6.05 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 The Category 1 submission requested an Authority Required (Streamlined) listing for nivolumab for treatment of advanced or metastatic oesophageal squamous cell carcinoma (OSCC) in patients who have failed one fluoropyrimidine and platinum (FP)-based chemotherapy treatment regimen, with a World Health Organisation (WHO) performance status (PS) of 0 or 1.

1.2 The requested basis for listing is a cost-effectiveness analysis compared to single agent chemotherapy of docetaxel, paclitaxel or irinotecan (Table 1). The submission referred to monotherapy with docetaxel or paclitaxel as investigator's choice (IC) and this terminology will be used herein for consistency. Despite irinotecan being nominated as one of the main comparators, the submission did not present any clinical evidence comparing nivolumab to irinotecan nor include irinotecan in the economic analysis (paragraph 5.2).

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

Component	Description
Population	Patients with oesophageal squamous cell carcinoma refractory to prior fluoropyrimidine and platinum-based chemotherapy.
Intervention	Nivolumab (NIVO) 240 mg administered as an IV infusion over 30 minutes at 2-week intervals; or NIVO 480 mg administered as an IV infusion over 30 minutes at 4 week intervals. Treatment to be continued until progressive disease as assessed according to the RECIST guidelines.
Comparator	Single agent chemotherapy (docetaxel/paclitaxel/irinotecan).
Outcomes	Overall survival, progression free survival, objective response rate. Quality of life during treatment. Safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation.
Clinical claim	NIVO is superior in terms of efficacy compared to single agent chemotherapy and has a favourable safety profile for the treatment of refractory oesophageal squamous cell carcinoma after prior fluoropyrimidine and platinum-based chemotherapy.

Source: Table 1, p12 of the submission.
AE = adverse event; SAE = serious adverse event; IV = intravenous; NIVO = nivolumab; RECIST= Response Evaluation Criteria in Solid Tumour

2 Background

Registration status

2.1 Nivolumab was TGA registered on 22 February 2021 for the following indication:

OPDIVO, as monotherapy, is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior FP-based chemotherapy.

Previous PBAC consideration

2.2 This was the first submission for OSCC. Nivolumab is currently PBS listed for non-small lung cancer, renal cell carcinoma, malignant melanoma, and carcinoma of the oral cavity, pharynx or larynx.

3 Requested listing

3.1 The requested listing for nivolumab is provided below. Suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT Form	**PBS item code**	**Maximum amount**	**No. of Repeats**
NIVOLUMAB Injection	New (Public) New (Private)	480 mg	8
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒ *Medical Practitioners*			
Restriction type: ☒Authority Required – Streamlined [New 2]			
~~**Administrative Advice:** No increase in the maximum number of repeats may be authorised.~~			
Administrative Advice: Special Pricing Arrangements apply.			
Episodicity: [blank]			
Severity: Advanced or metastatic			
Condition: ~~oesophageal~~ squamous cell carcinoma *of oesophagus*			
Indication: Advanced or metastatic ~~oesophageal~~ squamous cell carcinoma *of oesophagus*			
Treatment Phase: Initial treatment			
~~**Clinical criteria**~~:			
~~Patient must have failed one fluoropyrimidine and platinum based chemotherapy treatment regimen~~			
~~**AND**~~			
Clinical criteria:			
Patient must have a WHO performance status of 0 or 1			
AND			
~~**Clinical criteria:**~~			
~~The treatment must be the sole PBS-subsidised therapy for this condition~~			
~~Patient must not have received prior PBS funded treatment with a programmed cell death-1 (PD-1) inhibitor for this condition.~~			
Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition.			
AND			
Treatment criteria:			
Patient must be undergoing treatment with this drug only after having disease progression/recurrence following treatment with chemotherapy that contains at least each of: (i) a platinum drug, (ii) a fluoropyrimidine drug			
AND			
Treatment criteria:			
Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy for this PBS indication			
Administrative Advice:			

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
Administrative Advice: *Up to 17 repeats may be sought if dosing at 240 mg every 2 weeks. Where an increase is sought, the benefit is no longer a Streamlined benefit. Seek approval prior to issuing the prescription.*

MEDICINAL PRODUCT **Form**	**PBS item code**	**Maximum amount**	**No. of Repeats**
NIVOLUMAB Injection	New (Public) New (Private)	480 mg	11
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒ *Medical Practitioners*			
Restriction type: ☒ Authority Required – Streamlined [New 4]			
Indication: Advanced or metastatic ~~oesophageal~~ squamous cell carcinoma *of oesophagus*			
Treatment Phase: Continuing treatment			
~~**Clinical criteria:**~~			
~~Patient must have previously received PBS-subsidised treatment with this drug for this condition~~			
~~**AND**~~			
Clinical criteria:			
Patient must have stable or responding disease			
AND			
~~**Clinical criteria:**~~			
~~The treatment must be the sole PBS-subsidised therapy for this condition.~~			
Treatment criteria:			
Patient must be undergoing continuing PBS treatment with this drug for this PBS-indication, evidenced by at least one completed PBS claim under the 'Initial treatment' phase			
AND			
Treatment criteria:			
Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy for this PBS indication			
Administrative Advice: *Up to 23 repeats may be sought if dosing at 240 mg every 2 weeks. Where an increase is sought, the benefit is no longer a Streamlined benefit. Seek approval prior to issuing the prescription.*			

3.2 The sponsor proposed a Special Pricing Arrangement (SPA).

3.3 The proposed PBS listing did not restrict use to only second line (2L) (the target population described in the submission). Patients who have previously failed treatment with FP-based chemotherapy treatment regimen, and then failed 2L taxane or irinotecan monotherapy (the proposed comparator), would still be eligible for treatment with nivolumab under the proposed restriction.

3.4 The Pre-Sub-Committee Response (PSCR) stated that the requested PBS restriction is consistent with the circumstances of use in ATTRACTION-3 the pivotal clinical trial, with patient eligibility based on disease stage (advanced or metastatic) and response to prior therapy (refractory or intolerant to one previous FP chemotherapy). The PSCR stated that approximately 32-34% of patients enrolled in the ATTRACTION-3 trial had

received more than one prior line of therapy at baseline. The PBAC agreed with the ESC that most of the use would be in the 2L setting and that the requested listing was reasonable. The PBAC and the ESC acknowledged that few 3L patients would satisfy the criterion of WHO PS 0 or 1, and that clinicians will be unlikely to use 2L single agent chemotherapy if nivolumab is available.

3.5 The Product Information stated that the dosing in this condition is either 240 mg administered every 2 weeks or 480 mg administered every 4 weeks. The requested maximum amount of 480 mg would facilitate either dosing regimen, however, the requested number of repeats is intended for 4-weekly dosing and a patient receiving 240 mg every 2 weeks would utilise repeat prescriptions more frequently than a patient being administered the drug every 4 weeks. A separate listing for the 240 mg every 2 weeks dosing regimen was not recommended. A prescriber dosing their patient at 240 mg every 2 weeks could either write prescriptions more frequently, or, request an increase in repeats from Services Australia.

3.6 The Secretariat had suggested that the PBS indication refer to the condition using the fully specified name in SNOMED CT (Systematised Nomenclature of Medicine – Clinical Terms), which is 'squamous cell carcinoma of oesophagus'.

3.7 The submission did not identify any trial subjects requiring transitioning to PBS supply arrangements ('grandfather' patients).

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

4 Population and disease

4.1 Oesophageal cancer (OC) is estimated as the 19th most commonly diagnosed type of cancer in Australia and the 12th leading cause of cancer death (Australian Institute of Health and Welfare, 2018). It typically occurs in one of two histological forms, OSCC arising predominantly in the middle and lower thirds of the oesophagus, and oesophageal adenocarcinoma (OAC) predominating in the distal oesophagus (Zhang, 2015). The submission estimated that OSCC accounts for 35% of OCs in Australia. The five-year survival rate for distant (metastasised) OC was estimated as 4.9% using the US Surveillance, Epidemiology and End Results (SEER) data.

4.2 The target population for this submission is patients with OSCC of good performance status (WHO/ECOG 0-1) being considered for second line (2L) systemic anticancer treatment following failure of prior FP treatment. The submission stated that for eligible patients, nivolumab will substitute for current single agent 2L systemic chemotherapy options and may also substitute best supportive care for some patients. It was noted that a number of immunotherapies (intended as monotherapy,

or in combination with chemotherapy) are in development for the treatment of OC for various treatment settings[1].

5 Comparator

5.1 The submission nominated single agent chemotherapy (one of paclitaxel, docetaxel or irinotecan) as the main comparator. The nominated comparators have unrestricted listings on the PBS and are not TGA-approved for OSCC. The main arguments provided in support of this nomination were that:

- These represent the most commonly prescribed agents in Australian clinical practice for the treatment of 2L OSCC as advised by an expert advisory board gathered by the sponsor.
- Use of these chemotherapy agents were consistent with category 1 recommendations in the National Comprehensive Cancer Network (NCCN) clinical practice guidelines (NCCN, 2020) for 2L OSCC; and
- Taxane monotherapy (i.e. paclitaxel or docetaxel) is indicated for 2L treatment of OC by the European Society for Medical Oncology (ESMO) clinical practice guidelines.

5.2 Overall, the nomination of single agent chemotherapy as the comparator was appropriate. However, though irinotecan was nominated as one of the main comparators, the submission did not present any clinical evidence comparing nivolumab to irinotecan nor include irinotecan in the economic analysis. Additionally, it was noted that though best supportive care was included in the clinical management algorithm as a possible alternative to both 2L chemotherapy and nivolumab, and the submission substituted best supportive care with nivolumab in their financial estimates, it was not nominated as a comparator in the submission. The PBAC and the ESC considered the use of irinotecan in clinical practice would be low.

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 organisations (3) via the Consumer Comments facility on the PBS website.

[1] Kelly RJ. The emerging role of immunotherapy for esophageal cancer. Curr Opin Gastroenterol. 2019;35(4):337-343. doi:10.1097/MOG.0000000000000542

6.3 The PBAC noted the advice received from Rare Cancers Australia and the Pancare Foundation clarifying the likely use of nivolumab in 2L OSCC in clinical practice. Rare Cancers Australia stated that patients treated with nivolumab compared with chemotherapy in the 2L setting experienced significantly better overall survival and improved quality of life. The Pancare Foundation similarly emphasised improved survival and tolerance with nivolumab treatment and commented that the poor survival rate and concern regarding chemotherapy side effects urgently mandates more effective and tolerable treatment options. The PBAC noted that this advice was supportive of the evidence provided in the submission.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the nivolumab in 2L OSCC submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the ATTRACTION-3 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab in 2L OSCC, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[2], based on a comparison with taxane therapy.

Clinical trials

6.5 The submission was based on one head-to-head trial, ATTRACTION-3 (N=419) comparing nivolumab (N=210) to IC (N=208) of docetaxel or paclitaxel, in patients with OSCC refractory or intolerant to combination therapy with FP-based therapy.

6.6 Details of the trial presented in the submission are provided in Table 2.

[2] 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: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ATTRACTION-3 (CA209-473, ONO-4538)	Pelosof, L et al. Benefit-risk summary of nivolumab for the treatment of patients with unresectable, advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.	*The Oncologist* 2021; 25: 1-7.
	Thuss-Patience, P et al. Nivolumab versus chemotherapy in advanced esophageal squamous cell carcinoma (AESCC): The phase 3 attraction-2 study.	*Oncol Research and Treatment* 2020; 43: S1-67.
	Takahashi, M et al. Nivolumab versus chemotherapy in Japanese patients with advanced esophageal squamous cell carcinoma: a subgroup analysis of a multicentre, randomized, open-label, phase 3 trial (ATTRACTION-3).	*Esophagus* 2021; 18: 90-99.
	Kato, K et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial.	*Lancet Oncol* 2019; 20 (11): 1506-1517.
	Cho, BC et al. Nivolumab versus chemotherapy in advanced esophageal squamous cell carcinoma (ESCC): The phase III ATTRACTION-3 study.	*Ann of Oncol* 2019; 30: S5 (v873-874).
	Chin K, Kate, K, Byoung CC et al. Three-year followup of ATTRACTION-3: A phase 3 study of nivolumab in patients with advanced esophageal squamous cell carcinoma that is refractory or intolerant to previous chemotherapy.	Presented at ASCO Gastrointestinal Cancers Symposium January 2021, poster 204.
	ATTRACTION-3 Clinical Study Report: A multicentre, randomized, open-label study in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs.	CSR Dated 12 March 2019 (Full ITT analysis).
	ATTRACTION-3 Addendum 01 to the Clinical Study Report: A multicentre, randomized, open-label study in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs.	CSR Dated 25 June 2019 (Modified ITT analysis, excludes non-GCP compliant sites)
	ATTRACTION-3 Early Death Analysis Report	Dated 13 Dec 2019.
	ATTRACTION-3: 3 year update.	Dated January 2021. (selected updates for ITT population only)

Source: Table14, p33 of the submission.
ASCO = American Society of Clinical Oncology; CSR = clinical study report; GCP = Good Clinical Practice; ITT = intention-to-treat.

6.7 The key features of the direct randomised trial are summarised in Table 3. Overall, there was a low to moderate risk of bias in the ATTRACTION-3 trial. Although the primary outcome of overall survival (OS) was objective, the open label design may have influenced key secondary outcomes of objective response rate (ORR), progression-free survival (PFS) and quality of life.

Table 3: Key features of the included evidence

Trial, N	Trial Design	Interventions	Population	Main Outcomes
ATTRACTION-3 N=419	Phase 3, R, OL, MC, MN	NIVO: 240 mg, IV, Q2W vs. DOC: 75 mg/m^2, IV, Q3W or PAC: 100 mg/m^2 IV, Q1W x 6 with 2W off Treatment until progression or unacceptable toxicity. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression was permitted if the subject had investigator-assessed clinical benefit and tolerated study drug.	OSCC refractory or intolerant to combination therapy with fluoropyrimidine and platinum based drugs.	Primary: OS Key secondary: ORR, PFS

Source: Table 15, p35 of the submission.

DOC = docetaxel; IV = intravenous; MC = multicentre; MN = multinational; NIVO = nivolumab; OL= open-label; ORR = objective response rate; OS = overall survival; OSCC = oesophageal squamous cell carcinoma; PAC = paclitaxel; PFS = progression-free survival; Q1W = every week; Q2W = every 2 weeks; Q3W = every 3 weeks; R: randomised; RECIST: Response Evaluation Criteria In Solid Tumors Version 1.1; 2W = 2 weeks.

6.8 Two separate clinical study reports (CSRs) from two intention-to-treat (ITT) populations were available for ATTRACTION-3 for the 18 month data cut off. In addition to the full ITT population which included all enrolled patients (n=419), analysis of a modified ITT population (n=388) was also presented. The modified ITT population analysis was based on the same data cut-off date, but it excluded 31 patients from 6 Taiwanese sites due to non-compliance with Good Clinical Practice (GCP) procedures. The sponsor presented the full ITT analysis as the primary clinical dataset and considered that the GCP non-compliance did not compromise patient safety or the interpretation or scientific value of the reported trial results. The submission provided a comparison of the full-ITT and modified-ITT analyses as an exploratory analysis which indicated no substantial differences.

6.9 During the preparation of the submission, a three-year partial update on the full-ITT population became available, providing an additional 1.5 years of follow-up to the initial analysis. Where applicable, this information was included along with the presentation of the full-ITT results in the submission. Not all relevant information (e.g. PFS rates) from the three-year update was provided, which was only presented in the form of a 17-page report.

6.10 In ATTRACTION-3, treatment was to continue until disease progression, though patients were allowed to continue treatment beyond progression under certain circumstances. Approximately 50% (83/167) of patients treated with nivolumab continued nivolumab treatment beyond progression. Comparatively, only 1.9% (3/162) of patients treated with IC continued with taxane therapy beyond progression.

6.11 Aside from treatment beyond progression with the randomised therapy, patients in ATTRACTION-3 were eligible to receive any subsequent cancer treatment deemed appropriate by the investigator after experiencing disease progression on the trial. As noted by the [redacted]

[redacted]

6.12 ATTRACTION-3 enrolled predominantly an Asian population (401/419, 95.7%), with only a small number of non-Asian patients (18/419, 4.3%) who were all of Western origin. This is a potential applicability issue given a much higher proportion of Western patients is expected to be treated in Australian clinical practice. The PSCR stated that both the European Medicines Agency (EMA) and the National Institute for Health and Care Excellence (NICE) have accepted that the results from ATTRACTION-3 are generalisable to their respective Western OSCC populations, i.e. with a lower proportion of Asian patients than included in the trial. The PSCR noted that the NICE final approval document stated: "…although the trials were mainly done in Asia, there is no difference in the underlying biology of oesophageal squamous cell cancer compared with people in the UK".[3]

6.13 The primary outcome of ATTRACTION-3 was OS, with objective response rate (ORR) and progression free survival (PFS) being secondary outcomes. If superiority in OS was demonstrated for patients randomised to the nivolumab group, a hierarchical testing procedure was implemented to test for the secondary endpoints preserving the study-wise type 1 error rate at 5% in the following order: ORR, PFS. Two-sided testing was performed with a 5% significance level.

6.14 The sponsor proposed that the minimal clinically important difference (MCID) for the primary outcome was an OS HR ≤0.8, corresponding to 2.5-6 months gain in median OS versus the current standard of care (Ellis et al 2014, p1278). This was based on recommended targets for clinically important differences in clinical trial endpoints of OS proposed for various solid tumour types (colon, pancreatic, lung, breast), developed by the American Society of Clinical Oncology (ASCO) (Ellis et al 2014), as targets specific to OSCC have not been published. The evaluation noted the recommended target HRs in Ellis et al 2014 ranged from 0.6 to 0.8 and a HR of 0.70 was used in the sample size calculation of the trial. As OSCC has not been previously considered by PBAC, previous MCID thresholds were not available for reference.

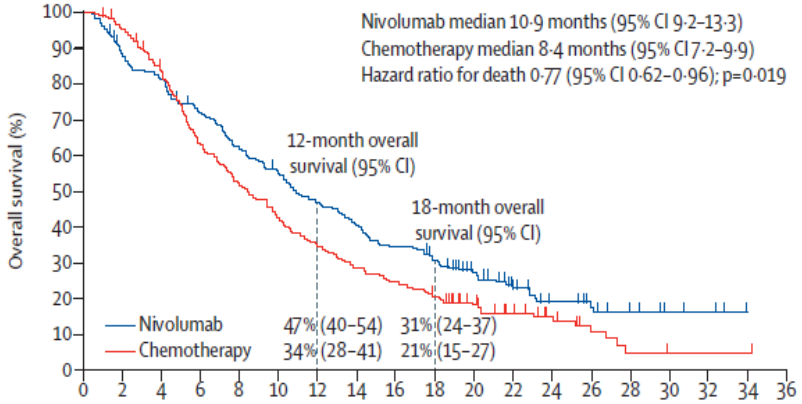
[3] https://www.nice.org.uk/guidance/gid-ta10222/documents/final-appraisal-determination-document-2

Comparative effectiveness

Primary outcome

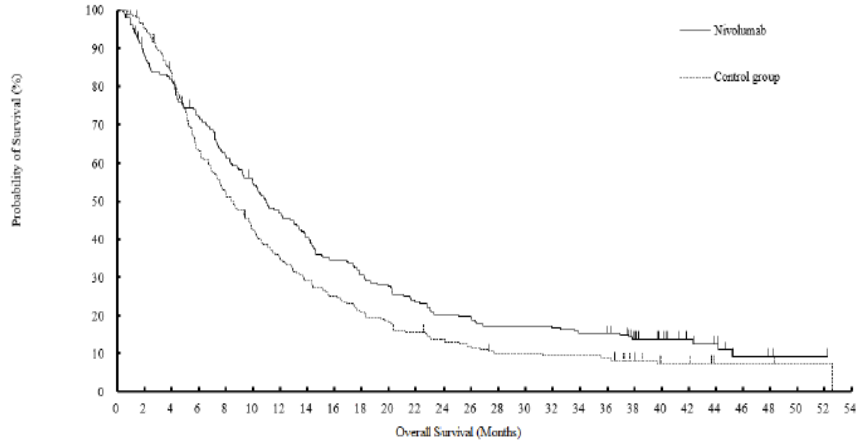
6.15 Figure 1 shows the OS Kaplan-Meier at both data cuts and Table 4 summarises the OS results for the ITT population.

Figure 1: Kaplan-Meier curve for overall survival at 18 month data cut (top) and 3 year data cut (bottom)



Number at risk (number censored)

Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
	(0)	(4)	(4)	(5)	(5)	(6)	(6)	(6)	(6)	(8)	(19)	(31)	(35)	(38)	(43)	(46)	(47)	(50)	(50)
Chemotherapy	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0
	(0)	(3)	(7)	(8)	(8)	(9)	(9)	(9)	(9)	(10)	(19)	(26)	(30)	(33)	(34)	(35)	(35)	(35)	(36)



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54
Nivolumab	210	182	167	147	126	111	95	82	70	62	56	48	41	39	35	35	34	31	31	22	17	12	9	3	2	1	1	0
Control group	209	196	170	127	106	85	69	58	50	42	36	31	26	22	18	18	17	17	16	11	7	6	2	2	2	1	1	0

Source: Figure 2A, Kato 2019 and Figure 6, p61 of the submission

Table 4: Results of overall survival in the trial

Efficacy parameter	NIVO (n=210)	IC		
		Total (n=209)	DOC (n=65)	PAC (n=144)
18 month data cut				
Events, n (%)	160 (76.2)	173 (82.8)	52 (80.0)	121 (84.0)
Median[a], months (95% CI)	10.91 (9.23, 13.34)	8.38 (7.20, 9.86)	7.62 (6.11, 10.68)	8.51 (6.87, 9.89)
Difference, months	NA	-2.53	-3.29	-2.4
HR (95% CI)[b], p-value[c]	NA	**0.77 (0.62, 0.96), p=0.0189**	0.78 (0.56, 1.07), p=NE	0.76 (0.60, 0.97), p=NE
OS rates[d]				
12-month	46.9 (39.9, 53.5)	34.4 (27.8, 40.9)	34.6 (23.1, 46.3)	34.3 (26.4, 42.1)
24-month	19.1 (13.3, 25.6)	15.1 (10.3, 20.9)	19.3 (10.4, 30.1)	13.1 (7.5, 20.1)
36-month	NR	NR	NR	NR
3 year data cut				
Events, n (%)	179 (85.2)	186 (89.0)	NR	NR
Median[a], months (95% CI)	10.91 (9.23, 13.34)	8.51 (7.29, 9.86)	NR	NR
Difference, months	NA	-2.4	NR	NR
HR (95% CI)[b], p-value[c]	NA	**0.79 (0.64, 0.97), p=0.0264**	NR	NR
OS rates[d]				
12-month	46.9 (39.9, 53.5)	34.7 (28.2, 41.2)	NR	NR
24-month	20.2 (15.0, 26.0)	13.5 (9.2, 18.6)	NR	NR
36-month	15.3 (10.7, 20.6)	8.7 (5.3, 13.2)	NR	NR

Source: Table 28, p59 of the submission and Table 1, p5 of the 3 year update report.
CI = confidence interval; DOC = docetaxel; IC = investigator's choice; NA = not applicable; NE = not evaluated; NIVO = nivolumab; NR = not reported; OS= overall survival; PAC = paclitaxel.
1 month = 30.4375 days
a This estimation was conducted by using the KM method.
b Hazard ratio and the corresponding two-sided 95% CI for the nivolumab group relative to each column group was calculated by using the stratified Cox proportional-hazards model stratified by the three stratification factors (IWRS source); 1) Location (Japan vs. Rest of the world) 2) The number of organs with metastases (<=1 vs. >=2) 3) PD-L1 expression (>=1% vs. <1% or indeterminate).
c Nivolumab group and total of control group were used for the calculation of p-value. The calculation of p-value was conducted by using the two-sided stratified log-rank test stratified by the three stratification factors (IWRS source) presented 1)-3).
d the estimation of the survival rate was derived from the Kaplan-Meier estimate and corresponding CI was derived based on Greenwood formula for variance and on log-log transformation.
Values in bold indicate statistical significant differences.

6.16 At both data cuts, statistically significant improvements in median OS associated with nivolumab versus IC were reported (18 months: HR = 0.77, 95% confidence interval [CI] 0.62, 0.96; p= 0.0189; 3 years: HR = 0.79, 95% CI 0.64, 0.97; p= 0.0264). The resulting point estimate for the OS HR met the submission's nominated MCID of ≤0.8 at both data cuts, however the upper 95% CI did not meet the MCID at either data cut.

6.17 The Kaplan-Meier OS curves crossed around the five-month time point. Before crossing, the OS curve for nivolumab was under the IC curve, suggesting there was an increased hazard of death associated with nivolumab which was reversed after approximately five months. The crossing over of the OS curves suggests that the assumption of proportional hazards was violated and given this, the ESC considered HRs may not provide the best measure of relative benefit.

6.18 The PSCR stated that a delayed treatment effect versus chemotherapy is a well-characterised feature of immunotherapy (Ferrara 2018) and claimed that this does not

negate the significance of the long-term, durable OS demonstrated by nivolumab treatment in ATTRACTION-3. The ESC acknowledged that this is a common issue for immunotherapy versus chemotherapy studies, and the higher HR for nivolumab prior to 5 months likely reflects a poor prognosis population, increased time to response for immunotherapy, and/or a subgroup that will not respond to immunotherapy.

Secondary outcomes

6.19 Table 5 summarises the ORR statistics for the ITT population and response evaluable set (RES) population (which included all patients except those with incomplete target lesion measurements) at the 18 month and 3 year data cut respectively. Additional detail around responses achieved and duration of response were not provided for the 3 year data cut. Only ORR statistics for the RES population were available for this time point.

Table 5: Results of objective response rate in the trial

Efficacy parameter	NIVO (n=210)	IC		
		Total (n=209)	DOC (n=65)	PAC (n=144)
18 month data cut				
Responses achieved, n (%)				
Complete response	1 (0.5)	2 (1.0)	0	2 (1.4)
Partial response	32 (15.2)	32 (15.3)	8 (12.3)	24 (16.7)
Stable disease	31 (14.8)	65 (31.1)	19 (29.2)	46 (31.9)
Progressive disease	94 (44.8)	51 (24.4)	20 (30.8)	31 (21.5)
Not evaluated	52 (24.8)	59 (28.2)	18 (27.7)	41 (28.5)
Objective response rate				
ORR, n (%) (CR+PR)	33 (15.7)	34 (16.3)	8 (12.3)	26 (18.*1*)
95% CI	(11.1, 21.4)	(11.5, 22.0)	(5.5, 22.8)	(12.1, 25.3)
Duration of response for objective response rate				
Median (95%CI)	6.93 (5.39, 11.14)	3.91 (2.79, 4.17)	4.37 (2.56, 7.06)	3.25 (2.79, 4.17)
Min-max	2.1-18.0[a]	2.5[a] -18.0[a]	2.6-12.6	2.5[a] -18.0[a]
Disease control rate				
DCR, n (%) (CR+PR+SD*)*	64 (30.5)	99 (47.4)	27 (41.5)	72 (50.0)
95% CI	(24.3, 37.2)	(40.4, 54.4)	(29.4, 54.4)	(41.6, 58.4)
3 year data cut				
Objective response rate				
ORR, n (%) (CR+PR)	33 (15.7)	34 (16.3)	NR	NR
95% CI	(13.7, 26.0)	(15.4, 28.8)	NR	NR

Source: Table 30, p63 of the submission, Table 14.2.2-5-1 & 14.2.2-5-2, p341&342 of Clinical Study Report dated 12 March 2019, and Table 1, p5 of the 3 year update report.

CI = Confidence interval; CR = complete response; DCR=disease control rate; DOC = docetaxel; IC=investigator choice; NA = not applicable; NIVO = nivolumab; NR=not reported; ORR = objective response rate; PAC = paclitaxel; PR = partial response; SD = stable disease

1 month = 30.4375 days

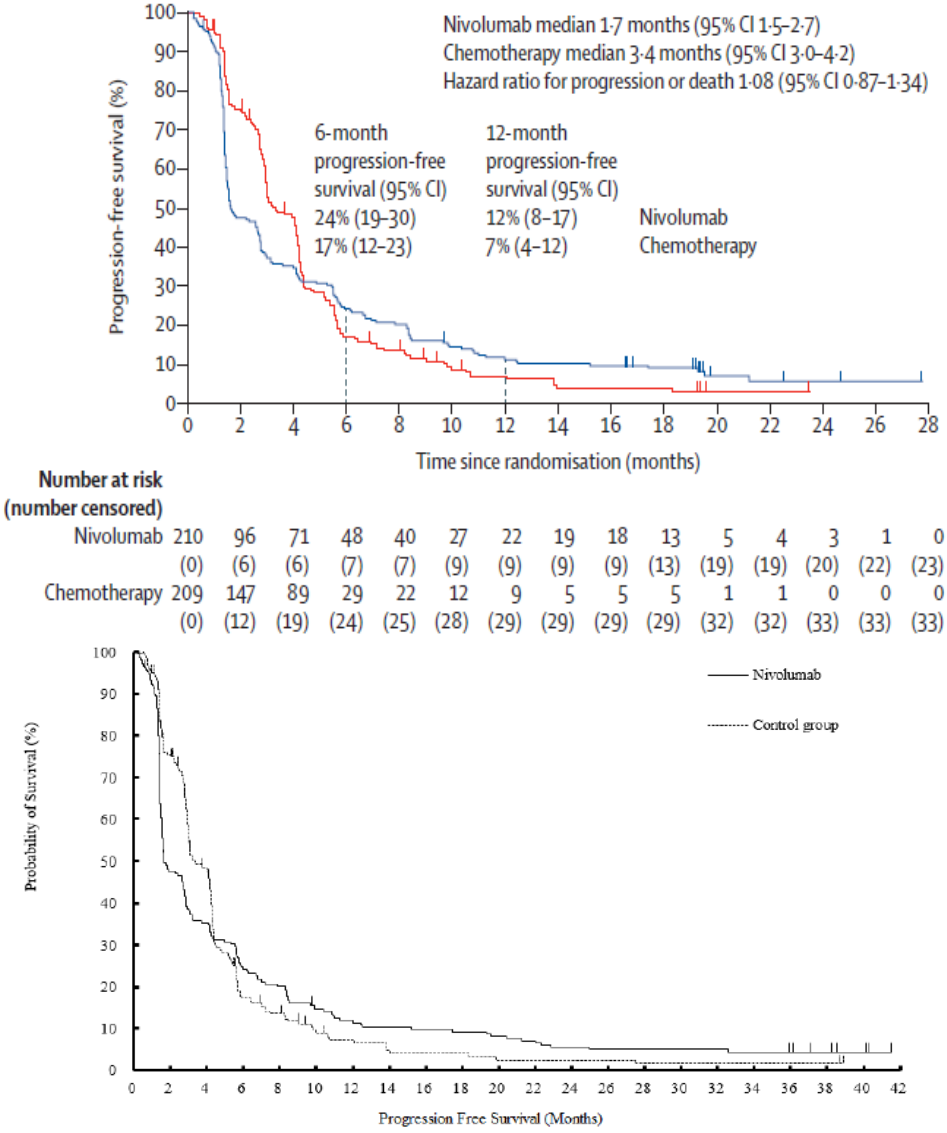
a Censored

6.20 A similar proportion of patients across treatment arms achieved a complete or partial response (p=0.6323, using response evaluable population at 18 month and 3 year data cut). The ESC noted that while the ORR for the nivolumab and chemotherapy treatment arms was similar, the median duration of response was longer for the nivolumab arm (6.9 months vs 3.9 months).

6.21 Overall, a larger proportion of patients randomised to the IC group achieved disease control (complete response + partial response + stable disease), compared to patients randomised to the nivolumab group (difference = -25.41%, 95% CI -35.64, -15.19, response evaluable population), though formal hypothesis testing was not conducted.

6.22 Figure 2 shows the PFS Kaplan-Meier at both data cuts and Table 6 summarises the PFS statistics for the ITT population.

Figure 2: Kaplan-Meier curve for progression free survival at 18 month data cut (top) and 3 year data cut (bottom)



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
Nivolumab	210	96	71	48	40	27	22	19	18	17	15	12	10	9	9	9	9	8	7	5	3	0
Control group	209	147	89	29	22	12	9	5	5	5	3	3	3	3	2	2	2	2	2	2	0	0

Source: Figure 2C, Kato 2019 and Figure 7, p65 of the submission

Table 6: Results of progression free survival in the trial

Efficacy parameter	NIVO (n=210)	IC		
		Total (n=209)	DOC (n=65)	PAC (n=144)
18 month data cut				
Number of events, n (%)	187 (89.0)	176 (84.2)	55 (84.6)	121 (84.0)
Progression	167 (79.5)	162 (77.5)	53 (81.5)	109 (75.7)
Deaths	20 (9.5)	14 (6.7)	2 (3.1)	12 (8.3)
Number of censored	23 (11.0)	33 (15.8)	10 (15.4)	23 (16.0)
Median, months (95%CI)[a]	1.68 (1.51, 2.73)	3.35 (2.99, 4.21)	3.02 (2.46, 4.21)	4.11 (2.99, 4.27)
HR (95% CI)[b]	NA	1.08 (0.87, 1.34)	0.97 (0.71, 1.33)	1.15 (0.91, 1.46)
PFS rate[c]				
3-month	38.2 (31.5, 44.8)	56.6 (49.4, 63.3)	52.5 (39.2, 64.1)	58.6 (49.7, 66.4)
6-month	24.2 (18.6, 30.3)	17.2 (12.1, 23.1)	16.3 (8.0, 27.3)	17.6 (11.5, 24.8)
12-month	11.9 (7.8, 16.8)	7.2 (3.8, 12.0)	7.7 (2.3, 17.4)	6.9 (3.1, 12.8)
18-month	9.0 (5.5, 13.6)	4.0 (1.6, 8.2)	2.6 (0.2, 11.1)	4.6 (1.6, 10.1)
3 year data cut				
Events, n (%)	193 (91.9)	178 (85.2)	NR	NR
Median, months (95%CI)[a]	1.68 (1.51, 2.73)	3.35 (2.99, 4.21)	NR	NR
HR (95%CI)[b]	NA	1.07 (0.87, 1.33)	NR	NR

Source: Table 31, p64 of the submission and Table 1, p5 of the 3 year update report.
CI = Confidence interval; DOC = docetaxel; KM = Kaplan Meier; NA = not applicable; NIVO = nivolumab; NR=not reported; PAC = paclitaxel
1 month = 30.4375 days
a This estimation was conducted by using the KM method
b Hazard ratio and the corresponding two-sided 95% CI for the nivolumab group relative to the each column group was calculated by using the stratified Cox proportional-hazards model stratified by the following three stratification factors (IWRS source). 1) Location (Japan vs. Rest of the world) 2) The number of organs with metastases (<=1 vs. >=2) 3) PD-L1 expression (>=1% vs. <1% or indeterminate). Because nivolumab did not demonstrate a significant improvement in ORR, PFS was not formally compared between the two treatment groups using the stratified logrank test with the randomisation factors as the stratification factors.
c The estimation of the PFS rate was derived from the Kaplan-Meier estimate and corresponding CI was derived based on Greenwood formula for variance and on log-log transformation.

6.23 As with OS, the Kaplan-Meier curves for PFS crossed around the four-month time point. Before crossing, there was an increased hazard of progression or death associated with nivolumab. As with OS, the crossing of the curves indicate that the assumption of proportion hazards was violated, and given this, HRs may not provide the best measure of relative benefit. As nivolumab did not demonstrate a significant improvement in ORR, PFS was not formally compared between the two treatment groups.

6.24 General health status was measured using the EQ-5D. The publication for ATTRACTION-3 (Kato 2019, p1513) reported an overall significant on-treatment improvement in quality of life for patients given nivolumab compared to patients given IC for VAS scores (least square mean=6.9, 95%CI: 3.0, 10.9; p<0.001) and utility index (least square mean=0.076, 95%CI: 0.011, 0.142; p=0.023) calculated for on treatment data through week 42.

6.25 The baseline mean EQ-5D in the nivolumab arm was higher than the mean EQ-5D in the IC arm (0.835 vs 0.787), suggesting that patients in the nivolumab arm already had a better quality of life at baseline, and any incremental quality of life benefits which did not adjust for the difference in baseline quality of life may be biased in favour of

nivolumab. Patient reported outcomes in ATTRACTION-3 may also have been biased due to the open label design of the trial.

6.26 The PBAC noted there was no significant treatment effect interaction by age (<65 years, ≥ 65 years), PD-L1 expression (<1% TPS, ≥1% TPS) or race (Asian, White) but noted the small number of non-Asian patients in the trial.

Comparative harms

6.27 Nivolumab has been available in Australia since 2016 and has been approved by the TGA for use in multiple indications, and as such nivolumab's safety profile is well characterised. The safety profile for IC is also well characterised.

6.28 The three-year data cut summary of adverse events (AEs) in ATTRACTION-3 is presented in Table 7. Results indicated patients treated with nivolumab had a significantly lower risk of experiencing all causality or drug-related AEs associated compared to patients treated with IC.

Table 7: Summary of adverse events in the trial (3 year data cut)

n, (%)		NIVO n= 209	IC n= 208	RR (95% CI)	RD (95% CI)
All causality					
AEs	Any grade	189 (90.4)	205 (98.6)	0.92 (0.88,0.96)	-0.08 (-0.12,-0.04)
	Grade 3-4	83 (39.7)	148 (71.2)	0.56 (0.47,0.68)	-0.31 (-0.40,-0.22)
SAEs	Any grade	70 (33.5)	78 (37.5)	0.89 (0.69,1.16)	-0.04 (-0.13,0.05)
	Grade 3-4	45 (21.5)	64 (30.8)	0.70 (0.50,0.97)	-0.09 (-0.18,-0.01)
AEs leading to discontinuation	Any grade	30 (14.4)	34 (16.3)	0.88 (0.56,1.38)	-0.02 (-0.09,0.05)
	Grade 3-4	11 (5.3)	22 (10.6)	0.50 (0.25,1.00)	-0.05 (-0.10,0.00)
Drug-related					
AEs	Any grade	138 (66.0)	198 (95.2)	0.69 (0.63,0.77)	-0.29 (-0.36,-0.22)
	Grade 3-4	40 (19.1)	131 (63.0)	0.30 (0.23,0.41)	-0.44 (-0.52,-0.35)
SAEs	Any grade	35 (16.7)	47 (22.6)	0.74 (0.50,1.10)	-0.06 (-0.13,0.02)
	Grade 3-4	22 (10.5)	39 (18.8)	0.56 (0.35,0.91)	-0.08 (-0.15,-0.01)
AEs leading to discontinuation	Any grade	18 (8.6)	20 (9.6)	0.90 (0.49,1.64)	-0.01 (-0.07,0.05)
	Grade 3-4	8 (3.8)	12 (5.8)	0.66 (0.28,1.59)	-0.02 (-0.06,0.02)
Deaths					
Overall (all treated population)		178 (85.2)	186 (89.4)	0.95 (0.89,1.02)	-0.04 (-0.11,0.02)
Within 28 days of the last dose		19 (9.1)	9 (4.3)	2.10 (0.97,4.54)	0.05 (0.00,0.10)
Within 100 days of the last dose		62 (29.7)	65 (31.3)	0.95 (0.71,1.27)	-0.02 (-0.10,0.07)

Source: Table 33, p67 of the submission.

AEs = adverse events; CI = confidence interval; IC = investigators choice; NIVO = nivolumab; SAEs = serious adverse events; RD = risk difference; RR = relative risk

6.29 A summary of the drug-related AEs which were significantly different between treatment arms at the 18 month follow up is presented in Table 8.

Table 8: Drug-related adverse events which were significantly different between nivolumab and IC in ATTRACTION-3 at 18 month follow up

Adverse Event		NIVO (N=209), n (%)	IC (N=208), n (%)	RR (95%CI)	RD (95%CI)
Any adverse event	Any grade	137 (65.6)	198 (95.2)	0.69 (0.62, 0.76)	-0.30 (-0.37, -0.30)
	Grade 3-4	38 (18.2)	131 (62.7)	0.29 (0.21, 0.39)	-0.45 (-0.53, -0.36)
Hypothyroidism	Any grade	18 (8.1)	1 (0.5)	16.92 (2.27, 125.98)	0.08 (0.04, 0.11)
	Grade 3-4	0 (0)	0 (0)	-	-
Decreased Appetite	Any grade	16 (7.7)	56 (26.9)	0.28 (0.17, 0.48)	-0.19 (-0.26, -0.12)
	Grade 3-4	2 (1)	10 (4.8)	0.20 (0.04, 0.90)	-0.03 (-0.07, -0.01)
Fatigue	Any grade	15 (7.2)	43 (20.7)	0.35 (0.20, 0.61)	-0.13 (-0.20, -0.07)
	Grade 3-4	1 (0.5)	9 (4.3)	0.11 (0.01, 0.87)	-0.04 (-0.07, -0.01)
Malaise	Any grade	9 (4.3)	45 (21.6)	0.20 (0.10, 0.40)	-0.17 (-0.24, -0.11)
	Grade 3-4	0 (0)	0 (0)	-	-
Anaemia	Any grade	5 (2.4)	49 (23.6)	0.10 (0.04, 0.25)	-0.21 (-0.27, -0.15)
	Grade 3-4	4 (1.9)	19 (9.1)	0.21 (0.07, 0.61)	-0.07 (-0.12, -0.03)
Stomatitis	Any grade	5 (2.4)	25 (12)	0.20 (0.08, 0.51)	-0.10 (-0.15, 0.05)
	Grade 3-4	1 (0.5)	1 (0.5)	1.00 (0.06, 15.81)	0.00 (-0.01, 0.01)
Constipation	Any grade	4 (1.9)	16 (7.7)	0.25 (0.08, 0.73)	-0.06 (-0.10, -0.02)
	Grade 3-4	0 (0)	0 (0)	-	-
Lymphocyte count decreased	Any grade	4 (1.9)	18 (8.7)	0.22 (0.08, 0.64)	-0.07 (-0.11, -0.02)
	Grade 3-4	2 (1)	12 (5.7)	0.17 (0.04, 0.73)	-0.05 (-0.08, -0.01)
Nausea	Any grade	4 (1.9)	34 (16.3)	0.12 (0.04, 0.32)	-0.14 (-0.20, -0.09)
	Grade 3-4	0 (0)	1 (0.5)	0.33 (0.01, 8.10)	0.00 (-0.02, 0.01)
Alopecia	Any grade	3 (1.4)	98 (47.1)	0.03 (0.01, 0.09)	-0.46 (-0.53, -0.39)
	Grade 3-4	0 (0)	0 (0)	-	-
Arthralgia	Any grade	3 (1.4)	21 (10.1)	0.14 (0.04, 0.47)	-0.09 (-0.13, -0.04)
	Grade 3-4	0 (0)	1 (0.5)	0.33 (0.01, 9.10)	0.00 (-0.02, 0.01)
Dysgeusia	Any grade	3 (1.4)	14 (6.7)	0.21 (0.06, 0.73)	-0.05 (-0.09, -0.02)
	Grade 3-4	0 (0)	0 (0)	-	-
Myalgia	Any grade	3 (1.4)	18 (8.7)	0.17 (0.05, 0.55)	-0.07 (-0.11, -0.03)
	Grade 3-4	1 (0.5)	0 (0)	2.99 (0.12, 72.87)	0.00 (-0.01, 0.02)
Neutrophil count decreased	Any grade	3 (1.4)	76 (36.5)	0.04 (0.01, 0.12)	-0.35 (-0.42, -0.28)
	Grade 3-4	1 (0.5)	59 (28.2)	0.02 (0.00, 0.12)	-0.28 (-0.34, -0.22)
Lung infection	Any grade	3 (1.4)	11 (5.3)	0.27 (0.08, 0.96)	-0.04 (-0.07, 0.00)
	Grade 3-4	1 (0.5)	6 (2.9)	0.17 (0.02, 1.37)	-0.02 (-0.05, 0.00_
WBC count decreased	Any grade	2 (1)	72 (34.6)	0.03 (0.01,0.11)	-0.34 (-0.40,-0.27)
	Grade 3-4	1 (0.5)	46 (22)	0.02 (0.00,0.16)	-0.22 (-0.27,-0.16)
Neutropenia	Any grade	1 (0.5)	40 (19.2)	0.02 (0.00,0.18)	-0.19 (-0.24,-0.13)
	Grade 3-4	0 (0)	29 (13.9)	0.02 (0.00,0.27)	-0.14 (-0.19,-0.09)
Peripheral sensory neuropathy	Any grade	1 (0.5)	47 (22.6)	0.02 (0.00,0.15)	-0.22 (-0.28,-0.16)
	Grade 3-4	0 (0)	1 (0.5)	0.33 (0.01,8.10)	0.00 (-0.02,0.01)
Vomiting	Any grade	1 (0.5)	14 (6.7)	0.07 (0.01,0.54)	-0.06 (-0.10,-0.03)
	Grade 3-4	0 (0)	1 (0.5)	0.33 (0.01,8.10)	0.00 (-0.02,0.01)
Febrile neutropenia	Any grade	0 (0)	22 (10.6)	0.02 (0.00,0.36)	-0.11 (-0.15,-0.06)
	Grade 3-4	0 (0)	22 (10.5)	0.02 (0.00,0.36)	-0.11 (-0.15,-0.06)
Leukopenia	Any grade	0 (0)	17 (8.2)	0.03 (0.00,0.47)	-0.08 (-0.12,-0.04)
	Grade 3-4	0 (0)	14 (6.7)	0.03 (0.00,0.57)	-0.07 (-0.10,-0.03)
Neuropathy peripheral	Any grade	0 (0)	22 (10.6)	0.02 (0.00,0.36)	-0.11 (-0.15,-0.06)
	Grade 3-4	0 (0)	1 (0.5)	0.33 (0.01,8.10)	0.00 (-0.02,0.01)

Source: Table 36, p76-77 of the submission

6.30 Overall, with the exception of hypothyroidism, patients treated with nivolumab were significantly less likely to experience drug-related adverse events. The ESC considered hypothyroidism was not a clinically significant adverse event and could be managed in clinical practice.

Benefits/harms

6.31 A summary of the comparative benefits for nivolumab versus IC is presented in the table below. A summary of the comparative harms was presented in Table 8.

Table 9: Summary of comparative benefits for nivolumab versus investigator's choice chemotherapy

Benefits			
Overall survival (median duration of follow up 10.55 months for nivolumab and 8.02 months for IC chemotherapy, at 18 month data cut)			
Event	**Nivolumab**	**IC chemotherapy**	**HR (95% CI)**
Deaths, n/N (%)	160/210 (76.2%)	173/209 (82.8%)	0.77 (0.62, 0.96) P=0.0189
Overall survival (at 3-year data cut)			
Deaths, n/N (%)	179/210 (85.2%)	186/209 (89.0%)	0.79 (0.64, 0.97) P=0.0264
Overall survival rates at various time points			**Difference**
12-month (95% CI)	46.9 (39.9, 53.5)	34.7 (28.2, 41.2)	12.2
24-month (95% CI)	20.2 (15.0, 26.0)	13.5 (9.2, 18.6)	6.7
36-month (95% CI)	15.3 (10.7, 20.6)	8.7 (5.3, 13.2)	6.6

CI = confidence interval; HR = hazard ratio; NR = not reported
Source: Table 28, p59 of the submission and Table 1, p5 of the 3 year update report.

6.32 On the basis of the direct evidence presented by the submission, for every 100 patients treated with nivolumab in comparison to IC, 13 additional people will be alive at 12 months and 7 additional people will be alive at 24 and 36 months.

6.33 On the basis of the direct evidence presented by the submission, for every 100 patients treated with nivolumab in comparison to IC and over a median duration of follow-up of 10.55 months (for nivolumab) and 8.02 months (for IC):

- Approximately 45 fewer patients will experience any adverse event (grade 3-4);
- Approximately 8 additional patients will experience hypothyroidism (any grade);
- Approximately 7 fewer patients will experience anaemia (grade 3-4);
- Approximately 14 fewer patients will experience neutropenia (grade 3-4);
- Approximately 11 fewer patients will experience febrile neutropenia (grade 3-4);

Clinical claim

6.34 The submission described nivolumab as superior in terms of effectiveness compared with IC (docetaxel or paclitaxel). The evaluation considered the therapeutic conclusion presented in the submission was subject to the following uncertainty:

- In ATTRACTION-3, while there was a statistically significant OS benefit (OS HR = 0.79, 95%CI 0.64, 0.97) there was a higher hazard of death associated with nivolumab in the beginning of treatment, with the Kaplan-Meier OS curves crossing around the five-month time point (paragraph 6.17).

- The incremental benefit of nivolumab in non-Asian patients was uncertain. Trial results were based on a trial population made up of mostly (~96%) Asian patients, with only a small number of Western patients. The PSCR stated that both the EMA and NICE have accepted that the results from ATTRACTION-3 are generalisable to their respective western OSCC populations (paragraph 6.12).
- Even though the OS HR point estimates met the submission's nominated MCID (OS HR ≤0.8) at both data cuts, the MCID targets provided by Ellis et al. ranged from 0.6-0.8 (a HR of 0.7 was assumed in the sample size calculation for ATTRACTION-3).
- No significant difference in ORR was reported between the two treatment groups in ATTRACTION-3. While ORR was comparable between nivolumab and IC, a larger proportion of patients randomised to the nivolumab group compared to the IC group experienced progressive disease as best response.
- As with OS, Kaplan-Meier PFS curves crossed around the four-month time point, before which there was an increased hazard of progression or death associated with nivolumab. The PSCR stated that PFS favours nivolumab after 4 months and is durable over the 3 years of available trial data. The PSCR further stated that, whilst ORR and PFS are not driving the OS results for patients treated with nivolumab, there is a marked difference in the median duration of response between treatment arms, which was substantially longer with nivolumab compared to IC (Table 5).

6.35 The PBAC considered that nivolumab provided a small OS benefit and improved quality of life in a poor prognosis patient group with a moderate clinical need. The PBAC noted the concerns raised in the evaluation but had high confidence that, overall, nivolumab is superior in terms of effectiveness compared with IC (docetaxel or paclitaxel). While the PBAC noted that there was a higher hazard of death with nivolumab up until approximately 5 months, it acknowledged that this has been observed for immunotherapy versus chemotherapy studies in other indications.

6.36 With regards to safety, the submission described nivolumab as favourable in terms of safety compared to IC. The ESC noted that TEAE rates were generally significantly reduced in the nivolumab arm, with the exception of hypothyroidism (which was a clinically manageable AE). The PBAC considered that nivolumab has an improved safety profile over chemotherapy and that the claim of superior comparative safety was reasonable.

Economic analysis

6.37 The submission presented a stepped economic evaluation based on the ATTRACTION-3 trial. The type of economic evaluation presented was a cost-utility analysis.

6.38 Table 10 and Table 11 present the summary of the model structure and the utilities used in the economic evaluation presented in the submission, respectively.

Table 10: Summary of model structure and rationale

Component	Description	Evaluation comments
Outcomes	Life years gained, quality-adjusted life years	Appropriate
Time horizon	Seven years in the model base case vs. minimum follow-up time of three years in the key trial	Given the nature of the disease and low 5-year survival rate, the evaluation considered a 7 year time horizon might be optimistic.
Health states	Alive without progression, alive following progression, death	Appropriate
Cycle length	1 week	Likely to be reasonable
Methods used to generate results	OS and PFS curves from ATTRACTION-3 were used to estimate the proportion of patients who are in each health state. KM estimates based on individual patient data was used for 40.2 months (174 cycles, median follow-up), after which an extrapolated function was used, until the time horizon of 7 years. TTD curves from ATTRACTION-3 were used to inform duration of therapy (up to 44.6 months (cycle 194) for nivolumab and 40.2 months (cycle 174) for IC). The expected costs of treating AEs were applied upfront at week 0. Ongoing costs for disease management differed by alive health states but were same for both treatment arms. Patients who died in a cycle had a terminal cost applied to that cycle. Utilities were assigned depending on the proportion of patients in each health state, as well as what treatment arm the patient was in, but was independent of whether the patient was on treatment or not. No disutility on AEs was considered.	The use of OS and PFS curves to inform partition survival analysis is reasonable. However, the submission's nominated extrapolations (as determined by the lowest AIC) appeared to have favoured nivolumab for both OS and PFS. e.g. for OS, it appeared to have overestimated OS in the nivolumab arm and underestimated OS in the IC arm when compared to the observed ATTRACTION-3 data up to 3.35 years. It was noted that clinical data from ATTRACTION-3 did not support a PFS benefit associated with nivolumab. The ESC considered it was not appropriate to assume a PFS benefit for nivolumab over the time horizon of the model and noted assuming the same IC PFS for both treatment arms increased the ICER by ~10%. No convergence of survival was assumed, which was optimistic and favoured nivolumab. Use of PFS to inform treatment duration rather than TTD was tested in a sensitivity analysis by the submission and was shown to have a moderate impact (19.5% increase) on the ICER. Applying the AE costs upfront will result in the cost of managing AEs not being discounted correctly, though this is not expected to have a large impact on the estimated ICER. Inclusion of terminal costs may not be appropriate given patients are not expected to be cured from the disease. The economic model did not adjust for disutility associated with AEs – this was assumed to be captured via the treatment-based health state.
Utilities	See Table 11	The evaluation considered the assumption that all patients in the nivolumab arm of the model would have higher utility irrespective of whether they remained on treatment or not was unlikely.

Source: Table 53, p112 of the submission, and complied during evaluation.

AE = adverse event; AIC = Akaike's information criteria; IC = investigator's choice; ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation.

Table 11: Utility values used in the economic evaluation

Health state utility Mean (95%CI)	NIVO	IC	Difference[a] (95% CI)	Overall
Alive without progression	0.796 (0.762, 0.830)	0.737 (0.705, 0.769)	0.059 (0.023, 0.095)[b]	0.767 (0.739, 0.794)[b]
Alive following progression	0.583 (0.530, 0.636)	0.519 (0.465, 0.572)	0.064 (0.005, 0.124)[b]	0.551 (0.506, 0.595)

Source: Table 66, p136 of the submission.
CI = confidence interval; IC = investigator's choice; NIVO = nivolumab
a Based on standard unpaired t-test.
b The PSCR provided corrected utility values from ATTRACTION-3 (PSCR p6)

6.39 Table 12 summarises the key drivers for the economic model. It was noted that the benefit in OS of nivolumab compared to IC was likely to be a key driver of the model; however, this was difficult to test during sensitivity analysis and its impact could not be quantified.

Table 12: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Utilities	Values for model health states taken from ATTRACTION-3 and scored using Australian tariffs (Viney 2011). Differential utility applied for same health state depending on treatment arm, but independent to whether patient was on treatment or not.	Moderate, favoured nivolumab. Assuming no differential utility between treatment arms increased the ICER to $[redacted][2].
Time horizon	Base case time horizon was 7 years but given the nature of the disease and low five-year survival rates (4.9%), it might be optimistic.	Moderate, favoured nivolumab. Changing time horizon to 5 years increased the ICER to $[redacted][2].
Adverse events	The costs of managing drug-related grade 3 or 4 AEs that occurred in ≥5% of patients in either arm of ATTRACTION-3 that were statistically significantly different between treatment arms were included, and it was assumed each AE involved hospitalisation. While it was reasonable to assume a reduction in cost of managing AE with nivolumab to be consistent with a claim of superior safety, the unit costs of managing AEs may have been overestimated by the submission.	Moderate, favoured nivolumab. Removal of AE costs in the economic model increased the estimated ICER to $[redacted][2]. While this was an implausible scenario (it would be reasonable to assume higher AE management costs for IC compared to nivolumab) it illustrates the upper limit of the impact of the estimate for AE management costs.

Source: Complied during evaluation.
AE = adverse event; AIC = Akaike's information criteria; BIC = Bayesian information criteria; IC = investigator's choice; ICER = incremental cost effectiveness ratio; PFS = progression free survival; OS = overall survival
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$75,000 to < $95,000*

6.40 Table 13 summaries the results of the stepped economic evaluation presented in the submission.

Table 13: Results of the stepped economic evaluation

Step and component	NIVO	IC	Increment
Step 1: trial-based costs and outcomes (LYs), time horizon of 4.35 years, using only observed KM[a]			
Costs	$[redacted]	$33,325	$[redacted]
LYs	1.311	1.066	0.245
Incremental cost/extra LY gained			$[redacted][1]
Step 2: trial-based costs and outcomes (QALYs), time horizon of 4.35 years, using only observed KM[a]			
Costs	$[redacted]	$33,325	$[redacted]
QALYs	0.874	0.646	0.228
Incremental cost/extra QALY gained			$[redacted][2]
Step 3: time horizon extended to 7 years, modelled evaluation using extrapolation beyond 174 weeks (40.2 months)			
Costs	$[redacted]	$34,542	$[redacted]
QALYs	0.974	0.668	0.306
Incremental cost/extra QALY gained (base case)			**$**[redacted][3]

Source: Table 77, p149 of the submission.

KM = Kaplan-Meier data; LYs = life years; IC = investigator's choice; NIVO = nivolumab; QALYs = quality adjusted life years

a Based on end of Kaplan-Meier data for ATTRACTION-3 three year follow up

The redacted values correspond to the following ranges:

[1] *$75,000 to < $95,000*

[2] *$95,000 to < $115,000*

[3] *$55,000 to < $75,000*

6.41 Univariate and multivariate sensitivity analyses considered by the PBAC are summarised in Table 14.

Table 14: Results of key sensitivity analyses

Variable	Base case	Scenario	Cost	QALY	ICER	%
Base case			$[redacted]	0.306	$[redacted][1]	-
Univariate analyses						
Time horizon	7 years	Within trial **(#1)**	$[redacted]	0.228	$[redacted][2]	+32.9%
		5 years **(#2)**	$[redacted]	0.261	$[redacted][3]	+14.2%
Parametric function	NIVO OS: Log-logistic; NIVO PFS: Gen gamma IC OS: Log-logistic; IC PFS: Log-logistic	All extrapolations Log-logistic	$[redacted]	0.303	$[redacted][1]	+0.8%
		All extrapolations Weibull	$[redacted]	0.271	$[redacted][3]	+13.5%
Utilities	Per treatment arm	Overall results **(#3)**	$[redacted]	0.226	$[redacted][2]	+35.7%
		Treatment-specific utilities apply pre-progression and overall utilities apply post-progression **(#4)**	$[redacted]	0.255	$[redacted][3]	+20.0%
DOT	TTD	PFS curve	$[redacted]	0.306	$[redacted][3]	+19.5%
Dosing[a]	NIVO: 240 mg Q2W	NIVO: 480 mg Q4W	-	-	$[redacted][1]	-8.9%
IC costs	31% of patients on DOC	100% of patients on DOC	$[redacted]	0.306	$[redacted][3]	+5.2%
Terminal care[b]	Terminal costs included	Removal of terminal costs	$[redacted]	0.306	$[redacted][3]	+4.3%
AEs (gr 3/4)	AEs as hospitalisations	Removal of AEs	$[redacted]	0.306	$[redacted][3]	+16.3%
PFS	PFS extrapolated separately	Assume PFS for IC applied to both treatment arms **(#5)**	$[redacted]	0.274	$[redacted][3]	+10.4%
Multivariate analyses						
Time horizon and utilities	Time horizon of 7 years and utilities per treatment arm	Within trial time horizon and utilities using overall results **(#1 + #3)**	$[redacted]	0.154	$[redacted][4]	+96.9%
Time horizon, PFS and utilities	Time horizon of 7 years and PFS extrapolated separately and utilities per treatment arm	5 year time horizon, treatment-specific utilities apply pre-progression and overall utilities apply post-progression assume PFS for IC applied to both treatment arms, **(#2 + #4 + #5)**	$[redacted]	0.185	$[redacted][5]	+59.4%
Time horizon, PFS and OS, and utilities	Time horizon of 7 years, no convergence of OS and PFS, and utilities per treatment arm	5-year time horizon, treatment-specific utilities apply pre-progression and overall utilities apply post-progression, and curve convergence from 3-5 years	$[redacted]	0.191	$[redacted][5]	+61.3%

AE = adverse event; DOC = docetaxel; DOT = duration of treatment; gr = grade; IC = investigator's choice; KM = Kaplan-Meier; NIVO = nivolumab; OS = overall survival; PAC = paclitaxel; PD = progressive disease; PFS = progression-free survival; Q2W = every 2 weeks; Q4W = every 4 weeks; TTD = time to treatment discontinuation.

a This could not be verified during evaluation.

The redacted values correspond to the following ranges:

[1] $55,000 to < $75,000

[2] $95,000 to < $115,000

[3] *$75,000 to < $95,000*
[4] *$135,000 to < $155,000*
[5] *$115,000 to < $135,000*

6.42 The assumption of differential utility based on treatment arm and the extrapolation to seven-year time horizon (step 3) from 'within trial' (step 2) had the largest potential impacts on the ICER (increasing to estimated ICER by 35.7% and 32.9%, respectively). Multivariate sensitivity analyses combining these two scenarios increased the estimated ICER by 96.9%, and likely represents the upper estimates of the ICER.

6.43 The ESC considered the base case ICER presented by the submission was uncertain and likely underestimated, given:

- A differential utility based on ATTRACTION-3 EQ-5D results that favoured patients in the nivolumab arm was applied, with patients in the nivolumab arm experiencing higher utility than patients in the IC arm in all alive health states irrespective of whether patients were receiving treatment or not. Additionally, patients randomised to nivolumab in ATTRACTION-3 had a higher baseline utility (0.835) compared to patients randomised to IC (0.787) which likely overestimating any utility benefit from nivolumab. The ESC considered the use of treatment-specific utilities was not well justified.
- The base case time horizon of seven years, particularly for a 2L treatment, may be optimistic given the SEER data indicated that the five-year survival for OSCC with distant metastasis was only 4.9%. The ESC considered a time horizon of 5 years would be appropriate.

6.44 The ESC considered the multivariate sensitivity analysis with a 5 year time horizon, PFS for IC applied to both treatment arms and utilities using overall results for PD only with an associated ICER of $115,000 to < $135,000 was a more appropriate base case.

6.45 The PSCR stated that the application of treatment-specific utilities was appropriate for use in the modelled economic evaluation, as the higher pre-progression utilities for the nivolumab treatment group (0.796) compared with the IC group (0.737) was expected given both the preferential AE profile and mechanism of action of the immunotherapy agent nivolumab. The PSCR also claimed that the post-progression utility values used which were higher for the nivolumab treatment group (0.583 compared with 0.519 for IC) was reasonable given that a high proportion of nivolumab patients (49.7%) were treated beyond progression as per the ATTRACTION-3 trial protocol. The PBAC considered that applying a higher utility for patients treated with nivolumab in the progressed health state for the duration of the model was likely to substantially overestimate the utility benefit. The PBAC also noted the restriction criteria allows for continuing treatment only when patients have stable or responding disease. The pre-PBAC response acknowledged the ESC's rationale for the application of overall utility values for the progressed treatment state, but considered it overly conservative as the high proportion of nivolumab patients (49.7%) who received

treatment beyond progression have not been accounted for. The response stated that these patients have a continued benefit and higher quality of life compared to the IC arm for a certain period of the post-progression state. The sponsor considered it more appropriate to apply treatment-specific utilities for the progressed health state for the duration of time supported by evidence (median follow-up for OS from the ATTRACTION-3 trial, 40.2 months), with an average utility applied thereafter.

6.46 The PSCR and pre-PBAC response stated that a seven-year time horizon was appropriate for the base case because the maturity of the OS data seen in the ATTRACTION-3 trial indicates that the long-lasting and durable effect of nivolumab therapy compared to chemotherapy can potentially change the survival landscape of OSCC. The PSCR rejected a five-year time horizon based on the SEER data (five-year survival for OC with distant metastasis 4.9%; paragraph 4.1) as being historical (2013-2017). The ESC noted the five year survival reported in the SEER data is from time of diagnosis, not the time of second line treatment and therefore likely to be an overestimate.

6.47 The pre-PBAC response rejected the ESC's proposal that a revised base case should apply PFS for the IC arm to both treatment arms. The response stated that the PFS HR varies over time; i.e. while PFS data favour IC over nivolumab up until 4.5 months (PFS >1), PFS thereafter favours nivolumab over IC (PFS <1). The PBAC agreed with the pre-PBAC response that economic models previously accepted for immunotherapy have modelled PFS using trial data although there was not a significant PFS benefit. However, the PBAC considered extrapolating the PFS curves over the model time horizon without convergence potentially overestimated the PFS benefit and considered the curves should be converged from 3 to 5 years. The PBAC considered the OS curves should be similarly converged.

6.48 The pre-PBAC response stated that an upper range of cost-effectiveness should be reflected in a 7-year time horizon with curve convergence from 5-7 years, and overall utility values applied in the post progression health state from 40.2 months (ICER = $75,000 to < $95,000 per QALY gained).

6.49 The PBAC considered that a reasonable base case incorporated a 5-year time horizon, curve convergence for both PFS and OS from 3-5 years, and assumed treatment-specific utilities apply pre-progression and overall utilities apply post-progression. The PBAC noted the ICER applying these assumptions was $115,000 to < $135,000 per QALY gained at the sponsor's requested price.

Drug cost/patient/course

6.50 Drug acquisition costs of nivolumab and IC (docetaxel and paclitaxel) are summarised in Table 15 below.

Table 15: Drug cost per patient for proposed and comparator drugs

	Nivolumab	Docetaxel	Paclitaxel
Mean dose (number of infusions per course)[a]	13.01 (240 mg Q2W) or 6.51 (480 mg Q4W)	4.96 (Q3W)	12.68 (6 weeks on, 2 weeks off)
Dispensed price per infusion[b]	$[redacted]	$161.35[c]	$146.07[c]
Mean duration[d]	182.14 days	104.1 days	
Cost/patient/course[e]	$[redacted]	$1,526.24[f]	

Source: Table76, p149 of the submission.
Q2W = every 2 weeks; Q3W = every 3 weeks Q4W = every 4 weeks
a Calculated based on the number of infusions required for the mean duration.
b Calculated based on a 33.83% public weighting and 66.17% private weighting used in the economic and financial model.
c Calculated assuming 75 mg/m^2 docetaxel, 100 mg/m^2 paclitaxel and 1.6025 mean body surface area (from the ATTRACTION-3 trial), consistent with dosing used in the economic and financial model. Irinotecan was not included in the ATTRACTION-3 trial nor the economic model, but was included in the financial estimates, which assumed 250 mg/m^2 irinotecan every 3 weeks (frequency assumed to be same as docetaxel) and 1.6025 mean body surface area.
d Based on mean time to treatment discontinuation from the ATTRACTION-3 trial.
e Undiscounted and excludes administration costs.
f Calculated based on weighting of 31% of patients on docetaxel and 69% of patients on paclitaxel as observed in the ATTRACTION-3 trial and applied in the economic model. Split of use differed in the financial model, which included irinotecan.

Estimated PBS usage & financial implications

6.51 This submission was considered by DUSC.

6.52 The submission used an epidemiological approach to estimate the utilisation and financial impact of listing nivolumab on the PBS for 2L OSCC. A summary of the key assumptions used to calculate the financial estimates is presented in Table 16.

Table 16: Data sources and parameter values applied in the utilisation and financial estimates

<table>
<tr><th>Data</th><th>Value and Source</th><th>Comment</th></tr>
<tr><td colspan="3">Eligible population</td></tr>
<tr><td>Estimated incident patients with OC</td><td>Calculated based on estimated number of patients (1,587) diagnosed with OC in 2020 (AIHW, 2020), applying a population growth rate of 1.3% per annum (ABS, 2020)</td><td>Reasonable.</td></tr>
<tr><td>Proportion of patients with OSCC</td><td>35.3%
Source: Based on sponsor commissioned report using AIHW data for the proportion of OC with OSCC histology in 2016.</td><td>Appears reasonable. Ranged between 35.3%-37.9% from 2013-2016 according to AIHW data. The evaluation considered using the lowest proportion may lead to underestimates of eligible patients.</td></tr>
<tr><td>Disease stage at diagnosis</td><td>Stage I: 10.4%
Stage II/III: 56.8%
Stage IV: 27.2%
Source: Nguyen 2019, a pattern of care study of OC patients in SA between 2012 – 2015 (OC N=375, OSCC N=93). High grade disease excluded from the financial model as patients are unlikely to progress to palliative treatment options.</td><td>The proportion of disease stages were based on overall OC patients (OSCC and OAC), rather than just OSCC.</td></tr>
<tr><td>Proportion of patients eligible for 1L chemotherapy</td><td>Proportion eligible for 1L chemotherapy
<table>
<tr><th></th><th>Eligible at diagnosis</th><th>Become eligible</th><th>Total eligible</th></tr>
<tr><td>Stage I</td><td>10.3%</td><td>25.8%</td><td>36.1%</td></tr>
<tr><td>Stage II/III</td><td>36.2%</td><td>25.8%</td><td>62.0%</td></tr>
<tr><td>Stage IV</td><td>99.0%</td><td>NA</td><td>99.0%</td></tr>
</table>
Source: Calculated by adding the proportion of patients offered 1L chemotherapy at time of diagnosis (Nguyen 2019) and the proportion of patients offered 1L chemotherapy following recurrence on curative treatment options. Recurrence of 25.8% assumed based on results of Knight 2018, a study of patients undergoing resection of the oesophagus, who reported 31/120 patients had systemic recurrence. The same recurrence rate was applied for each disease stage.</td><td>The proportion of patients offered 1L chemotherapy at time of diagnosis was based on overall OC patients (OSCC and OAC). The proportion of patients offered 1L chemotherapy following recurrence on curative treatment options were not differentiated via disease stage, but the evaluation considered it was possible that recurrence rate in Stage I and stage II/III disease may be different.</td></tr>
<tr><td>Proportion of patients electing 1L FP based chemotherapy</td><td>61% of OSCC patients.
Source: Jaffe 2019, global retrospective treatment patterns study of 1809 patients with advanced or metastatic unresectable OC from Asian and Western countries conducted between September and October 2018. Of these patients, 1049 had OSCC and 760 had OAC</td><td>Based on a global statistic which did not include Australia, therefore usage patterns may not be applicable. Availability of nivolumab as 2L treatment may alter usage patterns of 1L FP based chemotherapy as it is a requirement of 2L nivolumab use. The DUSC considered it is likely that the 2L nivolumab requirement for prior fluoropyrimidine + platinum chemotherapy will change 1L patterns and considered 70% a better estimate than 61%.</td></tr>
</table>

Data	Value and Source	Comment
ECOG status	Assumption only. 100% of patients electing 1L treatment with FP based chemotherapy considered to have ECOG 0-1 (with all patients with ECOG ≥2 electing treatment with BSC) and will have the same ECOG performance score when initiating 2L treatment.	This was inappropriate and likely overestimated. Jaffe 2019 reported that 50.5% and 62.9% of patients in Asia and the West, respectively, had ECOG of 0 or 1 at the initiation of 2L therapy. The DUSC considered 70% would be a more appropriate estimate than 100%.
Proportion of patients electing 2L therapy	[redacted]% before nivolumab listing [redacted]% after nivolumab listing Source: Expert advice BMS advisory board chair 2020/2021	Assumption only. It is reasonable to expect market growth with nivolumab listing.
Treatment utilisation		
Uptake rate	[redacted]%, remaining [redacted]% electing chemotherapy Source: Expert opinion, BMS advisory board chair 2020/2021	It is noted that the submission did not account for the [redacted]% of patients who will continue to receive 2L chemotherapy, and as such, the cost offsets provided by the submission were overestimated. These have been corrected during the evaluation. The DUSC considered that the [redacted]% who elect 2L chemotherapy will be potentially eligible for 3L nivolumab, and this will effectively increase the nivolumab uptake rate to [redacted]%.
Dosing and frequency split for nivolumab	240mg Q2W: 10% 480mg Q4W: 90% Calculated from prior PBAC determination (Nivolumab, March 2019 PSD), adjusted to 100% (based on removal of weight-based dosing option).	The dosage used in the pivotal clinical trial (ATTRACTION-3) was Q2W.
Costs		
MBS costs	$111.40 (MBS rebate rate of 80% used) Source: MBS 13950, Cytotoxic Chemotherapy Administration	Appropriate.

Source: Tables 85, 92, 95, 97,100&102, p155, 163, 166, 167, 171&172 of the submission.
1L = first-line; 2L = second-line; ABS = Australian Bureau of Statistics; AOC = adenocarcinoma; AIHW = Australian Institute of Health and Welfare; BSA = body surface area; DOC = docetaxel; FP = fluoropyrimidine and platinum; IC = investigator's choice; NIVO = nivolumab, OAC = oesophageal adenocarcinoma OC = oesophageal carcinoma; OSCC = oesophageal squamous cell carcinoma; PAC = paclitaxel; PSD=public summary document; TTD = time to treatment discontinuation

6.53 The estimated financial impact of PBS listing nivolumab is summarised in Table 17.

Table 17: Estimated net financial implications of the proposed nivolumab listing (using proposed effective price of nivolumab)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Incident OC patients	1,629	1,650	1,671	1,693	1,715	1,737
Incident OSCC patients (35.3%)	575	583	590	598	606	614
Total OSCC patients receiving 1L FP chemo[a]	231	234	238	240	244	247
Patients treated with nivolumab	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of nivolumab scripts						
240 mg Q2W	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
480 mg Q4W	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total nivolumab scripts	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
PBS/RPBS cost of nivolumab less co-pay						
Total	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Total change in number of scripts of chemotherapy	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
PBS/RPBS cost of chemotherapy substituted less co-pay (DPMA)[c]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net MBS costs	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to Government health budget	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Revised estimates provided in pre-PBAC response[d]						
Patients treated with nivolumab	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS/RPBS cost of nivolumab (less copay)	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Table 93, 94, 96, 98, 99,101&103-107, p165-168&170-176 of the submission.

1L = first line; 2L = second line; chemo = chemotherapy; DOC = docetaxel; DPMA = dispensed price for maximum amount; ECOG = Eastern Cooperative Oncology Group; FP = fluoropyrimidine and platinum; Oesophageal carcinoma; OSCC = Oesophageal Squamous Cell Carcinoma; PAC = paclitaxel; eff = effective; Q2W = every 2 weeks; Q4W = every 4 weeks

a The submission assumed that all patients would fail 1L FP- based chemotherapy and assumed that all patients would have maintained with an ECOG performance status of 0 or 1 at initiation of 2L treatment.

b The submission inappropriately did not account for the [redacted]% of patients who will continue to receive 2L chemotherapy post introduction of nivolumab. This was corrected during the evaluation.

c Several errors regarding RPBS estimates, copayments and number of chemotherapy scripts were corrected during evaluation to derive this estimate

d Estimate was updated in the pre-PBAC response to (i) include a prevalent patient pool in Year 1; (ii) increase the estimated proportion of palliative patients electing 1L FP to 70% (from 61%); (iii) decrease the estimated proportion of patients with ECOG = 0-1 at the start of 2L treatment to 70% (from 100%); and (iv) increase the estimated uptake rate of nivolumab for eligible patients to [redacted]% (from [redacted]%). The revised model did not correct for errors outlined in (c).

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

[3] $0 to < $10 million

6.54 The submission estimated the net cost to the government budget of listing nivolumab on the PBS/RPBS at the proposed effective price was $0 to < $10 million in Year 1,

increasing to $0 to < $10 million in Year 6. The total cost over the six year period was $20 million to < $30 million.

6.55 The DUSC noted the submission estimated that the proportion of patients electing 1L FP-based chemotherapy to be 61%. The DUSC considered it is likely that the availability of nivolumab in the 2L setting would increase the proportion of patients electing treatment with FP-based chemotherapy in the 1L setting and 70% would be a more appropriate estimate.

6.56 The DUSC noted the submission estimated that the uptake rate of nivolumab for eligible patients would be [redacted]%. The DUSC considered that the [redacted]% who elect 2L chemotherapy will be potentially eligible for 3L nivolumab, and this will effectively increase the nivolumab uptake rate to [redacted]%.

6.57 The DUSC noted the submission assumed that 100% of patients electing 1L FP-based chemotherapy were considered to have ECOG 0-1 and will have the same ECOG performance score when initiating 2L treatment. However, Jaffe 2019 reported that 50.5% and 62.9% of patients in Asia and the West, respectively, had ECOG of 0 or 1 at the initiation of 2L therapy. The DUSC considered that progression is often rapid and symptomatic in upper gastrointestinal tract cancers and considered 70% a better estimate than 100%.

6.58 The DUSC noted the submission estimates were based on the number of incident oesophageal cancer patients reported by the Australian Institute of Health and Welfare (AIHW). The submission assumed the prevalent population to be same as the incident population. That is, it assumed that all newly diagnosed patients relapsed from Stages 1, 2 and 3 to advanced/metastatic disease in the same year as diagnosis. The DUSC considered this was not consistent with the survival patterns in oesophageal cancer and there would be a prevalent pool of eligible patients in the first year of PBS listing that were not included in the estimates (i.e., patients that were diagnosed in previous years and reached advanced/metastatic disease prior to or during the first year of listing).

6.59 The pre-PBAC response provided updated financial estimates that (i) included a prevalent patient pool in Year 1; (ii) increased the estimated proportion of palliative patients electing 1L FP to 70% (from 61%); (iii) decreased the estimated proportion of patients with ECOG = 0-1 at the start of 2L treatment to 70% (from 100%); (iv) and increased the estimated uptake rate of nivolumab for eligible patients to [redacted]% (from [redacted]%). The estimated net cost to the government budget was revised to $0 to < $10 million in Year 1, decreasing to $0 to < $10 million in Year 6. The total cost over the six year period was $20 million to < $30 million.

6.60 The pre-PBAC response stated the Year 1 prevalent population was calculated based on the total number of patients eligible for nivolumab in the two years prior to PBS listing and survival rates from the IC arm of the ATTRACTION-3 clinical trial. The pre-PBAC response stated that the methodology to derive the number of eligible patients

in the two years prior to PBS listing replicated those used to estimate the number of treated nivolumab patients in Years 1-6. The PBAC considered the estimated number of prevalent patients that would access treatment (~< 500) was reasonable.

6.61 The PBAC considered there was risk of use in patients with WHO/ ECOG scores greater than 1 and earlier in the treatment setting, given the emerging evidence of a benefit for immunotherapy in the first line and adjuvant treatment setting.

Quality Use of Medicines

6.62 The submission noted that the sponsor has implemented the following initiatives:

- Currently runs regular local meetings around physician education and organises national meetings that aim to address identified key educational needs;
- Previously provided sponsorship for Immune-Oncology preceptorship for oncologists and oncology nurses;
- Previously provided sponsorship of a peer-to-peer support mentorship program connecting clinicians with leading oncologists;
- Continues to offer nursing and pharmacy in-services to sites where nivolumab is used;
- Has a Risk Management Plan in place for nivolumab in Australia;
- Has made available a range of educational materials and tools for health care professionals (such as the immune-related adverse reactions (irAR) Management Guide with algorithms and irAR symptom checklist, and Prescribers Guide) and patients (such as mediband bracelets, a Patient Information Booklet and irAR wallet alert card nivolumab).

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required (Streamlined) listing of nivolumab for the treatment of patients with advanced or metastatic oesophageal squamous cell carcinoma (OSCC) who have disease progression following treatment with a fluoropyrimidine and platinum (FP)-based chemotherapy regimen. The PBAC considered there is a moderate need for more effective therapies in this patient population and acknowledged the moderate added benefit provided by nivolumab. The PBAC considered that the incremental cost effectiveness ratio (ICER) was high at the proposed price and a price reduction would be required to ensure nivolumab is cost-effective in this population.

7.2 The PBAC was satisfied that nivolumab provided, for some patients, a significant improvement in efficacy and reduction in toxicity over the nominated comparator of single agent chemotherapy (paclitaxel, docetaxel or irinotecan). The PBAC noted that although irinotecan was nominated as a comparator, the submission did not present

any clinical evidence comparing nivolumab to irinotecan or include it in the economic analysis; however, the PBAC considered this was reasonable as most patients would receive docetaxel or paclitaxel as a 2L treatment.

7.3 The PBAC considered there is a moderate need for more effective treatments in advanced or metastatic OSCC, given the poor prognosis for patients and the poor efficacy and high toxicity of current treatments. The PBAC noted this was supported by the consumer comments received for this submission.

7.4 The PBAC noted that the proposed PBS listing did not restrict nivolumab use to 2L treatment only, and patients could access nivolumab as 3L therapy. The PBAC considered that the majority of use would be in the 2L setting, consistent with the clinical evidence provided in the submission, and that the requested listing was reasonable.

7.5 The submission was based on one head-to-head randomised, phase 3, open-label multi-centre trial (ATTRACTION-3; N=419) comparing nivolumab to investigator's choice (IC) of docetaxel or paclitaxel, in patients with OSCC refractory or intolerant to combination therapy with FP-based therapy. The PBAC noted that there was a statistically significant OS benefit associated with nivolumab (HR=0.79, 95% CI: 0.64, 0.97) with the median survival improving from 8.5 to 10.9 months, and the 24-month survival rate improving from 13.5% to 20.2%. The PBAC noted that there was a higher hazard of death associated with nivolumab in the first few months of treatment, with the survival curves crossing around the five-month time point; however, it acknowledged this has been observed in other immunotherapy versus chemotherapy studies, and considered that the survival benefit was meaningful for those patients who responded to immunotherapy. The PBAC noted there was no difference in ORR, DCR or PFS between nivolumab and IC. However, the PBAC considered there was likely to be quality of life benefits given the lower rate of AEs observed in patients treated with nivolumab compared to IC chemotherapy. The PBAC considered nivolumab provided a moderate added benefit with a small increase in median OS, some improvement in quality of life, and a moderate reduction in adverse events.

7.6 The PBAC noted the base case ICER presented in the submission was $55,000 to < $75,000 per QALY gained. The PBAC considered this ICER was of low certainty with the economic model sensitive to time horizon and utility assumptions. The PBAC noted the base case ICER assumed a modelled time horizon of 7 years and applied treatment-specific utilities in the pre-progression and post-progression health states. The PBAC considered a 5 year time horizon was appropriate in this patient population and that applying curve convergence between 3 and 5 years was appropriate. The PBAC considered it was reasonable to use treatment-specific utilities in the pre-progression health state but not in the post-progression health state as that would substantially overestimate the utility gain over the time horizon of the model. The PBAC noted the revised ICER applying these assumptions to the economic model was $115,000 to < $135,000 and considered this was of high certainty. The PBAC considered nivolumab

would be cost-effective in this population with an ICER less than $55,000 to < $75,000.

7.7 The PBAC considered the revised estimates of utilisation provided in the pre-PBAC response, which incorporated revisions recommended by the DUSC (paragraph 6.55 to paragraph 6.58), were reasonable. The PBAC noted an error in the calculation of cost-offsets identified during evaluation had not been corrected in the estimates provided with the pre-PBAC response. The PBAC considered the financial estimates provided in the pre-PBAC response were of moderate certainty with the initial patient population reasonably well defined.

7.8 The PBAC considered the restriction criteria in paragraph 3.1 was appropriate with the following amendments:

- Tumour flares at the start of therapy in the context of this condition are unlikely to occur. Therefore, the administrative note in the initial restriction criteria regarding transient tumour flare was not required.
- The addition of 'PBS subsidised' to the clinical criteria "Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition" to ensure patients currently on treatment are not precluded from accessing nivolumab.

7.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for nivolumab:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies. The PBAC considered this criteria was not met as the available evidence showed a clinically relevant but small improvement in overall survival for some patients;

b) The treatment is not expected to address a high and urgent unmet clinical need. The PBAC considered this criteria was not met as other PBS-subsidised therapies were available;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add indication (advanced or metastatic squamous cell carcinoma of oesophagus) as follows:

MEDICINAL PRODUCT Form	**PBS item code**	**Maximum amount**	**No. of Repeats**
NIVOLUMAB Injection	New (Public) New (Private)	480 mg	8
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			

Restriction Summary [New 1] / Treatment of Concept: [New 2]	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒Authority Required – Streamlined [New 2]
	Episodicity: [blank]
	Severity: Advanced or metastatic
	Condition: Squamous cell carcinoma of oesophagus
	Indication: Advanced or metastatic squamous cell carcinoma of oesophagus
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must have a WHO performance status no greater than 1 at treatment initiation
	AND
	Patient must not have received prior treatment with a PBS-subsidised programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug only after having disease progression/recurrence following treatment with chemotherapy that contains at least each of: (i) a platinum drug, (ii) a fluoropyrimidine drug
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy for this PBS indication
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Up to 17 repeats may be sought if dosing at 240 mg every 2 weeks. Where an increase is sought, the benefit is no longer a Streamlined benefit. Seek authority approval prior to issuing the prescription.

MEDICINAL PRODUCT Form	**PBS item code**	**Maximum amount**	**No. of Repeats**
NIVOLUMAB Injection	New (Public) New (Private)	480 mg	11
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			

Restriction Summary [new 3] / Treatment of Concept: [new 4]	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required – Streamlined [New 4]
	Indication: Advanced or metastatic squamous cell carcinoma of oesophagus

Restriction Summary [new 3] / Treatment of Concept: [new 4]	
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have stable or responding disease
	AND
	Treatment criteria:
	Patient must be undergoing continuing treatment with this drug for this PBS-indication, with PBS subsidised treatment having commenced under the 'Initial treatment' phase listing – do not commence PBS subsidised treatment through this treatment phase
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy for this PBS indication
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Up to 23 repeats may be sought if dosing at 240 mg every 2 weeks. Where an increase is sought, the benefit is no longer a Streamlined benefit. Seek authority approval prior to issuing the prescription.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.