

**6.06 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 submission

- 1.1 The Category 2 submission requested Section 100 (Efficient Funding of Chemotherapy Program) Authority Required listing for the adjuvant treatment of patients with oesophageal carcinoma (OC) or gastroesophageal junction carcinoma (GOJC) who have received platinum-based chemoradiotherapy and surgery.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus standard of care (watch and wait surveillance).
- 1.3 A summary of key components of the clinical issue addressed by the submission is presented in Table 1.

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

Component	Description
Population	Patients with stage II or III oesophageal carcinoma (OC) or gastro-oesophageal junction carcinoma (GOJC) who have received chemoradiotherapy (CRT) prior to surgery who then subsequently have complete surgical resection and have residual disease of either ypT1 or greater or ypN1 or greater in the resected specimen.
Intervention	Nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks for the first 16 weeks, followed by nivolumab 480 mg administered every 4 weeks. Treatment is to be continued until disease progression or unacceptable toxicity, to a maximum 1-year duration of treatment.
Comparator	Standard of care (SOC) - watch and wait surveillance.
Outcomes	Disease-free survival, overall survival, quality of life during treatment, safety (based on frequency of deaths, AEs, SAEs and AEs leading to discontinuation).
Clinical claim	Nivolumab is superior in terms of efficacy and has an inferior safety profile compared with SOC for the treatment of patients with OC or GOJC who have received CRT prior to surgery.

Source: Table 1, p13 of the submission.

AE = adverse event; SAE = serious adverse events

2 Background

Registration status

- 2.1 Nivolumab was approved by the TGA on 29 November 2021 for the following indication:

- as monotherapy, for the adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer in patients who have received neoadjuvant chemoradiotherapy

2.2 Nivolumab was evaluated by the TGA via the Project Orbis pathway. The TGA Delegate’s Overview was provided with the submission.

2.3 Nivolumab is currently TGA-approved as a treatment for several other types of cancer, including for the first line treatment of patients with HER2 negative advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma and for the second line treatment of patients with unresectable, advanced, recurrent or metastatic oesophageal squamous cell carcinoma.

3 Requested listing

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

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
NIVOLUAB Injection 100 mg in 10 mL (vial)	480mg	3 (initial treatment) 8	\$ [Published, Private Hospital]	Opdivo® Bristol-Myers Squibb Australia Pty Ltd [BQ]
			\$ [Published, Public Hospital]	
NIVOLUMAB Injection 40 mg in 4 mL (vial)		(continuing treatment)	\$ [Effective, Private Hospital]	
			\$ [Effective, Public Hospital]	

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Administrative Advice: <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: No increase in the maximum quantity amount or number of units may be authorised.
Administrative Advice: The treatment must not exceed 12 months for this PBS indication.
Administrative Advice: Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks. Up to an additional 4 repeat prescriptions (7 in total) may be sought only where dosing is on a 2-weekly schedule. This listing's stated number of repeat prescriptions is based on 4-weekly dosing.
Episodicity: <i>Adjuvant treatment of</i>
Severity: stage II/ or III
Condition: oesophageal carcinoma (OC) or gastro-oesophageal carcinoma (GOJC)
Indication: <i>Adjuvant treatment of stage II or III oesophageal carcinoma (OC) or gastro-oesophageal carcinoma (GOJC)</i>

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Treatment Phase: Initial treatment
Clinical criteria:
Patient The condition must have histological evidence confirming a diagnosis of a least one of: (i) ed adenocarcinoma, or (ii) squamous cell carcinoma; document this evidence in the patient's medical records histology
AND
Clinical criteria:
Patient The condition must have received been treated with platinum-based chemoradiotherapy (CRT)
AND
Clinical criteria:
Patient The treatment must have had be for the purposes of adjuvant use following complete surgical resection AND have residual disease of either ypT1 or greater or ypN1 or greater in the resected specimen
AND
Clinical criteria:
The condition must have evidence, through resected specimen, that residual disease is present to the extent of either: (i) at least ypT1, (ii) at least ypN1
AND
Clinical criteria:
Patient must have a be in a state that they either: (i) have a current WHO performance status of 0 or 1 no higher than 1 at treatment initiation, (ii) had a WHO performance status no higher than 1 where treatment was initiated as non-PBS subsidised supply
AND
Clinical criteria:
Patient must not have experienced disease recurrence
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must not have received prior PBS-subsidised treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition or
The condition must have been treated with PD-1/PD-L1 inhibitor therapy obtained only through non-PBS supply, but at the time of treatment initiation, the condition was untreated with PD-1/PD-L1 inhibitor therapy
Treatment criteria:
Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks. Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information
Treatment criteria:
Initial treatment
Prescribing Instructions:
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 quantity or number of units may be authorised. Up to 7 repeats may be authorised if dosing at 240mg every 2 weeks. The treatment must not exceed 12 months for this PBS indication.

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Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Indication: <i>Adjuvant treatment of stage II or III oesophageal carcinoma (OC) or gastro-oesophageal carcinoma (GOJC)</i>
Treatment Phase: Continuing treatment
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria: Patient must not have experienced disease recurrence.
AND
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria: <i>The treatment must be for the purposes of adjuvant use following complete surgical resection</i>
Treatment criteria: Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks. <i>Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information</i>
AND
Treatment criteria: Continuing treatment <i>Patient must not be undergoing continuing PBS-subsidised treatment where this benefit is extending treatment beyond 12 cumulative months from the first administered dose, once in a lifetime</i>
Prescribing Instructions: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. The treatment must not exceed 12 months for this PBS indication.

- 3.2 The requested ex-manufacturer price (EMP) for each 100 mg vial is \$ [REDACTED]. The proposed PBS restriction was consistent with the approved TGA indication and the enrolment criteria of the pivotal CM-577 trial, with one exception. The requested restriction was broader than the enrolment criteria of the pivotal CM-577 trial, which required patients to have had complete resection in a window of 4 to 16 weeks prior to randomisation. The evaluation noted there were no restrictions on the time elapsed between resection and nivolumab initiation in the requested restriction. The PBAC considered a time restriction for treatment initiation post-surgical resection was appropriate for inclusion in the restriction and considered it should align with the Checkmate 577 trial (16 weeks).
- 3.3 The PBAC noted 70.9% of trial participants had adenocarcinoma histology and 29.0% of participants had squamous cell carcinoma histology and considered it was

appropriate for the restriction criteria to include reference to histology. The PBAC also considered that the prescriber instruction for a confirmatory scan, taken at least 4 weeks after progression / transient tumour flare, was not required for an adjuvant listing in and advised it could be removed from the restriction.

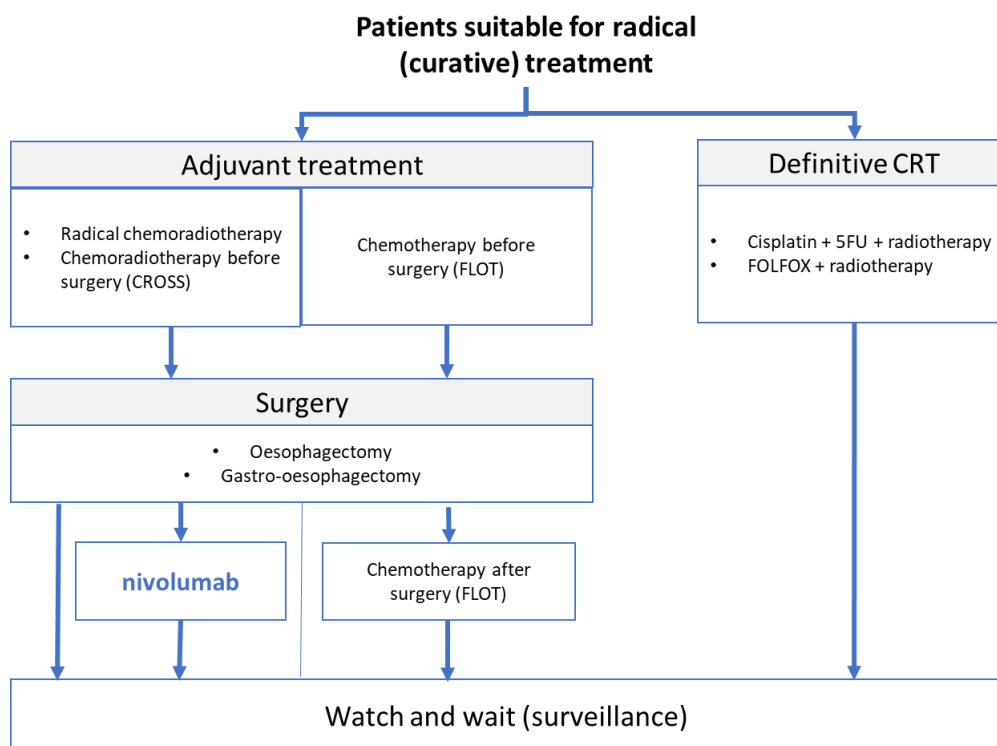
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 OC and GOJC are diseases in which malignant (cancer) cells form in the tissues of the oesophagus, or the gastro-oesophageal junction (GOJ), the place where the oesophagus is connected to the stomach. Survival data specific to OC and GOJC patients from the Surveillance, Epidemiology and End Results (SEER)¹ program in the United States indicate a similar 24% and 32% 5-year relative survival for OC and GOJC respectively.
- 4.2 Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. This leads to the restoration of immune response against the tumour.
- 4.3 Nivolumab is proposed as an adjuvant therapy after chemoradiation therapy (CRT) and surgery in patients with Stage II or III disease (Figure 1).

¹ Surveillance, Epidemiology, and End Results (SEER) Program Populations (1969-2020) (www.seer.cancer.gov/popdata), National Cancer Institute, DCCPS, Surveillance Research Program (accessed on 8 November 2021)

Figure 1: Proposed clinical management algorithm



5FU = Fluorouracil; CROSS = Chemoradiotherapy for oesophageal cancer followed by surgery study; CRT = chemoradiation therapy; FLOT = Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel

4.4 The most likely prescribed treatment regimens prior to nivolumab treatment are:

- The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) protocol which includes weekly administration of carboplatin and paclitaxel with concurrent radiotherapy, prior to surgery (Van Hagen, 2012)²; or
- Use of fluorouracil+leucovorin, oxaliplatin and docetaxel (FLOT) before and after surgery (Al-Batran, 2019)³ (evidence base in adenocarcinoma of the GOJ, not OC).

4.5 The sponsor’s advisory board reported that of patients with locally advanced OC and GOJC, approximately 8% have surgery alone (typically patients with early stage I) and approximately 20% have definitive CRT (dCRT). There would then be an equal split between neoadjuvant CRT/CROSS and perioperative FLOT. The ESC noted that based

² Van Hagen P, Hulshof MCM, van Lanschot JJB. et. al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. NEJM 2012; 366:2074-84

³ Al-Batran, S. Hormann, N, Pauvlig, C et al. Perioperative Chemotherapy with fluorouracil plus leucovorin, oxaliplatin and docetaxel for locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma (FLOT4) a randomised trial. NEJM, 2019 393: 1948-1958

on current NCCN⁴ and ESMO⁵ guidelines, both neoadjuvant CRT/CROSS and perioperative FLOT are currently standard practice for adenocarcinomas and also noted that these regimens are currently being assessed in a head-to-head trial (the ESOPEC⁶ study), due to report in 2023. The ESC noted patients with squamous histology would be treated with the CROSS protocol.

- 4.6 Given that patients who received the FLOT protocol would not be eligible for adjuvant nivolumab as no radiation therapy was used, listing nivolumab could lead to higher uptake of CROSS treatment in anticipation of accessing nivolumab after surgery. The ESC agreed with the evaluation that the listing of nivolumab is likely to lead to an increase in adenocarcinoma patients receiving the CROSS protocol over FLOT but the extent of the increase may depend on the outcome of the ESOPEC study directly comparing FLOT and CROSS in oesophageal adenocarcinoma.
- 4.7 It was noted that since the lodging of the submission, nivolumab has received positive PBAC recommendations for the following gastro-oesophageal cancers as specified in the TGA approved product information:
- non-HER2 positive advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma (in combination with platinum-containing plus fluoropyrimidine-containing chemotherapy) (6.10 March 2022 PBAC Public Summary Document (PSD)); and
 - second-line treatment of oesophageal squamous cell carcinoma (OSCC) after fluoropyrimidine and platinum (FP) based chemotherapy. (6.14 March 2022 PBAC PSD)
- 4.8 Consequently, it would be expected that at least a proportion of patients with stage II or III OC or GOJC who progress after CRT and surgery, in both the current and proposed (i.e., with adjuvant nivolumab) scenarios, would access nivolumab either as monotherapy or in combination with chemotherapy. However, it was unknown if failure (progression) during or after nivolumab adjuvant therapy within the scope of the current submission would affect the efficacy (and cost effectiveness) of nivolumab in post progression treatment.
- 4.9 Pembrolizumab in combination with chemotherapy was recommended at the May 2022 intracycle PBAC meeting for the first line treatment of advanced or metastatic

⁴ National Comprehensive Cancer Network (NCCN) (2022) Esophageal and Esophagogastric Junction Cancers V2.2022 Available at: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1433>

⁵ Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016 Sep;27(suppl 5):v50-v57.

⁶ <https://www.clinicaltrials.gov/ct2/show/NCT02509286>

gastro-oesophageal cancers as defined by the specific tumour types included in the approved Therapeutic Goods Administration indications.

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

5 Comparator

- 5.1 The submission nominated standard of care (SOC) or 'watch and wait' surveillance as the appropriate main comparator. The ESC affirmed that this was reasonable.
- 5.2 The submission stated that 'watch and wait' surveillance was identified as the standard treatment provided post CRT + surgery for patients in international treatment guidelines (NCCN, 2020⁷; Lordick, 2016⁸) and as identified by the sponsor's multidisciplinary advisory board (minutes provided with the submission).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician noted that while neo-adjuvant chemoradiation (CROSS) in this setting was associated with improved health outcomes, the prognosis of patients with oesophageal cancer remained poor. The clinician considered the improvement in disease free survival (DFS) observed for nivolumab patients in the adjuvant setting is a meaningful outcome that is likely to translate into long-term improvement in overall survival (OS). In making this claim, the clinician referenced a study in oesophago-gastric cancer demonstrating a correlation between DFS and OS (Ronellenfitsch et al 2019). The clinician emphasised that improvement in DFS is also a meaningful outcome for patients, noting that the maintenance of good health and overall quality of life was especially important to patients. The clinician considered that the benefit to risk ratio of adjuvant nivolumab was highly favourable and argued that preventing future recurrence with adjuvant therapy was preferable to delivering immunotherapy in the metastatic setting where long term remission may be less likely.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The health professional stated that despite the availability of

⁷ National Comprehensive Cancer Network (NCCN) Esophageal and Esophogastric Junction Cancers V5 2020

⁸ Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016 Sep;27(suppl 5):v50-v57.

chemoradiotherapy prior to surgery (CROSS), further treatment options were needed for patients with early GOJC. The health professional noted that adjuvant nivolumab was associated with improved DFS and relatively low rates of serious adverse events. The health professional also noted disadvantages associated with adjuvant nivolumab, including that it remains a costly medication and there is no known overall survival benefit associated with the therapy. Comments from an individual and those quoted from the health consumer organisation described a range of benefits associated with receiving nivolumab, including improved clinical outcomes and quality of life while experiencing minimal side effects. Pancare also provided support for the PBS listing of adjuvant nivolumab, noting that nivolumab was likely to improve survival and quality of life for this group of patients.

- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the use of nivolumab as an adjuvant treatment for patients with oesophageal cancer or gastro-oesophageal cancer, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the Checkmate 577 (CM-577) trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab, which was a Grade A, the highest grade (on a scale from A to C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies).⁹

Clinical trial

- 6.4 The submission was based on one randomised placebo-controlled trial (CM-577; N=794) of adjuvant nivolumab in resected oesophageal or gastro-oesophageal junction cancer following neoadjuvant chemoradiotherapy (CRT).
- 6.5 Details of CM-577 presented in the submission are provided in Table 2.

⁹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CM-577	CheckMate-577 primary CSR	October 2020
(NCT02743494)	CheckMate-577 ad-hoc descriptive analysis	February 2021
	Kelly, R. J., Ajani, J. A., Kuzdzal, J., et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer.	<i>NEJM</i> 2021; 384: 1191-1203
	Moehler, M., Ajani, J. A., Kuzdzal, J., et al. 2021. 1381P Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): 14-month follow-up of CheckMate 577.	<i>Annals of Oncology</i> 2021; 32: S1045-S1046.
	Lawrance, R., Singh, P., Leso, A., et al. PCN83 Healthcare Resource Utilization (HCRU) of Patients with Resected Esophageal Cancer or Gastroesophageal Junction Cancer (EC/GEJC) Receiving Adjuvant Nivolumab Treatment Versus Placebo.	<i>Value in Health</i> 2021; 24: S34-S35.
	Van Cutsem, E., Singh, P., Cleary, J. M., et al. Checkmate 577: Health-related quality of life (HRQoL) in a randomized, double-blind phase III study of nivolumab (NIVO) versus placebo (PBO) as adjuvant treatment in patients (pts) with resected esophageal or gastroesophageal junction cancer (EC/GEJC).	<i>Journal of Clinical Oncology</i> 2021; 39: 167-167.
	Zander, T., Kelly, R. J., Ajani, J. A., et al. Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): Expanded efficacy and safety analyses from CheckMate 577.	<i>Oncology Research and Treatment</i> 2021; 44: 80-81.
	Kelly, R. J., Ajani, J. A., Kuzdzal, J., et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study.	<i>Annals of Oncology</i> 2020; 31: S1193-S1194.
	Kelly, R. J., Lockhart, A. C., Jonker, D. J., et al. CheckMate 577: A randomized, double-blind, phase 3 study of nivolumab (Nivo) or placebo in patients (Pts) with resected lower esophageal I or gastroesophageal junction (GEJ) cancer.	<i>Journal of Clinical Oncology</i> 2017; 35: TPS212-TPS212

Source: Table 14, p39-40 of the submission.

6.6 The key features of the CM-577 trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Nivolumab versus placebo						
CM-577	794	R, DB, MC, median follow-up time 32.2 months ^a	Low ^b	OC and GOJC after surgery and CRT	DFS, DMFS	TTR ^c

Source: constructed during evaluation

CRT = chemoradiation therapy; DB = double blind; DFS = disease free survival; DMFS = distant metastasis free survival; GOJC = gastro-oesophageal cancer; MC = multi-centre; OC = oesophageal cancer; R = randomised; TTR = time to recurrence

^a February 2021 Data cut

^b The trial adequately concealed randomisation from participants and study staff, and outcome assessors, and intention to treat study sets were used in efficacy analyses. The submission noted that the reporting of outcomes was prespecified before the trial. The submission also noted the protocol amendment of changing overall survival (OS) from a primary outcome to a secondary endpoint due to low uptake of participants during enrolment.

^c not a pre-specified outcome in CM-577

6.7 The original trial protocol listed DFS and OS as dual primary endpoints for CM-577. The submission stated that, due to slower than expected enrolment, a protocol amendment was made in June 2019, demoting OS from a dual primary endpoint to an exploratory secondary endpoint. The projected enrolment period was also revised to

26 months from 15 months. At the time of this amendment, there were already 700 participants randomised into the study. Consequently, DFS became the single primary endpoint with OS changing from the coprimary end point to the first secondary end point to be assessed hierarchically.

- 6.8 The submission stated that the OS data were not mature (49.6% of total OS events were observed) and did not meet the prespecified boundary for declaring statistical significance of 0.003; therefore, OS efficacy analyses were not released to the sponsor.
- 6.9 The *ad-hoc* descriptive analysis (database lock 18-Feb-21, CSR update February 2021) was performed to provide longer term data to support the previously reported DFS, distant metastasis free survival (DMFS) and progression-free survival after subsequent systemic therapy (PFS2) efficacy endpoints. The submission stated data for OS remained immature at the time of this submission and as such, OS was not available.

Comparative effectiveness

- 6.10 The interim analysis (October 2020) data demonstrated a statistically significant improvement in DFS for nivolumab compared to placebo (HR = 0.69, 95%CI 0.56, 0.85, p=0.0003), with a median DFS of 22.41 months in the nivolumab arm compared to 11.04 months in the placebo arm. This was based on a median follow-up of 24.4 months and a maximum follow-up of 44.9 months.
- 6.11 The submission stated that the difference in DFS (HR = 0.67, 95% CI 0.55, 0.81, p-value not reported) was sustained over longer-term follow-up (median 32.2 months, maximum 52.7 months) and was supported with improvements in DMFS and PFS2 with nivolumab treatment compared with placebo.
- 6.12 Results for DFS, DMFS and PFS2 from October 2020 and February 2021 analyses of CM-577 are presented in Table 4.

Table 4: Summary of the efficacy results of CM-577

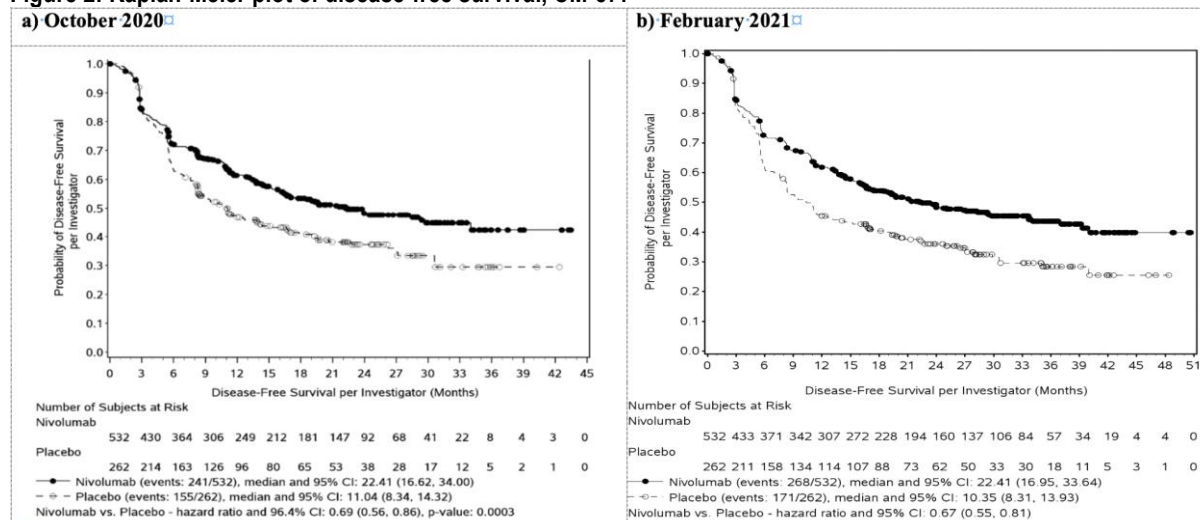
Trial ID	October 2020 (interim analysis)		February 2021 (<i>ad hoc</i> analysis)	
	Nivolumab (N=532)	Placebo (N=262)	Nivolumab (N=532)	Placebo (N=262)
DFS				
Events, n (%)	241 (45.3)	155 (59.2)	268 (50.4)	171 (65.3)
Median DFS, months (95% CI)	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)	22.41 (16.95, 33.64)	10.35 (8.31, 13.93)
Hazard ratio (95% CI)	0.69 (0.56, 0.85) [p=0.0003]		0.67 (0.55, 0.81) [NR]	
DMFS				
Events, n (%)	218 (41.0)	134 (51.1)	253 (47.6)	154 (58.8)
Median DMFS, months (95% CI)	28.32 (21.26, N/a)	17.61 (12.45, 25.40)	29.37 (23.66, 36.63)	16.62 (11.37, 24.87)
Hazard ratio (95% CI)	0.74 (0.60, 0.92)		0.71 (0.58, 0.87)	
PFS2				
Events, n (%)	163 (30.6)	100 (38.2)	203 (38.2)	120 (45.8)
Median PFS2, months (95% CI)	N/a (34.00, N/a)	32.07 (24.15, N/a)	N/a (36.63, N/a)	30.72 (24.15, N/a)
Hazard ratio (95% CI)	0.77 (0.60, 0.99)		0.77 (0.61, 0.96)	

Source: Table 29, p75 of the submission.

CI = confidence interval; DFS = disease-free survival; DMFS = distant metastasis free survival; N/a = not achieved; NR = not reported; PFS2 = progression-free survival after subsequent systemic therapy

6.13 Kaplan-Meier (KM) curves for DFS are presented in Figure 2.

Figure 2: Kaplan-Meier plot of disease-free survival, CM-577



Source: Figure 8, p80 of the submission.

6.14 Three monthly DFS survival rates per investigator are presented in Table 5.

Table 5: 3-monthly DFS survival rates per investigator, CM-577 (February 2021)

Disease-free survival (DFS) rate, % (95% CI)	Nivolumab (N=532)	Placebo (N=262)
3-month	84.3 (80.9, 87.2)	82.1 (76.9, 86.3)
6-month	72.6 (68.5, 76.3)	61.5 (55.3, 67.1)
9-month	67.3 (63.1, 71.2)	52.5 (46.2, 58.4)
12-month	61.8 (57.4, 65.8)	45.5 (39.3, 51.4)
15-month	57.9 (53.5, 62.0)	43.4 (37.3, 49.4)
18-month	53.9 (49.5, 58.2)	40.4 (34.4, 46.4)
21-month	51.1 (46.6, 55.5)	37.6 (31.5, 43.6)
24-month	48.3 (43.7, 52.8)	36.0 (29.9, 42.0)

Source: Table 34, p81 of the submission.

CI = confidence interval; DFS = disease-free survival

6.15 The evaluation noted that the base case economic analysis did not use DFS to model clinical outcomes, but rather time to recurrence (TTR), which was not a defined outcome in CM-577 and appears to have been constructed specifically for the purpose of the economic model and as such was associated with more uncertainty than the primary outcome of DFS. DFS was used only in a sensitivity analysis. This modelling choice is further discussed below in paragraph 6.37.

6.16 The submission noted that DFS benefit with nivolumab over placebo was observed in the prespecified subgroups regardless of histology, pathologic lymph node status, and

PD-L1 status. These data, reported in Moehler 2021¹⁰, were from a separate data cut (4 January 2021) to the interim analysis (October 2020) and the ad hoc analysis (February 2021) described above.

- 6.17 It was acknowledged by the evaluation that subgroup results should be interpreted with caution due to the lack of OS results, immaturity of the data, and the lack of tests for interactions provided for any of the subgroups. Nonetheless, the baseline characteristics of the proposed Australian patient population could differ to that observed in CM-577 and this could lead to lower efficacy of nivolumab in the proposed PBS population as the Australian population may be older at diagnosis and more patients may have higher tumour staging (discussed below).
- 6.18 On the basis of the presented subgroup DFS HRs, for which no confidence intervals were reported, there may be treatment effect differences in relation to age, tumour status, tumour location, time from complete resection to randomisation, and PD-L1 combined positive score. Gordon et al 2011¹¹ and Nguyen et al 2019¹² reported the Australian population was generally older than in the clinical trial. Nguyen et al 2019 also reported more T3 and T4 (65.3%) patients compared with CM-577 (54.9%), suggesting that the efficacy of nivolumab could potentially be lower in the proposed PBS population than in CM-577. The PBAC agreed with the ESC that, overall, the trial population was unlikely to be significantly different from the Australian patient population, with the exception that patients treated in Australia are likely to be older.
- 6.19 Regarding EuroQoL 5 dimension (EQ-5D) results, except for a large jump in nivolumab patient scores between week 62 and 65, likely due to small patient numbers, there did not appear to be a clear difference in scores or trends between the two treatments.
- 6.20 The ESC noted that 253/268 (94%) events in the nivolumab arm and 154/171 (90%) events in the placebo arm (February 2021 data cut) were distant metastatic events.
- 6.21 The ESC noted the use of subsequent immunotherapy was low with 2.9% of all randomised patients receiving immunotherapy (0.8% in the nivolumab arm and 7.3% in the placebo arm). The ESC considered that given the recent PBAC recommendations for the listing of immunotherapy in the advanced or metastatic treatment settings it would be expected that subsequent immunotherapy in the placebo arm would be substantially higher in the Australian setting. The ESC considered this condition is not so responsive to immunotherapy that it is likely to provide benefit in patients who

¹⁰ Moehler, M., Ajani, J. A., Kuzdzal, J., et al. 2021. 1381P Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): 14-month follow-up of CheckMate 577. *Annals of Oncology*, 32, S1045-S1046.

¹¹ Gordon, L. G., Eckermann, S., Hirst, N. G., et al. 2011. Healthcare resource use and medical costs for the management of oesophageal cancer. *Br J Surg*, 98, 1589-98.

¹² Nguyen TMN, Hummel R, Bright T et al. Pattern of care for cancer of the oesophagus in a western population. *ANZ J Surg* 2019; 89: E15 – 19.

recur after having received it in the adjuvant setting. The ESC considered access to immunotherapy should be restricted to one course of treatment per lifetime unless there is adequate clinical and economic evidence available to support retreatment. The sponsor did not support restricting nivolumab to one course of treatment per patient lifetime (pre-PBAC response). As an alternative, the sponsor proposed a revised restriction criterion that only excludes patients who progress within 6 months of completing adjuvant immunotherapy from retreatment (pre-PBAC response).

Comparative harms

6.22 A summary of safety outcomes in CM-577 is presented in Table 6.

Table 6: Adverse event summary in the CM577 trial (all treated patients)

Safety outcome, n (%)	Any grade			Grade 3-4		
	Nivolumab (n=532)	Placebo (n=260)	Risk difference (95% CI)	Nivolumab (n=532)	Placebo (n=260)	Risk difference (95% CI)
Any AEs	513 (96)	243 (93)	0.03 (-0.00, 0.06)	186 (35)	84 (32)	0.03 (-0.04, 0.10)
Serious AEs	160 (30)	81 (31)	-0.01 (-0.08, 0.06)	109 (20)	53 (20)	0.00 (-0.06, 0.06)
AEs leading to discontinuation	71 (13)	21 (8)	0.05 (0.01, 0.10)	39 (7)	16 (6)	0.01 (-0.02, 0.05)
Any TRAEs	379 (71)	122 (47)	0.24 (0.17, 0.32)	74 (14)	16 (6)	0.08 (0.04, 0.12)
Serious TRAEs	41 (8)	7 (3)	0.05 (0.02, 0.08)	31 (6)	3 (1)	0.05 (0.02, 0.07)
TRAEs leading to discontinuation	49 (9)	8 (3)	0.06 (0.03, 0.09)	26 (5)	7 (3)	0.02 (-0.00, 0.05)
TRAEs in ≥10% of treated patients in either arm						
Fatigue	92 (17)	29 (11)	0.06 (0.01, 0.11)	6 (1)	1 (<1)	0.01 (-0.00, 0.02)
Diarrhoea	89 (17)	39 (15)	0.02 (-0.04, 0.07)	2 (<1)	2 (<1)	-0.00 (-0.02, 0.01)
Pruritis	53 (10)	9 (3)	0.07 (0.03, 0.10)	2 (<1)	0	0.00 (-0.00, 0.01)
Rash	51 (10)	10 (4)	0.06 (0.02, 0.09)	4 (<1)	1 (<1)	0.00 (-0.01, 0.01)
Hypothyroidism	51 (10)	4 (2)	0.08(0.05, 0.11)	0	0	0.00 (-0.01, 0.01)

Source: Table 38, p96 of the submission.

AE = adverse event; CI = confidence interval; TRAE = treatment related adverse event

Text in **bold** indicate statistically significant differences

The submission stated that RDs were calculated post-hoc using Review Manager Ver 5

6.23 It was noted in the evaluation that there was an approximate 8% increase of grade 3 or 4 treatment related AEs associated with nivolumab treatment compared with placebo.

Benefits/harms

6.24 A summary of the comparative benefits and harms for nivolumab versus placebo is presented in Table 7.

Table 7: Summary of comparative benefits and harms for nivolumab versus placebo

Disease free survival					
Interim analysis*					
Event	Nivolumab (N=532)	Placebo (N=262)	Absolute Difference		HR (95% CI) [p-value]
Events, n (%)	241 (45.3)	155 (59.2)	-		0.69 (0.56, 0.85) [p=0.0003]
Median DFS, months (95% CI)	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)	11.37		
February 2021 update*					
% Disease free at:	% (95% CI)	% (95% CI)	Absolute difference (%)		
3-month	84.3 (80.9, 87.2)	82.1 (76.9, 86.3)	2.2		
6-month	72.6 (68.5, 76.3)	61.5 (55.3, 67.1)	11.1		
9-month	67.3 (63.1, 71.2)	52.5 (46.2, 58.4)	14.8		
12-month	61.8 (57.4, 65.8)	45.5 (39.3, 51.4)	16.3		
15-month	57.9 (53.5, 62.0)	43.4 (37.3, 49.4)	14.5		
18-month	53.9 (49.5, 58.2)	40.4 (34.4, 46.4)	13.5		
21-month	51.1 (46.6, 55.5)	37.6 (31.5, 43.6)	13.5		
24-month	48.3 (43.7, 52.8)	36.0 (29.9, 42.0)	12.3		
Harms					
	Nivolumab (n=532)	Placebo (n=260)	Event rate/100 patients*		RD (95% CI)
			Nivolumab	Placebo	
Any TRAEs, n (%)	379 (71)	122 (47)	71%	47%	0.24 (0.17, 0.32)
Any severe (Grade 3 or 4) TRAEs, n (%)	74 (14)	16 (6)	14%	6%	0.08 (0.04, 0.12)

Source: Table 29, p75, Table 34, p81 and Table 38, p96 of the submission.

DFS = disease free survival; HR = hazard ratio; RD = risk difference; TRAE = treatment related adverse event

* the interim October 2020 analysis had minimum follow-up 6.2 months; median follow-up time was 24.4 months. The updated February 2021 database lock had minimum follow-up time of 14.0 months; median follow-up time was 32.2 months

6.25 On the basis of the CM-577 trial, it is estimated for every 100 patients treated with nivolumab in comparison with placebo over a median follow-up time of 32.2 months:

- 12 more patients would be disease free at 24 months.
- 24 more patients would have treatment related adverse events.
- 8 more patients would have severe (grade 3 or 4) treatment related adverse events.

Clinical claim

6.26 The submission claimed that adjuvant nivolumab demonstrated superior efficacy and inferior safety compared to placebo in patients with resected OC or GOJC whom had received prior CRT.

6.27 The submission stated that this claim was demonstrated by a statistically significant and clinically meaningful DFS benefit as well as a consistent benefit across DMFS and PFS2 for adjuvant nivolumab treatment versus placebo.

6.28 On the basis of DFS, there appeared to be a benefit of nivolumab compared with placebo in this treatment setting. However, the clinical relevance of this benefit was unclear due primarily to the lack of currently available OS data. The Pre-Sub

Committee Response (PSCR) stated that OS data will be available when 460 events are observed (estimated to occur in 2024). The ESC noted the pooled analyses in the treatment of OC and GOJC (Leung et al 2021 and Ronellenfitch et al 2019) and gastric cancer (Oba et al 2013) referenced in the PSCR to support the claim of a strong positive correlation between DFS and OS in this setting. However, it also noted these studies were conducted for chemotherapies and considered that the studies may not be applicable to immunotherapy. The PBAC agreed with the ESC that the relationship between DFS and OS observed for adjuvant chemotherapy does not necessarily hold for adjuvant immunotherapy, and further the relationship will be impacted by subsequent therapy, including immunotherapy, received in the metastatic setting for patients who have disease recurrence.

- 6.29 Based on the CM-577 trial results the ESC considered a claim of inferior safety was reasonable.
- 6.30 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.31 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.32 The submission presented a stepped economic evaluation based on the direct randomised trial (CM-577). The type of economic evaluation presented was a cost-utility analysis. The key components of the economic evaluation are presented in Table 8.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Nivolumab for up to one year compared to standard of care ('watch and wait')
Outcomes	Life years gained, quality-adjusted life years
Time horizon	25 years in the model base case versus a median follow-up of 32.2 months in the CM-577 trial (the February 2021 data cut).
Methods used to generate results	A three-health state Markov model; costs and health effects (utility values).
Health states	Pre-recurrence, post-recurrence, death. The ESC considered it reasonable to combine locoregional and distant metastases into one disease health state, as it was considered that a recurrence, local or distant, in this setting is generally non-curative and therefore a similar progression of disease can be assumed for all patients. The ESC noted only a small proportion of recurrences would be local in this population given the nature of the surgical resection.
Cycle length	4 weekly for one year; 3 monthly thereafter.
Transition probabilities	Individual patient data for TTR from the CM-577 trial (from the February 2021 analysis) was used until up to month 27 (which was the median follow-up for TTR from the updated February 2021 database lock) followed by extrapolation of TTR applied to individual treatment arms was used to determine the transitions from pre-recurrence to post-recurrence for a period of 5 years. After 5 years, patients in the pre-recurrence state were assumed to be cured and will not transition to post-recurrence but can still die. Given there was no OS data available from CM-577 at the time of submission, transitions from post-recurrence to death were independent of treatment and informed in the base case by a real-world data registry set from the Netherlands (van Putten et al 2018). It was assumed that patients in the post-recurrence health state could not be cured and maintained a constant death rate, calculated from van Putten et al, 2018. The ESC noted that the Netherlands Cancer registry sourced for the transition

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Component	Summary
	<p>between post-recurrence and death was based on 2010–2014 data. As these data do not reflect current practice with immunotherapy in the metastatic setting these transitions are likely to have been overestimated.</p> <p>In the base case, Australian population mortality data were elevated with an SMR of x2.5 up to the assumed point of cure (5 years). After this point, those remaining in the pre-recurrence health state were assumed to have the same mortality as the general population. The ESC advised that it is not reasonable to assume the same mortality as the general population for the subset of patients who have not recurred at 5 years (cured fraction), as these patients suffer from complications associated with a complete surgical resection and risk factors associated with OC and GOJC that do not reflect the risk profile of the general population.</p>
Extrapolation method	In the base case, KM estimates were used until the median TTR follow-up of 27 months, at which point independently fit generalised gamma curves were applied to both the nivolumab and SOC arms up to 5 years, at which point cure was assumed and the Australian background mortality was applied exclusively.
Health related quality of life	<p>Based on mean EQ-5D scores by health state in the CM-577 trial, with Australian preference weights applied.</p> <p>Pre-recurrence: 0.840 Post-recurrence: 0.771</p> <p>The pooling of utility weights pre- and post-regression might not be appropriate given relative safety profiles. The ESC noted the inclusion of disutility associated with AEs, but considered that arm-specific utility scores would be informative, at least as part of a sensitivity analysis. The sponsor provided a revised economic evaluation in the pre-PBAC response. The revised economic model included treatment specific utilities that led to a 3.7% increase in the base case ICER (\$\$35,000 to < \$45,000/QALY gained).</p>

Source: Table 50, p127 of the submission.

TTR: time to treatment recurrence; OS = overall survival; SMR = standardised mortality ratio

6.33 While the PSCR maintained that the appropriate time horizon is 25 years, the ESC considered that it was not reasonable given the long-term complications associated with complete surgical resection and risk factors associated with OC and GOJC. The ESC advised that a 15–20 year time horizon represents a more realistic maximum life expectancy for this patient population.

6.34 The average recurrence or death events per patient in CM-577 versus in the economic model are presented in Table 9.

Table 9: Average recurrence or death events per patient in the trial versus the economic model

	CM-577 (Median follow-up: 32.2 months)			Economic model (Over 25 years, undiscounted)		
	Nivolumab	Placebo	Increment	Nivolumab	Placebo	Increment
Recurrence or death, %	50.4%	65.3%	14.9%	80.3%*	87.9%**	7.6%
Proportion assumed cured	Not assumed in CM-577			36.1%^	22.2%^	13.9%
Death at 5 years	Not available (68% ^ψ for non-metastatic OC patients in van Putten et al 2018)			61.3% ^ψ	75.4% ^ψ	14.1% ^ψ
Life years (undiscounted)	-	-		9.075	6.199	2.876

Source: Model worksheet of attached economic evaluation and Table 29, p75 of the submission.

*Calculated as =sum(W209:X:209) in model worksheet of economic model.

** Calculated as =sum(AO209:AP209) in model worksheet of economic model.

^ Cell V130 in model worksheet of attached economic model

^^Cell AN130 in model worksheet of attached economic model

ψ Inputs calculated during the evaluation.

6.35 The base case of the economic model (25-year time horizon) estimated for every patient treated with nivolumab:

- a primary drug cost of \$| per patient (undiscounted); and
 - a mean gain of 2.876 life years (LY) per patient (undiscounted).
- 6.36 The probability of recurrence or death in both treatment arms was higher in the economic model than in CM-577 (Table 9). This was expected given the longer time horizon (lifetime horizon) used in the model compared to the trial. van Putten et al 2018¹³ estimated that 5-year survival for non-metastatic oesophageal cancer was 32% between 2010 and 2014. The economic evaluation estimated a 5-year survival of 24.6% and 38.7% for standard of care and nivolumab, respectively. It was likely that the van Putten et al 2018 estimates were not directly comparable as they included all non-metastatic patients as opposed to only those included in the trial but, nevertheless, these differences might suggest an underestimation of overall survival in the SOC arm.
- 6.37 In the base case analysis, TTR is utilised to determine transitions from recurrence free to recurred with DFS data utilised in a sensitivity analysis. The submission stated that the rationale for the use of TTR over DFS in the base case was that the use of DFS may lead to a potential double counting of deaths for nivolumab. Therefore, this is utilised in the base case for the economic evaluation. DFS is the primary endpoint for CM-577 and allows for external validation with clinical experts and published literature. Therefore, DFS is utilised as the data source to estimate the transition from pre-recurrence to post-recurrence in a sensitivity analysis. It was noted in the evaluation that TTR estimates were calculated post hoc and therefore may be associated with more uncertainty compared with DFS, the primary outcome of CM-577. The PSCR reiterated that TTR is equal in its validity to DFS, and a more accurate approach to modelling recurrence, as DFS includes both recurrence and death events in CM-577 and its use in the economic model leads to the double counting of death in the pre-recurrence health state. The ESC considered that the TTR curves used for the base case in the submission may be reasonable, and further noted that the choice of data source for this transition (TTR versus DFS) was not a key driver of the economic model.
- 6.38 The key limitation of the model was the absence of comparative overall survival data to assess the magnitude of benefit of nivolumab. The submission relied on calculating the transition from post-recurrence to death on a one-year overall survival of 22% from a Dutch registry dataset (van Putten et al 2018; also referred to as IKNL data). The data from van Putten et al 2018 may not be applicable to the proposed Australian population due to differences in previous treatment, as only 29% had surgical resection between 2010–2014 in the IKNL data whereas all patients were required to have had complete surgical resection with the requested restriction. Furthermore, the ESC noted that the Netherlands Cancer registry was based on 2010–2014 data and

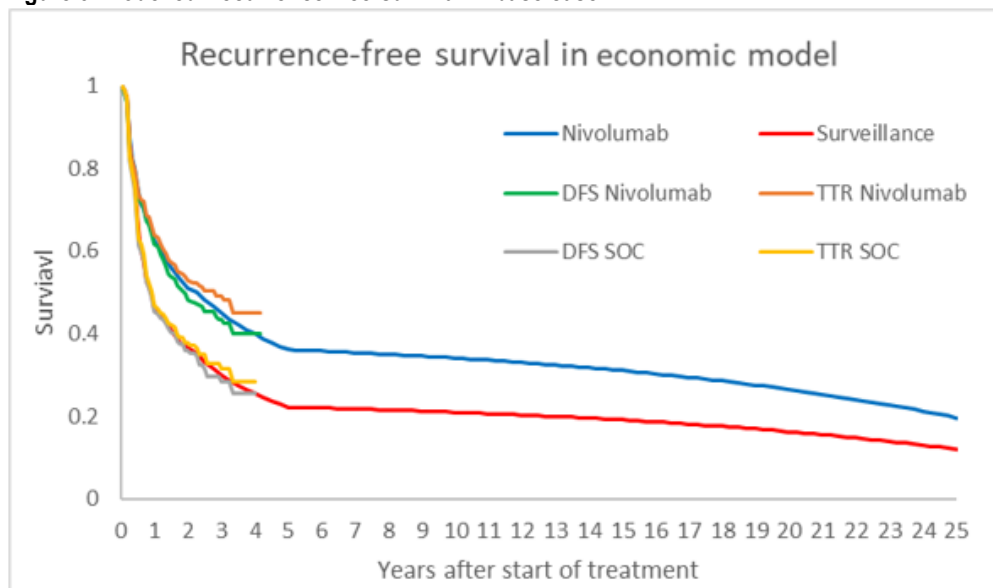
¹³ van Putten, M., de Vos-Geelen, J., Nieuwenhuijzen, G.A.P. et al. Long-term survival improvement in oesophageal cancer in the Netherlands. *European Journal of Cancer* 94(2018) 138-147.

would not include immunotherapy as a treatment option in the metastatic setting (which would be current clinical practice in the placebo arm). The ESC considered using these transitions for post-recurrence to death may overestimate the incremental OS benefit associated with nivolumab.

- 6.39 In comparison, Lou et al 2013, which was used in the NICE evaluation of nivolumab in OC and GOJC (NICE TA746)¹⁴ to inform post recurrence mortality, would be more relevant to the current submission. Lou et al 2013 reported a one-year survival of 46.9% in 1147 patients in the US who had surgery (93.3% R0 resection), of whom 63% also had neoadjuvant CRT. The ESC advised that Lou et al (2013) was the preferable dataset for populating this transition, however noted that the choice of data (Lou et al 2013 versus the Netherlands Cancer registry) was not a driver of the economic model (see paragraph 6.55).
- 6.40 The modelled recurrence-free survival and overall survival in the base case are presented in Figure 3 and Figure 4.

¹⁴ <https://www.nice.org.uk/guidance/ta746/evidence/committee-papers-pdf-10887317533>, accessed 12/4/22

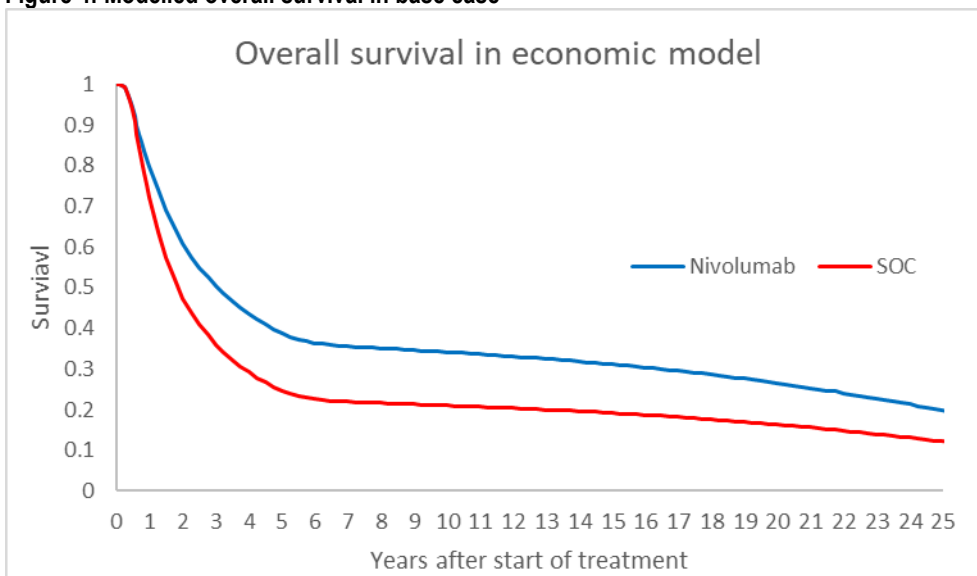
Figure 3: Modelled Recurrence-free-survival in base case



SOC = standard of care

Source: 'Model' worksheet of attached economic model.

Figure 4: Modelled overall survival in base case



SOC = standard of care

Source: 'Model' worksheet of attached economic model.

- 6.41 In its consideration of nivolumab for melanoma in the adjuvant setting (paragraph 7.11, nivolumab PSD, March 2019 PBAC meeting), the PBAC had considered that in light of unavailable OS data in the trial, the PBAC had requested modelling OS (and DMFS and regression free survival) with converging curves, with the convergence occurring at 15 years.
- 6.42 The nivolumab model in the OC GOJC setting did not include operability for modelling convergence of survival curves. Ideally, the economic model would allow for OS

convergence through adjustment to the probability of mortality over time. However, during the evaluation, it was found that selection of a loglogistic extrapolation for TTR in the nivolumab arm, while retaining the generalised gamma curve for the SOC arm, and assuming cure at 15 years, resulted in an approximate OS convergence at 15 years. The PSCR argues that manipulations of the model to assume OS convergence conducted in the evaluation were inappropriate. The sponsor considered it unreasonable to assume that economic modelling of adjuvant melanoma should also apply to adjuvant OC or GOJC. It was argued by the sponsor that the plot of DFS hazards over time indicated a convergence of the hazards for the nivolumab arm with general mortality at 3 years, supporting an assumption of cure at 5 years, which was also supported by a local advisory board. The sponsor also maintained that the most appropriate parametric functions were applied to TTR, both visually and as reported by the lowest AIC/BIC and that the choice of parametric functions to force OS convergence in the evaluation was not appropriate. While acknowledging that the multivariate analyses presented were ad-hoc and not a precise method to estimate an ICER in an OS convergence scenario, the ESC noted it resulted in substantial differences in modelled OS with an increase to the incremental cost effectiveness ratio (ICER) of over 100% (Table 12). The ESC considered OS curve convergence would be reasonable at a point when background mortality would be assumed to dominate over prior treatment benefit. The ESC considered that this would likely occur towards the end of the model time horizon (which the ESC considered should be between 15 and 20 years).

6.43 It should be noted that the cure assumption at a particular timepoint was based on assumption only reflecting the cured proportion rather than being a meaningful clinical marker. That is, setting a cure at 5 years instead of 15 years is analogous to assuming that nivolumab was associated with 36% of patients cured in the base case (cure rate at 5 years) and 11.4% in this alternative case (cure rate at 15 years).

6.44 Key drivers of the model are presented in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: \$11/QALY gained
Assumption of no convergence of TTR curves	No convergence for TTR (and by extension, OS) applied in the base case. Based on PBAC consideration of nivolumab in the melanoma adjuvant setting, an <i>ad-hoc</i> approach to converge survival curves at 15 years was conducted by using different extrapolation functions for each arm (and altering the cure assumption).	High, favours nivolumab Use of a log logistic curve for nivolumab and a cure set at 15 years to model convergence increased the ICER to \$11 ² /QALY gained (151% increase) Use of a Gompertz extrapolation for SOC and a cure set at 15 years increased the ICER to \$11 ³ /QALY gained (123% increase)
Time horizon	25-year time horizon was selected in the base case, this was compared to a median follow up of 32.2 months using the latest data cut.	High, favours nivolumab Use of a 15-year time horizon increases the ICER to \$11 ⁴ /QALY gained (29% increase)

Source: Table 86, p186 of the submission and the attached economic model.

ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; SOC = standard of Care; TTR = time to recurrence

The redacted values correspond to the following ranges:

- ¹ \$35,000 to < \$45,000
- ² \$95,000 to < \$115,000
- ³ \$75,000 to < \$95,000
- ⁴ \$45,000 to < \$55,000

6.45 Based on the model assumptions, patients do not remain in the post-recurrence health state for long before they die due to a high mortality rate assumed (one year survival of 22.0%, sourced from van Putten et al 2018), and as such, the TTR was a key driver of the model due to its effect on predicting overall survival rather than the incremental differences in utility assumed between health states (0.84 in pre recurrence and 0.771 in post recurrence). For example, assuming there was no difference in utility between pre and post recurrence increased the ICER by only 0.5%.

6.46 Results of the economic evaluation are presented in Table 11.

Table 11: Results of the stepped economic evaluation

Step and component	Nivolumab	Standard care	Increment
Step 1: Trial based cost per recurrence avoided			
Costs	\$█	\$22,510	\$█
Recurrence	44.9%	61.5%	16.6%
Incremental cost/recurrence avoided			\$█ ¹
Step 2: Trial based cost per life year gained^a			
Costs	\$█	\$22,510	\$█
LY	1.845	1.653	0.193
Incremental cost/ LYG			\$█ ¹
Step 3: Trial based cost per QALY gained^a			
Costs	\$█	\$22,510	\$█
QALY	1.528	1.360	0.168
Incremental cost/ QALY gained			\$█ ¹
Step 4: Cost per QALY gained, extrapolated to 25 years			
Costs	\$█	\$29,507	\$█
QALY	5.050	3.587	1.463
Incremental cost/ QALY gained			\$█ ²

Source: Table 79, p181 of the submission.

LYG = life year gained; QALY = Quality adjusted life-year

^a Time horizon set to median follow-up of trial of 32.2 months = 2.68 years

The redacted values correspond to the following ranges:

- ¹ \$255,000 to < \$355,000
- ² \$35,000 to < \$45,000

6.47 The incremental cost of nivolumab treatment contributed to the largest component of the incremental cost (\$█, 98% of incremental cost). The incremental QALY gained in the pre-recurrence health state in the nivolumab arm (1.542, 105% of incremental QALY gain) was the largest component of the incremental QALYs, with the post recurrence health state decrement (-0.079, -5% of incremental QALY gain) contributing only a small proportion to the overall incremental QALYs.

6.48 The submission assumed that adjuvant nivolumab would not preclude use of immunotherapy (assumed to be pembrolizumab plus chemotherapy in the submission) in the metastatic setting. The economic model allowed for a sensitivity

analysis in which post-recurrence survival from KEYNOTE 590 of pembrolizumab in the metastatic setting was used. A per cycle post-progression mortality risk of 0.05 (based on a one-year survival of 55% reported in KEYNOTE 590) instead of 0.126 in the base case (based on results from van Putten et al 2018) was applied to both treatment arms in the model and a total cost of \$¹⁵ was also applied for each recurrence. The ESC noted this sensitivity analysis should include the use of immunotherapy in the metastatic setting in the standard care arm only to better reflect likely Australian clinical practice (as discussed in paragraph 6.21). The PBAC noted that the cost applied to this sensitivity analysis was substantially higher than the recommended cost per patient for nivolumab in the advanced/metastatic setting. Further to this, the PBAC advised that immunotherapy should be restricted to one course of treatment per lifetime for OC and GOJC (see paragraph 7.4), and therefore considered that the sensitivity analysis was not informative.

- 6.49 The results of key univariate and multivariate sensitivity analyses are summarised in Table 12.

¹⁵ Based on the published price of pembrolizumab.

Table 12: Results of sensitivity analyses

Analyses		Incremental cost	Incremental QALY	ICER	% Change in ICER from BC
Base case		\$█	1.463	\$█ ¹	-
Discount rate (5% in BC)	3.5%	\$█	1.679	\$█ ²	-12.6%
	0%	\$█	2.422	\$█ ³	-38.7%
Time horizon (25 years in BC)	30	\$█	1.531	\$█ ¹	-4.1%
	20	\$█	1.333	\$█ ¹	+9.3%
	15	\$█	1.128	\$█ ⁴	+28.8%
Pre-recurrence to post-recurrence transitions (based on TTR in BC)	Based on DFS	\$█	1.351	\$█ ¹	+8.7%
Cure assumption (5 years in BC – Nivo 36.1%, SOC 22.2%)	3 years (44.7%, 29.9%)	\$█	1.493	\$█ ¹	-2.6%
	7 years (31.3%, 18.3%)	\$█	1.426	\$█ ¹	+3.2%
	10 years (26.5%, 14.7%)	\$█	1.386	\$█ ¹	+6.9%
	15 years (20.7%, 10.9%)	\$█	1.354	\$█ ¹	+10.2%
	25 years (no cure)	\$█	1.356	\$█ ¹	+10.7%
Post -recurrence mortality (22% one-year survival in BC)	46.9% (Lou et al 2013)	\$█	1.393	\$█ ¹	+4.3%
Terminal care costs (\$25,547 in BC)	Removed	\$█	1.463	\$█ ¹	+4.8%
Utilities (mean estimates in BC)	Lower 95% bounds	\$█	1.446	\$█ ¹	+1.2%
	Upper 95% bounds	\$█	1.478	\$█ ¹	-1.0%
	Assume 0.84 for post recurrence	\$█	1.456	\$█ ¹	+0.5%
Multivariate analyses					
Cure at 15 years, Gompertz for SOC		\$█	0.691	\$█ ⁵	+122.7%
Cure at 15 years, and loglogistic for Nivolumab		\$█	0.614	\$█ ⁶	+150.7%
15-year time horizon, DFS for transition, 46.9% post recurrent one year mortality		\$█	0.975	\$█ ⁷	+48.73%

Source: Table 86, p186 of the submission and the attached economic model.

BC = base case; DFS = disease free survival; ICER = incremental cost-effectiveness ratio SOC = standard of care; TTR = time to recurrence

The redacted values correspond to the following ranges:

- ¹ \$35,000 to < \$45,000
- ² \$25,000 to < \$35,000
- ³ \$15,000 to < \$25,000
- ⁴ \$45,000 to < \$55,000
- ⁵ \$75,000 to < \$95,000
- ⁶ \$95,000 to < \$115,000
- ⁷ \$55,000 to < \$75,000

6.50 The model was overall most sensitive to variables which affected the time spent in pre-recurrence. This increased OS by proxy, as patients who transitioned to the post-recurrence health state die at an accelerated rate (22% survival at one year in the model).

6.51 Notably, increasing the required amount of time to a cured status from 5 to 25 years (assuming no cure) only increased the ICER by approximately 10%. This may be driven by the fact that the TTR extrapolations already are modelled to plateau substantially after 5 years, essentially already assuming a cure for many patients.

- 6.52 When applying the same extrapolation function to each arm of the model for TTR, the only extrapolation resulting in a substantial increase in the ICER was the exponential curve resulting in a 12% increase. All other extrapolations resulted in decreases to the ICER.
- 6.53 Generalised Gamma extrapolations were used in both arms for TTR in the base case. Even though the statistical fit with the generalised gamma extrapolation seemed reasonable and had the lowest AIC and BIC among the parametric models fitted, it was noted that both the CADTH¹⁶ and NICE evaluation of nivolumab in adjuvant GOJC used different extrapolations. In the CADTH evaluation, which appeared to also have used the earlier data cut of CM-577 (see paragraph 6.16), a spline odds 2 knots model was used in the base case to predict DFS and a spline hazards 2 knots model was used as part of the reanalysis by CADTH, who noted that the parametric model used to extrapolate DFS data was a driver of the model. In the NICE evaluation, a log normal 1 knot spline fit for nivolumab and a log normal 2 knot spline for SOC were assessed to be the most robust in the base case, however subsequently a generalised F distribution using data from a later database lock was used.
- 6.54 The choice of the parametric function for extrapolation as opposed to spline models may have favoured nivolumab but the exact impact was unclear as spline models could not be tested during evaluation. When assuming the same discount rate (1.5% per year) and time horizon (30 years) as in the CADTH evaluation, the resulting incremental QALY gained estimated from the model was 2.22 QALYs compared to 1.11 QALYs in the CADTH model. Comparing landmark DFS proportions at up to two years in the model with those considered by NICE also showed that the DFS in the submission were higher in model at all time points compared to the model presented to NICE.
- 6.55 Using post-recurrence mortality estimates from Lou et al (2013) rather than van Putten et al (2018) in the base case (46.9% instead of 22%) resulted in an increase to the ICER of 4.3%. The moderate impact of this sensitivity analysis was due to two reasons. Firstly, post-recurrence mortality was assumed to be independent of treatment. Secondly, and more importantly, as discussed in paragraph 6.47, only a small fraction of the treatment effect (QALYs and LYGs) was accrued in the post-recurrence state, so even doubling this estimate did not have a large impact on the overall ICER.
- 6.56 In response to a number of concerns raised by the ESC, the sponsor provided a revised economic evaluation in the pre-PBAC response. The revised economic evaluation included the following steps (based on a 25 year time horizon):

¹⁶ https://www.cadth.ca/sites/default/files/DRR/2022/PC0253-Opdivo_combined.pdf , accessed 22 April 2022

- Step 1: Use of a Gompertz extrapolation for TTR (reducing the ICER to \$35,000 to < \$45,000/QALY gained).
- Step 2: Cure assumption removed (increasing the ICER to \$35,000 to < \$45,000/QALY gained).
- Step 3: Use of Lou et al (2013) for post-recurrence survival (increasing the ICER to \$35,000 to < \$45,000/QALY gained).
- Step 4: Use of treatment specific utilities (increasing the ICER to \$35,000 to < \$45,000/QALY gained).
- Step 5: Use of continuous background mortality multiplier of x2.5 (increasing the ICER to \$35,000 to < \$45,000/QALY gained). The sponsor stated that for this scenario 9% of patients in the nivolumab arm and 5% of patients in the ‘watch and wait’ arm remain alive at 25 years.

6.57 The ESC considered it would be informative for the PBAC to be provided with a summary of key clinical data and economic and financial assumptions for submissions associated with adjuvant treatments.

6.58 The PBAC noted it had previously considered an ICER of less than \$30,000/ QALY to be reasonable in an adjuvant treatment setting (paragraph 5.11, nivolumab PSD, July 2019 PBAC meeting).

Drug cost/patient/course

Table 13: Nivolumab cost per patient/ course (applies to clinical, economic and financial estimates)

	Nivolumab 240mg every 2 weeks over first 16 weeks	Nivolumab 480mg every 4 weeks for remainder of 1 year of treatment	Total
Infusions per Treatment course	7.07	5.23	12.3
DPMA per infusion	\$	\$	\$
Drug cost/patient/course	\$	\$	\$

^a weighted by number of infusions for 240mg and 480mg

Source: Table 78, p180 of the submission. DPMA = dispensed price per maximum amount; mg = milligram

6.59 The submission estimated drug cost per patient by estimating the number of 240 mg infusions and the number of 480 mg infusions based on the distribution in the CM-577 trial, each was multiplied by the DPMA per infusion, and summed for a total cost/ per patient per course. As treatment is not to exceed one year, which was covered by the trial period, there were no differences between the clinical, financial and economic sections. As the comparator was watch and wait standard of care, this was assumed to have no associated treatment costs. The PBAC noted the requested price for each 100 mg vial of nivolumab was substantially higher than the price recommended for advanced/ metastatic gastro-oesophageal cancers.

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

Estimated PBS usage & financial implications

6.60 This submission was not considered by DUSC.

6.61 The submission took an epidemiological approach to estimating financial impact. Key inputs of the financial estimates are presented in Table 14.

Table 14: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
OC and GC incidence	OC: 1,649 GC: 2,392	AIHW 2020 estimate (Cancer Australia, 2021)	It appeared that the estimates only included incidence and did not factor in a prevalent population.
% Of GC with GOJC	35.70%	AIHW 2021 - Sponsor commissioned report, referenced year 2016	The AIHW worksheet calculated this by dividing the number of new cases with the C16.0 – cardia subsite classification in 2016 (n=784) by the total number of new stomach cancer cases in 2016 (N= 2,197). It was unclear if the C.16.0 classification tracked exactly to the Gastro-oesophageal junction, or whether this may include additional stomach cancer patients, but this likely constituted the best available evidence, and was otherwise reasonable.
% Receiving neoadjuvant CRT plus surgery	42.35%	Nguyen et al (2019)	The submission adjusted the estimate from Nguyen et al 2019 (35.29%) to account for an expected 20% increase in patients accessing nCRT as a result of nivolumab listing. The additional 20% was based on advice from the sponsor’s advisory board. It was unclear on what basis it would increase by 20% as opposed to more than this, but accounting for this change was a reasonable approach. The ESC noted that estimates from Nguyen et al 2019 were based on data (2012–2015) prior to evidence of FLOT peri-operative chemotherapy and therefore may overestimate the proportion of patients currently receiving nCRT vs peri-operative chemotherapy. The ESC also considered that it is likely that the percentage increase in nCRT uptake due to the listing of nivolumab would be higher than 20%. The PSCR stated that the percentage increase was based on the most reliable evidence available, and the sponsor was willing to work with the Department of Health to determine the most appropriate estimate. The PBAC and ESC acknowledged the lack of local real world data to inform this input and considered that the overall estimate of those receiving neoadjuvant CRT + surgery may be reasonable.
% Patients with WHO PS 0 or 1	100%	NCCN (2020)	The submission argued that, as an adjustment had already been made to remove patients who have not received nCRT + surgery, the financial model implicitly assumes that those patients who did not receive nCRT + surgery included those with WHO performance status of 2 or higher. It was unclear if performance status could change between initiation of surgery and nivolumab initiation. The ESC advised that performance status can deteriorate post-surgery and therefore it is likely that there is a percentage of patients who have nCRT + surgery who would subsequently not be eligible for nivolumab. The ESC considered that these patients may be accounted for in the selected uptake rate.
% Complete surgical resection and residual disease	71%	Van Hagen (2012)	These estimates were generally similar to those of other sources identified by the submission (Bossett 1997: 74%; Reynolds 2007: 81%)
Treatment utilisation			

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Data	Value	Source	Comment
Uptake rate	%	Sponsor advisory board (attachment 2 of the submission).	The ESC considered an estimate of % uptake was reasonable and accounted for patients that may decline treatment post-surgery or those not fit due to a decline in health.
Costs			
Nivolumab infusion costs	\$112.40	MBS item 13950	The submission estimated costs associated with a likely increase in the number of patients prescribed a radiotherapy containing neo-adjuvant regimen. The submission based these estimates on consultation with the sponsor's advisory board and relevant MBS items. Overall, this approach appeared reasonable.
IMRT dosimetry plan preparation	\$3,338.10	MBS Item 1565	
Radiation oncology tx verification	\$79.70	MBS Item 15715	
Radiation oncology treatment (IGRT)	\$190.35	MBS Item 15275	

Source: Table 87, p188 of the submission and '2a- patients incident' worksheet of attached financial model.

AIHW = Australian Institute for Health and Wellness; CRT = chemoradiotherapy; DPMA = dispensed price per maximum amount; GC = gastric cancer; GOJC = gastro-oesophageal junction cancer; IGRT = image guided radiotherapy; IMRT = intensity modulated radiotherapy; NCCN = National Comprehensive Cancer Network; nCRT = neoadjuvant chemoradiotherapy; MBS = Medicare benefits Schedule; mg = milligram; OAC= oesophageal adenocarcinoma; SCC= squamous cell cancer

6.62 The financial estimates did not account for reduction in later line use of immunotherapies. Though this was consistent with the economic evaluation, the evaluation considered it may not be appropriate. The ESC considered that the listing of nivolumab in the adjuvant setting would reduce the use of nivolumab in later lines of therapy, particularly for first line metastatic treatment among early relapsing patients. The ESC considered access to immunotherapy should be restricted to one course of treatment per lifetime unless there is adequate clinical and economic evidence available to support retreatment. The sponsor agreed that the PBS listing of nivolumab in the adjuvant treatment setting for OC/GOJC may reduce the use of metastatic immunotherapy (pre-PBAC response), however noted that the post-PBAC recommendation process for nivolumab in the advanced metastatic setting is ongoing. For this reason, the sponsor did not account for this potential cost saving in the financial estimates. The sponsor did not support restricting nivolumab to one course of treatment per patient lifetime and suggested a listing, similar to adjuvant melanoma, that only excludes patients who progress within 6 months of completing adjuvant immunotherapy from retreatment.

6.63 The calculation of number of treated patients is presented in Table 15.

Table 15: Estimation of number of treated patients

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Patients diagnosed with OC or GOJC	2,569	2,602	2,636	2,670	2,705	2,740
B	Growth rate	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%
C	% Stage II/III disease at diagnosis	A x 56.8%	1459	1478	1497	1517	1536
D	% adeno/squamous histology	C x 90.5%	1320	1337	1354	1372	1390
E	% Receiving neoadjuvant CRT + surgery	D x 42.35%	559	566	574	581	589
F	% Complete resection and residual disease	E x 71%	397	402	407	412	418
G	% WHO performance status 0 or 1	F x 100%	397	402	407	412	418
H	Total eligible patients	-	397	402	407	412	418
I	Uptake rate	-	%	%	%	%	%
J	Treated patients	H x %	1	1	1	1	1

Source: Table 99, p201 of the submission and '2a- patients incident' worksheet of attached financial model

CRT = chemoradiation therapy; GOJC = gastro-oesophageal junction cancer; OC = oesophageal cancer; WHO = World Health Organisation

The redacted values correspond to the following ranges:

¹ < 500

6.64 The estimated use and financial implications are presented in Table 16.

Table 16: 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	1	1	1	1	1	1
Number of infusions Q2W ^a	2	2	2	2	2	2
Number of infusions Q4W ^b	2	2	2	2	2	2
Estimated financial implications of nivolumab						
Cost to PBS/RPBS less copayments	\$3	\$3	\$3	\$3	\$3	\$3
Net financial implications						
Net cost to PBS/RPBS	\$3	\$3	\$3	\$3	\$3	\$3
Net cost to MBS	\$4	\$4	\$4	\$4	\$4	\$4
Net cost to PBS/RPBS/MBS	\$3	\$3	\$3	\$3	\$3	\$3

Source: Table 99, p201 to Table 107, p 210 of the submission.

^a Assuming 7.07 infusions per year as estimated by the submission.

^b Assuming 5.23 infusions per year as estimated by the submission

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$20 million to < \$30 million

⁴ 0 to < \$10 million

6.65 At year 6, the estimated number of patients initiating treatment was < 500 and the net cost to the PBS/RPBS of listing nivolumab was estimated to be \$20 million to < \$30 million, and a total of \$125.2 million in the first 6 years of listing.

6.66 The ESC noted that the submission did not include a prevalent population of patients. A prevalent population would be expected given the time interval from diagnosis to nCRT/surgery/post-surgery recovery prior to nivolumab commencement may be up to 6 months. Therefore, patients in this treatment phase at the time of nivolumab listing would be in addition to the incident population. The ESC advised that it would be reasonable for approximately 40% of the incident patients projected in year 1 to be

used as an estimate for the prevalent population. The sponsor agreed with the ESC that there may be additional patients during this treatment phase and provided revised financial estimates (pre-PBAC response). The net cost to PBS/RPBS (less copayments) during the first year of listing was revised from \$20 million to < \$30 million to \$20 million to < \$30 million.

- 6.67 Overall, the ESC considered the sources of the epidemiological approach seemed appropriate, and the approach generally reasonable.

Quality Use of Medicines

- 6.68 The submission noted that immunotherapy may be associated with a risk of immune-related adverse reactions (irARs), which may require a specific course of management. The submission described several initiatives to provide peer-to-peer education as well as established guidelines on the management of irARs.

- 6.69 These initiatives include physician education, immune-oncology preceptorship for oncologists and oncology nurses, peer-to-peer support, nursing and pharmacy in-services, a risk management plan (RMP), additional educational materials for awareness and management of irARs, educational materials and tools, as well as guidance on monitoring and treating immune related adverse reactions.

Financial Management – Risk Sharing Arrangements

- 6.70 The submission stated that the sponsor is willing to enter a risk-sharing arrangement (RSA) related to expenditure in this disease state, including the potential for subsidisation caps. The PSCR noted the positive recommendation of the broad listing resubmission encompassing OC, GOJC and GC is currently proceeding through the post-PBAC process to pursue PBS listing. The PSCR acknowledged there is some overlap between patients who will be able to access nivolumab in the adjuvant treatment setting for OAC and GOJC based on this submission and those who would be eligible for treatment in the metastatic setting. The PSCR stated that given the potential for a cure if patients reach 5 years without recurrence it is anticipated that less patients would require treatment for advanced/metastatic disease.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend nivolumab for the adjuvant treatment of patients with oesophageal cancer (OC) or gastro-oesophageal junction cancer (GOJC) who have received platinum-based chemoradiotherapy and surgery. The PBAC considered nivolumab provided moderate clinical benefit over 'watch and wait' surveillance in terms of disease free survival, however it was uncertain if it provided an overall survival benefit as clinical data for this outcome was unavailable. The PBAC considered the ICER presented in the submission was highly uncertain and likely to be substantially underestimated. The PBAC considered the estimated number of patients

- likely to be treated was reasonable but the financial estimates should account for reduced use of immunotherapy in the advanced/ metastatic treatment setting.
- 7.2 The PBAC noted the consumer comments highlighted that patients diagnosed with OC and GOJC have a poor prognosis and a low probability of 5-year survival due to limited efficacy of existing therapies. The PBAC noted that the comments emphasised the need for effective new adjuvant therapies and the quality of life benefits gained by reducing the burden associated with cancer recurrence.
- 7.3 The PBAC agreed with the suggestions and additions to the restriction proposed by the Secretariat. The PBAC considered a time restriction for treatment initiation post-surgical resection was appropriate for inclusion in the restriction and considered it should align with the Checkmate 577 trial (16 weeks). The PBAC considered that the prescriber instruction for a confirmatory scan, taken at least 4 weeks after progression / transient tumour flare, was not relevant to a PBS listing in the adjuvant setting and advised it should be removed from the restriction.
- 7.4 The PBAC agreed with the ESC that immunotherapy should be restricted to one course of treatment per lifetime for OC and GOJC given there is currently no clinical and economic evidence available to support retreatment and it advised an amendment to the proposed restriction would be required. The PBAC noted the sponsor requested consideration be given to excluding retreatment only if recurrence occurs within 6 months of completing adjuvant treatment (see paragraph 6.62) consistent with the PBS listings for immunotherapy to treat melanoma. However, the PBAC considered retreatment for patients with OC and GOJC in the metastatic setting was not justified, given lack of evidence of benefit for retreatment, and a range of other potentially effective PBS-reimbursed systemic therapies for this condition.
- 7.5 The PBAC considered the nominated comparator of ‘watch and wait’ surveillance, as standard of care, was appropriate.
- 7.6 The PBAC noted the submission was based on the Checkmate 577 study, a randomised, double blind trial comparing nivolumab (n=532) and placebo (representing standard of care) (n=262) in patients with resected OC or GOJC following neoadjuvant chemoradiotherapy. The submission presented data from an interim analysis (data cut October 2020, median follow up 24 months) and an *ad hoc* analysis (data cut February 2021, median follow up 32 months). The PBAC noted no OS data was presented in the submission for either analysis as the data has not yet been released to the sponsor.
- 7.7 The PBAC was satisfied that nivolumab was superior to the nominated comparator in improving DFS with a hazard ratio of 0.67 (95% CI: 0.55, 0.81) and a median DFS of approximately 22 months compared to 10 months in the standard of care arm. The PBAC noted 90% - 95% of the recurrence events observed in the clinical trial were metastatic and the outcomes for patients with metastatic disease are generally poor.

- 7.8 The PBAC considered that a claim of inferior safety was reasonable. The PBAC noted that there was an approximate 8% increase in grade 3 or 4 treatment related AEs associated with nivolumab compared with placebo in the Checkmate 577 trial. However, the PBAC considered the overall safety associated with nivolumab treatment in the adjuvant setting was acceptable.
- 7.9 The PBAC noted the base case ICER in the submission was \$35,000 to < \$45,000/QALY gained and considered this was likely to be substantially underestimated. The PBAC noted the economic model resulted in an average gain of 2.9 life years per patient treated with nivolumab over the 25 year time horizon of the model (see paragraph 6.35). The PBAC considered this was highly uncertain given the model was based on a surrogate outcome from clinical trial data with a relatively short median follow-up and the economic model did not account for OS benefits gained from immunotherapy that would be received by patients in the ‘watch and wait’ arm post-recurrence.
- 7.10 The PBAC noted the following issues with the economic model:
- The time horizon of the base case in the economic model was 25 years. The PBAC agreed with the ESC that a 15 to 20 year time horizon represented a more reasonable maximum life expectancy for this patient population.
 - In addition to overestimating the cost of subsequent immunotherapy, the model did not allow use of immunotherapy in the metastatic setting in the standard care arm only to better reflect Australian clinical practice (see paragraph 6.48).
 - The model lacked operability for modelling convergence of survival curves to test the sensitivity of assumptions regarding the modelled OS benefit (particularly in the context of no OS data being available).
- 7.11 The PBAC noted that, despite excluding the operability to model convergence, the evaluation was able to approximate convergence of the survival curves in the economic model by changing extrapolation functions and the time at which cure occurs (see paragraph 6.42). The PBAC noted that this adjustment to the economic model did not specifically address the issues regarding the time horizon and subsequent use of immunotherapy (as discussed in the paragraph above) but considered it provided a conservative basis to assess the cost effectiveness of nivolumab in this treatment setting. The PBAC noted that the average life years gained per patient with assumptions that approximate convergence was 0.614 and considered this to be a less uncertain estimate of the overall survival gained by adjuvant nivolumab, particularly in a scenario where immunotherapy is restricted to once per lifetime in both arms of the model. The PBAC noted that with this adjustment to the economic model the ICER was very high (\$95,000 to < \$115,000/QALY gained). It considered that a reasonable ICER for adjuvant OC or GOJC therapy would be less than \$30,000 per QALY.
- 7.12 The PBAC considered the estimated number of patients likely to be treated with nivolumab in Table 15 was reasonable and the addition of a prevalent patient

population as proposed in the sponsor's pre-PBAC response was appropriate. The PBAC noted that the financial estimates did not account for a reduction in use of immunotherapy in the advanced/ metastatic setting.

- 7.13 The PBAC noted that the sponsor stated in the submission that it was willing to enter an RSA including the potential for subsidisation caps in order to provide additional certainty to government. The PBAC considered this was appropriate and it would be reasonable for use to be included in the RSA recommended in the advanced/ metastatic setting with the expenditure caps revised to account for the estimated financial impact (after accounting for offsets associated with reduced use in the advanced/ metastatic setting).
- 7.14 The PBAC considered that the outstanding issues could be resolved in a simple resubmission for nivolumab using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- Amend the restriction as outlined in paragraphs 7.3–7.4;
 - Using the economic model specified in paragraph 7.11, propose a price that results in an ICER of \$30,000/QALY gained or less;
 - Provide revised financial estimates incorporating the new proposed price and accounting for the reduced use of immunotherapy in the advanced/ metastatic treatment setting; and
 - Propose an RSA addressing the issues raised in paragraph 7.13.
- 7.15 The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.
- 7.16 The PBAC advised that its acceptance of an early re-entry pathway was in the context of accepting the economic model referred to in paragraph 7.11 which, while it does not address all the modelling issues, provides a conservative basis to estimate cost effectiveness. Alternatively, the issues with the economic model (as discussed generally in the Economic analysis section above and specifically in paragraph 7.10) could be addressed in a standard re-entry resubmission.
- 7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

9 Sponsor's Comment

The Sponsor welcomes the PBAC's decision to resubmit via an early re-entry pathway and looks forward to continuing to work with the PBAC and the Department of Health to provide access of nivolumab for the adjuvant treatment of patients with oesophageal carcinoma (OC) or gastro-oesophageal junction carcinoma (GOJC) who have received previous platinum based chemoradiotherapy (CRT) and surgery.