7.06 DURVALUMAB, Solution concentrate for I.V. infusion, 120 mg in 2.4 mL, 500 mg in 10mL, Imfinzi®, AstraZeneca Pty Ltd

1 Purpose of Application

1.1 The resubmission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required (Streamlined) listing for durvalumab for treatment of Stage III unresectable non-small cell lung cancer (NSCLC) in patients who have not progressed after platinum-based chemoradiation therapy (CRT).

1.2 The requested listing for durvalumab was based on a cost-utility analysis comparing durvalumab to placebo or 'watch and wait' monitoring plus best supportive care. The key components of the clinical issues addressed by the resubmission are summarised in Table 1.

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

Component	Description
Population	Patients with unresectable Stage III NSCLC who have not progressed following platinum-based chemoradiation therapy.
Intervention	Durvalumab 10mg/kg via a 60-minute infusion q2w as maintenance therapy after chemoradiation for up to 12 months or until disease progression
Comparator	'Watch-and-wait' monitoring plus best supportive care (represented in the key trial by a matched placebo infusion q2w for up to 12 months or until disease progression)
Outcomes	OS, PFS as primary endpoints and TTDM, OS24, ORR, DOR, APF12; APF18; PFS2, HRQOL as secondary endpoints
Clinical claim	Durvalumab demonstrated superior efficacy, similar quality of life and manageable safety compared with watch-and-wait monitoring of patients with Stage III NSCLC whose disease has not progressed following definitive chemoradiation therapy.

APF12/APF18= proportion of patients alive and progression-free at 12/18 months from randomisation; DOR=duration of response; HRQOL = health related quality of life; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; OS24 = overall survival at 24 months; PFS = progression-free survival; PFS2 = time from randomisation to second progression; q2w = every two weeks; TTDM = time to death or distant metastasis.
Source: Table 1.1.2, p34 of the resubmission.

1.3 The resubmission presented updated overall survival (OS) results from the PACIFIC trial from a 31 January 2019 data cut (10 months longer follow-up compared with the previous submission), and also presented additional analyses of OS, adjusted for treatment switching (or lack of). This was to address previous PBAC concerns regarding the limited applicability of OS results observed in the PACIFIC trial to Australian clinical practice, since the use of subsequent therapies in PACIFIC did not reflect clinical practice.

2 Requested listing

2.1 The requested listing is presented below. Amendments by the Secretariat are included with additions in italics and deletions in strikethrough.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Durvalumab 500mg/10mL; 10mL 120mg/2.4mL; 10mL	~~1240~~*1200*mg	8 (initial) 8 (continuing)	$[redacted] published (public) $[redacted] published (private) $[redacted] effective (public) $[redacted] effective (private)	Imfinzi, AstraZeneca Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy (Public and Private Hospital)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Unresectable
Condition:	Stage III Non-small cell lung cancer
PBS Indication:	Unresectable Stage III non-small cell lung cancer
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	Initial The patient must have received platinum-based chemoradiation therapy AND The condition must not have progressed following platinum-based chemoradiation therapy AND ~~The p~~*P*atient must have a *WHO* performance status of 0 or 1 AND ~~The p~~*P*atient must not have received prior *treatment with a programmed cell death-1* (PD-1) *inhibitor* or *programmed cell death ligand-1 (PD-L1)* inhibitor for this condition AND The treatment must be the sole PBS-subsidised treatment for this condition Continuing Patient must have stable or responding disease AND Patient must have previously been issued with an Authority prescription for this indication AND The treatment must be the sole PBS subsidised treatment for this condition AND Treatment must not exceed 12 months in total, *at a maximum dose of* 10 mg *per kg* every 2 weeks, with this drug for this condition Grandfathering The patient must have stable or responding disease AND The patient must have received treatment with this drug for this condition prior to [DATE] AND The treatment must be the sole PBS subsidised treatment for this condition AND Treatment must not exceed 12 months in total, *at a maximum dose of* 10 mg *per kg* every 2 weeks, with this drug for this condition
Administrative Advice:	No increase in the maximum number of repeats will be authorised. Special pricing arrangement apply

2.2 The resubmission proposed a special pricing arrangement (SPA), and therefore the requested prices include both a published price and an effective price.

2.3 The PBAC considered it was appropriate to add the following wording to the grandfathering restriction: "Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria" and "Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS subsidised treatment with this drug for this condition". The PBAC also considered it appropriate to change "Patient must have stable or responding disease" to "The condition must not have progressed while receiving PBS-subsidised treatment with this drug for this condition."

2.4 The resubmission proposed a grandfathering restriction to allow patients in the sponsor's compassionate access program (initiated October 2017) to receive durvalumab upon PBS listing. The Sponsor estimated that 600 patients would be accessing durvalumab under the grandfathering restriction by the time of PBS listing. The PBAC considered that the number of grandfathered patients is overestimated, noting that estimates of the number of grandfathered patients should account for the number of patients accessing treatment at the time of PBAC consideration and not the number of patients expected to be part of the access program by the time of PBS listing.

2.5 The proposed restriction had the following wording to preclude prior and subsequent use of PD-(L)1 therapies for all stages of NSCLC: "The patient must not have received prior PD 1 or PD L1 inhibitor therapy for this condition". The word "condition" could easily be misinterpreted to mean stage. The PBAC considered the wording of the restriction should be modified to clarify that a patient can only be administered one course of treatment with PD-(L)1 inhibitors per life time and that restrictions for other listed PD-(L)1 inhibitors should also be amended.

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

3 Background

Registration status

3.1 Durvalumab was approved by the TGA on 23 October 2018 for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum based chemoradiation therapy.

3.2 The PBAC noted that the European Medicines Agency (EMA) excluded PD-(L)1 negative patients from its approved authorisation and considered that if in future it was established that biomarkers identify subgroups without benefit, then the PBS listing should be amended to exclude these subgroups.

Previous PBAC consideration

3.3 Durvalumab was previously considered by the PBAC in November 2018. Table 2 summarises the outstanding PBAC concerns raised during the November 2018 consideration of durvalumab, and how the resubmission addressed these.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern (durvalumab PSD, November 2018)	How the resubmission addresses it
Sequential use of PD-(L)1 inhibitors	The PBAC considered there is potential for a NSCLC listing that allows patients of WHO PS 0 and 1 access to a single course of treatment with a PD-(L)1 inhibitor per lifetime. (paragraph 7.2 and 7.14)	The intent of the proposed restriction is to limit treatment with a PD-(L)1 inhibitor to once per lifetime.
Maturity of OS data from the PACIFIC trial	The OS data in the PACIFIC trial was immature, with median OS not yet reached in the durvalumab arm. Although there was an incremental improvement in OS that favoured patients receiving durvalumab in the trial, the magnitude of the difference in overall survival beyond the trial duration was uncertain (paragraph 7.4).	Update of the OS data (data cut-off: 31 January 2019) was provided, with an additional 10 months of follow up. The OS benefit associated with durvalumab remains statistically significant however the OS data remain immature for the durvalumab arm.
Impact of subsequent therapy with PD-(L)1 inhibitors on OS results	Subsequent therapy upon progression with PD-(L)1 inhibitors in the PACIFIC trial may not reflect Australian clinical practice, particularly if the restrictions for PD-(L)1 therapies limit treatment with a PD-(L)1 to once per lifetime. This difference possibly affected the OS associated with durvalumab compared with placebo. (paragraphs 6.7 and 7.5).	A RPSFT-adjusted analysis of OS to account for the impact of subsequent therapies in PACIFIC was provided. There was considerable uncertainty associated with the assumptions on which the RPSFT analysis was based. These included that the immunotherapy effect was the same, regardless of the time point and stage of disease when immunotherapy was received, and that all types of immunotherapies have an equivalent effect.
Modelled OS benefit of durvalumab	The PBAC considered the choice of extrapolation method to be highly uncertain given: • The immaturity of the survival data • The likelihood that use of subsequent PD-(L)1 inhibitors in both arms of the trial did not match Australian clinical practice, and • That the trial population may be younger than the average patient diagnosed with lung cancer in Australia. Overall, the PBAC was concerned that the modelled benefit beyond the duration of the trial was likely overestimated, and that the ICER was consequently underestimated. (paragraphs 7.4, 7.5, 7.6, 7.7, 7.8 and 7.12)	• Updated observed OS data were used in the base case economic evaluation. • A scenario analysis was presented which used adjusted OS estimates from a RPSFT model. • The economic evaluation included background mortality to account for the potential difference in age of patients between the PACIFIC trial and Australian clinical practice.
Extrapolation of OS and time horizon	The PBAC noted that the ICER was sensitive to the choice of parametric extrapolation for overall survival and considered the model's time horizon was poorly justified in the context of this uncertainty. The PBAC agreed that an alternative extrapolation method may be more plausible, particularly as the log-logistic function used in the durvalumab arm in the base case may not adequately capture the increasing rate of background mortality over the model's time horizon. (paragraph 7.9)	The model's time horizon and the parametric function to extrapolate OS for durvalumab were unchanged from the previous submission on the basis of the long-term OS data from clinical studies in similar patient populations.
Selection of parametric function	The PBAC noted the ESC advice that AIC estimates for the PACIFIC trial OS curves, may not be helpful for fitting parametric functions as there was little difference between the estimates,	The selection of the parametric model to inform the base case analysis in the resubmission was based on goodness of fit statistics which were more informative in view of the updated OS data. The resubmission did not justify that the parametric function that best fitted the

Component	Matter of concern (durvalumab PSD, November 2018)	How the resubmission addresses it
	and they likely reflect differences in the earlier portions of OS data. (paragraph 7.10)	observed data would give accurate predictions in the unobserved period. The continued survival benefit of durvalumab throughout the modelled time horizon was also not justified.
Utility values	The PBAC agreed with the ESC that the utilities derived from the PACIFIC trial were likely to be higher than in the Australian setting and considered that a lower estimate should be applied, or a robust analysis of the collection of quality of life in the PACIFIC study should be presented to rule out responder bias. (paragraph 7.10)	The resubmission maintained that the utility values for the PFS health state from PACIFIC were informative given that the patients in PACIFIC were responders to prior chemoradiation therapy and were potentially cured. Hence, the utility for PFS being only slightly lower than that observed in the general Australian population was claimed to be reasonable by the resubmission. Regarding the PD state, the resubmission assumed lower health state utility values from the literature, compared with those used in the previous submission.
Eligible patient population	The PBAC and DUSC considered that the estimated eligible patient population was inaccurate: • The proportion of NSCLC of all lung cancers is likely to be closer to 80% than the 70.3% applied in the estimates. • The DUSC considered that the proportion of patients receiving chemoradiation was reasonable for year 1 (70%), but was overestimated for subsequent years (80-90%). (paragraph 6.40) The DUSC had considered that '…the proportion of patients receiving first-line chemoradiation therapy should be at least 70-80% in all years' [5.04.DUSC ADV.6].	The resubmission updated the proportion of NSCLC of all lung cancers to 86.6%, consistent with Mitchell et al 2013, as quoted in the briefing document for the PD-(L)1 Stakeholder Meeting, 8th February 2019. The resubmission assumed that the uptake rate of chemoradiation in this population was 70% in year 1, increasing to 80% in year 2-6. This uptake rate was reflective of a patient population irrespective of performance status (i.e. PS 0-4). However, the resubmission applied these estimates to a population that was limited to a PS 0-1.
Cost offsets associated with the reduced use of immuno-therapies	The PBAC considered that the financial impact was overestimated as it did not account for a reduction in the use of subsequent lines of PD-(L)1 therapies. The PBAC considered that there would be substantial cost offsets from PD-(L)1 use in later stage NSCLC resulting from a PBS listing of durvalumab in stage III NSCLC, which would affect the current RSA in the current joint Deed of Agreement for atezolizumab, nivolumab and pembrolizumab in NSCLC. The PBAC considered that if durvalumab was made available on the PBS, there would only be a modest increase in the overall number of patients treated for NSCLC, provided sequential treatment with different PD-(L)1 therapies was precluded as recommended above (paragraph 7.14)	The base case analysis has been revised to include cost-savings associated with the reduction in PD-(L)1 use in later stages of NSCLC if durvalumab is listed on the PBS. A number of concerns remain regarding the estimation of the cost-savings related to a decrease in the use of immunotherapies.

AIC = Akaike information criterion; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; NSCLC = non-small cell lung cancer; OS = overall survival; PSD = Public Summary Document; PD = progressive disease; PD-(L)1 = programmed cell death (ligand) 1; PFS = progression-free survival; PS = performance status; RPSFT = rank-preserving structural failure time; WHO = World Health Organization
Source: Table compiled during the evaluation, based on Table 1.1.1, pp31-33, the table on p46, the table on pp85-87, and Table 4.1.1, pp163-164 of the resubmission

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

4 Population and disease

4.1 Lung cancer was estimated to be the leading cause of death from cancer in Australia in 2017, the fifth most commonly diagnosed cancer in Australia, and one of the most lethal cancer types (AIHW 2017). NSCLC accounts for approximately 80% of lung cancer cases in Australia and is usually diagnosed at an advanced stage when it is no longer amenable to surgical resection (AIHW 2011; NCCN 2016). Around 20% of these cases are Stage III disease, and while surgery remains a viable treatment option for patients, some tumours cannot be resected, and in these cases non-surgical treatments are indicated.

4.2 Consistent with the previous submission, the resubmission proposed durvalumab for use in unresectable Stage III NSCLC as a consolidation therapy for patients who have not progressed after platinum-based CRT.

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

5 Comparator

5.1 The resubmission nominated placebo, representing 'watch-and-wait' monitoring plus best supportive care, as the main comparator. The PBAC has previously agreed that this was the appropriate comparator (paragraph 7.3, durvalumab Public Summary Document (PSD), November 2018 PBAC meeting).

5.2 Restrictions for all anti PD-(L)1 therapies, in all stages of NSCLC, are likely to preclude prior and subsequent use of anti PD-(L)1 therapies (until evidence to support sequential use is forthcoming). The listing of durvalumab would substitute for placebo, followed by PD-(L)1 inhibitors for eligible patients. Subsequent PD-(L)1 inhibitors may include "first" subsequent therapy (for example with pembrolizumab for patients with PD-L1 ≥50%) or later line subsequent therapy (with, for example, nivolumab or atezolizumab). The PBAC has also recommended the listing of atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) (March 2019 PBAC meeting) and reconsidered pembrolizumab in combination with pemetrexed and platinum chemotherapy (July 2019 PBAC meeting) for the first line treatment of patients with stage IV metastatic NSQ NSCLC.

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 the advice received from The Lung Foundation clarifying the likely use of durvalumab in clinical practice. The PBAC specifically noted the advice that the use of durvalumab results in important and clinically meaningful outcomes for patients with unresectable Stage III NSCLC, extending both PFS and OS. The Lung Foundation considered that this regime would be offered as routine standard of care for these patients. The PBAC noted that this advice was supportive of the evidence provided in the submission.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the durvalumab submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the PACIFIC trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) grading with two scores for durvalumab, which was A (best, if it is considered potentially curative) or 3 (out of a maximum of 5, if it is considered a non-curative treatment, where 5 and 4 represent the grades with substantial improvement)[a], based on a comparison with placebo.

Clinical trials

6.4 The resubmission was based on one randomised placebo controlled trial comparing durvalumab with placebo in patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following platinum based CRT (PACIFIC; n=713). The resubmission provided updated OS data compared to the November 2018 submission with an additional 10 months follow-up provided.

6.5 Details of the trials presented in the resubmission are provided in Table 3.

[a] Herny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
PACIFIC	Clinical Study Protocol. A Phase III, Randomised, Double blind, Placebo controlled, Multi centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum based, Concurrent Chemoradiation Therapy (PACIFIC).	24 February 2016.
	Clinical Study Report. A Phase III, Randomized, Double blind, Placebo controlled, Multi center, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum based, Concurrent Chemoradiation Therapy (PACIFIC).	21 July 2017[§] 17 August 2018[×].
	Updated OS data Additional data outputs 2 [folder in PBAC Attachment 1]. Data cut-off 31 January 2019.	
	Antonia SJ et al. Durvalumab after Chemoradiotherapy in Stage III Non–Small Cell Lung Cancer.	*NEJM* 2017; 377(20):1919–1929
	Antonia SJ, Villegas A, Daniel D, Vincente Baz D, Murakami S, Hui R, et al. Pacific: A double blind, placebo controlled phase 3 study of durvalumab as consolidation therapy after chemoradiation in patients with locally advanced, unresectable non small cell lung cancer.	*International Journal of Radiation Oncology Biology Physics* 2017; 99(5): 1314–1315.
	Antonia SJ. Clinical activity, patient reported outcomes, and safety with durvalumab after chemoradiation in locally advanced, unresectable NSCLC: Pacific study.	*Asia Pacific Journal of Clinical Oncology* 2017; 13: 145.
	Hui R, Özgüroğlu M, Daniel D, Baz D, Murakami S, Yokoi T, et al. Patient reported outcomes with durvalumab after chemoradiation in locally advanced, unresectable NSCLC: Data from PACIFIC.	*Journal of Thoracic Oncology*. 2017; 12(11): S1604.
	Antonia SJ et al. Overall Survival with Durvalumab Versus Placebo After Chemoradiotherapy in Stage III NSCLC: updated Results from PACIFIC.	*Journal of Thoracic Oncology* 2018; 13(10): S184
	Laack HE, Schulz C, Wolff T, Rückert A, Reck M, Faehling M, et al. PACIFIC: A double blind, placebo controlled phase III study of durvalumab after chemoradiation therapy in patients with stage III, locally advanced, unresectable NSCLC.	*Oncology Research and Treatment* 2018; 41 (Suppl 1): 186–187.
	Hui R et al. Time to deterioration of symptoms with durvalumab in stage III, locally advanced, unresectable NSCLC: post-hoc analysis of PACIFIC patient-reported outcomes.	*Journal of Thoracic Oncology* 2018; 13(4): S71
	Antonia SJ, et al. Overall survival with durvalumab versus placebo after chemoradiotherapy in Stage III NSCLC: updated results from PACIFIC.	*Journal of Thoracic Oncology* 2018; 13(10): S184

[§]Data cutoff for July 2017 CSR was February 2017;
[×]Data cutoff for August 2018 CSR was March 2018'
NSCLC = non-small cell lung cancer.
Source: Tables 2.2.1 and 2.2.2, pp50-52 of the resubmission.

6.6 The key features of the direct randomised trial are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Durvalumab vs. placebo						
PACIFIC	713	R, DB, MC 50 mths	Low	Unresectable Stage III NSCLC who have not progressed after CRT	OS, PFS	Used

DB=double blind; MC=multi-centre; OS=overall survival; PFS=progression-free survival; R=randomised; NSCLC = non-small cell lung cancer; CRT = chemoradiation therapy.
Source: Compiled during the evaluation based on Sections 2.2-2.4 of the submission.

6.7 When considering the previous submission in November 2018, the PBAC noted that there was uncertainty as to whether post-progression treatments with immunotherapy in both the active and placebo arms in the PACIFIC trial were reflective of Australian clinical practice, particularly if PD-(L)1 immunotherapy use is limited to one course per lifetime. To address this concern raised by the PBAC, the resubmission conducted a rank preserving structural failure of time (RPSFT) analysis to adjust for the impact of subsequent immunotherapy on OS.

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

Comparative effectiveness

6.8 The results for OS (March 2018 and January 2019 data cutoffs) from the PACIFIC trial are summarised below. No updated PFS data were presented in the resubmission. The OS results presented in the previous submission are also reproduced in Table 5.

Table 5: Summary of OS in PACIFIC for the March 2018 and January 2019 data cutoffs

	Durvalumab n/N (%)	Placebo n/N (%)	Absolute difference	HR (95% CI)
Data cutoff March 2018: **Total duration of follow-up: ~ 40 months** **Median duration of follow-up durvalumab: 25.9 months** **Median duration of follow-up placebo: 23.8 months**				
Patients with event	183/476 (38.4)	116/237 (48.9)		-
Median months OS (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)	NR	0.68 (0.53, 0.87)
Survival rate at 12 months, (95% CI)§	83.1% (79.4%, 86.2%)	75.3% (69.2%, 80.4%)	7.8%	
Survival rate at 24 months, (95% CI)§	66.3% (61.7%, 70.4%)	55.6% (48.9%, 61.8%)	10.7%	
Data cutoff January 2019 (10 additional months of data) **Total duration of follow-up: ~ 50 months** **Median duration of follow-up durvalumab: 33.9 months** **Median duration of follow-up placebo: 26.4 months**				
Patients with event	210/476 (44.1)	134/237 (56.5)		-
Median months OS (95% CI)	NR (38.4, NR)	29.1 (22.1, 35.1)	NR	0.69 (0.55, 0.86)
Survival rate at 12 months, (95% CI)β	83.1% (79.4%, 86.2%	74.6% (68.5%, 79.7%)	8.5%	
Survival rate at 24 months, (95% CI)β	66.3% (61.8%, 70.4%)	55.3% (48.6%, 61.4%)	11.0%	

Shaded: Previously considered by PBAC (November 2018 Meeting)

§Reproduced during the evaluation from p21 of the PACIFIC clinical study report (CSR), data cutoff March 2018, interim OS analysis: statistical significance level of ≤0.00274. The CSR noted that rates were determined using the Kaplan-Meier technique.

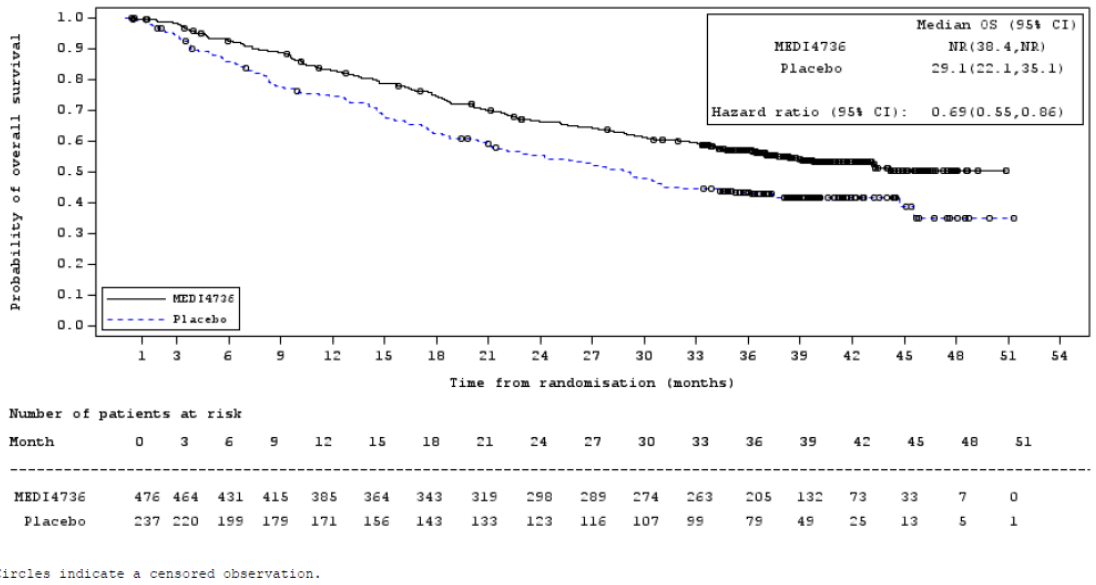
βReproduced during the evaluation from Table 11.2.2.2.OS_UP1, p24 of updated OS report accompanying the resubmission (PACIFIC_OS_Update1_HLR_05Mar2019), data cutoff January 2019.

CI = confidence interval; HR = hazard ratio; NR = not reached; OS = overall survival;

Source: Relevant CSR and updated efficacy reports accompanying the resubmission and Table 2.5.1, p60 of the resubmission.

6.9 The updated OS Kaplan Meier curves are presented in Figure 1.

Figure 1: OS Kaplan Meier curves in PACIFIC – January 2019 data cutoff



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
MEDI4736	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1

Circles indicate a censored observation.

Source: Figure 2.5.2, p61 of the resubmission

6.10 The updated OS data presented in the resubmission remain immature for the durvalumab group with median survival not being reached. The OS results were similar for both data cutoffs, demonstrating a statistically significant reduction in the hazard of death associated with durvalumab compared with placebo (approximately 30%: HR = 0.69 [95%CI: 0.55, 0.86]). The PBAC noted the outcomes reported in Table 5 were consistent between the March 2018 and January 2019 data cutoffs.

6.11 Table 6 presents a summary of the proportion of patients who had post-progression immunotherapies in the PACIFIC trial. Data from the previous submission are included for comparison. In the placebo arm, 46% of patients who had subsequent therapy received immunotherapy. Of these, the majority (83%) received nivolumab and 13% received pembrolizumab. In the durvalumab arm, 22% of patients who had subsequent therapy received immunotherapy. Of these, the majority (72%) received nivolumab and 22% received pembrolizumab. The ESC considered that the effect of subsequent therapies, including immunotherapies, is likely to have impacted the OS results. The subsequent immunotherapy in the durvalumab arm is likely to have resulted in OS in the durvalumab arm being overestimated (and hence the incremental benefit of durvalumab being overestimated). The subsequent immunotherapy in the placebo arm being less than that expected in clinical practice is likely to have resulted in OS being underestimated (and hence the incremental benefit of durvalumab being overestimated).

Table 6: PACIFIC trial - subsequent therapy post-treatment discontinuation (data cutoff January 2019)

Number (%) of patients who received subsequent therapy post discontinuation of allocated treatment	Durvalumab (N=476)	Placebo (watch and wait) (N=237)
March 2018 data cutoff (provided in the previous submission)		
Post-discontinuation disease-related anti-cancer therapy, n	195 (41% of 476)	128 (54.0% of 237)
• Of post anti-cancer therapy, who received immunotherapy [β]	38 (19.5% of 195)	53 (41.4% of 128)
January 2019 data cutoff (provided in the resubmission)		
Post-discontinuation disease-related anti-cancer therapy n	206 (43% of 476)	137 (57.8% of 237)
• Of post anti-cancer therapy, who received immunotherapy [β,]	46/206 (22.3%)	63/137 (46.0%)
○ Of immunotherapy who received it as 1st subsequent treatment	21/46 (46.0%)	29/63 (46.0%)
○ Of immunotherapy who received it as ≥2nd subsequent treatment	25/46 (54.0%)[§]	34/63 (54.0%)[§]

Shaded: Considered by the PBAC from the previous submission.

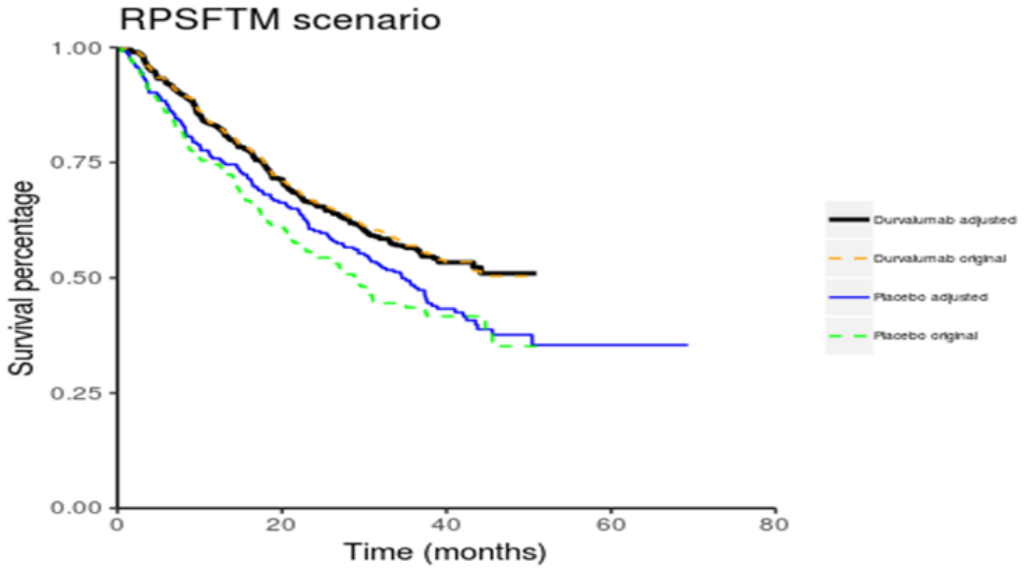
[β]If durvalumab gets listed, it would be expected that the proportion of patients who would receive a subsequent PD-(L)1 inhibitor upon progression would be much less given PBS restrictions preclude sequential use of PD-(L)1 therapies.

[§]Calculated during the evaluation assuming this subgroup is a complement of those who received immunotherapy as 1st subsequent treatment, post discontinuation/progression.

Source: Compiled during the evaluation from Section 3.2 of treatment switching report (trtSwitchReport_ITT_27_March_2019), the resubmission, the November 2018 PBAC Minutes for durvalumab and the updated CSR accompanying the resubmission

6.12 The resubmission presented OS estimates from the RPSFT-adjusted analysis which assumed that all patients in the placebo arm who subsequently received any anticancer treatment, received immunotherapy at the start of their first subsequent treatment, and that all patients in the durvalumab arm received no subsequent immunotherapy. The observed and RPSFT-adjusted Kaplan-Meier curves for OS are presented in Figure 2. Based on the January 2019 data cutoff, the HR for the RPSFT-adjusted analysis indicated a smaller reduction in the hazard of death associated with durvalumab, over placebo (HR = 0.78; 95% CI: 0.62, 0.97), compared to the observed non-adjusted hazard reduction in the PACIFIC trial (HR = 0.69; 95% CI: 0.55, 0.86). The PBAC noted the RPSFT-adjusted analysis supported a lower benefit of treatment with durvalumab.

Figure 2: Observed and adjusted Kaplan-Meier curves for OS



Source: Figure 3, Section 3.3.2 of the updated treatment switching report "trtSwitch Report_ITT_27_March_2019" provided during the evaluation

6.13 There is high uncertainty associated with the RPSFT approach.

- The key assumptions underlying the RPSFT adjustment approach were that 1) the immunotherapy effect is the same, regardless of the time point and stage of disease when immunotherapy was received, and 2) all types of immunotherapies have an equivalent effect. These assumptions are very difficult to verify. Given that treatment switching is often only permitted after disease progression – at which time the capacity for a patient to benefit may be different compared to pre-progression – the "common treatment effect" assumption may be clinically implausible. The ESC considered these assumptions were a key source of uncertainty for the RPSFT-adjusted analysis.
- In PACIFIC, of progressed patients in the placebo arm who received subsequent immunotherapy, 46% received it as first subsequent treatment. Although this estimate in clinical practice is uncertain, the assumption that 100% of progressed patients would receive immunotherapy, as first subsequent treatment, is likely an overestimate. Depending on eligibility, some 'watch and wait' patients upon progression, would have radiotherapy, chemotherapy, or targeted therapy. Currently, patients can only access pembrolizumab in Australia if they express a PD-(L)1 tumour proportion score (TPS) of ≥50% and access to nivolumab or atezolizumab is contingent on failure of prior platinum-based chemotherapy and patients' performance status. For patients who progressed on durvalumab, and who went on to receive further immunotherapy, there is currently no evidence that such sequential therapy is associated with any benefit (or lack of). The ESC agreed with the PSCR's claim that the RPSFT-adjusted analysis may be conservative

in terms of clinical benefit as it overestimated the proportion of patients in the placebo arm being treated with subsequent PD-(L)1 inhibitor which favoured placebo and reduced the incremental benefit of durvalumab. However ESC also noted if 100% of PD-(L)1 use was assumed in the placebo arm for the economic model this would result in more cost-offsets downstream, thereby reducing the incremental cost and producing a lower ICER (favouring durvalumab).

- The resubmission did not present OS analyses using other adjustment methods to enable a comparison with results from the RPSFT model.

6.14 The ESC considered that although the RPSFT-adjusted analysis did not fully address the concerns raised previously by the PBAC the RPSFT-adjusted analysis was informative.

6.15 There were no updated quality-of-life data presented in the resubmission. The PBAC recalled that the previous submission demonstrated there was no difference in quality of life between the two treatment arms.

Comparative harms

6.16 The resubmission presented some updated safety data from the March 2018 data cutoff (Table 7). The updated safety data in the resubmission was consistent with the safety data presented in the previous submission.

Table 7: Summary of key adverse events in the PACIFIC trial

Adverse event	Durvalumab, n (%) N=476	Placebo, n (%) N=234	Relative risk (95% CI)	Risk difference (95% CI)
Any AE related to treatment	322 (67.8)	125 (53.4)	**1.27 (1.11, 1.45)**	**0.14 (0.07, 0.22)**
Any AE of CTCAE Grade 3 or 4	155 (32.6)	66 (28.2)	1.15 (0.91, 1.47)	0.04 (-0.03, 0.11)
Any AE of CTCAE Grade 3 or 4 related to treatment	59 (12.4)	11 (4.7)	**2.64 (1.41, 4.92)**	**0.08 (0.04, 0.12)**
Any SAE	138 (29.1)	54 (23.1)	1.26 (0.96, 1.65)	0.06 (-0.01, 0.13)
Any SAE related to treatment	41 (8.6)	9 (3.8)	**2.24 (1.11, 4.53)**	**0.05 (0.01, 0.08)**
Any AE leading to discontinuation	73 (15.4)	23 (9.8)	1.56 (1.00, 2.43)	**0.06 (0.01, 0.11)**
Any AE leading to discontinuation related to treatment	47 (9.9)	8 (3.4)	**2.89 (1.39, 6.01)**	**0.06 (0.03, 0.10)**
Any AE leading to dose delay	203 (42.7)	72 (30.8)	**1.39 (1.11, 1.72)**	**0.12 (0.04, 0.19)**
Any AESI	317 (66.7)	115 (49.1)	**1.36 (1.17, 1.57)**	**0.17 (0.10, 0.25)**
Any ImAEs	166 (34.9)	39 (16.7)	**2.09 (1.53, 2.86)**	**0.18 (0.12, 0.25)**

Bolded = statistically significant.
AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; CTCAE = Common terminology criteria for adverse events; ImAE = immune mediated adverse events; SAE = serious adverse events;
Source: Table 2.5.2, pp64-7 of the resubmission.

6.17 Overall, durvalumab was associated with greater toxicity than placebo.

Benefits/harms

6.18 A summary of the comparative benefits and harms for durvalumab compared with placebo is presented in Table 8.

Table 8: Summary of comparative benefits and harms for durvalumab versus placebo

Data cutoff January 2019 (updated 10 additional months of data - total duration of follow-up approximately 50 months)				
Benefits				
	Durvalumab	**Placebo**	**Absolute difference**	**HR (95% CI)**
Deaths, n/N (%)	210/476 (44.1%)	134/237 (56.5%)		0.69 (0.55, 0.86)
Median OS (months)	NR (38.4, NR)	29.1 (22.1, 35.1)	-	
Survival rate at 12 months, (95% CI)[β]	83.1% (79.4%, 86.2%	74.6% (68.5%, 79.7%)	8.5%	
Survival rate at 24 months, (95% CI)[β]	66.3% (61.8%, 70.4%)	55.3% (48.6%, 61.4%)	11.0%	

Harms						
	Durvalumab n/N	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Durvalumab	**Placebo**	
Adverse event						
Any Grade 3/4 AE related to treatment	59/476	11/234	2.64 (1.41, 4.92)	12.4	4.7	0.08 (0.04, 0.12)
Any SAE related to treatment	41/476	9/234	2.24 (1.11, 4.53)	8.6	3.8	0.05 (0.01, 0.08)

[β]Reproduced during the evaluation from Table 11.2.2.2.OS_UP1, p24 of updated OS report accompanying the resubmission (PACIFIC_OS_Update1_HLR_05Mar2019), data cutoff January 2019.
OS = overall survival; PFS = progression-free survival; CI = confidence interval; NR = not reached, HR = hazard ratio; RR = risk ratio; RD = risk difference; AE = adverse event; SAE = serious adverse event.
Source: compiled during the evaluation based on Table 2.5.1, p60, and Table 2.5.2, pp64-7, of the resubmission.

6.19 On the basis of the direct evidence presented by the resubmission, for every 100 patients treated with durvalumab in comparison to placebo and followed over a maximum duration of 50 months:

- Approximately 9 more patients remained alive at 12 months and 11 more patients remained alive at 24 months. The ESC noted this may be potentially overestimated because of the expected different use of subsequent immunotherapy in clinical practice;
- Approximately 8 additional patients would experience a Grade 3 or 4 treatment-related adverse event;
- Approximately 5 additional patients would experience a serious adverse event related to durvalumab.

6.20 The benefits and harms of durvalumab compared with placebo remained similar to that presented in the previous submission.

Clinical claim

6.21 The resubmission described durvalumab as superior in terms of effectiveness, with similar quality of life, and manageable safety compared with "watch and wait" monitoring in patients with Stage III NSCLC whose disease has not progressed following CRT.

6.22 The therapeutic conclusion for effectiveness was adequately supported by the evidence presented in the resubmission although there is some residual uncertainty regarding the applicability of the observed OS benefit from the PACIFIC trial to the OS benefit that would be observed in Australian clinical practice should durvalumab be approved. The PBAC considered the OS data for durvalumab remain immature but noted that further OS data was not anticipated until mid-2020.

6.23 The therapeutic conclusion for safety was adequately supported with data from the PACIFIC trial demonstrating that durvalumab was associated with an inferior safety profile compared to placebo.

6.24 The PBAC considered that, although the data remain immature, the claim of superior comparative effectiveness versus placebo was reasonable.

6.25 The PBAC considered that durvalumab had inferior comparative safety compared to placebo and that overall, the claim of a manageable safety profile was reasonable.

Economic analysis

6.26 The resubmission presented a cost-utility analysis with a three-state (progression-free disease, progressive disease and death) partitioned survival model. The model structure and the key components of the economic evaluation in the current resubmission were largely unchanged from the previous submission. The model structure and rationale are summarised in Table 9.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 50 months in the PACIFIC trial. Additional 10 months trial data became available since the previous submission.
Outcomes	Life years and quality adjusted life years. Unchanged from the previous submission
Methods used to generate results	Partitioned survival analysis. Unchanged from the previous submission
Health states	Progression-free disease, progressive disease and death. Unchanged from the previous submission
Cycle length	2 weeks for the first 12 months and 4 weeks thereafter. Unchanged from the previous submission
Allocation to health states	The proportion of patients in each health state was based on the PFS and OS curves. In the base case, the Kaplan-Meier estimates for PFS and OS from the PACIFIC trial were used up to the extrapolation point§. Thereafter, parametric distributions fitted to the observed Kaplan-Meier estimates were used for PFS and OS extrapolation to the end of the model time horizon. In the scenario analysis, RPSFT-adjusted OS estimates, instead of observed OS data, were applied to the model. This is unchanged from the previous submission, except that updated OS from PACIFIC and RPSFT-adjusted OS were used in the resubmission's base case and scenario analysis respectively.

OS = overall survival; PFS = progression-free survival; RPSFT = rank-preserving structural failure time.
§In the base case, 34.5 months for durvalumab PFS extrapolation, 30 months for placebo PFS extrapolation, 45.1 months for durvalumab OS extrapolation, and 46.1 months for placebo OS extrapolation
Source: Table 3.1.1, p91 of the resubmission.

6.27 When the previous submission for durvalumab was considered in November 2018, the PBAC raised concerns over the high degree of uncertainty surrounding the choice of extrapolation, "given the immaturity of the survival data, the likelihood that use of subsequent line PD-(L)1 inhibitors in the active and placebo arms of the trial will not match Australian clinical practice, and that the trial population may be younger than the average patient diagnosed with lung cancer in Australia" (paragraph 7.7, durvalumab PSD, November 2018 PBAC meeting).

6.28 To address the PBAC's concerns above, the resubmission made the following changes to the economic evaluation:

- The updated OS data at the most recent data cutoff (January 2019) were used to inform the within-trial and extrapolated OS data associated with durvalumab and placebo; however, the updated OS data remained immature with median overall survival not yet reached in the durvalumab arm.
- In addition to the economic model that used the updated ITT data for OS and for subsequent anti-cancer therapies from PACIFIC as the base case, a scenario analysis was also presented in the resubmission, where OS was adjusted using a RPSFT-adjusted analysis. The RPSFT model removed the benefit of subsequent treatment with a PD-(L)1 inhibitor in patients in the durvalumab arm, whilst assuming that 100% of patients who have progressed in the placebo arm would receive the benefit of subsequent PD-(L)1 therapy. As discussed above, the underlying 'common treatment effect' assumption of the RPSFT method is not verifiable. In addition, the assumption that 100% of patients who have progressed would be given a PD-(L)1 inhibitor is likely to be an overestimate. It is possible that

some progressed patients may no longer be eligible for PD-(L)1 inhibitors. No sensitivity analyses were conducted using different statistical methods/assumptions for adjustment to address the uncertainty associated with the estimated treatment effect of durvalumab; and

- The economic model has been updated to include background mortality to account for potential difference in age of patients between PACIFIC and Australian settings.

6.29 Apart from the above revisions, the current economic evaluation also made the following changes:

- Included an age-related utility decrement;
- Used lower utility values for the progressive disease health state (0.68-0.71), sourced from the literature, compared with the previous submission (0.785-0.789), to address the PBAC's concern that the utility value for progressive state was likely to be overestimated. The utility values for the progression-free state in the base case, which were sourced from the PACIFIC trial, remained unchanged from the previous submission. At the November 2018 meeting, the PBAC noted that the estimates for utility for the PFS health state (0.810 in the durvalumab arm and 0.814 in the placebo arm) were only marginally lower than the average Australian utility estimate for all adults >18 years (paragraph 6.29, durvalumab PSD, November 2018 PBAC meeting). However, the resubmission cited an Australian study reporting a mean utility of 0.91 for the Australian general population (McCaffrey 2016) and claimed that a reduction of 0.1 in the utility for the progression-free disease state, as observed from the PACIFIC trial, remain reasonable for patients with Stage III unresectable NSCLC whose disease has not progressed following chemoradiation therapy.
- Assumed that 100% patients treated with durvalumab would receive pathology services and diagnostic imaging services (compared with 70% and 90%, respectively, in the original submission). This was consistent with the explicit recommendation in the Product Information (PI) and the comments in the November 2018 Commentary; and
- Proposed a lower effective price for durvalumab compared with that in the previous submission (ex-manufacturer price of $[redacted] for a 500mg/10mL vial and $[redacted] for a 120mg/2.4mL vial vs. $[redacted] and $[redacted] respectively in the previous submission). Costs of other health resources were also updated on the basis of current PBS, MBS, and Efficient Funding of Chemotherapy (EFC) mark-ups.

6.30 The PBAC previously noted that the ICER was sensitive to the choice of parametric extrapolation for OS. The choice of parametric functions in the extrapolation of OS remained as a source of uncertainty in the resubmission.

6.31 The resubmission assumed that the PFS and OS benefit of durvalumab compared with placebo continued over the modelled 10-year period. The PBAC guidelines (v5.0) suggest that, in the absence of ongoing treatment effect, if the proposed approach to extrapolating time-to-event results does not result in a convergence of the two extrapolated curves, a forced convergence should be considered from the point of median follow up to a point that is clinically plausible.

6.32 The key drivers of the model are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Ongoing OS benefits of durvalumab within the model time horizon of 10 years	Moderate, favours durvalumab
	The choice of parametric functions to extrapolate OS curves	Moderate, favours durvalumab
	Time point of extrapolation when observed data became unreliable as a result of small number of patients remaining at risk of the event	Moderate, favours durvalumab
Time horizon	10 years	Moderate, favours durvalumab
Utilities	High values for model health states sourced from the PACIFIC trial for progression-free state and from the literature for progressive disease state	Moderate, favours durvalumab

OS = overall survival
Source: Compiled during the evaluation, based on sensitivity analyses presented in Section 3.9.

6.33 The results of the stepped economic analysis for the base case are presented in Table 11.

6.34 Nivolumab was used as a proxy for all subsequent immunotherapy in the economic model as it was most commonly used in the PACIFIC trial. The economic evaluations used the published price for nivolumab which did not take into account the existing SPA. Additionally, the economic evaluation assumed that patients received 7.5 doses of nivolumab but the PBAC recalled it had previously considered that it was appropriate to assume patients received 24 weeks (12 doses) of nivolumab treatment in the second line setting (paragraph 6.37, agenda item 6.06 pembrolizumab PSD, November 2018 meeting). The results of the economic evaluations using the effective price for nivolumab and adjusted duration of treatment are provided in the committee in confidence (CIC) section.

Table 11: Results of the stepped economic evaluation (base case)

Step and component	Durvalumab	Placebo	Increment
Step 1: trial-based, time horizon of 50 months, cost for durvalumab therapy only			
Costs	$	$	$
LYs gained			
Incremental cost/extra LY gained			$
Step 2: time horizon extended to 10 years			
Costs	$	$	$
LYs gained			
Incremental cost/extra LY gained			$
Step 3: incorporation of medical resource costs			
Costs	$	$	$
LYs gained			
Incremental cost/extra LY gained			$
Step 4: utility weights applied			
Costs	$	$	$
QALYs			
Incremental cost/extra QALY gained (base case)			**$**

LY = life-year; QALY = quality-adjusted life-year
Source: Table 3.8.1, p155 of the resubmission

The redacted table shows ICER in the range of $45,000/LY -$75,000/LY to $105.000/LY - $200,000/LY and $45,000/QALY - $75,000/QALY.

6.35 Extrapolation of health outcomes from the trial-based 50 months to 10 years had the most impact on the ICER, since the life years gained from durvalumab compared with placebo almost doubled (to). As noted earlier, given the immaturity of trial data, the extrapolation assuming ongoing survival benefits of durvalumab introduced substantial uncertainty to the estimated treatment effect of durvalumab.

6.36 The results of the scenario analysis, where OS data from PACIFIC were adjusted using RPSFT method, are summarised in Table 12.

Table 12: Results of the stepped economic evaluation (scenario analysis)

Step and component	Durvalumab	Placebo	Increment
Step 1: trial-based, time horizon of 50 months, cost for durvalumab therapy only			
Costs	$	$	$
LYs gained			
Incremental cost/extra LY gained			$
Step 2: time horizon extended to 10 years			
Costs	$	$	$
LYs gained			
Incremental cost/extra LY gained			$
Step 3: incorporation of medical resource costs			
Costs	$	$	$
LYs gained			
Incremental cost/extra LY gained			$
Step 4: utility weights applied			
Costs	$	$	$
QALYs			
Incremental cost/extra QALY gained (base case)			**$**

LY = life-year; QALY = quality-adjusted life-year

Source: Table 2, p5 of the 'UpdatedRPSFT_ScenarioAnalysis' document provided during the evaluation

The redacted table shows ICERs in the range of $15,000/LY - $200,000/LY and $$15,000/QALY $45,000/QALY.

6.37 The incremental quality-adjusted life-years (QALYs) for durvalumab versus placebo in the scenario analysis ( ) were reduced, compared with that in the base case analysis ( ), as the RPSFT method suggested a better OS in the placebo arm.

6.38 The application of the effective price of nivolumab and the adjusted duration of treatment in the base case and the scenario analysis resulted in greater incremental cost of durvalumab compared with placebo and increased the ICER (see CIC).

6.39 The key sensitivity analyses for the base case model are presented in Table 13.

Table 13: Results of key sensitivity analyses (base case)

	Costs			QALYs			ICER
	DUR	PBO	Incr.	DUR	PBO	Incr.	($/QALY)
Base case	$	$	$				$
Time horizon (base case: 10 years)							
1. 5 years[a]	$	$	$				$
2. 7.5 years[a]	$	$	$				$
3. 15 years	$	$	$				$
OS extrapolation method (base case: independent log-logistic in both arms)							
4. Independent log-normal in both arms	$	$	$				$
5. Independent generalised gamma in both arms	$	$	$				$
6. Independent exponential in both arms[a]	$	$	$				$
7. Independent Weibull in both arms[a]	$	$	$				$
8. Independent Gompertz in both arms[a]	$	$	$				$
9. Independent exponential in durvalumab arm[a,b]	$	$	$				$
Convergence of OS curves of the two treatment arms within time horizon (base case: no)							
10. OS curves start to converge at Year 5 and converge at Year 10[a,c]	$	$	$				$
Convergence of survival curves of the two treatment arms for both PFS and OS within time horizon (base case: no)							
11. For both PFS and OS, survival curves start to converge at Year 5 and converge at Year 10[a,c]	$	$	$				$
Extrapolation time point for OS (45.1 months for durvalumab and 46.1 months for placebo)							
12. 35 months in both arms[a]	$	$	$				$
13. 40 months in both arms[a]	$	$	$				$
14. 45 months in both arms[a]	$	$	$				$
Utility weights (base case: PACIFIC for PFS and Chouaid 2013 for PD[d])							
15. PACIFIC for PFS and Khan 2015 for PD[d]	$	$	$				$
16. Chouaid 2013 for both PFS and PD[a,e]	$	$	$				$
17. Khan 2015 for both PFS and PD[a,e]	$	$	$				$

DUR = durvalumab; ICER = incremental cost-effectiveness ratio; OS = overall survival; PBO = placebo; PD = progressive disease; PFS = progression-free survival; QALY = quality-adjusted life-year

[a] Sensitivity analyses performed during the evaluation

[b] The parametric function to extrapolate OS for placebo did not change from the base case (independent log-logistic)

[c] In the placebo arm, selected parametric functions in the base case were used from the extrapolation point to the end of the time horizon. As for durvalumab, the parametric functions were used until the point at which convergence started, then a linear decrease of PFS and OS estimates was assumed until the convergence time point.

[d] The utility value for the PFS health state reported in the literature was applied to the PD (≥180 days prior to death) state in the economic model. The utility for the PD health state reported in the literature was applied to the PD (<180 days prior to death) state in the economic

model.
[e] The utility values for the PFS and PD health states reported in the literature were used for the PFS and PD (both ≥180 and <180 days prior to death) states, respectively, in the economic model.
Source: Table 3.9-1, p158 of the resubmission. Results presented in italics are additional sensitivity analyses performed during the evaluation.

The redacted table shows ICERs in the range of $45,000/QALY - $105,000/QALY.

6.40 Results of the sensitivity analyses around the base case indicated that the model was sensitive to the selection of the extrapolation model for OS. The use of an independent exponential function to extrapolate OS in the durvalumab arm, but an independent log-logistic function in the placebo arm (not changed from the base case), would result in the survival curves of the two treatment arms converging at the end of 10-year time horizon. The ICER would increase from the base case $45,000/QALY - $75,000/QALY to $45,000/QALY - $75,000/QALY .

6.41 The resubmission set a late time point for OS extrapolation at which the survival curve became unstable, in both the base case and the scenario analysis models. It was noted that, for the base case model, a slight change of the extrapolation point in the placebo arm from the base case 46.1 months to 45 months, the ICER increased from $45,000/QALY - $75,000/QALY to $45,000/QALY - $75,000/QALY. The ESC noted that at the time point at which extrapolation starts the sample size was small and considered extrapolation at an earlier time point (40 months) would be more reasonable. The PBAC agreed with the ESC that extrapolation from 40 months would be more appropriate.

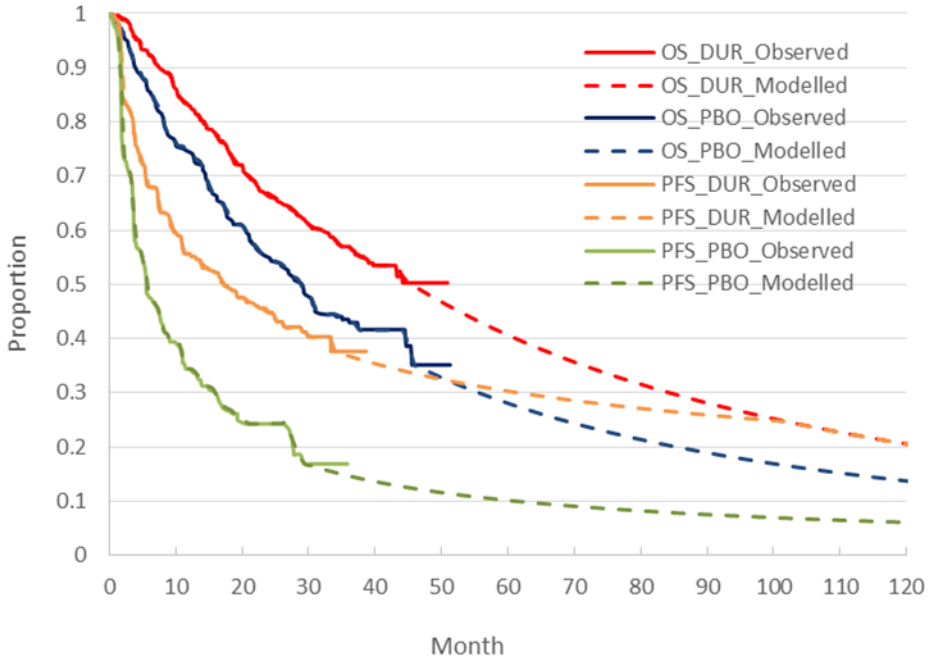
6.42 The 10 year time horizon of the economic model was previously considered poorly justified (paragraph 7.9, durvalumab PSD, November 2018 PBAC meeting) and is longer than the PBAC has considered reasonable for other NSCLC treatments (7.5 years). The ESC noted durvalumab is used earlier in the treatment pathway (Stage III) than other NSCLC treatments (Stage IIIb and IV) previously considered by the PBAC, and the patient population has responded to CRT. The PBAC considered a 10 year time horizon was reasonable.

6.43 The economic model was moderately sensitive to the change in health state utility values. Using lower utility values from published literature for both progression-free and progressive disease health states, the ICER would exceed $45,000/QALY - $75,000/QALY. However, it is acknowledged that the utilities reported in the literature were for a later stage of disease than the proposed PBS population for durvalumab, and may be underestimates. The ESC noted the utility values for the PFS health state remained unchanged in the resubmission and considered that using the utility values derived from the PACIFIC study remained an area of uncertainty, as they were likely to be higher than those expected in the Australian setting.

6.44 The modelled PFS and OS curves compared with the observed Kaplan-Meier curves for PFS and OS are presented below in Figure 3. Visual inspection indicated that the

modelled PFS and OS benefit appeared optimistic, with continued benefit of durvalumab being assumed throughout the modelled time horizon. Setting the PFS and OS curves of the two treatment arms to begin converging at Year 5 and completely converging at Year 10, the ICER would increase to $45,000/QALY - $75,000/QALY . The PBAC agreed with the ESC that the assumed continued PFS and OS benefit of durvalumab compared with placebo over 10 years was not justified and considered the OS and PFS curves should be made to converge at 10 years, with convergence starting at year 5.

Figure 3: Kaplan Meier and modelled curves for PFS and OS (base case)



DUR = durvalumab; PBO = placebo; OS = overall survival; PFS = progression-free survival
Source: Figure constructed during the evaluation, based on the "Imfinzi (durvalumab) Economic Evaluation – ITT" Excel workbook

6.45 The ICER from the RPSFT-adjusted scenario analysis was also sensitive to the time horizon of the model, the assumed duration of survival benefits associated with durvalumab versus placebo, and the time point for OS extrapolation, particularly in the placebo arm.

6.46 The ESC considered that additional multivariate analysis accounting for convergence of PFS and OS (refer to paragraph 6.44, Step B in Table 14), adjustment of OS extrapolation in both treatment arms (refer paragraph 6.41, Step C in Table 14), the effective nivolumab price and adjusted nivolumab duration of treatment was likely to result in the most appropriate revised base case (see CIC section, Table 15 for Step D).

Table 14: Results of the additional multivariate analysis

			ITT	RPSFT
A.	Base case in submission	No convergence Extrapolation from 45.1 months for durvalumab and 46.1 months for placebo in ITT; 45.1 months for durvalumab and 51 months for placebo in RPSFT. Published nivolumab price and duration of treatment	$[redacted]	$[redacted]
B.	Add convergence	Convergence of PFS and OS at 10 years, starting at 5 years	$[redacted]	$[redacted]
C.	Add change OS extrapolation time point	Extrapolation from 40 months for all treatment arms in both scenarios	$[redacted]	$[redacted]
D	Add effective nivolumab price and adjusted duration of treatment	Refer to CIC section		

Committee-In-Confidence information

6.47 The ICERs for the base case and RPSFT-adjusted scenario multivariate analysis incorporating the effective nivolumab price and adjusted duration of treatment are summarised in Table 15.

Table 15: Results of the additional multivariate analysis (refer to Table 14 for analyses A-C)

			Base case	*RPSFT*
D.	Add effective nivolumab price and adjusted duration of treatment	Convergence of PFS and OS at 10 years, starting at 5 years Extrapolation from 40 months for all treatment arms in both scenarios	$[redacted]	$[redacted]

End Committee-In-Confidence information

6.48 The ESC considered the true ICER is likely to lie between the respecified base case and the scenario analysis that was based on the RPSFT-adjusted OS curves, although given the uncertainty introduced with the RPSFT adjustment, the true ICER may be more closely aligned with the respecified base case.

6.49 The Pre-PBAC response noted and verified the multivariate analyses undertaken by the ESC (Table 14). The sponsor acknowledged the ESC's advice that the true ICER is likely to be more closely aligned with the respecified base case.

Drug cost/patient/course

6.50 The costs of durvalumab per patient per treatment-course are summarised in Table 16. There was a minor difference between the mean treatment duration reported in Section 2 and that used in the model of the submission, although both of these data were claimed to be sourced from the PACIFIC trial.

Table 16: Drug cost per patient for durvalumab

	Trial dose and duration	Model	Financial estimates
Mean dose	711mg[a] every 2 weeks	711mg every 2 weeks	711mg every 2 weeks
Mean duration	35.5 weeks[b]	35.0 weeks[c]	35.5 weeks[d]
Cost/patient/2-week cycle	$ [redacted]	$ [redacted]	$ [redacted]
Cost/patient/course	$ [redacted]	$ [redacted]	$ [redacted]

[a] Equal to the recommended dose regimen (10mg/kg) multiplied by the average body weight of patients in the PACIFIC trial (71.07kg)
[b] Sourced from Table 2.4.2, p57 of the resubmission
[c] Estimated on the basis of the time-to-treatment discontinuation curve from the PACIFIC trial
[d] Sourced from Table 4.1.9, Section 4 of the resubmission
[e] 'Imfinzi (durvalumab) Section 4 – Subsequent IO – ITT' Excel workbook
[f] Undiscounted drug cost from the economic model
Source: Table compiled during the evaluation, based on Table 2.4.2, pp56-57 of the resubmission, the "Imfinzi (durvalumab) Economic Evaluation – ITT" Excel workbook, and the 'Imfinzi (durvalumab) Section 4 – Subsequent IO – ITT' Excel workbook

Estimated PBS usage & financial implications

6.51 This submission was not considered by DUSC.

6.52 Consistent with the original submission, the resubmission used an epidemiological approach to estimate the expected financial implications of listing durvalumab as consolidation therapy for patients with unresectable Stage III NSCLC whose disease has not progressed following definitive chemoradiation therapy.

6.53 It was uncertain whether the size of the eligible patient population is under or overestimated because:

- The proportion of patients receiving first-line therapy with chemoradiation was uncertain as the estimates of treatment uptake for chemoradiation previously considered reasonable by the DUSC (70-80% in all years) were not limited by performance status. The resubmission limited patients to a performance status of 0 or 1 and therefore, the proportion of patients with Stage III unresectable NSCLC with a WHO PS of 0 or 1 that would receive chemoradiation is likely to be underestimated. The ESC considered the update rate was reasonable but noted it increased from 70% to 80% and considered the number of eligible patients receiving CRT would not increase because of the availability of durvalumab. The PBAC considered a CRT uptake rate of 70% across all years was reasonable.
- The high treatment uptake of durvalumab following treatment with CRT (90% in year 1, increasing to 95% in years 2-6) may not take into consideration the proportion of patients whose PS worsened while on chemoradiation. The PBAC agreed with the ESC that a 90% uptake rate of durvalumab across all years was

appropriate.

6.54 The resubmission presented two alternative analyses for estimating the cost offsets associated with the reduced use of PD-(L)1 inhibitors as subsequent therapy:

- Base case: Based on the survival curves from the ITT analysis in the PACIFIC trial and extrapolated as described for the economic model and applying the proportion of patients in the PACIFIC trial that received subsequent therapy with a PD-(L)1 inhibitor (22% for the durvalumab and 46% for the placebo arms). The proportion of patients who progressed and the proportion of progressed patients who received subsequent immunotherapy may not represent clinical practice. The PBAC previously considered that it was appropriate for the restrictions for PD-(L)1 therapies in all stages of NSCLC to preclude prior and subsequent use of PD-(L)1 therapies until evidence to support their sequential use is forthcoming (paragraph 7.2, 5.04 durvalumab PSD, November 2018 PBAC Meeting).
- An RPSFT scenario analysis (provided as a sensitivity analysis): based on the RPSFT-adjusted survival curves and extrapolated as described for the economic model, and assuming that no patients will receive subsequent treatment with a PD-(L)1 inhibitor in the durvalumab arm, while 70% of progressed patients in the placebo arm will receive subsequent therapy with a PD-(L)1 inhibitor. However, the RPSFT model was subject to high uncertainty as noted above. The assumed 70% of progressed patients in current clinical practice receiving subsequent immunotherapy was inconsistent with the assumption of 100% of progressed patients receiving subsequent immunotherapy in the RPSFT-based economic model. The ESC considered the implications of using the RPSFT-based survival curve which assumed 100% of progressed patients receive a PD-(L)1 inhibitor to identify progressed patients but only off-setting 70% of them was unclear.

6.55 The PBAC have previously considered that if durvalumab was made available on the PBS, there would only be a modest increase in the number of patients treated with PD-(L)1 inhibitors, provided sequential treatment with different PD-(L)1 therapies was precluded as recommended above. The PBAC recalled it had previously noted that some patients (~25%) are cured by chemo-radiotherapy (paragraph 7.1, durvalumab PSD, November 2018 PBAC meeting) and therefore considered that most patients treated with durvalumab would have been treated with a PD-(L)1 inhibitor in the metastatic setting.

6.56 The ESC noted that the submission assumed grandfathered patients would receive a full 12 months' worth of durvalumab treatment, resulting in the financial estimates being overestimated in Year 1.

6.57 The estimated use and financial implications of listing durvalumab are provided in Table 17. The ESC noted that a discount of [redacted]% on the published price of nivolumab was assumed for the cost-offsets.

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of durvalumab						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for the reduced use of PD-(L)1s as subsequent therapy (assumed [redacted]% discount on published list price)						
Number of patients no longer treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Assuming an average of 17.65 scripts per patient per year as estimated by the submission.

[b] Assuming an average of 7.5 scripts per patient per treatment course based on IQVIA Utilisation Report

Source: Table 4.2.2, Table 4.2.3, Table 4.2.4, Table 4.2.6, Table 4.2.7, Table 4.2.9, Table 4.3.1, Table 4.3.5, Table 4.3.6, and Table 4.3.8, Table 4.5.2

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

6.58 The estimated cost offsets associated with subsequent therapy based on the RPSFT scenario analysis are summarised in Table 18.

Table 18: Cost offsets associated with subsequent therapy based on the RPSFT scenario analysis

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients no longer treated with PD-(L)1 therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total original prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated Financial implications (assumed 45% discount on published list price)						
Cost offset to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Offset patient copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost offset to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Imfinzi (durvalumab) Section 4 – Subsequent IO – RPSFT'.xlsx provided during the evaluation

The redacted table shows that the estimated cost offset to PBS at year 6 would be $10 - $20 million.

Quality Use of Medicines

6.59 The resubmission provided a brief description of activities to support the quality use of medicines. The resubmission stated that as part of the launch of durvalumab, the sponsor will undertake to provide appropriate education to the clinical community about the drug, its use and the appropriate management of any adverse events experienced by patients.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of durvalumab as a consolidation treatment in Stage III unresectable NSCLC in patients who have not progressed after platinum-based CRT. The PBAC considered the revised ICER, based on the PBAC's preferred assumptions, was high and potentially underestimated. The PBAC also considered the total cost of subsidising durvalumab in this setting to be very high and uncertain.

7.2 The PBAC noted the proposed listing was updated to address the comments made by the ESC and the PBAC following review of the previous submission (paragraph 7.2, durvalumab PSD, November 2018 meeting). The PBAC considered the listing should be revised as suggested by the Secretariat (paragraph 2.1). In addition, the listing should be revised to clarify the grandfathering restriction (paragraph 2.3), include appropriate wording to restrict access to patients that have not progressed (paragraph 2.3) and limit patients to one course of treatment with PD-(L)1 inhibitors per lifetime (paragraph 2.4).

7.3 The PBAC recalled that when it previously considered durvalumab in November 2018, it considered the OS in the PACIFIC trial was immature, with median OS not yet reached in the durvalumab arm. The PBAC noted the current resubmission provided an updated OS analysis using data with an additional 10 months of follow-up (an overall median duration of follow-up of 33 months). The PBAC noted with only a 6% increase in the number of events, there was minimal change in the OS hazard ratio or the proportion alive at 24 months (paragraph 6.8). The PBAC considered there was evidence that durvalumab was likely to prolong OS in patients who respond to CRT; however, the magnitude of the benefit remained uncertain with median OS not yet reached in the durvalumab arm.

7.4 The PBAC noted that the updated safety data presented in the submission was consistent with the previous safety data considered by the PBAC. The PBAC reaffirmed its previous consideration that durvalumab has an inferior safety profile compared to placebo. The PBAC noted approximately 25% of patients would be cured with CRT alone and, for these patients, treatment with durvalumab resulted in additional toxicity.

7.5 The PBAC considered that the benefit of durvalumab if it is listed on the PBS may be less than that observed in the PACIFIC trial, with the OS in the trial likely to be overestimated due to higher subsequent immunotherapy use in the durvalumab arm and lower use in the placebo arm (paragraph 6.11). The PBAC recalled that only 8% of patients in the PACIFIC trial were aged > 70 years and considered this was not reflective of Australian clinical practice, with a greater proportion of treated patients anticipated to be aged > 70 years (paragraph 7.6, durvalumab PSD, November 2018 PBAC meeting). The PBAC considered this may result in a lower OS benefit and a higher rate of adverse events amongst Australian patients, compared to the trial population.

7.6 The PBAC noted the submission presented a RPSFT-adjusted analysis in an attempt to address the applicability issue resulting from the use of post-progression immunotherapies in the PACIFIC trial. The RPSFT-adjusted analysis assumed that no patients in the durvalumab arm received subsequent immunotherapy and all patients in the placebo arm, who subsequently received any anticancer treatment, received immunotherapy as their first subsequent treatment. The PBAC considered the RPSFT-adjusted analysis did not completely mitigate the applicability concerns as the assumptions underpinning the analysis were unverifiable (paragraph 6.13). The PBAC also considered that the analysis likely overestimated the extent of immunotherapy use in the placebo arm and noted that this would underestimate the incremental benefit, with the corresponding assumption regarding immunotherapy use in the economic model underestimating the incremental cost.

7.7 The PBAC agreed with the ESC that the assumed continued PFS and OS benefit of durvalumab compared with placebo over the economic model's 10-year time horizon was not justified given the available trial data. The PBAC considered that although a 10-year time horizon was appropriate, given durvalumab's earlier line in therapy compared to currently PBS-listed PD-(L)1 inhibitors in NSCLC, the OS and PFS curves of the two treatment arms should be made to converge at 10 years, with convergence starting at year 5 (paragraph 6.44). The PBAC further agreed with the ESC that OS extrapolation should commence at 40 months in both treatment arms (paragraph 6.41).

7.8 The PBAC recalled it had previously considered the utility values derived from the PACIFIC trial to be high when compared with Australian norms and that a lower estimate should be applied (paragraph 7.11, durvalumab PSD, November 2018 meeting). The PBAC noted the utility values for the PFS health state remained the same as in the previous submission but the utility values for the PD health state were lower. The PBAC further noted that sensitivity analyses assuming lower utility values resulted in ICERs that were 25% higher than the base case. The PBAC considered there was still some uncertainty regarding the appropriate utility values to apply in the economic model.

7.9 The PBAC noted that the published price for nivolumab as a second line treatment was used in the resubmission's economic model. Additionally, a shorter duration of treatment was used than previously accepted as reasonable by the PBAC (paragraph 6.37, pembrolizumab PSD, November 2018 meeting). The PBAC considered that the respecified base case incorporating the effective price and adjusted duration of treatment for nivolumab, as well as the changes for convergence and extrapolation (paragraph 7.7), provided a more appropriate basis for determining cost-effectiveness. The PBAC noted that the ICER for the respecified base case (Table 15) was substantially higher than the ICER provided in the resubmission's base case (Table 11).

7.10 The PBAC agreed with the ESC that the true ICER is likely to lie between the respecified base case and the RPSFT–adjusted analysis, however given the uncertainty of the RPSFT–adjusted analysis, the true ICER may be more closely aligned with the respecified base case analysis. Additionally, the PBAC considered the respecified base case was uncertain given the continued immaturity of the clinical data (paragraph 7.3) and the uncertainty regarding the appropriateness of the utilities (paragraph 7.8).

7.11 The PBAC considered that a reasonable base case ICER in this treatment setting would be less than $45,000-$74,000 per QALY, noting the uncertainties discussed above.

7.12 The PBAC noted the high estimated financial impact of subsidising durvalumab in the proposed treatment setting, although it considered that the financial impact was overestimated in terms of the eligible patient population and inadequate inclusion of cost-offsets associated with avoiding subsequent immunotherapy.

7.13 The PBAC considered it would be appropriate for the patient estimates to apply an uptake of CRT of 70% and an uptake rate for durvalumab of 90% across all years (paragraph 6.53).

7.14 The PBAC recalled that in November 2018, it considered that there would be substantial cost-offsets from PD-(L)1 inhibitor use in later stage NSCLC resulting from a PBS listing of durvalumab in stage III NSCLC, which would affect the current RSA in the shared subsidisation cap in the Deeds of Agreement for atezolizumab, nivolumab and pembrolizumab in NSCLC (paragraph 7.13, durvalumab PSD, November 2018 meeting). The PBAC considered the cost-offsets were underestimated in the financial estimates and that it would be appropriate to assume that 70% of patients that initiate treatment with durvalumab would avoid subsequent use of PD-(L)1 inhibitors in the metastatic setting.

7.15 The PBAC reaffirmed its November 2018 advice that if durvalumab was made available on the PBS, there would only be a modest increase in the overall number of patients treated for NSCLC, provided sequential treatment with different PD-(L)1 therapies was precluded (paragraph 6.55). The PBAC also reaffirmed its previous advice that due to a lack of evidence to support the sequential use of immunotherapies, precluding prior and subsequent use of PD-(L)1 inhibitors remained appropriate. The PBAC further considered it was appropriate for durvalumab to share the RSA subsidisation cap in the current Deeds of Agreement for locally advanced/metastatic NSCLC for PD-(L)1 therapies.

7.16 The PBAC considered that any resubmission could be a minor resubmission and would be required to:

- Use the respecified economic model outlined in paragraph 6.46 to provide a base case ICER of less than $45,000 - $75,000 per QALY. The PBAC noted that the use of the published price of nivolumab as a subsequent treatment decreased the ICER compared to using the effective price, and advised that this would need to be taken into account when considering any revised proposal from the sponsor.
- Revise the patient estimates applying the uptake rates outlined in paragraph 7.13.
- Revise the financial estimates for grandfathered patients to take into account only the number of patients accessing treatment at the time of PBAC reconsideration (paragraph 2.3) and a reduced cost per patient to account for treatment already received (paragraph 6.56).
- Increase cost-offsets associated with avoiding subsequent lines of immunotherapy as outlined in paragraph 7.14.

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

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.