

5.04 DURVALUMAB, Solution for I.V. infusion 120 mg in 2.4 mL; Solution for I.V. infusion 500 mg in 10 mL, Imfinzi[®], AstraZeneca Pty Ltd

1 Purpose of Application

- 1.1 The submission 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). This was the first submission for durvalumab.
- 1.2 The submission requested PBS listing on the basis of a cost-utility analysis comparing durvalumab to placebo or ‘watch and wait’ monitoring plus best supportive care.

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

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 every two weeks 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 every two weeks 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.

Source: Table 1.1.1, p2 of the submission.

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; TTDM = time to death or distant metastasis.

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

2 Requested listing

- 2.1 The listing proposed by the submission is given below with wording changes suggested by the Secretariat marked (additions in italics, deletions struck through).
- 2.2 The Pre-PBAC response provided a revised effective price for durvalumab, which was approximately ■■■% lower than in the original submission (see also section 6).

Public Summary Document – November 2018 PBAC meeting

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	1240mg	8	\$ [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:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	<i>Unresectable</i>
Condition:	Stage III Non-small cell lung cancer
PBS Indication:	Unresectable Stage III non-small cell lung cancer
Treatment phase:	<i>Initial treatment</i>
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The patient must have received platinum-based chemoradiation therapy AND The condition must not have progressed following platinum-based chemoradiation therapy AND The patient must not have received prior PD-1 or PD-L1 inhibitor therapy for this condition AND The treatment must be the sole PBS-subsidised treatment for this condition AND The condition must be Stage III non-small cell lung cancer AND The condition must be unresectable
Administrative Advice:	<i>No increase in the maximum number of repeats will be authorised. Special pricing arrangement apply</i>

Source: Tables 1.4.2 -1.4.4, pp12-17, with Sec additions.

- 2.3 The submission proposed a special pricing arrangement (SPA).
- 2.4 The patients in the proposed population were broader than those enrolled in the PACIFIC trial where eligibility for the trial required patients to have (i) not progressed after at least two rounds of concurrent platinum-based chemoradiation therapy; and (ii) a WHO performance status of 0 or 1.
- 2.5 The ESC considered that the restriction should specify that treatment should continue until disease progression or up to a maximum of 12 months consistent with the pivotal clinical trial. The ESC further advised that the issue of sequential treatment with checkpoint inhibitors at different stages of NSCLC required consideration by the PBAC.

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

3 Background

Registration status

- 3.1 The submission was made under the TGA/PBAC Parallel Process. The TGA delegate's Summary was finalised on 8 August 2018. The TGA delegate noted "Currently there are no approved consolidation therapies for patients with locally advanced, unresectable NSCLC after definitive cCRT [concurrent chemoradiotherapy], and if progression occurs after cCRT, patients are no longer considered curable. Durvalumab in the proposed indication is more effective than placebo on both PFS and OS measures, and has a manageable safety profile similar to that of other PD-L1/PD-1 inhibitors."
- 3.2 The Pre-PBAC response informed the PBAC that durvalumab had been approved by the TGA on 22 October 2018, for the following indication:

IMFINZI (durvalumab) is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.

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). Non-small cell lung cancer (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 The submission proposed durvalumab for use in unresectable Stage III NSCLC as a consolidation therapy for patients who have not progressed after platinum-based chemoradiation treatment (CRT).
- 4.3 The submission noted that in the current management algorithm, if progression to Stage IIIb/c or IV disease occurs after CRT, a patient's treatment path is informed by the molecular phenotype of the tumour.
- Those with wild type disease (presumed to be EGFR or ALK wild type) will receive platinum-based chemotherapy followed by nivolumab or atezolizumab on progression; or the recently recommended, but not yet PBS-listed use of pembrolizumab as a first-line treatment of Stage IV NSCLC if PD-L1 expression is $\geq 50\%$.
 - Those with mutations such as EGFR or ALK will receive an agent specific to the relevant mutation.
 - A proportion of patients may receive supportive palliative care with no active therapy, depending on their overall health, prognosis and personal choice.

- 4.4 The submission also observed that in the proposed management algorithm, patients with Stage III NSCLC, whose wild-type disease progresses on or following durvalumab maintenance therapy are expected to receive platinum-based chemotherapy. The submission stated that the nivolumab and atezolizumab PBS restrictions exclude patients who have received prior treatment with a PD-(L)1 inhibitor, and thus durvalumab treated patients would not have access to subsequent PD-(L)1 inhibitors after progression.

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

5 Comparator

- 5.1 The submission nominated placebo, representing 'watch-and-wait' monitoring plus best supportive care as the main comparator, based on the absence of PBS-listed maintenance therapies after chemoradiation treatment (CRT) in Stage III 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 and welcomed the input from two individuals via the Consumer Comments facility on the PBS website.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the durvalumab submission for the treatment of Stage III NSCLC following chemoradiation on the basis of comparative benefit observed in the PACIFIC study. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for durvalumab, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)^[1], based on a comparison with placebo.¹ The ESMO-MCBS did not account for benefits in overall survival due to the immaturity of the survival data in the PACIFIC study.

Clinical trials

6.4 The submission was based on one randomised placebo controlled trial comparing durvalumab to placebo (PACIFIC; n=713).

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PACIFIC (NCT02125461)	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.
	Antonia SJ et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer.	NEJM 2017; 377(20):1919–1929 [plus supplementary material].
	Antonia SJ, Villegas A, Daniel D, Vicente 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.
	Hui R, 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.
	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.

Source: Table 2.2.1, p22-23 of the submission. NSCLC = non-small cell lung cancer;

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

The key features of the PACIFIC 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
Durvalumab vs. placebo						
PACIFIC	713	R, DB, MC 40-43 months	Low	Have not progressed after CRT	OS, PFS	Used in the model

CRT = chemoradiation treatment; DB=double blind; MC=multi-centre; OS=overall survival; PFS=progression-free survival; R=randomised. Source: pp24-37 of the submission.

6.6 The PACIFIC trial participants were adequately randomised and the overall risk of bias was low.

6.7 The proportion of patients receiving subsequent PD-(L)1 inhibitors in both the durvalumab arm and watch-and-wait arm of the PACIFIC trial may not reflect Australian clinical practice, and the impact of this on the applicability of the treatment effect remains unclear.

- If the use of subsequent PD-(L)1 inhibitors in Australia is limited due to restrictions against sequential use of nivolumab, atezolizumab and pembrolizumab, then the effect of the use of PD-(L)1 inhibitors following treatment with durvalumab, as occurred in the PACIFIC trial, may influence OS in a way that would not occur in the Australian setting.

Comparative effectiveness

6.8 Table 4 presents a summary of the overall survival (OS) estimates in the PACIFIC trial.

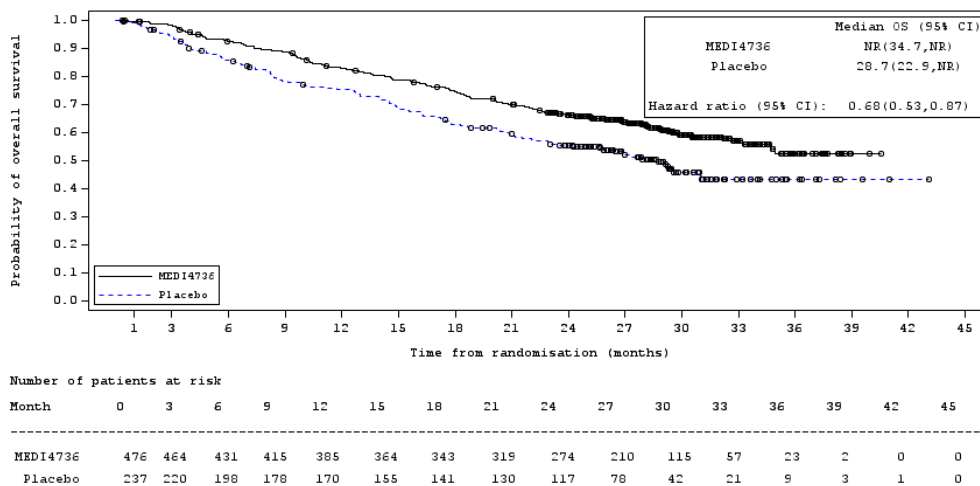
Table 4: Summary of OS in PACIFIC

	Durvalumab; n/N (%)	Placebo; n/N (%)	Absolute difference	HR (95% CI)
Overall survival				
Patients with event	183/476 (38.4)	116/237 (48.9)	10.5%	-
Median months OS (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)	NR	0.68 (0.53, 0.87)

Source: Table 2.5.1, p40 of the submission. CI = confidence interval; HR = hazard ratio; NR = not reported; OS = overall survival

6.9 Figure 1 presents the OS Kaplan Meier curve in the PACIFIC trial.

Figure 1: OS Kaplan Meier curve in PACIFIC



Source: Figure 2.5.1, p40 of the submission. BICR = blinded independent central review; FAS = full analysis set; OS = overall survival; RECIST = response evaluation criteria in solid tumours

6.10 The PBAC noted that results of the PACIFIC trial were immature, with median OS not reached in the durvalumab arm. The main findings were:

- OS among patients in the durvalumab arm of the trial was significantly longer than those in the placebo arm (HR = 0.68 [95% CI: 0.53, 0.87]). The submission did not indicate when final OS data from the PACIFIC trial would be expected.
- The submission noted that 22.4% of patients randomised to the placebo arm received immunotherapy treatment following progression during the post study follow up, and that 8% of durvalumab patients received immunotherapy following progression (see Table 5).
- The Pre-Sub-Committee Response (PSCR) addressed the possibility of second-line PD-(L)1 inhibitors in the durvalumab arm of the PACIFIC trial affecting the estimates of overall survival with an analysis that adjusted for these subsequent treatments. The PSCR described a rank-preserving structural failure time model (RPSFTM), which was applied to remove the effect of second line PD-(L)1 inhibitors in the durvalumab arm. The analysis reported an adjusted hazard ratio of [REDACTED], 95% CI [REDACTED], [REDACTED]. This result is consistent with the primary analysis.

6.11 Table 5 presents a summary of post-progression therapies in the PACIFIC trial.

Table 5: Post-progression therapies in the PACIFIC trial

Subsequent therapy	PACIFIC (ITT population)		PACIFIC (patients treated with subsequent therapy)	
	Durvalumab (N=476)	Placebo (N=237)	Durvalumab (N=195)	Placebo (N=128)
Radiotherapy	17.2%	23.6%	42.1%	43.8%
Immunotherapy	8.0%	22.4%	19.5%	41.4%
Chemotherapy	26.9%	30.0%	65.6%	55.5%
Systemic therapy	9.9%	13.1%	24.1%	24.2%
Other therapies	0.2%	0.4%	0.5%	0.8%

Source: Table 2.7.3, p70 of the submission. ITT = intention to treat

6.12 Table 6 presents a summary of PFS outcomes in the PACIFIC trial at two data cuts. The estimates from 22 March 2018 could not be located in the CSR or references provided by the submission.

Table 6: Summary of PFS outcomes in PACIFIC

	Durvalumab n/N (%)	Placebo n/N (%)	Absolute difference	HR (95% CI)
Progression-free survival by BICR (primary analysis, 22 March 2018 data cut)				
Patients with event	243/476 (51.1)	173/237 (73.0)	21.9%	-
Median PFS months (95% CI)	17.2 (13.1, 23.9)	5.6 (4.6, 7.7)	11.6 months	0.51 (0.41, 0.63)
Progression-free survival by BICR (primary analysis; CSR, 21 July 2017)				
Patients with event	214/476 (45.0)	157/237 (66.2)	21.2%	-
Median months PFS (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)	11.2 months	0.52 (0.42, 0.65)
Progression-free survival by investigator assessment (CSR, 21 July 2017)				
Patients with event	252/476 (52.9)	167/237 (70.5)	17.6%	-
Median months PFS (95% CI)	13.6 (11.0, 14.0)	7.4 (5.6, 9.0)	6.2 months	0.61 (0.50, 0.76)

Source: Table 2.5.4, p42 of the submission and corrected in the PSCR.

BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival

6.13 In the 21 July 2017 data cut, the hazard ratios and differences in median progression-free survival showed that the benefit in the investigator assessed results were substantially smaller than the benefit assessed by blinded independent central review (BICR). The PBAC had previously expressed a preference for BICR PFS estimates as a less biased estimate (Palbociclib March 2017 PSD; paragraphs 7.9, 7.13).

- 6.14 The PACIFIC trial also collected results of the EuroQol 5D (EQ-5D). The submission noted that the mean and median baseline scores from the EQ-5D were similar in the two treatment groups and the scores remained similar across the arms of the trial over time.

Comparative harms

- 6.15 The submission considered that a similar proportion of patients in each treatment group in the PACIFIC trial experienced adverse events, and that the majority were not severe in nature, see Table 7. The submission noted that durvalumab patients experienced more treatment related AEs than placebo patients (67.8% and 53.4%, respectively), but that for most AEs, the difference was not significant.
- 6.16 The submission noted adjusting for duration of exposure did not substantially alter the unadjusted results, but that the rate of AEs leading to discontinuation was no longer significant after this adjustment.

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

Adverse event	Durvalumab, n (%) N=475	Placebo, n (%) N=234	Relative risk (95% CI) p-value	Risk difference (95% CI) (%) p-value
Any AE	460 (96.8)	222 (94.9)	1.02 (0.99, 1.06) p=0.21	1.97 (-1.03, 5.57) p=0.21
Any AE related to treatment	322 (67.8)	125 (53.4)	1.27 (1.11, 1.46) p=0.0002	14.37 (6.73, 22.00) p=0.0002
Any AE of CTCAE Grade 3 or 4 related to treatment	59 (12.4)	11 (4.7)	2.64 (1.48, 5.22) p=0.001	7.72 (3.52, 11.68) p=0.001
Any SAE related to treatment	41 (8.6)	9 (3.8)	2.24 (1.17, 4.86) p=0.01	4.79 (1.05, 8.26) p=0.01
Any AE leading to discontinuation related to treatment	47 (9.9)	8 (3.4)	2.89 (1.48, 6.53) p=0.0012	6.48 (2.75, 10.00) p=0.0012
Any AE leading to death	21 (4.4)	15 (6.4)	0.69 (0.36, 1.34) p=0.26	-1.99 (-5.97, 1.43) p=0.26
Any AE leading to death related to treatment	7 (1.5)	4 (1.7)	0.86 (0.26, 3.26) p=0.81	-0.24 (-2.63, 1.62) p=0.81
Any AESI	317 (66.7)	115 (49.1)	1.36 (1.18, 1.58) p<.0001	17.59 (9.89, 25.22) p<.0001
Any ImAEs	166 (34.9)	39 (16.7)	2.10 (1.56, 2.91) p<.0001	18.28 (11.69, 24.54) p<.0001
Cough	167 (35.2)	59 (25.2)	1.39 (1.09, 1.81) p=0.01	9.94 (2.78, 16.83) p=0.01
Pyrexia	72 (15.2)	22 (9.4)	1.61 (1.05, 2.60) p=0.03	5.76 (0.61, 10.56) p=0.03
Pneumonia	63 (13.3)	18 (7.7)	1.72 (1.07, 2.93) p=0.02	5.57 (0.78, 10.03) p=0.02
Pneumonitis	60 (12.6)	18 (7.7)	1.64 (1.02, 2.80) p=0.04	4.94 (0.18, 9.35) p=0.04
Pruritus	59 (12.4)	12 (5.1)	2.42 (1.38, 4.65) p=0.001	7.29 (3.01, 11.32) p=0.001
Hypothyroidism	55 (11.6)	4 (1.7)	6.77 (2.82, 22.17) p<.0001	9.87 (6.49, 13.26) p<.0001
Myalgia	38 (8.0)	10 (4.3)	1.87 (0.99, 3.91) p=0.054	3.73 (-0.07, 7.20) p=0.054
Oedema peripheral	37 (7.8)	9 (3.8)	2.03 (1.04, 4.41) p=0.04	3.94 (0.27, 7.32) p=0.04
Hyperthyroidism	35 (7.4)	4 (1.7)	4.31 (1.75, 14.30) p=0.001	5.66 (2.65, 8.59) p=0.001

Source: Table 2.5.8, pp52-55 of the submission and corrected by sponsor. 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.

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 versus placebo is presented in Table 8.

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

Trial	Durvalumab n/N	Placebo n/N	Absolute difference	HR (95% CI)		
Benefits						
Overall survival						
Patients with event	183/476 (38.4)	116/237 (48.9)	10.5%	-		
Median months OS (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)	NR	0.68 (0.53, 0.87)		
Overall survival at 24 months						
Patients alive at 24 months, % (95% CI)	66.3 (61.7, 70.4)	55.6 (48.9, 61.8)	10.7% p=0.005	--		
Progression-free survival by BICR (primary analysis, 22 March 2018 data cut)						
Patients with event	242/247 (51.1)	173/237 (73.0)	21.9%	-		
Median PFS months (95% CI)	17.2 (13.1, 23.9)	5.6 (4.6, 7.7)	11.6 months	0.51 (0.41, 0.63)		
Harms						
	Durvalumab n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI) (%)
				Durvalumab	Placebo	
Adverse event						
Any AE of CTCAE Grade 3 or 4 related to treatment	59/475	11/234	2.64 (1.48, 5.22)	12.4	4.7	7.72 (3.52, 11.68)
Pneumonia	63/475	18/234	1.72 (1.07, 2.93)	13.3	7.7	5.57 (0.78, 10.03)
Pneumonitis	60/475	18/234	1.64 (1.02, 2.80)	12.6	7.7	4.94 (0.18, 9.35)

* maximum duration of follow-up for durvalumab= 40.5 months; placebo=43.1 months

CTCAE = Common terminology criteria for adverse events; HR = hazard ratio; NR = not reported; PBO = placebo; RD = risk difference; RR = risk ratio

Source: Table 2.5.1, p40, Table 2.5.4, p42 and Table 2.5.8, pp52-55 of the submission and corrected by the sponsor.

6.19 On the basis of the direct evidence presented by the submission, for every 100 patients treated with durvalumab in comparison to placebo and followed over a maximum duration of 40-43 months:

- Approximately 22 more patients remained progression-free;
 - Approximately 8 additional patients would have a common terminology criteria for adverse events (CTCAE) grade 3 (severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living) or grade 4 (life-threatening consequences; urgent intervention indicated) treatment-related adverse event;
- Approximately 6 additional patients would experience pneumonia; and

- Approximately 5 additional patients would experience pneumonitis.

6.20 On the basis of the direct evidence presented by the submission, for every 100 patients treated with durvalumab in comparison to placebo, between 10 and 11 additional patients will be alive at 24 months.

Clinical claim

6.21 The submission described durvalumab as superior in terms of effectiveness with a similar quality of life and a manageable safety profile compared with watch-and-wait monitoring of patients with Stage III NSCLC whose disease has not progressed following definitive chemoradiation therapy.

6.22 The PBAC considered that the claim of superior comparative effectiveness was reasonable. However, the magnitude of comparative benefit was difficult to determine due to the lack of mature OS data and due to the issues with the applicability of the PACIFIC trial to the Australian setting (see Section 7). The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.23 The submission presented a cost-utility analysis with a three-state partitioned survival model including the health states, progression-free disease, progressive disease and death.

6.24 Table 9 presents a summary of the model structure and rationale.

Table 9: Summary of model structure and rationale

Component	Description
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Outcomes	Life years and quality-adjusted life years
Time horizon	10 years based on 40 months in the clinical trial
Methods used to generate results	Partitioned survival model. Kaplan-Meier estimates for progression-free and overall survival were derived directly from the PACIFIC trial. Parametric distributions fitted to the observed KM survival estimates were used for extrapolation beyond the trial time.
Health states	Progression-free, progressive disease and dead
Cycle length	2 weeks for first 12 months, and 4 weeks thereafter
Software package	Microsoft Excel 2016

Source: Table 3.1.1, p81 of the submission

6.25 Table 10 presents a summary of the key drivers of the model.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Time horizon	40-43 month trial period for up to 10 years	High, favours durvalumab
Extrapolation function	OS - LogLogistic and exponential for durvalumab and placebo, respectively. PFS - Generalised gamma for both durvalumab and placebo	High, favours durvalumab
Utility values	Selected utility values were similar to population values.	Moderate, favours durvalumab
Assumed maximum treatment duration of 12 months or until disease progression	Maximum of 12 months of treatment was suggested in the submission, but not specified in the restriction - removal of this maximum treatment duration and assuming treatment until disease progression.	Low to moderate, favours durvalumab

Source: Table 3.9.1, p137-138 of the submission.

6.26 The evaluation noted the model was most sensitive to the selection of the time horizon.

6.27 The evaluation and ESC noted the results were also sensitive to the various extrapolation methods tested in sensitivity analyses (see Table 12). The base case was among the most favourable methods for durvalumab, further suggesting that the base case ICER was likely to be underestimated.

6.28 The ESC noted that the utilities applied in progression-free survival and in the progressive disease health states were high, and similar to general population utility values. The utility in the post-progressive state was based on limited EQ-5D data from the PACIFIC trial collected soon after progression. It would be expected that the quality of life of patients in a progressive state would continue to decline over time until death. For this reason, the ESC considered that the utility applied in the post progressive state was likely overestimated.

6.29 The ESC noted that the submission had provided sensitivity analyses using alternative utility values from published literature, and suggested that sensitivity analyses using the Chouaid 2013 and Khan 2015 values may be informative. The Pre-PBAC response noted that the utilities from Chouaid 2013 were derived from patients with Stage IIIb and IV lung cancer, and not from patients with Stage III lung cancer who have not progressed following chemoradiotherapy. However, the PBAC agreed with the ESC that the utilities derived from the PACIFIC trial are likely to overestimate the utilities in the Australian setting. The PBAC noted that the estimate for utility for non-progressed health state (0.81 for durvalumab) was only marginally lower than the average Australian utility estimate for all adults >18 years. In the absence of robust consideration of the response rates to patient reported outcomes, and a comparison of responders and non-responders, to rule out response bias, the utility estimates remain uncertain. The PBAC also noted that the average age of patients in the PACIFIC trial may be lower than in the Australian setting, which also may impact the average utility across health states.

6.30 Table 11 presents the results of the economic evaluation at the initial proposed price.

Table 11: Results of the submissions stepped economic evaluation at the initial proposed price

Step and component	Durvalumab	Placebo	Increment
Step 1: PACIFIC trial Time horizon: 42 months			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	2.41	2.08	0.33
Incremental cost/extra LY gained			\$ [REDACTED]
Step 2: PACIFIC trial extrapolated to 10 years			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	3.38	2.85	0.98
Incremental cost/LY gained			\$ [REDACTED]
Step 3: Including all resource use			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	3.38	2.85	0.98
Incremental cost/LY gained			\$ [REDACTED]
Step 4: Transformed to QALYs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	3.08	2.29	0.79
Incremental cost/QALY gained			\$ [REDACTED]

Source: Table 3.8.1, p134. Incr = increment; LY = life years; QALY = quality adjusted life year.

The redacted table shows ICERs in the range of \$45,000/LY – \$75,000/LY to more than \$200,000/LY, and \$75,000/QALY – \$105,000/QALY.

Table 12: Results of sensitivity analyses

Analyses		Incremental cost*	Incremental QALY	ICER
Base case		\$ [REDACTED]	0.79	\$ [REDACTED]
Overall survival	LogLogistic for both curves	\$ [REDACTED]	0.55	\$ [REDACTED]
	Weibull for both curves	\$ [REDACTED]	0.53	\$ [REDACTED]
	Gompertz for both curves	\$ [REDACTED]	0.41	\$ [REDACTED]
	LogLogistic – Dependent	\$ [REDACTED]	0.64	\$ [REDACTED]
	Weibull – Dependent	\$ [REDACTED]	0.69	\$ [REDACTED]
	Gompertz – Dependent	\$ [REDACTED]	0.64	\$ [REDACTED]
Progression-free survival	Exponential for both curves	\$ [REDACTED]	0.78	\$ [REDACTED]
	Exponential – Dependent	\$ [REDACTED]	0.78	\$ [REDACTED]
Time horizon	15 years	\$ [REDACTED]	1.05	\$ [REDACTED]
	20 years	\$ [REDACTED]	1.20	\$ [REDACTED]
	7.5 years	\$ [REDACTED]	0.61	\$ [REDACTED]
	5 years	\$ [REDACTED]	0.41	\$ [REDACTED]
Utility values	Chouaid C et al., 2013	\$ [REDACTED]	0.71	\$ [REDACTED]
	Khan I et al., 2015	\$ [REDACTED]	0.69	\$ [REDACTED]
Treatment duration	<i>Using progression-free status as proxy for time on treatment</i>	\$ [REDACTED]	0.79	\$ [REDACTED]
Subsequent therapy	<i>Set nivolumab use to 0% in the durvalumab arm</i>	\$ [REDACTED]	0.79	\$ [REDACTED]
Multivariate	LogLogistic for OS, exponential for PFS, Chouaid 2013 utilities	\$ [REDACTED]	0.49	\$ [REDACTED]
	Weibull for OS, exponential for PFS, Chouaid 2013 utilities	\$ [REDACTED]	0.48	\$ [REDACTED]
	Gompertz for OS, exponential for PFS, Chouaid 2013 utilities	\$ [REDACTED]	0.37	\$ [REDACTED]

Source: Table 3.9.1, pp137-139 of the submission. ICER = incremental cost-effectiveness ratio; QALY = Quality Adjusted life year; Note: sensitivity analyses conducted during the evaluation are *italicized*.

The redacted table shows ICERs in the range of \$45,000/QALY - \$75,000/QALY and \$105,000/QALY - \$200,000/QALY.

6.31 Sensitivity analyses in which the overall survival data for the durvalumab and placebo arms were fitted independently had a marked impact on the ICER, with estimates ranging from \$105,000/QALY - \$200,000/QALY for independently fitted log-logistic curves to \$150,492/QALY for independently fitted Gompertz curves. When combined with using an exponential function fitted to PFS curves and alternative utility values sourced from Chouaid C et al., 2013, the ICERs ranged from \$105,000/QALY - \$200,000/QALY.

6.32 The PBAC considered that there was a high degree of uncertainty associated with all of the extrapolations presented in the submission, due to the limited follow up duration in the trial, concern that the use of subsequent therapies in the trial may not match Australian clinical practice and the observation that patients diagnosed in Australia may be, on average, older than the population enrolled into the PACIFIC trial (and would therefore be exposed to a higher rate of background mortality). The PBAC noted that the ICER is highly sensitive to the selection of parametric function. The PBAC noted that using Gompertz extrapolations resulted in a crossing of the

extrapolated curves at approximately 7.5 years, and considered the analysis to be overly conservative.

6.33 The Pre-PBAC response presented a revised price for durvalumab and included re-estimated ICERs for the base case and selected sensitivity analyses. These are presented in Table 13.

Table 13: Results of sensitivity analyses with the price proposed in the pre-PBAC response.

Analyses		Incremental cost*	Incremental QALY	ICER
Base case		\$ [REDACTED]	0.79	\$ [REDACTED]
Overall survival	Log-logistic for both curves	\$ [REDACTED]	0.55	\$ [REDACTED]
	Weibull for both curves	\$ [REDACTED]	0.53	\$ [REDACTED]
	Gompertz for both curves	\$ [REDACTED]	0.41	\$ [REDACTED]
	Log-logistic – Dependent	\$ [REDACTED]	0.64	\$ [REDACTED]
	Weibull – Dependent	\$ [REDACTED]	0.69	\$ [REDACTED]
	Gompertz – Dependent	\$ [REDACTED]	0.64	\$ [REDACTED]
Progression-free survival	Exponential for both curves	\$ [REDACTED]	0.78	\$ [REDACTED]
	Exponential – Dependent	\$ [REDACTED]	0.78	\$ [REDACTED]
Time horizon	15 years	\$ [REDACTED]	1.05	\$ [REDACTED]
	20 years	\$ [REDACTED]	1.20	\$ [REDACTED]
	7.5 years	\$ [REDACTED]	0.61	\$ [REDACTED]
	5 years	\$ [REDACTED]	0.41	\$ [REDACTED]
Utility values	Chouaid C et al 2013	\$ [REDACTED]	0.71	\$ [REDACTED]
	Khan I et al 2015	\$ [REDACTED]	0.69	\$ [REDACTED]
Subsequent therapy	Set nivolumab use to 0% in the durvalumab arm	\$ [REDACTED]	0.79	\$ [REDACTED]

Source: Table 2, Pre-PBAC response. ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years.

The redacted table shows ICERs in the range of \$15,000/QALY - \$45,000/QALY to \$105,000/QALY - \$200,000/QALY.

6.34 The reduction in the price proposed in the Pre-PBAC response resulted in a reduction in the base case ICER of 25%.

Drug cost/patient/course

- 6.35 At the initially proposed price, the cost of durvalumab was stated by the submission to be \$ [REDACTED] per administration. With a maximum total number of administrations of 26 (every two weeks for 12 months), the resulting total cost per course was \$ [REDACTED]. When the cost associated with intravenous administration was considered, the total cost per treatment increased to \$ [REDACTED]. This differs to the costs estimated in the model of \$ [REDACTED] as a number of patients died or progressed before 12 months, so they did not receive 26 administrations. The average number of administrations used in the model and financial estimates is 17.75 (35.5 weeks of treatment).
- 6.36 The cost per patient per 12 months applying the Pre-PBAC revised price per administration of durvalumab (\$ [REDACTED]) was \$ [REDACTED], including the cost of administration. The estimated cost per course, applying the model estimated rate of treatment discontinuation, is \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.37 The submission's initial estimates of use and financial implications are presented in Table 14. The DUSC of PBAC provided advice on the estimated extent of use and financial implications on this item.
- 6.38 The PBAC noted that the DUSC considered the estimates of utilisation presented in the submission to be inaccurate. The main issues identified by the DUSC were:
- The proportion of NSCLC of all lung cancers is likely to be closer to 80% than the 70.3% applied in the estimates.
 - No justification was provided for the estimate of the proportion of patients undergoing first-line chemoradiation. The submission assumed that 70%, 80% and 90% of eligible patients would receive chemoradiation in year 1, year 2 and years 3-6. The DUSC did not agree that the numbers of patients receiving chemoradiation would substantially change with the introduction of durvalumab. The DUSC considered that the proportion of patients receiving chemoradiation was reasonable for year 1, but was overestimated for subsequent years.

Table 14: Estimated use and financial implications (at effective price prior to revised price in Pre-PBAC response)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Treated patients	████	████	████	████	████	████
Total prescriptions ^a	████	████	████	████	████	████
Estimated financial implications of durvalumab						
Cost to PBS/RPBS	\$████	\$████	\$████	\$████	\$████	\$████
Co-payments	\$████	\$████	\$████	\$████	\$████	\$████
Cost to PBS/RPBS less co-payments	\$████	\$████	\$████	\$████	\$████	\$████
Net financial implications						
Net PBS/RPBS cost	\$████	\$████	\$████	\$████	\$████	\$████
MBS costs	\$████	\$████	\$████	\$████	\$████	\$████
Total costs to government	\$████	\$████	\$████	\$████	\$████	\$████

^a Assuming 17.75 scripts per year as estimated by the submission.

Source: Tables 4.2.1-4.2.3, 4.2.6 4.2.7, 4.2.9, and 4.5.2, pp153-161 of the submission. MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS/RBPS would be more than \$100 million per year.

6.39 The submission initially estimated that the total cost to Government would be more than \$100 million in year 6. However, the DUSC noted that the financial implications did not account for cost-offsets associated with the lower use of subsequent immunotherapies.

6.40 The Pre-PBAC response included a revised estimated use and financial implications based on applying the following changes as well as the lower price offered as part of the Pre-PBAC response:

- 80% of lung cancers are assumed to be NSCLC.
- Proportion of patients receiving first line chemoradiation 70% in year 1, 75% in year 2 and 80% in years 3-6.

The Pre-PBAC response did not include cost-offsets from later line immunotherapy use.

The PBAC considered the DUSC advice on the proportion of patients who would receive first-line chemoradiation to be reasonable.

The initial and revised financial implications calculated by the sponsor are presented in Table 15.

Table 15: Estimated use and financial implications following DUSC advice, applying the effective price in the submission and the revised effective price in the Pre-PBAC response

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Treated patients	█	█	█	█	█	█
Total prescriptions ^a	█	█	█	█	█	█
Estimated financial implications of durvalumab (submission proposed effective price)						
Cost to PBS/RPBS (less co-payment)	\$█	\$█	\$█	\$█	\$█	\$█
Cost to government	\$█	\$█	\$█	\$█	\$█	\$█
Estimated financial implications of durvalumab (Pre-PBAC proposed effective price)						
Cost to PBS/RPBS (less co-payment)	\$█	\$█	\$█	\$█	\$█	\$█
Cost to government	\$█	\$█	\$█	\$█	\$█	\$█

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS/RPBS would be \$60 - \$100 million per year.

Quality Use of Medicines

- 6.41 The submission stated that the sponsor would undertake to provide appropriate education to the clinical community about the drug, its use and appropriate management of any adverse event experienced by patients as part of the launch of durvalumab.
- 6.42 The submission stated no post-marketing surveillance studies were planned.

Financial Management – Risk Sharing Arrangements

- 6.43 No risk sharing arrangements (RSA) were proposed by the submission. The PSCR stated that the sponsor was open to managing uncertainty in expected use of durvalumab through Commonwealth expenditure caps within a RSA.

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 an adjuvant (consolidation) treatment for Stage III non-small-cell lung cancer (NSCLC) in patients who have not progressed following chemoradiotherapy. The PBAC noted that some patients (~25%) are cured by chemo-radiotherapy and hence consolidation treatment with durvalumab would expose this group of patients to treatment without benefit. The PBAC however acknowledged that adjuvant treatment with durvalumab may reduce the risk of recurrence of NSCLC in some patients who have not been cured by chemo-radiotherapy. However, given the immaturity of the trial data and the unknown impact of subsequent treatment with an immunotherapy agent on progression, the extent of effect on overall survival could not be determined. The Committee considered that the uncertainty surrounding the

magnitude of benefit of durvalumab in this setting resulted in a highly uncertain and potentially very high incremental cost-effectiveness ratio. The PBAC also noted the high total cost of subsidising durvalumab in this setting.

- 7.2 The PBAC considered the proposed listing was appropriate, but agreed with the ESC that a maximum treatment duration of 12 months should be included to reflect the key study. The PBAC also considered that it was appropriate for the restrictions for all 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.
- 7.3 The PBAC agreed that best supportive care (placebo) was the appropriate comparator.
- 7.4 The PBAC noted that overall survival in the PACIFIC trial was immature, with median overall survival not yet reached in the durvalumab arm. The PBAC acknowledged there was an incremental improvement in overall survival that favoured patients receiving durvalumab in the trial, however the magnitude of the difference in overall survival beyond the trial duration was uncertain.
- 7.5 The PBAC noted that the use of durvalumab may affect the subsequent efficacy of PD-(L)1 therapies, and would affect the usage of PD-(L)1 agents in the metastatic/recurrent setting. The PBAC agreed with its ESC that the proportion of patients receiving subsequent PD-(L)1 therapies in the PACIFIC trial will not reflect the use of immunotherapies in later disease stages in the Australian setting if durvalumab is subsidised, particularly if subsidy is limited to one course of PD-(L)1 immunotherapy as recommended above. The PBAC noted that this difference affects the applicability of the PACIFIC trial results, possibly affecting incremental overall survival as use of PD-(L)1 therapies upon progression in the active and placebo arms of the PACIFIC trial was different to what can be expected in Australia.
- 7.6 The PBAC noted that only 8% of patients in the key study were older than 70 years, and that in Australian clinical practice, this proportion is likely to be higher. The PBAC considered that the overall survival gains may be reduced in a population that is, on average, older and hence is subject to competing mortality from other diseases.
- 7.7 The PBAC considered the choice of extrapolation to be highly uncertain 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.

- 7.8 The PBAC noted that the economic model assumed an additional 13% of patients entering the model would remain alive at 10 years following treatment with durvalumab compared with standard of care. The estimate was based on an average of 40 months follow up in the key study, at which time median OS had not been reached in the durvalumab arm, and represents more than a trebling of survival at 10 years (18% in the durvalumab arm vs 5% in the placebo arm). The PBAC considered that the absolute gain in survival would likely reduce with further follow-up.
- 7.9 The PBAC noted that the ICER was sensitive to the choice of parametric extrapolation for overall survival and considered the model time horizon was poorly justified in the context of this uncertainty. The PBAC agreed that an alternative extrapolation may be more plausible, particularly as the log-logistic function used in the durvalumab in the base case may not adequately capture the increasing rate of background mortality over the model time horizon.
- 7.10 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, and they likely reflect differences in the earlier portions of OS data.
- 7.11 The PBAC agreed with the ESC that the utilities derived from the PACIFIC trial are 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.
- 7.12 Overall, the PBAC was concerned that the modelled benefit beyond the duration of the trial is likely overestimated, and that the ICER was consequently underestimated.
- 7.13 The PBAC noted the high estimated financial impact of subsidising durvalumab for the proposed listing, although 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 risk sharing arrangements (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.
- 7.14 The PBAC advised the Minister examine the potential for a broad PBS subsidy listing for PD-(L)1 inhibitors for NSCLC, as substantial evidence and experience is now available for four PD-(L)1 medicines in this setting. The PBAC considered there is potential for a NSCLC listing that allows patients of WHO performance status 0 and 1 access to a single course of treatment with a PD-(L)1 inhibitor, irrespective of disease stage (unresectable stage III or IV), biomarker status, line of treatment (adjuvant, 1st or later line), and with or without concomitant cytotoxic therapy. This would allow

the decision regarding timing the PD-(L)1 inhibitor to be determined by the clinician and patient. The PBAC noted a lack of robust evidence to support the efficacy of sequential courses of PD-(L)1 checkpoint inhibitors, and considered limiting treatment with a PD-(L)1 to once per lifetime appropriate at this time.

7.15 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.