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

1 Purpose of Application

1.1 The resubmission requested Section 100 Authority Required (Streamlined) (Efficient Funding of Chemotherapy) listing of durvalumab for the treatment of unresectable Stage III non-small cell lung cancer (NSCLC) for patients whose disease has not progressed following chemoradiation therapy (CRT).

1.2 The resubmission aimed to address issues raised by the PBAC in its July 2019 rejection of durvalumab for this indication.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are in italics and deletions are in strikethrough.

2.2 The resubmission proposed a maximum amount of 1120 mg; however, the maximum amount for medicines listed as Section 100 (Efficient Funding of Chemotherapy) items with weight-based dosing generally reflects the dose for a 120 kg patient at the maximum recommended dose (1.2 mg per kg).

2.3 In its Pre-PBAC response, the Sponsor noted the Secretariat's comments relating to the restriction wording and maximum amount and had no objection to the proposed changes .

2.4 The PBAC previously considered it would be clinically appropriate to limit patients to one course of treatment with PD-(L)1 inhibitors per lifetime. The PBAC previously noted that the current restrictions for first-line and second-line treatment of Stage IV NSCLC included sufficient provisions to ensure that the PBS does not subsidise sequential immunotherapy for NSCLC (paragraph 7.15, durvalumab Public Summary Document (PSD), July 2019 PBAC meeting). The PBAC previously noted that should any PD-(L)1 inhibitors be listed in an earlier disease stage, additional restriction wording for all PD-(L)1 inhibitors may be warranted (paragraph 6.10, pembrolizumab PSD, July 2018 PBAC meeting). Flow-on changes to PBS restrictions for PD-(L)1 inhibitors in first-line Stage IV (metastatic) NSCLC and second-line locally advanced or metastatic NSCLC are provided in Section 6.

Name, Restriction, Manner of administration and form	Max. amount	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DURVALUMAB Solution concentrate for I.V. infusion 120 mg/ 2.4 mL; 10 mL 500 mg/ 10 mL; 10 mL	*1200mg*	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 {Related Benefits}
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 Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒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 Patient must have a WHO performance status of 0 or 1 AND *Patient must not have previously received PBS-subsidised treatment with this drug for this condition* ~~Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or programmed cell death ligand-1 (PD-L1) inhibitor.~~ ~~Patient can only be administered one course of treatment with PD-1/PD-L1 inhibitors per life time~~ AND ~~The treatment must be the sole PBS-subsidised treatment for this condition~~ *The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition* Continuing ~~Patient must have stable or responding disease~~ *Patient must not have developed disease progression while being treated with this drug for this condition* AND ~~Patient must have previously been issued with an Authority prescription for this indication~~ *Patient must have previously received PBS-subsidised treatment with this drug for this condition* AND ~~The treatment must be the sole PBS-subsidised treatment for this condition~~ *The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition* AND *The treatment* must not exceed 12 months *duration* ~~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 received *non-PBS subsidised* treatment with this drug for this condition prior to [DATE] 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 AND ~~The condition must not have progressed while receiving PBS-subsidised treatment with this drug for this condition~~. *Patient must not have developed disease progression while being treated with this drug for this condition* AND ~~The treatment must be the sole PBS-subsidised treatment for this condition~~ *The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition*
Administrative Advice:	No increase in the maximum number of repeats will be authorised. Special pricing arrangement apply *Note (applies to 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"*

3 Background

Registration status

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

Previous PBAC consideration

3.2 The PBAC considered two previous submissions for durvalumab for the treatment of patients with unresectable stage III NSCLC whose disease has not progressed following chemoradiation therapy (November 2018 and July 2019).

3.3 The PBAC previously considered that, although the data remain immature, the claim that durvalumab was of superior comparative effectiveness versus 'watch-and-wait' monitoring plus best supportive care (best supportive care) was reasonable. The PBAC previously considered that durvalumab had inferior comparative safety compared to best supportive care and that overall, the claim of a manageable safety profile was reasonable.

3.4 The July 2019 resubmission was rejected, with the PBAC advising that any resubmission could be a minor resubmission and would be required to address issues around the estimated incremental cost-effectiveness ratio (ICER), patient estimates, overall financial implications related to grandfathered patients and the cost offsets associated with avoiding subsequent lines of immunotherapy. The PBAC considered the ICER, based on the PBAC's preferred assumption, was high and likely underestimated. The PBAC considered that a reasonable base case ICER in this treatment setting would be less than $45,000 - $75,000 per quality adjusted life year (QALY), noting the uncertainties surrounding the continued immaturity of the clinical data and the uncertainty regarding the appropriateness of the utilities (paragraphs 7.10 & 7.11, durvalumab PSD, July 2019 PBAC meeting).

3.5 A summary of the outstanding matters of concern from the July 2019 consideration are provided in the table below.

Table 1: PBAC matters of concern in previous consideration (July 2019)

Component	Matters of concern (durvalumab PSD, July 2019 PBAC meeting)	How the resubmission addresses it
Requested listing	PBAC Secretariat recommended change to DPMA from 1240mg to 1200 mg (paragraph 2.1). Changes to clinical criteria for durvalumab restrictions (paragraph 2.1, 2.3, 2.5).	Changed DPMA to 1120 mg. Addressed
Requested price	AEMP: $[redacted]/500 mg vial	AEMP: $[redacted]/500 mg vial ([redacted]% reduction)
Economic evaluation	The PBAC considered there were significant uncertainties with both the ITT and RPSFT economic models that likely underestimated the ICER. The PBAC considered that the respecified base case incorporating the effective price and adjusted duration of treatment for nivolumab, as well as the changes for convergence and extrapolation (paragraph 7.7), provided a more appropriate basis for determining cost-effectiveness. Re-specified base case ICER=$[redacted](ITT) and $[redacted] (RPSFT-adjusted) using published nivolumab price.	ICER= $[redacted]/QALY (RPSFT-adjusted) - $[redacted]/QALY (ITT) The following changes were made to the economic model: • Extrapolation of KM OS curves from 40 months (paragraph 6.46) • Convergence of KM PFS and OS curves beginning Year 5 with full convergence by Year 10 (paragraph 6.46) • Subsequent nivolumab duration of treatment changed from 7.5 to 12 doses (paragraph 6.34) • nivolumab discount assumption of [redacted]% • durvalumab effective price per mg changed to $[redacted]
Utilisation/ Overall financial impact	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. 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 (paragraph 7.14). The PBAC considered the financial estimates for grandfathered patients required revision 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).	The following changes were made to the utilisation (Section 4) model: • Uptake of CRT to 70% all years (paragraph 6.53, 7.13) • Uptake of durvalumab to 90% in all years (paragraph 6.53, 7.13) Assumed that 70% of progressed patients treated with durvalumab receive subsequent immunotherapy costs offset as they are no longer eligible for immunotherapy in later stage disease. The minor resubmission increased the number of expected grandfathered patients by November 2019 to [redacted], however no adjustment was made to reduce treatment duration, therefore the cost per patient is overestimated.

AEMP approved ex-manufacturer price; CIC committee in confidence; CRT chemoradiation therapy; DPMA dispensed price for maximum amount; ICER incremental cost effectiveness ratio; ITT intention to treat; KM Kaplan Meier; OS overall survival; QALY quality adjusted life year; RPSFT rank preserving structural failure of time

Source: Compiled during the evaluation. Paragraph references refer to the durvalumab PSD, July 2019 PBAC meeting.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (2), and organisations (2) via the Consumer Comments facility on the PBS website. The comments supported the listing of durvalumab based on patient experience and its potential to be considered a treatment with curative intent.

4.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the durvalumab resubmission, 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) 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 the progression free survival (PFS) outcome compared with best supportive care (BSC).

Economic analysis

4.4 The minor resubmission presented a re-specified economic model for an intention to treat (ITT) population and a rank preserving structural failure of time (RPSFT)-adjusted analysis, consistent with the multivariate analysis considered reasonable by the PBAC in July 2019.

4.5 The re-specified economic model in the minor resubmission converged PFS and overall survival (OS) from 5 years to 10 years, extrapolated OS from 40 months in both treatment arms and adjusted the duration of treatment with nivolumab from 7.5 to 12 doses as advised by the PBAC (paragraph 6.46 & 6.47, durvalumab PSD, July 2019 PBAC meeting). The model assumed a [redacted]% rebate on the published price of nivolumab.

4.6 As with the July 2019 resubmission, the ITT analysis assumed that 22% and 46% of progressed patients treated with durvalumab and BSC respectively received subsequent treatment with another PD-(L)1 inhibitor. The RPSFT-adjusted analysis assumed 0% and 100% of progressed patients treated with durvalumab and BSC respectively received subsequent treatment with another PD-(L)1 inhibitor.

[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

4.7 The PBAC considered that a reasonable base case ICER in this treatment setting would be less than $45,000 - $75,000 per QALY (paragraph 7.11, durvalumab PSD, July 2019 PBAC meeting).

4.8 The re-specified economic models resulted in an ICER of between $15,000 - $45,000 (RPSFT-adjusted analysis) and $45,000 - $75,000 per QALY (ITT analysis) (Table 2) (applying the published price of nivolumab with an assumed [redacted]% discount). The ICERs applying the effective nivolumab price are provided in paragraph 4.10.

4.9 The resubmission also presented ICERs for the ITT analysis and RPSFT-adjusted analysis assuming post-progression PD-(L)1 use in 0% of progressed patients in the durvalumab treatment arm and 70% of progressed patients in the BSC treatment arm (Table 2) (to provide consistency with the financial estimates). These analyses changed the costs only and did not change the outcomes.

Table 2: Results of the re-specified economic evaluation with and without adjustments for subsequent PD-(L)1 use

	Cost			Outcomes			ICER ($/QALY)
	Durvalumab	BSC	Incremental	Durvalumab	BSC	Incremental	
ITT population analysis							
Re-specified model with subsequent PD-(L)-1 use: Durvalumab = 22% and BSC = 46% of progressed patients	$[redacted]	$[redacted]	$[redacted]	3.08	2.45	0.63	$[redacted]
Re-specified model with subsequent PD-(L)-1 use: Durvalumab = 0% and BSC = 70%[a] of progressed patients	$[redacted]	$[redacted]	$[redacted]	3.08	2.45	0.63	$[redacted]
RPSFT-adjusted analysis							
Re-specified model with subsequent PD-(L)-1 use: Durvalumab = 0% and BSC = 100% of progressed patients	$[redacted]	$[redacted]	$[redacted]	3.07	2.59	0.48	$[redacted]
Re-specified model with subsequent PD-(L)-1 use: Durvalumab = 0% and BSC = 70%[a] of progressed patients	$[redacted]	$[redacted]	$[redacted]	3.07	2.59	0.48	$[redacted]

Source: Attachment 2 Imfinzi (durvalumab) Economic Evaluation – ITT - minor.xlsx worksheet "Results" and Attachment 3 Imfinzi (durvalumab) Economic Evaluation – RPSFT - Minor.xlsx worksheet "Results"
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
a: The absolute change in the use of subsequent PD-(L)1 inhibitors from that observed in PACIFIC trial is proportionally re distributed across the other categories to ensure that the total use of subsequent therapies remains unchanged.

The redacted table shows ICERs in the range of $15,000/QALY – $75,000/QALY.

4.10 The minor resubmission considered the ITT analysis with the costs adjusted for subsequent PD-(L)1 use in progressed patients, with an ICER of $15,000/QALY - $45,000/QALY, to be the most appropriate base case for consideration by the PBAC. This analysis changed the costs in both treatment arms but did not change the outcomes in either treatment arm. Decreasing the proportion of subsequent PD-(L)1 use in progressed patients in the durvalumab arm from 22% to 0% would be expected to result in a lower survival benefit. Increasing the proportion of subsequent PD-(L)1 use in the BSC arm from 46% to 70% would be expected to result in a higher survival benefit. Overall, the incremental benefit of treatment with durvalumab would be expected to be lower and the ICER from this analysis ($15,000/ QALY - $45,000/QALY) is likely to be an underestimate of the true ICER.

Committee-in-Confidence information

4.11 The ICERs for the base case (ITT) and RPSFT-adjusted scenario analyses incorporating the effective nivolumab price (ex-manufacturer prices of $[redacted] per 40 mg/4 mL vial and $[redacted] per 100 mg/10 mL vial) were $[redacted] and $[redacted], respectively. The PBAC noted the cost of treatment with PD-(L)1 inhibitors after disease progression was based on the nivolumab treatment cost per course but there were a number of other PD-(L)1 inhibitors available (atezolizumab, pembrolizumab) [redacted]

End Committee-In-Confidence information

For more detail on PBAC's view, see section 5 PBAC outcome.

Drug cost/patient/course: $[redacted]

4.12 The minor resubmission estimated that the cost of durvalumab per prescription was $[redacted] (effective) and $[redacted] (published). This was based on a revised effective approved ex-manufacturer price (AEMP) per vial of $[redacted] for 120 mg/2.4 mL injection and $[redacted] for 500 mg/10 mL injection.

4.13 Using the effective drug cost per prescription ($[redacted]) and an average of 17.75 prescriptions per patient, the estimated cost per patient is $[redacted]. This compares with $[redacted] per course in the July 2019 submission ($[redacted]/500mg and $[redacted]/120mg effective price per vial).

Estimated PBS usage & financial implications

4.14 The minor resubmission estimated that less than 10,000 patients would be eligible for grandfathering at the time of PBAC consideration in November 2019.

Accordingly, the revised estimates for grandfathered patient numbers in Year 1 were increased to less than 10,000(from less than 10,000 in the July 2019 resubmission).

4.15 In July 2019, the PBAC noted a reduced cost of treatment for grandfathered patients should be applied, to take into account the treatment already received (paragraph 7.16, durvalumab PSD, July 2019 PBAC meeting). As with the July 2019 resubmission, the minor resubmission calculated the cost of treatment for the grandfathered patients based on the mean duration of treatment (35.5 weeks, 17.75 prescriptions) from the PACIFIC trial. In its pre-PBAC response , the Sponsor provided revised financial estimates assuming grandfathered patients are treated for 17.75 weeks (8.875 prescriptions).

4.16 Based on the PBAC's advice in July 2019, the minor resubmission updated its estimated total number of eligible patients for durvalumab treatment, revising the CRT uptake rate to 70% for all years, and adjusting the durvalumab uptake rate from 90% in Year 1 and 95% in Year 2 to 6 to 90% for all years. The PBAC considered the uptake of durvalumab in Year 1 should be lower to account for the fact that not all eligible (non-grandfathered) patients will receive a full treatment course in Year 1 as some patients will commence treatment later in the year. The PBAC considered an uptake of 75% of that anticipated (i.e., 75% x 90%) in Year 1 would be more reasonable (see Table 4 for revised patient numbers).

4.17 The minor resubmission estimated a net cost to the health budget of $30 - $60 million in Year 6 of listing, with a total net cost of more than $100 million over the first 6 years of listing (applying the published price of nivolumab with an assumed [redacted]% discount). Revised financial estimates were included in the Sponsor's pre-PBAC response and are presented in Table 3 below.

4.18 To calculate cost offsets from reduced PD-(L)1 inhibitor use in the Stage IV setting, the total number of patients who would have been treated with a PD-(L)1 inhibitor subsequent to CRT for Stage III disease in each year was estimated using the modelled PFS from the economic evaluation. The resubmission assumed that 70% of progressed patients treated with CRT would have received subsequent treatment with a PD-(L)1 inhibitor. Over 6 years, it was estimated that 57% of the less than 10,000 patients treated in Year 1 would no longer require PD-(L)1 inhibitor therapy for Stage IV disease. The PBAC previously considered it would be appropriate to assume that 70% of patients who initiate treatment with durvalumab (not just 70% of progressed patients) would avoid subsequent use of PD-(L)1 inhibitors in the Stage IV setting. The pre-PBAC response presented revised financial estimates , assuming that 70% of patients who initiate treatment with durvalumab avoid subsequent use of PD-(L)1 inhibitors rather than only those who progressed following durvalumab treatment (Table 3).

4.19 The revised financial estimates presented in the pre-PBAC response , assuming a reduced treatment duration for grandfathered patients in Year 1 and cost offsets for 70% of patients who initiate treatment with durvalumab, resulted in a net cost of durvalumab to the health budget of $20 - $30 million in Year 1, increasing to $20 - $30 million by Year 6, with a total net cost of more than $100 million over the first 6 years of listing (using the published price of nivolumab with an assumed [redacted]% discount) (Table 3).

Table 3. Revised financial estimates changed duration of treatment for grandfathered patients in Year 1 and cost offsets for 70% of all patients initiating durvalumab treatment

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of durvalumab treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of nivolumab patients with cost offsets (70%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of durvalumab						
Net cost to PBS/RPBS (effective price minus co-payments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net reduction in cost of PD-L1 medicines (at nivolumab rebate of [redacted]%)						
Net cost to PBS/RPBS (effective price)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS (effective price)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to health budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: pre-PBAC response, Table 2, p2

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

For more detail on PBAC's view, see section 5.

Proposed increase in current Risk Sharing Arrangement caps for NSCLC

4.20 In July 2019, the PBAC considered that if durvalumab was to be PBS listed, there would only be a modest increase in the overall number of patients treated for NSCLC, provided sequential use with PD-(L)1 inhibitor therapies was precluded. The PBAC also 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) inhibitor therapies (paragraphs 7.15 & 6.55, durvalumab PSD, July 2019 PBAC minutes).

4.21 The resubmission estimated the number of patients treated with durvalumab who would not be covered by the current Deeds of Agreement for NSCLC.

4.22 Based on the modelled PFS curves at 72 months (6 years), a timeframe considered relevant for the financial estimates, the resubmission estimated approximately 25% of durvalumab treated patients remain progression-free. Of the 75% of patients who have progressed at 72-months, the resubmission assumed approximately 70% would have been candidates for subsequent immunotherapy, which equated to 52% of patients who initiate durvalumab treatment (75%*70% = 52%).

4.23 The PBAC previously noted that some patients (~25%) are cured by CRT (paragraph 6.55, durvalumab PSD, July 2019 PBAC meeting). Therefore, it may be reasonable to assume that 25% of the patients estimated to initiate treatment with durvalumab would not have progressed to Stage IV disease and are not covered by the current Deed(s). In the pre-PBAC response , the Sponsor provided revised estimates assuming 25% of patients who initiate on durvalumab treatment would not have progressed to Stage IV disease and are not already covered by the Deeds of Agreement for NSCLC. The PBAC noted the revised number of durvalumab patients not included in the RSA subsidisation cap in the current Deeds of Agreement for NSCLC presented in Table 4, taking into account a reduced uptake in Year 1 (paragraph 4.16).

Table 4: Estimated incremental increase in patient numbers over the existing risk-sharing arrangement for PD-(L)1 drugs for NSCLC – REVISED

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Total eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab uptake	90% x 75%	90%	90%	90%	90%	90%
Number of durvalumab treated patients	[redacted] eligible [redacted] GF [redacted] total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of durvalumab patients not currently included in RSA caps (25%)	[redacted] eligible [redacted] GF [redacted] total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Year 1: calculated Year 2 to 6: pre-PBAC response, Table 3, p3

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the listing of durvalumab, on the basis that it should be available only under special arrangements under Section 100 (Efficient funding of chemotherapy). The PBAC recommended durvalumab be made available for the treatment of unresectable Stage III NSCLC in patients whose disease had not progressed following CRT, under the circumstances shown in Section 6. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of durvalumab would be acceptable with a small (around 5%) reduction to the price proposed in the resubmission.

5.2 The PBAC was satisfied that durvalumab provides, for some patients, a significant improvement in efficacy over "watch and wait" monitoring plus best supportive care (best supportive care).

5.3 The PBAC recalled that it had previously considered the Sponsor's claims of superior comparative effectiveness (in terms of OS and PFS), relative to best supportive care (BSC) in patients with stage III NSCLC whose disease had not progressed following CRT was reasonable and that the trial data presented demonstrated durvalumab was likely to prolong OS in patients who respond to CRT (paragraph 7.3, durvalumab PSD, July 2019 PBAC meeting).

5.4 The PBAC considered that the minor resubmission had adequately addressed the Committee's concerns from the July 2019 resubmission in relation to the economic evaluation. The PBAC noted the minor resubmission presented a re-specified economic model based on the ITT trial population and a RPSFT-adjusted analysis, consistent with the multivariate analysis considered reasonable by the PBAC in July 2019, as well as incorporating an additional [redacted]% reduction to the price of durvalumab compared to that in the July 2019 resubmission.

5.5 The PBAC recalled that in July 2019, it considered a reasonable base case ICER in this treatment setting would be less than $45,000 - $75,000 per QALY (paragraph 7.11, durvalumab PSD, July 2019 PBAC meeting). The PBAC previously considered that the true ICER is likely to lie between the ITT analysis and the RPSFT–adjusted analysis, however given the uncertainty of the RPSFT–adjusted analysis, the true ICER may be more closely aligned with the ITT analysis (paragraph 7.10, durvalumab PSD, July 2019 PBAC meeting). The PBAC noted the ICERs for the respecified economic model using the effective price for nivolumab (paragraph 4.10) and considered a small (around 5%) reduction to the price proposed in the resubmission was required to ensure durvalumab was of acceptable cost-effectiveness.

5.6 The PBAC reaffirmed its July 2019 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 (paragraph 7.15, durvalumab PSD, July 2019 PBAC meeting). The PBAC previously noted that should any PD-(L)1 inhibitors be listed in an earlier disease stage, additional restriction wording for all PD-(L)1 inhibitors may be warranted (paragraph 6.10, pembrolizumab PSD, July 2018 PBAC meeting). The PBAC considered flow-on restriction changes were required for first-line listings of Stage IV NSCLC (pembrolizumab and atezolizumab), as well as second-line listings in locally advanced or metastatic NSCLC (nivolumab and atezolizumab), to include sufficient provisions to ensure that the PBS does not subsidise sequential immunotherapy for NSCLC.

5.7 The PBAC reaffirmed its July 2019 advice that it was appropriate for durvalumab to share the RSA subsidisation cap in the current Deed(s) of Agreement for locally

advanced/metastatic NSCLC for PD-(L)1 therapies (paragraph 7.15, durvalumab PSD, July 2019 PBAC meeting). The PBAC recalled its previous advice that some patients (~25%) are cured by CRT (paragraph 7.1, durvalumab Public Summary Document, November 2018 PBAC meeting). The PBAC considered that, based on this assumption, 25% of patients who initiate treatment with durvalumab would not have progressed to Stage IV disease (in the absence of durvalumab) and are therefore not covered by the current Deed(s). The PBAC considered it may be reasonable to further increase the cap to account for the small proportion of patients who would have progressed after CRT but would not have been treated with PD-(L)1 inhibitors for Stage IV disease and hence are not covered by the current Deed(s). The PBAC considered this would be the case for less than 5% of patients who initiate treatment with durvalumab. The PBAC noted that assuming 30% (i.e., 25% + 5%) of patients who initiate treatment with durvalumab would not have progressed to Stage IV disease is consistent with applying an offset for 70% of patients who initiate treatment with durvalumab in the financial estimates. The PBAC considered the financial estimates in Table 3 (revised to account for paragraph 4.15 and paragraph 5.8), should be consistent with multiplying the number of eligible patients not covered by the current cap by the durvalumab treatment cost per patient. The cost for the additional grandfathered patients not currently covered by the existing RSA caps should take into account the reduced cost per patient (paragraph 4.14).

5.8 The PBAC noted the revised financial estimates in Table 3 applied the treatment cost per patient for nivolumab to estimate the net reduction in cost of PD-(L)1 inhibitors but there are alternative PD-(L)1 inhibitors available in the first-line and second-line setting (pembrolizumab, atezolizumab). The PBAC noted the PD-(L)1 inhibitor costs for the offset patients (in both the first-line or second-line setting) are already accounted for in current subsidisation caps for NSCLC. The PBAC was also of the view that nivolumab should not be considered the most likely therapy for the purposes of the estimated offset population, as the PBAC has previously considered that the majority of patients were likely to switch to first line treatment with PD-(L)1 inhibitors once these are available.

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

(a) The treatment may not provide a substantial and clinically relevant improvement in efficacy over alternative therapies given the uncertainty in the magnitude of the overall survival benefit (due to immaturity of the clinical data and uncertainty regarding the impact of post-progression treatment with PD-(L)1 inhibitors in the clinical trial).

(b) The treatment is expected to address a high and urgent unmet clinical need.

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

5.10 The PBAC advised that under subsection 101(3BA) of the National Health Act 1953, durvalumab should not be treated as interchangeable on an individual patient basis with any other drugs.

5.11 The PBAC advised that durvalumab was not suitable for prescribing by nurse practitioners.

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

Outcome:
Recommended

6 Recommended Listing

Add new item:

Name, Restriction, Manner of administration and form	Max. amount	№.of Rpts	Proprietary Name and Manufacturer	
DURVALUMAB Solution concentrate for I.V. infusion 120 mg/ 2.4 mL; 10 mL 500 mg/ 10 mL; 10 mL	1200mg	8	Imfinzi	AstraZeneca Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy {Related Benefits}
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 Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒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 Patient must have a WHO performance status of 0 or 1 AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition Continuing Patient must not have developed disease progression while being treated with this drug for this condition AND Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition AND *The* treatment must not exceed 12 months duration Grandfathering The patient must have received *non-PBS subsidised* treatment with this drug for this condition prior to [DATE] 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 AND Patient must not have developed disease progression while being treated with this drug for this condition AND The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition
Administrative Advice:	No increase in the maximum number of repeats will be authorised. Special pricing arrangement apply [For grandfathering restriction only]: 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.

Flow-on Restriction changes

Pembrolizumab- 11494Y (Public)/ 11492W (Private)

Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised Special Pricing Arrangements apply. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
Indication:	Previously untreated Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment Phase:	Initial treatment
Clinical criteria:	~~Patient must not have previously been treated for this condition in the metastatic setting~~ *Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for non-small cell lung cancer* AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have a WHO performance status of 0 or 1 AND The condition must express programmed cell death ligand (PD-L1) with a tumour score of at least 50% in the tumour sample; and The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material AND The treatment must not exceed a total of 7 doses at a maximum dose of 200mg every 3 weeks for this condition under this restriction
Prescribing Instructions:	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised Special Pricing Arrangements apply. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. A patient may only qualify for PBS-subsidised treatment under this restriction once Following completion of the initial PBS subsidised course, further applications for treatment will be assessed under the continuing restriction
Indication:	Previously untreated Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment Phase:	Grandfathering treatment
Clinical criteria:	Patient must not have previously received non-PBS subsidised treatment with this drug for this condition prior to 1 November 2018, AND *Patient must not have received prior PBS-subsidised treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for non-small cell lung cancer.* *AND* Patient must have stable or responding disease

	AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have a WHO performance status of 0 or 1 prior to initiation of non-PBS subsidised treatment with this drug for this condition AND The condition must express programmed cell death ligand (PD-L1) with a tumour score of at least 50% in the tumour sample prior to initiation of non-PBS subsidised treatment with this drug for this condition ; and The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material AND The treatment must not exceed 35 doses in total or up to 24 months of treatment, at a dose of 200mg every 3 weeks, with this drug for this condition

Nivolumab- 11158G (Public) / 11143L (Private)

Administrative Advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment Phase:	Initial treatment
Clinical criteria:	Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for ~~this condition~~ *non-small cell lung cancer*. AND Patient must have a WHO performance status of 0 or 1 AND The treatment must be the sole PBS subsidised treatment for this condition AND The condition must have progressed on or after prior platinum based chemotherapy
Prescribing Instructions:	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated. Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.

Atezolizumab- 11284 (Public) / 11309F (Private)

Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment Phase:	Initial treatment

Clinical criteria:	Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for ~~this condition~~ *non-small cell lung cancer.* **AND** Patient must have a WHO performance status of 0 or 1 **AND** The treatment must be the sole PBS subsidised treatment for this condition **AND** The condition must have progressed on or after prior platinum based chemotherapy
Administrative Advice:	No increase in the maximum number of repeats may be authorised. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. Special Pricing Arrangements apply.

11284 (Public) / 11309F (Private)

Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment Phase:	Initial treatment
Clinical criteria:	Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for ~~this condition~~ *non-small cell lung cancer.* **AND** Patient must have a WHO performance status of 0 or 1 **AND** The treatment must be the sole PBS subsidised treatment for this condition **AND** The condition must have progressed on or after prior platinum based chemotherapy
Administrative Advice:	No increase in the maximum number of repeats may be authorised. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. Special Pricing Arrangements apply.

11807K (Public) / 11792P (Private)

Administrative Advice:	No increase in the maximum number of repeats may be authorised. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. Special Pricing Arrangements apply.
Indication:	Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment Phase:	Initial treatment 1
Treatment criteria:	Patient must be undergoing combination treatment with bevacizumab and platinum-doublet chemotherapy **AND**

Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC) **AND** Patient must not have previously been treated for this condition in the metastatic setting ***AND*** *Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for ~~this condition~~ non-small cell lung cancer.* **AND** Patient must have a WHO performance status of 0 or 1 **AND** The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material

Treatment Phase:	Initial treatment 2
Treatment criteria:	Patient must be undergoing combination treatment with bevacizumab and platinum-doublet chemotherapy **AND**
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC) **AND** Patient must have a WHO performance status of 0 or 1 **AND** Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material **AND** Patient must have progressive disease following treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) OR an anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) **AND** Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for ~~this condition~~ *non-small cell lung cancer*

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

7 Context for Decision

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

8 Sponsor's Comment

The sponsor had no comment.