

7.07 NIVOLUMAB,

Injection concentrate for I.V. infusion 40 mg in 4 mL

Injection concentrate for I.V. infusion 100 mg in 10 mL

Opdivo[®],

Bristol-Myers Squibb Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor resubmission sought to remove the rebate for patients initiating treatment at the age of 75 years or older in the Deed of Agreement (the Deed) for nivolumab for the treatment of non-small cell lung cancer (NSCLC) following progression or after prior chemotherapy (herein referred to as 2L NSCLC).
- 1.2 The resubmission sought to address the PBAC's previous concerns about the incremental effectiveness of nivolumab in patients aged 75 years or older.

2 Background

Previous PBAC consideration

- 2.1 The PBAC considered nivolumab for the treatment of squamous NSCLC and non-squamous NSCLC with progression on or after prior chemotherapy at its March 2016 (not recommended) and November 2016 (deferred) PBAC meetings. Nivolumab was subsequently recommended for 2L NSCLC at the March 2017 PBAC meeting.
- 2.2 A summary of prior PBAC considerations is provided below.

Table 1: Previous PBAC considerations

Meeting date	Request	Outcome	Detail
March 2016	<p>Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the treatment of locally advanced or metastatic squamous NSCLC with progression on or after prior chemotherapy.</p> <p>Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the treatment of locally advanced or metastatic non-squamous NSCLC with progression on or after prior chemotherapy.</p>	Not recommended	<p>The PBAC decided not to recommend on the basis that acceptable cost-effectiveness had not been adequately demonstrated. The PBAC considered that the economic model presented in the submission included numerous assumptions that favoured nivolumab, and that the resulting incremental cost-effectiveness ratio was too high and likely to be significantly underestimated.</p> <p>Further, for the non-squamous submission, the PBAC considered that the cost-effectiveness against pemetrexed, which the PBAC considered to be a relevant main comparator, could not be determined because an economic comparison</p>

Public Summary Document – March 2021 PBAC Meeting

			was not presented; and that acceptable cost-effectiveness against the submission's nominated main comparator, docetaxel, had not been adequately demonstrated.
November 2016	<p>Resubmission to request a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the treatment of locally advanced or metastatic squamous NSCLC with progression on or after prior chemotherapy.</p> <p>Resubmission to request a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the treatment of locally advanced or metastatic non-squamous NSCLC with progression on or after prior chemotherapy.</p>	Deferred	The PBAC deferred its decision as there were concerns regarding the variation in the extent of effectiveness in patients over 75 years, especially given the high ICERs presented in the resubmission and doubts about the ability of the proposed RSA to achieve the sponsor's intended effect on these ICERs. The PBAC requested that the Department hold discussions with the sponsor in order to develop a proposal for a Managed Entry Scheme (MES) to address these concerns.
March 2017	To address issues raised by the PBAC in its November 2016 deferral of nivolumab for NSCLC.	Recommended	The PBAC recommended the Authority Required (STREAMLINED) listing of nivolumab for the treatment of locally advanced or metastatic, squamous or non-squamous, non-small cell lung cancer (NSCLC). The PBAC considered that, with its suggested modifications, the risk sharing arrangements proposed by the sponsor adequately addressed concerns regarding the possible variation in the extent of effectiveness in patients aged 75 years or older, and uncertainties regarding the ICERs presented in the November 2016 submissions, the overall numbers using nivolumab in NSCLC, the risk of leakage of nivolumab outside of the intended restriction, and the duration of nivolumab treatment.

Source: Public Summary Documents for nivolumab: March 2016, November 2016, March 2017

2.3 Nivolumab was listed on the PBS for 2L NSCLC from 1 August 2017.

2.4 In November 2016, the PBAC was concerned about the variation in the extent of effectiveness of nivolumab in patients over 75 years of age, with the prespecified subgroup analyses of CA209-057 suggesting that nivolumab may not have an incremental benefit over docetaxel in patients aged over 75 years (unstratified HR 0.90, 95% CI: 0.43, 1.87), and the pre-specified subgroup analyses of CA209-017 suggesting that nivolumab may possibly be inferior to docetaxel in patients aged over 75 years (unstratified HR 1.85, 95% CI: 0.76, 4.51). The PBAC also noted the abstract

Public Summary Document – March 2021 PBAC Meeting

of an analysis (Landre et al, J Clin Oncol 34, 2016 (suppl; abstr 3070)) which indicated that the survival benefit of nivolumab in patients older than 75 years appears uncertain. The PBAC had considered that it was plausible that nivolumab, and other immunotherapies relying on stimulating an immune response, may prove to be less effective in older patients whose immune systems may no longer be able to respond to such a stimulus. The PBAC previously considered this likely reduced effectiveness in patients over 75 years of age to be a significant issue, given that a large proportion of patients in Australian clinical practice would belong to this age group, with over 50% of patients being over the age of 70 at diagnosis (Nivolumab Public Summary Documents, November 2016, item 7.06 (para 7.6) & 7.07 (para 7.7)).

- 2.5 In March 2017, the PBAC considered that the meta-analyses of randomised trials of nivolumab provided in the sponsor’s submission, in both NSCLC alone and combined with other cancers, did not adequately resolve the uncertainties regarding the comparative effectiveness of nivolumab in patients aged 75 years or older, and considered that the other analyses presented were less informative (Nivolumab Public Summary Document, March 2017, item 4.02, para 6.44).
- 2.6 In its March 2017 recommendation, the PBAC advised that the sponsor’s proposed RSA would address its concerns regarding the uncertainty around age as a treatment effect modifier in nivolumab treatment. The Deed for nivolumab includes an annual rebate for patients aged 75 years or older, consistent with the March 2017 PBAC advice, which applies if the proportion of patients first supplied nivolumab in that year is over ██████%.
- 2.7 The threshold of ██████% was proposed by the sponsor in its pre-PBAC response to the March 2017 PBAC meeting, based on the proportion of squamous NSCLC patients aged 75 years or over upon treatment initiation in the sponsor’s Australian named patient program. The rebate of ██████% was calculated as the rebate down to the cost of the weighted comparator price of docetaxel and pemetrexed.
- 2.8 The following outlines the amounts that have been payable in relation to the above rebate:

Table 2: ≥75 year old Rebates under current Deed

Year	≥75 year old Rebate	% of patients ≥ 75 years first supplied nivolumab in that Year	No of patients ≥ 75 years first supplied nivolumab in that Year
August 2017 – July 2018	\$ ██████	██████%	█████ ¹
August 2018 – July 2019	\$ ██████	██████%	█████ ²
August 2019 – July 2020	\$ ██████	██████%	█████ ²

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

- 2.9 Nivolumab is subject to RSA subsidisation caps which are shared by all PBS-listed PD-1/PD-L1 inhibitors for NSCLC, namely nivolumab, atezolizumab, pembrolizumab and durvalumab.
- 2.10 Nivolumab with ipilimumab for first-line treatment of squamous Stage IV NSCLC was recommended at the November 2020 PBAC meeting, but not yet listed at the time of the March 2021 PBAC meeting.

3 Requested listing

- 3.1 No change to the current listing was requested.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted that no consumer comments were received for this item.

Equity with other PBS listed immunotherapy agents

- 4.3 The submission requested the removal of the age-related RSA to ensure equity with other PBS listed immunotherapies, stating that “the Sponsor understands that nivolumab is the only immunotherapy listed on the PBS for the treatment of NSCLC (Without driver mutation) with an age-related RSA to address uncertainty in the extent of effectiveness in patients aged 75 years or older”.

Clinical management

- 4.4 The submission claimed that the uptake of nivolumab in patients aged 75 and over potentially reflects growing clinician confidence in the use and outcomes associated with 2L nivolumab in elderly patients, and that the increasing uptake is likely to be affected by the changing treatment landscape.
- 4.5 Since nivolumab was listed for 2L NSCLC in August 2017, several other agents have also been listed on the PBS for NSCLC: atezolizumab (2L NSCLC), pembrolizumab monotherapy (1L NSCLC), atezolizumab + bevacizumab + chemotherapy (1L NSCLC), pembrolizumab + chemotherapy (1L NSCLC) and durvalumab (Stage III NSCLC).
- 4.6 The submission claimed that the relative uptake of nivolumab in elderly patients appears to be increasing since the introduction of pembrolizumab plus chemotherapy.
- 4.7 The submission referred to the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (Planchard et al 2020) which state that “it can be inferred that ORRs and survival are not different between patients ≤ 65 years and those > 65 , based on subgroup analysis of the randomised second-line trials”. The submission also proposed that the absence of age in the National Comprehensive Cancer Network

NSCLC guidelines suggests that NSCLC patients should be treated irrespective of age and based on other factors (e.g. PD-L1 expression and ECOG status).

Clinical evaluation

4.8 The submission presented three main sources of data to support effectiveness of nivolumab in patients aged 75 years or older for 2L NSCLC:

- The United States Food and Drug Administration (FDA) analyses supporting the use of immune-oncology in elderly patients;
- real world evidence assessing the effectiveness of nivolumab; and
- longer term follow up data from the pivotal trials for nivolumab and atezolizumab for 2L NSCLC.

Marur et al (2018) meta-analyses

4.9 The submission presented Marur et al (2018) pooled data from four clinical trials submitted to the FDA in relation to NSCLC trials for nivolumab, pembrolizumab and atezolizumab. The paper states that the analysis suggested that older adults, including those aged over 75, derive similar benefits as younger patients in overall survival with PD-1/PD-L1 blocking antibodies for the treatment of advanced NSCLC.

Table 3: Pooled Kaplan-Meier overall survival by treatment and age group

	PD-1/L1 blocking antibodies			Docetaxel			Difference
	n	Median (mth)	95%CI	n	Median (mth)	95%CI	Median (mth)
<65 years	921	14.5	(10.8, 14.2)	699	8.8	(8.3, 9.9)	5.7
≥65 years	659	14.2	(11.0, 15.3)	545	9.0	(8.3, 9.6)	5.2
≥70 years	300	14.1	(9.7, 15.0)	240	9.2	(8.2, 10.5)	4.9
≥75 years	211	14.7	(9.1, 20.4)	149	9.5	(8.3, 15.5)	5.2

Source: Table 5 minor submission

Abbreviations: CI = confidence interval; mth = month; PD-1 = programmed cell death 1 receptor; PD-L1 = programmed death ligand 1.

References: Marur et al 2018 (Table 3).

Real world evidence

4.10 The submission presented a systematic review identifying real world data relevant to assessing the relative efficacy of nivolumab in 2L NSCLC for the relevant different age groups, which included two studies that collected data from patients in an early access/expanded access program (Italy and Canada) and one study based on a retrospective medical chart review (Japan).

Table 4: List of relevant studies presented as real world evidence

Country	Database	Publication
Italy	Expanded access program	Grossi et al. Use of nivolumab in elderly patients with advanced squamous non-small cell lung cancer: results from the Italian cohort of an expanded access programme. <i>Eur J Cancer</i> 2018; 100: 126-134.
Japan	Electronic health record data	Okishio et al. Nivolumab treatment of elderly Japanese patients with non-small cell lung cancer: sub analysis of a real-world retrospective observational study (CA209-9CR). <i>ESMO Open</i> 2020; 5: e000656. Additional study details available in: Morita et al. Real world effectiveness and safety of nivolumab in patients with non-small cell lung cancer: A multicentre retrospective observational study in Japan. <i>Lung Cancer</i> 2020: 8-18.
Canada	Expanded access program	Juergens et al. Real world benefit of nivolumab in a Canadian non-small cell lung cancer cohort. <i>Curr Oncol</i> 2018; 25: 384-392.

Source: Table 6, minor submission

4.11 A reduced mean OS was reported for patients who were ≥ 75 years of age in Grossi et al (2018). However, the submission contends that the difference was not statistically different from patients aged 65-75 years old, and that the population in the publication had only squamous NSCLC and that the ≥ 75 age subgroup was more likely to have other comorbidities that may have contributed to an increased risk of death.

Table 5: Median overall survival reported in included studies

Characteristic	Median OS (95%CI), mths		
	Grossi et al (2018) n=371	Okishio et al (2020) n=901	Juergens et al (2018) n=472
Total patients			
<65 years	8.6 (5.2, 11.9)	NR	11.50 (9.04, 14.10)
65-<75 years	8.0 (5.6, 10.4)	NR	12.60 (10.97, 17.70)
<75 years	NR	14.7 (12.5, 16.5)	NR
≥ 75 years	5.8 (3.5, 8.1)	12.3 (8.3, 16.0)	12.10 (6.60, NA)
Test for association between age and survival, HR (95% CI)			
Age ≥ 75 vs. 65-<75	1.15 (0.82, 1.61), P=0.42	-	-
Age ≥ 75 vs. <75	-	NR, p=0.3272 (LR test)	-
Age <65 vs. ≥ 75	-	-	0.89 (0.60, 1.44), p=0.57

Source: Table 7, minor submission

Abbreviations: CI = confidence interval; LR = log rank; mths = months; NA = not applicable; NR = not reported; OS = overall survival.

Longer term trial data from pivotal 2L NSCLC trials

4.12 At the time of the initial PBS listing of nivolumab for the treatment of 2L NSCLC, the submission stated that the overall survival data available was relatively immature (17-18 months follow-up) and atezolizumab had not yet been considered by the PBAC for use in this indication. Longer term overall survival data has since been provided for the pivotal clinical trials which supported the existing PBS listings for nivolumab and atezolizumab in 2L NSCLC.

4.13 Details of the trials presented in the submission are provided in the table below.

Public Summary Document – March 2021 PBAC Meeting

Table 6: Trials and associated reports presented in the re-submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
CM017	Brahmer et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer.	<i>New Engl J Med</i> 2015; 373: 123-35.
CM057	Borghaei et al. Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer.	<i>N Engl J Med</i> 2015; 373: 1627-39.
CM017/CM057 pooled	<p>Gettinger et al. Five-year outcomes from the randomized, phase 3 trials CheckMate 017/057: Nivolumab vs docetaxel in previously treated NSCLC.</p> <p>Horn et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: Tow-year outcome from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057).</p> <p>Vokes et al. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases.</p>	<p>Poster presented at <i>Florida Society of Clinical Oncology</i> 2019.</p> <p><i>J Clin Oncol</i> 2017; 35 (35): 3924-3933.</p> <p><i>Annals of Oncol</i> 2018; 29: 959-965.</p>
OAK	<p>Fehrenbacher et al. Updated efficacy analysis including secondary population results for OAK: A randomised phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer.</p> <p>Rittmeyer et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial.</p>	<p><i>J Thorac Oncol</i> 2018; 18 (8): 1156-70.</p> <p><i>Lancet</i> 2017; 389: 255-65.</p>
POPLAR	Fehrenbacher et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial.	<i>Lancet</i> 2016; 387: 1837-46.
OAK/POPLAR pooled	Mazieres et al. 4-year survival in randomised phase II (POPLAR) and phase II (OAK) studies of atezolizumab (atezo) vs docetaxel (doc) in pre-treated NSCLC.	<i>Annals of Oncol</i> 2020; 31 (4): abstract 1271P.

4.14 The submission presented data comparing the longer term overall survival outcomes of nivolumab and atezolizumab across the 2L studies to support the claim that there is no evidence of difference in the primary efficacy outcomes between the treatments, and that conditions should be equitable.

Table 7: Overall survival for patients in the 2L included studies

	% patients treated with ATEZO or NIVO alive					Median OS (95%CI), mths
	1-year	2-year	3-year	4-year	5-year	
OAK	54.7% ³	30.9% ³	NR	14.8% ¹	NR	13.8 (11.8, 15.7) ³
POPLAR	~52% ⁷	32.2% ⁴	18.7% ⁴	15.5% ¹	NR	9.7 (8.6, 12.0) ⁷
CM017/057 ²	48.0%	26.9%	17.1%	14.2%	13.4%	11.1 (9.2, 13.1)
CM017	42% ⁵	23% ⁸	16% ⁹	13.1% ¹⁰	12.3% ¹⁰	9.2 (7.3, 12.6) ⁹
CM057	51% ⁶	29% ⁸	18% ⁹	14.7% ¹¹	14.0% ¹¹	12.2 (9.7, 15.1) ⁹

Source: Table 11 minor submission

Abbreviations: ATEZO = atezolizumab; CI = confidence interval; CM017 = Checkmate017; CM057 = Checkmate 057; mths = months; OS = overall survival; NIVO = nivolumab; NR = not reported.

References: 1. Mazieres et al 2020, 2. Gettinger et al 2020, 3. Fehrenbacher et al 2018, 4. Mazieres et al 2018; 5. Brahmer et al 2015; 6. Borghaei et al 2015; 7. Fehrenbacher et al 2016; 8. Horn et al 2017; 9. Vokes et al 2018 (Fig S3AB); 10. CM017 Clinical Study Report Addendum 04 dated 18 Jul 19 (Section 5.1); 11. CM057 Clinical Study Report Addendum 02 dated 18 Jul 19 (Section 5.1).

4.15 The minor submission stated that longer term follow up data from the pivotal trials (CA209-017) and (CA209-057) for PBS listed IO agents for 2L NSCLC demonstrate comparable median overall survival across the pooled nivolumab trials (CM017/CM057) and OAK trial between the < and ≥65 year old age groups.

Pricing considerations

4.16 Nivolumab was originally recommended for 2L NSCLC on the basis of a risk sharing arrangement intended to address concerns regarding the possible variation in the extent of effectiveness in patient 75 years or older, uncertainties regarding the ICERs presented in the November 2016 submissions, the overall number of patients using nivolumab in NSCLC, the risk of leakage outside the intended population, and the duration of treatment.

4.17 The PBAC recommended an overall cap on patient numbers and cost per patient to ensure that the estimated ICER was not exceeded. The total cost per patient was to be based on an average of █ infusions per patient. It should be noted that Commonwealth expenditure on nivolumab to date has been significantly lower than estimated at the time of listing and for the basis of the RSA caps (█% of the cap was reached in Year 1 and reducing in subsequent years). It is likely that the target cost per patient (~\$█) to achieve the intended ICERs has not yet been achieved as the RSA caps were significantly overestimated. Previous analysis (from July 2019) by the Department post-PBS listing showed that the mean number of scripts per patient for nivolumab was 14.4, equivalent to 6.6 months of treatment, which resulted in a cost higher than what was originally accepted by the PBAC.

Estimated PBS usage & financial implications

4.18 The minor submission did not provide any information on the financial implications of removing the age-related RSA rebate. Given that a rebate has been payable in relation to the age-related RSA for nivolumab each year since listing, removal of the rebate is likely to result in a cost to the Commonwealth. While there is a subsidisation cap arrangement in place, the expenditure in Year 1 and 2 was significantly below the caps and has only been slightly exceeded in Year 3 of the

Deed (the most recent complete year). The pre-PBAC response claimed that it is likely that the Year 4 cap will be exceeded by approximately \$20 million to < \$30 million, and therefore that removal of the age-related RSA rebate would not result in additional cost to the Commonwealth.

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

5 PBAC Outcome

- 5.1 The PBAC advised against the removal of the rebate for patients initiating treatment at the age of 75 years or older in the Deed of Agreement for nivolumab for the treatment of NSCLC (as second-line drug therapy). The PBAC considered that, while the submission presented some evidence to support similar overall survival benefit in patients aged 75 years and older compared with those under 75 years, any amendment to the risk sharing arrangements for nivolumab should be considered with regard to its overall cost-effectiveness and in the broader context of the subsidisation caps and the total cost per patient.
- 5.2 The PBAC considered that the Marur et al (2018) meta-analyses of the pooled FDA trials provided some support that the OS benefit of nivolumab would be similar in patients 75 years and over compared with patients under 75 years. However, the PBAC also noted that patients included in clinical trials are likely to derive more benefit compared to the PBS population.
- 5.3 The PBAC noted that the Grossi et al (2018) and Okishio et al (2020) studies, provided by the submission as real world evidence, reported numerically lower OS in patients 75 years and over, although the PBAC noted that the differences were not statistically significant.
- 5.4 The PBAC found the comparison of median OS between patients under 65 years and 65 years and over in the 2L NSCLC trials for nivolumab and atezolizumab less informative as it did not address the key issue regarding effectiveness in patients aged 75 years and over.
- 5.5 The PBAC recalled that nivolumab for 2L NSCLC was originally recommended in conjunction with various arrangements to achieve cost-effectiveness, including an overall cap on patient numbers and cost per patient, to ensure that the estimated ICERs were not exceeded. The PBAC noted that it is likely that the target cost per patient required to achieve the intended ICERs has not been realised, as the RSA caps were significantly overestimated and were therefore not an adequate device to ensure the target cost per patient. Previous Departmental analysis of PBS data showed a longer actual duration of treatment with nivolumab compared to the basis of the RSA caps (14.4 (mean) prescriptions per patient vs ■ infusions per patient).
- 5.6 Overall, the PBAC considered that while the Marur et al (2018) meta-analyses presented by the submission provided some support in addressing the Committee's previous concerns about the incremental effectiveness of nivolumab in patients aged

75 years or older, there remained a concern about the broader cost-effectiveness of nivolumab in this setting, since the actual cost per patient in practice was likely higher than the target cost recommended to achieve the intended ICERs.

- 5.7 The PBAC therefore considered that removal of the age-related rebate would need to be considered as part of a broader review of the subsidisation caps and a potential price reduction to reach alignment with the target cost per patient.
- 5.8 The pre-PBAC response contended that if the subsidisation caps were to be exceeded, removal of the rebate would not result in any additional cost to government. The PBAC considered that removal of the age related rebate may result in a cost to the Commonwealth, given that the rebate had been payable in relation to the age-related RSA for nivolumab each year since listing.
- 5.9 The PBAC noted that it was also open to the sponsor to propose a corresponding price reduction to facilitate the removal of the age-related RSA rebate.
- 5.10 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:

Rejected

6 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.

7 Sponsor's Comment

The sponsor had no comment.