

## 5.11 RELATLIMAB WITH NIVOLUMAB, Injection concentrate for I.V. infusion containing 80 mg relatlimab and 240 mg nivolumab in 20mL, Opdualag<sup>®</sup>, Bristol-Myers Squibb Australia Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing of the fixed dose combination product of relatlimab plus nivolumab (RELA+NIVO), for the treatment of patients with unresectable Stage III or IV malignant melanoma.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus nivolumab monotherapy.

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

Component	Description
Population	Patients with unresectable Stage III or IV malignant melanoma previously untreated with a PD-1 inhibitor for this indication.
Intervention	Relatlimab 160 mg IV plus nivolumab 480 mg IV as fixed dose combination every 4 weeks.
Comparator	Main comparator: Nivolumab 480 mg IV every 4 weeks. Secondary comparator: Nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV every 3 weeks for 4 doses followed by Nivolumab 3 mg/kg IV every 2 weeks.
Outcomes	Primary: PFS Secondary: OS, ORR, HRQoL, and Safety
Clinical claim	Relatlimab plus nivolumab is superior in terms of efficacy compared to nivolumab monotherapy, with an inferior safety profile. Relatlimab plus nivolumab is non-inferior in terms of efficacy compared to nivolumab plus ipilimumab, with a superior safety profile.

Source: Table 1, p18 of the submission.

HRQoL = health related quality of life, IV = intravenous, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PD-1 = programmed death-1.

### 2 Background

#### Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process. The application was identified for consideration under the United States Food and Drug Administration's (FDA) Project Orbis. The TGA Delegate's overview was available at the time of the PBAC consideration. The TGA Delegate proposed to approve the registration of RELA+NIVO for the:

‘treatment of adults and adolescent patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma’.

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

### 3 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Amt. (units)	No. of Repeats	DPMA	Proprietary Name and Manufacturer
RELATLIMAB/NIVOLUMAB 80 mg/240 mg injection, 1 vial x 20 mL	160 mg/480 mg	Initial: 8 Continuing: 11	Published: \$ Effective: \$	OPDUALAG® Bristol Myers Squibb Australia Pty Ltd

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Administrative Advice:</b> <i>No increase in the maximum amount or number of units may be authorised</i>
<b>Episodicity:</b> [blank]
<b>Severity:</b> Unresectable Stage III or Stage IV
<b>Condition:</b> Malignant melanoma
<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b> Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma
<b>AND</b>
<b>Clinical criteria:</b> Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma
<b>AND</b>
<b>Clinical criteria:</b> Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
<b>AND</b>
<b>Clinical criteria:</b> The condition must not be uveal melanoma
<b>AND</b>
<b>Clinical criteria:</b> The treatment must be the sole PBS-subsidised therapy for this condition

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<b>Population criteria:</b>
Patient must weigh at least 40 kg.
<b>Population criteria:</b>
<i>Patient must be 12 years of age or older</i>
<b>Prescribing Instructions:</b>
<i>Patients must only receive a maximum of 160 mg relatlimab and 480 mg nivolumab every four weeks under a weight based or flat dosing regimen</i>
<b>Prescribing Instructions:</b> <i>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.</i>
<b>Caution:</b> <i>Combination treatment with relatlimab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with nivolumab monotherapy. Monitoring at least prior to each dose is recommended</i>
<b>Caution:</b> <i>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.</i>

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Administrative Advice:</b> <i>No increase in the maximum amount or number of units may be authorised</i>
<b>Episodicity:</b> [blank]
<b>Severity:</b> Unresectable Stage III or Stage IV
<b>Condition:</b> Malignant melanoma
<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment Phase</b> Continuing <i>treatment</i>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised therapy for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have previously <del>been issued with an authority prescription for</del> received PBS-subsidised treatment with this drug for this condition.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
<b>Population criteria:</b>
Patient must weigh at least 40 kg

**Prescribing Instructions:**

Patients must only receive a maximum of 160 mg relatlimab and 480 mg nivolumab every four weeks under a weight based or flat dosing regimen

**Prescribing Instructions:**

The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

**Caution:** Combination treatment with relatlimab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with nivolumab monotherapy. Monitoring at least prior to each dose is recommended.

- 3.2 The submission proposed a Special Pricing Arrangement and provided proposed published and effective prices.
- 3.3 The requested restriction was consistent with the eligibility criteria for the key trial for RELA+NIVO (CA224047), which included patients who had not previously received systemic anti-cancer therapy for unresectable or metastatic melanoma and who had an ECOG performance status of  $\leq 1$ . Of note, the requested restriction did not exclude patients with active brain metastases, which was an exclusion criterion in CA224047.
- 3.4 The requested restriction did not specify any age criteria and did not require a Lansky Performance Score of  $\geq 80\%$  for adolescents, whereas the proposed TGA indication and the key trial (CA224047) restricted use to patients aged 12 years or older. Adolescents were eligible to participate in CA224047, but the trial did not recruit any patients younger than 18 years old.
- 3.5 The requested restriction was consistent with the current PBS listing for NIVO+IPI for the treatment of unresectable Stage III or IV malignant melanoma.
- 3.6 The submission did not request a grandfather restriction given that patients currently receiving RELA+NIVO will not align with the proposed PBS listing. The sponsor currently provides RELA+NIVO to patients who have experienced disease progression after treatment with all PBS-listed therapies.

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

## 4 Population and disease

- 4.1 Australia and New Zealand have the highest incidence and mortality rates from melanoma in the world<sup>1</sup>. It has been estimated that the incidence of melanoma was 16,878 cases in 2018, with 1,315 deaths<sup>2</sup>. Based on 2011-2016 data, the overall 5-year

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<sup>1</sup> Cancer Australia, (2021), Melanoma of the skin, <https://www.canceraustralia.gov.au/cancer-types/melanoma/statistics>

<sup>2</sup> Australian Institute of Health and Welfare (AIHW), (2021), Cancer data in Australia, <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation>

survival rate of patients diagnosed with Stage III and IV melanoma was approximately 61.1% and 26.2%, respectively<sup>3</sup>.

- 4.2 The submission proposed RELA+NIVO as a first line alternative to currently available PBS subsidised programmed cell death protein 1 (PD-1) based treatments in the management of patients with unresectable stage III or IV malignant melanoma. The submission’s proposed place in therapy for RELA+NIVO is presented in Figure 1.

**Figure 1: Proposed clinical management algorithms for patients with previously untreated unresectable Stage III or IV malignant melanoma in Australia**

		BRAF-negative			BRAF-positive				
1L / 2L		anti-PD-1 based treatment*			IPI#	anti-PD-1 based treatment*			BRAF inhibitor-based treatment#
		NIVO	PEMBRO	NIVO+IPI		NIVO	PEMBRO	NIVO+IPI	
		NIVO+RELA				NIVO+RELA			

Source: Figure 6, p28 of the submission.

BRAF= B-Raf proto-oncogene, IPI= ipilimumab, PEMBRO= pembrolizumab, PD-1= programmed cell death protein 1, NIVO= nivolumab, NIVO+IPI= nivolumab plus ipilimumab, RELA= relatlimab, RELA+NIVO= relatlimab plus nivolumab.

\*PBS allows treatment with one anti-PD1 based treatment per patient. Choice between those listed above. Prior treatment with IPI excludes anti-PD1 treatment.

#PBS allows treatment with IPI and BRAF inhibitor-based treatment as either 1st or 2nd line treatment.

- 4.3 Relatlimab is a fully human antibody specified for human lymphocyte activation gene (LAG)-3, which binds to a defined epitope on LAG-3 and blocks the interaction of LAG-3 with its ligand. Relatlimab enhances activation human T-cells in superantigen simulation assays when added alone or in combination with nivolumab. Nivolumab acts as an immunomodulating agent by blocking the interaction between PD-1 and its ligands (PD-L1 and PD-L2), resulting in activation of T-cells and cell-mediated immune responses against tumour cells or pathogens.
- 4.4 For B-Raf proto-oncogene (BRAF)-negative (wild-type) patients, immunotherapy with nivolumab, pembrolizumab or combination of NIVO+IPI is recommended for the first-line setting. The National Comprehensive Cancer Network (NCCN) recently recommended the use of RELA+NIVO in the first line of therapy for unresectable Stage III or IV metastatic melanoma<sup>4</sup>.
- 4.5 BRAF-positive (mutant) patients can receive sequential treatment with PD-1 and BRAF inhibitors, with clinical factors dictating the optimal sequence of treatment.

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

<sup>3</sup> National Cancer Control Indicators, (2019), Relative survival by stage at diagnosis (melanoma), <https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/relative-survival-stage-diagnosis-melanoma>

<sup>4</sup> National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology, Melanoma: Cutaneous, Version 3.2022, [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf)

## 5 Comparator

- 5.1 The submission nominated nivolumab monotherapy, a proxy for treatment with PD-1 inhibitor monotherapy, as the main comparator. Nivolumab plus ipilimumab (NIVO+IPI) was nominated as a secondary comparator. The main arguments provided by the submission in support these nominations were:
- PD-1 inhibitor monotherapy is predominantly used as first-line treatment of unresectable Stage III or IV melanoma in Australia. The Pre-Sub-Committee Response (PSCR) stated that 49% of patients are initiated on PD-1 monotherapy.
  - The choice between PD-1 based or BRAF-based treatment is mainly based on patients' individual disease and circumstances.
  - Head-to-head evidence comparing RELA+NIVO and nivolumab monotherapy is available. The ESC noted the available evidence does not dictate the comparator.
- 5.2 The nominated main comparator (nivolumab monotherapy) and secondary comparator (NIVO+IPI) were used to determine the comparative effectiveness and safety of RELA+NIVO. However, only the main comparator (nivolumab monotherapy) was used in the economic model and financial estimates.
- 5.3 The ESC considered that the choice of nivolumab monotherapy as the main comparator was not appropriate, with the most appropriate comparator for RELA+NIVO being NIVO+IPI for the following reasons:
- Based on the improved progression-free survival (PFS) and overall survival (OS) with combination therapy (e.g., NIVO+IPI) compared with nivolumab alone, clinical guidelines recommend the use of combination therapy over PD-1 inhibitor monotherapy for the treatment of unresectable Stage III or IV metastatic melanoma if tolerated<sup>5</sup>. The ESC noted that combination therapy (i.e. NIVO+IPI) was increasingly the preferred first-line treatment for patients in Australia especially as the management of the adverse events associated with ipilimumab has improved.
  - Combination therapy is also preferred in aggressive disease including patients with elevated lactate dehydrogenase (LDH) or American Joint Committee on Cancer (AJCC) baseline metastasis stage of M1c. Notably, 43% of the patients in CA224047 trial (RELA+NIVO) and 59% of the patients in CA209067 (NIVO+IPI) had M1c stage.
- 5.4 The pre-PBAC response (p1) stated that analysis of PBS data for PD-1 monotherapy and NIVO+IPI initiation/induction did not indicate any increase in preference to initiate patients on combination NIVO+IPI over PD-1 monotherapy. The pre-PBAC

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<sup>5</sup> National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology, Melanoma: Cutaneous, Version 2.2022, [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf)

response further stated that since March 2020, when PBS eligibility for PD-1 based treatments was expanded to include first line treatment for BRAF-mutant melanoma, PD-1 monotherapy has represented approximately 60% of patient initiations, while the proportion of combination NIVO+IPI therapy has remained stable at approximately 40%.

- 5.5 The Pre-PBAC response disagreed that the NCCN Guidelines unambiguously recommend the use of combination therapy if tolerated. The pre-PBAC response reiterated that the Guidelines refer to a range of factors that should be considered when deciding upon combination therapy.

*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 individuals (6), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from individuals, the Melanoma and Skin Cancer Advocacy Network (MSCAN) and Melanoma Patients Australia supported the submission and highlighted the demand for alternate effective therapies.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the RELA + NIVO submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for RELA + NIVO, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>6</sup>, based on a comparison with nivolumab.

### **Clinical trials**

- 6.4 The submission was based on one head-to-head randomised, double-blind, phase III trial comparing RELA+NIVO combination therapy to nivolumab monotherapy in patients with previously untreated unresectable Stage III or IV metastatic melanoma (CA224047).
- 6.5 An indirect treatment comparison (ITC) of RELA+NIVO and NIVO+IPI, using nivolumab monotherapy as the common reference, was presented based on two phase III randomised controlled trials (RCTs): CA224047 which compared RELA+NIVO with nivolumab monotherapy and CA209067 which compared nivolumab monotherapy or

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<sup>6</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

NIVO+IPI with ipilimumab monotherapy, in patients with previously untreated unresectable or metastatic melanoma.

6.6 Details of the clinical trials 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
CA224047	A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with NIVO versus NIVO in Participants with Previously Untreated Metastatic or Unresectable Melanoma	May 2021
	Addendum 01 to the Primary Clinical Study Report for Study CA224047: A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with Nivolumab Versus Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma	Jan 2022
	Schadendorf D, Tawbi HA, Lipson EJ et al. Health-related quality of life with relatlimab plus nivolumab versus nivolumab in patients with previously untreated metastatic or unresectable melanoma: RELATIVITY-047	18 <sup>th</sup> International Congress of the Society for Melanoma Research (SMR) 2021; 59
	Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma.	NEJM 2022; 386(1): 24–34.
	Hodi FS, Tawbi HA, Lipson EJ et al. 1036O Relatlimab (RELA) + nivolumab (NIVO) vs. NIVO in previously untreated metastatic or unresectable melanoma: Additional efficacy in RELATIVITY-047.	Annals of Oncology 2021; 32: S867-S868
CA209067	Lipson EJ, Long GV, Tawbi HA et al. A randomized, double-blind, phase II/III study of relatlimab (anti-LAG-3) in combination with nivolumab (anti-PD-1) versus nivolumab alone in previously untreated metastatic or unresectable melanoma.	Annals of Oncology 2018; 29: viii464-viii465
	Lipson EJ, Tawbi HA, Schadendorf D et al. Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: Primary phase III results from RELATIVITY-047 (CA224-047).	Journal of Clinical Oncology 2021; 39(15_suppl).
	A Phase 3, Randomized, Double-blind Study of NIVO Monotherapy or NIVO Combined with IPI Versus IPI Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma	June 2015
	Hodi FS, Chiarion-Sileni V, Gonzalez R et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial.	The Lancet Oncology 2018; 19(11): 1480-1492.
	Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined nivolumab and ipilimumab or monotherapy in untreated Melanoma.	New England Journal of Medicine 2015; 373(1): 23-34.
CA209067	Larkin J, Chiarion-Sileni V, Gonzalez R et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma.	New England Journal of Medicine 2019; 381(16): 1535-1546.
	Wolchok JD, Chiarion-Sileni V, Gonzalez R et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma.	New England Journal of Medicine 2017; 377(14): 1345-1356.

Source: Table 14, p46-47 and Attachment 10a\_2.2 of the submission.

IPI = ipilimumab, LAG-3 = lymphocyte activation gene 3, NIVO = nivolumab, PD-1 = programmed cell death protein 1, RELA = relatlimab.

6.7 The key features of the included evidence are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Used in modelled evaluation
<b>RELA+NIVO versus nivolumab monotherapy</b>						
CA224047	714	R, MC, MN, DB Median follow-up of 19.27 months <sup>c</sup>	Low	Previously untreated unresectable or metastatic melanoma	PFS, OS, ORR, FACT-M, FACIT GP5, EQ-5D-3L and safety	PFS, OS, EQ-5D-3L, and safety
<b>NIVO+IPI versus nivolumab monotherapy</b>						
CA209067 <sup>a</sup>	630 <sup>b</sup>	R, MC, MN, DB Median follow-up of 12.2-12.5 months <sup>d</sup> Long-term analyses at 3-, 4-, 5- and 6.5 years.	Low	Previously untreated unresectable or metastatic melanoma	PFS, OS, ORR, EORTC QLQ-C30, EQ-5D-3L and safety	Not used

Source: Table 15, p50 and Table 19, p68 of the submission.

DB = double blind, EORTC-QLQ C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, EQ-5D-3L = 3-level version of the EQ-5D health status measure, FACT-M = Functional Assessment of Cancer Therapy – Melanoma, FACIT GP5 = Functional Assessment of Chronic Illness Therapy - GP 5, MC = multi-centre, MN = multi-national, ORR = overall response rate, OS = overall survival, PFS = progression-free survival R = randomised.

<sup>a</sup> CA209067 also had an ipilimumab monotherapy arm. Data from this arm were not considered by the submission

<sup>b</sup> The number of patients is the total in the NIVO+IPI and nivolumab monotherapy arms (314 and 316, respectively).

<sup>c</sup> Data cut-off: October 2021

<sup>d</sup> Data cut-off: February 2015

6.8 For CA224047, the results were based on the final PFS analysis (median duration of follow-up of 13.21 months; data cut-off: March 2021) and an updated OS analysis (median duration of follow-up of 19.27 months; data cut-off: October 2021). For the CA209067 trial, results were based on an interim analysis (median duration of follow-up of 12.2-12.5 months; data cut-off: February 2015). Updated results were available for CA209067 at 3-, 4-, 5-, and 6.5 years of follow-up.

6.9 The primary objective of CA209067 was to evaluate the safety and effectiveness of nivolumab monotherapy and NIVO+IPI in comparison with ipilimumab monotherapy. The OS, PFS, and overall response rate (ORR) between the NIVO+IPI group and the nivolumab monotherapy group were secondary endpoints evaluated using descriptive analysis (i.e., no hypothesis testing).

6.10 The eligibility criteria were largely similar for the CA224047 and CA209067 trials. However, there were key differences across the trials that may affect transitivity. These included:

- A higher proportion of patients in the CA224047 trial were aged 75 years or above compared with the CA209067 trial (17.6% versus 11.8%). Age was not found to be a statistically significant treatment effect modifier based on subgroup analyses.
- More patients in the CA209067 trial were classified as being fully active, i.e., ECOG performance status of 0 compared with the CA224047 trial (74.3% versus 67.0%),
- A higher proportion of patients in the CA224047 trial had a PD-L1 positive status compared with the CA209067 trial at 1% cut-off (41.0% versus 23.5%). Response

to the nivolumab single agent appeared to be more favourable in patients with PD-L1 expression  $\geq 1\%$  compared with those with PD-L1  $< 1\%$ ; however, the potential impact on the trial comparison is not clear.

- A higher proportion of patients in the CA224047 trial had a BRAF positive status compared with the CA209067 trial (38.5% versus 31.9%). As patients with a BRAF positive status showed a better response to treatment in the CA209067 trial but not in the CA224047 trial, the impact of this potential confounding factor is unclear.
- More patients in the CA209067 trial had AJCC M1c/d disease compared with CA224047 (59% versus 40%), suggesting that patients in the CA209067 trial represent a sicker population.

6.11 The PSCR noted that a matching-adjusted indirect comparison (MAIC) was presented to account for the known key differences between trials.

### **Comparative effectiveness**

#### Overall Survival

6.12 A summary of the OS results across the CA224047 and CA209067 trials is provided in Table 4.

**Table 4: Results of OS across trials**

<b>CA224047<sup>a</sup></b>	<b>RELA+NIVO</b>	<b>Nivolumab</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>
Patients with event, n (%)	137/355 (38.6%)	160/359 (44.6%)	-	-
Median OS, months (95% CI)	NA (32.2, NR)	34.1 (25.23, NR)	NE	0.80 (0.64, 1.01)
<b>CA209067<sup>b</sup></b>	<b>NIVO+IPI</b>	<b>Nivolumab</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>
Patients with event, n (%)	182/314 (58%)	164/316 (52%)	-	-
Median OS, months (95% CI)	NR (NR, NR)	37.6 (29.1, NR)	NE	0.85 (0.68, 1.07)

Source: Table 26, p90 and Table 29, p101 of the submission.

CI = confidence interval, HR = hazard ratio, IPI = ipilimumab, n = number of participants reporting data, N = total participants in group, NA = not applicable, NE = not estimable, NIVO = nivolumab, NR = not reported, OS = overall survival, RELA = relattimab.

<sup>a</sup> Data cut-off: October 2021

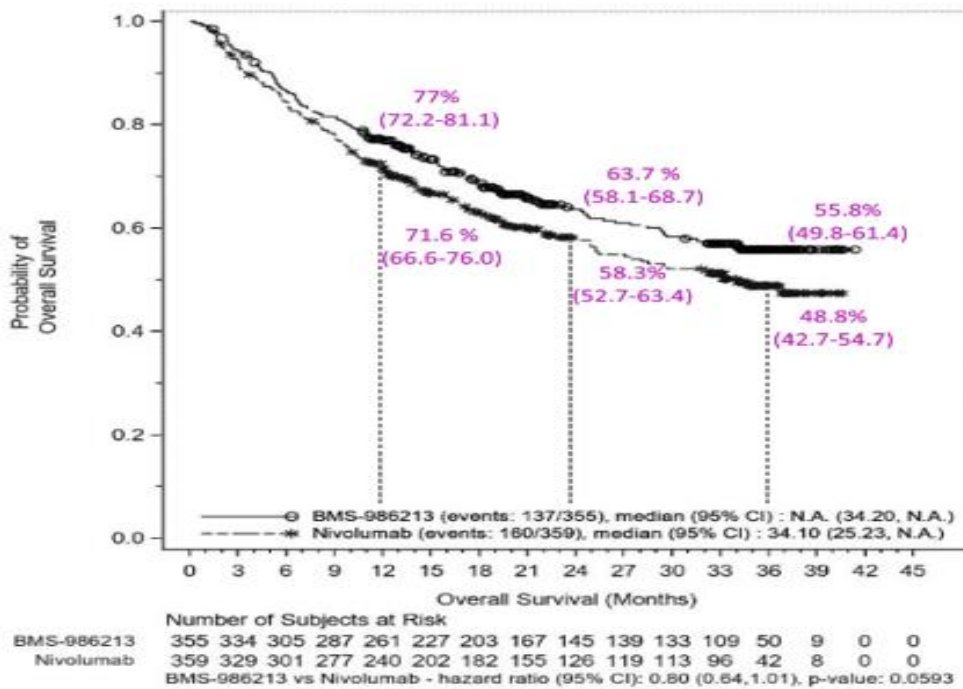
<sup>b</sup> Data cut-off: May 2017 (3-years follow-up)

6.13 At a median follow up of 19.27 months, the median OS for the RELA+NIVO arm was not reached. Median OS in the nivolumab monotherapy arm was 34.1 months. Overall, the change in OS was not statistically significant (HR = 0.80; 95% CI: 0.64, 1.01). Given the immaturity of the data, the survival benefit of RELA+NIVO compared with nivolumab monotherapy was uncertain. The PSCR (p2) noted that OS was included as secondary endpoint in the main trial CA2244047. The PSCR disagreed that the OS benefit was uncertain, arguing that the OS benefit favouring RELA+NIVO approached statistical significance ( $p=0.0593$ ), that the magnitude of the OS benefit (5%) was durable and clinically meaningful, and that the OS result was supported by the primary outcome of a statistically significant improvement in PFS for RELA+NIVO (HR = 0.75; 95% CI: 0.62, 0.92;  $p=0.0055$ ). The ESC noted the relatively short duration of follow-up duration (up to 36 months) and the difficulties associated with

interpreting immature data. The ESC considered that more mature data would be informative for better estimating the magnitude and durability of the OS gain. The pre-PBAC response (p2) claimed the magnitude of benefit was considered clinically meaningful, given that the Kaplan Meier OS estimates at 12, 24 and 36 months for RELA+NIVO were more than 5% higher than for nivolumab monotherapy.

- 6.14 In the CA209067 trial, the median OS at a minimum follow-up of 3 years, was not reached in the NIVO+IPI arm and was 37.6 months for the nivolumab arm. Updated data from an extended 6.5-year follow-up for this trial demonstrated that NIVO+IPI was associated with a non-statistically significant improvement in OS compared with nivolumab monotherapy (HR: 0.84; 95% CI: 0.67, 1.04).
- 6.15 The Kaplan Meier OS plots for the CA224047 (data cut-off: October 2021) and CA209067 (data cut-off: October 2020) trials are presented in Figure 2 and Figure 3, respectively.

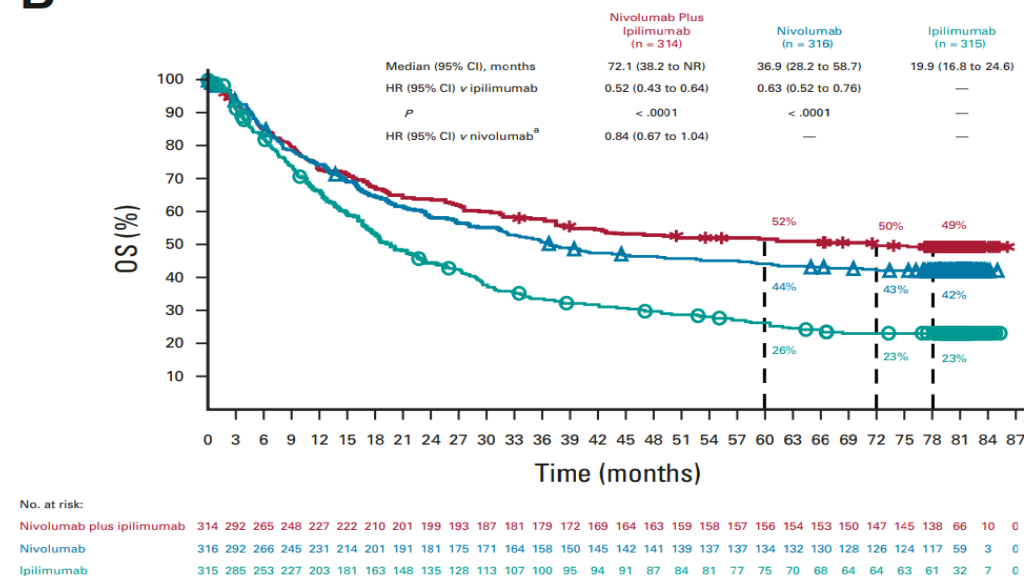
Figure 2: KM analysis of OS in the CA224047 trial (Data cut-off: October 2021)



Source: Figure 14, p90 of the submission.

Figure 3: KM analysis of OS in the CA209067 trial (Data cut-off: October 2020)

**B**



Source: Figure 25, p101 of the submission.

6.16 At 6.5 years (78 months), the OS rate was 49% in the NIVO+IPI arm and 42% in the nivolumab monotherapy arm. The results from the extended follow-up of the CA209067 trial demonstrate plateaued OS curves.

Progression-Free Survival

6.17 A summary of the PFS results across the CA224047 and CA209067 trials is provided in Table 5.

Table 5: Results of PFS across the trials

CA224047	RELA+NIVO	Nivolumab	Absolute difference	HR (95% CI)
<b>Data cut-off = March 2021 (median follow up = 13.21 months)</b>				
PFS event, n/N (%)	180/355 (50.7%)	211/359 (58.8%)	-	-
Median PFS, months (95% CI)	10.12 (6.37, 15.74)	4.63 (3.38, 5.62)	5.49 months	<b>0.75 (0.62, 0.92)</b>
<b>Data cut-off = October 2021 (median follow up = 19.27 months)</b>				
PFS event, n/N (%)	204/355 (57.5%)	233/359 (64.9%)	-	-
Median PFS, months (95% CI)	10.22 (6.51, 14.75)	4.63 (3.48, 6.44)	5.59 months	<b>0.78 (0.64, 0.94)</b>
CA209067 <sup>a</sup>	NIVO+IPI	Nivolumab	Absolute difference	HR (95% CI)
<b>Data cut-off = May 2015 (minimum follow up = 9 months)</b>				
Patients with event	151/314 (48.1%)	174/316 (55.1%)	-	-
Median PFS, months (95% CI)	11.5 (8.9, 16.72)	6.87 (4.34, 9.46)	4.63 months	<b>0.74 (0.60, 0.92)</b>

Source: Table 25, p87 and Table 28, p99 of the submission

CI = confidence interval, HR = hazard ratio, IPI = ipilimumab, n = number of participants reporting data, N = total participants in group, NIVO = nivolumab, PFS = progression-free survival, RELA = relatlimab.

<sup>a</sup> PFS per BICR were descriptively updated at the October 2021-cut-off.

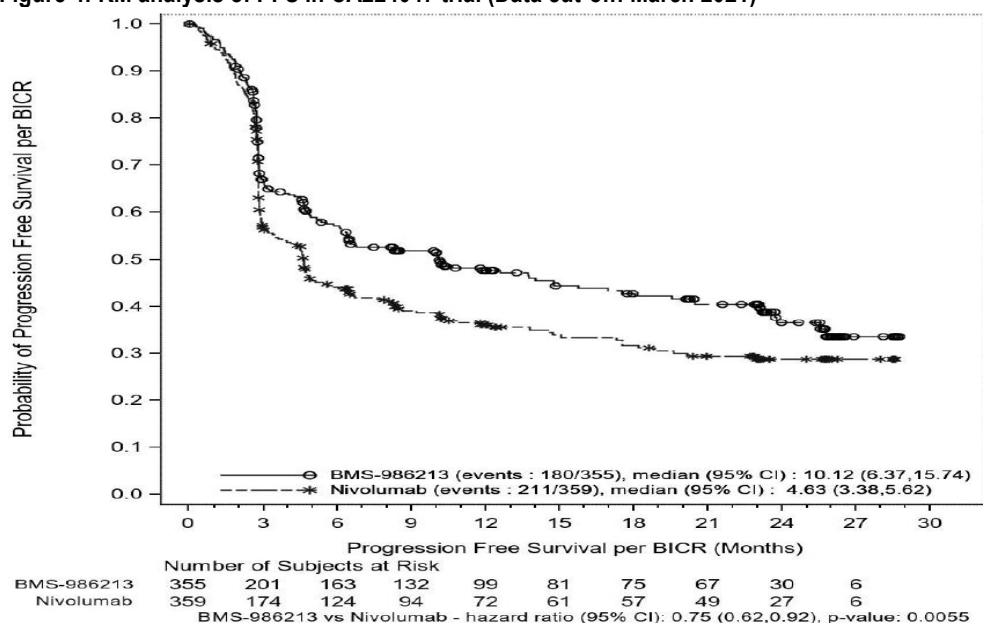
**Bold** indicates statistically significant results.

6.18 In the CA224047 trial, at a median duration of follow-up of 13.21 months (data cut-off: March 2021), RELA+NIVO was associated with a statistically significant

improvement in PFS compared with nivolumab monotherapy (HR = 0.75; 95% CI: 0.62, 0.92), with an absolute difference of 5.49 months. The improvement in PFS associated with RELA+NIVO from the updated analysis (median duration of follow-up of 19.27 months; data cut-off: October 2021) was similar to the original analysis, with an HR of 0.78 (95% CI: 0.64, 0.94).

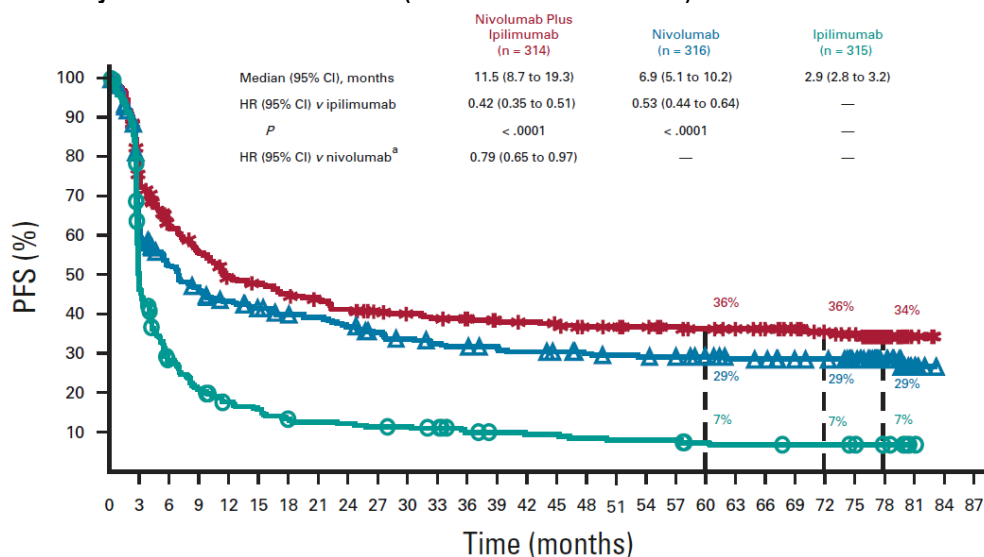
- 6.19 In the CA209067 trial, based on a minimum follow-up of 9 months (data cut-off: February 2015), NIVO+IPI was associated with a statistically significant improvement in median PFS of 4.6 months over nivolumab monotherapy (HR = 0.74; 95% CI: 0.60, 0.92). Updated data from extended 3-, 4-, 5- and 6.5-years follow-up continued to demonstrate significant improvement in PFS for NIVO+IPI compared to nivolumab monotherapy, with an HR of 0.79 (95% CI: 0.65, 0.97) in the most recent data cut-off (October 2020; 6.5-year follow-up; see Figure 5 below).
- 6.20 The Kaplan Meier PFS plots for the CA224047 (data cut-off: March 2021) and CA209067 (data cut-off: October 2020; 6.5-year follow-up) trials are presented in Figure 4 and Figure 5, respectively.

Figure 4: KM analysis of PFS in CA224047 trial (Data cut-off: March 2021)



Source: Figure 12, p87 of the submission.

Figure 5: KM analysis of PFS in CA209067 trial (Data cut-off: October 2020)



No. at risk:

	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87
Nivolumab plus ipilimumab	314	218	174	155	136	131	124	117	110	104	101	98	96	92	90	88	83	82	80	77	74	72	69	64	58	52	29	3	0
Nivolumab	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	68	66	65	64	60	55	54	51	49	42	24	7	0
Ipilimumab	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	12	11	11	10	10	9	7	1	0	

Source: Figure 24, p100 of the submission.

6.21 The separation of the PFS curves occurred at approximately 3 months in both trials and appeared to be sustained.

### Overall Response Rate

6.22 A summary of the ORR results across the CA224047 and CA209067 trials is provided in Table 6.

Table 6: Results of ORR across the trials

	CA224047		CA209067	
	RELA+NIVO n (%)	Nivolumab n (%)	NIVO+IPI n (%)	Nivolumab n (%)
Complete response	58 (16.3%)	51 (14.2%)	36 (11.5%)	28 (8.9%)
Partial response	95 (26.8%)	66 (18.4%)	145 (46.2%)	110 (34.8%)
Stable disease	61 (17.2%)	59 (16.4%)	41 (13.1%)	34 (10.8%)
Non-complete response or non-progressive disease	9 (2.5%)	6 (1.7%)	NR	NR
Progressive disease	105 (29.6%)	149 (41.5%)	71 (22.6%)	119 (37.7%)
Unable to determine	27 (7.6%)	28 (7.8%)	21 (6.7%)	25 (7.9%)
ORR <sup>a</sup> , n (%) (95% CI)	153 (43.1%) (37.9, 48.4)	117 (32.6%) (27.8, 37.7)	181 (57.6%) (52, 63.2)	138 (43.7%) (38.1, 49.3)
Difference of ORR (95% CI)	10.3% (3.4, 17.3)		13.8% (6.3, 21.3)	
Odds ratio (95% CI)	<b>1.58 (1.16, 2.15)</b>		<b>1.8 (1.3, 2.49)</b>	

Source: Table 27, p91 and Table 30, p102 of the submission.

CI = confidence interval, IPI = ipilimumab, n = number of participants reporting data, NIVO = nivolumab, NR = not reported, ORR = overall response rate, RELA= relatlimab.

<sup>a</sup> ORR = Complete response (CR) + Partial response (PR)

**Bold** indicates statistically significant results.

- 6.23 In CA224047, treatment with RELA+NIVO was associated with statistically significant increase in objective response compared with nivolumab monotherapy, with an odds ratio of 1.58 (95% CI: 1.16, 2.15). In CA209067, treatment with NIVO+IPI was also associated with statistically significant increase in objective response compared with nivolumab monotherapy, with an odds ratio of 1.8 (95% CI: 1.3, 2.49).

#### Patient Reported Outcomes

- 6.24 Health-related quality of life (HRQoL) was measured using EQ-5D-3L in both the trials. Additionally, the submission presented Functional Assessment of Cancer Therapy - Melanoma (FACT-M) and Functional Assessment of Cancer Therapy - General (FACT-GP5) results for the CA224047 trial and EORTC QLQ-C30 results for the CA209067 trial. Clinically meaningful changes from baseline were determined using pre-specified minimally important differences (MIDs) of 5 for the FACT-G Total and FACT-M Total scores based on Askew 2009, 0.08 for the health utility index and 7 for the visual analogue scale (VAS) based on Pickard 2007.
- 6.25 In CA224047, least-squares mean changes from baseline over time in the FACT-M total score and the EQ-5D-3L utility index remained stable and did not exceed the minimal clinically important differences within each treatment arm. No clinically meaningful difference was observed for the VAS or the utility index score between RELA+NIVO and nivolumab.
- 6.26 In CA209067, least-squares mean changes from baseline for EORTC QLQ-30 were slightly higher in the NIVO+IPI arm when compared to nivolumab; however, it did not reach clinically meaningful thresholds. No clinically meaningful difference was observed for the VAS or the utility index score between NIVO+IPI and nivolumab.

#### Subgroup Analyses

- 6.27 The submission also conducted subgroup analysis to inform the exchangeability of the CA224047 and CA209067 trials included in the indirect comparison of RELA+NIVO and NIVO+IPI.
- 6.28 In the CA224047 trial, median PFS was longer with RELA+NIVO compared with nivolumab monotherapy among patients with PD-L1 <1% (6.4 months compared with 2.9 months), with a HR of 0.66 (95% CI: 0.51, 0.84). This difference in PFS was not observed among patients with PD-L1 ≥1%, with a median PFS in the RELA+NIVO arm of 15.7 months compared to 14.7 months in the nivolumab monotherapy arm (HR = 0.95; 95% CI: 0.68, 1.33). The submission stated that although the results for the 1% PD-L1 status cut-off may be suggestive of PD-L1 expression status as a potential treatment modifier, with a negative expression of PD-L1 being associated with a better PFS outcome for RELA+NIVO compared to nivolumab monotherapy, the results should be viewed with caution. The submission noted that the relative effect of higher PD-L1 expression (5% and 10%) was not directionally consistent and that there was

substantial overlap between each of the complementary subgroupings in terms of the 95% confidence intervals.

- 6.29 In the subgroup of patients with LAG-3  $\geq 1\%$  expression, the median PFS was 12.58 months in the RELA+NIVO arm and 4.76 months in nivolumab arm (HR = 0.75; 95% CI: 0.59, 0.95); in the subgroup of patients with LAG-3  $< 1\%$ , the median PFS was 4.83 months in the RELA+NIVO arm and 2.79 months in nivolumab arm (HR = 0.78; 95% CI: 0.54, 1.15).
- 6.30 In the CA209067 trial, a statistically significant treatment modification effect was associated with the BRAF mutation ( $I^2=72\%$ ,  $p=0.06$ ) with respect to the PFS outcome, with greater treatment effect observed in patients who carry the mutation. Among patients with BRAF mutant tumours, OS was not reached in the NIVO+IPI arm and was 45.5 months in the nivolumab arm.

### Indirect Treatment Comparison

- 6.31 The submission presented an ITC, using the Bucher method, between RELA+NIVO and NIVO+IPI using nivolumab as the common comparator. The results of the ITC are summarised in Table 7.

**Table 7: Results of OS and PFS indirect comparison of RELA+NIVO and NIVO+IPI**

	RELA+NIVO	Nivolumab	Absolute difference	HR (95% CI)
<b>CA224047<sup>a</sup></b>				
OS event, n/N (%)	137/355 (38.6%)	160/359 (44.6%)	-	-
Median OS, months (95% CI)	NA (32.2, NR)	34.1 (25.23, NR)	-	0.80 (0.64, 1.01)
PFS event, n/N (%)	180/355 (50.7%)	211/359 (58.8%)	-	-
Median PFS, months (95% CI)	10.12 (6.37, 15.74)	4.63 (3.38, 5.62)	5.49 months	<b>0.75 (0.62, 0.92)</b>
	NIVO+IPI	Nivolumab	Absolute difference	HR (95% CI)
<b>CA209067<sup>b</sup></b>				
OS event, n/N (%)	182/314 (58%)	164/316 (52%)	-	-
Median OS, months (95% CI)	NR (NR, NR)	37.6 (29.1, NR)	-	0.85 (0.68, 1.07)
PFS event, n/N (%)	151/314 (48.1%)	174/316 (55.1%)	-	-
Median PFS, months (95% CI)	11.5 (8.9, 16.72)	6.87 (4.34, 9.46)	4.63 months	<b>0.74 (0.6, 0.92)</b>
<b>ITC</b>				
RELA+NIVO vs. NIVO+IPI for OS (95% CI)				0.94 (0.68, 1.30)
RELA+NIVO vs. NIVO+IPI for PFS (95% CI)				1.01 (0.76, 1.36)

Source: Table 25, p87, Table 26, p90, Table 28, p99, Table 29, p101, Table 38, p142 and Table 39, p144 of the submission.

CI = confidence interval, HR = hazard ratio, IPI = ipilimumab, ITC = indirect treatment comparison, n = number of participants reporting data, N = total participants in group, NIVO = nivolumab, NR = not reported, OS = overall survival, PFS = progression free survival, RELA = relatlimab.

**Bold** indicates statistically significant results.

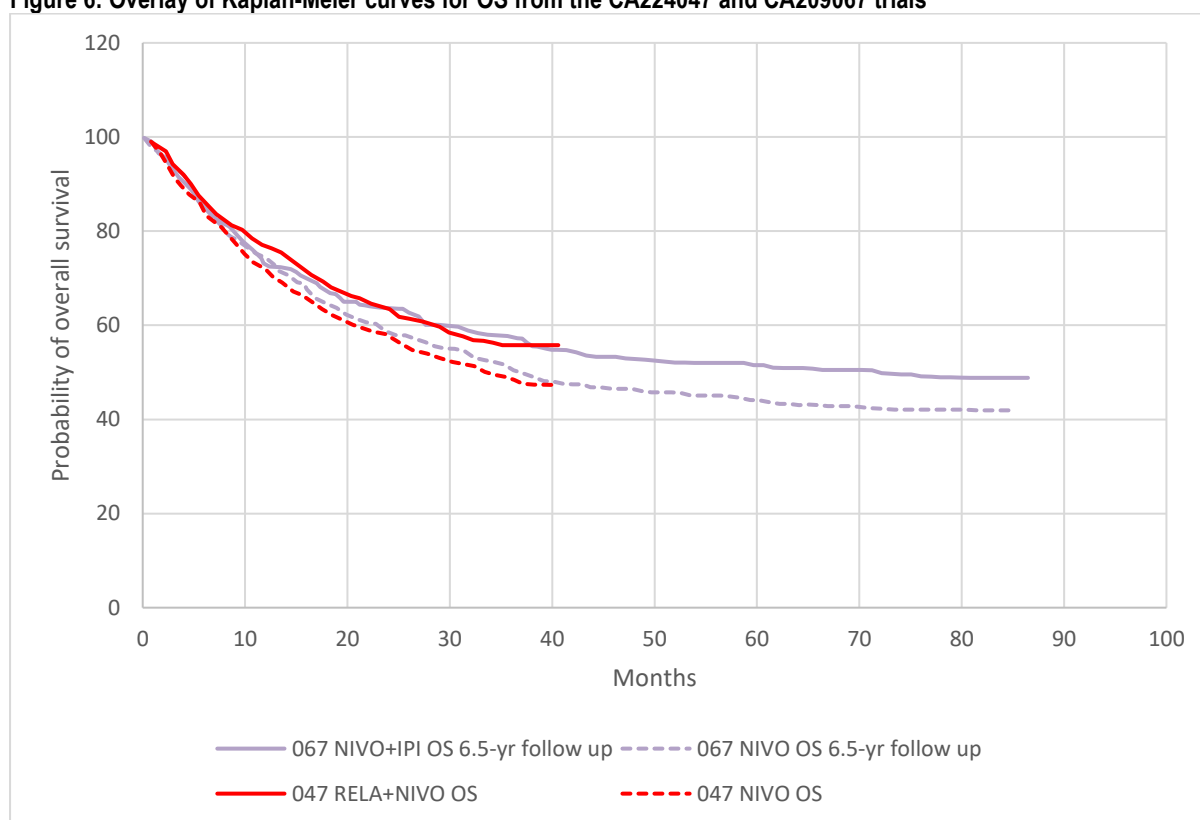
<sup>a</sup> In CA224047, data cut-off for PFS: March 2021 and data cut-off for OS: October 2021.

<sup>b</sup> In CA209067, data cut-off for PFS: February 2015 and data cut-for OS: May 2017.

- 6.32 The ITC analysis showed no statistically significant differences between RELA+NIVO and NIVO+IPI in terms of OS (HR = 0.94; 95% CI: 0.68, 1.30) or PFS (HR = 1.01; 95% CI: 0.76, 1.36). However, the results were uncertain given the transitivity issues identified in paragraph 6.7.

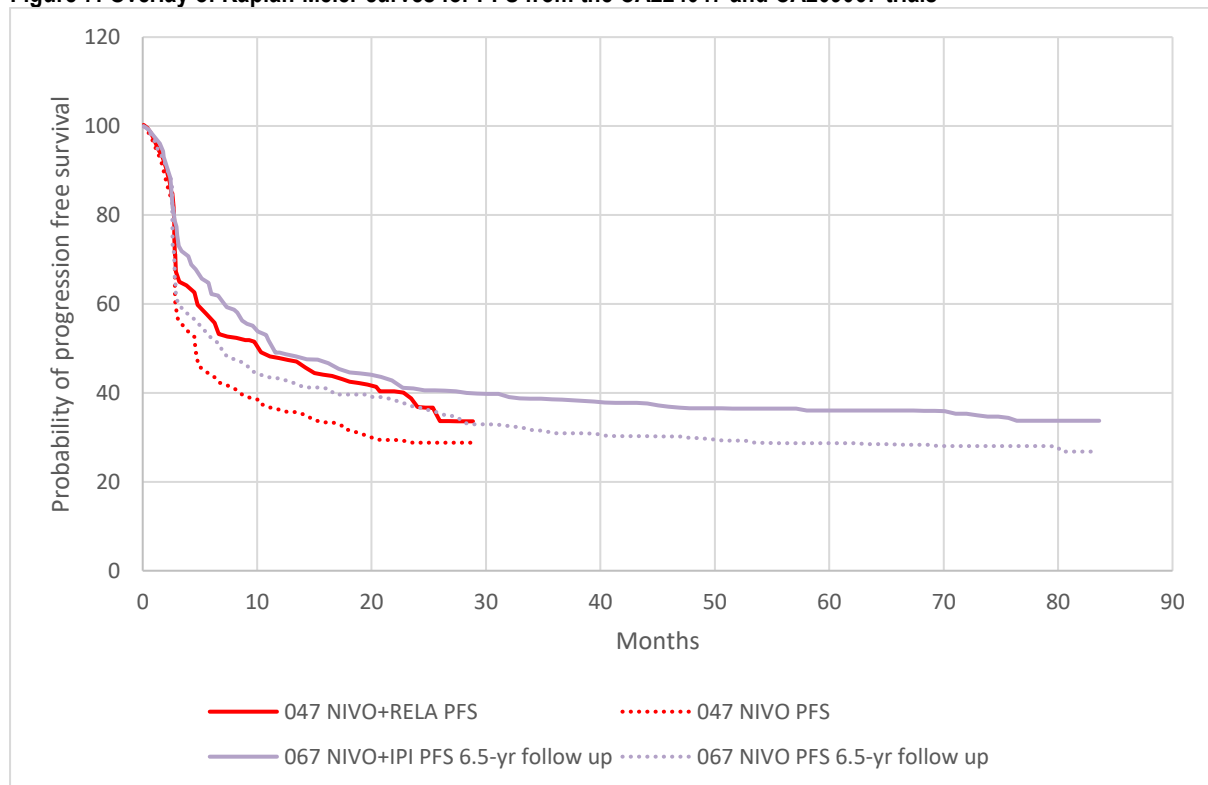
- 6.33 The median PFS of nivolumab monotherapy (i.e., the common comparator) was longer in the CA209067 trial than in the CA224047 trial (6.87 vs 4.63 months respectively). This could suggest differences in patient characteristics across the two trials.
- 6.34 The submission also presented sensitivity analyses, which compared results from the CA224047 trial with the extended data from the CA209067 trial at 4-, 5- and 6.5-years follow-up. The results of the sensitivity analyses were consistent with the main ITC analyses, showing no statistically significant differences in OS and PFS between RELA+NIVO and NIVO+IPI.
- 6.35 Figure 6 and Figure 7 present an overlay of the OS and PFS curves from the CA224047 and CA209067 trials, respectively.

**Figure 6: Overlay of Kaplan-Meier curves for OS from the CA224047 and CA209067 trials**



Source: Figure 42, p145 of the submission.

Figure 7: Overlay of Kaplan-Meier curves for PFS from the CA224047 and CA209067 trials



Source: Figure 40, p143 of the submission.

- 6.36 The submission presented a MAIC to adjust for differences in baseline characteristics between the trials. The submission used an inverse probability treatment weighting approach to adjust for differences in baseline characteristics between patients from the CA209067 and CA224047 trials.
- 6.37 The data cut-offs applied in the main ITC analysis were not consistent with those applied in the adjusted ITC analysis for the PFS, OS and safety estimates. For PFS, the main ITC used the March 2021 cut-off for the CA224047 trial and the February 2015 cut-off for the CA209067 trial, whereas the adjusted ITC used the October 2021 cut-off for the CA224047 trial.
- 6.38 For OS and safety, the main ITC used the October 2021 cut-off for the CA224047 trial and the 2017 cut-off for the CA209067 trial, whereas the adjusted ITC used the October 19, 2020, database lock from CA209067. Moreover, the OS outcomes from the October 2020 cut-off were truncated to emulate the first per protocol analysis and to align the median follow-up duration from the CA224047 trial. Accordingly, patients in the CA209067 trial who did not have an event by August 1, 2016, were censored at this date. After truncation the minimum follow-up in the CA209067 trial was 28 months, and median follow-up was 32 months. The truncation of data and the censoring to align median follow-up times may not be appropriate and could result in biased results. The submission could have used the data from the May 2017 cut-off (3

years median follow-up) from the CA209067 trial in the MAIC. The PSCR (p3) stated that comparing time-to-event endpoints across two trials with different follow up periods would create bias, particularly if data from one or both trials was not yet mature. The PSCR also stated that the decision to align end point definitions in the ITC and to truncate the data was to reduce the risk of bias in the ITC given the time-to-event nature of the endpoints being compared. The ESC considered the results from the MAIC reasonable but agreed for consistency, a 3-year median follow up (2017 data cut off) for the MAIC might be more appropriate although, based on the proportional hazards assumption, variation in the follow-up times between the trials would not have a significant effect on the results. The pre-PBAC response (p2) maintained that the most robust comparison was presented, given the data available and, on balance, demonstrated non-inferiority of RELA+NIVO compared with NIVO+IPI.

- 6.39 The submission presented the factors that could potentially affect the exchangeability of the results between the CA224047 and CA209067 trials, including age, AJCC M stage, ECOG Performance Status, discontinuation criteria, prior systemic therapy, and treatment setting. However, the ESC noted that the submission did not include subsequent treatments or differences in follow up duration as transitivity issues.
- 6.40 The MAIC estimates for efficacy were similar to the ITC estimates. Key findings from the MAIC were as follows:
- There was no significant difference in the OS between RELA+NIVO and NIVO+IPI, with HR of 0.87 (95% CI: 0.68, 1.12).
  - There was no significant difference in the PFS between RELA+NIVO and NIVO+IPI, with HR of 1.00 (95% CI: 0.79, 1.25).

### Comparative harms

- 6.41 The submission presented safety data based on *post-hoc* analyses from the CA224047 and CA209067 trials. A summary of key adverse events (AEs) in trials CA224047 and CA209067 is presented in Table 8.
- 6.42 In the CA224047 trial, RELA+NIVO was associated with more Grade  $\geq 3$  treatment-related AEs when compared with nivolumab (40.3% compared with 33.4%) and statistically significantly more AEs leading to discontinuation from the trial (19.4% vs 11.4%; RR = 1.70; 95% CI: 1.19, 2.43). RELA+NIVO was also associated with more pruritis (23.4% vs 15.9%), fatigue (23.1% vs 12.8%) and arthralgia (14.4% vs 7.2%) than nivolumab monotherapy.
- 6.43 In the CA209067 trial, NIVO+IPI was associated with statistically significantly more Grade  $\geq 3$  treatment-related AEs when compared with nivolumab monotherapy (68.7% compared with 43.5%). NIVO+IPI was also associated with more diarrhoea (44.1% vs 19.2%), pruritis (33.2% vs 18.9%), nausea (25.9% vs 13.1%) and pyrexia (18.5% vs 5.8%) than nivolumab monotherapy. The PBAC previously considered that combination treatment with NIVO+IPI has a significantly inferior safety profile

compared to pembrolizumab monotherapy, nivolumab monotherapy or ipilimumab monotherapy (paragraph 7.5, nivolumab plus ipilimumab Public Summary Document [PSD], November 2015).

**Table 8: Summary of key adverse events in the CA224047 (data cut-off: March 2021) and CA209067 (data cut-off: February 2015) trials**

<b>CA224047</b>	<b>RELA+NIVO N=355, n (%)</b>	<b>Nivolumab N=359, n (%)</b>	<b>RR (95% CI)</b>
Any severe AE (Grade ≥3)	143 (40.3%)	120 (33.4%)	1.21 (0.99, 1.46)
AE leading to discontinuation	69 (19.4%)	41 (11.4%)	<b>1.70 (1.19, 2.43)</b>
Death due to study drug toxicity	3 (0.9%)	2 (0.6%)	1.52 (0.25, 9.02)
Most frequent study drug related AEs (>5% in any treatment arm)			
• Pruritus	83 (23.4%)	57 (15.9%)	<b>1.47 (1.09, 1.99)</b>
• Fatigue	82 (23.1%)	46 (12.8%)	<b>1.80 (1.30, 2.51)</b>
• Rash	55 (15.5%)	43 (12.0%)	1.29 (0.89, 1.87)
• Arthralgia	51 (14.4%)	26 (7.2%)	<b>1.98 (1.27, 3.11)</b>
• Hypothyroidism	51 (14.4%)	43 (12.0%)	1.20 (0.82, 1.75)
• Diarrhoea	48 (13.5%)	33 (9.2%)	1.47 (0.97, 2.23)
<b>CA209067</b>	<b>NIVO+IPI N=313, n (%)</b>	<b>Nivolumab N=313, n (%)</b>	<b>RR (95% CI)</b>
Any cause severe AE (Grade ≥3)	215 (68.7%)	136 (43.5%)	<b>1.58 (1.36, 1.83)</b>
AE leading to discontinuation	135 (43.1%)	43 (13.7%)	<b>3.14 (2.31, 4.26)</b>
Death due to study drug toxicity	0	1 (0.3%)	0.33 (0.01, 8.15)
Most frequent study drug related AEs (>5% in any treatment arm)			
• Diarrhoea	138 (44.1%)	60 (19.2%)	<b>2.30 (1.77, 2.98)</b>
• Fatigue	110 (35.1%)	107 (34.2%)	1.03 (0.83, 1.27)
• Pruritus	104 (33.2%)	59 (18.9%)	<b>1.76 (1.33, 2.33)</b>
• Rash	89 (28.4%)	68 (21.7%)	1.31 (1.00, 1.72)
• Nausea	81 (25.9%)	41 (13.1%)	<b>1.98 (1.40, 2.78)</b>
• Pyrexia	58 (18.5%)	18 (5.8%)	<b>3.22 (1.94, 5.34)</b>

Source: Table 31, p108, Table 33, pp113-114 of the submission, Table 8.1-1, p68 of CA224047 CSR v1.0; Table 34, p118 and Table 36, pp125-126 of the submission; Table 8.1-2, p126 of CA209067 CSR v1.0.

AE = adverse event, NIVO= nivolumab, NR = not reported, RELA = relatlimab, TEAE = treatment emergent adverse event.

**Bold** indicates statistically significant results.

6.44 The ESC considered the comparison of adverse events in the CA224047 and CA209067 trials somewhat unclear. The ESC noted that in the nivolumab monotherapy treatment arms, there were more Grade 3 or higher AEs in trial CA209067 (43%) than trial CA224047 (33%) and that the rates of the common most frequent drug related AEs were also higher for nivolumab in CA209067 than CA224047 (diarrhoea 19.2% vs 9.2%; pruritis 18.9% vs 15.9%; fatigue 34.2% vs 12.8%; rash 21.7% vs 12.0%). The ESC considered that these differences demonstrated potential transitivity issues between the trial populations and the investigator assessment of AEs.

6.45 To support the claim that RELA+NIVO was superior in terms of safety compared to NIVO+IPI, the submission presented indirect comparisons of safety based on the data from the CA224047 and CA209067 trials. The indirect analysis of safety demonstrated that NIVO+IPI was associated with statistically significantly more any drug-related AEs,

any Grade 3 or 4 AEs, drug-related Grade 3 or 4 AEs, any SAEs, drug-related SAEs, any AEs leading to discontinuation, and drug-related AEs leading to discontinuation, compared with RELA+NIVO.

- 6.46 The submission also presented an adjusted ITC for safety using an inverse probability treatment weighting approach to adjust for differences in baseline characteristics. After weighting, NIVO+IPI was associated with higher Grade 3 or 4 AEs compared with RELA+NIVO (78.5% compared with 40.2%). The submission did not present a comparison of treatment related deaths between the two trials.

### Benefits/harms

- 6.47 A summary of the comparative benefits and harms for RELA+NIVO versus nivolumab monotherapy is presented in Table 9. No comparison of benefits and harms was presented for RELA+NIVO versus NIVO+IPI as submission presented an ITC with a claim of non-inferior efficacy.

**Table 9: Summary of comparative benefits and harms for RELA+NIVO and nivolumab monotherapy**

<b>Benefits</b>						
<b>Event</b>	<b>RELA+NIVO</b>		<b>Nivolumab</b>		<b>Absolute difference</b>	<b>HR (95% CI)</b>
<b>Progression-free survival (median duration of follow-up 13.21 months)</b>						
Progressed, n (%)	180/355 (50.7%)		211/359 (58.8%)		-	<b>0.75 (0.62, 0.92)</b>
Median PFS, months (95% CI)	10.12 (6.37, 15.74)		4.63 (3.38, 5.62)		5.49 months	
% not progressed at 6 months (95% CI)	57.2% (51.5%, 62.5%)		44.1% (38.5%, 49.5%)		13.1%	
% not progressed at 12 months (95% CI)	47.7% (41.8%, 53.2%)		36.0% (30.5%, 41.6%)		11.7%	
<b>Overall survival (median duration of follow-up 19.27 months)</b>						
Deaths, n/N (%)	137/355 (38.6%)		160/359 (44.6%)		-	<b>0.80 (0.64, 1.01)</b>
Median OS, months (95% CI)	NA (32.2, NR)		34.1 (25.23, NR)		-	
% alive at 12 months (95% CI)	77.0% (72.2%, 81.1%)		71.6% (66.6%, 76.0%)		5.4%	
% alive at 24 months (95% CI)	63.7% (58.1%, 68.7%)		58.3% (52.7%, 63.4%)		5.4%	
<b>Harms</b>						
	<b>RELA+NIVO n/N (%)</b>	<b>Nivolumab n/N (%)</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients*</b>		<b>RD (95% CI)</b>
				<b>RELA+NIVO</b>	<b>Nivolumab</b>	
Pruritus	83 (23.38%)	57 (15.88%)	<b>1.47 (1.09, 1.99)</b>	23.4	15.9	<b>0.08 (0.02, 0.13)</b>
Fatigue	82 (23.10%)	46 (12.81%)	<b>1.80 (1.30, 2.51)</b>	23.1	12.8	<b>0.10 (0.05, 0.16)</b>
Rash	55 (15.49%)	43 (11.98%)	1.29 (0.89, 1.87)	15.5	12	0.04 (-0.02, 0.09)
Arthralgia	51 (14.37%)	26 (7.24%)	<b>1.98 (1.27, 3.11)</b>	14.4	7.2	<b>0.07 (0.03, 0.12)</b>
Hypothyroidism	51 (14.37%)	43 (11.98%)	1.20 (0.82, 1.75)	14.3	12.0	0.02 (-0.03, 0.07)
Diarrhoea	48 (13.52%)	33 (9.19%)	1.47 (0.97, 2.23)	13.5	9.2	0.04 (0.00, 0.09)
Any cause TEAE leading to Discontinuation	69 (19.44%)	41 (11.42%)	<b>1.87 (1.23, 2.84)</b>	19.4	11.4	<b>0.08 (0.03, 0.13)</b>
Death due to study drug toxicity	3 (0.85%)	2 (0.56%)	1.52 (0.25, 9.02)	0.8	0.6	0.00 (-0.01, 0.02)

Source: Table 25, p87, Table 26, p90, Table 31, p108, Table 33, pp113-114 of the submission.

AE = adverse event, CI = confidence interval, n = number of participants reporting data, N = total participants in group, NIVO = nivolumab, OS = overall survival, HR = hazard ratio, PBO = placebo, PFS = progression-free survival, RD = risk difference, RELA = relatlimab, RR = risk ratio, TEAE = treatment emergent adverse event.

**Bold** indicates statistically significant results.

- 6.48 On the basis of direct evidence presented by the submission, for every 100 patients treated with RELA+NIVO in comparison to nivolumab monotherapy:
- Approximately 5 additional patients will remain alive after 24 months.
  - Approximately 12 additional patients will remain progression-free after 12 months.
- 6.49 For every 100 patients treated with RELA+NIVO in comparison with nivolumab over a median duration of follow-up of 13.21 months:
- Approximately 8 additional patients would experience pruritus.
  - Approximately 10 additional patients would experience fatigue.
  - Approximate 7 additional patients would experience arthralgia.
  - Approximately 8 additional patients would discontinue treatment due to AEs.

### **Clinical claim**

- 6.50 The submission described RELA+NIVO as superior in terms of effectiveness and inferior in terms of safety compared to nivolumab monotherapy. The ESC considered that nivolumab monotherapy was not the appropriate primary comparator.
- 6.51 The ESC and PBAC considered that the efficacy claim was supported; however, the magnitude of the treatment effect was uncertain as:
- there was no statistically significant difference in the OS benefit observed between RELA+NIVO and nivolumab monotherapy (HR = 0.80; 95% CI: 0.64, 1.01); and
  - the CA224047 trial data were immature as median OS for the RELA+NIVO arm had not been reached at the October 2021 data cut.
- 6.52 The PBAC considered that the claim of inferior safety versus nivolumab monotherapy was supported by the data presented.
- 6.53 The submission described RELA+NIVO as non-inferior in terms of effectiveness and superior in terms of safety compared to NIVO+IPI based on the results of the ITC between RELA+NIVO and NIVO+IPI, using nivolumab monotherapy as a common reference arm. The ESC noted that this was the more relevant clinical comparison.
- 6.54 The ESC and PBAC considered that the clinical claim that RELA+NIVO was non-inferior in terms of effectiveness was uncertain as:
- there were transitivity issues between the CA224047 and CA209067 trials used in the ITC including differences in PD-L1 status and BRAF mutation status; and

- the use of different data cut-offs and truncation with censoring to align follow-up durations across trials in the adjusted ITC may not have been appropriate. The submission could have used the data from the 2017 cut-off data (3 years median follow-up) in the MAIC.
- 6.55 The ESC considered the claim of a superior safety profile for RELA+NIVO (trial CA224047) compared to NIVO+IPI (trial CA209067) was also uncertain noting that there were potential transitivity issues between the trials as there were more Grade 3 or higher AEs in the nivolumab monotherapy arm of CA209067 (43%) than in CA224047 (33%).
- 6.56 The PBAC considered that the claim of superior comparative safety versus NIVO+IPI was not adequately supported by the data.

### ***Economic analysis***

- 6.57 The submission presented a cost-utility analysis (CUA) of RELA+NIVO compared to nivolumab monotherapy based on the results of the direct randomised trial, CA224047. Key components of the economic evaluation are presented in Table 10.
- 6.58 The ESC noted that the submission did not present an economic evaluation of RELA+NIVO compared with NIVO+IPI, based on the claim of non-inferior efficacy.
- 6.59 The PSCR argued (p4) and the pre-PBAC response (p2) reiterated that it was reasonable to present only an economic evaluation of RELA+NIVO versus nivolumab monotherapy as it allowed for the assessment of the cost-effectiveness of RELA+NIVO to be based on direct RCT evidence. The ESC considered that the CUA analysis presented in the submission was not informative as nivolumab monotherapy was not the appropriate comparator. Overall, the ESC considered that a cost minimisation approach for NIVO+RELA versus NIVO+IPI for the main economic evaluation would be more appropriate as NIVO+IPI was considered to be the more appropriate comparator.
- 6.60 NIVO+IPI was recommended by the PBAC in July 2018 for the treatment of unresectable Stage III or IV malignant melanoma on the basis of cost neutrality to the PBS, that is, that the total sum of expenditure by the Australian Government for PD-1 inhibitors plus ipilimumab would not increase following the listing of NIVO+IPI compared to nivolumab monotherapy (paragraphs 7.1 and 7.09, NIVO+IPI PSD, July 2018).

**Table 10: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	RELA+NIVO vs nivolumab
Time horizon	20 years in the model base case versus 19 months in trial
Outcomes	Life years and Quality-adjusted life years
Methods used to generate results	Cohort analysis of partitioned survival (i.e., area under the curve);
Health states	Pre-progression, Post-progression and Death
Cycle length	1 month
Allocation to health states (if partitioned survival model)	Health state over time was determined by PFS and OS KM data based on the CA224047 trial extrapolated using parametric curve fitting. Allocation of treatment and AE costs and disutilities were determined by time-to-treatment discontinuation data based on the CA224047 trial extrapolated using parametric curve fitting.
Extrapolation method	Parametric model fitted to each treatment arm with log-normal distribution selected in base case for OS, generalised gamma distribution selected in base case for PFS, and Weibull distribution selected in base case for TTD based on goodness of fit and visual inspection. 92% of the life-years gained, 91% of the incremental QALYs (discounted) and 26% of incremental costs (discounted) occurred in the extrapolated period.
Health related quality of life	Trial-based Progression-free = 0.80 Progressed = 0.75

Source: Table 59, p200 and Table 65, p217 of the submission; 'NIVO\_RELA\_Section3model' workbook

AE = adverse event, KM = Kaplan-Meier, NIVO = nivolumab, OS = overall survival, PFS = progression-free survival, QALY = Quality-adjusted life years, RELA = relatlimab, TTD = time-to treatment discontinuation.

- 6.61 The submission presented a partitioned survival model with three mutually exclusive health states: pre-progression, post-progression, and death to model the costs and health outcomes for RELA+NIVO versus nivolumab monotherapy for the treatment of unresectable Stage III or IV malignant melanoma.
- 6.62 The median duration of follow-up was 19 months for both the RELA+NIVO and nivolumab monotherapy arms, based on the CA224047 trial. Parametric distributions with best relative fit according to Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) were used to extrapolate the KM function curves (OS, PFS, TTD) from the median follow-up time over a time horizon of 20 years.
- 6.63 A 20-year time horizon may be too long in the population of advanced melanoma. Of note, the PBAC has previously accepted a five-year time horizon in the context of recommending PBS listing of pembrolizumab for melanoma (March 2015 PBAC meeting). The PBAC had also noted that a time horizon of ten years was not supported by the clinical evidence and favoured nivolumab significantly in its consideration of nivolumab (July 2015 PBAC meeting) and NIVO+IPI in melanoma (November 2015 PBAC meeting). The PSCR (p3) argued that the 20-year time horizon was appropriate as treatment with RELA+NIVO affects the long-term/ongoing quality of life of patients and the starting age of the modelled cohort was 61 years, consistent with the baseline characteristics of trial CA224047 and the target population. The ESC noted the inconsistency of the proposed time horizon with previously PBAC accepted time horizons for immunotherapy in a population with advanced melanoma. The ESC

acknowledged that immunotherapy is continuing to evolve and that historically accepted time horizons may no longer be reasonable; however, the ESC remained uncertain as to whether immunotherapy is achieving a cure or a significant delay in disease recurrence. The ESC considered a modelled 10–15-year time horizon would be more appropriate. The pre-PBAC response (p2) argued that the modelled 20 year time horizon was potentially conservative.

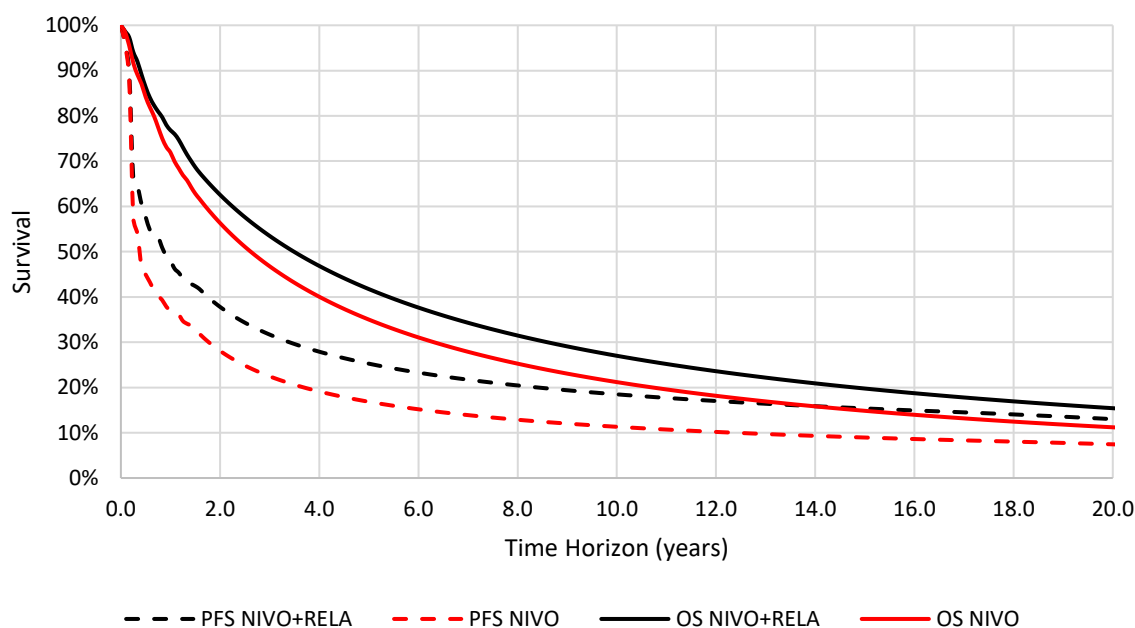
6.64 The results of sensitivity analyses indicate that the model was sensitive to a reduction in the time horizon (the ICER increased by 16% when the time horizon was reduced to 15 years). A graph plotting the estimated incremental cost-effectiveness ratio against changes in the time horizon is presented in Figure 8.

Figure 8: A trace of ICER over time



6.65 Figure 9 summarises the extrapolated curves for RELA+NIVO and nivolumab monotherapy used in the economic evaluation.

Figure 9: Partitioned survival model curves



Source: Figure 51, p201 of the submission.

NIVO = nivolumab, OS = overall survival, PFS = progression-free survival, RELA = relatlimab.

6.66 In the partitioned model, extrapolation of the hazard was based only on the time trend in the hazard observed for the within-trial period (up until 19 months in this model) which was unrealistically assumed to generalise throughout the extrapolation period (up to 20 years). The relative treatment effect was maintained beyond the trial duration, and hence, the survival curves did not converge. The ESC considered that maintaining a survival benefit based on the non-statistically significant difference in

the observed OS was inappropriate and resulted in highly uncertain outcomes. Notably, 92% of the incremental life-years gained and 91% of the QALYs gained occurred in the extrapolation period. The pre-PBAC response stated that the modelled incremental PFS benefit in favour of RELA+NIVO peaked at 19 months and gradually decreased during the extrapolation phase, similar to the modelled OS benefit. The pre-PBAC response further stated that the modelled OS benefit was conservative, given the incremental OS benefit of NIVO+IPI over nivolumab monotherapy in the CA209067 trial at 5 and 6 years was approximately 7.4% and 8.1%, respectively, compared to an incremental OS benefit of RELA+NIVO over nivolumab monotherapy equal to 6.7% and 6.6%, respectively, in the base case model.

- 6.67 Furthermore, OS and PFS curves generated for the nivolumab arm may have been underestimated compared with OS and PFS curves observed in the nivolumab arm in the extended follow-up (data cut-off: October 2020; 6.5-years follow-up) of the CA209067 trial. At 6.5-years follow-up, PFS curve for nivolumab plateaued, with PFS rate of 29% at Year 5 and Year 6. This was different from the PFS probabilities generated by the economic model, which were approximately 16.7% at Year 5 and 15.1% at Year 6. Similarly, at 6.5-years follow-up, the OS curve for nivolumab plateaued, with OS rate of 44% at Year 5 and 43% at Year 6. This was different from the OS probabilities generated by the economic model, which were approximately 36% at Year 5 and 31% at Year 6. The ESC considered that the model likely underestimated the OS and PFS outcomes for the nivolumab monotherapy arm, overestimating the incremental benefit of NIVO+RELA. The ESC also considered that the modelled 15% survival at 20 years in the RELA+NIVO arm and 11% survival in the nivolumab monotherapy arm was highly optimistic for a population of advanced cancer patients.
- 6.68 With immunotherapy, complex hazard function shapes can arise both within and beyond the trial period because of delayed responses to treatment and the existence of long-term survivors (plateaued survival curves). The submission did not plot the assumed long-term hazard in each trial arm and the assumed treatment effect in the short and long-term, which made it difficult to assess the suitability of the parametric models used. The submission also did not consider flexible parametric survival methods along with the standard parametric models presented. The PSCR (p3) disagreed that the extrapolation of survival curves was uncertain and claimed that the base case economic evaluation used conservative extrapolations of the survival curves, noting that the sensitivity analyses using the generalised gamma and Gompertz parametric distribution for OS resulted in lower base case ICERs. The pre-PBAC response (p3) noted that extrapolation of OS also incorporated Australian life table data and applied the higher of the mortality rates at each time point between the parametric model and the lifetable data. The ESC considered that application of more complex/flexible parametric functions to the trial data may have improved the plausibility and credibility of the extrapolation to inform decision making. The ESC

agreed with the evaluation that the extrapolations conducted in the model should be validated using external data, such as the extended follow up of the CA 209067 trial.

6.69 Based on the CA224047 trial, the submission estimated a utility of 0.80 in the progression-free state and 0.75 in the progressive disease state. Although these values were similar to those presented previously for nivolumab monotherapy (July 2015) and NIVO+IPI (November 2015), the PBAC has previously considered that the application of absolute utility values of approximately 0.8 for non-progressive and progressive disease states appeared to be high for a population with advanced cancer (paragraph 6.49, Nivolumab plus Ipilimumab, PSD, November 2015 PBAC meeting). The trial-based utility values for the progression health state appeared high for a population with advanced cancer. This may be due to collection of EQ-5D data during the earlier stages of progressive disease rather than across the entire period from disease progression to palliative care and death.

6.70 A summary of the key drivers of the model is presented in Table 11.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact Base case: \$ <sup>1</sup> /QALY gained.
Time horizon	20 years in the model base case versus 19 months in trial.	High, favours RELA+NIVO. Decreasing the time horizon from 20 years to 10 years increased the ICER by 53.6% to \$ <sup>2</sup> /QALY.
Extrapolation	Parametric model fitted to each treatment arm with log-normal distribution selected in base case for OS, generalised gamma distribution selected in base case for PFS, and Weibull distribution selected in base case for TTD based on goodness of fit and visual inspection.	Moderate. The submission did not consider flexible parametric survival methods and did not validate the model using external data. The submission tested generalised gamma and Gompertz parametric distribution for overall survival (the next best fits according to AIC and BIC values), this decreased the ICER by 21.5% and 18.3%, respectively.
Subsequent treatment	A one-off subsequent cost of \$ <sup>3</sup> for RELA+NIVO and \$25,290.10 for nivolumab was applied when a patient discontinued treatment.	Low. Assuming no difference in the subsequent treatment received by patients in the RELA+NIVO arm and the nivolumab arm, the ICER increased by 10.05% to \$ <sup>3</sup> /QALY.

Source: Table 59, p200 and Table 60, p205, Table 80, pp236-237 of the submission.

EQ-5D = EuroQol five-dimensional instrument, ICER = incremental cost-effectiveness ratio, NIVO = nivolumab, OS = overall survival, PFS = progression-free survival, QALY = quality-adjusted life years, RELA = relatimab, TTD = time-to treatment discontinuation.

The redacted values correspond to the following ranges:

<sup>1</sup>\$55,000 to < \$75,000

<sup>2</sup>\$95,000 to < \$115,000

<sup>3</sup>\$75,000 to < \$95,000

6.71 The total health care resource use cost, consisting of hospital-based costs and medical benefits schedule (MBS) cost of care, applied to the economic model for both pre-progression and post-progression health states, was \$<sup>1</sup>. This cost is based on 2013 data and was not adjusted to 2022 prices but is not expected to significantly impact the results of the economic evaluation.

6.72 The results of the modelled economic evaluation are summarised in Table 12.

**Table 12: Results of the stepped economic evaluation**

Step and component	RELA+NIVO	Nivolumab	Increment
<b>Step 1: trial-based costs and outcomes (drug acquisition cost)</b>			
Costs (\$)			
LYG	1.326	1.263	0.063
Incremental cost/extra LYG gained			\$ <sup>1</sup>
<b>Step 2: time horizon extended to 20 years</b>			
Costs (\$)			
LYG	6.777	5.681	1.097
Incremental cost/extra LYG gained			\$ <sup>2</sup>
<b>Step 3: discounting (5%) included</b>			
Costs (\$)			
LYG	4.962	4.249	0.713
Incremental cost/extra LYG gained			\$ <sup>3</sup>
<b>Step 4: incorporation of medical resource costs (health care resource use, drug administration, subsequent treatment and AEs)</b>			
Costs (\$)			
LYG	4.962	4.249	0.713
Incremental cost/extra LYG gained			\$ <sup>3</sup>
<b>Step 5: utility weights applied</b>			
Costs (\$)			
QALYs	3.880	3.299	0.582
Incremental cost/extra QALY gained (base case)			\$ <sup>3</sup>

Source: NIVO\_RELA\_Section3model economics workbook.

LYG = life-years gained, NIVO = nivolumab, QALY = quality-adjusted life years, RELA = relatlimab.

*Italics corrected during evaluation (using correct AEMP for RELA+NIVO (\$<sup>1</sup> instead of \$<sup>2</sup>), private hospital mark-up fee for RELA+NIVO (\$108.62 instead of \$68.21) and public weighting of 32.01% for RELA+NIVO and nivolumab. DPMA of \$<sup>3</sup> (inclusive of % SPR) for nivolumab.*

The redacted values correspond to the following ranges:

<sup>1</sup>\$455,000 to < \$555,000

<sup>2</sup>\$45,000 to < \$55,000

<sup>3</sup>\$55,000 to < \$75,000

6.73 For patients treated with RELA+NIVO, the economic evaluation estimated the following when a 20-year time horizon was applied:

- Cost of RELA+NIVO drug was \$<sup>1</sup> (undiscounted), resulting in an additional cost of \$<sup>1</sup> over nivolumab monotherapy.
- Approximately 6.7 life-years gained (undiscounted), resulting in an improvement of approximately 1.1 life-years over nivolumab monotherapy.
- Approximately 5.3 QALYs gained (undiscounted), resulting in an improvement of approximately 0.9 QALYs gained over nivolumab monotherapy.

6.74 Based on the economic model presented in the submission, treatment with RELA+NIVO was associated with a cost per QALY gained of \$55,000 to < \$75,000 compared to nivolumab monotherapy, for the treatment of patients with unresectable stage III or IV malignant melanoma.

6.75 The results of key sensitivity analyses are summarised in Table 13.

Table 13: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)
<b>Base case</b>		<b>0.582</b>	<b>1</b>
<b>Univariate sensitivity analyses</b>			
% and Discount rate (base case 5% costs and outcomes)			
• 0%		0.894	2
• 3.5%		0.656	3
Time horizon (base case 20 years)			
• 5 years		0.205	4
• 10 years		0.383	5
• 15 years		0.502	6
OS extrapolation (base case log-normal)			
• Generalised gamma		0.745	1
• Gompertz		0.715	1
• Log-log		0.535	6
TTD Extrapolation (base case Weibull)			
• Generalised gamma		0.582	1
Subsequent treatment costs (different treatment cost)			
• No difference between arms		0.582	6
<b>Multivariate sensitivity analyses</b>			
Assuming no difference between arms in subsequent treatment and varying time horizon			
• 5 years		0.205	4
• 10 years		0.383	7
• 15 years		0.502	5

Source: Table 80, pp236-237 of the submission.

ICER = incremental cost-effectiveness ratio, NIVO = nivolumab, OS = overall survival, RELA = relatlimab, TTD = time-to-discontinue. *Italics corrected during evaluation (using correct AEMP for RELA+NIVO (\$█████ instead of \$█████), private hospital mark-up fee for RELA+NIVO (\$█████ instead of \$█████) and public weighting of 32.01% for RELA+NIVO and nivolumab and DPMA of \$█████ (inclusive of █████% SPR) for nivolumab.*

The redacted values correspond to the following ranges:

<sup>1</sup>\$55,000 to < \$75,000

<sup>2</sup>\$45,000 to < \$55,000

<sup>3</sup>\$55,000 to < \$75,000

<sup>4</sup>\$155,000 to < \$255,000

<sup>5</sup>\$95,000 to < \$115,000

<sup>6</sup>\$75,000 to < \$95,000

<sup>7</sup>\$155,000 to < \$255,000

6.76 The results of sensitivity analyses indicate that the model was most sensitive to a reduction in the time horizon. The model was also sensitive to subsequent treatment, the choice of parametric extrapolation for overall survival and time-to-treatment discontinuation.

6.77 In terms of the model presented, the ESC considered that the base case ICER was highly uncertain and optimistic as:

- the 20-year time horizon was too long and was inconsistent with what had been previously accepted by the PBAC in this setting. The ESC considered that a 10 to 15-year time horizon would be more reasonable;
- maintenance of a survival benefit based on the non-statistically significant difference in observed OS was not appropriate;
- OS and PFS in the nivolumab monotherapy arm were underestimated; and
- the utility values applied for non-progressive and progressed disease were high and not representative of a population with advanced cancer.

### Drug cost/patient/course

Table 14: Drug cost per patient for proposed and comparator drugs

	RELA+NIVO			NIVO monotherapy		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose/infusion	NR	640 mg FDC Q4W	640 mg FDC Q4W	NR	480 mg Q4W	480 mg Q4W
Mean duration (months), (undiscounted) <sup>a</sup>	11.01	18.5	16.15	11.38	21.2	17.43
Cost/patient/month <sup>b</sup> (\$)	[REDACTED]					
Cost/patient/course <sup>c</sup> (\$)	[REDACTED]					

Sources: Table 6.1-1, p31 and Table 6.1-2, p32 of CA224047 CSR v2, 'NIVO\_RELA\_Section3model.xls' and 'Section4\_BIM.xls'  
 DPMA = dispensed price for maximum amount; FDC = fixed dose combination; NIVO = nivolumab; NR = not reported; Q4W = every 4 weeks; RELA+NIVO = relatlimab + nivolumab

<sup>a</sup> Mean duration estimated during financial estimates were based on weighted duration of treatment for first line and second line

<sup>b</sup> Cost/patient/month calculated using proposed relatlimab + nivolumab effective DPMA (weighted) of \$ [REDACTED] assuming 32.01% public/67.99% private split at a dose of 640 mg every 4 weeks, and nivolumab effective DPMA (weighted) of \$ [REDACTED] assuming 32.01% public/67.99% private split at a dose of 480 mg every 4 weeks, for approximately 1.087 cycles (1 month).

<sup>c</sup> Cost/patient/course = cost/patient/month × mean duration

6.78 For the financial estimates, the submission estimated the average duration of RELA+NIVO (first line) based on the time-to-treatment discontinuation (TTD) curve extrapolated at 6 years from the economic model. The extrapolated average TTD at 6 years (16.46 months for RELA+NIVO; undiscounted) was chosen to align with the time horizon of the financial estimates. However, this was shorter than the average TTD from the extrapolation presented over the entire time horizon of 20 years (18.5 months, undiscounted). Similarly, the average duration for nivolumab used in the financial estimates was different from the economic model (17.43 months compared with 21.2 months).

### Estimated PBS usage & financial implications

6.79 This submission was considered by DUSC.

6.80 The submission presented a mixed epidemiological and market share approach to estimate the use of RELA+NIVO for the treatment of unresectable Stage III or IV malignant melanoma. The estimated use and financial implications of listing RELA+NIVO are summarised in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
<b>Eligible population</b>		
Incident patients commencing treatment in 1L	1,964 in 2023 increasing to 2,004 in 2028; projection was generated based on the 10% PBS service data log trend from Mar 2020.	The submission assumed the market size for melanoma was to remain relatively flat due to saturation of the market uptake of the new treatments. DUSC considered that the growth rate in melanoma cases (< 1%) was underestimated compare to AIHW projections (2.9% to 3.7%).
Incident patients commencing treatment in 2L <sup>a</sup>	159 across Year 1 to 6; projection based on the 12-month historical average of the available 10% PBS data sample, from Jan 2021 to Dec 2021	
Total incident patients	2,123 in 2023 increasing to 2,164 in 2028	
<b>Treatment utilisation</b>		
Substitution rate	Substitution rate of 68% for PD-1 and 28% for NIVO+IPI based on expert opinion.	The substitution rate of 80% for PD-1 monotherapy and 33% for NIVO+IPI based on expert opinion was adjusted down by 15%. DUSC considered that the substitution rates were difficult to estimate.
<b>Duration of treatment</b>		
RELA+NIVO	16.15 months based on extrapolated KM TTD data at Year 6 from CA224047 trial and persistence data available from Prospecion (10% PBS data sample data).	DUSC considered that this was possibly underestimated (see paragraph 6.59)
PD-1 monotherapy	17.43 months based on extrapolated KM TTD data at Year 6 from CA224047 trial and persistence data available from Prospecion (10% PBS data sample data).	-
NIVO+IPI induction	1.81 months based on persistence data available from Prospecion (10% PBS data sample data).	-
NIVO maintenance	20.1 months derived by adjusting 10% PBS data sample data, by 112% in the first line and 116% in the second-line setting, to reflect the proportional use between PD-1 monotherapy and nivolumab in the maintenance phase of NIVO+IPI.	DUSC considered that this was possibly overestimated (see paragraph 6.59). Conservatively, the submission could have used either the extrapolated duration of treatment (17.76 months) or the data from the CA224047 trial.
<b>Costs</b>		
MBS item 13950	\$112.40	This was consistent with the economic model.
PBS/RPBS split	PBS = 96%, RPBS = 4%	-
Public/Private split	Public = 32.01%, Private = 67.99%	This was inconsistent with the public/private split used in Section 3, which was 31.3% for public weighting.
Co-payment	PBS = \$22.50, RPBS = \$6.28	-

Source: Table 81, p240, Table 82, p245, Table 84, p247 of the submission.

AIHW = Australian Institute of Health and Welfare, IPI = ipilimumab, KM = Kaplan Meier, NIVO = nivolumab, PD-1 = programmed death protein-1, RELA = relatlimab, TTD = time-to-treatment discontinuation.

<sup>a</sup> Includes patients who have previously received BRAF inhibitor treatment

6.81 The estimated net financial implications to the PBS/RPBS and MBS are summarised in Table 16.

**Table 16: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	■* <sup>1</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>
Total number of infusions <sup>a</sup>	■ <sup>2</sup>	■ <sup>3</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>
<b>Estimated financial implications of RELA+NIVO</b>						
Cost to PBS/RPBS less co-payments (\$)	■ <sup>5</sup>	■ <sup>6</sup>	■ <sup>7</sup>	■ <sup>7</sup>	■ <sup>7</sup>	■ <sup>7</sup>
<b>Estimated financial implications for PD-1 monotherapy and NIVO+IPI</b>						
Cost to PBS/RPBS less co-payments (\$)	■ <sup>b 5</sup>	■ <sup>b 8</sup>	■ <sup>b 9</sup>	■ ■ <sup>b 7</sup>	■ ■ <sup>b 7</sup>	■ <sup>b 7</sup>
<b>Net financial implications</b>						
<b>Net cost to PBS/RPBS (\$)</b>	■ <sup>b 5</sup>	■ <sup>b 10</sup>	■ <sup>b 11</sup>	■ <sup>b 11</sup>	■ <sup>b 11</sup>	■ <sup>b 11</sup>
Net cost to MBS (\$)	■ <sup>12</sup>	■ <sup>12</sup>	■ <sup>12</sup>	■ <sup>12</sup>	■ <sup>12</sup>	■ <sup>12</sup>
<b>Net cost to PBS/RPBS/MBS (\$)</b>	■ <sup>b 5</sup>	■ <sup>b 10</sup>	■ <sup>b 11</sup>	■ <sup>b 11</sup>	■ <sup>b 11</sup>	■ <sup>b 11</sup>

Source: Table 82, p245, Table 84, p247, Table 86, p249 and Table 102, p261 of the submission, Table 103, p261, Table 105, p262, Table 106, p263; 'Section 4\_BIM.xls' financial workbook.

\* The submission assumed Year 1 began in August 2023

<sup>a</sup> Assuming 17.55 infusions per treatment course as estimated by the submission. Infusions were amortised across years.

<sup>b</sup> Calculated during evaluation using DPMA of \$■ (inclusive of ■% SPR) for nivolumab.

The redacted values correspond to the following ranges:

<sup>1</sup>< 500

<sup>2</sup>500 to < 5,000

<sup>3</sup>5,000 to < 15,000

<sup>4</sup>15,000 to < 25,000

<sup>5</sup>\$0 to < \$10 million

<sup>6</sup>\$60 million to < \$70 million

<sup>7</sup>\$100 million to < \$200 million

<sup>8</sup>\$40 million to < \$50 million

<sup>9</sup>\$90 million to < 100 million

<sup>10</sup>\$20 million to < 30 million

<sup>11</sup>\$50 million to < 60 million

<sup>12</sup>net cost saving

6.82 The submission estimated there would be a decrease in expenditure to the MBS due to the decreased number of administrations.

6.83 The overall net cost to the Government of listing RELA+NIVO was estimated to be \$50 million to < \$60 million in Year 6, and a total of \$200 million to < \$300 million over the first 6 years of listing.

- The DUSC considered that the main sources of uncertainty relating to the estimated financial implications of RELA+NIVO in the unresectable Stage III or IV melanoma setting were: that the submission underestimated the growth rate in melanoma cases (< 1%) compared to Australian Institute of Health and Welfare's projections (2.9% to 3.7%);

- that the substitution rates of PD-1 monotherapy (nivolumab and pembrolizumab) and NIVO+IPI were uncertain as they were based on expert opinion, and then adjusted downwards by 15% (the submission stated that the substitution rates represented a more aggressive uptake of new treatments and would not reflect actual clinical practice). DUSC considered that the substitution rates were difficult to estimate and agreed with the submission that the expert opinion estimates of 80% substitution of PD-1 monotherapy and 33% substitution of NIVO+IPI treatment seemed to be an overestimate. This was particularly true for certain subgroups of patients with poor clinical prognostic risk factors who would still likely be treated with IPI+NIVO (e.g. high LDH, BRAF+, patients brain metastases, etc.)
- regarding the submissions forecast of the number of first-line metastatic therapy patients initiating PD-1 (based on PBS items for “Unresectable Stage III or Stage IV malignant melanoma”), DUSC agreed that the availability of adjuvant PD-1 treatments (i.e. for resected stage malignant melanoma) on the PBS from March 2020 meant that after this, patients were likely to have been treated earlier in their disease and may not have developed metastatic disease. Thus, it was appropriate to use the number of initiating first-line metastatic patients from March 2020 as the basis for the forecast. However, DUSC considered that some of these patients would relapse (i.e. those who have late relapses, greater than 6 months after adjuvant PD-1 inhibitor treatment) and be eligible for RELA+NIVO and that these patients had not been accounted for in the estimates; and
- that the methods for estimating duration of treatment with RELA+NIVO and the substituted therapies, PD-1 monotherapy and NIVO+IPI, were complex and the estimates could not be verified by DUSC. The durations of treatment for RELA+NIVO and PD-1 monotherapy were based on the economic model plus some adjustments based on the 10% PBS sample analysis. The duration of treatment for NIVO+IPI was based on the 10% PBS sample analysis with some adjustments based on the economic model. Overall DUSC considered that the duration of RELA+NIVO treatment was possibly underestimated as the extrapolated average time to treatment discontinuation at 6 years was used as compared to 20 years in the economic model. The duration of nivolumab maintenance phase as part of NIVO+IPI treatment was likely overestimated as the submission estimated it to be 20.01 months, whereas the CA209067 trial calculated it as 8.07 months over 3 years of follow-up. The overestimation of the duration of treatment for a substituted therapy would have resulted in an underestimate of the net cost to the PBS.

6.84 The pre-PBAC response stated that:

- the utilisation estimates reflect a reasonable estimate of long-term, real-world use of the intervention and comparator medicines; and

- duration of treatment was estimated utilising time-to-treatment-discontinuation Kaplan Meier curves from the economic model and the clinical trial evidence. In addition, duration of treatment estimates for all therapies were based on the number of months of treatment for nivolumab monotherapy derived from the time-to-treatment discontinuation curve and adjusted (i) for a proportion of patients receiving treatment with BRAF inhibitors in the second line setting; and (ii) to maintain the relative relationship of treatment duration between RELA+NIVO and PD-1 monotherapy as per the CA224047 trial and between NIVO+IPI and PD-1 monotherapy as per PBS utilisation data. Further, the pre-PBAC response stated that (i) updated duration of treatment data from CM209067 at 7.5 years follow-up for nivolumab monotherapy supported the validity of the treatment duration proposed in the submission as both were equivalent at 17.4 months and (ii) CA209067 likely underestimated the duration of treatment for NIVO+IPI due to high discontinuation rates at the time of the trial; however, as management of adverse events associated with ipilimumab has improved, it would be reasonable to anticipate longer duration of treatment with NIVO+IPI in the current setting.

### **Quality Use of Medicines**

- 6.85 The submission included an extensive quality use of medicines approach to ensure the appropriate use of RELA+NIVO in the treatment of metastatic melanoma. The submission's approach included physician education, immune-oncology preceptorship, peer to peer support, nursing and pharmacy in-services, a risk management plan, educational materials and tools, and guidance on monitoring and treating immune related adverse reactions.

### **Financial Management – Risk Sharing Arrangements**

- 6.86 The sponsor proposed to work with the Department to implement an appropriate Risk Sharing Arrangement to accompany the PBS listing of RELA+NIVO including the possible restructure of the existing melanoma PBS expenditure caps to reflect the evolving melanoma market.

*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 relatlimab with nivolumab (RELA+NIVO) fixed dose combination product for the treatment of patients with unresectable Stage III or IV malignant melanoma. The PBAC considered that there is a low clinical need for RELA+NIVO as there are existing effective treatment options available on the PBS (programmed cell death protein 1 (PD-1) monotherapy (nivolumab and pembrolizumab) and combination therapy (nivolumab plus ipilimumab (NIVO+IPI)). The PBAC considered that the nominated primary comparator of nivolumab

monotherapy was not appropriate and that the cost utility analysis versus nivolumab monotherapy was therefore not informative. The PBAC noted that the estimated financial impact of RELA+NIVO was high and uncertain.

- 7.2 The PBAC considered that the proposed place in therapy of RELA+NIVO, as a first line alternative to currently available PD-1 based therapies (i.e. pembrolizumab, nivolumab or NIVO+IPI) was reasonable.
- 7.3 The PBAC considered that the nomination of nivolumab monotherapy as the primary comparator was not appropriate. The PBAC noted that the submission nominated NIVO+IPI as a secondary comparator. The PBAC considered that NIVO+IPI would have been a more reasonable primary comparator as clinical guidelines recommend the use of combination therapy over PD-1 inhibitor monotherapy if tolerated and, as a combination treatment, RELA+NIVO is more likely to replace combination treatment (NIVO+IPI) rather than monotherapy.
- 7.4 The PBAC noted that the submission was based on one randomised controlled trial comparing RELA+NIVO with nivolumab monotherapy (CA224047) and an indirect treatment comparison (ITC) between RELA+NIVO (CA224047) and NIVO+IPI (CA209067) using nivolumab monotherapy as the common reference.
- 7.5 The PBAC noted that the submission described RELA+NIVO as superior in terms of effectiveness compared to nivolumab monotherapy. The PBAC considered that this claim was supported by the data but noted that given the difference in overall survival (OS) observed between RELA+NIVO and nivolumab monotherapy was not statistically significant (HR = 0.80; 95% CI: 0.64, 1.01) and as the data were immature (median OS for the RELA+NIVO arm was not reached after a median follow up of 19.27 months), the magnitude of the treatment effect was uncertain.
- 7.6 The PBAC considered that the claim that RELA+NIVO was inferior compared to nivolumab monotherapy in terms of safety was appropriate, noting that RELA+NIVO was associated with more Grade  $\geq 3$  treatment-related adverse events (AEs) and more AEs resulting in discontinuation from the CA224047 trial.
- 7.7 The PBAC considered that the ITC between RELA+NIVO and NIVO+IPI was the more appropriate comparison. The PBAC noted that the results of the ITC showed no statistically significant differences between RELA+NIVO and NIVO+IPI in terms of OS (HR = 0.94; 95% CI: 0.68, 1.30) or progression free survival (PFS; HR = 1.01; 95% CI: 0.76, 1.36). However, considered that the clinical claim that RELA+NIVO was non-inferior in terms of effectiveness compared to NIVO+IPI was uncertain due to the transitivity issues between the trials (paragraph 6.10). The PBAC noted the submission presented a matching-adjusted indirect comparison (MAIC) to adjust for differences in baseline characteristics between the trials. The PBAC noted that although the MAIC estimates for efficacy were similar to the ITC estimates, the data cut-offs applied were not consistent with those applied in the ITC analysis for PFS, OS and safety which may have biased the results.

- 7.8 In addition, in comparing the populations recruited in CA224047 and CA209067, the PBAC noted patients with metastatic melanoma disease with higher risk features would have been unlikely to have been enrolled in trial CA224047, as the standard of care for these patients is NIVO+IPI. The PBAC therefore considered that the CA224047 population likely had a lower risk profile and that it was unclear whether RELA+NIVO was as effective in higher risk patients.
- 7.9 The PBAC considered that the claim that RELA+NIVO was superior compared to NIVO+IPI in terms of safety was not adequately supported by the data. The PBAC noted the differences in rates of Grade  $\geq 3$  AEs and other drug-related AEs were higher in the nivolumab monotherapy arm of CA209067 compared to the nivolumab monotherapy arm of CA224047. The PBAC considered that these differences were possibly a result of the transitivity issues between the trial populations and differences in the investigator assessment of AEs, meaning that a meaningful comparison of AEs between the trials was difficult.
- 7.10 The PBAC noted that the submission presented a cost utility analysis comparing RELA+NIVO with nivolumab monotherapy. No economic comparison versus NIVO+IPI was presented in the submission. The PBAC considered that the economic model presented was not informative as nivolumab monotherapy was not the appropriate primary comparator.
- 7.11 The PBAC considered that a more appropriate economic evaluation would be a cost minimisation approach comparing RELA+NIVO with NIVO+IPI.
- 7.12 The PBAC noted that the estimated financial impact of listing RELA+NIVO was high (\$200 million to < \$300 million over the first 6 years). The PBAC noted the uncertainties in the estimates highlighted by DUSC (paragraph 6.60). In particular, the PBAC considered that the substitution rates of PD-1 monotherapy and NIVO+IPI were highly uncertain, noting that the submission considered the expert opinion sought was unlikely to reflect clinical practice, and the substantially higher substitution of monotherapy versus that for NIVO+IPI was not justified.
- 7.13 The PBAC noted that the proposed restriction was generally consistent with the current PBS listing for NIVO+IPI for the treatment of unresectable Stage III or IV malignant melanoma and considered that this was reasonable.
- 7.14 The PBAC considered a resubmission for RELA+NIVO should:
- nominate NIVO+IPI as the primary comparator and present a clinical comparison of RELA+NIVO versus NIVO+IPI that addresses the transitivity issues raised in the evaluation;
  - present an economic evaluation between RELA+NIVO and NIVO+IPI using a cost minimisation approach;

- present revised financial impact estimates addressing the issues raised in the evaluation and by DUSC.
- 7.15 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.16 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

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

## **9 Sponsor's Comment**

The sponsor had no comment.