An addendum to this public summary document has been included at the end of the document

7.03 RELATLIMAB AND NIVOLUMAB, Solution concentrate for I.V. infusion containing 80 mg relatlimab and 240 mg nivolumab in 20 mL vial, Opdualag®, Bristol-Myers Squibb Australia Pty Ltd.

1 Purpose of submission

1.1 The Standard Re-Entry 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 based on a cost-minimisation approach versus nivolumab in combination with ipilimumab (NIVO+IPI).

Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	Patients with unresectable Stage III or IV malignant melanoma previously untreated with a PD-1 inhibitor for this indication.
Intervention	RELA + NIVO fixed-dose combination (160 mg / 480 mg IV every 4 weeks)
Comparator	NIVO + IPI combination - Induction period: IPI 3 mg/kg IV plus NIVO 1 mg/kg IV every 3 weeks for 4 doses. Maintenance period: NIVO 3 mg/kg or 240 mg IV every 2 weeks or 480 mg IV every 4 weeks (After 6 weeks from the last dose of the induction period)
Outcomes	Primary: PFS Secondary: OS, ORR, HRQoL, and safety
Clinical claim	RELA+NIVO is non-inferior to NIVO+IPI regarding clinical efficacy RELA+NIVO has a different, potentially more favourable, safety profile than NIVO+IPI For CMA, RELA+NIVO is non-inferior to NIVO+IPI in terms of comparative safety.

Source: Table 16, pp50-51, Table 18, p53, Table 19, p54, of the resubmission, and table 31 of the original submission.
FU= follow-up, PD-L1= programmed death-ligand, RELA= relatlimab, NIVO= nivolumab, IPI= ipilimumab, PFS= progression-free survival, OS= overall survival, ORR= overall response rate, AEs= adverse events, HRQoL= health-related quality of life, CMA=Cost-minimisation analysis

2 Background

Registration Status

2.1 OPDUALAG® was TGA approved on the 7th of October of 2022 for the treatment of patients with unresectable or metastatic melanoma who are at least 12 years old.

Previous PBAC consideration

2.2 This resubmission is the second submission for RELA+NIVO for the treatment of unresectable Stage III or IV melanoma. The first submission was considered at the July

2022 PBAC meeting and was not recommended. The first submission requested a listing based on a cost-utility analysis versus NIVO monotherapy. The PBAC considered NIVO monotherapy inappropriate as the primary comparator. Therefore, the cost-utility analysis and the estimated financial impact were not informative.

2.3 The PBAC nominated a resubmission via the standard re-entry pathway. The PBAC considered that a resubmission for this treatment should (paragraph 7.14, RELA+NIVO, Public Summary Document (PSD), July 2022 PBAC meeting):

- Nominate NIVO+IPI as the primary comparator and present a clinical comparison of RELA+NIVO versus NIVO+IPI that addressed 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.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical Claim	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 was more likely to replace combination treatment (NIVO+IPI) rather than monotherapy (paragraph 7.3, RELA+NIVO PSD, July 2022) The PBAC considered that the clinical claim that RELA+NIVO was non-inferior in terms of effectiveness versus NIVO+IPI was uncertain due to transitivity issues between the trials used in the ITC (paragraph 7.7, RELA+NIVO PSD, July 2022) The PBAC considered that the data did not adequately support the claim of superior comparative safety versus NIVO+IPI. (paragraph 7.9, RELA+NIVO PSD, July 2022).	Addressed. The resubmission nominated NIVO+IPI as the primary comparator. The resubmission presented an aITC of RELA+NIVO vs. NIVO+IPI using the IPTW method to account for imbalances in the distribution of baseline characteristics between the CA209067 and CA224047 trials. The resubmission modified the clinical claim to: - RELA+NIVO is non-inferior to NIVO+IPI in terms of clinical efficacy - RELA+NIVO has a different, potentially more favourable, safety profile compared to NIVO+IPI. - RELA+NIVO is non-inferior to NIVO+IPI in terms of comparative safety (for CMA purposes)
Clinical effectiveness	The PBAC noted that the clinical effectiveness and safety results were uncertain, given the transitivity issues. (paragraph 6.44 and 7.7, RELA+NIVO PSD, July 2022). The ESC and PBAC considered that using different data cut-offs and truncation with censoring to align follow-up durations across trials in the adjusted ITC may not have been appropriate.(paragraphs 6.54 and 7.7, RELA+NIVO PSD, July 2022).	Partially Addressed. Transitivity issues introduced by differences in the trials noted by the PBAC in the original submission, such as PD-L1 status, BRAF mutation status, prior therapy and AJCC staging criteria were addressed in the adjusted ITC using IPTW The resubmission kept the same truncation and censoring as used in the previous submission. The truncation of the CA209067 used a 6.5-year database lock with various data-cuts to align the median follow-up times with the available data for CA224047.
Economic Evaluation	The PBAC advised that a cost-minimisation of RELA+NIVO against NIVO+IPI would be a more appropriate form of economic evaluation (paragraphs 7.11 and 7.14, RELA+NIVO PSD, July 2022)	Addressed. The resubmission presented an economic evaluation between RELA+NIVO and NIVO+IPI using a cost-minimisation approach.
Financial Impact	The PBAC considered the estimated financial impact of RELA+NIVO was high and uncertain. (paragraph 7.14, RELA+NIVO PSD, July 2022)	Addressed. The resubmission presented revised financial impact estimates addressing the issues raised in the evaluation and by DUSC.

Source: Table 11, pp31-33; item 3, p66; item 4, p80; and table 33, pp 81-82 of the resubmission

PBAC= Pharmaceutical Benefits Advisory Committee; PSD=public summary document DUSC= Drug Utilisation Sub Committee; RELA= relatlimab; IPI= ipilimumab; NIVO= nivolumab; PD-1= programmed death-ligand; CMA= cost-minimisation approach; ITC= indirect treatment comparison; aITC= adjusted indirect treatment comparison; IPTW= inverse probability treatment weighting

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

3 Requested listing

Medical Product Form	DPMA	Maximum Amount	№ of Repeats
Nivolumab / Relatlimab, 240 mg / 80 mg in 20 mL vial	Published: $38,600.48 Effective: $[redacted]	2	8 initial, 11 continuing
Available brands			
OPDUALAG ®. Bristol-Myers Squibb Australia Pty Ltd			
Restriction for relatlimab/nivolumab - initial treatment			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED)			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangements apply.			
Administrative Advice: *No increase in the maximum amount or number of units may be authorised*			
Episodicity: [blank]			
Severity: Unresectable Stage III or Stage IV			
Condition: Malignant melanoma			
Indication: Unresectable Stage III or Stage IV malignant melanoma			
Treatment Phase: Initial treatment			
Clinical criteria:			
Patients must not have received prior treatment with ipilimumab or a PD-1 inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma.			
AND			
Clinical criteria:			
Patients 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.			
AND			
Clinical criteria:			
Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1			
AND			
Clinical criteria:			
The condition must not be uveal melanoma.			
AND			
Clinical criteria:			
The treatment must be the sole PBS-subsidised therapy for this condition.			
Population criteria:			
Patients must weigh at least 40 kg.			
Population criteria:			
Patients must be 12 years of age or older.			
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.			

Cautions: - 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. - In the first few months after the 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 scan taken at least 4 weeks later.
Restriction for relatlimab/nivolumab – continuing treatment
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required – Streamlined
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: *No increase in the maximum amount or number of units may be authorised.*
Episodicity: [blank]
Severity: Unresectable Stage III or Stage IV
Condition: Malignant melanoma
Indication: Unresectable Stage III or Stage IV malignant melanoma
Treatment Phase Continuing *treatment*
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria:
Patients must have previously ~~been issued with an authority prescription for~~ *received PBS-subsidised treatment with this* drug for this condition.
AND
Clinical criteria:
Patients must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.
Population criteria:
~~Patients 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.*

Source: Table 8, p24, table 9, pp26-27 of the resubmission
Suggestions PBAC from the July 2022 meeting are added in italics and suggested deletions are crossed out with a strikethrough. Additional changes proposed by the Sponsor are in bold strikethrough

3.1 The resubmission proposed a Special Pricing Arrangement. The requested effective price was % lower than in the previous submission ($ versus $ in July 2022).

3.2 The resubmission included additional clinical criteria which required the patient to be 12 years of age or older and to weigh at least 40 kg. This was in accordance with the recommendations made by PBAC (paragraph 3.1, RELA+NIVO PSD, July 2022) and the

TGA registration for OPDUALAG®. The resubmission also removed the prescription instruction of maximum doses under a weight-based dosing regimen.

3.3 The requested restriction was consistent with the TGA registration and the maximum quantity and maximum number of repeats requested was consistent with the dosing schedule.

3.4 ESC noted, that if recommended, RELA+NIVO would be the first fixed dose combination therapy listed on the Section 100 Efficient Funding of Chemotherapy (EFC). It was noted that the addition of a Section 100 EFC combination product presented system challenges for Services Australia, prescribing software vendors and dispensing software vendors around correct dose calculation and payment as per the EFC algorithm as these systems were not designed to accommodate combination dose EFC medicines. This would require significant changes to software, the EFC calculation algorithm and Services Australia. The Secretariat advised that this would be a lengthy process.

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 from melanoma worldwide. It was estimated that melanoma would become the 3rd most-diagnosed cancer in Australia in 2022, with an estimated 17,756 new cases. Based on 2011-2016 data, the overall 5-year survival rate of patients diagnosed with Stage III and IV melanoma was approximately 61.1% and 26.2%, respectively[1].

4.2 The resubmission proposed RELA+NIVO as an 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 resubmission's proposed place in therapy for RELA+NIVO remains unchanged from the original submission. The current guidelines are presented in Figure 1 and the resubmission's proposed to place in therapy for RELA+NIVO is presented in Figure 2.

Figure 1: Current metastatic melanoma treatments available in Australia

	BRAF-negative				BRAF-positive				
1L / 2L	PD-1 inhibitor treatment[a]			IPI[b]	PD-1 inhibitor treatment[a]			IPI[b]	BRAF inhibitor-based treatment[b]
	NIVO	PEMBRO	NIVO+IPI		NIVO	PEMBRO	NIVO+IPI		

Source: Figure 1, p22 of the resubmission.
BRAF= B-RAF protein, IPI= ipilimumab, PEMBRO= pembrolizumab, PD1= programmed cell death protein 1, NIVO= nivolumab.
[a] PBS allows treatment with one PD-1 inhibitor-based treatment per patient. Prior therapy with IPI excludes PD-1 inhibitor treatment.
[b] PBS allows treatment with IPI and BRAF inhibitor-based treatment as either 1st or 2nd line treatment.

[1] 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

Figure 2: Future metastatic melanoma treatments available in Australia

	BRAF-negative				BRAF-positive				
1L / 2L	PD-1 inhibitor treatment[a]			IPI[b]	PD-1 inhibitor treatment[a]			IPI[b]	BRAF inhibitor-based treatment[b]
	NIVO	PEMBRO	NIVO+IPI		NIVO	PEMBRO	NIVO+IPI		
	RELA+NIVO				RELA+NIVO				

Source: Figure 2, p22 of the resubmission

BRAF= B-RAF protein, IPI= ipilimumab, PEMBRO= pembrolizumab, PD1= programmed cell death protein 1, NIVO= nivolumab, RELA= relatlimab.

[a] PBS allows treatment with one PD-1 inhibitor-based treatment per patient. The choice between those listed above. Prior therapy with IPI excludes PD-1 inhibitor treatment.

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

4.3 Melanoma treatment guidelines from Australia[2] and overseas[3,4] recommend the use of combination therapy over PD-1 inhibitor monotherapy to treat unresectable stage III or IV metastatic melanoma in patients with good performance status and aggressive diseases, regardless of BRAF mutation status.

4.4 The resubmission also recommended that first-line systemic therapy be individualised based on clinical factors. The National Comprehensive Cancer Network (NCCN) suggests that for patients with BRAF mutation and who would benefit from a more rapid response, BRAF/MEK inhibition may be preferred.

4.5 Relatlimab is a fully human antibody specified for LAG-3, which binds to a defined epitope on LAG-3 and blocks the interaction of LAG-3 with its ligand. This enhances the activation of 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), activating T-cells and cell-mediated immune responses against tumour cells or pathogens.

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

5 Comparator

5.1 The resubmission nominated NIVO+IPI as the main comparator, (paragraph 7.3, RELA+NIVO PSD, July 2022 PBAC meeting). The ESC considered that the main comparator was appropriate.

5.2 NIVO+IPI was recommended by the PBAC in July 2018 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 and ipilimumab would not increase following the listing of NIVO+IPI for unresectable Stage III or IV melanoma (paragraph 7.9, NIVO+IPI PSD, July 2018).

[2] Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of melanoma. https://wiki.cancer.org.au/australia/Guidelines:Melanoma

[3] National Comprehensive Cancer Network (NCCN), (2022). Clinical Practice Guidelines in Oncology. Cutaneous Melanoma (V.3). https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

[4] European Society for Medical Oncology (ESMO), Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2019, Annals of Oncology, 30. Available from: https://www.annalsofoncology.org/article/S0923-7534(20)32563-1/pdf

5.3 Under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: NIVO and PEMBRO monotherapy. Results of the head-to-head trial comparing RELA+NIVO with NIVO monotherapy indicated that RELA+NIVO was statistically superior in terms of PFS (HR = 0.75; 95% CI: 062, 0.92) and numerically superior in terms of OS (HR = 0.80; 95% CI: 0.64, 1.01).

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from two organisations via the Consumer Comments facility on the PBS website. Rare Cancers Australia stated that there remains an unmet need to continue to improve the survival outcomes for patients with metastatic melanoma and that the two checkpoint inhibitors (RELA and NIVO) target distinct immune checkpoint pathways and RELA+NIVO offers the potential for clinically meaningful survival with a manageable safety profile.

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)[5], based on a comparison with nivolumab.

Clinical trials

6.4 The resubmission was based on the same two head-to-head, randomised, double-blinded trials presented in the original submission.

- Trial CA224047 compared RELA+NIVO (n=355) to NIVO monotherapy (n=359), with a follow-up of 3 years.
- Trial CA209067 compared NIVO+IPI (n=314) or NIVO monotherapy (n=316) to IPI monotherapy (n=315), with a truncation cut-off of 6.5-year follow-up.

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

6.5 Details of the CA224047 and CA209067 trials presented in the submission are provided in Table 3.

Table 3: Trials CA224047 and CA209067, and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
CA224047	A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with NIVO v/s 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 v/s Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma	Jan 2022
	Tawbi, H. A., et al. Relatlimab and Nivolumab v/s Nivolumab in Untreated Advanced Melanoma.	*New England Journal of Medicine* 2022; 386(1): 24-34
CA209067	A Phase 3, Randomized, Double-blind Study of NIVO Monotherapy or NIVO Combined with IPI v/s IPI Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma	June 2015
	Wolchok JD., et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma	*New England Journal of Medicine* 2017; 377(14): 1345-1356
	Regan, M. M., et al. Treatment-free survival over an extended follow-up of patients with advanced melanoma treated with immune checkpoint inhibitors in CheckMate 067	*Journal for Immunotherapy of Cancer* 2021; 9(11): 1-8
	Wolchok, J. D., et al. Long-Term Outcomes with Nivolumab Plus Ipilimumab or Nivolumab Alone v/s Ipilimumab in Patients with Advanced Melanoma	*Journal of Clinical Oncology* 2021; 40(2): 127-137

Source: Table 12, pp 36-40 of the resubmission

6.6 Regan (2021) and Wolchok (2021) were not included in the previous submission; however, they did not add any additional data or information to what was presented in the original submission.

6.7 The key features of the CA224047 and CA209067 trials are summarised in Table 4.

Table 4: Key features of the included evidence – direct comparison

Trial	N	Design / duration	Risk of bias	Patient population	Outcome(s)
RELA+NIVO vs. NIVO					
CA224047	RELA+NIVO arm: 355 NIVO arm: 359	R, DB, MC 3 years	Low	Unresectable or metastatic melanoma	OS, PFS, ORR, HRQol, AEs
NIVO+IPI vs. NIVO					
CA209067	NIVO+IPI arm: 314 NIVO arm: 316 IPI arm: 315	R, DB, MC 6.5 years[a]	Low	Unresectable or metastatic melanoma	OS, PFS, ORR, HRQol, AEs

Source: Table 22, pp75-77, Table 23, pp79-82, Table 24, pp84 of the submission

R= randomised. DB= double-blind; MC= multi-centre, PFS= progression-free survival, OS= overall survival, ORR= overall response rate, AEs= adverse events, HRQoL= health-related quality of life

[a] total duration of followup is 6.5 years (utilised for the adjusted clinical comparison) and 7.5 years (time on treatment utilised in the economic modelling)

6.8 Adequate randomisation and double blinding techniques in both trials minimised the risk of selection, performance, and detection bias. There was no evidence of selective reporting across both trials. The risk of attrition bias was also low across trials. Overall, the risk of bias across both trials was low.

6.9 There were no direct head-to-head trials comparing RELA+NIVO with NIVO+IPI for the treatment of patients with unresectable stage III or IV malignant melanoma.

Therefore, the resubmission presented an adjusted indirect treatment comparison (aITC) of RELA+NIVO versus NIVO+IPI to support the claim that RELA+NIVO is non-inferior to NIVO+IPI in terms of clinical efficacy.

6.10 The methodology used to conduct the aITC was an inverse probability treatment weighting (IPTW) to account for imbalances in the distribution of baseline characteristics between the CA209067 and CA224047 trials. The IPTW is recommended[6,7] for treating imbalances in the distribution of baseline characteristics in an ITC. This methodology creates weights based on a propensity score to remove the presence of confounding, allowing a comparison of outcomes directly in the weighted sample. The IPTW builds a synthetic sample standardising each of the treated and control samples to a common reference sample. The same approach was presented as a secondary comparison in the first submission. While the approach is the same, more information was presented in the resubmission. The use of IPTW to conduct the aITC in this resubmission to address the transitivity issues was appropriate.

6.11 The baseline factors included in the propensity score model are presented in Table 5.

Table 5: Baseline factors included in the propensity score model

Demographics	Age (continuous)
	Sex (male vs female)
	Geographic region (Rest of World vs USA)
Disease characteristics	ECOG performance status (≥1 vs 0)
	Time from advanced melanoma diagnosis until randomisation (continuous, yrs)
	Prior adjuvant therapy (yes vs no)
	AJCC M stage with LDH category 1 (M1any [1] vs M0/M1any [0])
	AJCC disease stage at study entry (Stage III vs stage IV)
	Melanoma subtype (cutaneous acral vs non-acral; mucosal vs cutaneous non-acral; other vs cutaneous non-acral)
	BRAF mutation status (positive vs wild type)
	Baseline LDH category 1 (> ULN vs ≤ ULN)
	Baseline LDH category 2 (> 2 X ULN vs ≤ 2 X ULN)
	PD-L1 expression category (≥ 1% vs < 1%/non-quantifiable)

Source: Table 13, pp43-44 of the resubmission.
AJCC= American Joint Committee on Cancer, BRAF= B-Raf proto-oncogene, ECOG= Eastern Cooperative Oncology Group, LDH= lactate dehydrogenase, PD-L1= programmed death-ligand 1

6.12 The selection of these baseline factors as predictors and variables (PD-L1 expression and BRAF mutation status) in the propensity score model was consistent subgroup analyses that suggested that PD-L1 expression and BRAF mutation status could be potential treatment effect modifiers on the outcomes of interest. LAG-3 status at baseline was also noted to be a potential treatment effect modifier on the outcomes; however, was not included in the propensity score model.

[6] Austin, P, 2011. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies.
[7] Austin, P, et al., 2021. Applying Propensity Score Methods in Clinical Research in Neurology.

6.13 A summary of baseline characteristics before and after weighting is shown in Table 6.

Table 6: Summary baseline characteristics before and after weighting

Characteristics	RELA+NIVO		NIVO+IPI		SMD	
	Before	After[a]	Before	After[a]	Before	After
N	**349**	**340**	**307**	**298**	-	-
Demographics						
Mean age, years (SD)	61.22 (13.98)	60.62 (14.15)	59.50 (13.63)	60.44 (13.59)	0.125	0.013
Sex, n/N (%)					0.139	0.025
Male	205/349 (58.7%)	204/340 (60.0%)	201/307 (65.5%)	185/298 (62.2%)		
Female	144/349 (41.3%)	136/340 (39.0%)	106/307 (34.5%)	113/298 (37.8%)		
Race, n/N (%)					0.196	0.171
White	336/349 (96.3%)	329/340 (96.8%)	303/307 (98.7%)	294/298 (98.6%)		
Non-white	7/349 (2.0%)	6/340 (1.8%)	4/307 (1.3%)	4/298 (1.4%)		
Missing	6/349 (1.7%)	5/340 (1.4%)	0/307	0/298		
Geographic region, n/N (%)					0.26	0.039
Rest of world	312/349 (89.4%)	292/340 (86.0%)	246/307 (80.1%)	252/298 (84.6%)		
USA	37/349 (10.6%)	48/340 (14.0%)	61/307 (19.9%)	46/298 (15.4%)		
History of smoking, n/N (%)					0.198	0.220
Never smoked	211/349 (60.5%)	205/340 (60.2%)	156/307 (50.8%)	147/298 (49.4%)		
Current/former	123/349 (35.2%)	121 (35.5%)	137/307 (44.6%)	136/298 (45.6%)		
Missing	15/349 (4.3%)	14 (4.3%)	14/307 (4.6%)	15/298 (5.0%)		
Disease characteristics						
Mean time from diagnosis to randomisation, years (SD)	2.85 (4.85)	3.18 (5.42)	3.57 (4.48)	3.34 (4.16)	0.154	0.031
Prior adjuvant therapy, n/N (%)					0.367	0.074
Not received	315/349 (90.3%)	291/340 (85.6%)	236/307 (76.9%)	247/298 (83.0%)		
Received	34/349 (9.7%)	49/340 (14.4%)	71/307 (23.1%)	51/298 (17.0%)		
AJCC M stage with LDH category 1, n/N (%)					0.036	0.013
M0/M1 any [0]	230/349 (65.9%)	225/340 (66.2%)	197/307 (64.2%)	196/298 (65.6%)		
M1 any [1]	119/349 (34.1%)	115/340 (33.8%)	110/307 (35.8%)	102/298 (34.4%)		
AJCC disease stage, n/N (%)					0.182	0.034
Stage III	35/349 (10.0%)	28/340 (8.1%)	16/307 (5.2%)	22/298 (7.2%)		
Stage IV	314/349 (90.0%)	312/340 (91.9%)	291/307 (94.8%)	276/298 (92.8%)		
Melanoma subtype, n/N (%)					0.328	0.100
Cutaneous acral	39/349 (11.2%)	26/340 (7.7%)	11/307 (3.6%)	16/298 (5.3%)		
Cutaneous non-acral	245/349 (70.2%)	252/340 (74.0%)	242/307 (78.8%)	228/298 (76.5%)		
Mucosal	23/349 (6.6%)	24/340 (7.2%)	27/307 (8.8%)	23/298 (7.7%)		
Other	42/349 (12.0%)	38/340 (11.1%)	27/307 (8.8%)	31/298 (10.5%)		
History of brain metastases, n/N (%)					0.078	0.077
Presence of history	342/349 (98.0%)	333/340 (98.0%)	297/307 (96.7%)	288/298 (96.8%)		
Absence of history	7/349 (2.0%)	7/340 (2.0%)	10/307 (3.3%)	10/298 (3.2%)		
ECOG PS, n/N (%)					0.135	0.027
≥1	116/349 (33.2%)	104/340 (30.6%)	83/307 (27.0%)	87/298 (29.3%)		
0	233/349 (66.8%)	236/340 (69.4%)	224/307 (73.0%)	211/298 (70.7%)		
BRAF mutation status, n/N (%)					0.109	0.010
Wild type	216/349 (61.9%)	216/340 (63.6%)	206/307 (67.1%)	191/298 (64.1%)		
Mutation positive	133/349 (38.1%)	124/340 (36.4%)	101/307 (32.9%)	107/298 (35.9%)		
LDH category 1, n/N (%)					0.015	0.009
≤ULN	223/349 (63.9%)	220/340 (64.6%)	194/307 (63.2%)	191/298 (64.2%)		
>ULN	126/349 (36.1%)	120/340 (35.4%)	113/307 (36.8%)	107/298 (35.8%)		
LDH category 2, n/N (%)					0.094	0.010
> 2 X ULN	31/349 (8.9%)	33/340 (9.7%)	36/307 (11.7%)	30/298 (10.0%)		

Characteristics	RELA+NIVO		NIVO+IPI		SMD	
	Before	After[a]	Before	After[a]	Before	After
≤ 2 X ULN	318/349 (91.1%)	307/340 (90.3%)	271/307 (88.3%)	268/298 (90.0%)		
PD-L1 expression category, n/N (%)					0.186	0.027
<1%/non-quantifiable	205/349 (58.7%)	186/340 (54.7%)	152/307 (49.5%)	159/298 (53.4%)		
≥1%	144/349 (41.3%)	154/340 (45.3%)	155/307 (50.5%)	139/298 (46.7%)		

Source: Table 14, pp 44-46 of the resubmission.
AJCC= American Joint Committee on Cancer, BRAF= B-Raf proto-oncogene, IPI= ipilimumab, LDH= lactate dehydrogenase, ECOG PS= Eastern Cooperative Oncology Group Performance Status, NIVO= nivolumab, PD-L1= programmed death-ligand 1, RELA= relatlimab, SD= standard deviation, SMD= standard mean difference, ULN= upper limit of normal.
[a] n is back-calculated from the percentage (only percentages were reported in the indirect comparison study report).

6.14 The propensity score model aimed to balance the characteristics reported at the baseline. The baseline characteristics were well matched following the IPTW approach, except for the smoking status, where the standard mean difference (SMD) after weighting was higher (0.220) than before this treatment (0.198). Overall, the IPTW analysis improved the comparability between the trials (CA224047 and CA209067) and addressed the transitivity issues between baseline status allowing the aITC of RELA+NIVO versus NIVO+IPI to be performed.

6.15 The resubmission did not present any further information regarding unbalancing smoking status as this factor was not considered a relevant issue in the subgroup analysis.

6.16 The ESC considered that the use of the IPTW approach in the ITC was appropriate considering the differences between the trials at baseline.

Comparative effectiveness

6.17 The aITC was presented, based on the results of the IPTW. The results from the July 2022 submission's unadjusted ITC using the Bucher method are also presented for comparison.

6.18 The resubmission used truncation of data to align the median follow-up times in the two trials (median follow up in CA224047 = 33 months; median follow up in CA209067 = 32 months).

6.19 In July 2022, the PBAC noted that the truncation of data and censoring to align median follow-up times may not have been appropriate and could have resulted in biased results (paragraphs 6.38 and 6.54, RELA+NIVO PSD, July 2022).

6.20 The resubmission stated that the truncation of CA209067 at the 6.5-year database lock was the most appropriate to emulate the available data for CA224047. The resubmission reported cut-offs for the aITC as follows:

- For the CA224047 trial:
  - For OS and PFS: Data from October 2021 cut-off (19.27 months OS median follow-up).
- For the CA209067 trial:
  - For PFS: Data from 2015 cut-off (PFS median extent of follow-up was 12.2 to 12.5 months).

- For OS: Data from October 2020 cut-off. However, this was truncated to August 2016 to emulate the first per-protocol analysis of OS and to align the median follow-up duration from the CA224047 trial (after truncation, the minimum follow-up in the CA209067 trial was 28 months, and the median follow-up was 32 months). Patients who did not have events by the 1st of August 2016 were censored at this date.

6.21 The key reasons stated in the resubmission for this choice were:

- Using the truncated, unweighted data set, the resulting OS ITC hazard ratio (95% CI) was 0.98 (0.76, 1.25), confirming that differences in follow-up have not created a bias in favour of RELA+NIVO. The slightly higher hazard ratio (aITC HR = 0.98 versus ITC HR = 0.91 to 0.96 provided in the unadjusted analysis) suggested a possible bias against RELA+NIVO. Table 2.6.7 in the main body provides all data-cut points in the unadjusted ITC. Results from the 6.5 year data-cut are provided in Table 8.
- The median follow-up typically reported in publications and clinical study reports represents the median extent of follow-up for OS.
- Truncation of the 6.5-year data on 1st August 2016 resulted in a more comparable median follow-up (32 months for CA209067 versus 33 months for CA224047). The minimum follow-up was shorter for CA224047 (28 months for CA209067 versus 9 months for CA224047). Using the May 2017 data-cut would have resulted in a greater discrepancy between the minimum follow-up (36 months for CA209067 versus 9 months for CA224047.

6.22 Although the submission provided further support for the selection of the follow-up and truncation cut-offs, the same issue of possible bias due to aligning median follow-up remains. It was not clear why different truncations were used for PFS and OS. Data from the May 2017 cut-off (median follow up = 3 years) from the CA209067 trial could have been used.

6.23 Censoring of propensity score model weights occurred at the 5th and 95th percentiles. Trimming of extreme values is routinely used in statistical modelling and it is considered appropriate to limit the impact of very small or large values on the overall estimates. However, it was not clear whether the 5th and 95th percentiles were appropriate as no alternative values were explored.

Indirect Comparison of Effectiveness

Progression-Free Survival (PFS)

6.24 The aITC results for PFS are presented in Table 7 and

6.25 Figure 3.

6.26 PFS with RELA+NIVO, after weighting, demonstrated a non-statistically significant hazard ratio for progression-free survival compared to NIVO+IPI (HR = 1.00; 95% CI = 0.79, 1.25).

Table 7: Indirect analyses of RELA+NIVO vs. NIVO+IPI: PFS

Progression-free survival (PFS)	Direct HR (95% CI) Result < 1 favour combination therapy		Indirect HR (95% CI; p-value) Result < 1 favours RELA+NIVO
	RELA+NIVO vs NIVO[a]	NIVO+IPI vs NIVO	RELA+NIVO vs NIVO+IPI
Adjusted indirect analysis			
Feb 2015 DBL[b] truncated *(unweighted)*	NR	NR	1.08 (0.86, 1.35)
Feb 2015 DBL[b] *truncated (weighted)*[c]	NR	NR	1.00 (0.79, 1.25)
Unadjusted indirect analysis from July 2022 submission			
2020 data-cut. 6.5-year follow-up	0.75 (0.62, 0.92)	0.79 (0.65, 0.97)	0.95 (0.72, 1.26; p = 0.7171)

Source: Table 16, pp50-51 of the resubmission

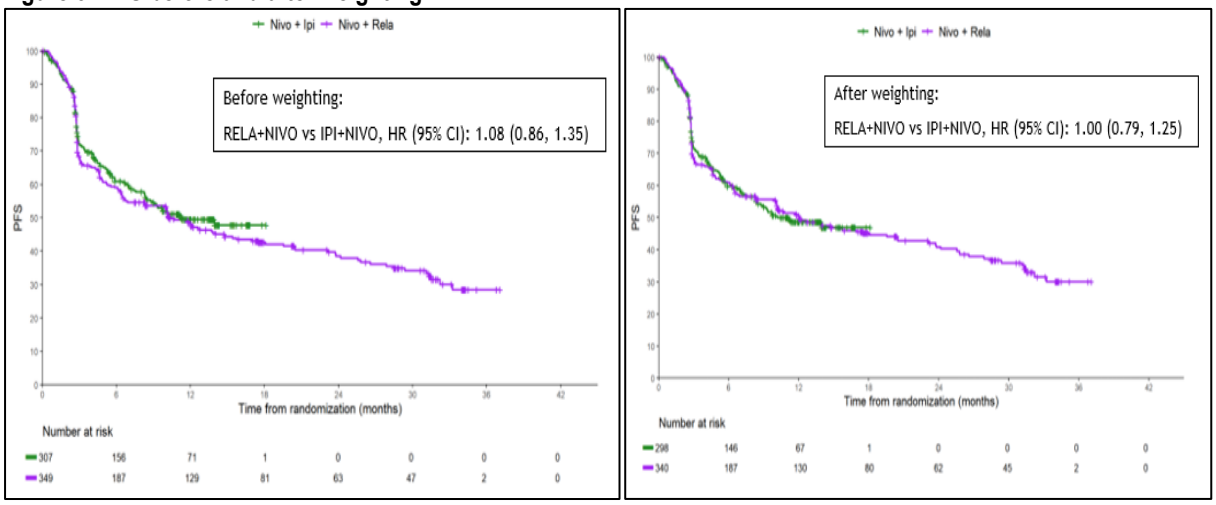
DBL= database lock, CI= confidence interval, HR= hazard ratio, IPI= ipilimumab, NIVO= nivolumab, NR= not reported, PFS= progression-free survival, RELA= relatlimab.

[a] PFS per BICR data March 2021 data-cut CA224047 CSR version 1 Section 7.2 pg. 72

[b] PFS per BICR data were only available from February 17, 2015, DBL (minimum 9-month follow-up).

[c] per IPTW (inverse probability treatment weighting) analysis

Figure 3: PFS before and after weighting



Source: Figure 6, p47 of the resubmission

Overall Survival (OS)

6.27 The aITC results for OS are presented in Table 8 and Figure 4.

6.28 OS with RELA+NIVO, after weighting, demonstrated a numerically lower death hazard compared to NIVO+IPI; however, the result was not statistically significant (HR = 0.87; 95% CI: 0.68, 1.12).

Table 8: Indirect analyses of RELA+NIVO vs. NIVO+IPI: OS (adjusted versus unadjusted)

Overall survival (OS)	Direct HR (95% CI) Result < 1 favour combination therapy		Indirect HR (95% CI; p-value) Result < 1 favours RELA+NIVO
	RELA+NIVO vs NIVO[a]	NIVO+IPI vs NIVO	RELA+NIVO vs NIVO+IPI
Adjusted indirect analysis			
August 2016[b]. truncated (unweighted)	NR	NR	0.98 (0.76, 1.25)
August 2016[b]. truncated (weighted)[c]	NR	NR	0.87 (0.68, 1.12)
Unadjusted indirect analysis from July 2022 submission			
2020 data-cut. 6.5-years follow-up	0.80 (0.64, 1.01)	0.84 (0.67, 1.04)	0.952 (0.694, 1.307; p = 0.7628)

Sources: Table 16, pp 50-51 of the resubmission

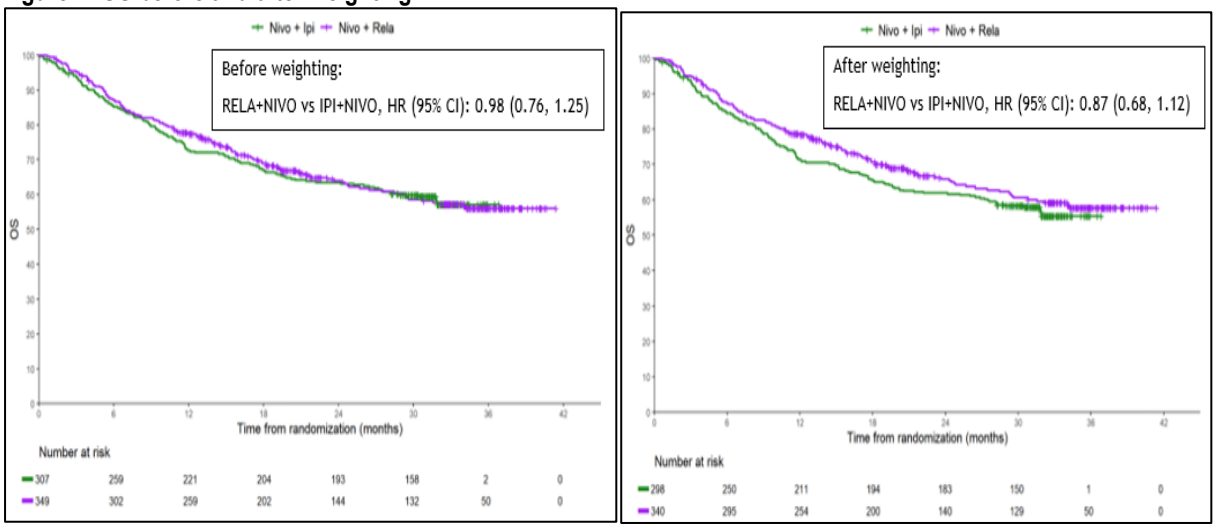
CI= confidence interval, HR= hazard ratio, IPI= ipilimumab, NIVO= nivolumab, NR= not reported, OS= overall survival, RELA= relatlimab.

[a] October 2021 data-cut median follow-up 19.94 months; CA224047 CSR version 2 Section 7.3 pg. 42

[b] November 2021 6.5-year data cut-off truncated at 1-Aug-16 to emulate the median follow-up of the CA224047 Oct-21 data cut-off.

[c] per IPTW (inverse probability treatment weighting) analysis

Figure 4: OS before and after weighting



Source: Figure 7, p48 of the resubmission

6.29 Overall, given the lack of statistically significant results for weighted and unweighted PFS and OS, the resubmission concluded that there was no statistically significant difference between RELA+NIVO and NIVO+IPI in terms of effectiveness. The ESC considered that this conclusion was reasonable; however, there remained some uncertainty given the different duration of the trials (3 versus 7.5 years) and the truncation points chosen. Additionally, the CA224047 trial was initiated in 2018, whereas the CA209067 trial was initiated 2013. The last cut-off for both trials was in 2021.

6.30 Furthermore, a non-inferiority margin was not specified in the indirect comparison.

Comparative harms

Indirect Comparison of Safety

6.31 The resubmission presented the same safety data as the original submission. The data was presented before weighting, using the Bucher (unadjusted) ITC methodology and after weighting, using the IPTW approach. In July 2022, the PBAC noted differences in the rates of Grade ≥ 3 adverse events (AEs) and other drug-related AEs were higher in the NIVO monotherapy arm of CA209067 than in the NIVO 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, stating that comparison of AEs between the trials was difficult (paragraphs 6.44 and 6.45, RELA+NIVO PSD, July 2022).

6.32 The resubmission stated that the safety analysis cut-offs were the same as used in the aITC for efficacy analyses (33 months median follow-up for the CA224047 trial and 32 months median follow-up after truncation for the CA209067 trial).

6.33 The results of the safety comparison for the aITC are provided in Table 9.

Table 9: Safety of RELA+NIVO vs NIVO+IPI before and after weighting

AEs categories	RELA+NIVO		NIVO+IPI	
	Before	After[a]	Before	After[a]
N	349	340	307	298
Any cause AEs (all grades)	339/349 (97.1%)	329/340 (96.9%)	306/307 (99.7%)	297/298 (99.7%)
Any cause AEs (Grade 3 or 4)	142/349 (40.7%)	137/340 (40.1%)	233/307 (75.9%)	234/298 (78.5%)
Study drug-related AEs (all grades)	285/349 (81.7%)	277/340 (81.6%)	294/307 (95.8%)	285/298 (95.6%)
Study drug-related AEs (Grade 3 or 4)	67/349 (19.2%)	65/340 (19.1%)	179/307 (58.3%)	181/298 (60.8%)
Study drug-related AEs leading to discontinuation of treatment	52/349 (14.9%)	50/340 (14.7%)	120/307 (39.1%)	120/298 (40.1%)

Source: Table 19, p54 of the resubmission

AE= adverse event, IPI= ipilimumab, NIVO= nivolumab, RELA= relatlimab.

[a] Using adjusted indirect treatment comparison. n is back-calculated from the percentage (only percentages were reported in the indirect comparison study report).

6.34 The safety outcomes did not change markedly with weighting. Patients treated with NIVO+IPI had higher rates of AEs compared to those treated with RELA+NIVO, particularly for any cause Grade 3 or 4 AEs (78.5% versus 40.2%), study drug-related Grade 3 or 4 AEs (60.8% versus 19.1%), and study drug-related AEs leading to discontinuation of treatment (40.1% versus 14.7%).

6.35 Although the safety outcomes presented above suggest that RELA+NIVO has a better safety profile than NIVO+IPI, uncertainties remain as different AEs are experienced with the different combinations. For example, hypothyroidism was experienced by 14.4% of RELA+NIVO patients, but experienced by < 5% of NIVO+IPI patients.

Benefits/harms

6.36 A benefits and harms table is not presented as the submission claimed non-inferiority.

Clinical claim

6.37 The resubmission claimed that RELA+NIVO was non-inferior to NIVO+IPI in terms of effectiveness as there were no statistically significant differences between RELA+NIVO and NIVO+IPI in terms of PFS and OS. The ESC considered that this claim was reasonable; however, noted that there were uncertainties relating to the:

- differences in the follow up periods of the trials, with less mature OS data available from CA224047;
- use of truncated data from CA209067 to align medium follow up times with CA224047; and
- absence of a nominated non-inferiority margin. The lack of statistically significant differences in the outcomes of the aITCs may not be sufficient to establish non-inferiority.

6.38 The resubmission claimed that RELA+NIVO had a different but non-inferior safety profile and that, on balance, RELA+NIVO was likely to have a more favourable safety profile than NIVO+IPI. The ESC considered that although, the claim of non-inferior safety was adequately supported, the claim the RELA+NIVO was likely to have a more favourable safety profile was not adequately supported as different AEs are experienced with the different combinations.

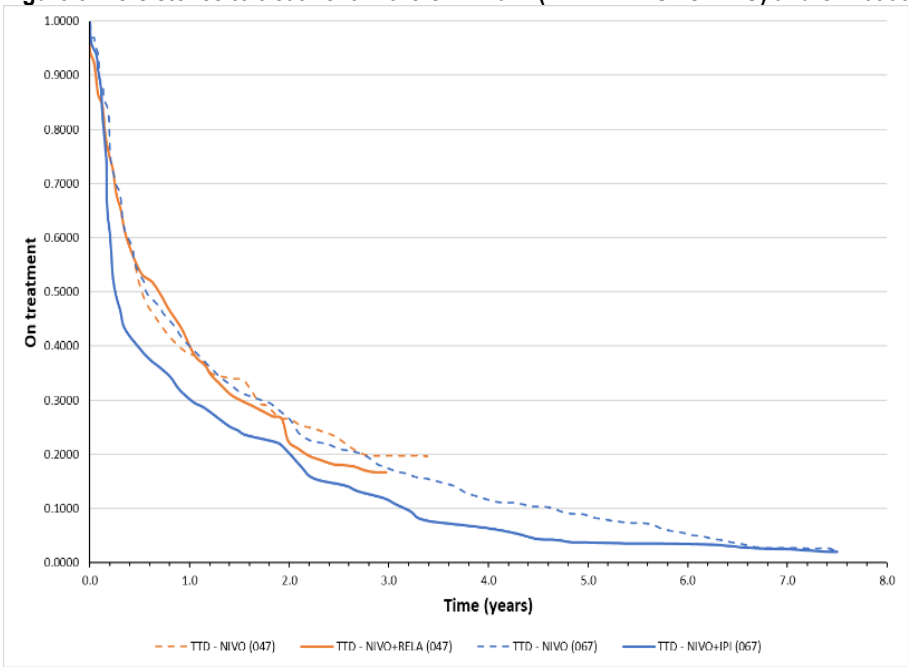
6.39 The PBAC considered that the claims of non-inferior comparative effectiveness and safety were reasonable.

Economic analysis

6.40 The resubmission presented a cost-minimisation approach between RELA+NIVO and NIVO+IPI. This was in contrast to the July 2022 submission, which presented a cost-effectiveness analysis between RELA+NIVO and NIVO monotherapy.

6.41 The equi-effective doses for treatment were calculated based on an unadjusted indirect comparison of treatment utilisation across the CA224047 and the CA209067 trials. Due to the previously identified transitivity issues, it may have been more appropriate to use adjusted results. It was not possible to conduct a sensitivity analysis using adjusted results as the required individual patient data was not available; however, given the differences in the aITC in terms of OS and PFS were small compared to the July 2022 ITC results, use of adjusted data would not be expected to result in a large change. The Pre-Sub-Committee Response (PSCR) presented Figure 5 below, which demonstrated that the time to treatment discontinuation was similar in the NIVO monotherapy arms of the respective trials. The PSCR states that this provided assurance that the differences in the amount of, or persistence to, treatment use in the NIVO+IPI and RELA+NIVO arms of the trials were due to the treatments themselves and not underlying differences in the patient populations. The ESC considered that this was reasonable.

Figure 5: Persistence to treatment in the CA224047 (RELA+NIVO vs NIVO) and CA209067 (NIVO+IPI vs NIVO) trials



Source: Figure 1, p2 of the PSCR
NIVO = nivolumab; NIVO+IPI = nivolumab + ipilimumab; NIVO+RELA/RELA+NIVO = relatlimab + nivolumab; TTD = time to treatment discontinuation

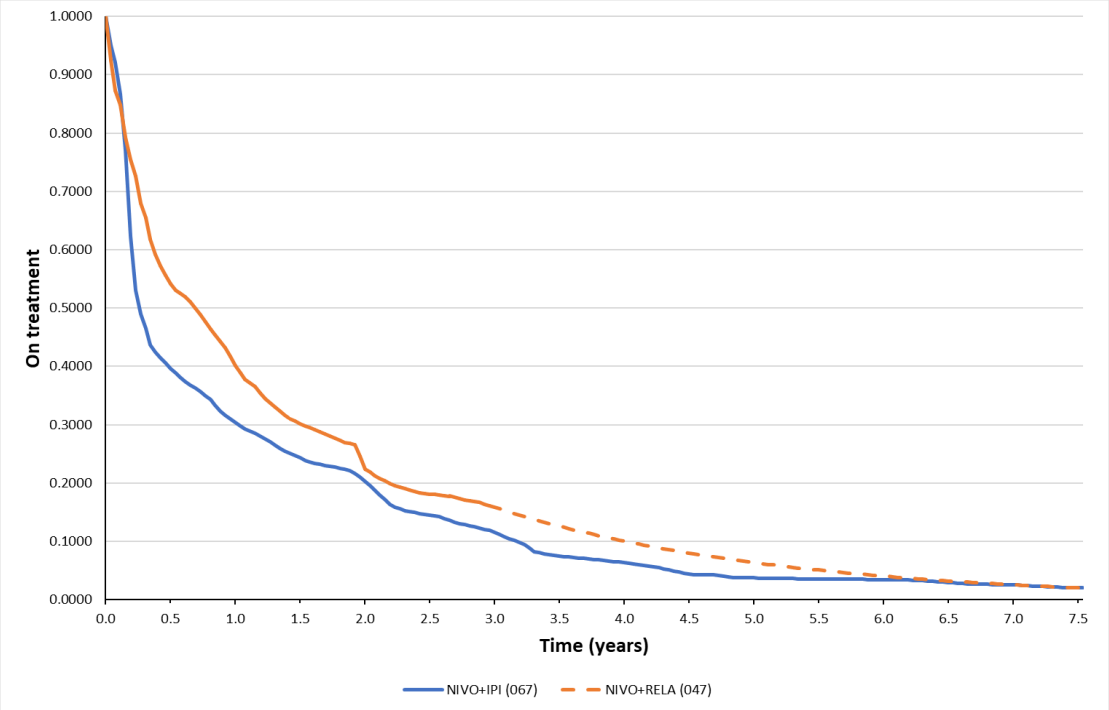
6.42 Due to (i) differences in the treatment regimens (the IPI component of the NIVO+IPI combination is given for a fixed interval with a lower dose of NIVO prior to NIVO monotherapy, whereas RELA+NIVO combination used continuously until disease progression), and (ii) the differences in time to treatment discontinuation (TTD) between the trials, the resubmission stated that patients receiving RELA+NIVO were likely to remain on treatment for longer and utilise more NIVO than patients treated with the NIVO+IPI combination.

6.43 The resubmission calculated the equi-effective doses of RELA+NIVO and NIVO+IPI over a 7.5-year time horizon. Sensitivity analysis revealed the use of a 7.5 year time horizon was conservative compared to shorter time horizons.

6.44 The equi-effective doses calculated for the CMA were the total amount of drug a patient treated with NIVO+IPI or RELA+NIVO would be expected to receive over a 7.5-year period. This expected amount of drug was based on the dosage regimens for each agent, TTD and the relative dose intensities as reported in the clinical trials. As only 2.9 years of TTD data were available for RELA+NIVO (compared to 7.5 years of data for NIVO+IPI), this was extrapolated to 7.5 years (Figure 6). The extrapolated RELA+NIVO curve followed a simple multiplicative function with a rate of discontinuation set to equate to the NIVO+IPI treatment persistence of 2% at 7.5 years. The discontinuation rate applied in the extrapolated period was 1.7% per 2 weeks to result in the same proportion remaining on treatment as for NIVO+IPI at 7.5 years (i.e. convergence of the TTD curves). As this rate was lower than the discontinuation rate observed in the clinical trial of 2.4% per 2 weeks, the ESC noted

that it may have increased the assumed use of RELA+NIVO and hence, resulted in a lower unit price for RELA+NIVO. The resubmission noted that there was uncertainty in the rate of discontinuation in the extrapolation and appropriately provided a sensitivity analysis around the rate of RELA+NIVO treatment discontinuation in the extrapolated period. No sensitivity analyses were provided in the resubmission applying different extrapolation methods. During the evaluation an alternate analysis was conducted using a linear forecast to converge TTD at 7.5 years. This resulted in a lower cost-minimisation price for RELA+NIVO. Due to the extrapolation of the RELA+NIVO TTD data, the mean duration of treatment was highly uncertain.

Figure 6: Time to treatment discontinuation curves with RELA+NIVO and NIVO+IPI used in the calculation of equi-effective doses for the CMA



CMA = cost minimisation approach; NIVO+IPI = nivolumab plus ipilimumab; RELA+NIVO = relatlimab plus nivolumab
Source: Figure 11, p73 of the resubmission.
Dashed line reflects the extrapolated data for RELA+NIVO

6.45 Patients in the RELA+NIVO arm of CA224047 received RELA 160 mg + NIVO 480 mg intravenously (IV) as a fixed-dose combination (FDC) every four weeks (Q4W) until disease progression, treatment discontinuation, withdrawal of consent, or end of the study. This dosing regime was used in the calculation of equi-effective doses.

6.46 Patients in the NIVO+IPI arm of CA209067 received IPI 3 mg/kg and NIVO 1 mg/kg intravenously (IV) every three weeks (Q3W) for four doses as induction therapy. Thereafter, NIVO monotherapy was administered intravenously at 3 mg/kg every two weeks (Q2W) until treatment discontinuation. In the calculation of equi-effective doses, the dosing was assumed to be identical to the clinical trial for the induction period (i.e. when patients received NIVO+IPI); however, for the maintenance period, when patients received NIVO monotherapy, patients were assumed to receive NIVO

480 mg Q4W. The resubmission noted that 3 mg/kg NIVO Q2W and 480 mg NIVO Q4W were both consistent with the TGA Product Information. The ESC considered that the assumption that NIVO monotherapy would be administered as 480 mg Q4W was reasonable and likely aligned with clinical practice and noted that a 6-week break prior to commencing NIVO 480 mg Q4W dose is recommended in the TGA PI. The PSCR acknowledged that as the analysis is based on an average of 3.2 doses of IPI per patient, the final IPI dose for most patients will be at Week 6 and therefore it was appropriate for NIVO monotherapy to commence at Week 12 after incorporating a 6 week interval. The ESC noted that a significant portion of patients receive four NIVO+IPI doses before commencing NIVO monotherapy. The pre-PBAC response provided further analyses in which (i) patients commenced NIVO monotherapy at Week 15 (i.e. after 4 doses of NIVO+IPI induction), and (ii) a weighted cost minimisation approach in which 43% of patients commence NIVO monotherapy at Week 12 and 57% of patients commence NIVO monotherapy at Week 15 (weighting was based on the number of doses of IPI received in CA209067 – 57% of patients received 4 doses, 43% received 3 or less).

6.47 Relative dose intensity (RDI) was applied to calculate the expected number of doses. The RDIs for RELA+NIVO (96.03%) and NIVO+IPI (90.16%) were sourced from the respective clinical trials.

6.48 The resubmission assumed an administration cost of $114.20 (MBS item 13950) for each dose. For NIVO+IPI the cost minimisation approach assumed one administration fee for NIVO+IPI. As patients remained on RELA+NIVO treatment for longer, they incurred more administrative costs.

6.49 The equi-effective doses were estimated as:

2,869 mg of RELA + 8,608 mg of NIVO = 800 mg of IPI + 5,412 mg of NIVO.

6.50 Given the time horizon and significant up-front costs of NIVO+IPI, the resubmission applied a 5% discount rate to all drug and administration costs. Table 10 presents the results of the CMA.

Table 10: Results of the cost-minimisation approach[a]

Component	RELA+NIVO	NIVO+IPI
Effective AEMP	NIVO 240 mg + RELA 80 mg cost per vial: $[redacted]	IPI 200 mg unit: $[redacted] NIVO 100 mg unit: $[redacted]
Equi-effective dose	2,869 mg of RELA + 8,608 mg of NIVO	800 mg of IPI + 5,412 mg of NIVO
Total drug cost per patient[b]	NIVO: $[redacted] RELA: $[redacted]	NIVO: $[redacted] IPI: $[redacted]
Administrative cost per patient[b]	$1,927.74	$1,509.00
Total cost per patient over the whole treatment course[b]	$[redacted]	$[redacted]

AEMP = approved ex-manufacturer price; NIVO+IPI = nivolumab plus ipilimumab; RELA+NIVO = relatlimab plus nivolumab
Source: Table 29, 30, pp76-77 of the resubmission.
[a] Corrected values applying a 6 week break between NIVO+IPI and NIVO monotherapy are presented in italics
[b] Values are discounted at a 5% annual discount rate and adjusted for relative dose intensity

6.51 The submission calculated the price per vial of RELA+NIVO vial to be $[redacted].

6.52 The results of key univariate sensitivity analyses are summarised in Table 11.

6.53 In addition, the resubmission applied a cost of NIVO of $[redacted] per 100 mg. This was the original effective price of nivolumab in the unresectable Stage III or IV malignant melanoma setting. Following the recommendation of NIVO in the adjuvant setting, an effective weighted price for NIVO was calculated of $[redacted] per 100 mg (inclusive of 5% statutory price reduction). Using the weighted effective price for NIVO resulted in a price per vial of RELA+NIVO of $[redacted].

Table 11: Sensitivity analyses

Variable	Value for sensitivity analysis	Cost minimising price ($)	% change
Base case		[redacted]	
Duration of analysis (base case = 7.5 years)	5.0 years	[redacted]	+2.1%
	2.5 years	[redacted]	+14.9%
Discount rate (base case = 5%)	3.5%	[redacted]	-0.7%
	0%	[redacted]	-2.5%
Dose intensity: NIVO (post IPI) and RELA+NIVO (base case = 90.16%, 96.03% respectively)	90.16%, 100%	[redacted]	-4.1%
	100%, 96.03%	[redacted]	+5.5%
	100%, 100%	[redacted]	+1.3%
Duration of RELA+NIVO TTD data (base case = 2.9 years)	1.75 years	[redacted]	-0.4%
RELA+NIVO discontinuation rate in the extrapolated period (base case = 0.0174 per 2 weeks)	0.01	[redacted]	-7.0%
	0.02	[redacted]	+1.9%
	0.024	[redacted]	+4.6%
	0.03	[redacted]	+7.5%
RELA+NIVO extrapolation (base case = multiplicative)	linear	[redacted]	-6.4%
NIVO price (base case = $[redacted] /100 mg)	$[redacted] /100 mg	[redacted]	-8.6%
Pre-PBAC analyses			
Commencement of NIVO monotherapy (base case = Week 12)	Week 15	[redacted]	-1.9%
Weighted CMA: 43% of patients commence NIVO monotherapy at Week 12, 57% at Week 15 (base case = 100% at Week 12)[a]	-	[redacted]	-1.1%

CMA = cost minimsation approach; IPI = ipilimumab; NIVO = nivolumab; RELA+NIVO = relatlimab plus nivolumab; TTD = time to treatment discontinuation

Source: Table 31, p78 of the resubmission and calculated during the commentary from 'Section 3_RELA NIVO_CMA.xlsx' CMA workbook and the pre-PBAC response.

[a] Weighting was based on the number of IPI doses received in CA209067 – 56.9% of patients received 4 doses, and 43.1% received 3 or less.

6.54 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with RELA+NIVO would be no more than the cost per patient of NIVO+IPI. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe. In this case, the PBAC should consider the uncertainty in the extrapolation of the RELA+NIVO time to treatment discontinuation, the average number of NIVO+IPI induction doses received and the pricing applied.

Drug cost/patient/course

6.55 The drug cost per patient for proposed and comparator drugs are shown in Table 12.

Table 12: Drug cost per patient for proposed and comparator drugs

	RELA+NIVO			
	Drug	**Trial dose and duration**	**Cost-minimisation**	**Financial estimates[c]**
Dose regimen	RELA	160 mg Q4W	160 mg Q4W	160 mg Q4W
	NIVO	480mg Q4W	480mg Q4W	480mg Q4W
Mean number of infusions[a]	RELA	12.3[b]	17.93	17.33
	NIVO			
Mean duration[a]	RELA	11.01 months[b]	16.51 months	15.95 months
	NIVO			
Cost/patient/ course[d]	RELA[e]	$	$	$
	NIVO	$	$	$
	Σ	**$**	**$**	**$**
	NIVO+IPI			
Dose regimen	NIVO	Induction: 1 mg/kg Q3W Ongoing: 3 mg/kg Q2W	Induction: 80 mg Q3W Ongoing: 480 mg Q4W	Induction: 80 mg Q3W Ongoing: 480 mg Q4W
	IPI	Induction: 3 mg/kg Q3W	Induction: 250 mg Q3W	Induction: 250 mg Q3W
Mean number of infusions[a]	NIVO+IPI induction	3.2[f]	3.2[f]	3.2[f]
	NIVO ongoing	21.7[f]	10.74	10.83
Mean duration[a]	NIVO+IPI induction	2.12 months[f]	2.12 months[f]	2.21 months[f]
	NIVO ongoing	9.99 months[g]	9.89 months	9.97 months
	Total duration	12.11 months	12.01 months	12.18 months
Cost/patient/ course	NIVO	$	$	$
	IPI	$	$	$
	Σ	**$**	**$**	**$**

Source: Table 26, p70, Table 27, p75 of the resubmission. "Attachment 16_DoT for BIM"

Notes: Data from CA224047 was collected for 3 years for RELA+NIVO and 3 years for NIVO, data from CA209067 was collected for 7.5 years.

[a] Mean number of infusions and duration has been adjusted for Relative Dose Intensity

[b] Sourced from CA224047 CSR V2

[c] Financial estimate mean number of infusions and mean duration is calculated assuming only first line usage and adjusted for monthly commencement. Sourced from attachment 16_DoT for BIM

[d] cost/patient/course was drug cost/infusion x # of infusions. Costs were not discounted and costs only consider the drug costs

[e] Calculated using the RELA price calculated by the resubmission in Section 3

[f] Sourced from CA209067 CSR

[g] Value was calculated from the mean number of infusions

Estimated PBS usage & financial implications

6.56 This resubmission was not considered by DUSC.

6.57 The resubmission 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 13.

Table 13: Key inputs for financial estimates

	Value applied and source	Comment
Total incident patients	2,139 in 2023 increasing to 2,472 in 2028. Historical market data based on DUSC analysis. Market Growth aligned with AIHW estimate of a 2.9% annual growth rate.	Likely underestimated. The resubmission used the lower end of the AIHW estimate. Use of the higher end growth estimate of 3.7% was tested in a sensitivity analysis.
Substitution rate	PD-1 monotherapy: [redacted] % in Year 1, and [redacted] % from Year 2 onwards NIVO+IPI: [redacted] % in Year 1, [redacted] % in Year 2, and [redacted] % from Year 3 onwards	Values were highly uncertain but were in line with the PBAC recommendations from July 2022.
Duration of treatment[a]	RELA+NIVO: 15.95 months NIVO+IPI induction: 2.21 months + NIVO maintenance: 9.97 months PD-1 monotherapy: 17.08 months Based on the economic analysis up to 6 years.	The TTD was greater than 6 years for relatively more RELA+NIVO patients compared to NIVO+IPI and PD-1 monotherapy patients in the economic analysis when a 7.5 year time horizon was used. Therefore, the cost of RELA+NIVO may be underestimated compared to the cost-offsets of NIVO+IPI applied (see paragraph 6.60).
2L usage	2% of patients were estimated to receive treatment in the 2L setting. Treatment duration was estimated to be 65% of 1L duration. Based on 10% sample PBS data provided by Prospection	The duration of RELA+NIVO, NIVO+IPI and PD-1 monotherapy was adjusted to account for decreased second line usage. This approach was reasonable, but the values were uncertain due to the small sample (10%) used.
MBS item 13950	$112.40	Appropriate, but not consistent with the economic evaluation. The economic evaluation conservatively assumed that one administration fee was required for NIVO+IPI induction, whereas the financial estimates assumed 2 administrative fees were required.

Source: Table 33, pp81,82 of the resubmission and Attachment 16_DoT for BIM
AIHW = Australian Institute of Health and Welfare, DUSC = Drug Utilisation Sub-Committee, IPI = ipilimumab, NIVO = nivolumab, PBAC = Pharmaceutical Benefits Advisory Committee, PD-1 = programmed death protein-1, RELA = relatlimab
[a] Values were adjusted for monthly commencement and relative dose intensity

6.58 The substitution rates were revised compared to the July 2022 submission to reflect that the majority of substitution would be from the primary comparator, NIVO+IPI. The PBAC has previously indicated that the standard of care for patients with metastatic melanoma disease with higher risk features is NIVO+IPI (paragraph 7.8, RELA+NIVO, PSD, July 2022 PBAC meeting), hence the resubmission assumed NIVO+IPI was likely to remain the preferred treatment for patients with poorer prognostic features. In line with this, the resubmission proposed that patients with the most advanced stage IV melanoma, classified as M1d by AJCC version 8, would receive NIVO+IPI. Based on the NIVO+IPI patient access program [redacted] % of patients were classified as M1d, resulting in a maximum substitution rate of [redacted] % for RELA+NIVO to substitute NIVO+IPI. The resubmission assumed that [redacted] % of PD-1 inhibitor monotherapy would be substituted by RELA+NIVO resulting in the relative substitution rates of [redacted] % NIVO+IPI: [redacted] % PD-1 inhibitor monotherapy.

6.59 The duration of NIVO+IPI induction therapy was calculated based on the number of reported doses in the CA209067 trial. The duration of NIVO maintenance therapy and

PD-1 monotherapy was based on the Kaplan Meier TTD data used in the economic analysis from the CA209067 trial.

6.60 RELA+NIVO duration was derived from the extrapolated Kaplan Meier TTD data used in the economic analysis; however, a 6-year duration was used in the financial estimates compared to 7.5 years in the economic analysis. As the TTD was greater than 6 years for relatively more RELA+NIVO patients compared to NIVO+IPI patients, the use of a 6-year time horizon failed to capture some of the costs associated with RELA+NIVO. As a result, the cost-savings for RELA+NIVO compared to NIVO+IPI were unlikely to occur in practice if the time-horizon was extended past 6 years.

6.61 The duration of treatment was adjusted by the relative dose intensities sourced from the CA209067 and CA224047 clinical trials.

6.62 The resubmission stated that BRAF-positive patients who had received BRAF inhibitor treatment would be able to receive PD-1-based treatment in the second line. Given that the DUSC data did not separate into lines of therapy, the resubmission applied a reduction to the duration of treatment in the second line. The resubmission assumed that 2% of patients would receive second line treatment and the duration of treatment would be 65% of that in the first line. These values were based on 10% sample PBS data provided by Prospection and may be uncertain due to the small sample size.

6.63 The estimated utilisation and cost impact of listing RELA+NIVO on the PBS is presented below.

Table 14: Estimated use and financial implications

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted] 1	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2
Number of scripts dispensed[a]	[redacted] 2	[redacted] 2	[redacted] 6	[redacted] 8	[redacted] 8	[redacted] 8
Estimated financial implications of RELA+NIVO						
Cost to PBS/RPBS less copayments	[redacted] 3	[redacted] 5	[redacted] 7	[redacted] 9	[redacted] 10	[redacted] 11
Estimated financial implications for PD-1 monotherapy and NIVO+IPI						
Cost to PBS/RPBS less copayments[b] ($)	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4
Net financial implications						
Net cost to PBS/RPBS[b] ($)	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4
Net cost to MBS[c] ($)	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4
Net cost to PBS/RPBS/MBS[b,c] ($)	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4	[redacted] 4
Previous submission - July 2022						
Net cost to PBS/RPBS ($)	[redacted] 3	[redacted] 5	[redacted] 7	[redacted] 7	[redacted] 7	[redacted] 7
Net cost to PBS/RPBS/MBS ($)	[redacted] 3	[redacted] 5	[redacted] 7	[redacted] 7	[redacted] 7	[redacted] 7

Source: Table 39, p97, Table 41, p99, Table 57, p110, Table 58, p111, Table 62, p113 of the resubmission. Table 16 of PBAC PSD Jul-22 Item 5.11.

[a] Assuming 17.33 infusions per treatment course as estimated by the resubmission.

[b] During the evaluation, an error in the financial workbook where the change in utilisation of 11532Y was switched with 11543M was corrected. This had a flow on effects to the cost to the PBS and RPBS. 11532Y = NIVO induction therapy delivered with IPI in private setting, 11543M = NIVO induction therapy delivered with IPI in public setting.

[c] Values were recalculated during the evaluation to correct an error in the calculation of total RELA+NIVO services. In the original workbook only, the initiating scripts were considered for RELA+NIVO in the calculation of MBS costs.

The redacted values correspond to the following ranges:

[1] < 500
[2] 500 to < 5,000
[3] $0 to < $10 million
[4] net cost saving
[5] $20 million to < $30 million
[6] 5,000 to < 10,000
[7] $50 million to < $60 million
[8] 10,000 to < 20,000
[9] $60 million to < $70 million
[10] $80 million to < $90 million
[11] $90 million to < $100 million

6.64 The total cost to the PBS/RPBS of listing RELA+NIVO was estimated to be $90 million to < $100 million in Year 6, and $300 million to < $400 million over the first 6 years of listing. The net cost to the PBS/RPBS of listing RELA+NIVO, including cost offsets due to reduced NIVO+IPI and PD-1 monotherapy use, was estimated to be net cost saving in Year 6, and net cost saving over the first 6 years of listing.

6.65 The financial estimates may over-estimate the net cost savings to the PBS/RPBS as the TTD was greater than 6 years for relatively more RELA+NIVO patients compared to NIVO+IPI patients. In addition, the high cost of IPI is incurred at the beginning of NIVO+IPI treatment. If a longer time-horizon was used, the cost savings of RELA+NIVO would be decreased. The PSCR stated that it was anticipated that over a longer time horizon the of RELA+NIVO would be cost neutral, in line with the approach applied in the economic model. The ESC noted that although the substitution of RELA+NIVO for NIVO+IPI would become cost neutral, there would be some cost associated with the substitution of NIVO and PEMBRO monotherapy.

Quality Use of Medicines

6.66 The resubmission proposed the same quality use of medicine activities for RELA+NIVO as in the original submission. This 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

6.67 The resubmission stated that existing melanoma risk sharing arrangements could possibly be restructured if RELA+NIVO was recommended. Currently the costs associated with the affected medicines are covered by two different expenditure caps, one for PD-1 monotherapies (i.e., NIVO and PEMBRO) and one for IPI expenditure. Although the resubmission does not recommend creating a third expenditure cap pertaining to melanoma treatments, incorporation of RELA+NIVO into the PD-1 cap would not adequately address cost offsets as a result of the substitution of IPI. One option proposed in the resubmission was the amalgamation of the existing expenditure caps, which would reduce the impact of uncertainty regarding actual versus forecast NIVO+IPI substitution rates and preserve the existing total expenditure exposure for the Government.

6.68 The pre-PBAC response agreed that the incorporation of RELA+NIVO into the existing PD-1 monotherapy cap would not adequately address the cost offsets as a result of the substitution of IPI. The pre-PBAC response noted that the existing cap for IPI lapses in November 2023 and proposed that, if recommended, this would be an opportune time to re-evaluate the melanoma cap structure.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of relatlimab and nivolumab (RELA+NIVO), a fixed-dose combination treatment, for the treatment of patients with unresectable Stage III or IV malignant melanoma, on the basis that it should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy). The PBAC was satisfied the RELA+NIVO was non-inferior in terms of efficacy and safety compared to nivolumab plus ipilimumab (NIVO+IPI) and therefore, recommended RELA+NIVO on a cost-minimisation basis. The PBAC considered that the financial uncertainty relating to the substitution rates of RELA+NIVO for NIVO+IPI and programmed cell death protein (PD-1) inhibitor monotherapies may be mitigated by including RELA+NIVO in the existing PD-1 inhibitor risk sharing arrangement (RSA) for melanoma.

7.2 The PBAC again considered that the proposed place in therapy for RELA+NIVO, as a first line alternative to currently available PD-1 inhibitor based therapies (i.e. pembrolizumab (PEMBRO), NIVO or NIVO+IPI) was reasonable.

7.3 The PBAC considered that the nomination of NIVO+IPI as the comparator was appropriate. The PBAC recalled that in July 2022 it considered that NIVO+IPI would be a reasonable comparator as clinical guidelines recommend the use of combination therapy over PD-1 inhibitor monotherapy if tolerated, and therefore as a combination treatment, RELA+NIVO was more likely to replace NIVO+IPI rather than PD-1 monotherapy.

7.4 The PBAC noted that the resubmission was based on an adjusted indirect treatment comparison (aITC) between RELA+NIVO (trial CA224047) and NIVO+IPI (trial CA209067), with NIVO monotherapy as the common comparator. The PBAC considered that the use of inverse probability treatment weighting (IPTW) method to adjust for imbalances in the distribution of baseline characteristics was reasonable to address the key transitivity issues between the trials.

7.5 The PBAC noted that the aITC resulted in no statistically significant or clinically meaningful differences between RELA+NIVO and NIVO+IPI in terms of progression free survival (PFS; HR = 1.00; 95% CI: 0.79, 1.25) or overall survival (OS; HR = 0.87; 95% CI: 0.68, 1.12). The PBAC considered that the claim that RELA+NIVO was non-inferior in terms of effectiveness compared to NIVO+IPI was adequately supported by the data.

7.6 The PBAC considered that the claim that RELA+NIVO had a different but non-inferior safety profile compared with NIVO+IPI was reasonable.

7.7 The PBAC noted that the resubmission presented a cost minimisation approach between RELA+NIVO and NIVO+IPI which was based on a 7.5 year time horizon. As only 2.9 years of treatment discontinuation data were available for the RELA+NIVO arm (compared to 7.5 years for the NIVO+IPI arm) the PBAC noted that the resubmission extrapolated the RELA+NIVO arm and then applied a discontinuation rate to result in the same proportion of patients remaining on treatment in both arms at 7.5 years. The PBAC considered that this approach was reasonable.

7.8 The PBAC considered that the assumption that all patients, following the period of NIVO+IPI induction, would receive 480 mg NIVO monotherapy every 4 weeks was reasonable and aligned with clinical practice. The PBAC noted that the pre-PBAC response presented a revised weighted base case, which was based on the number of IPI doses received in CA209067, in which 43% of patients received 3 doses of NIVO+IPI induction before commencing NIVO monotherapy and 57% received 4 doses. The PBAC considered that the use of this weighted approach was appropriate and resulted in the following equi-effective doses:

2,869 mg of RELA + 8,608 mg of NIVO = 800 mg IPI + 5,315 mg of NIVO

7.9 The PBAC noted that the utilisation and financial impact estimates were based on the cost minimisation model and that the substitution rates of RELA+NIVO for PD-1 monotherapy and NIVO+IPI were updated in line with the recommendations provided

in July 2022. The PBAC considered that the substitution rates remained an area of uncertainty.

7.10 Overall, the PBAC considered that the utilisation and financial impact estimates were reasonable, noting that the cost savings associated with RELA+NIVO substituting for NIVO+IPI were due to the higher cost of IPI being incurred early in treatment and that there would be costs associated with the substitution of RELA+NIVO for PD-1 monotherapy.

7.11 The PBAC recommended RELA+NIVO be included in the existing PD-1 inhibitor RSA for melanoma. Further, the PBAC advised that as the existing RSA for IPI is approaching its nominal 5 year term this provided an opportunity for amalgamating the melanoma RSAs and would be a pragmatic way forward to contain the total expenditure exposure to the Commonwealth.

7.12 The PBAC noted that flow-on restriction changes stating that patients must not have received prior treatment with RELA+NIVO would be required to the initial treatment phases for NIVO, PEMBRO and NIVO+IPI.

7.13 The PBAC advised that RELA+NIVO was not suitable for prescribing by nurse practitioners.

7.14 The PBAC advised that the Early Supply Rule should not apply to RELA+NIVO.

7.15 The PBAC advised that RELA+NIVO should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because RELA+NIVO is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over NIVO+IPI, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new medicinal product as follows:

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№. of Rpts**
RELATLIMAB + NIVOLUMAB Injection	{NEW (Public)} {NEW (Private)}	480 mg/160 mg (relatlimab – 160 mg)	8
Available brands			

Opdualag (relatlimab 80 mg/20 mL + nivolumab 240 mg/20 mL, 20 mL vial)		
Restriction Summary / Treatment of Concept:		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (STREAMLINED) [new]
Prescribing rule level		**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
Prescribing rule level		**Administrative Advice:** Special Pricing Arrangements apply.
Prescribing rule level		**Administrative Advice:** No increase in the maximum amount or number of units may be authorised
		Episodicity: [blank]
		Severity: Unresectable Stage III or Stage IV
		Condition: Malignant melanoma
		Indication: Unresectable Stage III or Stage IV malignant melanoma
		Treatment Phase: Initial treatment
		Clinical criteria:
		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
		AND
		Clinical criteria:
		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
		AND
		Clinical criteria:
		Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
		AND
		Clinical criteria:
		The condition must not be uveal melanoma
		AND
		Clinical criteria:
		The treatment must be the sole PBS-subsidised therapy for this condition
		Population criteria:
		Patient must weigh at least 40 kg.
		Population criteria:
		Patient must be at least 12 years of age
		Prescribing Instructions: Patients must only receive a maximum of 160 mg relatlimab and 480 mg nivolumab every four weeks under a flat dosing regimen
		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

	Caution: 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.

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№. of Rpts**
RELATLIMAB + NIVOLUMAB Injection	{NEW (Public)} {NEW (Private)}	480 mg/160 mg (relatlimab -160 mg)	11
Available brands			
Opdualag (relatlimab 80 mg/20 mL + nivolumab 240 mg/20 mL, 20 mL vial)			
Restriction Summary / Treatment of Concept:			

Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required – Streamlined [new code]
Prescribing rule level		**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: No increase in the maximum amount or number of units may be authorised
		Episodicity: [blank]
		Severity: Unresectable Stage III or Stage IV
		Condition: Malignant melanoma
		Indication: Unresectable Stage III or Stage IV malignant melanoma
		Treatment Phase Continuing treatment
		Clinical criteria:
		The treatment must be the sole PBS-subsidised therapy for this condition
		AND
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition.
		AND
		Clinical criteria:
		Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
		Prescribing Instructions: Patients must only receive a maximum of 160 mg relatlimab and 480 mg nivolumab every four weeks under a flat dosing regimen
		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.

8.2 Flow on changes to the clinical criteria for the following PBS item codes/listings will be requried:

- 2641B / ipilimumab
- 2638W / ipilimumab
- 10475H / pembrolizumab

- 10493G / pembrolizumab
- 10764M / nivolumab
- 10775D / nivolumab
- 11532Y / nivolumab
- 11543M / nivolumab
- 12122B / pembrolizumab
- 12128H / pembrolizumab

	Patient must not have received prior treatment with *relatlimab plus nivolumab,* ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma.

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

9 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.

10 Sponsor's Comment

The sponsor had no comment.

Addendum to the March 2023 PBAC Public Summary Document:

4.08 RELATLIMAB WITH NIVOLUMAB, Solution concentrate for I.V. infusion containing 80 mg relatlimab and 240 mg nivolumab in 20 mL vial, Opdualag®, Bristol-Myers Squibb Australia Pty Ltd.

11 Background

11.1 In March 2023, the PBAC recommended the listing of relatlimab and nivolumab (RELA+NIVO), a fixed-dose combination treatment, for the treatment of patients with unresectable Stage III or IV malignant melanoma, on the basis that it should be available only under special arrangements under Section 100 Efficient Funding of Chemotherapy (EFC).

11.2 RELA+NIVO is the first fixed dose combination therapy recommended for listing on the Section 100 EFC Program. At present, the EFC legislative instrument and pricing algorithm are not designed to accommodate combination products. Further, the addition of a Section 100 EFC combination product presents system challenges for Services Australia, prescribing software vendors and dispensing software vendors around correct dose calculation and payment as per the EFC algorithm as these systems are also not currently equipped to manage combination dose EFC medicines. It is expected that significant changes to software, the EFC calculation algorithm and Services Australia systems would be required, potentially delaying implementation of a PBS listing.

11.3 One of the goals of the EFC Program is to minimise wastage and reduce costs to patients and the Commonwealth by funding the lowest cost combination of vials for prescription chemotherapy medicines. However, the recommended dose for RELA+NIVO is fixed at RELA 160 mg + NIVO 480 mg, equivalent to two vials, every four weeks. Therefore, there is no requirement to calculate an “efficient” combination of vials in practice for this medicine.

11.4 Following the PBAC recommendation, the sponsor provided options to the Department to progress a listing ahead of required changes being made to relevant legislative instruments and IT systems. One of these options included an interim listing on the Section 100 Highly Specialised Drugs (HSD) Program.

11.5 It is noted that other products for intravenous infusion are available under S100 HSD arrangements (e.g. rituximab, doxorubicin – pegylated liposomal).

12 PBAC Outcome

12.1 The PBAC recommended the listing of RELA+NIVO under the Section 100 Highly Specialised Drugs (HSD) Program, while implementation issues relating to a Section 100 EFC listing were being worked through.

12.2 The PBAC noted that under S100 EFC, patients are not required to pay a co-payment for repeat prescriptions, but would be required to do so under S100 HSD. The PBAC noted that this arrangement was unique to S100 EFC and that for listings under the General Schedule and most other S100 programs, patients are required to pay a co-payment for each script and repeat. The PBAC therefore considered that this should not be a barrier to a S100 HSD listing, noting that absence of any PBS access was a greater equity issue than a S100 HSD vs S100 EFC listing.

12.3 The PBAC further noted that RELA+NIVO was to be supplied as a fixed dose, and did not require titration for individual patients, which meant it did not require the S100 EFC algorithm to calculate the most suitable number of vials to be supplied, which made it suitable for listing on the S100 HSD program, and could be listed with a Dispensed Price for Maximum Quantity.

12.4 The PBAC noted that the recommended dose is RELA 160 mg + NIVO 480 mg, equivalent to two vials, every four weeks (Q4W). The PBAC considered that under a S100 HSD listing, the maximum quantity should be 2 vials.

Outcome:
Recommended

13 Recommended Listing

13.1 Add new medicinal product as follows:

MEDICINAL PRODUCT Form	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
RELATLIMAB WITH NIVOLUMAB					
relatlimab 80mg/20 mL plus nivolumab 240 mg/20 mL injection, 20 mL vial	{NEW (Public)} {NEW (Private)}	2	2	8	Opdualag
Restriction Summary / Treatment of Concept:					
Concept ID	**Category / Program:** Section 100 – Highly Specialised Drugs Program				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (STREAMLINED) [new]				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Administrative Advice: No increase in the maximum amount or number of units may be authorised				
	Episodicity: [blank]				
	Severity: Unresectable Stage III or Stage IV				
	Condition: Malignant melanoma				
	Indication: Unresectable Stage III or Stage IV malignant melanoma				
	Treatment Phase: Initial treatment				

	Clinical criteria:
	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
	AND
	Clinical criteria:
	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
	AND
	Clinical criteria:
	Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	AND
	Clinical criteria:
	The condition must not be uveal melanoma
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	Population criteria:
	Patient must weigh at least 40 kg.
	Population criteria:
	Patient must be at least 12 years of age
	Prescribing Instructions: Patients must only receive a maximum of 160 mg relatlimab and 480 mg nivolumab every four weeks under a flat dosing regimen
	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
	Caution: 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.

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
RELATLIMAB WITH NIVOLUMAB					
relatlimab 80mg/20 mL plus nivolumab 240 mg/20 mL injection, 20 mL vial	{NEW (Public)} {NEW (Private)}	2	2	11	Opdualag

Restriction Summary / Treatment of Concept:		
Concept ID		**Category / Program:** Section 100 – Highly Specialised Drugs Program
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required – Streamlined [new code]
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: No increase in the maximum amount or number of units may be authorised
		Episodicity: [blank]

	Severity: Unresectable Stage III or Stage IV
	Condition: Malignant melanoma
	Indication: Unresectable Stage III or Stage IV malignant melanoma
	Treatment Phase Continuing treatment
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
	Prescribing Instructions: Patients must only receive a maximum of 160 mg relatlimab and 480 mg nivolumab every four weeks under a flat dosing regimen
	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.

13.2 Flow on changes to the clinical criteria 24875 for the following PBS item codes/listings will be requried:

- 2641B / ipilimumab
- 2638W / ipilimumab
- 10475H / pembrolizumab
- 10493G / pembrolizumab
- 10764M / nivolumab
- 10775D / nivolumab
- 11532Y / nivolumab
- 11543M / nivolumab
- 12122B / pembrolizumab
- 12128H / pembrolizumab

Edit	Patient must not have received prior treatment with *relatlimab plus nivolumab,* ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma.

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

14 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.

15 Sponsor's Comment

The sponsor had no comment.