

Technology Guidance

Nivolumab and relatlimab

for first-line treatment of unresectable or metastatic melanoma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended nivolumab and relatlimab fixed-dose combination (FDC) for inclusion on the MOH List of Subsidised Drugs for first-line treatment of unresectable or metastatic melanoma. The decision was based on the uncertain extent of clinical benefit and inferior safety compared with nivolumab monotherapy. The nivolumab and relatlimab FDC is also unlikely to represent an acceptable use of healthcare resources, and the price-volume agreement proposed by the company was unacceptable.

Clinical indication, subsidy class and MediShield Life claims eligibility for nivolumab and relatlimab FDC are provided in the Annex.

Technology Evaluation

- 1.1. At the July 2026 meeting, the MOH Drug Advisory Committee (“the Committee”) considered the technology evaluation of nivolumab and relatlimab fixed-dose combination (FDC) for first-line treatment of unresectable or metastatic melanoma. The evaluation considered the company’s evidence submission by Bristol Myers Squibb for nivolumab and relatlimab FDC (Opdualag), and a review conducted by one of ACE’s evidence review centres.
- 1.2. Expert opinion from clinicians at healthcare institutions helped ACE ascertain the clinical value of nivolumab and relatlimab FDC. Members of local patient and voluntary organisations were also invited to provide their lived experiences to inform the evaluation, however, no submissions were received.
- 1.3. The evidence was used to inform the Committee’s deliberations around four core decision-making criteria:
 - Clinical need of patients and nature of the condition;
 - Clinical effectiveness and safety of the technology;
 - Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
 - Estimated annual technology cost and the number of patients likely to benefit from the technology.
- 1.4. Additional factors, including social and value judgments, may also inform the Committee’s funding considerations.

Clinical need

- 2.1. In Singapore, approximately 15 patients diagnosed with unresectable or metastatic melanoma require first-line systemic treatment each year. Of these, about 57% have tumour cell PD-L1 expression <1%. Nivolumab and relatlimab FDC comprises a programmed cell death protein 1 inhibitor and a lymphocyte activation gene 3 inhibitor that work together to enhance T-cell activation and antitumour immune responses.
- 2.2. The Committee noted that current subsidised first-line treatment options are nivolumab plus ipilimumab, nivolumab or pembrolizumab monotherapy and dabrafenib plus trametinib for BRAF-positive, fast-growing disease. If funded, nivolumab and relatlimab FDC may replace nivolumab plus ipilimumab as well as nivolumab and pembrolizumab monotherapy in selected patients.

Clinical effectiveness and safety

- 3.1. The company requested a listing for patients with unresectable or metastatic melanoma irrespective of tumour cell PD-L1 expression, in line with the pivotal trial (RELATIVITY-047). This was broader than the HSA-approved indication, which is restricted to patients with tumour cell PD-L1 expression <1%.

Nivolumab + relatlimab versus nivolumab monotherapy

- 3.2. The Committee reviewed clinical evidence from a Phase II/III, double-blind, randomised controlled trial (RCT; RELATIVITY-047) that compared nivolumab + relatlimab with nivolumab monotherapy in patients with untreated unresectable or metastatic melanoma.
- 3.3. After a median follow-up of 13.2 months, nivolumab + relatlimab demonstrated a statistically significant improvement in progression-free survival (PFS) compared with nivolumab monotherapy in the intention-to-treat (ITT) population (Table 1). However, PFS benefit was confined to the PD-L1 <1% subgroup, with no clear benefit in the PD-L1 ≥1% subgroup. The Committee also noted that the magnitude of PFS benefit may not be fully generalisable to the local population, given the higher prevalence of acral melanoma in Singapore, which is generally less responsive to immunotherapy. At the final overall survival (OS) analysis, no statistically significant difference in OS was observed between treatment arms.

Table 1: Results for PFS and OS in RELATIVITY-047

Population / subgroup	NIVO+RELA		NIVO monotherapy		Absolute difference, months	HR (95% CI), p-value
	Event, n / N (%)	Median time to event, months (95% CI)	Event, n / N (%)	Median time to event, months (95% CI)		
PFS at primary analysis (DCO 9 March 2021, median follow-up = 13.21 months)						
ITT	180/355 (50.7%)	10.1 (6.4 to 15.7)	211/359 (58.8%)	4.6 (3.4 to 5.6)	5.5	0.75 (0.62 to 0.92); p=0.0055
PD-L1 <1%	112/209 (53.4%)	6.4 (4.6 to 11.8)	144/212 (53.7%)	2.9 (2.8 to 4.5)	3.5	0.66 (0.51 to 0.84)
PD-L1 ≥1%	68/146 (46.6%)	15.7 (10.1 to 25.8)	67/147 (45.6%)	14.7 (5.1 to NR)	1.0	0.95 (0.68 to 1.33)
OS at prespecified final analysis (DCO 21 October 2021, median follow-up = 19.3 months)						
ITT	137/355 (38.6%)	NR (34.2 to NR)	160/359 (44.6%)	34.1 (25.2 to NR)	NE	0.80 (0.64 to 1.01) p=0.0593 ^a
PD-L1 <1%	89/209 (42.6%)	NR (27.4 to NR)	104/212 (49.1%)	27.0 (17.1 to NR)	NE	0.78 (0.59 to 1.04)
PD-L1 ≥1%	48/146 (32.9%)	NR (NR to NR)	56/147 (38.1%)	NR (32.0 to NR)	NE	0.84 (0.57 to 1.24)

Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; ITT, intention-to-treat; NIVO, nivolumab; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; RELA, relatlimab.

^a The 2-sided boundary for statistically significant p-value would be < 0.04302, with a cumulative design power of 69%.

- 3.4. In terms of safety, nivolumab + relatlimab was associated with higher rates of grade ≥ 3 drug-related serious adverse events (11.3% vs. 5.3%) and drug-related adverse events (AEs) leading to discontinuation (17.7% vs. 9.5%). The Committee also noted immune-mediated AEs, including thyroiditis, colitis and hepatitis, were more frequent with nivolumab + relatlimab.

Nivolumab + relatlimab versus nivolumab + ipilimumab

- 3.5. In the absence of direct comparative evidence, the Committee reviewed an inverse probability treatment weighting (IPTW) indirect treatment comparison of nivolumab + relatlimab versus nivolumab + ipilimumab, based on two RCTs (RELATIVITY-047 and CHECKMATE-067). The results suggested similar PFS and OS between the two treatments. However, the Committee considered the results uncertain given several methodological limitations, including insufficient transparency to assess the validity of the IPTW approach, residual cross-trial differences despite weighting, and potential confounding from unmeasured prognostic factors.
- 3.6. The submission described nivolumab plus relatlimab as non-inferior in efficacy and superior in safety compared with nivolumab + ipilimumab. The Committee considered that the comparative efficacy and safety of nivolumab + relatlimab versus nivolumab + ipilimumab remained uncertain, and that the submission's claims were not adequately supported.

Cost effectiveness

Nivolumab + relatlimab versus nivolumab monotherapy

- 4.1. The Committee noted that no cost-utility analysis was presented for nivolumab + relatlimab versus nivolumab monotherapy.

Nivolumab + relatlimab versus nivolumab + ipilimumab

- 4.2. The submission presented a cost-minimisation analysis (CMA) between nivolumab + relatlimab and nivolumab + ipilimumab based on a non-inferiority claim. The base case results indicated that the total healthcare costs were lower with nivolumab + relatlimab compared with nivolumab + ipilimumab. Key components of the CMA are summarised in Table 2.

Table 2: Key components of the company-submitted CMA

Component	Description
Therapeutic claim: effectiveness	Based on evidence in the submission, effectiveness was assumed to be non-inferior by the company.
Therapeutic claim: safety	Based on evidence in the submission, safety was assumed to be superior by the company.
Evidence base	Adjusted indirect comparison of nivolumab + relatlimab and nivolumab + ipilimumab based on randomised controlled trials (CHECKMATE-067 and RELATIVITY-047) with a common reference arm (nivolumab monotherapy).

Component	Description
Equi-effective doses	480 mg nivolumab + 160 mg relatlimab = 1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W for up to 4 doses, followed by 3 mg/kg nivolumab maintenance monotherapy Q2W (based on the dosing regimens in the clinical trials without any adjustment for baseline differences)
Direct medicine costs, other costs, or cost offsets	• Drug and AE management costs • Administration and monitoring requirements and costs were assumed to be the same between the intervention and comparator

Abbreviations: AE, adverse event; CMA, cost-minimisation analysis; Q2W, every two weeks; Q3W, every three weeks.

- 4.3. The Committee considered that a CMA approach was not appropriate to compare nivolumab + relatlimab with nivolumab + ipilimumab, as the claim of non-inferiority was not adequately supported. The Committee also noted that the CMA results were highly uncertain and likely overestimated, mainly due to the use of unadjusted trial dosing and median treatment duration.
- 4.4. Given these uncertainties, the Committee compared nivolumab + relatlimab versus nivolumab + ipilimumab based on drug, administration and testing costs using mean number of doses from the ITT population. Nivolumab + relatlimab was associated with higher total treatment costs than nivolumab + ipilimumab.
- 4.5. The Committee also noted that a comparison of treatment costs for patients with PD-L1 expression <1% was not feasible, as the mean treatment duration was not reported for this subgroup.
- 4.6. Overall, the Committee considered that nivolumab + relatlimab did not represent an acceptable use of healthcare resources for first-line treatment of unresectable or metastatic melanoma at the price proposed by the company.

Estimated annual technology cost

- 5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would be less than SG\$1 million over the first five years of listing nivolumab and relatlimab FDC on the MOH List of Subsidised Drugs for first-line treatment of unresectable or metastatic melanoma.
- 5.2. The Committee considered that the submission estimates were uncertain and likely overestimated, most notably because the submission base case did not restrict nivolumab and relatlimab FDC to patients with tumour cell PD-L1 expression <1%, which the Committee viewed as more appropriate and in line with the HSA-approved indication. Additional sources of uncertainty included the use of median rather than mean treatment duration, overestimated melanoma incidence, uncertain proportions of eligible patients, and uptake rate.

- 5.3. Based on the respecified budget impact model, the annual cost impact to the public healthcare system was estimated to be less than SG\$1 million over the first five years of listing. However, the Committee noted that the respecified estimates remained uncertain and were likely overestimated, primarily because treatment duration was based on the trial ITT population and may be longer than that expected in the PD-L1 <1% subgroup.
- 5.4. The Committee also considered that the price-volume agreement (PVA) caps were unacceptably high.

Recommendations

- 6.1. Based on available evidence, the Committee recommended not listing nivolumab and relatlimab FDC on the MOH List of Subsidised Drugs for the first-line treatment of unresectable or metastatic melanoma. The decision was based on the uncertain extent of clinical benefit and inferior safety compared with nivolumab monotherapy. The nivolumab and relatlimab FDC is also unlikely to represent an acceptable use of healthcare resources, and the PVA proposed by the company was unacceptable.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Company-proposed clinical indication	Subsidy class	Eligible for MediShield Life claims
Nivolumab / relatlimab 240 mg/80 mg concentrate for solution for infusion	Nivolumab and relatlimab for the first-line treatment of unresectable or metastatic melanoma.	Not recommended for subsidy	No

 Agency for Care Effectiveness - ACE  Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidelines, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at <https://www.ace-hta.gov.sg/about-us/>

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