EE395

Cost-effectiveness analysis of nivolumab plus relatlimab (NIVO+RELA) versus current standard of care (SOC) for patients with unresectable or metastatic melanoma in Canada

Elsa Mameri[1], Laura McDonald[2], Julie Villeneuve[1], Flavia Ejzykowicz[3], Barbara Baginska-Dudek[4], Anna Tokarz[4], Georgia Yates[5], Rui Cai[6]

[1] Bristol Myers Squibb, St. Laurent, QC, Canada; [2] Bristol Myers Squibb, Uxbridge, UK; [3] Bristol Myers Squibb, West Windsor, NJ, US; [4] Parexel International, Krakow, Poland; [5] Parexel International, London, LON, UK; [6] Parexel International, Gouda, ZH, Netherlands;

Background

- Melanoma is the fourth most common cancer in Canadians aged between 30 and years.[1] The age-standardized incidence rate is 23.5 per 100,000.[1] An estimated 9,000 people were diagnosed with melanoma in 2022.[2] Melanoma accounted for 3.8% of new cancer cases and 1.5% of cancer deaths in 2021 in Canada.[1]
- The treatment landscape for advanced, unresectable melanoma has shifted in the past decade, with the introduction of immuno-oncology (IO) therapies.[3] However, there remains an unmet need for novel IO therapies with more favorable risk-benefit profiles.
- Programmed cell death 1 (PD-1) and lymphocyte-activation gene 3 (LAG-3) are distinct inhibitors immune checkpoints. In preclinical models, dual inhibition of PD-1 and LAG-3 showed synergistic antitumor activity.[4-5]
- Combined PD-1 and LAG-3 inhibition with nivolumab plus relatlimab (NIVO+RELA) as a new fixed-dose combination (FDC) was evaluated in the phase 2/3, randomized, open label, double blind RELATIVITY-047 clinical trial:
  - NIVO+RELA demonstrated a statistically significant and clinically meaningful progression free survival (PFS) benefit vs nivolumab monotherapy (NIVO) (hazard ratio (HR) = 0.75 for intent-to-treat (ITT) population at the primary endpoint analysis in March 2021, median follow-up: 13.2 months).[6]
  - A clinically meaningful (not statistically significant) overall survival (OS) improvement vs NIVO with no delayed effect was observed (HR = 0.80 at the OS final analysis in October 2021, median follow-up: 19.3 months).[7]
- NIVO+RELA received notice of compliance for patients with unresectable or metastatic melanoma from Health Canada [8] and has been recommended for reimbursement by the local health technology assessment (HTA) body, i.e. Canadian Agency for Drugs and Technologies in Health (CADTH).[9]

Objective

- To evaluate the cost-effectiveness (CE) of NIVO+RELA versus SOC for unresectable or metastatic melanoma from a healthcare payer perspective in Canada. Current SOC includes IOs: NIVO, pembrolizumab (PEMBRO), nivolumab+ipilimumab (NIVO+IPI), IPI, and BRAF/MEK inhibitors: vemurafenib+cobimetinib (VEM+COBI), dabrafenib+trametinib (DAB+TRAM) and encorafenib+binimetinib (ENCO+BINI).

Methods

Structure and modeling approach

- A partitioned survival model (PSM) was developed with three health states: progression-free (PF), progressed disease (PD), and death.
- Population: age (62 years), gender (58.3% male), in line with baseline characteristics of patients in RELATIVITY-047.
- Perspective: payer.
- Time horizon: 25 years.
- Discount rates: costs (1.5%) and outcomes (1.5%), in line with CADTH guidelines.[10]
- Base case analysis: probabilistic with 4,000 Monte Carlo iterations.

Clinical inputs to inform health-state occupancy

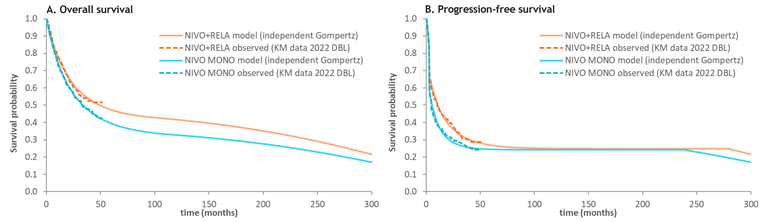
- For within trial comparison (NIVO+RELA vs NIVO), OS and PFS data from the ITT population of RELATIVITY-047 were used (October-2022 database lock [DBL] with minimum follow-up of 21 months).[11]
  - Standard parametric (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalized gamma) and spline-based models with 1 or 2 knots for PFS and OS were fitted separately to the NIVO+RELA and NIVO arms.
  - In addition, flexible piecewise (Kaplan-Meier, KM plus parametric) modelling was explored for PFS owing to the observed change in hazards at 3-months in both treatment arms which corresponded to the first per-protocol progression assessment, 12-weeks after randomization.
  - Independent standard parametric models were used to extrapolate time to treatment discontinuation (TTD) for NIVO+RELA and NIVO.
  - Curve selection was based on NICE decision support unit guidance[12] and considered long-term data and smoothed hazards in addition to statistical criteria to ensure the most plausible model was selected. The base case curve selection is shown in Table 1.
- For comparators external to RELATIVITY-047, a fractional polynomial network meta-analysis (FPNMA) was performed as the proportional hazards assumption did not hold for all studies.
  - To estimate PFS and OS for the external comparators, time-varying HRs based on the best-fitting FP model were applied to the modelled PFS and OS NIVO curves from RELATIVITY-047.
  - TTD for other IOs and BRAF/MEK inhibitors utilized data from the pivotal trials, where available, or the most appropriate assumptions (Table 1).

Table 1. Base-case curve selection and rationale

	Curve selection	Rationale
Within trial comparation (NIVO+RELA vs NIVO)		
OS	Gompertz	• A superior visual fit to the KM data and smoothed hazards • Estimated survival and hazards in line with long-term data from CheckMate-067 • A good statistical fit in terms of AIC/BIC
PFS	Piecewise model: KM (first 3 months) + Gompertz	• The best visual fit to both the KM data and observed smoothed hazards • The closest alignment to long term data from CheckMate-067 • A good statistical fit in terms of AIC/BIC
TTD	Weibull	• NIVO arm: the improved visual fit to the long-term CheckMate-067 TTD data • NIVO+RELA arm: preferred to use the same TTD distributions for both treatment arms
Comparison external to RELATIVITY-047 (NIVO+RELA vs other IOs and BRAF/MEK inhibitors)		
OS	• Other IOs: FPNMA IO network • BRAF/MEK inhibitors: FPNMA complete network (included patients from the BRAF/MEK inhibitors and IO trials irrespective of BRAF status)	• Due to heterogeneity in study design and patient characteristics in the complete network • To maximize sample size as the relative treatment effects from the NMA based on BRAF subgroup from the IO trials were consistent with those from the NMA based on the ITT population
PFS	• Other IOs: FPNMA IO network • BRAF/MEK inhibitors: FPNMA complete network	• Same as above
TTD	• NIVO+IPI: CM067 • IPI: CM067 • PEMBRO: NIVO TTD as a proxy • BRAF/MEK inhibitors: PFS as a proxy	• CM067 data were very (96%) mature therefore no extrapolation was required • PEMBRO TTD was not available and PEMBRO has the similar mechanism of action as NIVO • BRAF/MEK inhibitors TTD was not available. Unlike for IOs, PFS was used as a proxy due to different mechanism of action and different administration mode compared to IOs

AE, adverse event; AIC, Akiak information criteria; BIC, Bayesian information criteria; BRAF, V-raf murine sarcoma viral oncogene homolog B1; CM, CheckMate; FP, fractional polynomial; HR, hazard ratio; IO, Immuno-oncology; IPI, ipilimumab; ITC, indirect treatment comparison; KM, Kaplan-Meier; MEK, mitogen-activated extracellular signal-regulated kinase; NIVO, nivolumab; NMA, network meta-analysis; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; RELA, Relatlimab; TTD, Time to treatment discontinuation.

Figure 1. Survival models used for within trial comparison (NIVO+RELA vs NIVO) and KM data from RELATIVITY-047 October 2022 DBL



DBL, data base lock; KM, Kaplan-Meier; NIVO, nivolumab; RELA, relatlimab.
Note: the OS and PFS curves were adjusted with the background (general population) mortality

Cost inputs

- Costs were obtained from official Canadian sources and literature and were inflated to 2023 values where relevant. Drug acquisition costs were based on list prices.
- Cost categories included in the base-case analysis were:
  - Disease management costs (PF/PD health state costs, one time progression related costs, and end-of-life care costs).
  - Drug acquisition and administration costs
  - Costs associated with the management of adverse events (AEs)
  - Subsequent treatment costs
- Maximum treatment duration of 2 years for all IO-drugs was selected for the base case.

Quality of life

- Utility analyses were conducted based on the EQ-5D-3L questionnaire collected from the RELATIVITY-047 trial and used Canadian-specific tariffs.[13]
- Overall health-state utilities were used (PF: 0.81; PD:0.79), given the absence of statistical difference in health-state values between the treatment groups (p=0.752).
- The model included grade 3-5 TRAEs. A one-off cost and utility decrement was applied in the first model cycle to account for the expected impact of these AEs on utility.

Probabilistic base case

- In line with CADTH guidelines, the model was built probabilistically.
- A probability distribution was defined for each probabilistic input (Table 2), and when the model was run, a value for each probabilistic input was randomly selected from the associated probability distribution.
- Mean model results over the 4,000 iterations were reported.

Table 2. Distributions and sources of stochasticity

Type of parameter	Distribution	Source of stochasticity
Clinical data	Multivariate normal distribution	SE based on RELATIVITY-047 and FPNMA
Model state utility values and disutility	Beta	SE based on RELATIVITY-047
AE disutility	Beta	Proxy: SE equals 20% of mean
Average weight	Normal	SE based on RELATIVITY-047
Adverse event costs	Gamma	Combination of sourced SE from official Canadian websites and proxy SE
HCRU costs	Gamma	Proxy: SE equals 20% of mean
Mortality costs	Gamma	Proxy: SE equals 20% of mean
Base patient characteristic values	Log-normal or Beta	SE sourced from RELATIVITY-047
Frequencies of AEs	Beta	Proxy: SE equals 20% of mean

AE, Adverse events; FPNMA, fractional polynomial network meta-analysis; HRU, Health resource use; SE, Standard error.

Results

Cost-effectiveness probabilistic base case results

- NIVO+RELA generated higher QALYs compared to all IOs; total QALYs were 5.74, 4.93, 3.40, 6.38, and 6.89 for NIVO, PEMBRO, IPI, NIVO+IPI, and NIVO+RELA, respectively (Table 3).
- The total costs were $235,576, $268,007, $268,964, $274,002, and $371,036 for NIVO, PEMBRO, IPI, NIVO+IPI, and NIVO+RELA, respectively (Table 3). The disaggregated costs by treatment are shown in Table 4.
- In the pairwise comparison, NIVO+RELA was more costly and more effective than IO comparators. With comparison against BRAF/MEK inhibitors NIVO+RELA was less costly and more effective.
  - For IOs, NIVO+RELA resulted in an incremental cost-effectiveness ratio (ICER) of $117,838/QALY vs NIVO; $187,138/QALY vs NIVO+IPI; $52,559/QALY vs PEMBRO and $29,249/QALY vs IPI (Table 3).
  - For BRAF/MEK inhibitors, NIVO+RELA dominated all BRAF/MEK inhibitors, generating higher QALYs with cost savings (Table 3).

Table 3. Pairwise incremental results for cost-effectiveness frontier in 1L advanced, unresectable melanoma

Treatment	Total costs, $	Total QALYs	Inc. cost / QALYG, $
Within trial comparison (RELATIVITY-047)			
NIVO+RELA	371,036	6.894	-
NIVO	235,576	5.745	117,838
FPNMA IO network			
NIVO+IPI	274,002	6.376	187,138
PEMBRO	268,007	4.934	52,559
IPI	268,964	3.405	29,249
FPNMA complete network			
VEM+COBI	712,242	3.146	Dominated
DAB+TRAM	779,511	3.729	Dominated
ENCO+BINI	1,090,092	4.028	Dominated

BINI, binimetinib; COBI, cobimetinib; DAB, dabrafenib; ENCO, encorafenib; Inc, incremental; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYG, quality-adjusted life-years gained; RELA, Relatlimab; TRAM, trametinib; VEM, vemurafenib.

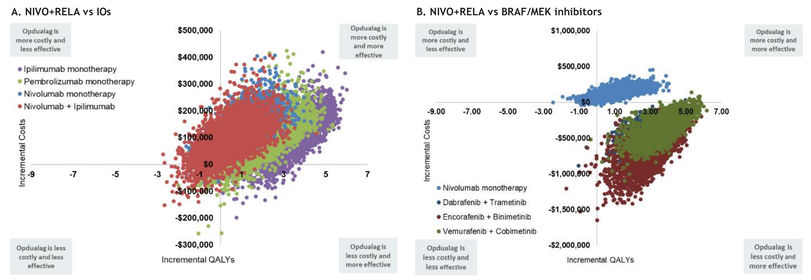
Table 4. Disaggregated costs by treatment

Treatment	Total cost, $	Cost breakdown, $				
		Disease management	Treatment acquisition	Treatment admin	AEs	Subsequent treatment
NIVO+RELA	371,036	158,638	199,578	657	475	11,689
NIVO	235,576	116,739	104,694	2,285	173	11,685
NIVO+IPI	274,002	94,780	166,535	2,063	4,639	5,985
PEMBRO	268,007	115,524	137,488	1,974	752	12,269
IPI	268,964	147,148	109,012	192	2,283	10,328

BINI, binimetinib; COBI, cobimetinib; DAB, dabrafenib; ENCO, encorafenib; Inc, incremental; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYG, quality-adjusted life-years gained; RELA, Relatlimab; TRAM, trametinib; VEM, vemurafenib.

- The CE planes for ICERs (cost per QALY gained) are displayed in Figure 2.
  - NIVO+RELA was more effective and more costly compared to other IOs: most (70%-94%) of probabilistic ICERs fell in the northeast (NE) quadrant (Figure 2A).
  - NIVO+RELA was always the most cost-effective treatment against BRAF/MEK inhibitors: over 99% of probabilistic ICERs fell in southeast (SE) quadrant (Figure 2B).

Figure 2. Cost-effectiveness plane of probabilistic ICER results ($/QALY)



Discussion

- For comparison with IOs, NIVO+RELA was the most effective and costly treatment. Between 70%-94% of probabilistic ICERs of NIVO+RELA vs IOs fell in NE quadrant.
- For comparison with BRAF/MEK inhibitors, NIVO+RELA dominated all BRAF/MEK inhibitors, generating higher QALYs with cost savings. Over 99% of probabilistic ICERs of NIVO+RELA vs BRAF/MEK inhibitors fell in SE quadrant.
- Due to similar efficacy between NIVO+RELA and NIVO+IPI, a small incremental QALY difference was observed, and as such, the ICER presented for NIVO+RELA vs NIVO+IPI should be interpreted with caution.
- Although the relative treatment effects from the NMA used the ITT population, a sensitivity analysis showed results based on BRAF subgroup from the IO trials were consistent with those from the NMA based on the ITT population. Thus, the robustness of the results was confirmed.

Conclusion

- This study provides robust modeling evidence that suggests NIVO+RELA is expected to be a life-extending and cost-effective new therapy compared to SOC treatments for unresectable or metastatic melanoma in Canada.

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Email: Laura.McDonald@bms.com