Cost-effectiveness analysis of nivolumab plus relatlimab (NIVO+RELA) versus nivolumab monotherapy (NIVO) for patients with advanced melanoma in the Netherlands

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Background

- Rates of malignant melanoma are rapidly increasing globally, ranking fifth in incidence and among the top 15 causes of cancer death in Europe.[1] Incidence and mortality rates in the Netherlands are ranked second for incidence (27.0 per 100,000 person-years) and seventh for mortality (2.3 per 100,000 person-years) in 2020.[2]
- The treatment landscape for advanced, non-resectable melanoma has shifted in the past decade.[3] However, there remains a need for highly effective combination immuno-oncology (IO) therapies with manageable safety profiles.
- Programmed cell death 1 (PD-1) and lymphocyte-activation gene 3 (LAG3) are distinct inhibitory 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 RELATIVITY-047 clinical trial:[6]
- NIVO+RELA demonstrated a statistically significant and highly clinically meaningful progression free survival (PFS) benefit vs NIVO (hazard ratio (HR) = 0.78 and 0.68 for intent-to-treat (ITT) and PD-L1 < 1% population [October-2021 database lock (DBL)]).
 A clinically meaningful (but not statistically significant) overall survival (OS) improvement vs NIVO with no delayed effect was observed (HR = 0.80 and 0.78) for ITT and PD-L1 < 1% population [October-2021 DBL].
 NIVO+RELA has received marketing authorization for patients with PD-L1 < 1% from the European Medicines Agency (EMA) [7] and is now being assessed for reimbursement by the local health technology assessment (HTA) body, Zorginstituut Nederland (ZIN).

Cost inputs

- Costs obtained from official Dutch websites were conducted in 2022. Other costs from literature were inflated to 2023.
- 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 costs and drug administration costs.
- Cost of treatment-related AEs.
- Societal costs, including travel costs, productivity loss (based on friction costs), and informal care costs.
- $\circ~$ Subsequent treatment costs.
- Biomarker (PD-L1) test costs.
- A conservative maximum treatment duration of 1.5 years for both arms was chosen for the base case.
- Research has shown sustained tumor response after early discontinuation of PD-1 inhibitors is observed in patients who achieve complete response (CR), partial response (PR) and

Probabilistic sensitivity analyses

- Results from the PSA (Figure 3B) show that the majority of the 1,000 iterations were in the northeast quadrant, meaning that NIVO+RELA provided QALY gains at an incremental total cost compared with NIVO.
- Applying a WTP threshold of €50,000 per QALY gained, NIVO+RELA had a 60% probability of being cost-effective compared with NIVO (Figure 3A).
- The deterministic and probabilistic analyses produced similar ICERs (€41,896 vs €42,081 per QALY gained).

Figure 3. Cost-effectiveness acceptability curve (A) and cost-effectiveness plane (B): NIVO+RELA vs NIVO



Objectives

• To evaluate the cost-effectiveness (CE) of NIVO+RELA versus NIVO for 1L treatment of advanced, non-resectable melanoma for the PD-L1 < 1% population from a societal perspective in the Netherlands.

Methods

Structure and modeling approach

- A partitioned survival cohort model (PSM) was developed. The model structure comprised three key health states: progression-free (PF), progressed disease (PD), and death.
- **Population:** starting age (60.8 years), gender (58.3% male), in line with baseline characteristics of patients in RELATIVITY-047.
- Perspective: societal perspective.
- Time horizon: lifetime (40 years).
- **Discount rates:** costs (4.0%) and outcomes (1.5%), in line with ZIN pharmacoeconomic guidelines.[8]

Clinical inputs to inform health-state occupancy

- OS and PFS data for patients with PD-L1<1% from the RELATIVITY-047 trial (October-2021 DBL, minimum follow-up: 8.7 months) were used to inform the model.
- Dependent standard parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalized gamma) were fitted to both PFS and OS since proportional hazards held. The base case extrapolations fitted to Kaplan-Meier (KM) data are shown in Figure 1.
- Independent spline models with 1 or 2 knots (proportional odds model, proportional hazards model, and probit model) were also explored for PFS in a scenario analysis, in order to better capture the initial sharp drop in PFS observed in the KM curve, which reflects the first on-study tumor assessment (scheduled at 12 ± 1 weeks from randomization) commonly seen in IO trials.

- stable disease (SD).[10][11][12] As such, under routine clinical practice in the Netherlands, treatment is typically stopped on an individual basis after achieving CR or PR.[13]
- The median time to objective response is approximately 3 months in patients with advanced melanoma, and the preferred treatment duration is considered to be at least 3-6 months.[13] According to Dutch clinical expert opinion, IO treatment for patients with CR and PR is typically around 6 months of initiating IO therapy, while for SD this is 1 to 1.5 years.

Quality of life

- Utility analyses were conducted based on the EQ-5D-3L questionnaire collected from the RELATIVITY-047 trial and on the prespecified country-specific utility values.[14]
- Given an absence of statistical difference in health-state utility values between the treatment groups (p=0.9840), overall health-state utilities were used (PF: 0.86; PD:0.80).
- Treatment-related adverse events (AEs) with NIVO+RELA and NIVO were obtained from RELATIVITY-047.[6] The model included grade 3-5 treatment-related AEs. 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.

Sensitivity analysis

- One-way deterministic sensitivity analysis (DSA) was undertaken by varying key parameters by their standard error, 95% confidence interval (CI), or ±20% of their point estimate (e.g., value used in base-case analysis) depending on data availability.
- A probabilistic sensitivity analysis (PSA) was performed with 1,000 simulations. The willingness-to-pay (WTP) threshold applicable in this CEA was €50,000/QALY gained, calculated based on the proportional shortfall method.[15]

Scenario analysis

- Scenario analysis was conducted to investigate the effect of a maximum treatment duration of 1 year, which is in line with clinical practice for SD.
- Additionally, the second curve choices for PFS (independent spline 2 knots odds for both treatments), OS (dependent generalized gamma) and for TTD (independent log-logistic for both treatments) were investigated in scenario analyses.
- For PFS, spline models were presented as an alternative scenario as SPMs were unable to capture the initial sharp drop in the PFS KM curve. Spline models, however, underpredicted long-term survival when compared to observed data from CheckMate-067.
- For OS, although generalized gamma exhibited a good visual and statistical fit to the observed RELATIVITY-047 data and smoothed hazards, but underestimated the tail of the KM curve, particularly for NIVO+RELA and overestimated the underlying hazards at early time points and tail.

QALY, quality adjusted life years; WTP, willingness to pay

Scenario analysis

Table 4 presents the results for the scenario analyses. The highest impact was seen for the second-best fitting OS curve (€ 56,592/QALY) and treatment duration cap of 1 year (€ 33,860/QALY). All other scenarios resulted in minor ICER changes.

Table 4. Scenario analysis results for NIVO+RELA vs NIVO in 1L advance, non-resectable melanoma

Scenario's	Inc. Costs, €	Inc. LYs	Inc. QALYs	Inc. cost per LYG, €	lnc. cost per QALYG, €	Difference in ICER vs base case
Base case	65,278	1.74	1.56	37,500	41,896	-
1: PFS (independent 2 knots spline odds)	67,235	1.74	1.47	38,624	45,742	3,847
2: OS (dependent generalized gamma)	61,504	1.20	1.09	51,389	56,592	14,697
3: TTD (independent loglogistic)	63,386	1.74	1.56	36,413	40,681	-1,214
4: treatment duration cap (1 year)	52,757	1.74	1.56	30,307	33,860	-8,036

CEA: cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; NIVO: nivolumab; NIVO+RELA: nivolumab + relatlimab; TTD: time to treatment discontinuation; PFS: progression free survival; OS: overall survival; Inc, incremental; QALY: quality adjusted life years; LY: life years; LYG: life year gained; QALYG: quality adjusted life years

- Independent standard parametric models were used to extrapolate time to treatment discontinuation (TTD), as a constant treatment effect could not reasonably be assumed given the various factors that influence time on treatment.
- Curve selection was based on NICE decision support unit guidance.[9] The base case curve selection is shown in Table 1. Notably, model selection for the base case considered long-term data and smoothed hazards in addition to statistical criteria to ensure the most plausible model was selected.

Table 1. Base-case curve selection and rationale

	Curve selection	Rationale
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	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
OS: overall surv	ival; PFS: progression free survival	; TTD: time to treatment discontinuation

Figure 1. Survival models used in the base case vs KM data from RELATIVITY-047 October 2021 DBL



Results

Base-case cost-effectiveness results

- In the PD-L1 <1% advanced, non-resectable melanoma population, NIVO+RELA and NIVO resulted in 7.95 vs. 6.39 QALYs, respectively, yielding an incremental benefit of 1.56 QALYs for NIVO+RELA.
- The total costs for NIVO+RELA and NIVO were estimated at € 262,216 and € 196,938, respectively, an increment of € 65,278.
- The resulting ICER of €41,896/QALY gained is below the WTP threshold of €50,000/QALY gained (Table 2).
- The disaggregated costs by treatment are shown in Table 3.

Table 2. Base-case incremental results for NIVO+RELA vs NIVO in 1L advanced, non-resectable melanoma

NIVO+RELA vs	'O+RELA vs Inc. costs, €		Inc. LYs	lnc. cost / QALYG, €	Inc. cost / LYG, €	
NIVO	65,278	1.56	1.74	41,896	37,500	
Inc, incremental; LYG, life-years gained; QALYG, quality-adjusted life-years gained.						

Table 3. Disaggregated costs by treatment

	Total cost, €	Cost breakdown, €						
Treat- ment		Disease manage- ment	Treatment acquisition	Treatment admin	AEs	Subse- quent treatment	Transpor- tation	Producti- vity loss & informal care
NIVO+REL A	262,216	80,309	108,687	3,579	73	38,465	714	30,388
NIVO	196,938	66,306	46,635	3,511	92	50,745	580	29,067
Admin, administration.								

Deterministic sensitivity analyses

Discussion

- The calculated QALY gain of 1.56 QALYs for NIVO+RELA vs. NIVO is substantial, in light of the remaining QALYs of 6.39 for NIVO in this population. The resulting ICER of €41,896/QALY is below the WTP threshold of €50,000/QALY gained.
- Most importantly, the deterministic and probabilistic mean ICERs were in close agreement (€41,896 vs €42,081 per QALY gained), demonstrating that the base case analysis was robust to variations in key parameters. Applying a WTP threshold of €50,000 per QALY gained, NIVO+RELA had a 60% probability of being cost-effective compared with NIVO.
- Scenario analyses indicated that a realistic maximum treatment duration of 1 year further reduces the ICER to €33,860/QALY.
- Scenario analysis including the generalized gamma distribution should be interpreted with caution as this model underestimated long-term survival.

Conclusion

• This study provides robust modeling evidence that confirms NIVO+RELA as a clinically valuable and cost-effective addition to the first-line treatment options for patients with advanced, unresectable melanoma with PDL1 expression <1% in the Netherlands.

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 The ICER was found to be most sensitive to changes in the disease management costs for the PF and average starting age (related to productivity loss costs), but all calculated ICERs were below the WTP threshold of €50,000 per QALY gained (Figure 2).

Figure 2. DSA tornado diagram showing the impact of individual input parameters on the NIVO+RELA vs NIVO ICER (€ per QALY gained)



AE: adverse event; ICER, incremental cost-effectiveness ratio; PF: progression free; PD: progressed disease.

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