Temporal Trends in Adverse Event Costs with Nivolumab + Relatlimab Combination Therapy or Nivolumab Monotherapy for Patients with Unresectable or Metastatic Melanoma

EE268

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Introduction

- Melanoma is one of the deadliest malignant cancers in the United States, accounting for approximately 75% of skin cancer deaths despite only representing 4% of skin cancer cases.[1] In 2023, approximately 97,610 people will be diagnosed and 7,990 people are expected to die from melanoma[2]
- The introduction of novel therapies and immuno-oncology agents has greatly improved survival outcomes over the last 10 years[3]
- Lymphocyte-activation gene 3 (LAG-3) and programmed cell death protein 1 (PD-1), two distinct immune checkpoints often co-expressed on tumor-infiltrating lymphocytes (TILs), contribute to tumor-mediated T-cell dysfunction. Nivolumab (NIVO) is an anti-PD-1 antibody that relieves T-cell dysfunction and restores cytotoxic function,[4] and has been a standard of care for treating unresectable or metastatic melanoma. Relatlimab (RELA) is a human LAG-3 blocking antibody that restores the effector function of dysfunctional T-cells[5]
- RELATIVITY-047 (NCT03470922) investigated NIVO + RELA as a fixed-dose combination therapy in patients with unresectable or metastatic melanoma.[5] NIVO + RELA was approved by the FDA in 2022[6]
  - At a median follow-up of 13.2 months, NIVO + RELA demonstrated superior progression free survival (PFS) versus NIVO (hazard ratio, 0.75; 95% CI, 0.62 to 0.92; P=0.006)[4]
  - At a median follow-up of 19.3 months, sustained PFS benefit, clinically meaningful improvement in overall survival (OS), and numerically higher objective response rate (ORR) were observed with NIVO + RELA compared to NIVO (median PFS: 10.2 vs. 4.6 months, hazard ratio [HR]: 0.78 [95% CI: 0.64, 0.94]; median OS: not reached [NR] vs. 34.1 months, HR: 0.80 [95% CI: 0.64, 1.01]; ORR: 43.1% [95% CI: 37.9, 48.4] vs. 32.6% [95% CI: 27.8, 37.7])[7]
- NIVO + RELA showed a manageable safety profile with no new or unexpected safety signals and a positive benefit/risk profile. The impact of treatment-related adverse events (TRAEs) on health-related quality of life was similar between the treatment arms, suggesting a perceived treatment tolerance with NIVO + RELA[8]
- To inform decision-making, it is important to fully understand the safety profile of treatment options and the economic burden associated with adverse events (AEs), including temporal patterns and cost drivers

Objectives

- The present study summarized the hospitalization costs of grade 3 or 4 all-cause AEs and TRAEs among treatment naïve patients with unresectable or metastatic melanoma treated with NIVO + RELA or NIVO in RELATIVITY-047 as follows:
  - Estimated the per-patient costs within 6, 12, and 24 months, and the entire study period
  - Described temporal trends of per-patient per-month (PPPM) costs over the entire study period
  - Identified the top drivers of costs over different time periods (i.e., entire study period, and within 1-6, 7-12, 13-24, and 25-35 months)

Methods

Data sources

- AEs were identified from individual-level patient data (IPD) from the RELATIVITY-047 intention-to-treat (ITT) population (NIVO + RELA: N = 355; NIVO N = 359; October 28, 2021 database lock; 19.3 months median follow-up)[4]
  - All grade 3 or 4 all-cause AEs or TRAEs occurring in either treatment arm between treatment initiation date and 30 days after the last dose of study drug (i.e., 30-day treatment-emergent AEs) were included; no minimum threshold was imposed on the AE rates for inclusion into the analyses
  - Patients at risk were defined as patients who were still on treatment or within the above 30-day safety window after ending treatment
- Inpatient AE unit costs were identified from the US 2019 Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) database[9] based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes, and were inflated to 2021 USD[10] (the most recent price year available within inflation index at the time when this study was conducted)

AE cost calculation

- The cost for a given AE was calculated by multiplying its unit cost by its frequency within the relevant period
- Time to AE, which was used to allocate an AE to its given month, was calculated as the difference between AE start date and date of first exposure to treatment
- If the time periods of two or more AEs overlapped (i.e., one AE's start date fell between another AE's start and end date), the cost of the most expensive AE was used to represent all AEs in that period
  - A sensitivity analysis was conducted by using costs of all overlapping AEs without adjustment

Statistical analyses

- Per-patient AE costs were calculated by dividing total AE costs by number of patients in each arm
- Temporal trends
  - PPPM AE costs were calculated for each month by dividing the sum of AE costs by the sum of person-months at risk, and then graphically depicted over the entire study period. A non-parametric local polynomial regression (LOESS) method was used to plot smooth curves
- AE cost drivers
  - Per-patient AE costs were summarized for each AE category defined by body system or organ class based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (e.g., vascular disorders, gastrointestinal disorders, laboratory investigations)
  - For each specific period, AE costs per category were calculated by dividing the total AE costs for each AE category over the time period by the sum of person-months at risk within that period
  - The AE categories associated with the highest costs were identified as the top cost drivers

Results

Per-patient AE costs

- NIVO + RELA was associated with higher per-patient costs of all-cause AEs compared to NIVO ($8,911 vs. $7,072, cost difference of $1,839) and TRAEs ($2,349 vs. $1,855, cost difference of $494) over the entire study period (**Table 1**)

Table 1: Per-patient grade 3 or 4 hospitalization AE costs over each period

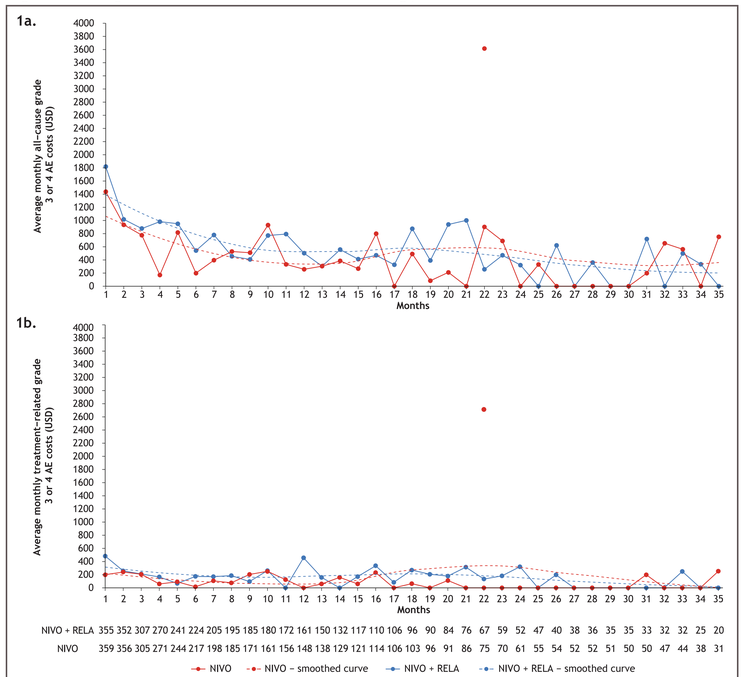
	Per-patient AE cost (USD)	
	NIVO + RELA	NIVO
All-cause grade 3 or 4 AE costs		
Up to 6 months	$5,160	$3,708
Up to 12 months	$7,026	$5,068
Up to 24 months	$8,610	$6,700
Over the entire study period	**$8,911**	**$7,072**
Treatment-related grade 3 or 4 AE costs		
Up to 6 months	$1,167	$703
Up to 12 months	$1,741	$1,056
Up to 24 months	$2,307	$1,808
Over the entire study period	**$2,349**	**$1,855**

Abbreviations: AE, adverse event; NIVO, nivolumab; RELA, relatlimab; USD, US Dollars.

Temporal trends in all-cause AE and TRAE costs

- Both NIVO + RELA and NIVO followed similar trends of PPPM AE costs
  - All-cause AE costs were highest in the first 6 months, decreased during the first year (72% reduction for NIVO + RELA; 82% reduction for NIVO), and plateaued through the second and third years (**Figure 1a**)
  - TRAE costs were much lower initially compared to all-cause AEs, and remained stable throughout the study (**Figure 1b**)
- Average PPPM all-cause AE and TRAE costs were slightly higher for NIVO + RELA than NIVO, especially in the first year, and became more similar through the second and third years
  - All-cause AE: $825 for NIVO + RELA and $608 for NIVO in year 1, and $385 for NIVO + RELA and $406 for NIVO for the remaining period
  - TRAE: $211 for NIVO + RELA and $132 for NIVO in year 1, and $122 for NIVO + RELA and $167 for NIVO for the remaining period

Figure 1. PPPM grade 3 or 4 AE hospitalization costs among patients in RELATIVITY-047



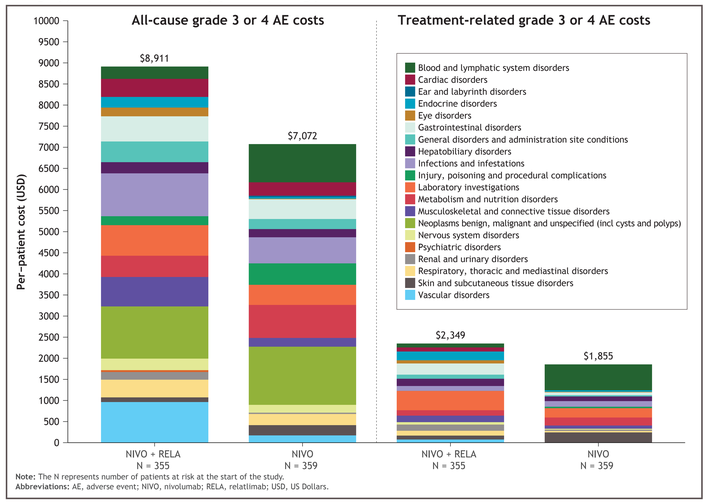
Notes:
1. The numbers at the bottom of the figure represent patients at risk at the start of each month.
2. One patient in the NIVO arm had a treatment-related acquired haemophilia event at month 22, which is associated with a large unit cost ($193,564 in 2021 USD). The red outlier represents the total PPPM costs including the cost of this event. This event's cost was included in the smooth curve estimation and overall results.
3. AEs were captured at the onset months, and cost for each AE was applied at the AE start date. The temporal trend does not reflect the duration of AEs.

Abbreviations: AE, adverse event; NIVO, nivolumab; PPPM, per-patient per-month; RELA, relatlimab; USD, US Dollars.

Top drivers of all-cause AE and TRAE costs

- Over the entire study period, top all-cause AE cost-driver categories were neoplasms ($1,236), infections and infestations ($1,016), and vascular disorders ($963) for NIVO + RELA, accounting for 36% of total costs; and neoplasms ($1,374), blood and lymphatic system disorders ($902), and metabolism and nutrition disorders ($780) for NIVO (43% of total costs) (**Figure 2**)
- Over the entire study period, top TRAE cost-driver categories were laboratory investigations ($461), gastrointestinal disorders ($264), and endocrine disorders ($208) for NIVO + RELA, accounting for 40% of costs; and blood and lymphatic system disorders ($612), skin and subcutaneous tissue disorders ($244), and laboratory investigations ($216) for NIVO (58% of total costs) (**Figure 2**)

Figure 2. Per-patient all-cause and treatment-related grade 3 or 4 AE hospitalization costs (by AE category) over the entire study period among patients in RELATIVITY-047



Note: The N represents number of patients at risk at the start of the study.
Abbreviations: AE, adverse event; NIVO, nivolumab; RELA, relatlimab; USD, US Dollars.

Sensitivity analysis

- The results and conclusions were similar with and without adjustment for overlapping AEs (data not shown)

Limitations

- Costs associated with grade 1 and 2 AEs and the non-inpatient costs (e.g., outpatient or community services) associated with grade 3 or 4 AEs were not included in this analysis because the standard US unit costs are unavailable in the HCUP NIS data. These events are usually of relatively low-cost impact compared to inpatient costs
- This analysis assumed all grade 3 or 4 AEs resulted in hospitalization, which may potentially overestimate the costs of these AEs

Conclusions

- The AE cost trends over the study period were similar for the NIVO + RELA and NIVO arms, with slightly higher cost associated with NIVO + RELA (approximately $500 difference per patient in TRAE costs)
- NIVO + RELA has demonstrated significant improvement in PFS, clinically meaningful improvement in OS, and numerically higher confirmed ORR compared to NIVO monotherapy. Patients had similar health-related quality of life in the NIVO + RELA and NIVO arms. The results of this analysis suggest that these benefits are achieved with minimal incremental economic burden associated with AE management

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Disclosures

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