First-Line Nivolumab Plus Relatlimab Versus Nivolumab Plus Ipilimumab in Advanced Melanoma: An Indirect Treatment Comparison Using RELATIVITY-047 and CheckMate 067 Trial Data

Georgina V. Long, PhD, MBBS[1]; Evan J. Lipson, MD[2]; F. Stephen Hodi, MD[3]; Paolo A. Ascierto, MD[4]; James Larkin, MD, PhD[5]; Christopher Lao, MD[6]; Jean-Jacques Grob, MD, PhD[7]; Flavia Ejzykowicz, PhD[8]; Andriy Moshyk, MD, MSc[8]; Viviana Garcia-Horton, PhD[9]; Zheng-Yi Zhou, PhD[9]; Yiqiao Xin, PhD, MSc[9]; Jennell Palaia, PharmD, MS[8]; Laura McDonald, PhD, MSc[8]; Sarah Keidel, BM BCh[8]; Anthony Salvatore, PharmD, MBA[8]; Divya Patel, PharmD[8]; Leon A. Sakkal, PharmD[8]; Hussein Tawbi, MD, PhD[10]; and Dirk Schadendorf, MD[11,12,13]

DOI https://doi.org/10.1200/JCO.24.01125

ABSTRACT

PURPOSE Nivolumab plus relatlimab and nivolumab plus ipilimumab have been approved for advanced melanoma on the basis of the phase II/III RELATIVITY-047 and phase III CheckMate 067 trials, respectively. As no head-to-head trial comparing these regimens exists, an indirect treatment comparison was conducted using patient-level data from each trial.

METHODS Inverse probability of treatment weighting (IPTW) adjusted for baseline characteristic differences. Minimum follow-ups (RELATIVITY-047, 33 months; CheckMate 067, 36 months) were selected to best align assessments. Outcomes included progression-free survival (PFS), confirmed objective response rate (cORR), and melanoma-specific survival (MSS) per investigator; overall survival (OS); and treatment-related adverse events (TRAEs). A Cox regression model compared PFS, OS, and MSS. A logistic regression model compared cORRs. Subgroup analyses were exploratory.

RESULTS After IPTW, key baseline characteristics were balanced for nivolumab plus relatlimab (n = 339) and nivolumab plus ipilimumab (n = 297). Nivolumab plus relatlimab demonstrated similar PFS (hazard ratio [HR], 1.08 [95% CI, 0.88 to 1.33]), cORR (odds ratio, 0.91 [95% CI, 0.73 to 1.14]), OS (HR, 0.94 [95% CI, 0.75 to 1.19]), and MSS (HR, 0.86 [95% CI, 0.67 to 1.12]) to nivolumab plus ipilimumab. Subgroup comparisons showed larger numerical differences favoring nivolumab plus ipilimumab with acral melanoma, *BRAF*-mutant melanoma, and lactate dehydrogenase >2 × upper limit of normal, but were limited by small samples. Nivolumab plus relatlimab was associated with fewer grade 3-4 TRAEs (23% *v* 61%) and any-grade TRAEs leading to discontinuation (17% *v* 41%).

CONCLUSION Nivolumab plus relatlimab demonstrated similar efficacy to nivolumab plus ipilimumab in the overall population, including most—but not all—subgroups, and improved safety in patients with untreated advanced melanoma. Results should be interpreted with caution.

ACCOMPANYING CONTENT

Editorial, p. 3891

Data Supplement

Accepted July 10, 2024
Published August 13, 2024

J Clin Oncol 42:3926-3934

View Online Article

INTRODUCTION

Nivolumab plus relatlimab and nivolumab plus ipilimumab are dual immune checkpoint inhibitor (ICI) regimens that were approved for treating patients with advanced melanoma on the basis of the phase II/III RELATIVITY-047 (ClinicalTrials.gov identifier: NCT03470922) and phase III CheckMate 067 (ClinicalTrials.gov identifier: NCT01844505) trials, respectively.[1-4] Nivolumab plus relatlimab is the only dual PD-1 and lymphocyte-activation gene 3 (LAG-3) inhibitor regimen approved for treating patients with advanced melanoma, and relatlimab is a first-in-class human IgG4 LAG-3–blocking antibody.[1,2] Nivolumab plus ipilimumab is a dual PD-1 and cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor regimen.[3,4] After regulatory approvals, the National Comprehensive Cancer Network

CONTEXT

Key Objective

How do efficacy and safety compare between nivolumab plus relatlimab and nivolumab plus ipilimumab in patients with untreated advanced melanoma in the absence of a randomized, head-to-head trial?

Knowledge Generated

In this indirect treatment comparison, which used patient-level trial data from the phase II/III RELATIVITY-047 and phase III CheckMate 067 trials, nivolumab plus relatlimab demonstrated similar efficacy to nivolumab plus ipilimumab in the overall population, including most—but not all—subgroups, and improved safety in patients with untreated advanced melanoma.

Relevance *(G.K. Schwartz)*

With the exception of patients with acral melanoma and brain metastases, nivolumab plus relatlimab represents a reasonable alternative to nivolumab and ipilimumab in the treatment of patients with metastatic melanoma.*

*Relevance section written by *JCO* Associate Editor Gary K. Schwartz, MD, FASCO.

(NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommended both nivolumab plus relatlimab and nivolumab plus ipilimumab as preferred, category 1, first-line systemic therapy options for unresectable or metastatic melanoma.[5] At a long-term follow-up of RELATIVITY-047 (median follow-up, 33.8 months), progression-free survival (PFS) per blinded independent central review (hazard ratio [HR], 0.79 [95% CI, 0.66 to 0.95]) and overall survival (OS; HR, 0.80 [95% CI, 0.66 to 0.99]) data were consistent with previous reports.[2] At a long-term follow-up of CheckMate 067 (minimum follow-up, 7.5 years), a descriptive analysis of nivolumab plus ipilimumab versus nivolumab monotherapy suggested benefits for PFS per investigator (INV; HR, 0.79 [95% CI, 0.65 to 0.97]) and OS (HR, 0.84 [95% CI, 0.68 to 1.04]) in patients with previously untreated advanced melanoma.[4]

No randomized, head-to-head trial comparing nivolumab plus relatlimab with nivolumab plus ipilimumab as first-line therapy exists for patients with advanced melanoma, resulting in an evidence gap for determining which dual ICI regimen to administer. Indirect treatment comparisons (ITCs) that evaluated published data across trials using unadjusted analyses suggest that nivolumab plus relatlimab may have similar efficacy and improved safety versus nivolumab plus ipilimumab.[6-8] However, there is a need for a robust ITC that uses patient-level data, allowing adjustment of covariates across trials. Consequently, an exploratory, post hoc ITC was conducted using patient-level data from RELATIVITY-047 and CheckMate 067.[1-4]

METHODS

Data Sources

Characteristics of RELATIVITY-047 and CheckMate 067 are presented in the Data Supplement (Table S1, online only).[1-4] In RELATIVITY-047, patients were randomly assigned (1:1) to receive either nivolumab 480 mg and relatlimab 160 mg as a fixed-dose combination once every 4 weeks or nivolumab 480 mg once every 4 weeks.[1] In CheckMate 067, patients were randomly assigned (1:1:1) to receive nivolumab 1 mg/kg once every 3 weeks plus ipilimumab 3 mg/kg once every 3 weeks for four doses followed by nivolumab 3 mg/kg once every 2 weeks, nivolumab 3 mg/kg once every 2 weeks, or ipilimumab 3 mg/kg once every 3 weeks for four doses.[3]

Outcomes

Outcomes were selected from available common data. Efficacy outcomes included PFS per INV, OS, confirmed objective response rate (cORR) per INV, duration of response (DOR) per INV, and melanoma-specific survival (MSS) per INV. Safety outcomes included all-cause adverse events (AEs) and treatment-related AEs (TRAEs). Select TRAEs (ie, those with a potential immunologic etiology related to ICIs) were evaluated for the following categories: endocrine, GI, hepatic, pulmonary, renal, skin, and hypersensitivity/infusion reactions.

Statistical Analysis

In RELATIVITY-047, outcomes were analyzed using a database lock (DBL) of October 19, 2023 (the latest available DBL at the time of the analysis), with a minimum follow-up time of 33.0 months and a median follow-up time of 33.8 months.[2] In CheckMate 067, outcomes were analyzed using a DBL of November 12, 2021, with a minimum follow-up time of 90 months (7.5 years).[4] To best align the follow-up times between the two trials, the follow-up time for CheckMate 067 was truncated at the date of April 13, 2017 (the data cutoff date corresponding to the CheckMate 067 DBL of May 24, 2017). Patients in CheckMate 067 without an event were censored on the date of truncation, resulting in a minimum

follow-up time of 36 months and a median follow-up time of 37 months.

A propensity score model was used to generate inverse probability of treatment weighting (IPTW),[9] which adjusted for any imbalances in the distribution of baseline characteristics between the two trials (Data Supplement). The distribution of baseline characteristics was compared between the weighted cohorts using a standardized mean difference (SMD) of <0.2 to indicate balance between treatments.[10,11]

PFS, OS, DOR, and MSS were estimated using the Kaplan-Meier method and compared for nivolumab plus relatlimab versus nivolumab plus ipilimumab in a Cox regression model using HRs before and after weighting. Violations to the proportional hazards assumption for PFS, OS, and MSS were determined using the Schoenfeld residual test, as indicated by a *P* value of <.05. cORRs were compared for nivolumab plus relatlimab versus nivolumab plus ipilimumab in a logistic regression model using odds ratios (ORs) before and after weighting. Efficacy outcomes were similar between the two treatment groups if the 95% CIs for the HRs/ORs included 1.

PFS, cORR, and OS were summarized descriptively in prespecified subgroups. HRs/ORs for PFS, cORR, and OS are presented for each subgroup in forest plots. Kaplan-Meier curves for PFS and OS are presented for selected subgroups.

In a sensitivity analysis that was conducted using the untruncated data from CheckMate 067, PFS, OS, and MSS were compared for the nivolumab plus relatlimab versus nivolumab plus ipilimumab groups while retaining the minimum follow-up time (7.5 years) for CheckMate 067. As an internal validation of the ITC, PFS, cORR, OS, and MSS were compared between the nivolumab monotherapy groups from each trial using the truncated follow-up time for CheckMate 067.

AEs were analyzed descriptively. To allow comparability in follow-up times between the trials, AEs were restricted to events occurring within 30 days of the last dose of study drug (ie, 30-day treatment-emergent) during the first 36 months of follow-up in both trials. Time to onset of any-grade and grade 3-4 select TRAEs were evaluated at various intervals over 36 months before and after weighting for both treatments.

RESULTS

Baseline Characteristics

Data for all covariates were available for 349 of 355 patients in the nivolumab plus relatlimab group and 307 of 314 patients in the nivolumab plus ipilimumab group; the remaining six and seven patients, respectively, were excluded (Data Supplement, Fig S1). Before weighting, geographic region, previous adjuvant therapy, and melanoma subtype were unbalanced between the two treatments (SMD ≥0.2) and tumor PD-L1 expression approached the threshold (SMD = 0.18; Data Supplement, Table S2). After weighting, effective sample sizes were 339 for the nivolumab plus relatlimab group and 297 for the nivolumab plus ipilimumab group, and all covariates were balanced (SMD <0.2; Data Supplement, Table S2).

Efficacy

Overall, PFS per INV was similar between nivolumab plus relatlimab and nivolumab plus ipilimumab after weighting (36-month PFS, 36% *v* 39%; HR, 1.08 [95% CI, 0.88 to 1.33]; Fig 1). Proportional hazards assumptions were not violated before or after weighting (Schoenfeld residual test *P* = .54 and *P* = .75, respectively). Across most subgroups, PFS per INV was similar between the treatments after weighting, although larger numerical differences were observed in the subgroup with acral melanoma (HR, 1.42 [95% CI, 0.69 to 2.93] favoring nivolumab plus ipilimumab; Data Supplement, Fig S2). Kaplan-Meier PFS curves by *BRAF* status, tumor PD-L1 expression, baseline lactate dehydrogenase (LDH) level, and presence/absence of liver metastasis after weighting are shown in the Data Supplement (Figs S3-S7).

cORR per INV was similar between nivolumab plus relatlimab and nivolumab plus ipilimumab after weighting (48% *v* 50%; OR, 0.91 [95% CI, 0.73 to 1.14]; Data Supplement, Table S3). Across most subgroups, cORRs per INV were similar between the treatments after weighting, although larger numerical differences were observed favoring nivolumab plus ipilimumab with *BRAF*-mutant disease (OR, 0.65 [95% CI, 0.44 to 0.96]), acral melanoma (OR, 0.59 [95% CI, 0.21 to 1.61]), mucosal melanoma (OR, 0.63 [95% CI, 0.25 to 1.61]), and LDH >2 × upper limit of normal (ULN; OR, 0.28 [95% CI, 0.10 to 0.83]; Data Supplement, Fig S8). Median DOR per INV was similar for the two treatments after weighting (HR, 0.88 [95% CI, 0.60 to 1.28]; Data Supplement, Fig S9).

OS was similar between nivolumab plus relatlimab and nivolumab plus ipilimumab after weighting (36-month OS, 57% for both treatments; HR, 0.94 [95% CI, 0.75 to 1.19]; Fig 2). Proportional hazards assumptions were not violated before or after weighting (Schoenfeld residual test *P* = .12 and *P* = .13, respectively). Across most subgroups, OS was similar between the treatments after weighting, although larger numerical differences were observed favoring nivolumab plus ipilimumab with acral melanoma (HR, 1.72 [95% CI, 0.76 to 3.91]) and LDH >2 × ULN (HR, 1.50 [95% CI, 0.85 to 2.66]; Data Supplement, Fig S10). Kaplan-Meier OS curves by *BRAF* status, tumor PD-L1 expression, LDH level, and presence/absence of liver metastasis after weighting are shown in the Data Supplement (Figs S11-S15).

MSS per INV was similar between nivolumab plus relatlimab and nivolumab plus ipilimumab after weighting (36-month

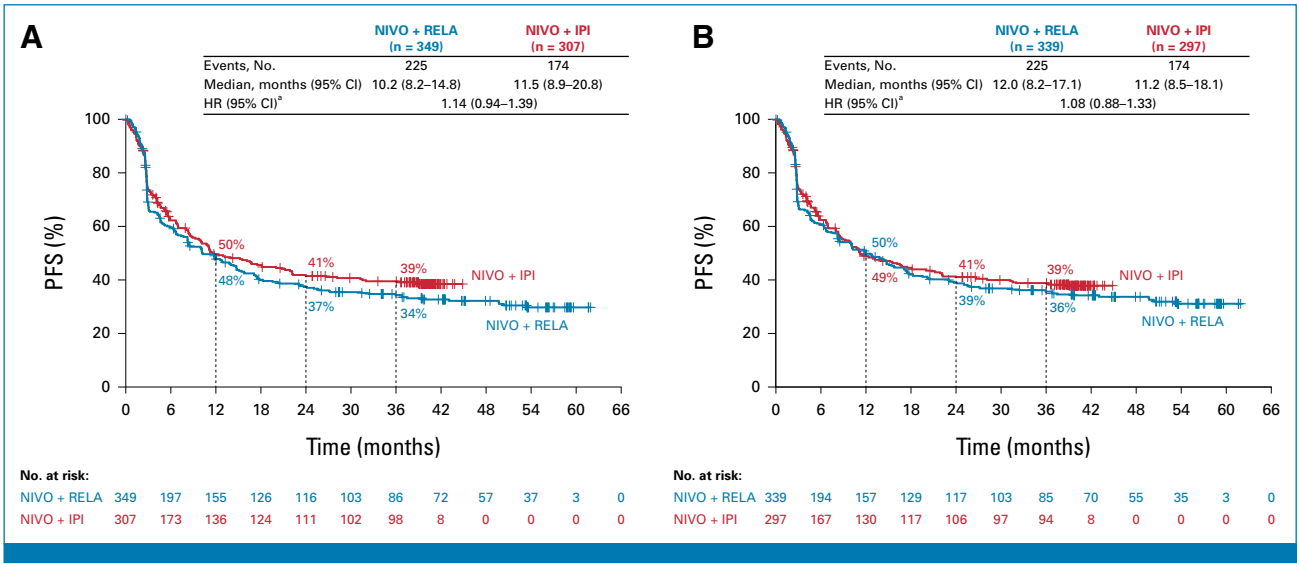

FIG 1. PFS per INV (A) before and (B) after weighting. To align with the follow-up for RELATIVITY-047 (median follow-up, 33.8; minimum follow-up, 33 months), follow-up for CheckMate 067 was truncated (median follow-up, 37 months; minimum follow-up, 36 months). [a]Comparison of NIVO + RELA with NIVO + IPI. HR, hazard ratio; INV, investigator; NIVO + IPI, nivolumab plus ipilimumab; NIVO + RELA, nivolumab plus relatlimab; PFS, progression-free survival.

MSS, 65% *v* 62%; HR, 0.86 [95% CI, 0.67 to 1.12]; Fig 3). Proportional hazards assumptions were not violated before or after weighting (Schoenfeld residual test $P = .22$ and $P = .27$, respectively).

Consistent with the primary analysis, PFS, OS, and MSS were similar between nivolumab plus relatlimab and nivolumab plus ipilimumab in the analysis that retained the untruncated minimum follow-up time of 7.5 years (Data Supplement, Figs S16-S18).

Nivolumab Monotherapy Comparisons

In the internal validation analysis, data were available for 355 of 359 patients in the nivolumab monotherapy group from RELATIVITY-047 and 303 of 316 patients in the nivolumab monotherapy group from CheckMate 067 for all covariates included in the propensity score model. After weighting, all variables were balanced (SMD <0.2), and the effective sample sizes were 338 for RELATIVITY-047 and 288 for CheckMate 067. PFS (Fig 4), cORR (Data Supplement, Table S4), OS

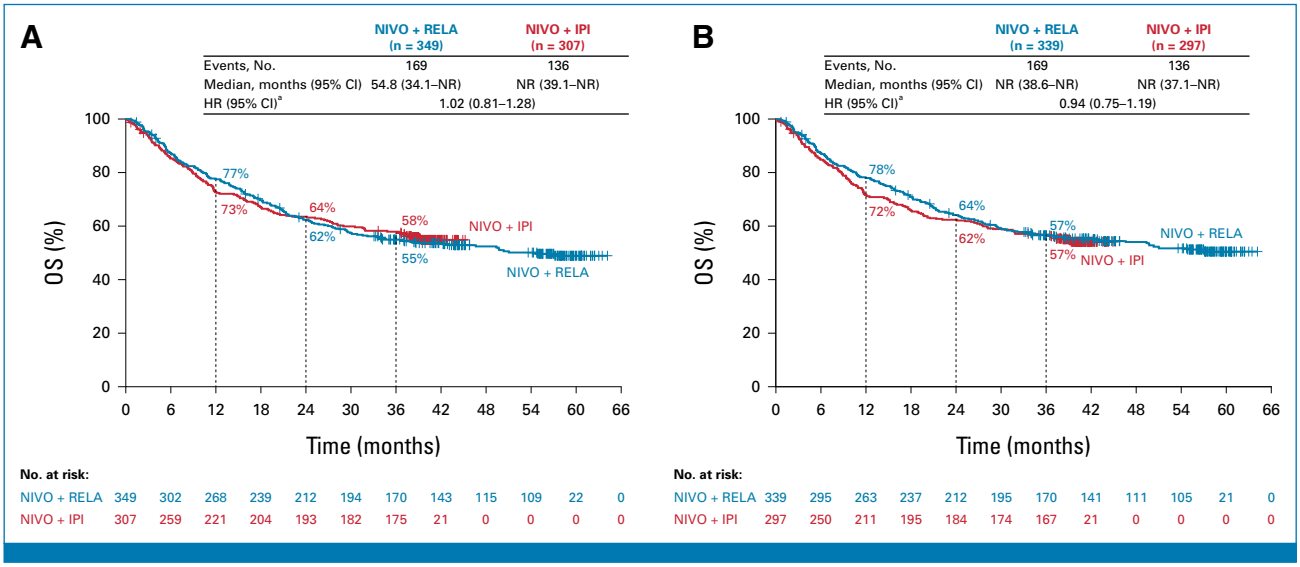

FIG 2. OS (A) before and (B) after weighting. To align with the follow-up for RELATIVITY-047 (median follow-up, 33.8; minimum follow-up, 33 months), follow-up for CheckMate 067 was truncated (median follow-up, 37 months; minimum follow-up, 36 months). [a]Comparison of NIVO + RELA with NIVO + IPI. HR, hazard ratio; NIVO + IPI, nivolumab plus ipilimumab; NIVO + RELA, nivolumab plus relatlimab; NR, not reached; OS, overall survival.

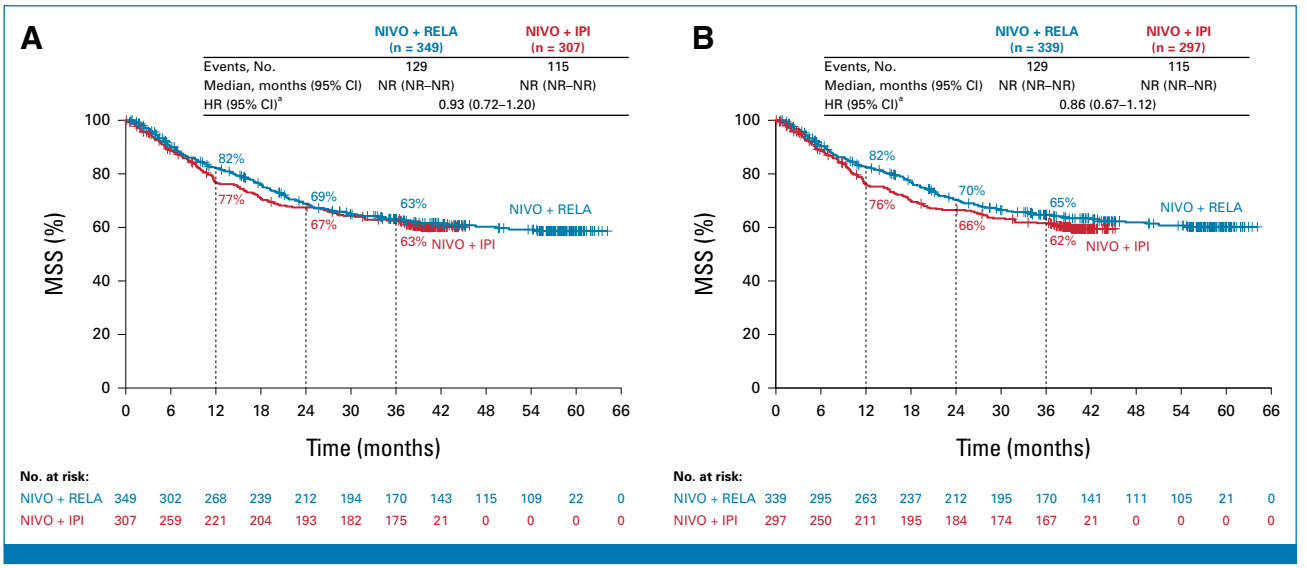

FIG 3. MSS per INV (A) before and (B) after weighting. To align with the follow-up for RELATIVITY-047 (median follow-up, 33.8; minimum follow-up, 33 months), follow-up for CheckMate 067 was truncated (median follow-up, 37 months; minimum follow-up, 36 months). [a]Comparison of NIVO + RELA with NIVO + IPI. HR, hazard ratio; INV, investigator; MSS, melanoma-specific survival; NIVO + IPI, nivolumab plus ipilimumab; NIVO + RELA, nivolumab plus relatlimab; NR, not reached.

(Fig 5), and MSS (Fig 6) were similar between the nivolumab monotherapy groups after weighting. Weighting brought the PFS and OS Kaplan-Meier curves for the nivolumab monotherapy groups closer together (Figs 4 and 5).

Safety

After weighting, nivolumab plus relatlimab was associated with fewer grade 3 or 4 TRAEs (23% *v* 61% for nivolumab plus ipilimumab) and any-grade TRAEs leading to discontinuation (17% *v* 41% for nivolumab plus ipilimumab; Data Supplement, Table S5). Rates of any-grade select TRAEs after weighting were lower for nivolumab plus relatlimab than for nivolumab plus ipilimumab in several categories (endocrine, 28% *v* 35%; GI, 19% *v* 48%; hepatic, 14% *v* 31%; renal, 5% *v* 8%; and skin, 47% *v* 62%, respectively; Data Supplement, Fig S19), as were rates of grade 3 or 4 select TRAEs (endocrine, 2% *v* 7%; GI, 3% *v* 16%; hepatic, 4% *v* 20%; and skin, 1% *v* 6%, respectively; Data Supplement, Fig S20). Percentages of patients with onset of any-grade endocrine, GI, hepatic, or skin TRAEs were

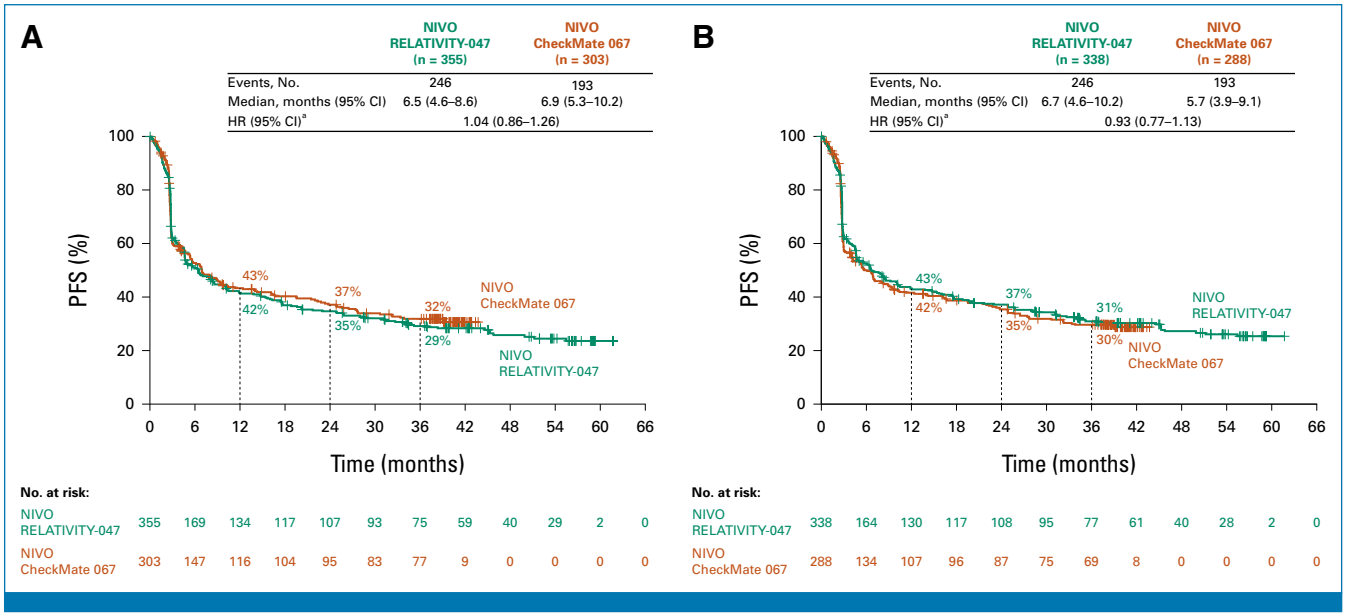

FIG 4. PFS per INV (A) before and (B) after weighting in the nivolumab monotherapy groups (sensitivity analysis). [a]Comparison of nivolumab RELATIVITY-047 with nivolumab CheckMate 067. HR, hazard ratio; INV, investigator; NIVO, nivolumab; PFS, progression-free survival.

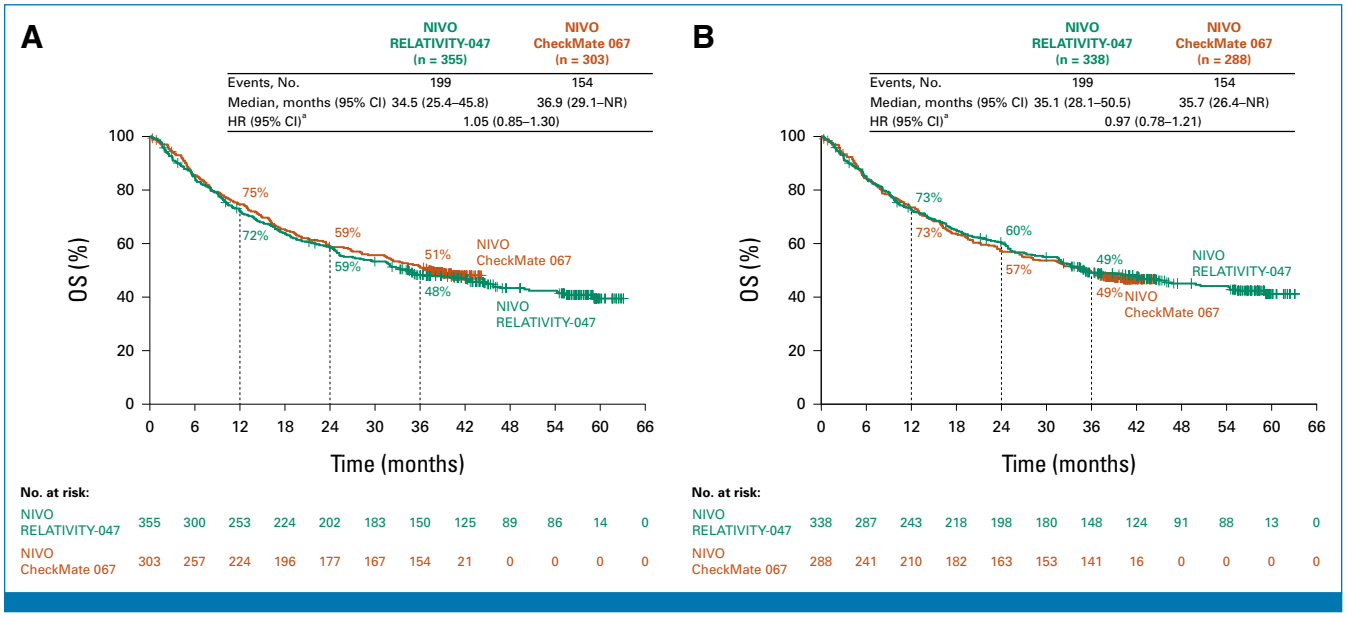

FIG 5. OS (A) before and (B) after weighting in the nivolumab monotherapy groups (sensitivity analysis). [a]Comparison of nivolumab RELATIVITY-047 with nivolumab CheckMate 067. HR, hazard ratio; NIVO, nivolumab; NR, not reached; OS, overall survival.

greatest early in both treatments (≤3 months from random assignment), before and after weighting (Data Supplement, Figs S21 and S22). During that time interval, percentages of patients with onset of any-grade TRAEs were greater for nivolumab plus ipilimumab than for nivolumab plus relatlimab.

DISCUSSION

Results from this ITC suggest that nivolumab plus relatlimab may have similar efficacy to nivolumab plus ipilimumab in patients with advanced melanoma that were previously untreated, although some subgroups showed larger numerical differences favoring nivolumab plus ipilimumab. This finding was noted across multiple outcomes (PFS, cORR, DOR, OS, and MSS) after weighting. The ITC benefited from access to patient-level data from both trials, and the propensity score model successfully adjusted for differences in key prognostic factors. Although the model was limited to observed baseline characteristics, reported baseline characteristics across the two trials had a high level of consistency, and few patients were excluded from the final analysis because of missing values.

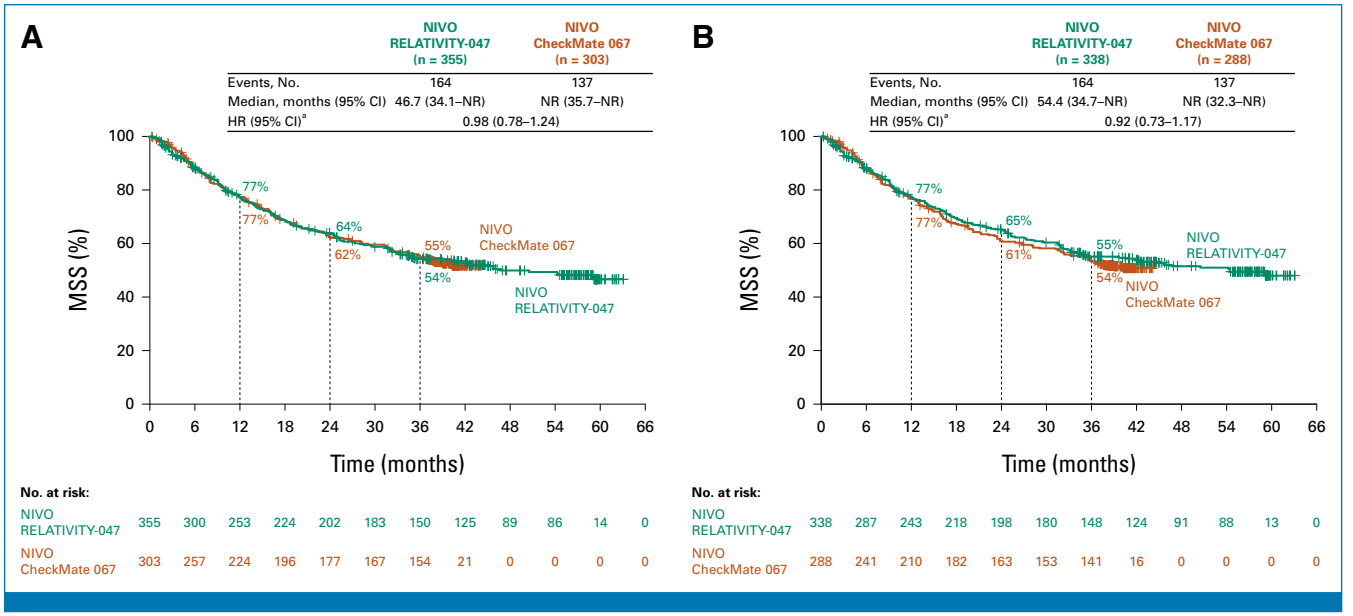

FIG 6. MSS (A) before and (B) after weighting in the nivolumab monotherapy groups (sensitivity analysis). [a]Comparison of nivolumab RELATIVITY-047 with nivolumab CheckMate 067. HR, hazard ratio; MSS, melanoma-specific survival; NIVO, nivolumab; NR, not reached.

These findings were expected, given data from the RELATIVITY-047 and CheckMate 067 trials,[2,4] as well as other ITCs.[6-8] Efficacy improved similarly with nivolumab plus relatlimab over nivolumab monotherapy in RELATIVITY-047 (PFS HR, 0.79 [95% CI, 0.66 to 0.95]; OS HR, 0.80 [95% CI, 0.66 to 0.99]; median follow-up, 33.8 months)[2] and nivolumab plus ipilimumab over nivolumab monotherapy in CheckMate 067 (PFS HR, 0.79 [95% CI, 0.65 to 0.97]; OS HR, 0.84 [95% CI, 0.68 to 1.04]; minimum follow-up, 7.5 years),[4] suggesting that the dual ICI regimens exhibited similar benefit over nivolumab monotherapy across the two trials. A previous unadjusted ITC, which used published Kaplan-Meier curves from RELATIVITY-047 and CheckMate 067 to generate pseudo individual patient data and different statistical methods to compare end points, suggested that PFS was similar between the two regimens and that nivolumab plus relatlimab had fewer TRAEs.[6] Two separate network meta-analyses, which indirectly compared several ICIs across multiple trials identified in systematic literature reviews, suggested that nivolumab plus relatlimab may have similar efficacy and improved safety to nivolumab plus ipilimumab as first-line therapy for advanced melanoma.[7,8] Findings from this ITC confirm those from previous ITCs.[6-8] To our knowledge, this ITC was the first to use patient-level data from RELATIVITY-047 and CheckMate 067, allowing adjustment of covariates, and it extends previous findings by including additional efficacy end points (eg, MSS) and comprehensive subgroup analyses.

Although nivolumab plus relatlimab appeared to have similar efficacy to nivolumab plus ipilimumab in the overall treatment groups in this ITC, there were larger numerical differences observed favoring nivolumab plus ipilimumab for PFS in the subgroup with acral melanoma; cORR in the subgroups with *BRAF*-mutant disease, acral melanoma, mucosal melanoma, and LDH >2 × ULN; and OS in the subgroups with acral melanoma and LDH >2 × ULN. However, these analyses could not determine which subgroup would definitively benefit from one therapy over the other owing to the small sample sizes and wide CIs.

Melanoma brain metastases (MBM) have historically been associated with a poor prognosis.[12] Although patients with controlled MBM were allowed to enroll in RELATIVITY-047 and CheckMate 067, their numbers were too low for assessment. By contrast, patients with active MBM were excluded from both trials and thus could not be evaluated in this ITC. To date, data on the use of nivolumab plus relatlimab in active MBM have not been reported. Investigation of nivolumab plus relatlimab in active MBM is underway in a single-arm, open-label, phase II trial (ClinicalTrials.gov identifier: NCT05704647).[13] On the basis of existing data,[14-18] nivolumab plus ipilimumab remains the standard ICI therapy for patients with active MBM.

Despite the observed similarity in efficacy between nivolumab plus relatlimab and nivolumab plus ipilimumab in this ITC, trial data demonstrate that these regimens may also be effective when administered sequentially.[19,20] For instance, patients whose disease progresses on or after treatment with nivolumab plus relatlimab may subsequently respond to nivolumab plus ipilimumab, as evidenced by second-line data from RELATIVITY-047.[19] Conversely, the phase I/IIa RELATIVITY-020 trial demonstrated that after disease progression on first-line anti–PD-1 plus anti–CTLA-4 therapy, patients may respond to subsequent treatment with nivolumab plus relatlimab.[20]

Nivolumab plus relatlimab was associated with less frequent and less severe toxicity than nivolumab plus ipilimumab in this ITC. Notably, rates of hepatic and GI grade 3 or 4 select TRAEs were lower with nivolumab plus relatlimab than with nivolumab plus ipilimumab. Although the onset of any-grade endocrine, GI, hepatic, or skin TRAEs occurred most frequently early in both treatments (≤3 months from randomization), percentages of patients with onset of those TRAEs during that time interval were greater with nivolumab plus ipilimumab.

This ITC had several limitations. First, differences in the design and conduct of the two trials may have affected the ITC. Specifically, RELATIVITY-047 and CheckMate 067 differed with regard to staging criteria, tumor assessment schedules (potentially affecting PFS results), geographic regions (potentially affecting access to subsequent therapy), and AE classifications.[1,3] Also, at the time of conduct of RELATIVITY-047, there was substantial familiarity with the management of AEs associated with ICIs compared with the time period in which CheckMate 067 was conducted, possibly accounting for an increased rate of TRAEs with nivolumab monotherapy in Checkmate 067 than with nivolumab monotherapy in RELATIVITY-047.[21,22] Furthermore, although the propensity score model successfully adjusted for differences in baseline characteristics, other important differences may not have been measured. Accordingly, the ITC included a comparison of the nivolumab monotherapy groups from both trials as an internal validation of the approach, and no differences were observed in PFS, cORR, OS, and MSS between those groups after weighting, indicating that unobserved factors were unlikely to have confounded the results. Additionally, differences in chronologic timing of CheckMate 067 and RELATIVITY-047 (enrollment, 2013-2014 and 2018-2020, respectively)[1,3] may have resulted in some patients in RELATIVITY-047 having access to more effective subsequent treatments, thereby providing potential survival advantages to nivolumab plus relatlimab. Nivolumab plus ipilimumab may have been available (pending local reimbursement) as subsequent therapy in RELATIVITY-047,[23] whereas nivolumab plus relatlimab was not available as subsequent therapy in CheckMate 067. Although ICIs were administered less frequently as subsequent therapy in the nivolumab plus relatlimab group in RELATIVITY-047 (15%) than in the nivolumab plus ipilimumab group in CheckMate 067 (19%), 5% of patients in the nivolumab plus relatlimab group received nivolumab plus ipilimumab as subsequent

therapy.[2,4] Of note, subsequent therapy data from CheckMate 067 were not truncated. Despite differences in subsequent therapy, survival advantages were not observed in the nivolumab monotherapy group from RELATIVITY-047 compared with the nivolumab monotherapy group from CheckMate 067. Although minimum follow-up time was shorter for RELATIVITY-047 than for CheckMate 067 (33 months[2] *v* 7.5 years,[4] respectively), this difference was controlled by truncating follow-up time in CheckMate 067. Because the ITC involved trials with a particular set of eligibility criteria, results may not be generalizable to all patients with advanced melanoma. Finally, as this was a post hoc analysis, no formal power calculation was conducted.

In this exploratory, post hoc ITC, nivolumab plus relatlimab demonstrated similar efficacy to nivolumab plus ipilimumab in the overall population, including most—but not all—subgroups, and improved safety in patients with previously untreated advanced melanoma. Findings from this ITC, which, to our knowledge, was the first to use patient-level data from RELATIVITY-047 and CheckMate 067, confirm those from previous ITCs.[6-8] The ITC did not include patients with active MBM, and nivolumab plus ipilimumab remains the standard ICI therapy for these patients.[14-18] Although this ITC incorporated the IPTW methodology to adjust for any imbalances in the distribution of baseline characteristics, results should be interpreted with caution, given limitations of the cross-trial analysis.

AFFILIATIONS

[1]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia
[2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD
[3]Dana-Farber Cancer Institute, Boston, MA
[4]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italy
[5]The Royal Marsden NHS Foundation Trust, London, United Kingdom
[6]University of Michigan, Ann Arbor, MI
[7]Aix-Marseille University, Hôpital de la Timone, Marseille, France
[8]Bristol Myers Squibb, Princeton, NJ
[9]Analysis Group, Inc, Boston, MA
[10]The University of Texas MD Anderson Cancer Center, Houston, TX
[11]University of Essen and the German Cancer Consortium, Partner Site, Essen, Germany
[12]National Center for Tumor Diseases (NCT-West), Campus Essen, Essen, Germany
[13]University Alliance Ruhr, Research Center One Health, University Duisburg-Essen, Essen, Germany

CORRESPONDING AUTHOR

Georgina V. Long, PhD, MBBS; e-mail: georgina.long@sydney.edu.au.

EQUAL CONTRIBUTION

H.T. and D.S. contributed equally as cosenior authors to this work.

PRIOR PRESENTATION

Presented in part at the 2024 ASCO Annual Meeting, Chicago, IL, May 31-June 4, 2024.

SUPPORT

Supported by Bristol Myers Squibb (Princeton, NJ).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.24.01125.

DATA SHARING STATEMENT

The Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

AUTHOR CONTRIBUTIONS

Conception and design: Georgina V. Long, Evan J. Lipson, Flavia Ejzykowicz, Andriy Moshyk, Viviana Garcia-Horton, Zheng-Yi Zhou, Jennell Palaia, Laura McDonald, Sarah Keidel, Anthony Salvatore, Leon A. Sakkal, Dirk Schadendorf
Provision of study materials or patients: Evan J. Lipson, F. Stephen Hodi, Hussein Tawbi, Dirk Schadendorf
Collection and assembly of data: Georgina V. Long, Evan J. Lipson, F. Stephen Hodi, James Larkin, Jean-Jacques Grob, Zheng-Yi Zhou, Sarah Keidel, Anthony Salvatore, Hussein Tawbi, Dirk Schadendorf
Data analysis and interpretation: Georgina V. Long, Evan J. Lipson, F. Stephen Hodi, Paolo A. Ascierto, James Larkin, Christopher Lao, Flavia Ejzykowicz, Andriy Moshyk, Viviana Garcia-Horton, Zheng-Yi Zhou, Jennell Palaia, Laura McDonald, Sarah Keidel, Anthony Salvatore, Divya Patel, Leon A. Sakkal, Hussein Tawbi, Dirk Schadendorf
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors acknowledge Ono Pharmaceutical Company, Ltd (Osaka, Japan) for contributions to nivolumab development. Assistance with the data analysis was provided by Dana Christensen and Matthew Mattera of Analysis Group, Inc, and funded by Bristol Myers Squibb. Professional medical writing and editorial assistance were provided by Mark Palangio and Kathleen Blake of Ashfield MedComms, an Inizio company, and funded by Bristol Myers Squibb; specifically, Mark Palangio assisted with the development of the first draft and subsequent revisions, under the direction of the authors, and Kathleen Blake provided editorial support for formatting and submission.

REFERENCES

1. Tawbi HA, Schadendorf D, Lipson EJ, et al: Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med 386:24-34, 2022
2. Tawbi HA, Hodi FS, Lipson EJ, et al: Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma (RELATIVITY-047): Overall survival (OS) and melanoma-specific survival (MSS) outcomes at 3 years. Presented at 2024 American Society of Clinical Oncology (ASCO) Annual Meeting. Presentation number 9524, Chicago, IL, & online, May 31-June 4, 2024
3. Larkin J, Chiarion-Sileni V, Gonzalez R, et al: Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373:23-34, 2015
4. Hodi FS, Chiarion-Sileni V, Lewis KD, et al: Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. J Clin Oncol 40, 2022 (suppl 16; abstr 9522)
5. National Comprehensive Cancer Network, Inc: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma: Cutaneous (V.2.2024). 2024. 2024. http://NCCN.org
6. Zhao B-W, Zhang F-Y, Wang Y, et al: LAG3-PD1 or CTLA4-PD1 inhibition in advanced melanoma: Indirect cross comparisons of the CheckMate-067 and RELATIVITY-047 trials. Cancers (Basel) 14: 4975, 2022
7. Boutros A, Tanda ET, Croce E, et al: Activity and safety of first-line treatments for advanced melanoma: A network meta-analysis. Eur J Cancer 188:64-79, 2023
8. Thosar M, Khankhel Z, McDonald L, et al: Network meta-analysis (NMA) of immuno-oncology (IO) treatments for first-line (1L) advanced or metastatic melanoma. Presented at 2023 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe Annual Meeting. Poster CO62, Copenhagen, Denmark, November 12-15, 2023
9. Austin PC: Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med 35:5642-5655, 2016
10. Cohen J: Statistical Power Analysis for the Behavioral Sciences (ed 2). Hillsdale, NJ, Erlbaum, 1988
11. Stuart EA: Matching methods for causal inference: A review and a look forward. Stat Sci 25:1-21, 2010
12. Janavicius M, Lachej N, Anglickiene G, et al: Outcomes of treatment for melanoma brain metastases. J Skin Cancer 2020:7520924, 2020
13. Phillips S, Burton EM, Kreidieh FY, et al: Phase II study of nivolumab (nivo) in combination with relatlimab (rela) in patients (pts) with active melanoma brain metastases (MBM). J Clin Oncol 41, 2023 (suppl 16; abstr TPS9605)
14. Long GV, Atkinson V, Lo S, et al: Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: A multicentre randomised phase 2 study. Lancet Oncol 19:672-681, 2018
15. Long GV, Atkinson V, Lo S, et al: Five-year overall survival from the anti-PD1 brain collaboration (ABC Study): Randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets). J Clin Oncol 39, 2021 (suppl 15; abstr 9508)
16. Tawbi HA, Forsyth PA, Algazi A, et al: Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 379:722-730, 2018
17. Tawbi HA, Forsyth PA, Hodi FS, et al: Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): Final results of an open-label, multicentre, phase 2 study. Lancet Oncol 22:1692-1704, 2021
18. Di Giacomo AM, Chiarion-Sileni V, Del Vecchio M, et al: Nivolumab plus ipilimumab in melanoma patients with asymptomatic brain metastases: 7-year outcomes and quality of life from the multicenter phase III NIBIT-M2 trial. Eur J Cancer 199:113531, 2024
19. Tawbi HA, Hodi FS, Lipson EJ, et al: Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047. J Clin Oncol 41, 2023 (suppl 16; abstr 9502)
20. Ascierto PA, Lipson EJ, Dummer R, et al: Nivolumab and relatlimab in patients with advanced melanoma that had progressed on anti-programmed death-1/programmed death ligand 1 therapy: Results from the phase I/IIa RELATIVITY-020 trial. J Clin Oncol 41:2724-2735, 2023
21. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al: Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol 40: 127-137, 2022
22. Long GV, Stephen Hodi F, Lipson EJ, et al: Overall survival and response with nivolumab and relatlimab in advanced melanoma. NEJM Evid 2:EVIDoa2200239, 2023
23. Menzies AM, Pires da Silva I, Trojaniello C, et al: CTLA-4 blockade resistance after relatlimab and nivolumab. N Engl J Med 386:1668-1669, 2022

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

First-Line Nivolumab Plus Relatlimab Versus Nivolumab Plus Ipilimumab in Advanced Melanoma: An Indirect Treatment Comparison Using RELATIVITY-047 and CheckMate 067 Trial Data

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Georgina V. Long
This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.
Honoraria: BMS, Pierre Fabre
Consulting or Advisory Role: Agenus, Amgen, Array BioPharma, Boehringer Ingelheim, Bristol Myers Squibb, Evaxion Biotech, Hexal, Highlight Therapeutics, Innovent Biologics, Merck Sharp & Dohme, Novartis, OncoSec, PHMR, Pierre Fabre, Regeneron, AstraZeneca, IO Biotech, Immunocore Ireland Limited

Evan J. Lipson
Honoraria: Bristol Myers Squibb
Consulting or Advisory Role: Bristol Myers Squibb, Novartis, Merck, Instil Bio, Nektar, OncoSec, Pfizer, Rain Therapeutics, Regeneron, CareDX, Immunocore, Replimune, HUYA Bioscience International
Research Funding: Bristol Myers Squibb (Inst), Merck (Inst), Regeneron (Inst), Sanofi (Inst)

F. Stephen Hodi
Employment: Dana-Farber Cancer Institute
Leadership: Bicara Therapeutics
Stock and Other Ownership Interests: Apricity Health, Torque, Pionyr, Bicara Therapeutics
Consulting or Advisory Role: Merck Sharp & Dohme, Novartis, Genentech/Roche, Bristol Myers Squibb, Compass Therapeutics, Rheos Medicines, Checkpoint Therapeutics, Bioentre, Gossamer Bio, Iovance Biotherapeutics, Catalym, Immunocore, Kairos Therapeutics, Zumutor Biologics, Corner Therapeutics, AstraZeneca, Curis, Pliant, Solu Therapeutics, Vir Biotechnology, 92Bio
Research Funding: Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst), Genentech/Roche (Inst), Novartis (Inst)
Patents, Royalties, Other Intellectual Property: Patent pending as per institutional policy, patent pending royalties received on MICA related disorders application to institution per institutional IP policy, Angiopoietin-2 Biomarkers Predictive of Anti-immune checkpoint response (Inst), Compositions and Methods for Identification, Assessment, Prevention, and Treatment of Melanoma using PD-L1 Isoforms, Methods of Using Pembrolizumab and Trebananib (Inst)
Travel, Accommodations, Expenses: Novartis, Bristol Myers Squibb
Other Relationship: Bristol Myers Squibb, Genentech/Roche

Paolo A. Ascierto
Consulting or Advisory Role: Bristol Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre Fabre, AstraZeneca, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Italfarmaco, Nektar, Boehringer Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, OncoSec, Nouscom, Lunaphore Technologies, Seagen, ITeos Therapeutics, Medicenna, Bio-AI Health, ValoTx, Replimune, Bayer, Erasca, Inc, Philogen, BioNTech SE, Anaveon
Research Funding: Bristol Myers Squibb (Inst), Roche/Genentech (Inst), Sanofi (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Pfizer, Bio-AI Health, Replimune, MSD Oncology, Pierre Fabre

James Larkin
Honoraria: Bristol Myers Squibb, Pfizer, Novartis, Incyte, Merck Serono, Eisai, touchIME, touchEXPERTS, Royal College of Physicians, Cambridge Healthcare research, RCGP, VJOncology, Agence Unik
Consulting or Advisory Role: Bristol Myers Squibb, Incyte, iOnctura, Apple Tree Partners, Merck Serono, Eisai, Debiopharm Group, Pierre Fabre, Ipsen, Roche, EUSA Pharma, Novartis, Aptitude Health, AstraZeneca, GlaxoSmithKline, Calithera Biosciences, Ultimovacs, eCancer, Insel Gruppe, Pfizer, Goldman Sachs, MSD Oncology, Agence Unik, Philogen, Telix Pharmaceuticals, Syncona
Research Funding: Pfizer (Inst), Novartis (Inst), MSD (Inst), Bristol Myers Squibb (Inst), Achilles Therapeutics (Inst), Roche (Inst), Nektar (Inst), Covance (Inst), Immunocore (Inst), Aveo (Inst), Pharmacyclics (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, GlaxoSmithKline, Pierre Fabre, Immatics, ESMO, Bristol Myers Squibb/Roche

Christopher Lao
Employment: Bristol Myers Squibb
Research Funding: Bristol Myers Squibb, Genentech, Oncosec

Jean-Jacques Grob
Consulting or Advisory Role: BMS, MSD Oncology, Roche/Genentech, Novartis, Amgen, Pierre Fabre, Sun Pharma, Merck KGaA, Sanofi, Roche, Philogen, Ultimovacs
Speakers' Bureau: Novartis, Pierre Fabre
Travel, Accommodations, Expenses: BMS, MSD Oncology, Novartis, Pierre Fabre

Flavia Ejzykowicz
Employment: Bristol Myers Squibb
Stock and Other Ownership Interests: Bristol Myers Squibb

Andriy Moshyk
Employment: Bristol Myers Squibb/Celgene
Stock and Other Ownership Interests: Bristol Myers Squibb/Celgene

Viviana Garcia-Horton
Consulting or Advisory Role: Analysis Group

Yiqiao Xin
Consulting or Advisory Role: Bristol Myers Squibb (Inst)
Research Funding: Bristol Myers Squibb (Inst)

Jennell Palaia
Employment: Bristol Myers Squibb PPK
Stock and Other Ownership Interests: Bristol Myers Squibb
Research Funding: Bristol Myers Squibb

Laura McDonald
Employment: Bristol Myers Squibb
Stock and Other Ownership Interests: Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb

Sarah Keidel
Employment: Bristol Myers Squibb/Celgene, GlaxoSmithKline
Stock and Other Ownership Interests: Bristol Myers Squibb/Celgene, GlaxoSmithKline, AbbVie

Anthony Salvatore
Employment: Bristol Myers Squibb/Medarex
Stock and Other Ownership Interests: Bristol Myers Squibb/Medarex

Divya Patel
Employment: Bristol Myers Squibb
Stock and Other Ownership Interests: Bristol Myers Squibb

Leon A. Sakkal
Employment: Bristol Myers Squibb
Stock and Other Ownership Interests: Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb

Hussein Tawbi
Consulting or Advisory Role: Novartis, Bristol Myers Squibb, Genentech/Roche, Merck, Eisai, Iovance Biotherapeutics, Karyopharm Therapeutics, Boxer Capital, Jazz Pharmaceuticals, Pfizer, Medicenna
Research Funding: Bristol Myers Squibb (Inst), Novartis (Inst), Merck (Inst), GlaxoSmithKline (Inst), Genentech/Roche (Inst), Celgene (Inst), Dragonfly Therapeutics (Inst), RAPT Therapeutics (Inst)

Dirk Schadendorf
Honoraria: Roche/Genentech, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Immunocore, Merck Serono, Pfizer, Pierre Fabre, Philogen, Regeneron, 4SC, Sanofi/Regeneron, NeraCare GmbH, Sun Pharma, InflarxGmbH, Ultimovacs, Daiichi Sankyo Japan, LabCorp, Replimune, Agenus, AstraZeneca, Erasca, Inc, Immatics, Novigenix, Pamgene, Seagen
Consulting or Advisory Role: Roche/Genentech, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Sanofi/Regeneron, Agenus, AstraZeneca, Daiichi Sankyo, Erasca, Inc, Immatics, Immunocore, NeraCare GmbH, Replimune
Speakers' Bureau: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sanofi/Regeneron, Merck KGaA
Research Funding: Bristol Myers Squibb (Inst), Novartis (Inst), Roche (Inst), MSD Oncology (Inst), Array BioPharma/Pfizer (Inst), Amgen (Inst), Regeneron (Inst), Agenus (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, Bristol Myers Squibb, Merck Serono, Novartis, Merck Sharp & Dohme, Pierre Fabre, Sanofi/Regeneron

No other potential conflicts of interest were reported.