ORIGINAL ARTICLE

Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma

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ABSTRACT

BACKGROUND

Lymphocyte-activation gene 3 (LAG-3) and programmed death 1 (PD-1) are distinct inhibitory immune checkpoints that contribute to T-cell exhaustion. The combination of relatlimab, a LAG-3–blocking antibody, and nivolumab, a PD-1–blocking antibody, has been shown to be safe and to have antitumor activity in patients with previously treated melanoma, but the safety and activity in patients with previously untreated melanoma need investigation.

METHODS

In this phase 2–3, global, double-blind, randomized trial, we evaluated relatlimab and nivolumab as a fixed-dose combination as compared with nivolumab alone when administered intravenously every 4 weeks to patients with previously untreated metastatic or unresectable melanoma. The primary end point was progression-free survival as assessed by blinded independent central review.

RESULTS

The median progression-free survival was 10.1 months (95% confidence interval [CI], 6.4 to 15.7) with relatlimab–nivolumab as compared with 4.6 months (95% CI, 3.4 to 5.6) with nivolumab (hazard ratio for progression or death, 0.75 [95% CI, 0.62 to 0.92]; P=0.006 by the log-rank test). Progression-free survival at 12 months was 47.7% (95% CI, 41.8 to 53.2) with relatlimab–nivolumab as compared with 36.0% (95% CI, 30.5 to 41.6) with nivolumab. Progression-free survival across key subgroups favored relatlimab–nivolumab over nivolumab. Grade 3 or 4 treatment-related adverse events occurred in 18.9% of patients in the relatlimab–nivolumab group and in 9.7% of patients in the nivolumab group.

CONCLUSIONS

The inhibition of two immune checkpoints, LAG-3 and PD-1, provided a greater benefit with regard to progression-free survival than inhibition of PD-1 alone in patients with previously untreated metastatic or unresectable melanoma. Relatlimab and nivolumab in combination showed no new safety signals. (Funded by Bristol Myers Squibb; RELATIVITY-047 ClinicalTrials.gov number, NCT03470922.)

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Immunotherapy with checkpoint inhibitors, including programmed death 1 (PD-1) inhibitors and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, has transformed treatment outcomes in patients with advanced melanoma.[1,2] However, other immune checkpoints inhibit T-cell activation and function, and new combinations of checkpoint inhibitors need to be explored to improve outcomes and enhance the benefit–risk profiles of immunotherapy combinations.

Lymphocyte-activation gene 3 (LAG-3) is a cell-surface molecule that is expressed on immune cells, including T cells, and negatively regulates T-cell proliferation and effector T-cell function. LAG-3 is upregulated in many tumor types, including melanoma.[3-5] LAG-3 and PD-1 are distinct inhibitory immune checkpoints that are often coexpressed on tumor-infiltrating lymphocytes, thus contributing to tumor-mediated T-cell exhaustion.[6,7] In preclinical models, dual inhibition of LAG-3 and PD-1 showed synergistic antitumor activity.[6,7]

Relatlimab is a first-in-class human IgG4 LAG-3–blocking antibody that binds to LAG-3 and restores the effector function of exhausted T cells.[8] In a phase 1–2 dose-escalation and cohort-expansion trial, the combination of relatlimab and nivolumab, a PD-1 inhibitor, showed antitumor activity, including durable objective responses in patients with melanoma that relapsed after, or was refractory to, PD-1 inhibition.[9] RELATIVITY-047, a phase 2–3, global, double-blind, randomized trial, evaluated combined LAG-3 and PD-1 inhibition with relatlimab–nivolumab as a new fixed-dose combination as compared with nivolumab alone in patients with previously untreated metastatic or unresectable melanoma.

METHODS

PATIENTS

Patients were eligible if they were 12 years of age or older and had previously untreated, histologically confirmed, unresectable stage III or IV melanoma; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[10]; and expression of LAG-3 and programmed death ligand 1 (PD-L1) that could be evaluated in tumor tissue. Patients who had received previous adjuvant or neoadjuvant therapies containing a PD-1, CTLA-4, BRAF, or MEK inhibitor (or a combination of BRAF and MEK inhibitors) were eligible if the therapy was completed at least 6 months before the date of recurrence; patients who received previous treatment with interferon were eligible if the last dose was received at least 6 weeks before randomization. Key exclusion criteria were uveal melanoma and active, untreated brain or leptomeningeal metastases. Full eligibility criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

A Quick Take is available at NEJM.org

TRIAL DESIGN AND TREATMENTS

In this phase 2–3, double-blind trial, patients were randomly assigned in a 1:1 ratio to receive 160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination or 480 mg of nivolumab; both therapies were administered in a single 60-minute intravenous infusion every 4 weeks (Fig. S1 in the Supplementary Appendix). Patient group assignments were stratified according to LAG-3 expression (≥1% or <1%), PD-L1 expression (≥1% or <1%), *BRAF* V600 mutation status, and metastasis stage (M0 or M1 with normal lactate dehydrogenase [LDH] levels vs. M1 with elevated LDH levels) as defined in the *Cancer Staging Manual* of the American Joint Committee on Cancer (AJCC), 8th edition.[11] Treatment continued until the occurrence of disease progression, unacceptable adverse effects, or withdrawal of consent. Treatment beyond initial progression (as defined by investigators according to RECIST, version 1.1)[10] was permitted if the investigators assessed that the patient had clinical benefit and if the patient did not have unacceptable side effects.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival assessed according to RECIST, version 1.1,[10] by blinded independent review and defined as the time between the date of randomization and the earliest date of documented disease progression or the date of death from any cause, whichever occurred first. Secondary end points included overall survival and objective response. Tumor response, according to RECIST, version 1.1,[10] was assessed by blinded independent review at 12 weeks, followed by every 8 weeks up

to 52 weeks, and then every 12 weeks until disease progression or treatment discontinuation.

Exploratory end points included progression-free survival in prespecified subgroups and health-related quality of life as measured with the Functional Assessment of Cancer Therapy–Melanoma (FACT-M) questionnaire[12] and the three-level version of the EuroQol Group–5 Dimensions (EQ-5D-3L) survey.[13] Additional information on health-related quality-of-life end-point assessments is provided in the Supplementary Appendix. Adverse events were assessed continuously throughout the trial and for at least 100 days after treatment was discontinued and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

PD-L1 expression on tumor cells was assessed by means of an immunohistochemistry assay (PD-L1 IHC 28-8 pharmDx, Agilent), as described previously.[14] LAG-3 expression was assessed, with the use of an analytically validated immunohistochemistry assay (developed in collaboration with LabCorp), as the percentage of immune cells with positive staining that had a morphologic resemblance to lymphocytes within the tumor region (consisting of the tumor, intervening stroma, and invasive margin) relative to all nucleated cells in the tumor region in samples containing at least 100 viable tumor cells.[15]

TRIAL OVERSIGHT

All trial investigators received approval from their respective institutional review boards. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, and all patients provided written informed consent before participation. An independent data monitoring committee provided oversight to assess the efficacy and safety profile of relatlimab and nivolumab. The trial was designed by Bristol Myers Squibb, the trial sponsor, in conjunction with the trial steering committee. Data were collected by the sponsor and analyzed in collaboration with the authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org). All the authors contributed to drafting the manuscript, provided critical review, and gave final approval to submit the manuscript for publication. All the authors signed a confidentiality disclosure agreement with the sponsor. Professional medical writing and editorial assistance with an earlier version of the manuscript were funded by the sponsor.

STATISTICAL ANALYSIS

This trial included an interim analysis after phase 2, conducted by the data monitoring committee, to determine whether the hazard ratio in the analysis of progression-free survival met the prespecified threshold of 0.8 or less. The prespecified threshold was met and the trial proceeded to phase 3 enrollment. The trial investigators and sponsor were unaware of the results of the interim analysis. For the final analysis of progression-free survival, we estimated that at least 365 progression events or deaths would yield 85% power to detect a hazard ratio of 0.73 with an overall type I error of 0.05. (The two-sided final analysis used an alpha of 0.049 owing to an administrative alpha penalty of 0.001 for the interim analysis of progression-free survival.) A comparison of progression-free survival between treatment groups was performed with a two-sided log-rank test stratified according to LAG-3 status, AJCC metastasis stage, and BRAF status; a Cox proportional-hazards model was used to estimate hazard ratios and two-sided 95% confidence intervals. Kaplan–Meier methods were used to estimate additional progression-free survival end points. The confidence intervals for the reported end points have not been adjusted for multiplicity. The proportional-hazards assumption was tested by the addition of a time-dependent covariate, defined by treatment-by-time interaction, to the stratified Cox regression model. A two-sided Wald chi-square P value of less than 0.1 may indicate a potential nonconstant treatment effect. The P value in this analysis was 0.1497, indicating no evidence of a nonconstant hazard. The changes from baseline in FACT-M total score and EQ-5D-3L health utility index were analyzed with the use of a longitudinal mixed model for repeated measures (details are provided in the Supplementary Appendix). Minimal clinically important differences of 5 in the FACT-M total score and 0.08 in the EQ-5D-3L health utility index were considered to be clinically meaningful.[16,17]

At the final analysis of progression-free sur-

vival, the data monitoring committee conducted a prespecified interim analysis of overall survival, which at that time point had not reached significance. Until additional analyses of overall survival are conducted, data on overall survival and on objective response rate will remain blinded. The objective response rate will be assessed after all patients have had a minimum of 28 weeks of follow-up and will be tested after overall survival, in accordance with the statistical hierarchy.

RESULTS

PATIENTS

From May 2018 through December 2020, a total of 714 patients were randomly assigned to receive relatlimab–nivolumab (355 patients) or nivolumab (359 patients) (Fig. S2) at 111 sites in North America, Central America, South America, Europe, Australia, and New Zealand.

The characteristics of the patients at baseline were well balanced between the treatment groups (Table 1). Fewer patients in the relatlimab–nivolumab group than in the nivolumab group had stage M1a or M1b disease, more had stage M1c disease, and a larger proportion had three or more sites with at least one lesion. Across both treatment groups, a total of 60 patients (8.4%) had received previous adjuvant or neoadjuvant treatment, of which interferon was the most common (45 patients [6.3%]), followed by CTLA-4 inhibitors (7 patients [1.0%]) and PD-1 inhibitors (5 patients [0.7%]) (Table S1).

As of the database lock on March 9, 2021, the median follow-up was 13.2 months. A total of 470 patients (65.8%) discontinued treatment (237 patients [66.8%] in the relatlimab–nivolumab group and 233 patients [64.9%] in the nivolumab group), with most discontinuations due to disease progression (36.3% and 46.0%, respectively) (Table S2). The use of subsequent therapies was similar in the two groups (Table S1), including the use of BRAF or MEK inhibitors as monotherapy or in combination (11.5% of patients in the relatlimab–nivolumab group and 13.9% of those in the nivolumab group) and PD-1 or CTLA-4 inhibitors as monotherapy or in combination (9.0% of patients in the relatlimab–nivolumab group and 12.8% of those in the nivolumab group).

EFFICACY

The median progression-free survival was 10.1 months (95% confidence interval [CI], 6.4 to 15.7) with relatlimab–nivolumab as compared with 4.6 months (95% CI, 3.4 to 5.6) with nivolumab (hazard ratio for progression or death, 0.75 [95% CI, 0.62 to 0.92]; P=0.006 by the log-rank test). The percentage of patients with progression-free survival at 12 months was 47.7% (95% CI, 41.8 to 53.2) with relatlimab–nivolumab and 36.0% (95% CI, 30.5 to 41.6) with nivolumab (Fig. 1). Progression-free survival, assessed by blinded independent review of 391 events, was significantly longer with relatlimab–nivolumab than with nivolumab (Fig. 1).

In prespecified exploratory analyses, progression-free survival also favored relatlimab–nivolumab over nivolumab across key subgroups (Fig. 2). In both treatment groups, the median progression-free survival estimates were longer for patients with LAG-3 expression of 1% or greater; however, a benefit was seen with relatlimab–nivolumab over nivolumab regardless of LAG-3 expression (Fig. 3).

Among patients with PD-L1 expression of 1% or greater, median progression-free survival was similar in the two groups: 15.7 months (95% CI, 10.1 to 25.8) in the relatlimab–nivolumab group and 14.7 months (95% CI, 5.1 to not reached) in the nivolumab group (hazard ratio for progression or death, 0.95 [95% CI, 0.68 to 1.33]). Among patients with PD-L1 expression of less than 1%, the median progression-free survival with relatlimab–nivolumab was 6.4 months (95% CI, 4.6 to 11.8) as compared with 2.9 months (95% CI, 2.8 to 4.5) with nivolumab (hazard ratio, 0.66 [95% CI, 0.51 to 0.84]) (Fig. 2).

The benefit of treatment with relatlimab–nivolumab was observed regardless of patients' *BRAF* mutation status. In the subgroup of patients with *BRAF* mutations, the median progression-free survival was 10.1 months (95% CI, 4.6 to 23.1) in the relatlimab–nivolumab group and 4.6 months (95% CI, 3.0 to 6.5) in the nivolumab group (hazard ratio for progression or death, 0.74 [95% CI, 0.54 to 1.03]); in the subgroup of patients with wild-type *BRAF*, the median progression-free survival was 10.1 months (95% CI, 5.9 to 17.0) with relatlimab–nivolumab and 4.6 months (95% CI, 2.9 to 6.6) with nivolumab

Table 1. Patient Demographics and Disease Characteristics at Baseline.*

Characteristic	Relatlimab–Nivolumab (N=355)	Nivolumab (N=359)	Total (N=714)
Median age (range) — yr	63.0 (20–94)	62.0 (21–90)	63.0 (20–94)
Female sex — no. (%)	145 (40.8)	153 (42.6)	298 (41.7)
Previous systemic therapy — no. (%)			
Adjuvant	31 (8.7)	26 (7.2)	57 (8.0)
Neoadjuvant	2 (0.6)	1 (0.3)	3 (0.4)
Unknown or other	0	2 (0.6)	2 (0.3)
Metastasis stage — no. (%)†			
M0	35 (9.9)	23 (6.4)	58 (8.1)
M1a or b	162 (45.6)	195 (54.3)	357 (50.0)
M1c	151 (42.5)	127 (35.4)	278 (38.9)
M1d	6 (1.7)	11 (3.1)	17 (2.4)
Melanoma subtype classification — no. (%)			
Cutaneous acral	41 (11.5)	41 (11.4)	82 (11.5)
Cutaneous nonacral	249 (70.1)	254 (70.8)	503 (70.4)
Mucosal	23 (6.5)	28 (7.8)	51 (7.1)
Other	42 (11.8)	36 (10.0)	78 (10.9)
ECOG performance status — no. (%)‡			
0	236 (66.5)	242 (67.4)	478 (66.9)
1	119 (33.5)	117 (32.6)	236 (33.1)
LDH level — no. (%)			
> ULN	130 (36.6)	128 (35.7)	258 (36.1)
>2× ULN	32 (9.0)	31 (8.6)	63 (8.8)
Median tumor burden (range) — mm§	59.0 (10–317)	54.5 (10–548)	
Sites with ≥1 lesion — no. (%)¶			
1	127 (35.8)	158 (44.0)	285 (39.9)
2	111 (31.3)	102 (28.4)	213 (29.8)
≥3	112 (31.5)	87 (24.2)	199 (27.9)
Stratification factors — no. (%)			
LAG-3 expression			
≥1%	268 (75.5)	269 (74.9)	537 (75.2)
<1%	87 (24.5)	90 (25.1)	177 (24.8)
PD-L1 expression			
≥1%	146 (41.1)	147 (40.9)	293 (41.0)
<1%	209 (58.9)	212 (59.1)	421 (59.0)
BRAF mutation status			
Patients with *BRAF* mutations	136 (38.3)	139 (38.7)	275 (38.5)
Patients without *BRAF* mutations	219 (61.7)	220 (61.3)	439 (61.5)
Metastasis stage with LDH level			
M0, M1 and normal LDH level	232 (65.4)	237 (66.0)	469 (65.7)
M1 and elevated LDH level	123 (34.6)	122 (34.0)	245 (34.3)

* LAG-3 denotes lymphocyte-activation gene 3, LDH lactate dehydrogenase, PD-L1 programmed death ligand 1, and ULN upper limit of the normal range.
† Metastasis stages are defined according to the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, 8th edition.[11]
‡ The Eastern Cooperative Oncology Group (ECOG) performance status is assessed on a 5-point scale, with 0 indicating no performance restrictions and higher scores indicating greater disability.
§ Measurements shown are the sums of the reference diameters of the target lesions.
¶ Included are both target and nontarget lesions.

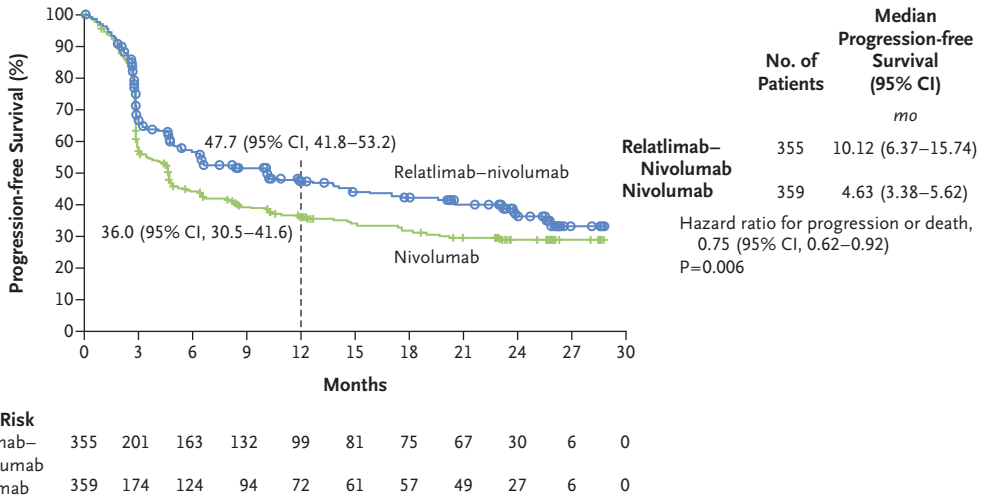

Figure 1. Progression-free Survival.

Data shown include all patients who underwent randomization. Hazard ratios were estimated with a stratified Cox proportional-hazards model. P values were calculated with the use of a log-rank test stratified according to expression of lymphocyte-activation gene 3 (LAG-3) (≥1% vs. <1%), *BRAF* mutation status (mutant vs. wild-type), and American Joint Committee on Cancer metastasis stage (M0 or M1 with normal LDH level vs. M1 with elevated LDH level). Programmed death ligand 1 was not used for stratification because it resulted in subgroups with fewer than 10 patients. Tick marks indicate censored data.

(hazard ratio, 0.76 [95% CI, 0.59 to 0.98]). Similarly, patients who received relatlimab–nivolumab had longer progression-free survival regardless of key prognostic indicators, such as the AJCC metastasis stage of the tumor, LDH level, and tumor burden (Fig. 2).

EXPOSURE AND SAFETY

The median duration of treatment was 5.6 months with relatlimab–nivolumab and 4.9 months with nivolumab. The median time to treatment discontinuation was 8.3 months (95% CI, 6.5 to 11.0) in the relatlimab–nivolumab group and 6.5 months (95% CI, 5.5 to 9.2) in the nivolumab group. The most frequent treatment-related adverse events are shown in Table 2. Infusion-related adverse reactions occurred in 5.9% of patients who received relatlimab–nivolumab and 3.6% of patients who received nivolumab. Grade 3 or 4 treatment-related adverse events occurred in 18.9% of the patients in the relatlimab–nivolumab group and in 9.7% in the nivolumab group. The most common grade 3 or 4 treatment-related adverse events in the relatlimab–nivolumab group included increased levels of lipase (in 1.7% of the patients), alanine aminotransferase (in 1.4%), and aspartate aminotransferase (in 1.4%), as well as fatigue (in 1.1%). Treatment-related adverse events (of any grade) leading to discontinuation occurred in 14.6% of patients in the relatlimab–nivolumab group as compared with 6.7% of those in the nivolumab group (Table 2). Overall, three deaths among patients who received relatlimab–nivolumab (0.8%) were considered by investigators to be treatment-related (hemophagocytic lymphohistiocytosis, acute pulmonary edema, and pneumonitis), and two deaths in the nivolumab group (0.6%) were considered by investigators to be treatment-related (sepsis and myocarditis in one patient and pneumonia in one patient).

The most common categories of immune-mediated adverse events that occurred in the relatlimab–nivolumab group were hypothyroidism or thyroiditis (in 18.0% of the patients), rash (in 9.3%), and diarrhea or colitis (in 6.8%) (Table 2). Routine troponin monitoring was conducted during the first 2 months of treatment, as specified in the protocol. Myocarditis occurred in 1.7% of the patients in the relatlimab–

Subgroup	Relatlimab–Nivolumab	Nivolumab	Unstratified Hazard Ratio for Progression or Death (95% CI)
	no. of events (no. of patients)		
Overall	180 (355)	211 (359)	0.76 (0.62–0.92)
Age			
≥18 and <65 yr	99 (187)	117 (196)	0.83 (0.64–1.09)
≥65 and <75 yr	50 (102)	60 (103)	0.69 (0.47–1.00)
≥65 yr	81 (168)	94 (163)	0.69 (0.51–0.93)
≥75 yr	31 (66)	34 (60)	0.69 (0.42–1.13)
Sex			
Male	98 (210)	123 (206)	0.68 (0.52–0.89)
Female	82 (145)	88 (153)	0.88 (0.65–1.19)
Melanoma subtype			
Cutaneous acral	31 (41)	29 (41)	0.84 (0.50–1.39)
Cutaneous nonacral	111 (249)	139 (254)	0.73 (0.57–0.93)
Mucosal	14 (23)	19 (28)	0.72 (0.36–1.45)
Other	24 (42)	24 (36)	0.77 (0.44–1.36)
LDH			
≤ULN	100 (224)	127 (231)	0.70 (0.54–0.91)
>ULN	79 (130)	84 (128)	0.80 (0.59–1.09)
≤2× ULN	158 (322)	186 (328)	0.75 (0.60–0.92)
>2× ULN	21 (32)	25 (31)	0.75 (0.42–1.35)
ECOG performance-status score			
0	108 (236)	136 (242)	0.74 (0.57–0.95)
1	72 (119)	75 (117)	0.78 (0.56–1.07)
Tumor burden			
<Q1	26 (74)	37 (82)	0.62 (0.37–1.03)
Q1 to <Q3	84 (161)	96 (153)	0.80 (0.60–1.07)
≥Q3	53 (84)	53 (75)	0.72 (0.49–1.06)
BRAF mutation status			
Mutant	67 (136)	83 (139)	0.74 (0.54–1.03)
Wild-type	113 (219)	128 (220)	0.76 (0.59–0.98)
Metastasis stage			
M0, M1 and normal LDH level	104 (232)	130 (237)	0.71 (0.55–0.92)
M1 and elevated LDH level	76 (123)	81 (122)	0.79 (0.58–1.09)
PD-L1			
≥1%	68 (146)	67 (147)	0.95 (0.68–1.33)
<1%, nonquantifiable	112 (209)	144 (212)	0.66 (0.51–0.84)
≥5%	33 (88)	36 (86)	0.86 (0.54–1.38)
<5%, nonquantifiable	147 (267)	175 (273)	0.73 (0.58–0.90)
LAG-3			
≥1%	131 (268)	151 (269)	0.75 (0.59–0.95)
<1%	49 (87)	60 (90)	0.78 (0.54–1.15)

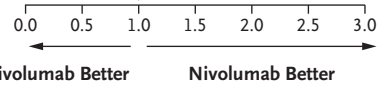

Figure 2. Progression-free Survival, According to Subgroup.

The exploratory and descriptive analyses and proportional-hazards assumptions were not tested for the subgroup exploratory analyses, so hazard ratios should be interpreted with caution. The Eastern Cooperative Oncology Group (ECOG) performance status is assessed on a 5-point scale, with 0 indicating no performance restrictions and higher scores indicating greater disability. The tumor burden was measured by blinded independent central review. Q1 denotes the middle value between the smallest value and the median; 25% of data are below Q1. Q3 denotes the middle value between the median and the highest value; 75% of data are below Q3. LDH denotes lactate dehydrogenase, PD-L1 programmed death ligand 1, and ULN upper limit of the normal range.

nivolumab group and in 0.6% of those in the nivolumab group; grade 3 or 4 events occurred in 0.6% of patients in the relatlimab–nivolumab group and in no patients in the nivolumab group. Myocarditis events in the relatlimab–nivolumab group resolved completely.

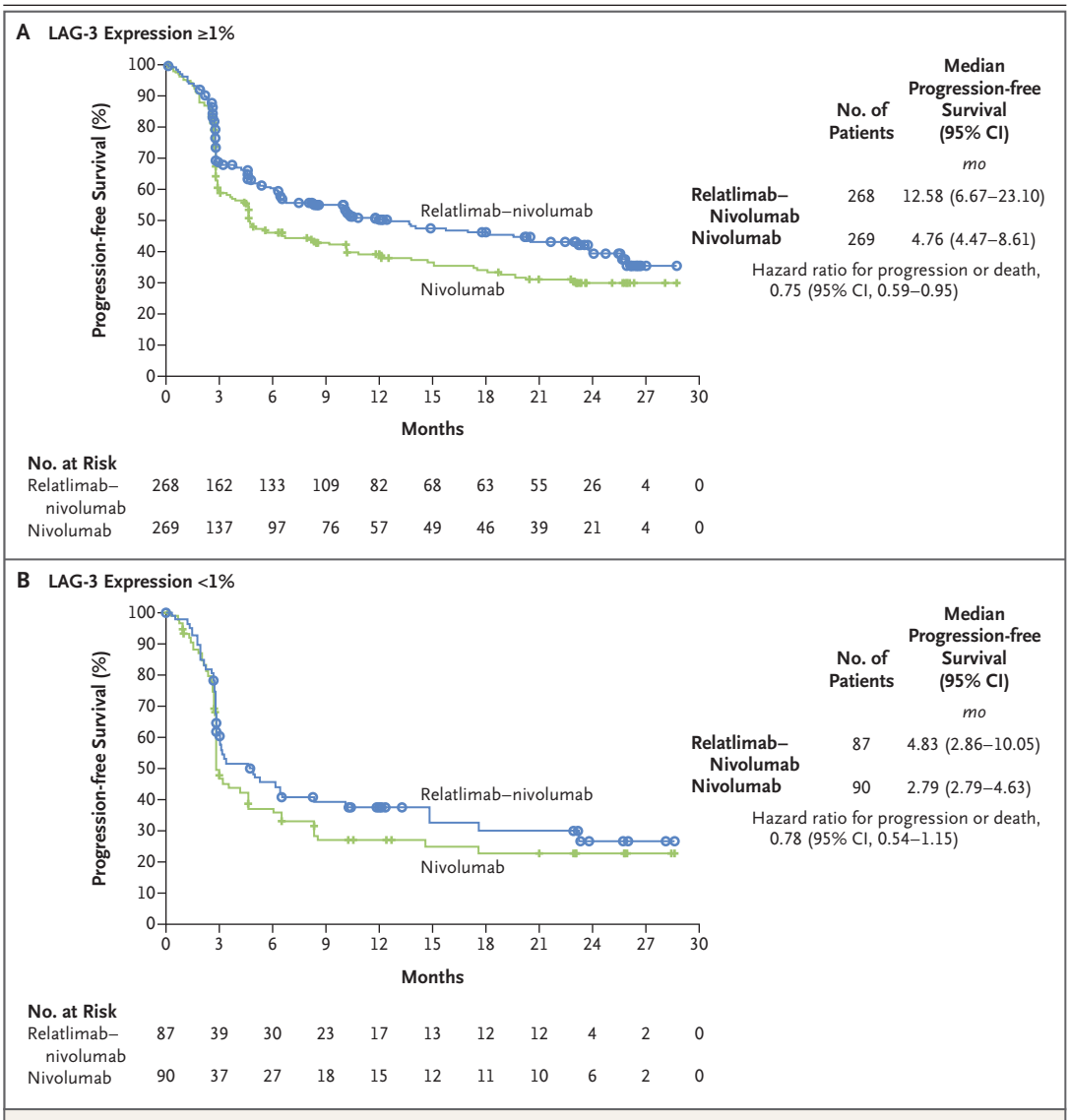

Figure 3. Progression-free Survival, According to LAG-3 Expression.
Hazard ratios were estimated with an unstratified Cox proportional-hazards model.

HEALTH-RELATED QUALITY OF LIFE

The percentage of patients with completed health-related quality-of-life assessments was high (≥86% of the number of patients expected at all on-treatment visits) and was similar in the two treatment groups. Within each treatment group, least-squares mean changes from baseline over time in the FACT-M total score and the EQ-5D-3L utility index remained stable and did not exceed the minimal clinically important differences. (Details regarding the quality-of-life assessments are provided in the Supplementary Appendix.) Overall, no substantial differences in health-related quality of life were noted between the treatment groups (Figs. S3 and S4).

DISCUSSION

RELATIVITY-047 is a phase 3 trial that evaluated the dual inhibition of LAG-3 and PD-1 using a new combination of relatlimab, a human IgG4 LAG-3–blocking antibody, and nivolumab, a PD-1–blocking antibody, as compared with nivolumab alone, which is a current standard therapy for

Table 2. Summary of Adverse Events.

Adverse Event	Relatlimab–Nivolumab (N=355)		Nivolumab (N=359)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	number of events (percent)			
Any adverse event	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
Treatment-related adverse event	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Led to discontinuation of treatment	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
Treatment-related adverse event in ≥10% of patients in the relatlimab–nivolumab group				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0
Immune-mediated adverse event*				
Hypothyroidism or thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea or colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	4 (1.1)	0	4 (1.1)	0

* Immune-mediated adverse events included adverse events of any grade that occurred in at least 1% of patients in the relatlimab–nivolumab group, that were considered by investigators to be potentially immune-mediated, and that met the following criteria: occurred within 100 days after the last dose (regardless of causality) and were treated with immune-modulating medication with no clear alternate cause or had an immune-mediated component.

patients with melanoma. Blinded independent assessment of the primary end point showed that progression-free survival was longer with relatlimab–nivolumab than with nivolumab. Relatlimab–nivolumab dual checkpoint inhibition had twice the median progression-free survival and a 25% lower risk of disease progression or death than nivolumab alone (hazard ratio, 0.75; P=0.006 by the log-rank test). The separation of the progression-free survival curves occurred at the initial postbaseline assessment (at approximately 12 weeks) and was sustained thereafter, with a 12% difference in progression-free survival between the groups at 12 months. The longer progression-free survival with relatlimab–nivolumab than with nivolumab came with a slightly greater incidence of adverse events and a health-related quality of life similar to that observed with nivolumab.

Relatlimab–nivolumab also had a progression-free survival benefit over nivolumab in prespecified subgroups. Patients with characteristics that are typically associated with a worse prognosis, such as visceral metastases, high tumor burden, elevated levels of serum LDH, or mucosal or acral melanoma, had better outcomes with

relatlimab–nivolumab than with nivolumab. A benefit of relatlimab–nivolumab over nivolumab was also observed across *BRAF* mutant and wild-type subgroups. Expression of LAG-3 or PD-L1 was not useful in predicting a benefit of relatlimab–nivolumab over nivolumab and does not have a clear role in the selection of treatment.

Dual checkpoint inhibition in melanoma is a well-established treatment option for achieving the benefit of long-term overall survival. The phase 3 CheckMate 067 trial showed the benefit of dual checkpoint inhibition with a CTLA-4 inhibitor and PD-1 inhibitor over monotherapy with a CTLA-4 inhibitor, with long-term data confirming durable disease control and improved overall survival with dual checkpoint inhibition. These results led to approval of the combination immunotherapy by the Food and Drug Administration and widespread adoption as standard of care in the first-line treatment of metastatic melanoma.[2,18-21] The trial reported here shows a significantly longer median progression-free survival with dual checkpoint inhibition of LAG-3 and PD-1 than with PD-1 inhibition monotherapy. These results suggest that dual checkpoint inhibition should be considered as a treatment option over PD-1 inhibition monotherapy as first-line therapy. Nivolumab monotherapy was chosen as the comparator for this trial because it is standard of care for previously untreated metastatic or unresectable melanoma. In addition, combining relatlimab with nivolumab allowed for direct assessment of the clinical and translational effects of the combination treatment as compared with nivolumab monotherapy. Although cross-trial comparisons should be made with caution, the median progression-free survival observed with nivolumab in this trial was consistent with the initial results from previous trials with PD-1 inhibitor monotherapy in patients with previously untreated metastatic or unresectable melanoma (median, 4.1 to 6.9 months).[22-25] Furthermore, the benefit seen with relatlimab–nivolumab is similar to that reported with the combination of a CTLA-4 inhibitor and PD-1 inhibitor in patients with advanced melanoma who had not received treatment previously; 12-month progression-free survival was 47.7% with relatlimab–nivolumab in this trial and 49% with ipilimumab–nivolumab in CheckMate 067.[19] Follow-up evaluation of survival and long-term benefit in this trial is ongoing. Although grade 3 or 4 treatment-related adverse events were more frequent among patients who received relatlimab–nivolumab than among patients who received nivolumab, no new safety signals associated with relatlimab–nivolumab were identified, and the safety profile appeared favorable as compared with that reported with dual checkpoint inhibition with a CTLA-4 inhibitor and PD-1 inhibitor.[22] Additional studies are needed to understand the efficacy of relatlimab–nivolumab in patient populations that are often excluded from clinical trials for the treatment of melanoma, such as patients with active or untreated brain metastases or with rare melanoma subtypes (e.g., uveal melanoma).

Relatlimab and nivolumab in this trial were administered as a single intravenous infusion. This single infusion has the potential to reduce preparation and infusion times and minimize the risk of errors related to administration.

We report a phase 3 trial investigating the dual checkpoint inhibition of LAG-3 and PD-1. These results validate blocking LAG-3 in combination with PD-1 as a therapeutic strategy for patients with melanoma and establish LAG-3 as the third immune checkpoint pathway the inhibition of which shows clinical benefit. These data further support the added benefit of dual checkpoint inhibition over monotherapy, add another immune checkpoint combination to the therapeutic armamentarium, and establish relatlimab–nivolumab as a potential new treatment option for patients with previously untreated metastatic or unresectable melanoma.

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APPENDIX

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