original reports

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

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abstract

PURPOSE Nivolumab and relatlimab activity in advanced melanoma with prior progression on anti–programmed death-1/programmed death ligand 1 (PD-(L)1)-containing regimens is under investigation. RELATIVITY-047 demonstrated significantly improved progression-free survival (PFS) for nivolumab and relatlimab over nivolumab in previously untreated advanced melanoma.

METHODS The phase I/IIa, open-label RELATIVITY-020 trial part D assessed efficacy and safety of nivolumab and relatlimab in advanced melanoma with progression during, or within 3 months of, 1 (D1) or ≥ 1 (D2) anti–PD-(L)1-containing regimens. Safety was a primary end point. Objective response rate (coprimary end point) and PFS by blinded independent central review (BICR) were assessed.

RESULTS Five hundred eighteen patients (D1 = 354; D2 = 164) received nivolumab and relatlimab. Among evaluable patients, the objective response rate by BICR was 12.0% (95% CI, 8.8 to 15.8) in D1 (n = 351) and 9.2% (95% CI, 5.2 to 14.7) in D2 (n = 163). Responses appeared to be enriched among patients with tumors expressing programmed death ligand 1 or lymphocyte activation gene 3; however, responses were observed regardless of programmed death ligand 1 and lymphocyte activation gene 3 expression (1%). The median duration of response was not reached (95% CI, 12.9 to not reached) in D1 and 12.8 months (95% CI, 6.9 to 12.9) in D2. The median PFS by BICR was 2.1 months (95% CI, 1.9 to 3.5) in D1 and 3.2 months (95% CI, 1.9 to 3.6) in D2; the 6-month PFS rate was 29.1% (95% CI, 24.2 to 34.1) and 27.7% (95% CI, 20.5 to 35.4), respectively. The grade 3-4 treatment-related adverse event incidence was 15.0% in D1 and 12.8% in D2. One case of grade 3 myocarditis and no treatment-related deaths occurred across part D.

CONCLUSION Nivolumab and relatlimab had a manageable safety profile and demonstrated durable clinical activity in a proportion of patients with heavily pretreated advanced melanoma with prior progression on anti–PD-(L)1-containing regimens.

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INTRODUCTION

Immune checkpoint inhibitors have transformed the treatment landscape for patients with advanced melanoma.[1,2] However, despite the availability of effective immunotherapies, treatment for patients with melanoma that had progressed while on anti–programmed death (PD)-ligand (L)-containing therapies remains an area of high unmet need.[3,4] Approximately 40% of patients with melanoma do not derive sustained clinical benefit from existing frontline combination immunotherapies; therefore, novel immunotherapy combinations are needed to improve patient outcomes.[5,6]

RELATIVITY-047, a phase II/III, randomized, double-blind trial, demonstrated a statistically significant and clinically meaningful benefit in the primary end point of progression-free survival (PFS) by blinded independent central review (BICR) for nivolumab and relatlimab versus nivolumab alone in patients with previously untreated metastatic or unresectable

CONTEXT

Key Objective

What are the safety and efficacy of nivolumab and relatlimab in patients with advanced melanoma with documented prior progression on one or more anti–programmed death-1/programmed death ligand 1 therapies?

Knowledge Generated

Nivolumab and relatlimab had a manageable safety profile that was consistent across study cohorts, with no treatment-related deaths. Objective response rate by blinded independent central review ranged from 9.2% to 12.0% across cohorts, and responses were seen regardless of lymphocyte activation gene 3 or programmed death ligand 1 expression (1%). Responses were durable; the percentage of responders who remained in response at 6 months ranged from 84.6% to 92.3%, the median progression-free survival by blinded independent central review ranged from 2.1 to 3.2 months (95% CI, 1.9 to 3.5 and 1.9 to 3.6, respectively), and progression-free survival rates at 6 months ranged from 27.7% to 29.1% (95% CI, 20.5 to 35.4 and 24.2 to 34.1, respectively) across patient cohorts.

Relevance *(G.K. Schwartz)*

Nivolumab and relatlimab represent a safe and reasonable treatment option for patients with advanced melanoma who progressed on a prior anti–programmed death-1/programmed death ligand 1 therapy.*

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

melanoma (median follow-up time, 13.2 months; hazard ratio for progression or death, 0.75; 95% CI, 0.62 to 0.92; $P = .006$).[7] This PFS benefit was consistent when reassessed with a median follow-up time of 19.3 months.[8] Furthermore, treatment with nivolumab and relatlimab versus nivolumab alone was associated with a clinically meaningful, although not statistically significant, improvement in overall survival (OS) (hazard ratio, 0.80; 95% CI, 0.64 to 1.01; $P = .0593$), with numerically increased confirmed objective response rates (ORRs) by BICR for nivolumab and relatlimab (43.1%; 95% CI, 37.9 to 48.4) versus nivolumab alone (32.6%; 95% CI, 27.8 to 37.7).[8] In RELATIVITY-047, the incidence of grade 3-4 events was 21.1% for nivolumab and relatlimab versus 11.1% for nivolumab, with no new or unexpected safety signals.[8]

Taken together, RELATIVITY-047 validated combined PD-1 and lymphocyte activation gene 3 (LAG-3) blockade as an effective strategy for treating patients with advanced melanoma.[7] Nivolumab and relatlimab fixed-dose combination (FDC) was approved for patients with unresectable or metastatic melanoma by the US Food and Drug Administration in March 2022.[9]

RELATIVITY-020 is a phase I/IIa dose-escalation and cohort-expansion trial evaluating the efficacy, safety, and tolerability of relatlimab alone and in combination with nivolumab in patients with advanced solid tumors. A cohort in RELATIVITY-020 part C assessed the efficacy and safety of sequential infusion of nivolumab and relatlimab 240/80 mg once every 2 weeks in patients with advanced melanoma that had progressed on prior anti–programmed death-1/programmed death ligand 1 (PD-(L)1) therapy.[10,11] Nivolumab and relatlimab demonstrated clinically meaningful antitumor activity in this setting.[10,11] Here, we report the results of RELATIVITY-020 part D, which assessed the efficacy and safety of nivolumab and relatlimab in two distinct cohorts of patients with advanced melanoma with documented progression on one or more anti–PD-(L)1 therapies, including a cohort of patients with broader inclusion criteria that may present challenges in clinical practice.

METHODS

Trial Design

RELATIVITY-020 (ClinicalTrials.gov identifier: NCT01968109) is an ongoing, phase I/IIa, dose-escalation and cohort-expansion, open-label trial evaluating relatlimab as monotherapy or in combination with nivolumab in patients with advanced solid tumors. Here, we report results from parts D1 and D2.

The trial was conducted in accordance with the Declaration of Helsinki. The study protocol and amendments were approved by an institutional review board or independent ethics committee at each site. All patients provided written informed consent.

Patients

Eligibility. Patients eligible for enrollment in RELATIVITY-020 had histologic or cytologic confirmation of an advanced (metastatic and/or unresectable) solid malignancy. Part D included patients with advanced unresectable or metastatic melanoma (as assessed by American Joint Committee on Cancer, version 7, criteria) and documented disease progression while on a prior anti–PD-(L)1-containing regimen.

Part D1 allowed only one line of a prior anti–PD-1-containing regimen, and eligibility criteria were more restrictive (Data Supplement, online only). Patients were required to have

documented, unequivocal disease progression within 3 months after the last dose of a prior PD-1–containing regimen (limited to nivolumab or pembrolizumab) in the advanced/metastatic setting. Documentation of prior anti–PD-1 therapy included unequivocal progression and a radiologic progression date not more than 3 months after the last dose of anti–PD-1 therapy. Patients who received prior anti–cytotoxic T lymphocyte antigen-4 (CTLA-4)-containing regimens were also allowed, including in combination with anti–PD-1 therapy. Prior anti–LAG-3 or anti–programmed death ligand 1 (PD-L1) therapy was not allowed, and adjuvant (or neoadjuvant) anti–PD-1 or anti–PD-L1 therapy was also not allowed. *BRAF*-mutant patients were eligible but must have been treated with, and progressed on, one prior line of BRAF inhibitor therapy in the advanced/metastatic setting. Eligible patients had an Eastern Cooperative Oncology Group performance status of 0-1. There were no further limits to the number of prior therapies.

Eligibility criteria in part D2 were broader compared with those in part D1 (Data Supplement). Patients were allowed multiple prior lines of anti–PD-1-containing regimens, and an anti–PD-L1-containing regimen could substitute for anti–PD-1 therapy. Patients who received prior adjuvant or neoadjuvant anti–PD-1 therapy were allowed if one of the following two conditions was met: progression occurred during or within 6 months of the last dose of adjuvant anti–PD-1 therapy or subsequent progression occurred on additional anti–PD-1 therapy in the metastatic setting. Multiple prior lines of BRAF inhibitor therapy were allowed, but *BRAF*-mutant patients were not required to have progressed on prior BRAF inhibitor therapy. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0-2.

Dosing. In part D1 (Data Supplement), patients were treated with nivolumab and relatlimab 240/80 mg once every 2 weeks single-agent vial (SAV; part D1 once every 2 weeks) or randomly assigned 1:1 to receive nivolumab and relatlimab 480/160 mg once every 4 weeks SAV or nivolumab and relatlimab 480/160 mg once every 4 weeks FDC (part D1 once every 4 weeks). In part D2, patients were treated with nivolumab and relatlimab 480/160 mg once every 4 weeks SAV (part D2 once every 4 weeks).

Primary Objectives

A primary objective in part D was to assess safety as measured by the rates of adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation of treatment, deaths, and laboratory abnormalities. Safety outcomes were assessed during treatment and for up to 135 days after the last treatment. The coprimary objective in part D1 once every 2 weeks was to demonstrate preliminary clinical evidence of the treatment effect, measured by ORR, as determined by BICR using RECIST, version 1.1, in patients with advanced melanoma with LAG-3 expression that had progressed while on prior anti–PD-1 therapy. The coprimary objective in part D1 once every 4 weeks was the safety of SAV (nivolumab and relatlimab coadministered in a single intravenous bag) and FDC (containing nivolumab and relatlimab in a single vial at a protein-mass ratio of 3:1), as measured by the incidence of hypersensitivity/infusion-related reactions (defined by a broad list of AE terms) that occurred within 2 days after dosing. Another coprimary objective was the safety of nivolumab and relatlimab 240/80 mg once every 2 weeks dosing relative to nivolumab and relatlimab 480/160 mg once every 4 weeks dosing.

Key Secondary Objectives

Key secondary objectives for which results are presented are listed in the Data Supplement along with a complete list of secondary objectives for part D (Data Supplement).

Statistical Analysis

Efficacy and safety data were assessed separately by individual cohorts for parts D1 and D2, and an exploratory pooled analysis was conducted across all cohorts in part D1. Pharmacokinetic and pharmacodynamic analysis methods are described in the Data Supplement.

Safety. All AEs, SAEs, treatment-related AEs (TRAEs), and treatment-related SAEs were summarized using the worst grade per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, by system organ class and preferred term. Incidence of AEs and the difference in rates between arms were reported descriptively.

Efficacy. ORR, duration of response (DOR), disease control rate (DCR), best overall response, and PFS were determined on the basis of RECIST, version 1.1, for the primary and secondary analyses. Time to event distributions (eg, PFS, DOR, and OS) were estimated using the Kaplan-Meier method. Best overall response outcomes were summarized using frequency tables together with two-sided 95% CIs.

RESULTS

Patient Demographics and Baseline Characteristics

All results are based on a database lock of February 25, 2021, and a clinical cutoff date (last patient, last visit) of January 4, 2021. The minimum potential follow-up (time from the last patient, first treatment date to the last patient, last visit date) was 19.4 months. In part D1, 189 patients received nivolumab and relatlimab 240/80 mg once every 2 weeks SAV, 83 patients received 480/160 mg once every 4 weeks SAV, and 82 patients received 480/160 mg once every 4 weeks FDC. In part D2, 164 patients received 480/160 mg once every 4 weeks SAV. In total, 518 patients from D1 pooled (n = 354) and D2 (n = 164) received nivolumab and relatlimab. The median duration of nivolumab and relatlimab treatment was approximately 16 weeks across the SAV arms (range, 2-160 weeks) and 19.8 weeks in the FDC arm (range, 4-128 weeks).

Baseline characteristics were generally similar between D1 pooled (Table 1) and three D1 cohorts (Data Supplement).

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	D1 Pooled[a] (n = 354)	D2[b] (n = 164)
Age, years, median (range)	63.0 (17-92)	62 (21-91)
< 65, No. (%)	186 (52.5)	93 (56.7)
Male, No. (%)	218 (61.6)	85 (51.8)
Race, No. (%)		
White	328 (92.7)	156 (95.1)
Black	3 (0.8)	1 (0.6)
Asian	20 (5.6)	7 (4.3)
Others	3 (0.8)	0
ECOG PS, No. (%)		
0	244 (68.9)	111 (67.7)
1	109 (30.8)	44 (26.8)
2	1 (0.3)	9 (5.5)
Melanoma subtype, No. (%)		
Mucosal	35 (9.9)	11 (6.7)
Cutaneous	240 (67.8)	122 (74.4)
Acral	50 (14.1)	18 (11.0)
Others	28 (7.9)	11 (6.7)
Unknown	1 (0.3)	2 (1.2)
LDH, No. (%)		
Normal	183 (51.7)	85 (51.8)
Normal to < 2 × ULN	124 (35.0)	55 (33.5)
≥ 2 × ULN	45 (12.7)	23 (14.0)
Unknown	2 (0.6)	1 (0.6)
Liver metastases, No. (%)		
Yes	121 (34.2)	49 (29.9)
No	233 (65.8)	115 (70.1)
Disease stage at entry, No. (%)		
III	22 (6.2)	15 (9.1)
IV	332 (93.8)	149 (90.9)
M status at entry,[c] No. (%)		
M1a	39 (11.0)	27 (16.5)
M1b	59 (16.7)	17 (10.4)
M1c with brain metastases	36 (10.2)	23 (14.0)
M1c without brain metastases	198 (55.9)	81 (49.4)
Unknown	22 (6.2)	16 (9.8)
LAG-3 status, No. (%)[d]		
≥1%	199 (56.2)	88 (53.7)
<1%	93 (26.3)	48 (29.3)
PD-L1 status, No. (%)[d]		
≥1%	134 (37.9)	57 (34.8)
<1%	147 (41.5)	74 (45.1)
BRAF status, No. (%)		
Mutation	68 (19.2)	62 (37.8)
No mutation	275 (77.7)	98 (59.8)
Unknown	0[e]	0[f]
Time from initial diagnosis to treatment, years, median	3.2	4.3
Prior surgery, No. (%)	324 (91.5)	153 (93.3)
Prior radiotherapy, No. (%)	146 (41.2)	84 (51.2)
Prior systemic therapy, No. (%)	353 (99.7)	164 (100.0)
Immunotherapy	352 (99.4)	164 (100.0)
CTLA-4	139 (39.3)	98 (59.8)
BRAF	57 (16.1)	39 (23.8)
Prior anti–PD-(L)1	352 (99.4)	164 (100.0)
Chemotherapy	107 (30.2)	81 (49.4)
Prior systemic regimens		
1, No. (%)	164 (46.3)	28 (17.1)
2, No. (%)	123 (34.7)	40 (24.4)
≥3, No. (%)	66 (18.6)	96 (58.5)
Median (range)	2 (1-6)	3 (1-10)

Abbreviations: AJCC, American Joint Committee on Cancer; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; FDC, fixed-dose combination; LAG-3, lymphocyte activation gene 3; LDH, lactate dehydrogenase; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PD-(L)1; programmed death-1/programmed death ligand 1; SAV, single-agent vial; ULN, upper limit of normal.

[a]D1 pooled includes the nivolumab and relatlimab 240/80 mg once every 2 weeks SAV, nivolumab and relatlimab 480/160 mg once every 4 weeks SAV, and nivolumab and relatlimab 480/160 mg once every 4 weeks FDC cohorts.

[b]D2 includes the nivolumab and relatlimab 480/160 mg once every 4 weeks SAV cohort.

[c]As assessed by AJCC, version 7, criteria.

[d]LAG-3 and PD-L1 status was not available for all patients.

[e]Eleven patients had missing *BRAF* status.

[f]Four patients had missing *BRAF* status.

In D1 pooled, 53.3% of patients had ≥ 2 lines of prior therapy and 58.5% of patients in D2 had ≥ 3 lines of prior therapy. In D1 pooled and D2, 39.3% and 59.8% of patients had prior anti–CTLA-4 therapy, 16.1% and 23.8% of patients had prior BRAF inhibitor therapy, and 30.2% and 49.4% had prior chemotherapy, respectively.

Patient Disposition/Follow-Up

Patient disposition and follow-up are presented in the Data Supplement.

Efficacy

The ORR by BICR was 12.0% (95% CI, 8.8 to 15.8) in D1 pooled and 9.2% (95% CI, 5.2 to 14.7) in D2 (Table 2). The

TABLE 2. Comparison of ORR by BICR, BOR by BICR, Median PFS by BICR, Median OS, Median DOR by BICR, and DCR by BICR

End Point	D1 Pooled[a] (n = 351)[c]	D2[b] (n = 163)[d]
Minimum follow-up, months	19.4	26.9
Confirmed ORR, No. (%)	42 (12.0)	15 (9.2)
95% CI	8.8 to 15.8	5.2 to 14.7
BOR, No. (%)		
CR	15 (4.3)	4 (2.5)
PR	27 (7.7)	11 (6.7)
SD	100 (28.5)	50 (30.7)
SD ≥12 weeks	94 (26.8)	46 (28.2)
Non-CR/non-PD	6 (1.7)	4 (2.5)
PD	174 (49.6)	68 (41.7)
Unable to determine	28 (8.0)	25 (15.3)
Confirmed DCR (CR + PR + SD), No. (%)	142 (40.5)	65 (39.9)
95% CI	35.3 to 45.8	32.3 to 47.8
Confirmed DCR ≥12 weeks,[e] No. (%)	136 (38.7)	61 (37.4)
95% CI	33.6 to 44.1	30.0 to 45.3
Median DOR, months (95% CI)	NR (12.9 to NR)	12.8 (6.9 to 12.9)
6-Month DOR rate	92.3 (78.0 to 97.5)	84.6 (51.2 to 95.9)
12-Month DOR rate	70.9 (53.5 to 82.7)	52.7 (23.4 to 75.5)
Median PFS, months (95% CI)	2.1 (1.9 to 3.5)	3.2 (1.9 to 3.6)
6-Month PFS rate	29.1 (24.2 to 34.1)	27.7 (20.5 to 35.4)
12-Month PFS rate	21.4 (17.0 to 26.1)	16.0 (10.0 to 23.0)
Median OS, months (95% CI)	14.7 (12.4 to 16.9)	17.1 (13.4 to 21.0)
12-Month OS rate	56.0 (50.6 to 61.1)	60.0 (52.0 to 67.0)
ORR, % (95% CI)		
LAG-3 ≥1%	14.1 (9.6 to 19.8)[f]	11.4 (5.6 to 19.9)[g]
LAG-3 <1%	5.4 (1.8 to 12.2)[h]	4.2 (0.5 to 14.3)[i]
DCR (12 weeks),[e] % (95% CI)		
LAG-3 ≥1%	42.9 (35.9 to 50.1)[f]	38.6 (28.4 to 49.6)[g]
LAG-3 <1%	26.1 (17.5 to 36.3)[h]	29.2 (17.0 to 44.1)[i]
Median PFS, months (95% CI)		
LAG-3 ≥1%	3.5 (1.9 to 3.6)[f]	3.5 (1.8 to 5.1)[g]
LAG-3 <1%	1.9 (1.8 to 2.0)[h]	1.9 (1.8 to 3.5)[i]
Median OS, months (95% CI)		
LAG-3 ≥1%	16.2 (13.1 to 18.9)[j]	17.2 (11.9 to 22.8)[g]
LAG-3 <1%	10.3 (8.3 to 13.7)[k]	14.3 (7.1 to 22.4)[i]

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; FDC, fixed-dose combination; LAG-3, lymphocyte activation gene 3; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SAV, single-agent vial; SD, stable disease.

[a]D1 pooled includes the nivolumab and relatlimab 240/80 mg once every 2 weeks SAV, nivolumab and relatlimab 480/160 mg once every 4 weeks SAV, and nivolumab and relatlimab 480/160 mg once every 4 weeks FDC cohorts.

[b]D2 includes the nivolumab and relatlimab 480/160 mg once every 4 weeks SAV cohort.

[c]Response-evaluable patients; OS end point was assessed in all treated patients (n = 354).

[d]Response-evaluable patients; OS end point was assessed in all treated patients (n = 164).

[e]DCR was defined as the total number of patients whose best overall response was CR, PR, or SD for at least 12 weeks divided by the total number of response-evaluable patients in the population of interest.

[f]n = 198.

[g]n = 88.

[h]n = 92.

[i]n = 48.

[j]n = 199.

[k]n = 93.

ORR by BICR in individual D1 cohorts is shown in the Data Supplement. The confirmed DCR by BICR was 40.5% in D1 pooled and 39.9% in D2 (Table 2).

For patients with LAG-3 expression ≥ 1% and < 1% in D1 pooled, the ORR by BICR was 14.1% (95% CI, 9.6 to 19.8) and 5.4% (95% CI, 1.8 to 12.2), respectively (Table 2). A similar pattern of ORR by LAG-3 expression was observed in the individual D1 cohorts (Data Supplement). Similarly, for patients with PD-L1 expression ≥ 1% and < 1%, the ORR by BICR was 15.7% (95% CI, 10.0 to 23.0) and 8.2% (95% CI, 4.3 to 13.8), respectively (Table 3).

In patients with and without prior CTLA-4 exposure (as monotherapy or in combination with PD-1 blockade) in D1 pooled, the ORR by BICR was 11.7% (95% CI, 6.8 to 18.3)

TABLE 3. ORR by BICR in Subgroups

D1 Pooled[a]

Subgroup	No.	Responders, No. (%)	95% CI
Overall	351	42 (12.0)	8.8 to 15.8
BOR on prior (anti–PD-(L)1) therapy			
CR + PR + SD	157	19 (12.1)	7.4 to 18.3
CR	12	2 (16.7)	—
PR	69	9 (13.0)	—
SD	76	8 (10.5)	—
PD	152	18 (11.8)	7.2 to 18.1
PD-L1 ≥1%	134	21 (15.7)	10.0 to 23.0
PD-L1 <1%	147	12 (8.2)	4.3 to 13.8
Prior BRAF/MEK inhibitor, *BRAF*-mutant patients	52	7 (13.5)	5.6 to 25.8
No prior BRAF/MEK inhibitor, *BRAF*-mutant patients	16	2 (12.5)	1.6 to 38.3
Prior CTLA-4 therapy	137	16 (11.7)	6.8 to 18.3
No prior CTLA-4 therapy	214	26 (12.1)	8.1 to 17.3
One prior systemic regimen	162	19 (11.7)	7.2 to 17.7
First-line PD-1 and CTLA-4 inhibitors	25[b]	3 (12.0)	2.5 to 31.2
≥2 prior systemic regimens	188	23 (12.2)	7.9 to 17.8
Mucosal	35	6 (17.1)	6.6 to 33.6
Cutaneous	238	28 (11.8)	8.0 to 16.6
Acral	49	7 (14.3)	5.9 to 27.2
M1a	39	11 (28.2)	15.0 to 44.9
M1b	57	8 (14.0)	6.3 to 25.8
M1c with brain metastases	36	5 (13.9)	4.7 to 29.5
M1c without brain metastases	197	16 (8.1)	4.7 to 12.9
LDH > ULN	167	17 (10.2)	6.0 to 15.8
LDH < ULN	182	25 (13.7)	9.1 to 19.6
LDH ≥2 × ULN	43	2 (4.7)	0.6 to 15.8
LDH <2 × ULN	306	40 (13.1)	9.5 to 17.4
Presence of liver metastases	121	10 (8.3)	4.0 to 14.7
No presence of liver metastases	230	32 (13.9)	9.7 to 19.1
Time from initial diagnosis to treatment, ≥ median	176	18 (10.2)	6.2 to 15.7
Time from initial diagnosis to treatment, < median	175	24 (13.7)	9.0 to 19.7

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T lymphocyte antigen-4; FDC, fixed-dose combination; LAG-3, lymphocyte activation gene 3; LDH, lactate dehydrogenase; ORR, objective response rate; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PD-(L)1; programmed death-1/programmed death ligand 1; PR, partial response; SAV, single-agent vial; SD, stable disease; ULN, upper limit of normal.

[a]D1 pooled includes the nivolumab and relatlimab 240/80 mg once every 2 weeks SAV, nivolumab and relatlimab 480/160 mg once every 4 weeks SAV, and nivolumab and relatlimab 480/160 mg once every 4 weeks FDC cohorts.

[b]Of these 25 patients, 24 received nivolumab and ipilimumab and one received pembrolizumab and ipilimumab.

and 12.1% (95% CI, 8.1 to 17.3), respectively (Table 3). Patients with and without a prior BRAF/MEK inhibitor in D1 pooled had a similar ORR by BICR of 13.5% (95% CI, 5.6 to 25.8) and 12.5% (95% CI, 1.6 to 38.3), respectively (Table 3).

In patients with M1c stage disease with and without brain metastases in D1 pooled, the ORR by BICR was 13.9% (95% CI, 4.7 to 29.5) and 8.1% (95% CI, 4.7 to 12.9), respectively (Table 3). Patients with lactate dehydrogenase levels greater or lower than the upper limit of normal in D1 pooled had an ORR by BICR of 10.2% (95% CI, 6.0 to 15.8) and 13.7% (95% CI, 9.1 to 19.6), respectively (Table 3).

The median DOR by BICR was not reached (NR; 95% CI, 12.9 to NR) for patients in D1 pooled and was 12.8 months (95% CI, 6.9 to 12.9) in D2 (Table 2 and Fig 1). In D1 pooled, the percentage of responders who remained in response was 92.3% (95% CI, 78.0 to 97.5) at 6 months and 70.9% (95% CI, 53.5 to 82.7) at 12 months (Table 2). In D2, the percentage of responders who remained in response was 84.6% (95% CI, 51.2 to 95.9) at 6 months and 52.7% (95% CI, 23.4 to 75.5) at 12 months (Table 2). Waterfall plots of best changes in target lesion tumor burden by BICR are presented in the Data Supplement.

In D1 pooled, the median PFS by BICR was 2.1 months (95% CI, 1.9 to 3.5). The 6-month PFS rate was 29.1% (95% CI, 24.2 to 34.1), and the 12-month PFS rate was 21.4% (95% CI, 17.0 to 26.1; Table 2 and Fig 2A). Similar BICR-assessed PFS rates were observed across the individual D1 cohorts (Data Supplement). In D2, the median PFS by BICR was 3.2 months (95% CI, 1.9 to 3.6). The 6-month PFS rate was 27.7% (95% CI, 20.5 to 35.4), and the 12-month PFS rate was 16.0% (95% CI, 10.0 to 23.0; Table 2 and Fig 2B).

The median OS was 14.7 months (95% CI, 12.4 to 16.9), and the 12-month OS rate was 56.0% (95% CI, 50.6 to 61.1) for patients in D1 pooled (Table 2 and Fig 2C). OS rates were similar across the individual D1 cohorts (Data Supplement). In D2, the median OS was 17.1 months (95% CI, 13.4 to 21.0) and the 12-month OS rate was 60.0% (95% CI, 52.0 to 67.0) (Table 2 and Fig 2D).

Safety

Incidences of any-grade and grade 3-4 AEs were similar across individual part D cohorts (Table 4 and Data Supplement). There were no treatment-related deaths in part D.

The incidence of any-grade and grade 3-4 TRAEs was 67.5% and 15.0% in D1 pooled and 68.9% and 12.8% in D2, respectively (Table 4). Incidence of any-grade TRAEs leading to discontinuation was 5.1% in D1 pooled and 4.3% in D2 (Table 4).

The most common immune-mediated AEs were rash (7.3%), hypothyroidism/thyroiditis (5.9%), and diarrhea/colitis (5.4%)

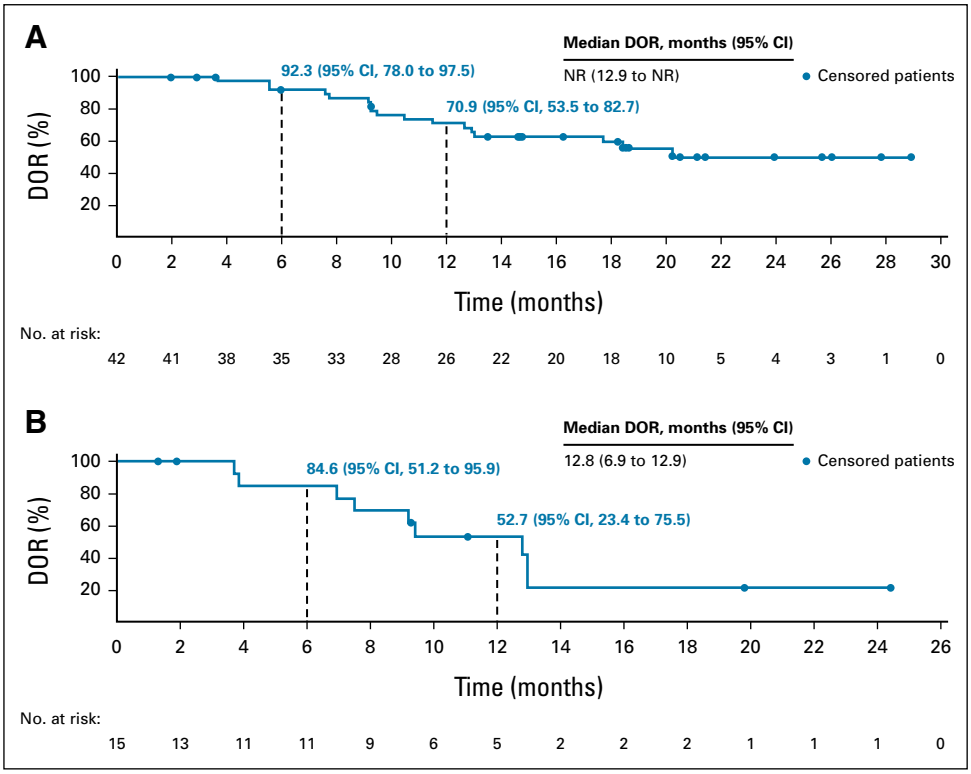

FIG 1. DOR Kaplan-Meier curve by BICR for (A) D1 pooled and (B) D2. The database lock date was February 25, 2021. The minimum follow-up time was 19.4 months in D1 pooled and 26.9 months in D2. BICR, blinded independent central review; DOR, duration of response; NR, not reached.

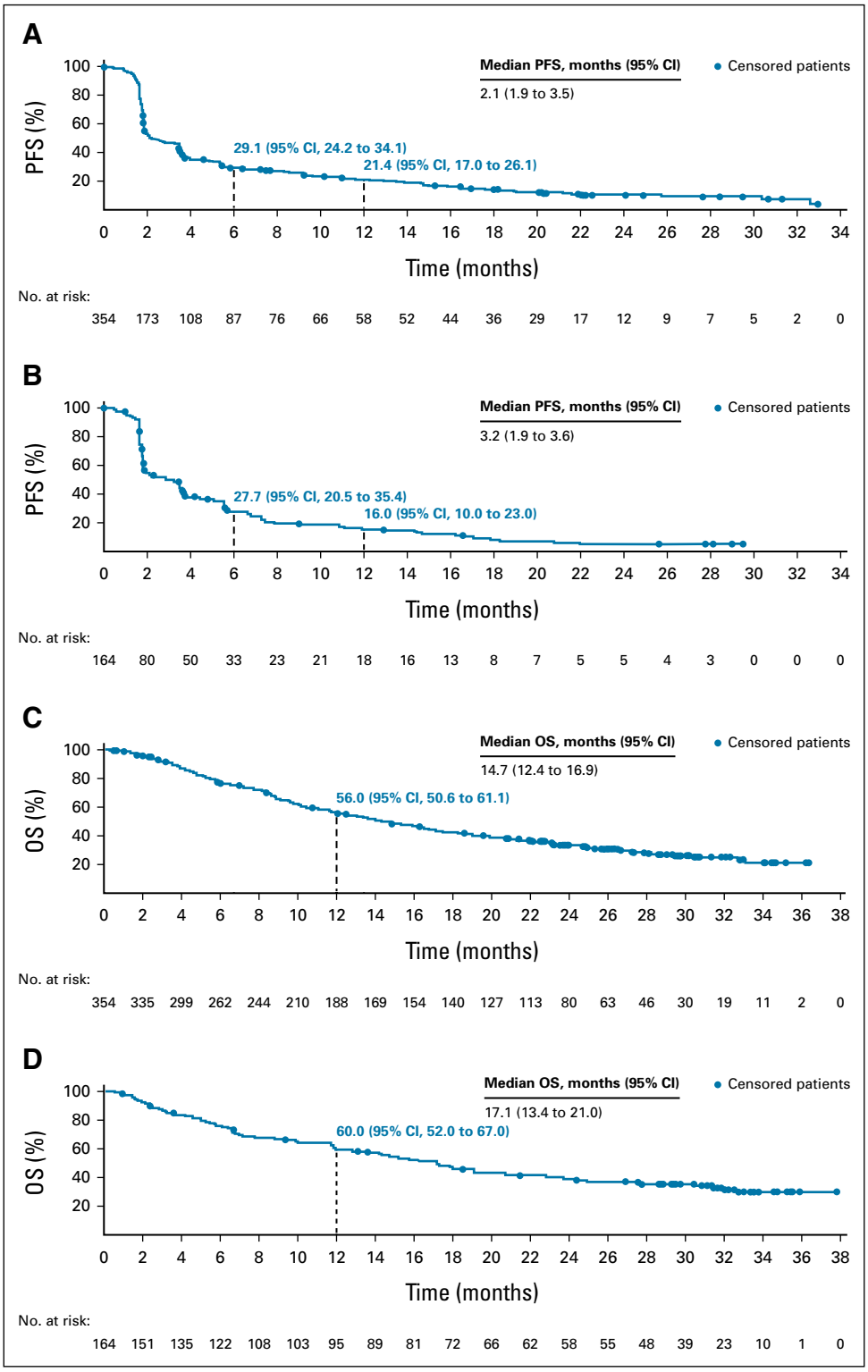

FIG 2. PFS by BICR for (A) D1 pooled and (B) D2 and OS Kaplan-Meier curve for (C) D1 pooled and (D) D2. The database lock date was February 25, 2021. The minimum follow-up time was 19.4 months in D1 pooled and 26.9 months in D2. BICR, blinded independent central review; OS, overall survival; PFS, progression-free survival.

in D1 pooled and rash (8.5%), hypothyroidism/thyroiditis (4.3%), and hepatitis (4.3%) in D2 (Table 4). There was one case of grade 3 myocarditis in D1 pooled (0.3%) and no cases in D2. In part D1, the incidence of treatment-related hypersensitivity/infusion-related reactions was 8.5% (16 of 189) in the 240/80 mg once every 2 weeks SAV cohort, 3.6%

TABLE 4. Safety Outcomes

	D1 Pooled[a] (n = 354)		D2[b] (n = 164)	
Safety[c]	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
AEs, No. (%)	343 (96.9)	146 (41.2)	159 (97.0)	70 (42.7)
TRAEs, No. (%)	239 (67.5)	53 (15.0)	113 (68.9)	21 (12.8)
TRAEs, ≥10%,[d] No. (%)				
Fatigue	55 (15.5)	1 (0.3)	21 (12.8)	0
Diarrhea	38 (10.7)	5 (1.4)	12 (7.3)	1 (0.6)
Pruritus	33 (9.3)	0	20 (12.2)	0
SAEs, No. (%)	131 (37.0)	93 (26.3)	69 (42.1)	53 (32.3)
Treatment-related SAEs, No. (%)	27 (7.6)	21 (5.9)	11 (6.7)	10 (6.1)
AEs leading to discontinuation, No. (%)	41 (11.6)	29 (8.2)	16 (9.8)	13 (7.9)
Treatment-related AEs leading to discontinuation, No. (%)	18 (5.1)	11 (3.1)	7 (4.3)	7 (4.3)
IMAEs,[e] No. (%)				
Rash	26 (7.3)	5 (1.4)	14 (8.5)	0
Diarrhea/colitis	19 (5.4)	14 (4.0)	4 (2.4)	2 (1.2)
Hypothyroidism/thyroiditis	21 (5.9)	0	7 (4.3)	0
Hypophysitis	8 (2.3)	5 (1.4)	1 (0.6)	0
Pneumonitis	8 (2.3)	0	0	0
Hepatitis	7 (2.0)	4 (1.1)	7 (4.3)	7 (4.3)
Adrenal insufficiency	6 (1.7)	3 (0.8)	3 (1.8)	0
Hyperthyroidism	2 (0.6)	0	1 (0.6)	0
Nephritis and renal dysfunction	2 (0.6)	0	1 (0.6)	1 (0.6)
Diabetes mellitus	1 (0.3)	1 (0.3)	1 (0.6)	0
Hypersensitivity/infusion reactions[f]	0	0	1 (0.6)	0

NOTE. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Abbreviations: AE, adverse event; FDC, fixed-dose combination; IMAE, immune-mediated adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SAV, single-agent vial; SMQ, standardized MedDRA query; TRAE, treatment-related adverse event.

[a]D1 pooled includes the nivolumab and relatlimab 240/80 mg once every 2 weeks SAV, nivolumab and relatlimab 480/160 mg once every 4 weeks SAV, and nivolumab and relatlimab 480/160 mg once every 4 weeks FDC cohorts.

[b]D2 includes the nivolumab and relatlimab 480/160 mg once every 4 weeks SAV cohort.

[c]There were no treatment-related deaths.

[d]Includes events reported after first dose and within 100 days after last dose of study therapy.

[e]IMAEs were defined as AEs consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) were ruled out. IMAEs could have included events with an alternative etiology that were exacerbated by the induction of autoimmunity. Events reported after first dose and within 100 days after last dose of study therapy were included.

[f]IMAEs of hypersensitivity/infusion reactions are distinct from the events in the broad scope MedDRA hypersensitivity/infusion-related reaction SMQ, which occurred within 2 days of any doses of study therapy.

(3 of 83) in the 480/160 mg once every 4 weeks SAV cohort, and 7.3% (6 of 82) in the 480/160 mg once every 4 weeks FDC cohort (Data Supplement). None of the hypersensitivity/infusion-related reactions (all causality or treatment-related) were grade 3 or 4.

Pharmacokinetics, Pharmacodynamics, and Immunogenicity

The results for key pharmacokinetic parameters were similar in patients receiving nivolumab and relatlimab as SAV or FDC, indicating that combination as an FDC drug product had no effect on pharmacokinetics (Data Supplement). Free soluble LAG-3 (sLAG-3) levels decreased after treatment with nivolumab and relatlimab (SAV and FDC; Data Supplement). There was an approximately 50% decrease in sLAG-3 level at trough concentration (day 29) for the 480/160 mg once every 4 weeks SAV and FDC arms. No difference between SAV and FDC in sLAG-3 change from baseline to day 15 was observed. An approximately 100% (or two-fold) increase in serum interferon-gamma levels in the nivolumab and relatlimab SAV and FDC arms was observed on treatment compared with that in baseline (Data Supplement).

Administration of nivolumab and relatlimab as FDC compared with SAV, or as different dosing regimens, had no detectable effect on immunogenicity. All pharmacokinetic,

pharmacodynamic, and immunogenicity results are presented in the Data Supplement.

DISCUSSION

RELATIVITY-020 part D demonstrated the durable clinical benefit of nivolumab and relatlimab in heavily pretreated patients with melanoma that previously progressed on anti–PD-(L)1-containing regimens. Previous studies of immunotherapies in patients with melanoma who had been treated with anti–PD-(L)1 therapy largely relied on retrospective data, did not include heavily pretreated patients, and/or included few patients.[12-17] Conversely, RELATIVITY-020 part D included more than 500 heavily pretreated patients with advanced melanoma, more than half of whom had received two or more prior lines of therapy, including anti–PD-(L)1, anti–CTLA-4, and BRAF/MEK inhibitors. Although the single-arm nature of this phase I/IIa trial is a limitation, part D generally represents a patient population with unique challenges in routine practice. These results provide a valuable data set for understanding nivolumab and relatlimab efficacy and safety in patients with melanoma that previously progressed on PD-(L)1 inhibitor–containing regimens.

In RELATIVITY-020 part D, the ORR by BICR was 12.0% in D1 pooled and 9.2% in D2. Patients who experienced responses had durable disease control, with longer median DOR observed in D1 pooled relative to D2. The median DOR by BICR was NR in D1 pooled and was 12.8 months in D2. Among patients who experienced a response, 92.3% and 70.9% had ongoing responses at 6 and 12 months in D1 pooled, respectively, and 84.6% and 52.7% in D2, respectively. The median OS was 14.7 months and 17.1 months in D1 pooled and D2, respectively. Results also demonstrate a manageable safety profile for nivolumab and relatlimab in this patient population. Generally consistent safety profiles were seen across cohorts, including equivalent dosing regimens of once every 2 weeks and once every 4 weeks and FDC and SAV administration.

Response rates appeared to be enriched among patients with tumors expressing PD-L1 or LAG-3; however, responses were observed regardless of PD-L1 and LAG-3 expression (1% cutoff). These results are in line with those from RELATIVITY-047,[7] suggesting that LAG-3 and PD-L1 may not be appropriate as sole markers for treatment selection. In addition, nivolumab and relatlimab efficacy was observed regardless of the presence of controlled brain metastases, lactate dehydrogenase, and prior therapy with or without a CTLA-4 inhibitor (ORR, 11.7% and 12.1%, respectively, for D1 pooled) or a BRAF/MEK inhibitor (ORR, 13.5% and 12.5%, respectively, for D1 pooled).

RELATIVITY-020 part D is one of several recent investigations into the safety and efficacy of escalation to combination therapy for patients with advanced melanoma that had progressed on prior anti–PD-(L)1 therapy.[18] Key trials in this clinical setting include LEAP-004, a phase II study of lenvatinib and pembrolizumab (n = 103),[19] SWOG S1616, a phase II study of ipilimumab and nivolumab (n = 69) versus ipilimumab (n = 23)[15] and a phase II study of lifileucel (n = 66).[20] ORRs were 21% for lenvatinib and pembrolizumab in LEAP-004, 28% for ipilimumab and nivolumab in SWOG S1616, and 36% for lifileucel.[15,19,20] The median DOR was 8.2 months for lenvatinib and pembrolizumab (median follow-up of 15.3 months), 18.9 months for ipilimumab and nivolumab (median follow-up of 28.3 months), and NR for lifileucel (median follow-up of 18.7 months).[15,19,20] Median OS values were 14.0 months for lenvatinib and pembrolizumab, 21.7 months for ipilimumab and nivolumab, and 17.4 months for lifileucel.[15,19,20] AEs were observed at an incidence of 46% for lenvatinib and pembrolizumab (grade 3-4 treatment-related), 56% for ipilimumab and nivolumab (all-causality treatment-emergent), and 97% for lifileucel (grade 3-4 treatment-related).[15,19,20] Of note, S1616 did not include patients who progressed on prior anti–CTLA-4 therapy.[15] Published results highlight potential emerging options for patients with advanced melanoma that has progressed on anti–PD-(L)1 therapy; however, cross-trial comparisons should be made with caution because of differences in study design and median follow-up.

Nivolumab and relatlimab treatment induced immune activation in patients with melanoma previously treated with anti–PD-(L)1. An increase in soluble interferon-gamma levels was observed in the nivolumab and relatlimab SAV and FDC arms after treatment, demonstrating immune activation and pharmacodynamic activity with this combination.

sLAG-3 levels were also evaluated as a pharmacodynamic end point. The observed dose-dependent decrease from baseline of sLAG-3 in circulation at day 15 (week 2) indicates target engagement during treatment with nivolumab and relatlimab.

Additional studies may be needed to confirm the use of nivolumab and relatlimab in later lines of therapy and determine whether biomarkers have utility to predict response. In particular, LAG-3 in combination with another biomarker such as PD-L1, PD-1, or a LAG-3 ligand (eg, major histocompatibility complex class II) may better differentiate the efficacy of combination anti–LAG-3 and anti–PD-1 therapy over anti–PD-1 monotherapy as compared with a single biomarker. There may also be value in assessing immunohistochemical markers across a broader dynamic range versus at single cutoffs although such innovative approaches present novel challenges for diagnostic development. Further research is also needed to determine the relative contributions of nivolumab and relatlimab to the efficacy observed in this setting. However, the durability of the responses to nivolumab and relatlimab in this study is suggestive of benefit beyond anti–PD-1 rechallenge.

These results demonstrate the safety and clinical activity of nivolumab and relatlimab in patients with advanced

melanoma that had progressed on anti–PD-(L)1-containing regimens, including patients who were heavily pretreated, received prior CTLA-4 inhibitors, and had multiple poor prognostic factors. Taken together with the results from RELATIVITY-047,[7] these findings demonstrate the activity of dual immunotherapy with nivolumab and relatlimab in advanced melanoma across lines of therapy.

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Bristol Myers Squibb will honor legitimate requests for our clinical trial data from qualified researchers with a clearly defined scientific objective. We consider data sharing requests for phase II-IV interventional clinical trials that completed on or after January 1, 2008. In addition, primary results from these trials must have been published in peer-reviewed journals and the medicines or indications approved in the United States, EU, and other designated markets. Sharing is also subject to protection of patient privacy and respect for the patient's informed consent. Data considered for sharing may include nonidentifiable patient-level and study-level clinical trial data, full clinical study reports, and protocols. Bristol Myers Squibb reserves the right to update and change criteria at any time. Other criteria may apply; for details, visit Bristol Myers Squibb at www.vivli.org.

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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

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