Relatlimab and nivolumab vs nivolumab in previously untreated metastatic or unresectable melanoma: overall survival and response rates from RELATIVITY-047 (CA224-047)

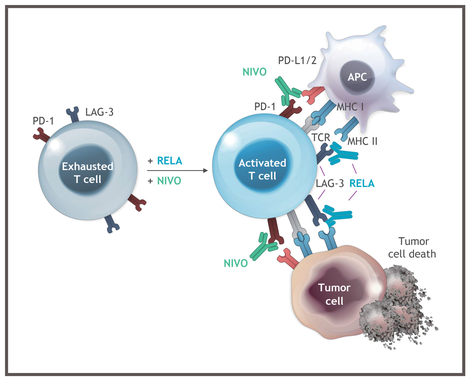
Georgina V. Long,[1] F. Stephen Hodi,[2] Evan J. Lipson,[3] Dirk Schadendorf,[4] Paolo A. Ascierto,[5] Luis Matamala,[6,7] Pamela Salman,[6,*] Erika Castillo Gutiérrez,[8] Piotr Rutkowski,[9] Helen J. Gogas,[10] Christopher D. Lao,[11] Juliana Janoski De Menezes,[12] Stéphane Dalle,[13] Ana Arance,[14] Jean-Jacques Grob,[15] Sarah Keidel,[16] Anadil Shaikh,[16] Anne Marie Sobiesk,[16] Sonia Dolfi,[16] Hussein A. Tawbi[17]

[1]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [4]Department of Dermatology, University Hospital Essen, Essen, Germany & German Cancer Consortium, Partner Site Essen, Germany; [5]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Napoli, Italy; [6]Department of Oncology, Instituto Oncologico Fundacion Arturo Lopez Perez, Santiago, Chile; [7]Department of Oncology, Instituto Nacional del Cancer, Santiago, Chile; [8]FAICIC Clinical Research, Veracruz, Mexico; [9]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10]Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [11]Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI, USA; [12]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [13]Unit of Dermatology, Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; [14]Department of Medical Oncology, Hospital Clinic Barcelona and IDIBAPS, Barcelona, Spain; [15]Aix-Marseille University, CHU Timone, Marseille, France; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; *Affiliation during the time of the trial

Introduction

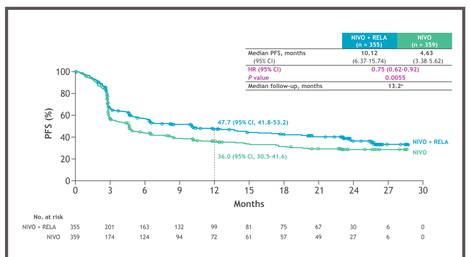
- Immune checkpoint inhibitors have revolutionized treatment options for patients with advanced melanoma.
- New combinations are needed to improve benefit-risk profiles.[1-5]
- Relatlimab (RELA) is a human LAG-3-blocking antibody that restores the effector function of exhausted T cells (**Figure 1**).[6]

Figure 1. Mechanism of relatlimab in combination with nivolumab



- RELATIVITY-047, a global, randomized, double-blind, phase 2/3 study, met its primary endpoint of progression-free survival (PFS) (**Figure 2**).[7]
  - Nivolumab and relatlimab (NIVO + RELA) as a fixed-dose combination (FDC) demonstrated a significant PFS benefit, with a manageable safety profile, compared to NIVO alone in patients with previously untreated metastatic or unresectable melanoma.[7]

Figure 2. Primary endpoint: PFS by BICR[7]



Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3, *BRAF*, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: March 9, 2021.

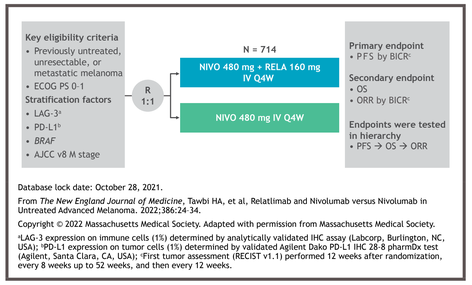
[a]Minimum potential follow-up (time from last patient randomized to last patient, last visit) was 1.3 months.

- Here we report updated PFS and the first results of secondary endpoints, overall survival (OS) and overall response rate (ORR).

Methods

- Patients were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg FDC or NIVO 480 mg alone, given intravenously every 4 weeks, as previously described (**Figure 3**).[7]
- The primary endpoint of PFS per RECIST v1.1 was assessed by blinded independent central review (BICR).
- Secondary endpoints were OS and ORR by BICR, to be tested hierarchically.

Figure 3. RELATIVITY-047 study design



Database lock date: October 28, 2021.

From *The New England Journal of Medicine*, Tawbi HA, et al, Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. 2022;386:24-34.

[a]LAG-3 expression on immune cells (1%) determined by analytically validated IHC assay (Labcorp, Burlington, NC, USA); [b]PD-L1 expression on tumor cells (1%) determined by validated Agilent Dako PD-L1 IHC 28-8 pharmDx test (Agilent, Santa Clara, CA, USA); [c]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks.

Results

Patients

- Baseline characteristics have been previously reported[7] and were balanced between treatment groups (**Table 1**).

Table 1. Baseline characteristics

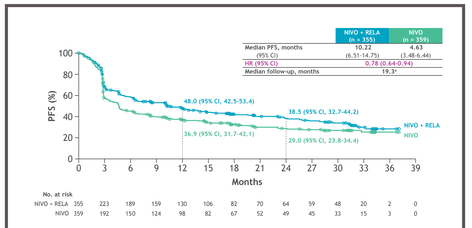
Characteristic	NIVO + RELA (n = 355)	NIVO (n = 359)	Total (N = 714)
Median age, years	63	62	63
Female, n (%)	145 (40.8)	153 (42.6)	298 (41.7)
AJCC v8 M stage, n (%)			
M1A	77 (21.7)	107 (29.8)	184 (25.8)
M1B	85 (23.9)	88 (24.5)	173 (24.2)
M1C	151 (42.5)	127 (35.4)	278 (38.9)
M1D	6 (1.7)	11 (3.1)	17 (2.4)
ECOG PS, n (%)			
0	236 (66.5)	242 (67.4)	478 (66.9)
1	119 (33.5)	117 (32.6)	236 (33.1)
Serum LDH level, n (%)			
> ULN	130 (36.6)	128 (35.7)	258 (36.1)
> 2 × ULN	32 (9.0)	31 (8.6)	63 (8.8)
Prior neoadjuvant/adjuvant,[a] n (%)	33 (9.3)	27 (7.5)	60 (8.4)
Tumor burden,[b] median (min-max), mm	59.0 (10-317)	54.5 (10-548)	-
Stratification factor, n (%)			
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			
Mutant	136 (38.3)	139 (38.7)	275 (38.5)
Wild-type	219 (61.7)	220 (61.3)	439 (61.5)
AJCC M stage			
M0/M1any[0][c]	232 (65.4)	237 (66.0)	469 (65.7)
M1any[1]d	123 (34.6)	122 (34.0)	245 (34.3)

[a]Most common therapy was interferon; [b]Sum of reference diameters of target lesions in mm; [c]AJCC M stage M0/M1any (LDH not elevated); [d]AJCC M stage M1any (elevated LDH).

Efficacy

- Updated median PFS was 10.2 mo (95% CI 6.5–14.8) with NIVO + RELA vs 4.6 mo (95% CI 3.5–6.4) with NIVO (HR 0.78 [95% CI 0.6–0.9]) (**Figure 4**).
  - PFS favored NIVO + RELA across stratification factors, including LAG-3 (1%) and PD-L1 (1%) expression (**Figure 5**).
- Median OS was not reached (NR) (95% CI 34.2–NR) with NIVO + RELA vs 34.1 mo (95% CI 25.2–NR) with NIVO (HR 0.80 [95% CI 0.6–1.0]; *P* = 0.0593) (**Figure 6**).
  - OS favored NIVO + RELA across stratification factors, including LAG-3 (1%) and PD-L1 (1%) expression (**Figure 7**).
- Subsequent systemic therapy rates and types were generally similar between treatment groups (**Table 2**).
- Confirmed ORR per BICR was 43.1% (95% CI 37.9–48.4) with NIVO + RELA vs 32.6% (95% CI 27.8–37.7) with NIVO (**Table 3**).

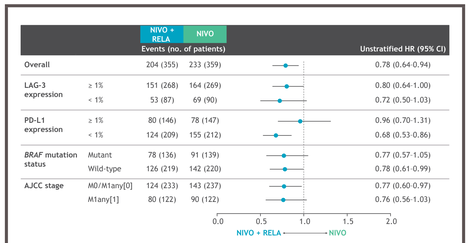
Figure 4. Updated PFS by BICR



Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF*, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: October 28, 2021.

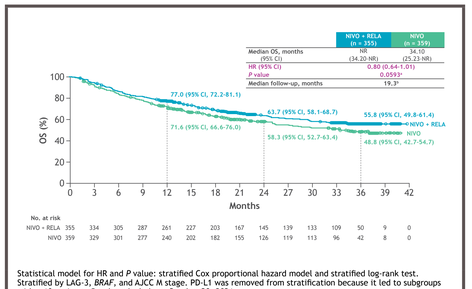
[a]Minimum potential follow-up (time from last patient randomized to last patient, last visit) was 8.7 months.

Figure 5. PFS across stratification factors



Exploratory/descriptive analyses. Database lock date: October 28, 2021. AJCC M stage for 1 patient was revised from M1any[1] to M0/M1any[0] between the database lock on March 9, 2021 and October 28, 2021, following correction of a rounding error.

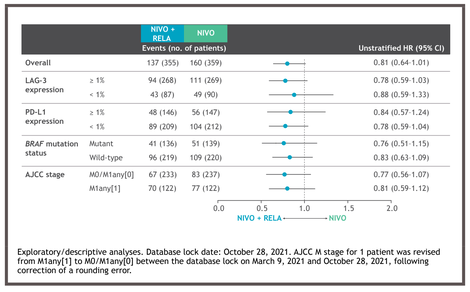
Figure 6. Secondary endpoint: overall survival



Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3, *BRAF*, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: October 28, 2021.

[a]OS boundary for statistical significance was *P* < 0.04302 (2-sided) analyzed at 69% power; target HR, 0.75; [b]Minimum potential follow-up (time from last patient randomized to last patient, last visit) was 8.7 months.

Figure 7. Overall survival across stratification factors



Exploratory/descriptive analyses. Database lock date: October 28, 2021. AJCC M stage for 1 patient was revised from M1any[1] to M0/M1any[0] between the database lock on March 9, 2021 and October 28, 2021, following correction of a rounding error.

Table 2. Subsequent therapy

Subsequent therapy	NIVO + RELA (n = 355)	NIVO (n = 359)
Any subsequent therapy,[a] n (%)	145 (40.8)	153 (42.6)
Systemic therapy	116 (32.7)	124 (34.5)
PD-(L)1 and/or CTLA-4 inhibitors	42 (11.8)	57 (15.9)
NIVO and ipilimumab	15 (4.2)	24 (6.7)
NIVO monotherapy	15 (4.2)	20 (5.6)
Ipilimumab monotherapy	13 (3.7)	19 (5.3)
Pembrolizumab monotherapy	6 (1.7)	10 (2.8)
Avelumab monotherapy	0	1 (0.3)
BRAF and/or *MEK* inhibitor therapies	44 (12.4)	53 (14.8)
Other	49 (13.8)	55 (15.3)
Radiotherapy[b]	52 (14.6)	44 (12.3)
Surgery[b]	25 (7.0)	29 (8.1)

Database lock date: October 28, 2021.

[a]Patients may have received > 1 subsequent therapy; [b]Radiotherapy and surgery subsequent therapies were allowed during study therapy.

Table 3. Secondary endpoint: confirmed ORR by BICR

Overall response	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR, n (%) 95% CI	153 (43.1) 37.9-48.4	117 (32.6) 27.8-37.7
Difference of ORR, % (95% CI)	10.3 (3.4-17.3)	
Odds ratio, (95% CI)	1.6 (1.2-2.2)	
Confirmed best overall response, n (%)		
Complete response	58 (16.3)	51 (14.2)
Partial response	95 (26.8)	66 (18.4)
Stable disease	61 (17.2)	59 (16.4)
Progressive disease	105 (29.6)	149 (41.5)
Unknown	27 (7.6)	28 (7.8)
DCR, n (%) 95% CI	223 (62.8) 57.6-67.9	182 (50.7) 45.4-56.0
Median DOR, months 95% CI	NR 29.57-NR	NR 29.93-NR

ORR could not be formally tested and was descriptively analyzed. Median follow-up, 19.3 months. Database lock date: October 28, 2021. Strata adjusted difference in ORR based on Cochran-Mantel-Haenszel method of weighting. Stratified by LAG-3, *BRAF*, AJCC M stage.

Safety

- Grade 3/4 treatment-related adverse events (TRAEs) were observed in 75 (21.1%) patients on NIVO + RELA and 40 (11.1%) on NIVO (**Table 4**).
- The most common categories of immune-mediated adverse events that occurred in the NIVO + RELA group were hypothyroidism or thyroiditis (18.6% of the patients), rash (11.0%), and diarrhea or colitis (7.0%) (**Table 5**).
  - Myocarditis (any grade) occurred in six (1.7%) patients with NIVO + RELA and two (0.6%) with NIVO. Troponin monitoring was performed for the first 2 months of treatment per protocol.

Table 4. Safety summary

Overall response	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	352 (99.2)	154 (43.4)	344 (95.8)	126 (35.1)
TRAE	297 (83.7)	75 (21.1)	260 (72.4)	40 (11.1)
Leading to discontinuation	54 (15.2)	32 (9.0)	26 (7.2)	13 (3.6)
TRAE ≥ 10%				
Pruritus	87 (24.5)	0	59 (16.4)	2 (0.6)
Fatigue	83 (23.4)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	55 (15.5)	0	46 (12.8)	0
Arthralgia	53 (14.9)	3 (0.8)	29 (8.1)	1 (0.3)
Diarrhea	53 (14.9)	4 (1.1)	36 (10.0)	2 (0.6)
Vitiligo	45 (12.7)	0	42 (11.7)	0
Treatment-related deaths[a]	4 (1.1)	0	2 (0.6)	0

Includes events reported between first dose and 30 days after last dose of study therapy. Other grade 3-4 TRAEs that were associated with any-grade TRAEs occurring in < 10% of patients not shown. Database lock date: October 28, 2021.

[a]Treatment-related deaths: NIVO + RELA (n = 4) - hemophagocytic lymphohistiocytosis, acute edema of the lung, pneumonitis, and multiorgan failure; NIVO (n = 2) - sepsis and myocarditis, and worsening pneumonia.

Table 5. Immune-mediated adverse events

Immune-mediated AE category,[a] n(%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3- 4
Hypothyroidism/thyroiditis	66 (18.6)	0	53 (14.8)	0
Rash	39 (11.0)	3 (0.8)	28 (7.8)	5 (1.4)
Diarrhea/colitis	25 (7.0)	5 (1.4)	12 (3.3)	5 (1.4)
Hyperthyroidism	23 (6.5)	0	25 (7.0)	0
Hepatitis	21 (5.9)	15 (4.2)	11 (3.1)	6 (1.7)
Adrenal insufficiency	19 (5.4)	6 (1.7)	4 (1.1)	0
Pneumonitis	14 (3.9)	2 (0.6)	7 (1.9)	2 (0.6)
Hypophysitis	10 (2.8)	2 (0.6)	4 (1.1)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	5 (1.4)	0	5 (1.4)	0

Database lock date: October 28, 2021.

[a]Includes AEs of any grade occurring in ≥ 1% of patients considered by investigators to be potentially immune-mediated that met the following criteria: occurred within 100 days of the last dose, regardless of causality; treated with immune-modulating medication with no clear alternate etiology; or had an immune-mediated component.

Conclusions

- RELATIVITY-047 met its primary endpoint and demonstrated a superior PFS benefit vs NIVO
  - NIVO + RELA continued to demonstrate consistent PFS benefit with longer follow-up
  - 22% reduction in risk of progression or death (HR, 0.78 [95% CI, 0.64-0.94])
- NIVO + RELA demonstrated a clinically meaningful improvement in OS (secondary endpoint), but was not statistically significant
  - 20% reduction in risk of death (HR, 0.80 [95% CI, 0.64-1.01]; *P* = 0.0593)
  - OS rates numerically improved at 12, 24, and 36 months vs NIVO alone
  - OS favored NIVO + RELA across stratification factors, including LAG-3 (1%) and PD-L1 (1%) expression
- NIVO + RELA showed increased ORR by BICR (secondary endpoint) vs NIVO alone
- NIVO + RELA had a manageable safety profile with no new or unexpected safety signals
- These data further validate NIVO + RELA as a potential new treatment option in patients with advanced melanoma and support the benefit of dual checkpoint inhibition

References

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Acknowledgments

- The patients and families who have made the study possible
- The clinical study teams who participated in this study
- Scientists who pioneered the research and discovery of LAG-3
- Dako, an Agilent Technologies, Inc. company (Santa Clara, CA, USA), for collaborative development of the PD-L1 IHC 28-8 pharmDx assay
- Labcorp (Burlington, NC, USA) for collaborative development of LAG-3 IHC assay, including analytical and clinical validations
- The study was supported by Bristol Myers Squibb
- All authors contributed to, and approved, the presentation; medical writing support and editing support were provided by Ryan Staudt, PhD, and Adam Paton, BA, of Complete HealthVizion, IPG Health Medical Communications, funded by Bristol Myers Squibb

Glossary

AE, adverse event
AJCC, American Joint Committee on Cancer
APC, antigen-presenting cell
CTLA-4, cytotoxic T lymphocyte antigen-4
DCR, disease control rate
DOR, duration of response
IHC, immunohistochemistry
LAG-3, lymphocyte-activation gene 3
LDH, lactate dehydrogenase
PD-1, programmed death-1
PD-L1/2, programmed death ligand 1/2
PS, performance status
R, randomization
TCR, T-cell receptor
ULN, upper limit of normal