RP1 Combined With Nivolumab in Advanced Anti–PD-1–Failed Melanoma (IGNYTE)

Michael K. Wong, MD, PhD, FRCPC[1]; Mohammed M. Milhem, MBBS[2]; Joseph J. Sacco, PhD, MBChB, FRCP[3,4]; Judith Michels, MD, PhD[5]; Gino K. In, MD, MPH[6]; Eva Muñoz Couselo, MD, PhD[7]; Dirk Schadendorf, MD[8]; Georgia M. Beasley, MD[9]; Jiaxin Niu, MD, PhD[10]; Bartosz Chmielowski, MD, PhD[11]; Trisha M. Wise-Draper, MD, PhD[12]; Tawnya Lynn Bowles, MD[13]; Katy K. Tsai, MD[14]; Céleste Lebbé, MD, PhD[15]; Caroline Gaudy-Marqueste, MD, PhD[16]; Mark R. Middleton, PhD, FRCP[17]; Aglaia Skolariki, MD[17]; Adel Samson, PhD, MBChB[18]; Jason A. Chesney, MD, PhD[19]; Ari M. VanderWalde, MD[20]; Yousef Zakharia, MD[2]; Kevin J. Harrington, PhD, MBBS[21]; Elizabeth Appleton, PhD, MBChB[21]; Praveen K. Bommareddy, PhD, MS, BPharm[22]; Junhong Zhu, PhD[22]; Marcus Viana, MD[22]; Jeannie W. Hou, MD[22]; Robert S. Coffin, PhD[22]; and Caroline Robert, MD, PhD[23]

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ABSTRACT

PURPOSE Effective treatment options for melanoma after immune checkpoint blockade failure are limited. RP1 (vusolimogene oderparepvec) is a herpes simplex virus type 1–based oncolytic immunotherapy, here evaluated in combination with nivolumab in anti–PD-1–failed melanoma.

METHODS Patients had advanced melanoma that had confirmed progression on anti–PD-1 (≥8 weeks, last prior treatment). RP1 was administered intratumorally (≤8 doses, ≤10 mL/dose; additional doses allowed) with nivolumab (≤2 years). The objective response rate (ORR) was assessed by independent central review using Response Evaluation Criteria in Solid Tumors version 1.1.

RESULTS Of 140 patients enrolled, 48.6% had stage IVM1b/c/d disease, 65.7% had primary anti–PD-1 resistance, 56.4% were PD-L1 negative, and 46.4% received prior anti–PD-1 and anti–cytotoxic T-lymphocyte antigen-4 therapy (43.6% in combination and 2.9% sequentially). Confirmed ORR (95% CI) was 32.9% (95% CI, 25.2% to 41.3%; 15.0% complete response). Responses occurred with similar frequency, depth, duration, and kinetics for injected and noninjected, including visceral lesions. The median (95% CI) duration of response was 33.7 (95% CI, 14.1 to not reached) months. Overall survival rates (95% CI) at 1 and 2 years were 75.3% (95% CI, 66.9% to 81.9%) and 63.3% (95% CI, 53.6% to 71.5%), respectively. Biomarker analysis demonstrated broad immune activation associated with response, including increased $CD8^+$ T-cell infiltration and PD-L1 expression. Treatment-related adverse event rates were 77.1% grade 1/2, 9.3% grade 3, 3.6% grade 4, and no grade 5 events.

CONCLUSION RP1 combined with nivolumab provided deep and durable systemic responses in patients with anti–PD-1–failed melanoma, including those with poor prognostic factors. The safety profile was favorable, with mostly grade 1/2 adverse events.

ACCOMPANYING CONTENT

Editorial, p. 3552, and understanding the pathway, p. 3622

Appendix

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have improved outcomes for patients with unresectable or metastatic melanoma.[1-3] However, primary resistance to anti–PD-1 therapy occurs in approximately 30%-50% of patients, with an additional 25% of patients developing secondary resistance.[4-8] Outcomes after progression on anti–PD-1 therapy remain poor, with a median overall survival (OS) of approximately 1 year in real-world clinical practice.[9,10] Subsequent treatment options are limited by patients' medical conditions, suboptimal efficacy, and/or toxicity.[11-15] Tumor-infiltrating lymphocyte therapy (lifileucel) is the only US Food and Drug Administration (FDA)–approved therapy for melanoma in patients previously treated with anti–PD-1 therapy[16,17] and provided an objective response rate (ORR) of 31.4%.[18] However, nearly all patients experienced grade 3/4 treatment-emergent adverse events,[18,19] and the treatment-related mortality rate was 7.5%.[17] Nivolumab plus ipilimumab is an alternative option, although the combination is also associated with high toxicity with grade ≥3 adverse events in 57% of patients.[20,21] BRAF/MEK

CONTEXT

Key Objective

This trial sought to determine the safety and efficacy of RP1 (vusolimogene oderparepvec) in combination with nivolumab in patients with advanced anti–PD-1–failed melanoma.

Knowledge Generated

RP1 combined with nivolumab demonstrated an objective response rate of 32.9% by RECIST 1.1, with reductions seen in both injected and noninjected lesions and a median duration of response of 33.7 months, with a 2-year survival of 63.3% in patients with advanced melanoma that had confirmed progression while being treated with an anti–PD-1–containing regimen. Treatment-related adverse events were primarily grade 1/2 with no treatment-related deaths.

Relevance *(G. McArthur)*

The RP1 oncolytic immunotherapy combined with nivolumab provides safe and effective activity in melanoma progressing on anti–PD-1–based therapy. If randomized trials demonstrate significant activity, this would be a new standard approach for these patients with high unmet need.*

*Relevance section written by *JCO* Associate Editor Grant McArthur, PhD, MBBS.

inhibition is an option for the approximately 50% of patients with *BRAF*-mutant melanoma, but responses may not be durable and treatment can diminish the response to subsequent immunotherapy[15,22,23]; additionally, grade ≥3 treatment-related adverse events (TRAEs) occur in up to 60% of patients on combination therapy.[22,23] Therefore, there is an unmet need for effective and less toxic therapies that provide clinically meaningful benefit for patients with anti–PD-1–progressed melanoma.

RP1 (vusolimogene oderparepvec) is a next-generation, replication-selective, oncolytic immunotherapy that is administered intratumorally. RP1 is engineered from a new clinical strain of herpes simplex virus type 1 (HSV-1) that was selected for its enhanced oncolytic activity. RP1 expresses granulocyte-macrophage colony-stimulating factor (GM-CSF) and the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R$^-$) to enhance direct oncolytic activity, promote immunogenic cell death, and increase the overall systemic antitumor effect.[24] Preclinical data demonstrated that RP1 provides antitumor activity in both injected and noninjected tumors, which is enhanced through the inclusion of GALV-GP-R$^-$ and further increased in combination with anti–PD-1 therapy.[24,25] RP1 was designed to provide enhanced clinical efficacy compared with talimogene laherparepvec (T-VEC), the first FDA-approved oncolytic immunotherapy,[26] in particular through the multimodal activity of GALV-GP-R$^-$ to increase both direct tumor killing and the immunogenicity of tumor cell death. T-VEC, which is also an HSV-based oncolytic immunotherapy, received approval in melanoma based on data from anti–PD-1–naïve patients,[27] but subsequent studies in patients with melanoma that progressed on anti–PD-1 therapy demonstrated only limited activity outside of disease that had progressed on or after adjuvant anti–PD-1 therapy.[28,29]

IGNYTE is a phase I/II clinical trial evaluating the safety and efficacy of RP1 as monotherapy or in combination with nivolumab in patients with advanced tumors. Here, we report data from the registrational phase II cohort of patients with advanced melanoma with confirmed progression while being treated with an anti–PD-1–containing regimen.

METHODS

Patients

Patients age ≥18 years with unresectable stage IIIB-IV cutaneous melanoma were eligible if they had confirmed progression while being treated for ≥8 weeks with anti–PD-1 alone or combined with another anticancer therapy, including in the adjuvant setting, as their last prior therapy. At least one measurable tumor per RECIST 1.1 and injectable lesions comprising ≥1 cm in the longest diameter were required. Key exclusion criteria included prior oncolytic therapy, current antiviral therapy, or a history of serious complications from ICI therapy.

Study Design and Treatment

The registration-intended cohort assessed RP1 combined with nivolumab in patients with advanced melanoma and confirmed progression while being treated with a prior anti–PD-1–containing regimen. Patients received an initial intratumoral dose of RP1 (1×10^6 plaque-forming units [PFU]/mL; each dose ≤10 mL), followed by up to seven additional doses at 1×10^7 PFU/mL every 2 weeks. Nivolumab (240 mg once every 2 weeks) was initiated with the second dose of RP1 for up to eight cycles and then continued at 480 mg once every 4 weeks for up to an additional 21 cycles. Nivolumab was given within a ± 2-day window of each dose

TABLE 1. Baseline Characteristics

Characteristic	All Patients (N = 140)
Age, years, median (range)	62.0 (21.0-91.0)
≥65	57 (40.7)
Male sex	95 (67.9)
White race	103 (73.6)
Stage	
IIIB/IIIC/IVM1a	72 (51.4)
IVM1b/c/d	68 (48.6)
BRAF status	
Wild-type *BRAF*	87 (62.1)
Mutant *BRAF*	53 (37.9)
LDH level	
LDH ≤ULN	92 (65.7)
LDH >ULN	47 (33.6)
LDH ≥2 × ULN	9 (6.4)
LDH unknown	1 (0.7)
PD-L1 tumor expression	
Positive (≥1%)	44 (31.4)
Negative (<1%)	79 (56.4)
Undetermined or missing	17 (12.1)
Prior therapy	
Anti–PD-1	
Anti–PD-1 only as adjuvant therapy	36 (25.7)
Anti–PD-1 other than as adjuvant therapy	104 (74.3)
Anti–CTLA-4	
Anti–PD-1 combined with anti–CTLA-4	61 (43.6)
Anti–PD-1 treated with anti–CTLA-4 sequentially	4 (2.9)
Wild-type *BRAF* and received combination anti–PD-1 and anti–CTLA-4	37 (26.4)
Received BRAF/MEK therapy	17 (12.1)
Other disease characteristics	
Primary resistance to prior anti–PD-1[a]	92 (65.7)
Secondary resistance to prior anti–PD-1[b,c]	48 (34.3)

NOTE. Data are presented as No. (%) unless otherwise indicated.
Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a]Primary resistance was defined as progression within 6 months of starting the immediate prior course of anti–PD-1 therapy.[30]
[b]Secondary resistance was defined as progression after 6 months of starting the immediate prior course of anti–PD-1 therapy.[30]
[c]Includes one patient with unknown resistance status.

of RP1. RP1 was directly injected into superficial lesions and/or into deeper lesions using appropriate imaging guidance. Multiple lesions, including both superficial and deep lesions (up to the 10-mL maximum allowable dose), could be injected on each treatment day and different lesions could be injected on different treatment occasions. Additional doses of RP1 beyond eight could be given if clinically indicated (Data Supplement and Fig S1). This study was registered with EudraCT (number 2016-004548-12) before enrollment of the first patient and subsequently registered with ClinicalTrials.gov (identifier: NCT03767348).

End Points

The primary end point of the registration-intended cohort was ORR using a modified RECIST 1.1 (mRECIST) by blinded independent central review (BICR). The key modification of mRECIST was that progression needed to be confirmed by further tumor increase to allow for the potential of pseudoprogression. ORR was also analyzed using RECIST 1.1 by BICR to allow better comparison with other clinical trials. Secondary end points included duration of response (DOR), complete response (CR) rate, and progression-free survival (PFS), each by BICR, and 1- and 2-year OS. Responses of injected and noninjected lesions, biomarker analysis of tumor biopsies, and clinical subgroup analyses were exploratory and are detailed in the Data Supplement. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Study Oversight

The study protocol was approved by institutional review boards or independent ethics committees at each participating site and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and in compliance with Good Clinical Practice. All patients provided written informed consent before enrollment. The investigators collected data, which were analyzed by statisticians employed by the study sponsor.

Statistical Analysis

A sample size of 125 patients was estimated to provide >97% power to reject the null hypothesis of an ORR <15% (given a two-sided 5% or one-sided 2.5% alpha), which would not be considered clinically relevant. The sample size was also considered to provide sufficient characterization of the safety profile. For the primary efficacy analysis of ORR, the point estimate and the two-sided 95% Clopper-Pearson exact CI were computed. The DOR, PFS, and OS were estimated using Kaplan-Meier methodology. Exploratory analyses and safety data were summarized descriptively.

RESULTS

Patient Baseline Clinical Characteristics

A total of 140 patients with anti–PD-1–failed melanoma were enrolled and treated with RP1 combined with nivolumab (Data Supplement, Fig S2). The cutoff date for the primary data analysis reported here was March 8, 2024, when all patients had the potential for at least 12 months of follow-up. The median (range) age was 62.0 (21.0-91.0) years, 67.9% of patients were male, and 73.6% were White

TABLE 2. BOR Among All Patients and Across Subgroups by Blinded Independent Central Review Using RECIST 1.1

		Prior Anti–PD-1		Stage		Anti–PD-1 Resistance		Anti–PD-1 Adjuvant		*BRAF*		PD-L1 Expression[a]	
BOR	All Patients (N = 140)	Without Anti–CTLA-4[b] (n = 75)	With Anti–CTLA-4 (n = 65)	IIIB/IIIC/ IVM1a (n = 72)	IVM1b/c/d (n = 68)	Primary (n = 92)	Secondary (n = 48)[c]	Yes (n = 36)	No (n = 104)	Mut (n = 53)	WT (n = 87)	Pos. (n = 44)	Neg. (n = 79)
CR, No. (%)	21 (15.0)	16 (21.3)	5 (7.7)	17 (23.6)	4 (5.9)	16 (17.4)	5 (10.4)	11 (30.6)	10 (9.6)	8 (15.1)	13 (14.9)	11 (25.0)	10 (12.7)
PR, No. (%)	25 (17.9)	13 (17.3)	12 (18.5)	12 (16.7)	13 (19.1)	16 (17.4)	9 (18.8)	5 (13.9)	20 (19.2)	10 (18.9)	15 (17.2)	12 (27.3)	9 (11.4)
SD, No. (%)	31 (22.1)	16 (21.3)	15 (23.1)	17 (23.6)	14 (20.6)	15 (16.3)	16 (33.3)	8 (22.2)	23 (22.1)	17 (32.1)	14 (16.1)	7 (15.9)	19 (24.1)
PD, No. (%)	54 (38.6)	28 (37.3)	26 (40.0)	25 (34.7)	29 (42.6)	39 (42.4)	15 (31.3)	11 (30.6)	43 (41.3)	15 (28.3)	39 (44.8)	11 (25.0)	36 (45.6)
NE, No. (%)	9 (6.4)	2 (2.7)	7 (10.8)	1 (1.4)	8 (11.8)	6 (6.5)	3 (6.3)	1 (2.8)	8 (7.7)	3 (5.7)	6 (6.9)	3 (6.8)	5 (6.3)
ORR (95% CI)	32.9 (25.2 to 41.3)	38.7 (27.6 to 50.6)	26.2 (16.0 to 38.5)	40.3 (28.9 to 52.5)	25.0 (15.3 to 37.0)	34.8 (25.1 to 45.4)	29.2 (17.0 to 44.1)	44.4 (27.9 to 61.9)	28.8 (20.4 to 38.6)	34.0 (21.5 to 48.3)	32.2 (22.6 to 43.1)	52.3 (36.7 to 67.5)	24.1 (15.1 to 35.0)

Abbreviations: BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen 4; Mut, mutant; NE, not evaluable; Neg, negative; ORR, objective response rate; PD, progressive disease; Pos, positive; PR, partial response; SD, stable disease; WT, wild-type.

[a]There were 17 patients with unknown PD-L1 expression status.

[b]Includes 66 patients receiving anti–PD-1 as monotherapy (ORR 40.9%, CR rate 22.7%). Nine patients received anti–PD-1 in combination with other therapeutic agents.

[c]Includes one patient with unknown resistance status.

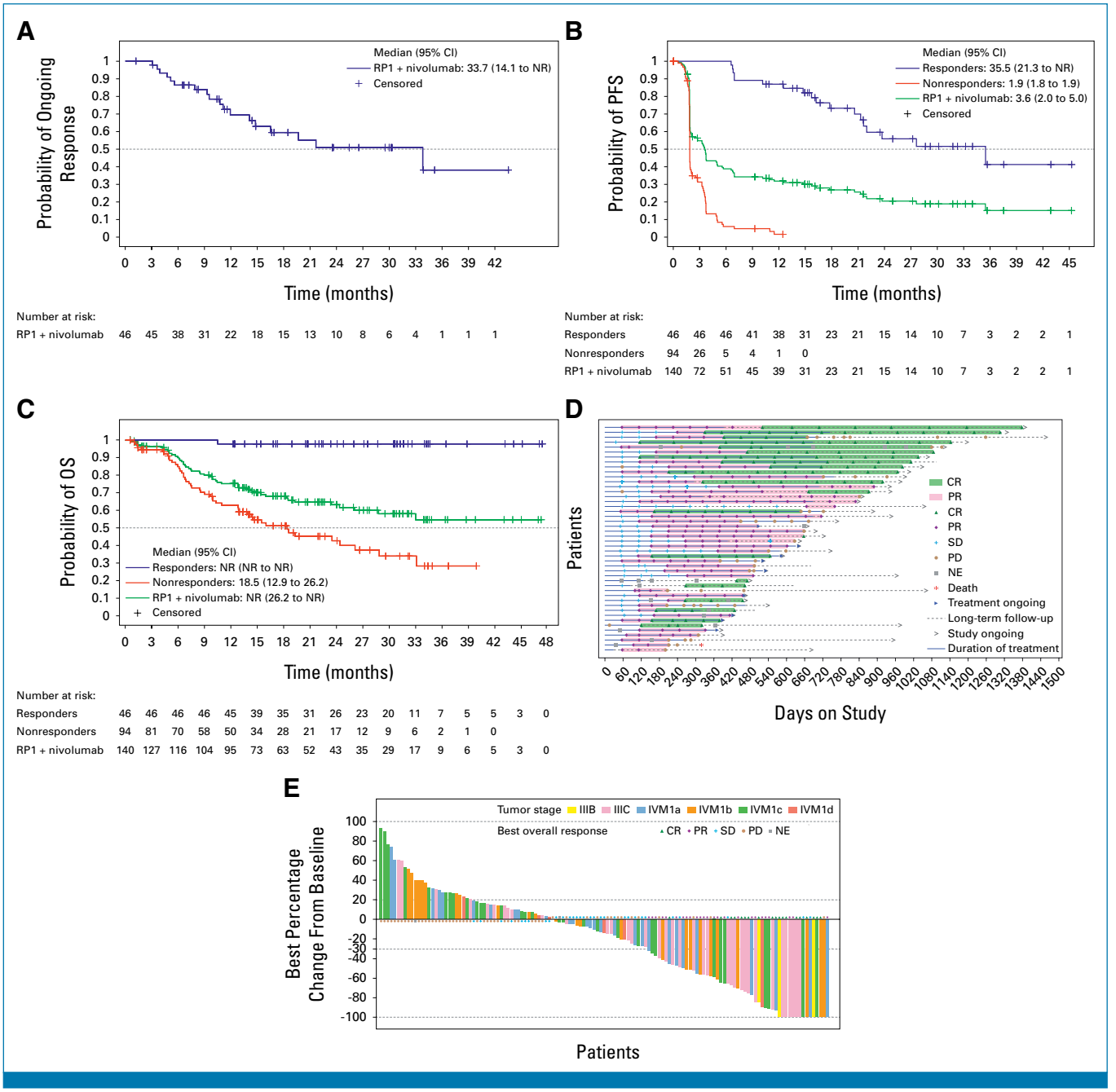

FIG 1. Duration of response and survival outcomes for RP1 combined with nivolumab. (A) Duration of response by RECIST 1.1. (B) PFS for all patients and according to response subgroup (responders and nonresponders) by RECIST 1.1. (C) OS for all patients and according to response subgroup (responders and nonresponders). (D) Clinical course for all responding patients. (E) Percentage change from baseline in target lesions for all patients measured by BICR. Patients who did not have target lesions measured at baseline and/or post-baseline are not included in the figure. BICR, blinded independent central review; CR, complete response; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

(Table 1). Primary resistance (defined as progression within 6 months of starting the prior course of anti–PD-1 therapy[30]) had occurred in 65.7% of patients and secondary resistance (progression after 6 months of prior anti–PD-1 therapy[30]) in 34.3% of patients. The median (range) duration of the immediate prior anti–PD-1 therapy was 4.6 (1.0-55.2) months. Overall, 46.4% of patients received prior anti–PD-1 therapy either in combination (43.6%) or sequentially (2.9%) with anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) therapy, 48.6% of patients had stage IVM1b/c/d disease, 37.9% had *BRAF*-mutant tumors, 33.6% had a lactate dehydrogenase (LDH) level greater than the upper limit of normal (ULN), and 56.4% had PD-L1–negative (<1%) tumors. A summary of the RP1 volume administered in the initial course is detailed in the Data Supplement (Table S1).

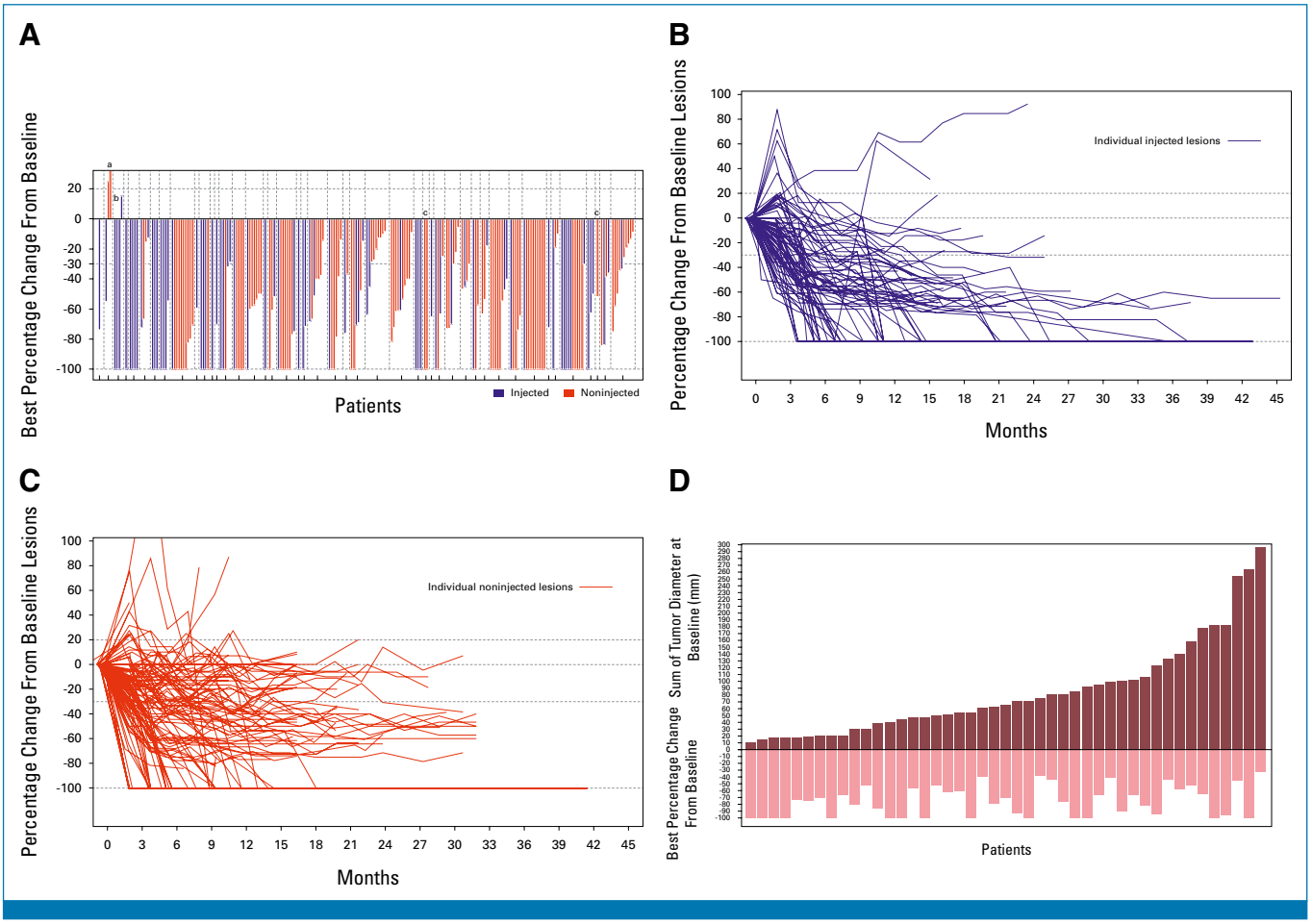

FIG 2. Tumor reduction among responding patients by RECIST 1.1. (A) Best percentage change in individual injected and noninjected lesions from baseline, (B) change in size of individual injected lesions over time, (C) change in size of individual noninjected lesions over time, and (D) overall baseline tumor burden and best reduction in tumor burden. (A) [a]Patient had a CR as a radical resection of all three lesions on the skin of the left foot confirmed full regression; [b]the sum of diameters of four target lesions met the criteria for a PR; and [c]the patient only had noninjected lesions measured. (A and D), One patient was not included because lesions were not measurable by BICR. (B and C) All measurable lesions were measured by BICR for each patient with a best response of confirmed CR or PR by RECIST 1.1. (D) Total tumor burden was plotted above the line for each patient (maroon bars) with percent reduction in tumor burden plotted below the line (pink bars). BICR, blinded independent central review; CR, complete response; PR, partial response.

Clinical Efficacy

The median (range) follow-up at the primary analysis was 15.5 (0.5-47.6) months, with all patients having the potential to be followed for at least 12 months. The median (range) time to response was 4.5 (1.7-21.9) months. Among all patients (N = 140), the ORR (95% CI) was 33.6% (95% CI, 25.8% to 42.0%) by mRECIST (the primary end point) and 32.9% (95% CI, 25.2% to 41.3%) by RECIST 1.1, both according to BICR. The additional end points and analyses are reported here using RECIST 1.1 to allow better comparison with other clinical trials. By RECIST 1.1, the CR rate (95% CI) was 15.0% (95% CI, 9.5% to 22.0%; Table 2), and the median (95% CI) DOR was 33.7 (14.1 to not reached [NR]) months (Fig 1A) with 69.5% of responses ongoing at 1 year after response initiation. The median (95% CI) PFS for all patients was 3.6 (95% CI, 2.0-5.0) months, with 35.5 (95% CI, 21.3 to NR) months for responders and 1.9 (95% CI, 1.8-1.9) months for nonresponders (Fig 1B). The 1- and 2-year OS rates (95% CI) were 75.3% (95% CI, 66.9% to 81.9%) and 63.3% (95% CI, 53.6% to 71.5%), respectively, with the median OS NR. The median (95% CI) OS was NR (95% CI, NR to NR) for responders and 18.5 (95% CI, 12.9-26.2) months for nonresponders (Fig 1C). The overall clinical course for responders is shown in Figure 1D. A waterfall plot showing the overall reduction in target tumor burden is shown in Figure 1E.

Responses in Injected and Noninjected Lesions

Responses occurred among both injected and noninjected lesions (Data Supplement, Fig S3) with a similar frequency, depth, durability, and kinetics, including noninjected lesions in visceral organs (Figs 2A-2C). Among RECIST 1.1 responders, there was a ≥30% reduction in 93.6% (73/78) of injected lesions and 79.0% (94/119) of noninjected lesions

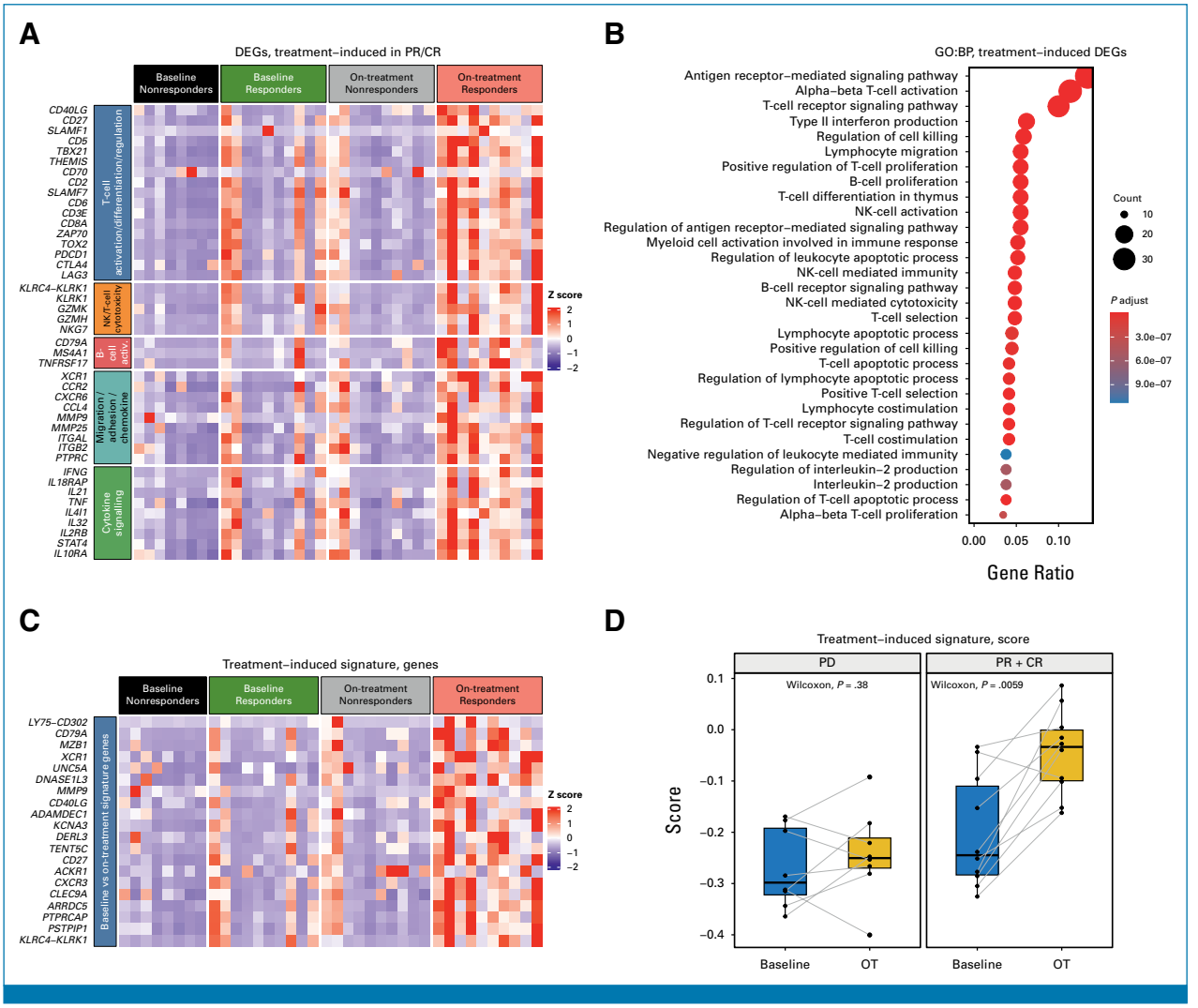

FIG 3. RNA Sequencing–Based Biomarker Analysis. (A) Heatmap demonstrating relative gene expression of selected DEGs between baseline and on-treatment (day 43) tumor samples in responders, representing diverse immune activation, including T, B, and NK cells, cell adhesion, and cytokine/chemokine signaling; each column represents an individual patient. (B) GO:BP terms enriched with genes differentially upregulated between baseline and on-treatment samples in responders. (C) Heatmap demonstrating relative gene expression of treatment-induced signature genes (P adj <.05, $\log_2$FC >1.5). (D) Treatment-induced signature gene score in pretreatment versus on-treatment samples in groups by response. activ, activation; CR, complete response; DEG, differentially expressed gene; GO:BP, Gene Ontology: Biological Processes; NK, natural killer; OT, on-treatment; PD, progressive disease; PR, partial response.

(Figs 2A-2C and Data Supplement, Table S2). Pseudoprogression (initial tumor increase before response) was frequently seen in both the injected and noninjected lesions of responding patients (Figs 2B and 2C). Of the 52 noninjected visceral organ lesions in responding patients (including in the lung and liver), 96.2% showed any reduction from baseline, with 65.4% reduced by ≥30% (Data Supplement, Table S3). Responses were also observed irrespective of injection route, with a 29.8% ORR following only superficial injection, a 40.9% ORR for only deep/visceral injections, and a 42.9% ORR for patients receiving both superficial and deep/visceral injections (Data Supplement, Table S4). Response was also independent of baseline tumor burden (Fig 2D).

Subgroup Analyses

The ORR by BICR using RECIST 1.1 was also assessed across clinical subgroups (Table 2). The ORR (95% CI) was 26.2% (95% CI, 16.0% to 38.5%) in patients having prior anti–PD-1 and anti–CTLA-4 therapy, 34.8% (95% CI, 25.1% to 45.4%) for patients with primary anti–PD-1 resistance, and 29.2% (95% CI, 17.0% to 44.1%) for those with secondary anti–PD-1 resistance. The ORR (95% CI) was 44.4% (95% CI, 27.9% to 61.9%) for patients who received anti–PD-1 in the adjuvant setting and 28.8% (95% CI, 20.4% to 38.6%) for patients who received nonadjuvant anti–PD-1. The ORR (95% CI) was 25.0% (95% CI, 15.3% to 37.0%) for stage IVM1b/c/d disease and 34.0% (95% CI, 21.5% to 48.3%) for *BRAF*-mutant

TABLE 3. Treatment-Related Adverse Events

Event	All Patients (N = 140)	
	Any Grade, No. (%)	Grade ≥3, No. (%)
Any TRAEs	126 (90.0)	18 (12.9)
TRAEs occurring in ≥5% of patients		
Fatigue	46 (32.9)	1 (0.7)
Chills	45 (32.1)	0
Pyrexia	43 (30.7)	0
Nausea	31 (22.1)	0
Influenza-like illness	25 (17.9)	0
Injection-site pain	21 (15.0)	0
Diarrhea	20 (14.3)	1 (0.7)
Vomiting	19 (13.6)	0
Headache	18 (12.9)	0
Pruritus	18 (12.9)	0
Asthenia	14 (10.0)	1 (0.7)
Arthralgia	10 (7.1)	1 (0.7)
Decreased appetite	9 (6.4)	1 (0.7)
Myalgia	9 (6.4)	0
Cough	8 (5.7)	0
Rash	8 (5.7)	0
Injection-site reaction	7 (5.0)	0
Vitiligo	7 (5.0)	0

NOTE. TRAEs were graded according to CTCAE version 5.0.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; TRAE, treatment-related adverse event.

tumors versus 32.2% (95% CI, 22.6% to 43.1%) for *BRAF* wild-type tumors. The ORR was 25.5% (95% CI, 13.9% to 40.3%) for patients with LDH levels >ULN versus 35.9% (95% CI, 26.1% to 46.5%) for LDH levels ≤ULN and 24.1% (95% CI, 15.1% to 35.0%) for patients with PD-L1–negative tumors versus 52.3% (95% CI, 36.7% to 67.5%) for those with PD-L1–positive tumors. Similar subgroup response rates were observed according to BICR using mRECIST (Data Supplement, Table S5).

Biomarkers

Tumors were biopsied at screening or on day 1 and day 43. Immunohistochemistry for available biopsies demonstrated increased $CD8^+$ T-cell infiltration with a higher $CD8^+$ T-cell score in 37 of 78 (47.4%) samples and increased PD-L1 expression in 39 of 68 (57.4%) samples at day 43 relative to baseline (Data Supplement, Fig S4). Differential gene expression between 10 responders (five CR and five partial response) and nine nonresponders (best response of progressive disease) was analyzed using RNA sequencing. A total of 313 genes were significantly upregulated in responders (adjusted $P<.05$, logFC >1) versus only five genes in nonresponders compared with their respective baseline. These differentially expressed genes (DEGs) included a wide range of genes encompassing T-cell, B-cell, and natural killer–cell function, as well as chemokine and cytokine signaling. The 313 upregulated DEGs in responders were not significantly changed in nonresponders (Fig 3A). Gene set enrichment analysis further confirmed the diversity of the immune pathways involved (Fig 3B). We then generated an unbiased signature using the DEGs from responders with the highest fold change (log_2FC >1.5, excluding T-cell receptor and immunoglobulin genes; Fig 3C); the expression of genes was more commonly differentially represented in responders compared with baseline (Fig 3D). The treatment-induced gene signature among responders suggests that the induction of a diverse, antiviral-type immune signature may contribute to responsiveness to RP1 therapy. These data further support the immune-mediated mechanism of action of RP1, with the increased expression of immune-related genes being associated with response to treatment, a pattern not observed in nonresponding patients.

Safety

Overall, 90.0% (126/140) of patients experienced at least one TRAE of any grade and 12.9% (18/140) experienced a grade 3/4 TRAE (3.6% grade 4; Table 3 and Data Supplement, Table S6). The most common all-grade TRAEs occurring in >20% of patients were fatigue (32.9%), chills (32.1%), pyrexia (30.7%), and nausea (22.1%). Hypophysitis and rash maculopapular were the only grade 3 TRAEs to occur in more than one patient (n = 2 each). In total, there were five grade 4 TRAEs (cytokine release syndrome, hepatic cytolysis, lipase increased, myocarditis, and splenic rupture [n = 1 each]). No treatment-related deaths were observed.

DISCUSSION

The introduction of ICIs has greatly improved outcomes for patients with advanced melanoma.[1–3] However, many patients experience disease progression on anti–PD-1 therapy given as monotherapy or in combination with other ICIs.[4,5,31] The prognosis after progression remains poor, with a median OS of approximately 1 year,[9,10] and available treatment options have significant limitations. Lifileucel, the only FDA-approved therapy after anti–PD-1 therapy,[16] requires strict patient selection criteria[32] and is associated with significant toxicity.[18,19] Additionally, the efficacy of combined anti–PD-1 and anti–CTLA-4 therapy is limited in this setting, and 57% of patients with anti–PD-1/PD-L1–refractory melanoma given this combination experience grade ≥3 TRAEs.[21] In this study, RP1 combined with nivolumab provided clinically meaningful rates and durability of response when evaluated in the context of historical data for patients with advanced melanoma that progressed on treatment with anti–PD-1 alone or combined with anti–CTLA-4. Approximately one in three patients had a confirmed objective response by RECIST 1.1 (32.9%) and 15.0% had a CR. Although CR rates were notably higher among patients with stage III–IVM1a disease (23.6%) versus stage IVM1b–d disease (5.9%), this is not surprising given that CRs with approved therapies are uncommon among patients

with more advanced disease, even in the first-line setting. The median DOR was 33.7 months, and more than 50% of responses were maintained at 2 years. The median OS was NR. Clinically meaningful rates of response were also observed across all subgroups analyzed, including those with poorer prognoses. This included an ORR of at least 25% in patients with melanoma that progressed on both prior anti–PD-1 and anti–CTLA-4 therapy and in stage IVM1b/c/d, primary resistant, and PD-L1–negative disease. Responses of injected and noninjected, including distant and visceral, lesions were seen with similar frequency, depth, duration, and kinetics, demonstrating a durable, systemic benefit.

The IGNYTE clinical trial was a single-arm study, and the results should therefore be contextualized with historical data for patients with melanoma that progressed while being treated with anti–PD-1 therapy. Previous studies have shown that only 6% to 7% of patients are expected to respond to continued anti–PD-1 monotherapy after confirmed progression on an anti–PD-1–containing regimen.[33] An ORR of 32.9% with 69.5% of responses ongoing for at least 1 year demonstrates a clear benefit of RP1 combined with nivolumab compared with expectations for nivolumab alone. RP1 combined with nivolumab also demonstrated a favorable safety profile, with generally transient grade 1/2 TRAEs consistent with systemic immune activation. There was a low incidence of grade 3/4 TRAEs (12.9%) with 3.6% being grade 4. The safety profile of RP1 combined with nivolumab generally overlapped with that of nivolumab monotherapy[3,7] and demonstrated no evidence of additive toxicity. Hence, the safety profile of RP1 combined with nivolumab compares favorably with lifileucel or the combination of anti–PD-1 and anti–CTLA-4 that may be used following anti–PD-1 therapy.[19–21,32]

RP1 is unique and distinct from previous oncolytic immunotherapies. RP1 was constructed from a new clinical isolate of HSV-1 selected for its enhanced ability to kill a range of human tumor cell lines[24] and encodes the transgenes for GM-CSF and GALV-GP-R$^-$. Expression of GALV-GP-R$^-$ is unique to RP1 and enhances tumor killing by causing cell-to-cell fusion, the primary effect of which is to greatly increase immunogenic cell death and thereby enhance systemic immune activation (shown in preclinical models),[24] which is further enhanced when combined with immune checkpoint blockade.[24] Consistent with preclinical data and the intended mechanism of action of RP1, biomarker data from patients in the IGNYTE study demonstrated broad-spectrum immune activation after treatment with RP1 combined with nivolumab in responding patients, which was not seen in nonresponders. This supports the hypothesis that the induction of an immune-inflamed tumor microenvironment by RP1 is critical for achieving the responses observed.

The key limitation of this study is the single-arm study design. The rationale for conducting this phase II study as a single-arm trial was based on ethical and practicality considerations, stemming from the lack of a well-established standard of care in this patient population to serve as a control arm. Based on the results of this phase II study, a randomized phase III confirmatory study evaluating RP1 combined with nivolumab versus treatment of physician's choice in patients with unresectable or metastatic melanoma that has progressed on anti–PD-1 and anti–CLTA-4 therapy is underway and enrolling (IGNYTE-3; NCT06264180).

In conclusion, RP1 combined with nivolumab demonstrated clinically meaningful and durable responses with a favorable safety profile in patients with advanced melanoma that progressed while being treated with an anti–PD-1–containing regimen.

AFFILIATIONS

[1]Roswell Park Comprehensive Cancer Center, Buffalo, NY
[2]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA
[3]The Clatterbridge Cancer Centre, Wirral, United Kingdom
[4]University of Liverpool, Liverpool, United Kingdom
[5]Département de Médecine Oncologique, Gustave Roussy, Villejuif, France
[6]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA
[7]Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron Hospital Medical Oncology Department, Barcelona, Spain
[8]Department of Dermatology, West German Cancer Center, University Hospital Essen, Essen & National Center for Tumor Diseases (NCT-West), Campus Essen & University Alliance Ruhr, Research Alliance Ruhr, Research Center One Health, University Duisburg-Essen, Campus Essen, Germany
[9]Duke Cancer Institute, Duke University, Durham, NC
[10]Banner MD Anderson Cancer Center, Gilbert, AZ
[11]Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA
[12]University of Cincinnati Cancer Center, University of Cincinnati, Cincinnati, OH
[13]Intermountain Medical Center, Murray, UT
[14]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA
[15]Université Paris Cité, AP-HP Dermato-Oncology and CIC, Cancer Institute APHP. Nord–Université Paris Cité, INSERM U976, Saint Louis Hospital, Paris, France
[16]Aix-Marseille Université, APHM, Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM, U1068, CNRS, UMR7258, UM105, Hôpital Timone, CEPCM, Dermatology and Skin Cancer Department, Marseille, France
[17]Churchill Hospital and University of Oxford, Oxford, United Kingdom
[18]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, United Kingdom
[19]James Graham Brown Cancer Center, University of Louisville, Louisville, KY
[20]West Cancer Center and Research Institute, Germantown, TN
[21]The Institute of Cancer Research/Royal Marsden NIHR Biomedical Research Centre, London, United Kingdom
[22]Replimune, Inc, Woburn, MA

[23]Gustave Roussy and Paris-Saclay University, Villejuif, France

CORRESPONDING AUTHOR

Michael K. Wong, MD, PhD, FRCPC; e-mail: Michael.Wong@RoswellPark.org.

EQUAL CONTRIBUTION

M.K.W. and M.M.M. are co-first authors.

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AUTHOR CONTRIBUTIONS

Conception and design: Michael K. Wong, Mohammed M. Milhem, Joseph J. Sacco, Bartosz Chmielowski, Mark R. Middleton, Ari M. VanderWalde, Kevin J. Harrington, Praveen K. Bommareddy, Junhong Zhu, Jeannie W. Hou, Robert S. Coffin, Caroline Robert
Administrative support: Dirk Schadendorf, Marcus Viana
Provision of study materials or patients: Michael K. Wong, Mohammed M. Milhem, Joseph J. Sacco, Judith Michels, Gino K. In, Dirk Schadendorf, Georgia M. Beasley, Jiaxin Niu, Trisha M. Wise-Draper, Tawnya Lynn Bowles, Katy K. Tsai, Céleste Lebbé, Caroline Gaudy-Marqueste, Mark R. Middleton, Aglaia Skolariki, Adel Samson, Jason A. Chesney, Kevin J. Harrington, Caroline Robert
Collection and assembly of data: Michael K. Wong, Joseph J. Sacco, Judith Michels, Gino K. In, Dirk Schadendorf, Georgia M. Beasley, Bartosz Chmielowski, Katy K. Tsai, Céleste Lebbé, Caroline Gaudy-Marqueste, Mark R. Middleton, Aglaia Skolariki, Adel Samson, Jason A. Chesney, Yousef Zakharia, Kevin J. Harrington, Elizabeth Appleton, Praveen K. Bommareddy, Junhong Zhu, Marcus Viana, Jeannie W. Hou, Robert S. Coffin, Caroline Robert
Data analysis and interpretation: Michael K. Wong, Mohammed M. Milhem, Joseph J. Sacco, Judith Michels, Gino K. In, Eva Muñoz Couselo, Dirk Schadendorf, Georgia M. Beasley, Jiaxin Niu, Bartosz Chmielowski, Trisha M. Wise-Draper, Tawnya Lynn Bowles, Katy K. Tsai, Céleste Lebbé, Caroline Gaudy-Marqueste, Mark R. Middleton, Adel Samson, Jason A. Chesney, Ari M. VanderWalde, Yousef Zakharia, Kevin J. Harrington, Elizabeth Appleton, Praveen K. Bommareddy, Junhong Zhu, Marcus Viana, Jeannie W. Hou, Robert S. Coffin, Caroline Robert
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Michael K. Wong
Consulting or Advisory Role: Regeneron, Castle Biosciences, Replimune, Sun Pharma

Mohammed M. Milhem
Research Funding: Amgen (Inst), Novartis (Inst), Merck (Inst), Pfizer (Inst), E.R. Squibb Sons, LLC (Inst), Prometheus (Inst)

Joseph J. Sacco
Honoraria: Immunocore
Consulting or Advisory Role: Immunocore (Inst), MSD, BMS, Immunocore
Research Funding: AstraZeneca (Inst), Immunocore (Inst), Replimune (Inst), BMS (Inst)
Travel, Accommodations, Expenses: BMS, MSD

Judith Michels
Consulting or Advisory Role: GlaxoSmithKline, Regeneron Pharmaceuticals, Inc;
Research Funding: Merck (Inst)
Travel, Accommodations, Expenses: Merck, Merck

Gino K. In
Honoraria: Array BioPharma/Pfizer, regeneron, Bristol Myers Squibb, Sanofi, Pfizer
Consulting or Advisory Role: Bristol Myers Squibb, Castle Biosciences, Novartis, Sanofi, Pfizer, Replimune
Speakers' Bureau: Merck, Rockpointe CME, Regeneron, Targeted Oncology
Research Funding: Regeneron (Inst), Xencor (Inst), Checkmate Pharmaceuticals (Inst), Replimune (Inst), Instil Bio (Inst), Idera (Inst), Iovance Biotherapeutics (Inst), Pfizer (Inst), Bicara Therapeutics (Inst), Obsidian Therapeutics (Inst), Merck (Inst), Immunocore (Inst), Georgiamune (Inst)
Travel, Accommodations, Expenses: Regeneron, Bristol Myers Squibb/Pfizer, Pfizer

Eva Muñoz Couselo
Honoraria: BMS, Novartis, Pierre Fabre, MSD, Regeneron, Immunocore
Consulting or Advisory Role: Bristol Myers Squibb/Celgene, Novartis, Pierre Fabre, MSD, Sanofi, Regeneron, Immunocore, Menarini
Speakers' Bureau: Bristol Myers Squibb/Celgene, Pierre Fabre, Sanofi, MSD, Novartis

Dirk Schadendorf
Honoraria: Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Immunocore, Merck Serono, Pfizer, Pierre Fabre, Philogen, Regeneron, NeraCare GmbH, Sun Pharma, InflarxGmbH, Daiichi Sankyo Japan, LabCorp, Replimune, Agenus, AstraZeneca, immatics, Novigenix, Ipsen, Boehringer Ingelheim, BioNTech SE, IO Biotech, Iovance Biotherapeutics, Skyline Diagnostics
Consulting or Advisory Role: Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, AstraZeneca, Daiichi Sankyo, immatics, Immunocore, NeraCare GmbH, Replimune, BioNTech SE, IO Biotech, Boehringer Ingelheim, Iovance Biotherapeutics, Skyline Diagnostics, Sun Pharma, Philogen
Speakers' Bureau: Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Merck KGaA, Regeneron
Research Funding: Bristol Myers Squibb (Inst), MSD Oncology (Inst), Regeneron (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, Bristol Myers Squibb, Merck Serono, Novartis, Merck Sharp & Dohme, Pierre Fabre, Sanofi/Regeneron

Georgia M. Beasley
Honoraria: National Comprehensive Cancer Network
Consulting or Advisory Role: Cardinal Health, Regeneron, Bristol Myers Squibb
Research Funding: Istari Oncology (Inst), Oncosec (Inst), Delcath Systems (Inst), Replimune (Inst), Checkmate Pharmaceuticals (Inst), Skyline Diagnostics (Inst)

Jiaxin Niu
Consulting or Advisory Role: AstraZeneca, Bristol Mers Squibb, Daiichi Sankyo, Johnson & Johnson, Mirati Therapeutics, Takeda, Sanofi, Pfizer, G1 Therapeutics

Bartosz Chmielowski
Consulting or Advisory Role: Atreca, Regeneron, Treeline Biosciences, SpringWorks Therapeutics, SERVIER
Research Funding: Bristol Myers Squibb (Inst), Macrogenics (Inst), Infinity Pharmaceuticals (Inst), Advenchen Laboratories (Inst), Xencor (Inst), Compugen (Inst), Iovance Biotherapeutics (Inst), RAPT Therapeutics (Inst), IDEAYA Biosciences (Inst), Ascentage Pharma (Inst), Atreca (Inst), Replimune (Inst), Instil Bio (Inst), Adagene (Inst), TriSalus Life Sciences (Inst), Kinnate Biopharma (Inst), PTC Therapeutics (Inst), Xilio Therapeutics (Inst), Kezar Life Sciences (Inst), Immunocore (Inst), AskGene Pharma (Inst), Krystal Biotech (Inst), Regeneron (Inst), Nested Therapeutics (Inst), Pierre Fabre (Inst), Georgiamune (Inst), immatics (Inst)
Travel, Accommodations, Expenses: immatics

Trisha M. Wise-Draper
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.
Stock and Other Ownership Interests: High Enroll
Consulting or Advisory Role: Merck, Caris Life Sciences, Need, EMD Serono, Adlai Nortye, Replimune, Adaptimmune, Genmab
Research Funding: Merck, AstraZeneca/MedImmune, Bristol Myers Squibb, GlaxoSmithKline, Caris Life Sciences, GlaxoSmithKline, Janssen Oncology
Travel, Accommodations, Expenses: Caris Life Sciences

Tawnya Lynn Bowles
Research Funding: Amgen (Inst), Replimune (Inst), Genentech (Inst), Natera (Inst)

Katy K. Tsai
Consulting or Advisory Role: Bristol Myers Squibb, Bristol Myers Squibb/Celgene
Research Funding: Oncosec (Inst), Bristol Myers Squibb (Inst), Pfizer (Inst), Replimune (Inst), Genentech (Inst), ABM (Inst), OnKure (Inst), BioAtla (Inst), AstraZeneca (Inst), IDEAYA Biosciences (Inst), Innovent Biologics (Inst), Georgiamune (Inst), Merck (Inst)

Céleste Lebbé
Honoraria: Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, Pfizer, Sanofi
Consulting or Advisory Role: Bristol Myers Squibb, MSD, Novartis, Amgen, Merck Serono, Sanofi, Pierre Fabre, Inflax
Speakers' Bureau: Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, Sanofi
Research Funding: Roche (Inst), Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD, Novartis, Sanofi, Pierre Fabre, Roche
Other Relationship: InflaRx, Sanofi, BMS, MSD, Pierre Fabre, Novartis, Jazz Pharmaceuticals

Caroline Gaudy-Marqueste
Honoraria: BMS france, Pierre Fabre, UCB
Consulting or Advisory Role: Pierre Fabre, MSD Oncology, Bristol Meyer Squib, Regeneron, Sun Pharma, Iovance Biotherapeutics
Research Funding: Day One Biopharmaceuticals (Inst), Immunocore (Inst), Merck (Inst), Sairopa (Inst), DOT therapeutics (Inst), Dragonfly Therapeutics (Inst), Incyte (Inst), Daiichi Sankyo Europe GmbH (Inst), Microbiotica (Inst), Erasca, Inc (Inst), Bristol Myers Squibb (Inst), Pfizer (Inst), Amgen (Inst), GlaxoSmithKline (Inst), Roche (Inst), Novartis (Inst), Pierre Fabre (Inst), Replimune (Inst), MSD (Inst), Janssen (Inst), Kartos Therapeutics (Inst), IFX (Inst), HUYA Bioscience International (Inst), Regeneron (Inst), IO Biotech (Inst), Philogen (Inst), Sotio (Inst), Kinnate Biopharma (Inst), AstraZeneca (Inst), Cytovation (Inst)
Travel, Accommodations, Expenses: Pierre Fabre, BMS France, MSD Oncology

Mark R. Middleton
Consulting or Advisory Role: GRAIL (Inst)
Research Funding: Immunocore (Inst), Novartis (Inst), AstraZeneca (Inst), Roche (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Merck (Inst), Pfizer (Inst), Replimune (Inst), Regeneron (Inst), GRAIL (Inst), Infinitopes (Inst), Moderna Therapeutics (Inst)
Uncompensated Relationships: GenesisCare

Aglaia Skolariki
Employment: University of Oxford
Research Funding: Cancer Research UK, Hellenic Society of Medical Oncology
Travel, Accommodations, Expenses: Roche, Nucana

Adel Samson
Consulting or Advisory Role: Roche, Chugai/Roche
Research Funding: Transgene (Inst), Transgene (Inst), Stratosvir

Jason A. Chesney
Consulting or Advisory Role: Iovance Biotherapeutics
Research Funding: Amgen, Replimune, Iovance Biotherapeutics, Bristol Myers Squibb
Patents, Royalties, Other Intellectual Property: University of Louisville US Patents

Ari M. VanderWalde
Employment: Caris Life Sciences
Consulting or Advisory Role: West Clinic, George Clincal
Research Funding: Amgen (Inst), Merck (Inst), Genentech/Roche (Inst), Millennium (Inst), AstraZeneca (Inst), Lilly (Inst), Bristol Myers Squibb (Inst), Replimune (Inst), Caris Life Sciences (Inst), EMD Serono (Inst), Immunomedics/Gilead (Inst)

Yousef Zakharia
Consulting or Advisory Role: Eisai, Novartis, Exelixis, Pfizer, Bayer, Janssen, EMD Serono, Bristol Myers Squibb/Medarex, Genzyme, Gilead Sciences, AstraZeneca
Research Funding: Pfizer (Inst), Exelixis (Inst), Eisai (Inst)
Travel, Accommodations, Expenses: Newlink Genetics

Kevin J. Harrington
Honoraria: AstraZeneca (Inst), BMS (Inst), Boehringer Ingelheim (Inst), Merck Serono (Inst), MSD (Inst), Replimune (Inst), Scenic Biotech, Johnson and Johnson (Inst), Nanobiotix (Inst), ALX Oncology (Inst), BeiGene (Inst), GlaxoSmithKline (Inst), Bicara Therapeutics (Inst), Merus (Inst), PDS Biotechnology (Inst), Exelixis (Inst), Flamingo Pharma (Inst), PsiVac Ltd (Inst), Abbvie (Inst)
Consulting or Advisory Role: AstraZeneca (Inst), BMS (Inst), Boehringer Ingelheim (Inst), Merck Serono (Inst), MSD (Inst), Replimune (Inst), Nanobiotix (Inst)
Speakers' Bureau: BMS (Inst), Merck Serono (Inst), MSD (Inst)
Research Funding: AstraZeneca (Inst), Replimune (Inst), Boehringer Ingelheim (Inst)

Elizabeth Appleton
Research Funding: Replimune (Inst)

Praveen K. Bommareddy
Employment: Replimune
Stock and Other Ownership Interests: Replimune

Junhong Zhu
Employment: Replimune
Stock and Other Ownership Interests: Replimune

Marcus Viana
Employment: Replimune
Stock and Other Ownership Interests: Replimune
Travel, Accommodations, Expenses: Replimune

Jeannie W. Hou
Employment: Replimune
Stock and Other Ownership Interests: agenus, Day One Biopharmaceuticals

Robert S. Coffin
Employment: Replimune
Leadership: Replimune
Stock and Other Ownership Interests: Replimune
Consulting or Advisory Role: Replimune
Patents, Royalties, Other Intellectual Property: I am the inventor on all Replimune's patents
Travel, Accommodations, Expenses: Replimune

Caroline Robert
Stock and Other Ownership Interests: RiboNexus
Honoraria: Pierre Fabre, Sanofi, Bristol Myers Squibb, MSD, Novartis, Merck, Roche, Pfizer, Sun Pharma, Ultimovacs, Regeneron, Egle, Philogen, MaaT Pharma, IO Biotech
Consulting or Advisory Role: Bristol Myers Squibb, Roche, Novartis, Pierre Fabre, MSD, Sanofi, Pfizer, Sun Pharma, Merck, Ultimovacs, Regeneron, Egle, Philogen, MaaT Pharma
Travel, Accommodations, Expenses: Pierre Fabre

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of Participating Investigators and Study Sites

Principal Investigator	Site Name
Dr Jason A. Chesney	University of Louisville
Dr Jiaxin Niu	Banner MD Anderson Cancer Center
Dr Terence Rhodes	Intermountain Cancer Center of St George
Dr Katy K. Tsai	UCSF/Helen Diller Family Comprehensive Cancer Center
Dr Ari M. VanderWalde	West Cancer Clinic and Research Institute
Dr Evan Hall	University of Washington Seattle Cancer Care Alliance
Dr Tawnya Lynn Bowles	Intermountain Medical Center
Dr Mohammed M. Milhem	University of Iowa
Dr Gregory Daniels	Moores UCSD Cancer Center
Dr Bartosz Chmielowski	University of California, Los Angeles
Dr John Fruehauf	University of California, Irvine
Dr Gino K. In	USC Norris Comprehensive Cancer Center
Dr Georgia M. Beasley	Duke Cancer Institute
Dr Trisha M. Wise-Draper	University of Cincinnati Cancer Center
Dr Robert McWilliams	Mayo Clinic in Minnesota
Dr Mahesh Seetharam	Mayo Clinic in Arizona
Dr Aleksandar Sekulic	Mayo Clinic in Arizona
Dr Issam Makhoul	CARTI Cancer Center
Dr Michael K. Wong	MD Anderson Cancer Center
Dr Céleste Lebbé	Hôpital Saint Louis APHP
Dr Sophie Dalac-Rat	CHU Dijon-Bourgogne
Dr Caroline Gaudy-Marqueste	CHU de La Timone Aix-Marseille University
Dr Charlée Nardin	CHU Besancon Hôpital Jean Minjoz
Dr Antoine Italiano	Institut Bergonié
Dr Mona Amini-Adle	Center Léon Bérard
Dr Judith Michels	Institut Gustave Roussy
Dr Ana María Arance Fernandez	Hospital Clinic Barcelona
Dr Eva Muñoz Couselo	Hospital Universitari Vall d'Hebron
Dr Pablo Cerezuela	Hospital Universitario Virgen de la Arrixaca
Dr Miguel Sanmamed	Clinica Universitaria de Navarra
Dr Maria Luisa Limon	Hospital Universitario Virgen del Rocio
Dr Mark R. Middleton	Oxford University Hospital
Dr Kevin J. Harrington	Royal Marsden Hospital
Dr Joseph J. Sacco	Clatterbridge Cancer Centre
Dr Adel Samson	University of Leeds
Dr Patricia Roxburgh	The Beatson West of Scotland Cancer Center
Dr Dirk Schadendorf	University Hospital Essen