Abstract: 1661P

Efficacy and safety of RP1 + nivolumab (nivo) in patients with non-melanoma skin cancer (NMSC)

Dirk Schadendorf[1], Michael K. Wong[2], Georgia M. Beasley[3], Anna C. Pavlick[4], Kevin J. Harrington[5], Bartosz Chmielowski[6], Jiaxin Niu[7], Ari M. VanderWalde[8], Tawnya Lynn Bowles[9], Katy K. Tsai[10], Evan T. Hall[11], Trisha M. Wise-Draper[12], Judith Michels[13], Ana Arance[14], Mona Amini-Adle[15], Junhong Zhu[16], Marcus Viana[16], Jeannie W. Hou[16], Mohammed M. Milhem[17]

[1]Department of Dermatology, West German Cancer Center, University Hospital 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, Essen, Germany; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [3]Duke Cancer Institute, Duke University, Durham, NC, USA; [4]Weill Cornell Medical College, New York, NY, USA; [5]The Institute of Cancer Research/Royal Marsden NIHR Biomedical Research Centre, London, UK; [6]Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA, USA; [7]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [8]West Cancer Center and Research Institute, Germantown, TN, USA; [9]Intermountain Medical Center, Murray, UT, USA; [10]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [11]Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA; [12]University of Cincinnati Cancer Center, University of Cincinnati, Cincinnati, OH, USA; [13]Département de Médecine Oncologique, Gustave Roussy, Villejuif, France; [14]Medical Oncology Department, Hospital Clinic, Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain; [15]Centre Léon Bérard, Lyon, France; [16]Replimune, Inc., Woburn, MA, USA; [17]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA

Background

- NMSC is a common group of malignancies that includes basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (CSCC), as well as less common cancers, such as Merkel cell carcinoma (MCC) and angiosarcoma[1,2]
- Although easily treatable in early stages, some NMSCs recur or metastasize and require systemic treatments such as immune checkpoint inhibitors.[3] Furthermore, patients with advanced NMSC that progressed on an anti–programmed cell death protein 1 (PD-1) or anti–programmed death-ligand 1 (PD-L1)-containing therapy have poor clinical outcomes and limited treatment options[4-7]
  - There is currently no standard of care for NMSC that has progressed on anti–PD-1/PD-L1 therapy[3-7]
- RP1 (vusolimogene oderparepvec) is a replication-selective herpes simplex virus type 1–based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R$^-$), which substantially increases the degree and immunogenicity of tumor cell death[8]
- In the phase 1/2 IGNYTE trial (NCT03767348), RP1 combined with nivolumab showed clinically meaningful and durable efficacy (objective response rate [ORR] 32.9% and duration of response 33.7 months by Response Evaluation Criteria in Solid Tumors version 1.1) in 140 patients with advanced anti–PD-1–failed melanoma[9]
- The IGNYTE trial also evaluated the safety and efficacy of RP1 alone or combined with nivolumab in cohorts of other patients with advanced tumors, including a cohort of patients with NMSC

Objective

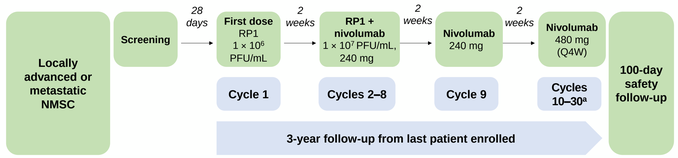
To report the efficacy and safety of RP1 plus nivolumab in the NMSC cohort from the IGNYTE trial

Methods

Study design and treatment

- The trial enrolled patients with anti–PD-1–naïve and –failed NMSC, including MCC, BCC, angiosarcoma, and CSCC
- RP1 was administered intratumorally into superficial and/or deep/visceral tumors at 1 × 10^6 plaque-forming units (PFU)/mL initially, then at 1 × 10^7 PFU/mL once every 2 weeks for up to 7 doses (≤10 mL per cycle) with intravenous nivolumab (240 mg); nivolumab was then given alone (240 mg every 2 weeks or 480 mg every 4 weeks) for up to 2 years, with further RP1 allowed if indicated (**Figure 1**)
- The data cutoff date for this study was October 15, 2024

Figure 1. Study design



Primary objective

- Safety and efficacy using mRECIST[b] 1.1 by investigator assessment

Key eligibility

Advanced NMSC[c] considered not treatable with surgical excision; measurable disease; adequate organ function; no prior oncolytic therapy; ECOG performance status 0–1

Patients with **anti–PD-1–naïve NMSC** for whom anti–PD-1 is indicated, or for whom currently available therapies are not appropriate

Patients with **anti–PD-1–failed NMSC** whose disease progressed while being treated with at least 8 weeks of anti–PD-1 therapy; anti–PD-1 must be the last prior therapy

[a]RP1 could be reinitiated beyond 8 cycles if protocol-specified criteria were met.
[b]For mRECIST, PD must be confirmed by further progression at least 4 weeks after initial PD; intended to better allow for pseudoprogression than RECIST 1.1.
[c]NMSC includes basal cell carcinoma, cutaneous squamous cell carcinoma, basosquamous carcinoma, Merkel cell carcinoma, high-grade dermatofibrosarcoma protuberans, angiosarcoma of the skin, non–HIV-related Kaposi's sarcoma, sebaceous gland carcinoma, and eccrine carcinomas.
ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; mRECIST, modified RECIST 1.1; NMSC, non-melanoma skin cancer; PD, progressive disease; PD-1, programmed cell death protein 1; PFU, plaque-forming units; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Results

Baseline demographics and clinical characteristics

- Among 105 patients with NMSC, 73 (69.5%) patients had disease progression on prior anti–PD-1 therapy (**Table 1**)

Table 1. Baseline demographics and clinical characteristics of patients with NMSC

Characteristic	MCC (n = 28)		BCC (n = 14)		Angiosarcoma (n = 14)		CSCC (n = 49)	
	Anti–PD-1 naïve (n = 6)	Anti–PD-1 failed (n = 22)	Anti–PD-1 naïve (n = 4)	Anti–PD-1 failed (n = 10)	Anti–PD-1 naïve (n = 6)	Anti–PD-1 failed (n = 8)	Anti–PD-1 naïve (n = 16)	Anti–PD-1 failed (n = 33)
Age, median (range), y	72.5 (46.0–90.0)	72.5 (48.0–89.0)	70.0 (44.0–83.0)	66.0 (44.0–93.0)	74.0 (43.0–97.0)	72.0 (60.0–88.0)	67.5 (47.0–87.0)	69.0 (48.0–90.0)
Sex, n (%)								
Male	5 (83.3)	18 (81.8)	2 (50.0)	8 (80.0)	5 (83.3)	3 (37.5)	12 (75.0)	26 (78.8)
Female	1 (16.7)	4 (18.2)	2 (50.0)	2 (20.0)	1 (16.7)	5 (62.5)	4 (25.0)	7 (21.2)
Stage, n (%)								
M0	3 (50.0)	12 (54.5)	2 (50.0)	5 (50.0)	3 (50.0)	5 (62.5)	5 (31.3)	8 (24.2)
M1	3 (50.0)	7 (31.8)	2 (50.0)	3 (30.0)	2 (33.3)	3 (37.5)	11 (68.8)	25 (75.8)
Missing	0	3 (13.6)	0	2 (20.0)	1 (16.7)	0	0	0
ECOG performance status, n (%)								
0	5 (83.3)	8 (36.4)	0	9 (90.0)	1 (16.7)	3 (37.5)	5 (31.3)	15 (45.5)
1	1 (16.7)	14 (63.6)	4 (100.0)	1 (10.0)	5 (83.3)	5 (62.5)	11 (68.8)	18 (54.5)
PD-L1 tumor expression, (%)								
Positive (≥1%)	0	5 (22.7)	0	3 (30.0)	3 (50.0)	1 (12.5)	8 (50.0)	16 (48.5)
Negative (<1%)	3 (50.0)	9 (40.9)	1 (25.0)	6 (60.0)	2 (33.3)	5 (62.5)	3 (18.8)	8 (24.2)
Undetermined or missing	3 (50.0)	8 (36.4)	3 (75.0)	1 (10.0)	1 (16.7)	2 (25.0)	5 (31.3)	9 (27.3)

BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; MCC, Merkel cell carcinoma; NMSC, non-melanoma skin cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Results

Efficacy

- Among all patients with NMSC, 99 were included in the efficacy analysis; 6 patients did not have post-baseline assessments and were excluded
- Responses to RP1 plus nivolumab occurred across the NMSC tumor types enrolled, with confirmed responses seen in patients with both anti–PD-1–naïve and –failed disease, as well as both in locally advanced and metastatic disease (**Table 2**)
  - The ORR was 100.0%, 33.3%, 66.7%, and 56.3% in patients with anti–PD-1–naïve MCC, BCC, angiosarcoma, and CSCC, respectively
  - The ORR was 26.3%, 30.0%, 37.5%, and 15.2% in patients with anti–PD-1–failed MCC, BCC, angiosarcoma, and CSCC, respectively
- Response profiles for individual patients are shown in **Figure 2**

Table 2. Confirmed response by NMSC type

BOR, n (%)	MCC		BCC		Angiosarcoma		CSCC anti–PD-1 naïve			CSCC anti–PD-1 failed		
	Anti–PD-1 naïve (n = 4)	Anti–PD-1 failed (n = 19)	Anti–PD-1 naïve (n = 3)	Anti–PD-1 failed (n = 10)	Anti–PD-1 naïve (n = 6)	Anti–PD-1 failed (n = 8)	LA (n = 5)	Met (n = 11)	Total (n = 16)	LA (n = 8)	Met (n = 25)	Total (n = 33)
CR	4 (100.0)	3 (15.8)	1 (33.3)	0	2 (33.3)	2 (25.0)	2 (40.0)	4 (36.4)	6 (37.5)	1 (12.5)	1 (4.0)	2 (6.1)
PR	0	2 (10.5)	0	3 (30.0)	2 (33.3)	1 (12.5)	1 (20.0)	2 (18.2)	3 (18.8)	1 (12.5)	2 (8.0)	3 (9.1)
SD	0	3 (15.8)	1 (33.3)	5 (50.0)	2 (33.3)	3 (37.5)	1 (20.0)	2 (18.2)	3 (18.8)	3 (37.5)	7 (28.0)	10 (30.3)
PD	0	10 (52.6)	1 (33.3)	2 (20.0)	0	2 (25.0)	1 (20.0)	2 (18.2)	3 (18.8)	1 (12.5)	12 (48.0)	13 (39.4)
NE	0	1 (5.3)	0	0	0	0	0	1 (9.1)	1 (6.3)	2 (25.0)	3 (12.0)	5 (15.2)
ORR[a]	4 (100.0)	5 (26.3)	1 (33.3)	3 (30.0)	4 (66.7)	3 (37.5)	3 (60.0)	6 (54.5)	9 (56.3)	2 (25.0)	3 (12.0)	5 (15.2)

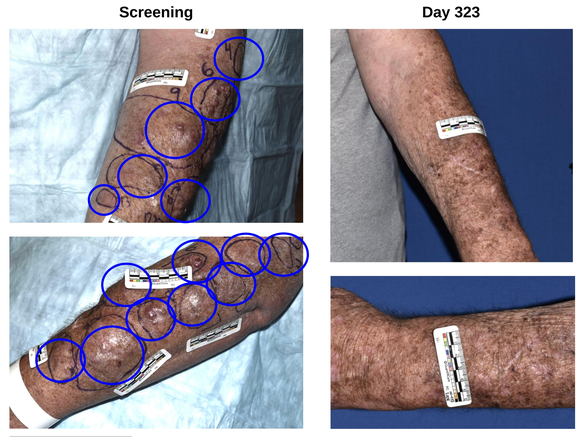
[a]The ORR for efficacy-evaluable patients is shown; ORR based on the full analysis set including all patients is identical except for anti–PD-1–naïve MCC (66.7% [4/6]), anti–PD-1–failed MCC (22.7% [5/22]), and anti–PD-1–naïve BCC (25.0% [1/4]).
BCC, basal cell carcinoma; BOR, best overall response; CR, complete response; CSCC, cutaneous squamous cell carcinoma; LA, locally advanced; MCC, Merkel cell carcinoma; Met, metastatic; NE, not evaluable; NMSC, non-melanoma skin cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

Figure 2. Response profile for individual patients with (A) MCC, (B) BCC, (C) angiosarcoma, (D) locally advanced CSCC, and (E) metastatic CSCC

BCC, basal cell carcinoma; CR, complete response; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; NE, not evaluable; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

- An example of a patient with anti–PD-1–failed MCC and partial response to RP1 + nivolumab is shown in **Figure 3**

Figure 3. Patient example: Partial response to RP1 + nivolumab in a patient with anti–PD-1 failed MCC



MCC, Merkel cell carcinoma; PD-1, programmed cell death protein 1.

Safety

- RP1 plus nivolumab had a tolerable safety profile in patients with NMSC; most treatment-related adverse events (TRAEs) were grade 1/2 in severity (**Table 3**)
- The most common TRAEs among all patients (≥15%) were fatigue, chills, and pyrexia
- The most common grade ≥3 TRAEs (≥2 events in patients with anti–PD-1–naïve or –failed disease) were fatigue, rash maculo-papular, abdominal pain, diarrhea, hyponatremia, and pyrexia. There were 2 grade 5 TRAEs (disease hyperprogression and capillary leak syndrome)

Table 3. TRAEs in patients with anti–PD-1–naïve and –failed NMSC (related to RP1 or nivolumab)[a]

TRAEs, n (%)	Anti–PD-1–naïve NMSC (n = 32)		Anti–PD-1–failed NMSC (n = 83)	
	All grades	Grades 3/4	All grades	Grades 3/4
All TRAEs	29 (90.6)	14 (43.8)	66 (79.5)	19 (22.9)
Fatigue	12 (37.5)	2 (6.3)	24 (28.9)	1 (1.2)
Nausea	9 (28.1)	0	5 (6.0)	0
Pruritus	9 (28.1)	1 (3.1)	6 (7.2)	0
Pyrexia	8 (25.0)	1 (3.1)	17 (20.5)	1 (1.2)
Influenza-like illness	7 (21.9)	0	9 (10.8)	1 (1.2)
Diarrhea	7 (21.9)	2 (6.3)	8 (9.6)	0
Chills	5 (15.6)	0	22 (26.5)	0
Rash	5 (15.6)	0	4 (4.8)	0
Rash maculo-papular	3 (9.4)	2 (6.3)	4 (4.8)	1 (1.2)
Hyponatremia	2 (6.3)	1 (3.1)	2 (2.4)	1 (1.2)
Abdominal pain	0	0	3 (3.6)	2 (2.4)

[a]The safety population includes additional patients with other NMSC subtypes (basosquamous carcinoma [n = 2], non-HIV–related Kaposi's sarcoma [n = 2], sebaceous gland carcinoma [n = 2], eccrine carcinomas [n = 3], and missing [n = 1]).
HIV, human immunodeficiency virus; NMSC, non-melanoma skin cancer; PD-1, programmed cell death protein 1; TRAE, treatment-related adverse event.

Conclusions

- RP1 plus nivolumab provided responses across multiple advanced NMSC tumor types, including anti–PD-1–failed disease
- RP1 plus nivolumab represents a promising treatment option for patients with advanced NMSC for whom no other safe and effective treatments are available

References:

1. Sendín-Martín M, et al. *Clin Transl Oncol*. 2025. doi: 10.1007/s12094-025-03985-z.
2. Deinlein T, et al. *J Dtsch Dermatol Ges*. 2016;14(2):144-51.
3. Ascierto PA, et al. *J Immunother Cancer*. 2022;10(12):e005082.
4. NCCN clinical practice guidelines® for basal cell skin cancer. Version 2.2025.
5. NCCN clinical practice guidelines® for squamous cell skin cancer. Version 1.2026.
6. NCCN clinical practice guidelines® for Merkel cell carcinoma. Version 2.2025.
7. Nghiem P, et al. *J Immunother Cancer*. 2021;9(4):e002478.
8. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.
9. Wong MK, et al. *J Clin Oncol*. 2025. doi:10.1200/JCO-25-01346.

Presenter disclosure:

DS received research funding from Amgen, Bristol Myers Squibb, Merck Sharpe & Dohme, and Novartis; received consulting fees from 4SC, AstraZeneca, BioAtla, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Erasca, Formycon, Immatics, Immunocore, InflaRx, IO BioTech, Iovance Therapeutics, Ipsen, Labcorp, Merck-Serono, Merck Sharpe & Dohme, NeraCare, Novartis, Pfizer, Philogen, Pierre Fabre, Regeneron, Replimune, Sanofi, Seagen, SkylineDx, and Sun Pharma; received honoraria from Bristol Myers Squibb, InflaRx, Merck Sharpe & Dohme, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi, and Sun Pharma; received travel support from Bristol Myers Squibb, Merck Sharpe & Dohme, Novartis, Pierre Fabre, Regeneron, and Sanofi; served on advisory boards for 4SC, AstraZeneca, Bristol Myers Squibb, BioNTech, Daiichi Sankyo, Immatics, Immunocore, InflaRx, Iovance Therapeutics, Labcorp, Merck Sharpe & Dohme, NeraCare, Novartis, Pfizer, Philogen, Pierre Fabre, Regeneron, Replimune, Sanofi, SkylineDx, and Sun Pharma; and had a leadership role in Dermatologic Cooperative Oncology Group (DeCOG), Deutsche Hautkrebsstiftung/Hiege-Stiftung, EUMelaReg, and NVKH.

The IGNYTE study is currently continuing to recruit patients with NMSC. To learn more about enrolling your patient, contact clinicaltrials@replimune.com or +1 (781) 222 9570.

Additional information can be obtained by visiting ClinicalTrials.gov (NCT03767348).

Acknowledgments:

The authors would like to thank the patients and their families for their participation in the trial. Medical writing and editorial support were provided by June F. Yang, PhD, of Red Nucleus, and were funded by Replimune, Inc.

Study sponsor:

This study is sponsored by Replimune, Inc. (Woburn, MA). Nivolumab was supplied by Bristol Myers Squibb.

Contact:

Dirk Schadendorf: Dirk.Schadendorf@uk-essen.de

Presented at the 2025 European Society for Medical Oncology (ESMO) Annual Meeting; October 17–21, 2025; Berlin, Germany