Abstract: 9553

# Updated results from the skin cancer cohorts from an ongoing phase 1/2 multi-cohort study of RP1, an enhanced potency oncolytic HSV, combined with nivolumab (IGNYTE)

**Mohammed M. Milhem**,[1] Ari M. Vanderwalde,[2] Tawnya Lynn Bowles,[3] Joseph J. Sacco,[4] Jiaxin Niu,[5] Katy K Tsai,[6] Jason Alan Chesney,[7] Bartosz Chmielowski,[8] Adel Samson,[9] Terence Duane Rhodes,[10] Gino K. In,[11] Anna C. Pavlick,[12] Trisha Wise-Draper,[13] Miguel F. Sanmamed,[14] Praveen K. Bommareddy,[15] Junhong Zhu,[15] Robert S. Coffin,[15] Kevin Harrington,[16] Mark R. Middleton[17]

[1]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA; [2]West Cancer Center and Research Institute, Germantown, TN; [3]Intermountain Med Ctr, Murray, UT; [4]Clatterbridge Cancer Centre, Wirral, United Kingdom and University of Liverpool, Liverpool, UK; [5]Banner MD Anderson Cancer Center, Gilbert, AZ; [6]Helen Diller Family Comprehensive Cancer Center Cutaneous Oncology San Francisco, CA; [7]James Graham Brown Cancer Center, University of Louisville, Louisville, KY; [8]University of California Los Angeles, Los Angeles, CA; [9]University of Leeds, Leeds, UK; [10]Intermountain Med Ctr, St George, UT; [11]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [12]Weill Cornell Medical College, New York, NY; [13]University of Cincinnati, Cincinnati, OH; [14]Clínica Universidad de Navarra, Pamplona, ES; [15]Replimune Inc., Woburn, MA; [16]Royal Marsden NHS Foundation Trust, The Institute of Cancer Research, London, UK; [17]Churchill Hospital, Oxford, UK

## Background

- RP1 is an enhanced potency oncolytic version of herpes simplex virus 1 that expresses the human granulocyte macrophage colony stimulating factor and the fusogenic protein GALV-GP R− [1]
- IGNYTE is a phase 1/2 open label, multicenter, dose escalation and expansion trial (NCT03767348) evaluating the safety and efficacy of RP1 in combination with the anti–PD-1 inhibitor nivolumab in a range of tumor types [2]
- Here, we present updated results from the melanoma and anti–PD-1–naïve non-melanoma skin cancer (NMSC) cohorts with RP1 combined with nivolumab

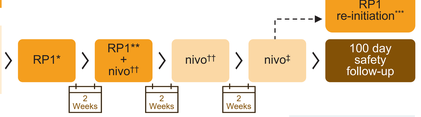
## Objective

To evaluate the safety, tolerability, and preliminary efficacy of RP1 alone and in combination with nivolumab in adult subjects with advanced and/or refractory solid tumors

## Methods

| Cohorts | Target N |
|---|---|
| Melanoma[a] | 30 |
| Non-melanoma skin cancer anti–PD-1/PD-L1–failed and –naïve[b] | 60 |
| Anti–PD-1–failed cutaneous melanoma[c] | 125 |
| Non-small cell lung cancer anti–PD-1/PD-L1–failed | 30 |
| Micro Satellite Instability and deficient Mis-match Repair anti–PD-1/PD-L1–failed | 30 |

[a]Melanoma (N = 30) is fully enrolled and not recruiting.
[b]Anti–PD-1/PD-L1–naïve is fully enrolled and not recruiting; anti–PD-1/ PD-L1–failed (N = 30).
[c]Registration-directed cohort.




### Dosing

RP1
*First dose = 1 x $10^6$ PFU/mL
**Subsequent doses = 1 x $10^7$ PFU/mL

Nivo
†Dosing with nivo begins at Dose 2 of RP1; therefore, a maximum of 29 cycles of nivo will be given
††240 mg (Q2W)
‡480 mg (Q4W)

### RP1 re-initiation***

Re-initiation of up to 8 additional doses of RP1 Q2W in combination with nivo 480 mg Q4W if the protocol specific criteria are met

### Objectives

Primary: ORR, safety and tolerability

Secondary: DOR, CR, DCR, PFS and OS

Exploratory: Biomarker analysis using tumor biopsies and peripheral blood, including the assessment of RP1 biodistribution and shedding

CR, complete remission; DCR, disease control rate; DOR, duration of response; nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, stable disease.

## Melanoma

### Table 1. Demographics

| | All | Cutaneous melanoma | Mucosal melanoma | Uveal melanoma |
|---|---|---|---|---|
| Patients (N) | 36 | 24 | 6 | 6 |
| Age: Range | 28–95 | 28–95 | 40–78 | 44–85 |
| **Prior Tx** | | | | |
| Prior anti–PD-1 (alone or combined) | 25 | 24[a] | 5 | 4 |
| Prior single agent anti–PD-1 | 9 | 7 | 1 | 1 |
| Prior anti–PD-1/anti–CTLA-4 | 16 | 9 | 4 | 3 |
| Prior anti–PD-1 (%) | 69% | 67% | 83% | 75% |
| **Disease Characteristics** | | | | |
| Stage IIIc | 2 | 2 | 0 | 0 |
| Stage IV M1a | 7 | 3 | 4 | 0 |
| Stage IV M1b | 11 | 10 | 1 | 0 |
| Stage IV M1c | 16 | 9 | 1 | 6 |
| Stage IV M1b/c (%) | 75% | 79% | 33% | 100% |

[a]87.5% of anti–PD-1-failed patients had stage IV M1b/c (visceral) disease.
CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1.

- 36 patients with melanoma had been enrolled: 24 had cutaneous, 6 mucosal and 6 uveal melanoma (enrollment complete in January 2020; **Table 1**)

## Results

### Melanoma

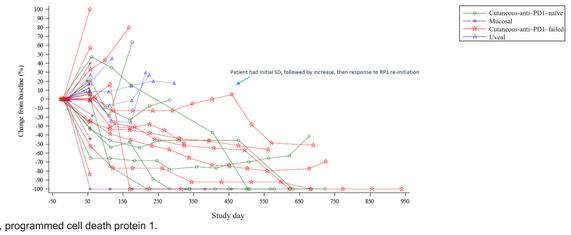
#### Table 2. Melanoma: Efficacy

| | Cutaneous: Anti–PD-1–naïve | Cutaneous: Anti–PD-1–failed | Mucosal: Anti–PD-1–naïve | Mucosal: Anti–PD-1–failed | Uveal: Anti–PD-1–naïve | Uveal: Anti–PD-1–failed |
|---|---|---|---|---|---|---|
| Patients (N) | 8 | 16 | 1 | 5 | 3 | 3 |
| **Best overall response n (%)** | | | | | | |
| CR | 3 (37.5) | 2 (12.5) | 1 (100.0) | 1 (20.0) | 0 | 0 |
| PR | 2 (25.0) | 4 (25.0)[a] | 0 | 0 | 0 | 0 |
| SD | 2 (25.0) | 1 (6.3)[b] | 0 | 0 | 1 (33.3) | 3 (100.0) |
| PD | 1 (12.5) | 8 (50.0) | 0 | 4 (80.0) | 2 (66.7) | 0 |
| ORR | 5 (62.5) | 6 (37.5) | 1 (100.0) | 1 (20.0) | 0 | 0 |
| CR+PR+SD | 7 (87.5) | 7 (43.8) | 1 (100.0) | 1 (20.0) | 1 (33.3) | 3 (100.0) |

[a]One anti–PD-1–naïve PR patient is being treated with re-initiated RP1 with the aim of achieving a CR; One anti–PD-1–failed PR patient is a CR by PET scan (no metabolic activity seen) and PET scans are being scheduled for two others suspected to be NED at 18 and 23 months.
[b]One SD patient has the potential for response following ongoing RP1 re-initiation; The second SD patient is a surgical CR (residual tumor removed at 4 months, ongoing at 18 months). CR, complete remission; NED, no evidence of disease; ORR, overall response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

- The ORR and CR for the anti–PD-1–failed cutaneous melanoma cohort increased from 31.3% to 37.5% and from 6.3% to 12.5%, respectively from when last presented in June 2021
- Disease control (CR+PR+SD) was achieved in 87.5% and 43.8% of patients in the anti–PD-1–naïve and anti–PD-1–failed cutaneous melanoma, respectively

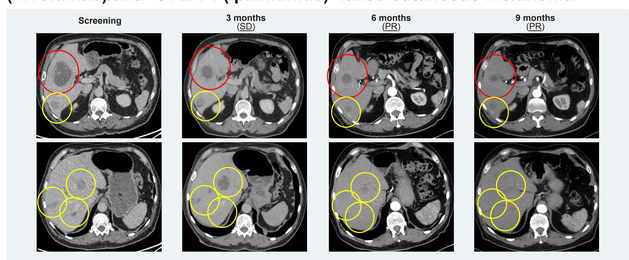
#### Figure 1. Melanoma: Change in sum of tumor diameters




PD-1, programmed cell death protein 1.

- Durability was maintained, with general deepening of response over time

#### Figure 2. Patient example: Systemic response in anti–PD-1 (nivolumab)/anti–CTLA-4 (ipilimumab)–failed cutaneous melanoma




Red circle, injected; Yellow circle, un-injected.
Melanoma (Patient 1122-2007): PR. Ongoing at 19 months from first RP1 dose. All lesions show no evidence of metabolic activity by PET.
CTLA-4, cytotoxic T-lymphocyte antigen 4; PET, positron emission tomography; PD-1, programmed death protein 1; PR, partial response.

### NMSC

#### Table 3. Anti–PD-1–naïve NMSC: Efficacy

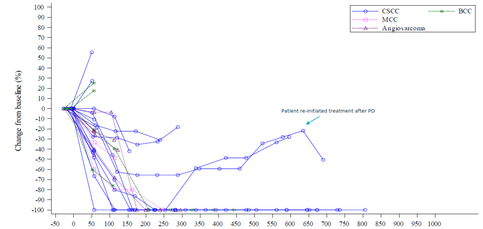
| | CSCC | BCC | MCC | Angiosarcoma |
|---|---|---|---|---|
| Patients (N)* | 17 | 4 | 4 | 6 |
| **Best overall response n (%)** | | | | |
| CR | 8 (47.1) | 1 (25.0) | 2 (50.0) | 1 (16.7) |
| PR | 3 (17.6) | 0 | 1 (25.0) | 3 (50.0) |
| SD | 1 (5.9) | 2 (50.0) | 0 | 1 (16.7) |
| PD | 4 (23.5) | 1 (25.0) | 1 (25.0) | 1 (16.7) |
| ORR | 11 (64.7) | 1 (25.0) | 3 (75.0) | 4 (66.7) |
| CR+PR+SD | 12 (70.6) | 3 (75.0) | 3 (75.0) | 5 (83.3) |

*Patients with follow up assessments (n = 31), on study with no follow up currently for the other patient (MCC).
BCC, basal cell carcinoma; CR, complete remission; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; ORR, overall response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

- The ORR for the CSCC cohort increased from 60.0% (last data cut, March 2022) to 64.0%, with 47.1% of patients achieving a CR
- CR rates increased from 46.0% to 47.1% in CSCC, from 0% to 25.0% in BCC, to 50.0% in MCC, and to 16.7% in angiosarcoma
- Overall, disease control (CR+PR+SD) was achieved in >70.0% of patients in each subtype

#### Figure 3. Anti-PD1–naïve NMSC: Change in sum of tumor diameters

- A high frequency of deep and durable responses continues to be observed, with treatment ongoing in 12 patients

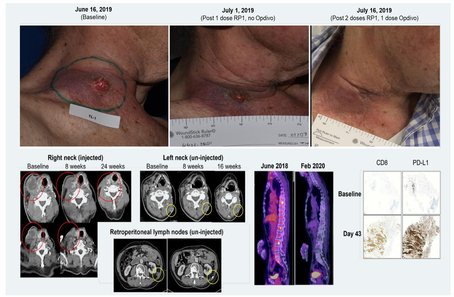



BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; NMSC, nonmelanoma skin cancer; PD, progressive disorder.

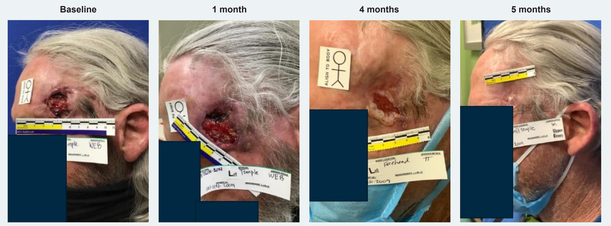
#### Figure 4. Patient example: Systemic response in CSCC

- Both the large-injected tumor and the contralateral tumor in the neck reduced before the first nivolumab dose
- Resolution of bone metastases was observed

CSCC (Patient 4402-2001): CR - the patient had recurrent CSCC of the neck (bilateral) and bone metastases, previously treated with cisplatin-based chemoradiation and six cycles of carboplatin/5-FU. 5-FU, 5-fluorouracil; CD8, cluster of differentiation 8; CR, complete remission; CSCC, cutaneous squamous cell carcinoma; PD-L1, programmed death-ligand 1.




#### Figure 5. Patient example: Anti–PD-1–naïve CSCC




Anti–PD-1–naïve CSCC (Patient 101 1121 2009): new ongoing PR. Last CSCC patient enrolled into anti–PD-1–naïve CSCC cohort (ie new from last data cut). CSCC, cutaneous squamous cell carcinoma; PD-1, programmed cell death protein 1; PR, partial response.

### Safety

#### Table 4. Updated safety data for patients with skin cancer treated with RP1 combined with nivolumab

| | N = 84 | | | |
|---|---|---|---|---|
| Preferred Term | Grade 1–2 (>10%) | Grade 3 (all) | Grade 4/5 (all) | Total |
| Chills | 25 (29.8) | 0 | 0 | 25 (29.8) |
| Pyrexia | 24 (28.6) | 1 (1.2) | 0 | 25 (29.8) |
| Fatigue | 19 (22.6) | 5 (6.0) | 0 | 24 (28.6) |
| Pruritus | 19 (22.6) | 2 (2.4) | 0 | 21 (25.0) |
| Influenza like illness | 18 (24.1) | 0 | 0 | 18 (21.4) |
| Nausea | 17 (20.2) | 0 | 0 | 17 (20.2) |
| Diarrhea | 9 (10.7) | 1 (1.2) | 0 | 10 (11.9) |
| Injection site pain | 9 (10.7) | 0 | 0 | 9 (10.7) |
| Decreased appetite | 7 (8.3) | 1 (1.2) | 0 | 8 (9.5) |
| Rash maculo-papular | 3 (3.6) | 2 (2.4) | 0 | 5 (6.0) |
| Immune-mediated arthritis | 3 (3.6) | 1 (1.2) | 0 | 4 (4.8) |
| Lipase increased | 2 (2.4) | 2 (2.4) | 0 | 4 (4.8) |
| Dyspnea, hypotension | 1 (1.2) | 2 (2.4) | 0 | 3 (3.6) |
| Eczema | 2 (2.4) | 1 (1.2) | 0 | 3 (3.6) |
| Amylase increased, aspartate aminotransferase increased, hyponatremia, vertigo | 1 (1.2) | 1 (1.2) | 0 | 2 (2.4) |
| Immune-mediated hepatitis | 0 | 2 (2.4) | 0 | 2 (2.4) |
| Alanine aminotransferase increased, cancer pain, confusional state, delirium, hypovolemic shock, immune-mediated enterocolitis, injection site necrosis, liver function test increased, localized oedema, lymph node pain, oedema, oral candidiasis, prostate cancer, uveitis | 0 | 1 (1.2) | 0 | 1 (1.2) |
| Immune-mediated myocarditis | 0 | 0 | 1 (1.2) Gr5 | 1 (1.2) |

## Conclusions

- A high frequency of durable response continues to be seen in patients with skin cancers, including in anti–PD-1, anti–CTLA-4–failed melanoma, and in CSCC
  - Promising evidence of activity continues to also be observed in BCC, MCC and angiosarcoma
- Systemic overall responses were seen irrespective of the sites of disease and the site of injection
- RP1 combined with nivolumab continued to be well tolerated, irrespective of injection route
- The data highlights the potential for RP1 combined with nivolumab across different type of skin cancer

**Acknowledgements:**
The authors would like to thank the patients for their participation in the trial. The authors would also like to acknowledge the contributions of Taylor Jew, Kristen Catron, Jacqueline Matczak, Dharmendra Chaudhari, Atula Godwin, Heather Cong, and April Dovholuk. Medical writing and editorial support was provided by Elisabetta Lauretti, PhD, of AlphaBioCom, LLC (King of Prussia, PA, USA) and funded by Replimune Inc. (Woburn, MA, USA).

**References:**
1. Thomas S, et al. *J Immunother Cancer.* 2019;7(1):214.
2. Middleton M, et al. *J Clinical Oncol.* 2020;38(15):e22050-e22050.

**Study Sponsor:**
The study is sponsored by Replimune Inc, Woburn MA, USA.



**Presented at the 2022 American Society of Clinical Oncology (ASCO) meeting, June 3–7, 2022; Chicago, IL, USA**