Abstract: 705

Biodistribution and shedding analysis following RP1 oncolytic immunotherapy dosing in patients from the IGNYTE clinical trial

Praveen K. Bommareddy[1*], Alina Monteagudo[1], Mohammed M. Milhem[2], Joseph J. Sacco[3], Tawnya Lynn Bowles[4], Katy K. Tsai[5], Gino K. In[6], Eva Muñoz-Couselo[7], Ari M. VanderWalde[8], Jason Alan Chesney[9], Judith Michels[10], Adel Samson[11], Georgia M. Beasley[12], Trisha M. Wise-Draper[13], Dirk Schadendorf[14], Fade Mahmoud[15], Michael K. Wong[16], Walter Hong[1], Jeannie W. Hou[1], Aaron Clack[1], Robert S. Coffin[1], Mark R. Middleton[17], Bartosz Chmielowski[18]

[1]Replimune, Inc., Woburn, MA, USA; [2]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA; [3]The Clatterbridge Cancer Centre, Wirral, UK and University of Liverpool, Liverpool, UK; [4]Intermountain Medical Center, Murray, UT, USA; [5]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [6]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [7]Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron Hospital Medical Oncology Department, Barcelona, Spain; [8]West Cancer Center and Research Institute, Germantown, TN, USA; [9]James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA; [10]Gustave Roussy, Département de Médecine Oncologique, Villejuif, France; [11]Leeds Institute of Medical Research at St. James, University of Leeds, Leeds, UK; [12]Duke Cancer Institute, Duke University, Durham, NC, USA; [13]University of Cincinnati, Cincinnati, OH, USA; [14]West German Cancer Center, University Hospital Essen, Essen, Germany; [15]The T.W. Lewis Melanoma Center of Excellence, Banner MD Anderson Cancer Center at Banner Gateway Medical Center, Gilbert, AZ, USA; [16]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [17]Churchill Hospital and the University of Oxford, Oxford, UK; [18]Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA, USA

*Presenting author

Background

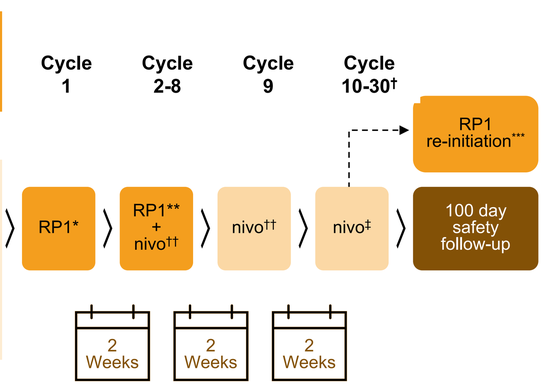
- RP1 is an enhanced potency oncolytic version of herpes simplex virus 1 that expresses the human granulocyte macrophage colony stimulating factor and the fusogenic protein GALV-GP R− [1].
- IGNYTE is a phase 1/2 open label, multicenter, dose escalation and expansion trial (NCT03767348) evaluating the safety and efficacy of RP1 in combination with anti–PD-1 inhibitor nivolumab in a range of tumor types [2].
- Here, we present the biodistribution and shedding analysis from patients (n=285) enrolled in phase 1 dose expansion (n=14) and phase 2 (n=271) cohorts from the ongoing IGNYTE trial.

Objective

To assess the biodistribution and shedding patterns of RP1 from the patients enrolled in the phase 1 dose expansion and phase 2 cohorts from the ongoing IGNYTE trial.

Methods

Cohorts	Target N
Melanoma	30[a]
Non-melanoma skin cancer anti–PD-1/PD-L1–failed and –naïve	110[b]
Anti–PD-1–failed cutaneous melanoma	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



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

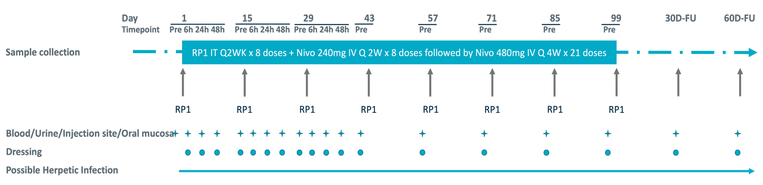
Exploratory: Biomarker analysis using tumor biopsies and peripheral blood, including the assessment of RP1 biodistribution and shedding

[a]Melanoma (N=30) is fully enrolled and not recruiting.
[b]Anti–PD-1/PD-L1–naïve is fully enrolled and not recruiting (N=32); anti–PD-1/PD-L1–failed currently recruiting.

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; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q4W, every 4 weeks.

Sample collection schema

Figure 1: Sample type and collection schedule

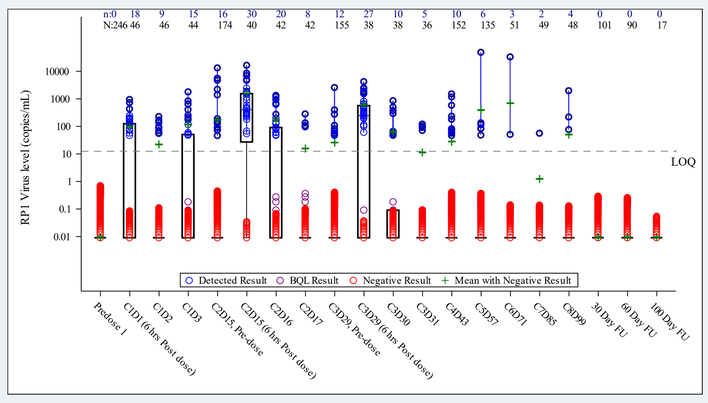


FU=follow up; IT=intratumoral; IV=intravenous; Nivo=nivolumab; Q2W=every 2 weeks; Q4W=every 4 weeks.

Blood, urine, and swabs from the exterior of occlusive dressings, the surface of injection sites, the oral mucosa, and any areas of suspected herpetic infection origin were collected throughout the study (Figure 1). The presence of RP1 DNA was assessed using an RP1-specific and sensitive qPCR assay. qPCR-positive swab samples were further tested for infectious virus in validated 50% tissue culture infective dose (TCID50) assay.

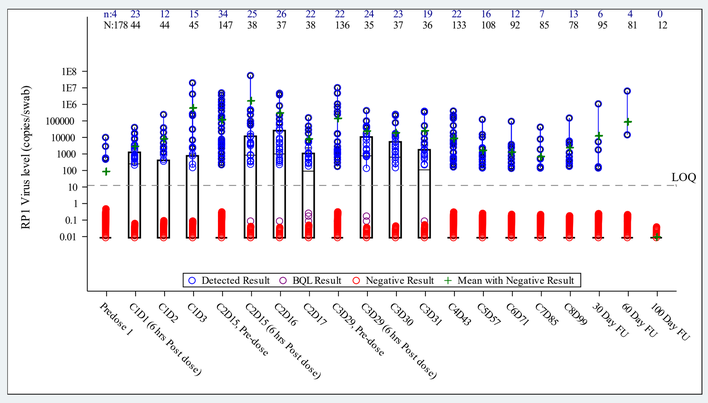
Results

Figure 2. RP1 DNA levels in blood



BQL=below quantitation limit; C#D#=cycle number, study day number; FU=follow-up; hrs=hours; LOQ=limit of quantification; N=number of patients tested; n=number of patients with RP1 DNA Virus Level equal to or above the lower limit of quantification.

Figure 3. RP1 DNA levels at the site of injection



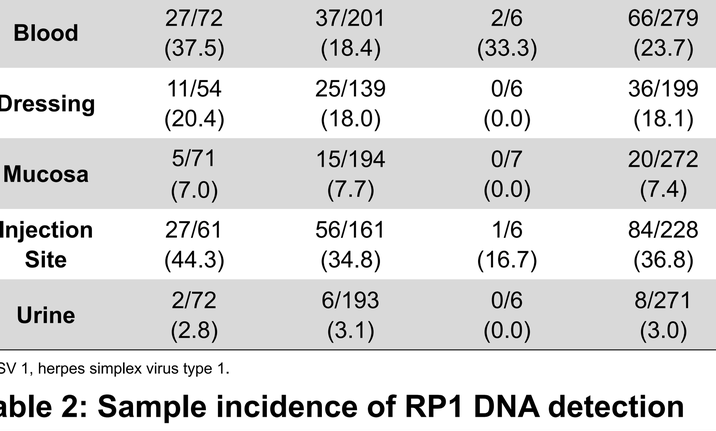
BQL=below quantitation limit; C#D#=cycle number, study day number; FU=follow-up; hrs=hours; LOQ=limit of quantification; N=number of patients tested; n=number of patients with RP1 DNA Virus Level equal to or above the lower limit of quantification.

Blood: The highest levels of RP1 DNA copy numbers were detectable in blood shortly (6-hrs) after injection. A subset of patients showed continued presence of RP1 DNA throughout to the next injection, 15 days later, with kinetics indicative of RP1 replication in tumors (Figure 2).

Urine: Throughout the eight cycles, RP1 DNA was rarely detected in urine samples: 8/271 patients and 11/1834 samples (Table 1-2).

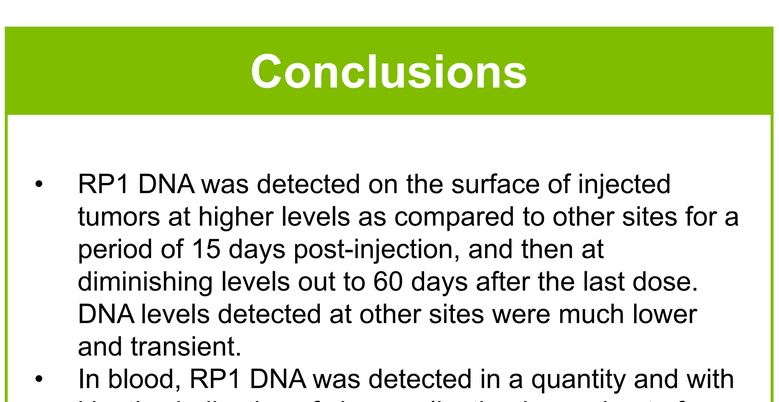
Injection site: The incidence of RP1 DNA was highest during cycle 2 with approximately 15.0% of patients having detectable levels at the injection site after 15 days post RP1 injection (Figure 3). During the safety follow-up period, RP1 DNA was only detected on the surface of injected lesions and not at any other sites, except for one oral/mucosa patient.

Figure 4. RP1 DNA levels from the exterior dressing



BQL=below quantitation limit; C#D#=cycle number, study day number; FU=follow-up; hrs=hours; LOQ=limit of quantification; N=number of patients tested; n=number of patients with RP1 DNA Virus Level equal to or above the lower limit of quantification.

Figure 5. RP1 DNA levels from oral mucosa/saliva



BQL=below quantitation limit; C#D#=cycle number, study day number; FU=follow-up; hrs=hours; LOQ=limit of quantification; N=number of patients tested; n=number of patients with RP1 DNA Virus Level equal to or above the lower limit of quantification.

Exterior dressings: RP1 DNA copies detected from the dressing are lower compared to the number of copies detected at the site of injection (Table 1-2 and Figure 4). RP1 DNA remain undetectable from all dressing samples collected post Cycle 8 Day 99.

Oral mucosa: RP1 DNA was rarely detected and mostly at low levels on oral mucosa (Figure 5), with 20/272 patients and 24/1909 samples testing positive for RP1 DNA (Table 1-2).

Sample and patient incidence of RP1 DNA detection

Table 1: Patient incidence of RP1 DNA detection

	Baseline HSV-1 seronegative N=75 n1/n2 (%)	Baseline HSV-1 seropositive N=203 n1/n2 (%)	Baseline HSV-1 unknown N=7 n1/n2 (%)	Overall N=285 n1/n2 (%)
Blood	27/72 (37.5)	37/201 (18.4)	2/6 (33.3)	66/279 (23.7)
Dressing	11/54 (20.4)	25/139 (18.0)	0/6 (0.0)	36/199 (18.1)
Mucosa	5/71 (7.0)	15/194 (7.7)	0/7 (0.0)	20/272 (7.4)
Injection Site	27/61 (44.3)	56/161 (34.8)	1/6 (16.7)	84/228 (36.8)
Urine	2/72 (2.8)	6/193 (3.1)	0/6 (0.0)	8/271 (3.0)

HSV 1, herpes simplex virus type 1.

Table 2: Sample incidence of RP1 DNA detection

	Baseline HSV-1 seronegative n3/n4 (%)	Baseline HSV-1 seropositive n3/n4 (%)	Baseline HSV-1 unknown n3/n4 (%)	Overall n3/n4 (%)
Blood	94/459 (20.5)	98/1094 (9.0)	3/37 (8.1)	195/1590 (12.3)
Dressing	24/321 (7.5)	51/690 (7.4)	0/14 (0.0)	75/1025 (7.3)
Mucosa	5/549 (0.9)	19/1323 (1.4)	0/37 (0.0)	24/1909 (1.3)
Injection Site	122/450 (27.1)	206/1022 (20.2)	1/27 (3.7)	329/1499 (21.9)
Urine	2/545 (0.4)	9/1258 (0.7)	0/31 (0.0)	11/1834 (0.6)

HSV 1, herpes simplex virus type 1.

$TCID_{50}$ From positive qPCR swab samples

We have only detected 1 positive live virus from injection site swab sample that tested positive for RP1 DNA. This sample came from an injection site sample collected 48hr post Cycle 1 RP1 injection visit. All follow-up samples for that patient were negative.

Conclusions

- RP1 DNA was detected on the surface of injected tumors at higher levels as compared to other sites for a period of 15 days post-injection, and then at diminishing levels out to 60 days after the last dose. DNA levels detected at other sites were much lower and transient.
- In blood, RP1 DNA was detected in a quantity and with kinetics indicative of virus replication in a subset of patients, as would be expected based on the mechanism of action of RP1.
- No RP1 DNA has been detected in samples collected 30 days and 60 days after the final dose of RP1 except for site of injection samples and one oral/mucosa sample, where low levels of RP1 DNA below the LOQ was detected.
- RP1 virus was detected by TCID50 from (1) injection site swab sample collected at 48 hr post injection; all samples collected thereafter were negative.
- Overall, the data suggests that the possibility of transmission of RP1 to patient's or their close contacts is minimal. No evidence of transmission having been reported to date in patient's caregivers or study staff.

IGNYTE trial is now recruiting patients.
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)

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.

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