Abstract: 611

Biodistribution and shedding analysis following treatment with RP1 oncolytic immunotherapy in the skin cancer patients from the IGNYTE clinical trial

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Background

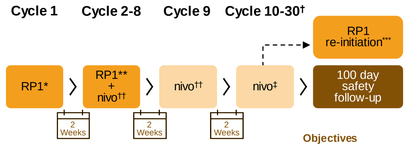
- RP1 is an enhanced potency oncolytic version of herpes simplex virus 1 that expresses the human granulocyte macrophage colony stimulating factor and the fusogenic protein GALV-GP R− [1].
- IGNYTE is a phase 1/2 open label, multicenter, dose escalation and expansion trial (NCT03767348) evaluating the 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=61) enrolled in the phase 2 cutaneous melanoma and anti-PD-1 naïve non-melanoma skin cancer (NMSC) cohorts of IGNYTE trial.

Objective

To assess the biodistribution and shedding patterns of RP1 from the patients enrolled in the cutaneous melanoma and anti-PD-1 naïve non-melanoma skin cancer (NMSC) cohorts in the IGNYTE trial.

Methods

Cohorts	Target N
Melanoma	30[a]
Non-melanoma skin cancer anti–PD-1/PD-L1–failed and –naïve	60[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

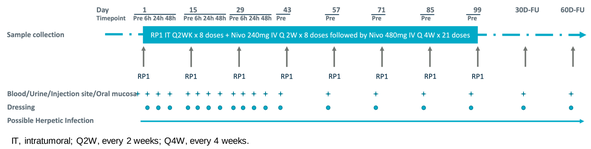
Exploratory: Biomarker analysis using tumor biopsies and peripheral blood, including the assessment of RP1 biodistribution and shedding

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

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.

Sample collection schema

Figure 1: Sample type and collection schedule

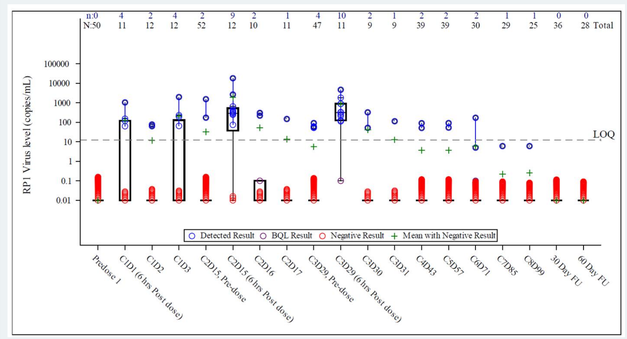


IT, intratumoral; Q2W, every 2 weeks; Q4W, every 4 weeks.

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

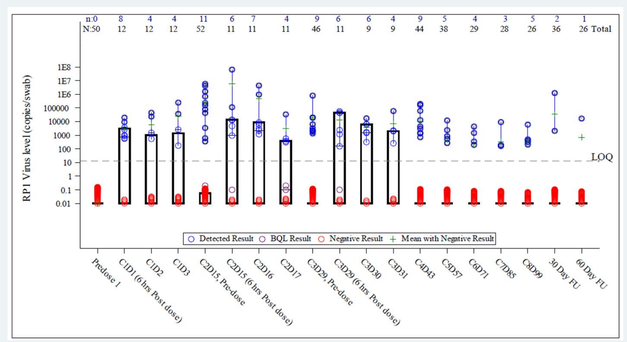


BQL=below quantitation limit; C#D#=cycle number, study day number; FU=follow-up; hrs=hours; N=number of patients tested; n=number of patients with VO DNA Virus Level equal to or above the lower limit of quantification; LOQ: limit of quantification

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 of tumors (Figure 2).

Urine: Throughout the eight cycles, RP1 DNA was undetectable in urine samples: 0/53 patients and 0/453 samples (Table 1-2).

Figure 3. RP1 DNA levels at the site of injection



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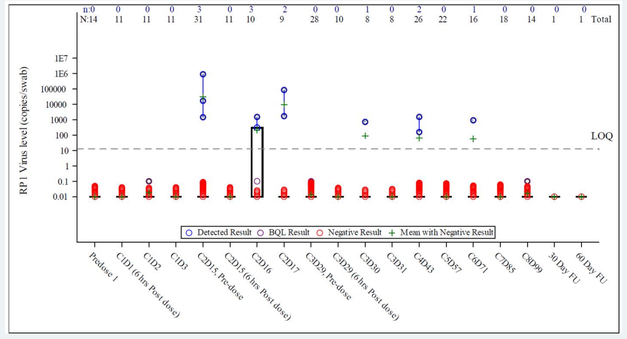
Injection site: The incidence of RP1 DNA was highest during cycle 2 with approximately 20.0% of patients having detectable levels at the injection site after 15 days post RP1 injection (Figure 3). During the safety follow-up period, RP1 DNA was only detected on the surface of injected lesions and not at any other sites.

Figure 4. RP1 DNA levels from the exterior dressing



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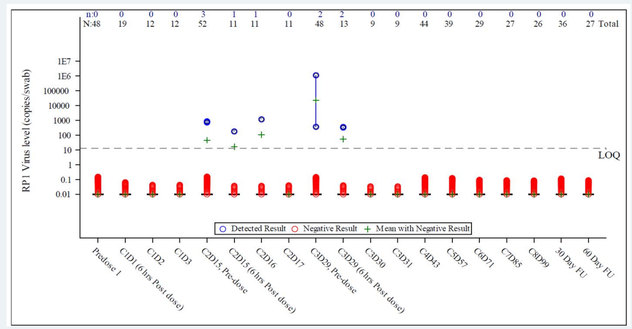
Exterior dressings: RP1 DNA copies detected from the dressing are lower compared to the number of copies detected at the site of injection (Table 1-2 and Figure 4). RP1 DNA remain undetectable from all dressing samples collected post Cycle 6 Day 71.

Figure 5. RP1 DNA levels from oral mucosa/saliva



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Oral mucosa: RP1 DNA was rarely detected and only at low levels on oral mucosa (Figure 5), with 8/53 (15.1%) patients and 9/483 (1.9%) samples testing positive for RP1 DNA (Table 1-2).

No live virus has been detected from the swab samples that tested positive for RP1 DNA: All swab samples (107 from the surface of injection site, 16 swabs from the exterior dressings, 9 from the oral mucosa) which tested positive for RP1 DNA were assessed for the presence of infectious virus by the TCID50 assay and all tested negative for infectivity.

Sample and patient incidence of RP1 DNA detection

Table 1: Patient incidence of RP1 DNA detection

	HSV-1 seronegative N=14, n1/n2 (%)	HSV-1 seropositive N=14, n1/n2 (%)	Overall N=61, n1/n2 (%)
Blood	8/11 (72.7)	9/42 (21.4)	17/53 (32.1)
Urine	0/11 (0.0)	0/42 (0.0)	0/53 (0.0)
Mucosa	1/11 (9.1)	7/42 (16.7)	8/53 (15.1)
Injection site	10/11 (90.9)	17/42 (40.5)	27/53 (50.9)
Dressing exterior	3/11 (27.3)	5/28 (17.9)	8/39 (20.5)

Table 2: Sample incidence of RP1 DNA detection

	HSV-1 seronegative N=14, n1/n2 (%)	HSV-1 seropositive N=14, n1/n2 (%)	Overall N=61, n1/n2 (%)
Blood	34/140 (24.3)	18/332 (5.4)	52/472 (11.0)
Urine	0/135 (0.0)	0/318 (0.0)	0/453 (0.0)
Mucosa	1/138 (0.7)	8/345 (2.3)	9/483 (1.9)
Injection site	48/138 (34.8)	59/334 (17.7)	107/472 (22.7)
Dressing exterior	10/101 (9.9)	6/157 (3.8)	16/258 (6.2)

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 both urine and mucosa samples collected 30 days and 60 days after the final dose of RP1.
- No RP1 virus was detected by TCID50 from any swab sample, and therefore only residual RP1 DNA was concluded to be present.
- Overall, the data suggests that the possibility of transmission of RP1 to patients close contacts is minimal, with no evidence of transmission having been reported to date in patients 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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