Poster #: CR02

Biodistribution and shedding analysis following RP1 oncolytic immunotherapy dosing in patients from the IGNYTE clinical trial: Implications for oncology pharmacists

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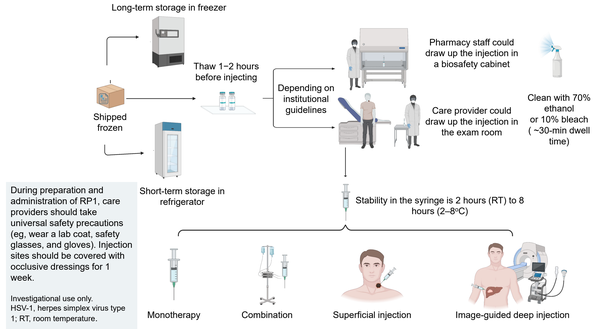
Background

- RP1 is a genetically modified herpes simplex virus type 1 (HSV-1)–based oncolytic immunotherapy (OI) that selectively replicates in and kills tumors[1,2]
- IGNYTE is a phase 1/2 open-label, multicenter, dose-escalation and dose-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[3]
- RP1 is delivered intratumorally via injection into superficial lesions or deeper tumors using image guidance. As the field of OIs continues to grow, the importance of understanding biosafety considerations is essential for pharmacy and nursing staff

Figure 1. Example handling of HSV-1 oncolytic immunotherapies[4]



During preparation and administration of RP1, care providers should take universal safety precautions (eg, wear a lab coat, safety glasses, and gloves). Injection sites should be covered with occlusive dressings for 1 week.

Investigational use only. HSV-1, herpes simplex virus type 1; RT, room temperature.

Figure adapted from: Robilotti E, et al. *Front Mol BioSci*. 2023. doi: 10.3389/fmolb.2023.1178382. © 2023 Robilotti, Zeitouni and Orloff.

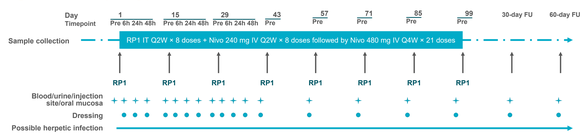
Objective

To assess the biodistribution and shedding patterns of RP1 from the patients (N=285) enrolled in the phase 1 dose-expansion (n=14) and phase 2 (n=271) cohorts from the ongoing IGNYTE trial

Methods

Sample collection schema

Figure 2. Sample type and collection schedule

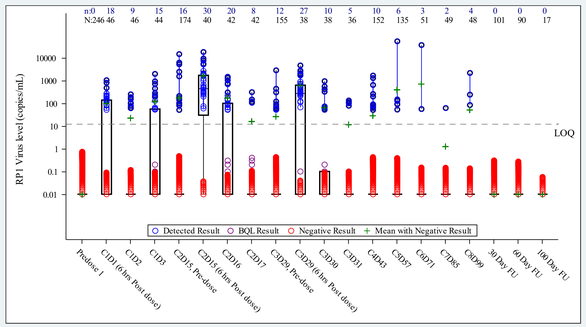


FU, follow-up; h, hours; IT, intratumoral; IV, intravenous; Nivo, nivolumab; Q2W, every 2 weeks; Q4W, every 4 weeks.

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 2**). 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 ($TCID_{50}$) assay.

Results

Figure 3. RP1 DNA levels in blood

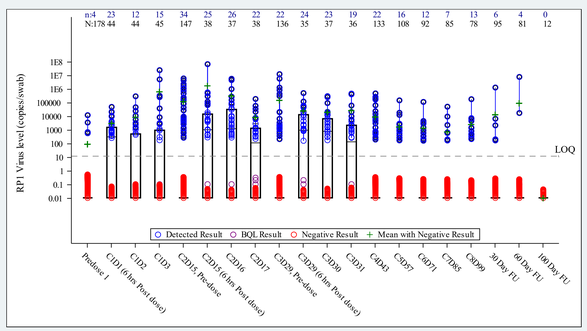


BQL, below quantitation limit; C, cycle number; D, day; FU, follow-up; hrs, hours; LOQ, limit of quantification; N, number of patients tested; n, number of patients with DNA virus level equal to or above the lower LOQ.

Blood: The highest levels of RP1 DNA copy numbers were detectable in blood shortly (6 hours) after injection. A subset of patients showed continued presence of RP1 DNA up to the next injection 15 days later, with kinetics indicative of RP1 replication in tumors (**Figure 3**).

Urine: Throughout the 8 cycles, RP1 DNA was detected in 8/271 patients and 11/1834 samples (**Tables 1** and **2**).

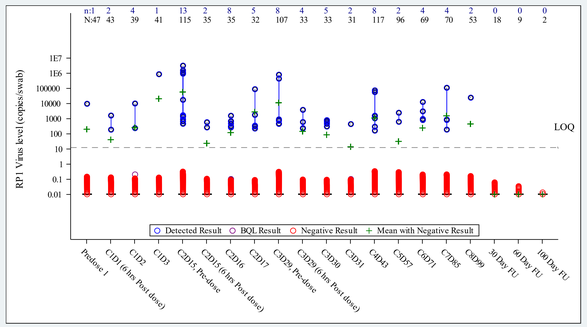
Figure 4. RP1 DNA levels at the site of injection



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

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 4**). 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 the oral mucosa from 1 patient.

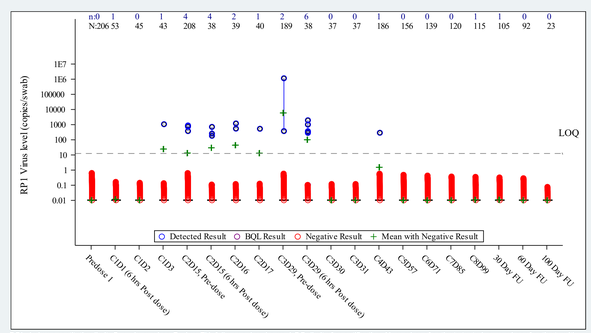
Figure 5. RP1 DNA levels from the exterior dressing



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

Exterior dressings: RP1 DNA copies detected from the dressing are lower compared to the number of copies detected at the site of injection (**Tables 1** and **2; Figure 5**). RP1 DNA remained undetectable from all dressing samples collected post-cycle 8 day 99.

Figure 6. RP1 DNA levels from oral mucosa/saliva



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

Oral mucosa: RP1 DNA was rarely detected and mostly at low levels on oral mucosa (**Figure 6**), with 20/272 patients and 24/1909 samples testing positive for RP1 DNA (**Tables 1** and **2**).

Sample and patient incidence of RP1 DNA detection

Table 1: Patient incidence of RP1 DNA detection[a]

	Baseline HSV-1 seronegative N=75	Baseline HSV-1 seropositive N=203	Baseline HSV-1 unknown N=7	Overall N=285
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)	36/199 (18.1)
Mucosa	5/71 (7.0)	15/194 (7.7)	0/7 (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)	8/271 (3.0)

[a]Data indicate number of patients positive/number of patients tested (%).
HSV-1, herpes simplex virus type 1.

Table 2: Sample incidence of RP1 DNA detection[a]

	Baseline HSV-1 seronegative	Baseline HSV-1 seropositive	Baseline HSV-1 unknown	Overall
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)	75/1025 (7.3)
Mucosa	5/549 (0.9)	19/1323 (1.4)	0/37 (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)	11/1834 (0.6)

[a]Data indicate number of samples positive/number of samples tested (%).
HSV-1, herpes simplex virus type 1.

$TCID_{50}$ from positive qPCR swab samples

Live virus was only detected from 1 injection-site swab (from the right neck) that tested positive for RP1 DNA. This sample came from an injection-site sample collected 48 hours post-cycle 1 RP1 injection visit. All follow-up samples for that patient were negative.

Figure 7. Differences between wild-type HSV and HSV-based OIs[4]

Wild-type HSV may replicate and transmit to others, potentially resulting in community spread. Attenuated HSV-based OIs are limited to replication within tumors and do not show evidence of transmission to close contacts.

HSV, herpes simplex virus; OI, oncolytic immunotherapy.

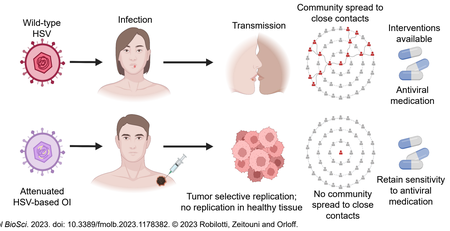


Figure adapted from: Robilotti E, et al. *Front Mol BioSci*. 2023. doi: 10.3389/fmolb.2023.1178382. © 2023 Robilotti, Zeitouni and Orloff.

Conclusions

- RP1 live virus was only detected from 1 injection-site swab sample in the entire study; otherwise, only residual RP1 DNA (noninfectious) was present
- Low presence of DNA on exterior dressing samples suggests that dressings act as an effective barrier
- Overall, RP1 showed negligible potential for viral transmission to pharmacy staff and other caregivers, patients, and their families, with no evidence of transmission or herpetic infection reported
- Evaluating and understanding biodistribution and shedding data of viral OIs will be critical for developing internal handling protocols as pharmacy staff and other caregivers incorporate their use into patient care

The 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. Chmielowski B, et al. *J Clin Oncol.* 2023;41(16_suppl):9509-9509.
3. Middleton M, et al. *J Clin Oncol.* 2020;38(15):e22050.
4. Robilotti E, et al. *Front Mol BioSci.* 2023. doi:10.3389/fmolb.2023.1178382

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