Poster Number: 575

Safety and feasibility of intratumoral injection of the RPx family of oncolytic immunotherapies in patients with liver metastasis

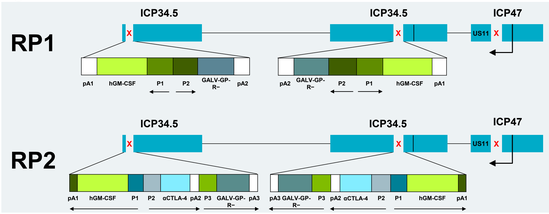
Scott L Baum[1], Andrew Price[2], Tze Y Chan[3], **Tom Hash[4]**, Jeannie Hou[4], Johannes Wolff[4], Robert Coffin[4], Joseph J Sacco[5], Ari M VanderWalde[1], Jiaxin Niu[2]

[1]West Cancer Center and Research Institute, Germantown, TN, USA; [2]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [3]Interventional Radiology, Royal Liverpool University Hospital, Liverpool, UK; [4]Replimune Inc., Woburn, MA, USA; [5]Clatterbridge Cancer Centre, Wirral, UK and University of Liverpool, Liverpool, UK

BACKGROUND

- The liver is a common site of metastasis (mets) for various tumors; liver mets have been linked with resistance to immune checkpoint inhibitors (ICIs) by reducing systemic and tumoral T-cell diversity and numbers[1,2]
  - Furthermore, liver mets are associated with lower rates of overall survival among patients treated with ICIs[3]
- The RP1–3 family of oncolytic immunotherapies (OIs) was developed from a potent clinical strain of herpes simplex virus type 1 (HSV-1) selected for its ability to kill a panel of human cancer cells[4]
  - RP1 is an enhanced-potency oncolytic HSV-1 that expresses a fusogenic glycoprotein (GALV-GP-R−) and granulocyte-macrophage colony–stimulating factor (GM-CSF; **Figure 1**); RP2 additionally expresses an anti-cytotoxic T-lymphocyte–associated antigen 4 (αCTLA-4) antibody-like molecule (**Figure 1**), and RP3 expresses αCTLA-4, 4-1BBL, and CD40L but lacks GM-CSF (not shown)
- RP1–3 OIs are currently being investigated in Phase 1–2 clinical trials, either alone or in combination with anti-programmed cell death protein 1 (PD-1) therapy, in a range of advanced and metastatic solid tumors, including in patients with liver mets[5]
- Intratumoral (IT) OI with RP1–3 is intended to directly provide immunogenic killing of tumors and to induce systemic innate and T-cell–mediated adaptive immune responses to convert immunologically cold tumors to immunologically hot[6]
  - Local immune response: RP1–3 OIs selectively replicate in injected tumors, resulting in local oncolysis. Genetic modifications in RP1–3 trigger key immune pathways, resulting in the activation of a local immune response
  - Distant/systemic immune response: Activated immune cells proliferate and migrate to metastatic tumor locations, causing a systemic immune response resulting in the lysis of noninjected tumors (abscopal effects)
- Here, we report initial findings from a subset of patients who received direct IT injections in liver mets of RP1 (NCT03767348) or RP2 (NCT04336241) alone or combined with nivolumab

Figure 1. RP1 and RP2 backbones



αCTLA-4, anti-cytotoxic T-lymphocyte–associated antigen 4; GALV-GP-R−, gibbon ape leukemia virus surface glycoprotein with the R sequence deleted; hGM-CSF, human granulocyte-macrophage colony–stimulating factor; ICP, infected cell protein; P, promoter; pA, polyA signal; US11, unique short 11.

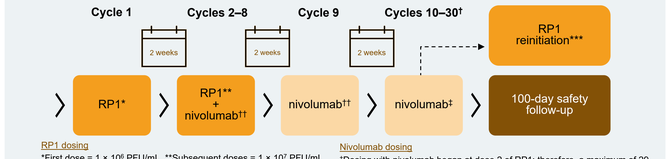
METHODS

- Enrolled patients received up to 10 mL of RP1–2 by IT injection (**Table 1**) into one or more superficial or deep-seated/visceral lesions (Dose: 1 × 10^6 plaque-forming unit [PFU]/mL × 1 followed by ≤7 doses of 1 × 10^7 PFU/mL every 2 weeks [Q2W]; recommended Phase 2 dosing was determined by a prior Phase 1/2 study [NCT03767348])
- From the second dose of RP1–2, nivolumab (anti–PD-1) was administered at a dose of 240 mg Q2W for 8 cycles, followed by 480 mg every 4 weeks for the remaining cycles (**Figures 2** and **3**)
- Primary endpoints included safety, tolerability, and overall response rate; secondary endpoints included duration of response, disease control rate, and progression-free survival

Table 1. Injection volume based on size of tumor to be injected

Tumor diameter, cm	0 to 1	>1 to 2	>2 to 3	>3 to 4	>4 to 5	>5 to 7	>7
Volume of RP1, mL	Up to 0.1	Up to 0.5	Up to 1.0	Up to 3.0	Up to 4.0	Up to 6.0	Up to 10.0
Tumor diameter, cm	**≤2**			**>2–5**		**>5**	
Volume of RP2, mL	Up to 1.0			Up to 5.0		Up to 10.0	

Figure 2. RP1 study design (IGNYTE)

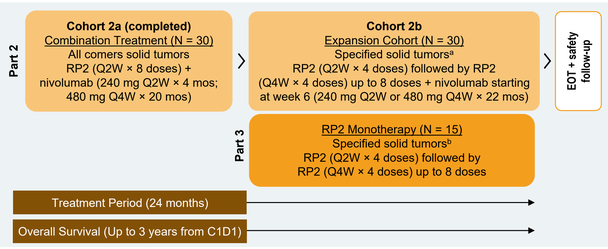


RP1 dosing
*First dose = 1 × 10^6 PFU/mL. **Subsequent doses = 1 × 10^7 PFU/mL. ***Reinitiation of up to 8 additional doses of RP1 Q2W in combination with nivolumab 480 mg Q4W if protocol-specific criteria were met.

Nivolumab dosing
†Dosing with nivolumab began at dose 2 of RP1; therefore, a maximum of 29 cycles of nivolumab were given. ††240 mg (Q2W). ‡480 mg (Q4W).

PFU, plaque-forming units; Q2W, every 2 weeks; Q4W, every 4 weeks.

Figure 3. RP2 study design



[a]Includes advanced/metastatic uveal melanoma, lung cancer, breast cancer, squamous cell carcinoma of the head and neck, or gastrointestinal cancer. [b]Solid tumors (excluding skin cancers) deemed suitable for RP2 monotherapy, including ≥10 patients with liver tumors from lung, breast, squamous cell carcinoma of the head and neck, or gastrointestinal cancer. C1D1, day 1 of treatment cycle 1; EOT, end of treatment; mo, month; Q2W, every 2 weeks; Q4W, every 4 weeks.

RESULTS

Table 2. Demographics and baseline characteristics of patients with liver lesion and IT injection in liver mets

	RP1			RP2		
	Liver mets* injected (n = 30)	Liver mets not injected (n = 27)	All liver mets (N = 57)	Liver mets* injected (n = 10)	Liver mets not injected (n = 5)	All liver mets (N = 15)
Age, median (min–max)	60.5 (28–87)	62.0 (22–81)	61.0 (22–87)	62.5 (38–78)	55.0 (39–64)	57.0 (38–78)
Male, n (%)	23 (76.7)	18 (66.7)	41 (71.9)	6 (60.0)	5 (100.0)	11 (73.3)
Female, n (%)	7 (23.3)	9 (33.3)	16 (28.1)	4 (40.0)	0	4 (26.7)
ECOG PS, n (%)						
0	20 (66.7)	16 (59.3)	36 (63.2)	9 (90.0)	4 (80.0)	13 (86.7)
1	10 (33.3)	11 (40.7)	21 (36.8)	1 (10.0)	1 (20.0)	2 (13.3)
Tumor types, n (%)						
Melanoma	14 (46.7)	16 (59.3)	30 (52.6)	8 (80.0)	4 (80.0)	12 (80.0)
Colon	5 (16.7)	1 (3.7)	6 (10.5)	1 (10.0)	0	1 (6.7)
Head and neck	2 (6.7)	0	2 (3.5)	0	0	0
Other/missing	9 (30.0)	10 (37.0)	19 (33.3)	1 (10.0)	1 (20.0)	2 (13.3)
Prior PD-1 and PD-L1 inhibitors, n (%)						
Yes	13 (43.3)	19 (70.4)	32 (56.1)	6 (60.0)	4 (80.0)	10 (66.7)
Prior CTLA-4 antagonists, n (%)						
Yes	4 (13.3)	10 (37.0)	14 (24.6)	4 (40.0)	4 (80.0)	8 (53.3)
Doses administered, n median (min–max)	5.0 (1–8)	5.0 (2–8)	5.0 (1–8)	6.0	6.0	6.0
Treatment duration, months (median)	1.9	2.3	1.9	2.36	4.00	2.38
Nivolumab doses administered, n median (min–max)	6.0 (2–29)	4.0 (1–28)	5.0 (1–29)	8.0	11.0	9.0
Nivolumab treatment duration, months (median)	2.7	1.9	1.9	4.66	5.82	4.66

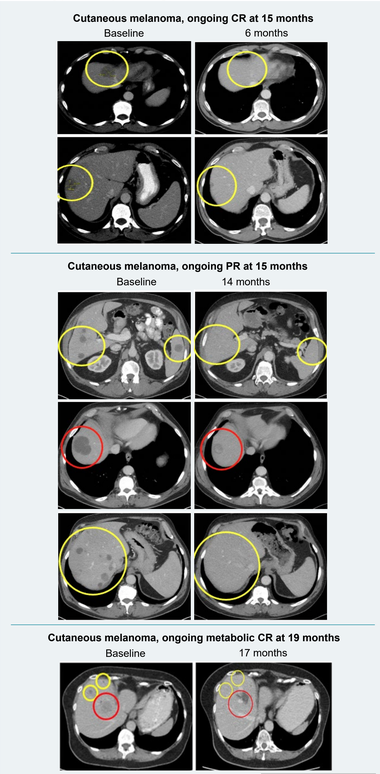
Data extraction: June 2022 for RP1 study and January 2022 for RP2 study. RP1 and RP2 were administered +/- nivolumab.
*RP1 and RP2 injection volume ranged from 0.5 mL to 10 mL in 1–2 liver lesions.
CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; IT, intratumoral; max, maximum; mets, metastases; min, minimum; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Table 3. Any-grade TEAEs (>15%)

	RP1			RP2		
Preferred term, n (%)	Liver mets injected (n = 30)	Liver mets not injected (n = 27)	All liver mets (N = 57)	Liver mets injected (n = 10)	Liver mets not injected (n = 5)	All liver mets (N = 15)
Pyrexia	20 (66.7)	5 (18.5)	25 (43.9)	7 (70.0)	3 (60.0)	10 (66.7)
Nausea	17 (56.7)	8 (29.6)	25 (43.9)	2 (20.0)	3 (60.0)	5 (33.3)
Chills	18 (60.0)	5 (18.5)	23 (40.4)	2 (20.0)	4 (80.0)	6 (40.0)
Hypotension	-	-	-	3 (30.0)	2 (40.0)	5 (33.3)
Fatigue	14 (46.7)	10 (37.0)	24 (42.1)	2 (20.0)	2 (40.0)	4 (26.7)
Back pain	-	-	-	2 (20.0)	2 (40.0)	4 (26.7)
Constipation	7 (23.3)	7 (25.9)	14 (24.6)	0	2 (40.0)	2 (13.3)
Vomiting	12 (40.0)	4 (14.8)	16 (28.1)	0	3 (60.0)	3 (20.0)
Influenza-like illness	8 (26.7)	6 (22.2)	14 (24.6)	1 (10.0)	1 (20.0)	2 (13.3)
Abdominal pain	8 (26.7)	4 (14.8)	12 (21.1)	2 (20.0)	2 (40.0)	4 (26.7)
Pruritus	-	-	-	2 (20.0)	1 (20.0)	3 (20.0)
Arthralgia	6 (20.0)	5 (18.5)	11 (19.3)	0	2 (40.0)	2 (13.3)
Cough	-	-	-	3 (30.0)	0	3 (20.0)
Diarrhea	7 (23.3)	4 (14.8)	11 (19.3)	0	1 (20.0)	1 (6.7)
Decreased appetite	4 (13.3)	5 (18.5)	9 (15.8)	0	1 (20.0)	1 (6.7)
Injection site pain	9 (30.0)	2 (7.4)	11 (19.3)	2 (20.0)	0	2 (13.3)

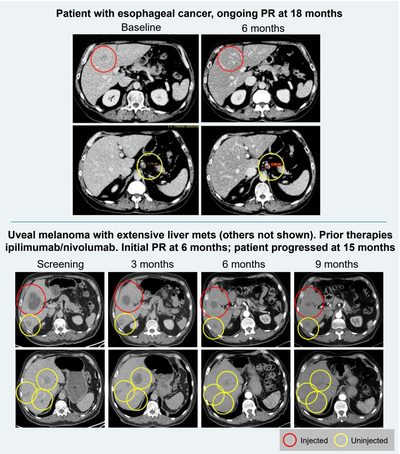
Data extraction: June 2022 for RP1 study and January 2022 for RP2 study. RP1 and RP2 were administered +/- nivolumab. Grade ≥3 TEAEs in all patients with liver mets (injected or not injected): **RP1** (occurring in >1 patient): Abdominal pain (n = 4); lipase increased (n = 4); disease progression (n = 3); anemia, ALT increased, hyperglycemia, pyrexia, and urinary tract infection (n = 2 each; all injected only). **RP2:** Hepatic pain, infusion-related reaction, syncope (n = 1 each; all injected only); abscess limb, acute myeloid leukemia, anemia, arthralgia, hemorrhage, pain, and pancytopenia (n = 1 each; all not injected only).
ALT, alanine aminotransferase; mets, metastases; TEAE, treatment-emergent adverse event.

Figure 4. Example patients with liver mets across tumor types responding to RP1 + nivolumab



CR, complete response; mets, metastases; PR, partial response.

Figure 5. Example patients with liver mets across tumor types responding to RP2 monotherapy



mets, metastases; PR, partial response.

CONCLUSIONS

- RP1–2 ± nivolumab demonstrated good tolerability and clinical activity in patients with heavily pretreated and anti–PD-1 progressed advanced cancers, including in patients with liver mets
- The adverse event profile did not differ from the known safety of the drug class irrespective of administration route, although the incidence of pyrexia, nausea, chills, and fatigue did appear to increase with RP1 following injection into liver mets versus when liver mets were not injected. For RP2, the number of patients dosed in each group is probably too small for any conclusions to be drawn
- IT injection of RP1–2 into liver mets may provide systemic clinical efficacy, including the potential to overcome the underlying resistance to immune checkpoint blockade in these patients

RP1−3 trials are 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, NCT04336241, and NCT04735978).

Corresponding Author Disclosure:
Scott L Baum
Scott L Baum has no conflicts of interest to report
Corresponding author email address: sbaum@WESTCLINIC.com
Author disclosures: Tom Hash, Jeannie Hou, Johannes Wolff, and Robert Coffin are employees of Replimune Inc.

References:
1. Riihimäki, et al. *Cancer Med*. 2018;7(11):5534-42.
2. Yu, et al. *Nat Med*. 2021;27(1):152-64.
3. Chen XJ, et al. *Front Immunol*. 2021;12:651086.
4. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.
5. Aroldi F, et al. *J Immunother Cancer*. 2020;8:421.
6. Melero I, et al. *Nat Rev Clin Oncol*. 2021;18(9):558-76.

Acknowledgements:
The authors would like to thank the patients for their participation in the trial. Medical writing and editorial support were provided by Tony Sallese, PhD, of AlphaBioCom, LLC (King of Prussia, PA, USA), and was funded by Replimune Inc. (Woburn, MA, USA).

Study Sponsor:
These studies are sponsored by Replimune Inc., Woburn, MA, USA.
Nivolumab was supplied by Bristol Myers Squibb.

Presented at the Society for Immunotherapy of Cancer (SITC) Congress 2022, November 8–12, 2022; Boston, MA