Abstract: TPS4178

Trial in progress: An open-label, multicenter study investigating RP3 oncolytic immunotherapy in combination with first- or second-line systemic atezolizumab and bevacizumab therapy in patients with locally advanced unresectable or metastatic hepatocellular carcinoma

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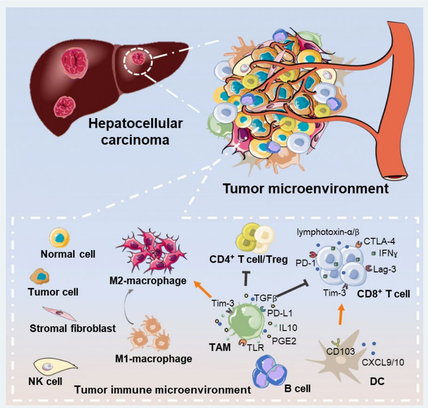
Background

- Primary liver cancer is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide[1]
- Hepatocellular carcinoma (HCC) accounts for ~90% of cases[2]
- Only a minority of patients with unresectable HCC achieve durable benefit from standard-of-care systemic therapies, as many develop resistance to available therapies, and long-term survival rates remain poor[3]
  - The combination of atezolizumab (anti–programmed death-ligand 1 [PD-L1]) and bevacizumab (anti–vascular endothelial growth factor [VEGF]) is the preferred first-line (1L) therapy for advanced HCC,[4] but less than a third of patients respond and approximately half progress within 6 months[5,6]
- The immunosuppressive tumor microenvironment of HCC (**Figure 1**), mediated in part by activated immune checkpoint signaling and angiogenesis pathways,[7] likely contributes to therapeutic resistance and provides the rationale to explore combination-based approaches in this disease state
  - HCC is amenable to lesion-directed therapy, as this is the standard of care until systemic therapy is initiated[4]

Figure 1. Immunosuppressive tumor microenvironment in HCC



Adapted from Zhou J, et al. Potential therapeutic targets in the tumor microenvironment of hepatocellular carcinoma: reversing the protumor effect of tumor-associated macrophages. *J Exp Clin Cancer Res*. 2021;40(1):73. CC BY 4.0 license: https://creativecommons.org/licenses/by/4.0/.
CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte antigen 4; CXCL9/10, CXC motif chemokine ligand 9/10; DC, dendritic cell; HCC, hepatocellular carcinoma; IL, interleukin; IFN, interferon; Lag-3, lymphocyte activation gene 3; M1, type 1 macrophage; M2, type 2 macrophage; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PGE2, prostaglandin E2; TAM, tumor-associated macrophage; TGFβ, transforming growth factor β; Tim-3, T-cell immunoglobulin and mucin domain-containing protein 3; TLR, toll-like receptor; Treg, regulatory T cell.

- Tumor-directed oncolytic immunotherapies (TDOIs) consist of naturally occurring or genetically modified viruses designed to kill tumors via a dual mechanism of action[8]:
  1) Direct viral killing of the tumor and alteration of the tumor microenvironment
  2) Release of tumor antigens to potentially ignite a strong and durable systemic immune response (**Figure 2**)
- The RP1–3 family of TDOIs was developed from a potent clinical strain of herpes simplex virus type 1 (HSV-1) selected for its ability to kill human cancer cells[9]; a series of genetic modifications further enhance oncolytic activity (**Table 1**)

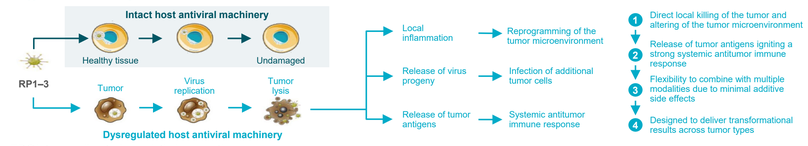
Table 1. RP1–3 HSV-1–based TDOIs

		Clinical program		
		RP1	RP2	RP3
RH018A viral strain	Optimized tumor infectivity and lytic activity; engineered for selective replication	✓	✓	✓
GALV-GP-R−	Increased tumor killing and immunogenic cell death	✓	✓	✓
GM-CSF	Dendritic cell expansion and maturation	✓	✓	
Anti–CTLA-4	Blockade of APC/T-cell feedback loop		✓	✓
CD40L	APC maturation, T-cell costimulation, inflammatory cytokine release (IFN-γ)			✓
4-1BBL	T-cell costimulation, NK cell ADCC, APC maturation, inflammatory cytokine release (IL-2, IL-8, IL-12, IFN-γ)			✓

4-1BBL, 4-1BB ligand; ADCC, antibody-dependent cellular cytotoxicity; APC, antigen-presenting cell; CD40L, cluster of differentiation 40 ligand; CTLA-4, cytotoxic T-lymphocyte antigen 4; GALV-GP-R−, gibbon ape leukemia virus glycoprotein with the R sequence deleted; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV-1, herpes simplex virus type 1; IFN, interferon; IL, interleukin; NK, natural killer; TDOI, tumor-directed oncolytic immunotherapy.

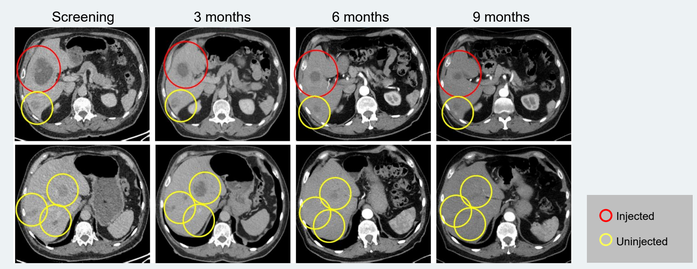
- Intratumoral administration of RP1 and RP2 alone or in combination with immune checkpoint inhibition demonstrated antitumor activity in a variety of tumor types; delivery to metastatic liver lesions can induce an abscopal effect in uninjected hepatic and extrahepatic lesions (**Figure 3**)
- RP3 expresses the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R−), an anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody-like molecule, and costimulatory CD40 and 4-1BB activating ligands (**Table 1** and **Figure 4**)
  - Boosting immune activation with RP3 may help overcome therapeutic resistance, which might be further enhanced through combination with atezolizumab, alone or combined with bevacizumab, to improve outcomes in patients with advanced HCC

Figure 2. Proposed dual mechanism of action of TDOI



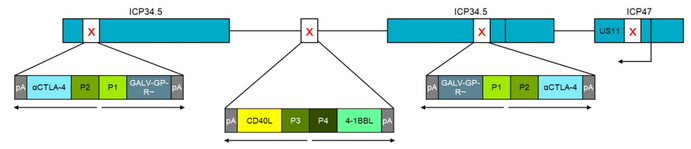
TDOI, tumor-directed oncolytic immunotherapy.

Figure 3. Response of liver metastases to RP2 monotherapy



Representative example of a patient with uveal melanoma with extensive liver metastases who responded to RP2 monotherapy in a phase 1 study. Prior therapies included ipilimumab/nivolumab. The patient had initial partial response at 6 months and ultimately progressed at 15 months.

Figure 4. RP3 backbone



αCTLA-4, anti–cytotoxic T-lymphocyte antigen 4; 4-1BBL, 4-1BB ligand; CD40L, cluster of differentiation 40 ligand; GALV-GP-R−, gibbon ape leukemia virus glycoprotein with the R sequence deleted; ICP, infected cell protein; P, promoter; pA, polyA signal; US11, unique short 11; X, denotes inactivation of viral protein.

Objective

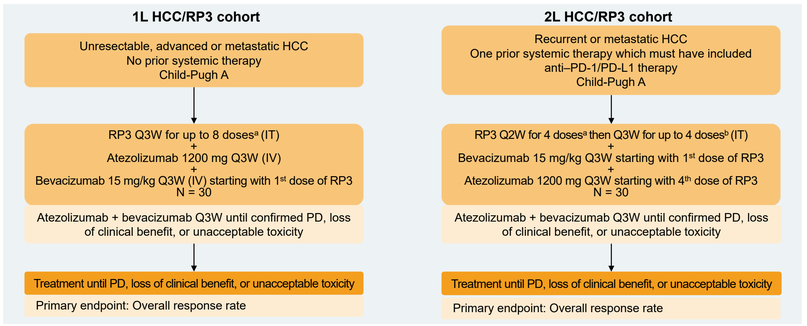
- To assess the efficacy and safety of RP3 in combination with atezolizumab and bevacizumab as 1L or second-line (2L) systemic treatment in patients with locally advanced unresectable or metastatic HCC

Trial design

Trial design

- Phase 2, open-label, multicenter, 2-cohort trial (**Figure 5**)
- Patients will be assigned based on their disease characteristics and prior therapy; up to 30 patients will be enrolled in each cohort
  - 1L: Patients with locally advanced unresectable or metastatic HCC eligible for 1L treatment with atezolizumab + bevacizumab combination therapy, who have not previously received systemic treatment, will receive atezolizumab + bevacizumab combined with RP3
  - 2L: Patients with recurrent or metastatic HCC who progressed on 1 prior systemic treatment, which must have included anti–programmed cell death protein 1 (PD-1)/PD-L1 therapy, will receive atezolizumab + bevacizumab combined with RP3

Figure 5. Study design of 1L and 2L cohorts



[a]First dose at a concentration of 1×10^6 PFU/mL with subsequent doses at 1×10^7 PFU/mL.
[b]At 1×10^7 PFU/mL.
Re-initiation of up to 8 additional doses of RP3 Q3W in combination with atezolizumab + bevacizumab is permitted in both cohorts, provided all criteria for second course are met.
1L, first line; 2L, second line; HCC, hepatocellular carcinoma; IT, intratumoral; IV, intravenous; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFU, plaque-forming unit; Q2W, every 2 weeks; Q3W, every 3 weeks.

Treatment administration

- RP3 will be administered by direct or image-guided injection into visceral and/or nodal solid tumors, with multiple tumors injected whenever possible; injections are made into the largest suitable lesion(s) at volumes dependent on tumor size (**Table 2**)

Table 2. RP3 injection volume by tumor size

Tumor diameter (cm)	RP3 injection volume (mL)
<2	Up to 1.0
2–5	Up to 5.0
>5	Up to 10.0

Key eligibility criteria

Inclusion (both cohorts)

- ≥18 years of age
- Locally advanced unresectable, recurrent, and/or metastatic HCC confirmed by histologic or cytologic analysis or clinical features plus imaging criteria
- Child-Pugh A, determined within 14 days before first study treatment
- At least 1 measurable tumor of ≥1 cm in longest diameter (or ≥1.5 cm shortest diameter for lymph nodes) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- Injectable tumor(s), which alone or in aggregate, total ≥1 cm in diameter
- Eastern Cooperative Oncology Group performance status 0 or 1
- Adequate hematologic, hepatic, and renal function

Exclusion (both cohorts)

- Child-Pugh B or C
- Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding
- Macroscopic intravascular invasion into the hepatic and/or segmental portal vein(s), hepatic vein, vena cava, and/or other major blood vessel(s), or into the hepatic and/or common bile duct(s)
- Known acute or chronic hepatitis B (surface antigen [HBsAg] reactive) or C (HCV RNA detected) virus
  - Patients who have been effectively treated are eligible for enrollment if negative for HBsAg and HCV RNA
- Active significant herpetic infections or prior complications of HSV-1 infection or requirement for intermittent or chronic use of systemic antivirals with known antiherpetic activity

Key endpoints

Primary

- Overall response rate (ORR), defined as the proportion of patients achieving a best overall response of complete response (CR) or partial response per RECIST v1.1 as modified for use in this study

Secondary

- Frequency, nature, and severity of treatment-emergent adverse events and serious adverse events
- ORR per RECIST modified for HCC (HCC-mRECIST)[10]
- Duration of response
- CR rate
- Clinical benefit rate
- Progression-free survival
- Overall survival

Enrollment

This study is currently 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 (NCT05733598).

Acknowledgments

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Study sponsor

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