Abstract: TPS3628

Trial in progress: An open-label clinical trial of RP2 and RP3 oncolytic immunotherapy in combination with atezolizumab and bevacizumab for the treatment of patients with advanced colorectal carcinoma

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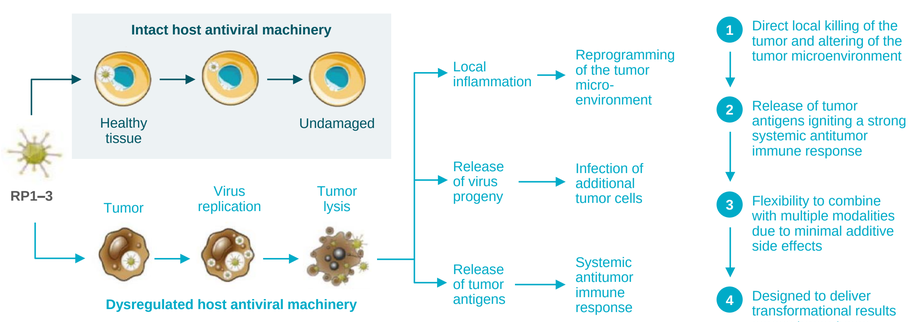
Background

- Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer-related mortality worldwide[1]
- Programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibition, alone or in combination with other modalities, has demonstrated significant benefit in patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC[2,3]
  - However, these agents have limited, if any, clinical benefit in patients with microsatellite stable (MSS) or mismatch repair proficient (pMMR) CRC[4]
- The first line of therapy for patients with advanced/unresectable pMMR/MSS CRC who had disease progression on checkpoint inhibitor immunotherapy (such as anti–PD-1) is chemotherapy in combination with targeted therapies, such as the anti–vascular endothelial growth factor antibody bevacizumab[5]
- Tumor-directed oncolytic immunotherapies (TDOIs) consist of naturally occurring or genetically modified viruses proposed to kill tumors via a dual mechanism of action intending to provide[6] (**Figure 1**):
  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 1. Proposed dual mechanism of action of TDOI



TDOI, tumor-directed oncolytic immunotherapy.

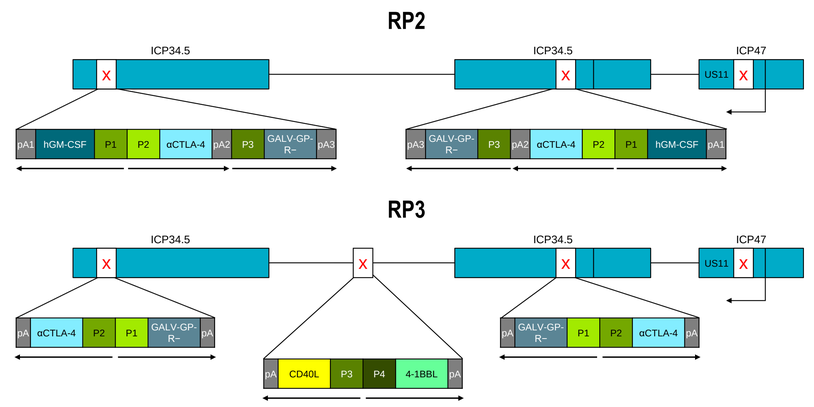
- RP2 is an enhanced potency oncolytic herpes simplex virus type 1 (HSV-1) that expresses the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R–), granulocyte-macrophage colony-stimulating factor (GM-CSF), and an anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody-like molecule (**Table 1**, **Figure 2**)
- RP3 expresses GALV-GP-R–, an anti–CTLA-4 antibody-like molecule, and 4-1BB and CD40 activating ligands; RP3 does not express GM-CSF (**Table 1**, **Figure 2**)
- RP2 has demonstrated preliminary safety and efficacy in patients with solid tumors[7] and RP3 has shown efficacy in a preclinical study[8]

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.

Figure 2. RP2 and 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; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; ICP, infected cell protein; P, promoter; pA, polyA signal; US11, unique short 11; X, denotes inactivation of viral protein.

Objective

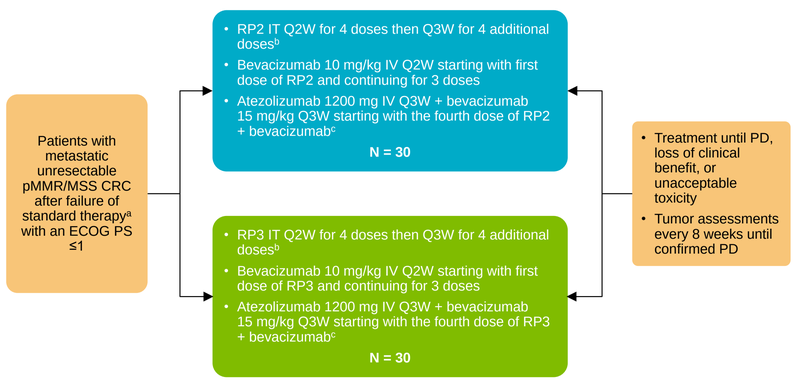
- To assess the efficacy and safety of RP2 or RP3 in combination with atezolizumab and bevacizumab in patients with advanced MSS and pMMR CRC

Trial design

Trial design

- This is an open-label, nonrandomized, phase 2 trial (NCT05733611)
- Patients will be allocated to 2 groups and receive either RP2 or RP3 in combination with atezolizumab and bevacizumab (**Figure 3**)
- Treatment groups will enroll patients simultaneously; each treatment group will consist of 30 patients (**Figure 3**)
  - At clinical trial sites that have both groups open, patients will be automatically assigned by central allocation after screening assessments are completed

Figure 3. Study design



[a]Patients must have had PD or were intolerant to treatment protocols that included irinotecan and oxaliplatin. Epidermal growth factor receptor or vascular endothelial growth factor receptor–directed therapies are allowed as part of the previous therapy if indicated. Other prior therapies are not allowed. [b]Additional courses of up to 8 doses of RP2/RP3 Q3W per course as monotherapy or in combination with atezolizumab/bevacizumab if protocol-specified criteria are met. [c]After completion of a course(s) of RP2/RP3, atezolizumab and bevacizumab treatment will continue Q3W until confirmed PD, loss of clinical benefit, or unacceptable toxicity.
CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IT, intratumoral; IV, intravenous; MSS, microsatellite stable; PD, progressive disease; pMMR, proficient mismatch repair; Q2W, once every 2 weeks; Q3W, once every 3 weeks.

Treatment administration

- RP2 or RP3 will be injected by direct (including via colonoscope) or image-guided injection into injectable tumors (including subcutaneous, visceral, and nodal tumors)
- When RP2 or RP3 and atezolizumab and bevacizumab are administered the same week, atezolizumab and bevacizumab must be given within ± 72 hours of RP2/RP3

Key eligibility criteria

Inclusion

- ≥18 years of age
- Histological or cytologic diagnosis of colorectal adenocarcinoma that is unresectable or metastatic
- Had disease progression or were intolerant to treatment protocols that included irinotecan and oxaliplatin. Epidermal growth factor receptor or vascular endothelial growth factor receptor–directed therapies are allowed as part of the previous therapy if indicated. Other prior therapies are not allowed
- At least 1 measurable tumor of ≥1 cm in longest diameter (or ≥1.5 cm shortest diameter for lymph nodes)
- Has injectable tumor(s) of ≥1 cm in aggregate total diameter
- Eastern Cooperative Oncology Group performance status 0 to 1
- Adequate hematologic, hepatic, and renal function

Exclusion

- Receipt of more than 3 lines of therapy for CRC
- MSI-H/dMMR disease
- Known acute or chronic hepatitis B or C virus or HIV infection
- Presence of a systemic infection requiring intravenous antibiotics or other serious infection within 14 days prior to dosing
- Active significant herpetic infections or prior complications of HSV-1 infection
- Active or history of central nervous system metastases and/or carcinomatous meningitis
- Macroscopic intravascular invasion into any large blood vessel such as the main portal vein, hepatic vein, pulmonary arteries or veins, aorta, or vena cava
- Significant bleeding event within the last 12 months that places the patient at unjustifiable risk for bleeding from deep intratumoral injection procedures based on investigator assessment or interventional radiologist assessment

Key endpoints

Primary

- Objective response rate, defined as the proportion of patients achieving a best overall response of complete or partial response (per Response Evaluation Criteria in Solid Tumors v1.1 as modified for the study) among those that are evaluable for response

Secondary

- Frequency, nature, and severity of treatment-emergent adverse events and serious adverse events
- Overall survival
- Progression-free survival
- Duration of response
- Duration of clinical benefit
- Complete response rate

Exploratory

- Health-related quality of life
- Changes in biomarkers after initiation of treatment
- Biodistribution and shedding of RP2/RP3
- Changes in levels of anti–HSV-1 antibodies
- Antitumor response in injected vs uninjected tumors

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 (NCT05733611).

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References

1. International Agency for Research on Cancer. Colorectal cancer. Globocan 2020; https://gco.iarc.f r/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf.
2. Andre T, et al. *N Engl J Med*. 2020;383:2207-18.
3. Li Y, et al. *BMC Gastroenterol*. 2022;22:431.
4. Marmorino F, et al. *Cancers*. 2020;12:2317.
5. NCCN Clinical Practice Guidelines in Oncology, Colon Cancer, version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
6. Kaufman HL, et al. *Nat Rev Drug Discov*. 2015;14:642-62.
7. Harrington KJ, et al. *Ann Oncol*. 2022;33:S926-7.
8. Bommareddy PK, et al. *Cancer Res*. 2023;83:S7:6639.

Study sponsor

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