Abstract: TPS2705

An open-label, multicenter, phase 1 study of RP3 as a single agent and in combination with nivolumab in patients with solid tumors

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Background

- Oncolytic immunotherapies act through a dual mechanism of action involving direct killing of tumors and the induction of an anticancer immune response to provide overall systemic benefit (**Figure 1**) [1]
- RP3 is a genetically modified herpes simplex virus 1 (HSV-1) that encodes for the gibbon ape leukemia virus surface glycoprotein with the R-sequence deleted (GALV-GP-R−), an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody-like molecule, cluster of differentiation 40 ligand (CD40L), and 4-1BB ligand (4-1BBL) [2,3]
- Together, these encoded genes are intended to increase oncolytic potency, cell-to-cell spread, immunogenic cell death, and systemic immune activation
- RP3 is the third in a series of HSV-based oncolytic immunotherapies under clinical development by Replimune (**Table 1**)
- Antitumor activity was demonstrated in preclinical models using viruses similar to RP3 expressing murine versions of anti–CTLA-4, CD40L, and 4-1BBL, both alone and in combination with programmed cell death protein 1 (PD-1) blockade [4]

Objectives

- Evaluate the safety and tolerability of RP3 as monotherapy or in combination with anti–PD-1 therapy (nivolumab) in patients with solid tumors
- Determine the recommended phase 2 dose (RP2D) of RP3

Figure 1. Dual mechanism of oncolytic virus therapy

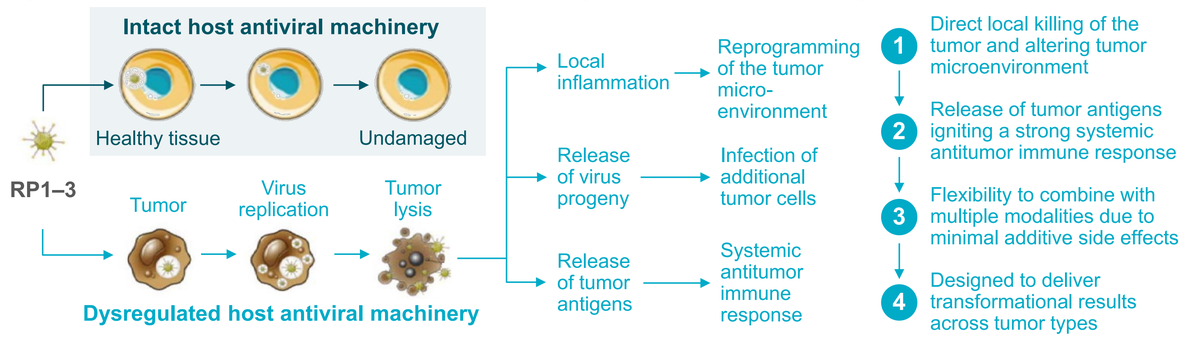


Table 1. Product candidates in clinical development

		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-ɣ)			✓
4-1BBL	T-cell costimulation, NK cell ADCC, APC maturation, inflammatory cytokine release (IL-2, IL-8, IL-12, IFN-ɣ)			✓

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

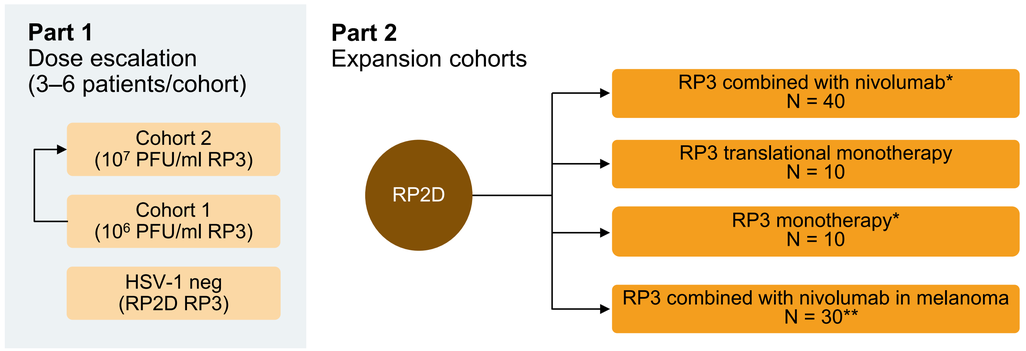
Trial Design

- This is an open-label, multicenter, phase 1 clinical trial evaluating RP3 as monotherapy or in combination with nivolumab in patients with solid tumors (NCT04735978)
- Part 1 evaluated escalating doses of RP3 in a 3+3 dose escalation design
- Patients in Part 1 received intratumoral (IT) injections of ≤10 ml RP3 into superficial, nodal, or visceral lesions once every 2 weeks (Q2W) x 5 doses across two dose levels (**Table 2**)
  - Dose level 1: 1 x 10^5 plaque-forming units (PFU)/ml once, then 1 x 10^6 PFU/ml x 4
  - Dose level 2: 1 x 10^6 PFU/ml once, then 1 x 10^7 PFU/ml x 4
  - RP2D: 1 x 10^6 PFU/ml once, followed by 1 x 10^7 PFU/ml IT Q2W

Table 2. RP3 injection volume by tumor size

Tumor diameter	RP3 injection volume
≤2 cm	Up to 1 ml
>2–5 cm	Up to 5 ml
>5 cm	Up to 10 ml

Figure 2. Study design



*Patients in Cohorts 1 & 3 must have squamous cell carcinoma of head and neck, lung cancer, breast cancer, or gastrointestinal cancers (including hepatocellular carcinoma, colorectal cancer, gastric cancer, esophageal cancer, etc) and 50% must have injections to liver tumors.
**Not yet open for enrollment.
HSV-1, herpes simplex virus 1; PFU, plaque-forming units; RP2D, recommended phase 2 dose.

- In Part 2, patients are being enrolled into expansion cohorts of patients with gastrointestinal cancer (including hepatocellular carcinoma [HCC]), lung cancer, breast cancer, and squamous cell carcinoma of the head and neck treated with RP3 combined with nivolumab
- Additional cohorts will enroll patients treated with RP3 monotherapy, including to further explore biomarkers in both injected and uninjected tumors
- There is also the potential to open a cohort in melanoma
- Patients receive up to 8 doses of RP3 and may receive up to 8 additional doses of RP3 if protocol-specified criteria are met

Key Eligibility Criteria

Inclusion

- Male or female ≥18 years of age
- Patients with histologically or cytologically confirmed advanced or metastatic non-neurological solid tumors, who have received all appropriate standard-of-care (SOC) anticancer therapies for advanced or metastatic disease, as defined by applicable guidelines and deemed by the Investigator to be in the best interest of the patient
  - Transarterial chemoembolization is counted as a systemic therapy for HCC
  - Patients who have received nonSOC therapies may be eligible after discussion with Medical Monitor
  - Patients who, in the opinion of the Investigator, are deemed not appropriate candidates for SOC systemic anticancer therapy for advanced or metastatic disease, or the patient has refused SOC therapy, may be eligible after discussion with the Medical Monitor
  - For patients who are not appropriate candidates or who refused SOC therapy (or therapies), the therapy, rationale, and justification for the lack of appropriateness and/or refusal must be documented
- Cohorts 1 & 3: Patients must have a diagnosis of head and neck cancer, lung cancer, breast cancer, or gastrointestinal cancer (including but not limited to HCC, colorectal, gastric, and esophageal cancers)
  - Half of patients must have ≥1 liver tumor intended for injection

Exclusion

- Prior oncolytic virus therapy
- History of hepatitis B virus (HBV), hepatitis C virus (HCV) other than per the below for HCC, or human immunodeficiency virus infection
  - HCC patients with a diagnosis of HBV must be off antiviral therapy for ≥4 weeks prior to enrollment, and HBV load by real-time polymerase chain reaction must be below the limit of quantitation
  - HCC patients with past or ongoing HCV infection must have completed treatment for HCV ≥1 month prior to enrollment, and HCV viral load must be undetectable
  - Patients with a diagnosis of HBV or HCV must be expected to not require antiviral therapy during the RP3 treatment period
- Liver metastasis exceeding 1/3 of the liver volume
- Prior major liver resection (remnant liver <50% of the initial liver volume; patients with a biliary stent can be included)
- Prior chemoembolization, radioembolization, or other local/liver-directed procedures to the lesion selected for virus injection
- Macroscopic intravascular invasion by tumors of the main portal vein, hepatic vein, or vena cava
- Significant bleeding event within the last 12 months that places the patient at risk for complication during intrahepatic IT injection procedure based on Investigator assessment

Key Endpoints

Primary

- Objective response rate per cohort as assessed by the Investigator using modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- Safety and tolerability of RP3 monotherapy as assessed by the incidence of dose-limiting toxicities
- Determine the RP2D of RP3
- Safety of RP3 in combination with nivolumab as assessed by the incidence of adverse events and laboratory abnormalities

Secondary

- Complete response rate, disease control rate, duration of response, and progression-free survival per cohort as assessed by the Investigator using RECIST v1.1 as modified for use in this study
- 1-year and 2-year overall survival rates

Exploratory

- Biological activity per cohort as assessed by individual tumor responses
- Presence and patient incidence of RP3 in blood and urine
- Presence and patient incidence of RP3 in saliva/oral mucosa, at the injection sites, on the exterior of dressings, and on lesions that appear to be herpetic
- Changes in levels of anti–HSV-1 antibodies compared with baseline
- Safety and tolerability of RP3 monotherapy in HSV-1 seronegative patients
- Assess local and systemic immune responses and immunologically relevant molecular changes through biomarker analysis of tumor biopsies from both injected and uninjected tumor lesions and blood specimens

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 (NCT04735978).

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Study Sponsor

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