Abstract: TPS6106

Trial in progress: A phase 2, open-label, multicenter study investigating efficacy and safety of RP3 oncolytic immunotherapy combined with other therapies in patients with locoregionally advanced or recurrent squamous cell carcinoma of the head and neck

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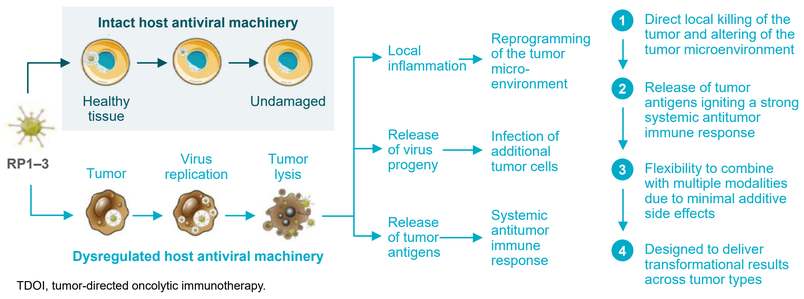
Background

- Head and neck cancers were estimated to account for >50,000 new cancer diagnoses and >11,000 deaths in the US in 2022[1]
- Squamous cell carcinoma of the head and neck (SCCHN) comprises about 90% of head and neck cancers[2,3]
- Standard initial therapy for locally advanced (LA) SCCHN is concurrent chemoradiation therapy (CCRT) or definitive resection followed by adjuvant radiation ± chemotherapy[3]; standard first-line therapy for recurrent/metastatic (R/M) SCCHN includes immune checkpoint inhibitors (anti–programmed cell death protein 1 [PD-1]) ± chemotherapy, chemotherapy ± cetuximab, or salvage surgery[3,4]
  - Even with standard-of-care frontline therapy, >50% of patients with LA SCCHN relapse within 2 years of initial treatment[4-6]; those with R/M SCCHN also have poor prognoses, and the benefits of frontline anti–PD-1 therapy are generally limited to patients with programmed death-ligand 1 (PD-L1) combined positive score (CPS) positivity[7,8]
- Standard chemoimmunotherapy regimens have generally shown limited efficacy in patients with SCCHN to date, highlighting an unmet need for new immunotherapies that can be safely combined with standard-of-care treatments to improve clinical outcomes
  - Combination of standard-of-care chemoradiotherapy (CRT) with anti–PD-1/PD-L1 in patients with LA SCCHN did not prolong event-free survival (KEYNOTE-412)[9] or progression-free survival (PFS; JAVELIN Head and Neck 100)[10] vs CRT control arms in 2 randomized phase 3 trials
- Tumor-directed oncolytic immunotherapies (TDOIs) consist of naturally occurring or genetically modified viruses proposed to kill tumors via a dual mechanism of action (**Figure 1**)[11]:
  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
- An early-phase clinical study in patients with LA SCCHN showed that a modified herpes simplex virus type 1 (HSV-1)–based TDOI combined with CRT induced high response rates without major safety concerns[12]
- RP3 is the third agent in a series of HSV-1–based TDOIs under clinical development by Replimune (**Table 1**, **Figure 2**); it is an enhanced potency, modified version of HSV-1 expressing 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
  - RP1–3 are designed to exert antitumor activity at several steps in the cancer-immunity cycle, which may be further augmented by combination with other treatment modalities (**Figure 3**)
  - Preliminary activity has been demonstrated in advanced solid tumors, including SCCHN, in an ongoing phase 1 clinical trial

Figure 1. Proposed dual mechanism of action of TDOI



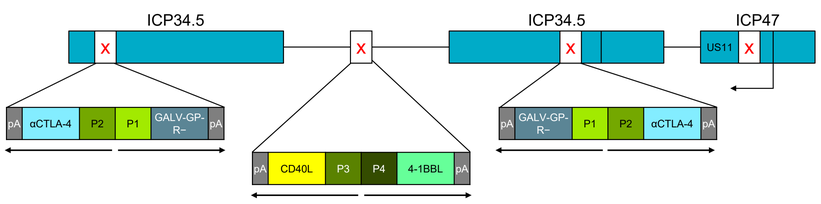
TDOI, tumor-directed oncolytic immunotherapy.

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)			✓

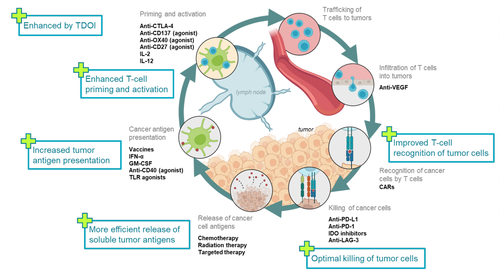
4-1BBL, 4-1BB ligand; ADCC, antibody-dependent cellular cytotoxicity; APC, antigen-presenting cell; CD40L, cluster of differentiation 40 ligand; CTLA-4, cytotoxic T-lymphocyte antigen 4; GALV-GP-R−, gibbon ape leukemia virus glycoprotein with the R sequence deleted; GM-CSF, granulocyte-macrophage colony-stimulating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

Figure 2. 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.

Figure 3. The cancer-immunity cycle: Potential for combination therapies with TDOI



CAR, chimeric antigen receptor; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte antigen 4; GM-CSF, granulocyte-macrophage colony-stimulating factor; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; IFN-α, interferon-alpha; LAG-3, lymphocyte activation gene-3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TDOI, tumor-directed oncolytic immunotherapy; TLR, toll-like receptor; VEGF, vascular endothelial growth factor.

Objective

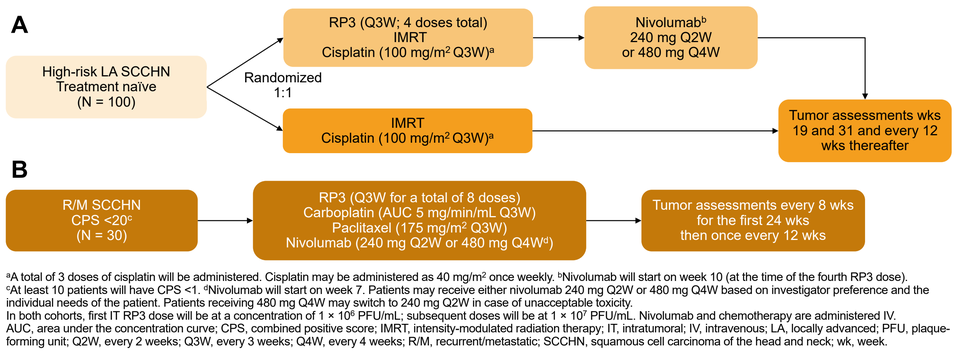
- To describe the study design of an open-label phase 2 trial evaluating the efficacy and safety of RP3 combined with other therapies in patients with advanced, inoperable, treatment-naïve LA or R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx (NCT05743270)

Trial design

Trial design

- The study schema is illustrated in **Figure 4**
- The LA cohort will enroll up to 100 patients; the R/M cohort will enroll up to 30 patients
- Patients in the LA cohort will be randomized 1:1 to receive RP3 + standard-of-care cisplatin-based CCRT, followed by nivolumab, vs CCRT alone
  - Stratification factors used in randomization are CPS (all patients; ≥20 vs <20) and human papillomavirus (HPV) status for patients with oropharyngeal tumors (based on p16 expression; positive vs negative)
- Patients in the R/M cohort will receive RP3 + nivolumab + carboplatin/paclitaxel
- A formal safety evaluation will be performed by an independent data monitoring committee (IDMC) approximately 30 days after the first 3 patients have completed 2 RP3 doses and every 6 months thereafter for both cohorts

Figure 4. Study design



[a]A total of 3 doses of cisplatin will be administered. Cisplatin may be administered as 40 mg/m² once weekly. [b]Nivolumab will start on week 10 (at the time of the fourth RP3 dose). [c]At least 10 patients will have CPS <1. [d]Nivolumab will start on week 7. Patients may receive either nivolumab 240 mg Q2W or 480 mg Q4W based on investigator preference and the individual needs of the patient. Patients receiving 480 mg Q4W may switch to 240 mg Q2W in case of unacceptable toxicity.
In both cohorts, first IT RP3 dose will be at a concentration of 1 × 10^6 PFU/mL; subsequent doses will be at 1 × 10^7 PFU/mL. Nivolumab and chemotherapy are administered IV.
AUC, area under the concentration curve; CPS, combined positive score; IMRT, intensity-modulated radiation therapy; IT, intratumoral; IV, intravenous; LA, locally advanced; PFU, plaque-forming unit; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck; wk, week.

Treatment administration

- LA SCCHN cohort
  - Patients in the RP3 group will receive up to 4 doses of RP3 intratumorally every 3 weeks (Q3W)
  - Nivolumab will be given intravenously after CCRT completion, starting concurrent with the fourth RP3 dose, for up to 1 year
- R/M SCCHN cohort
  - RP3 will be injected for up to 8 doses Q3W
  - Carboplatin/paclitaxel will be given concurrent with RP3 doses
  - Nivolumab will be given, starting concurrent with third RP3 dose, for up to 2 years
- RP3 will be administered via direct (visualization/palpation) or image-guided (eg, computerized tomography scan, ultrasound), laryngoscopic, or endoscopic intratumoral injection into superficial, subcutaneous, nodal, visceral, or deep soft tissue lesions, at the discretion of the treating investigator

Key eligibility criteria

Inclusion

- Adults (≥18 years of age) with histological diagnosis of SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx and/or of lymph node(s) in the neck
- Patients with nodal disease only and no identified primary site will be allowed after appropriate exclusion of potential non–head and neck sources
- Injectable tumors of ≥1 cm in aggregate longest overall diameter
- Eastern Cooperative Oncology Group performance status 0−1
- LA cohort
  - High-risk disease eligible for curative CCRT
  - p16-positive oropharynx cancer must be ≥T3 and/or N2 with smoking history or T4 and/or N3 irrespective of tobacco use
- R/M cohort
  - R/M SCCHN eligible for first-line therapy for locoregional recurrence and/or distant metastases
  - PD-L1 CPS <20

Exclusion

- Primary tumors of nasopharynx, paranasal sinuses, nasal passages, salivary gland, thyroid or parathyroid gland, or skin
- Life expectancy of ≤6 months
- Prior radiotherapy or systemic therapy for SCCHN (for the LA cohort only)
- Eligible for radiation (R/M cohort only) and/or surgery (both cohorts) with curative intent
- Prior systemic therapy for recurrence or new distant metastases of SCCHN (for the R/M cohort only)

Enrollment

This study is registered with recruitment expected to commence Q3 2023. 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 (NCT05743270)

Key endpoints

Primary

- LA cohort: PFS
- R/M cohort: Overall response rate (ORR) based on investigator-assessed Response Evaluation Criteria in Solid Tumors version 1.1

Secondary

- LA cohort: Overall survival (OS), ORR, metabolic ORR, complete response rate (CRR), metabolic CRR, incidence of locoregional and distant metastatic failure, duration of clinical benefit, patient-reported quality of life (QoL), safety (treatment-emergent adverse events [TEAEs], serious adverse events [SAEs])
- R/M cohort: PFS, OS, duration of response, duration of clinical benefit, CRR, disease control rate, number of patients who undergo attempted definitive resection, patient-reported QoL, safety (TEAEs, SAEs)

Study highlights

- This study will evaluate the addition of novel TDOI RP3 to standard treatment and nivolumab, with the goal of improving outcomes in both LA and R/M SCCHN
- Focus on airway and nutrition, including serial assessments of airway stability, swallow function, and nutritional status, to maximize safety and chances for cure
- Randomization (LA cohort only) via double stratification (CPS and HPV status), to reflect key current understanding of tumor biology
- Allowance of unknown primaries, to better address growing unmet needs
- Overall and disease-specific QoL assessments, using patient-reported outcomes, to better understand and address issues of concern to actual patients
- Formal safety reviews (both cohorts) by an IDMC to ensure objectivity; IDMC to monitor efficacy and safety in the LA cohort
- Variable dosing options offered for both cisplatin and nivolumab, to preempt and mitigate toxicity and potentially improve convenience for patients and care providers
- Treatment regimen for the R/M cohort designed on a carboplatin/paclitaxel backbone, to avoid the toxicities associated with a platinum-5 fluorouracil regimen

Acknowledgments

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Study sponsor

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