Abstract: TPS2704

# A phase 1 trial of RP2, a first-in-class, enhanced potency oncolytic HSV expressing an anti–CTLA-4 antibody as a single agent and combined with nivolumab in patients with advanced solid tumors

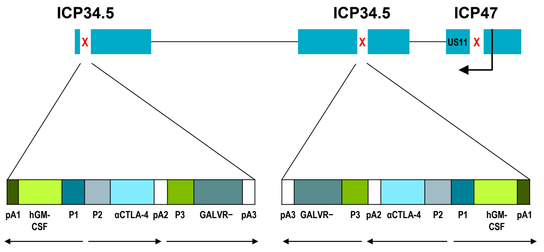
**Kevin Harrington**,[1] Joseph J. Sacco,[2] Anna Olsson-Brown,[2] Tze Y. Chan,[2] Pablo Nenclares,[1] Isla Leslie,[1] Imran Saleem,[3] Praveen K. Bommareddy,[3] Christoph M. Ahlers,[3] Robert S. Coffin,[3] Mark R. Middleton[4]

[1]The Institute of Cancer Research, London, UK; [2]The Clatterbridge Cancer Centre, Wirral UK & University of Liverpool, Liverpool, UK; [3]Replimune, Inc., Woburn, MA; [4]University of Oxford, Oxford, UK

## Background

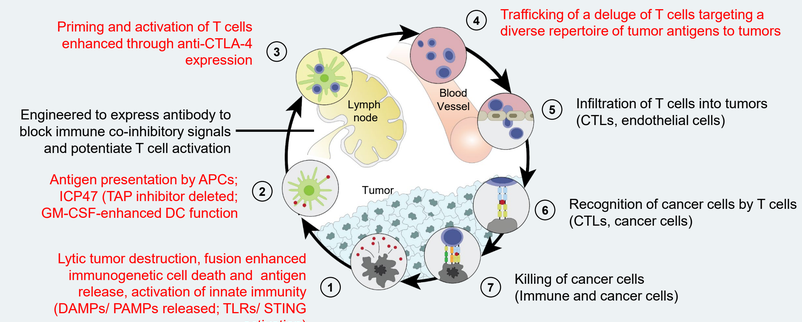
- RP2 is a selectively replication-competent herpes simplex virus-1 (HSV-1) that encodes a codon-optimized sequence for human granulocyte-macrophage colony-stimulating factor, the gibbon ape leukemia virus surface glycoprotein (GALV-GP) with the R− sequence deleted (R−), and an anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody-like molecule (**Figure 1**) [1,2]
- These modifications are intended to increase oncolytic potency through GALV-GP R- expression which mediates cell-to-cell fusion and immunogenic cell death, and to increase systemic immune activation including through the effects of the expression of anti−CTLA-4 (**Figure 2**)
- RP2 has demonstrated antitumor activity in the initial patients treated with RP2 monotherapy (n = 9) and in combination with nivolumab (n = 30)

### Figure 1. RP2




αCTLA-4, α cytotoxic T lymphocyte antigen 4; GALVR−, leukemia virus surface glycoprotein; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; ICP34.5, infected cell protein 34.5; ICP47, infected cell protein 47.

### Figure 2. Intended MOA of RP2




APC, antigen presenting cell; CTL, cytotoxic T cell; CTLA-4, cytotoxic T lymphocyte antigen 4; DAMPs, damage-associated molecular pattern; DC, dendritic cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; ICP47, infected cell protein 47; MOA, mechanism of action; PAMPs, pathogen-associated molecular patterns; STING, stimulator of interferon genes; TAP, transporter associated with antigen processing; TLRs, toll-like receptors.

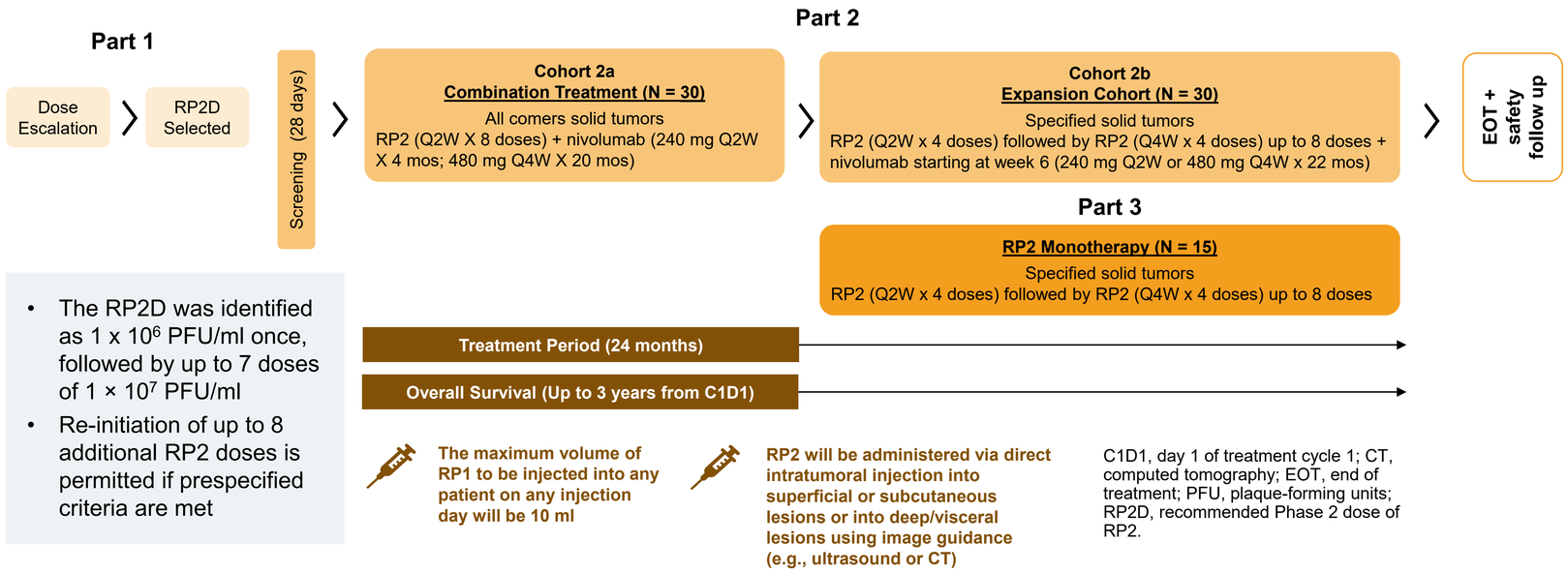
## Objective

Evaluate the safety and tolerability, biodistribution, shedding, including biomarker data, and preliminary efficacy of RP2 alone and in combination with nivolumab in adult patients with advanced solid tumors

## Trial Design

- This is a phase 1 multicenter, open-label, study evaluating RP2 in combination with nivolumab (NCT04336241)
  - Part 1 - Dose Escalation (completed; N = 9) - Patients were enrolled into three sequential RP2 dose level cohorts
  - Part 2 - RP2 at the RP2D in combination with nivolumab
    - Cohort 2a (N = 30; completed) - Patients with solid tumors having failed or refused alternative options
    - Cohort 2b (n = 30) is open for enrollment for patients with advanced or metastatic uveal melanoma, non-small cell lung cancer (NSCLC), breast cancer, head and neck cancer, or gastrointestinal (GI) cancers (NSCLC, breast or GI cancers with liver tumors intended for injection)
  - Part 3 (monotherapy) - Patients will receive RP2 at the RP2D
    - Up to 15 evaluable patients to be enrolled to further evaluate RP2 monotherapy including ≥10 patients with NSCLC, breast or GI cancers with liver tumors intended for injection

### Part 2 Combination Cohorts and Part 3 Monotherapy Phase




- The RP2D was identified as 1 x $10^6$ PFU/ml once, followed by up to 7 doses of 1 × $10^7$ PFU/ml
- Re-initiation of up to 8 additional RP2 doses is permitted if prespecified criteria are met

**The maximum volume of RP1 to be injected into any patient on any injection day will be 10 ml**

**RP2 will be administered via direct intratumoral injection into superficial or subcutaneous lesions or into deep/visceral lesions using image guidance (e.g., ultrasound or CT)**

C1D1, day 1 of treatment cycle 1; CT, computed tomography; EOT, end of treatment; PFU, plaque-forming units; RP2D, recommended Phase 2 dose of RP2.

## Key Eligibility Criteria

### Inclusion

- Male or female ≥18 years of age
- Patients with histologically or cytologically confirmed advanced or metastatic non-neurological solid tumors (tumor types as specified per cohort), who have progressed on standard therapy or cannot tolerate standard therapy
- At least one measurable and injectable tumor ≥1 cm in longest diameter (or shortest diameter for lymph nodes)
- Adequate hematologic, hepatic, and renal function
- Eastern Cooperative Oncology Group performance status 0-1

### Exclusion

- Prior treatment with an oncolytic therapy
- Known history of hepatitis B, or known active hepatitis C virus, or human immunodeficiency virus infection
- Systemic infection requiring IV antibiotics or other serious infection within 14 days prior to dosing
- Active significant herpetic infections or prior complications of HSV-1 infection
- Requires intermittent or chronic use of systemic (oral or IV) antivirals with known antiherpetic activity
- Systemic anticancer therapies within four weeks of first dose
- Known active central nervous system metastases
- Conditions requiring treatment with immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement therapy within 14 days after enrollment

## Key Endpoints

### Primary

- Assess the safety and tolerability of RP2 alone and in combination with nivolumab in all patients, as determined by the incidence of all treatment-emergent adverse events, including immune-mediated and serious adverse events
- Assess the objective response rate following RP2 alone and in combination with nivolumab by investigator review

### Secondary

- Estimate duration of response, complete response rate, disease control rate, and progression-free survival by investigator review
- Evaluate efficacy by one-year and two-year overall survival rates

### Exploratory

- Assess the changes in levels of anti–HSV-1 antibodies during the RP2 treatment period compared to baseline
- Explore the biodistribution and viral shedding of RP2
- Assess the biological activity of RP2 alone and in combination with nivolumab as determined by individual tumor responses
- Assess the safety and tolerability of RP2 alone in HSV-1 seronegative patients

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 (NCT04336241).

### Acknowledgements

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

### References

1. Aroldi F, et al. *J Immunother Cancer.* 2020;8: A421.
2. Middleton M, et al. *J Immunother Cancer.* 2021;9: A507.

### Study Sponsor

The study is sponsored by Replimune Inc, Woburn MA, USA.

### Disclaimer



**Presented at the 2022 American Society of Clinical Oncology (ASCO) meeting, June 3–7, 2022; Chicago, IL, USA**