ARTACUS: An open-label, multicenter, Phase 1b/2 study of RP1 in solid organ transplant recipients with advanced cutaneous malignancies

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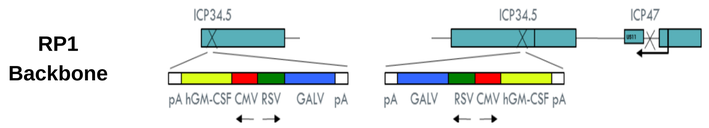
Background

- Solid organ transplantation (SOT) has emerged as an important lifesaving procedure for patients with end-organ diseases characterized by dysfunction or specific organ function failure.
- For SOT recipients, transplant rejection is a major complication and commits patients to a life-long immunosuppressive therapy to prevent rejection.
- Chronic immunosuppression required to prevent rejection of a transplanted organ impairs immune surveillance, allowing tumor cells to proliferate unchecked, and increases the risk of a wide range of cutaneous tumors.
- Non-melanoma skin cancer (NMSC) is the most common post-transplant malignancies that arise in majority of SOT recipients [1].
- Cutaneous squamous cell carcinoma (CSCC) and basal cell carcinoma (BCC) account for more than 90% of all cases of NMSC [2].
- CSCC is associated with a higher mortality rate than breast or colon cancer in SOT recipients [3].
- The management of locally advanced and metastatic CSCC to skin, soft tissue, or lymph nodes in SOT patients is not established, but generally follows therapeutic approaches used in non-SOT patients. This includes localized radiation therapy, systemic chemotherapy, and targeted therapy.
- Withdrawal of immunosuppressive therapy may be required for the management of CSCC but may be associated with high rates of graft failure.
- Thus, there is a high unmet need for a safe and effective treatment for SOT recipients who experience cutaneous malignancies that also protects patients from allograft rejection.
- RP1 is an oncolytic virus (HSV-1) that expresses a fusogenic glycoprotein (GALV-GP R-) and granulocyte macrophage colony stimulating factor (GM-CSF) [4].



- In preclinical studies, RP1 induced immunogenic tumor cell death and provided potent systemic anti-tumor activity [4] and clinical data in combination with nivolumab (a PD-1 inhibitor) has demonstrated a high rate of deep and durable response in patients with advanced skin cancers (SCs) [5].

Objective

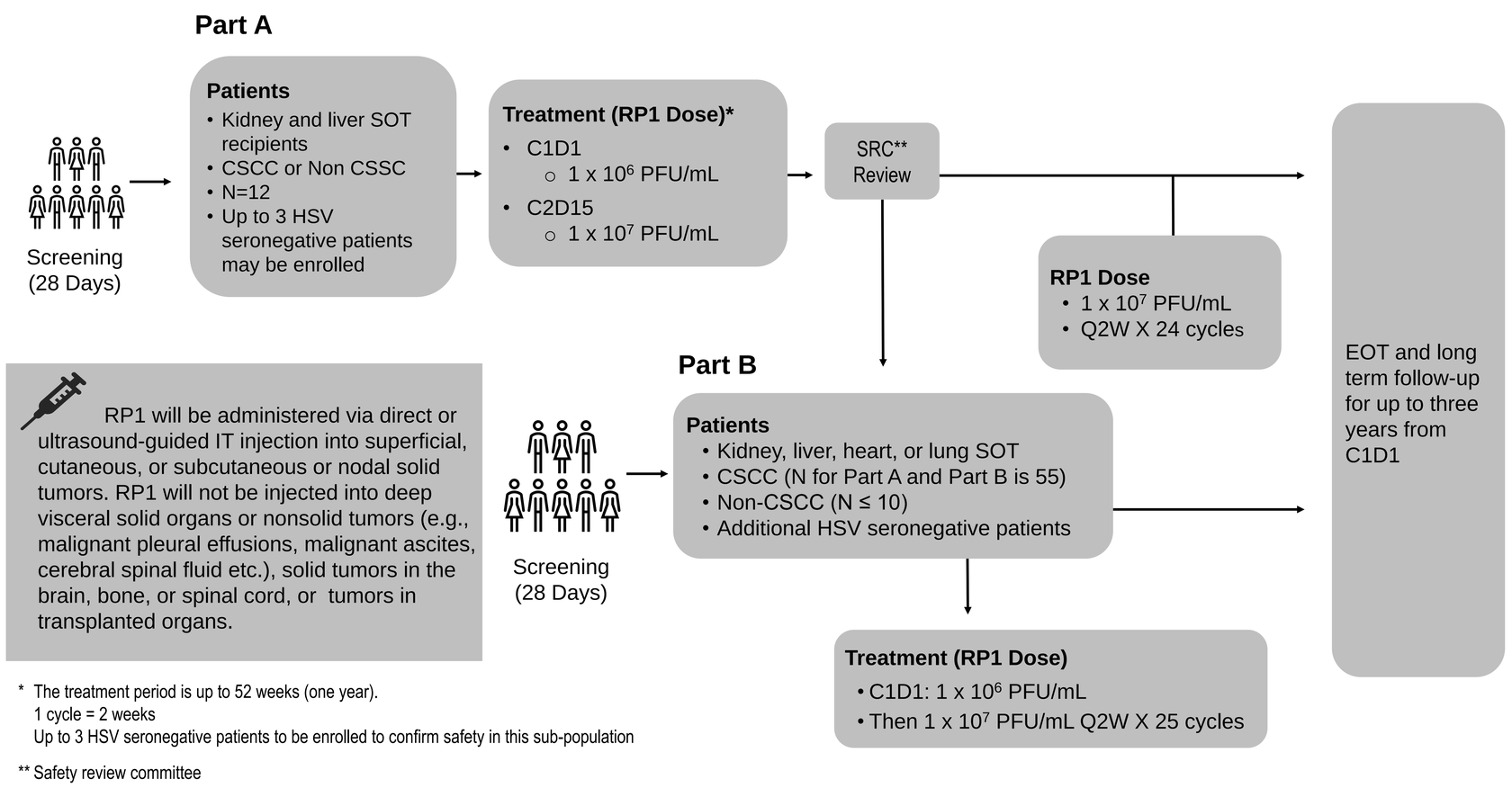
The objective of this study is to assess the safety and efficacy of single agent RP1 in organ transplant recipients (kidney, liver, heart and lung) with skin cancers, with focus on CSCC.

Methods

Study Design

- This is a Phase 1b/2, multicenter, open-label study, evaluating efficacy and safety of RP1 for the treatment of locally advanced or metastatic cutaneous malignancies (to skin, soft tissue, or lymph nodes) in up to 65 evaluable SOT patients.
- The study will have two parts (Parts A and B) and patients in both parts will receive RP1 via direct or ultrasound-guided intratumoral (IT) injection into superficial, cutaneous, or subcutaneous or nodal solid tumors to assess the safety and tolerability of RP1 treatment.
- The primary efficacy population in Parts A and B (combined) is up to 55 SOT patients with CSCC. The enrollment of SOT patients with CSCC will determine study duration.
- Up to 10 additional SOT patients with non-CSCC skin cancers may enroll concurrently with the 55 CSCC patients to explore preliminary safety and efficacy of RP1 in this patient population.

Trial Design



* The treatment period is up to 52 weeks (one year).
1 cycle = 2 weeks
Up to 3 HSV seronegative patients to be enrolled to confirm safety in this sub-population

** Safety review committee

Key Eligibility Criteria

Inclusion

- SOT patients with recurrent, locally advanced or metastatic cutaneous malignancies including CSCC, BCC, Merkel cell carcinoma (MCC), and melanoma.
- Patients must have progressed following local resection, prior radiation, or topical or systemic therapies. One prior line of systemic therapy is allowed in up to 30% of patients enrolled in either Parts A or B.
- Documentation that the patient's allograft is stable.
- At least one measurable tumor of ≥1 cm in longest diameter or ≥1.5 cm in shortest diameter for lymph nodes and injectable lesions which in aggregate comprise ≥1 cm in longest diameter.
- ECOG ≤ 1 and adequate hepatic, renal and hematologic function.

Exclusion

- Prior treatment with an oncolytic therapy. Active significant herpetic infections or prior complications of HSV-1 infection.
- A history of transplant-related viral infections, such as BKV, EBV or CMV within three months of study entry. Patients with BKV may be eligible if the BKV viral load is $<1 \times 10^7$ copies/mL by urine PCR or ≤4 log IU/mL by BKV plasma testing.
- Patients with autoimmune disease that requires systemic immunosuppressive treatment beyond immunosuppressive medications required for maintenance of allograft rejection prevention.
- Patients with a history of any positive test result for hepatitis B virus (HBV) or hepatitis C (HCV) indicating the presence of the virus.
- Hematologic malignancy; stable CLL not on active treatment is permitted.

Key Endpoints

Primary

- Safety and tolerability.
- Objective response rate (ORR) by investigator review.

Secondary

- Duration of response, complete response rate, disease control rate, progression-free survival (PFS), one-year and two-year overall survival rate by investigator review.
- Quality of life (QoL) score using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).

Exploratory

- Biodistribution and viral shedding of RP1.
- Activation of tumor infiltrating lymphocytes (TILs).
- Expression levels of PD-L1 and tumor mutation burden (TMB)

ARTACUS is now recruiting SOT recipient patients. To learn more about enrolling your patient contact: clinicaltrials@replimune.com or +1 (781) 222 9570.

Additional information could be obtained by visiting clinicaltrials.gov (NCT04349436).

Reference
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