Poster: D326

Initial results from an open-label, multicenter, phase 1b/2 study of RP1 oncolytic immunotherapy in solid organ and hematopoietic cell transplant recipients with advanced cutaneous malignancies (ARTACUS)

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Background

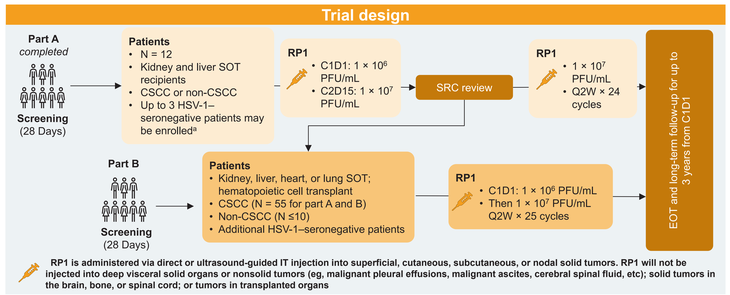
- Solid organ transplantation (SOT) is an important, lifesaving procedure for patients with end-organ diseases characterized by dysfunction or specific organ function failure[1]
  - Allograft rejection is a major complication of SOT that commits patients to lifelong immunosuppressive therapy to prevent rejection[1]
  - Chronic immunosuppression impairs immune surveillance, allowing tumors to proliferate unchecked, and increases the risk of a wide range of cutaneous tumors[2]
- Nonmelanoma skin cancer (NMSC) is the most common post-transplant malignancy in SOT recipients[3]
  - Cutaneous squamous cell carcinoma (CSCC) and basal cell carcinoma account for >90% of all cases of NMSC[3,4]
  - Systemic immune checkpoint blockade is contra-indicated in the setting of SOT-associated NMSC given the documented risk of allograft rejection[2]
- Management of locally advanced and metastatic CSCC that has spread to other areas of the skin, soft tissue, or lymph nodes in SOT patients is not well established[2,5]
  - Withdrawal of immunosuppressive therapy may be required for the management of CSCC but may increase the risk of organ transplant rejection
- RP1 is a tumor-directed oncolytic immunotherapy (herpes simplex virus type 1) that expresses granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (gibbon ape leukemia virus glycoprotein with the R sequence deleted [GALV-GP-R−]; **Figure 1**)[6]
  - When used in combination with an anti−programmed cell death protein 1 antibody, RP1 demonstrated a high rate of deep and durable responses in non-SOT patients with advanced skin cancers[7]
- **Objective:** To assess the safety and efficacy of single agent RP1 in SOT and hematopoietic cell transplant patients with skin cancers (NCT04349436)

Figure 1. RP1 backbone

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; pA, polyA signal; X, denotes inactivation of viral protein.

Methods

Figure 2. ARTACUS study design



Key eligibility criteria

Inclusion
- SOT patients with recurrent, locally advanced, or metastatic cutaneous malignancies including CSCC, BCC, Merkel cell carcinoma, and melanoma
- At least 1 measurable tumor ≥1 cm in longest diameter or ≥1.5 cm in shortest diameter for lymph nodes and injectable lesions that, in aggregate, comprise ≥1 cm in longest diameter
- ECOG performance status ≤1 and adequate hepatic, renal, and hematologic function
- Documentation that the patient's allograft is stable

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 requiring treatment or modification to immunosuppression, such as BKV, EBV, or CMV, within 3 months of study entry
- Patients with visceral metastases
- Other active malignancy (other than the disease under study) within 3 years of the first dose of RP1

Key endpoints

Primary
- Objective response rate by investigator review
- Safety and tolerability

Secondary
- Duration of response, complete response rate, disease control rate, and progression-free survival by investigator review; 1-year and 2-year overall survival rate
- Quality of life score using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

[a]After 3 seronegative patients were enrolled, safety in this population was assessed by SRC, who approved continued enrollment of seronegative patients.
One cycle = 2 weeks. The treatment period is up to 52 weeks (one year).
BCC, basal cell carcinoma; BKV, BK virus; C, cycle; CMV, cytomegalovirus; CSCC, cutaneous squamous cell carcinoma; D, day; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HSV-1, herpes simplex virus type 1; IT, intratumoral; PFU, plaque-forming unit; Q2W, every 2 weeks; SOT, solid organ transplantation; SRC, safety review committee.

Results

Patients

- The trial enrolled 13 kidney transplant recipients with skin cancers (median age, 68.0 years; **Table 1**)

Table 1. Patient demographics and baseline disease characteristics

Characteristic	All patients (N = 13)
Age, years, median (range)	68.0 (57–81)
Female	4 (30.8)
Race	
White	13 (100.0)
Ethnicity	
Not Hispanic or Latino	13 (100.0)
Allograft type	
Kidney	13 (100.0)
Liver	0
Cutaneous malignancies	
CSCC[a]	12 (92.3)
MCC[b]	1 (7.7)
Stage at study baseline	
Locally advanced	7 (53.8)
Metastatic[c]	6 (46.2)

All data presented as n (%) unless otherwise indicated.
[a]One patient had BCC as a new primary tumor. [b]One patient had CSCC as a new primary tumor. [c]Per protocol, metastatic to skin, soft tissue, or lymph nodes.
BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma.

Efficacy

- The preliminary objective response rate (ORR) for the 11 evaluable patients was 27.3%, with 3 patients (27.3%) achieving a confirmed complete response (**Table 2**)
  - One of the non-evaluable patients showed a clear reduction in tumor size before death due to COVID-19–related pneumonia at 7 weeks following initiation of RP1 (ie, prior to the first formal efficacy assessment)

Table 2. Efficacy

	All patients (N = 13)	CSCC (n = 12)	MCC[a] (n = 1)
Evaluable patients[b], n	11	10	1
Best overall response			
CR	3 (27.3)	2[c] (20.0)	1 (100.0)
PR	0	0	0
SD	1 (9.1)	1 (10.0)	0
PD	7 (63.6)	7 (70.0)	0
ORR (CR + PR)	3 (27.3)	2 (20.0)	1 (100.0)
DCR (CR + PR + SD)	4 (36.4)	3 (30.0)	1 (100.0)

All data presented as n (%) unless otherwise indicated.
[a]Patient had CSCC as a new primary tumor. [b]Two patients were not evaluable for efficacy; both died before the first assessment (COVID-19, n = 1; CVA, n = 1). [c]One patient had CR in a new primary tumor (BCC).
BCC, basal cell carcinoma; CR, complete response; CSCC, cutaneous squamous cell carcinoma; CVA, cerebrovascular accident; DCR, disease control rate; MCC, Merkel cell carcinoma; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety

- The most common treatment-emergent adverse events (TEAEs) were fatigue (46.2%), pyrexia (38.5%), and chills (30.8%; **Table 3**)
  - One patient died from COVID-19–related pneumonia, one died from progressive disease, and one died from a cerebrovascular accident
  - No evidence of allograft rejection or immune-mediated adverse events were seen

Table 3. All-grade TEAEs (>20% of patients)

	All patients (N = 13)
Fatigue	6 (46.2)
Pyrexia	5 (38.5)
Chills	4 (30.8)
Injection-site pain	3 (23.1)
Nausea	3 (23.1)
UTI	3 (23.1)
Vomiting	3 (23.1)

All data presented as n (%). Grade 3 TEAEs included UTI, cerebrovascular accident, anemia, aspiration, calciphylaxis, sepsis, staphylococcal infection, WBC-count increased, and *Pseudomonas* wound infection (n = 1 each); grade 4 TEAEs included mental status changes and seizure (n = 1 each); grade 5 TEAEs included cerebrovascular accident, COVID-19–related pneumonia, and disease progression (n = 1 each).
TEAE, treatment-emergent adverse event; UTI, urinary tract infection; WBC, white blood cell.

Figure 3. Patients with confirmed complete response

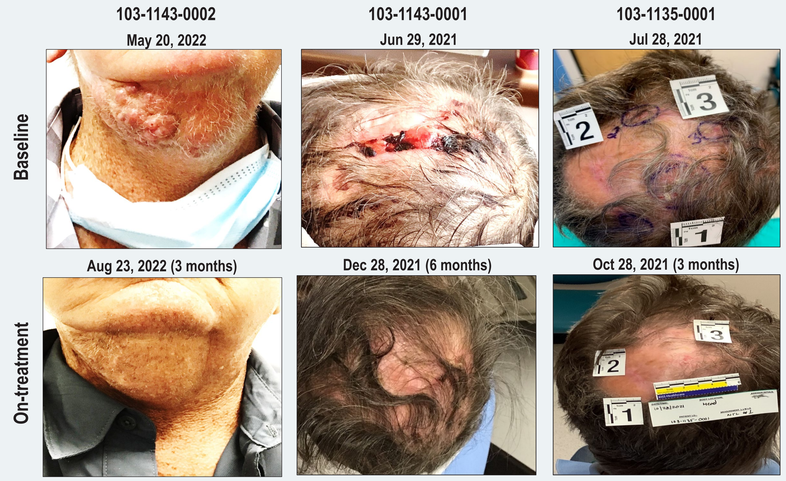
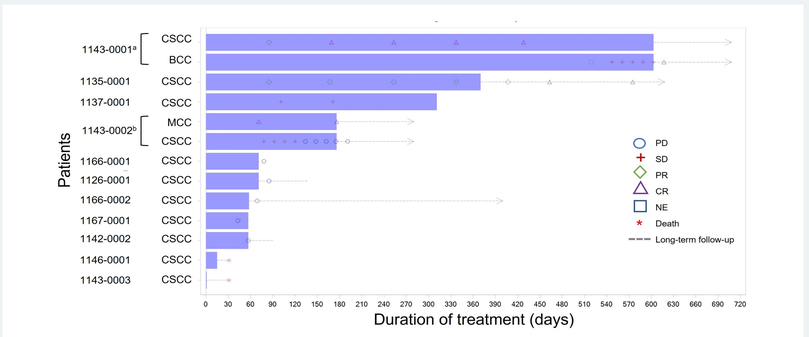


Figure 4. Duration of response



[a]BCC was a new primary tumor. [b]CSCC was a new primary tumor.
BCC, basal cell carcinoma; CR, complete response; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions

- **This is the first clinical trial assessing single-agent RP1 in SOT patients**
- **RP1 monotherapy showed clear anti-tumor activity, with an ORR of 27.3% (all CR) in evaluable patients, and all responses ongoing to date**
- **No immune-mediated adverse events or evidence of allograft rejection were observed**
- **RP1 monotherapy was well tolerated, and the safety profile was similar to non-immunocompromised patients with advanced skin cancers (IGNYTE study)**

ARTACUS is now 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 (NCT04349436).

Presenter disclosures:

MRM received clinical trial support, medical writing support, and served on a steering committee and safety review committee for Replimune; received consulting fees from Regeneron and Replimune; received support for attending meetings from Regeneron; and is a board member for the International Society of Dermatologic Oncology.

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References:

1. Black C, et al. *Ann Transl Med.* 2018;6(20):409.
2. Mittal A and Colegio O. *Am J Transplant.* 2017;17(10):2509-30.
3. Friman T, et al. *Int J Cancer.* 2022;150(11):1779-91.
4. Garrett G, et al. *JAMA Dermatol.* 2017;153(3):296-303.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Squamous Cell Skin Cancer. Version 1. 2023.
6. Thomas S, et al. *J Immunother Cancer.* 2019;7(1):214.
7. Milhem M, et al. *J Clin Oncol.* 2022;40(suppl 16):9553.

Study Sponsor:

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