Initial results from an open-label 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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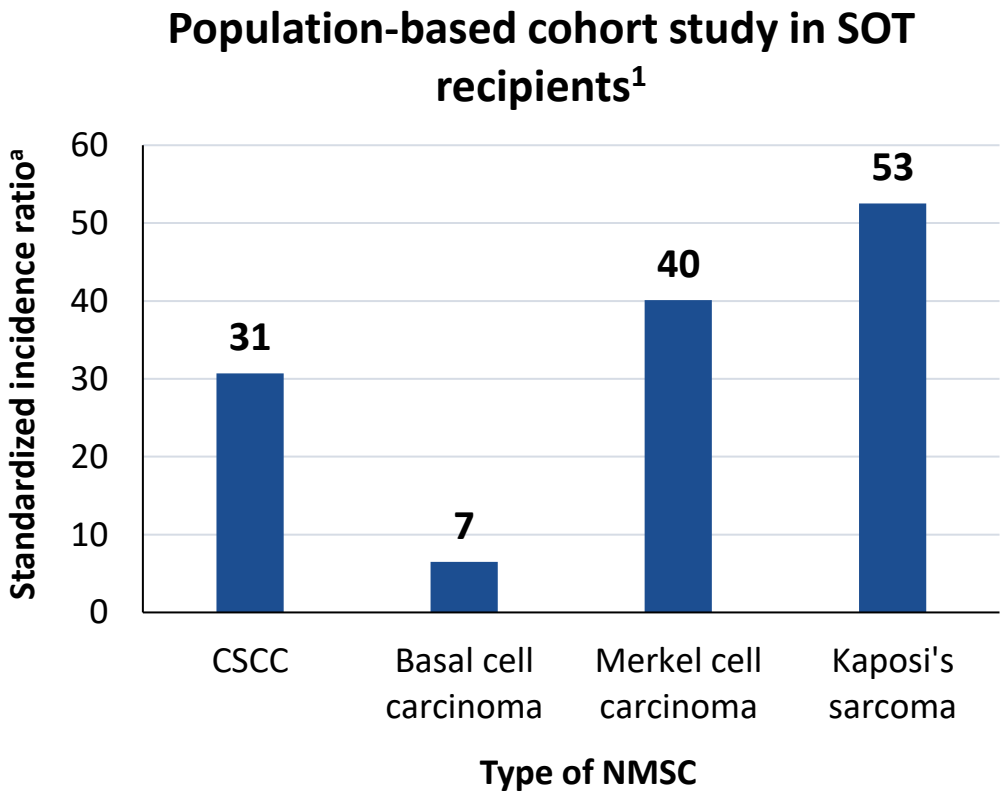
Solid organ transplantation and non-melanoma skin cancer

- Non-melanoma skin cancer (NMSC) is the most common post-transplant malignancy in solid organ transplant (SOT) recipients and occurs at a 7-53x higher incidence vs the general population[1]
  - >90% of NMSC in SOT recipients is cutaneous squamous cell carcinoma (CSCC) and basal cell carcinoma[1,2]
  - Systemic immune checkpoint blockade is contra-indicated in the setting of SOT-associated NMSC given the documented risk of allograft rejection[3,4]
- Optimal management of NMSC in SOT is not well established[3,4]

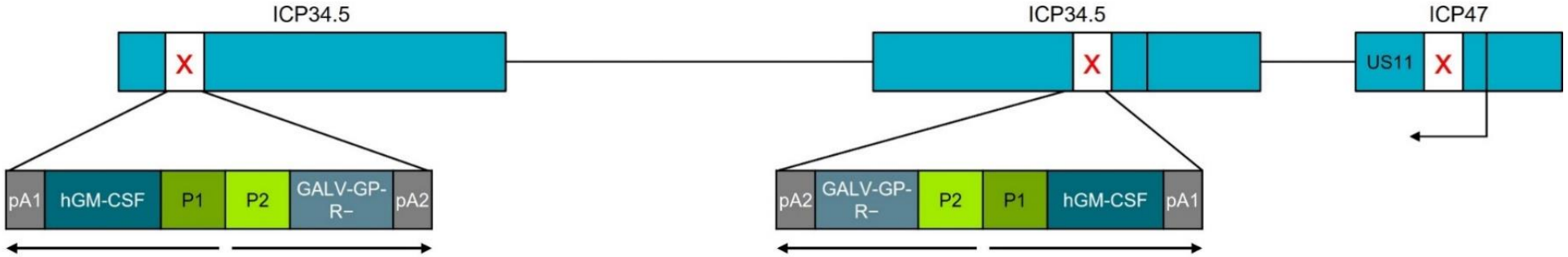


[a]Standardized incidence ratios were calculated by dividing the observed number of NMSC cases by the expected number of cases based on the general population.

1. Friman T, et al. *Int J Cancer*. 2022;150(11):1779-91. 2. Garrett G, et al. *JAMA Dermatol*. 2017;153(3):296-303. 3. Mittal A and Colegio O. *Am J Transplant*. 2017;17(10):2509-30.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Squamous Cell Skin Cancer. Version 1. 2023.

RP1

- RP1 is an oncolytic immunotherapy (HSV-1) that expresses GM-CSF and a fusogenic glycoprotein (GALV-GP-R–)[1]



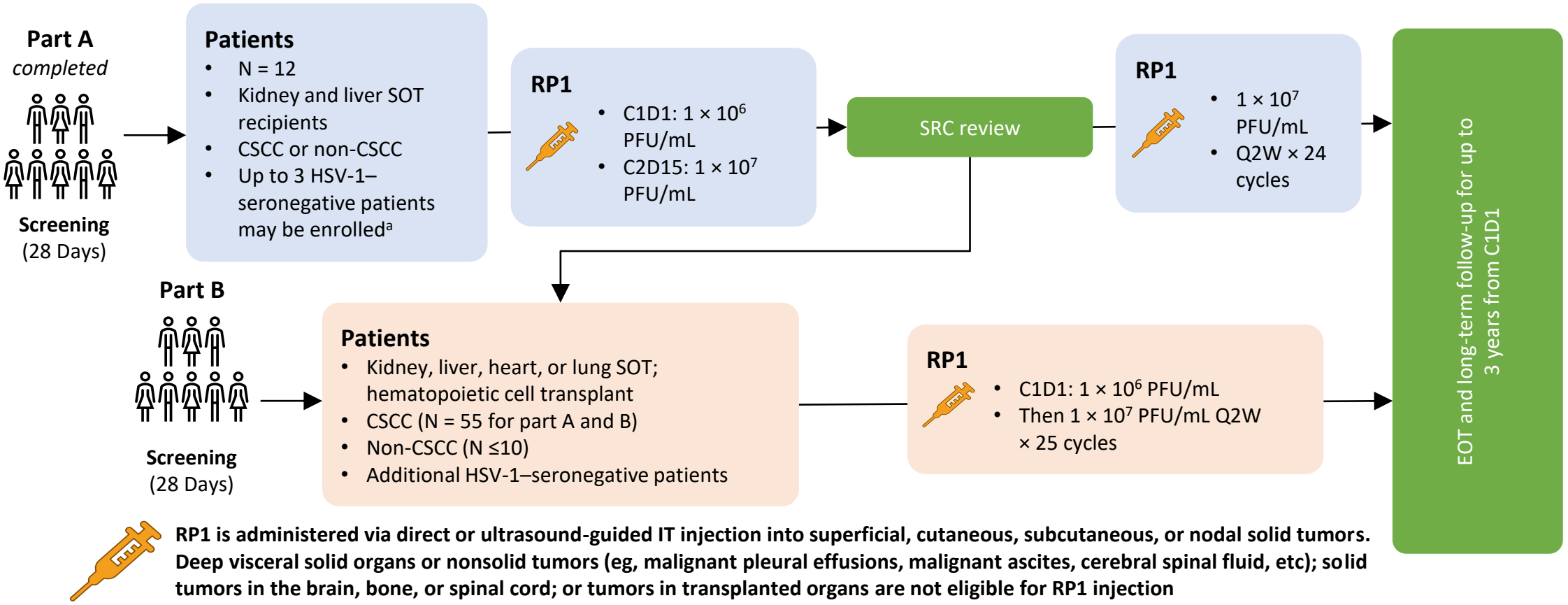
- When used in combination with intravenous nivolumab, intratumoral RP1 demonstrated a high rate of deep and durable responses in non-SOT patients with advanced skin cancers (IGNYTE study)[2]

Objective: To assess the safety and efficacy of single-agent RP1 in SOT and hematopoietic cell transplant patients with skin cancers (NCT04349436)

GALV-GP-R–, gibbon ape leukemia virus glycoprotein with the R sequence deleted; GM-CSF, granulocyte-macrophage colony-stimulating factor; hGM-CSF, human GM-CSF; HSV-1, herpes simplex virus type 1; ICP, infected cell protein; pA, polyA signal; SOT, solid organ transplantation; X, denotes inactivation of viral protein.

1. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214. 2. Milhem M, et al. *J Clin Oncol*. 2022;40(suppl 16):9553.

Study design



[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).
C, cycle; CSCC, cutaneous squamous cell carcinoma; D, day; 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.

Key eligibility and endpoints

Key eligibility criteria

Inclusion

- Solid organ or hematopoietic cell transplant recipients 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 PS ≤1 and adequate hepatic, renal, and hematologic function
- Stable allograft function including allograft cfDNA
- No more than 1 prior systemic therapy for cutaneous malignancy

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

- Investigator-assessed ORR per modified RECIST 1.1
- 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 (EORTC QLQ-C30)

Exploratory

- Biomarker analysis

BKV, BK virus; cfDNA, cell-free DNA; CMV, cytomegalovirus; Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HSV-1, herpes simplex virus type 1; OI, oncolytic immunotherapy; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors..

Patient demographics and baseline characteristics

Characteristic	All patients (N = 27)
Age, years, median (range)	68.0 (48–86)
Male, n (%)	21 (77.8)
Race, n (%)	
White	26 (96.3)
Native Hawaiian/Pacific Islander	1 (3.7)
Allograft type, n (%)	
Kidney	22 (81.5)
Liver	4 (14.8)
Lung	1 (3.7)
Heart	0

Characteristic	All patients (N = 27)
Cutaneous malignancies, n (%)	
CSCC	24 (88.9)
MCC	3 (11.1)
Stage at study baseline, n (%)	
Locally advanced	15 (55.6)
Metastatic[a]	12 (44.4)
Primary tumor location, n (%)	
Skin	26 (96.3)
Lymph node	1 (3.7)

Data cutoff: September 18, 2023

[a]Per protocol, metastatic to skin, soft tissue, or lymph nodes.
CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma.

Efficacy

	Evaluable patients[a] (N = 23)
Best overall response per modified RECIST 1.1	n (%)
CR	5 (21.7)[b]
PR	3 (13.0)[c]
SD	1 (4.3)
PD	14 (60.9)
ORR (CR + PR)	8 (34.8)
DCR (CR + PR + SD)	9 (39.1)

	Responders (n = 8)
Characteristics of responders	n
Tumor type	
CSCC	6
MCC	2
Stage at study baseline	
Locally advanced	6
Metastatic	2

[a]Enrolled ≥3 months before the data cut; 4 patients who went off study for reasons unrelated to NMSC or RP1-related adverse events (1 death each from COVID-19, stroke, and pneumonia and 1 withdrawal because of injection pain) were excluded from the efficacy analysis. The median study follow-up time for all enrolled patients (N = 27) was 18.7 weeks as of September 18, 2023.

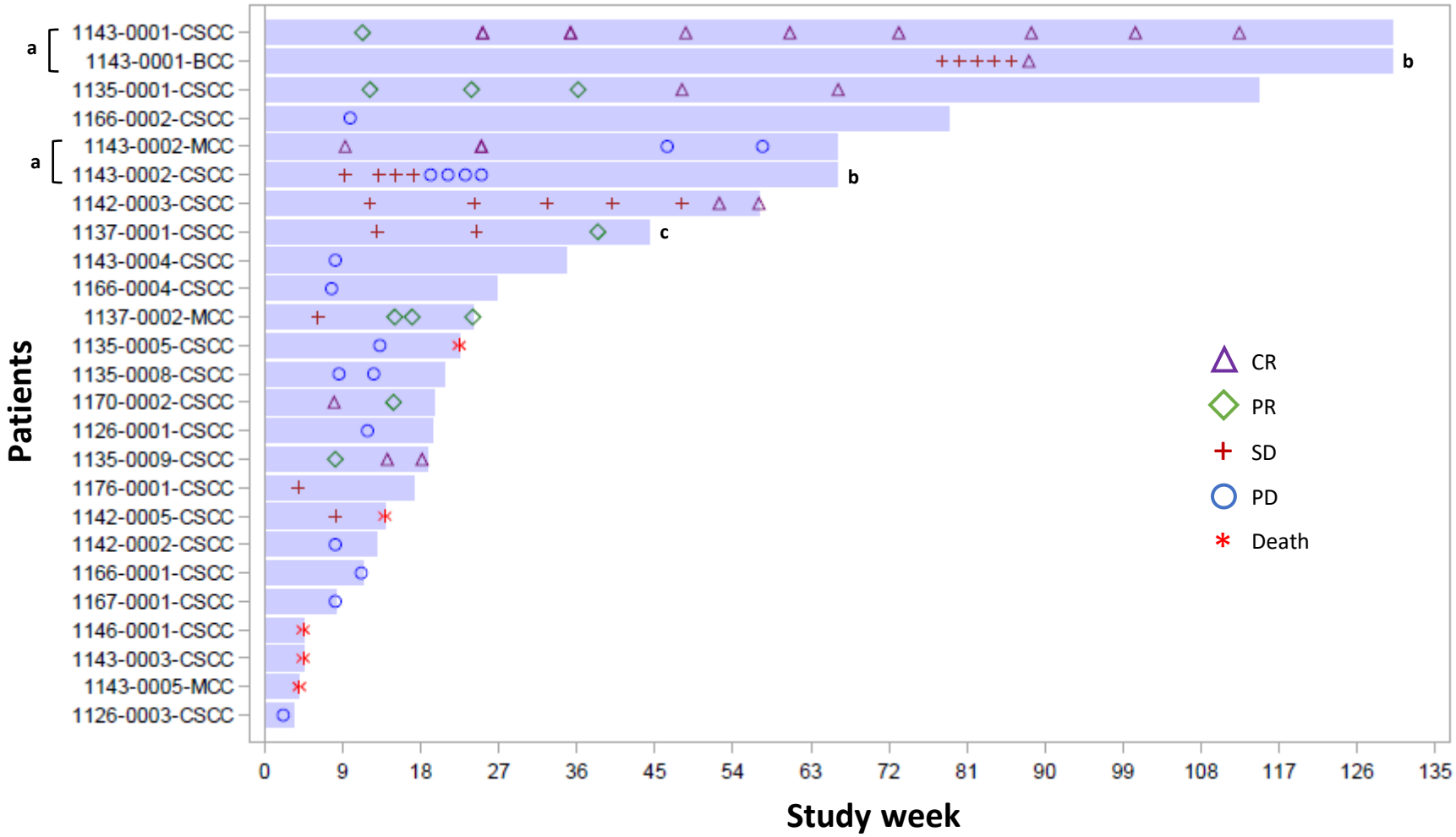
[b]One patient with CSCC also had CR of a new primary BCC which appeared post baseline and was also treated with RP1.

[c]One PR could not be confirmed because the patient withdrew consent; all other responses are confirmed.

BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; COVID-19, coronavirus disease 2019; CR, complete response; DCR, disease control rate; MCC, Merkel cell carcinoma; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

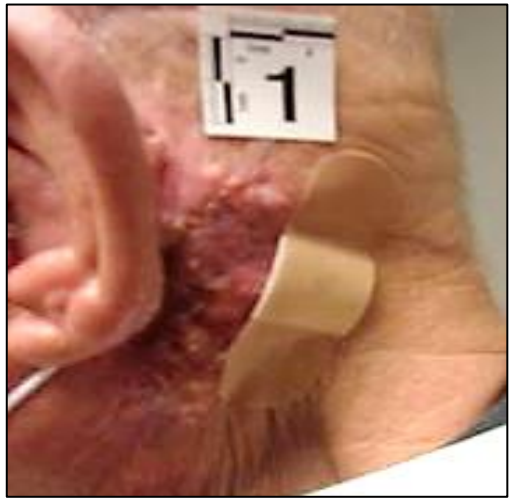
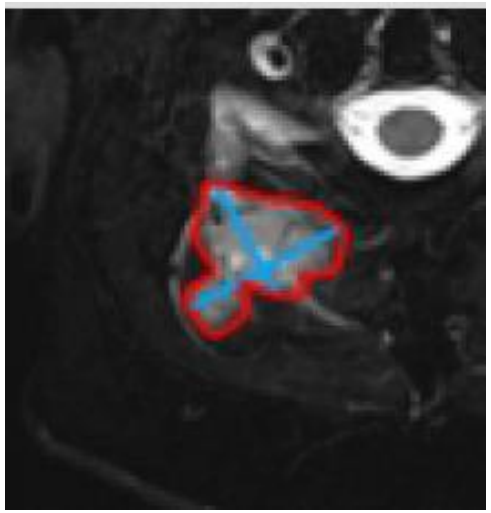
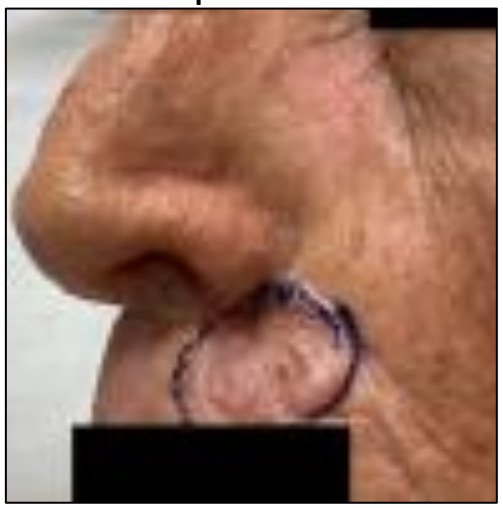
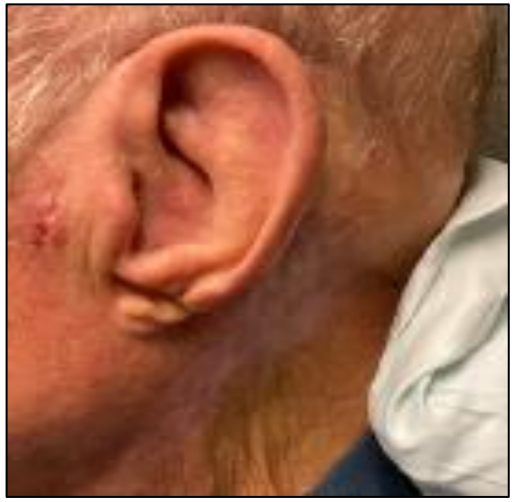
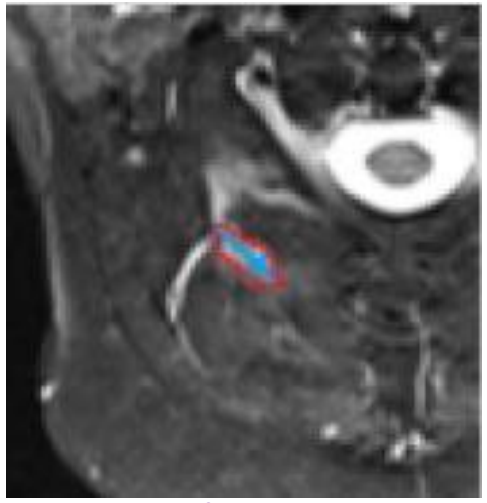
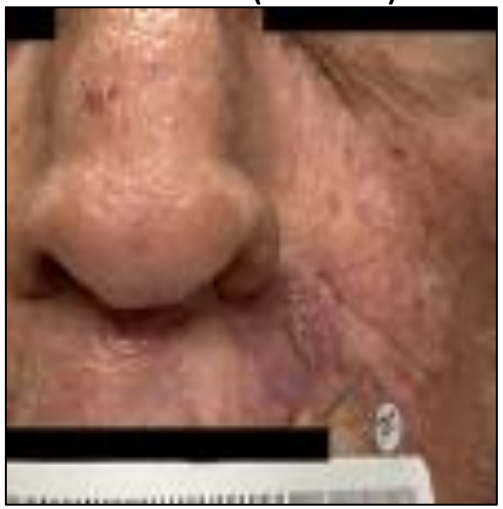
Results

Response profile over time



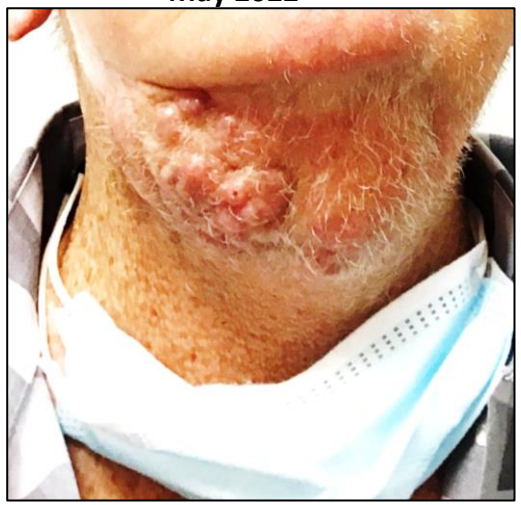
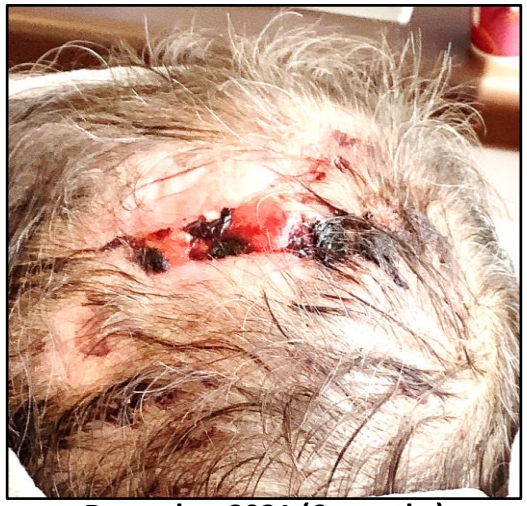
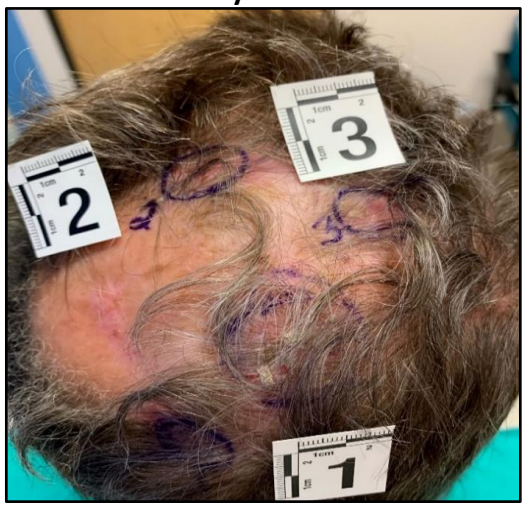
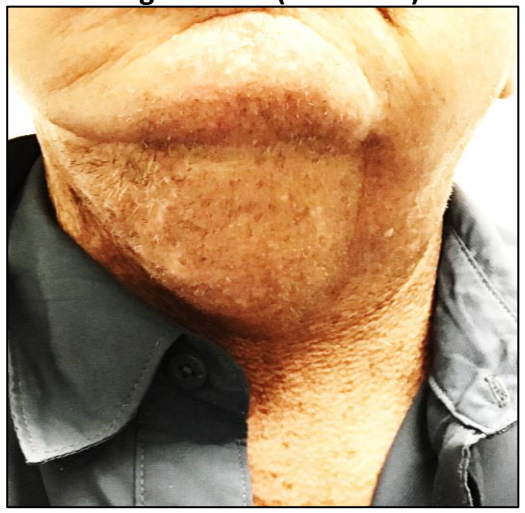
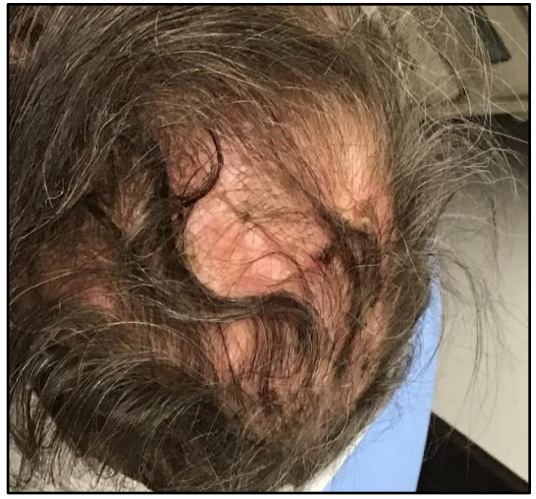
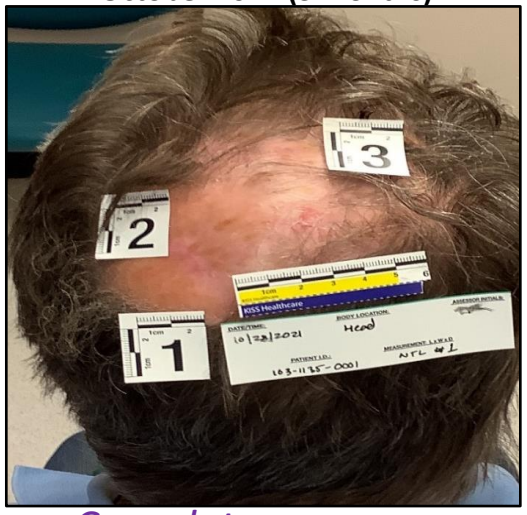
[a]A second primary skin cancer that developed on study was allowed to be treated with RP1, per protocol. [b]Second primary malignancy. [c]Withdrew consent.
CR, complete response; BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; PD, progressive disease; PR, partial response; SD, stable disease.

Examples of patients with confirmed response

	1142-0003 August 2022	1137-0002[a] March 2023	1135-0009 April 2023
Baseline			
Best response	September 2023 (13 months) 	September 2023 (6 months) 	June 2023 (2 months) 
	Complete response	*Partial response*	*Complete response*

[a]Right paraspinal muscle metastasis at C1–C2 level.

Examples of patients with confirmed response

	1143-0002 May 2022	1143-0001 June 2021	1135-0001 July 2021
Baseline			
	August 2022 (3 months)	December 2021 (6 months)	October 2021 (3 months)
Best response			
	Complete response	*Complete response*	*Complete response*

Safety profile

All-grade TEAEs (>10% of patients), n (%)	All patients (N = 27)		
	Grade 1/2	Grade ≥3	Total
Fatigue	9 (33.3)	0	9 (33.3)
Chills	7 (25.9)	0	7 (25.9)
Pyrexia	7 (25.9)	0	7 (25.9)
Anemia	2 (7.4)	3 (11.1)	5 (18.5)
Blood creatinine increased	5 (18.5)	0	5 (18.5)
Nausea	5 (18.5)	0	5 (18.5)
Urinary tract infection	3 (11.1)	2 (7.4)	5 (18.5)
Decreased appetite	4 (14.8)	0	4 (14.8)
Diarrhea	4 (14.8)	0	4 (14.8)

All-grade TEAEs (>10% of patients), n (%)	All patients (N = 27)		
	Grade 1/2	Grade ≥3	Total
Headache	4 (14.8)	0	4 (14.8)
Injection-site pain	4 (14.8)	0	4 (14.8)
Cellulitis	2 (7.4)	1 (3.7)	3 (11.1)
Confusional state	3 (11.1)	0	3 (11.1)
Constipation	3 (11.1)	0	3 (11.1)
Facial pain	3 (11.1)	0	3 (11.1)
Hypercalcemia	3 (11.1)	0	3 (11.1)
Hyperglycemia	2 (7.4)	1 (3.7)	3 (11.1
Sepsis	0	3 (11.1)	3 (11.1)
Tumor pain	2 (7.4)	1 (3.7)	3 (11.1)

- The most common TEAEs were fatigue (33.3%), chills (25.9%), and pyrexia (25.9%)
  - No evidence of allograft rejection
  - Seventeen patients had at least one grade ≥3 AE, all unrelated to RP1
  - Eight deaths were reported: disease progression (n = 3); pneumonia (n = 2); sepsis, stroke, and pulmonary hypertension (each n = 1); none were related to RP1

Other grade 3 TEAEs were encephalopathy and hyperkalemia (n = 2 each) and COVID-19, cerebrovascular accident, hematuria, hypertension, hyponatremia, mental status changes, tumor hemorrhage, aspiration, calciphylaxis, infusion-related reaction, lipase increased, pneumonia aspiration, staphylococcal infection, and *Pseudomonas* wound infection (n = 1 each). Grade 4 TEAEs were sepsis, cerebrovascular accident, mental status changes, COVID-19 pneumonia, and seizure (n = 1 each). Grade 5 TEAEs were disease progression (n = 2) and sepsis, cerebrovascular accident, and COVID-19 pneumonia (n = 1 each).
AE, adverse event; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent AE.

Conclusions

- This is the first clinical trial assessing single-agent intratumoral RP1 in solid organ/hematopoietic cell transplant patients on chronic immunosuppressive treatment with advanced skin cancer in whom systemic immunotherapy is typically contra-indicated
- RP1 monotherapy showed clear anti-tumor activity, with an ORR of 34.8% (5/23 [21.7%] confirmed CR) in evaluable patients, with most responses ongoing as of the data cutoff[a]
- No allograft rejection was observed as of the data cutoff[a] including in hepatic and lung allografts
- RP1 monotherapy was well tolerated, and the safety profile was similar to the profile in non-immunocompromised patients with advanced skin cancers (IGNYTE study)

[a]September 18, 2023.
CR, confirmed response; ORR, objective response rate.

Acknowledgments

- The authors would like to thank the patients, their families, and site staff/investigators for their participation in the trial

ARTACUS 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 (NCT04349436).

Footnote holder

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