Safety, efficacy, and biomarker assessment of RP1 in combination with nivolumab in patients with advanced skin cancers

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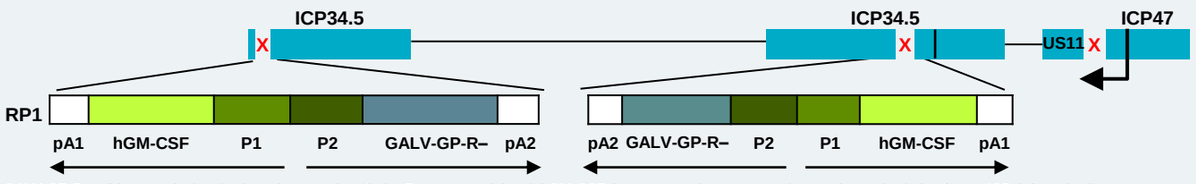
Background

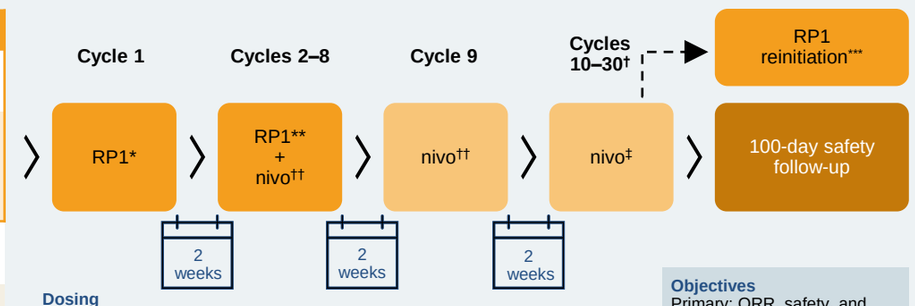
- RP1 is an enhanced potency oncolytic herpes simplex virus type 1 (HSV-1) that expresses[1]:
  - A codon-optimized sequence for human granulocyte-macrophage colony-stimulating factor (hGM-CSF)
  - The fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R–)
- RP1 was selected for its ability to kill a panel of human cancer cell types
- Preclinical studies with RP1 demonstrated that GALV-GP-R– potently enhanced antitumor activity and immunogenic cell death
- RP1 contains additional genetic modifications to ensure safety
  - ICP34.5 deletion renders HSV-1 nonpathogenic/limits replication to the tumor
  - ICP47 deletion improves antigen presentation
  - US11 upregulation improves tumor-selective replication



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; P, promoter; pA, polyA signal; US11, unique short 11; X, denotes inactivation of viral protein.

Study design

Cohorts	Target N
Melanoma (all-comers)[a]	30
Non-melanoma skin cancer anti–PD-1/PD-L1–failed and –naïve[b]	60
Cutaneous melanoma anti–PD-1–failed[c]	138
Non-small cell lung cancer anti–PD-1/PD-L1–failed	30
Microsatellite instability-high and deficient mismatch repair anti–PD-1/PD-L1–failed	30



Dosing
RP1
*First dose = 1 x 10^6 PFU/mL.
**Subsequent doses = 1 x 10^7 PFU/mL
Nivo
†Dosing with nivo begins at Dose 2 of RP1; therefore, a maximum of 29 cycles of nivo will be given
††240 mg (Q2W)
‡480 mg (Q4W)

*****RP1 reinitiation**
Reinitiation of up to 8 additional doses of RP1 Q2W in combination with nivo 480 mg Q4W if the protocol-specified criteria are met

Objectives
Primary: ORR, safety, and tolerability
Secondary: DOR, CR, DCR, PFS, and OS
Exploratory: biomarker analyses using tumor biopsies and peripheral blood, including the assessment of RP1 biodistribution and shedding

[a]Melanoma (N = 30) is fully enrolled and not recruiting; an additional 6 patients with melanoma from the phase 1 expansion study were included in this analysis (36 patients with melanoma in total). [b]Anti–PD-1/PD-L1–naïve is fully enrolled and not recruiting; anti–PD-1/ PD-L1–failed (N = 30). [c]Registration-directed cohort.
CR, complete response; DCR, disease control rate; DOR, duration of response; nivo, nivolumab; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFU, plaque-forming unit; PFS, progression-free survival; Q2W, every 2 weeks; Q4W, every 4 weeks.

Results

Melanoma

Table 1. Patient demographics and clinical characteristics

	All	Cutaneous	Mucosal	Uveal
Patients, N[a]	36[b]	24	6	6
Age range, years	28–95	28–95	40–78	44–85
Prior therapy				
Anti–PD-1 (alone or combined), n	25	16[c]	5	4
% of patients	69	67	83	67
Single agent anti–PD-1, n	9	7	1	1
Anti–PD-1/anti–CTLA-4, n	16	9	4	3
Disease characteristics				
Stage IIIc, n	2	2	0	0
Stage IV M1a, n	7	3	4	0
Stage IV M1b, n	11	10	1	0
Stage IV M1c, n	16	9	1	6
% of patients with stage IV M1b/c	75	79	33	100

Data snapshot date: March 2022.
[a]Enrollment completed in January 2020. [b]6 additional patients were added as part of a phase 1 expansion study. [c]87.5% of anti–PD-1-failed patients had stage IV M1b/c (visceral) disease.
CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1.

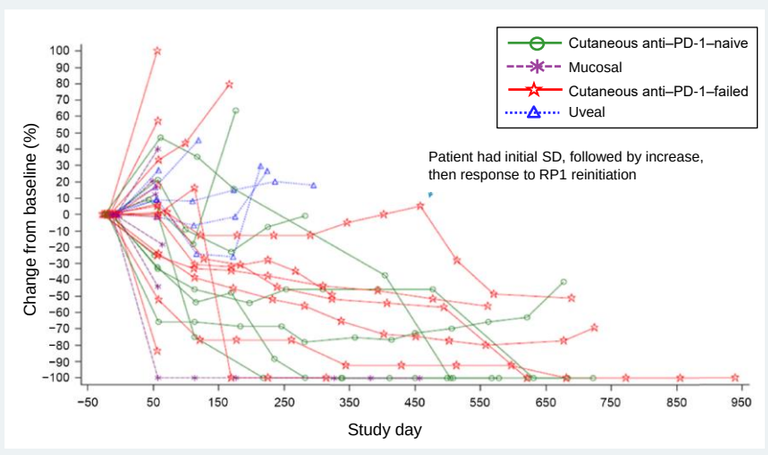
Table 2. Efficacy: Melanoma

	Cutaneous anti–PD-1–naïve	Cutaneous anti–PD-1–failed	Mucosal anti–PD-1–naïve	Mucosal anti–PD-1–failed	Uveal anti–PD-1–naïve	Uveal Anti–PD-1–failed
Patients, N	8	16	1	5	3	3
Best overall response, n (%)						
CR	3 (37.5)	2 (12.5)	1 (100.0)	1 (20.0)	0	0
PR	2 (25.0)[a]	4 (25.0)[b]	0	0	0	0
SD	2 (25.0)	1 (6.3)[c]	0	0	1 (33.3)	3 (100.0)
PD	1 (12.5)	8 (50.0)	0	4 (80.0)	2 (66.7)	0
ORR (CR + PR)	5 (62.5)	6 (37.5)	1 (100.0)	1 (20.0)	0	0
DCR (CR + PR + SD)	7 (87.5)	7 (43.8)	1 (100.0)	1 (20.0)	1 (33.3)	3 (100.0)

Data snapshot date: March 2022.
[a]One anti–PD-1–naïve PR patient is being treated with reinitiated RP1 with the aim of achieving a CR. [b]One anti–PD-1–failed PR patient is a CR by PET scan (no metabolic activity seen), and PET scans are being scheduled for 2 others suspected to be NED at 18 and 23 months. [c]One SD patient has the potential for response following ongoing RP1 reinitiation.
CR, complete response; DCR, disease control rate; NED, no evidence of disease; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PET, positron emission tomography; PR, partial response; SD, stable disease.

- Durability was maintained, with general deepening of response to treatment over time (**Figure 1**)
- The median duration of response (DOR) was 13.27 months (range, 3.67–16.93 months); follow-up is ongoing
- 12 of 13 responders maintained responses by last assessment (12/30/2022)

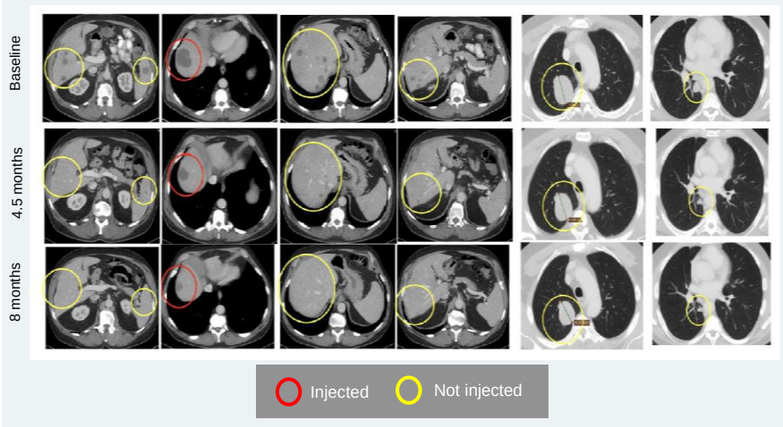
Figure 1. Change in sum of melanoma tumor diameters



Data snapshot date: March 2022.
PD-1, programmed cell death protein 1; SD, stable disease.

- Responses were observed in locoregional and distant visceral lesions, including the lung (**Figure 2**)

Figure 2. Systemic response in a patient with anti–PD-1 (nivolumab)/anti–CTLA-4 (ipilimumab)–failed cutaneous melanoma



Melanoma (patient 1122-2007): PR; ongoing at 19 months from first RP1 dose. All lesions show no evidence of metabolic activity by PET.
CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; PET, positron emission tomography; PR, partial response.

Non-melanoma skin cancer (NMSC)

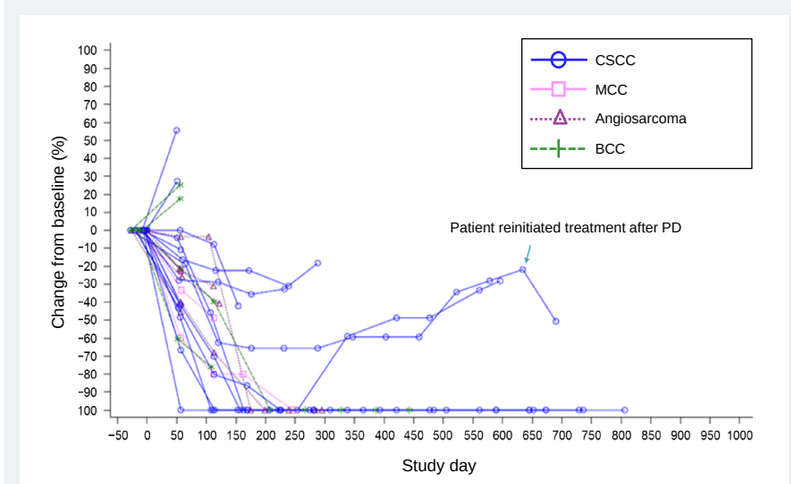
Table 3. Efficacy: Anti–PD-1–naïve NMSC

	CSCC	BCC	MCC	Angiosarcoma
Patients, N[a]	17	4	4	6
Best overall response, n (%)				
CR	8 (47.1)	1 (25.0)	2 (50.0)	1 (16.7)
PR	3 (17.6)	0	1 (25.0)	3 (50.0)
SD	1 (5.9)	2 (50.0)	0	1 (16.7)
PD	4 (23.5)	1 (25.0)	1 (25.0)	1 (16.7)
ORR (CR + PR)	11 (64.7)	1 (25.0)	3 (75.0)	4 (66.7)
DCR (CR + PR + SD)	12 (70.6)	3 (75.0)	3 (75.0)	5 (83.3)

Data snapshot date: March 2022.
[a]Patients with follow-up assessments (n = 31), on study with no follow-up currently for the other patient (MCC).
BCC, basal cell carcinoma; CR, complete response; CSCC, cutaneous squamous cell carcinoma; DCR, disease control rate; MCC, Merkel cell carcinoma; NMSC, non-melanoma skin cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

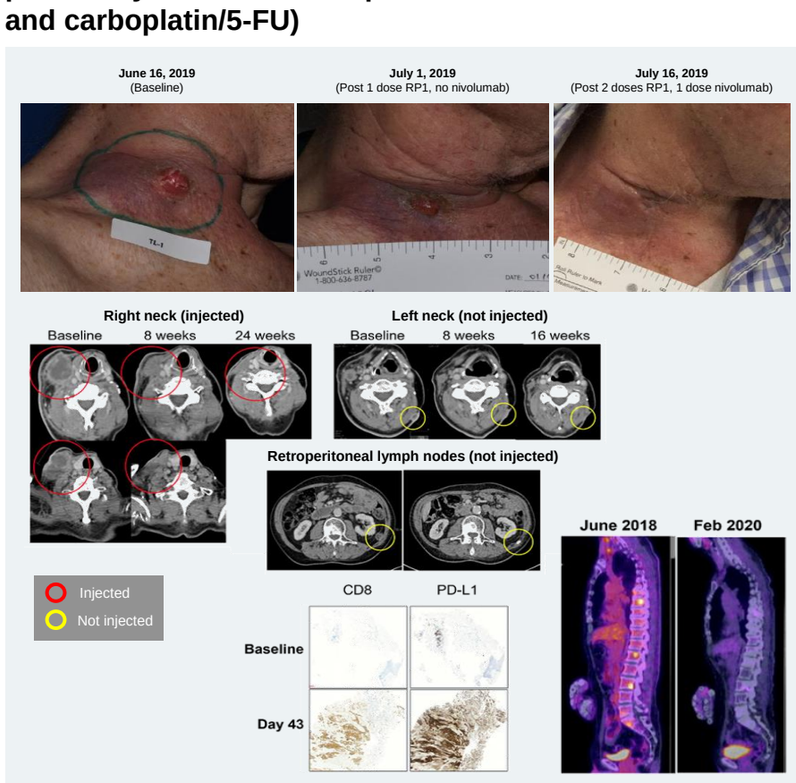
- A high frequency of deep and durable responses continues to be observed, with treatment ongoing in 12 patients
- The median DOR was 7.32 months (range, 1.88–23.11 months); follow-up is ongoing

Figure 3. Change in sum of NMSC tumor diameters



Data snapshot date: March 2022.
BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; NMSC, non-melanoma skin cancer; PD, progressive disease.

Figure 4. Systemic response in a patient with CSCC previously treated with cisplatin-based chemoradiation and carboplatin/5-FU)



CSCC (patient 4402-2001): CR; the patient had recurrent CSCC of the neck (bilateral) and bone metastases, previously treated with cisplatin-based chemoradiation and 6 cycles of carboplatin/5-FU.
5-FU, 5-fluorouracil; CD8, cluster of differentiation 8; CR, complete response; CSCC, cutaneous squamous cell carcinoma; PD-L1, programmed death-ligand 1.

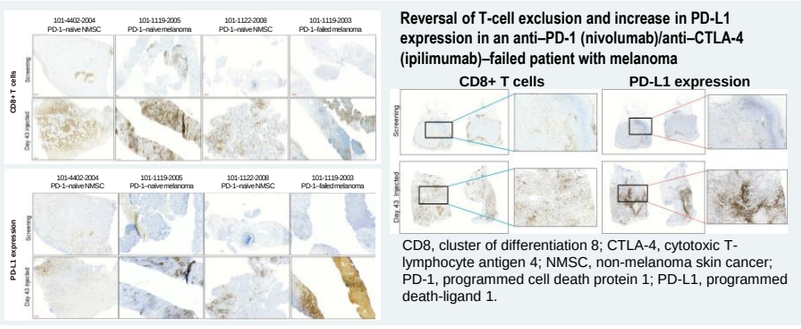
Figure 5. Partial response in Anti–PD-1–naïve CSCC

CSCC (patient 101 1121 2009): new ongoing PR. Last CSCC patient enrolled into anti–PD-1–naïve CSCC cohort.
CSCC, cutaneous squamous cell carcinoma; PD-1, programmed cell death protein 1; PR, partial response.

Biomarker (melanoma and NMSC cohorts)

- At baseline, CD8+ T-cell infiltration and PD-L1 expression are restricted to the tumor margins (**Figure 6**)
- RP1 treatment resulted in an intratumoral CD8+ T-cell influx and an increase in PD-L1 expression

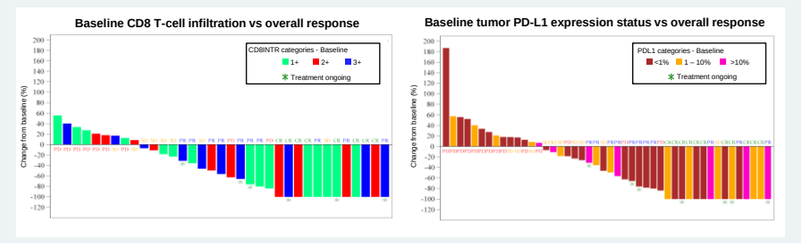
Figure 6. Increase in CD8+ T-cell infiltration and PD-L1 expression post-treatment



CD8, cluster of differentiation 8; CTLA-4, cytotoxic T-lymphocyte antigen 4; NMSC, non-melanoma skin cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

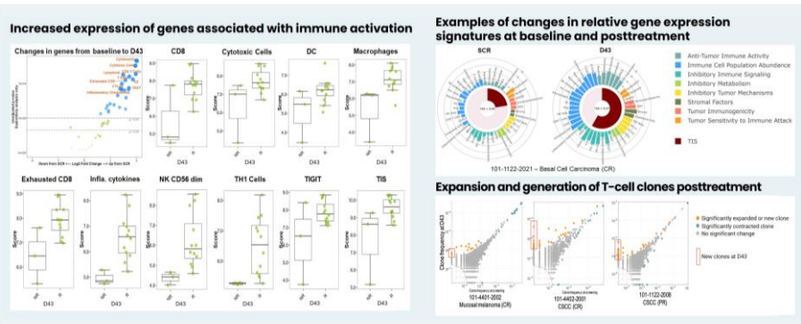
- Waterfall plots indicate no association between baseline CD8+ T-cell infiltration status or tumor PD-L1 expression with percent change in tumor volume (**Figure 7**)

Figure 7. Overall response by baseline CD8+ T-cell status and PD-L1 expression



CD8, cluster of differentiation 8; CD8INTR, intratumoral CD8; CR, complete response; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

Figure 8. RP1 + nivolumab reverses the immunologically cold tumor microenvironment



CD, cluster of differentiation; CR, complete response; CSCC, cutaneous squamous cell carcinoma; D, day; DC, dendritic cell; Infla, inflammatory; NK, natural killer cell; NR, nonresponder; ORR, objective response rate; PR, partial response; R, responder; SCR, screening; TH, T helper; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains; TIS, tumor inflammation signature.

Safety (melanoma and NMSC cohorts)

- RP1 combined with nivolumab continues to be well tolerated, irrespective of injection route
- This highlights the potential for combination with other anticancer therapies
- Most of the adverse events were low grade and indicative of systemic immune activation

Table 4. Treatment-related adverse events

	N = 84			
Preferred term, n (%)	Grade 1/2 (>10%)	Grade 3 (all)	Grade 4/5 (all)	Total
Chills	25 (29.8)	0	0	25 (29.8)
Pyrexia	24 (28.6)	1 (1.2)	0	25 (29.8)
Fatigue	19 (22.6)	5 (6.0)	0	24 (28.6)
Pruritus	19 (22.6)	2 (2.4)	0	21 (25.0)
Influenza-like illness	18 (21.4)	0	0	18 (21.4)
Nausea	17 (20.2)	0	0	17 (20.2)
Diarrhea	9 (10.7)	1 (1.2)	0	10 (11.9)
Injection site pain	9 (10.7)	0	0	9 (10.7)
Decreased appetite	7 (8.3)	1 (1.2)	0	8 (9.5)
Rash maculopapular	3 (3.6)	2 (2.4)	0	5 (6.0)
Immune-mediated arthritis	3 (3.6)	1 (1.2)	0	4 (4.8)
Lipase increased	2 (2.4)	2 (2.4)	0	4 (4.8)
Dyspnea, hypotension	1 (1.2)	2 (2.4)	0	3 (3.6)
Eczema	2 (2.4)	1 (1.2)	0	3 (3.6)
Amylase increased, AST increased, hyponatremia, vertigo	1 (1.2)	1 (1.2)	0	2 (2.4)
Immune-mediated hepatitis	0	2 (2.4)	0	2 (2.4)
ALT increased, cancer pain, confusional state, delirium, hypovolemic shock, immune-mediated enterocolitis, injection site necrosis, liver function test increased, localized edema, lymph node pain, edema, oral candidiasis, prostate cancer, uveitis	0	1 (1.2)	0	1 (1.2)
Immune-mediated myocarditis	0	0	1 (1.2)[a]	1 (1.2)

[a]Grade 5; deemed related to nivolumab
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Conclusions

Efficacy
- A high frequency of durable response continues to be seen in patients with skin cancers, including in anti–PD-1/anti–CTLA-4–failed melanoma and in anti–PD-1–naïve cutaneous squamous cell carcinoma (CSCC)
  - Promising evidence of activity also continues to be observed in anti–PD-1–naïve basal cell carcinoma, Merkel cell carcinoma, and angiosarcoma
- Systemic overall responses were seen, irrespective of sites of disease and the site of injection

Safety
- RP1 combined with nivolumab continues to be well tolerated, irrespective of injection route

Biomarker
- Overall, the biomarker data demonstrated that treatment with RP1 + nivolumab increased immune activation in patients with skin cancer
- Responses were observed irrespective of baseline CD8+ T-cell infiltration or PD-L1 expression

Ongoing studies
- Additional RP1 studies include ARTACUS (RP1 in solid organ transplant patients with advanced skin cancers; NCT04349436) and CERPASS (RP1 ± cemiplimab in CSCC; NCT04050436)

Additional information can be obtained by visiting Clinicaltrials.gov (NCT03767348).

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References:
1.Thomas S, et al. *J Immunother Cancer.* 2019;7(1):214.

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