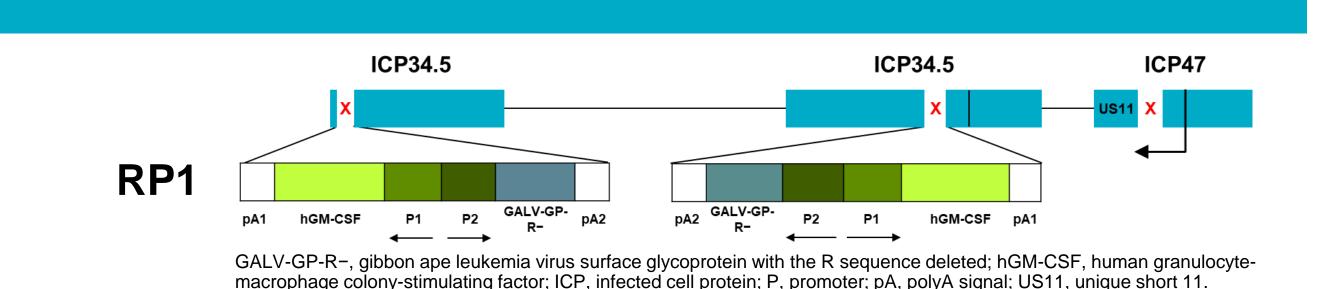
Updated data from the ongoing phase 1/2 clinical trial of RP1 combined with nivolumab (IGNYTE) in patients with melanoma

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Background

- RP1 is an enhanced potency oncolytic version of herpes simplex virus type 1 that expresses human granulocyte macrophage colony stimulating factor and the fusogenic protein GALV-GP-R-[1]
- IGNYTE is a phase 1/2 open-label, multicenter, dose escalation and expansion trial (NCT03767348) evaluating the safety and efficacy of RP1 in combination with the anti-programmed cell death protein 1 (PD-1) inhibitor nivolumab in a range of tumor types [2]
- Here, we present updated results from the melanoma and anti-PD-1-naïve non-melanoma skin cancer (NMSC) cohorts with RP1 combined with nivolumab



Methods

		Cycle 1	Cycles 2–8	Cycle 9	Cycles 1	0_30†	
Cohorts	Target N	Cycle 1	Cycles 2	Oyole 3			RP1 re-initiation***
Melanoma ^a	30						
Non-melanoma skin cancer anti–PD-1/PD-L1–failed and –naïve ^b	60	> RP1*	> RP1** + nivolumab††	> nivolumab ^{††}	> nivolum	nab [‡]	100-day safety follow-up
Non-meianoma skin cancer anti-PD-1/PD-L1-laneu and -naive-	00	<u> </u>		' 			
Cutaneous melanoma anti–PD-1–failed ^c	125	Dosing	Weeks	2 Weeks	2 Weeks	Objectives	
Non-small cell lung cancer anti–PD-1/PD-L1–failed	30	*First dose = 1 x 10 ⁶ PFU **Subsequent doses = 1 x		RP1 re-initiation* Re-initiation of up to 8		Secondary: D	R, safety and tolerability OR, CR, DCR, PFS, and OS Biomarker analyses using tumor
Microsatellite instability-high and deficient mismatch repair anti–PD-1/PD- L1–failed	30		egins at Dose 2 of RP1; therefor of nivolumab will be given.	of RP1 Q2W in combine, nivolumab 480 mg Q4	ination with 4W if the protocol-	biopsies and assessment of	peripheral blood, including the of RP1 biodistribution and
^a Melanoma (N = 30) is fully enrolled and not recruiting. ^b Anti–PD-1/PD-L1–naïve is fully enrolled and not recruiting; anti–PD-1/PD-L1–failed (N = 30).		††240 mg (Q2W). ‡480 mg (Q4W).		specified criteria are r	net	shedding	

CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFU, plaque-forming units; PR, partial response; Q2W, every 2 weeks; Q4W, every 4 weeks.

Results

Melanoma

^cRegistration-directed cohort.

Table 1. Demographics

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

	All	Cutaneous	Mucosal	Uveal
Patients, N	36	24	6	6
Age range, years	28–95	28–95	40–78	44–85
Prior Tx				
Prior anti-PD-1 (alone or combined), n	25	24 ^a	5	4
Prior single agent anti–PD-1, n	9	7	1	1
Prior anti-PD-1/anti-CTLA-4, n	16	9	4	3
Prior anti–PD-1, %	69	67	83	75
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
Stage IV M1b/c, %	75	79	33	100

^a87.5% 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; Tx, treatment.

• 36 patients with melanoma were enrolled: 24 had cutaneous, 6 mucosal, and 6 uveal melanoma (enrollment complete in January 2020; **Table 1**)

Table 2. Melanoma: Efficacy

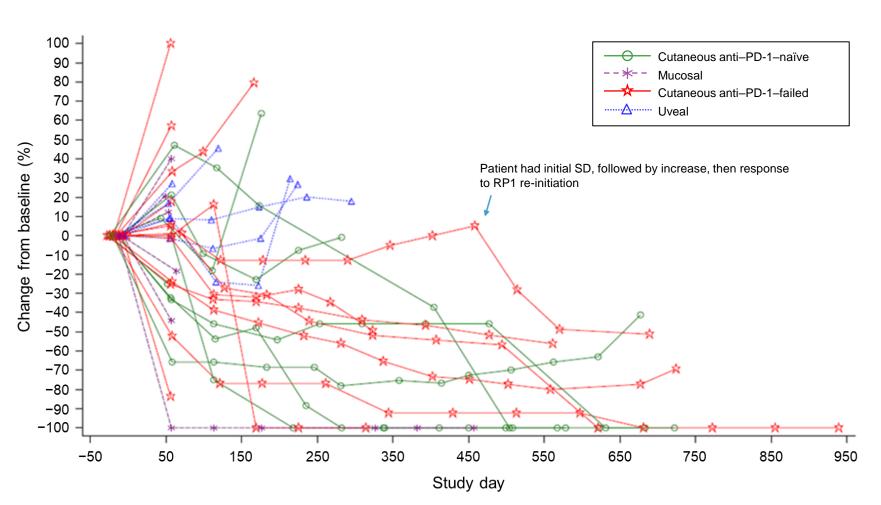
	Cutaneous: Anti-PD-1- naïve	Cutaneous: Anti-PD-1- failed	Mucosal: Anti–PD-1– naïve	Mucosal: Anti–PD-1– failed	Uveal: Anti–PD-1– naïve	Uveal: Anti–PD-1– failed
Patients, N	8	16	1	5	3	3
Best overall i	response, n ('	%)				
CR	3 (37.5)	2 (12.5)	1 (100.0)	1 (20.0)	0	0
PR	2 (25.0)	4 (25.0) ^a	0	0	0	0
SD	2 (25.0)	1 (6.3) ^b	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
CR+PR+SD	7 (87.5)	7 (43.8)	1 (100.0)	1 (20.0)	1 (33.3)	3 (100.0)
^a One anti–PD-1–naïve PR patient is being treated with re-initiated RP1 with the aim of achieving a CR; one anti–PD-1–						

suspected to be NED at 18 and 23 months ^bOne SD patient has the potential for response following ongoing RP1 re-initiation; the second SD patient is a surgical CR (residual tumor removed at 4 months, ongoing at 18 months). CR, complete response; 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.

failed PR patient is a CR by PET scan (no metabolic activity seen) and PET scans are being scheduled for two others

- The objective response rate (ORR) and complete response (CR) rate for the anti-PD-1-failed cutaneous melanoma cohort increased from 31.3% to 37.5% and from 6.3% to 12.5%, respectively
- Disease control (CR+ partial response [PR] + stable disease [SD]) was achieved in 87.5% and 43.8% of patients in the anti-PD-1-naïve and anti-PD-1-failed cutaneous melanoma, respectively

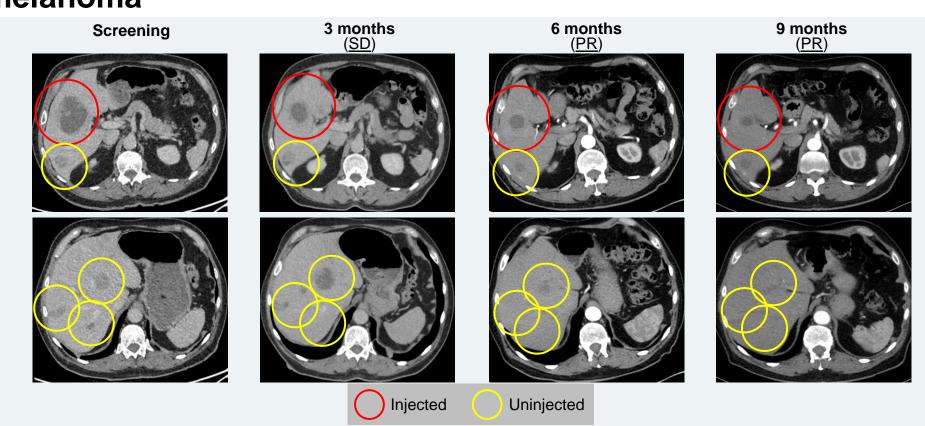
Figure 1. Melanoma: Change in sum of tumor diameters



PD-1, programmed cell death protein 1; SD, stable disease

Durability was maintained, with general deepening of response over time

Figure 2. Patient example: Systemic response in 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 CTLA-4, cytotoxic T-lymphocyte antigen 4; PET, positron emission tomography; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

NMSC

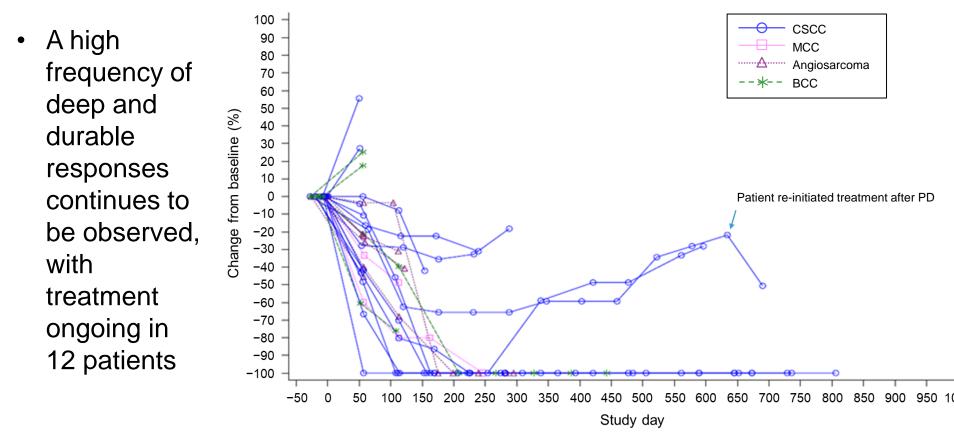
Table 3. Anti-PD-1-naïve NMSC: Efficacy

	CSCC	ВСС	MICC	Angiosarcoma
Patients, N ^a	17	4	4	6
Best overall respon	nse, 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)
CR+PR+SD	12 (70.6)	3 (75.0)	3 (75.0)	5 (83.3)

^aPatients 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; 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.

- The ORR for the cutaneous squamous cell carcinoma (CSCC) cohort increased from 60.0% (last data cut, March 2022) to 64.0%, with 47.1% of patients achieving a CR
- CR rates increased from 46.0% to 47.1% in CSCC, from 0% to 25.0% in basal cell carcinoma (BCC), to 50.0% in Merkel cell carcinoma (MCC), and to 16.7% in angiosarcoma
- Overall, disease control (CR+PR+SD) was achieved in >70.0% of patients in each subtype

Figure 3. Anti-PD-1—naïve NMSC: Change in sum of tumor diameters



BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; NMSC, nonmelanoma skin cancer; PD, progressive disease; PD-1, programmed cell death protein 1.

Figure 4. Patient example: Systemic response in CSCC

- Both the large-injected tumor and the contralateral tumor in the neck were reduced before the first nivolumab dose
- Resolution of bone metastases was observed

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

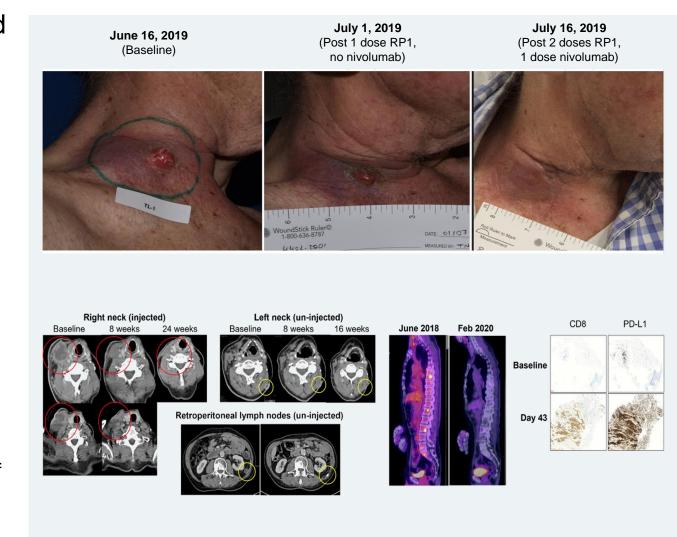


Figure 5. Patient example: Anti–PD-1–naïve CSCC



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

Safety

Table 4. Updated safety data for patients with skin cancer treated with RP1 combined with nivolumab

	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 (24.1)	0	0	18 (21.4	
Nausea	17 (20.2)	0	0	17 (20.2	
Diarrhoea	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 maculo-papular	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)	
Dyspnoea, hypotension	1 (1.2)	2 (2.4)	0	3 (3.6)	
Eczema	2 (2.4)	1 (1.2)	0	3 (3.6)	
Amylase increased, aspartate aminotransferase increased, hyponatraemia, vertigo	1 (1.2)	1 (1.2)	0	2 (2.4)	
Immune-mediated hepatitis	0	2 (2.4)	0	2 (2.4)	
Alanine aminotransferase increased, cancer pain, confusional state, delirium, hypovolaemic shock, immune-mediated enterocolitis, injection site necrosis, liver function test increased, localized oedema, lymph node pain, oedema, 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)	

Conclusions

- 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 CSCC - Promising evidence of activity continues to also be observed in BCC, MCC, and angiosarcoma
- Systemic overall responses were seen irrespective of the sites of disease and the site of injection
- RP1 combined with nivolumab continued to be well tolerated, irrespective of injection route
 - Based on these data, enrollment into a registration-directed cohort of patients who have anti–PD-1–failed cutaneous melanoma (N = 125) is currently ongoing



The IGNYTE 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 (NCT03767348).

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Study sponsor:

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