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Efficacy and safety of RP1 plus nivolumab in patients with advanced anti–PD-1–failed acral melanoma

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Background

- Acral melanoma is a rare and aggressive type of cutaneous melanoma (2%–3% of all melanoma cases) that frequently occurs on the palms of the hands, soles of the feet, and nailbeds; acral melanoma often has poor outcomes, with many patients presenting with in-transit metastases[1-3]
  - This melanoma subtype is typically not related to ultraviolet exposure and has a low mutational burden and programmed cell death-ligand 1 (PD-L1) expression[1,2]
- Acral melanoma typically does not respond well to available therapies, such as immune checkpoint inhibitors (objective response rate [ORR] of ~20%–40% to first-line anti–PD-1 ± anti–cytotoxic T-lymphocyte antigen 4 [CTLA-4] treatment)[4-6]
  - Following progression on first-line therapy, aside from targeted therapy for a subset of patients with *BRAF* mutation-positive tumors, few viable treatment options exist[7-9]
- RP1 (vusolimogene oderparepvec) is an oncolytic immunotherapy expressing human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R$^-$) designed to enhance the local and systemic anti-tumor response through increased immunogenic cell death[10]
- In a registrational cohort of patients with advanced melanoma and confirmed progression during anti–PD-1 ± anti–CTLA-4 treatment from the IGNYTE trial (NCT03767348), RP1 combined with nivolumab demonstrated an ORR of 32.9% (15.0% complete response) by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; primary analysis, data cutoff: March 8, 2024)[11]

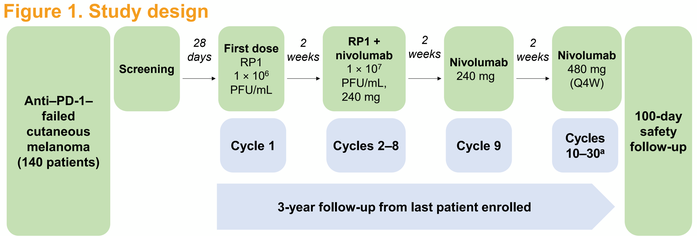
Objective

To assess the efficacy and safety of RP1 plus nivolumab in an ad hoc analysis of patients with anti–PD-1–failed acral melanoma from the IGNYTE clinical trial

Methods

- The IGNYTE phase 2 registrational cohort enrolled patients with stage IIIB–IV cutaneous melanoma and confirmed progression on anti–PD-1 ± CTLA-4 therapy for ≥8 weeks as the last prior treatment (N = 140)
- RP1 was administered intratumorally into superficial and/or deep/visceral tumors at 1 × 10^6 plaque-forming units (PFU)/mL initially, then at 1 × 10^7 PFU/mL once every 2 weeks for up to 7 doses (≤10 mL per cycle) with intravenous nivolumab (240 mg); nivolumab was then given alone (240 mg every 2 weeks or 480 mg every 4 weeks) for up to 2 years, with further RP1 allowed if indicated (**Figure 1**)
- The data cutoff date was March 8, 2024

Figure 1. Study design



***Tumor response assessment**: Radiographic imaging at baseline, every 8 weeks from first dose, and every 12 weeks after confirmation of response*

Primary objective
- Safety and efficacy using mRECIST[b] by independent central review (also assessed by RECIST 1.1)

Secondary objectives
- ORR by investigator assessment (mRECIST[b])
- DOR, CR rate, and PFS by central and investigator assessment, 1-year and 2-year OS

Key eligibility
Anti–PD-1–failed advanced melanoma (including acral), measurable disease, adequate organ function, no prior oncolytic therapy, ECOG performance status 0–1

Criteria for prior anti–PD-1 failure
Confirmed progression while being treated with at least 8 weeks of anti–PD-1 therapy, alone or in combination; anti–PD-1 must be the last prior therapy. Patients on prior adjuvant therapy must have confirmed progression while being treated with adjuvant treatment (PD can be confirmed by biopsy)

Primary analysis was conducted when all patients had ≥12 months of follow-up

[a]Additional doses of RP1 can be given beyond 8 cycles if protocol-specified criteria are met.
[b]For mRECIST, PD must be confirmed by further progression at least 4 weeks after initial PD; intended to better allow for pseudoprogression than RECIST 1.1.
CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; mRECIST, modified RECIST 1.1; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; PFU, plaque-forming units; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Results

Patients

- Of 140 patients with anti–PD-1–failed cutaneous melanoma, 18 (12.9%) had acral melanoma
- Of these 18 patients, 50.0% (9/18) had stage IVM1b–d disease, 94.4% (17/18) had *BRAF* wild-type tumors, and 72.2% (13/18) had programmed death-ligand 1 (PD–L1)–negative (<1%) tumors (**Table 1**)
- Most patients (61.1% [11/18]) had prior treatment with both anti–PD-1 and anti–CTLA-4, and 72.2% (13/18) had primary resistance to anti–PD-1 therapy

Table 1. Baseline demographics and clinical characteristics of patients with acral melanoma

Patients, n (%)	N = 18
Age, median (range), y	62.0 (31.0–81.0)
Sex	
Male	11 (61.1)
Female	7 (38.9)
Stage	
IIIB/IIIC/IVM1a	9 (50.0)
IVM1b/c/d	9 (50.0)
***BRAF* status**	
Wild-type	17 (94.4)
Mutant	1 (5.6)
LDH level	
LDH ≤ULN	15 (83.3)
LDH >ULN	3 (16.7)
Baseline PD-L1 tumor expression	
Positive (≥1%)	4 (22.2)
Negative (<1%)	13 (72.2)
Undetermined or missing	1 (5.6)
Prior therapy	
Anti–PD-1	
Anti–PD-1 only as adjuvant therapy	3 (16.7)
Anti–PD-1 other than as adjuvant therapy	15 (83.3)
Anti–CTLA-4	
Anti–PD-1 combined with anti–CTLA-4	9 (50.0)
Anti–PD-1 treated with anti–CTLA-4 sequentially	2 (11.1)
Received BRAF/MEK therapy	0
Unique prior regimens for advanced/metastatic disease	
1	9 (50.0)
2	4 (22.2)
>2	1 (5.6)
Anti–PD-1 resistance category	
Primary resistance[a]	13 (72.2)
Secondary resistance[b]	5 (27.8)

[a]Primary resistance: progressed within 6 months of starting the immediate prior course of anti–PD-1 therapy.
[b]Secondary resistance: progressed after 6 months of starting the immediate prior course of anti–PD-1 therapy.
CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

Efficacy

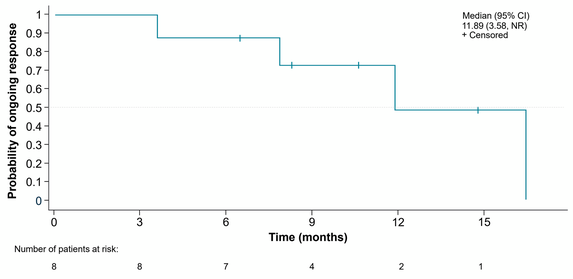
- Following treatment with RP1 plus nivolumab, the confirmed ORR in patients with acral melanoma was 44.4% (8/18) by BICR using RECIST 1.1, including 16.7% (3/18) of patients with complete response and 27.8% (5/18) with partial response (**Table 2**)
- Median (95% confidence interval) duration of response (DOR) was 11.9 (3.6, not reached) months (**Figure 2**)

Table 2. Response by BICR using RECIST 1.1

Confirmed BOR, n (%)	All patients (N = 18)
CR	3 (16.7)
PR	5 (27.8)
SD	3 (16.7)
PD	6 (33.3)
NE	1 (5.6)
ORR (CR + PR)	8 (44.4)

Data were centrally reviewed by RECIST 1.1 (per protocol).
BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

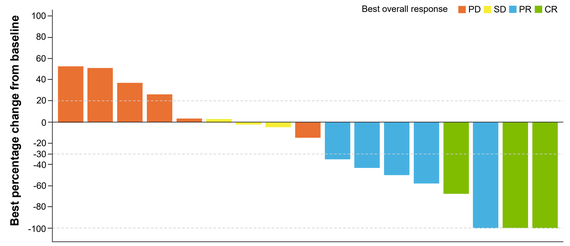
Figure 2. Duration of response



CI, confidence interval; NR, not reached.

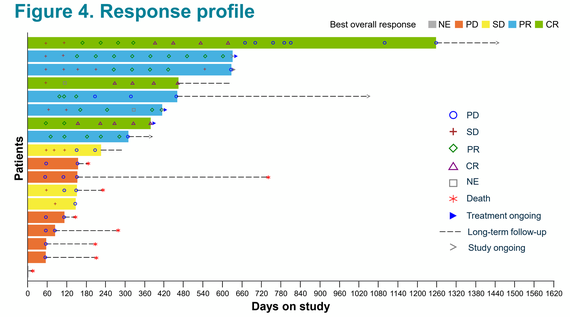
- Best percentage change from baseline for each patient is shown in **Figure 3**, and the kinetics of response for each patient in **Figure 4**
- Responses were seen in both injected and non-injected tumors (**Figure 5**)

Figure 3. Best percentage change from baseline



One patient was not evaluable for response.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

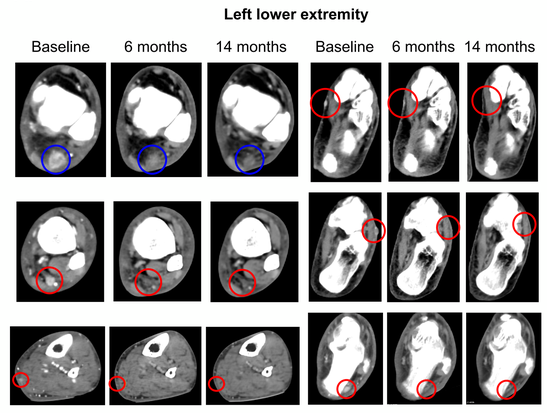
Figure 4. Response profile



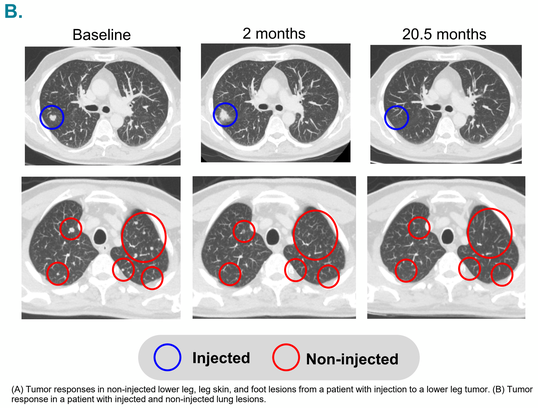
CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5. Patient examples of responses in injected and non-injected tumors

A.



B.



(A) Tumor responses in non-injected lower leg, leg skin, and foot lesions from a patient with injection to a lower leg tumor. (B) Tumor response in a patient with injected and non-injected lung lesions.

Safety

- Most treatment-related adverse events (TRAEs) were grade 1/2; the most common TRAEs (any grade) were chills, pyrexia, fatigue, injection-site pain, and nausea (**Table 3**)
  - Grade ≥3 TRAEs were reported in 2 (11.1%) patients

Table 3. TRAEs (any grade occurring in >1 patient and all grade ≥3; related to RP1)

Preferred term, n (%)	Patients with anti–PD-1–failed acral melanoma (N = 18)	
	All grades	Grade 3/4
Any TRAE	14 (77.8)	2 (11.1)
Chills	5 (27.8)	0
Pyrexia	5 (27.8)	0
Fatigue	4 (22.2)	0
Injection-site pain	4 (22.2)	0
Nausea	3 (16.7)	0
Decreased appetite	2 (11.1)	1 (5.6)
Headache	2 (11.1)	0
Vomiting	2 (11.1)	0
Acute left ventricular failure	1 (5.6)	1 (5.6)
Asthenia	1 (5.6)	1 (5.6)
Hyponatremia	1 (5.6)	1 (5.6)
Left ventricular dysfunction	1 (5.6)	1 (5.6)
Myocarditis	1 (5.6)	1 (5.6)[a]
Sinus arrythmia	1 (5.6)	1 (5.6)
Tricuspid valve incompetence	1 (5.6)	1 (5.6)

There were no grade 5 TRAEs.
[a]Grade 4.
PD-1, programmed cell death protein 1; TRAE, treatment-related adverse event.

Conclusions

- **RP1 combined with nivolumab** demonstrated **notable efficacy** and was **well tolerated** in patients with **advanced anti–PD-1–failed acral melanoma**
  - The **ORR** was **44.4%**, with a median **DOR** of **11.9 months**
- The **safety profile** was **favorable**, with generally transient grade 1/2 TRAEs
- RP1 plus nivolumab represents a **promising treatment approach** for this rare, aggressive melanoma subtype, for which effective therapies are limited
- The **IGNYTE-3 confirmatory phase 3 trial** evaluating **RP1 plus nivolumab** vs physician's choice of treatment in melanoma that has progressed on anti–PD-1 and anti–CTLA-4 is currently recruiting (NCT06264180)

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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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