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Retreatment with RP1 in combination with nivolumab in patients with advanced anti–PD-1–failed melanoma

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Background

- Immune checkpoint inhibitors have improved outcomes for patients with advanced melanoma; however, a large proportion of patients experience disease progression on anti–programmed cell death protein 1 (PD-1) therapy, and there is no generally established standard of care following progression[1-6]
- Treatment options following progression on anti–PD-1 therapy are limited by suboptimal efficacy and toxicity[6-9]
  - Further treatment with anti–PD-1 monotherapy after disease progression yields a 6%–7% response rate[10,11]
- RP1 (vusolimogene oderparepvec) is a fusion-enhanced herpes simplex virus type 1–based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R$^-$)[12]
- In a registration-intended cohort from the IGNYTE trial, RP1 in combination with nivolumab demonstrated clinically meaningful and durable responses in patients with anti–PD-1–failed melanoma
  - As of October 15, 2024, the objective response rate (ORR) was 33.6%, with a complete response rate of 16.4% by blinded independent central review using Response Evaluation Criteria in Solid Tumors version 1.1
  - The median duration of response was 24.8 months
  - Mainly grade 1/2 constitutional-type side effects
- IGNYTE allowed retreatment with RP1 beyond the initial 8 doses when believed by the investigator to be in the best clinical interest of the patient

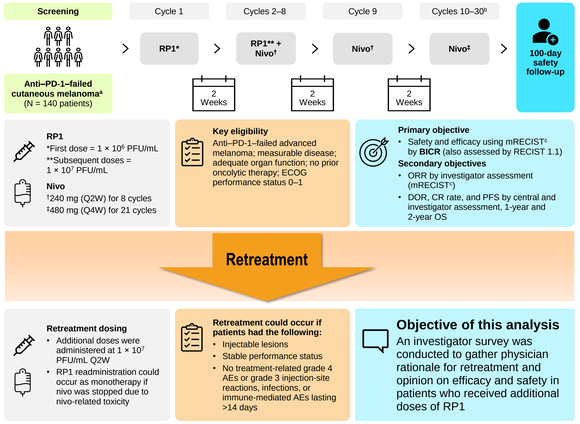
Objective

To present the investigator assessment of patients with anti–PD-1–failed melanoma who were treated with RP1 beyond the initial course of 8 doses in the IGNYTE trial

Methods

- The anti–PD-1–failed melanoma cohort from IGNYTE (NCT03767348) enrolled patients with melanoma and confirmed progression on anti–PD-1 ± anti–cytotoxic T-lymphocyte antigen 4 therapy for ≥8 weeks as the last prior treatment (**Figure 1**)
- Patients received RP1 in combination with nivolumab for up to 8 doses in the initial course of treatment; patients could receive additional courses of up to 8 RP1 injections per course if specific criteria were met (**Figure 1**)
- An investigator survey was performed to gather physician rationale for retreatment and opinion on efficacy and safety in patients who received additional doses of RP1

Figure 1. Study design



[a]Confirmed progression while being treated with ≥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). [b]Additional courses of RP1 beyond the initial 8 cycles could be given if protocol-specified criteria were met. [c]For mRECIST, PD must be confirmed by further progression ≥4 weeks after initial PD; this is intended to better allow for pseudoprogression than RECIST 1.1.
AE, adverse event; BICR, blinded independent central review; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; mRECIST, modified RECIST 1.1; nivo, nivolumab; 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; Q2W, every 2 weeks; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Results

Summary of investigator survey of retreatment

- To supplement clinical data and capture the potentially multifactorial rationale and clinical benefits of RP1 retreatment, investigators from the IGNYTE trial who administered RP1 beyond the initial course of 8 doses were surveyed (**Table 1**)

Table 1. Survey questions and overview of responses

Question	Response
What was the rationale for re-initiating RP1?	Investigator responses included various reasons for administering RP1 beyond the initial 8-dose course, including disease control, deepening or gaining a response, delaying progression, avoiding more toxic therapies, and lack of alternative treatment options
In your clinical opinion, did the patient benefit from the additional course(s) of RP1?	Among the 25 patients who received additional doses of RP1, **64% (16 patients)** were considered to have derived clinical benefit based on investigator assessment
Based on your experience, would you consider re-initiating RP1 again in a similar context?	All participating investigators confirmed they would consider re-initiating RP1 in similar circumstances and would value having this treatment option available in the future

Patients

- Of 140 enrolled patients, 25 (18%) received treatment with RP1 beyond the initial 8 doses
- Demographics and baseline characteristics for patients who re-initiated RP1 are provided in **Table 2**
- As of the October 15, 2024, data cutoff, patients received a median (range) of 8.0 (2.0–24.0) additional RP1 doses with a median (range) volume of 13.1 (1.0–148.0) mL (**Table 2**)
  - Primary reasons for further treatment included aiming for deepening of response or delay of disease progression

Table 2. Demographics and baseline characteristics of patients who received RP1 retreatment

Characteristic	Patients receiving >8 doses (N = 25)
Age, years, median (range)	60.0 (31.0–83.0)
≥65 years	8 (32.0)
Male sex	18 (72.0)
White race	22 (88.0)
Stage	
IIIB/IIIC/IVM1a	15 (60.0)
IVM1b/c/d	10 (40.0)
***BRAF* status**	
Wild-type *BRAF*	14 (56.0)
Mutant *BRAF*	11 (44.0)
LDH level	
LDH ≤ULN	18 (72.0)
LDH >ULN	7 (28.0)
PD-L1 tumor expression	
Positive (≥1%)	9 (36.0)
Negative (<1%)	11 (44.0)
Undetermined or missing	5 (20.0)
Prior therapy	
Anti–PD-1	
Anti–PD-1 only as adjuvant therapy	8 (32.0)
Anti–PD-1 as advanced/metastatic therapy	17 (68.0)
Anti–CTLA-4	
Anti–PD-1 combined with anti–CTLA-4	7 (28.0)
Wild-type *BRAF* and received combination anti–PD-1 and anti–CTLA-4	4 (16.0)
Received BRAF/MEK therapy	3 (12.0)
Other disease characteristics	
Primary resistance to prior anti–PD-1[a]	11 (44.0)
Secondary resistance to prior anti–PD-1[b]	14 (56.0)
Number of additional RP1 doses, median (range)	8.0 (2.0–24.0)
Volume of additional RP1 doses, mL, median (range)	13.1 (1.0–148.0)

Data are presented as n (%) unless otherwise indicated.
[a]Primary resistance was defined as progression within 6 months of starting the immediate prior course of anti–PD-1 therapy.
[b]Secondary resistance was defined as progression 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.

Survey efficacy summary

- Of the 25 patients who received additional doses of RP1, 16 patients (64%) experienced a deepened or maintained response, extended time to progression, or extended time to subsequent anticancer therapy as assessed by the investigators (**Table 3**)

Safety summary

- Twelve patients had treatment-related adverse events during retreatment with RP1 (**Table 3**)
  - One patient had grade 3 worsening tumor pain and grade 4 splenic rupture that were considered related to RP1 by the investigator upon initial assessment; however, further evaluation by the study sponsor determined that splenic rupture was likely unrelated to RP1, and no other grade 3 tumor pain events occurred with additional injections

Table 3. Individual responses and benefits of re-initiation (N = 25)

Patient #	BOR by RECIST 1.1	Investigator rationale for administering RP1 beyond the initial 8-dose course[a]	Investigator assessment of benefit (yes/no)	TRAEs
Patient 1	CR	Deepen response	Yes	None
Patient 2	PR	Limited treatment options, tolerated treatment well, and wanted to induce response	Yes	None
Patient 3	SD	Deepen response	Yes	None
Patient 4	CR	Deepen response	Yes	None
Patient 5	PR	Delay progression	Yes	G1 vitiligo G2 eczema
Patient 6	PR	Deepen response	Yes	None
Patient 7	SD	Disease stability and potential conversion from SD to PR	Yes	None
Patient 8	SD	Disease stability and potential conversion from SD to PR	No	G2 injection-site reaction G2 rash (acne form) G1 rash (acne form) G1 desquamation/tumor site
Patient 9	PR	Deepen response	Yes	G1 hair loss G1 hair greying G1 fever (2 events) G1 joint pain G1 chills
Patient 10	SD	Deepen response	No	G1 pain at injection sites (right thigh and scalp) G1 fatigue (3 events)
Patient 11	PR	Deepen response	Yes	G1 flu-like symptoms G1 fatigue G1 malaise
Patient 12	PR	Deepen response	Yes	G1 RP1 injection-site pain, intermittent G3 tumor pain G2 worsening tumor pain G1 chills, intermittent G4 splenic rupture
Patient 13	PR	Slow progression and try to induce a response	No	G1 serum amylase increased G1 C-reactive protein 1 G1 increased troponin
Patient 14	CR	Delay progression and treat progressive sites	Yes	G1 nausea after injection alone
Patient 15	SD	Deepen response	Yes	G1 flu syndrome (2 events) G1 asthenia
Patient 16	PR	Deepen response	Yes	None
Patient 17	SD	No alternative therapy	No	None
Patient 18	PR	Deepen response	Yes	None
Patient 19	PD	Deepen response	Yes	None
Patient 20	SD	Deepen response and delay progression	Yes	None
Patient 21	CR	Avoid initiating a more toxic therapy and benefit in initial cycles	No	G1 fever (2 events) G1 diarrhea
Patient 22	PD	Gain response	Possibly	None
Patient 23	PR	Control disease	Possibly	G1 fatigue G2 bone pain (knee) G1 bone pain (knee)
Patient 24	SD	Deepen response	Possibly	None
Patient 25	PR	Deepen response	No	G1 decreased hemoglobin G1 lipase increase G1 gamma-glutamyl transferase elevation G1 vitiligo G1 TSH elevation (2 events)

[a]Responses recorded as provided by investigators.
BOR, best overall response; CR, complete response; G, grade; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TRAE, treatment-related adverse event; TSH, thyroid-stimulating hormone.

IGNYTE trial of RP1 + nivolumab in patients with anti–PD-1–failed melanoma (N = 140)
8 initial doses of RP1, with option for additional doses
Overall Efficacy: 33.6% ORR (16.4% CR), DOR of 24.8 months

Survey of investigators
who administered additional RP1 doses to determine the rationale and clinical benefits of RP1 retreatment

What was the rationale for re-initiating RP1?

In your clinical opinion, did the patient benefit from the additional course(s) of RP1?

Based on your experience, would you consider re-initiating RP1 again in a similar context?

Median age: 60 years
72% male
40% stage M1b–d
44% primary resistance to anti–PD-1

Median (range) of 8.0 (2.0–24.0) additional RP1 doses
Median (range) volume of 13.1 (1.0–148.0) mL

Reasons for retreatment
- Disease control
- Deepening or gaining a response
- Delaying progression
- Avoiding more toxic therapies
- Lack of alternative treatment options

64% of patients derived clinical benefit based on investigator assessment

All participating investigators would consider re-initiating RP1 in similar circumstances

In the opinion of the investigators, retreatment with RP1 provided clinical benefit in the majority (64%) of patients and was generally well tolerated

Conclusions

- **Treatment with RP1 beyond 8 doses was feasible** and in the opinion of the investigators, the majority of patients to whom it was given experienced **clinical benefit** (16/25 patients [64%])
- Findings from this study indicate that additional treatment with RP1 is **well tolerated** in patients with anti–PD-1–failed melanoma, with the **opportunity for continued clinical benefit**
- These results suggest a favorable risk-benefit profile for treating patients with RP1 beyond 8 doses; **treating physicians should determine whether additional doses should be administered using their clinical judgement**

The IGNYTE study is currently recruiting patients with anti–PD-1–failed NMSC and anti–PD-1–failed MSI-H/dMMR solid tumors. 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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