Abstract: 9537

Response analysis for injected and non-injected lesions and of the safety and efficacy of superficial and deep/visceral RP1 injection in the registrational cohort of anti–PD-1–failed melanoma patients of the IGNYTE trial

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Background

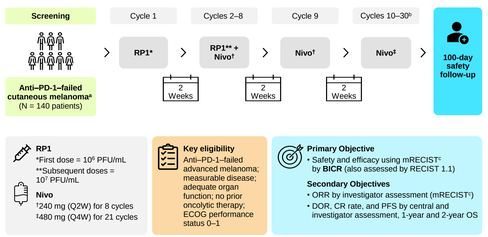
- Immune checkpoint inhibitors have improved outcomes for patients with advanced melanoma, but the majority of patients experience disease progression on anti–programmed cell death protein 1 (PD-1) therapy[1-6]
  - Outcomes following progression are poor, with a median overall survival (OS) of approximately 1 year in real-world clinical practice[7,8]
  - There is no generally established standard of care following progression, and available treatment options are limited by suboptimal efficacy and/or high toxicity[9-13]
- RP1 (vusolimogene oderparepvec) is a selectively replication-competent herpes simplex virus type 1–based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor and the fusogenic GALV-GP-R$^-$ glycoprotein[14]
- In the registrational cohort from the IGNYTE trial, patients with advanced anti–PD-1–failed melanoma were treated with RP1 + nivolumab:
  - The **objective response rate (ORR)** was **32.9%** by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)
  - The **complete response** rate was **15.0%**
  - Landmark **OS** rates at **1**, **2**, and **3 years** were **75.3%**, **63.3%**, and **54.8%**, respectively; median OS was not reached

Objective

- Evaluate the efficacy of RP1 + nivolumab in injected and non-injected lesions
- Assess the safety and efficacy in patients receiving superficial and/or deep/visceral RP1 injections

Methods

Study design



The primary analysis was conducted when all patients had ≥12 months of follow-up.
[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]RP1 can be reinitiated beyond 8 cycles if protocol-specified criteria are 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.
BICR, blinded independent central review; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; mRECIST, modified RECIST; 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.

RP1 administration

- RP1 was injected into superficial and/or deep/visceral tumors
  - **Superficial tumors:** defined as those that could be visualized or palpated and accessed with standard-sized needles and syringes
  - **Deep/visceral tumors:** defined as those that could not be directly observed or palpated and required imaging guidance (eg, ultrasound, computed tomography, endoscopy, bronchoscopy) to inject
    - **Visceral tumors** are deep tumors associated with visceral organs
  - Both superficial and deep/visceral lesions could be injected on the same day (volume dependent on lesion size; ≤10 mL total/day)
  - Recommended needle gauges are 25–27 for superficial lesions and 20–23 for deep/visceral lesions

Patients

- A "real-world" anti–PD-1–failed melanoma population was enrolled (N = 140; data cutoff, March 8, 2024)
  - Median (range) age was 62 (21–91) years
  - The median (range) follow-up at the time of the primary analysis was 15.5 (0.5–47.6) months
  - Due to the requirement that patients must have confirmed progressive disease on an immediate prior anti–PD-1–based therapy, most patients had 1 or 2 prior lines of therapy
- Patient clinical characteristics are summarized below
  - Sixty-eight (48.6%) patients had stage IVM1b–d disease
  - Lactate dehydrogenase (LDH) levels were above the upper limit of normal in 47 (33.6%) patients[a]
  - Seventy-nine (56.4%) patients had PD-L1–negative tumors[b]
  - Sixty-one (43.6%) patients had prior anti–PD-1 combined with anti–CTLA-4 and 4 (2.9%) received both therapies sequentially
  - Most patients (92 [65.7%]) had primary resistance to anti–PD-1 therapy[c]

[a]LDH level was unknown in 1 (0.7%) patient. [b]PD-L1 status was undetermined or missing in 17 (12.1%) patients. [c]Primary resistance: Progressed within 6 months of starting the immediate prior course of anti–PD-1 therapy.

Efficacy in superficial and/or deep/visceral lesions

- Patients with deep/visceral (± superficial) injections had numerically higher response rates vs those who received superficial injections only (**Table 1**)
- The ORR was 40.0% (6/15) in patients receiving deep/visceral (± superficial) lung and liver injections
  - The median number of RP1 injections in the lung and liver was 8 and 6.5, respectively

Responses in injected vs non-injected lesions

- In an analysis of injected vs non-injected lesions, up to 10 lesions per patient were analyzed by BICR
- Among RECIST 1.1 responders (N = 46), robust responses were observed in both injected and non-injected lesions (**Table 2** and **Figure 1**)
  - There was a ≥30% reduction in 93.6% (73/78) of injected lesions and 79.0% (94/119) of non-injected lesions
  - The kinetics of response were similar in injected vs non-injected lesions (**Figure 2**)
  - Of the non-injected visceral lesions in responding patients, 96.2% (50/52) showed reduction from baseline, with 65.4% reduced by ≥30% (**Figure 3**)

Results

Table 1. Efficacy by injection type by BICR using RECIST 1.1 (patient-level data)

Confirmed BOR, n (%)	Total (N = 140)	Superficial only (n = 104)	Deep/visceral ± superficial (n = 36)	
			Deep/visceral plus superficial (n = 14)	Deep/visceral only (n = 22)
CR	21 (15.0)	18 (17.3)	0	3 (13.6)
PR	25 (17.9)	13 (12.5)	6 (42.9)	6 (27.3)
SD	31 (22.1)	19 (18.3)	4 (28.6)	8 (36.4)
PD	54 (38.6)	46 (44.2)	3 (21.4)	5 (22.7)
ORR	**46 (32.9)**	**31 (29.8)**	**6 (42.9)**	**9 (40.9)**

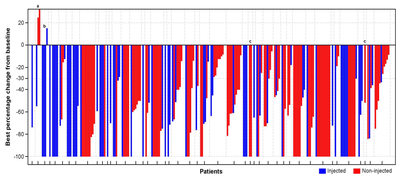
Eight (7.7%) patients in the superficial only group and 1 (7.1%) patient in the deep/visceral plus superficial group were not evaluable (discontinued prior to the first efficacy assessment).
BICR, blinded independent central review; BOR, best overall response; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Table 2. Responses in injected vs non-injected lesions from RECIST 1.1 responders (lesion-level data)

Number (%) of measured lesions for RECIST 1.1 responders (CR or PR; N = 46)	Injected lesions (n = 78)	Non-injected lesions (n = 119)
Number (%) of lesions with		
No reduction	1 (1.3)	4 (3.4)
Any reduction	**77 (98.7)**	**115 (96.6)**
Best reduction ≥0% to <30%	4 (5.1)	21 (17.6)
Best reduction ≥30% to <100%	31 (39.7)	47 (39.5)
Best reduction of 100%	**42 (53.8)**	**47 (39.5)**

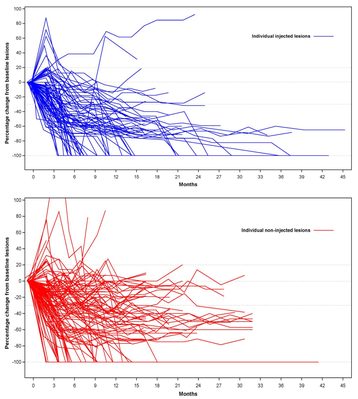
CR, complete response; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 1. Depth of response in injected vs non-injected lesions from RECIST 1.1 responders (N = 46; patient- and lesion-level data)



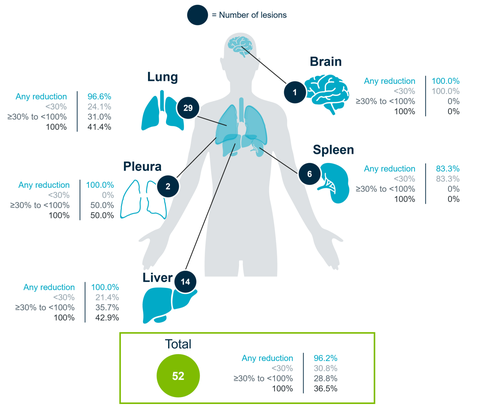
One patient was not included because lesions were not measurable by BICR.
[a]Patient had a CR as a radical resection of all 3 lesions on the skin of the left foot confirmed full regression. [b]The sum of diameters of 4 target lesions met the criteria for a PR. [c]Patient only had non-injected lesions measured.
BICR, blinded independent central review; CR, complete response; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 2. Kinetics of response in injected vs non-injected lesions from RECIST 1.1 responders (N = 46; lesion-level data)



RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 3. Responses in non-injected visceral lesions from RECIST 1.1 responders (N = 46; lesion-level data)



RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Safety in superficial and/or deep/visceral injections

- Patients with deep/visceral (± superficial) injections and patients with only superficial injections experienced comparable rates of treatment-related adverse events (**Table 3**)

Table 3. Safety by injection type (most common TRAEs related to RP1 or nivolumab)

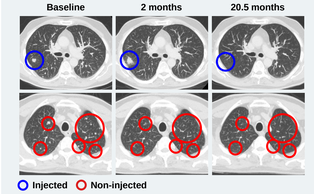
TRAEs, n (%)	Superficial only (n = 104)		Deep/visceral ± superficial (n = 36)			
			Deep/visceral plus superficial (n = 14)		Deep/visceral only (n = 22)	
	All grades	Grades 3/4	All grades	Grades 3/4	All grades	Grades 3/4
Total	93 (89.4)	15 (14.4)	12 (85.7)	2 (14.3)	21 (95.5)	1 (4.5)
Fatigue	33 (31.7)	1 (1.0)	6 (42.9)	0	7 (31.8)	0
Pyrexia	31 (29.8)	0	3 (21.4)	0	9 (40.9)	0
Chills	30 (28.8)	0	5 (35.7)	0	10 (45.5)	0
Nausea	22 (21.2)	0	3 (21.4)	0	6 (27.3)	0
Diarrhea	14 (13.5)	1 (1.0)	2 (14.3)	0	4 (18.2)	0
Vomiting	14 (13.5)	0	1 (7.1)	0	4 (18.2)	0
Headache	13 (12.5)	0	1 (7.1)	0	4 (18.2)	0
Influenza-like illness	13 (12.5)	0	2 (14.3)	0	10 (45.5)	0
Injection-site pain	13 (12.5)	0	3 (21.4)	0	5 (22.7)	0

TRAE, treatment-related adverse event.

RP1 lung and liver injections

- RP1 injections to lung and liver lesions were feasible and resulted in responses (**Figures 4** and **5**)
- Among 7 patients with lung injections, pneumothorax events were reported in 5.8% (3/52) of injections
  - One event was grade 1 and two events were grade 2; these events self-resolved, and further RP1 injections were given without additional events
    - For both grade 2 events, resolution occurred within 4 days
  - One (1.9%) lung injection led to pneumothorax requiring invasive intervention (chest tube insertion)
  - All events occurred within 7 days after RP1 injection

Figure 4. Patient example: RP1 lung injection in patient with prior ipilimumab + nivolumab



52 lung injections in 7 patients

Pneumothorax events: 3/52 (5.8%)
- Grade 1: 1/52 (1.9%)
- Grade 2: 2/52 (3.8%)
- Grade ≥3: 0

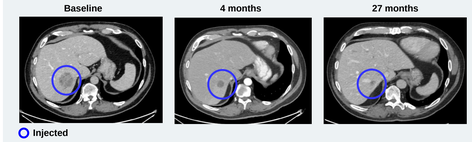
Management of pneumothorax

Grade 1 pneumothorax
- No treatment was required
- The event resolved after 13 days

Grade 2 pneumothorax
- The patient underwent a chest X-ray and received an opioid analgesic
- The event resolved on the same day

Grade 2 pneumothorax (prior patient example)
- The patient was treated with chest tube insertion, oxygen therapy, an analgesic, an opioid analgesic, and a NSAID
- The event resolved after 4 days
- The patient continued to receive lung injections without recurrence of pneumothorax

Figure 5. Patient example: RP1 liver injection in patient with prior pembrolizumab



48 liver injections in 8 patients
- No elevated liver function tests
- No liver or abdominal cavity bleeding events

Patients experienced numerically higher ORRs after receiving deep/visceral injections (± superficial) compared with superficial injections only. Deep responses were observed in injected and non-injected, including visceral, lesions.

RP1 injections directly into the lung and liver were generally well tolerated and resulted in few organ-specific adverse events that were easily managed.

Conclusions

- Both lesion-level and patient-level responses were seen independent of the injection status of individual lesions or their anatomical site
  - The overall response to RP1 was driven by the response of both injected and non-injected lesions
- The safety and efficacy profiles of deep/visceral injections were generally comparable to those of superficial injections
  - Numerically higher rates of response were observed after deep/visceral injections vs superficial injections only
  - Deep/visceral injections can be safely and reproducibly performed
- Liver and lung injections had a tolerable safety profile
  - No bleeding events were reported after liver injection
  - Lung injections were associated with low rates of pneumothorax events, which were typically of low grade and manageable
- Overall, these data support the safety and efficacy of deep/visceral injections and demonstrate the development of a robust systemic anti-tumor response following RP1 treatment
- The confirmatory phase 3 IGNYTE-3 trial (NCT06264180) is currently underway (see poster TPS9599)

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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Disclosures:

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