EFFICACY AND SAFETY OF RP1 COMBINED WITH NIVOLUMAB IN PATIENTS WITH ANTI–PD-1–FAILED MELANOMA FROM THE IGNYTE CLINICAL TRIAL


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Key takeaways

Clinical relevance
• Treatment of melanoma patients after progression on an anti-PD-1 containing regimen remains a considerable unmet need

IGNYTE data analysis by investigator review
• Efficacy
  ▪ RP1 combined with nivolumab provides deep and durable responses in patients with advanced melanoma who had confirmed disease progression, while on prior anti–PD-1 therapy for at least 8 weeks, including in combination with anti-CTLA-4
  ▪ The ORR was 33%, with a median duration of response of >36 months (N=156)
• Safety
  ▪ The treatment showed a favorable safety profile with generally ‘on target’ and transient grade 1–2 side effects indicative of systemic immune activation
Background

- There are limited options for melanoma patients who have progressed on anti–PD-1 therapy\(^1\) (including on adjuvant anti–PD-1 therapy)

- Further single agent anti-PD-1 for patients having confirmed PD on prior anti-PD-1 gives a response rate of 6-7\(^%\)\(^{1,2}\)

- For patients who have not received anti–CTLA-4 therapy, ipilimumab or nivolumab + ipilimumab or relatlimab are potential options\(^3\) but toxicity is high\(^4,5\)

- Adding anti-LAG3 to anti–PD-1 has not demonstrated meaningful efficacy in the anti–PD-1–failed setting\(^6\)

- For targeted therapy–naïve patients with BRAF mutant tumors, BRAF-targeted therapy responses are generally transient\(^7\)

- T-VEC + pembrolizumab in patients who progressed on prior anti–PD-1 therapy has limited activity outside of the adjuvant setting, with no responses seen in patients with visceral disease\(^8,9\)

- TIL therapy gives response rates of ~30%, but comes with toxicity (nearly all patients have grade 4 toxicity)\(^10\)

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CTLA-4, cytotoxic T-lymphocyte antigen 4; LAG3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; TIL, tumor infiltrating lymphocyte

PRESENTED BY: IGNYTE Study design (Anti-PD-1 failed melanoma cohort)

**Primary objectives**
- To assess the safety and efficacy (by independent central review [mRECIST]) of RP1 in combination with nivolumab

**Secondary objective**
- ORR by investigator review (mRECIST)
- To assess the efficacy of RP1 in combination with nivolumab as determined by DOR, CR rate, DCR, PFS, by central & investigator review, 1-year and 2-year OS

**Key eligibility**
Advanced melanoma having confirmed progression while on prior anti-PD-1 therapy; at least 1 measurable and injectable lesion (≥1 cm LD), including deep/visceral; adequate organ function; no prior treatment with oncolytic therapy; ECOG performance status 0–1

**Criteria for prior anti-PD-1 failure**
≥8 weeks of prior anti-PD-1, confirmed progression while on anti-PD-1; anti-PD-1 must be the last therapy before the clinical trial. Patients on prior adjuvant therapy must have progressed while on prior adjuvant treatment (progression can be confirmed by biopsy)

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

**3-year follow-up from last patient enrolled**

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### Study Design

- **Screening:** 28 days
- **First dose:**
  - RP1 1×10⁶ pfu/mL
  - RP1+nivolumab
    - 1×10⁷ pfu/mL, 240 mg
- **2 weeks:**
  - RP1+nivolumab
    - 1×10⁷ pfu/mL, 240 mg
  - Nivolumab 240 mg
- **2 weeks:**
  - Nivolumab 480 mg (Q4W)

**Cycle 1**
- RP1+nivolumab
- Nivolumab

**Cycles 2–8**
- RP1+nivolumab
- Nivolumab

**Cycle 9**
- Nivolumab

**Cycles 10–30b**
- Nivolumab

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*Dr. Michael K. Wong, MD, PhD, FRCPC*

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**Notes:**
- Dosing with nivolumab begins at dose 2 of RP1 (C2D15).
- Option to reinitiate RP1 for 8 cycles if criteria are met.
- Non-neurological solid tumors
- CR, complete response; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; LD, longest diameter; ORR, objective response rate; OS, overall survival; PD-1, programmed death protein 1; PFS, progression-free survival; pfu, plaque-forming unit; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
Baseline clinical characteristics

- A ‘real world’ anti-PD-1 failed melanoma population was enrolled
  - Good representation of each of the sub-groups of patients who progress on prior anti-PD-1 therapy

### Patients, n (%)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (N = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median [range])</td>
<td>62 (21-91)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52 (33.3)</td>
</tr>
<tr>
<td>Male</td>
<td>104 (66.7)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IIIb/IIIc/IVM1a</td>
<td>75 (48.1)</td>
</tr>
<tr>
<td>IVM1b/c/d</td>
<td>81 (51.9)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
</tr>
<tr>
<td>Anti–PD-1 only as adjuvant therapy</td>
<td>39 (25.0)</td>
</tr>
<tr>
<td>Anti–PD-1 not as adjuvant therapy</td>
<td>117 (75.0)</td>
</tr>
<tr>
<td>Anti–PD-1 &amp; anti–CTLA-4</td>
<td>74 (47.4)</td>
</tr>
<tr>
<td>Received BRAF-directed therapy</td>
<td>17 (10.9)</td>
</tr>
</tbody>
</table>

### Other disease characteristics

- Primary resistance to prior anti–PD-1\textsuperscript{a} 105 (67.3)
- Secondary resistance to prior anti–PD-1\textsuperscript{b,c} 51 (32.7)
- BRAF wt 103 (66.0)
- BRAF mutant 53 (34.0)
- LDH ≤ULN 105 (67.3)
- LDH >ULN 50 (32.1)
- LDH unknown 1 (0.6)

The median follow up for all patients on study is 15.4 months (range 0.5-55.5)

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\textsuperscript{a} Primary resistance: Progressed within 6 months of starting the immediate prior course of anti–PD-1 therapy; \textsuperscript{b} Secondary resistance: Progressed after 6 months of treatment on the immediate prior course of anti–PD-1 therapy; \textsuperscript{c} Includes 2 pt unknown resistance status. CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; ULN, upper limit of normal; wt, wild type.
Efficacy

- The data presented today is the **investigator assessed data with all patients having at least 12 months follow up**
  - Centrally reviewed, primary endpoint data, will be presented separately once available

Data cutoff: March 8th 2024. BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD, progressive disease; PR, partial response; ORR, objective response rate; SD, stable disease.

<table>
<thead>
<tr>
<th>BOR n (%)</th>
<th>All patients (n = 156)</th>
<th>Prior single-agent anti–PD-1 (n = 82)</th>
<th>Prior anti–PD-1/CTLA-4 Exposure (n = 74)a</th>
<th>Stage IIIb-IVM1a (n = 75)</th>
<th>Stage IVM1b-d (n = 81)</th>
<th>1o resistance to anti–PD-1 (n = 105)</th>
<th>2o resistance to anti–PD-1 (n = 51)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR 23 (14.7)</td>
<td>18 (22.0)</td>
<td>5 (6.8)</td>
<td>18 (24.0)</td>
<td>6 (7.8)</td>
<td>18 (17.1)</td>
<td>5 (9.8)</td>
<td></td>
</tr>
<tr>
<td>PR 28 (17.9)</td>
<td>13 (15.9)</td>
<td>15 (20.3)</td>
<td>13 (17.3)</td>
<td>15 (18.5)</td>
<td>18 (17.1)</td>
<td>10 (19.6)</td>
<td></td>
</tr>
<tr>
<td>SD 34 (21.8)</td>
<td>18 (22.0)</td>
<td>16 (21.6)</td>
<td>19 (25.3)</td>
<td>15 (18.5)</td>
<td>17 (16.2)</td>
<td>17 (33.3)</td>
<td></td>
</tr>
<tr>
<td>PD 63 (40.4)</td>
<td>31 (37.8)</td>
<td>32 (43.2)</td>
<td>24 (32.0)</td>
<td>39 (48.1)</td>
<td>47 (44.8)</td>
<td>16 (31.4)</td>
<td></td>
</tr>
<tr>
<td>ORR 51 (32.7)c</td>
<td>31 (37.8)</td>
<td>20 (27.0)</td>
<td>31 (41.3)</td>
<td>20 (24.7)</td>
<td>36 (34.3)</td>
<td>15 (29.4)</td>
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</table>

- Approximately 1 in 3 patients achieved an objective response (32.7%)
- Consistent ORR across subgroups, including:
  - 27% ORR in patients who had prior anti–PD-1 & anti–CTLA-4
  - 34% ORR in patients who are primary resistant to their prior anti-PD-1 therapy

*Eight patients were treated with sequential anti-CTLA-4 and anti-PD-1 (ORR for prior combined anti-CTLA-4/anti-PD-1 was 25.8%).

1Includes one patient with unknown resistance status.

2ORR for the 140 registration intended cohort was 32.1%.

Data cutoff: March 8th 2024.
Responses are Systemic
Change in Size of Individual Injected and Non-injected Lesions

- 70.4% of responding patients had non-injected lesions
  - Responders include patients with minority of lesions injected
  - Injected and non-injected lesions responded with similar duration and kinetics
  - Depth of response independent of whether injected

Responses in non-injected lesions demonstrate systemic benefit

Includes both target and non-target lesions for RECIST assessment, measured from CT/MRI scans for radiologically assessable lesions (responders from the first 75 patients enrolled into the registration intended cohort). 58/75 patients had ≥1 non-injected lesion, of whom 15 achieved a response based on those lesions only (excludes possible response in injected lesions); ORR of 25.9% on the basis of non-injected lesions only. First presented at ASCO 2023.
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Responses are durable, with a median DOR by Kaplan-Meier estimate of **36.6 months**

The median follow up for responders is 27.9 months (range 10.5-55.5)

<table>
<thead>
<tr>
<th>Duration</th>
<th>Probability (%)</th>
</tr>
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<tbody>
<tr>
<td>&gt;6 months</td>
<td>100%</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>84.2%</td>
</tr>
<tr>
<td>&gt;18 months</td>
<td>74.9%</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>65.2%</td>
</tr>
</tbody>
</table>

Data cutoff: March 8th 2024. Duration of response defined as time from baseline to end of response for responders. DOR, duration of response.
A substantial proportion of patients achieved durable clinical benefit, including those with SD, with a 55% disease control rate overall.

65% of responses are ongoing at the time of this analysis.

Data cutoff: March 8th 2024. The target lesion response is shown for patients with at least one post-baseline assessment. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Patient examples

Patient 1121-2011: Stage IVM1c, progressed on prior nivolumab (adjuvant) and pembrolizumab (1L); CR

Patient 1156-2008: Stage IVM1b, BRAF-mutant, progressed on prior nivolumab (1L); PR

Responses seen in non-injected distant & visceral tumors
Safety: Treatment-related AEs (N = 156)

RP1 combined with nivolumab continues to be a generally well tolerated regimen
- Predominantly grade 1 and 2 constitutional-type side effects
- Low incidence of grade 3 and 4 events
- No grade 5 events

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>TRAEs occurring in &gt;5% of patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade 1–2</td>
</tr>
<tr>
<td>Chills</td>
<td>53 (34.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (32.7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>49 (31.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (22.4)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>30 (19.2)</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>23 (14.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (13.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (13.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>20 (12.8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20 (12.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13 (8.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (7.1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>11 (7.1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>9 (5.8)</td>
</tr>
<tr>
<td>Rash</td>
<td>9 (5.8)</td>
</tr>
</tbody>
</table>

Additional grade 3 and 4 events <5%

Grade 3: Two each of rash maculo-papular and hypophysitis; 1 each of tumor pain, infusion-related reaction, muscular weakness, abdominal pain, amylase increased, dermatitis bullous, eczema, immune-mediated enterocolitis, immune-mediated hepatitis, paresthesia, acute left ventricular failure, arthritis, cancer pain, enterocolitis, extranodal marginal zone B-cell lymphoma (MALT type), hyponatremia, injection site necrosis, left ventricular dysfunction, memory impairment, meningitis aseptic, edema, palmar-plantar erythrodysesthesia syndrome, peripheral sensory neuropathy, radiculitis brachial, sinus arhythmia, tricuspid valve incompetence, and type 1 diabetes mellitus

Grade 4: One each of lipase increased, alanine aminotransferase increased, blood bilirubin increased, cytokine release syndrome, myocarditis, and hepatic cytolysis, splenic rupture

Data cutoff: March 8th 2024. MALT, mucosa-associated lymphoid tissue; TRAE, treatment-related adverse event.
Conclusions

RP1 combined with nivolumab in melanoma patients who had **confirmed progression** on prior anti-PD-1 continues to show:

- Deep and durable, systemic responses
- **A favorable safety profile**, with generally ‘on target’ and transient grade 1–2 side effects indicative of systemic immune activation

- **Approximately 1 in 3 patients experienced a response**
  - 27% ORR in patients had prior anti–PD-1/anti–CTLA-4
  - 34% ORR in patients who had primary resistance to their immediate prior anti-PD-1 therapy
  - Clinically meaningful activity was seen across all enrolled subgroups
  - Approximately 55% of patients experienced clinical benefit (CR + PR + SD)

- **Responses were highly durable**
  - All patients followed for at least 12 months
  - All responses lasted at least 6 months, with median DOR >36 months

*Based on these results, a confirmatory randomized phase 3 study is in the start-up phase (IGNYTE-3; NCT06264180); Poster #TPS9604 Centrally reviewed primary & secondary endpoint data from the study will be presented separately once available*
Acknowledgements

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• We would also like to thank the site staff and principal investigators for their critical contributions to this study.

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The IGNYTE study is currently recruiting patients, except for anti–PD-1–failed melanoma patients. To learn more about enrolling your patient, contact clinicaltrials@replimune.com or +1 (781) 222 9570.

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