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Biomarker and updated clinical data for RP1 plus nivolumab in anti–PD-1–failed melanoma from the IGNYTE trial demonstrate reversal of mechanisms of resistance to immune checkpoint blockade

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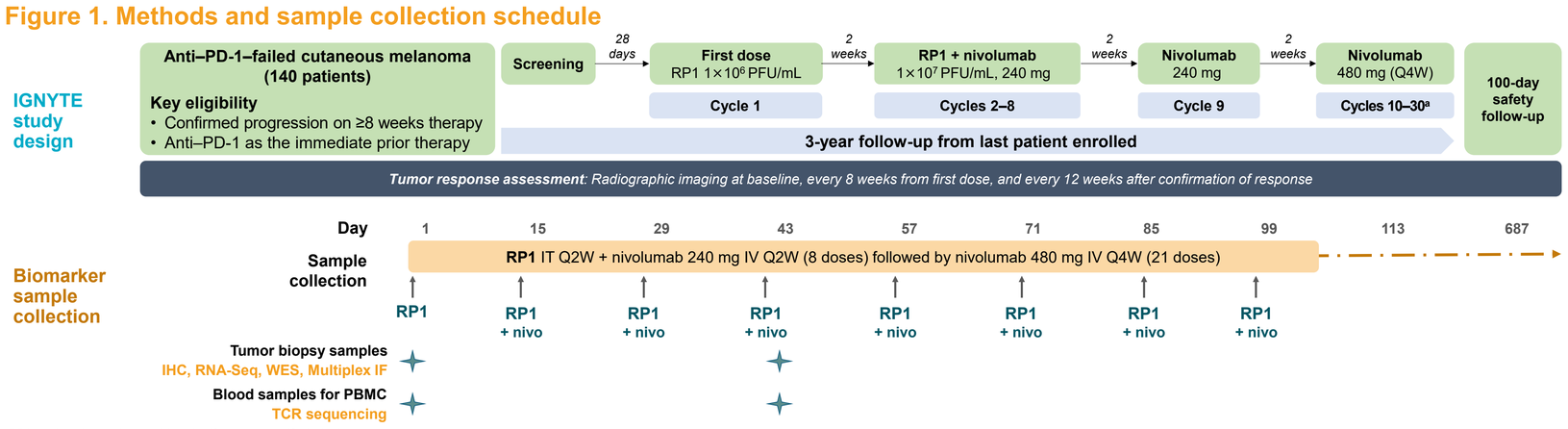
Background

- Resistance to anti–programmed cell death protein 1 (PD-1) ± anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) therapy can be attributed to multiple molecular mechanisms[1]
- T-cell infiltration, programmed death-ligand 1 (PD-L1) expression, and interferon (IFN)-γ signature can be used as biomarkers to assess the inflammatory state of the tumor microenvironment (TME) and potentially predict response to treatment[1,2]
- Treatment options for patients with anti–PD-1–failed melanoma are limited[3,4] and associated with suboptimal efficacy or high toxicity[4-10]
  - Anti–PD-1 retreatment is an option, but the TME state during retreatment may vary based on the timing of treatment and intervening therapy. Patients who experience disease progression during anti–PD-1 therapy are expected to derive minimal benefit from additional treatment[5]
- RP1 (vusolimogene oderparepvec) is a herpes simplex virus type 1 (HSV-1)–based oncolytic immunotherapy that expresses granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R$^-$)[11]
  - In the primary analysis of the IGNYTE trial (data cutoff: March 8, 2024), RP1 combined with nivolumab in patients with advanced melanoma that progressed during prior anti–PD-1 treatment resulted in an objective response rate (ORR) of 32.9% and duration of response (DOR) of 33.7 months[12]
- Here we present pharmacodynamic data from paired tumor biopsies and blood samples supporting a follow-up efficacy analysis with a data cutoff of October 15, 2024

Methods

Figure 1. Methods and sample collection schedule



[a]RP1 can be reinitiated beyond 8 cycles if protocol-specified criteria are met.
IF, immunofluorescence; IHC, immunohistochemistry; IT, intratumoral; IV, intravenous; nivo, nivolumab; PBMC, peripheral blood mononuclear cell; PD-1, programmed cell death protein 1; PFU, plaque-forming units; Q2W, every 2 weeks; Q4W, every 4 weeks; RNA-Seq, RNA sequencing; TCR, T-cell receptor; WES, whole exome sequencing.

Results

Patients

- A total of 140 patients were enrolled (**Table 1**)

Table 1. Baseline clinical characteristics

Patients, n (%)	N = 140
Age, median (range), y	62 (21–91)
Sex	
Female	45 (32.1)
Male	95 (67.9)
Stage	
IIIB/IIIC/IVM1a	72 (51.4)
IVM1b/c/d	68 (48.6)
***BRAF* status**[a]	
Wild-type	89 (63.6)
Mutant	51 (36.4)
Baseline PD-L1 tumor expression	
Positive (≥1%)	45 (32.1)
Negative (<1%)	78 (55.7)
Undetermined or missing	17 (12.1)
Prior therapy	
Anti–PD-1	
Anti–PD-1 only as adjuvant therapy	36 (25.7)
Anti–PD-1 as advanced/metastatic therapy	104 (74.3)
Anti–CTLA-4	
Anti–PD-1 combined with anti–CTLA-4	61 (43.6)
Anti–PD-1 treated with anti–CTLA-4 sequentially	4 (2.9)
Received BRAF/MEK therapy	17 (12.1)
Anti–PD-1 resistance category	
Primary resistance[b]	92 (65.7)
Secondary resistance[c,d]	48 (34.3)

Data cutoff: October 15, 2024 (7 months post the primary analysis).
[a]Two patients originally designated as *BRAF* mutant were recategorized as *BRAF* wild-type at extended follow-up. [b]Primary resistance: progressed within 6 months of starting the immediate prior course of anti–PD-1 therapy. [c]Secondary resistance: progressed after 6 months of treatment on the immediate prior course of anti–PD-1 therapy. [d]Includes 1 patient with unknown resistance status.
CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Efficacy

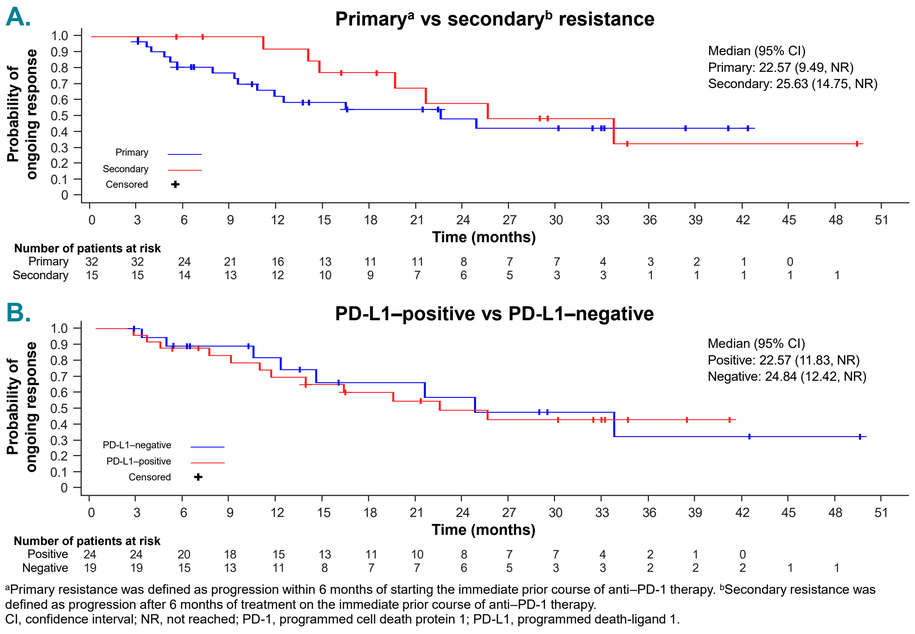
- Updated ORRs (all patients had ≥12 months of follow-up) showed clinically meaningful benefits across biological subgroups (**Table 2**)
- Consistent response rates were seen across clinical patient subgroups, including the following (**Table 2**):
  - **26.2% ORR** in patients who had **prior anti–PD-1 and anti–CTLA-4 therapy**
  - **34.8% ORR** in patients who had **primary resistance to anti–PD-1 therapy**
- Durable responses were seen across challenging-to-treat biological subgroups (**Figure 2**)

Table 2. Updated ORRs per central review using RECIST 1.1

BOR n (%)	All patients (N = 140)	Prior anti–PD-1 without anti–CTLA-4 (n = 75)	Prior anti–PD-1 with anti–CTLA-4 (n = 65)	Stage IVb–IVd (n = 68)	Primary resistance (n = 92)[a]	Secondary resistance (n = 48)[b,c]	PD-L1–positive (n = 45)	PD-L1–negative (n = 78)
CR	23 (16.4)	17 (22.7)	6 (9.2)	4 (5.9)	16 (17.4)	7 (14.6)	12 (26.7)	11 (14.1)
PR	24 (17.1)	13 (17.3)	11 (16.9)	13 (19.1)	16 (17.4)	8 (16.7)	12 (26.7)	8 (10.3)
SD	30 (21.4)	15 (20.0)	15 (23.1)	14 (20.6)	15 (16.3)	15 (31.3)	7 (15.6)	18 (23.1)
PD	54 (38.6)	28 (37.3)	26 (40.0)	29 (42.6)	39 (42.4)	15 (31.3)	11 (24.4)	36 (46.2)
ORR	**47 (33.6)**	**30 (40.0)**	**17 (26.2)**	**17 (25.0)**	**32 (34.8)**	**15 (31.3)**	**24 (53.3)**	**19 (24.4)**
DOR, median (95% CI), months	**24.8 (14.1, NR)**	**NR (19.6, NR)**	**16.5 (7.9, 25.6)**	**14.8 (7.9, 22.6)**	**22.6 (9.5, NR)**	**25.6 (14.8, NR)**	**22.6 (11.8, NR)**	**24.8 (12.4, NR)**

Data cutoff: October 15, 2024 (7 months post the primary analysis).
[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 treatment on the immediate prior course of anti–PD-1 therapy. [c]Includes 1 patient with unknown resistance status.
BOR, best overall response; CI, confidence interval; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen 4; DOR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Figure 2. Duration of response by (A) resistance type and (B) PD-L1 expression

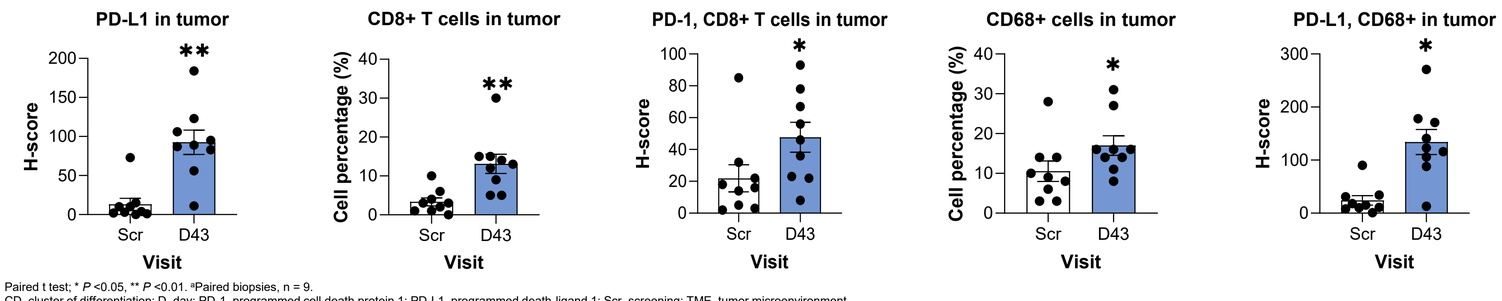


[a]Primary resistance was defined as progression within 6 months of starting the immediate prior course of anti–PD-1 therapy. [b]Secondary resistance was defined as progression after 6 months of treatment on the immediate prior course of anti–PD-1 therapy.
CI, confidence interval; NR, not reached; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Biomarkers

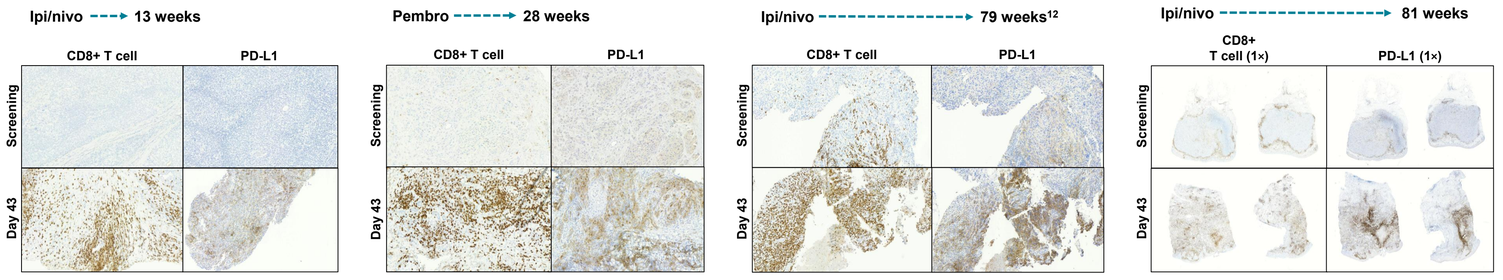
- RP1 plus nivolumab treatment resulted in reprogramming of the TME, with significant increases in intratumoral PD-L1 expression and CD8+ T cells post-treatment (**Figure 3** and **Figure 4**), with increases observed regardless of type and duration of prior treatment (**Figure 4**)
  - PD-L1 expression increased in 56% (25/45) and 57% (39/68) of paired and all lesions, respectively, and CD8+ T cells increased in 37% (17/46) and 47% (37/78) of paired and all lesions, respectively
- RP1 plus nivolumab increased the expression of the IFN-γ signature, evidence of resensitizing tumors to anti–PD-1 treatment (**Figure 5A**)
- Whole exome sequencing of day 0 biopsies demonstrated that clinical responses were observed irrespective of tumor mutational burden (**Figure 5B**)
- RP1 plus nivolumab expanded existing T-cell clones and generated new T-cell clones, indicating a systemic anti-tumor immune response
  - Many of the expanded clones (range, 20%–80%) were newly detected at day 43, demonstrating that treatment not only expanded existing T-cell clones, but also generated new T-cell clones
    - These included HSV-1– and melanoma-associated clones, such as those against BRAF V600 and melanoma-associated antigen at day 43 in the periphery, demonstrating treatment-driven systemic expansion of T-cell clones
    - A particularly striking expansion of T-cell clones (n = 170) was observed in a patient with ongoing complete response (data not shown—presented in original presentation)

Figure 3. RP1 plus nivolumab treatment reprograms the TME[a]



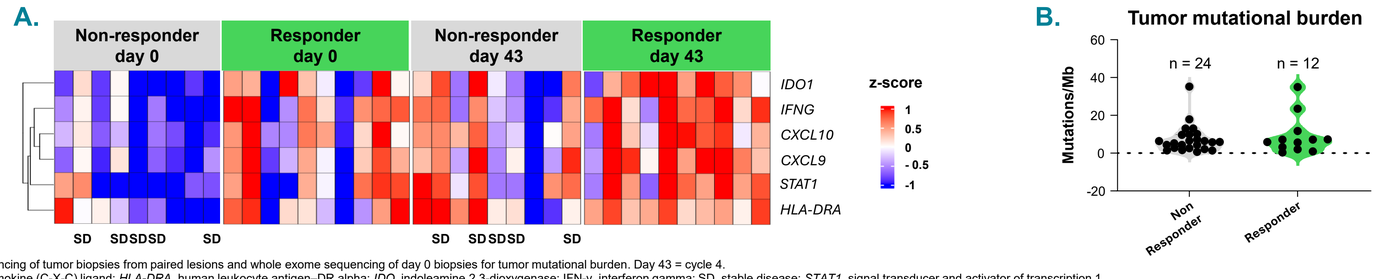
Paired t test; * P <0.05, ** P <0.01. [a]Paired biopsies, n = 9.
CD, cluster of differentiation; D, day; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Scr, screening; TME, tumor microenvironment.

Figure 4. RP1 plus nivolumab treatment increases CD8+ T-cell infiltration and PD-L1 expression



Treatment duration includes maintenance anti–PD-1 therapy.
CD, cluster of differentiation; ipi, ipilimumab; nivo, nivolumab; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pembro, pembrolizumab.

Figure 5. (A) Heatmap of the IFN-γ signature (days 0 and 43) and (B) tumor mutational burden (day 0) in non-responders vs responders



RNA sequencing of tumor biopsies from paired lesions and whole exome sequencing of day 0 biopsies for tumor mutational burden. Day 43 = cycle 4.
CXCL, chemokine (C-X-C) ligand; *HLA-DRA*, human leukocyte antigen–DR alpha; *IDO*, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; SD, stable disease; *STAT1*, signal transducer and activator of transcription 1.

Conclusions

Biomarkers

- **Treatment with RP1 plus nivolumab** led to upregulation of gene signatures associated with **responsiveness to PD-1 blockade**, including:
  - Increases in CD8+ T-cell infiltration, PD-L1 expression, and IFN-γ signature
  - Improved T-cell function and antigen presentation gene signature
  - Expansion of pre-existing and emergence of novel/tumor-specific T-cell clones
- These pharmacodynamic changes, which were not achieved during prior prolonged anti–PD-1 therapy, demonstrate that the addition of **RP1 reverses multiple resistance mechanisms to PD-1 blockade** and highlight the contribution of RP1 in anti–PD-1–failed melanoma
- Biomarker data provide mechanistic insight into the **systemic clinical responses** observed with RP1 plus nivolumab following definitive anti–PD-1 failure, highlighting efficacy independent of PD-L1 status or resistance type

Efficacy and safety

- RP1 combined with nivolumab continues to demonstrate a **clinically meaningful response rate (ORR, 33.6%)** and **durability (median DOR, 24.8 months)** in patients with advanced melanoma, with a consistent DOR across PD-L1–positive and –negative tumors, as well as in both primary and secondary resistance settings
- The safety profile remained consistent with the primary analysis; there were generally transient grade 1/2 side effects

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

Presenter disclosure

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Study sponsor

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Disclaimer

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