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RP1 plus nivolumab in patients with and without prior BRAF-directed therapy: A subgroup analysis of patients with anti–PD-1–failed *BRAF*-mutant melanoma from the IGNYTE clinical trial

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Background

- Approximately 50% of melanomas have *BRAF* mutations, which drive the proliferation and survival of tumor cells via constitutive activation of the MAPK pathway[1-3]
  - The majority of *BRAF* mutations occur at codon 600 (V600)[1,3]
- BRAF inhibitors (BRAFi) ± MEK inhibitors (MEKi) may be used to treat advanced *BRAF*-mutant (mut) melanoma as first-line therapy or after progression on anti–programmed cell death protein 1 (PD-1) therapy[1,4]
  - However, response to BRAFi/MEKi is often not durable, and prior treatment with BRAF-directed therapy can diminish the efficacy of subsequent treatment with anti–PD-1 therapy[1,5-7]
  - The DREAMseq study demonstrated that nivolumab/ipilimumab followed by BRAFi/MEKi should be the preferred treatment sequence for most patients with advanced *BRAF*-mut melanoma[5,6]
  - Similarly, the SECOMBIT study demonstrated the clinical benefit of initial immunotherapy followed by subsequent BRAFi-directed therapy (vs the reverse sequence) in this same patient population[7]
- RP1 (vusolimogene oderparepvec) is a replication-selective herpes simplex virus type 1 (HSV-1)-based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor (GM-CSF) and a fusogenic glycoprotein (GALV-GP-R$^-$) to enhance the direct lysis of tumor cells and increase systemic anti-tumor effects[8]
- RP1 combined with nivolumab demonstrated clinically meaningful and durable anti-tumor activity in the primary analysis of a registration-intended cohort of patients with melanoma that progressed on prior anti–PD-1 therapy from the IGNYTE clinical trial (NCT03767348)[9]
  - With further follow-up (data cutoff: October 15, 2024), the objective response rate (ORR) was 33.6% (16.4% complete response [CR]) by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), with a median duration of response (DOR) of 24.8 months (see late-breaking abstract #1327)

Objective

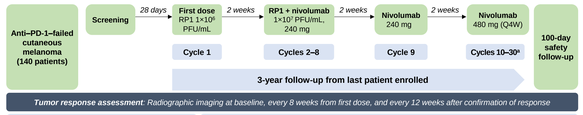
To assess the impact of *BRAF* mutation status and prior BRAFi/MEKi therapy on the efficacy of RP1 plus nivolumab from a post hoc subgroup analysis of the IGNYTE trial

Methods

Study design and treatment

- Eligible patients had advanced 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 had known and documented *BRAF* mutation status
  - Prior treatment with BRAFi ± MEKi therapy (before anti–PD-1 therapy) was allowed for *BRAF*-mut melanoma
- 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**)
- This post hoc analysis evaluated ORR, DOR, and progression-free survival (PFS) by BICR per RECIST 1.1, overall survival (OS), and safety in patients with *BRAF*–wild-type (WT) melanoma or *BRAF*-mut melanoma (data cutoff: October 15, 2024)
  - Patients with *BRAF*-mut melanoma were additionally analyzed by prior BRAFi treatment

Figure 1. Study design



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; 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 conducted when all patients had ≥12 months follow-up

[a]RP1 can be reinitiated 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 the 140 enrolled patients with anti–PD-1–failed melanoma, 89 (63.6%) had *BRAF*-WT and 51 (36.4%) had *BRAF*-mut melanoma, of whom 35 (68.6%) patients were BRAFi-naïve and 16 (31.4%) received BRAFi/MEKi prior to anti–PD-1 therapy (BRAFi-exposed; **Table 1**)

Table 1. Patient demographic and baseline characteristics

Patients, n (%)	*BRAF*-WT (n = 89)	*BRAF*-mut Total (n = 51)	*BRAF*-mut BRAFi-naïve (n = 35)	*BRAF*-mut BRAFi-exposed (n = 16)
Age, years, median (range)	62.0 (31.0–91.0)	60.0 (21.0–88.0)	60.0 (21.0–88.0)	52.0 (23.0–81.0)
Male sex	57 (64.0)	38 (74.5)	29 (82.9)	9 (56.3)
Stage				
IIIB/IIIC/IVM1a	49 (55.1)	23 (45.1)	17 (48.6)	6 (37.5)
IVM1b/c/d	40 (44.9)	28 (54.9)	18 (51.4)	10 (62.5)
LDH level				
LDH ≤ULN	56 (62.9)	36 (70.6)	30 (85.7)	6 (37.5)
LDH >ULN	32 (36.0)	15 (29.4)	5 (14.3)	10 (62.5)
Unknown	1 (1.1)	0	0	0
PD-L1 tumor expression				
Positive (≥1%)	28 (31.5)	17 (33.3)	14 (40.0)	3 (18.8)
Negative (<1%)	50 (56.2)	28 (54.9)	19 (54.3)	9 (56.3)
Unknown	11 (12.4)	6 (11.8)	2 (5.7)	4 (25.0)
Prior therapy				
Anti–PD-1				
Anti–PD-1 only as adjuvant therapy	22 (24.7)	14 (27.5)	13 (37.1)	1 (6.3)
Anti–PD-1 as advanced/metastatic therapy	67 (75.3)	37 (72.5)	22 (62.9)	15 (93.8)
Anti–CTLA-4				
Anti–PD-1 combined with anti–CTLA-4	37 (41.6)	24 (47.1)	14 (40.0)	10 (62.5)
Anti–PD-1 treated with anti–CTLA-4 sequentially	4 (4.5)	0	0	0
Anti–PD-1 resistance				
Primary resistance[a]	58 (65.2)	34 (66.7)	25 (71.4)	9 (56.3)
Secondary resistance[b]	31 (34.8)	17 (33.3)	10 (28.6)	7 (43.8)

[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.
BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; mut, mutant; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ULN, upper limit of normal; WT, wild-type.

Efficacy

- The confirmed ORR was 34.8% (31/89) and 31.4% (16/51) in patients with *BRAF*-WT and *BRAF*-mut melanoma, respectively
  - Among patients with *BRAF*-mut melanoma, the confirmed ORR was 40.0% (14/35; CR, 20.0% [7/35]; PR, 20.0% [7/35]) in the BRAFi-naïve group vs 12.5% (2/16; CR, 6.3% [1/16]; PR, 6.3% [1/16]) in the BRAFi-exposed group (**Table 2**)

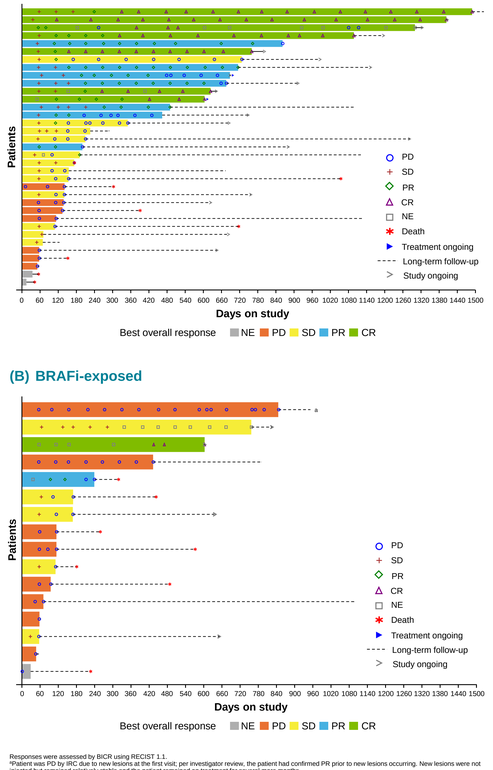
Table 2. Response by BICR using RECIST 1.1

	BRAF-WT (n = 89)	*BRAF*-mut Total (n = 51)	*BRAF*-mut BRAFi-naïve (n = 35)	*BRAF*-mut BRAFi-exposed (n = 16)
Confirmed BOR, n (%)				
CR	15 (16.9)	8 (15.7)	7 (20.0)	1 (6.3)
PR	16 (18.0)	8 (15.7)	7 (20.0)	1 (6.3)
SD	13 (14.6)	17 (33.3)	12 (34.3)	5 (31.3)
PD	39 (43.8)	15 (29.4)	7 (20.0)	8 (50.0)
NE	6 (6.7)	3 (5.9)	2 (5.7)	1 (6.3)
ORR (CR + PR), n (%)	31 (34.8)	16 (31.4)	14 (40.0)	2 (12.5)
95% CI	25.0, 45.7	19.1, 45.9	23.9, 57.9	1.6, 38.3

BICR, blinded independent central review; BOR, best overall response; BRAFi, BRAF inhibitor; CI, confidence interval; CR, complete response; mut, mutant; 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; WT, wild-type.

- The median DOR was 21.6 months among patients with *BRAF*-WT melanoma and 33.7 months among patients with *BRAF*-mut melanoma. Response profiles for individual patients with *BRAF*-mut melanoma by BRAFi status are shown in **Figure 2**

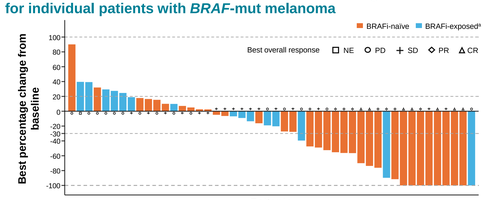
Figure 2. Clinical response profiles for individual patients with *BRAF*-mut melanoma by BRAFi status



Responses were assessed by BICR using RECIST 1.1.
[a]Patient was PD by IRC due to new lesions at the first visit; per investigator review, the patient had confirmed PR prior to new lesions occurring. New lesions were not injected but remained relatively stable and the patient remained on treatment for several more months.
BICR, blinded independent central review; BRAFi, BRAF inhibitor; CR, complete response; IRC, independent review committee; mut, mutant; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

- Change from baseline in target tumor lesions for individual patients with *BRAF*-mut melanoma is shown in **Figure 3**

Figure 3. Best percentage change from baseline in target tumor lesion for individual patients with *BRAF*-mut melanoma



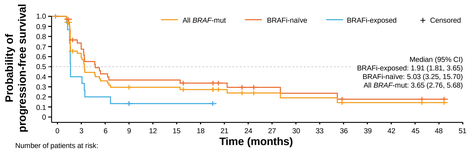
Responses were assessed by BICR using RECIST 1.1.
[a]One BRAFi-exposed patient who achieved a CR had no identified target lesions by IRC; however, CR was confirmed by biopsy.
BICR, blinded independent central review; BRAFi, BRAF inhibitor; CR, complete response; IRC, independent review committee; mut, mutant; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Survival outcomes for BRAF-mut melanoma

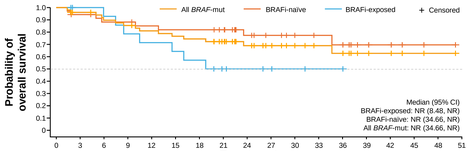
- Median PFS was 5.0 months in the BRAFi-naïve group vs 1.9 months in the BRAFi-exposed group (**Figure 4A**). The 12-month PFS rate was 36.7% vs 13.3%, respectively
- Median OS was not reached in either group (**Figure 4B**). The 1- and 2-year OS rates in the BRAFi-naïve vs BRAFi-exposed groups were 85.1% vs 71.4% and 77.4% vs 50.0%, respectively

Figure 4. Survival outcomes in patients with *BRAF*-mut melanoma

(A) Progression-free survival by BICR using RECIST 1.1



(B) Overall survival



BICR, blinded independent central review; BRAFi, BRAF inhibitor; CI, confidence interval; mut, mutant; NR, not reached; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Subsequent BRAFi treatment post-IGNYTE

- Following the IGNYTE trial, 15 BRAFi-naïve patients with *BRAF*-mut melanoma were subsequently treated with BRAFi ± MEKi for a median of 13.9 months; among these patients, the ORR on subsequent therapy was 66.7% (10/15)

Safety

- Overall, 86.5% (77/89) and 94.1% (48/51) of patients with *BRAF*-WT and *BRAF*-mut melanoma, respectively, experienced at least 1 treatment-related adverse event (TRAE) of any grade (**Table 3**)
  - The most common any-grade TRAEs included fatigue, chills, and pyrexia
  - Grade ≥3 TRAEs occurred in 14.6% (13/89) and 9.8% (5/51) of patients with *BRAF*-WT and *BRAF*-mut melanoma, respectively
  - TRAEs were similar across the BRAFi-naïve and BRAF-exposed groups (**data not shown**)

Table 3. Treatment-related adverse events

Event, n (%)	*BRAF*-WT (Total n = 89) Any grade	*BRAF*-WT (Total n = 89) Grade ≥3	*BRAF*-mut (Total n = 51) Any grade	*BRAF*-mut (Total n = 51) Grade ≥3
Any TRAE	77 (86.5)	13 (14.6)	48 (94.1)	5 (9.8)
TRAEs occurring in ≥10% of patients overall				
Fatigue	27 (30.3)	0	19 (37.3)	1 (2.0)
Chills	30 (33.7)	0	15 (29.4)	0
Pyrexia	29 (32.6)	0	14 (27.5)	0
Nausea	22 (24.7)	0	9 (17.6)	0
Influenza-like illness	13 (14.6)	0	12 (23.5)	0
Injection-site pain	13 (14.6)	0	8 (15.7)	0
Vomiting	14 (15.7)	0	5 (9.8)	0
Pruritus	11 (12.4)	0	8 (15.7)	0
Diarrhea	10 (11.2)	1 (1.1)	10 (19.6)	0
Headache	11 (12.4)	0	7 (13.7)	0
Asthenia	10 (11.2)	1 (1.1)	4 (7.8)	0

TRAEs could be related to RP1 or nivolumab.
mut, mutant; TRAE, treatment-related adverse event; WT, wild-type.

Conclusions

- **RP1 plus nivolumab** appeared to be **more effective in BRAFi-naïve patients compared with BRAFi-exposed patients**, consistent with the SECOMBIT and DREAMseq trials in patients with advanced *BRAF*-mut melanoma
- Overall, RP1 plus nivolumab demonstrated **comparable efficacy** in patients with ***BRAF*-WT and *BRAF*-mut advanced melanoma**
- Safety events were **comparable**, regardless of ***BRAF* mutation status**
- Altogether, these data support **treating with oncolytic immunotherapy** and reserving BRAF/MEK-targeted therapy as a subsequent option **to optimize treatment outcomes** in patients with *BRAF* mutations and disease progression on prior anti–PD-1–containing regimens

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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