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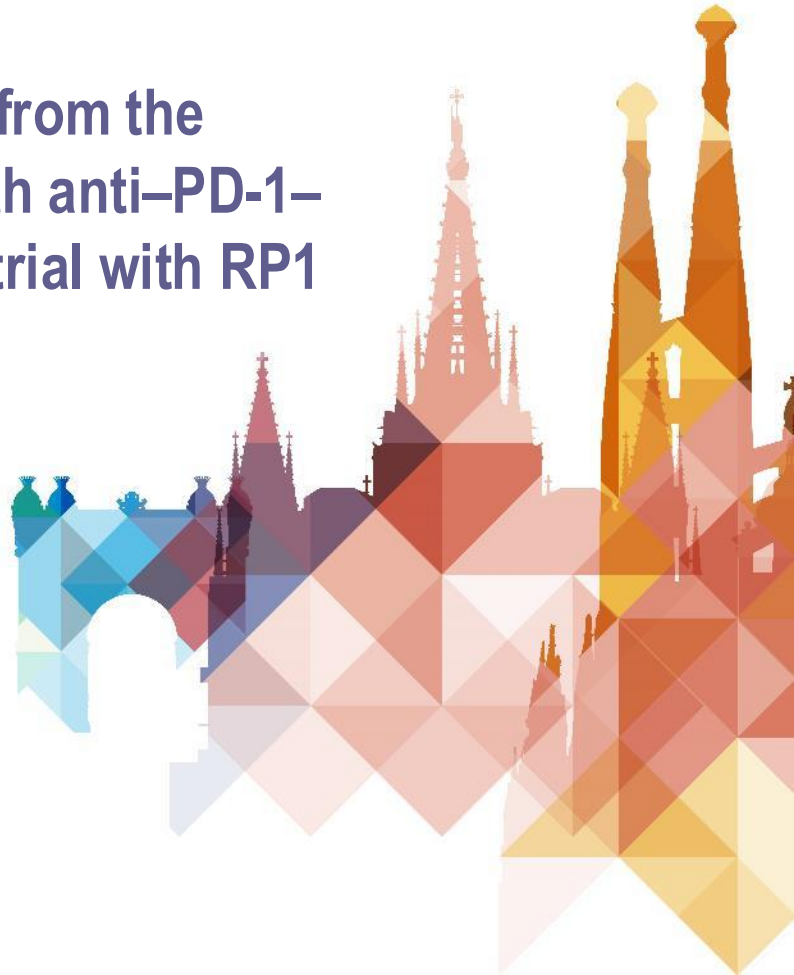
# Primary efficacy, safety, and survival data from the registration-intended cohort of patients with anti–PD-1–failed melanoma from the IGNYTE clinical trial with RP1 combined with nivolumab



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# Declaration of interest

**Caroline Robert**, MD, PhD

**Consulting fees**: BMS, Roche, Pierre Fabre, Novartis, Sanofi, Pfizer, MSD, Merck, Sun Pharma, Ultimovacs, Regeneron, Egle, Philogen, MaaT Pharma, IO Biotech and Replimune, Inc.

**Honoraria**: Pierre Fabre, Sanofi, BMS, MSD and Novartis

**Support for attending meetings and/or travel**: Pierre Fabre

**Data Safety Monitoring Board/Advisory Board**: BMS, Roche, Pierre Fabre, Novartis, Sanofi, Pfizer, MSD, Merck, Sun Pharma, Ultimovacs, Regeneron, Egle, Philogen, MaaT Pharma and Replimune, Inc.

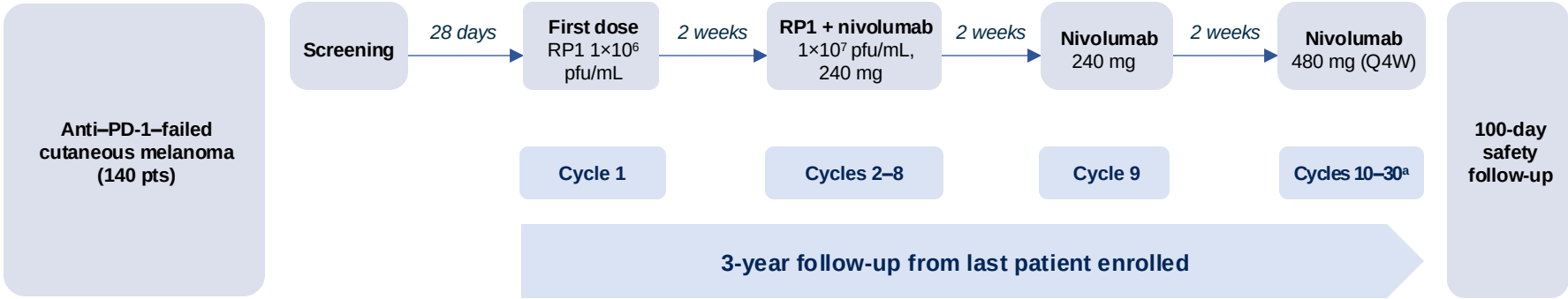
# Background

- There are limited treatment options for patients with anti–PD-1 progressed melanoma[1,2]
- Responses to targeted anti–BRAF+MEK for *BRAF*-mutant melanoma are usually not durable[3]
- Single-agent anti–PD-1 after confirmed progressive disease on anti–PD-1 yields a 6%–7% response rate[4,5]
- Nivolumab + ipilimumab is a potential option,[2] but toxicity is high[2,6]
- Nivolumab + anti–LAG-3 does not add meaningful efficacy[7]
- TIL therapy gives response rates of ~30%,[8] but nearly all patients have Grade 4 toxicity[9,10]

LAG-3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; TIL, tumor-infiltrating lymphocyte

1. Mooradian MJ, et al. *Oncology*. 2019;33(4):141-8. 2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Cutaneous. Version 2.2024. 3. Dixon-Douglas JR, et al. *Curr Oncol Rep*. 2022;24(8):1071-9. 4. Beaver JA, et al. *Lancet Oncol*. 2018;19(2):229-39. 5. Ribas A, et al. *Lancet Oncol*. 2018;19(5):e219. 6. Pires da Silva I, et al. *Lancet Oncol*. 2021;22(6):836-47. 7. Ascierto PA, et al. *J Clin Oncol*. 2023;41(15)2724-35. 8. Chesney J, et al. *Journal for ImmunoTherapy of Cancer*. 2022;10(12):e005755. 9. US Food and Drug Administration. BLA clinical review and evaluation - AMTAGVI. BLA 125773. Updated February 6, 2024. Accessed May 31, 2024.https://www.fda.gov/media/176951/download. 10. Sarnaik AA, et al. *J Clin Oncol* 2021; 39(24): 2656-66.

# Study design




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

**Primary objective**

- Safety and efficacy using mRECIST* v1.1 by independent central review (sensitivity analysis by RECIST v1.1)

**Secondary objectives**

- ORR by investigator assessment (mRECIST* v1.1)
- DOR, CR rate, DOCB, DCR, and PFS by central and investigator assessment, 1-year and 2-year OS

** For mRECIST, PD must be confirmed by further progression at least 4 weeks after initial PD; intended to better allow for pseudoprogression than RECIST v1.1*

**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.

CR, complete response; DCR, disease control rate; DOCB, duration of clinical benefit; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; 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; pt, patient; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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# Baseline clinical characteristics

- A ‘real world’ anti–PD-1–failed melanoma population was enrolled

| 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 | |
| Wild-type | 87 (62.1) |
| Mutant | 53 (37.9) |
| LDH level | |
| LDH ≤ULN | 92 (65.7) |
| LDH >ULN | 47 (33.6) |
| Unknown | 1 (0.7) |
| Baseline PD-L1 tumor expression | |
| Positive (≥1%) | 44 (31.4) |
| Negative (<1%) | 79 (56.4) |
| Undetermined or missing | 17 (12.1) |

| Patients, n (%) | N = 140 |
|---|---|
| Prior therapy | |
| Anti–PD-1 | |
| Anti–PD-1 only as adjuvant therapy | 36 (25.7) |
| Anti–PD-1 other than as adjuvant 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[a] | 92 (65.7) |
| Secondary resistance[b,c] | 48 (34.3) |

Due to the requirement that patients must have confirmed PD on an immediate prior anti–PD-1–based therapy, most patients had 1 or 2 prior lines of therapy

The median (range) follow-up at the time of the primary analysis was 15.4 months (0.5–47.6 months)

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[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 one patient with unknown resistance status. CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

# Primary efficacy analysis

*By blinded, independent central review*

| | Primary endpoint mRECIST v1.1 (N = 140) | Sensitivity analysis RECIST v1.1 (N = 140) |
|---|---|---|
| Confirmed best response, n (%) | | |
| CR | 21 (15.0) | 21 (15.0) |
| PR | 26 (18.6) | 25 (17.9) |
| SD | 41 (29.3) | 31 (22.1) |
| PD | 43 (30.7) | 54 (38.6) |
| **ORR (confirmed CR+PR), n (%)** | **47 (33.6)** | **46 (32.9)** |
| 95% CI | (25.8, 42.0) | (25.2, 41.3) |

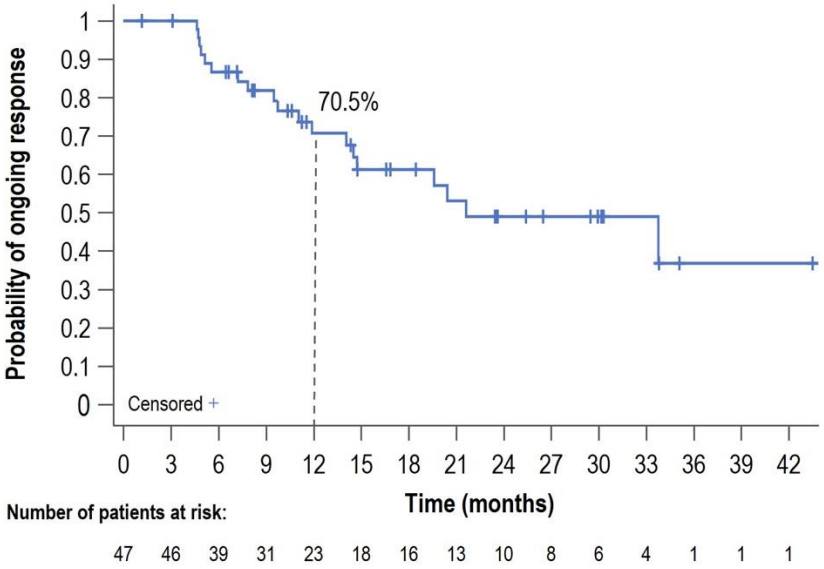
- 1 in 3 patients (33.6%) experienced a confirmed objective response,15.0% CR



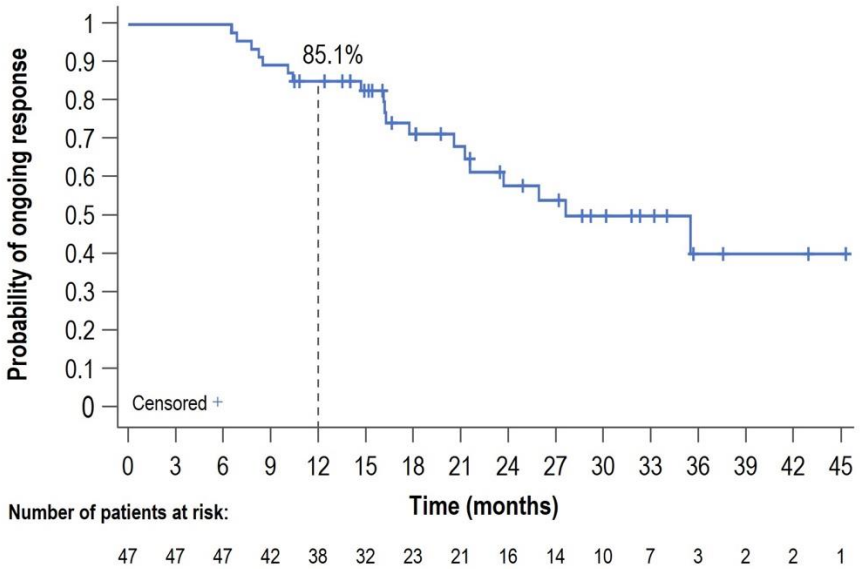
CR, complete response; mRECIST, modified RECIST; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

# Duration of response (mRECIST v1.1)

Duration from response initiation




Duration from treatment initiation




- Median (range) duration from response initiation was 21.6 months (1.2+ to 43.5+ months)
- Median (range) duration from treatment initiation was 27.6 months (6.6+ to 45.3+ months)
- ***85% of responses were ongoing ≥1 year from starting treatment***



mRECIST, modified Response Evaluation Criteria in Solid Tumors.

# Efficacy

- Centrally reviewed mRECIST v1.1 responses (per protocol); all patients have ≥12 months follow up

| BOR n (%) | All patients (N = 140) | Single-agent anti–PD-1 (n = 75) | Anti–PD-1/ CTLA-4 (n = 65) | Stage IIIb–IVa (n = 72) | Stage IVb–IVd (n = 68) | Primary resistance (n = 92) | Secondary resistance (n = 48[a]) | Anti–PD-1 adjuvant (n = 36) | Anti–PD-1 not adjuvant (n = 104) |
|---|---|---|---|---|---|---|---|---|---|
| CR | 21 (15.0) | 16 (21.3) | 5 (7.7) | 17 (23.6) | 4 (5.9) | 16 (17.4) | 5 (10.4) | 11 (30.6) | 10 (9.6) |
| PR | 26 (18.6) | 13 (17.3) | 13 (20.0) | 12 (16.7) | 14 (20.6) | 17 (18.5) | 9 (18.8) | 5 (13.9) | 21 (20.2) |
| SD | 41 (29.3) | 20 (26.7) | 21 (32.3) | 24 (33.3) | 17 (25.0) | 22 (23.9) | 19 (39.6) | 10 (27.8) | 31 (29.8) |
| PD | 43 (30.7) | 24 (32.0) | 19 (29.2) | 18 (25.0) | 25 (36.8) | 31 (33.7) | 12 (25.0) | 9 (25.0) | 34 (32.7) |
| **ORR** | **47 (33.6)** | **29 (38.7)** | **18 (27.7)** | **29 (40.3)** | **18 (26.5)** | **33 (35.9)** | **14 (29.2)** | **16 (44.4)** | **31 (29.8)** |

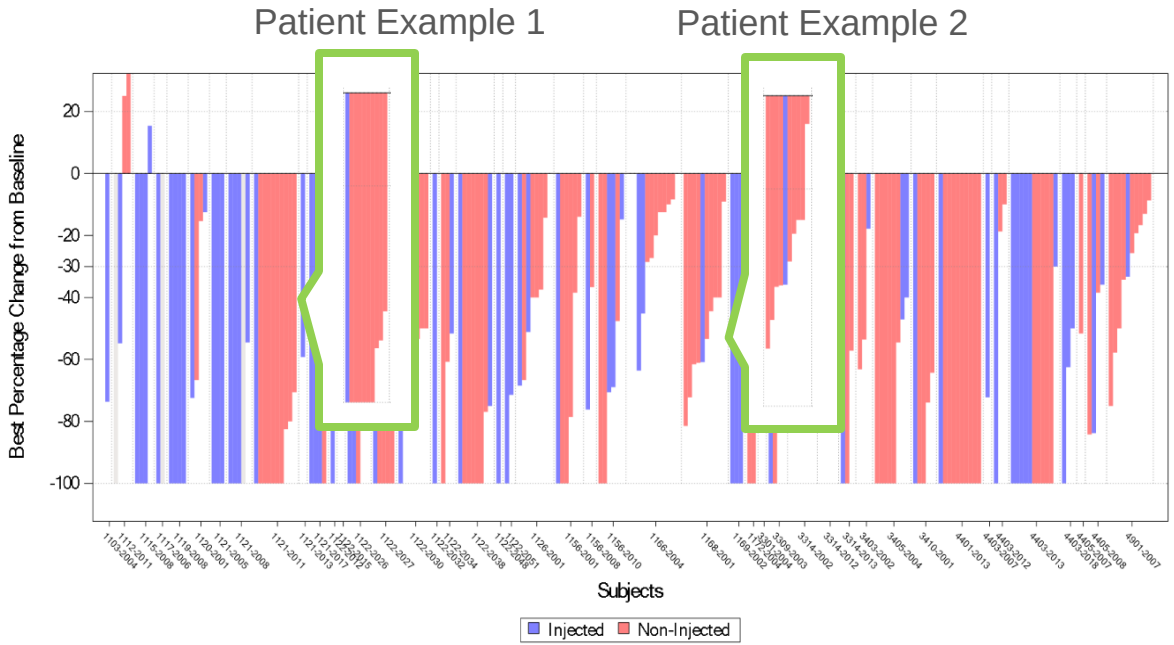
- Consistent response rates were seen across patient subgroups, including:
  - **27.7% ORR** in patients who had **prior anti–PD-1 and anti–CTLA-4**
  - **35.9% ORR** in patients who had **primary resistance to anti–PD-1**

[a]Includes one patient with unknown resistance status.

BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen 4; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD-1, programmed cell death protein 1; PD, progressive disease; PR, partial response; ORR, objective response rate; SD, stable disease.

# Responses in injected and non-injected lesions

## Responses observed including visceral non-injected lesions



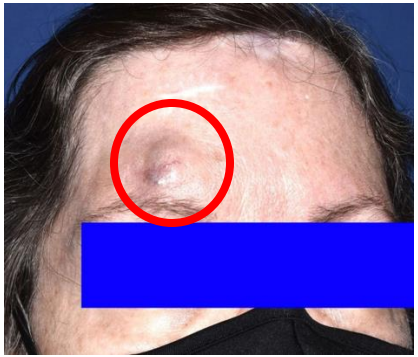

- Tumor reduction seen in 53 out of 60 non-injected visceral organ lesions
- Injected and non-injected lesions responded with similar frequency, depth and duration
- Responses not driven by injected lesions alone

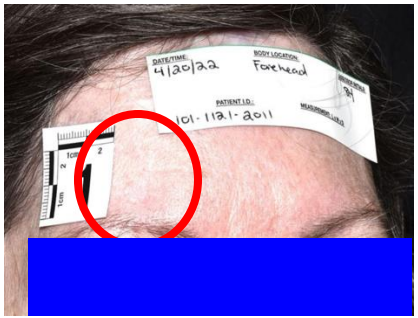
All measurable lesions (10 max if >10 were present) measured by central review for each patient with a best response of confirmed CR or PR. Central reviewers were blinded to lesion injection status.

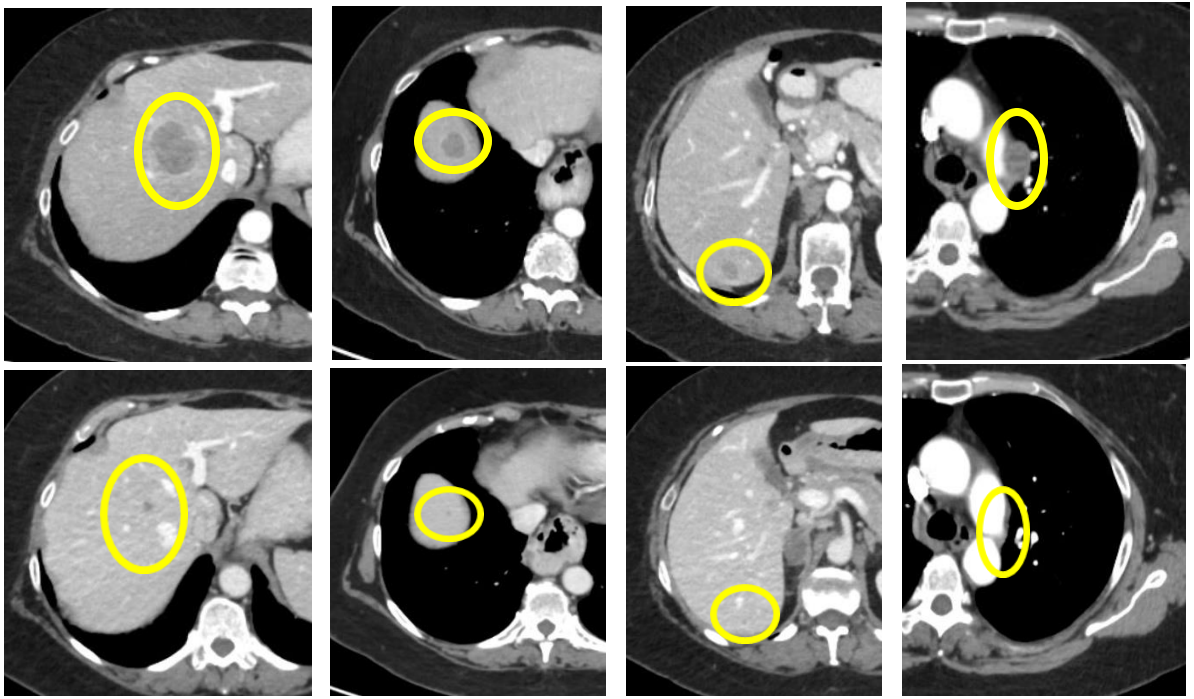
# Patient example: Prior adjuvant nivolumab followed by 1L pembrolizumab

Baseline

9 months



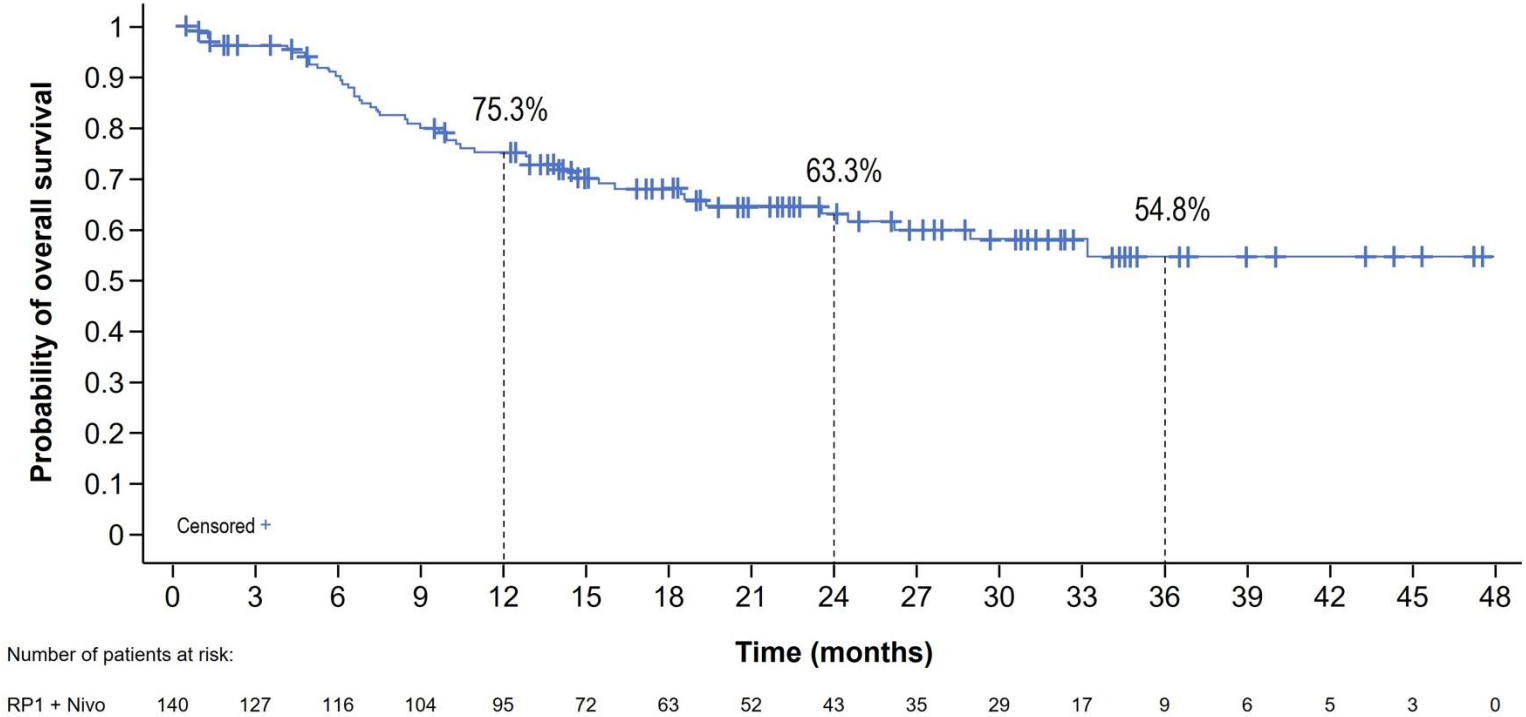


Injected Non-injected

1L, first line.

# Overall survival




- One-, two-, and three-year survival rates were 75.3%, 63.3%, and 54.8%, respectively
- Median overall survival has not been reached

# Safety: Treatment-related AEs (N = 141)

## Related to either RP1 or nivolumab

| Preferred term, n (%) | TRAEs occurring in ≥5% of patients (N = 141) | |
|---|---|---|
| | All Grades | Grade 3-4 |
| **≥1 TRAE** | **126 (89.4)** | **18 (12.8)** |
| Fatigue | 46 (32.6) | 1 (0.7) |
| Chills | 45 (31.9) | 0 (0.0) |
| Pyrexia | 43 (30.5) | 0 (0.0) |
| Nausea | 31 (22.0) | 0 (0.0) |
| Influenza-like illness | 25 (17.7) | 0 (0.0) |
| Injection-site pain | 21 (14.9) | 0 (0.0) |
| Diarrhoea | 20 (14.2) | 1 (0.7) |
| Vomiting | 19 (13.5) | 0 (0.0) |
| Headache | 18 (12.8) | 0 (0.0) |
| Pruritus | 18 (12.8) | 0 (0.0) |
| Asthenia | 14 (9.9) | 1 (0.7) |
| Arthralgia | 10 (7.1) | 1 (0.7) |
| Decreased appetite | 9 (6.4) | 1 (0.7) |
| Myalgia | 9 (6.4) | 0 (0.0) |
| Cough | 8 (5.7) | 0 (0.0) |
| Rash | 8 (5.7) | 0 (0.0) |
| Injection-site reaction | 7 (5.0) | 0 (0.0) |
| Vitiligo | 7 (5.0) | 0 (0.0) |

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AE, adverse event; MALT, mucosa-associated lymphoid tissue; TRAE, treatment-related adverse event.

RP1 combined with nivolumab is generally well tolerated

- Predominantly grade 1 and 2 constitutional-type side effects
- Low incidence of grade 3 events (none occurring in >5% of patients); five grade 4 events in total
- No grade 5 events

**Additional grade 3/4 TRAEs (grade 4 TRAEs are italicized):**

- **Two events each (1.4%):** Hypophysitis and rash maculo-papular
- **One event each (0.7%):** Abdominal pain, acute left ventricular failure, amylase increased, cancer pain, *cytokine release syndrome*, eczema, enterocolitis, extranodal marginal zone B-cell lymphoma (MALT type), *hepatic cytolysis*, hyponatraemia, immune-mediated enterocolitis, infusion-related reaction, left ventricular dysfunction, *lipase increased*, memory impairment, meningitis aseptic, muscular weakness, *myocarditis*, palmar-plantar erythrodysaesthesia syndrome, paraesthesia, peripheral sensory neuropathy, radiculitis brachial, sinus arrhythmia, *splenic rupture*, tricuspid valve incompetence, tumor pain, type 1 diabetes mellitus

# Conclusions

- **Efficacy**
  - RP1 combined with nivolumab following confirmed progression on prior anti–PD-1 therapy alone or combined with anti–CTLA-4 demonstrated a clinically meaningful rate and duration of response
    - ORR 33.6%; median DOR of 21.6 months
  - Responses were seen in patients with advanced disease, including in non-injected visceral lesions
  - Clinically meaningful activity was seen across all subgroups, including patients who had prior combined anti–PD-1/anti–CTLA-4 and with primary anti–PD-1 resistance
- **Safety**
  - The safety profile was favorable, with generally transient grade 1–2 side effects
- **Survival**
  - While the median OS has not been reached, 1- (75.3%), 2- (63.3%) and 3-year (54.8%) survival rates are promising, and further demonstrate long-term clinical benefit
- The IGNYTE-3 confirmatory phase 3 trial evaluating RP1 + nivolumab vs physician's choice in patients with advanced melanoma that has progressed on anti–PD-1 and anti–CTLA-4 is currently recruiting (NCT06264180)



CTLA-4, cytotoxic T-lymphocyte antigen 4; DOR, duration of response; PD-1, programmed cell death protein 1; ORR, objective response rate; OS, overall survival.

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- We would like to thank the patients for their participation in the trial, as well as their family members
- We would also like to thank the site staff and principal investigators for their critical contributions to this study

| | |
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| Dr. Patricia Roxburgh | The Beatson West of Scotland Cancer Center |
| Dr. Dirk Schadendorf | University Hospital Essen |


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).