2024 ASCO® ANNUAL MEETING

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

Michael K. Wong, Joseph J. Sacco, Caroline Robert, Judith Michels, Tawnya L. Bowles, Gino K. In, Katy K. Tsai, Céleste Lebbé, Caroline Gaudy-Marqueste, Eva Muñoz-Couselo, Mark R. Middleton, Adel Samson, Dirk Schadendorf, Georgia M. Beasley, Jiaxin Niu, Bartosz Chmielowski, Trisha M. Wise-Draper, Junhong Zhu, Marcus Viana, Mohammed M. Milhem

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

The University of Texas MD Anderson Cancer Center, Houston, TX, USA



Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# 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


Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# 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]

CTLA-4, cytotoxic T-lymphocyte antigen 4; LAG3, 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. Beaver JA, et al. Lancet Oncol. 2018;19(2):229-39. 3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Cutaneous. Version 2.2024. 4. Pires da Silva I, et al. Lancet Oncol. 2021;22(6):836-47. 5. VanderWalde AM, et al. Presented at the American Association of Cancer Research Annual Meeting 2022. New Orleans. 6. Ascierto PA, et al. J Clin Oncol. 2023;41(15)2724-35. 7. Dixon-Douglas JR, et al. Curr Oncol Rep. 2022;24(8):1071-9. 8. Gastman B, et al. J Clin Oncol. 2022;40(16_suppl):9518. 9. Hu-Lieskovan S, et al. Cancer Res. 2023;83(7_suppl):3275. 10. 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.



Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# IGNYTE Study design (Anti-PD-1 failed melanoma cohort)

**Anti–PD-1–failed cutaneous melanoma cohort (140 pts; 16 pts treated in prior cohorts: Total 156)**

**Screening** — *28 days* → **First dose** RP1 $1\times10^6$ pfu/mL — *2 weeks* → **RP1+nivolumab[a]** $1\times10^7$ pfu/mL, 240 mg — *2 weeks* → **Nivolumab** 240 mg — *2 weeks* → **Nivolumab** 480 mg (Q4W)

**Cycle 1** | **Cycles 2–8** | **Cycle 9** | **Cycles 10–30[b]**

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

**100-day safety follow-up**

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

**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***[c]; 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)

***Primary analysis to be conducted when all patients have ≥ 12 months follow up***

[a]Dosing with nivolumab begins at dose 2 of RP1 (C2D15). [b]Option to reinitiate RP1 for 8 cycles if criteria are met.
c. 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 cell death protein 1; PFS, progression-free survival; pfu, plaque-forming unit; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.


PRESENTED BY: **Dr. Michael K. Wong,** MD, PhD, FRCPC
Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

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

| Patients, n (%) | All patients (N = 156) |
|---|---|
| **Other disease characteristics** | |
| Primary resistance to prior anti–PD-1[a] | 105 (67.3) |
| Secondary resistance to prior anti–PD-1[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)**

Data cutoff: March 8th 2024. [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 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.


Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# 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

| | All patients enrolled in IGNYTE | | | | | | |
|---|---|---|---|---|---|---|---|
| BOR n (%) | All patients (n = 156) | Prior single-agent anti–PD-1 (n = 82) | Prior anti–PD-1/CTLA-4 Exposure (n = 74)[a] | Stage IIIb-IVM1a (n = 75) | Stage IVM1b-d (n = 81) | 1º resistance to anti–PD-1 (n = 105) | 2º resistance to anti–PD-1 (n = 51)[b] |
| CR | 23 (14.7) | 18 (22.0) | 5 (6.8) | 18 (24.0) | 5 (6.2) | 18 (17.1) | 5 (9.8) |
| PR | 28 (17.9) | 13 (15.9) | 15 (20.3) | 13 (17.3) | 15 (18.5) | 18 (17.1) | 10 (19.6) |
| SD | 34 (21.8) | 18 (22.0) | 16 (21.6) | 19 (25.3) | 15 (18.5) | 17 (16.2) | 17 (33.3) |
| PD | 63 (40.4) | 31 (37.8) | 32 (43.2) | 24 (32.0) | 39 (48.1) | 47 (44.8) | 16 (31.4) |
| **ORR** | **51 (32.7[c])** | **31 (37.8)** | **20 (27.0)** | **31 (41.3)** | **20 (24.7)** | **36 (34.3)** | **15 (29.4)** |

[a]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%). [b]Includes one patient with unknown resistance status.
[c]ORR for the 140 registration intended cohort was 32.1%

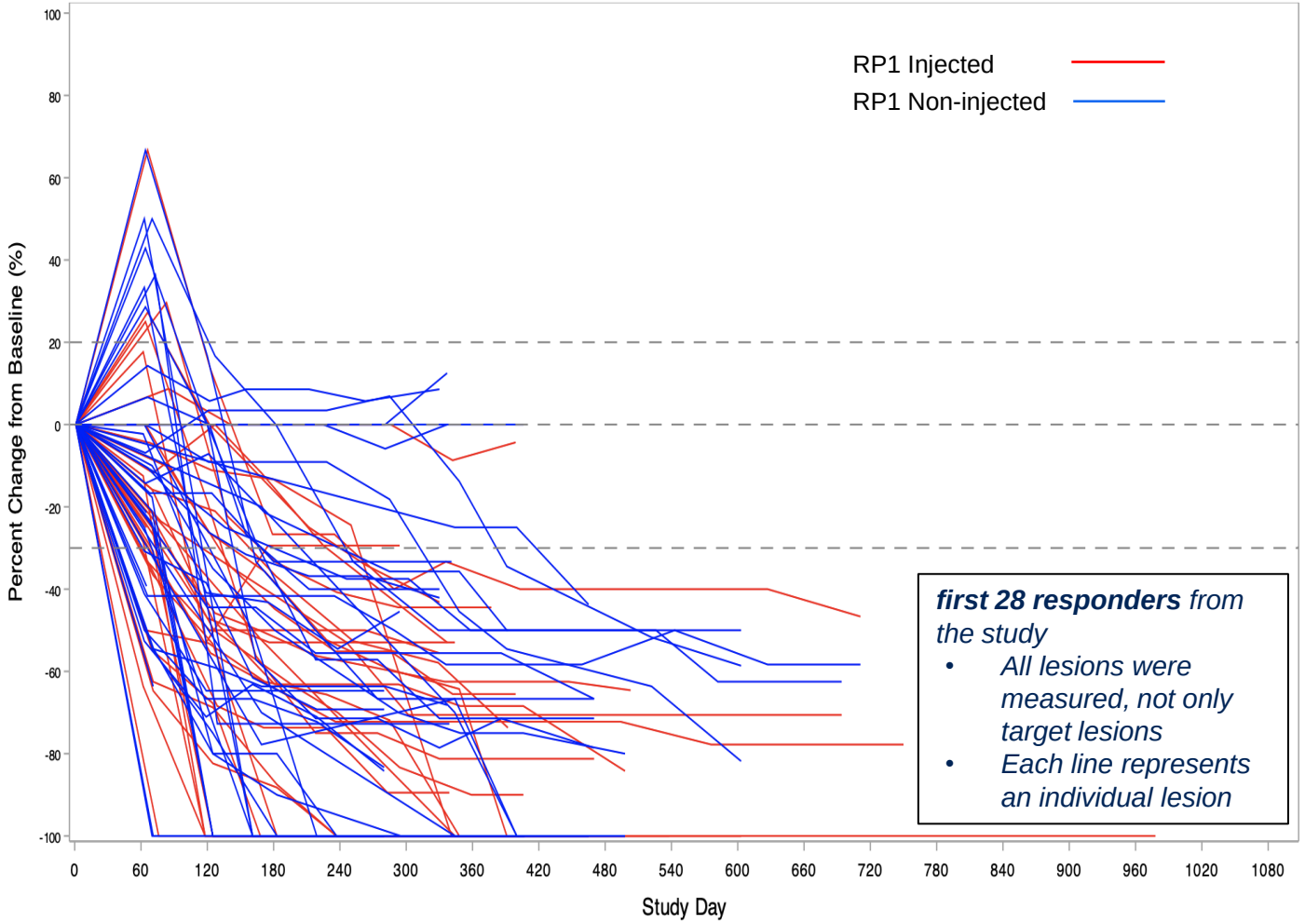
- Approximately 1 in 3 patients achieved an objective response (32.7%)
- Consistent ORR across subgroups, including:
  - 27% ORR in patients who had prior anti–PD-1 & anti–CTLA-4
  - 34% ORR in patients who are primary resistant to their prior anti-PD-1 therapy

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.


Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# Responses are Systemic

## Change in Size of Individual Injected and Non-injected Lesions



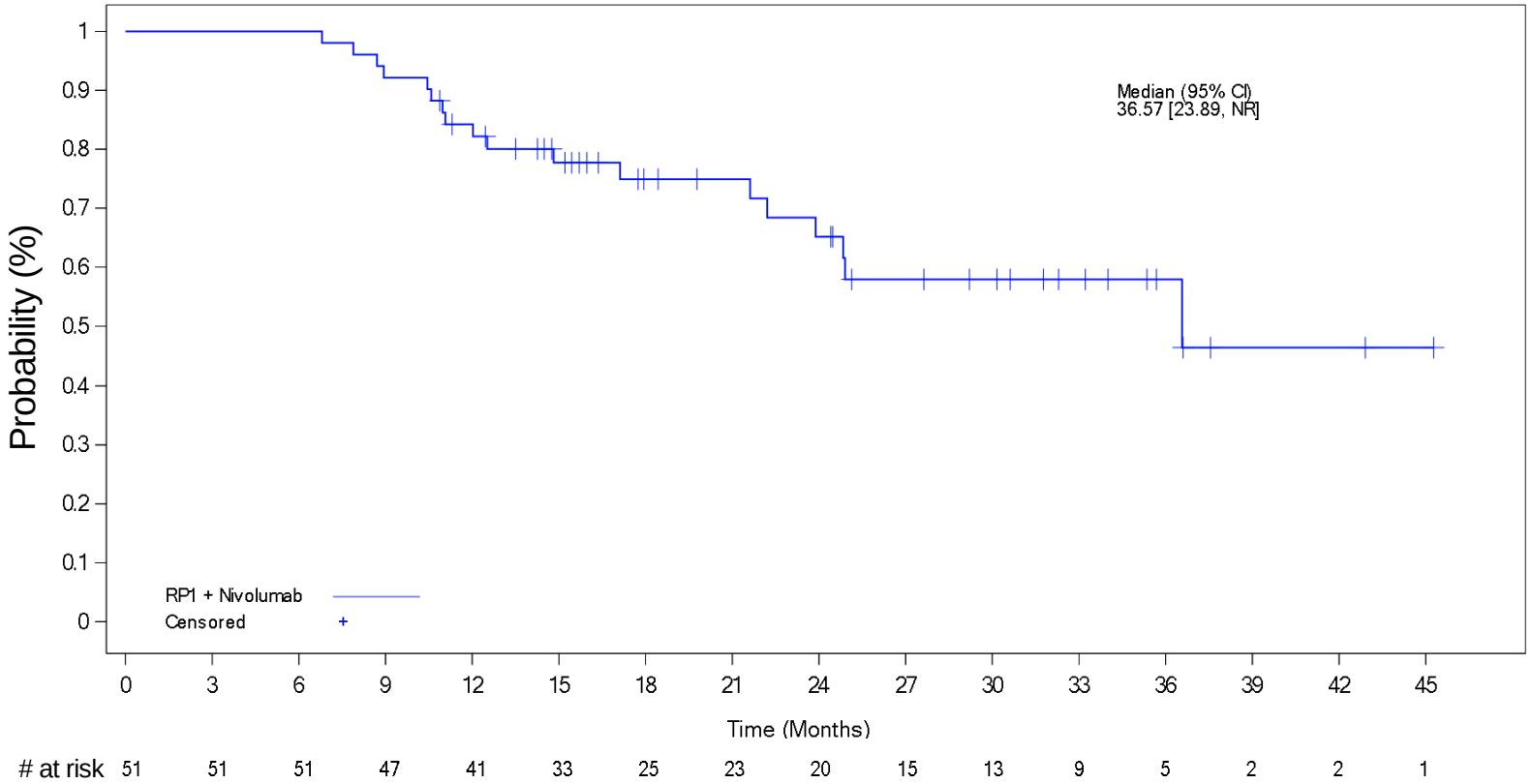

- 70.4% of responding patients had non-injected lesions
  - Responders include patients with minority of lesions injected
- Injected and non-injected lesions responded with similar duration and kinetics
- Depth of response independent of whether injected

**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 at ≥ 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.


Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# Duration of Response




- Responses are durable, with a **median DOR** by Kaplan-Meier estimate of **36.6 months**

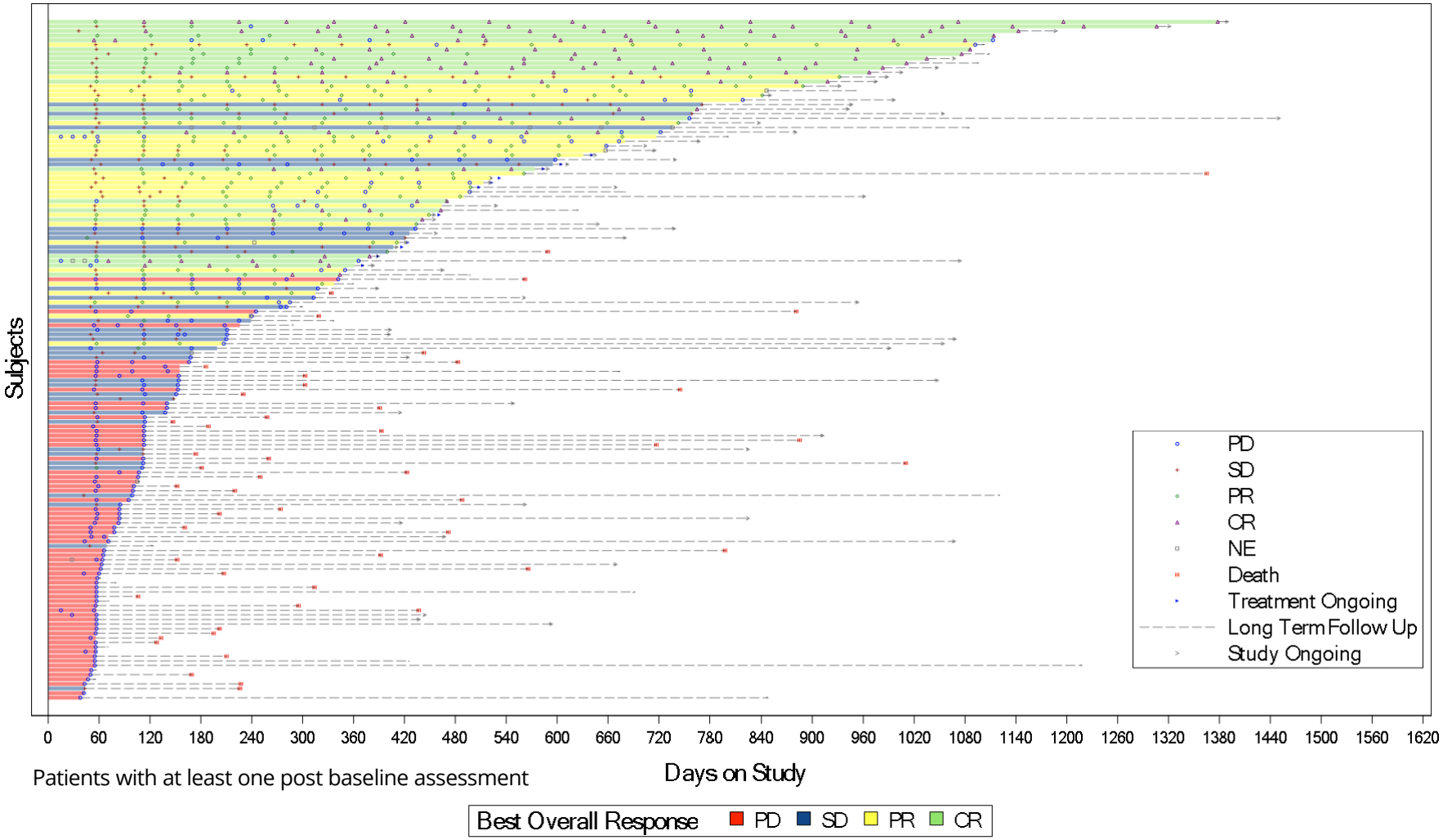
| >6 months | >12 months | >18 months | >24 months |
|---|---|---|---|
| 100% | 84.2% | 74.9% | 65.2% |

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

Data cutoff: March 8th 2024. Duration of response defined as time from baseline to end of response for responders. DOR, duration of response.


Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# Duration of Benefit




- 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

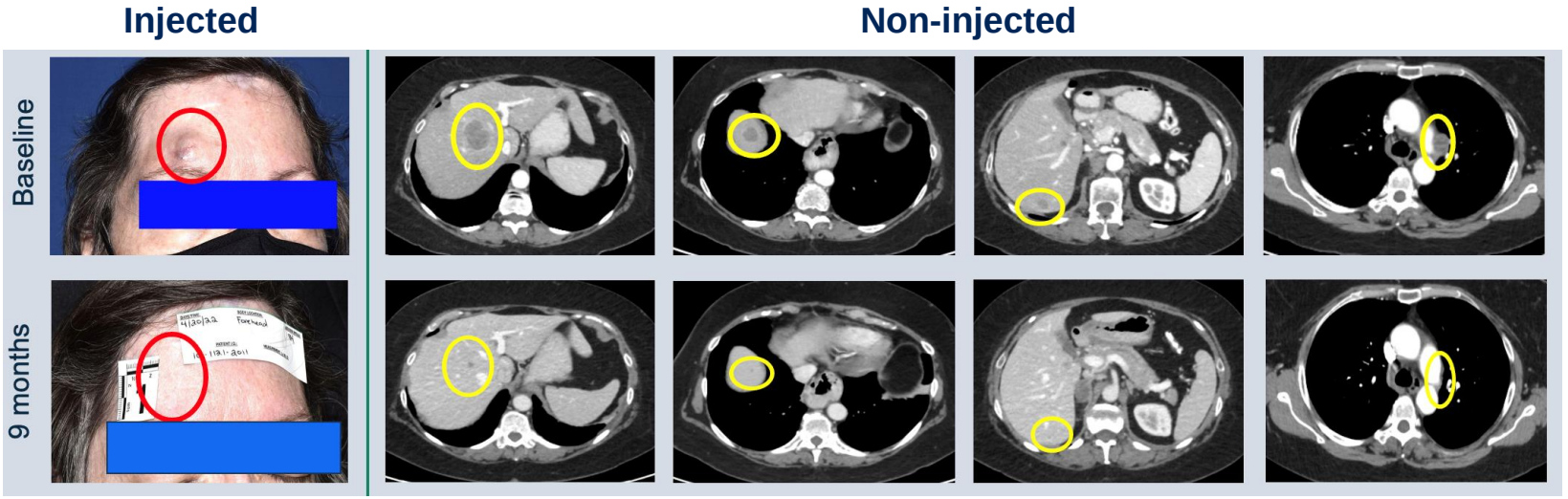
Data cutoff: March 8th 2024. The target lesion response is shown for patients with at least one post-baseline assessment. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.



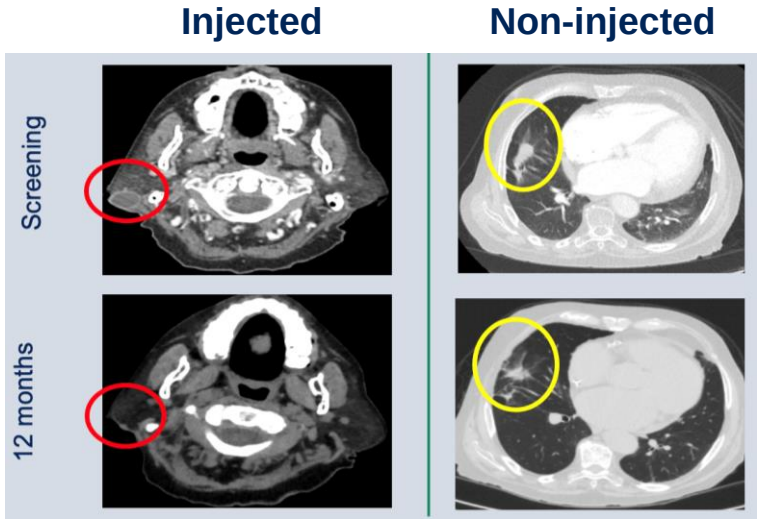
Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# 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**

RP1 injected  Non-injected

1L, first line; CR, complete response; PR, partial response


Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# Safety: Treatment-related AEs (N = 156)

| Preferred term, n (%) | TRAEs occurring in >5% of patients | | | | |
|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 | Total (N = 156) |
| Chills | 53 (34.0) | 1 (0.7) | 0 | 0 | 53 (34.0) |
| Fatigue | 51 (32.7) | 2 (1.3) | 0 | 0 | 52 (33.3) |
| Pyrexia | 49 (31.4) | 0 | 0 | 0 | 49 (31.4) |
| Nausea | 35 (22.4) | 0 | 0 | 0 | 35 (22.4) |
| Influenza-like illness | 30 (19.2) | 0 | 0 | 0 | 30 (19.2) |
| Injection-site pain | 23 (14.7) | 0 | 0 | 0 | 23 (14.7) |
| Diarrhea | 21 (13.5) | 1 (0.6) | 0 | 0 | 21 (13.5) |
| Vomiting | 21 (13.5) | 0 | 0 | 0 | 21 (13.5) |
| Headache | 20 (12.8) | 0 | 0 | 0 | 20 (12.8) |
| Pruritus | 20 (12.8) | 0 | 0 | 0 | 20 (12.8) |
| Asthenia | 13 (8.3) | 1 (0.6) | 0 | 0 | 14 (9.0) |
| Arthralgia | 11 (7.1) | 1 (0.7) | 0 | 0 | 11 (7.1) |
| Myalgia | 11 (7.1) | 0 | 0 | 0 | 11 (7.1) |
| Decreased appetite | 9 (5.8) | 1 (0.6) | 0 | 0 | 10 (6.4) |
| Rash | 9 (5.8) | 1 (0.6) | 0 | 0 | 10 (6.4) |

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

**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 arrhythmia, 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.


Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# 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*


Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

# Acknowledgements


- 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

| | | | | | |
|---|---|---|---|---|---|
| Dr. Jason Chesney | University of Louisville | Dr. Georgia Beasley | Duke Cancer Institute | Dr. Judith Michels | Institut Gustave Roussy |
| Dr. Jiaxin Niu | Banner MD Anderson | Dr. Trisha Wise-Draper | University of Cincinnati Medical Center | Dr. Ana Arance Fernandez | Hospital Clinic Barcelona |
| Dr. Terence Rhodes | Intermountain Cancer Center - Saint George | Dr. Robert McWilliams | Mayo Clinic - Rochester | Dr. Eva Munoz Couselo | Hospital Universitari Vall d'Hebron |
| Dr. Katy Tsai | UCSF/Helen Diller Family Comprehensive Cancer Center | Dr. Manesh Seetharam | Mayo Clinic - Arizona | Dr. Pablo Cerezuela | Hospital General Universitario de Valencia |
| Dr. Ari Vanderwalde | West Cancer Clinic | Dr. Issam Makhoul | Carti Cancer Center | Dr. Miguel Sanmamed | Clinica Universitaria de Navarra |
| Dr. Evan Hall | University of Washington Seattle Cancer Care Alliance | Dr. Mike Wong | MD Anderson Cancer Center | Dr. Maria Luisa Limon | Hospital Universitario Virgen del Rocio |
| Dr. Tanya Bowles | Intermountain Medical Center | Dr. Celeste Lebbe | Hôpital Saint Louis APHP | Dr. Mark Middleton | Oxford University Hospital |
| Dr. Mohammed Milhem | University of Iowa | Dr. Sophie Dalac-Rat | CHU Dijon | Dr. Kevin Harrington | Royal Marsden Hospital |
| Dr. Gregory Daniels | UCSD Moores Cancer Center | Dr. Caroline Gaudy | Cancerologie Cutanee Hopital de la Timone | Dr. Joseph Sacco | Clatterbridge Cancer Centre |
| Dr. Bartosz Chmielowski | University of California, Los Angeles | Dr. Charlee Nardin | CHU Besancon – Hopital Jean Minjoz | Dr. Adel Samson | University of Leeds |
| Dr. John Fruehauf | University of California, Irvine | Dr. Antoine Italiano | Institut Bergonié | Dr. Patricia Roxburgh | The Beatson West of Scotland Cancer Center |
| Dr. Gino In | USC Norris Comprehensive Cancer Center | Dr. Mona Amini Adle | Centre Léon Bérard | Dr. Dirk Schadendorf | University Hospital Essen |


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.

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




Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.