2026 ASCO® ANNUAL MEETING

RP2 ONCOLYTIC IMMUNOTHERAPY ALONE AND IN COMBINATION WITH NIVOLUMAB (NIVO) IN PATIENTS WITH ADVANCED SOLID TUMORS: FINAL SAFETY, EFFICACY, AND BIOMARKER RESULTS FROM THE PHASE 1 FIRST-IN-HUMAN (FIH) STUDY

Joseph J. Sacco, Kevin J. Harrington, Andrés Cervantes, María de Miguel, Guzmán Alonso, Sara Valpione, Anna Olsson-Brown, Tze Y. Chan, Pablo Nenclares, Isla Leslie, Praveen K. Bommareddy, Alireza Kalbasi, Ben Xie, Dishan Liu, Danielle Ulanet, Vineetha Edavana, Gary Vanasse, Francesca Aroldi, Aglaia Skolariki, Mark R. Middleton

Dr Joseph J. Sacco, MBChB, MSc, MRCP, PhD
The Clatterbridge Cancer Centre, Wirral, UK, and the University of Liverpool, Liverpool, UK

Key Takeaways

1

RP2 monotherapy and RP2 + nivo were **well tolerated,** with no unexpected toxicity in combination with nivo**.**

2

Durable responses were observed with RP2 monotherapy and RP2 + nivo in **heavily pretreated patients with diverse tumors.**

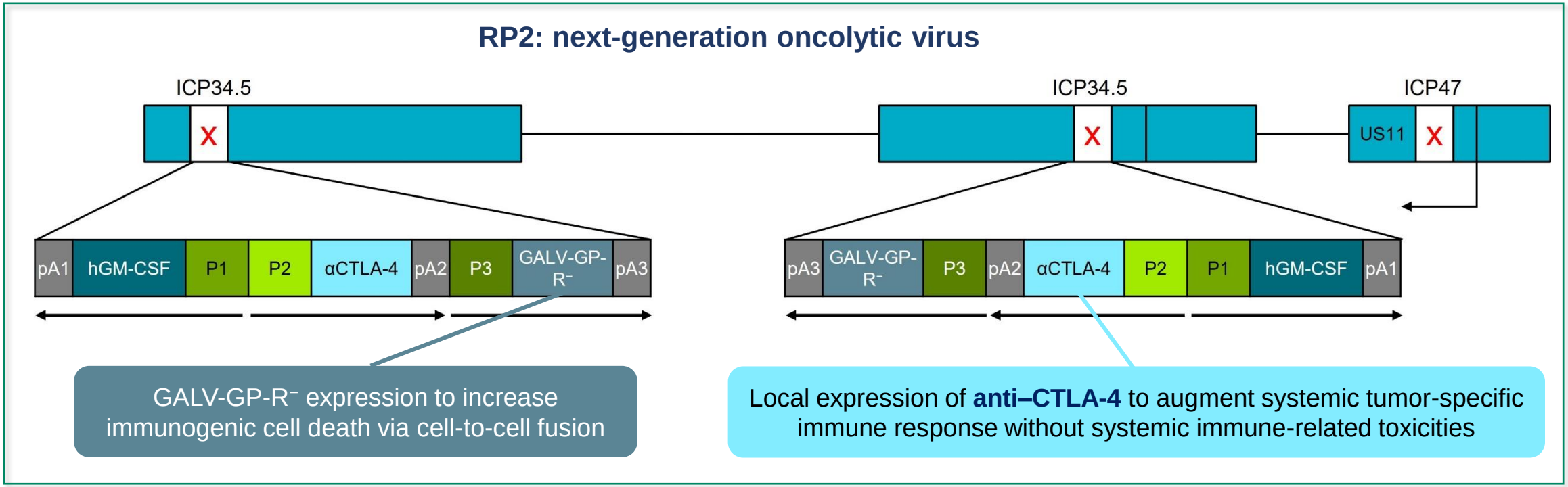
3

Meaningful tumor reductions in distant non-injected lesions were observed, with translational correlates supporting **systemic immune response**.

Nivo, nivolumab.

RP2 Oncolytic Immunotherapy

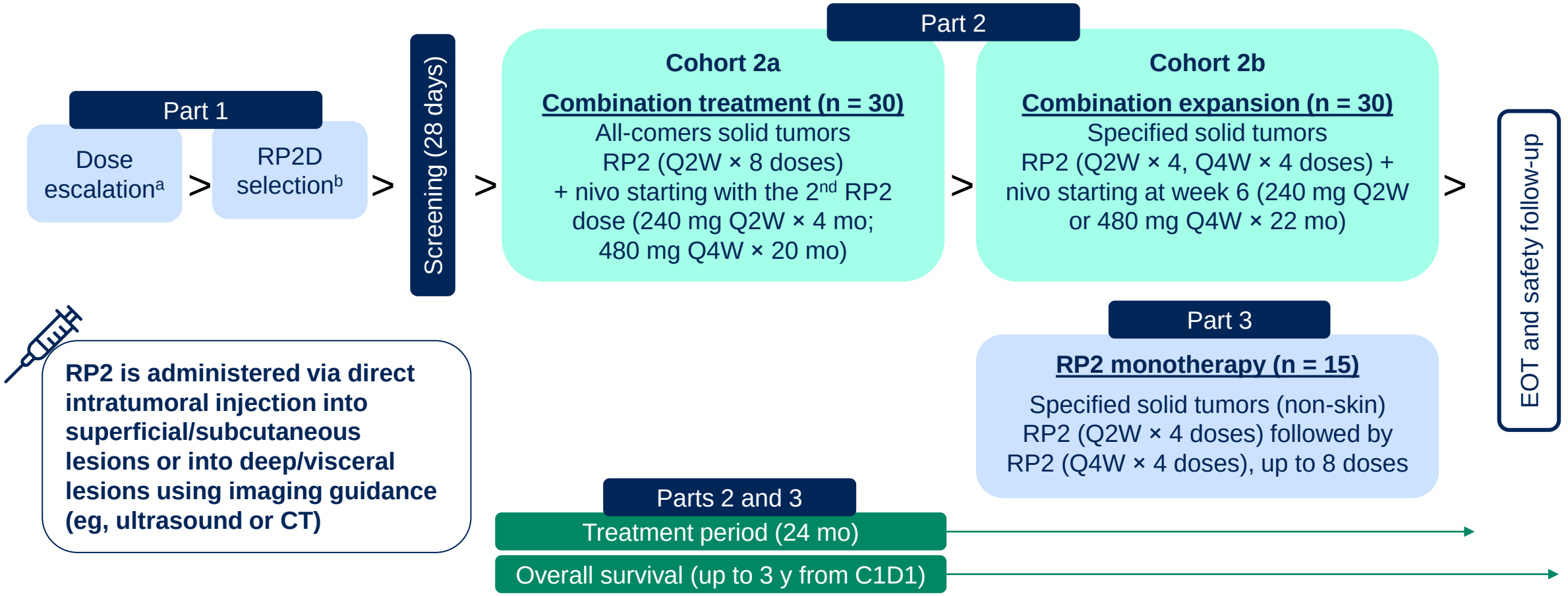
- RP2 is a genetically modified HSV-1 that encodes GM-CSF, the fusogenic protein GALV-GP-R⁻, and a human **anti–CTLA-4** antibody-like molecule[1]
  - RP2 was constructed using a potent new clinical strain of HSV-1 with superior oncolytic activity in vitro and further modified to enhance immunogenic tumor cell death[1]



αCTLA-4, anti–CTLA-4; CTLA-4, cytotoxic T-lymphocyte antigen 4; GALV-GP-R⁻, gibbon ape leukemia virus glycoprotein with the R sequence deleted; GM-CSF, granulocyte-macrophage colony-stimulating factor; hGM-CSF, human GM-CSF; HSV-1, herpes simplex virus type 1; ICP, infected cell protein; P, promoter; pA, polyA signal; US11, unique short 11; X, denotes inactivation of viral protein.

1. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.

RP2-001-18 FIH Study Design



[a]In the dose-escalation phase, cohort 1 received dose levels of 1 × 10^5 PFU/mL (day 1) followed by 1 × 10^6 PFU/mL (days 15, 29, 43, and 57), receiving up to 10 mL per dose. Cohort 2 received dose levels of 1 × 10^6 PFU/mL (day 1) followed by 1 × 10^7 PFU/mL (days 15, 29, 43, and 57), receiving up to 10 mL per dose. Cohort 3 received dose levels of 1 × 10^6 PFU/mL (day 1) followed by 1 × 10^8 PFU/mL (days 15, 29, 44, and 57), receiving up to 10 mL per dose. [b]The RP2D was identified as an initial dose of 1 × 10^6 PFU/mL, followed by up to 7 doses of 1 × 10^7 PFU/mL per dosing day. A second course of up to 8 additional RP2 injections is permitted if prespecified criteria are met.

C1D1, cycle 1 day 1; CT, computed tomography; EOT, end of treatment; FIH, first-in-human; mo, month; nivo, nivolumab; PFU, plaque-forming units; Q2W, every 2 weeks; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; y, year.

RP2-001-18 FIH Study

Key eligibility criteria

Inclusion

- Age ≥18 years
- Advanced or metastatic non-neurological solid tumors
- Progressed on or cannot tolerate standard therapy
- At least 1 measurable and injectable tumor ≥1 cm
- ECOG PS 0–1

Exclusion

- Prior treatment with oncolytic immunotherapy
- History of HBV, HCV, or HIV infection
- Active significant herpetic infections/prior complications of HSV-1 infection
- Active CNS metastases and/or carcinomatous meningitis
- Major surgery ≤2 weeks prior to starting the study drug[a]

Key endpoints

Primary

- Safety/tolerability of RP2 ± nivo (TEAEs, SAEs)
- ORR with RP2 ± nivo

Secondary

- Duration of response
- Disease control rate (CR + PR + SD)
- Progression-free survival

Exploratory

- Biomarker analyses from tumor biopsies and peripheral blood

[a]If a patient underwent major surgery, they must have recovered adequately prior to starting study treatment.

CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; nivo, nivolumab; ORR, objective response rate; PR, partial response; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event.

Baseline Characteristics

	RP2 monotherapy (n = 25)	RP2 + nivo (n = 60)	Total (N = 85)
Age, median (range), years	61.0 (27.0–80.0)	57.0 (27.0–83.0)	59.0 (27.0–83.0)
≥65, n (%)	11 (44.0)	22 (36.7)	33 (38.8)
Male sex, n (%)	17 (68.0)	37 (61.7)	54 (63.5)
ECOG PS, n (%)			
0	13 (52.0)	34 (56.7)	47 (55.3)
1	12 (48.0)	26 (43.3)	38 (44.7)
Cancer type, n (%)			
Uveal melanoma	3 (12.0)	14 (23.3)	17 (20.0)
Colorectal cancer	4 (16.0)	10 (16.7)	14 (16.5)
Head and neck	5 (20.0)	8 (13.3)	13 (15.3)
Pancreas	4 (16.0)	8 (13.3)	12 (14.1)
Cutaneous melanoma	2 (8.0)	9 (15.0)	11 (12.9)
Sarcoma	2 (8.0)	5 (8.3)	7 (8.2)
Other[a]	5 (20.0)	6 (10.0)	11 (12.9)

	RP2 monotherapy (n = 25)	RP2 + nivo (n = 60)	Total (N = 85)
Prior lines of systemic therapy, median (range)	2 (1–5)	2 (1–8)	2 (1–8)
>2 prior lines, n (%)	11 (44.0)	22 (36.7)	33 (38.8)
Prior ICI therapy, n (%)	10 (40.0)	26 (43.3)	36 (42.4)
ICI resistance type, n (%)[b]			
Primary	4 (40.0)	11 (42.3)	15 (41.7)
Secondary	5 (50.0)	5 (19.2)	10 (27.8)
Unknown	1 (10.0)	10 (38.5)	11 (30.6)
HSV-1 serostatus, n (%)[c]			
Positive	7 (58.3)	38 (74.5)	45 (71.4)
Negative	5 (41.7)	13 (25.5)	18 (28.6)

- Data cutoff: December 1, 2025

[a]Other cancer types include breast, SCLC, NSCLC, mesothelioma, liver, esophageal adenocarcinoma, anal gland, SCC of unknown primary, cholangiocarcinoma, thyroid, and gastroesophageal junction (n = 1 each).
[b]Percentages are calculated out of the totals of patients who received prior ICI therapy in each group. [c]HSV-1 serostatus was unknown for 22 patients; percentages are calculated out of the totals of patients with known serostatus in each group.
ECOG PS, Eastern Cooperative Oncology Group performance status; HSV-1, herpes simplex virus type 1; ICI, immune checkpoint inhibitor; nivo, nivolumab; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; SCLC, small cell lung cancer.

Safety Profile

Most common TRAEs (≥5% of all patients; related to RP2 or nivo)

	RP2 monotherapy (n = 35)		RP2 + nivo (n = 50)		Total (N = 85)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any TRAE, n (%)	21 (60.0)	2 (5.7)	47 (94.0)	15 (30.0)	68 (80.0)	17 (20.0)
Pyrexia	13 (37.1)	0	29 (58.0)	1 (2.0)	42 (49.4)	1 (1.2)
Chills	8 (22.9)	0	23 (46.0)	0	31 (36.5)	0
Fatigue	4 (11.4)	0	14 (28.0)	0	18 (21.2)	0
Influenza-like illness	1 (2.9)	0	12 (24.0)	0	13 (15.3)	0
Hypotension	5 (14.3)	0	7 (14.0)	2 (4.0)	12 (14.1)	2 (2.4)
Pruritus	1 (2.9)	0	9 (18.0)	0	10 (11.8)	0
Nausea	1 (2.9)	0	8 (16.0)	0	9 (10.6)	0
Headache	1 (2.9)	0	5 (10.0)	0	6 (7.1)	0
Injection-site pain	3 (8.6)	0	3 (6.0)	0	6 (7.1)	0
Vomiting	1 (2.9)	0	5 (10.0)	0	6 (7.1)	0
ALT increased	0	0	5 (10.0)	2 (4.0)	5 (5.9)	2 (2.4)

- The TRAE profile of RP2 is consistent with systemic immune activation
  - Additional TRAEs of CRS (one grade 2, two grade 3) and injection-related reaction (grade 2) were reported in 3 (3.5%) patients each
- No individual grade ≥3 TRAE was reported in >2 patients
- There were no grade 4 or 5 TRAEs
- RP2 + nivo did not result in increases in irAEs compared to the expected safety profile of nivo alone
- Patients received a median of 5 RP2 injections (range, 1–16)
  - Overall, 68.2% of injections were deep/visceral (liver, 51.8%; lung, 5.9%)

AE, adverse event; ALT, alanine aminotransferase; CRS, cytokine release syndrome; irAE, immune-related AE; nivo, nivolumab; TRAE, treatment-related AE.

Response Summary by Treatment

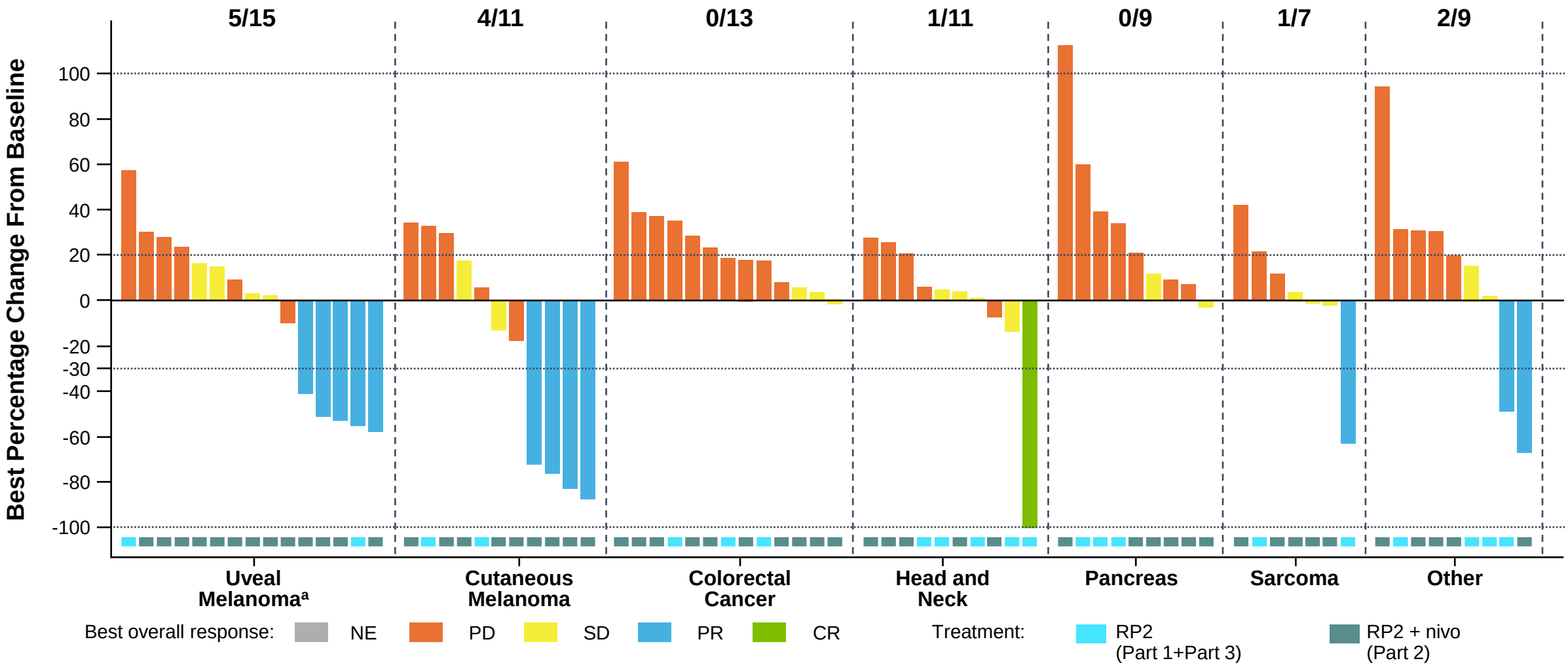
Efficacy-evaluable patients

	RP2 monotherapy[a] (n = 21)	RP2 + nivo (n = 47[b])
BOR, n (%)		
CR	1 (4.8)	0
PR	3 (14.3)	9 (19.1)
SD	5 (23.8)	14 (29.8)
PD	12 (57.1)	24 (51.1)
ORR (CR + PR), n (%)	**4 (19.0)**	**9 (19.1)**
95% CI	(5.4, 41.9)	(9.1, 33.3)
Disease control rate (CR + PR + SD), n (%)	9 (42.9)	23 (48.9)
95% CI	(21.8, 66.0)	(34.1, 63.9)
Duration of response, median, months	NR	22.1
Range	11.5–27.3+	2.8–35.2+

- Confirmed monotherapy responses were noted in 4 patients with the following tumor types:
  - Uveal melanoma
  - Esophagogastric adenocarcinoma (PR per RECIST 1.1; mCR by FDG-PET)
  - Chordoma
  - Mucoepidermoid (BOR of uCR)
- Monotherapy responses exhibited durability of 11 to 27+ months
- Tumor regression was observed in both injected and non-injected lesions, including in all 3 patients with monotherapy responses who had non-injected lesions

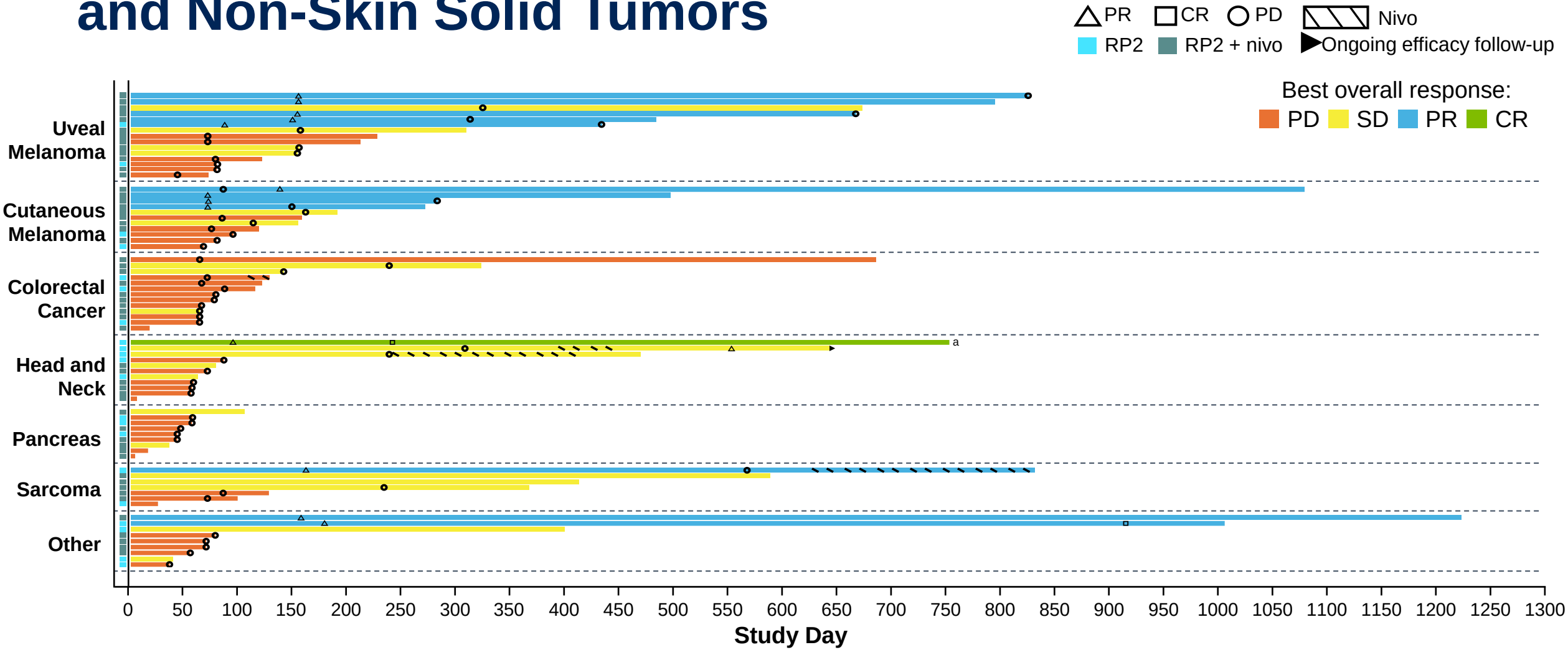
BOR includes confirmed and unconfirmed responses. One patient in the monotherapy group had best response of uCR (confirmatory scan not performed). One patient in the combination group had uPR due to new lesions at a subsequent scan (target lesions remained declined, and the patient continued on treatment post-PD with further target lesion decline).
[a]For patients enrolled in a monotherapy cohort that received nivo post-progression (n = 4), response assessments after the start of nivo are not included in the BOR derivation. One patient had a confirmed PR following re-initiation of RP2 treatment with nivo post-progression. [b]Seven additional efficacy-evaluable patients (4 pancreatic, 2 colorectal, 1 head and neck) enrolled in the RP2 + nivo cohort discontinued treatment early prior to receiving nivo and were not included in the efficacy analyses presented by treatment group. The ORR was 17.3% across all efficacy-evaluable patients.
BOR, best overall response; CI, confidence interval; CR, complete response; FDG-PET, fluorodeoxyglucose positron emission tomography; mCR, metabolic CR; nivo, nivolumab; NR, not reached; 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; uCR, unconfirmed CR; uPR, unconfirmed PR.

Anti-Tumor Activity by Tumor Type



Patients who had no post-baseline tumor measurement are not included in the waterfall plot.
[a]Data from the uveal melanoma subgroup previously presented at the 2024 ASCO annual meeting (data cutoff: August 2023); additional 2+ years of follow-up reported here.
CR, complete response; NE, not evaluable; nivo. nivolumab; PD, progressive disease; PR, partial response; SD, stable disease.

Durable Clinical Responses in Patients With Melanoma and Non-Skin Solid Tumors

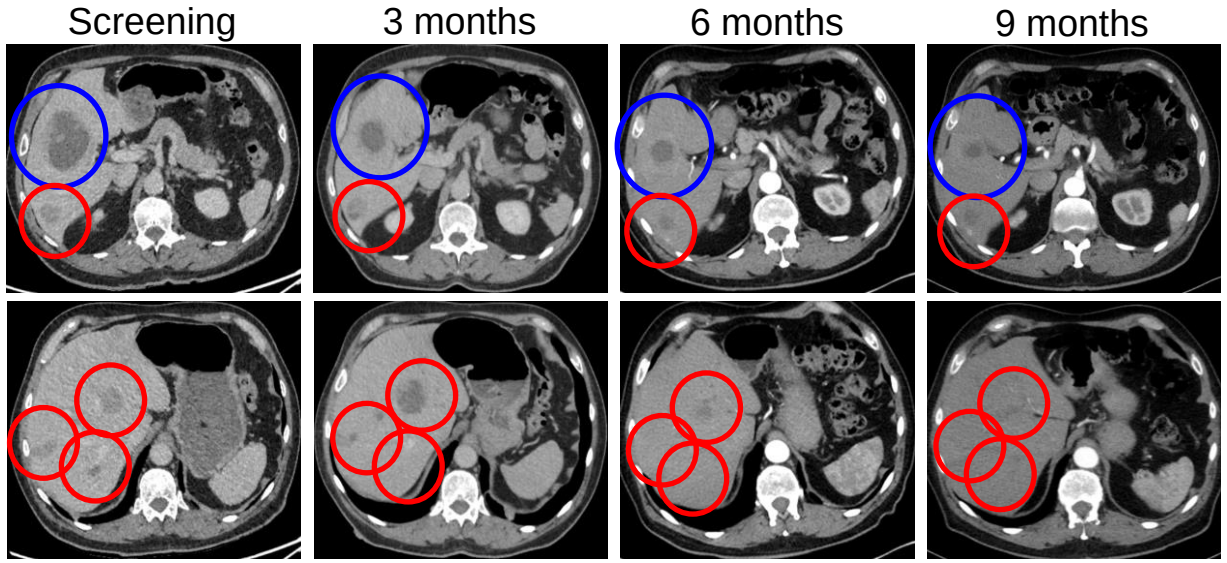


For patients who enrolled in a monotherapy group and received nivo following PD, the bar color represents the best overall response on monotherapy treatment. One of the 4 patients who received nivo following PD (head and neck group) had a PR following the start of nivo. [a]This patient with mucoepidermoid carcinoma had a durable PR deepening to a CR at 25 months. The patient had a best response of PD to 3 prior therapies. As of the data cutoff, the patient remained in overall survival follow-up with no subsequent therapy given after >5 years. CR, complete response; NE, not evaluable; nivo, nivolumab; PD, progressive disease; PR, partial response; SD, stable disease.

RP2 Monotherapy Drives Tumor Reduction in Non-Injected Target Lesions

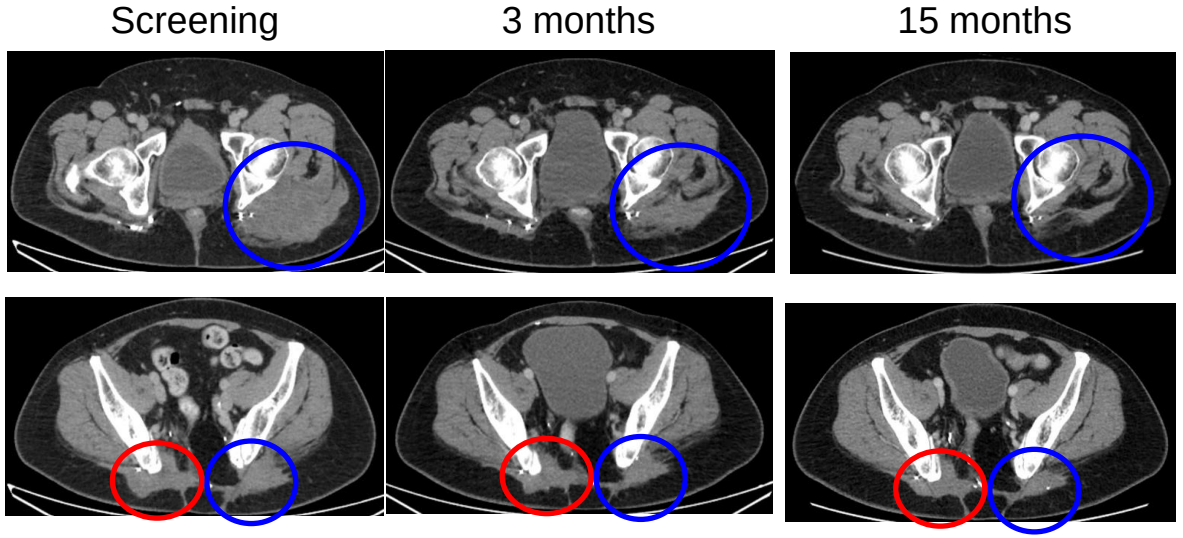
Injected Non-injected

A 64-year-old male patient with uveal melanoma[1]



- The patient had primary resistance to ICI treatment and liver metastases
- Achieved PR at 3 months
- The DOR was 11.5 months; PD occurred due to new lesions

A 48-year-old male patient with chordoma

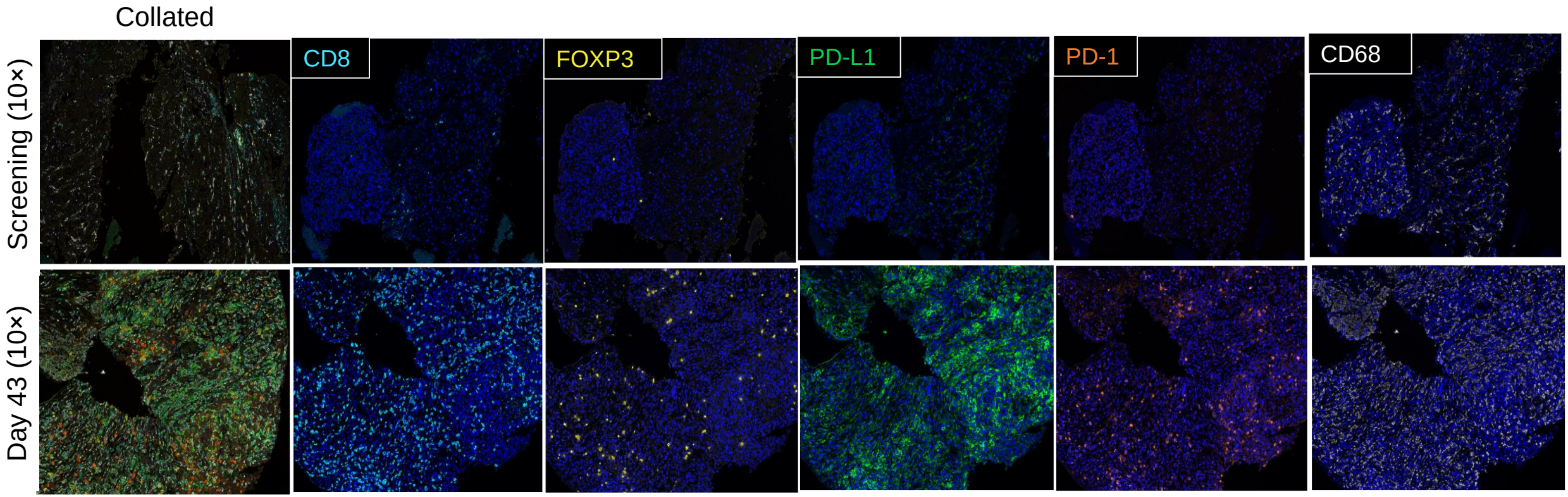


- The patient had prior therapy with imatinib and afatinib
- Extensive metastatic disease at baseline
- Achieved PR at 5 months (with disappearance of a solitary liver metastasis and multiple small lung lesions)
- The DOR was 13 months; PD occurred due to new lesions

DOR, duration of response; ICI, immune checkpoint inhibitor; PD, progressive disease; PR, partial response.

1.Sacco JJ, et al. Oral Presentation at the ASCO 2024 Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA.

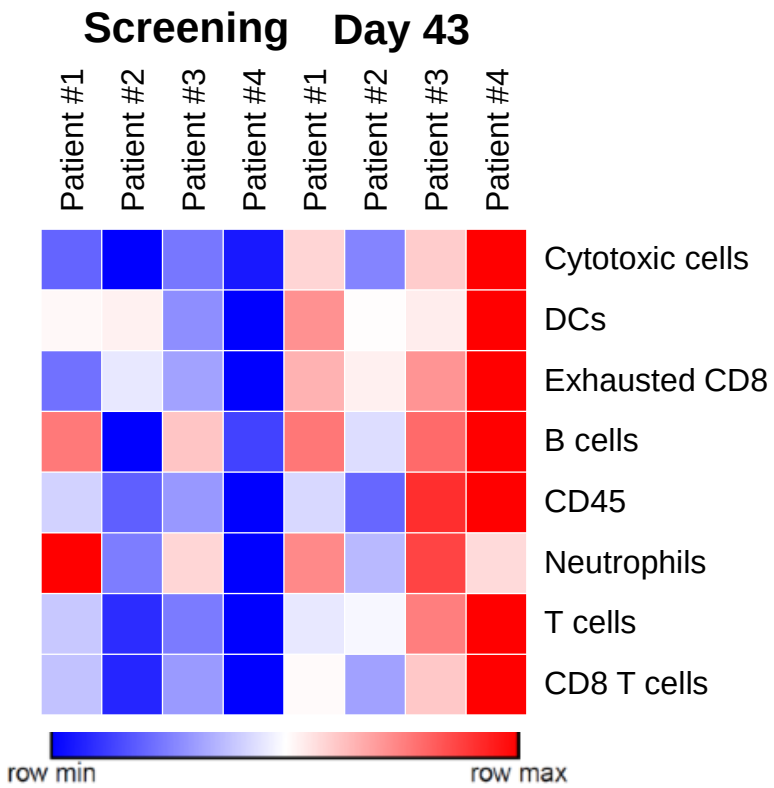
RP2 Monotherapy Reprograms the TME From Immunologically Silent to Immune-Inflamed



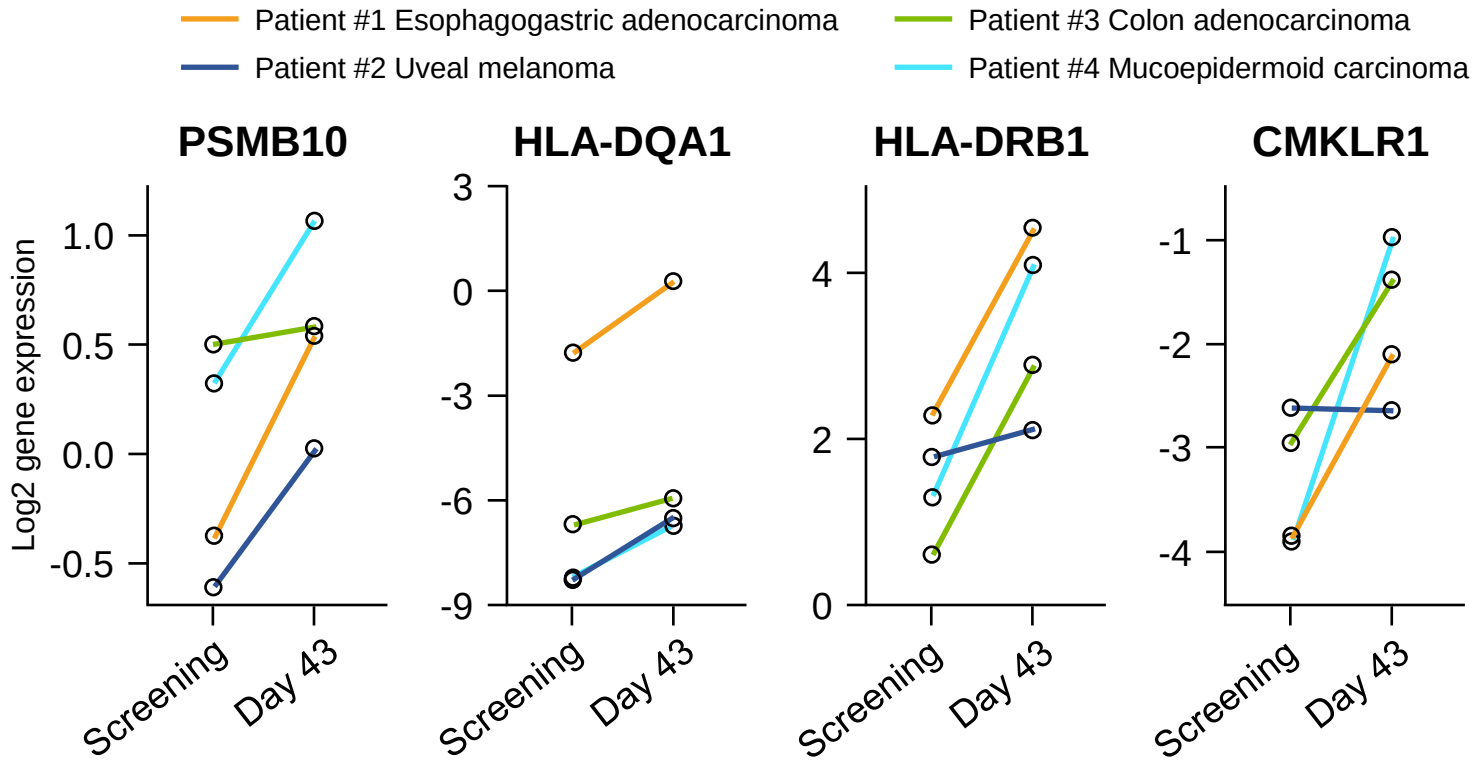
Multiplex IF.
FOXP3, forkhead box P3; IF, immunofluorescence; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TME, tumor microenvironment.

RP2 Monotherapy Upregulates Gene Expression Signatures of Key Immune Activation Pathways

Gene signatures



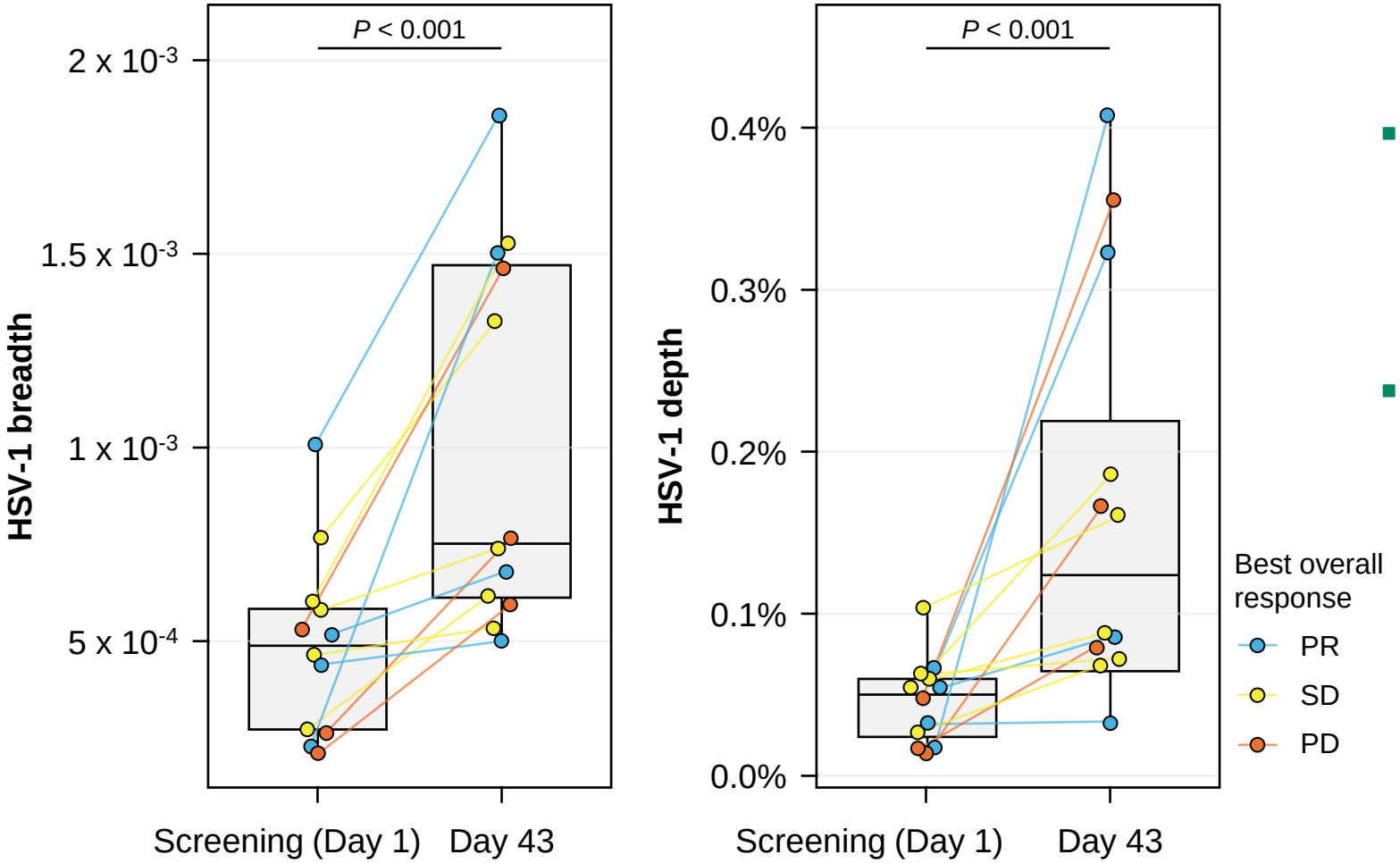
Antigen presentation



- Increases in gene signatures relevant to T-cell cytotoxicity, antigen presentation, and dendritic cells during RP2 monotherapy demonstrated the mechanism of action of the anti–CTLA-4 antibody-like molecule encoded by RP2

Gene signature and antigen presentation data are from patients who received monotherapy and had available samples pre- and post-dosing. Analysis was performed using NanoString.
CMKLR1, chemokine-like receptor 1; CTLA-4; cytotoxic lymphocyte antigen 4; DC, dendritic cell; HLA, human leukocyte antigen; PSMB10, proteasome subunit beta-type-10.

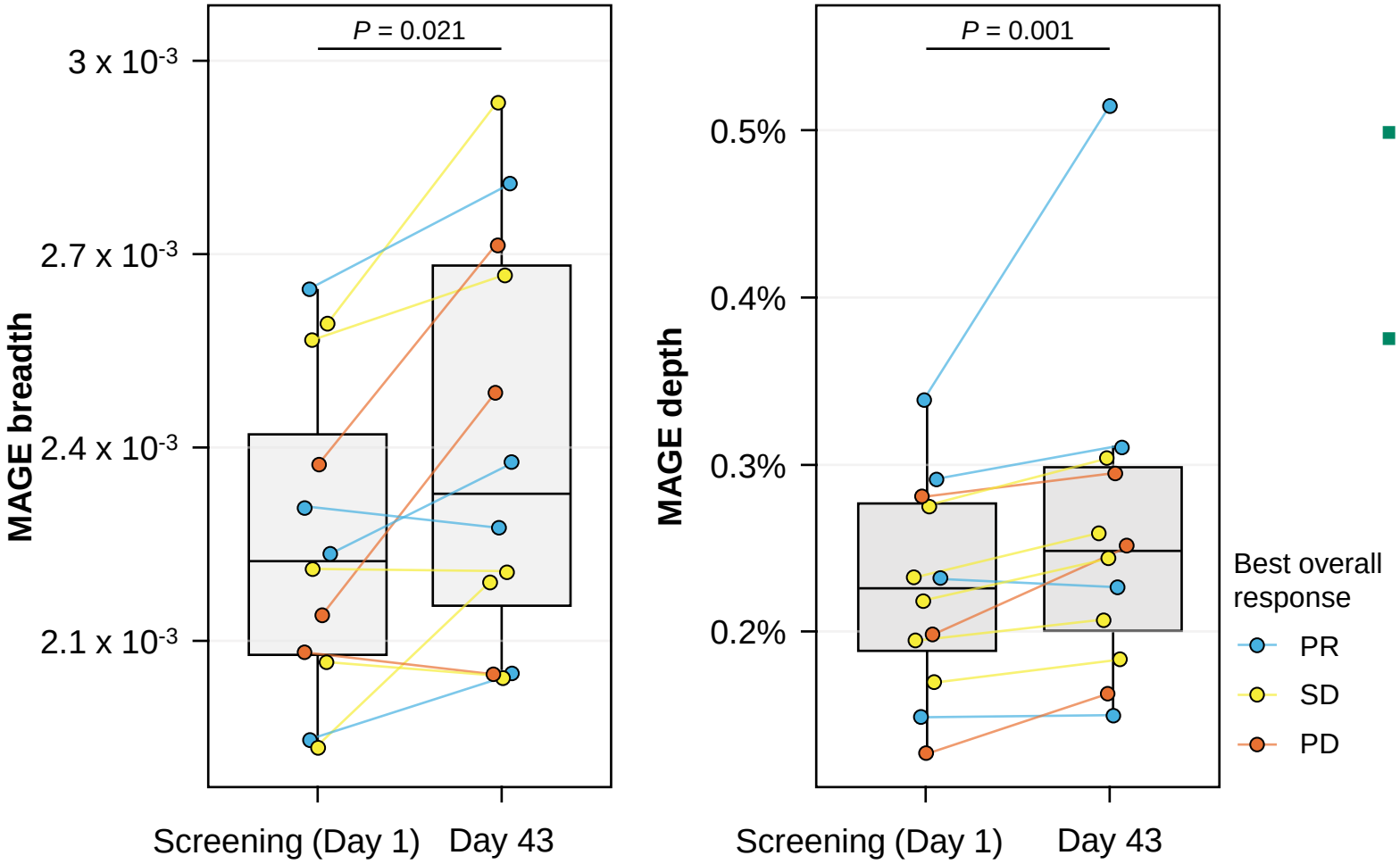
RP2 Treatment Increases Breadth and Depth of HSV-1 TCR Clones From Screening to Day 43



- Each patient exhibited increased breadth and depth of HSV-1 TCR clones at day 43 compared with day 1
- These trends were not seen in T-cell responses to other viral infections such as HSV-2, EBV, or SARS-CoV-2, indicating specificity to HSV-1

TCR sequencing was performed on peripheral blood and TCRs were annotated against publicly available HSV-1 epitopes. *P*-values from uncorrected paired Wilcox test.
EBV, Epstein-Barr virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; PD, progressive disease; PR, partial response; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, stable disease; TCR, T-cell receptor.

RP2 Treatment Increases Breadth and Depth of MAGE-Specific TCR Clones From Screening to Day 43



- Peripheral breadth and depth of MAGE TCR clones increased from screening to day 43
- There were no significant associations between MAGE breadth or depth and clinical response

TCR sequencing was performed on peripheral blood and TCRs were annotated against publicly available MAGE epitopes. *P*-values from uncorrected paired Wilcox test.
MAGE, melanoma-associated antigen; PD, progressive disease; PR, partial response; SD, stable disease; TCR, T-cell receptor.

Conclusions

1

RP2 monotherapy and RP2 + nivo were **well tolerated,** with no unexpected toxicity in combination with nivo.

2

Durable responses were observed with RP2 monotherapy and RP2 + nivo in **heavily pretreated patients with diverse tumors.**

3

Meaningful tumor reductions occurred in **distant non-injected lesions** and increases were seen in **HSV-1** and **tumor-specific TCRs.**

RP2 is being evaluated in combination with nivo in patients with **metastatic uveal melanoma** in a randomized phase 2/3 trial (NCT06581406)

Nivo, nivolumab; HSV-1, herpes simplex virus type 1; TCR, T-cell receptor.

Acknowledgments

- 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
- This study was sponsored by Replimune, Inc. Nivolumab was provided by Bristol Myers Squibb

Additional information can be obtained by visiting Clinicaltrials.gov (NCT04336241).