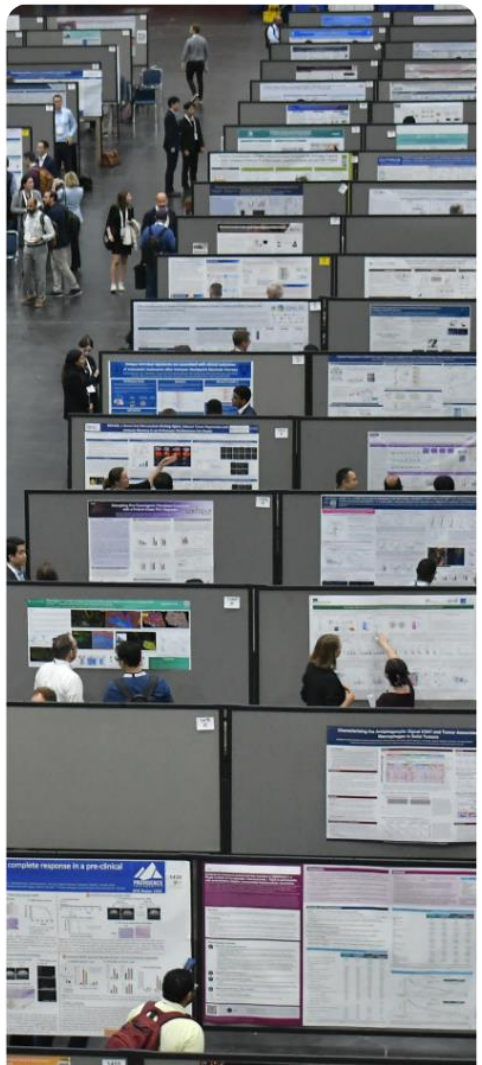

Society for Immunotherapy of Cancer

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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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Disclosure

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Background

- Resistance to anti–PD-1 ± anti–CTLA-4 therapy can be attributed to multiple molecular mechanisms[1]
- T-cell infiltration, PD-L1 expression, and IFN-γ signature can be used as biomarkers to assess the inflammatory state of the 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]
- RP1 (vusolimogene oderparepvec) is an HSV-1–based oncolytic immunotherapy that expresses GM-CSF and a fusogenic glycoprotein (GALV-GP-R$^-$)[11]

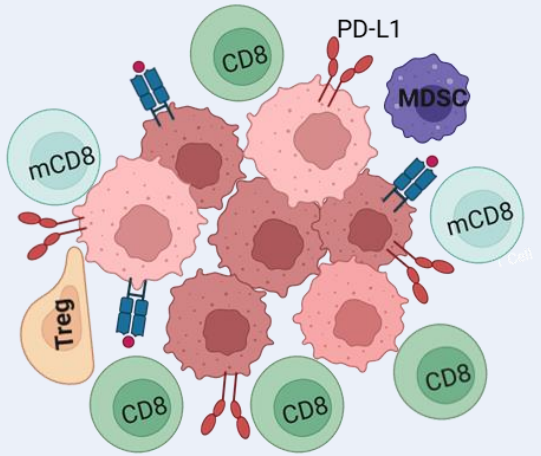
CTLA-4, cytotoxic T-lymphocyte antigen 4; GALV-GP-R$^-$, gibbon ape leukemia virus glycoprotein with the R sequence deleted; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV-1, herpes simplex virus type 1; IFN-γ, interferon gamma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TME, tumor microenvironment.

1. Alsaafeen BH, et al. *Mol Cancer*. 2025;24(1):20. 2. Sharma P, et al. *Cell*. 2017;168(4):707-23. 3. Mooradian MJ, et al. *Oncology*. 2019;33(4):141-8. 4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Cutaneous. Version 2.2025. 5. Beaver JA, et al. *Lancet Oncol*. 2018;19(2):229-39. 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. *J Immunother Cancer*. 2022;10(12):e005755. 9. US Food and Drug Administration. BLA clinical review and evaluation - AMTAGVI. BLA 125773. Updated February 6, 2024. Accessed October 7, 2025. https://www.fda.gov/media/176951/download. 10. Sarnaik AA, et al. *J Clin Oncol*. 2021;39(24):2656-66. 11. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.

TME state during anti–PD-1 retreatment may vary based on both the timing of treatment and intervening therapy

Stop → relapse → anti–PD-1 retreatment

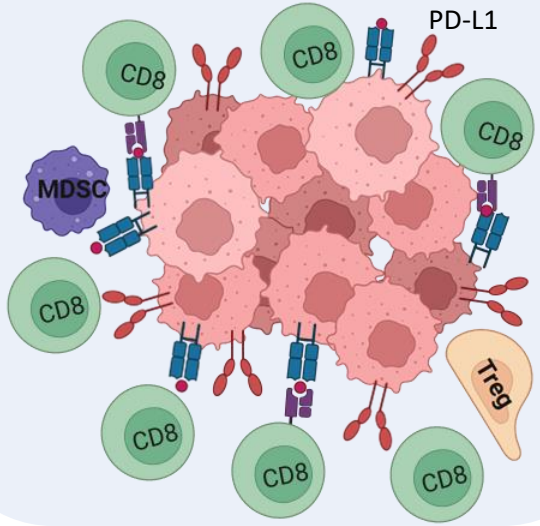
- Potentially immunologically active/sensitive TME
- Activated memory CD8+ T cells
- Mechanisms of resistance to anti–PD-1 may not be active



Potentially effective

Intervening therapy → anti–PD-1 retreatment

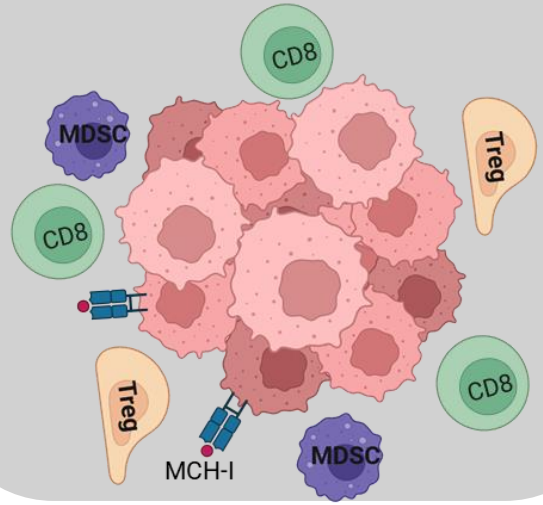
- Remodeled TME
- Potential for restored sensitivity to anti–PD-1



Potentially effective

Progression while on anti–PD-1 treatment

- Immune-suppressive TME
- Low/no T-cell infiltration and PD-L1 expression
- Low IFN-γ signature
- Low antigen presentation

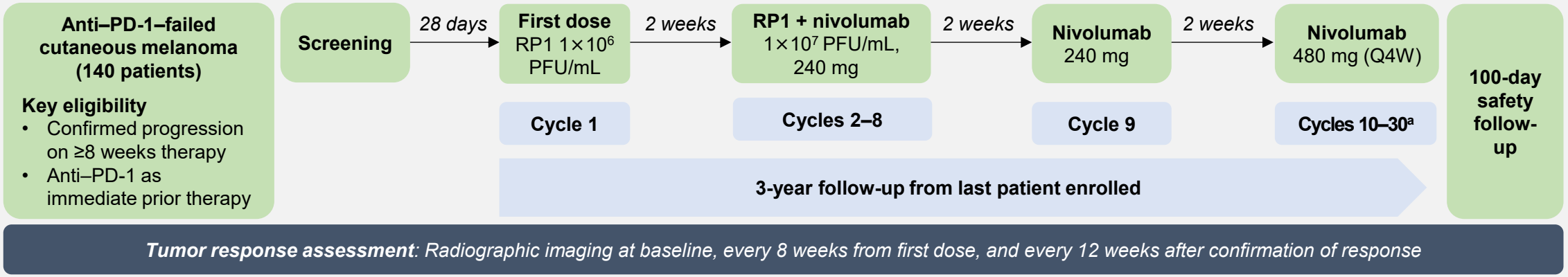


Minimally effective

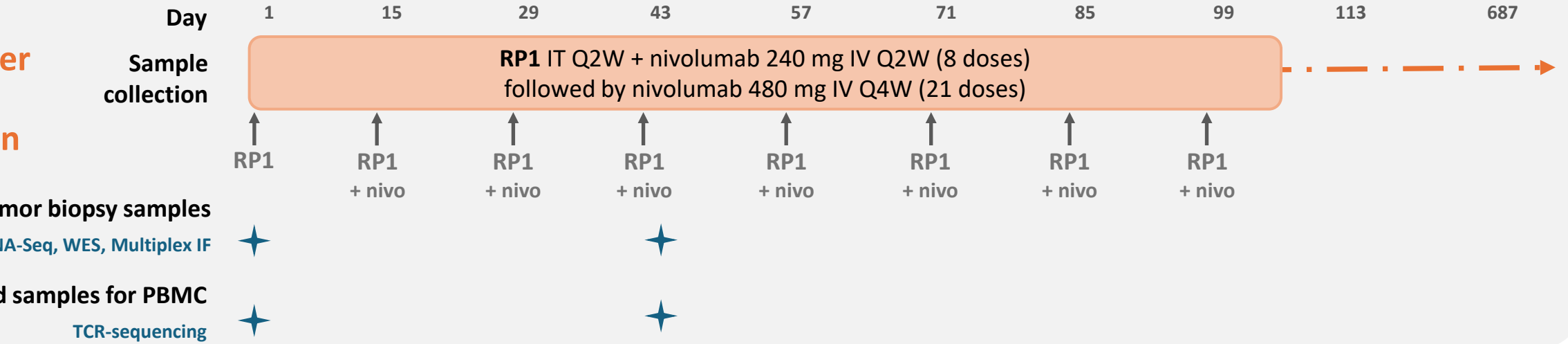
IFN-γ, interferon gamma; MDSC, myeloid-derived suppressor cell; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TME, tumor microenvironment; Treg, regulatory T cell.

Methods and sample collection schedule

IGNYTE study design



Biomarker sample collection



[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.

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)
LDH level	
LDH ≤ULN	92 (65.7)
LDH >ULN	47 (33.6)
Unknown	1 (0.7)

Patients, n (%)	N = 140
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; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

Updated ORRs show clinically meaningful benefits across biological subgroups

- Centrally reviewed RECIST 1.1 responses; all patients have ≥12 months follow-up

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)**

- Consistent response rates were also seen across clinical patient subgroups, including the following:
  - **26.2% ORR** in patients who had **prior anti–PD-1 and anti–CTLA-4**
  - **34.8% ORR** in patients who had **primary resistance to anti–PD-1**

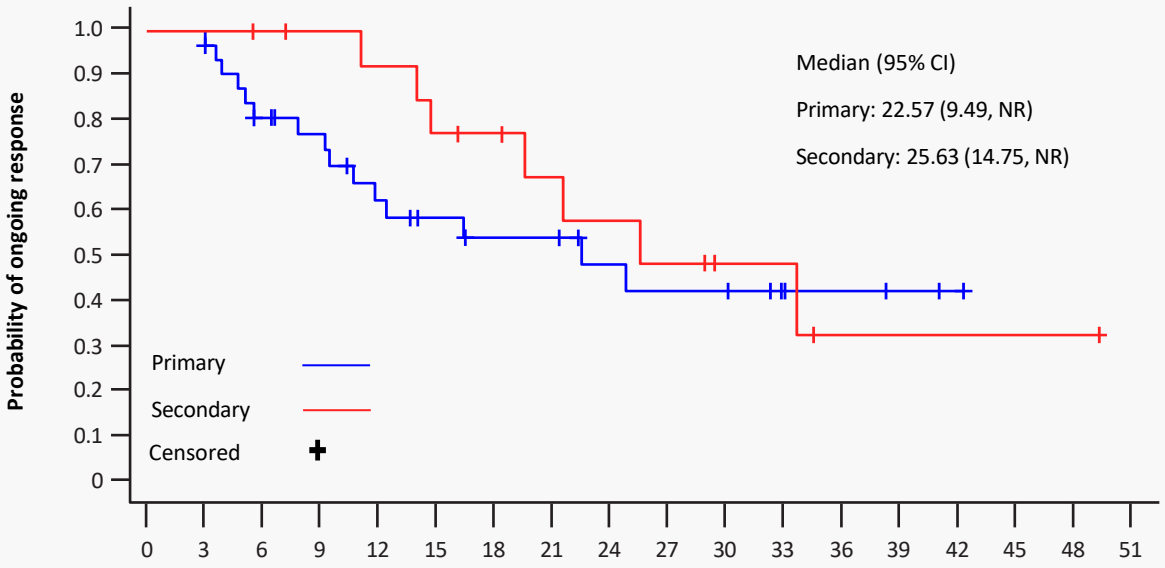
Data cutoff: October 15, 2024 (7 months post the primary analysis).

[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.

Durable responses observed across challenging-to-treat biological subgroups

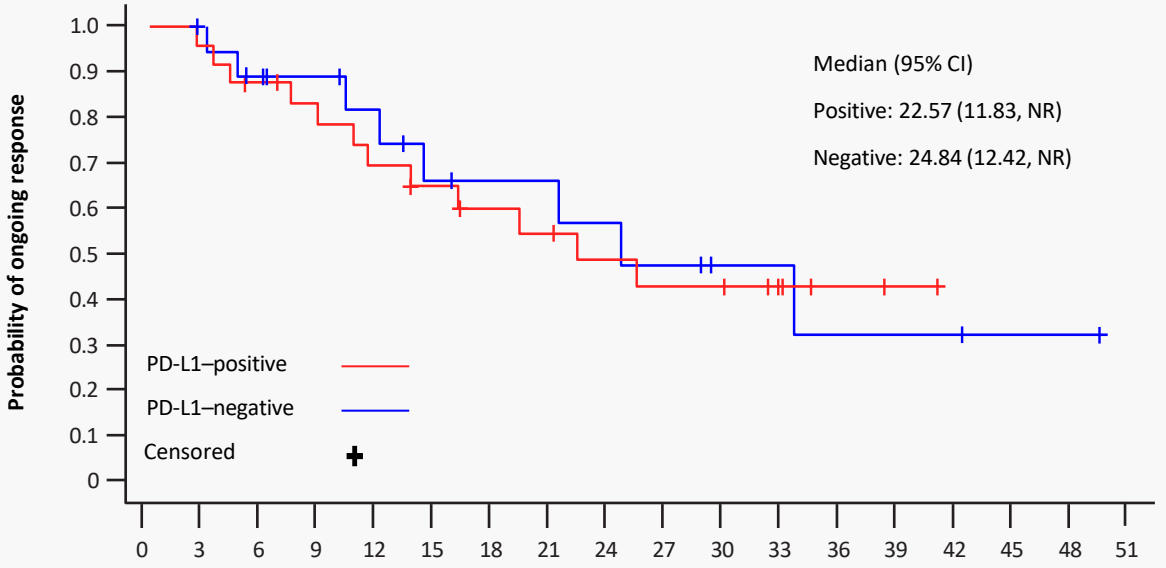
Primary[a] vs secondary[b] resistance



Number of patients at risk

Primary	32	32	24	21	16	13	11	11	8	7	7	4	3	2	1	0	
Secondary	15	15	14	13	12	10	9	7	6	5	3	3	1	1	1	1	1

PD-L1–positive vs PD-L1–negative

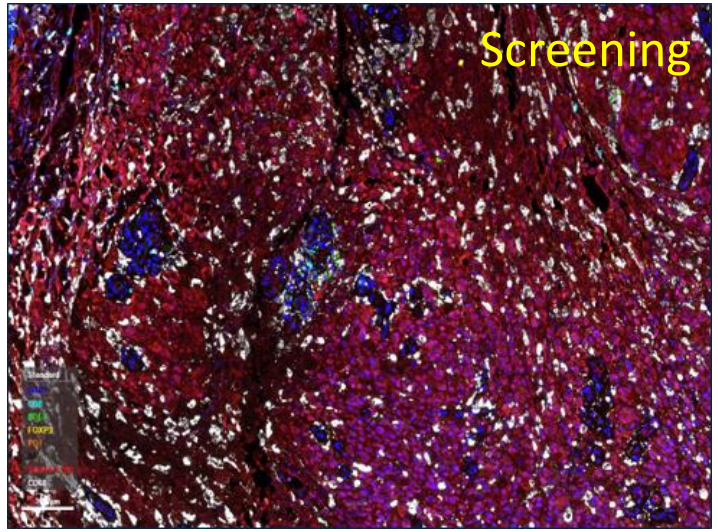


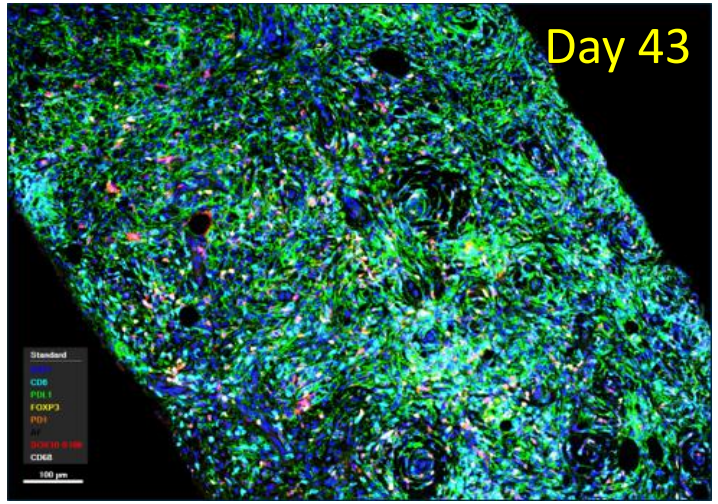
Number of patients at risk

Positive	24	24	20	18	15	13	11	10	8	7	7	4	2	1	0		
Negative	19	19	15	13	11	8	7	7	6	5	3	3	2	2	2	1	1

[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-L1, programmed death-ligand 1.

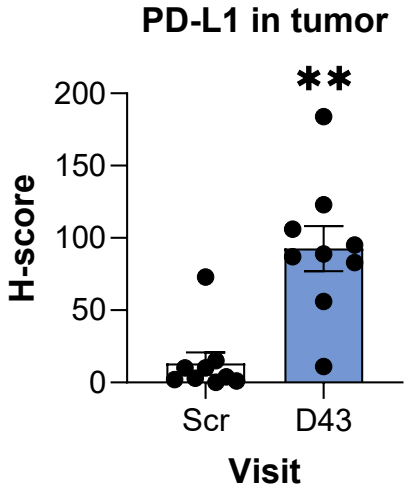
RP1 + nivo treatment reprograms the TME

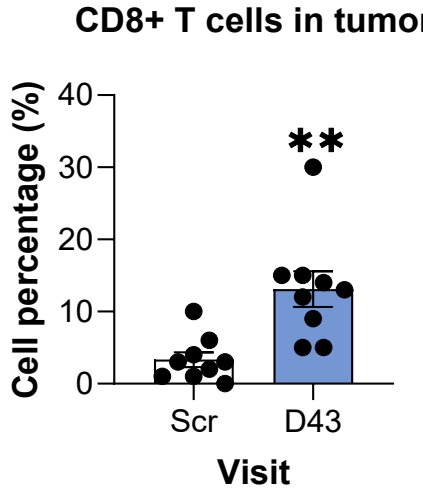


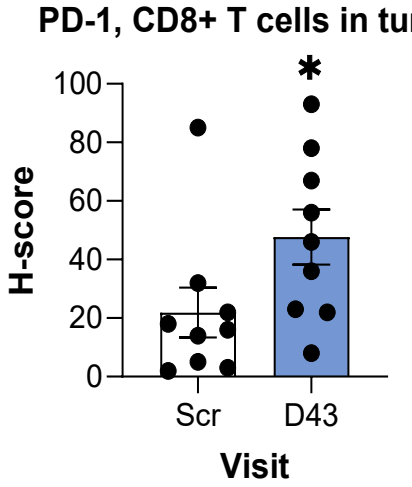


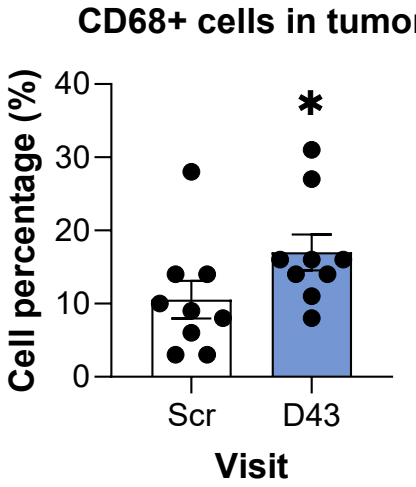
DAPI
PD-L1
CD8
FOXP3
PD-1
SOX10 S100
CD68

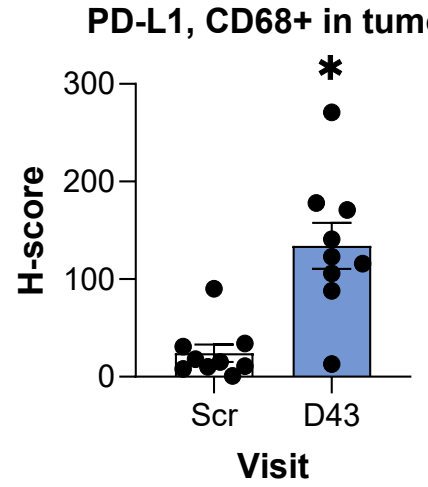
Paired biopsies n = 9







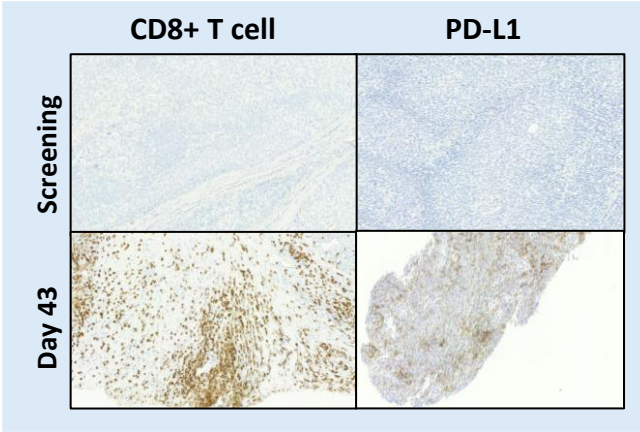




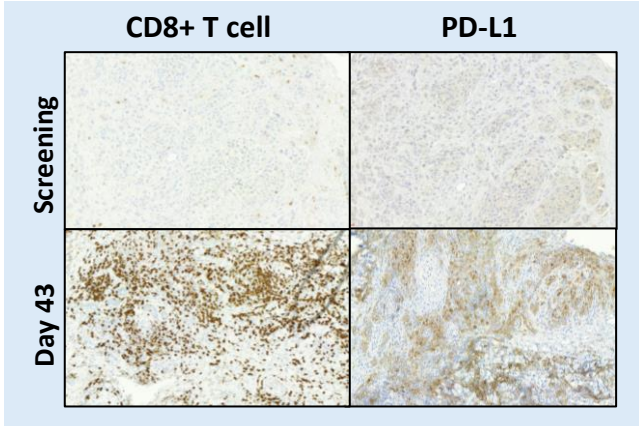
Paired t test, * *P*-value <0.05, ** *P*-value <0.01.
D, day; DAPI, 4′,6-diamidino-2-phenylindole; FOXP3, forkhead box P3; nivo, nivolumab; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Scr, screening; SOX10, SRY-box transcription factor 10; TME, tumor microenvironment.

RP1 + nivo treatment increases CD8+ T-cell infiltration and PD-L1 expression

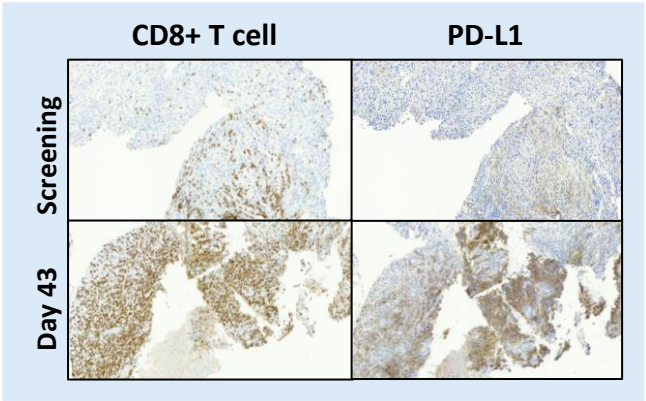
1 Ipi/nivo ----▸ 13 weeks



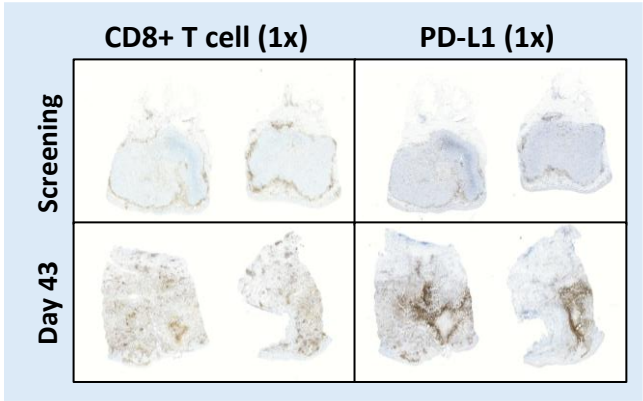
2 Pembro ------▸ 28 weeks



3[1] Ipi/nivo ----------▸ 79 weeks



4 Ipi/nivo ----------▸ 81 weeks



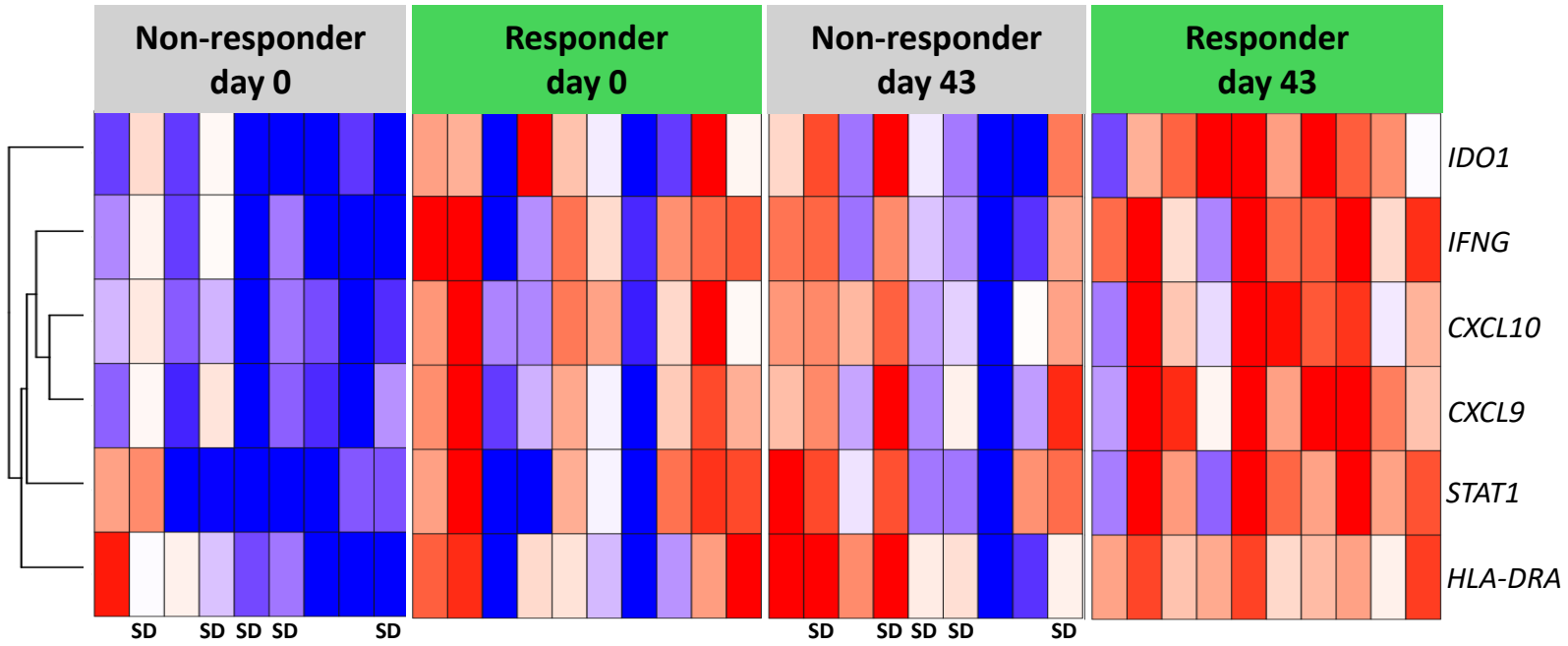
	All lesions (paired + non-paired) % (n/N)	Paired lesions % (n/N)
Increase in PD-L1	57 (39/68)	56 (25/45)
Increase in CD8+ T cells	47 (37/78)	37 (17/46)

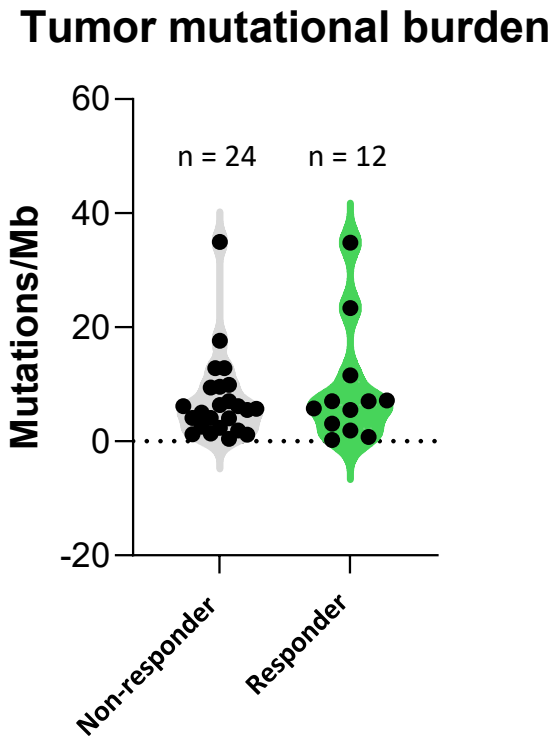
- Increases observed regardless of type and duration of prior treatment

Treatment duration includes maintenance anti–PD-1 therapy.
ipi, ipilimumab; nivo, nivolumab; PD-L1, programmed death-ligand 1; pembro, pembrolizumab.
1. Wong MK, et al. *J Clin Oncol*. 2025. doi: 10.1200/JCO-25-01346.

RP1 + nivo increases the expression of IFN-γ signature, evidence of resensitizing tumors to anti–PD-1 treatment

- Whole exome sequencing of day 0 biopsies demonstrated that clinical responses were observed irrespective of tumor mutation burden

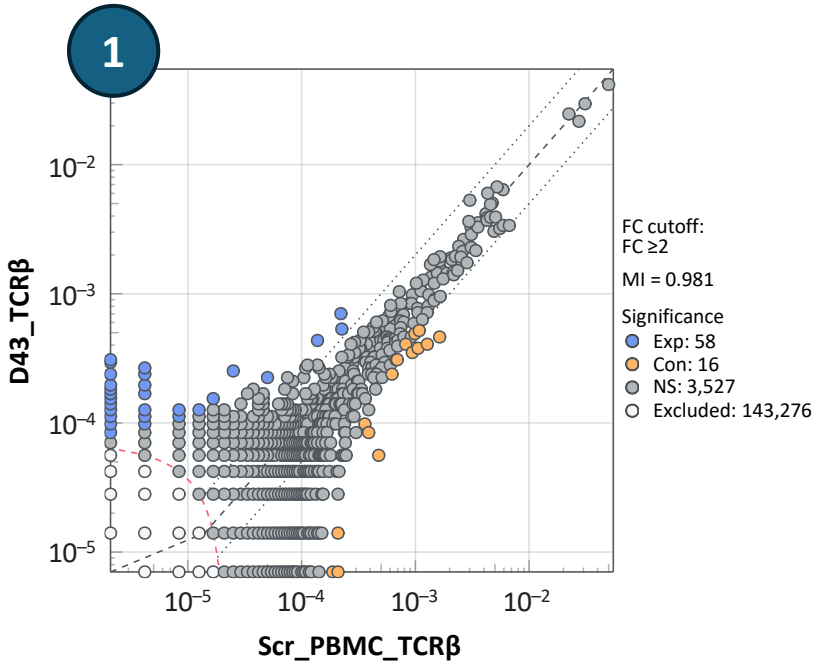




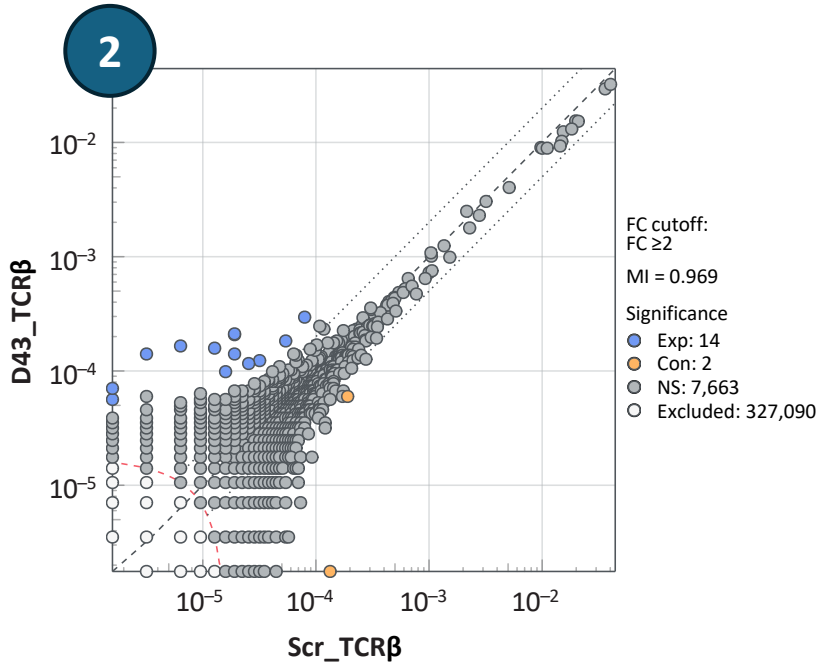
RNA-sequencing of tumor biopsies from paired lesions and whole exome sequencing of day 0 biopsies for tumor mutational burden. Day 43 = cycle 4.
IFN-γ, interferon gamma; nivo, nivolumab; PD-1, programmed cell death protein 1; SD stable disease

RP1 + nivo expanded existing T-cell clones and generated new T-cell clones, evidence of a systemic anti-tumor immune response

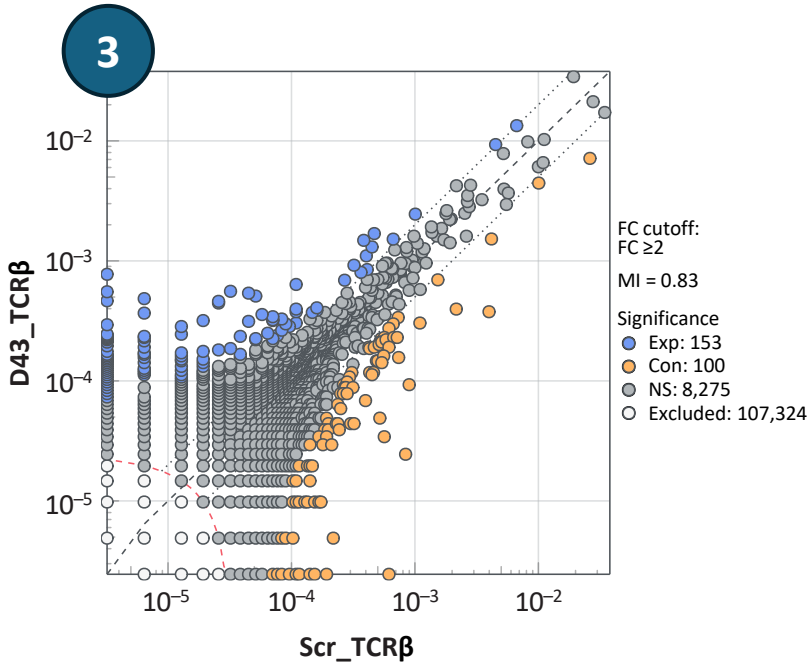
Patient 1



Patient 2



Patient 3



- Many of the expanded clones (range 20%–80%) were newly detected at day 43 (y-axis), 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 MAGE at day 43 in the periphery (y-axis), demonstrating treatment-driven systemic expansion of T-cell clones
  - A particularly striking expansion of T-cell clones (n = 170) was observed for **patient 3**, who had an ongoing complete response

D, day; FC, fold change; HSV-1, herpes simplex virus type 1; MAGE, melanoma-associated antigen; nivo, nivolumab; PBMC, peripheral blood mononuclear cell; NS, not significant; Scr, screening; TCRβ, T-cell receptor beta chain.

Conclusions

Biomarker

- **Treatment with RP1 + nivo led to upregulation of gene signatures associated with responsiveness to PD-1 blockade**, including:
  - Increase in CD8+ T-cell infiltration and PD-L1 expression
  - Increase in 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—absent during extended prior anti–PD-1 therapy—**demonstrate that the addition of RP1 can overcome multiple mechanisms of resistance to PD-1 blockade**, underscoring RP1's therapeutic contribution to the treatment of melanoma patients who previously failed such treatment.
- Biomarker data provide mechanistic insight into the systemic clinical responses observed with RP1 + nivo following definitive anti–PD-1 failure highlighting efficacy independent of PD-L1 status or resistance type

Efficacy and safety

- **RP1 combined with nivo continues to demonstrate a clinically meaningful response rate** (ORR: 33.6%) **and durability** (median DOR: 24.8 months) in patients with advanced melanoma with consistent duration of response 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

DOR, duration of response; IFN-γ, interferon gamma; nivo, nivolumab; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

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Dr Gregory Daniels	Moores UCSD Cancer Center
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Dr John Fruehauf	University of California, Irvine
Dr Gino K In	USC Norris Comprehensive Cancer Center
Dr Georgia M Beasley	Duke Cancer Institute
Dr Trisha M Wise-Draper	University of Cincinnati Cancer Center
Dr Robert McWilliams	Mayo Clinic - Minnesota
Dr Mahesh Seetharam	Mayo Clinic - Arizona
Dr Issam Makhoul	CARTI Cancer Center
Dr Michael K Wong	Roswell Park Comprehensive Cancer Center
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Dr Antoine Italiano	Institut Bergonié
Dr Mona Amini-Adle	Centre Léon Bérard
Dr Judith Michels	Institut Gustave Roussy
Dr Ana María Arance Fernandez	Hospital Clinic Barcelona
Dr Eva Muñoz Couselo	Hospital Universitari Vall d'Hebron
Dr Pablo Cerezuela	Hospital Universitario Virgen de la Arrixaca
Dr Miguel Sanmamed	Clinica Universitaria de Navarra
Dr Maria Luisa Limon	Hospital Universitario Virgen del Rocio
Dr Mark R Middleton	Oxford University Hospital
Dr Kevin Harrington	Royal Marsden Hospital
Dr Joseph J Sacco	Clatterbridge Cancer Centre
Dr Adel Samson	University of Leeds
Dr Patricia Roxburgh	The Beatson West of Scotland Cancer Center
Dr Dirk Schadendorf	University Hospital Essen

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