Research To Practice

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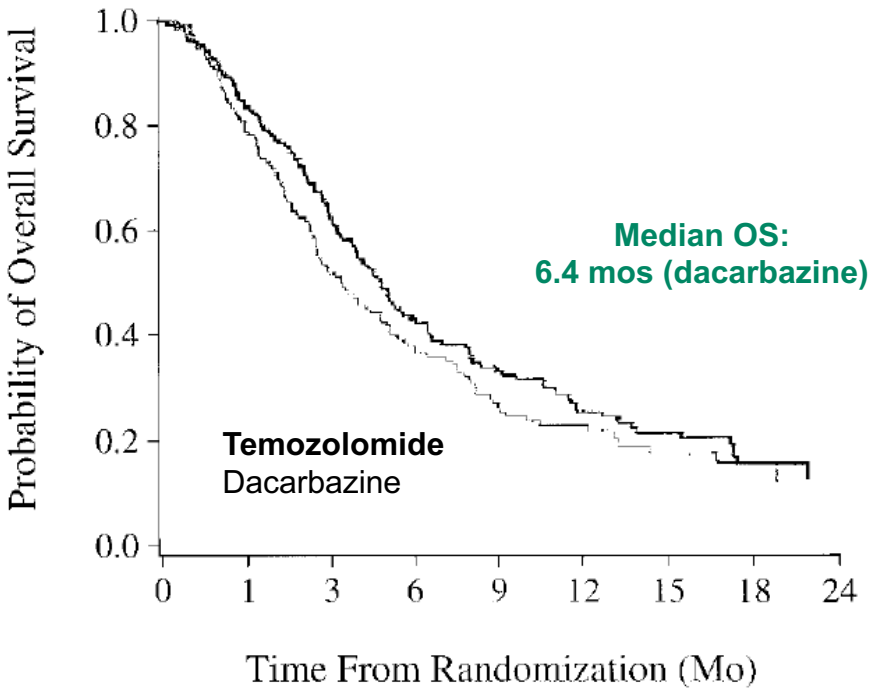
RTP
RESEARCH
TO PRACTICE

The Moving Overall Survival Bar for Metastatic Melanoma

Pre-Checkpoint Blockade/ BRAF-Targeted Therapy: Chemotherapy

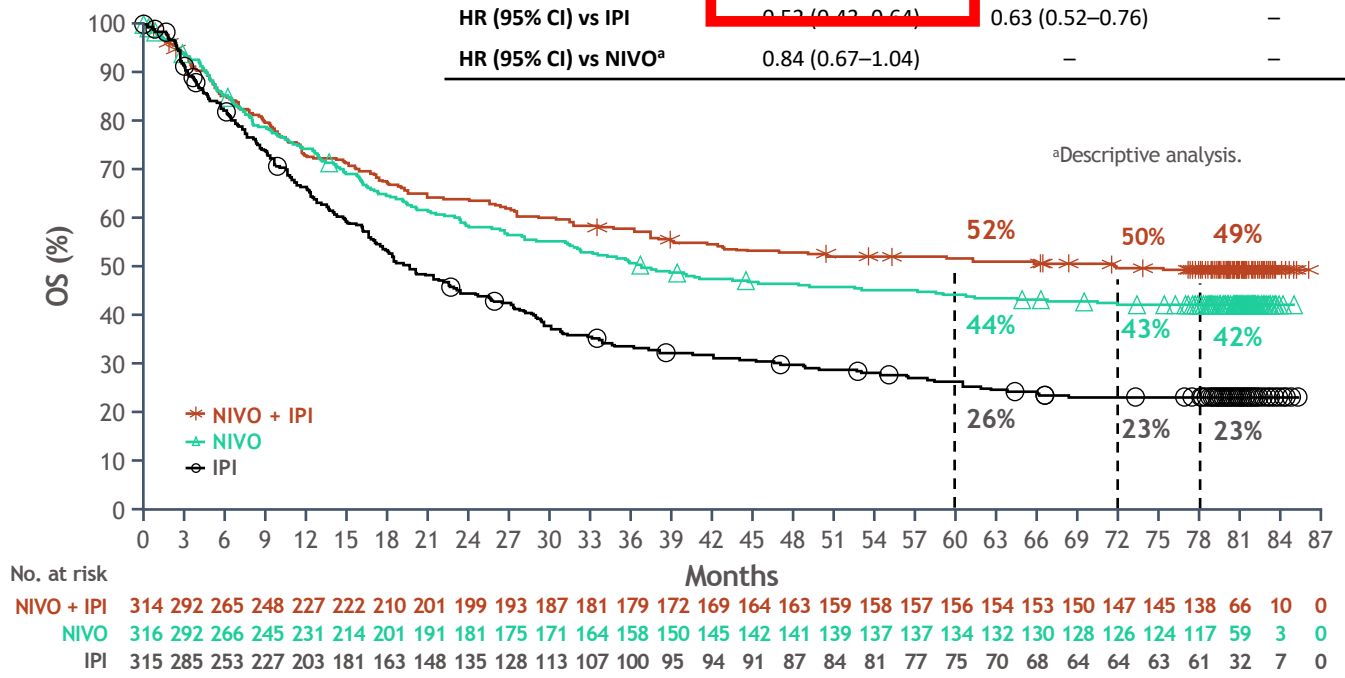


(Middleton MR et al. *J Clin Oncol* 2000)

PD-1 +/- CTLA-4 Inhibition

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.84 (0.67–1.04)	–	–

[a]Descriptive analysis.



(Wolchok et al. *ASCO* 2021)

COLUMBUS Part 1: 5-Year PFS, OS, and ORR

Columbus Part 1

Randomized 1:1:1

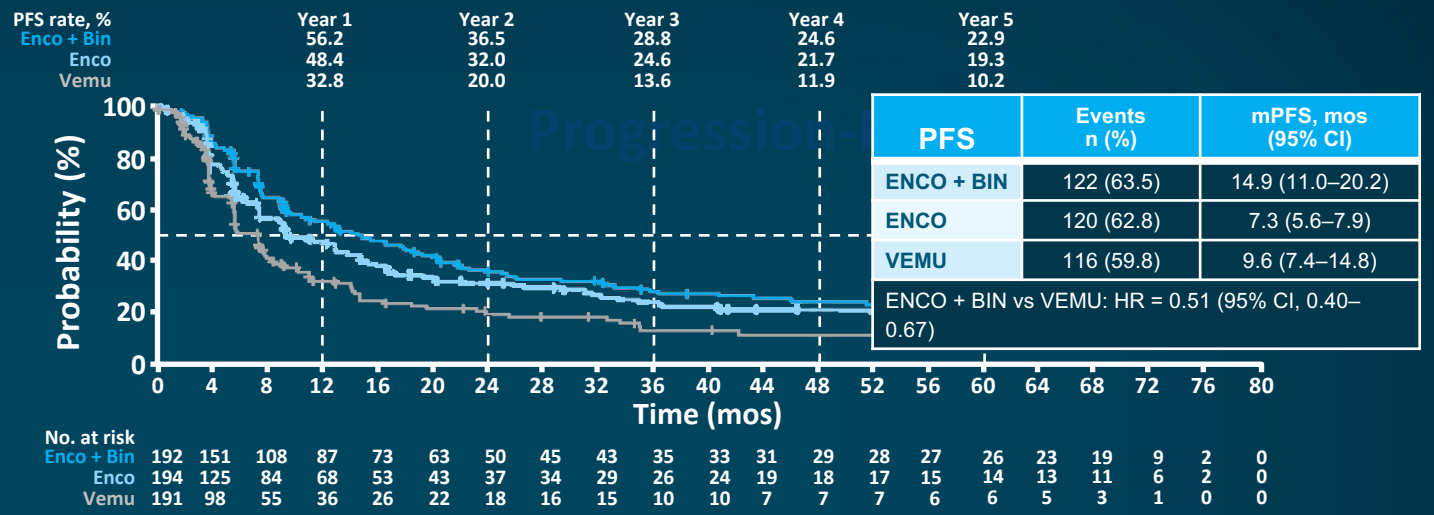
Encorafenib (ENCO) 450 mg QD + **Binimetinib (BIN)** 45 mg BID n = 192

Vemurafenib (VEMU) 960 mg BID n = 191

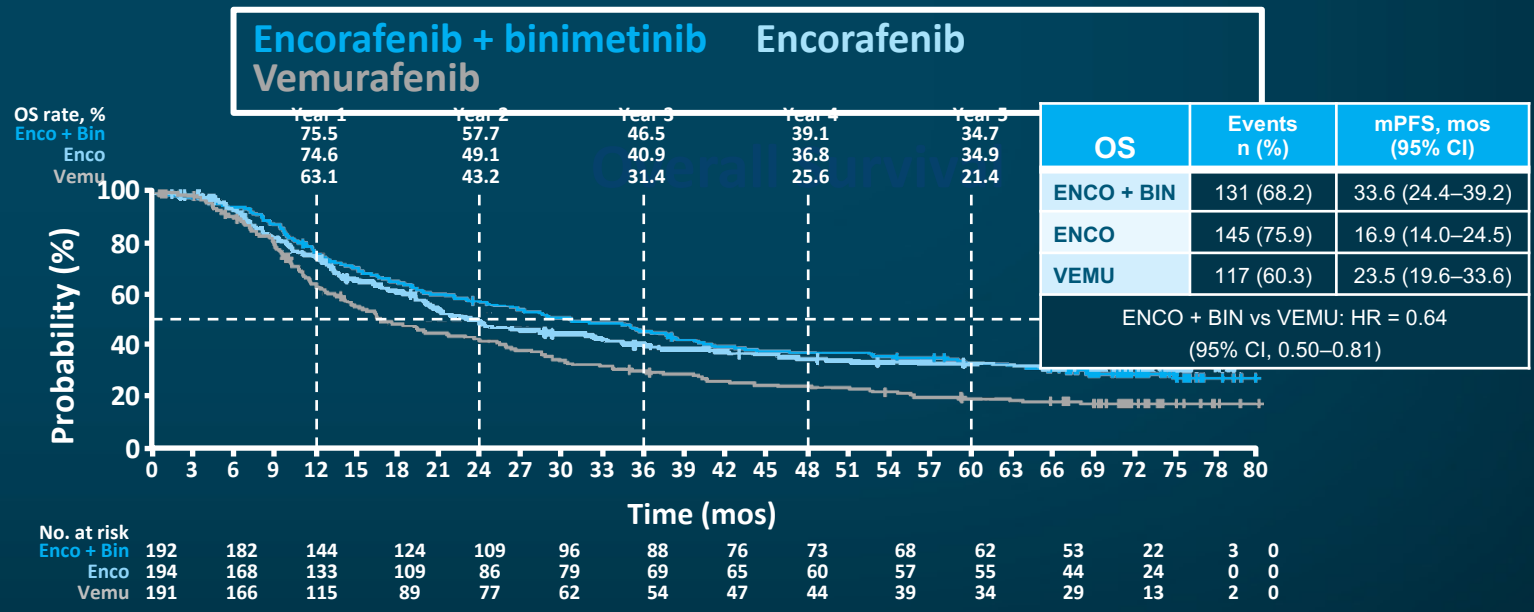
ENCO 300 mg QD n = 194

Overall response rate	ENCO + BIN (n = 192)	VEMU (n = 191)	ENCO (n = 194)
ORR	64.1%	40.8%	51.5%
95% CI	56.8–70.8	33.8–48.2	44.3–58.8

Median follow-up for all patients
PFS = 40.8 mos; OS = 70.4 mos



PFS	Events n (%)	mPFS, mos (95% CI)
ENCO + BIN	122 (63.5)	14.9 (11.0–20.2)
ENCO	120 (62.8)	7.3 (5.6–7.9)
VEMU	116 (59.8)	9.6 (7.4–14.8)
ENCO + BIN vs VEMU: HR = 0.51 (95% CI, 0.40–0.67)		



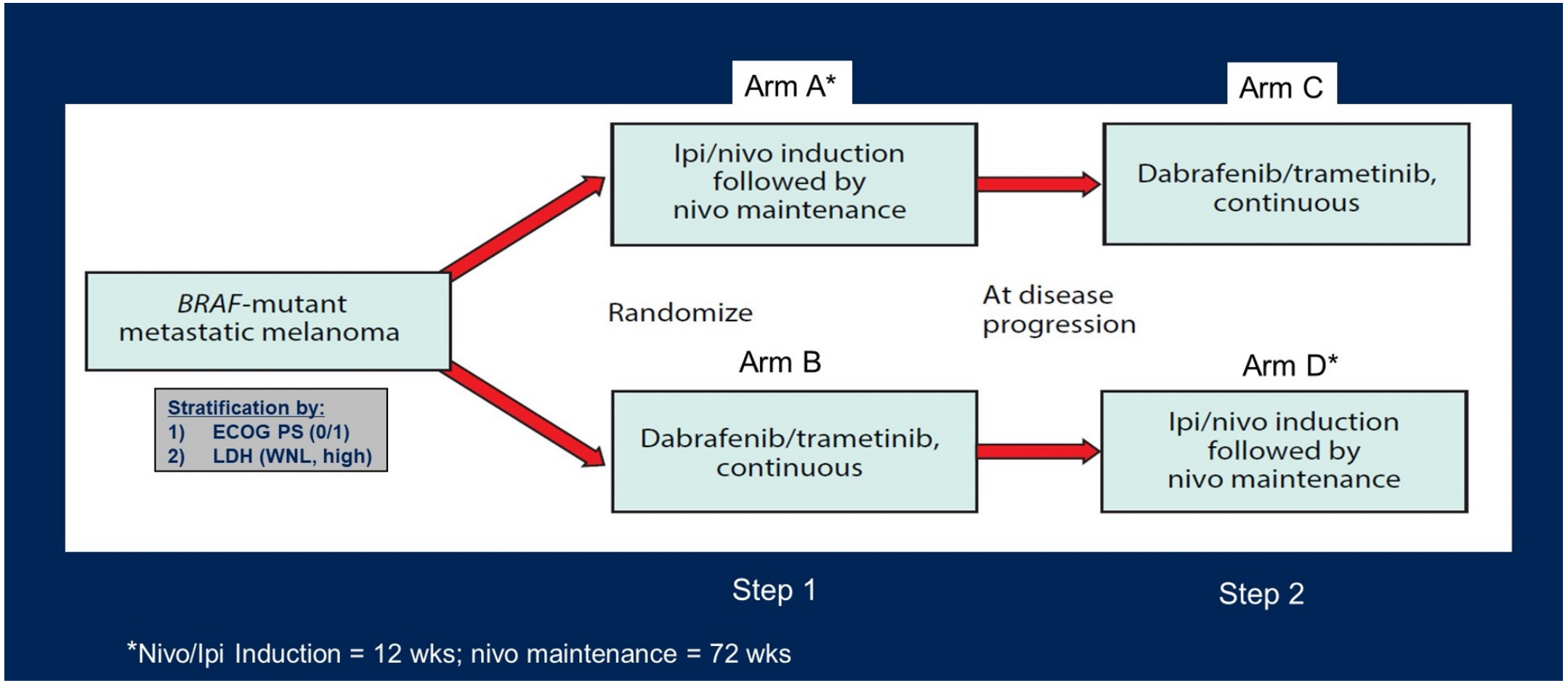
OS	Events n (%)	mPFS, mos (95% CI)
ENCO + BIN	131 (68.2)	33.6 (24.4–39.2)
ENCO	145 (75.9)	16.9 (14.0–24.5)
VEMU	117 (60.3)	23.5 (19.6–33.6)
ENCO + BIN vs VEMU: HR = 0.64 (95% CI, 0.50–0.81)		

BID = twice daily; QD = once daily.

Dummer R, et al. *J Clin Oncol.* 2022;40:4178-4188. Dummer R, et al. ESMO 2021; abstract 9507.

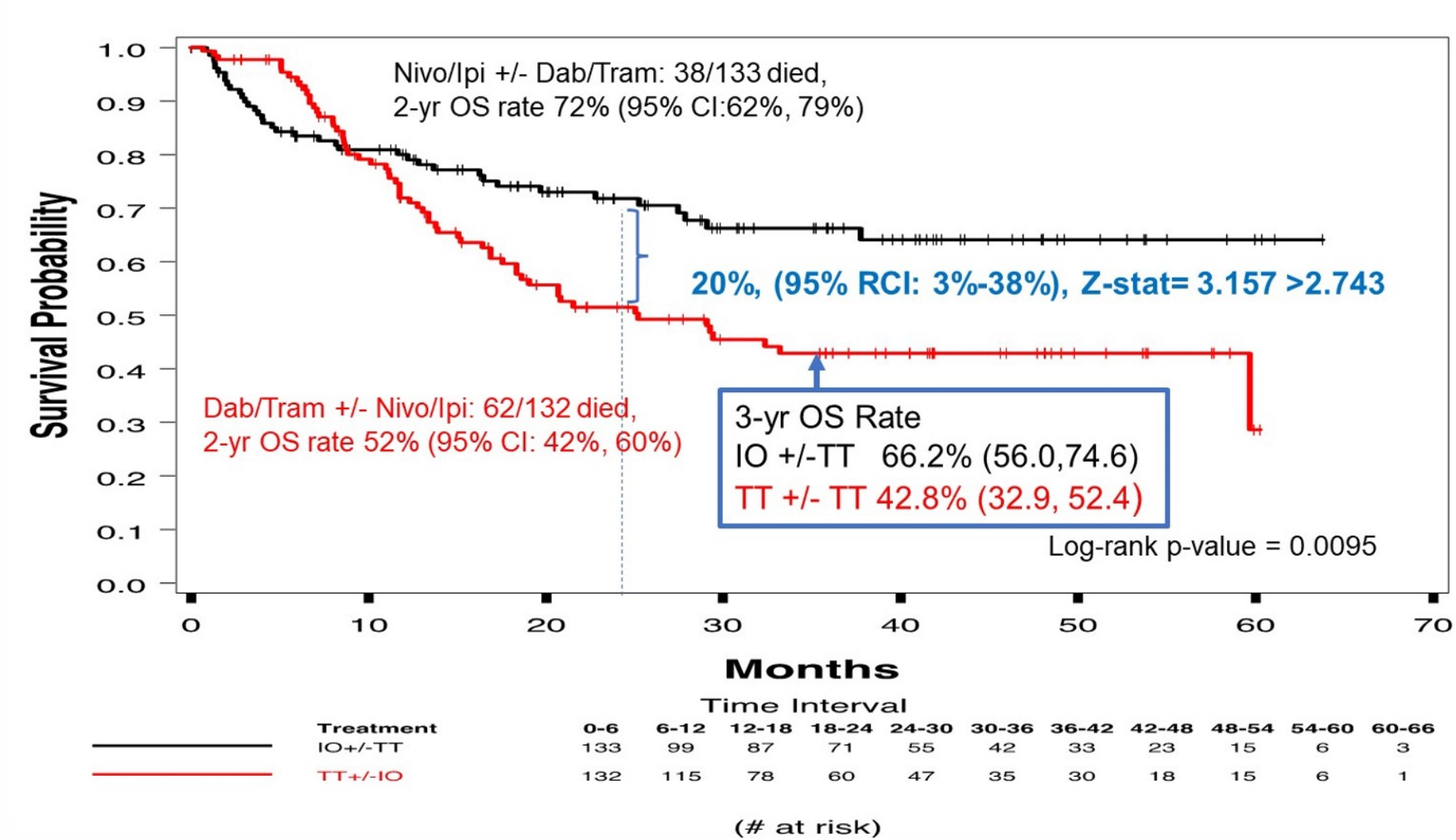
**Experimental arms not FDA-approved for the treatment of melanoma.*

DREAMseq: Sequencing Immune Checkpoint Inhibitors and BRAF-Targeted Therapies in BRAF-Mutant Advanced Melanoma



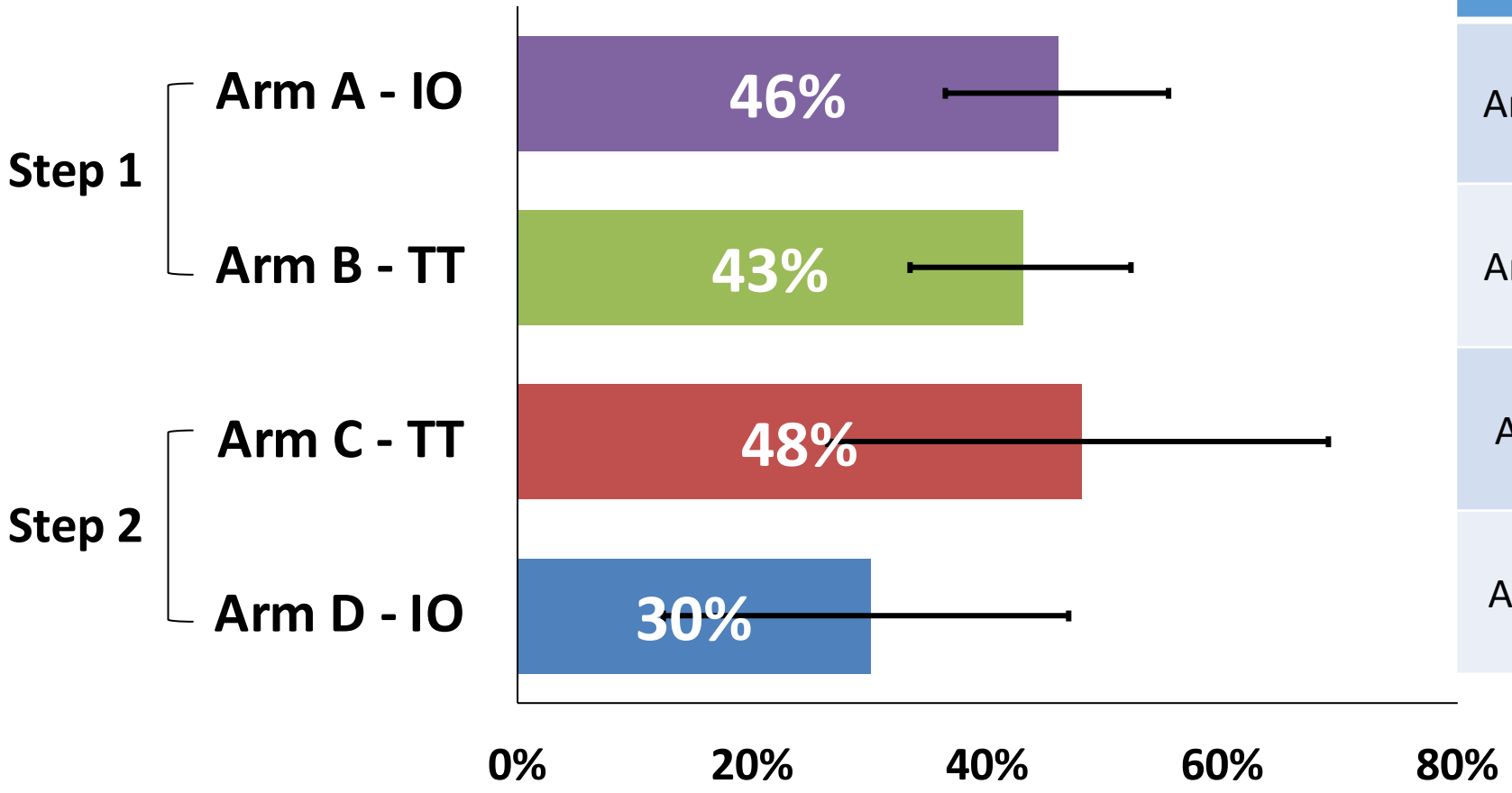
Atkins MB. ASCO 2022

DREAMseq: Overall Survival



Atkins MB. ASCO 2022; Atkins J Clin Oncol 2022

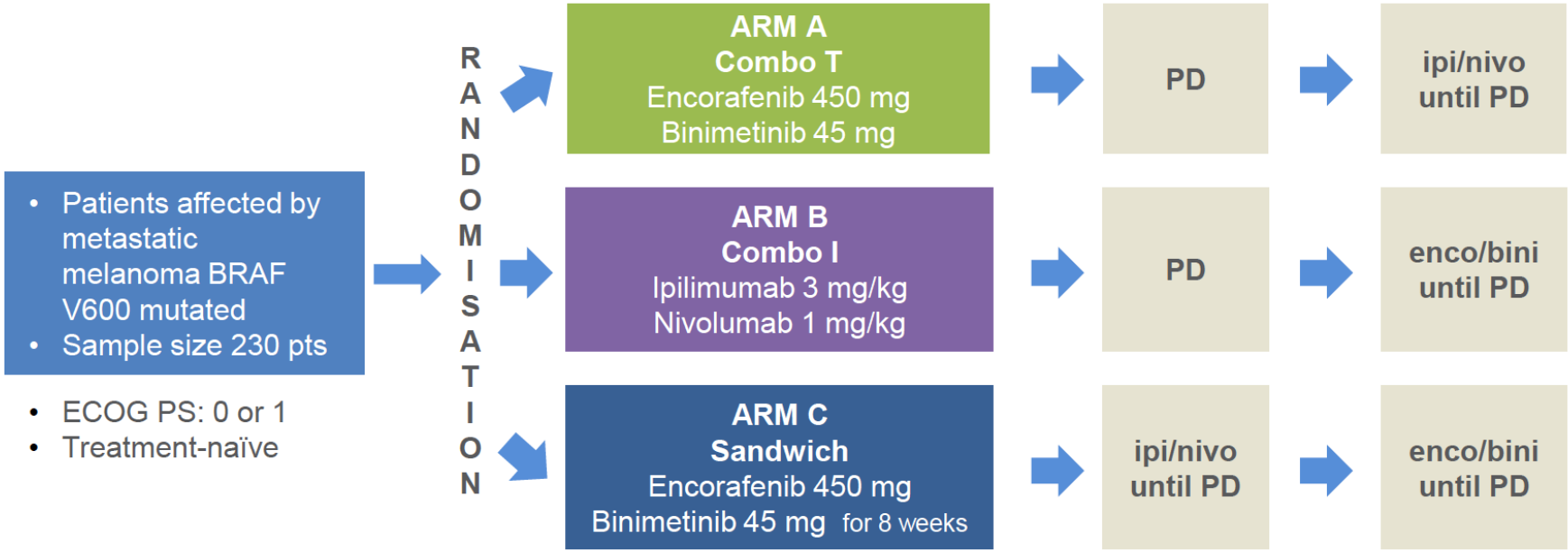
DREAMseq: Response by Treatment Arm



Median PFS Mos (95% CI)	
Arm A (n=133)	**11.8** (5.9, 33.5)
Arm B (n=132)	**8.5** (6.5, 11.3)
Arm C (n=27)	**9.9** (8.3, 20.8)
Arm D (n=46)	**2.9** (2.6, 8.9)

Atkins J Clin Oncol 2022

SECOMBIT Phase II Study: Sequencing Immunotherapy in BRAF-Mutant Advanced Melanoma



Primary endpoint:
- OS

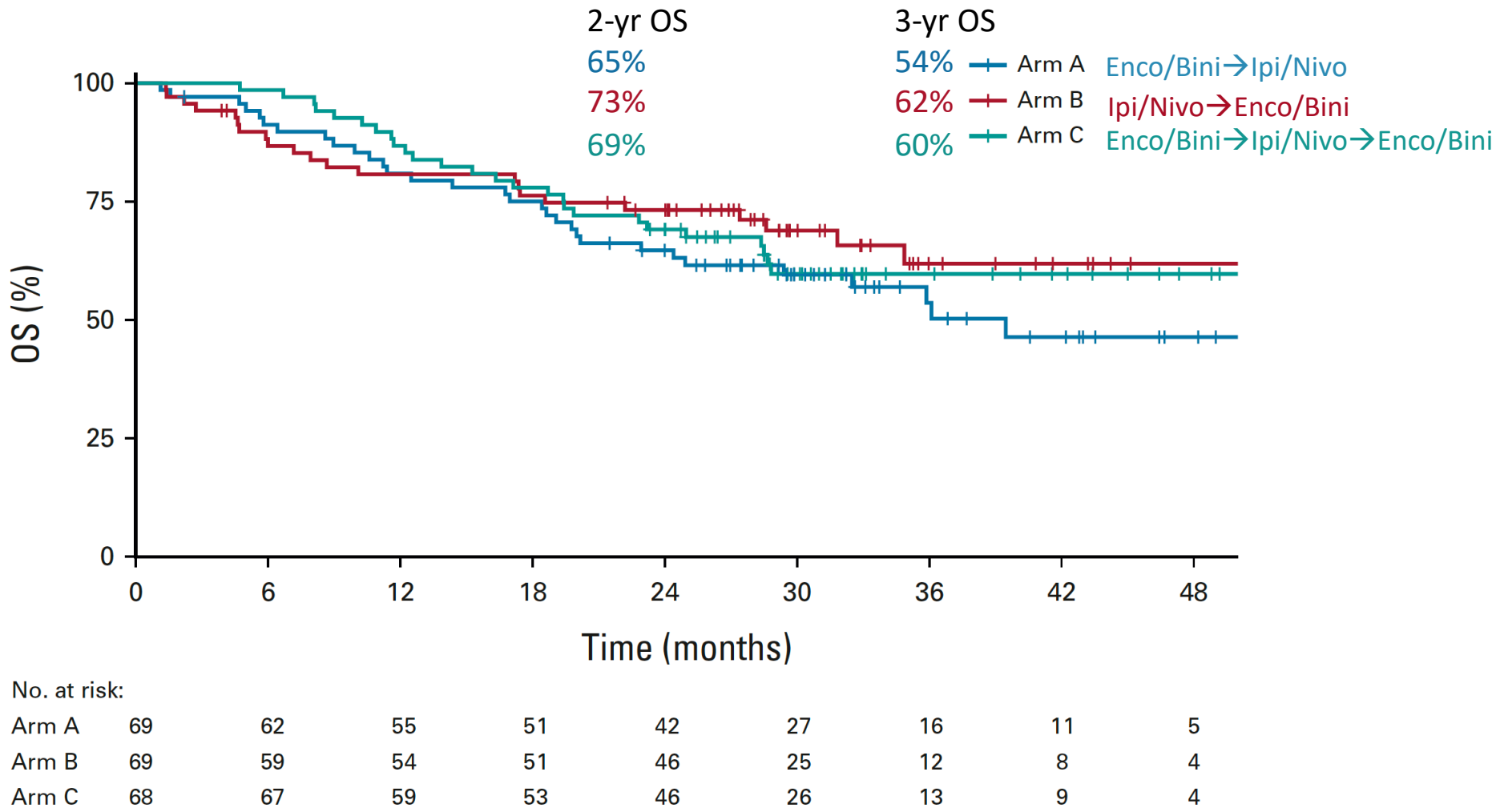
Secondary endpoints:
- PFS
- Total PFS
- Time to second progression
- % patients alive at 2–3 years
- Best ORR
- DOR

Stratification Factors:
- IIIb/c – M1a – M1b
- M1c with LDH ≤ 2ULN
- M1c with elevated LDH > 2 ULN

Current analysis: First patient randomized November 2016. Database lock 31st May 2021: 24- and 36-months PFS rate, total PFS at 24- and 36 months, OS at 24- and 36 months, Safety report. Duration of follow-up: the median follow-up estimated with the reverse Kaplan-Meier method is **32.2 months** (IQR= 27.9-41.6).

Ascierto PA et al. ESMO 2021;Abstract LBA1997.

SECOMBIT: Survival by Treatment Arm



Ascierto PA et al. *J Clin Oncol* 2023 Jan;41(2):212-221.

Durable clinical outcomes in patients with advanced melanoma who were progression-free at 3 years on nivolumab ± ipilimumab or ipilimumab in CheckMate 067

F. Stephen Hodi,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] Christopher D. Lao,[6] C. Lance Cowey,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Paola Queirolo,[11] Michael Smylie,[12] Marcus O. Butler,[13] Andrew G. Hill,[14] Iván Márquez-Rodas,[15] Corey Ritchings,[16] Leon A. Sakkal,[16] Peter Wang,[16] Jedd D. Wolchok,[17*] James Larkin[18*]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; [3]University of Colorado Cancer Center, Aurora, CO; [4]Aix Marseille University, Hôpital de la Timone, Marseille, France; [5]Maria Sklodowska-Curie National Institute of Oncology Center, Warsaw, Poland; [6]University of Michigan, Rogel Cancer Center, Ann Arbor, MI; [7]Texas Oncology-Baylor Charles A. Sammons Cancer Center

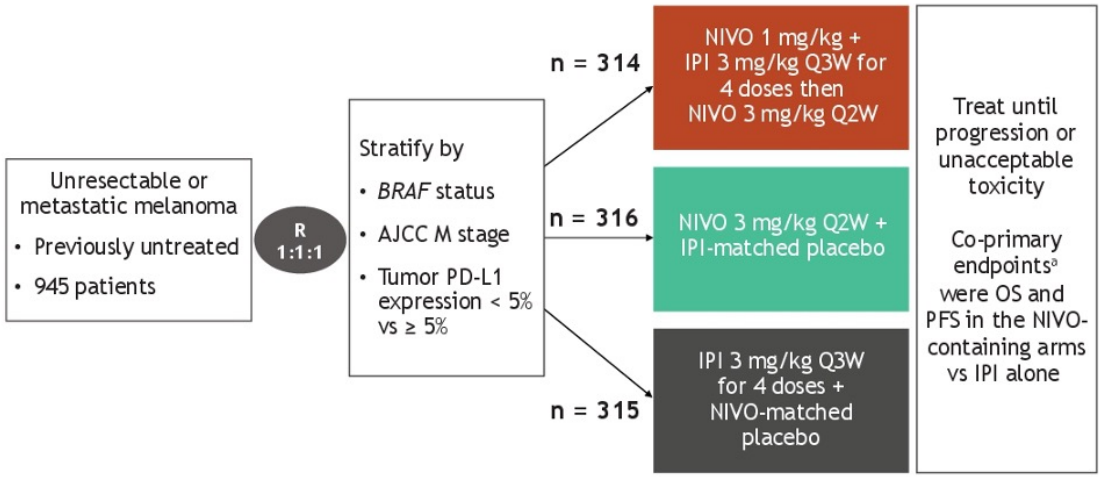
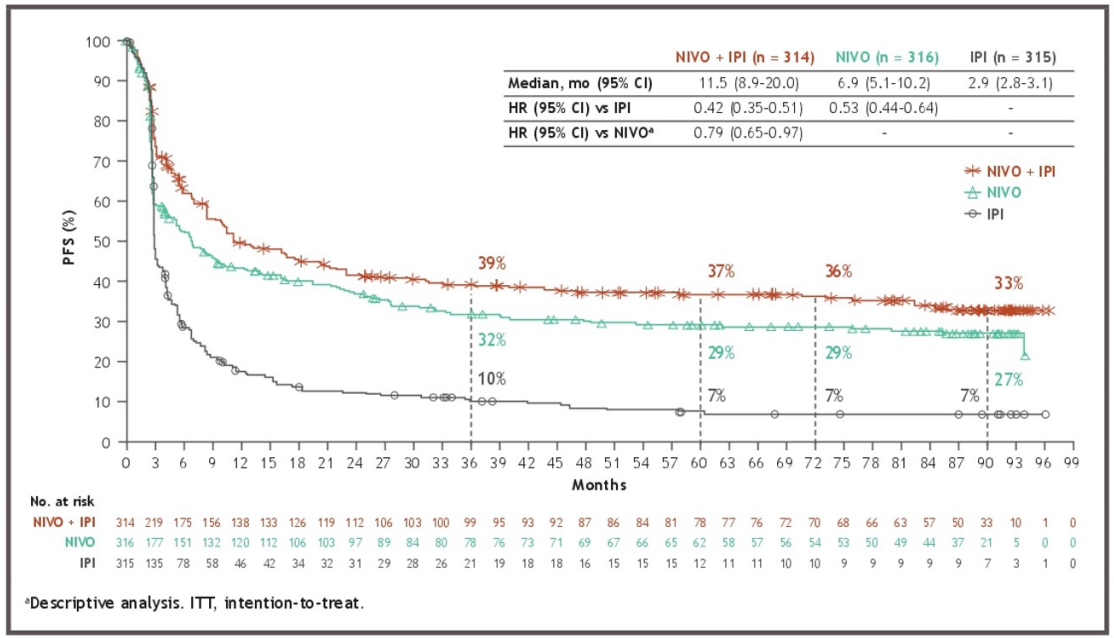
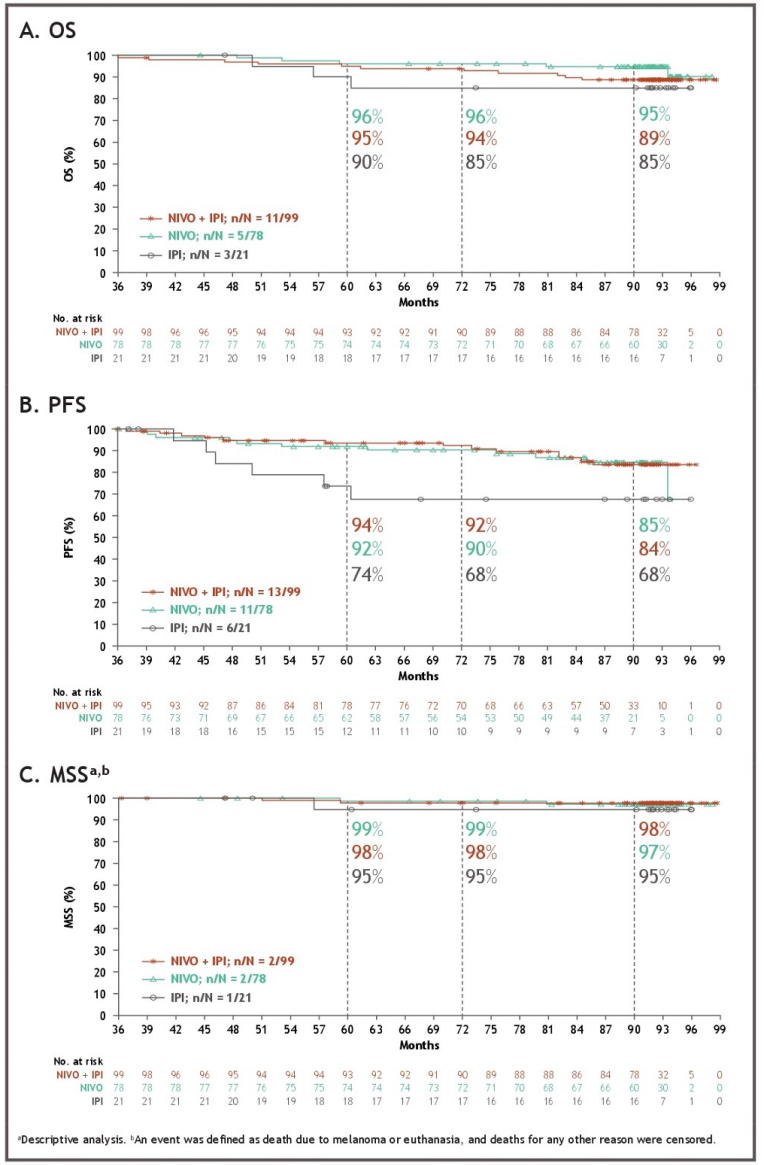


Figure 1. PFS in the ITT population of CheckMate 067[2]



	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	11.5 (8.9-20.0)	6.9 (5.1-10.2)	2.9 (2.8-3.1)
HR (95% CI) vs IPI	0.42 (0.35-0.51)	0.53 (0.44-0.64)	-
HR (95% CI) vs NIVO[a]	0.79 (0.65-0.97)	-	-

[a]Descriptive analysis. ITT, intention-to-treat.



[a]Descriptive analysis. [b]An event was defined as death due to melanoma or euthanasia, and deaths for any other reason were censored.

Wolchok ASCO 2023; Abstract 9542

Durable clinical outcomes in patients with advanced melanoma who were progression-free at 3 years on nivolumab ± ipilimumab or ipilimumab in CheckMate 067

F. Stephen Hodi,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] Christopher D. Lao,[6] C. Lance Cowey,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Paola Queirolo,[11] Michael Smylie,[12] Marcus O. Butler,[13] Andrew G. Hill,[14] Iván Márquez-Rodas,[15] Corey Ritchings,[16] Leon A. Sakkal,[16] Peter Wang,[16] Jedd D. Wolchok,[17]* James Larkin[18]*

- Patients with PFS at 3y in the NIVO-containing arms were less likely to receive subsequent systemic therapy than those treated with IPI alone (**Table 3**)
  - Subsequent systemic therapy was received by 4%, 5%, and 19% of patients treated with NIVO + IPI, NIVO, and IPI, respectively
- At a 7.5-year data cutoff, approximately 90% of patients in the NIVO-containing arms with PFS at 3y who were alive and in follow-up were treatment-free (**Figure 6**)

Conclusions

- This exploratory post hoc analysis suggested that PFS at 3y may be a useful surrogate for long-term MSS for NIVO + IPI or NIVO monotherapy
- In CheckMate 067, durable and sustained clinical benefit was observed for patients with PFS at 3y
  - 7.5-year MSS rates were 98%, 97%, and 95% for NIVO + IPI, NIVO, and IPI, respectively
  - Few deaths occurred overall, and only 5 deaths total across arms were related to melanoma
- Patients in the NIVO-containing arms spent the majority of time treatment-free with approximately 90% off treatment and free of subsequent systemic therapy at 7.5 years
- Further investigation of patients with PFS at 3y may shed additional light on the appropriate frequency of imaging and follow-up visits for this patient population

Wolchok ASCO 2023; Abstract 9542

2023 ASCO® ANNUAL MEETING

Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047

Hussein A. Tawbi,[1] F. Stephen Hodi,[2] Evan J. Lipson,[3] Dirk Schadendorf,[4] Paolo Antonio Ascierto,[5] Luis Matamala,[6] Erika Castillo Gutiérrez,[7] Piotr Rutkowski,[8] Helen Gogas,[9] Christopher D. Lao,[10] Juliana Janoski De Menezes,[11] Stéphane Dalle,[12] Ana Maria Arance,[13] Jean-Jacques Grob,[14] Barbara Ratto,[15] Saima Rodriguez,[15] Yuanfang Xu,[15] Peter Wang,[15] Sonia Dolfi,[15] Georgina V. Long[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [4]University of Essen and the German Cancer Consortium, Essen, Germany; [5]Istituto Nazionale dei Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; [6]Instituto Oncológico Fundación Arturo López Pérez and Department of Oncology, Instituto Nacional del Cáncer, Santiago, Chile; [7]FAICIC Clinical Research, Veracruz, Mexico; [8]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]National and Kapodistrian University of Athens, Athens, Greece; [10]Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI; [11]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [12]Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; [13]Hospital Clinic Barcelona and IDIBAPS, Barcelona, Spain; [14]Aix-Marseille University, CHU Timone, Marseille, France; [15]Bristol Myers Squibb, Princeton, NJ; [16]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Abstract number 9502

Study design

- RELATIVITY-047 is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria
- Previously untreated, unresectable, or metastatic melanoma
- ECOG PS 0–1

R 1:1

NIVO 480 mg + RELA 160 mg FDC IV Q4W

NIVO 480 mg IV Q4W

Primary endpoint
- PFS by BICR[a]

Secondary endpoints
- OS[b]
- ORR by BICR[c]

Stratified by: LAG-3,[d] PD-L1,[e] *BRAF,* and AJCC v8 M stage

Endpoints were tested in hierarchy: PFS → OS → ORR

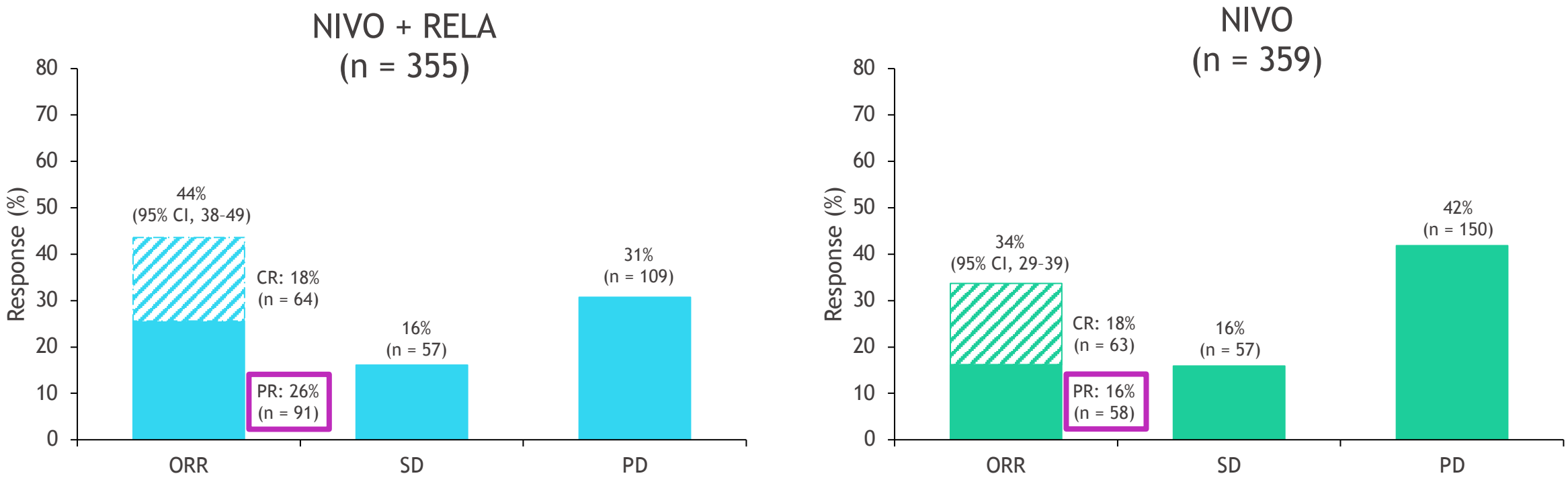
Database lock	**March 9, 2021**	**October 28, 2021**	**October 27, 2022**
Min. follow-up[f]	1.3 months	8.7 months	21.0 months
Median follow-up	13.2 months	19.3 months	25.3 months
Endpoint(s)	PFS per BICR	OS, ORR per BICR, and updated PFS per BICR	Updated PFS per BICR, OS, and ORR per BICR

RELATIVITY-047 (NCT03470922).
[a]First tumor assessment (RECIST v1.1) was performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. [b]OS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75. [c]ORR could not be formally tested and was descriptively analyzed. [d]LAG-3 expression on immune cells (1%) was determined by an analytically validated IHC assay (Labcorp, Burlington, NC, USA). [e]PD-L1 expression on tumor cells (1%) was determined by a validated Agilent Dako PD-L1 IHC 28-8 pharmDx test (Agilent, Santa Clara, CA, USA). [f]Minimum potential follow-up was defined as the time from last patient randomized to last patient, last visit.

Tawbi ASCO 2023;Abstract 9502

Best overall response per BICR

Updated secondary endpoint



- NIVO + RELA vs NIVO ORR difference of 9.8% (95% CI, 2.8–16.8)
- Median duration of response was not reached in both the NIVO + RELA (NR [95% CI, 39.4–NA]) and NIVO (NR [95% CI, 39.8–NA]) arms

RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. 26 patients (7.3%) in the NIVO + RELA arm and 26 patients (7.2%) in the NIVO arm were classified as unable to determine.

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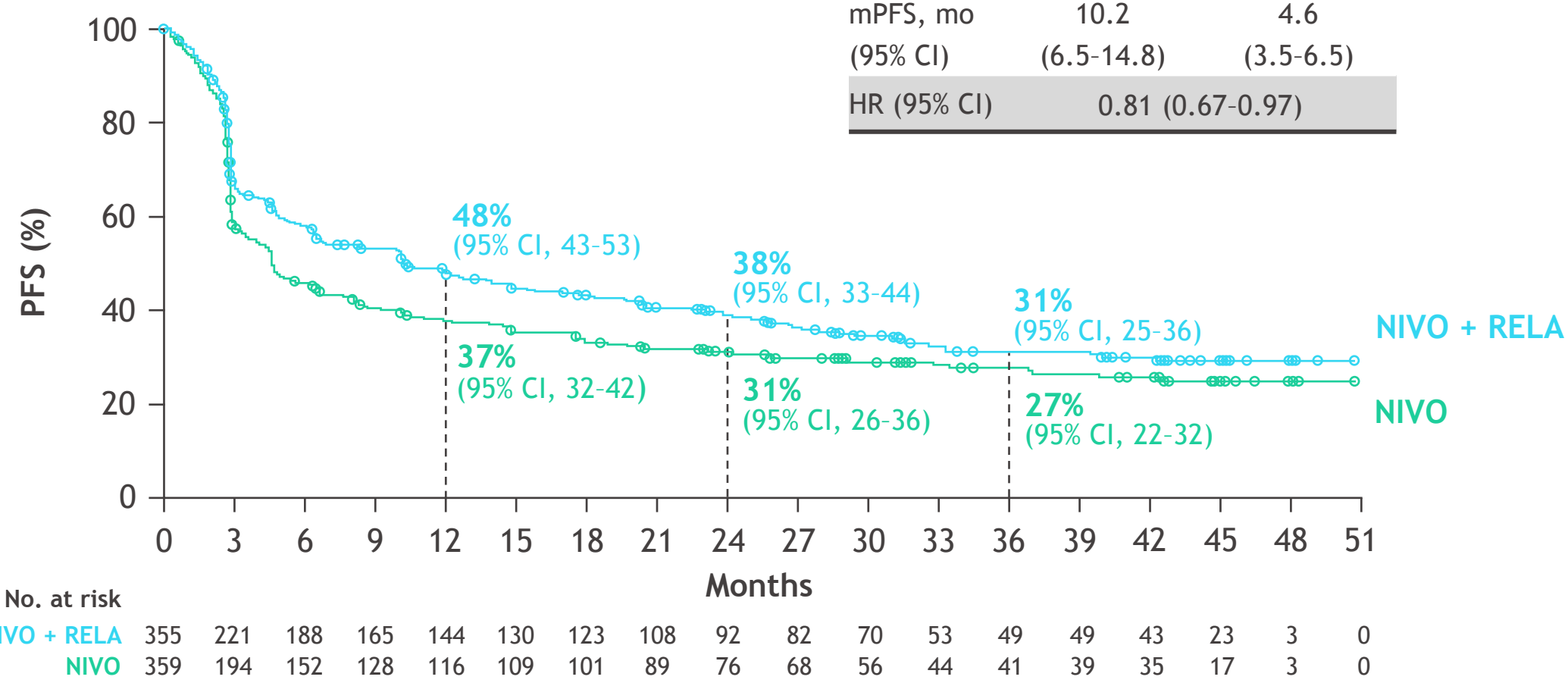
PFS by BICR

Updated primary endpoint

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo	10.2	4.6
(95% CI)	(6.5-14.8)	(3.5-6.5)
HR (95% CI)	0.81 (0.67-0.97)	



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

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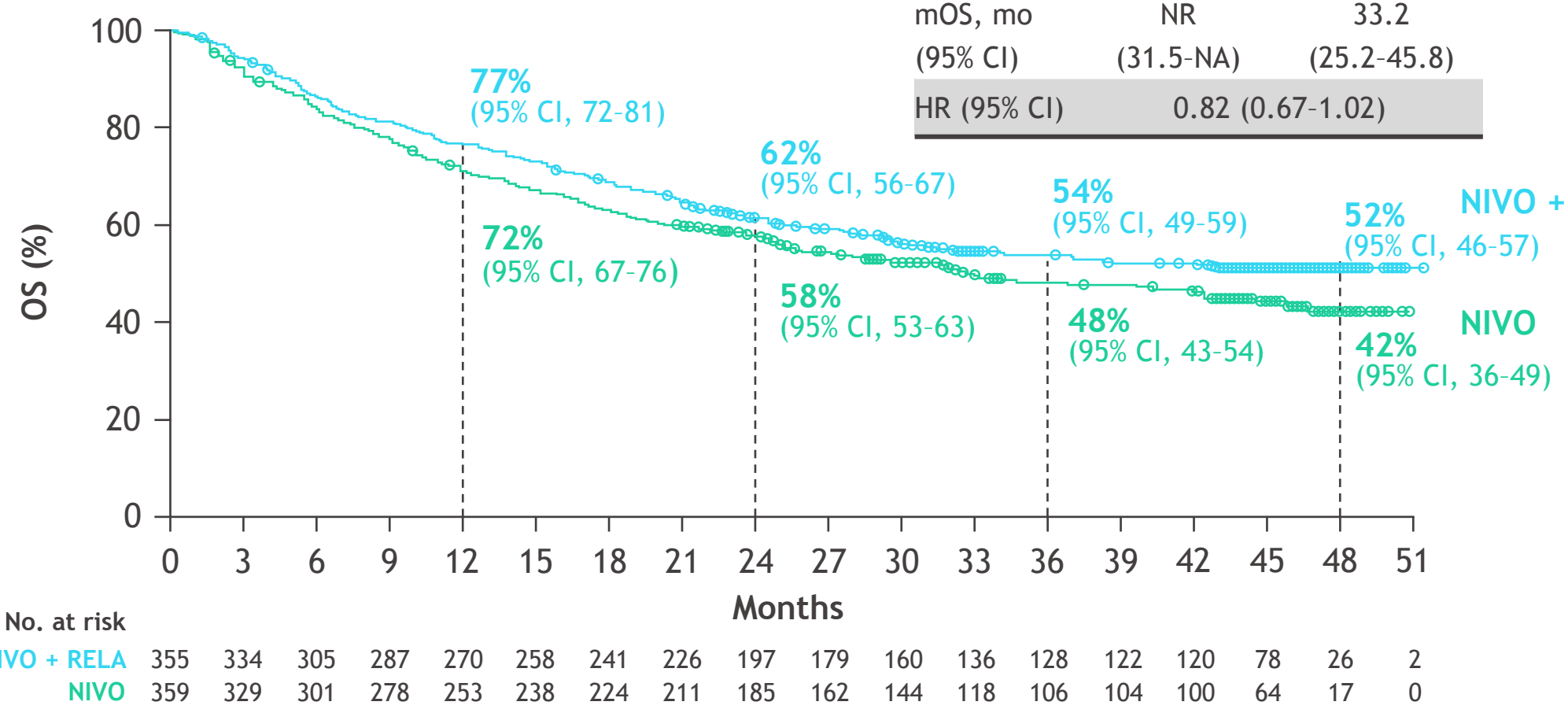
OS

Updated secondary endpoint

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo	NR	33.2
(95% CI)	(31.5-NA)	(25.2-45.8)
HR (95% CI)	0.82 (0.67-1.02)	



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

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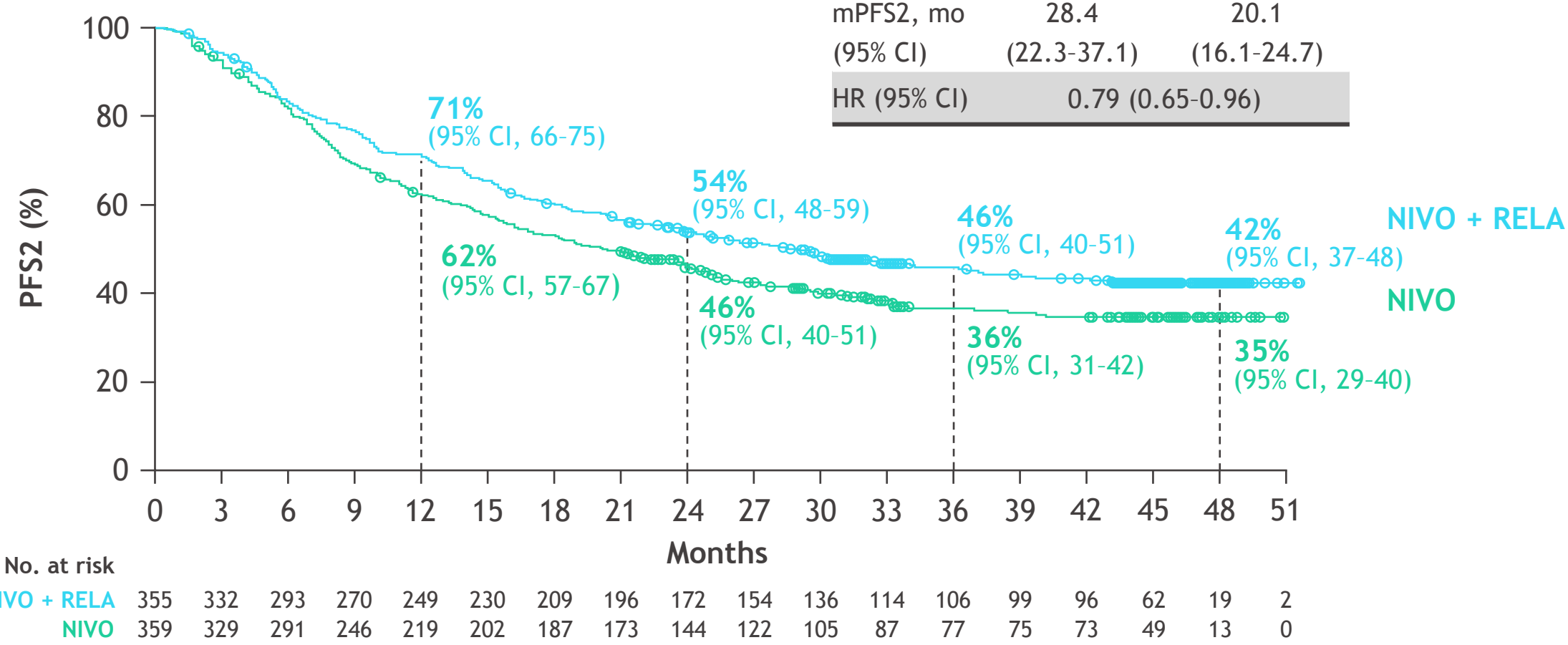
Progression-free survival 2 (PFS2)

Investigator assessed

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS2, mo	28.4	20.1
(95% CI)	(22.3-37.1)	(16.1-24.7)
HR (95% CI)	0.79 (0.65-0.96)	



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Progression-free survival 2 (PFS2) was an exploratory analysis and defined as the time from randomization to progression date after the next line of therapy, per investigator assessment, or to death from any cause.

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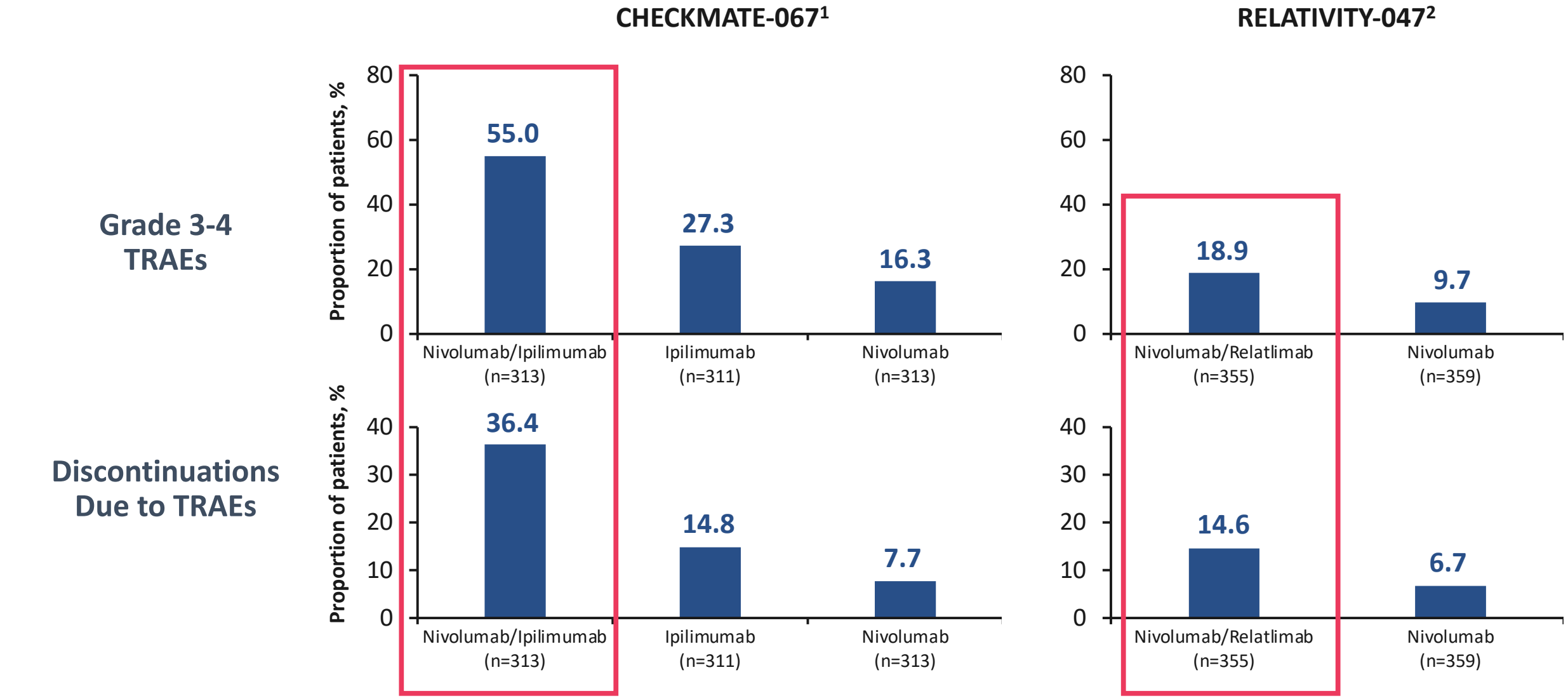
RELATIVITY-047: Subgroup Comparisons HR vs Nivolumab monotherapy

CM 067		Rela 047[a,b]	
PFS Nivo Ipi vs Nivo	HR	PFS Nivo Rela vs Nivo	HR
BRAF Mutant	0.59	BRAF Mutant	0.77
Wild Type	0.89	Wild Type	0.78
PDL-1. ≥ 1%	0.90	PDL-1. ≥ 1%	0.96
≤ 1%	0.67	≤ 1%	0.68

a. Tawbi HA, et al. N Engl J Med 2022;386:24–34. b: Long GV et al. NEJM Evid 2023;2(4)

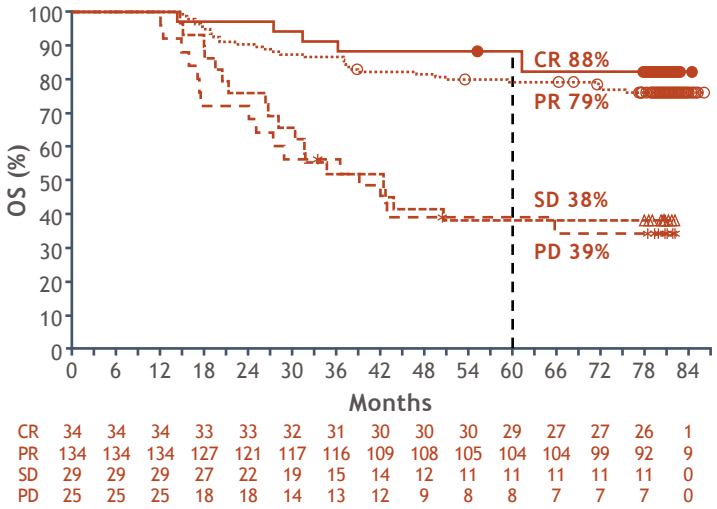
PD-1/LAG-3 Blockade May Be Associated With Fewer Severe Adverse Events and Discontinuations Due to TRAEs



1. Larkin J et al. *N Engl J Med*. 2015;373:23-34. 2. Tawbi HA et al. *N Engl J Med*. 2022;386:24-34.

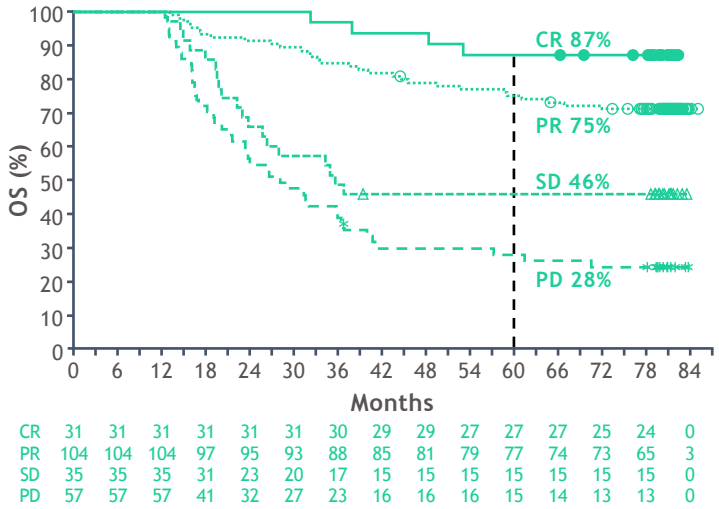
OS by best overall response, 12-month landmark analysis[a]

NIVO + IPI



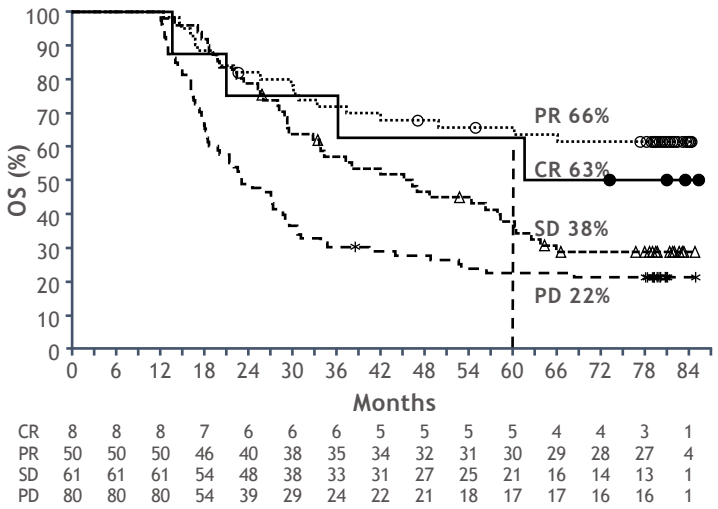
CR	34	34	34	33	33	32	31	30	30	30	29	27	27	26	1
PR	134	134	134	127	121	117	116	109	108	105	104	104	99	92	9
SD	29	29	29	27	22	19	15	14	12	11	11	11	11	11	0
PD	25	25	25	18	18	14	13	12	9	8	8	7	7	7	0

NIVO



CR	31	31	31	31	31	31	30	29	29	27	27	27	25	24	0
PR	104	104	104	97	95	93	88	85	81	79	77	74	73	65	3
SD	35	35	35	31	23	20	17	15	15	15	15	15	15	15	0
PD	57	57	57	41	32	27	23	16	16	16	15	14	13	13	0

IPI



CR	8	8	8	7	6	6	6	5	5	5	5	4	4	3	1
PR	50	50	50	46	40	38	35	34	32	31	30	29	28	27	4
SD	61	61	61	54	48	38	33	31	27	25	21	16	14	13	1
PD	80	80	80	54	39	29	24	22	21	18	17	17	16	16	1

- **Patients with a best overall response of a CR, PR, SD, or PD at 12 months were followed for OS**

[a]To address guarantee-time bias, landmark analysis excluded patients who had an event during the first 12 months.
PD, progressive disease.

Wolchok ASCO 2021;Abstract 9506

PARIS 2022 ESMO congress

Phase 1 study of fianlimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma

Omid Hamid,[1] Karl Lewis,[2] Amy Weise,[3] Meredith McKean,[4] Kyriakos P Papadopoulos,[5] John Crown,[6] Tae Min Kim,[7] Nehal J Lakhani,[8] John Kaczmar,[9] Ragini Kudchadkar,[10] Alexander Spira,[11] Guilherme Rabinowits,[12] Kevin Kim,[13] Richard Carvajal,[14] Stephen Williamson,[15] Ella Ioffe,[16] Shuquan Chen,[16] Jayakumar Mani,[16] Vladimir Jankovic,[16] Laura Brennan,[16] Glenn Kroog,[16] Tasha Sims,[16*] Israel Lowy,[16] Giuseppe Gullo[16]

[1]The Angeles Clinical and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [2]University of Colorado Hospital, CO, USA; [3]Henry Ford Hospital, Detroit, MI, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA; [5]START San Antonio, San Antonio, TX, USA; [6]St Vincent's University Hospital, Dublin, Ireland; [7]Seoul National University Hospital, Seoul, South Korea; [8]START Midwest, Grand Rapids, MI, USA; [9]MUSC Hollings Cancer Center, North Charleston, SC, USA; [10]Emory University School of Medicine, Atlanta GA, USA; [11]Virginia Cancer Specialists, Fairfax, VA, USA; [12]Miami Cancer Institute, Miami, FL, USA; [13]Sutter Health Research Enterprise, San Francisco, CA, USA; [14]Columbia University Medical Center, New York, NY, USA; [15]University of Kansas Medical Center, Fairway, KS, USA; [16]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

*Formerly with Regeneron Pharmaceuticals, Inc.

Tumour response among anti–PD-(L)1–naive patients (cohorts 6 + 15)†

% (n), unless otherwise stated	Anti–PD-(L)1 naive† Cohort 6 (N=40)	Anti–PD-(L)1 naive† Cohort 15 (N=40)	Cohorts 6 + 15 (N=80)
ORR, % (95% CI)	**62.5 (45.8, 77.3)**	**65 (48.3, 79.4)**	**63.8 (52.2, 74.2)**
Complete response	15.0 (6)	2.5 (1)	8.8 (7)
Partial response	47.5 (19)	62.5 (25)	55.0 (44)
Stable disease	17.5 (7)	15.0 (6)	16.3 (13)
Progressive disease	15.0 (6)	15.0 (6)	15.0 (12)
NE	5.0 (2)	5.0 (2)	5.0 (4)
DCR	80.0 (32)	80.0 (32)	80.0 (64)
KM-estimated PFS, median (95% CI), months	**24 (4.2, NE)**	**NR (7.5, NE)**	**24 (9.9, NE)**
DOR, median (95% CI), months	NR (11.9, NE)	NR (6.3, NE)	NR (22.6, NE)
ORR: baseline LDH, n/N1 (%)			
LDH > ULN	10/17 (58.8)	6/11 (54.5)	16/28 (57.1)
LDH normal	15/23 (65.2)	18/24 (75.0)	33/47 (70.2)
ORR: liver metastasis, n/N2 (%)			
Yes	6/14 (42.9)	3/5 (60.0)	9/19 (47.4)
No	19/26 (73.1)	23/35 (65.7)	42/61 (68.9)

% (n), unless otherwise stated	Anti–PD-(L)1 naive† Cohort 6 (N=40)	Anti–PD-(L)1 naive† Cohort 15 (N=40)	Cohorts 6 + 15 (N=80)
Patients completed planned treatment‡	15.0 (6)	5.0 (2)	10.0 (8)
Ongoing treatment	15.0 (6)	52.5 (21)	33.8 (27)
Discontinued treatment	70.0 (28)	42.5 (17)	56.3 (45)
Disease progression	45.0 (18)	17.5 (7)	31.3 (25)
AE	15.0 (6)	15.0 (6)	15.0 (12)
Patient decision	5.0 (2)	0	2.5 (2)
Death	2.5 (1)	5.0 (2)	3.8 (3)
Physician decision	2.5 (1)	5.0 (2)	3.8 (3)
Duration of exposure, median (range), weeks	**37.1 (2–110)**	**24.2 (3–56)**	**30.9 (2–110)**

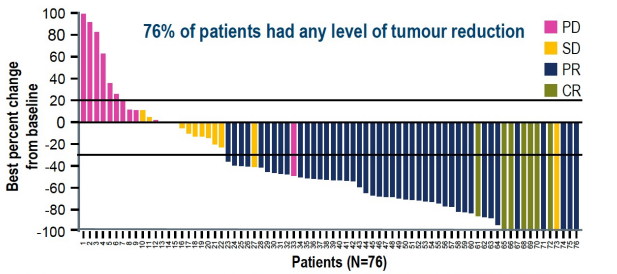
†Prior systemic therapies, including prior adjuvant therapies, excluded for cohort 15.
‡Planned treatment; 1 year + additional 1 year given based on investigator discretion.

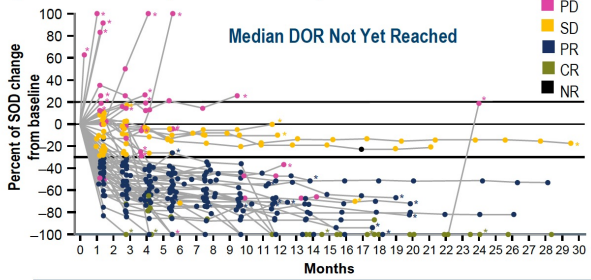
CI, confidence interval; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; LDH, lactase dehydrogenase; n, number; N1, proportion of patients with the listed LDH status; N2, proportion of patients with the listed liver metastasis status; NE, not evaluable; NR, not reached; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; ULN, upper limit of normal.

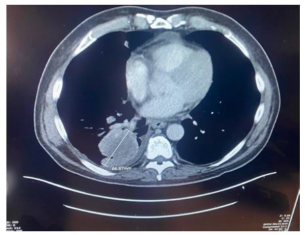
PARIS 2022 ESMO congress Dr Omid Hamid

Data cut-off date: 1 Jul 2022

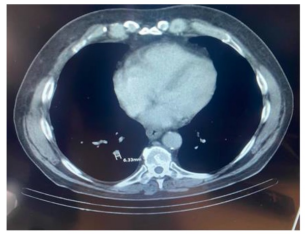
Efficacy overview among anti–PD-(L)1–naive patients (cohorts 6 + 15)†





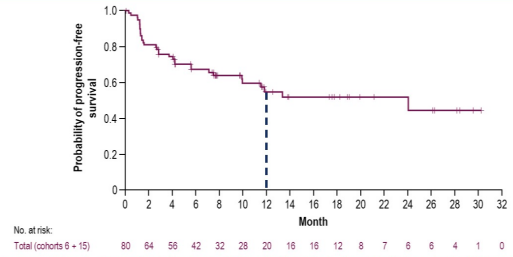


Baseline



On treatment (after 33 weeks)

Kaplan-Meier estimation of PFS by investigator assessment	Anti–PD-(L)1 naive† (N=80)
PFS, median (95% CI), months	24.0 (9.9, NE)
Estimated event-free probability at 12 months, % (95% CI)	55.0 (41.6, 66.5)



†Prior systemic therapies, including prior adjuvant therapies, excluded for cohort 15. ‡Patients with ongoing status (missing study complete status). CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; SOD, sum of diameters.

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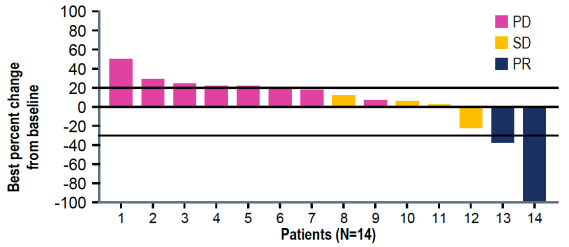
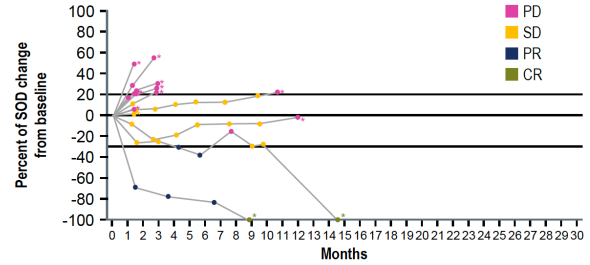
Data cut-off date: 1 Jul 2022

Clinical activity among anti–PD-(L)1–experienced patients (cohort 7)

% (n), unless otherwise stated	Total (N=15)
ORR, % (95% CI)	**13.3 (1.7–40.5)**
Complete response	0
Partial response	13.3 (2)
Stable disease	26.7 (4)
Progressive disease	53.3 (8)
NE	6.7 (1)
DCR	40.0 (6)
KM-estimated PFS, median (95% CI), months	1.5 (1.3–7.7)
DOR, median (95% CI), months	NR (3.4–NE)
ORR by LAG-3 expression, %	
<1%	NA
≥1%	18.2
ORR by PD-L1 expression, %	
<1%	18.2
≥1%	0





- Both patients that experienced CR had PD-L1 expression <1% and LAG-3 expression >1%.

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; LAG-3, lymphocyte activation gene-3; NA, not available; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; SOD, sum of diameters.

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Data cut-off date: 1 Jul 2022

2023 ASCO® ANNUAL MEETING

Significant durable response with fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: post adjuvant PD-1 analysis

Omid Hamid,[1] Karl D Lewis,[2] Amy Weise,[3] Meredith McKean,[4] Kyriakos P Papadopoulos,[5] John Crown,[6] Sajeve S Thomas,[7] Eugenia Girda,[8] John Kaczmar,[9] Kevin B Kim,[10] Nehal J Lakhani,[11] Melinda Yushak,[12] Tae Min Kim,[13] Guilherme Rabinowits,[14] Alexander Spira,[15] Jayakumar Mani,[16] Fang Fang,[16] Shuquan Chen,[16] JuAn Wang,[16] Laura Brennan,[16] Vladimir Jankovic,[16] Anne Paccaly,[16] Sheila Masinde,[16] Mark Salvati,[16] Matthew G Fury,[16] Israel Lowy,[16] Giuseppe Gullo[16]

[1]The Angeles Clinical and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [2]University of Colorado Cancer Center, Aurora, CO, USA; [3]Henry Ford Hospital, Detroit, MI, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA; [5]START, San Antonio, TX, USA; [6]St Vincent's University Hospital, Dublin, Ireland; [7]University of Florida Health Cancer Center at Orlando Health, Orlando, FL; [8]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [9]MUSC Hollings Cancer Center, North Charleston, SC, USA; [10]Center for Melanoma Research and Treatment, California Pacific Medical Center Research Institute, San Francisco, CA, USA; [11]START Midwest, Grand Rapids, MI, USA; [12]Department of Hematology and Medical Oncology at Emory University School of Medicine, Atlanta, GA, USA; [13]Seoul National University Hospital, Seoul, South Korea; [14]Department of Hematology and Oncology, Miami Cancer Institute/Baptist Health South Florida, Miami, FL, USA; [15]Virginia Cancer Specialists and US Oncology Research, Fairfax, VA, USA; [16]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Study design: three serial expansion cohorts in advanced melanoma setting

Treatment:
Fianlimab 1600 mg + cemiplimab 350 mg IV every 3 weeks, for up to 51 weeks*

Initial cohort MM1# (n=40)

1L or 2L advanced melanoma patients who have never received anti-PD-(L)1

Confirmatory cohort MM2# (n=40)

1L advanced melanoma patients who have never received anti-PD-(L)1

PD-1 experienced cohort MM3# (n=18)

1L advanced melanoma patients with prior (neo)adjuvant systemic therapy‡, including 13/18 patients who received anti-PD-1

Primary endpoint

- ORR per RECIST 1.1 criteria

Secondary endpoints

- PFS
- DoR
- DCR
- Safety
- PK

Key inclusion criteria

- Metastatic or inoperable locally advanced non-uveal melanoma
- ≥18 years of age
- ECOG PS of 0 or 1
- At least one lesion measurable by RECIST 1.1

Key exclusion criteria

- Uveal melanoma
- Prior treatment with a LAG-3 targeting agent
- Radiation therapy within 2 weeks prior to enrollment

‡: Prior exposure to (neo)adjuvant systemic treatment (including anti-PD-1) with recurrence >6 months after adjuvant therapy
MM1#, Cohort 6; MM2#, Cohort 15; MM3#, Cohort 16. *With an option for an additional 51 weeks.
1L, first-line; 2L, second-line; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; IV, intravenous; LAG-3, lymphocyte activation gene-3; MM, metastatic melanoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; PD-(L)1, programmed cell death-(ligand)1; PFS, progression-free survival; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Tumor response by cohort

Response endpoints	Initial cohort MM1[#] (n=40)	Confirmatory cohort MM2[#] (n=40)	PD-1 experienced cohort MM3[#] (n=18)*
Median follow-up (IQR), months	**20.8 (11.2–30.8)**	**11.5 (8.9–13.9)**	**9.7 (4.8–14.1)**
Treatment exposure, median (IQR), weeks	**37 (20–81)**	**35 (15–51)**	**23 (12–37)**
ORR, (n)	**63% (25)**	**63% (25)**	**56% (10)**
95% CI for ORR	(46–77)	(46–77)	(31–79)
DoR, median (95% CI), months	**NR (12–NE)**	**NR (NE–NE)**	**NR (6–NE)**
DCR, (n)	**80% (32)**	**80% (32)**	**67% (12)**
95% CI for DCR	(64–91)	(64–91)	(41–87)
Best overall response, (n)			
CR	15% (6)	13% (5)	6% (1)
PR	48% (19)	50% (20)	50% (9)
SD	18% (7)	18% (7)	11% (2)
PD	15% (6)	15% (6)	28% (5)
NE	5% (2)	5% (2)	6% (1)
KM-estimated PFS, median (95% CI), months	**24 (4–NE)**	**15 (7–NE)**	**12 (1–NE)**

MM1[#], Cohort 6; MM2[#], Cohort 15; MM3[#], Cohort 16. *17 patients in cohort MM3 received prior adjuvant therapy and 1 patient in cohort MM3 received prior neoadjuvant and adjuvant therapy.
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IQR, interquartile range; KM, Kaplan-Meier; n, number; MM, metastatic melanoma; NE, not estimated; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response;

Tumor responses compared with historical controls

Response endpoints	Cohorts MM1[#] + MM2[#] + MM3[#] Advanced Melanoma (N=98)	Nivo Relativity-047[1] (N=359)	Nivo + Rela Relativity-047[1] (N=355)	Ipi + Nivo CheckMate-067[2,3] (N=314)
Median follow-up, months	12.6	19.3	19.3	57.5
ORR, (95% CI)	61% (51–71)	33% (28–38)	43% (38–48)	58% (53–64)
DCR	78%	51%	63%	71%
DoR, median (95% CI), months	NR (23–NE)	NR (30–NR)	NR (30–NR)	NR (62–NR)
KM-estimated PFS, median (95% CI), months	15 (9–NE)	5 (3–6)	10 (7–15)	12 (9–19)

MM1[#], Cohort 6; MM2[#], Cohort 15; MM3[#], Cohort 16. CI, confidence interval; DCR, disease control rate; DoR, duration of response; Ipi, ipilimumab; KM, Kaplan-Meier; MM, metastatic melanoma; n, number; Nivo, nivolumab; ORR, objective response rate; PFS, progression-free survival; Rela, relatlimab.

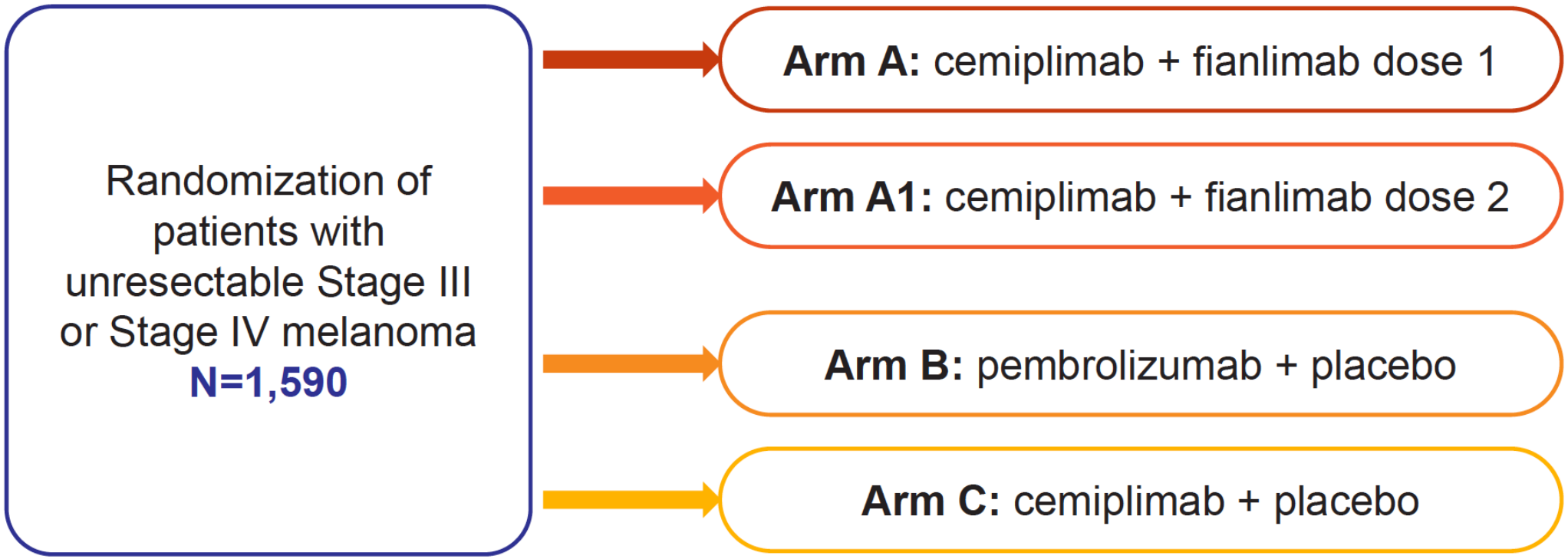
1. Long G et al. *NEJM Evid* 2023; 2 (4). 2. Larkin J et al. *N Engl J Med* 2019;381(16):1535–1546. *3.* Wolchok JD et al. *J Clin Oncol 2022 ;40(2):127-137*

Abstract TPS9602: A Phase 3 trial of fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) versus pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma

Ana Baramidze,[1] Miranda Gogishvili,[2] Tamta Makharadze,[3] Mariam Zhvania,[4] Khatuna Vacharadze,[5] John Crown,[6] Tamar Melkadze,[1] Omid Hamid,[7] Georgina V Long,[8] Caroline Robert,[9] Mario Sznol,[10] Hector Martinez-Said,[11] Jayakumar Mani,[12] Usman Chaudhry,[12] Mark Salvati,[12] Israel Lowy,[12] Matthew G Fury,[12] Giuseppe Gullo[12]

[1]Todua Clinic, Tbilisi, Georgia; [2]High Technology Medical Centre, University Clinic Ltd., Tbilisi, Georgia; [3]LTD High Technology Hospital Med Center, Batumi, Georgia; [4]Consilium Medullla, Tbilisi, Georgia; [5]LTD TIM Tbilisi Institute of Medicine, Tbilisi, Georgia; [6]St Vincent's University Hospital, Dublin, Ireland; [7]The Angeles Clinical and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [8]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; [9]Gustave Roussy and Paris Saclay University, Villejuif, France; [10]Yale Cancer Center, CT, USA; [11]Melanoma Clinic, Instituto Nacional de Cancerología, Mexico; [12]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Figure 1. Study design



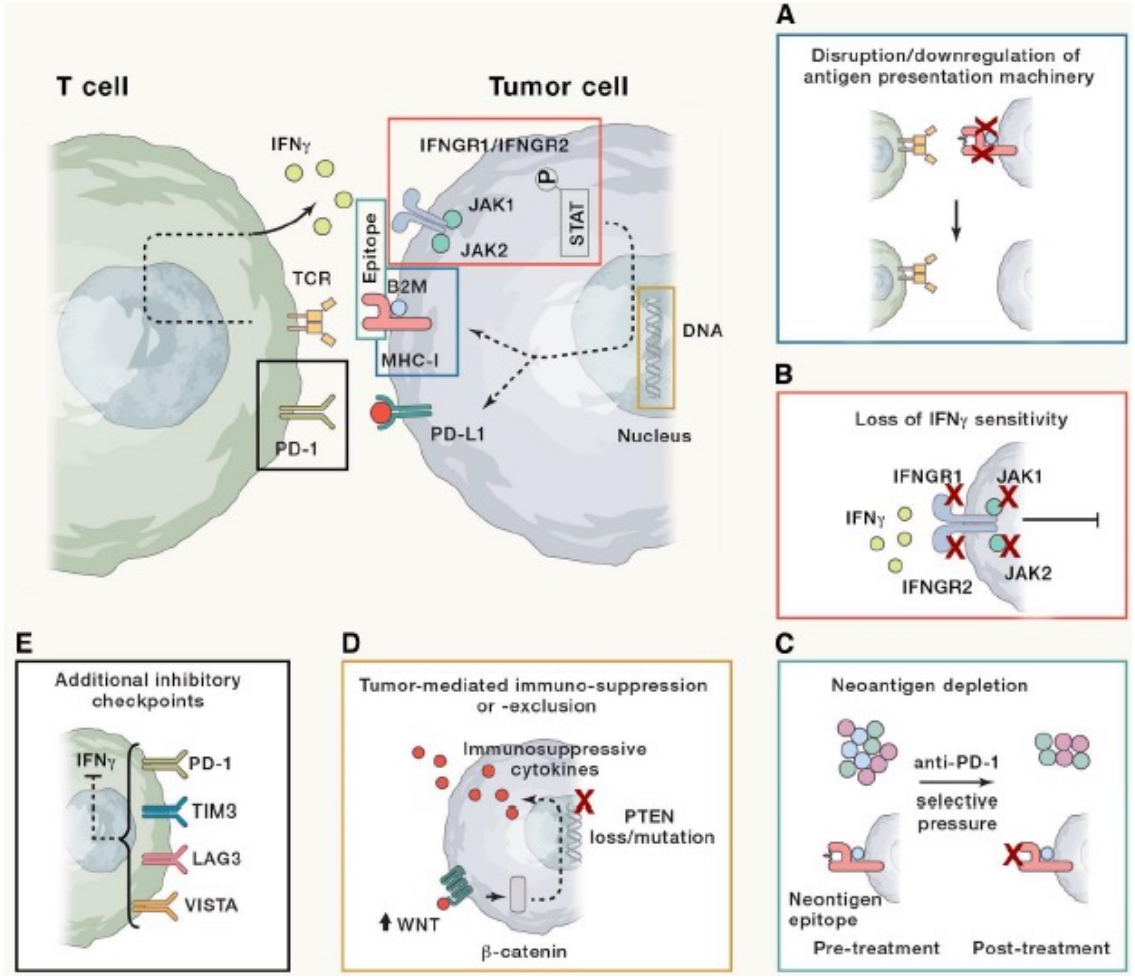
Stratification:

1. *M stage (Stage III vs. M1a–b vs. M1c vs. M1d)*
2. *LDH level (normal vs. elevated)*
3. *Prior exposure to anti-PD-1/PD-L1 therapy in the adjuvant setting.*

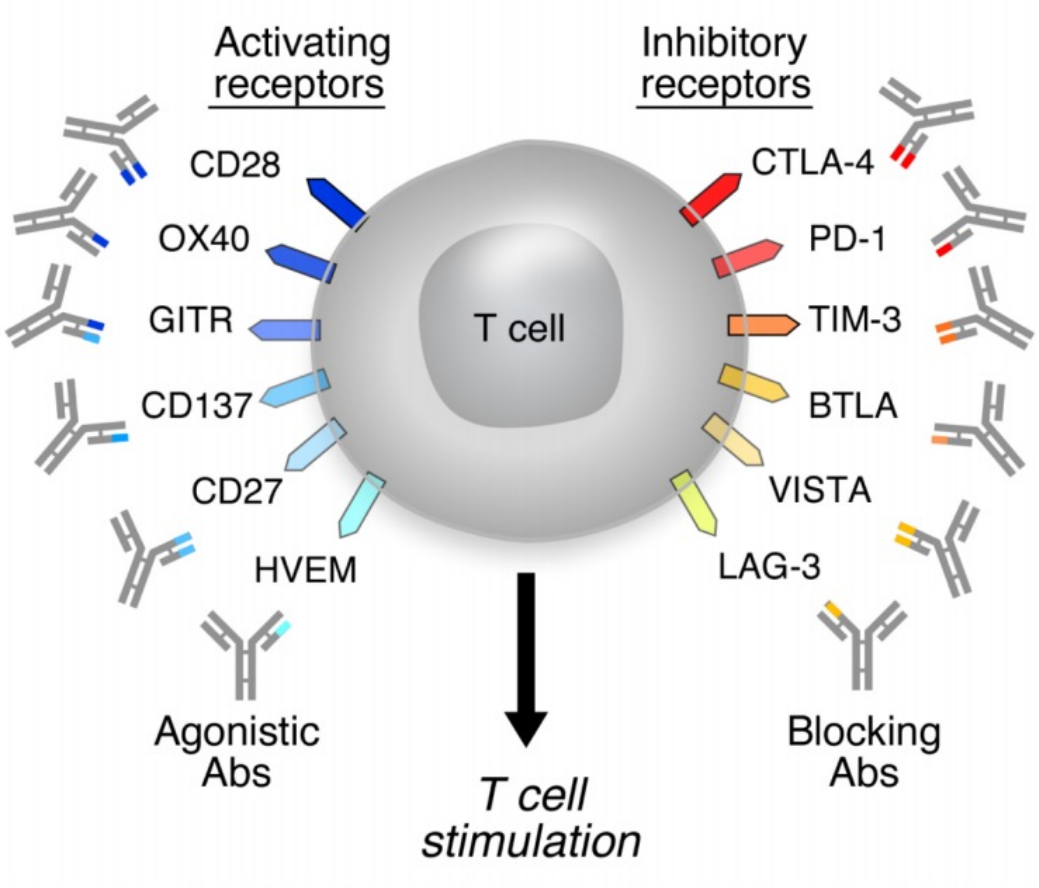
LDH, lactate dehydrogenase; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Loss of T-Cell Function Associated With Progressive Expression of Checkpoint Molecules

Mechanisms of Resistance[a]



Activating Receptors/Costimulatory Molecules[b]

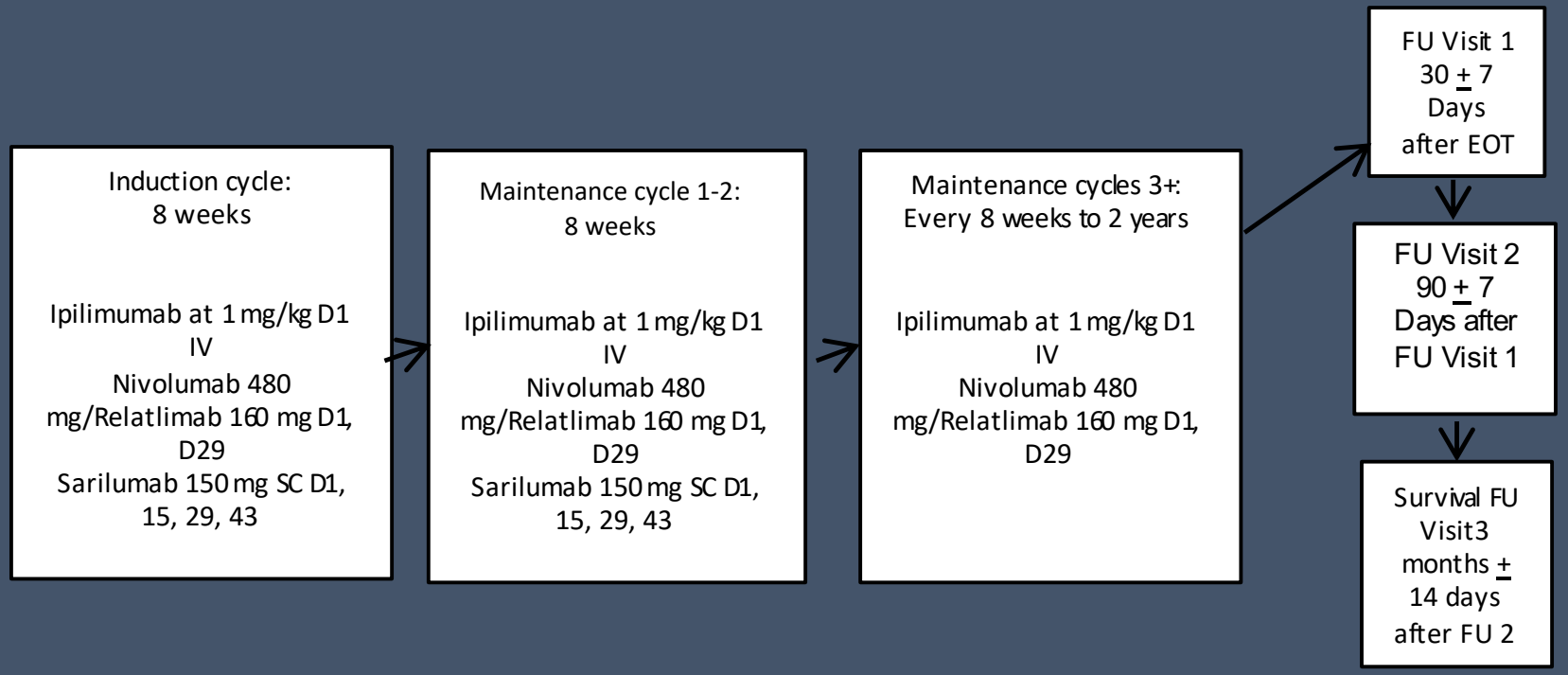


- a. Schoenfeld AJ, et al. *Cancer Cell*. 2020;37:443-455; b. Mellman I, et al. *Nature*. 2011;480:480-489.
- Wherry EJ. *Nat Immunol*. 2011;12:492-499; Wherry EJ, et al. *Nat Immunol*. 2011;12:492-499; Blackburn SD, et al. *Nat Immunol*. 2009;10:29-37; Paley MA, et al. *Science*. 2012;338:1220-1225.

NYU S22-00325

A Phase II Study of the Interleukin-6 Receptor Blocking Antibody Sarilumab in Combination with Ipilimumab, Nivolumab and Relatlimab in Patients with Unresectable Stage III or Stage IV Melanoma

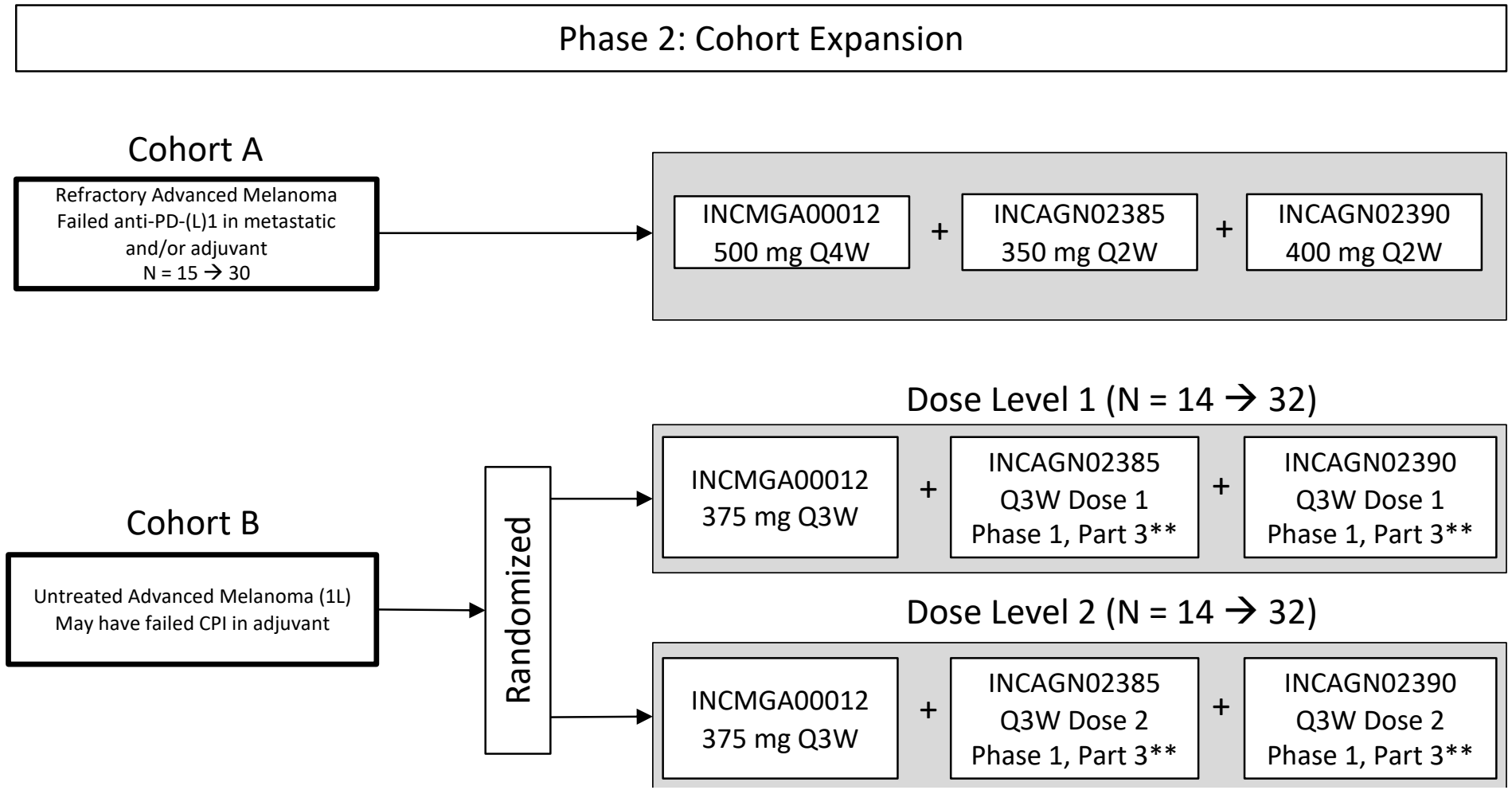
Abbreviations: C = cycle, D= day; FU = follow-up; Ipi = ipilimumab; Nivo = nivolumab; PD = progressive disease;.



clinicaltrials.gov/NCT05428007

STUDY SCHEMA

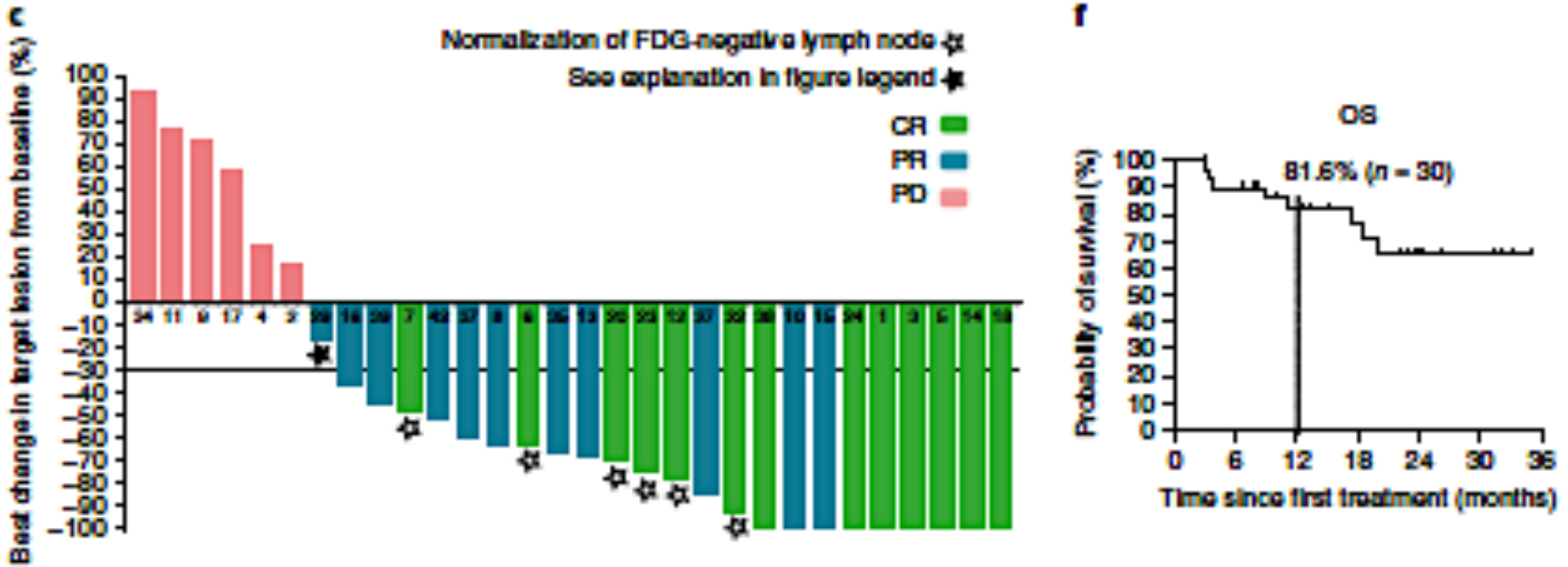
PHASE 2: EVALUATE SAFETY AND EFFICACY IN PATIENTS WITH MELANOMA



clinicaltrials.gov/NCT04370704

ARTICLES
https://doi.org/10.1038/s41591-021-01544-x
nature medicine
Check for updates

A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma



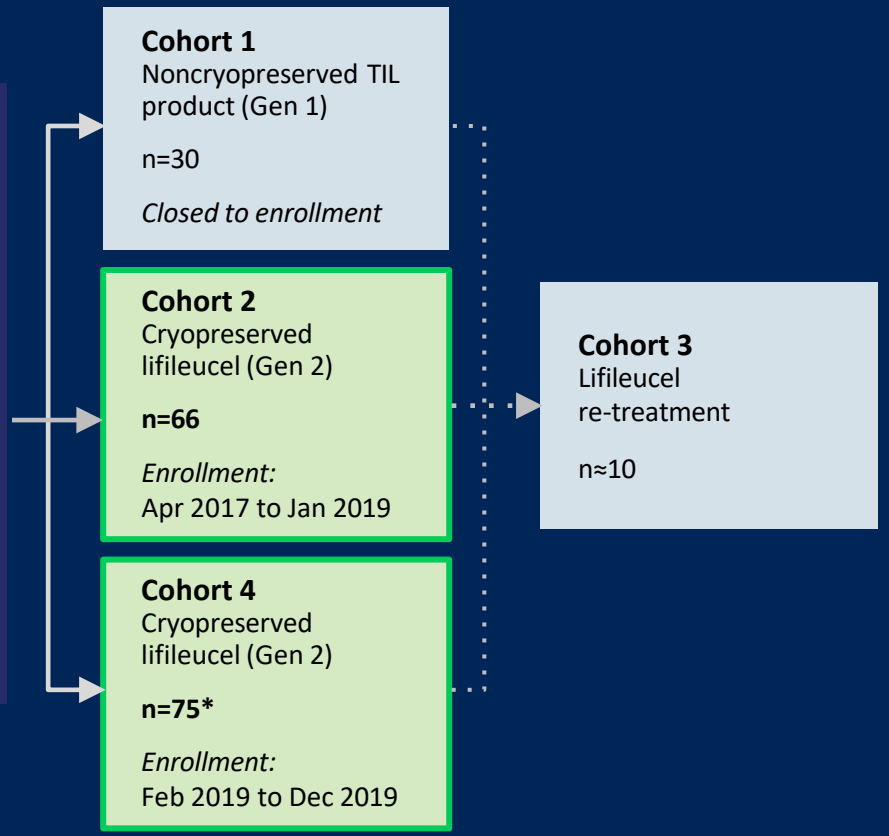
Kjeldsen JW et al. *Nat Med.* 2021;27(12):2212-2223.

C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous TIL (lifileucel) for treatment of patients with metastatic melanoma progressing on ICI and TC therapy (NCT02360579)

Patient Population

Unresectable or metastatic melanoma treated with ≥1 prior systemic therapy including a PD-1–blocking antibody and, if *BRAF* V600 mutation positive, a BRAF inhibitor ± MEK inhibitor



*The planned sample size for Cohort 4 was 75 per statistical plan, but the Full Analysis Set, defined as patients who received lifileucel that met specification, consisted of 87 patients due to rapid enrollment.

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IL-2, interleukin 2; IRC, Independent Review Committee; NMA-LD, nonmyeloablative lymphodepletion; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; RECIST, Response evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse events; TIL, tumor-infiltrating lymphocytes.

Key Endpoints

- Primary: ORR (IRC-assessed using RECIST v1.1)
- Secondary: DOR, PFS, OS, TEAE incidence and severity

Key Eligibility Criteria

- ≥1 tumor lesion resectable for TIL generation (≥1.5 cm in diameter) and ≥1 target tumor lesion for response assessment
- Age ≥18 years at time of consent
- ECOG performance status 0–1
- No limit on number of prior therapies

Treatment Regimen

- Lifileucel, a cryopreserved TIL cell therapy product, was used in Cohorts 2 and 4 and manufactured using the same 22-day Gen 2 process
- All patients received NMA-LD, a single lifileucel infusion, and up to 6 doses of high-dose IL-2

Data cutoff date: 15 July 2022

Sarnaik A. et al, SITC 2022

Objective Response Rate (IRC-assessed)

	Cohort 2 (n=66)	Cohort 4 (n=87)	Cohort 2+4 (N=153)
ORR, n (%)	**23 (34.8)**	**25 (28.7)**	**48 (31.4)**
(95% CI)	(23.5, 47.6)	(19.5, 39.4)	**(24.1, 39.4)**
Best overall response, n (%)			
CR	5 (7.6)	4 (4.6)	**9 (5.9)**
PR	18 (27.3)	21 (24.1)	**39 (25.5)**
SD	24 (36.4)	47 (54.0)	**71 (46.4)**
Non-CR/Non-PD*	1 (1.5)	0	**1 (0.7)**
PD	15 (22.7)	12 (13.8)	**27 (17.6)**
Nonevaluable†	3 (4.5)	3 (3.4)	**6 (3.9)**

- **IRC-assessed ORR** was **31.4%**
- The concordance rate between IRC- and investigator-assessed ORR was 91%
- Median number of TIL cells infused was 21.1×10^9 (range, 1.2×10^9 to 99.5×10^9)
- Lifileucel was manufactured within specification in 94.7% of patients
- Median time from resection to lifileucel infusion was 33 days

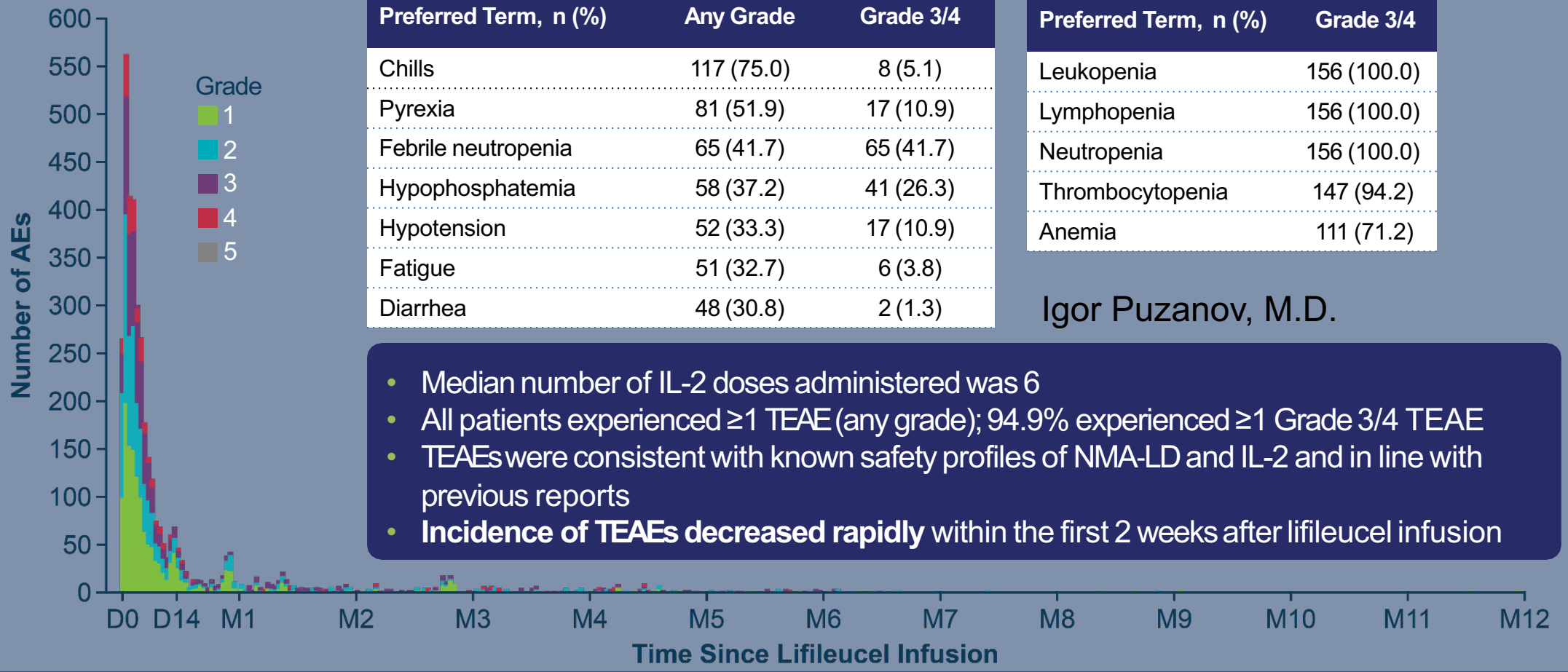
Safety

Non-Hematologic TEAEs in ≥30% of Patients*,†

Preferred Term, n (%)	Any Grade	Grade 3/4
Chills	117 (75.0)	8 (5.1)
Pyrexia	81 (51.9)	17 (10.9)
Febrile neutropenia	65 (41.7)	65 (41.7)
Hypophosphatemia	58 (37.2)	41 (26.3)
Hypotension	52 (33.3)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Diarrhea	48 (30.8)	2 (1.3)

Grade 3/4 Hematologic Lab Abnormalities*

Preferred Term, n (%)	Grade 3/4
Leukopenia	156 (100.0)
Lymphopenia	156 (100.0)
Neutropenia	156 (100.0)
Thrombocytopenia	147 (94.2)
Anemia	111 (71.2)

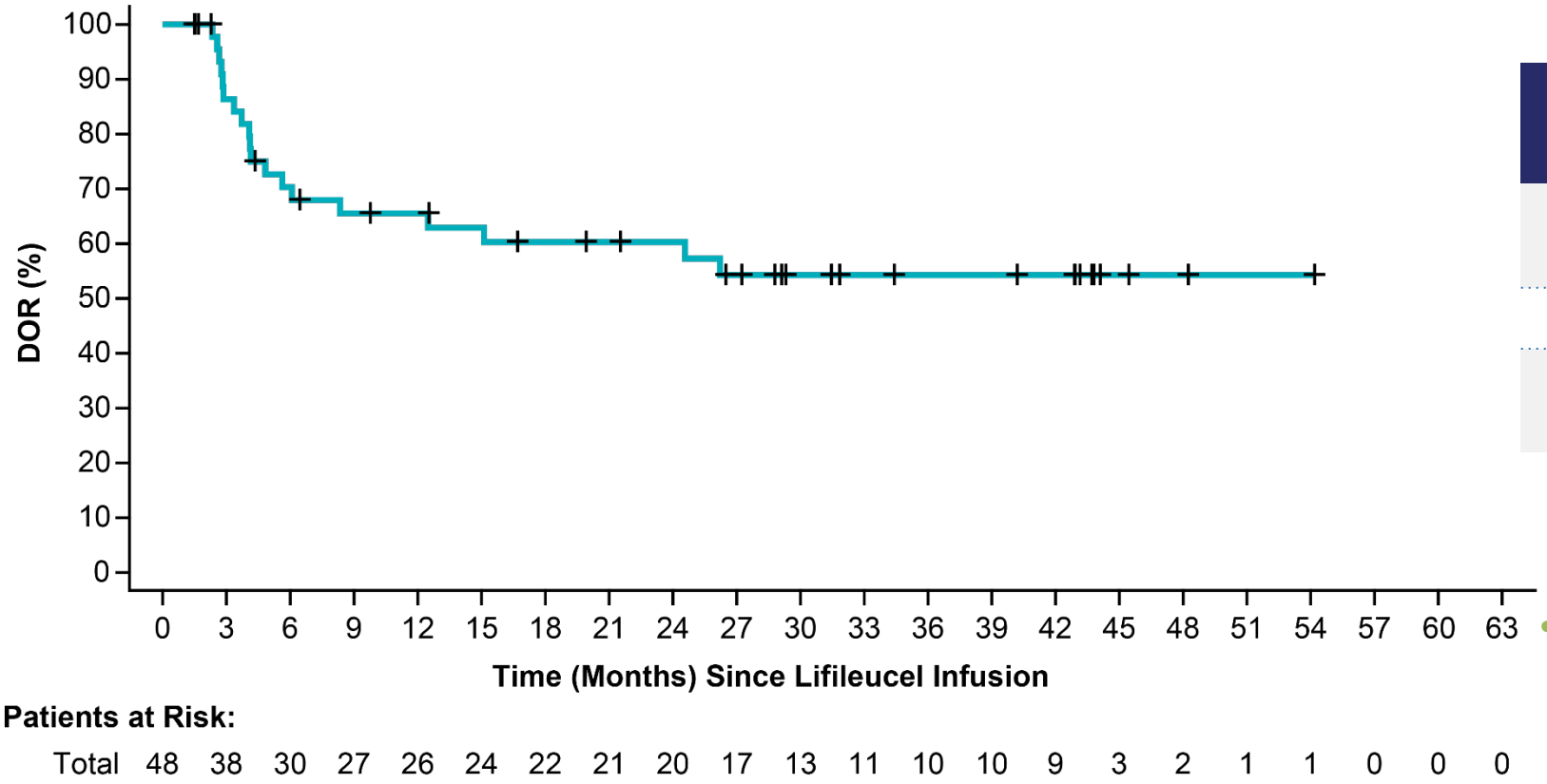


Igor Puzanov, M.D.

- Median number of IL-2 doses administered was 6
- All patients experienced ≥1 TEAE (any grade); 94.9% experienced ≥1 Grade 3/4 TEAE
- TEAEs were consistent with known safety profiles of NMA-LD and IL-2 and in line with previous reports
- **Incidence of TEAEs decreased rapidly** within the first 2 weeks after lifileucel infusion

*Per CTCAE v4.03; Safety Analysis Set (N=156).
†Grade 5 TEAEs included pneumonia (n=1), acute respiratory failure (n=1), arrhythmia (n=1), and intra-abdominal hemorrhage (n=1).
All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different timepoints. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that had not resolved, then the event was counted once with the highest grade reported.
15 events were reported after Month 12 (Grade 1, n=7; Grade 2, n=6; Grade 3, n=1; Grade 5, n=1).
AE, adverse event; D, day; IL-2, interleukin 2; M, month; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

Duration of Response



	Cohort 2 (n=23)	Cohort 4 (n=25)	Cohort 2+4 (N=48)
Median DOR*, months	NR	10.4	NR
95% CI	(NR, NR)	(4.1, NR)	(8.3, NR)
Min, max (months)	1.4+, 54.1+	1.4+, 34.3+	1.4+, 54.1+

- At a median study follow up of 36.5 months, **median DOR** was **not reached**
- 41.7% of responses maintained ≥24 months

PARIS 2022 ESMO congress

Treatment with tumor-infiltrating lymphocytes (TIL) versus ipilimumab for advanced melanoma: results from a multicenter, randomized phase 3 trial

John B.A.G. Haanen, Maartje W. Rohaan, Troels Holz Borch, Joost H. van den Berg, Özcan Met, Marnix H. Geukes Foppen, Joachim Stoltenborg Granhøj, Bastiaan Nuijen, Cynthia Nijenhuis, Jos H. Beijnen, Inge Jedema, Maaike van Zon, Inge Mansfield Noringriis, Rob Kessels, Sofie Wilgenhof, Johannes V. van Thienen, Ferry Lalezari, Alexander C.J. van Akkooi, Marco Donia, Inge Marie Svane

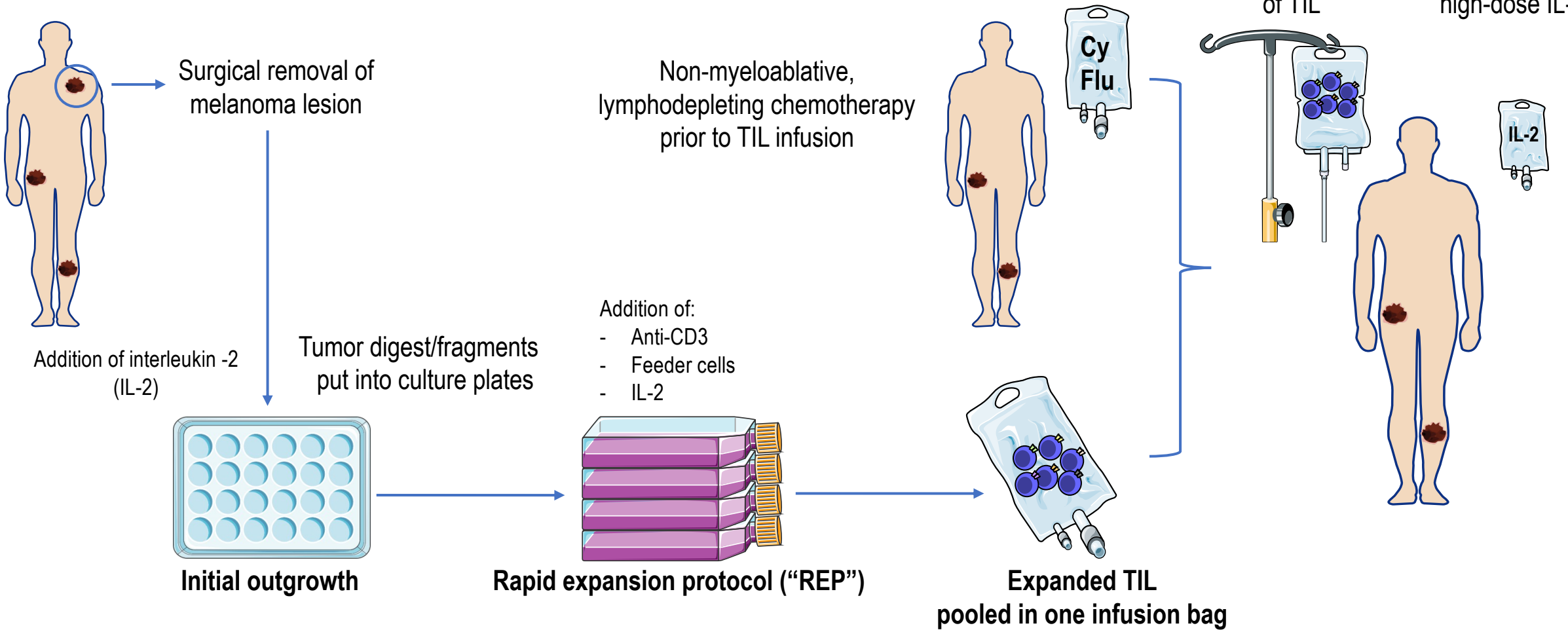
John B.A.G. Haanen

Paris, France, 10th September 2022

Presentation number LBA3

Tumor-infiltrating lymphocytes (TIL)

Preparation and treatment



Haanen, JBAG et al ESMO 2022

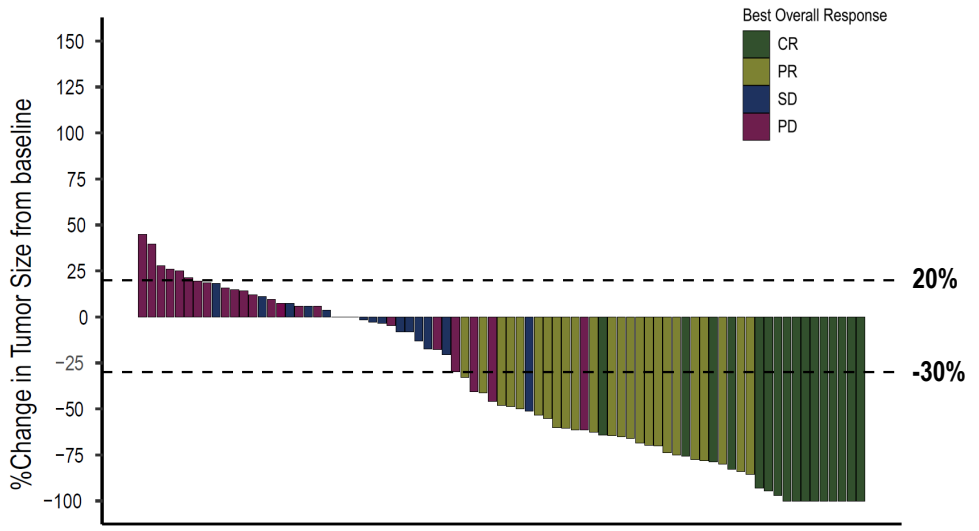
Results (3)

Best overall response according to RECIST 1.1*

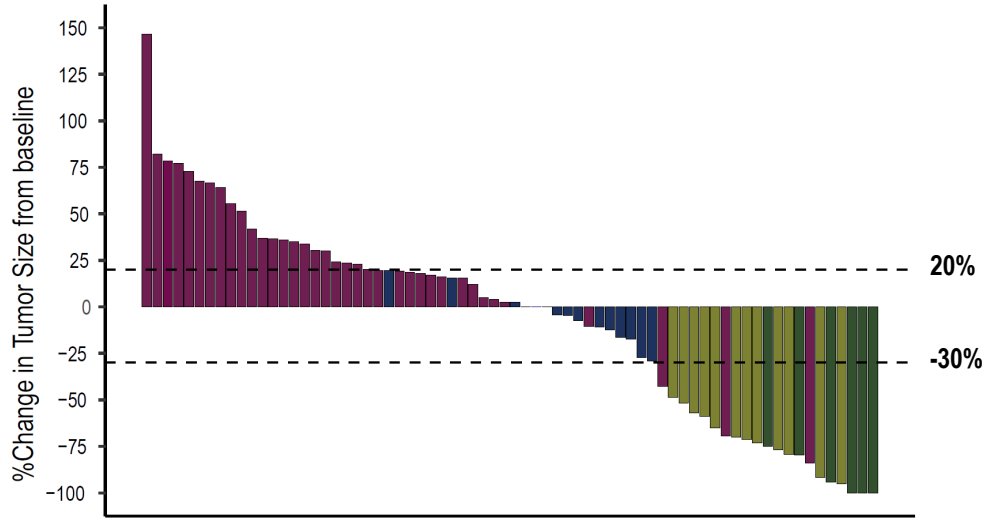
	TIL (n=84)	Ipilimumab (n=84)
Best overall response	**n (%)**	**n (%)**
Complete response	17 (20.2)	6 (7.1)
Partial response	24 (28.6)	12 (14.3)
Stable disease	16 (19.1)	15 (17.9)
Progressive disease	24 (28.6)	40 (47.6)
Not evaluable/done#	3 (3.6)	11 (13.1)
Overall response†	41 (48.8)	18 (21.4)
Clinical benefit‡	57 (67.9)	33 (39.3)

*In the intention-to-treat population. #In 3 (3.6%) and 11 (13.1%) of TIL and ipilimumab treated patients, respectively, best radiologic response could not be evaluated or was not done due to an event (death or need to start subsequent anticancer therapy) before the moment of first response evaluation or due to unevaluable target lesions in follow-up. †Defined as CR plus PR and ‡CR, PR plus SD according to RECIST 1.1.

TIL treatment

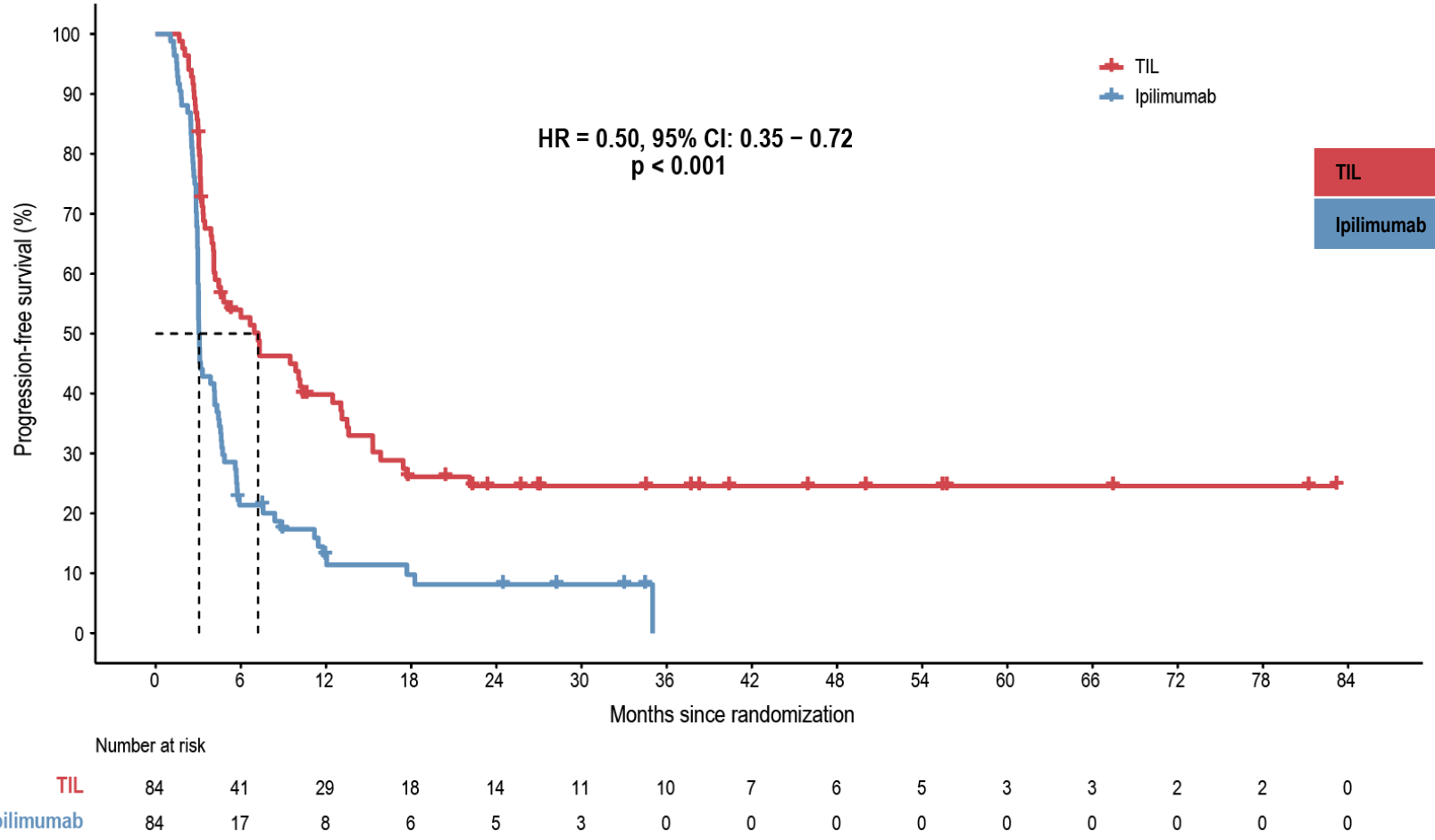


Ipilimumab treatment



Results (1)

Progression-free survival according to RECIST 1.1 in the ITT population



	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

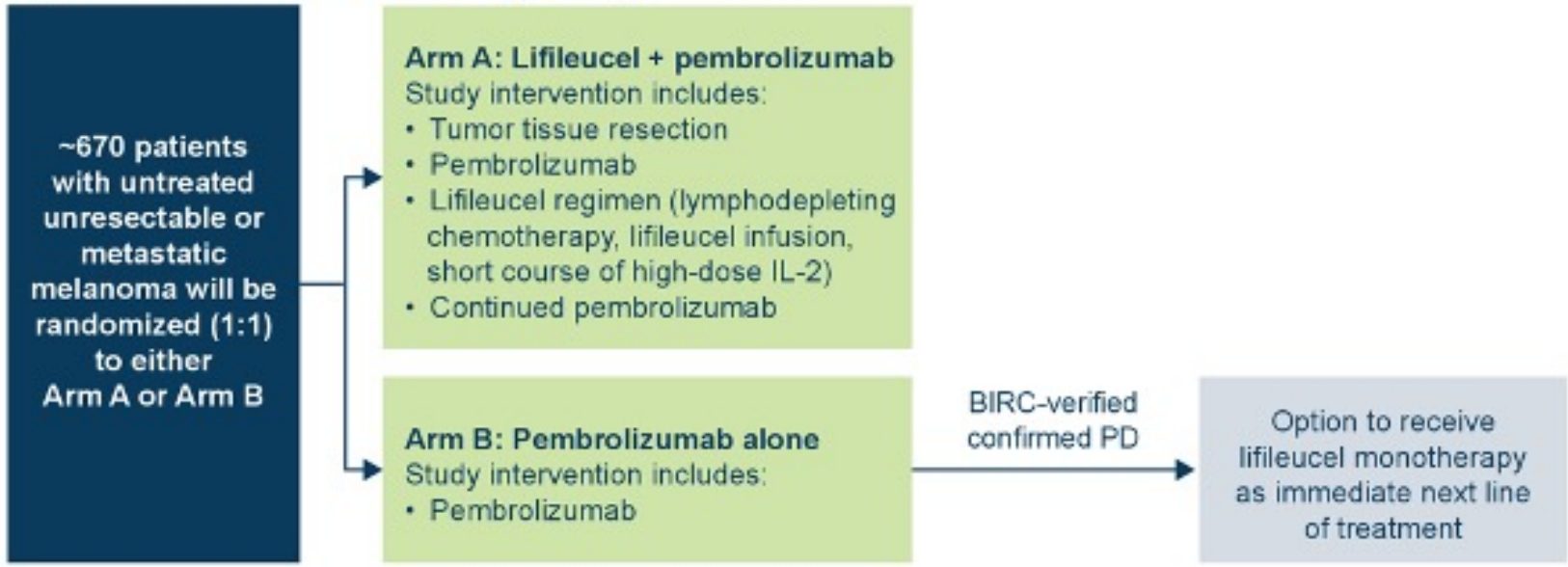
Trial in Progress: A Phase 3 Study (TILVANCE-301) to Assess the Efficacy and Safety of Lifileucel, an Autologous Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy, in Combination With Pembrolizumab Compared With Pembrolizumab Alone in Patients With Untreated Unresectable or Metastatic Melanoma

Daniel Olson, MD[1]; Young Hong, MD, MPH[2]; Sajeve Thomas, MD[3]; Juan Martin-Liberal, MD, PhD[4]; Friedrich Graf Finckenstein, MD[5]; Xiao Wu, PhD[5]; Giri Sulur, PhD[5]; Wen Shi, MD, PhD[5]; James Larkin, PhD, FRCP, F Med Sci[6]

[1]University of Chicago, Chicago, IL, USA; [2]Cooper University Hospital, Camden, NJ, USA; [3]Orlando Health Cancer Institute, Orlando, FL, USA; [4]ICO L'Hospitalet – Hospital Duran i Reynals, Barcelona, Spain; [5]Iovance Biotherapeutics Inc, San Carlos, CA, USA; [6]The Royal Marsden NHS Foundation Trust, London, UK

Corresponding author: Wen Shi; wen.shi@iovance.com

Figure 1. TILVANCE-301 Study Design



Study Endpoints

- **Dual primary efficacy endpoints**
  - ORR as assessed by BIRC per RECIST v1.1
  - PFS as assessed by BIRC per RECIST v1.1
- **Key secondary efficacy endpoint**
  - OS
- **Additional secondary endpoints**
  - BIRC-assessed CR rate, DOR, EFS per RECIST v1.1
  - Investigator-assessed ORR, PFS, CR rate, DOR, EFS PFS2 per RECIST v1.1
  - Safety (characterized by severity and seriousness of TEAEs, and relationship to study drug)
- **The study will enroll globally**

SITC 2021 WASHINGTON, D.C.
NOV. 10–14 *Join us in person or virtually*

Phase 2 Efficacy and Safety of Autologous Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy in Combination with Pembrolizumab in Immune Checkpoint Inhibitor-Naïve Patients with Advanced Cancers

David O'Malley,[1] Sylvia M Lee,[2] Amanda Psyrri,[3] Ammar Sukari,[4] Sajeve Thomas,[5] Robert M Wenham,[6] Helen Gogas,[7] Amir Jazaeri,[8] Bradley J Monk,[9] Peter G Rose,[10] Antonio Rueda,[11] Friedrich Graf Finckenstein,[12] Madan Jagasia,[12] Rana Fiaz,[12] Brigid Garelik,[12] Wen Shi,[12] Anjali Desai,[12] Giri Sulur,[12] Guang Chen,[12] Xiao Wu,[12] Antonio Jimeno[13]

1. Ohio State University, Columbus, OH, USA; 2. Fred Hutchinson Cancer Center, Seattle, WA, USA; 3. Attikon University Hospital, National Kapodistrian University of Athens, School of Medicine, Haidari, Athens, Greece; 4. Wayne State University, Karmanos Cancer Institute, Detroit, MI, USA; 5. Orlando Health Cancer Institute, Orlando, FL, USA; 6. Moffitt Cancer Center, Tampa, FL; 7. National and Kapodistrian University of Athens, Athens, Greece; 8. MD Anderson Cancer Center, Houston, TX, USA; 9. Arizona Oncology (US Oncology Network), Phoenix, AZ; 10. Cleveland Clinic, Cleveland, OH, USA; 11. Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; 12. Iovance Biotherapeutics, Inc., San Carlos, CA, USA; 13. University of Colorado School of Medicine, Aurora, CO, USA

Study Design and Eligibility

IOV-COM-202 (NCT03645928): A Phase 2, multicenter study of autologous TIL in patients with solid tumors

- **Cohort 1A: Unresectable or metastatic melanoma**
  Anti–PD-1 / PD-L1 naïve
  Lifileucel + pembrolizumab
  N=12
- **Cohort 2A: Advanced, recurrent, or metastatic HNSCC**
  Anti–PD-1 / PD-L1 naïve
  LN-145 + pembrolizumab
  N=19

C-145-04 (NCT03108495): A Phase 2, multicenter study of autologous TIL in patients with recurrent, metastatic, or persistent cervical cancer

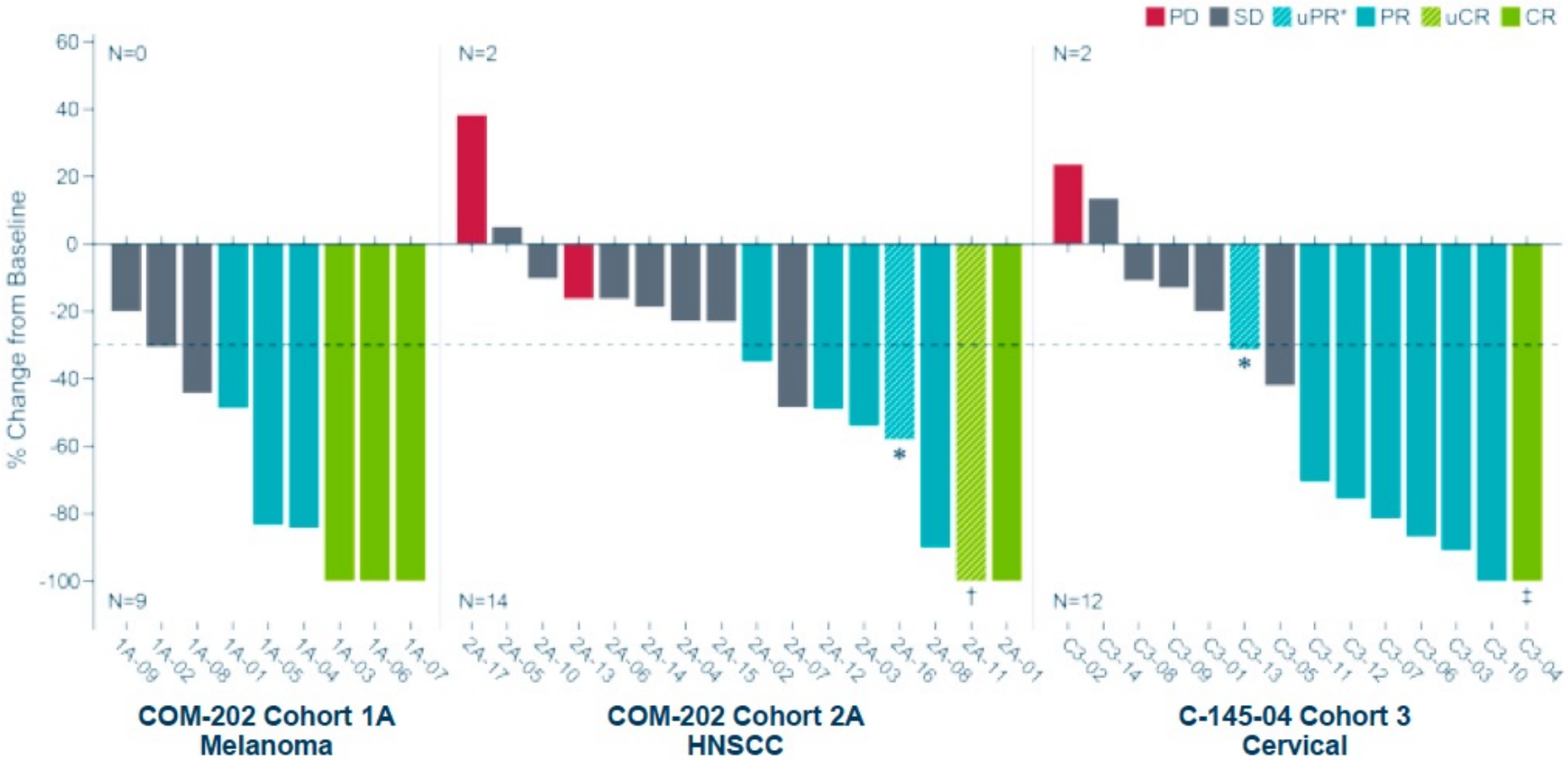
- **Cohort 3: Stage 4b, persistent, recurrent, or metastatic cervical cancer**
  No prior therapy (except chemoradiation or surgery for loco-regional disease)
  LN-145 + pembrolizumab
  N=24

Endpoints	IOV-COM-202	C-145-04
Primary	• ORR • Incidence of Grade ≥3 TEAEs	• Incidence of Grade ≥3 TEAEs
Secondary	• CR rate, DOR, DCR, PFS, OS	• ORR, DOR, DCR, PFS, OS

- **Key eligibility criteria**
  - ≥1 resectable lesion for TIL manufacturing (diameter ≥1.5 cm post-resection)
  - ≥1 measurable lesion for response assessment (by investigator per RECIST v1.1)
  - ECOG performance status 0–1
- **Methods**
  - Patients were enrolled from March 2019 to August 2021 at sites across North America and the EU
  - Concomitant anticancer therapy was not permitted
  - Responses were evaluated per RECIST v1.1
- **Data cutoff:** 22 September 2021

DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TEAEs, treatment-emergent adverse events; TIL, tumor-infiltrating lymphocytes.

Best Overall Response



COM-202 Cohort 1A Melanoma

COM-202 Cohort 2A HNSCC

C-145-04 Cohort 3 Cervical

- Nearly all efficacy-evaluable patients experienced a reduction in tumor burden:
  - Melanoma, 100%
  - HNSCC, 87.5%
  - Cervical, 85.7%

*Patients 2A-16 and C3-13 had a first PR assessment, but had not reached the confirmatory assessment at the time of the datacut. †Patient 2A-11 had a first CR assessment, but had not reached the confirmatory assessment at the time of the datacut. ‡For patient C3-04, –100% change from baseline includes lymph node lesions that resolved to <10 mm.

CR, complete response; HNSCC, head and neck squamous cell carcinoma; PD, progressive disease; PR, partial response; SD, stable disease; uCR, unconfirmed complete response; uPR, unconfirmed partial response.

IOV-4001 First-in-Human Study: IOV-GM1-201

Phase 1/2, Open-label Study of PD-1 Knockout Tumor-infiltrating Lymphocytes (IOV-4001) in Participants With Unresectable or Metastatic Melanoma or Stage III or IV Non-small-cell Lung Cancer (NCT05361174)

Phase 1 / 2 study to investigate the efficacy and safety of an infusion of IOV-4001 in adult participants with unresectable or metastatic melanoma or advanced non-small-cell lung cancer (NSCLC). N=53

Cohort 1: Unresectable or metastatic melanoma
Post-anti-PD-1/L1, post-BRAF/MEK inhibitor in patients with BRAF mutations

Cohort 2: Stage III or IV non-small-cell lung cancer
Post -anti-PD-1/L1 or
Post targeted therapy and either chemotherapy or anti-PD-1/L1

Endpoints

- Phase I: Safety
- Phase 2: Objective Response Rate (ORR) per RECIST v1.1 as assessed by the investigator
- Secondary endpoints include complete response (CR) rate, duration of response (DOR), disease control rate (DCR), progression free survival (PFS), overall survival (OS), safety and tolerability, feasibility

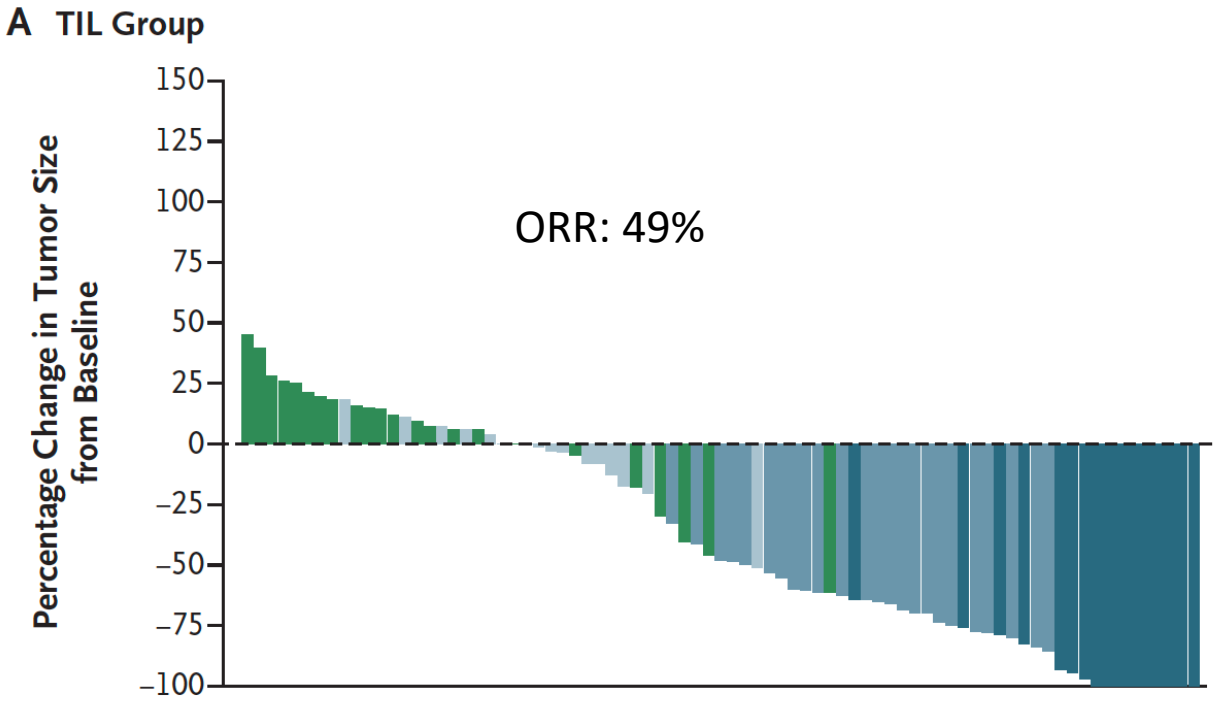
Study Updates

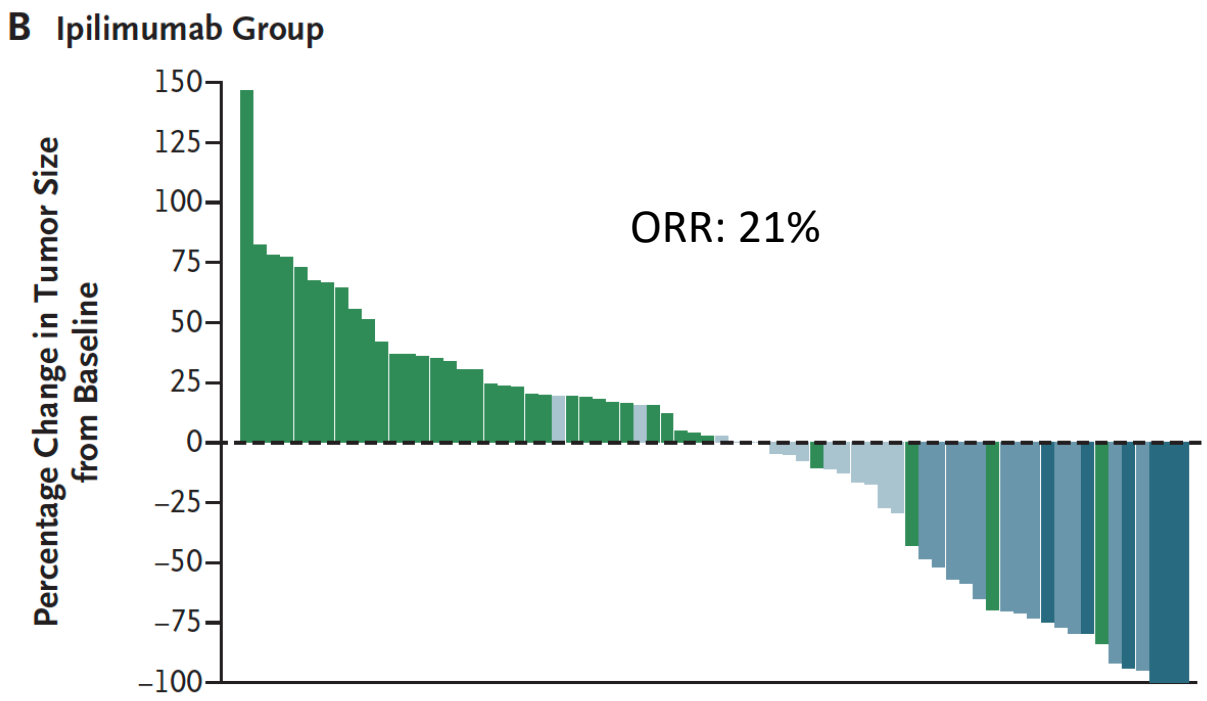
- Investigational New Drug (IND) Allowance March 2022

clinicaltrials.gov/NCT05361174

TIL Versus Ipilimumab

Phase III trial in patients (PS 0-1) with unresectable or metastatic melanoma
At least 1 prior line of systemic therapy, excluding ipilimumab





Rohaan MW et al. *N Engl J Med* 2022;387(23):2113-25.

TIL Versus Ipilimumab

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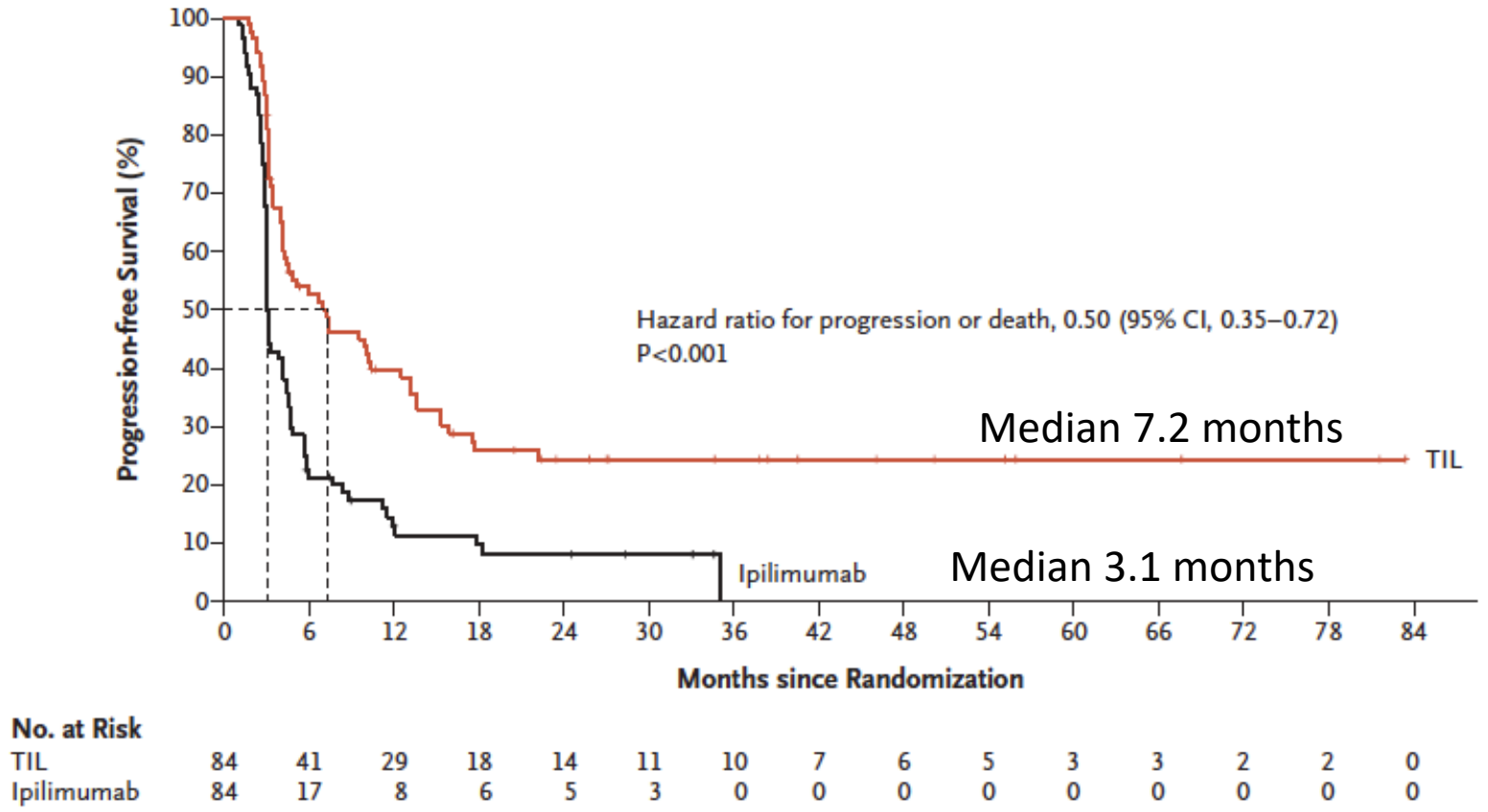


PFS @ 6 months

TIL	52.7%
Ipilimumab	21.4%

Median OS

TIL	25.8 months
Ipilimumab	18.9 months
HR 0.82	

2-year OS

TIL	54.3%
Ipilimumab	44.1%

Rohaan MW et al. *N Engl J Med* 2022;387(23):2113-25.

Systemic Therapy for Melanoma: ASCO Guideline Rapid Recommendation Update

Rahul Seth, MD[1]; Hans Messersmith, MPH[2]; and Pauline Funchain, MD[3]; for the Systemic Therapy for Melanoma Guideline Expert Panel

Outcome	Value	Absolute Effect Estimates (all numbers per 1,000)		Certainty of the Evidence	Plain Language Summary
		Single-Agent Immunotherapy or Dacarbazine	Tebentafusp		
Deaths at 1 year	OS HR: 0.51 (95% CI, 0.37 to 0.71)[a,b]	410	236	Moderate[d,e]	Tebentafusp probably improves OS[f]
		Difference: 174 fewer (95% CI, 233 fewer to 98 fewer)[c]			
Progressions or deaths at 6 months	PFS HR: 0.73 (95% CI, 0.58 to 0.94)[a,b]	810	702	Low[d]	Tebentafusp may improve PFS
		Difference: 108 fewer (95% CI, 192 fewer to 20 fewer)[g]			
Grade 3 or 4 treatment-related adverse events	Relative risk: 2.60 (95% CI, 1.69 to 4.01)[a,h]	172	447	Low[d]	Tebentafusp may produce more grade 3 or 4 treatment-related adverse events
		Difference: 275 more (95% CI, 119 more to 518 more)			

Seth R, Messersmith H, Kaur V, et al: Systemic therapy for melanoma: ASCO guideline. J Clin Oncol 38:3947-3970, 2020

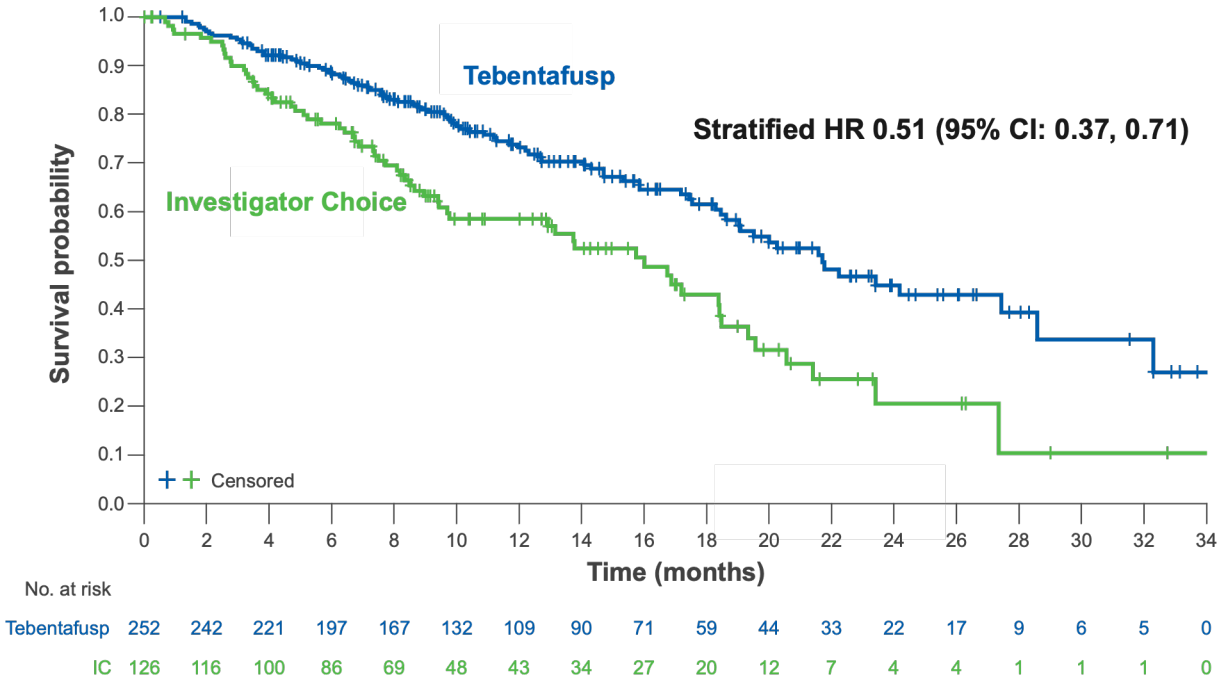
OS best captures benefit from tebentafusp (uveal melanoma)

Phase 3, first-line study (IMCgp100-202)[1]

RECIST response rate and PFS underestimate OS

	Tebentafusp vs Investigator Choice (IC)
RECIST response rate	9% vs 5%
Tumor shrinkage*	39% vs 24%
PFS (HR)	0.73 (95% CI: 0.58, 0.94)

Statistically and clinically significant OS benefit



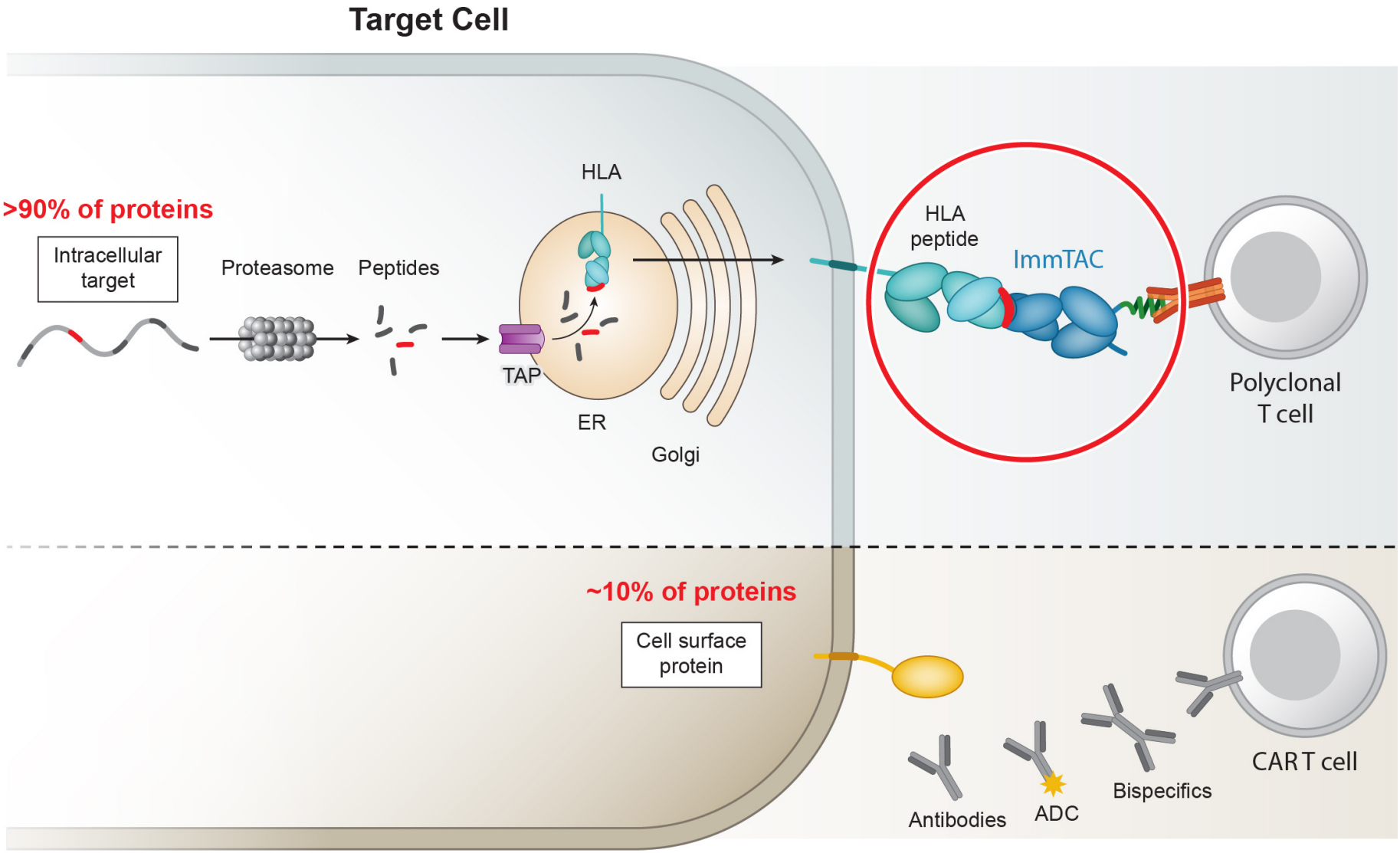
* In phase 2, any tumor shrinkage (44%)[2] and ctDNA reduction (70%)[3] were associated with OS

1. Nathan P, et al. *N Engl J Med* 2021;385:1196-206; 2. Sacco JJ, et al. *Ann Oncol* 2020;31:S1442–43; 3. Shoushtari A et al. *Ann Oncol* 2021;32:S1210

Professor M.R. Middleton

Middleton MR et al. ASCO 2022;Abstract 104

ImmTAC: T cell receptor (TCR) bispecifics target intracellular proteins



ImmTAC target >90% of proteome via soluble TCR

Antibody bispecifics target 10% of proteome

ImmTAC, Immune mobilizing T cell receptor Against Cancer

Middleton MR et al. ASCO 2022;Abstract 104

2022 ASCO® ANNUAL MEETING

Updated overall survival (OS) data from Phase 1b study of tebentafusp (tebe) as monotherapy or combination therapy with durvalumab (durva) and/or tremelimumab (treme) in metastatic cutaneous melanoma (mCM)

Authors: **M.R. Middleton**[1], O. Hamid[2], A.N. Shoushtari[3], F.E. Meier[4], T.M. Bauer[5], A.K.S. Salama[6], J.M. Kirkwood[7], P.A. Ascierto[8], P. Lorigan[9], C. Mauch[10], M.M. Orloff[11], T. R.J Evans[12], S.E. Abdullah[13], Y. Yuan[13], J. Mitchell[13], J.C. Hassel[14]

[1]University of Oxford, Oxford, UK; [2]The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA, USA; [3]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [4]University Hospital Carl Gustav Carus at the TU Dresden, Germany; [5]Tenessee Oncology, Nashville, TN, USA; [6]Duke University, Durham, NC, USA; [7]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [8]IRCCS National Cancer Institute Pascale Foundation, Naples, Italy; [9]The Christie NHS Foundation Trust, Manchester, UK; [10]University of Cologne, Cologne, Germany; [11]Thomas Jefferson University Hospitals, Philadelphia, PA, US; [12]Beatson West of Scotland Cancer Centre, Glasgow, UK; [13]Immunocore Ltd, Abingdon, UK; [14]Heidelberg University Hospital, Heidelberg, German

Abstract #104

Similar associations with OS between mUM and mCM

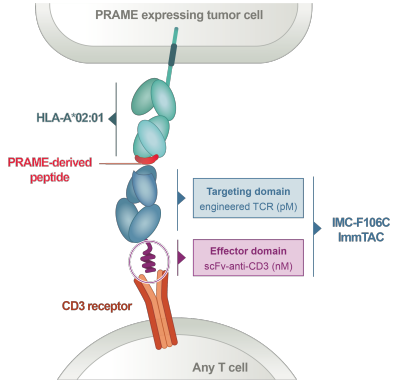
	IMCgp100-201	IMCgp100-202
Population	Previously treated mCM (n=52)	Previously untreated mUM (n=230)†
Treatment	Tebentafusp + durvalumab	Tebentafusp
RECIST response rate (%)	10%	12%
Patients with tumor decrease (%)	37%*	40%*
Alive at 1 yr (%)	89%	85%
Patients with tumor increase (%)	60%*	54%*
Alive at 1 yr (%)	58%	64%

* 3% and 6% of patients in Study 201 and Study 202, respectively, had no change in tumor size
† April 2022 data cut off for survival data. Tumor shrinkage and increase for IMCgp100-202 (N=230)

Middleton MR et al. ASCO 2022;Abstract 104

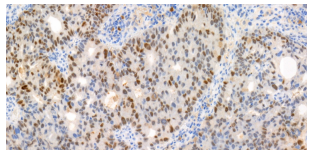
IMC-F106C: ImmTAC targeting HLA-A2-presented peptide from PRAME (PRAME × CD3)

- TCR bispecific proteins redirect polyclonal T cells to target intra- or extra-cellular cancer proteins (>90% of proteome)
- ImmTAC molecules are validated by tebentafusp (gp100 × CD3) with OS benefit in uveal melanoma (HR 0.51)[1]

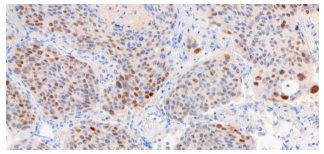


PRAME: most broadly expressed cancer-testis antigen in several tumor types but with minimal normal tissue expression

Adeno NSCLC



Squamous NSCLC

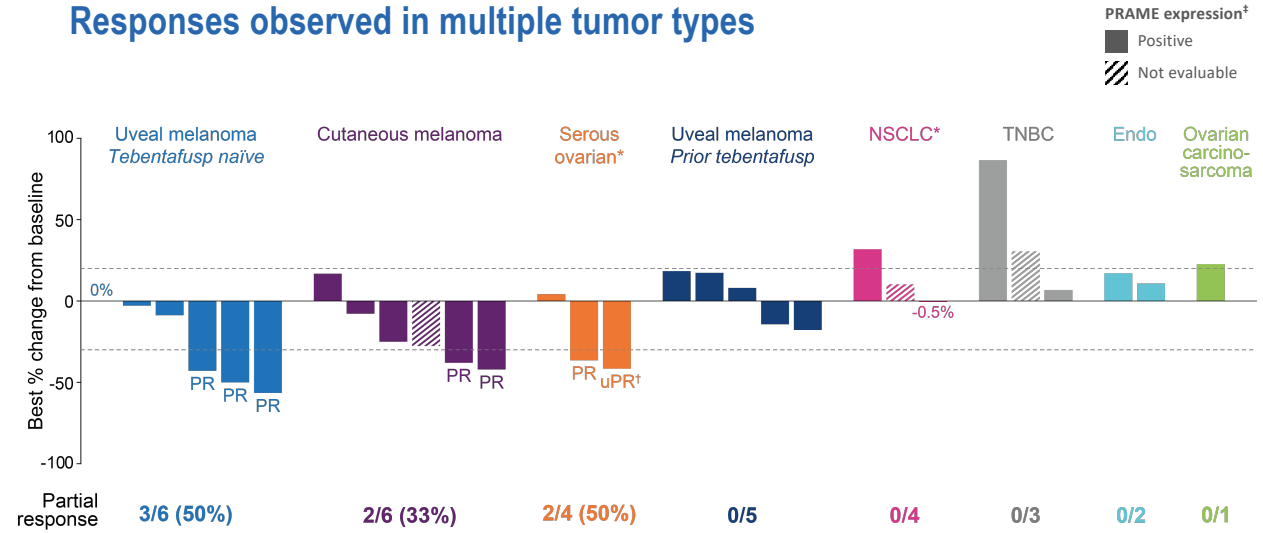


Tumor	Prevalence of PRAME expression
Melanoma, endometrial, NSCLC, TNBC, SCLC, ovarian	HIGH
RCC, esophageal, SCCHN, cervical	
Bladder, HCC, gastric	LOW

ImmTAC, Immune mobilizing T cell receptor Against Cancer; TCR, T cell receptor

1. Nathan P, et al. N Engl J Med 2021;385:1196-206;

Responses observed in multiple tumor types

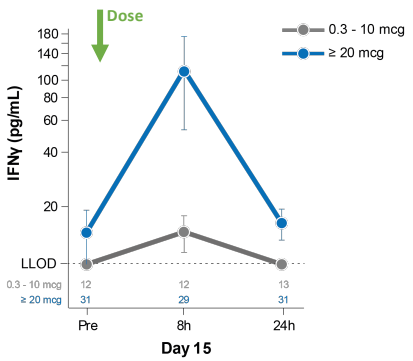


* Two patients (1 with NSCLC, 1 serous ovarian) discontinued treatment due to PD with scan data not available at DCO
† Ovarian cancer patient with unconfirmed PR (uPR) remains on treatment and eligible for confirmation
‡ PRAME expression assessed by IHC H-score
Two PRAME-negative patients both had PD (not shown)

Strong and Consistent Pharmacodynamic Activity at ≥20 mcg IMC-F106C

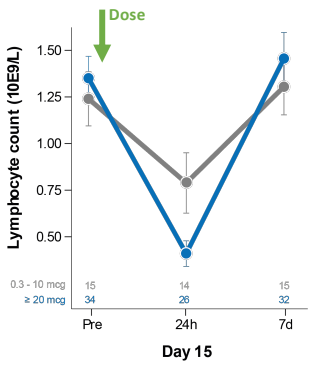
Interferon γ induction

Peripheral blood

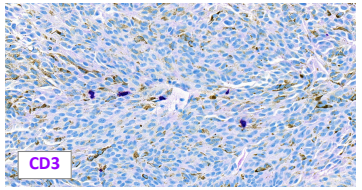


T cell trafficking

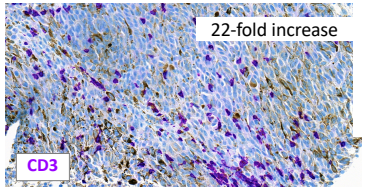
Peripheral blood ⇢ Tumor



Pre-treatment

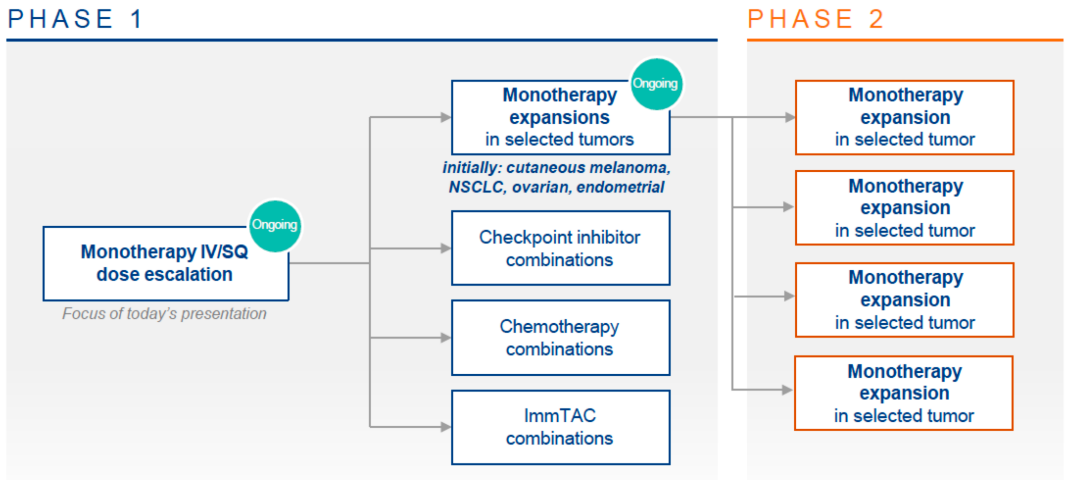


Day 28



Results plotted as mean ± SEM

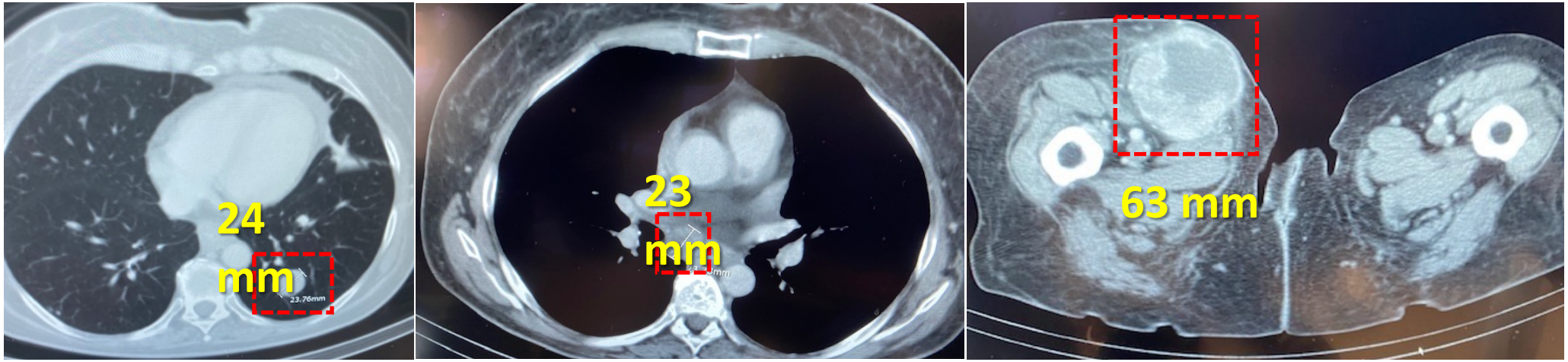
IMC-F106C-101 designed as an adaptive Phase 1/2 study



Single Agent: cutaneous melanoma

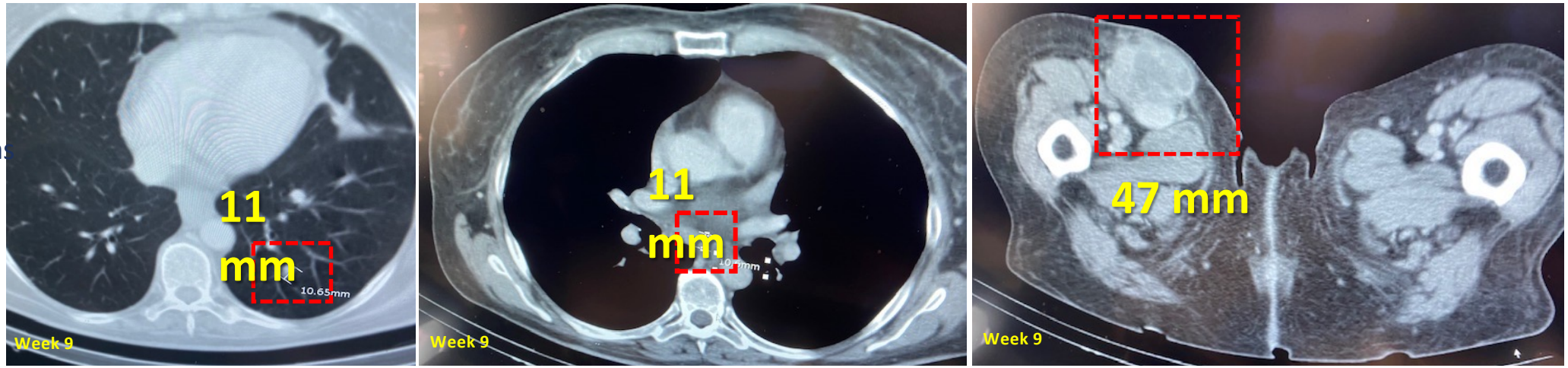
Prior anti-CTLA4, multiple anti-PD1s and oncolytic virus

Baseline



Confirmed PR

ongoing treatment 5+ months

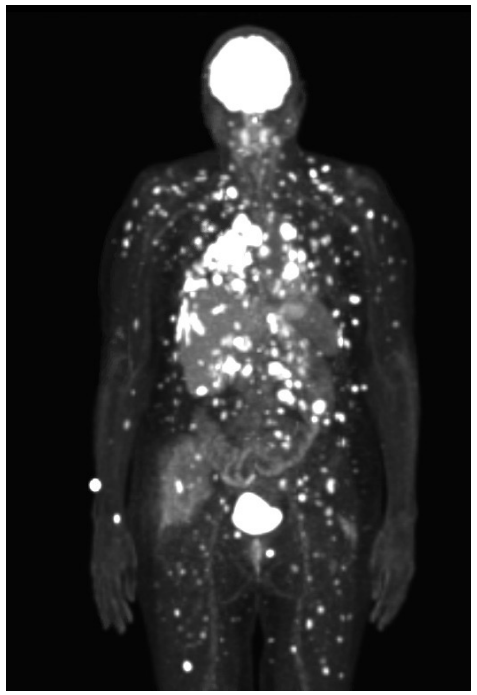


PARIS 2022 ESMO congress

Images courtesy of Dr. Omid Hamid (Angeles Clinic)

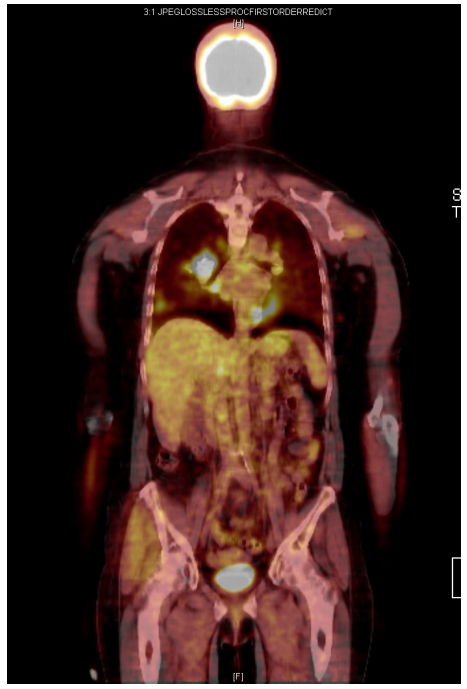
Response to Combined Checkpoint Blockade

52 year old female with Decision DX Class 2, GNA11 Q209L mutant, right ciliary body melanoma s/p enucleation with the development of metastatic disease 26 months later to the liver, lung, bone and soft tissue



12/2017

Ipi/Nivo



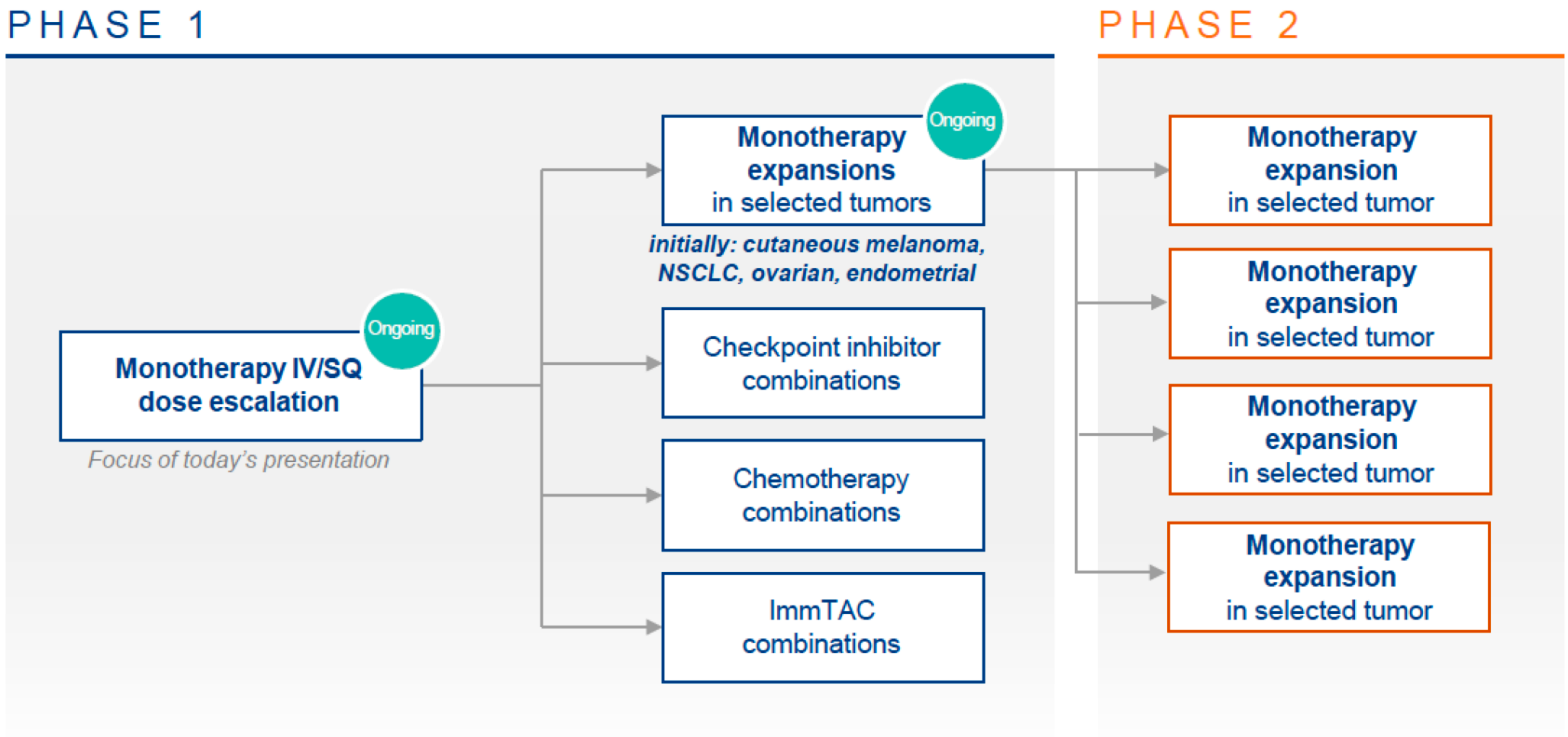
03/2018

Prior Therapies:

- Ipilimumab
- Pembrolizumab + radioembolization x 7 months
- IMCgp100 x 20 months
- **Ipi/Nivo**

Courtesy of Dr. Richard Carvajal

IMC-F106C-101 designed as an adaptive Phase 1/2 study



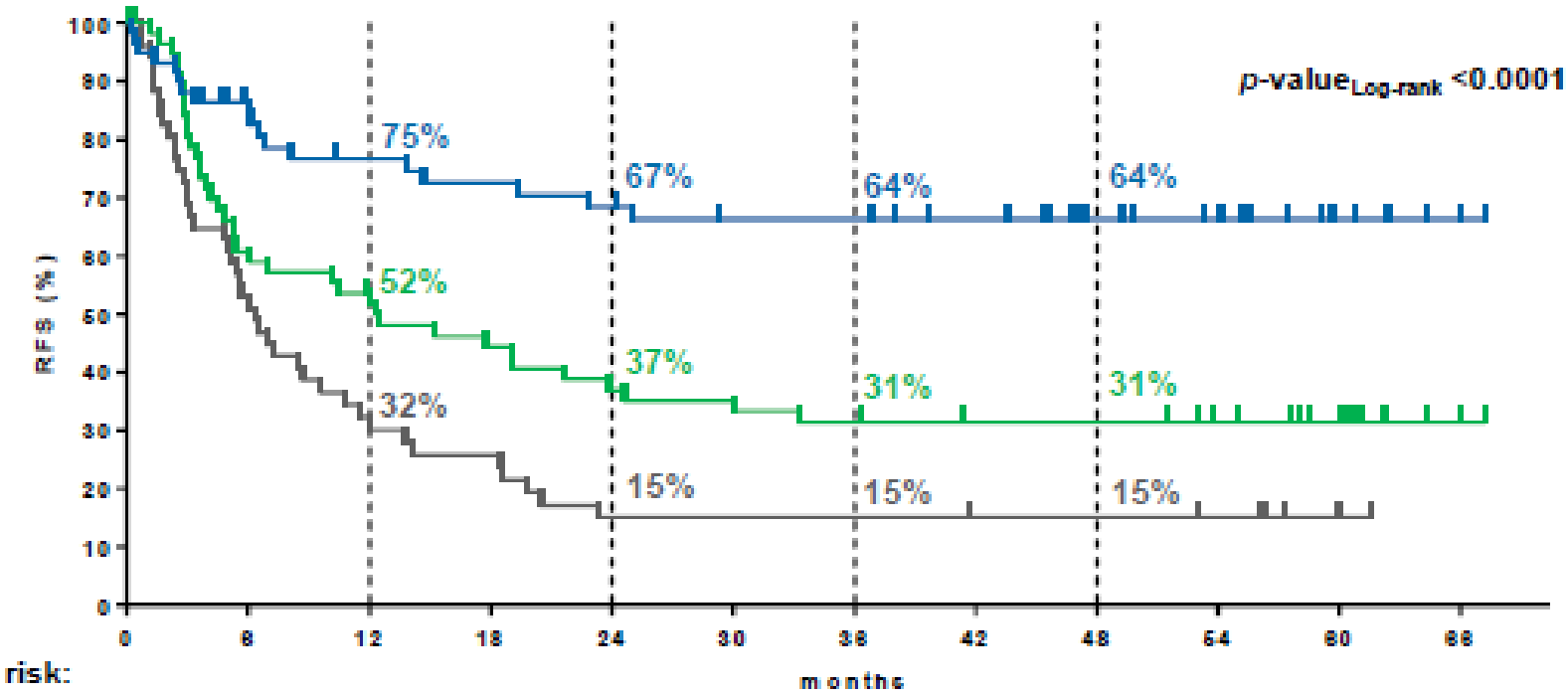
THE IMMUNED STUDY

Primary endpoint: RFS in all patients

Data cut-off date Sep 23, 2021
Median follow-up time: 49.2 months

	NIVO+IPI (n=56)	NIVO (n=59)	Placebo (n=52)
Median RFS, mo (95% CI)	NR[1] (25.0, NR)	12.3 (5.3, 23.9)	6.3 (3.3, 9.6)
HR (97.5% CI) vs placebo	0.25 (0.13, 0.48)	0.60 (0.36, 1.00)	-
HR (97.5% CI) vs NIVO	0.41 (0.22, 0.78)	-	-

[1]NR: not reached



Patients at risk:

NIVO + IPI	56	40	35	32	30	27	27	27	24	11	4	1
NIVO	59	34	28	24	20	19	17	15	15	12	7	2
Placebo	52	25	15	12	7	7	7	6	6	5	1	-

Schadendorf D et al. ESMO 2022;Abstract 7840

PARIS 2022 ESMO congress

Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01654-3/fulltext

Data cut-off date Sep 23, 2021
Median follow-up time: 45.2 months

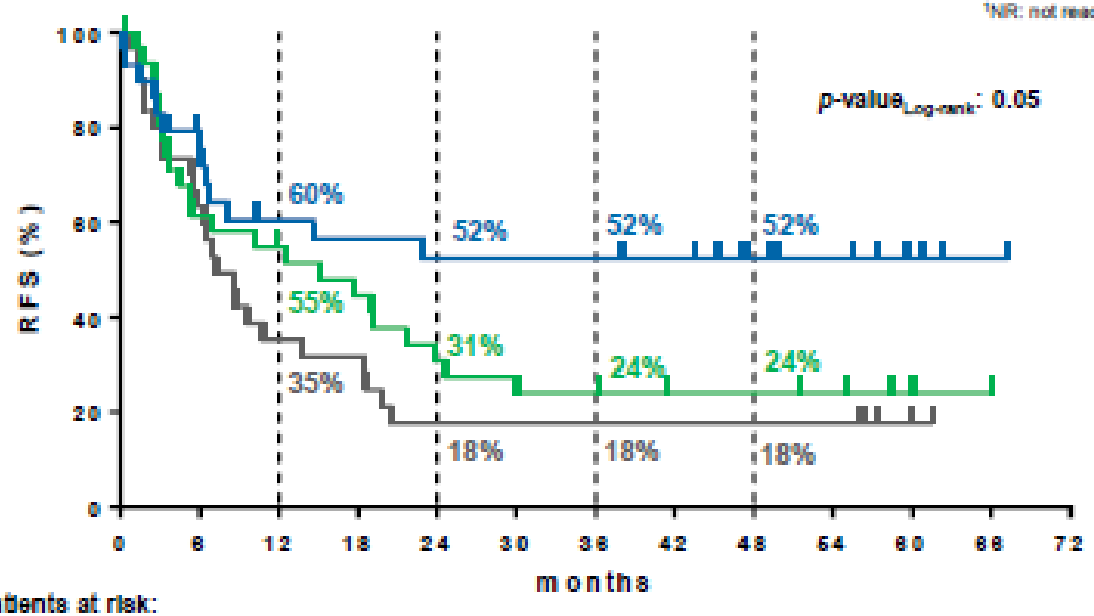
THE IMMUNED STUDY

RFS by BRAF mutation status

BRAF wildtype

	NIVO+IPI (n=29)	NIVO (n=32)	Placebo (n=31)
Median, mo (95% CI)	NR[1] (8.5, NR[1])	16.2 (4.6, 23.8)	7.3 (5.5, 13.8)
HR (95% CI) vs.placebo	0.46 (0.23, 0.89)	0.78 (0.43, 1.36)	–
HR (95% CI) vs. NIVO	0.58 (0.28, 1.11)	–	–

[1]NR: not reached.



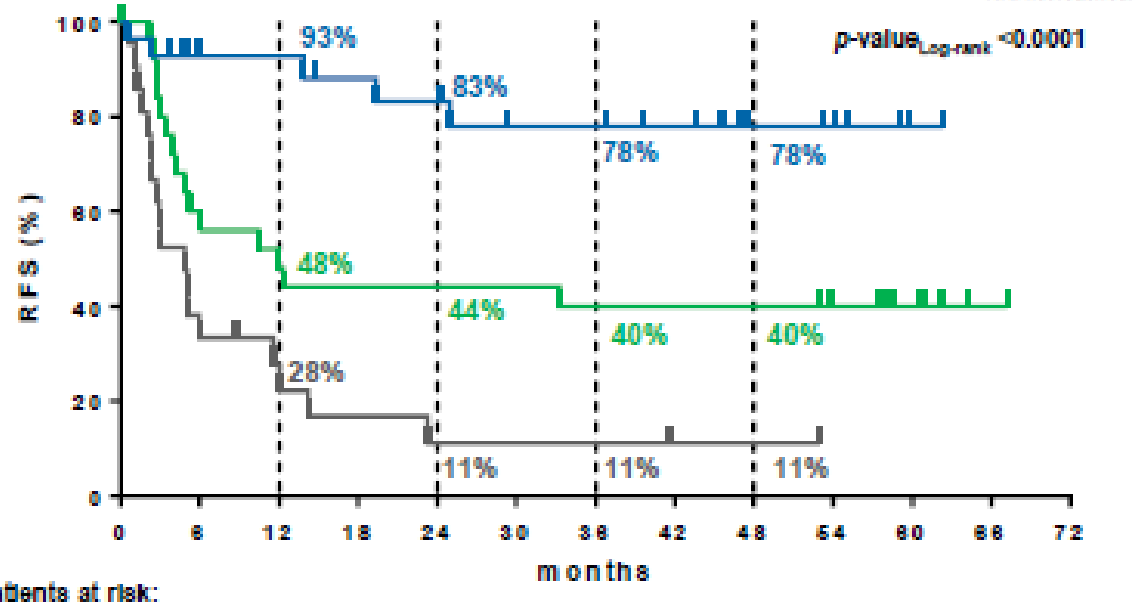
Patients at risk:

NIVO + IPI	29	20	15	14	13	13	13	12	8	6	3	1
NIVO	32	19	16	13	9	8	7	5	5	4	2	1
Placebo	31	18	10	9	5	5	5	5	5	5	1	-

BRAF mutated

	NIVO+IPI (n=27)	NIVO (n=27)	Placebo (n=21)
Median, mo (95% CI)	NR (NR[1])	11.9 (4.1, NR[1])	4.9 (2.3, 11.5)
HR (95% CI) vs.placebo	0.11 (0.04, 0.30)	0.46 (0.22, 0.90)	–
HR (95% CI) vs. NIVO	0.25 (0.09, 0.70)	–	–

[1]NR: not reached.



Patients at risk:

NIVO + IPI	27	20	20	18	17	14	14	12	6	5	1	-
NIVO	27	15	12	11	11	11	10	10	10	8	5	1
Placebo	21	7	5	3	3	2	2	1	1	-	-	-

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Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01654-3/fulltext

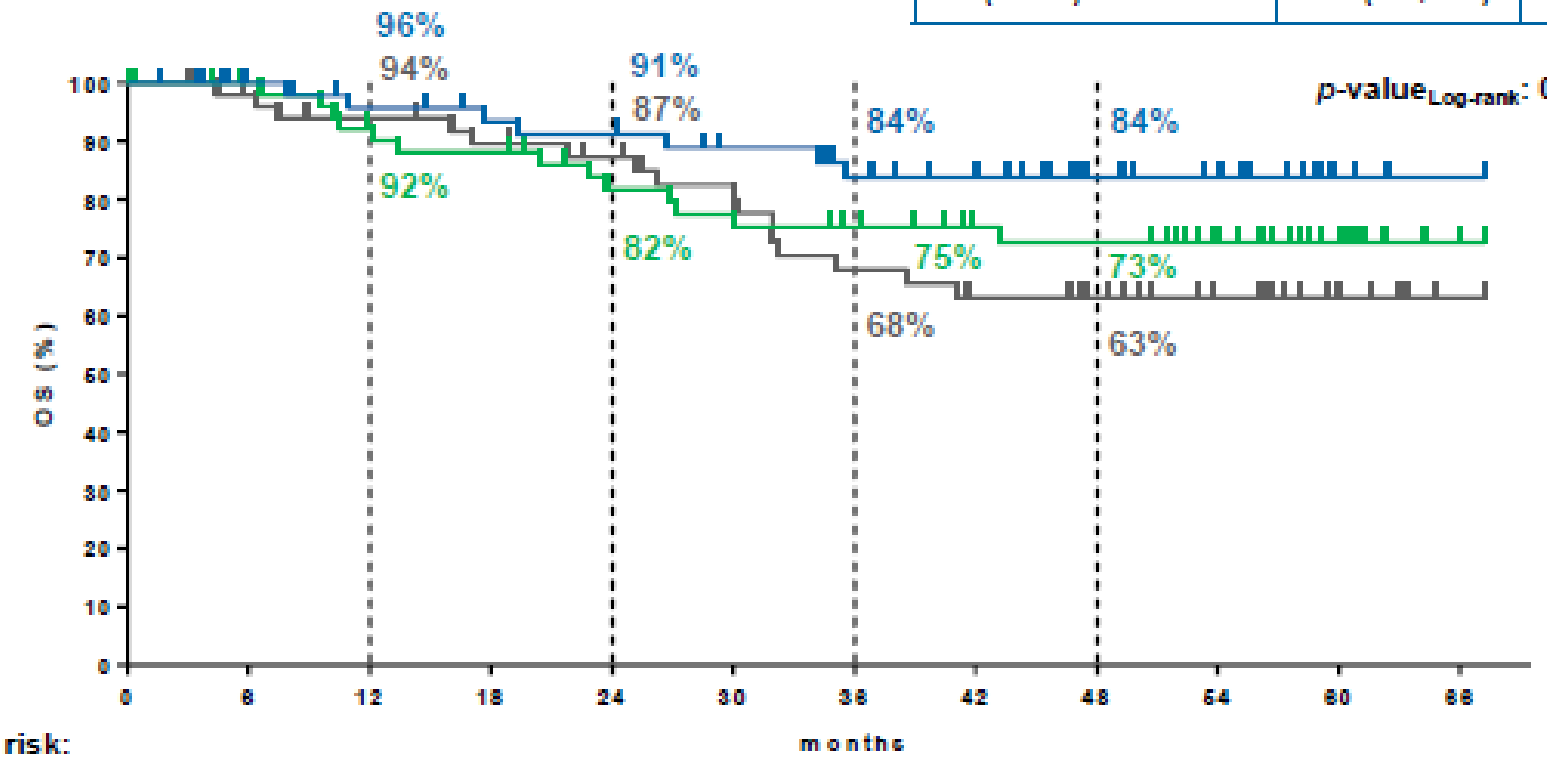
Schadendorf D et al. ESMO 2022;Abstract 7840

THE IMMUNED STUDY

Key secondary endpoint: OS in all patients

Data cut-off date Sep 23, 2021
Median follow-up time: 49.2 months

	NIVO+IPI (n=56)	NIVO (n=59)	Placebo (n=52)
Median OS, mo (95% CI)	NR[1]	NR[1]	NR[1] (38.59,NR)
HR (95% CI) vs placebo	0.41 (0.17, 0.98)	0.75 (0.36, 1.56)*	-
HR (95% CI) vs NIVO	0.55 (0.22, 1.38)	-	-



[1]NR: not reached
*Hazard ratio probably invalid due to violation of proportional hazard assumption.

Schadendorf D et al. ESMO 2022;Abstract 7840

- 36 events (22%) within 167 patients of the intention-to-treat population

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Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01654-3/fulltext

Conclusions:

- Checkpoint therapy has changed the outcome of advanced melanoma
- Standard therapy includes first-line PD1 based single agent or combinations
- Newer checkpoint combinations seek to overcome resistant mechanisms
- Adoptive T cell therapies will allow further improvements in outcomes
- Second- and third-line options are upcoming. Triplet, quadruplet, and more are coming
- Tumor Infiltrating Lymphocyte (TIL therapy) is at FDA for approval
- Clinical trials, clinical trials, clinical trials ….
- Complete response …

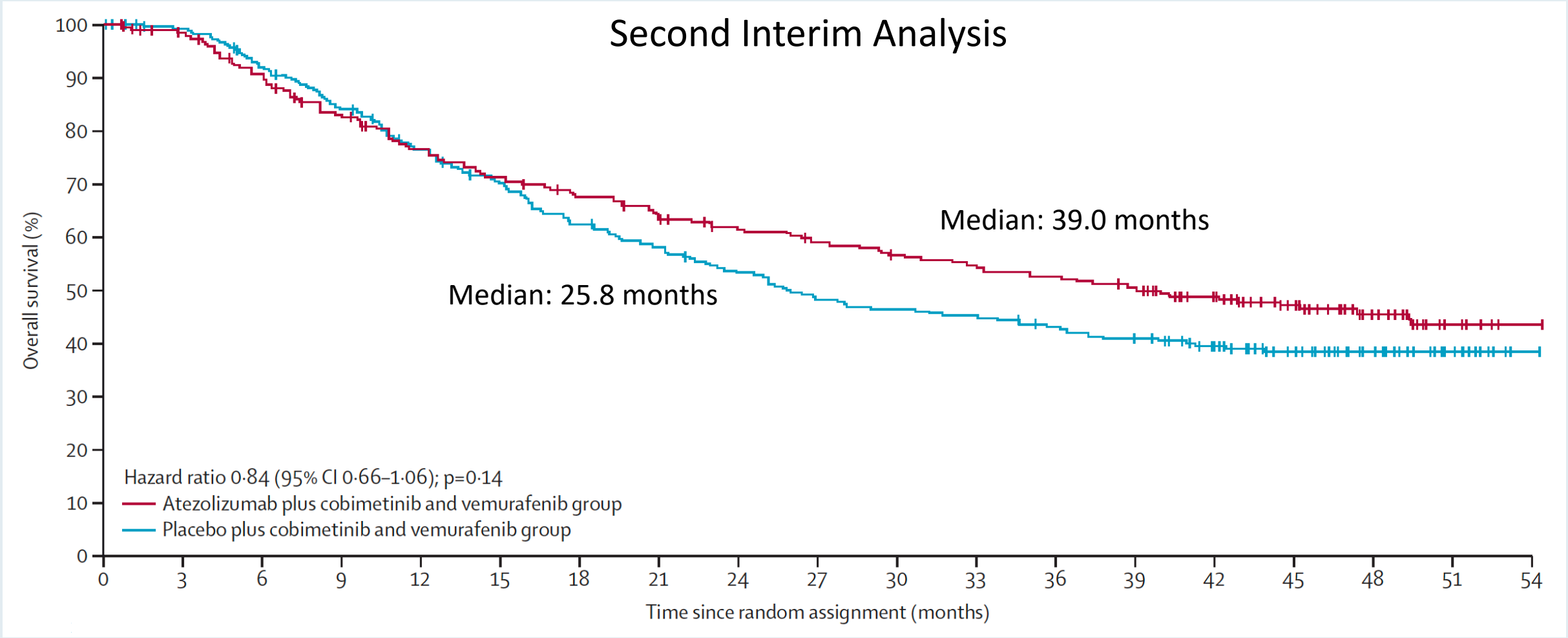
APPENDIX

Lancet Oncol 2023;24:33-44

Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in *BRAF*^{V600} mutation-positive advanced melanoma (IMspire150): second interim analysis of a multicentre, randomised, phase 3 study

Paolo A Ascierto, Daniil Stroyakovskiy, Helen Gogas, Caroline Robert, Karl Lewis, Svetlana Protsenko, Rodrigo P Pereira, Thomas Eigentler, Piotr Rutkowski, Lev Demidov, Natalia Zhukova, Jacob Schachter, Yibing Yan, Ivor Caro, Christian Hertig, Cloris Xue, Lieke Kusters, Grant A McArthur, Ralf Gutzmer**

IMspire150: Overall Survival with First-Line Atezolizumab and Cobimetinib for BRAFV600 Mutation-Positive Advanced Melanoma



Ascierto PA et al. *Lancet Oncol* 2023;24:33-44.

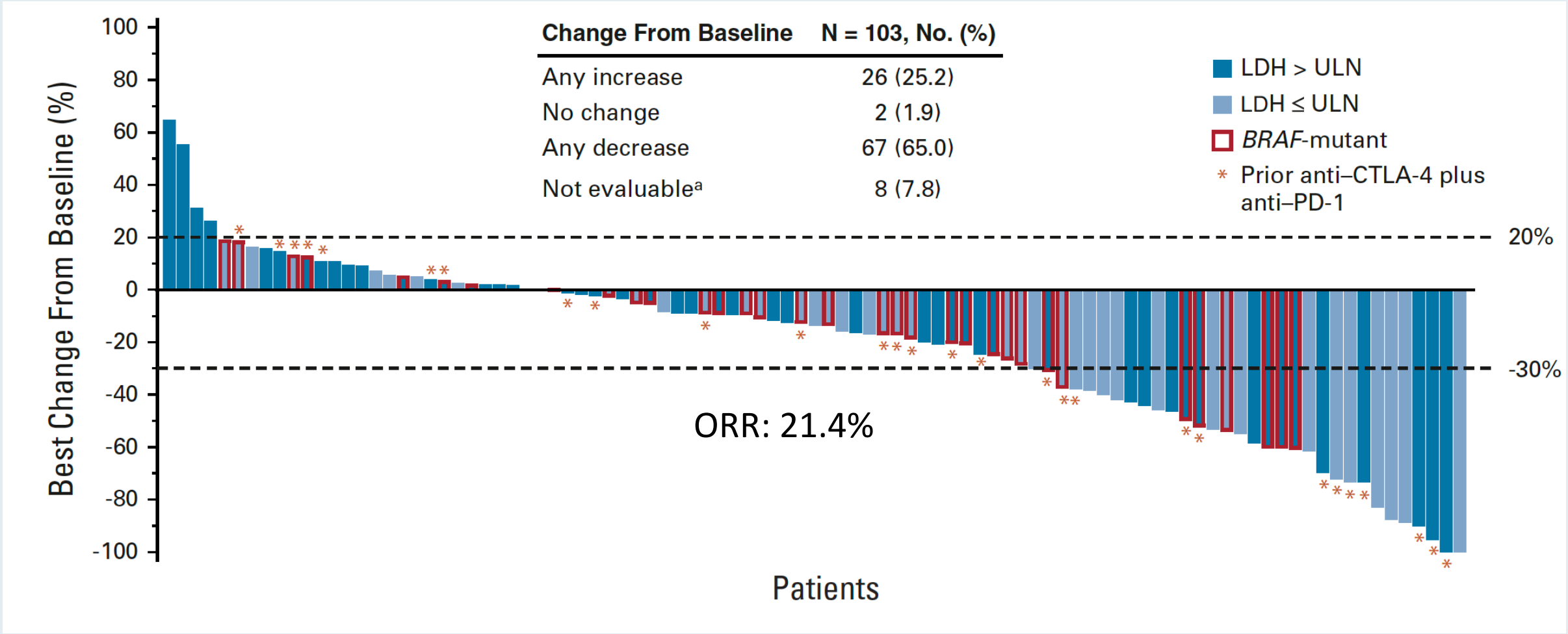
original reports

Phase II LEAP-004 Study of Lenvatinib Plus Pembrolizumab for Melanoma With Confirmed Progression on a Programmed Cell Death Protein-1 or Programmed Death Ligand 1 Inhibitor Given as Monotherapy or in Combination

Ana Arance, MD, PhD[1]; Luis de la Cruz-Merino, MD, PhD[2]; Teresa M. Petrella, MD[3]; Rahima Jamal, MD[4]; Lars Ny, MD, PhD[5]; Ana Carneiro, MD, PhD[6]; Alfonso Berrocal, MD[7]; Ivan Márquez-Rodas, MD, PhD[8]; Anna Spreafico, MD, PhD[9]; Victoria Atkinson, MD[10]; Fernanda Costa Svedman, MD, PhD[11]; Andrew Mant, MBBS[12]; Muhammad A. Khattak, MBBS, FRACP[13]; Catalin Mihalcioiu, MD[14]; Sekwon Jang, MD[15]; C. Lance Cowey, MD[16]; Alan D. Smith, MD[17]; Natalyn Hawk, MD, PhD[18]; Ke Chen, MS[19]; Scott J. Diede, MD, PhD[19]; Clemens Krepler, MD[19]; and Georgina V. Long, MBBS, PhD[20,21,22,23]

J Clin Oncol 2023;41(1):75-85

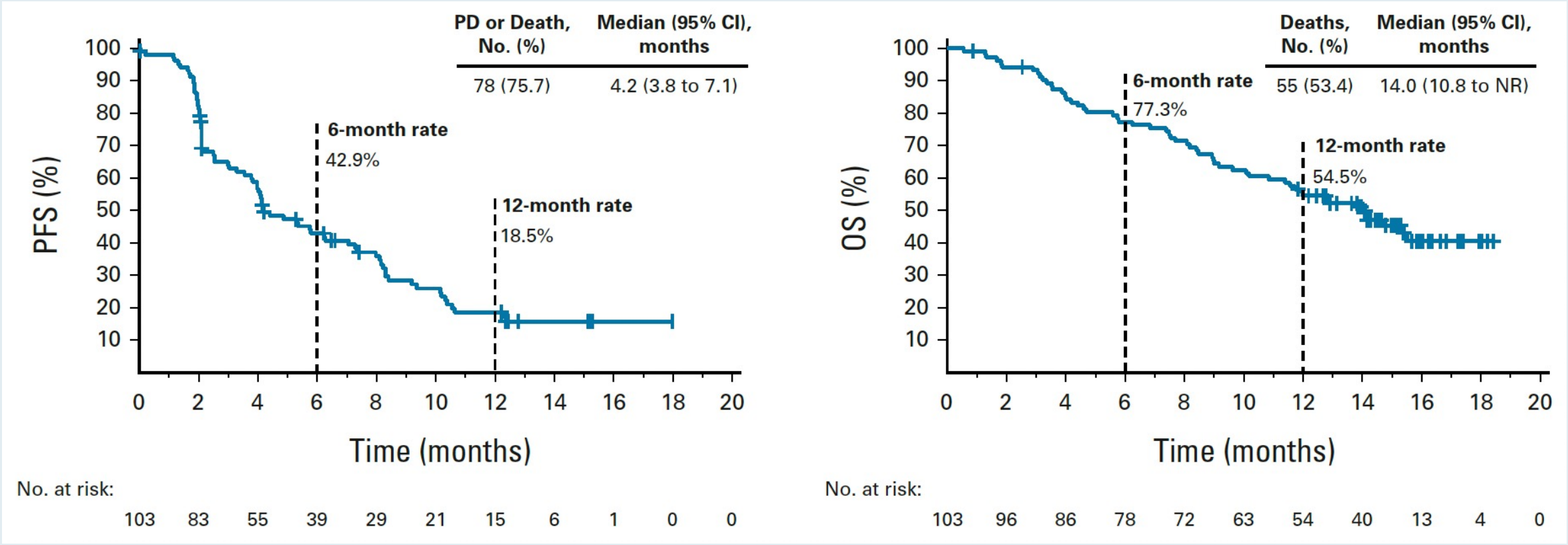
LEAP-004 Primary Endpoint: ORR by Independent Central Review



ORR = objective response rate

Arance A et al. *J Clin Oncol* 2023;41(1):75-85.

LEAP-004: PFS and OS



PFS = progression-free survival; OS = overall survival

Arance A et al. *J Clin Oncol* 2023;41(1):75-85.

LEAP-004: Treatment-Related AE summary

AE	All Patients (N = 103), No. (%)
Treatment-Related AE Summary	
Any	99 (96.1)
Grade 3	42 (40.8)
Grade 4	4 (3.9)
Grade 5	1 (1.0)[a]
Serious	19 (18.4)
Led to discontinuation of lenvatinib, pembrolizumab, or both	8 (7.8)
Led to interruption of lenvatinib, pembrolizumab, or both	61 (59.2)

AE = adverse event

Arance A et al. *J Clin Oncol* 2023;41(1):75-85.

Open access Original research

Journal for ImmunoTherapy of Cancer

Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study

Jason Chesney,[1] Karl D Lewis,[2] Harriet Kluger,[3] Omid Hamid,[4] Eric Whitman ,[5] Sajeve Thomas,[6] Martin Wermke,[7] Mike Cusnir,[8] Evidio Domingo-Musibay ,[9] Giao Q Phan,[10] John M Kirkwood,[11] Jessica C Hassel ,[12] Marlana Orloff,[13] James Larkin,[14] Jeffrey Weber ,[15] Andrew J S Furness,[14] Nikhil I Khushalani ,[16] Theresa Medina,[2] Michael E Egger,[1] Friedrich Graf Finckenstein,[17] Madan Jagasia,[17] Parameswaran Hari,[17] Giri Sulur,[17] Wen Shi,[17] Xiao Wu,[17] Amod Sarnaik [16]

J Immunother Cancer 2022;10(12):e005755.

Pooled Analysis of Patients Treated with Lifileucel in the Phase II C-144-01 Study

IRC assessment for Cohorts 2 and 4 and pooled Cohorts 2 and 4 (full analysis set)

Response (RECIST V.1.1)*	Cohort 2 (n=66)	Cohort 4 (n=87)	Pooled Cohorts 2+4 (N=153)
ORR, n (%)	23 (34.8)	25 (28.7)	48 (31.4)
(95% CI)	(23.5 to 47.6)	(19.5 to 39.4)	(24.1 to 39.4)
Best overall response, n (%)			
CR	5 (7.6)	3 (3.4)	8 (5.2)
PR	18 (27.3)	22 (25.3)	40 (26.1)
SD	24 (36.4)	47 (54.0)	71 (46.4)
Non-CR/non-PD†	1 (1.5)	0	1 (0.7)
PD	15 (22.7)	12 (13.8)	27 (17.6)
Non-evaluable‡	3 (4.5)	3 (3.4)	6 (3.9)
Median DOR,§ months (range)	NR (1.4+ to 45.0+)¶	10.4 (1.4+ to 26.3+)	NR (1.4+ to 45.0+)
Median study follow-up,** months	36.6	23.5	27.6

*Objective response refers to patients with the best overall response of CR and PR. 95% CI for ORR was calculated using the Clopper-Pearson exact test.
†Patient did not have measurable target lesions by IRC and had best overall response of non-CR/non-PD per IRC assessment.
‡Six patients were non-evaluable for response (five due to early death; one due to new anticancer therapy).
§Based on responders and using Kaplan-Meier product-limit estimates.
¶Note: + refers to censored.
**Based on the reverse Kaplan-Meier method.

Chesney J et al. *J Immunother Cancer* 2022;10(12):e005755.

RTP RESEARCH TO PRACTICE