AIBT Associazione Italiana di Immunogenetica e Biologia dei Trapianti
XXX Congresso Nazionale
Napoli, 10/12 ottobre 2024
"The programme of this event has been approved by the EFI Education Committee"

La rivoluzione dell'immunoterapia nel trattamento del melanoma

Margaret Ottaviano, MD, PhD

Unit of Melanoma, Cancer Immunotherapy and Innovative Therapies

Istituto Nazionale Tumori – Fondazione "G. Pascale"
Director Paolo A. Ascierto

DISCLOSURES

Speaker Fees, Travel and accommodation

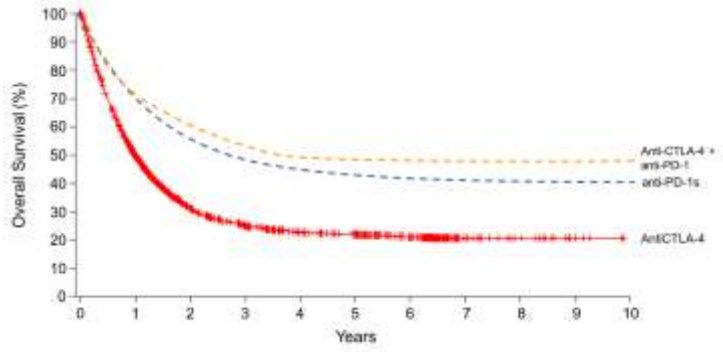
Bristol-Myers-Squibb
MSD
Sun Pharma
Pierre Fabre
Novartis
Regeneron

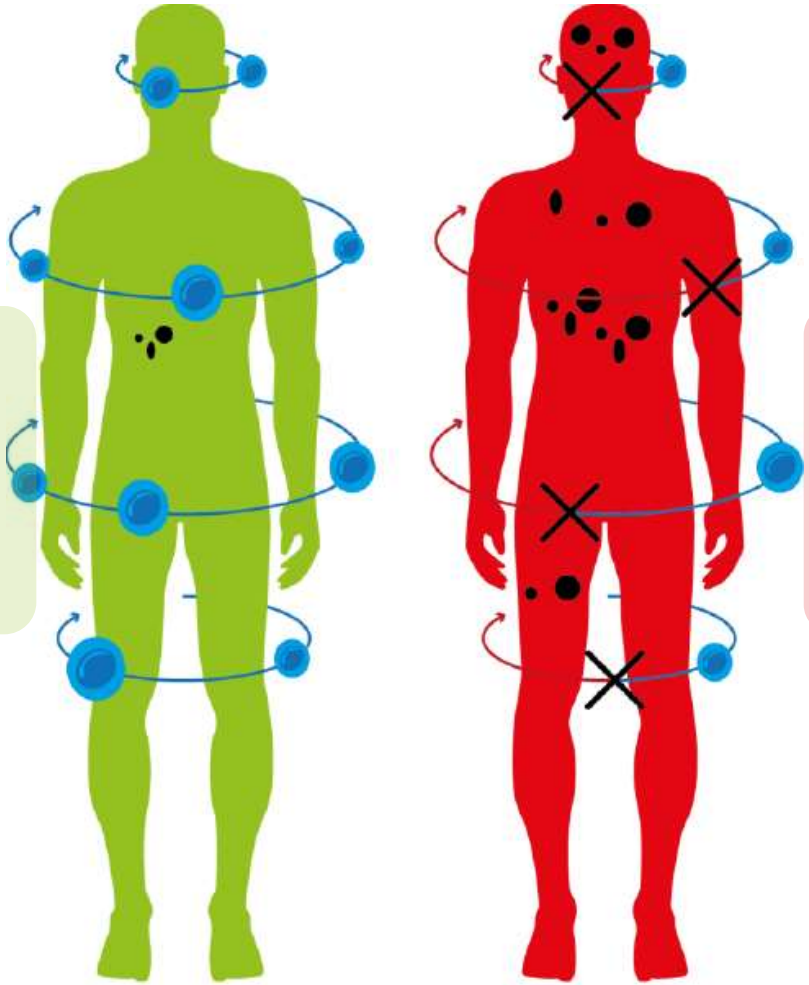
Patient characteristics affecting immune surveillance

Active immune surveillance

Long-term benefit patients

- ≤ 3 brain metastases (size < 2 cm)
- Low tumour burden (< 3 organ involved?)
- Normal LDH

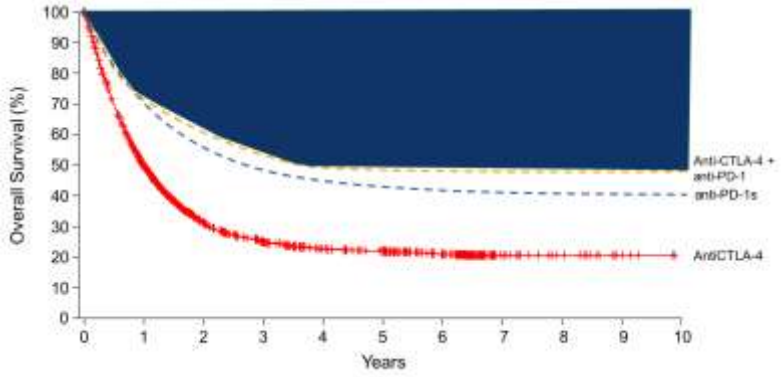




Inactive immune surveillance

No long-term benefit patients

- Multiple (>3) brain metastases
- High tumour burden (>3 organ involved?)
- High LDH



LDH, lactate dehydrogenase

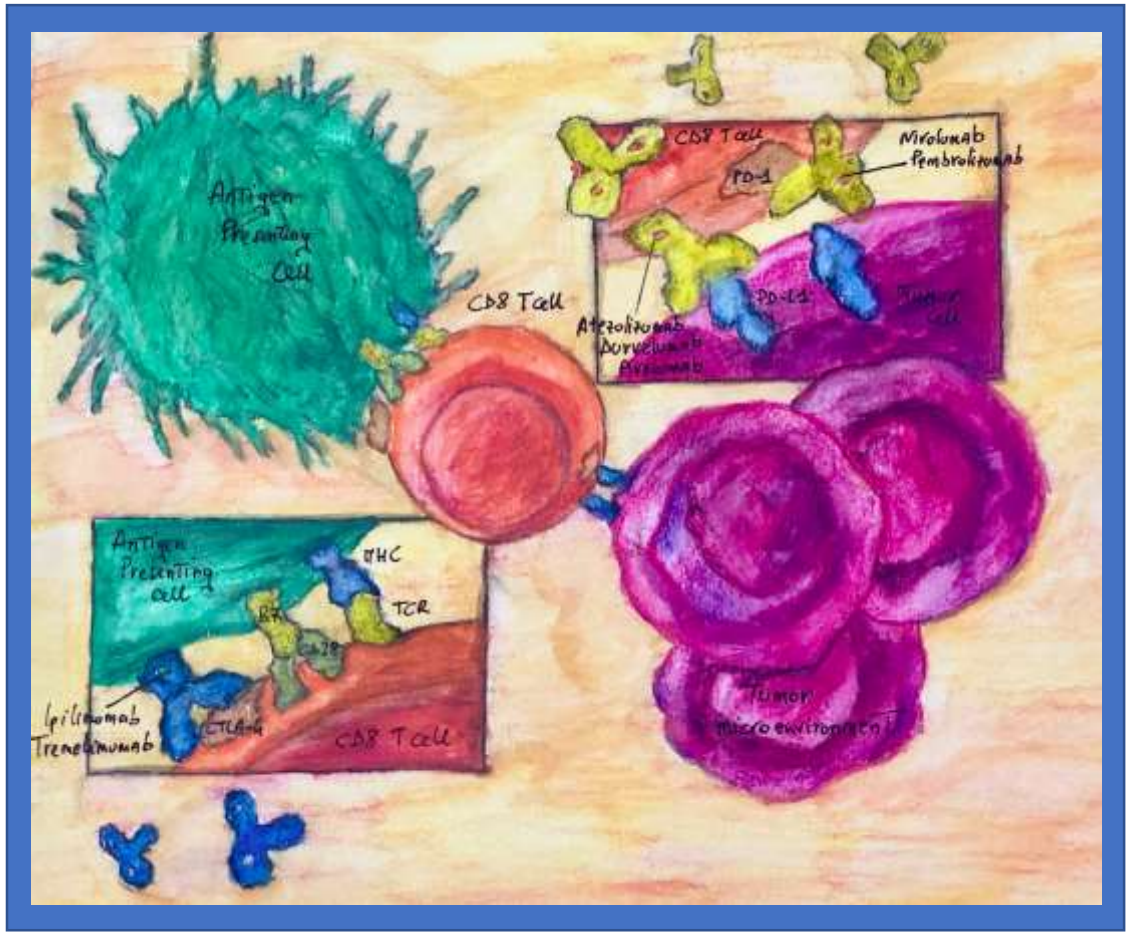
Ascierto P, Dummer R. Oncoimmunology. 2018; Ascierto P, Ed. Session ASCO. 2019

Agenda

Immune checkpoint inhibitors

TIL therapy

Oncolytic virus therapy



Cancer vaccines

CAR-T cells

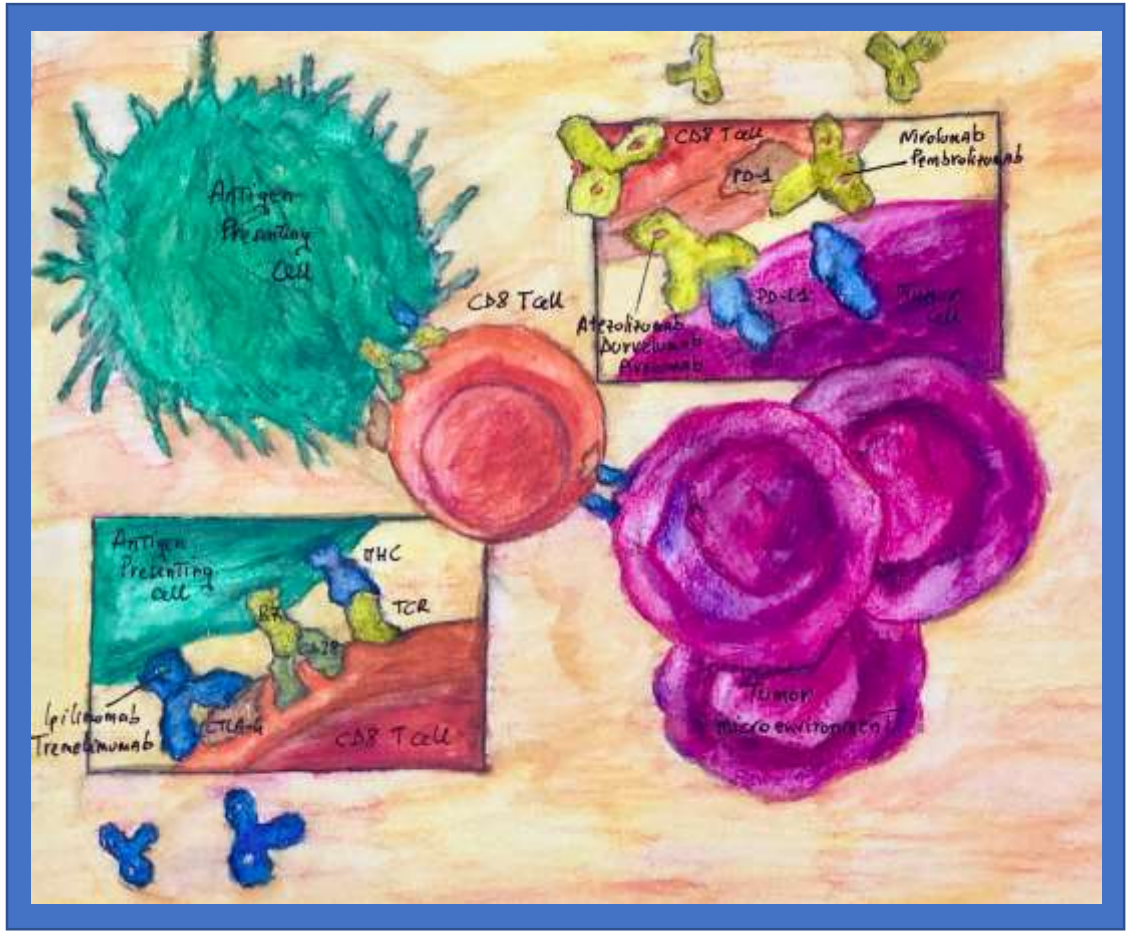
Ottaviano M. Virchows Arch 2019

Agenda

TIL therapy

Cancer vaccines

Immune checkpoint inhibitors



Oncolytic virus therapy

CAR-T cells

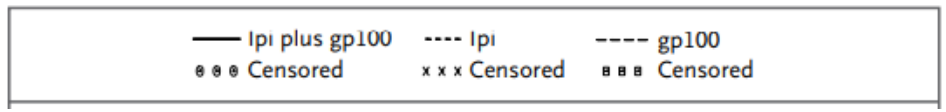
Ottaviano M. Virchows Arch 2019

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

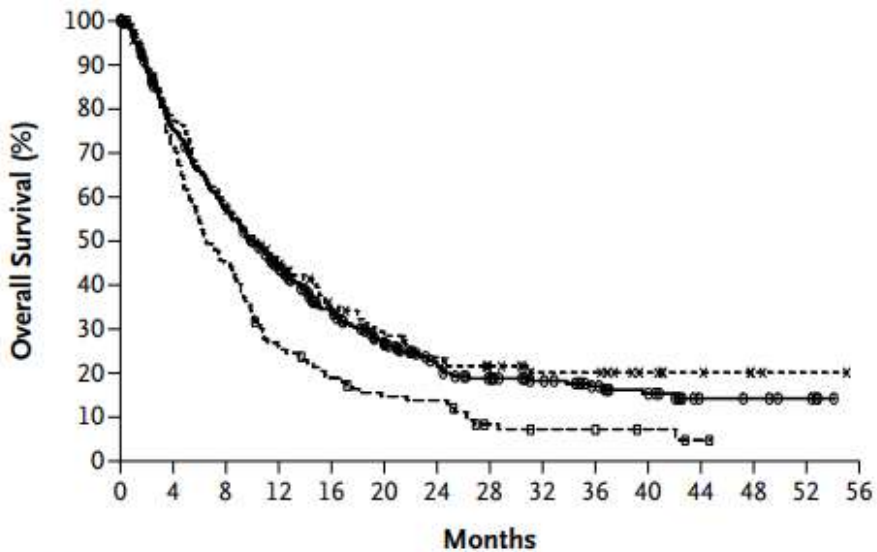
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

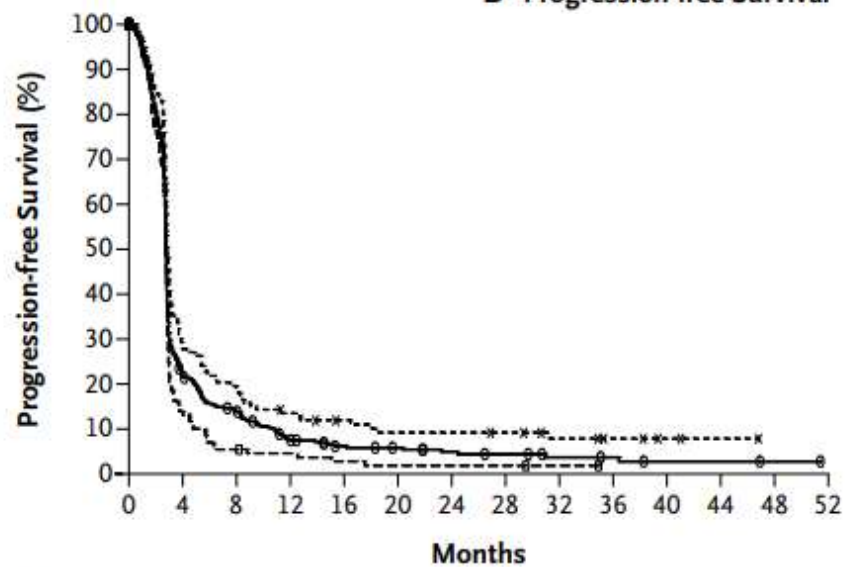


A Overall Survival



No. at Risk															
Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

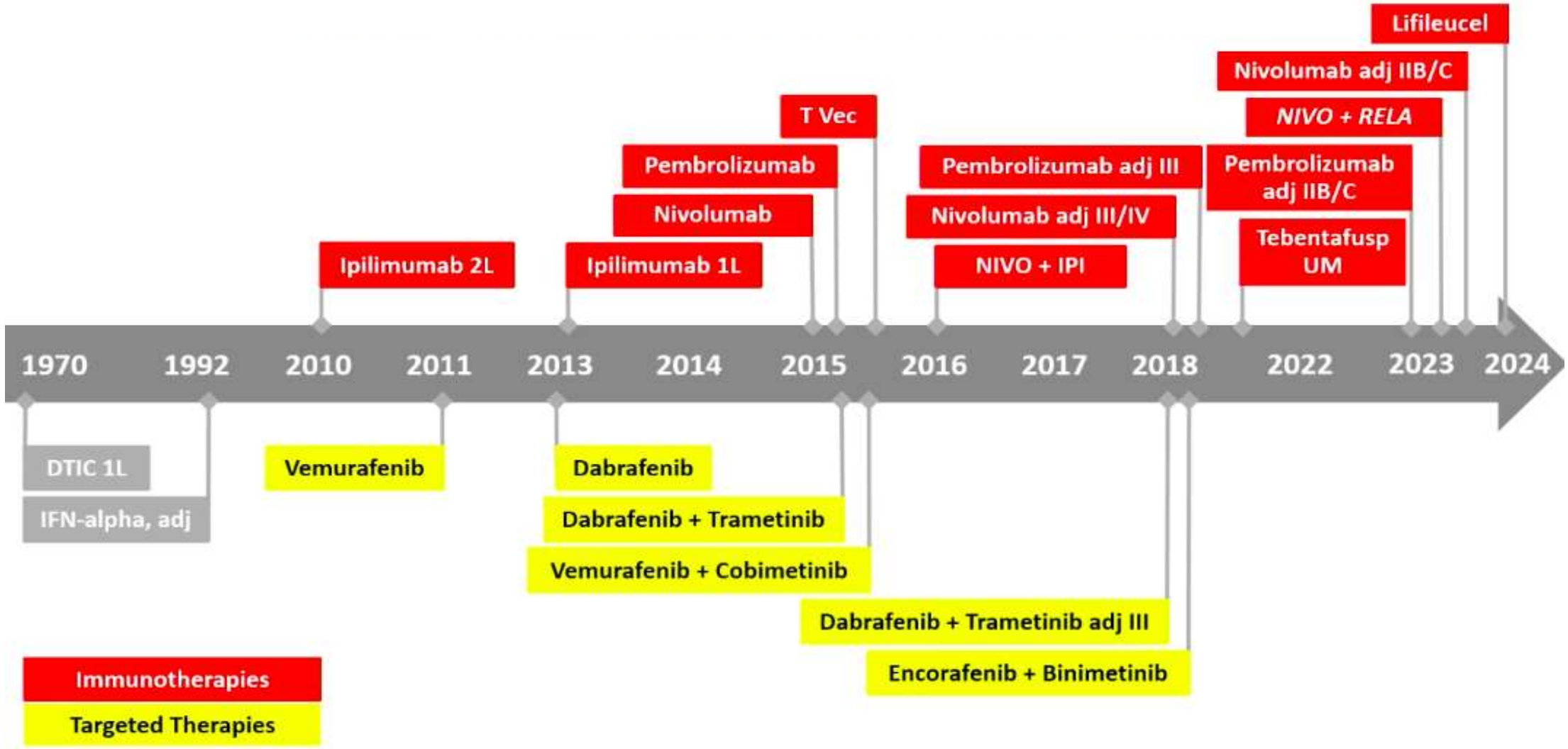
B Progression-free Survival



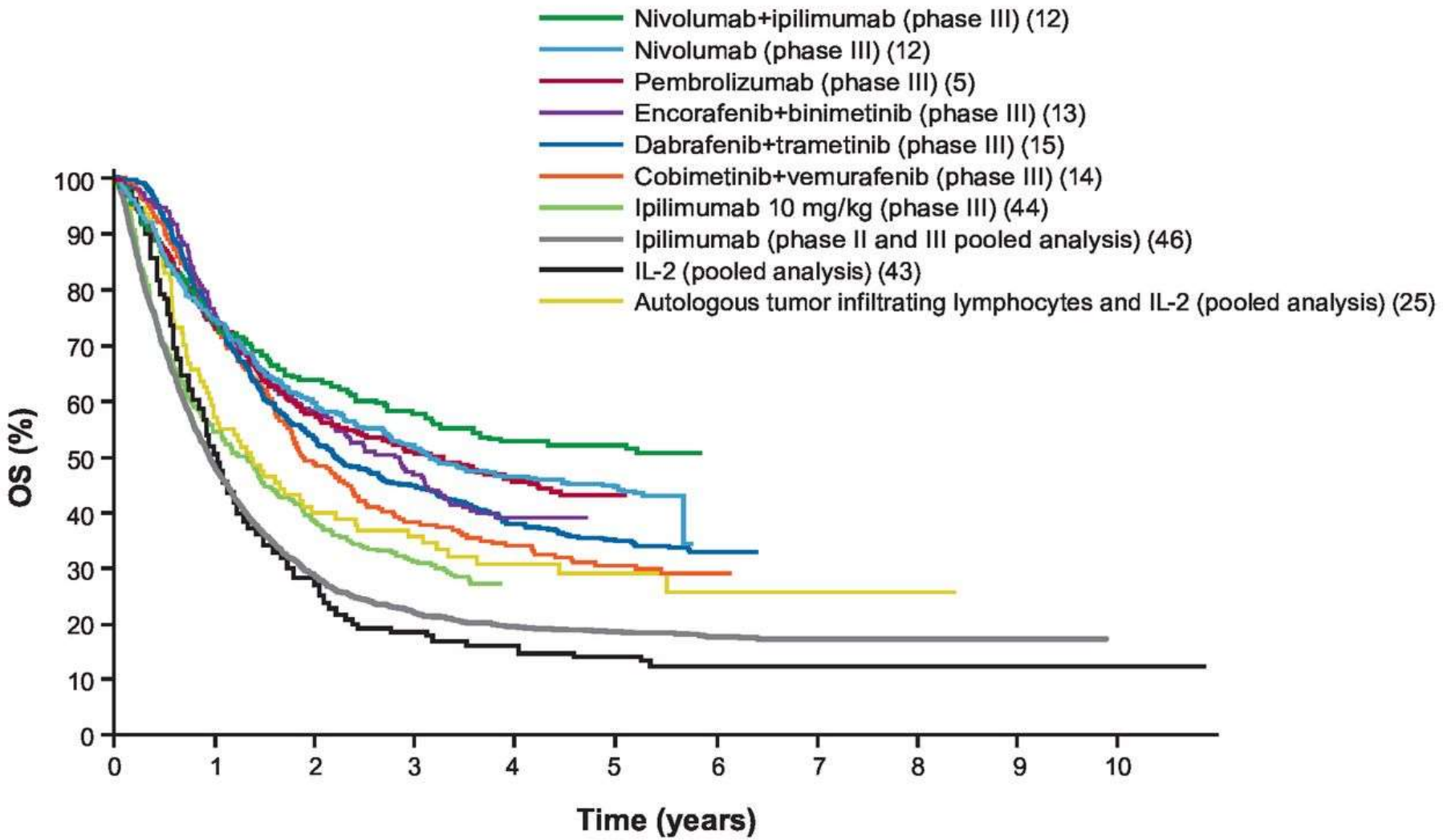
No. at Risk														
Ipi plus gp100	403	85	52	27	17	14	10	8	5	4	2	2	1	0
Ipi	137	37	26	17	13	10	10	9	6	4	2	1	0	0
gp100	136	18	7	5	3	2	2	2	1	0	0	0	0	0

N Engl J Med. 2010 Aug 19;363(8):711-23.

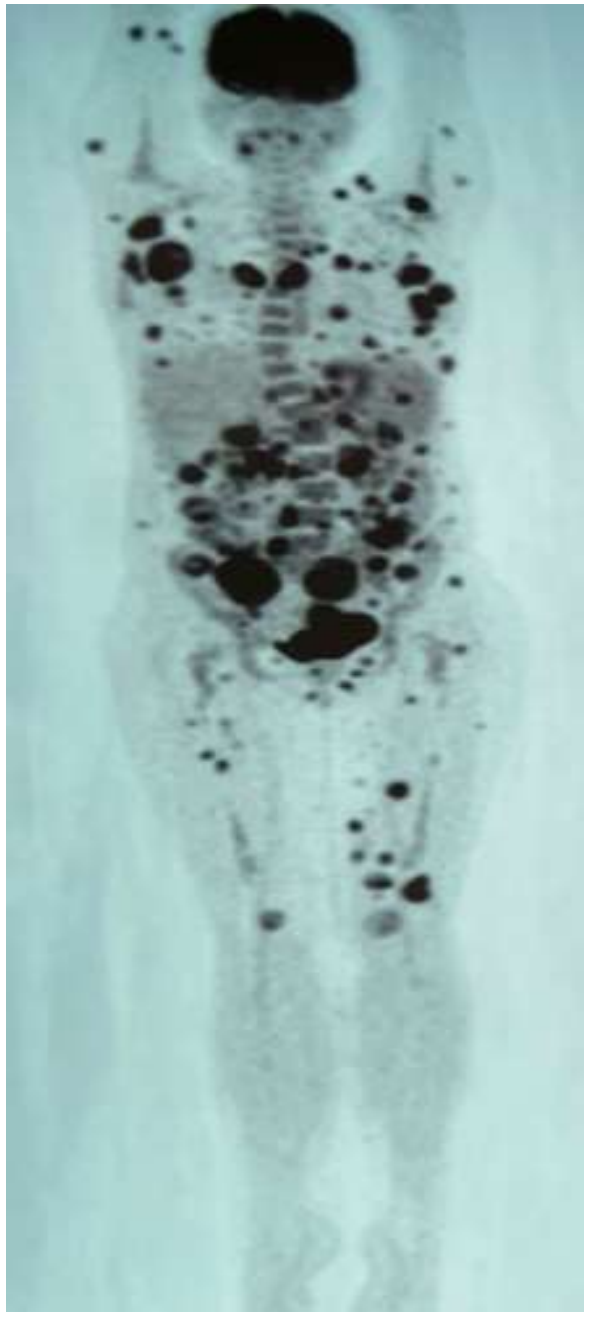
Therapeutic revolution



Long-term OS in clinical trials with immuno-oncology agents and TT In advanced melanoma



Olivier Michielin et al. J Immunother Cancer 2020

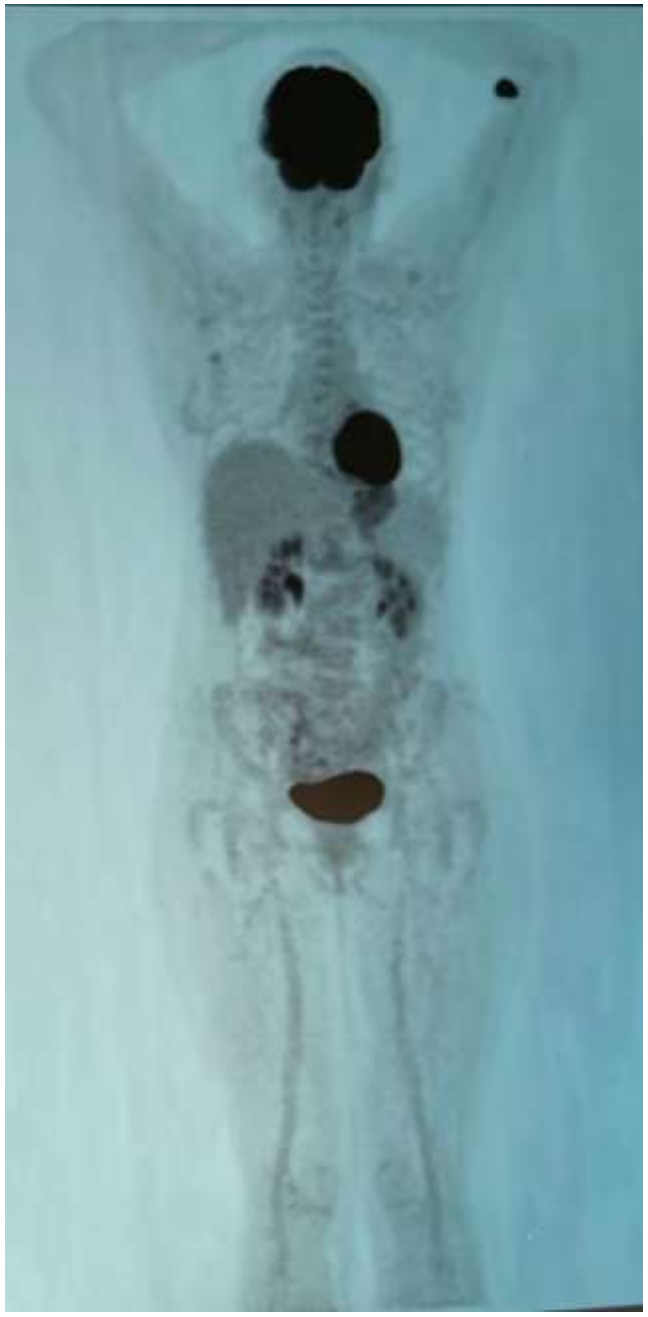


F.L. 47 Yo ♀

- ✓ June 2023: pT4b nodular cutaneous melanoma
- ✓ Basal CT scan: **multiple asymptomatic brain mets**; multiple bone, liver, splenic, lymphnodes, sub-cutaneous, bowel mets
- ✓ LDH > 2xULN
- ✓ PS ECOG 0

July 2023: start Nivolumab 1 mg/Kg plus Ipilimumab 3 mg/Kg x 4 cycles

CHECKMATE 067



December 2023:
4 cycle of combo ICIs
and 2 cycle of Nivolumab 480 mg…BUT
Hepatitis G2 and Colitis G2

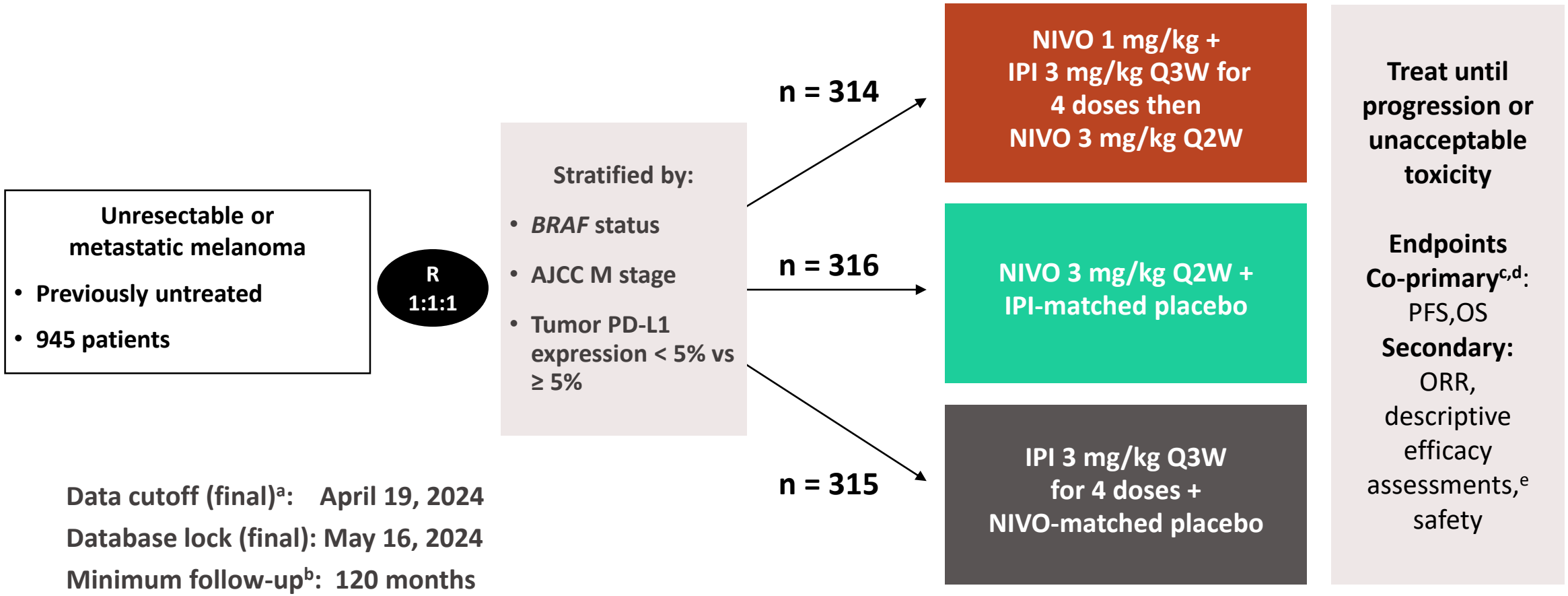
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma

J.D. Wolchok, V. Chiarion-Sileni, P. Rutkowski, C.L. Cowey, D. Schadendorf, J. Wagstaff, P. Queirolo, R. Dummer, M.O. Butler, A.G. Hill, M.A. Postow, C. Gaudy-Marqueste, T. Medina, C.D. Lao, J. Walker, I. Márquez-Rodas, J.B.A.G. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, S. Sandhu, C. Lebbé, P.A. Ascierto, G.V. Long, C. Ritchings, A. Nassar, M. Askelson, M.P. Benito, W. Wang, F.S. Hodi, and J. Larkin, for the CheckMate 067 Investigators*

CheckMate 067: study design and follow-up length



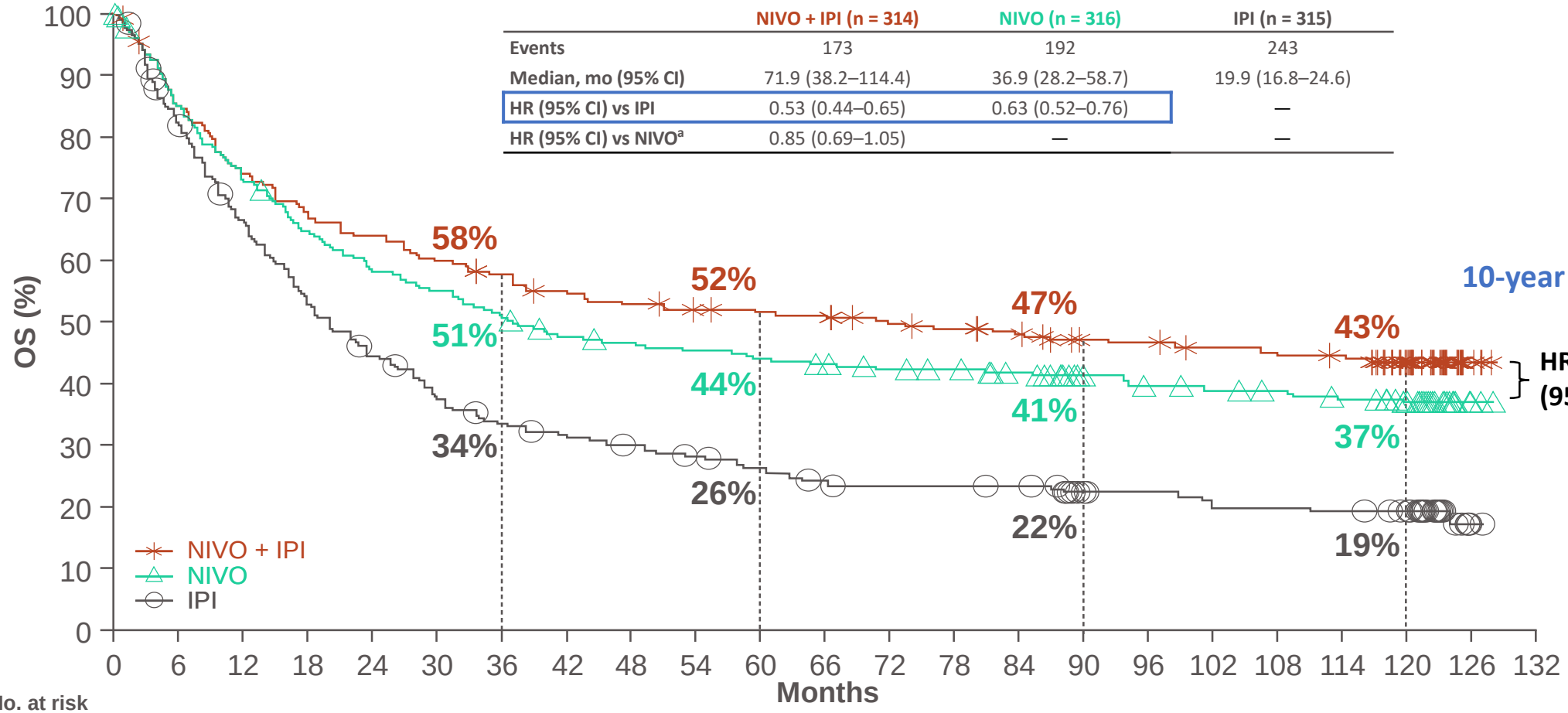
Data cutoff (final)[a]: April 19, 2024
Database lock (final): May 16, 2024
Minimum follow-up[b]: 120 months

[a]No patient was being treated on study at the time of the final DBL. [b]From the date the last patient was randomized. [c]The study was not powered for a comparison between NIVO + IPI and NIVO. [d]NIVO + IPI or NIVO alone vs IPI. [e]NIVO + IPI vs NIVO alone.

Courtesy of J. Larkin at ESMO 2024

Overall survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Events	173	192	243
Median, mo (95% CI)	71.9 (38.2–114.4)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.53 (0.44–0.65)	0.63 (0.52–0.76)	—
HR (95% CI) vs NIVO[a]	0.85 (0.69–1.05)	—	—



10-year **OS analysis**

HR = 0.85[a]
(95% CI, 0.69–1.05)

No. at risk

NIVO + IPI	314	265	227	210	199	187	179	169	163	158	156	153	147	144	139	126	124	120	117	115	92	10	0
NIVO	316	265	231	201	181	171	158	145	141	137	134	130	126	123	118	107	102	98	96	92	77	4	0
IPI	315	253	203	163	135	113	100	94	87	81	75	68	64	64	63	50	49	44	43	42	35	3	0

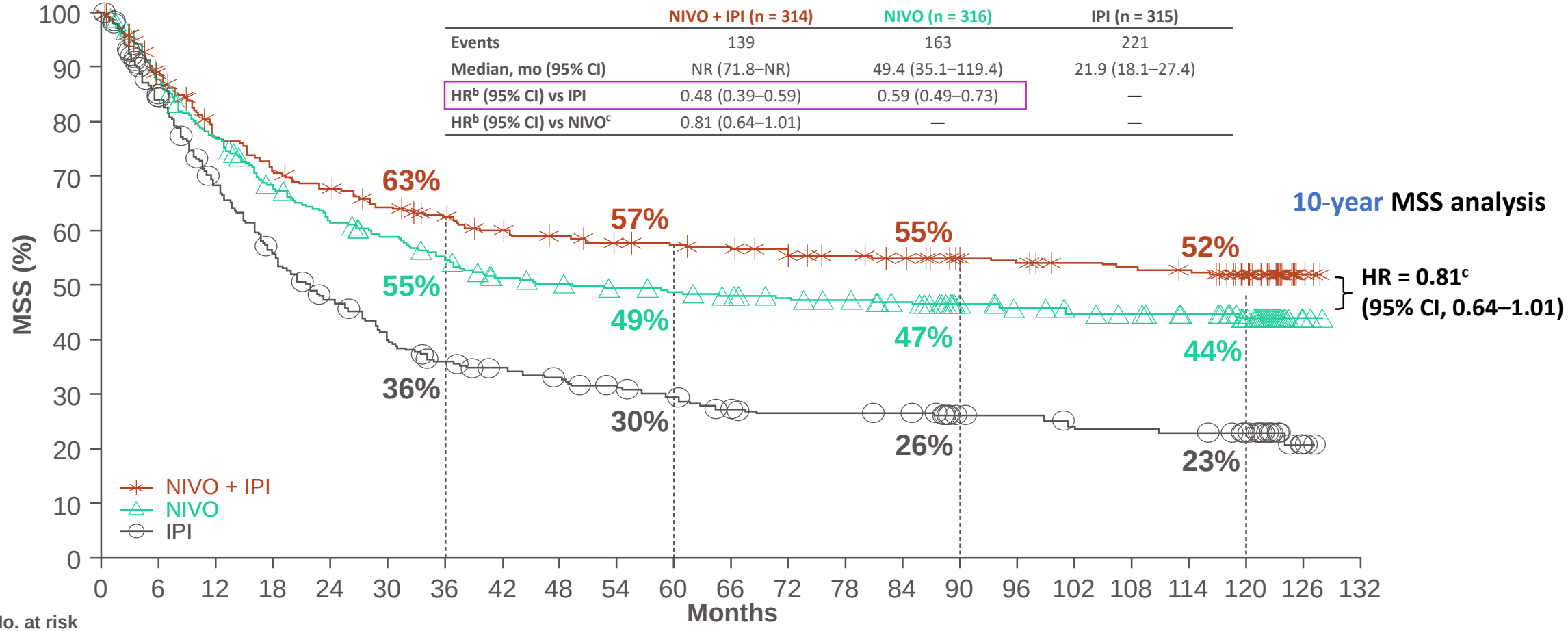
- At 10 years, NIVO + IPI and NIVO alone continued to demonstrate a significant and durable OS benefit

[a]Descriptive comparison.

Courtesy of J. Larkin at ESMO 2024

Melanoma-specific survival (MSS)a

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Events	139	163	221
Median, mo (95% CI)	NR (71.8–NR)	49.4 (35.1–119.4)	21.9 (18.1–27.4)
HR[b] (95% CI) vs IPI	0.48 (0.39–0.59)	0.59 (0.49–0.73)	—
HR[b] (95% CI) vs NIVO[c]	0.81 (0.64–1.01)	—	—



No. at risk

NIVO + IPI	314	265	227	210	199	187	179	169	163	158	156	153	147	144	139	126	124	120	117	115	92	10	0
NIVO	316	265	231	201	181	171	158	145	141	137	134	130	126	123	118	107	102	98	96	92	77	4	0
IPI	315	253	203	163	135	113	100	94	87	81	75	68	64	64	63	50	49	44	43	42	35	3	0

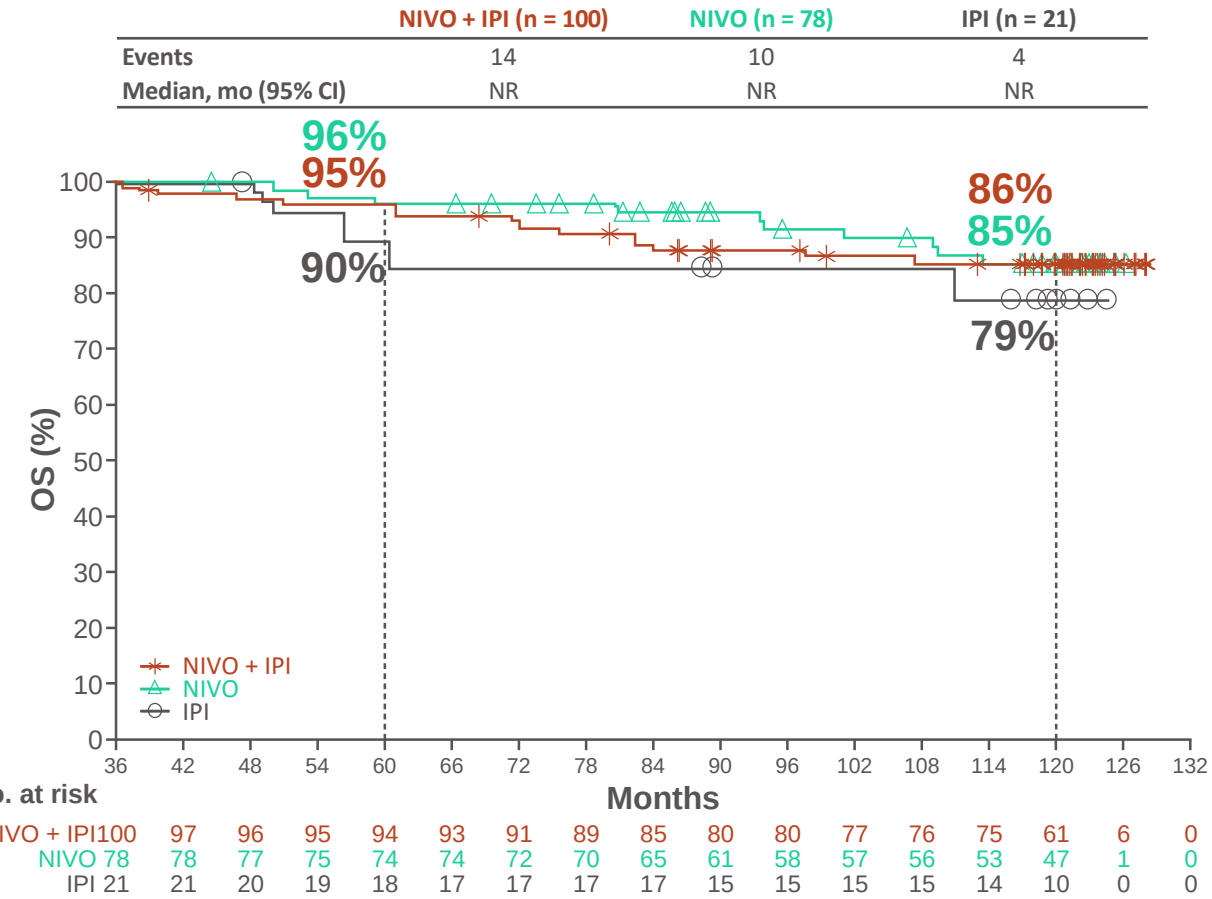
- After 10 years, median MSS was not reached (> 120 months) with NIVO + IPI and diverged from OS (52% vs 43%)
  - Results were consistent by BRAF mutation and PD-L1 expression status (Supplemental Figures S1 and S2)

[a]In this post hoc descriptive analysis, an event was defined as death due to melanoma or euthanasia due to disease progression; any other death was censored. [b]Unstratified. [c]Descriptive comparison.

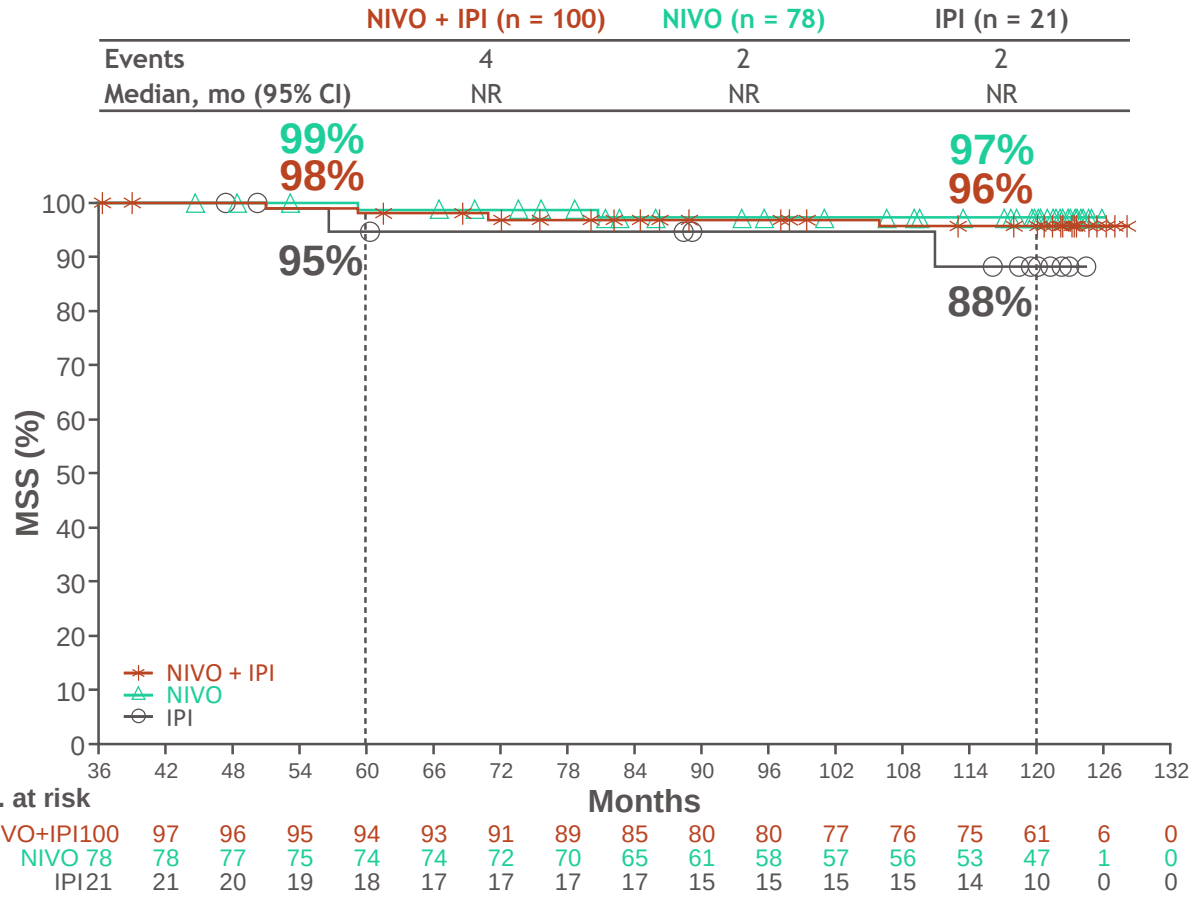
Courtesy of J. Larkin at ESMO 2024

OS and MSS in patients with PFS at 3 years

OS

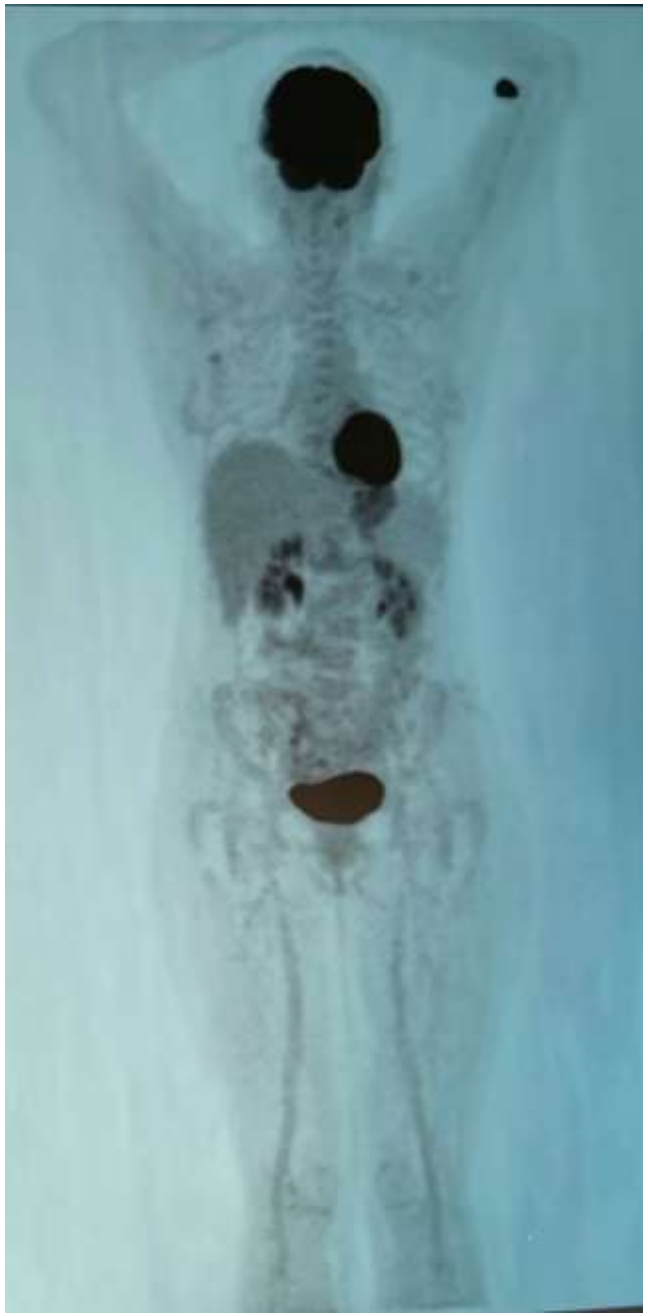


MSS



- PFS at 3 years may be a good surrogate for long-term survival, with 10-year MSS rates ≥ 96% in the NIVO-containing arms

Courtesy of J. Larkin at ESMO 2024



December 2023:
4 cycle of combo ICIs
and 2 cycle of Nivolumab 480 mg…

BUT

Hepatitis G2 and Colitis G2

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

Study design

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

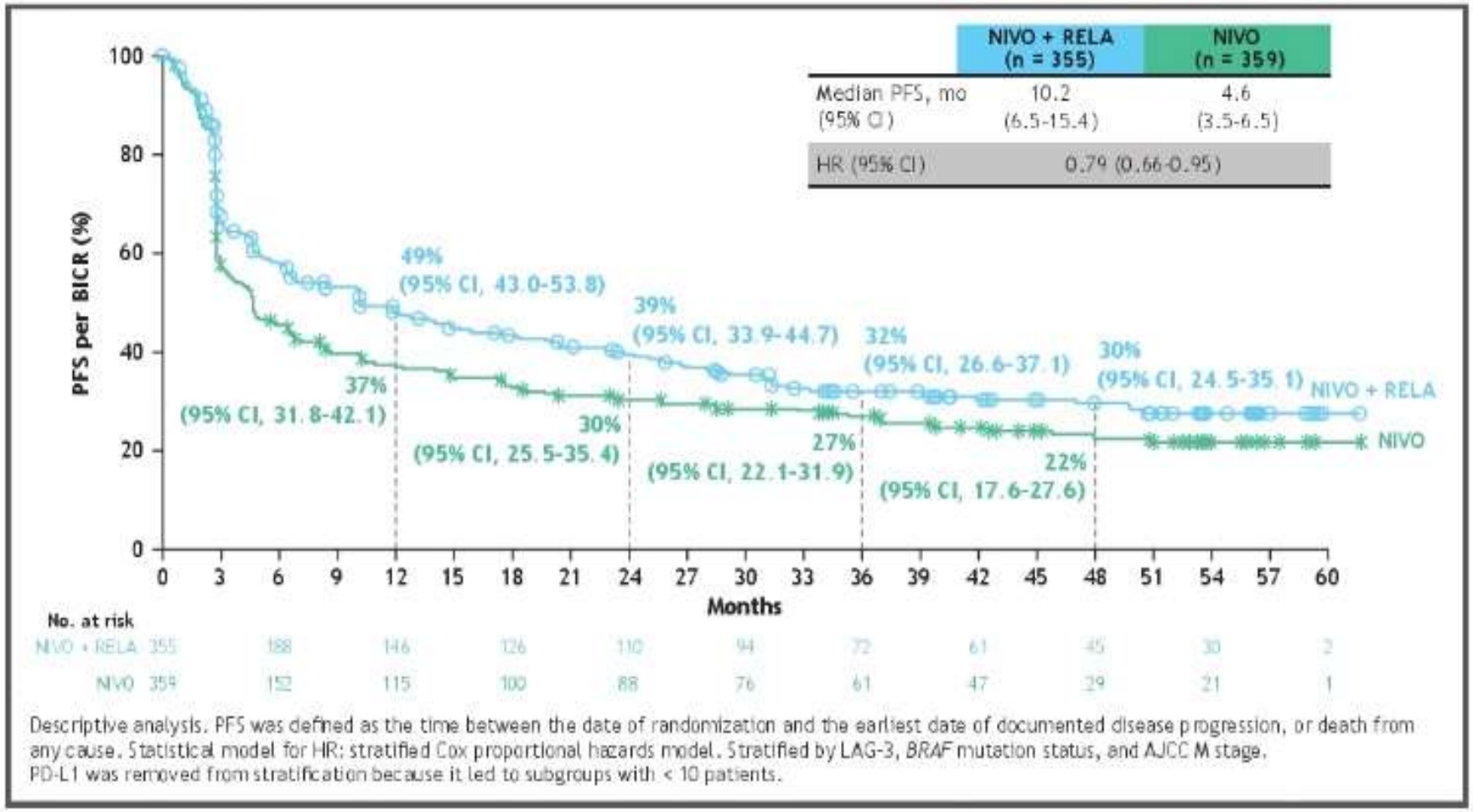
Endpoints were tested in hierarchy: PFS → OS → ORR

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.

RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO vs NIVO

Figure 2. PFS per BICR

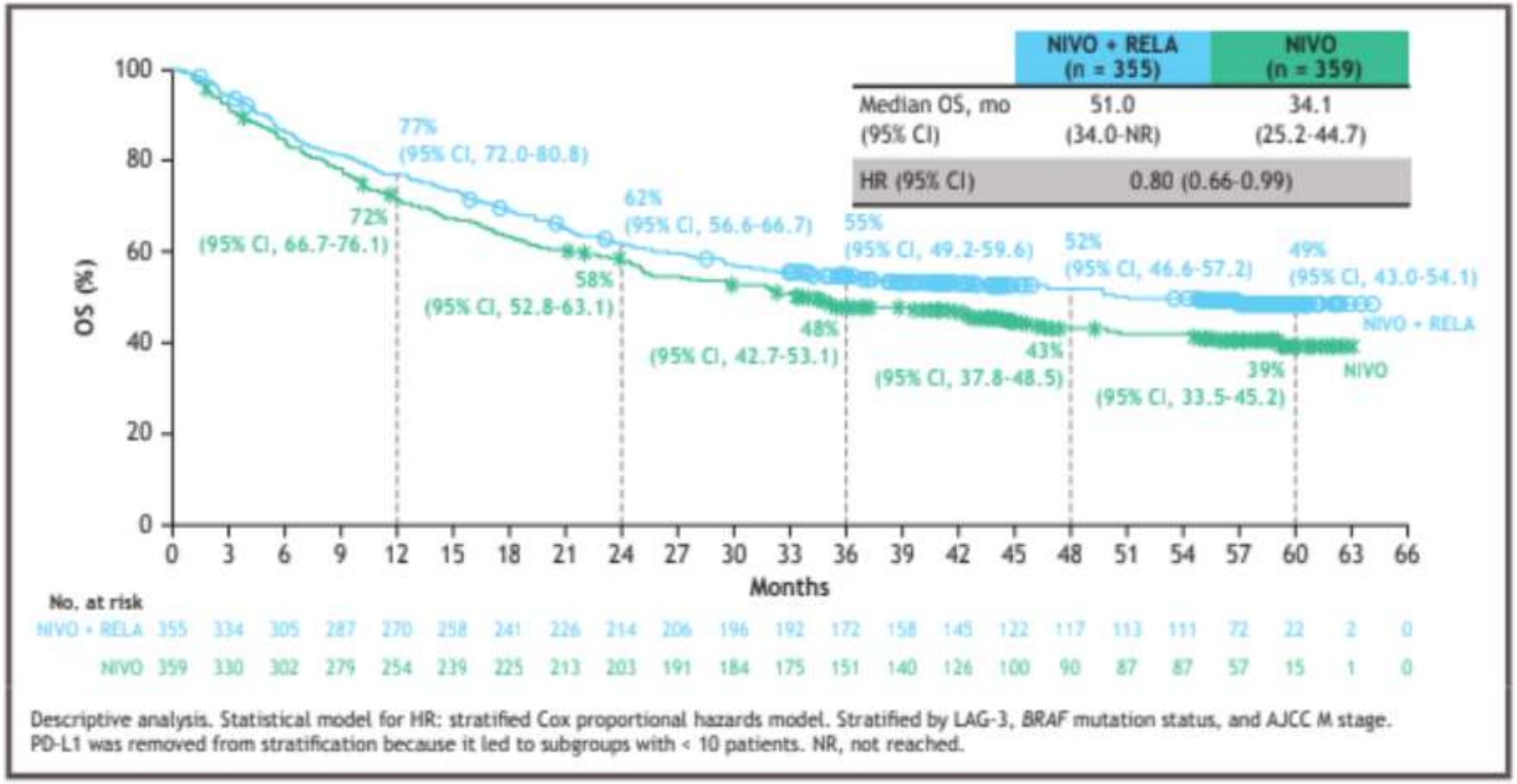


Descriptive analysis. PFS was defined as the time between the date of randomization and the earliest date of documented disease progression, or death from any cause. Statistical model for HR: stratified Cox proportional hazards model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

Tawbi et al, ASCO 2024

RELATIVITY 047 demonstrated superior OS benefit for RELA + NIVO vs NIVO

Figure 3. OS



Descriptive analysis. Statistical model for HR: stratified Cox proportional hazards 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. NR, not reached.

Tawbi et al, ASCO 2024

Safety summary

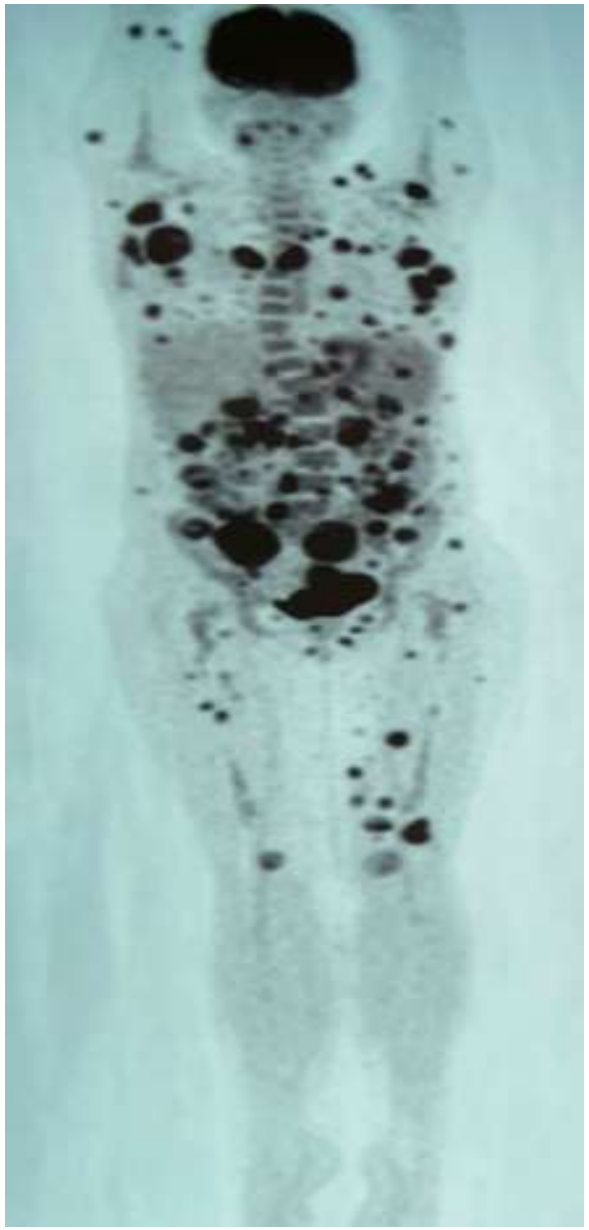
	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Treatment-related AE, %	96	63	87	25	86	30
Treatment-related AE leading to discontinuation, %	45	34	16	9	17	15
Treatment-related death,[a] n (%)	2 (1)		1 (< 1)		1 (< 1)	

AE, n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	352 (99)	164 (46)	345 (96)	141 (39)
TRAE	302 (85)	78 (22)	263 (73)	43 (12)
Leading to discontinuation	63 (18)	34 (10)	35 (10)	14 (4)
Treatment-related deaths[a]	4 (1)		2 (1)	

Courtesy of J. Larkin and D. Schadendorf at ESMO 2024

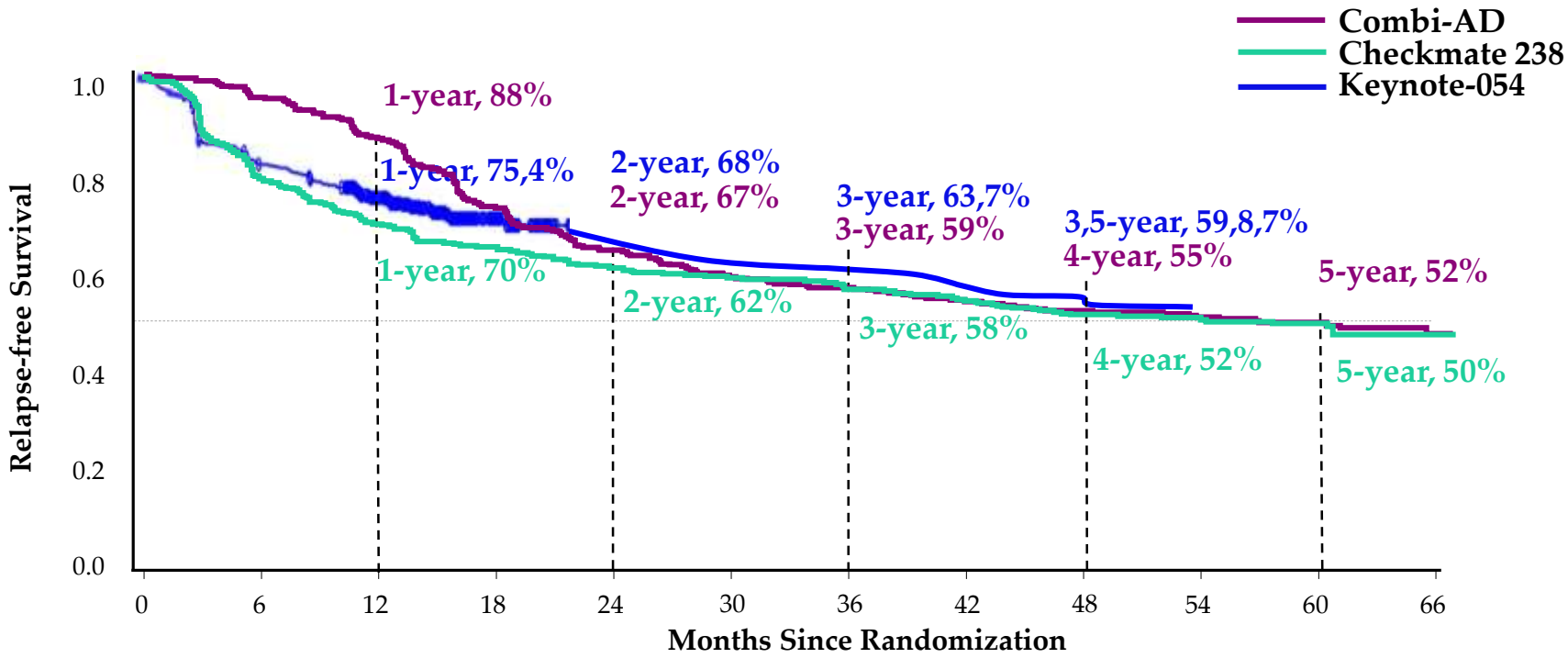
What can we do in future perspectives to avoid this ??

To implement screening campaigns



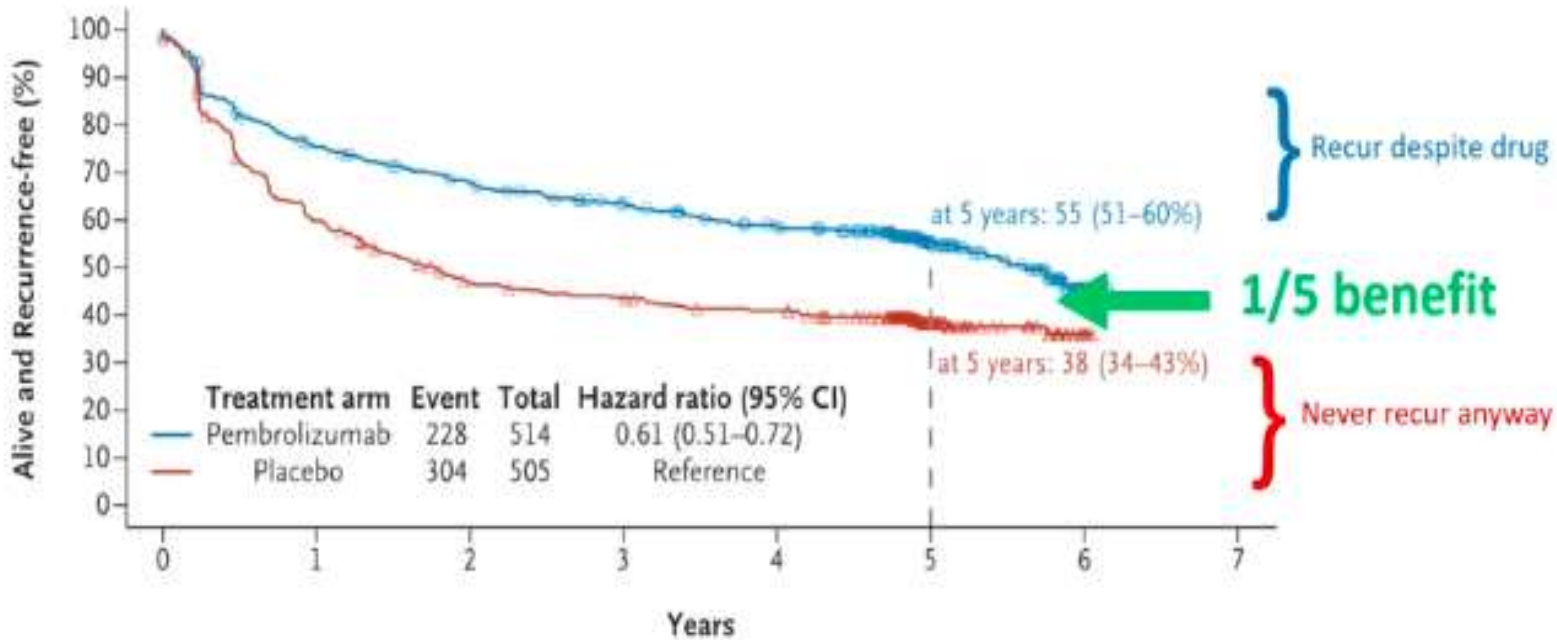
To impact on earlier stages of disease
Neoadjuvant/Adjuvant In melanoma

RFS curves in the current clinical practice of stage III Melanoma



Hauschild et al. ASCO 2020
Weber et al SMR 2021
Eggermont et al ESMO 2020

The problem with adjuvant therapy



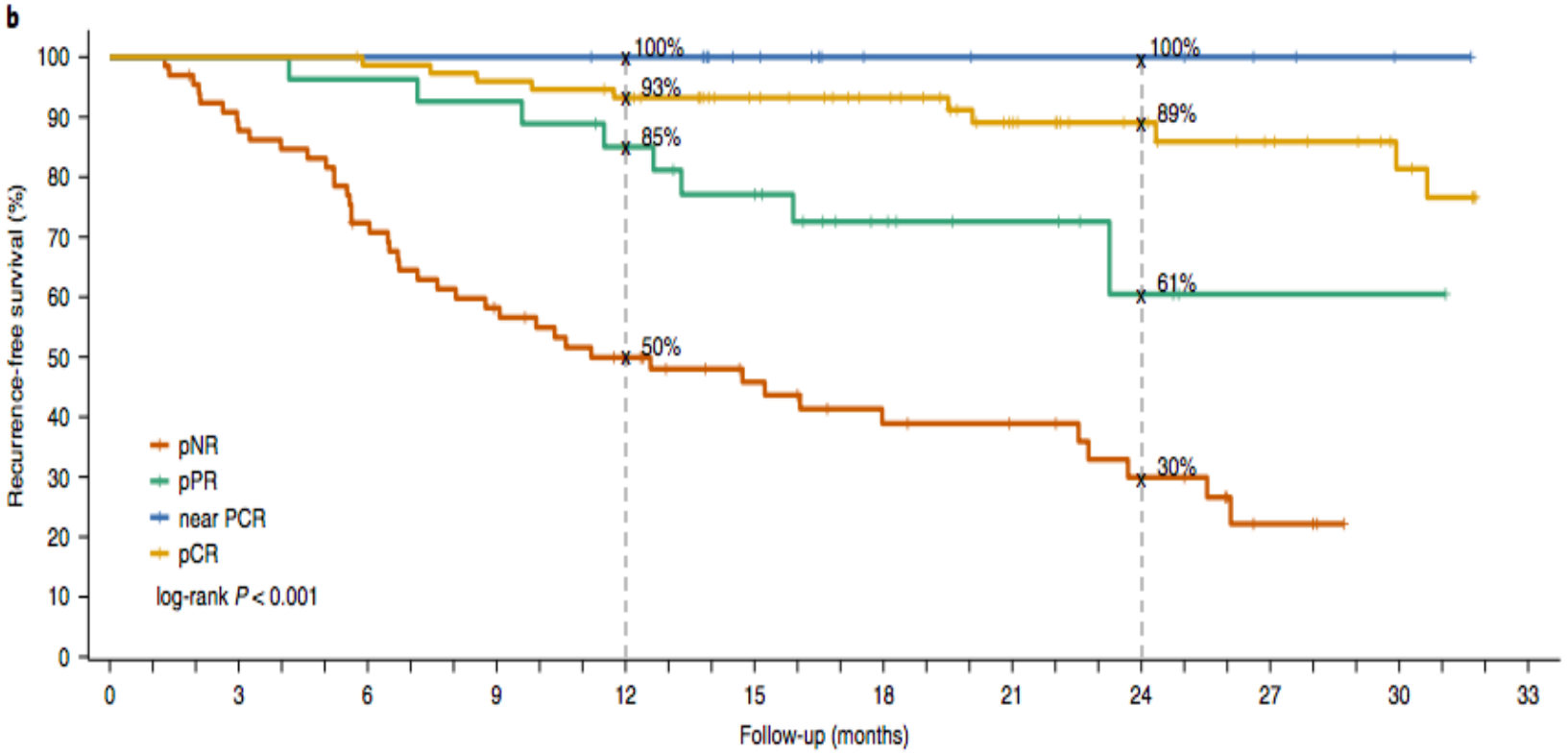
- ***ALL*** *get treated for 1 year*
- *Expensive (~$100,000 pp)*
- *q3-4w clinic visits*
- *3 monthly scans*

- *Toxicity*
- *No idea if treatment working*

Courtesy of A. Menzies at EADO 2023

Finally a flat line!!!

Pooled analysis: Neoadjuvant Immunotherapy in stage III melanoma



A. Menzies Nat Med 2021

Comment

https://doi.org/10.1038/s41591-023-02336-1

Neoadjuvant immunotherapy for melanoma is now ready for clinical practice

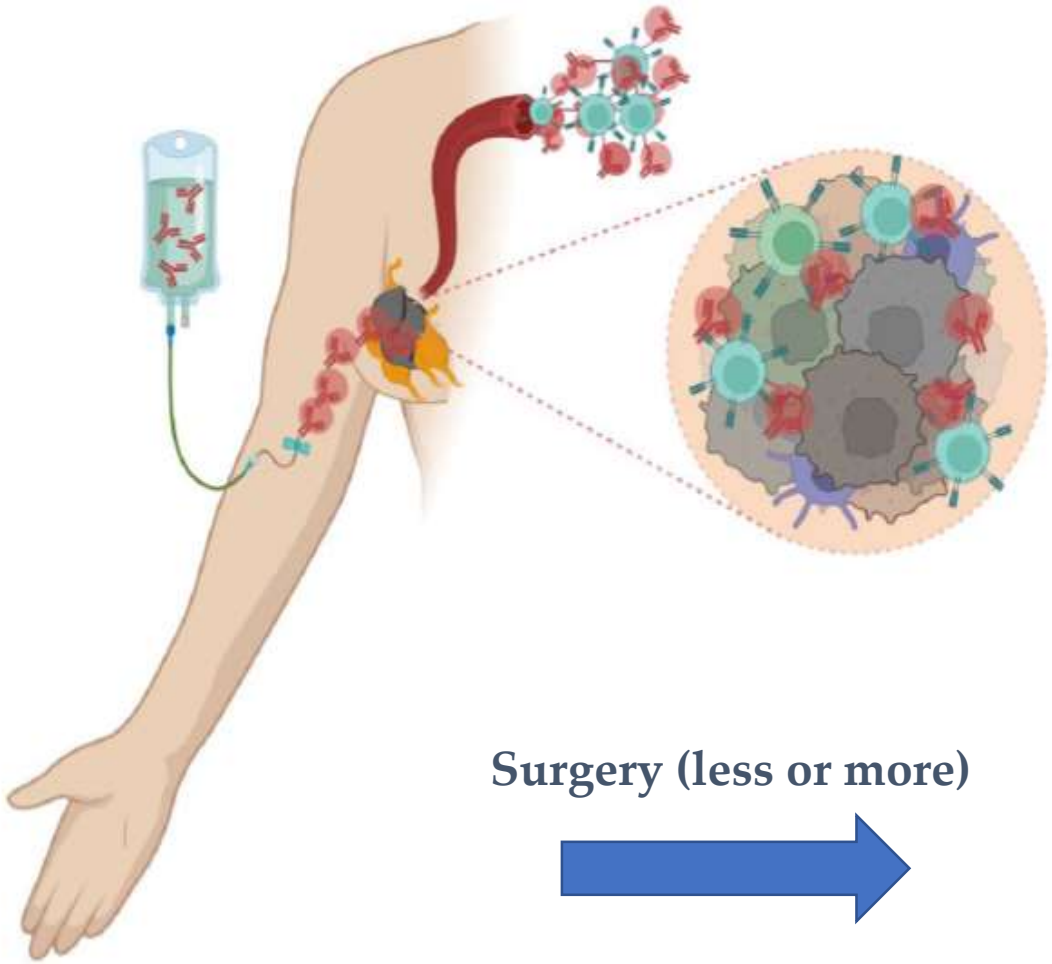
Claus Garbe, Reinhard Dummer, Teresa Amaral, Rodabe N. Amaria, Paolo A. Ascierto, Elizabeth M. Burton, Brigitte Dreno, Alexander M. M. Eggermont, Axel Hauschild, Christoph Hoeller, Roland Kaufmann, Celeste Lebbe, Mario Mandala, Alexander M. Menzies, David Moreno, Olivier Michielin, Paul Nathan, Sapna P. Patel, Caroline Robert, Dirk Schadendorf, Paul C. Lorigan, Richard A. Scolyer, Hussein A. Tawbi, Bart A. van de Wiel, Christian Blank & Georgina V. Long

Individuals with cutaneous melanoma who are treated with neoadjuvant immunotherapy show a substantial improvement; this should be incorporated into standard care.

Nat Med May 2023

Neoadjuvant Therapy

ICIs



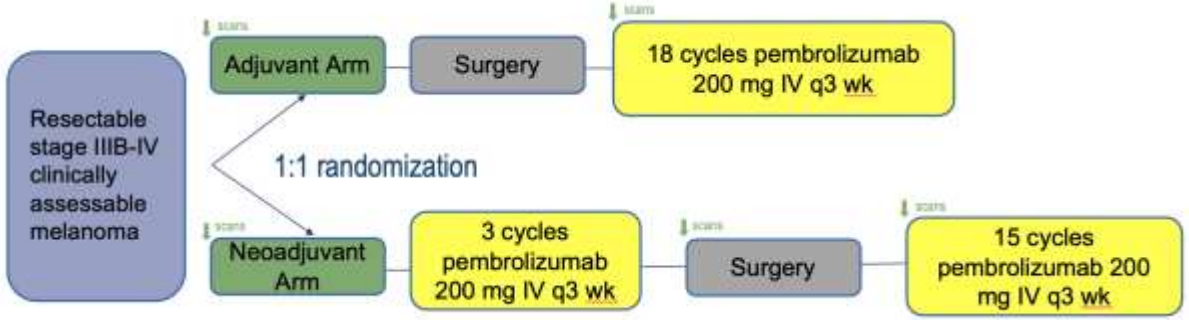
FINANCIAL TOXICITY

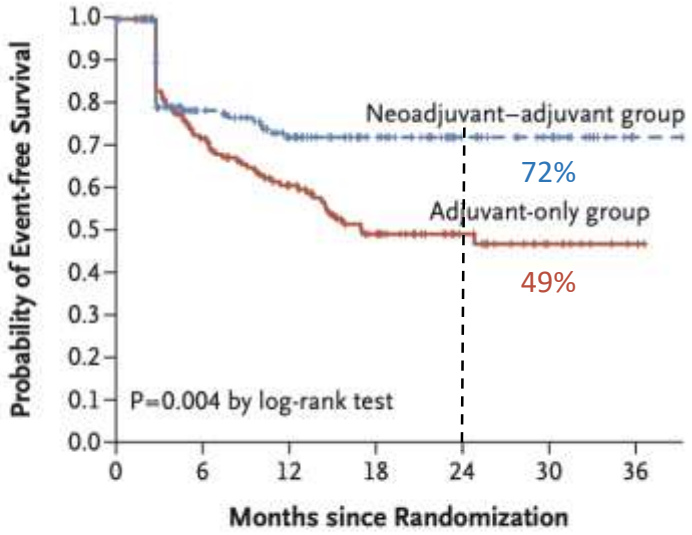
Surgery (less or more)

+/- Adjuvant

Immunotherapy before Surgery Appears Effective for Some with Melanoma
Carmen Phillips NCI

Neoadjuvant-adjuvant phase 2 and 3 trials in macroscopic stage 3 melanoma SWOG 1801 and NADINA

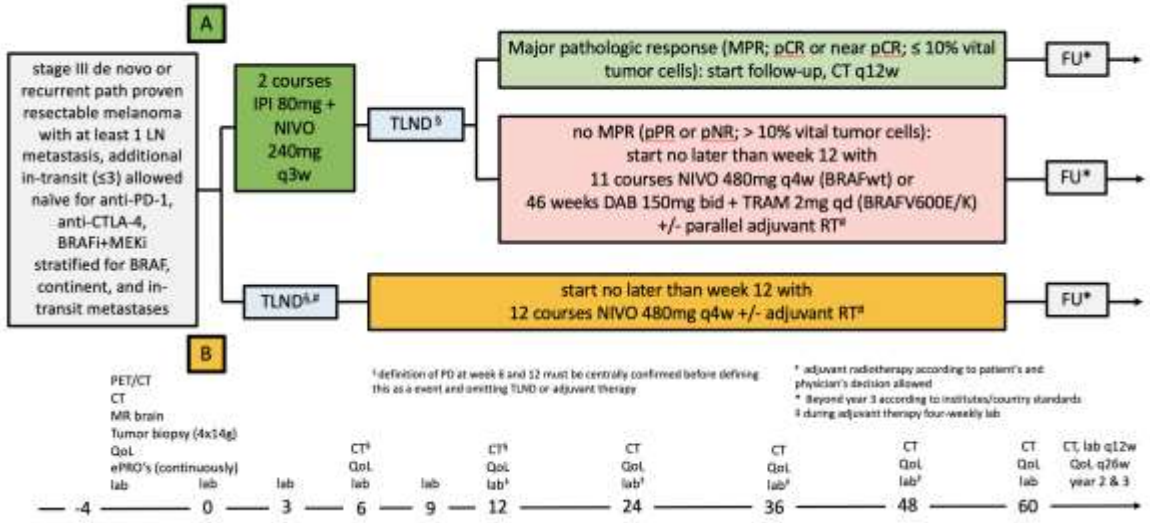




No. at Risk

Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

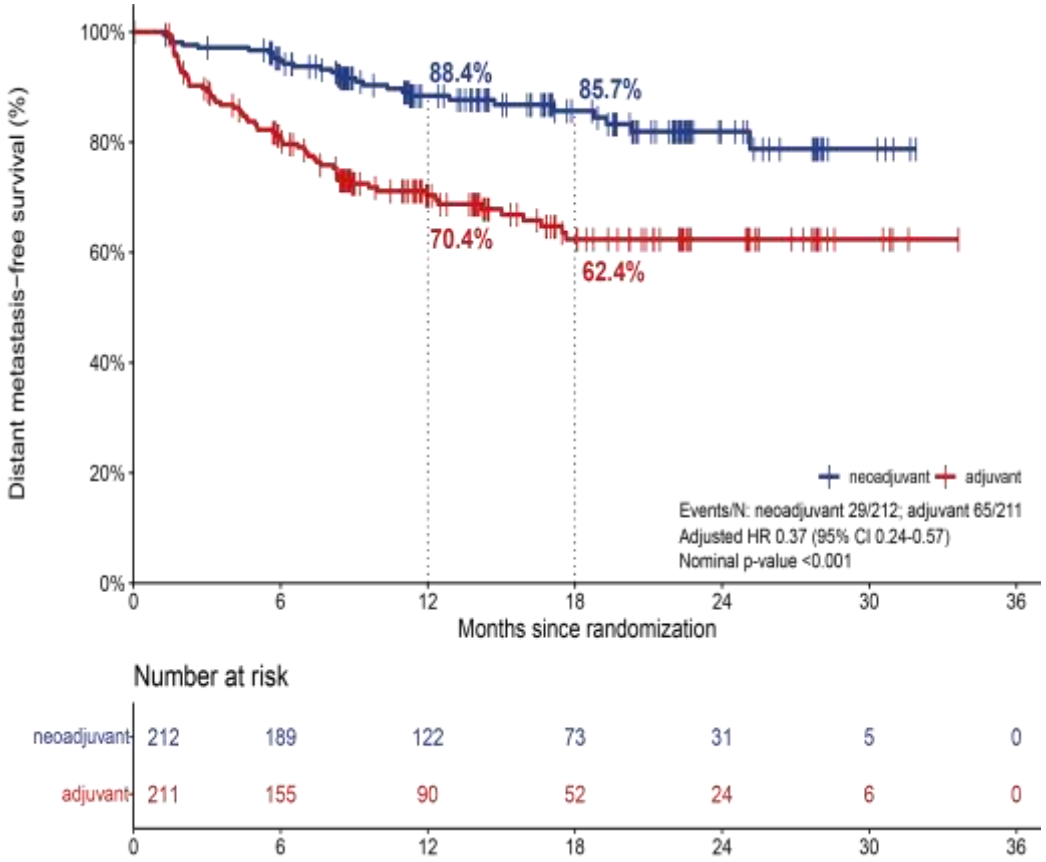
Patel et al. NEJM 2023



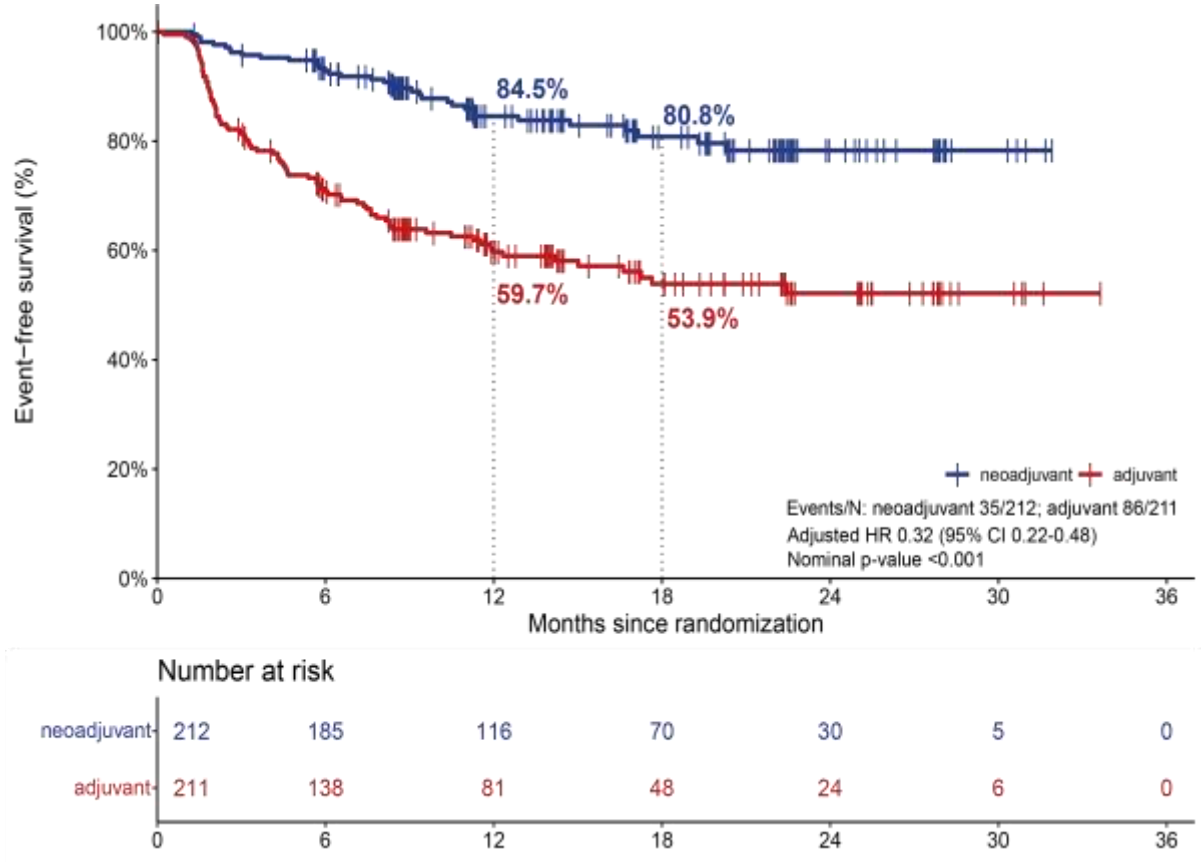
Patient 420 included November 30, 2023

Courtesy of Christian Blank

Distant metastasis-free survival



Updated event-free survival



BARCELONA 2024 ESMO congress

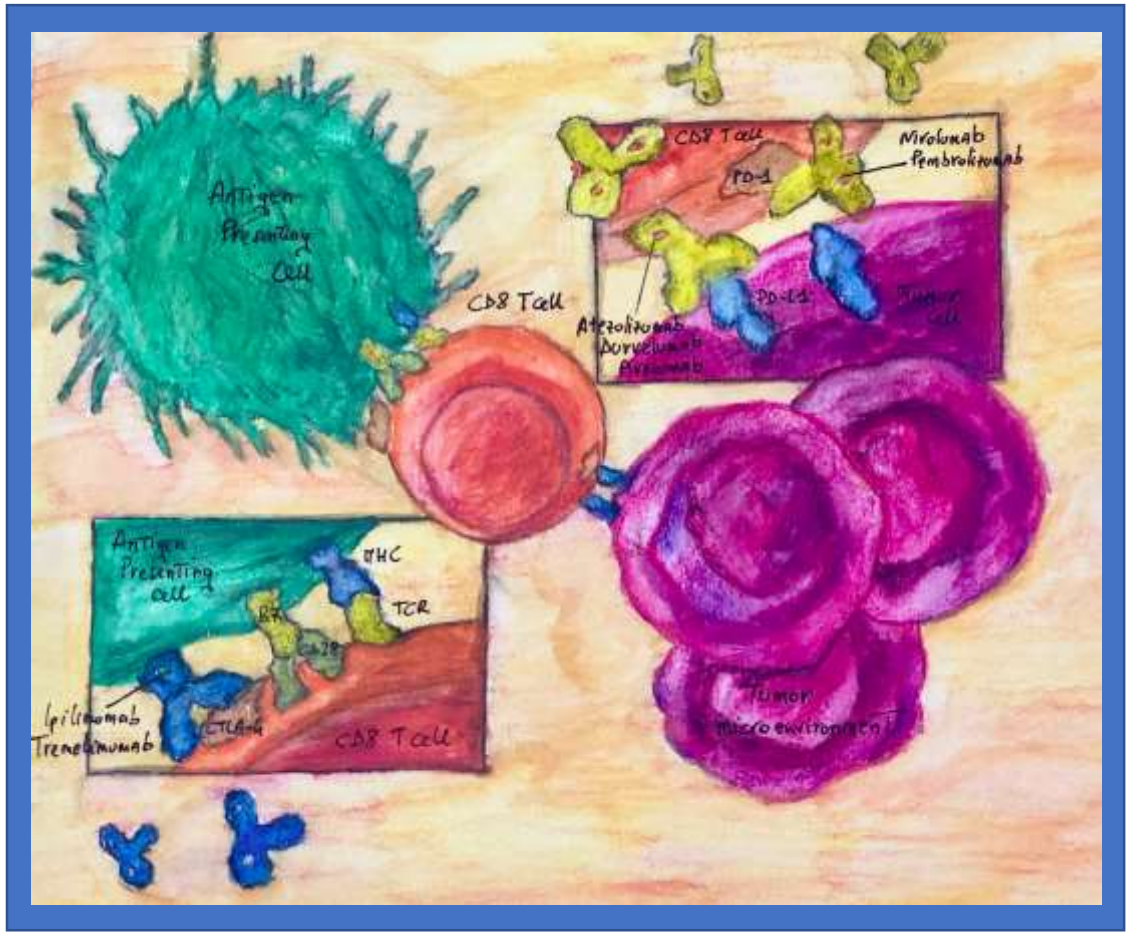
Courtesy of Lucas MW at ESMO 2024

Agenda

Immune checkpoint inhibitors

TIL therapy

Oncolytic virus therapy



Cancer vaccines

CAR-T cells

Ottaviano M. Virchows Arch 2019

Why CAR-T cells?

Nature review, Vol.2019 Sep 2019, pag 487

CAR-T cell therapy for solid cancers

Clinical trial status

- Nearly 500 clinical trials evaluating CAR-T cells in solid tumors have been registered, many still ongoing
- Most completed studies are phase I/II trials that have reported modest results, with only occasional and generally brief clinical responses
- Clinical research on CAR-T cells has mainly focused on glioblastoma, sarcoma, neuroblastoma, and gastrointestinal cancer.

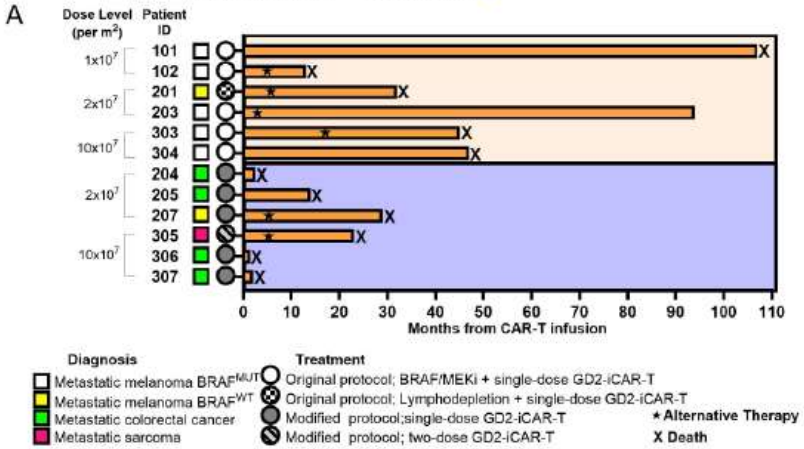
Albarran et al., Front Immunol **2024**

Potential CAR-T cell targets for metastatic melanoma

Open access Original research

Safety and biological outcomes following a phase 1 trial of GD2-specific CAR-T cells in patients with GD2-positive metastatic melanoma and other solid cancers

Tessa Gargett, Nga T H Truong, Bryan Gardam, Wenbo Yu, Lisa M Ebert, Amy Johnson, Erica C F Yeo, Nicole L Wittwer, Gonzalo Tapia Rico, Jesikah Logan, Purany Sivaloganathan, Maria Collis, Andrew Ruszkiewicz, Michael P Brown



5 MM patients with PR all treated with concomitant BRAFi/MEKi

2024;12:e008659. doi:10.1136/jitc-2023-008659

BARCELONA 2024 ESMO congress

Inge Marie Svane

nature communications

Article

https://doi.org/10.1038/s41467-024-45221-2

CAR-T cell therapy targeting surface expression of TYRP1 to treat cutaneous and rare melanoma subtypes

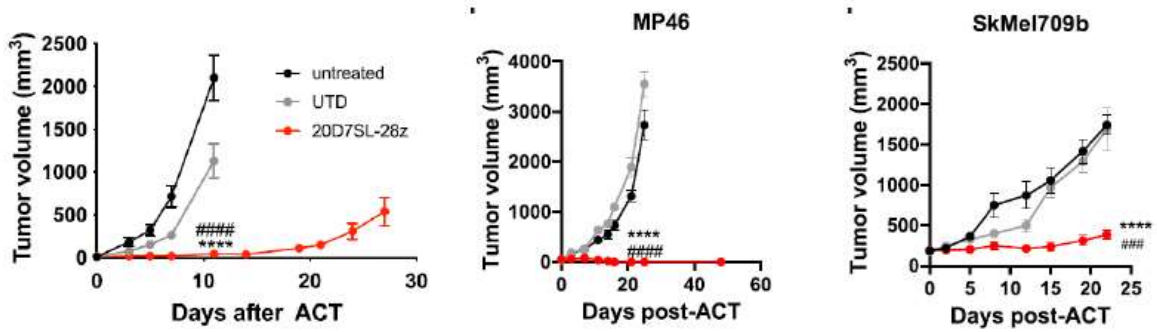
Received: 17 August 2023

Accepted: 18 January 2024

Published online: 09 February 2024

Check for updates

Sameeha Jilani, Justin D. Seco, Edurne Mugarza, Aleida Pujol-Morcillo, Jeffrey Chokry, Clement Ng, Gabriel Abril-Rodriguez, David Berger-Manerio, Ami Pant, Jane Hu, Rubi Gupta, Agustin Vega-Crespo, Ignacio Baselga-Carretero, Jia M. Chen, Daniel Sanghoon Shin, Philip Scumpia, Roxana A. Radu, Yvonne Chen, Antoni Ribas & Cristina Puig-Saus



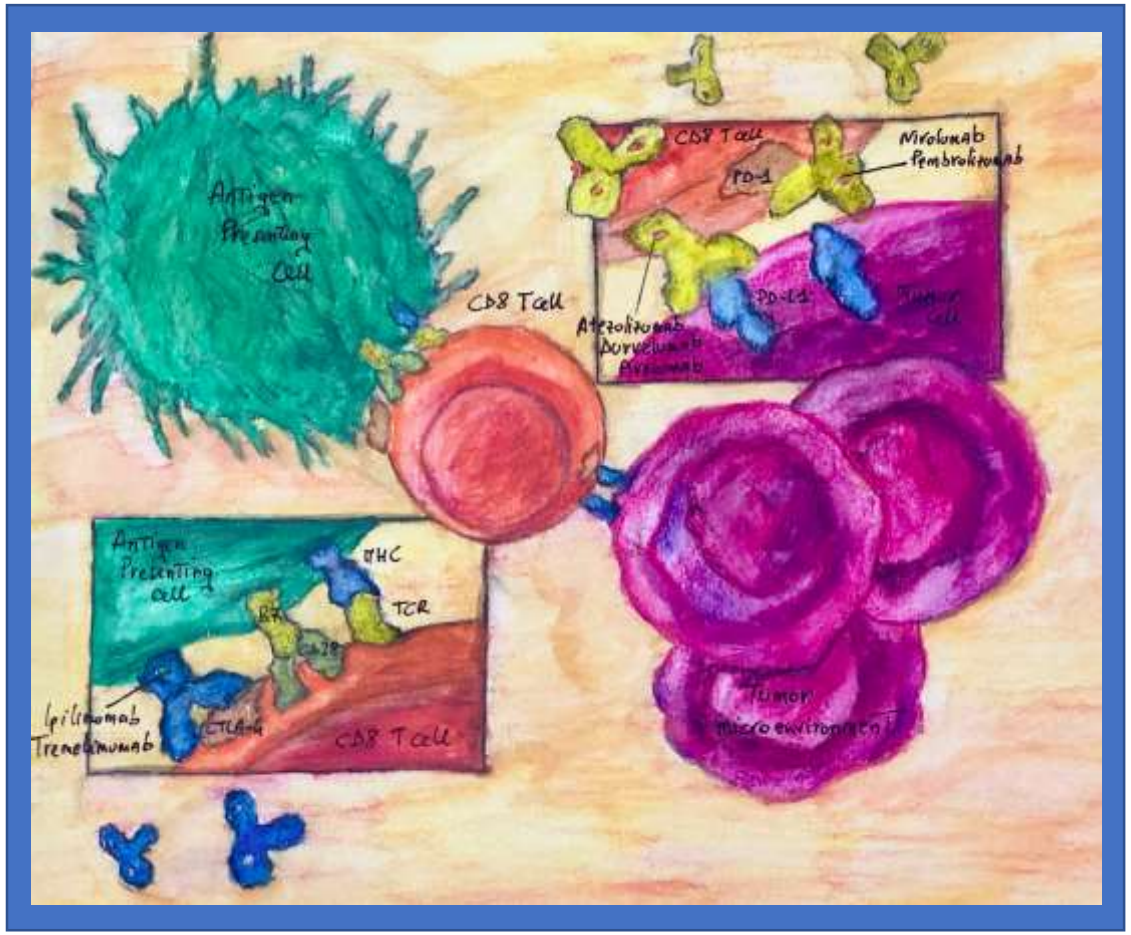
Antitumor activity in murine models on cutaneous, acral and uveal melanoma models with high TYRP1 overexpression

Agenda

Immune checkpoint inhibitors

TIL therapy

Oncolytic virus therapy



Cancer vaccines

CAR-T cells

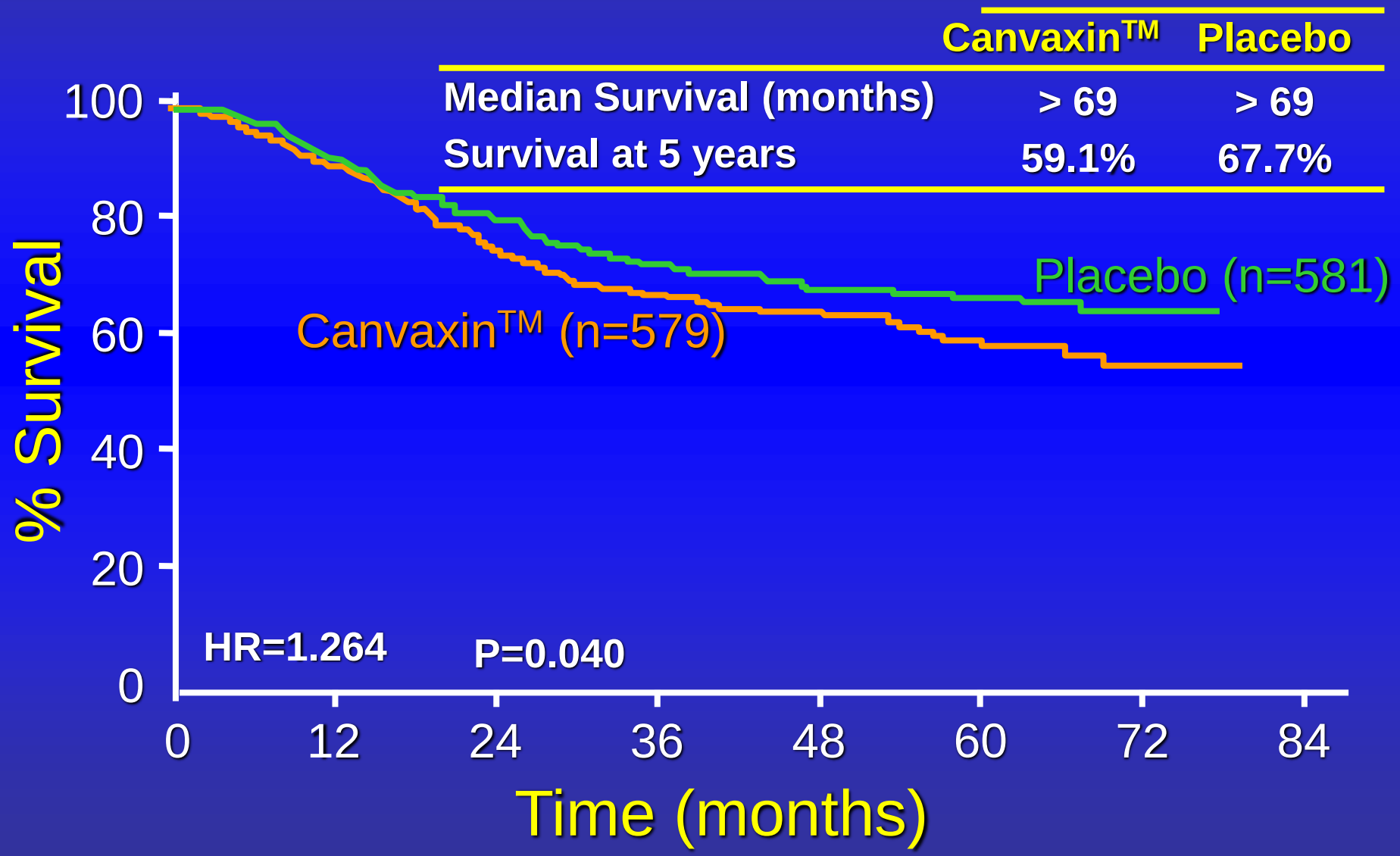
Ottaviano M. Virchows Arch 2019

Multicenter Double-Blind Phase 3 Trial of Canvaxin™ vs Placebo as Post Surgical Adjuvant in Metastatic Melanoma

Donald L. Morton, MD

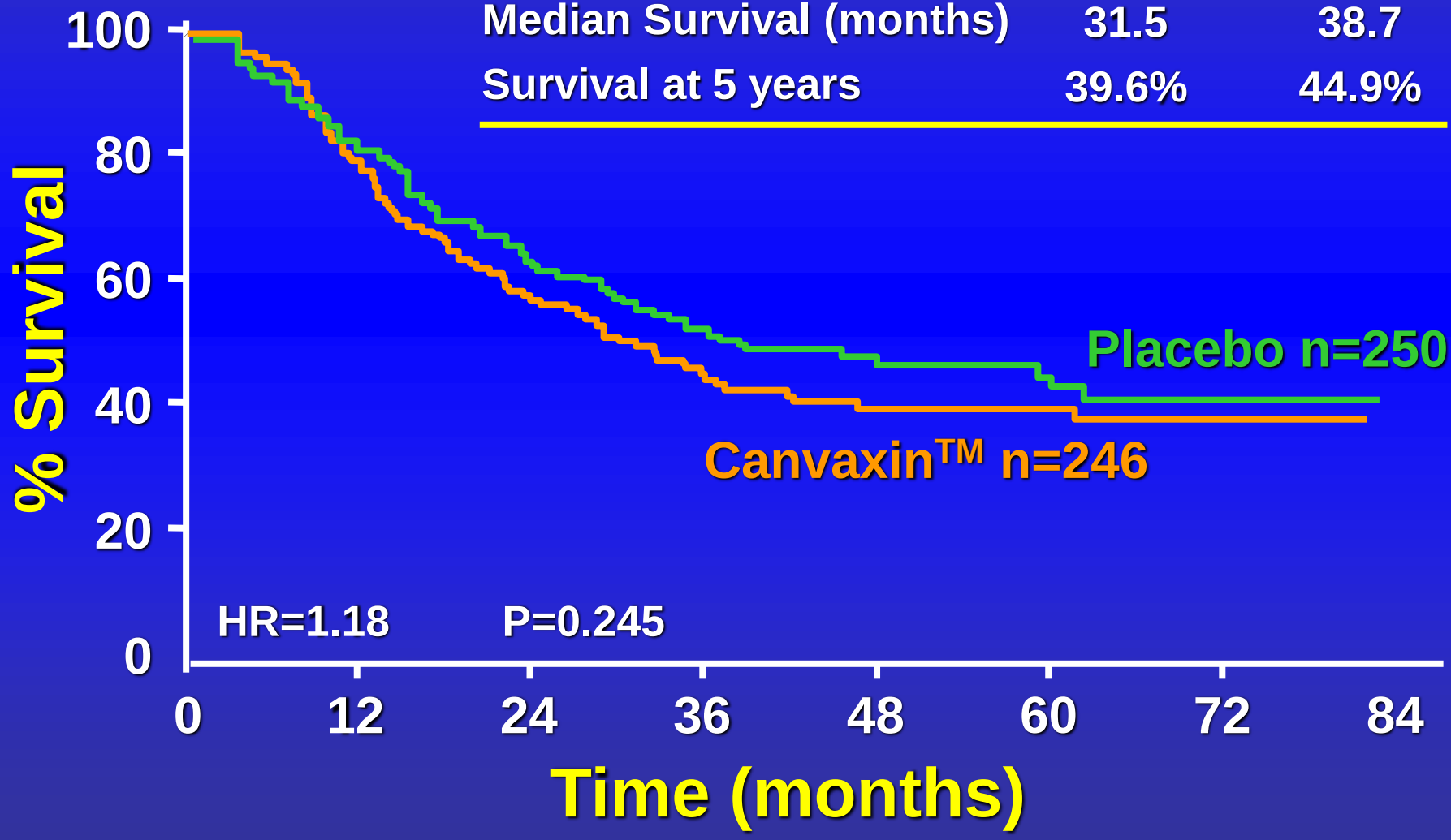
N. Mozzillo, J. F. Thompson, M. C. Kelley, M. Faries, S. Schneebaum, J. Wagner, E. Hersh, L. Schuchter, M. Ross, D. Pertschuk, C. Nardo, R. Elashoff, G. Gammon and the MMAIT-IV Clinical Trial Group

MMAIT-III Overall Survival (Intent To Treat)



MMAIT-IV Overall Survival (Intent To Treat)

	Canvaxin™	Placebo
Median Survival (months)	31.5	38.7
Survival at 5 years	39.6%	44.9%



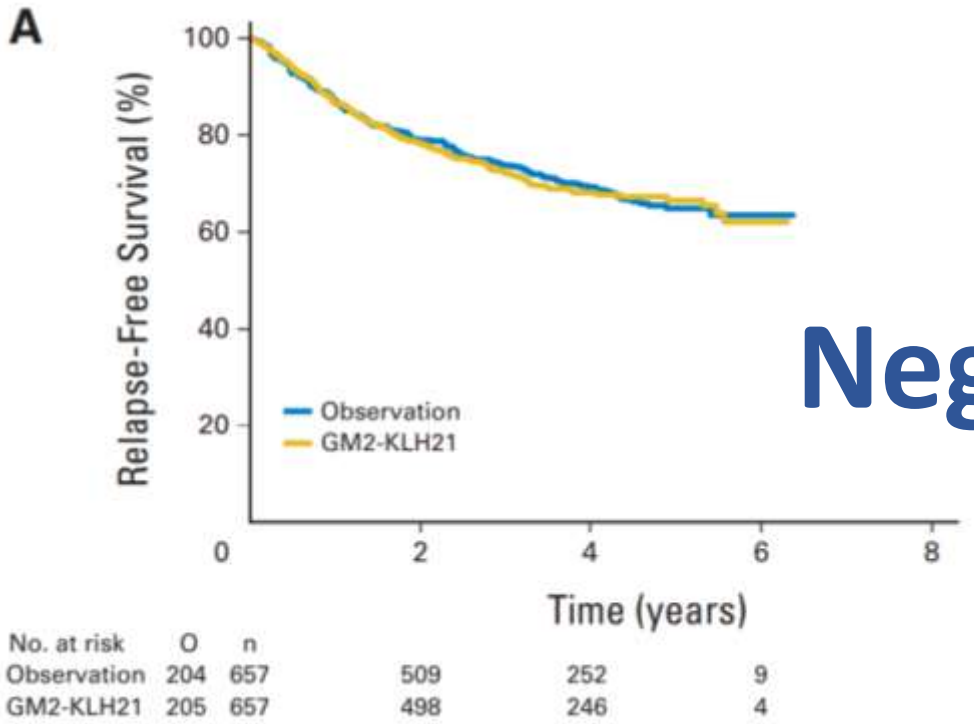
Adjuvant Ganglioside GM2-KLH/QS-21 Vaccination Versus Observation After Resection of Primary Tumor > 1.5 mm in Patients With Stage II Melanoma: Results of the EORTC 18961 Randomized Phase III Trial

VOLUME 31 · NUMBER 30 · OCTOBER 20 2013

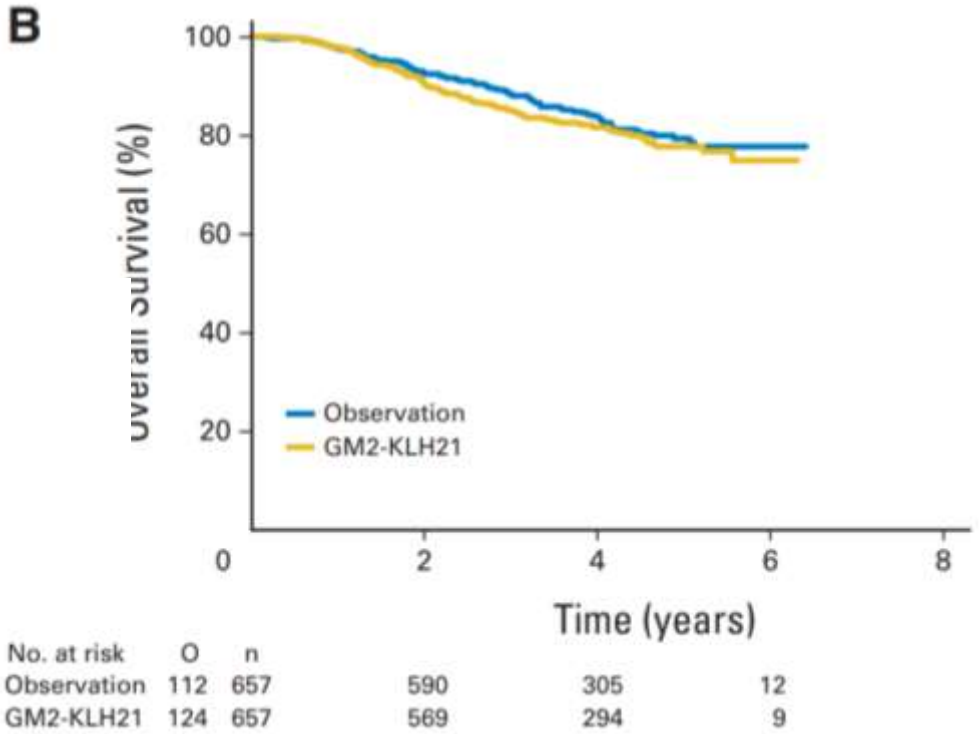
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Alexander M.M. Eggermont, Stefan Suciu, Piotr Rutkowski, Jeremy Marsden, Mario Santinami, Philippa Corrie, Steinar Aamdal, Paolo A. Ascierto, Poulam M. Patel, Wim H. Kruit, Lars Bastholt, Lorenzo Borgognoni, Maria Grazia Bernengo, Neville Davidson, Larissa Polders, Michel Praet, and Alan Spatz



Negative!



Journal of Clinical Oncology 31, no. 30 (October 20, 2013) 3831-3837

2024 ASCO® ANNUAL MEETING

Individualized neoantigen therapy mRNA-4157 (V940) plus pembrolizumab in resected melanoma: 3-year update from the mRNA-4157-P201 (KEYNOTE-942) trial

Jeffrey S. Weber,[1] Muhammad Adnan Khattak,[2] Matteo S. Carlino,[3] Tarek Meniawy,[4] Matthew H. Taylor,[5] George Ansstas,[6] Kevin B. Kim,[7] Meredith McKean,[8] Ryan J. Sullivan,[9] Mark B. Faries,[10] Thuy Tran,[11] C. Lance Cowey,[12] Theresa M. Medina,[13] Jennifer M. Segar,[14] Victoria Atkinson,[15] Geoffrey T. Gibney,[16] Jason J. Luke,[17] Elizabeth I. Buchbinder,[18] Georgina V. Long,[19] INT Research and Development Author Group,[20,21,a] Robert S. Meehan[20]

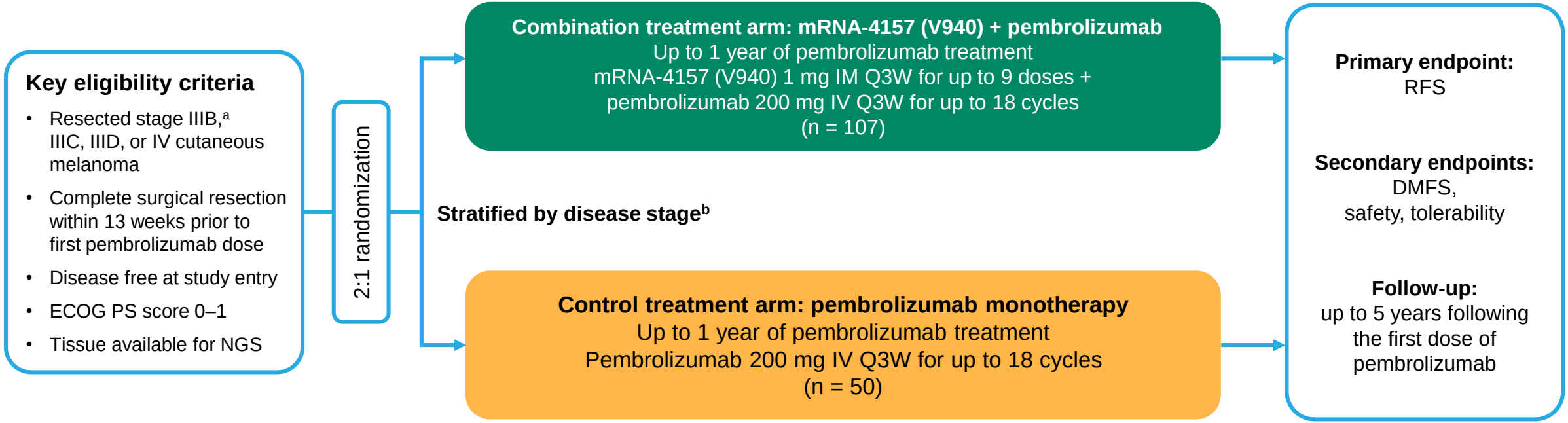
[a]Manju Morrissey,[20] Igor Feldman,[20] Vasudha Sehgal,[20] Huzhang Mao,[20] Jia Guo,[20] Min Liu,[20] Anjali Rao,[20] Wei Zheng,[20] Praveen Aanur,[20] Lakshmi Srinivasan,[20] Mo Huang,[21] Tal Zaks,[20] Michelle Brown,[20] Tracey Posadas[20]

[1]Laura and Isaac Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [2]Hollywood Private Hospital and Edith Cowan University, Perth, Australia; [3]Melanoma Institute Australia and Westmead Hospital, Sydney, Australia; [4]Saint John of God Subiaco Hospital, Subiaco, Australia; [5]Earle A. Chiles Research Institute, Portland, OR, USA; [6]Washington University School of Medicine, St Louis, MO, USA; [7]California Pacific Medical Center Research Institute, San Francisco, CA, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]Massachusetts General Hospital, Boston, MA, USA; [10]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [11]Yale-New Haven Hospital, New Haven, CT, USA; [12]Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [13]University of Colorado, Aurora, CO, USA; [14]University of Arizona Cancer Center, Tucson, AZ, USA; [15]Princess Alexandra Hospital, Woolloongabba, Australia; [16]Lombardi Comprehensive Cancer Center, Washington, DC, USA; [17]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [18]Dana-Farber Cancer Institute, Boston, MA, USA; [19]Melanoma Institute Australia, Sydney, Australia; [20]Moderna, Inc., Cambridge, MA, USA; [21]Merck & Co., Inc., Rahway, NJ, USA.

Sponsored by Moderna, Inc., in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

mRNA-4157-P201/KEYNOTE-942 (NCT03897881) study design

Randomized, phase 2, open-label study in patients with adjuvant resected melanoma at high risk of recurrence

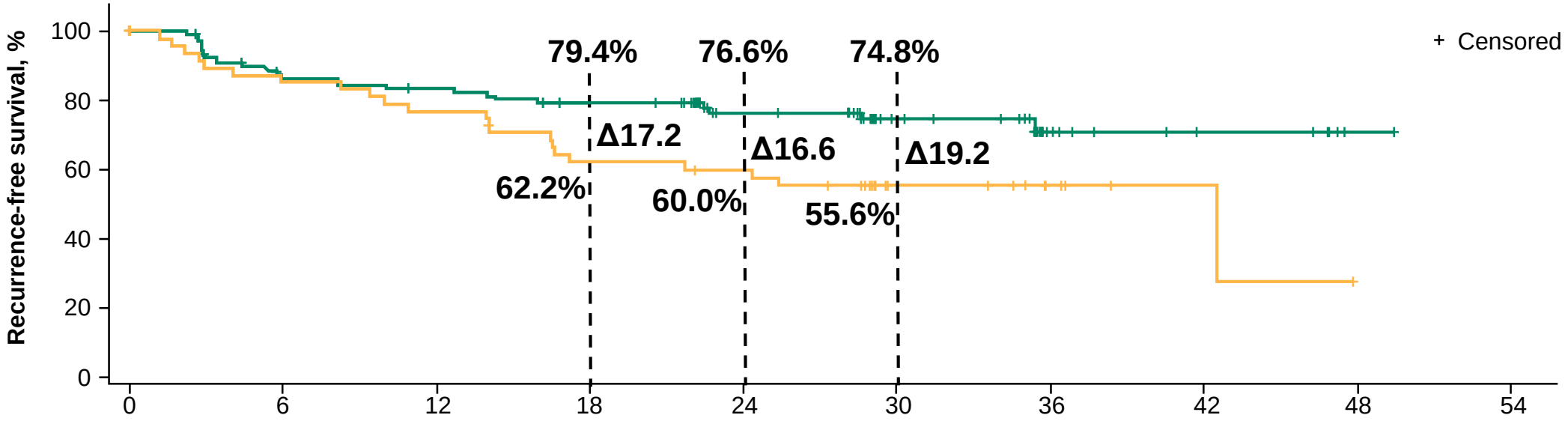


Designed with 80% power to detect a hazard ratio of 0.5 with 40 RFS events (with a 1-sided alpha of 0.1 per protocol)
Primary analysis **triggered after a minimum of 1-year planned follow-up[c]** (November 14, 2022 data cut) and at least 40 RFS events have been observed. DMFS analysis was prespecified for testing following positive RFS in the ITT population

Supportive analysis was **triggered after a minimum of 2 years of planned follow-up[c]** (November 3, 2023 data cut)
Median planned follow-up[c]: ~3yrs

[a]Patients with stage IIIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent; [b]According to the 8th edition of the American Joint Committee on Cancer Staging Manual [c]Defined as the time from the first dose date (or date of randomization if not treated) to date of clinical cut-off.
ECOG PS, Eastern Cooperative Oncology Group performance status; IM, intramuscular; ITT, intent-to-treat; IV, intravenous; NGS, next-generation sequencing; Q3W, every 3 weeks.

Sustained improvement of RFS primary efficacy endpoint



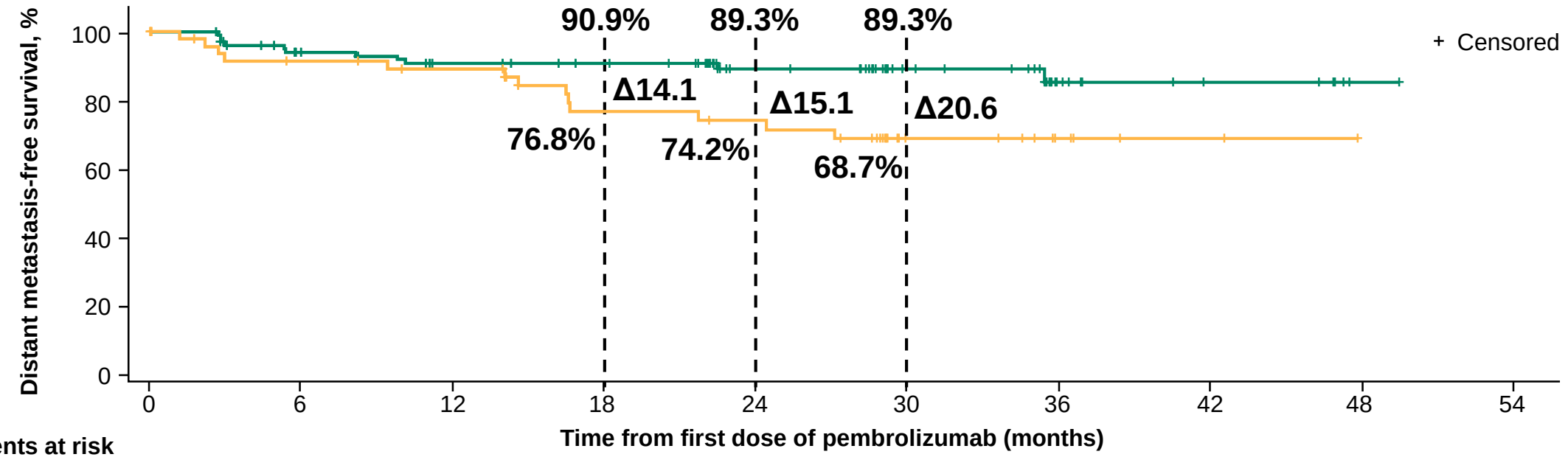
Patients at risk										
mRNA-4157 (V940) + pembrolizumab	107	87	83	77	52	29	12	6	1	0
Pembrolizumab	50	41	37	29	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	23.4 (25/107)	0.510 (0.288–0.906) *P* = 0.019[b]
pembrolizumab	42.51 (16.59–NE)	44.0 (22/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) + pembrolizumab versus pembrolizumab were estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization; [b]Formal hypothesis testing of RFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut; it's nominal and not for formal hypothesis testing. NE, not estimable.

Courtesy of Weber J ASCO 2023

Sustained improvement of DMFS secondary endpoint



Patients at risk

mRNA-4157 (V940) + pembrolizumab	107	89	82	78	52	30	12	6	1	0
Pembrolizumab	50	42	39	30	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	10.3 (11/107)	0.384 (0.172–0.858) *P* = 0.015[b]
Pembrolizumab	NE	26.0 (13/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab were estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization; [b]Formal hypothesis testing of DMFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut; it's nominal and not for formal hypothesis testing.

Courtesy of Weber J ASCO 2023

Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

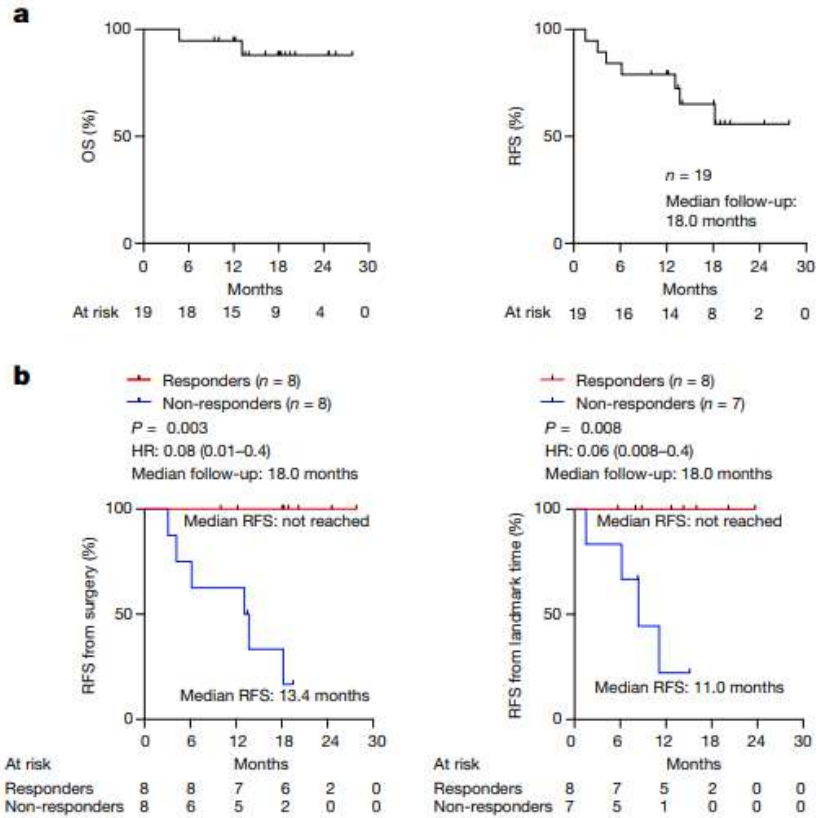


Fig. 3 | mRNA vaccine response correlates with delayed PDAC recurrence. **a**, OS and RFS in $n = 19$ patients in the safety-evaluable cohort. **b**, RFS from surgery and from landmark time (date of the last vaccine priming dose) stratified by vaccine response in patients in the biomarker-evaluable cohort. n indicates individual patients. HR indicates hazard ratio with 95% CI. P values calculated using two-tailed log-rank test.

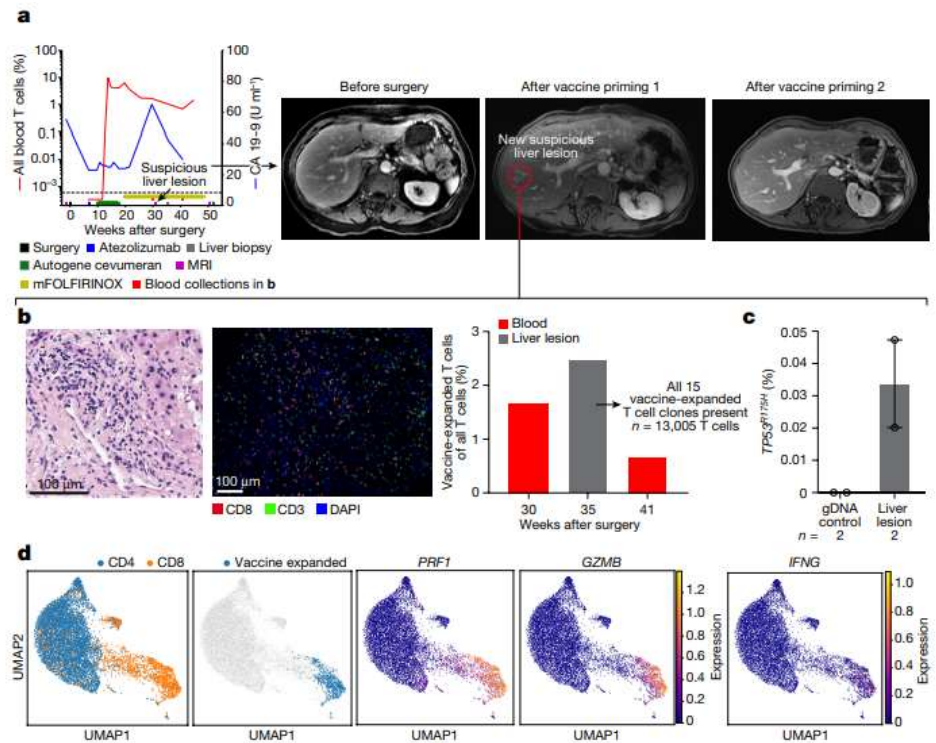
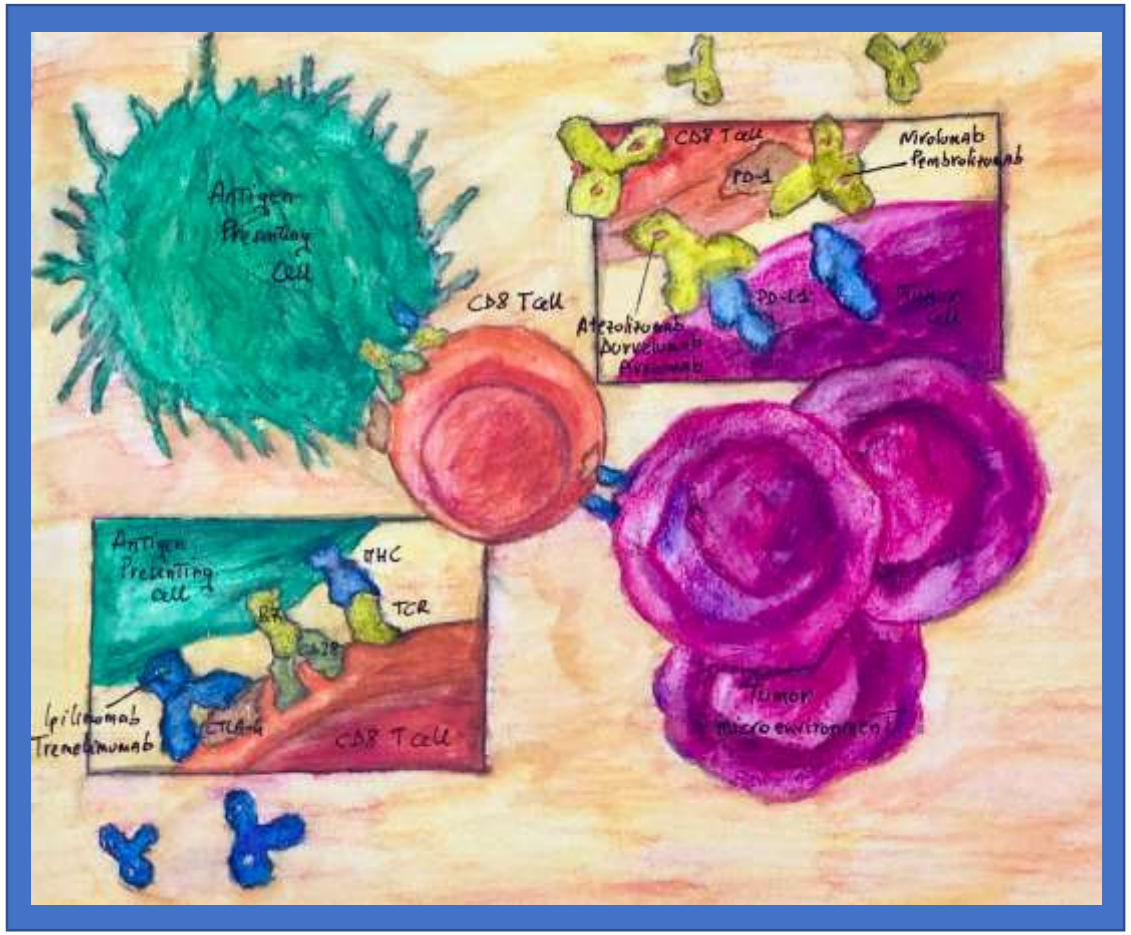


Fig. 4 | Vaccine-expanded T cells can infiltrate a micrometastasis. Clinical and immunological snapshot of a disappearing intrahepatic lymphoid aggregate after vaccination in a patient who responded to the vaccine. **a**, Serial percentage of vaccine-expanded T cells in blood analysed using CloneTrack and serum CA19-9 (left), and abdominal MRI (right) before and after vaccination. **b**, Haematoxylin and eosin staining (left), multiplexed immunofluorescence (middle) and percentage of vaccine-expanded T cells measured using CloneTrack (right, grey bar) in a new liver lesion that developed after vaccination detected by MRI as in **a**. All 15 vaccine-expanded T cell clones (**a**, red line) were present in liver lesion (right, grey bar). **c**, Percentage of mutant $TP53^{R175H}$ reads by digital droplet PCR in the liver lesion. The bar indicates the median, the error bars are the s.e.m. **d**, Uniform manifold approximation and projection (UMAP) plots of single-cell phenotypes of all blood T cells (left) and vaccine-expanded clones (middle), with effector markers (right). n indicates the number of T cells detected in liver lesion (**b**) or technical replicates (**c**). Data represent analyses of a single patient.

Agenda

Immune checkpoint inhibitors

TIL therapy



Oncolytic virus therapy

Cancer vaccines

CAR-T cells

Ottaviano M. Virchows Arch 2019

TIL Therapy

PARIS 2022 ESMO congress

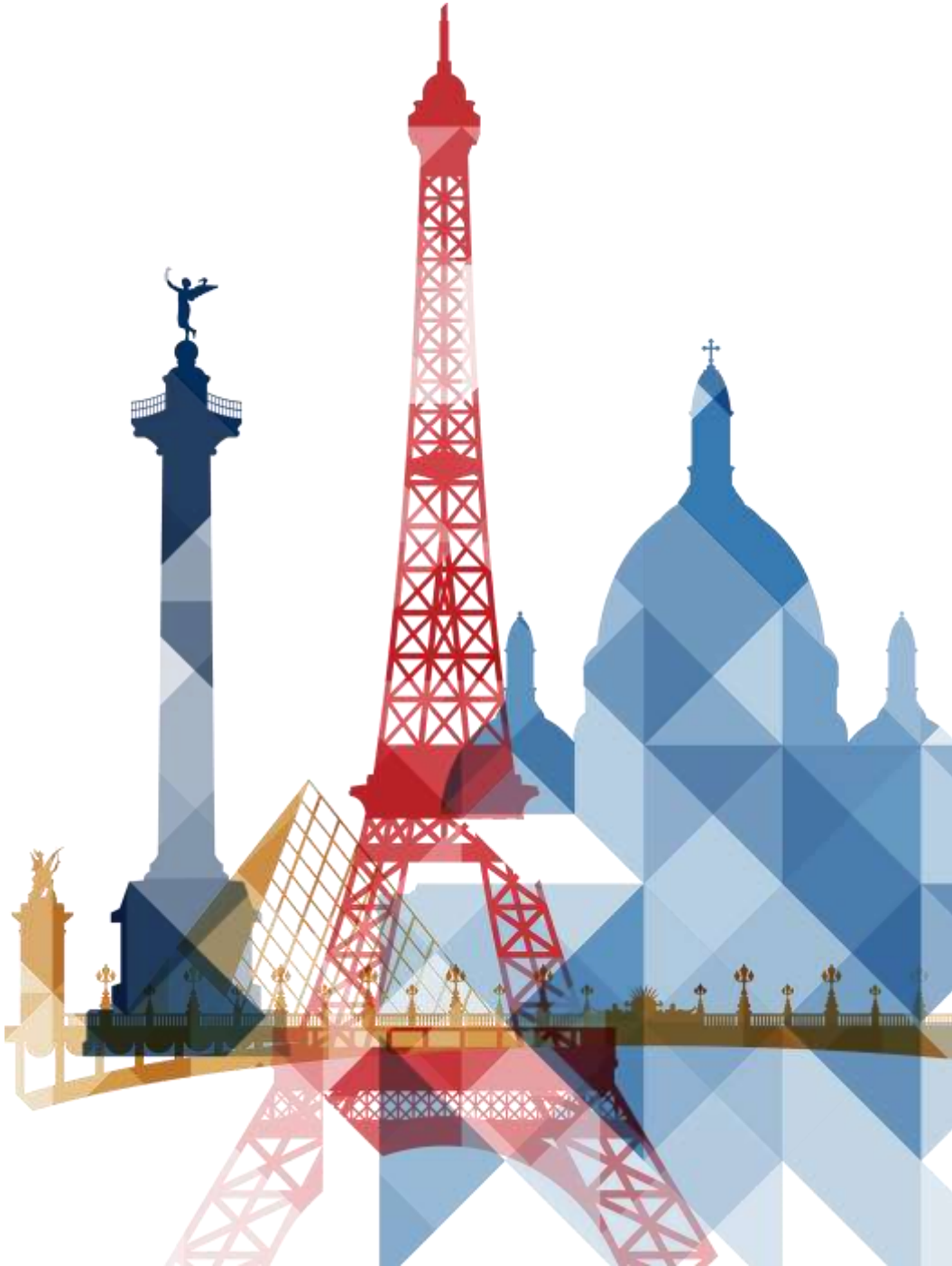
Treatment with tumor-infiltrating lymphocytes (TIL) versus ipilimumab for advanced melanoma: results from a multicenter, randomized phase 3 trial

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

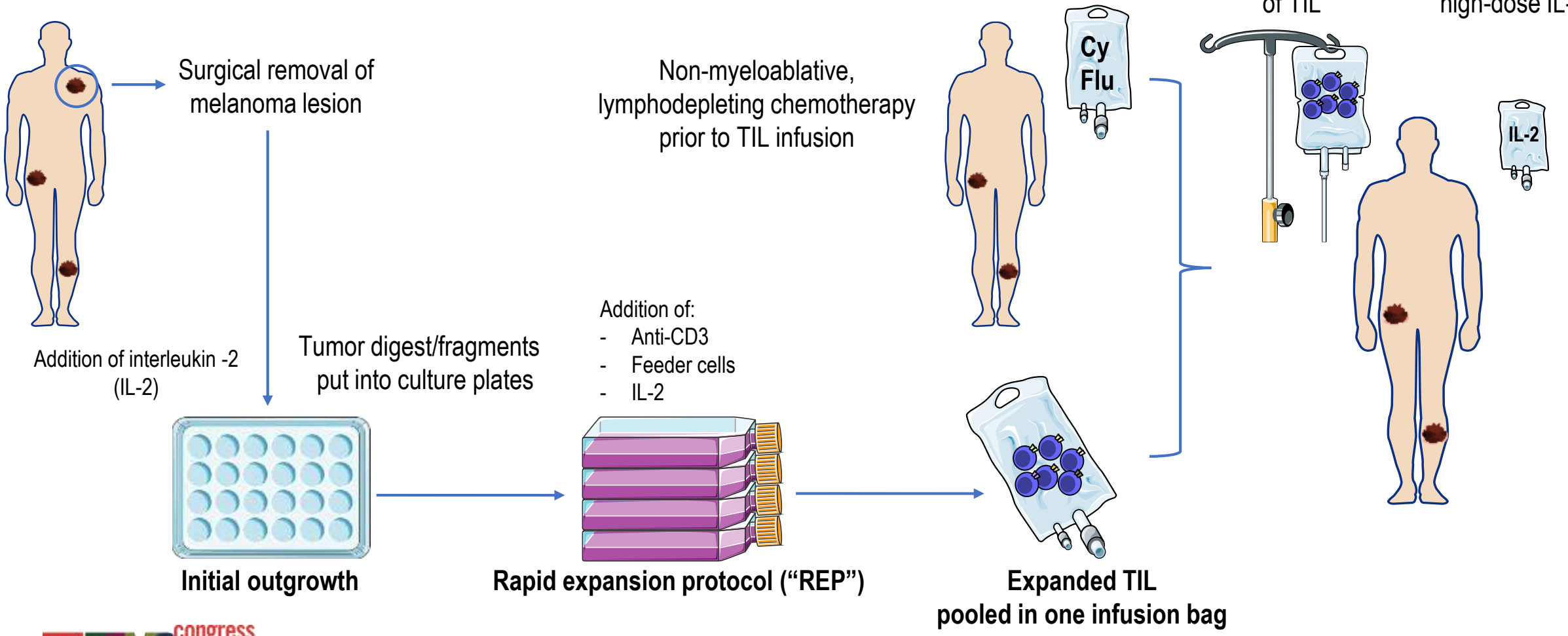
Paris, France, 10th September 2022

Presentation number LBA3



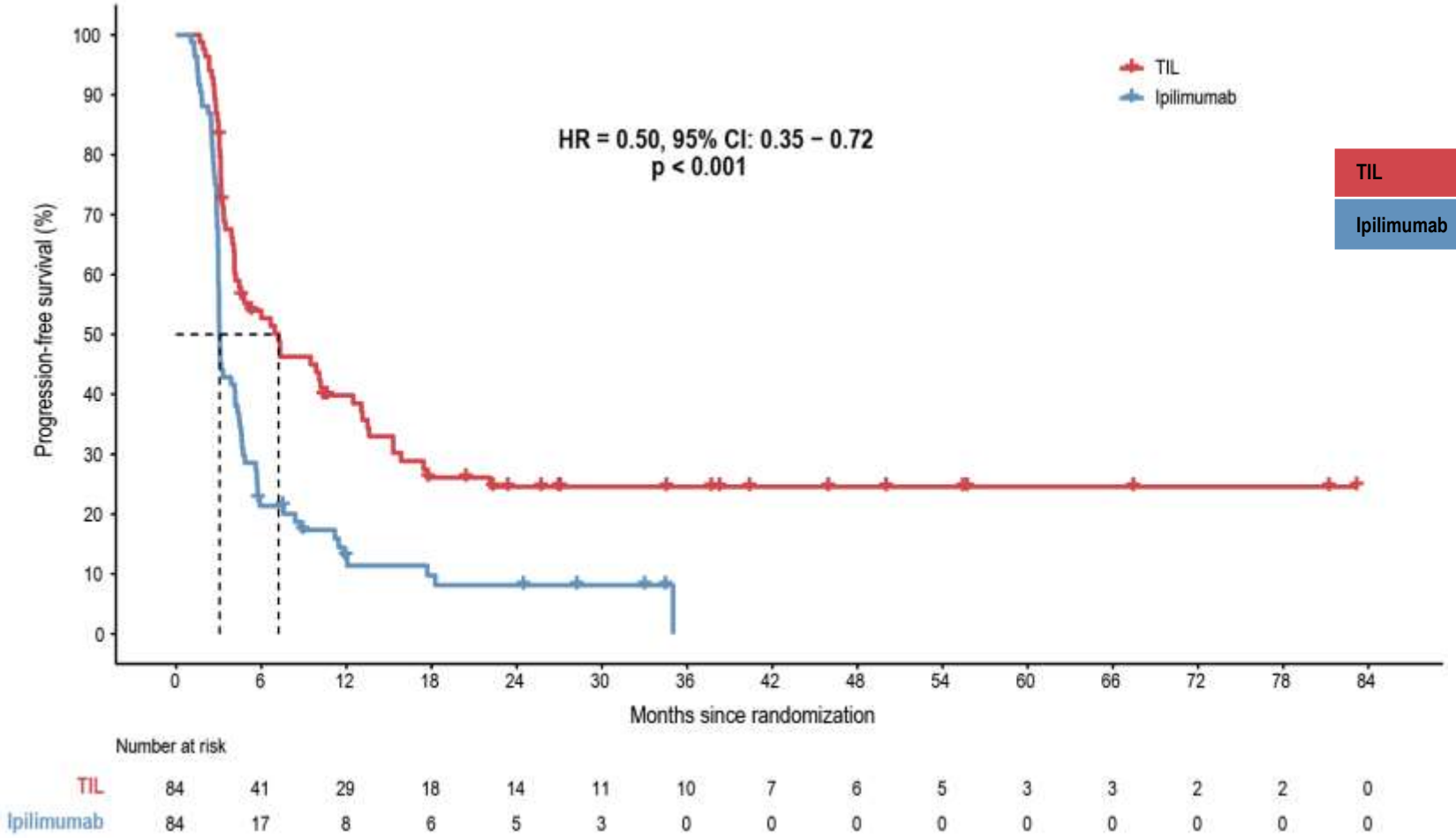
Tumor-infiltrating lymphocytes (TIL)

Preparation and treatment



Results (1)

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



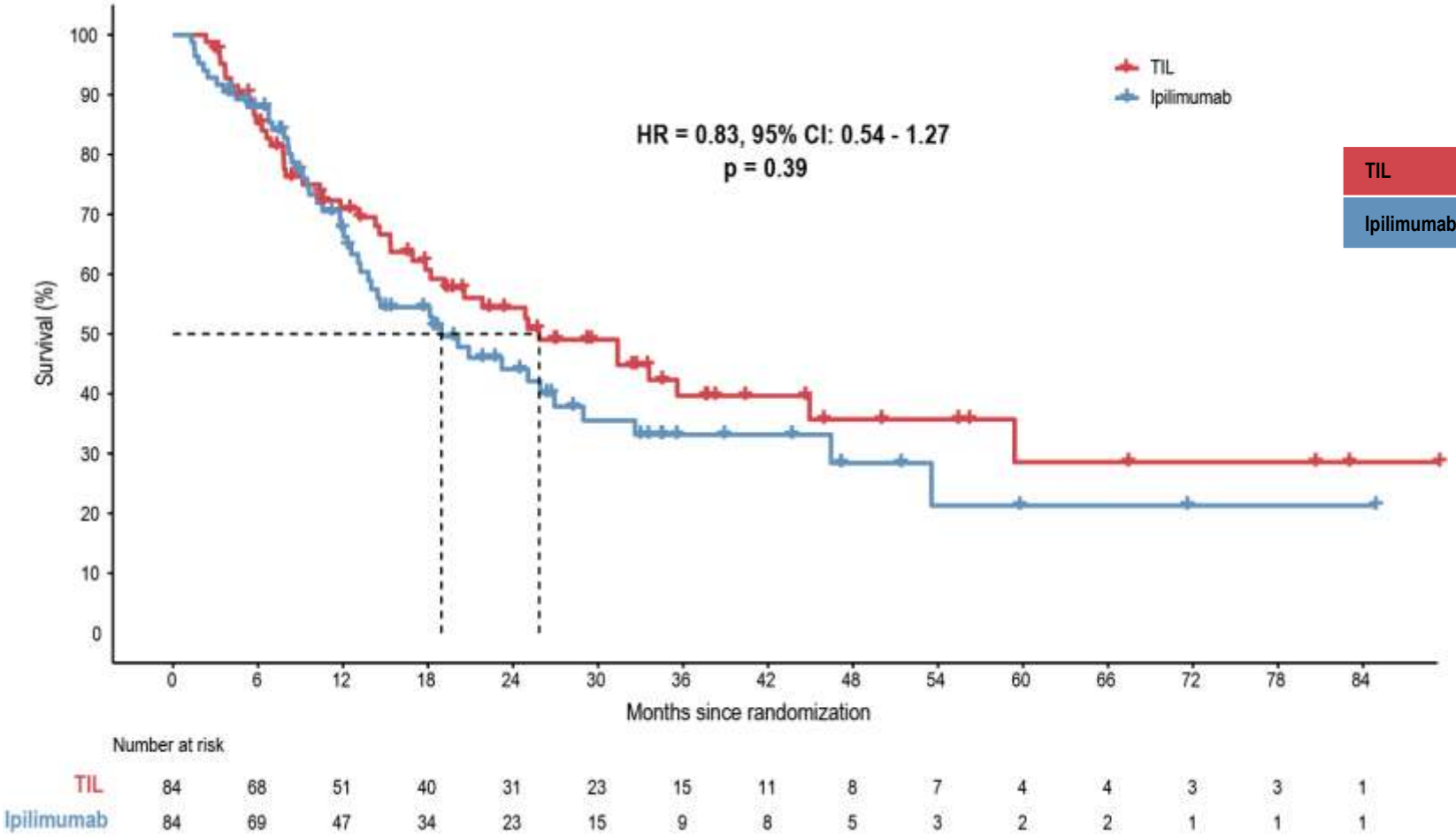
	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

2021 ESMO congress

John B.A.G. Haanen

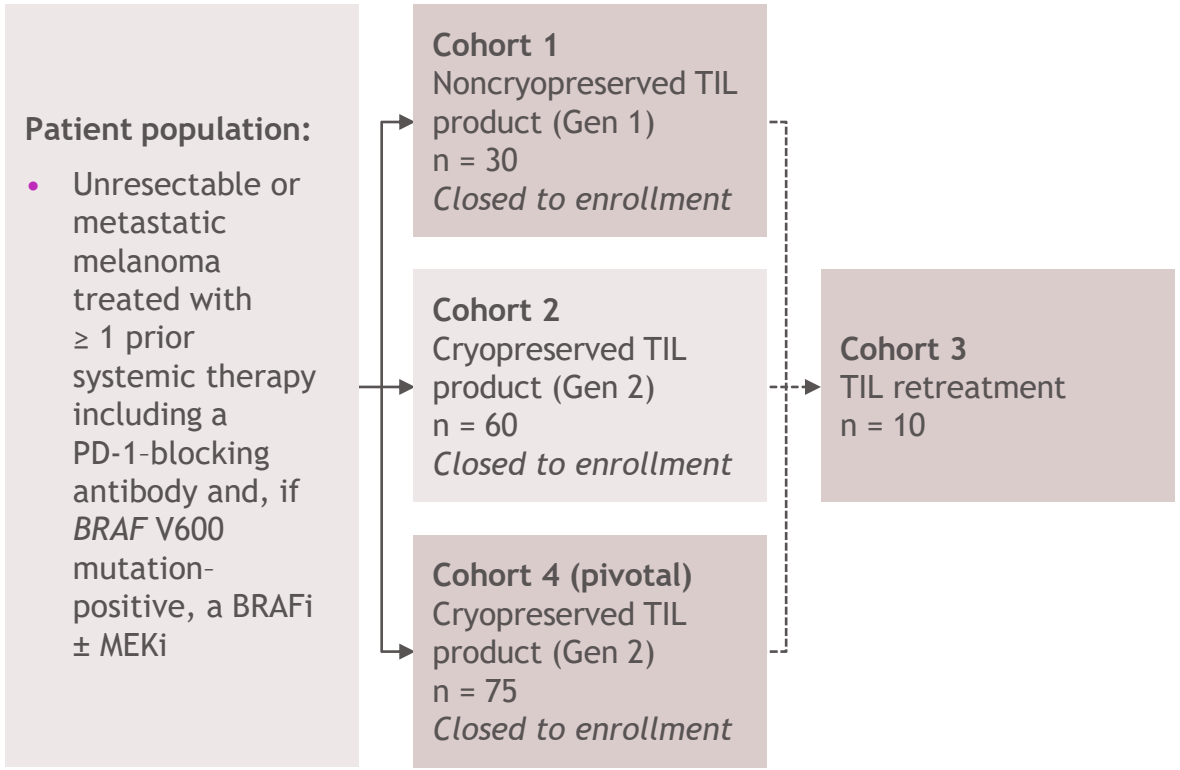
Results (4)

Overall survival in the ITT population



	Median overall survival (months)	95% CI	2 year overall survival (%)	95% CI
TIL	25.8	18.2 – NR	54.3	43.9 – 67.2
Ipilimumab	18.9	13.8 – 32.6	44.1	33.6 – 57.8

C-144-01 study design: autologous TIL therapy with lifileucel (LN-144) in advanced melanoma



Cohort 2 endpoints

- Primary: efficacy per investigator-assessed ORR using RECIST v1.1
- Secondary: safety and additional parameters of efficacy

Key eligibility criteria

- Radiographic confirmation of progression
- One tumor lesion resectable for TIL generation (~ 1.5 cm in diameter) and ≥ 1 target tumor lesion for RECIST v1.1 assessment
- Age ≥ 18 years at the time of consent
- ECOG PS 0-1

Methods

- Patients were enrolled from April 2017 to January 2019 at 26 sites across the US and EU
- Concomitant anticancer therapy was not permitted
- Imaging-evaluable disease was required
- All responses required confirmation
- Data cutoff: 22 April 2021

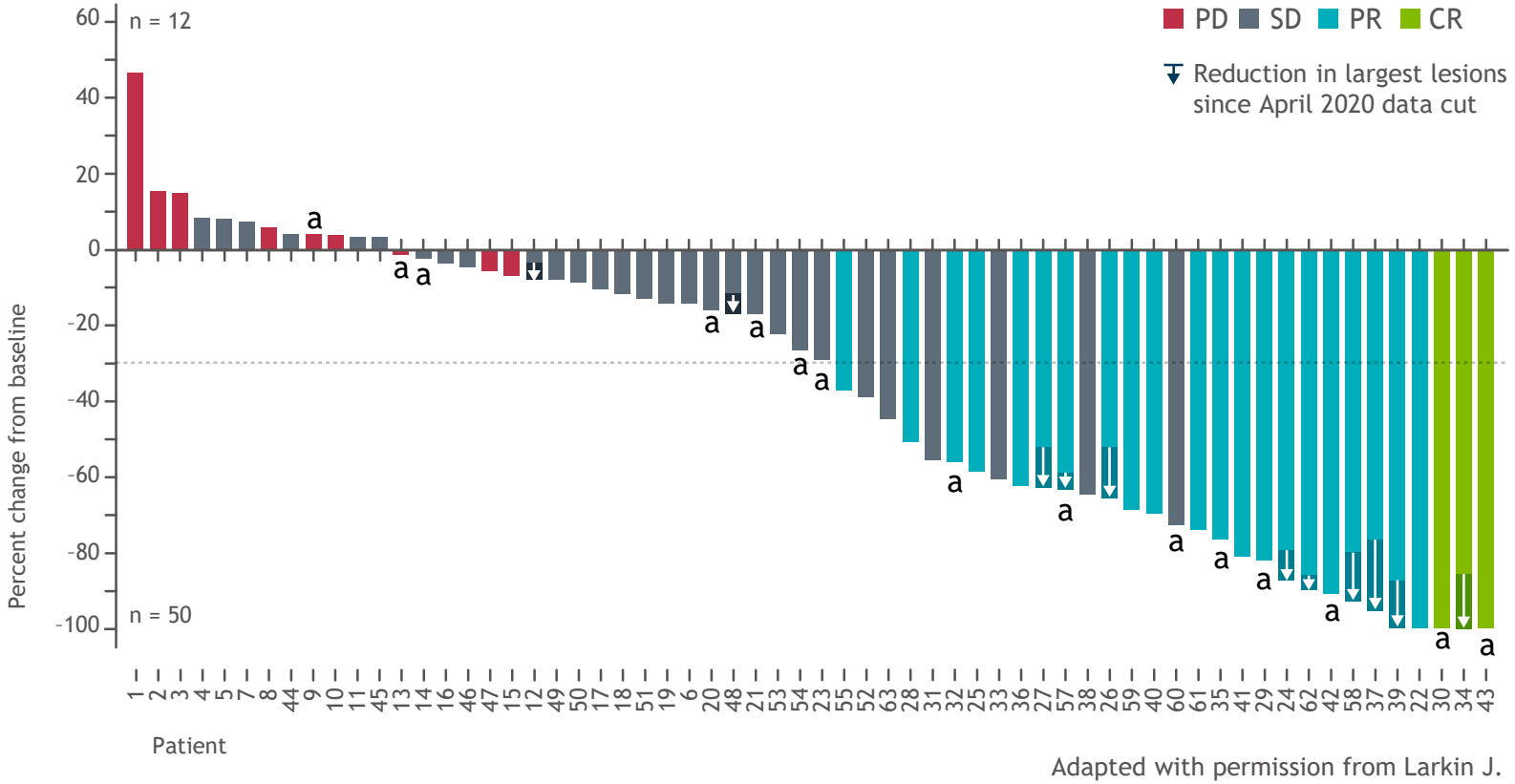
Adapted with permission from Larkin J.

BRAF, proto-oncogene B-Raf; Gen, generation; i, inhibitor; MEK, mitogen-activated protein kinase kinase; ORR, objective response rate; PD-1, programmed death 1; PFS, progression-free survival; PS, performance status; TIL, tumor-infiltrating leukocyte.

Larkin J et al. Presentation at the ASCO Annual Meeting; June 4–8, 2021; Virtual. Abstract 9505.

C-144-01: efficacy and safety

- 81% of patients had a reduction in tumor burden
- 17.7% of patients had further reduction of sum of diameters since the April 2020 data cutoff
- The ORR was 36.4% and the DCR was 80.3%
- Any-grade TEAEs were reported in 100% of patients
  - Grade 3–4: 97.0%
  - Grade 5: 3.0%



Adapted with permission from Larkin J.

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Median follow-up was 33.1 months (data cutoff, April 22, 2021). [a]Patients with *BRAF* V600 mutation. Three patients had no post-TIL disease assessments due to early death, and 1 due to start of new anticancer therapy.

BRAF, proto-oncogene B-Raf; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TIL, tumor-infiltrating leukocyte; TEAE, treatment-emergent adverse event.

Larkin J et al. Presentation at the ASCO Annual Meeting; June 4–8, 2021; Virtual. Abstract 9505.

FDA NEWS RELEASE

FDA Approves First Cellular Therapy to Treat Patients with Unresectable or Metastatic Melanoma

For Immediate Release: February 16, 2024

Today, the U.S. Food and Drug Administration approved Amtagvi (lifileucel), the first cellular therapy indicated for the treatment of adult patients with a type of skin cancer (melanoma) that is unable to be removed with surgery (unresectable) or has spread to other parts of the body (metastatic) that previously has been treated with other therapies (a PD-1 blocking antibody, and if *BRAF* V600 mutation positive, a *BRAF* inhibitor with or without a MEK inhibitor).

IOV-COM-202: Phase 2, Multicohort, Multicenter Study of Lifileucel + Pembrolizumab in Patients With Solid Tumors

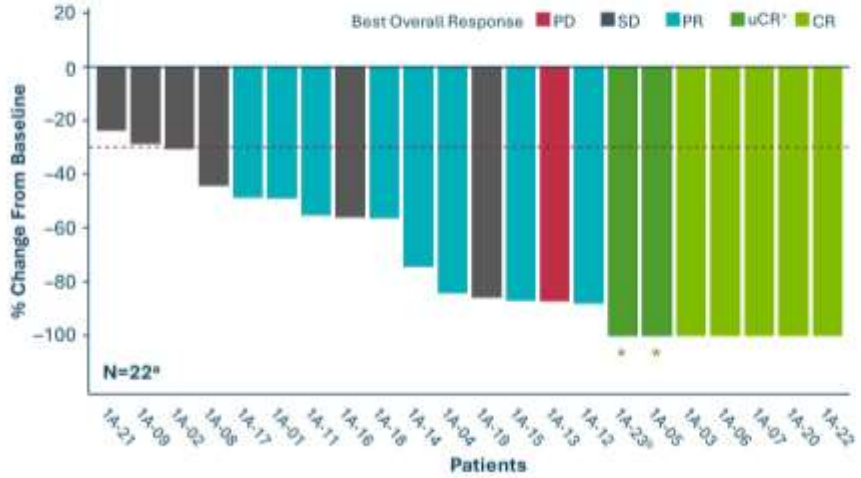
- Cohort 1A of IOV-COM-202 (NCT03645928) assesses the efficacy and safety of lifileucel + pembrolizumab in patients with ICI-naive unresectable or metastatic melanoma
  - Patients may have received BRAF/MEK inhibitor treatment if they are *BRAF* mutation positive
  - Eligible patients must have ≥1 resectable lesion (≥1.5-cm diameter) and ≥1 measurable lesion for response assessment per RECIST v1.1
- Trial designed as a proof-of-concept study to support a registrational study in the frontline treatment setting

Treatment Schema

[a]First administration of single-dose pembrolizumab IV 200 mg or 400 mg, followed by pembrolizumab IV 200 mg Q3W or 400 mg Q6W for 24 months or until disease progression or unacceptable toxicity. CY, cyclophosphamide; EOA, end of assessment; FLU, fludarabine; GMP, Good Manufacturing Practice; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; pembro, pembrolizumab; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

ORR was 65.2%; CR rate was 30.4%

Best Percentage Change From Baseline in Target Lesion SOD



Investigator-Assessed Response (RECIST v1.1)

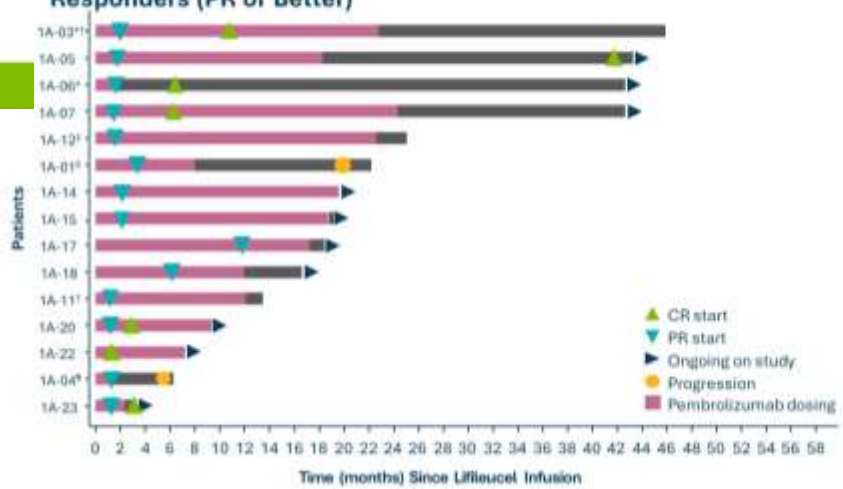
	N=23
ORR, n (%) (95% CI)	15 (65.2) (42.7, 83.6)
CR	7 (30.4)
PR	8 (34.8)
SD	6 (26.1)
PD	1 (4.3)
NE	1 (4.3)

All response-evaluable patients demonstrated regression of target lesions

*** The two uCRs have been confirmed post-data cut**

Lifileucel + pembrolizumab demonstrated durable and deepening responses

Time to Response and Time of Efficacy Assessment for Confirmed Responders (PR or Better)



Duration of Response

	Responders (N=15/23)
mDOR, months (95% CI)	Not reached (NR) (16.8, NR)
DOR, n (%)	
≥6 months	11 (73.3)
≥12 months	8 (53.3)

- Median follow-up was 21.7 months
- **mDOR was NR**
- Median time to initial response was 2.6 months
- 10 of 15 responders (66.7%) continue on study with ongoing response and 3 additional patients (20%) discontinued follow-up while in response

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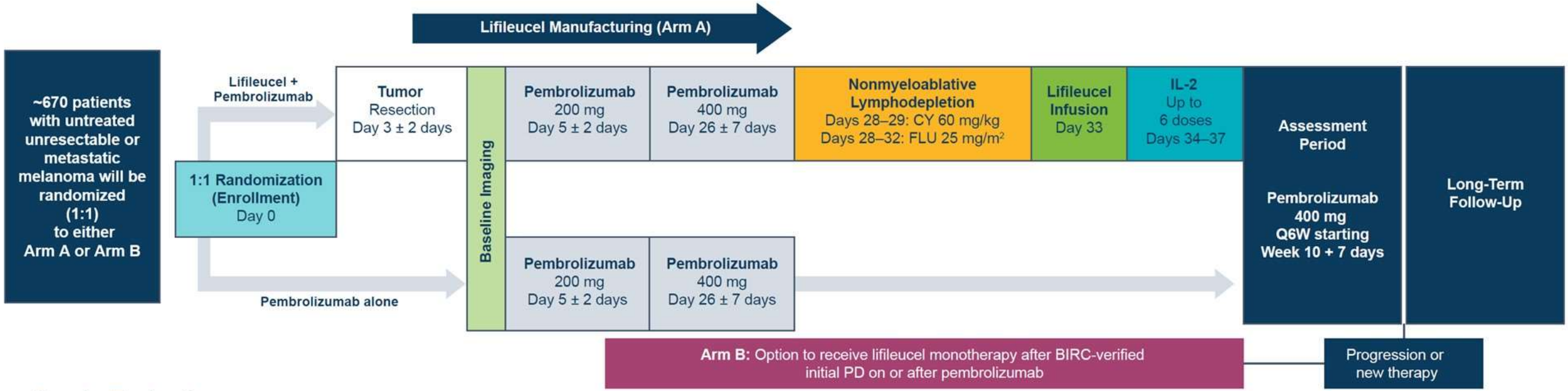
TILVANCE-301[a] Global Phase 3 and Confirmatory Trial

Randomized study to evaluate lifileucel + pembrolizumab in frontline advanced melanoma Enrolling in Europe, North America, and Australia



Study Endpoints

Dual primary efficacy endpoints

- BIRC-assessed ORR per RECIST v1.1
  - Potential for accelerated approval and confirmation of post anti-PD1 approval based on early interim analysis
- BIRC-assessed PFS 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

[a]NCT05727904.

BIRC, blinded independent review committee; CR, complete response; CY, cyclophosphamide; EFS, event-free survival; FLU, fludarabine; IL-2, interleukin-2; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; PFS, progression-free survival; PFS2, progression-free survival 2; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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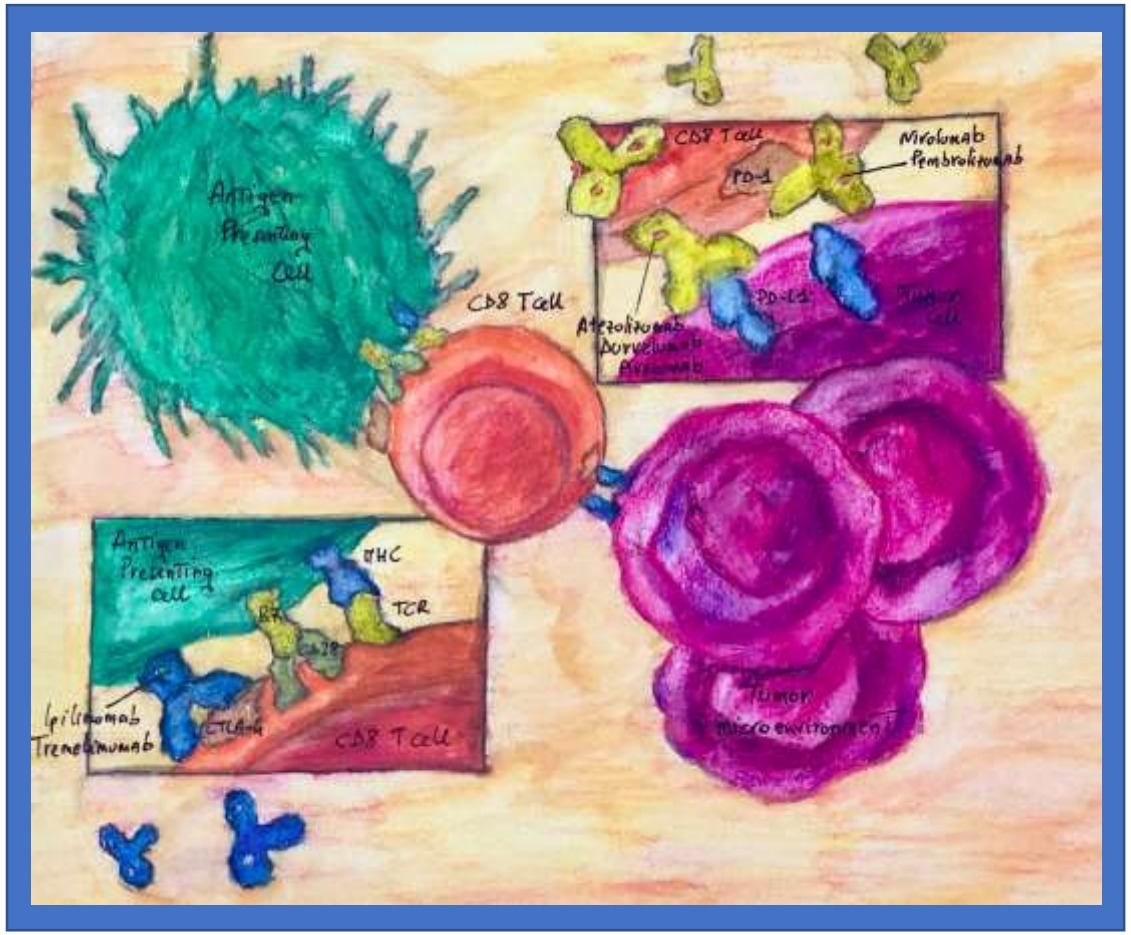
Agenda

Immune checkpoint inhibitors

TIL therapy



Oncolytic virus therapy

Cancer vaccines

CAR-T cells

Ottaviano M. Virchows Arch 2019

PARIS 2022 ESMO congress

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

Caroline Robert[1], Mohammed M Milhem[2], Joseph J Sacco[3], Judith Michels[4], Gino K In[5], Eva Muñoz Couselo[6], Dirk Schadendorf[7], Georgia M Beasley[8], Jiaxin Niu[9], Bartosz Chmielowski[10], Trisha M Wise-Draper[11], Tawnya Lynn Bowles[12], Katy K Tsai[13], Céleste Lebbé[14], Caroline Gaudy-Marqueste[15], Mark R Middleton[16], Adel Samson[17], Junhong Zhu[18], Marcus Viana[18], Michael K Wong[19]

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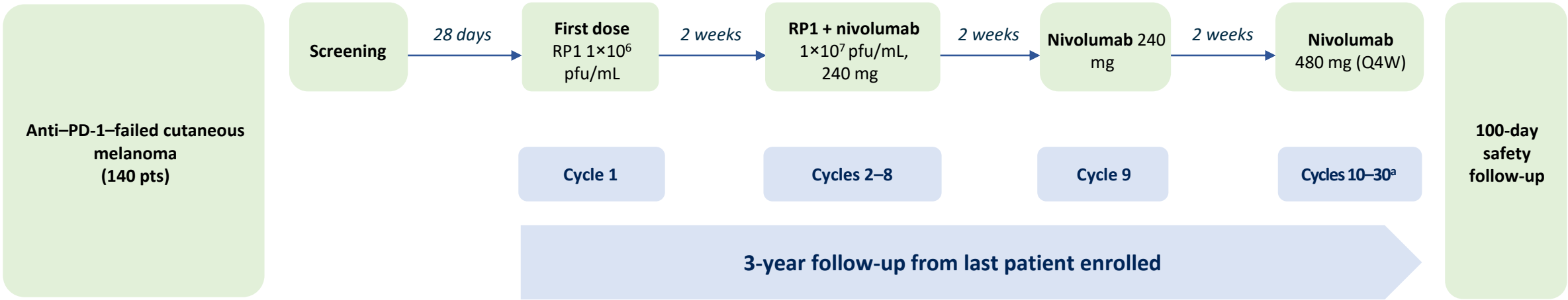
Study design



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

Primary objective

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

Secondary objectives

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

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

Key eligibility

Anti–PD-1–failed advanced melanoma; measurable disease; adequate organ function; no prior oncolytic therapy; ECOG performance status 0-1

Criteria for prior anti–PD-1–failure

Confirmed progression while being treated with at least 8 weeks of anti–PD-1 therapy, alone or in combination; anti–PD-1 must be the last prior therapy. Patients on prior adjuvant therapy must have confirmed progression while being treated with adjuvant treatment (PD can be confirmed by biopsy)

Primary analysis conducted when all patients had **≥12 months follow-up**

[a]RP1 can be reinitiated beyond 8 cycles if protocol-specified criteria are met.

CR, complete response; DCR, disease control rate; DOCB, duration of clinical benefit; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; pfu, plaque-forming units; pt, patient; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Primary efficacy analysis
By blinded, independent central review

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

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

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

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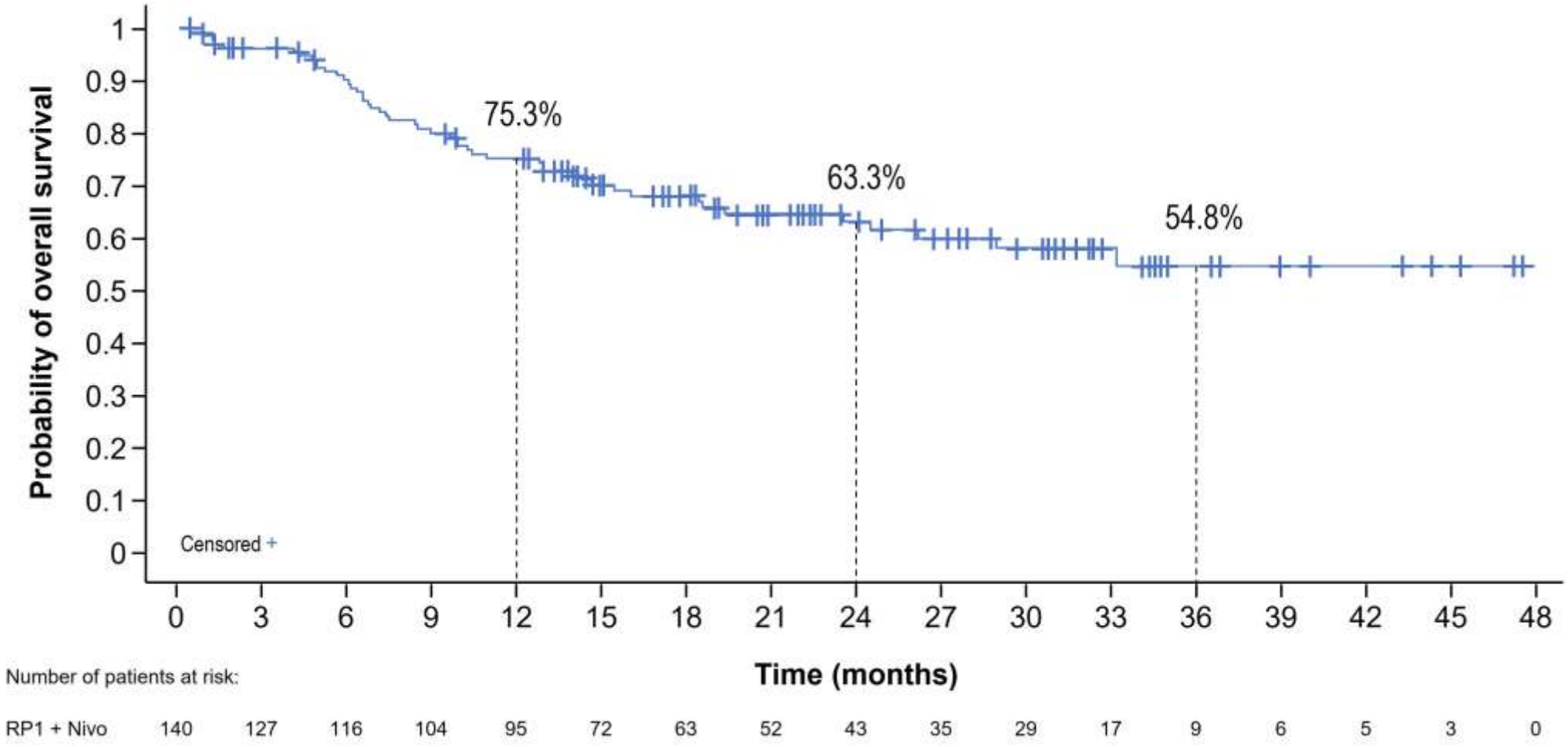
Overall survival



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

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My personal Considerations

- Neoadjuvant combo ICI practice chancing
- Still space for adjuvant therapy→ Ongoing Phase III adjuvant trials are investigating in individualized neoantigen therapy
- IO COMBO as first line of treatment for advanced disease→ something more to do for the safety profile
- Resistance to IO (BRAF wt)→ ???????? (CAR-T?, Oncolytic virus)
- TILs in front line setting…

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Patients, Families and Caregivers

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