ISTITUTO NAZIONALE TUMORI
IRCCS – Fondazione Pascale

Melanoma as a Paradigm for the Future of Immunotherapy

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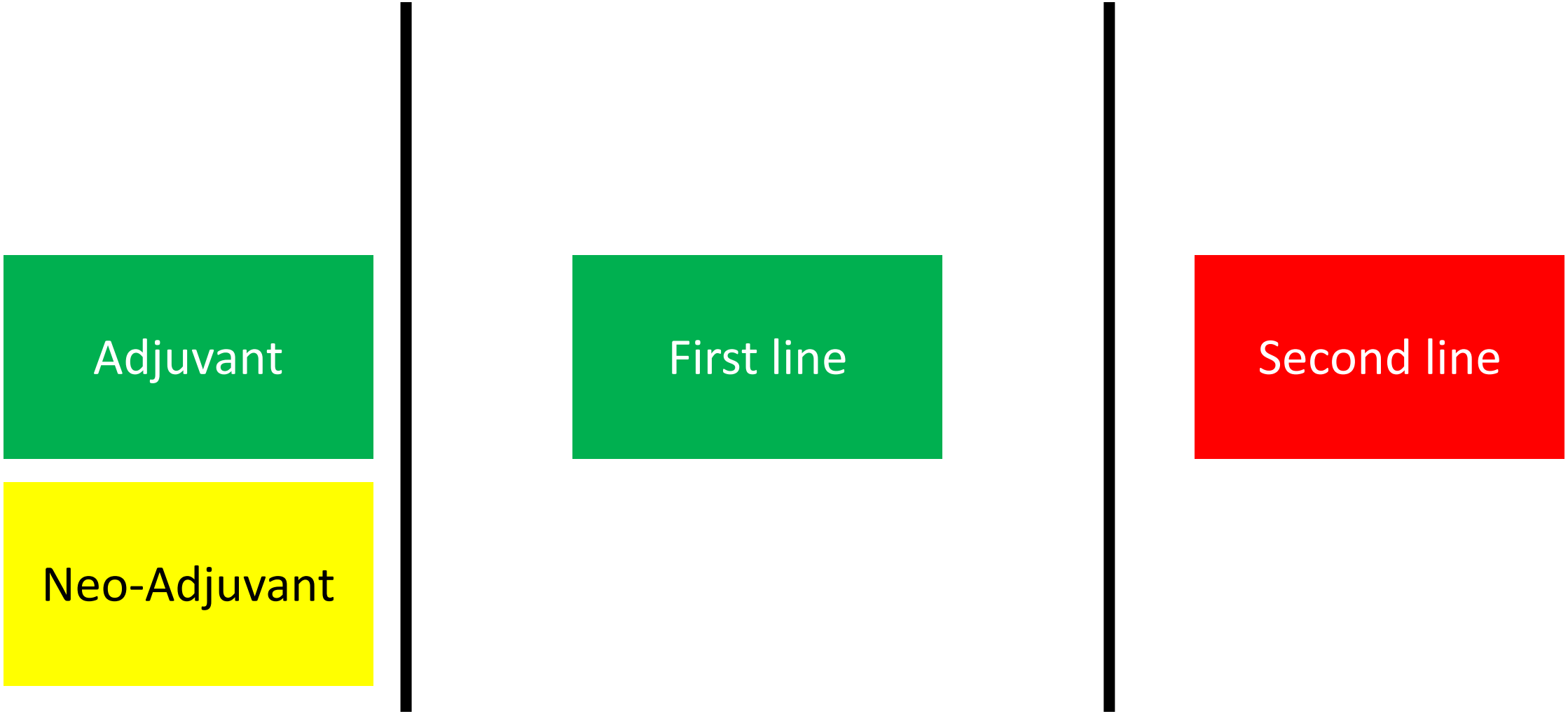
Istituto Nazionale Tumori – Fondazione "G. Pascale", Napoli

Melanoma landscape

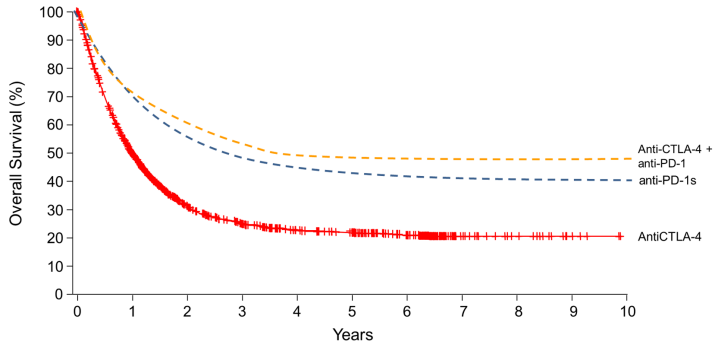


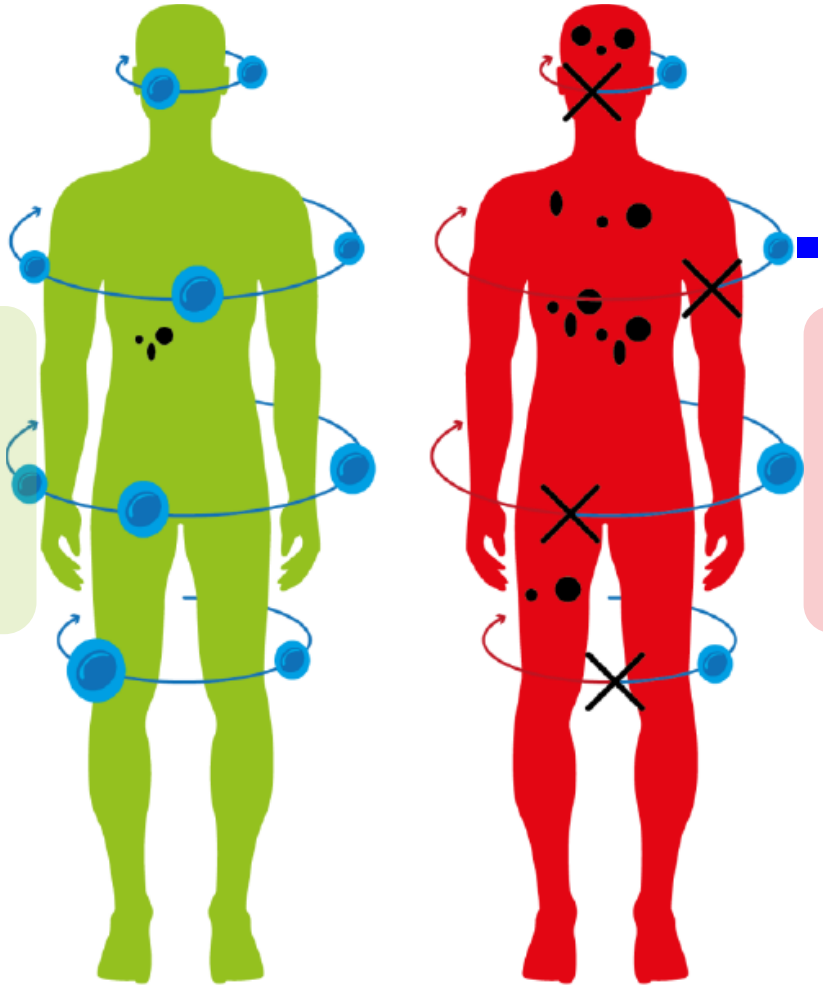
Patient characteristics affecting immune surveillance

Active immune surveillance

Long-term benefit patients

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

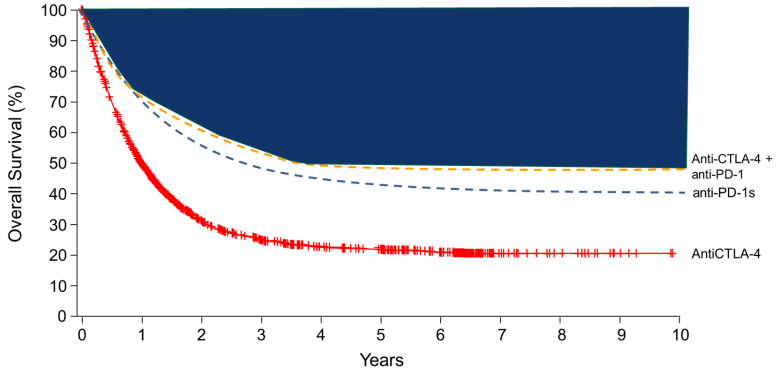




Inactive immune surveillance

No long-term benefit patients

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



LDH, lactate dehydrogenase

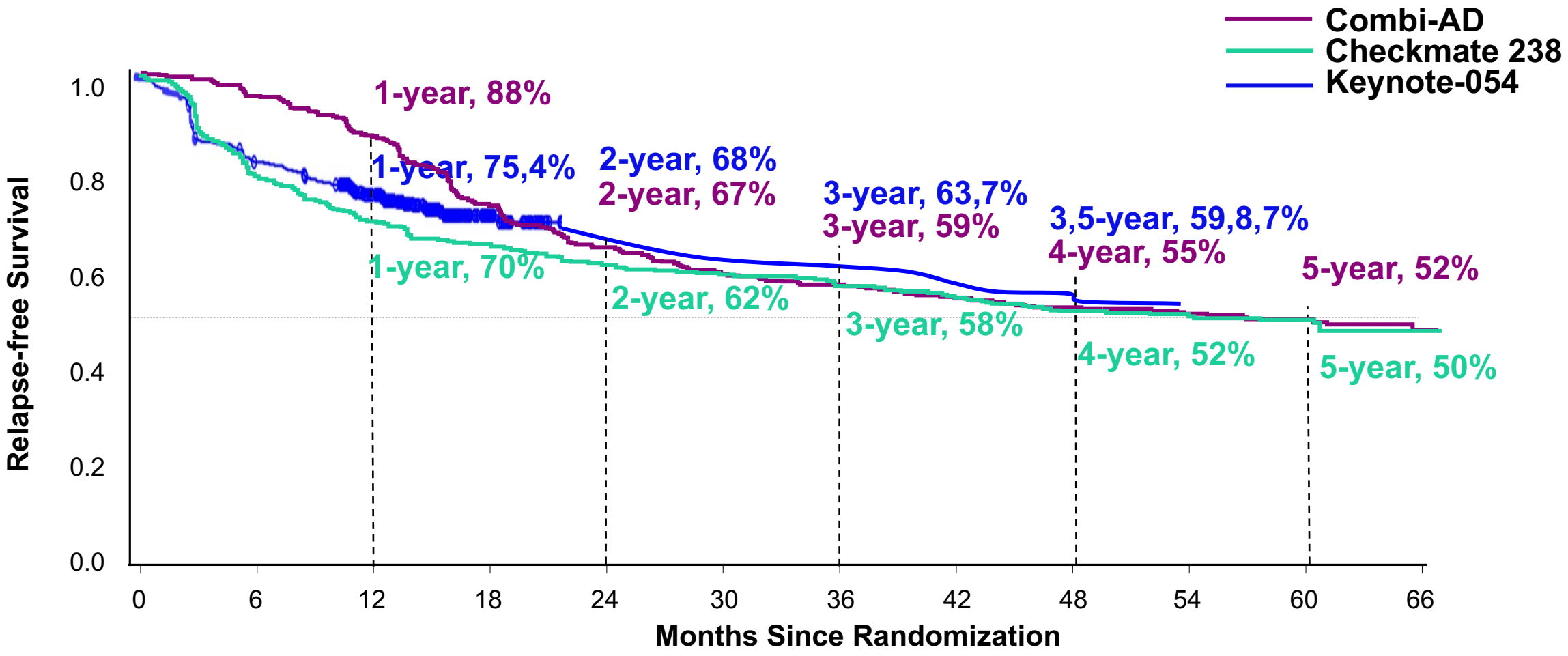
Ascierto P, Dummer R. Oncoimmunology. 2018; Ascierto P, Ed. Session ASCO. 2019

Melanoma landscape

Adjuvant

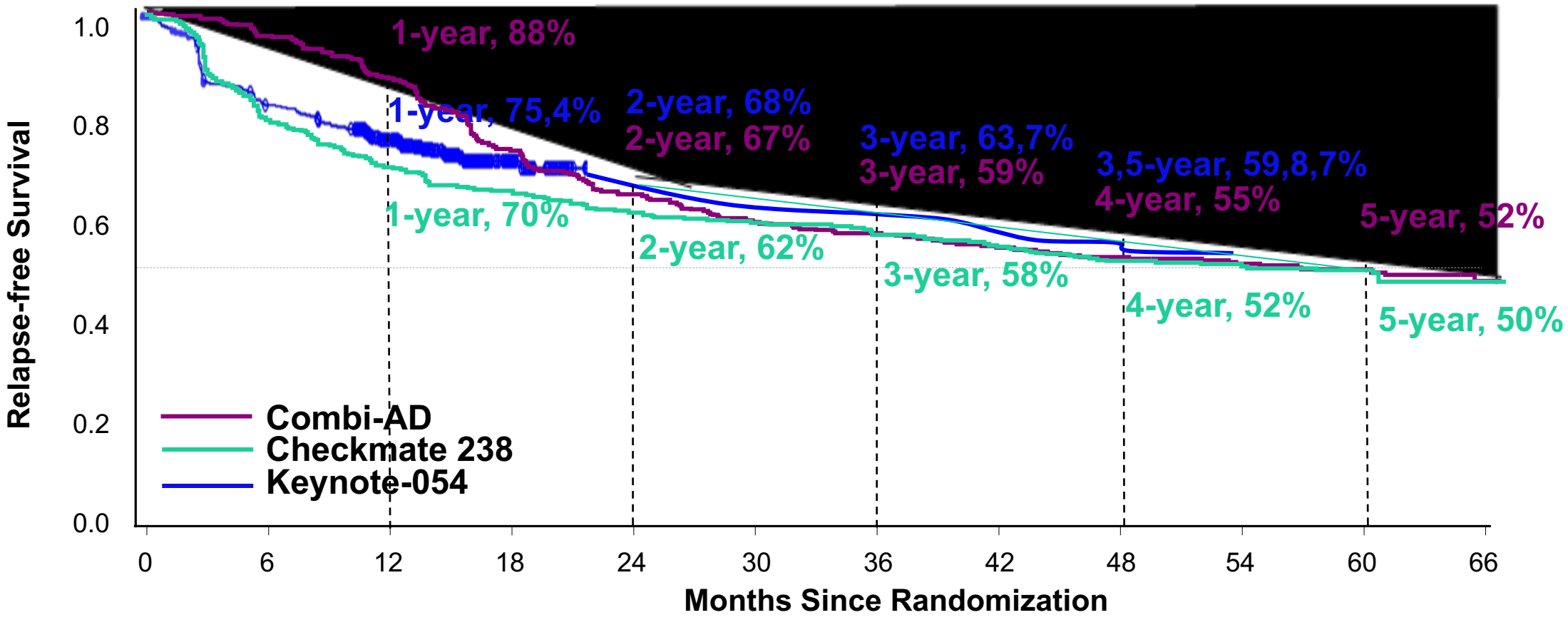
Stage III-IV NED

RFS curves in the recent adjuvant studies



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

RFS curves in the recent adjuvant studies



Hauschild et al. ASCO 2020
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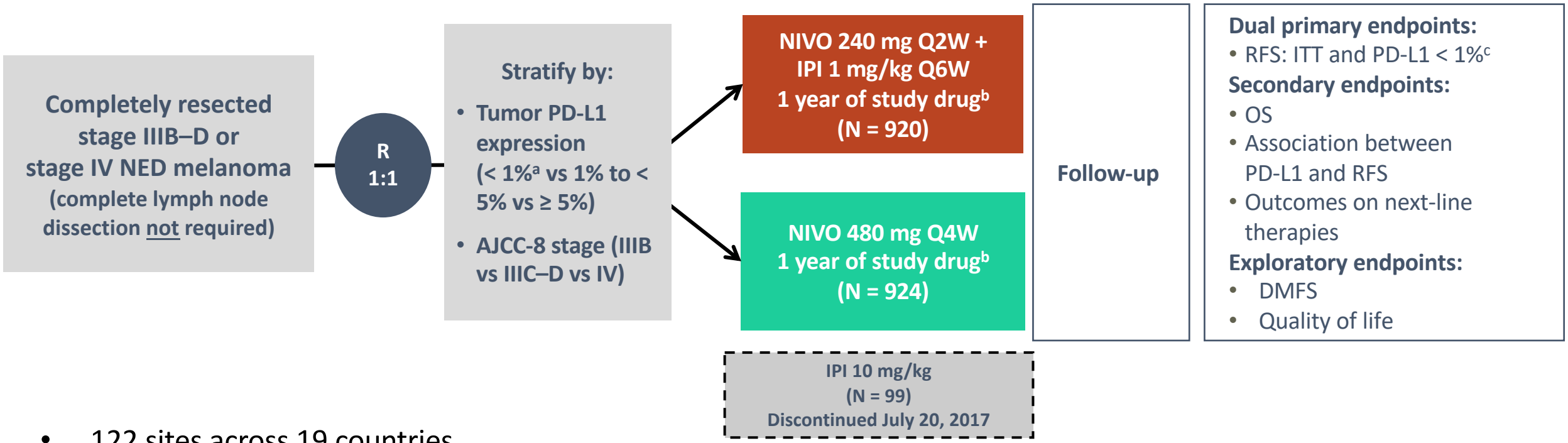
CheckMate 915 study design



- 122 sites across 19 countries
- Database lock Sept 8, 2020
- Minimum follow-up of approximately 24 months (median 28 months)

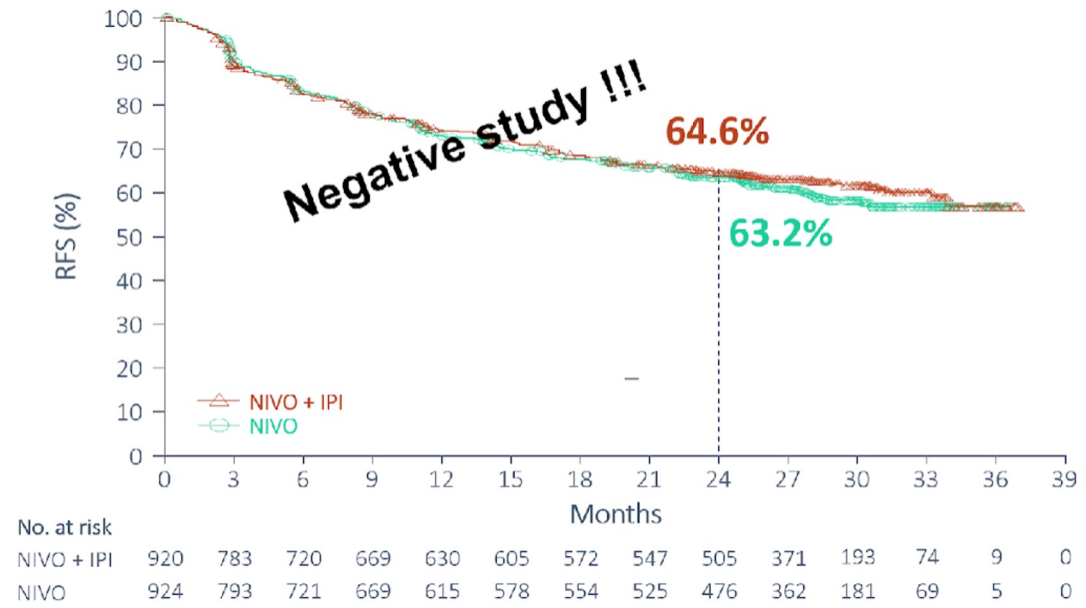
[a]Or indeterminate; [b]Until recurrence, unacceptable toxicity, or 1 year of treatment; [c]In November 2019, the data monitoring committee indicated that the dual primary endpoint of RFS in patients with tumor PD-L1 < 1% was not met; the study remained blinded until the ITT endpoint was evaluable. AJCC, American Joint Committee on Cancer; DMFS, distant metastasis-free survival; NED, no evidence of disease; PD-L1, programmed death-ligand 1.

Long et al. *AACR 2021*

Dual primary endpoint:

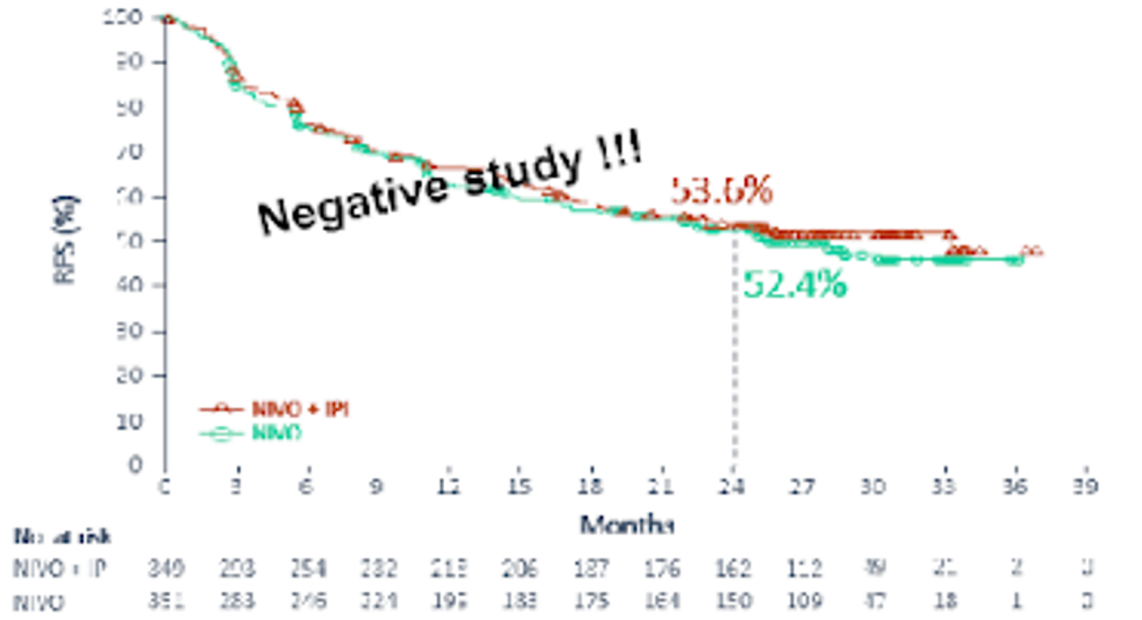
RFS in ITT population

	NIVO + IPI (n = 920)	NIVO (n = 924)
Events, n	327	347
Median, mo (95% CI)	NR	NR
HR (97.295% CI)[a]	0.92 (0.77–1.09)	
***P*[b]**	0.269	



RFS in patients with tumor PD-L1 < 1%

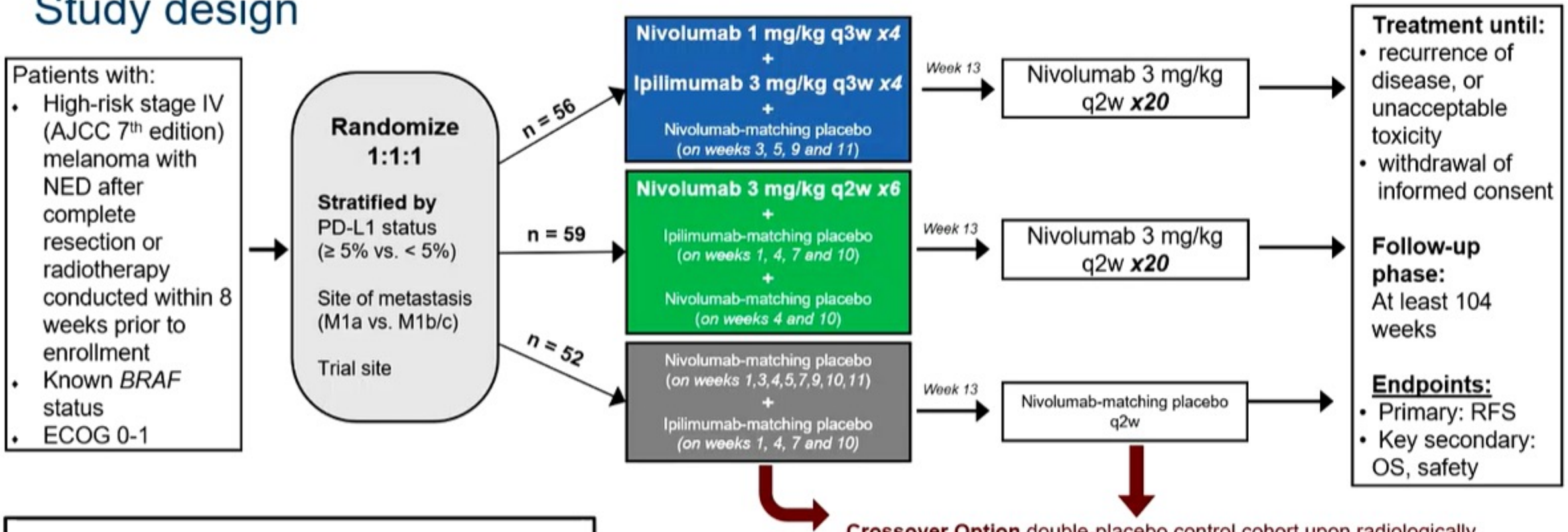
	NIVO + IPI (n = 349)	NIVO (n = 351)
Events, n	159	166
Median, mo (95% CI)	33.2 (22.2–NR)	25.3 (19.8–NR)
HR (95% CI)[a]	0.91 (0.73–1.14)	



Long et al. *AACR 2021*

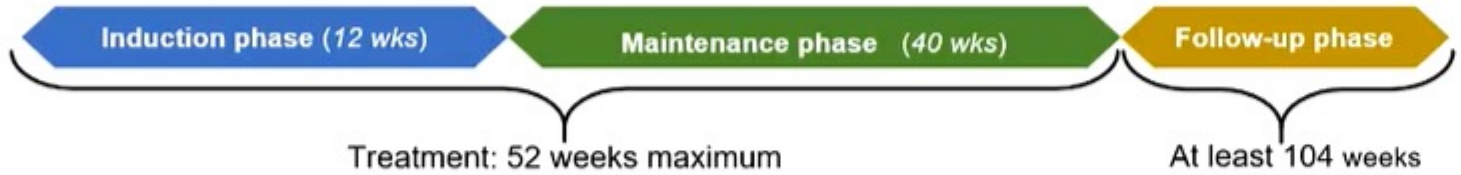
THE IMMUNED STUDY

Study design



Enrollment period: Sept. 2015 to Nov. 2018
Current median Follow-up: 49.2 months

Crossover Option double-placebo control cohort upon radiologically confirmed disease recurrence; nivolumab 3mg/kg monotherapy every 2 weeks until subsequent progression or for up to 1 year, whichever occurs first.



PARIS 2022 ESMO congress

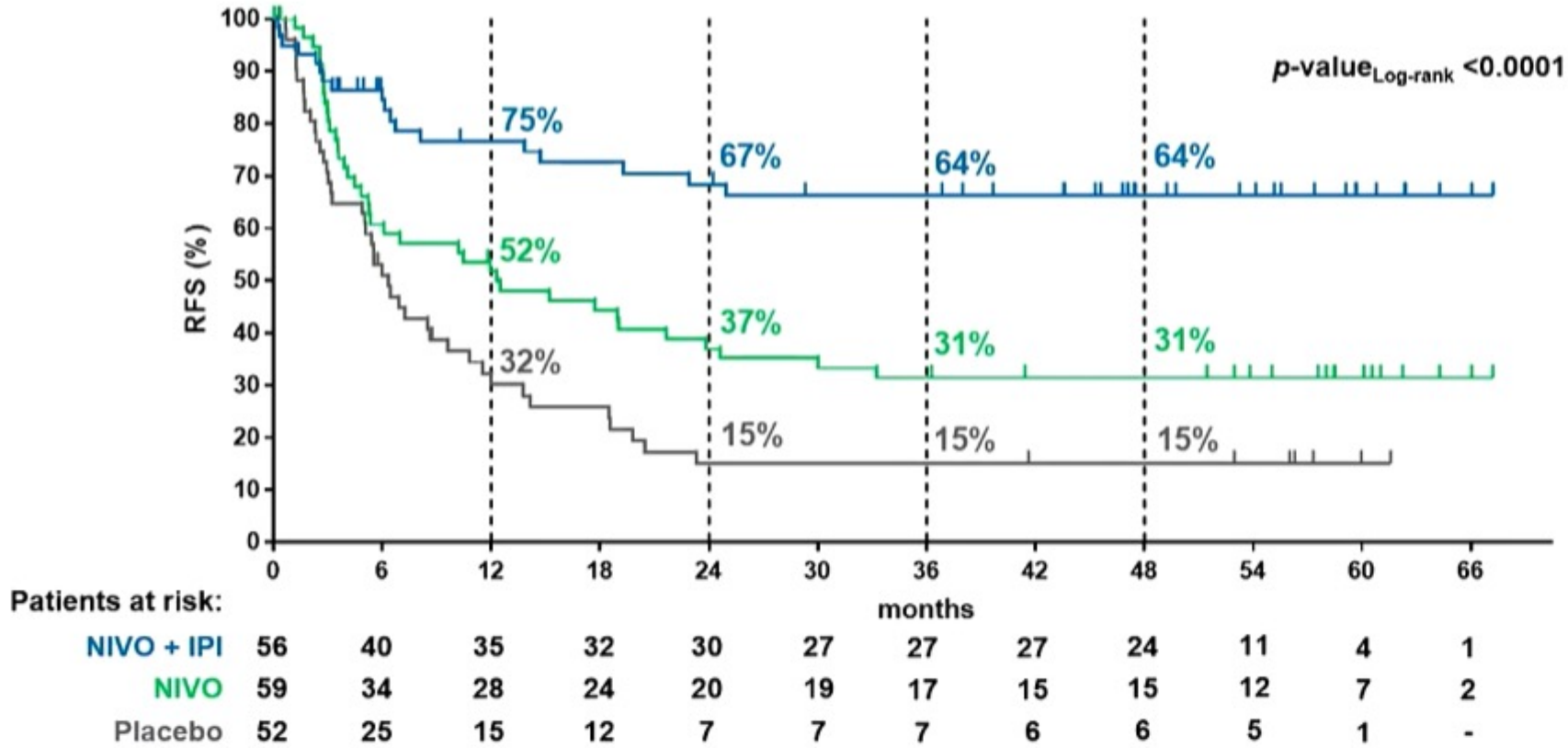
THE IMMUNED STUDY

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



PARIS 2022 ESMO congress

Dirk Schadendorf

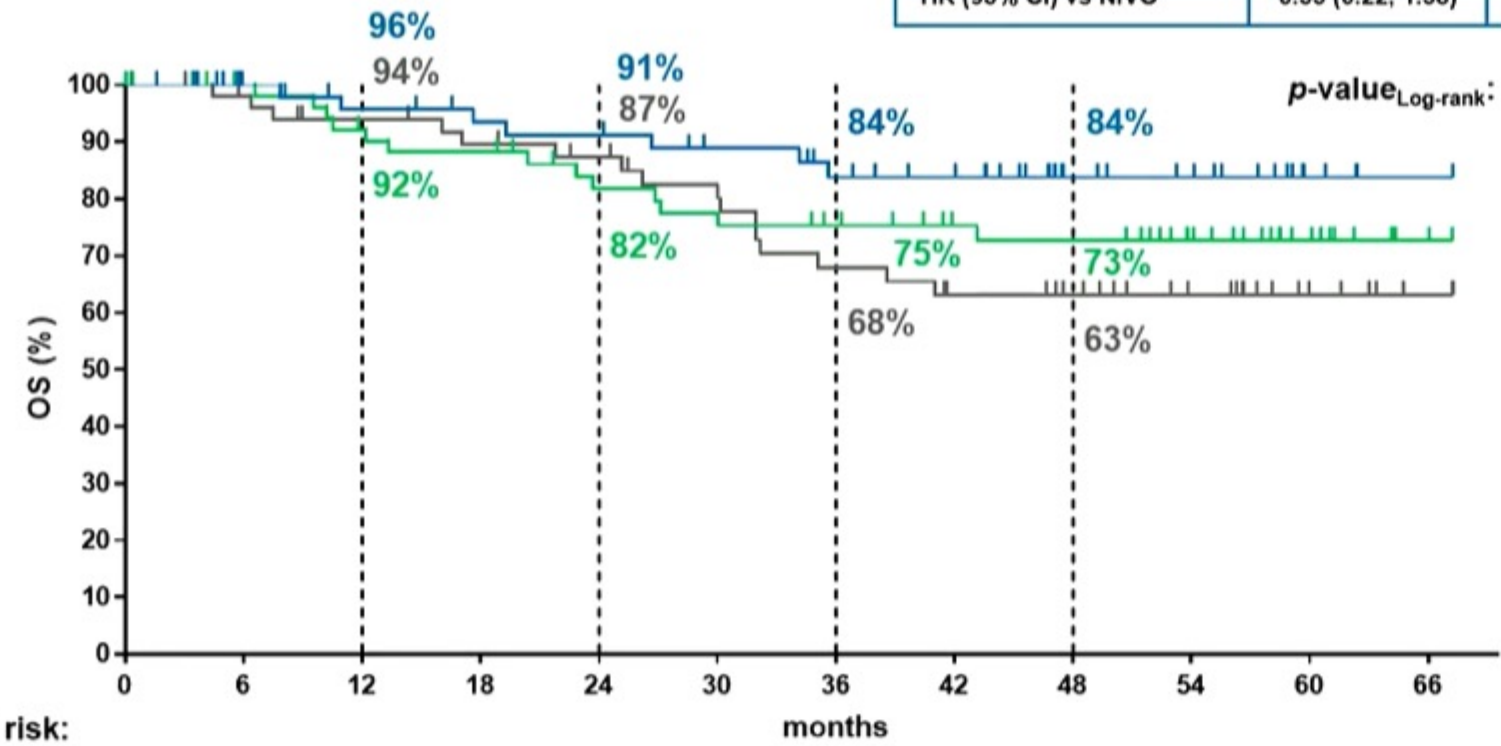
THE IMMUNED STUDY

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, 0.99)	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 proprtional hazard assumption.



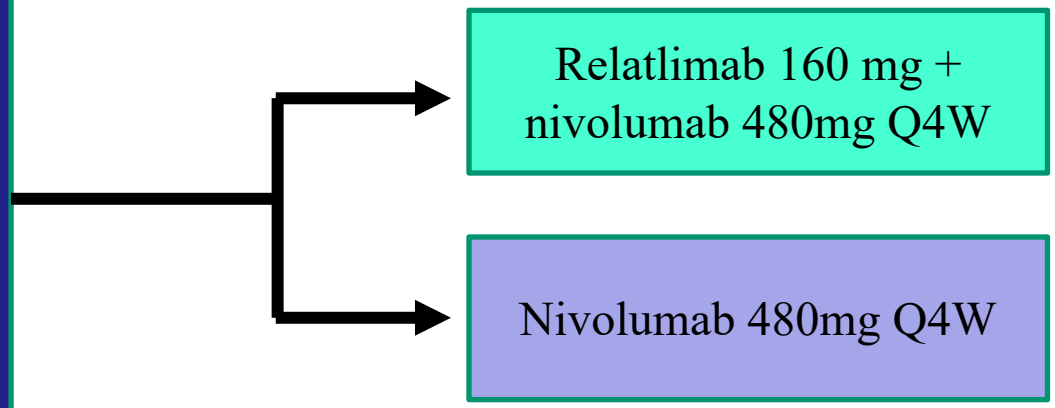
Patients at risk:

NIVO + IPI	56	48	44	41	40	36	32	29	16	13	4	1
NIVO	59	51	46	44	38	36	33	28	27	20	10	2
Placebo	52	48	44	41	38	33	28	23	20	14	6	2

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

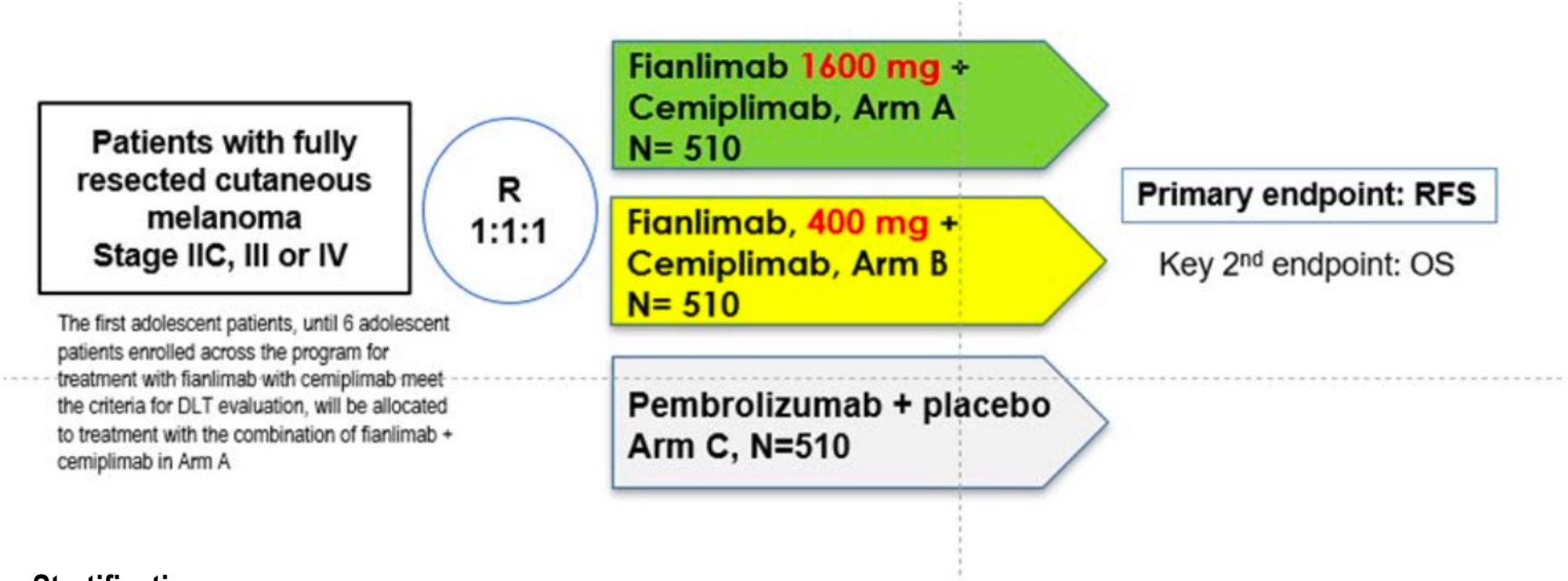
CA224-098 Study: Nivolumab plus relatlimab vs Nivolumab plus placebo

Key Elegibility Criteria
>> 18 Years of Age
Completely resected melanoma
Stage IIIA (>1mm tumor in LN)
Stage IIIB/C/D, or Stage IV NED
Melanoma
-no prior immuno-oncology agents
-ECOG 0-1
-Submission of FFPE tissue block or 20 unstained slides from surgical/biopsy speciment within 3 months of randomization.



Maximum treatment duration 1 year from first dose or maximum of 13 doses

Harmony-Adjuvant Study Design (Study 2055 – Phase 3)



Stratification

1. Stage: IIIA vs IIC- IIIB-IIIC vs IIID-IV[M1a/b] vs IV[M1c/d]
2. Geographical region: North America vs Europe vs Rest of World

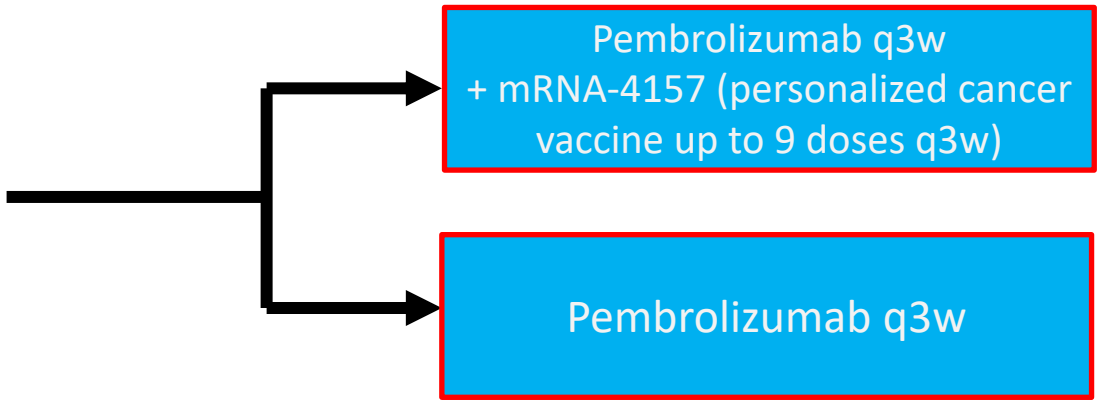
- The study will be conducted globally, at approximately 220 sites in Europe, North America, LATAM, and Australia.
- The study started enrolling in January 2023

A Phase 2 Randomized Study of Adjuvant Immunotherapy With the Personalized Cancer Vaccine mRNA-4157 and Pembrolizumab Versus Pembrolizumab Alone After Complete Resection of High-Risk Melanoma

Moderna TX ID	Clinicaltrials.gov ID
mRNA-4157-P201	NCT03897881

Key Elegibility Criteria:

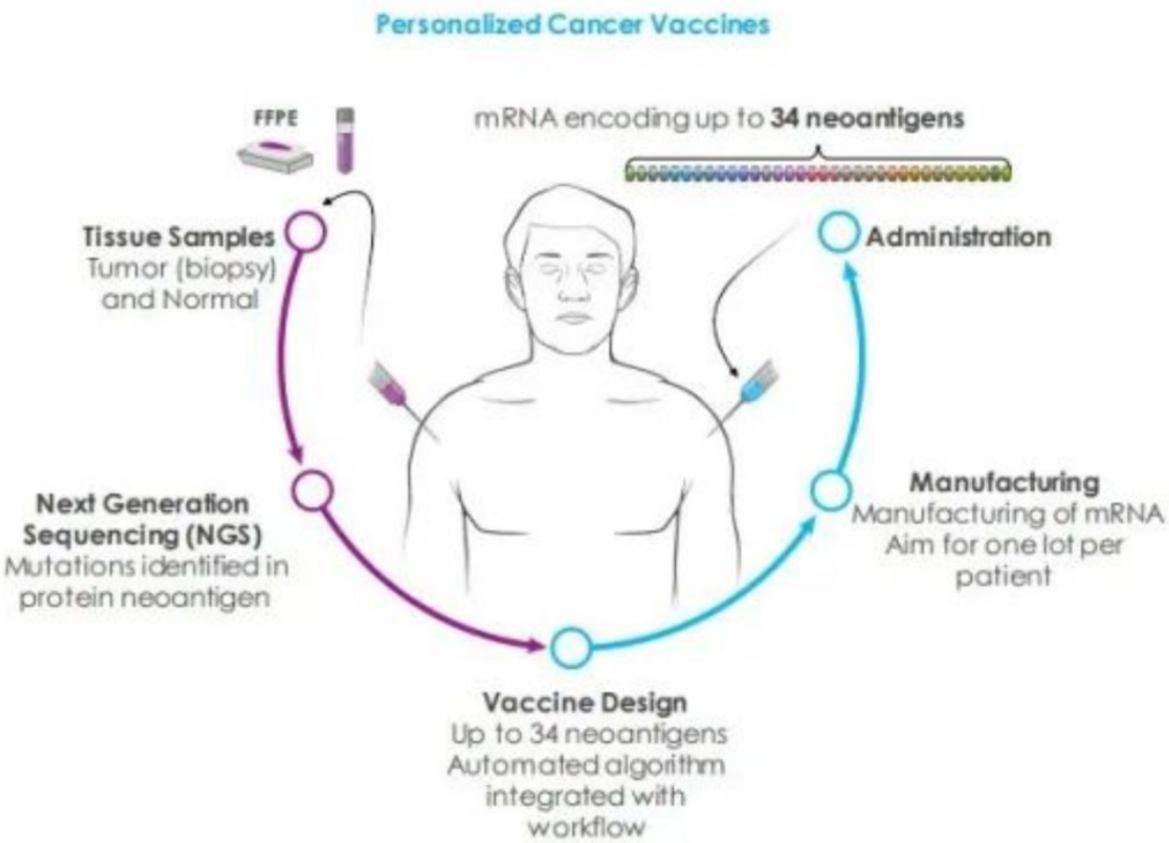
- Resectable cutaneous melanoma metastatic to a lymph node and at high risk of recurrence
- Complete resection within 13 weeks prior to the first dose of pembrolizumab
- Disease free at study entry (after surgery)
- Has an FFPE tumor sample available
- PS 0 or 1



Pt may continue until disease recurrence, unacceptable toxicity, or they undergo up to 18 total cycles (approximately 1 year of treatment.

Personalized cancer vaccine (mRNA-4157)

Designed to target an individual patient's unique tumor mutations



Personalized drug design

Rapid turnaround times

Needle-to-needle in just **weeks**

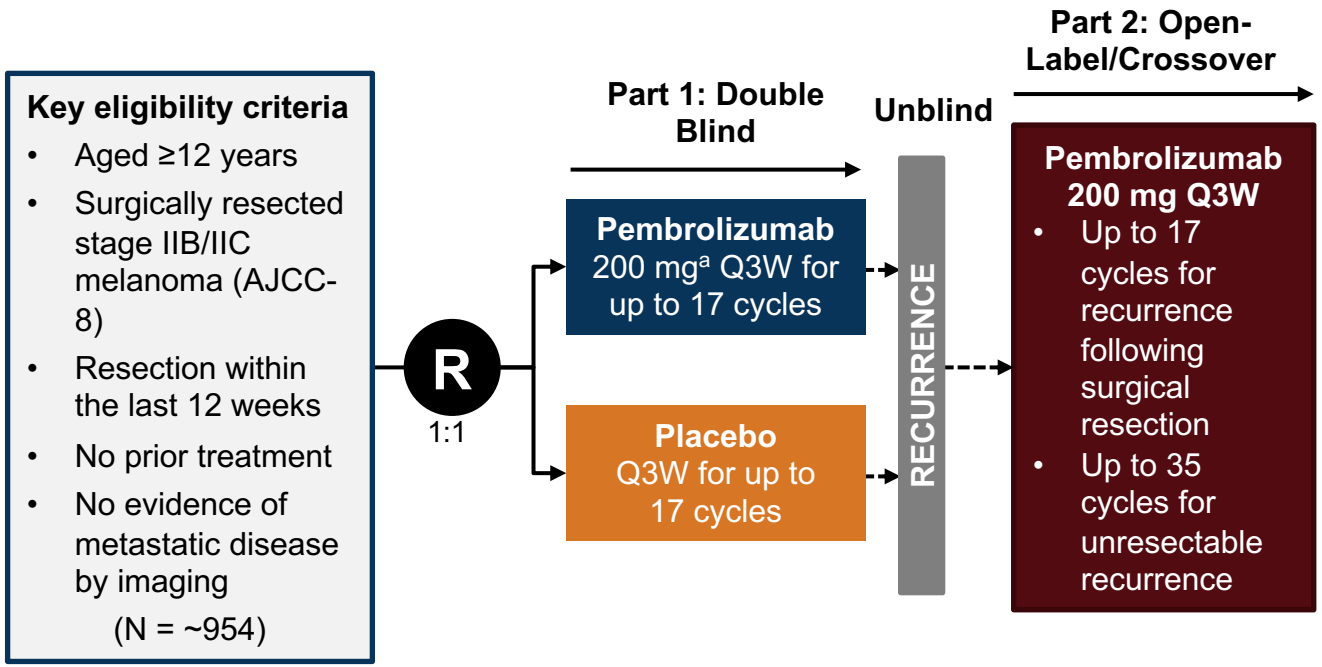
Melanoma landscape

Adjuvant

Stage IIB-IIC

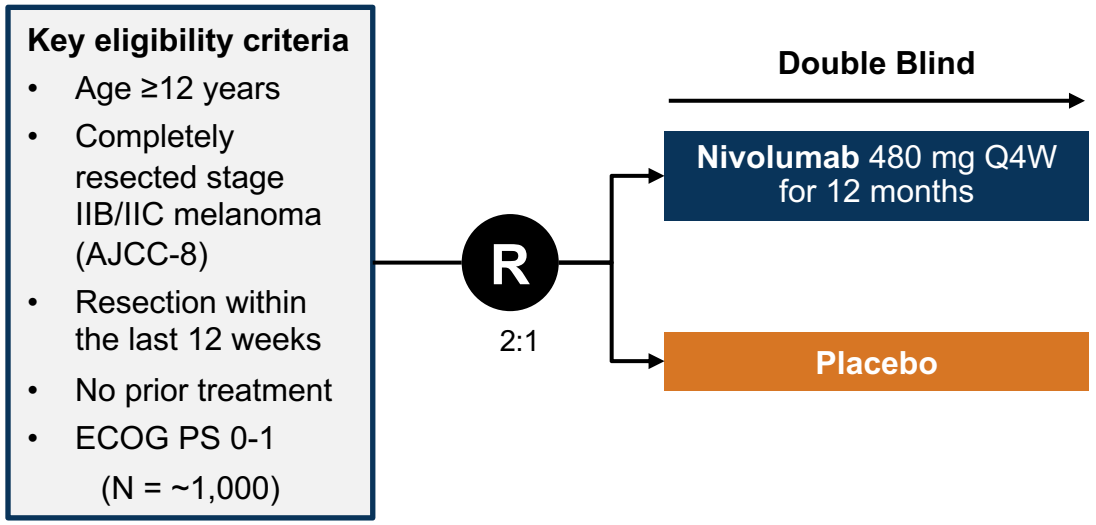
Ongoing Trials of Adjuvant Anti–PD-1 Antibodies for Stage IIB/C Melanoma

KEYNOTE-716[1]



- **Primary endpoint:** RFS
- **Key secondary endpoints:** DMFS, OS, and safety

CheckMate -76K[2,3]

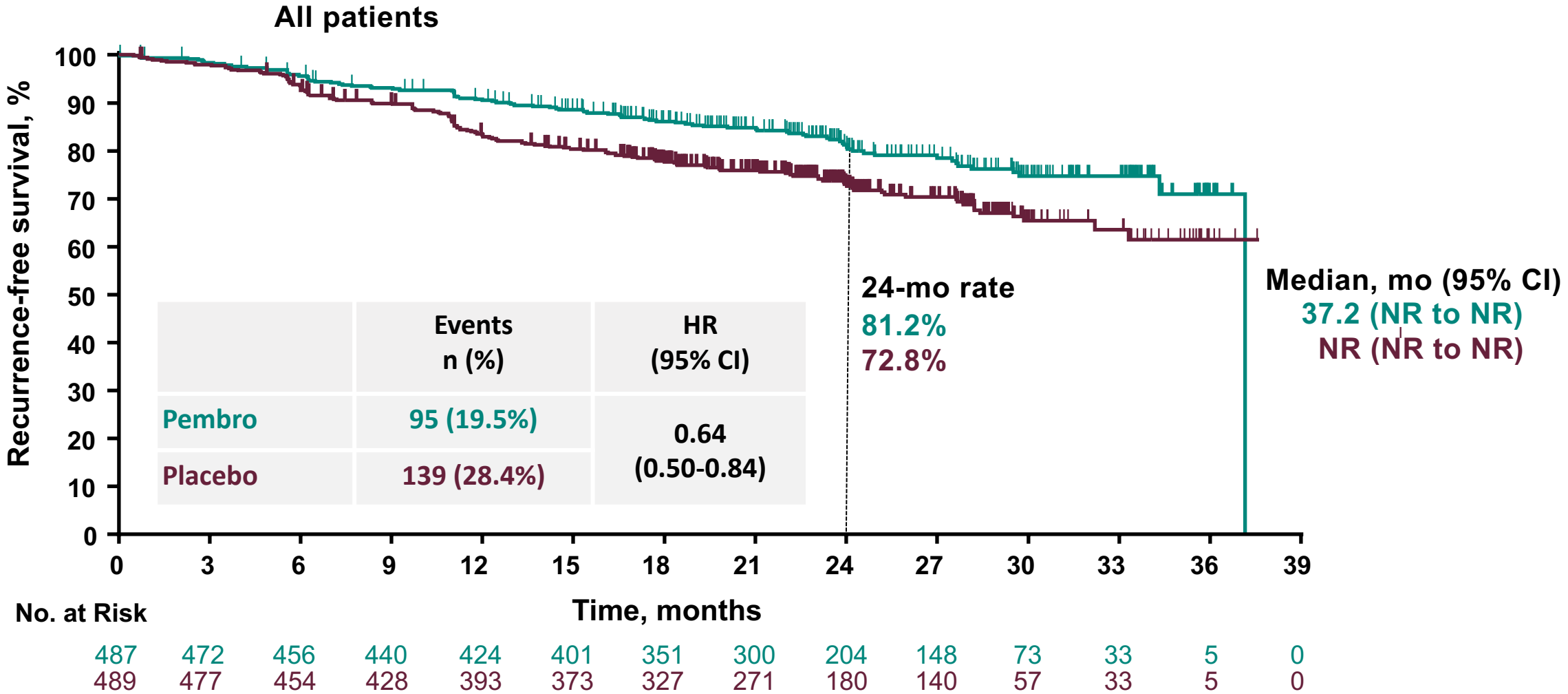


- **Primary endpoint:** RFS and safety biomarkers
- **Secondary endpoints:** OS, safety, DMFS, ORR, next-line outcomes (eg, PFS2), and biomarkers

[a] Adult dosage; eligible patients aged 12 to <18 years receive 2 mg/kg Q3W.

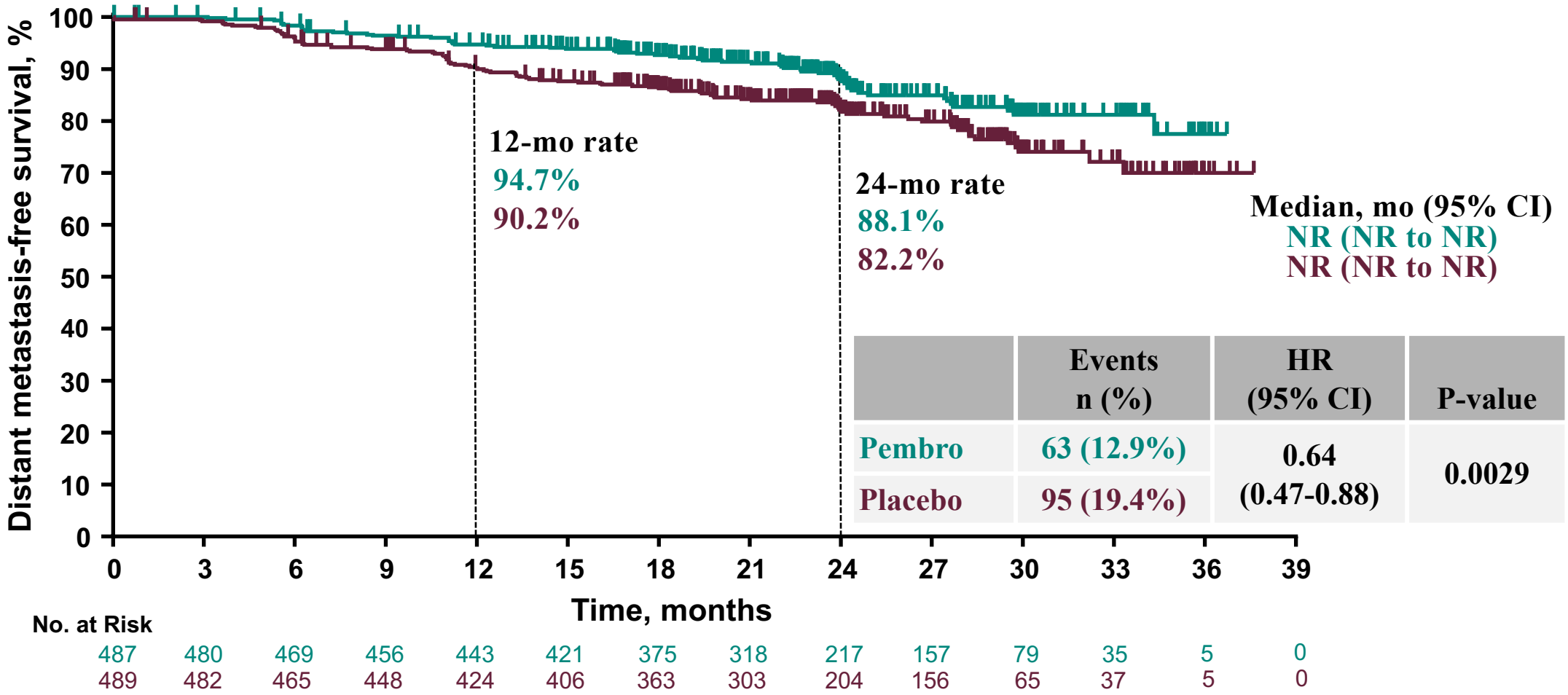
1. Carlino MS et al. 2019 American Society of Clinical Oncology Annual Meeting (ASCO 2019). Abstract TPS9596. 2. https://clinicaltrials.gov/ct2/show/NCT040992
https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001230-34/AT.

RFS With Longer Follow-up at IA3



HR for RFS with pembrolizumab versus placebo was 0.65 at IA1 and 0.61 at IA2; Median follow-up of 27.4 months (range, 14.0-39.4) at IA3; Data cut-off January 4, 2022.

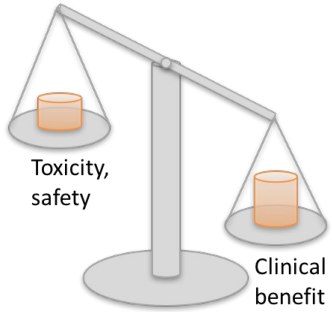
DMFS: Secondary Endpoint

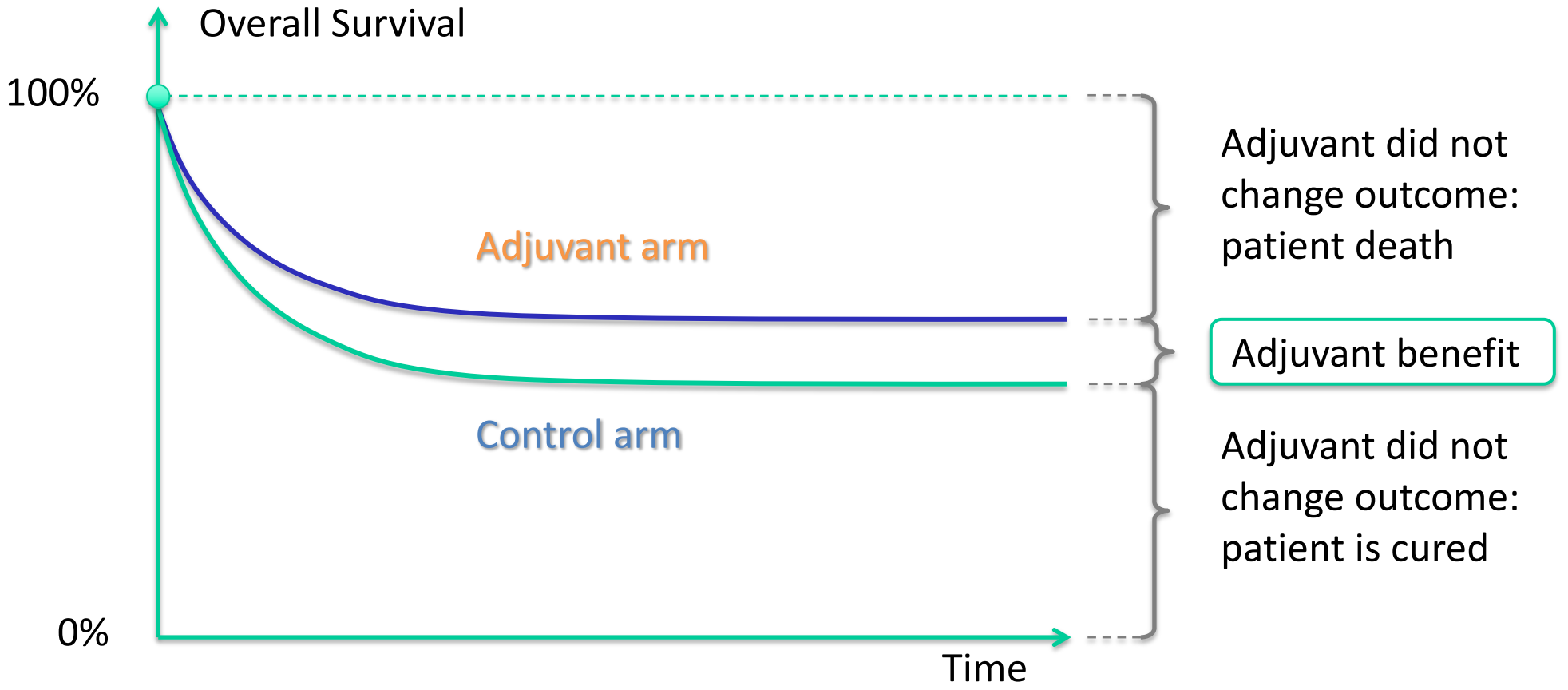


	Events n (%)	HR (95% CI)	P-value
Pembro	63 (12.9%)	0.64 (0.47-0.88)	0.0029
Placebo	95 (19.4%)		

Median follow-up of 27.4 months (range, 14.0-39.4); Data cut-off January 4, 2022.

Risk / benefit ratio: number needed to treat

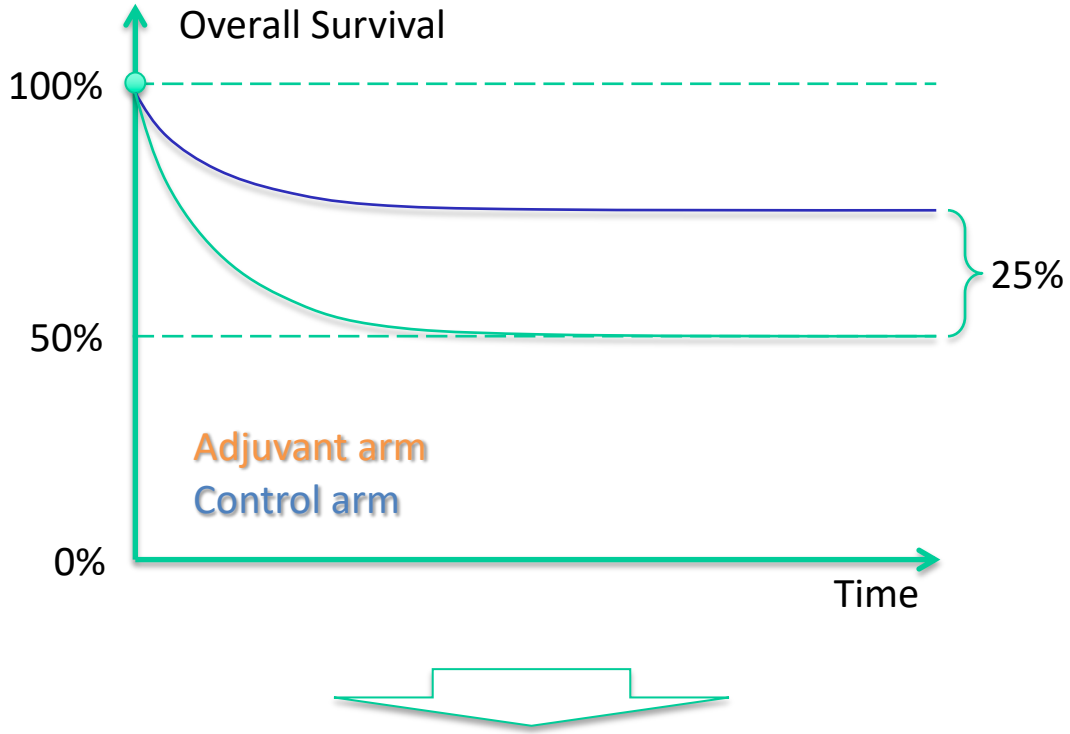




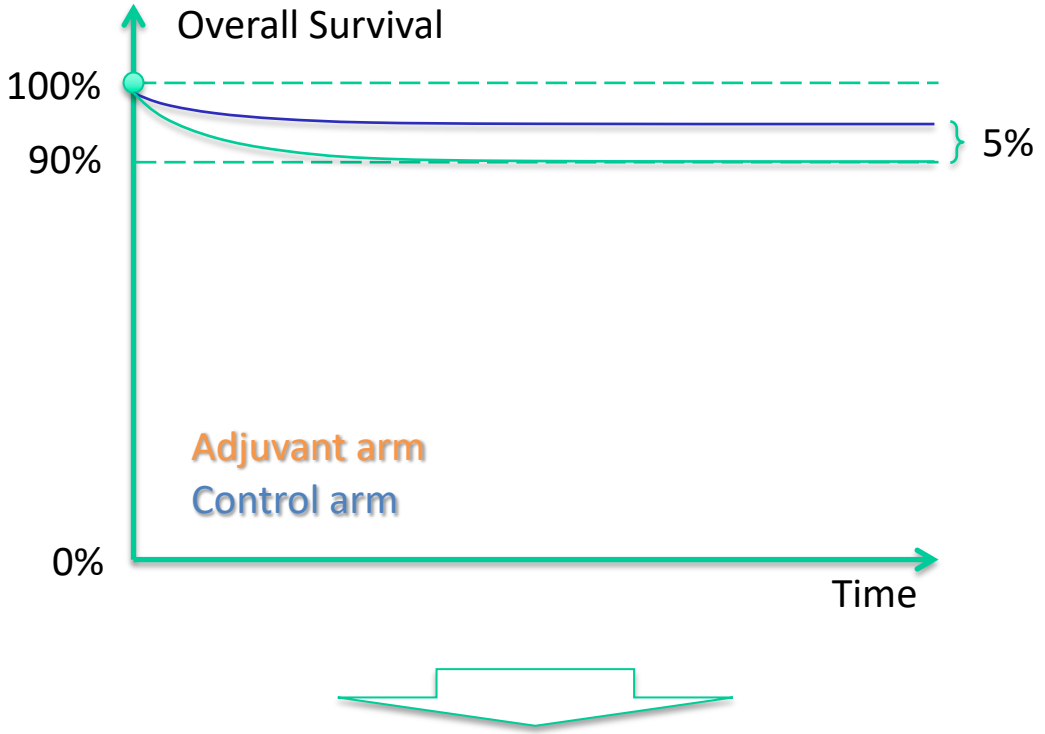
The number needed to treat (NNT) is defined as the number of patient, on average, that needs to be treated to prevent one bad outcome (progression, death, …)

Courtesy of Olivier Michielin

HR alone is not sufficient, absolute benefit also required to take a decision



HR 0.5
Absolute benefit: 25%
NNT[1]: 1/0.25 = 4



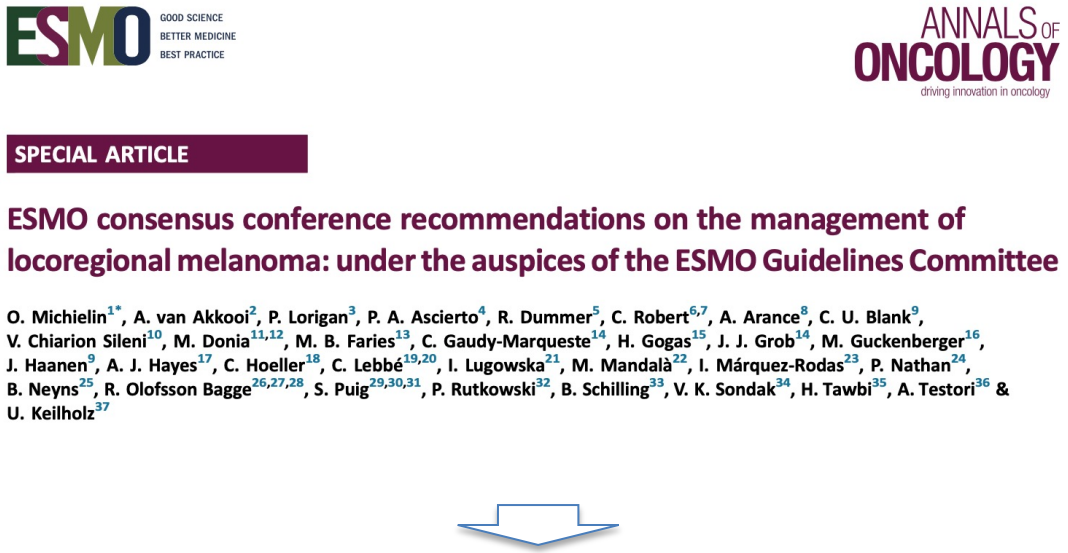
HR 0.5
Absolute benefit: 5%
NNT: 1/0.05 = 20

[1]NNT is computed as $1/(I_u-I_e)$, where I_e is the incidence of bad outcome in the exposed group and I_u that of the unexposed group

Courtesy of Olivier Michielin

Is there an absolute OS benefit to start discussing adjuvant?

- What is the absolute OS benefit needed to start discussing adjuvant with our patients?
- To answer this question, ESMO has organized a consensus conference, where experts were asked to vote on unresolved issues in the management of locoregional melanoma
- Recommendation 8.1 addresses the absolute benefit deemed necessary to start discussing adjuvant
- 5% was selected as the cutoff, level of consensus 100%:
  - **A 5% absolute gain correspond to an NNT of 20**
  - For a treatment with OS HR of 0.5, this translates to stages with a mortality of 10% or higher



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee

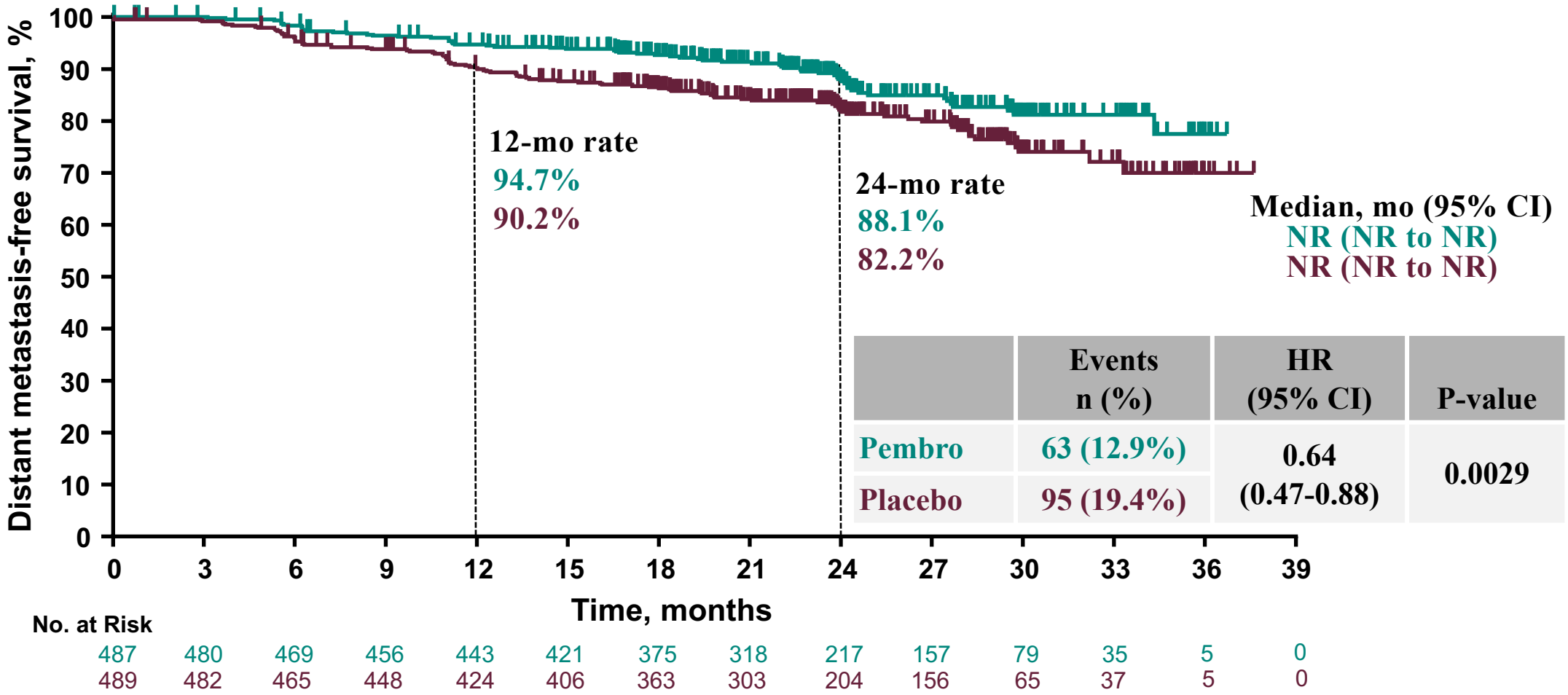
O. Michielin[1*], A. van Akkooi[2], P. Lorigan[3], P. A. Ascierto[4], R. Dummer[5], C. Robert[6,7], A. Arance[8], C. U. Blank[9], V. Chiarion Sileni[10], M. Donia[11,12], M. B. Faries[13], C. Gaudy-Marqueste[14], H. Gogas[15], J. J. Grob[14], M. Guckenberger[16], J. Haanen[9], A. J. Hayes[17], C. Hoeller[18], C. Lebbé[19,20], I. Lugowska[21], M. Mandalà[22], I. Márquez-Rodas[23], P. Nathan[24], B. Neyns[25], R. Olofsson Bagge[26,27,28], S. Puig[29,30,31], P. Rutkowski[32], B. Schilling[33], V. K. Sondak[34], H. Tawbi[35], A. Testori[36] & U. Keilholz[37]

Recommendation 8.1. An absolute survival benefit of 5% at 5 years would be considered strong evidence to recommend adjuvant therapy in stage III melanoma. However, surrogate markers of OS benefit are currently acceptable.
Level of evidence: I
Strength of recommendation: A
Level of consensus: 100% (30) yes (30 voters)

[1]Gershenwald, *CA Cancer J Clin* 2017

Courtesy of Olivier Michielin

DMFS: Secondary Endpoint



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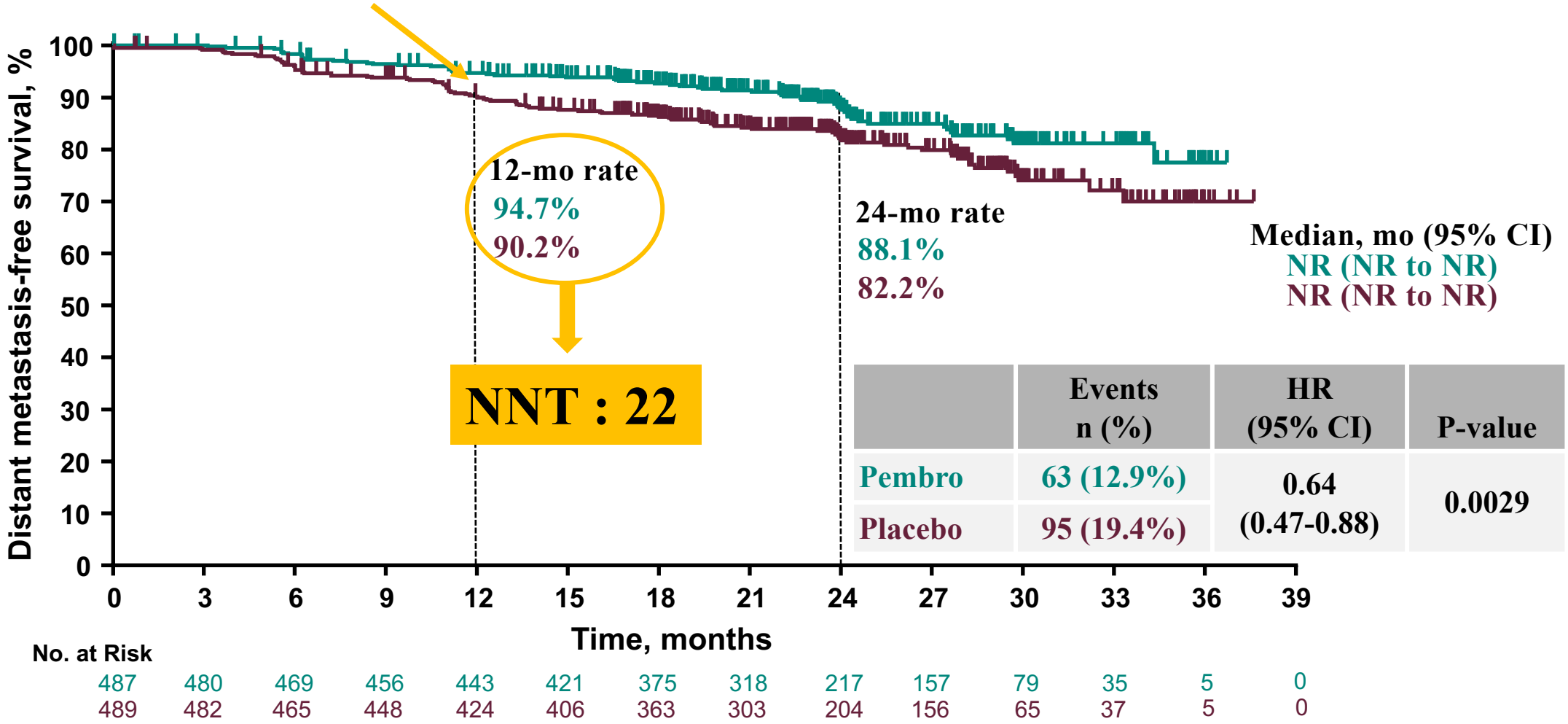
Median follow-up of 27.4 months (range, 14.0-39.4); Data cut-off January 4, 2022.

DMFS: Secondary Endpoint



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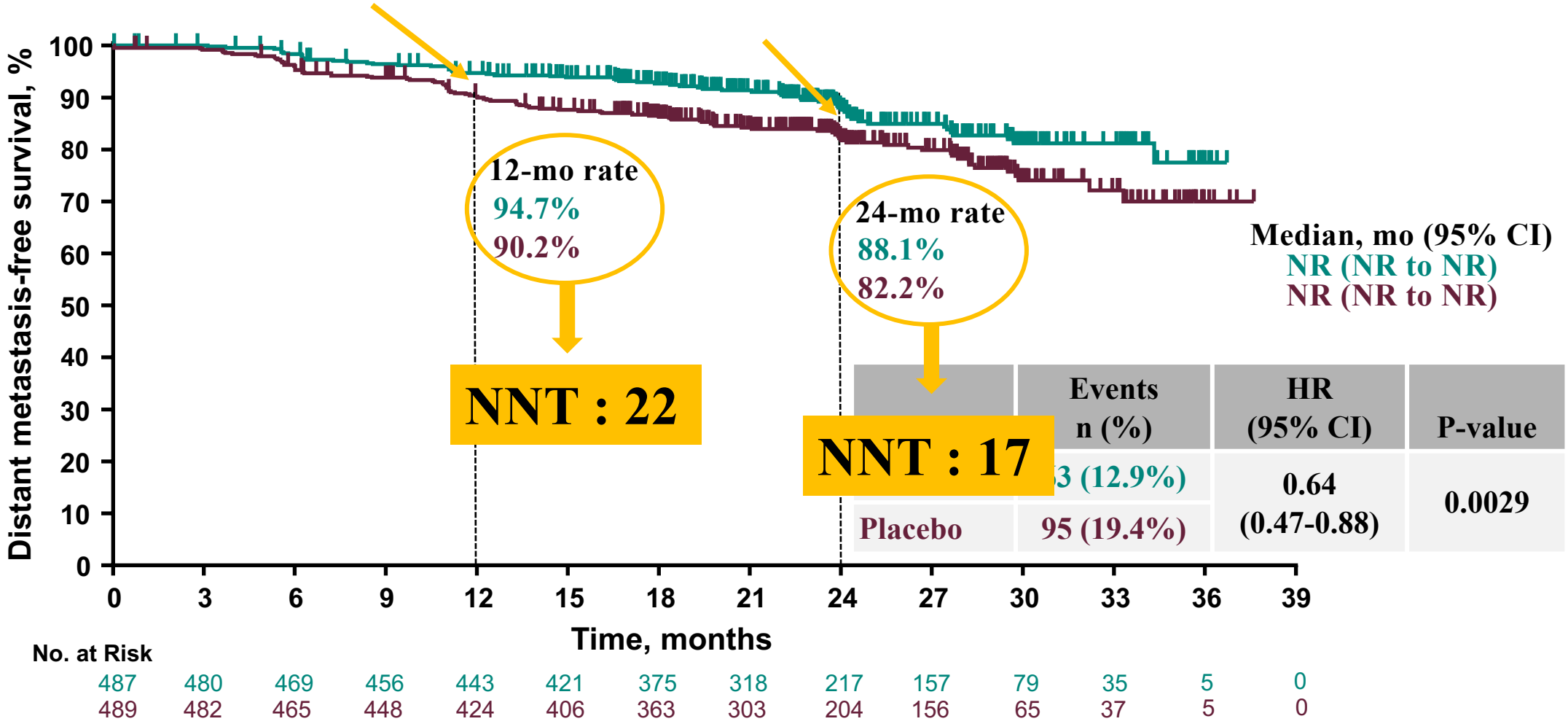
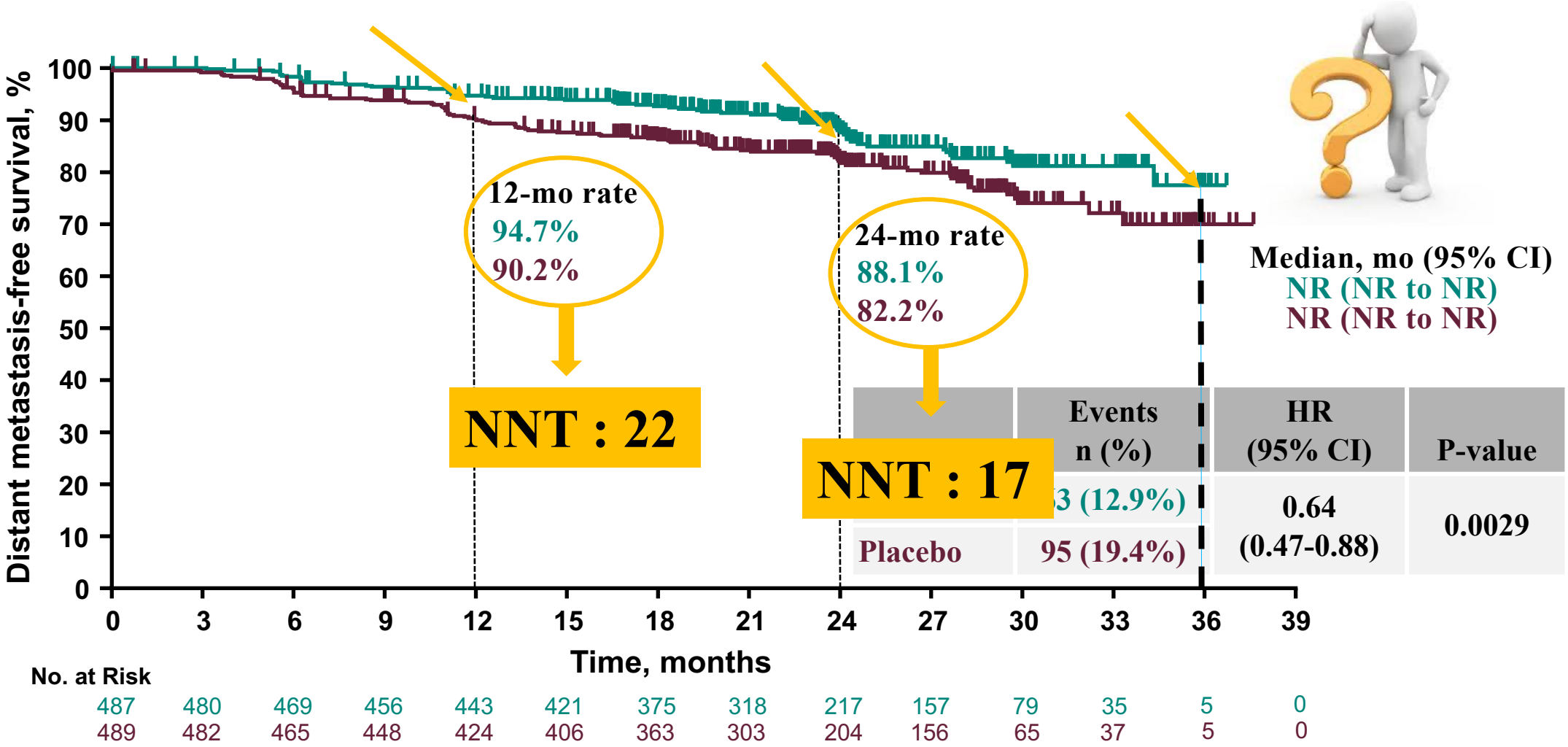
DMFS: Secondary Endpoint



	Events n (%)	HR (95% CI)	P-value
	3 (12.9%)	0.64 (0.47-0.88)	0.0029
Placebo	95 (19.4%)		

Median follow-up of 27.4 months (range, 14.0-39.4); Data cut-off January 4, 2022.

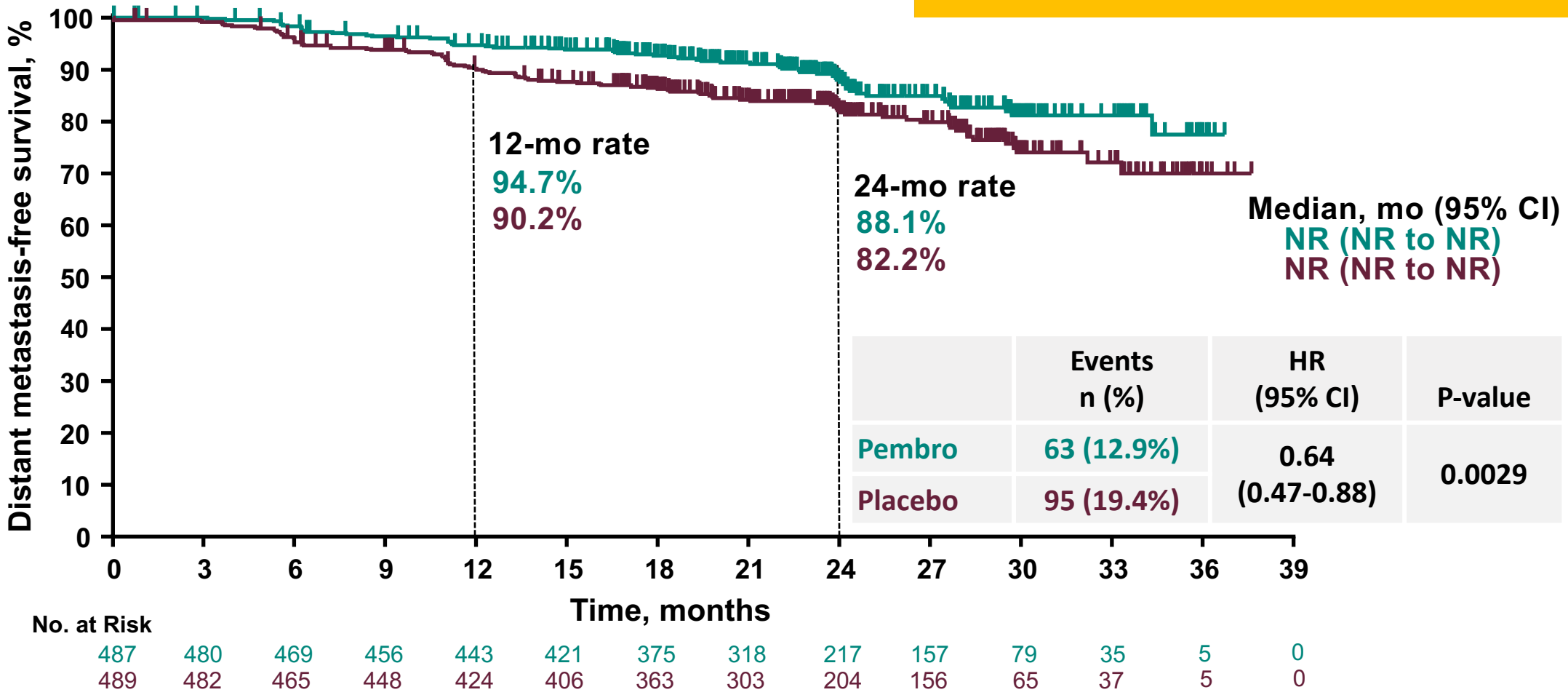
DMFS: Secondary Endpoint



Median follow-up of 27.4 months (range, 14.0-39.4); Data cut-off January 4, 2022.

DMFS: Secondary Endpoint

We need to find biomarkers to further refine the risk classification provided by the AJCC v8.



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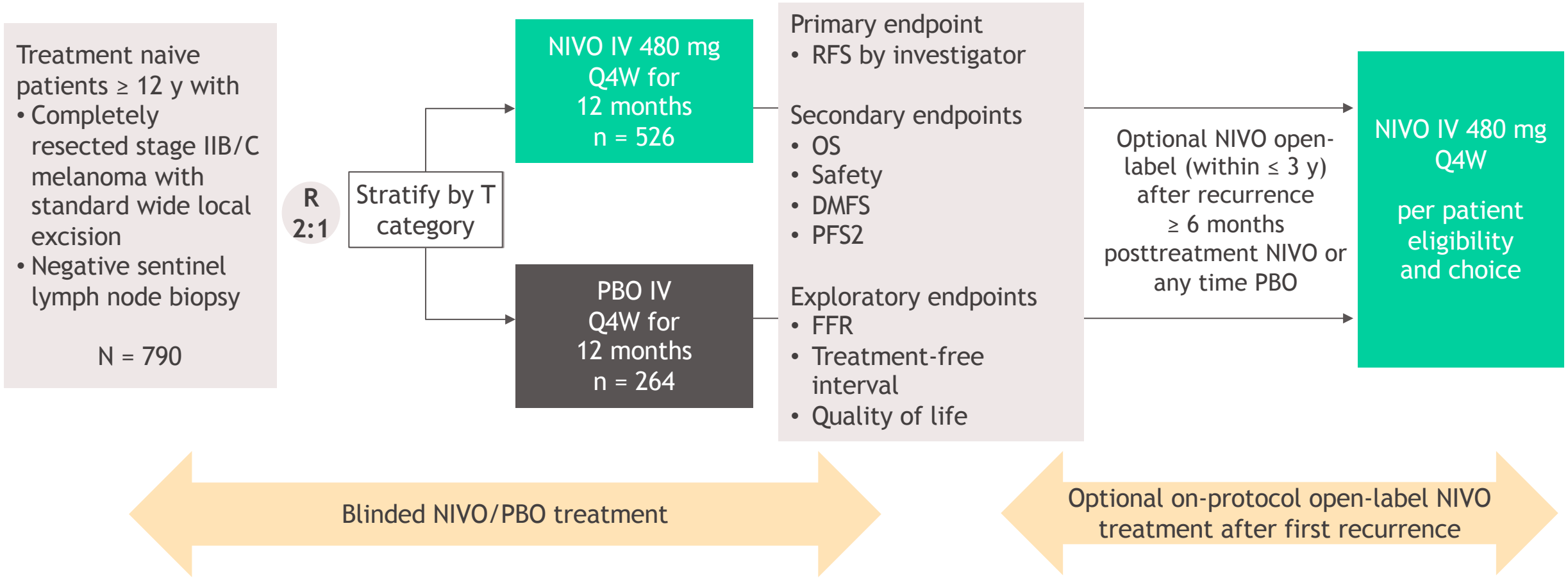
Placebo	95 (19.4%)		

PRESENTED BY:
Georgina V. Long, MD, PhD

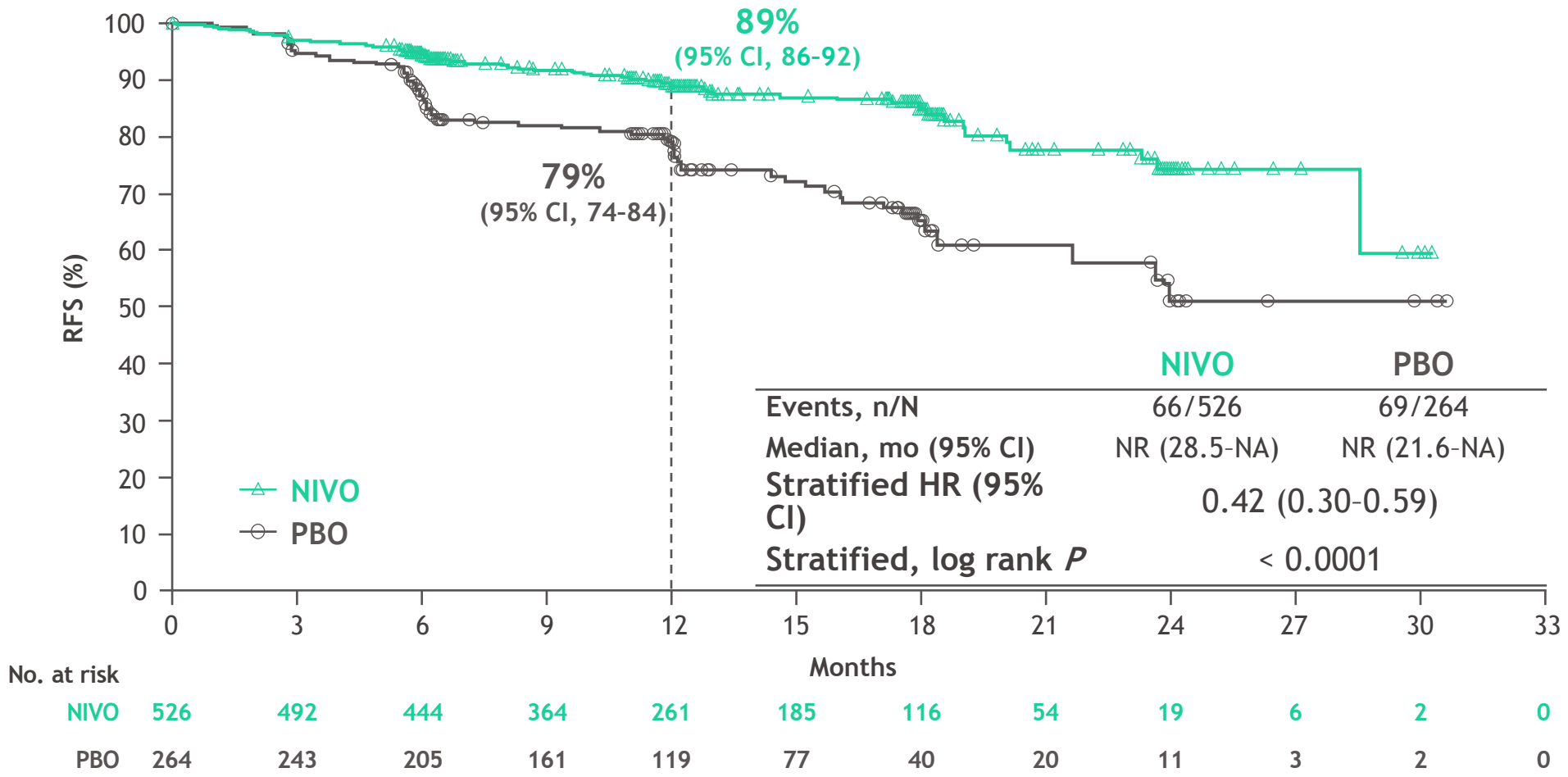
Median follow-up of 27.4 months (range, 14.0-39.4); Data cut-off January 4, 2022.

Study design



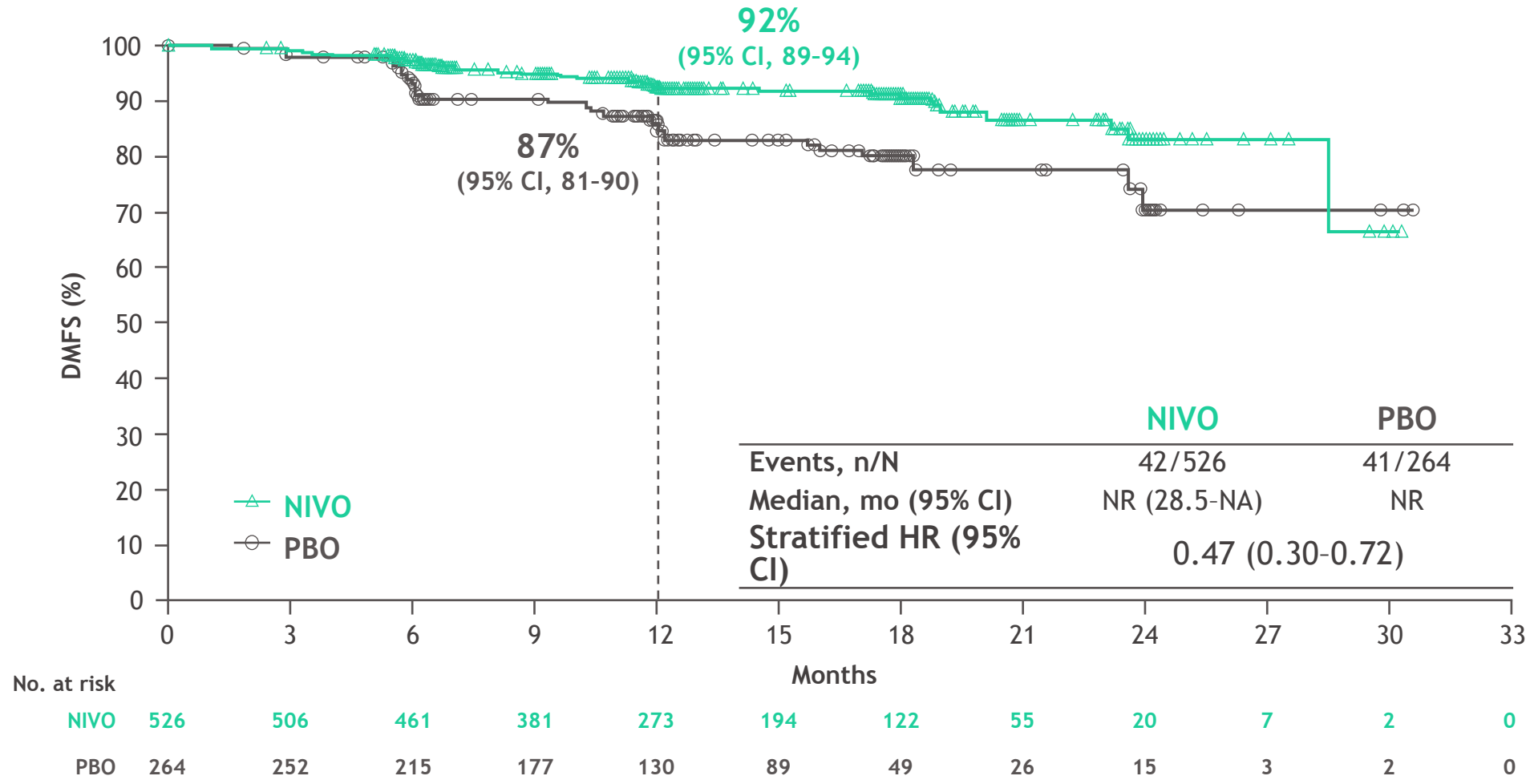
DMFS, distant metastasis-free survival; FFR, freedom from relapse (with censoring patients who died from causes other than disease); OS, overall survival; PFS2, progression-free survival through next-line therapy.

Primary endpoint: RFS



NA, not available; NR, not reached.

Secondary endpoint: DMFS



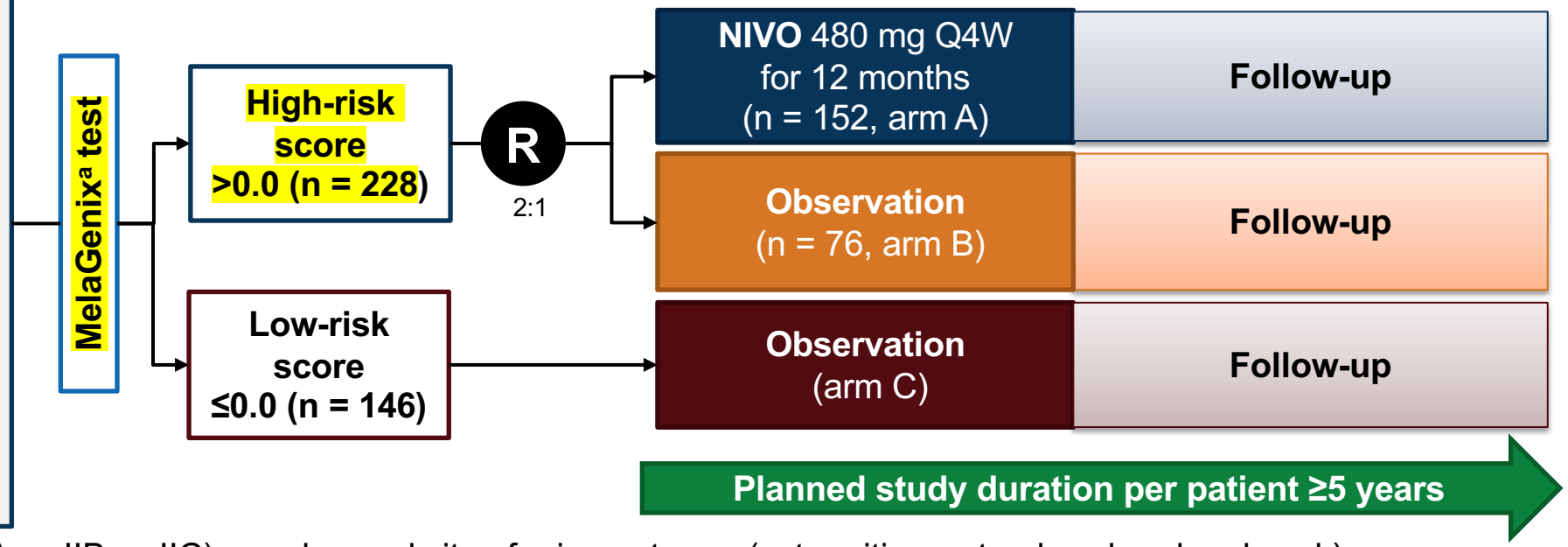
NivoMela: Adjuvant Treatment of High-Risk Stage II Melanoma[1]

- Adjuvant NIVO treatment in stage II high-risk melanoma: a randomized, controlled, phase 3 trial with biomarker-based risk stratification (investigator-initiated trial; sponsor: University Hospital Essen, Prof. Dr. Dirk Schadendorf; CA209-7DL)

Key eligibility criteria

- Aged ≥18 years
- Histologically confirmed, stage II (AJCC-8) cutaneous melanoma
- Negative SLNB
- Randomization ≤12 weeks after SLNB
- ECOG PS 0-1
- Adequate organ function
- Available tissue for MelaGenix test[2-4,a]

(N = ≈ 374)



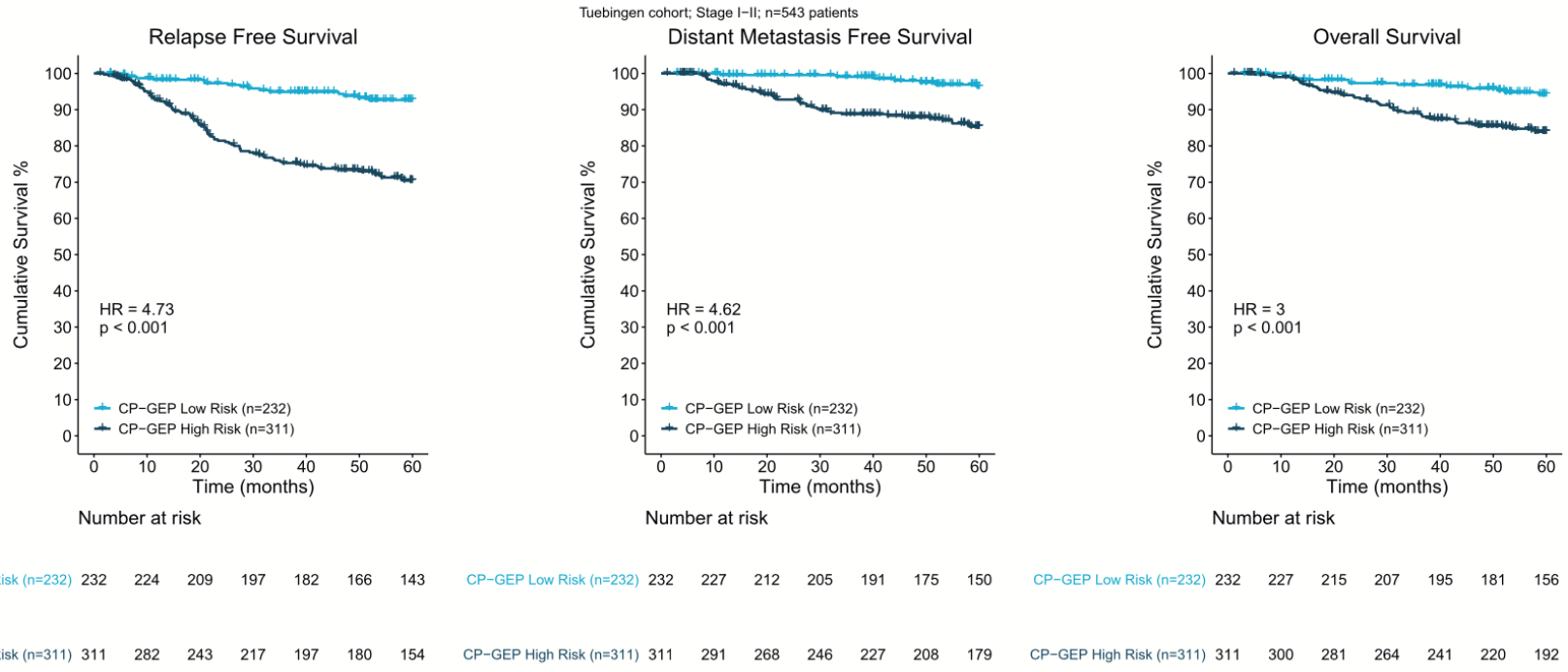
- **Stratification:** tumor stage (IIA vs IIB vs IIC), gender, and site of primary tumor (extremities vs trunk vs head and neck)
- **Primary endpoint:** RFS (at 36 and 60 months)
- **Secondary endpoints:** DMFS, MSS, and OS (at 36 and 60 months); safety; and clinical utility of the MelaGenix GEP score

[a] MelaGenix is an 11-gene prognostic signature.[2-4]

1. https://clinicaltrials.gov/ct2/show/NCT04309409. 2. Brunner G et al. *J Cancer Res Clin Oncol*. 2013;139:249-258. 3. Brunner G et al. 2018 American Society of C Oncology Annual Meeting (ASCO 2018). Abstract 9582. 4. Garbe C et al. ASCO 2019. Abstract 9518.

Identification of stage I/II melanoma patients at high risk for recurrence using a model combining clinicopathologic factors with gene expression profiling (CP-GEP)☆

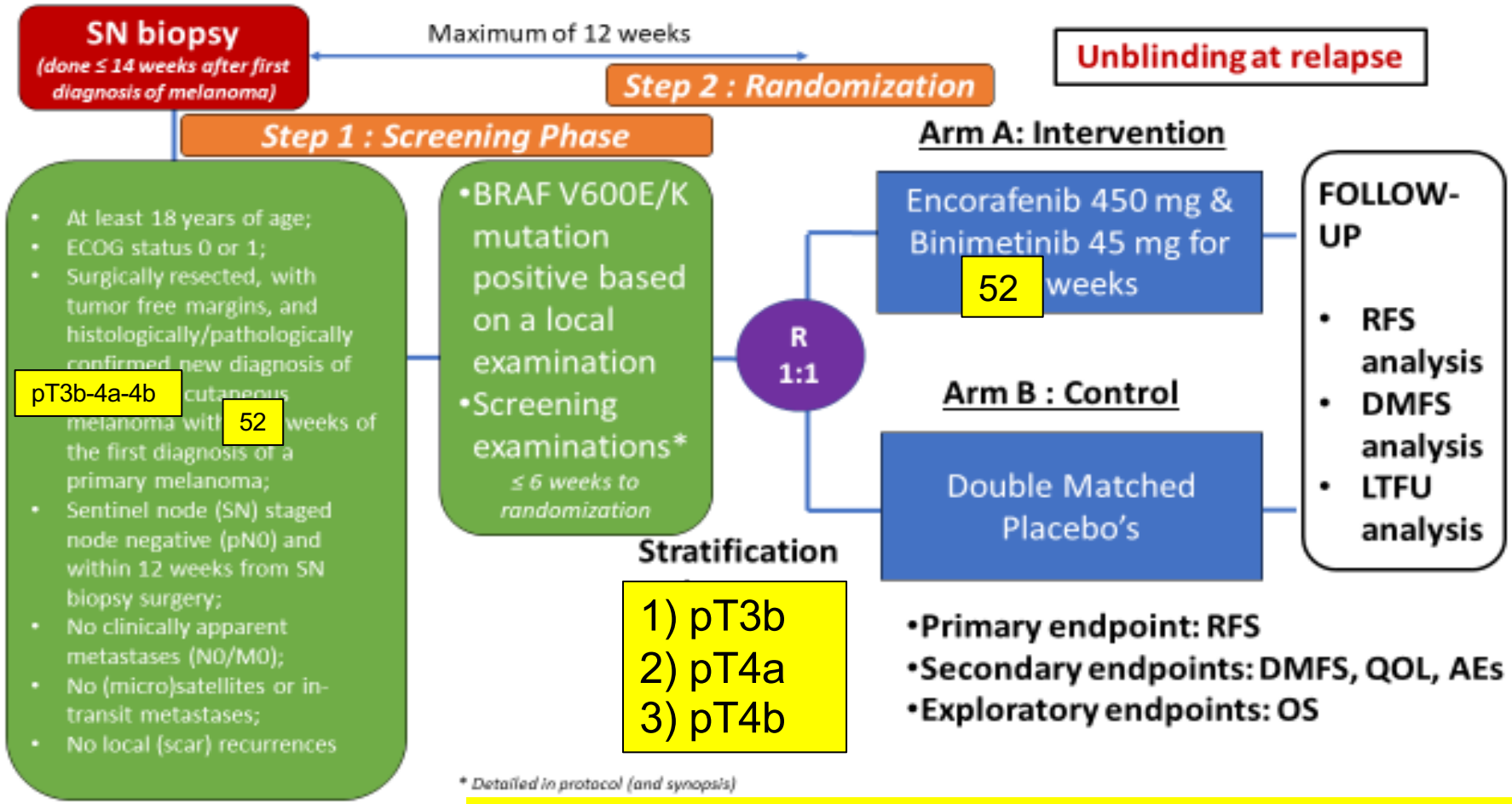
Teresa Amaral [a,b,*,1], Tobias Sinnberg [a,b,1], Eftychia Chatziioannou [a], Heike Niessner [a,b], Ulrike Leiter [a], Ulrike Keim [a], Andrea Forschner [a], Jvalini Dwarkasing [c], Félicia Tjien-Fooh [c], Renske Wever [c], Lukas Flatz [a], Alexander Eggermont [c,d,e,2], Stephan Forchhammer [a,2]



Analysis of the 543 stage I/II patients, stratification by CP-GEP classification.
Survival endpoints were relapse-free survival, distant metastasis-free survival and overall survival at five years of follow-up.

EORTC 2135 : Stage IIB/C

12 Months Adjuvant Encorafenib + Binimetinib vs Placebo



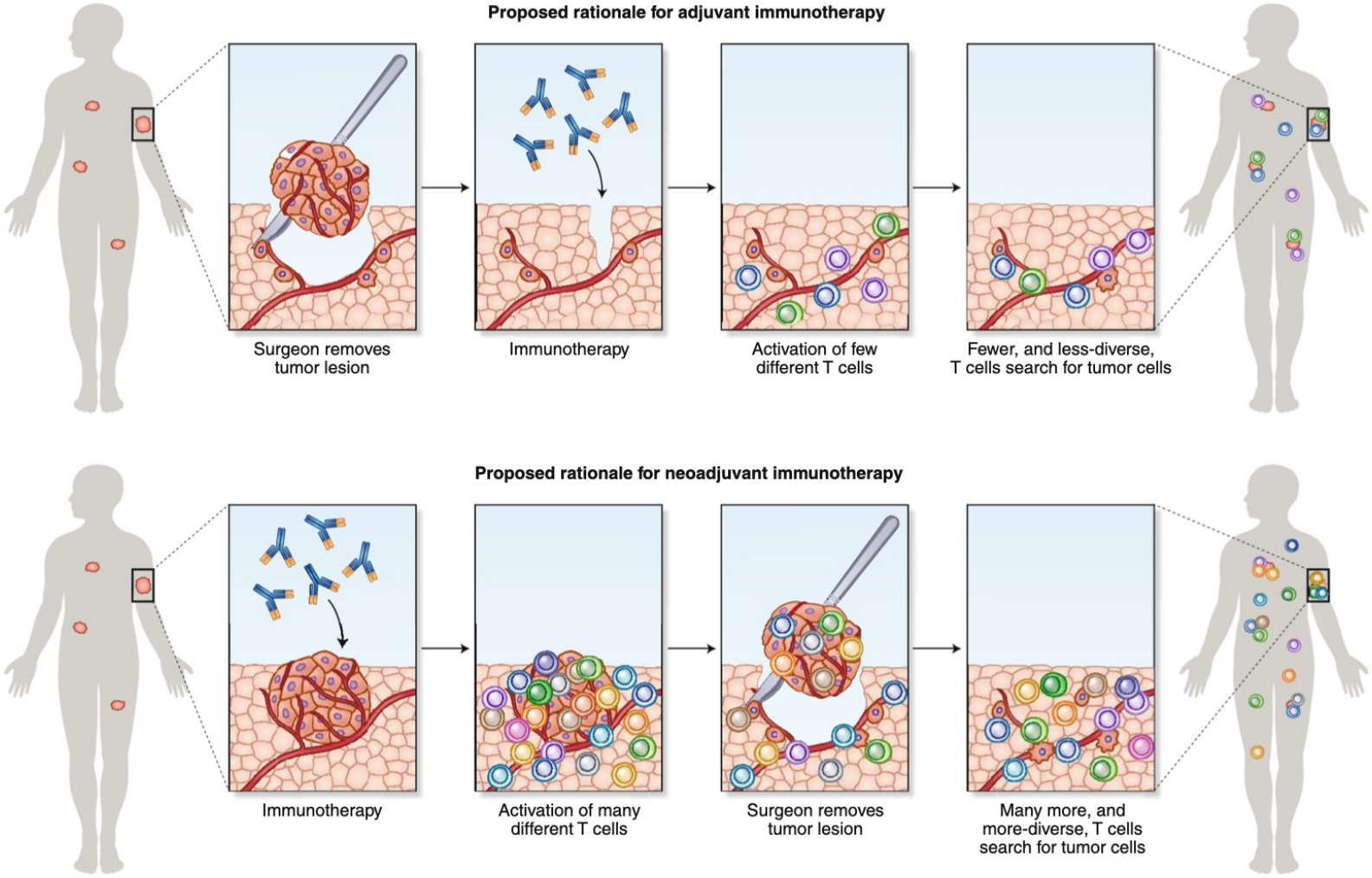
TR side project:
All Stages IIA-B/C: CP-GEP algorithm prospectively

Courtesy of Dr Eggermont

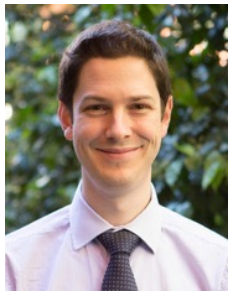
Melanoma landscape

Neo-Adjuvant

Neoadjuvant superior to adjuvant immunotherapy



Versluis, Long, and Blank, Nat Med 2020

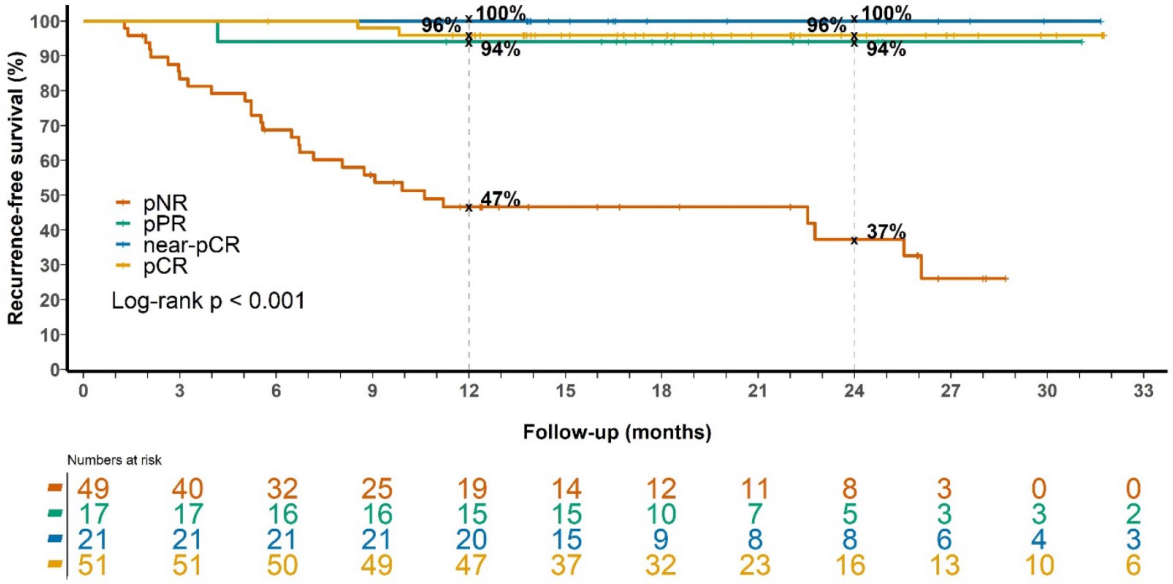


A. Menzies

INMC pooled analysis: Pathologic response better surrogate marker for immunotherapy than for targeted therapy

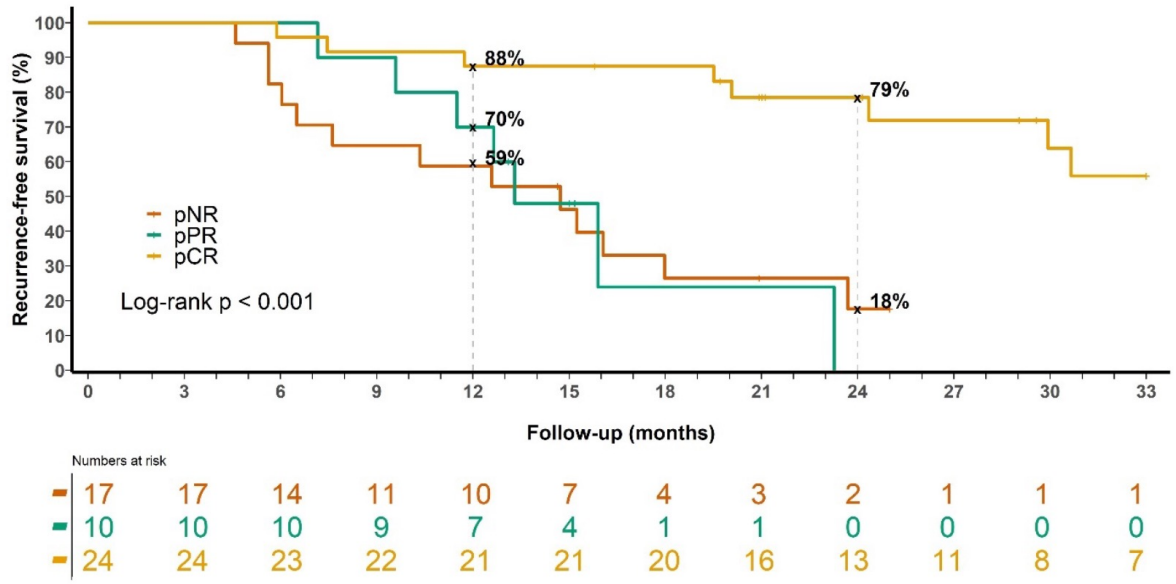
Immunotherapy

d) Immunotherapy cohort (all pathological response categories)



Targeted Therapy

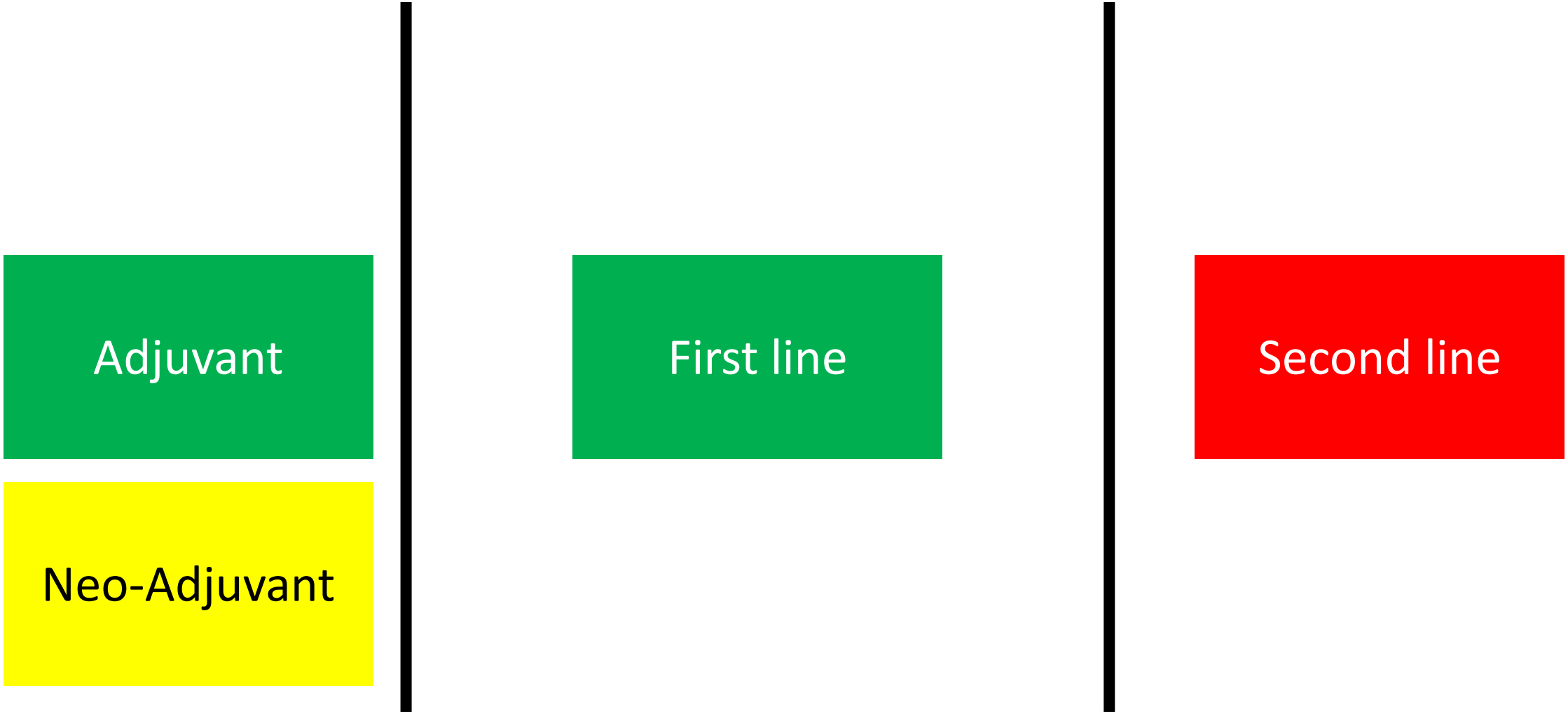
c) Targeted therapy cohort (all pathological response categories)



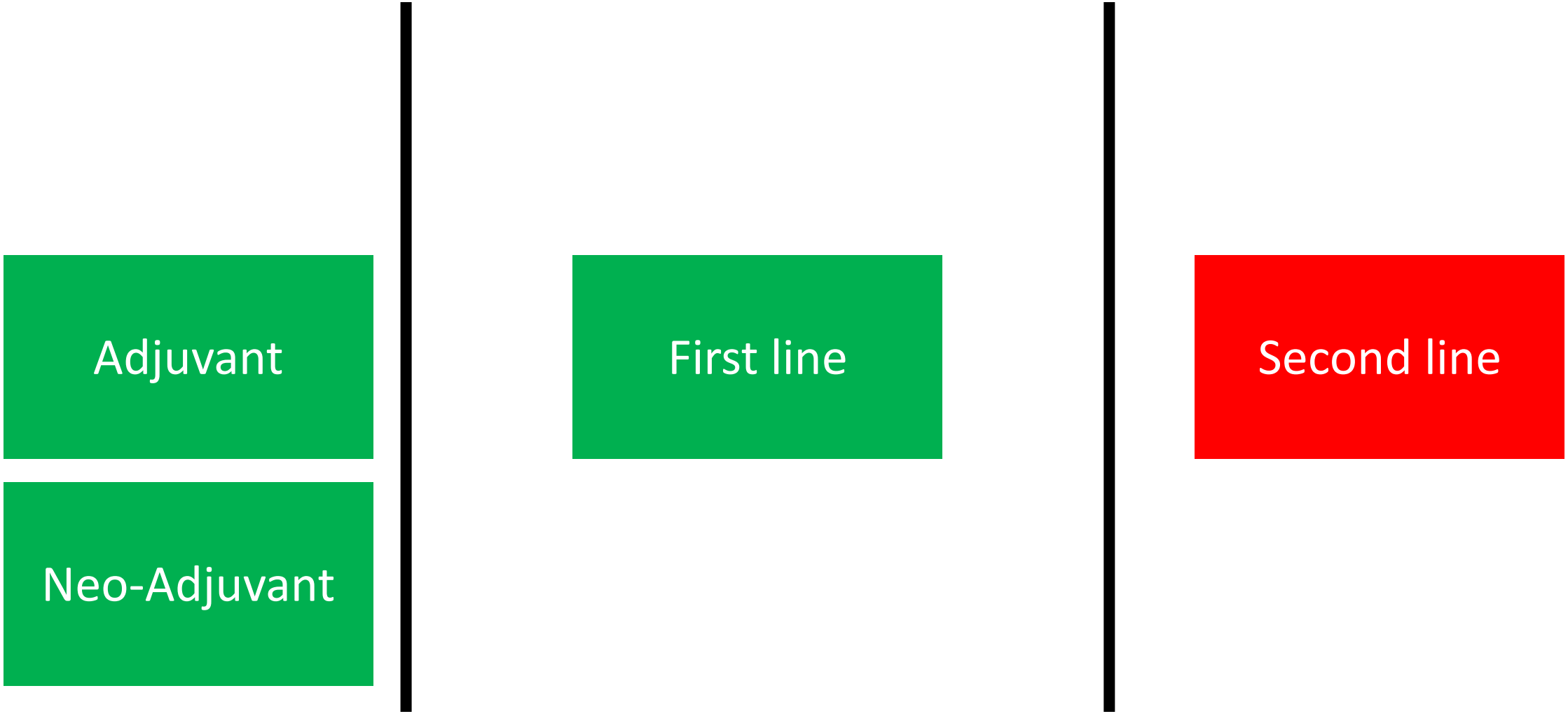
*No patient had a near-pCR

Menzies et al., Nat Med 2021

Melanoma landscape



Melanoma landscape



PARIS 2022 ESMO congress

Neoadjuvant versus adjuvant pembrolizumab for resectable stage III-IV melanoma (SWOG S1801)

Sapna P. Patel[1], Megan Othus[2,3], Victor G. Prieto[1], Michael C. Lowe[4], Elizabeth I. Buchbinder[5], Yuanbin Chen[6], John Hyngstrom[7], Christopher Lao[8], Thach-Giao Truong[9], Sunandana Chandra[10], Kari Kendra[11], Craig Devoe[12], Aparna Hegde[13], Ankit Mangla[14], Elad Sharon[15], Larissa Korde[15], James Moon[2,3], Vernon K. Sondak[16], Antoni Ribas[17]

1- University of Texas MD Anderson Cancer Center, Houston, TX; 2-SWOG Statistics and Data Management Center, Seattle, WA; 3-Fred Hutchinson Cancer Research Center, Seattle, WA; 4-Emory University, Atlanta, GA; 5-Dana-Farber Cancer Institute/Harvard Cancer Center, Boston, MA; 6-Cancer and Hematology Centers of Western Michigan/ CRC West MI NCORP, Grand Rapids, MI; 7-University of Utah Huntsman Cancer Institute, Salt Lake City, UT; 8-University of Michigan, Ann Arbor, MI; 9-Kaiser Permanente NCAL, Vallejo, CA; 10-Northwestern University, Chicago, IL; 11-Ohio State University Wexner Medical Center, Columbus, OH; 12-Northwell Health Cancer Institute, Lake Success, NY; 13-University of Alabama, Birmingham, AL; 14-University Hospitals Seidman Cancer Center, Cleveland, OH; 15-National Cancer Institute Cancer Therapy Evaluation Program, Bethesda, MD; 16-Moffitt Cancer Center, Tampa, FL; 17-UCLA/Jonsson Comprehensive Cancer Center, Los Angeles, CA

11 September 2022

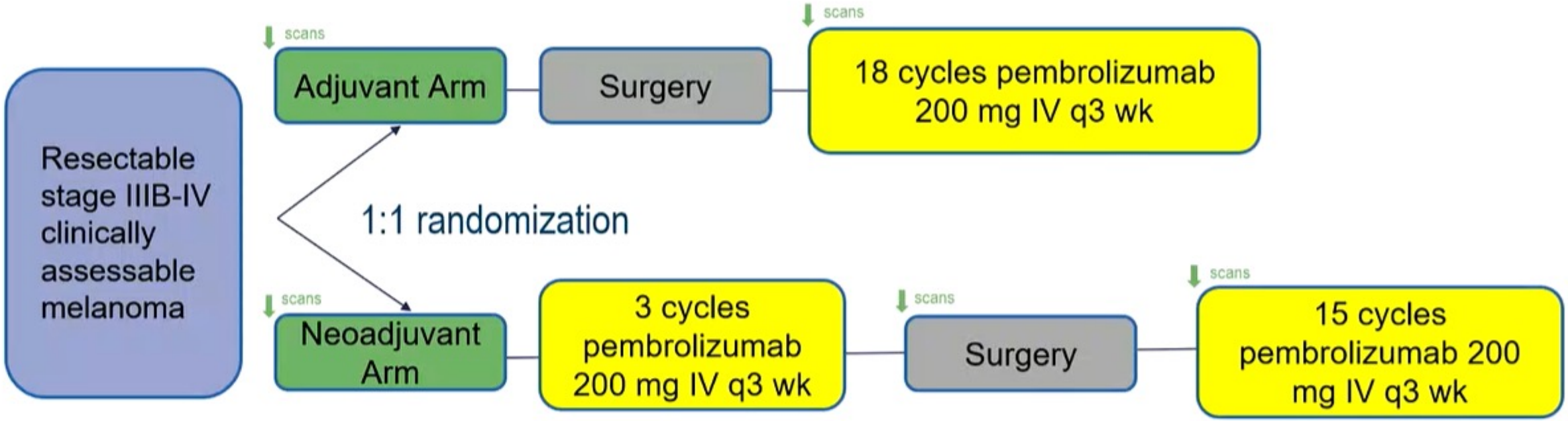
SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network
a National Cancer Institute program

NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

S1801 Study Schema

Primary endpoint: Event-free survival

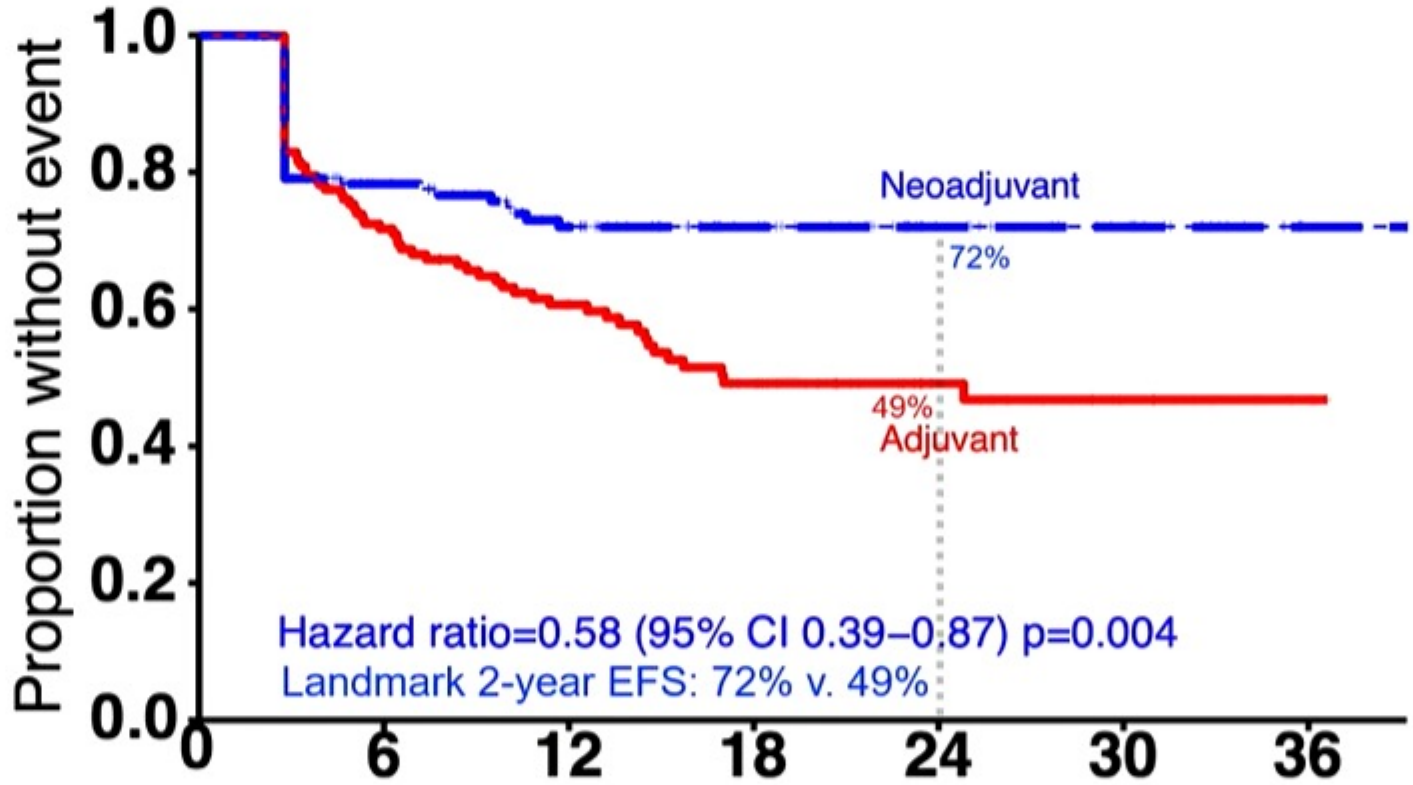


⬇ radiographic assessment (scans)

Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded

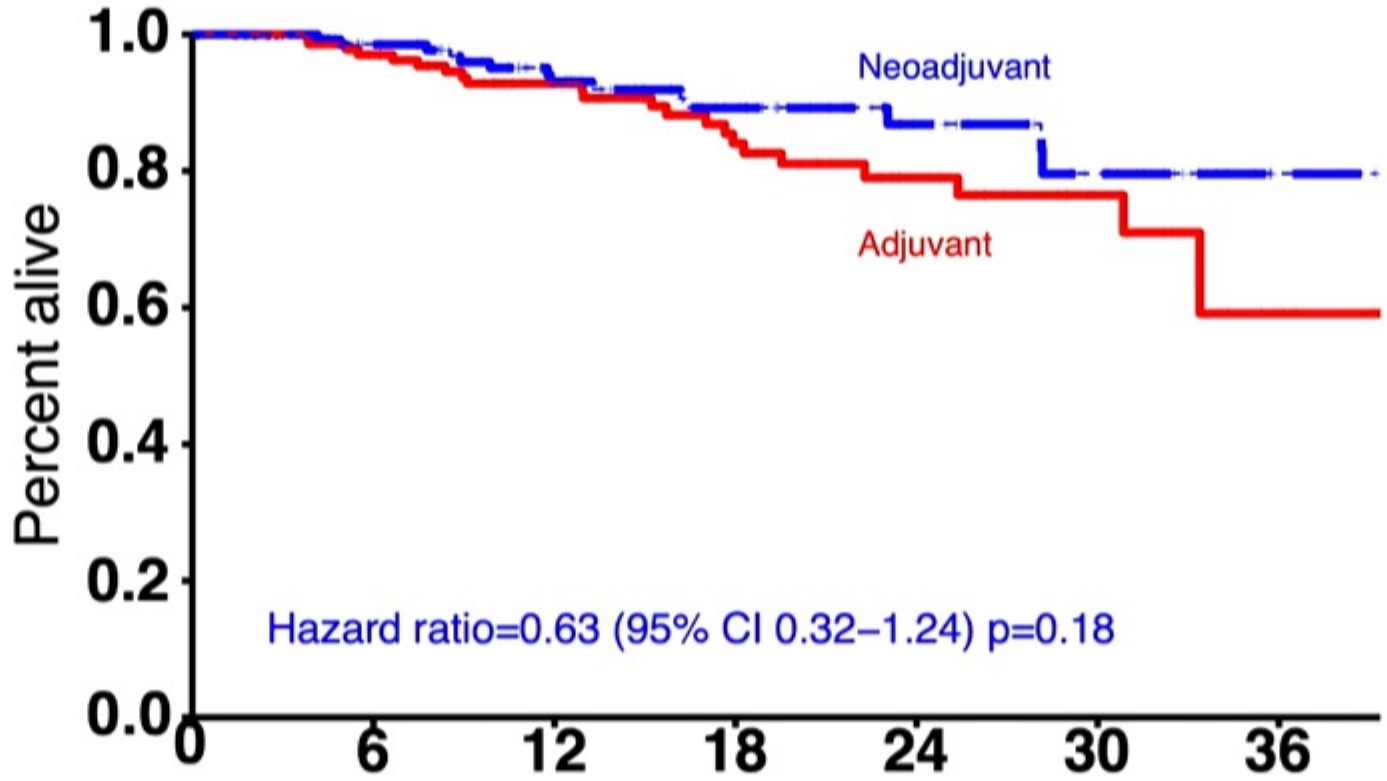
Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy

S1801 primary endpoint: Event-free survival



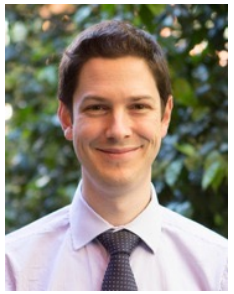
No. at Risk							
159	98	67	40	22	10	2	Adjuvant
154	96	69	46	25	17	1	Neoadjuvant

Overall survival



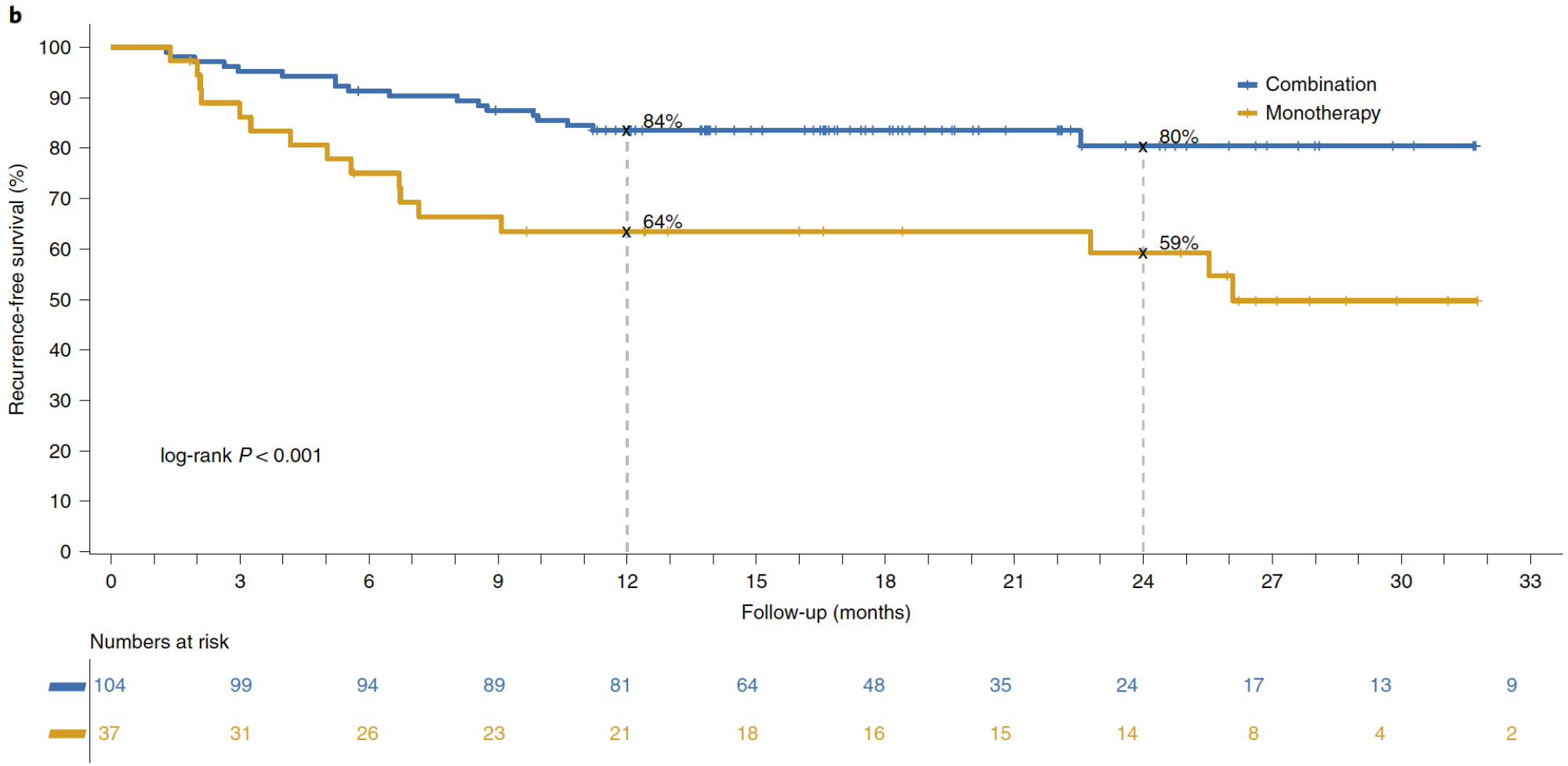
No. at Risk

159	124	93	60	33	15	3	Adjuvant
154	124	90	59	30	19	1	Neoadjuvant

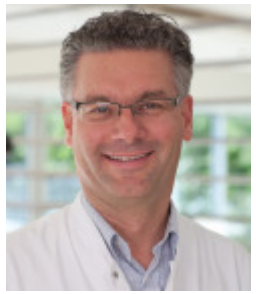


A. Menzies

INMC pooled analysis of neoadjuvant immunotherapy and targeted therapy



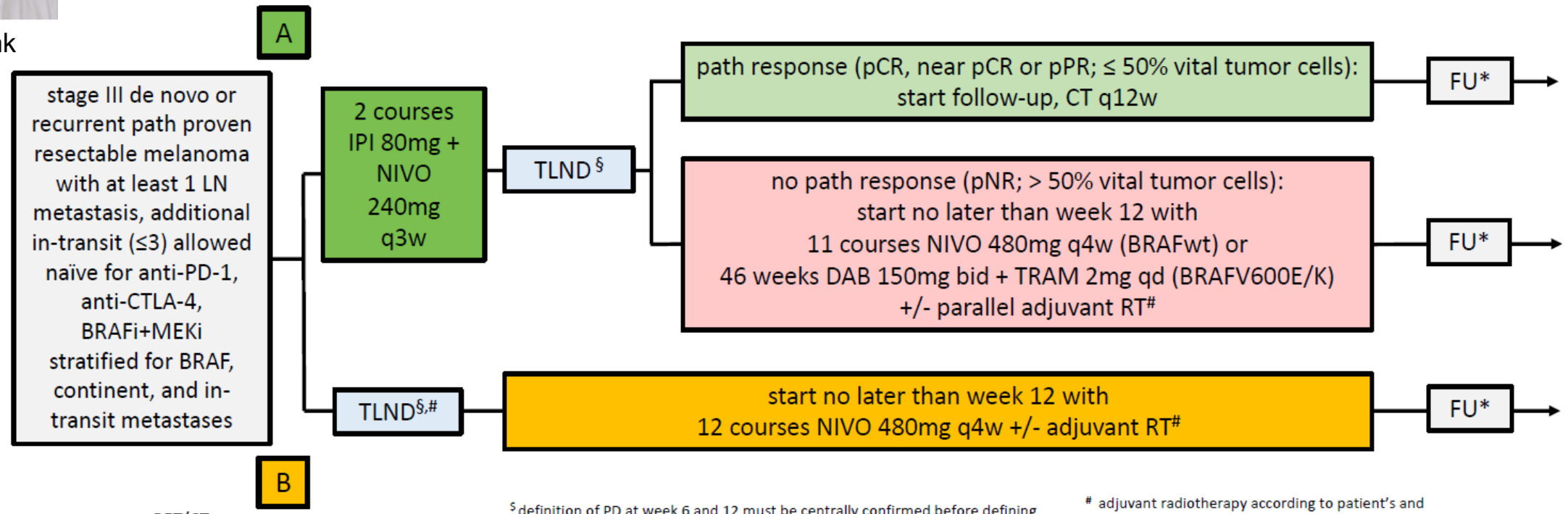
Menzies et al., Nat Med 2021



C.Blank

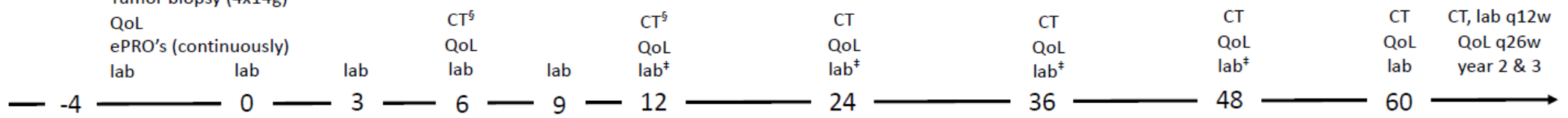
Phase 3 trial comparing response driven neo-adjuvant combination of ipilimumab + nivolumab versus adjuvant nivolumab (NADINA 2021)

(420 pts, EFS at 24 months 60%->75%, alpha two-sided 0.05, power 90%, cure model statistics)



§ definition of PD at week 6 and 12 must be centrally confirmed before defining this as a event and omitting TLND or adjuvant therapy

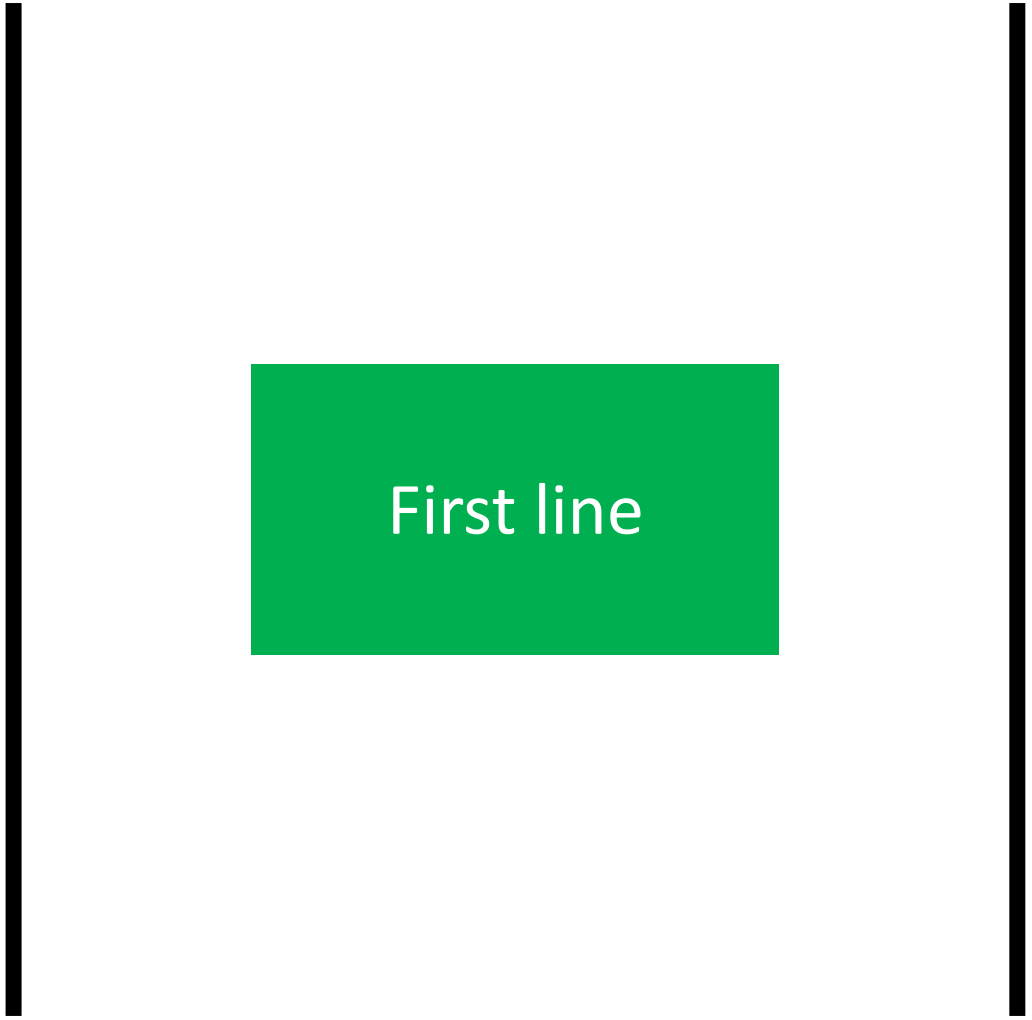
\# adjuvant radiotherapy according to patient's and physician's decision allowed
* Beyond year 3 according to institutes/country standards
‡ during adjuvant therapy four-weekly lab



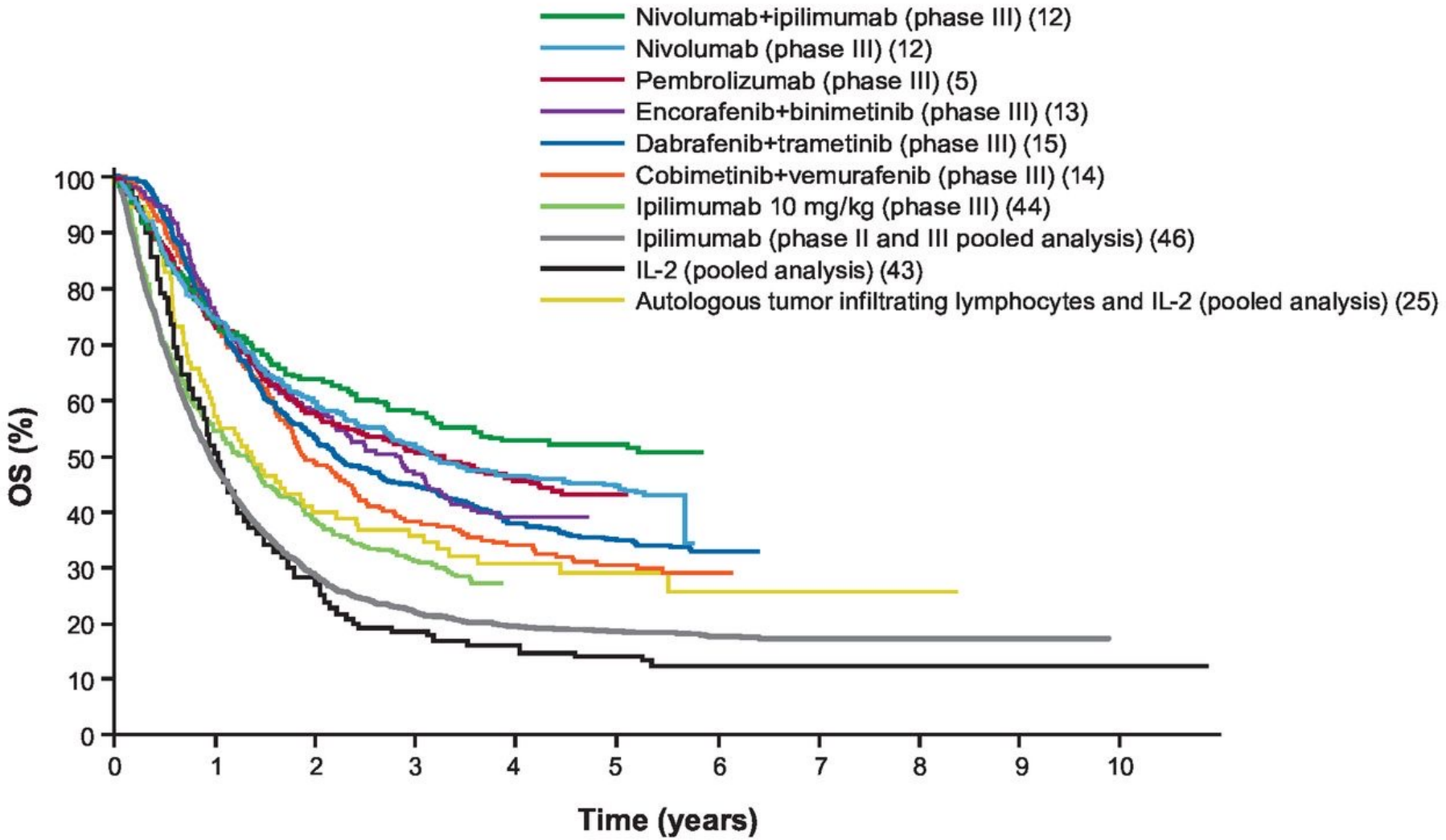
Courtesy of Christian Blank

2021 ESMO congress

Melanoma landscape



Long-term OS in clinical trials with immuno-oncology agents and targeted therapies in patients with advanced melanoma.



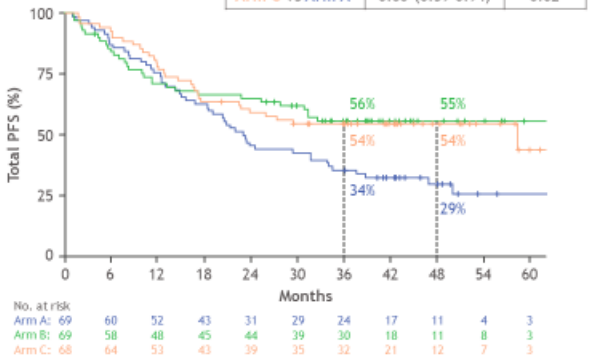
Olivier Michielin et al. J Immunother Cancer 2020;8:e000948

Journal for ImmunoTherapy of Cancer

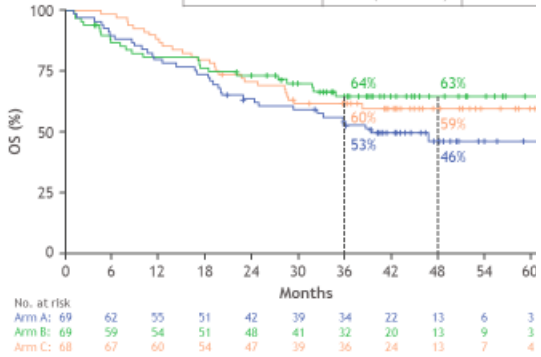
The best sequencing …

SECOMBIT: 4-year survival

Total PFS	HR (95% CI)[a]	*P* value
Arm B vs Arm A	0.58 (0.37-0.91)	0.01
Arm C vs Arm A	0.60 (0.39-0.94)	0.02



OS	HR (95% CI)[a]	*P* value
Arm B vs Arm A	0.66 (0.39-1.12)	0.13
Arm C vs Arm A	0.73 (0.44-1.21)	0.22

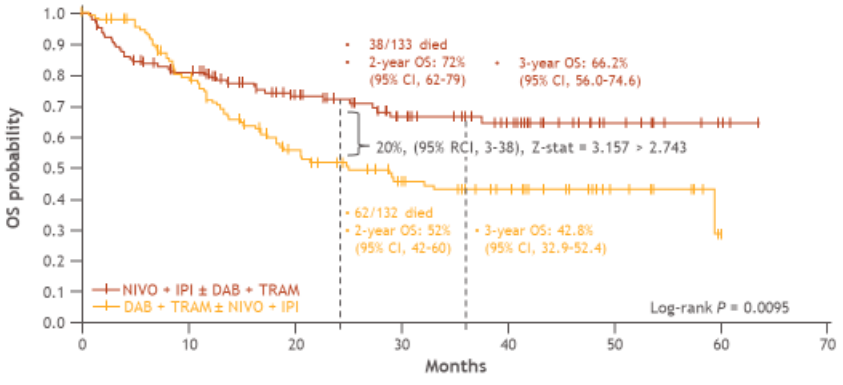


Adapted from Asclerto PA

This material may include information about investigational products and / or uses that are not approved for use in any country or in the country of your residence. Therefore, before prescribing any product, always refer to local materials such as the prescribing information and / or the Summary of Product Characteristics (SPC). Not all discussed therapies are approved for clinical use. Bristol Myers Squibb only recommends usage of approved products. Please check the product information of your country, approvals may vary. Refer to each country's local guidance for specific therapeutic strategies. Median follow-up was 43 months (estimated with the reverse Kaplan-Meier method). [a]Exploratory analysis. OS, overall survival; PFS, progression-free survival.

Asclerto PA et al. Presentation at the ESMO Congress; September 9-13, 2022; Paris, France. Abstract LBA41.

DREAMseq: overall survival (step 1 ± step 2)



No. at risk	Time interval										
	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66
NIVO + IPI ± DAB + TRAM	133	99	87	71	55	42	33	23	15	6	3
DAB + TRAM ± NIVO + IPI	132	115	78	60	47	35	30	18	15	6	1

Adapted from Atkins MB.

This material may include information about investigational products and / or uses that are not approved for use in any country or in the country of your residence. Therefore, before prescribing any product, always refer to local materials such as the prescribing information and / or the Summary of Product Characteristics (SPC). Not all discussed therapies are approved for clinical use. Bristol Myers Squibb only recommends usage of approved products. Please check the product information of your country, approvals may vary. Refer to each country's local guidance for specific therapeutic strategies.

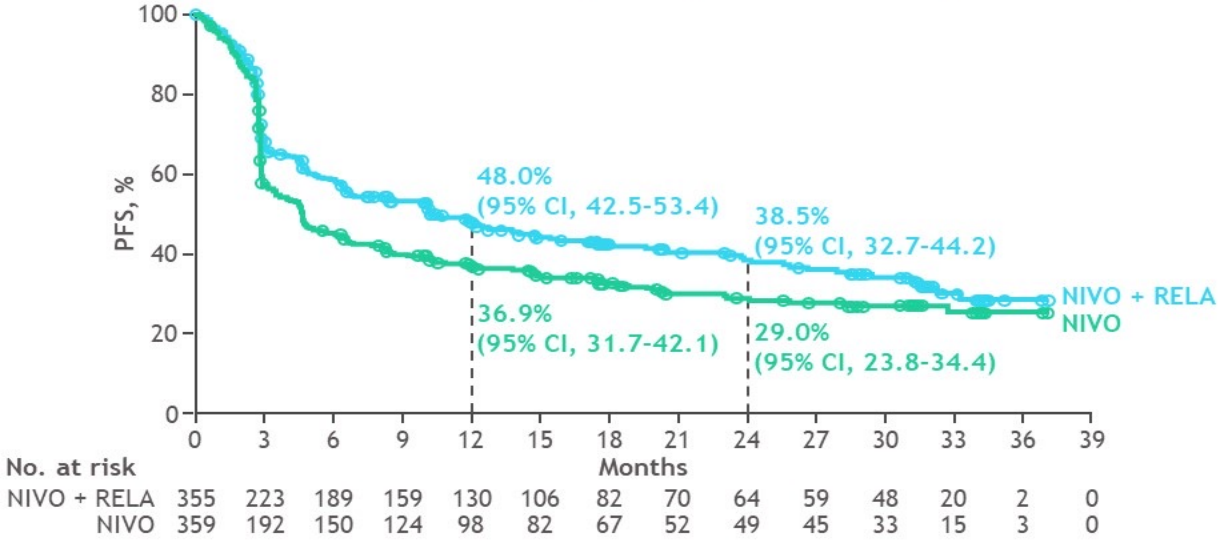
DAB, dabrafenib; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; TRAM, trametinib.

Atkins MB. Presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL. Updates on abstract 356154.

PFS, OS, and ORR in all randomized patients

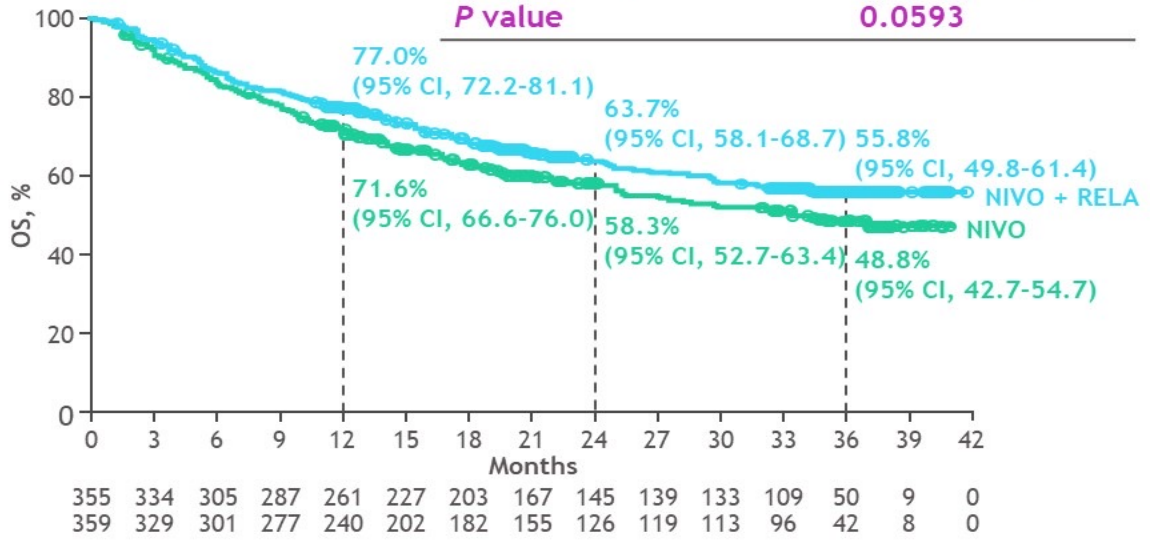
Updated PFS by BICR

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo (95% CI)	10.22 (6.51-14.75)	4.63 (3.48-6.44)
HR (95% CI)	0.78 (0.64-0.94)	



OS

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo (95% CI)	NR (34.20-NR)	34.10 (25.23-NR)
HR (95% CI)	0.80 (0.64-1.01)	
P value	0.0593	



Confirmed ORR by BICR	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR % (95% CI)	**43.1** (37.9-48.4)	**32.6** (27.8-37.7)

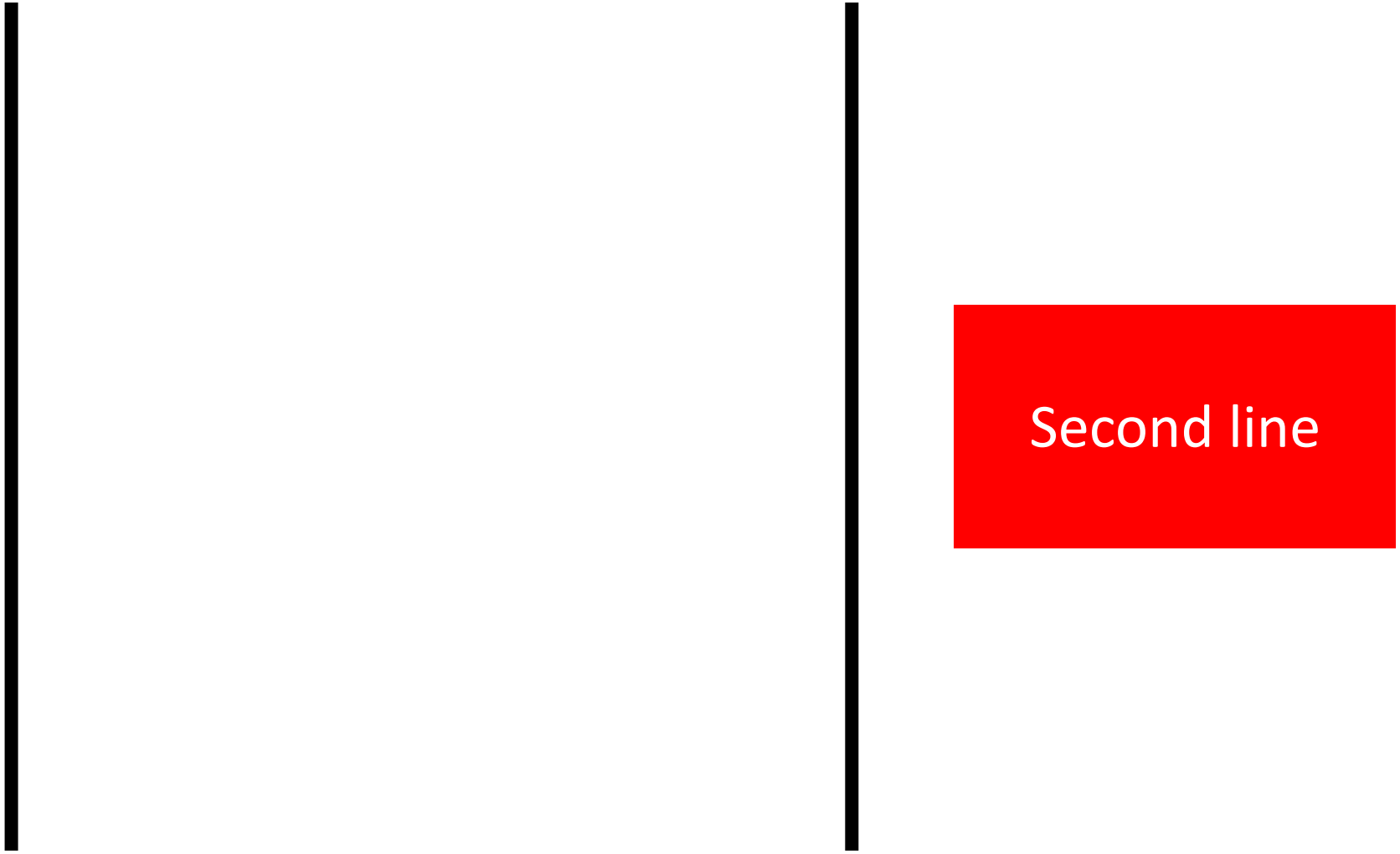
DBL date: October 28, 2021. Median follow-up: 19.3 mo

Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. 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; OS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75; ORR could not be formally tested and was descriptively analyzed. Minimum potential follow-up (time from last patient randomized to last patient last visit) was 8.7 mo.

Long GV, et al. Oral presentation at the American Society of Clinical Oncology (ASCO) 2022 March Plenary Series; March 15, 2022; Virtual. Abstract 360385.

Tawbi et al.
Asco 2022

Melanoma landscape



Best option is still a clinical trial!

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

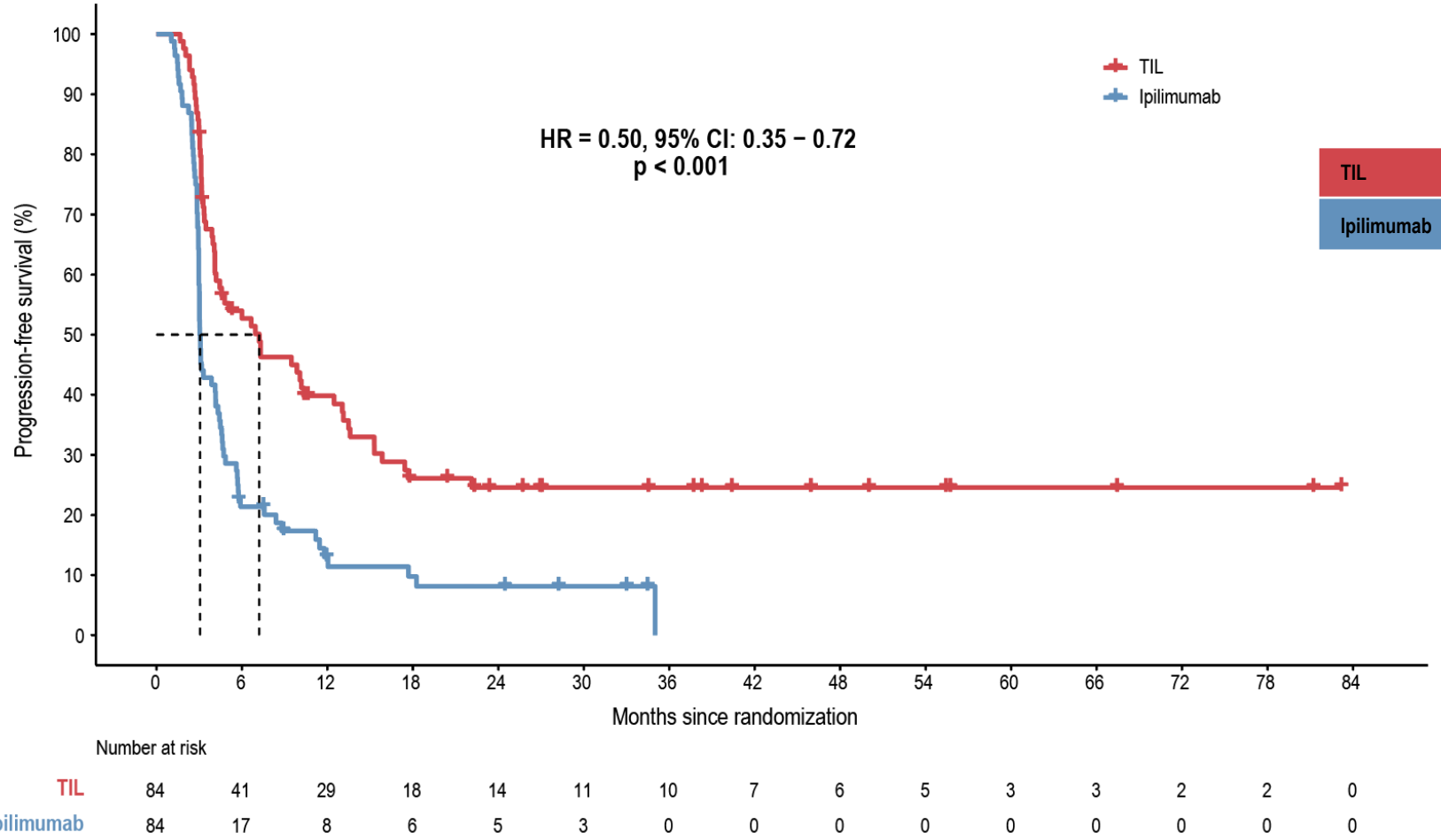
John B.A.G. Haanen

Paris, France, 10th September 2022

Presentation number LBA3

Results (1)

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

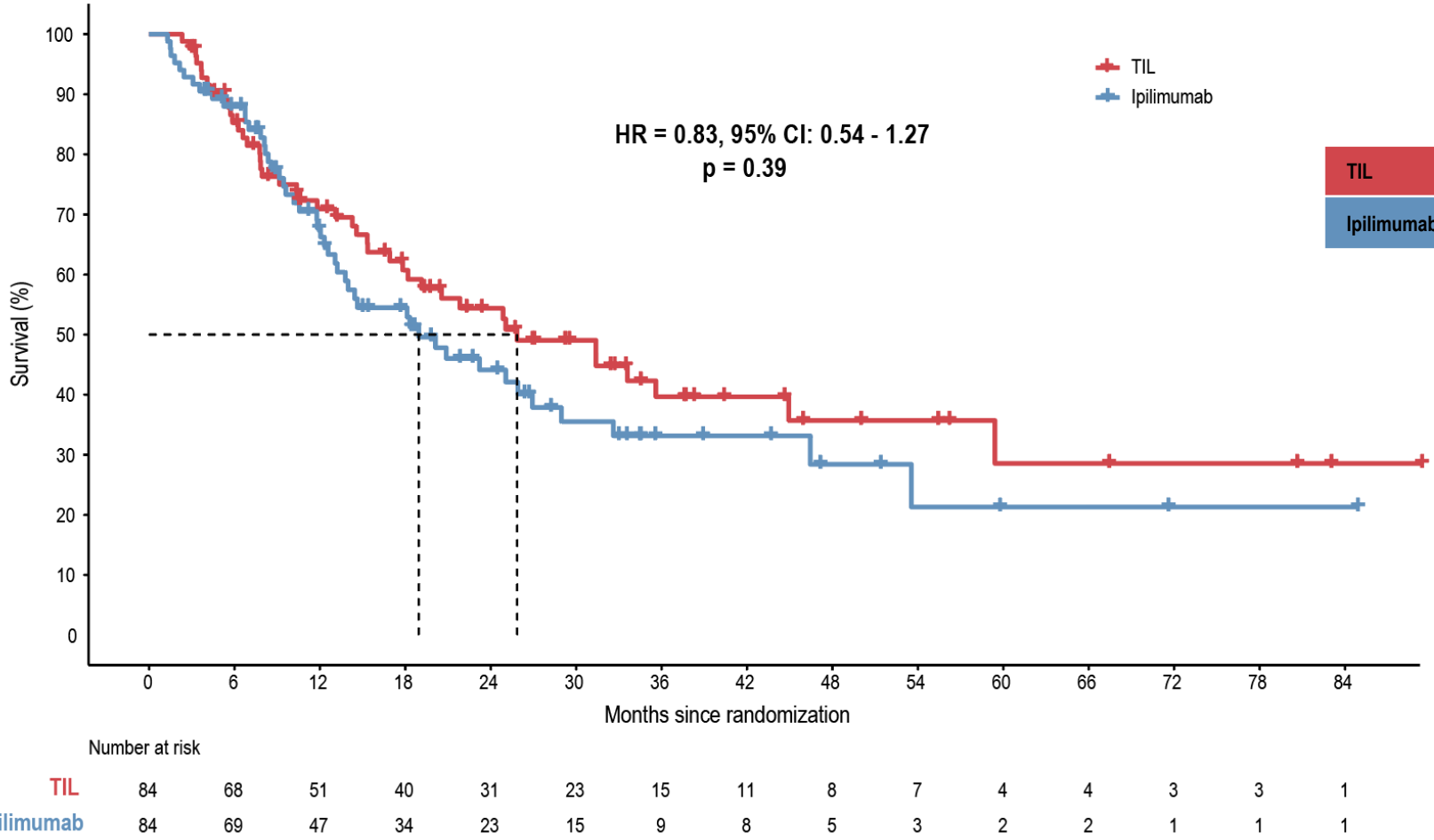


	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

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

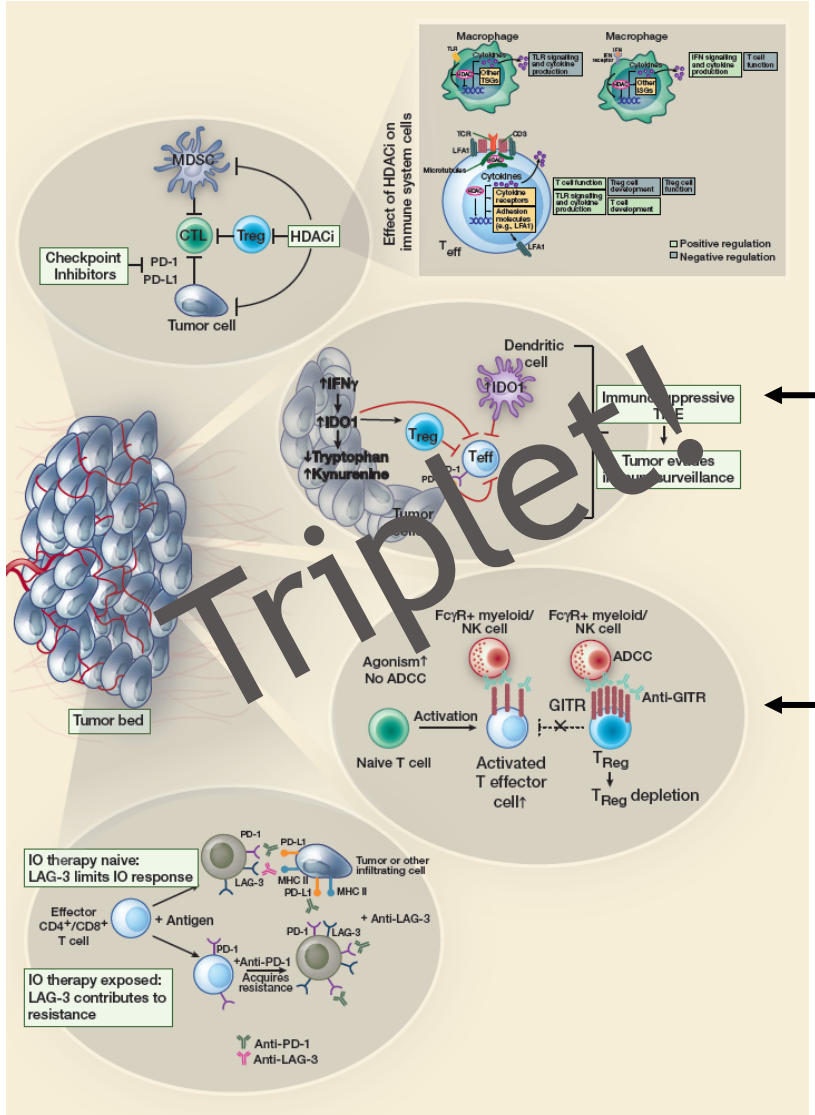
New emerging pathways for future combination with anti–PD-1 / PD-L1 compounds

HDAC inhibitors

IDO1 inhibitors

Anti-GITRs

Anti-LAG-3

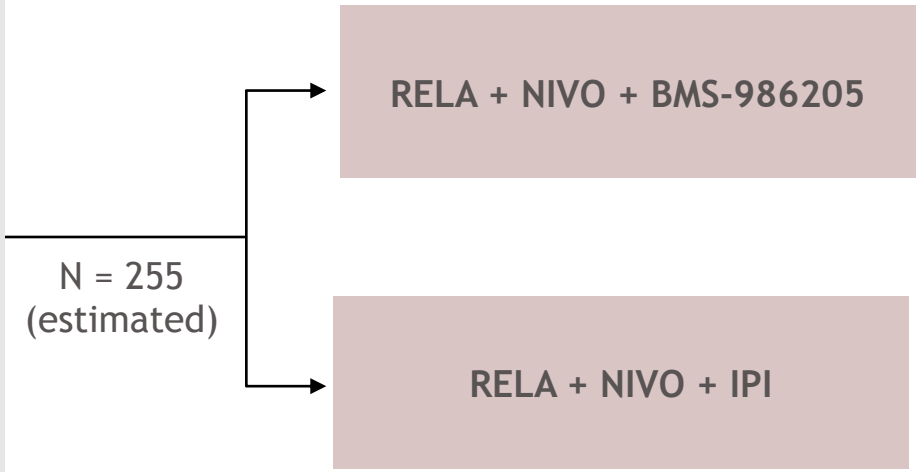


GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2, 3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3; PD-1, programmed death 1; PD-L1, programmed death ligand 1.
Ascierto PA, McArthur JA. *J Transl Med*. 2017;15:173.

Adapted with permission from *J Transl Med*.

CA224-048 study design: RELA + NIVO + BMS-986205 (IDO1 inhibitor) or RELA + NIVO + IPI in advanced disease[1,2]

- Metastatic and / or unresectable advanced solid tumors
  - Patients with known or suspected CNS metastases or with the CNS as the only site of active disease were not eligible for the study
- Includes I-O–naïve and I-O pretreated[a] populations
- Measurable disease per RECIST v1.1
- ECOG PS 0–1



- **Primary endpoints:** safety, ORR, DCR, median DOR
- **Secondary endpoint:** PFS

[a]Including but not limited to anti–PD-1 / PD-L1 and anti–CTLA-4 treatment.
CTLA-4, cytotoxic T-lymphocyte antigen 4; DCR, disease control rate; DOR, duration of response; I-O, immuno-oncology; IDO1, indoleamine 2, 3-dioxygenase 1; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PS, performance status; RELA, relatlimab.
1. ClinicalTrials.gov. Accessed August 10, 2022. https://clinicaltrials.gov/ct2/show/NCT03459222. 2. Ascierto PA. Metastatic melanoma treatment. Accessed August 30, 2022. https://oncologypro.esmo.org/content/download/434503/8350411/1/E-Learning-Metastatic-Melanoma-Treatment.pdf

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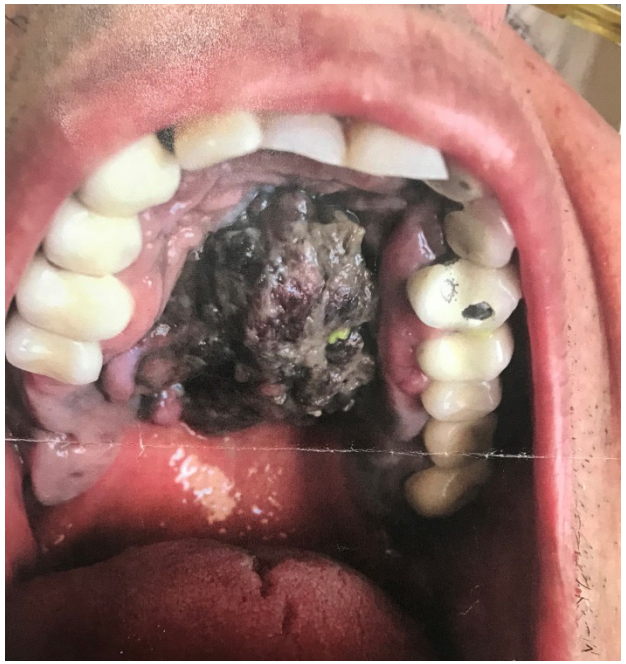
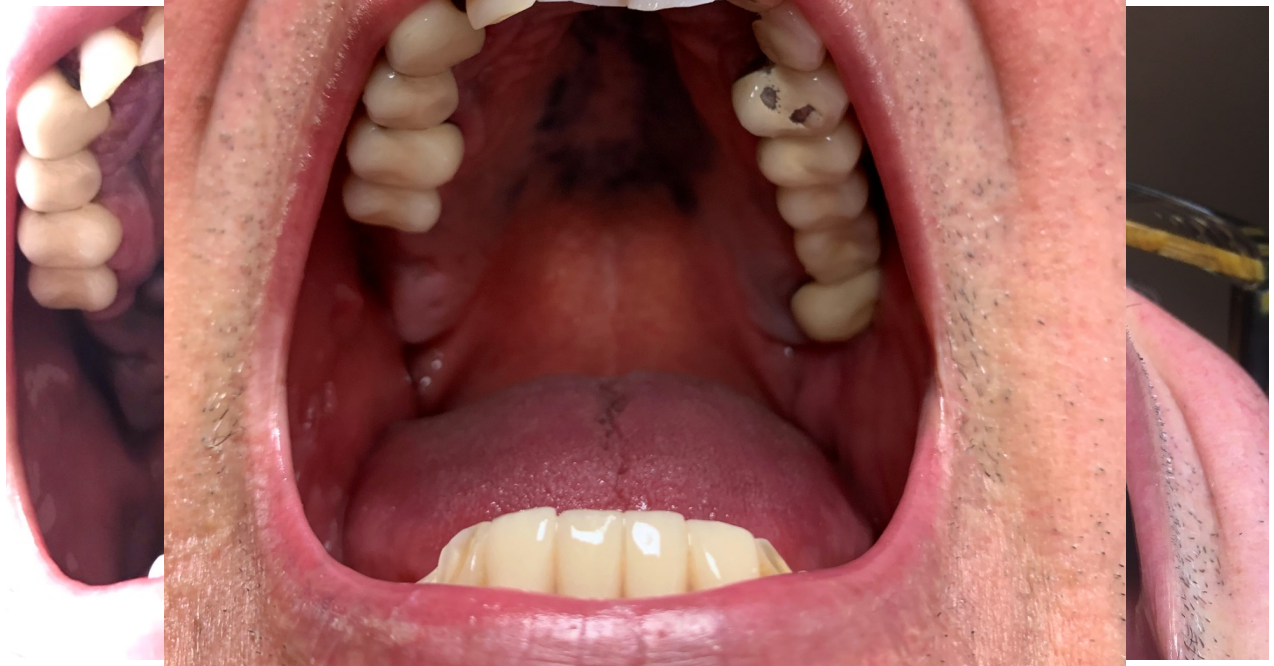


Baseline – cycle 1, day 1
IPI / NIVO / RELA
Date: 29 April, 2019



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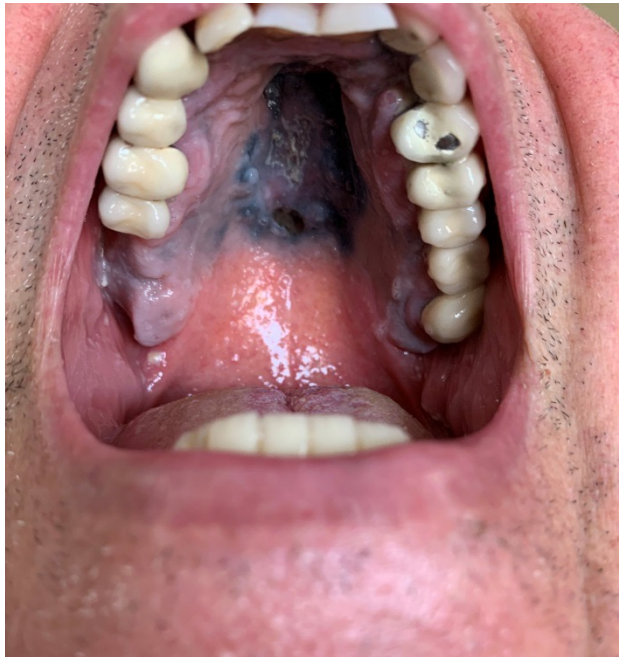
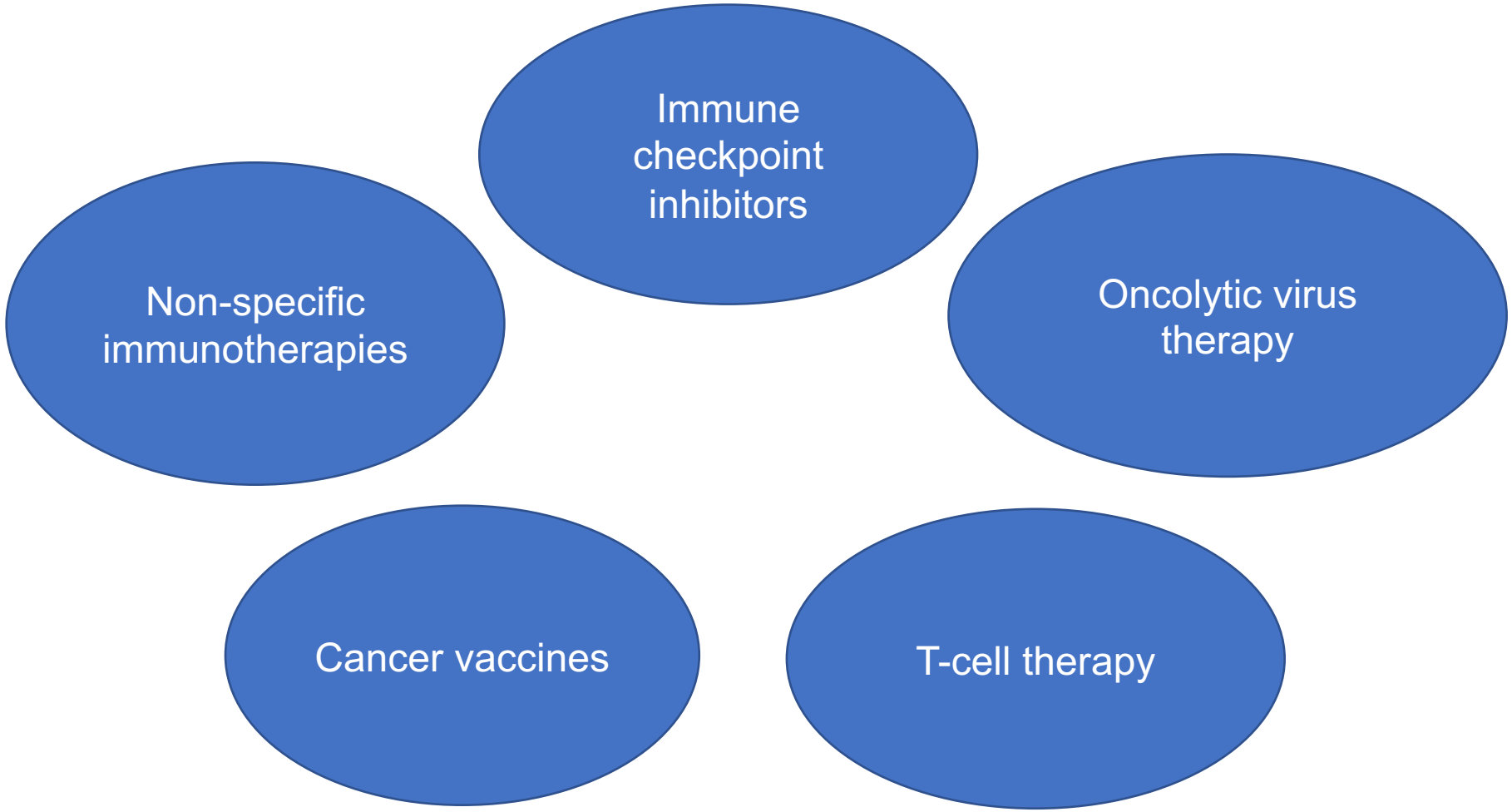
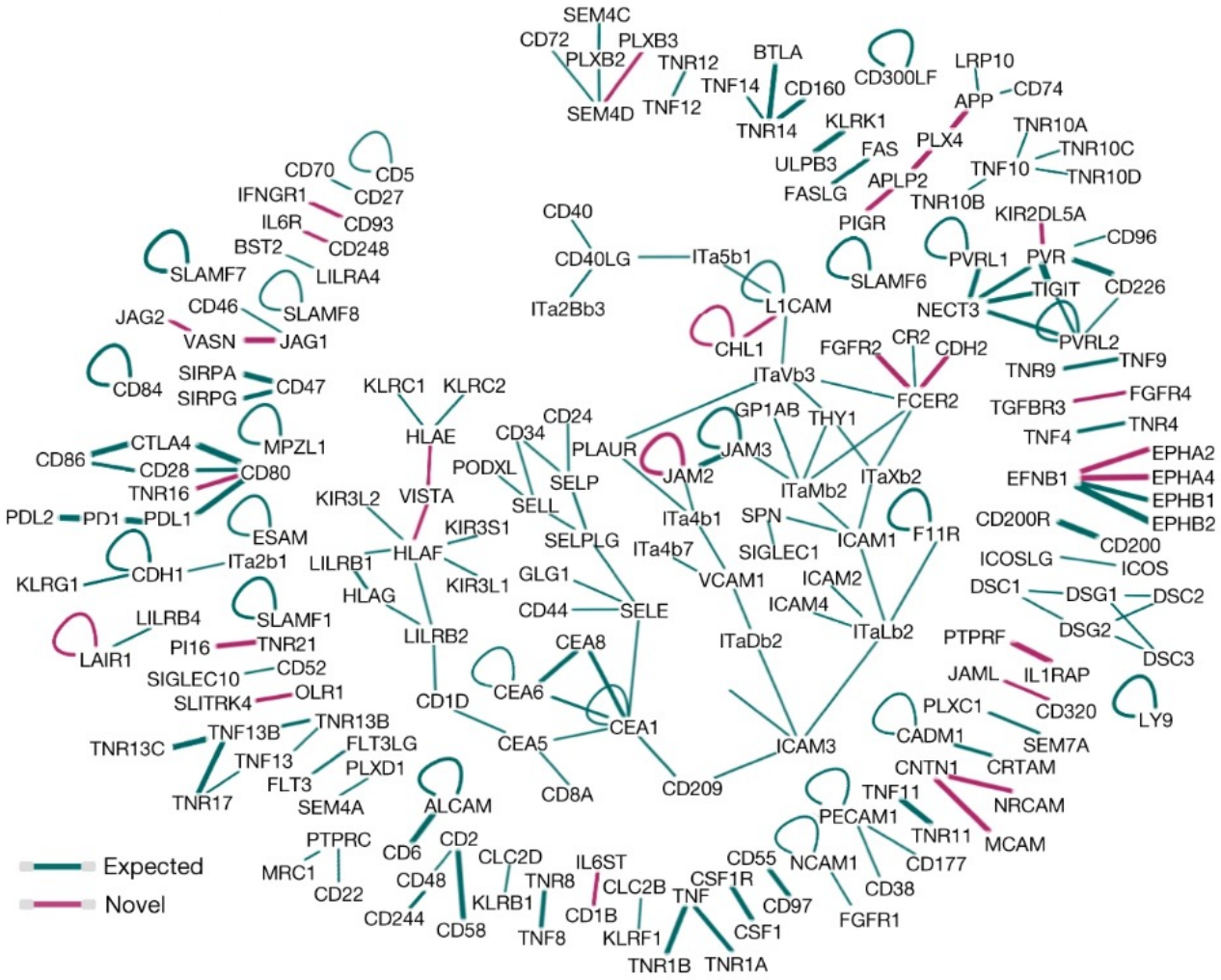


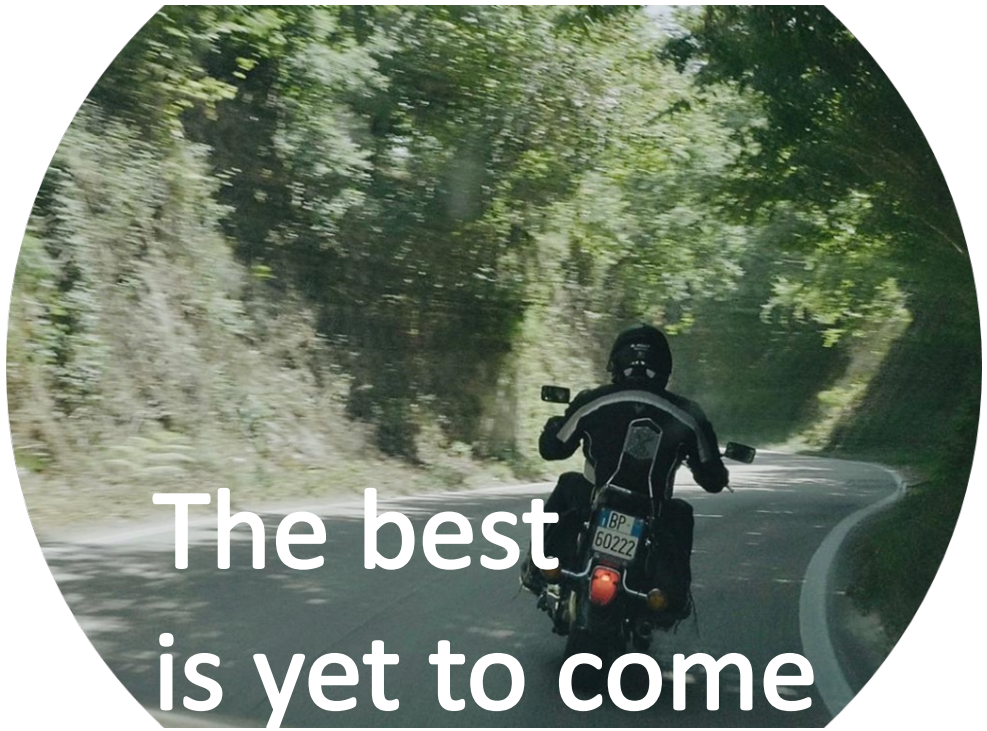
Re-evaluation
Date: 11 June, 2019

IPI, ipilimumab; NIVO, nivolumab; RELA, relatlimab.
Images provided by Ascierto PA. Istituto Nazionale Tumori IRCCS — Fondazione Pascale, Napoli, Italy.

Immunotherapy







Shilts, J., Severin, Y., Galaway, F. *et al.* A physical wiring diagram for the human immune system. *Nature* **608**, 397–404 (2022)

Thank you!

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