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 **SCUOLA DERMATOLOGICA**
SERGIO CHIMENTI

YES^{or} NO CONTEST 1° INCONTRO
Dermatology Update
ROMA 21-22 marzo 2025
NH ROMA CENTRO - Via dei Gracchi 324, Roma
RESPONSABILE SCIENTIFICO: **Ketty Peris**
COMITATO SCIENTIFICO: **Luca Bianchi, Maria Esposito**

Gemelli



TERAPIA MELANOMA

Ernesto Rossi

Medical Oncology

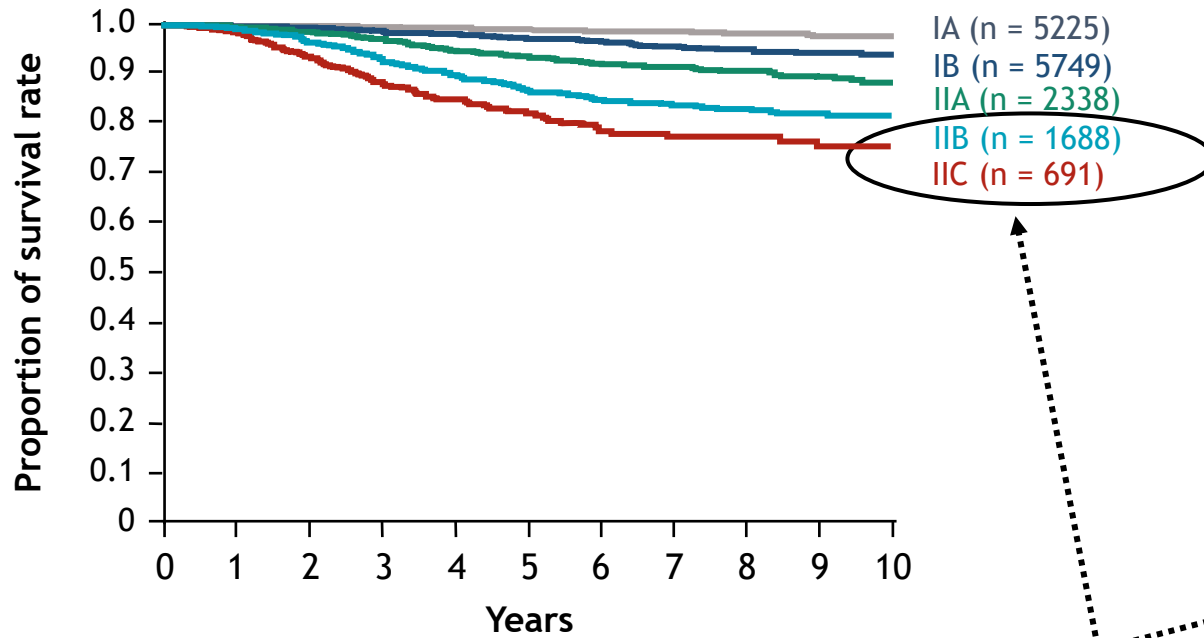
Fondazione Policlinico Universitario A. Gemelli IRCCS
Roma



I pazienti in stadio IIB-IIC radicalmente operato possono essere sottoposti a terapia adiuvante con Pembrolizumab?

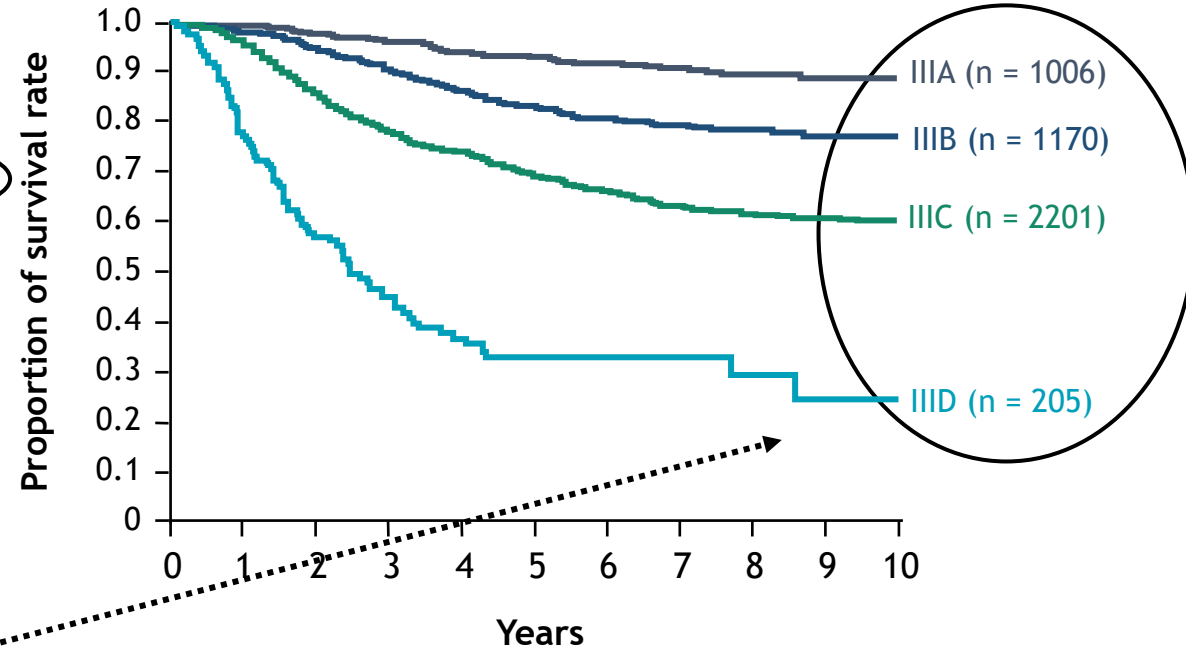
Survival by disease stage per AJCC 8th edition^a

Stage I/II melanoma¹



IA: 2%
IB: 6%
IIA: 12%
IIB: 18%
IIC: 25%

Stage III melanoma¹



IIIA: 12%
IIIB: 23%
IIIC: 40%
IIID: 76%

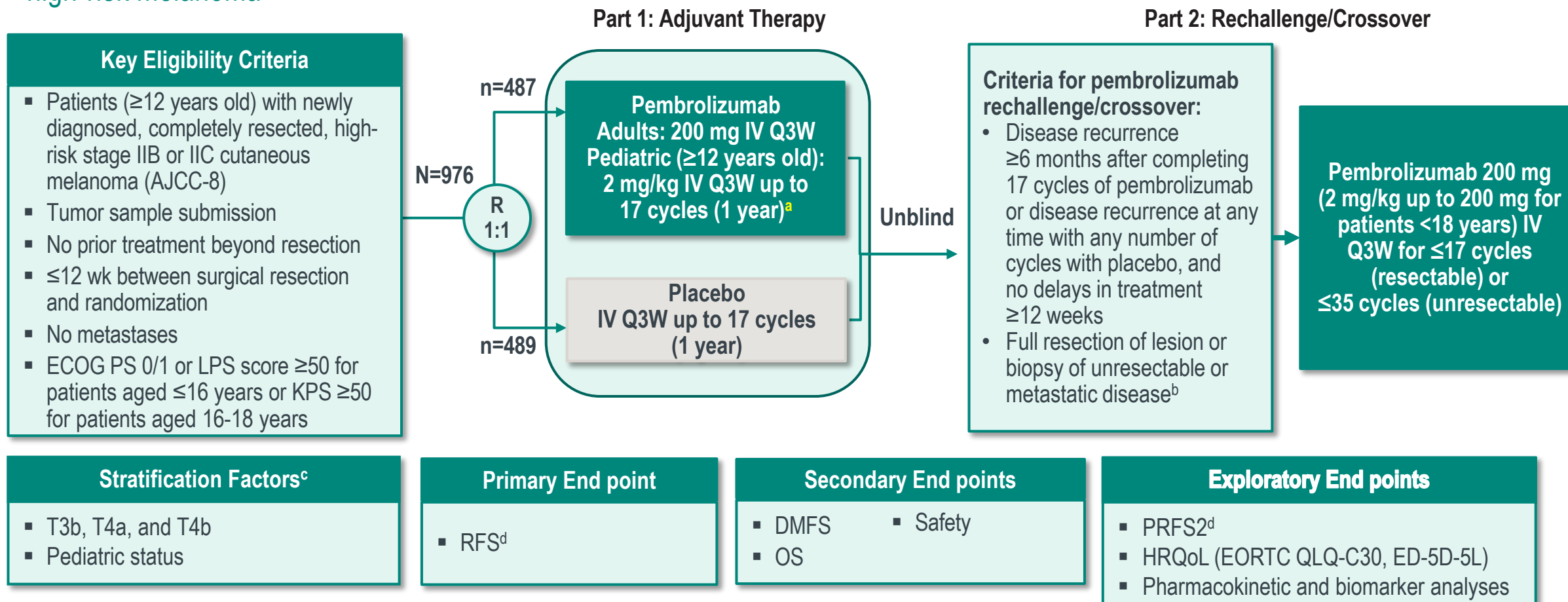
10 year mortality

^aBased on AJCC 8th Edition International Melanoma Database.
AJCC, American Joint Committee on Cancer.

1. Adapted from Gershenwald JE et al. *CA Cancer J Clin* 2017;67:472–492. 2. Davar D, Kirkwood JM. *Cancer Treat Res* 2016;167:181–208.

KEYNOTE-716: Study Design

A 2-arm, 2-part, randomized, controlled, phase 3 trial of pembrolizumab in stage IIB/C resected high-risk melanoma¹⁻⁵



^aTreatment was discontinued if patients experienced unacceptable toxicity, disease progression, or patient/physician decision to withdraw. ^bPatients may receive (neo)adjuvant radiotherapy and have an ECOG PS 0-2 (≥18 years).

^cBRAF-mutation status and PD-L1 status were not prespecified stratification factors due to tissue availability. ^dPer RECIST v1.1 by investigator assessment.

1. ClinicalTrials.gov. <https://www.clinicaltrials.gov/ct2/show/NCT03553836>. Accessed May 22, 2024. 2. Luke JJ, et al. *Future Oncol*. 2020;16:4429-4438. 3. Luke JJ, et al. *Lancet*. 2022; 399(10336):1718-1729.

4. Luke JJ, et al. Presented at ASCO 2023 (Abstract LBA9505). 5. Luke JJ, et al. Presented at ESMO 2024 (Abstract 1078MO).

Long-Term Follow-Up: RFS (Primary Endpoint)

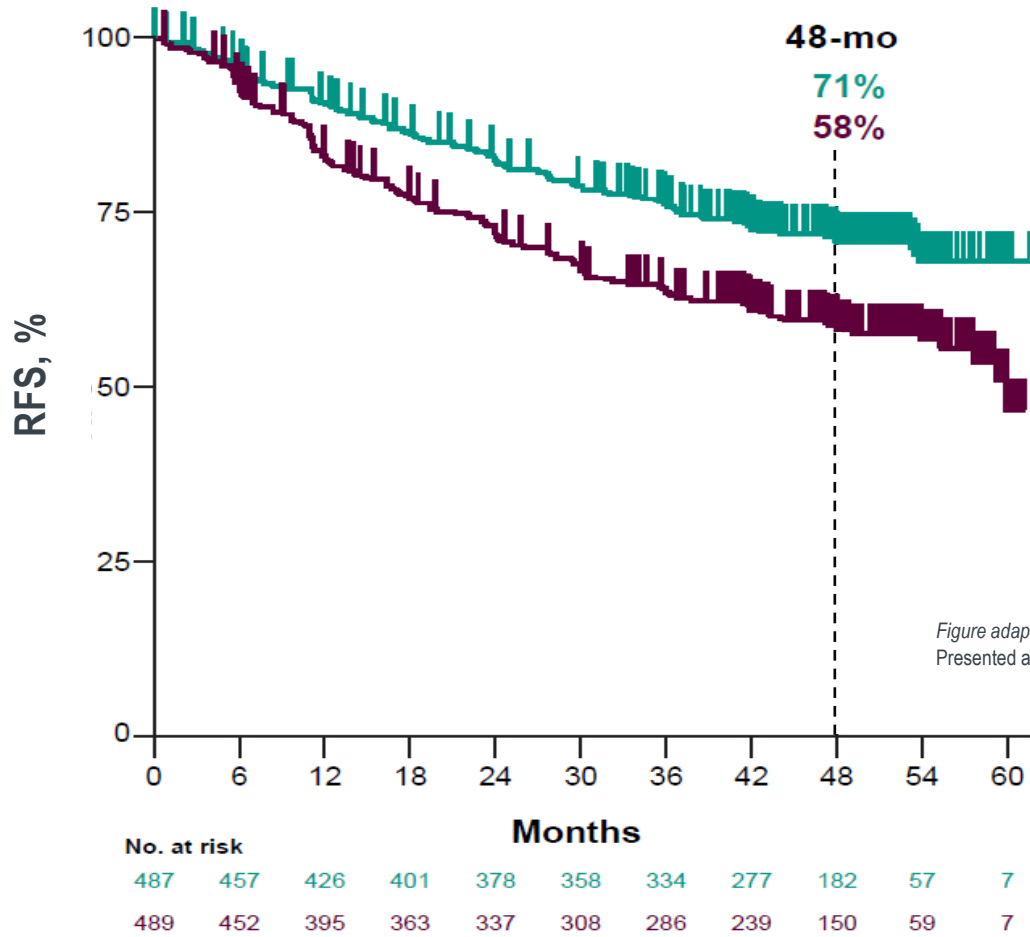


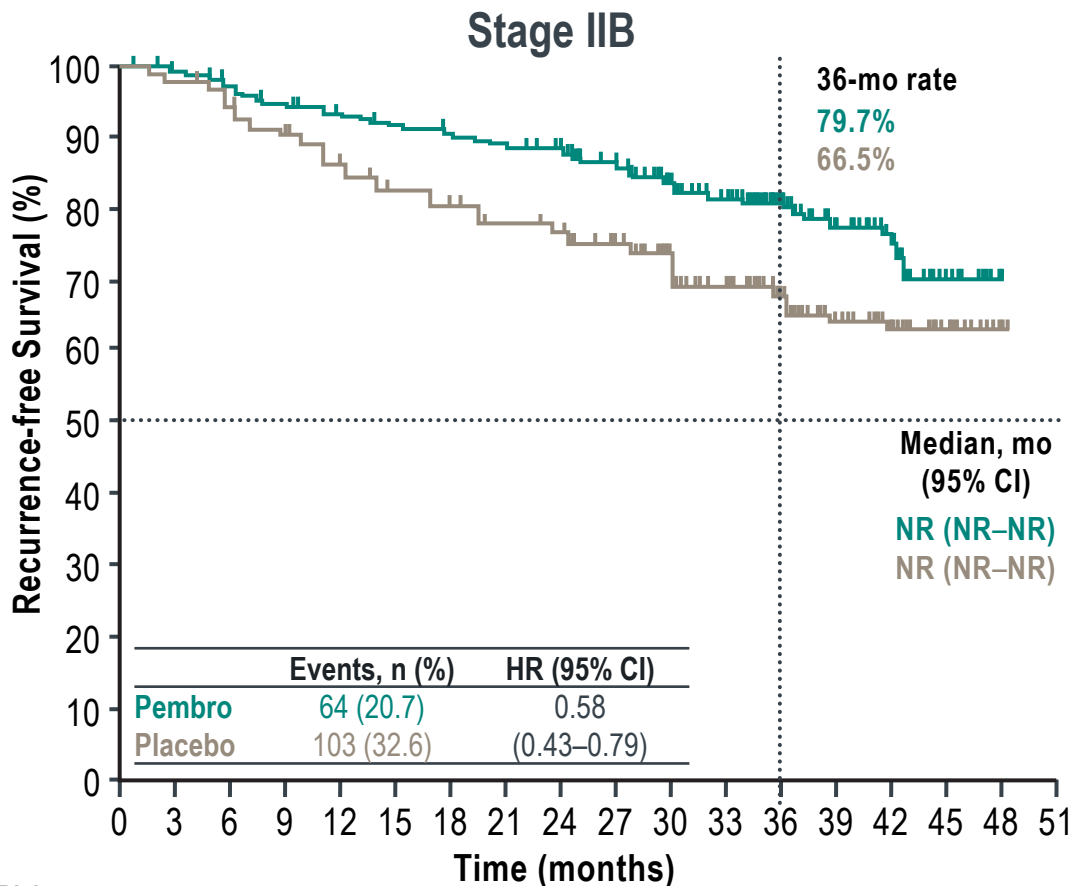
Figure adapted with permission from Luke, et al.
Presented at ESMO 2024. Abstract 1078MO.

	Events n/N (%)	Median (95% CI), months	HR (95% CI)
Pembrolizumab	134/487 (28)	NR (NR–NR)	0.62 (0.50–0.78)
Placebo	198/489 (40)	59.9 (57.6–NR)	

Median follow-up: 52.8 months (range, 39.4–64.8). Data cutoff: February 16, 2024.

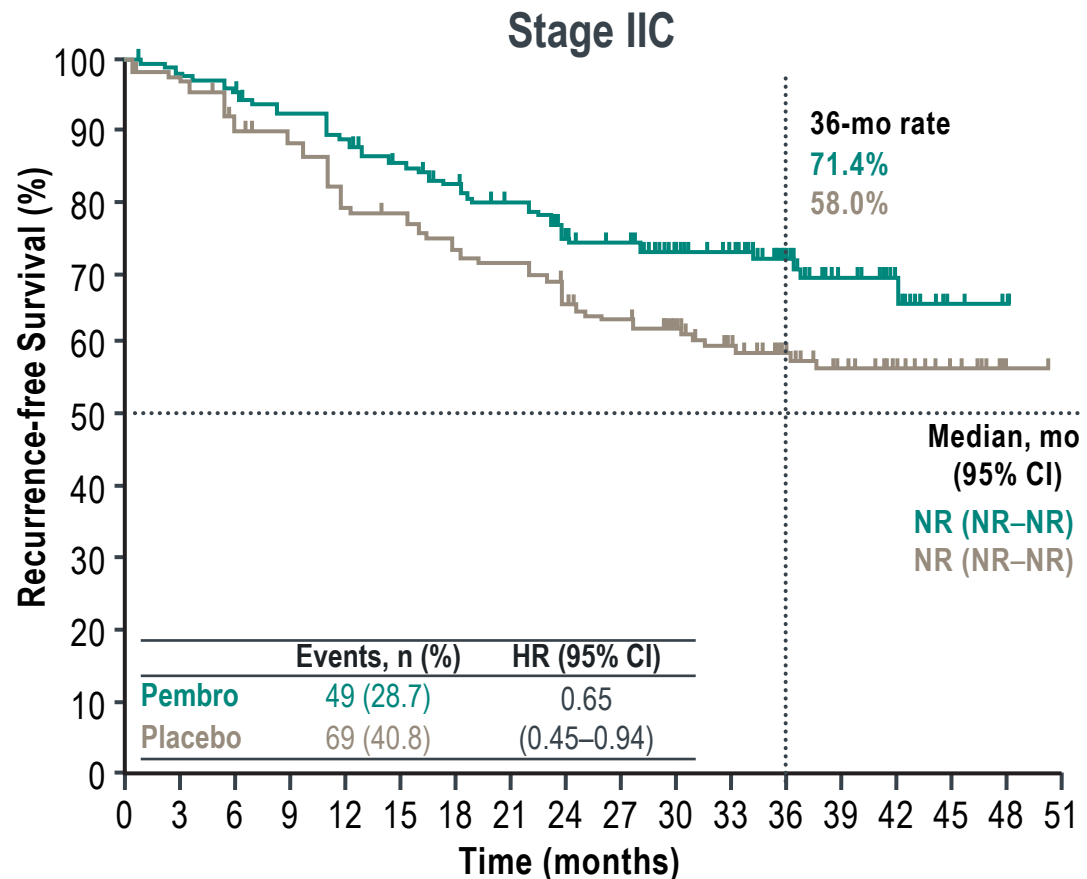
[Luke JJ, et al. Presented at ESMO 2024 \(Abstract 1078MO\).](#)

IA4: RFS by Disease Stage



No. at Risk

Pembrolizumab	309	301	293	285	276	272	266	263	255	242	204	169	115	77	43	12	2	0
Placebo	316	310	297	283	264	252	244	236	226	214	172	140	96	70	31	18	5	0



No. at Risk

Pembrolizumab	171	166	161	154	148	139	132	125	114	109	94	83	56	38	19	6	2	0
Placebo	169	164	152	145	130	125	118	114	105	97	80	70	53	43	20	12	2	0

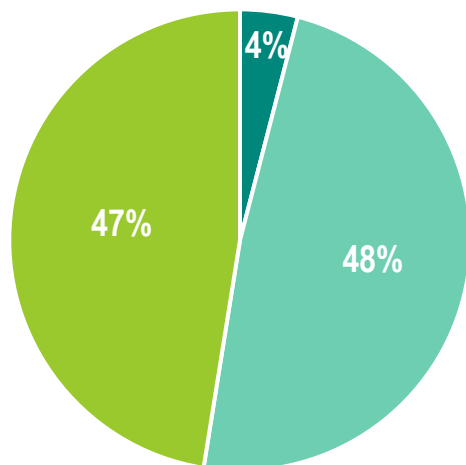
Median follow-up: 39.4 months (range 26.0-51.4). Data cutoff: January 4, 2023.
 Luke JJ, et al. *J Clin Oncol.* 2024;42(14):1619-1624.

Figure adapted with permission from AMERICAN SOCIETY OF CLINICAL ONCOLOGY.
 Luke JJ, et al. *J Clin Oncol.* 2024;42(14):1619-1624.

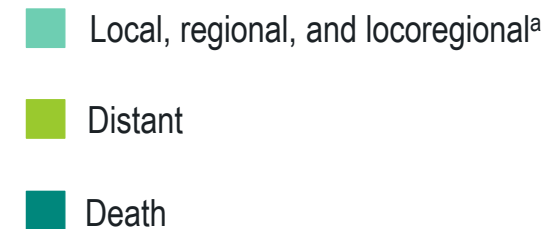
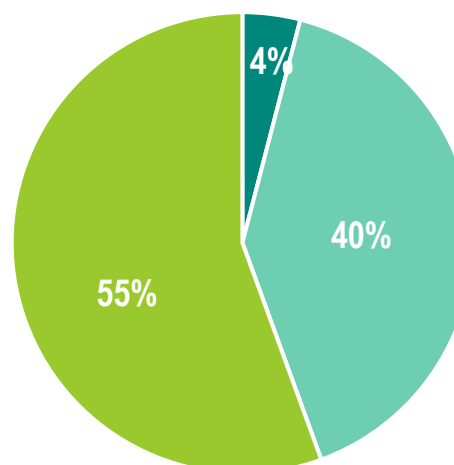
IA3: Pattern of First Recurrence

	Pembrolizumab n=487	Placebo n=489
Patients with an RFS event	95 (20)	139 (28)
Local/regional/locoregional recurrence ^a	46 (9)	56 (11)
Distant recurrence	45 (9)	77 (16)
Death	4 (1)	6 (1)

Pembrolizumab Recurrence, n=95



Placebo Recurrence, n=139



Median follow-up: 27.4 months (range 14.0–39.4 months). Data cutoff: January 4, 2022.

^aIncludes recurrence in the immediate vicinity of the primary tumor (local), regional lymph node basin involvement (regional), or in transit metastases (regional) or any combination of the aforementioned patterns of recurrence.
[Long GV, et al. Presented at ASCO 2022 \(Abstract LBA9500\).](#)

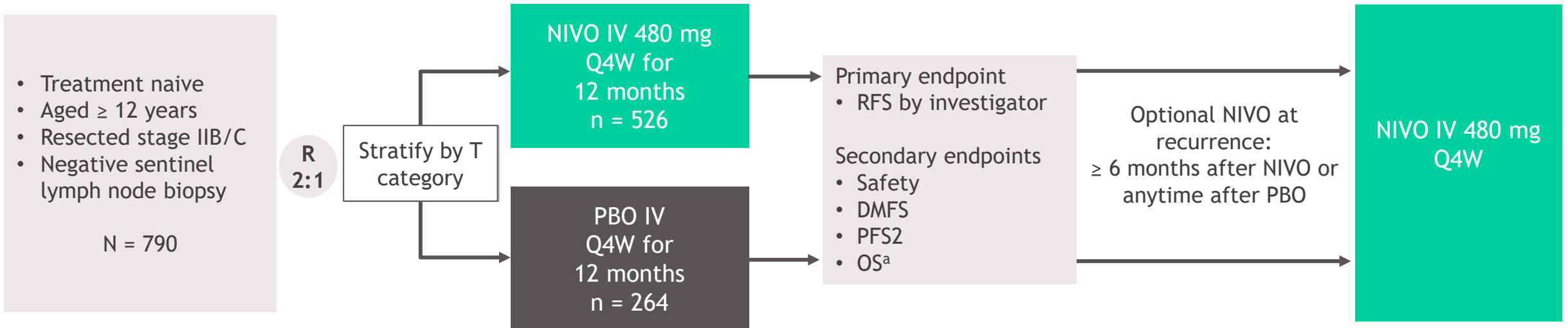
I pazienti in stadio IIB-IIC radicalmente operato possono essere sottoposti a terapia adiuvante con Pembrolizumab?

YES

La terapia adiuvante con Nivolumab è uno standard terapeutico per i pazienti con melanoma in stadio IIA operato?

CheckMate 76K

- CheckMate 76K is a global, randomized, double-blind, phase 3 study that led to the approval of NIVO treatment in patients with resected stage IIB/C melanoma



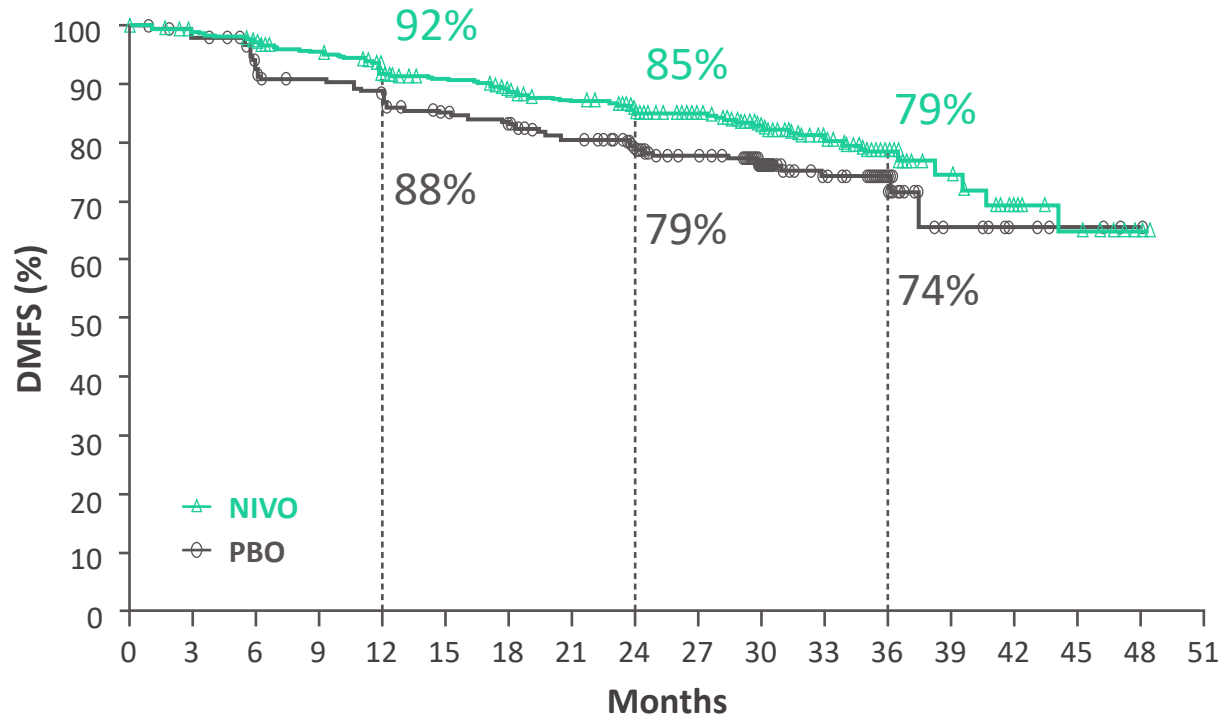
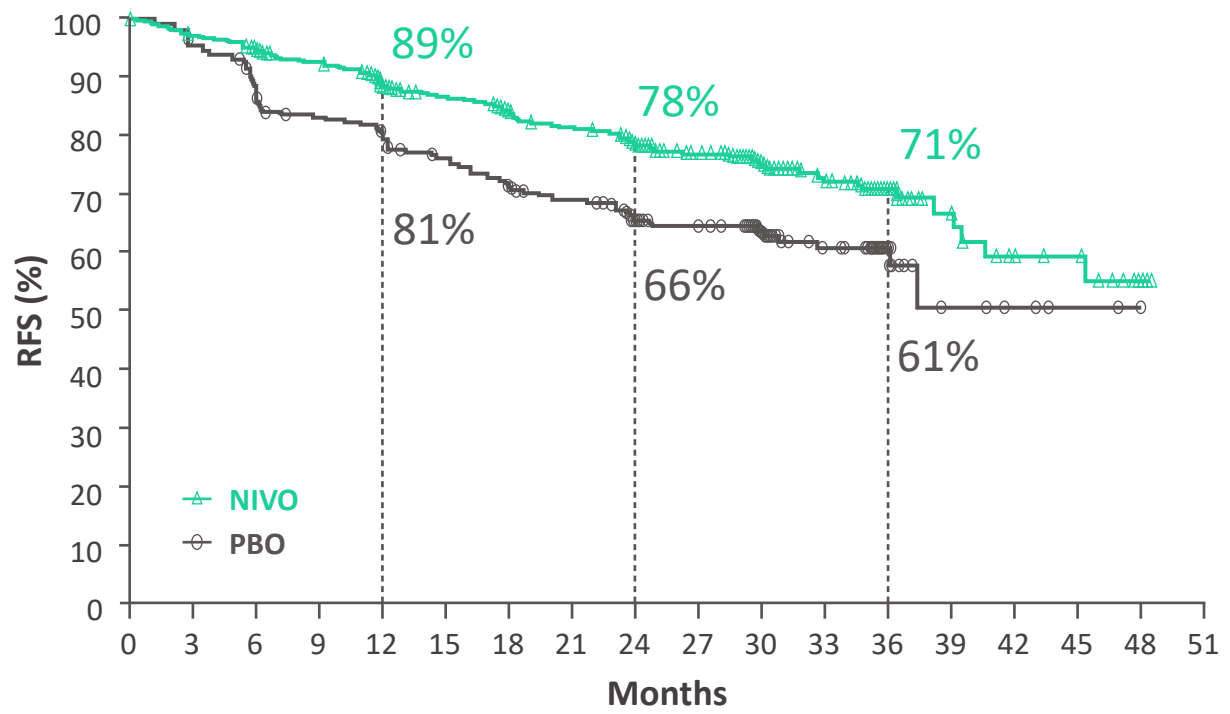
Clinical cutoff	June 28, 2022 ¹	February 21, 2023 ²	January 29, 2024
Months minimum follow-up ^b	7.8	15.6	26.9
Months median follow-up	NIVO: 15.8; PBO: 15.9	NIVO: 23.5; PBO: 23.0	NIVO: 34.2; PBO: 33.9
RFS HR (95% CI)	0.42 (0.30-0.59)	0.53 (0.40-0.71)	
DMFS HR (95% CI)	0.47 (0.30-0.72)	0.62 (0.43-0.89)	

^aOS was defined as the time between randomization and death from any cause. OS is event driven and follow-up is ongoing. ^bTime from the last patient's randomization date to the clinical cutoff date. 1. Kirkwood JM, et al. Nat Med 2023;29:2835-2843. 2. Kirkwood JM, et al. Presented at SMR November 6-9, 2023, Philadelphia PA.

RFS and DMFS

RFS ^a	NIVO	PBO
Events, n/N	133/526	95/264
Median, months (95% CI)	NR (40.7-NR)	NR (36.1-NR)
Stratified HR (95% CI)	0.62 (0.47-0.80)	

DMFS ^b	NIVO	PBO
Events, n/N	96/526	61/264
Median, months (95% CI)	NR	NR
Stratified HR (95% CI)	0.72 (0.52-1.00)	



No. at risk

NIVO	526	492	474	456	430	413	396	380	342	310	217	171	82	28	19	15	4	0
PBO	264	244	224	208	201	186	176	165	145	136	94	62	24	6	4	2	1	0

NIVO	526	505	493	478	452	442	428	413	375	345	242	190	91	31	21	15	4	0
PBO	264	253	236	226	219	207	202	190	170	156	112	79	33	9	5	3	1	0

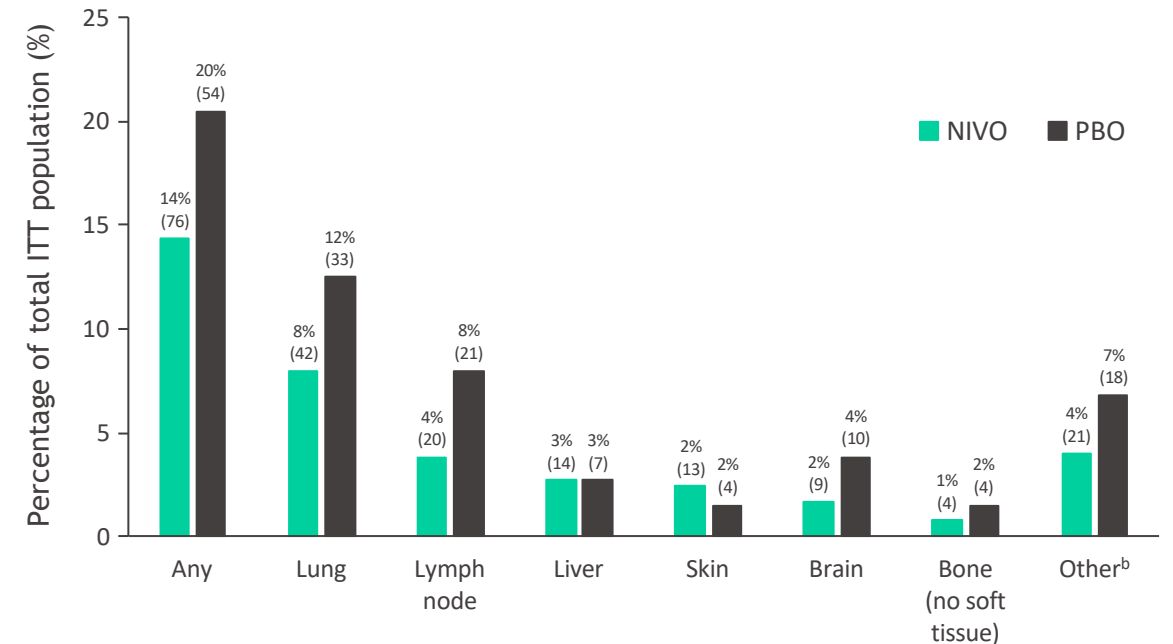
^aRFS was defined as the time between randomization and first recurrence (recurrence events included local, regional, or distant recurrence, new primary melanomas [including *in situ*], and death [due to any cause]). ^bDMFS was defined as time between randomization and first distant recurrence or death (due to any cause).

Patterns of events

Patterns of first RFS events

	NIVO (n = 526), n (%)	PBO (n = 264), n (%)
Number of patients with an event	133 (25%)	95 (36%)
Recurrence ^a		
Distant recurrence	59 (11%)	46 (17%)
Regional node recurrence	18 (3%)	24 (9%)
Local recurrence	11 (2%)	10 (4%)
<i>In transit</i> metastasis	9 (2%)	1 (< 1%)
New primary melanomas		
Melanoma <i>in situ</i>	11 (2%)	6 (2%)
New primary invasive melanoma	8 (2%)	4 (2%)
Death prior to recurrence	17 (3%)	4 (2%)

Location of distant metastases at any time



- 40 NIVO patients (8%) and 34 PBO patients (13%) had more than 1 new distant metastasis

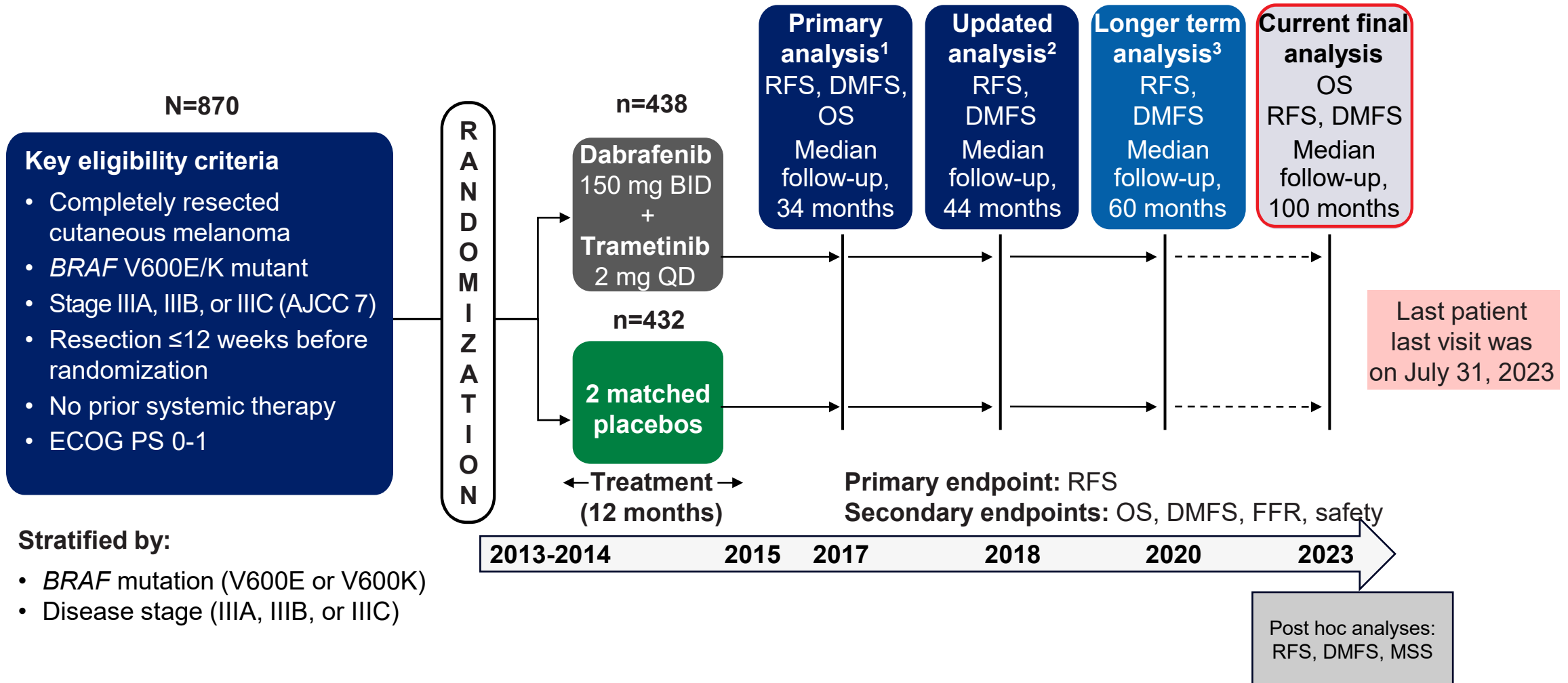
^aFor patients who had multiple recurrences identified on the same day, the most serious type is tabulated according to the displayed prespecified hierarchy. ^bOther (n NIVO v n PBO) includes the following: adrenal gland (3 vs 1), chest wall (3 vs 2), soft tissue (3 vs 3), intestine (2 vs 0), peritoneum (2 vs 1), bone with soft tissue component (1 vs 2), central nervous system (0 vs 1), pelvis (0 vs 1), spleen (0 vs 2) and “other” (7 vs 5).

La terapia adiuvante con Nivolumab è uno standard terapeutico per i pazienti con melanoma in stadio IIA operato?

NO

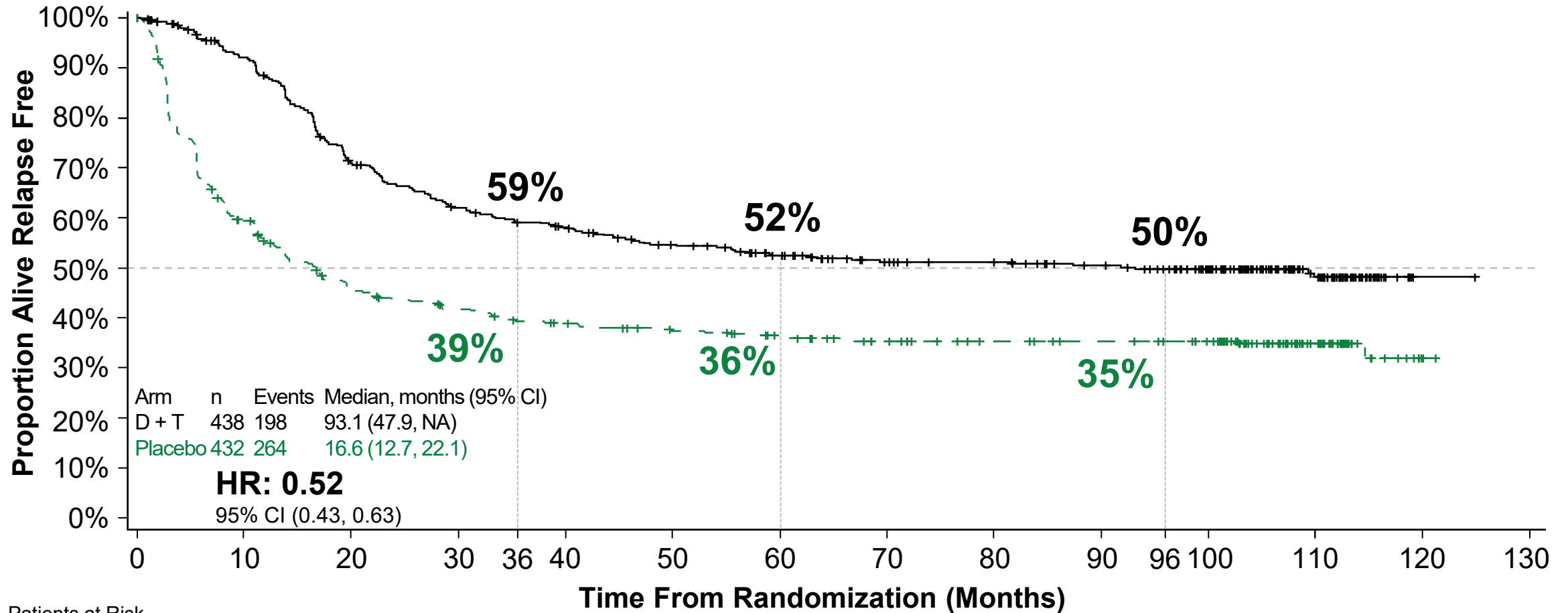
I pazienti con melanoma in stadio III radicalmente operato con mutazione BRAF V600 possono essere sottoposti a terapia adiuvante solo con Dabrafenib e Trametinib?

COMBI-AD: A Double-Blind, Placebo-Controlled, Phase 3 Study



1. Long GV, et al. *N Engl J Med.* 2017;377:1813-1823; 2. Hauschild A, et al. *J Clin Oncol.* 2018;4:1382-1388; 3. Dummer R, et al. *N Engl J Med.* 2020;383:1139-1148.

Relapse-Free Survival (ITT)



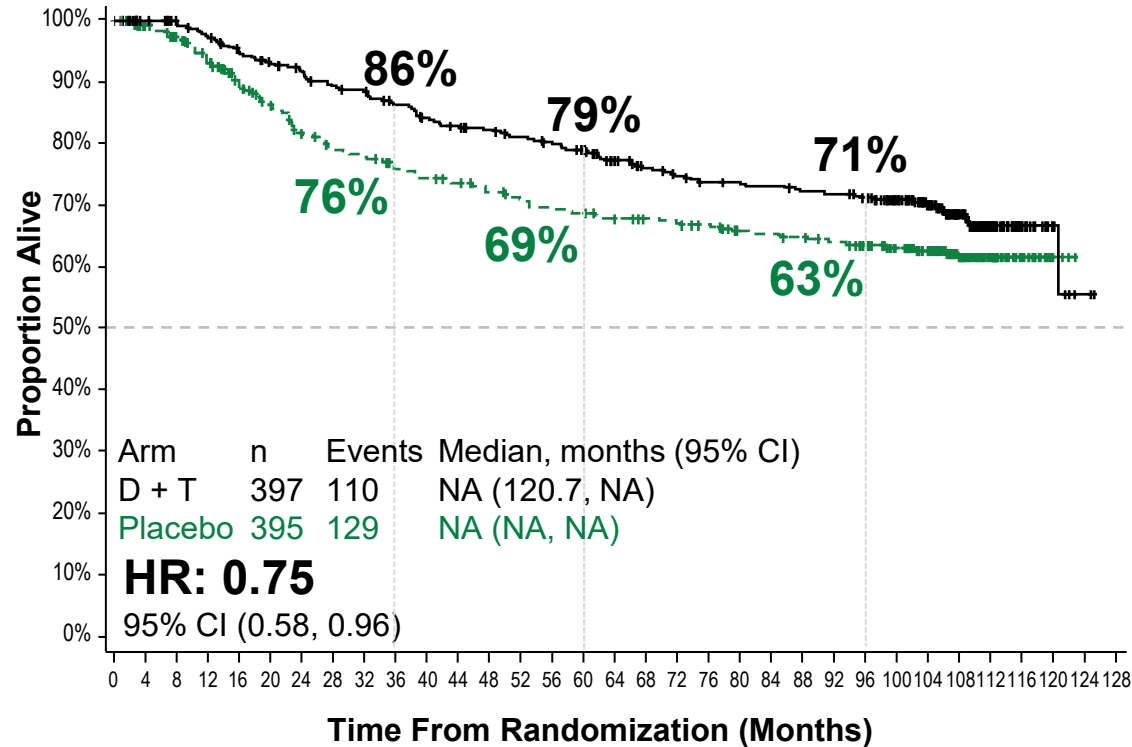
Patients at Risk

D+T	438	372	281	242	229	221	201	183	163	157	147	139	123	56	1	0
Placebo	432	243	178	158	147	143	133	123	112	103	99	96	92	39	2	0

End of study 31 July 2023. Median follow-up: D+T 100.0 (0–125) months; Placebo 82.5 (1–122) months.

Subgroup Analysis: Effect of Treatment on Overall Survival by *BRAF* V600 Mutations (ITT)

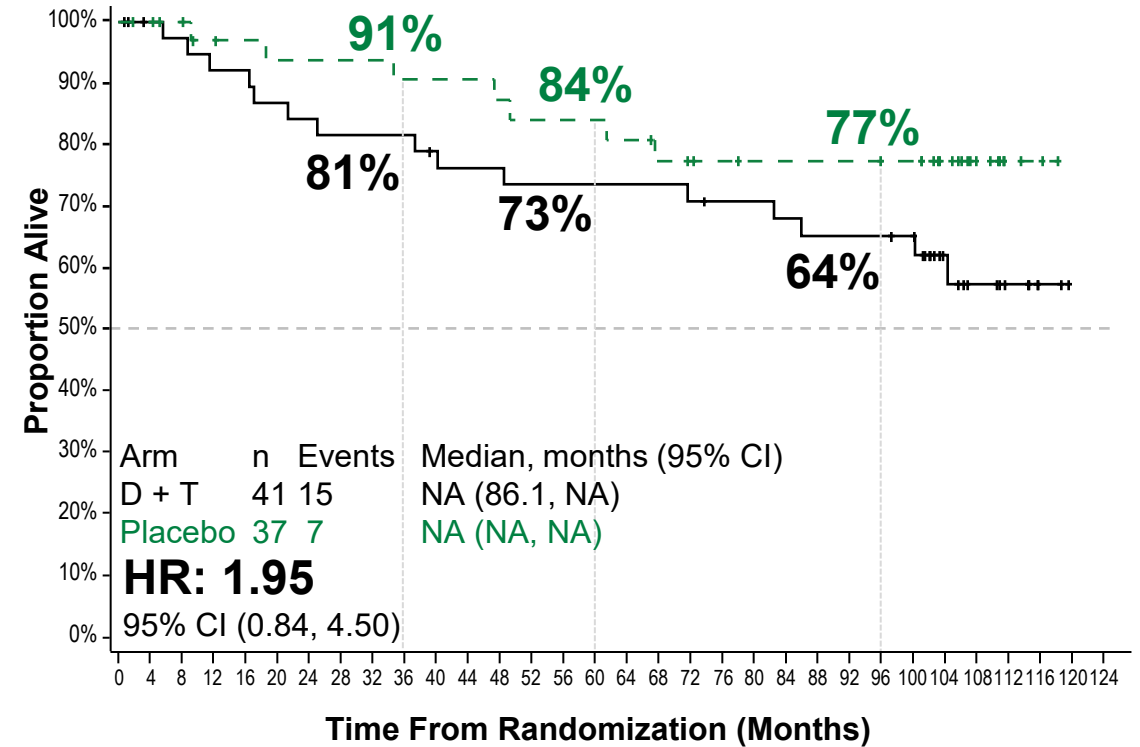
BRAF V600E Mutations



Patients at Risk

D + T	397	378	370	360	346	337	330	320	316	305	296	290	284	278	272	267	252	241	235	230	229	227	223	222	217	200	160	115	69	25	8	2	0
Placebo	395	379	366	346	316	299	279	268	263	254	246	242	237	229	225	222	216	213	211	207	198	196	193	188	181	166	143	106	64	24	4	0	0

BRAF V600K Mutations



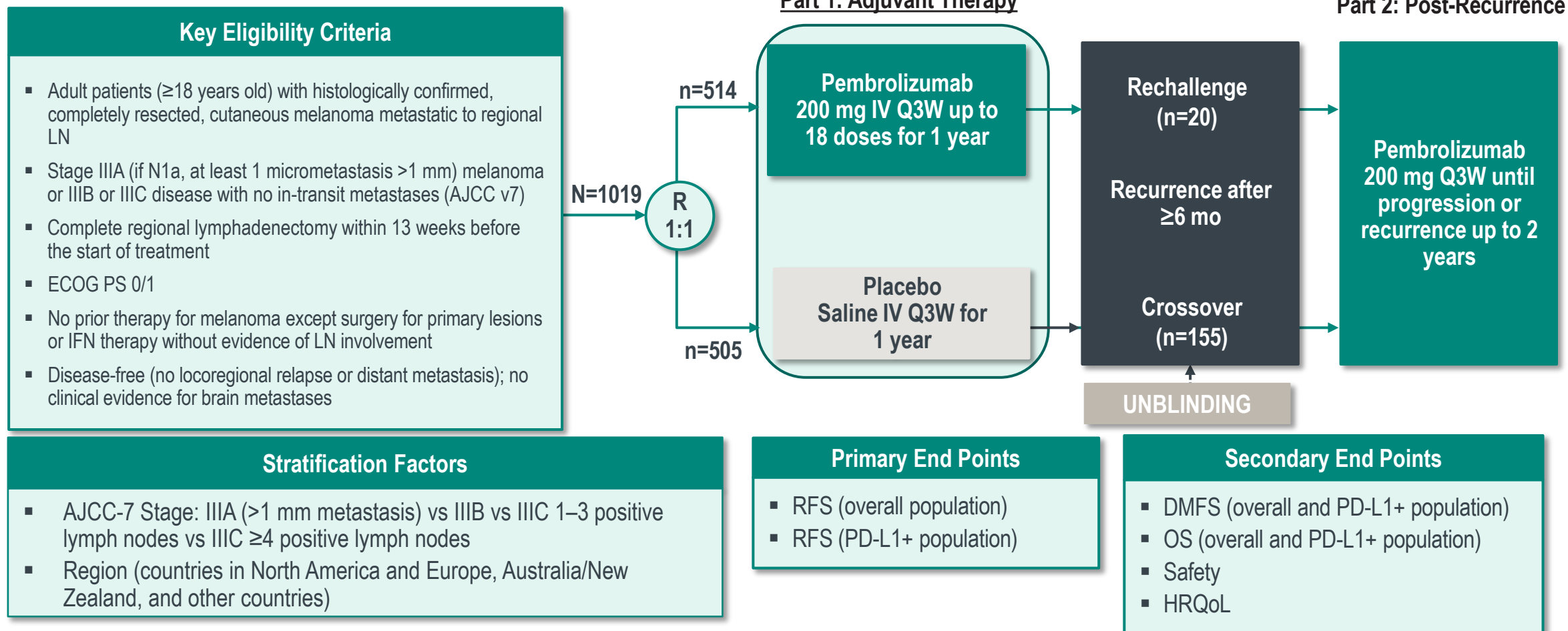
Patients at Risk

D + T	41	38	37	35	35	33	32	31	31	31	29	28	28	27	27	27	27	27	26	25	25	24	23	23	23	22	13	9	6	2	0	0
Placebo	37	36	34	31	30	29	29	29	29	28	28	28	27	26	26	26	25	23	22	21	20	20	20	20	20	19	14	9	3	2	0	0

End of study 31 July 2023. Median follow-up: D+T 100.0 (0–125) months; Placebo 82.5 (1–122) months.

EORTC 1325-MG/KEYNOTE-054: Study Design

A 2-arm, randomized, controlled, phase 3 trial of pembrolizumab in stage III resected high-risk metastatic melanoma¹⁻⁷



1. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02362594>. Accessed May 22, 2024. 2. Eggermont AMM, et al. *Eur J Cancer*. 2021;158:156-168. 3. Eggermont AMM, et al. *Eur J Cancer*. 2021;158:156-168 (Supplementary Appen...
4. Eggermont AAM, et al. *Lancet Oncol*. 2021;22(5):643-654. 5. Eggermont AMM, et al. *N Engl J Med*. 2018;378:1789-1801. 6. Eggermont AMM, et al. Presented at ESMO 2024 (Abstract 1095P).
7. Bühner E, et al. *Lancet Oncol*. 2024;25(9):1202-1212.

Recurrence-free Survival

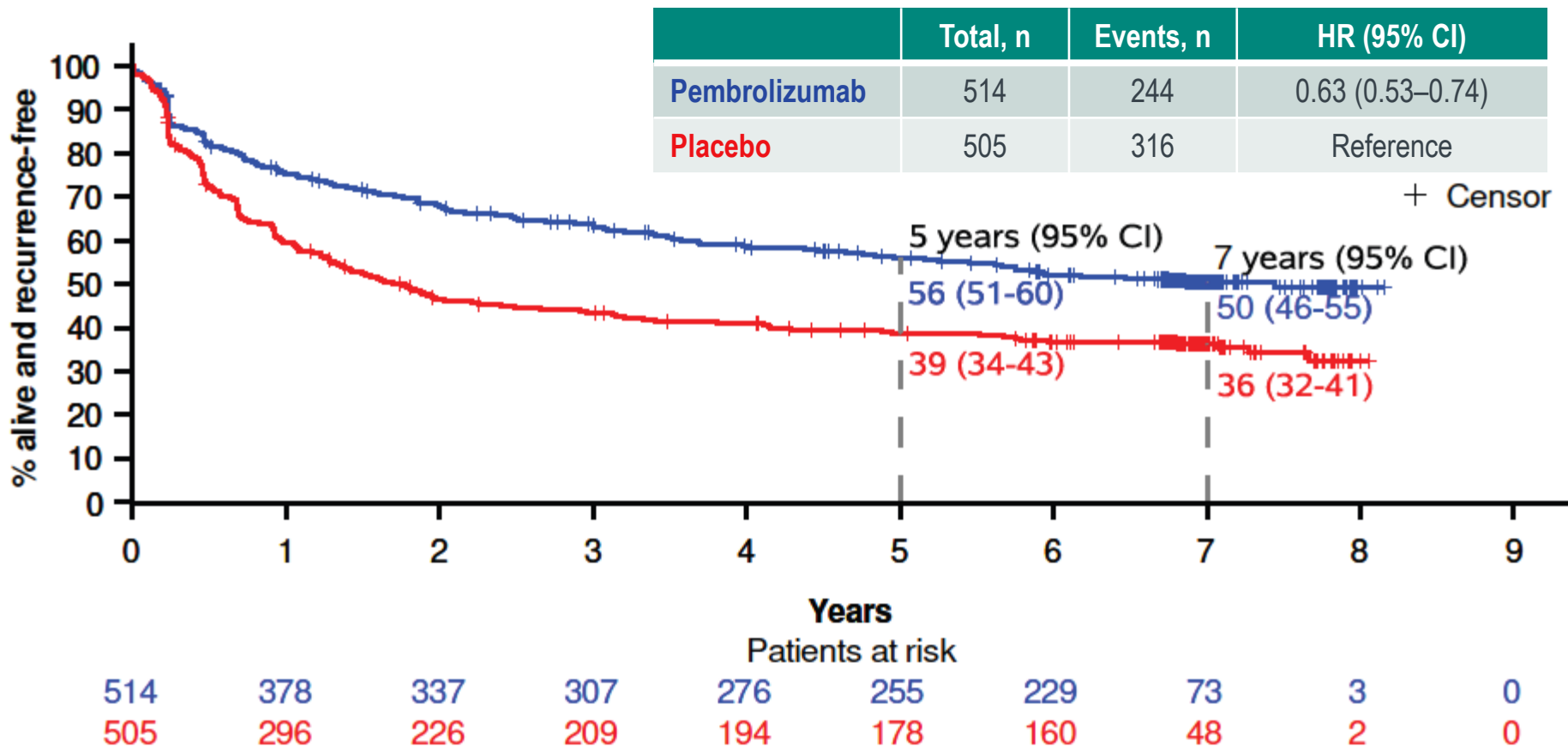


Figure adapted with permission from Eggermont, et al. Presented at ESMO 2024. Abstract 1095P.

Median follow-up: ~7 years.
[Eggermont AMM, et al. Presented at ESMO 2024 \(Abstract 1095P\).](#)

Part 1: DMFS by Treatment Group According to *BRAF* Mutation Status

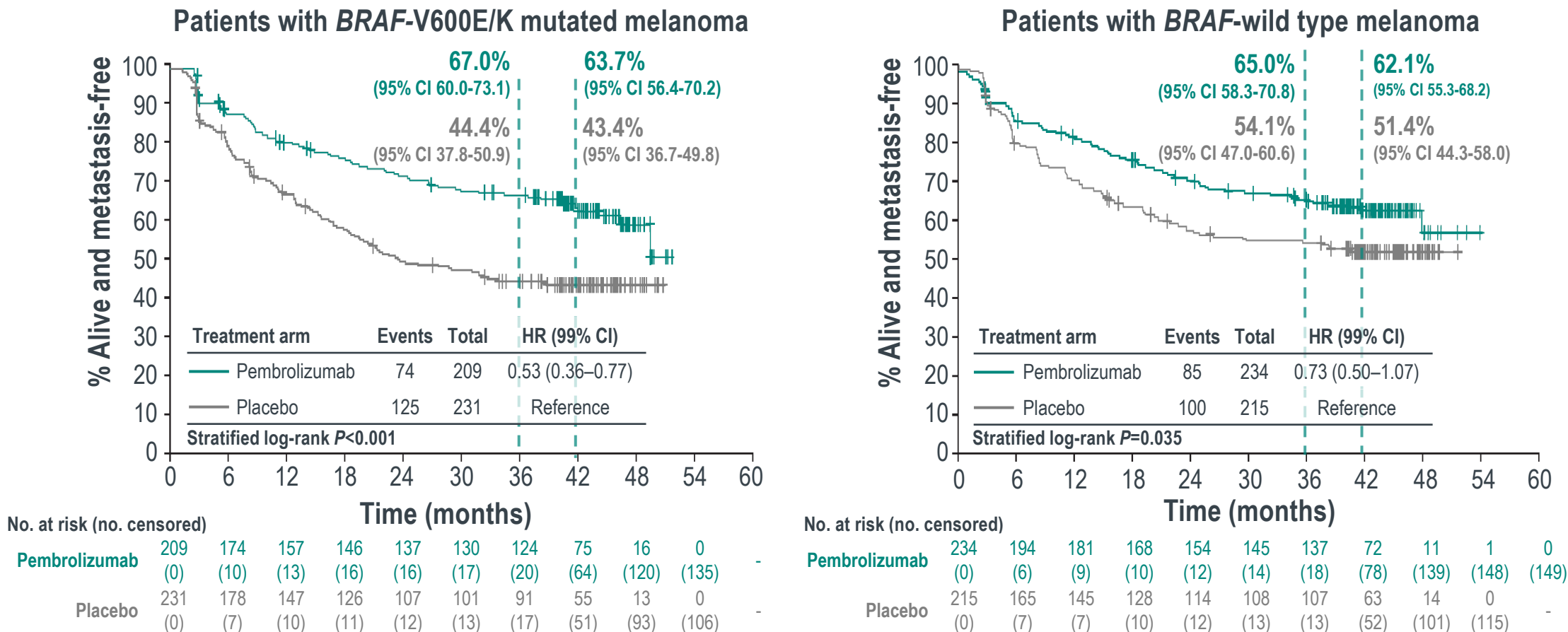
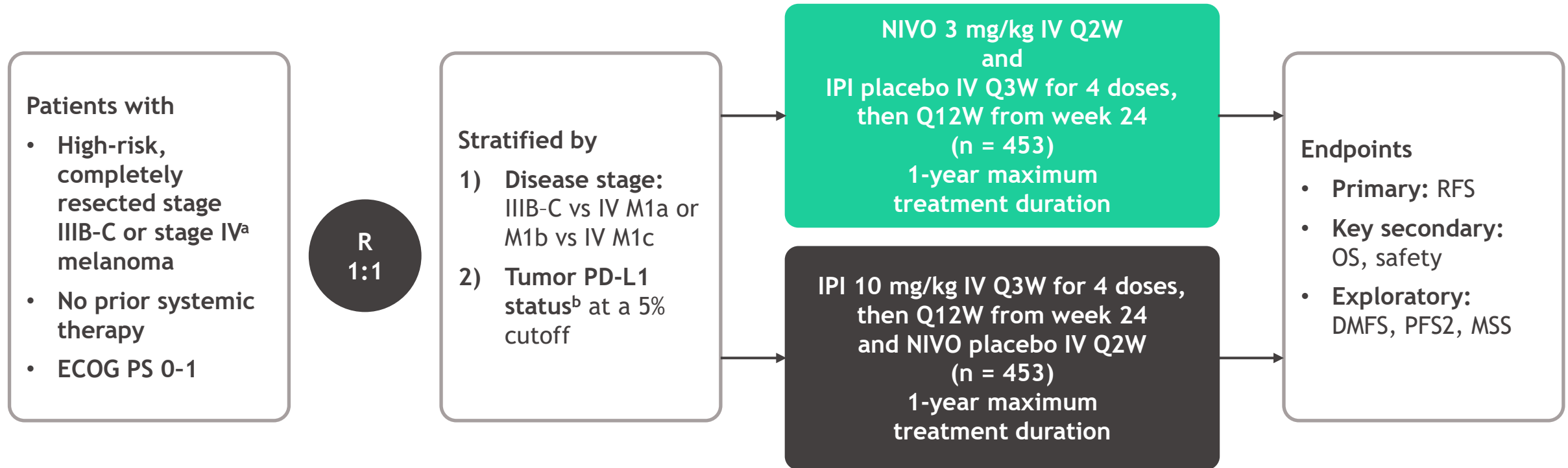


Figure adapted with permission from Lancet Publishing Group. Eggermont AMM, et al. *Lancet Oncol.* 2021;22:643-654 (supplementary appendix).

Median follow-up of 42.3 months (IQR 40.5-45.9); 42.2 months (40.2-45.6) in the pembrolizumab group and 42.5 months (40.6-46.0) in the placebo group. Data cutoff: April 3, 2020. The Cox model and the log-rank test were stratified by stage. Eggermont AMM, et al. *Lancet Oncol.* 2021;22:643-654 (supplementary appendix).

Figure 1. CheckMate 238 study design

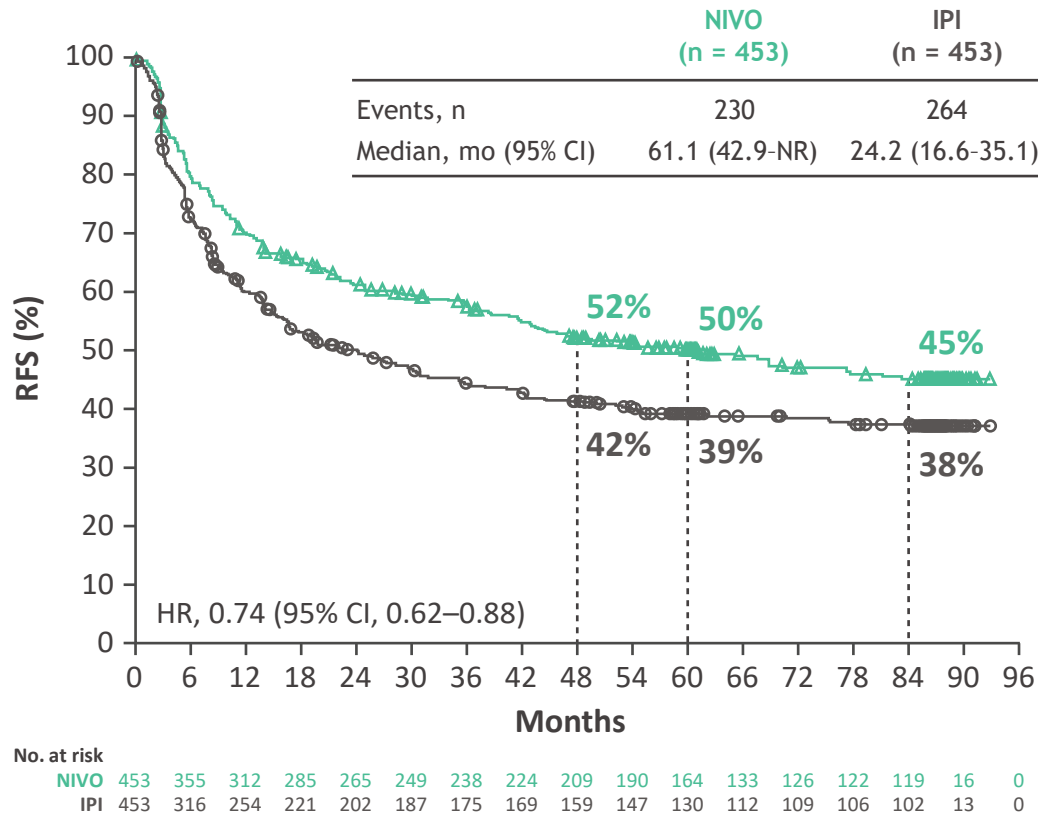


- 130 sites across 25 countries
 - Enrollment period: March 30, 2015, to November 30, 2015
 - Database lock Feb 24, 2023; minimum follow-up of 84 months

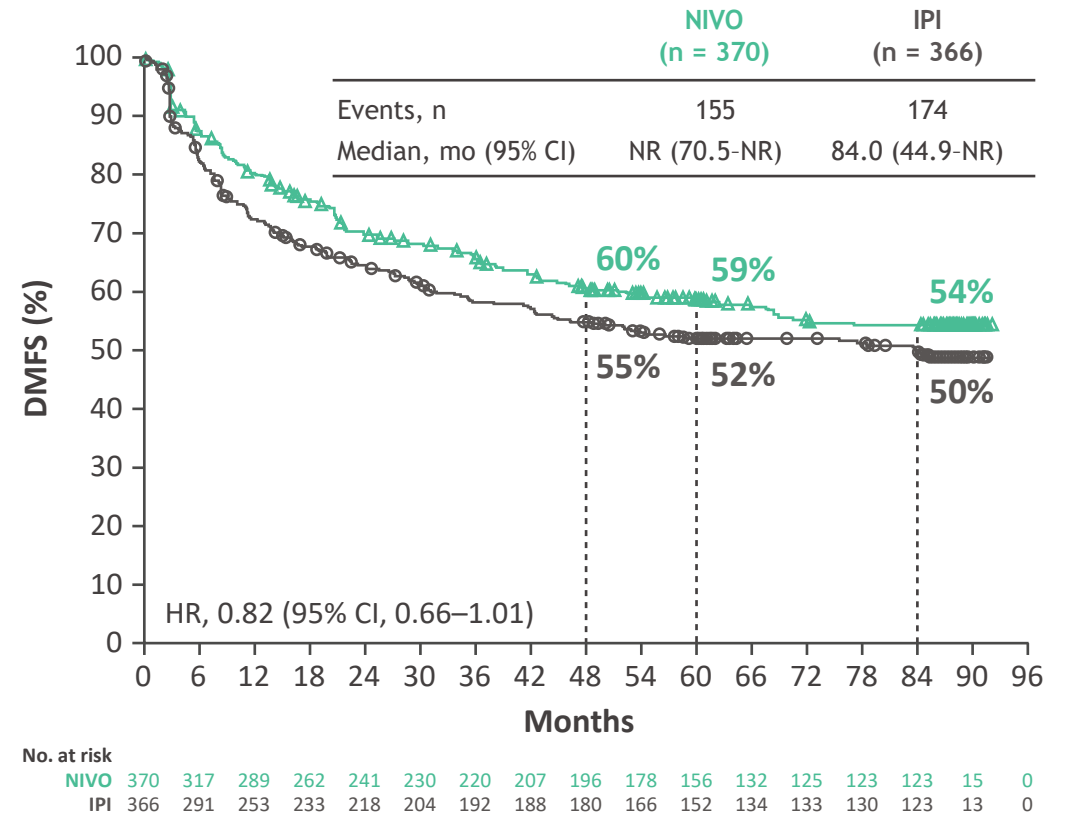
NCT02388906. ^aPer AJCC-7. ^bPD-L1 IHC 28-8 pharmDx assay. ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemical; IV, intravenously; M, meta Q2W, every 2 weeks; Q3W, every 3 weeks; Q12W, every 12 weeks; R, randomization.

Figure 2. RFS (A) and DMFS (B) at 7-year minimum follow-up

A. RFS in all patients



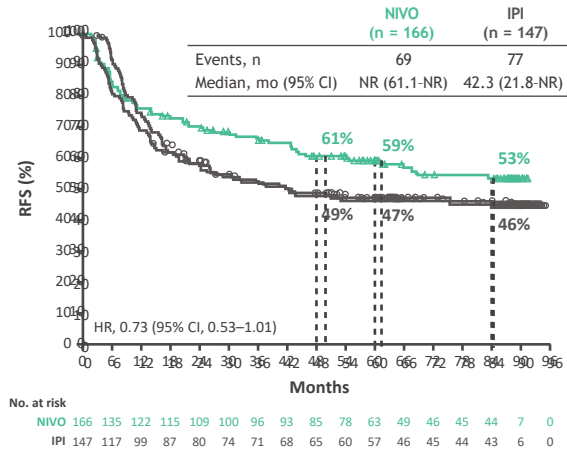
B. DMFS in all randomized stage III patients



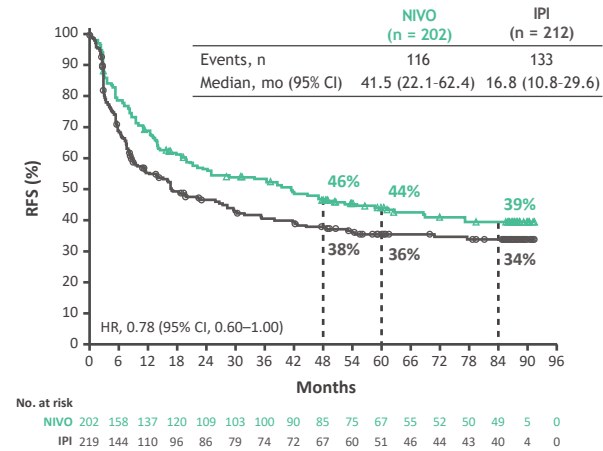
NR, not reached.

Figure 3. 7-year RFS update by disease stages IIIB and IIIC (A and B) and by *BRAF* mutation status (C and D)

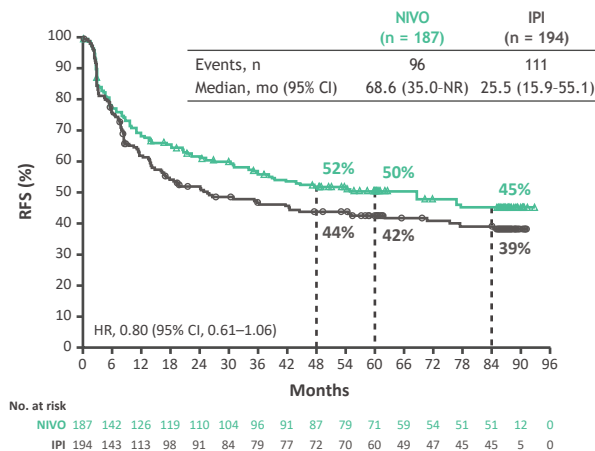
A. Stage IIIB



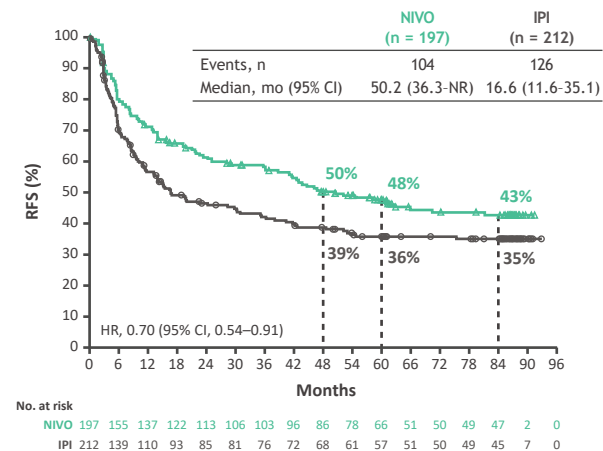
B. Stage IIIC



C. *BRAF* mutant



D. *BRAF* wild-type

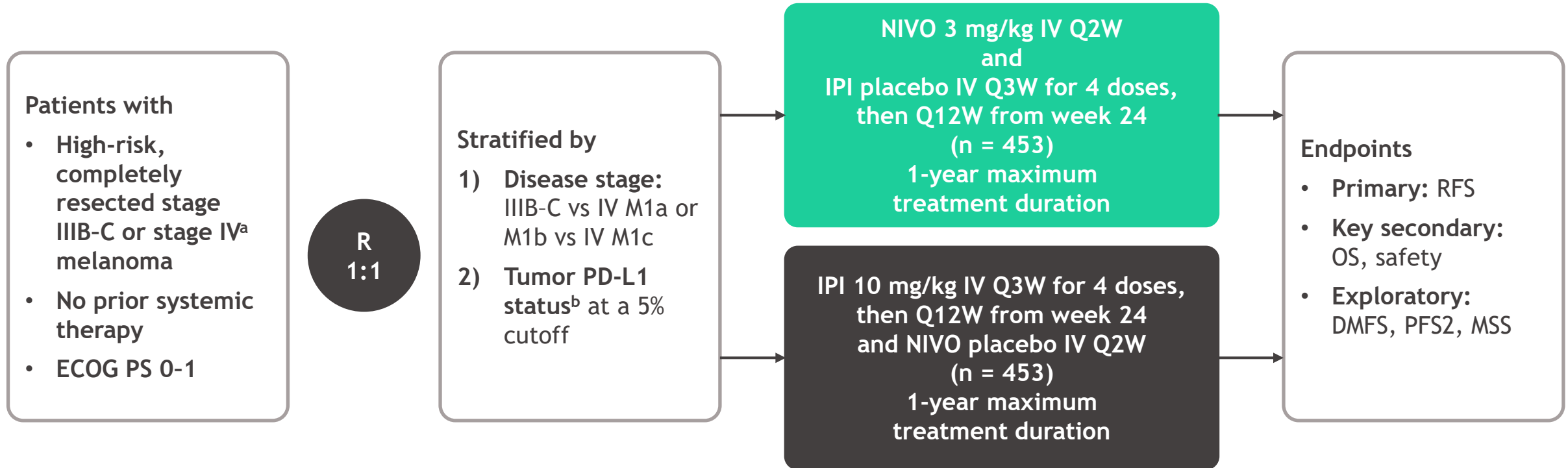


I pazienti con melanoma in stadio III radicalmente operato con mutazione BRAF V600 possono essere sottoposti a terapia adiuvante solo con Dabrafenib e Trametinib?

NO

In un paziente sottoposto all'asportazione di una metastasi a distanza da melanoma senza evidenza macroscopica di malattia (stadio IV NED), la terapia standard post-operatoria è Nivolumab-Ipilimumab?

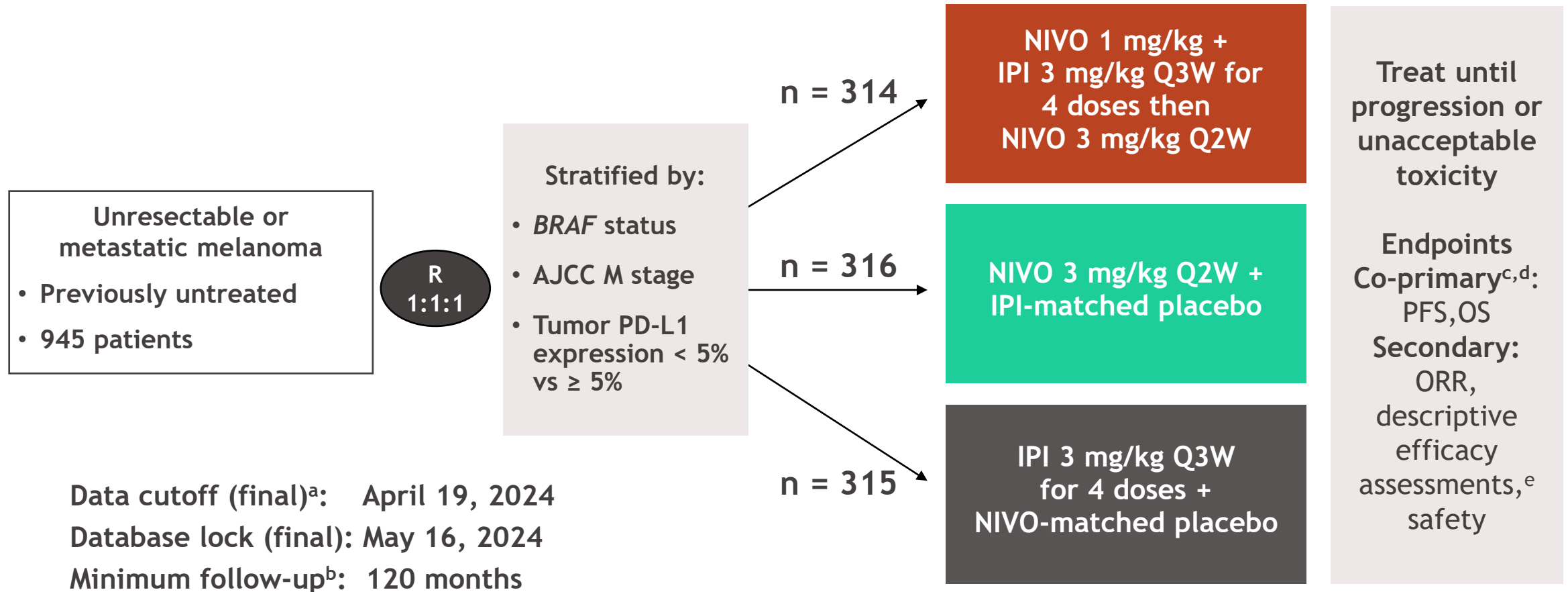
Figure 1. CheckMate 238 study design



- 130 sites across 25 countries
 - Enrollment period: March 30, 2015, to November 30, 2015
 - Database lock Feb 24, 2023; minimum follow-up of 84 months

NCT02388906. ^aPer AJCC-7. ^bPD-L1 IHC 28-8 pharmDx assay. ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemical; IV, intravenously; M, metastasis; Q2W, every 2 weeks; Q3W, every 3 weeks; Q12W, every 12 weeks; R, randomization.

CheckMate 067: study design and follow-up length



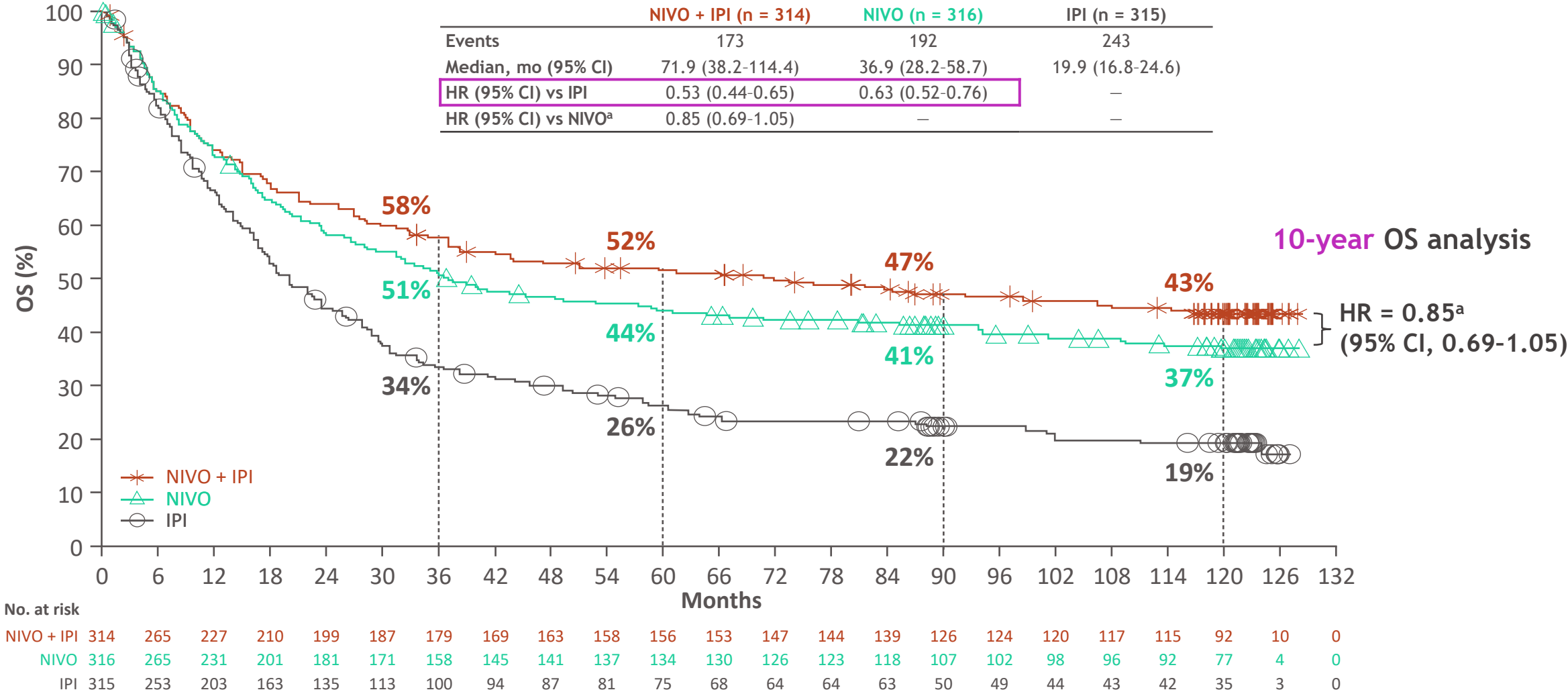
^aNo patient was being treated on study at the time of the final DBL. ^bFrom the date the last patient was randomized. ^cThe study was not powered for a comparison between NIVO + IPI and NIVO. ^dNIVO + IPI or NIVO alone vs IPI. ^eNIVO + IPI vs NIVO alone.

In un paziente sottoposto all'asportazione di una metastasi a distanza da melanoma senza evidenza macroscopica di malattia (stadio IV NED), la terapia standard post-operatoria è Nivolumab-Ipilimumab?

NO

Tra le opzioni di trattamento per i pazienti con melanoma metastatico PD-L1 negativo, può essere considerata la combinazione Nivolumab-Relatlimab?

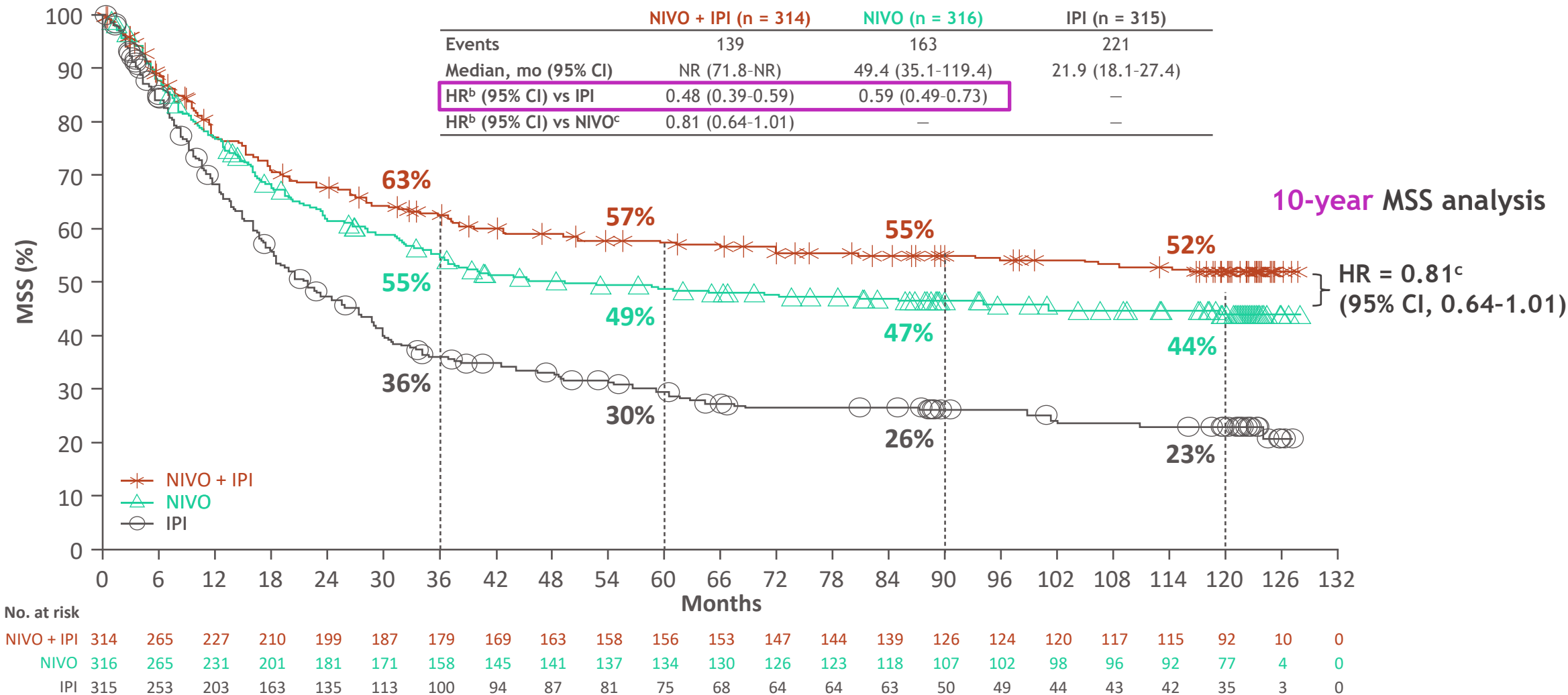
Overall survival



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

^aDescriptive comparison.

Melanoma-specific survival (MSS)^a

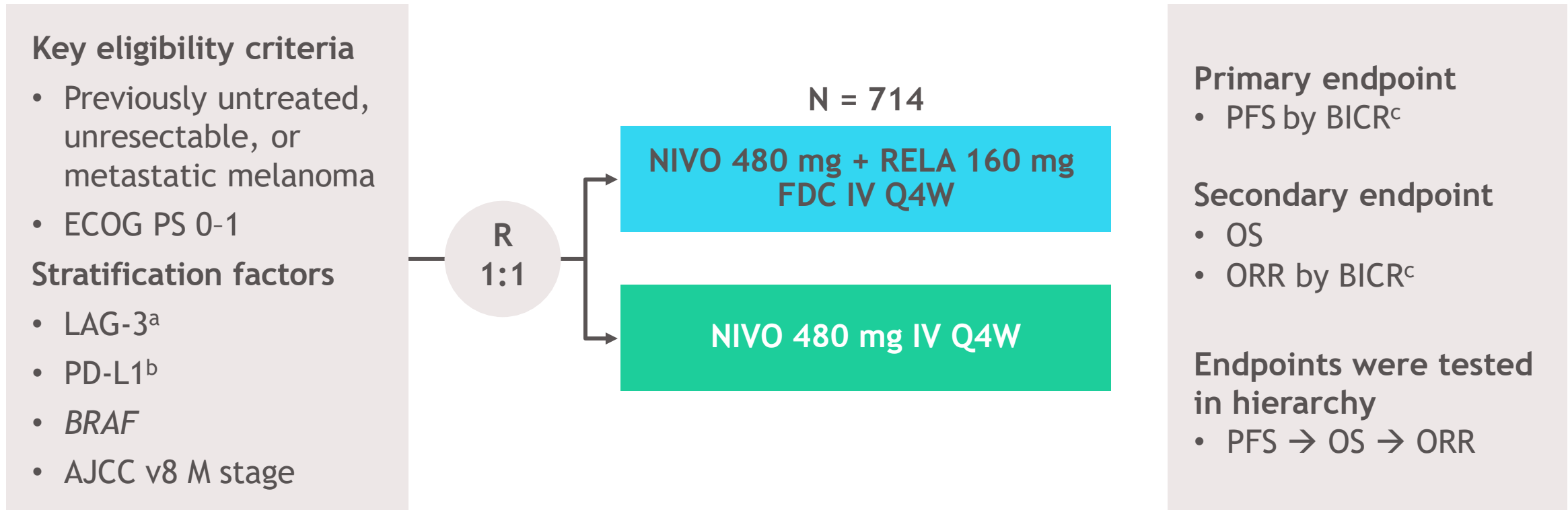


- After 10 years, median MSS was not reached (> 120 months) with NIVO + IPI and diverged from OS (52% vs 43%)
 - Results were consistent by BRAF mutation and PD-L1 expression status (Supplemental Figures S1 and S2)

^aIn 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. ^bUnstratified. ^cDescriptive comparison.

Study design

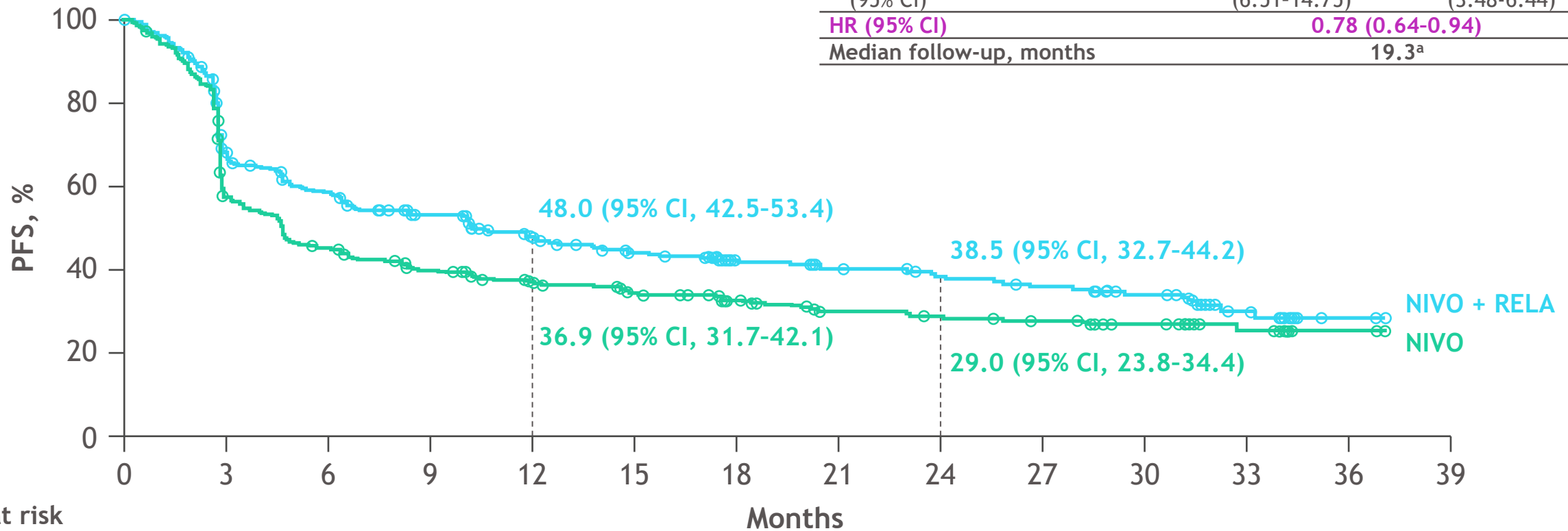
- **RELATIVITY-047** is a global, randomized, double-blind, gated, phase 2/3 study



^aLAG-3 expression on immune cells (1%) determined by analytically validated IHC assay (Labcorp, Burlington, NC, USA); ^bPD-L1 expression on tumor cells (1%) determined by validated Agilent Dako PD-L1 IHC 28-8 pharmDx test (Agilent, Santa Clara, CA, USA); ^cFirst tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. NCT03470922.

Primary endpoint: updated PFS by BICR

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median PFS, months (95% CI)	10.22 (6.51-14.75)	4.63 (3.48-6.44)
HR (95% CI)	0.78 (0.64-0.94)	
Median follow-up, months	19.3 ^a	



No. at risk

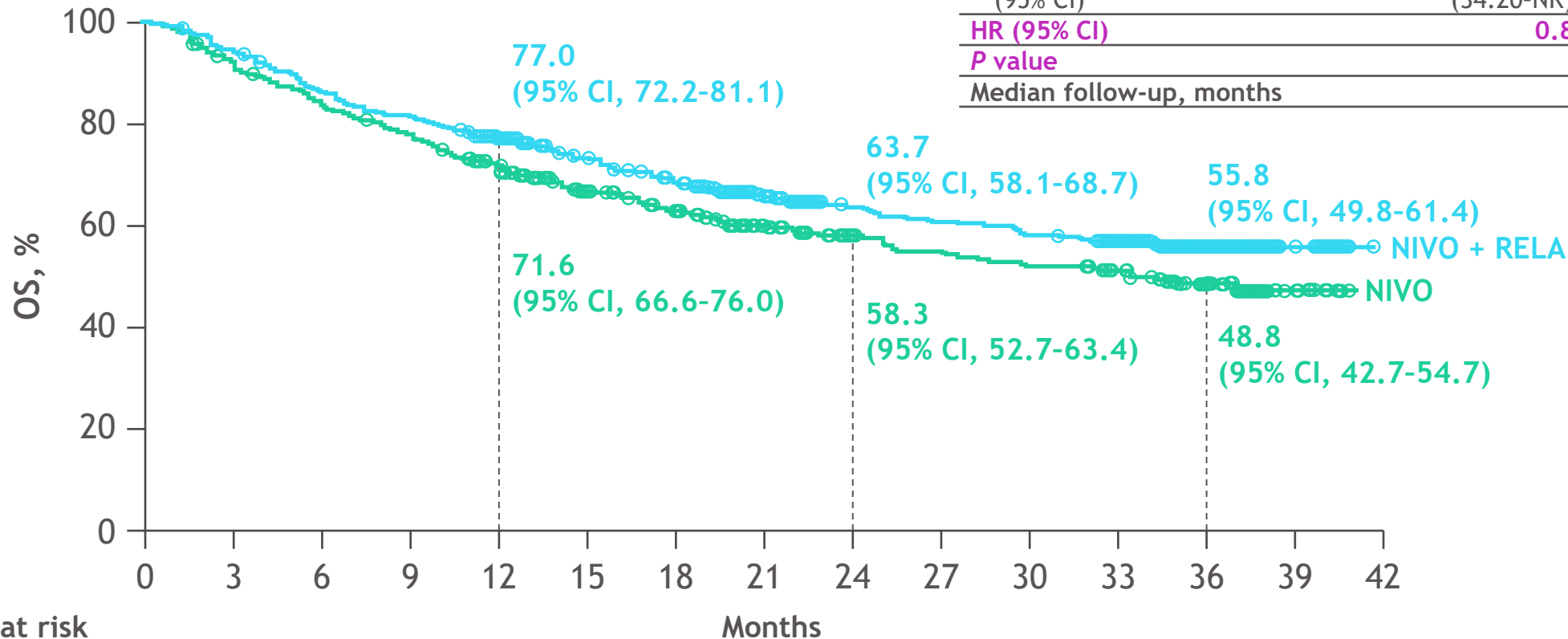
	0	3	6	9	12	15	18	21	24	27	30	33	36	39
NIVO + RELA	355	223	189	159	130	106	82	70	64	59	48	20	2	0
NIVO	359	192	150	124	98	82	67	52	49	45	33	15	3	0

Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF*, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: October 28, 2021.

^aMinimum potential follow-up (time from last patient randomized to last patient, last visit) was 8.7 months.

Secondary endpoint: overall survival

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median OS, months (95% CI)	NR (34.20-NR)	34.10 (25.23-NR)
HR (95% CI)	0.80 (0.64-1.01)	
P value	0.0593 ^a	
Median follow-up, months	19.3 ^b	



No. at risk	Months														
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
NIVO + RELA	355	334	305	287	261	227	203	167	145	139	133	109	50	9	0
NIVO	359	329	301	277	240	202	182	155	126	119	113	96	42	8	0

Statistical model for HR and P value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3, BRAF, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: October 28, 2021.

^aOS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75; ^bMinimum potential follow-up (time from last patient randomized to last patient last visit) was 8.7 months.

Tra le opzioni di trattamento per i pazienti con melanoma metastatico PD-L1 negativo, può essere considerata la combinazione Nivolumab-Relatlimab?

YES

THANK YOU FOR YOUR ATTENTION!