Avances en el Manejo de Melanoma

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Avances en el Manejo de Melanoma

- Adyuvancia E II – E III
- Neoadyuvancia
- Enfermedad avanzada

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Congratulations to James P. Allison & Tasuku Honjo

for winning
The 2018 Nobel Prize in
physiology or medicine

Immunotherapeutic Strategies in the Adjuvant Therapy Setting

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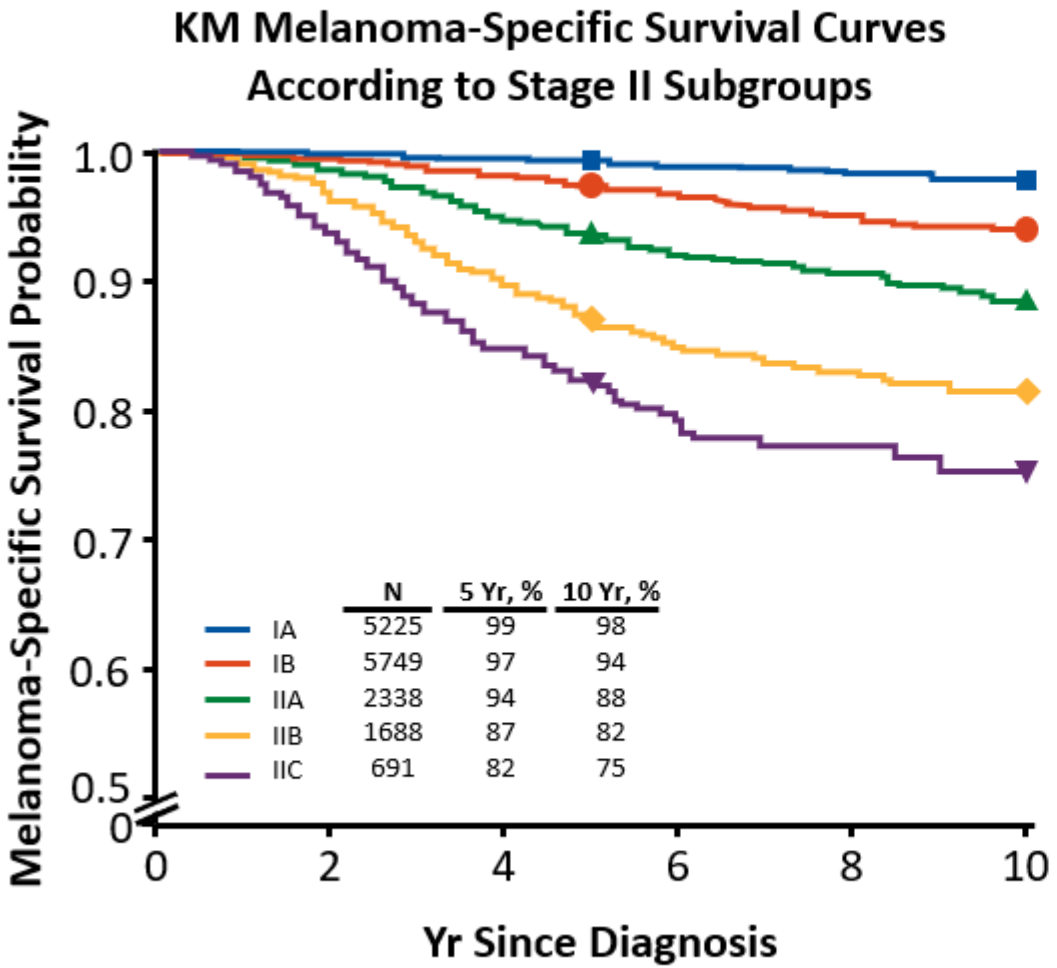
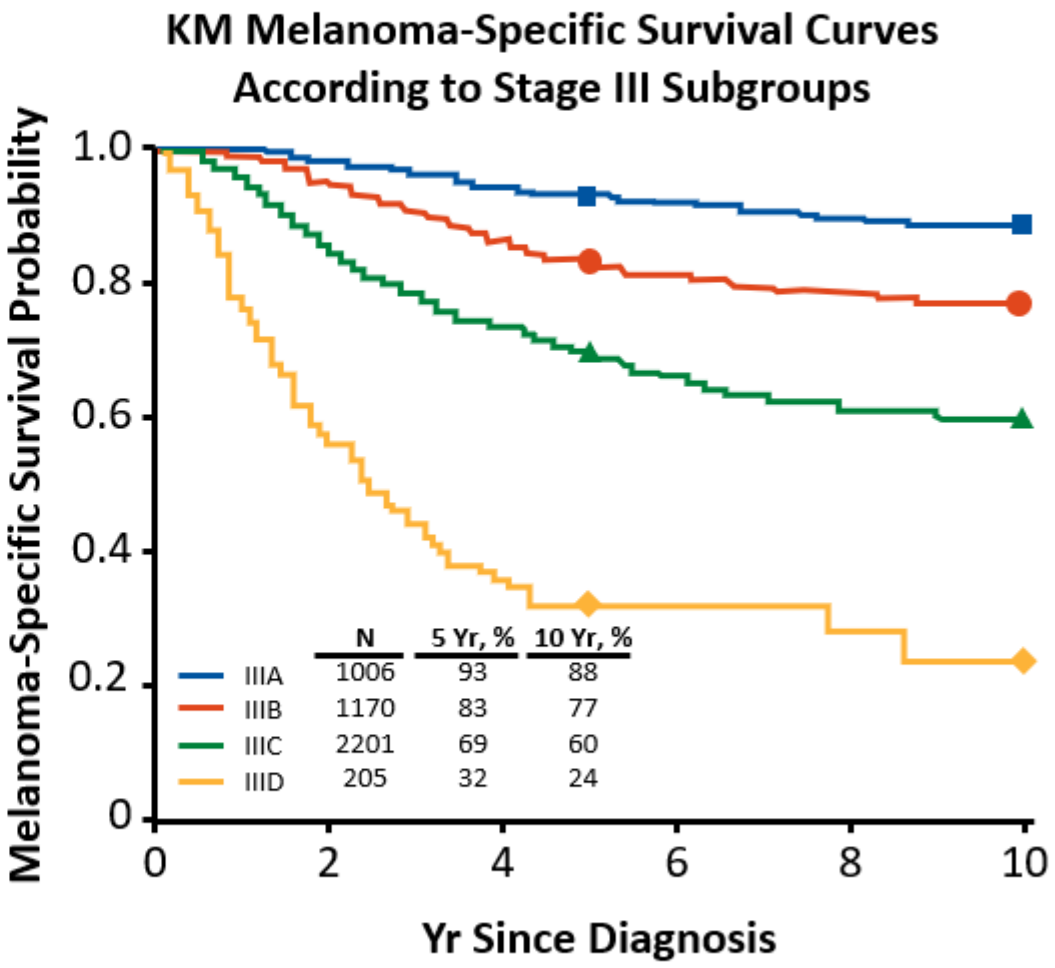
Melanoma-Specific Survival By Stage





Gershenwald. CA Cancer J Clin. 2017;67:472.

FDA-Approved Adjuvant Immunotherapy

Immunotherapy	Setting	Comparator	HR for 3-Yr RFS (95% CI)	HR for 3-Yr DMFS (95% CI)	Grade ≥3 TRAEs, %
Pembrolizumab[5,7,8]	IIB/C	Placebo	0.62 (0.49-0.79)	0.59 (0.44-0.79)	17

Immunotherapy	Setting	Comparator	HR for 1-Yr RFS (95% CI)	HR for 1-Yr DMFS (95% CI)	Grade ≥3 TRAEs, %
Nivolumab[2,9]	IIB/C	Ipilimumab	0.42 (0.30-0.59)	0.47 (0.30-0.72)	10.3

1. Larkin. Clin Cancer Res. 2023;29:3352. 2. Nivolumab PI. 3. Weber. NEJM. 2017;377:1824.
4. Eggermont. NEJM Evid. 2022;1. 5. Pembrolizumab PI. 6. Eggermont. JCO. 2020;38:3925.
7. Luke. ASCO 2023. Abstr LBA9505. 8. Long. Lancet Oncol. 2022;23:1378. 9. Kirkwood. Nature Med. 2023;29:2835.

FDA-Approved Treatments: Adjuvant Treatment for Stage III Melanoma

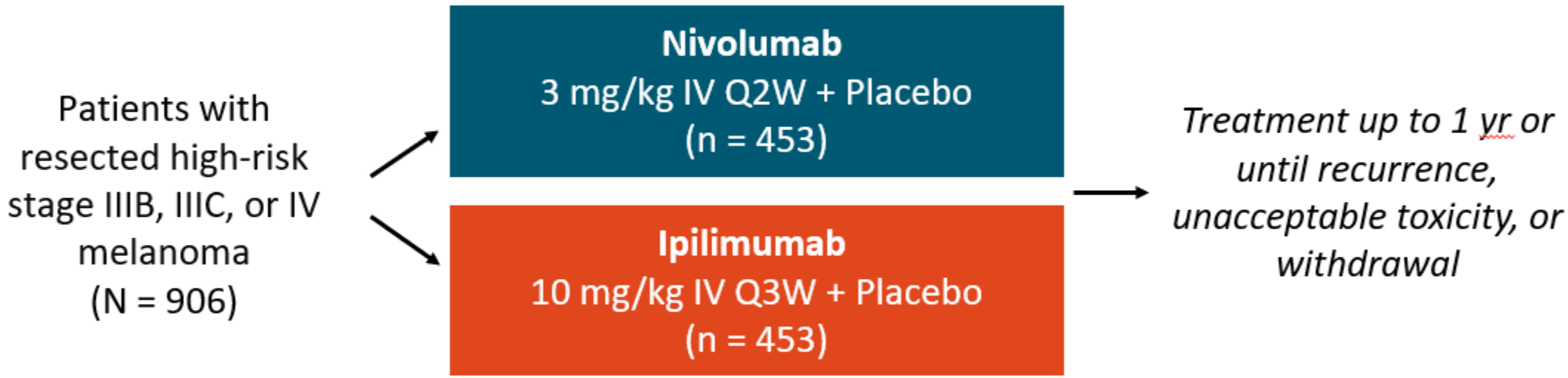
Immunotherapy	FDA Approval	Comparator	HR for 5-Yr RFS (95% CI)	HR for 5-Yr DMFS (95% CI)	Grade ≥3 TRAEs, %
Nivolumab[1]	2017[2]	Ipilimumab	0.72 (0.60-0.86)	0.79 (0.63-0.99)	14.4[3]
Pembrolizumab[4]	2019[5]	Placebo	0.61 (0.51-0.72)	0.62 (0.52-0.75)	14.5[6]

Targeted Therapy	FDA Approval	Comparator	HR for 5-Yr RFS (95% CI)	HR for 5-Yr DMFS (95% CI)	Any Cause Grade ≥3 AEs, %
Dabrafenib + trametinib[7]	2018[8]	Placebo	0.51 (0.42-0.61)	0.55 (0.44-0.70)	41[9]

1. Larkin. Clin Cancer Res. 2023;29:3352. 2. Nivolumab PI. 3. Weber. NEJM. 2017;377:1824.
4. Eggermont. NEJM Evid. 2022;1. 5. Pembrolizumab PI. 6. Eggermont. JCO. 2020;38:3925.
7. Dummer. NEJM. 2020;383:1139. 8. Trametinib PI. 9. Long. NEJM. 2017;377:1813.

CheckMate 238: Adjuvant Nivolumab vs Ipilimumab in Stage III-IV High-Risk Melanoma

- Randomized, double-blind phase III trial



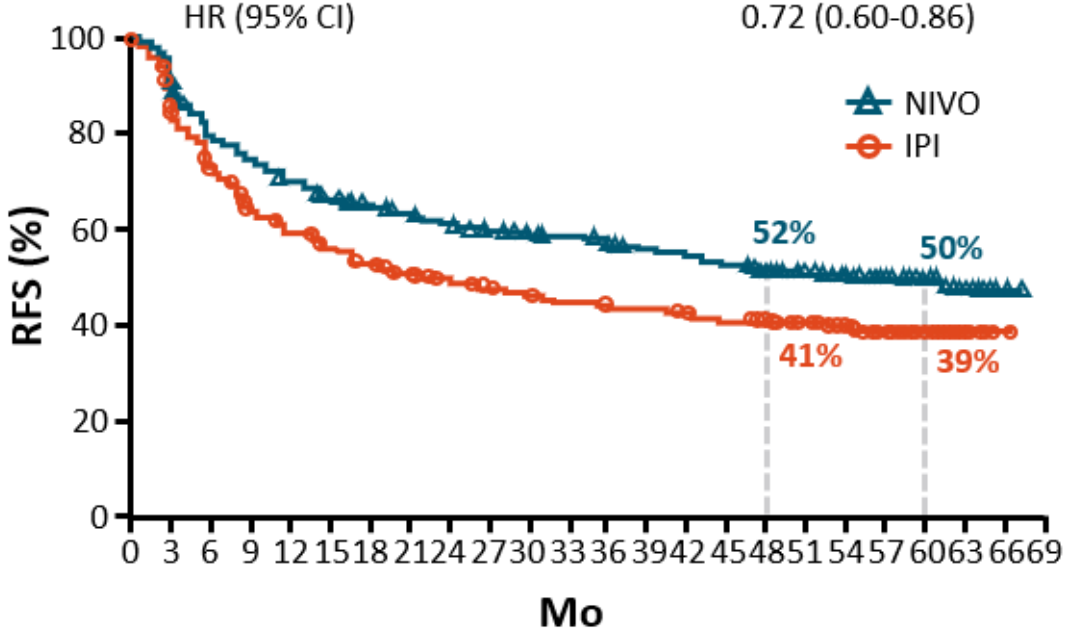
- **Primary endpoint**: RFS in ITT population
- **Secondary endpoints**: OS, safety, RFS by PD-L1 status, QoL
- **Exploratory endpoint**: DMFS

Larkin. Clin Cancer Res. 2023;[Epub]. Weber. NEJM. 2017;377:1824.

CheckMate 238: 5-Yr RFS and OS

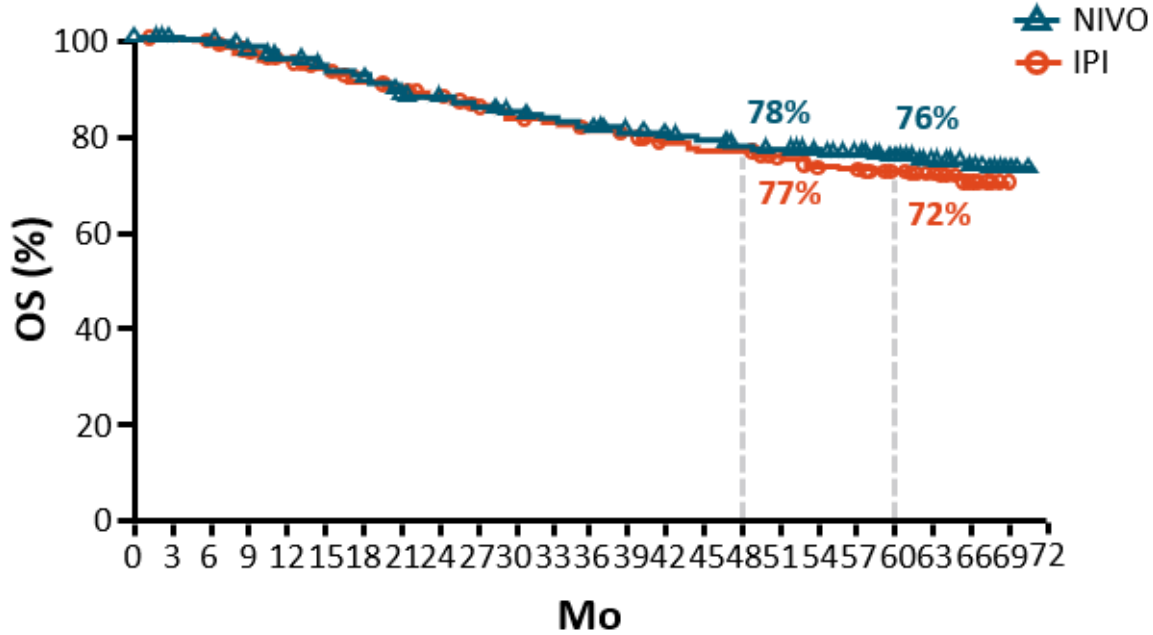
RFS

	Nivo (n = 453)	Ipi (n = 453)
Events, n	218	257
Median RFS, mo (95% CI)	61.0 (42.5-NR)	24.1 (16.6-35.1)
HR (95% CI)	0.72 (0.60-0.86)	



OS

	Nivo (n = 453)	Ipi (n = 453)
Events, n	108	120
Median OS, mo (95% CI)	NR	NR
HR (95% CI)	0.86 (0.66-1.12)	



KEYNOTE-054: Adjuvant Pembrolizumab vs Placebo for Stage III Melanoma

- Randomized, double-blind phase III study

Patients with resected high-risk stage IIIA, B, C melanoma (N = 1019)

Pembrolizumab
200 mg IV Q3W*
(n = 514)

Placebo
IV Q3W*
(n = 505)

Treatment administered 18 doses (~1 yr) or until recurrence, unacceptable toxicity, or withdrawal

*Patients with recurrence eligible for crossover or repeat treatment with pembrolizumab.

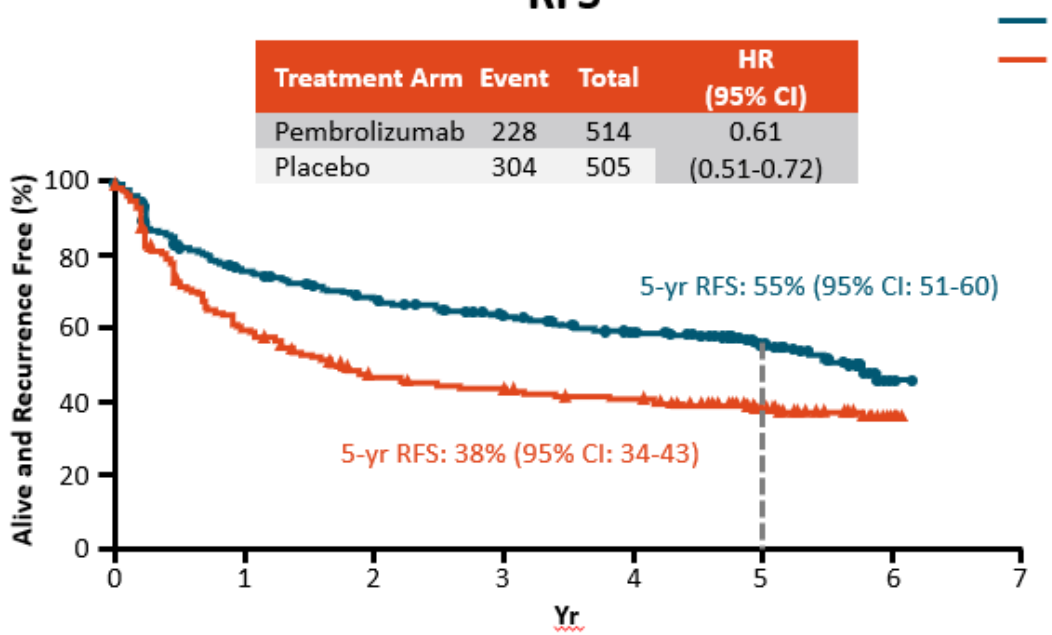
- **Coprimary endpoints:** RFS in ITT population, RFS in PD-L1+ subgroup
- **Secondary endpoints:** DMFS, OS, safety, QoL

Eggermont. NEJM. 2018;378:1789. Eggermont. NEJM Evid. 2022;1.

KEYNOTE-054: 5-Yr RFS and DMFS

RFS

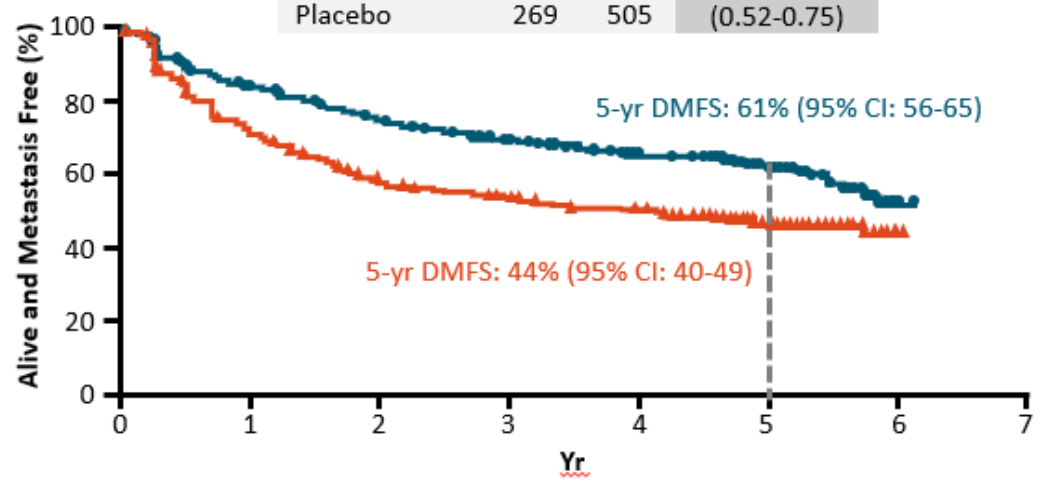
Treatment Arm	Event	Total	HR (95% CI)
Pembrolizumab	228	514	0.61
Placebo	304	505	(0.51-0.72)



Patients at Risk, n								
Pembrolizumab	514	377	336	305	272	92	4	0
Placebo	505	297	225	208	193	70	5	0

DMFS

Treatment Arm	Event	Total	HR (95% CI)
Pembrolizumab	201	514	0.62
Placebo	269	505	(0.52-0.75)

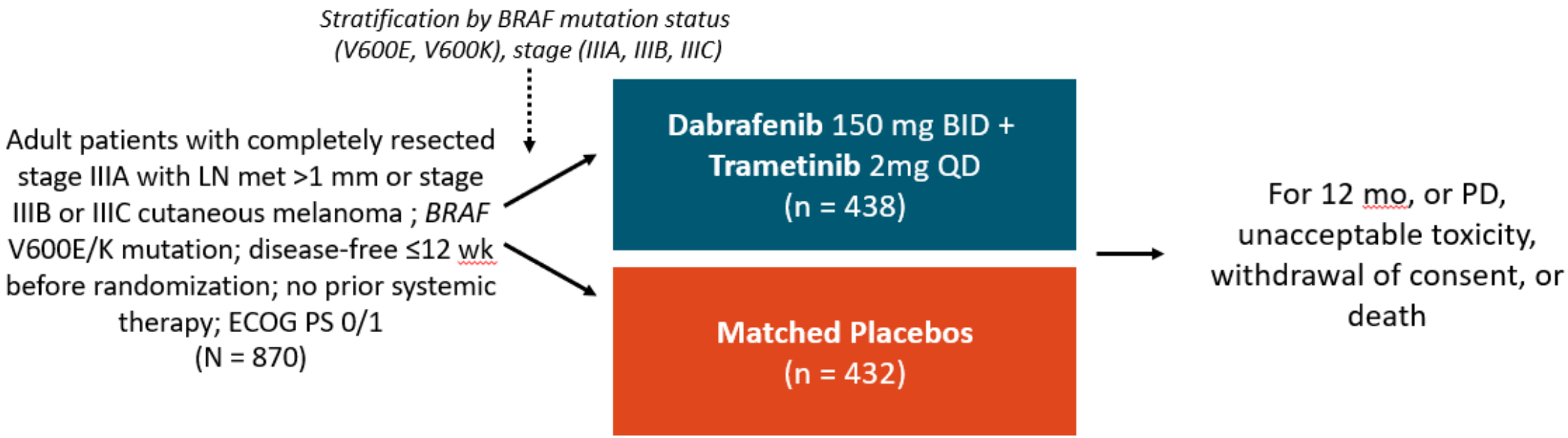


Patients at Risk, n								
Pembrolizumab	514	409	357	320	288	99	5	0
Placebo	505	341	266	239	220	84	5	0

Eggermont. NEJM Evid. 2022;1.

COMBI-AD: Adjuvant Dabrafenib/Trametinib vs Placebo in *BRAF* V600E/K–Mutant Melanoma

- Multicenter, randomized, double-blind, placebo-controlled phase III trial



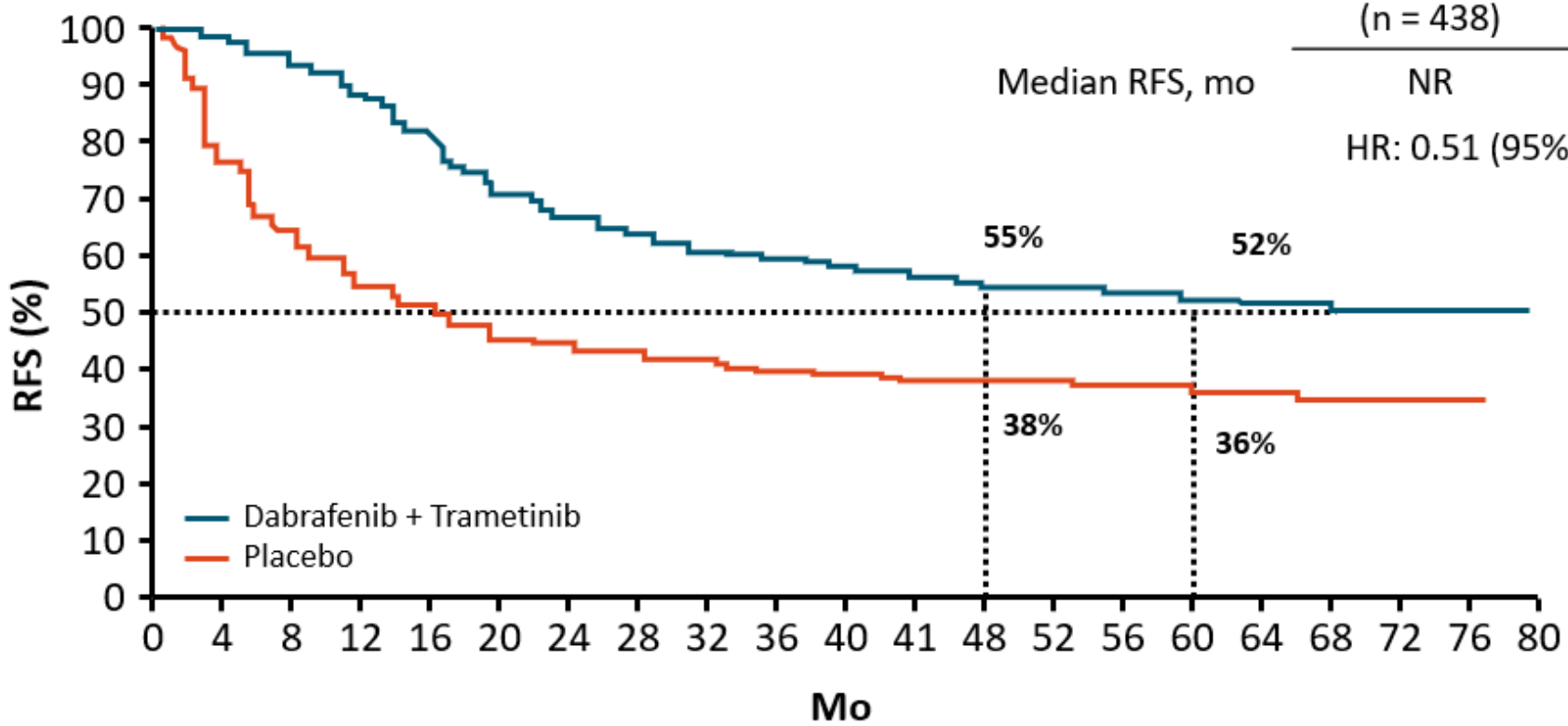
- **Primary endpoint**: RFS
- **Secondary endpoints**: OS, DMFS, FFR, safety

Dummer. NEJM. 2020;383:1139.

Phase III COMBI-AD Adjuvant Dabrafenib/Trametinib vs Placebo: 5-Yr RFS

	D + T (n = 438)	Placebo (n = 432)
Median RFS, mo	NR	16.6

HR: 0.51 (95% CI: 0.42-0.61)

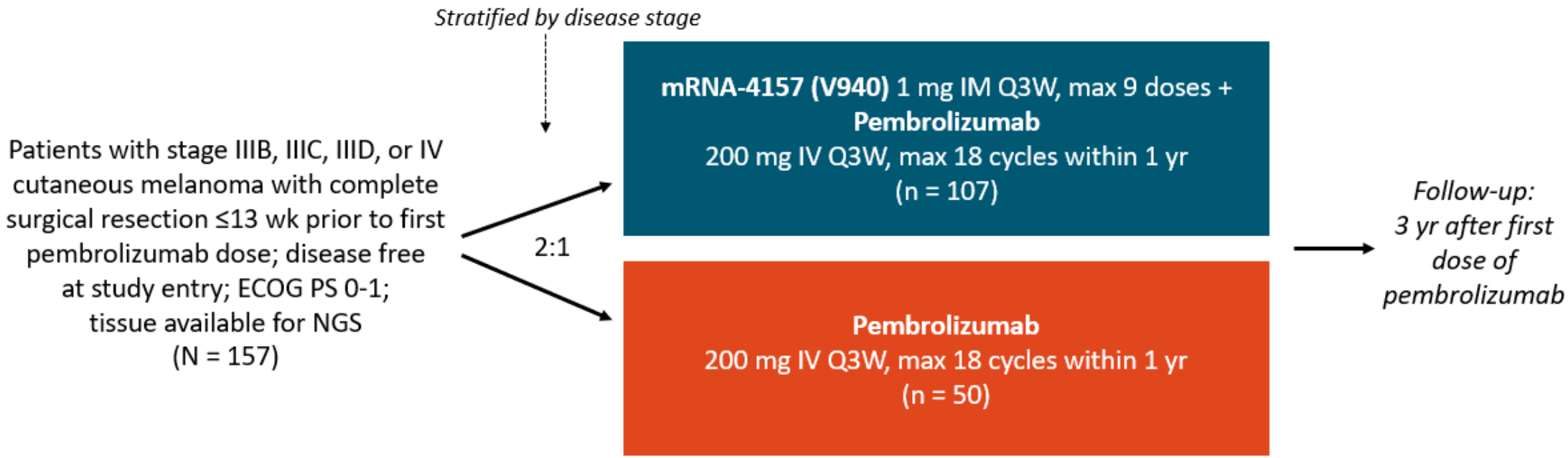


Patients at Risk, n

D + T	438	405	381	354	324	281	262	249	236	229	221	213	204	199	176	133	92	45	17	6	0
Placebo	432	322	263	219	199	178	168	164	157	147	143	139	136	133	121	99	69	35	13	1	0

KEYNOTE-942: Adjuvant Therapy With a Personalized Neoantigen Vaccine + Pembrolizumab vs Pembrolizumab

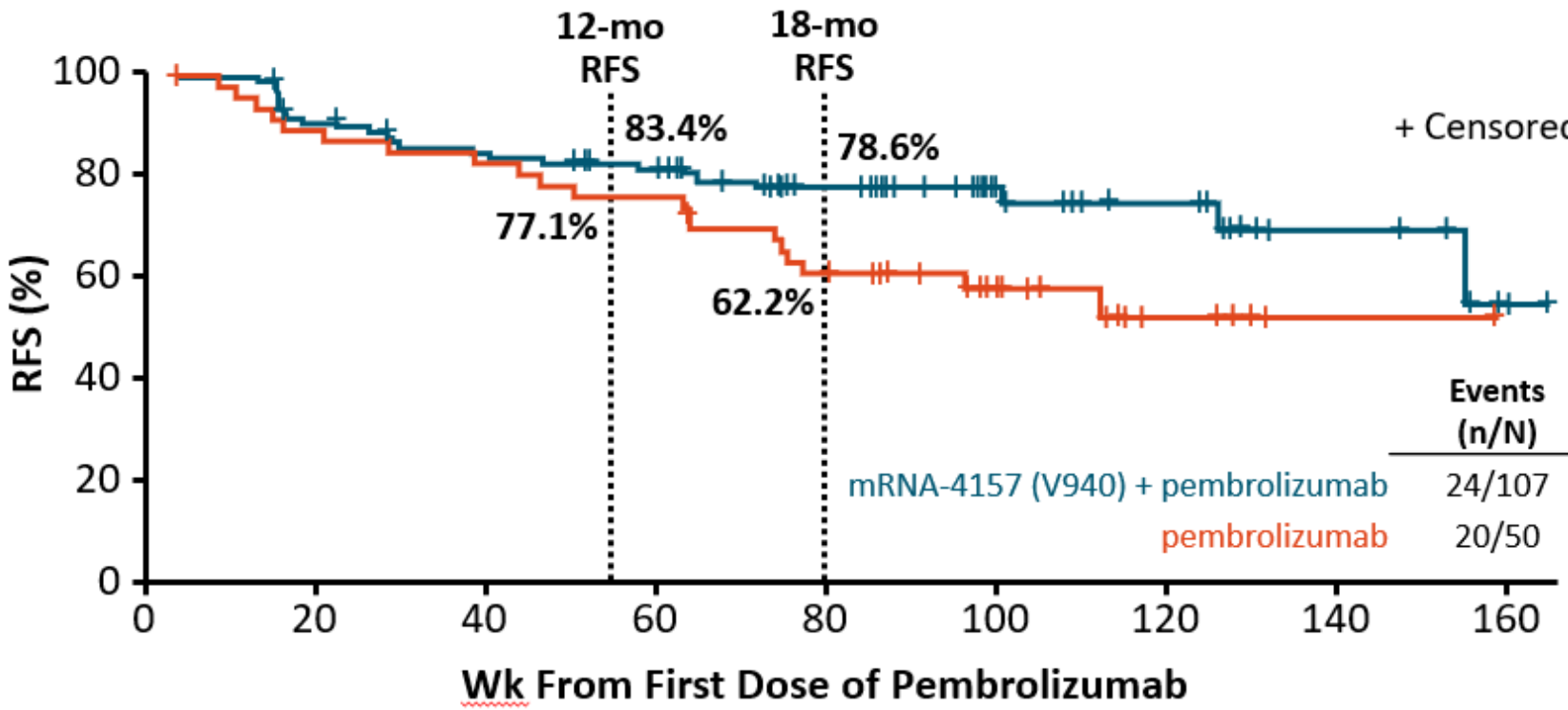
- Randomized, open-label phase II trial



- **Primary endpoint:** Investigator assessed RFS
- **Secondary endpoints:** DMFS, safety, tolerability

Khattak. AACR 2023. Abstr CT001. Khattak. ASCO 2023. Abstr LBA9503.

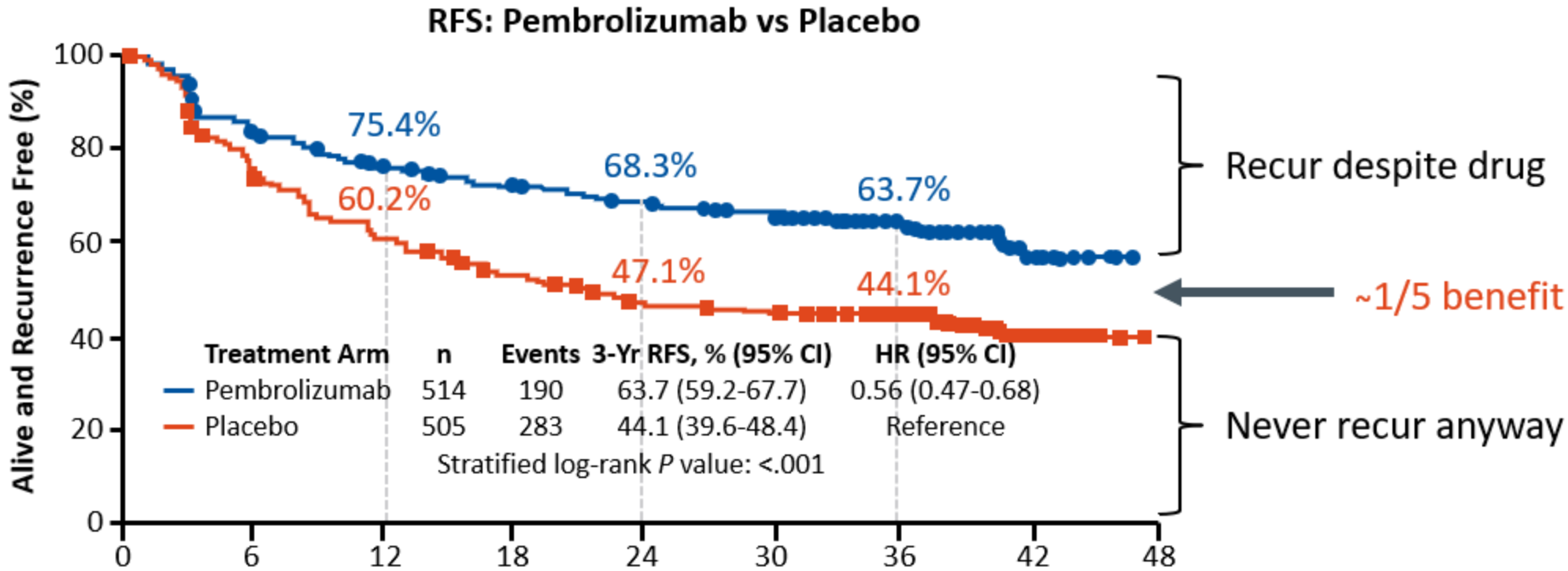
mRNA-4157-P201/KEYNOTE-942: RFS



	Events (n/N)	HR (95% CI)
mRNA-4157 (V940) + pembrolizumab	24/107	0.561 (0.309-1.017)
pembrolizumab	20/50	*P* = .0266

Patients at Risk, n									
mRNA-4157 (v940) + pembrolizumab	107	92	85	73	49	24	20	8	1
Pembrolizumab	50	42	40	37	28	13	6	1	0

Adjuvant Therapy for Stage III: Unmet Needs



- Risk of toxicity
- 1 yr of drug therapy ($$$)
- Regular clinic visits, infusions
- No proven impact on overall survival

Menzies. ASCO 2021 Discussion. Eggermont. JCO. 2020;33:3925.

Immunotherapeutic Strategies in the Neoadjuvant Therapy Setting

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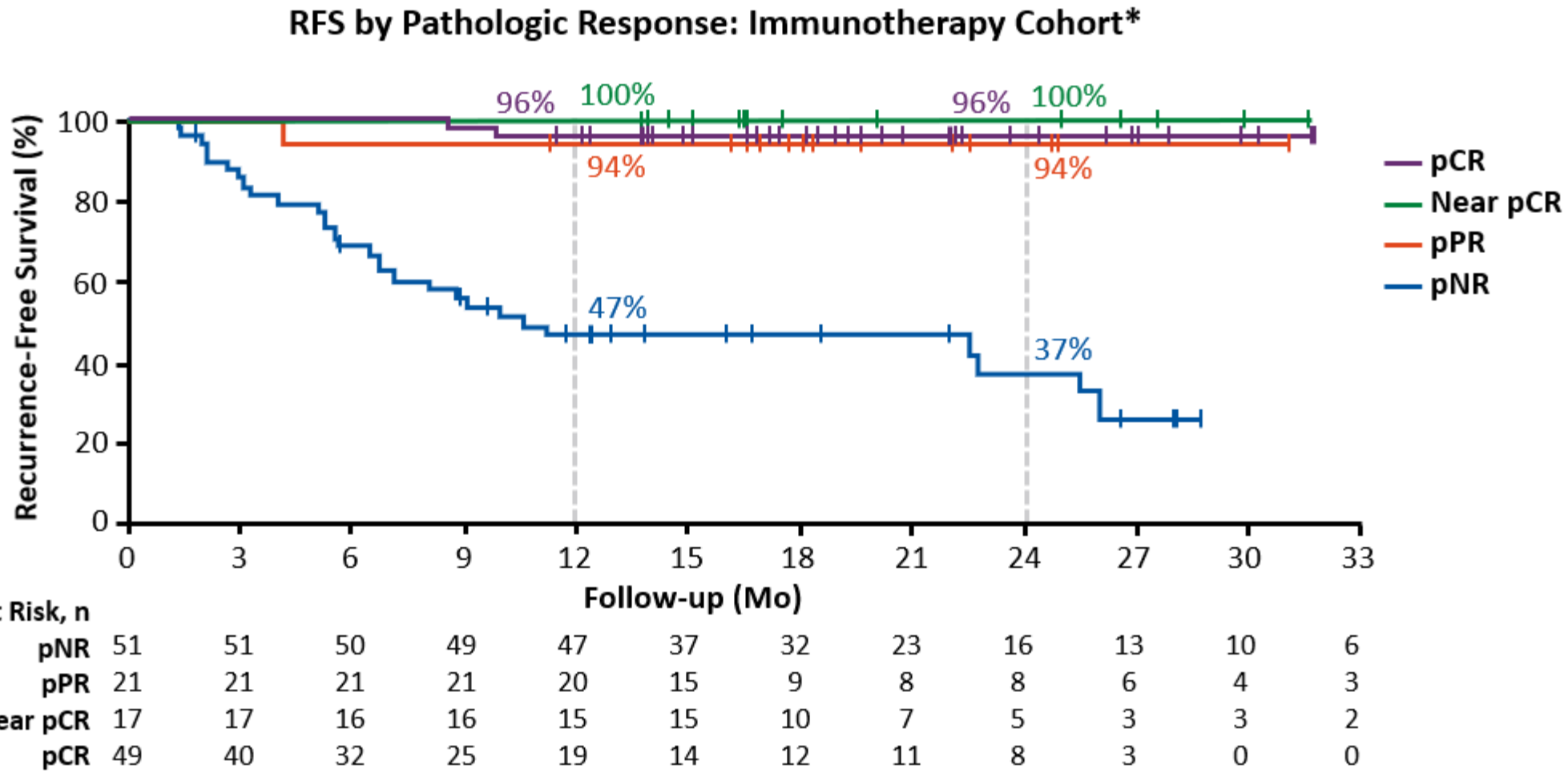
Prognostic Value of Pathologic Response



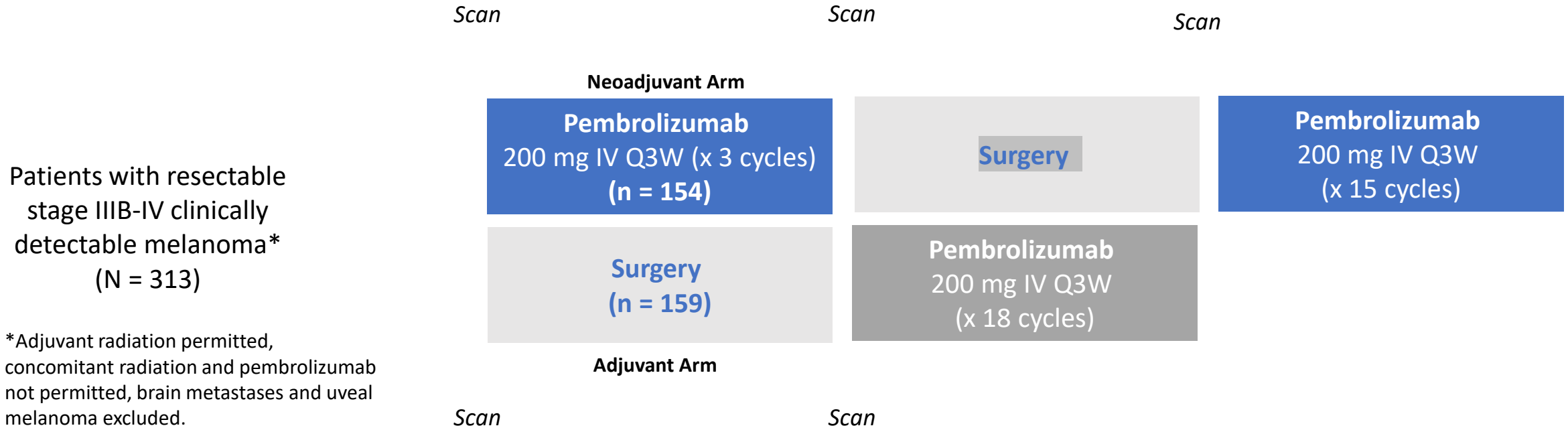
Patients at Risk, n												
pNR	51	51	50	49	47	37	32	23	16	13	10	6
pPR	21	21	21	21	20	15	9	8	8	6	4	3
Near pCR	17	17	16	16	15	15	10	7	5	3	3	2
pCR	49	40	32	25	19	14	12	11	8	3	0	0

*N = 141; n = 37 received anti–PD-1 monotherapy and n = 104 received ipilimumab/nivolumab; n = 138 with available pathologic data.

Menzies. Nature. 2021;27:301.

SWOG S1801: Adjuvant Pembrolizumab ± Neoadjuvant Pembrolizumab in Resectable Stage III-IV Melanoma

- Multicenter, randomized, open-label phase II study

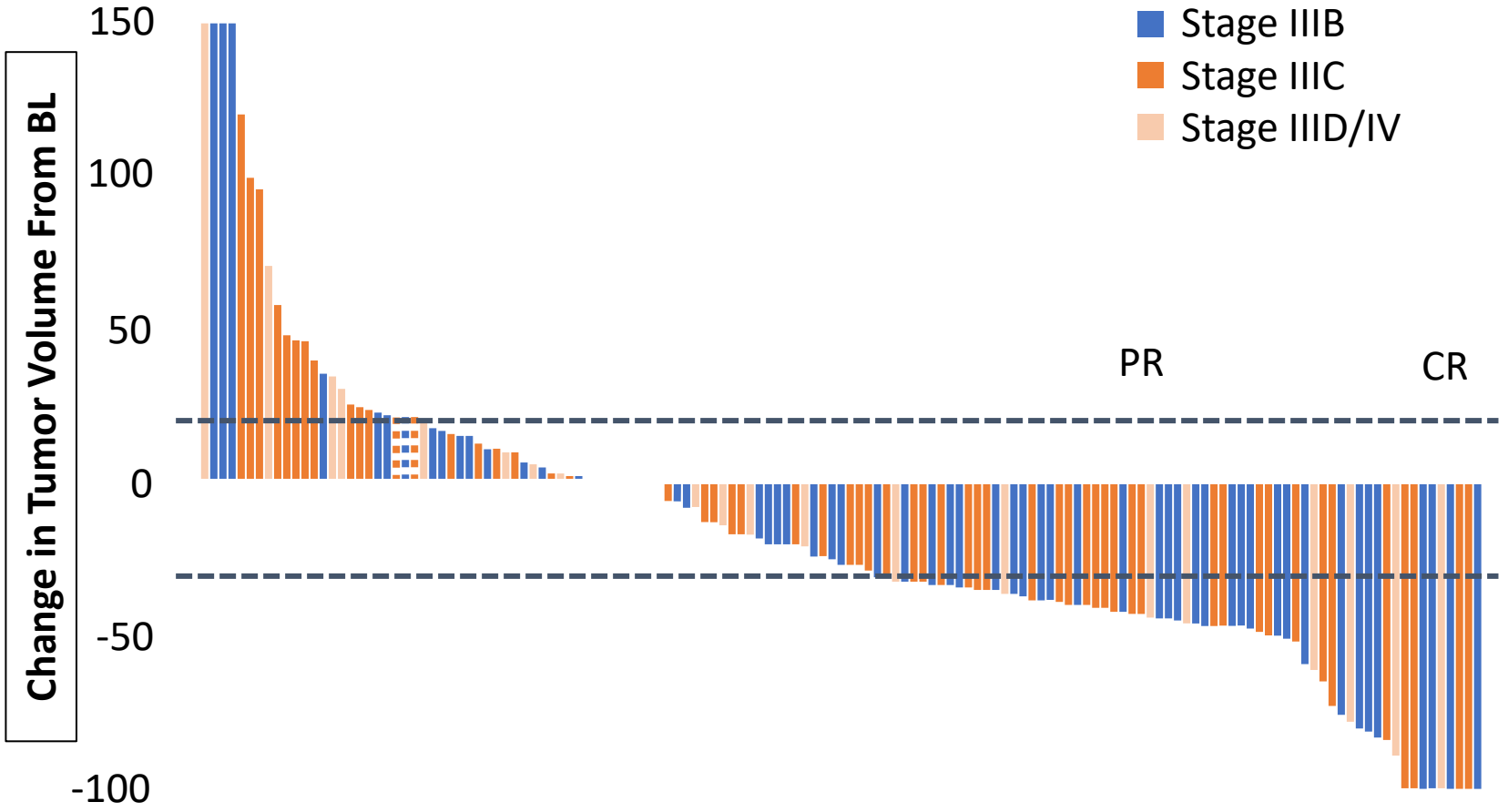


*Adjuvant radiation permitted, concomitant radiation and pembrolizumab not permitted, brain metastases and uveal melanoma excluded.

- **Primary endpoint:** EFS (time from randomization to first of: progression or toxicity preventing surgery; no adjuvant therapy within 84 days of surgery; postsurgery melanoma recurrence; death)
- **Secondary endpoints:** OS, safety

Patel. NEJM. 2023;388:813.

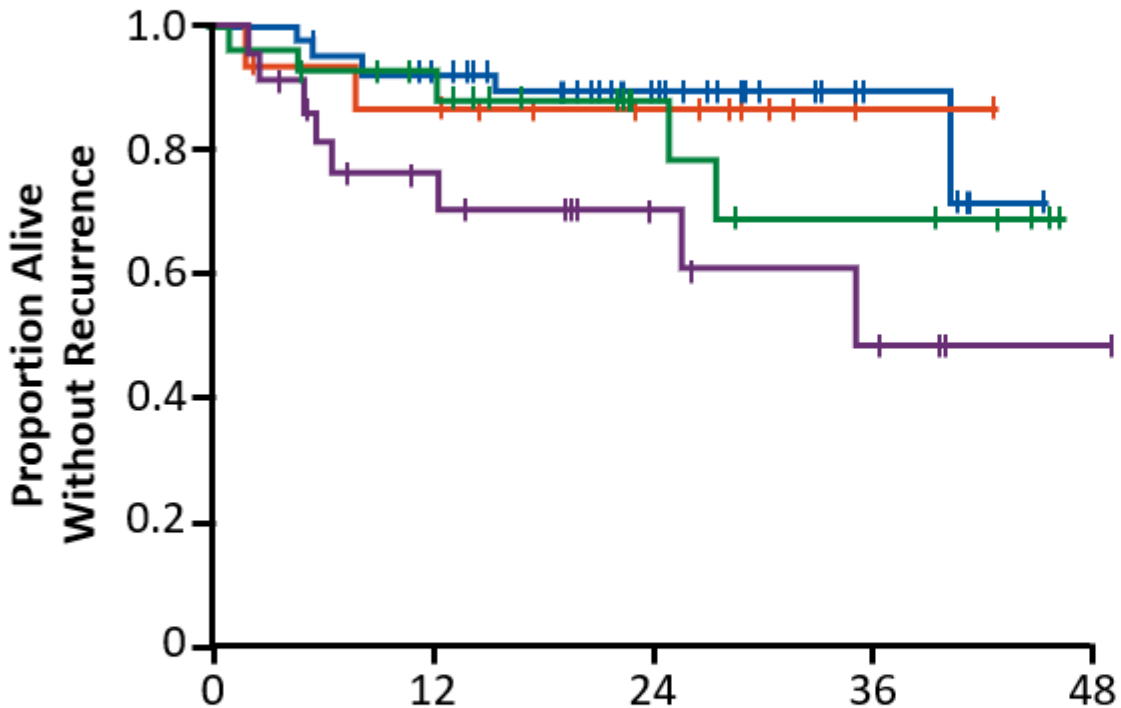
SWOG S1801: Radiographic Response Prior to Surgery



- 12 participants unable to undergo surgical resection due to PD
- 1 patient with CR refused surgery
- On local review:
  - 21% of patients with submitted pathology report achieved a pCR

Patel. NEJM. 2023;388:813.

SWOG S1801: RFS by Pathologic Response

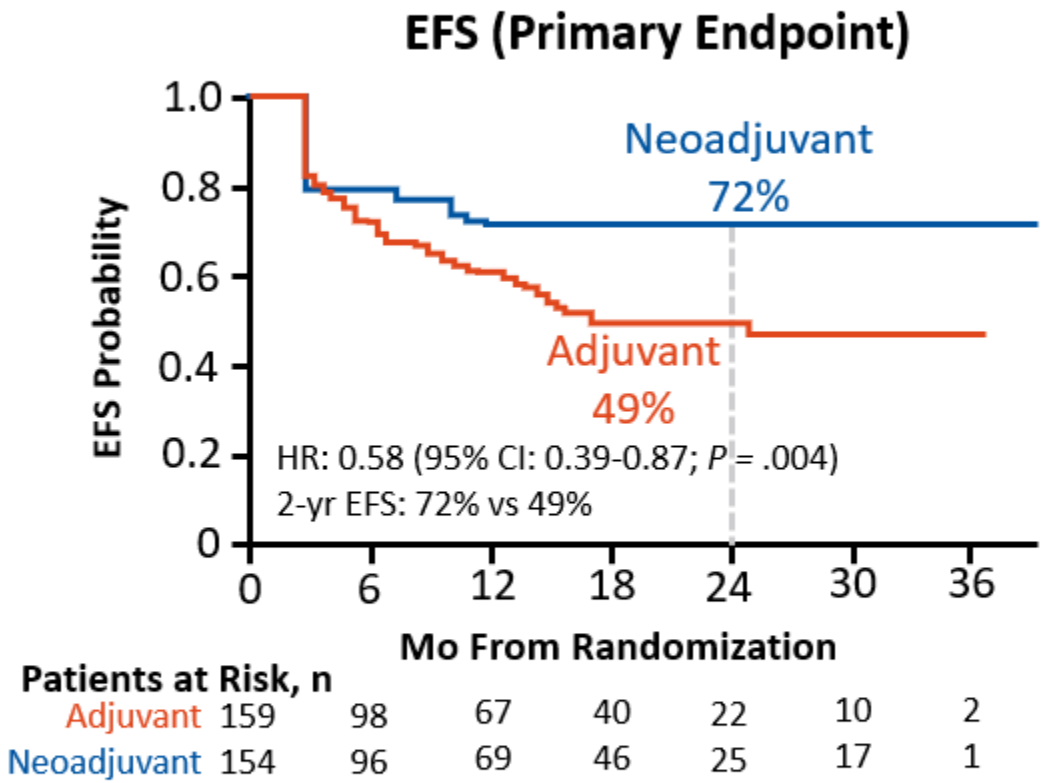


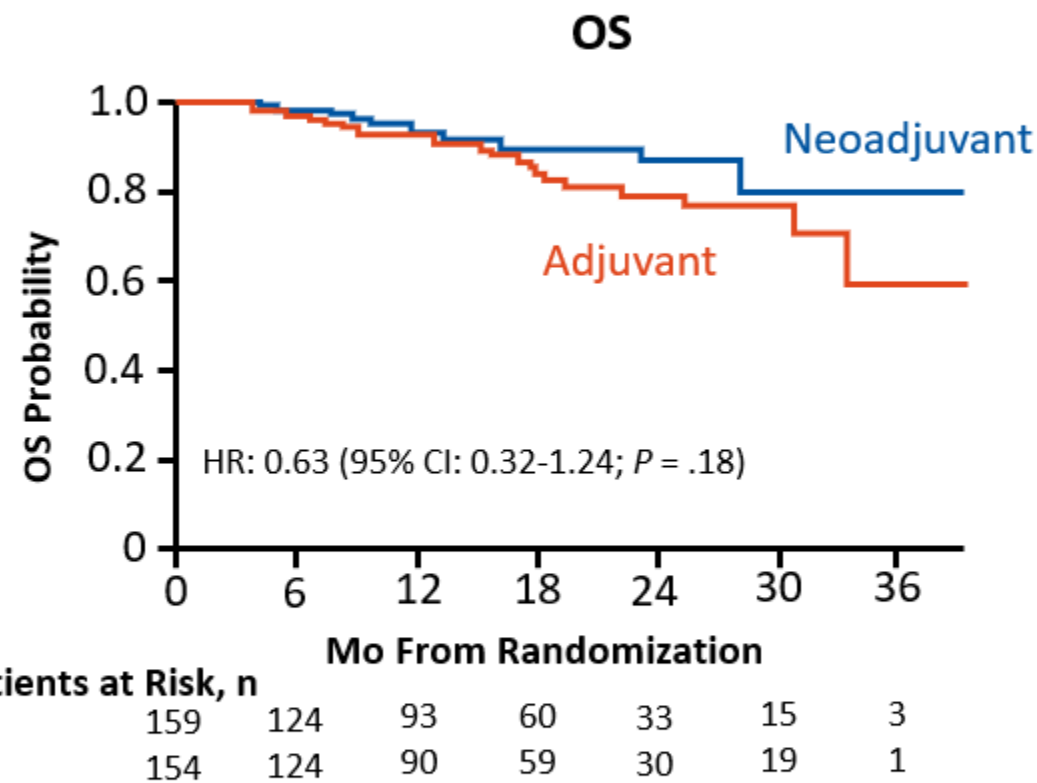
Patients at Risk, n					
pCR	40	34	17	5	
Near pCR	16	12	8	1	
pPR	27	22	9	6	
pNR	22	13	7	4	1

Response	24 Mo, % (95% CI)
pCR	89 (80-100)
Near pCR	87 (71-100)
pPR	88 (77-100)
pNR	70 (53-94)

Patel. ESMO 2023. Abstr LBA48.

SWOG S1801: Survival





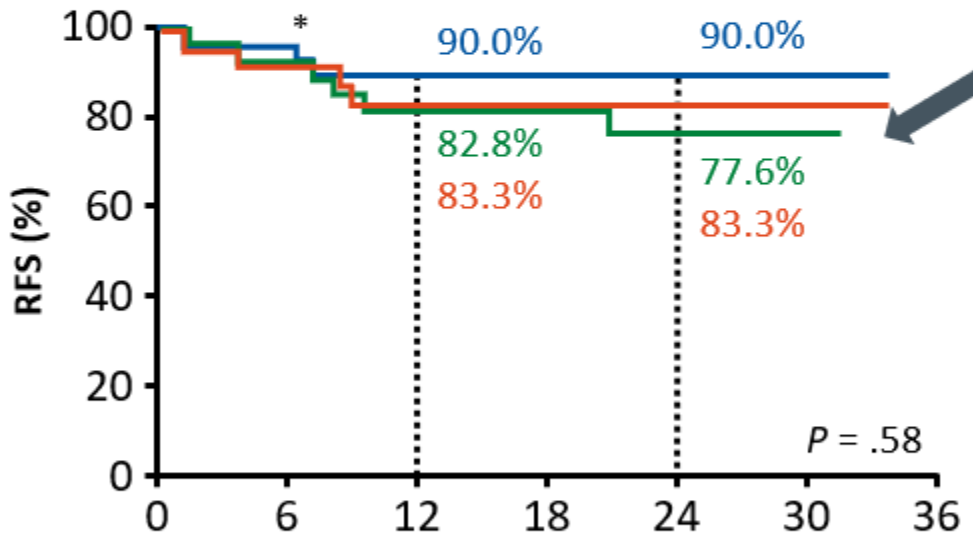
- Residual disease or metastasis occurred before adjuvant therapy in 10 (6.5%) patients in neoadjuvant arm and 18 (11%) in adjuvant arm

Patel. ESMO 2022. Abstr LBA6. Patel. NEJM. 2023;388:813.

OpACIN-neo Trial of Different Doses of Neoadjuvant Ipilimumab/Nivolumab: RFS

- Randomized phase II trial of 2 cycles of IPI3/NIVO1 vs 2 cycles of IPI1/NIVO3 vs 2 cycles of IPI3 followed by 2 cycles of NIVO3 in stage III melanoma

RFS by Immunotherapy Regimen

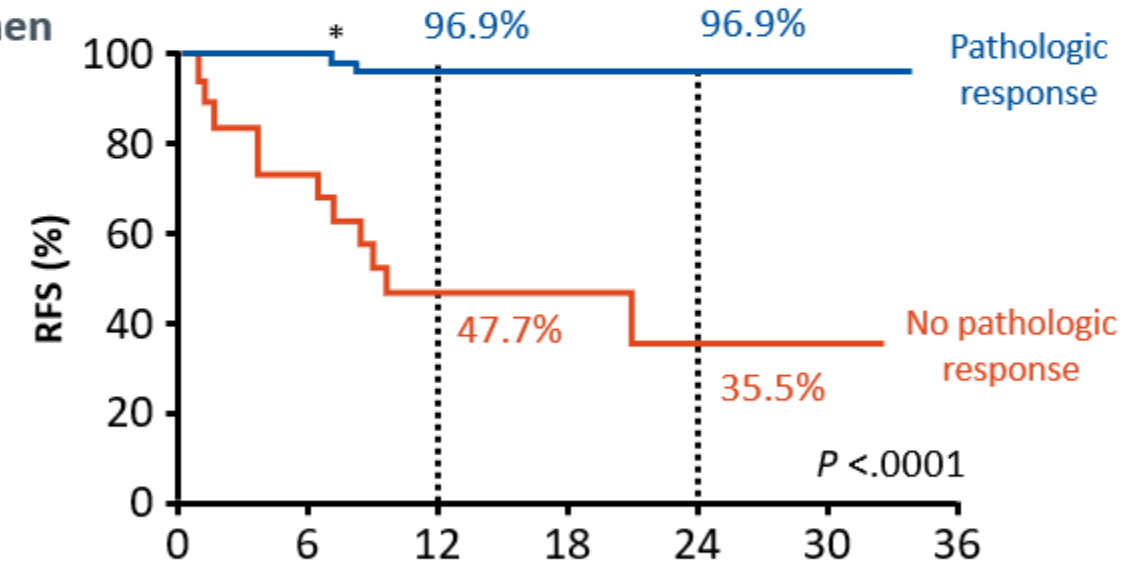


Patients at Risk, n							
IPI3/NIVO1	30	29	27	22	7	2	0
IPI1/NIVO3	29	27	24	16	7	1	0
IPI3 → NIVO3	24	22	20	16	8	3	0

*Patient died due to irAEs.

Rozeman. Nat Med. 2021;27:256.

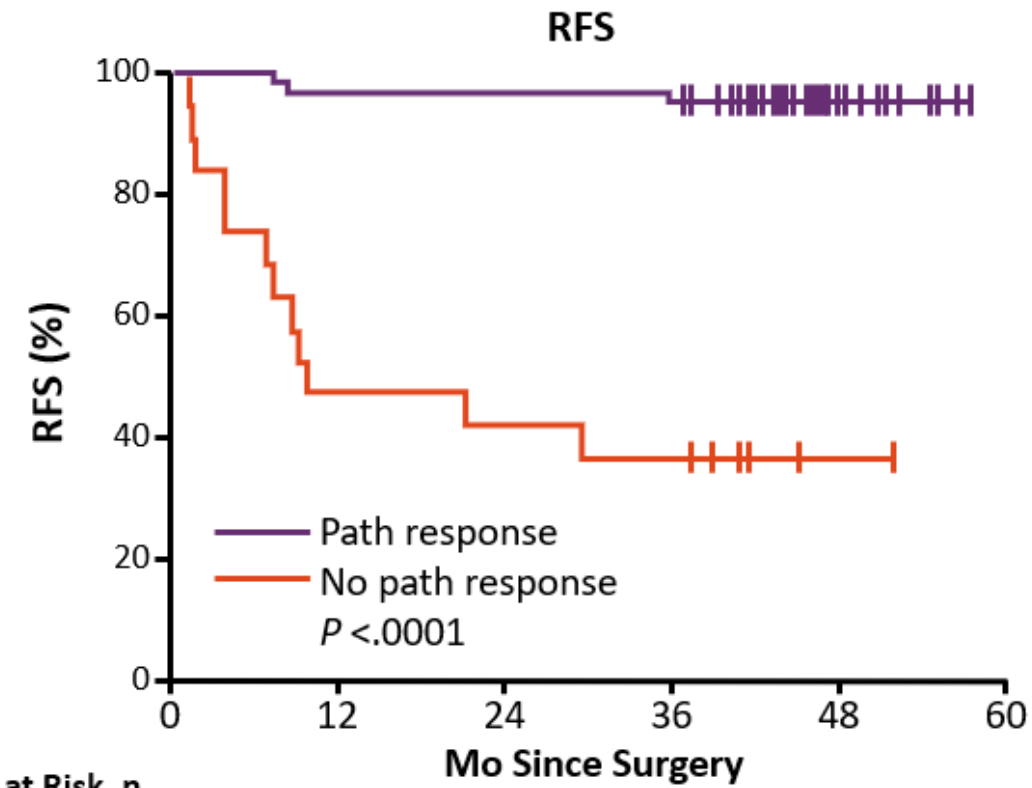
RFS by Pathologic Response†



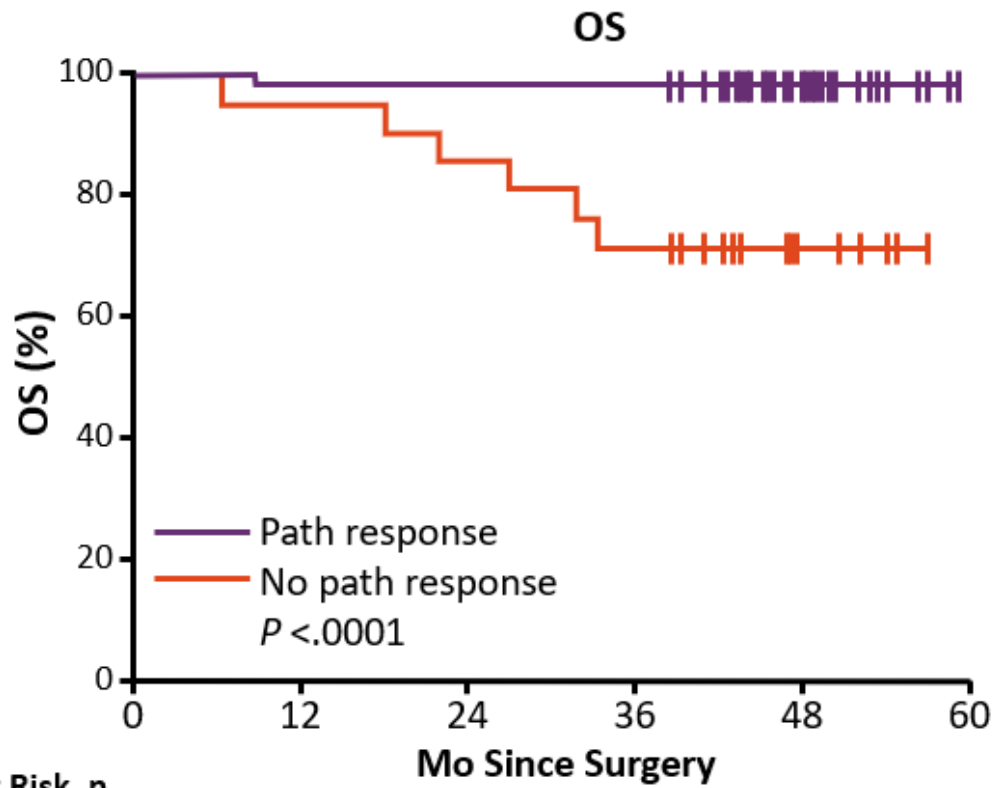
Patients at Risk, n							
Response	64	64	62	48	20	5	0
No response	19	14	9	6	2	1	0

†Pathologic response defined as <50% viable tumor cells.

OpACIN-neo: RFS and OS by Pathologic Response



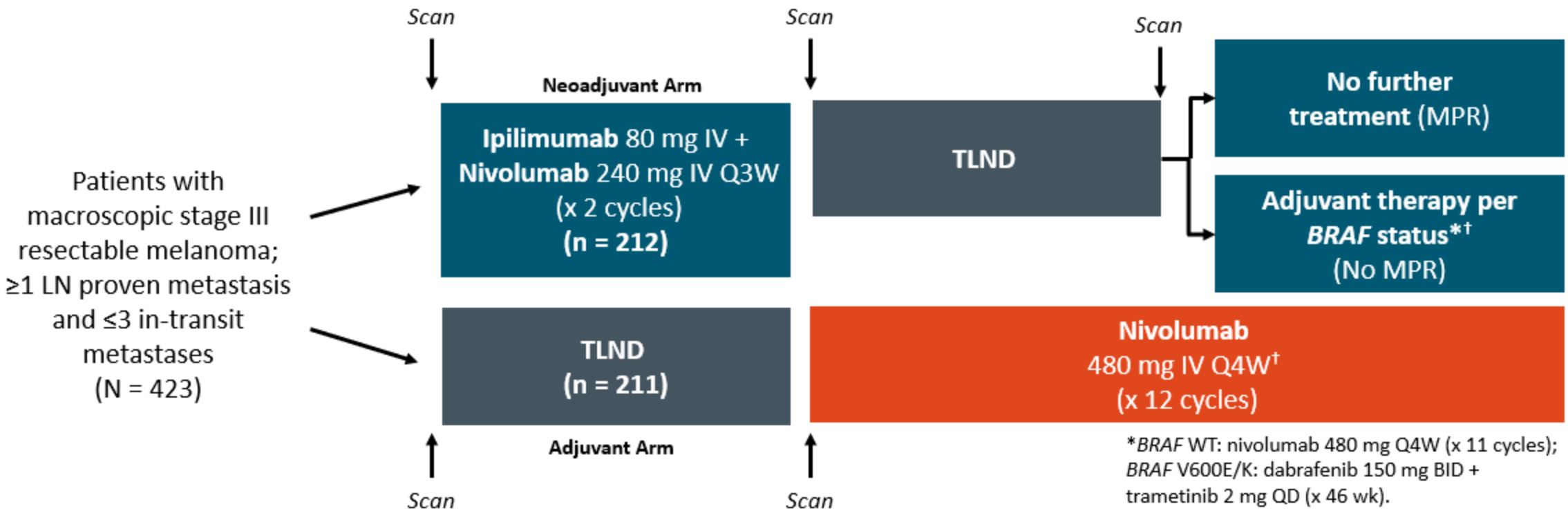
Patients at Risk, n						
Path response	64	63	62	61	14	0
No path response	19	9	8	7	1	0



Patients at Risk, n						
Path response	64	63	63	63	26	0
No path response	21	20	18	15	5	0

NADINA: Neoadjuvant Nivolumab + Ipilimumab vs Adjuvant Nivolumab in Macroscopic, Resectable Stage III Melanoma

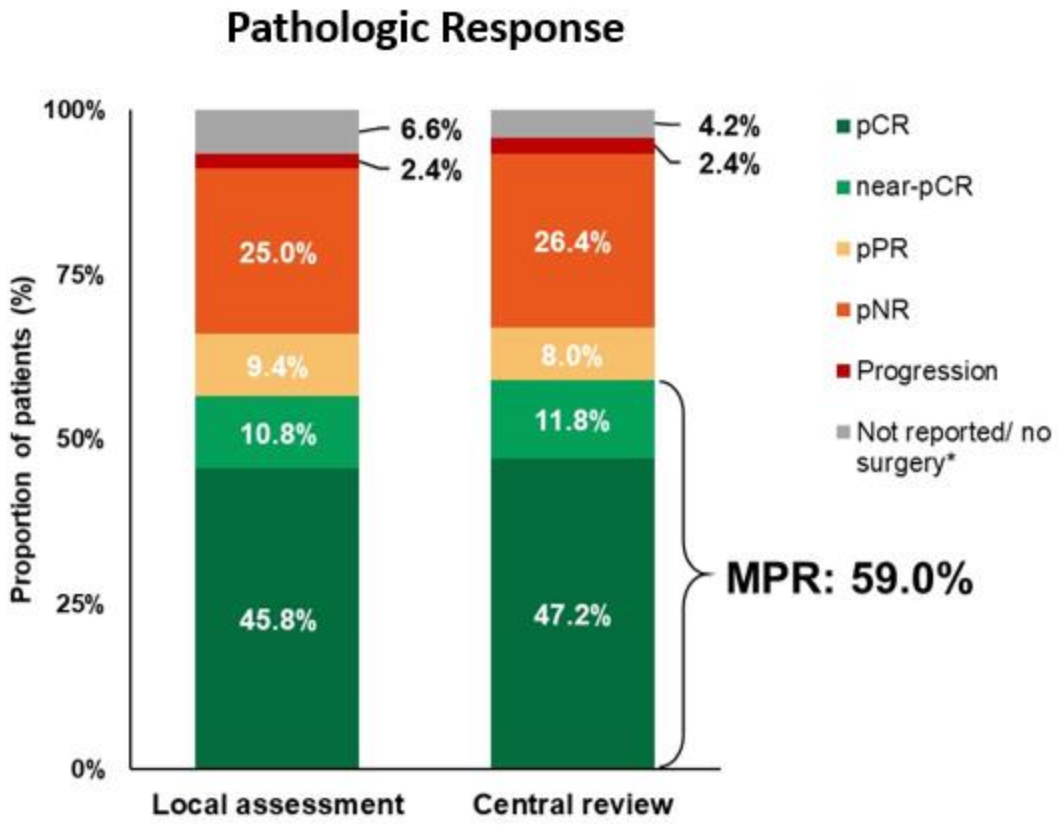
- Randomized, phase III trial

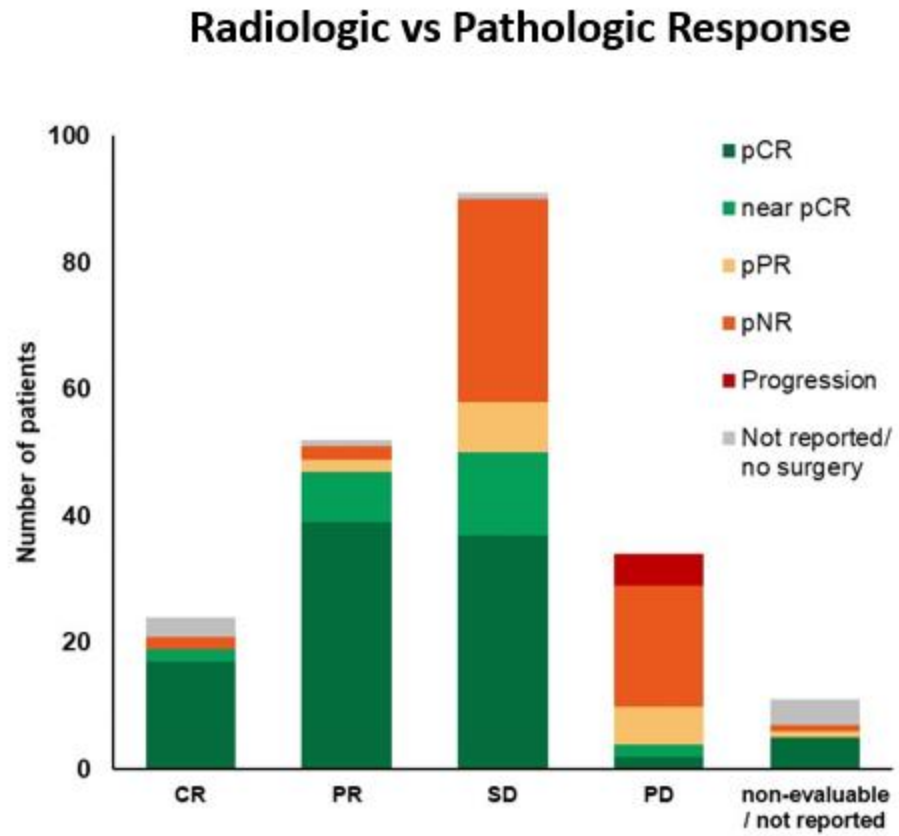


- **Primary outcome**: EFS
- **Secondary outcomes**: OS, pathologic response rate, RFS, DMFS, safety, surgical complications, QoL

Blank. ASCO 2024. Abstr LBA2. Blank. NEJM. 2024;[Epub].

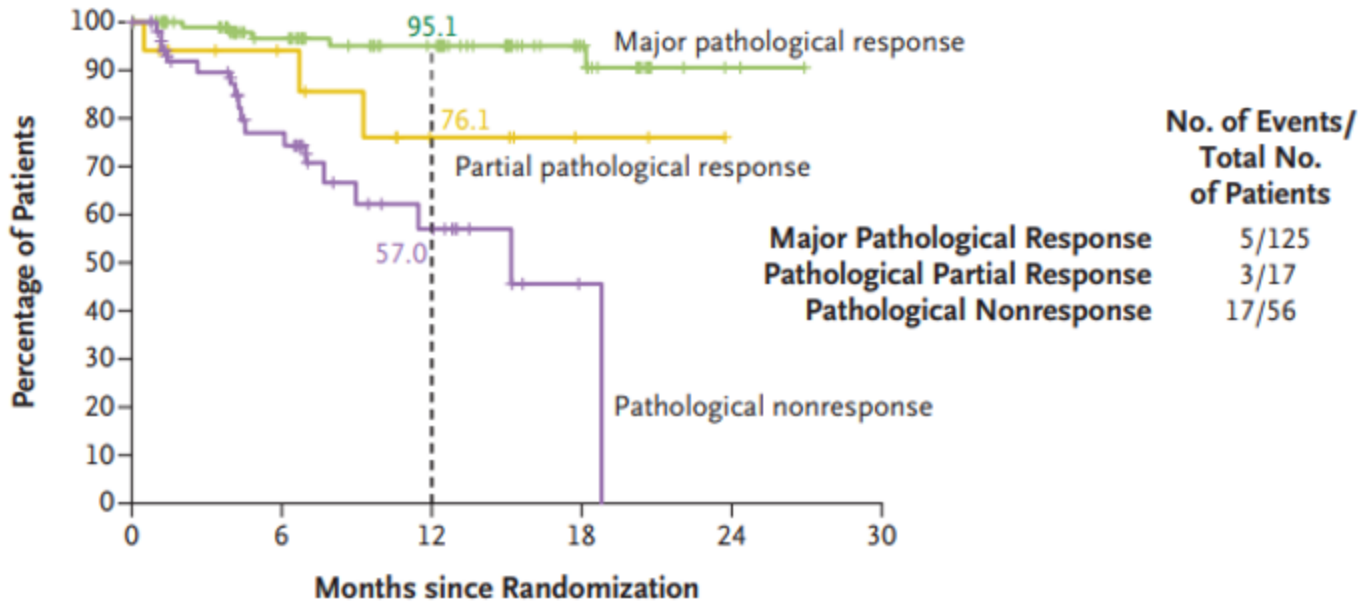
NADINA: Response





* Central review was completed for all patients who underwent surgery. At data cutoff, 9 patients had not (yet) undergone surgery (4.2%); 5 patients had surgery after data cutoff.

NADINA: RFS by Pathological Response in Patients Receiving Neoadjuvant Therapy



No. at Risk (no. censored)

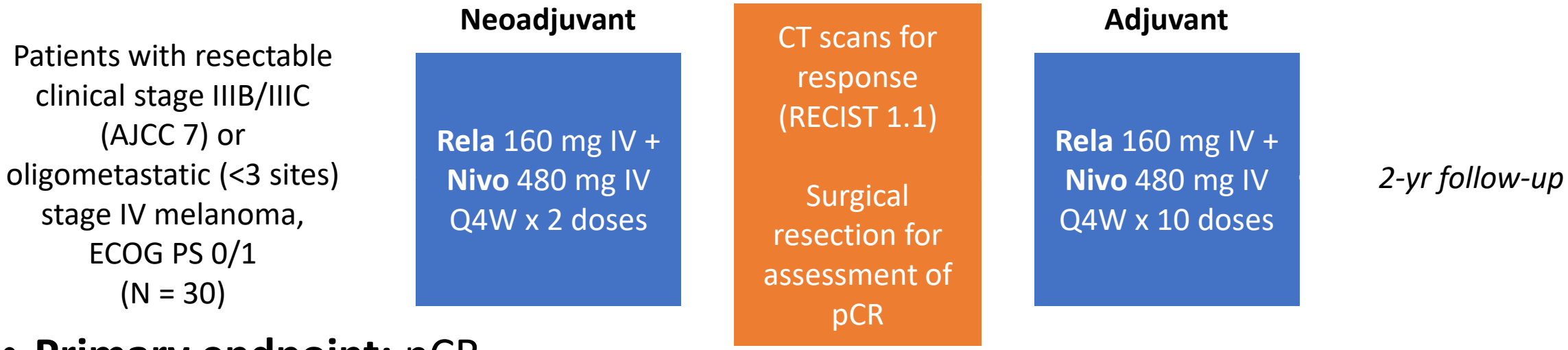
Major pathological response	125 (0)	76 (46)	55 (66)	22 (99)	2 (118)
Pathological partial response	17 (0)	11 (5)	5 (9)	2 (12)	
Pathological nonresponse	56 (0)	29 (17)	11 (30)	1 (39)	

NADINA: Clinical Implications

- More support for neoadjuvant immunotherapy for stage III melanoma, which is **now the standard of care**
- First randomized, neoadjuvant phase III ICI trial in melanoma
- Highly statistically significant EFS benefit compared with adjuvant PD-1 (HR: 0.32; *P* <.0001)
- 2 cycles of flipped-dose Ipi + Nivo (Ipi 1 mg/kg + Nivo 3 mg/kg) should now be considered for all fit patients with clinical stage III resectable melanoma
- If patients have MPR after neoadjuvant Ipi + Nivo, consider stopping immunotherapy

Neoadjuvant Relatlimab + Nivolumab for Stage III Melanoma: Study Design

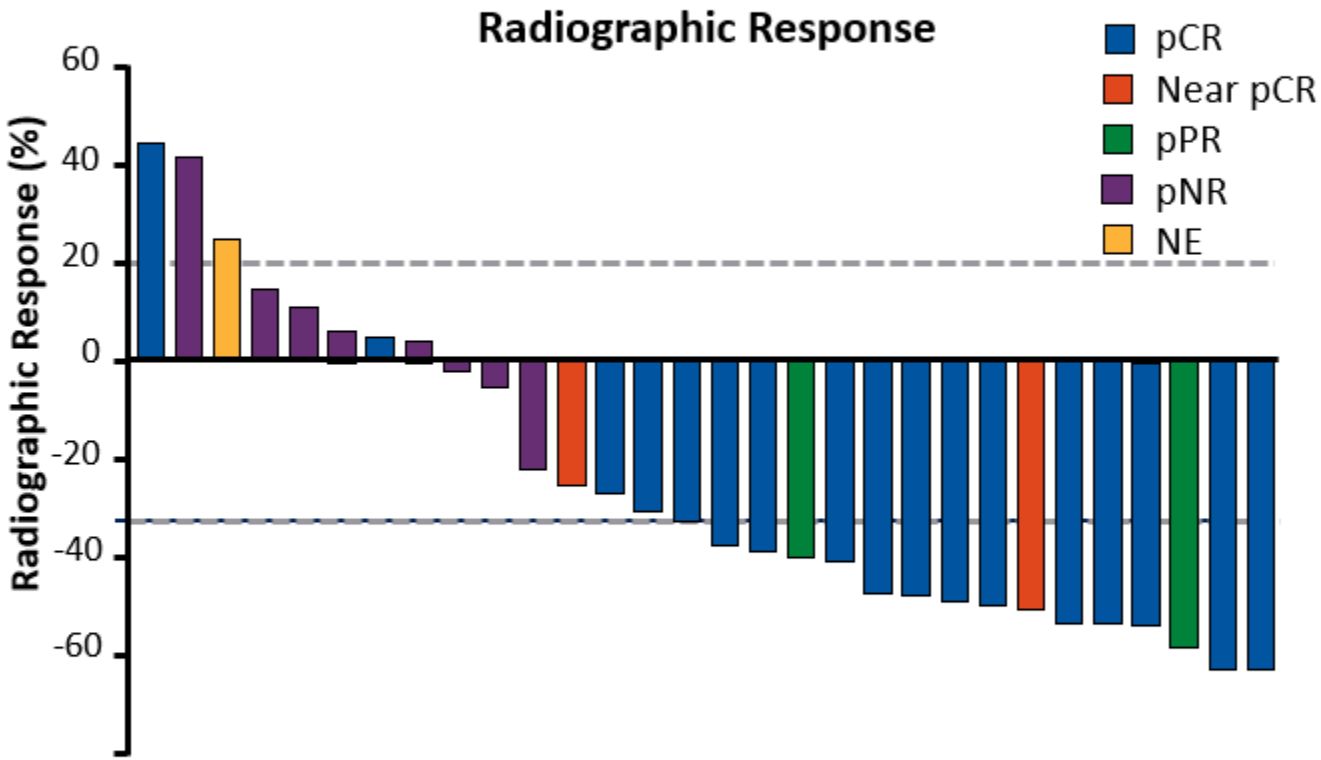
- Investigator-initiated, single-arm phase II study

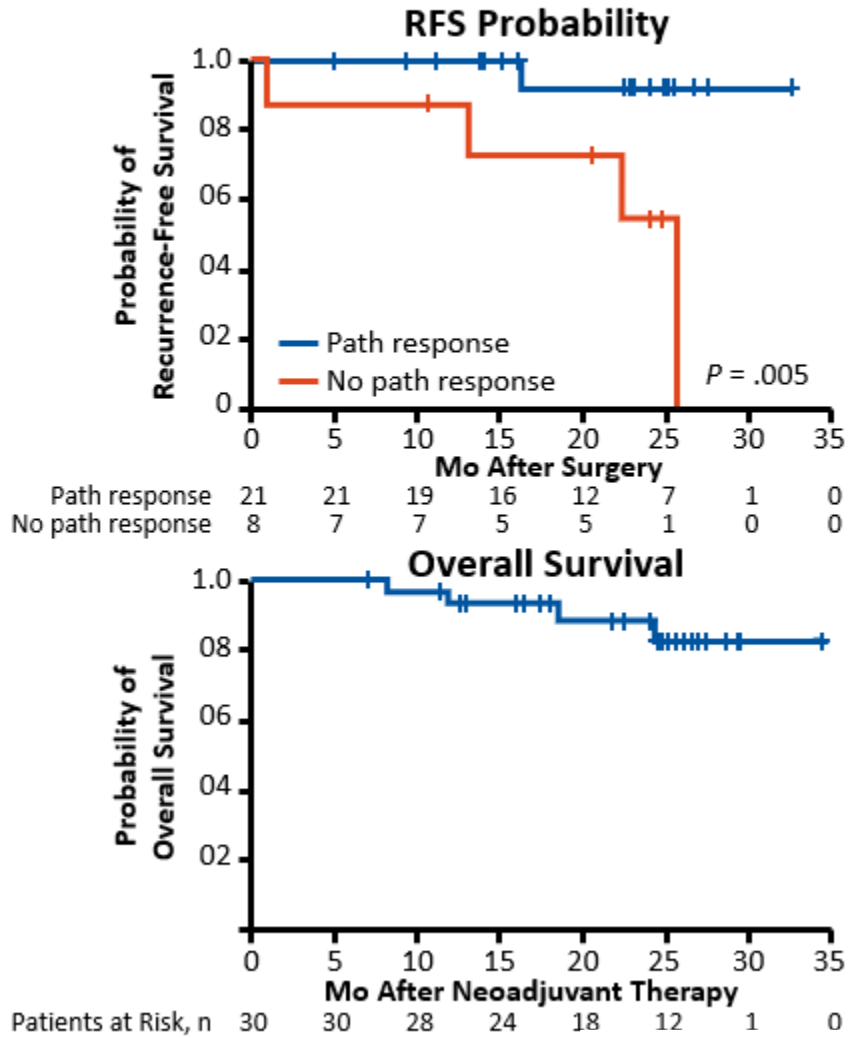


- **Primary endpoint:** pCR
- **Secondary endpoints:** ORR, RFS, EFS, OS, safety, mechanisms of response

Amaria. ASCO 2021. Abstr 9502. Amaria. Nature. 2022;611:155.

Neoadjuvant Relatlimab + Nivolumab for Stage III Melanoma: Efficacy





- Among patients with pCR/near pCR (n = 19) response of radiographic PR seen in 15, 3 SD, and 1 PD
- In patients with pNR (n = 8), only 1 had radiographic PD, 7 had SD
- No patients achieved a CR by RECIST 1.1

Amaria. ASCO 2021. Abstr 9502. Amaria. Nature. 2022;611:155.

Key Takeaways: Management of Clinically Detectable Stage III Melanoma

- RFS is improved in patients who receive neoadjuvant and adjuvant pembrolizumab compared with adjuvant pembrolizumab alone
- Safety appears to be similar with neoadjuvant approach
- Pathologic response to neoadjuvant therapy is robust predictor of subsequent RFS
- Patients who are candidates for systemic therapy should be considered for neoadjuvant approach
- Early multidisciplinary care coordination is key

Immunotherapeutic Strategies for Frontline Therapy in Unresectable/Metastatic Melanoma

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FDA-Approved Immunotherapy: Metastatic Melanoma

Immunotherapy	Trial Name; First Publication Date	Setting	ORR, %	5-Yr PFS, %	5-Yr OS, %	Grade ≥3 TRAEs, %
Ipilimumab[1-5]	2010[1]	Previously treated stage IV (or unresectable stage III)	11	8-14.4	26-31	20-28
Pembrolizumab[3,4,6,7]	KEYNOTE-006; 2015[6]	Previously treated stage IV (or unresectable stage III)	42	23*	39	17
Nivolumab[5,8,9]	CheckMate-067; 2015[8]	1L metastatic	45	29	44	23
Ipilimumab + nivolumab[5,8,9]	CheckMate-067; 2015[8]	1L metastatic	58	36	52	59
Nivolumab + relatlimab[10-12]	RELATIVITY-047; 2022[11]	1L metastatic	43	31†	52‡	22

*4-yr PFS rate. †3-yr PFS rate. ‡4-yr OS rate.

1. Hodi. NEJM. 2010;363:711. 2. Ipilimumab PI. 3. Robert. JCO. 2023;41:3998. 4. Robert. Lancet Oncology. 2019;20:1239.
5. Larkin. NEJM. 2019;381:1535. 6. Pembrolizumab PI. 7. Robert. NEJM. 2015;372:2521. 8. Nivolumab PI.
9. Larkin. NEJM. 2015;373:23. 10. Tawbi. ASCO 2023. Abstr 9052. 11. Relatlimab/nivolumab PI. 12. Tawbi. NEJM. 2022;386:24.

CheckMate 067: Nivolumab + Ipilimumab or Nivolumab vs Ipilimumab for First-line Treatment of Melanoma

- Randomized, double-blind phase III study

Stratified by PD-L1 expression (<5% vs ≥5%), BRAF status, and AJCC M stage

Previously untreated patients with unresectable or metastatic stage III/IV melanoma and ECOG PS 0/1 (N = 945)

Nivo 1 mg/kg + **Ipi 3 mg/kg Q3W for 4 doses**, then **Nivo 3 mg/kg Q2W** (n = 314)

Nivo 3 mg/kg Q2W + **Placebo** (n = 316)

Ipi 3 mg/kg Q3W for 4 doses + **Placebo** (n = 315)

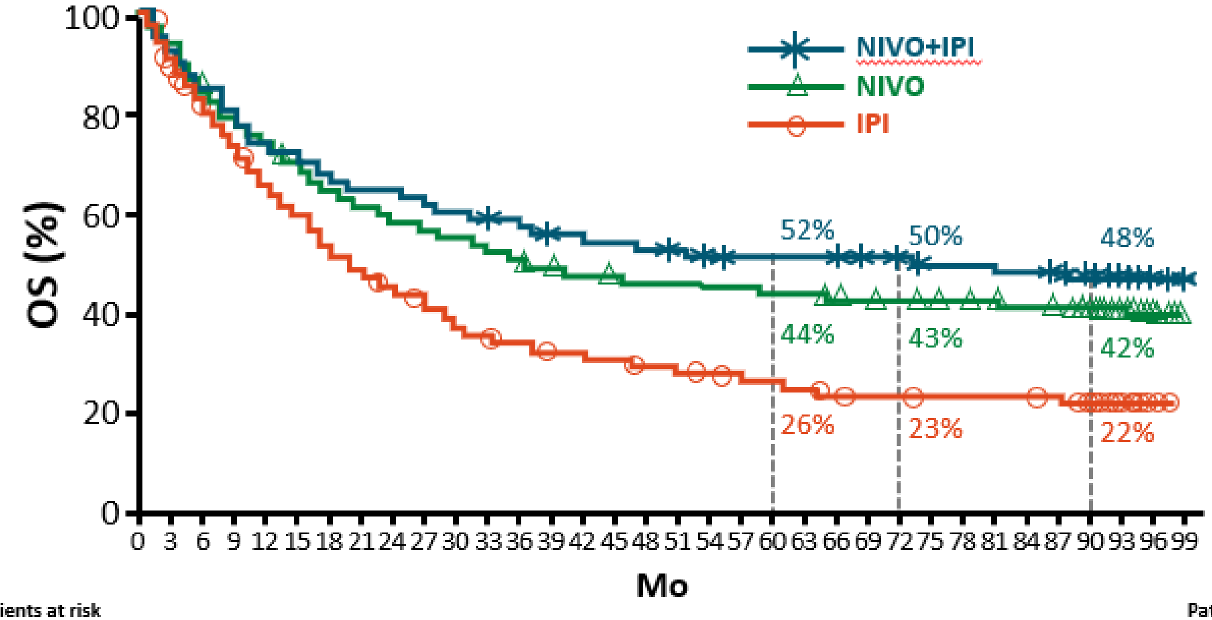
Until disease progression or unacceptable toxicity

- **Coprimary endpoints*:** PFS, OS
- **Secondary endpoints:** ORR, tumor PD-L1 expression and efficacy, safety

Larkin. NEJM. 2019:381:1535. Wolchok. JCO. 2022;40:127.

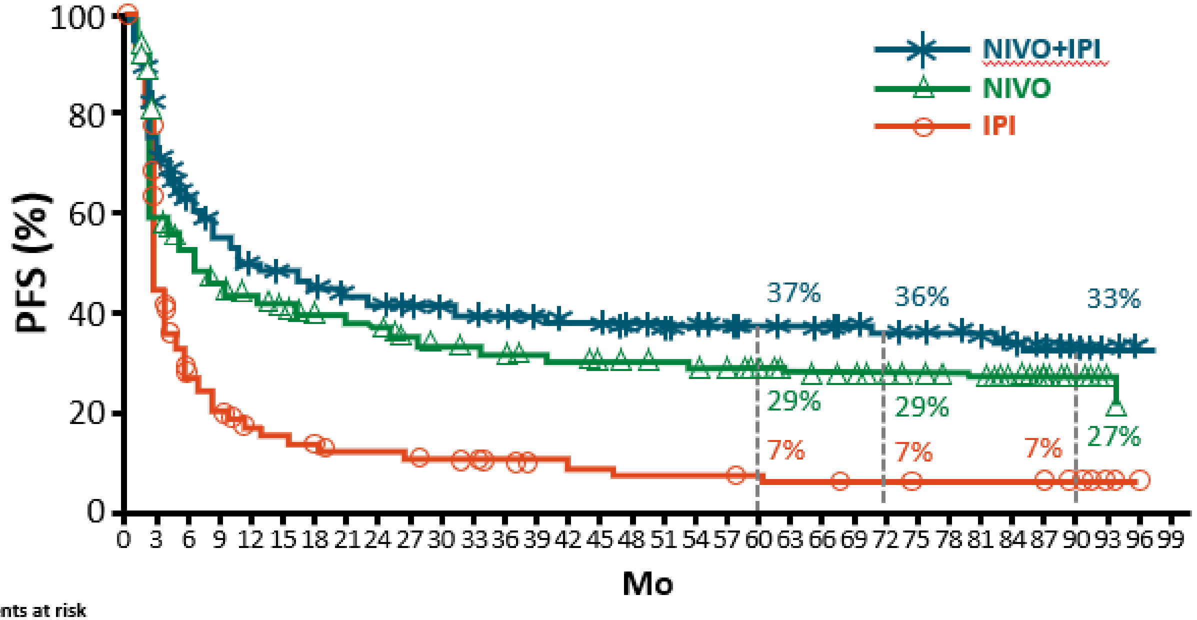
CheckMate 067: OS and PFS at 7.5-Yr Follow-up

OS	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median OS, mo (95% CI)	72.1 (38.2-NR)	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 (0.52-0.77)	–
HR (95% CI vs NIVO)	0.84 (0.68-1.04)	–	–



Patients at risk																																		
NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	144	143	141	138	129	58	7	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	123	121	120	118	107	54	4	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	63	63	63	62	57	24	5	0

PFS	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median PFS, mo (95% CI)	11.5 (8.9-20.0)	6.9 (5.1-10.2)	2.9 (2.8-3.1)
HR (95% CI vs IPI)	0.42 (0.35-0.51)	0.53 (0.44-0.64)	–
HR (95% CI vs NIVO)	0.79 (0.62-0.97)	–	–



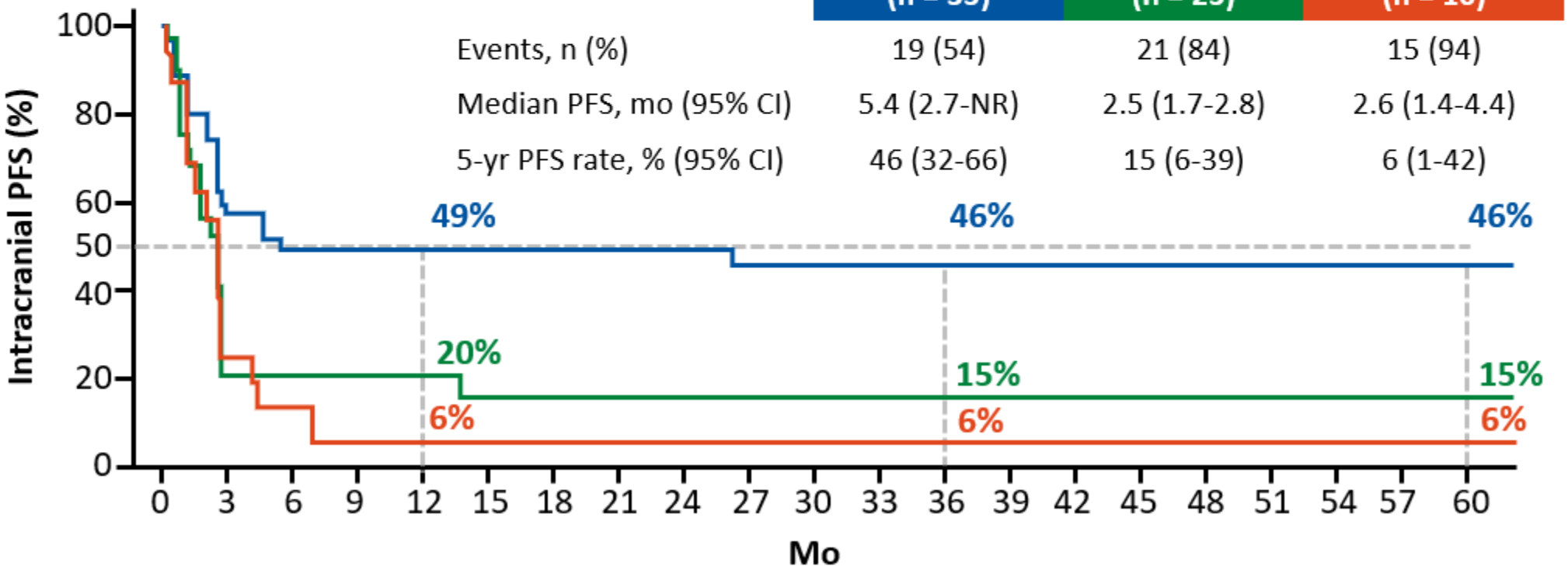
Patients at risk																																		
NIVO+IPI	314	219	175	156	138	133	126	119	112	106	103	100	99	95	93	92	87	86	84	81	78	77	76	72	70	68	66	63	57	50	33	10	1	0
NIVO	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	69	67	66	65	62	58	57	56	54	53	50	49	44	37	21	5	0	0
IPI	315	135	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	15	12	11	11	10	10	9	9	9	9	9	7	3	1	0

Hodi. ASCO 2022. Abstr 9522.

ABC Study of Nivolumab ± Ipilimumab in Patients With Melanoma Brain Metastases: Intracranial PFS at 5 Yr

- Open-label phase II trial, patients with asymptomatic brain metastases randomized to nivolumab ± ipilimumab and a nivolumab arm for patients with symptomatic brain metastases

	Asymptomatic		Symptomatic
Outcome	Nivo + Ipi (n = 35)	Nivo (n = 25)	Nivo (n = 16)
Events, n (%)	19 (54)	21 (84)	15 (94)
Median PFS, mo (95% CI)	5.4 (2.7-NR)	2.5 (1.7-2.8)	2.6 (1.4-4.4)
5-yr PFS rate, % (95% CI)	46 (32-66)	15 (6-39)	6 (1-42)



Long. ASCO 2021. Abstr 9508.

RELATIVITY-047: Relatlimab + Nivolumab vs Nivolumab in Previously Untreated Advanced Melanoma

- Randomized, global, double-blind open-label phase II/III study

Stratification by: LAG-3 expression, PD-L1 expression,† BRAF mutation status, AJCC v8 M stage*

Patients with previously untreated, unresectable, or metastatic melanoma; ECOG PS 0/1 (N = 714)

Nivolumab 480 mg + **relatlimab** 160 mg FDC IV Q4W (n = 355)

Nivolumab 480 mg IV Q4W (n = 359)

Until patient request, unacceptable toxicity, progression, or death

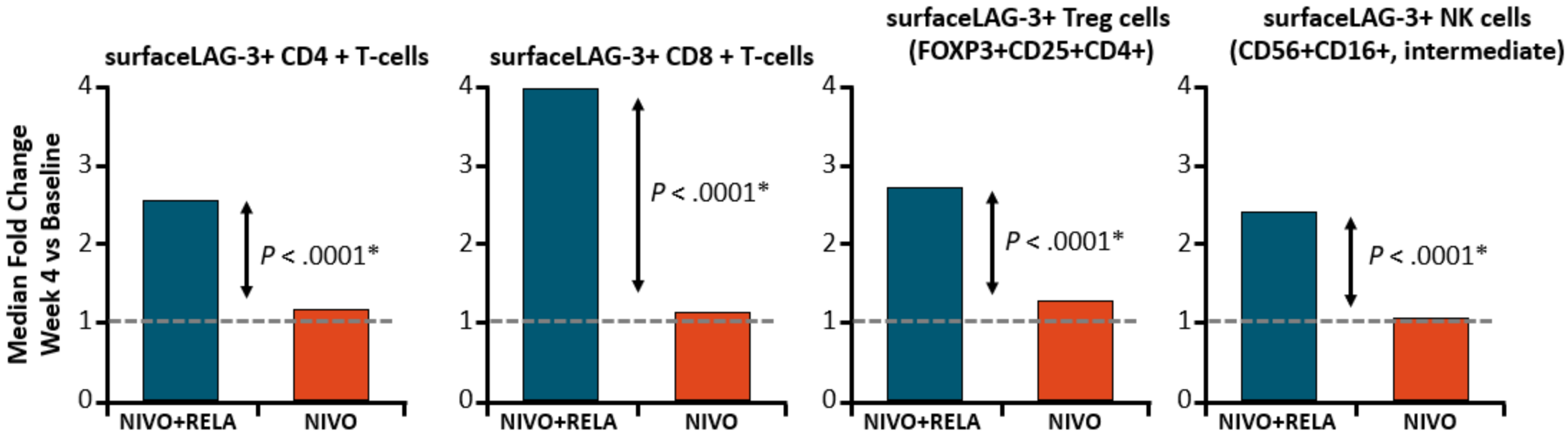
- **Primary endpoint:** PFS (BICR)
- **Secondary endpoints:** OS, ORR‡ (BICR)

*LAG-3 expression on immune cells (1%), determined by analytically validated IHC assay.
†PD-L1 expression on tumor cells (1%) determined by validated PD-L1 IHC 28-8 PharmDx assay.
‡Response assessed by RECIST v1.1 and confirmed with subsequent scan ≥28 days later.

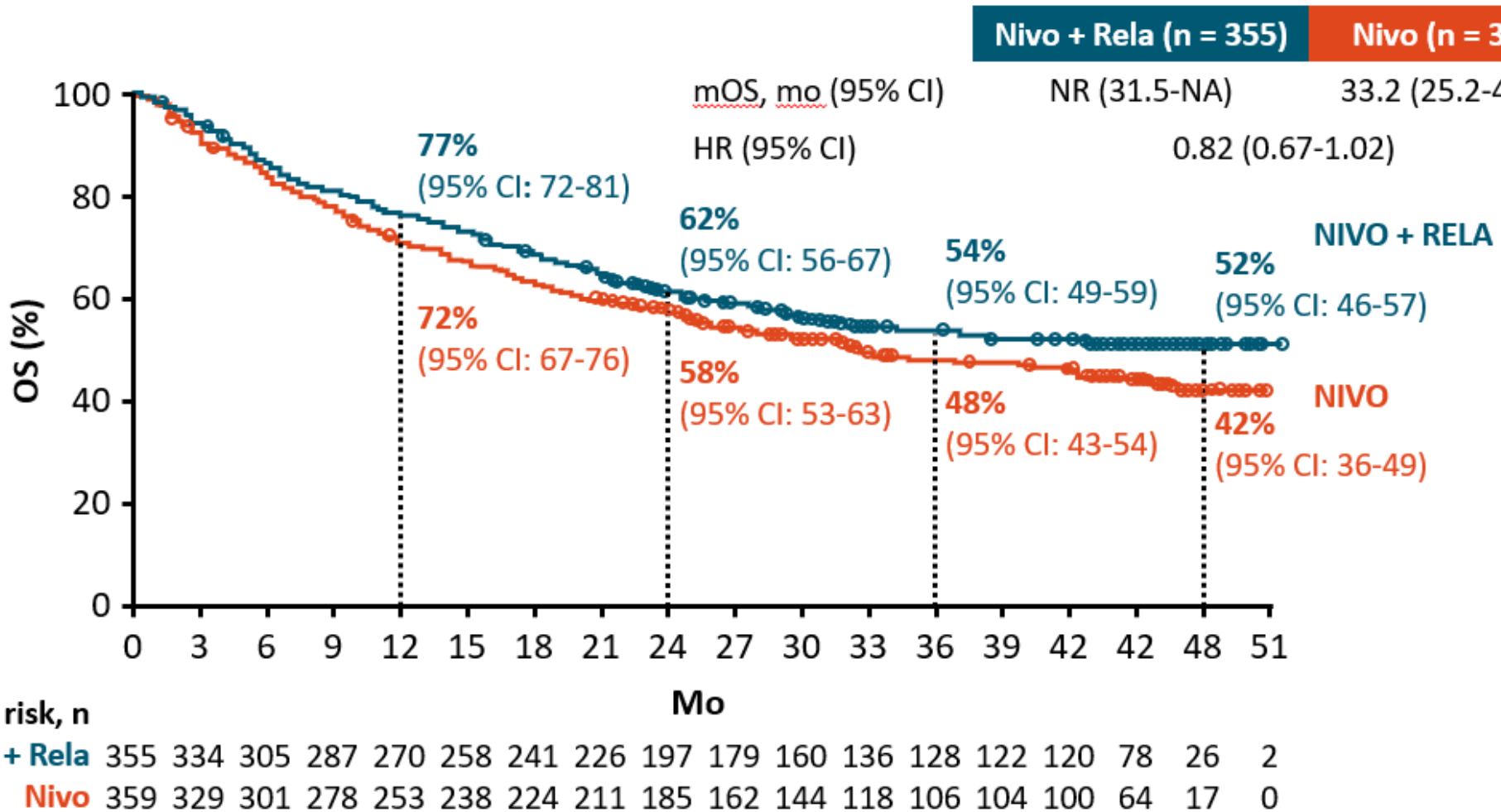
Tawbi. NEJM. 2022;386:24. Long. NEJM Evidence. 2023;2:4.

RELATIVITY-047 Biomarker Analysis: Changes in Peripheral Immune Cell Subsets

- Data include all patients with pre- and on-treatment PBMC samples (n = 236 NIVO + RELA; n = 231 NIVO)
- Significantly greater on-treatment changes in surface LAG-3+ CD4+ and CD8+ central memory, effector memory, and terminal effector T-cell populations with NIVO + RELA vs NIVO

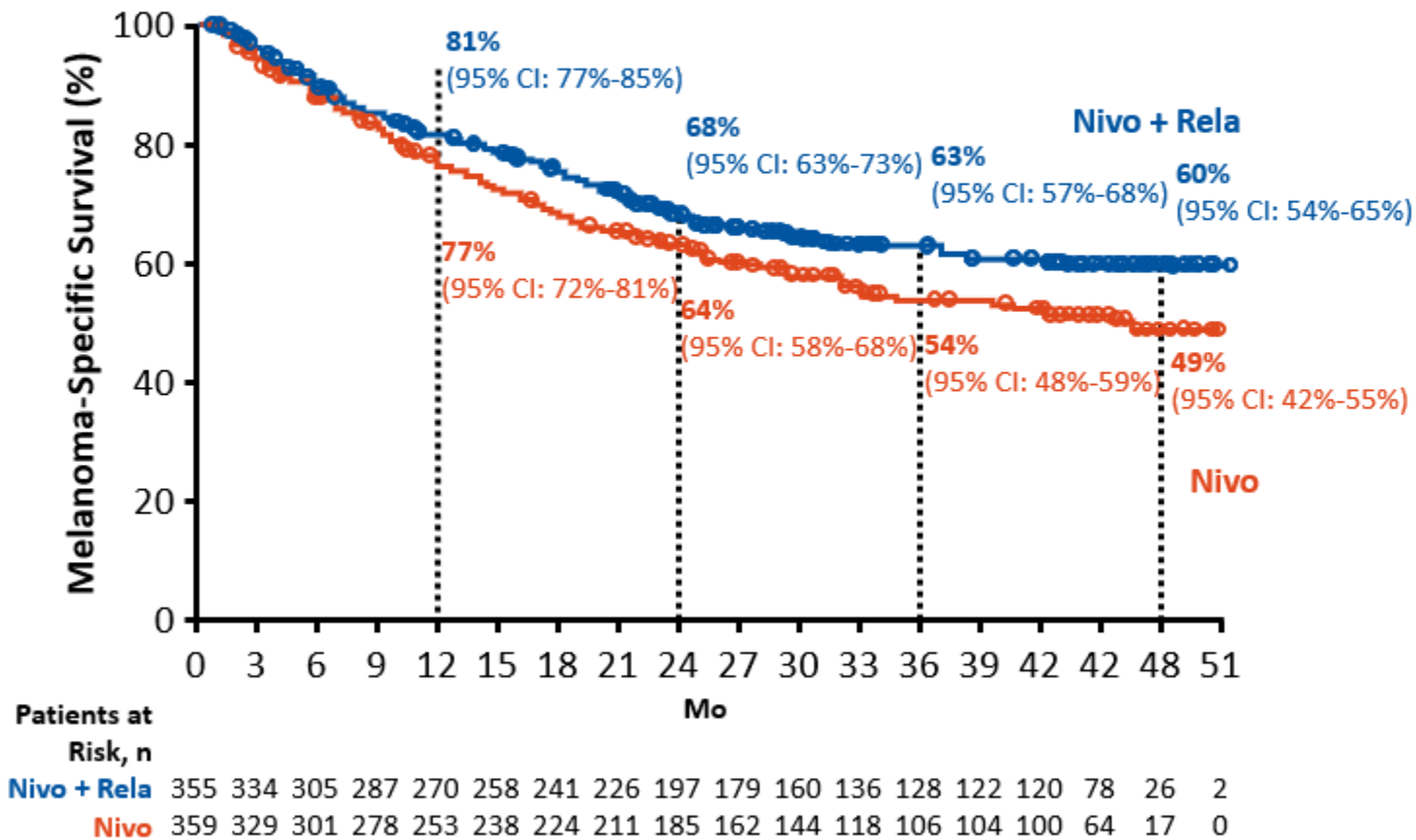


RELATIVITY-047: OS



Tawbi. ASCO 2023. Abstr 9502.

RELATIVITY-047: Post Hoc Exploratory Analysis of Melanoma-Specific Survival

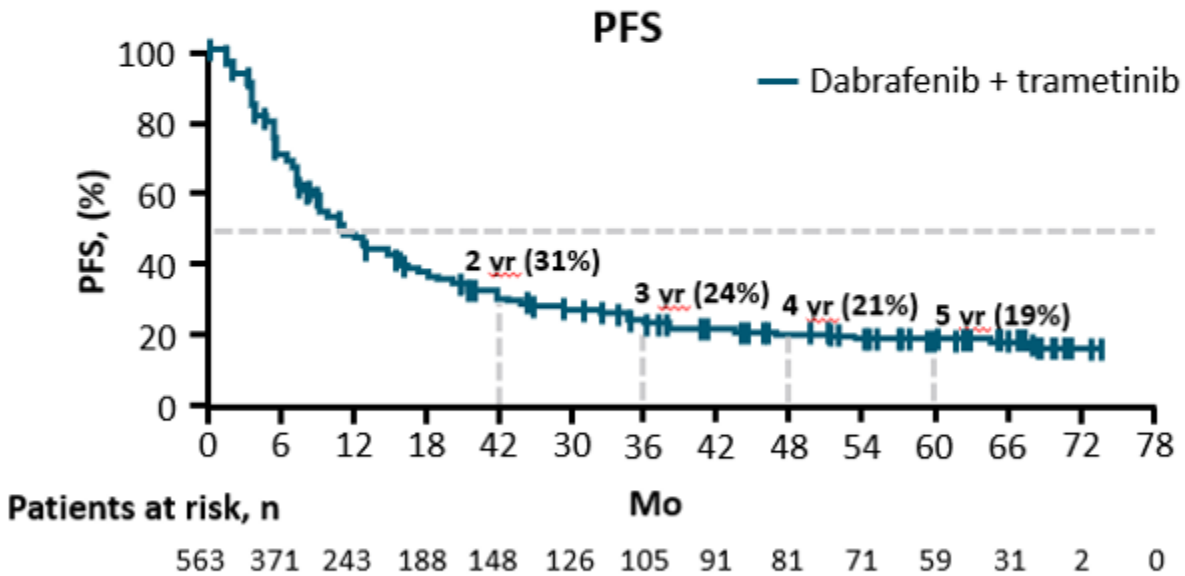


MSS Outcome	Nivolumab + Relatlimab (n = 355)	Nivolumab (n = 359)
Median, mo	NR	46.7
HR (95% CI)	0.77 (0.61-0.97)	
Melanoma deaths, n (%)	126 (35)	154 (43)
Censored patients, n (%)	229 (65)	205 (57)
▪ Nonmelanoma death	36 (10)	31 (9)
• Study drug toxicity	4 (1)	2 (1)
• Unknown	7 (2)	10 (3)
• Other	25 (7)	19 (5)

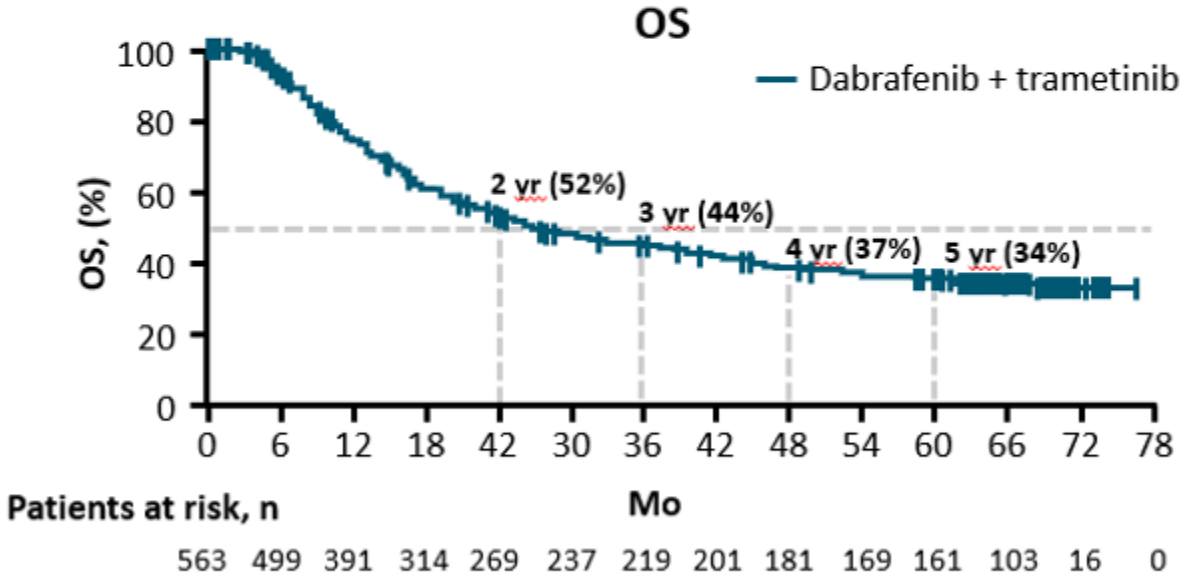
Tawbi. ASCO 2023. Abstr 9502.

Pooled Analysis of COMBI-d and COMBI-v Trials of Dabrafenib Plus Trametinib: 5-Yr OS

- **COMBI-d**: double-blind, randomized, phase III trial with primary outcome of PFS (N = 211)
- **COMBI-V**: open-label, randomized phase II trial with primary outcome of OS (N = 352)



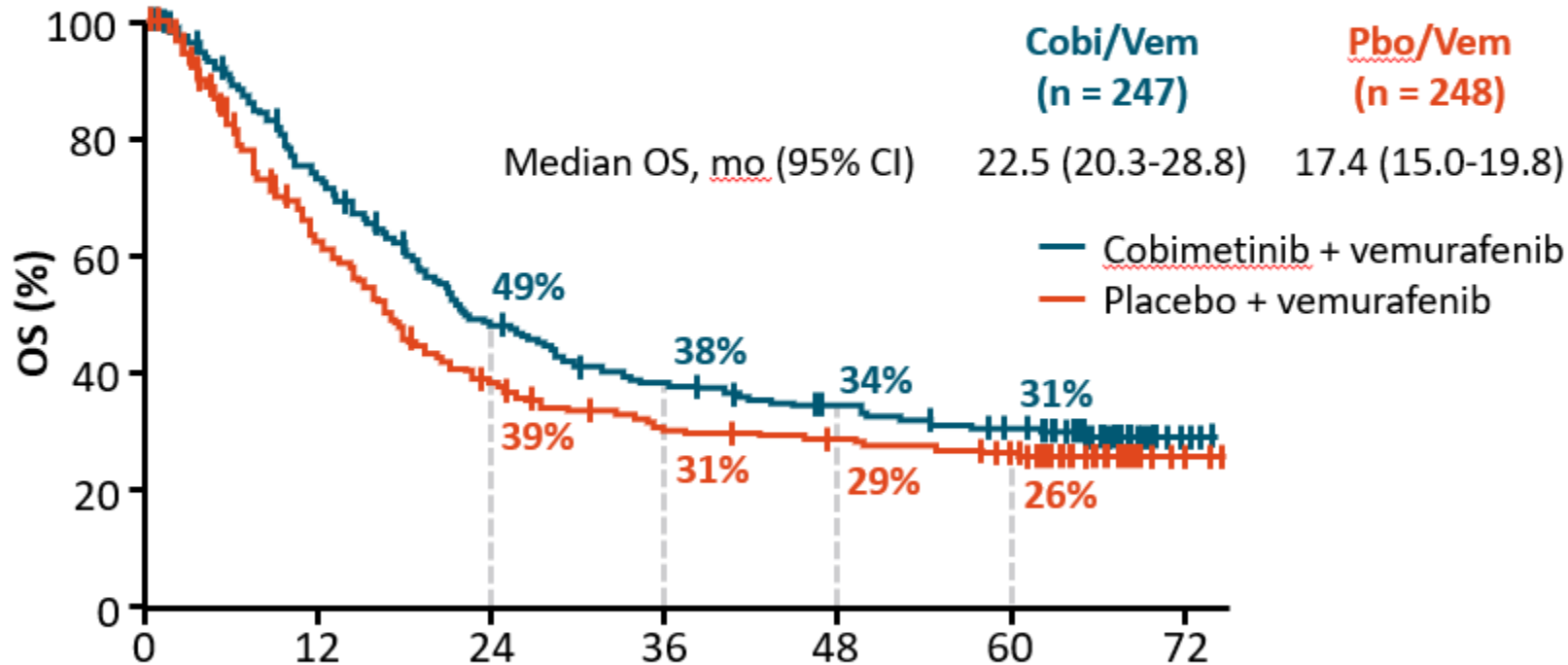
	Events, n (%)	Median PFS, Mo (95% CI)
Dabrafenib plus trametinib	417 (74)	11.1 (9.5-12.8)



	Events, n (%)	Median OS, Mo (95% CI)
Dabrafenib plus trametinib	351 (62)	25.9 (22.6-31.5)

coBRIM: OS With Vemurafenib ± Cobimetinib in *BRAF* Mutant Advanced Melanoma

- **coBRIM**: randomized, double-blind phase III trial of **vemurafenib + cobimetinib** vs **vemurafenib + placebo** for patients with unresectable stage IIIc/IV melanoma and *BRAF* V600E/K mutation (N = 495)

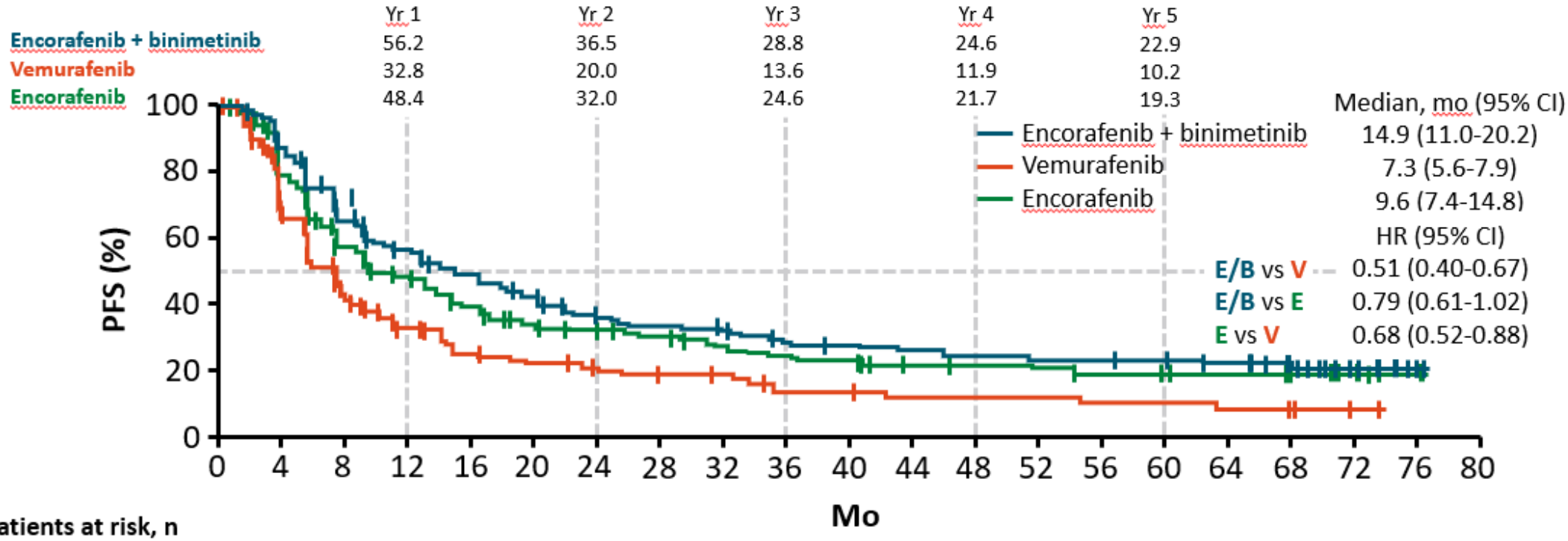


Patients at risk, n													
Cobimetinib + vemurafenib	247	210	169	139	109	91	83	76	70	66	60	33	3
Placebo + vemurafenib	248	194	142	104	84	72	65	62	59	56	52	25	3

Ascierto. Clin Cancer Res. 2022;27:5225.

COLUMBUS: Encorafenib + Binimetinib vs Vemurafenib or Encorafenib for *BRAF*-Mutant Melanoma – PFS

- Randomized, open-label phase III trial of **encorafenib + binimetinib** vs **vemurafenib** or **encorafenib** for patients with unresectable stage IIIB/C/IV melanoma and *BRAF* V600E/K mutation (N = 577)

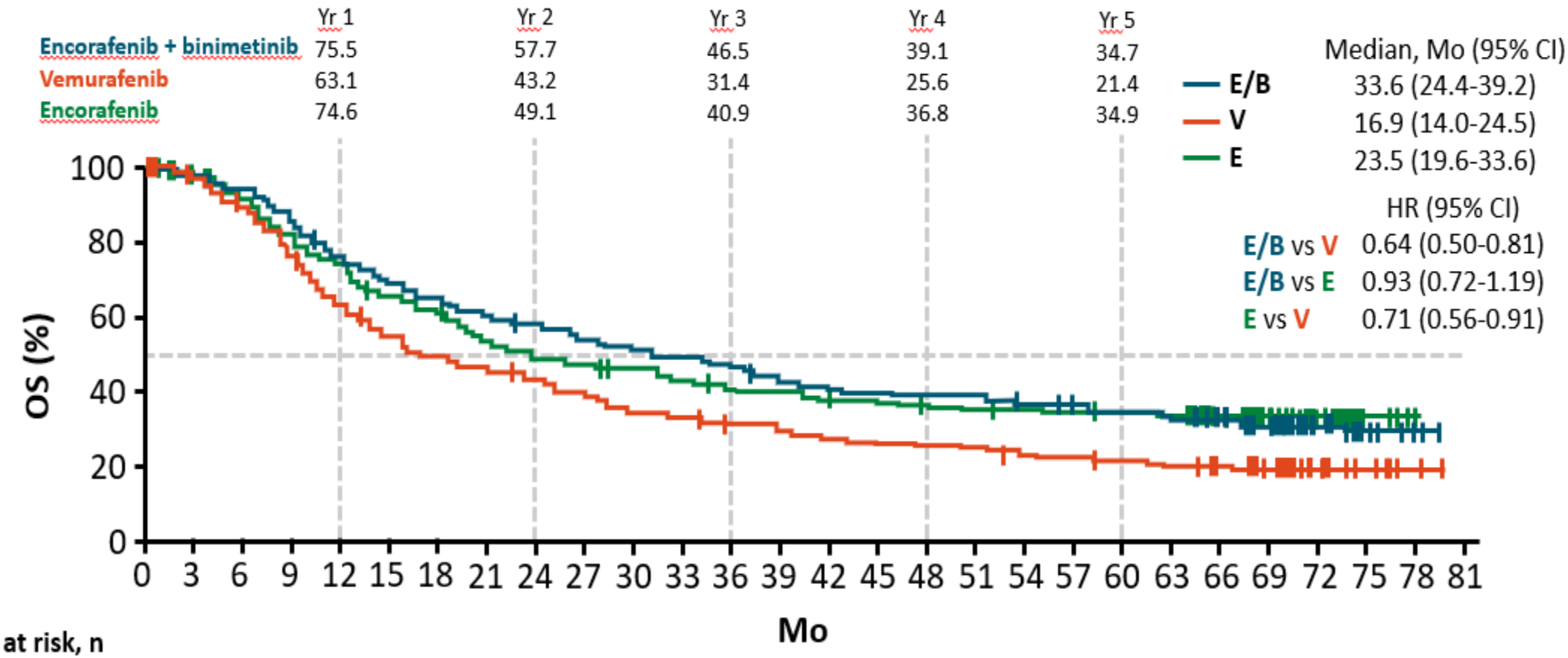


Patients at risk, n

Encorafenib + binimetinib	192	151	108	87	73	63	50	45	43	35	33	31	29	28	27	26	23	19	9	2	0
Vemurafenib	191	98	55	36	26	22	18	16	15	10	10	7	7	7	6	6	5	3	1	0	0
Encorafenib	194	125	84	68	53	43	37	34	29	26	24	19	18	17	15	14	13	11	6	2	0

Dummer. JCO 2022;40:4178.

COLUMBUS: OS



Patients at risk, n

Encorafenib + binimetinib	192	188	182	166	144	132	124	116	109	103	96	95	88	81	76	74	73	73	68	66	62	59	53	42	22	8	3	0
Vemurafenib	191	184	166	141	115	100	89	83	77	71	62	58	54	52	47	45	44	43	39	37	34	32	29	22	13	6	2	0
Encorafenib	194	181	168	147	133	117	109	94	86	83	79	74	69	68	65	62	60	58	57	56	55	53	44	35	24	5	0	0

DREAMseq: Nivo/Ipi → Dabrafenib/Trametinib vs Dabrafenib/Trametinib → Nivo/Ipi

- Randomized phase III trial of targeted therapy followed by immunotherapy and vice versa in stage III-IV *BRAF* V600 melanoma

Stratification factors: ECOG PS (0 vs 1), serum LDH (normal vs elevated)

Unresectable, treatment-naive for metastatic disease; stage III or IV melanoma; ECOG PS 0/1; *BRAF* V600E/K mutation; no active CNS metastases (N = 265)

Arm A
Nivo 1 mg/kg + **Ipi** 3 mg/kg, then **Nivo** 3 mg/kg*

Arm B
Dabrafenib 150 mg PO BID + **Trametinib** 2 mg PO QD

Progression

Arm C
Dabrafenib 150 mg PO BID + **Trametinib** 2 mg PO QD

Arm D
Nivo 1 mg/kg + **Ipi** 3 mg/kg, then **Nivo** 3 mg/kg*

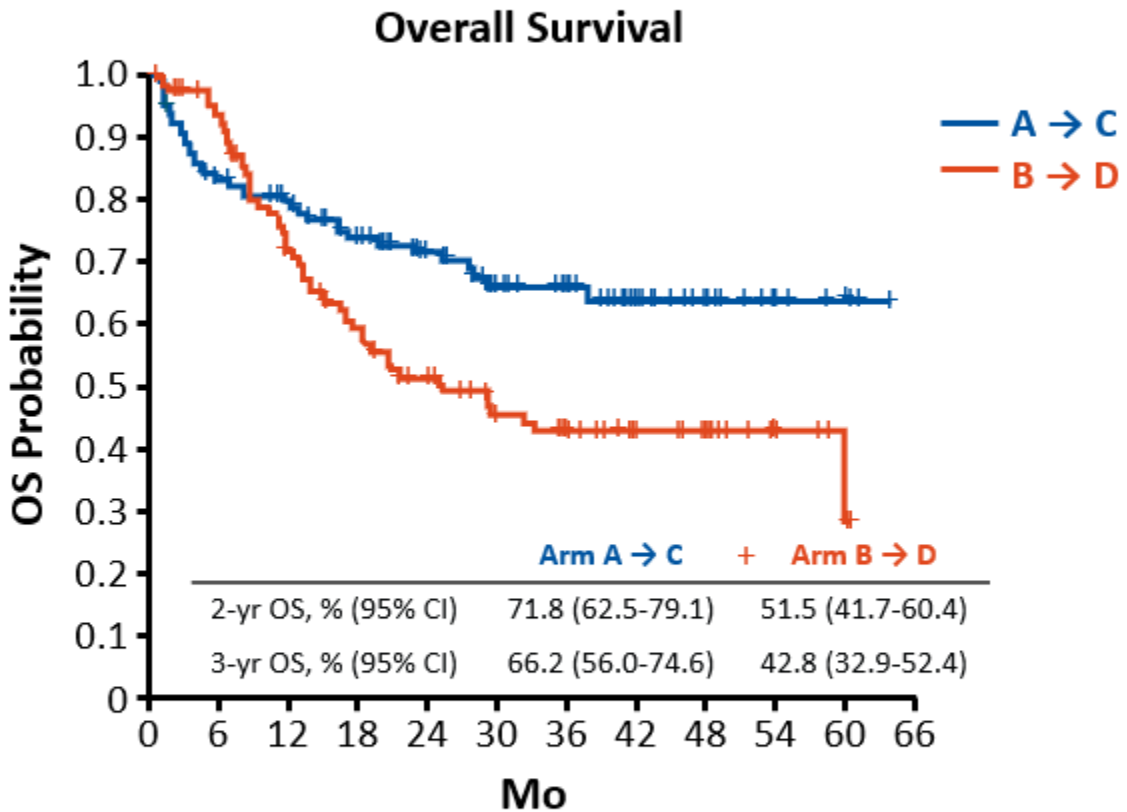
Continued until PD or unacceptable toxicity

*Ipi/Nivo on Days 1, 22 for 2 6-wk cycles; Nivo maintenance Days 1, 15, 29 cycles 3-14.

- **Primary endpoint**: 2-yr OS rate
- **Secondary endpoints**: PFS, ORR, safety

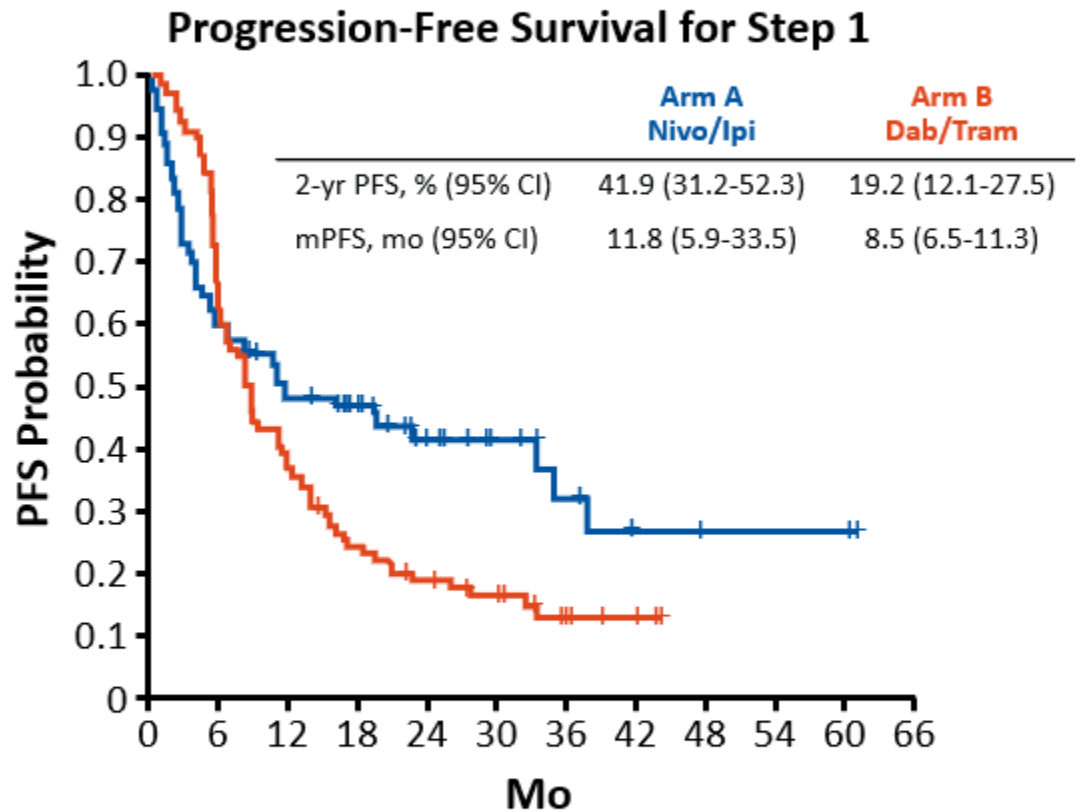
Atkins. JCO. 2023;41:186.

DREAMseq/EA6134: OS and PFS



Patients at Risk, n

Arm A → C	133	99	87	71	55	42	33	23	15	6	3
Arm B → D	132	115	78	60	47	35	30	18	15	6	1



Patients at Risk, n

Arm A	101	57	40	32	19	12	7	3	2	2	2
Arm B	113	66	38	23	17	13	6				

Atkins. JCO. 2023;41:186.

Phase III IMspire150: Anti–PD-L1 + Targeted Therapy in Newly Diagnosed, Advanced Melanoma

- Multicenter, double-blind, placebo-controlled phase III trial

Stratified by geography, LDH status

Patients with newly diagnosed unresectable, stage IIIc-IV, *BRAF* V600-positive advanced melanoma (N = 514)

Atezolizumab 840 mg IV on Days 1, 15 +
Vemurafenib 720 mg PO BID on Days 1-21 +
Cobimetinib 60 mg PO QD on Days 1-21
28-day cycles*
(n = 256)

Placebo IV on Days 1, 15
Vemurafenib 960 mg PO BID on Days 1-21 +
Cobimetinib 60 mg PO QD on Days 1-21
28-day cycles*
(n = 258)

Treatment continued until disease progression, death, unacceptable toxicity, or pregnancy

*Cycle 1: All patients received vemurafenib 960 mg PO BID on Days 1-21 + cobimetinib 60 mg PO QD, then vemurafenib 720 mg PO BID (if in atezolizumab group) or vemurafenib 960 mg PO BID (if in placebo group) for 7 days; cycles ≥2 as shown.

- **Primary endpoint**: PFS (investigator assessed)
- **Secondary endpoints**: PFS (IRC), ORR, DoR, OS, time to deterioration

Gutzmer. Lancet. 2020;395:1835.

Second-line and Later Therapy for Melanoma

SANATORIO ALLENDE

SWOG 1616 Trial of Ipilimumab ± Nivolumab in Anti–PD-1 Refractory Advanced Melanoma

- Randomized phase II trial

Patients with melanoma and no response to previous anti–PD-1/PD-L1 therapy (N = 92)

3:1

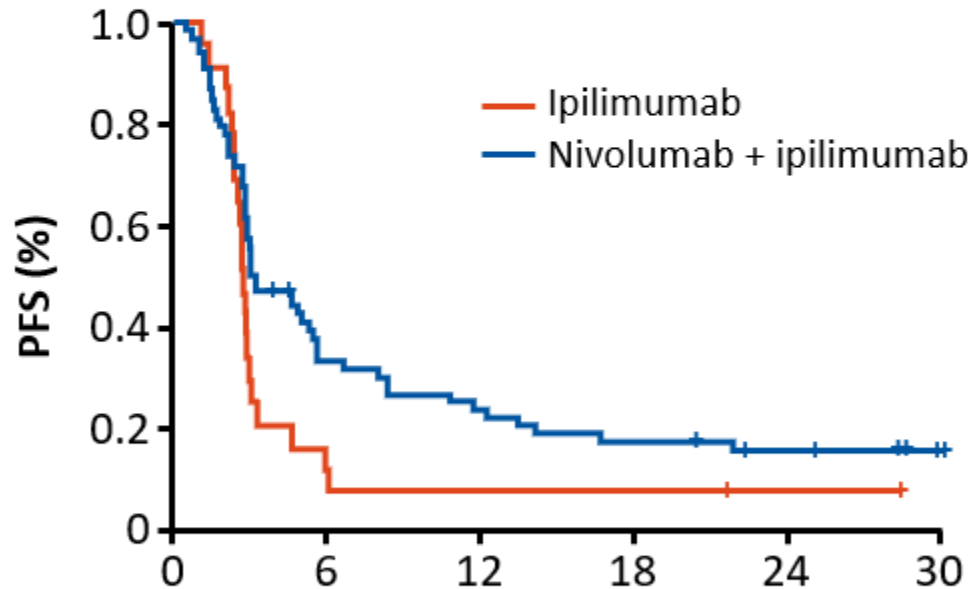
Ipilimumab + **Nivolumab** Q3W x 4 cycles → **Nivolumab** Q4W

Ipilimumab Q3W, 4 cycles

- **Primary endpoint:** PFS

PFS

	Nivo + Ipi (n = 69)	Ipi (n = 23)
6-mo PFS estimate, %	34	13
HR (90% CI)	0.63 (0.41-0.97); *P* = .04	



Patients at Risk, n					
Ipilimumab	23	3	2	2	1
Nivo + Ipi	69	22	16	12	

VanderWalde. Nat Med. 2023;29:2278.

RELATIVITY-020: 2L or Later Relatlimab/Nivolumab in Anti–PD-1/PD-L1 Refractory Melanoma

- Phase I/IIa trial of relatlimab/nivolumab in patients with progressive disease after anti–PD-1/PD-L1 therapy (n = 518)
  - Cohort D1 eligibility included ≤1 prior anti–PD-1 therapy
  - Cohort D2 eligibility included ≥1 prior anti–PD-1/PD-L1 therapy

Response	Cohort D1 (n = 351)	Cohort D2 (n = 163)
ORR, n (%)	42 (12.0)	15 (9.2)
Best overall response, n (%)		
▪ CR	15 (4.3)	4 (2.5)
PR	27 (7.7)	11 (6.7)
▪ SD	100 (28.5)	50 (30.7)
SD ≥12 wk	94 (26.8)	46 (28.2)
▪ Non-CR/non-PD	6 (1.7)	4 (2.5)
PD	174 (49.6)	68 (41.7)
▪ NE	28 (8.0)	25 (15.3)
Median DoR, mo (range)	NR (12.9-NR)	12.8 (6.9-12.9)

Cohort D1

mPFS: 2.1 mo

mOS: 14.7 mo

Cohort D2

mPFS: 3.2 mo

mOS: 17.1 mo

Ascierto. JCO. 2023;41:2724.

LEAP-004: Pembrolizumab + Lenvatinib for Anti–PD-1/PD-L1 Refractory Melanoma

- Multicenter, open-label, single-arm phase II trial

Patients with unresectable stage III/IV melanoma with confirmed PD per iRECIST ≤12 wk of last dose of anti–PD-1/PD-L1* therapy, and measurable disease by BICR (N = 103)

Pembrolizumab 200 mg IV Q3W for up to 35 cycles + **Lenvatinib 20 mg PO QD** (N = 103)

Until PD, unacceptable toxicity, or patient/physician decision

*Patients were eligible if last prior treatment involved anti-PD-1/L1 therapy given alone or in combination, including with anti-CTLA-4 agent for ≥2 doses. Maximum of 25% patients with PD on anti–PD-1/PD-L1 + anti–CTLA-4 enrolled. There was no limit to number of prior therapies permitted.

- **Primary endpoint**: ORR per RECIST v1.1 by BICR
- **Secondary endpoints**: DoR, PFS (per RECIST v1.1 by BICR), OS, safety
- Median follow-up at current analysis: 15.3 mo (range: 12.1-19.0)

Arance. JCO. 2023;41:75.

LEAP-004: BICR-Confirmed Response (Primary Endpoint)

BICR-Confirmed Response per RECIST v1.1	All Patients (N = 103)
ORR, % (95% CI)[1]	21.4 (13.9-30.5)
DCR, % (95% CI)[2]	66.0 (56.0-75.1)
Best overall response, n (%)[1]	
▪ CR	3 (2.9)
▪ PR	19 (18.4)
▪ SD	46 (44.7)
▪ PD	30 (29.1)
▪ Not assessed	5 (4.9)

- ORR the same as initial analysis
  - 1 additional patient with CR
- DCR increased from 65% at initial analysis to 66% with further follow-up
  - 1 additional patient with SD

1. Arance. JCO. 2023;41:75. 2. Arance. ASCO 2021. Abstr 9504.

C-144-01 Trial: Lifileucel in Previously Treated Metastatic Melanoma

- Multicenter, single-arm phase II study
- TILs were manufactured at centralized facility, and patients received treatment at regional centers
- Gen 2 TIL production time: 22 days

Patients with unresectable/metastatic melanoma; ≥1 prior systemic therapy including anti–PD-1; prior BRAF ± MEK inhibitors if *BRAF* V600 mutation positive; RECIST v1.1 measurable disease; ECOG PS 0-1 (N = 189)

Noncryopreserved lifileucel (Gen 1)*
(cohort 1; n = 30)

Cryopreserved lifileucel (Gen 2)*
(cohort 2; n = 66)

Cryopreserved lifileucel (Gen 2)*
(cohort 4; n = 87†)

Lifileucel retreatment*
(cohort 3; n = 10)

*Lifileucel 1 x 10^9 - 150 x 10^9 cells preceded by cyclophosphamide 60 mg/kg/d IV x 2 d + fludarabine 25 mg/m^2/d IV x 5 d and followed by to 6 doses of IL-2 600,000 IU/kg IV Q8-12h. †Planned n = 75 but rapid enrollment led to 87 patients receiving lifileucel and included in full analysis set (cohorts 2 + 4).

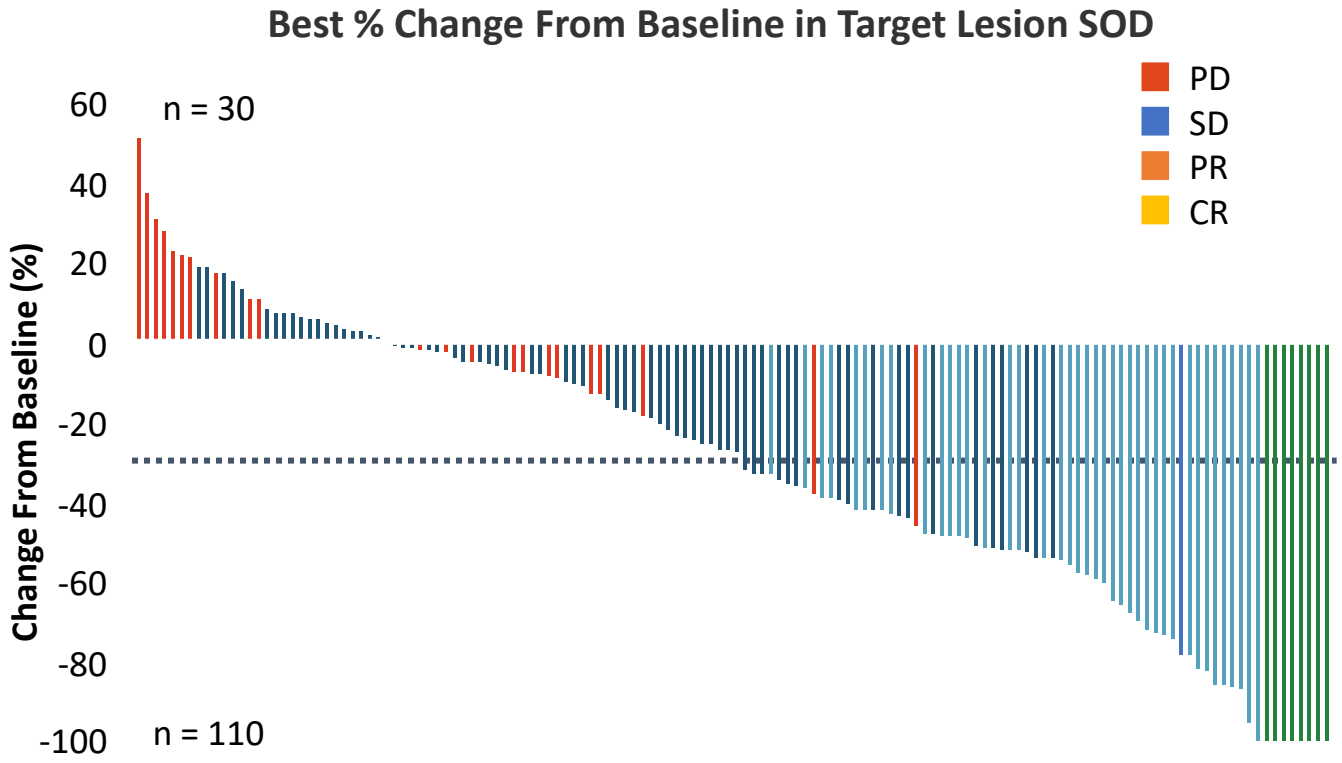
- **Primary endpoint:** IRC-assessed ORR (RECIST v1.1)
- **Secondary endpoints**: DoR, DCR, PFS, OS, safety

Sarnaik. JCO. 2021;39:2656. Chesney. J Immunother Cancer. 2022;10:e005755.

Lifileucel: Best Objective Response (Primary Endpoint)

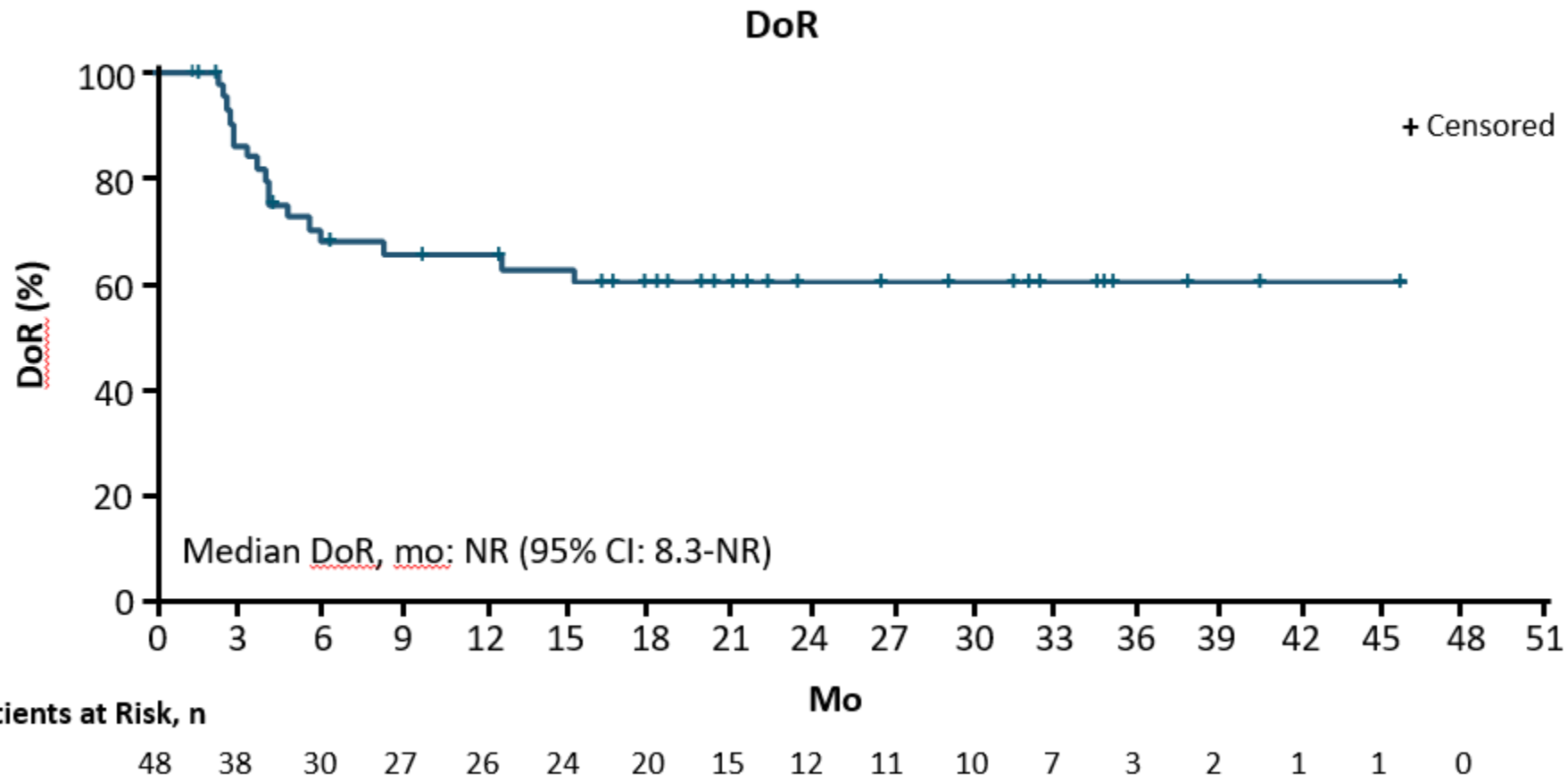
Response	Cohort 2 (n = 66)	Cohort 4 (n = 87)	Cohorts 2 + 4 (n = 153)
ORR, n (%)	23 (34.8)	25 (28.7)	48 (31.4)
Best overall response, n (%)			
▪ CR	5 (7.6)	3 (3.4)	8 (5.2)
PR	18 (27.3)	22 (25.3)	40 (26.1)
▪ SD	24 (36.4)	47 (54.0)	71 (46.4)
Non-CR/non-PD*	1 (1.5)	0	1 (0.7)
▪ PD	15 (22.7)	12 (13.8)	27 (17.6)
NE	3 (4.5)	3 (3.4)	6 (3.9)
Median DoR, mo (range)	NR (1.4+ to 45.0+)	10.4 (1.4+ to 26.3+)	NR (1.4+ to 45.0+)
Median follow-up, mo	36.6	23.5	27.6

*Patient did not have measurable target lesions by IRC and best overall response of non-CR/non-PD per IRC assessment.



Chesney. J Immunother Cancer. 2022;10:e005755.

Lifileucel: DoR in Patients With a Confirmed Response



- DoR ≥18 mo: 41.7%
- 39.6% of responses were ongoing at time of data cutoff

Chesney. J Immunother Cancer. 2022;10:e005755.

Lifileucel: Adverse Events

AEs	Safety Set (n = 156)	
Preferred Term, n (%)	Any Grade	Grade 3/4
Thrombocytopenia	129 (82.7)	120 (76.9)
Chills	117 (75.0)	8 (5.1)
Anemia	97 (62.2)	78 (50.0)
Pyrexia	81 (51.9)	17 (10.9)
Neutropenia	66 (42.3)	45 (28.8)
Febrile neutropenia	65 (41.7)	65 (41.7)
Hypophosphatemia	58 (37.2)	41 (26.3)
Leukopenia	54 (34.6)	42 (26.9)
Hypotension	52 (33.3)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Lymphopenia	49 (31.4)	38 (24.4)
Diarrhea	48 (30.8)	2 (1.3)

- 6 deaths occurred within 30 days after infusion
  - 4 deaths were determined to be due to AEs
    - 3 assessed by investigator to be related to NMA-LD and/or IL-2 (pneumonia, arrhythmia, acute respiratory failure)
    - 1 assessed by investigator to be related to all components (intra-abdominal hemorrhage)
  - 2 deaths due to PD
- TEAE were highest the first 2 wk post therapy, then rapidly decreased
- Safety profile was consistent with underlying disease and known safety profiles of NMA-LD and IL-2 regimens and was similar between cohorts

Chesney. J Immunother Cancer. 2022;10:e005755.

M14TIL: TIL vs Ipilimumab as Second-line Therapy for Patients With Advanced Melanoma

- Randomized, controlled phase III study at 2 centers (Denmark and Netherlands)

Stratification by BRAF V600 mutation status, line of treatment, and treatment center

Patients aged 18-75 yr with unresectable stage IIIC or IV cutaneous melanoma with PD after ≤1 line of systemic treatment; no prior ipilimumab treatment; RECIST v1.1 measurable disease; LDH ≤2 X ULN; WHO PS 0-1
(N = 168)

TIL
Single infusion of 5 x 10^9 - 2 x 10^{11} cells*
(n = 84)

Ipilimumab
3 mg/kg IV Q3W, maximum 4 doses
(n = 84)

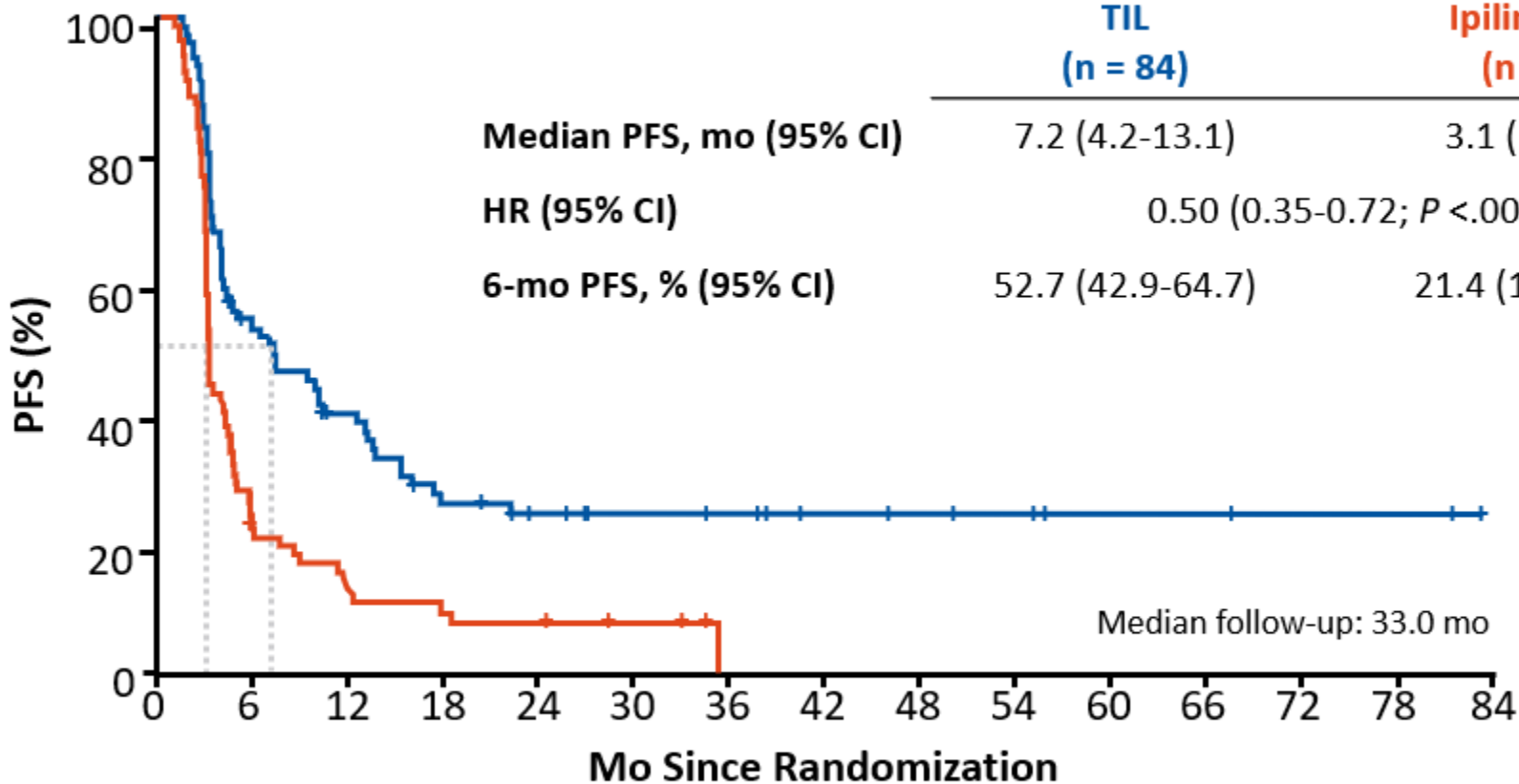
Follow-up according to protocol

*TIL infusion was preceded by NMA-LD with cyclophosphamide 60 mg/kg/d IV x 2 d + fludarabine 25 mg/m^2/d IV x 5 d and followed by up to 15 doses of IL-2 600,000 IU/kg IV Q8h.

- **Primary endpoint:** investigator-assessed PFS (RECIST v1.1, ITT population)
- **Secondary endpoints**: PFS (immune-related response criteria), ORR (RECIST v1.1 and immune-related response criteria), CR, OS, HRQoL, safety

Rohaan. NEJM. 2022;387:2113.

M14TIL: Progression-Free Survival (Primary Endpoint)



	TIL (n = 84)	Ipilimumab (n = 84)
Median PFS, mo (95% CI)	7.2 (4.2-13.1)	3.1 (3.0-4.3)
HR (95% CI)	0.50 (0.35-0.72; *P* <.001)	
6-mo PFS, % (95% CI)	52.7 (42.9-64.7)	21.4 (14.2-32.2)

Patients at Risk, n

TIL	84	41	29	18	14	11	10	7	6	5	3	3	2	2	0
Ipilimumab	84	17	8	6	5	3	0	0	0	0	0	0	0	0	0

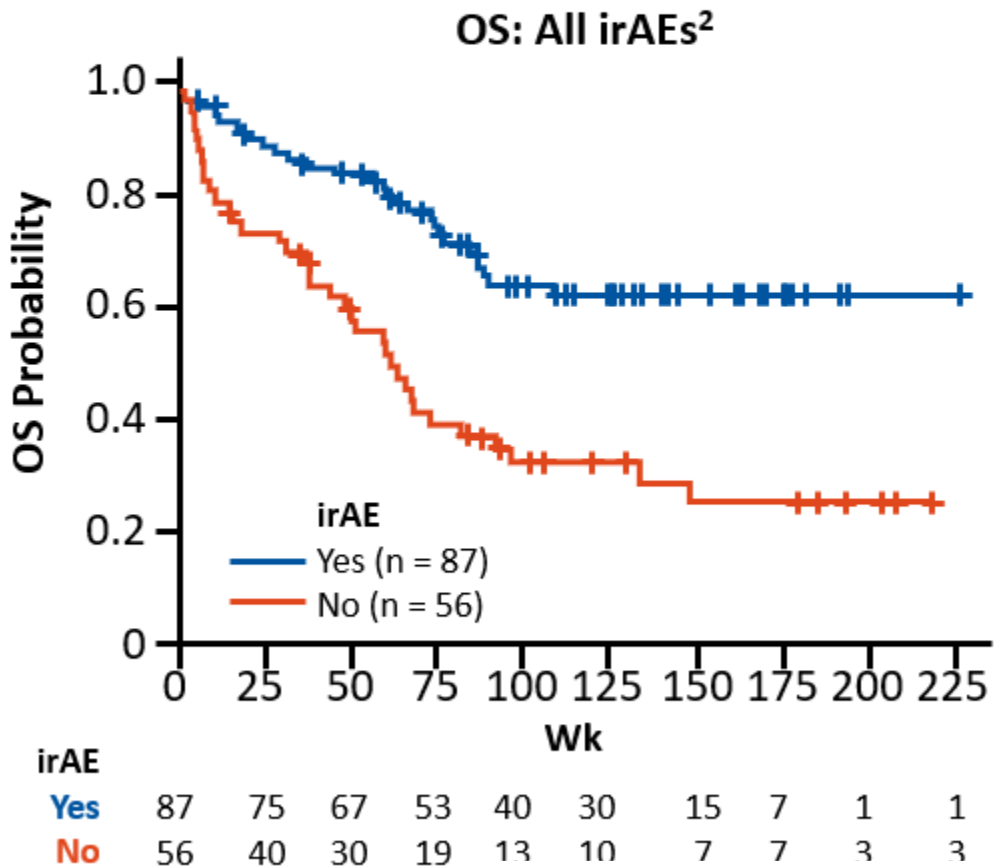
Rohaan. NEJM. 2022;387:2113.

Effect of TRAE on Survival

KEYNOTE-054 Trial[1]

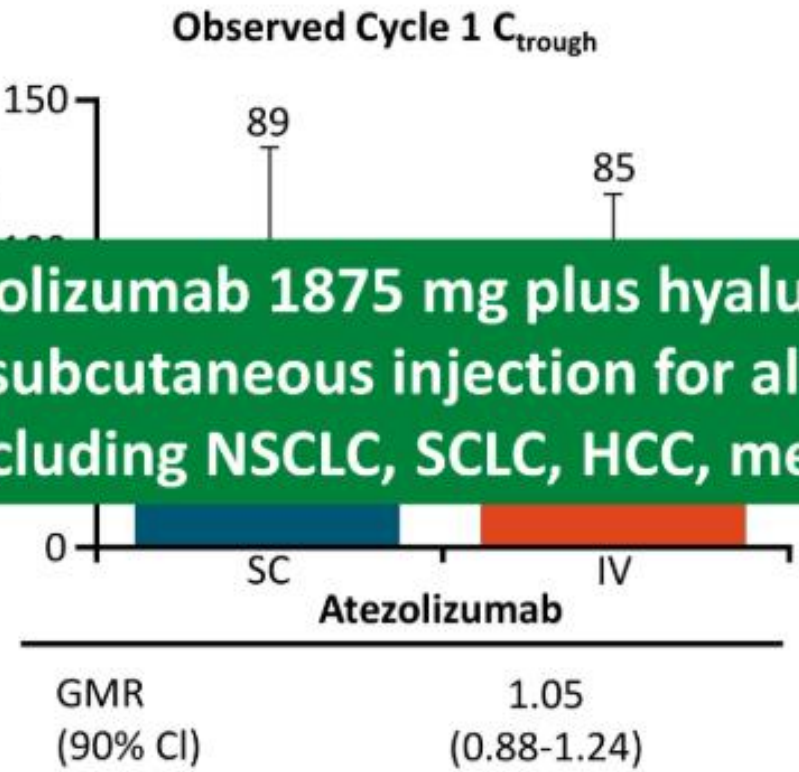
irAE by Treatment Arm	HR for RFS (95% CI)	*P* Value
Any irAE ▪ Placebo ▪ Pembro before irAE ▪ Pembro after irAE	1 0.62 (0.49-0.78) 0.37 (0.24-0.57)	.03
Endocrine irAE ▪ Placebo ▪ Pembro before irAE ▪ Pembro after irAE	1 0.60 (0.48-0.75) 0.34 (0.20-0.57)	.03
Vitiligo ▪ Placebo ▪ Pembro before irAE ▪ Pembro after irAE	1 0.57 (0.46-0.70) 0.13 (0.02-0.95)	.15
Any grade 3/4 irAE ▪ Placebo ▪ Pembro before irAE ▪ Pembro after irAE	1 0.55 (0.44-0.68) 0.78 (0.32-0.91)	.43

- Pooled analysis of irAEs and outcomes with nivolumab in metastatic melanoma



1. Eggermont. JAMA Oncol. 2020;6:519. 2. Freeman-Keller. Clin Cancer Res. 2016;22: 886.

IMscin001 Part 2: Cycle 1 C_{trough} and AUC on Days 0-21 (Coprimary Endpoints)



	SC	IV
GMR (90% CI)	1.05 (0.88-1.24)	

- **Cycle 1 C_{trough} SC vs IV:** 89 µg/mL vs 85 µg/mL; GMR: 1.05

AUC from Days 0-21

- SC atezolizumab: 2907 µg/mL
- IV atezolizumab: 3328 µg/mL

Atezolizumab 1875 mg plus hyaluronidase-tqjs is now approved by the FDA for subcutaneous injection for all the adult indications as IV atezolizumab, including NSCLC, SCLC, HCC, melanoma, and alveolar soft part sarcoma

(HR: 1.08; 90% CI: 0.82-1.41)

- **ORR SC vs IV:** 12% vs 10%
- **Antiatezolizumab antibody development for SC vs IV:** 19.5% vs 13.9%

NCT03735121. Felip. Clin Pharmacol Drug Dev. 2021;10:1142.

CheckMate 67T: Most Common AEs in Either Arm

Adverse Events, n (%)	Nivo SC + HuPH20 (n = 247)		Nivo IV (n = 245)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any	230 (93.1)	99 (40.1)	231 (94.3)	114 (46.5)
▪ Hypothyroidism	25 (10.1)	0	32 (13.1)	1 (0.4)
▪ Decreased appetite	24 (9.7)	0	32 (13.1)	3 (1.2)
▪ Fatigue	22 (8.9)	2 (0.8)	41 (16.7)	8 (3.3)

In December 2024, the FDA approved nivolumab as monotherapy and hyaluronidase-nvhy as SC injection across approved adult solid tumor indications, as monotherapy maintenance following completion of nivolumab and ipilimumab combination therapy, or in combination with chemotherapy or cabozantinib

Albiges. Ann Oncol. 2025;36:99.

RELATIVITY-048: Relatlimab + Nivolumab + Ipilimumab Triplet for Treatment-Naive Advanced Melanoma

- Nonrandomized phase I/II trial: advanced melanoma expansion cohort

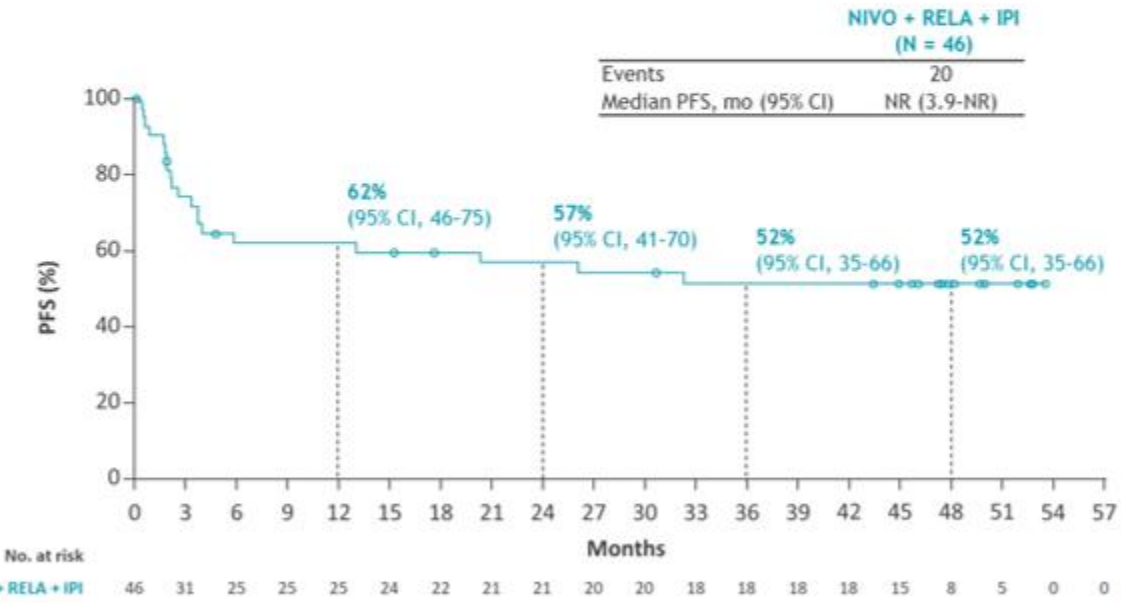
Previously untreated advanced unresectable or metastatic melanoma; ECOG PS 0/1; (neo)adjuvant immunotherapy ≥6 mo before permitted
(N = 46)

→ **Relatlimab** 160 mg + **Nivolumab** 480 mg Q4W + **Ipilimumab** 1 mg/kg Q8W

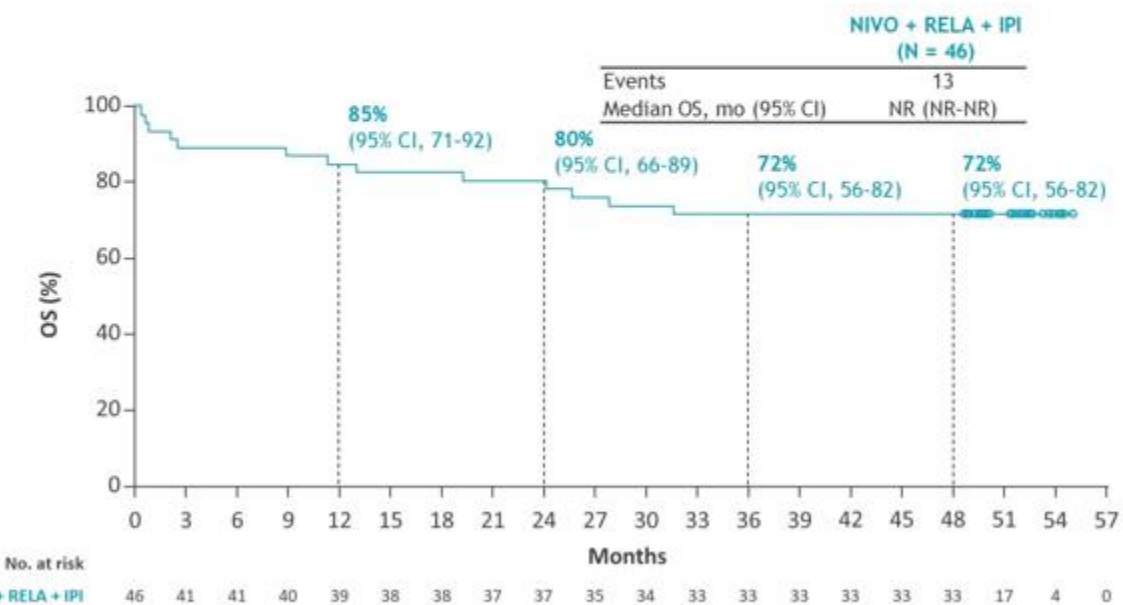
- **Primary endpoints:** safety, ORR, DCR, median DoR
- **Secondary endpoints:** PFS rates at 6 mo and 12 mo
- **Exploratory endpoints:** OS rates at 1 yr and 2 yr

RELATIVITY-048: PFS by Investigator and OS

PFS

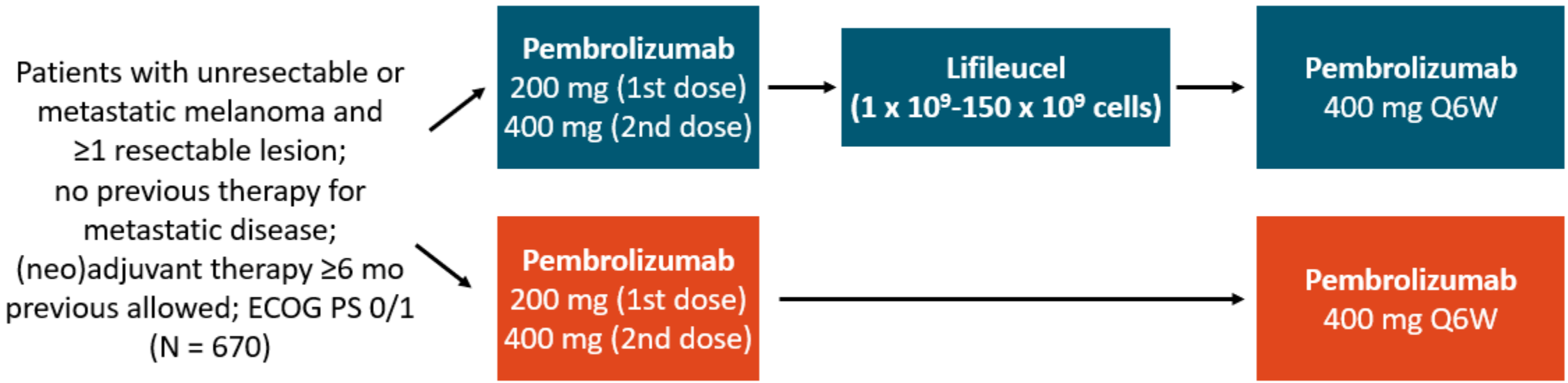


OS



TILVANCE-301: Lifileucel + Pembrolizumab as First-line Therapy for Advanced Melanoma

- Randomized phase III trial

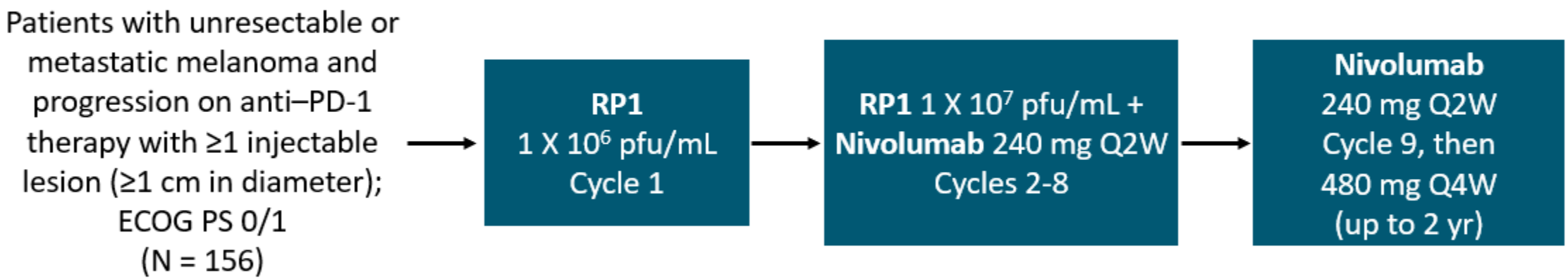


*Before lifileucel administration, patients undergo nonmyeloablative lymphodepletion with 2 days of cyclophosphamide followed by 5 days of fludarabine. **Lifileucel is infused as a 1-time treatment. Up to 6 doses of IL-2 are administered to boost treatment response.**

- **Primary endpoints:** ORR and PFS by BIRC
- **Secondary endpoints:** OS; CR, DoR, EFS by BIRC and INV; ORR, PFS, PFS2 by INV; safety

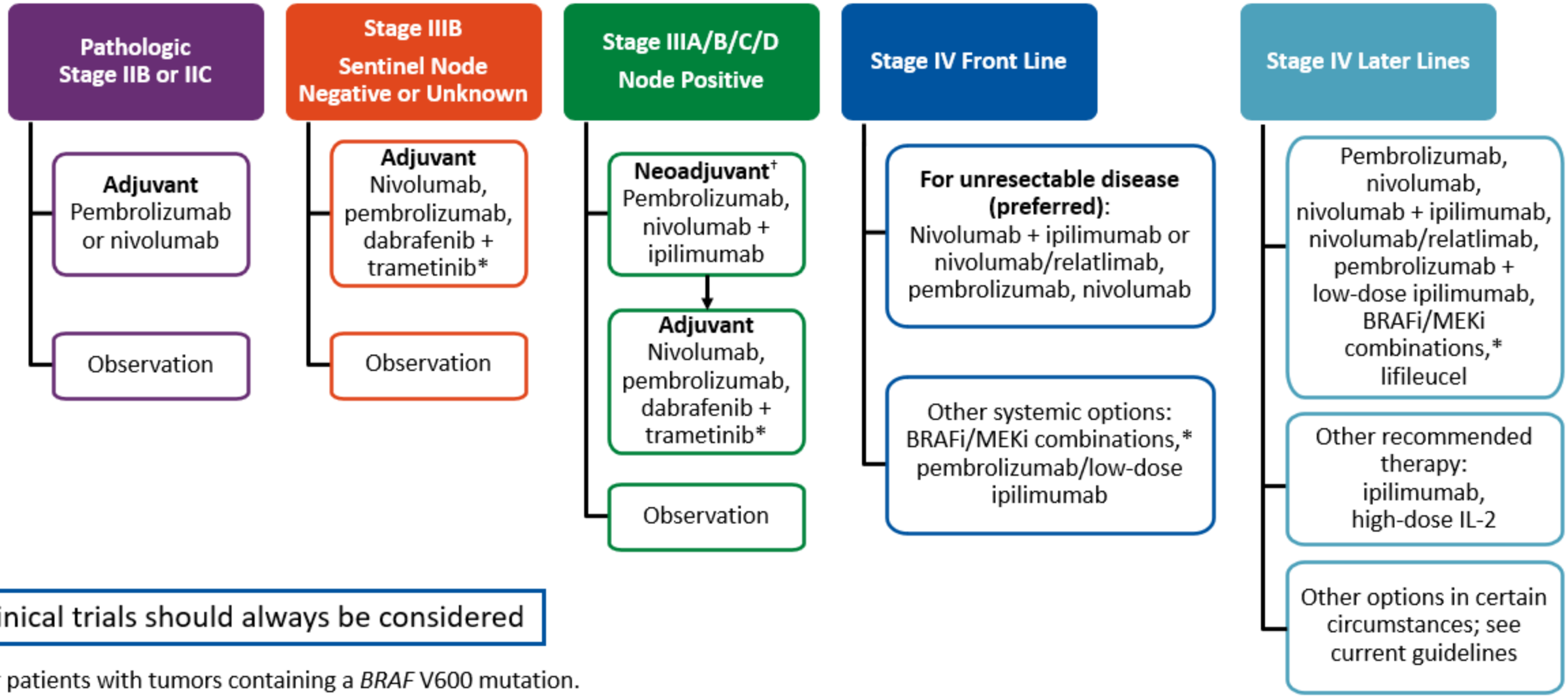
IGNYTE: RP1 + Nivolumab in Patients With Advanced Melanoma Progressing on Anti–PD-1 Therapy

- RP1: HSV-1–based oncolytic therapy expressing hGM-CSF and GALV-GP-R- fusion protein



- **Primary endpoint:** safety and efficacy by BIRC
- **Secondary endpoints:** ORR, DoR, CR rate, DCR, PFS, OS rate at 1 yr and 2 yr

Guideline Recommendations for Systemic Therapy



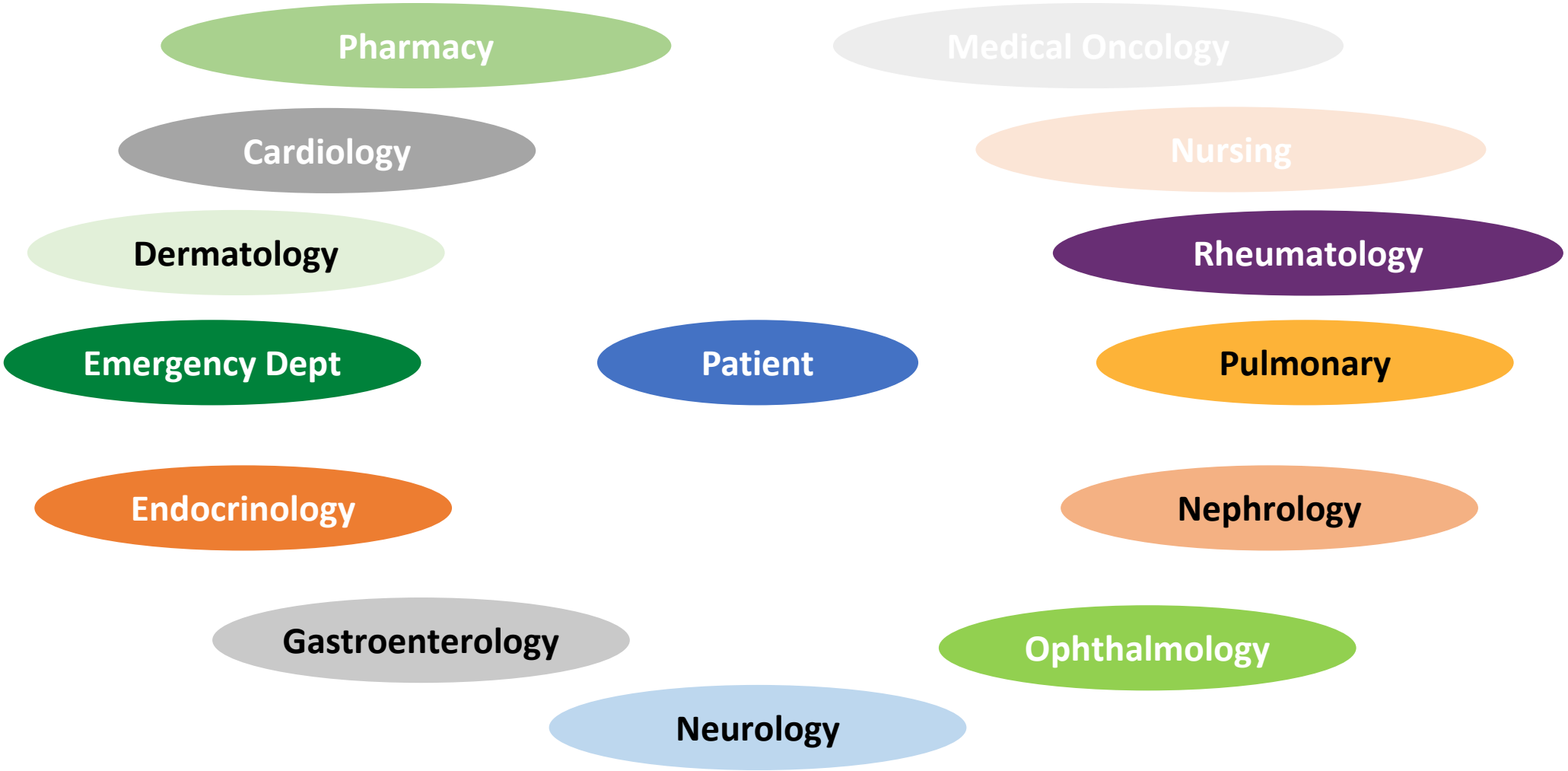
Clinical trials should always be considered

*For patients with tumors containing a *BRAF* V600 mutation.

†Other options include nivolumab, nivolumab/relatlimab, dabrafenib + trametinib.

NCCN. Clinical practice guidelines in oncology: melanoma: cutaneous. v.2.2024. nccn.org.

Multidisciplinary Approach to Patient Care



Gracias por su atención!

SANATORIO ALLENDE

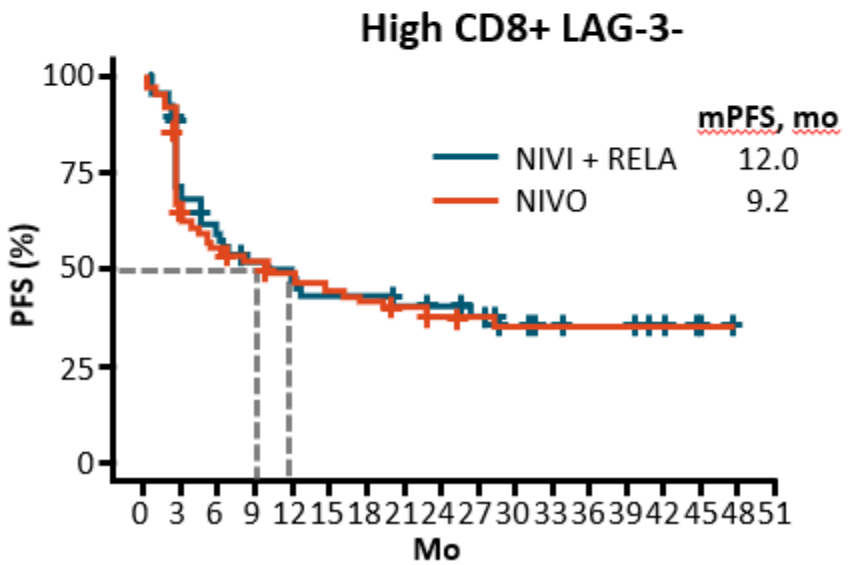
AJCC Version 8 Melanoma Staging

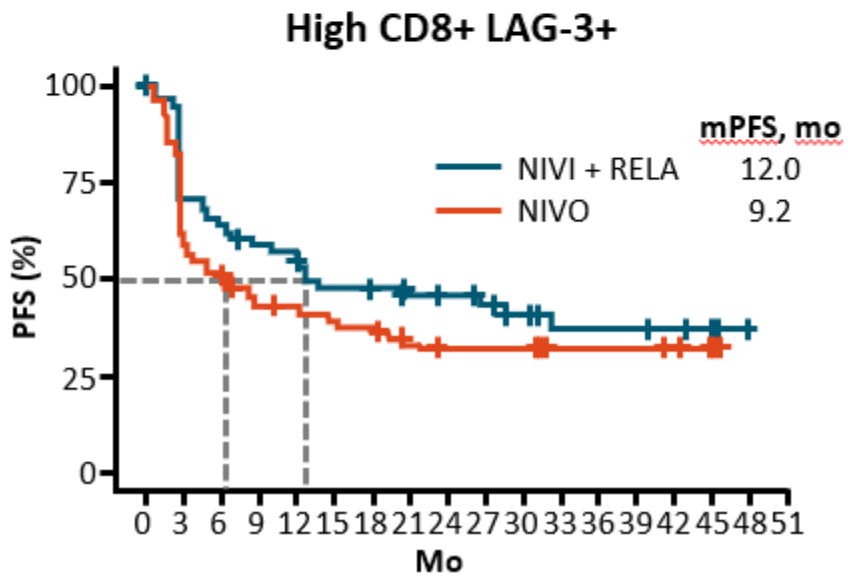
T	N	M	Clinical Stage
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥ N1	M0	III
Any T	Any N	M1	IV

Gershenwald. CA Cancer J Clin. 2017;67:472.

RELATIVITY-047 Biomarker Analysis: PFS Benefit According to Baseline LAG-3 Levels in High CD8+ Tumors

- PFS benefit observed with NIVO + RELA vs NIVO in patients with high CD8+ LAG-3+ tumors
- Data suggest LAG-3 expression may confer resistance to PD-1 inhibition that may be reversed with LAG-3 inhibition





M14TIL: Grade ≥3 Adverse Events in ≥5% of Patients

TIL (n = 80)			
AE, n (%)	**Chemotherapy**	**AE, n (%)**	**TIL + IL-2**
Neutropenia	80 (100)	Febrile neutropenia	59 (74)
Thrombocytopenia	71 (89)	Hypophosphatemia	48 (60)
Febrile neutropenia	69 (86)	Fever	36 (45)
Leukopenia	57 (71)	Dyspnea	15 (19)
Hypophosphatemia	20 (25)	Hypertension	11 (14)
Anemia	16 (20)	CPK increased	9 (11)
Elevated ALT	7 (9)	Rash	9 (11)
GGT increased	6 (8)	Elevated AST	8 (10)
Elevated AST	4 (5)	Elevated ALT	8 (10)
Fatigue	4 (5)	Fatigue	7 (9)
		Chills	6 (8)
		GGT increased	
		Hypotension	6 (8)
		Hypoxia	5 (6)

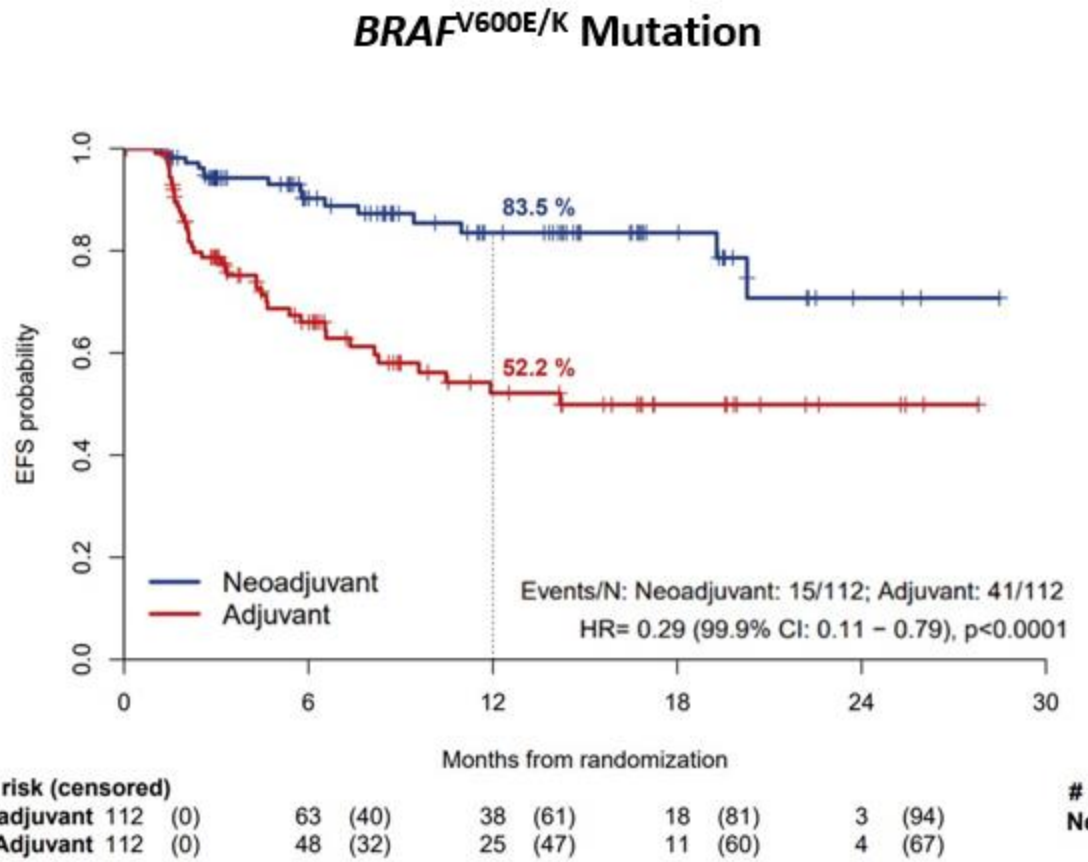
- Grade ≥3 AEs in 100% of patients receiving TIL therapy due to lymphodepletion

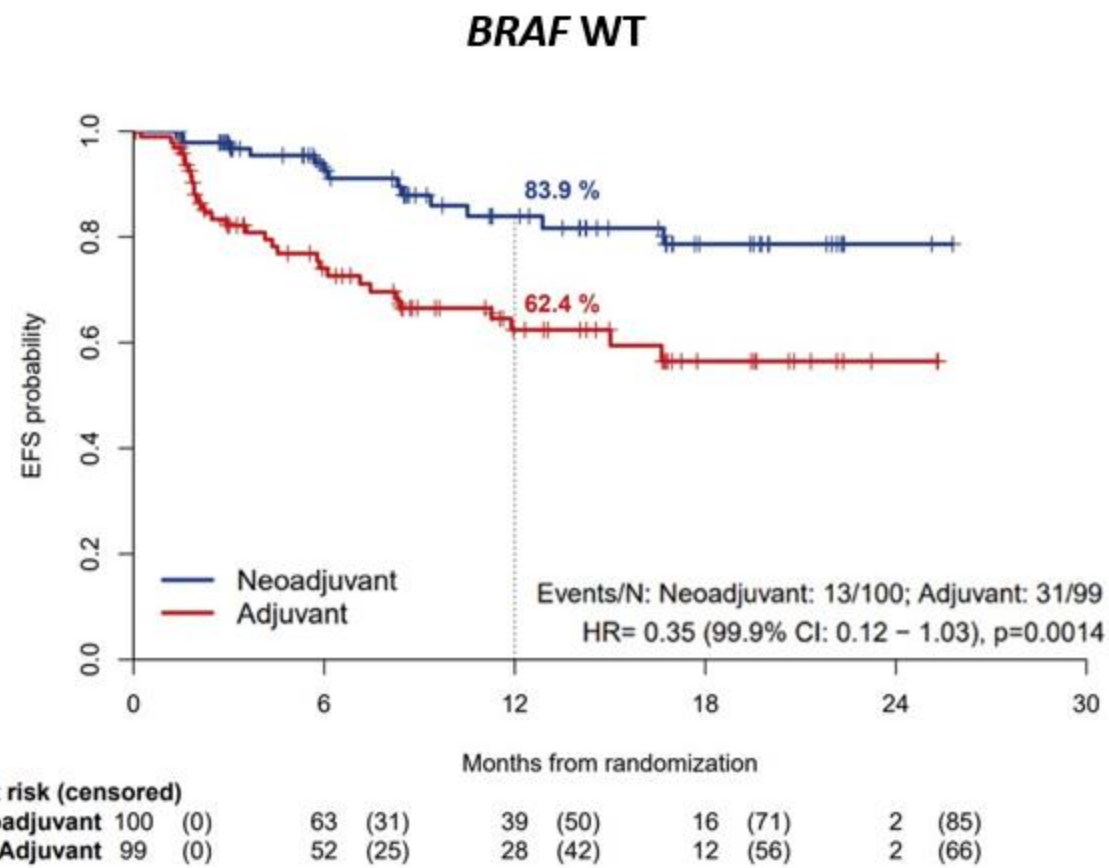
Ipilimumab (n = 82)	
AE	**n (%)**
Colitis	16 (20)
Diarrhea	12 (15)
Elevated ALT	8 (10)
Elevated AST	7 (9)
Rash	4 (5)
Elevated ALP	4 (5)

- Grade ≥3 AEs in 57% of patients receiving ipilimumab

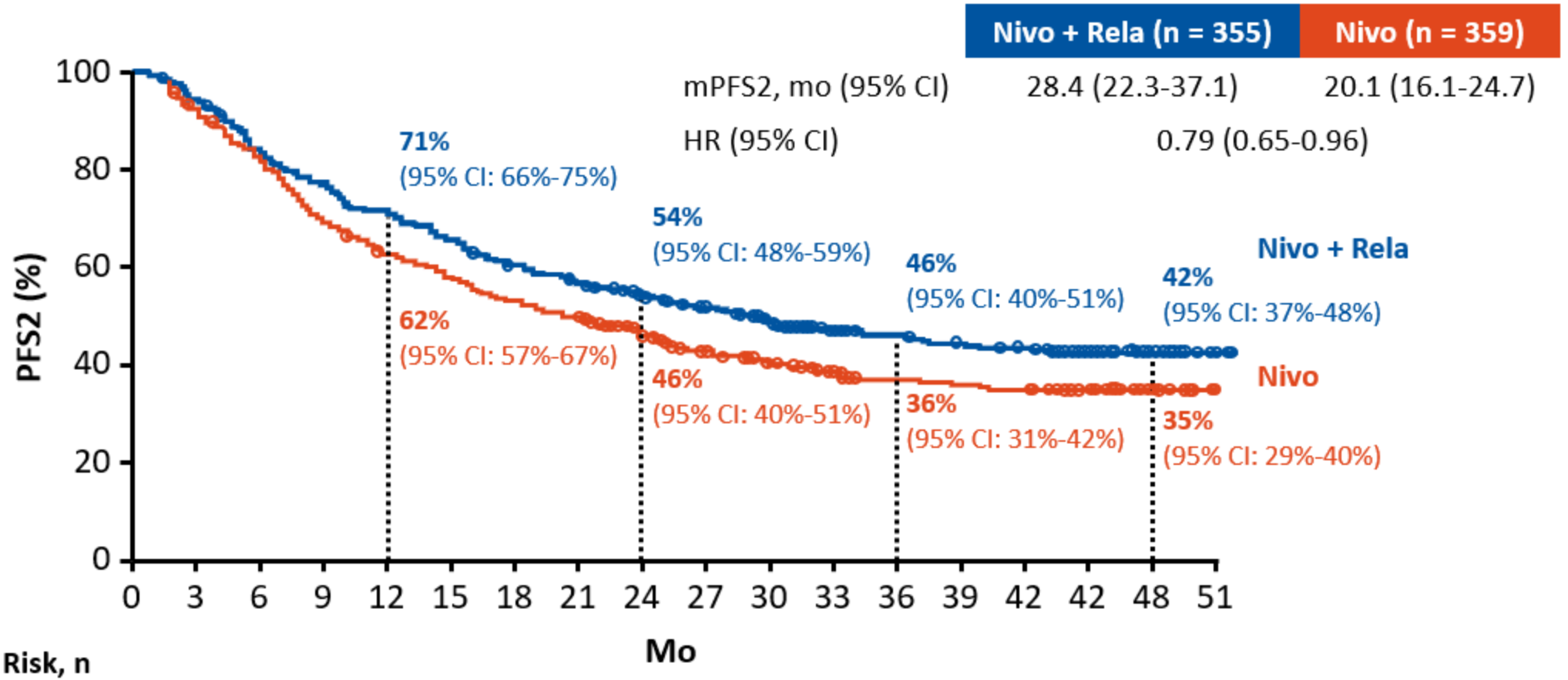
Rohaan. NEJM. 2022;387:2113.

NADINA: EFS by *BRAF* Mutational Status





RELATIVITY-047: Exploratory Endpoint of PFS2 by Investigator



Patients at Risk, n

Nivo + Rela	355	332	293	270	249	230	209	196	172	154	136	114	106	99	96	62	19	2
Nivo	359	329	291	246	219	202	187	173	144	122	105	87	77	75	73	49	13	0

Tawbi. ASCO 2023. Abstr 9502.