State-of-the-Art Management in Early and Metastatic Melanoma

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MOFFITT CANCER CENTER

Outline

i. Early stage (stage I, II) melanoma management

ii. Neoadjuvant/adjuvant therapy for stage III/IV resectable melanoma

iii. Systemic therapy for advanced/non-resectable stage III/IV melanoma

Case 1

A 66-year-old male with no past medical history presents for evaluation of the pigmented lesion over posterior trunk.

Invasive primary cutaneous melanoma? Yes
Tumor subtype: Nodular
Clark level: IV, at least
Breslow depth: 2.9 mm, at least
Ulceration: Present
Mitotic rate: 4 /mm2
Regression: Not identified
Vertical growth phase: Present
Angiolymphatic invasion: Not identified
Perineural invasion: Not identified
Microsatellites: Not evaluable
Tumor-infiltrating lymphocytes: Present, non-brisk
Precursor nevus: Not identified
Solar elastosis: 0
Tumor cell pigmentation: 1

T3b

Management of early-stage (I, II) melanoma

- **Wide excision**

T	Excision margin (cm)
Tis: In situ	0.5-1
T1: ≤1.0 mm	1
T2: 1.1-2.0 mm	1-2
T3-4: >2.0 mm	2

- **+/- Sentinel Lymph Node Biopsy (SLNB)**

Risk of positive SLN	Recommendation
<5% (<0.8mm+no ulceration)	Not recommended
5-10% 1. <0.8 mm with ulceration or 0.8–1 mm with or without ulceration 2. >0.5 mm and other adverse features (age ≤42 years, head/neck location, lymphovascular invasion, and/or mitotic rate ≥2/mm2)	Discuss and consider
>10% (>1mm)	Discuss and offer

NCCN Melanoma Guidelines v1, 2025

Case 1 continues

A 66-year-old male presents for discussion of adjuvant therapy after undergoing wide excision and sentinel lymph node biopsy. PET/CT and MRI Brain revealed no evidence of residual disease.

A. Lymph Node, "Sentinel Lymph Node #1, Right Axilla", Biopsy:
No evidence of melanoma in one lymph node (0/1).

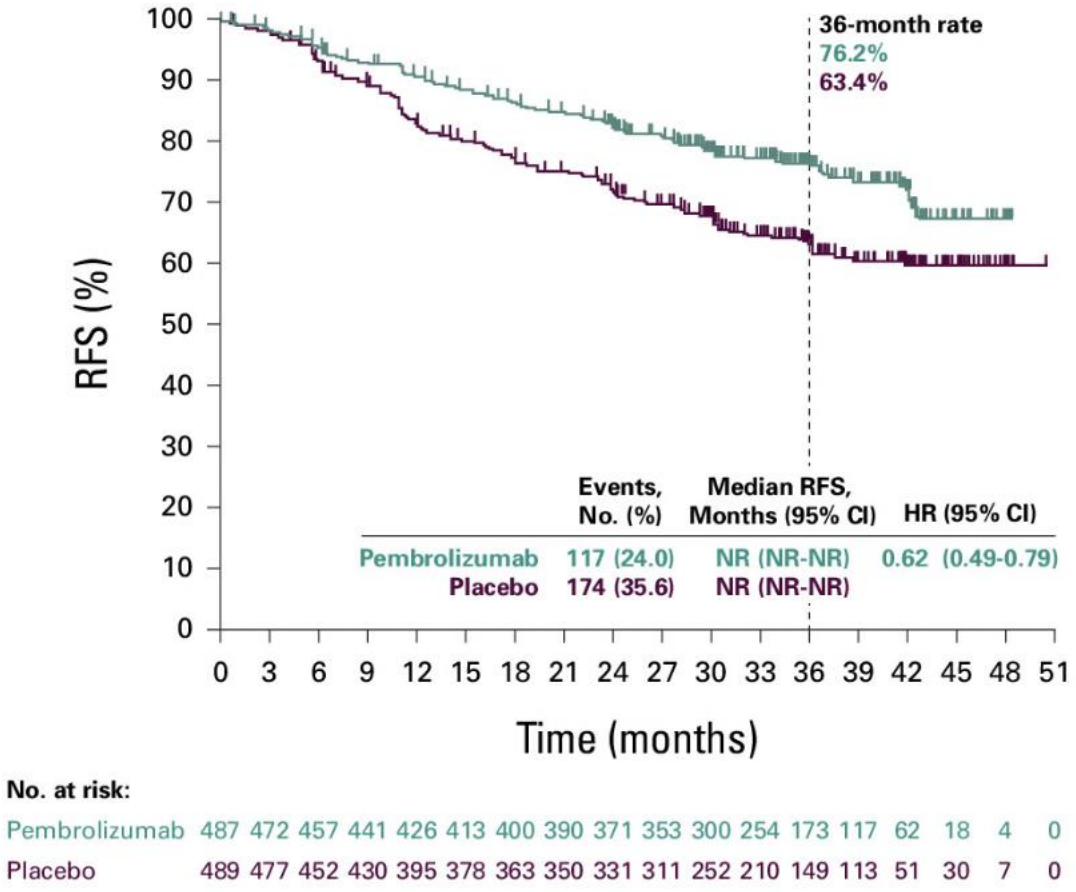
B. Lymph Node, "Sentinel Lymph Node #2", Right Axilla", Biopsy:
No evidence of melanoma in one lymph node (0/1).

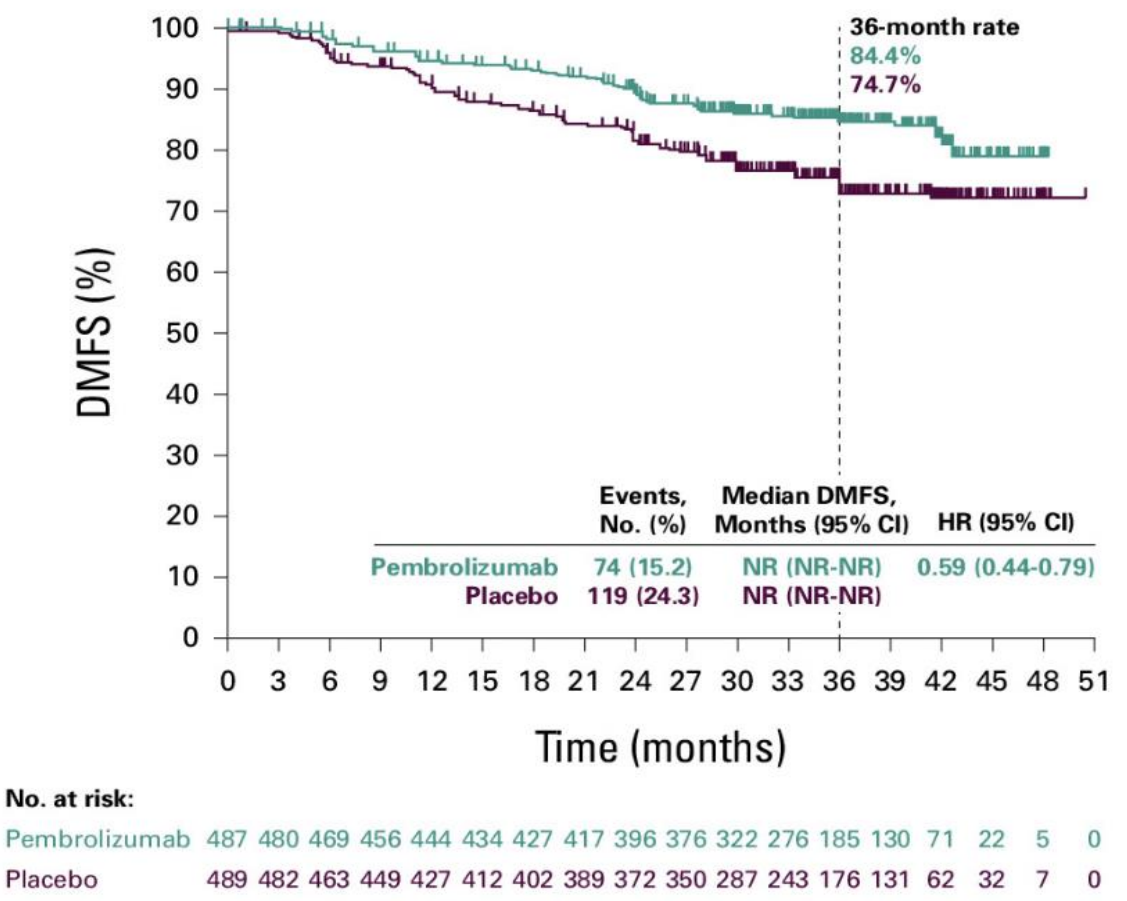
Stage IIB (T3bN0M0)

HMB-45 and SOX-10 immunostaining, with appropriate controls, were performed on the 3 sentinel lymph node tissue blocks, 1 from specimen A and 2 from specimen B, to evaluate for the presence of micrometastatic disease and fail to reveal evidence of metastatic malignant melanoma.

C. Skin, "Back, Right Upper", Excision:
Dermal scar, previous procedural site changes, residual malignant melanoma, Clark level IV, 2.9 mm in depth, margins clear.

Adjuvant Pembrolizumab for Stage IIB/IIC melanoma

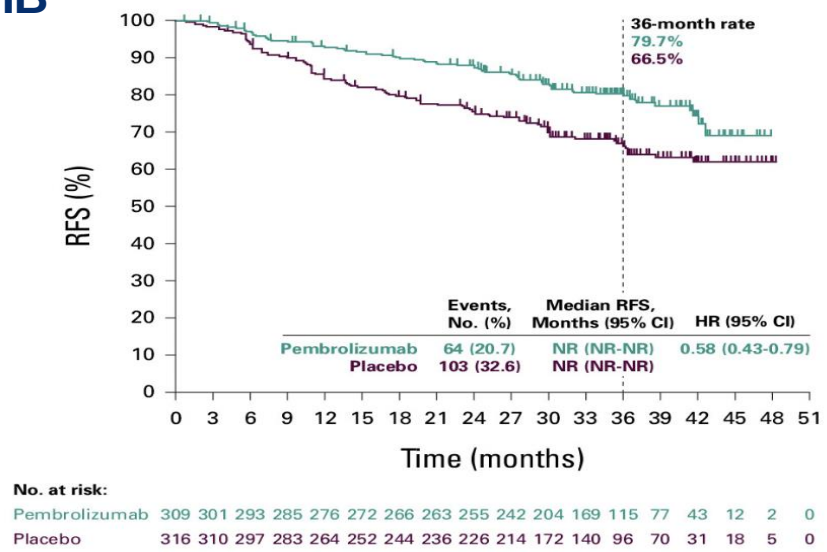




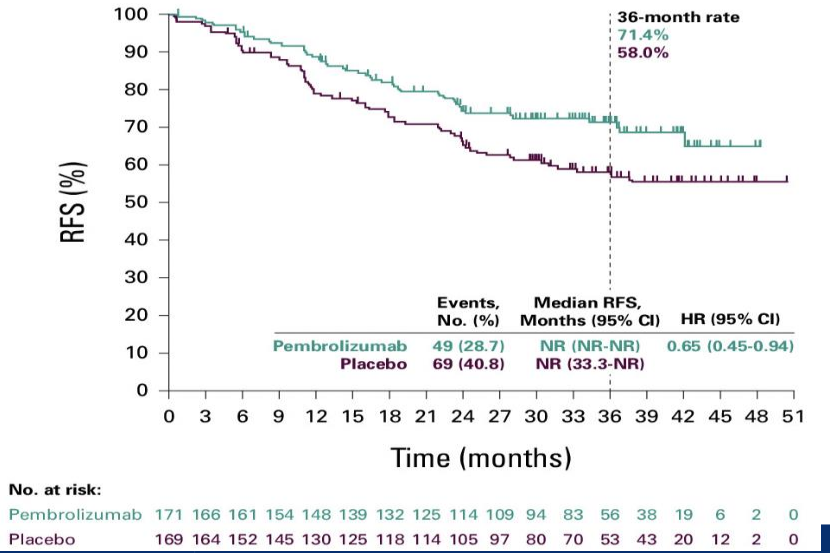
Luke et al, Journal of Clinical Oncology, 2024

Adjuvant Pembrolizumab for Stage IIB/IIC melanoma

IIB



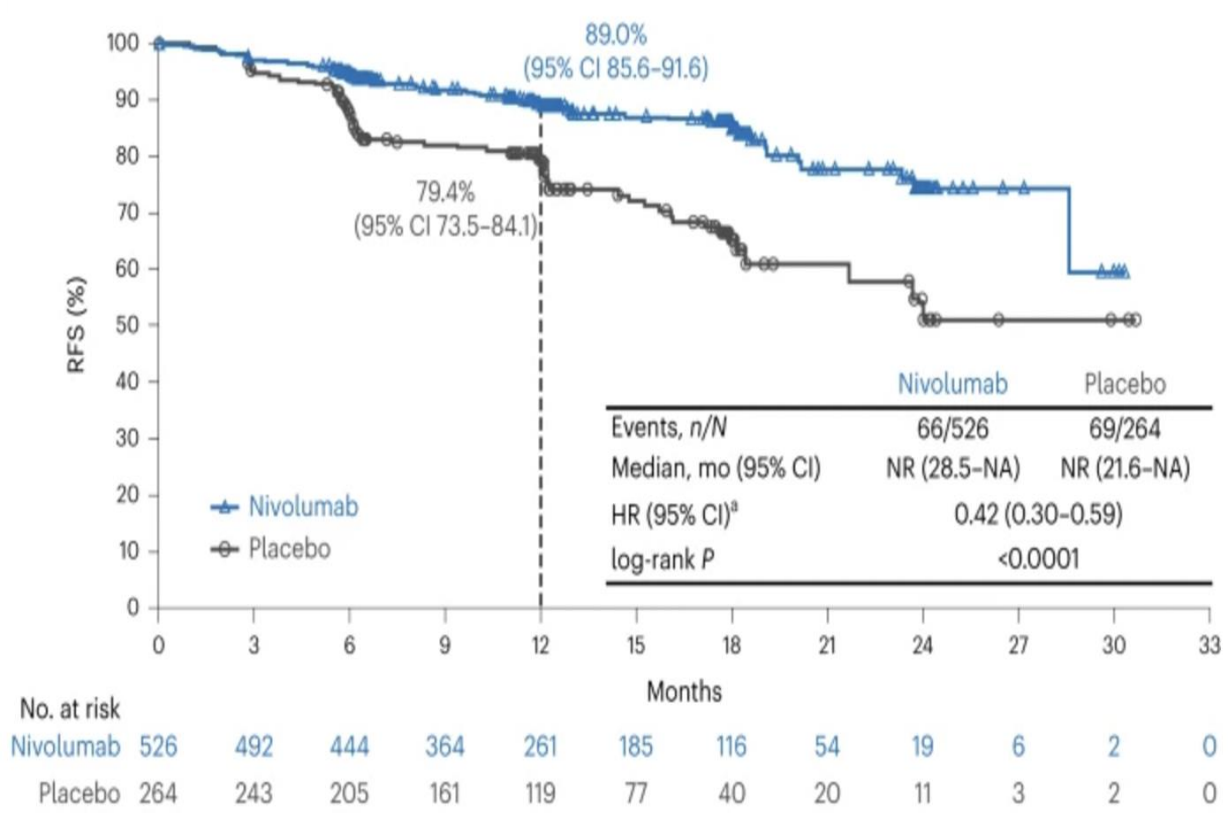
IIC

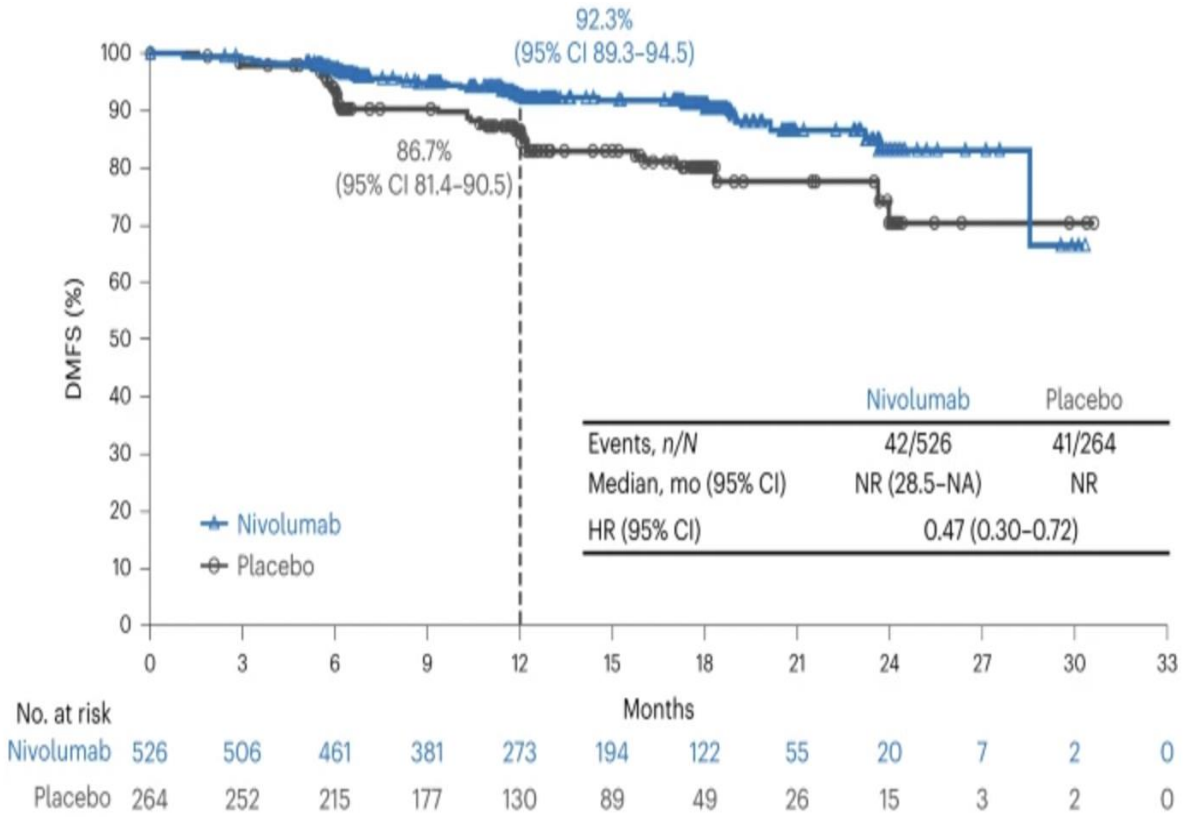


Treatment-related adverse event (TRAE)	Percent Any/≥G3
Any/≥G3 TRAE	82.6/17.2
Hypothyroidism	17.2/0
Hypophysitis	2.5/0.6
Adrenal Insufficiency	2.7/1.0
Hepatitis	2.3/1.9
Colitis	4.1/1.7
Myasthenic syndrome	0.4
Myocarditis	0.2
Type I Diabetes Mellitus	0.4

Luke et al, Journal of Clinical Oncology, 2024

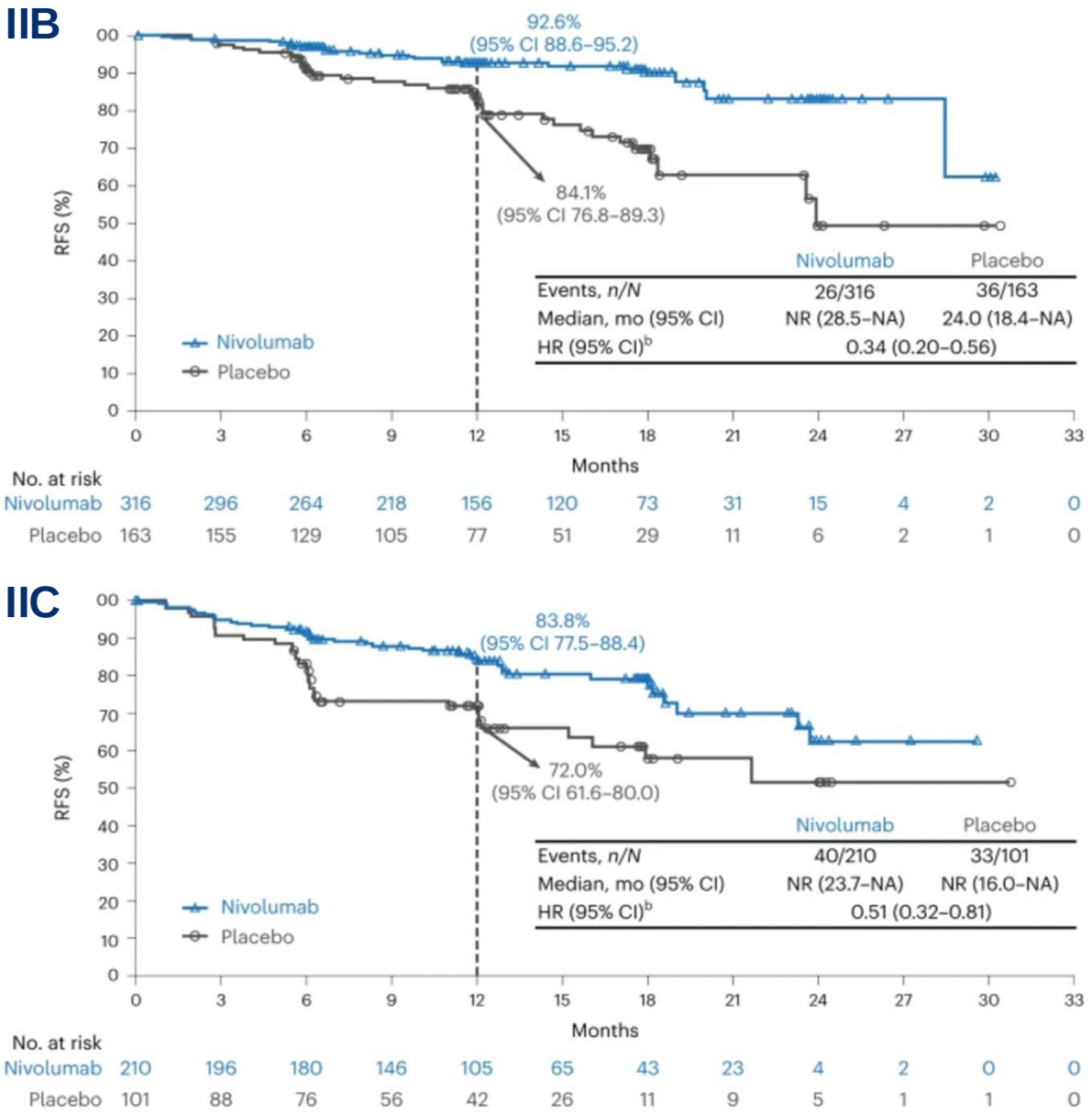
Adjuvant nivolumab for Stage IIB/IIC melanoma





Kirkwood et al, Nature Medicine, 2024

Adjuvant nivolumab for Stage IIB/IIC melanoma

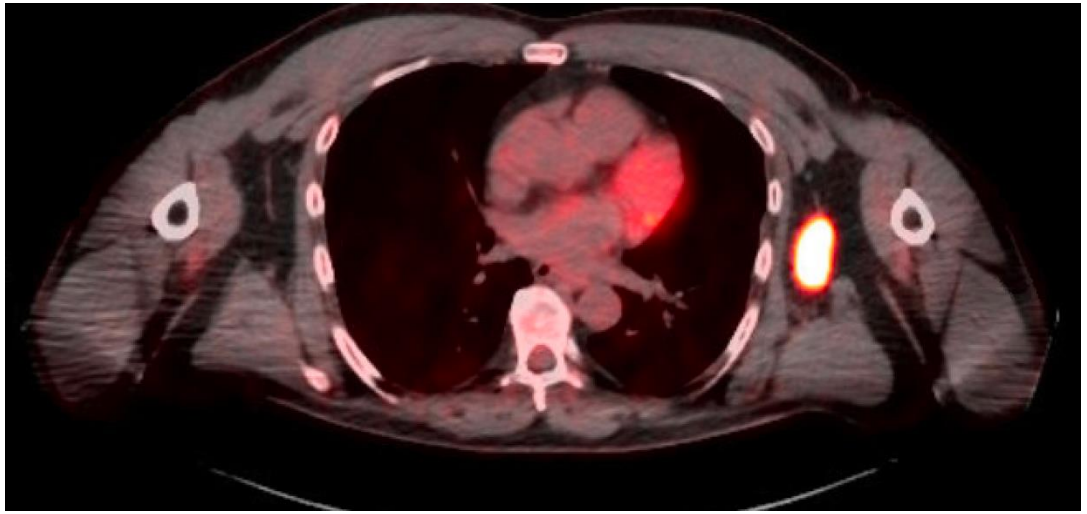


Treatment-related adverse event (TRAE)	Percent Any/≥G3
Any/≥G3 TRAE	82.6/10.3
Hypothyroidism	10.3/0
Adrenal Insufficiency	2.3/0.6
AST/ALT elevation	~6/1
Pneumonitis	0.8/0.2
Diarrhea	15.3/0.8
Rash	10.9/0.8
Myocarditis	0.5%
Myositis	1%

Kirkwood et al, Nature Medicine, 2024

Case 1 continues

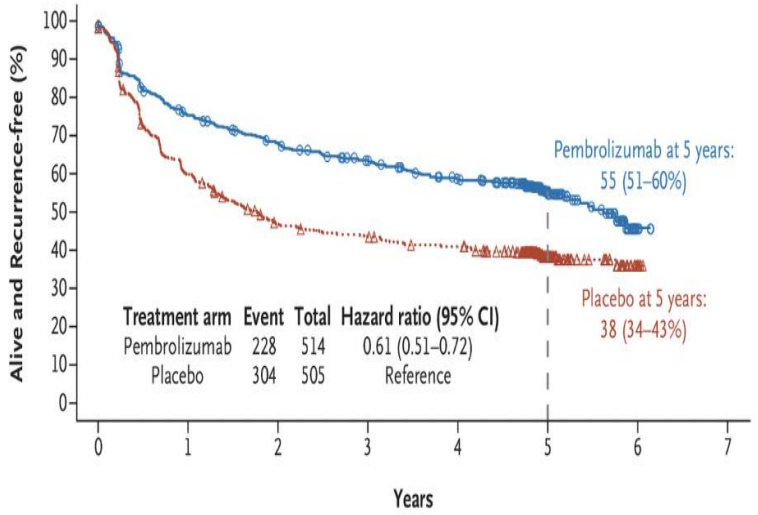
After discussion of benefits and risks related to adjuvant immunotherapy, patient opted NOT to proceed with adjuvant therapy. Patient presents 3 years later with palpable axillary mass.



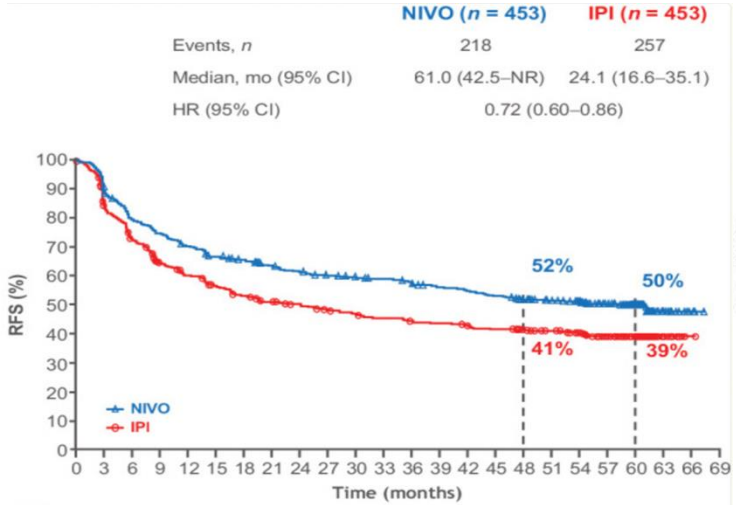
Core needle biopsy confirmed diagnosis of metastatic melanoma in axillary lymph node. *BRAF* wild type, *NF1* mutant. PET/CT and MRI brain revealed no evidence of other metastases.

Adjuvant anti-PD1 therapy for resected stage III/IV melanoma

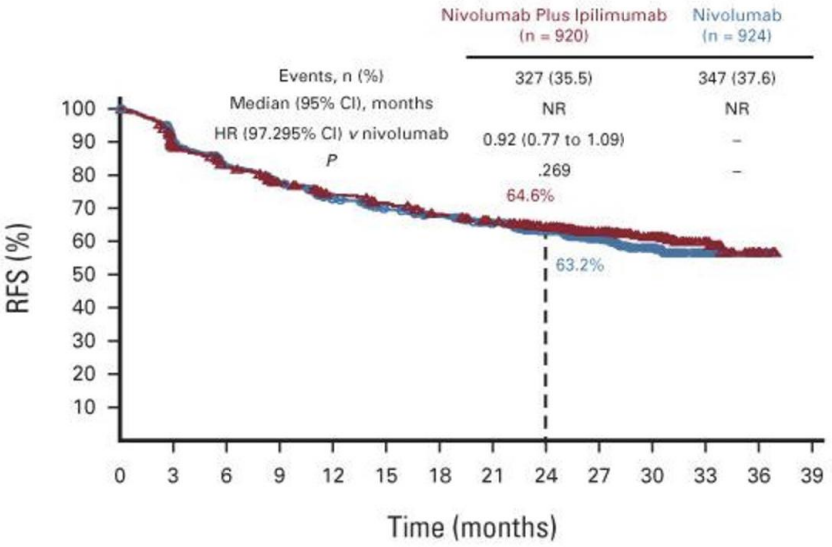
IIIA (>1mm) IIIB/C



IIIB–C/IV



IIIB–D/IV

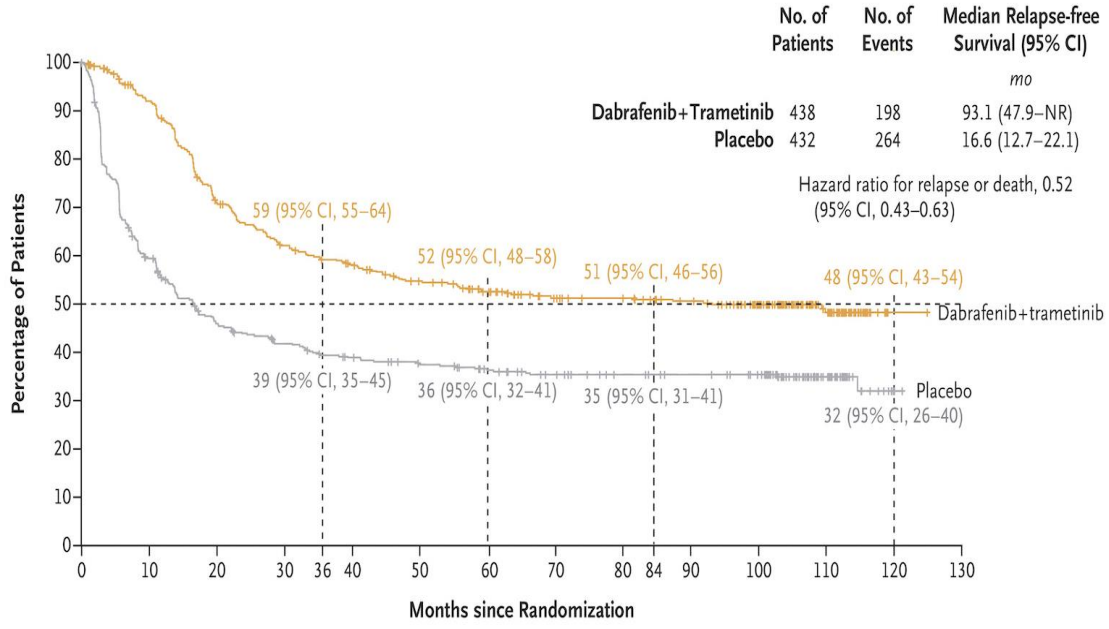


Eggermont et al, NEJM, 2021
Larkin et al, Clinical Cancer Research, 2023
Weber et al, J Clin Oncol, 2022

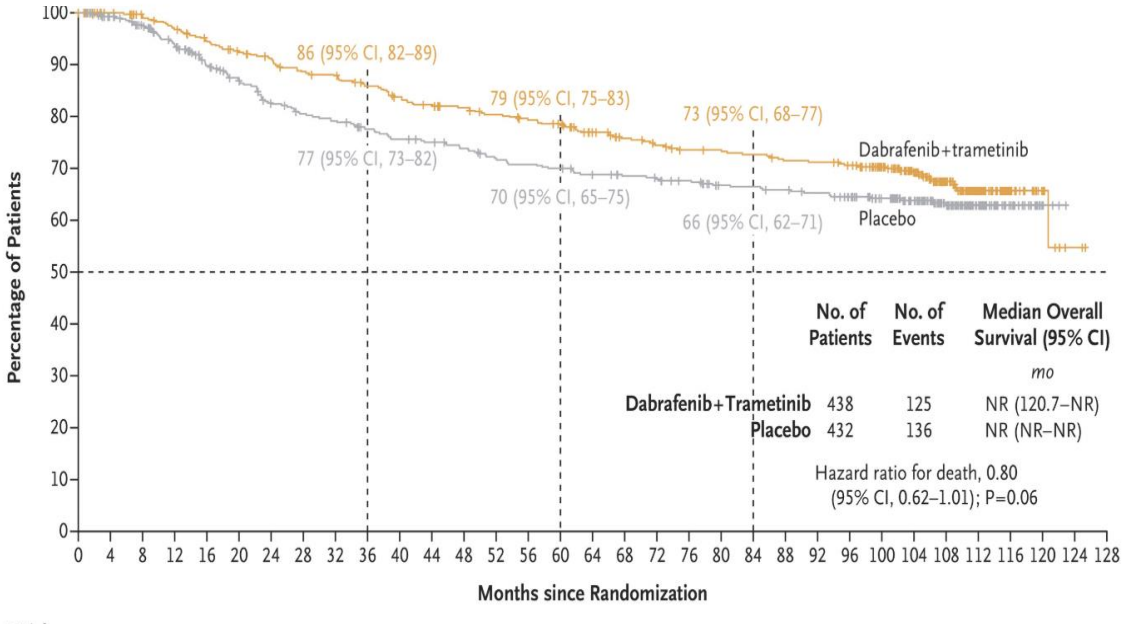
Adjuvant dabrafenib and trametinib for resected Stage III/IV BRAF mutant melanoma

IIIA (>1mm) IIIB/C

RFS

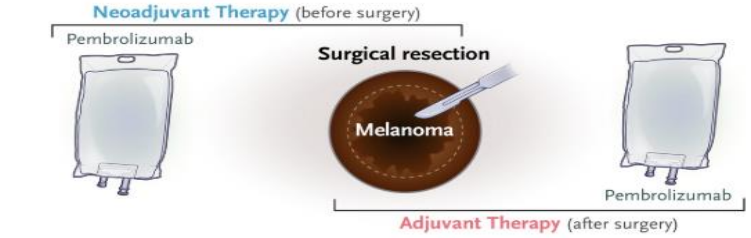


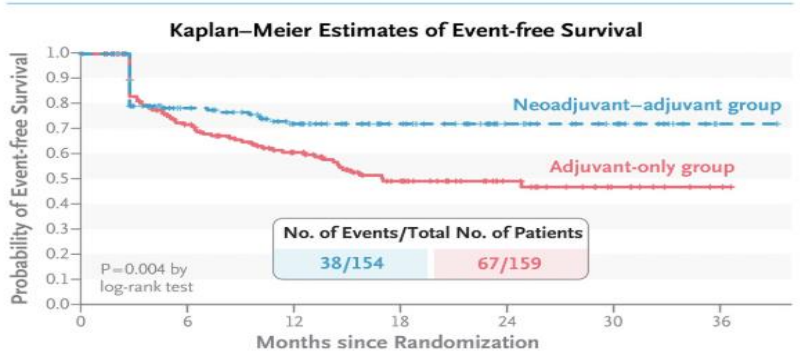
OS

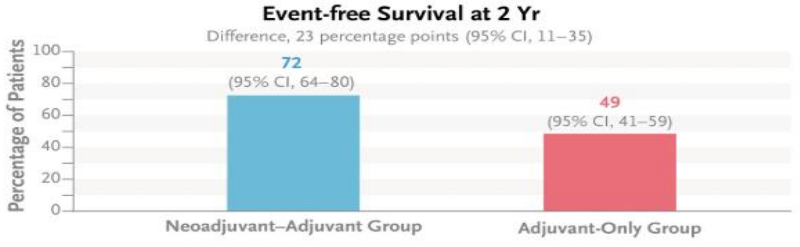


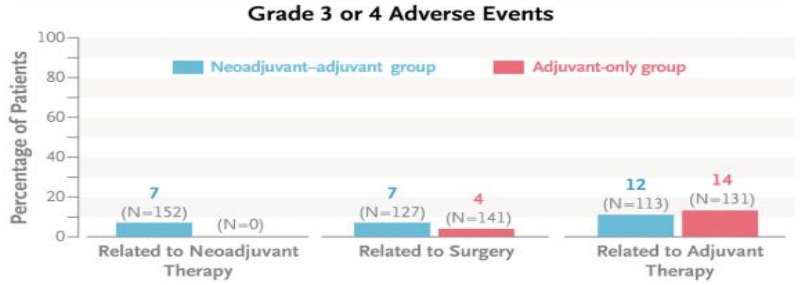
Long et al, NEJM, 2024

Neoadjuvant pembrolizumab (3 cycles) followed by adjuvant pembrolizumab (15 cycles)







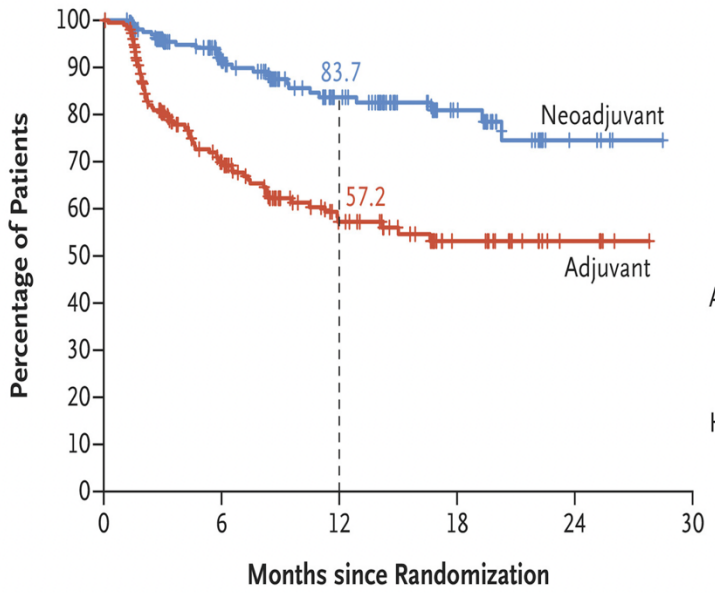


21% with complete pathological response

7% ≥G3 Pembrolizumab—related adverse events

Patel et al, NEJM, 2023

Neoadjuvant Ipilimumab 80mg/Nivolumab 240 mg q3 weeks for 2 cycles



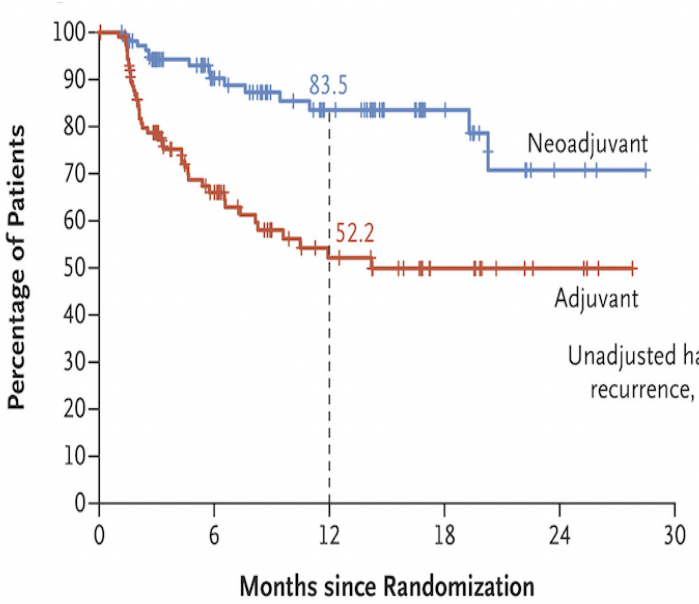
No. of Events/ Total No. of Patients	
Neoadjuvant	28/212
Adjuvant	72/211

Adjusted difference in restricted mean survival time, 8.00 mo (99.9% CI, 4.94–11.05); P<0.001

Hazard ratio for progression, recurrence, or death, 0.32 (99.9% CI, 0.15–0.66)

No. at Risk (no. censored)					
Neoadjuvant	212 (0)	126 (71)	77 (111)	34 (152)	5 (179)
Adjuvant	211 (0)	100 (57)	53 (89)	23 (116)	6 (133)

BRAF mutant melanoma



No. of Events/ Total No. of Patients	
Neoadjuvant	15/112
Adjuvant	41/112

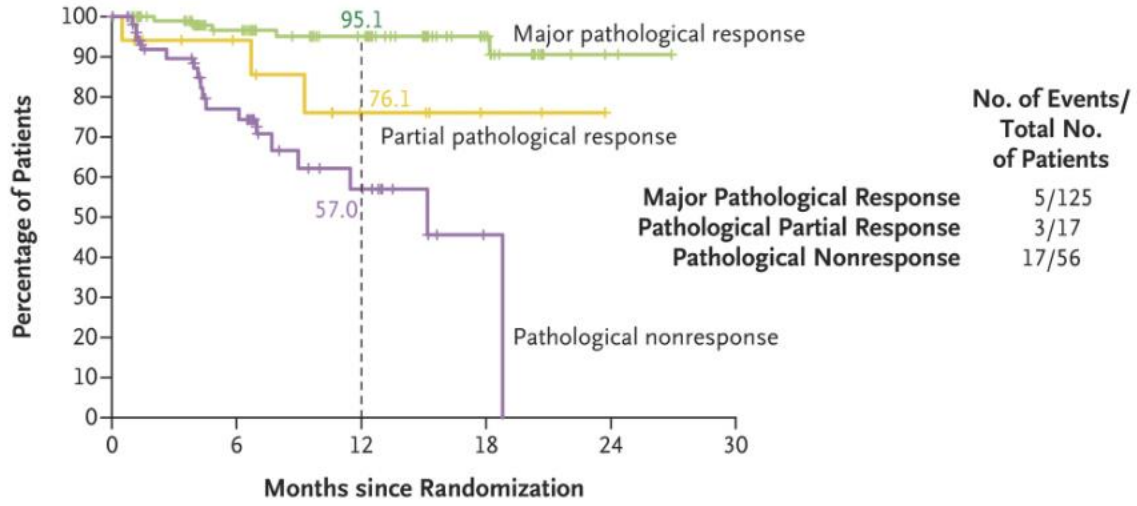
Unadjusted hazard ratio for progression, recurrence, or death, 0.29 (99.9% CI, 0.11–0.79)

No. at Risk (no. censored)					
Neoadjuvant	112 (0)	63 (40)	38 (61)	18 (81)	3 (94)
Adjuvant	112 (0)	48 (32)	25 (47)	11 (60)	4 (67)

Blank et al, NEJM, 2024

Pathologic response rate in association with recurrence-free survival

Response Type	Number (percent)
Major Pathological Response Pathological complete response Pathological near-complete response	125 (59) 100 (47.2) 23 (11.8)
Pathological partial response	17 (8)
Pathological nonresponse	56 (26.4)
Progression before surgery	5 (2.4)



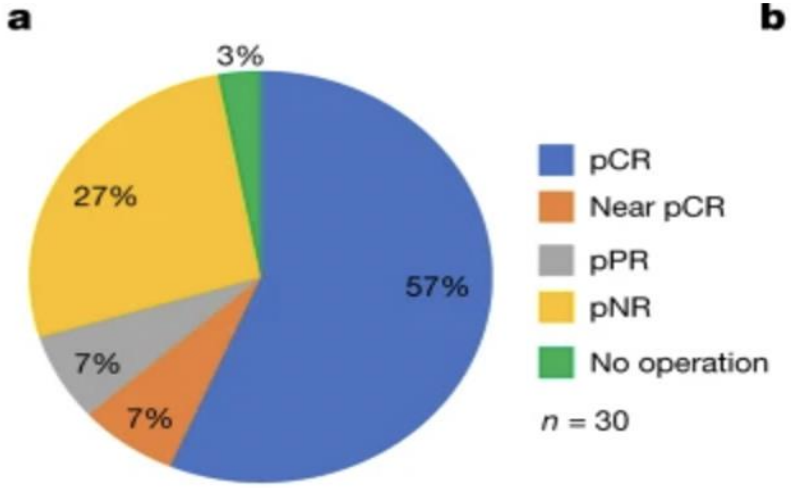
No. at Risk (no. censored)

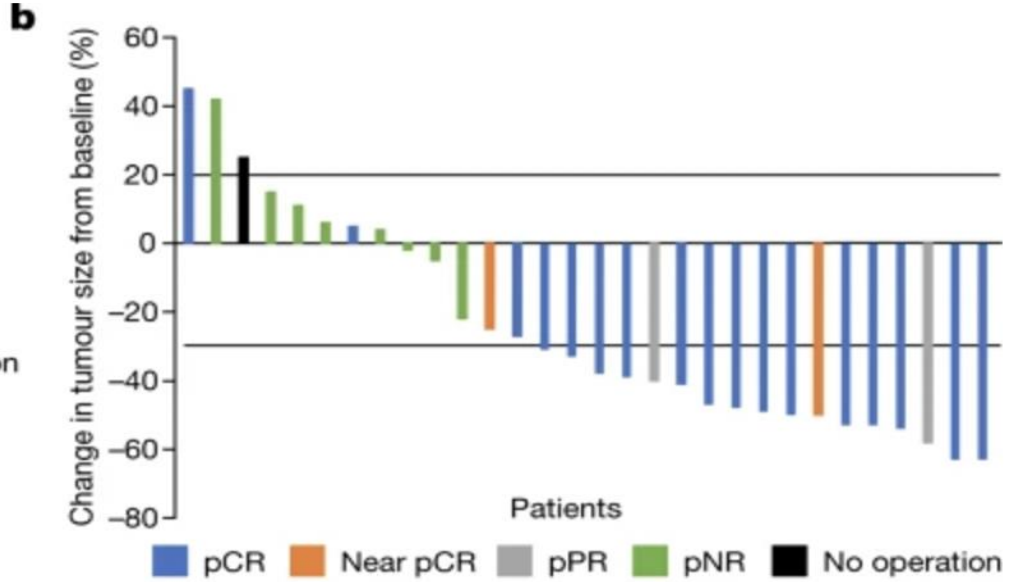
Major pathological response	125 (0)	76 (46)	55 (66)	22 (99)	2 (118)
Pathological partial response	17 (0)	11 (5)	5 (9)	2 (12)	
Pathological nonresponse	56 (0)	29 (17)	11 (30)	1 (39)	

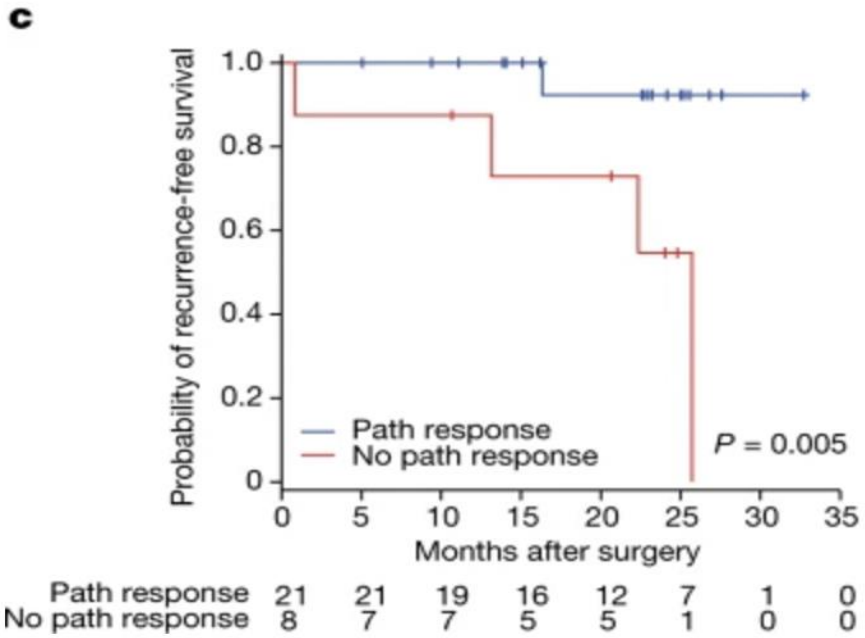
Adverse event (AE)	%
Any /≥G3 AE	96.2/47.2
Treatment-related any/≥G3 AE	92.5/38.7
AE due to systemic therapy any/≥G3	85.4/29.7

Blank et al, NEJM, 2024

Neoadjuvant Nivolumab/Relatlimab 2 cycles followed by adjuvant Nivolumab/Relatlimab 10 cycles







Adverse event (AE)	%
≥G3 treatment-related adverse event	26
Adrenal Insufficiency	23
≥G3 AST/ALT increase	7
Hypothyroidism	26.7
Discontinued therapy due to toxicity	33

Amaria et al, Nature, 2022

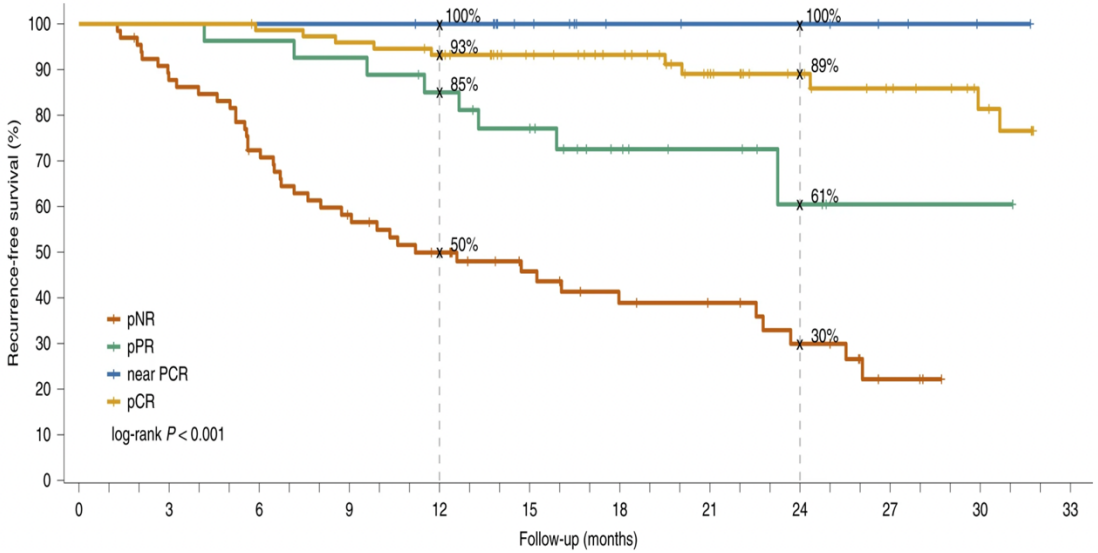
Case 1 continues

Patient received 2 cycles of Ipilimumab/Nivolumab and proceeded with LN dissection. Patient continued nivolumab therapy up to 1 year of total perioperative therapy.

A. Left axillary contents levels one and two, dissection:
Spindle cell melanoma, metastatic to two of fifteen (2/15) lymph nodes, 6.5 cm in greatest dimension, no extracapsular extension identified. See comment.

B. Left axillary contents level three, dissection:
Fibroadipose tissue, no lymph node or malignancy identified

99% viable tumor
0% tumor melanosis
0% necrosis
1% fibrosis/fibroinflammatory stroma
This represents pathologic non-response.



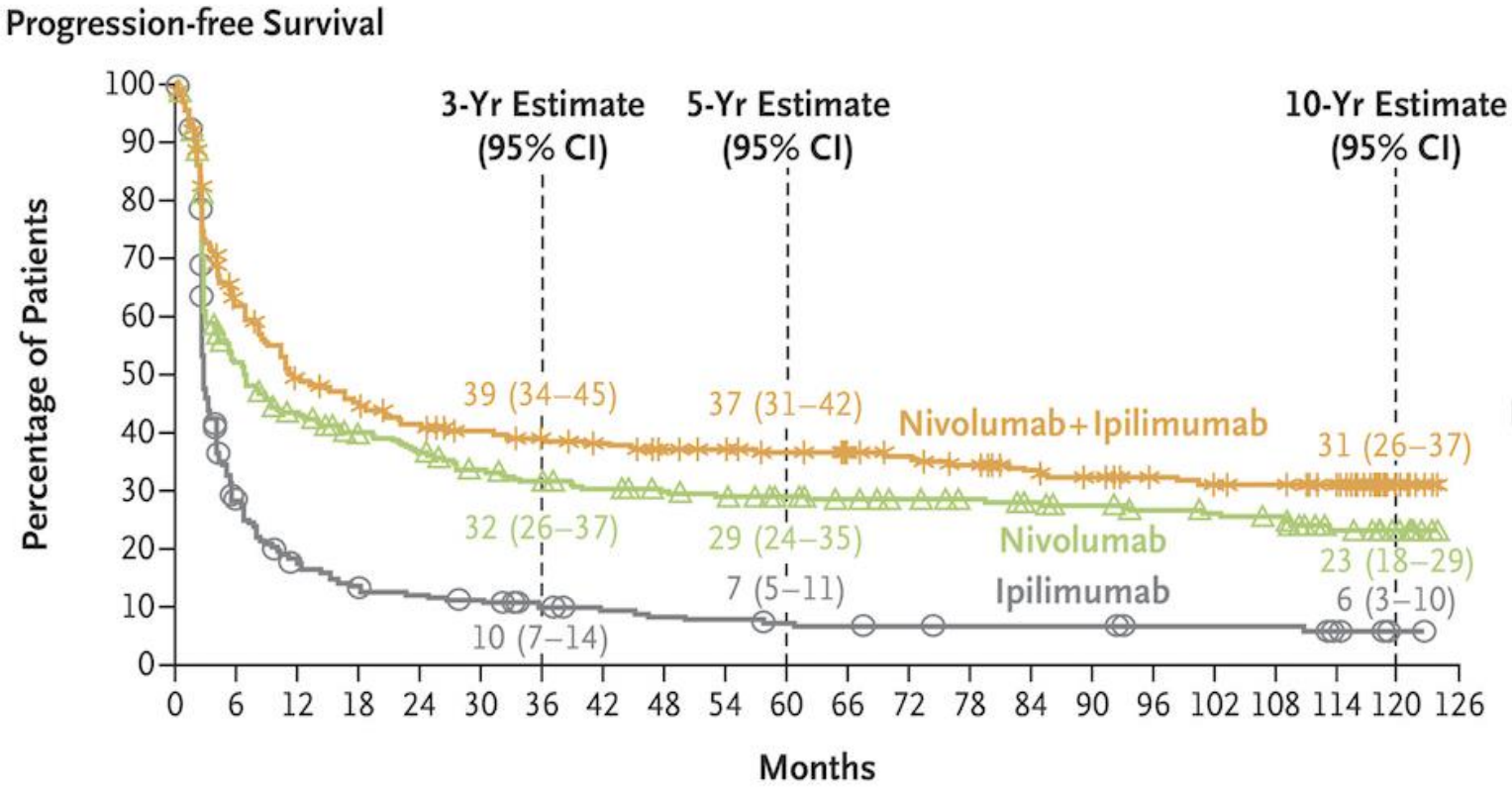
Menzies et al, Nature Medicine, 2021

Case 2

A 68-year-old male with h/o stage IIA melanoma in 2020 s/p wide excision and SLNB presented for scheduled follow up visit. CT NTAP demonstrated 3 new lung nodules largest with 2 cm, and lymph node metastatic disease. MRI brain revealed no evidence of inctracranial disease. LDH 230. US-guided core needle biopsy of axillary lymph node confirmed diagnosis of metastatic melanoma, BRAF*v600* wild type, NF1 mutant, TMB 70. PDL-1 >1%. Patient reports no symptoms related to disease. Medical comorbidities include hypertension, diabetes, hyperlipidemia. ECOG PS 0. What is recommended therapy for this patient?

A. Nivolumab and Ipilimumab
B. Nivolumab and Relatlimab
C. Dabrafenib and Trametinib
D. Tumor-infiltrating lymphocyte therapy
E. Chemotherapy with Temozolomide
F. A or B based on discussion with the patient

Ipilimumab 3mg/kg with Nivolumab 1mg/kg for patients with advanced melanoma



	No. of Patients with Event	Median Progression-free Survival (95% CI)
		mo
Nivo+Ipi (N=314)	192	11.5 (8.9–20.0)
Nivolumab (N=316)	212	6.9 (5.1–10.2)
Ipilimumab (N=315)	262	2.9 (2.8–3.1)

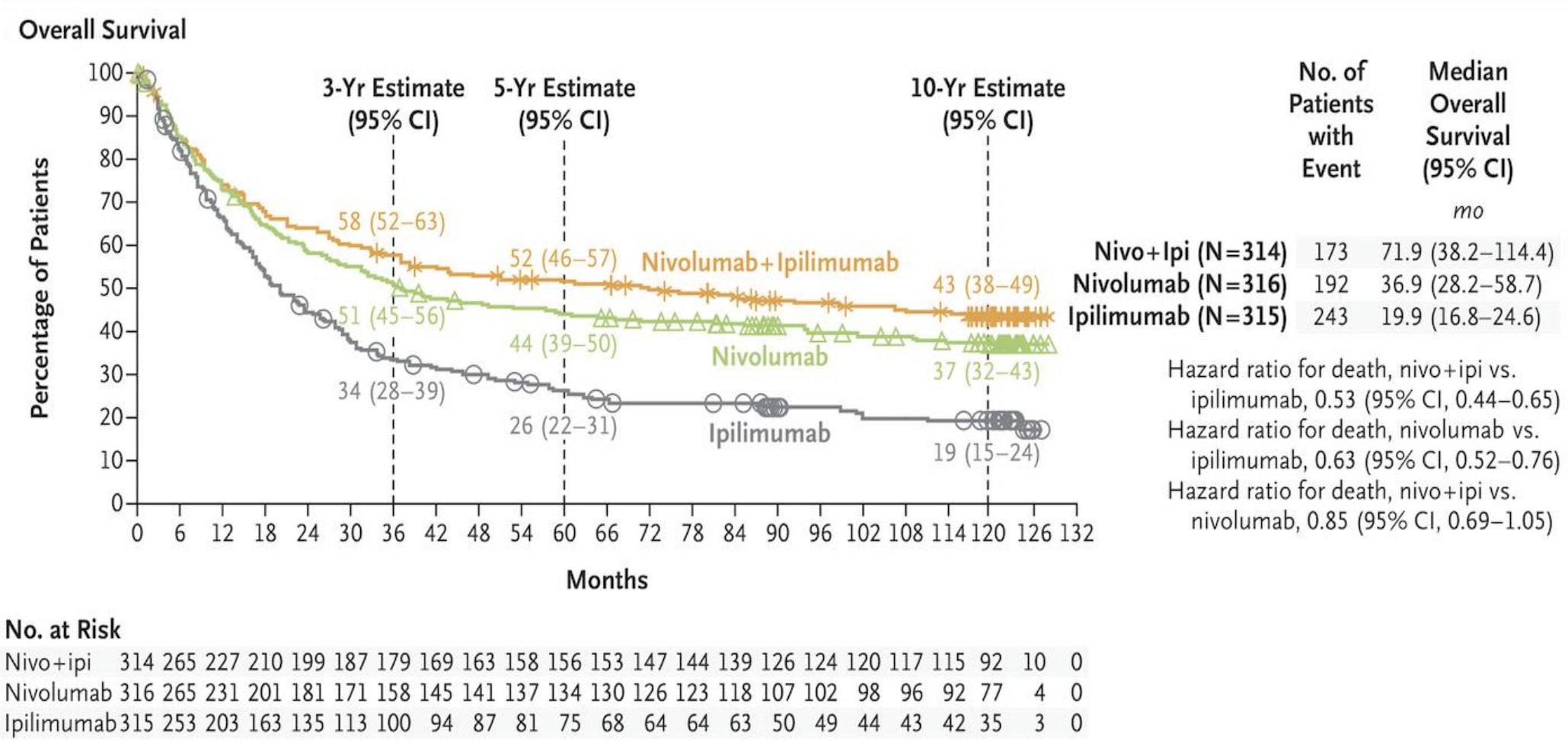
Hazard ratio for disease progression or death, nivo+ipi vs. ipilimumab, 0.42 (95% CI, 0.35–0.51)
Hazard ratio for disease progression or death, nivolumab vs. ipilimumab, 0.54 (95% CI, 0.45–0.65)
Hazard ratio for disease progression or death, nivo+ipi vs. nivolumab, 0.79 (95% CI, 0.65–0.96)

No. at Risk

Nivo+ipi	314	175	138	126	112	104	100	94	88	85	80	78	72	68	62	58	53	51	49	42	15	0
Nivolumab	316	151	120	106	97	84	78	73	69	66	62	58	55	52	49	45	42	40	38	24	12	0
Ipilimumab	315	78	46	34	31	28	21	18	16	15	13	12	11	10	10	10	8	8	8	4	1	0

Wolchok et al, NEJM, 2024

Ipilimumab 3mg/kg with Nivolumab 1mg/kg for patients with advanced melanoma



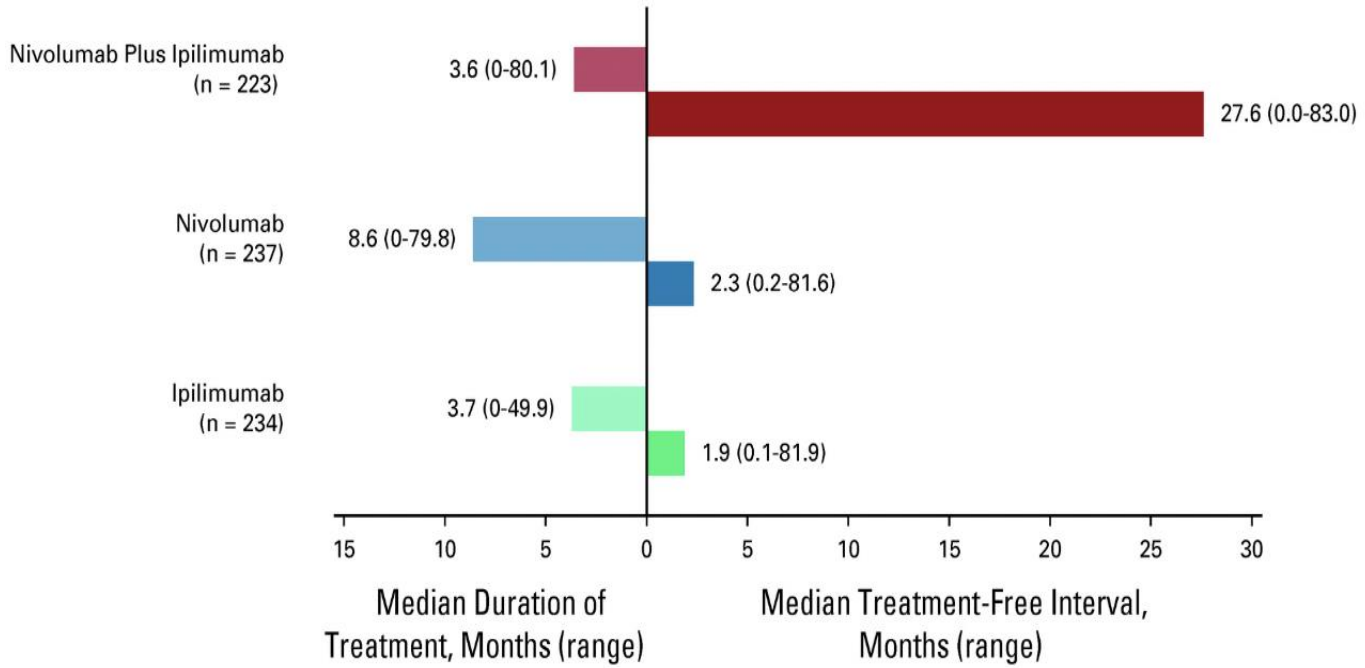
	No. of Patients with Event	Median Overall Survival (95% CI)
		mo
Nivo+Ipi (N=314)	173	71.9 (38.2–114.4)
Nivolumab (N=316)	192	36.9 (28.2–58.7)
Ipilimumab (N=315)	243	19.9 (16.8–24.6)

Hazard ratio for death, nivo+ipi vs. ipilimumab, 0.53 (95% CI, 0.44–0.65)
Hazard ratio for death, nivolumab vs. ipilimumab, 0.63 (95% CI, 0.52–0.76)
Hazard ratio for death, nivo+ipi vs. nivolumab, 0.85 (95% CI, 0.69–1.05)

Wolchok et al, NEJM, 2024

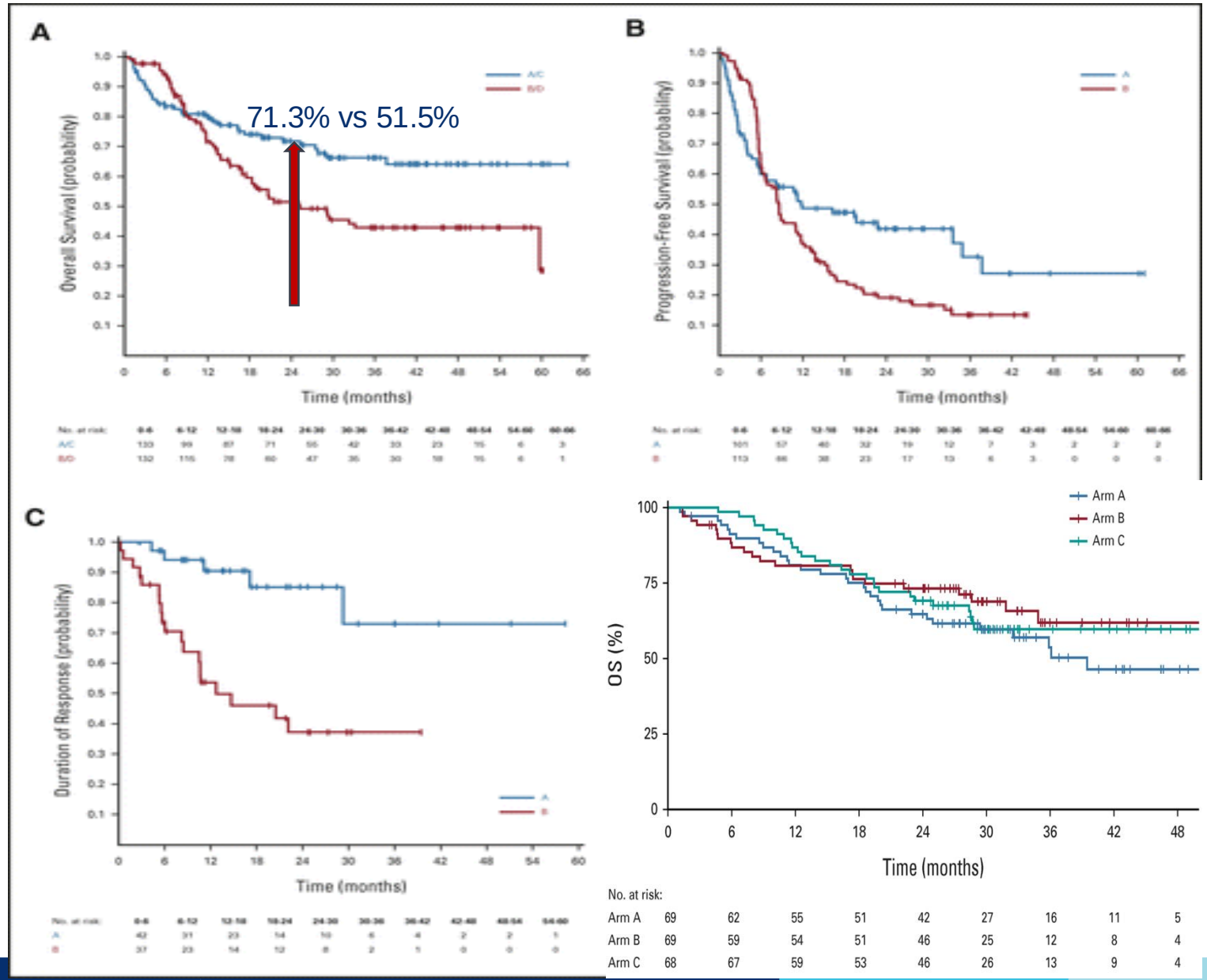
Adverse events related to Ipilimumab/Nivolumab

Treatment-related adverse event (TRAE)	Percent Any/≥G3
TRAE	**95.8/62.6**
TRAE leading to discontinuation of therapy	**44.7/33.5**



Wolchok et al, J Clin Oncol, 2021

Sequencing immunotherapy and targeting therapy for *BRAF v600* mutant melanoma

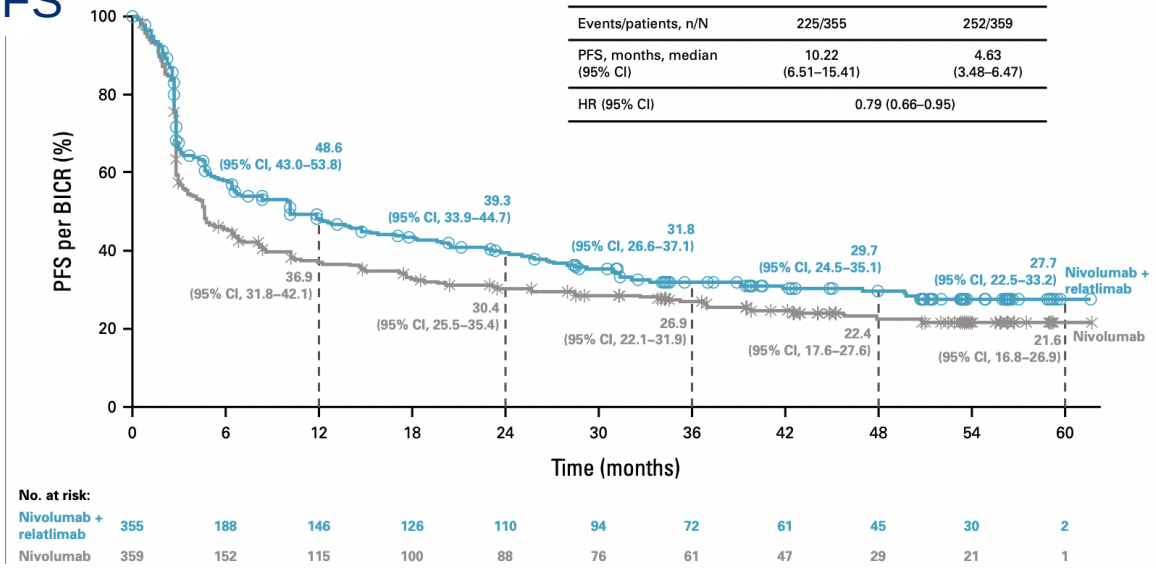


Atkins et al, J Clin Oncol, 2022
Ascierto et al, J Clin Oncol, 2023

Nivolumab and Relatlimab for patients with advanced melanoma

PFS

	Nivolumab + Relatlimab	Nivolumab
Events/patients, n/N	225/355	252/359
PFS, months, median (95% CI)	10.22 (6.51–15.41)	4.63 (3.48–6.47)
HR (95% CI)	0.79 (0.66–0.95)	

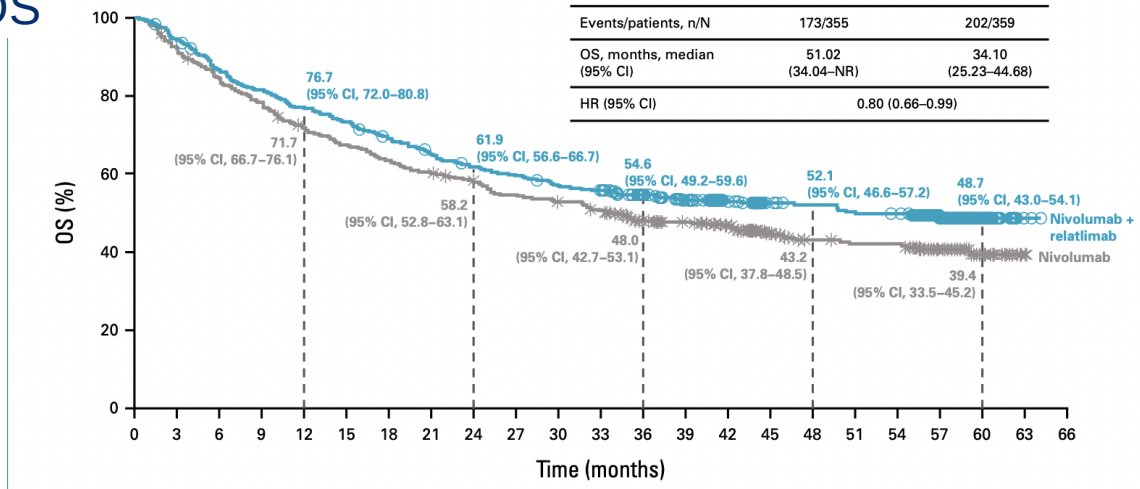


No. at risk:

Nivolumab + relatlimab	355	188	146	126	110	94	72	61	45	30	2
Nivolumab	359	152	115	100	88	76	61	47	29	21	1

OS

	Nivolumab + Relatlimab	Nivolumab
Events/patients, n/N	173/355	202/359
OS, months, median (95% CI)	51.02 (34.04–NR)	34.10 (25.23–44.68)
HR (95% CI)	0.80 (0.66–0.99)	

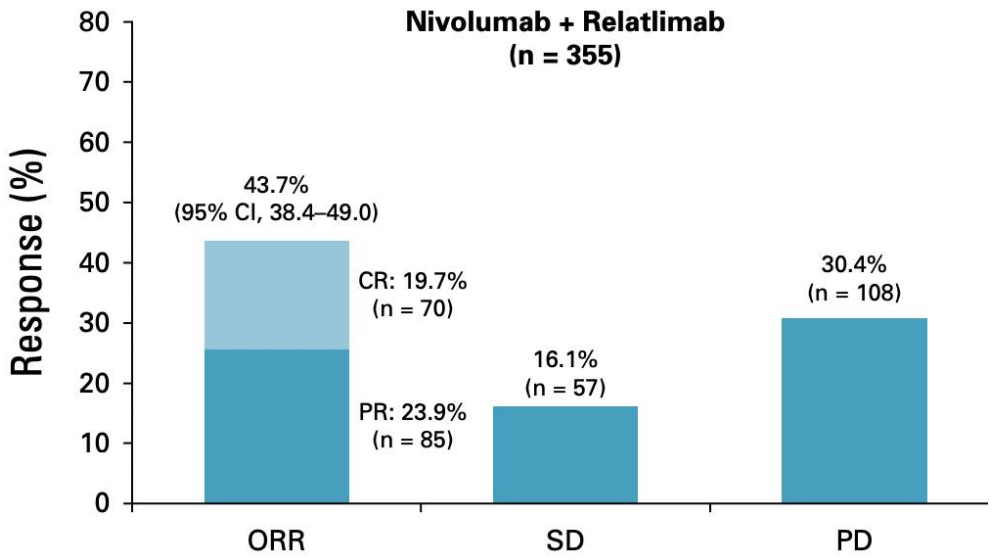


No. at risk:

Nivolumab + relatlimab	355	334	305	287	270	258	241	226	214	206	196	192	172	158	145	122	117	113	111	72	22	2	0
Nivolumab	359	330	302	279	254	239	225	213	203	191	184	175	151	140	126	100	90	87	87	57	15	1	0

Tawbi et al, J Clin Oncol, 2024

Nivolumab and Relatlimab for patients with advanced melanoma

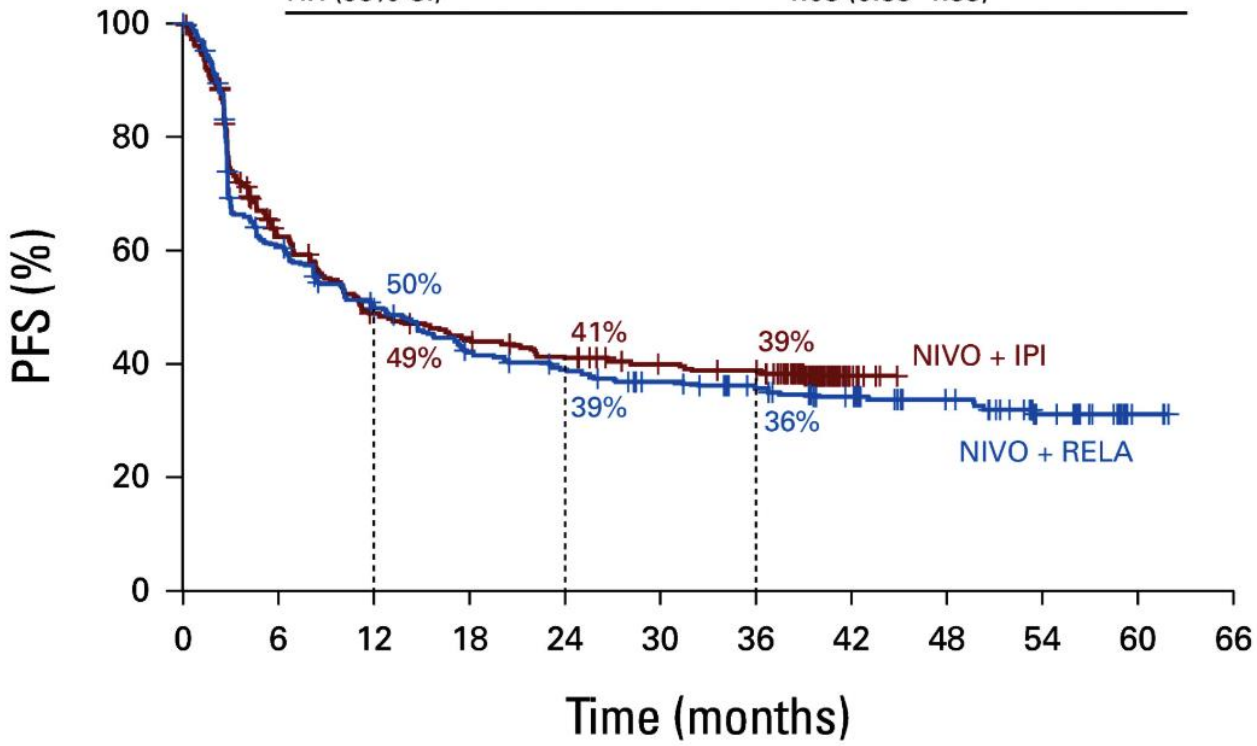


Treatment-related adverse event (TRAE)	Percent Any/≥G3
TRAE	**85.1/22**
TRAE leading to discontinuation of therapy	**17.7/9.6**

Tawbi et al, J Clin Oncol, 2024

Indirect treatment comparison between NIVO/RELA and NIVO/IPI

	NIVO + RELA (n = 339)	NIVO + IPI (n = 297)
Events, No.	225	174
Median, months (95% CI)	12.0 (8.2–17.1)	11.2 (8.5–18.1)
HR (95% CI)[a]	1.08 (0.88–1.33)	



No. at risk:

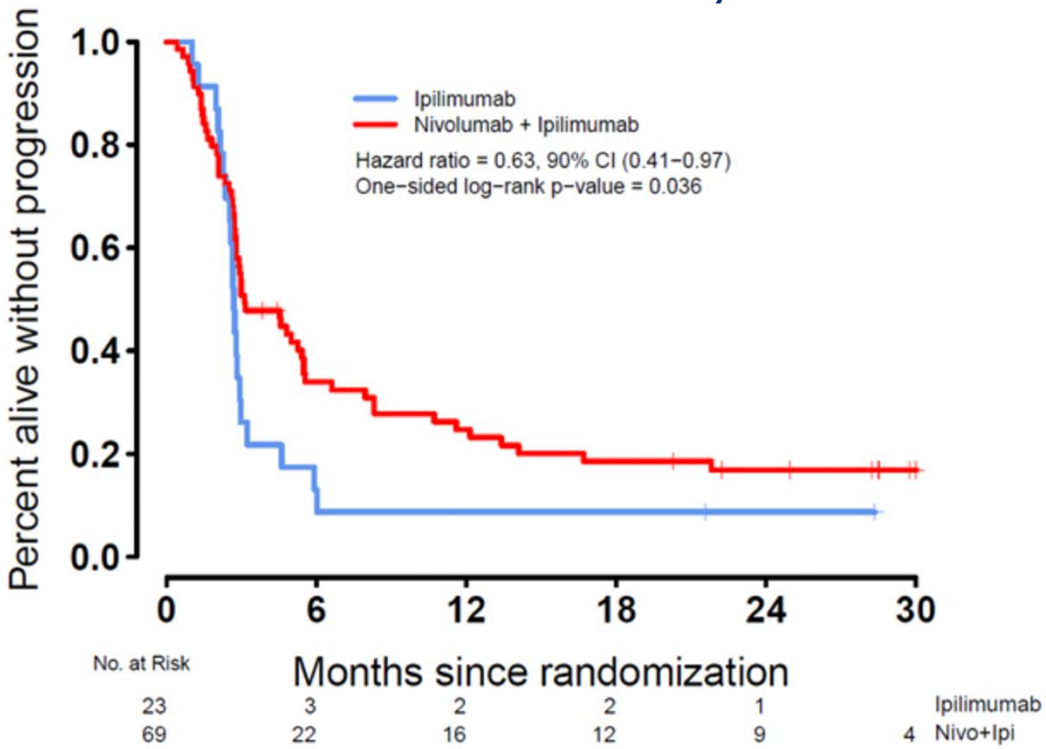
NIVO + RELA	339	194	157	129	117	103	85	70	55	35	3	0
NIVO + IPI	297	167	130	117	106	97	94	8	0	0	0	0

Long et al, J Clin Oncol, 2024

Objective response rate (ORR) and progression-free survival to subsequent immune-checkpoint blockade therapy

Anti-PD1	Anti-PD1+Anti-CTLA4	ORR=29%
Anti-PD1+/-anti-CTLA4	Anti-PD1+Anti-LAG3	ORR=12%
Anti-PD1+Anti-LAG3	Anti-CTLA4+/-Anti-PD1	ORR=11%

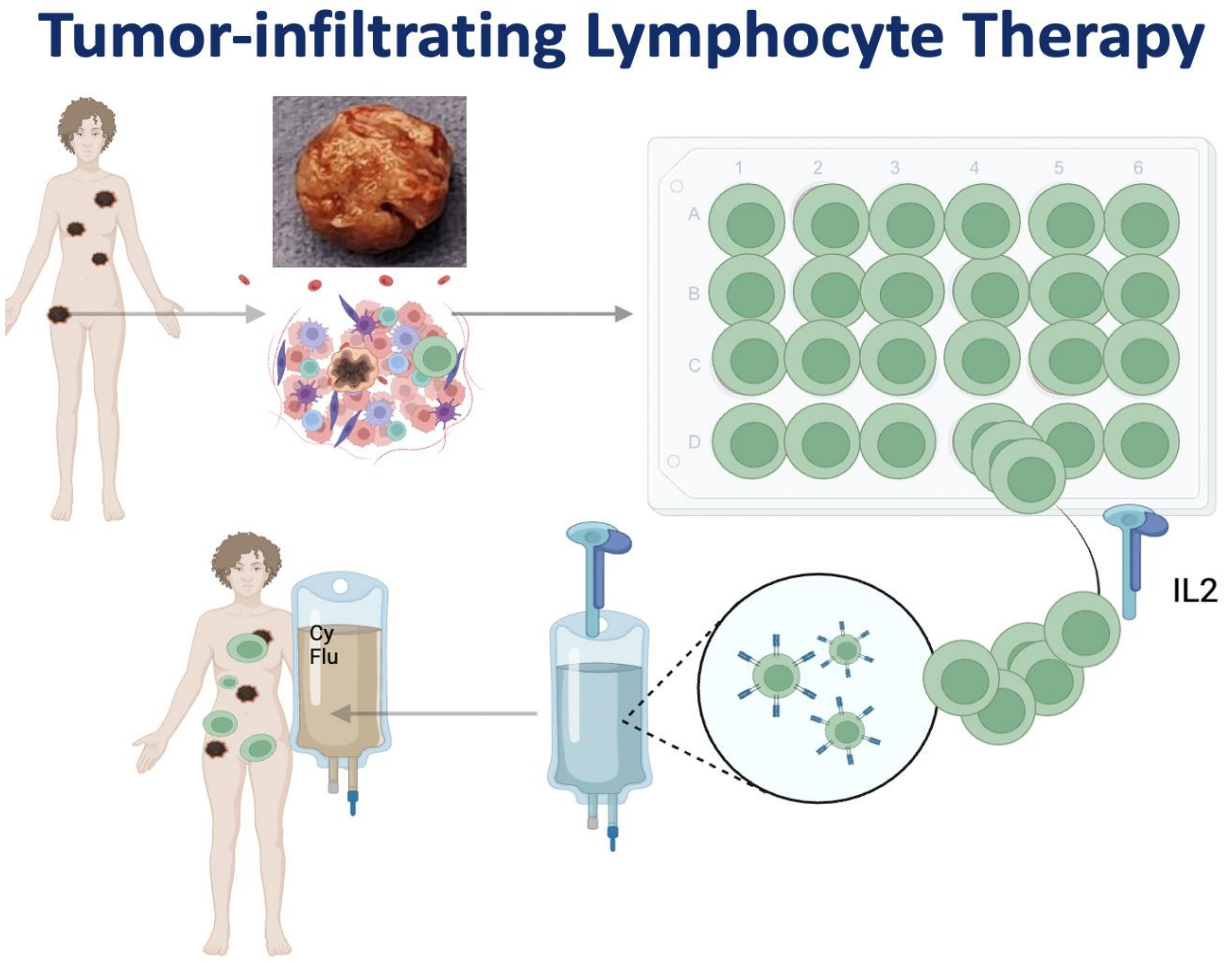
IPI/NIVO ORR=28%; IPI ORR=9%



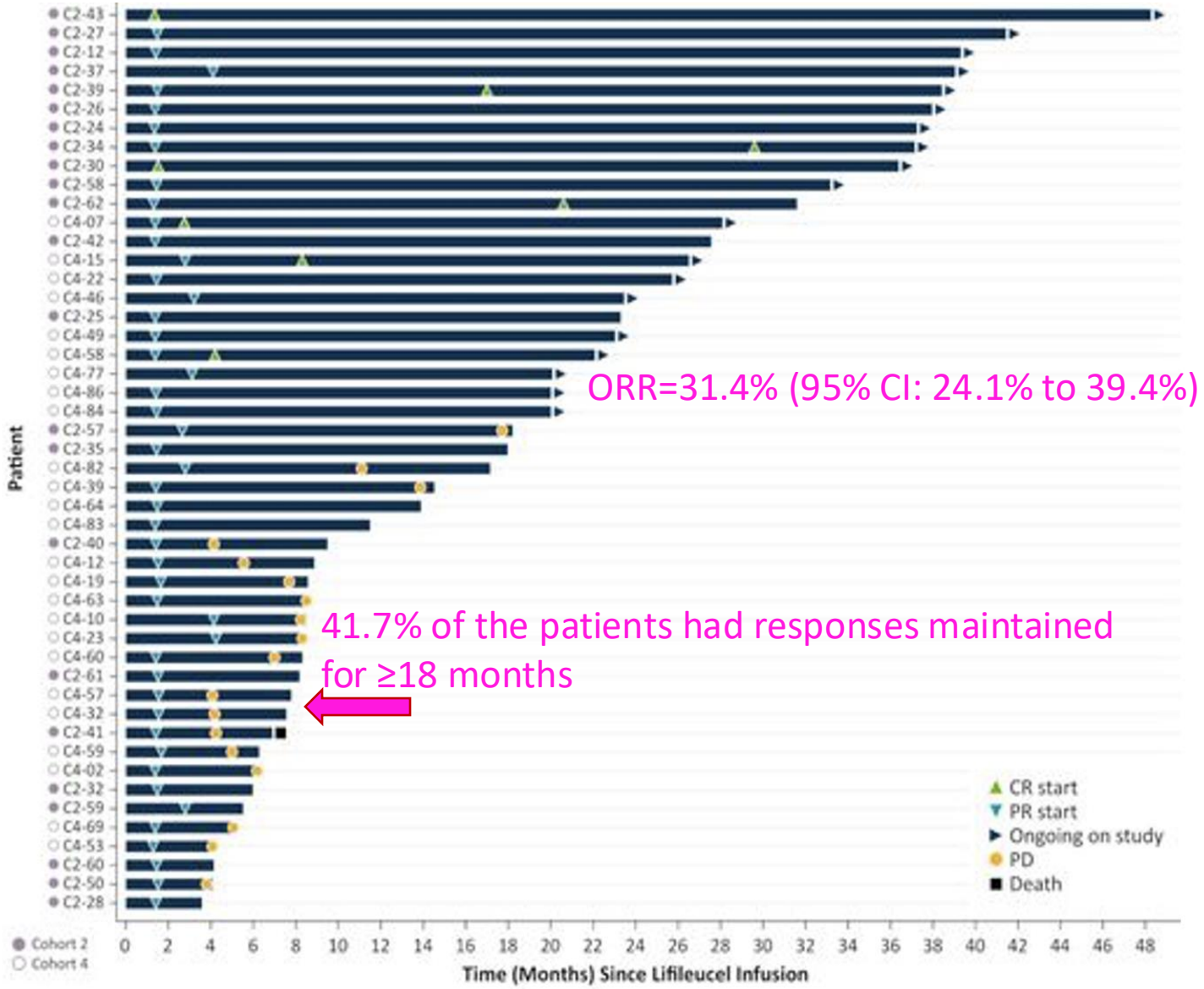
Olson et al, JCO 2021
Ascierto et al, JCO 2023
Menzies et al, NEJM, 2022
VanderWalde et al, Nat Med, 2023

Tumor infiltrating lymphocyte (TIL) therapy for advanced melanoma

- Lifileucel accelerated FDA approval in Feb, 2024
- Adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if *BRAF V600* mutation positive, a BRAF inhibitor with or without a MEK inhibitor

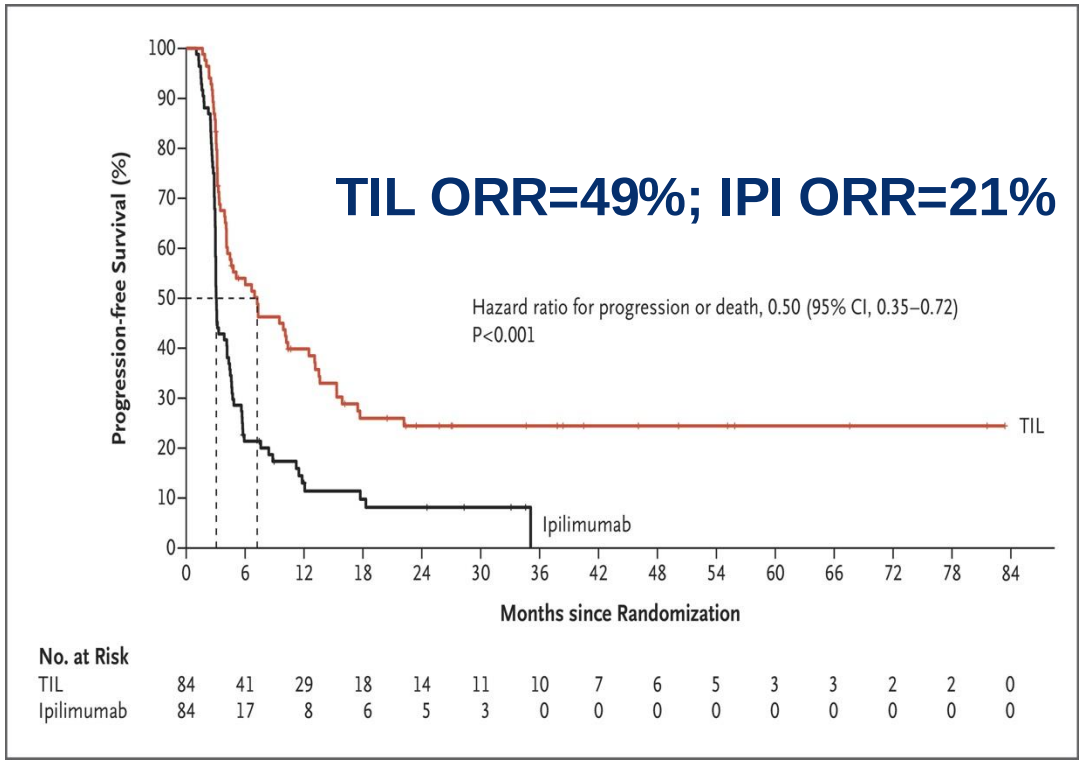


Efficacy of TIL in patients with advanced melanoma



ORR=31.4% (95% CI: 24.1% to 39.4%)

41.7% of the patients had responses maintained for ≥18 months



Rohaan MW et al. NEJM, 2022
Chesney J et al, J Immunother Cancer 2022

Take Home Points

- Wide excision, sentinel lymph node biopsy, and lymph node dissection remain important surgical basis for the management of resectable melanoma
- Regional -macroscopic resectable disease management includes incorporation of NEOADJUVANT Immunotherapy
- Pathologic response is a surrogate marker for long-term survival outcomes and *may* be used to guide adjuvant therapy
- First-line immunotherapy is preferred therapy for patients with *BRAF* mutant and wild-type advanced melanoma
- Ipi/nivo vs nivo/rela in first line melanoma remains discussion topic and choice of immunotherapy is based on shared discussion between provider and patient.
- Subsequent immune-checkpoint blockade therapy provides limited therapeutic benefit, consider tumor-infiltrating lymphocyte therapy.