MASSACHUSETTS GENERAL HOSPITAL

CANCER CENTER

Advances in Melanoma

14th Annual Winter Cancer Symposium

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Objectives: Advances in Melanoma

- Updates in 1L management in metastatic melanoma
- Evolution of treatment in the peri-operative setting
- Second-line and beyond advancements

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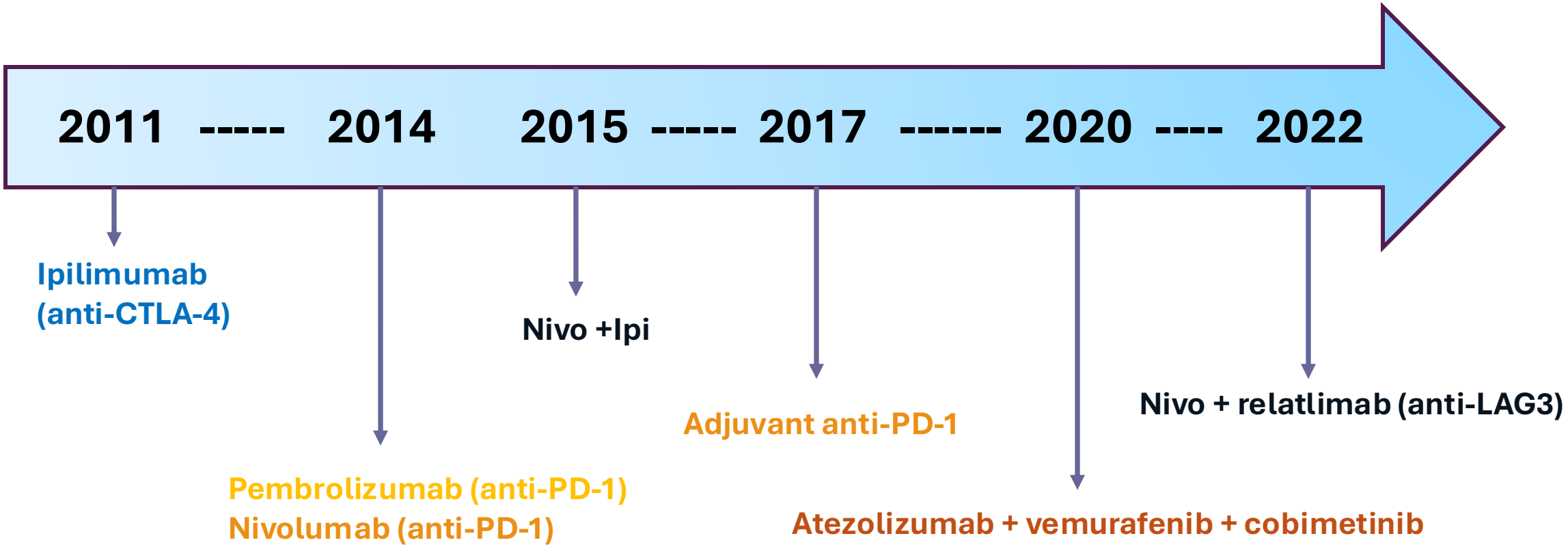
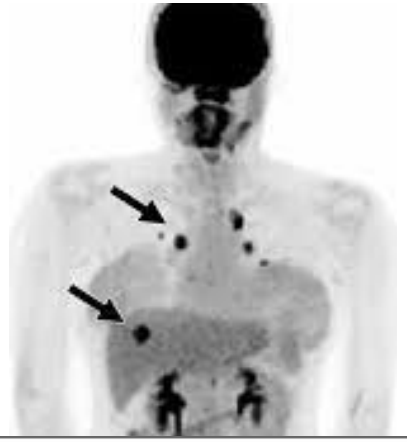
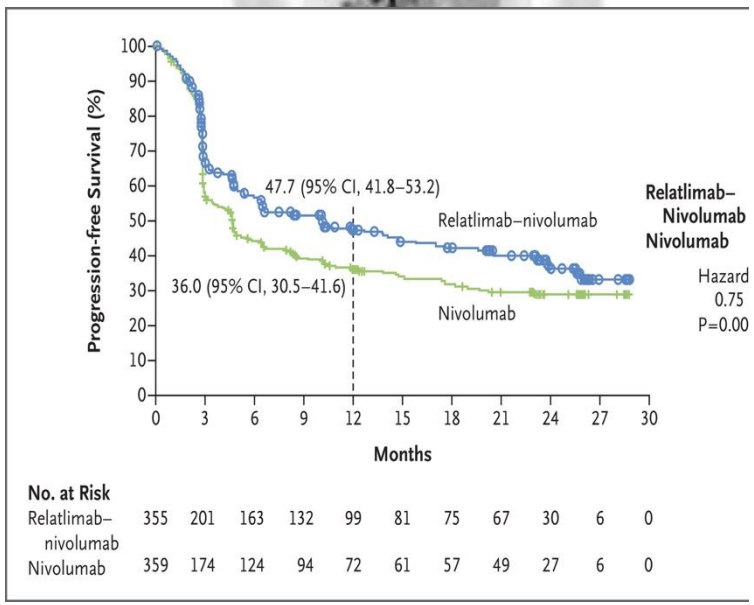
Immunotherapy timeline for cutaneous melanoma



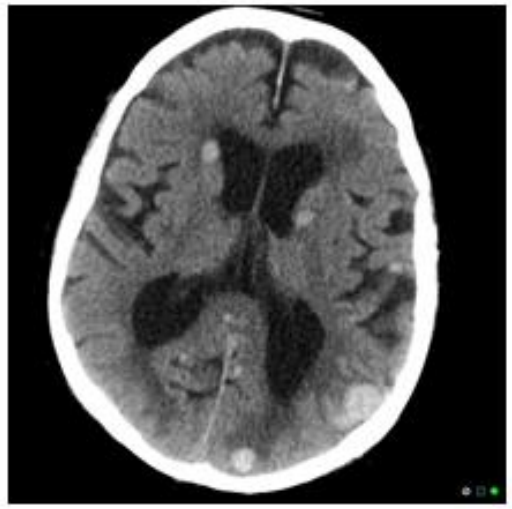
1L options for metastatic melanoma

Relatlimab-nivolumab





Ipilimumab-nivolumab



Post-adjuvant PD-1 inhibition

PD-1 inhibitor monotherapy

1L options for metastatic melanoma

Triplet ?? RELATIVITY-048

Key eligibility criteria

- Previously untreated metastatic melanoma
- Prior peri-operative ICI permitted if ≥6mths prior
- Pt with controlled brain mets allowed

N = 46

Nivo 480mg Q4W +
RELA 160mg Q4W +
IPI 1mg/kg Q8W

Primary endpoints

- Key safety (AE, SAE, etc)
- ORR, DCR, median DOR

Secondary endpoints

- PFS

Key exploratory endpoints

- OS at 1 and 2 years

Ascierto et al. Presented at ASCO 2024

RELATIVITY-048

	NIVO + RELA + IPI (n = 46)
Confirmed ORR, % (95% CI)	58.7 (43.2–73.0)
Confirmed DCR, % (95% CI)	76.1 (61.2–87.4)
Confirmed CR/PR/SD rates, %	17.4 / 41.3 / 17.4
Median DOR, mo (95% CI)	NR (NR–NR)
Median PFS, mo (95% CI)	NR (3.94–NR)
24-mo/48-mo PFS rates, % (95% CI)	57.2 (40.8–70.5) / 51.6 (35.3–65.6)
Median OS, mo (95% CI)	NR (NR–NR)
24-mo/48-mo OS rates, % (95% CI)	80.4 (65.8–89.3) / 71.7 (56.4–82.5)

Response rates by histology: cutaneous non-acral melanoma (64%) vs mucosal (33%) or acral (25%) melanoma

SAFETY
Grade 3-4 trAE: 39.1%
TrAE leading to d/c: 41.3%
Grade 5 trAE: 4.3%

Ipi/nivo: ~50-55%

Ascierto et al. Presented at ASCO 2024

Sarilumab in Combination with Ipi / Nivo / Rela

Phase 2 study of triplet +/- IL-6 receptor blocking Ab Sarilumab

Stage 1: up to 33 pts

- Single arm trial:
- Each tx cycle: 8 weeks
- Treatment: all four agents
  - Sarilumab SC (every 2wk) at 150 mg fixed dose
  - Nivolumab and relatlimab fixed dose of 480 mg/160 mg
  - Ipilimumab 1 mg/kg.

Stage 2: n=72

- Randomized (1:1)
  - Ipi/nivo/rela +/- sari

Co-primary endpoints:
- Rates of trAE grade 3-5
- ORR

Secondary endpoints:
- PFS for pt in Stage 1 vs PFS in Stage 2
- OS, DCR, DoR in all pts

Preliminary data likely to be presented at ASCO 2025!

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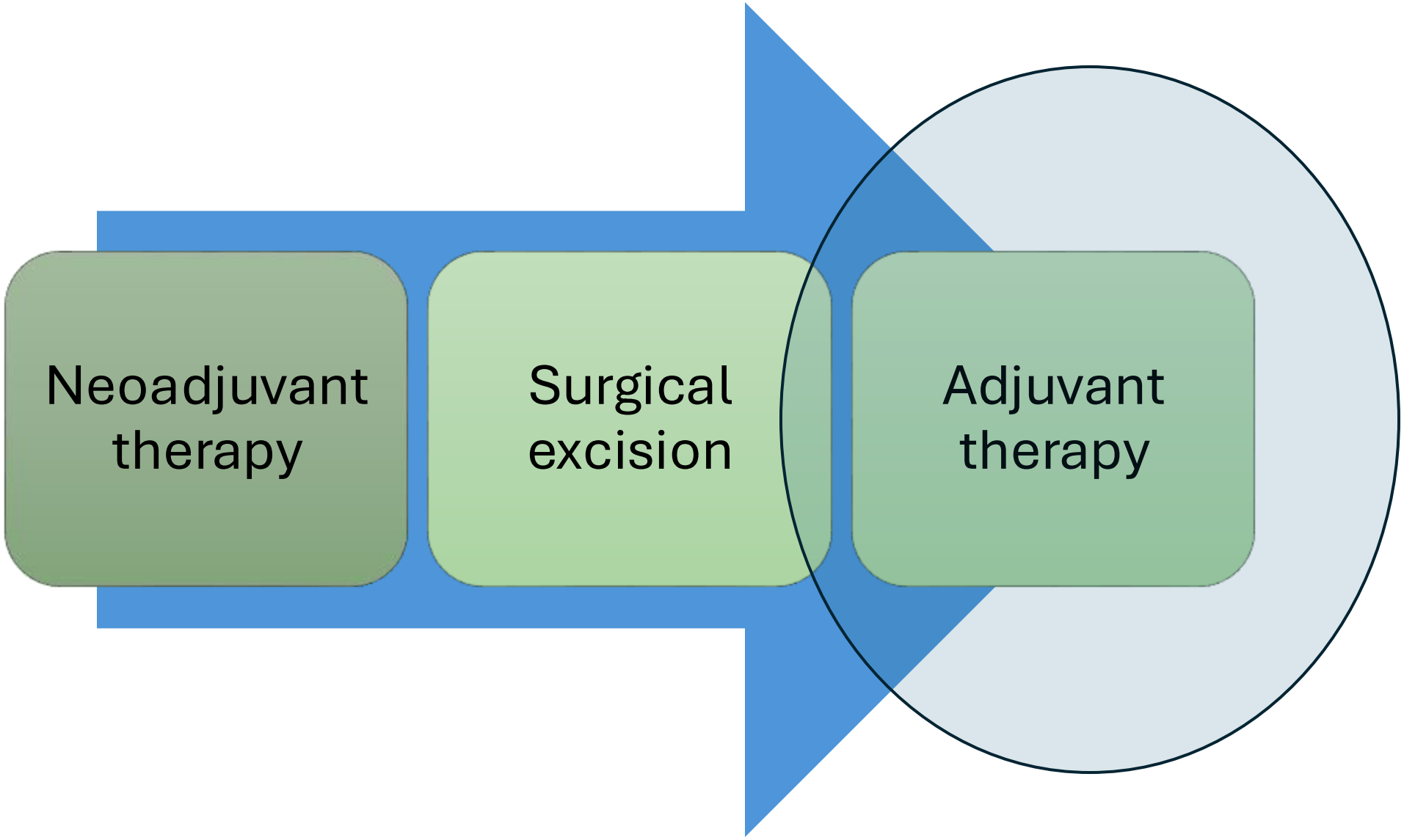
Peri-operative immunotherapy



Current adjuvant therapy landscape

<u>Stage IIB/C</u>
KEYNOTE716
CheckMate-76K

→ PD-1 inhibition

<u>Stage IIIA*-D</u>
KEYNOTE-054
CheckMate 238

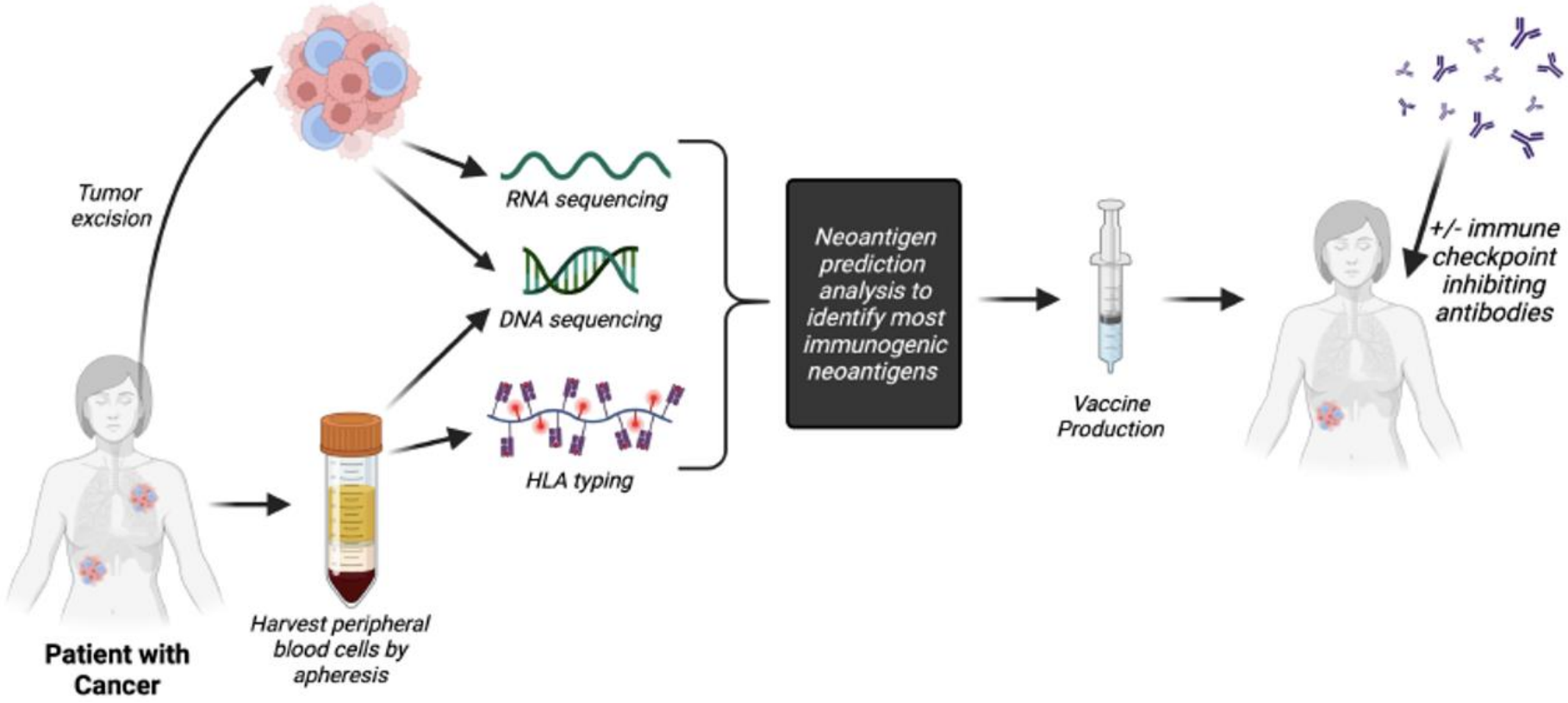
→ BRAF V600- → PD-1 inhibition

→ BRAF V600+ → PD-1 inhibition

→ BRAF V600+ → BRAF/MEK inhibition

* Omit Stage IIIA cases with <1mm of disease in SLNB

Neoantigen vaccination



Sullivan, ASCO 2022

Neoantigen vaccination

mRNA-4157-P201/KEYNOTE-942 (NCT03897881) Study Design

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

Key eligibility criteria

- Resected stage IIIB,[a] IIIC, IIID, or IV cutaneous melanoma
- Complete surgical resection within 13 weeks prior to first pembrolizumab dose
- Disease-free at study entry
- ECOG PS score 0-1
- Tissue available for NGS

2:1 Randomization

Stratified by disease stage[b]

Combination treatment arm: mRNA-4157 (V940) + pembrolizumab
Up to 1 year of pembrolizumab treatment
mRNA-4157 (V940) 1 mg IM Q3W for up to 9 doses +
pembrolizumab 200 mg IV Q3W for up to 18 cycles
(n = 107)

Control treatment arm: pembrolizumab monotherapy
Up to 1 year of pembrolizumab treatment
pembrolizumab 200 mg IV Q3W for up to 18 cycles
(n = 50)

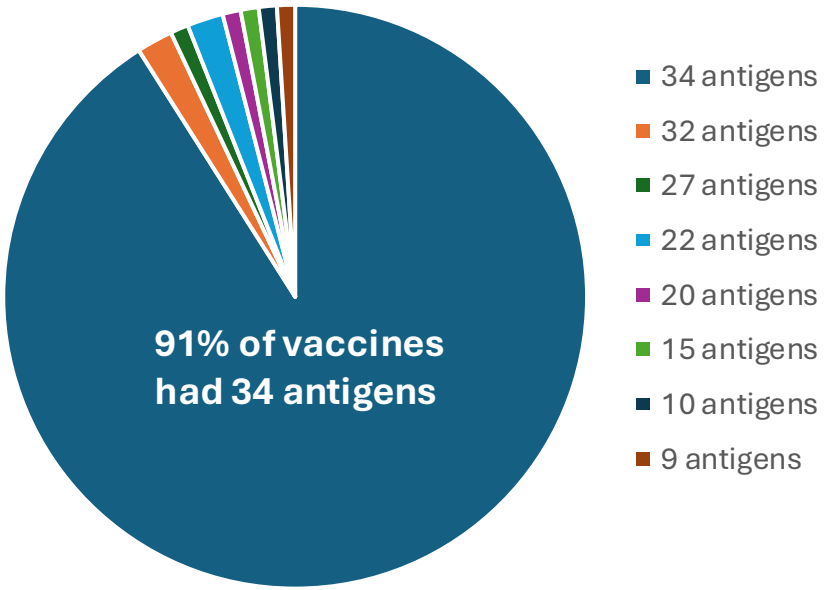
Primary endpoint:
RFS[c,d]

Secondary endpoints:
DMFS,[e]
safety, tolerability

Follow-up:
up to 3 years following the first dose of pembrolizumab

Designed with 80% power to detect an HR of 0.5 with ≥40 RFS events (with a 1-sided alpha of 0.1)
DMFS analysis was prespecified for testing following positive RFS in the ITT population[f]
Median follow-up[g]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab monotherapy

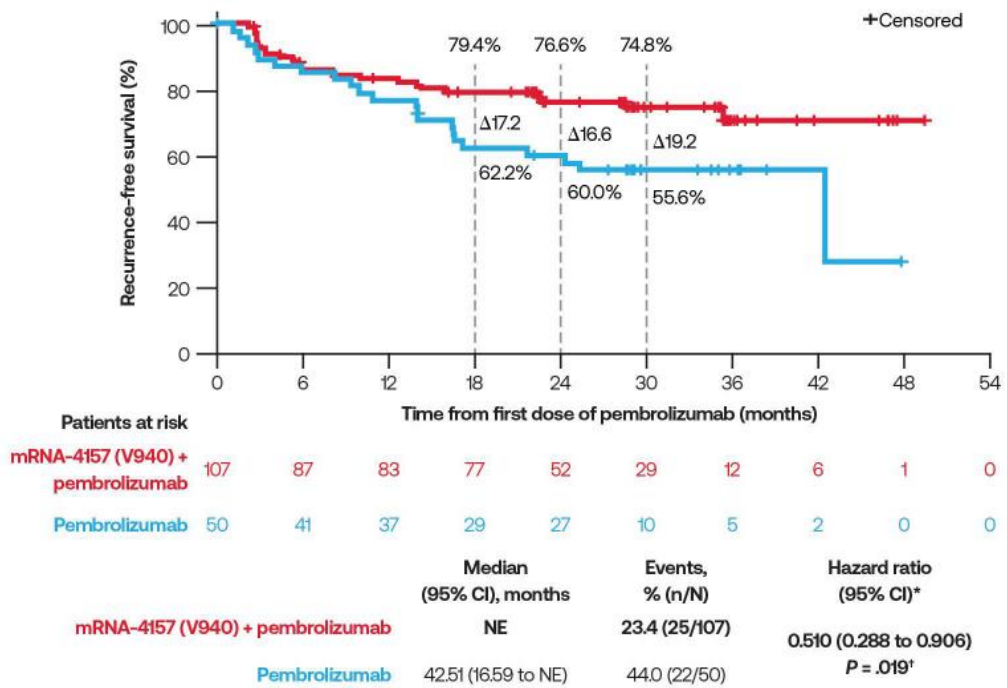
The median number of vaccine neoantigens was 34 (range: 9-34)



Weber et al. AACR 2023, Khattak et al ASCO 2023

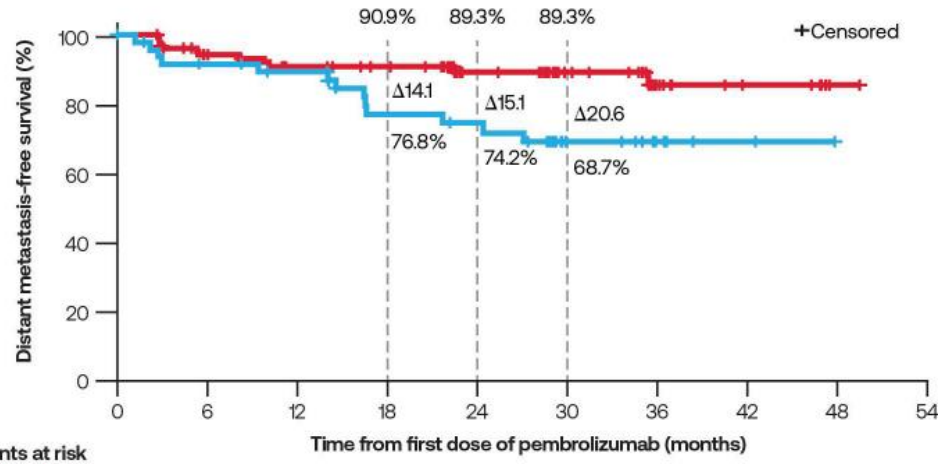
Neoantigen vaccination

Primary Efficacy Endpoint: PFS



	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)*
mRNA-4157 (V940) + pembrolizumab	NE	23.4 (25/107)	0.510 (0.288 to 0.906)
Pembrolizumab	42.51 (16.59 to NE)	44.0 (22/50)	*P* = .019†

Secondary Efficacy Endpoint: DMFS



	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)*
mRNA-4157 (V940) + pembrolizumab	NE	10.3 (11/107)	0.384 (0.172 to 0.858)
Pembrolizumab	NE	26.0 (13/50)	*P* = .015†

Weber et al. Lancet 2024

Neoantigen vaccination: Safety

	mRNA-4157 (V940) + pembrolizumab (n = 104)		Pembrolizumab (n = 50)	
Event, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	104 (**100%**)	36 (**34.6%**)	46 (**92.0%**)	18 (**36.0%**)
Any treatment-related AE	104 (**100%**)	26 (**25.0%**)	41 (**82.0%**)	10 (**20.0%**)
Serious AE	15 (**14.4%**)[a]	13 (12.5%)	5 (**10.0%**)	4 (8.0%)
Immune-related AE[b]	39 (**37.5%**)	11 (**10.6%**)	18 (**36%**)	7 (**14.0%**)

mRNA-4157 + pembrolizumab (n = 104)	Grade 1	Grade 2	Grade 3	Grade 4/5	TOTAL (n=104)
Patients with mRNA-4157–related AE[c]	**35 (33.7%)**	**51 (49.0%)**	**12 (11.5%)**	**0**	**98 (94.2%)**
Fatigue	40 (38.5%)	18 (17.3%)	5 (4.8%)	0	63 (60.6%)
Injection site pain	37 (35.6%)	22 (21.2%)	0	0	59 (56.7%)
Chills	48 (46.2%)	3 (2.9%)	0	0	51 (49.0%)
Pyrexia	34 (32.7%)	15 (14.4%)	1 (1.0%)	0	50 (48.1%)
Headache	20 (19.2%)	13 (12.5%)	0	0	33 (31.7%)
Injection site erythema	29 (27.9%)	4 (3.8%)	0	0	33 (31.7%)
Influenza like illness	21 (20.2%)	10 (9.6%)	0	0	31 (29.8%)
Nausea	23 (22.1%)	3 (2.9%)	0	0	26 (25.0%)
Myalgia	16 (15.4%)	5 (4.8%)	1 (1.0%)	0	22 (21.2%)

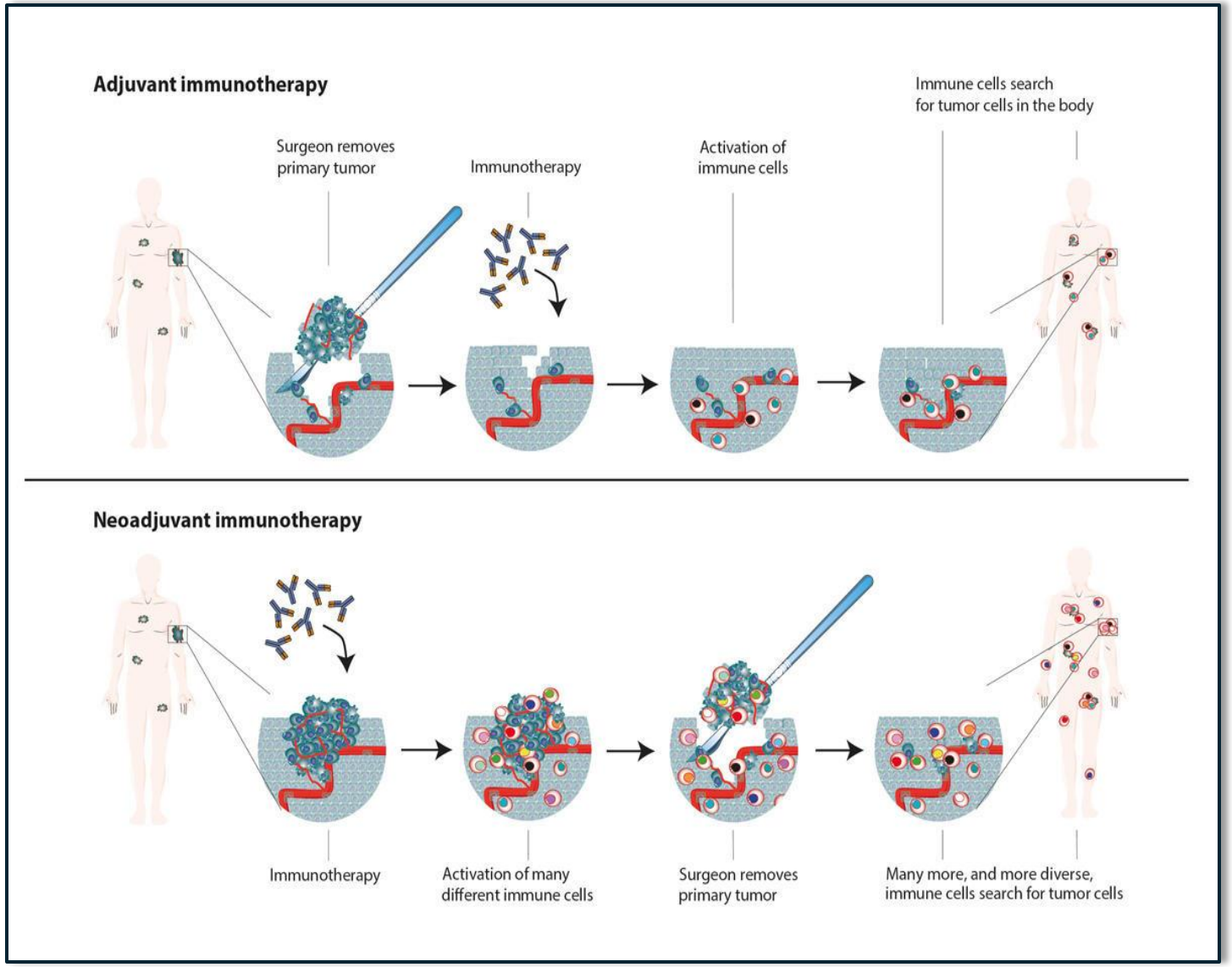
Neoantigen vaccination does not increase rates of irAEs

Weber et al. ASCO 2024

Slide courtesy of Ryan Sullivan

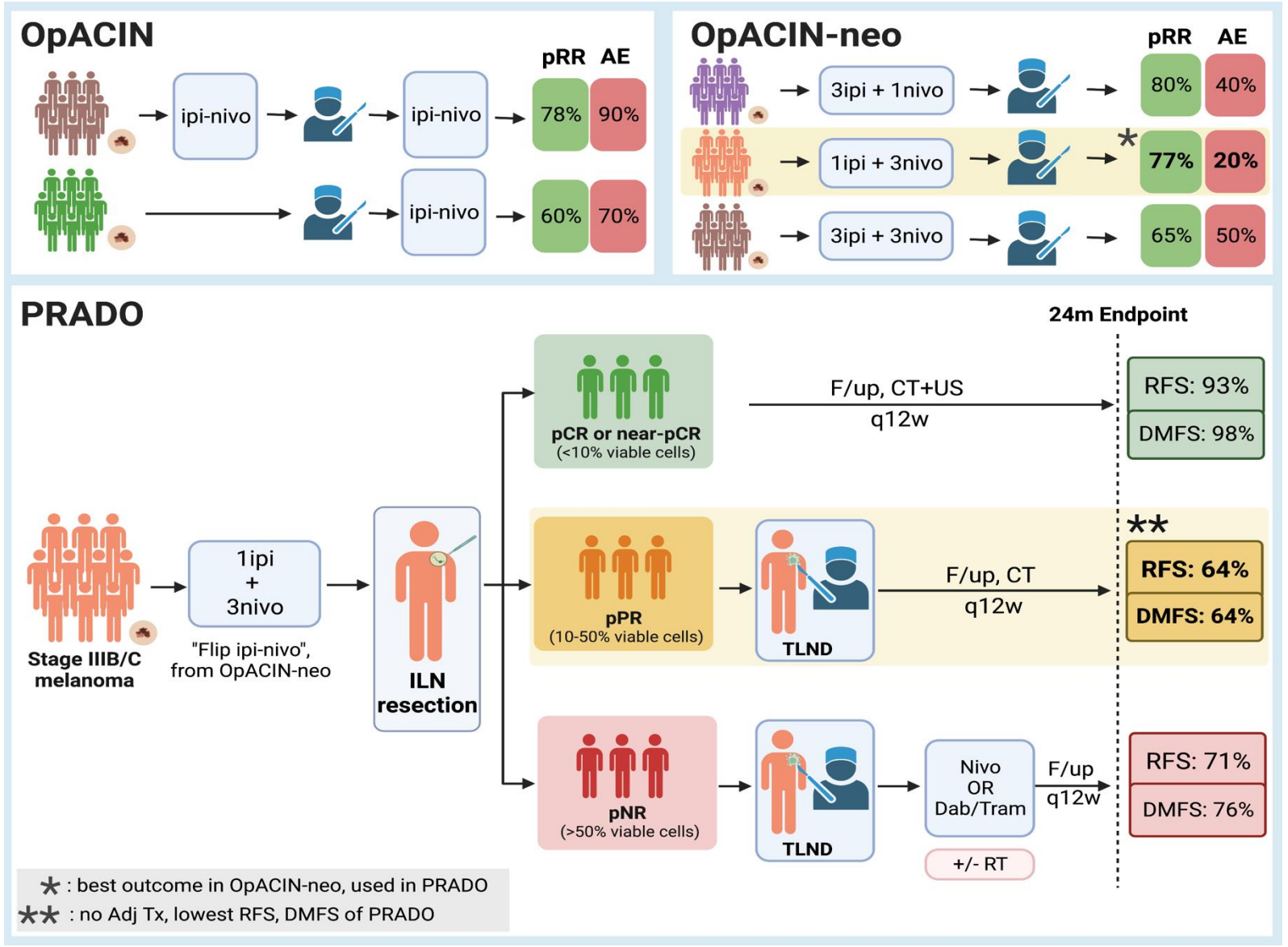
What about Neoadjuvant Therapy

- Tumor shrinkage → decreased surgical morbidity
- Objective measure of response & personalization of adjuvant therapy
- More effective activation of an immune response
  - Pathologic response correlates with RFS
- Understanding of drug response and resistance thru correlative analysis
- Potential pathway for new drug evaluation/registration



Versluis JM et al. Nature Medicine. 2020

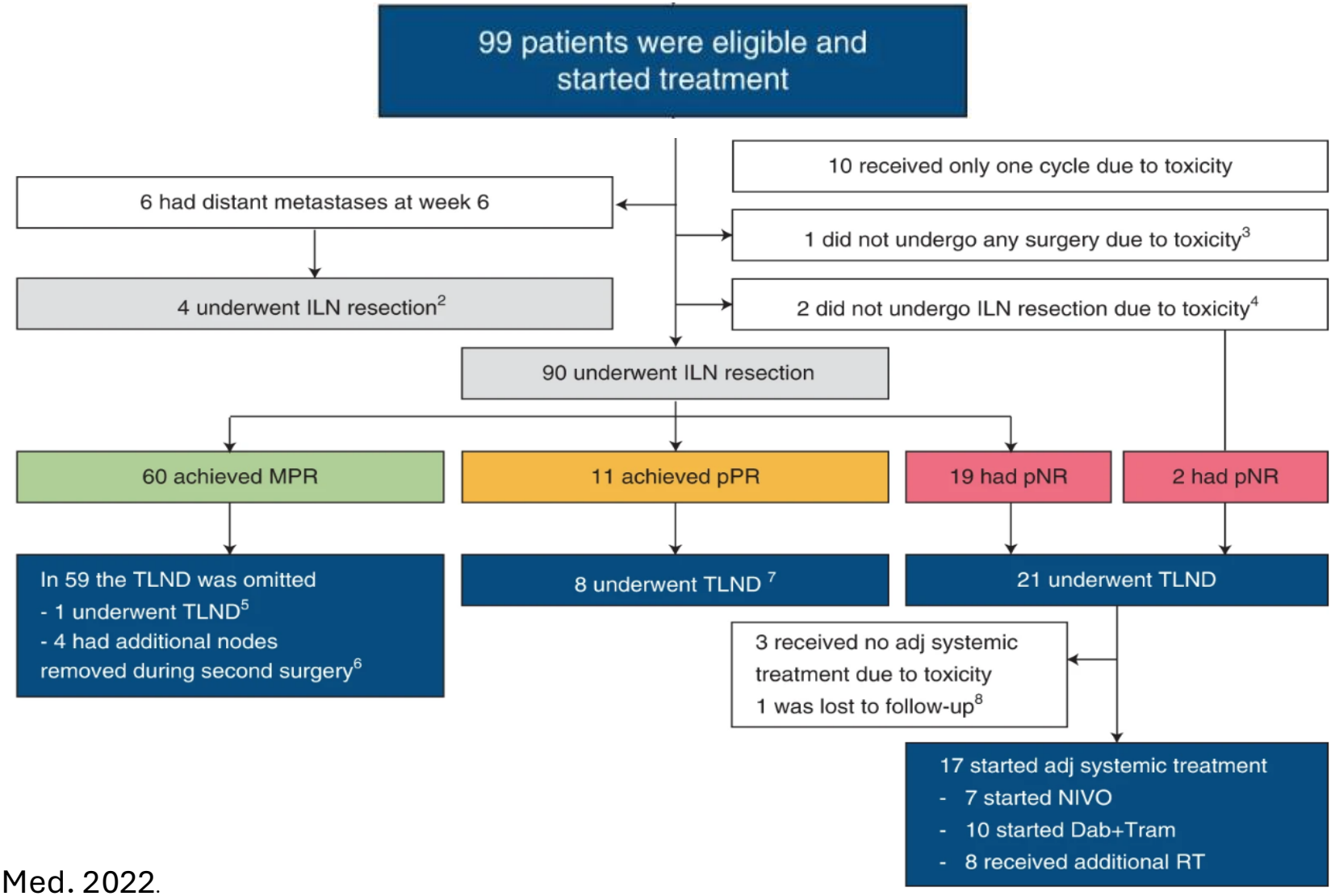
Early neoadjuvant studies



Reijers ILM et al. Nat Med. 2022. 2. Dedeilia A & Boland G. BJS Acad. 2022. https://www.bjsacademy.com/personalized-neoadjuvant-immunotherapy-for-stage-iii-malignant-melanoma-notes-on-the-prado-study.

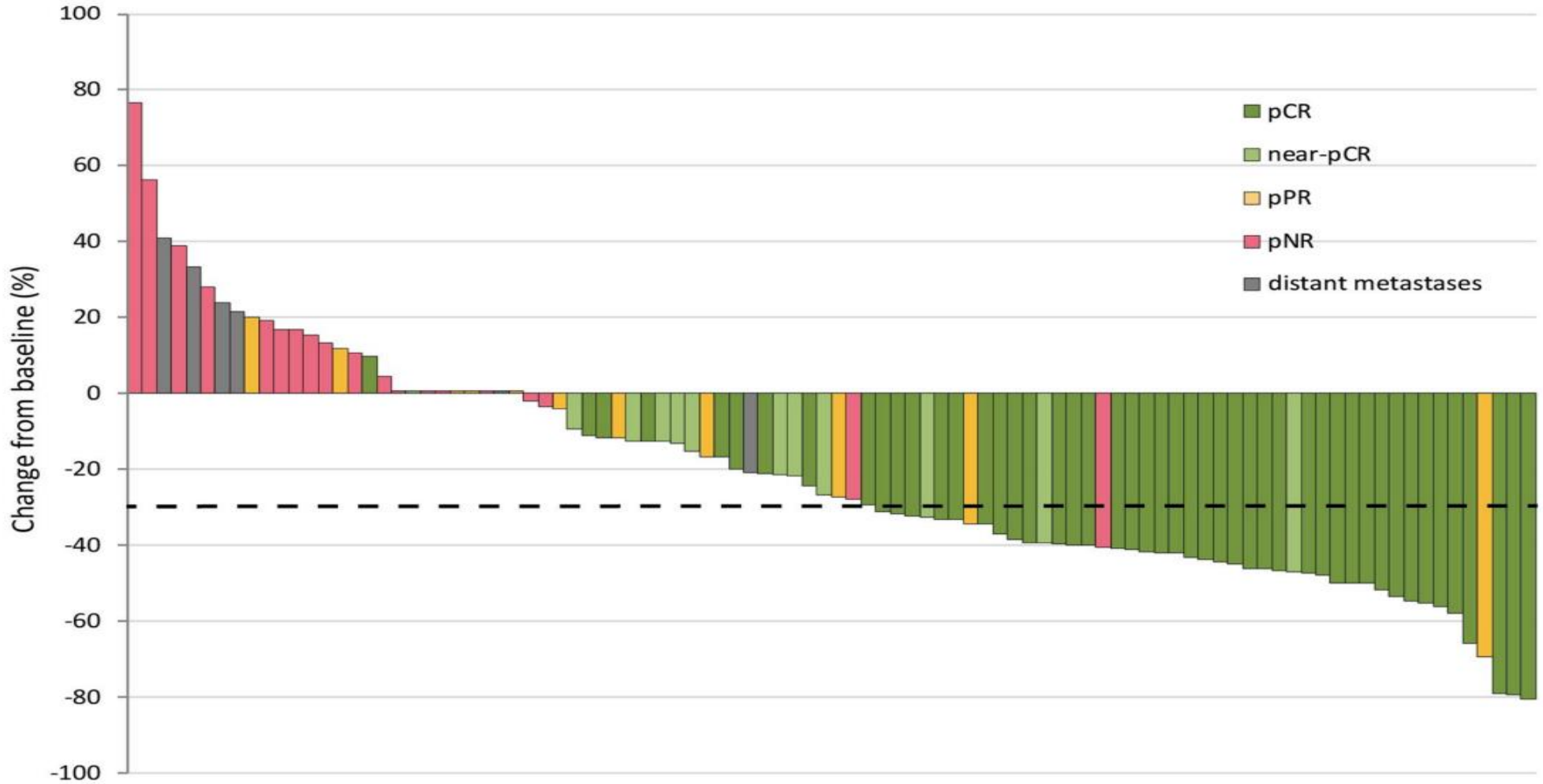
PRADO

Personalized response-directed surgery and adjuvant therapy



Reijers et al. NatureMed. 2022.

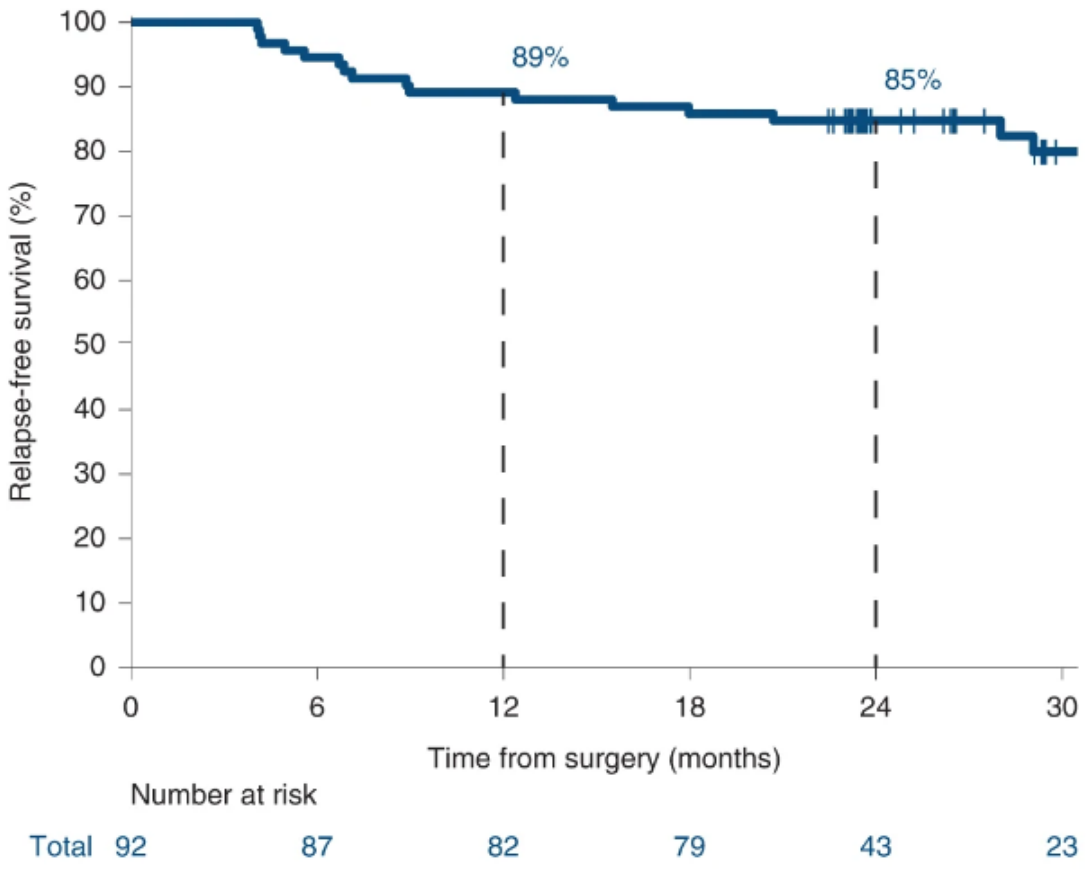
PRADO: ORR underestimate pathologic response



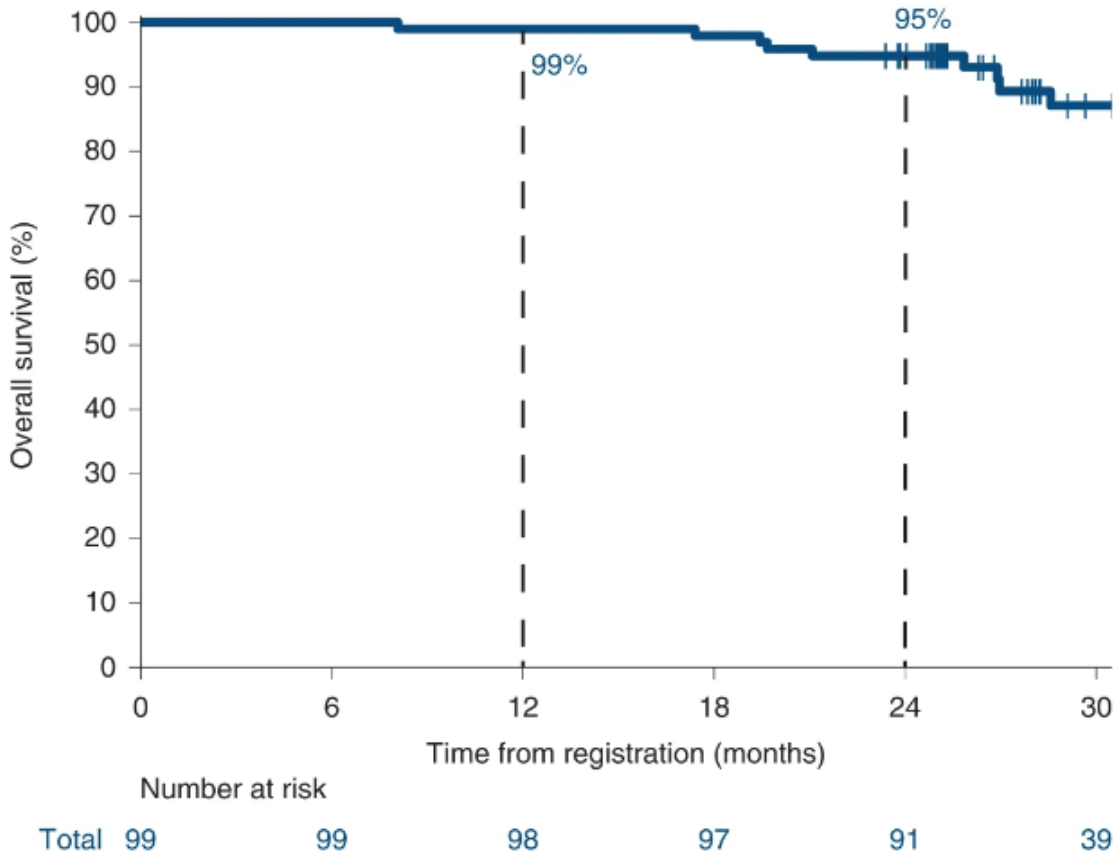
Reijers et al. NatureMed. 2022.

PRADO: RFS, OS

RFS of the entire population



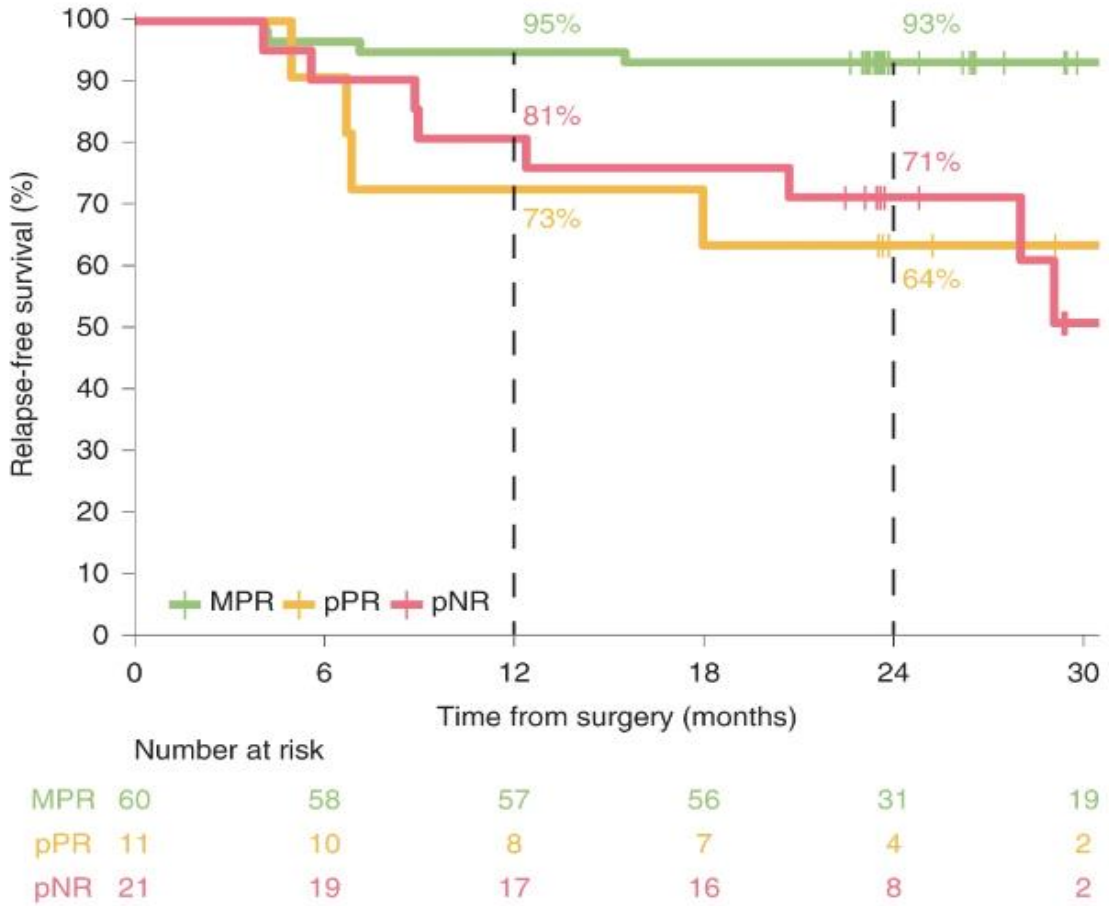
OS of the entire population



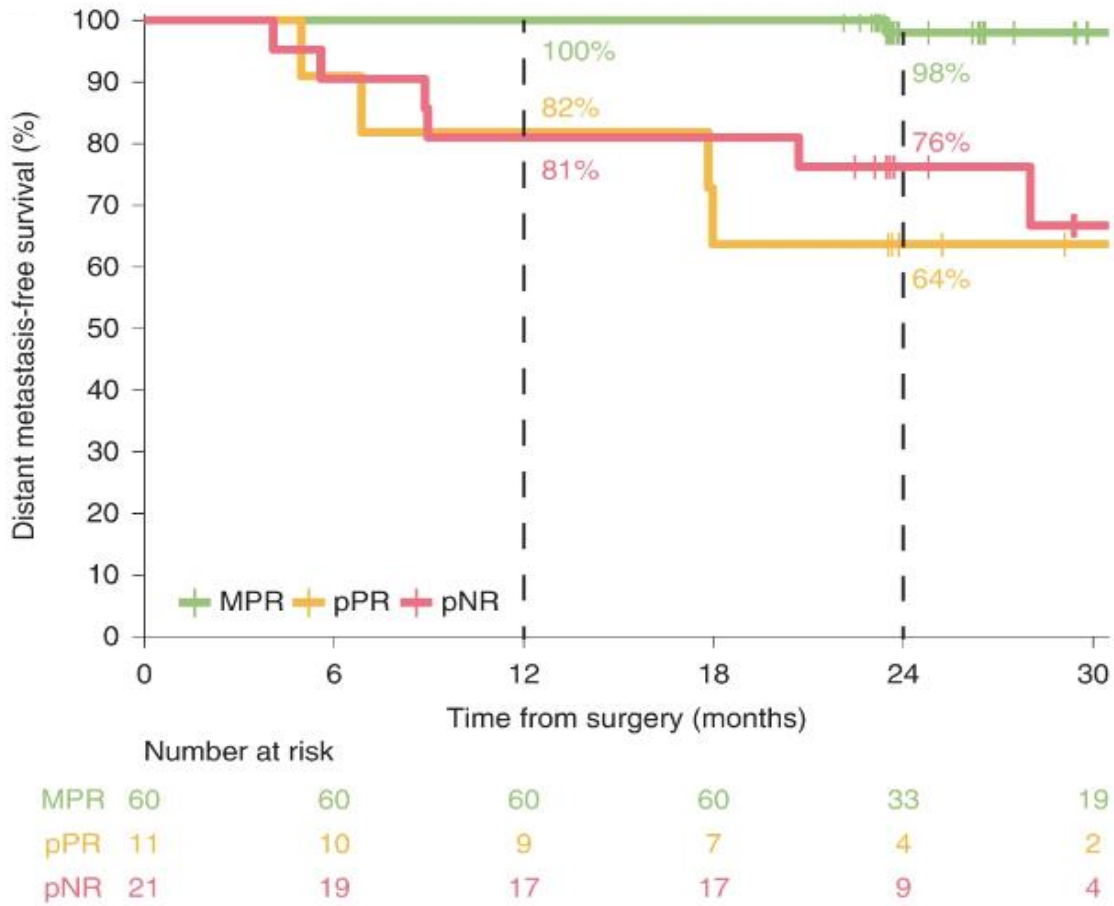
Reijers et al. NatureMed. 2022.

PRADO results by pathologic response

RFS by pathology response



DMFS by pathology response

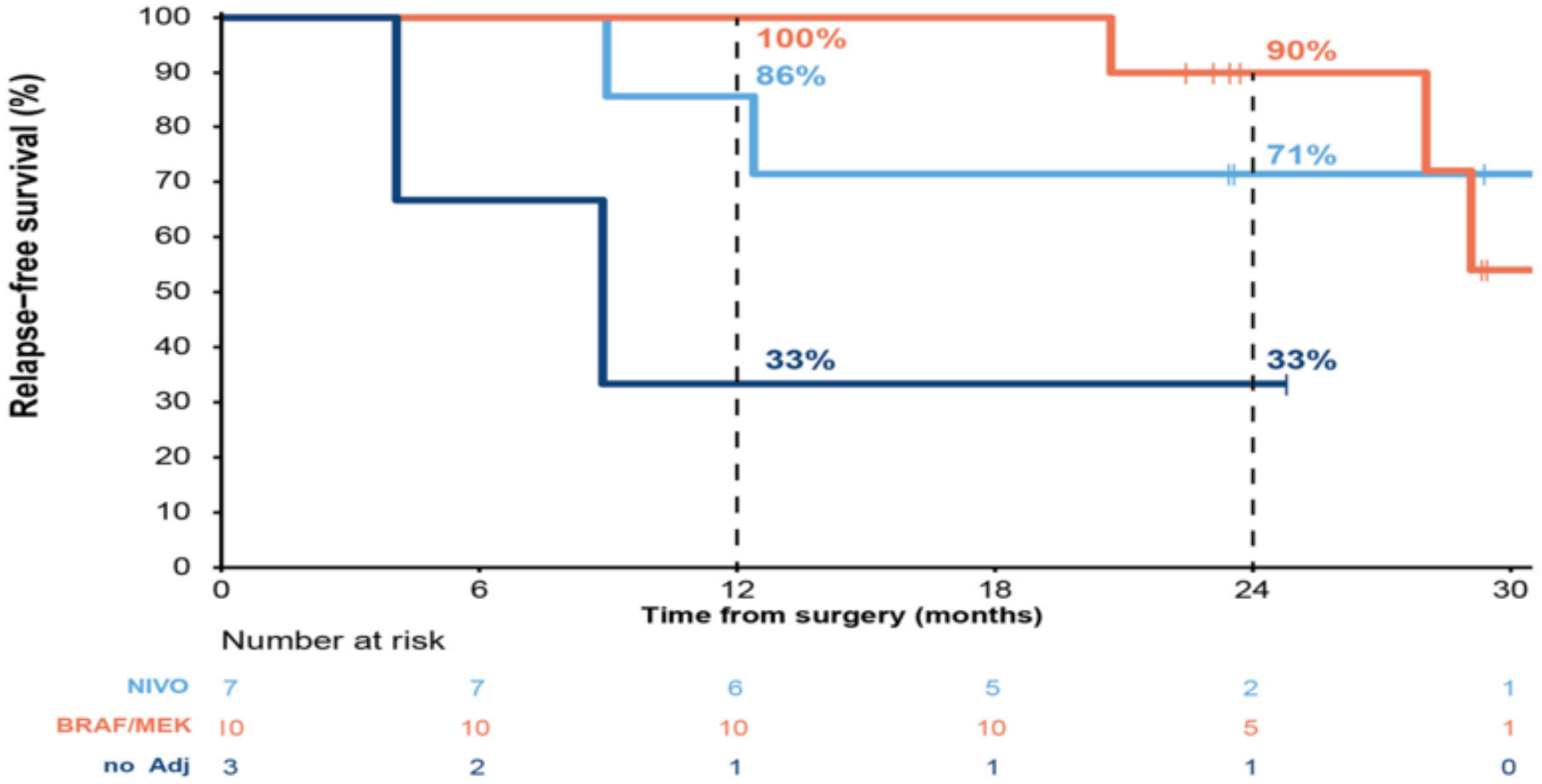


Reijers et al. NatureMed. 2022.

RFS by adjuvant therapy

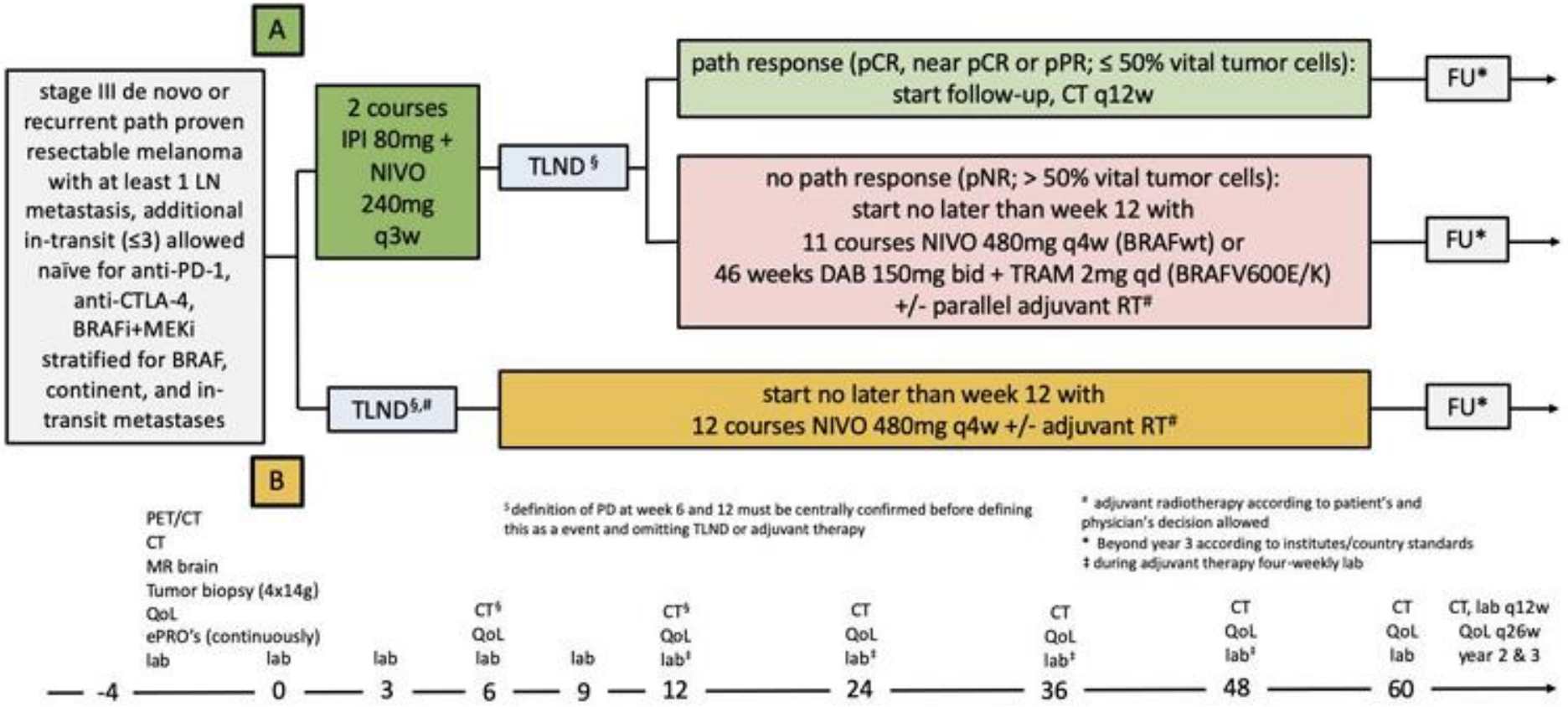
Adjuvant therapy improved RFS in pathology non-responders

Adjuvant strategies:
Nivolumab (light blue)
BRAF/MEK (orange)
Surveillance alone (dark blue)



Reijers et al. NatureMed. 2022.

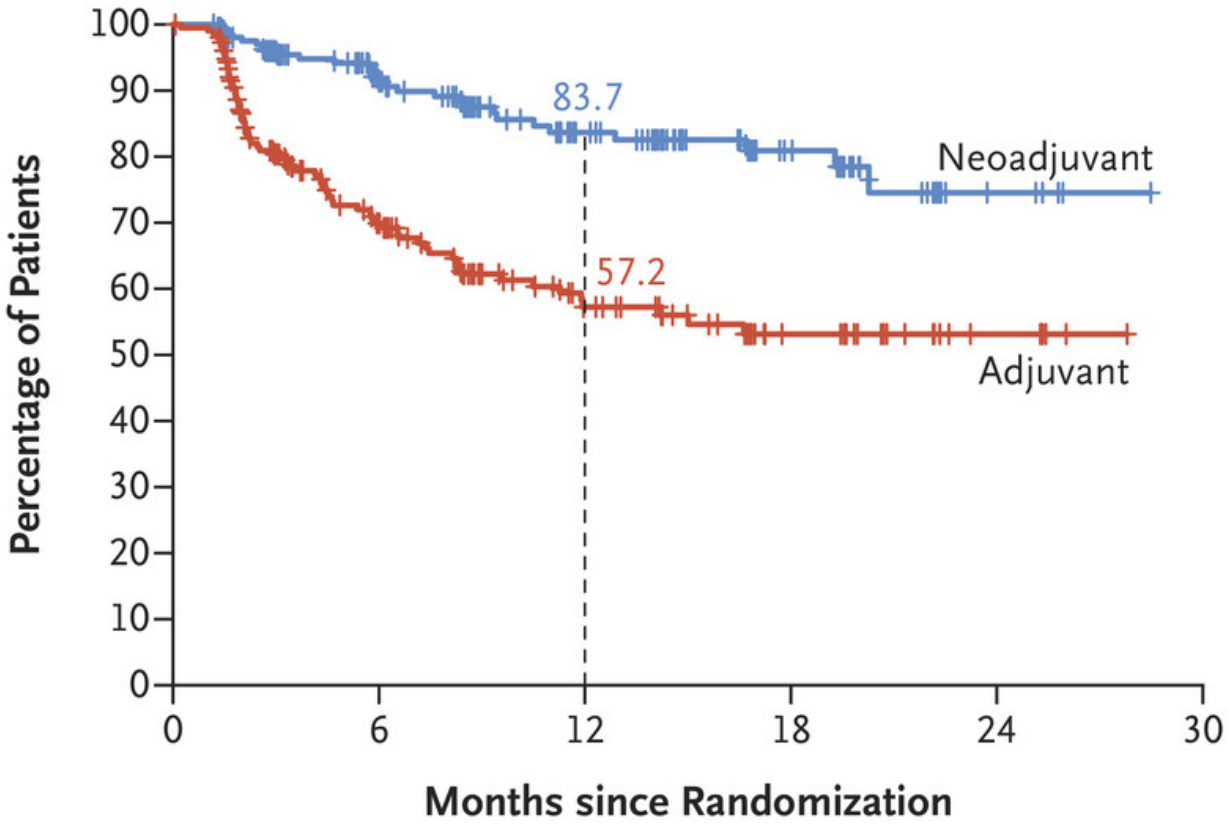
Phase III NADINA Trial – Design



Primary endpoint: event-free survival, event defined as the time from randomization to the occurrence of progression to unresectable melanoma before surgery, disease recurrence, or death due to melanoma or due to treatment

Blank CU et al. J Clin Oncol 42, 2024 (suppl 17; abstr LBA2). Blank CU, et al. N Engl J Med. 2024.

NADINA trial - Event-free Survival



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)

Blank CU et al. J Clin Oncol 42, 2024 (suppl 17; abstr LBA2). Blank CU, et al. N Engl J Med. 2024.

Pathologic Response and RFS

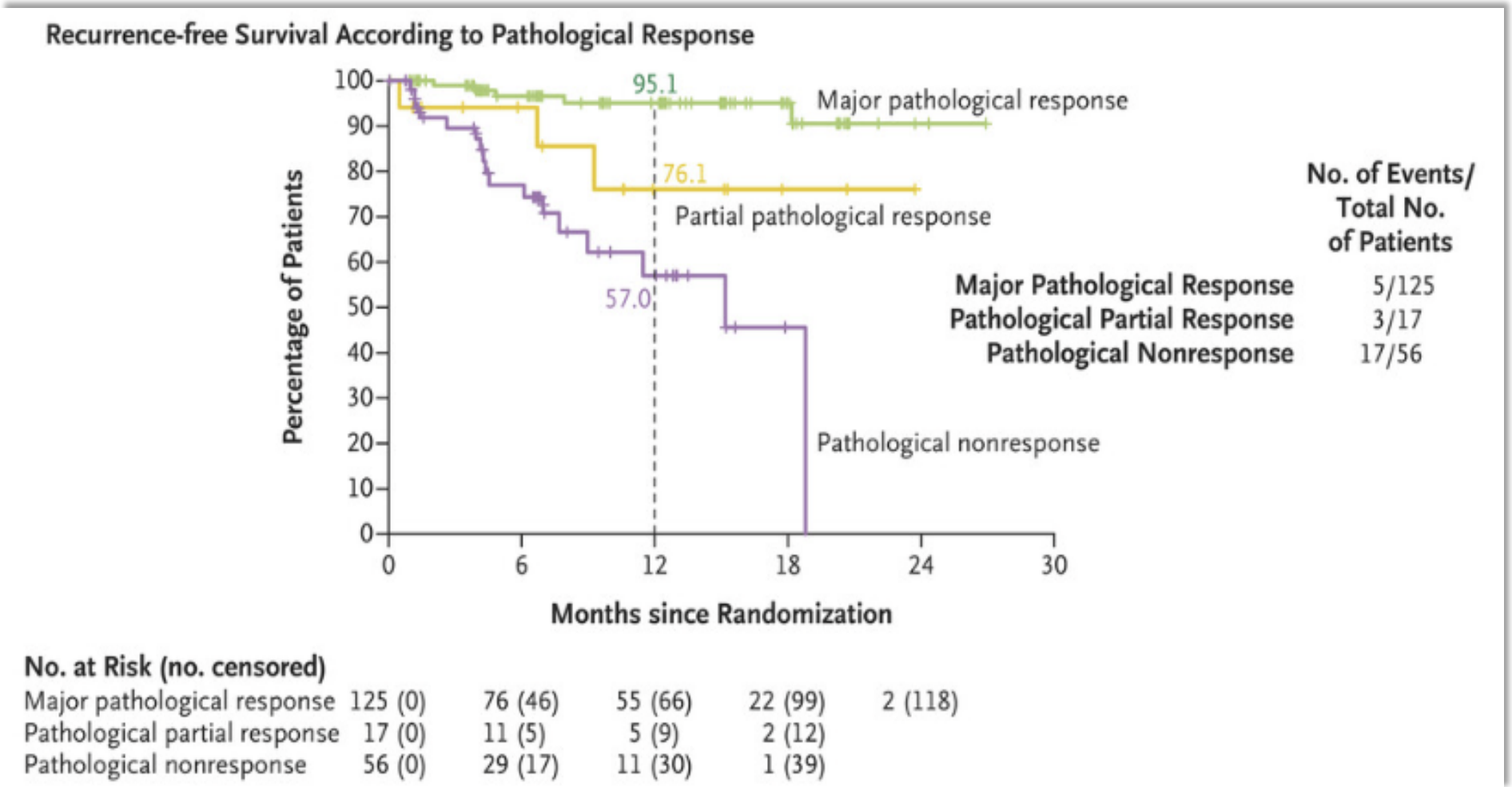
Pathologic response (by central review):

MPR: 59%
- pCR: 47%

pPR: 8%

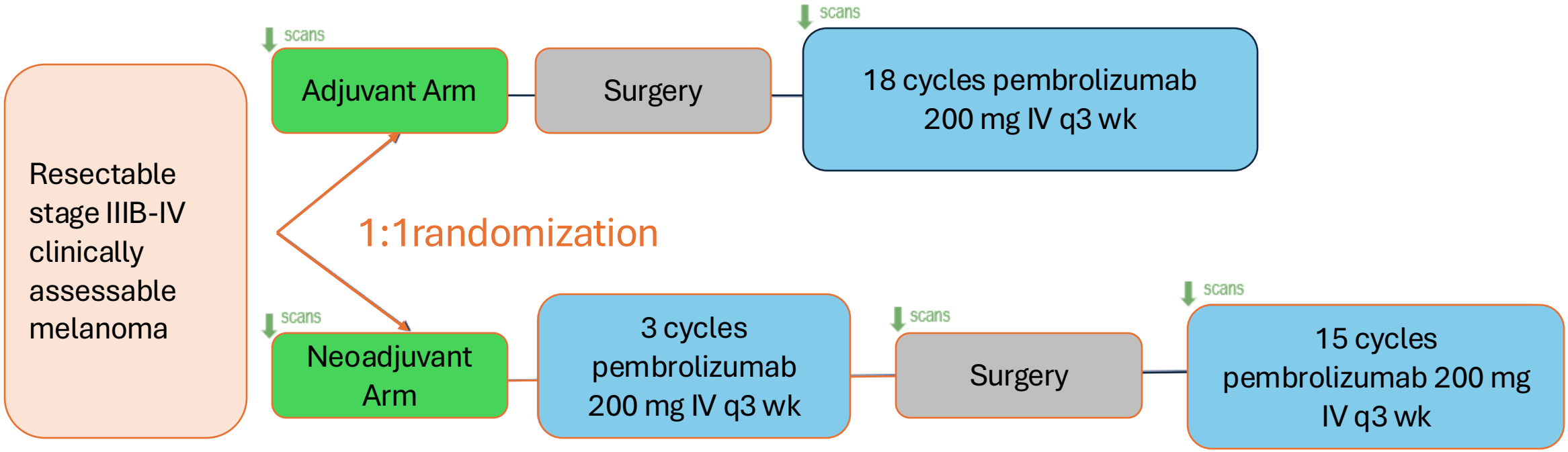
pNR:26%

PD prior to surgery: 2%



Blank CU et al. J Clin Oncol 42, 2024 (suppl 17; abstr LBA2). Blank CU, et al. N Engl J Med. 2024.

Phase II SWOG S1801: Neoadjuvant Pembrolizumab

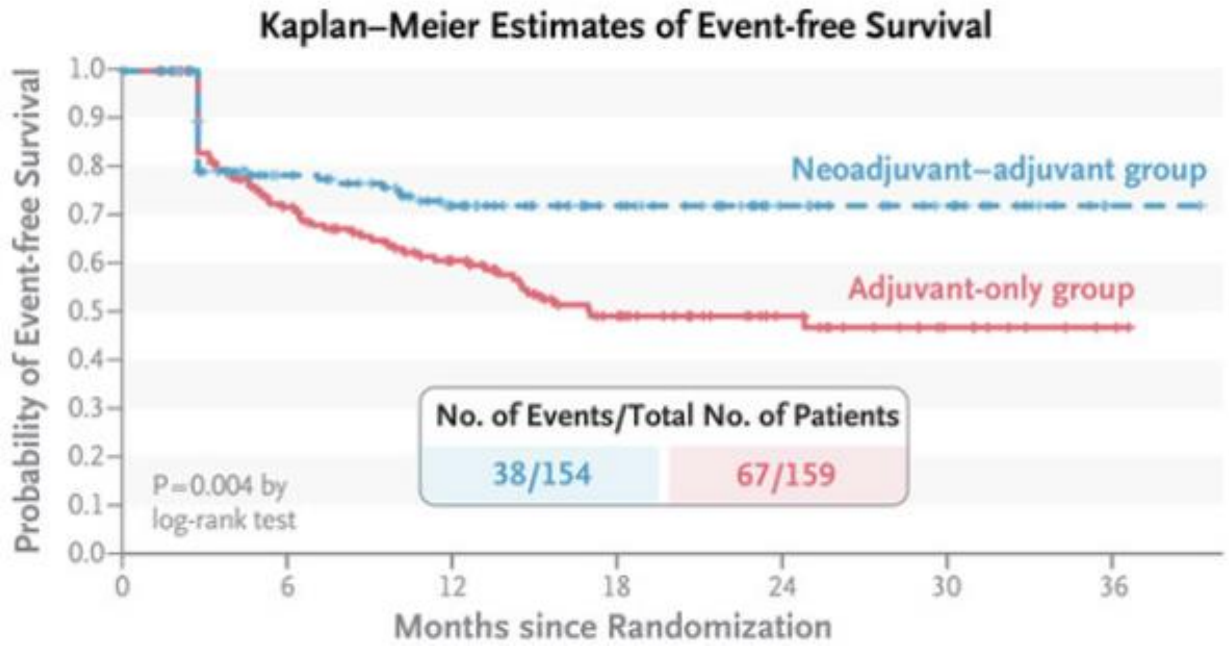


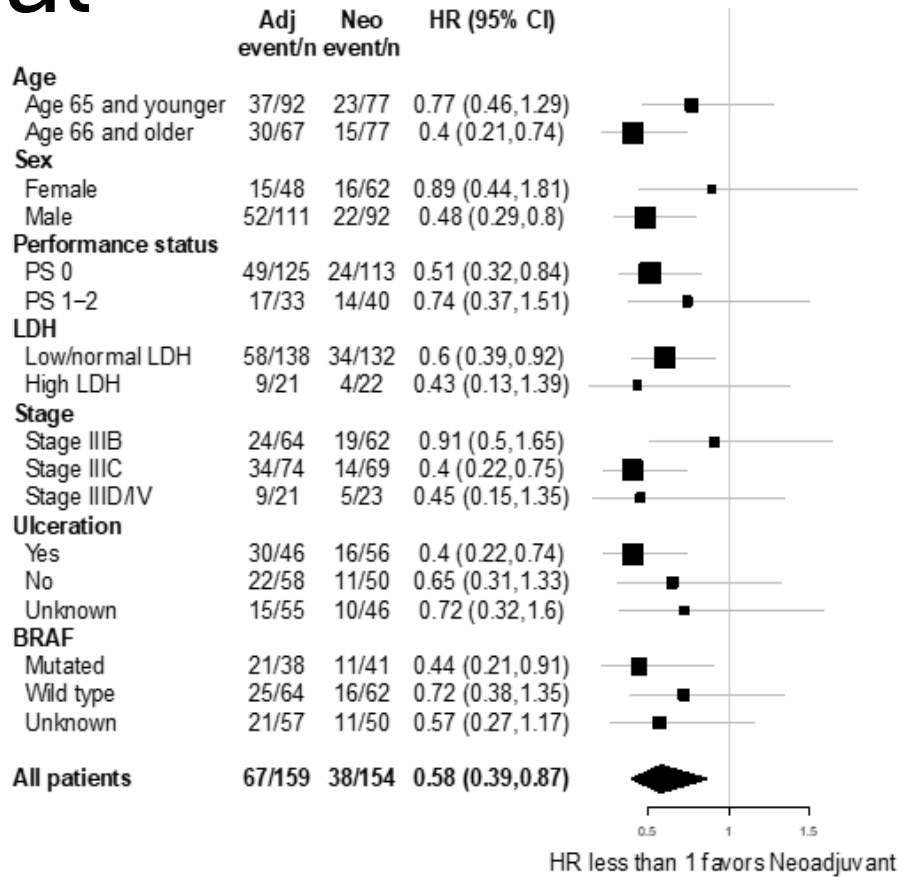
Primary endpoint: Event-free survival

Investigators assumed a 2yr RFS of 74% for neoadjuvant PD-1 vs. 64% for adjuvant PD-1

Patel SP et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. Patel SP et al.. N Engl J Med. 2023.

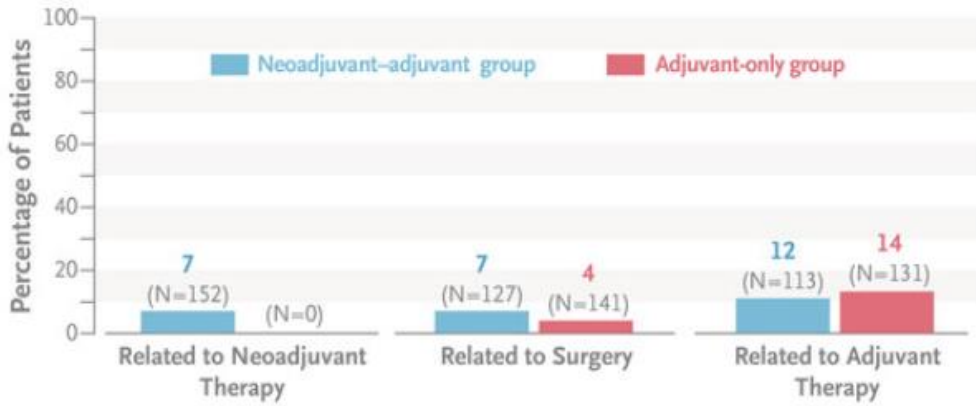
SWOG1801 – Event-free Survival





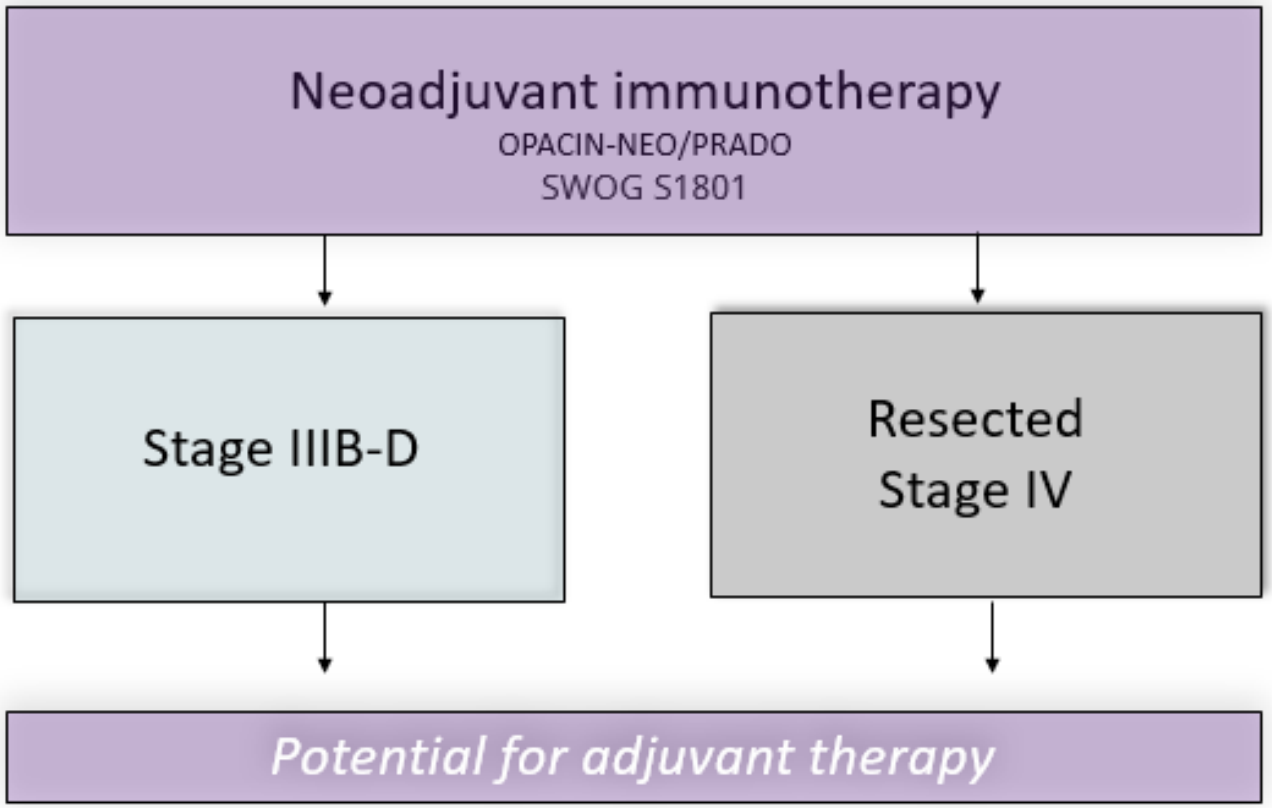
Neoadjuvant pembrolizumab:

- **Improved 2-year EFS: 72% vs 49%**
- **Benefit seen across subgroups**
- **No increased risk of toxicity in the surgical or adjuvant therapy for the neoadjuvant arm**



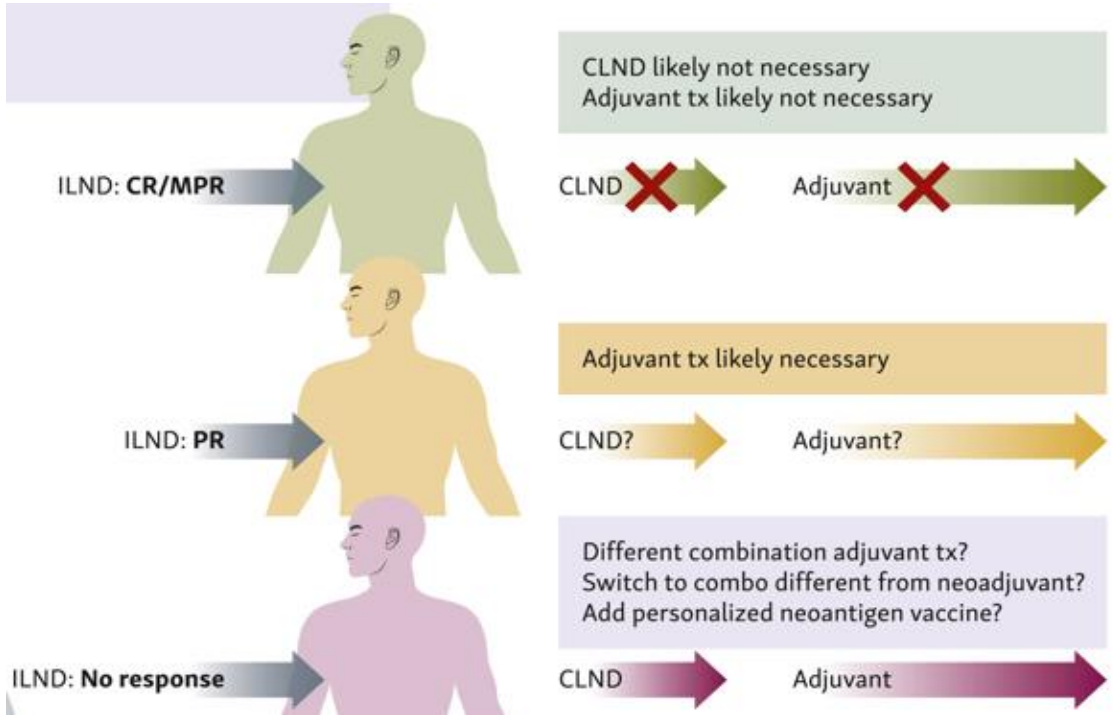
Patel SP et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. Patel SP et al. N Engl J Med. 2023;388(9):813-823.

Neoadjuvant therapy landscape



Outstanding Questions:

- Optimal neoadjuvant regimen
- Optimal duration
- Personalization of surgical & adjuvant strategy, especially for the non-responders!



Sussman and Ott. ESMO Open. 2024

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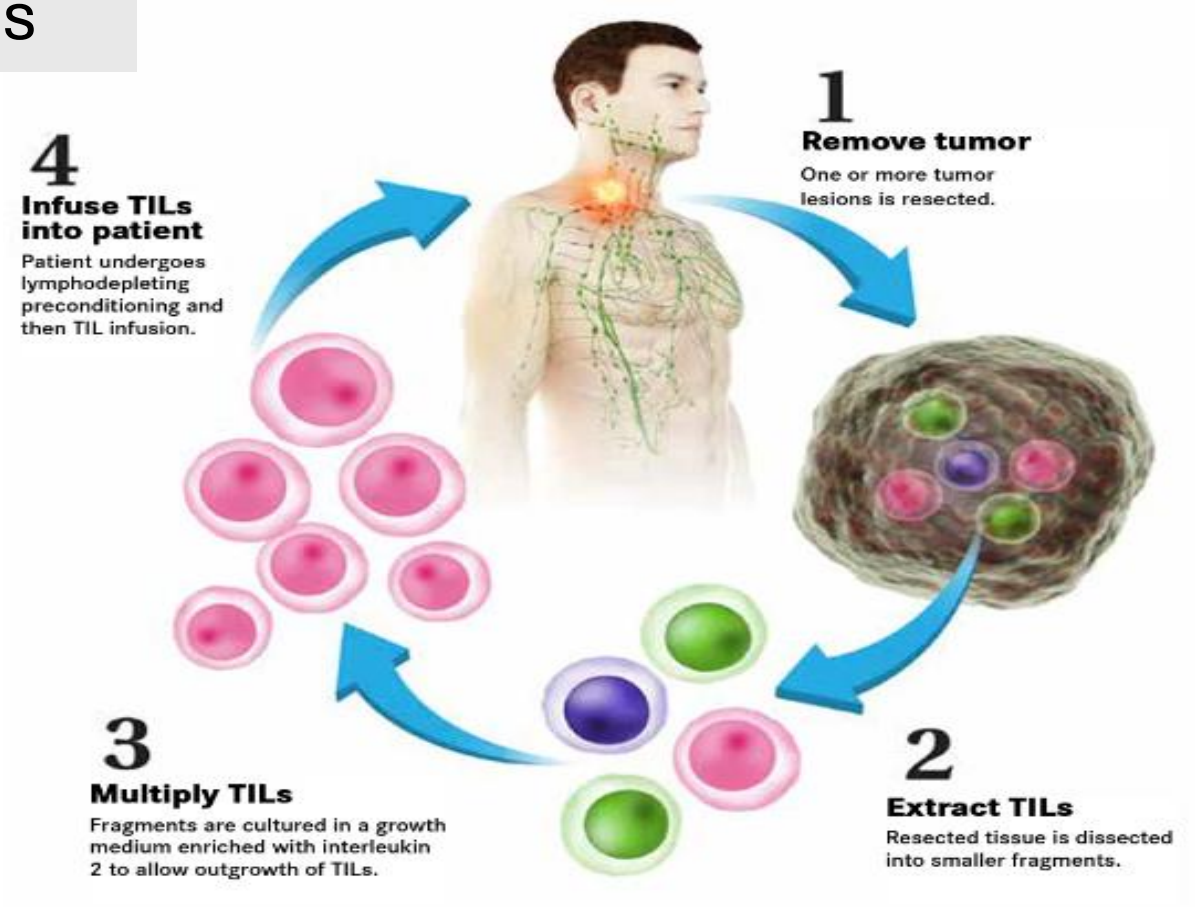
Tumor-infiltrating lymphocytes (TIL)

Key Steps

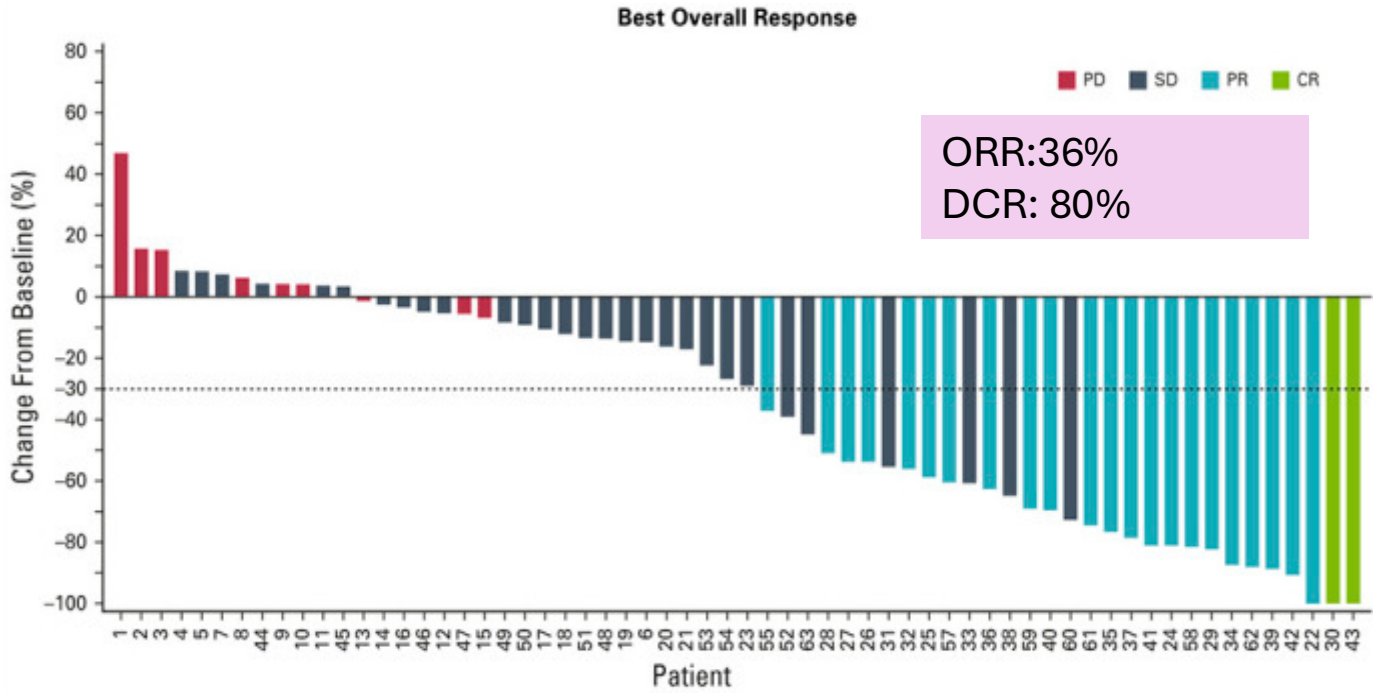


Salvage TIL with Lifileucel post-PD-1

Sixty-six patients (mean of 3.3 prior tx) enrolled on single arm study of TIL, Lifileucel

Prior therapies, No. (%)	
Mean No. of prior therapies (SD)	3.3 (1.69)
Anti–PD-1 or PD-L1[a]	66 (100)
Anti–CTLA-4[b]	53 (80)
Anti–PD-1 plus CTLA-4 combination	34 (52)
BRAF± MEK[c]	15/17 (88)
IL-2	7 (11)
Surgery	65 (99)
Radiotherapy	34 (52)
Progressive disease for at least one prior therapy, No. (%)	
Anti–PD-1 or PD-L1[d]	65/66 (99)
Anti–CTLA-4	41/53 (77)
Primary refractory to prior anti–PD-1 or anti–PD-L1, No. (%)	42 (64)
Patients with baseline liver lesions, No. (%)	23 (35)
Patients with baseline brain lesions, No. (%)	7 (11)
Patients with baseline liver and/or brain lesions, No. (%)	28 (42)

Primary endpoint: Objective Response Rate



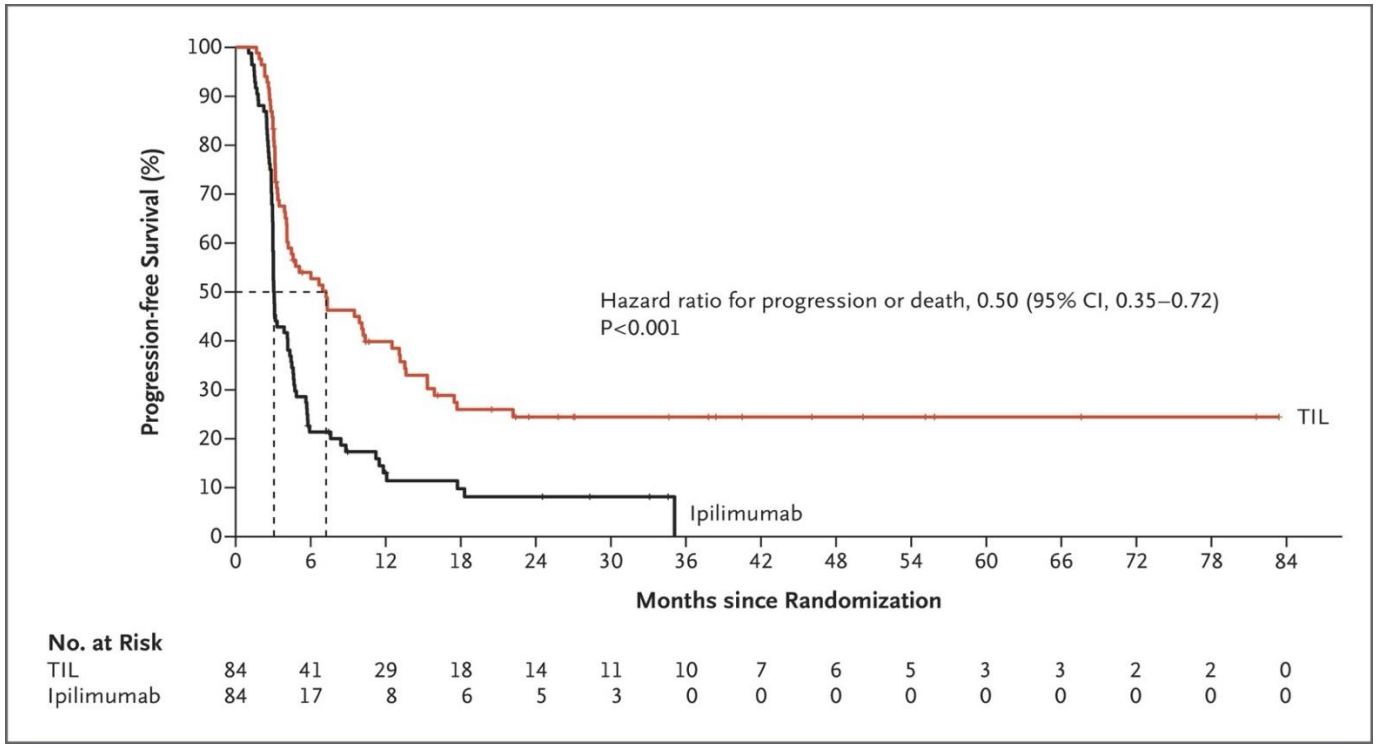
ORR:36%
DCR: 80%

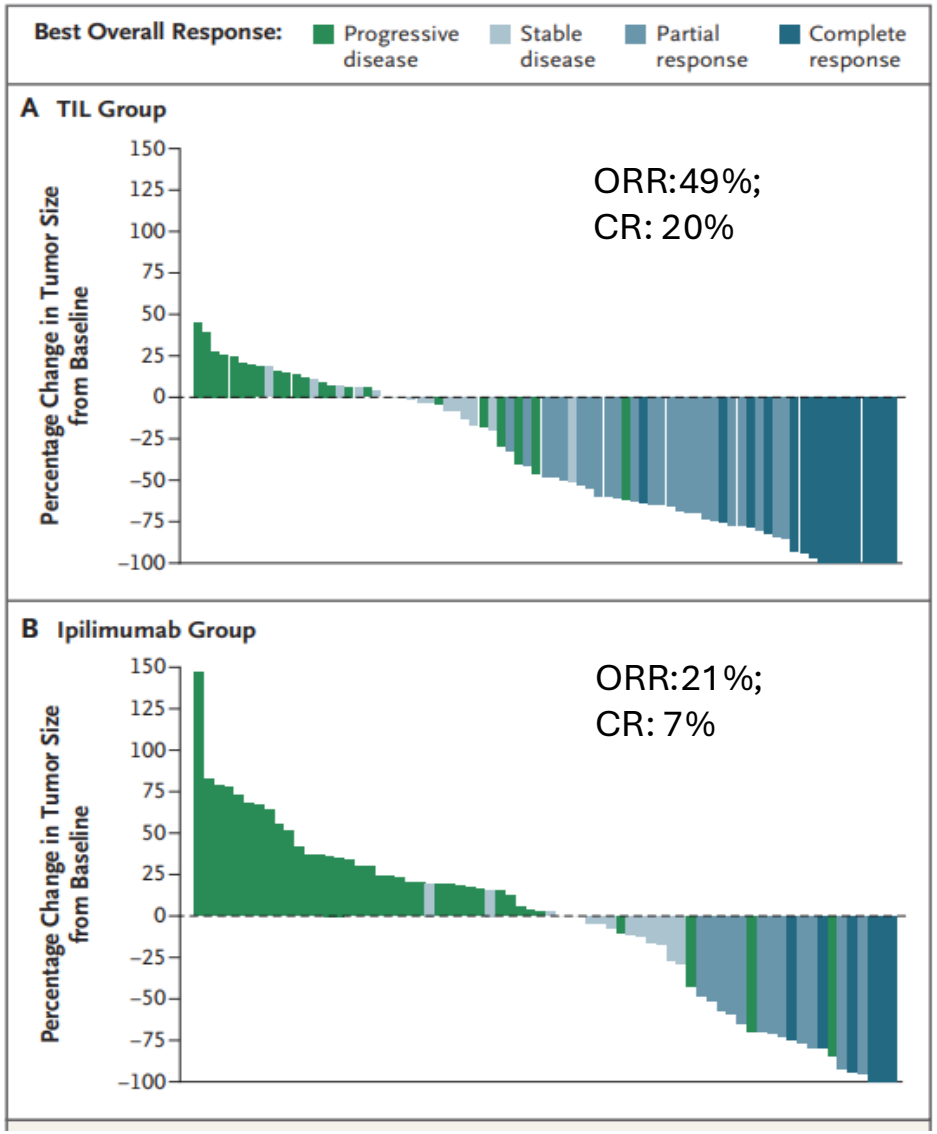
Sarnaik et el. JCO. 2021

TIL vs ipilimumab in unresectable melanoma

168 patients were randomly assigned to receive either TILs (84 pts) or ipilimumab (84 pts)
1 prior line of systemic treatment, excluding ipilimumab, was allowed
- 86% prior anti-PD-1 in the adjuvant or metastatic setting.

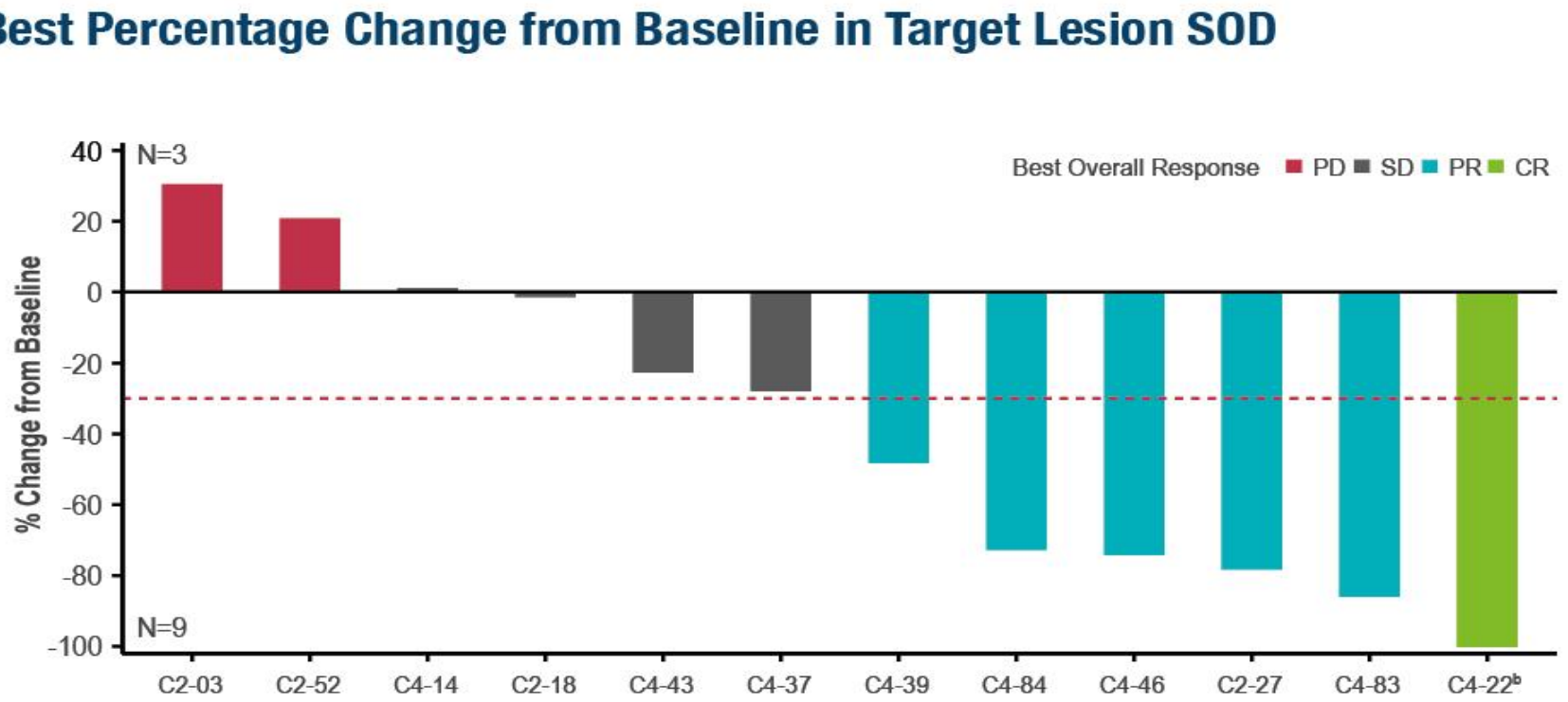
Primary endpoint: PFS





Rohaan MW et al. NEJM. 2022

TIL Activity in mucosal melanoma



After a median follow-up of 35.7 months:

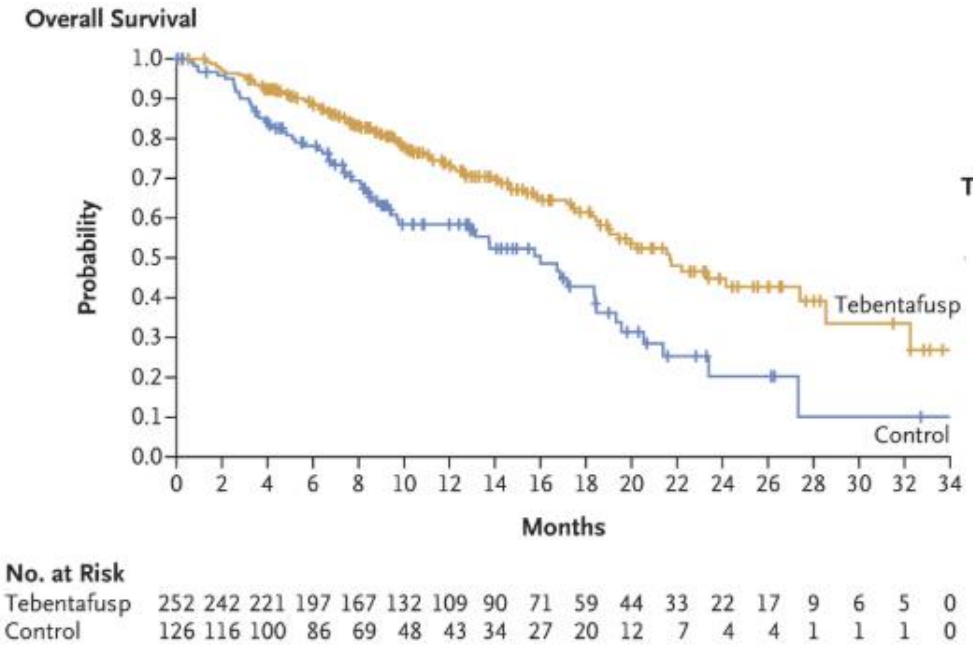
- ORR: was 50.0% (95% confidence interval [CI] 21.1–78.9) (n=12)
- Median duration of response (DoR) was not reached; 4 of 6 responders having durable and ongoing responses at data cutoff.

ESMO Congress 2023, Abstract 1086MO

Other promising strategies in the 2L space

ImmTAC: Tebentafusp

Improves OS in uveal melanoma

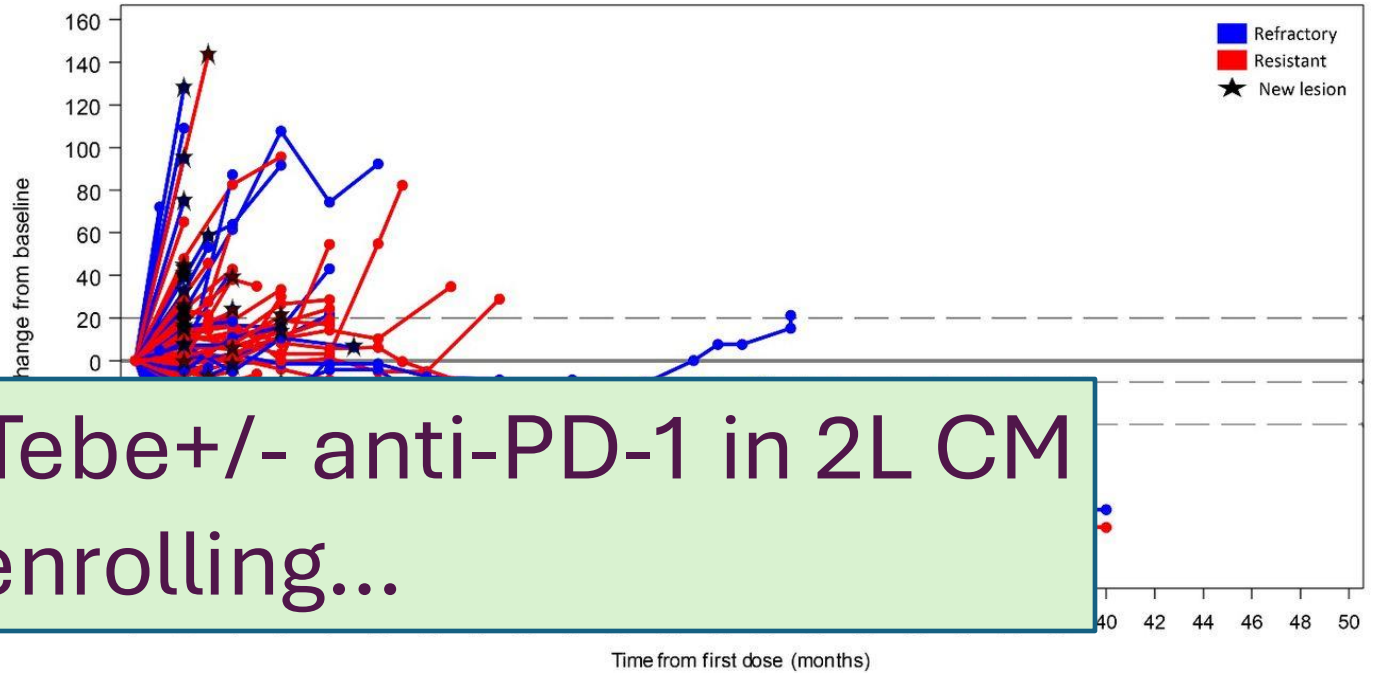


	Median Overall Survival (95% CI) *mo*
Tebentafusp	21.7 (18.6–28.6)
Control	16.0 (9.7–18.4)

Stratified hazard ratio for death, 0.51 (95% CI, 0.37–0.71)

Treatment beyond progression with tebentafusp may be associated with additional benefit

Encouraging efficacy in Tebentafusp (plus durva) post anti-PD1 in cutaneous melanoma (CM)



IMCgp100-203 Study: Tebe+/- anti-PD-1 in 2L CM
Now enrolling...

Sullivan et al. ASCO 2022

ImmTAC: Targeting PRAME

2024 ASCO ANNUAL MEETING

#9507

Phase 1 safety and efficacy of brenetafusp (IMC-F106C), a PRAME × CD3 ImmTAC bispecific, in post-checkpoint cutaneous melanoma (CM)

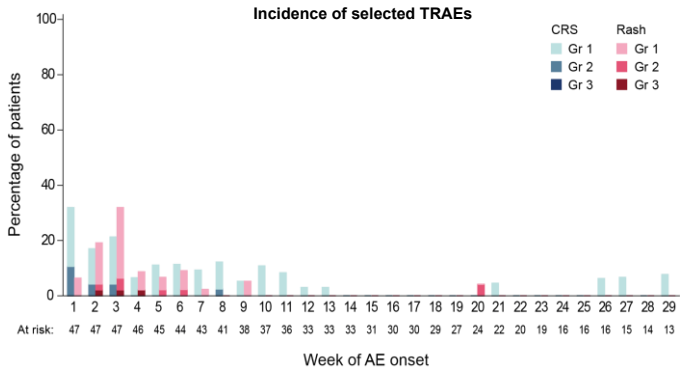
Omid Hamid[1], Anja Williams[2], Juanita Lopez[3], Daniel Olson[4], Takami Sato[5], Heather Shaw[6], Claire F. Friedman[7], Fiona Thistlethwaite[8], Mark R. Middleton[9], Celeste Lebbe[10], Vincent T. Ma[11], Benjamin Izar[12], Peter Lau[13], Oliver Bechter[14], Peter Kirk[15], Yuan Yuan[16], Shannon Marshall[16], and Diwakar Davar[17]

Brenetafusp monotherapy was well tolerated

TRAE in ≥ 15% of patients (N=47)

Preferred Term (%)	Any grade	Grade 3 / 4
ANY	43 (92%)	19 (40%)
Cytokine release syndrome*	24 (51%)	-
Rash (composite)†	23 (49%)	1 (2%)
Pyrexia	17 (36%)	1 (2%)
Chills	13 (28%)	-
Lymphocyte decrease	12 (26%)	11 (23%)
Pruritus	11 (23%)	-
Nausea	9 (19%)	-
Fatigue	7 (15%)	-

Includes patients receiving target doses ≥20mcg
* CRS graded per ASTCT 2019 criteria; all other AE per CTCAE v5.0
† Rash is a composite term for a list of skin toxicities of any grade (Nathan *et al.* 2021)
Other G3 treatment-related adverse events (TRAE, in 1 pt each): anemia, chronic inflammatory demyelinating polyneuropathy, fever, hypertension, hypotension, hypoxia, pain in extremity, tumor lysis syndrome, urticaria



- Safety consistent with previous report; no new signal with continued dosing
- Most frequent TRAE was G1/G2 CRS, consistent with mechanism
- TRAE frequency and severity attenuated over time
- The only G4 TRAEs were lymphocyte decrease (n=11) / lymphopenia (n=3), transient and related to mechanism
- No severe neutropenia observed
- 1 TRAE resulted in treatment discontinuation
- No treatment-related deaths

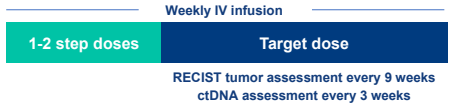
Brenetafusp Phase 1/2 Study Design

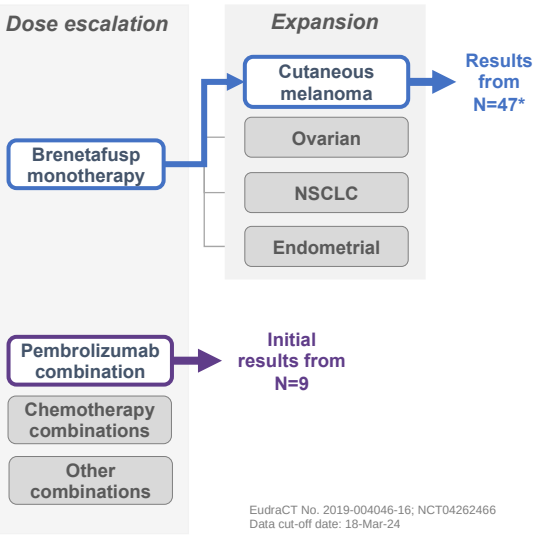
Key objectives:

Primary
- Safety
- MTD/expansion dose
- Efficacy (in expansion only)

Additional
- Pharmacokinetics
- Molecular response (ctDNA)
- Predictive biomarkers

Key eligibility criteria for CM:
- Unresectable or metastatic
- HLA-A*02:01 (central testing)
- Previously treated with
  - immune checkpoint inhibitors
  - BRAFi/MEKi, if applicable





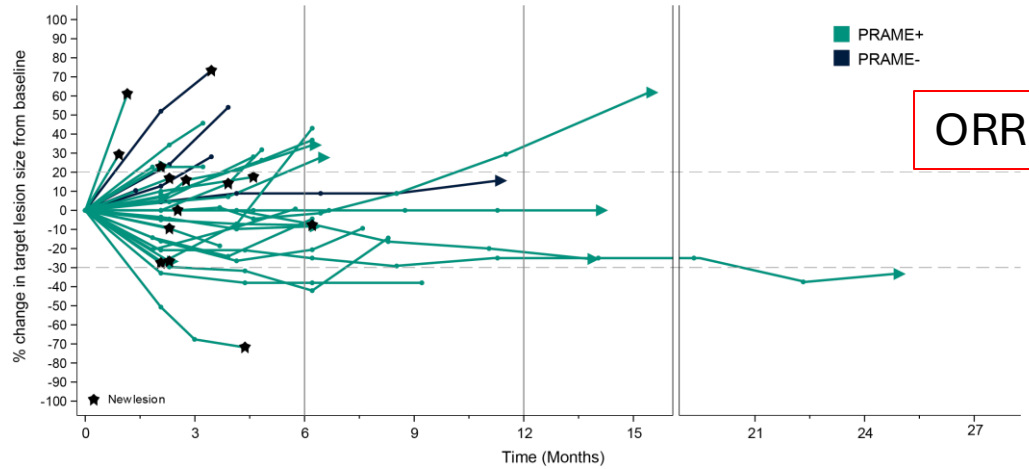
- Previously presented Ph1 data[1]
  - § Identified target doses ≥ 20 mcg as consistently pharmacodynamically and clinically active
  - § Included 7 efficacy-evaluable CM pts
- Tumor PRAME expression evaluated by IHC
- Gene expression in whole blood at baseline evaluated by bulk RNASeq

EudraCT No. 2019-004046-16; NCT04262466
Data cut-off date: 18-Mar-24

IV, intravenous; MTD, maximum tolerated dose; 1. Hamid O, *et al.* Ann Oncol 2022; 33 Suppl 7: S875
* 47 monotherapy patients at brenetafusp target dose of ≥ 20 mcg including 40 new patients and follow-up on 7 CM patients previously presented

Clinical benefit characterized by durable disease control

Brenetafusp monotherapy (n= 36 evaluable*)

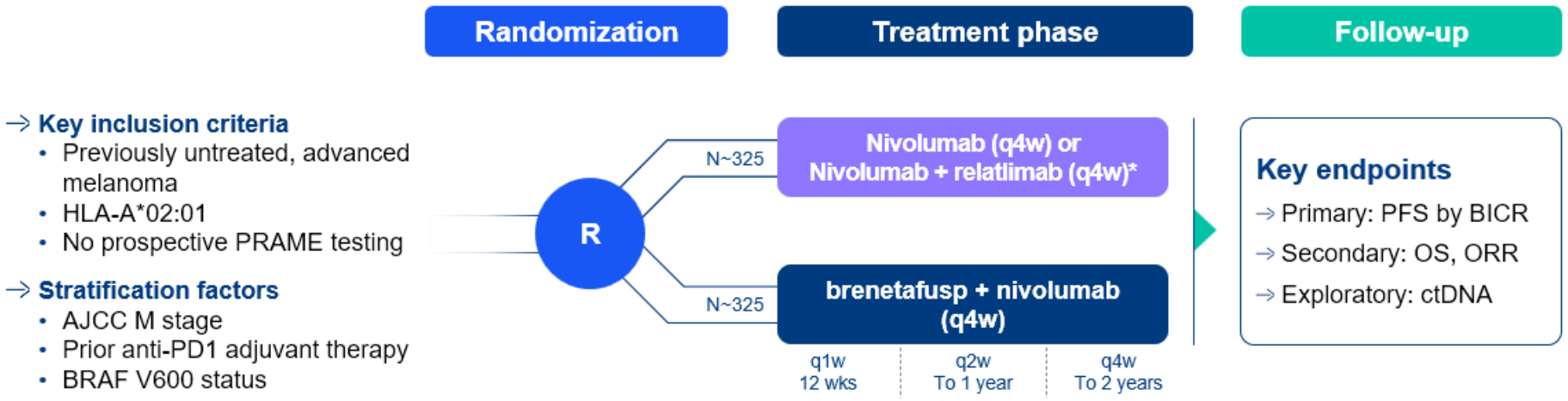


ORR 11%

PRAME positive group for efficacy analysis includes H-score ≥1 and pts with unknown PRAME IHC results
* 36/47 patients had baseline and at least one tumor assessment on treatment; 10 patients had no evaluable post-baseline tumor scans and 1 had non-target lesions only at baseline

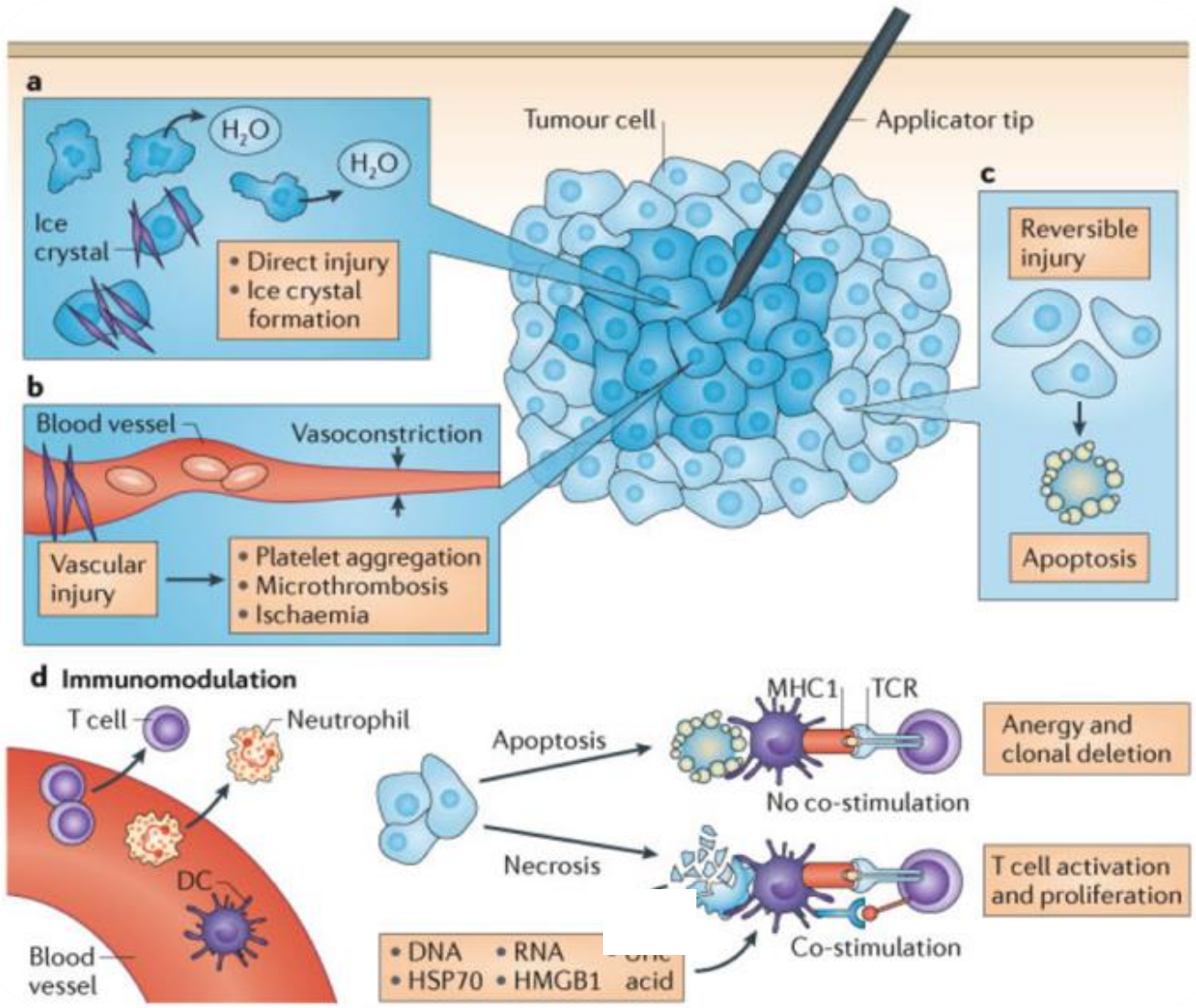
PRISM-MEL301: First-line advanced CM Phase 3

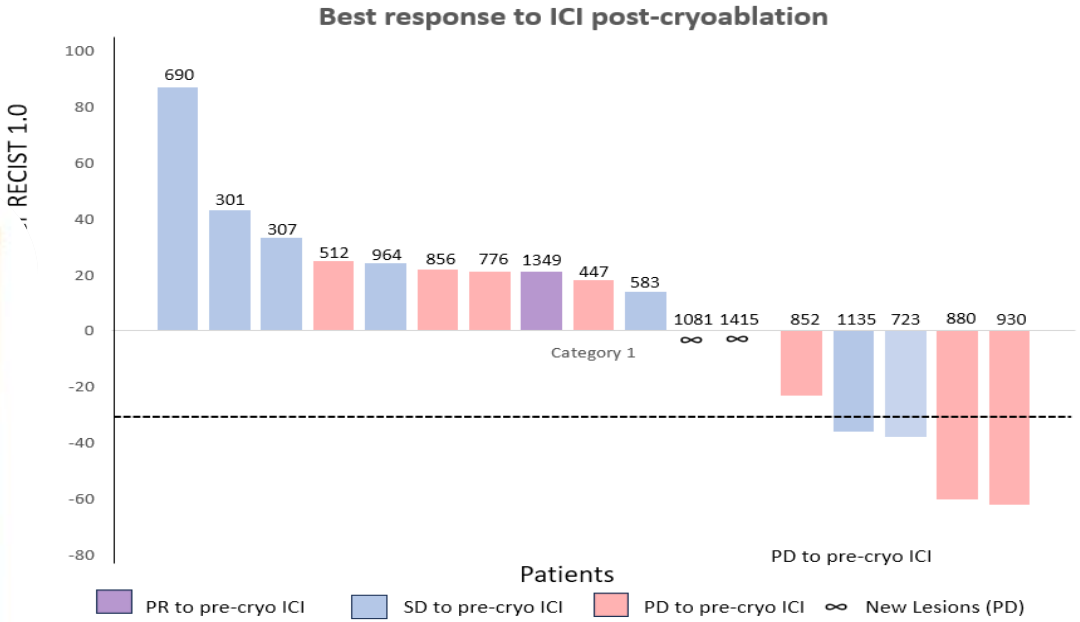
PRISM-MEL301: First-line advanced CM Phase 3

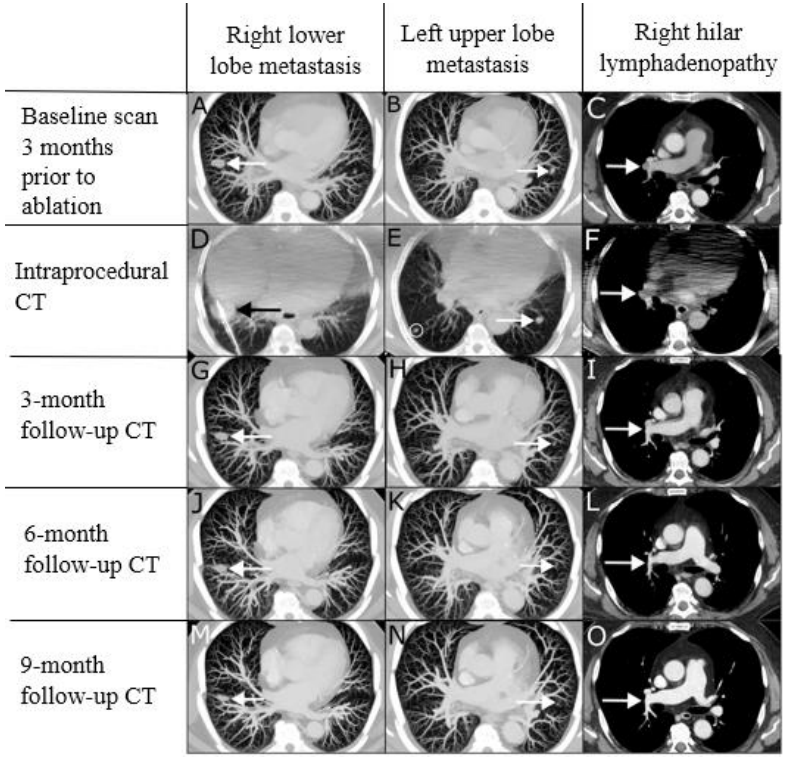


Initial randomization includes comparison of two brenetafusp regimens (~90 patients or 30/arm)

Cryoablation







Nature Reviews Cancer **14,** 2014. Mooradian et al. Nature Commun 2024.

Conclusions: Advances in Melanoma

- 1L SOC for metastatic melanoma centers on dual ICI
  - Single agent anti-PD1 still has a role in certain populations
  - Trials continue to explore optimal combinations to optimize efficacy & safety
- Peri-operative immunotherapy improves outcomes in high-risk melanoma
  - Adjuvant PD-1 inhibition approved in high-risk Stage IIB-IV melanoma; potential role for PCV
  - Neoadjuvant ICI with improved EFS compared to adjuvant therapy alone
  - Pathologic response correlates with RFS; further work needed to personalize adjuvant approaches
- 2L strategies in 2025
  - TIL: Encouraging efficacy signal in refractory disease; high rates of toxicity due to conditioning regimen required; eligibility limited to a select group of patients
  - Additional agents / strategies under investigation in clinical trials

Thank you!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