Neoadjuvant Immune Therapy in Melanoma

Updates from ASCO 2024

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Disclosures

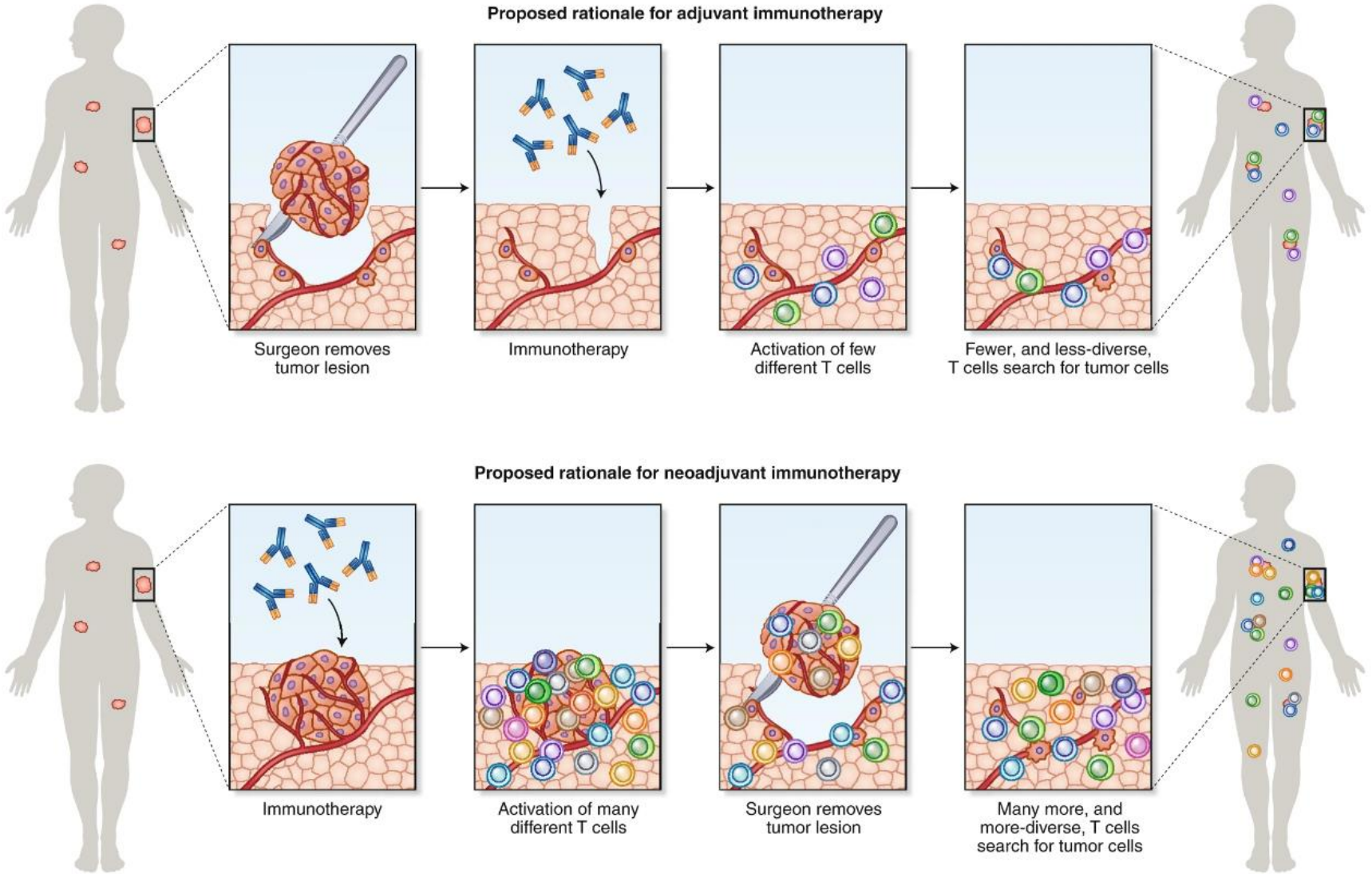
- Immunocore: Member, steering committee

Why consider a Neoadjuvant Approach?

- Resection of tumor bulk removes the **immunologic targets** as well as the **tumor-infiltrating lymphocytes** in the surgical specimen that would proliferate after treatment with immune therapy (Anti-PD1 therapy)

- Larger expansion of tumor-resident T cell clones occurs with Neoadjuvant immune therapy in melanoma, as compared to adjuvant immune therapy.

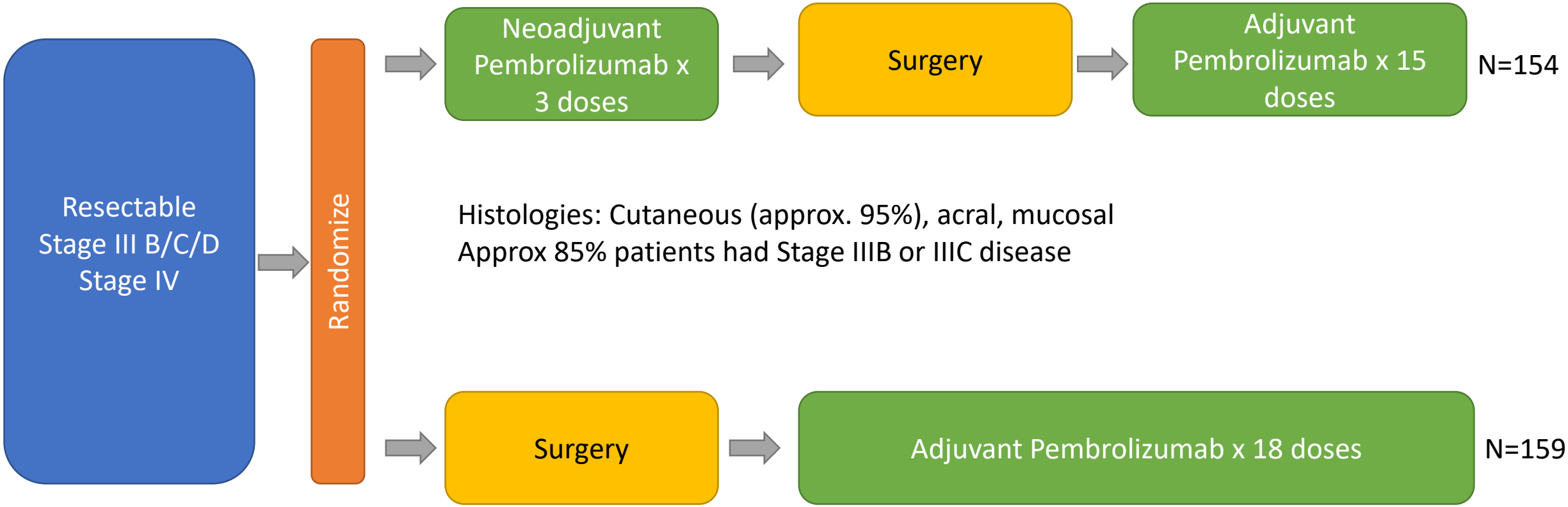
Blank et al. Nature Medicine 2018



In adjuvant approaches, shown above, immunotherapy (as indicated by the antibodies) is given after surgery, which results in the activation of T cells directed to different antigens, as indicated by the different colors. In neoadjuvant approaches, therapy is given before surgery, which results in the raising of a more diverse T cell response.

Versluis et al. Nature Medicine 2020

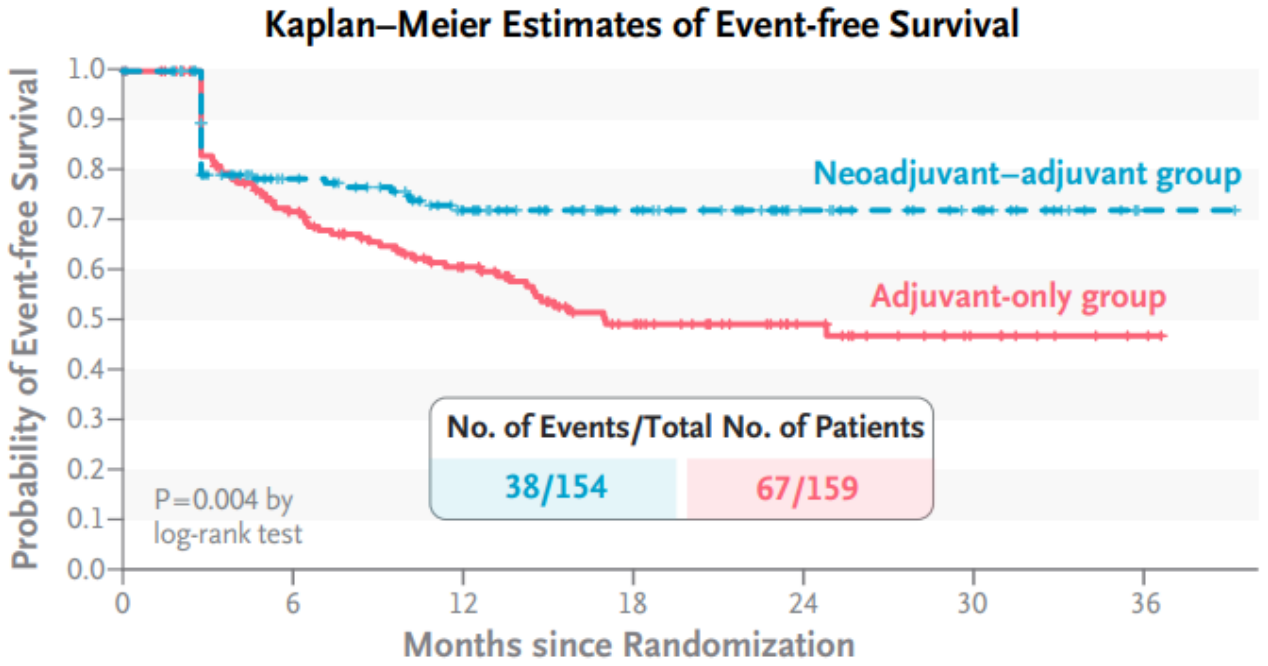
Neoadjuvant Pembrolizumab in Stage III Melanoma S1801 Phase II Trial



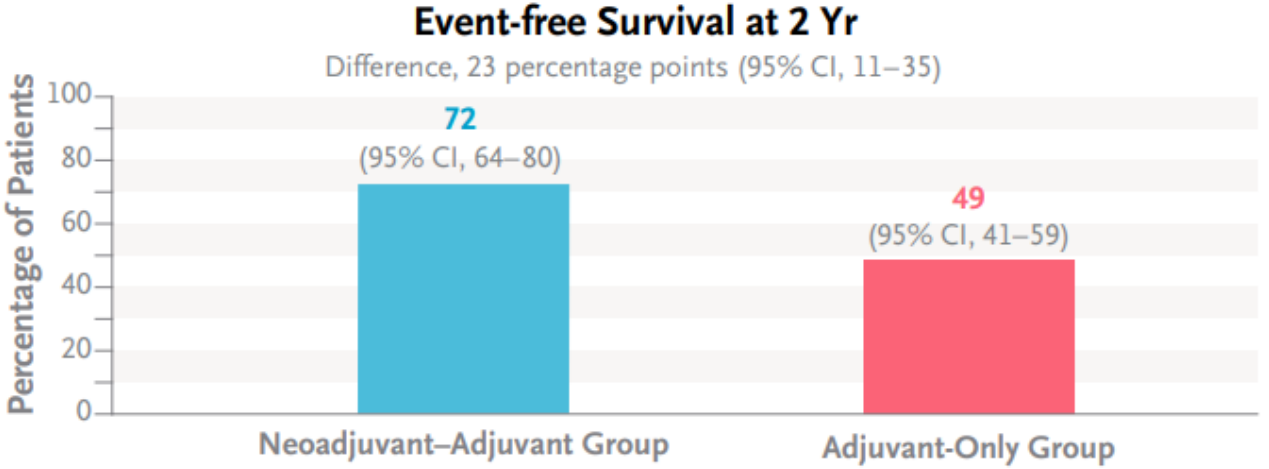
Results

- Events defined as:
  - Disease progression
  - Toxic effects that precluded surgery
  - Inability to resect all gross disease
  - Surgical complications

  -Toxicity that precluded initiation of adjuvant therapy
  - Post-op melanoma recurrence
  - Death from any cause



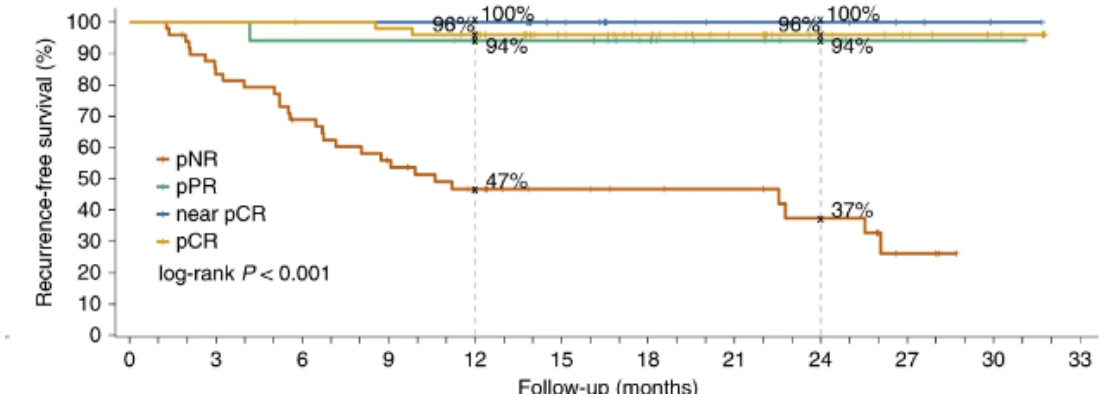
Other Notable findings
Disease Recurrence: 9 patients in the Neoadjuvant group and 41 in the adjuvant group had disease recurrence
21% of patients in the Neoadjuvant group had a pathologic complete response



Patel et al. NEJM March 2023

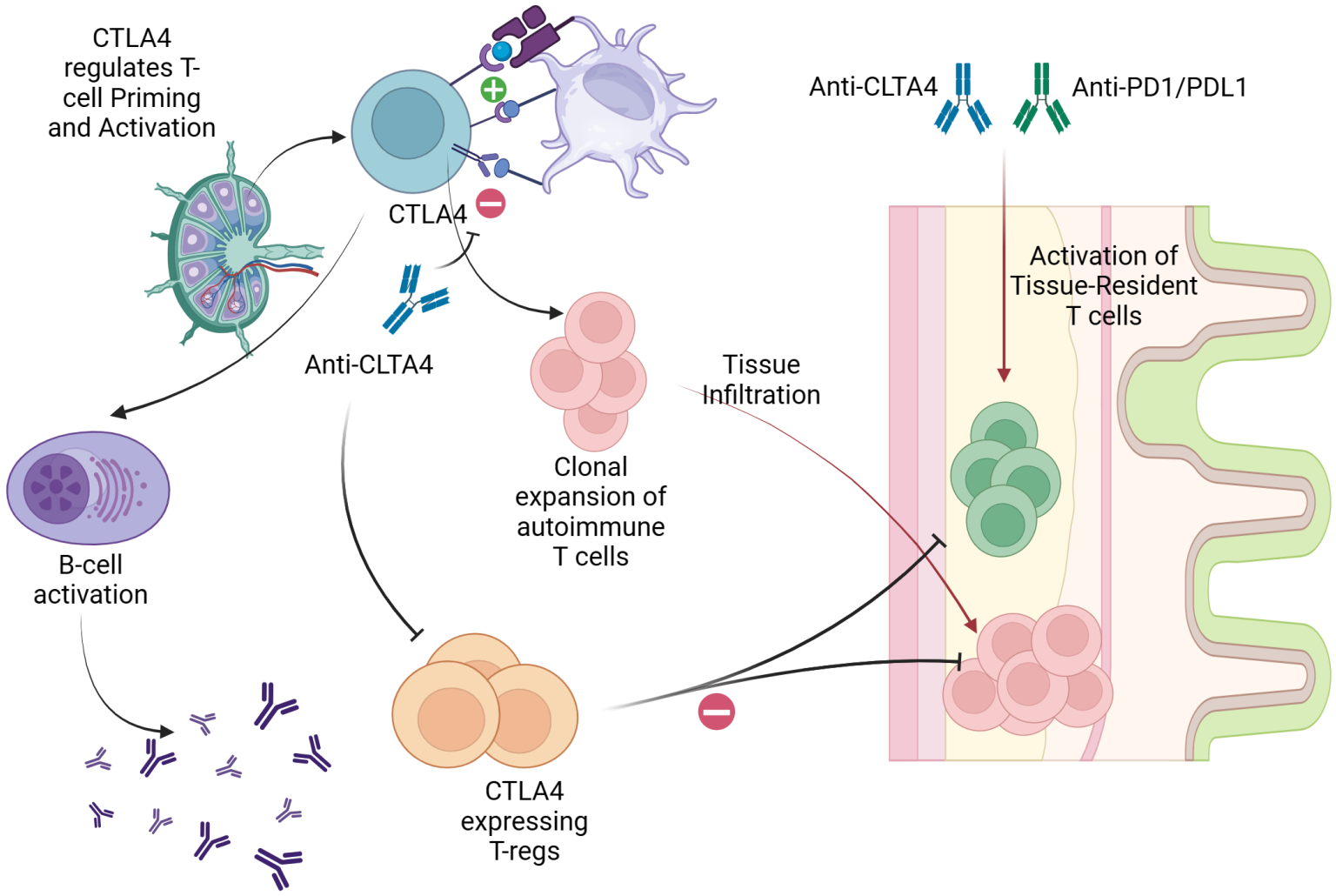
A note on Pathologic Complete Response with Neoadjuvant immune therapy In Melanoma

- Pooled data from six Melanoma clinical trials of anti-PD-1-based immunotherapy or BRAF/MEK targeted therapy.
- 141 patients received immunotherapy (104, combination of ipilimumab and nivolumab; 37, anti-PD-1 monotherapy)
- Pathological complete response (pCR) occurred in 33% with immunotherapy (43% combination and 20% monotherapy).
- pCR correlated with improved RFS and OS.
- In patients with pCR, near pCR or partial pathological response with immunotherapy, very few relapses were seen (2-year RFS 96%)



Menzies et al. Nature Medicine 2021

Why is Dual Check-point blockade more potent



Key points:

- Immune activation can occur more ‘proximal’ in the immune pathway (CTLA4).
- Immune activation can be driven at the tissue level (CTLA4, PD1/PDL1).
- Different types of ICI act on different check-points along the pathway

Adapted from: Sullivan et al. Immune- related toxicities of checkpoint inhibitors: mechanisms and mitigation strategies

The NEW ENGLAND JOURNAL of MEDICINE

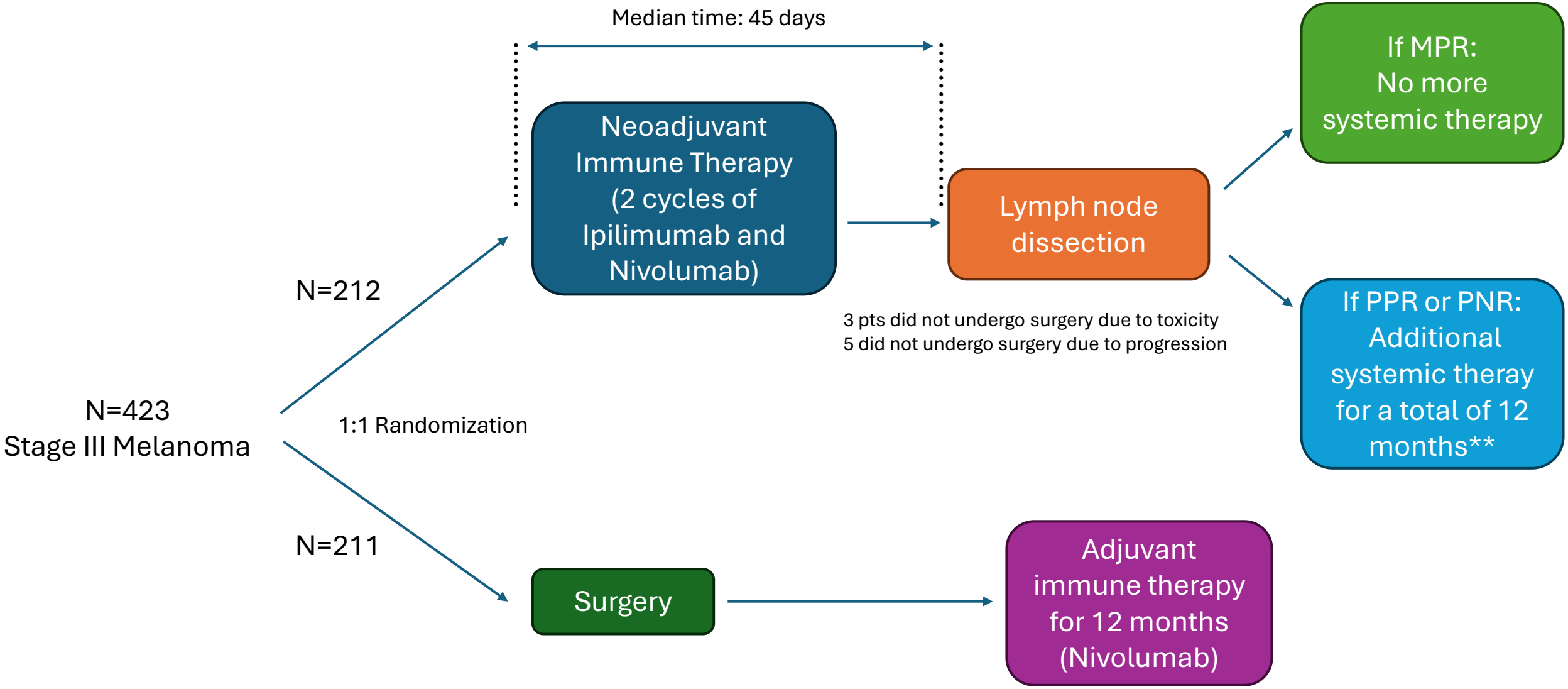
ORIGINAL ARTICLE

Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

Blank et al. June 2 2024

Inclusion Parameters

- Macroscopic, resectable, stage III [AJCC 8th ed] (Cutaneous or acral)
- At least one pathologically proven LN metastasis and up to 3 in-transit metastasis
- Macroscopic disease: Pathologically proven lymph-node metastasis that was palpable, positive according to PET, or measurable on imaging per RECIST 1.1



Neoadjuvant regimen: Ipilimumab: 80 mg, Nivolumab: 240 mg – every 3 weeks
MPR: Major Pathologic Response (≤ 10% of viable tumor cells on pathology)
PPR: Partial Pathologic Response (10-50% of viable tumor cells on pathology)
PNR: Pathologic Non-Response (>50% of viable tumor cells)
** Nivolumab or BRAF-MEK inhibitor therapy

Relevant Baseline Characteristics

Tumor stage — no. (%)§	Neoadjuvant Group	Adjuvant Group
T1	25 (11.8)	36 (17.1)
T2	41 (19.3)	39 (18.5)
T3	41 (19.3)	49 (23.2)
T4	52 (24.5)	46 (21.8)
Tx	7 (3.3)	6 (2.8)
Melanoma of unknown primary origin	46 (21.7)	35 (16.6)
Ulceration — no. (%)		
Yes	71 (33.5)	57 (27.0)
No	85 (40.1)	102 (48.3)
Melanoma of unknown primary origin	46 (21.7)	35 (16.6)
Unknown	10 (4.7)	17 (8.1)
In-transit metastases — no. (%)		
Yes	22 (10.4)	25 (11.8)
No	190 (89.6)	186 (88.2)
Location or locations of affected lymph nodes — no./total no. (%)‖		
Neck	55/211 (26.1)	57/211 (27.0)
Axilla	86/211 (40.8)	86/211 (40.8)
Groin	66/211 (31.3)	66/211 (31.3)
No. of lymph nodes positive for disease on PET — no./total no. (%)**		
1	126/200 (63.0)	122/205 (59.5)
2 or 3	52/200 (26.0)	64/205 (31.2)
>3	17/200 (8.5)	12/205 (5.9)
0	5/200 (2.5)	7/205 (3.4)
BRAF mutation status — no. (%)		
V600E	95 (44.8)	87 (41.2)
V600K	17 (8.0)	25 (11.8)

Blank et al. NEJM; 2024

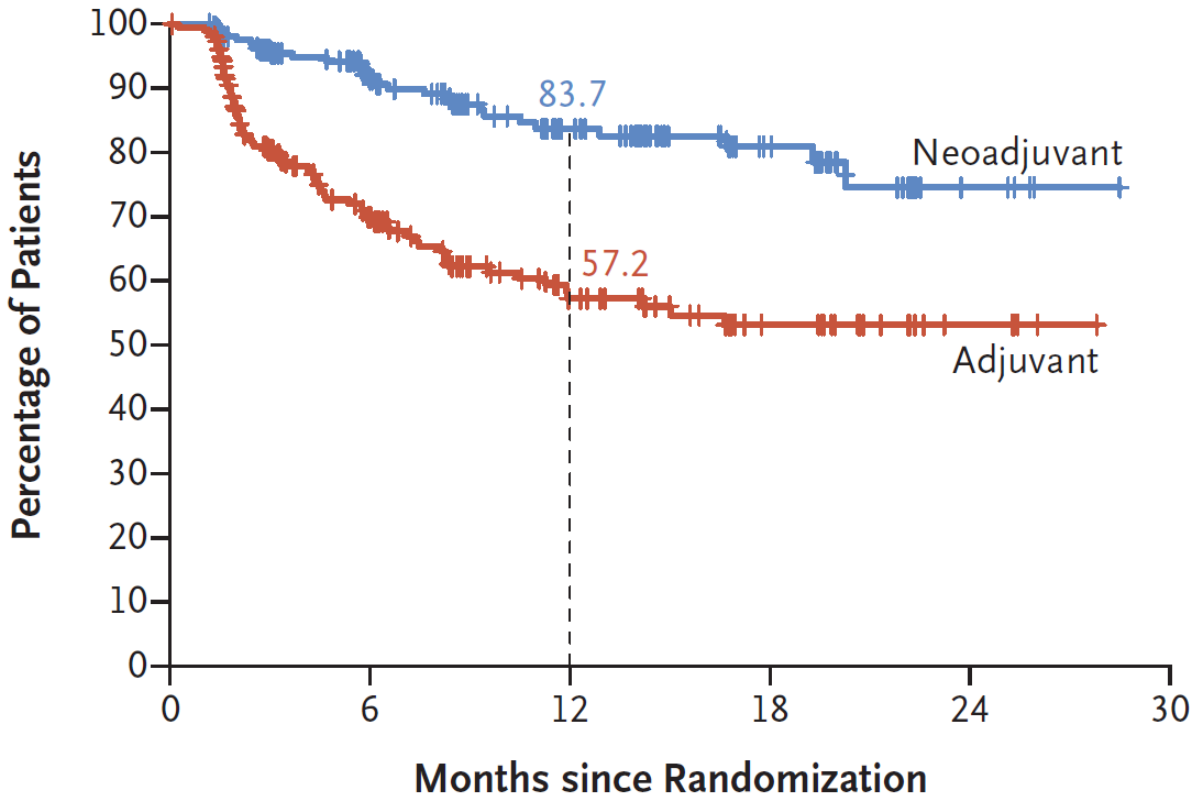
Median duration of follow-up was 10.6 months in the neoadjuvant group and 9.9 months in the adjuvant group.

Events: Progression, recurrence, or death from melanoma or treatment.

Events:

- 28 (neoadjuvant group)
- 72 (adjuvant group)

The estimated 12- month event-free survival was **83.7%** (99.9% confidence interval [CI], 73.8 to 94.8) and **57.2%** (99.9% CI, 45.1 to 72.7)



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 et al. NEJM; 2024

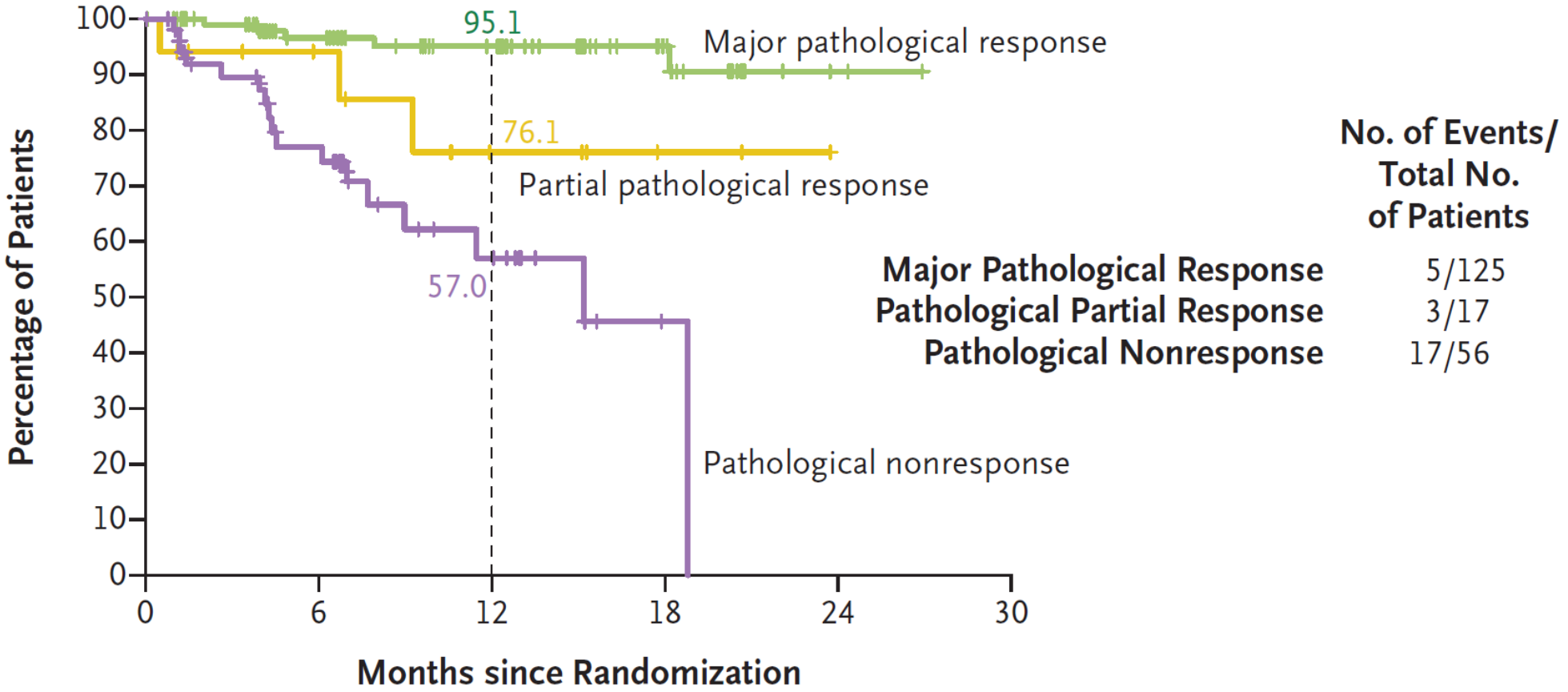
Pathological Responses in the Neoadjuvant Group.

Type of Response	Local Assessment (N = 212)	Central Review (N = 212)
	number (percent)	
Major pathological response	120 (56.6)	125 (59.0)
Pathological complete response†	97 (45.8)	100 (47.2)
Pathological near-complete response	23 (10.8)	25 (11.8)
Pathological partial response	20 (9.4)	17 (8.0)
Pathological nonresponse	53 (25.0)	56 (26.4)
Progression before surgery	5 (2.4)	5 (2.4)
Not reported	5 (2.4)	0
Not available‡	9 (4.2)	9 (4.2)

0% Viable Tumor

Blank et al. NEJM; 2024

Recurrence-free Survival According to Pathological Response



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)	

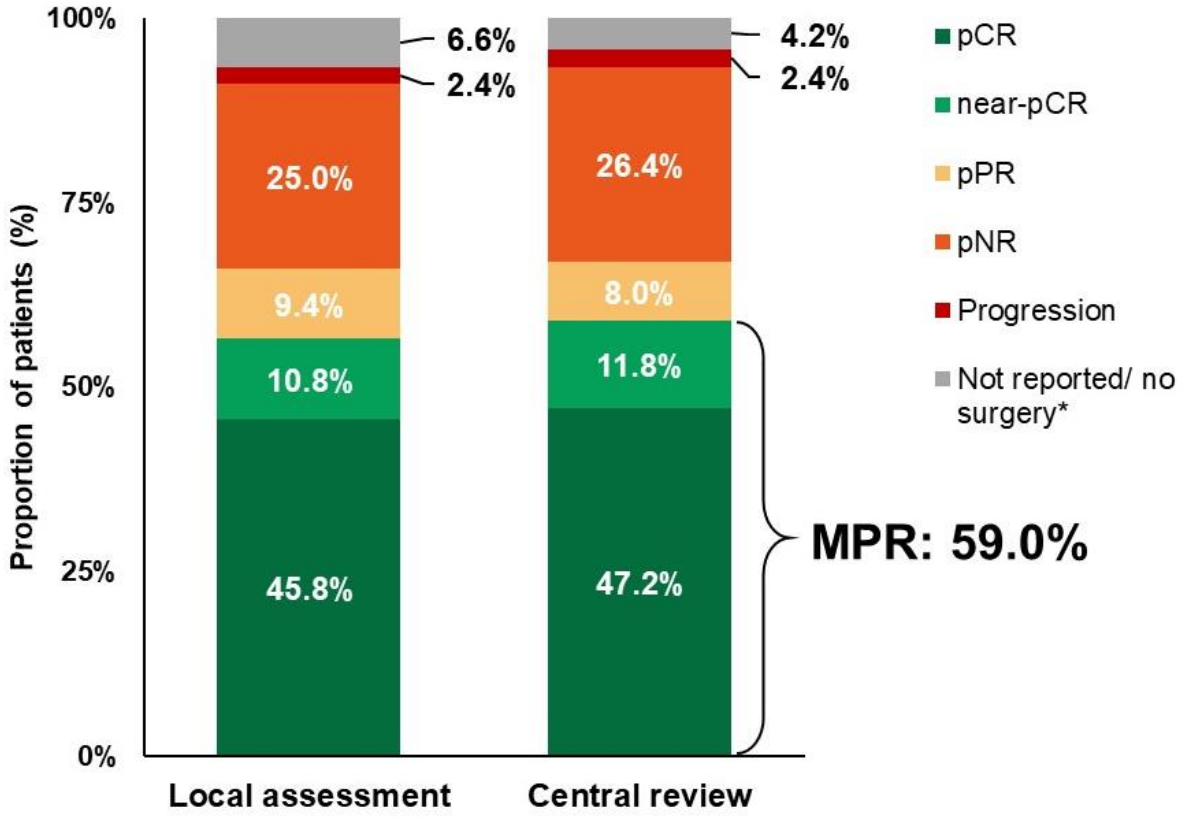
The estimated RFS at 12 mo was 95.1% (99.9% CI, 87.4 to 99.9) among patients who had a major pathological response, 76.1% (99.9% CI, 44.4 to 99.9) among those who had a pathological partial response, and 57.0% (99.9% CI, 33.3 to 97.6) among those who had a pathological nonresponse.
Among the patients who had a pathological complete response, the estimated RFS was 95.4% (99.9% CI, 87.0 to 99.9); among those who had a pathological near-complete response, the estimated RFS was 94.1% (99.9% CI, 77.1 to 99.9).

Blank et al. NEJM; 2024

Radiographic Response **Underestimates** Pathologic Response

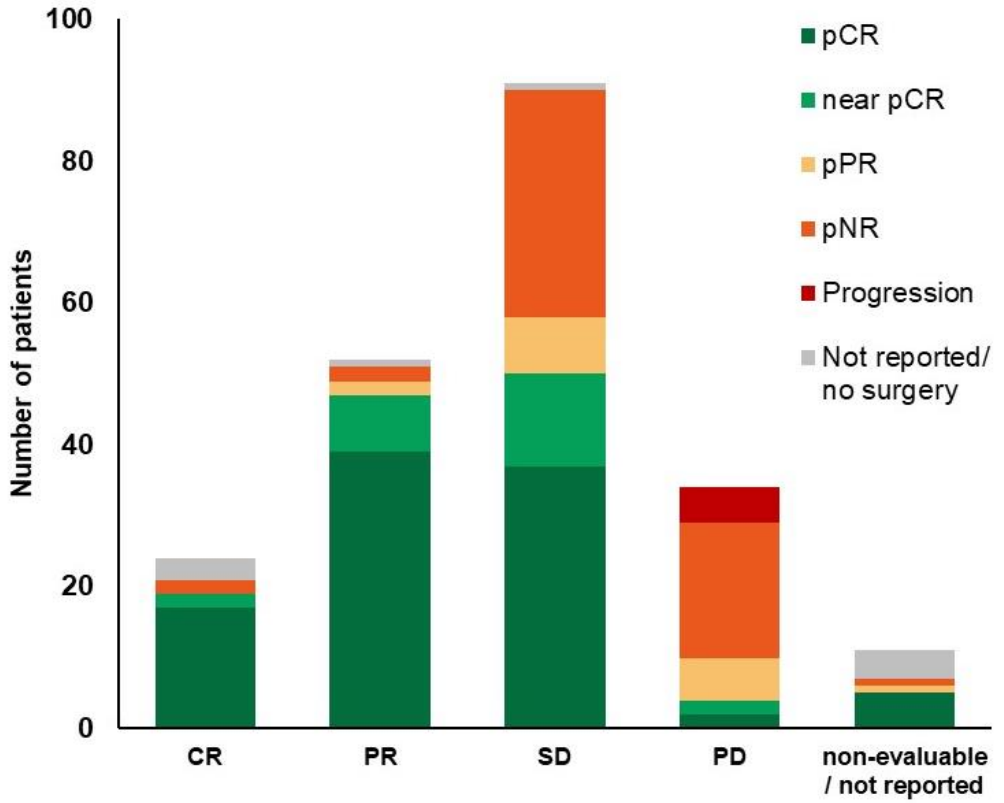
NADINA – Pathologic and Radiologic Response

Pathologic 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.

Radiologic- versus Pathologic Response



Presented by Christian Blank at ASCO 2024

Impact of Neo-adjuvant immune therapy on Overall Survival?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

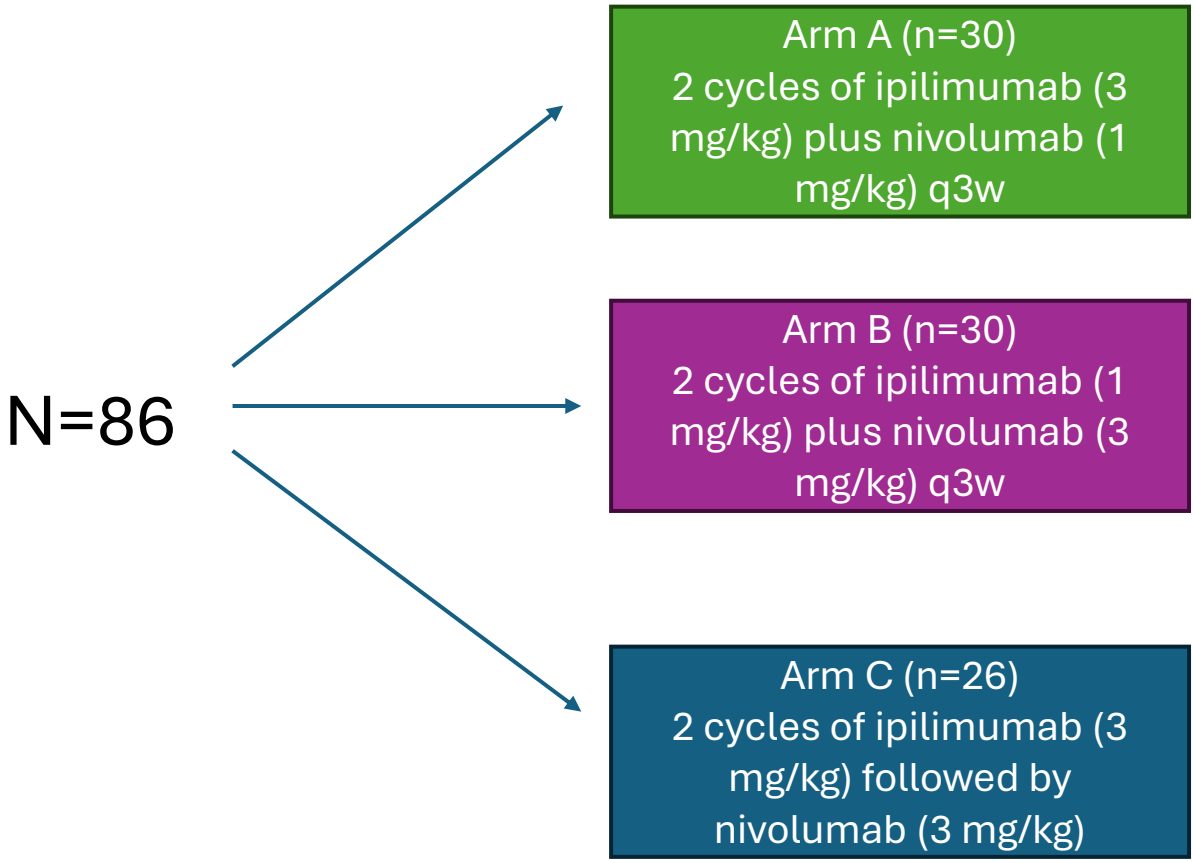
ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Survival update of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma in the OpACIN and OpACIN-neo trials☆

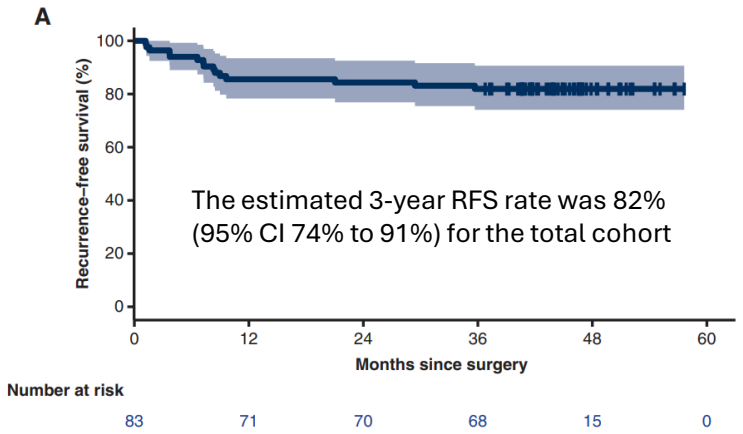
J.M. Versluis et al. 2023

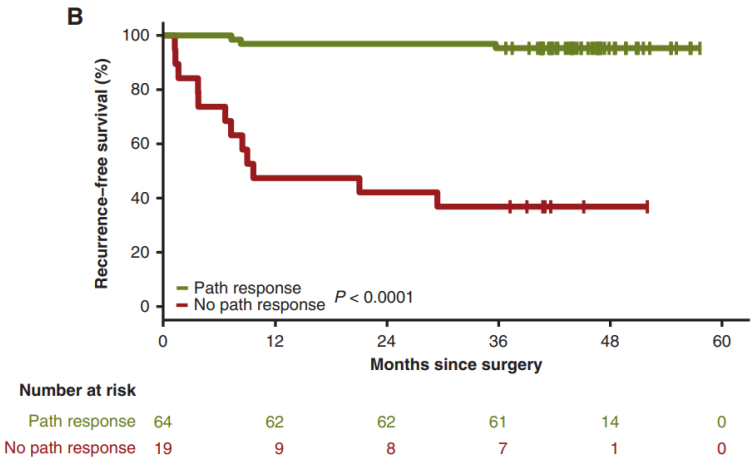
OpACIN-Neo Trial (Phase 2)

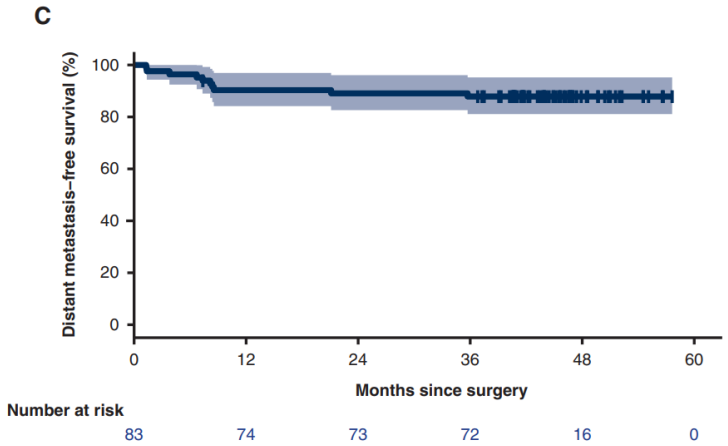


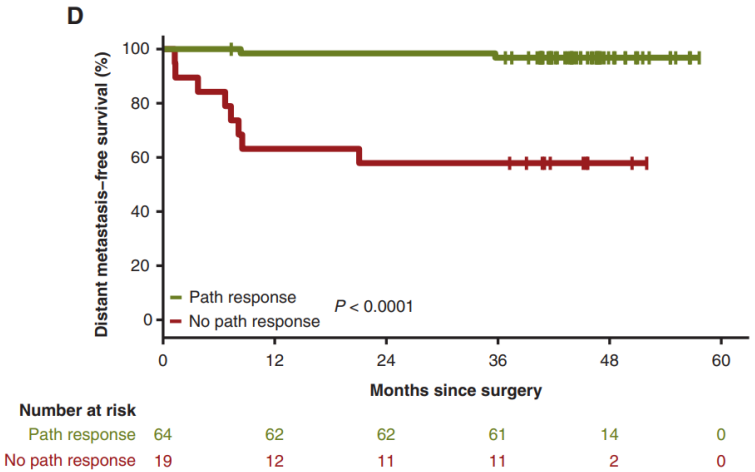
Therapeutic lymph node dissection was planned at week 6 and no adjuvant therapy was administered

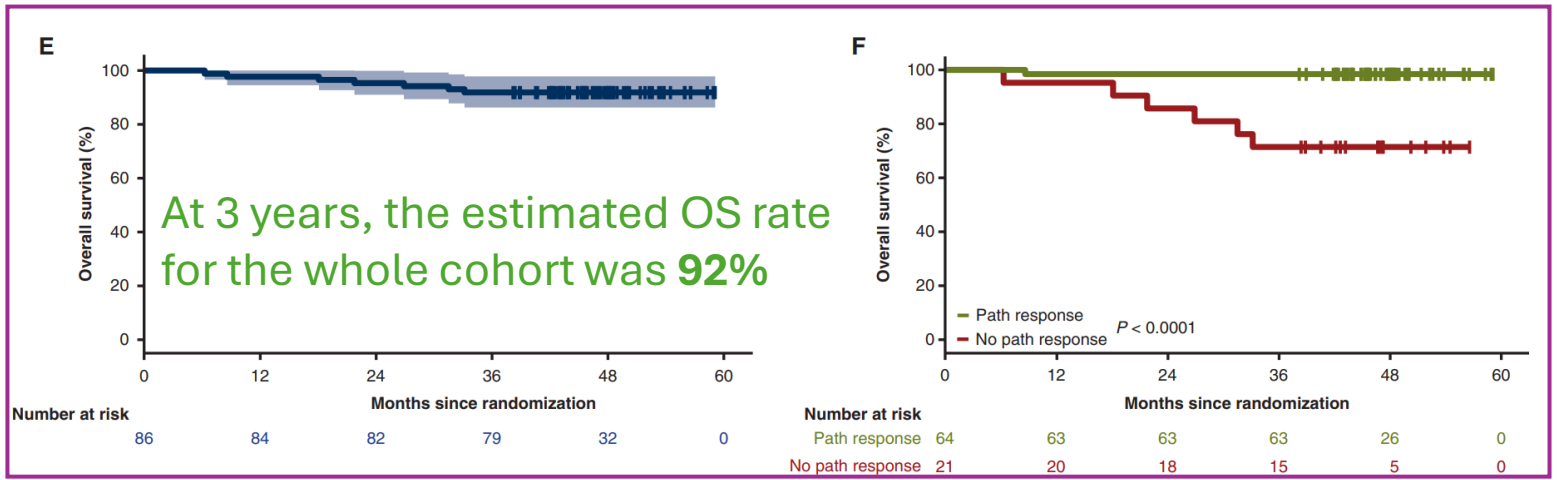
OpACIN-Neo Results











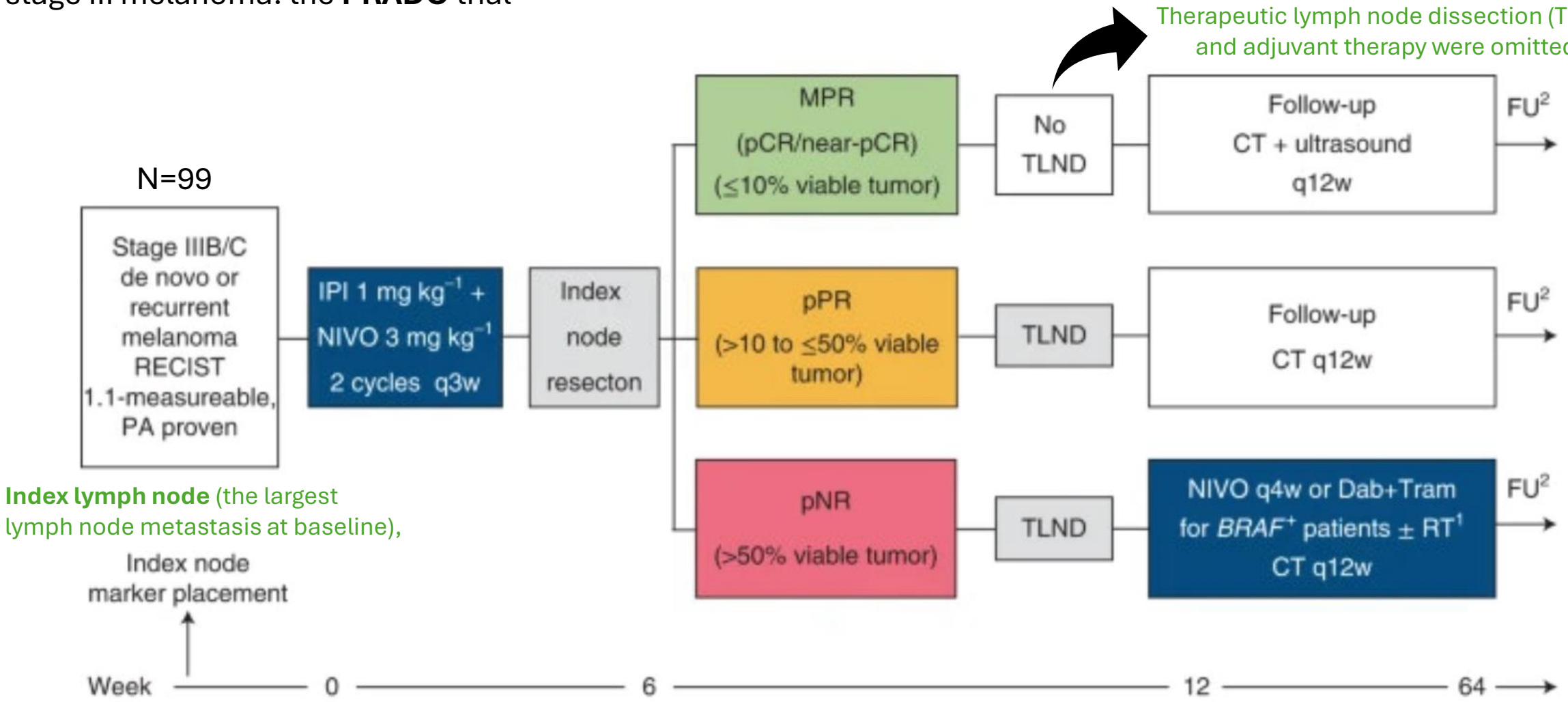
Median follow-up: 47 months

	Pathologic Response	No Path. Response
Est. 3 yr RFS	95%	37%
Est. 3 yr OS	98%	71%

J.M. Versluis et al. 2023

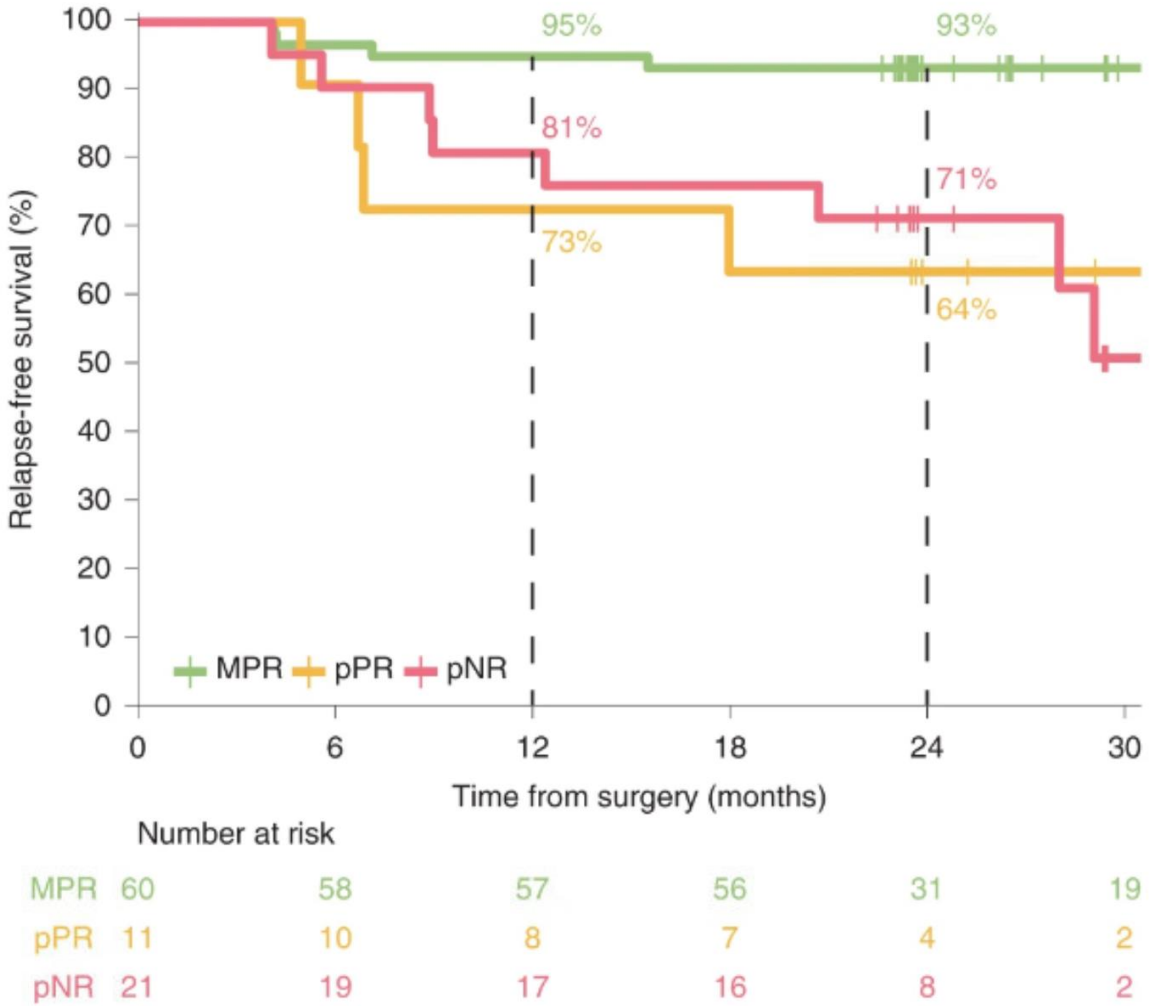
Do we need surgery?

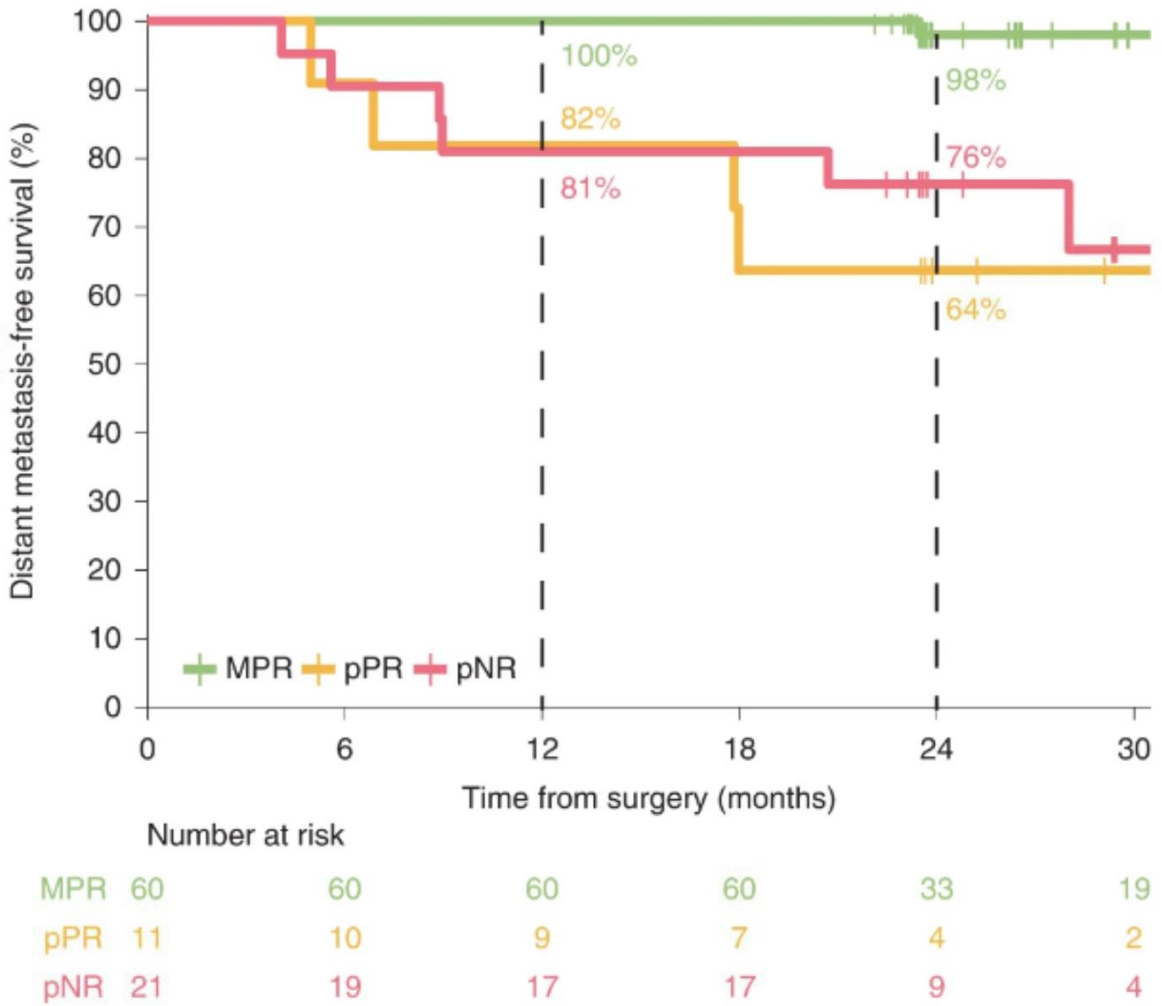
Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the **PRADO** trial



Nature Medicine 2022; Reijers et al.

PRADO Trial Results





Nature Medicine 2022; Reijers et al.

Putting OpACIN-Neo and PRADO Together

Three-year data of PRADO and OpACIN-neo.

Therapeutic lymph node dissection (TLND) and adjuvant therapy were omitted.

Therapeutic lymph node dissection (TLND) **done**, and adjuvant therapy omitted.

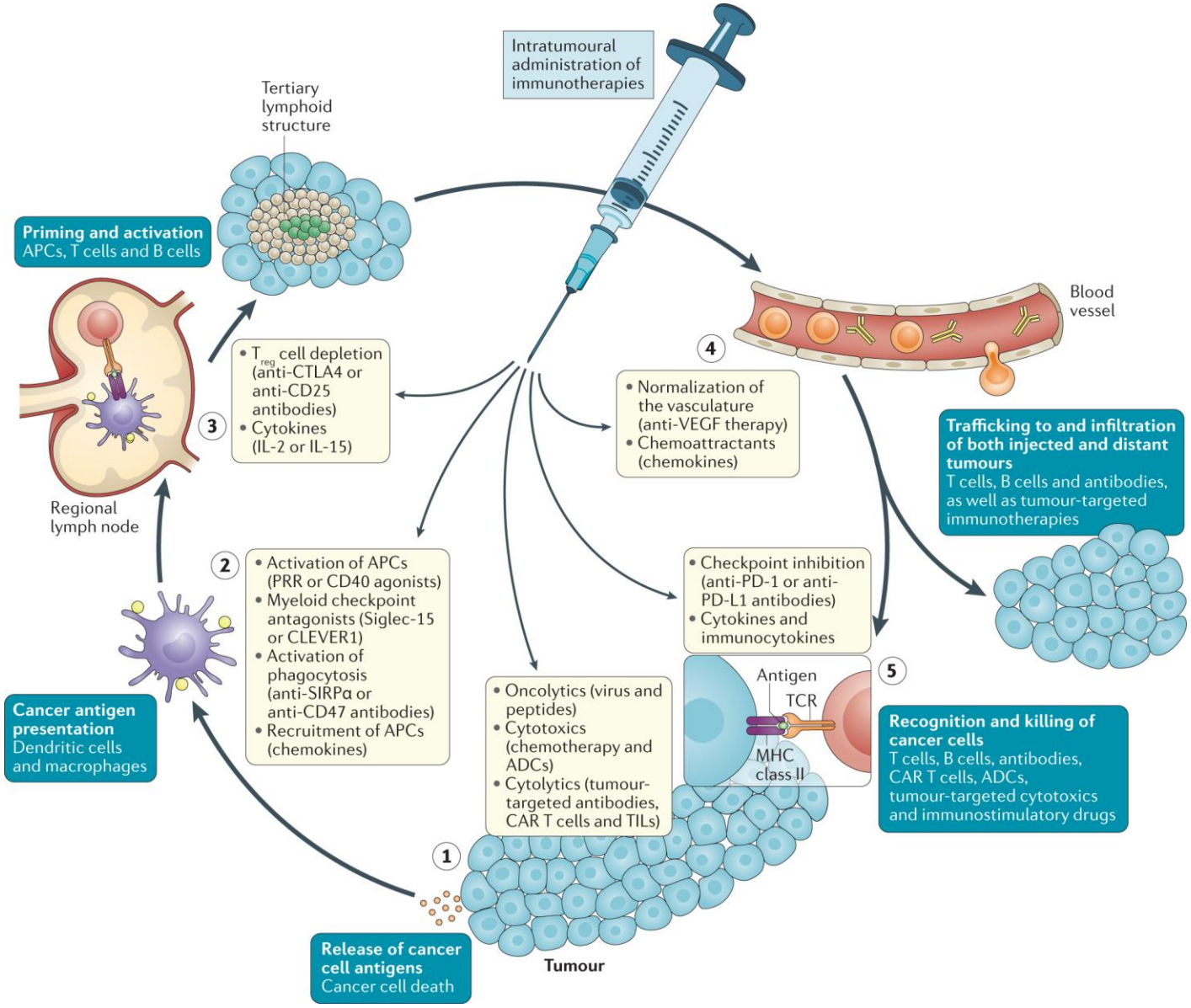
3y rates	Personalized	Non-personalized	p-value
MPR pts (n=112)	**No TLND (n=59)**	**TLND (n=53)**	
RFS	93%	96%	0.47
DMFS	98%	98%	0.92

Reijers et al. ASCO 2023

Intra-Tumoral (Oncolytic Immunotherapy)

- Used extensively in the past (e.g. intra-tumoral BCG)
- More novel agents capable of generating potent intra-tumoral oncolytic activity and abscopal effect at non-injected sites.
- Often combined with IV immune check point inhibitors

Benefits:
Ideal for Neoadjuvant strategy
Direct delivery of a concentrated drug dose into the tumor
Ideal for local symptom control from rapidly progressing tumors
Limited systemic toxicity
Capable of generating potent systemic immune responses (in combination with check-point inhibitors) to treat distant micro-metastatic disease.
Overcoming PD-1 resistance.



Ignacio Melero et al. Nature Reviews Clinical Oncology; 2021

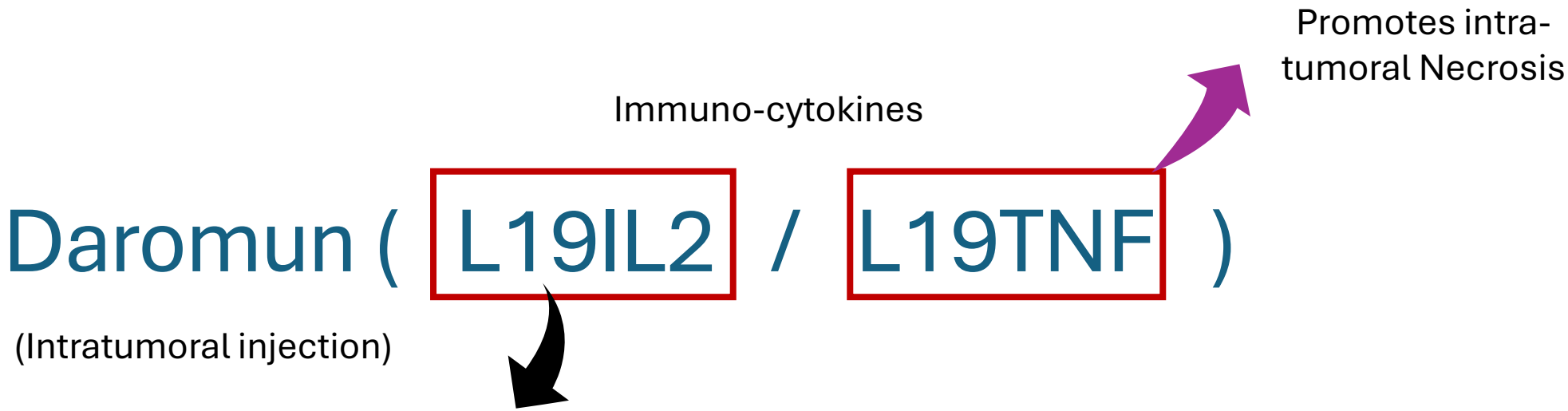
Examples of Novel agents used as Intra-tumoral injections	
Oncolytic Viruses (e.g. T-VEC)	Genetically modified viruses that ‘infect’ tumor cells, causing direct tumor lysis, release of tumor antigens and local expression of cytokines (GM-CSF), and check-point like molecules
Toll-like receptor 9 (TLR9) Agonists	Dendritic cell activation and maturation
Cytokines	Daromun

Neoadjuvant Intra-Tumoral Immune therapy

2024 ASCO® ANNUAL MEETING

#LBA9501 - Phase 3 study (PIVOTAL) of neoadjuvant intralesional Daromun versus immediate surgery in fully resectable melanoma with regional skin and/or nodal metastases

Hauschild et al. ASCO 2024



Overall, the drug enhances local ‘targeted’ delivery of pro-inflammatory cytokines

PIVOTAL - Trial design (1:1 Randomization)

Prior surgery, irradiation or any systemic treatment allowed!

ARM 1

- DAROMUN 1 weekly injection for 4 weeks
- Surgery of all lesions within 4 weeks

ARM 2

- Surgery of all lesions within 4 weeks

Post-Adjuvant therapy at investigator´s discretion

Primary Endpoint

- **RFS (time from randomization to progression or death)**

Secondary endpoints

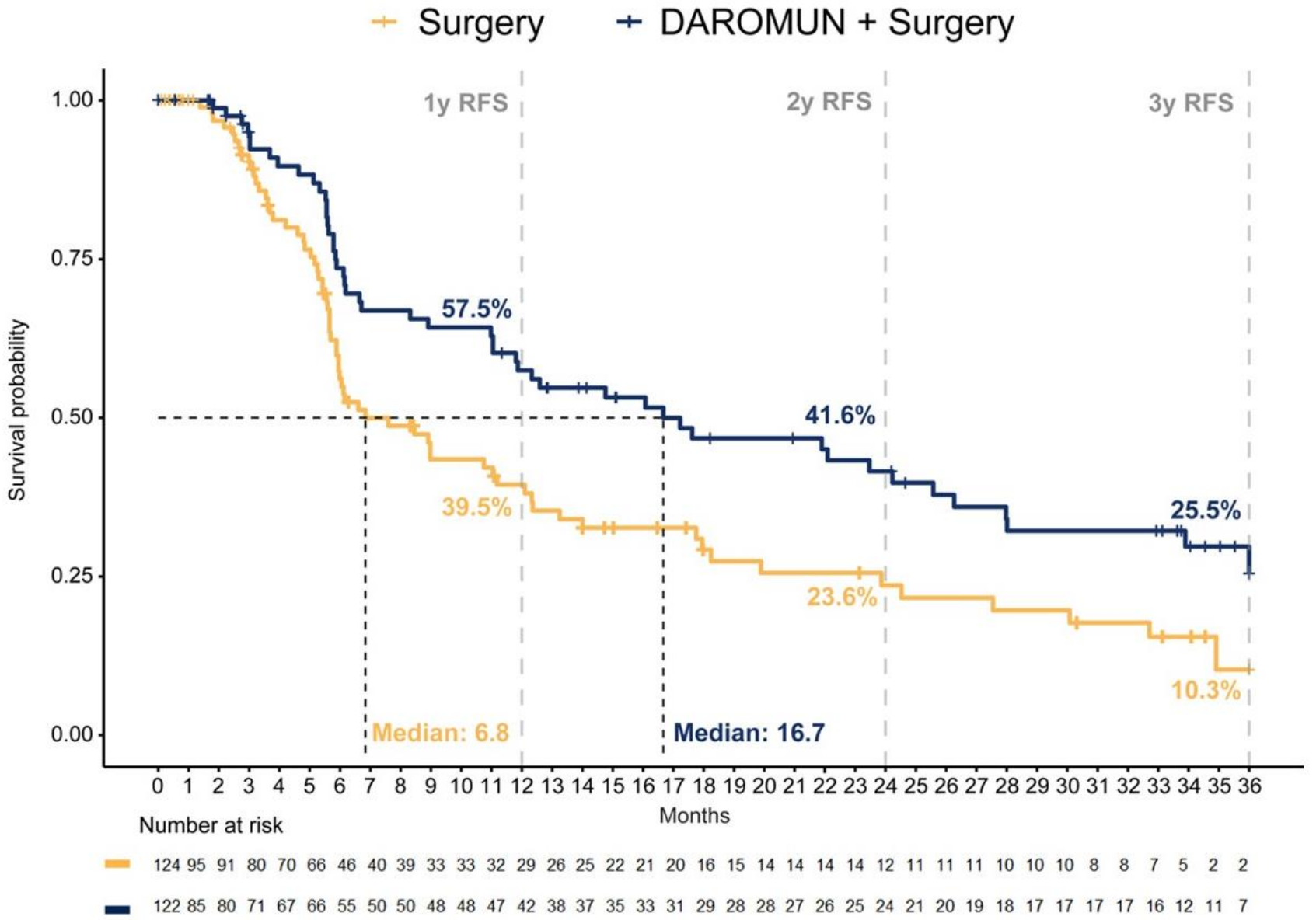
- OS
- DMFS
- LRFS
- Safety (AEs, ADA*)
- Pathological response *(study amendment)*

**Anti-Drug Antibody*

Danielli *et al., Cancer Immunol Immunother*, **2015**, 64, 999;

Hauschild et al. ASCO 2024

RFS - Blinded Independent Central Review



Data cut-off date
May 3rd, 2023

	Events / n
DAROMUN + Surgery	49/122
Surgery	66/124

p-value: 0.005 (log rank)

HR: 0.59 (95% CI: 0.41 - 0.86)

Median FU Time: 21.2 months (for all patients)

Median time to Surgery:
DAROMUN+surgery: 6.6 weeks (95% CI: 6.1 - 7.0)
Surgery: 2.3 weeks (95% CI: 2.0 - 2.9)

Hauschild et al. ASCO 2024

- Treatment with **Daromun** resulted in a **clinically meaningful and statistically significant longer RFS (primary study endpoint)** with a **HR of 0.59** and **DMFS (HR: 060, secondary endpoint)** compared to surgery alone in potentially pre-treated locally advanced melanoma patients.

- **Daromun showed a manageable safety profile with mainly local AEs.**

Overall Conclusions

- Neoadjuvant immune therapy is the new standard of care in locally advanced cutaneous melanoma
- Neoadjuvant approach limits extent of surgery and duration of immune therapy, and potentially limits the extent of immune related adverse events.
- Areas of unmet need: Management of patients who are non-responders to first-line immune therapy.

Thank you