

# **Neoadjuvant and Adjuvant Therapy in Melanoma**

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# Disclosures

- Research Support: Amgen, BMS, Castle Biosciences, Delcath, Merck, Philogen, Regeneron, SkylineDx, Vaccinex
- Advisory Board: Merck

# Objectives

- Describe recent neoadjuvant studies and how to incorporate them into practice for resectable advanced melanoma
- Understand the role of adjuvant therapy in patients with resected high risk melanoma
- Describe ongoing and future neoadjuvant and adjuvant investigations

# Outline

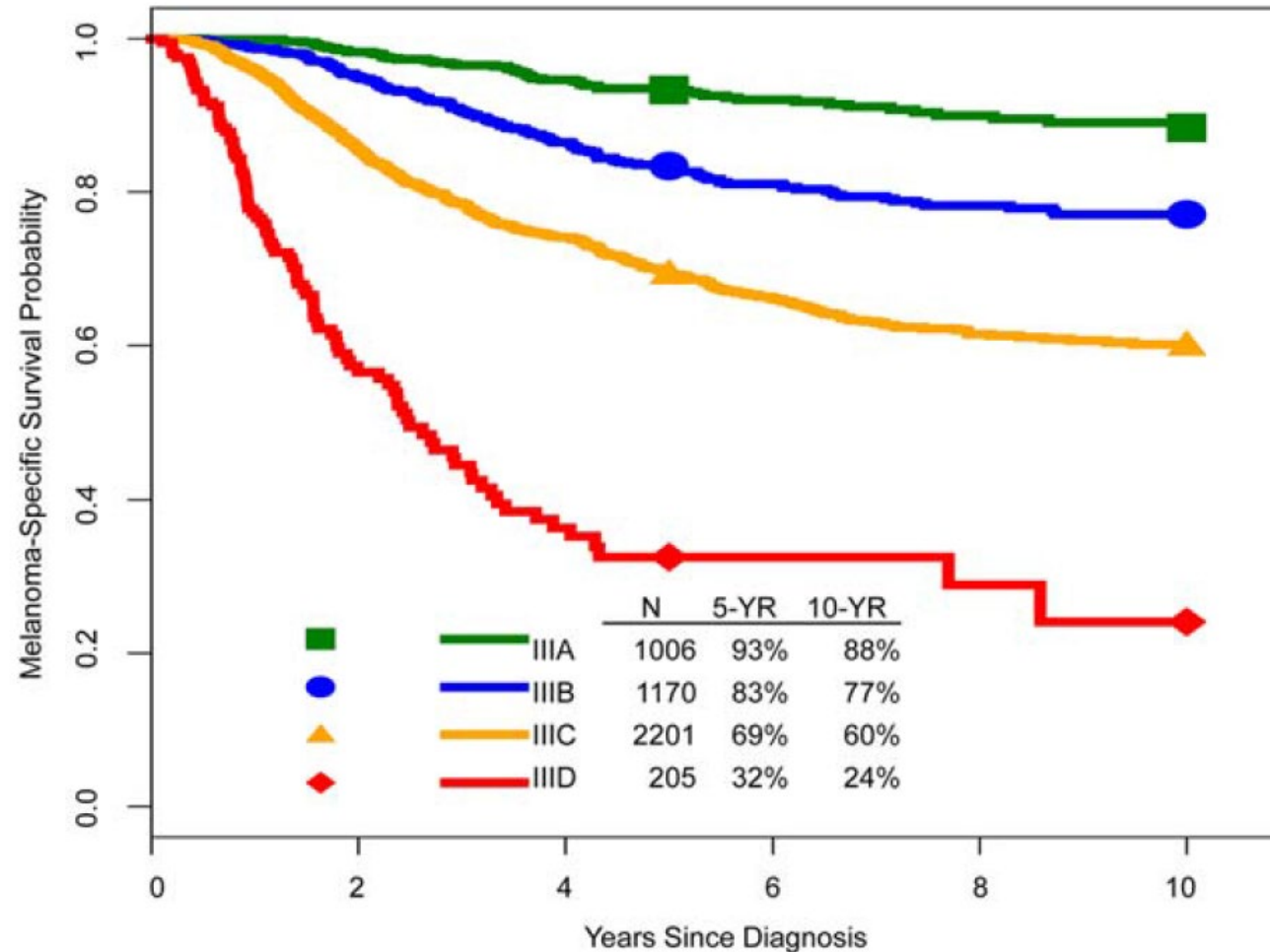
- Current landscape of adjuvant therapy
- Updates in neoadjuvant therapy
- Future directions for neoadjuvant and adjuvant therapy

# Outline

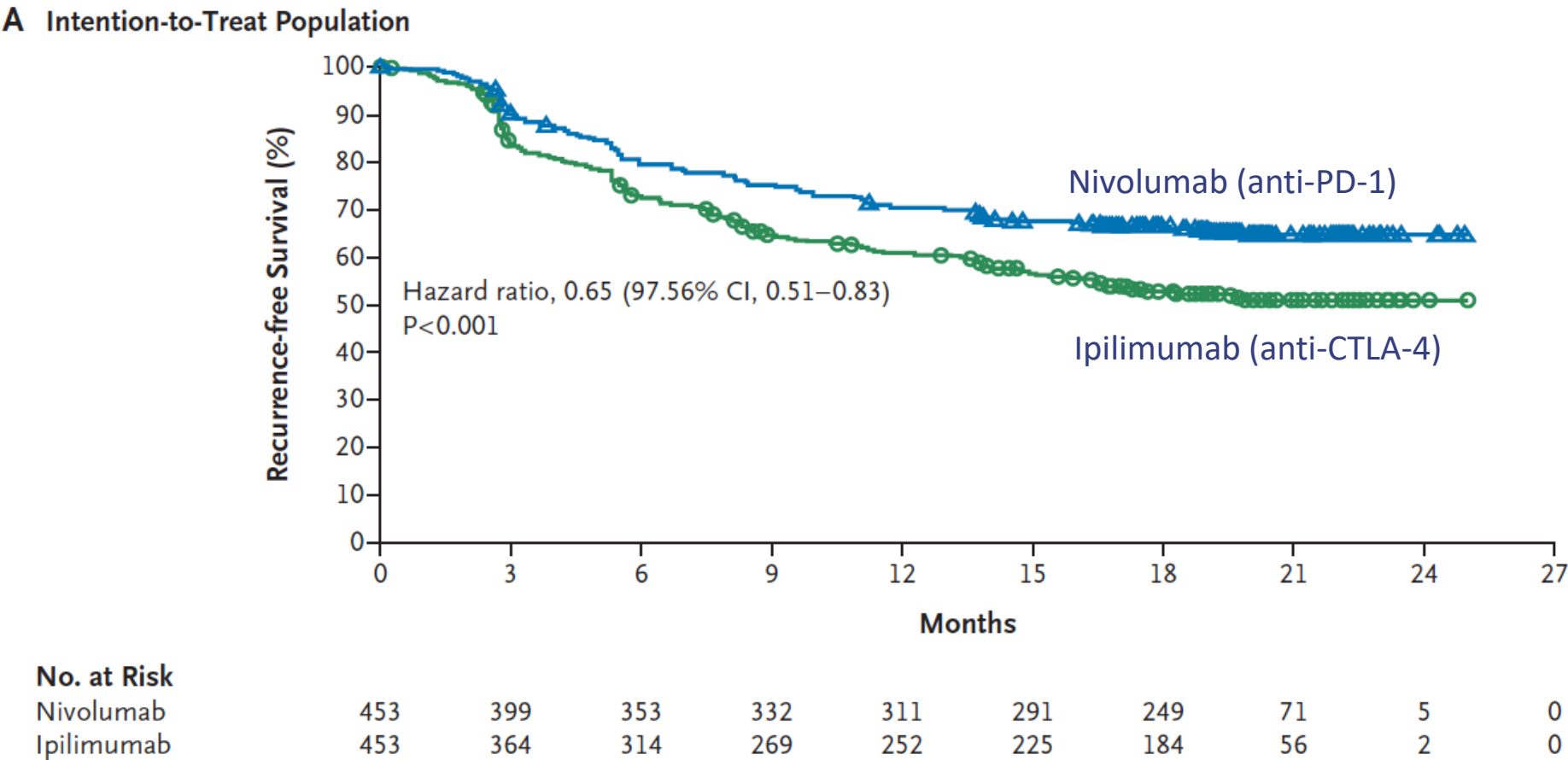
- **Current landscape of adjuvant therapy**
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# Adjuvant Therapy for Resected Stage III Melanoma

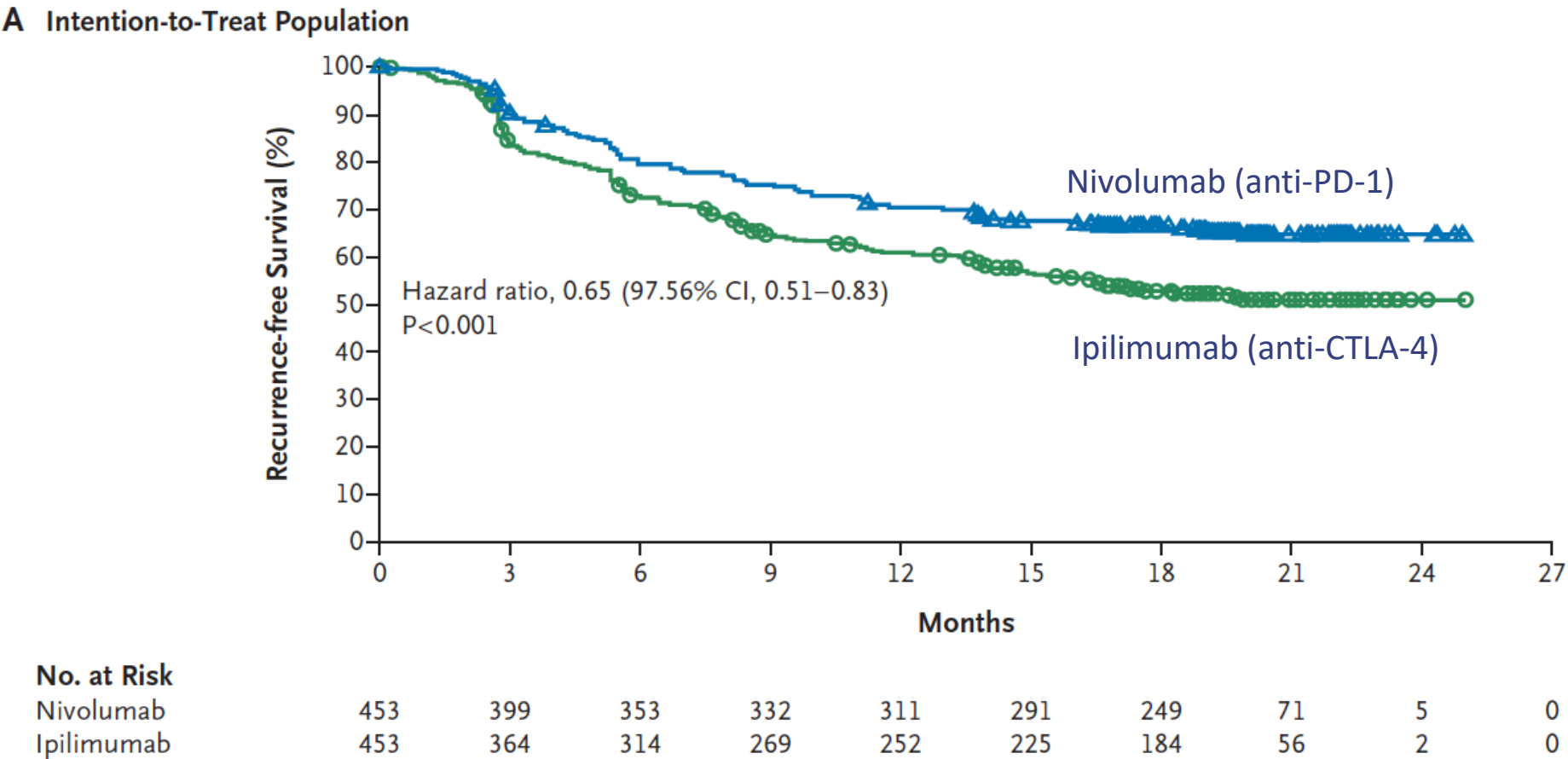
Survival by Substage – Stage III



# Adjuvant Therapy for Resected Stage III Melanoma – CheckMate 238

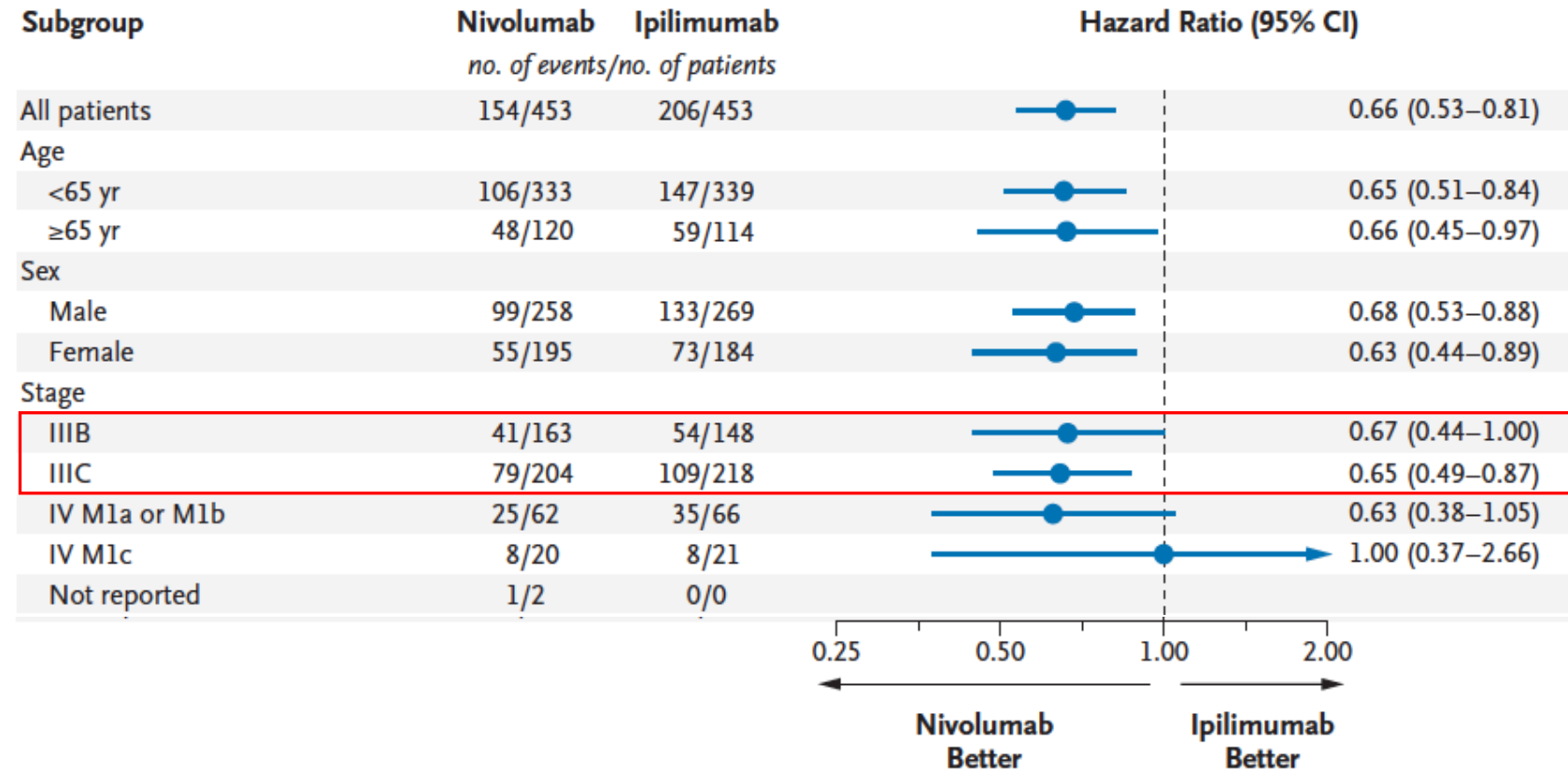


# Adjuvant Therapy for Resected Stage III Melanoma – CheckMate 238



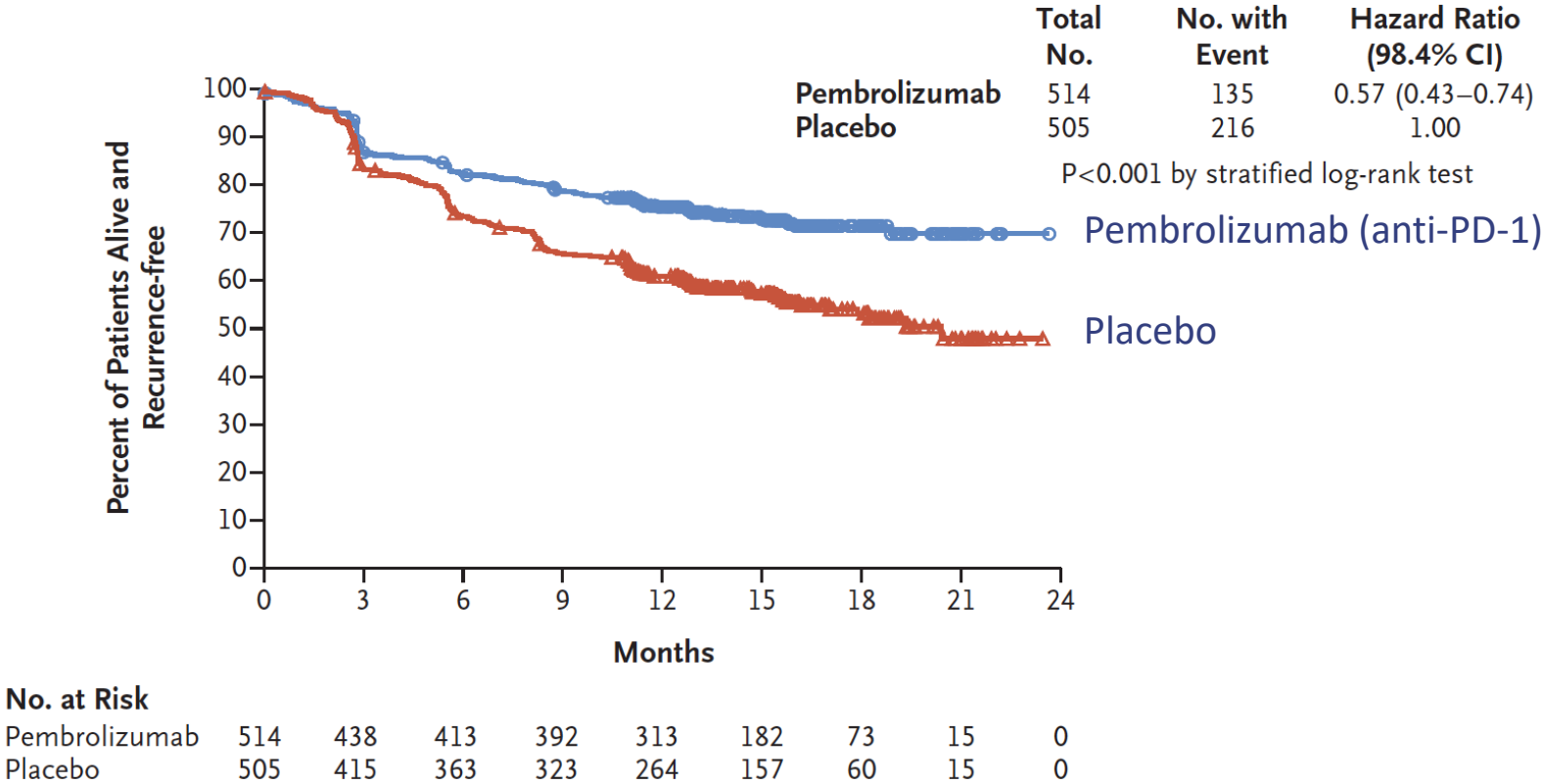


# Adjuvant Therapy for Resected Stage III Melanoma – CheckMate 238

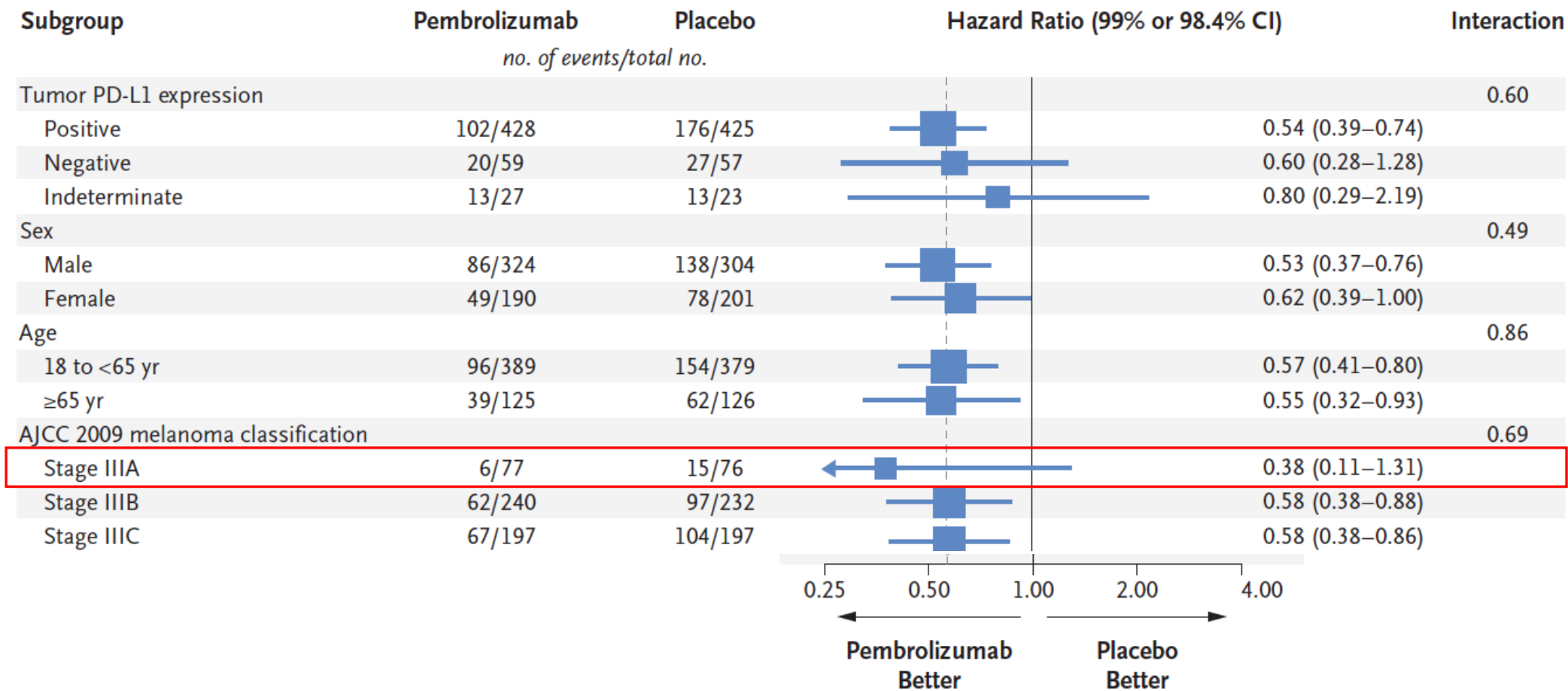


# Adjuvant Therapy for Resected Stage III Melanoma – KEYNOTE-054

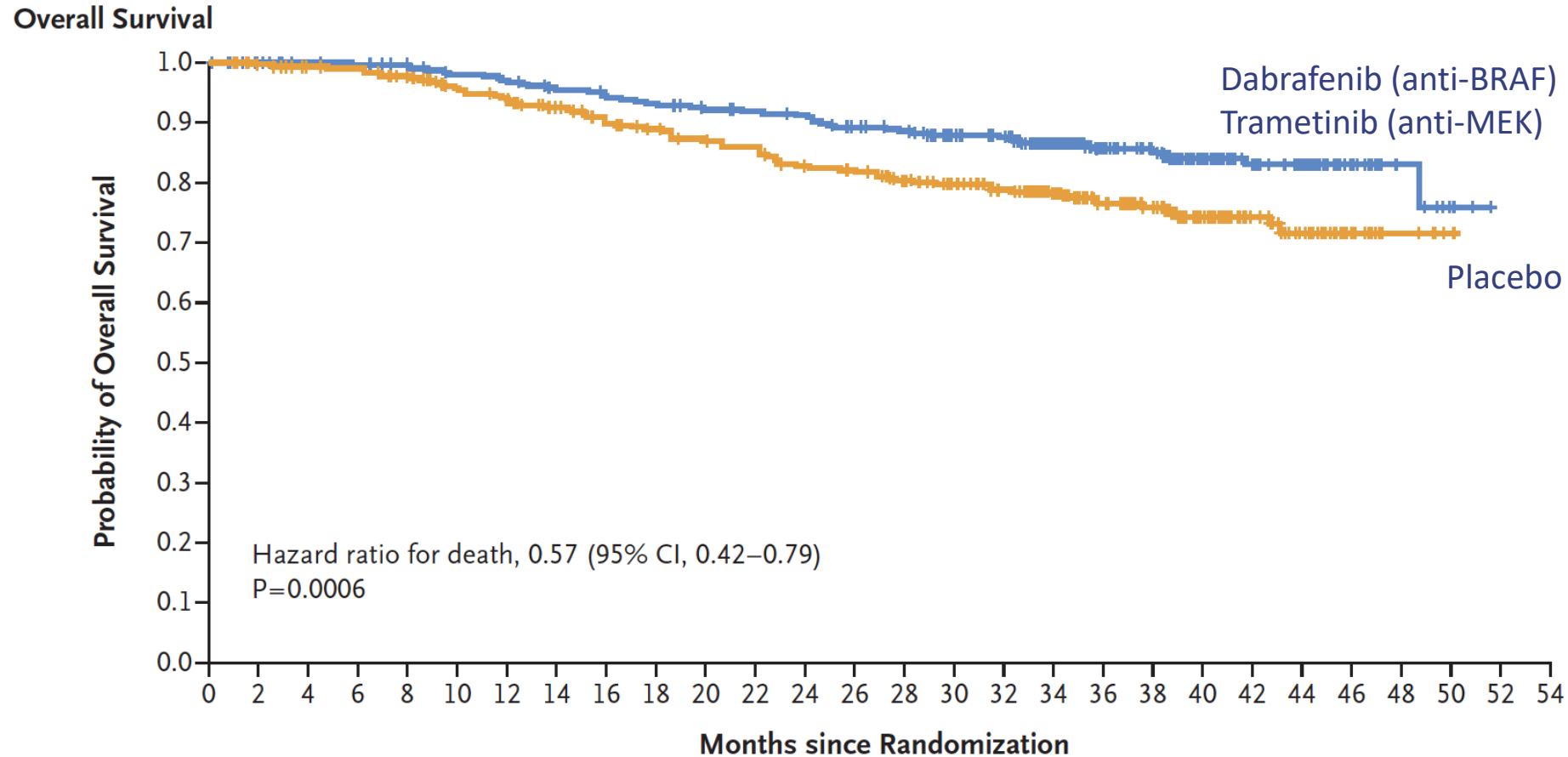
Overall Intention-to-Treat Population



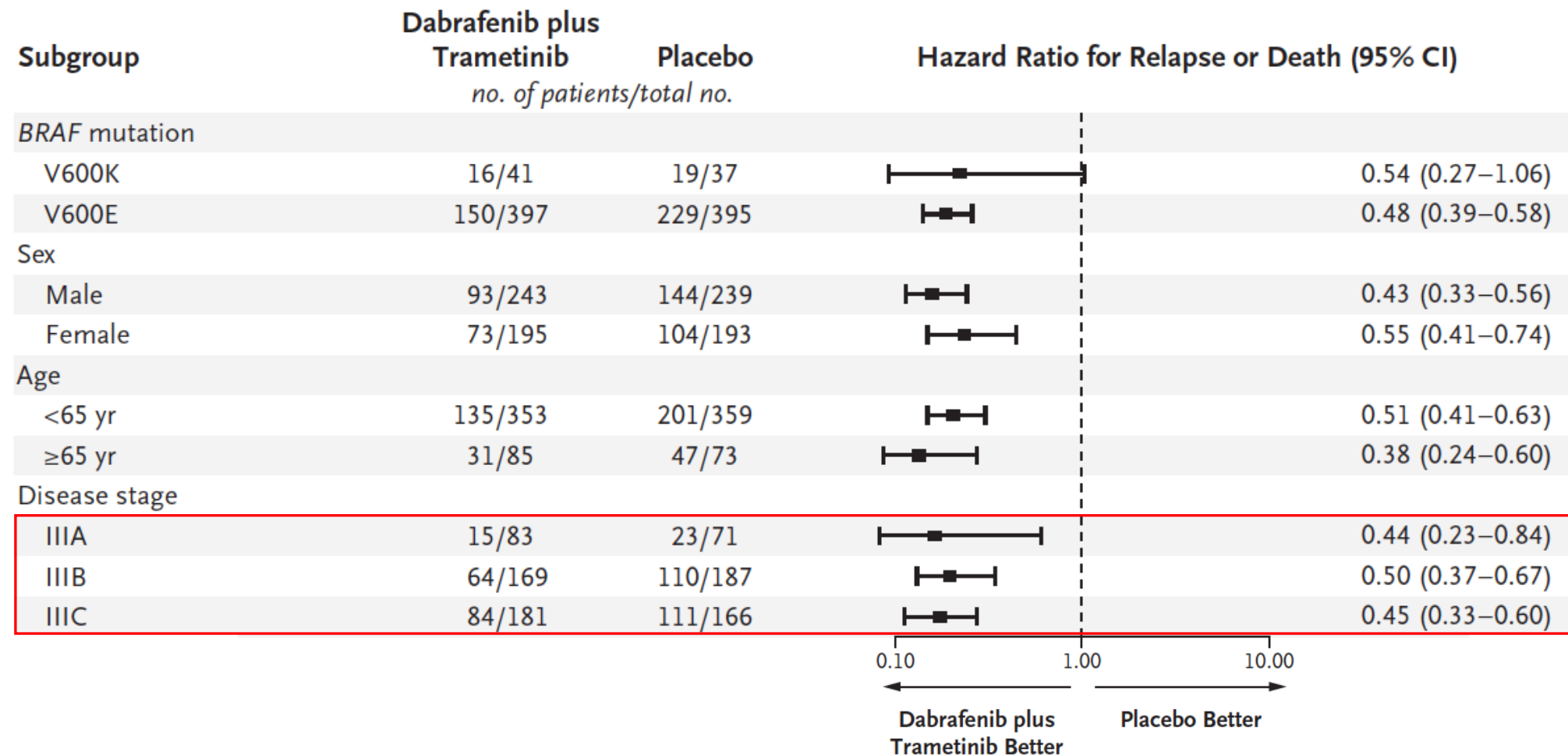
# Adjuvant Therapy for Resected Stage III Melanoma – KEYNOTE-054



# Adjuvant Therapy for Resected Stage III Melanoma – Combi-AD



# Adjuvant Therapy for Resected Stage III Melanoma – Combi-AD



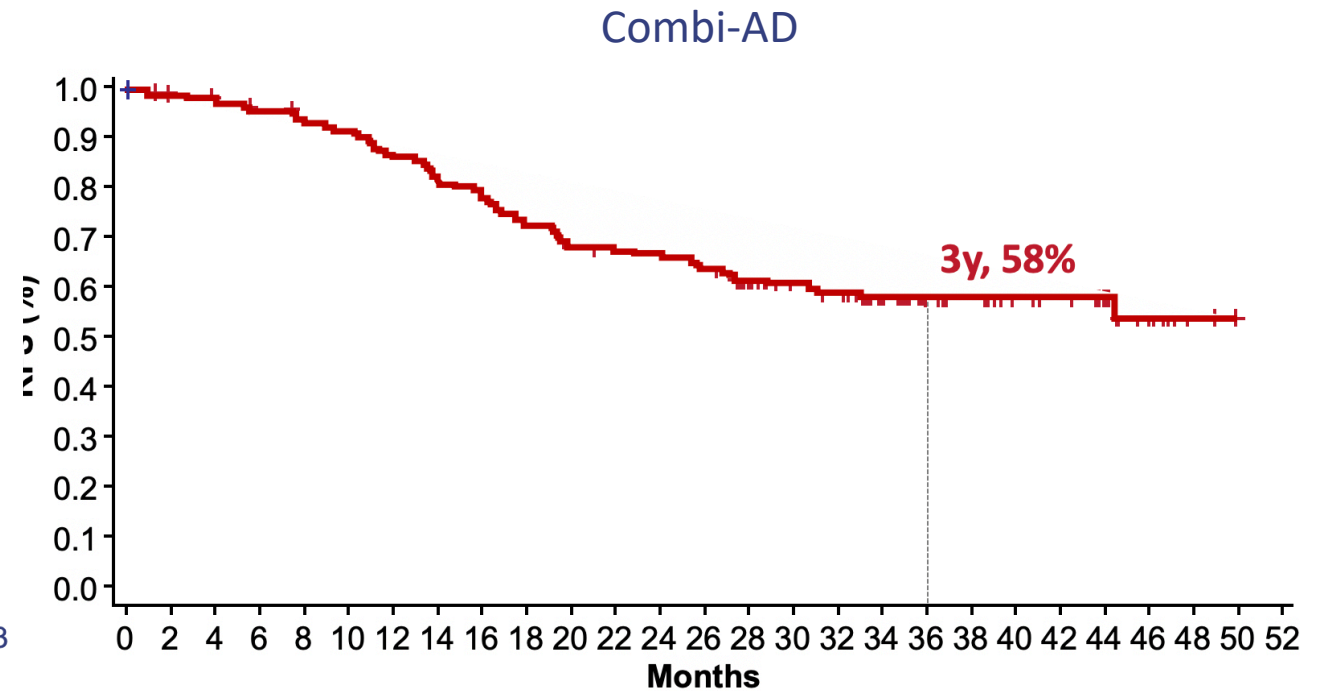
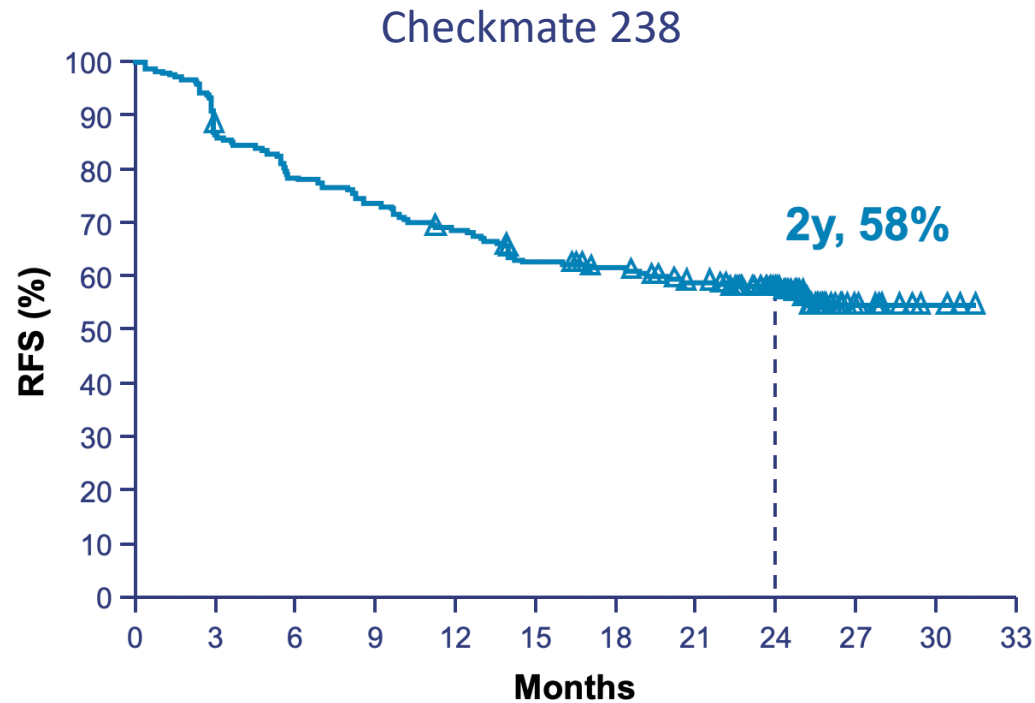
# Adjuvant Therapy for Resected Stage III Melanoma – Summary

- PD-1 inhibitors show improvement in **only** RFS
  - Checkmate 238 did not include stage IIIA patients
  - Keynote 054 included stage IIIA patients **only** if they had >1.0mm of disease in the SLN
  - FDA approval for both nivolumab and pembrolizumab for **all** stage III patients
- BRAF/MEK inhibitors have show improvement in RFS and OS for patients with IIIA/B/C

# Outline

- Current landscape of adjuvant therapy
- **Updates in neoadjuvant therapy**
- Future directions for neoadjuvant and adjuvant therapy

# Justification for Neoadjuvant Therapy

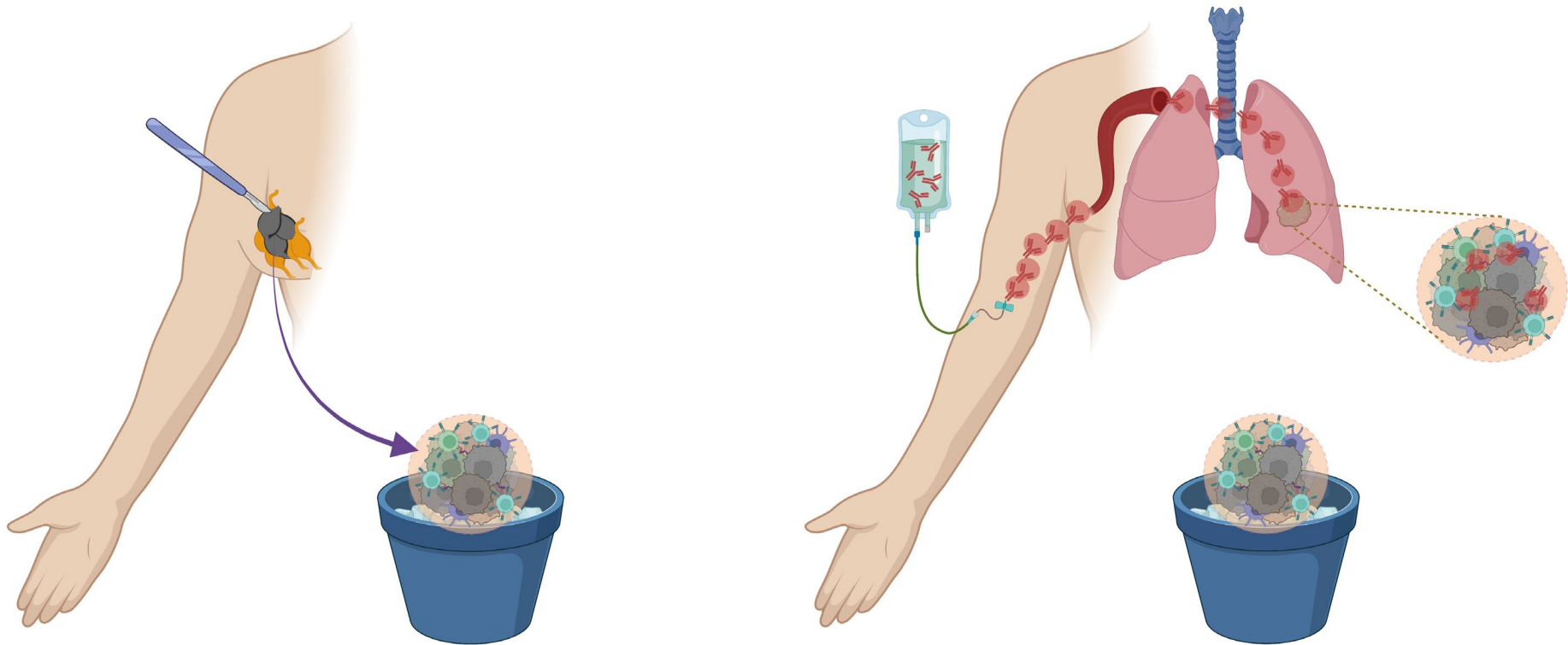


Outcomes for stage III disease remain relatively poor even with adjuvant therapies



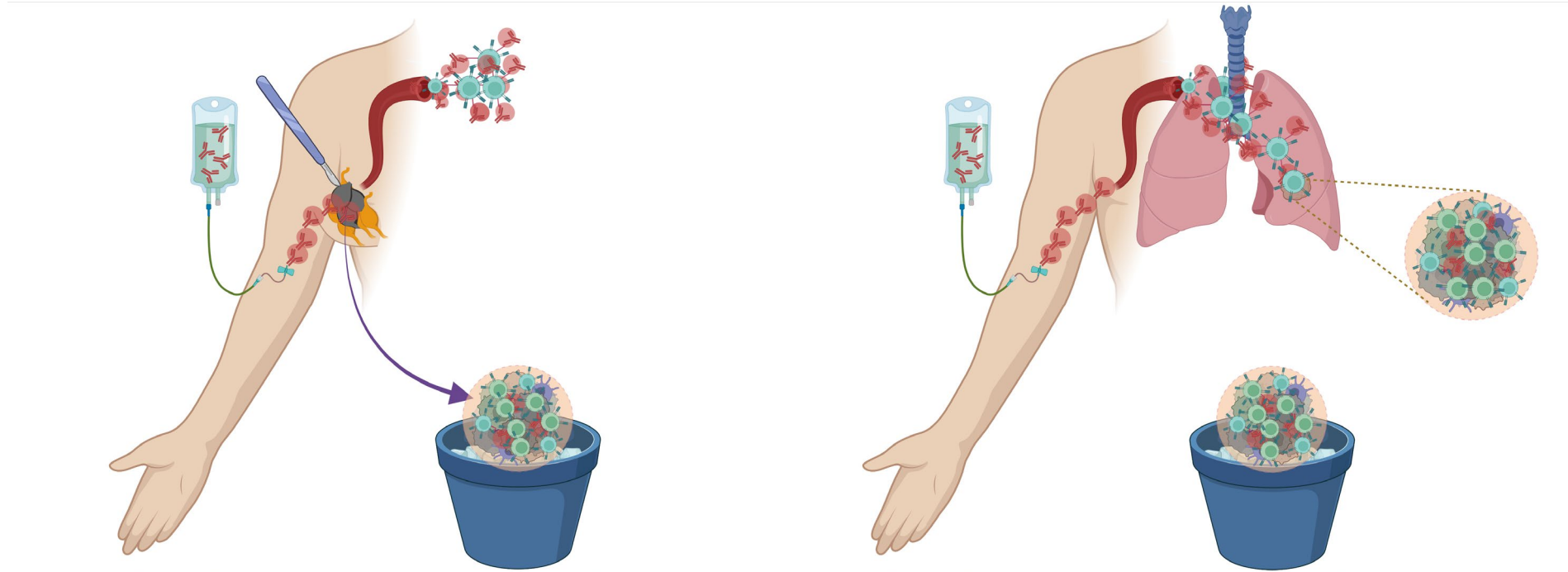
# Justification for Neoadjuvant Therapy

Surgical resection followed by adjuvant anti-PD-1 improves recurrence-free survival in patients with high-risk melanoma



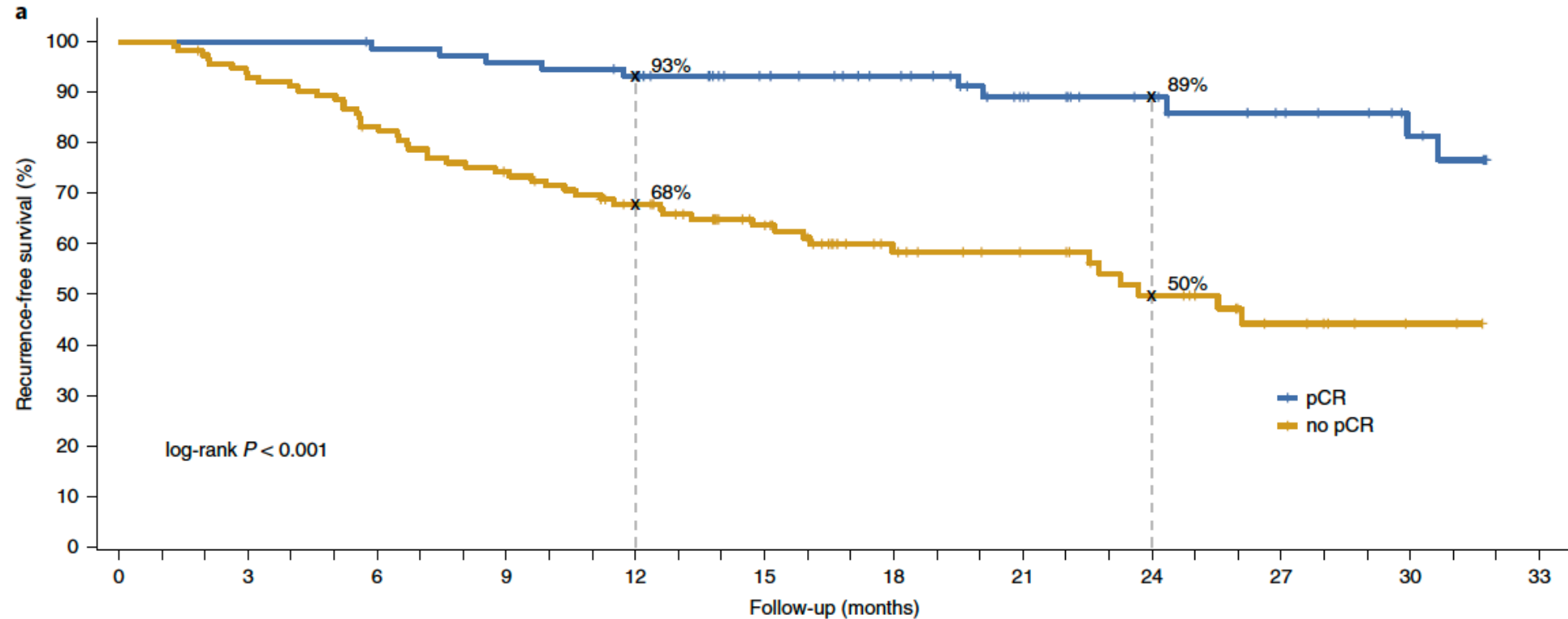
# Justification for Neoadjuvant Therapy

PD-1 blockade before surgery induces an immune response from a larger population of T cells that reside in the tumor and results in a systemic immune response at distant sites.

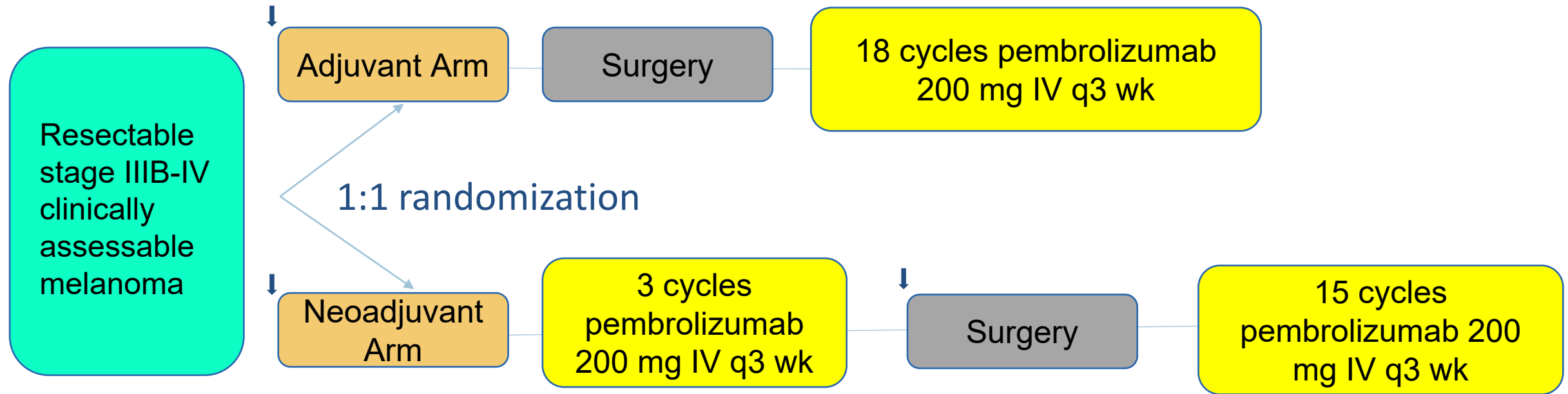


# Justification for Neoadjuvant Therapy

## INMC Pooled Analysis of Neoadjuvant Trials



# Neoadjuvant Therapy Updates – S1801



↓ radiographic assessment

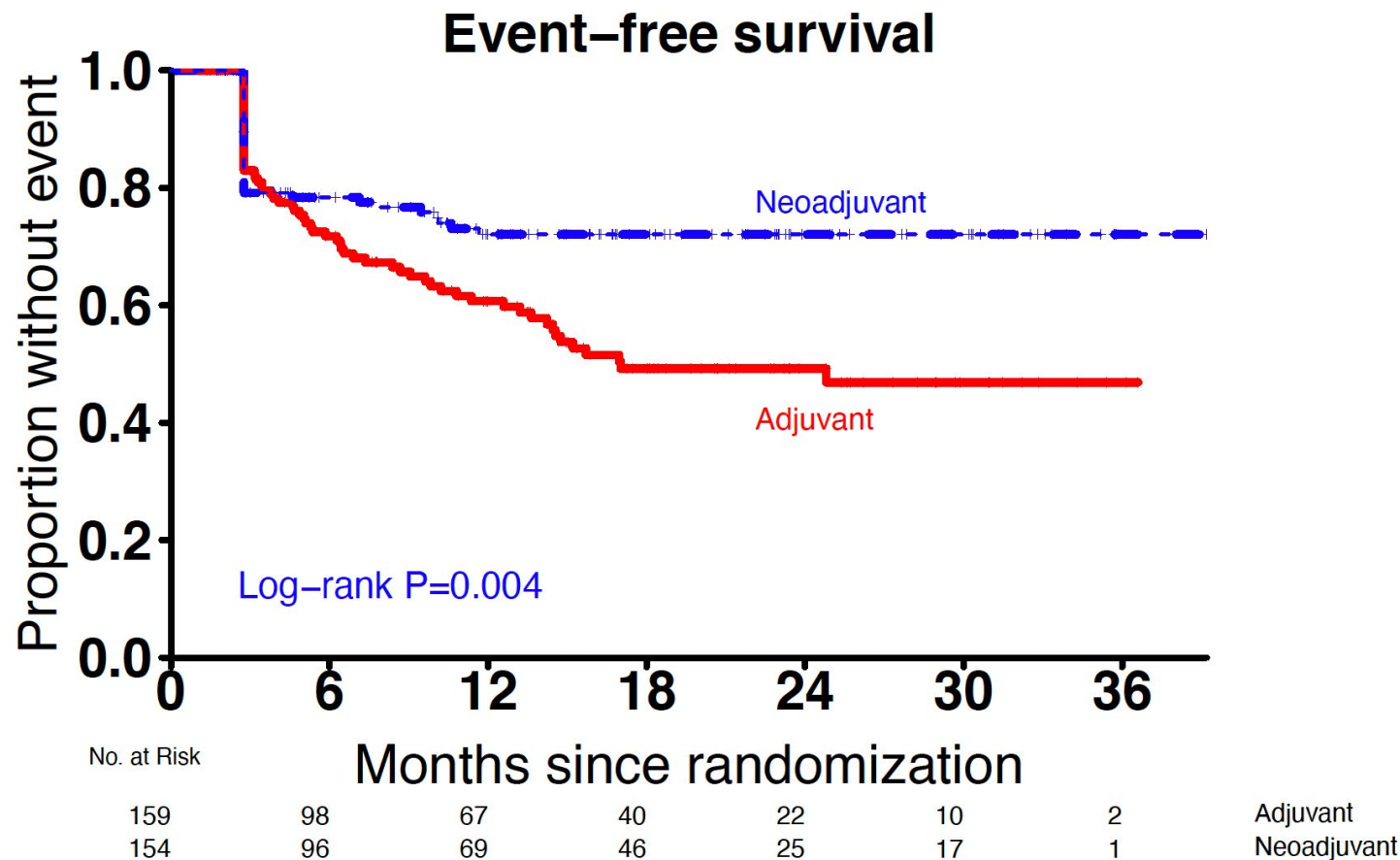
- Stratified by AJCC 8<sup>th</sup> ed. stage and LDH; adjuvant radiation allowed but not concomitantly with pembrolizumab; brain metastasis and uveal melanoma were excluded
- **Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy**

# Neoadjuvant Therapy Updates – S1801

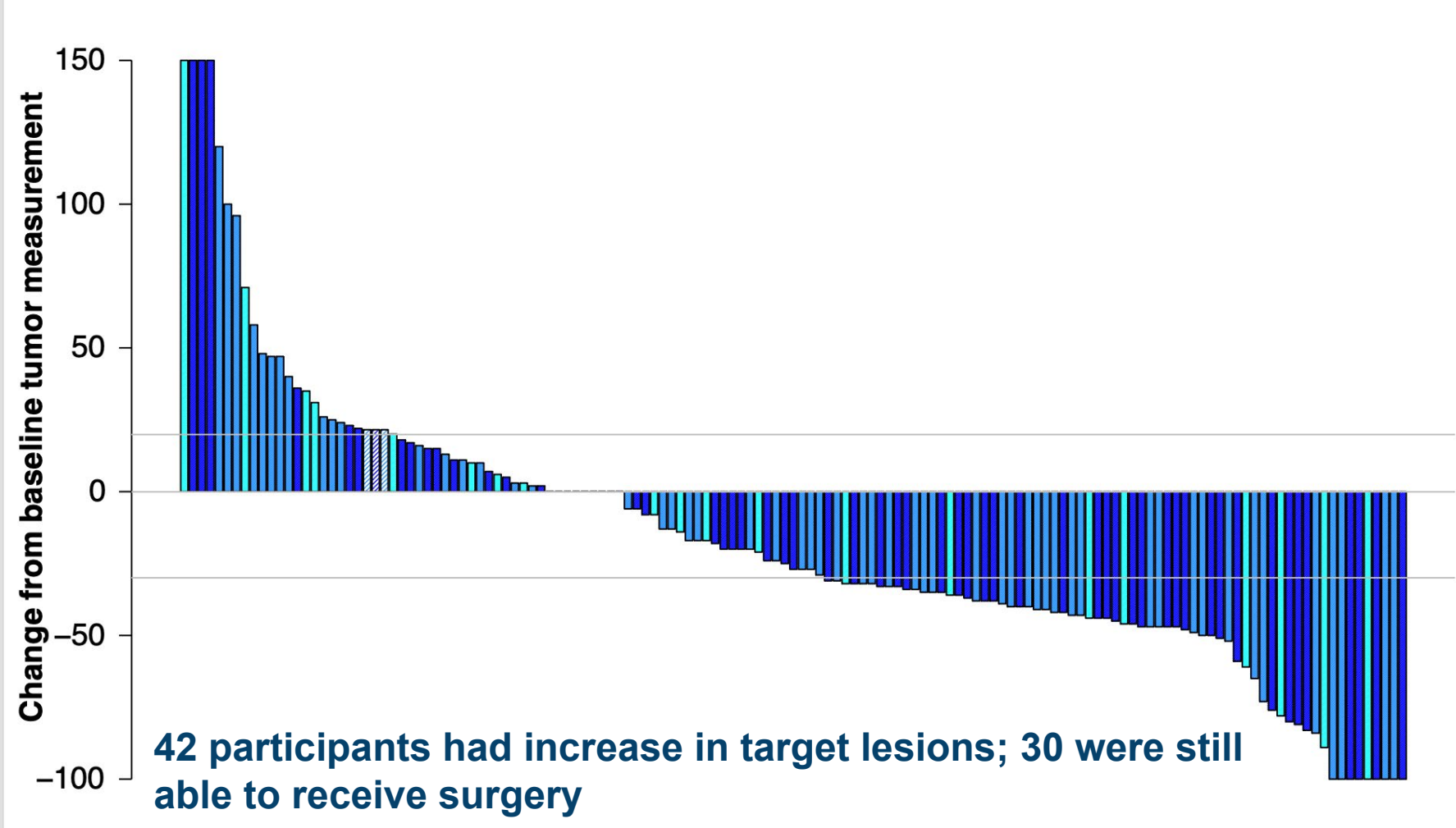
- Progression or toxicity that rendered a study participant unable to receive surgery
- Failure to begin adjuvant therapy within 84 days of surgery
- Melanoma recurrence after surgery (local, regional, or distant)
- Death from any cause

**Study participants who did not register to adjuvant therapy were assigned an EFS of 84 days\***

# Neoadjuvant Therapy Updates – S1801



# Neoadjuvant Therapy Updates – S1801



One study participant achieved a CR and refused surgery

# Neoadjuvant Therapy Updates – S1801

- 50 patients have experienced recurrence
  - Neoadjuvant: 9 (6%)
  - Adjuvant: 44 (28%)
- Median time to recurrence: 8.2 months
  - Neoadjuvant: 8.9 months
  - Adjuvant: 8.1 months
- Sites of Recurrence
  - Nodal only: 19%
  - In transit: 14%
  - Distant: 67%



# Neoadjuvant Therapy Updates

- Neoadjuvant therapy is safe and well-tolerated
- Nearly all patients underwent successful curative intent surgery as planned
- The ability to safely perform surgery was not affected by neoadjuvant treatment
- Based on EFS and safety of surgical intervention, all patients with resectable stage IIIB/C/D melanoma should be considered for neoadjuvant PD-1 blockade

# Adjuvant Therapy for Resected Stage II Melanoma – KEYNOTE-716

## Key Eligibility Criteria

- Age  $\geq 12$  years
- Newly diagnosed, resected, stage IIB or IIC melanoma
- Negative SLN biopsy
- No evidence of regional or distant metastases
- No prior treatment beyond resection
- ECOG PS 0 or 1

## Stratification<sup>b</sup>

- T category (T3b, T4a, T4b)
- Pediatric status

## Part 1 Adjuvant Therapy

R  
1:1  
n = 487  
n = 489

Pembrolizumab  
200 mg or 2 mg/kg  
(pediatric)<sup>a</sup> IV Q3W

Placebo IV Q3W

17 cycles

Follow-up

Unblinding

Recurrence

Recurrence

## Part 2 Rechallenge/Crossover

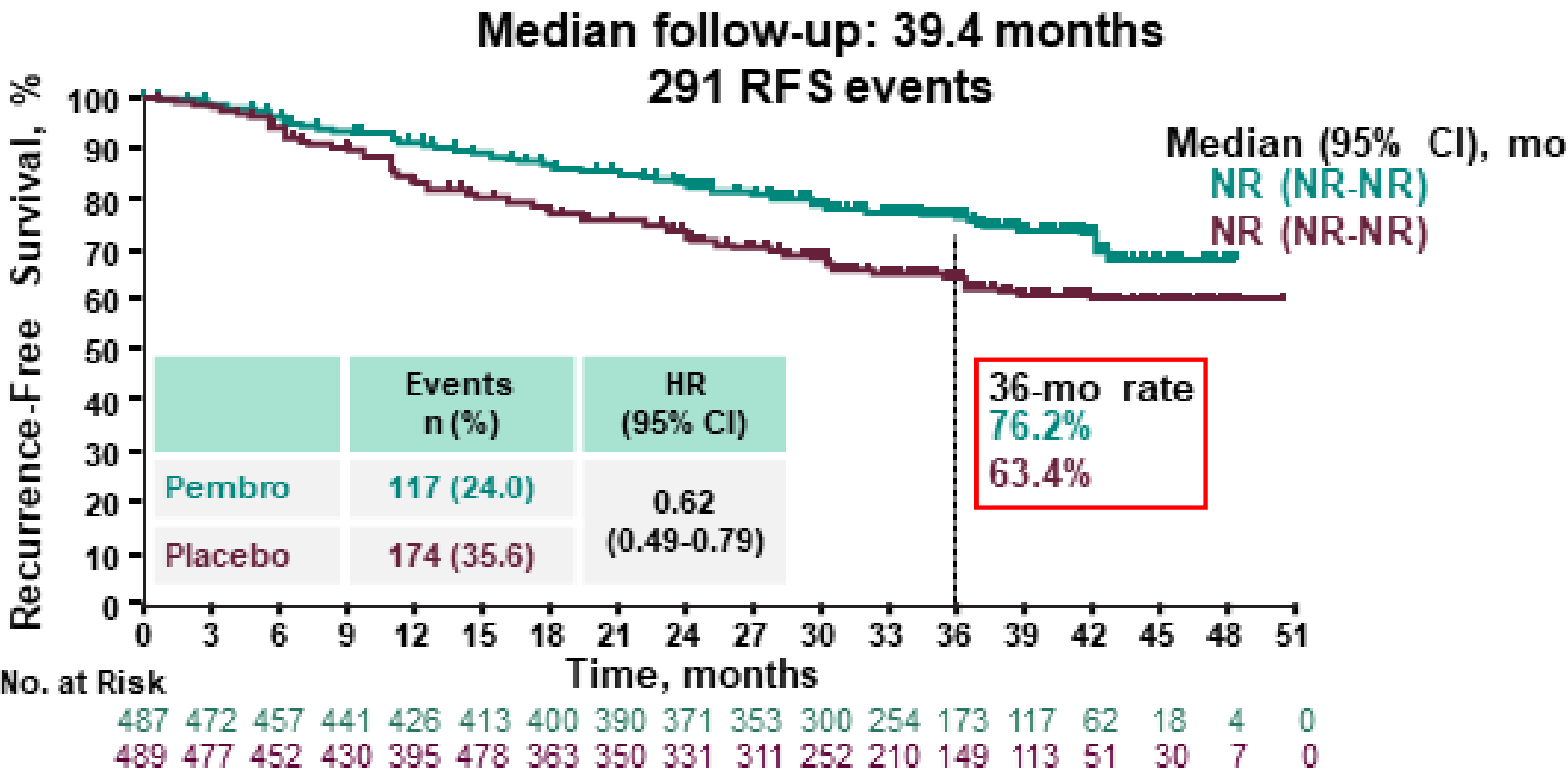
Pembrolizumab  
200 mg IV Q3W or  
2 mg/kg (pediatric)<sup>a</sup>

Until disease progression  
or recurrence, up to  
2 years

## End points

- **Primary:** RFS per investigator assessment
- **Secondary:** DMFS per investigator assessment

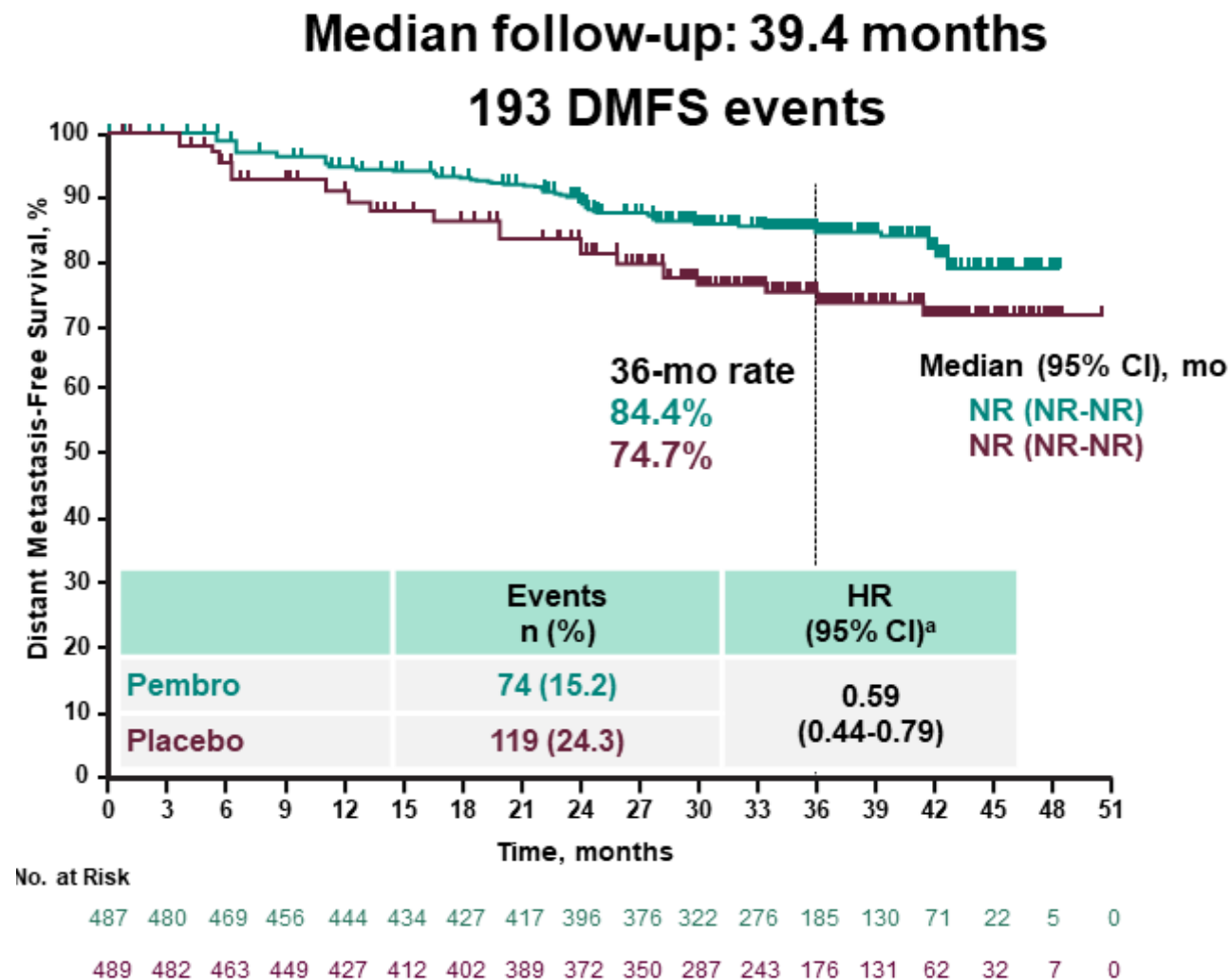
# Adjuvant Therapy for Resected Stage II Melanoma – KEYNOTE-716



# Adjuvant Therapy for Resected Stage II Melanoma – KEYNOTE-716

	Pembrolizumab n = 483	Placebo n = 486
<b>All AEs</b>	461 (95.4)	446 (91.8)
<b>Treatment-related AEs</b>	399 (82.6)	309 (63.6)
Grade 3/4	83 (17.2)	25 (5.1)
Led to discontinuation	77 (15.9)	12 (2.5)
Led to death	0 (0)	0 (0)
<b>Immune-mediated AEs and infusion reactions</b>	183 (37.9)	46 (9.5)
Grade 3/4	53 (11.0)	6 (1.2)

# Adjuvant Therapy for Resected Stage II Melanoma – KEYNOTE-716

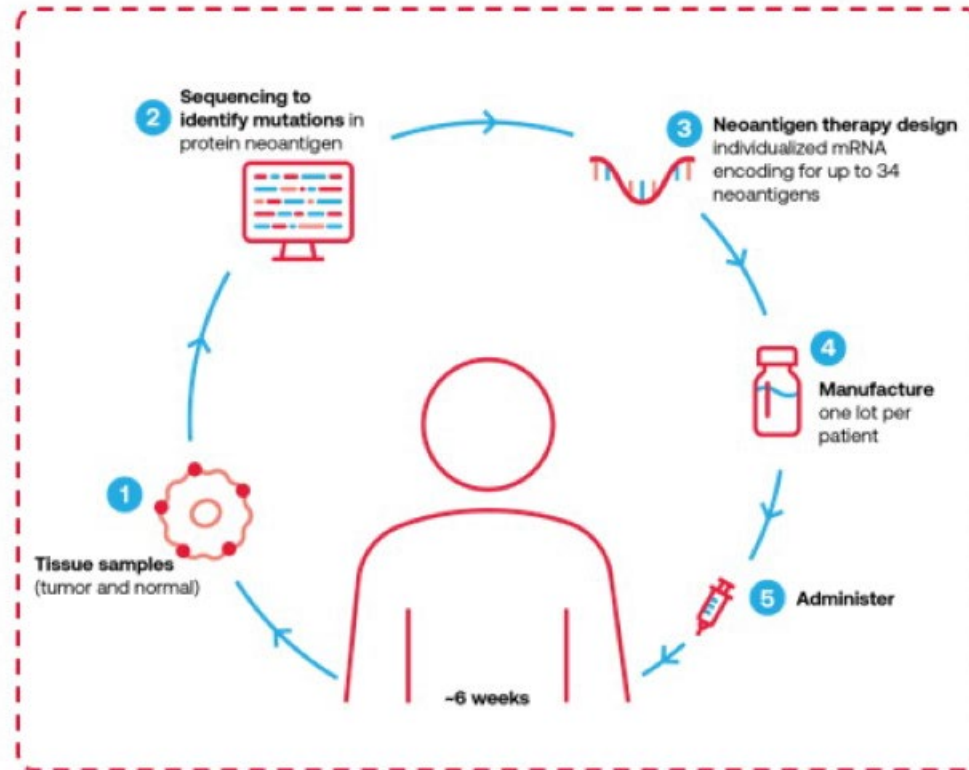


# Outline

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- Updates in neoadjuvant therapy
- **Future directions for neoadjuvant and adjuvant therapy**

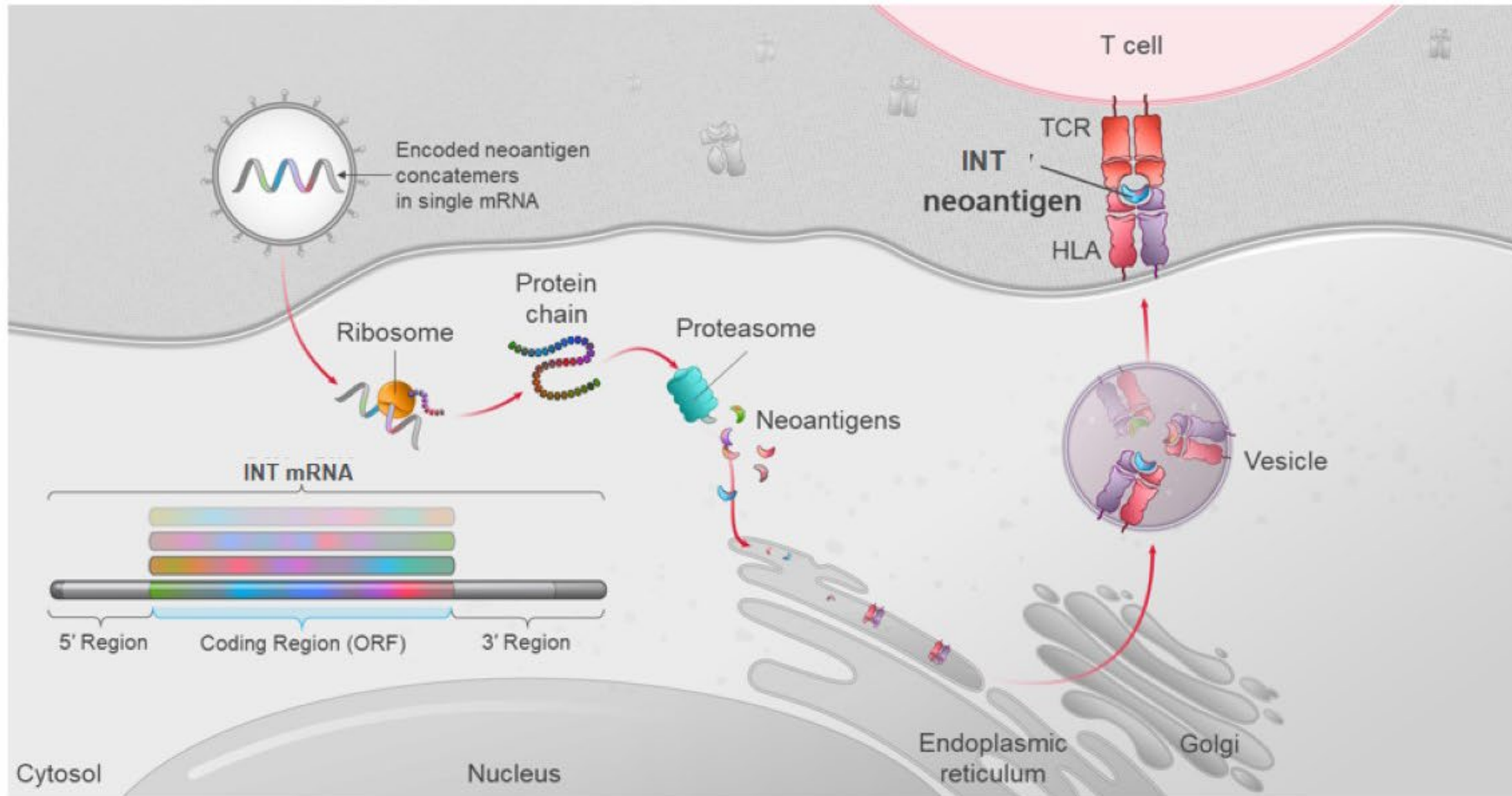
# Future Directions

## Individualized Neoantigen Therapy



# Future Directions

## Individualized Neoantigen Therapy



mRNA-4157 (V940) is a **customizable** individualized neoantigen therapy encoding up to 34 neoantigens

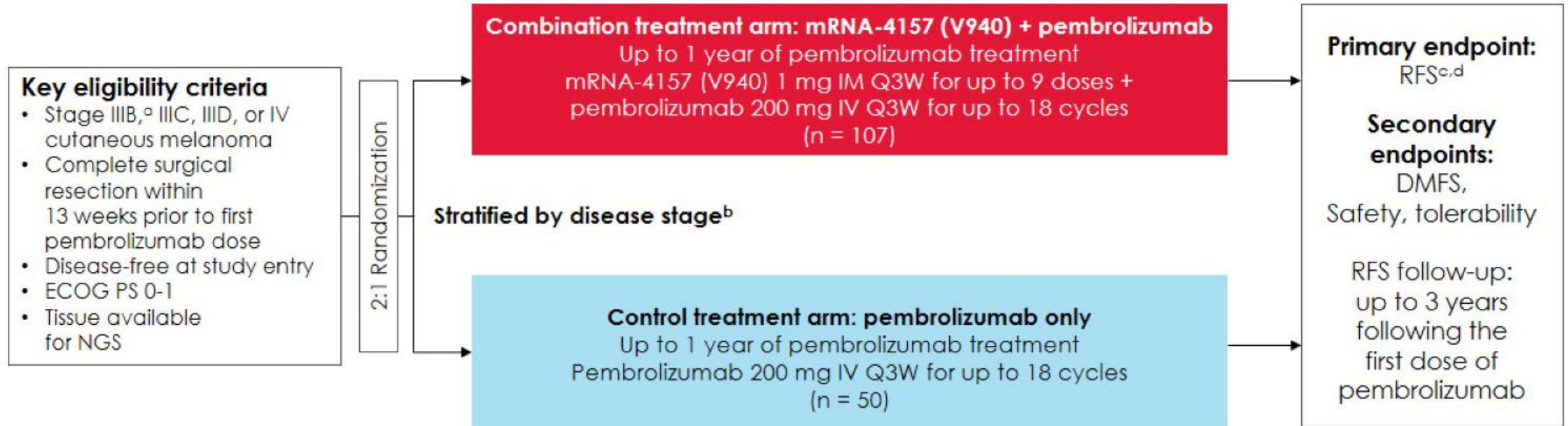
**Targeting of neoantigens** by T-cells has been demonstrated to **drive antitumor responses**<sup>1</sup>

The modified mRNA **platform** was implemented for the COVID-19 vaccine (mRNA-1273), demonstrating its **utility and adaptability**<sup>2</sup>



# Future Directions

## Individualized Neoantigen Therapy – KEYNOTE-942

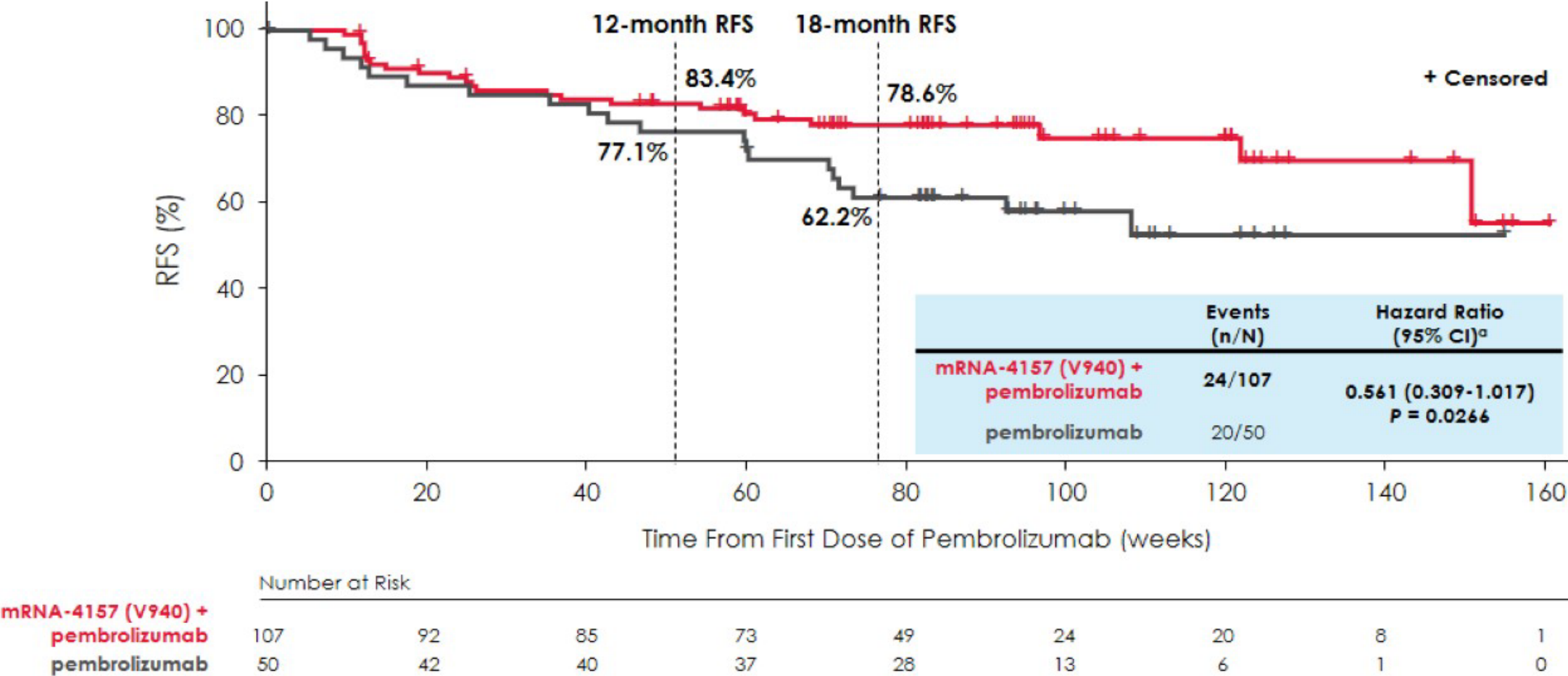


Designed with 80% power to detect an HR of 0.5 with  $\geq 40$  RFS events (with 1-sided alpha of 0.1)

**Median follow-up<sup>e</sup>:** 23 months for mRNA-4157 (V940) + pembrolizumab  
24 months for pembrolizumab only

# Future Directions

## Individualized Neoantigen Therapy – KEYNOTE-942



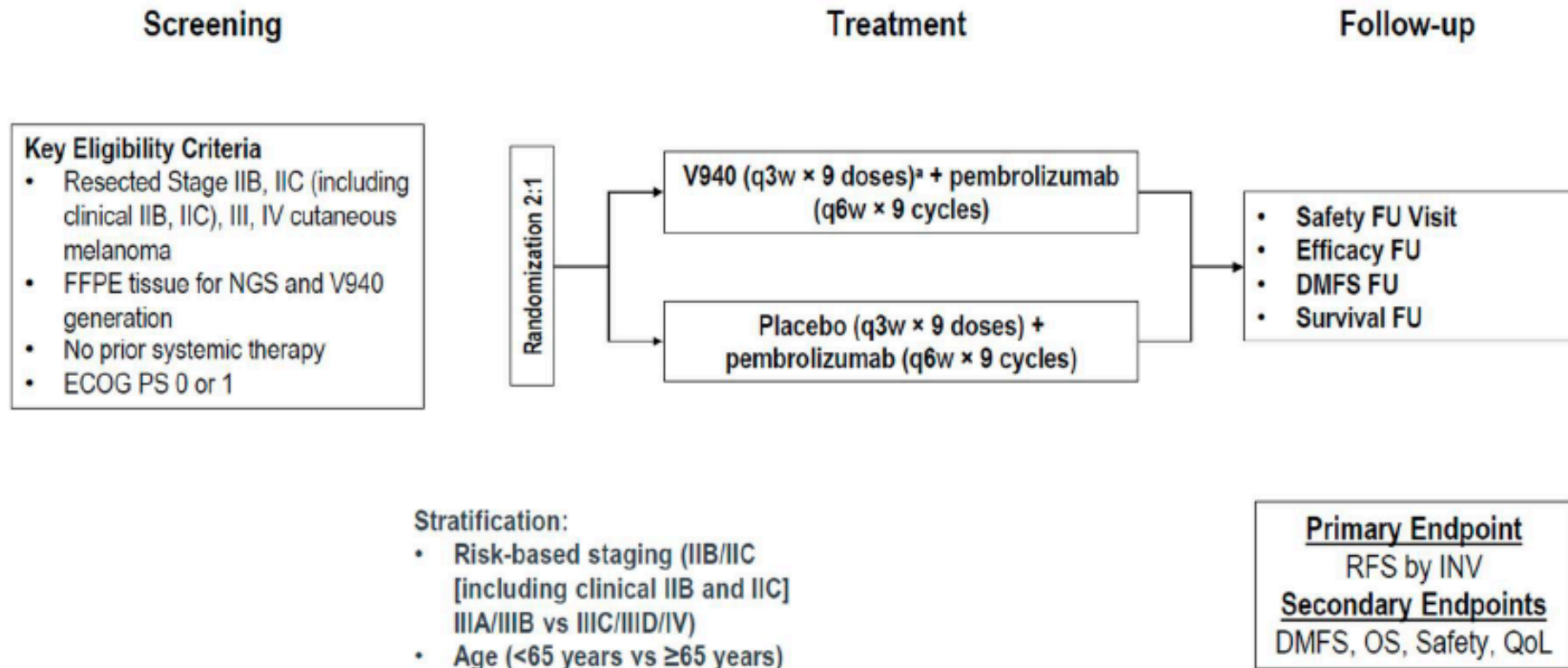
# Future Directions

## Individualized Neoantigen Therapy – KEYNOTE-942

	mRNA-4157 (V940) + pembro (n=104)		pembro (n=50)	
Event, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	104 (100.0)	36 (34.6)	47 (94.0)	18 (36.0)
Any treatment-related AE	104 (100.0)	26 (25.0)	41 (82.0)	9 (18.0)
Serious AE <sup>a</sup>	15 (14.4)		5 (10.0)	
Immune-mediated AEs	37 (35.6)	11 (10.6)	18 (36.0)	7 (14.0)
mRNA-4157 (V490) or combination-related AEs <sup>b</sup> occurring in >20% of patients				
Any	98 (94.2)	12 (11.5)	-	-
Fatigue	63 (60.6)	5 (4.8)	-	-
Injection site pain	58 (55.8)	0	-	-
Chills	52 (50.0)	0	-	-
Pyrexia	50 (48.1)	1 (1.0)	-	-
Headache	33 (31.7)	0	-	-
Injection site erythema	33 (31.7)	0	-	-
Influenza-like illness	32 (30.8)	0	-	-
Nausea	26 (25.0)	0	-	-
Myalgia	22 (21.2)	1 (1.0)	-	-

# Future Directions

- Phase III individualized neoantigen therapy trial



# Future Directions

- Phase III individualized neoantigen therapy trial
- Concepts under consideration
  - Neoadjuvant registry trial
  - Neoadjuvant nivo/ipi versus nivo/rela
  - Neoadjuvant PD-1 inhibitor for high-risk stage II melanoma with residual disease after biopsy



# **Neoadjuvant and Adjuvant Therapy in Melanoma**

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