A Role and Rationale for Neoadjuvant Therapy In the Melanoma Landscape

Suzanne Topalian, MD
Professor, Surgery and Oncology
Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy

#MelanomaNeoadjuvant

Disclosures

- Consultant for: Dragonfly Therapeutics, Five Prime Therapeutics, Immunocore, Merck; and (spouse) Amgen, Compugen, Janssen, MedImmune/AZ, Merck, Potenza
- Grant/Research support from: Bristol-Myers Squibb; and (spouse) Compugen, Potenza
- Stock/stock options: Dragonfly Therapeutics, Five Prime Therapeutics; and (spouse) Compugen, Potenza Therapeutics, Tizona, Trieza
- Royalties through institution (spouse): BMS, Immunomic Therapeutics, Potenza

- and -

- I will discuss investigational uses for anti-PD-1 drugs and TKIs in my presentation.

Advances in systemic therapy for stage IV melanoma (NCCN Guidelines)

2007

- Clinical trial
- Dacarbazine, temozolomide
- High-dose IL-2
- Chemoimmunotherapy
- Best supportive care

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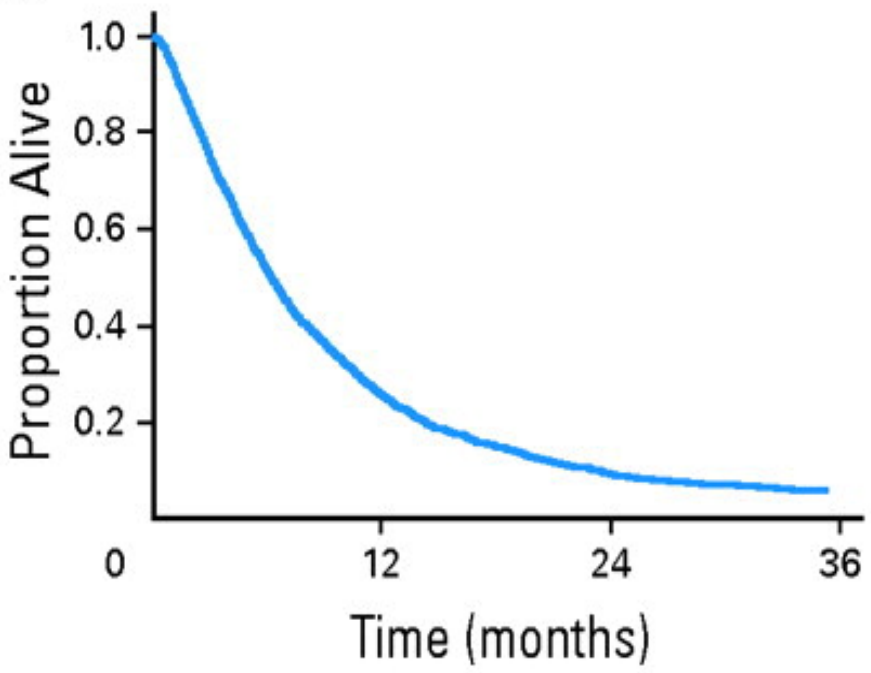
2019

- Clinical trial
- Pembrolizumab
- Nivolumab
- Nivolumab /ipilimumab
- Dabrafenib/trametinib (if BRAFmut)
- Vemurafenib/cobimetinib (if BRAFmut)
- Encorafenib/binimetinib (if BRAF mut)
- Ipilimumab
- High-dose IL-2
- Cytotoxic agents
- Imatinib (cKITmut)
- Best supportive care

Survival in advanced unresectable melanoma

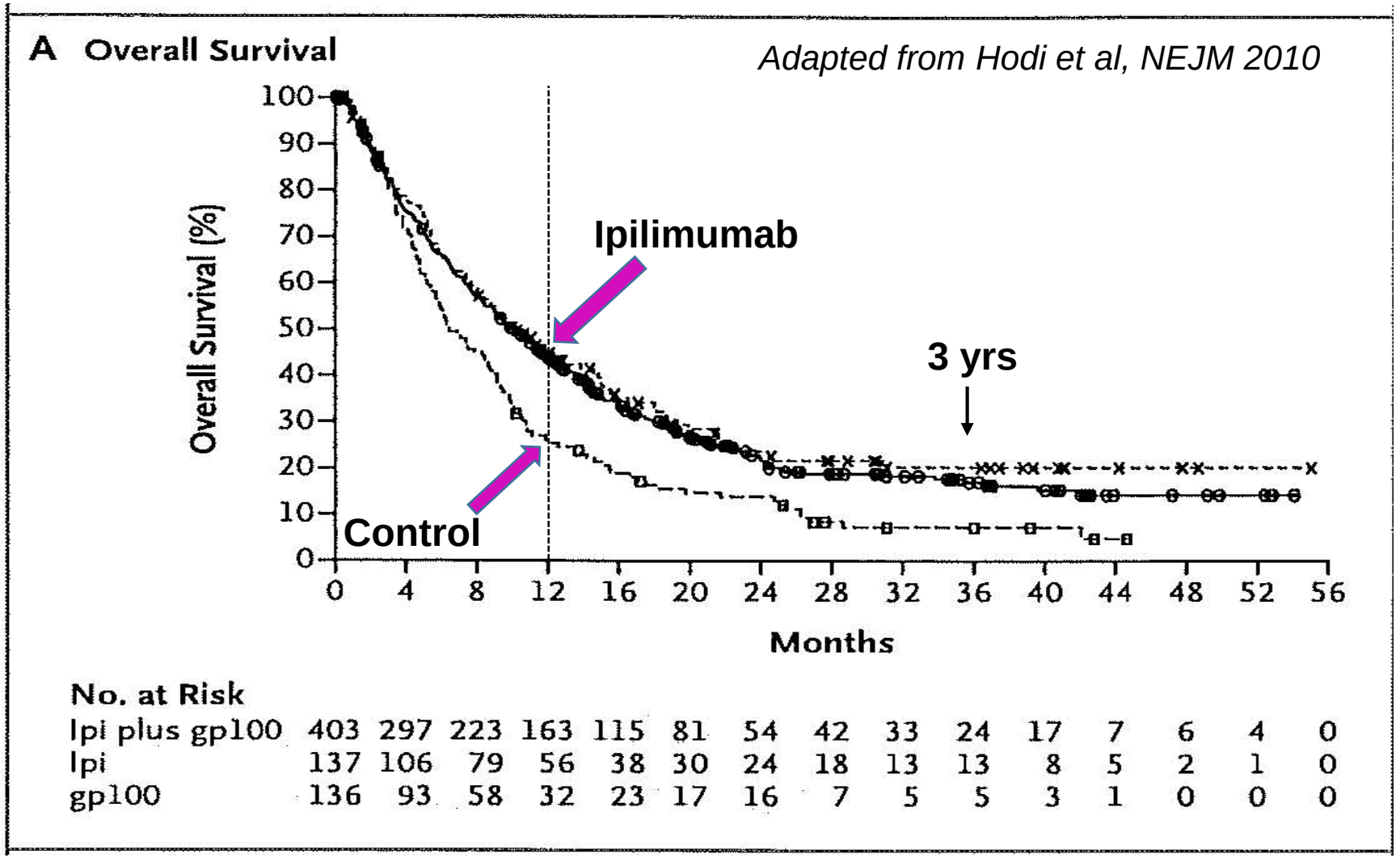
(Korn et al., JCO 2008)



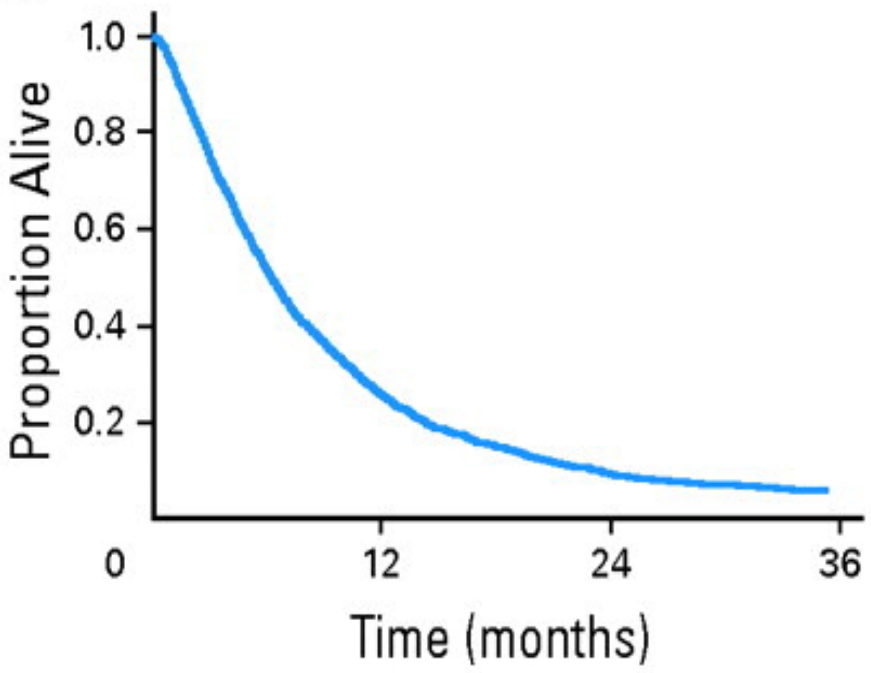
Meta-analysis of 2100 patients enrolled on 42 phase II cooperative group clinical trials, 1977-2005:

- "New agents are needed for the treatment of metastatic melanoma because ***no evidence of survival prolongation with existing therapy has been established***."
- Median overall survival = 6.2 months
- One-year overall survival = 26%

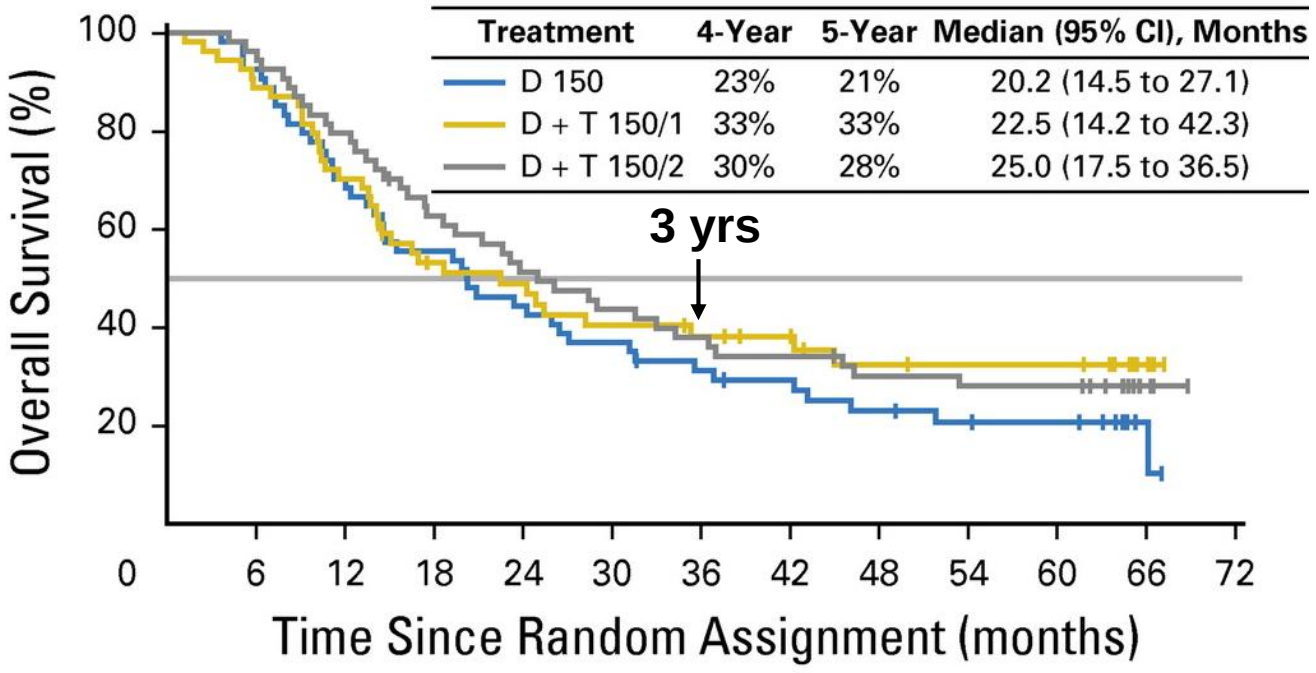
Ipilimumab in metastatic melanoma: first drug to improve overall survival in a randomized clinical trial



Survival in advanced unresectable melanoma: a decade of progress in targeted therapy



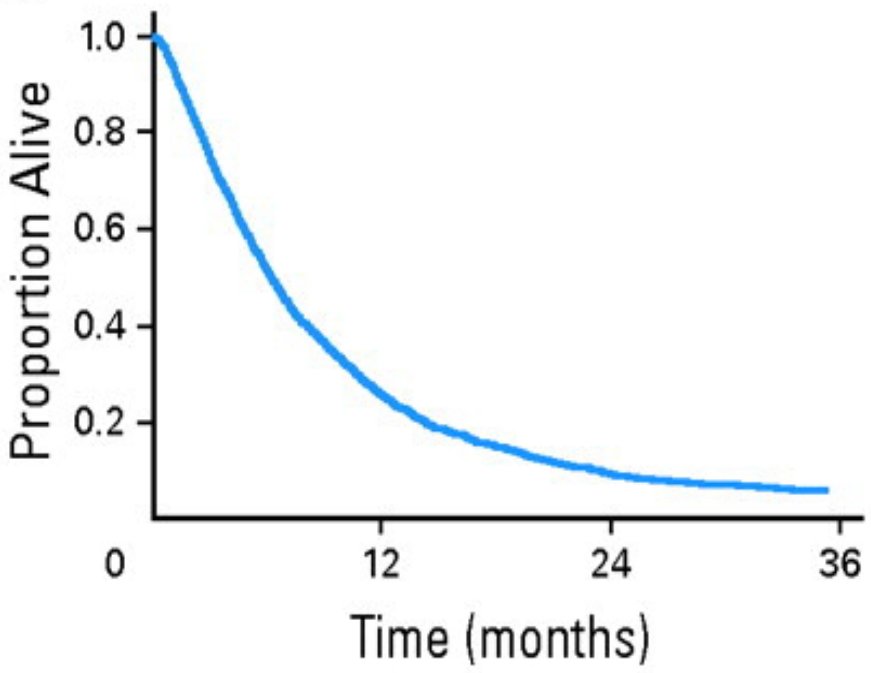
Korn et al., JCO 2008



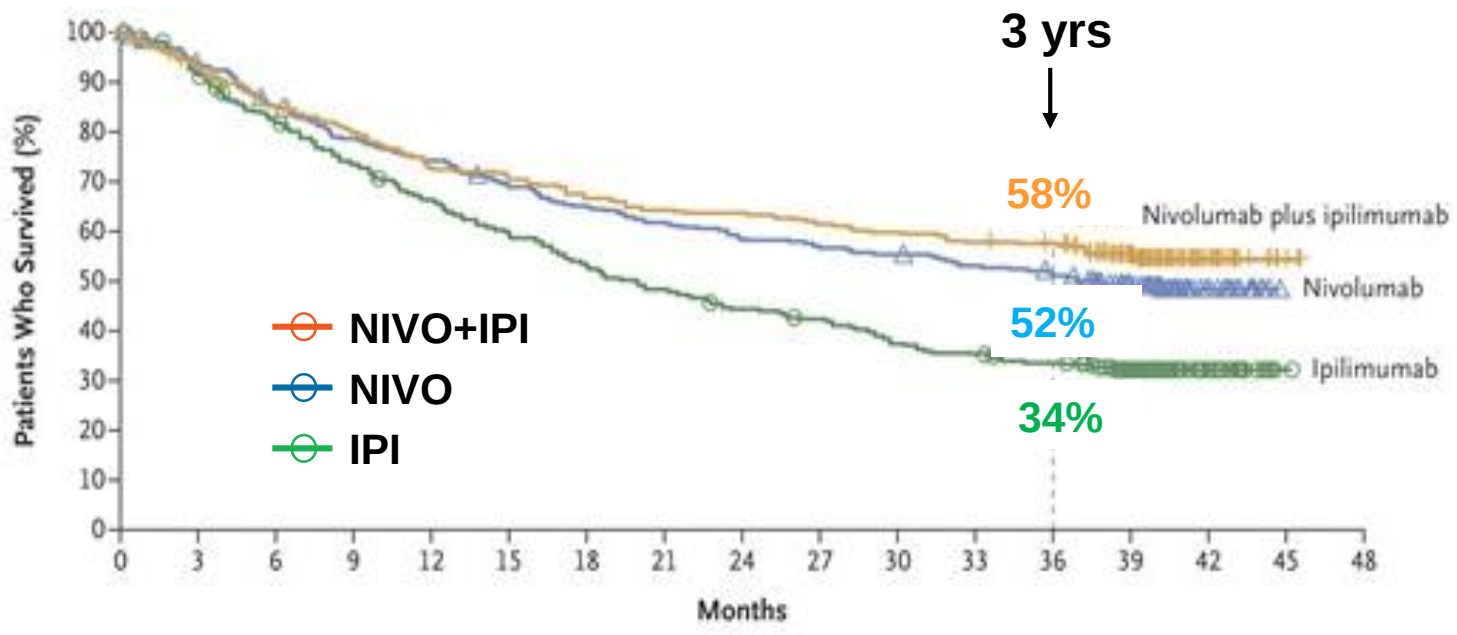
Treatment	4-Year	5-Year	Median (95% CI), Months
D 150	23%	21%	20.2 (14.5 to 27.1)
D + T 150/1	33%	33%	22.5 (14.2 to 42.3)
D + T 150/2	30%	28%	25.0 (17.5 to 36.5)

Long et al., JCO 2018

Survival in advanced unresectable melanoma: a decade of progress in immunotherapy



Korn et al., JCO 2008



Adapted from Wolchok et al., NEJM 2017

Advances in adjuvant therapy for stage III melanoma (NCCN Guidelines)

2007

After complete lymph node dissection (CLND),

- Clinical trial
- Interferon alfa
- Observation

Advances in adjuvant therapy for stage III melanoma (NCCN Guidelines)

"Complete overhaul" (A. Eggermont, EJC 2017)
"Head-spinning progress" (L. Schuchter, NEJM 2017)

2007

After complete lymph node dissection (CLND),

- Clinical trial
- Interferon alfa
- Observation

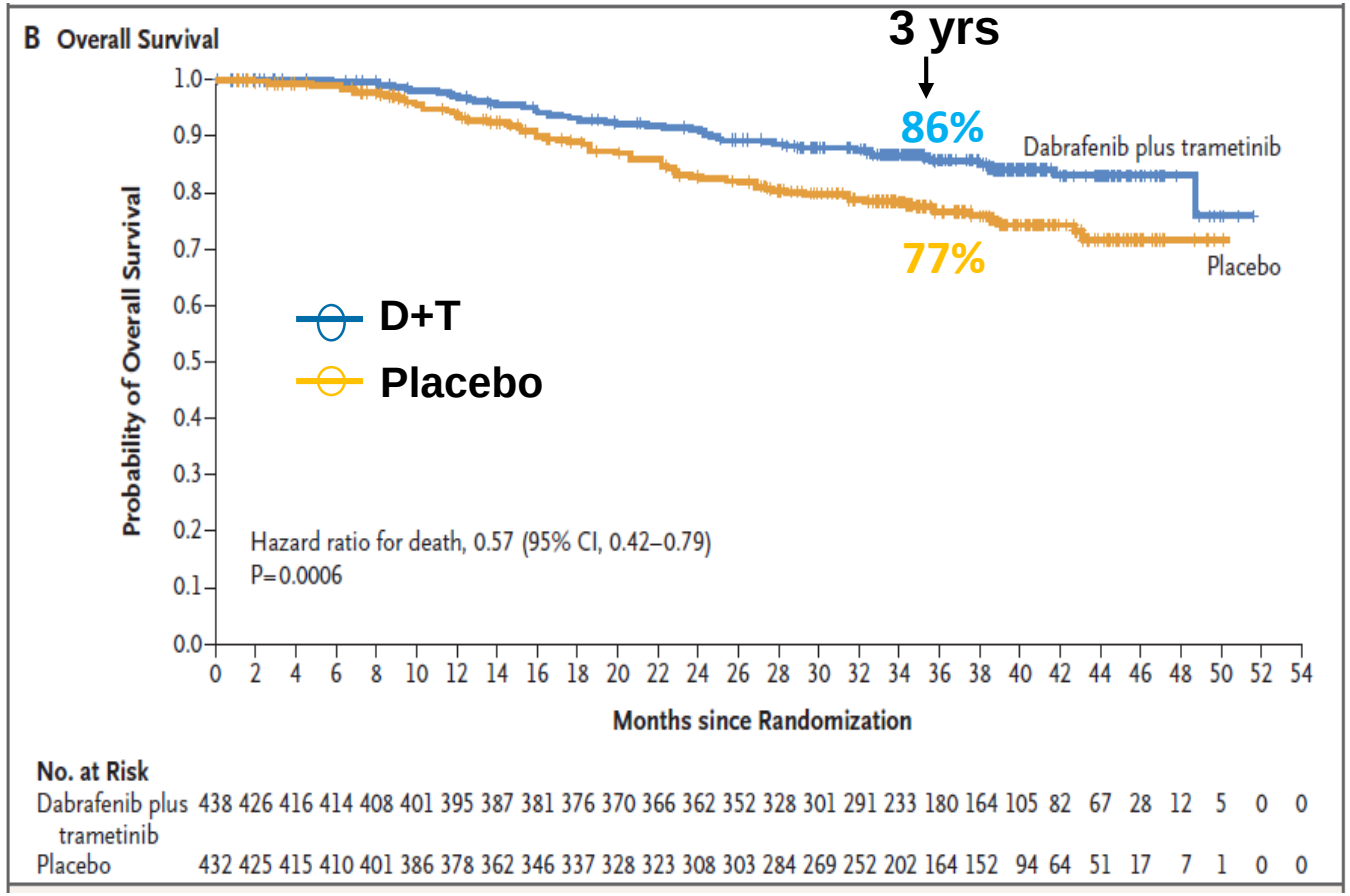
2019

CLND *not required* for positive SLNB.

- Nivolumab
- Pembrolizumab
- Dabrafenib/trametinib (if BRAFmut)
- Clinical trial
- Observation

Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma

Long et al., NEJM 2017



870 patients
stage IIIA/B/C, BRAFmut

D+T x 1 yr

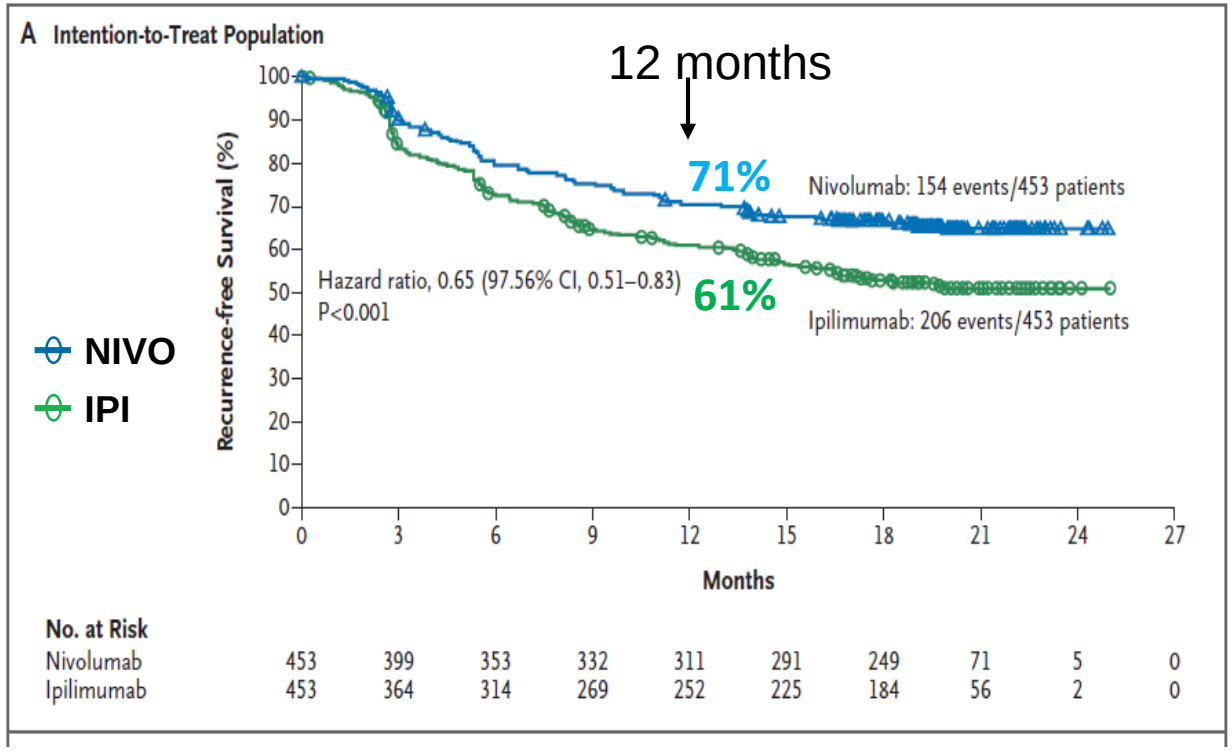
Placebo

***Results*: At 3 years, superior overall and recurrence-free survival with D+T compared to placebo**

- Grade 3-4 AEs with D+T = 41%

CheckMate 238: Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma

Weber et al., NEJM 2017



906 patients
melanoma stage IIIB/IIIC/IV

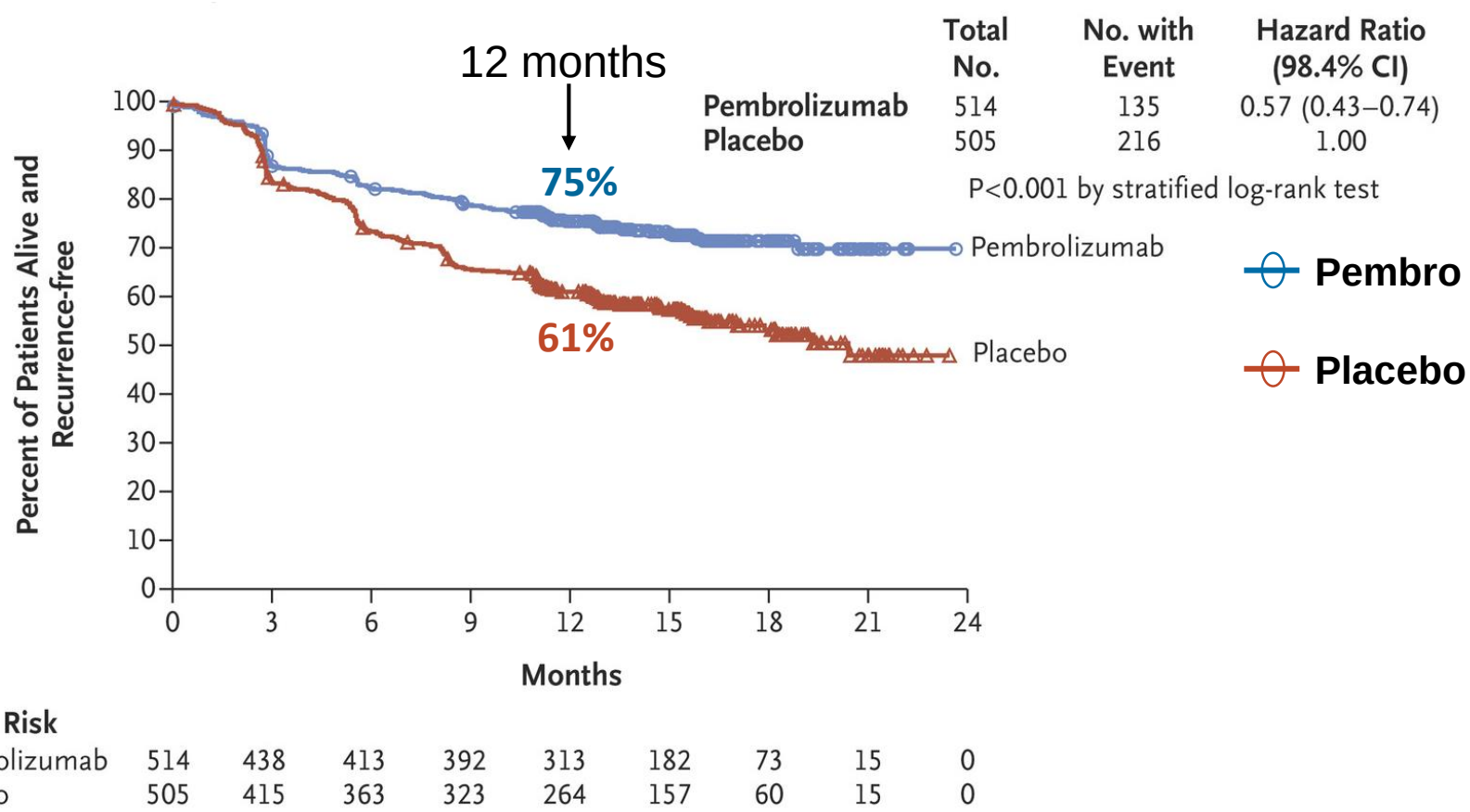
Nivo 3 mg/kg
x 1 yr

Ipi 10 mg/kg
X 1 yr

➢ Grade 3-4 AEs 14% nivo, 46% ipi

***Results*: At 12 months, adjuvant nivo improved recurrence-free survival compared to high-dose ipi, with less toxicity**

Keynote-054: Adjuvant pembrolizumab improves recurrence-free survival in stage III melanoma at 12 months, compared to placebo



Adapted from Eggermont et al., NEJM 2018

- Grade 3-5 toxicities with pembrolizumab = 15%, vs. placebo = 3%.

QUESTION:

- **Can we further improve patient outcomes by applying a *neoadjuvant (pre-surgical)* treatment approach in patients with high-risk resectable melanoma?**

Potential advantages of neoadjuvant therapies, compared to treating advanced unresectable melanoma

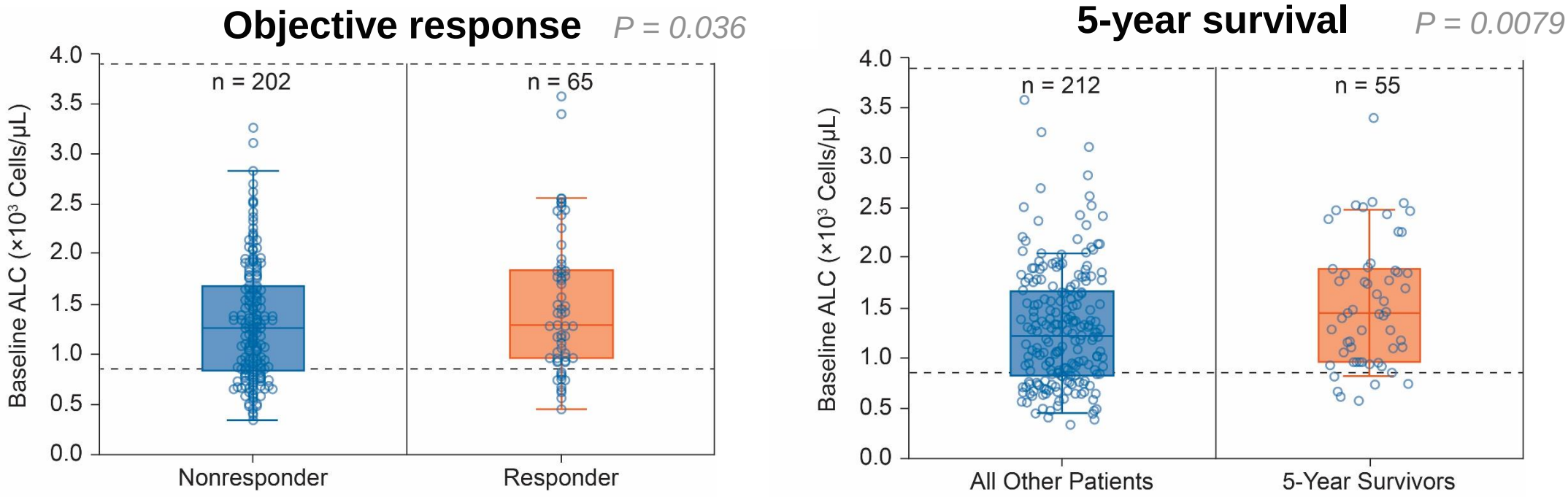
- Lower baseline tumor burden
- Intact immune system (for immunotherapy)

5-year OS after nivolumab therapy associated with lower baseline tumor burden in 270 patients on CA209-003

Tumor type, tumor burden (mm)	Alive at 5 yrs	Dead at 5 yrs	P-value
Melanoma	n = 30	n = 77	.043
median	75	111	
range	22-374	10-377	
RCC	n = 9	n = 25	.054
median	98	139	
range	42-236	43-615	
NSCLC	n = 16	n = 113	.508
median	83	95	
range	11-291	10-292	
All tumor types	**n = 55**	**n = 215**	**.024**
median	**88**	**109**	
range	**11-374**	**10-615**	

Topalian et al., JAMA Oncol 2019

Objective response and 5-year survival after nivolumab therapy significantly associated with higher baseline ALC



Patients with melanoma, RCC, or NSCLC

Topalian et al., JAMA Oncol 2019

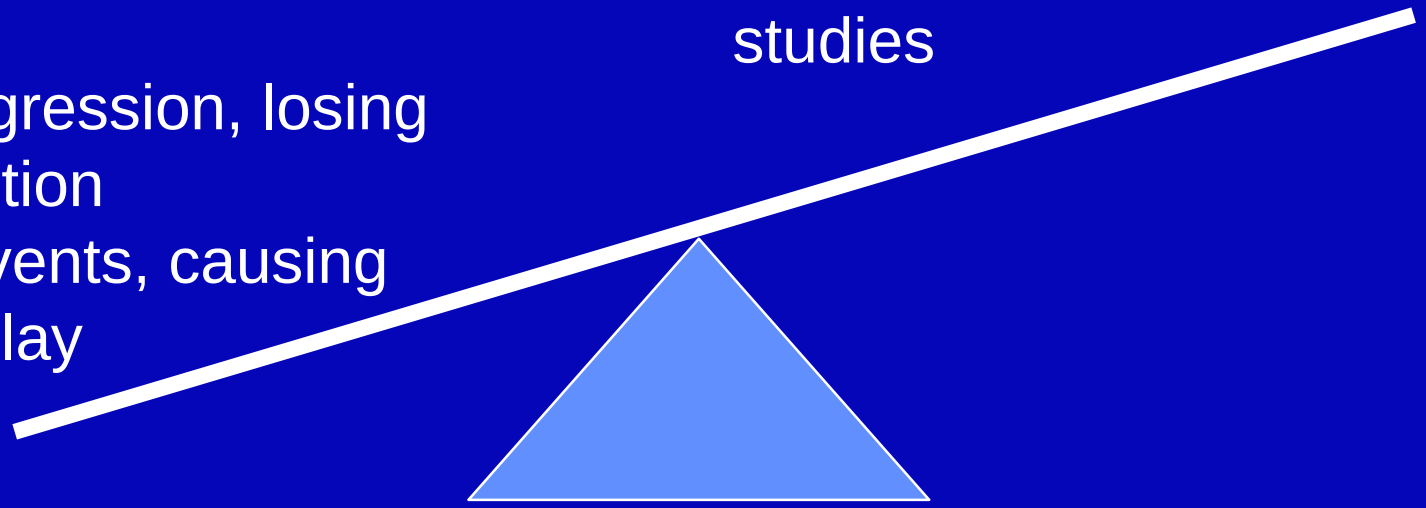
Neoadjuvant therapy trial design considerations

Benefits

- Tumor reduction before surgery
- Pathologic response as surrogate marker for RFS and OS
- Adequate tissues for in-depth biomarker studies

Risks

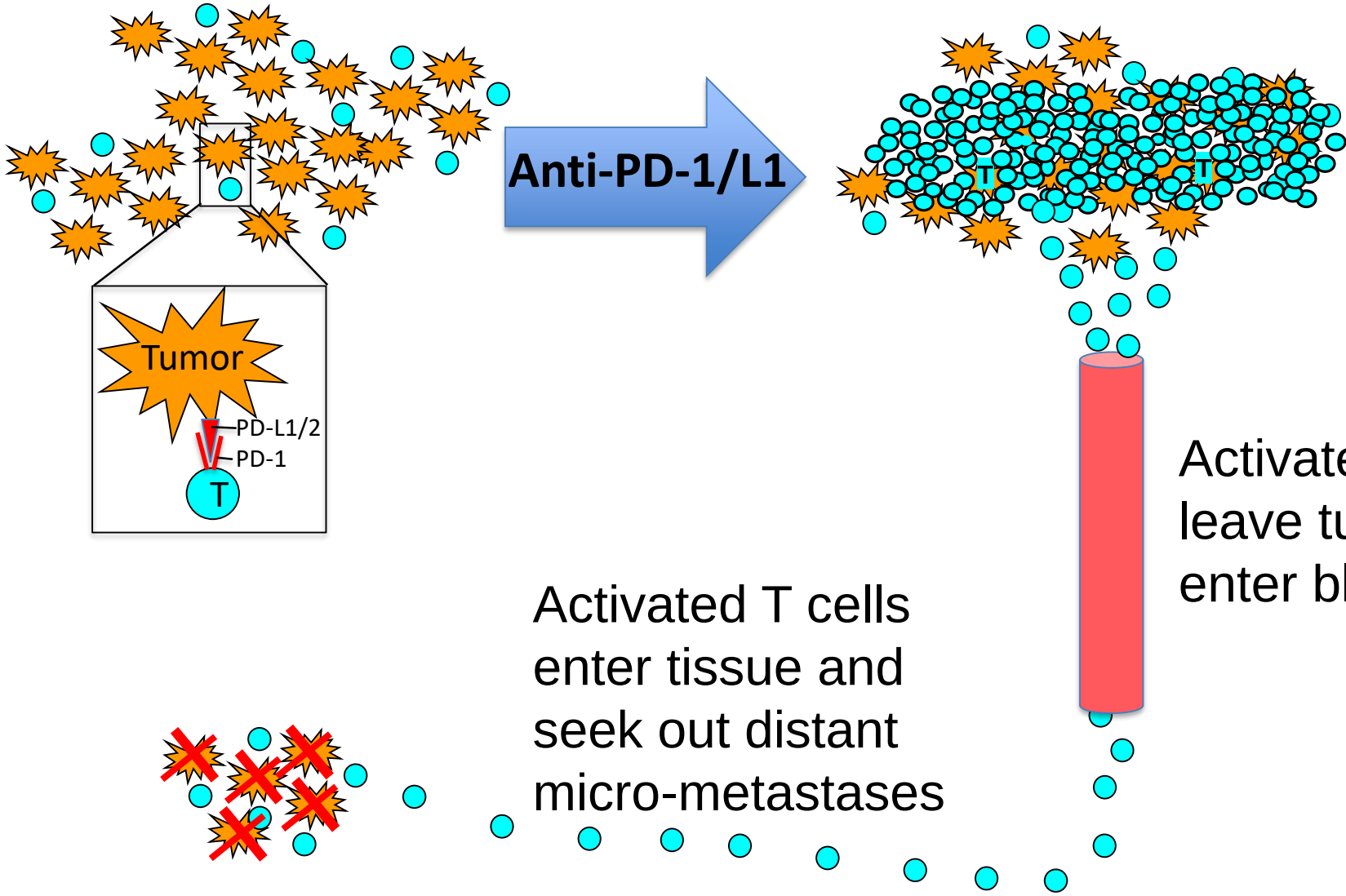
- Tumor progression, losing surgical option
- Adverse events, causing surgical delay



Surgical issues encountered with neoadjuvant therapies

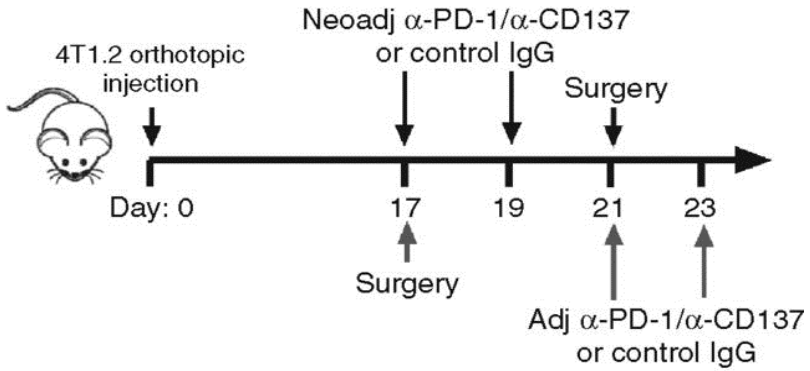
- What is a “safe” preoperative treatment interval?
- Regressed tumors may be difficult to locate for resection.
- In patients with regressing tumors, what should be the extent of surgery? Is surgery needed at all?
- Is there a role for SOC adjuvant therapy (TKI, immunotherapy)?

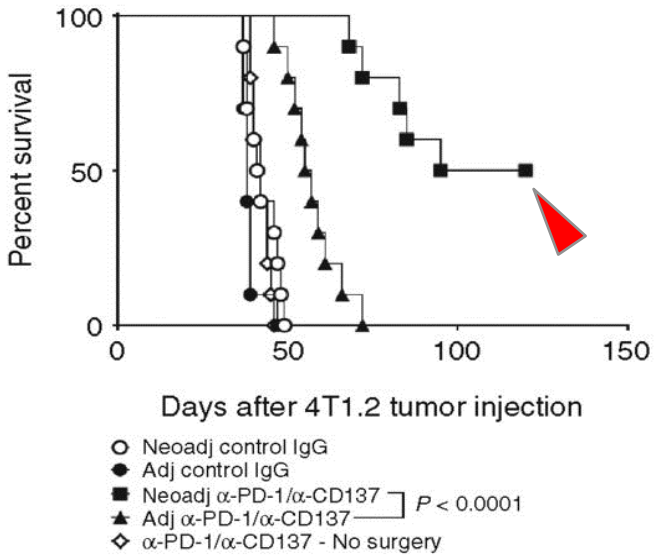
Special immunotherapy MOA considerations: neoadjuvant therapy as a primer for systemic antitumor T cell responses

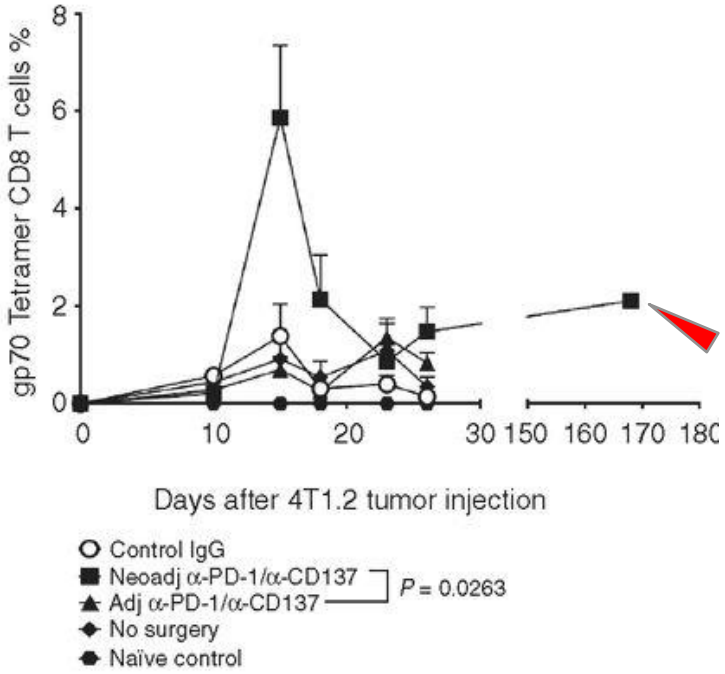


Pardoll, AACR 2018

Improved survival and heightened systemic antitumor immunity with neoadjuvant vs adjuvant immunotherapy in a metastatic breast cancer model

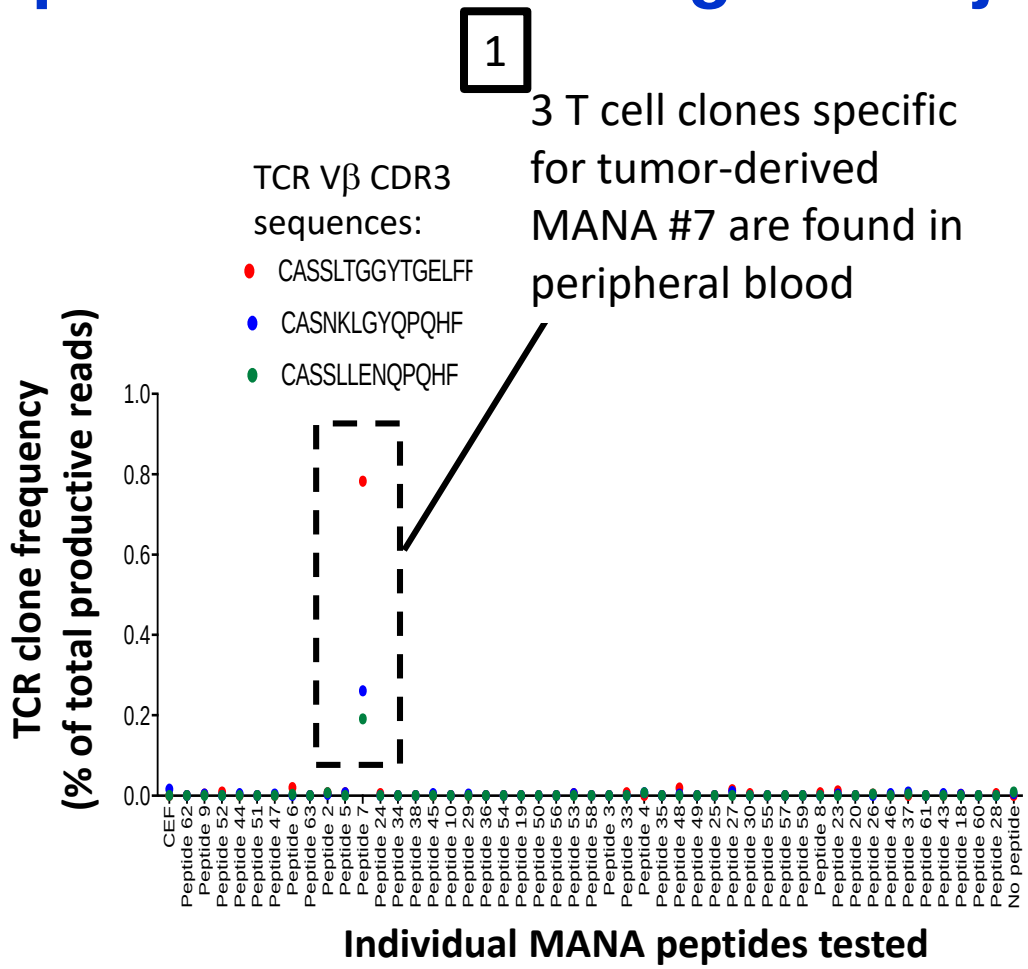






Liu et al., Cancer Discov 2016

T cells specific for a dominant tumor antigen expand in peripheral blood during neoadjuvant nivo treatment for NSCLC

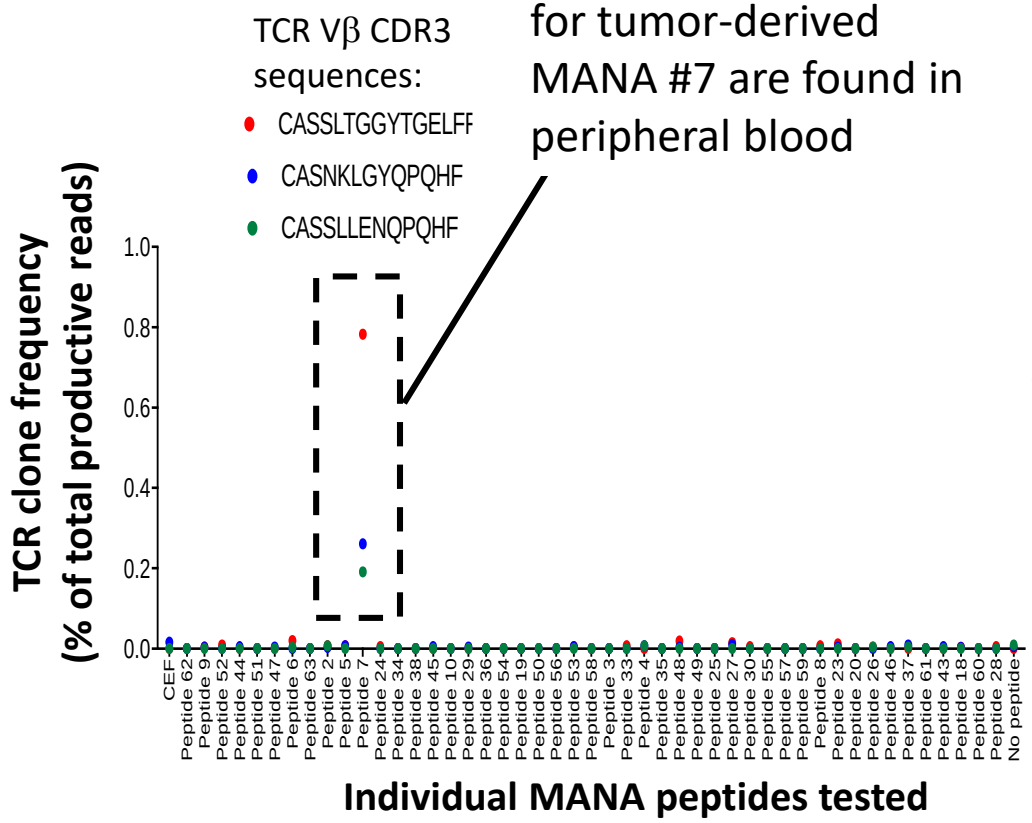


Forde, Chaft et al., NEJM 2018

T cells specific for a dominant tumor antigen expand in peripheral blood during neoadjuvant nivo treatment for NSCLC

1

3 T cell clones specific for tumor-derived MANA #7 are found in peripheral blood



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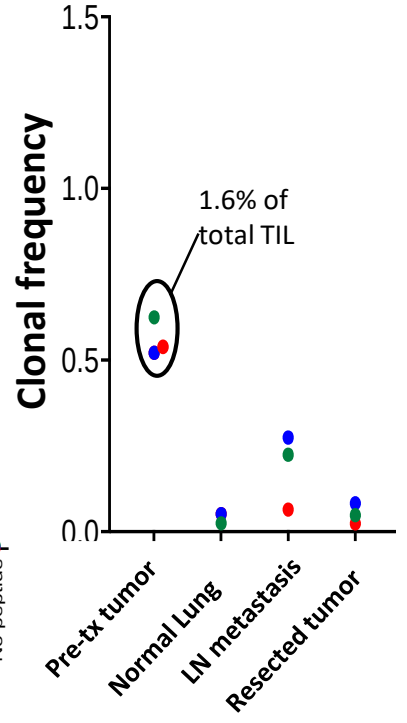
MANA#7-specific T cell clones found in tumor and LN



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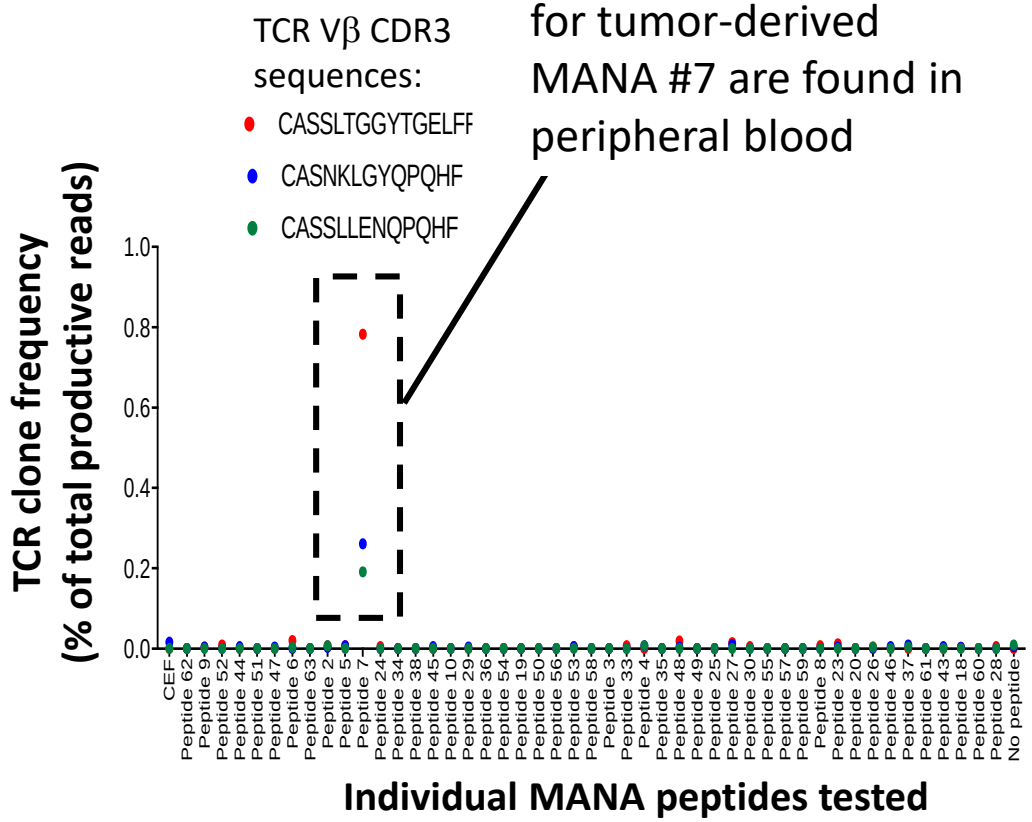

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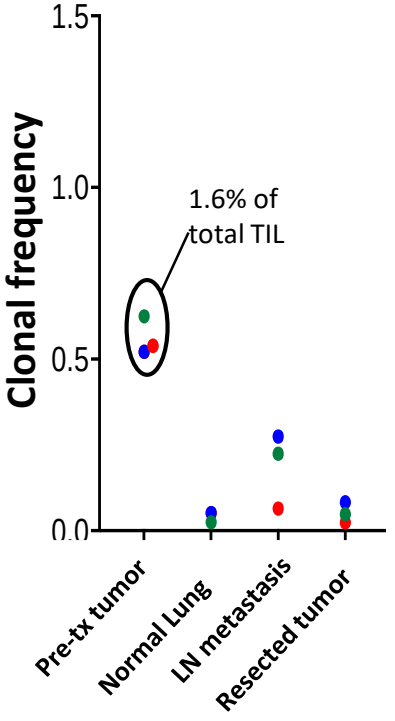
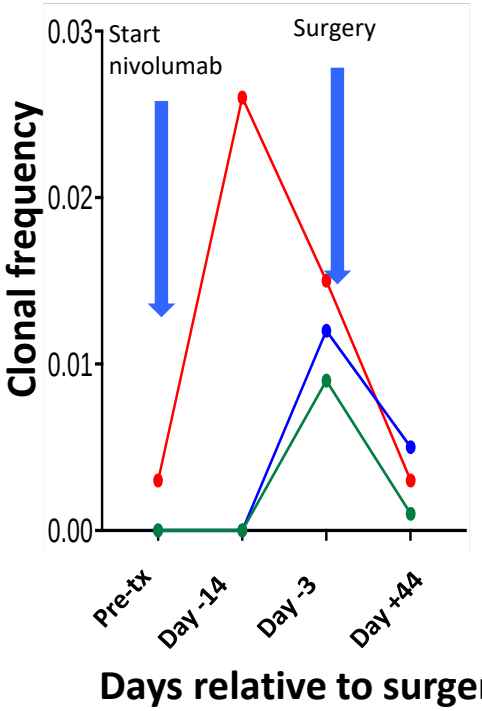


3

Frequency of MANA #7-specific T cell clones in peripheral blood changes over time



Forde, Chaft et al., NEJM 2018

Thirty-nine “neoadjuvant melanoma” trials listed in ClinicalTrials.gov (as of Feb. 2019)

- Trials cross the spectrum of systemic and localized approaches.
  - Immunotherapy, systemic + intratumoral (26)
  - Kinase inhibitor combos (9)
  - Kinase inhibitor and IO combos (2)
  - Radiotherapy, chemotherapy

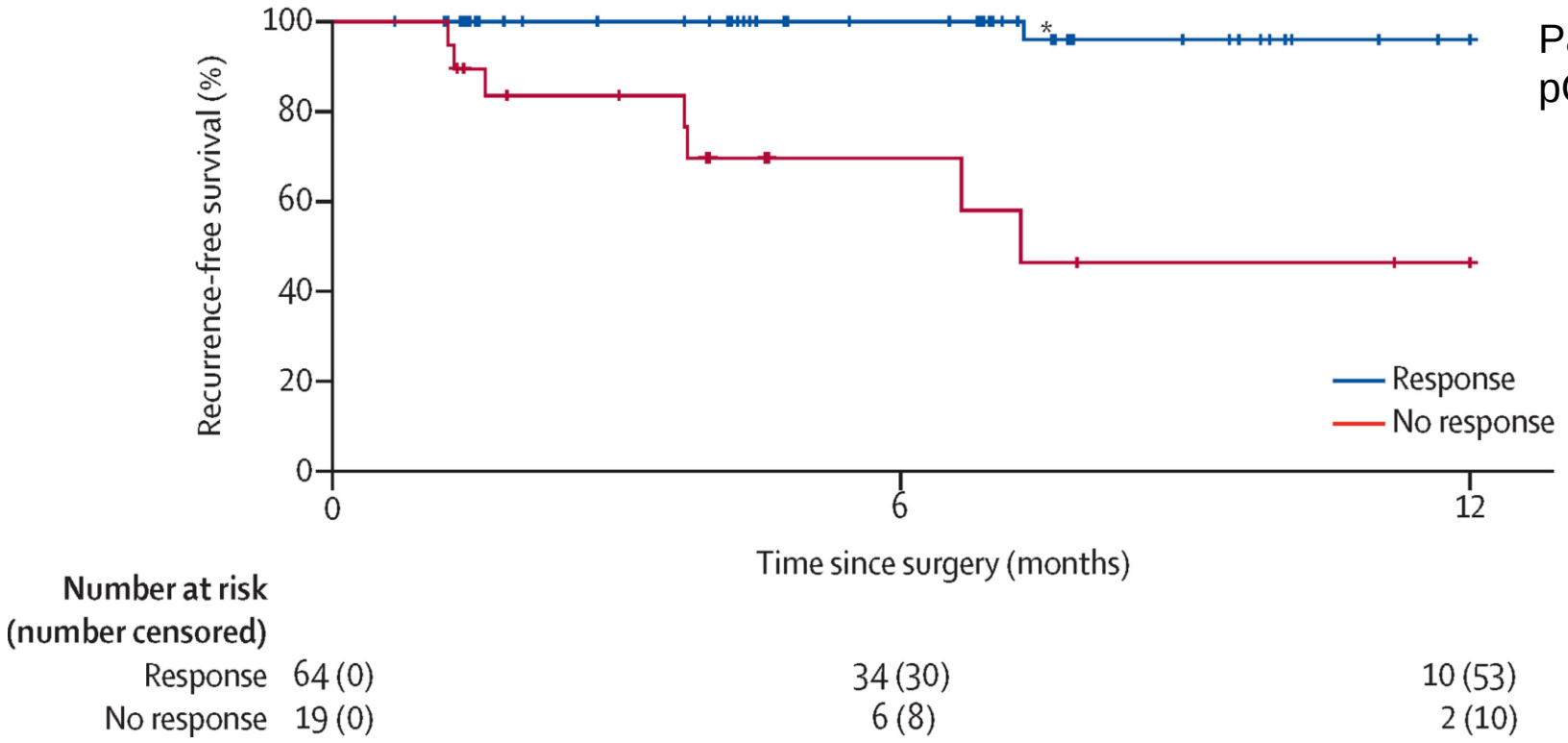
- Trials are at various stages of activity:
  - Not yet recruiting (1)
  - Recruiting (17)
  - Active, not recruiting (5)
  - Completed (8)
  - Suspended/terminated/withdrawn (8)

- Trial sponsors are primarily academic: investigator-sponsored (31), industry-sponsored (5), NCI (3)

Neoadjuvant immunotherapy in melanoma: striking a balance between risk and benefit

	Amaria, Nat Med 2018	Blank, Nat Med 2018	Huang, Nat Med 2019	Rozeman, Lancet Oncol 2019
No. patients, AJCC stage	23 pts, stage III-IV	10 pts, stage IIIB/C	27 pts, stage III-IV	86 pts, stage IIIB/C (LN mets only)
Treatment period	Preop 2 months, postop 6 months	Preop 6 weeks, postop 6 weeks	Preop 3 weeks, postop 1 year	Preop 6 weeks; 3 randomized arms
Anti-PD-1 mono: ORR	25%	[Not done]	Not provided	[Not done]
Pathologic response	25% pCR		30% = pCR + MPR	
Gr ≥3 AEs	8%		Not provided	
Ipi/nivo combo: ORR	73%	50%	[Not done]	35 – 63%
Pathologic response	45% pCR	78% = pCR + MPR + pPR		65-80% = pCR + MPR + pPR
Gr ≥3 AEs	73%	90%		20-50%
Risk:benefit	**Trial stopped early due to safety concerns**	**Only 1/10 patients completed therapy due to toxicity**	**Treatment safe and moderately effective.**	**6 wks nivo 3 + ipi 1 identified as optimal regimen**

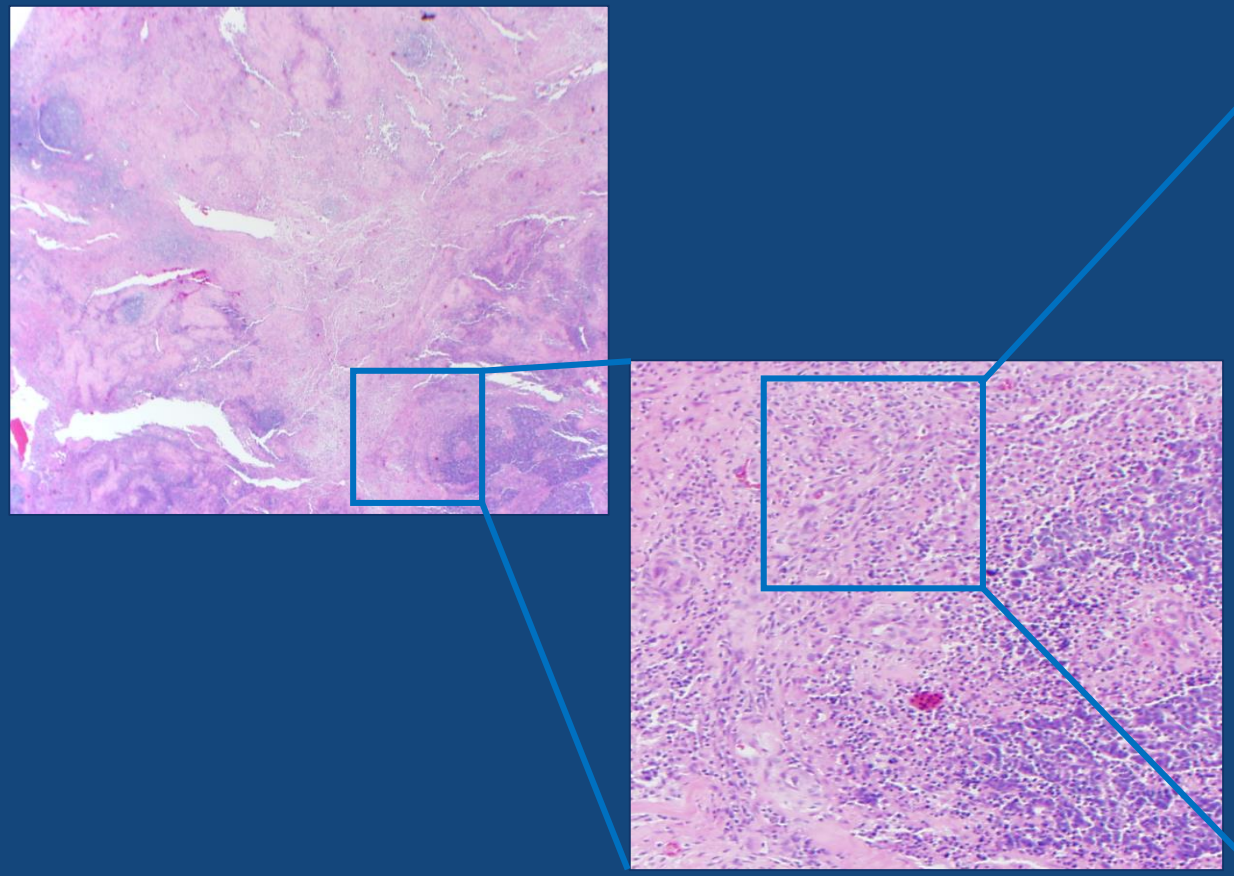
Pathologic response as an early surrogate marker for relapse-free survival after neoadjuvant anti-CTLA-4 + anti-PD-1 in stage 3 melanoma

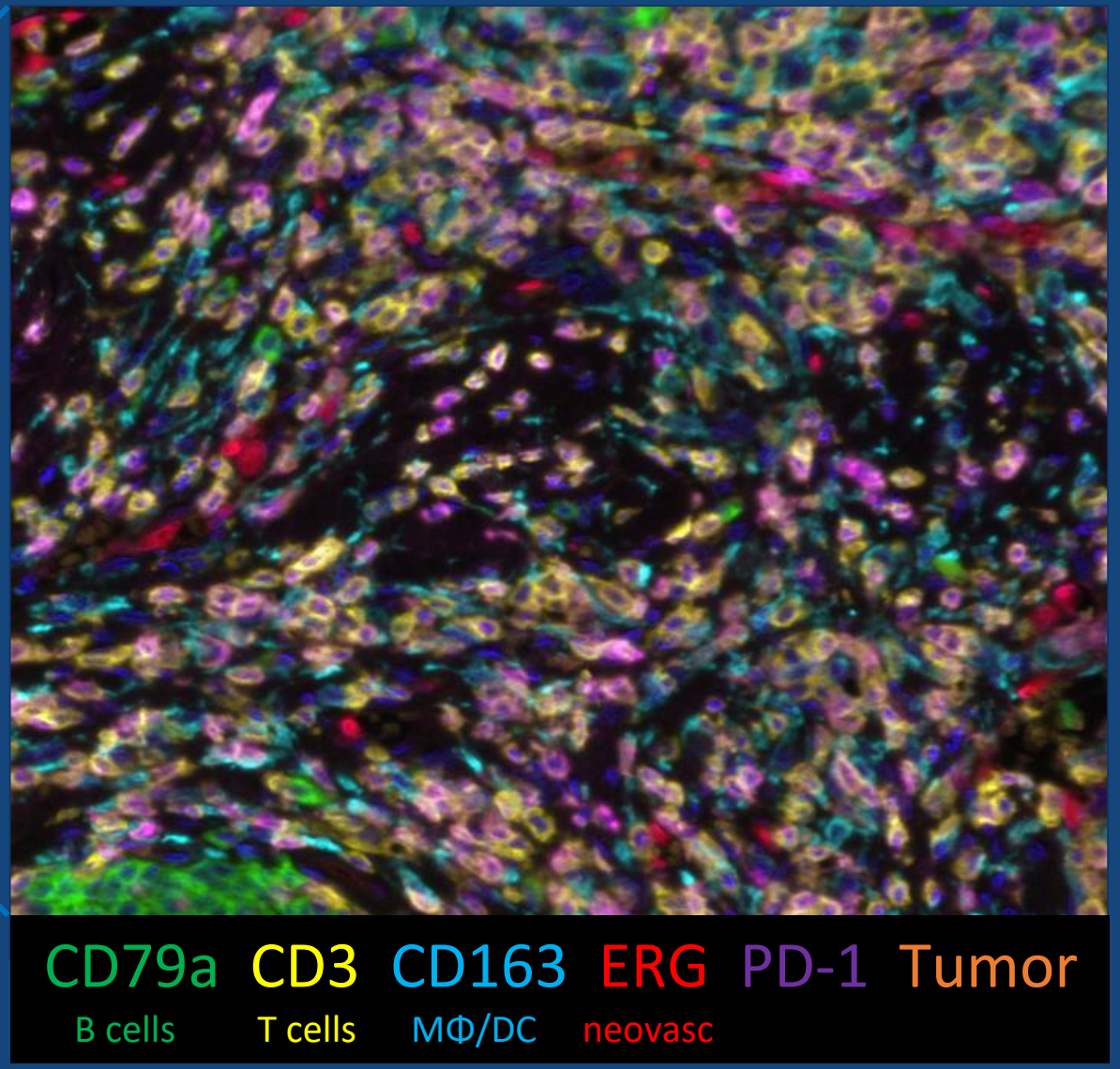


Pathologic response =
pCR + MPR + pPR

Rozeman et al., Lancet Oncol 2019

Neoadjuvant studies offer new opportunities to unravel therapeutic mechanism-of action





Major pathologic response of MCC lymph node metastasis to neoadjuvant nivo
(*J. Taube; ASCO 2018*)

Future development

- TKIs and modern immunotherapies provide safe and effective treatment options for melanoma in the advanced unresectable or adjuvant settings, and should be evaluated in the neoadjuvant setting.
- Risk:benefit is a primary consideration for neoadjuvant therapy in operable patients who might be cured by surgery alone.
- MOA considerations for neoadjuvant immunotherapies vs. TKIs probably differ.
- Pathologic response to neoadjuvant therapy provides a potential surrogate for RFS and OS.
- Future development of safe and effective neoadjuvant therapies for melanoma will require close collaborations among stakeholders from diverse clinical specialties and research sectors.