Neoadjuvant immune checkpoint blockade: a window into treatment response and primary resistance

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Disclosure Information
Suzanne L. Topalian

Consultant for: AstraZeneca, Dragonfly Therapeutics, Five Prime Therapeutics, Immunocore; and (spouse) Amgen, DNAtrix, Dracen Pharmaceuticals, Dynavax, Ervaxx, Immunomic Therapeutics, Janssen, RAPT, WindMIL

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Stock/stock options: Dragonfly Therapeutics, Five Prime Therapeutics; and (spouse) Aduro, DNAtrix, Dracen, Ervaxx, RAPT, Tizona, Trieza, WindMIL

Patents licensed through institution (spouse): Aduro, Arbor Pharmaceuticals, BMS, Immunomic Therapeutics, NexImmune, WindMIL

- and -

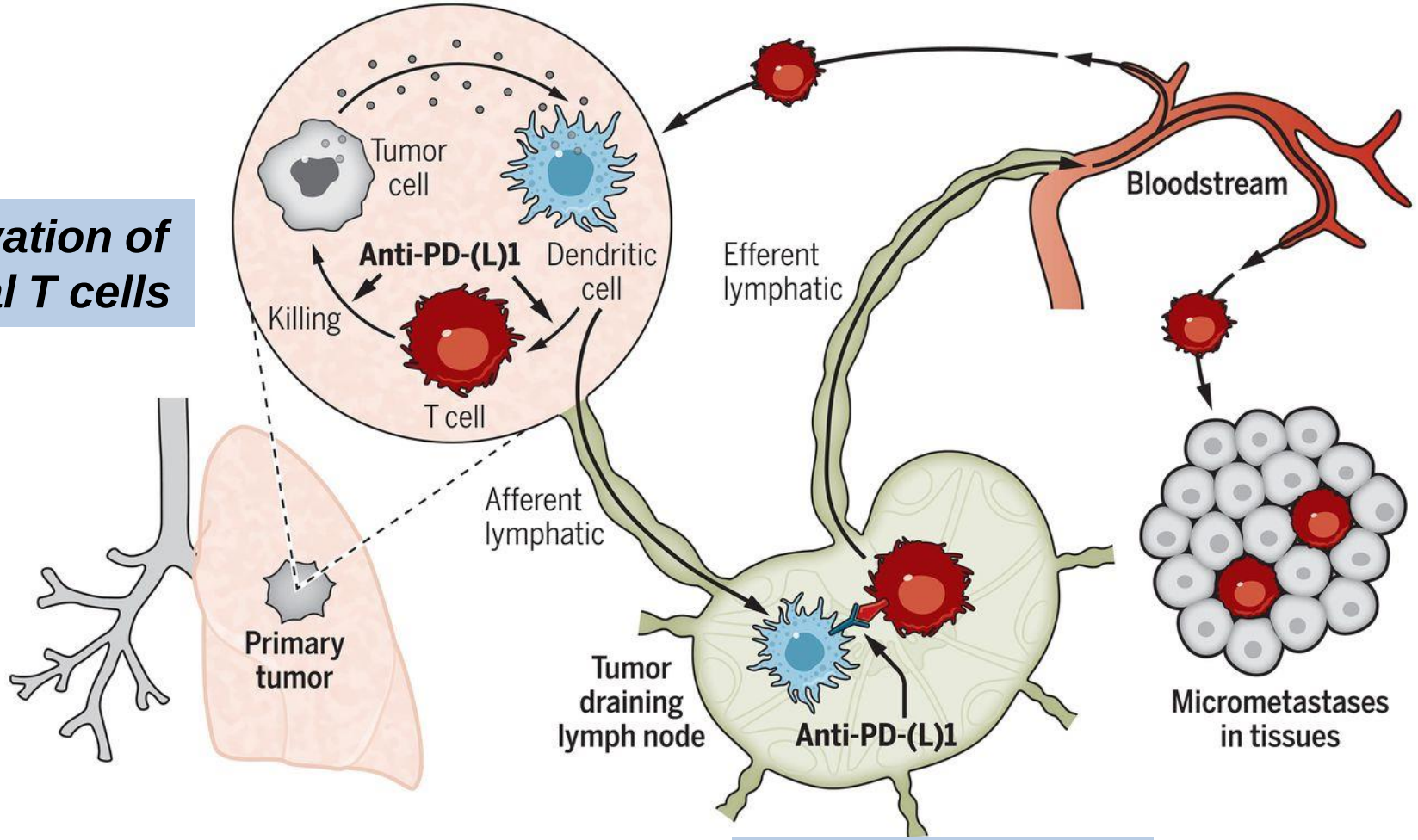
I will discuss investigational uses for anti-PD-(L)1 drugs in my presentation.

BACKGROUND: In the advanced unresectable disease setting, immune checkpoint blockade (ICB) benefits only ~20% of cancer patients across-the-board. Most studies of treatment response/resistance have been based on tumor needle biopsies.

NEW TREATMENT APPROACH: Prevent progression of early-stage high-risk cancers by targeting micrometastases with *neoadjuvant (pre-surgical)* ICB.

Neoadjuvant PD-(L)1 blockade as a primer for systemic antitumor T cell responses

In situ activation of intratumoral T cells

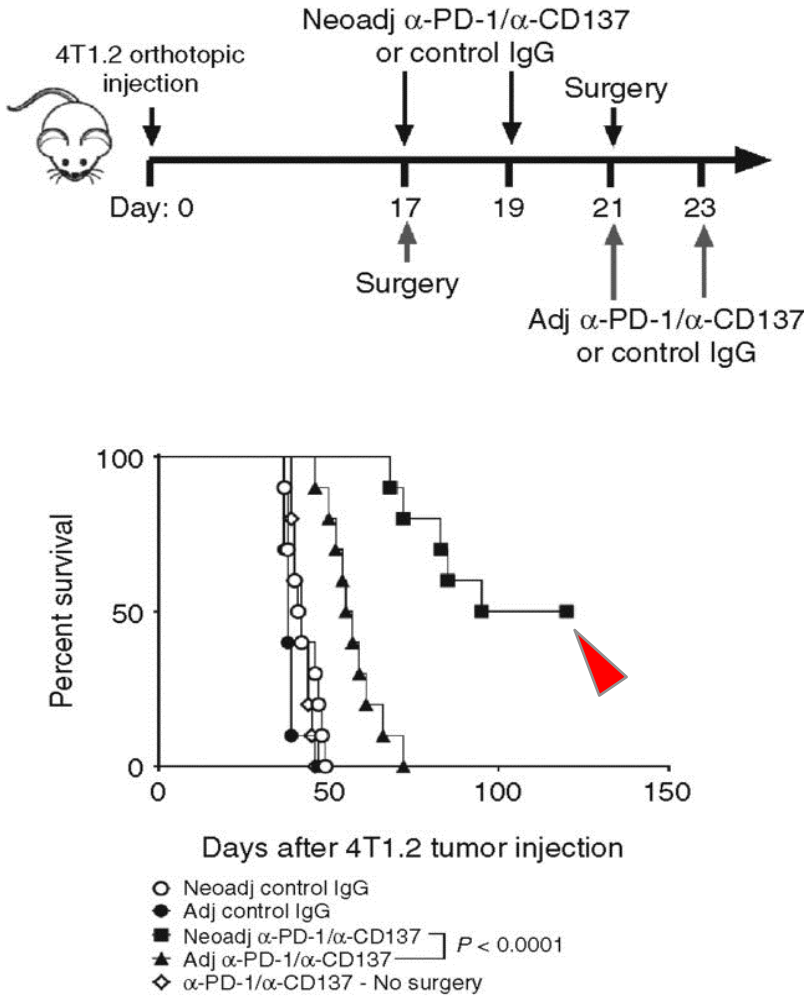


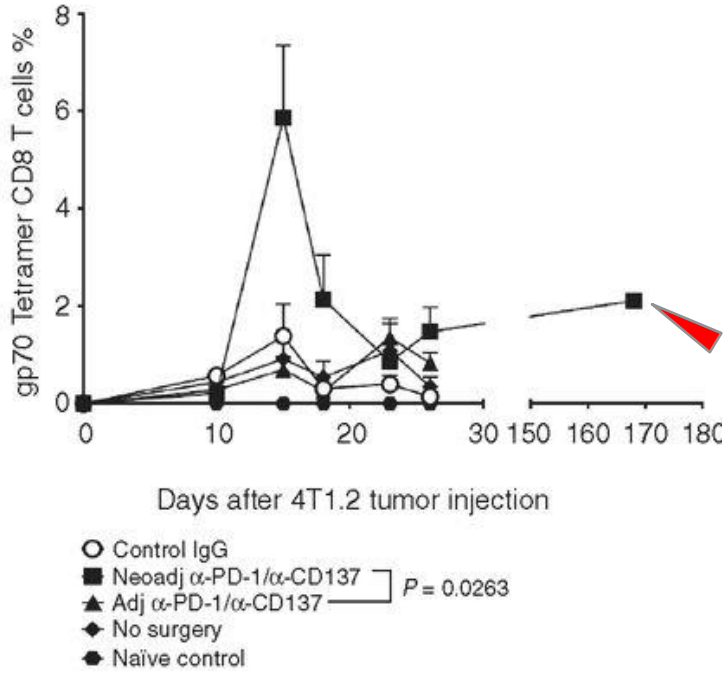
Enhanced DC stimulation of T cells in TDLN

Adapted from Topalian, Taube & Pardoll, Science 2020;367:eaax0182

Science AAAS

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





Liu et al., Cancer Discov 2016

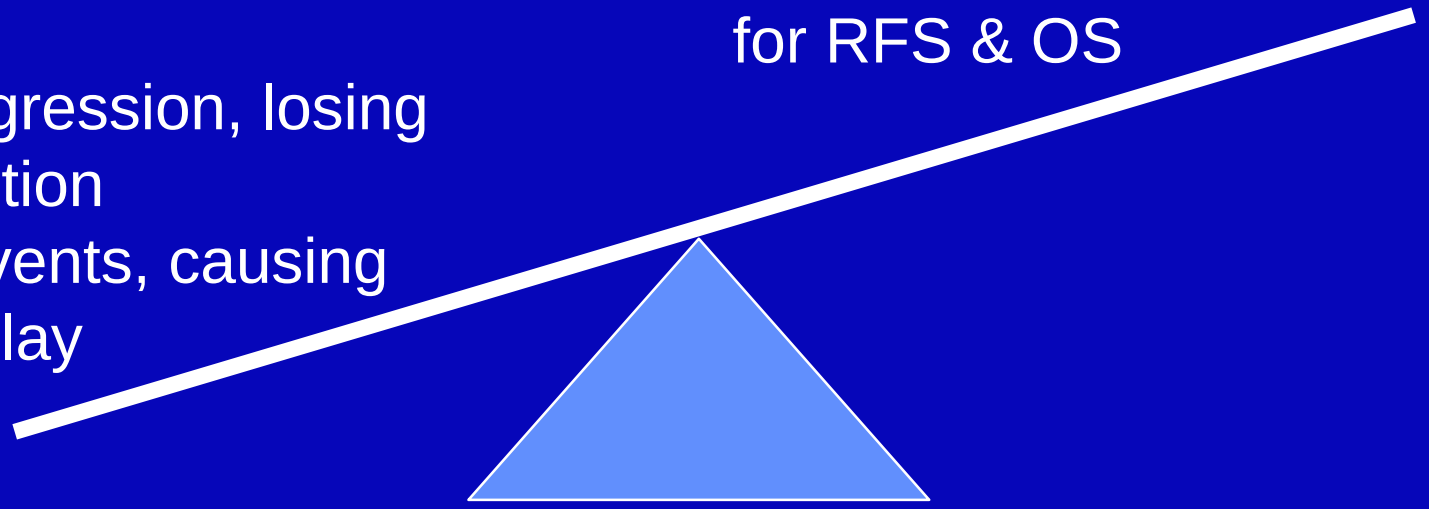
Neoadjuvant immunotherapy considerations

Benefits

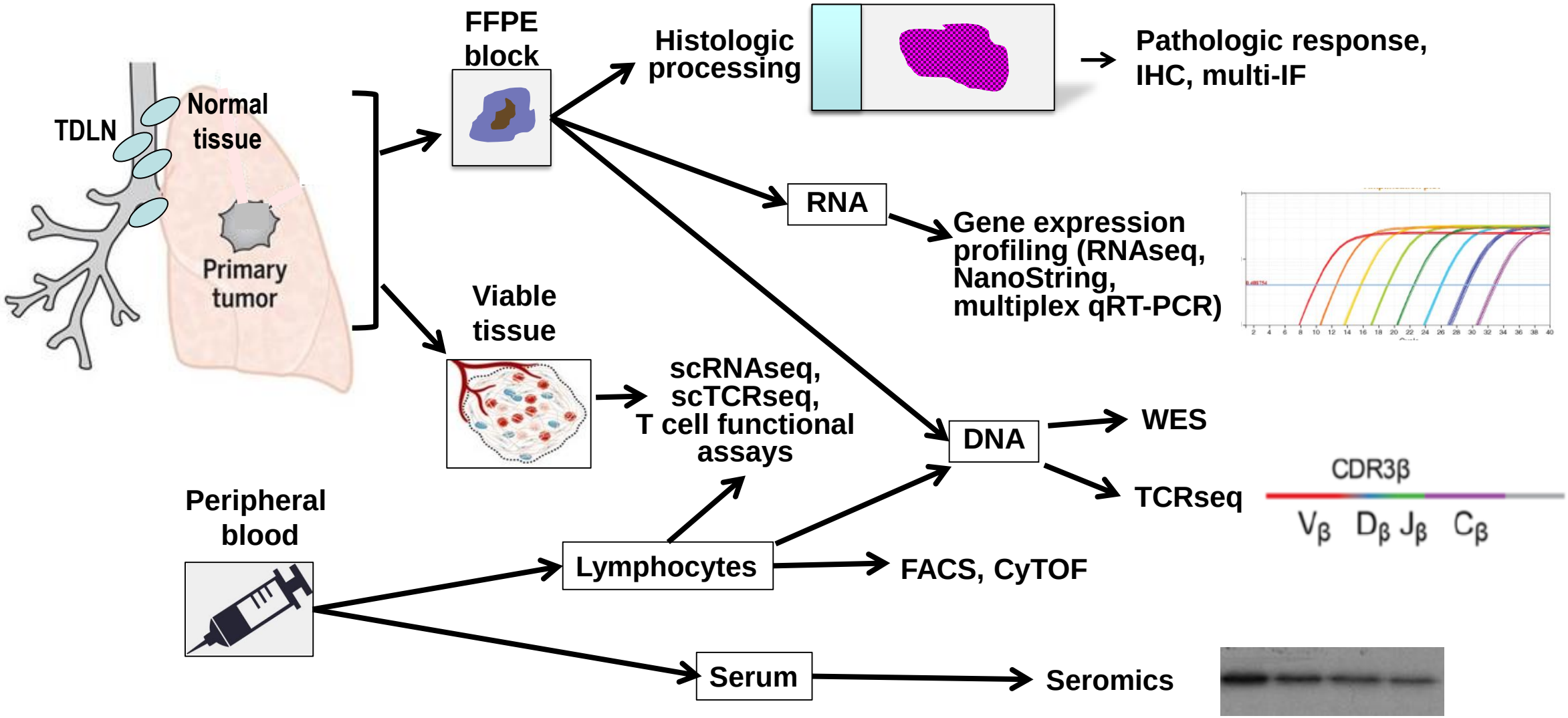
- Tumor reduction before surgery
- Adequate tissues for in-depth biomarker studies
- Pathologic response as a surrogate marker for RFS & OS

Risks

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

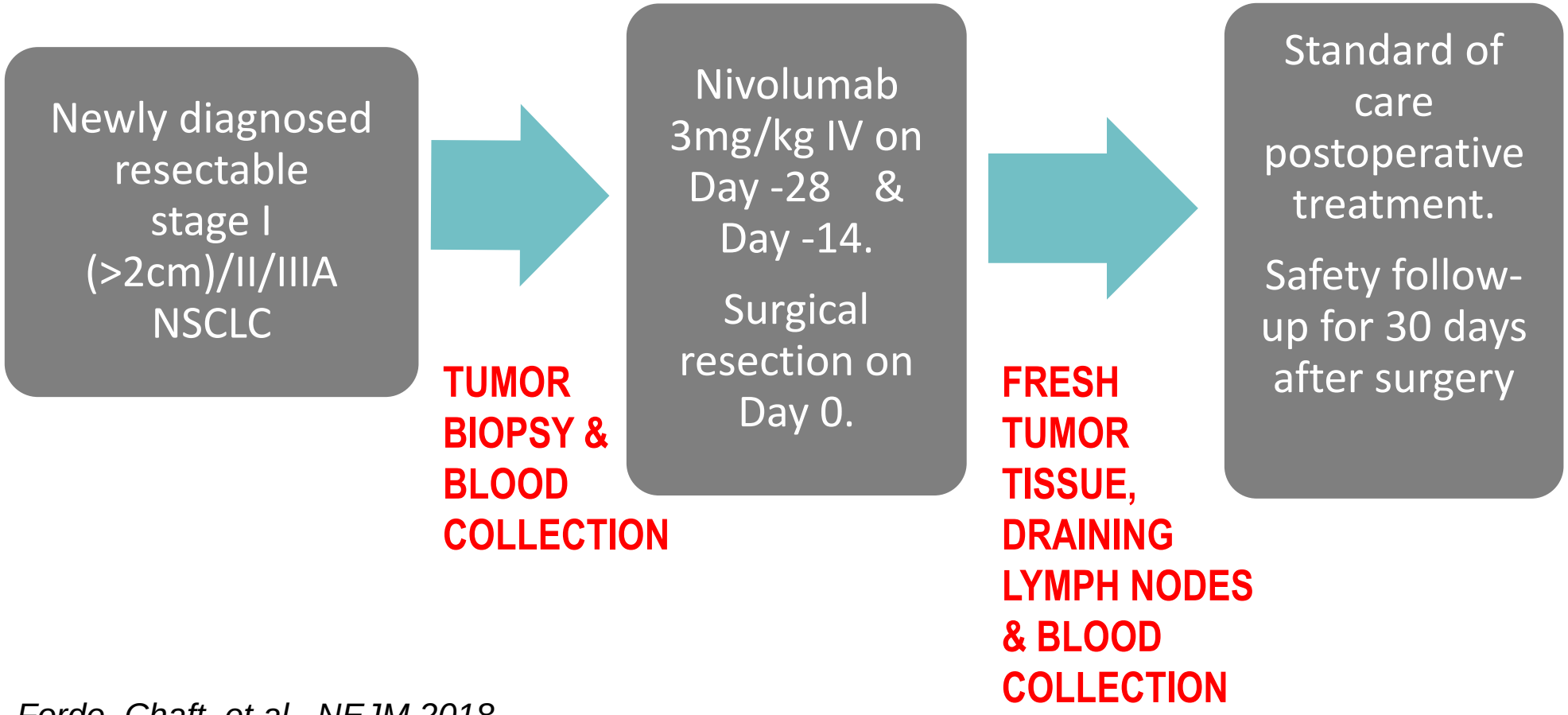


Neoadjuvant ICB opens new opportunities for correlative studies to understand treatment response and primary resistance



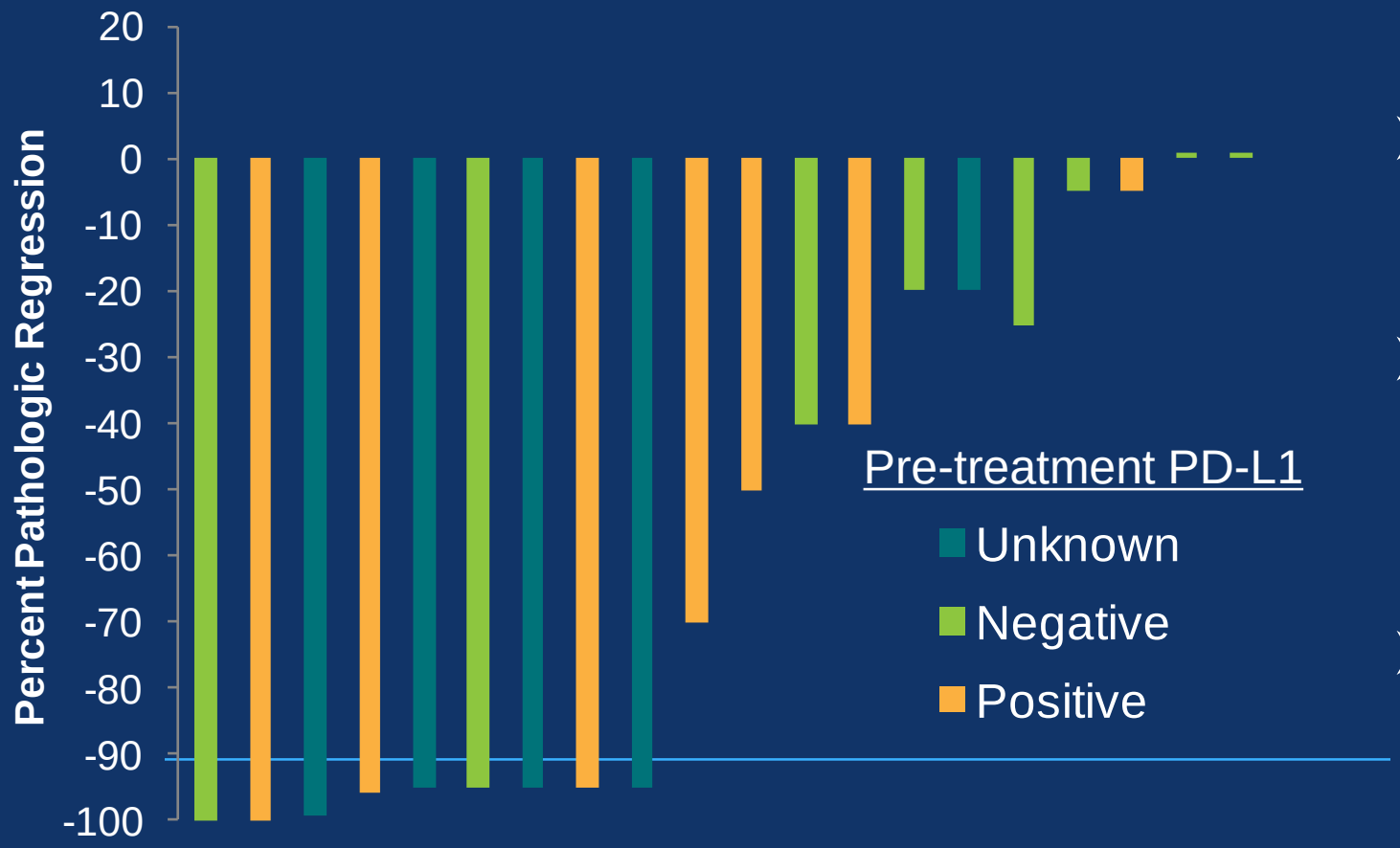
Neoadjuvant nivolumab in resectable non-small-cell lung cancer

STUDY DESIGN & ENDPOINTS



Forde, Chaft, et al., NEJM 2018

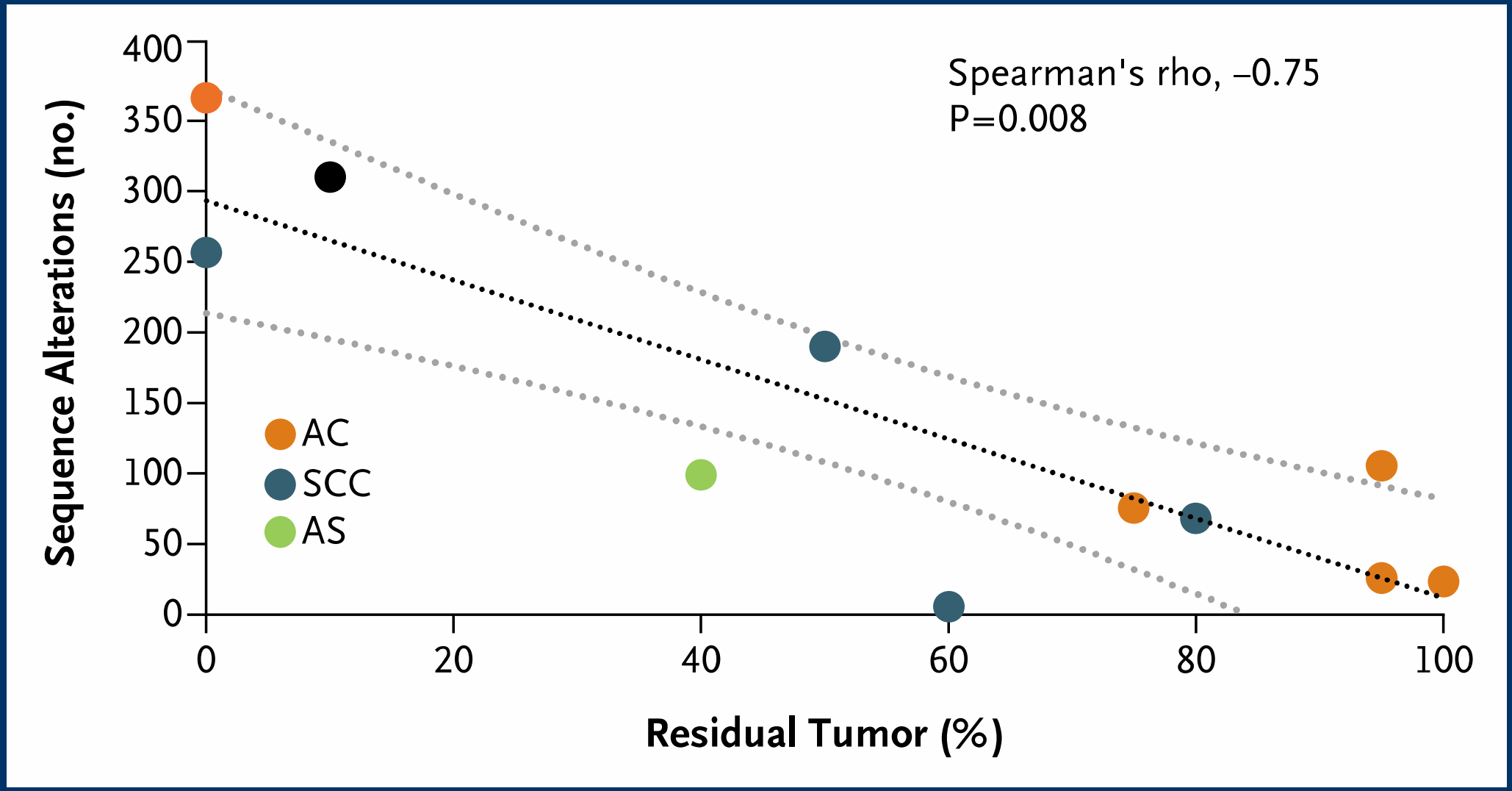
Pathologic response following 4 weeks of neoadjuvant nivolumab in NSCLC



- RECIST response occurred in **2/21 (*10%*)** patients
- Major Pathologic Response (MPR) was seen in **9/20 (*45%*)** cases
- MPR defined as ≤10% residual viable tumor cells (Pataer et al., JTO 2012; Hellmann et al., Lancet Oncol 2014)

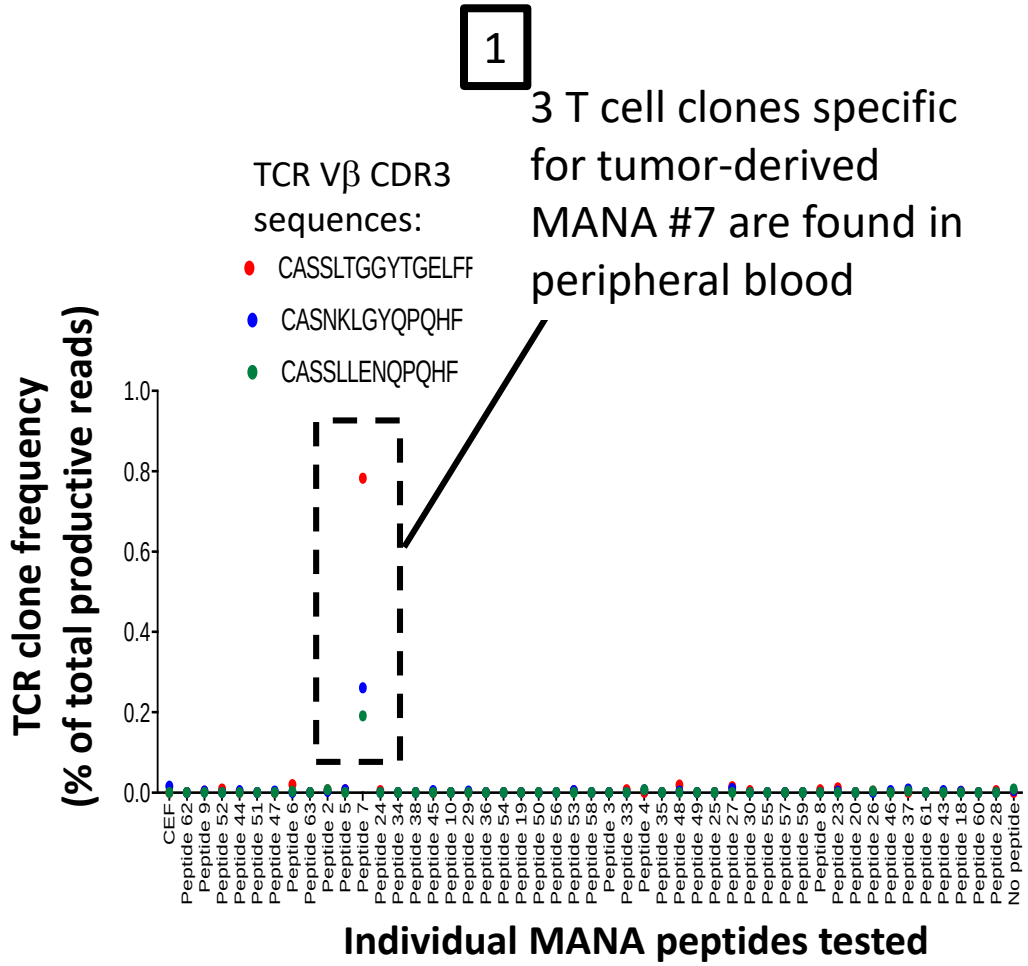
Adapted from Forde, Chaft et al., NEJM 2018

Association of tumor mutational burden with pathologic response to neoadjuvant nivolumab in NSCLC



Forde, Chaft et al., NEJM 2018

T cells specific for a dominant mutant tumor antigen expand in peripheral blood during neoadjuvant nivolumab treatment in a pathologic responder



Forde et al., NEJM 2018

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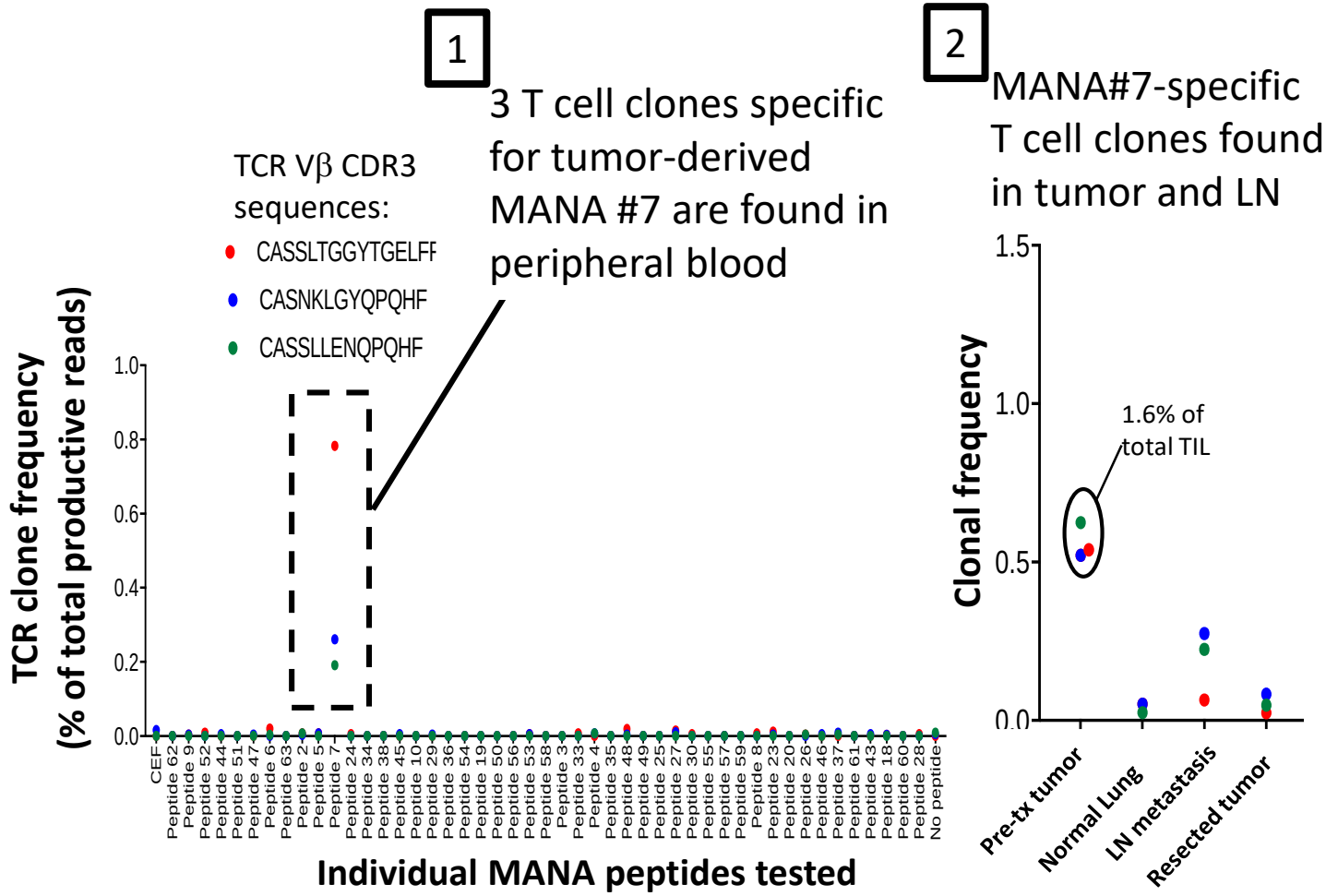
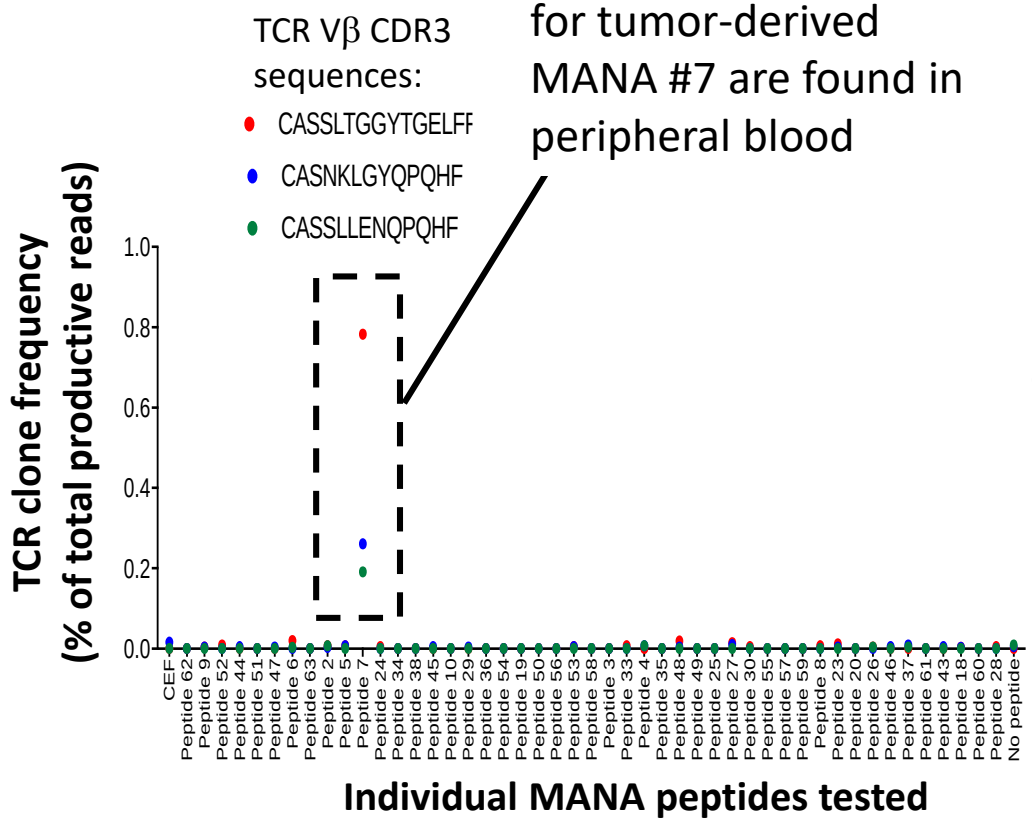


Forde et al., NEJM 2018

T cells specific for a dominant mutant tumor antigen expand in peripheral blood during neoadjuvant nivolumab treatment in a pathologic responder

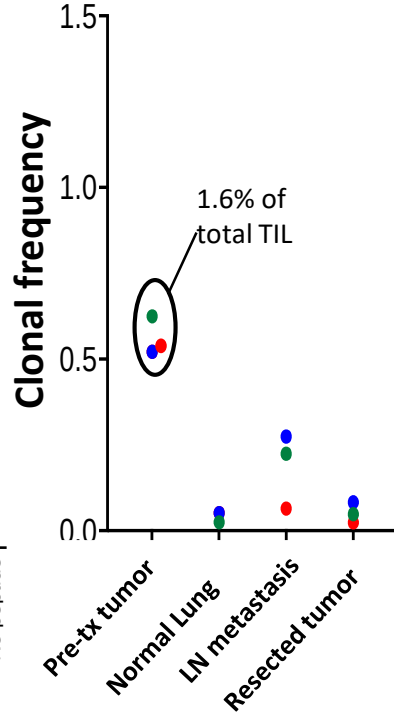
1

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



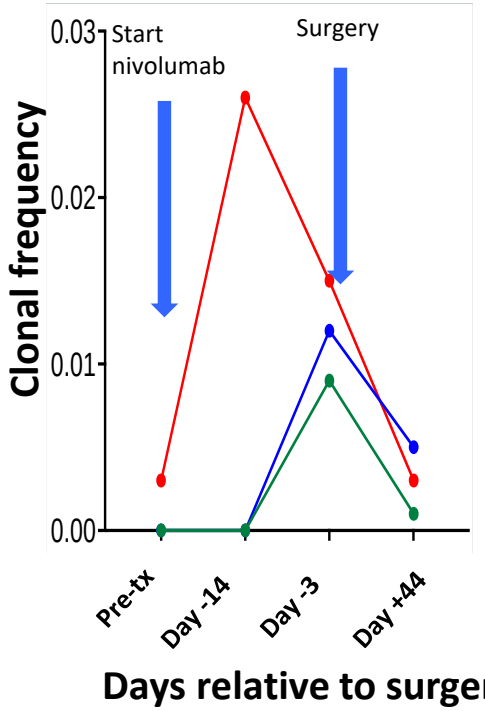
2

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



3

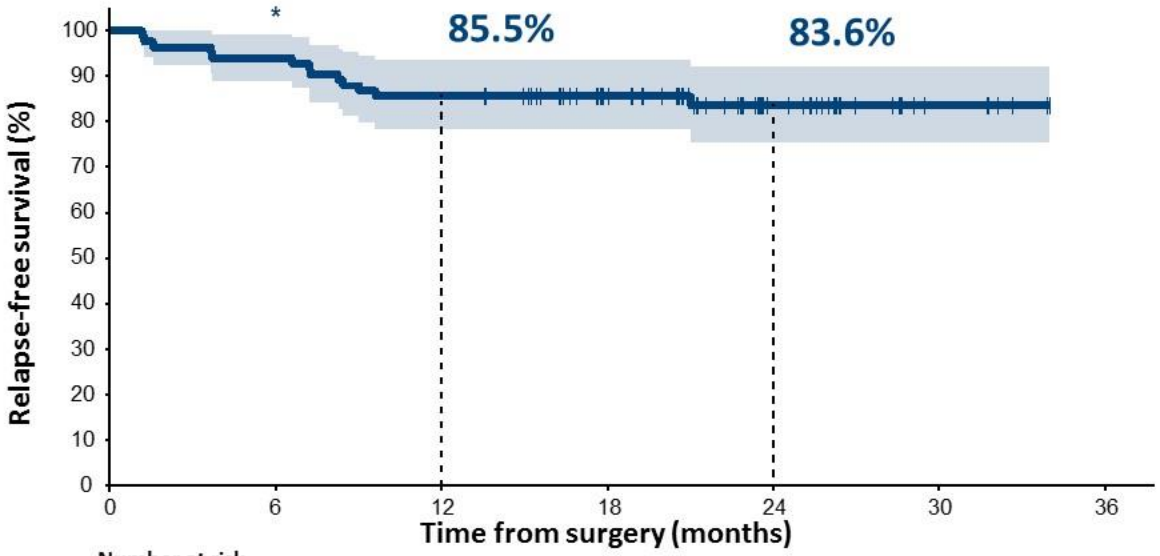
Frequency of MANA #7-specific T cell clones in peripheral blood changes over time

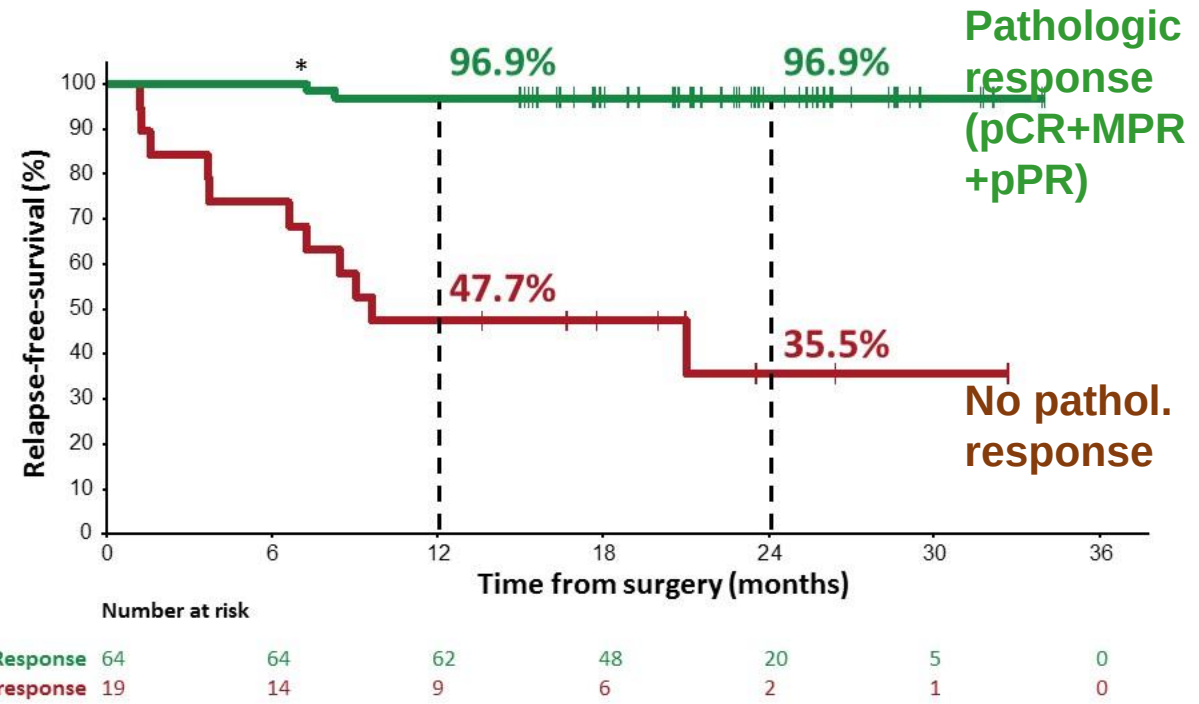


Forde et al., NEJM 2018

Neoadjuvant ipi+nivo for stage 3 melanoma: pathologic response at 6 weeks predicts RFS at 2 years

- **OpACIN-neo:** After a median follow-up of 24.6 months, only 1/64 (2%) patients with pathologic response has relapsed

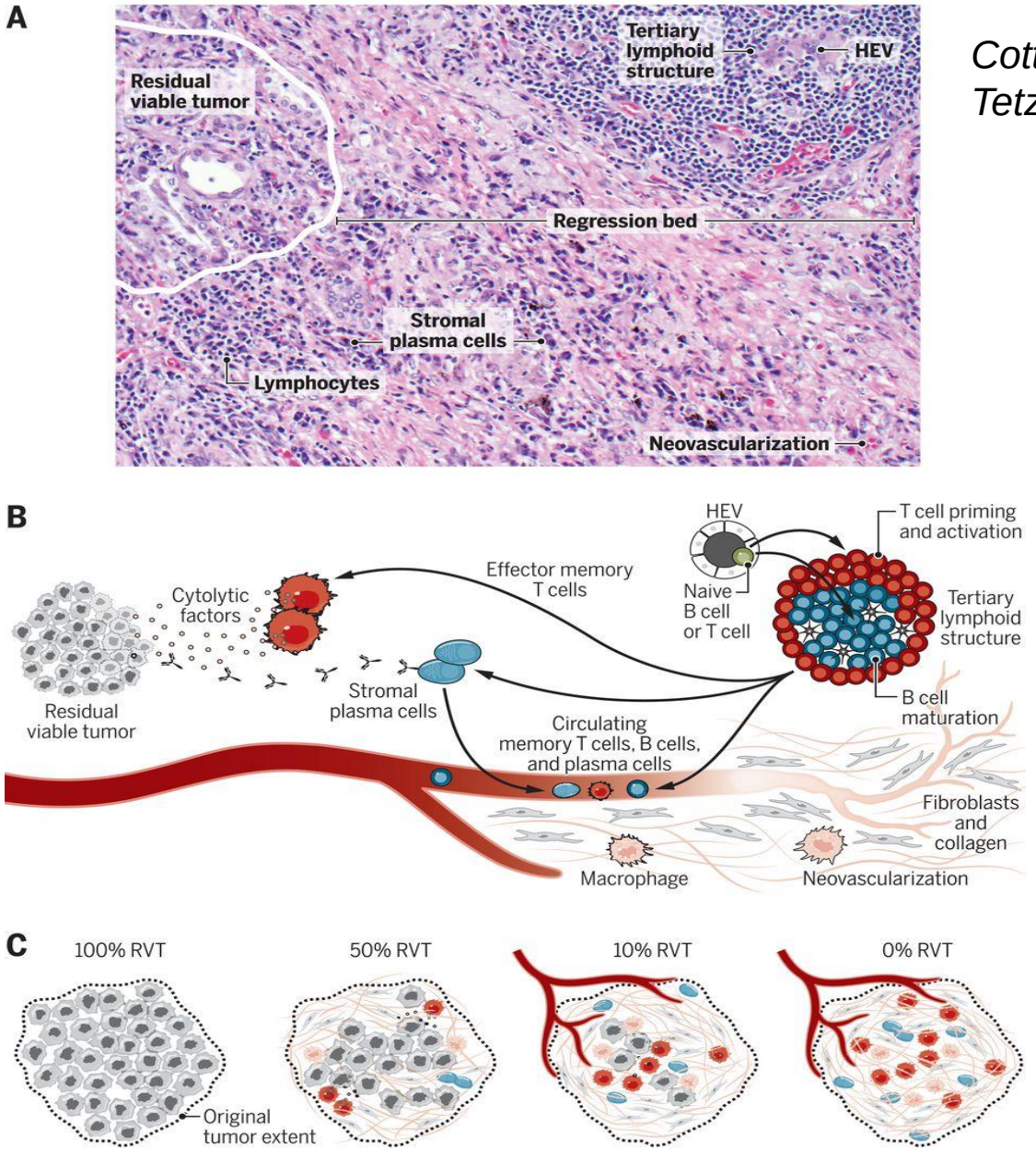




Rozeman et al., abstract 10015, ASCO 2020

* patient died due to toxicity without signs of melanoma relapse

Hallmarks of immune-mediated tumor regression

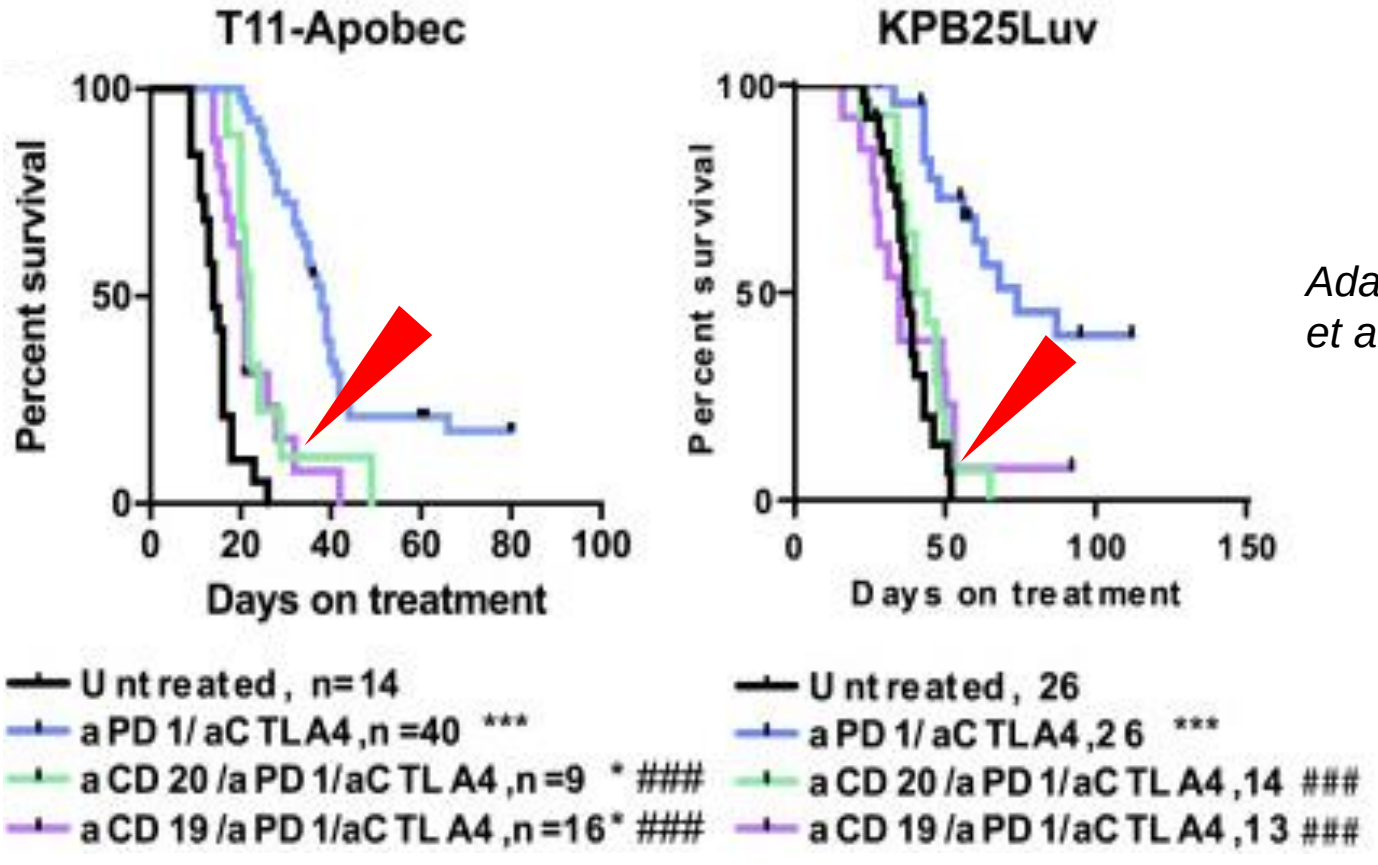


Cottrell, Taube et al., Ann Oncol 2018; Tetzlaff et al., Ann Oncol 2018.

Topalian, Taube & Pardoll, Science 2020;367:eaax0182

Science AAAS

Therapeutic effect of anti-PD-1/CTLA-4 in murine breast cancer models is *B-cell* dependent



Adapted from Hollern, Perou et al., Cell 2019

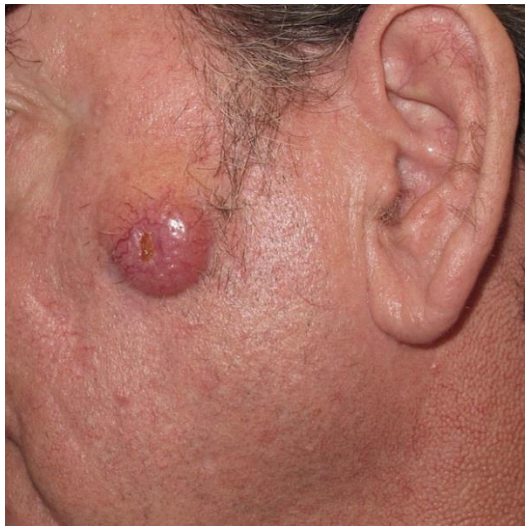
Immunologic correlates in melanoma neoadjuvant ICB studies

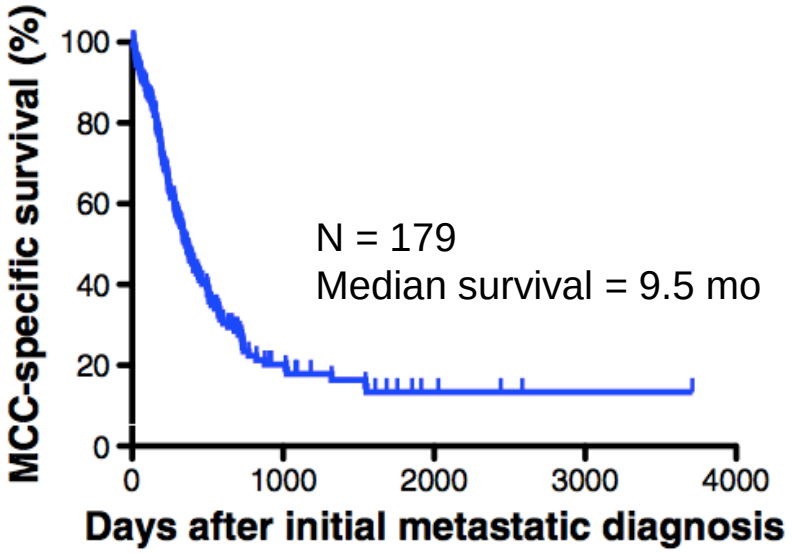
ClinicalTrials.gov identifier (citation)	NCT02519322 (Amaria et al., Nat Med 2018)	NCT02437279 (Blank et al., Nat Med 2018)	NCT02434354 (Huang et al., Nat Med 2019)	NCT02977052 (Rozeman et al., Lancet Oncol 2019)
Therapy	Anti-PD-1 +/- anti-CTLA-4	Anti-PD-1 + anti-CTLA-4	Anti-PD-1	Anti-PD-1 + anti-CTLA-4
Preoperative treatment interval	8-9 wks	6 wks	3 wks	6 wks
Immunologic correlates of clinical outcomes	CT response assoc. with ↑tumor PD-L1 at baseline, and ↑intratumoral CD8 density, lymphoid gene expression, & TCR clonality at 3-4 wks.	RFS assoc. with ↑intratumoral PD-L1, CD3, B2M, and ↑***IFNg GEP at baseline****;* and ↑ newly detected tumor-resident T cell clones in PBL at 6 wks.	RFS assoc. with ↑T cell activation & ↑***IFNg GEP in baseline tumor***; and ↑TILs with exhausted pheno at 3 wks, ↑intratumoral B cells & angiogenesis.	RFS assoc. with ↑***IFNg GEP in baseline tumor*****.**

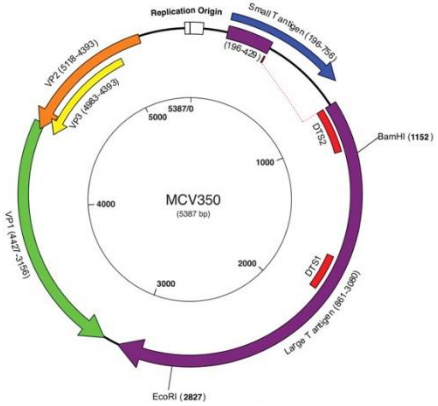
Adapted from Topalian et al., Science 2020

Merkel cell carcinoma

- ~ 2500 cases/year in the US
- Age >50, immune suppression
- **Merkel cell polyomavirus (MCPyV) present in ~80% of cases**
- >40% of MCC patients develop advanced disease







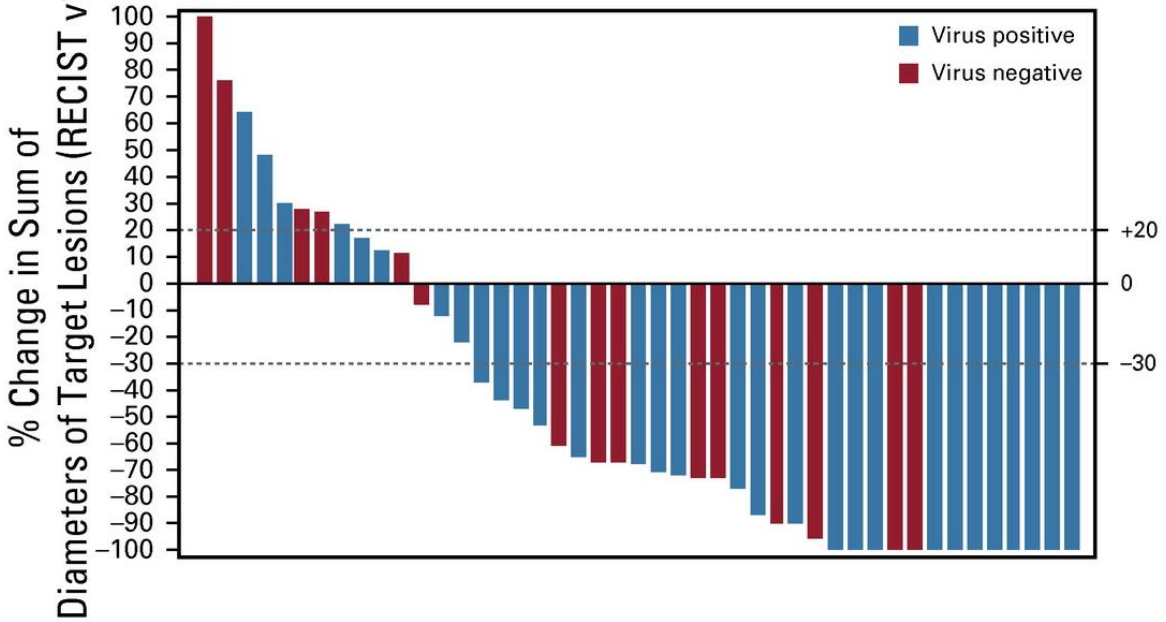
Feng et al., Science 2008

Miller, Curr Treat Options Oncol 2013

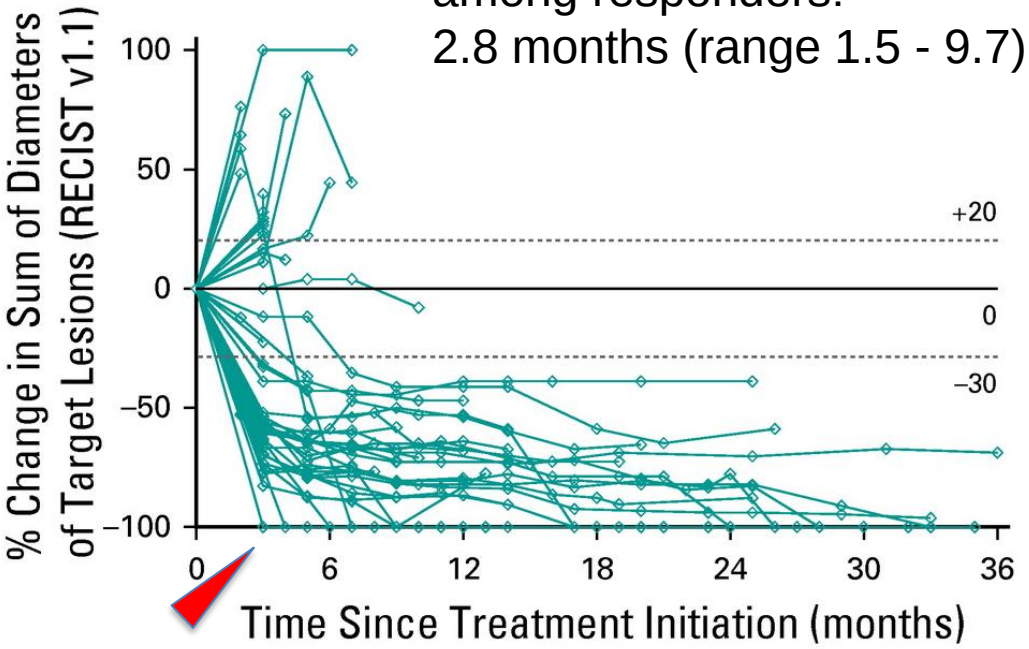
Adapted from Nghiem et al., AACR 2016

Quality vs quantity of tumor antigens: regardless of tumor viral status, advanced unresectable MCC responds rapidly and durably to first-line anti-PD-1 therapy (CITN-09, pembrolizumab)

ORR = 56%



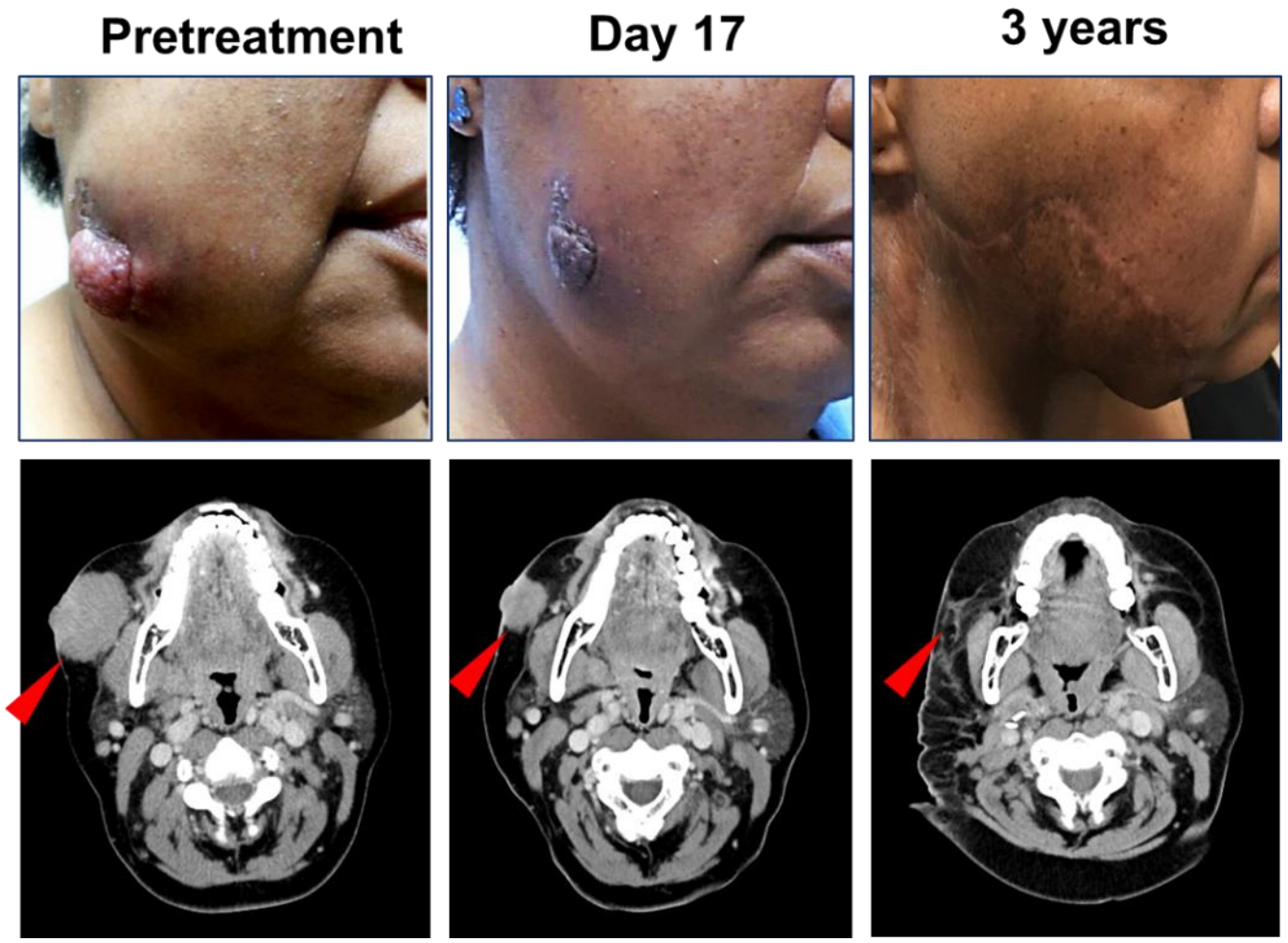
Median time to response among responders:
2.8 months (range 1.5 - 9.7)



Virus+ MCC has very low TMB
Virus- MCC has very high TMB

Nghiem et al., J Clin Oncol 2019

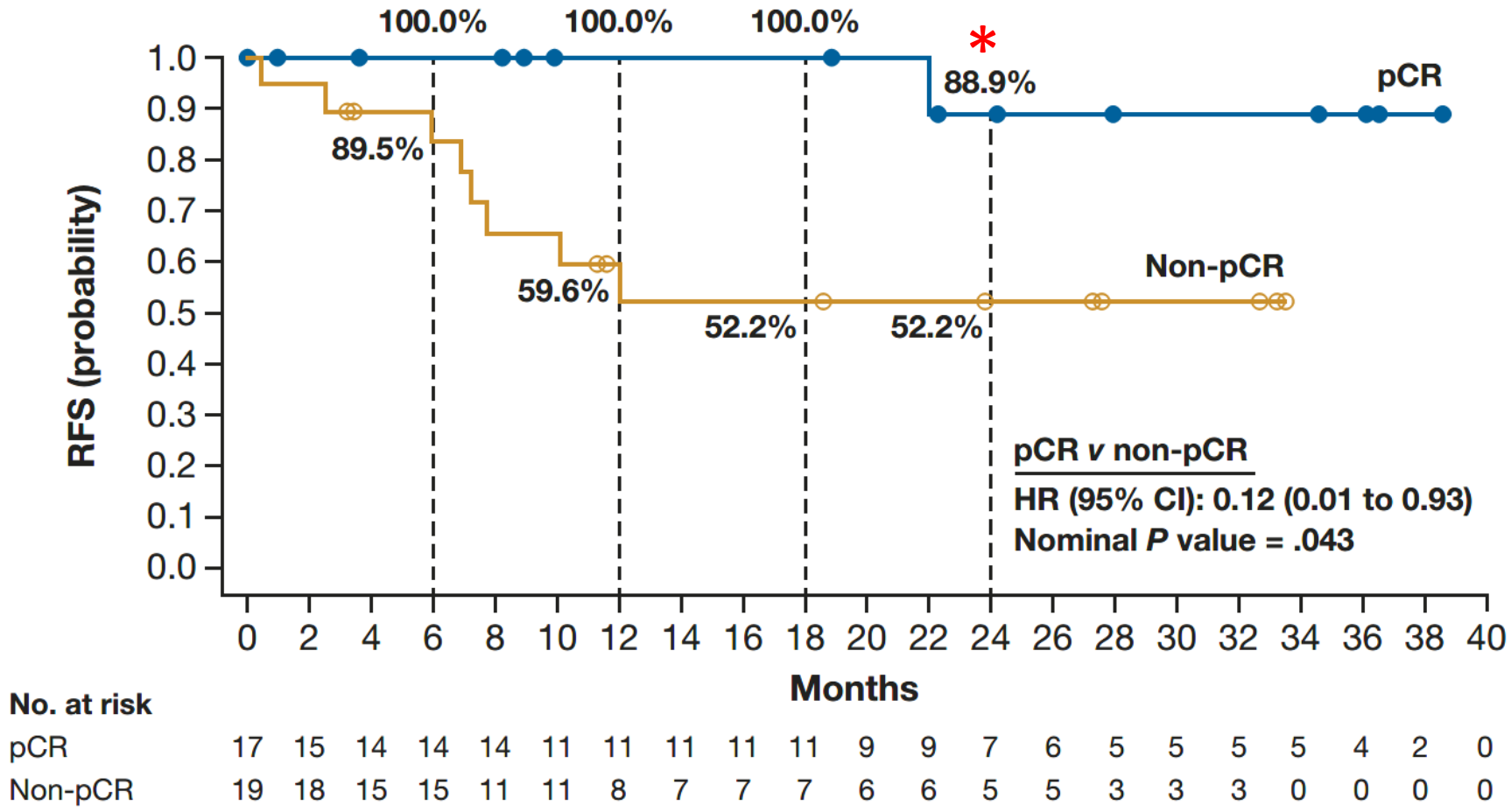
Neoadjuvant nivolumab for Merkel cell Ca: pathologic complete response in 47% of patients at ~4 weeks



- 53-year-old female with MCC T3N1
- MCPyV+, PD-L1 <1%
- Received 2 doses of Nivo (D1 & D15)
- Underwent surgery on D20 (radical cheek resection, parotidectomy, cervical LN dissection)
- Pathologic CR
- Postoperative radiotherapy to primary site
- No evidence of disease 3.5 years post-op

Topalian et al., JCO 2020

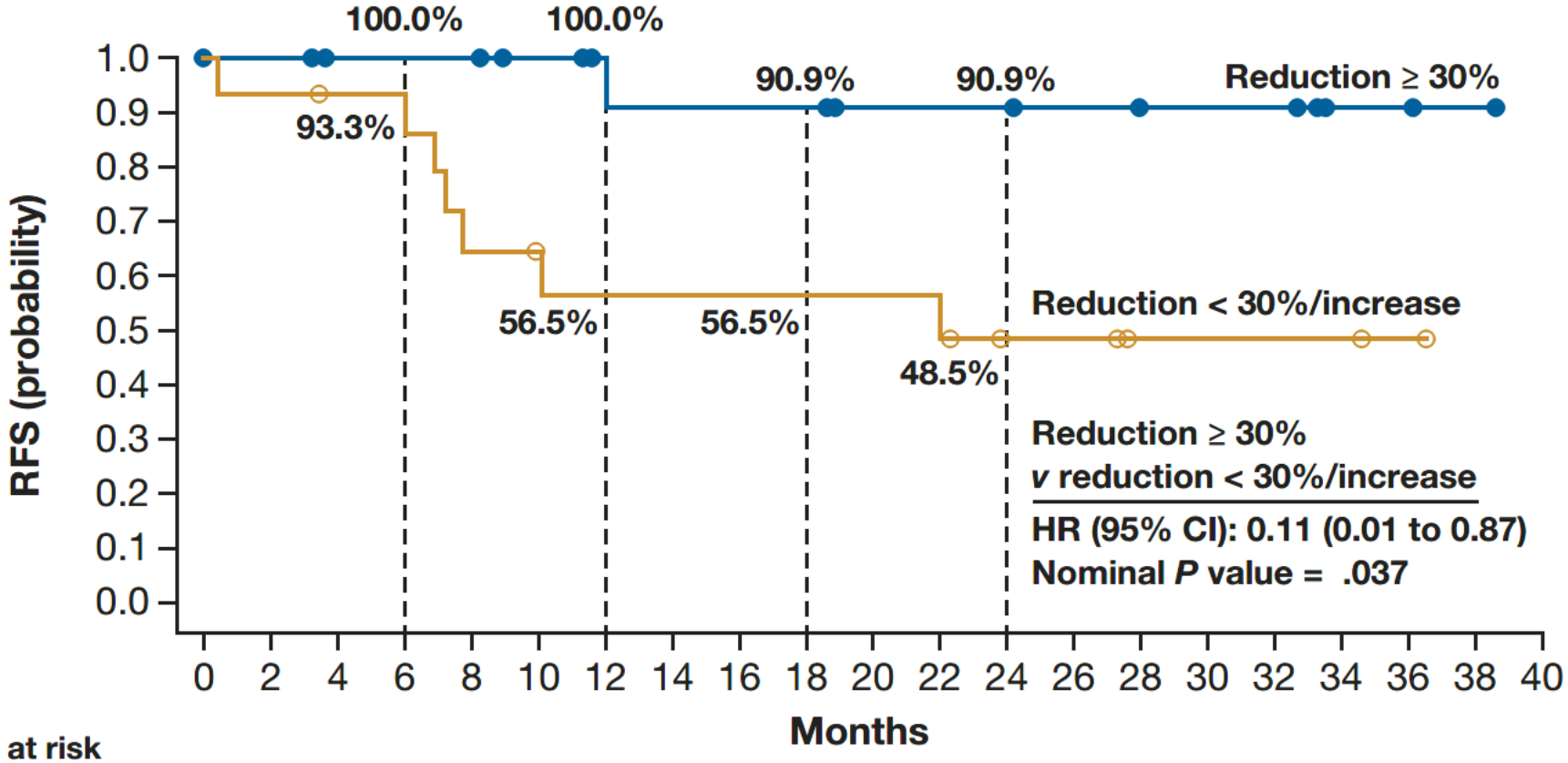
Neoadjuvant nivolumab for MCC: pathologic complete response (pCR) at ~4 wks correlates with RFS at 2 years



* There were *no* tumor relapses among pCRs. A single death occurred in the pCR group, *not* related to tumor relapse or study drug.

Topalian et al., JCO 2020

Neoadjuvant nivolumab for MCC: radiographic response (RECIST) at ~4 wks correlates with RFS at 2 years



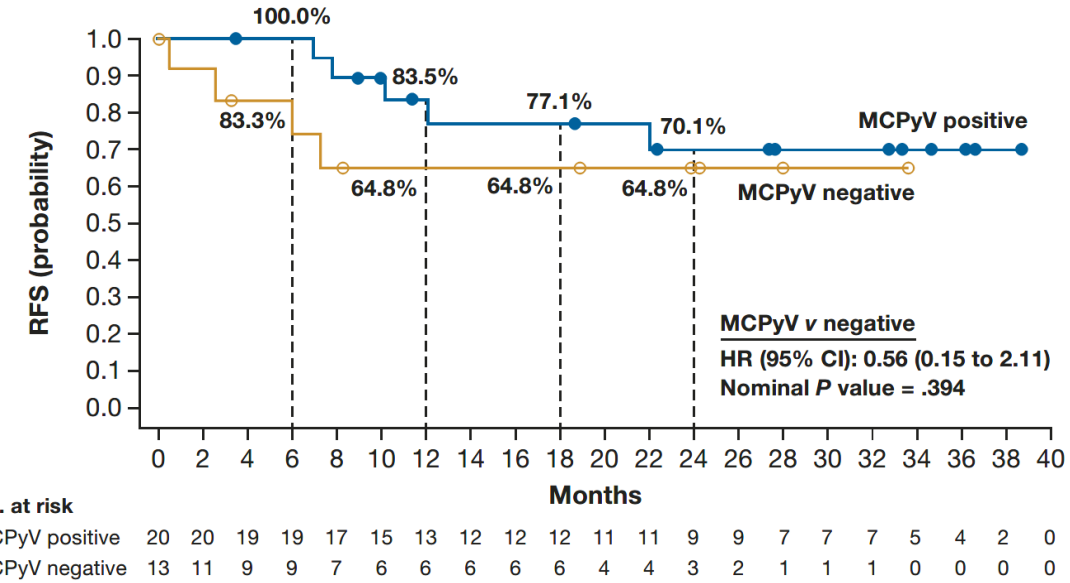
No. at risk																				
Tumor reduction ≥ 30%	18	17	15	15	15	13	11	10	10	10	8	8	8	7	6	6	6	3	3	2	0
Tumor reduction < 30%/increase	15	14	13	13	9	8	7	7	7	7	7	7	4	4	2	2	2	2	1	0	0

Topalian et al., JCO 2020

Neither tumor viral status nor PD-L1 expression predict RFS after neoadjuvant anti-PD-1 for MCC

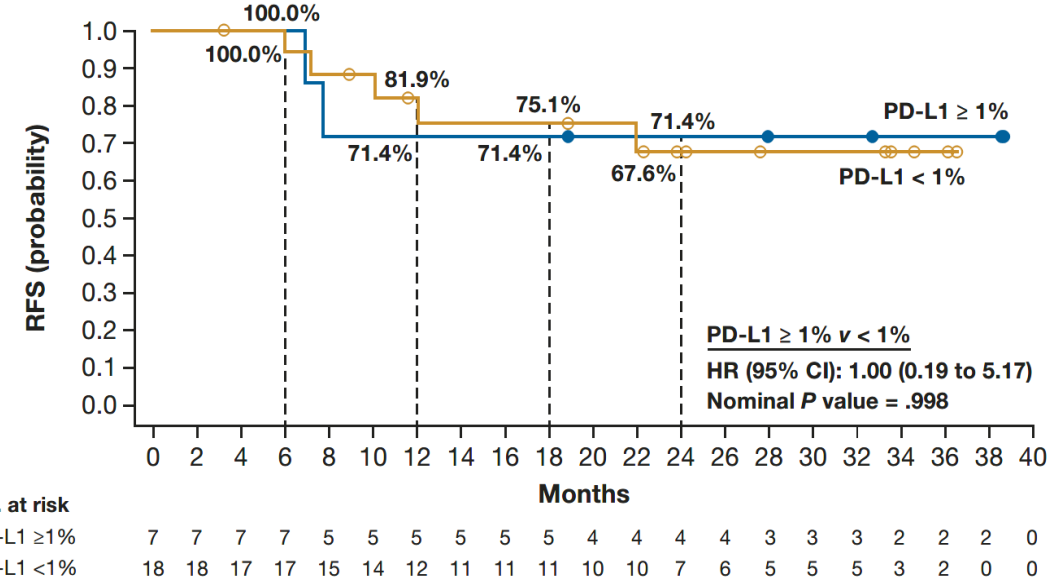
(*similar to PFS outcomes after anti-PD-1 in advanced unresectable MCC*)

MCPyV



No. at risk																				
MCPyV positive	20	20	19	19	17	15	13	12	12	12	11	11	9	9	7	7	7	5	4	2	0
MCPyV negative	13	11	9	9	7	6	6	6	6	6	4	4	3	2	1	1	1	0	0	0	0

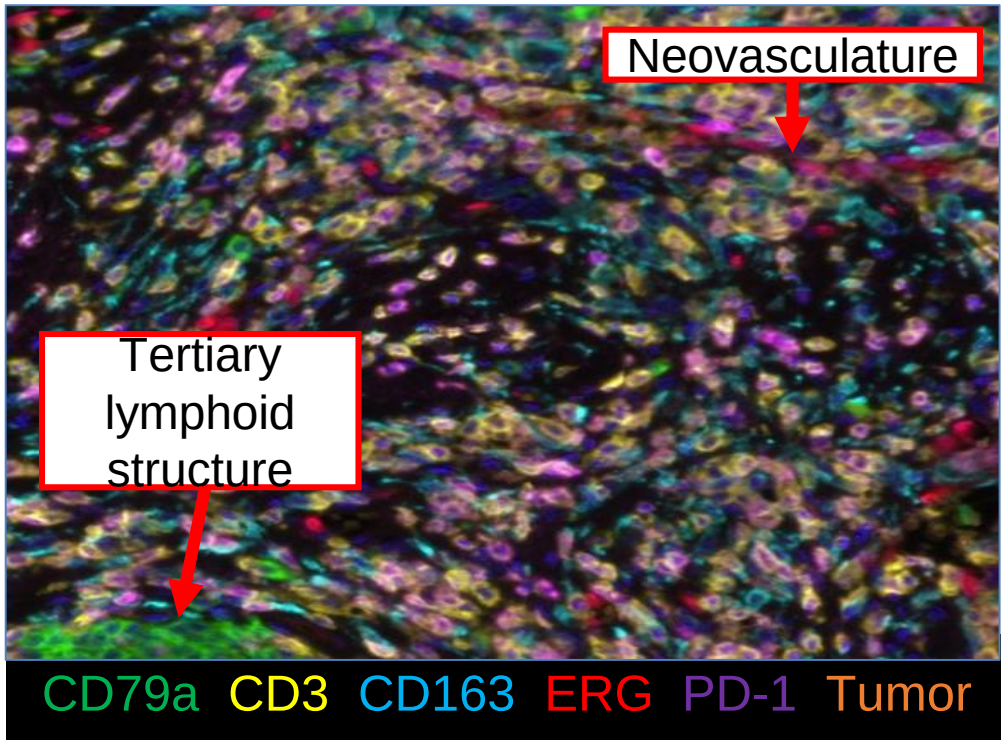
PD-L1



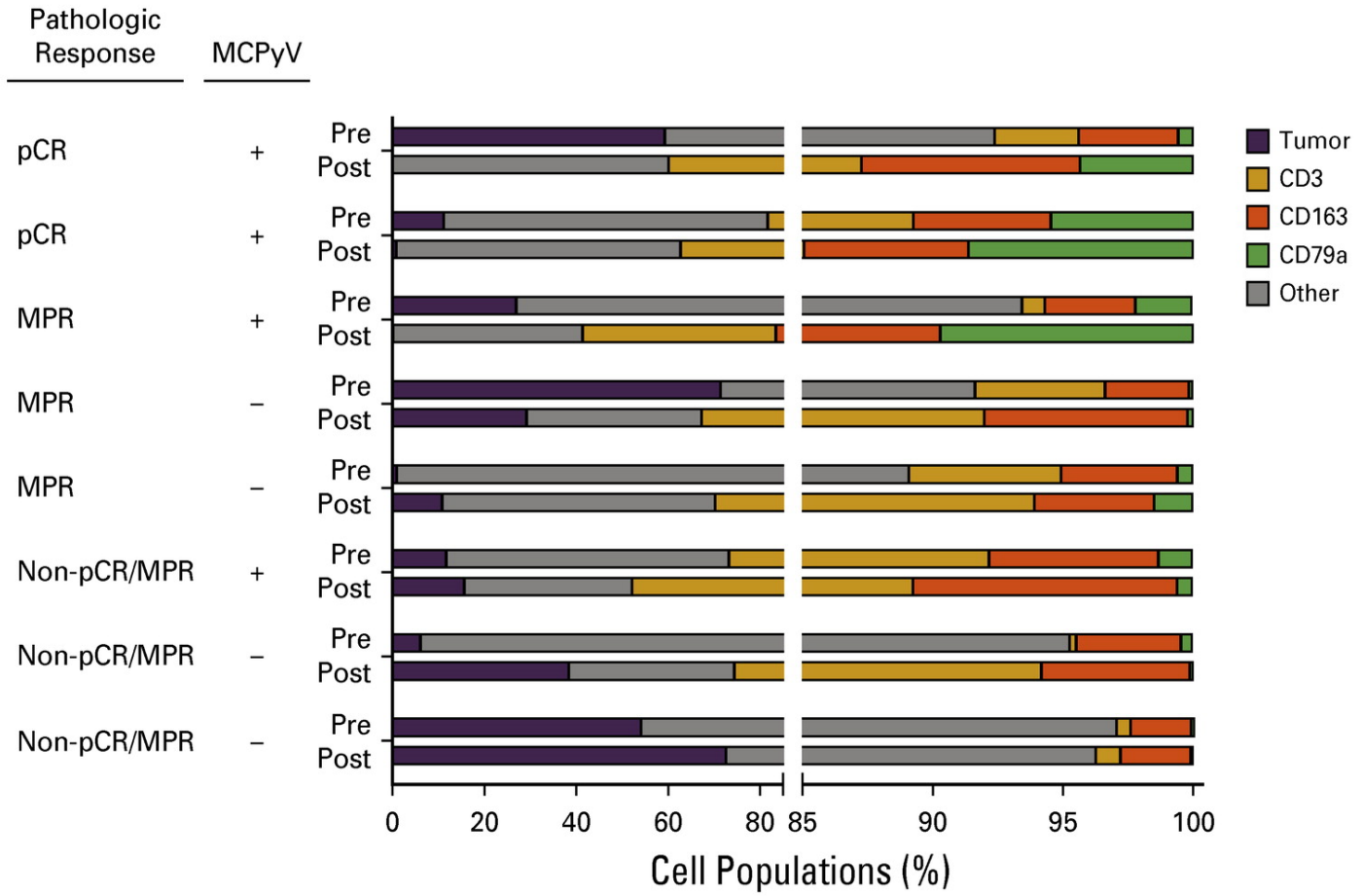
No. at risk																				
PD-L1 ≥1%	7	7	7	7	5	5	5	5	5	5	4	4	4	4	3	3	3	2	2	2	0
PD-L1 <1%	18	18	17	17	15	14	12	11	11	11	10	10	7	6	5	5	5	3	2	0	0

Topalian et al., JCO 2020

MCC demonstrates hallmarks of anti-PD-1-mediated tumor regression (multi-IF; J. Taube)



- Lymphoid infiltrates, prominent plasma cells
- Tertiary lymphoid structures
- Proliferative fibrosis
- Neovasculature



Topalian et al., J Clin Oncol 2020

Conclusions

- Neoadjuvant ICB may prime systemic anti-tumor immunity.
- Pathologic response after neoadjuvant ICB may provide an early on-treatment marker predicting long-term outcomes.
- Large quantities of viable on-treatment tissues from surgical specimens after neoadjuvant ICB enable in-depth correlative analyses to understand treatment response and primary resistance.

Hopkins PD-1 team ca. 2010

Thanks to collaborating clinical trial centers, esp. Nghiem et al. (U. Wash) for MCC studies.
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Moving for Melanoma, Barney Foundation, and others