Combination Immunotherapies

Leisha A. Emens, MD PhD
Professor of Medicine
Director of Translational Immunotherapy
Women's Cancer Research Center, Magee Women's Hospital
Co-Leader, Cancer Immunology and Immunotherapy
UPMC Hillman Cancer Center

Disclosure Information

I have the following financial relationships to disclose:

Consultant for: Vaccinex, Celgene, Bristol Meyers Squibb, AstraZeneca, Amgen, Syndax, Molecuvax, eTHeRNA, Peregrine, Bayer, Gritstone, Medimmune, Abbvie, Genentech/Roche, Macrogenics

Grant/Research support from: Genentech/Roche, EMD Serono, Maxcyte, Merck, AstraZeneca, Aduro, Corvus

Under a licensing agreement between Aduro Biotech, and the Johns Hopkins University, the University and Dr. Emens are entitled to milestone payments and royalty on sales of a GM-CSF-secreting breast cancer vaccine. The terms of these arrangements are being managed by the Johns Hopkins University in accordance with its conflict of interest policies

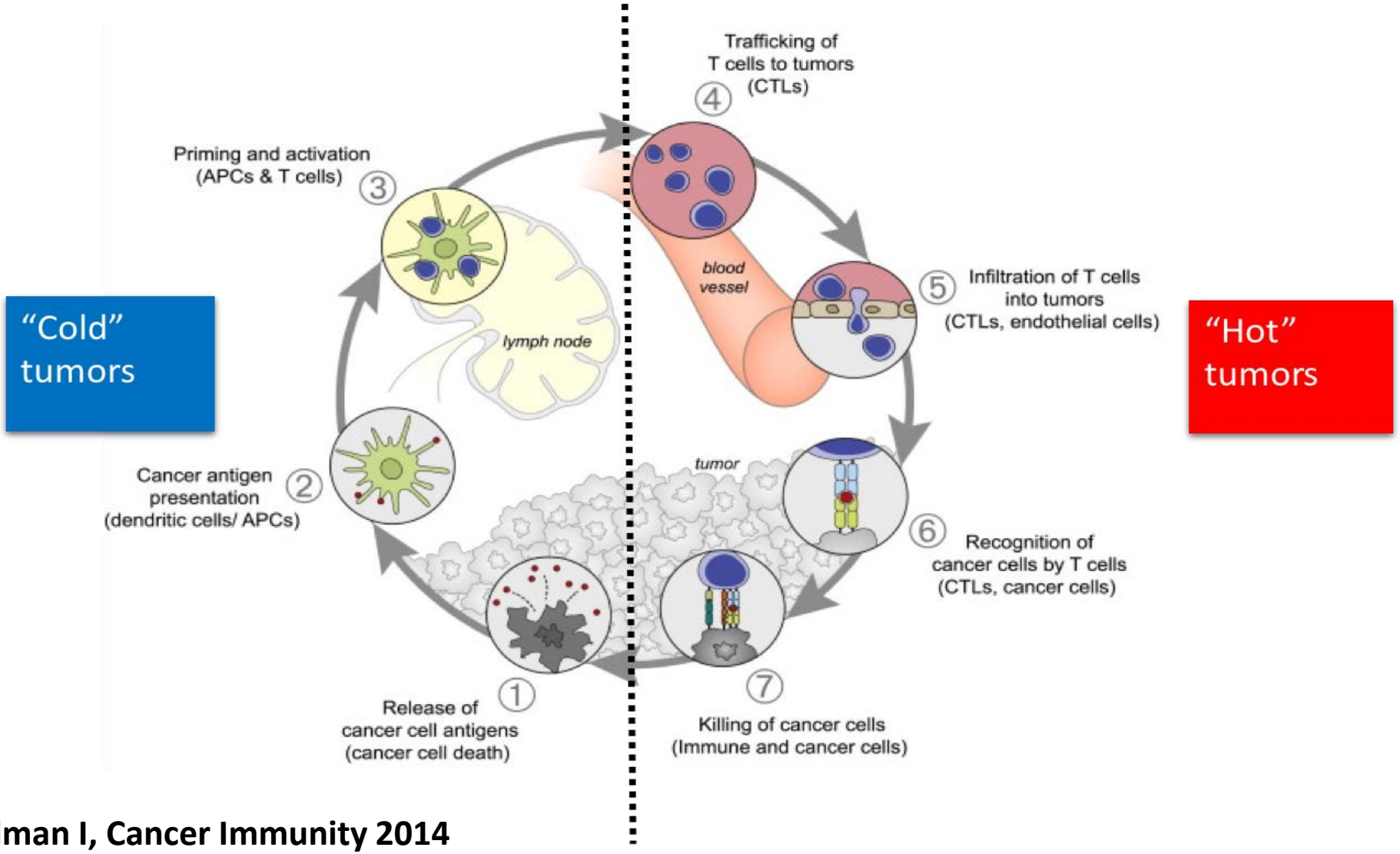
Key Features of Immune Checkpoint Blockade

- Response rates to single agent immune checkpoint blockade average only 10%-30%
  - Ipilimumab monotherapy in advanced melanoma has a response rate of ~10%
  - Nivolumab/Pembrolizumab monotherapy in advanced melanoma has a response rate of ~35-40%
- Response rates may range from <5% to ~90% across tumor types
- Many immunotherapy agents that target other pathways may have little single agent activity in the absence of PD-1/PD-L1 modulation

Why Immunotherapy Combinations?

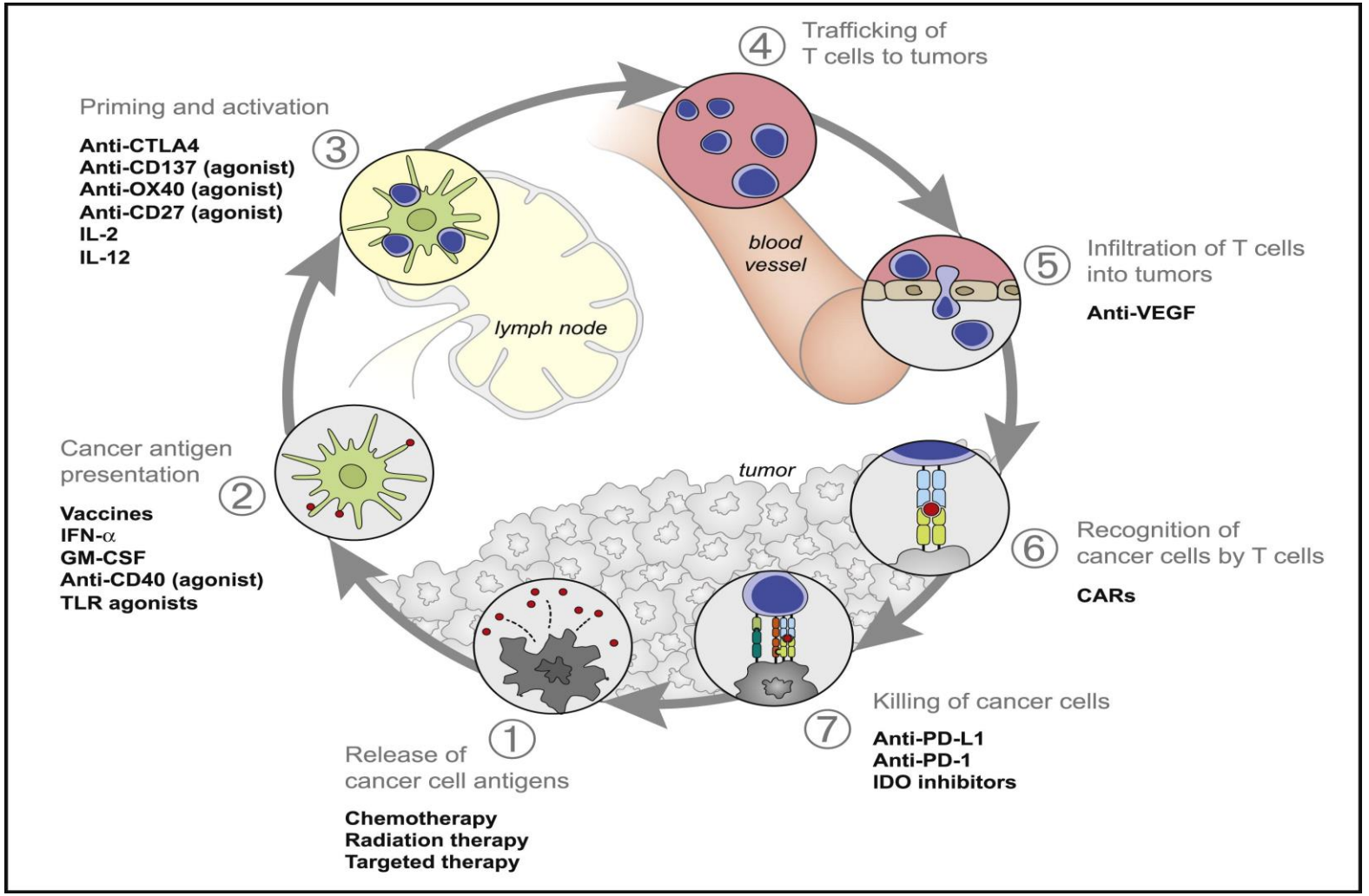
- Convert non-responders to responders
  - ✓overcome primary resistance
- Rescue patients who progress on immunotherapy
  - ✓overcome secondary resistance
- Deepen responses that do occur
  - ✓increase survival benefit
- Harness tumor biology to support immunotherapy
  - ✓monoclonal antibodies
  - ✓small molecule inhibitors
- Integrate with historical treatment modalities
  - ✓chemotherapy
  - ✓radiation

The Cancer Immunity Cycle



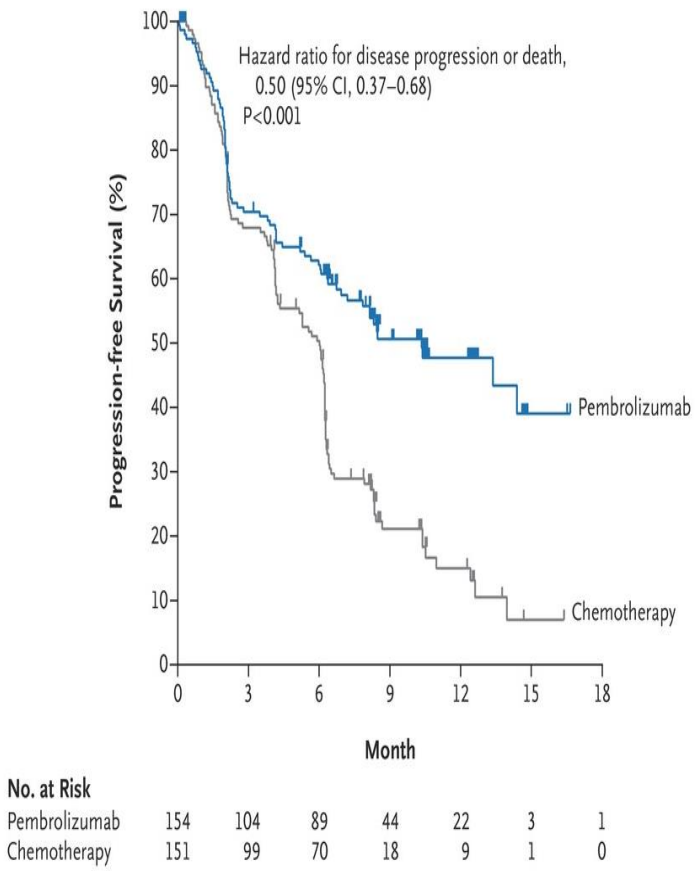
Chen DS, Mellman I, Cancer Immunity 2014

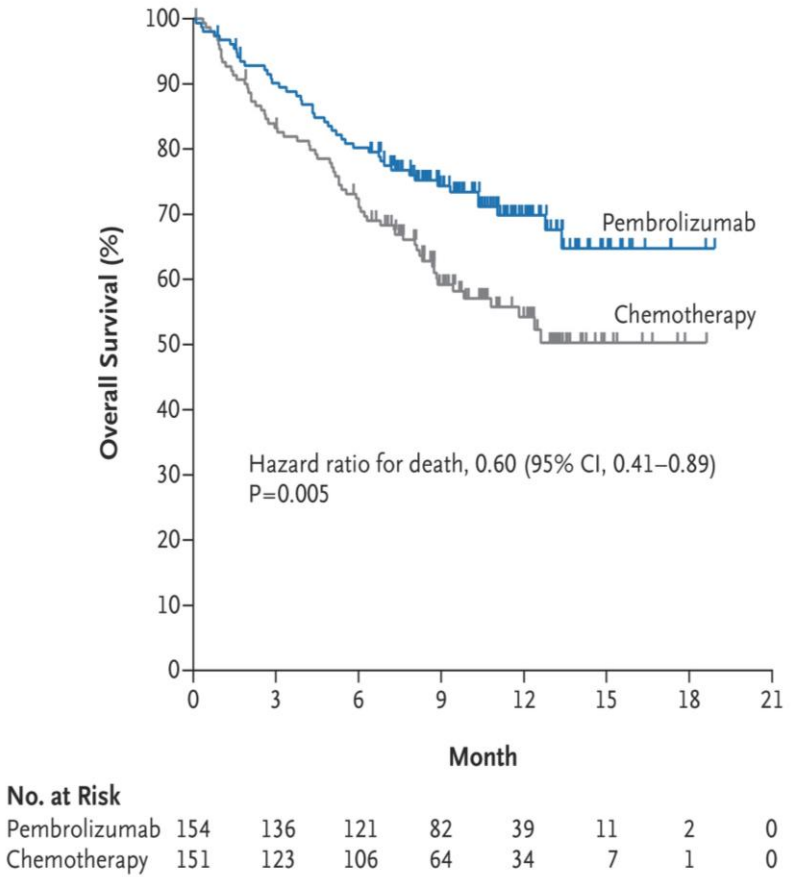
Harnessing the Cancer Immunity Cycle for Therapeutic Benefit



Chen DS, Mellman I, Cancer Immunity 2014

Single Agent Pembrolizumab for Untreated Metastatic NSCLC





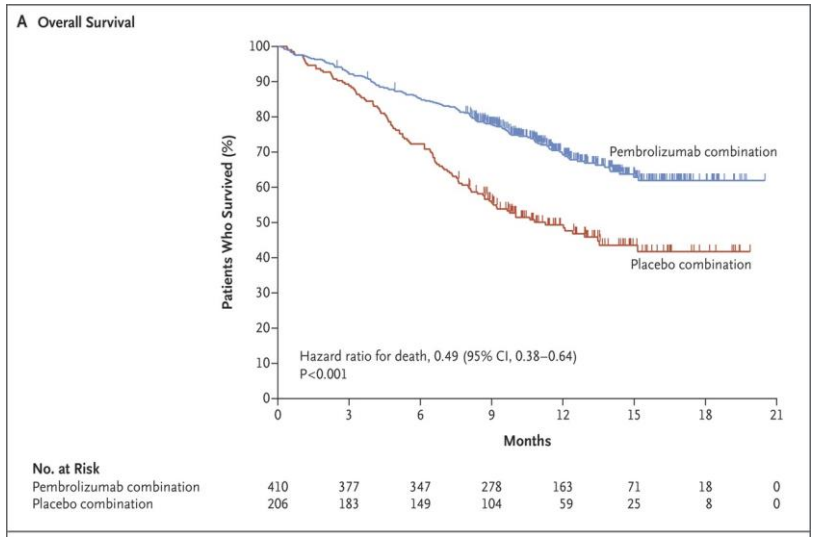
305 patients with untreated PD-L1+ TC >50% metastatic NSCLC w/o ALK or EGFR mutation were randomized 1:1 to pembrolizumab alone or platinum-based chemotherapy

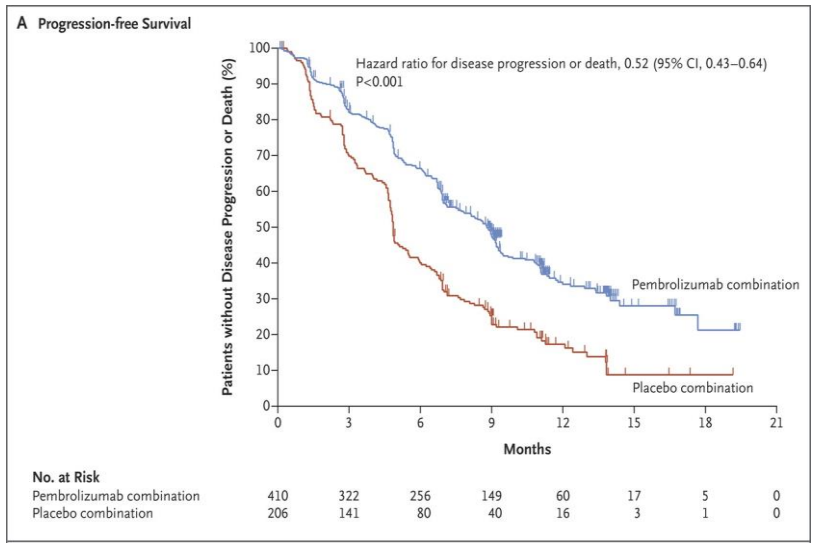
	Pembro	Platinum
ORR	44.8%	27.8%
mPFS	10.3 mo	6 mo
OS 6 mo	80.2%	72.4%
DOR	NR	6.3 mo

Pembrolizumab better tolerated than chemotherapy

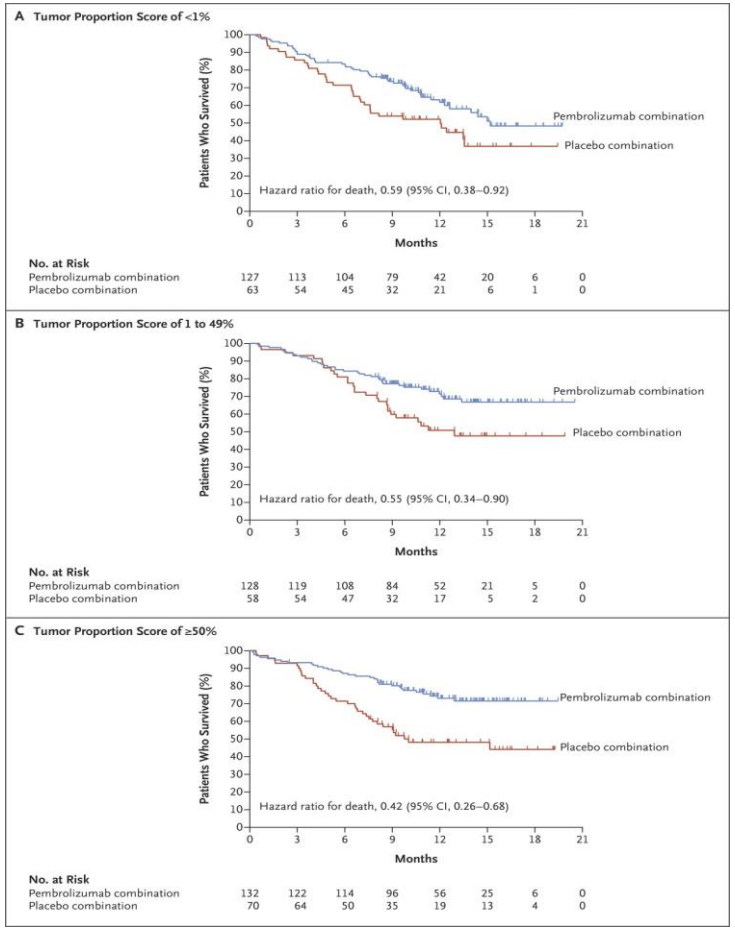
Reck M et al. N Engl J Med 2016;375:1823-1833

Pembrolizumab + Chemotherapy in NSCLC





616 patients with untreated metastatic NSCLC w/o ALK or EGFR mutation were randomized 2:1 to pemetrexed+platinum+placebo or pembrolizumab, regardless of PD-L1 TC expression (cut-point TC 1% and 50%)



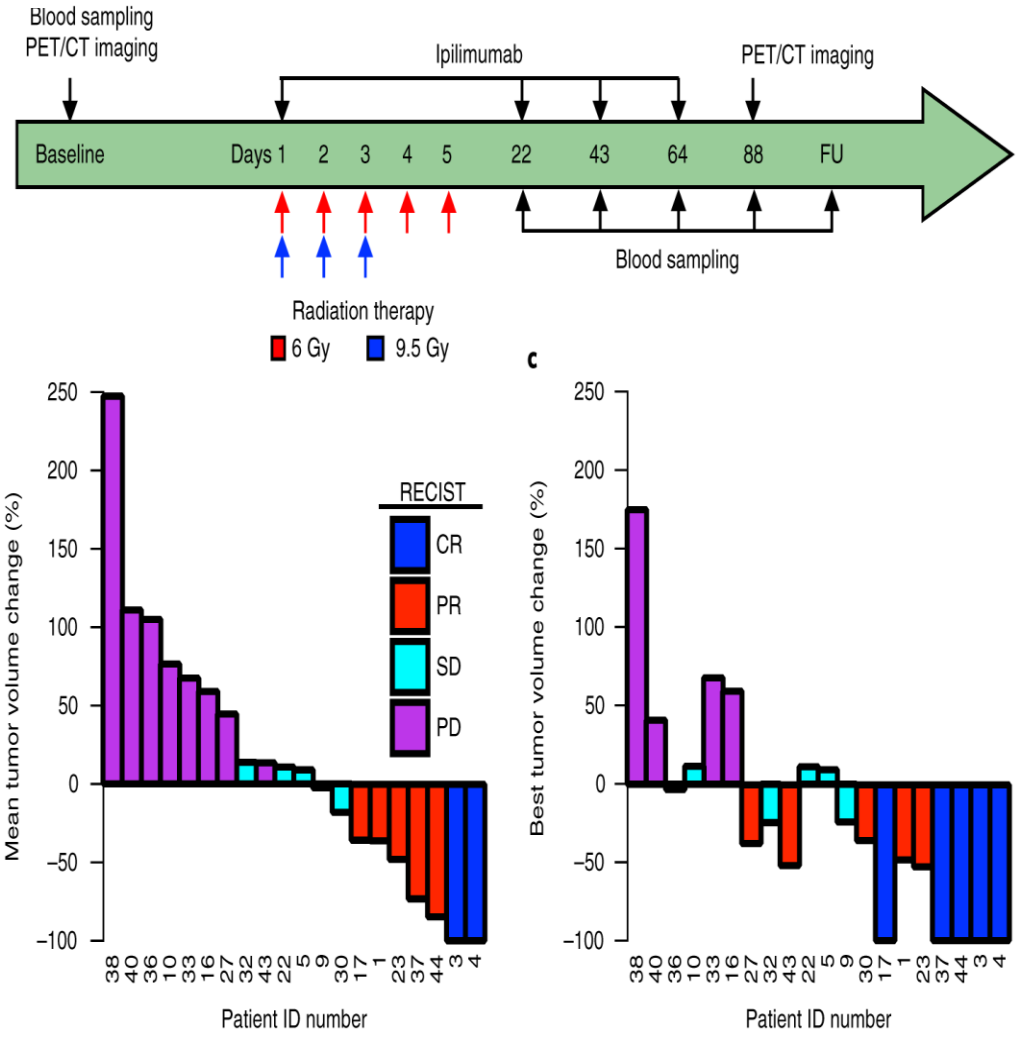
	Chemo+ Pembro	Placebo + Chemo
ORR	47.6 %	18.9 %
mPFS	8.8 mo	4 mo
OS 12 mo	69.2%	49.4%
DCR	84.6%	70.4%
DOR	11.2 mo	7.8 mo

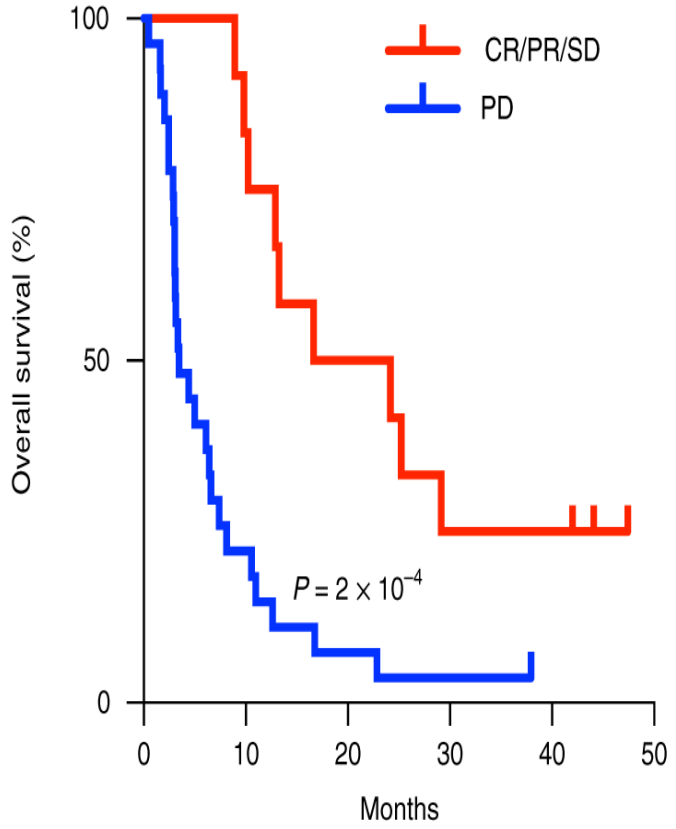
Similar adverse events except possibly more nephritis/AKI with pembro; twice as many irAEs in pembro group (22.7% vs 11.9%)

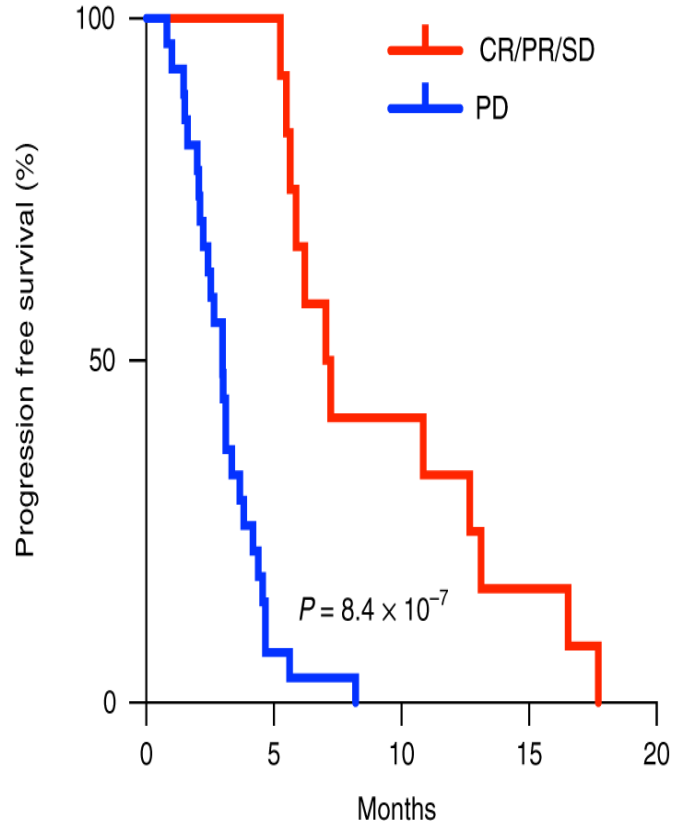
Gandhi L et al. N Engl J Med 2018;378:2078-2092

Radiotherapy Combined with CTLA-4 Blockade

Clinical response and survival



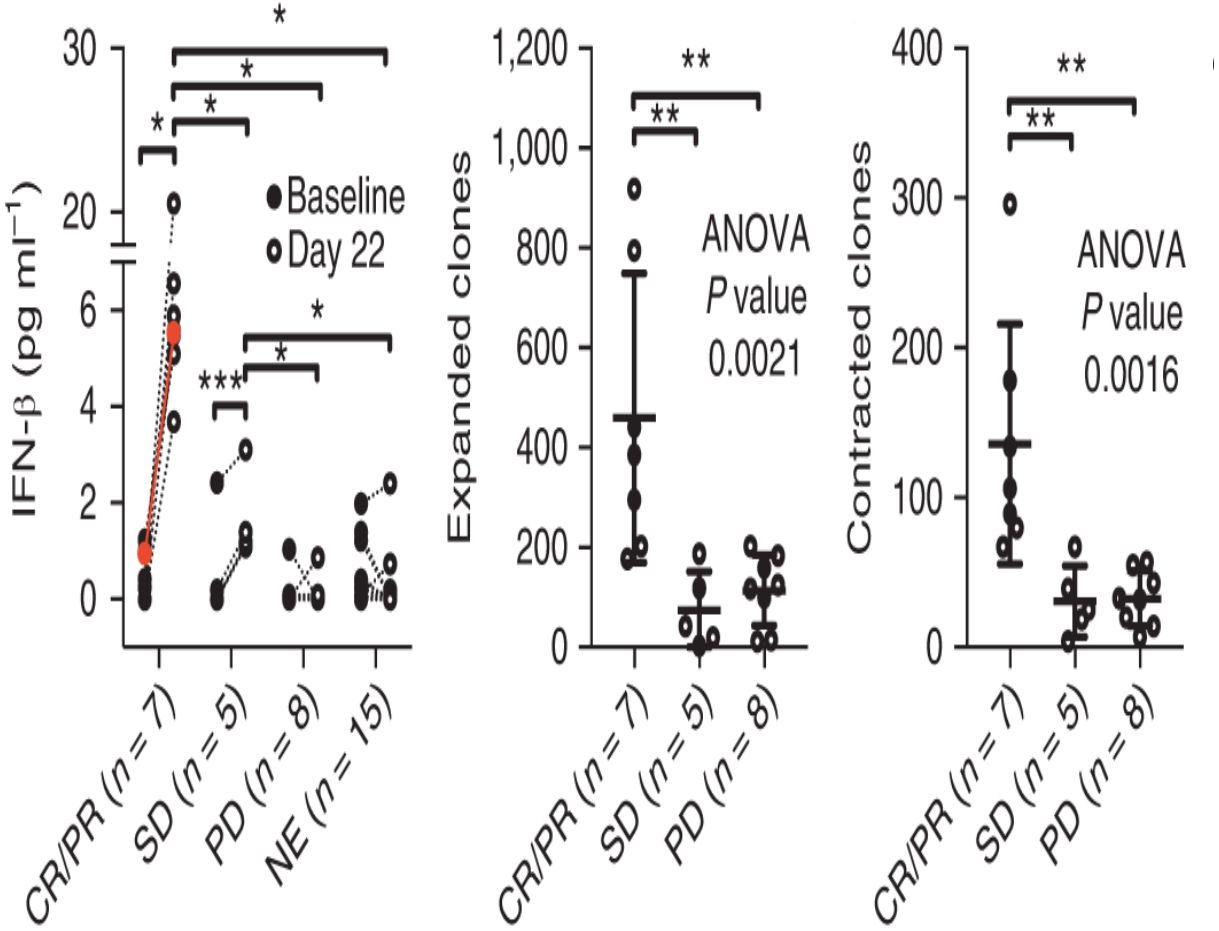


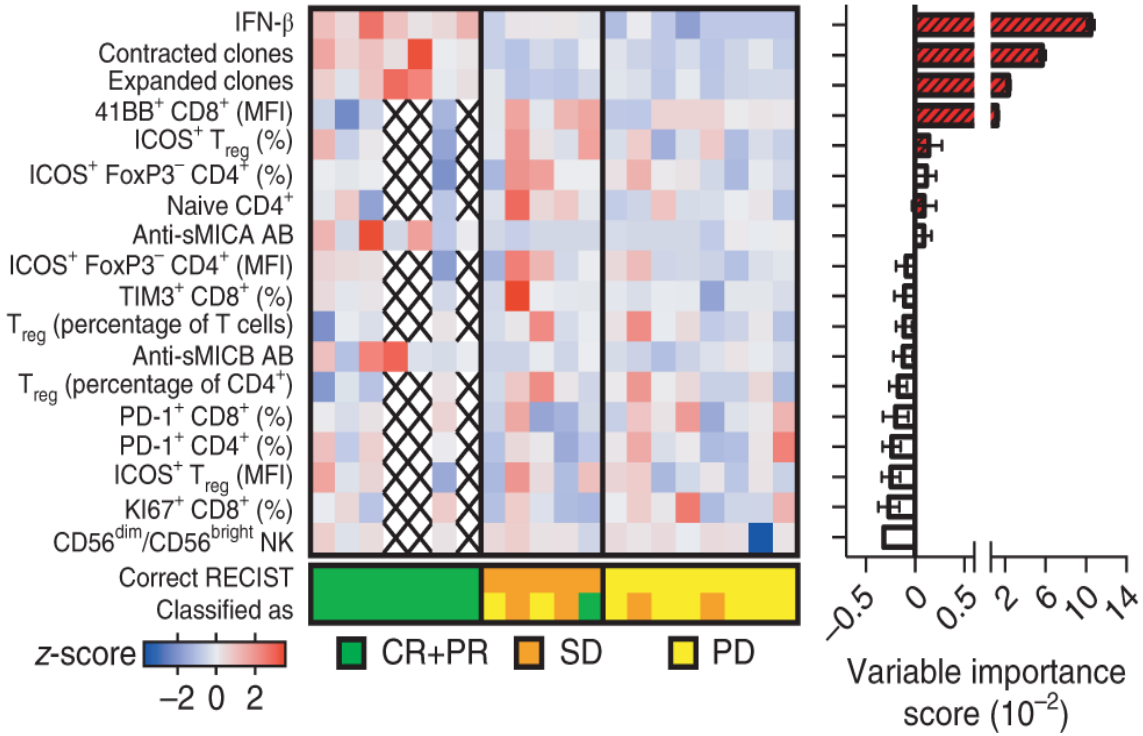


Formenti SC et al. Nature Med 2018; 24: 1845-1851

Radiotherapy Combined with CTLA-4 Blockade

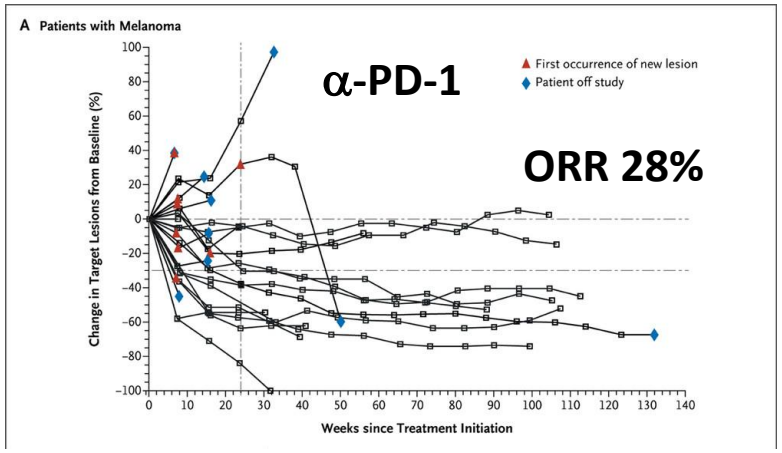
Increased IFN-β levels and TCR clonal dynamics predict for treatment response

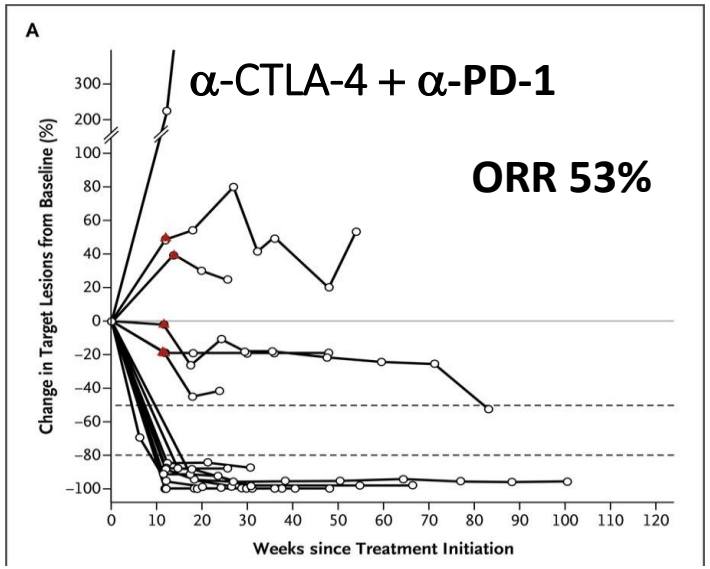




Formenti SC et al. Nature Med 2018; 24: 1845-1851

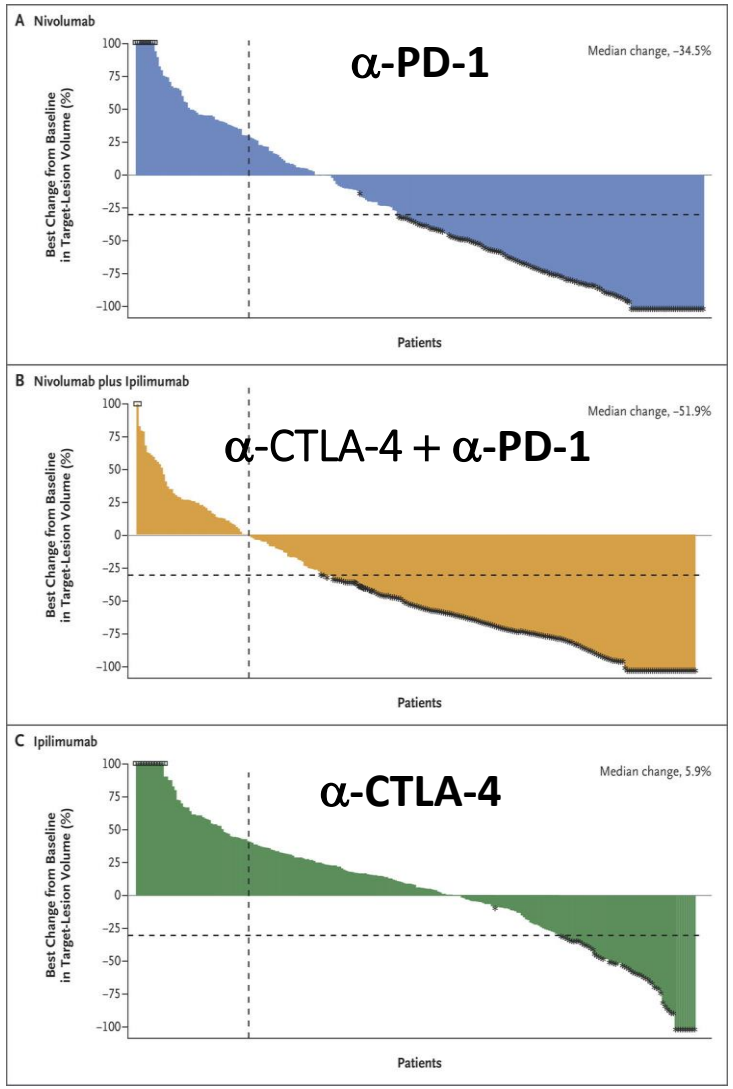
Dual Immune Checkpoint Blockade:
anti-CTLA-4 + anti-PD-1



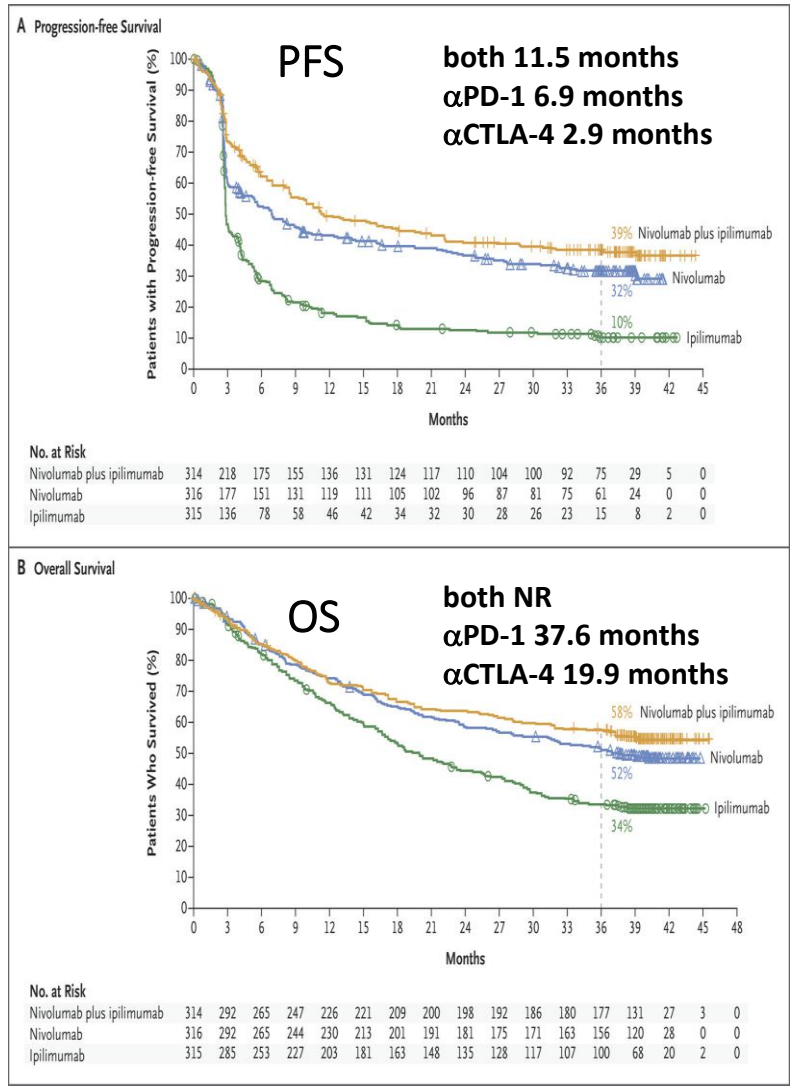


Topalian SL et al. N Engl J Med 2012;366:2443-2454.

Wolchok JD et al. N Engl J Med 2013;369:122-133.



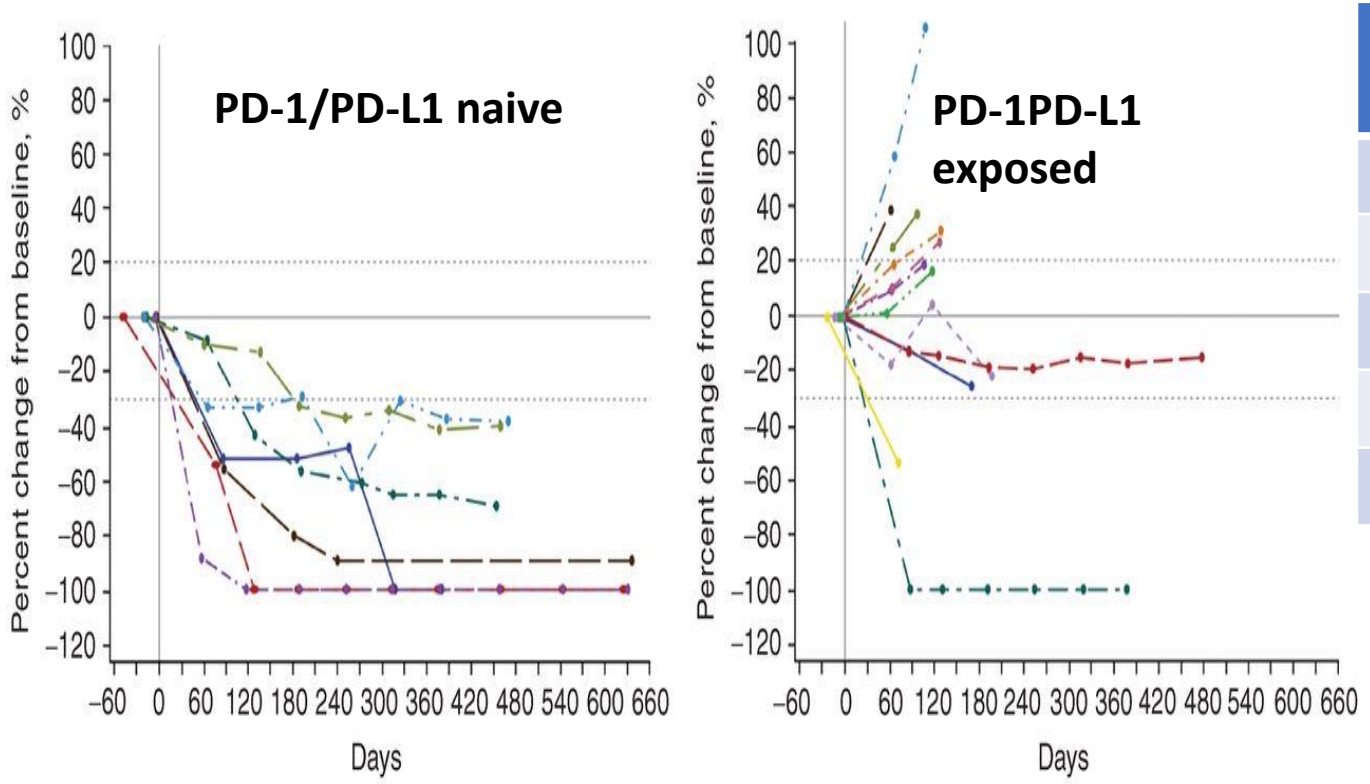
Larkin J et al. N Engl J Med 2015;373:23-34.



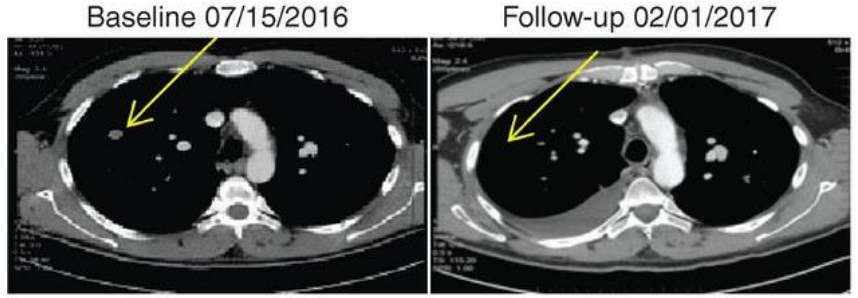
Wolchok JD et al. N Engl J Med 2017;377:1345-1356.

PD-1 Blockade + TLR-9 Activation

SD-101: CpG oligo that stimulates pDC by engaging TLR-9, inducing IFN-α, maturation, and support of innate and adaptive immunity

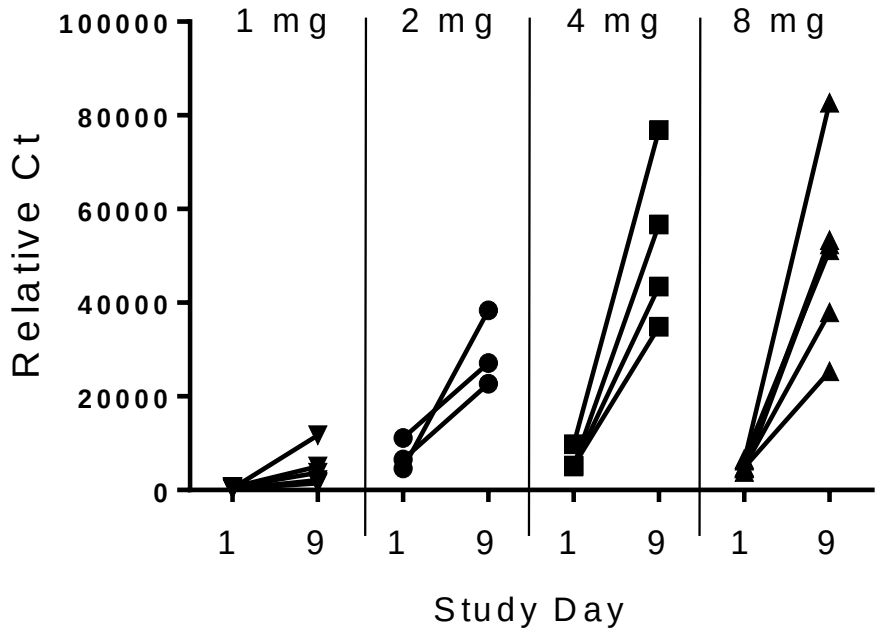


	PD-1/PD-L1 Naive [n=9]	PD-1/PD-L1 Exposed [n=13]
ORR	7 (78%)	2 (15%)
CR/PR	2/5	0/2
SD	0	5
DCR	7 (78%)	7 (54%)
PD	1 (11%)	5 (38%)

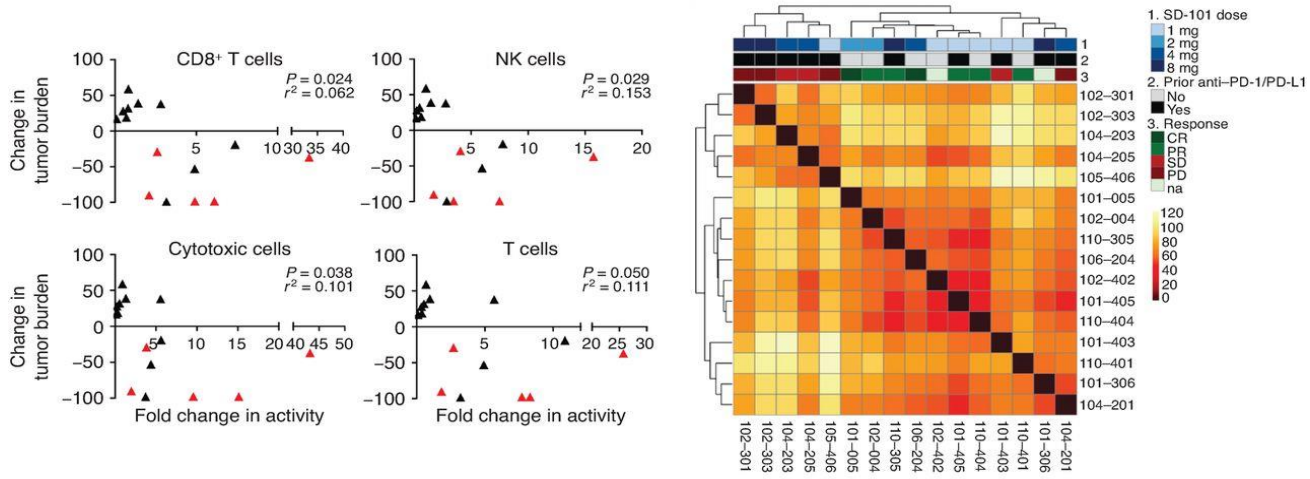


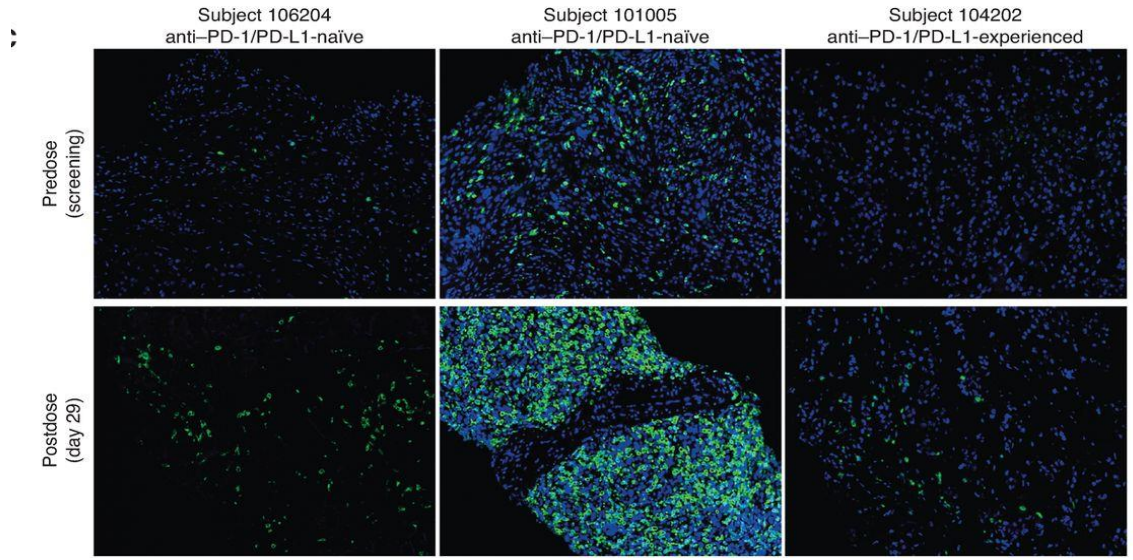
Antoni Ribas et al. Cancer Discov 2018;8:1250-1257

Pharmacodynamic Changes on SD-101 Therapy



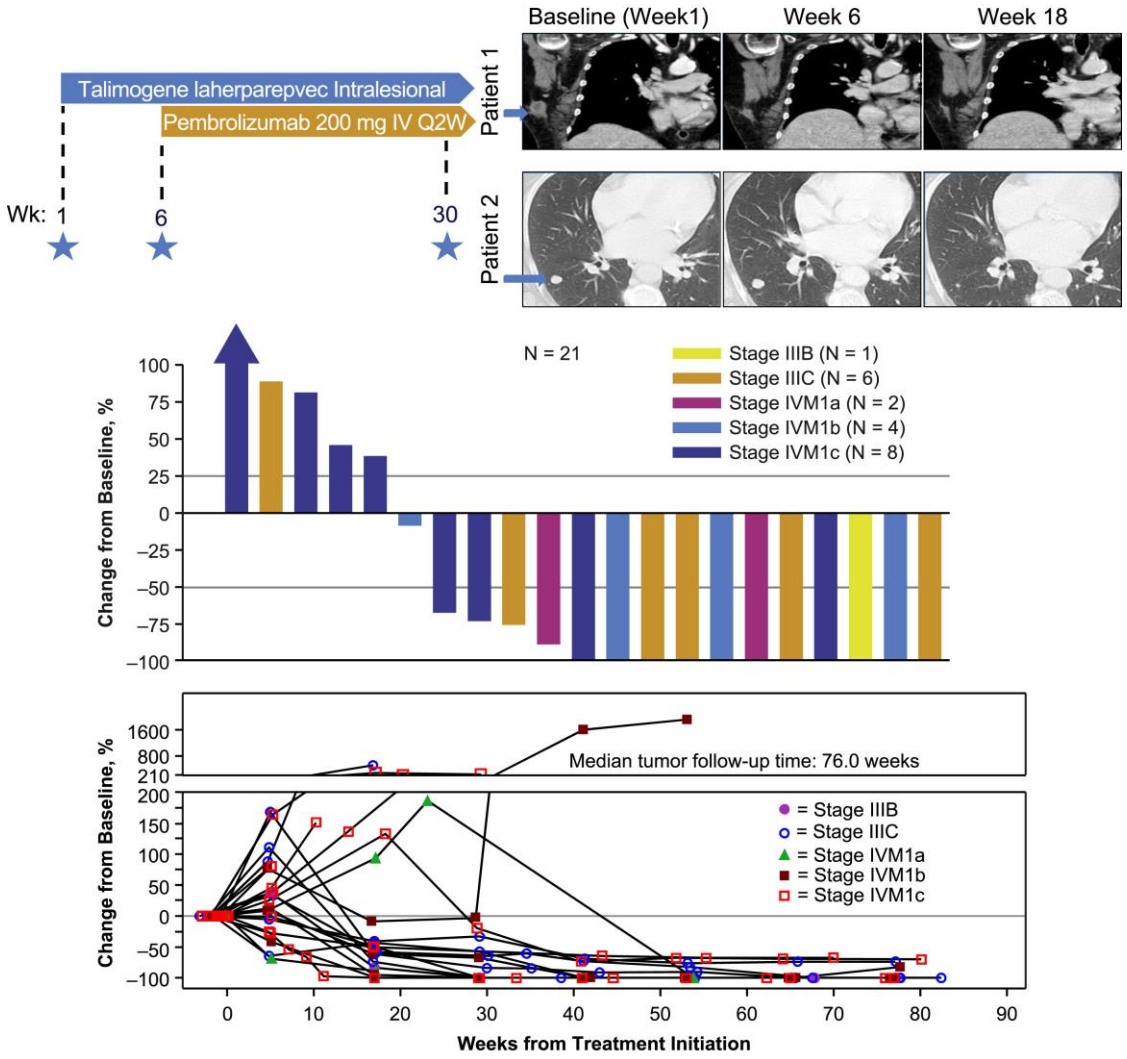
induction of IFN-α-responsive genes (GBP1, IFIT2, CCL2, MX2) in PBMC as a surrogate for intratumoral production, timepoint was 24 hours after second dose (day 9)

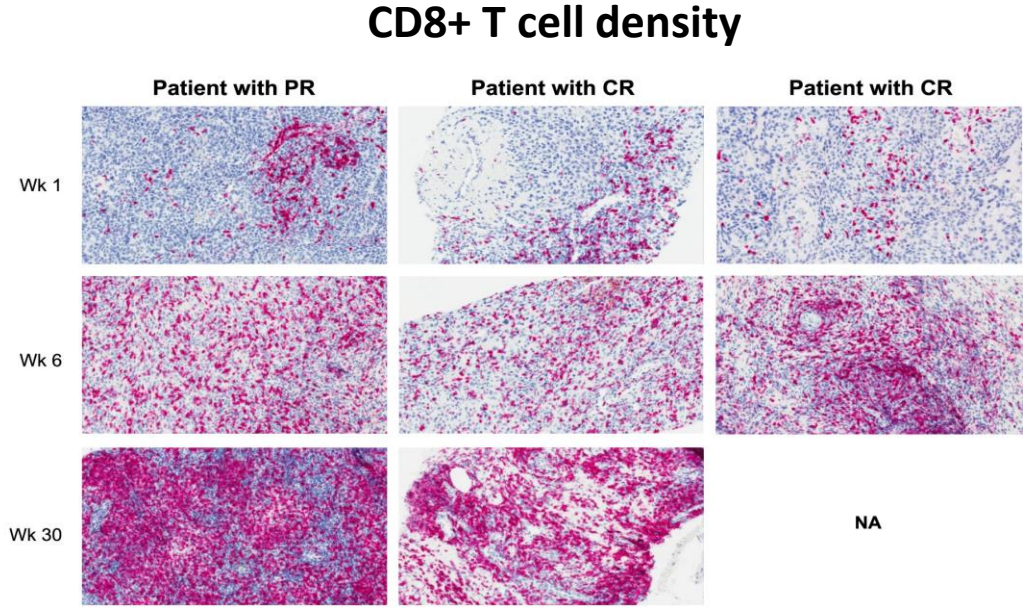




Antoni Ribas et al. Cancer Discov 2018;8:1250-1257

Oncolytic Virotherapy + Pembrolizumab in Metastatic Melanoma





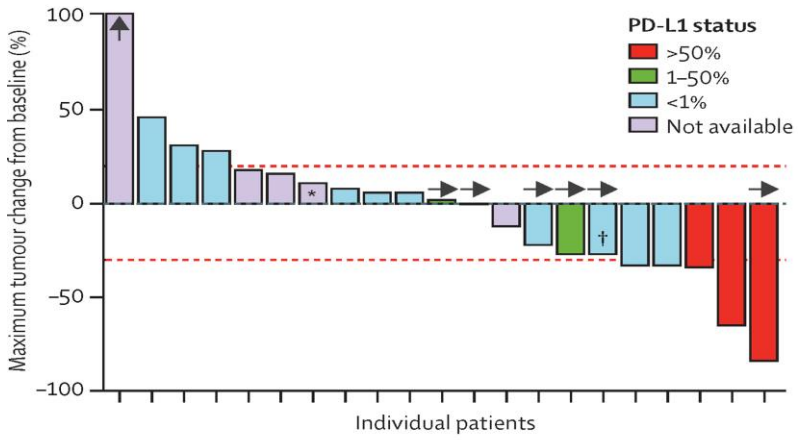
- High ORR of 62%
- High CR rate of 33%
- Therapy induced T cell infiltration, PD-L1 expression, and IFN-γ gene expression
- Clinical response independent of baseline T cell infiltration

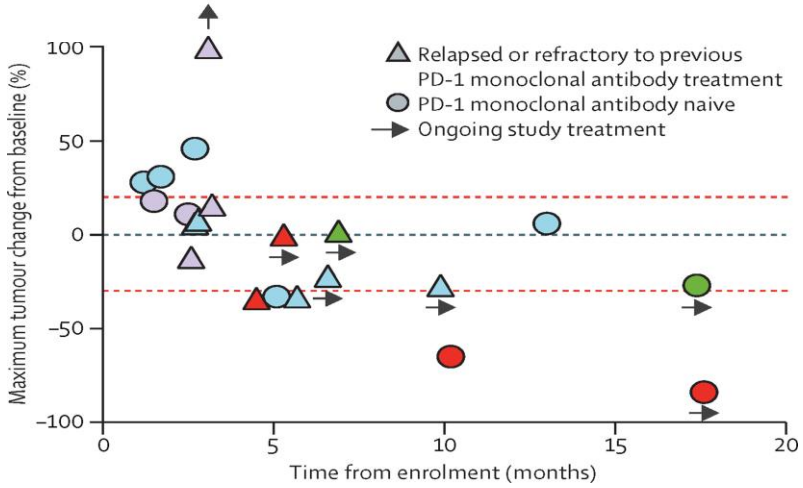
Ribas A et al. Cell 2017;170:1109-1119

Interleukin 15

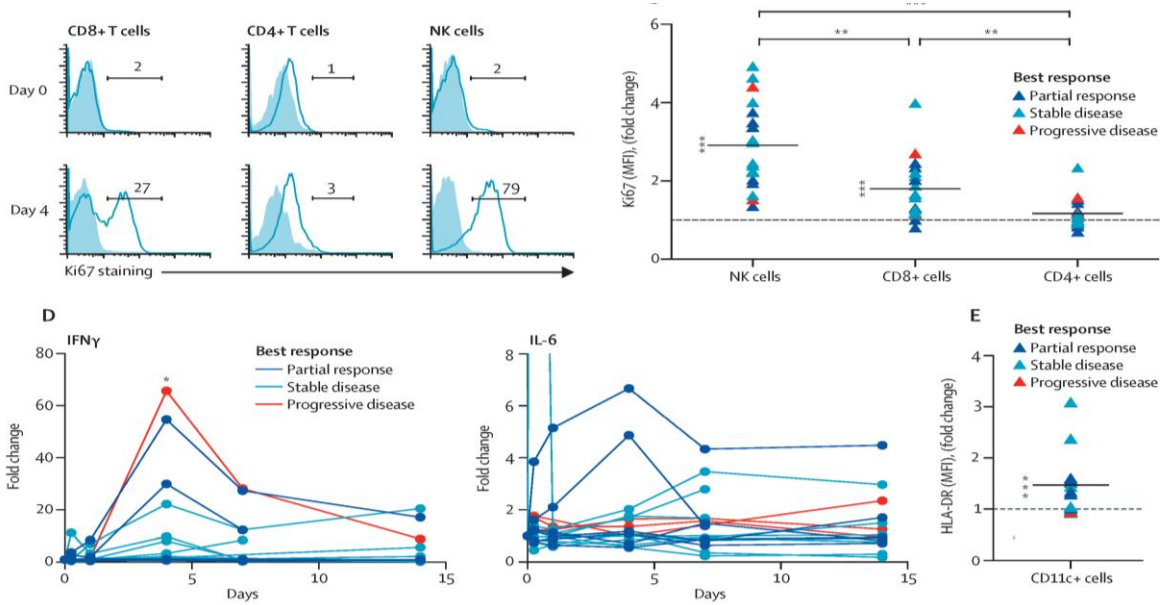
- IL-15 is a common γc receptor cytokine that shares the β chain with IL-2; the α chains are distinct
- Activates and expands NK cells (promotes survival) and CD8+ T cells (promotes memory development)
- DCs produce IL-15 and coordinately express the IL-15 α receptor, presenting IL-15 in *trans* via the α chain to cells expressing βγ receptors
- Advantages over IL-2: less activation induced cell death of CD8+ T cells, and less expansion of Treg
- ALT-803: IL-15/IL-15Rα complex fused to an IgG1Fc with an N72D mutation to increase activity (30X), serum half life (25X), and longer residence time in lymphoid tissues

ALT-305, an IL-15 Superagonist + Nivolumab





most common AEs: injection site reactions, flu-like sx, fever, fatigue



ΔKi67

n=21 (23 enrolled, 21 treated	ORR	DCR
All patients	6 (29%)	16 (76%)
PD-1 R/R	3 (27%)	10 (91%)
PD-L1 negative (<1%)	3 (30%)	7 (70%)
PD-L1 positive (>50%)	3 (75%)	4 (100%)

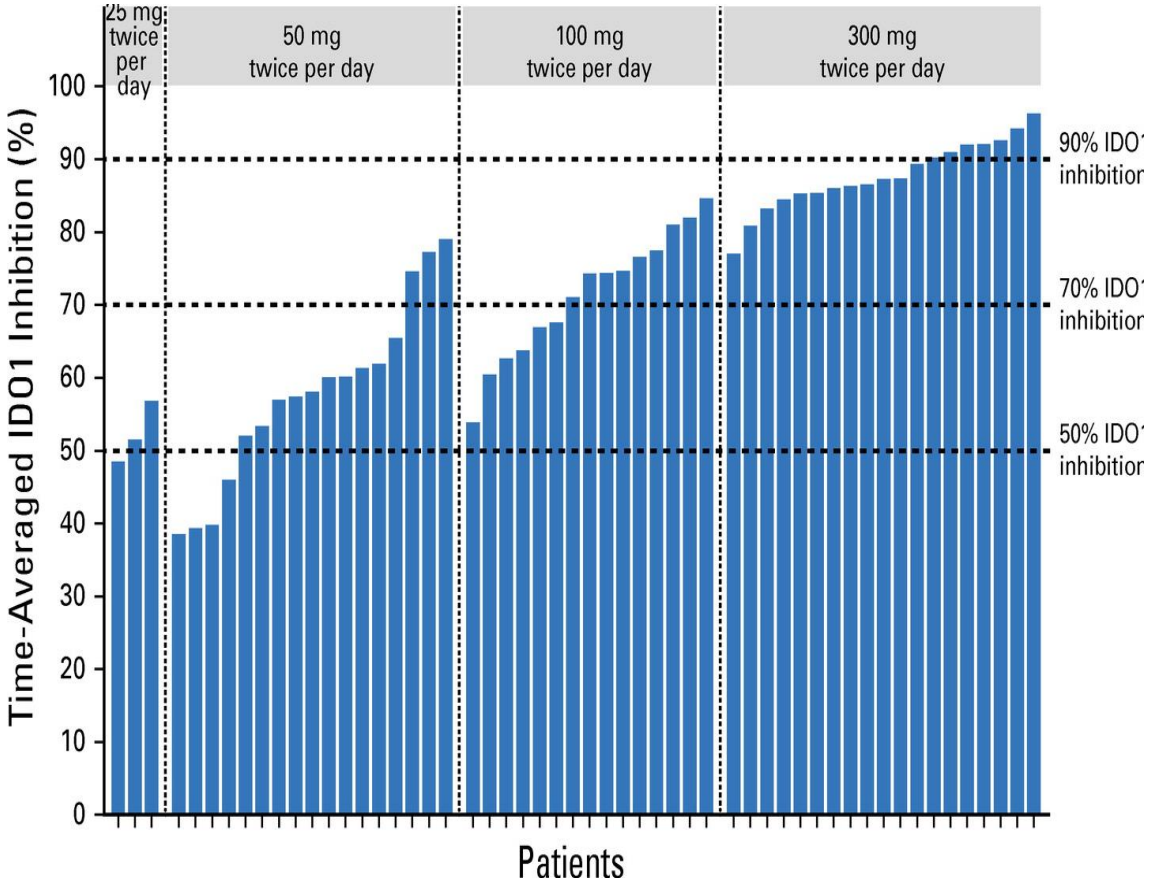
Wrangle JM et al. Lancet Oncology 2018;19:694-704

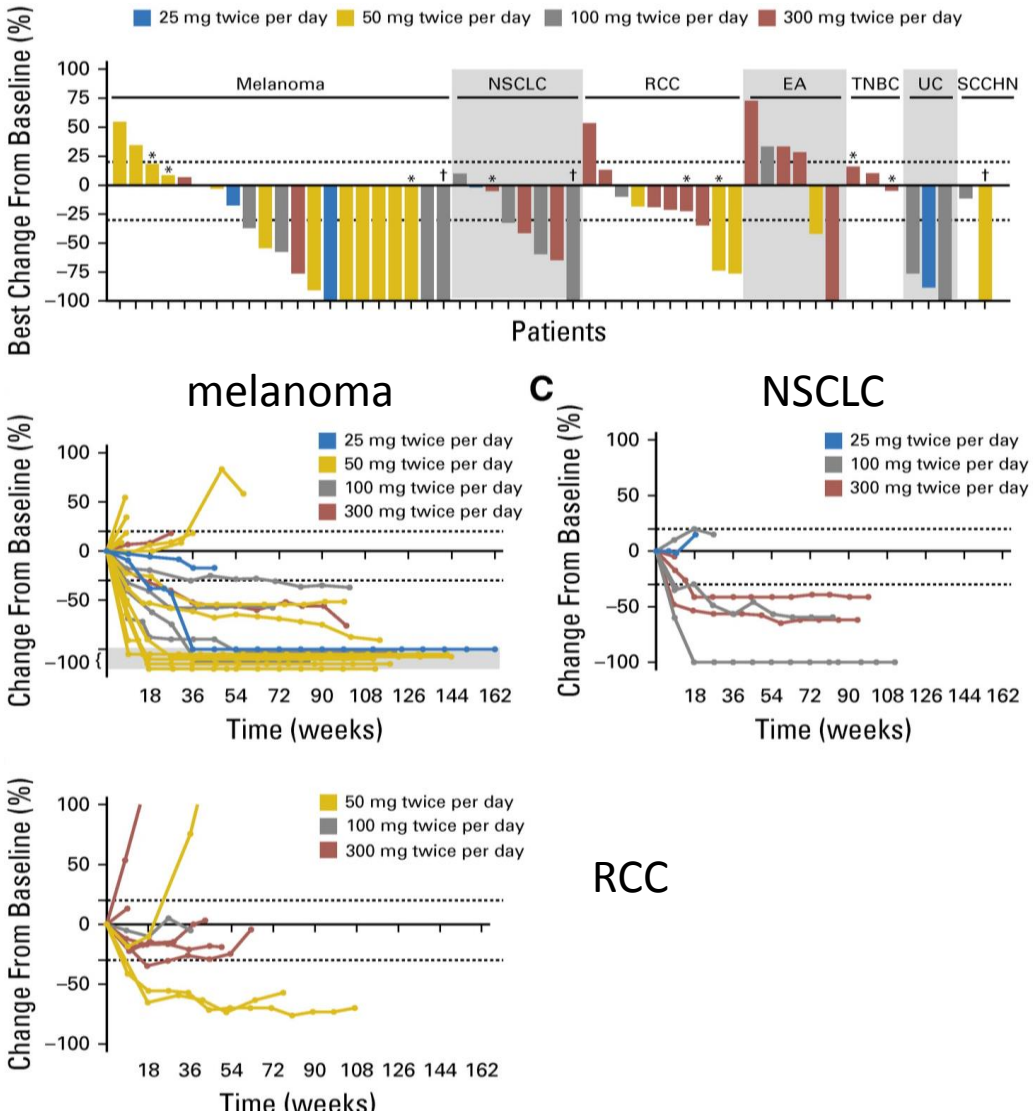
Epacadostat + Pembrolizumab in Advanced Solid Tumors

- IDO1 catalyzes the rate-limiting step in the degradation of tryptophan to kynurinine
- Expressed by tumor cells, endothelial cells, dendritic cells, and macrophages in the TME
- IDO1 depletes trytophan, resulting in anergy and apoptosis of effector T cells and the activation of suppressive cells (Treg, MDSC, macrophages)
- IDO1 is coordinately upregulated with PD-L1 by interferon-γ in the TME
- Epacadostat is a small molecule inhibitor of IDO1 that reverses this process and promotes the activation of $CD86^{high}$ dendritic cells
- Single agent epacadostat is well-tolerated in advanced cancer patients and has modest to no single agent activity
- These features support the testing of epacadostat (other IDO1i) with PD-1/PD-L1 blockade in cancer patients

Mitchell TC et al. J Clin Oncol 2018; epub ahead of print

Phase 1/2 Trial of Epacadostat + Pembrolizumab in Advanced Solid Tumors





Mitchell TC et al. J Clin Oncol 2018; epub ahead of print

Phase 3 ECHO 301 Pembro vs Pembro vs Epacadostat (n=706) Failed to Meet Primary PFS Endpoint: Why??

- TDO is expressed in addition to IDO in many tumors, including melanoma, and could make selective IDO inhibition insufficient to relieve the suppressive effect of kynurenine.
- IDO inhibition, at best, decreases kynurenine by 50% in serum
- Inhibiting downstream of IDO/TDO, where the pathways converge, would be a more potent way of impinging on this important pathway
- Epacadostat is an efflux substrate (PGP and BCRP) and tumor pharmacodynamics may be more informative than serum
- No biomarker selection
- Early data single arm, nonrandomized, small numbers of patients (n=62)

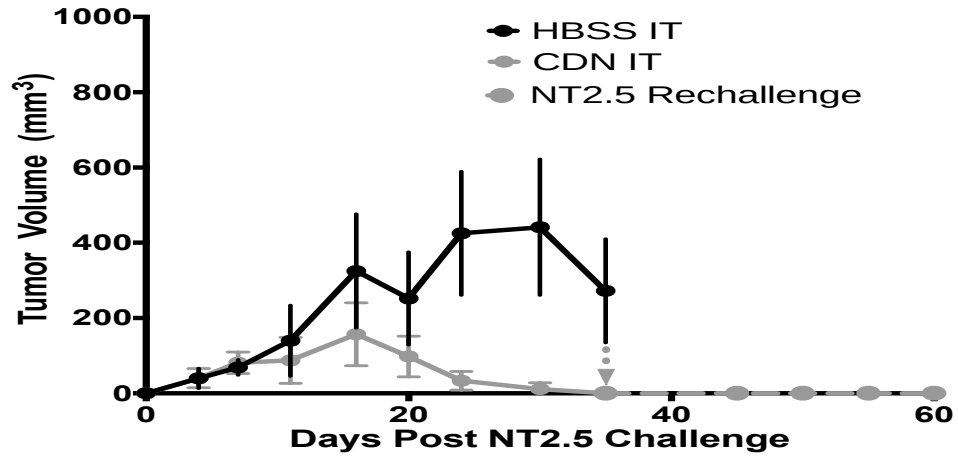
Optimizing the Development of Immunotherapy Combinations

- traditional development path is basic discovery to preclinical modeling to testing in patients
- modern development path interrogates human tumors, both at baseline and after exposure to drugs of interest, to rank the combinations of most interest to test--one drug may have limited activity in itself, but may sensitize tumors to a second agent—then tests both preclinically and in humans
- carefully set the bar for activity of a combination immunotherapy relative to the activity of either single agent in the context of the tumor type in which it is being tested
- evaluate pharmacodynamic changes with systems biology technologies (agnostic and high throughput)
- consider the impact of context and drug sequence (also drug dose)

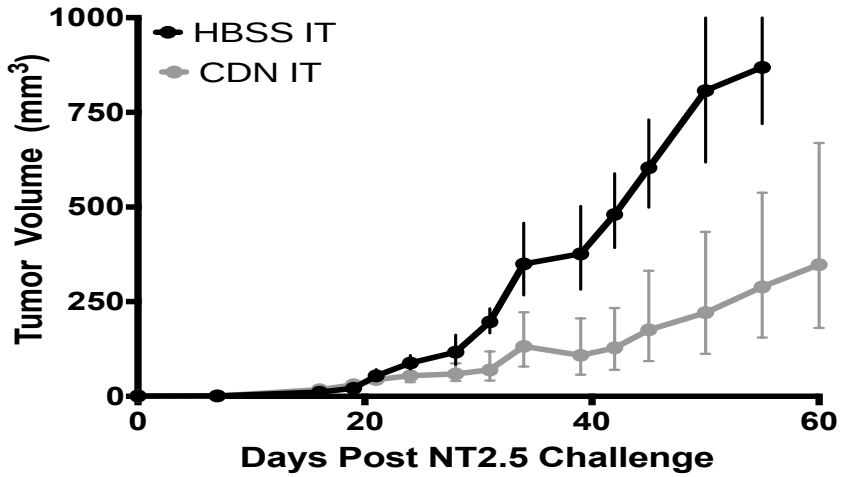
Mellman I et al. Cancer Immunol Res 2016;4:279-288

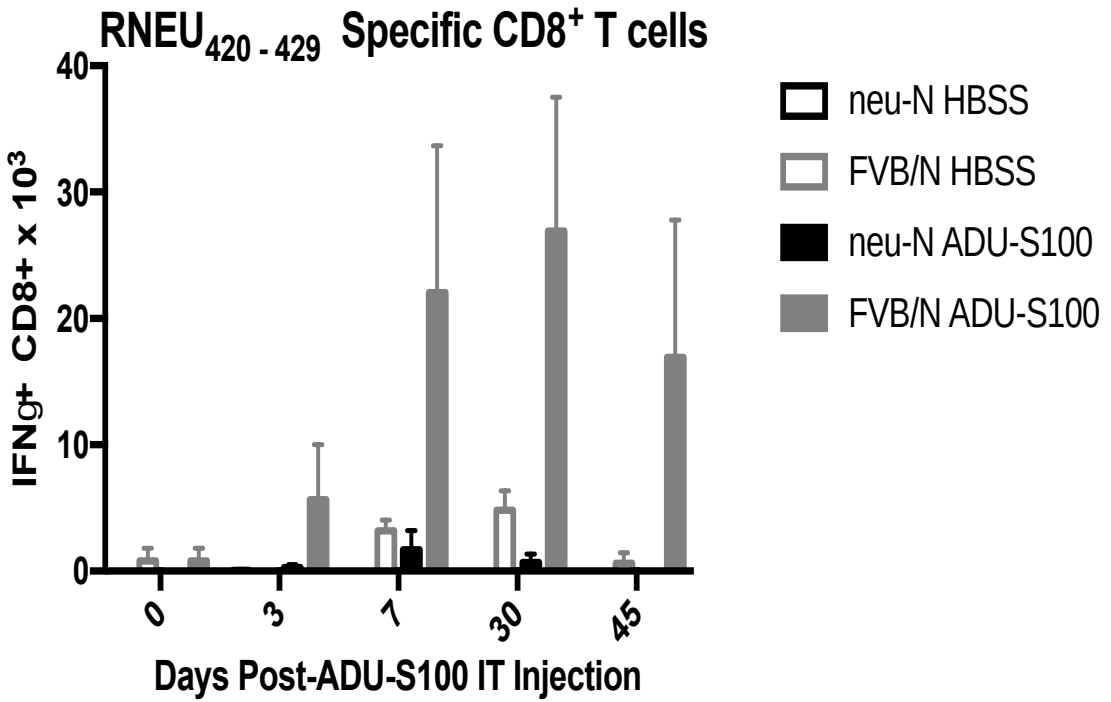
Differential Response to the STING Agonist ADU-S100 in FVB/N and neu/N Mice

FVB/N



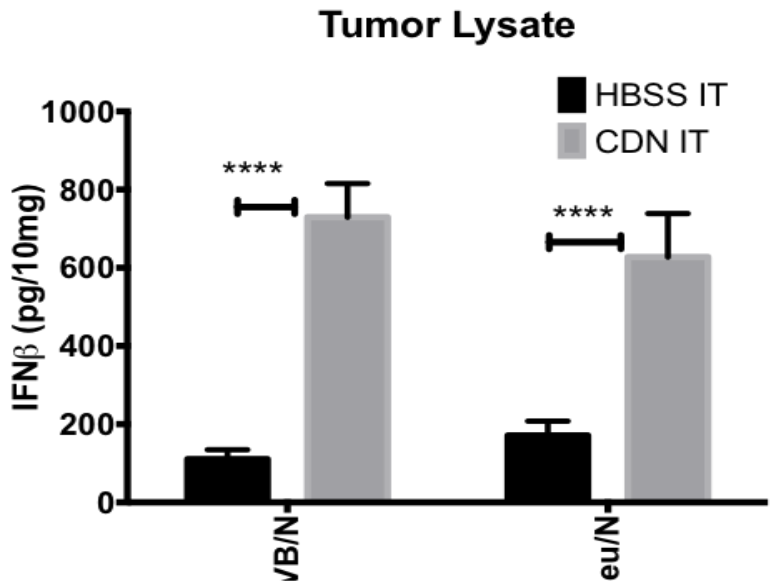
neu/N

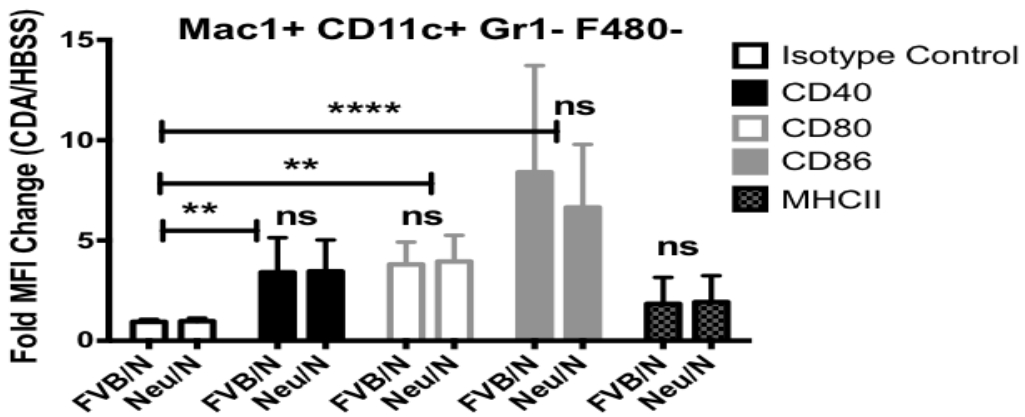


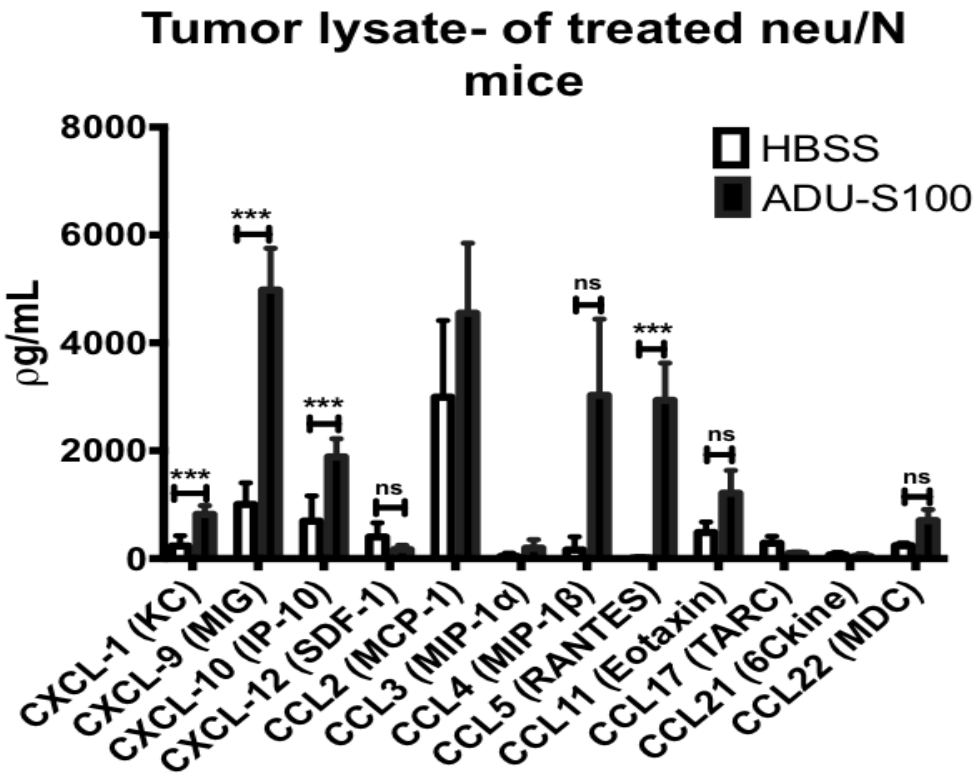


Foote JB/Emens LA at al, Cancer Immunol Res 2017

Proximal Innate Immune Activation is Intact in Neu/N Mice





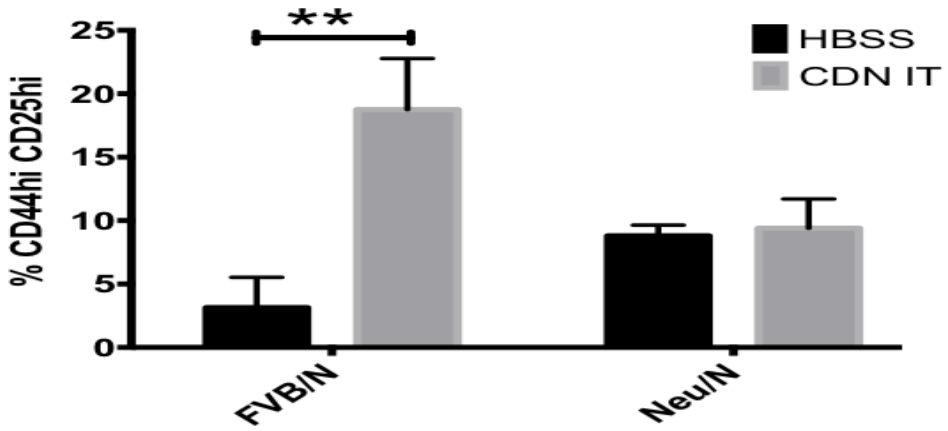


- **Proximal STING signaling events—type I IFN secretion, DC activation, chemokine production—are intact in neu/N mice.**

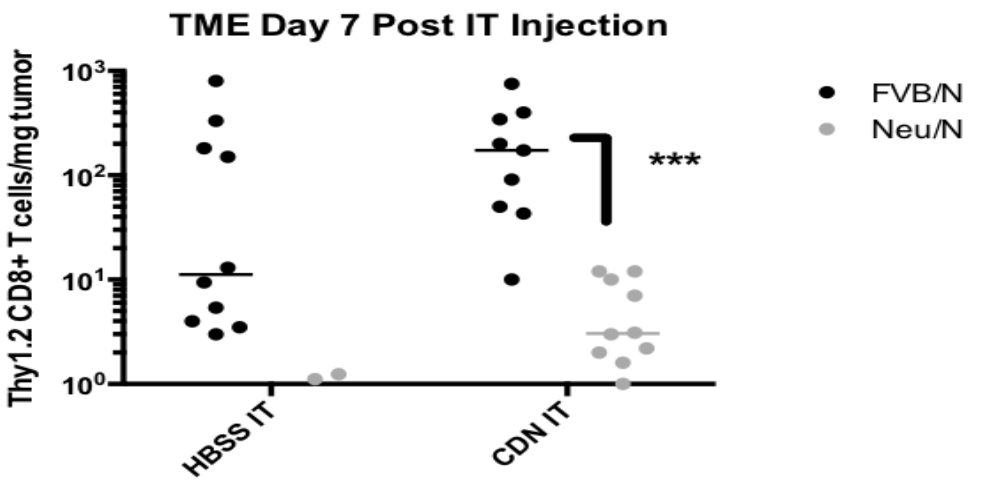
Foote JP/Emens LA Cancer Immunol Res, 2017.

Distal T Cell Priming is Deficient in Neu-N Mice

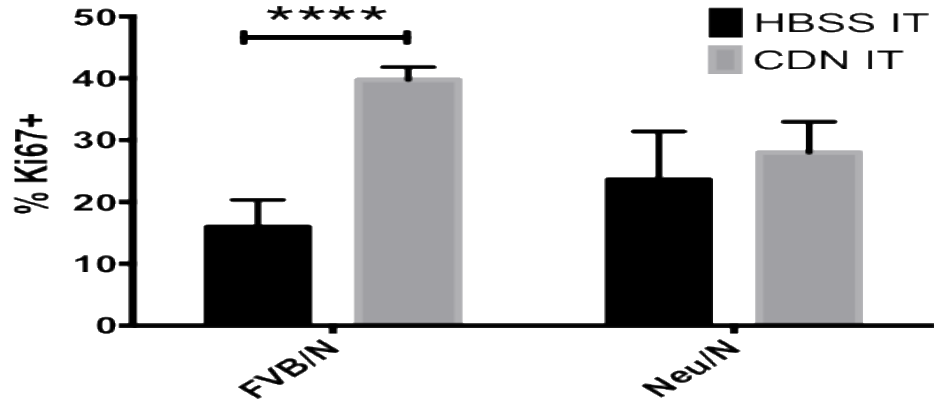
Activation



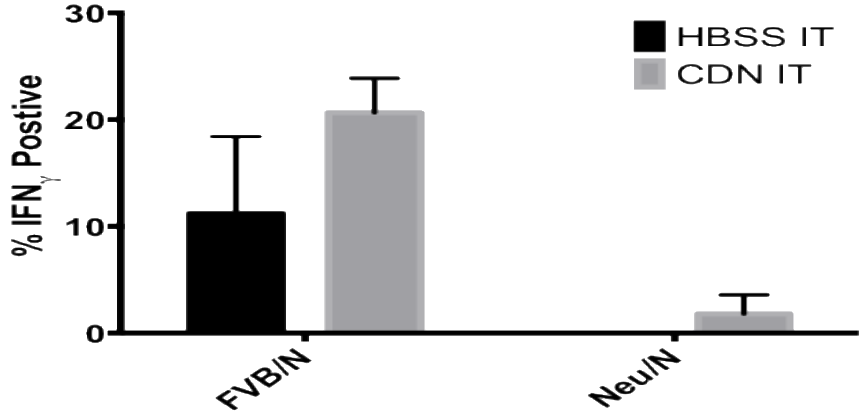
Migration



Proliferation

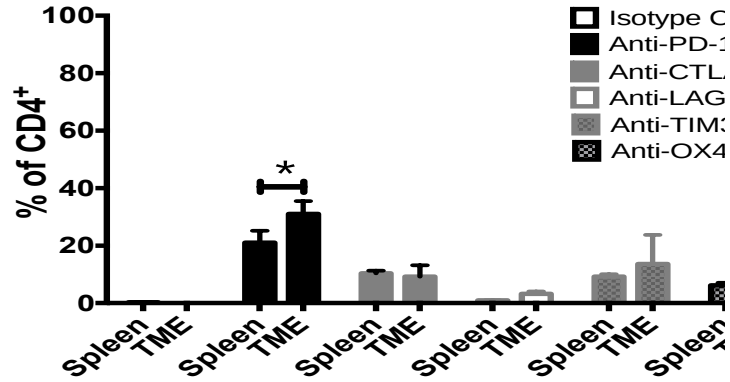


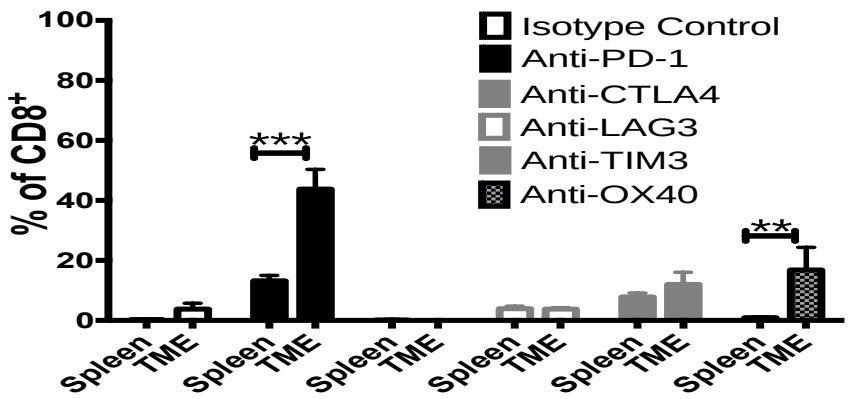
Function



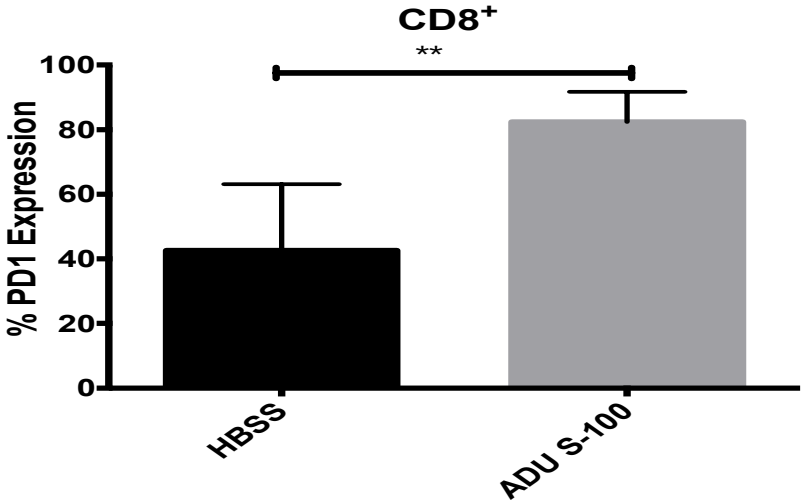
Foote JP/Emens LA Cancer Immunol Res, 2017.

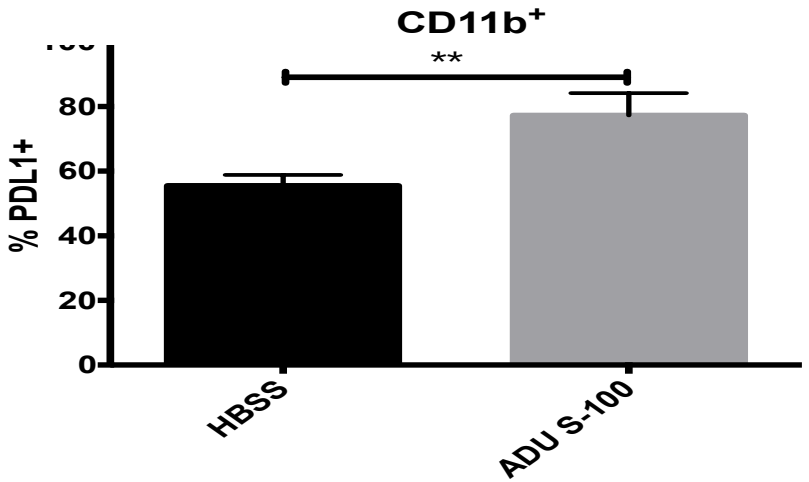
Immune Checkpoint Pathways in the TME of Neu Mice





Baseline



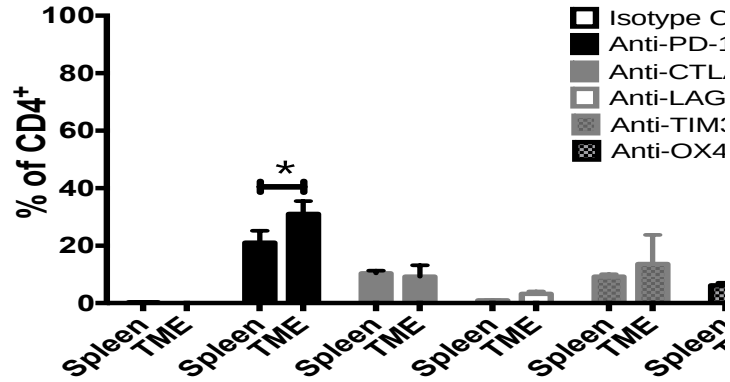


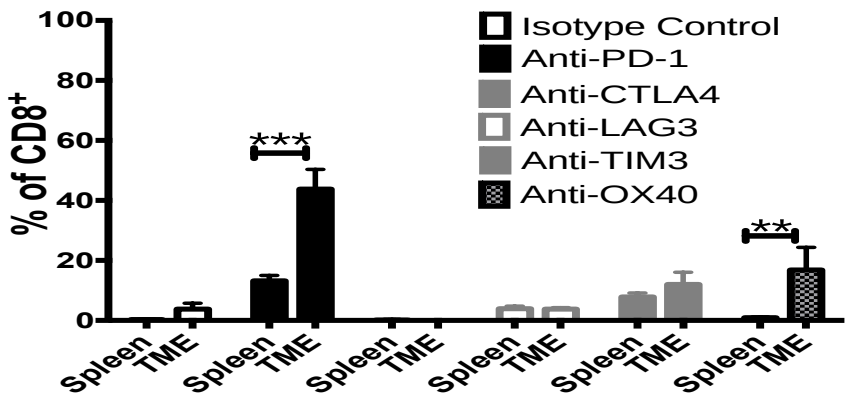
Post-ADU-S100

- **The PD-1 and OX-40 pathways are upregulated in neu/N mice.**

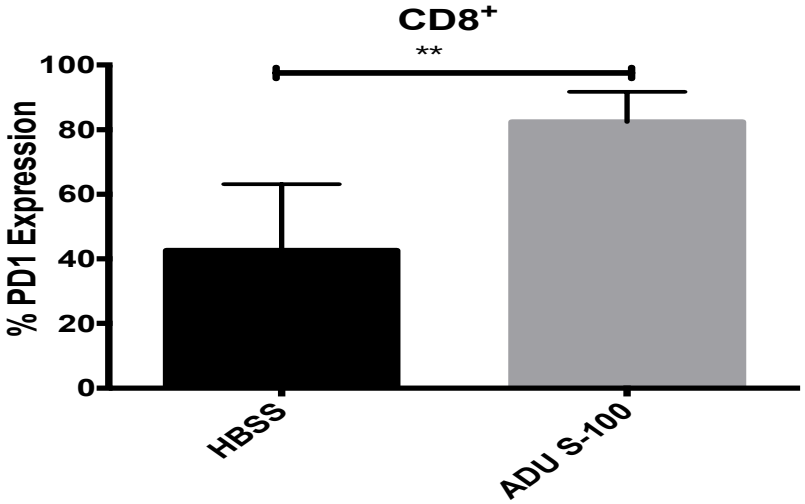
Foote JB/Emens LA at al, Cancer Immunol Res 2017

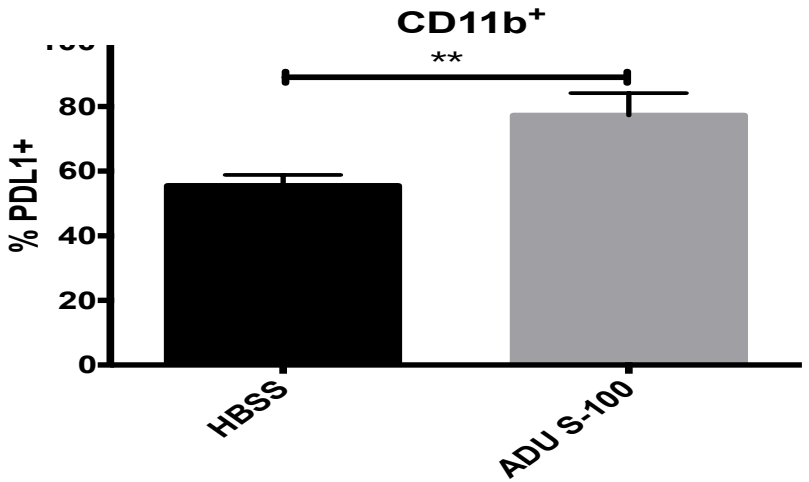
Immune Checkpoint Pathways in the TME of Neu Mice





Baseline



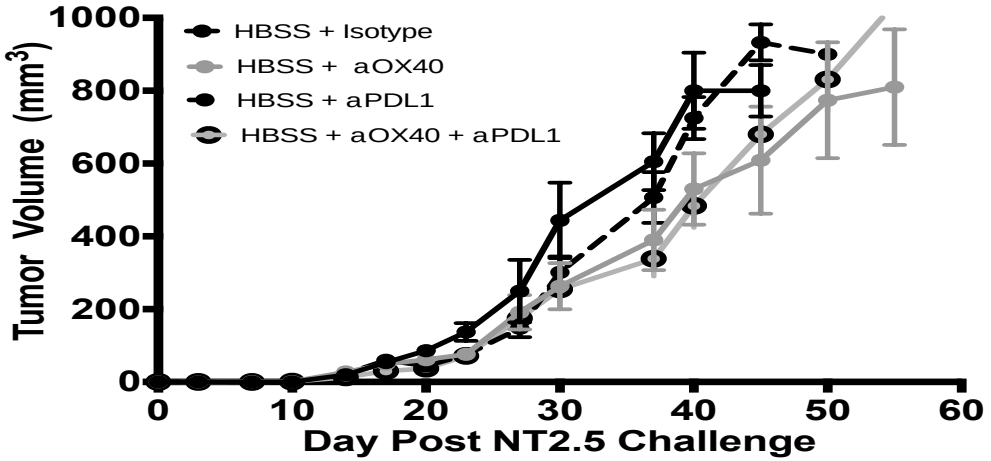


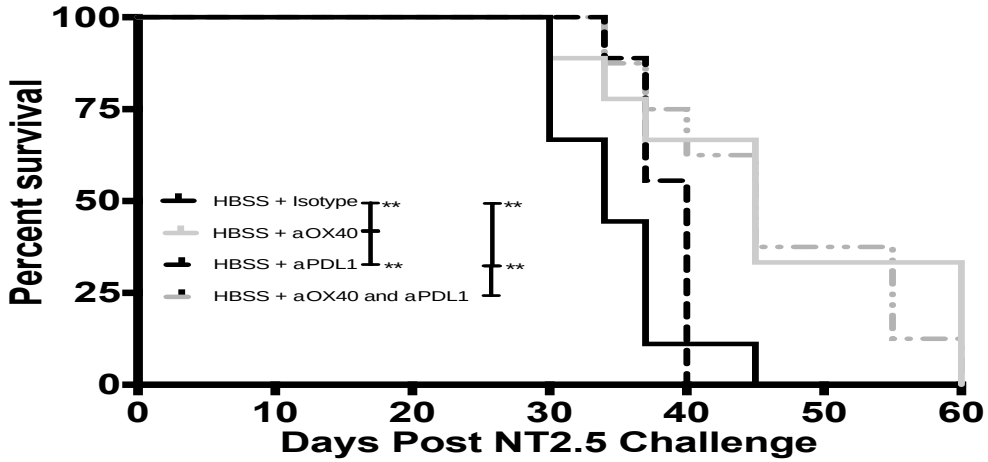
Post-ADU-S100

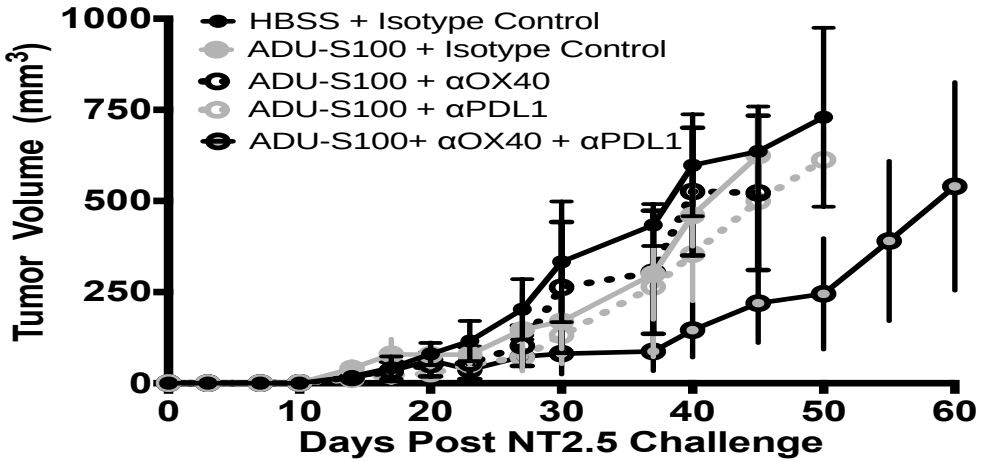
- **The PD-1 and OX-40 pathways are upregulated in neu/N mice.**

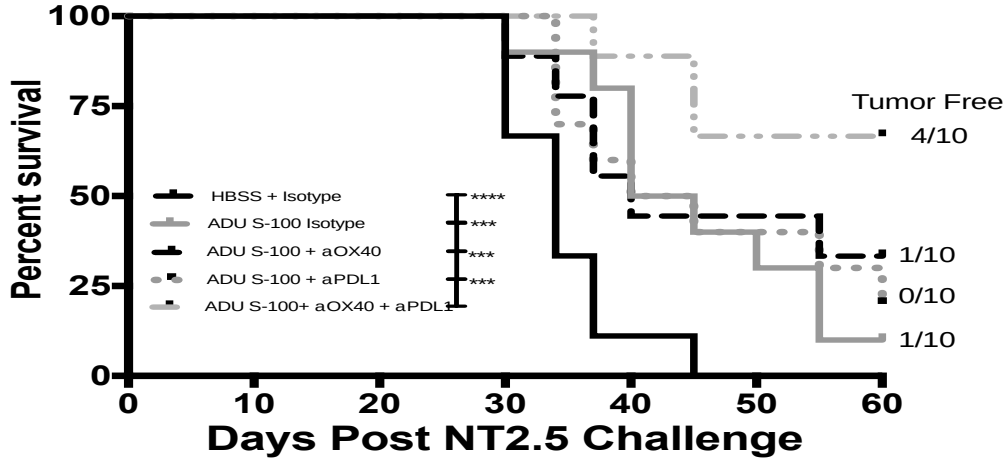
Foote JB/Emens LA at al, Cancer Immunol Res 2017

ADU-S100 Combined with PD-L1 Blockade and OX-40 Activation Prolongs Tumor-Free Survival in neu/N Mice



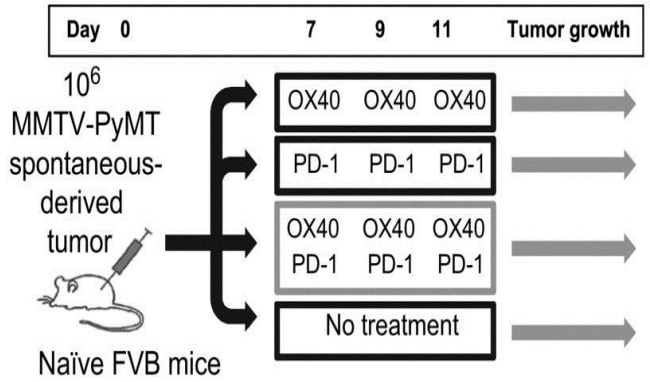


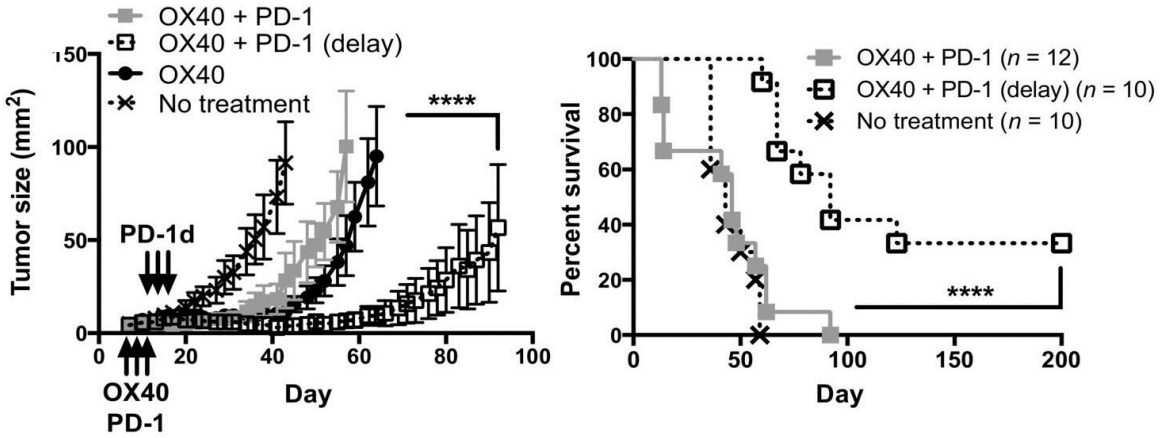


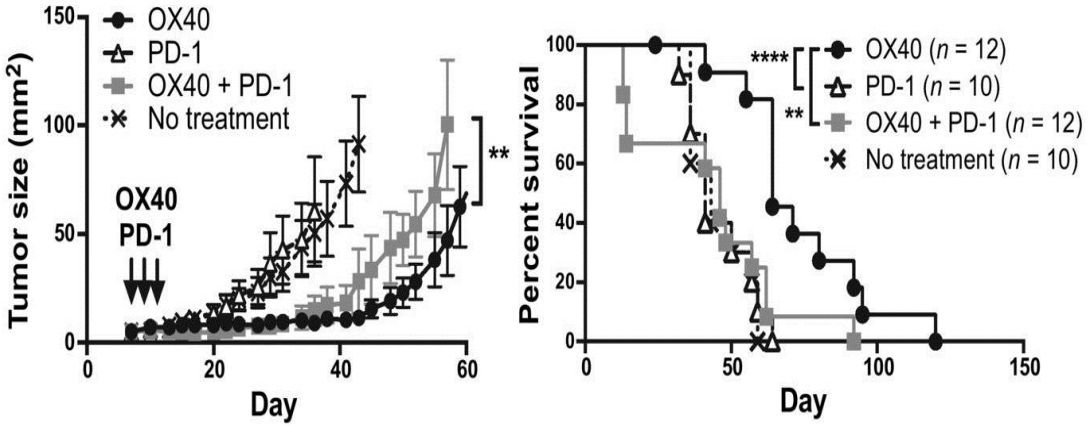


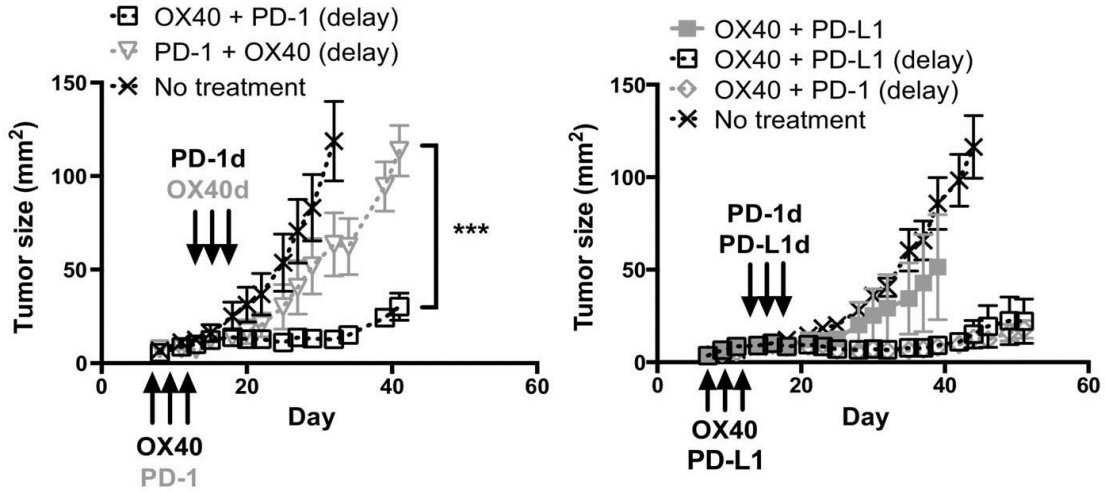
Foote JB/Emens LA at al, Cancer Immunol Res 2017

Timing of PD-1 Blockade and OX-40 Activation May Be Critical





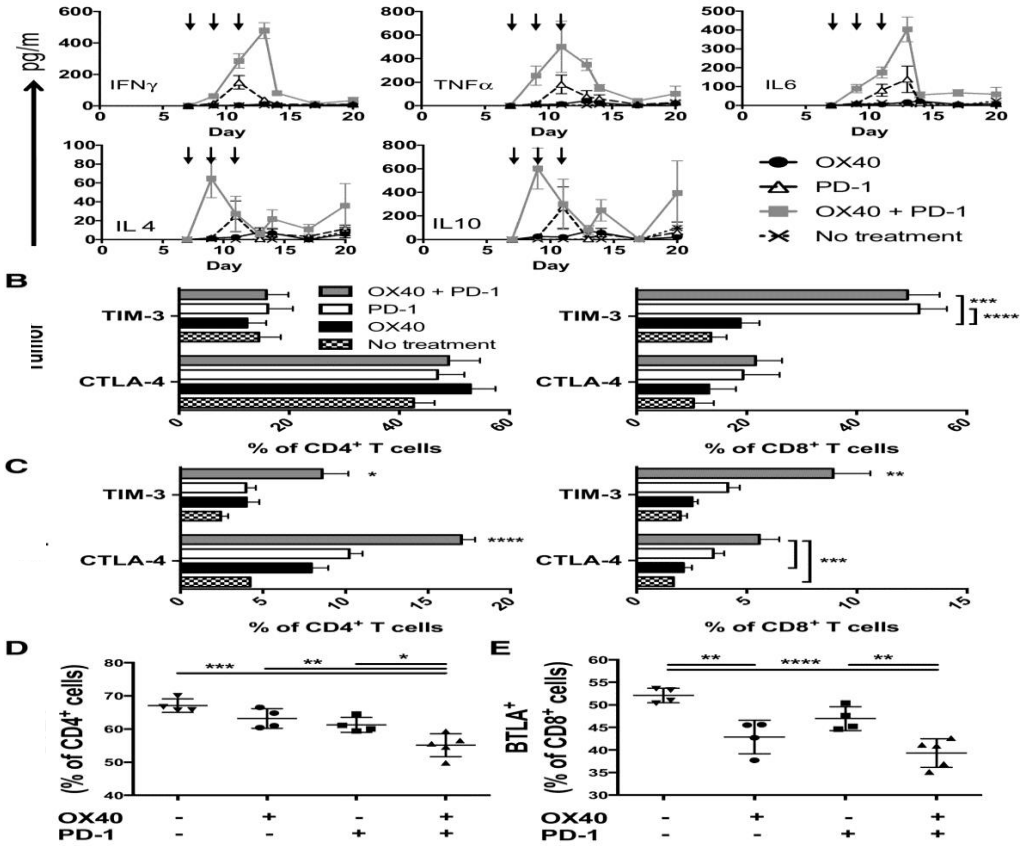




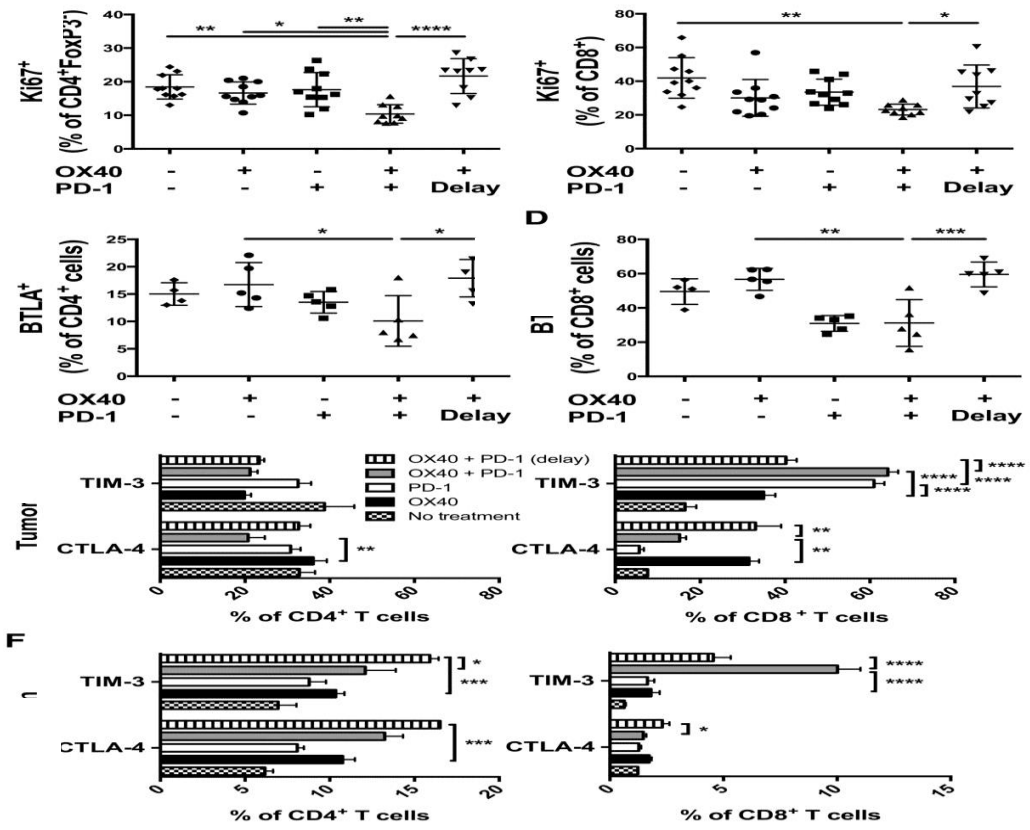
Messenheimer DJ et al. Clin Cancer Res 2017;23:6165-6177

Timing of PD-1 Blockade and OX-40 Activation May Be Critical

Concurrent



Sequential



increases proliferating T cells and increases circulating serum cytokines and inhibitory receptors

maintains proliferating T cells without increase in inhibitory receptors

Messenheimer DJ et al. Clin Cancer Res 2017;23:6165-6177

Conclusions

- Immunotherapy is transforming the lives of cancer patients who respond
- To date, a minority of cancer patients benefit from immunotherapy
- Combination immunotherapies could deliver the impact of immunotherapy to more patients
- The development of combinations should consider the immunobiology of the patient's tumor, the mechanism of each agent, and how they might interact when given together
- Trial designs should take into account the activity of monotherapy in the tumor type of interest for endpoints; incorporate baseline, on-treatment, and post-progression tumor biopsies, an agnostic, systems-based biomarker evaluation strategy to elucidate mechanisms of response and resistance
- Unexpected and/or synergistic toxicities may occur with combination immunotherapies

Thank you!