Combination Immunotherapies

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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, Replimune, Bristol-Myers Squibb, Roche, Genentech, Macrogenics, Lilly, Chugai, Silverback

Grant/Research support from: Genentech/Roche, EMD Serono, Maxcyte, Merck, AstraZeneca, Aduro, Corvus, Silverback, Bolt, Takeda, Bristol-Myers Squibb

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

I will discuss the following off-label use and/or investigational use:

Pembrolizumab, Atezolizumab

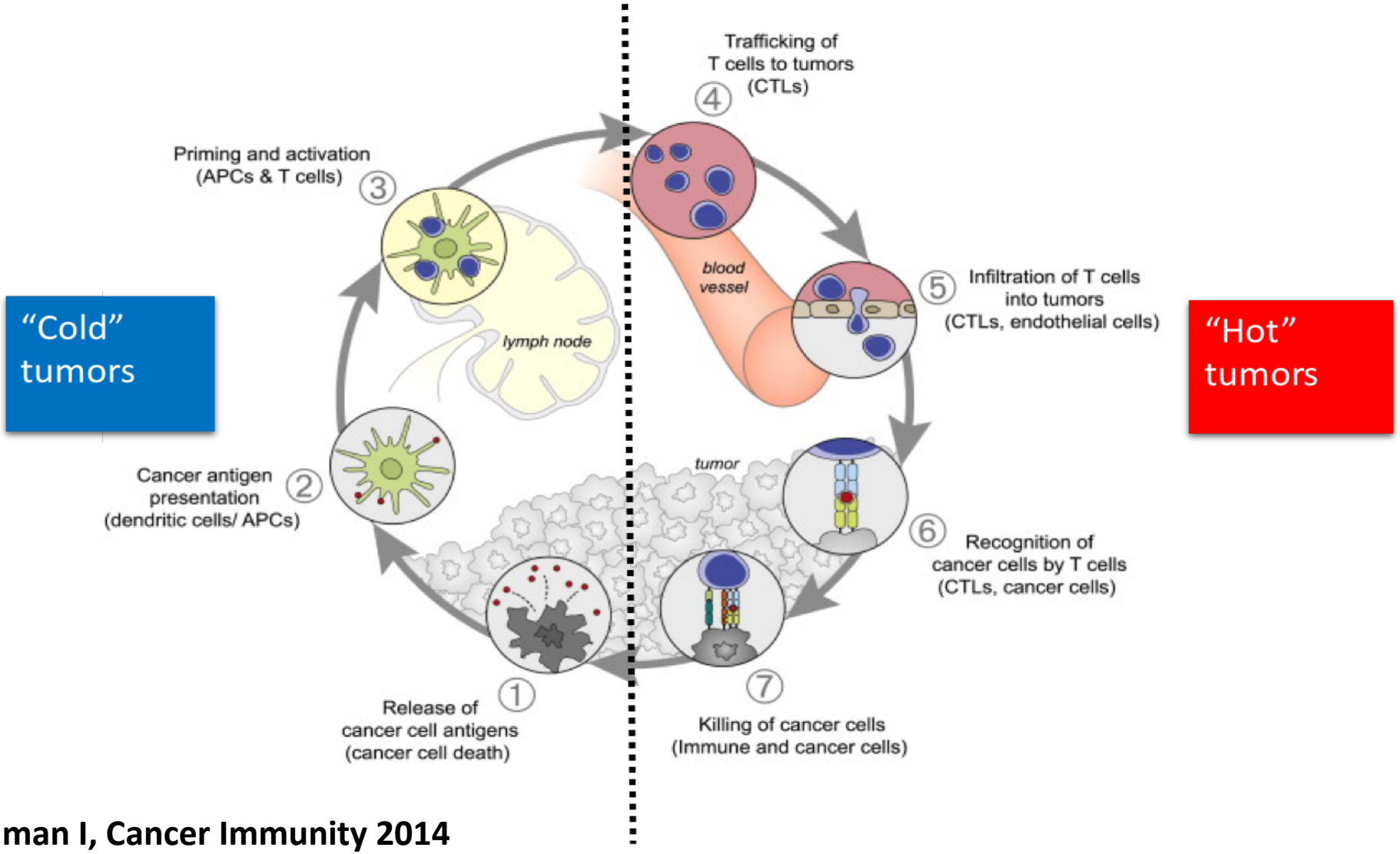
Key Features of Immune Checkpoint Blockade

- 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?

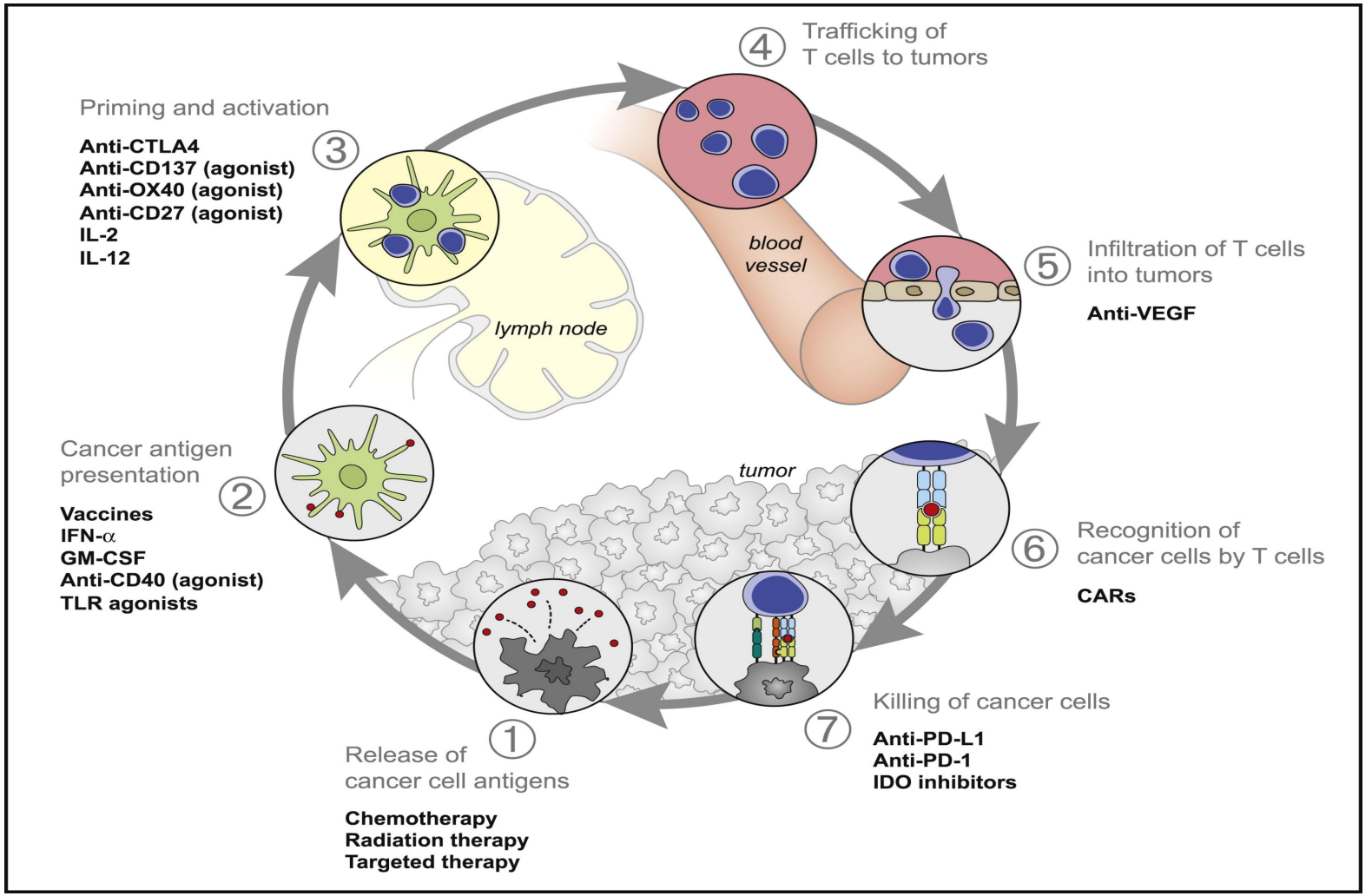
- Convert non-responders to responders
  - ✓overcome primary resistance
- Rescue patients who progress on immunotherapy
  - ✓overcome secondary resistance
- Deepen responses that do occur
  - ✓increase survival benefit
- Harness tumor biology to support immunotherapy
  - ✓monoclonal antibodies
  - ✓small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

The Cancer Immunity Cycle



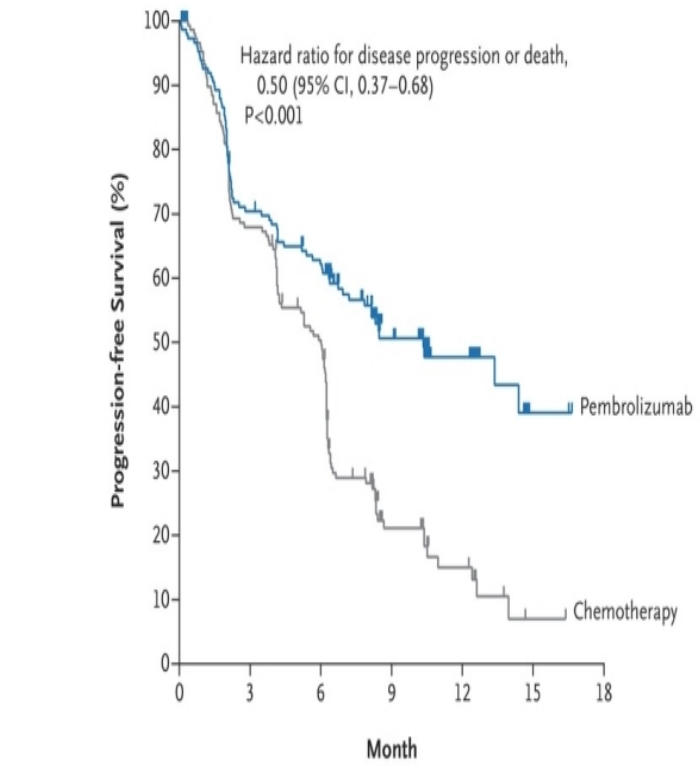
Chen DS, Mellman I, Cancer Immunity 2014

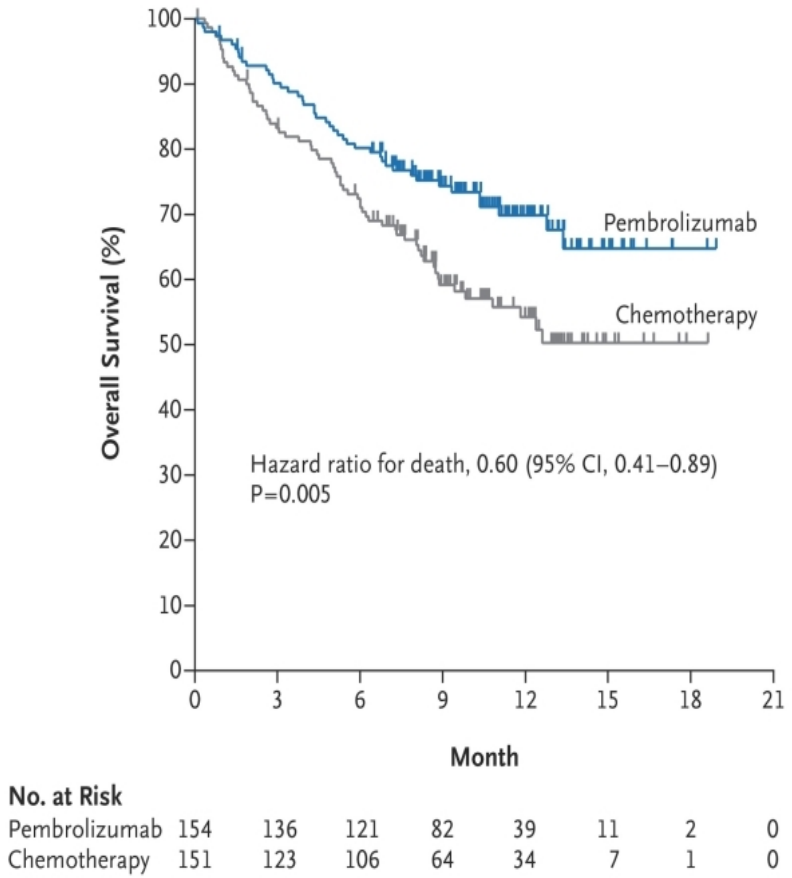
Harnessing the Cancer Immunity Cycle for Therapeutic Benefit



Chen DS, Mellman I, Cancer Immunity 2014

Single Agent Pembrolizumab for Untreated Metastatic NSCLC





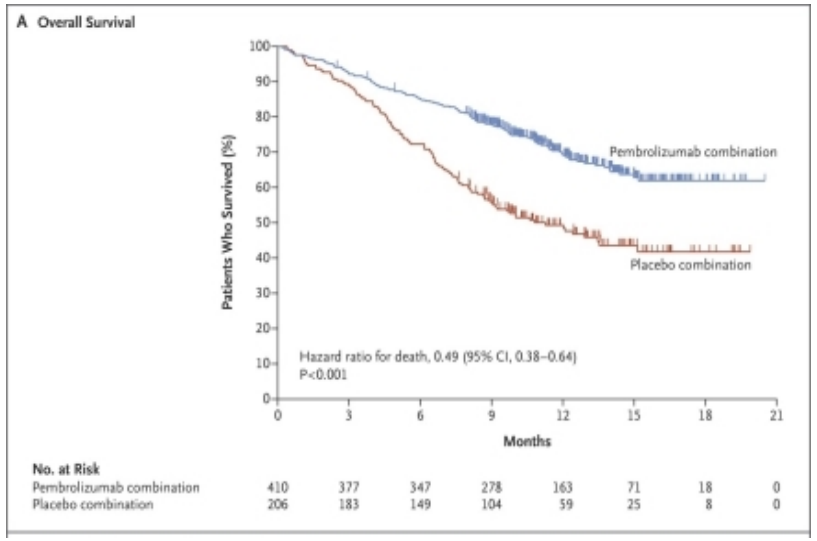
305 patients with untreated PD-L1+ TC >50% metastatic NSCLC w/o ALK or EGFR mutation were randomized 1:1 to pembrolizumab alone or platinum-based chemotherapy

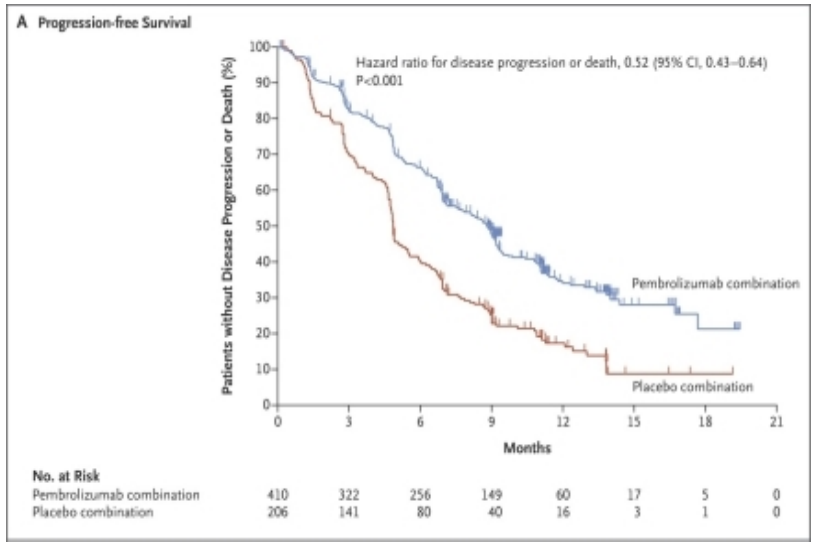
	Pembro	Platinum
ORR	44.8%	27.8%
mPFS	10.3 mo	6 mo
OS 6 mo	80.2%	72.4%
DOR	NR	6.3 mo

Pembrolizumab better tolerated than chemotherapy

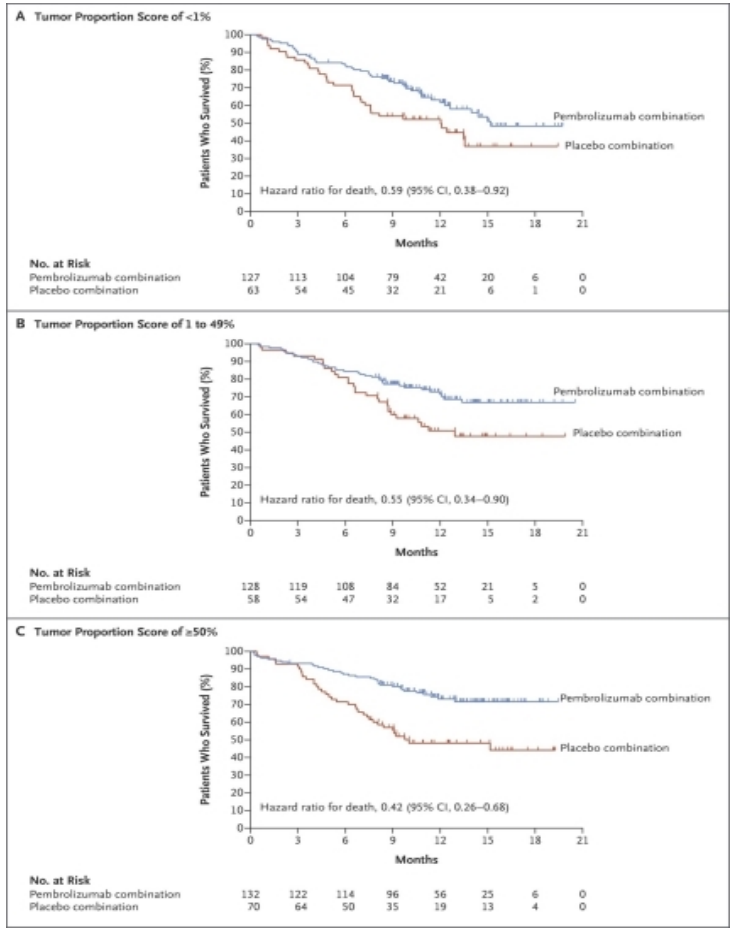
Reck M et al. N Engl J Med 2016;375:1823-1833

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%)

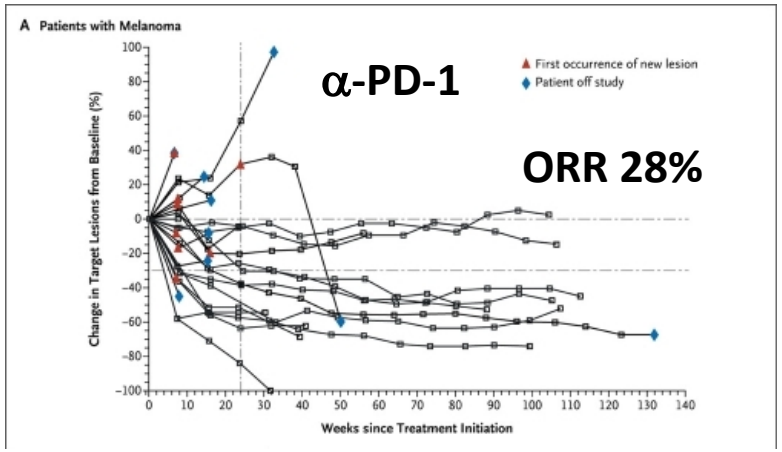


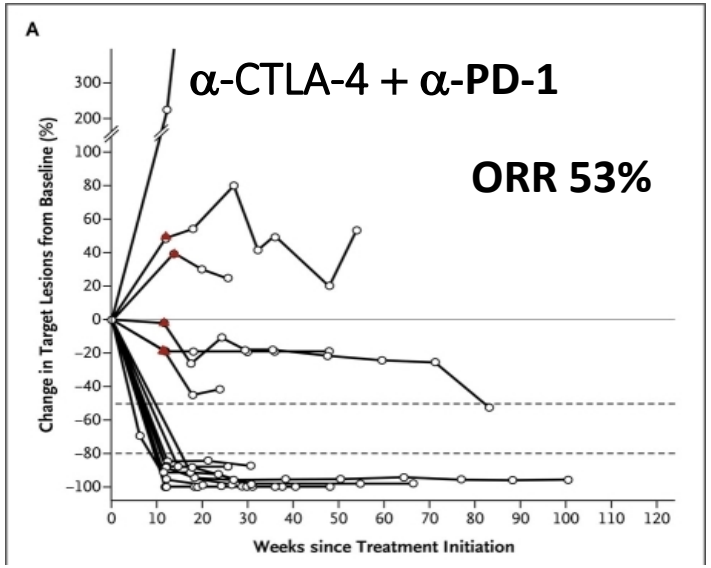
	Chemo+ Pembro	Placebo + Chemo
ORR	47.6 %	18.9 %
mPFS	8.8 mo	4 mo
OS 12 mo	69.2%	49.4%
DCR	84.6%	70.4%
DOR	11.2 mo	7.8 mo

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

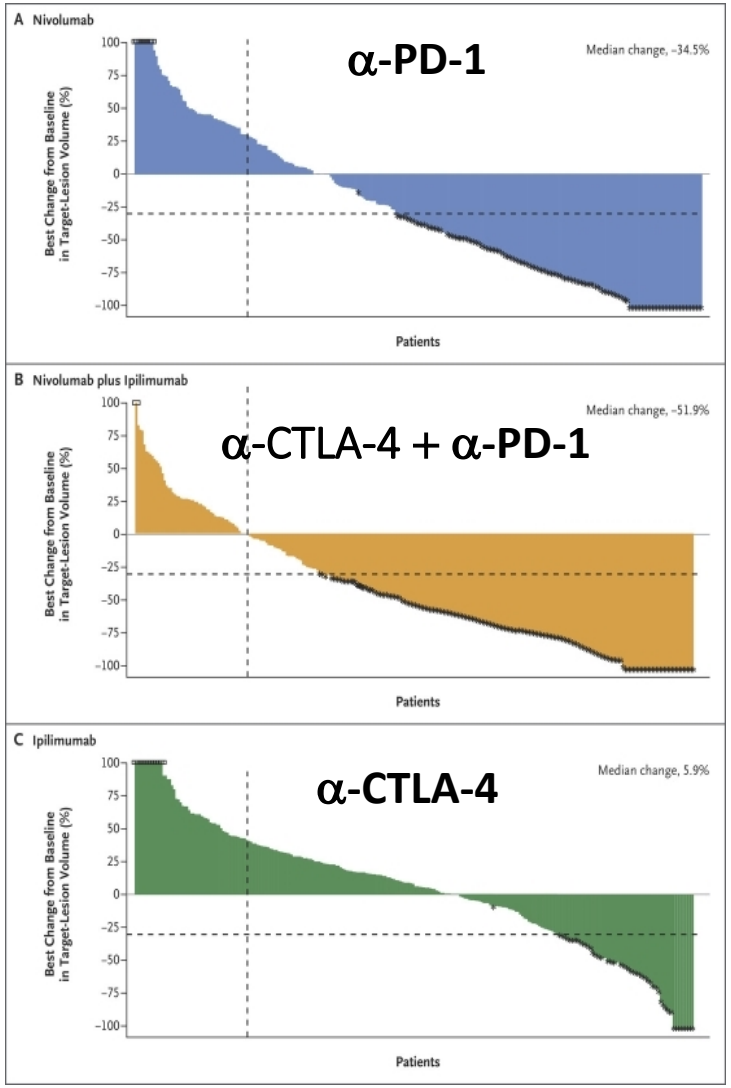
Dual Immune Checkpoint Blockade:
anti-CTLA-4 + anti-PD-1



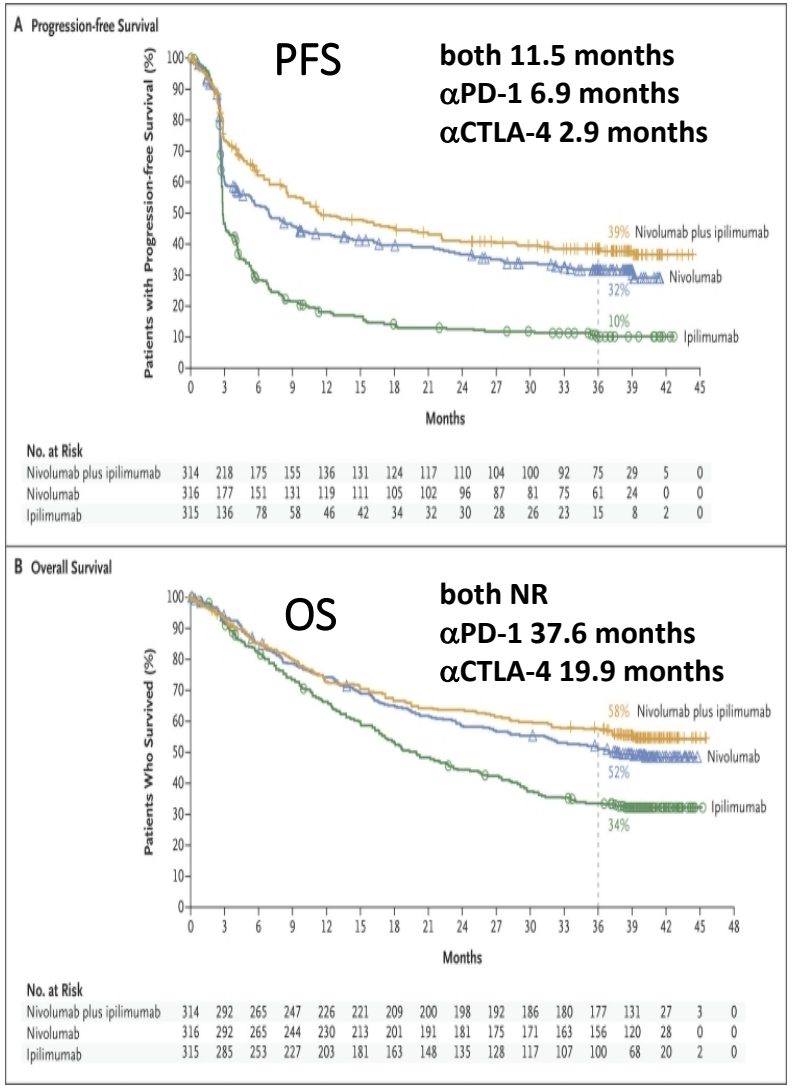


Topalian SL et al. N Engl J Med 2012;366:2443-2454.

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



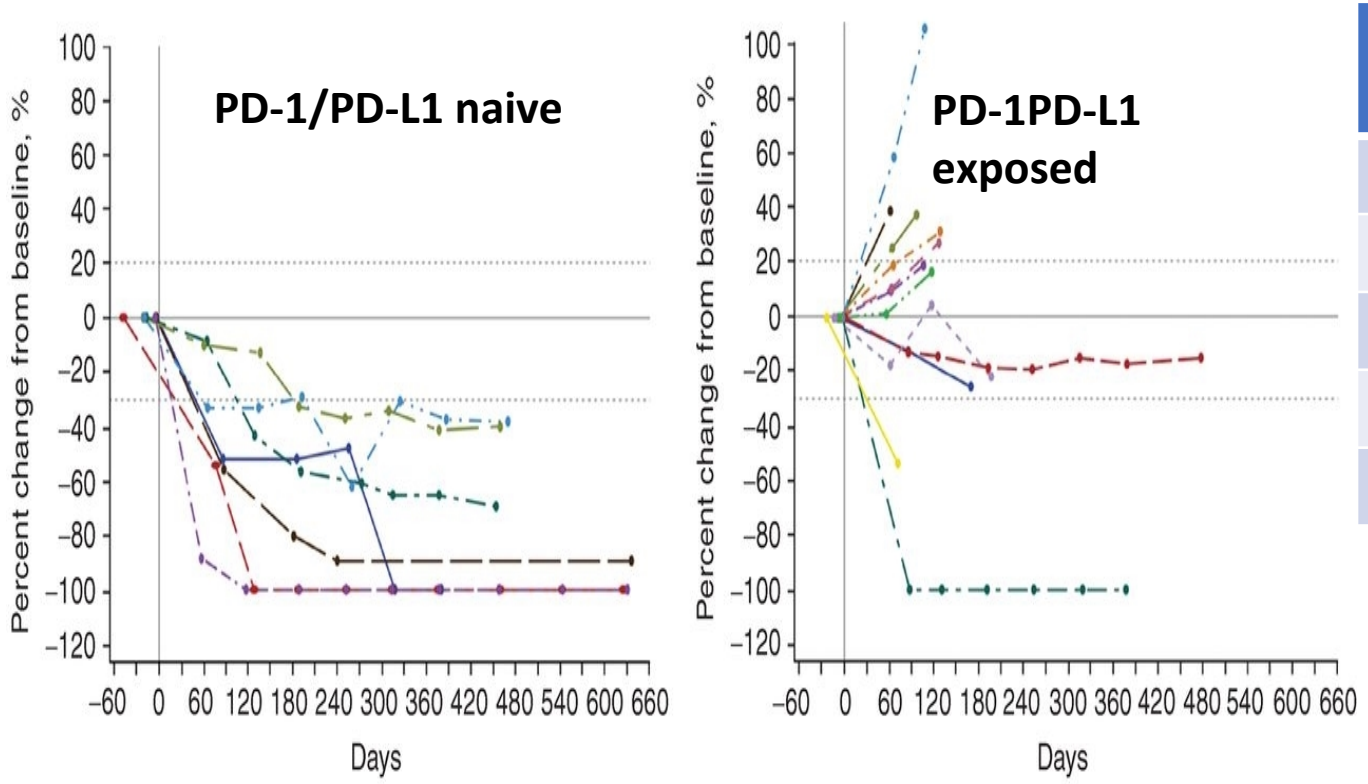
Larkin J et al. N Engl J Med 2015;373:23-34.



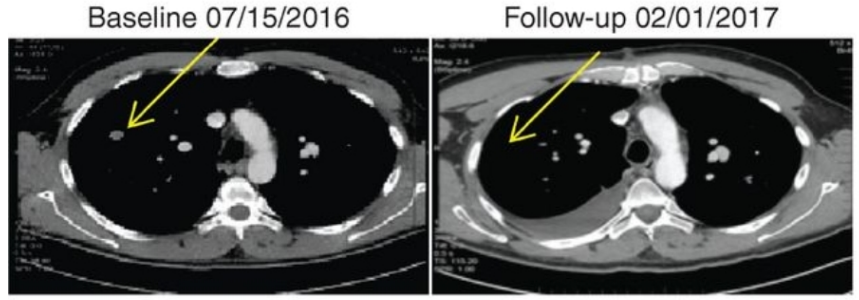
Wolchok JD et al. N Engl J Med 2017;377:1345-1356.

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

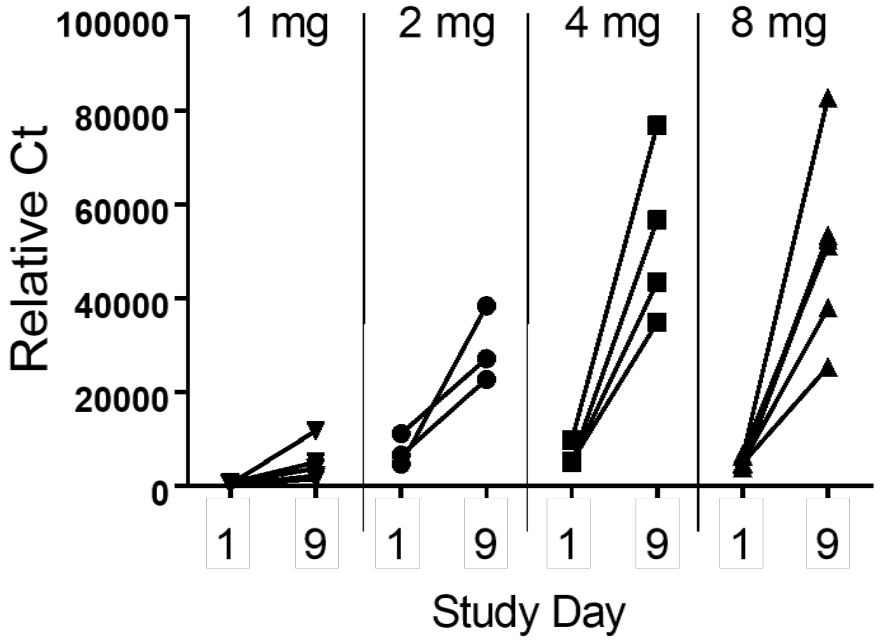


	PD-1/PD-L1 Naive [n=9]	PD-1/PD-L1 Exposed [n=13]
ORR	7 (78%)	2 (15%)
CR/PR	2/5	0/2
SD	0	5
DCR	7 (78%)	7 (54%)
PD	1 (11%)	5 (38%)

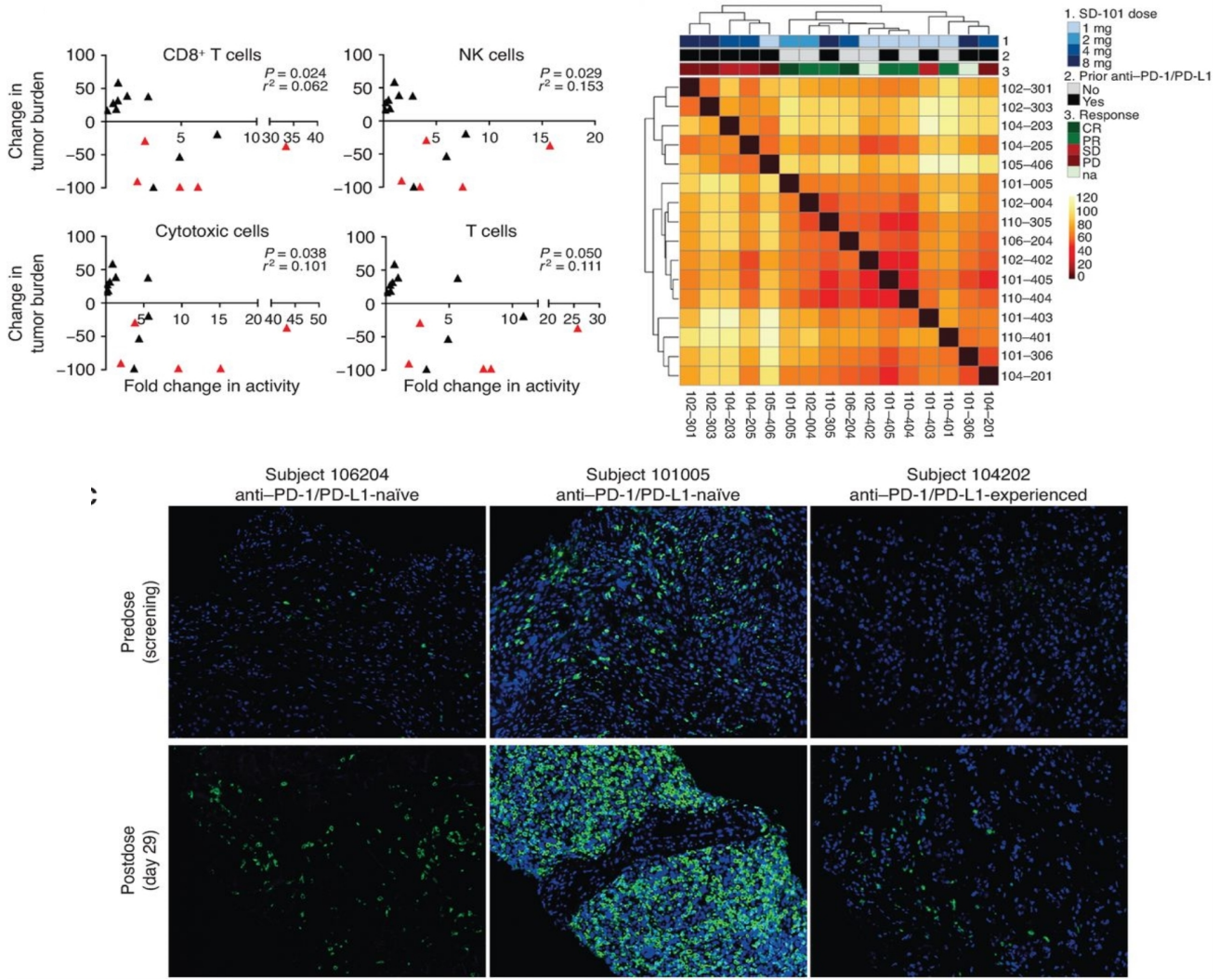


Antoni Ribas et al. Cancer Discov 2018;8:1250-1257

Pharmacodynamic Changes on SD-101 Therapy

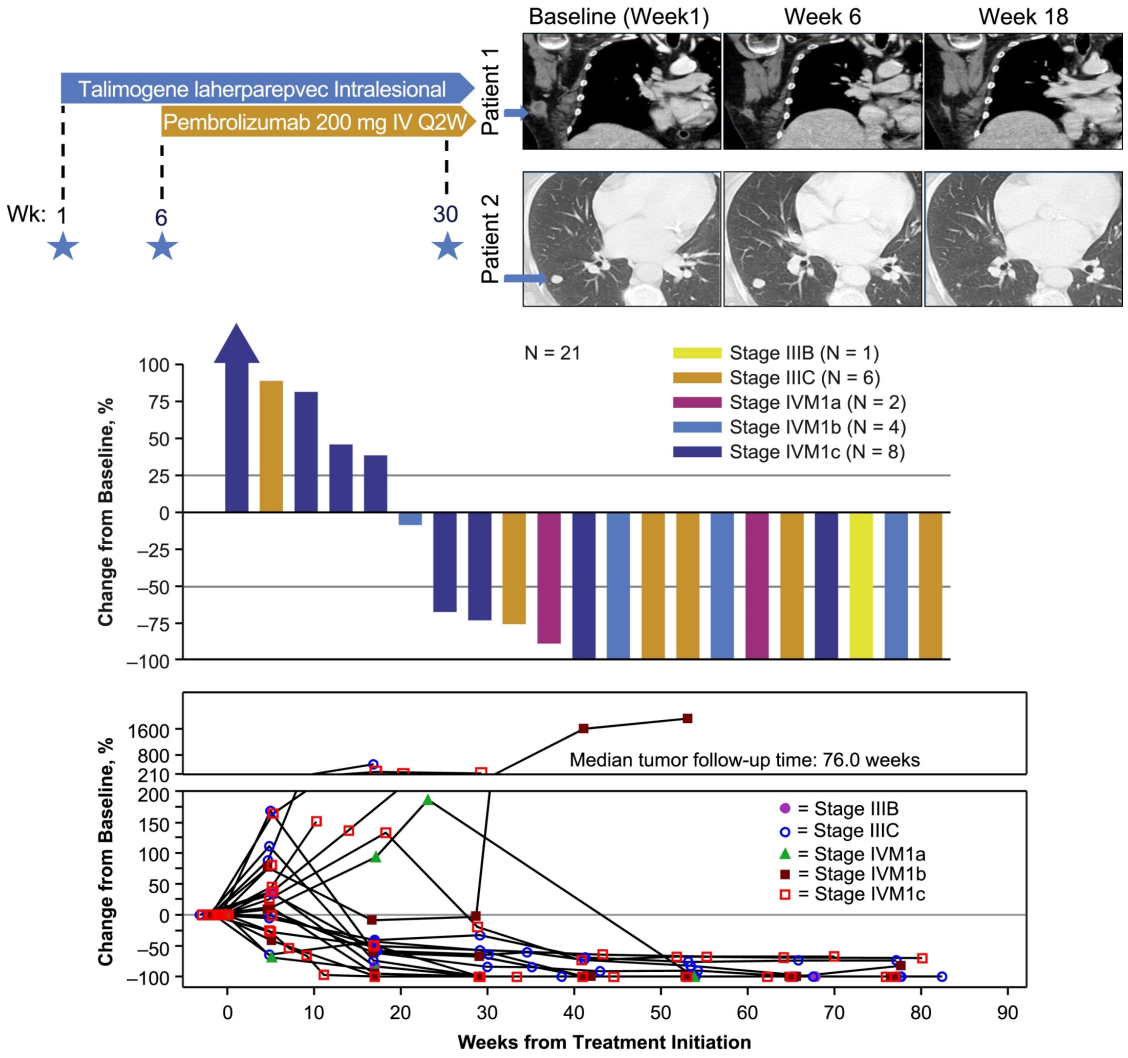


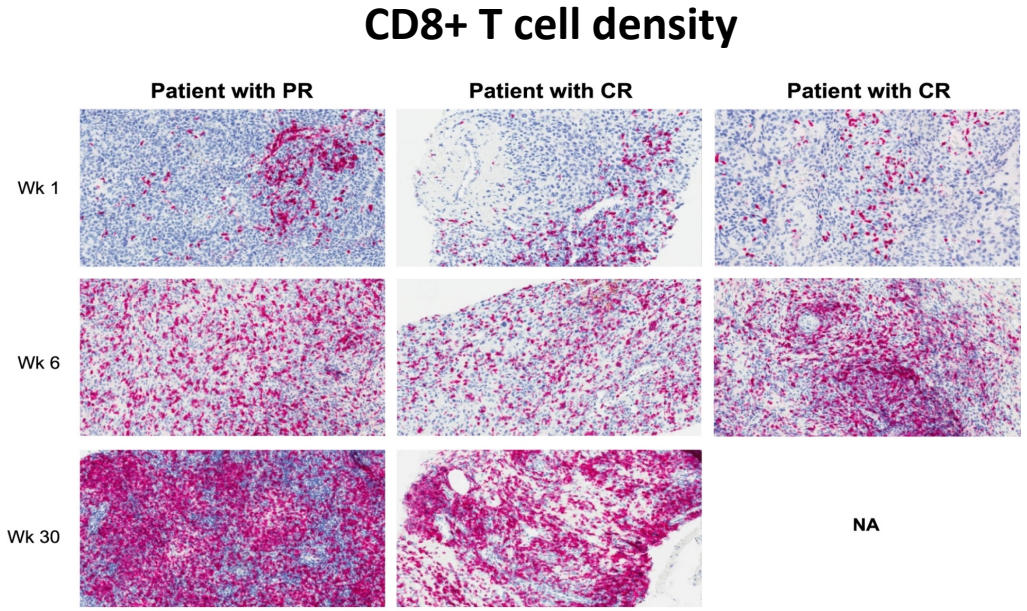
induction of IFN-α-responsive genes (GBP1, IFIT2, CCL2, MX2) in PBMC as a surrogate for intratumoral production, timepoint was 24 hours after second dose (day 9)



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

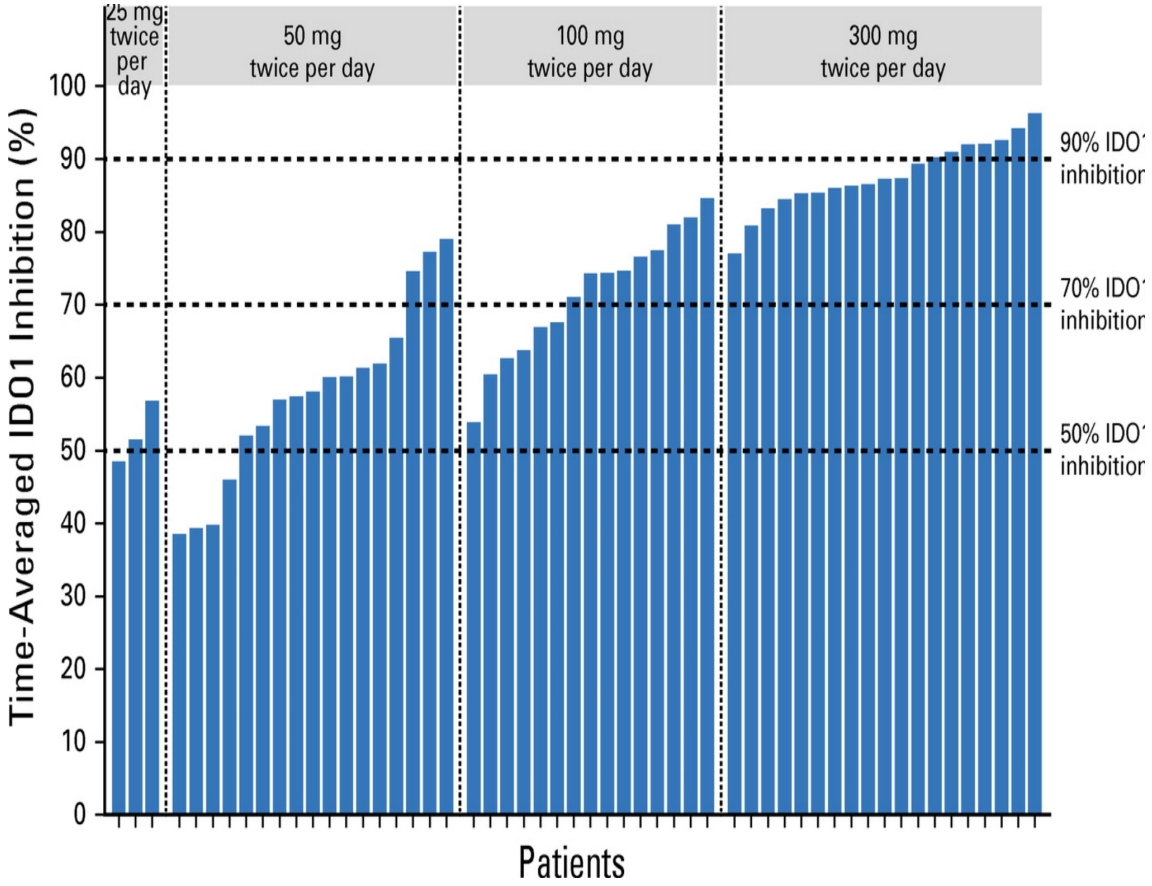
Ribas A et al. Cell 2017;170:1109-1119

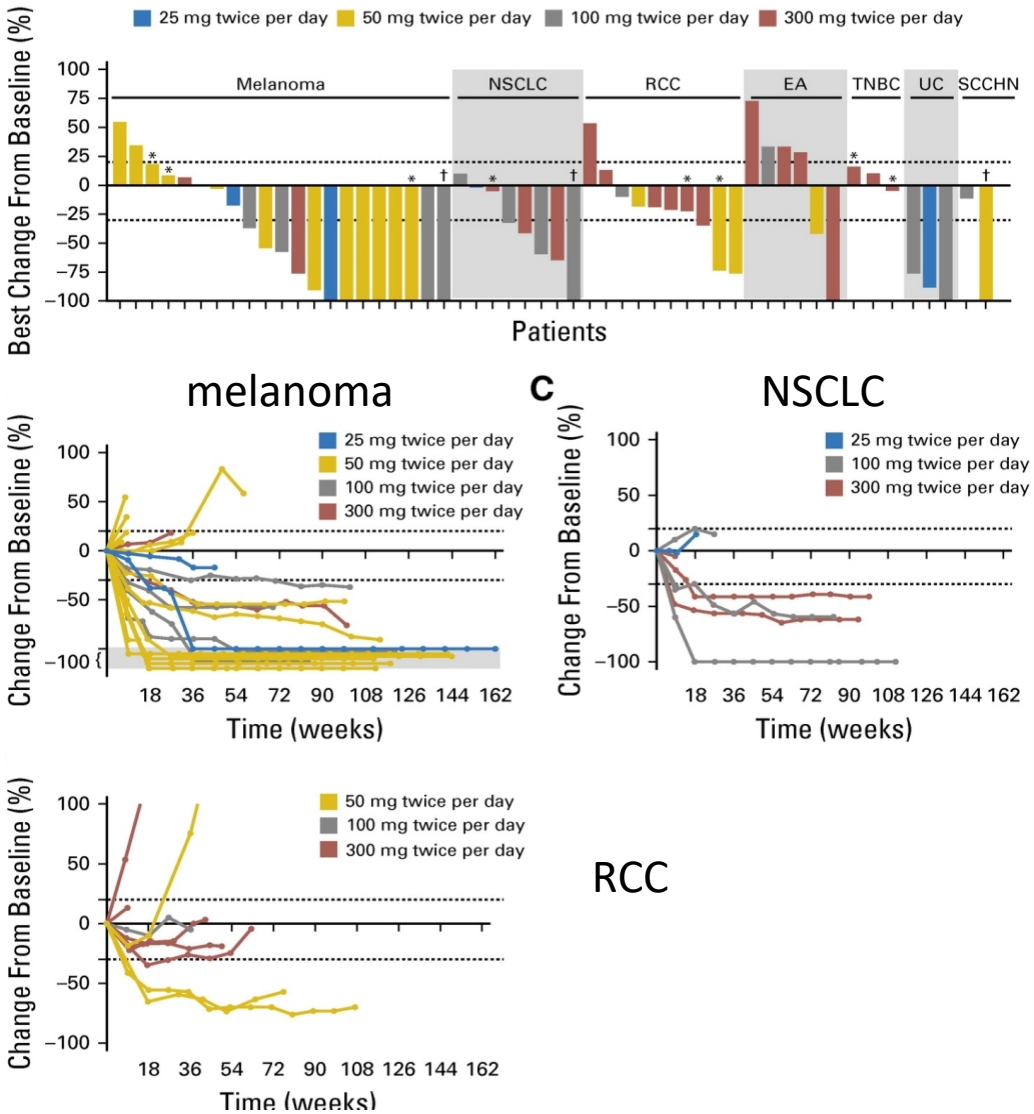
Epacadostat + Pembrolizumab in Advanced Solid Tumors

- 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??

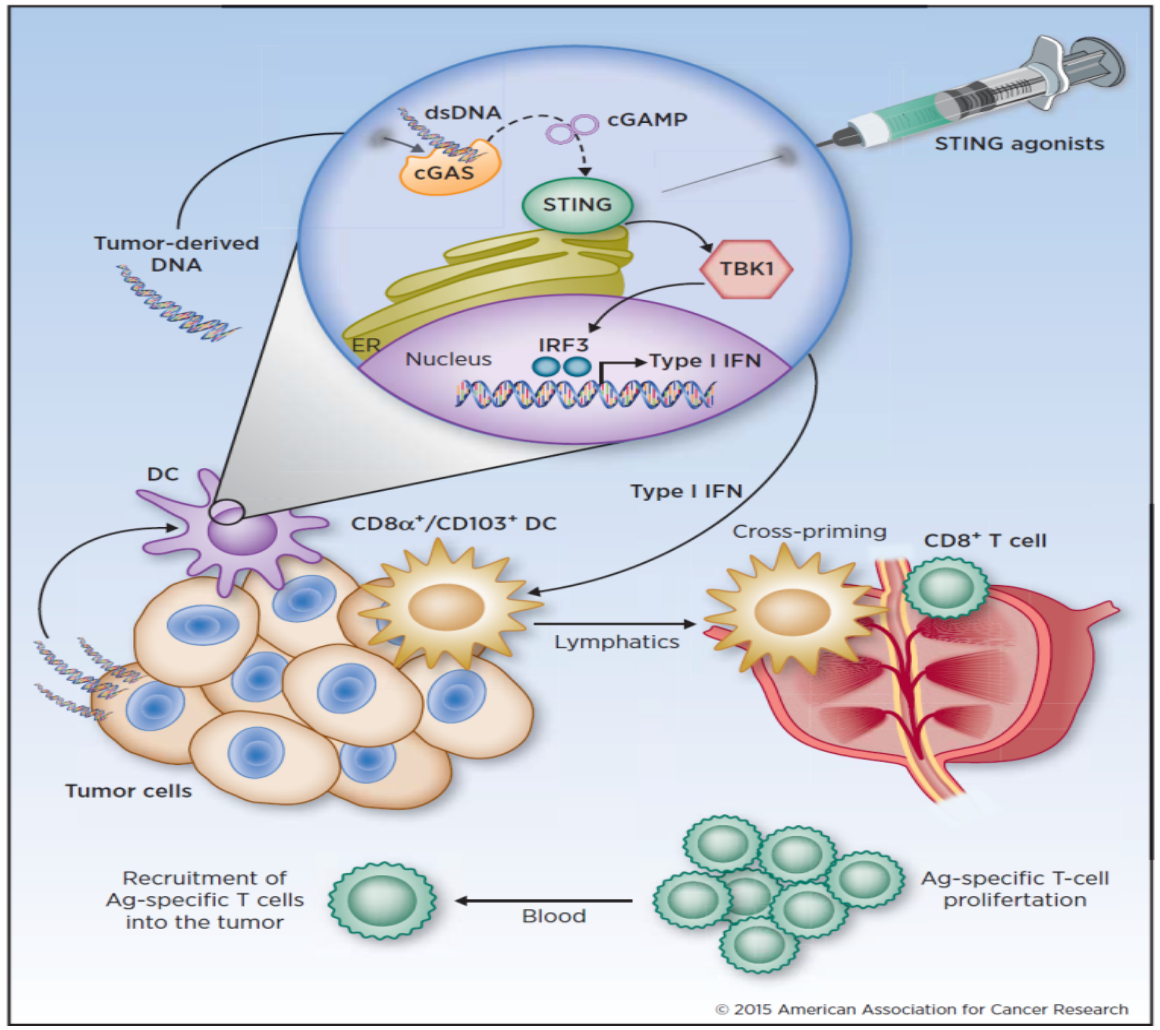
- TDO is expressed in addition to IDO in many tumors, including melanoma, and could make selective IDO inhibition insufficient to relieve the suppressive effect of kynurenine.
- IDO inhibition, at best, decreases kynurenine by 50% in serum
- Inhibiting downstream of IDO/TDO, where the pathways converge, 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

CDNs Activate STING Signaling to Initiate Intratumoral T cell Priming



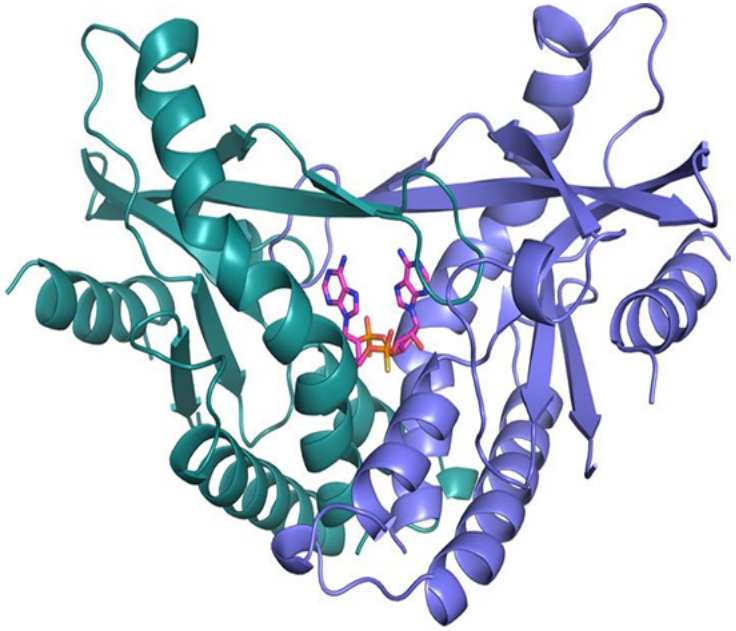
- T cell inflamed tumors in humans typically have an IFN-β transcriptional signature
- STING is the critical receptor to activate immune cells, including dendritic cells
- Tumor-derived DNA induces IFN-β by tumor resident DCs through STING signaling
- Intratumoral injection of CDNs induces IFN-β, activating tumor-resident DCs that stimulate tumor specific $CD8^+$ T cell priming

Corrales and Gajewski, Clin Cancer Res 2015

ADU-S100: An Improved CDN Agonist of STING

(R,R) dithio diastereoisomer, non-canonical mixed-linkage [2,3]-cyclic di-AMP analog

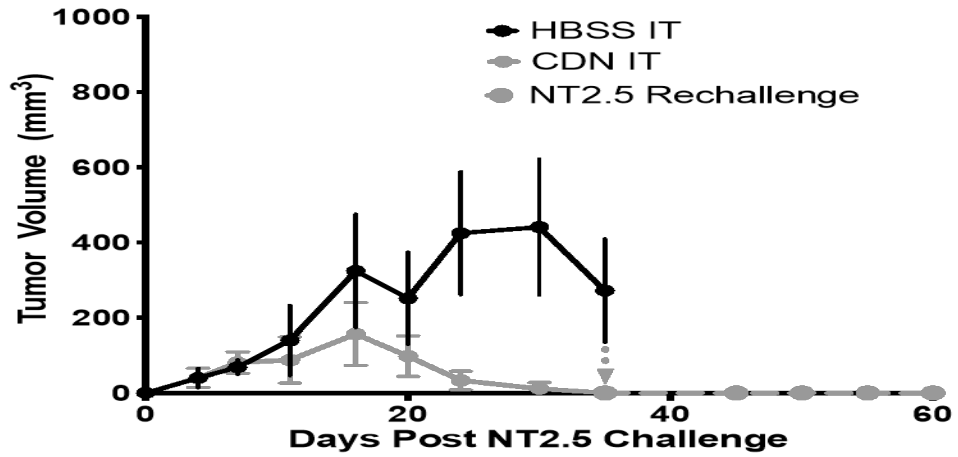
ADU-S100 STING
Co-Crystal Structure



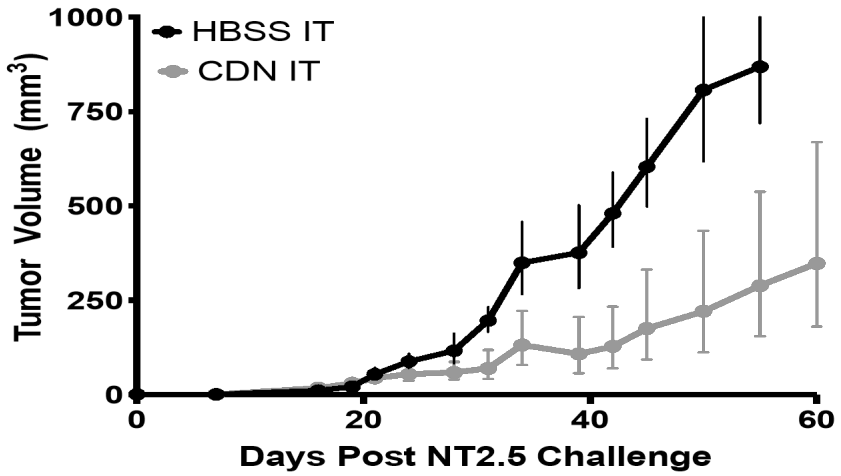
- ADU-S100 selected from series of CDN analogs based on balance of efficacy and tolerability/reduced toxicity
- Enhanced potency over natural CDN ligands
- Phosphorothioate increases resistance to phosphodiesterases to enhance potency
- ADU-S100 has activity in multiple mouse models, including melanoma (B16), colon cancer (CT26), pancreatic cancer (Panc02), triple negative breast cancer (4T1), squamous cell carcinoma (SCCVII)
- The efficacy of ADU-S100 in the setting of antigen-specific peripheral tolerance is poorly characterized

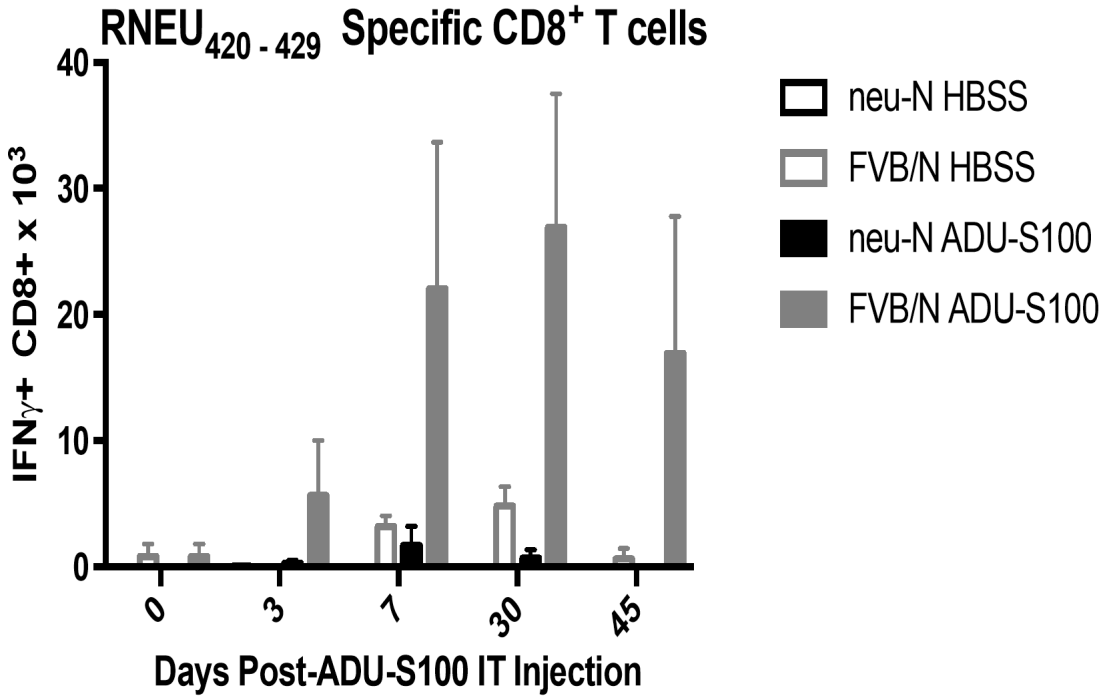
Differential Response to the STING Agonist ADU-S100 in FVB/N and neu/N Mice

FVB/N



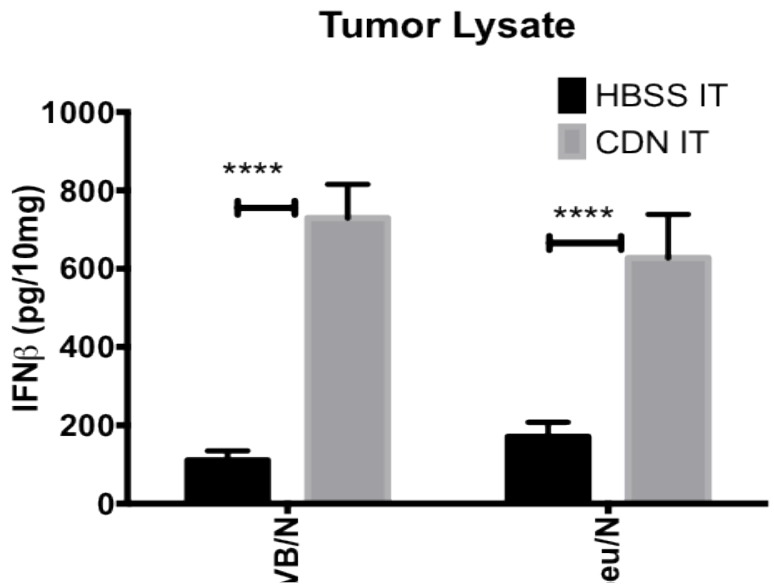
neu/N

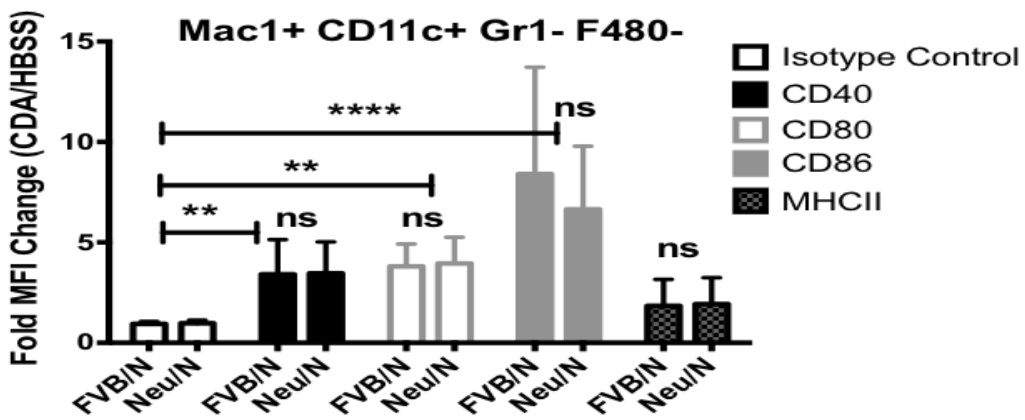


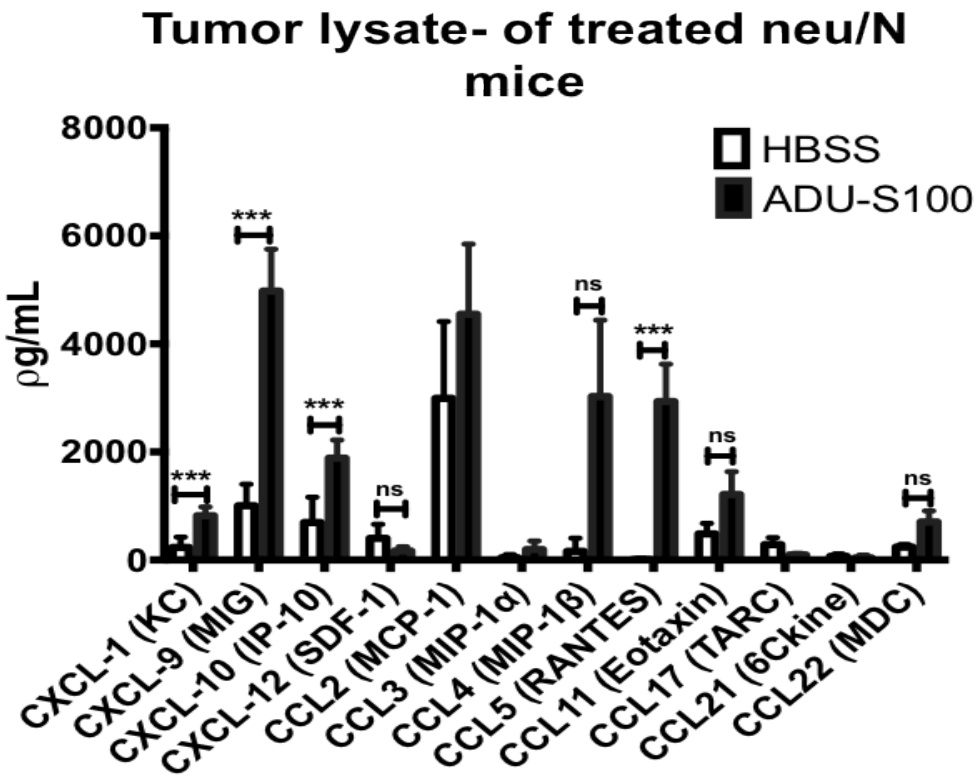


Foote JB/Emens LA at al, Cancer Immunol Res 2017

Proximal Innate Immune Activation is Intact in Neu/N Mice





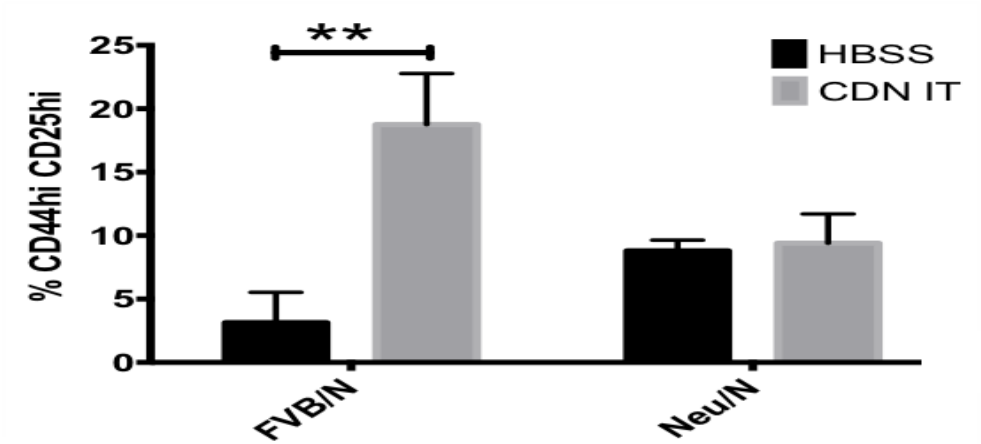


- **Proximal STING signaling events—type I IFN secretion, DC activation, chemokine production—are intact in neu/N mice.**

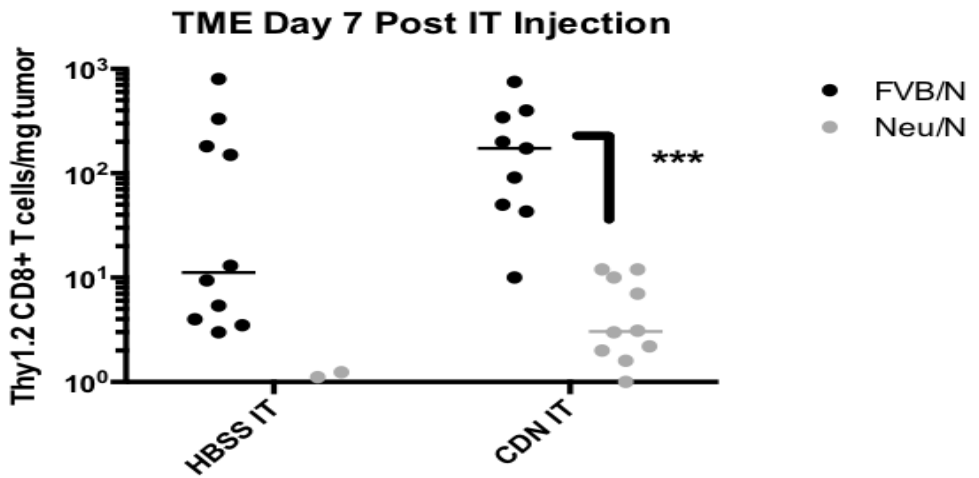
Foote JP/Emens LA Cancer Immunol Res, 2017.

Distal T Cell Priming is Deficient in Neu-N Mice

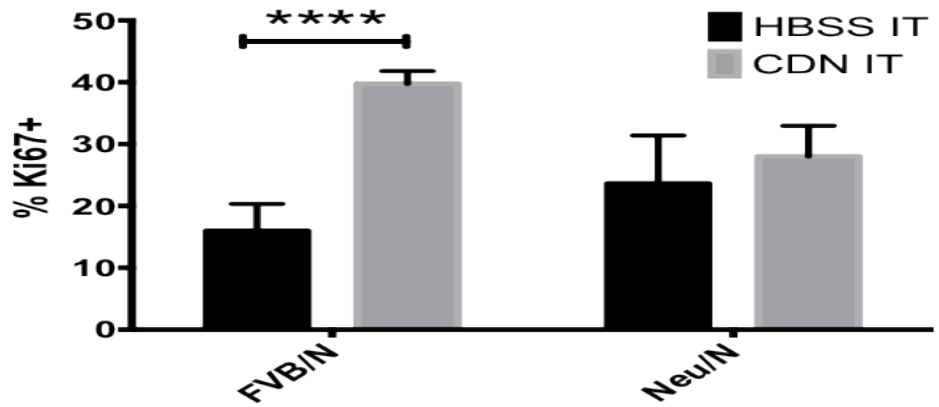
Activation



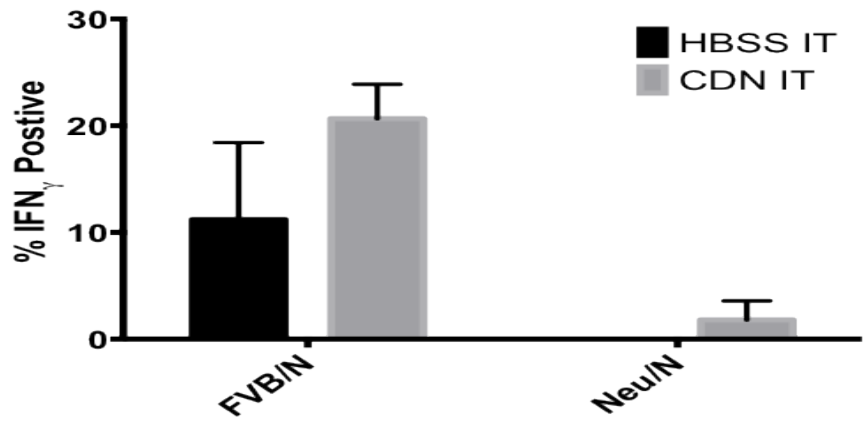
Migration



Proliferation

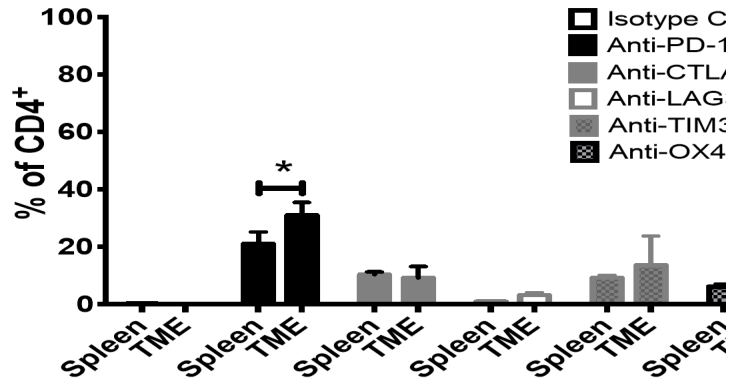


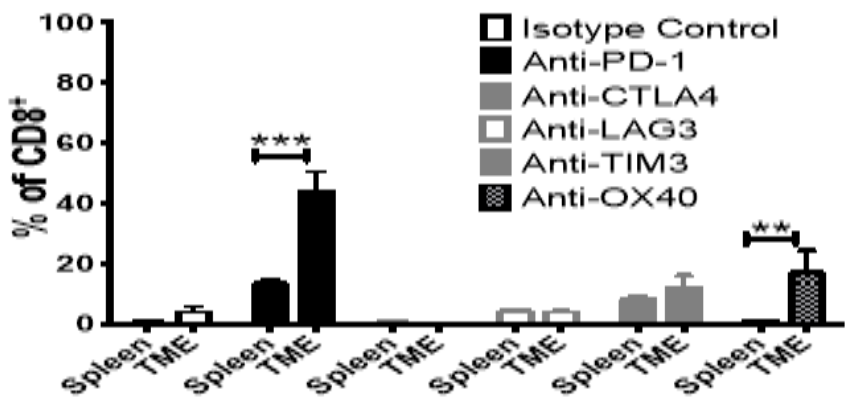
Function



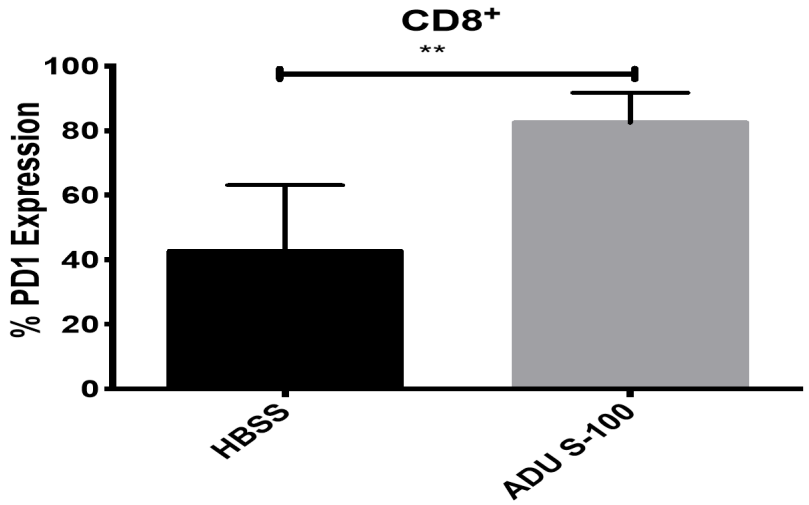
Foote JP/Emens LA Cancer Immunol Res, 2017.

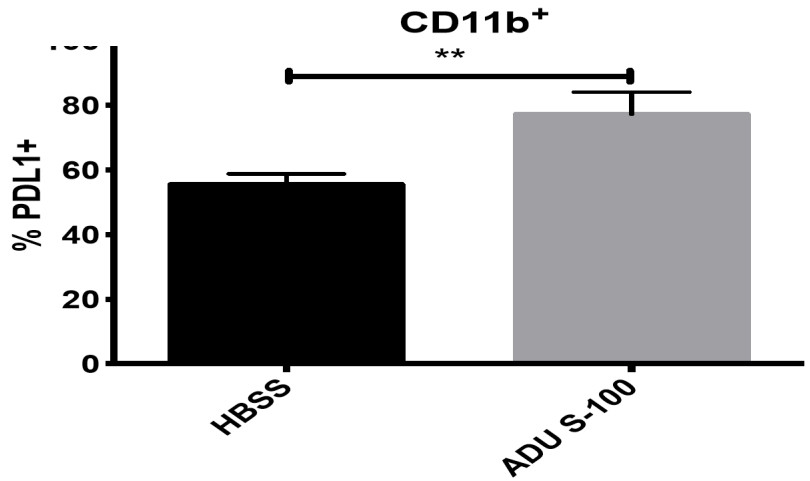
Immune Checkpoint Pathways in the TME of Neu Mice





Baseline



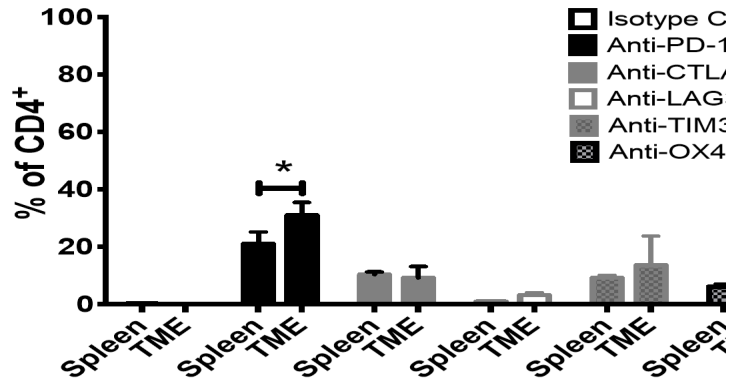


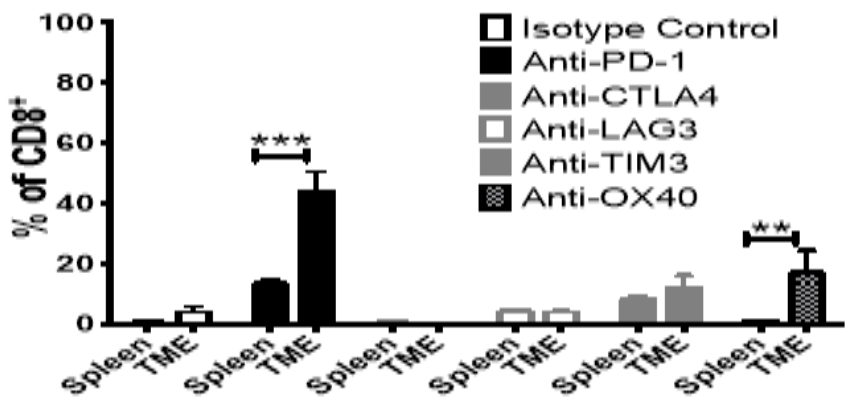
Post-ADU-S100

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

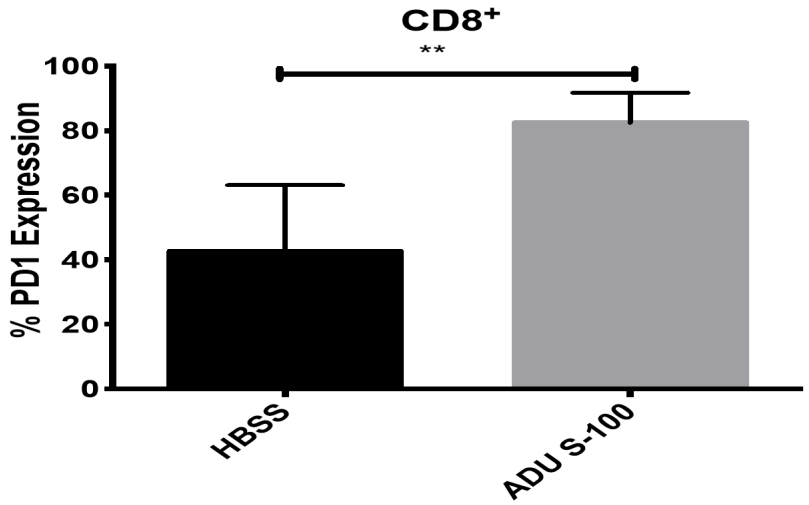
Foote JB/Emens LA at al, Cancer Immunol Res 2017

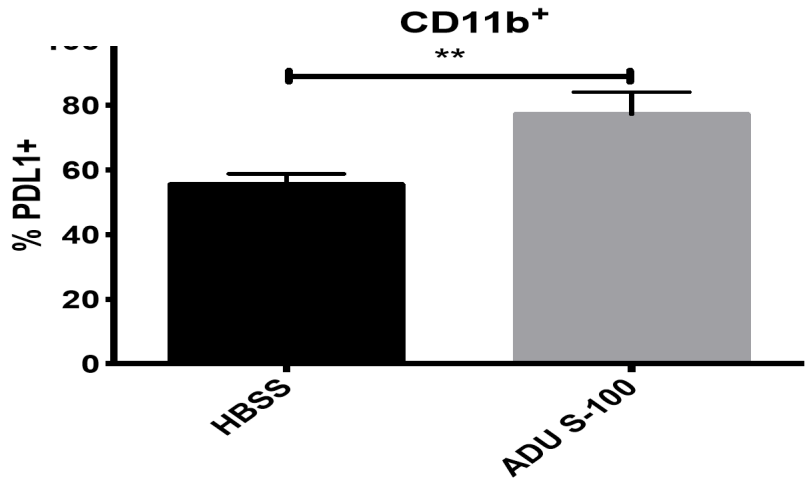
Immune Checkpoint Pathways in the TME of Neu Mice





Baseline



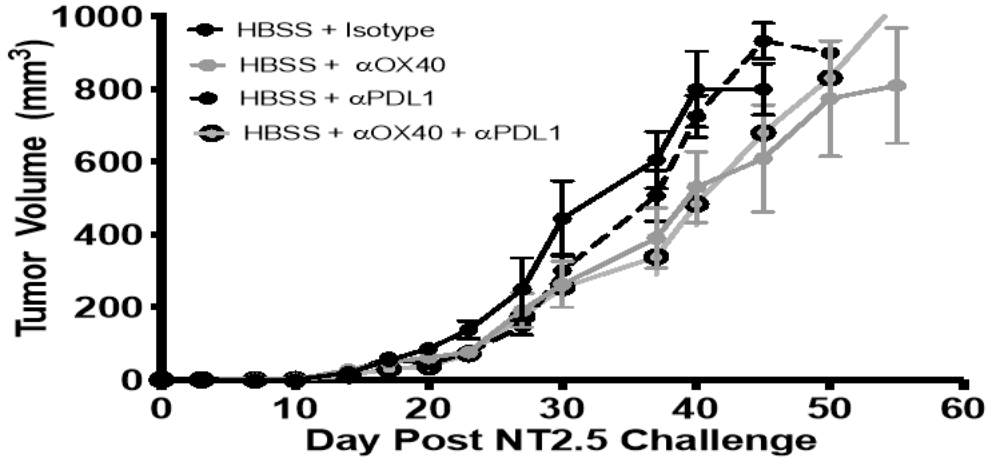


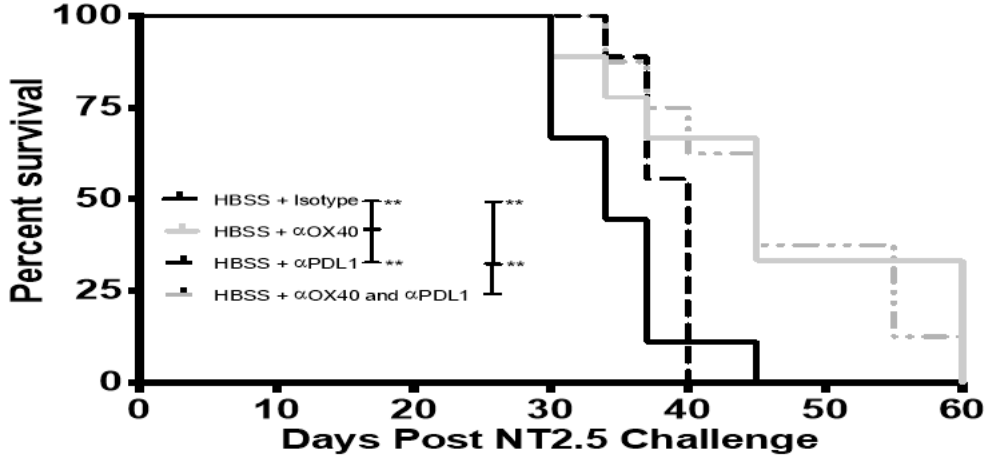
Post-ADU-S100

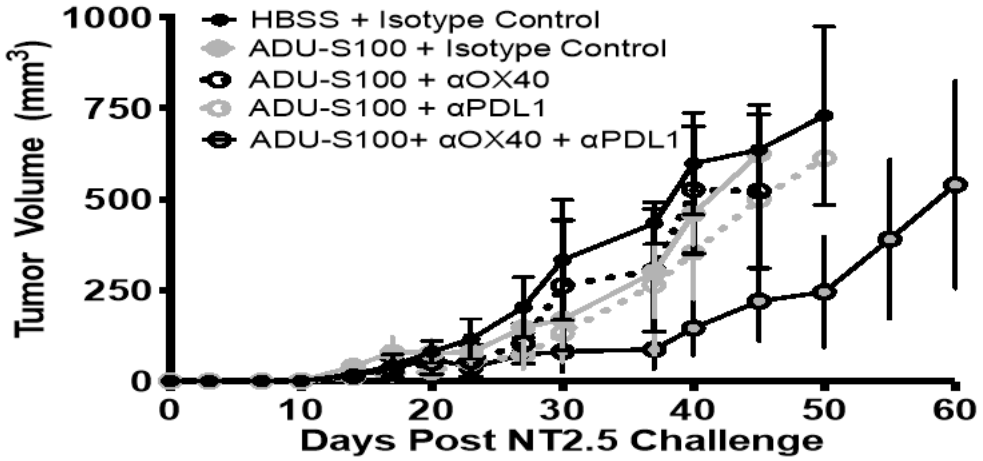
- **The PD-1 and OX -40 pathways are upregulated in neu/N mice.**

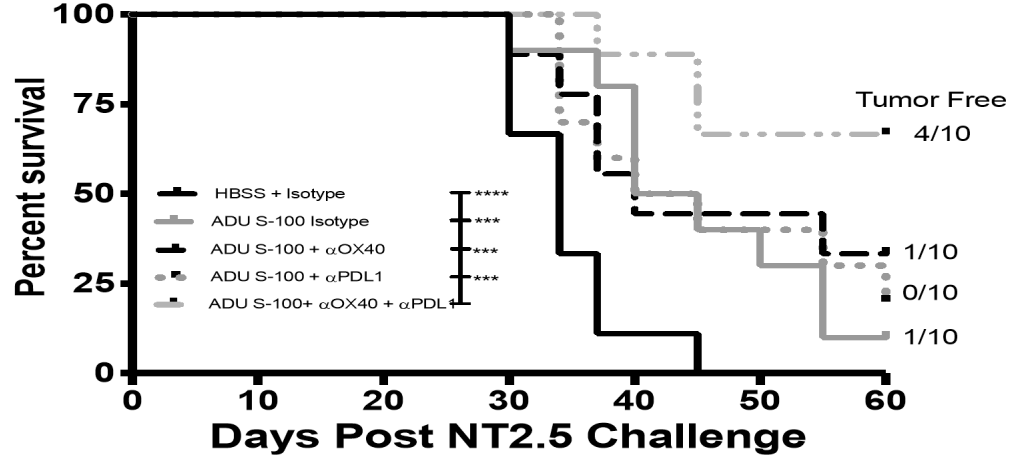
Foote JB/Emens LA at al, Cancer Immunol Res 2017

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



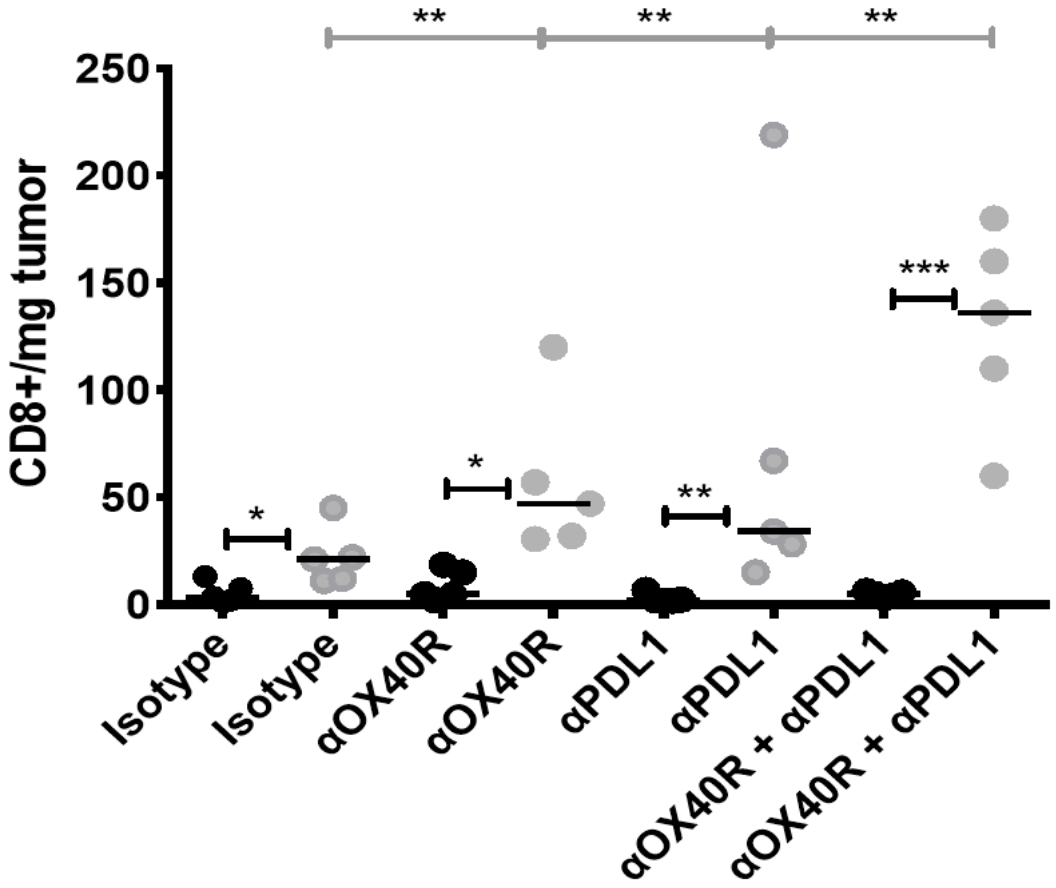


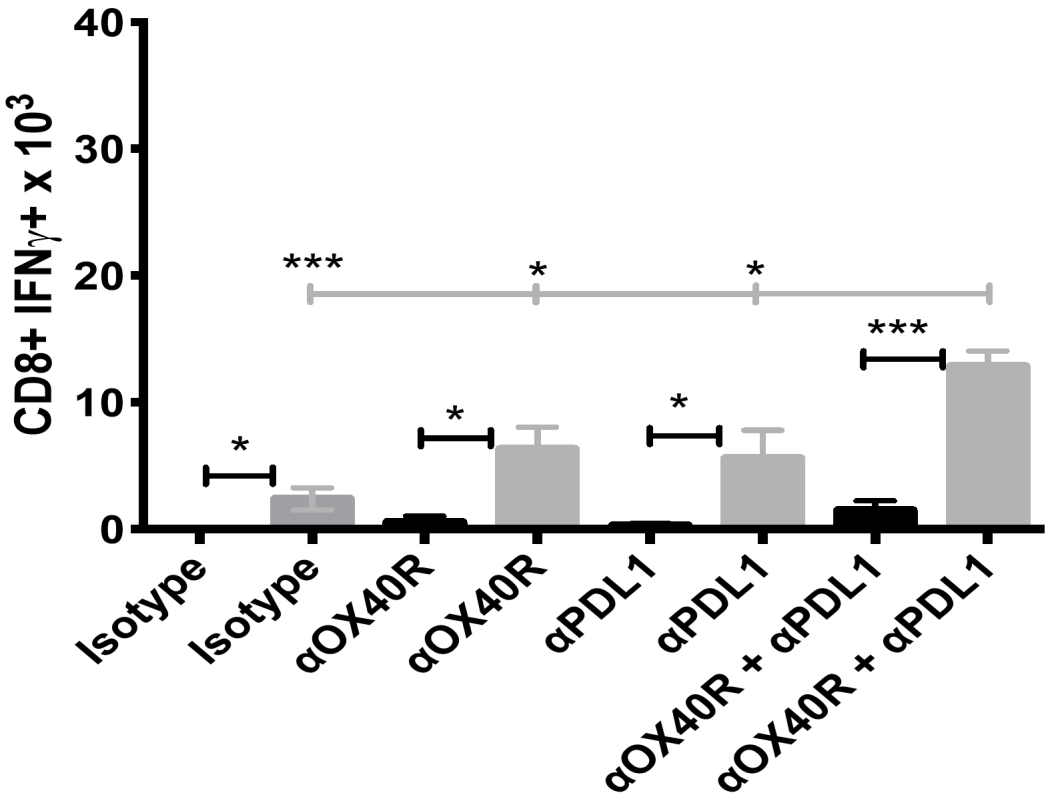




Foote JB/Emens LA at al, Cancer Immunol Res 2017

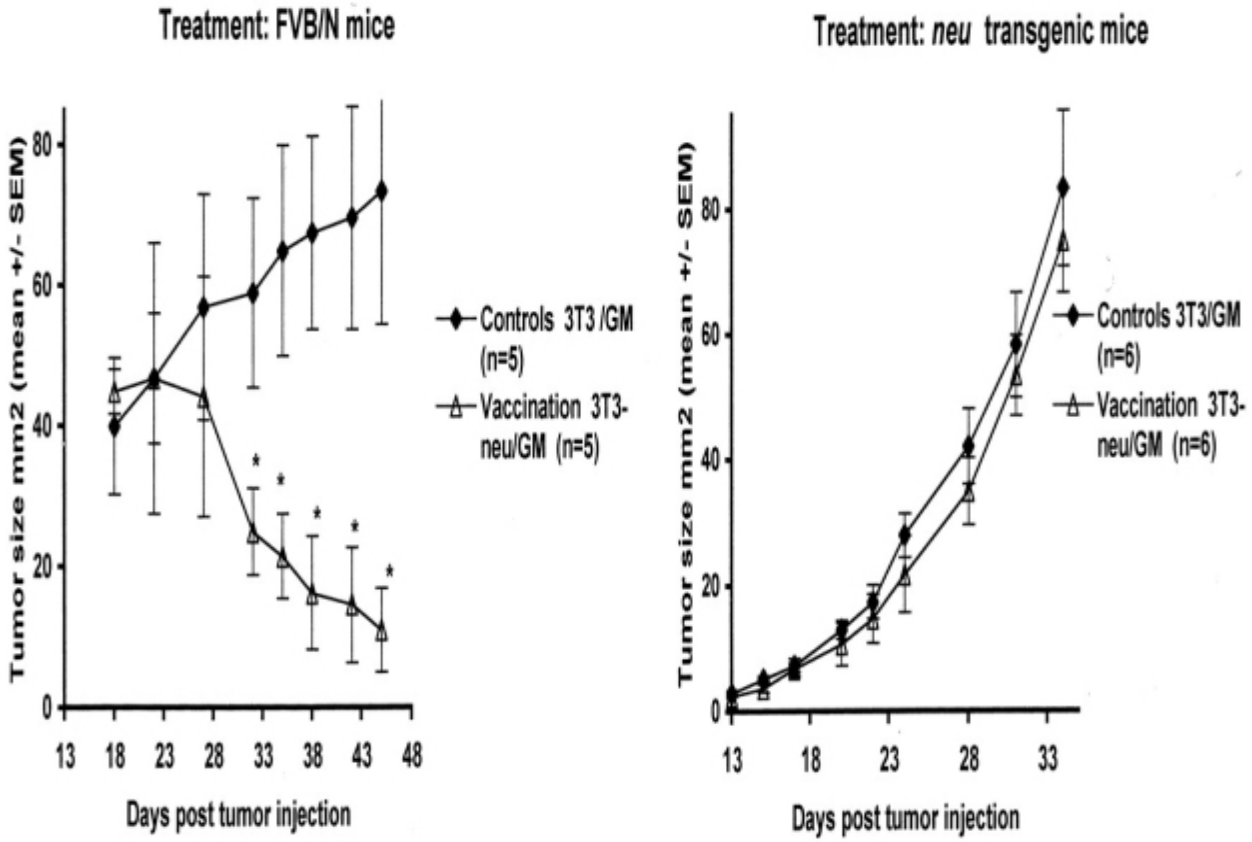
ADU-S100 Combined with PD-L1 Blockade and OX-40 Activation Induces Greater Numbers of Functional HER-2-specific T Cells in neu/N Mice





Foote JB/Emens LA at al, AACR 2017

Chemotherapy-Induced Immunomodulation Can Be Drug, Dose, and Schedule-Dependent

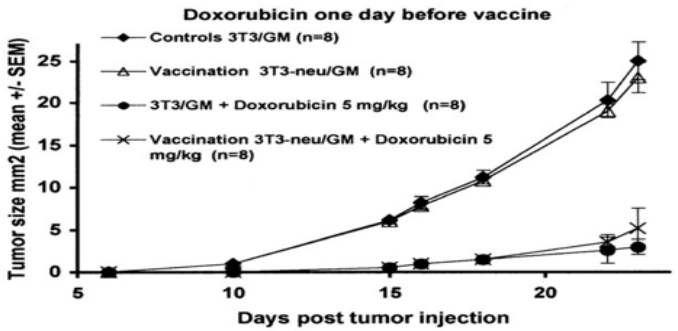


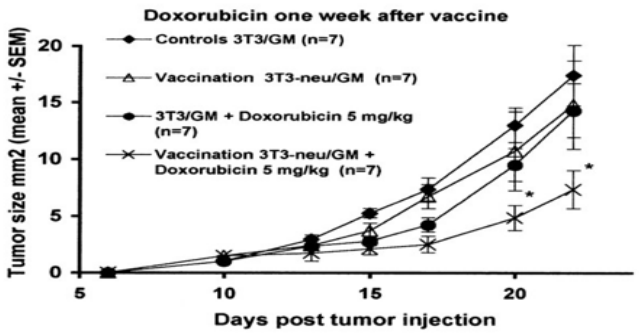
	T cell count (nadir) number/ μl ± SD (normal range, 4000–9000)[b]	Chemotherapy 1 day before vaccine	Chemotherapy 7 days after vaccine
CTX			
50 mg/kg	6128 ± 847	+[c]	–
100 mg/kg	5120 ± 1033	+	–
150 mg/kg	1559 ± 356	+	NT
200 mg/kg	1100 ± 478	+/–	NT
250 mg/kg	989 ± 122	+/–	NT
PTX			
20 mg/kg	4365 ± 501	+	–
30 mg/kg	4200 ± 675	+	NT
35 mg/kg	3600 ± 543	+/–	NT
40 mg/kg	3451 ± 345	+/–	NT
DOX			
4 mg/kg	6265 ± 1298	+/–	+/–
8 mg/kg	5586 ± 945	+/–	+/–
15 mg/kg	4180 ± 501	–	–
CIS			
2 mg/kg	6320 ± 903	+/–	+/–
3 mg/kg	6200 ± 674	+/–	+/–
5 mg/kg	3679 ± 455	–	–
10 mg/kg	3400 ± 697	–	–

Machiels JP et al Cancer Res 2001 61: 3689

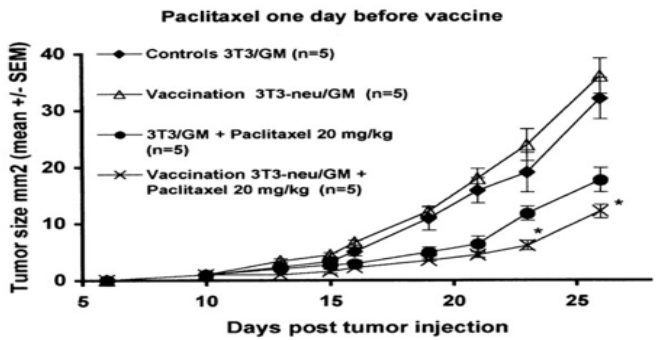
Dose and Schedule Dependent Impact of Chemotherapy on Vaccine Activity

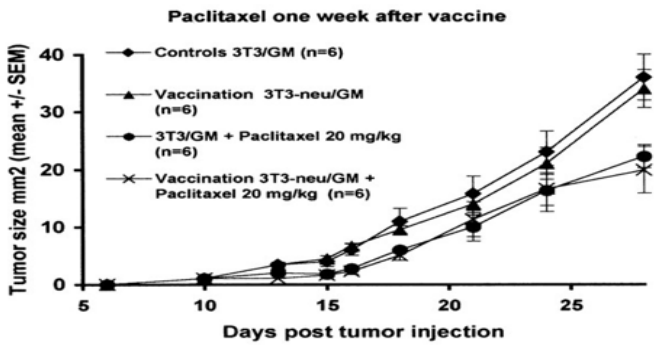
Doxorubicin



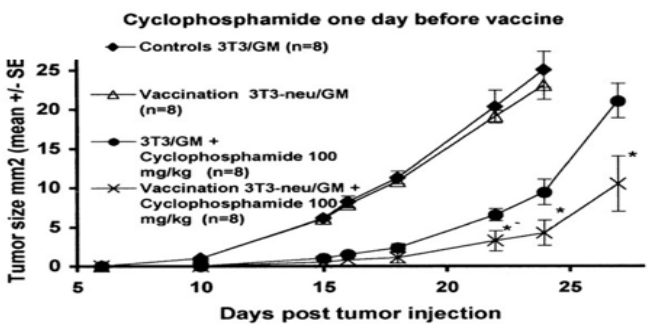


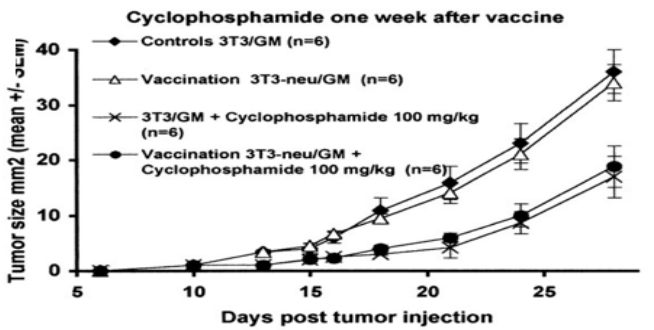
Paclitaxel





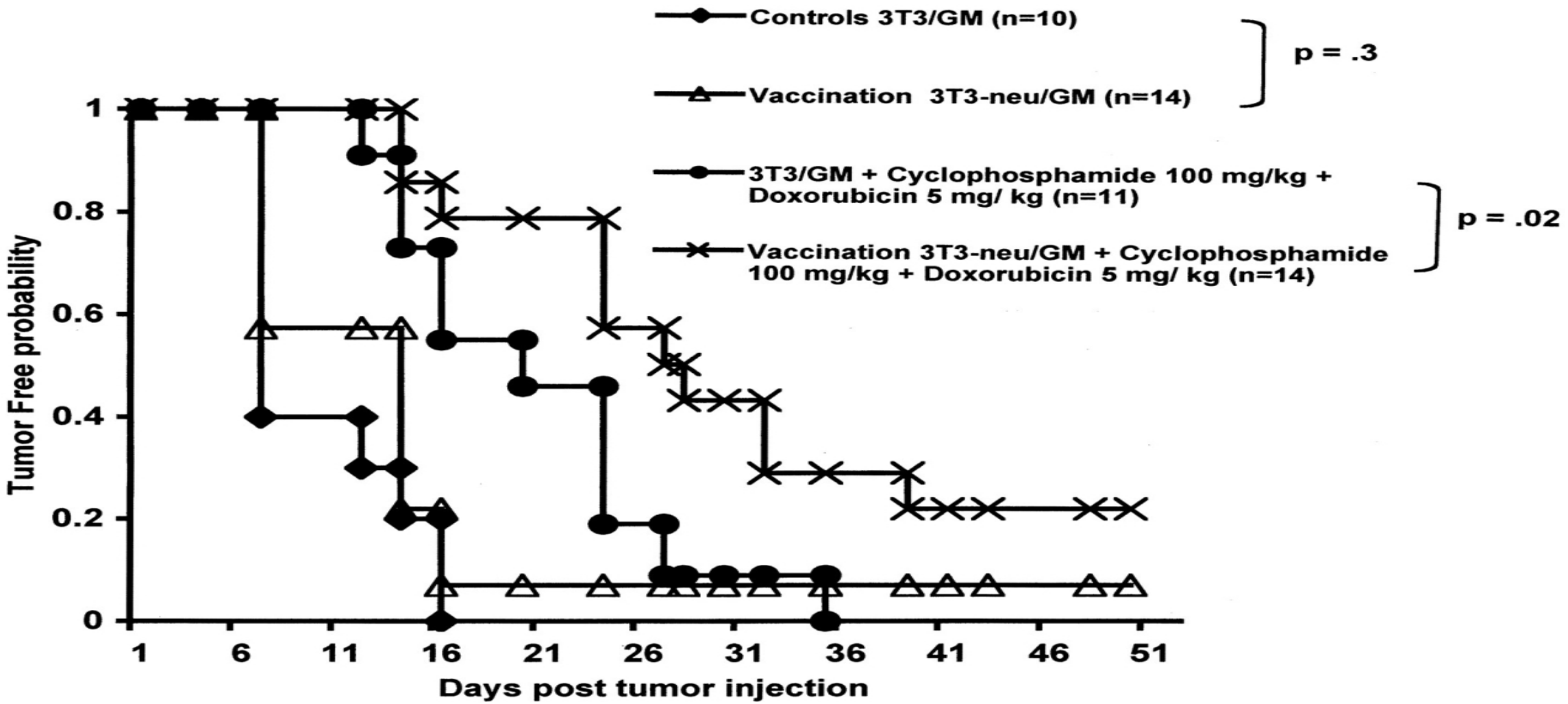
Cyclophosphamide





Machiels JP et al, Cancer Res 2001; 61: 3689

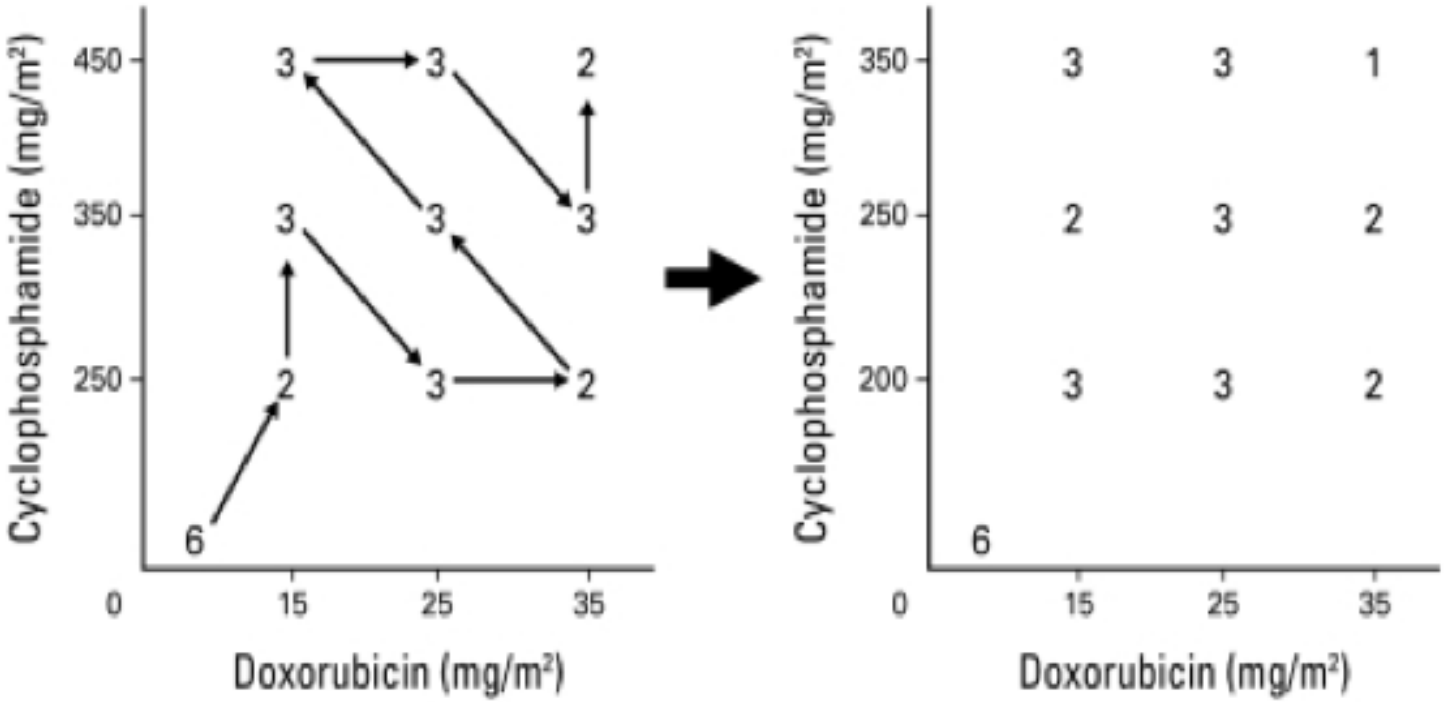
Polychemotherapy Enhances Vaccine Activity in Tolerant Neu-N Mice



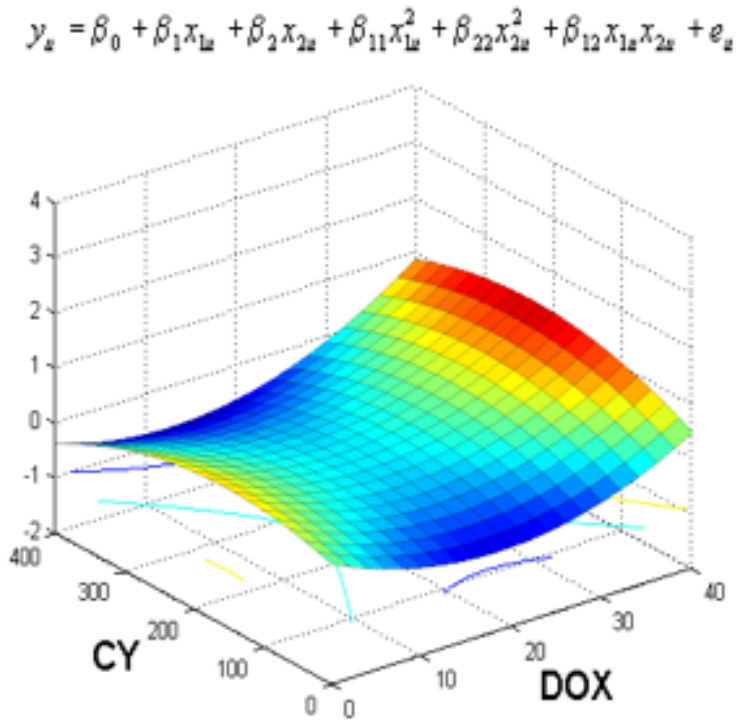
Jean-Pascal H. Machiels et al. Cancer Res 2001;61:3689-3697

Combination of Vaccination with Low Dose Chemotherapy

Novel Trial Designs to Explore Dose and Schedule



HER-2 Ab



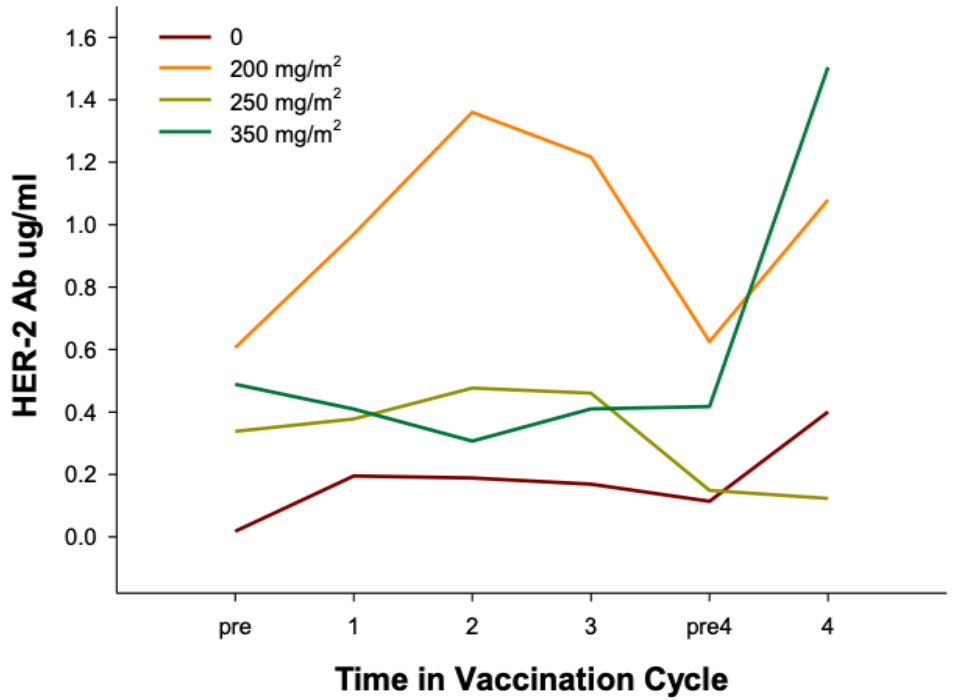
Possible Inputs: dose x dose
dose x schedule

Possible Outputs: immune response
clinical response
toxicity

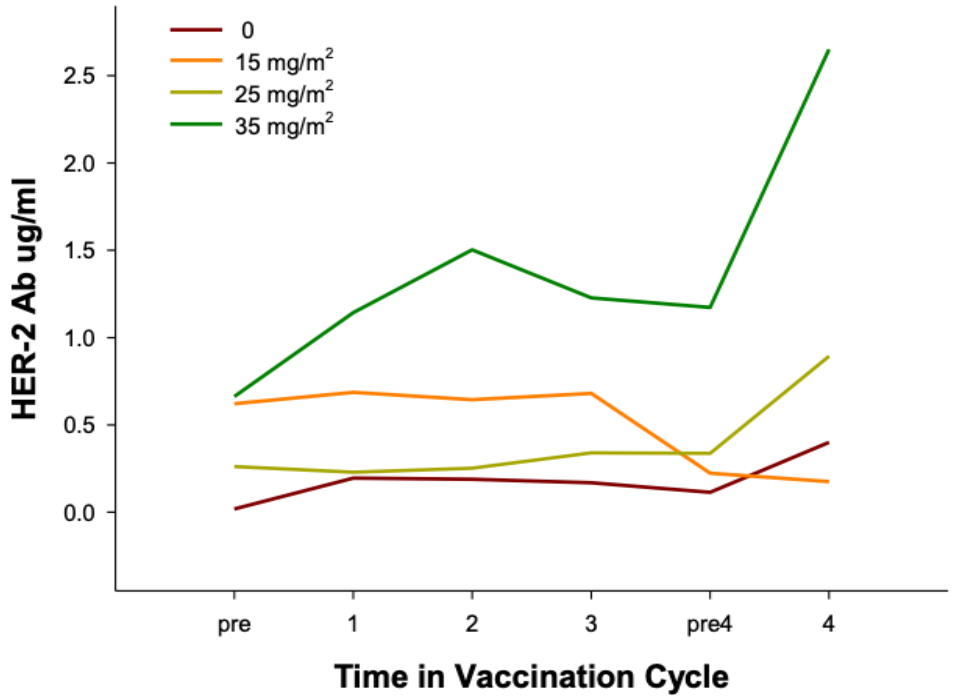
Emens LA, J Clin Oncol 2009;27: 5911-18

Impact of Increasing Chemotherapy Dose on Vaccine-Induced Immunity—Serum HER-2 Ab

CY



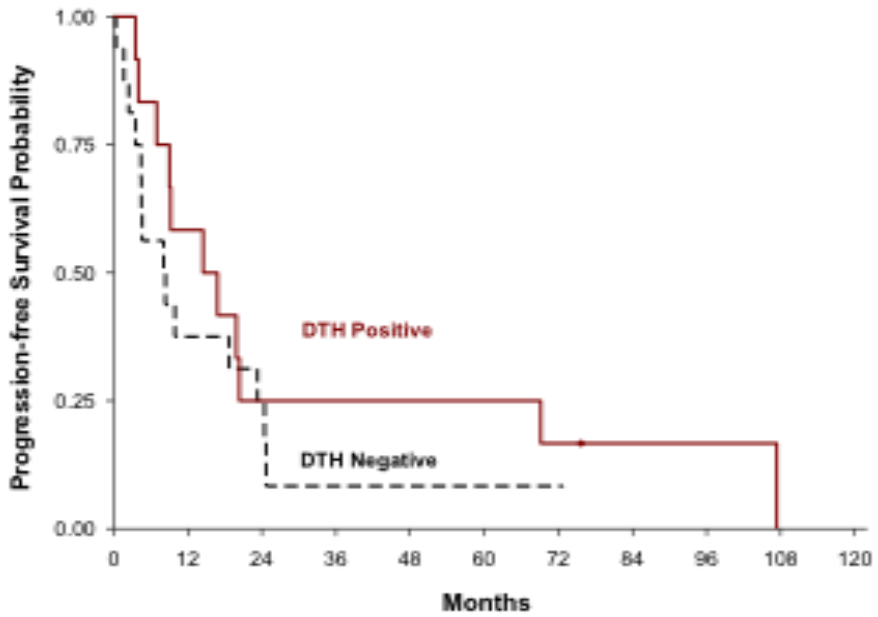
DOX



Emens et al, 2009, J Clin Oncol 151: 139-151

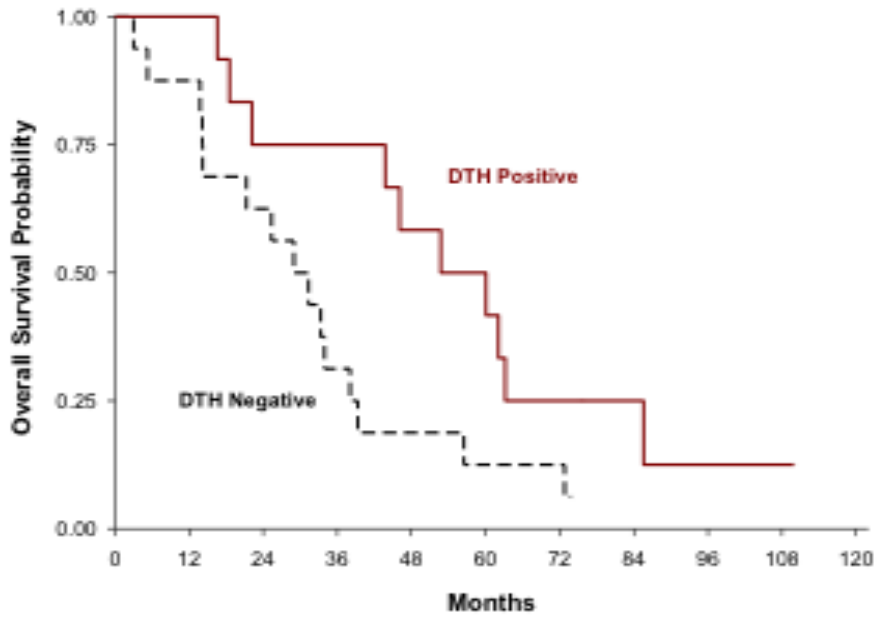
Survival Outcomes (n=28)

Total Progression-Free Survival: 10 months



DTH NR vs. R: 8 vs. 16 months

Total Overall Survival: 36 months

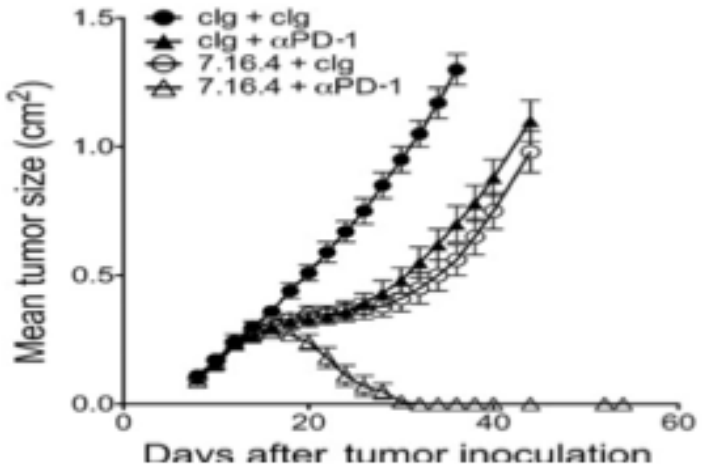


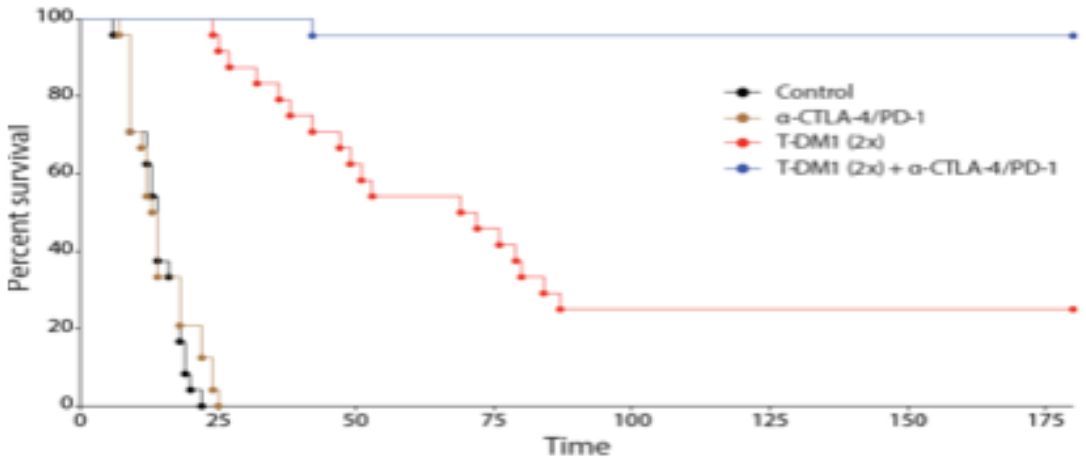
DTH NR vs. R 30 vs. 56 months

Emens LA, unpublished data

Combination of Immunotherapy with HER-2-directed Therapy

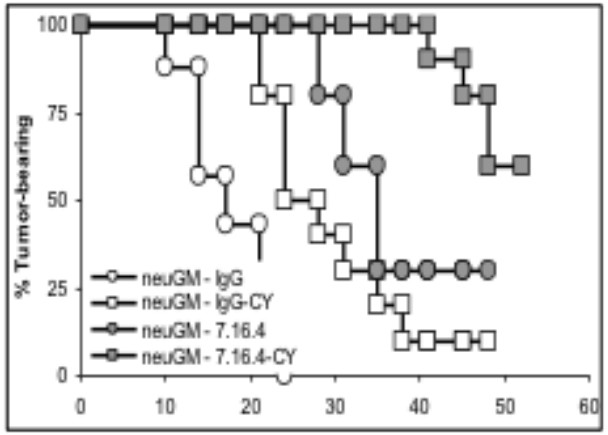
Checkpoint Blockade

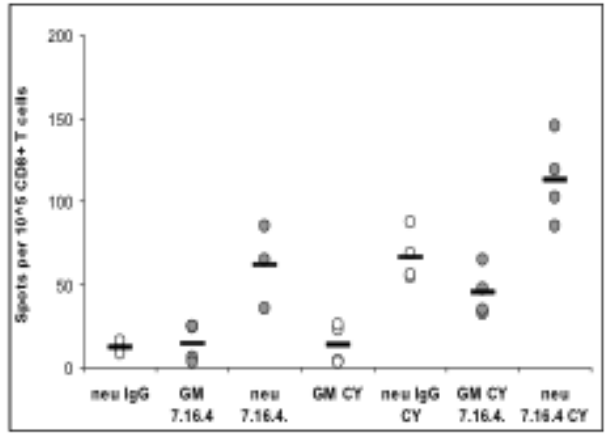


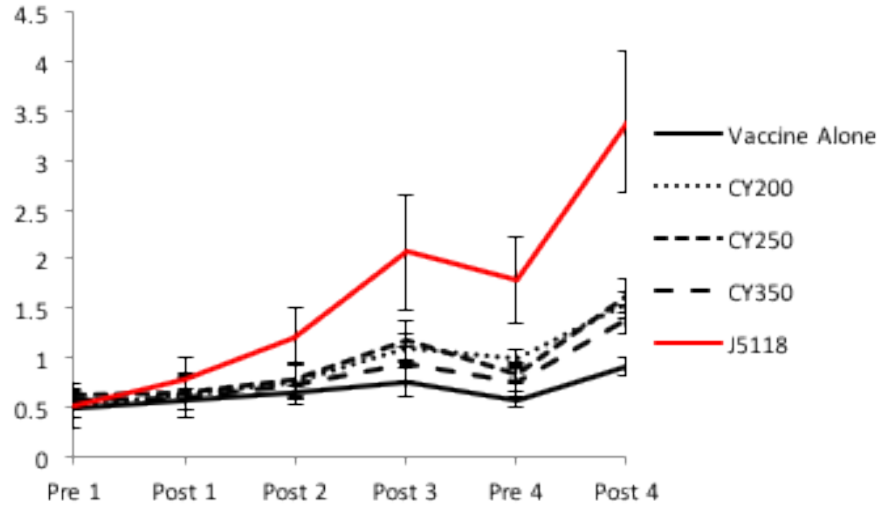


Stagg J et al, PNAS, 2011; 108: 7142-47
Müller P et al, Science Translation Medicine, 2015; 315:315ra188

Vaccination







Chen/Emens et al, Cancer Immunol Res 2014; 2: 949-961
Chen/Emens, unpublished data

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!