

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, 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

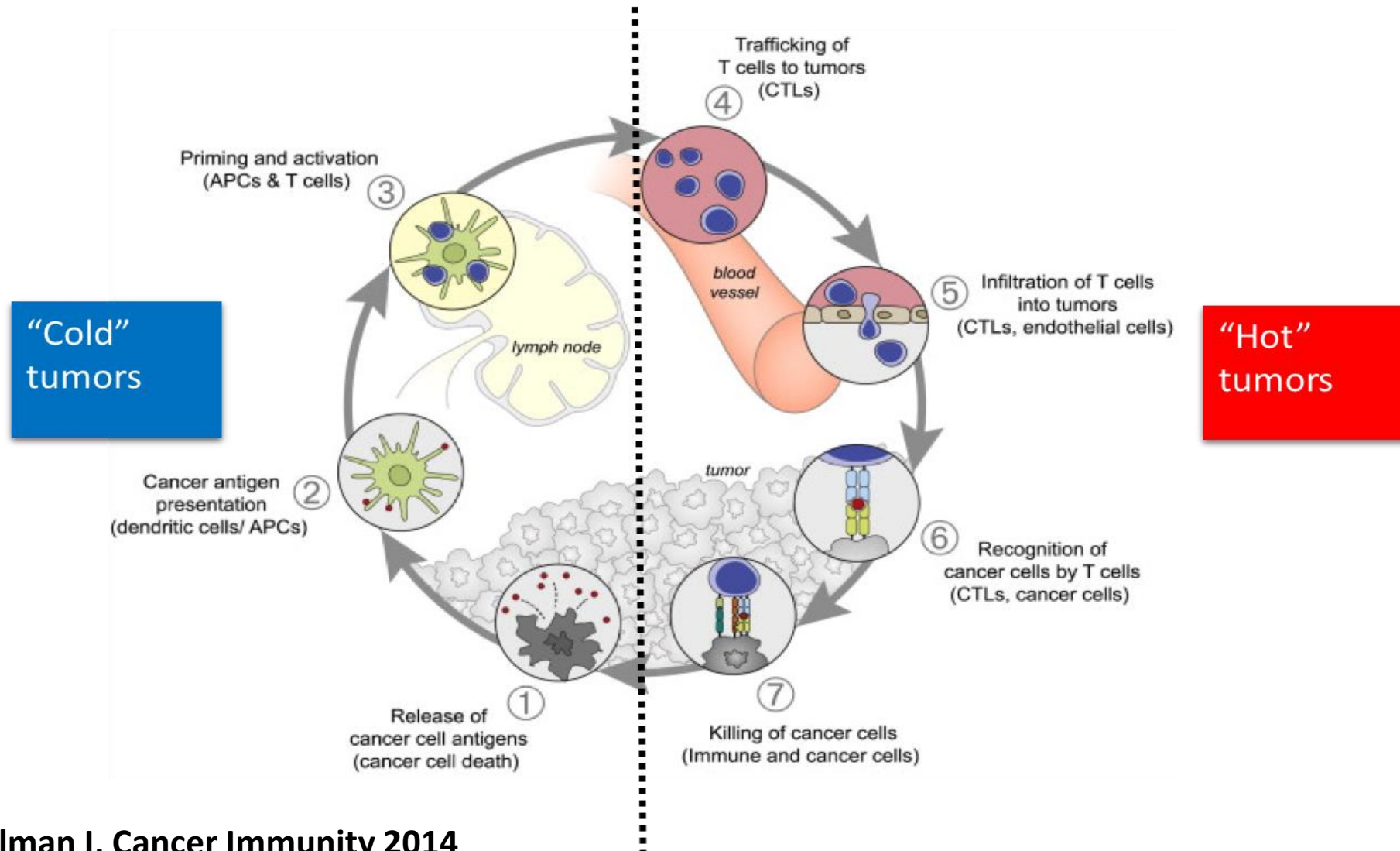
Key Features of Immune Checkpoint Blockade

- 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

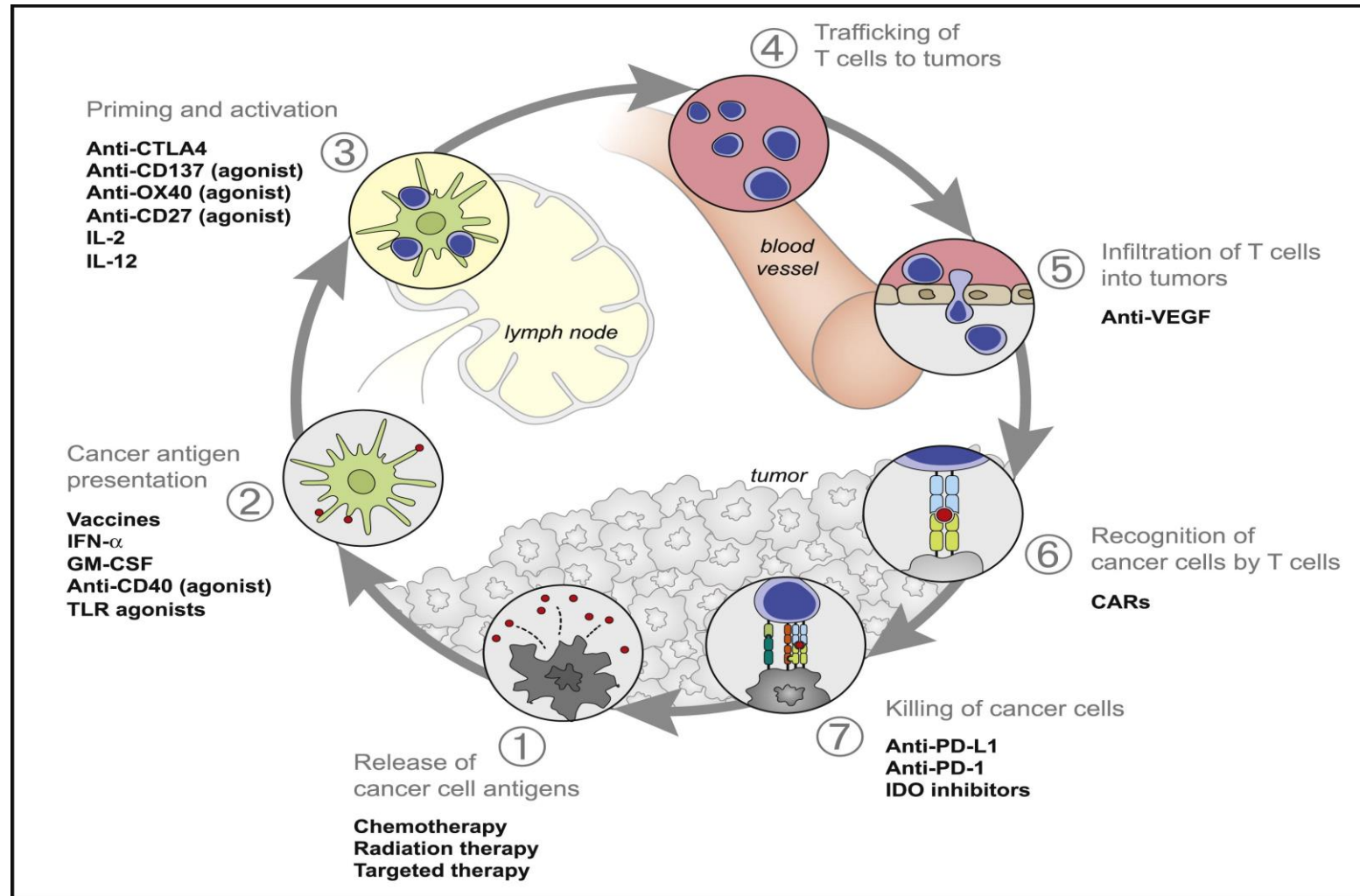
Why Immunotherapy Combinations?

- 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

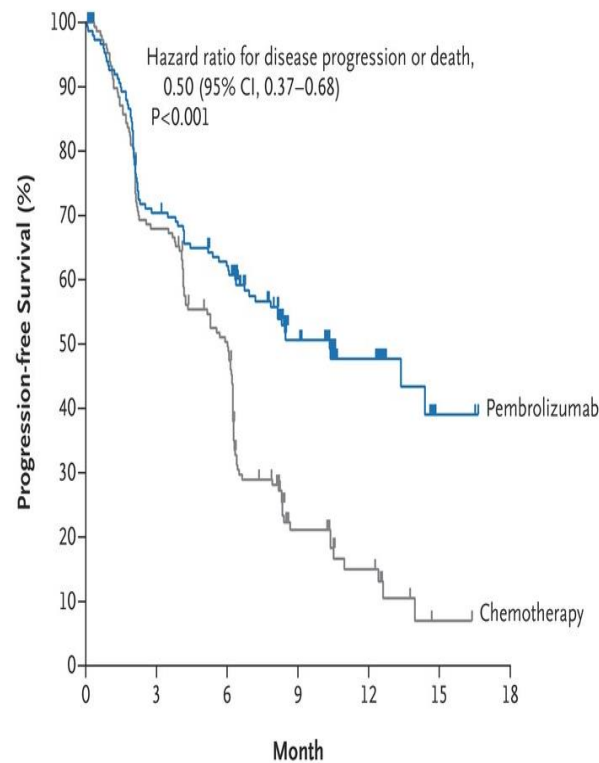


Harnessing the Cancer Immunity Cycle for Therapeutic Benefit

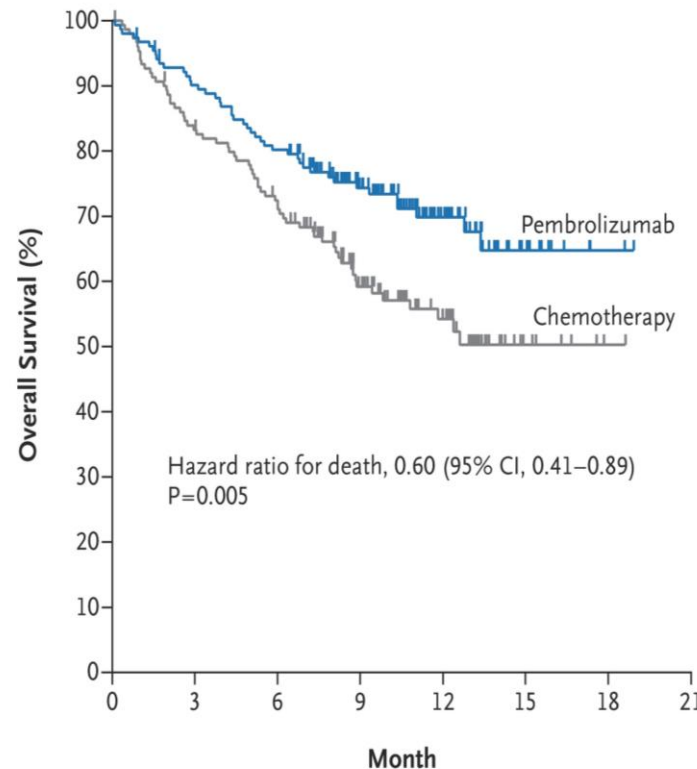


Single Agent Pembrolizumab for Untreated Metastatic NSCLC

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



No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0



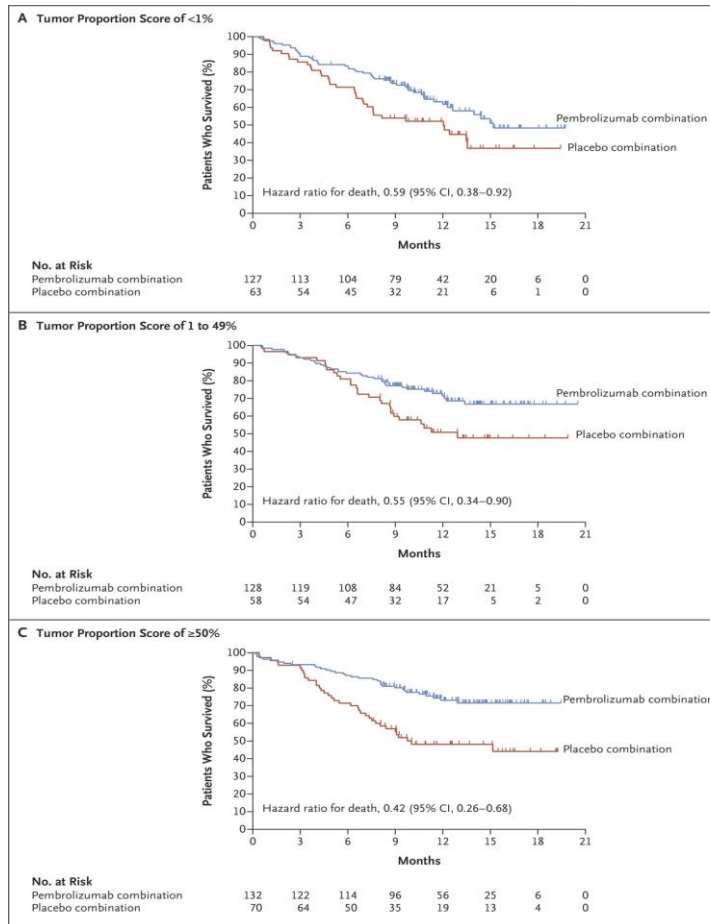
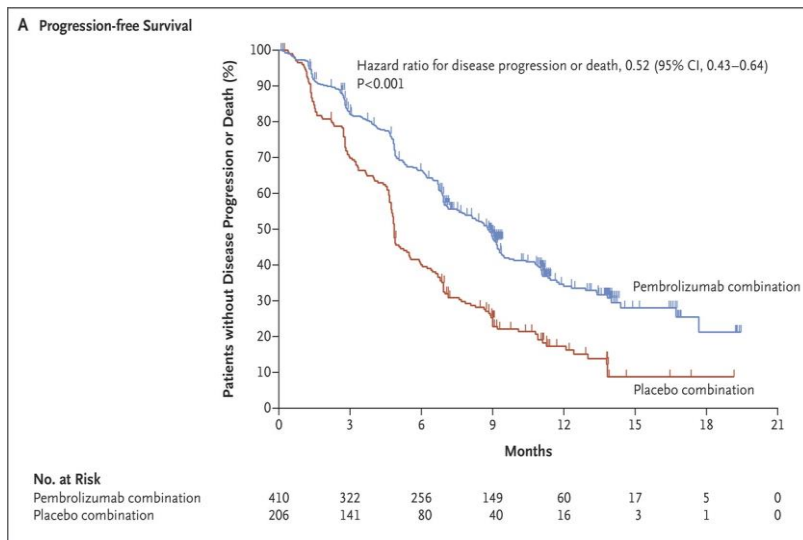
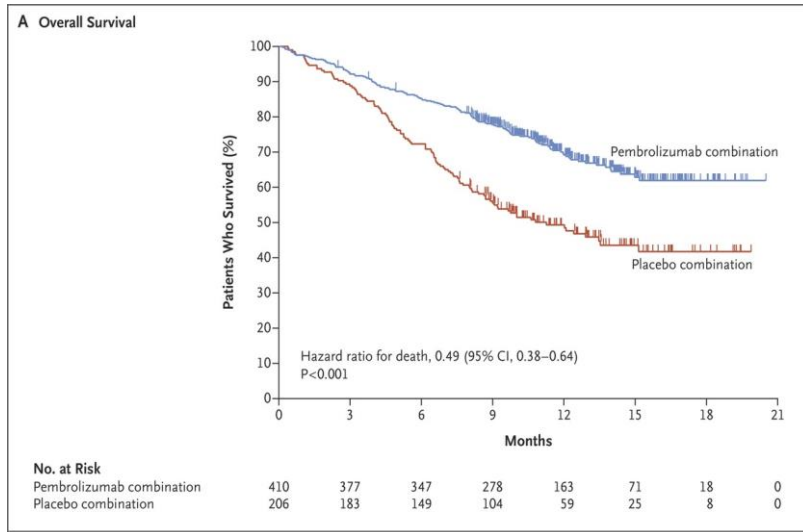
No. at Risk									
Pembrolizumab	154	136	121	82	39	11	2	0	
Chemotherapy	151	123	106	64	34	7	1	0	

	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

Pembrolizumab + Chemotherapy in NSCLC

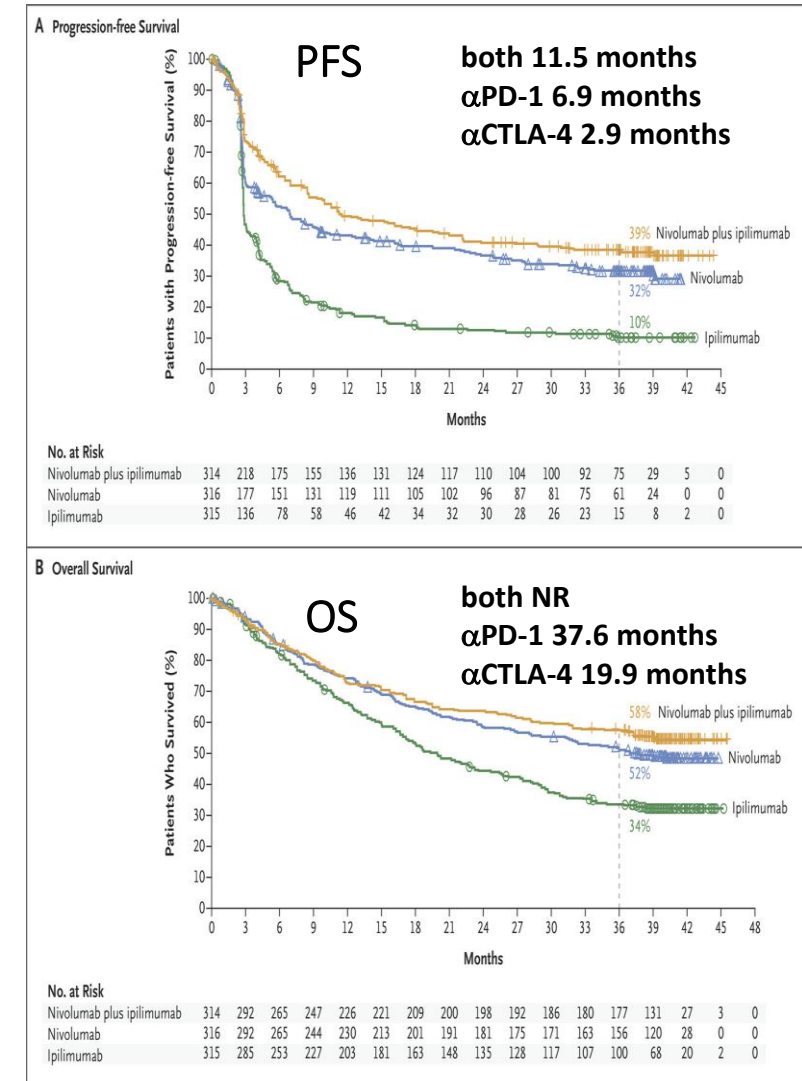
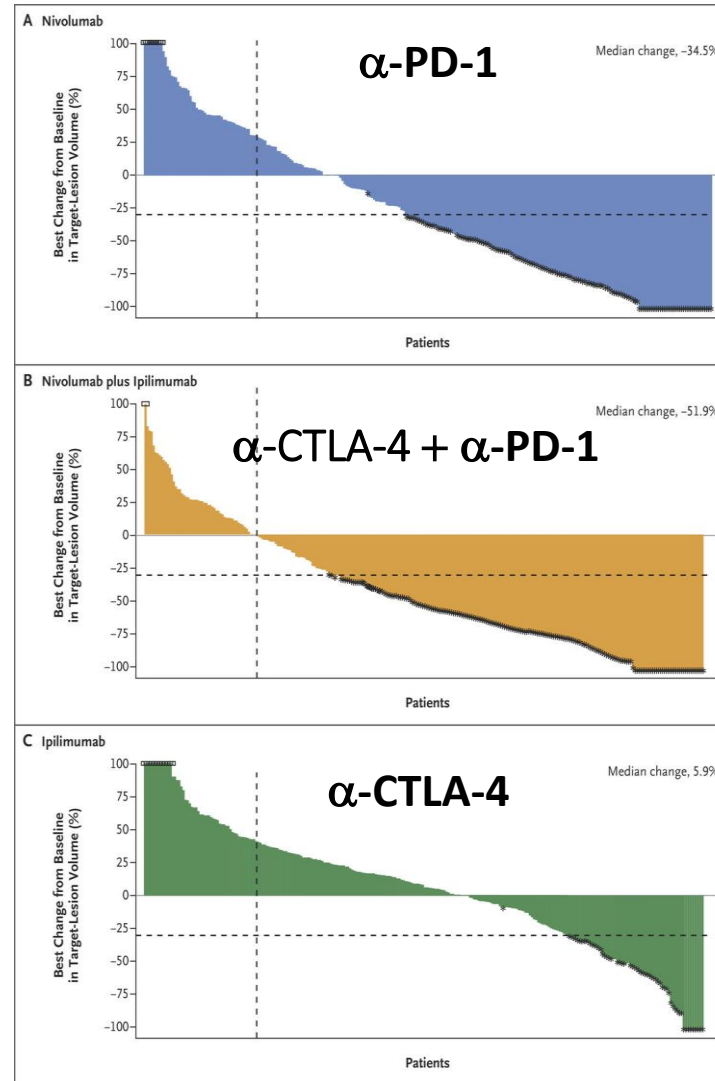
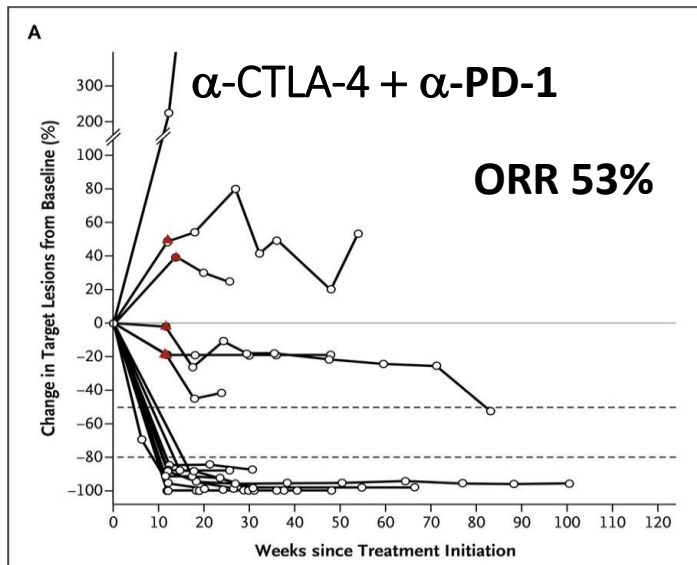
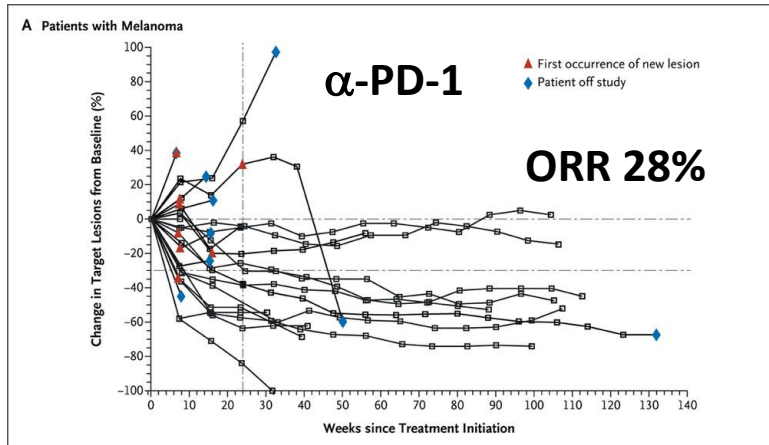
616 patients with untreated metastatic NSCLC w/o ALK or EGFR mutation were randomized 2:1 to pemetrexed+platinum+placebo or pembrolizumab, regardless of PD-L1 TC expression (cut-point TC 1% and 50%)



	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%)

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



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

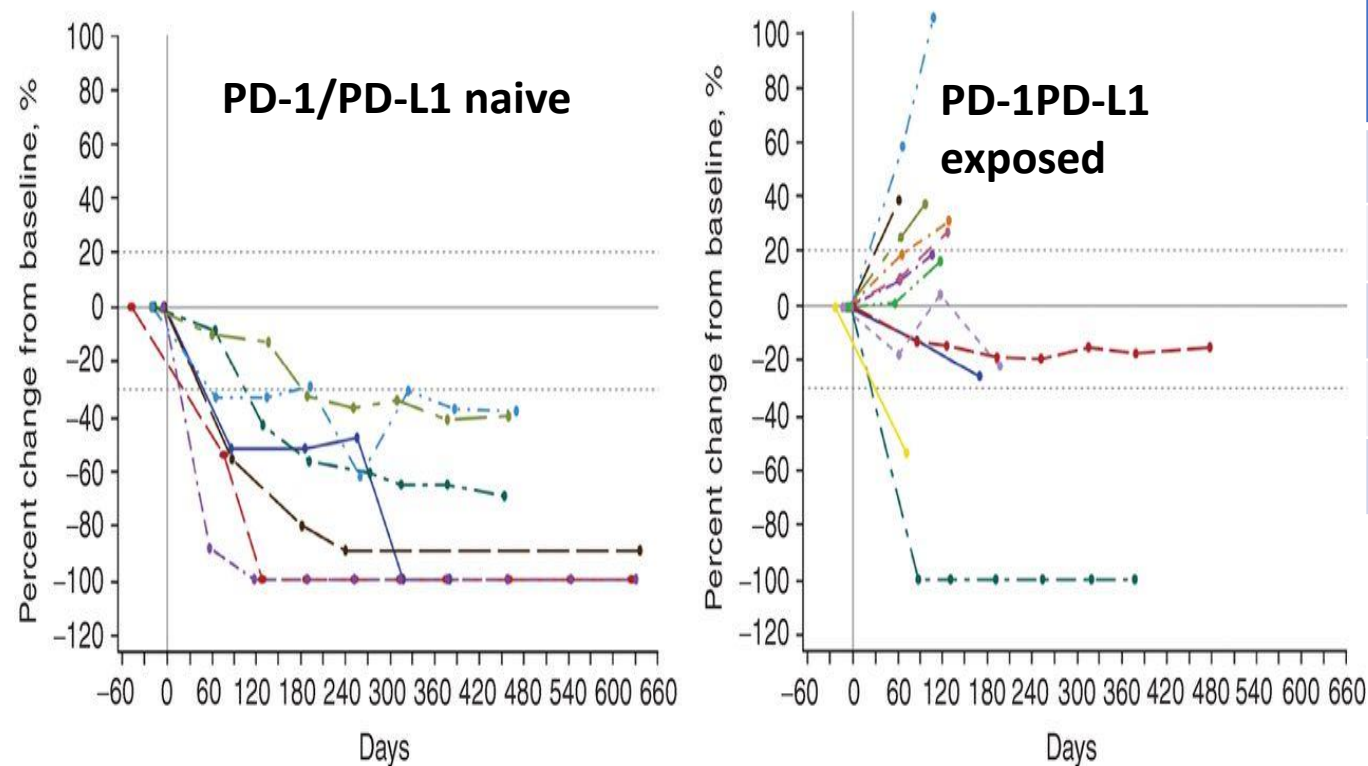
Wolchok JD et al. N Engl J Med 2013;369:122-133.

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

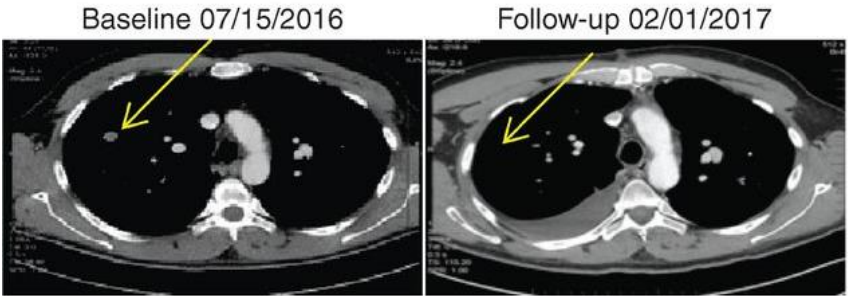
Wolchok JD et al. N Engl J Med 2017;377:1345-1356.

PD-1 Blockade + TLR-9 Activation

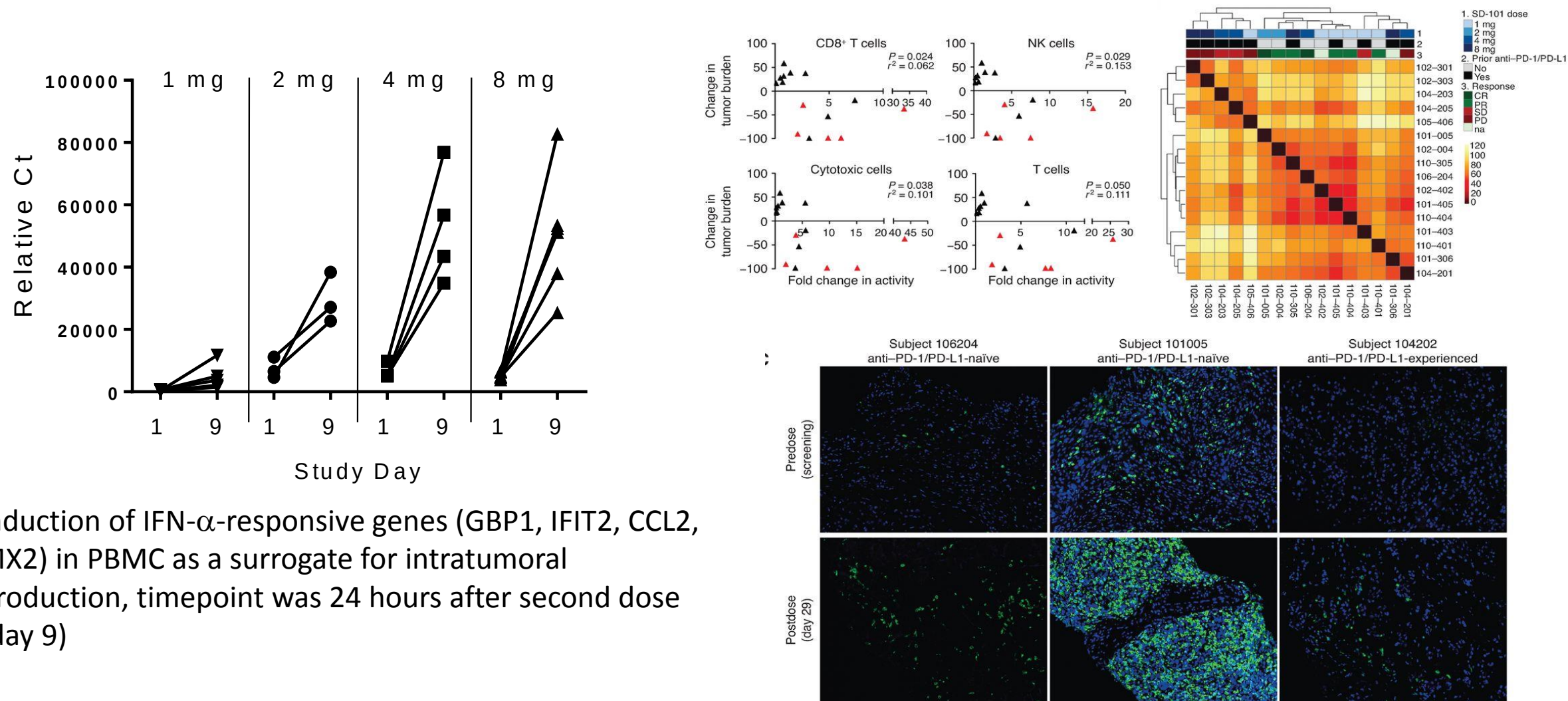
SD-101: CpG oligo that stimulates pDC by engaging TLR-9, inducing IFN- α , maturation, and support of innate and adaptive immunity



	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%)

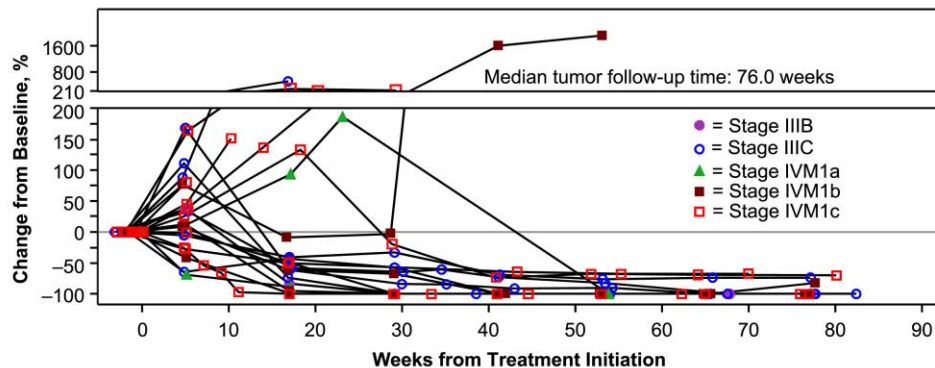
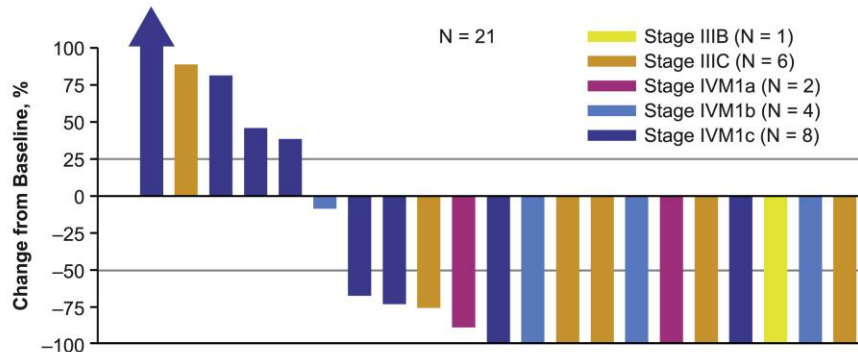
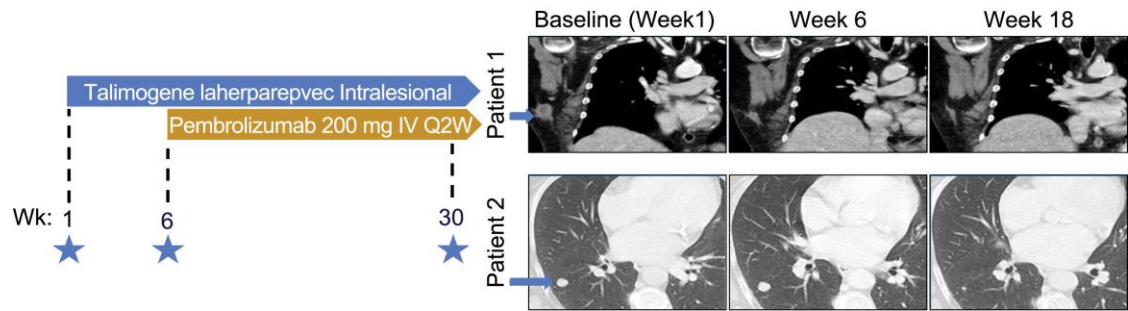


Pharmacodynamic Changes on SD-101 Therapy

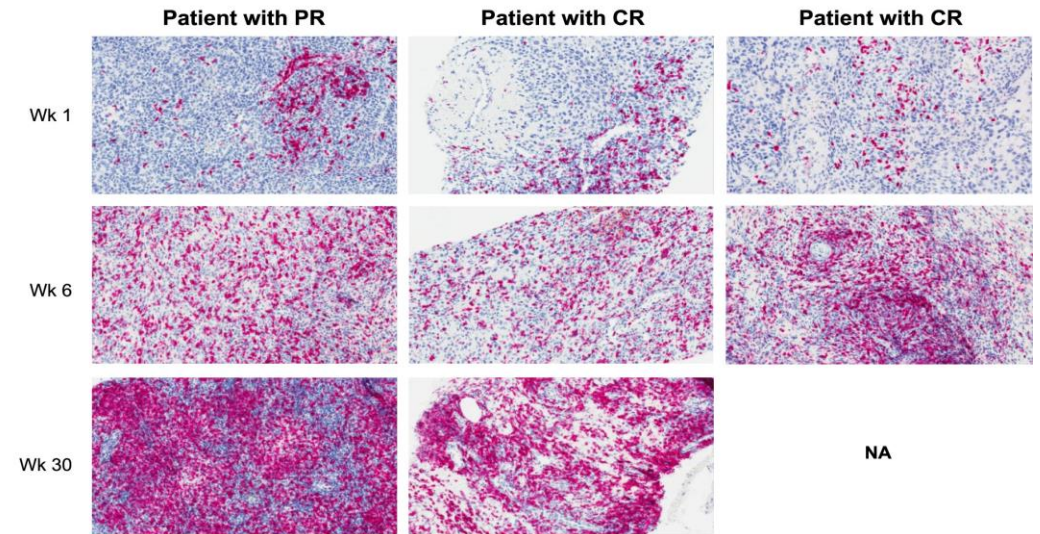


induction of IFN- α -responsive genes (GBP1, IFIT2, CCL2, MX2) in PBMC as a surrogate for intratumoral production, timepoint was 24 hours after second dose (day 9)

Oncolytic Virotherapy + Pembrolizumab in Metastatic Melanoma



CD8+ T cell density

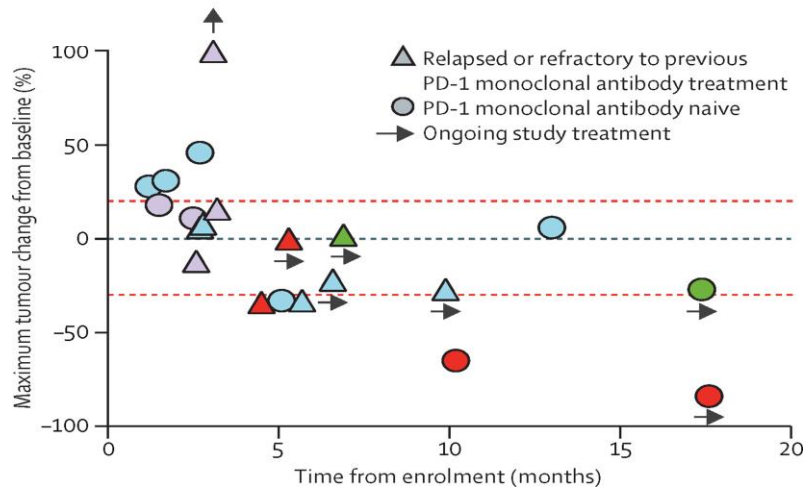
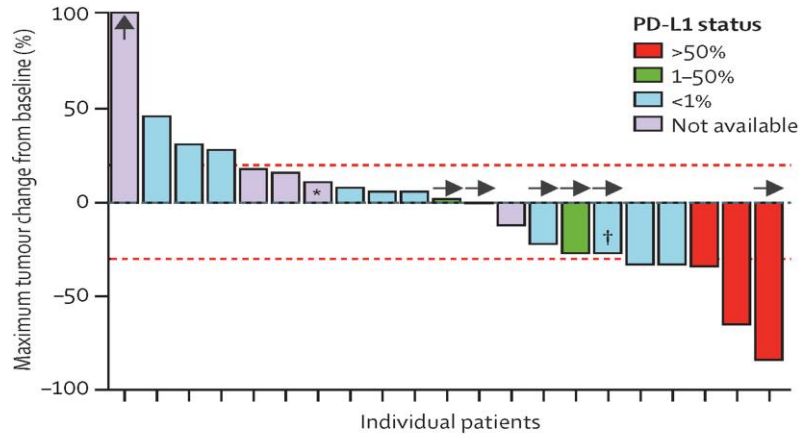


- High ORR of 62%
- High CR rate of 33%
- Therapy induced T cell infiltration, PD-L1 expression, and IFN- γ gene expression
- Clinical response independent of baseline T cell infiltration

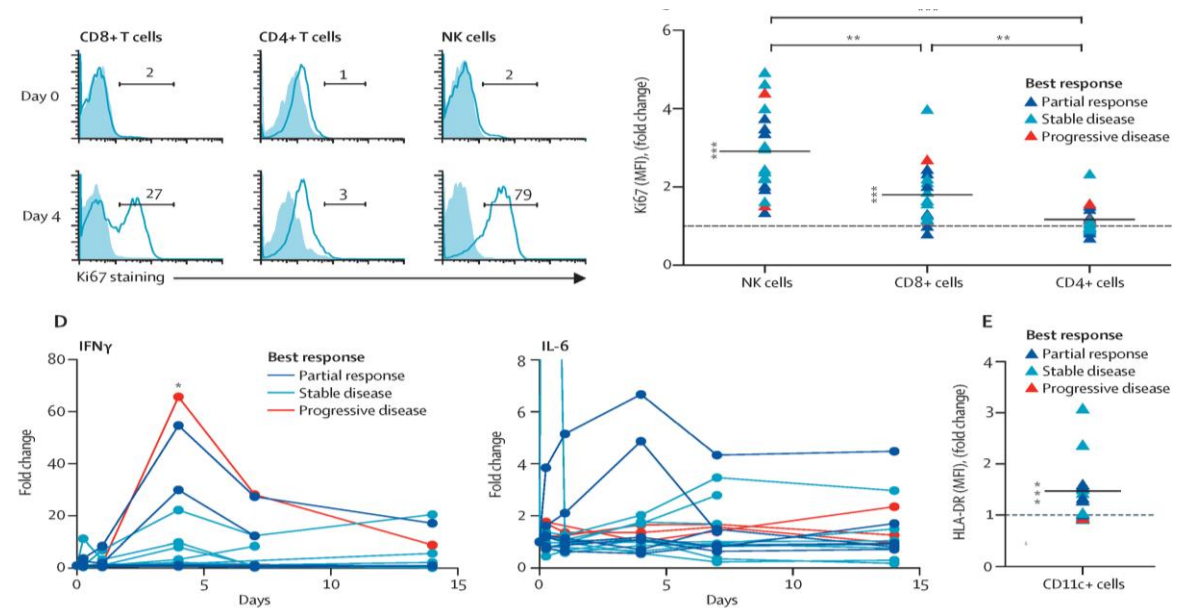
Interleukin 15

- IL-15 is a common $\gamma\epsilon$ 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 $\beta\gamma$ receptors
- Advantages over IL-2: less activation induced cell death of CD8+ T cells, and less expansion of Treg
- ALT-803: IL-15/IL-15R α 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

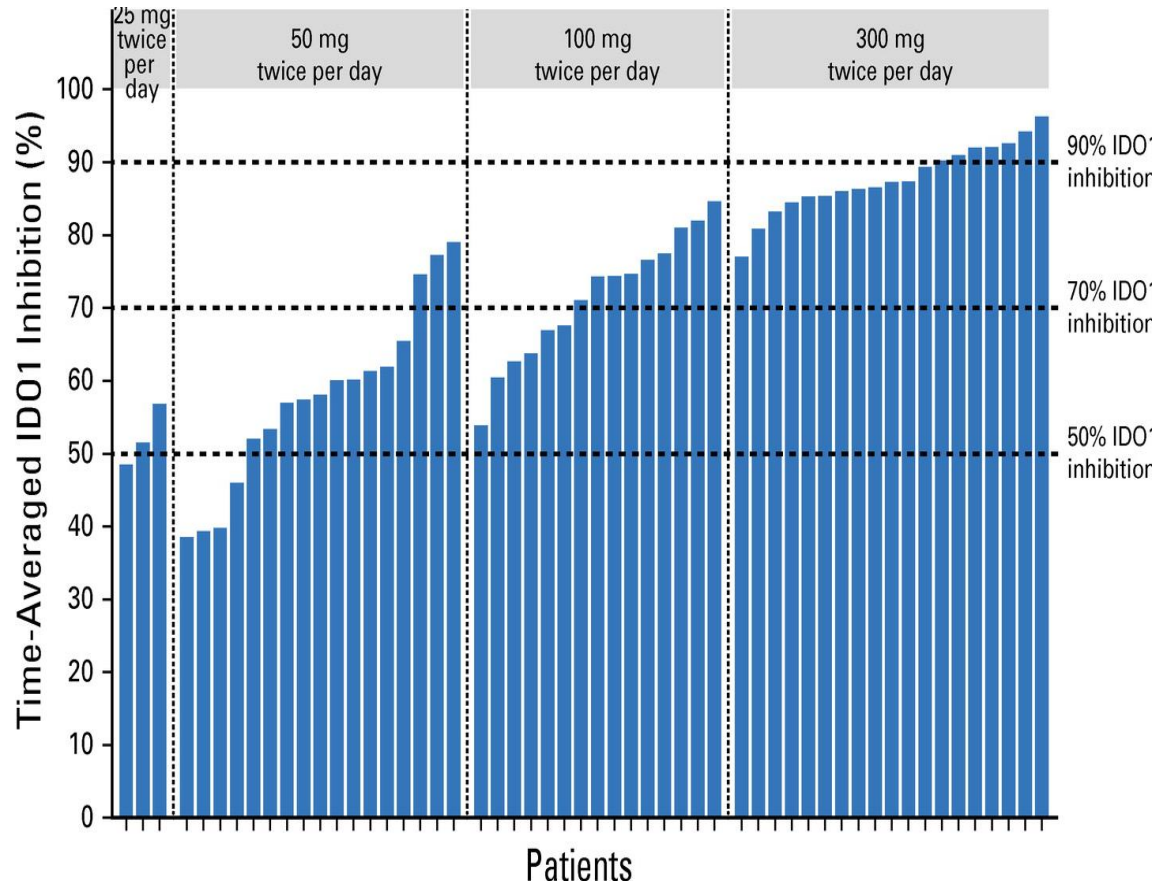


n=21 (23 enrolled, 21 treated)	ORR	DCR
All patients	6 (29%)	16 (76%)
PD-1 R/R	3 (27%)	10 (91%)
PD-L1 negative (<1%)	3 (30%)	7 (70%)
PD-L1 positive (>50%)	3 (75%)	4 (100%)

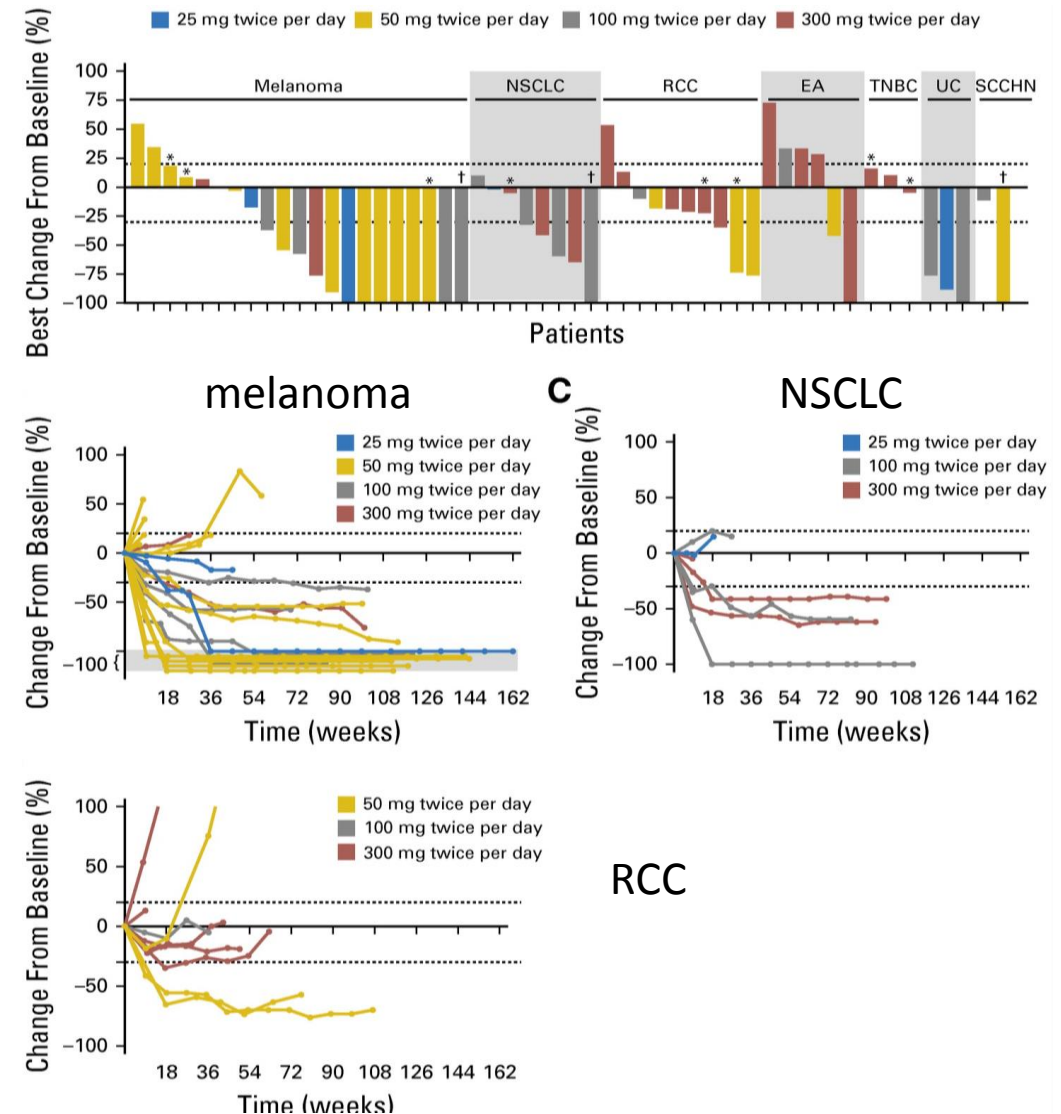
Epacadostat + Pembrolizumab in Advanced Solid Tumors

- 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 tryptophan, 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

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



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



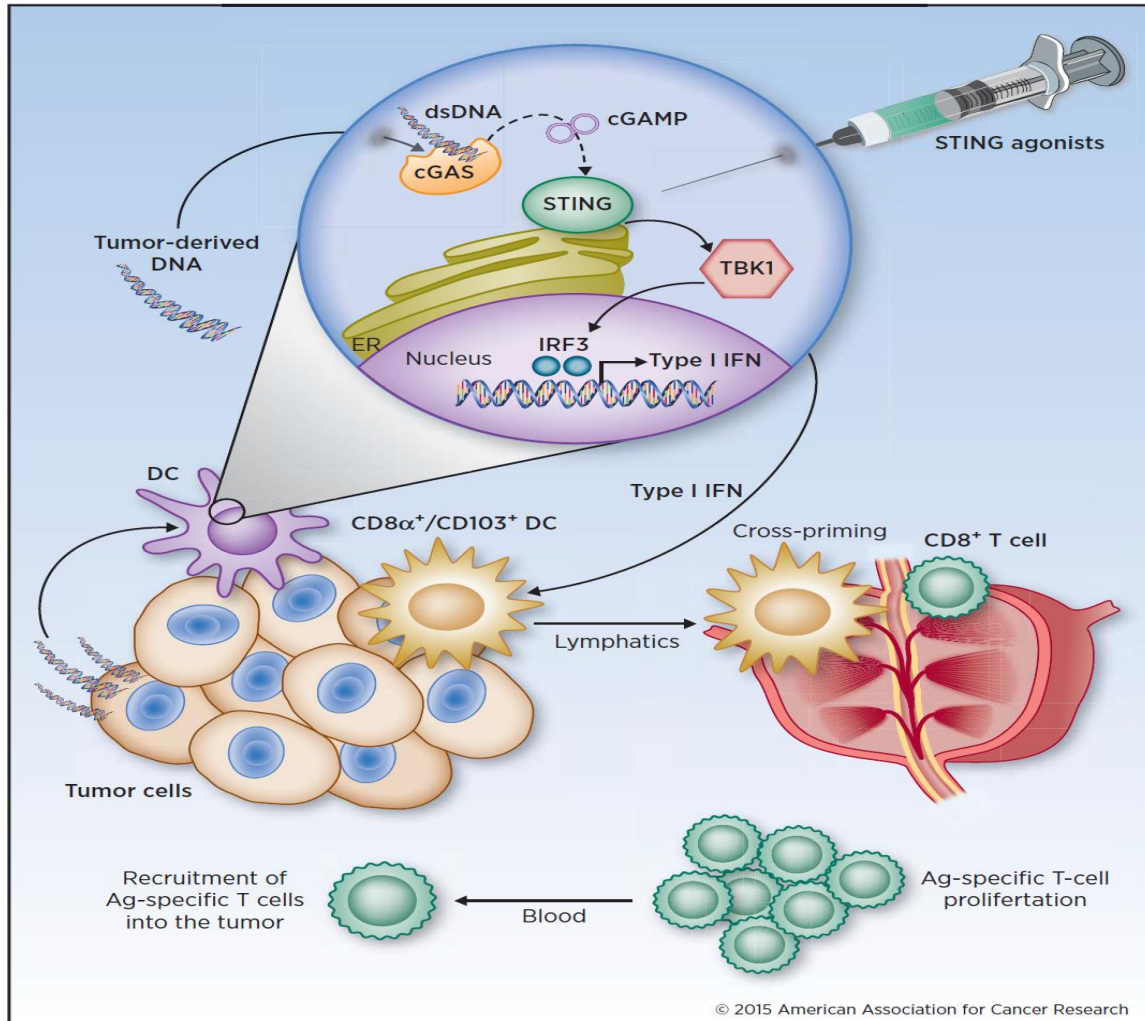
Phase 3 ECHO 301 Pembro vs Pembro vs Epacadostat (n=706) Failed to Meet Primary PFS Endpoint: Why??

- 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)

CDNs Activate STING Signaling to Initiate Intratumoral T cell Priming

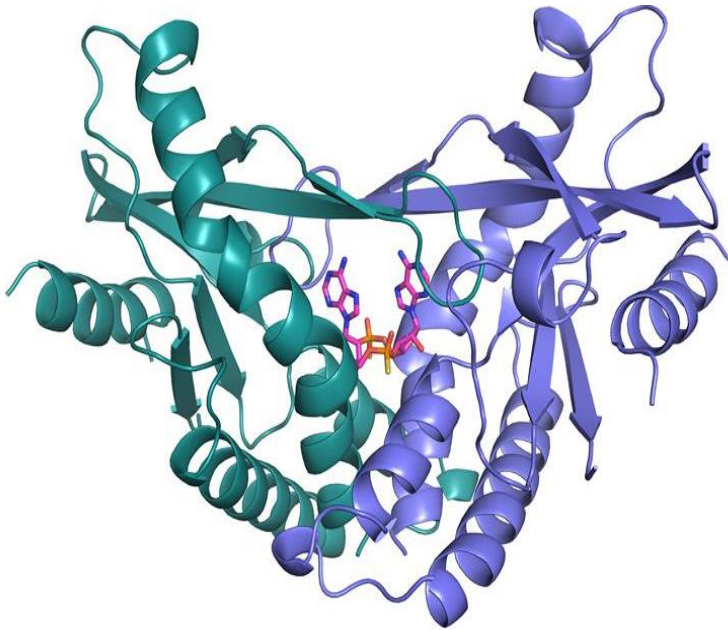


- T cell inflamed tumors in humans typically have an IFN- β transcriptional signature
- STING is the critical receptor to activate immune cells, including dendritic cells
- Tumor-derived DNA induces IFN- β by tumor resident DCs through STING signaling
- Intratumoral injection of CDNs induces IFN- β ,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

ADU-S100: An Improved CDN Agonist of STING

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

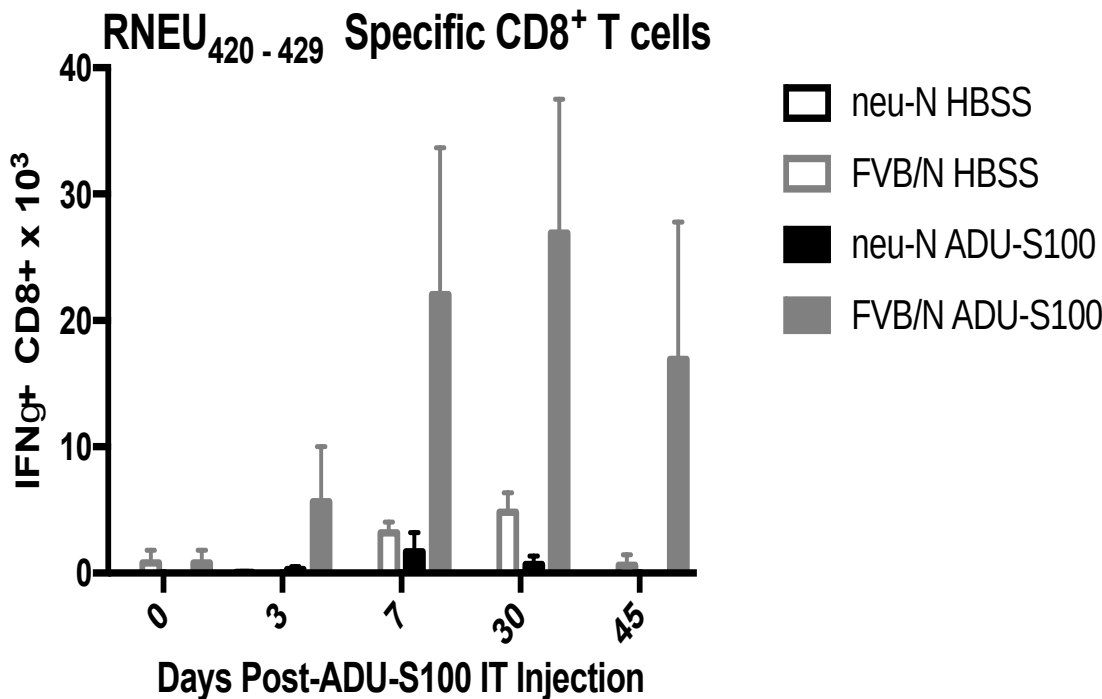
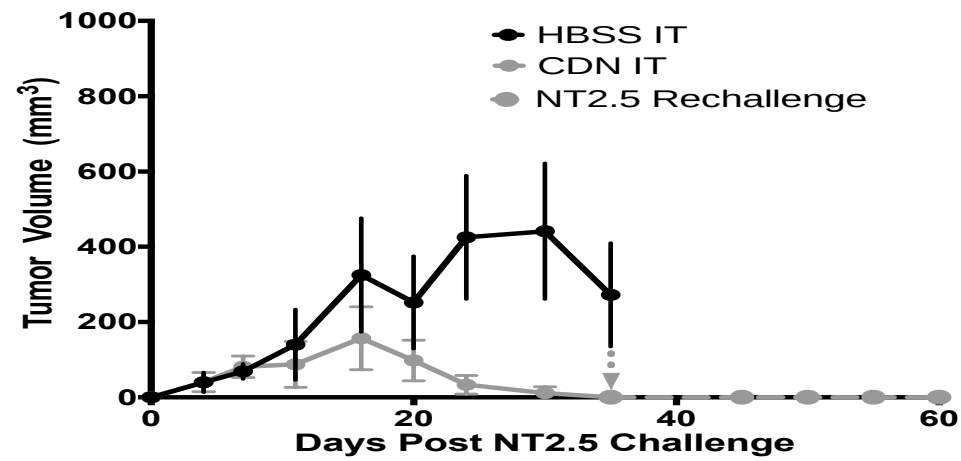
**ADU-S100 STING
Co-Crystal Structure**



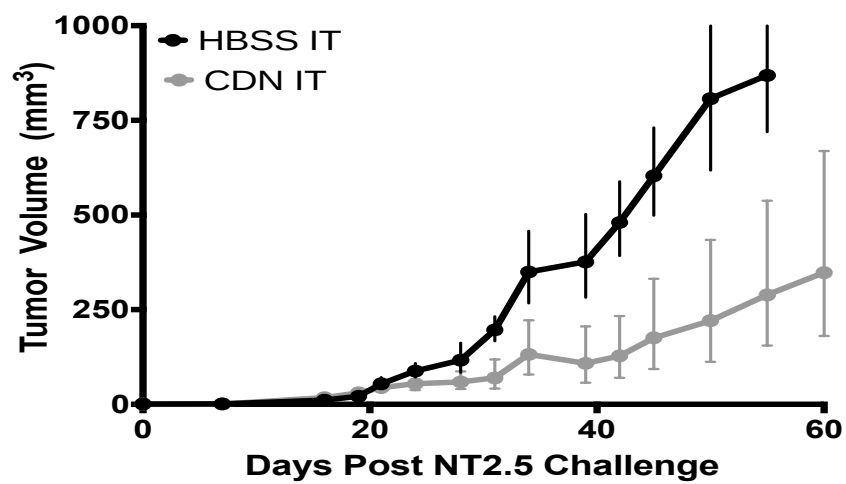
- ADU-S100 selected from series of CDN analogs based on balance of efficacy and tolerability/reduced toxicity
- Enhanced potency over natural CDN ligands
- Phosphorothioate increases resistance to phosphodiesterases to enhance potency
- ADU-S100 has activity in multiple mouse models, including melanoma (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

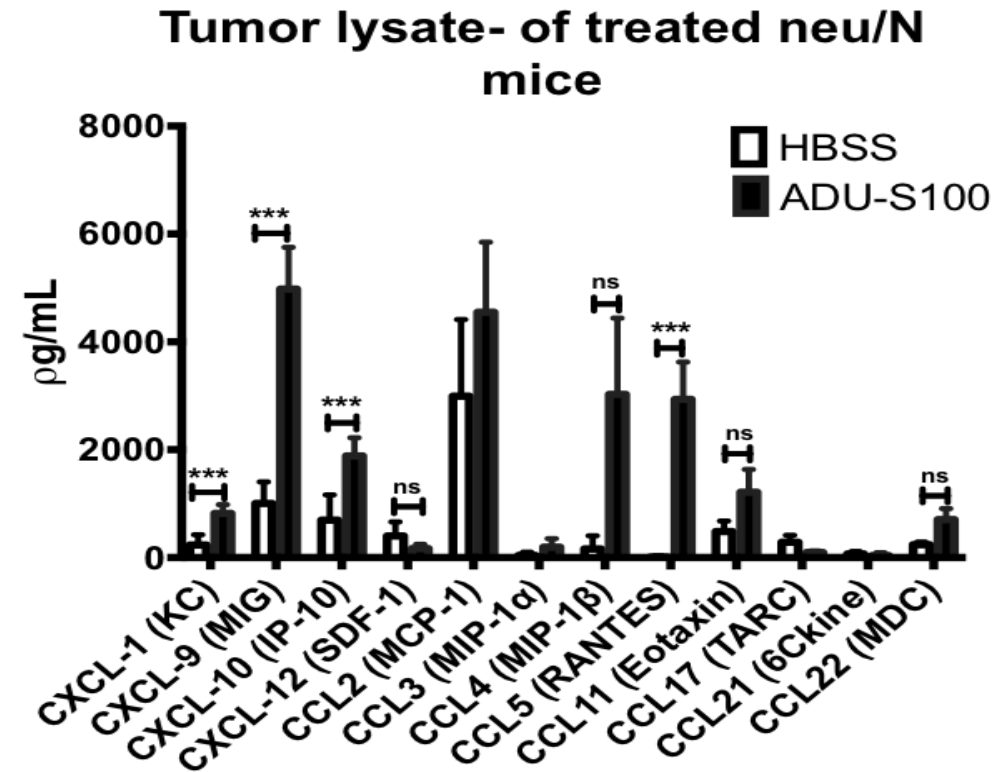
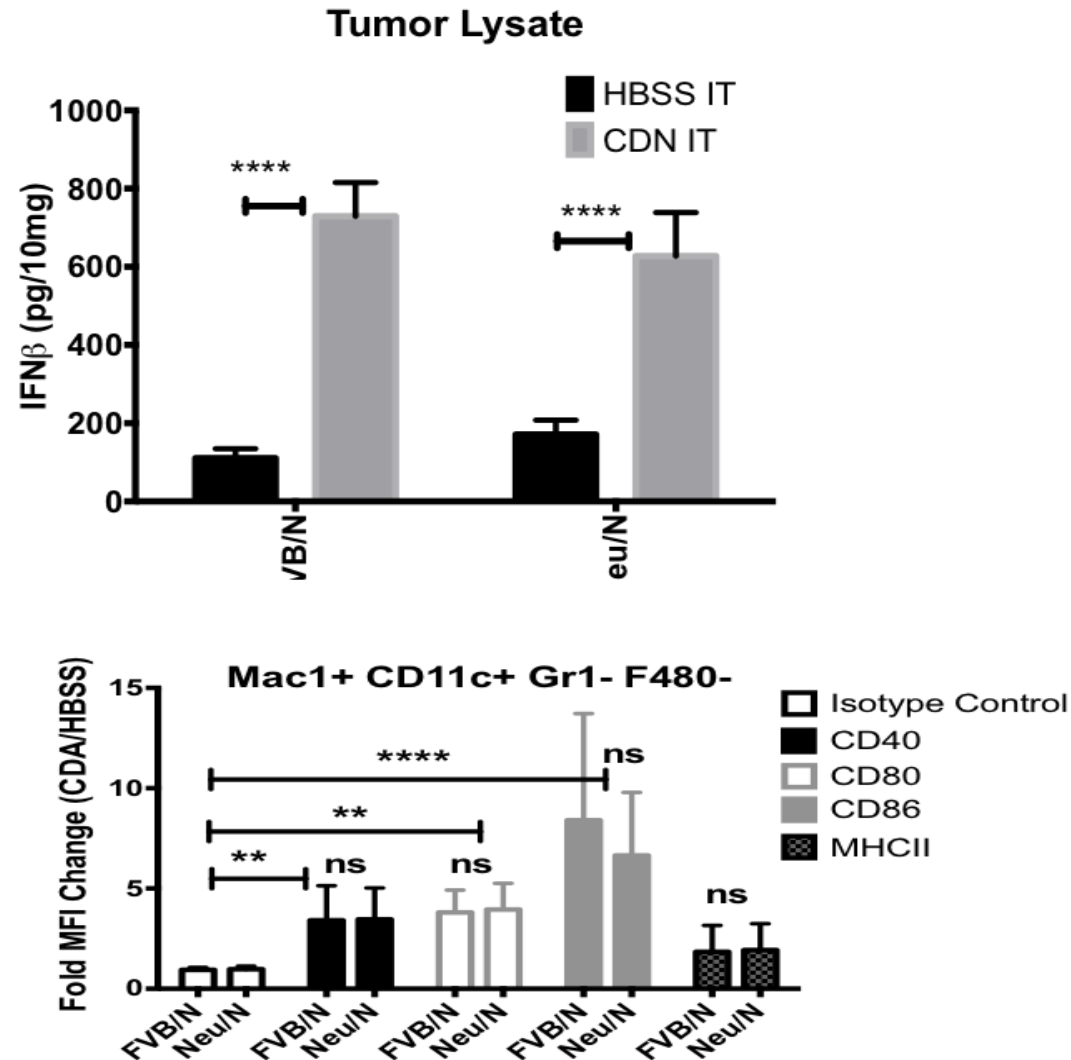
FVB/N



neu/N



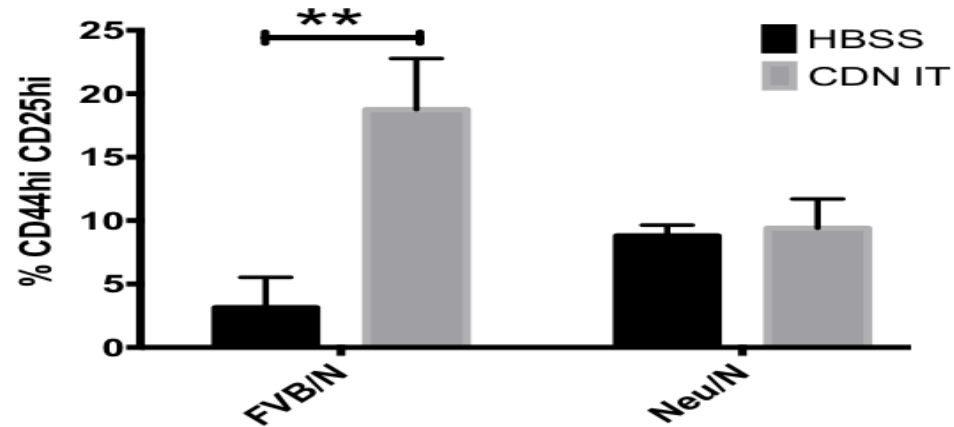
Proximal Innate Immune Activation is Intact in Neu/N Mice



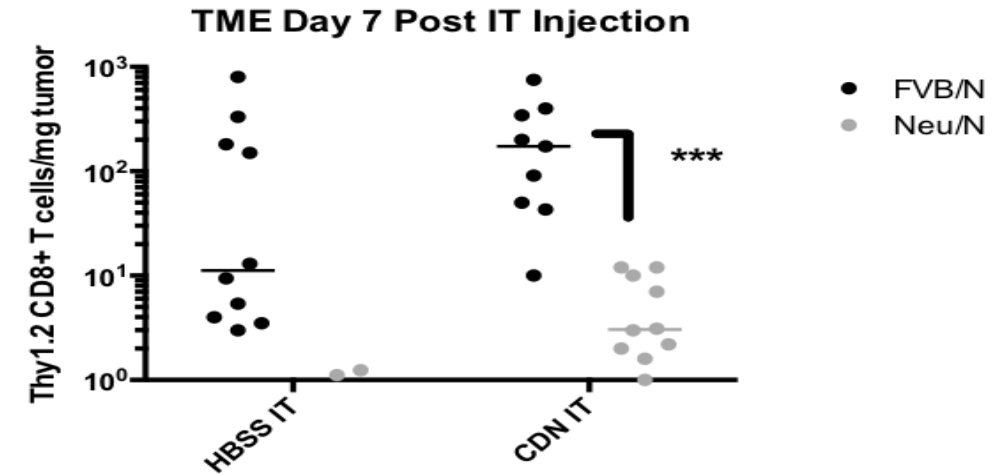
- Proximal STING signaling events—type I IFN secretion, DC activation, chemokine production—are intact in neu/N mice.

Distal T Cell Priming is Deficient in Neu-N Mice

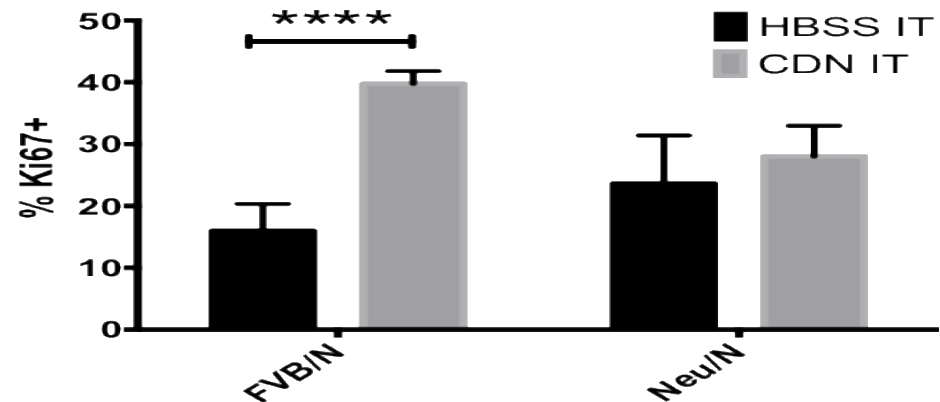
Activation



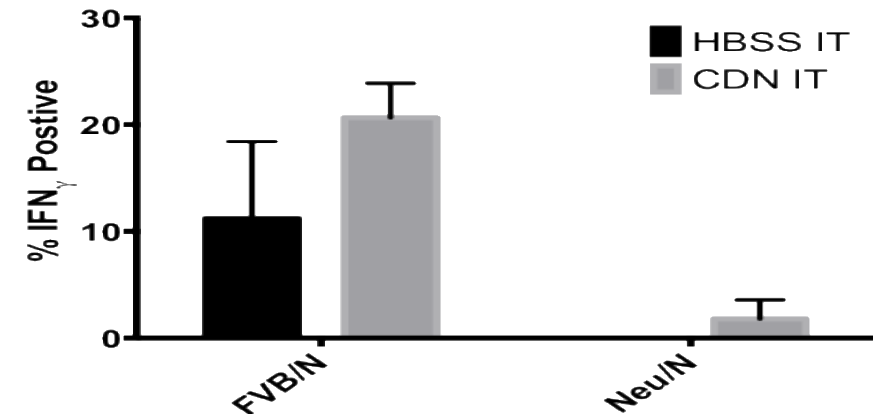
Migration



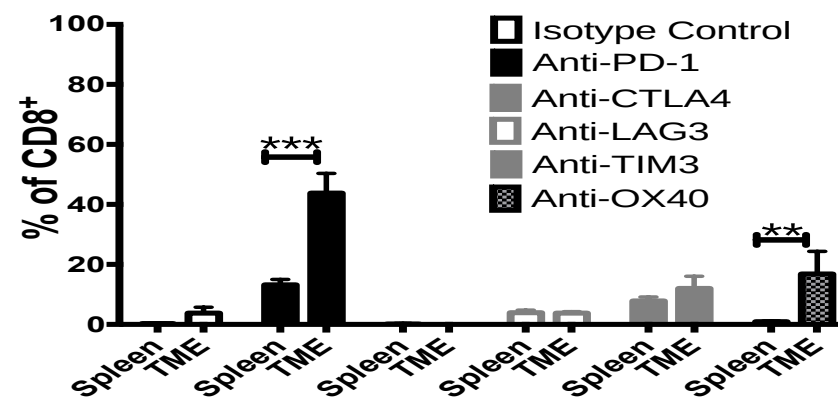
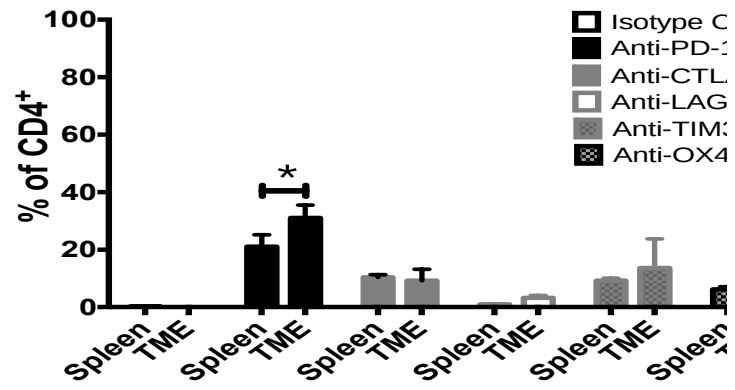
Proliferation



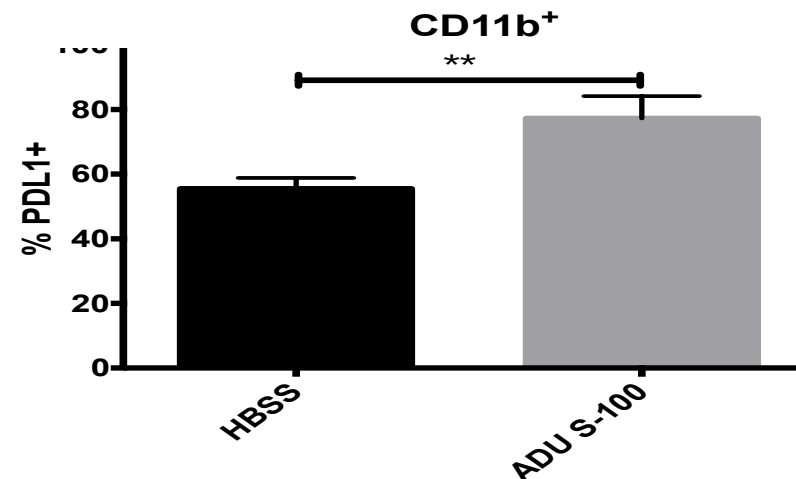
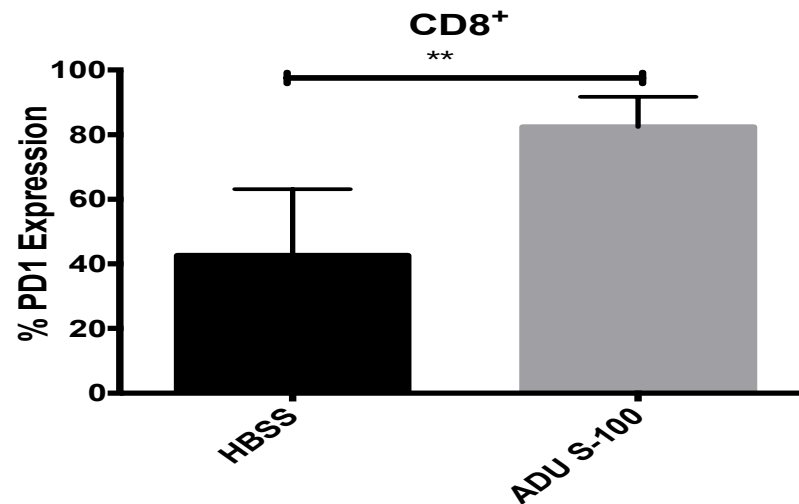
Function



Immune Checkpoint Pathways in the TME of Neu Mice



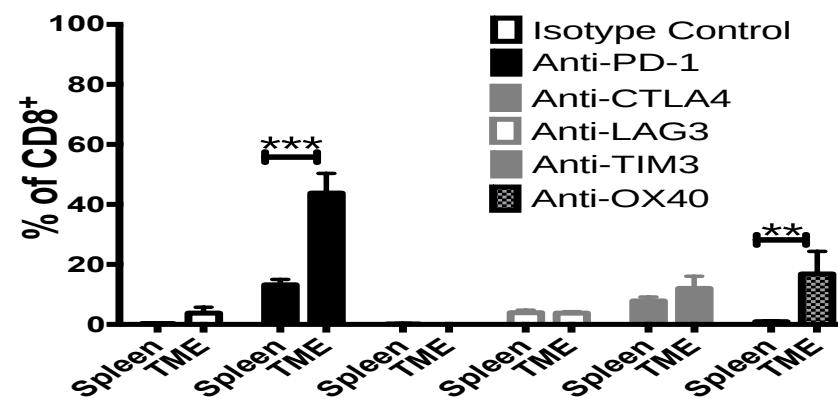
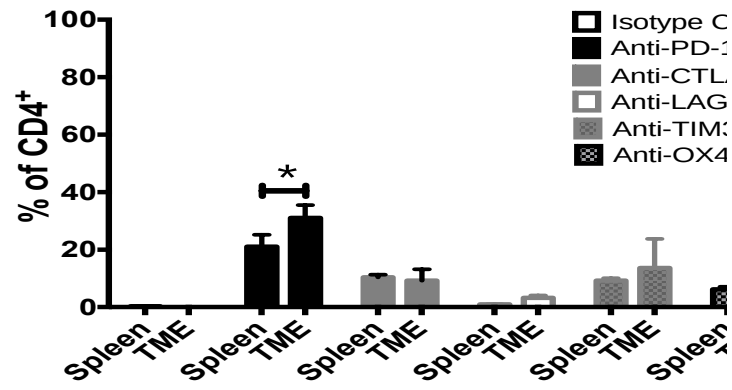
Baseline



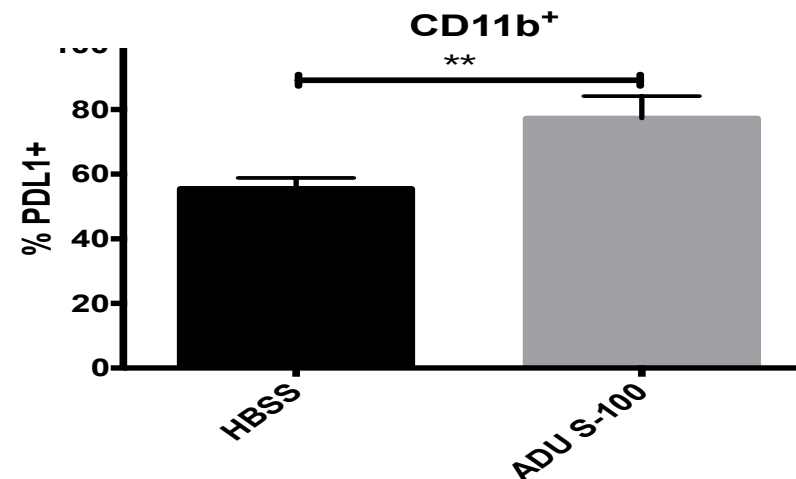
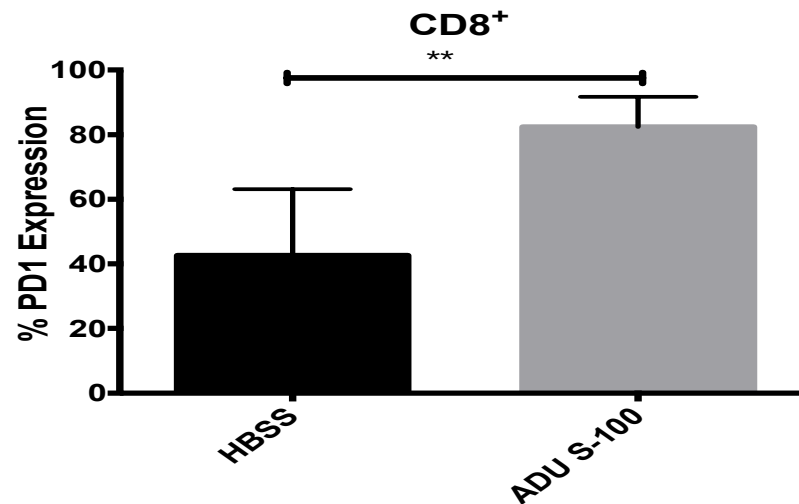
Post-ADU-S100

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

Immune Checkpoint Pathways in the TME of Neu Mice



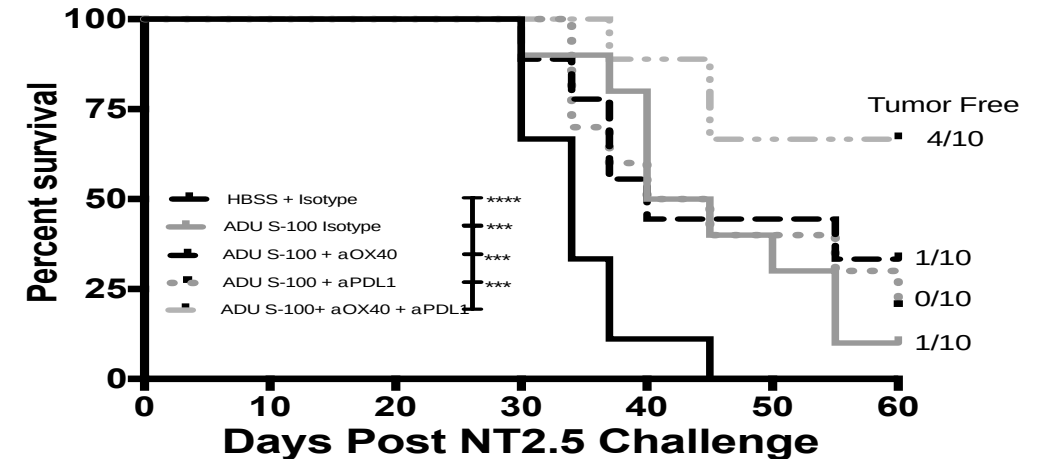
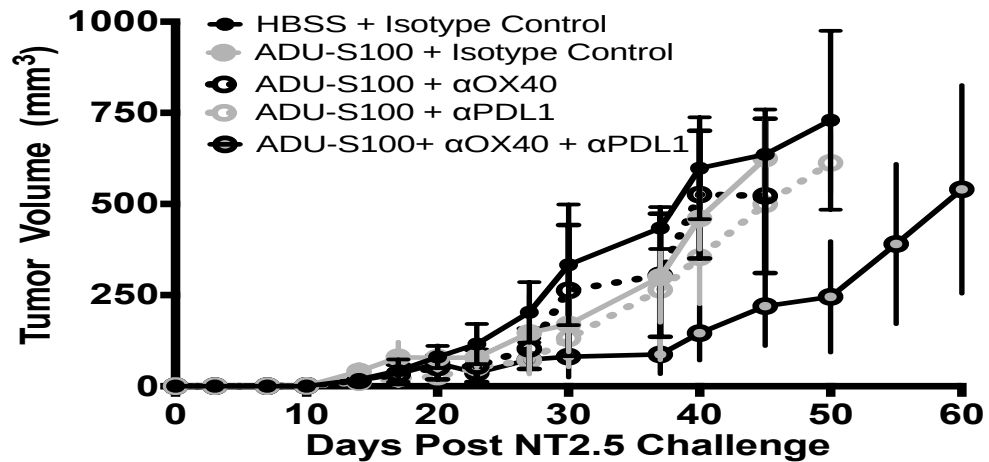
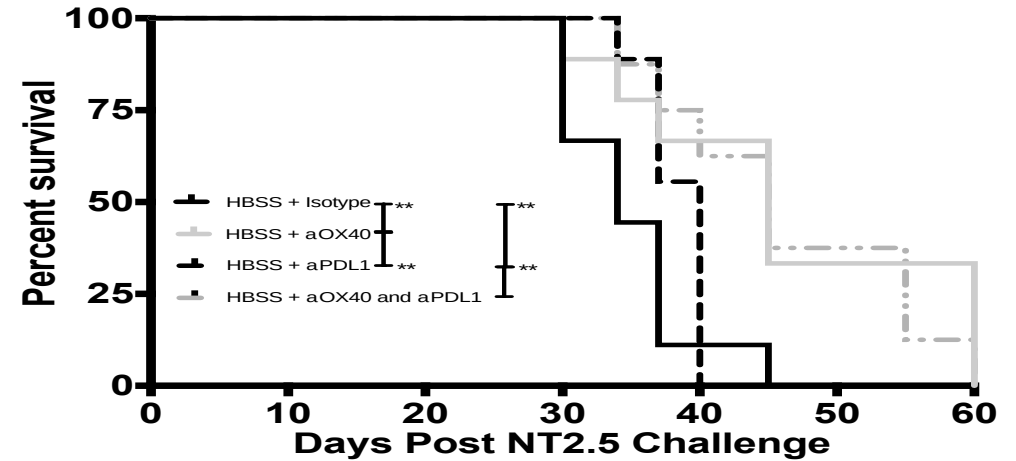
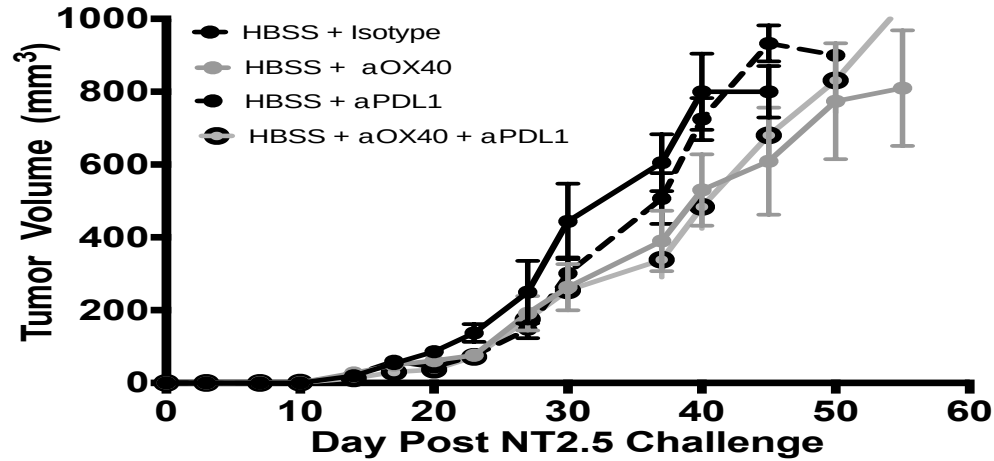
Baseline



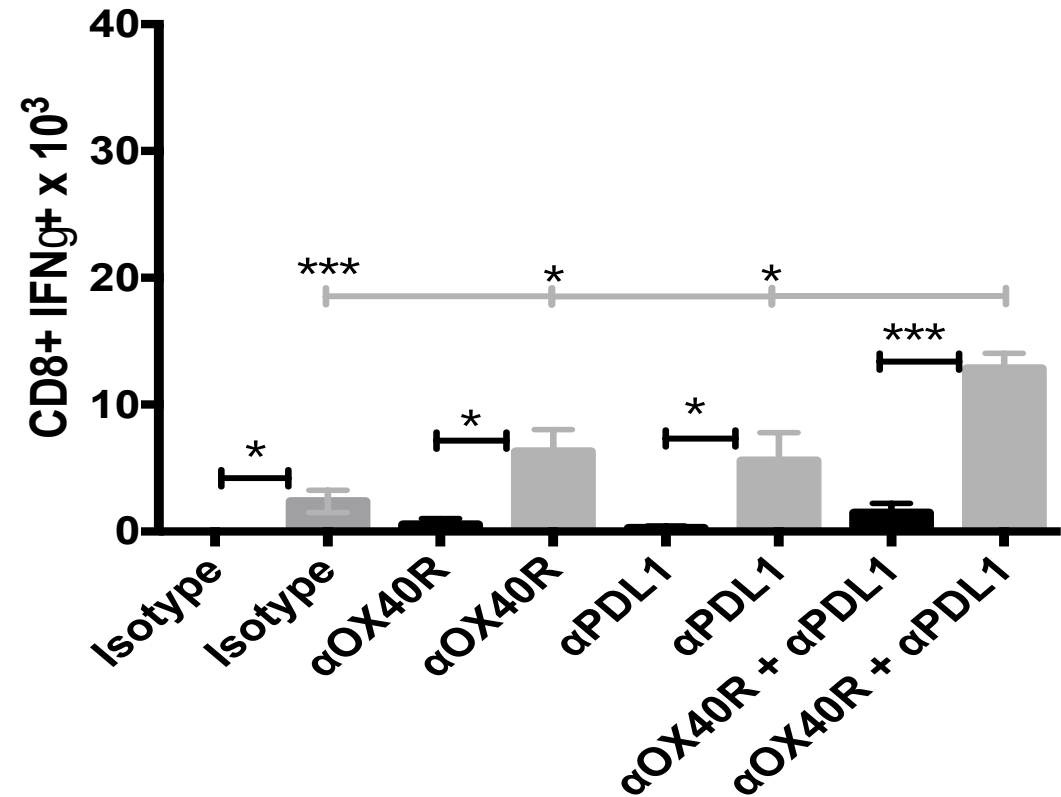
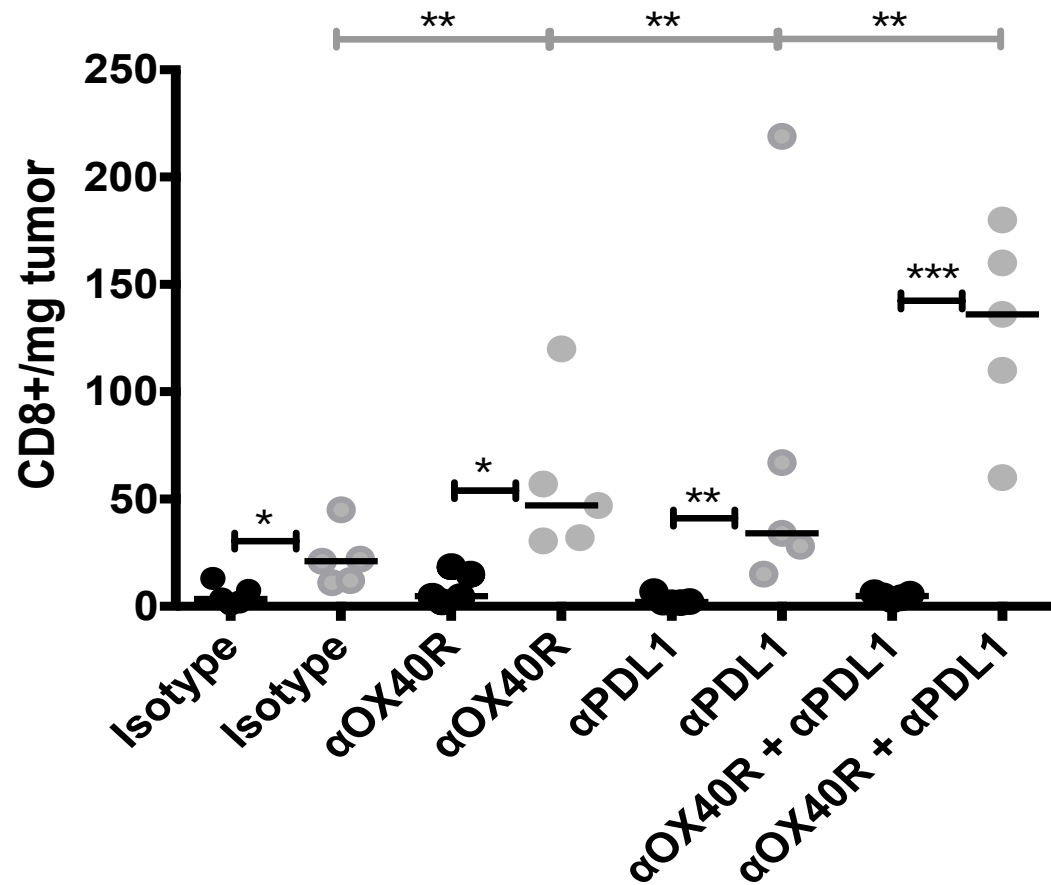
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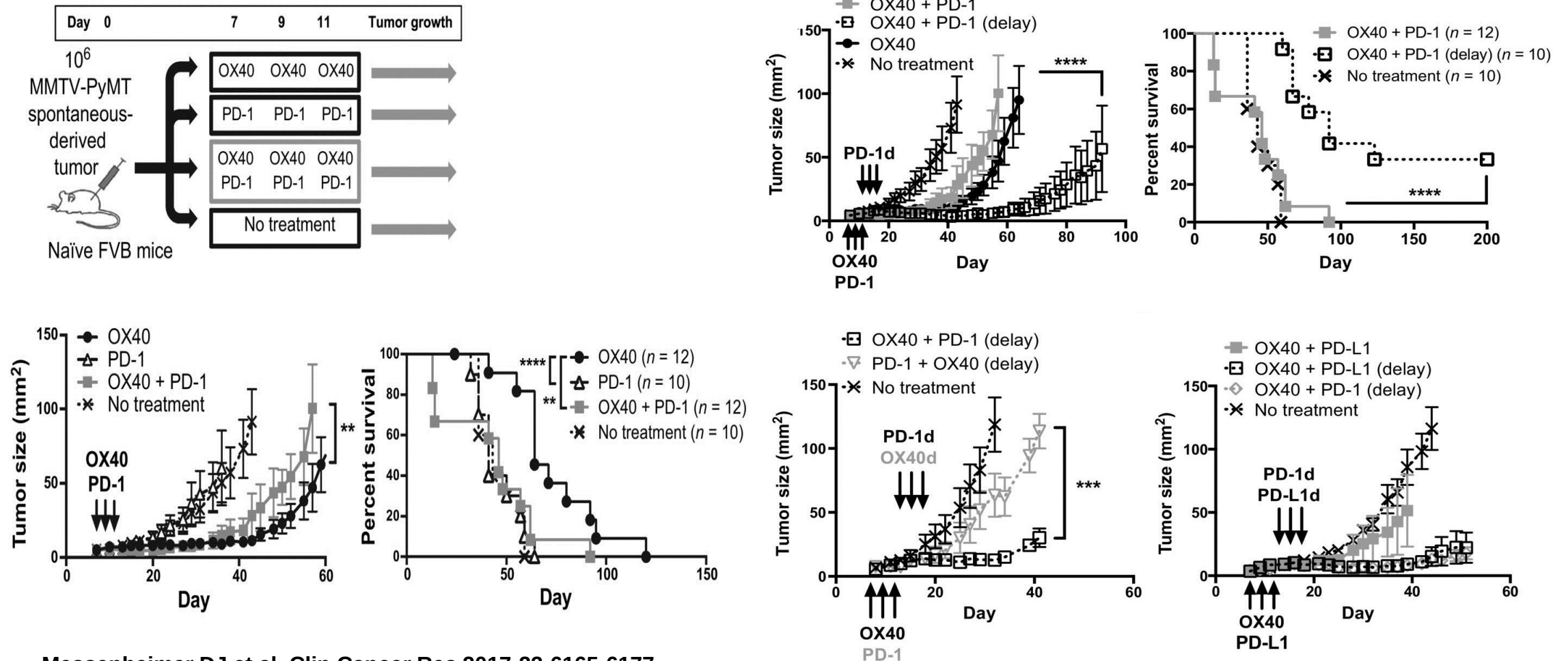
ADU-S100 Combined with PD-L1 Blockade and OX-40 Activation Prolongs Tumor-Free Survival in neu/N Mice



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

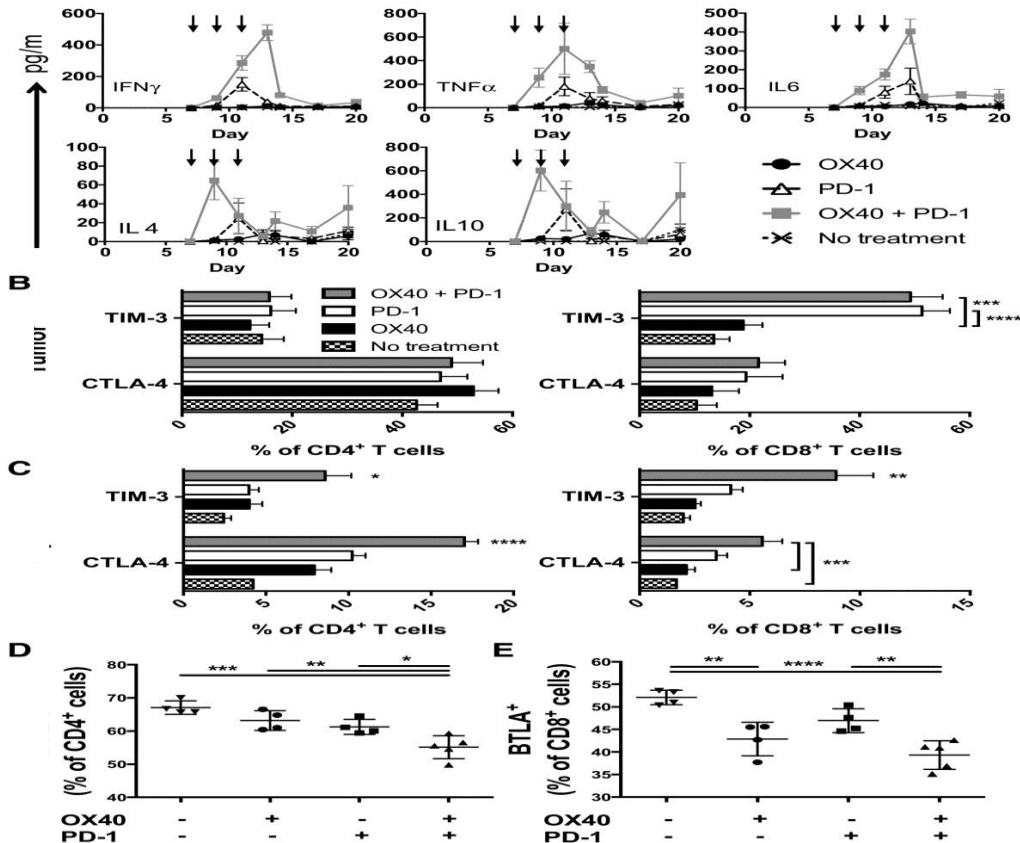


Timing of PD-1 Blockade and OX-40 Activation May Be Critical

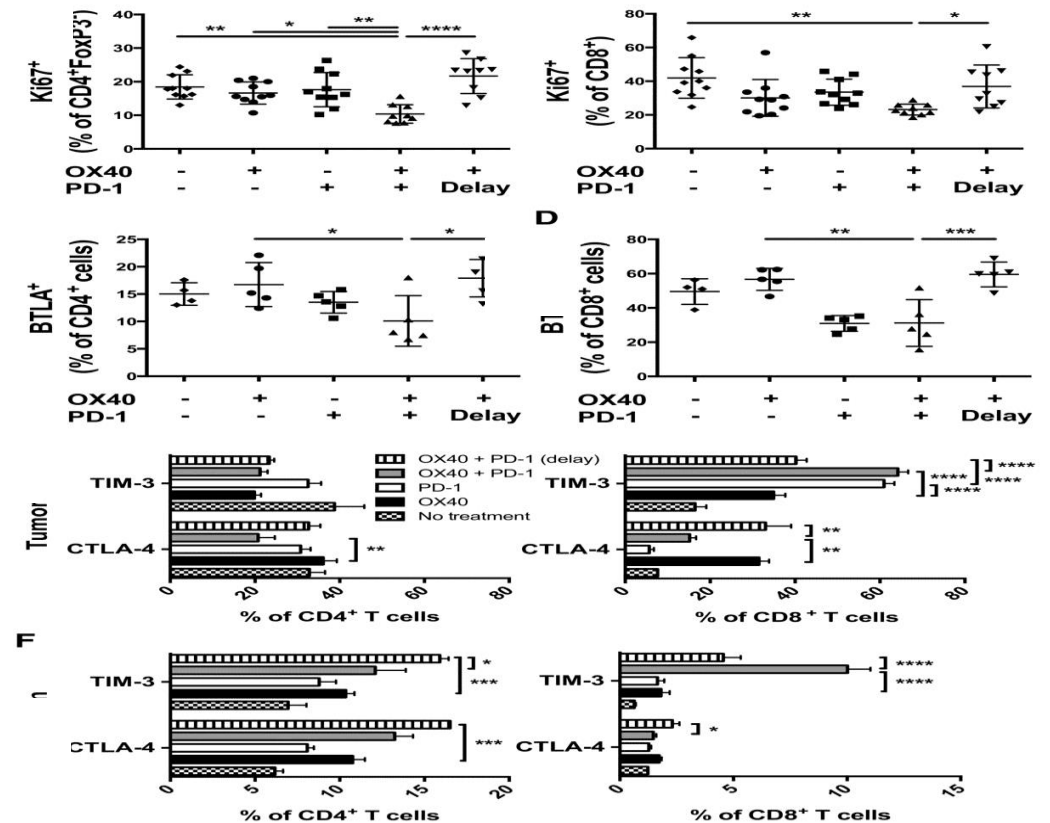


Timing of PD-1 Blockade and OX-40 Activation May Be Critical

Concurrent



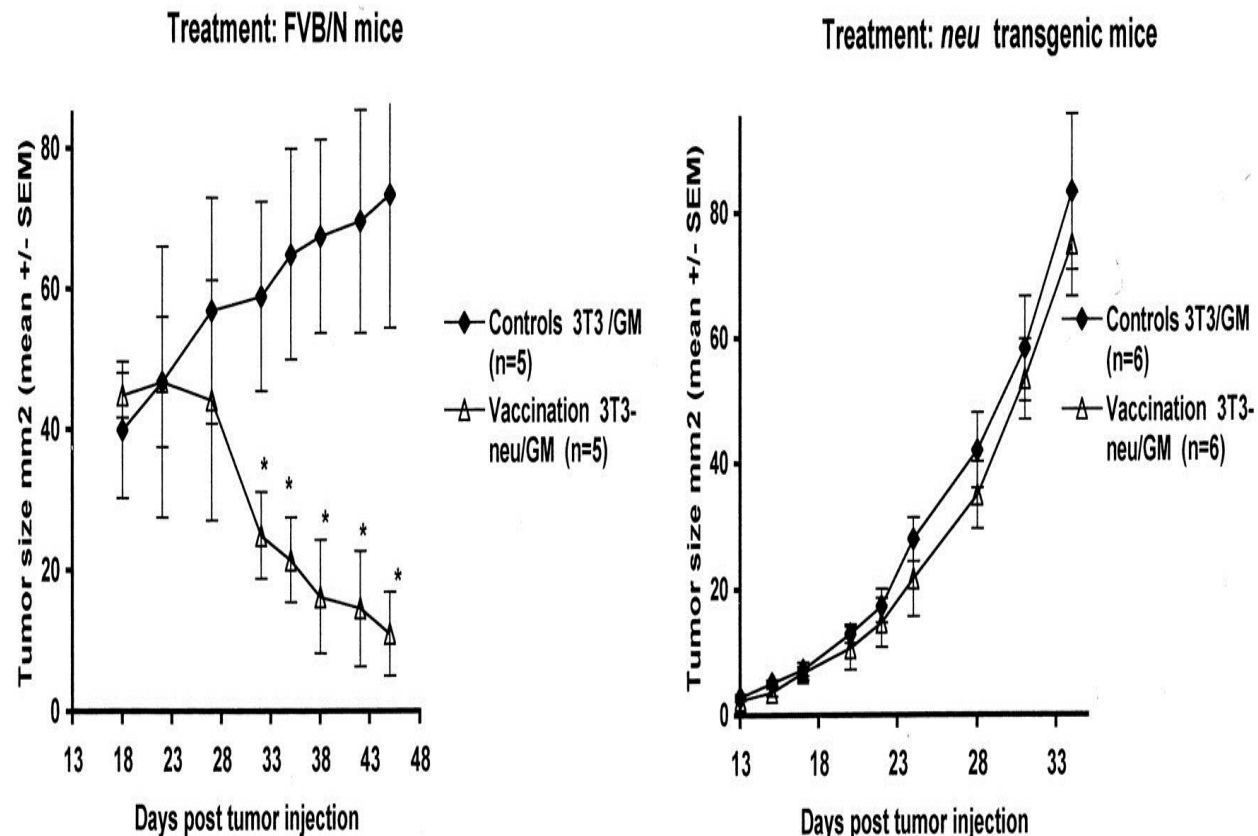
Sequential



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

maintains proliferating T cells without increase in inhibitory receptors

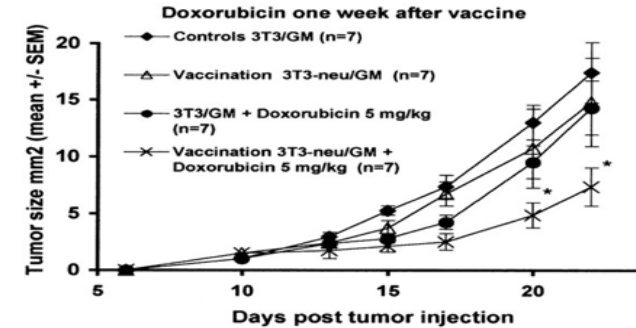
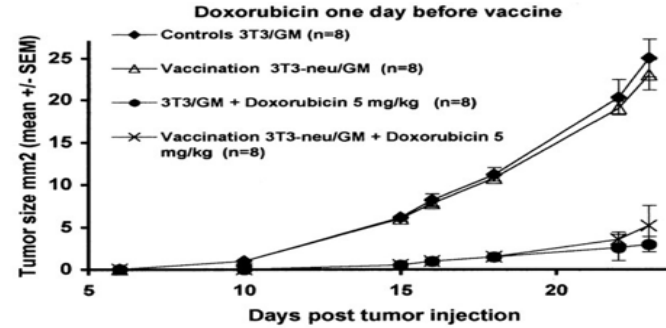
Chemotherapy-Induced Immunomodulation Can Be Drug, Dose, and Schedule-Dependent



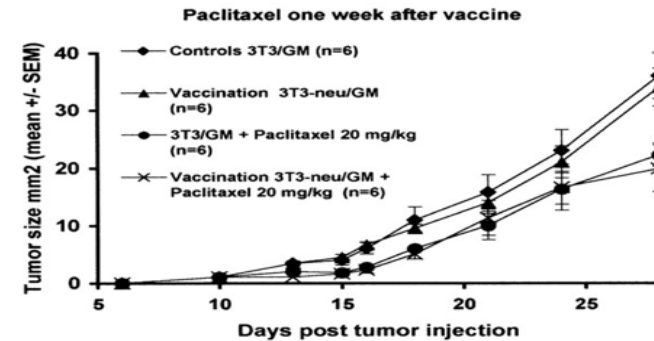
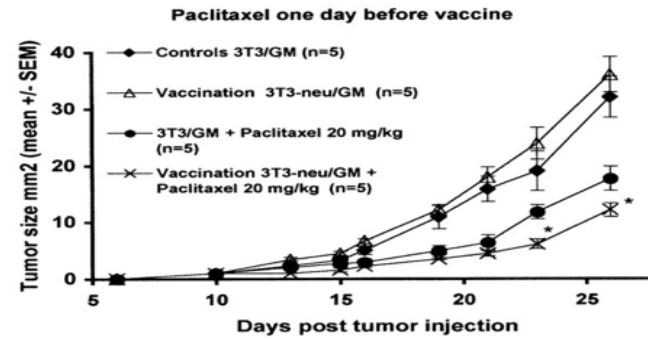
	T cell count (nadir) number/ μ l $\pm$ SD (normal range, 4000–9000) ^a	Chemotherapy 1 day before vaccine	Chemotherapy 7 days after vaccine
CTX			
50 mg/kg	6128 $\pm$ 847	+	–
100 mg/kg	5120 $\pm$ 1033	+	–
150 mg/kg	1559 $\pm$ 356	+	NT
200 mg/kg	1100 $\pm$ 478	+/-	NT
250 mg/kg	989 $\pm$ 122	+/-	NT
PTX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

Dose and Schedule Dependent Impact of Chemotherapy on Vaccine Activity

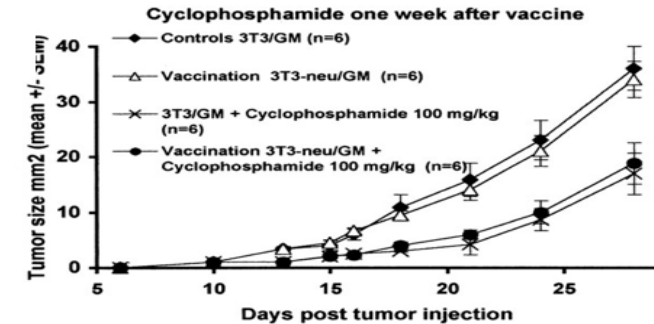
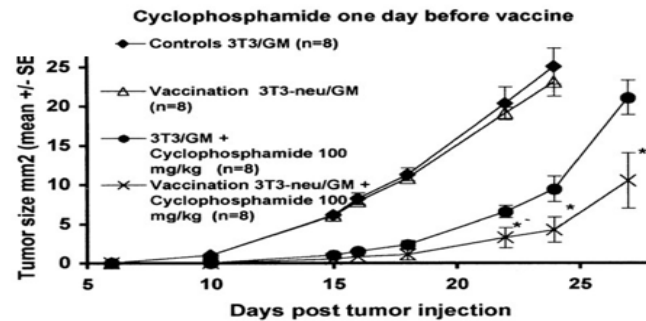
Doxorubicin



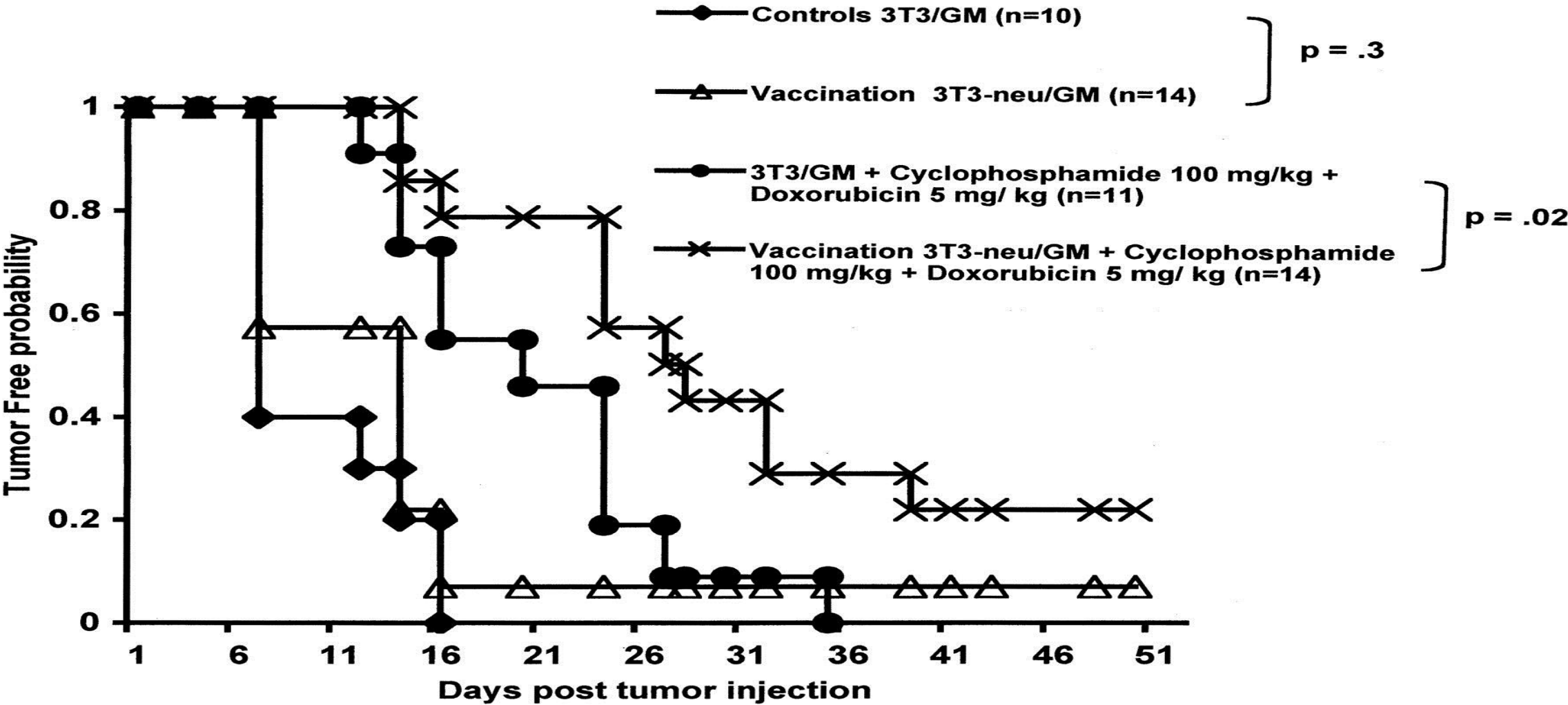
Paclitaxel



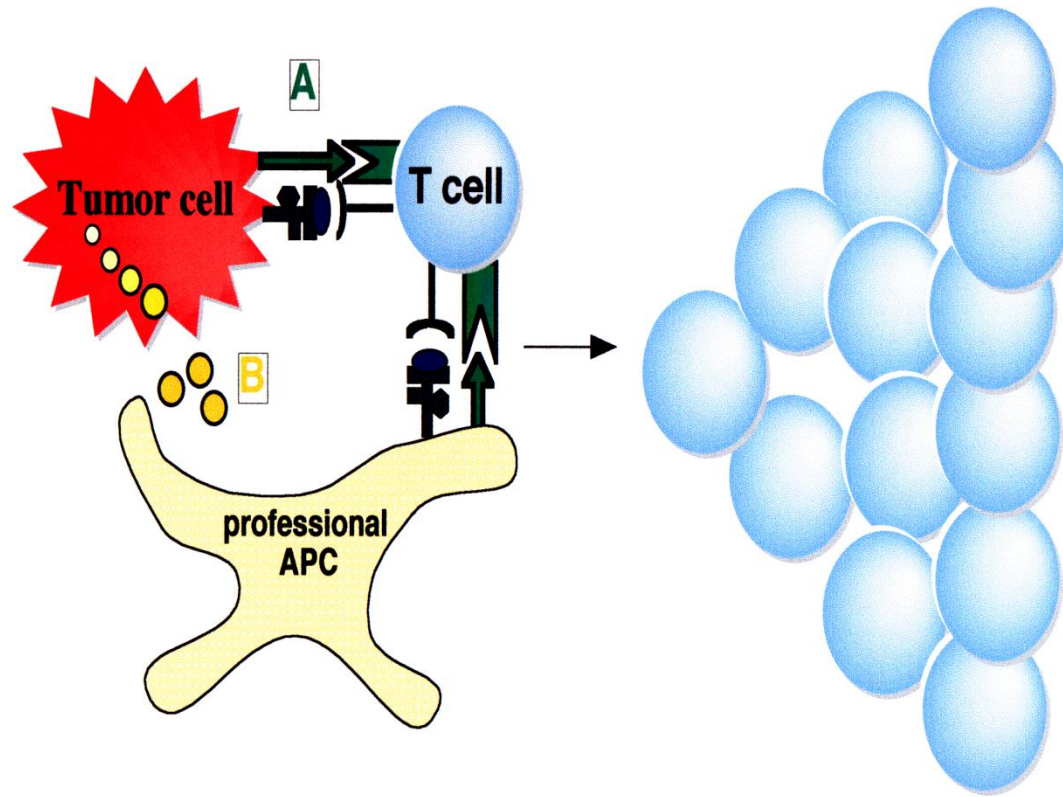
Cyclophosphamide



Polychemotherapy Enhances Vaccine Activity in Tolerant Neu-N Mice



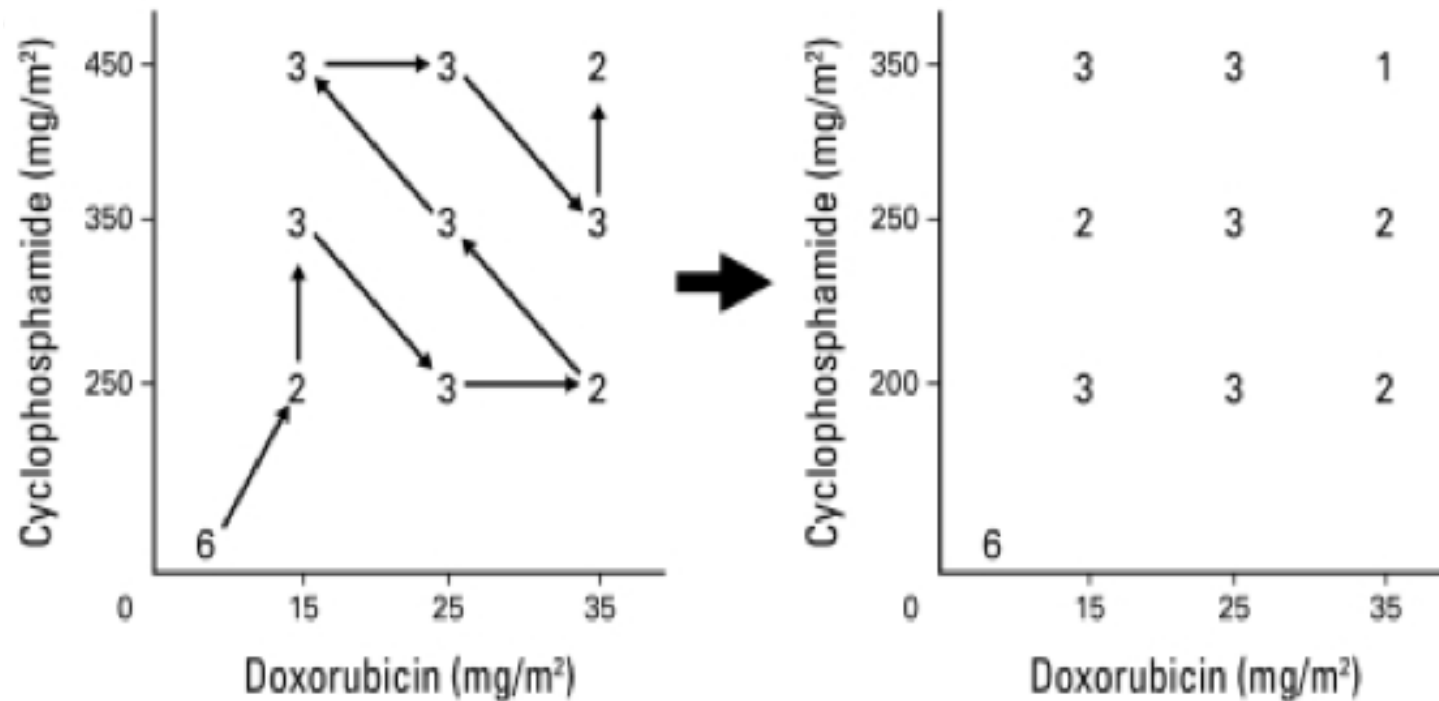
A Human GM-CSF-secreting Breast Cancer Vaccine



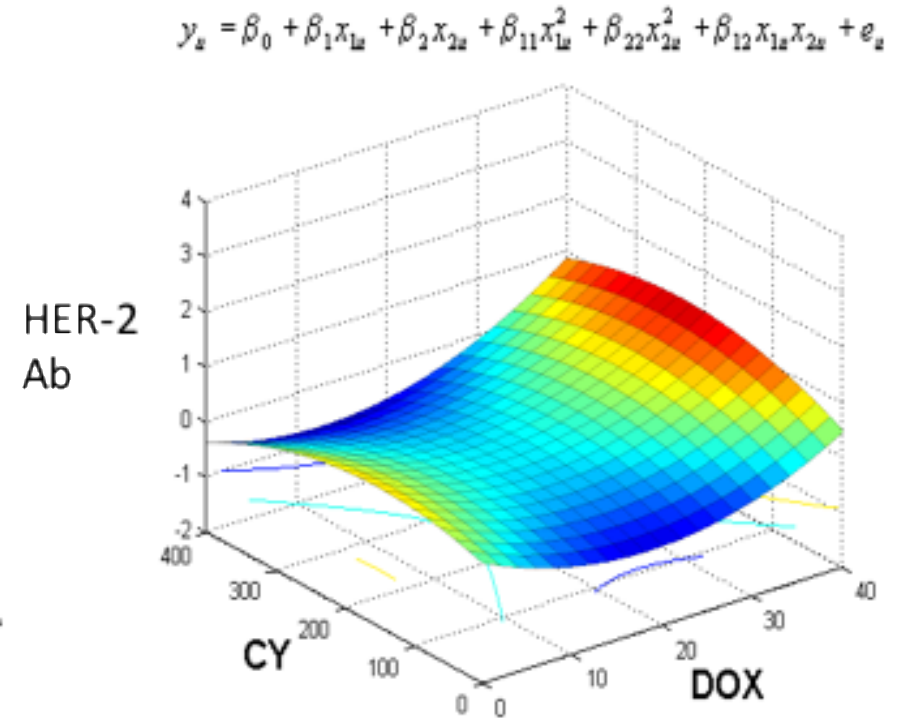
- Allogeneic breast tumor cells
 - SKBR3: HER-2+, ER-
 - T47D: HER-2-, ER+
- Generalizable
- Allows unbiased antigen delivery
- HER-2 for immune monitoring
- Secretes human GM-CSF 324 ng/10⁶ cells/24 hrs

Combination of Vaccination with Low Dose Chemotherapy

Novel Trial Designs to Explore Dose and Schedule



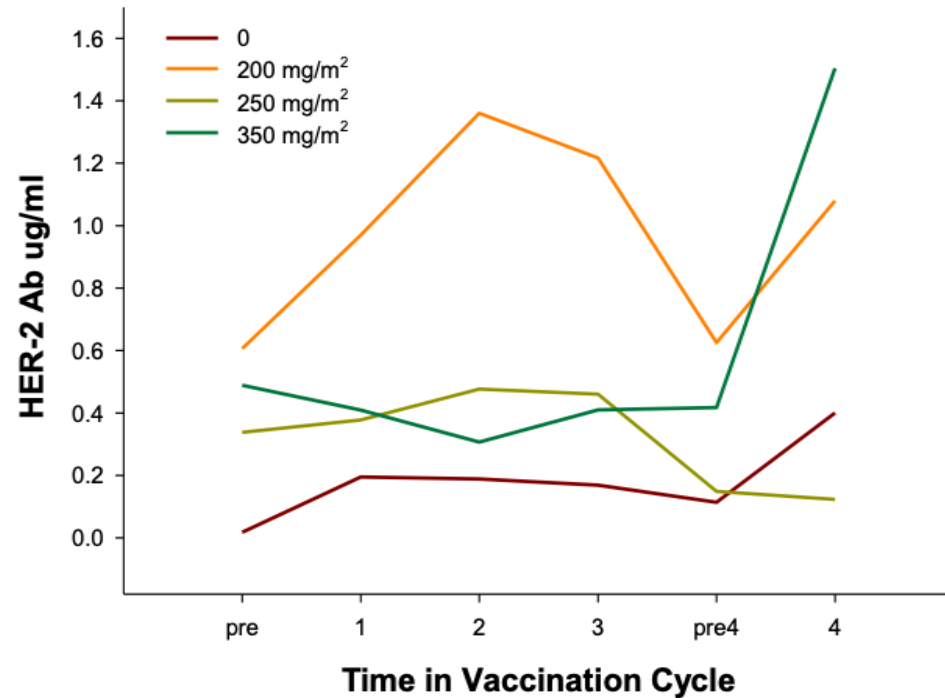
Possible Inputs: dose x dose
dose x schedule



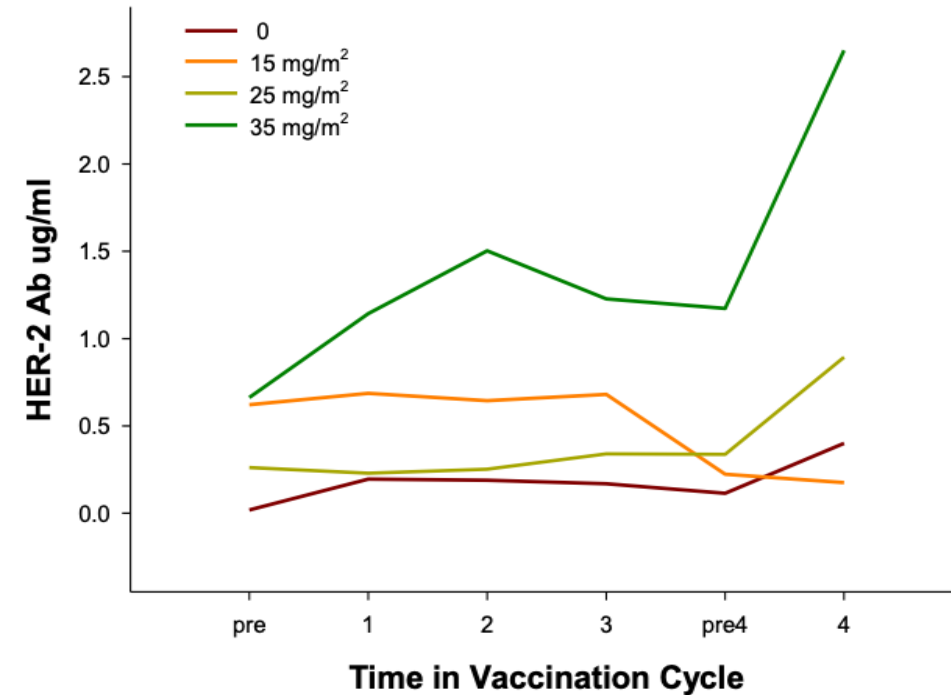
Possible Outputs: immune response
clinical response
toxicity

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

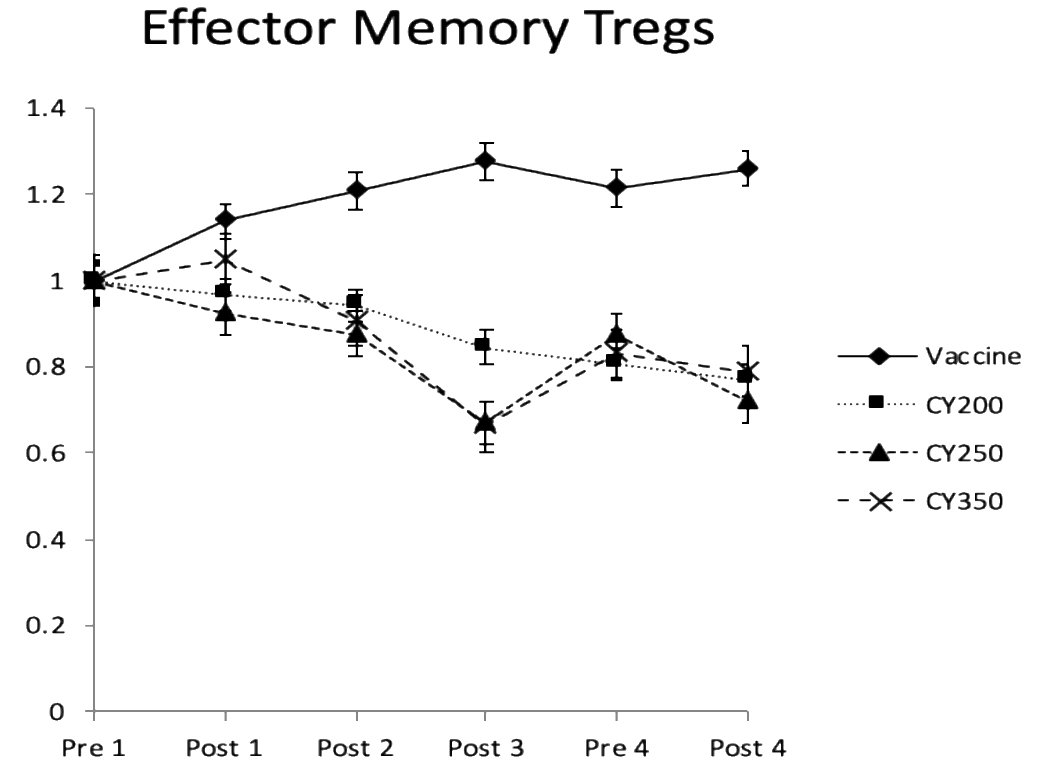
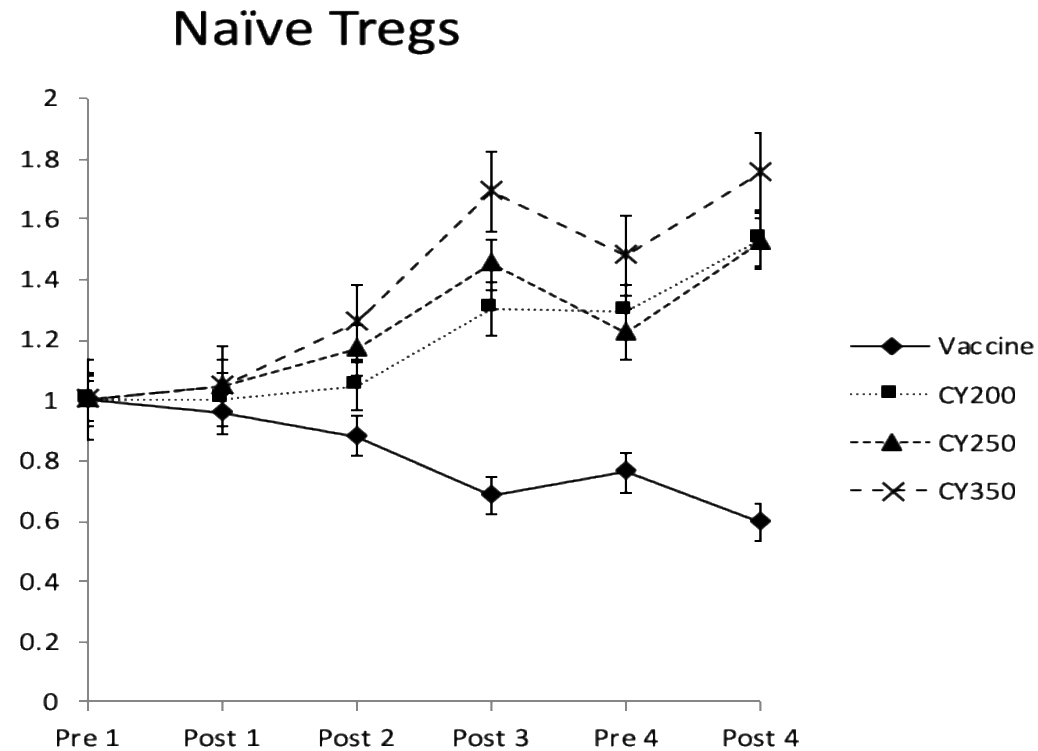
CY



DOX



Dose Dependent Impact of CY on Naïve and Effector Memory Tregs



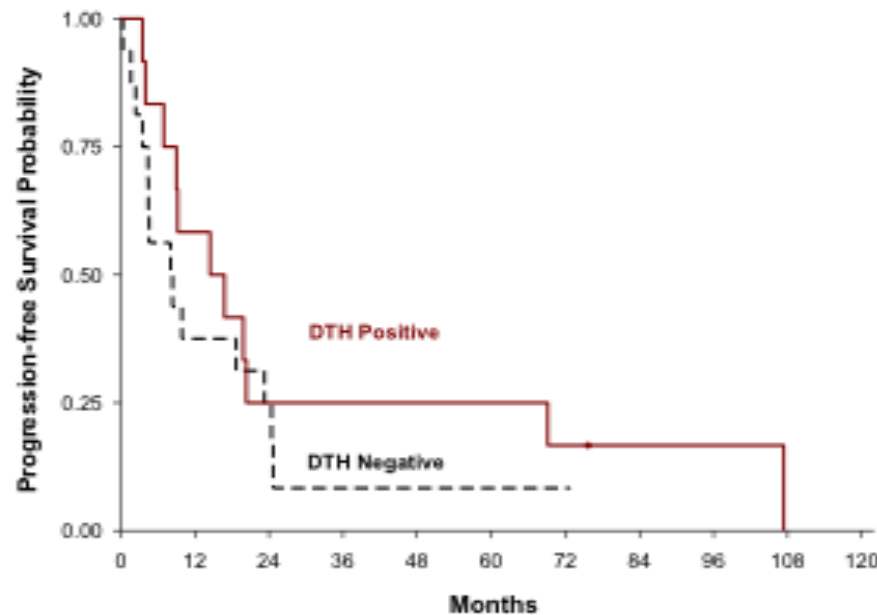
CY Preferentially Impacts Tregs Relative to Effector T Cells

	% Apoptotic Tregs	% Apoptotic Effector T Cells
No CY	8.61%	6.89%
CY 200	21.9%	7.16%
CY 250	28.4%	6.6%
CY 350	35.9%	15%

Chen/Emens, unpublished data

Survival Outcomes (n=28)

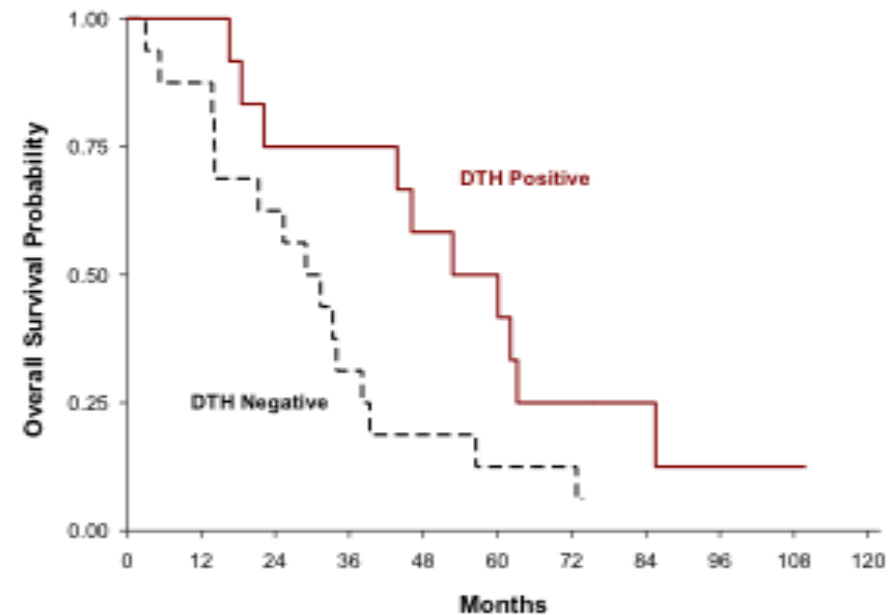
**Total Progression-Free
Survival: 10 months**



**DTH NR vs. R:
8 vs. 16 months**

Emens LA, unpublished data

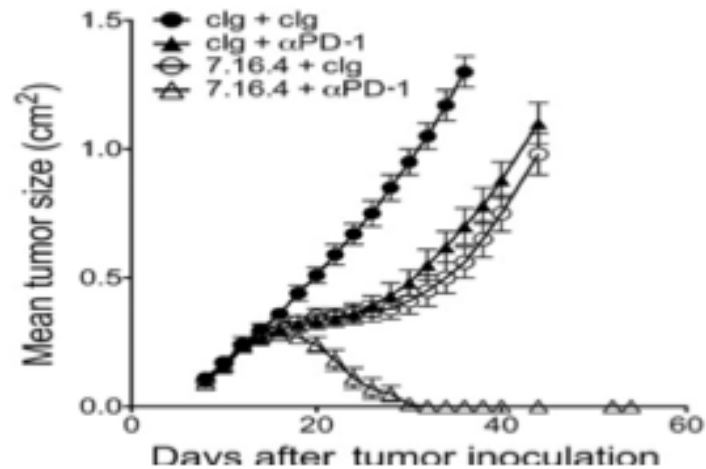
**Total Overall Survival:
36 months**



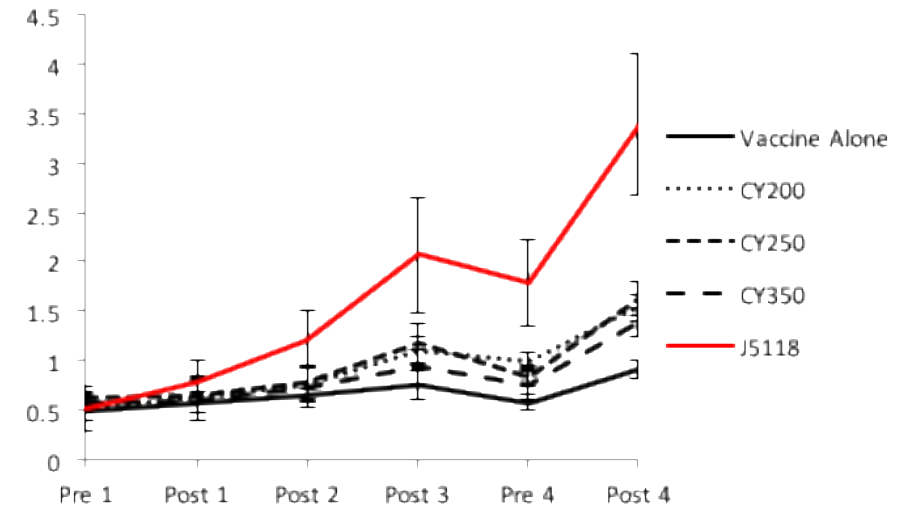
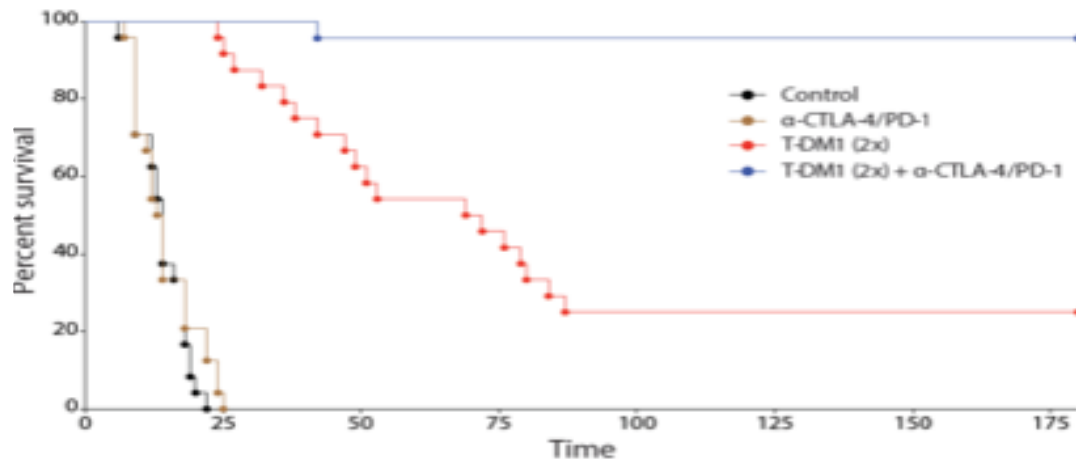
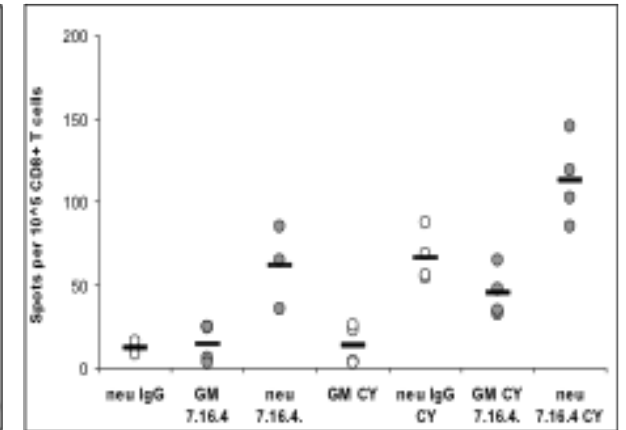
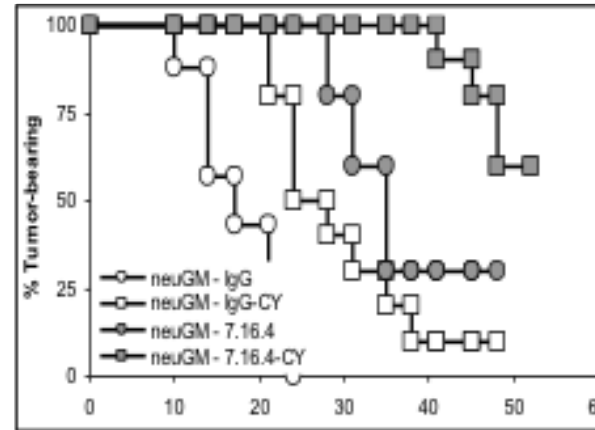
**DTH NR vs. R
30 vs. 56 months**

Combination of Immunotherapy with HER-2-directed Therapy

Checkpoint Blockade



Vaccination



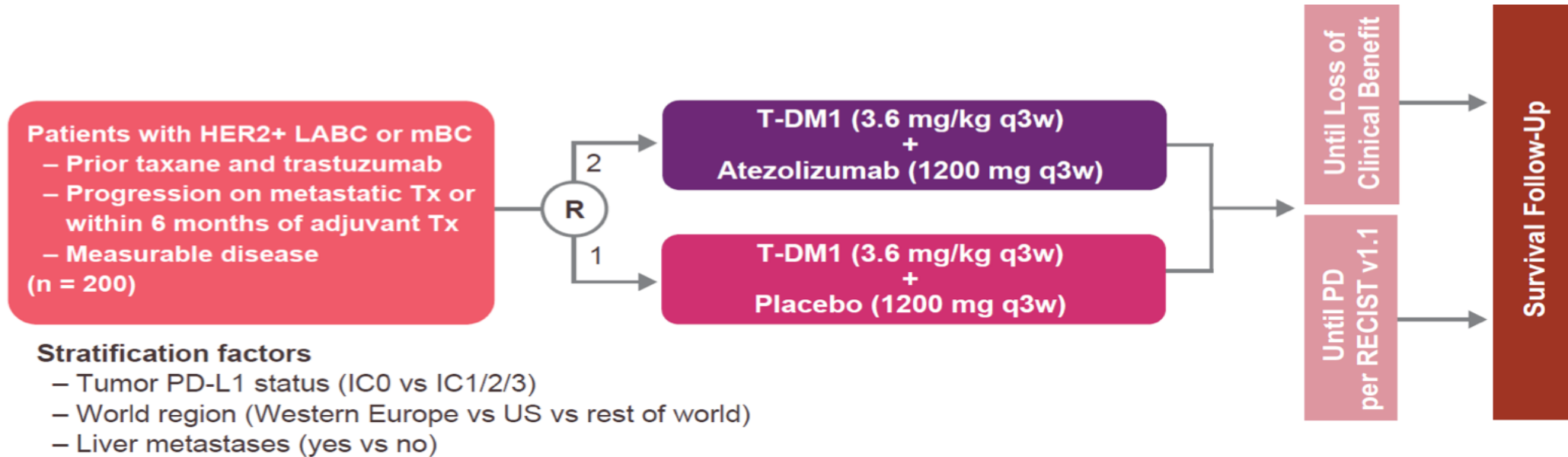
Stagg J et al, PNAS, 2011; 108: 7142-47

Müller P et al, Science Translation Medicine, 2015; 315:315ra188

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

Chen/Emens, unpublished data

KATE2: A randomized Phase II study of atezolizumab + trastuzumab emtansine (T-DM1) vs placebo + T-DM1 in previously treated HER2+ advanced breast cancer



Primary endpoint

- Investigator-assessed PFS per RECIST v1.1 (ITT)

Secondary endpoints

- OS, ORR, DOR (ITT)

Exploratory endpoints

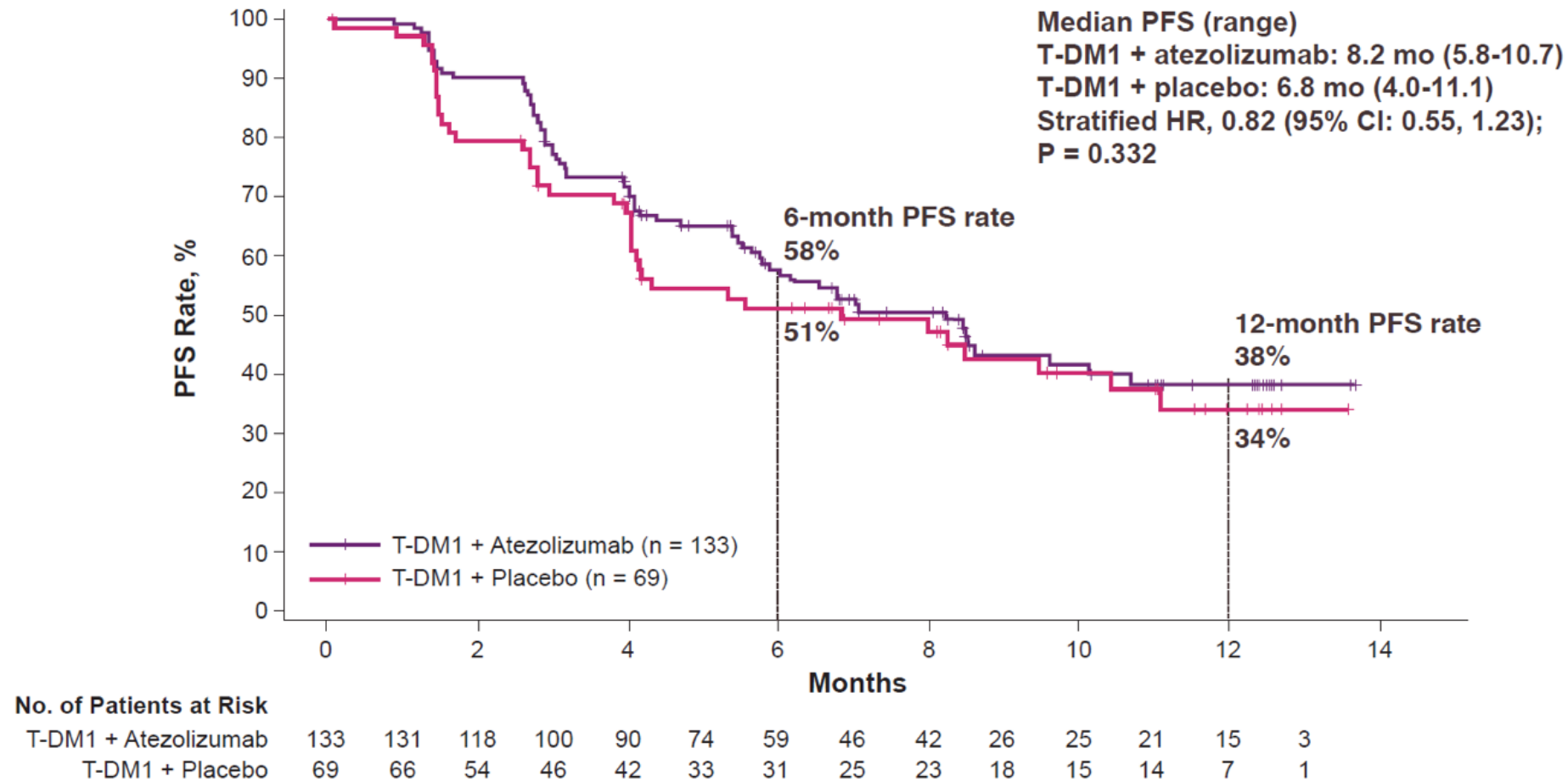
- PFS in the PD-L1+ (PD-L1 IC $\geq 1\%$) subgroup
- Efficacy in subgroups defined by immune-related (tumor-infiltrating lymphocytes and CD8 IHC expression) and HER2-related biomarkers

Safety endpoints

- AEs, SAEs, AEs leading to death, study discontinuation, or dose reduction and interruption

Emens LA et al SABCS 2018

Primary Endpoint PFS in ITT Patients



Data cutoff: 11 December 2017. Patients with PFS events: T-DM1 + atezolizumab, 68 (51%); T-DM1 + placebo, 39 (57%).

Emens LA et al SABCS 2018

- The study did not demonstrate a meaningful PFS benefit from the addition of atezolizumab to T-DM1 in the ITT population

Secondary Endpoint: ORR in ITT Patients

	T-DM1 + Atezolizumab (n = 132)^a	T-DM1 + Placebo (n = 69)
ORR, %	45.5	43.5
CR, %	6.1	7.2
PR, %	39.4	36.2
SD, %	37.9	29.0
PD, %	16.7	26.1

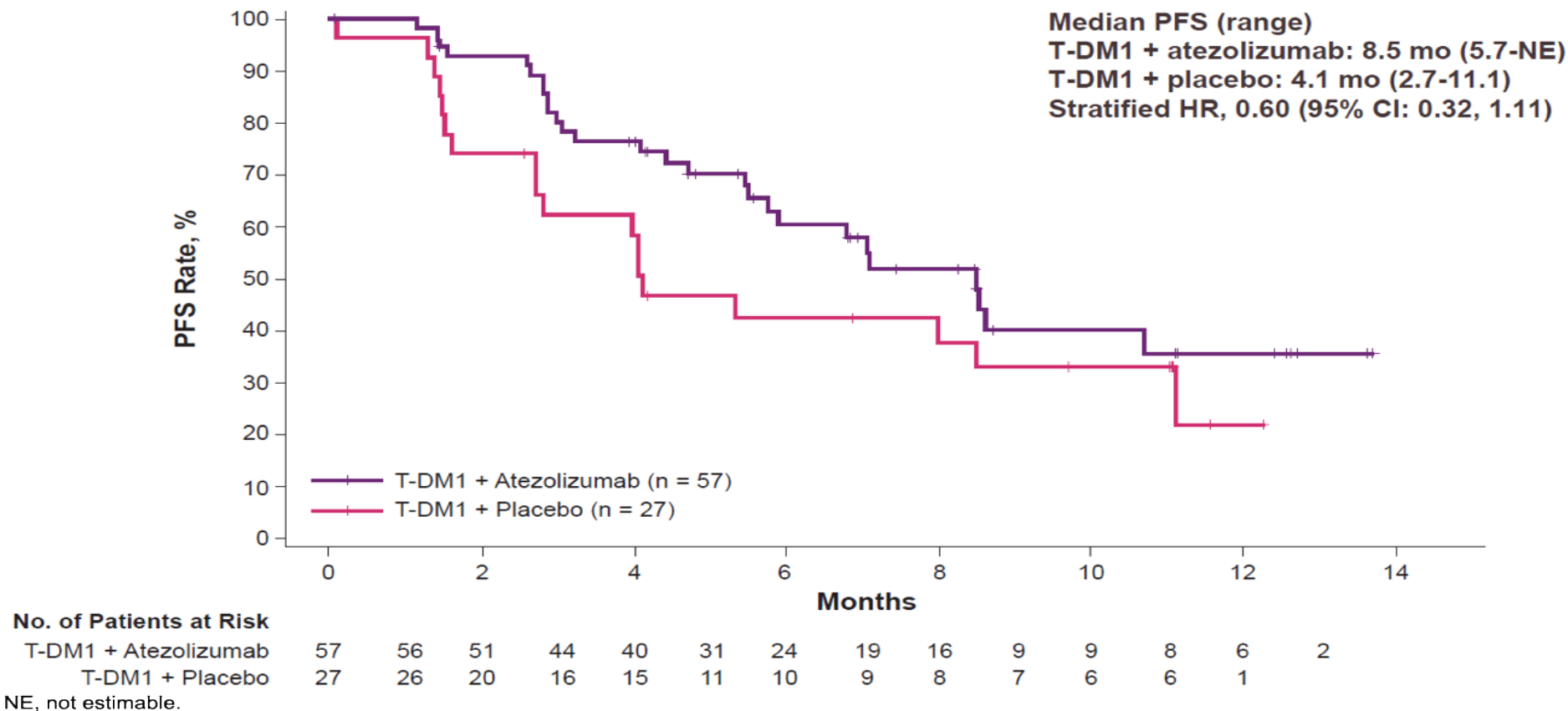
PD, progressive disease; PR, partial response; SD, stable disease.

Data cutoff: 11 December 2017.

^a Only 132 patients were evaluable for ORR (ie, had measurable disease at baseline).

- ORR and complete response (CR) rates in the ITT population were similar between arms
- OS data were not mature with 21 events (10%) in total. Median DOR was not reached

Primary Endpoint PFS in PD-L1+ Patients



- PFS in the PD-L1+ subgroup numerically favored atezolizumab + T-DM1 vs atezolizumab + placebo (HR, 0.60 [95% CI: 0.32, 1.11])
- The magnitude of the benefit is uncertain given the limited number of patients and the corresponding wide confidence interval of the hazard ratio

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!