# 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

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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

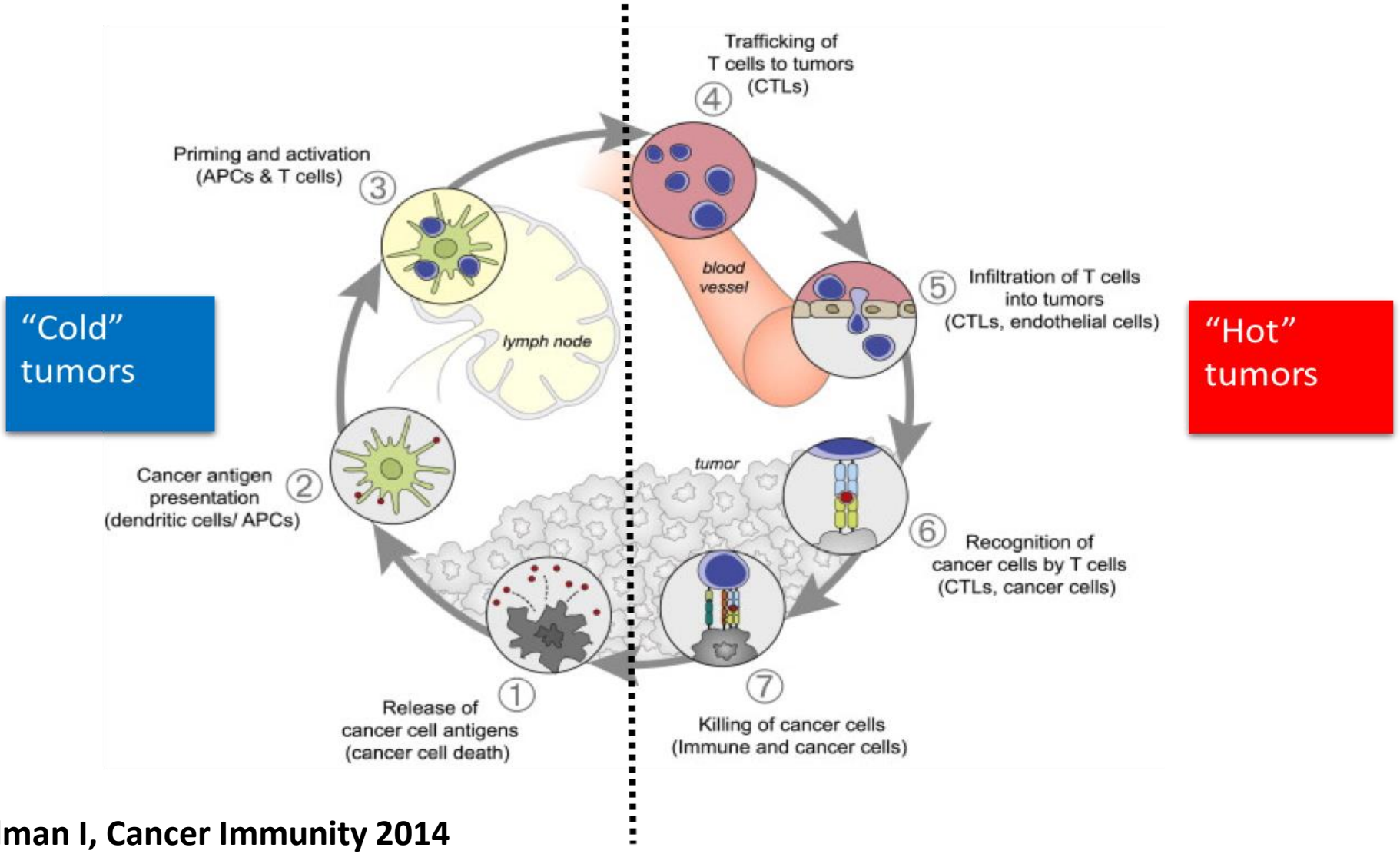
# Key Features of Immune Checkpoint Blockade

- 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?

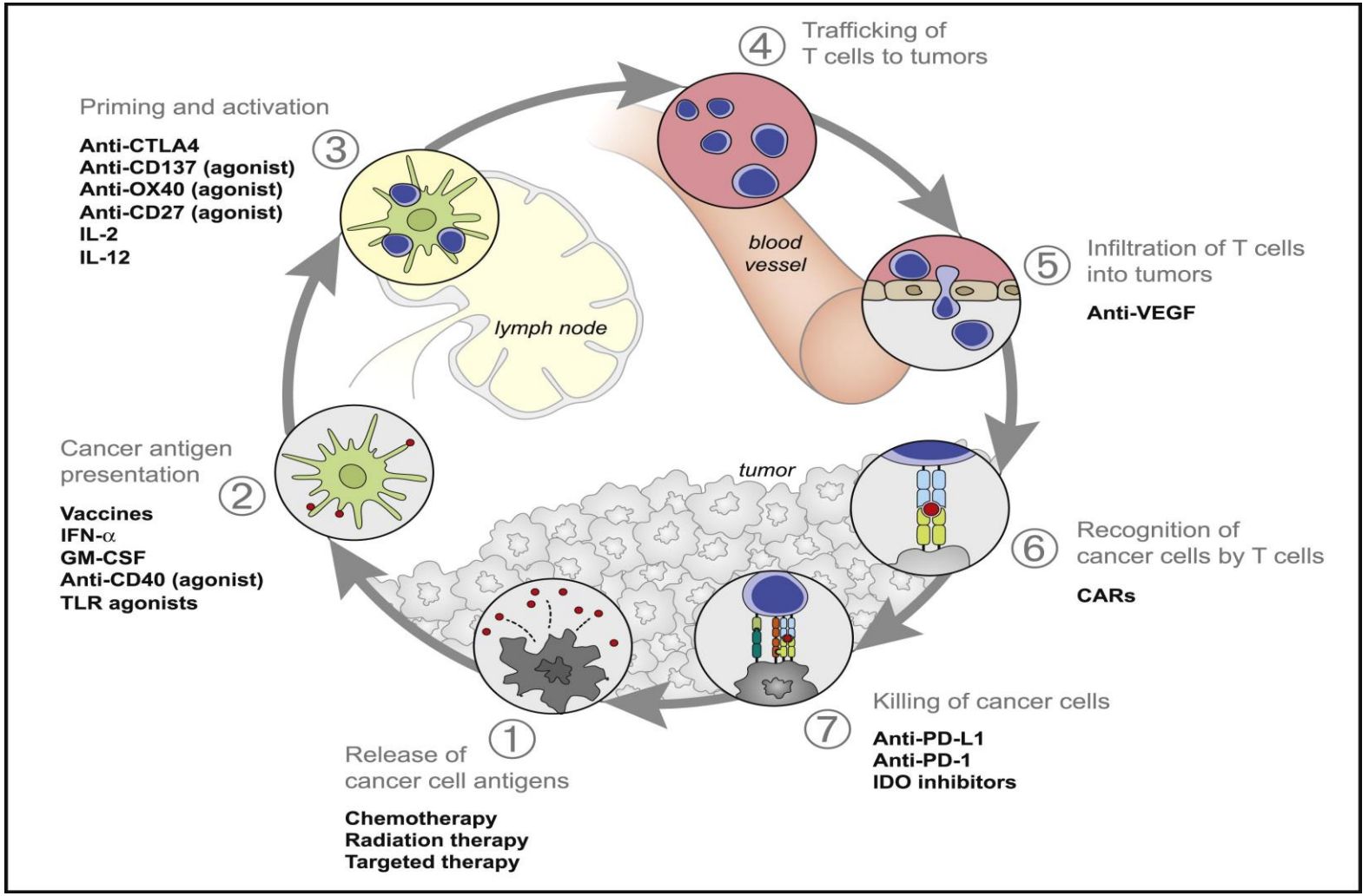
- Convert non-responders to responders
  - ✓overcome primary resistance
- Rescue patients who progress on immunotherapy
  - ✓overcome secondary resistance
- Deepen responses that do occur
  - ✓increase survival benefit
- Harness tumor biology to support immunotherapy
  - ✓monoclonal antibodies
  - ✓small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

# The Cancer Immunity Cycle



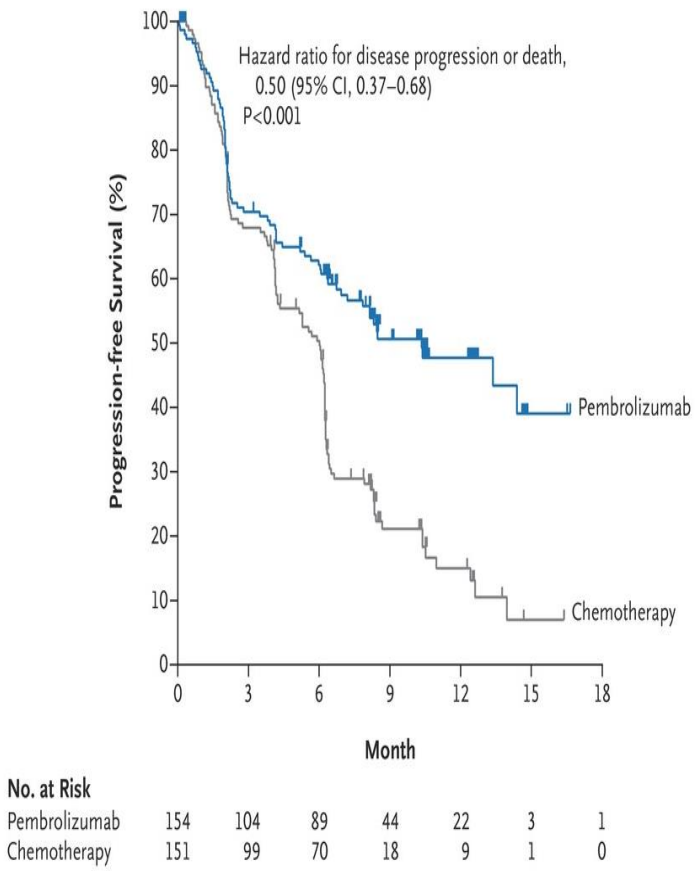

**Chen DS, Mellman I, Cancer Immunity 2014**

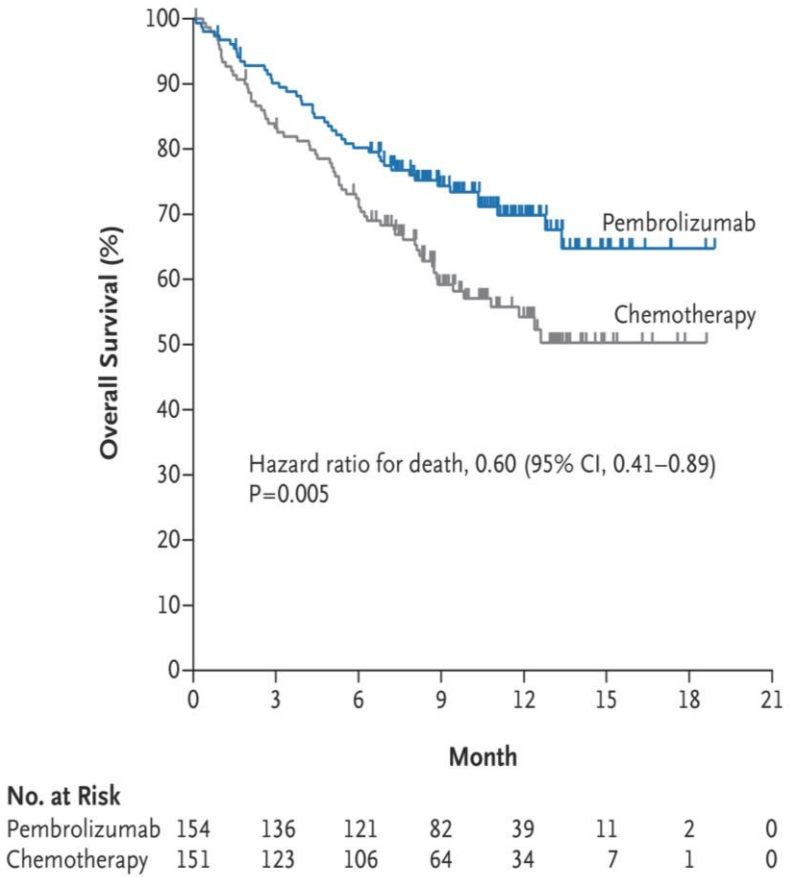
# Harnessing the Cancer Immunity Cycle for Therapeutic Benefit




**Chen DS, Mellman I, Cancer Immunity 2014**

# Single Agent Pembrolizumab for Untreated Metastatic NSCLC



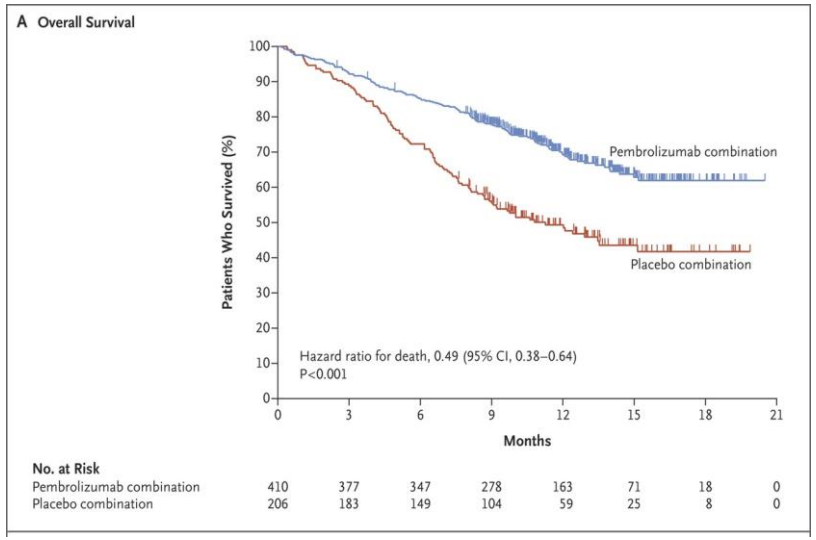

305 patients with untreated PD-L1+ TC >50% metastatic NSCLC w/o ALK or EGFR mutation were randomized 1:1 to pembrolizumab alone or platinum-based chemotherapy

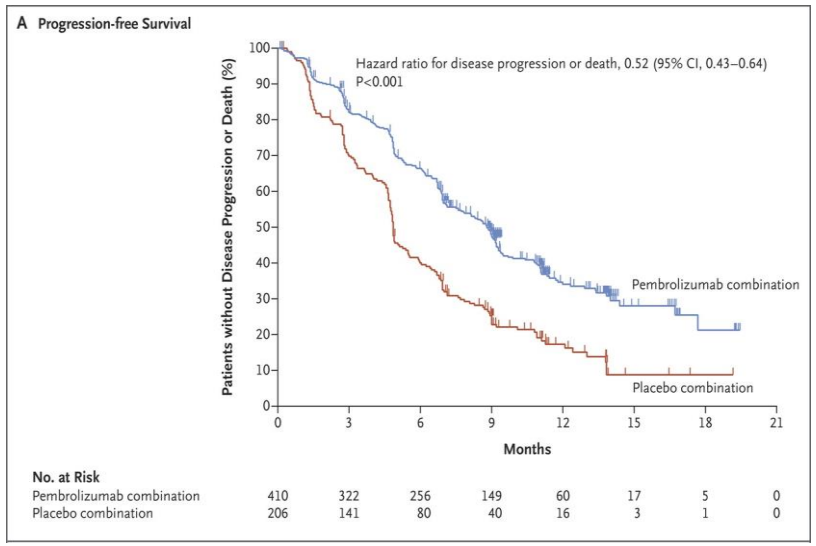
| | Pembro | Platinum |
|---|---|---|
| ORR | 44.8% | 27.8% |
| mPFS | 10.3 mo | 6 mo |
| OS 6 mo | 80.2% | 72.4% |
| DOR | NR | 6.3 mo |

Pembrolizumab better tolerated than chemotherapy

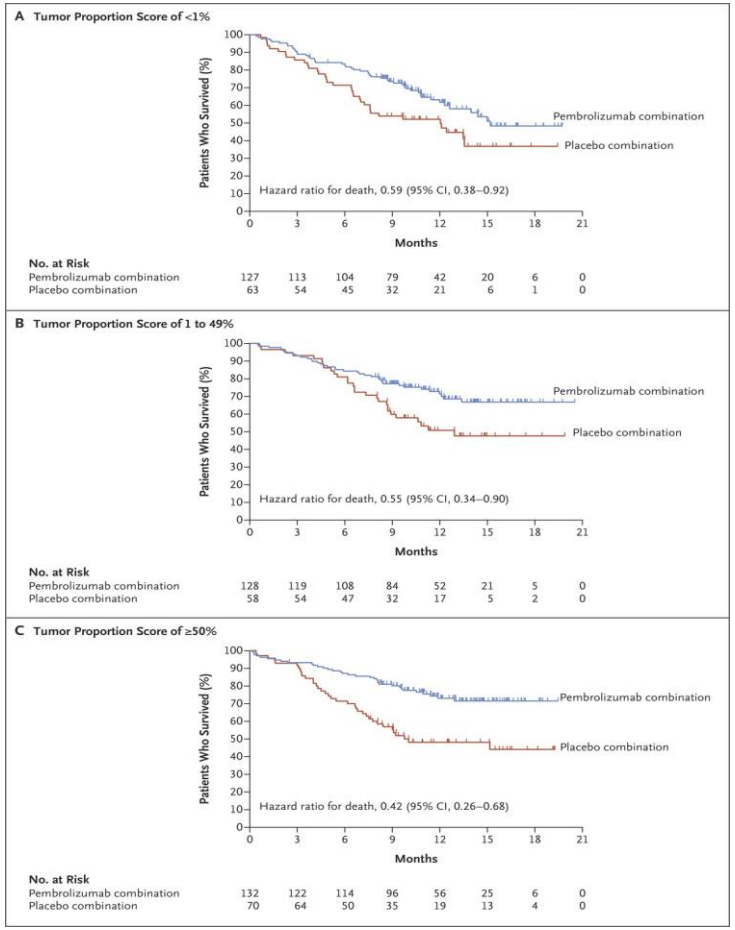
Reck M et al. N Engl J Med 2016;375:1823-1833

# 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%)

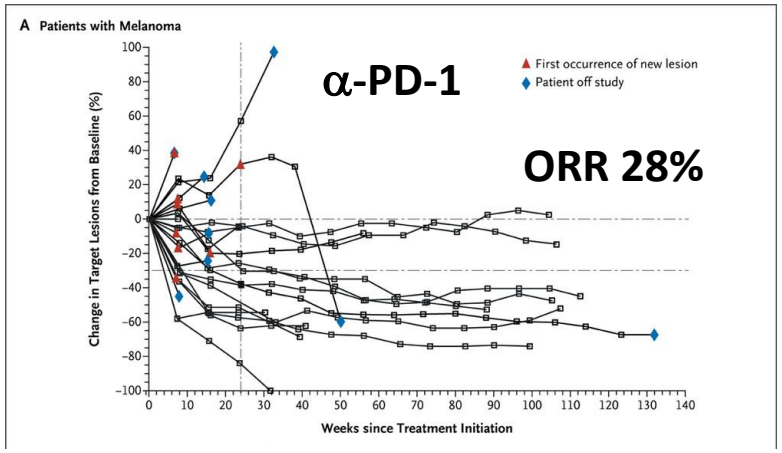


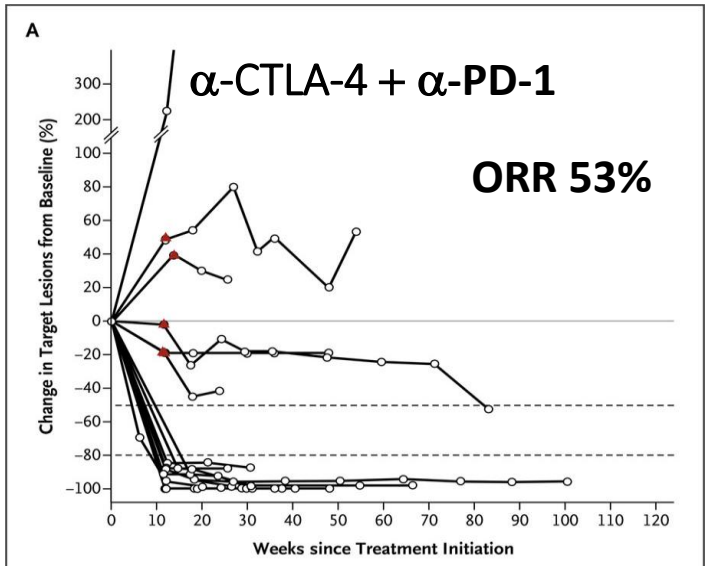

| | Chemo+ Pembro | Placebo + Chemo |
|---|---|---|
| ORR | 47.6 % | 18.9 % |
| mPFS | 8.8 mo | 4 mo |
| OS 12 mo | 69.2% | 49.4% |
| DCR | 84.6% | 70.4% |
| DOR | 11.2 mo | 7.8 mo |

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**

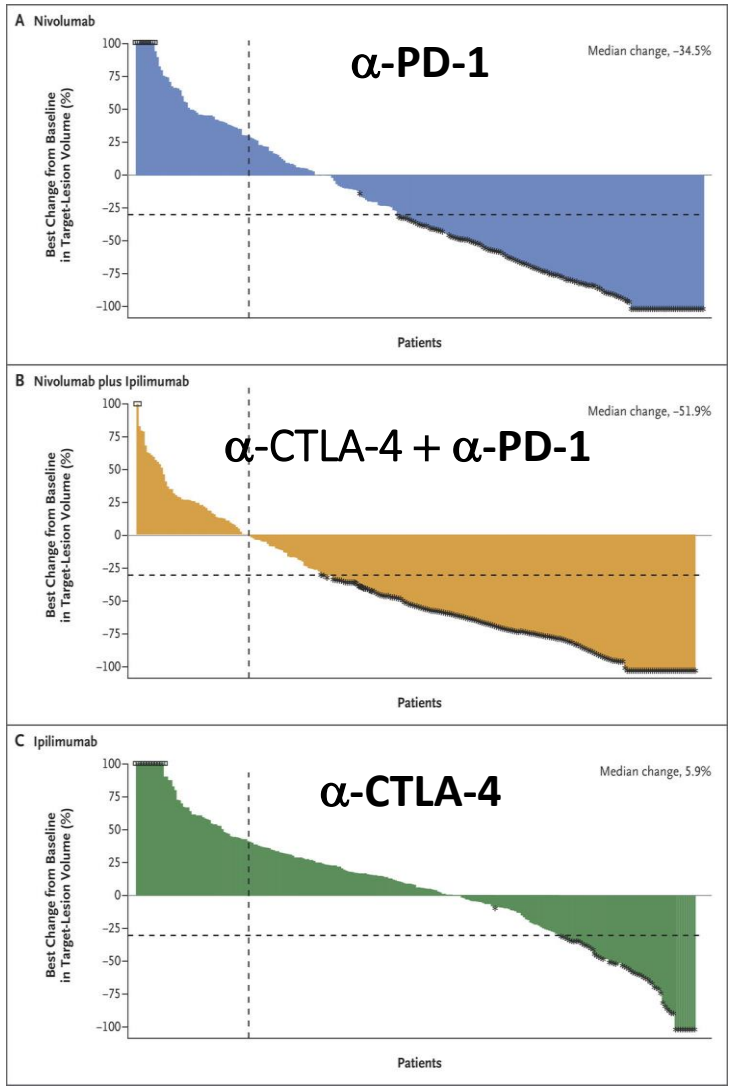
# Dual Immune Checkpoint Blockade:
## anti-CTLA-4 + anti-PD-1



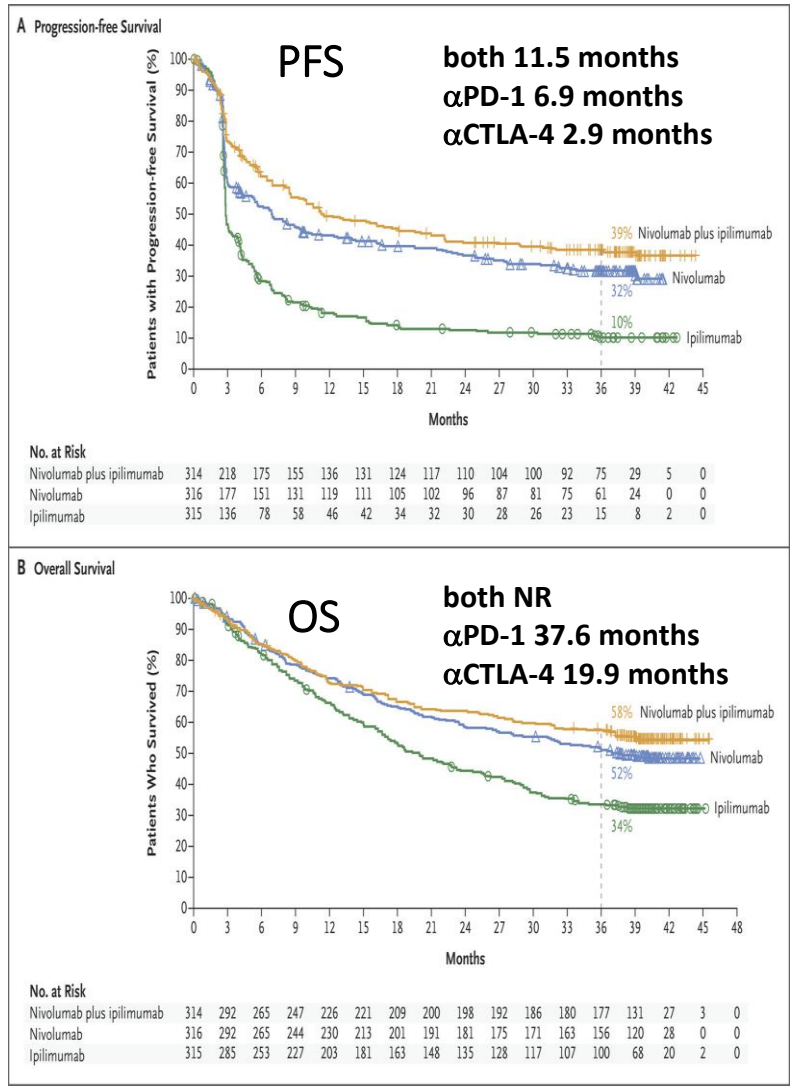




Topalian SL et al. N Engl J Med 2012;366:2443-2454.

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



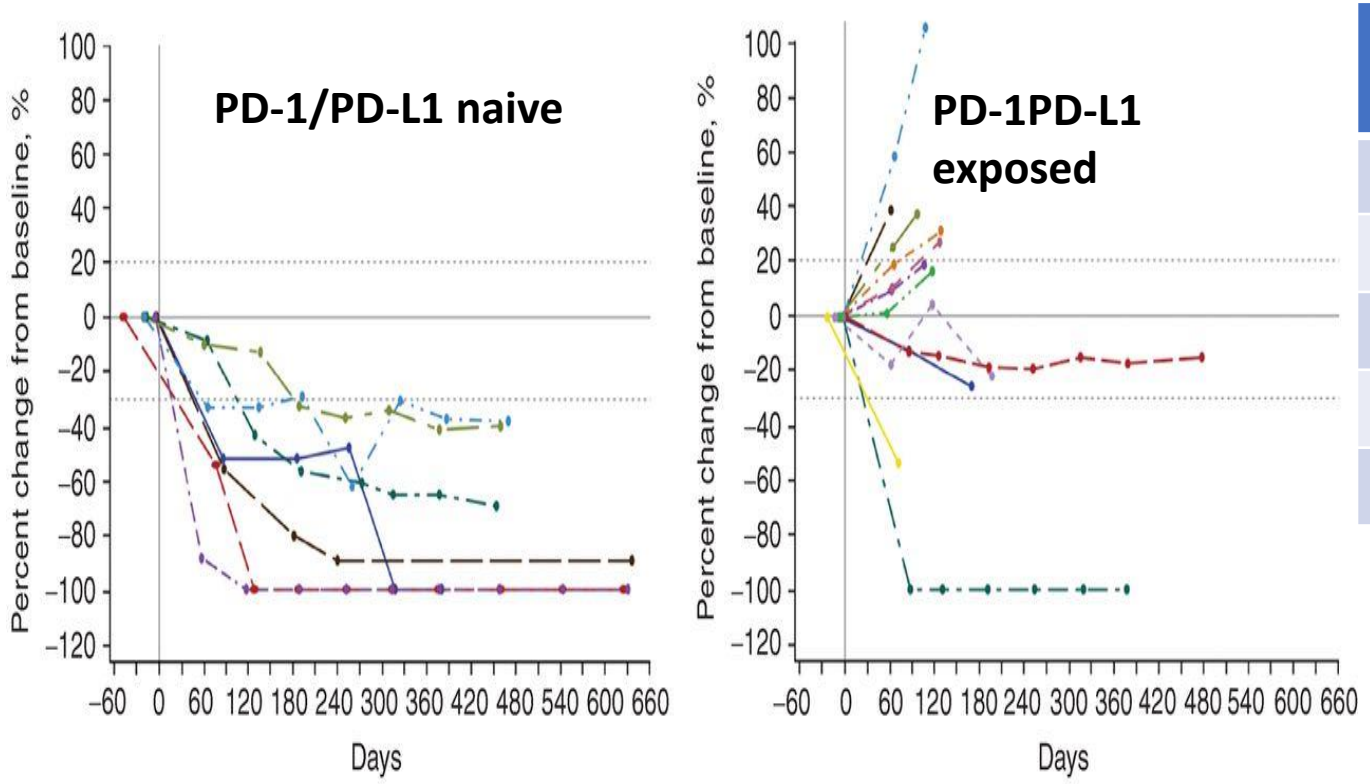

Larkin J et al. N Engl J Med 2015;373:23-34.



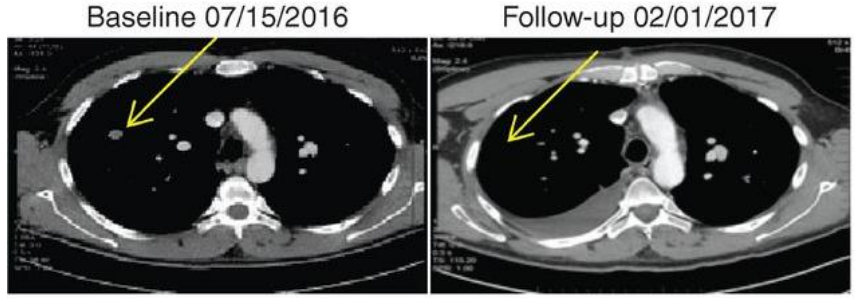

Wolchok JD et al. N Engl J Med 2017;377:1345-1356.

# PD-1 Blockade + TLR-9 Activation

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

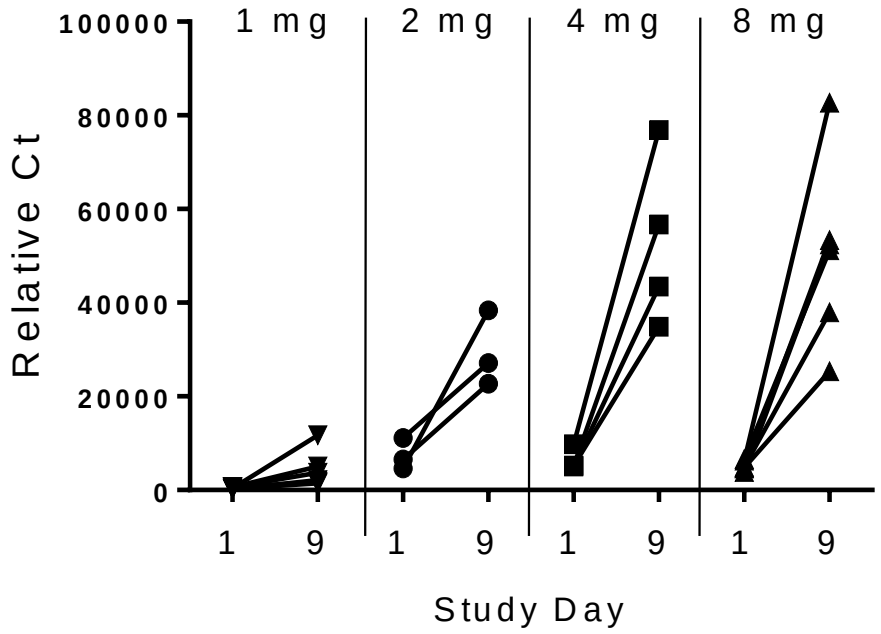



| | PD-1/PD-L1 Naive [n=9] | PD-1/PD-L1 Exposed [n=13] |
|---|---|---|
| ORR | 7 (78%) | 2 (15%) |
| CR/PR | 2/5 | 0/2 |
| SD | 0 | 5 |
| DCR | 7 (78%) | 7 (54%) |
| PD | 1 (11%) | 5 (38%) |

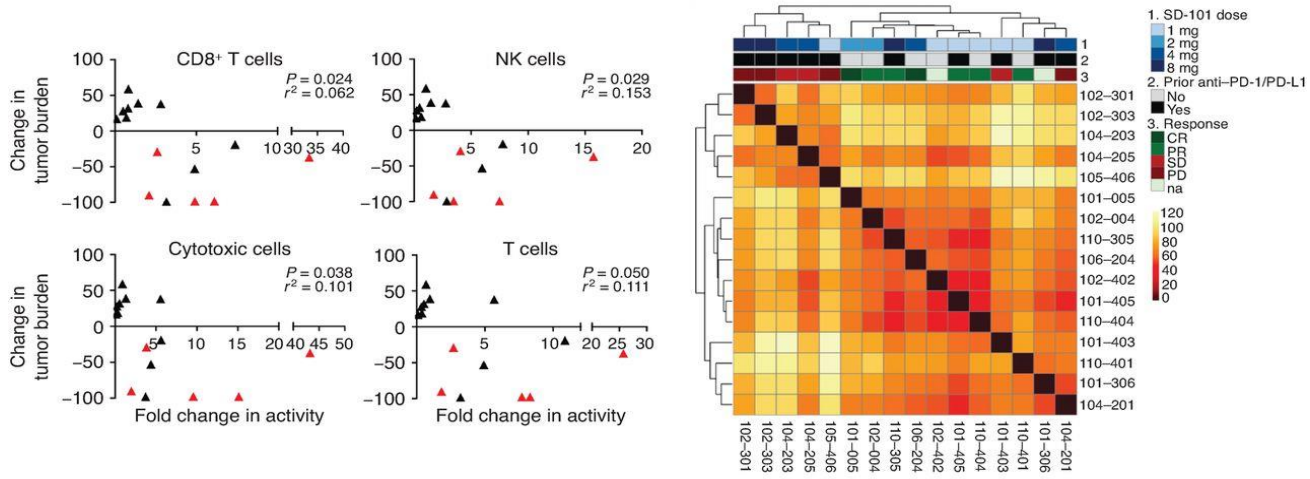


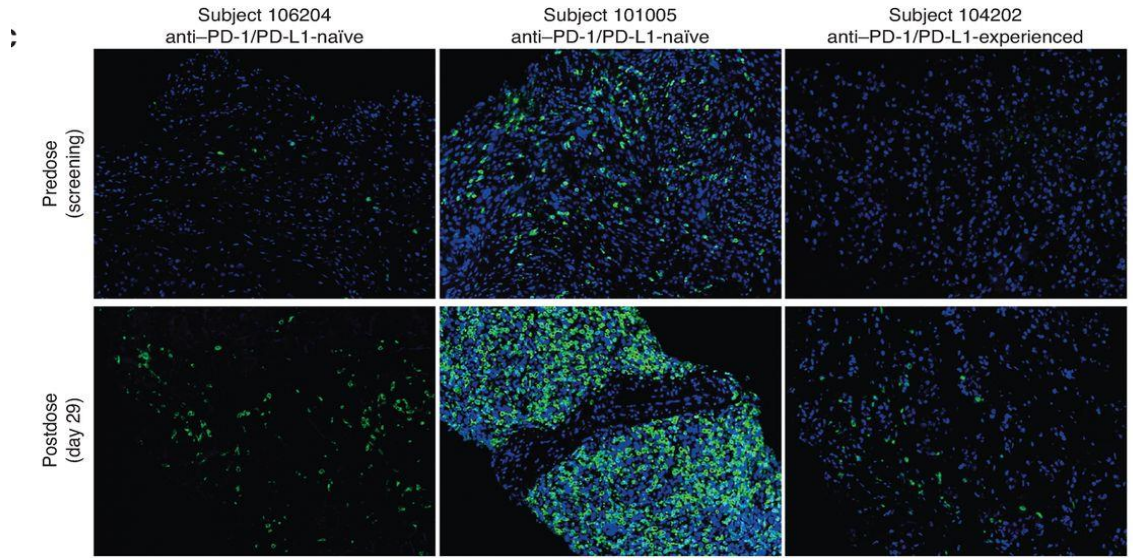

Antoni Ribas et al. Cancer Discov 2018;8:1250-1257

# Pharmacodynamic Changes on SD-101 Therapy



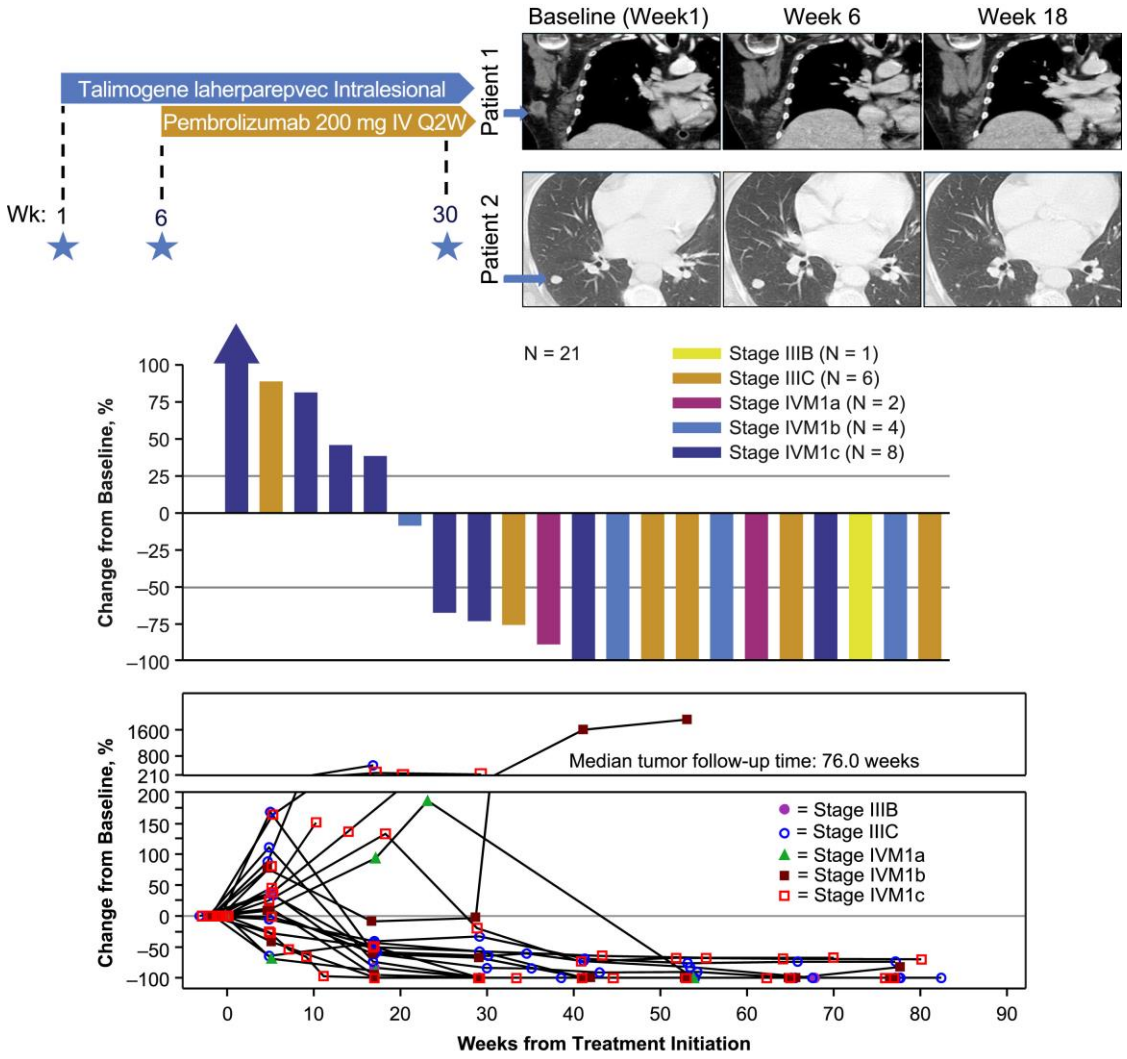

induction of IFN-α-responsive genes (GBP1, IFIT2, CCL2, MX2) in PBMC as a surrogate for intratumoral production, timepoint was 24 hours after second dose (day 9)

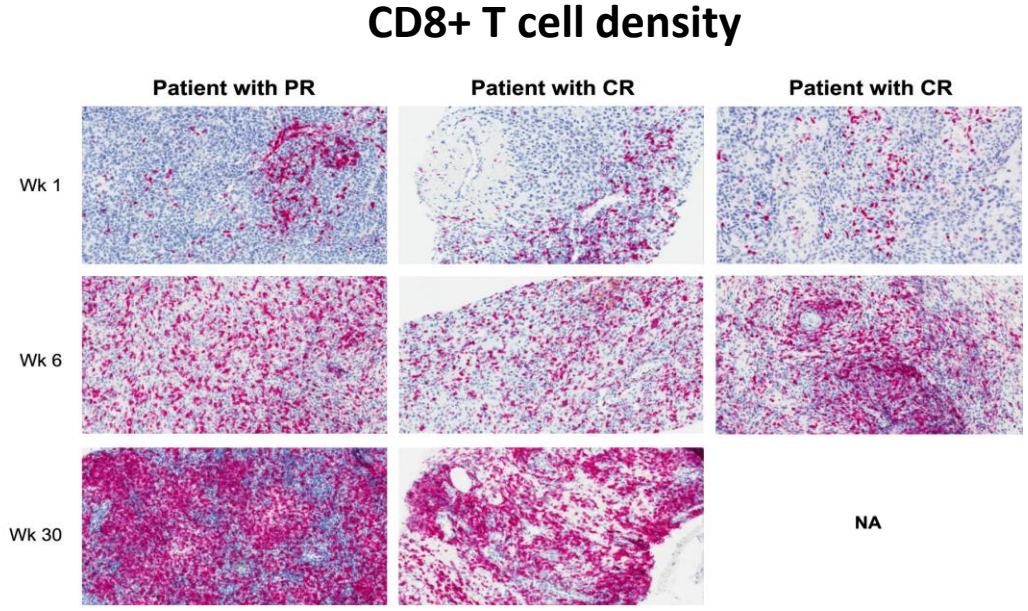



**Antoni Ribas et al. Cancer Discov 2018;8:1250-1257**

# Oncolytic Virotherapy + Pembrolizumab in Metastatic Melanoma



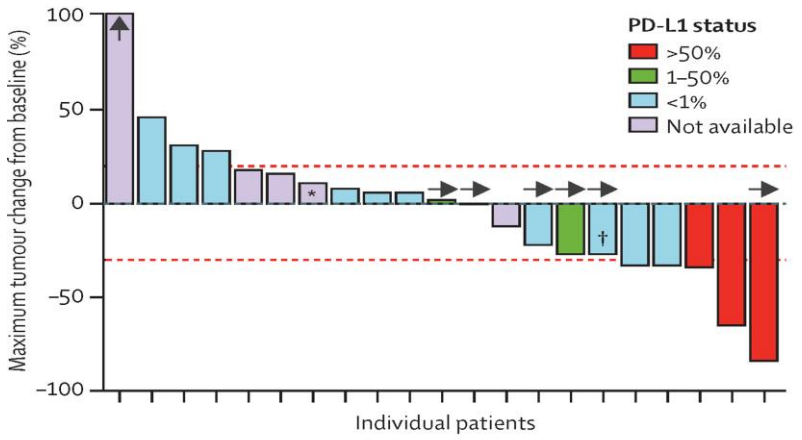

- High ORR of 62%
- High CR rate of 33%
- Therapy induced T cell infiltration, PD-L1 expression, and IFN-γ gene expression
- Clinical response independent of baseline T cell infiltration

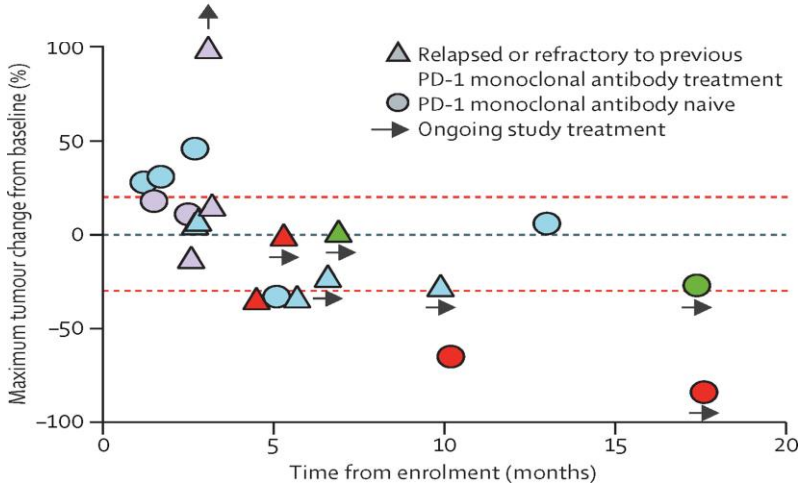
**Ribas A et al. Cell 2017;170:1109-1119**

# Interleukin 15

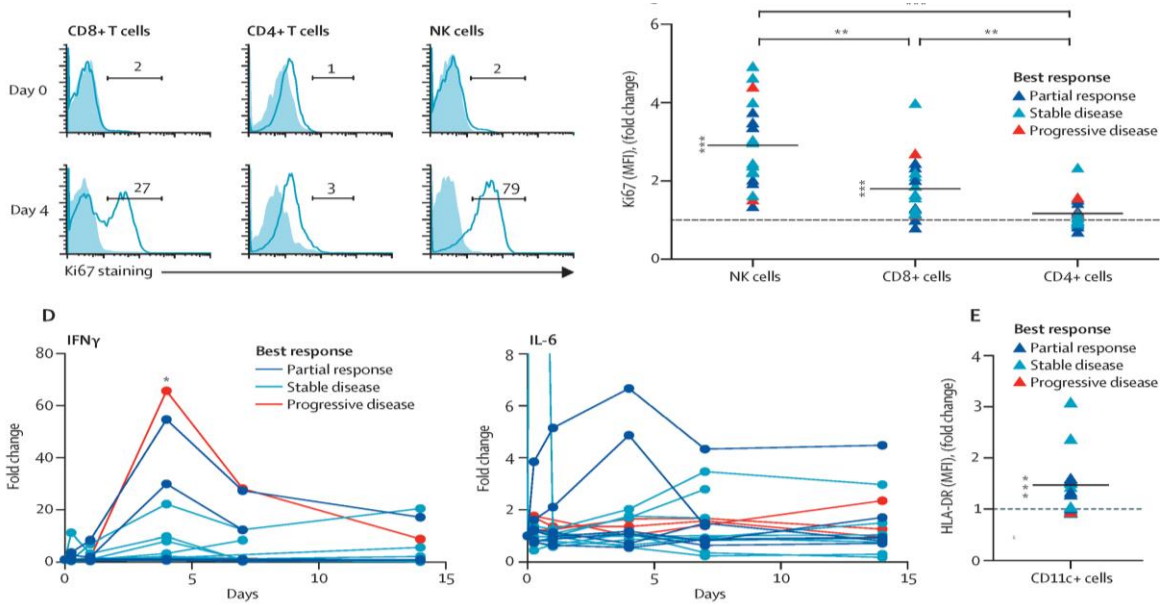
- IL-15 is a common γc receptor cytokine that shares the β chain with IL-2; the α chains are distinct
- Activates and expands NK cells (promotes survival) and CD8+ T cells (promotes memory development)
- DCs produce IL-15 and coordinately express the IL-15 α receptor, presenting IL-15 in *trans* via 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%) |

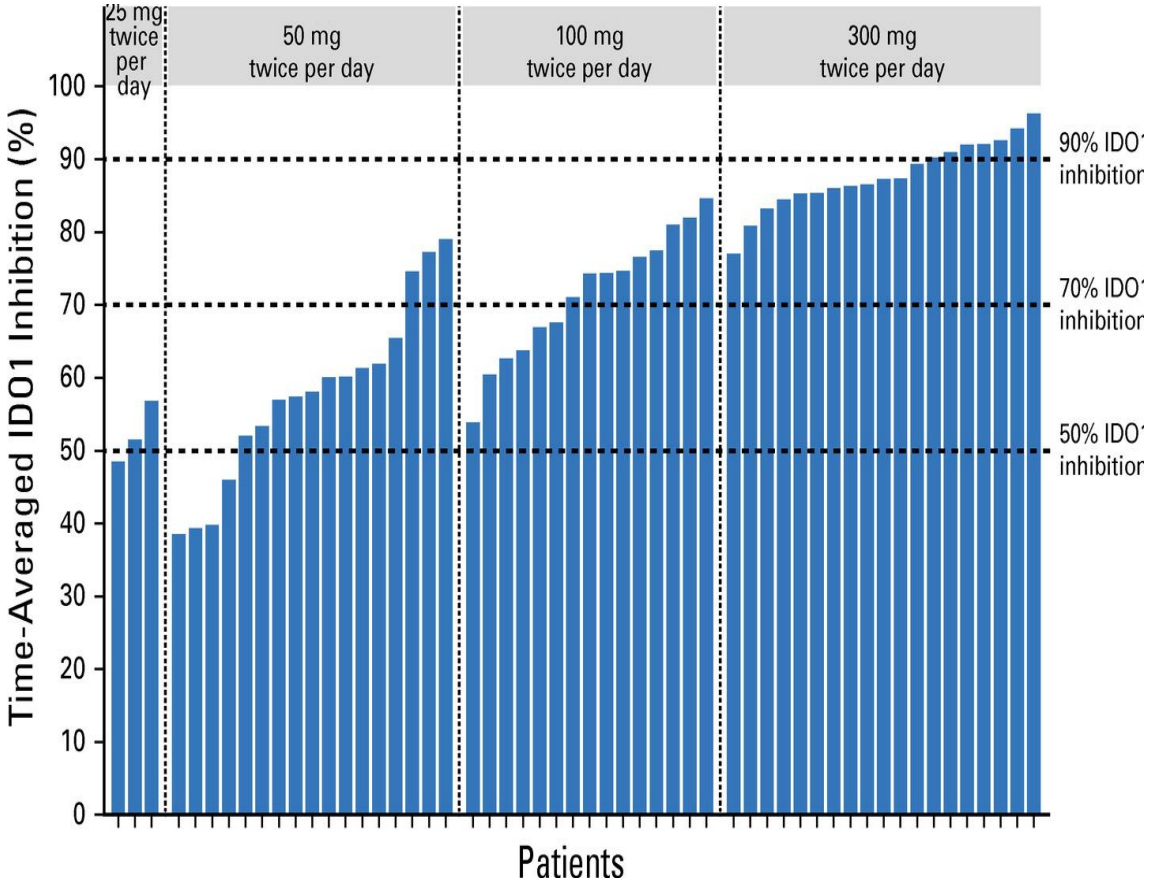
Wrangle JM et al. Lancet Oncology 2018;19:694-704

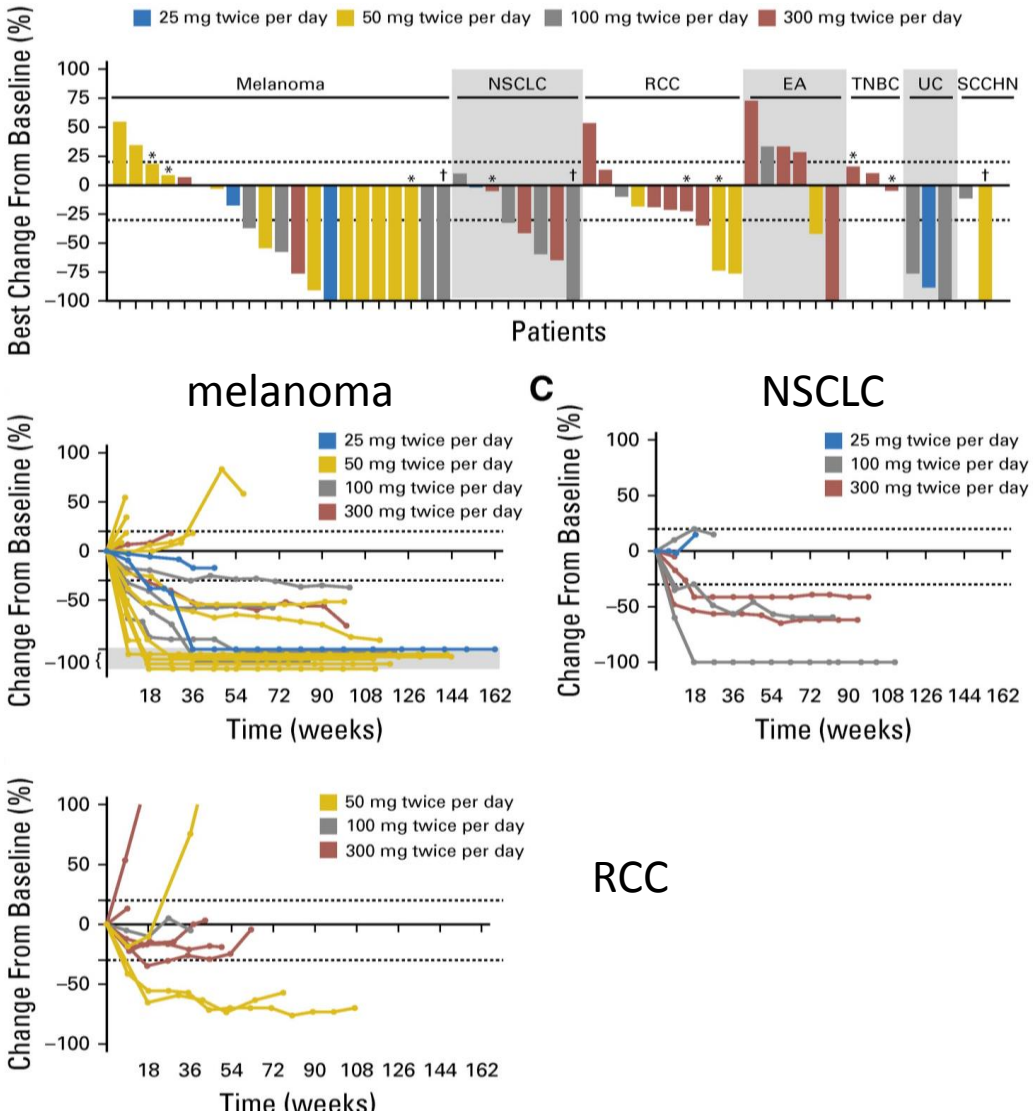
# Epacadostat + Pembrolizumab in Advanced Solid Tumors

- 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-$\gamma$ 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??

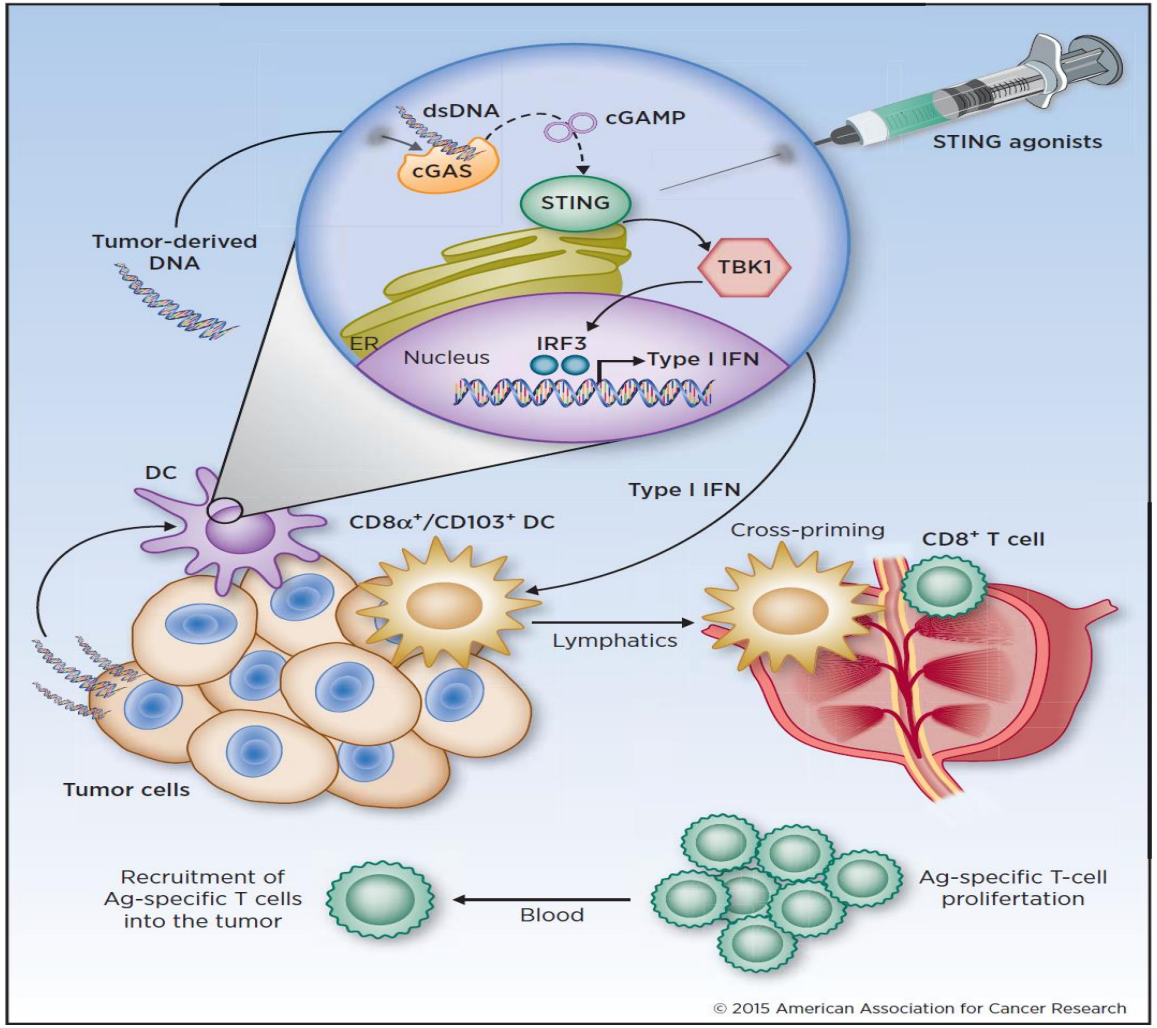
- TDO is expressed in addition to IDO in many tumors, including melanoma, and could make selective IDO inhibition insufficient to relieve the suppressive effect of kynurenine.
- IDO inhibition, at best, decreases kynurenine by 50% in serum
- Inhibiting downstream of IDO/TDO, where the pathways converge,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



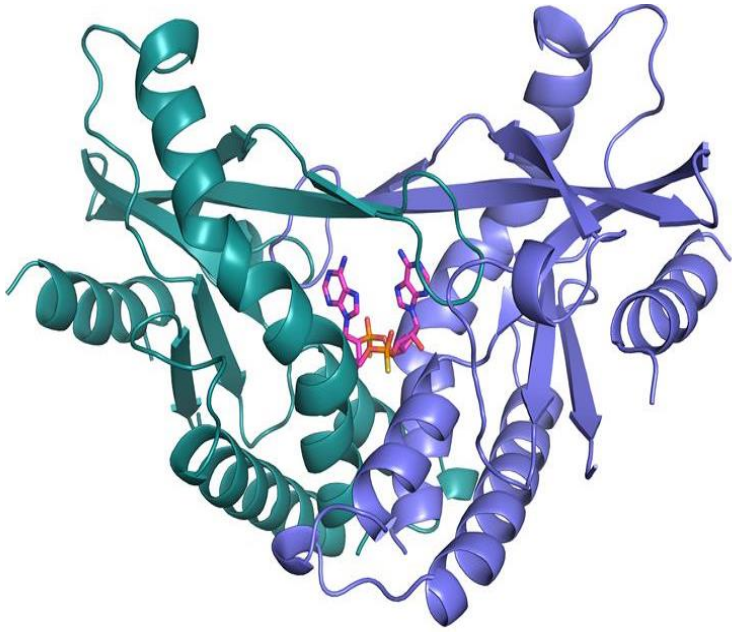

- T cell inflamed tumors in humans typically have an IFN-β transcriptional signature
- STING is the critical receptor to activate immune cells, including dendritic cells
- Tumor-derived DNA induces IFN-β by tumor resident DCs through STING signaling
- Intratumoral injection of CDNs induces IFN-β, activating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

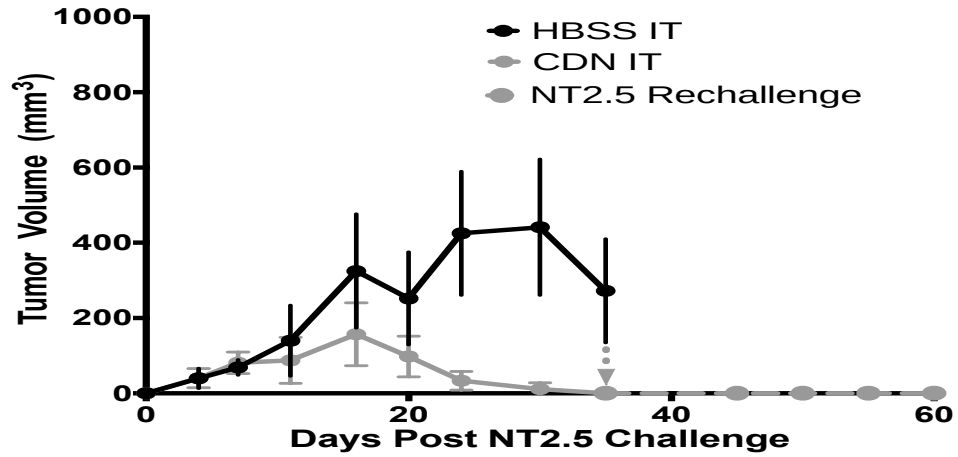
**ADU-S100 STING**
**Co-Crystal Structure**



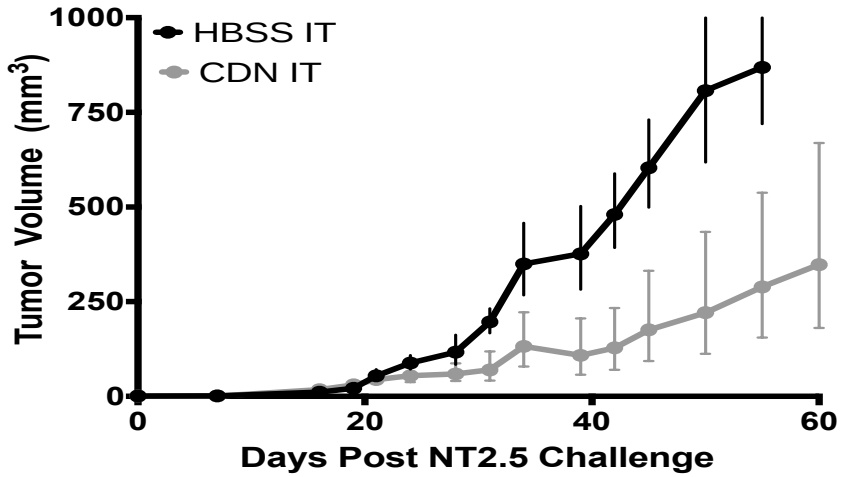
- ADU-S100 selected from series of CDN analogs based on balance of efficacy and tolerability/reduced toxicity
- Enhanced potency over natural CDN ligands
- Phosphorothioate increases resistance to phosphodiesterases to enhance potency
- ADU-S100 has activity in multiple mouse models, including melanoma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

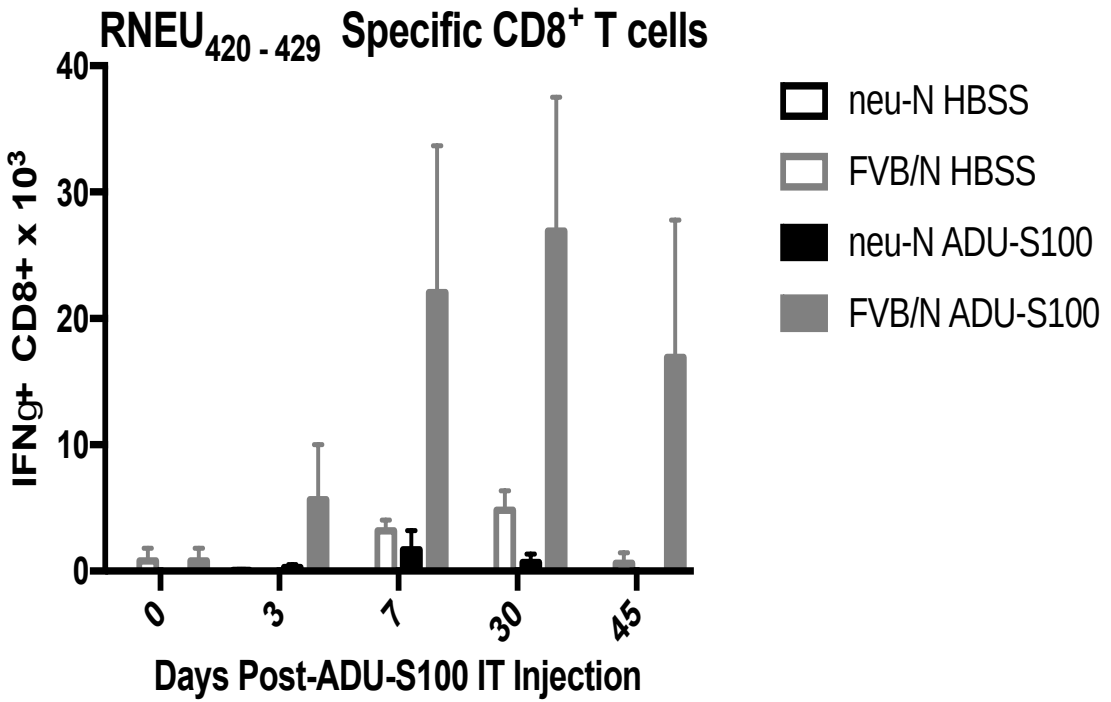
# Differential Response to the STING Agonist ADU-S100 in FVB/N and neu/N Mice

**FVB/N**



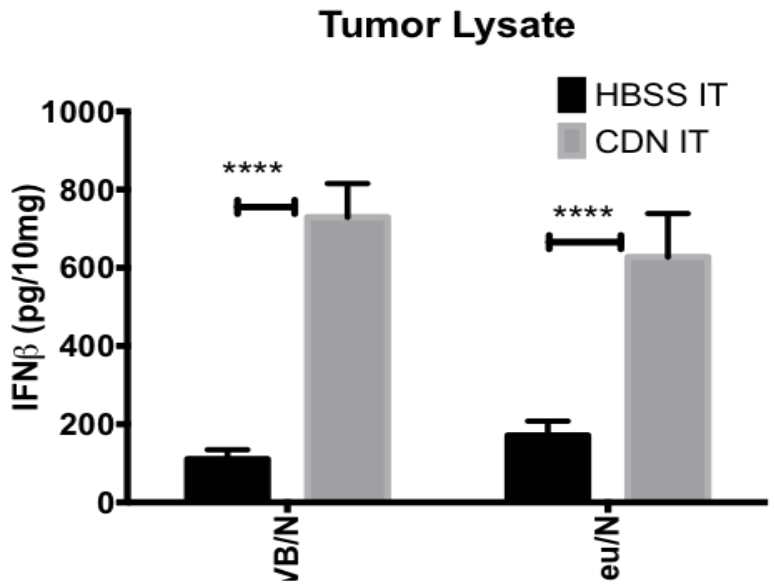

**neu/N**

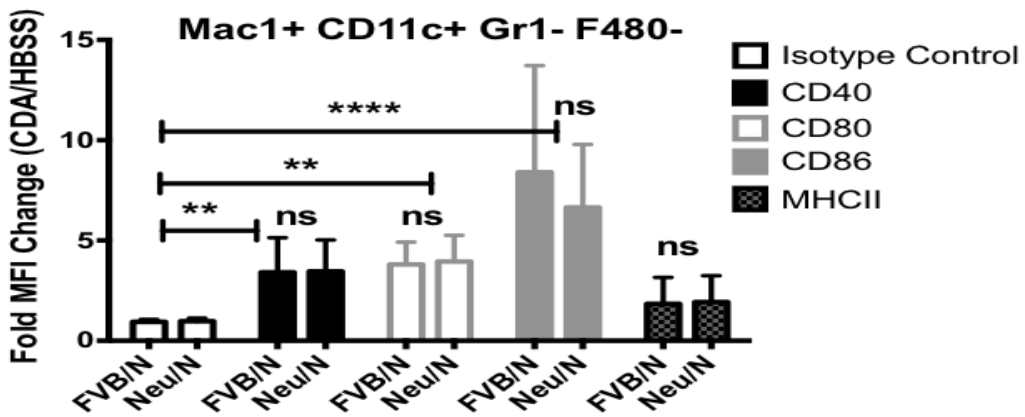


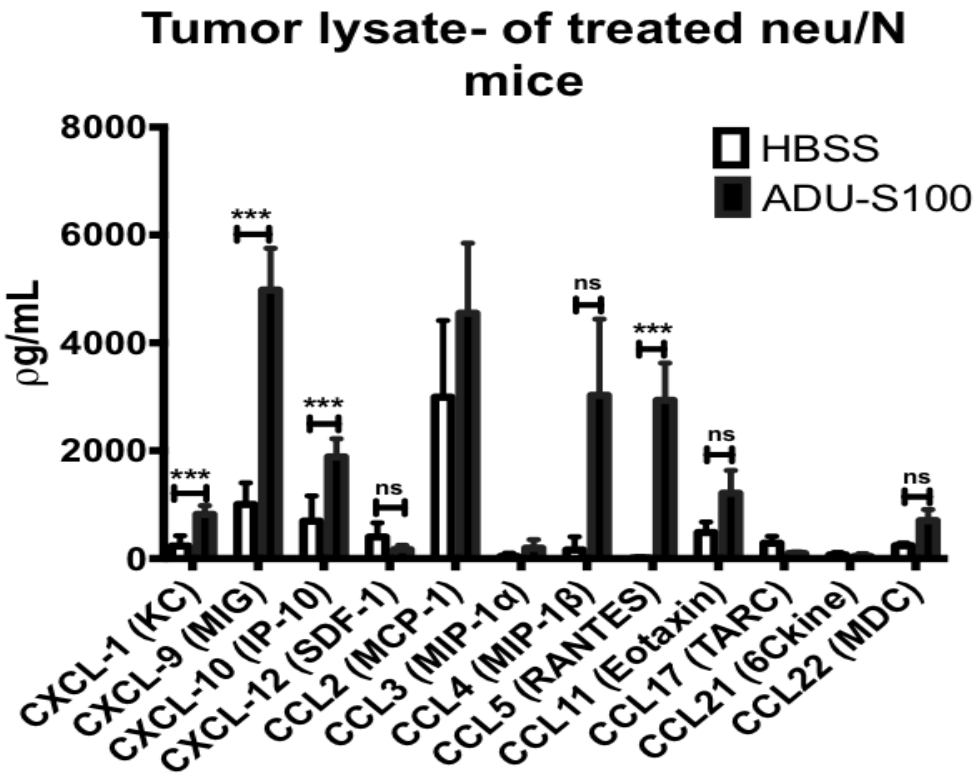




Foote JB/Emens LA at al, Cancer Immunol Res 2017

# Proximal Innate Immune Activation is Intact in Neu/N Mice



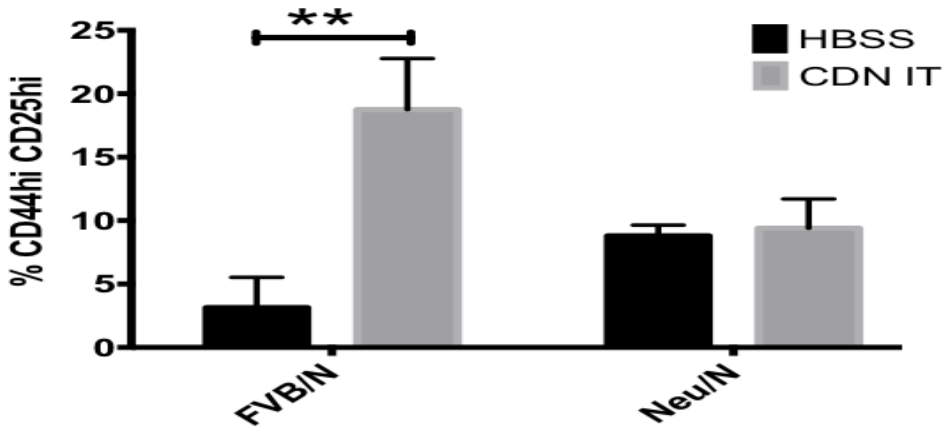




- **Proximal STING signaling events—type I IFN secretion, DC activation, chemokine production—are intact in neu/N mice.**

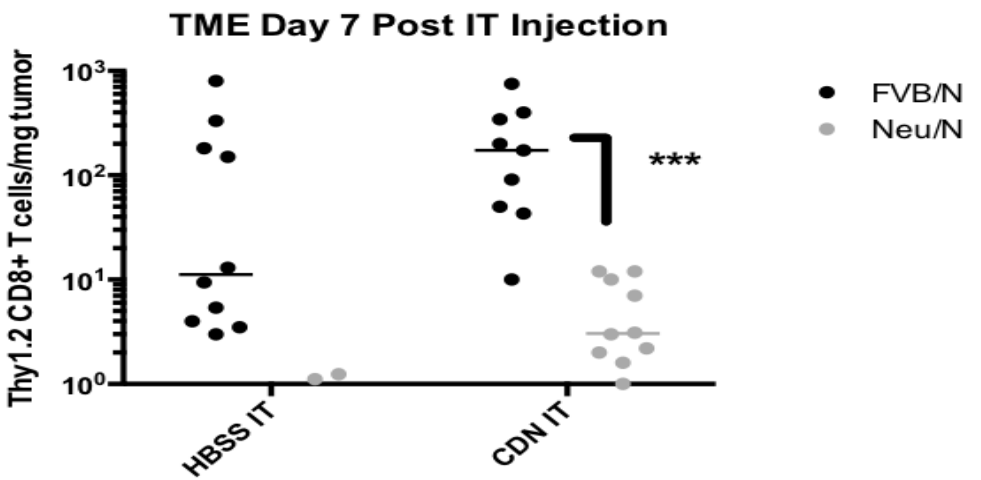
**Foote JP/Emens LA Cancer Immunol Res, 2017.**

# Distal T Cell Priming is Deficient in Neu-N Mice

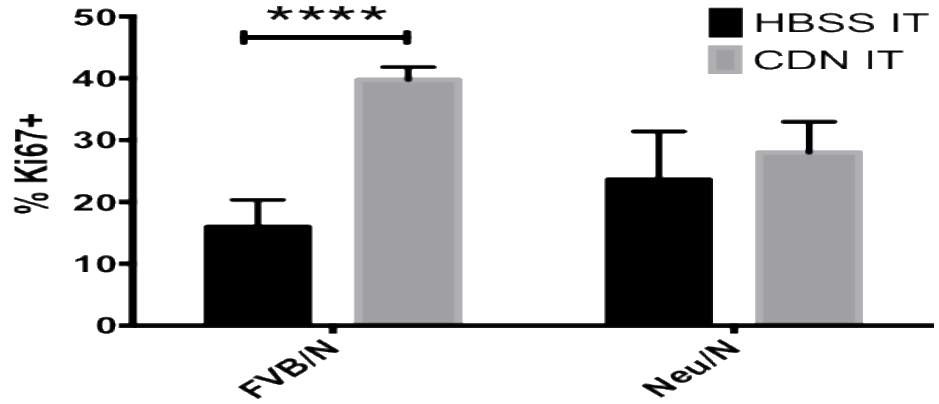
## Activation



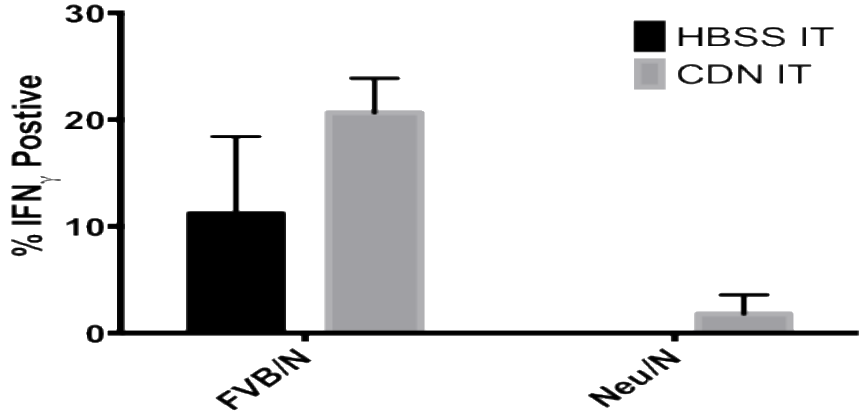

## Migration




## Proliferation

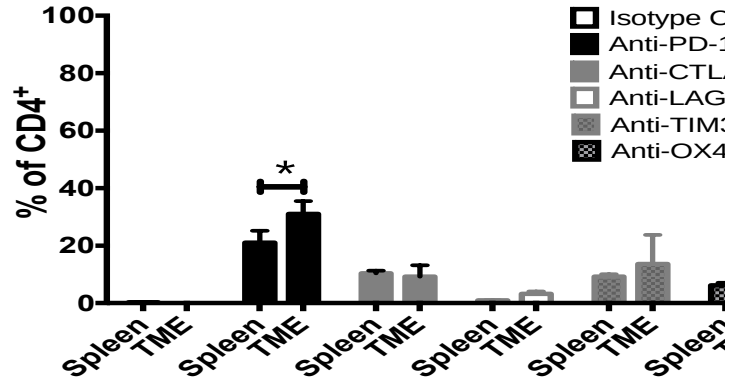


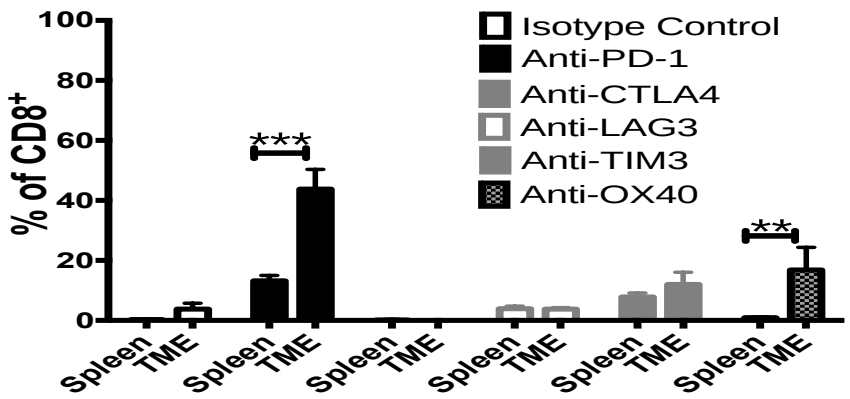

## Function



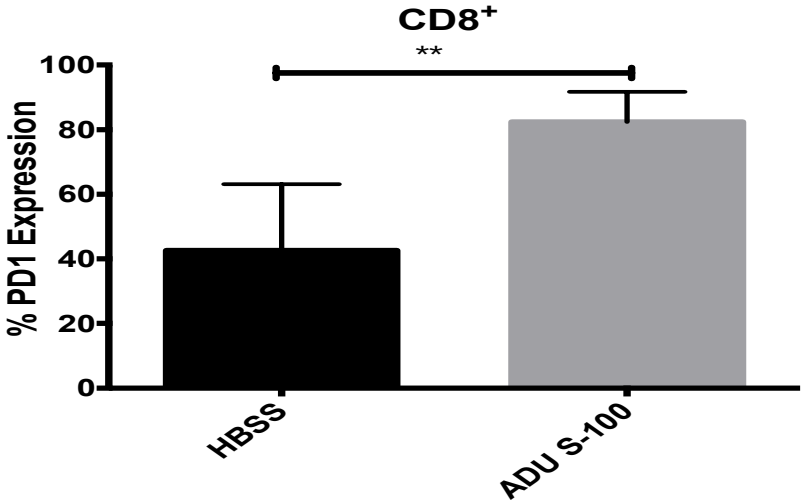

Foote JP/Emens LA Cancer Immunol Res, 2017.

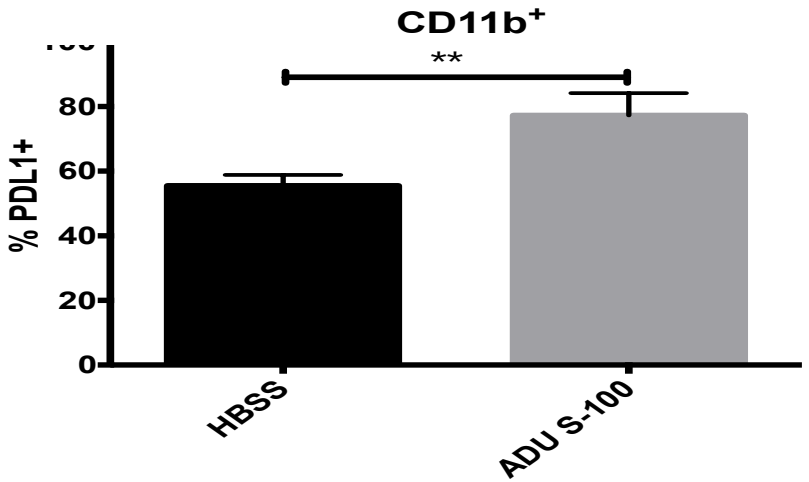
# Immune Checkpoint Pathways in the TME of Neu Mice




**Baseline**



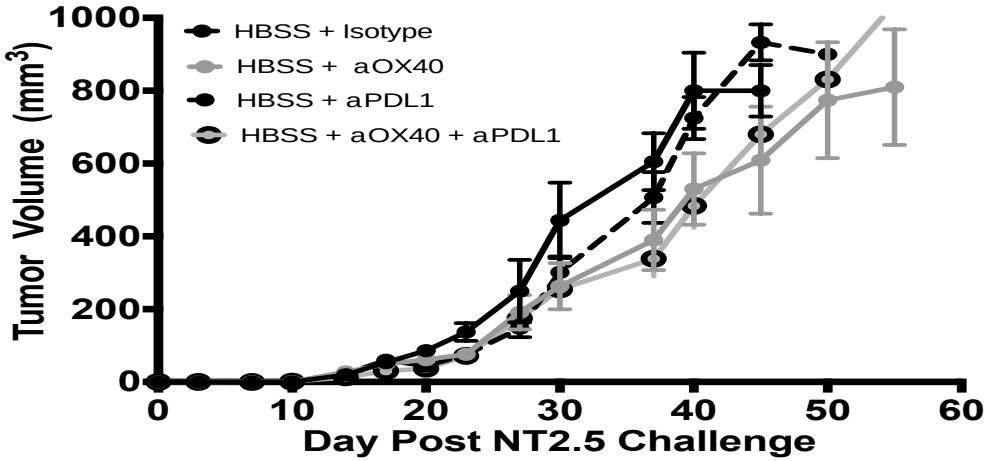



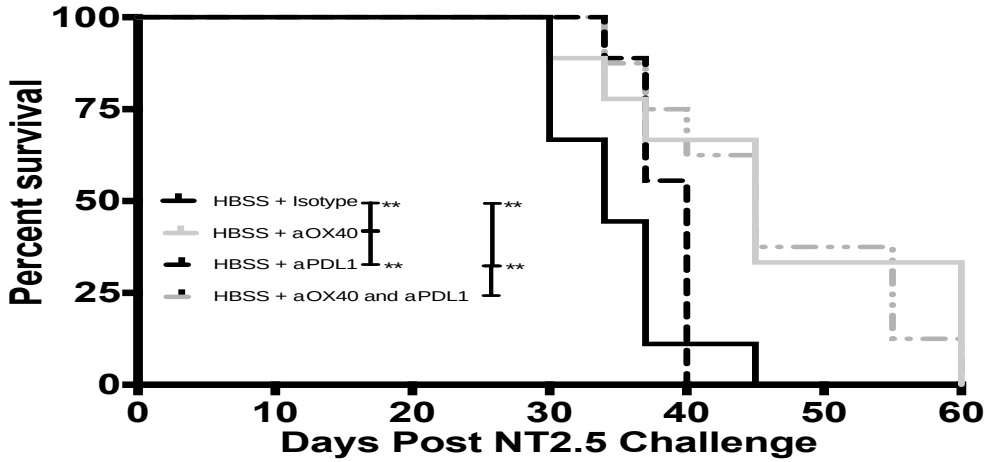

**Post-ADU-S100**

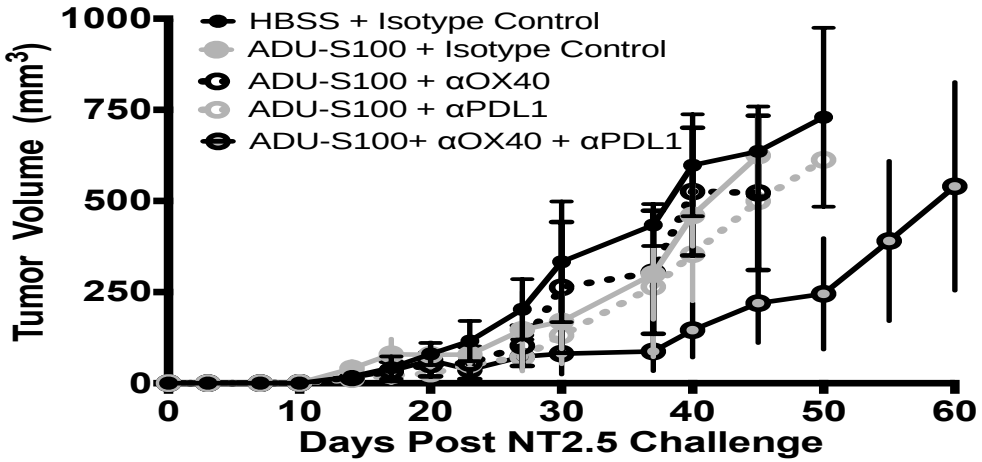
- **The PD-1 and OX-40 pathways are upregulated in neu/N mice.**

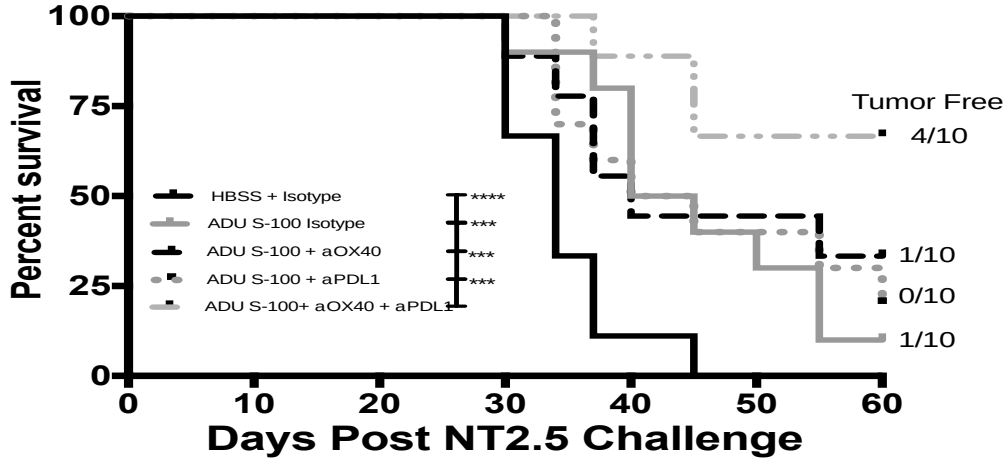
Foote JB/Emens LA at al, Cancer Immunol Res 2017

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



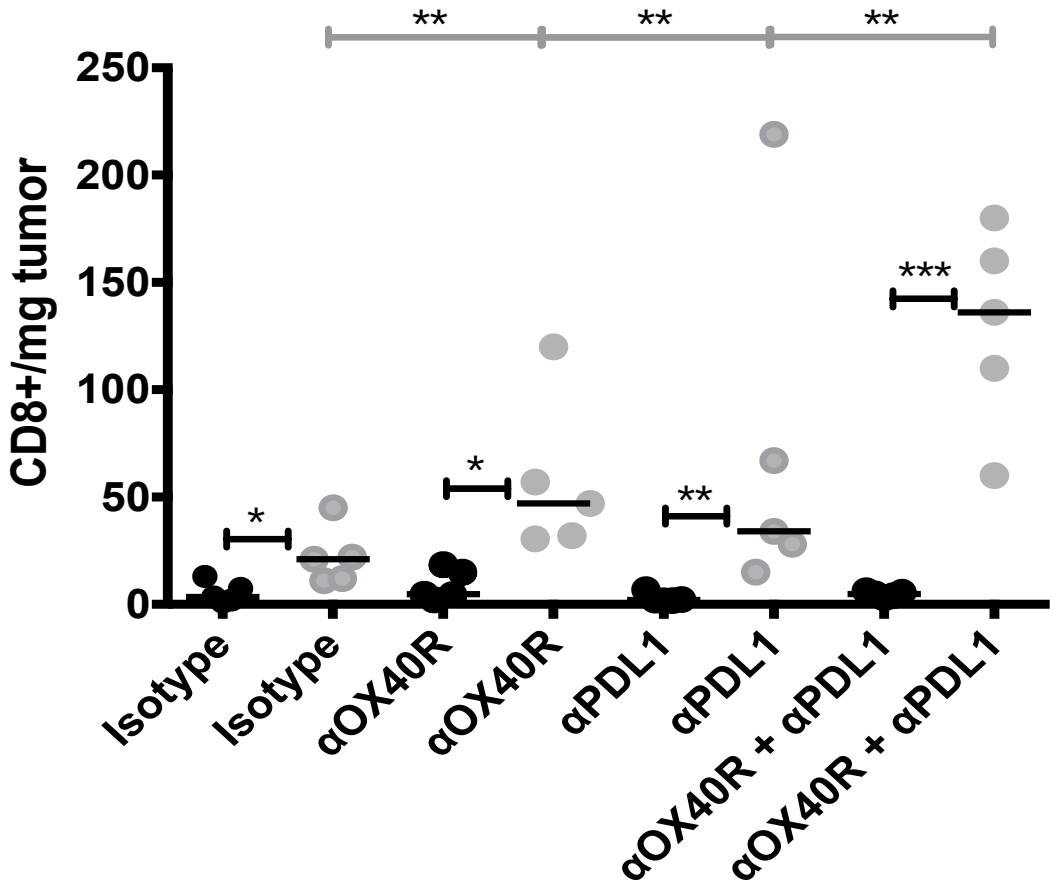



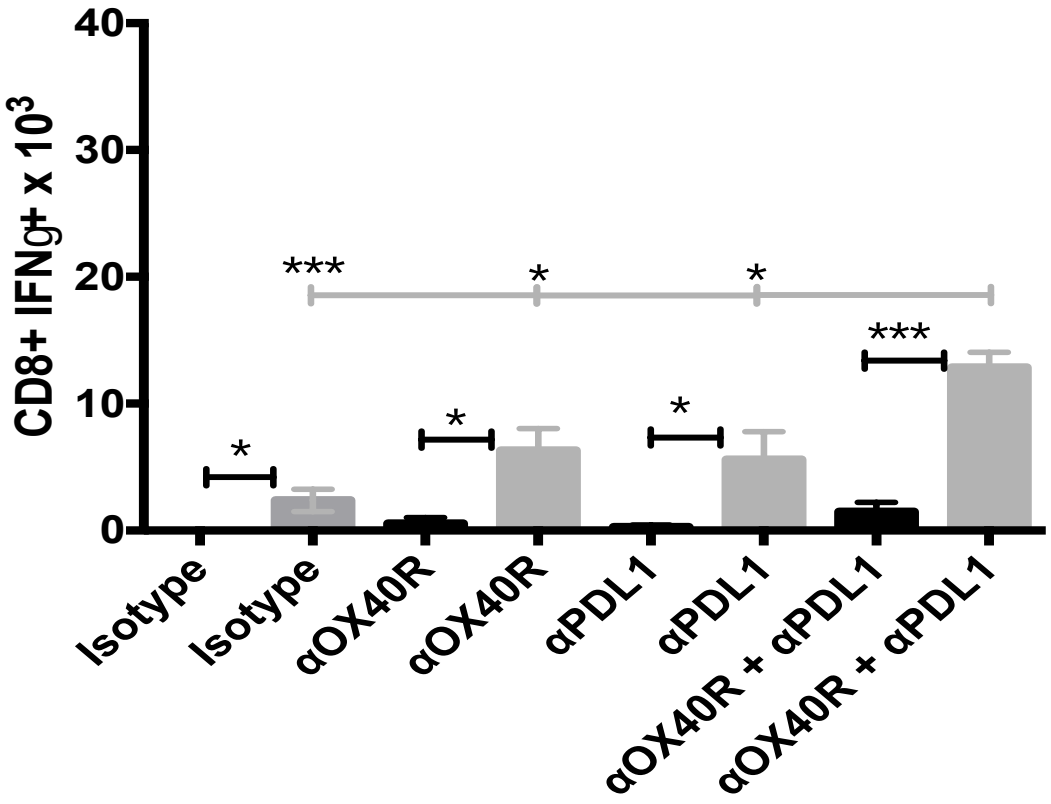




Foote JB/Emens LA at al, Cancer Immunol Res 2017

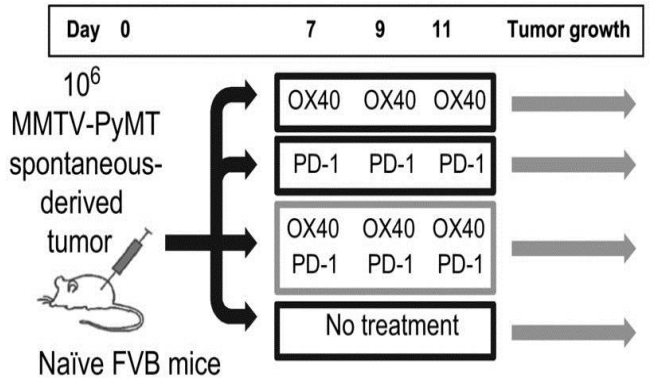
# ADU-S100 Combined with PD-L1 Blockade and OX-40 Activation Induces Greater Numbers of Functional HER-2-specific T Cells in neu/N Mice

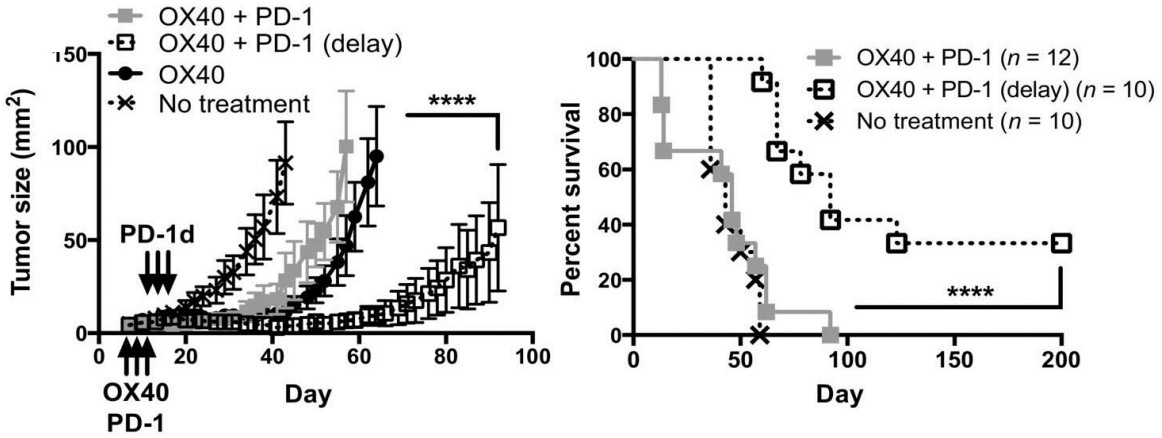


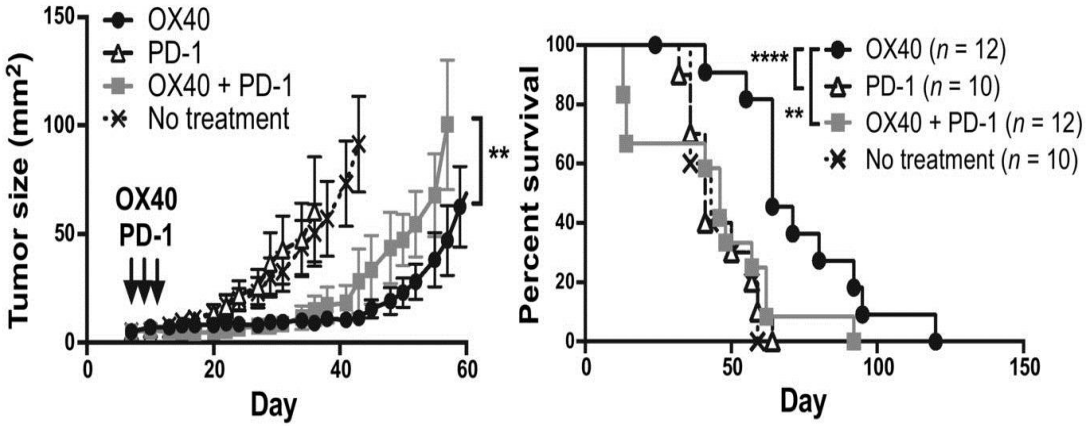



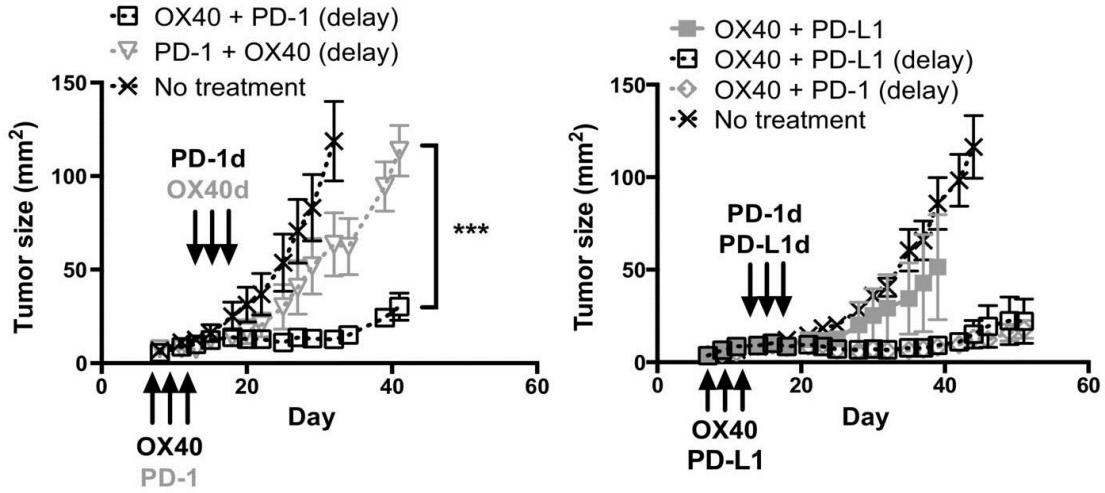

Foote JB/Emens LA at al, AACR 2017

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



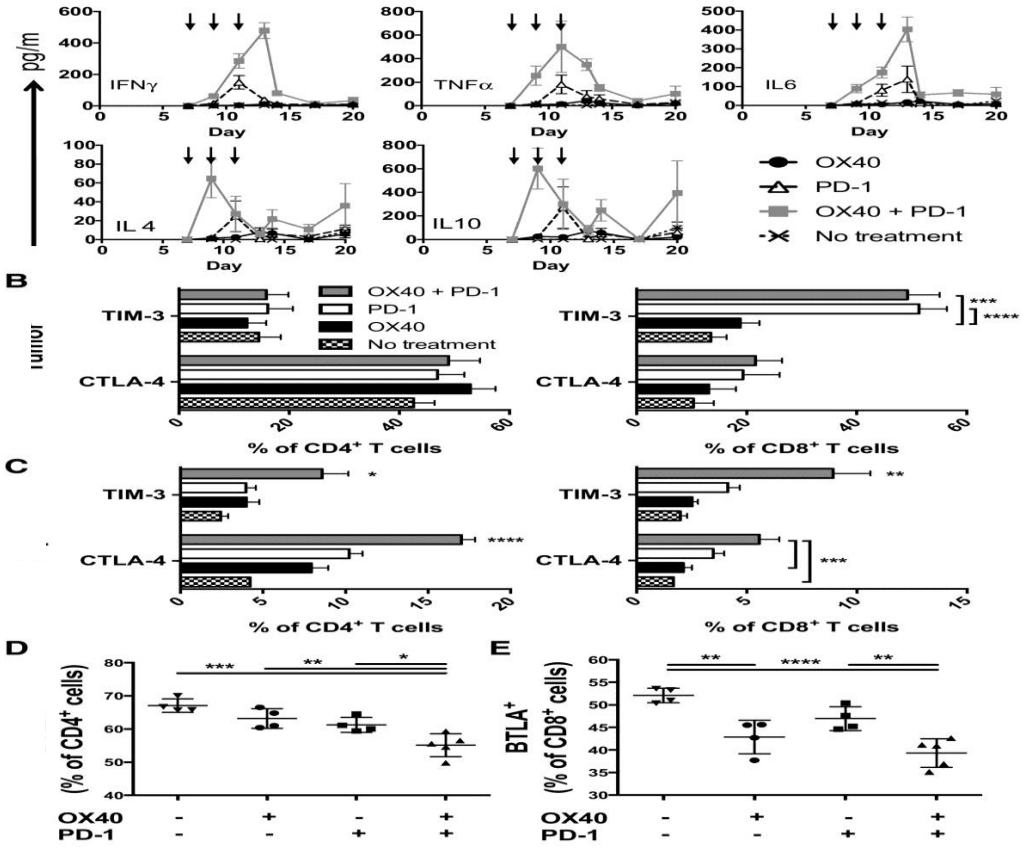



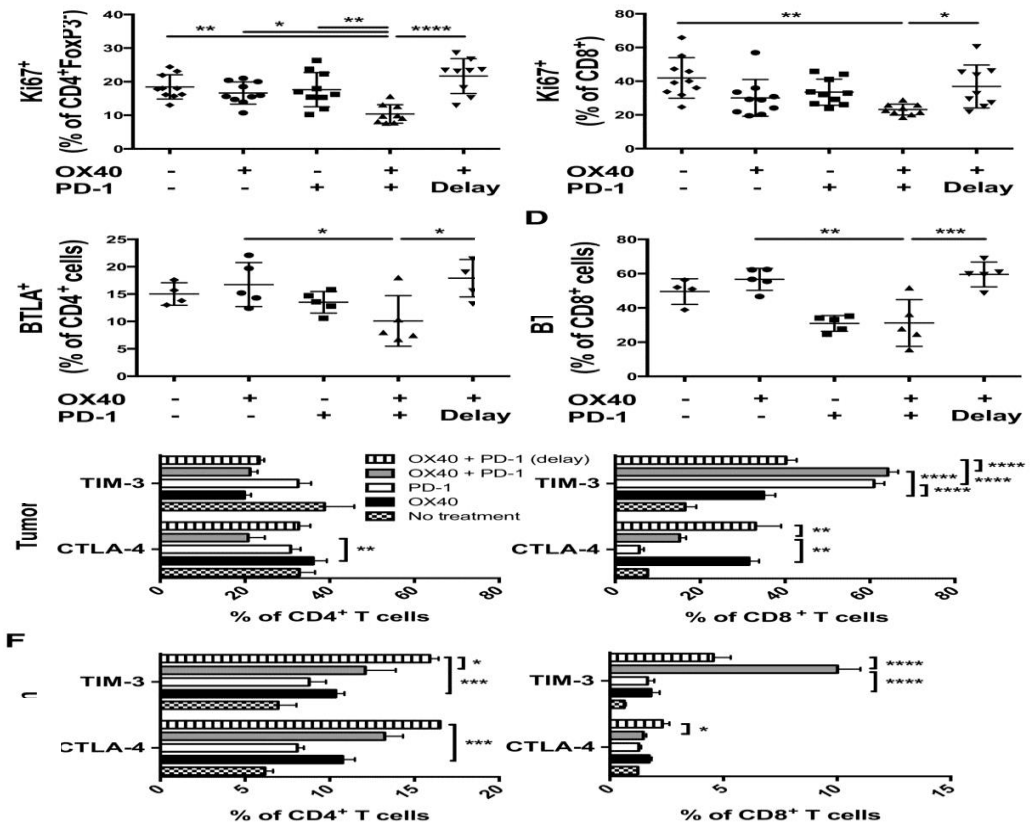

Messenheimer DJ et al. Clin Cancer Res 2017;23:6165-6177

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

**Concurrent**




**Sequential**

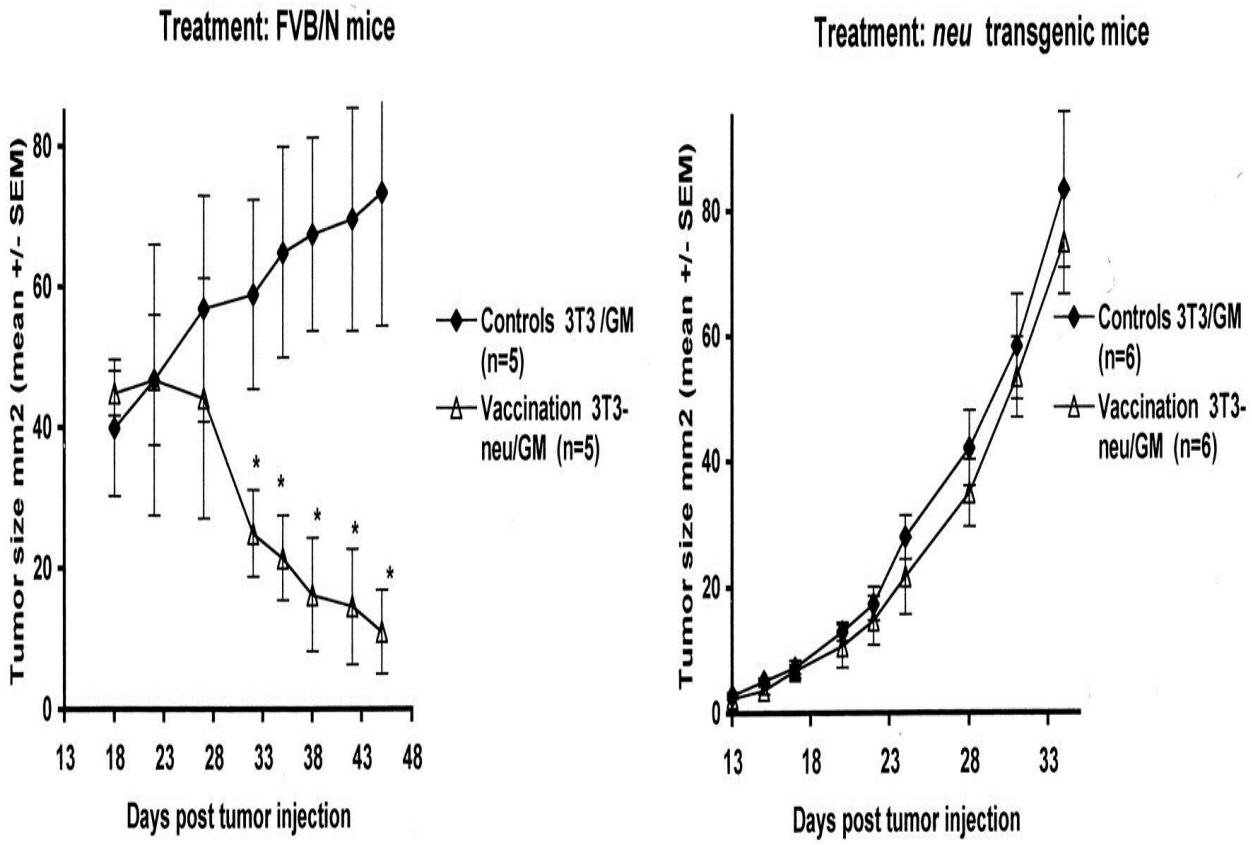



increases proliferating T cells and increases circulating serum cytokines and inhibitory receptors

maintains proliferating T cells without increase in inhibitory receptors

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

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

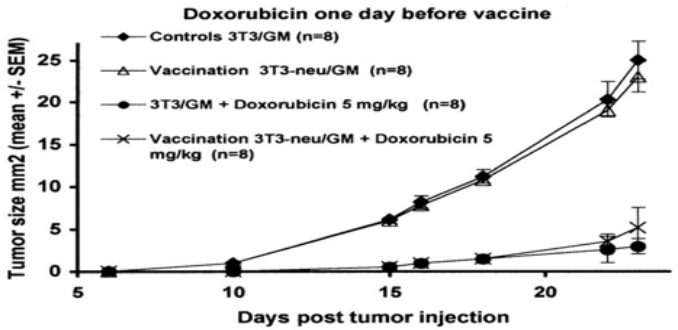


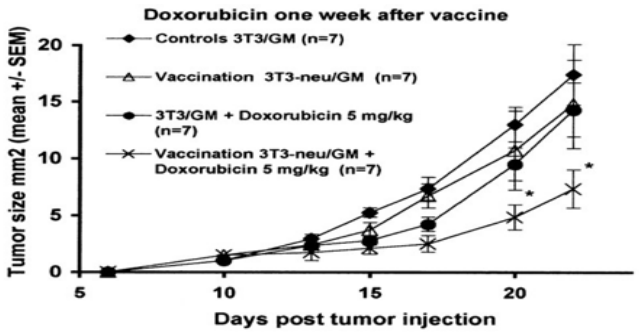

| | T cell count (nadir) number/ μl ± SD (normal range, 4000–9000)[b] | Chemotherapy 1 day before vaccine | Chemotherapy 7 days after vaccine |
|---|---|---|---|
| CTX | | | |
| 50 mg/kg | 6128 ± 847 | +[c] | – |
| 100 mg/kg | 5120 ± 1033 | + | – |
| 150 mg/kg | 1559 ± 356 | + | NT |
| 200 mg/kg | 1100 ± 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

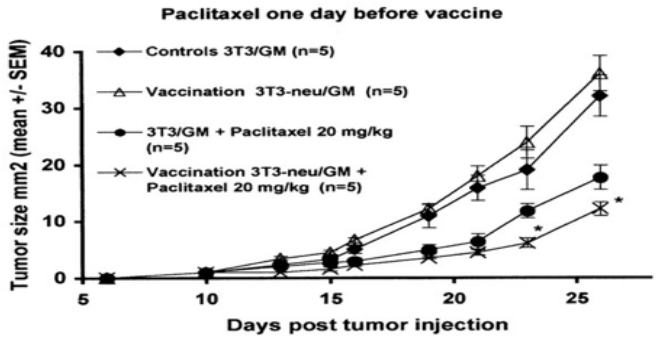
# Dose and Schedule Dependent Impact of Chemotherapy on Vaccine Activity

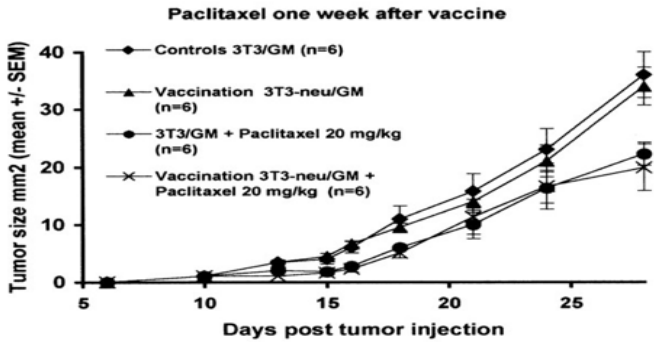
**Doxorubicin**



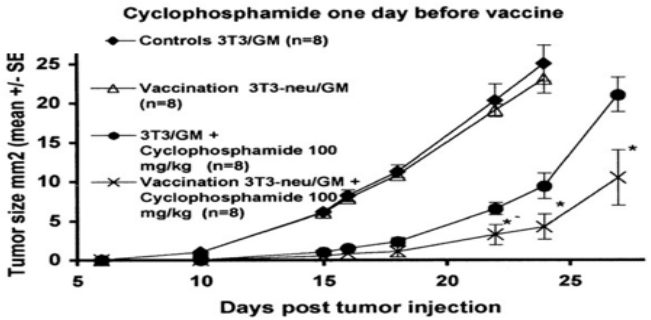



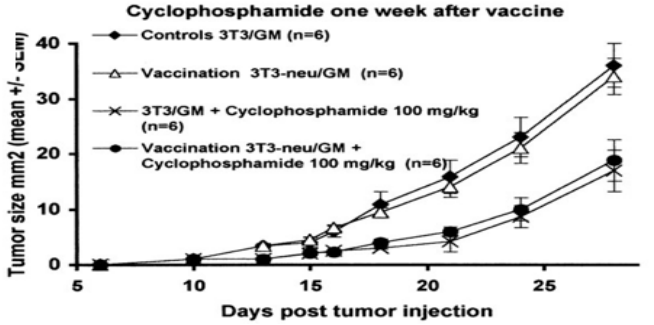

**Paclitaxel**



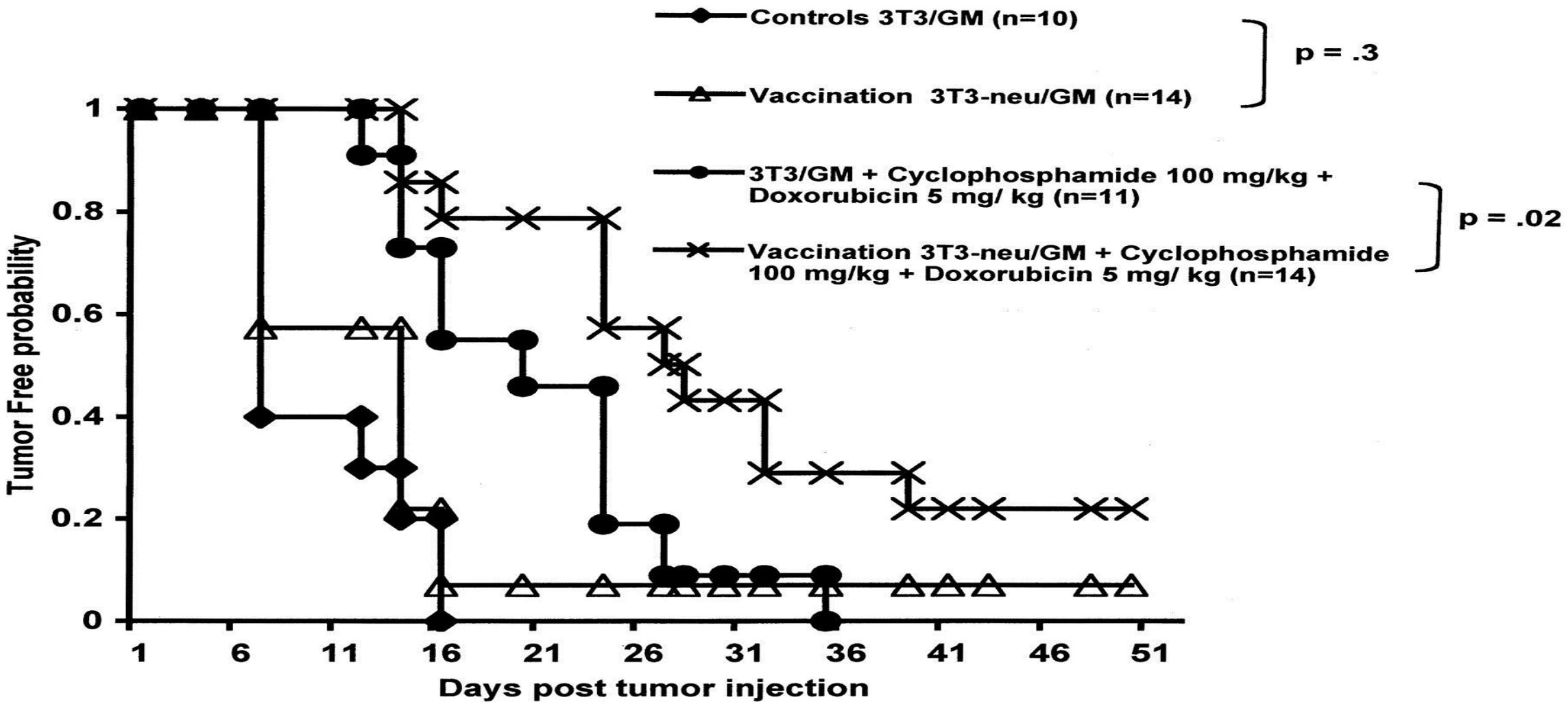

**Cyclophosphamide**



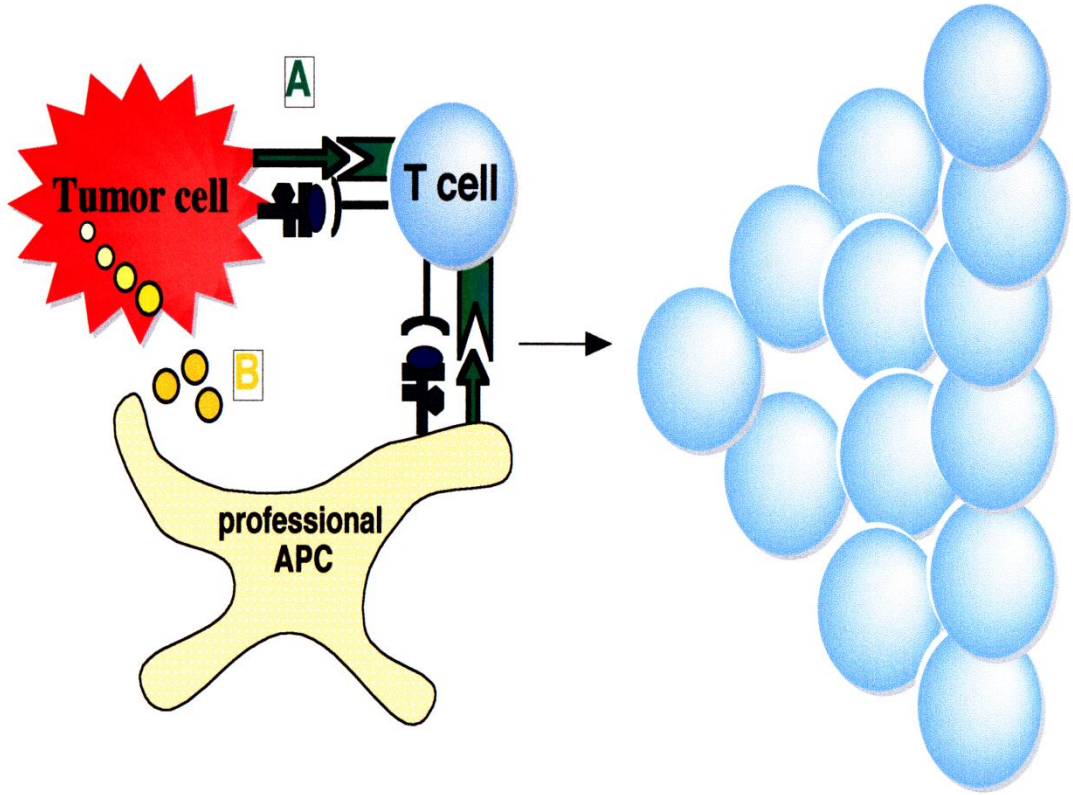

Machiels JP et al, Cancer Res 2001; 61: 3689

# Polychemotherapy Enhances Vaccine Activity in Tolerant Neu-N Mice




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

# A Human GM-CSF-secreting Breast Cancer Vaccine

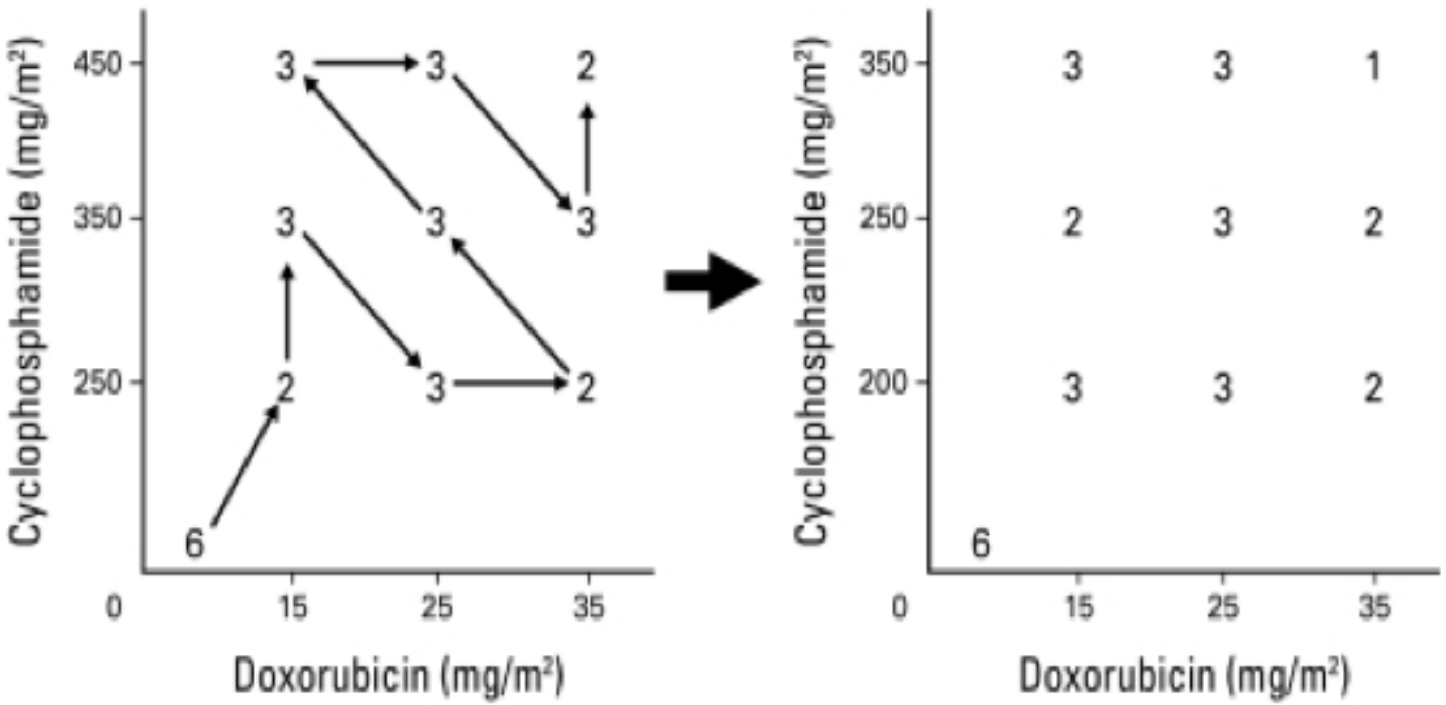



- Allogeneic breast tumor cells
  - SKBR3: HER-2+, ER-
  - T47D: HER-2-, ER+
- Generalizable
- Allows unbiased antigen delivery
- HER-2 for immune monitoring
- Secretes human GM-CSF 324 ng/$10^6$ cells/24 hrs

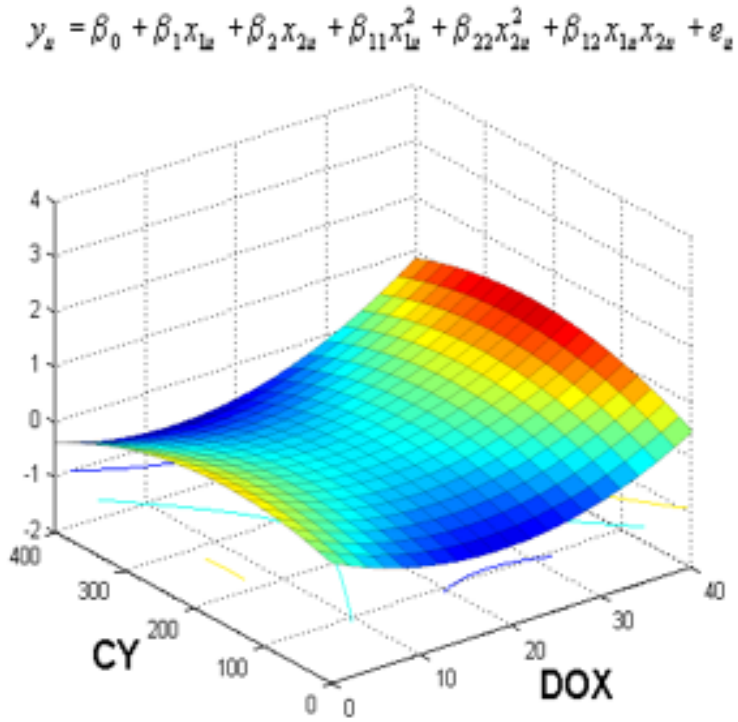
**Davis-Sproul et al, 2003, Cytotherapy, 7: 46-56**

# Combination of Vaccination with Low Dose Chemotherapy

## Novel Trial Designs to Explore Dose and Schedule




HER-2 Ab



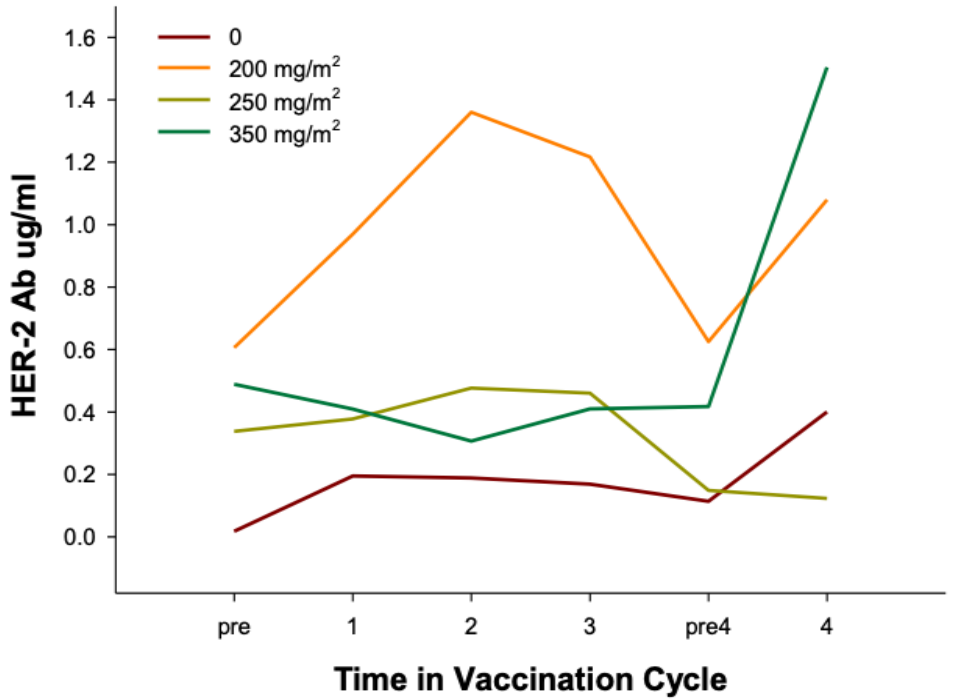

**Possible Inputs: dose x dose**
**dose x schedule**

**Possible Outputs: immune response**
**clinical response**
**toxicity**

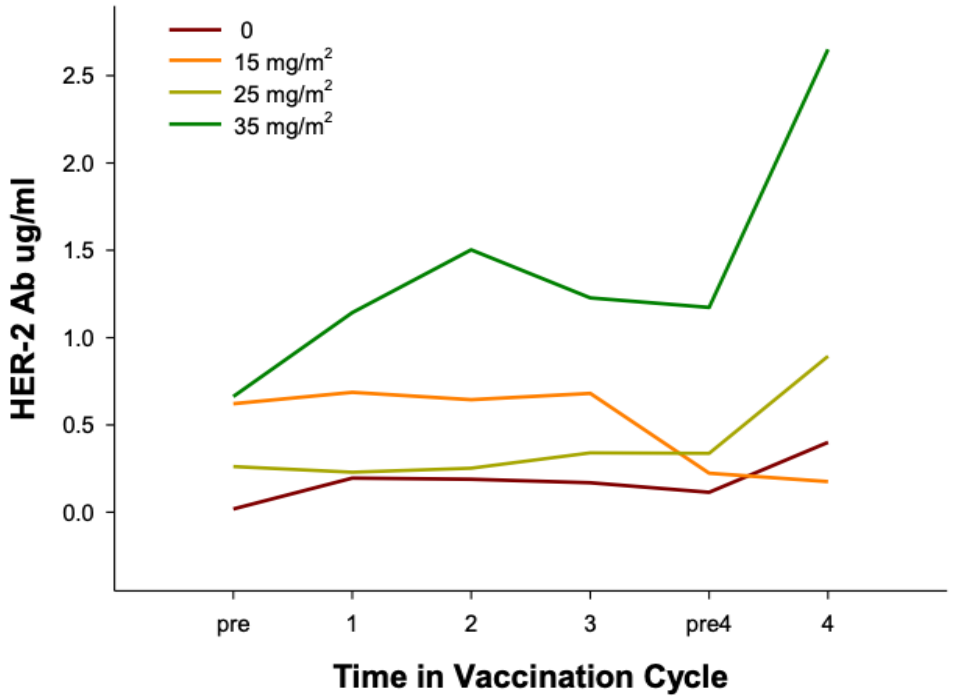
Emens LA, J Clin Oncol 2009;27: 5911-18

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

CY

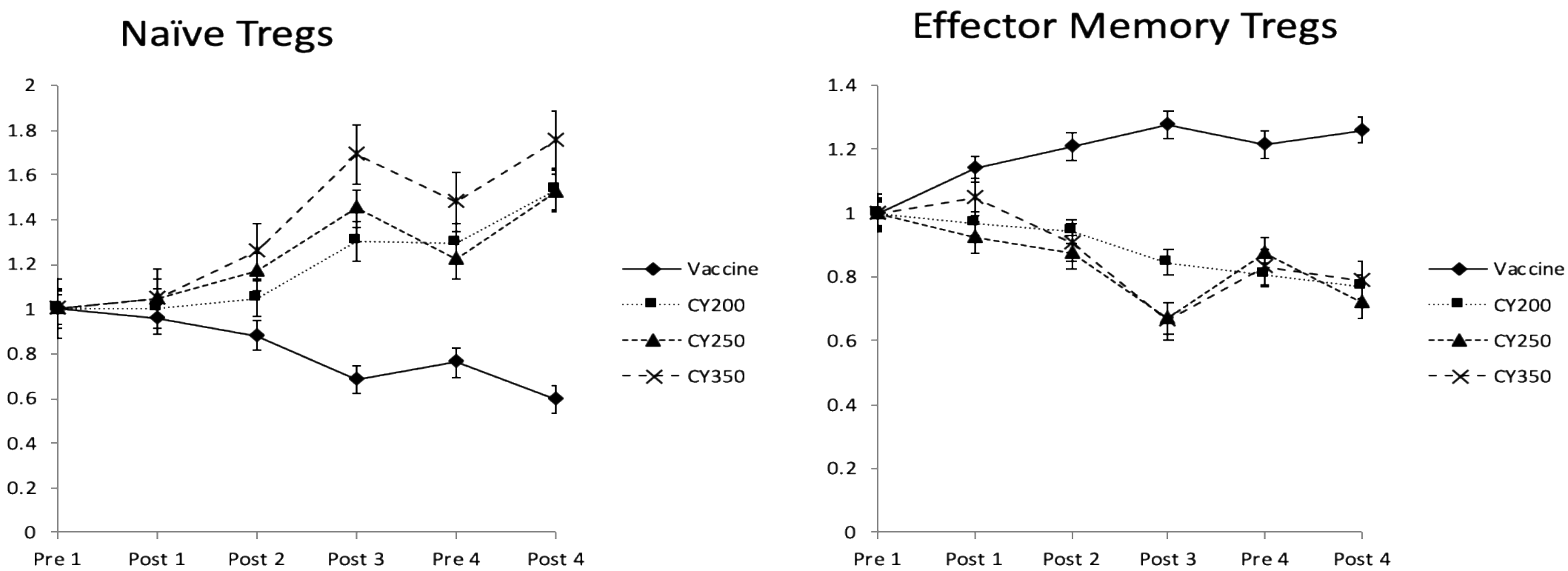



DOX




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

# Dose Dependent Impact of CY on Naïve and Effector Memory Tregs




**Chen/Emens, unpublished data**

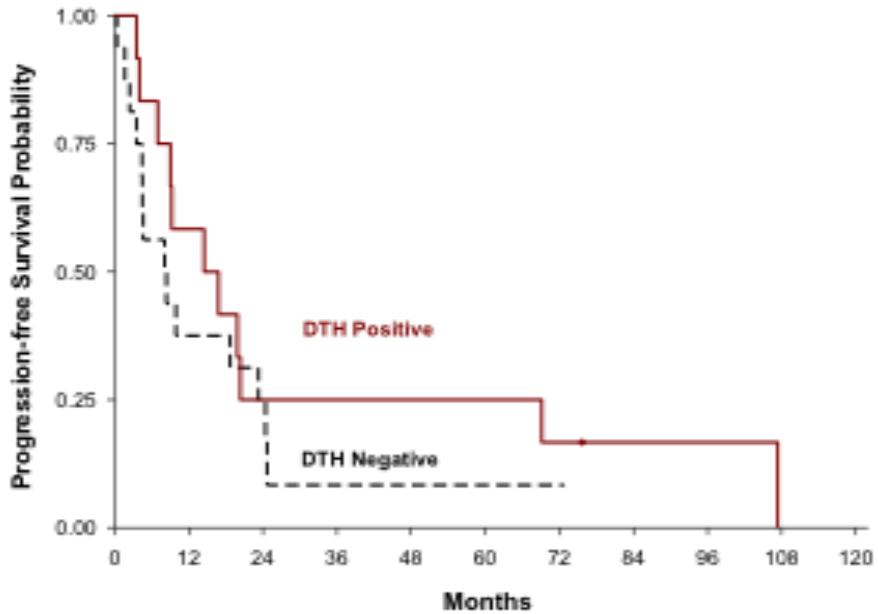
# CY Preferentially Impacts Tregs Relative to Effector T Cells

| | % 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

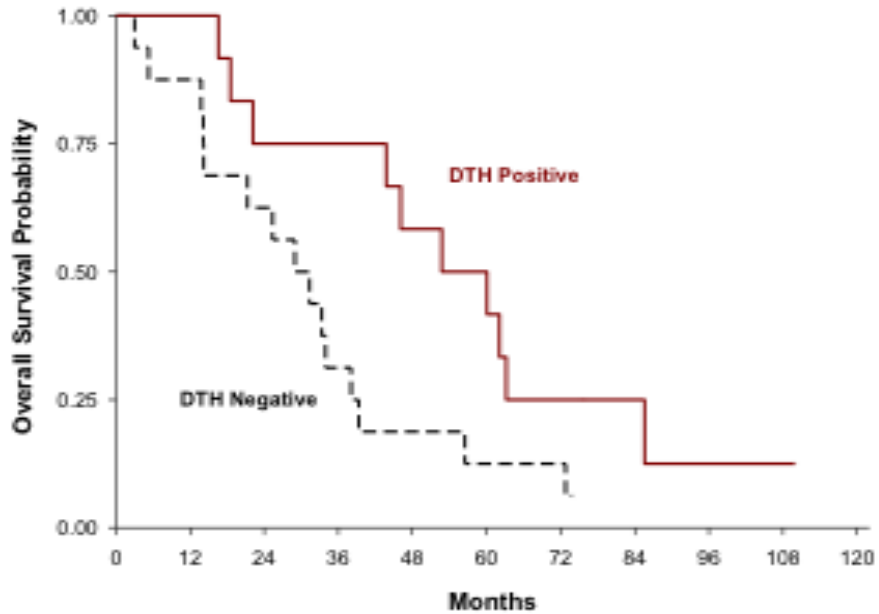
# Survival Outcomes (n=28)

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




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

**Total Overall Survival: 36 months**

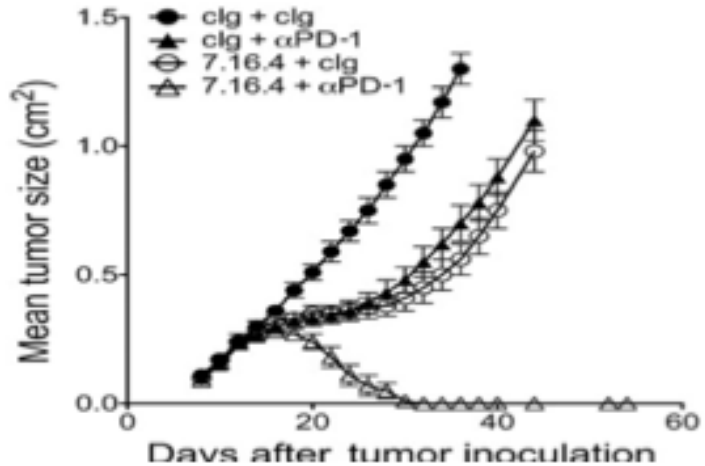


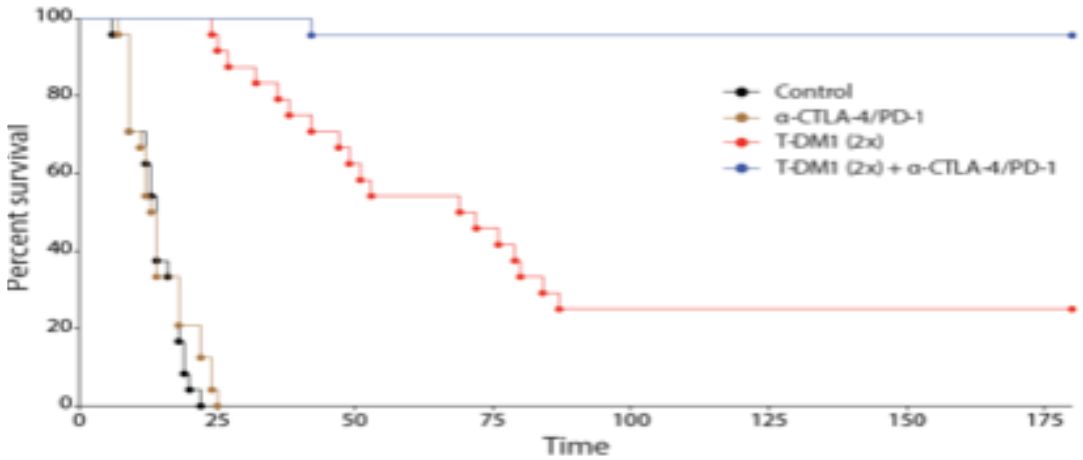

**DTH NR vs. R 30 vs. 56 months**

**Emens LA, unpublished data**

# Combination of Immunotherapy with HER-2-directed Therapy

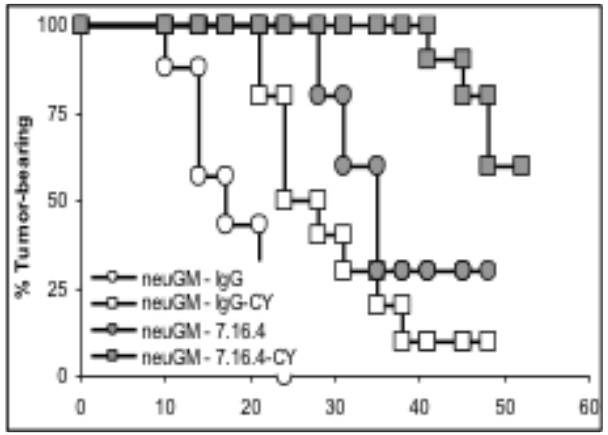
## Checkpoint Blockade

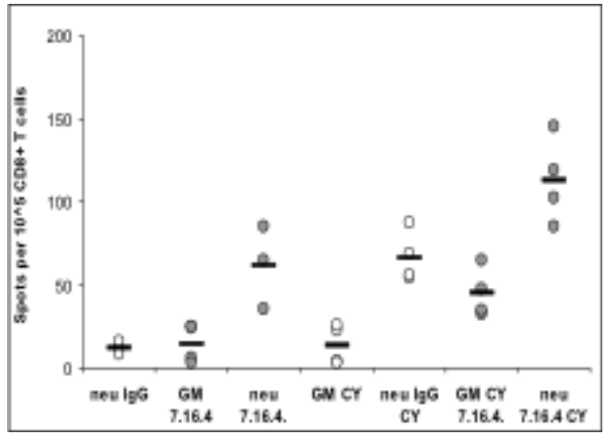


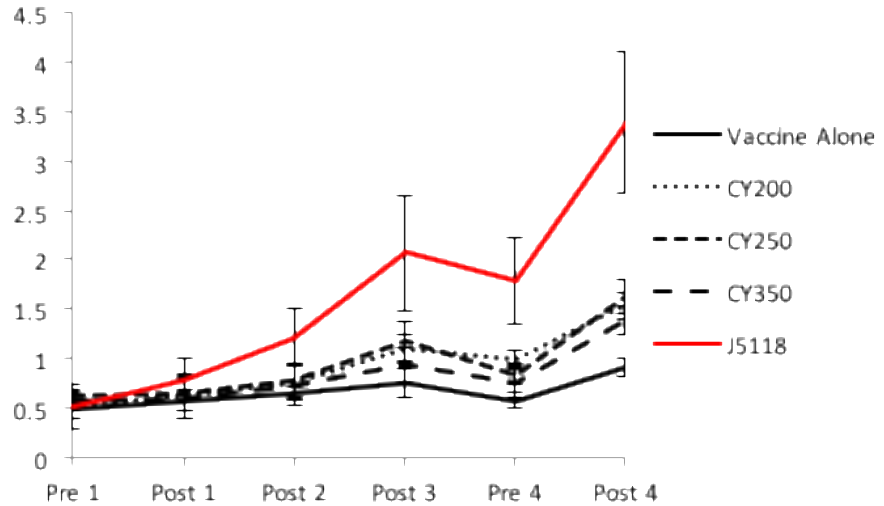




Stagg J et al, PNAS, 2011; 108: 7142-47
Müller P et al, Science Translation Medicine, 2015; 315:315ra188

## Vaccination

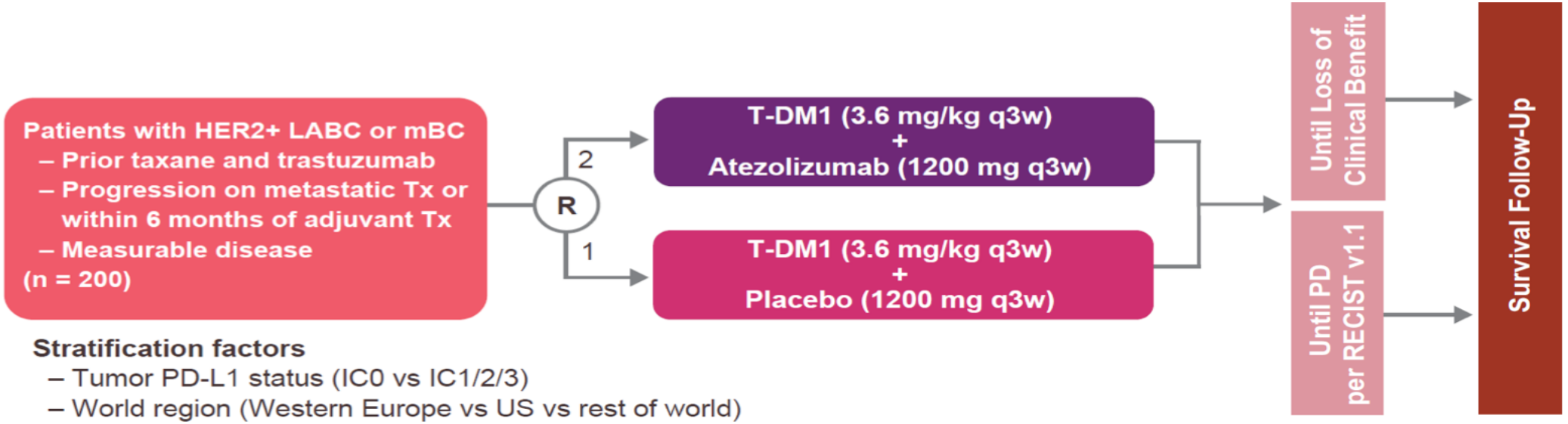



Chen/Emens et al, Cancer Immunol Res 2014; 2: 949-961
Chen/Emens, unpublished data

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




**Stratification factors**
- Tumor PD-L1 status (IC0 vs IC1/2/3)
- World region (Western Europe vs US vs rest of world)
- Liver metastases (yes vs no)

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

**Secondary endpoints**
- OS, ORR, DOR (ITT)

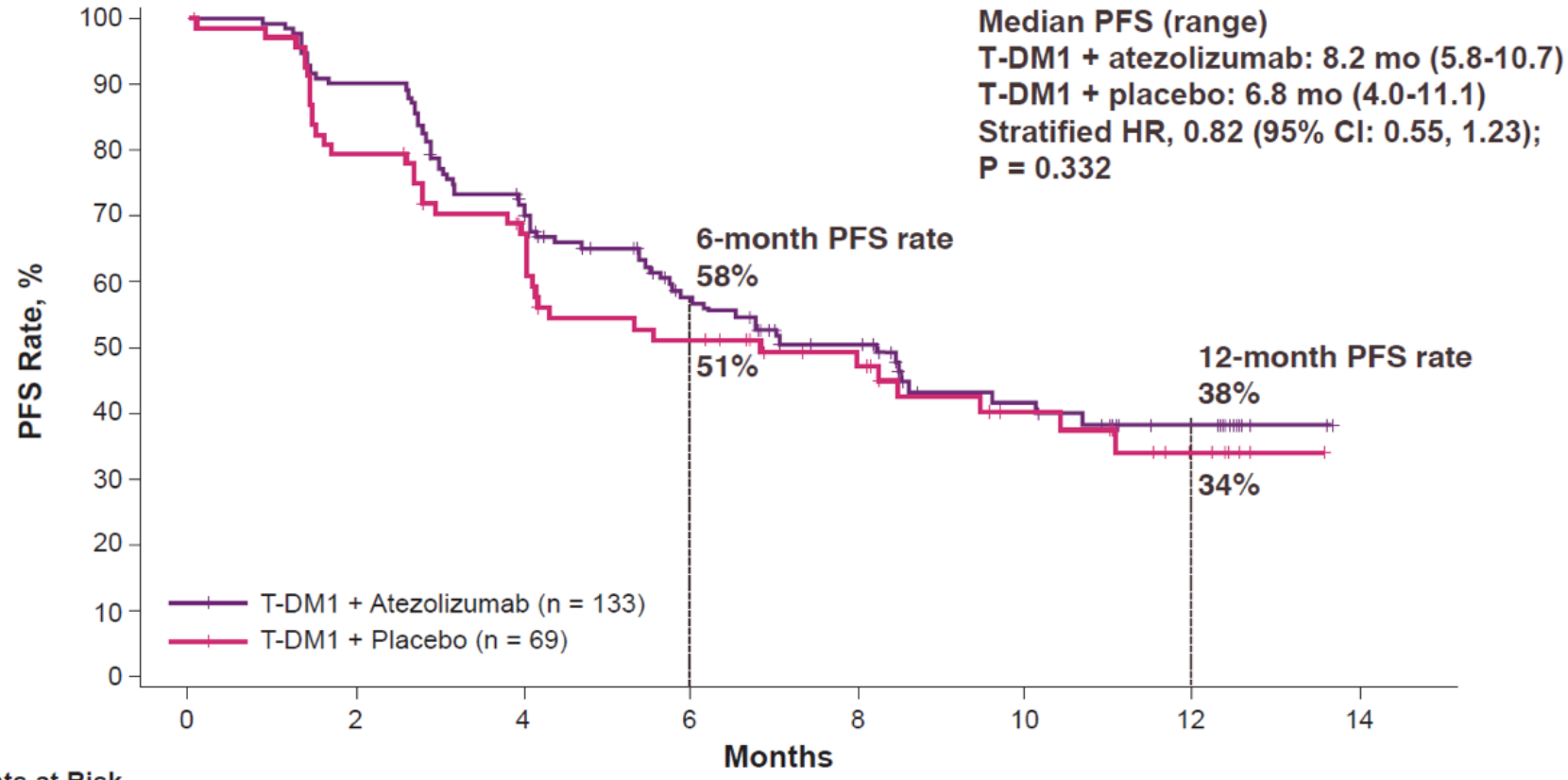
**Exploratory endpoints**
- PFS in the PD-L1+ (PD-L1 IC ≥ 1%) subgroup
- Efficacy in subgroups defined by immune-related (tumor-infiltrating lymphocytes and CD8 IHC expression) and HER2-related biomarkers

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

**Emens LA et al SABCS 2018**

IC, tumor-infiltrating immune cells; LABC, locally advanced breast cancer; mBC, metastatic breast cancer; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; Tx, treatment.

# Primary Endpoint PFS in ITT Patients




**No. of Patients at Risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DM1 + Atezolizumab | 133 | 131 | 118 | 100 | 90 | 74 | 59 | 46 | 42 | 26 | 25 | 21 | 15 | 3 |
| T-DM1 + Placebo | 69 | 66 | 54 | 46 | 42 | 33 | 31 | 25 | 23 | 18 | 15 | 14 | 7 | 1 |

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

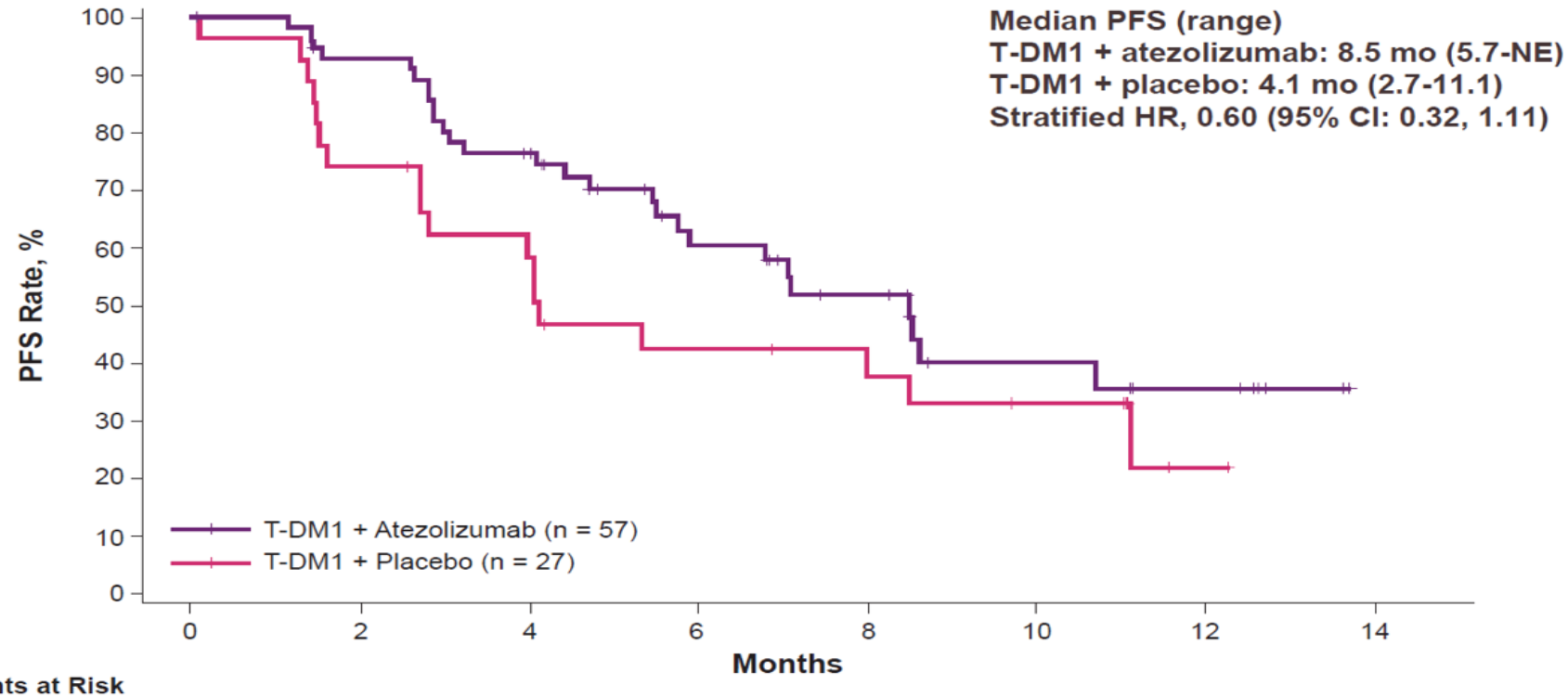
# Secondary Endpoint: ORR in ITT Patients

| | 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




**No. of Patients at Risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DM1 + Atezolizumab | 57 | 56 | 51 | 44 | 40 | 31 | 24 | 19 | 16 | 9 | 9 | 8 | 6 | 2 |
| T-DM1 + Placebo | 27 | 26 | 20 | 16 | 15 | 11 | 10 | 9 | 8 | 7 | 6 | 6 | 1 | |

NE, not estimable.

- 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

**Emens LA et al SABCS 2018**

# 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!