STANFORD
CANCER INSTITUTE

Incorporating Immunotherapy and Novel Biological Agents in Breast Cancer: New Horizons

21 JULY 2018

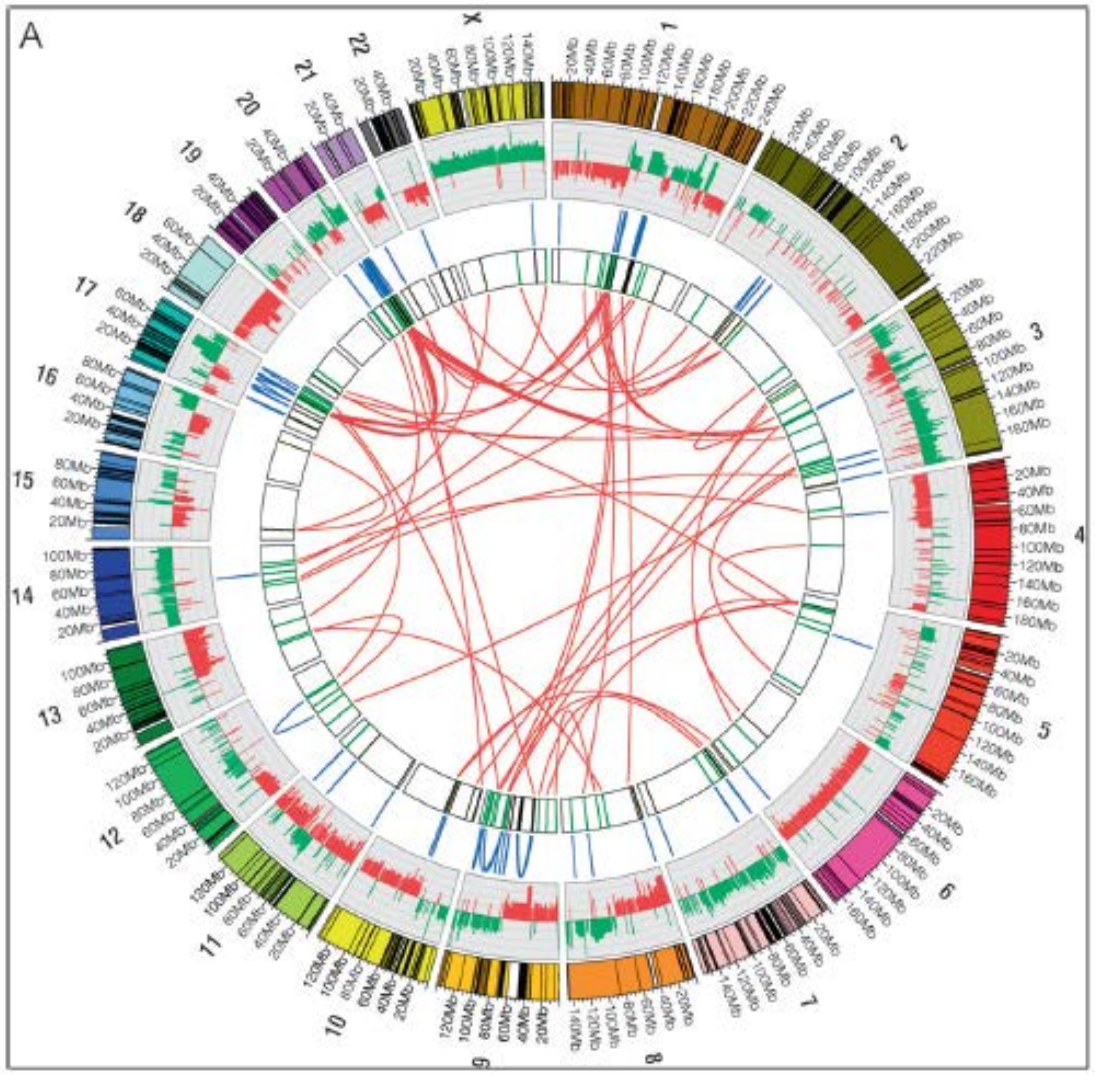
Mark Pegram, M.D.
Susy Yuan-Huey Hung Professor of Medical Oncology
Associate Director for Clinical Research
Director, Stanford Breast Oncology Program
Associate Dean for Clinical Research Quality
Stanford Comprehensive Cancer Institute

COI Declaration –
relevant to presentation topic

Roche/Genentech – consultant
Pfizer -- consultant

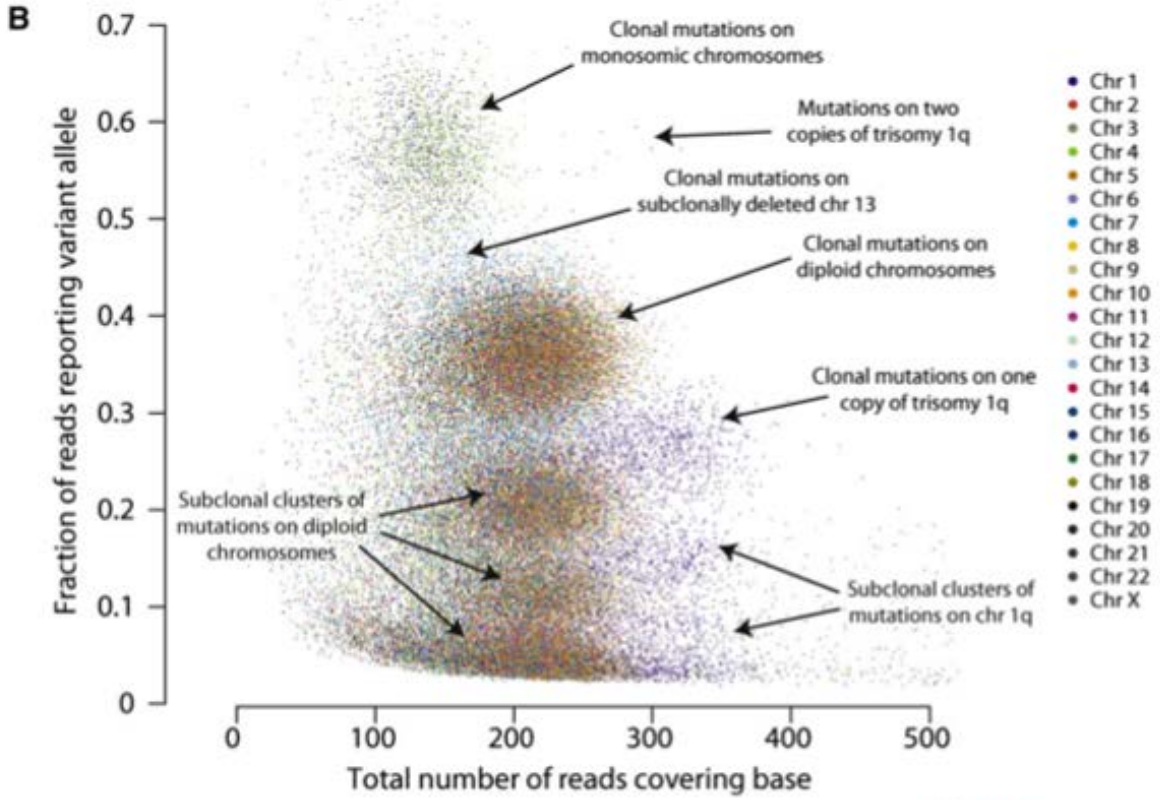
All of the clinical data shown in this presentation shall be considered as off-label.

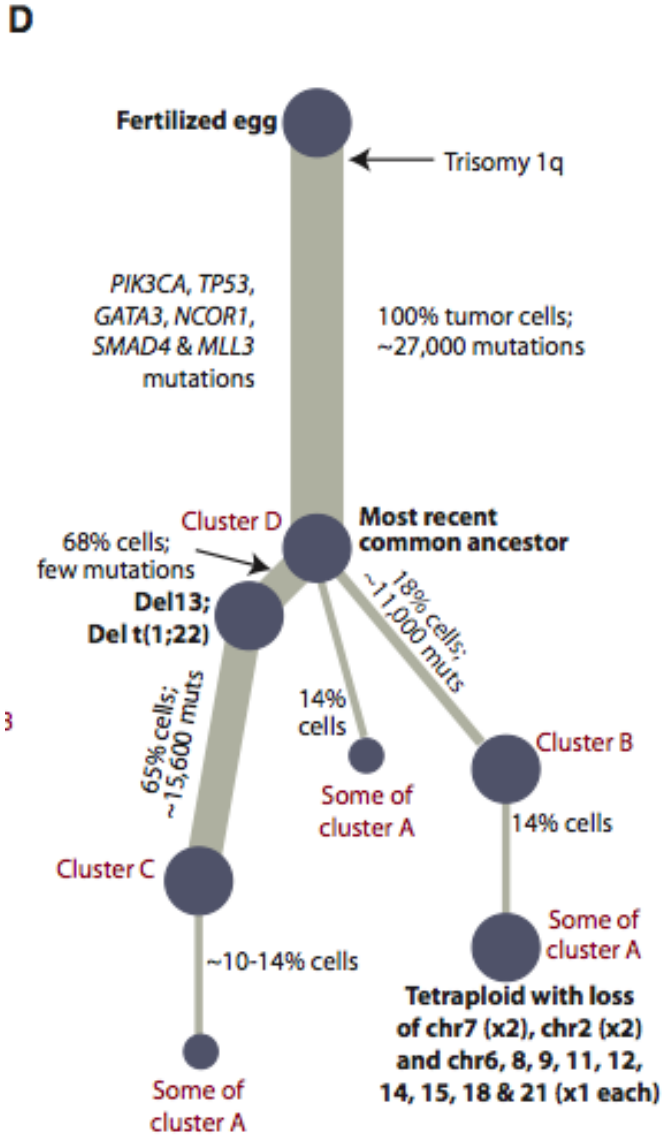
A sequence-level map of (MCF-7) human breast carcinoma cells reveals 157 chromosomal breakpoints in a single breast cancer cell line

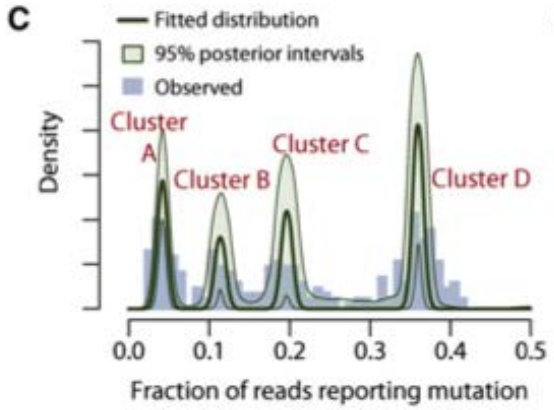


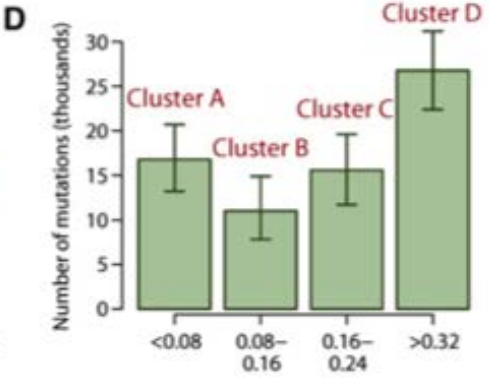
Hampton, et al., Genome Res (29 Jan 2009)

Genomic Architecture of PD4120a, a Breast Cancer Genome Sequenced to 188-Fold Coverage









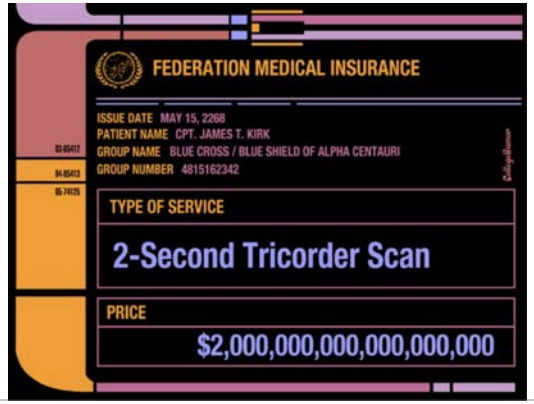
Nik-Zainal, et al., Cell *149,* 994–1007, 2012

Solutions to the Cancer Problem in the Genomic Era

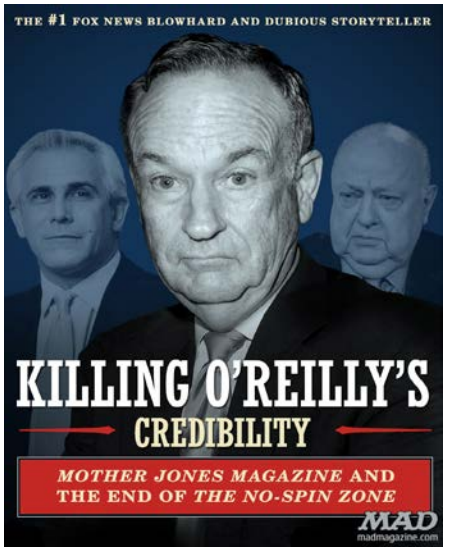
Prevention

"An ounce of prevention…"
-- B Franklin

Early Detection

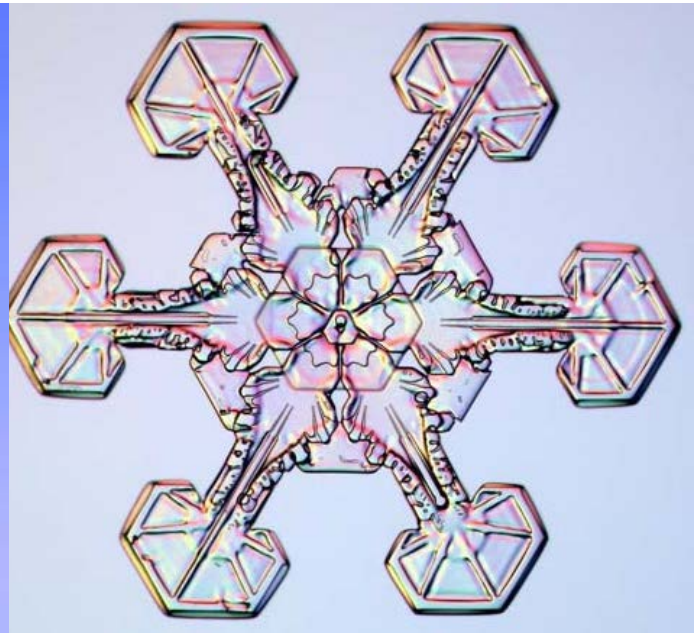


Immunotherapy

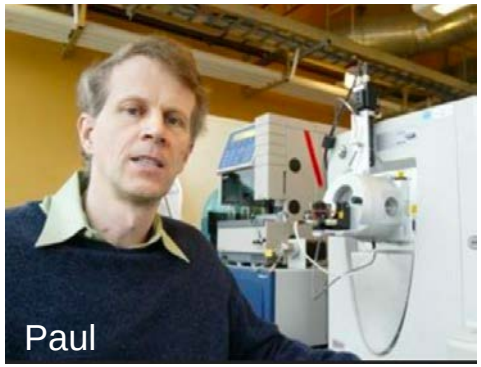


Sequel:
Killing Cancer with I/O
-- B O'Reilly

All Snowflakes are Different…
But they all Melt:
Immuno-oncology for Smart Tumors



“GENE CONVERSION MUTAGENESIS”



Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 4285–4289, May 1992
Immunology

Humanization of an anti-p185^{HER2} antibody for human cancer therapy

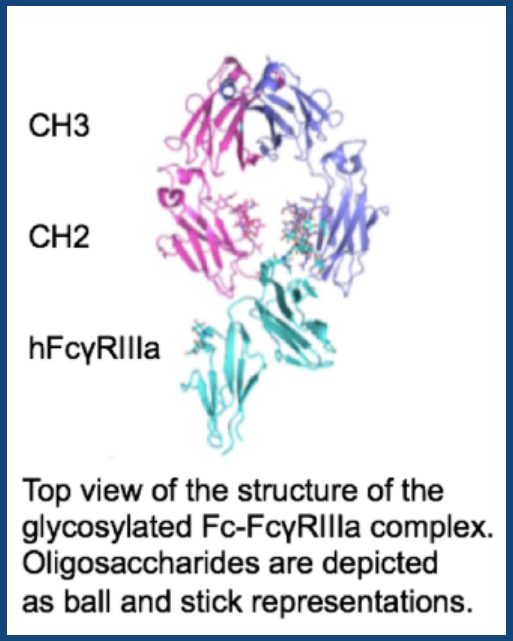
(antibody engineering/site-directed mutagenesis/c-*erbB-2*/*neu*)

PAUL CARTER*, LEN PRESTA*, CORNELIA M. GORMAN†, JOHN B. B. RIDGWAY†, DENNIS HENNER†, WAI LEE T. WONG‡, ANN M. ROWLAND‡, CLAIRE KOTTS‡, MONIQUE E. CARVER‡, AND H. MICHAEL SHEPARD§

Departments of *Protein Engineering, †Cell Genetics, ‡Medicinal and Analytical Chemistry, and §Cell Biology, Genentech Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080

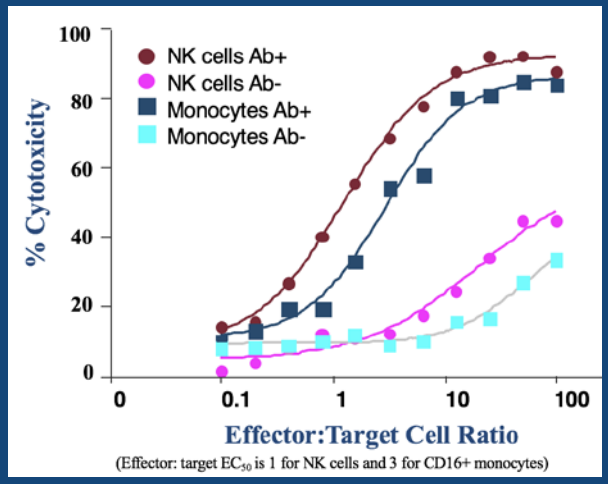
Communicated by Hilary Koprowski, January 16, 1992 (received for review February 15, 1991)

The trastuzumab Fc-domain/FcgRIIIa Complex is a Potent Mediator of ADCC*



Top view of the structure of the glycosylated Fc-FcγRIIIa complex. Oligosaccharides are depicted as ball and stick representations.

Trastuzumab Fc-domain binding to activating FcγRIIIa receptors elicits ADCC

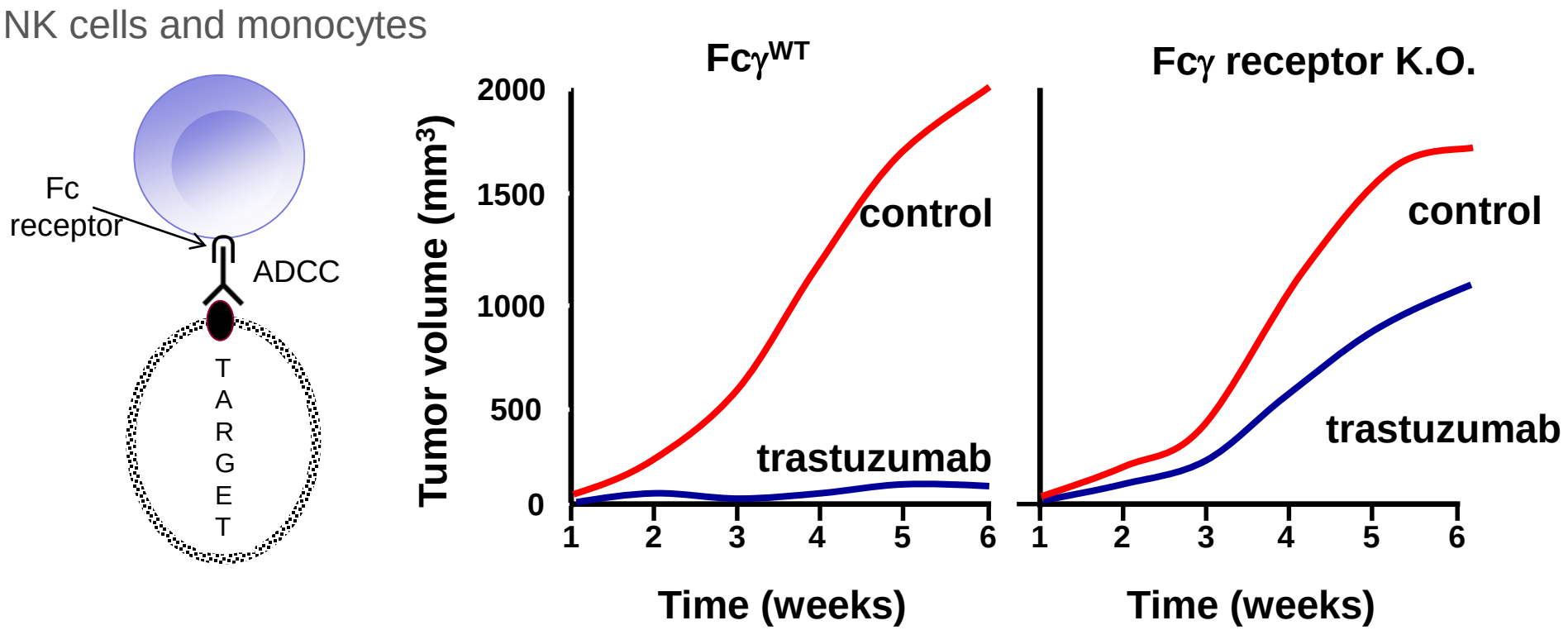


Pegram, et al., Proc Am Assoc Cancer Res 38: 602, 1997 (abstr 4044).

*ADCC = Antibody-Dependent Cell-mediated Cytotoxicity

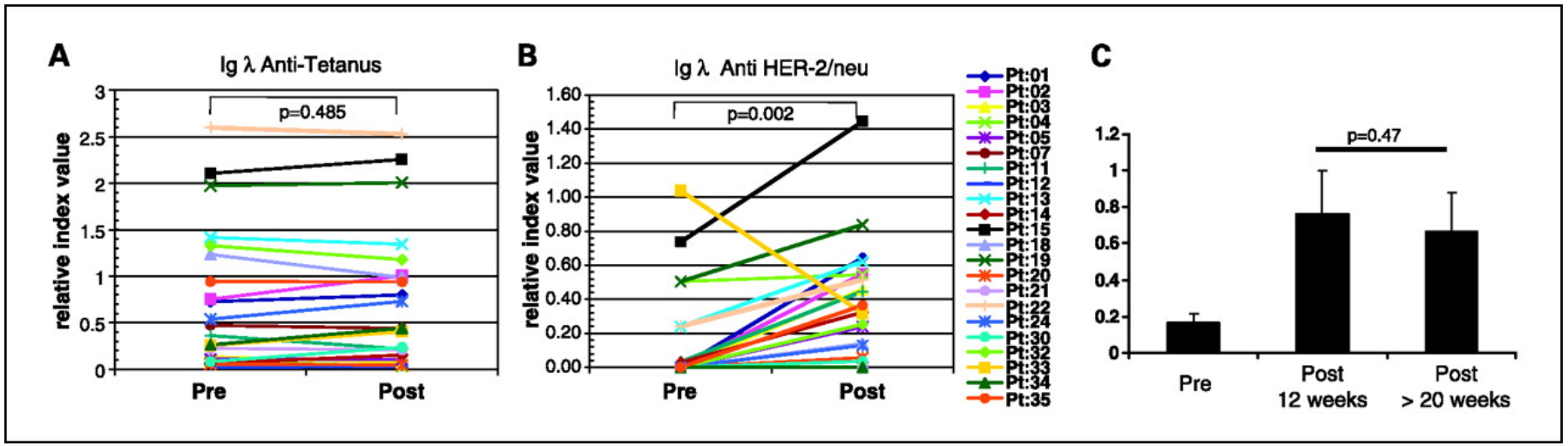
Fc Receptors Modulate Anti-tumor Activity of Trastuzumab

Breast Cancer Cell Growth Following Treatment with Trastuzumab in the Presence and Absence of Functional Fc Receptors

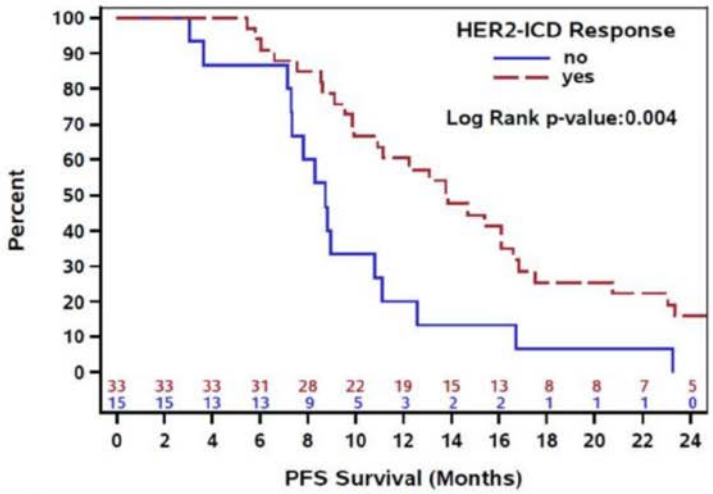


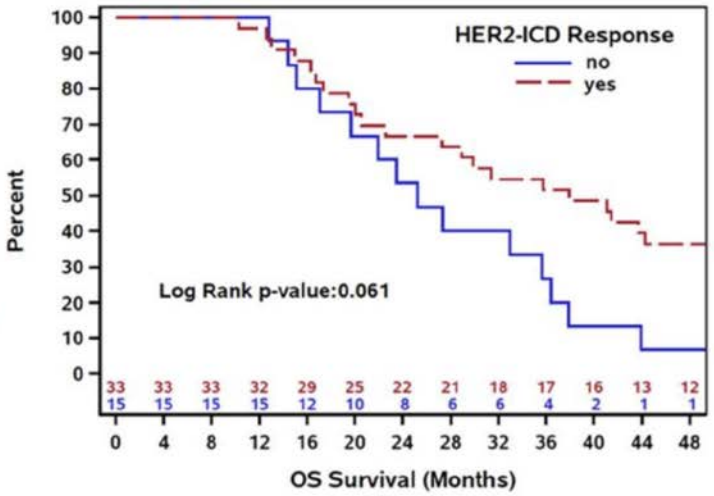
Adapted from Clynes et al. *Nature Med*. 2000;6:443-446

Patients develop increased anti-HER-2/neu Igλ and HER2-specific T-cell responses during trastuzumab therapy



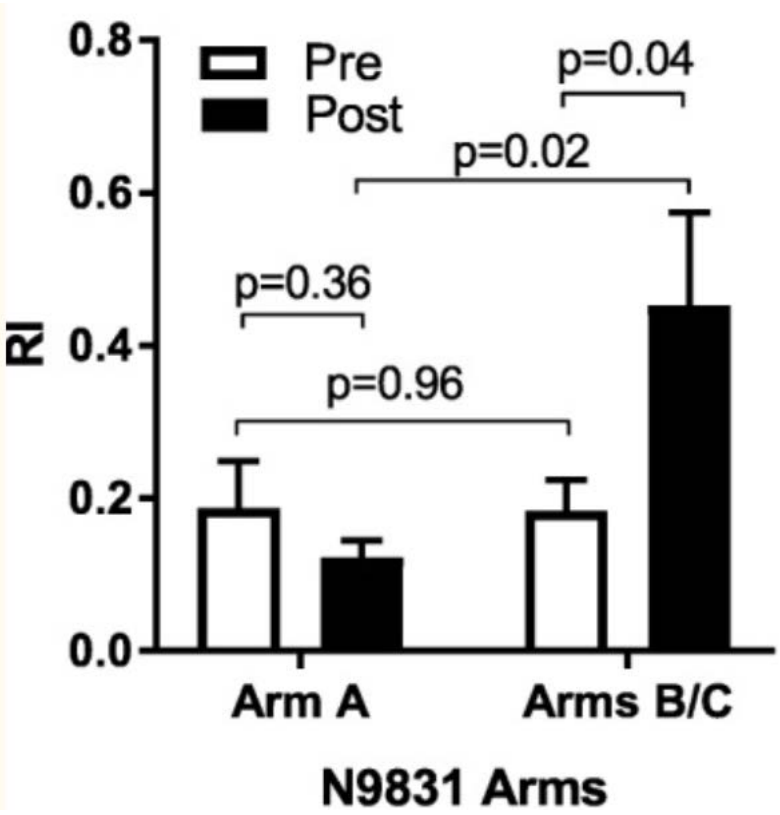
Taylor et al. Clin Cancer Res 2007;13:5133-5143.

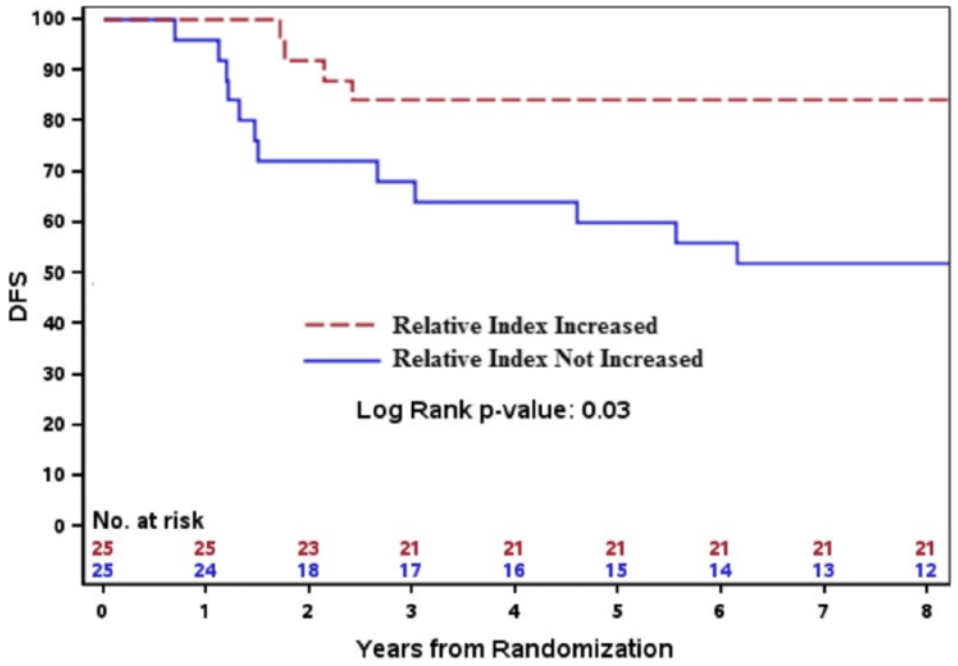




Knutson, et al., Cancer Res. 2016; 76(13): 3702–3710.

Generation of HER2-specific antibody immunity during trastuzumab adjuvant therapy associates with reduced relapse in resected HER2 breast cancer





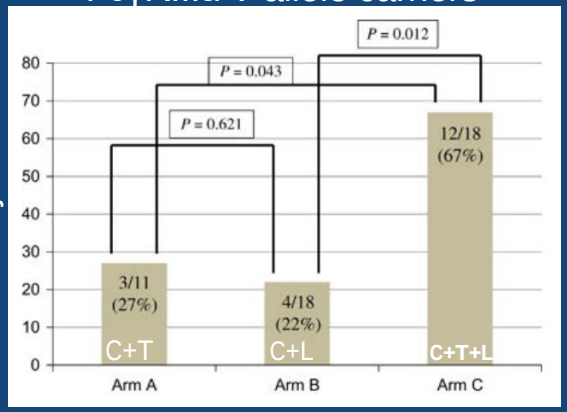
Higher levels of post-treatment antibodies are associated with improved disease-free survival. Kaplan-Meier curve showing disease-free survival (*DFS*) in all patients ($N = 50$) with antibody changes of ≥0.2 RI units (inclusive of all arms) compared with patients that did not experience increased antibodies

Norton, Fox, McCarl, Tenner, Ballman, Erskine, Necela, Northfelt, Tan, Calfa, Pegram, Colon-Otero, Perez, Clynes, Knutson. Breast Cancer Res. 2018; 20: 52.

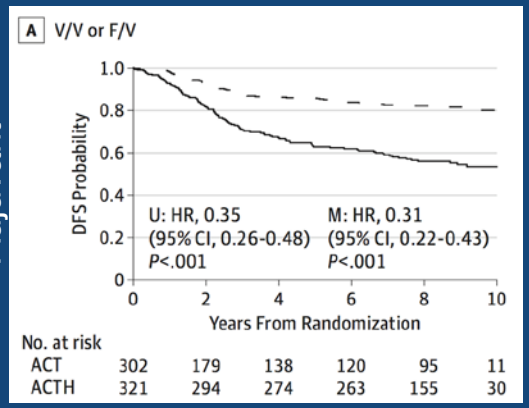
Improved Outcomes in Patients with High binding FcR Alleles

CHER-LOB trial
Neoadjuvant

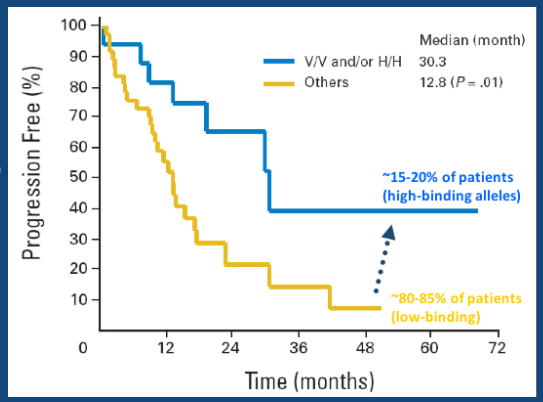
FcγRIIIa V allele carriers



NSABP B31
Adjuvant



Parma Data
MBC

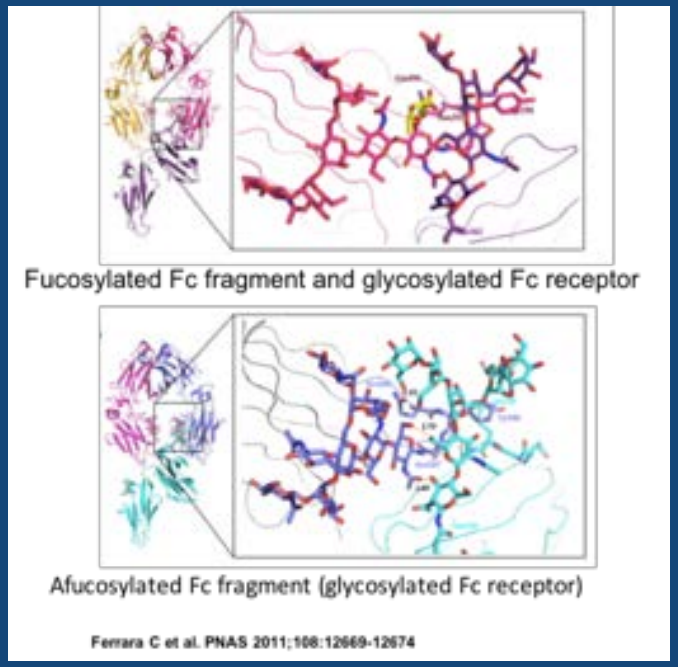


A Musolino, et al. The Pharmacogenomics Journal 16, 472–477 (2016).

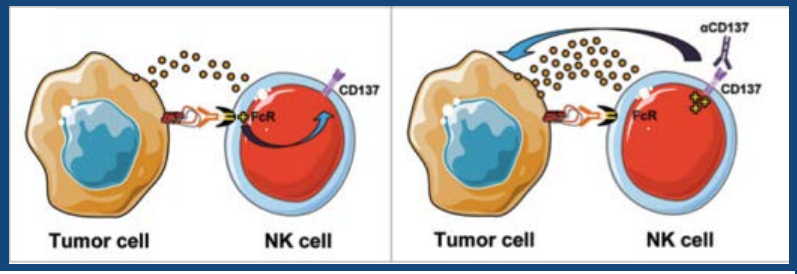
Gavin PG, et al. JAMA Oncol. 2017; 3(3): 335-341.

Musolino, A. et al. J Clin Oncol 26:1789-1796, 2008.

Fc-domain engineering for enhanced immune effector function, and CD137 agonist antibodies can potentiate ADCC *in vivo*



Margetuximab pivotal trial: SOPHIA
NCT02492711



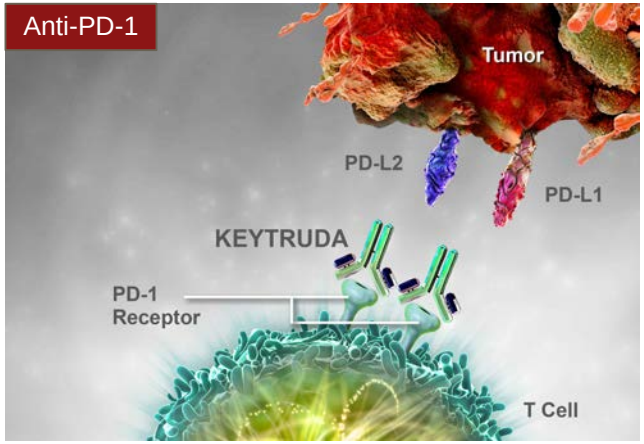
Stanford Phase IB/II IIT
NCT03364348

Kohrt, et al., J Clin Invest 122(5): 1066-75 (2012)

FDA Approval Status of Immune Checkpoint Inhibitors (anti-PD1/PDL1/CTLA-4)

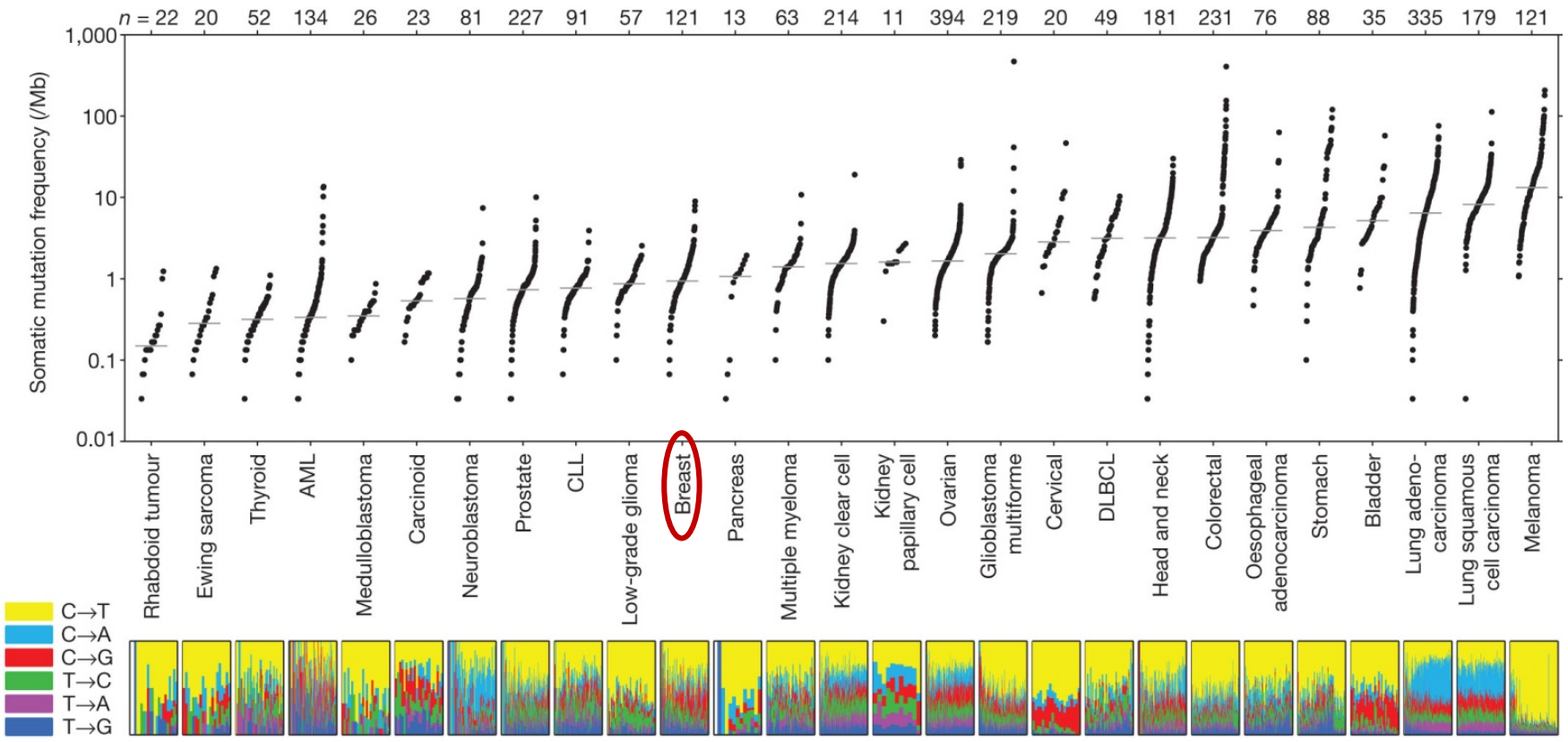
STANFORD MEDICINE

- Ipilumumab (CTLA-4):
  - *Melanoma (2011)*
- Pembrolizumab (PD-1):
  - *Melanoma (2014)*
  - *Non-small Cell Lung (2015)*
  - *Head and Neck cancers (2016)*
  - *Microsatellite-Instability High (MSI) solid tumors (2017)*
  - *Bladder cancers (2017)*
  - *Hodgkin lymphoma (2017)*
- Nivolumab (PD-1):
  - *Melanoma (2014)*
  - *Non-small Cell Lung (2015)*
  - *Renal (2015)*
  - *Hodgkin Lymphoma (2016)*
  - *Head and Neck Squamous (2016)*
  - *Bladder cancers (2017)*
- Atezolizumab (PD-L1):
  - *Urothelial cancers (2016)*
  - *Non-small Cell Lung Cancers (NSCLC), (2016)*
- Avelumab (PD-L1):
  - *NSCLC (2016)*
  - *Merkel Cell cancers (2017)*



Cancers Vary in Genomic Complexity:

Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.

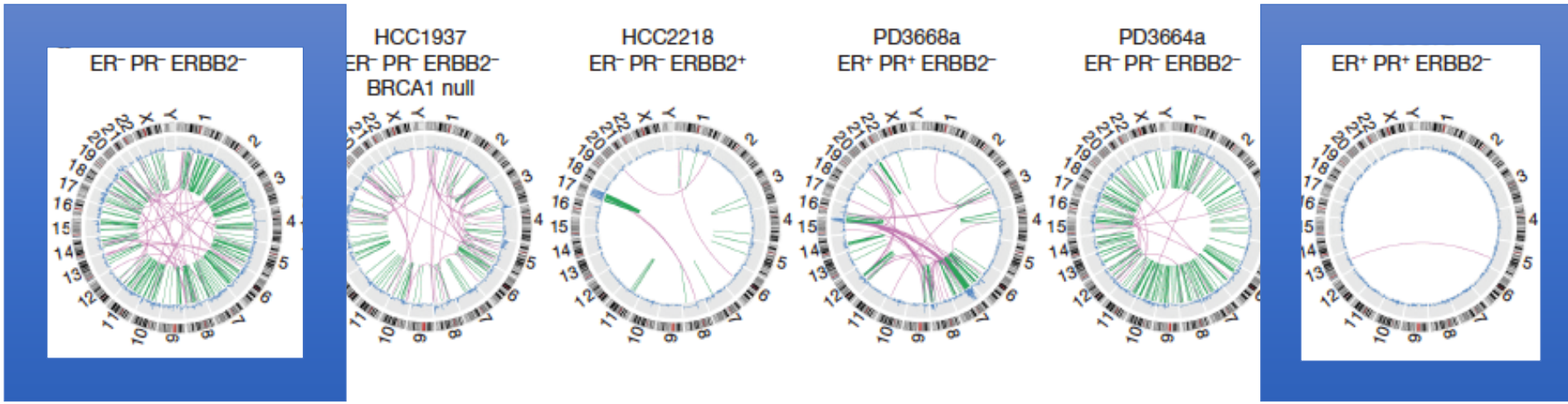


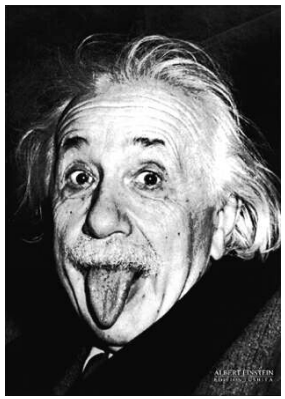
Lawrence MS, et al., Nature. 2013 Jul 11;499(7457):214-218.

Breast Cancer: Subtypes Reflect Genomic Complexity

SMART CANCERS

STUPID CANCERS



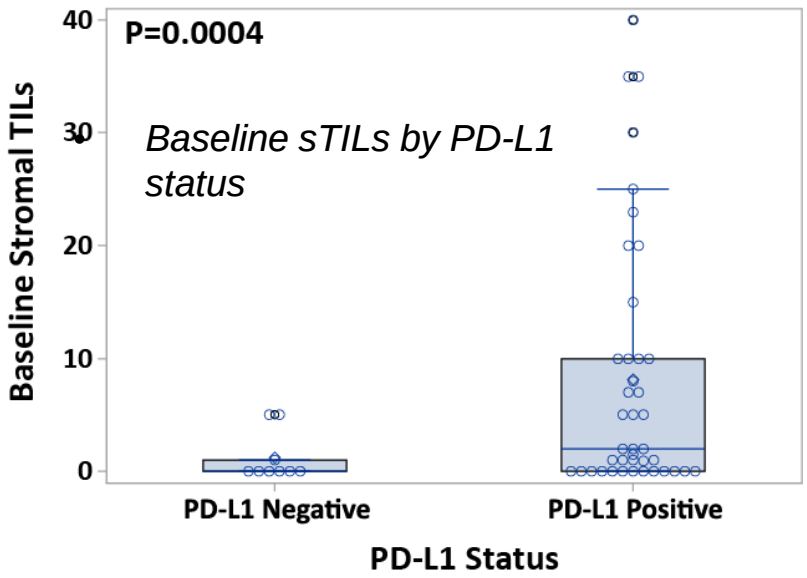


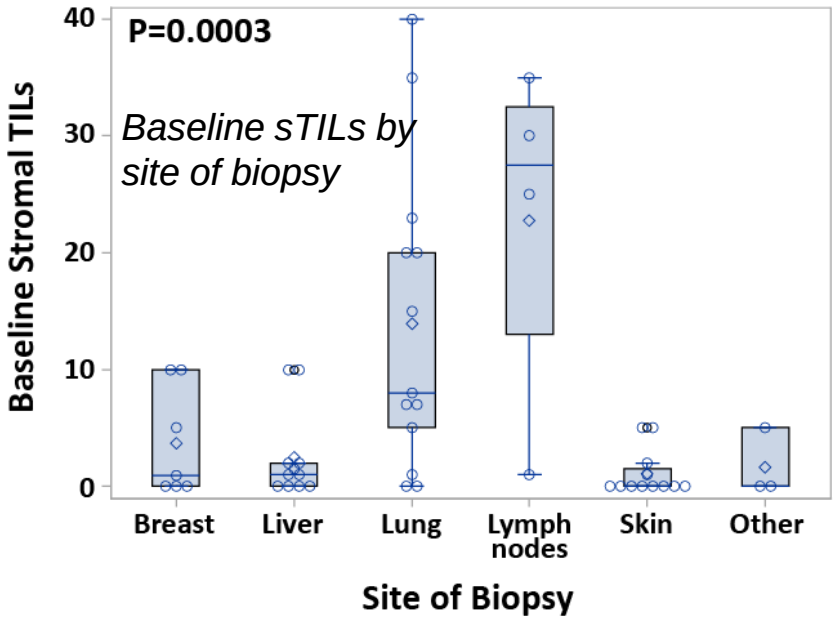
Genome-wide Circos plots
of somatic rearrangements

Stephens, PJ et al. Nature 462:1005-12, 2009.

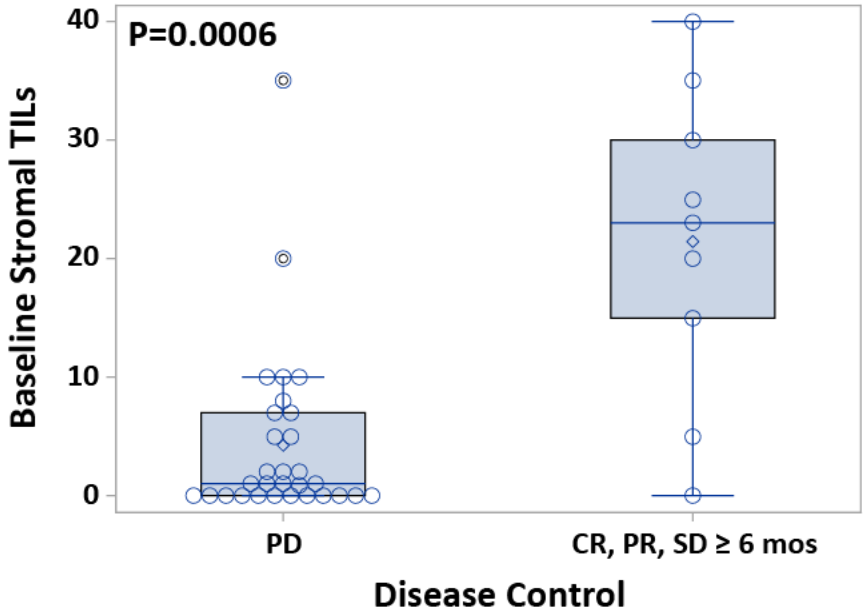
Panacea: Phase Ib/II Trial of Pembrolizumab and Trastuzumab

Loi et al., 2017 San Antonio Breast Cancer Symposium (Abstract GS2-06).

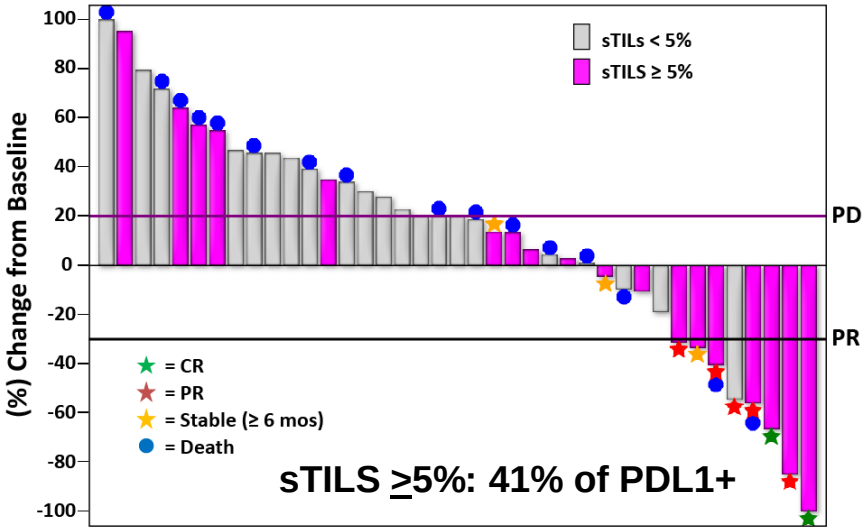




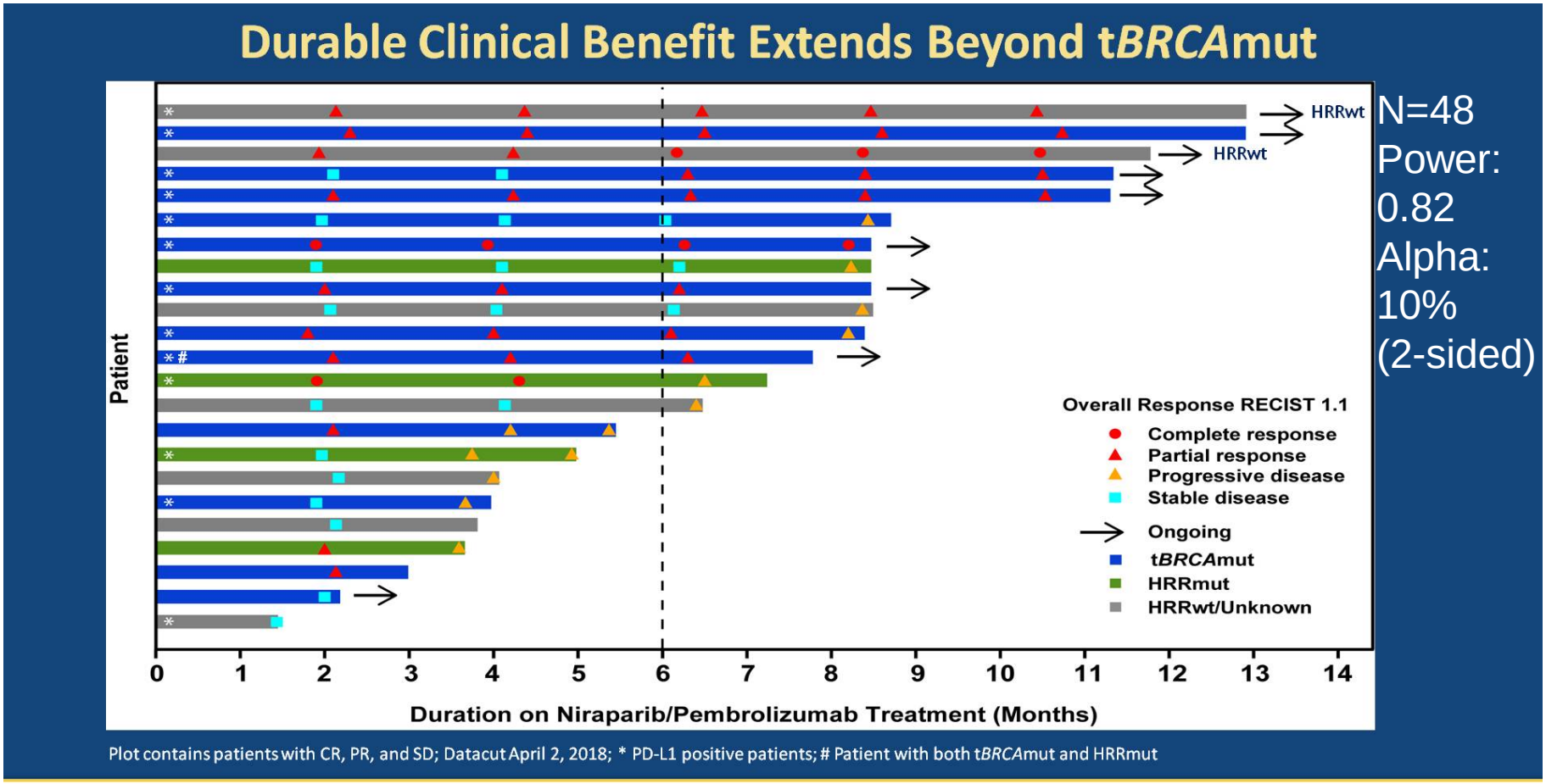
- *Baseline sTILs and DCR*



sTILs ≥ 5% as Potential Predictive Marker: PD-L1 Positive Cohort



TOPACIO: Phase II Trial of Niraparib and anti-PD-1 combination in metastatic TNBC (≤ 2 prior lines cytotoxic treatment for MBC)



N=48
Power: 0.82
Alpha: 10% (2-sided)

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Shaveta Vinayak, MD, MS

10

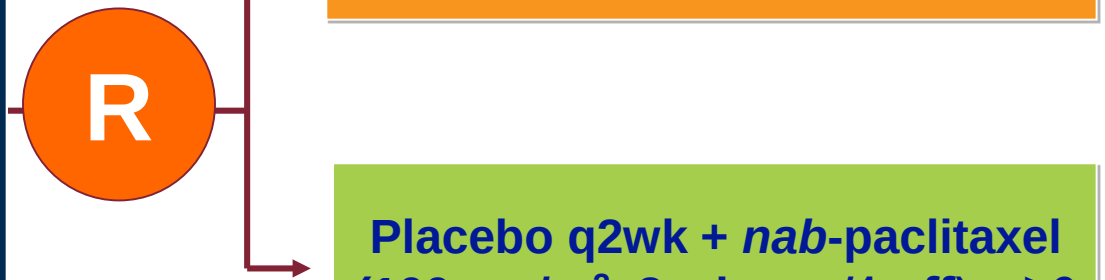
Prior platinum allowed if no progression while on or within 8 weeks of last platinum

IMpassion130: Phase III Randomized Trial of Atezolizumab with *Nab*-Paclitaxel for 1st-line Metastatic Triple-Negative Breast Cancer (mTNBC)

Target Accrual: 900 (completed)

Eligibility

- Locally advanced, measurable TNBC or mTNBC
- No prior systemic therapy for advanced TNBC
- ECOG PS 0-1
- No history of autoimmune disease



Primary Endpoints: PFS, OS

Stratification: Liver metastases; prior taxane; PD-L1 status

www.clinicaltrials.gov, September 2016. Identifier: NCT02425891
Emens LA et al. *Proc ASCO* 2016;Abstract TPS1104.

Media Release Basel, 02 July 2018:
Phase III IMpassion130 study showed Roche's Atezolizumab plus Albumin-bound paclitaxel significantly reduced the risk of disease worsening or death in people with metastatic triple negative breast cancer

- First Phase III immunotherapy study to demonstrate a statistically significant improvement in progression-free survival (PFS) in the intention-to-treat (ITT) and PD-L1 positive first-line metastatic triple negative breast cancer (TNBC) populations
- Encouraging overall survival (OS) benefit for PD-L1 positive population at interim analysis
- Data will be submitted to health authorities globally, including the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)

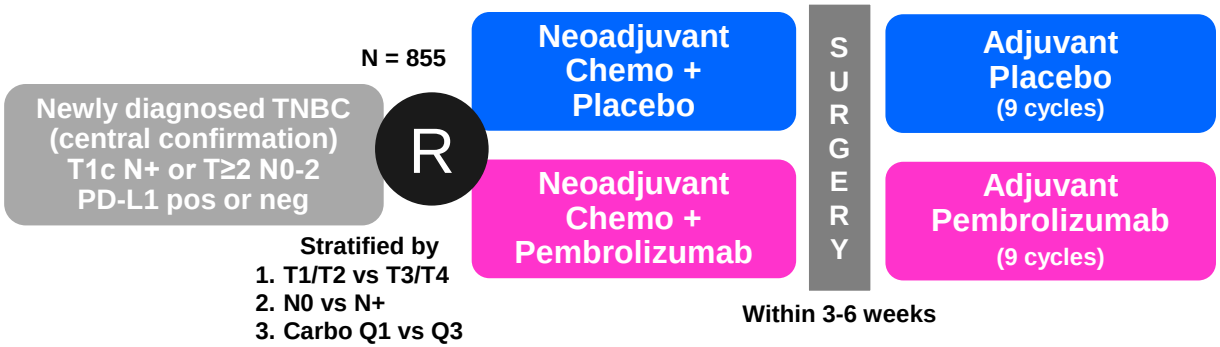
I-SPY 2 Trial: Paclitaxel vs. Paclitaxel + Pembro

Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	**> 99%**	**99%**
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	**>99%**	**>99%**
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	**>99%**	**88%**

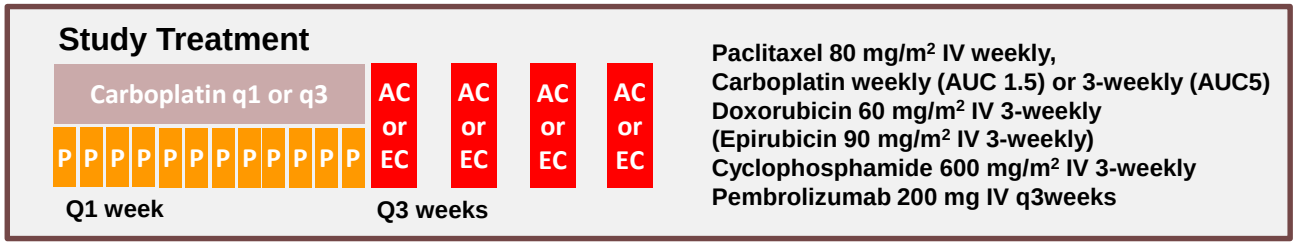
Nanda et al, ASCO 2017

Neoadjuvant Studies – KEYNOTE 522

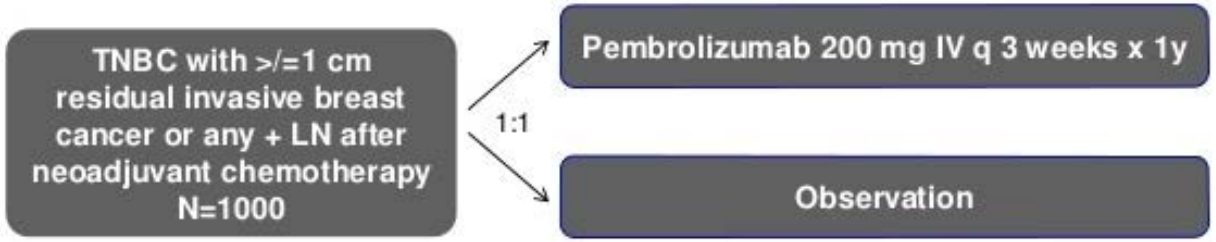


Primary Endpoints:
- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary Endpoints:
- Alternative pCR rate (ypT0 ypN0)
- pCR rate in PD-L1+
- EFS in PD-L1+
- OS



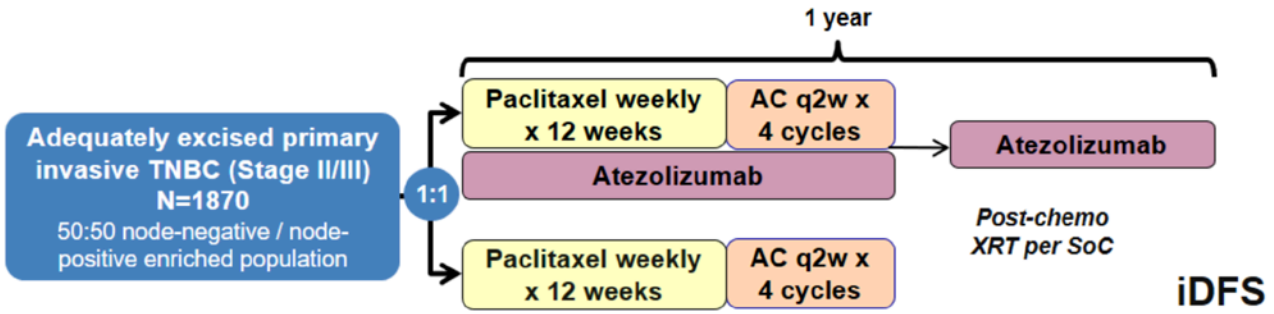
Post NAC residual disease: SWOG 1418



- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

IMpassion030: Phase III randomized, open label adjuvant TNBC trial (Alliance/BIG)



Stratification factors:

- Axillary nodal status (0 vs. 1-3 vs. ≥4 positive lymph nodes)
- Surgery (breast conserving vs mastectomy)
- PD-L1 IC0 vs IC1/2/3

Primary endpoint:

- iDFS in ITT

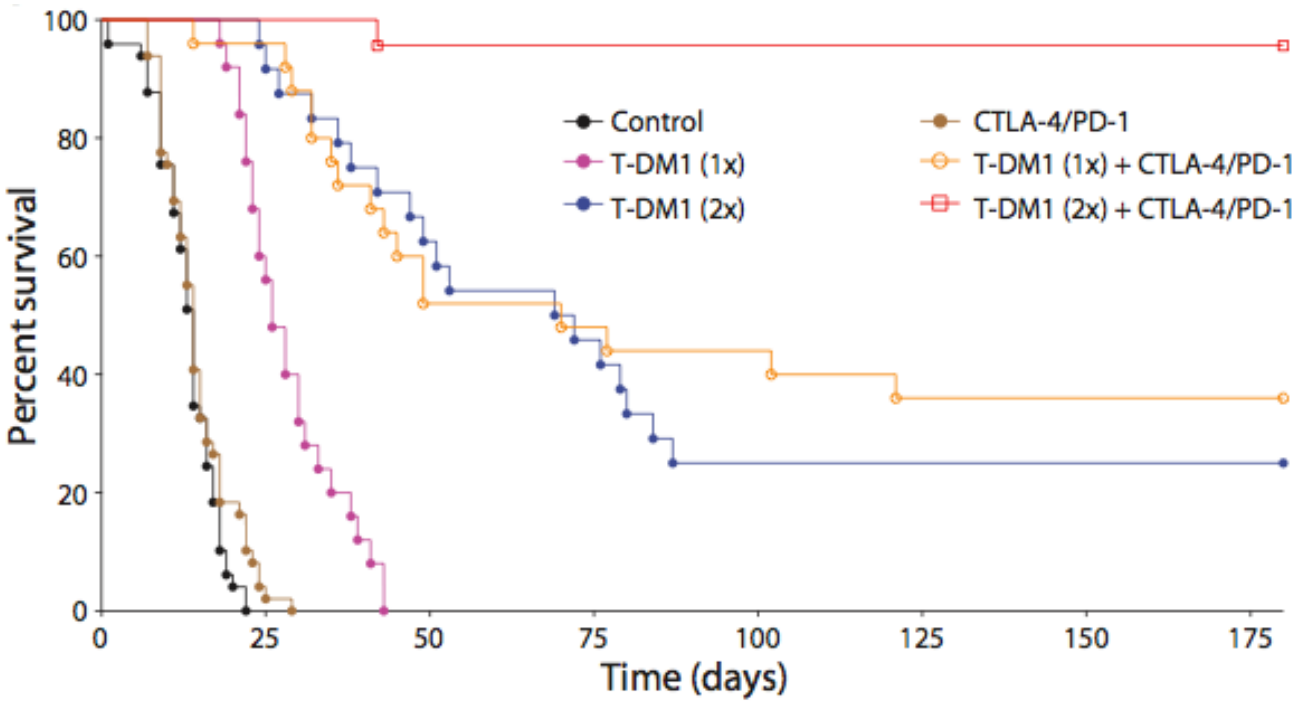
Assumptions:

- iDFS HR=0.75
- 3-yr iDFS +4.4% *(81% ➔ 85.4%)*
- 80% power, alpha =5% (two sided)

Secondary endpoints:

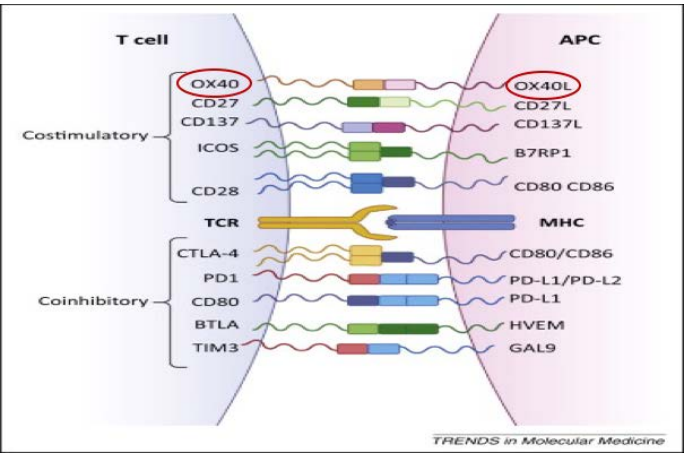
- iDFS PD-L1 IC1/2/3
- OS
- Recurrence-free interval (RFI)
- Distant RFI
- Safety
- Health-related QoL

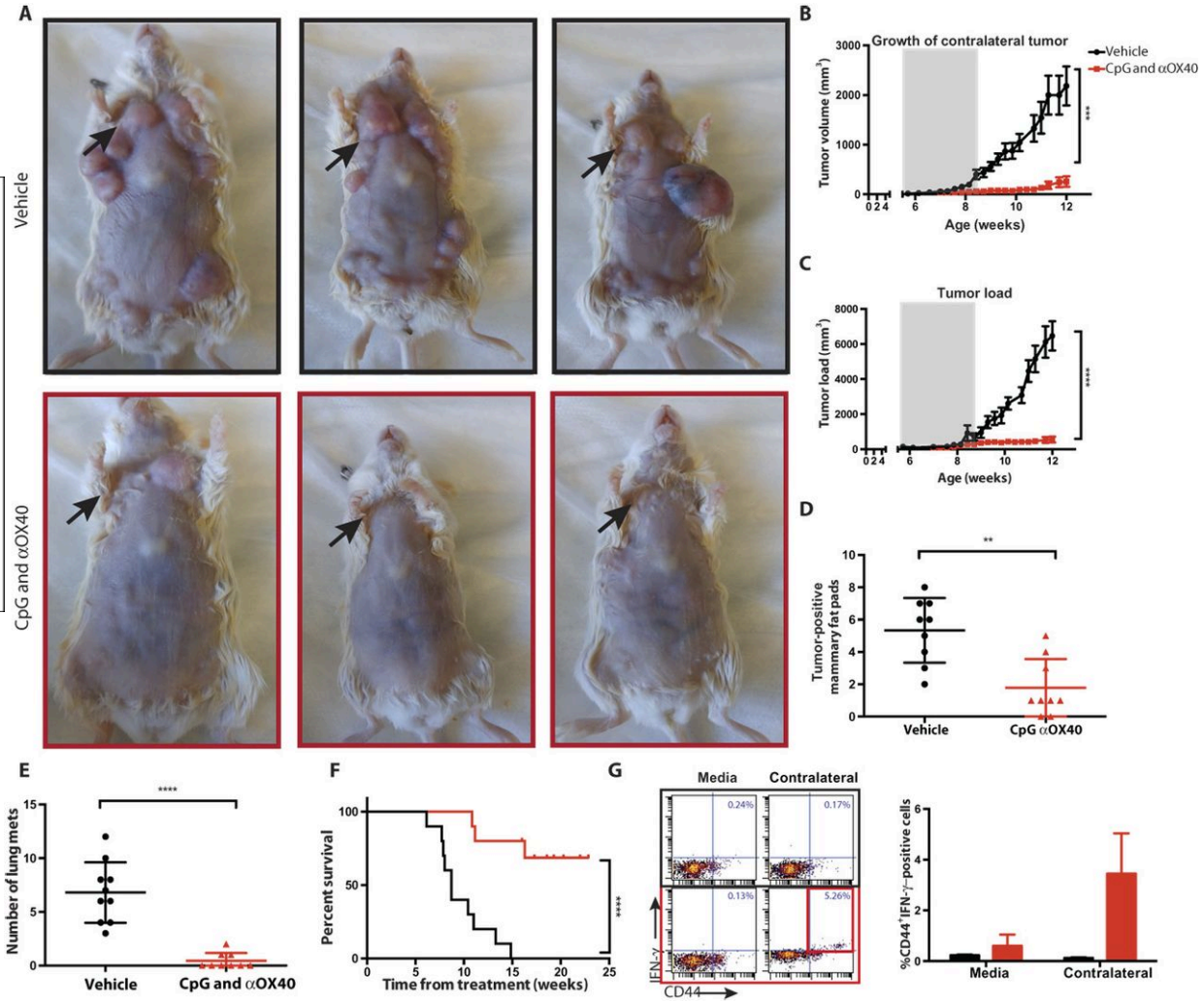
Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade



Muller P, et al., Science Translational Medicine November 2015 Vol 7 Issue 315 315ra188

In situ vaccination with CpG and anti-OX40 is therapeutic in a spontaneous tumor model





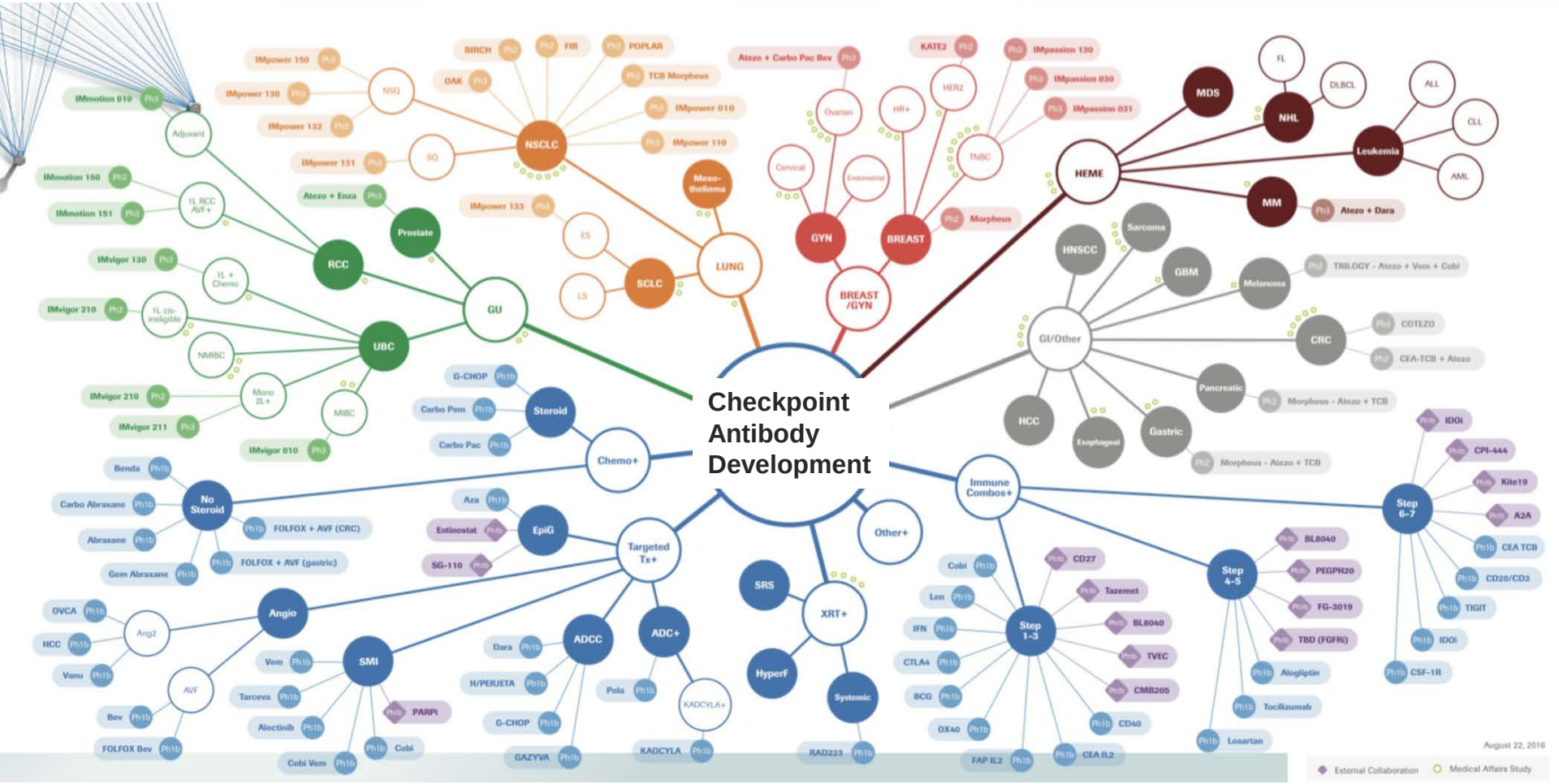
Idit Sagiv-Barfi et al., Sci Transl Med 2018;10:eaan4488

Published by AAAS

The Challenge of I/O Development:

- **Cancer and the immune system have a close and dynamic relationship**
- **The immune response and its modulation is probably most relevant in genetically unstable tumors**
- **Ideal schedule and duration of therapy?**
- **Biomarker(s) for patient selection?**
- **Optimal combinations and duration of treatment?**
- **Mechanisms of resistance?**
- **Managing toxicity?**

Development "Strategy" from a Single Sponsor for a Checkpoint MAb



I/O approaches litter the clinical trial landscape, but few have strong scientific rationale, and fewer still feature serial tumor tissue sample acquisition to begin to better understand dynamics of inflammatory cell infiltration into the tumor microenvironments


Questions/Comments
Discussion
Criticism
Debate
James H. Clark Center
Stanford University
Stanford Bio-X Program:
Biology, Medicine, Chemistry,
Physics and Engineering