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Immunotherapy for Breast Cancer: Updates and New Directions

Honolulu, HI February 2023

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Fc Receptors Modulate Antitumor Activity of Trastuzumab
2023 = 25th Anniversary of 1st FDA Approval of Trastuzumab

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*)

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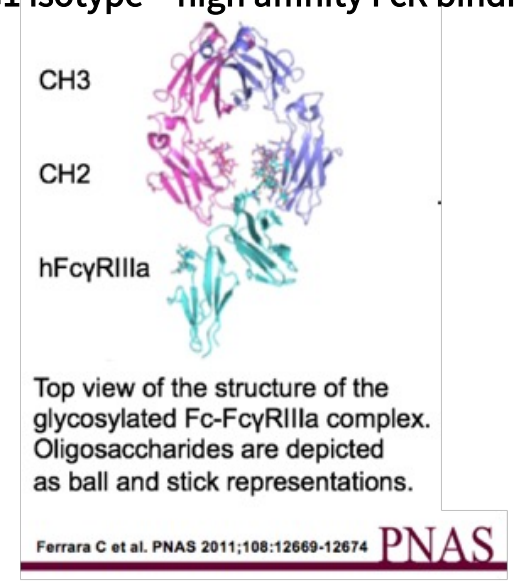
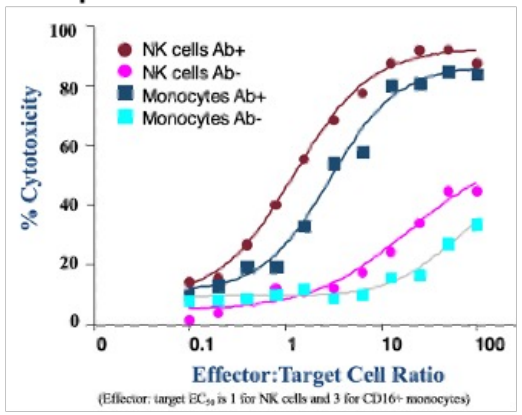
Communicated by Hilary Koprowski, January 16, 1992 (received for review February 15, 1991)

IgG1 isotype – high affinity FcR binding



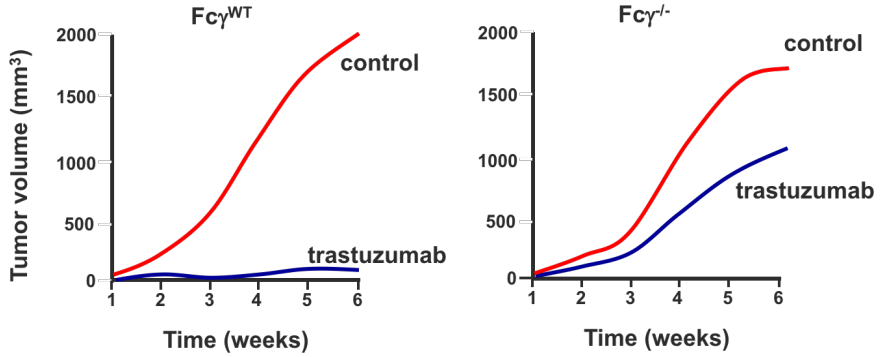
*ADCC = Antibody-Dependent Cell-mediated Cytotoxicity

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



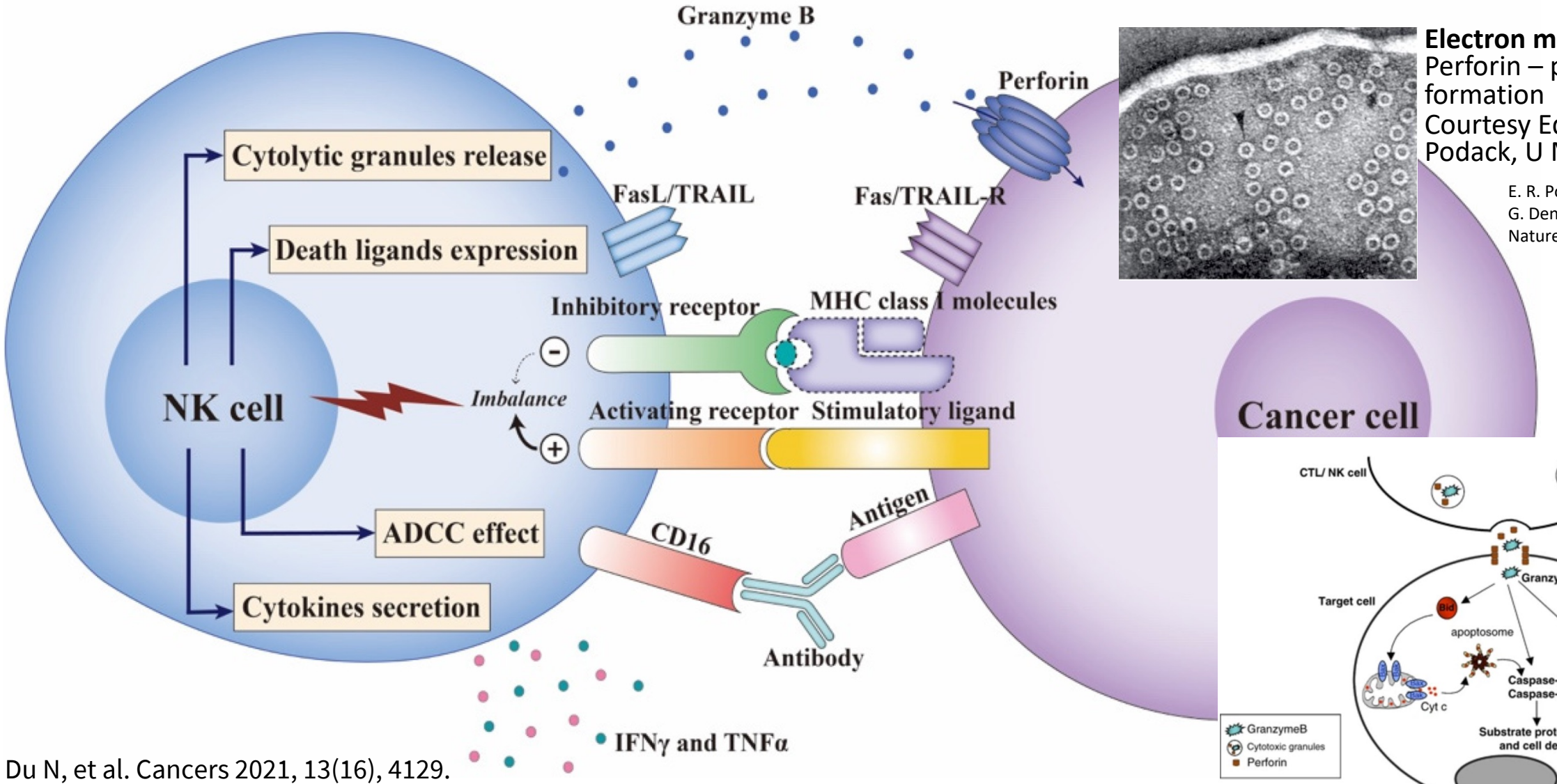
Pegram, et al., Proc Am Assoc Cancer Res 38: 602, 1997 (abstr 4044).

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

A specific function of NK cells in anti-cancer immunity is to exert ADCC by expressing CD16 to recognize antibody-coated cancer cells



Du N, et al. Cancers 2021, 13(16), 4129.

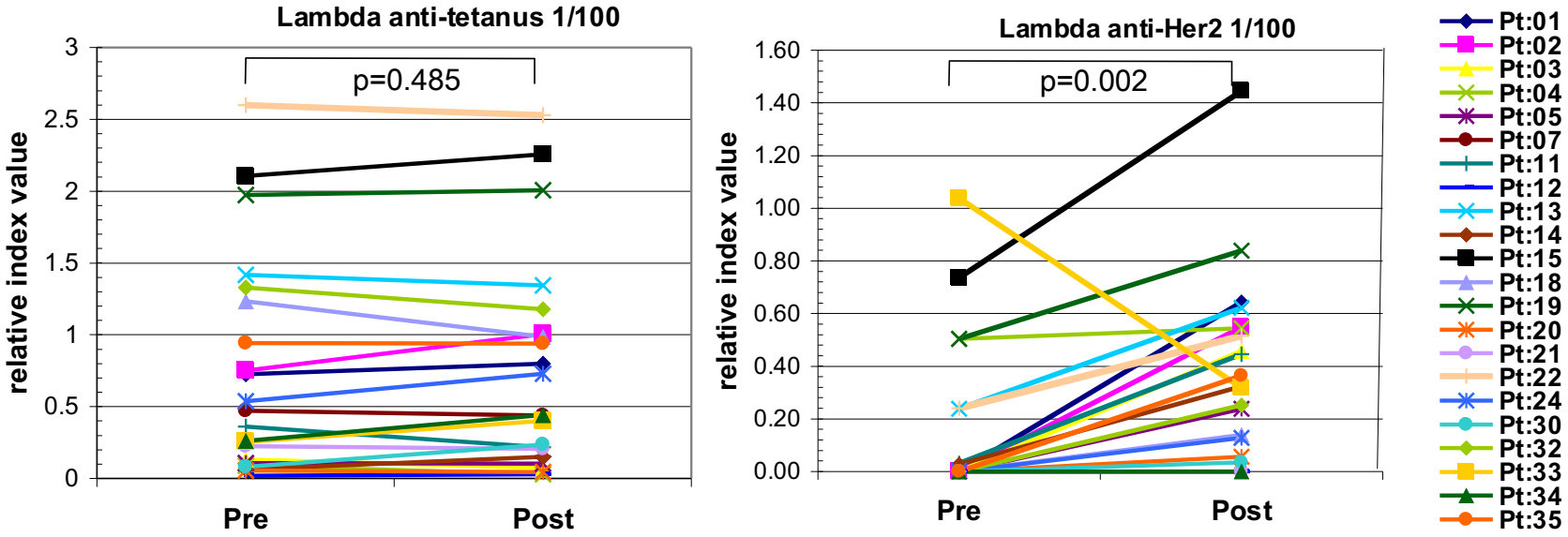
Activated NK cells rapidly synthesize and release cytolytic granules, perforin and granzymes, initiating cancer cell apoptosis

Electron microscopy
Perforin – pore formation
Courtesy Edgar Podack, U Miami

E. R. Podack and G. Dennert, 1983, Nature 301:442.

Cullen S, *et al. Cell Death Differ* **17**, 616–623 (2010).

Adaptive immune responses following trastuzumab: Patients develop increased anti HER2/neu Ig λ responses during trastuzumab therapy

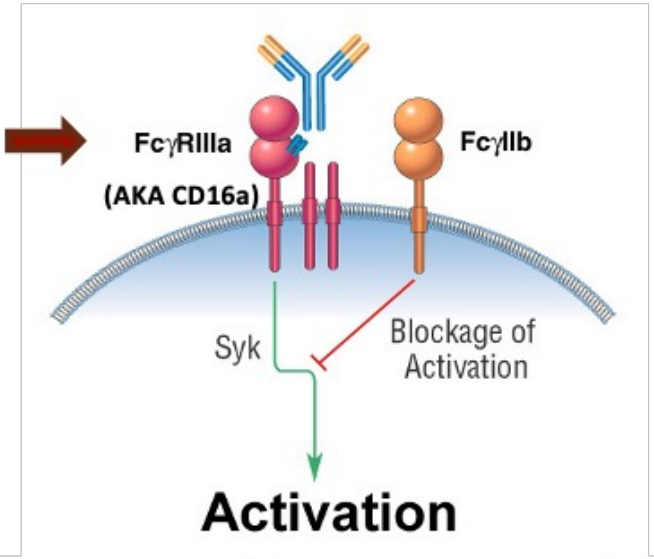


Those patients showing objective clinical responses exhibited more frequent (P = 0.004) and larger (P = 0.006) treatment-associated anti-HER-2/neu humoral responses. Also, augmented HER-2/neu-specific CD4 T-cell responses during therapy.

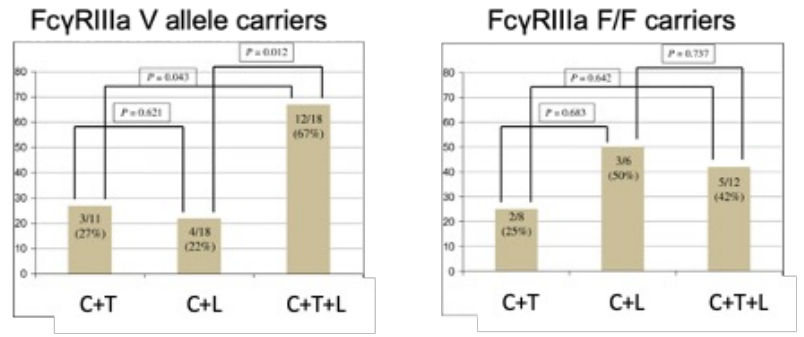
Taylor C, Hershman D, Shah N, Suciu-Foca N, Petrylak DP, Taub R, Vahdat L, Cheng B, Pegram M, Knutson KL, Clynes R. Clin Cancer Res. 2007 Sep 1;13(17):5133-43.

Improved Outcomes in Patients with High-binding FcR Alleles

FcγRIIIa amino acid # 158:
V/V = high affinity CD16a binding
F/F = lower affinity CD16a binding

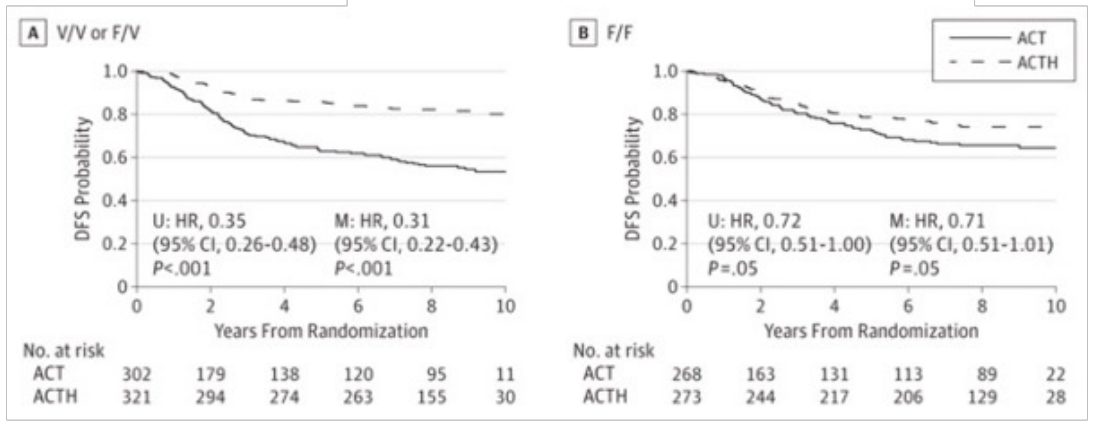


Pathological complete response (pCR) rate by treatment arm
CHER-LOB trial
Neoadjuvant



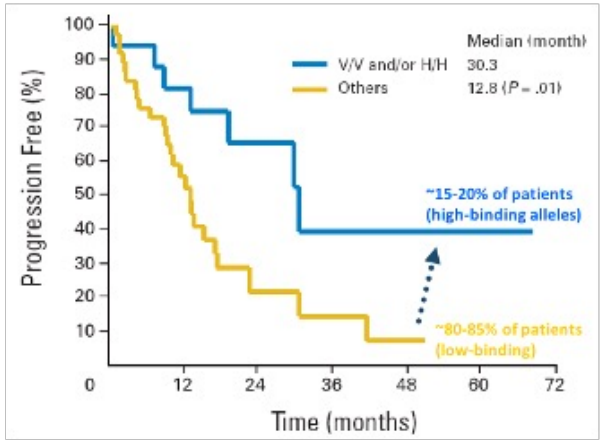
A Musolino, et al. The Pharmacogenomics Journal 16, 472–477 (2016).

NSABP B31
Adjuvant



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

Parma Data, MBC



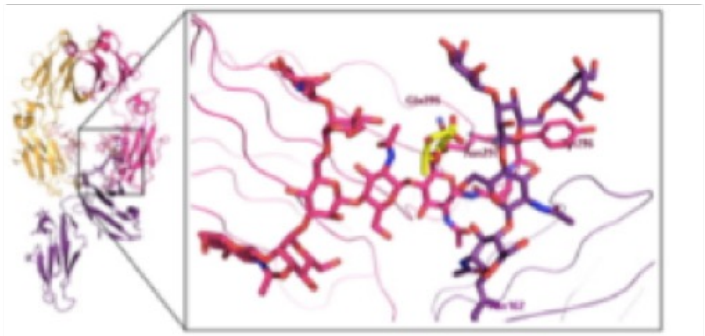
Musolino, A. et al. J Clin Oncol 26:1789-1796, 2008.

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

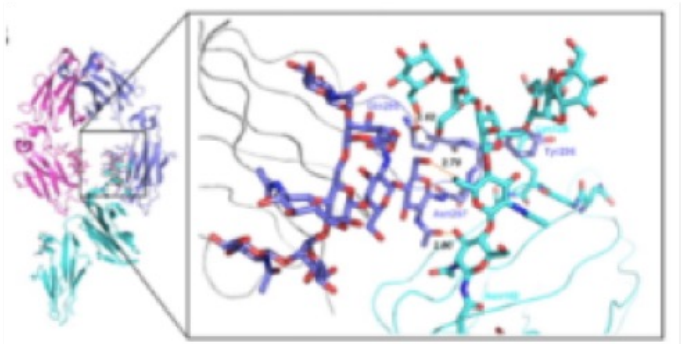
PRESENTED BY: M Pegram

Reviewed in: Musolino A,…Pegram MD. J Immunother Cancer. 2022 Jan;10(1):e003171.

NK Cell-Mediated Antibody-Dependent Cellular Cytotoxicity in Cancer Immunotherapy

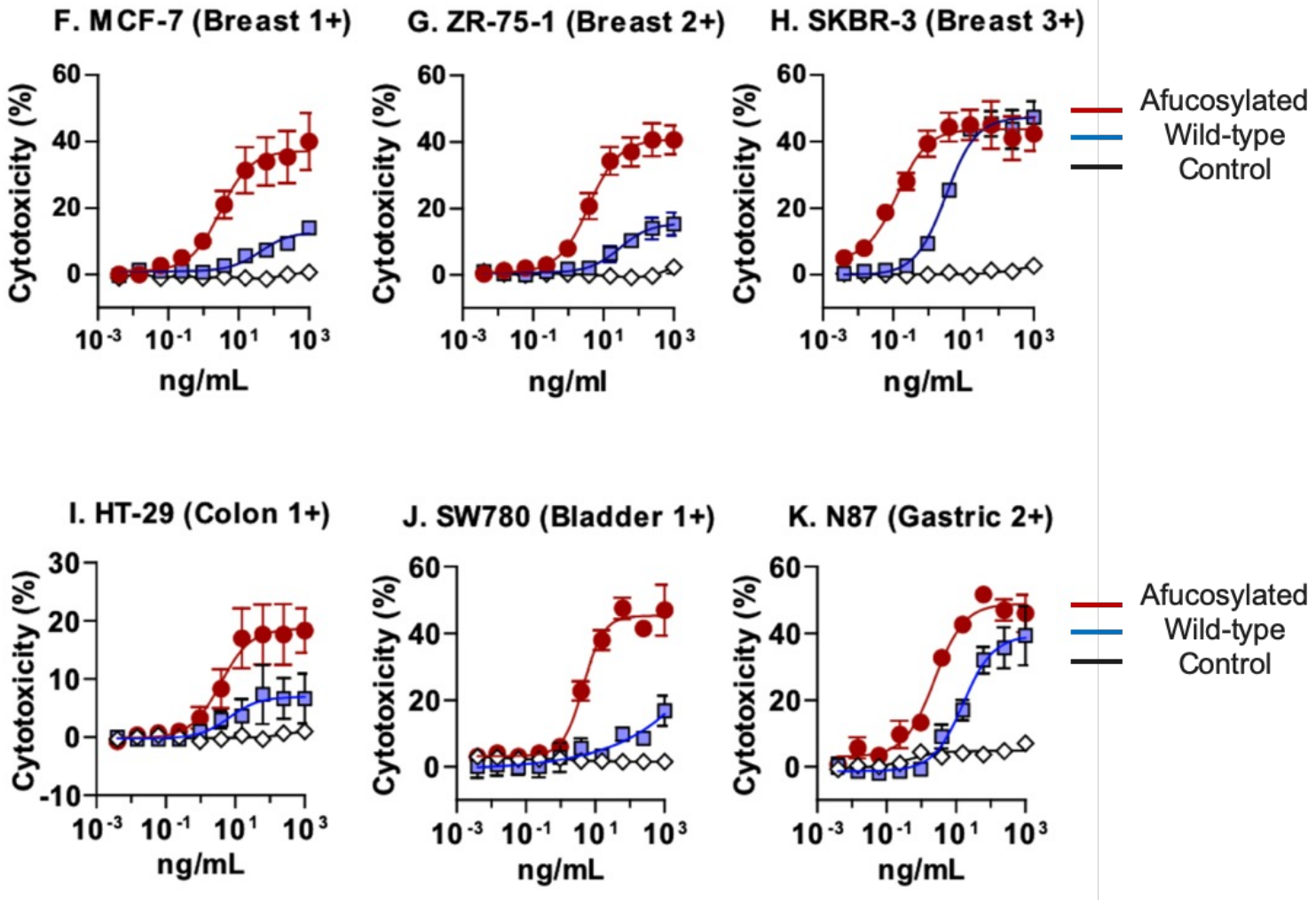


Fucosylated Fc fragment and glycosylated Fc receptor



Afucosylated Fc fragment (glycosylated Fc receptor)

Ferrara C et al. PNAS 2011;108:12669-12674

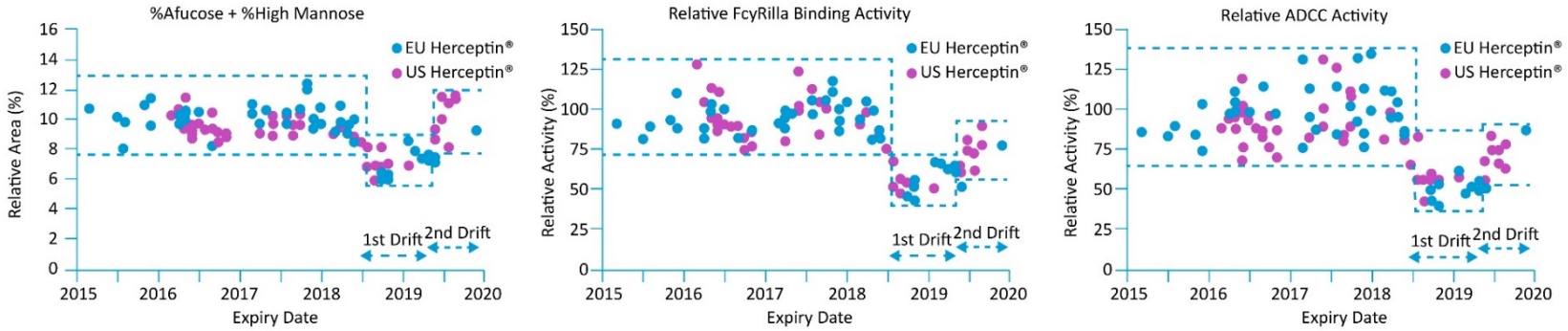


Nordstrom et al. Breast Cancer Research 2011, 13:R123.

Drift in Quality Profiles of Commercial Trastuzumab Associated with Clinical Outcome

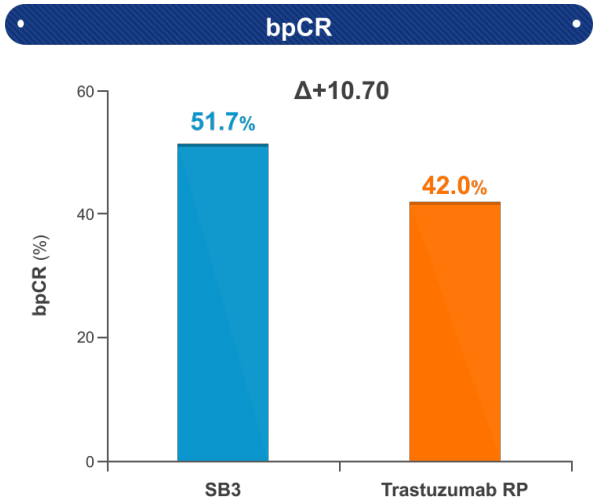
- Critical quality attributes of up to 103 Roche Trastuzumab lots marketed in the EU and the US were continually monitored for over 5 years by analyses[1]
- Changes in glycosylation, Fc receptor binding, and antibody-dependent cellular cytotoxicity (ADCC) activity were observed in lots manufactured during a select period of time[1]

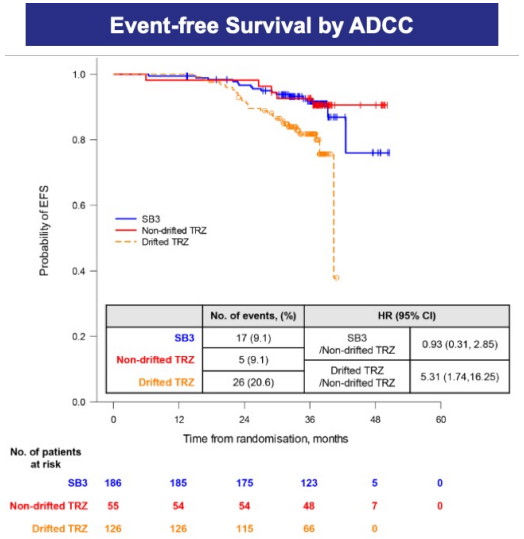
Drift in Glycosylation, Fc Receptor Binding, and ADCC of Trastuzumab Batches[1]



1. Kim S, et al. MAbs 2017;9(4): 704–714.

Three-year follow-up from a phase 3 study of SB3 (a trastuzumab biosimilar) versus trastuzumab in the neoadjuvant setting for HER2+ breast cancer.[2]

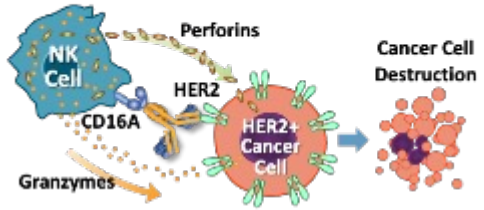




2. Pivot X, Pegram M, Cortes J, et al. Eur J Cancer. 2019 Oct;120:1-9.

Fc-Engineered HER2-Targeted Chimeric Monoclonal Antibody Margetuximab

Increased CD16A Affinity:
Enhanced Innate Immunity/More Potent ADCC Stimulation

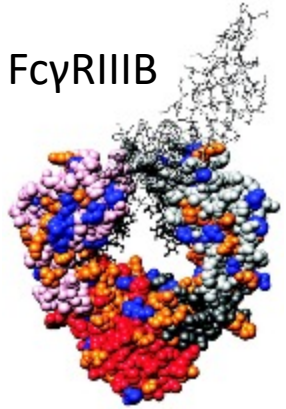


Musolino A, Gradishar WJ, Rugo HS, Nordstrom JL, Rock EP, Arnaldez F, Pegram MD. J Immunother Cancer. 2022 Jan;10(1):e003171.

Margetuximab: Increased affinity for activating Fcγ RIIIA (CD16A) and decreased affinity for inhibitory Fcγ RIIB (CD32B)

FcγRIIIB

IgG1 Fc



Co-crystal structure

Locations of Fc mutations (red, blue) identified by yeast surface display identify the variant F243L/R292P/Y300L/V305I/P396L

Stavenhagen. Cancer Res. 2007;67:8882.

SOPHIA:

HER2+ advanced BC with ≥ 2 previous anti-HER2 therapies; prior brain metastasis allowed if treated/stable

(N = 536)

Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy

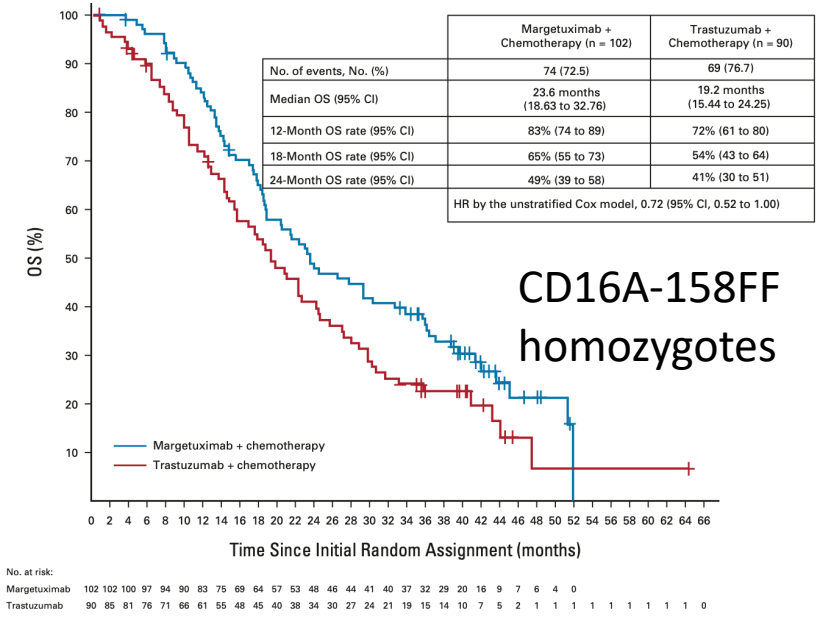
*Investigators choice of CT: capecitabine, eribulin, gemcitabine, or vinorelbine.

Sequential primary endpoint: PFS, OS
Secondary endpoints: ORR by central blinded analysis, investigator-assessed PFS
Tertiary and exploratory endpoints: investigator-assessed CBR, DoR, safety, effect of CD16A, CD32A, and CD32B alleles on margetuximab efficacy

Safety: ↑ in IRR, 14.4% vs 3.8%

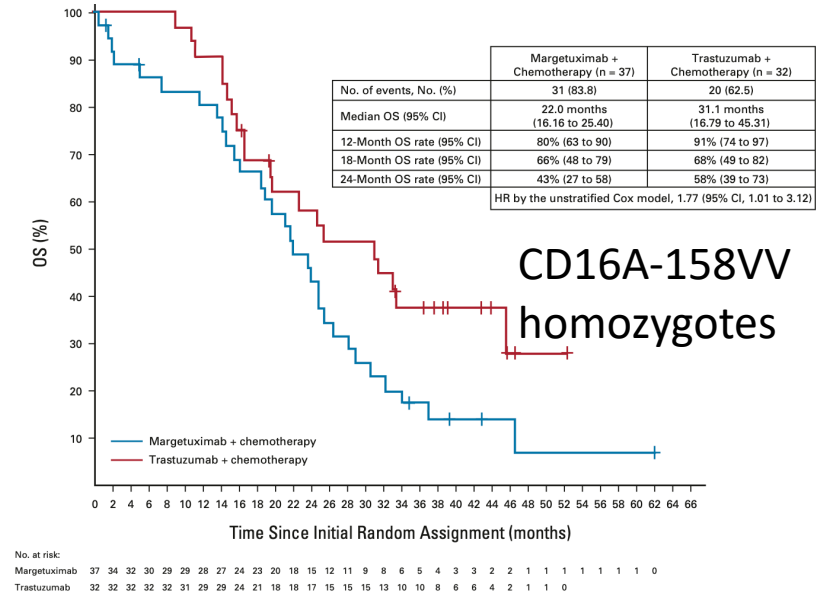
CD16A Genotype by Treatment Group

Prespecified Exploratory OS Analysis



	Margetuximab + Chemotherapy (n = 102)	Trastuzumab + Chemotherapy (n = 90)
No. of events, No. (%)	74 (72.5)	69 (76.7)
Median OS (95% CI)	23.6 months (18.63 to 32.76)	19.2 months (15.44 to 24.25)
12-Month OS rate (95% CI)	83% (74 to 89)	72% (61 to 80)
18-Month OS rate (95% CI)	65% (55 to 73)	54% (43 to 64)
24-Month OS rate (95% CI)	49% (39 to 58)	41% (30 to 51)
HR by the unstratified Cox model, 0.72 (95% CI, 0.52 to 1.00)		

CD16A-158FF homozygotes

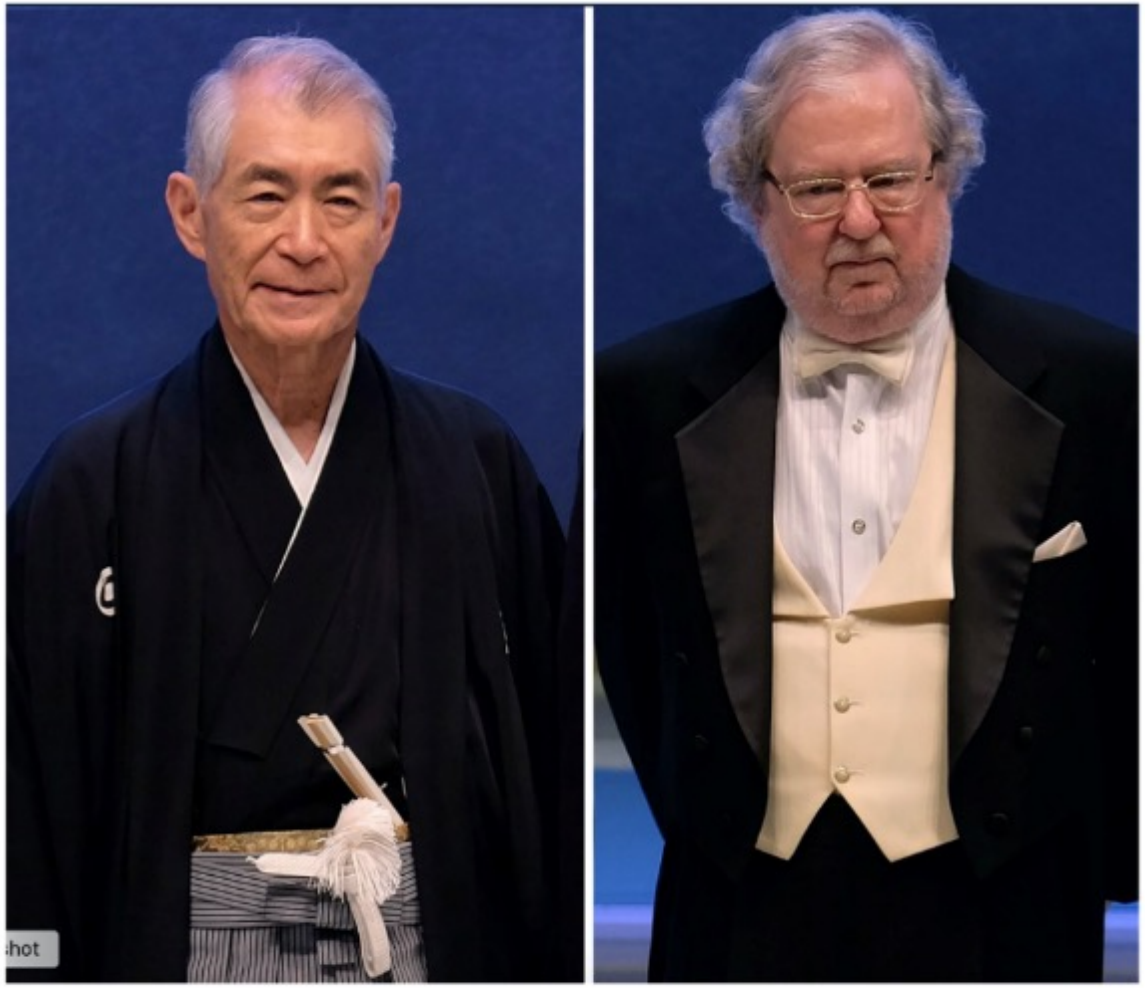


	Margetuximab + Chemotherapy (n = 37)	Trastuzumab + Chemotherapy (n = 32)
No. of events, No. (%)	31 (83.8)	20 (62.5)
Median OS (95% CI)	22.0 months (16.16 to 25.40)	31.1 months (16.79 to 45.31)
12-Month OS rate (95% CI)	80% (63 to 90)	91% (74 to 97)
18-Month OS rate (95% CI)	66% (48 to 79)	68% (49 to 82)
24-Month OS rate (95% CI)	43% (27 to 58)	58% (39 to 73)
HR by the unstratified Cox model, 1.77 (95% CI, 1.01 to 3.12)		

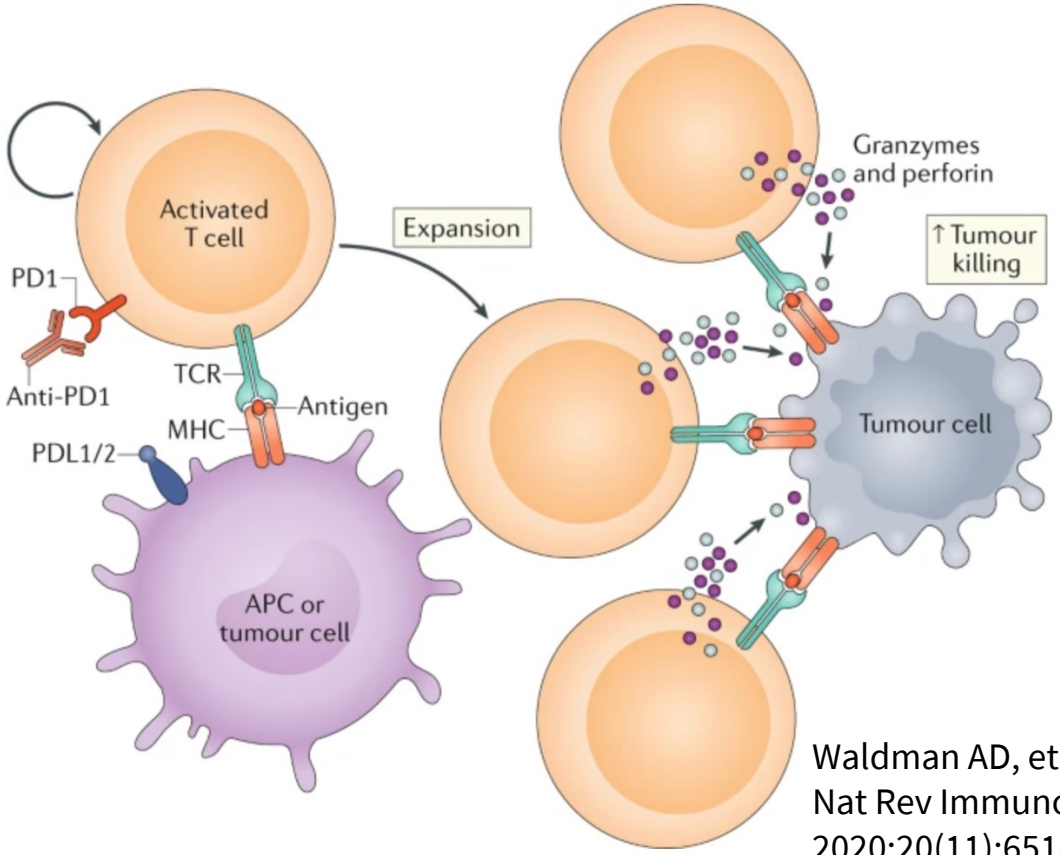
CD16A-158VV homozygotes

Rugo HS, et al. J Clin Oncol. 2023 Jan 10;41(2):198-205.

Nobel Prize in Medicine (2018) – Immune checkpoint blockade



Tasuku Honjo and James Allison



Waldman AD, et al. Nat Rev Immunol. 2020;20(11):651-668.

1. Huang P-W and Chang J W-C. *Biomed J.* 2019;42(5):299–306. 2. Cogdill AP, et al. *Br J Cancer.* 2017;117(1):1–7

Summary of Randomized, Phase 3, Double-Blind, Placebo-Controlled Chemoimmunotherapy Trials in Previously Untreated Metastatic Triple-Negative Breast Cancer

Trial	RR	Patients randomly assigned, N	PD-L1+, %	Treatment	ORR, %	Median PFS in PD-L1+, months	Median OS in PD-L1+, months
IMpassion130	1:1	902	41%	Atezolizumab + nab-paclitaxel vs control (placebo + nab-paclitaxel)	58.9 vs 42.6 $P = .0016$	7.5 vs 5.0 HR 0.62, 95% CI [0.49, 0.78]; $P < .001$	25.4 vs 17.9 HR 0.67, 95% CI [0.53, 0.86]; $P = .0016$
IMpassion131	2:1	651	45%	Atezolizumab + paclitaxel vs control (placebo + paclitaxel)	63.4 vs 55.4 $P = .18$*	6.0 vs 5.7 HR 0.82, 95% CI [0.6, 1.12]; $P = .20$	22.1 vs 28.3 HR 1.11, 95% CI [0.76, 1.64]; $P = .58$*
KEYNOTE-355	2:1	847	38% CPS ≥ 10)	Pembrolizumab + chemotherapy† vs control (placebo + chemotherapy)†	52.7 vs 40.8 $P =$ not available	9.7 vs 5.6 HR 0.65, 95% CI [0.49, 0.86]; $P = .0012$	23.0 vs 16.1 HR 0.73, 95% CI [0.55, 0.95]; $P = .0093$

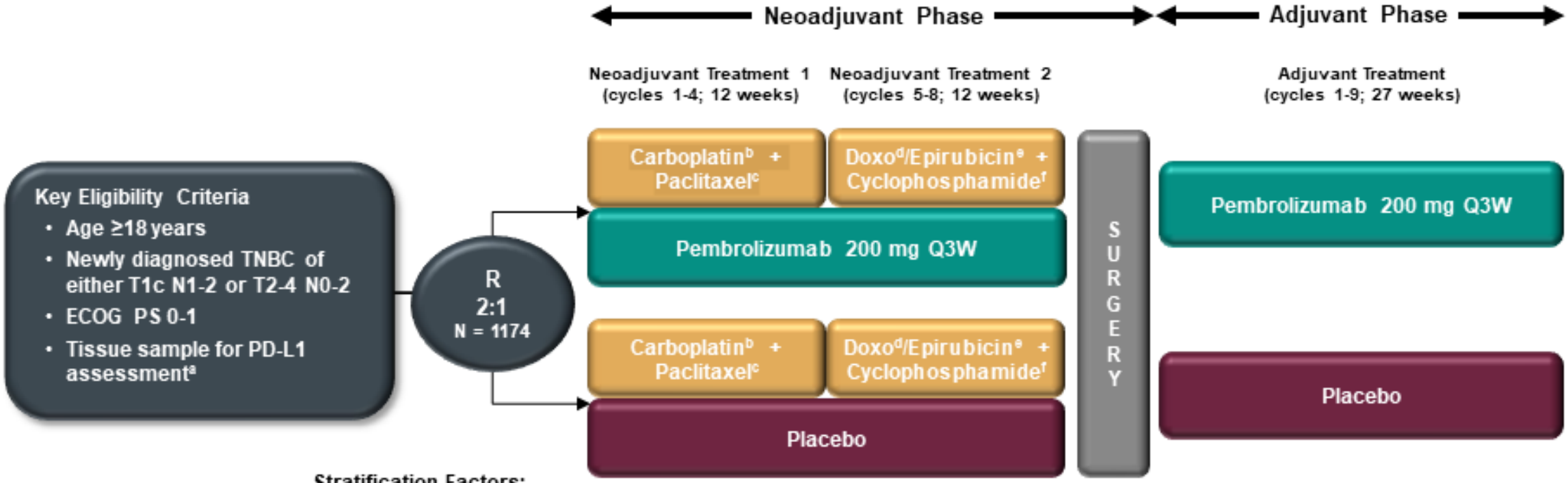
Abbreviations: CPS, combined positive score; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RR, randomization ratio.

*Not formally tested.

†Investigator's choice: nab-paclitaxel, paclitaxel, or gemcitabine and carboplatin.

Antoinette Tan. ASCO Daily News, February 23, 2022.

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

P Schmid, et al. N Engl J Med 2022; 386:556-567.

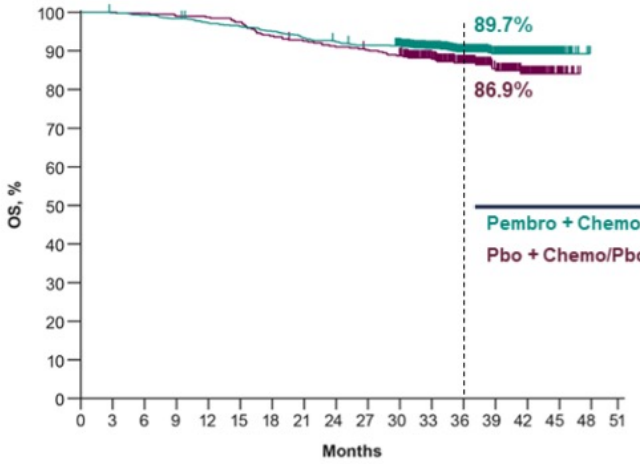
On July 26, 2021, the Food and Drug Administration approved pembrolizumab for high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

ESMO VIRTUAL PLENARY

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

Schmid KN522 ESMO Virtual Plenary 2021

Overall Survival



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

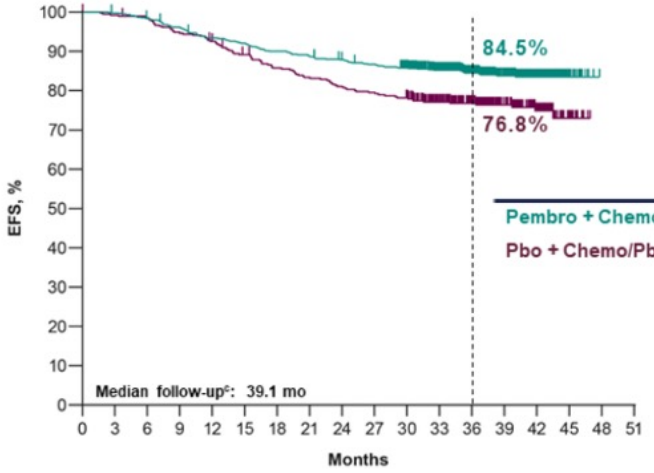
No. at Risk

Pembro + Chemo/Pembro	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Pbo + Chemo/Pbo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00086 not reached at this analysis.
Data cutoff date: March 23, 2021.

Schmid KN522 ESMO Virtual Plenary 2021

Statistically Significant and Clinically Meaningful EFS at IA4



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

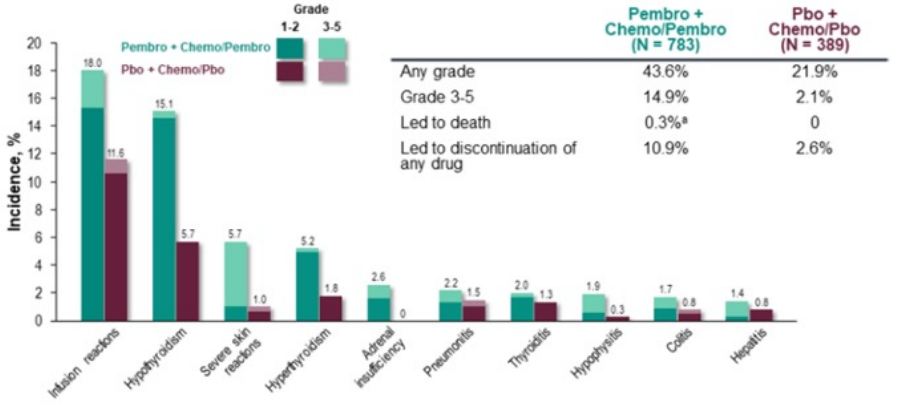
No. at Risk

Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Schmid KN522 ESMO Virtual Plenary 2021

Immune-Mediated AEs and Infusion Reactions in Combined Phases



	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

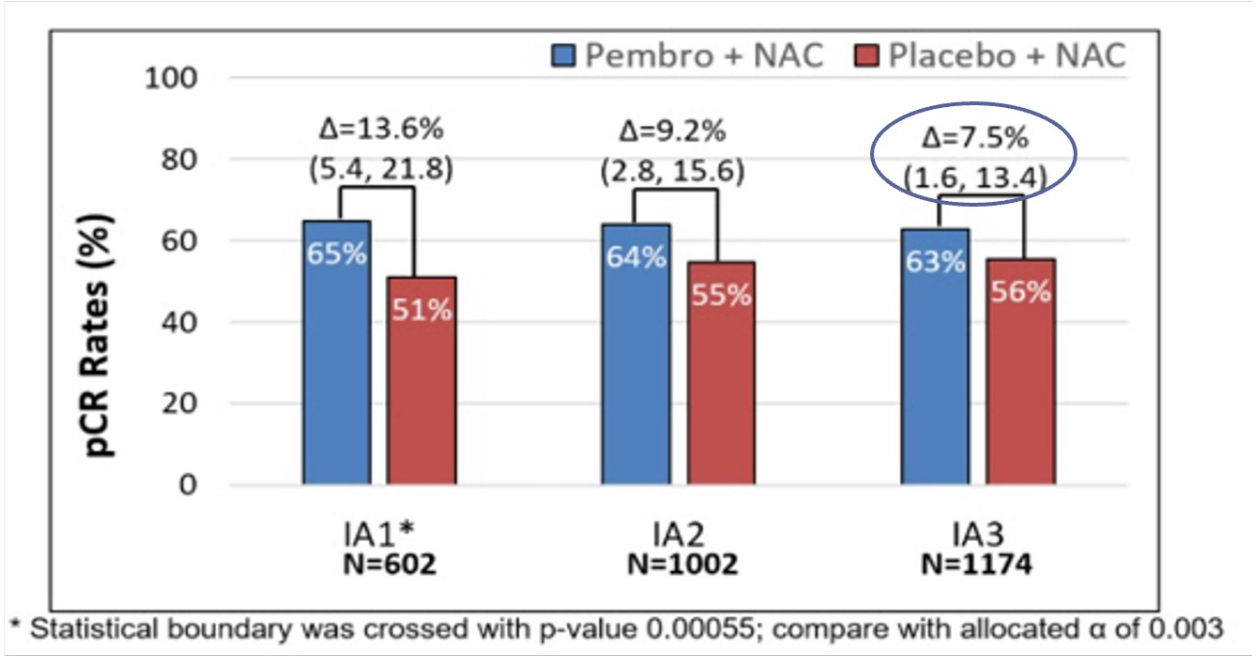
[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: March 23, 2021.

P Schmid, et al. N Engl J Med 2022; 386:556-567.

KEYNOTE-522: PCR

pCR: PD-L1 did not predict benefit to therapy

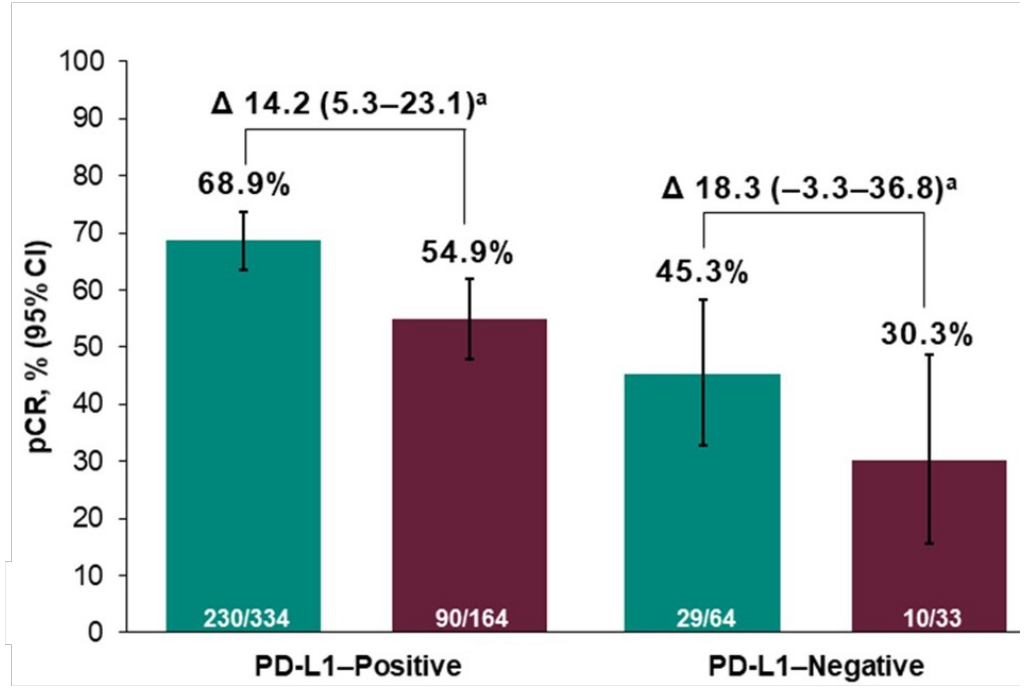
pCR across Interim analyses*



* Statistical boundary was crossed with p-value 0.00055; compare with allocated α of 0.003

*FDA ODAC meeting, 02/09/21

pCR by PD-L1 Status



Dent. ESMO Asia 2020. Abstr 10. Schmid. NEJM. 2020;382:810.

“Concordance” of Programmed Death-Ligand 1 Expression between SP142 and 22C3/SP263 Assays in Triple-Negative Breast Cancer

Journal of Breast Cancer JBC

Programmed Death-Ligand 1 SP142 Assay in Triple-Negative Breast Cancer

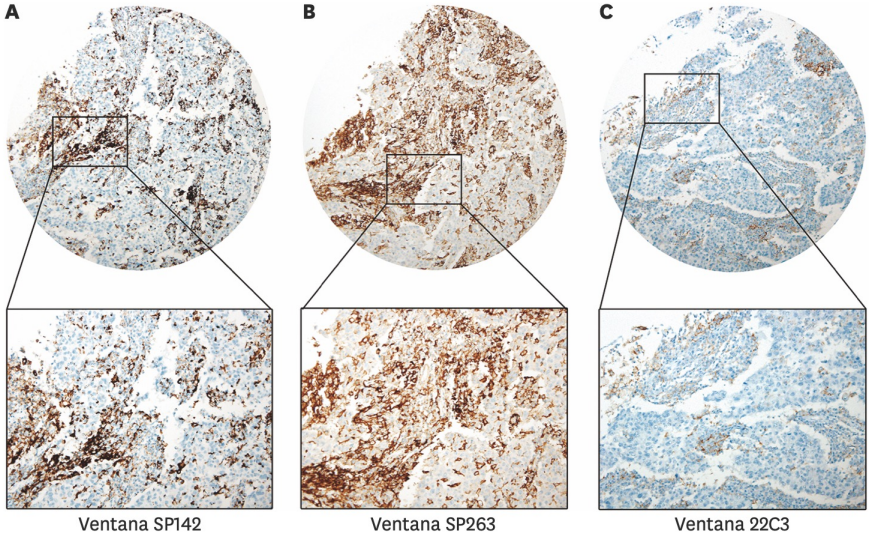
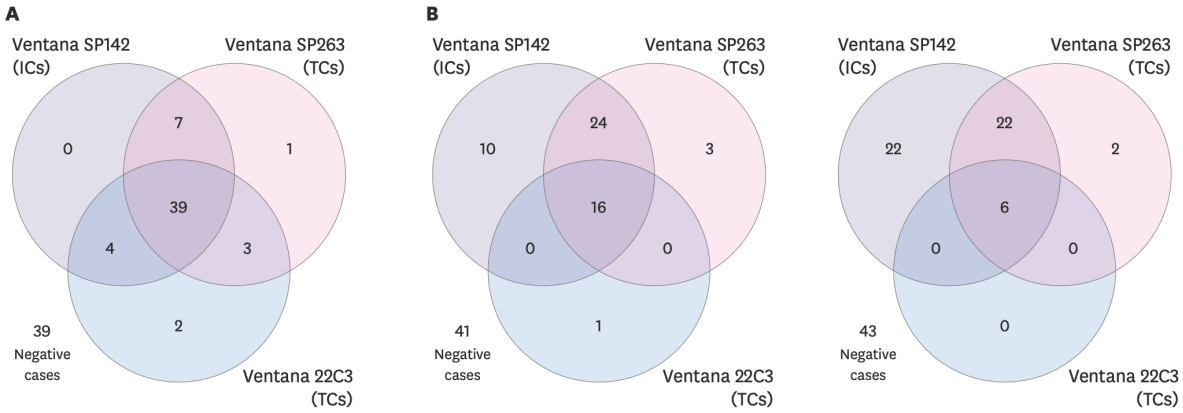


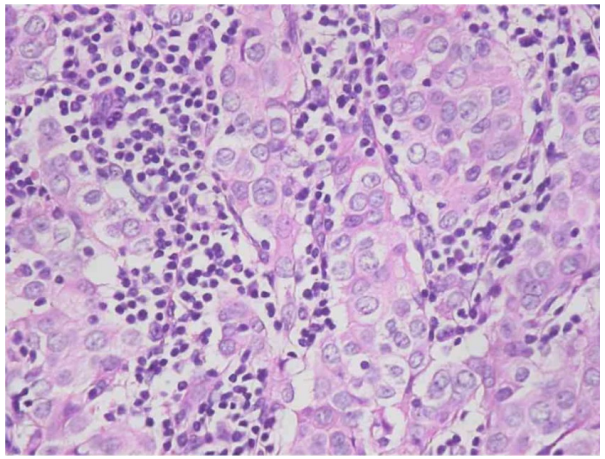
Figure 1. Representative IHC image of the same TMA core stained with 3 PD-L1 assays. (A) An SP142 assay on the Ventana platform showed prominent granular staining in infiltrating immune cells (IHC staining, 20× magnification). (B) An SP263 assay on the Ventana platform showed membranous staining in TCs (IHC staining, 20× magnification). (C) A 22C3 assay on the Ventana platform showed membranous staining in TCs (IHC staining, 20× magnification).
IHC = immunohistochemistry; TMA = tissue microarray; PD-L1 = programmed death-ligand 1; TC = tumor cell.



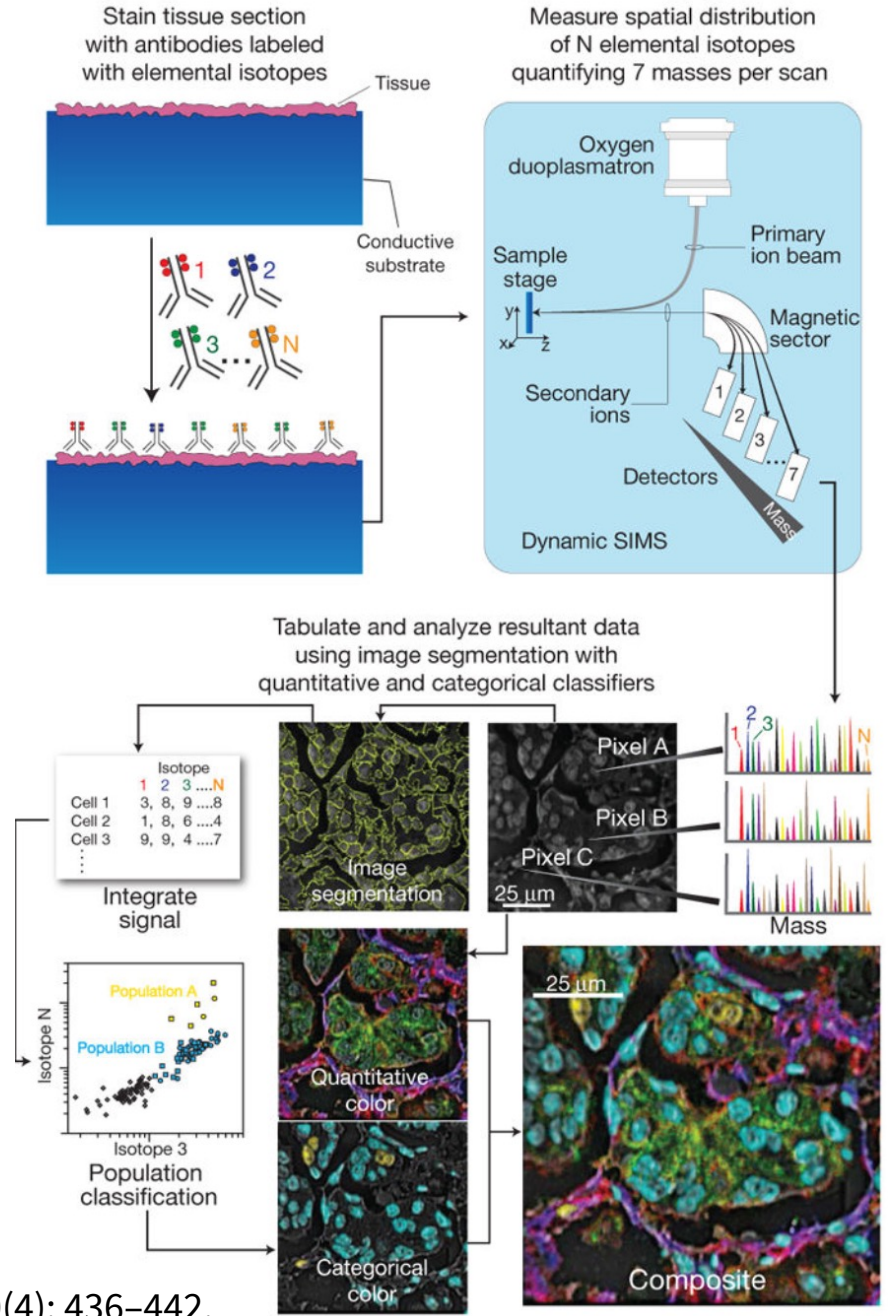
Venn diagram representing the concordance or discordance between the SP142 assay (≥ 1% of immune cells) and the 22C3/SP263 assays. (A) 22C3/SP263 assays at a 1% cut-off value, (B) 22C3/SP263 assays at a 5% cut-off value, (C) 22C3/SP263 assays at a 10% cut-off value.

Lee SE, et al. J Breast Cancer. 2020 Jun;23(3):303-313.

Multiplexed ion beam imaging (MIBI) of human breast tumors



H&E – TILs in breast CA



Multiplexed ion beam imaging (MIBI) is capable of analyzing up to 100 targets simultaneously over a five-log dynamic range. Here, we used MIBI to analyze formalin-fixed, paraffin-embedded (FFPE) human breast tumor tissue sections. The resulting data suggest that MIBI will provide new insights by integrating tissue microarchitecture with highly multiplexed protein expression patterns, and will be valuable for basic research, drug discovery and clinical diagnostics.

Angelo M, et al. Nat Med. 2014 April ; 20(4): 436–442.

Stanford University

NeoTRIP trial results and sample collection

OFFICIAL best of SABCS

Multiplexed ion beam imaging (MIBI) of human breast tumors

Angelo M, et al. Nat Med. 2014 April ; 20(4): 436–442.

TN high-risk **(T1cN1; T2N1; T3N0)** or locally advanced ***N=280***

R

Carboplatin+*nab*-paclitaxel

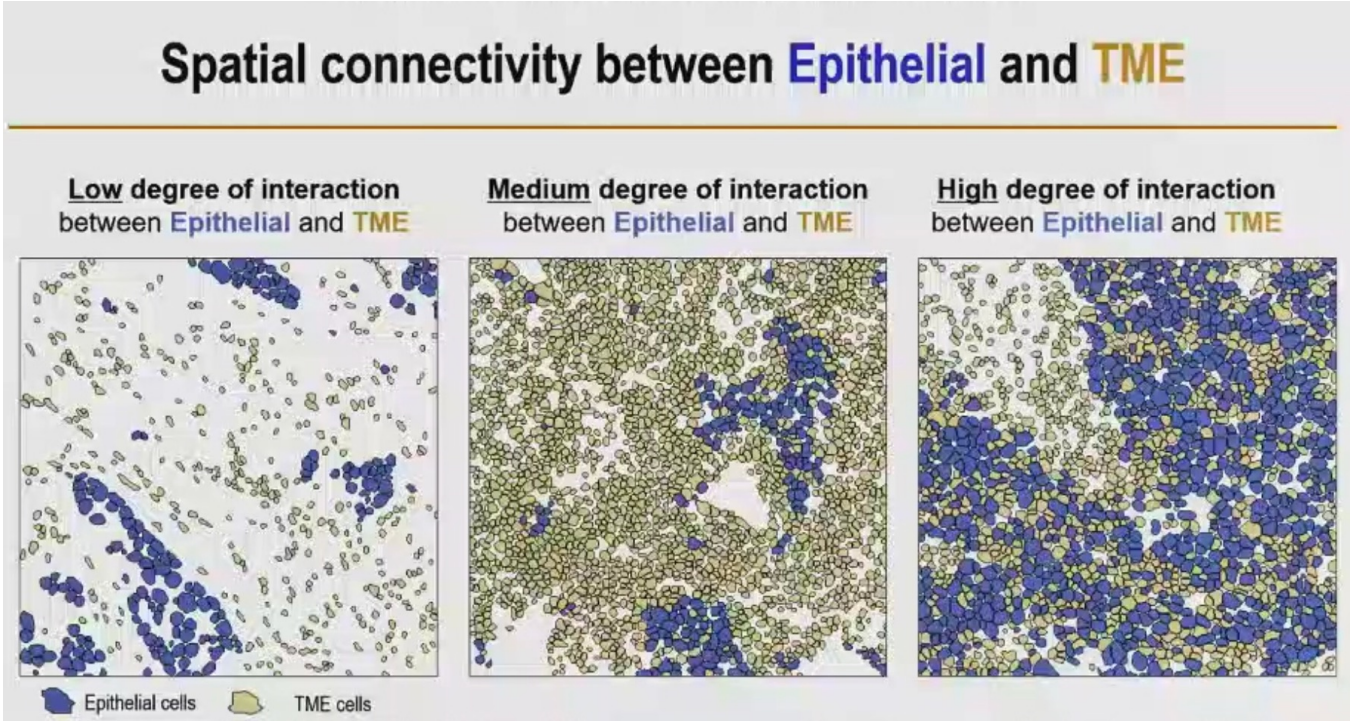
Carboplatin + *nab*-paclitaxel + Atezolizumab

Surgery

Pre-treatment tissue biopsies ***N=243*** (87%)
RNA-sequencing & Imaging Mass Cytometry of 43 proteins

Checkpoint	Lymphoid	Epithelial	Life & Death
PD-L1 (SP142)	CD56	CK5/14	c-PARP
PD-L1 (73-10)	CD20	CK8/18	pH2AX
IDO	CD79a	PanCK	Ki67
PD-1	CD3	Heterogeneity	DNA
OX40	CD4	AR	H3
ICOS	CD8	GATA3	Ir
Myeloid	FOXP3	CD15	
CD11c	GATA3	Mesenchymal	
CD15	Helios	Caveolin-1	
CD163	T-bet	CD31	
CD68	TCF	PDPN	
MPO	TOX	PDGFRB	
MHC I&II	GZMB	SMA	
HLA-ABC	Pan-Immune	Vimentin	
HLA-DR	CD45	Calponin	

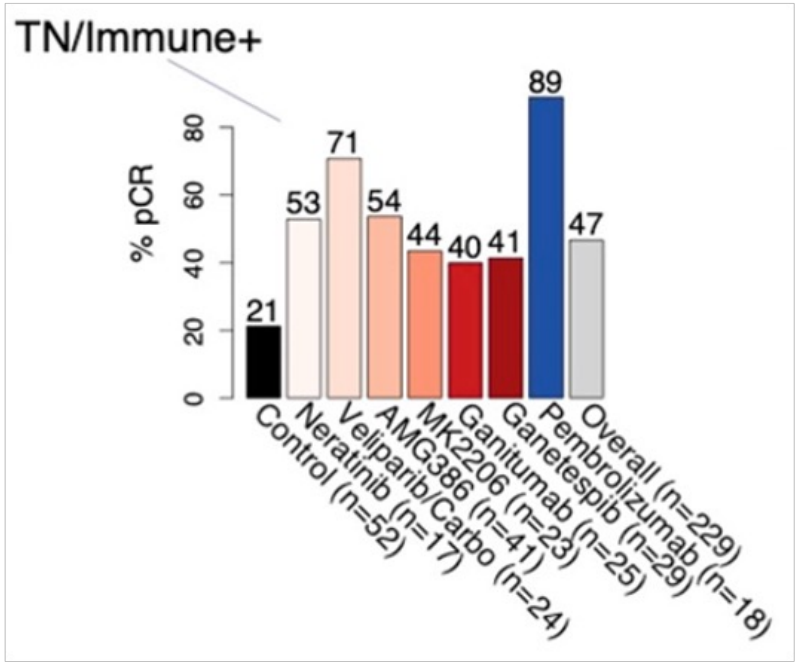
Is there a better marker than PDL1 to identify patients that selectively benefitted from ICI?



Giampaolo Bianchini, MD, et al. SABCS 2021.

1. **High degree of *spatial* connectivity between epithelial and specific TME cell phenotypes (e.g. CD8+PD1+T_{EX}; CD8+GZMB+; CD20+B) is predictive of higher pCR rate with the addition of atezolizumab, independently by PD-L1 and sTILs**
2. **Spatial Epithelial-TME interactions outperform cell phenotype density in predicting differential response to immunotherapy**

Immune response signature and pCR with ICI in I-SPY2



Yee D, et al. ASCO 2022, abstr 591, poster 362

UTSouthwestern Medical Center

CHAN LAB

InteractPrint predicts the degree of immune cell interaction for a patient's tumor

- We developed **InteractPrint**, a score that predicts the degree of immune cell interaction for a patient's tumor.

$$InteractPrint = \sum_{i=1}^{10} (e_i)(R_i)(w)$$

i = GE
e_i = GE expression
R_i = Number of predicted R-L pairs
w = Multiplier for activating GE (1) or inactivating GE (-1)

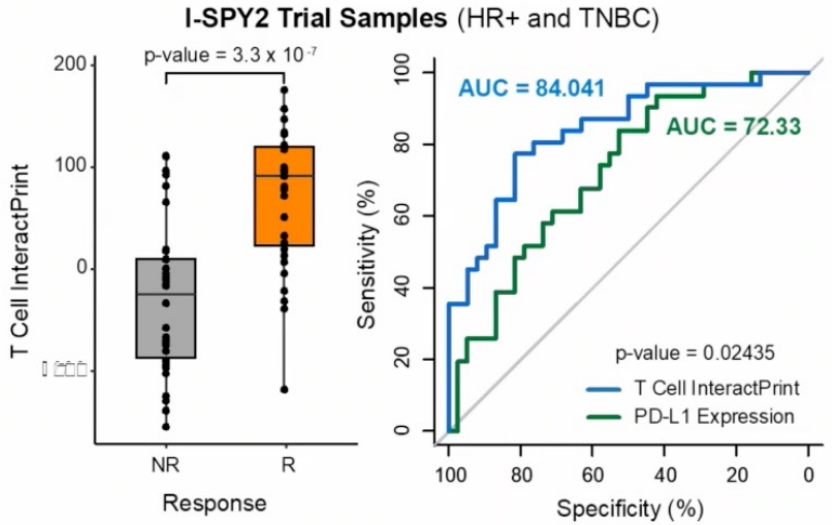
San Antonio Breast Cancer Symposium®, December 6-10, 2022

UTSouthwestern Medical Center

CHAN LAB

T Cell InteractPrint predicts response to anti-PD-1 therapy in I-SPY2

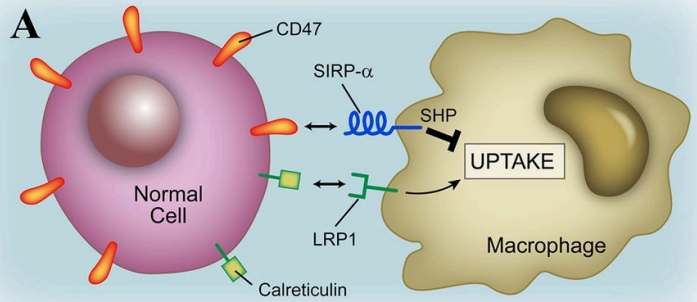
- In this trial, **T Cell InteractPrint predicted response to anti-PD-1 + neoadjuvant chemo with an AUC of 84.0** ($p < 1 \times 10^{-6}$).
- This was a **significant improvement over PD-L1** (assessed by average PD-L1 transcript levels; $p < 0.05$).

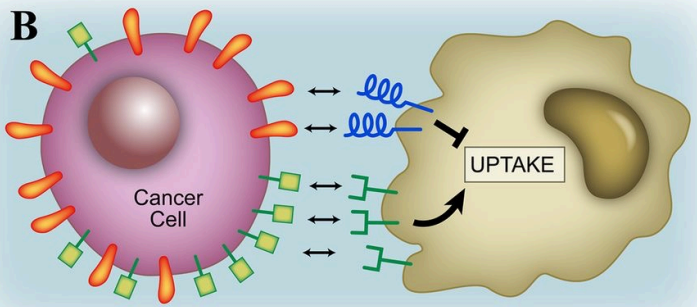


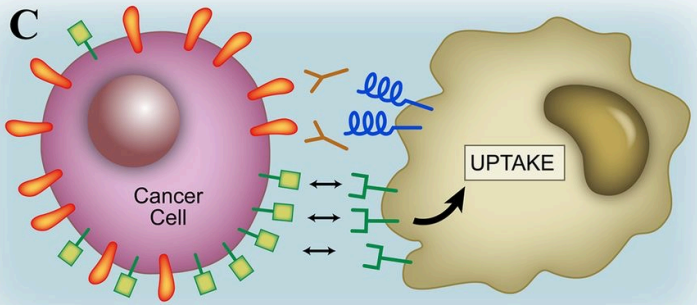
[5] Nanda et al., JAMA Oncol 2020.

Lily Xu, Isaac Chan lab, et al. UTSW, Single-cell RNAseq,…SABCS 2022, GS5-06.

Macrophages ignore CD47+ cells as a result of negative interactions in which the CD47–SIRP-α pair promote a “don’t eat me” signal; humanized CD47 antibody blocks SIRPα interaction

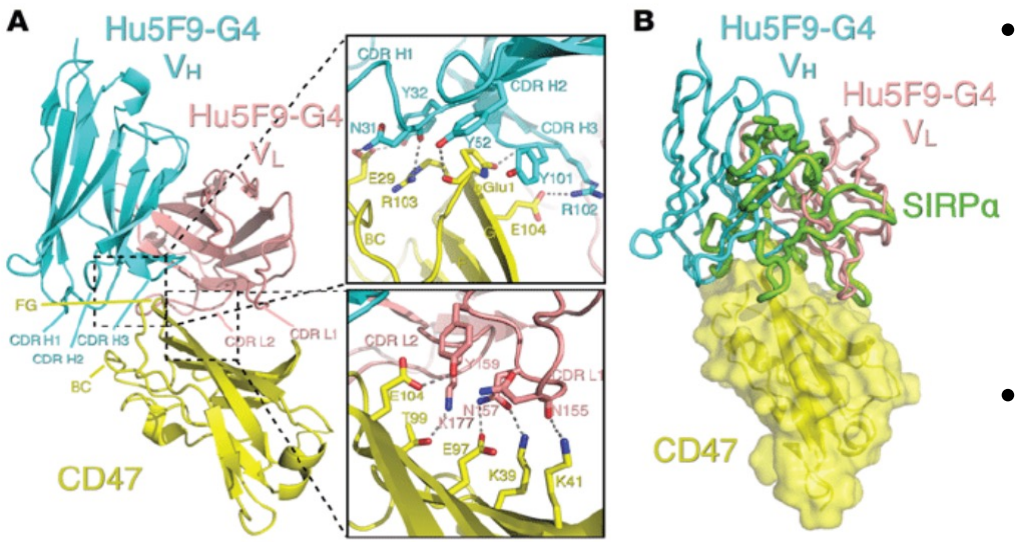






Unanue ER PNAS 2013;110:10886-10887.

The Journal of Clinical Investigation



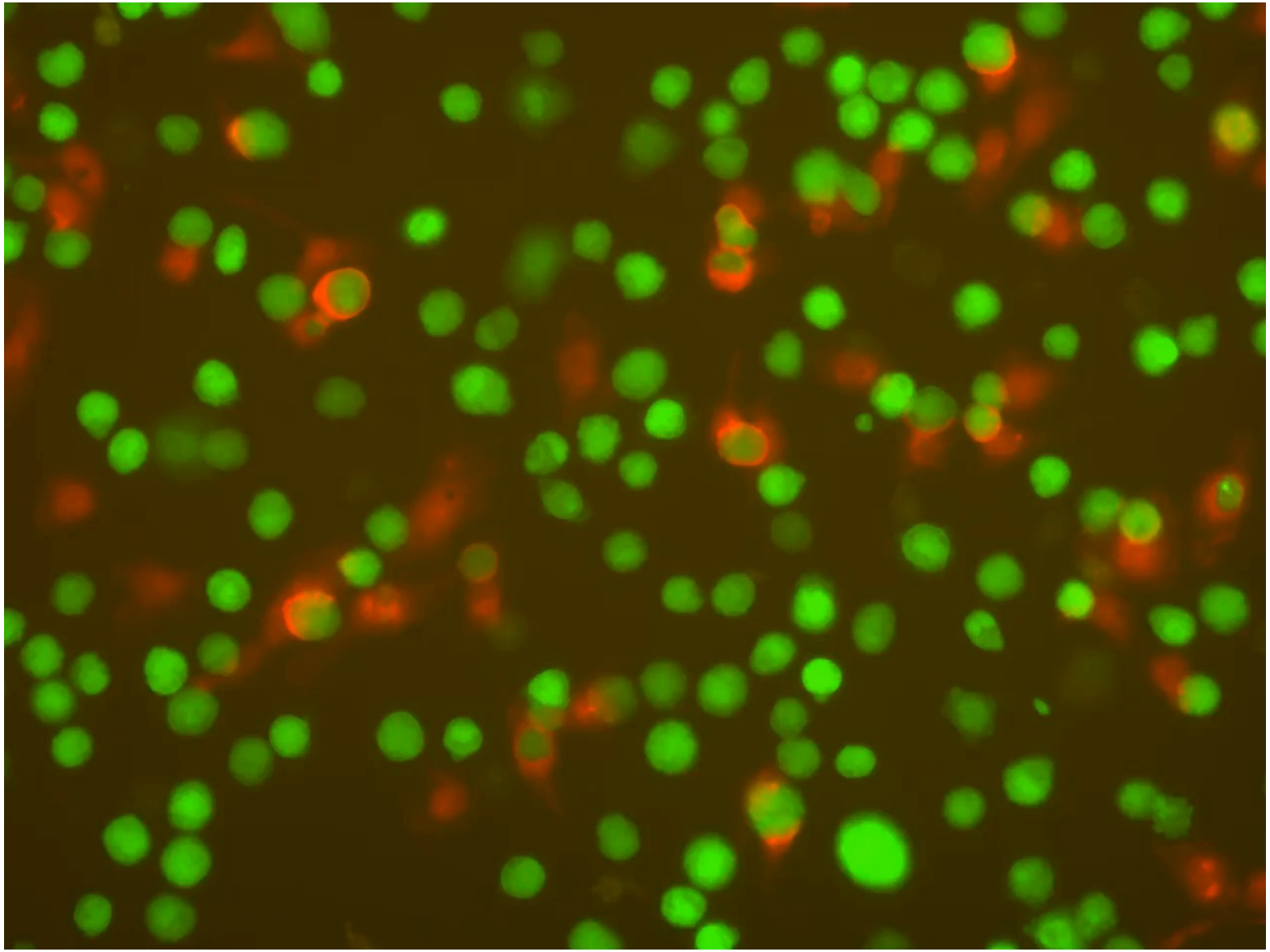
Crystal structure of CD47-ECD in complex with Hu5F9-G4: A) Hu5F9-G4/CD47 interface; B) Superposition of SIRPα demonstrating a shared binding interface.

Weiskopf K, et al. J Clin Invest. 2016;126(7):2610-2620.

- Hu5F9-G4 (magrolimab) binds human CD47 with high affinity by Biacore:
  - 8-10 nM for monomeric CD47
  - 8 pM for bivalent CD47
- Engineered into human IgG4 Fc (to avoid ADCC/CDC), with Ser-Pro substitution to reduce Fab arm exchange
- Humanized by CDR grafting

PNAS

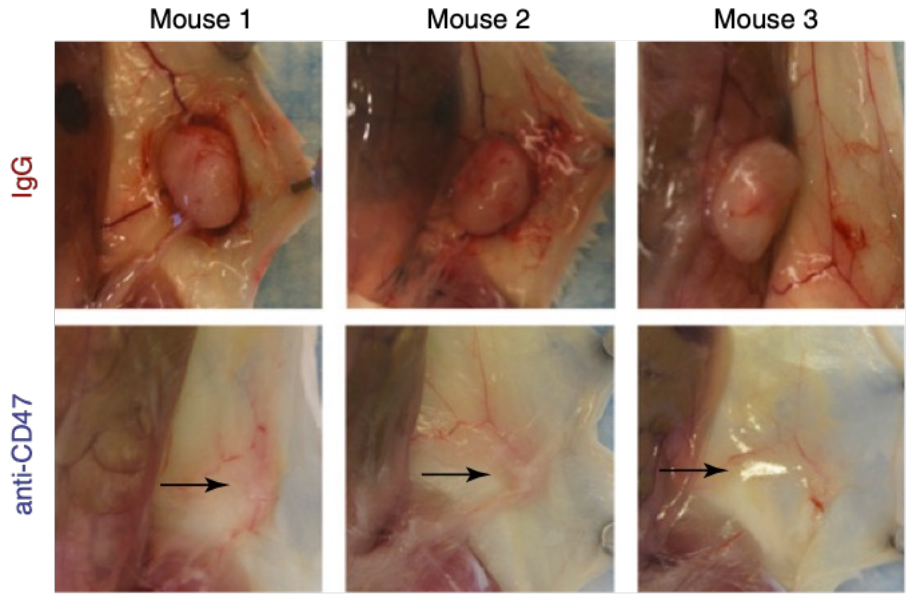
Macrophages (red) phagocytosing CD47+ tumor cells (green) in the presence of anti-CD47 antibody

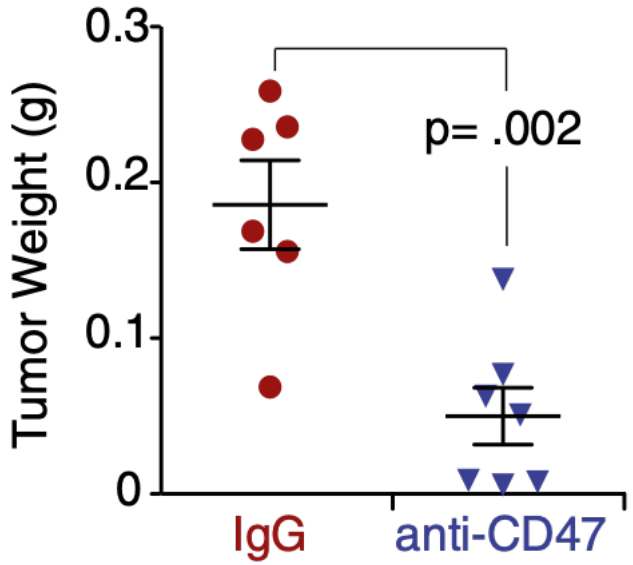


MΦ -- red
CD47+ tumor cells -- green

Edris, B. et al.. PNAS 109, 6656–6661 (2012).

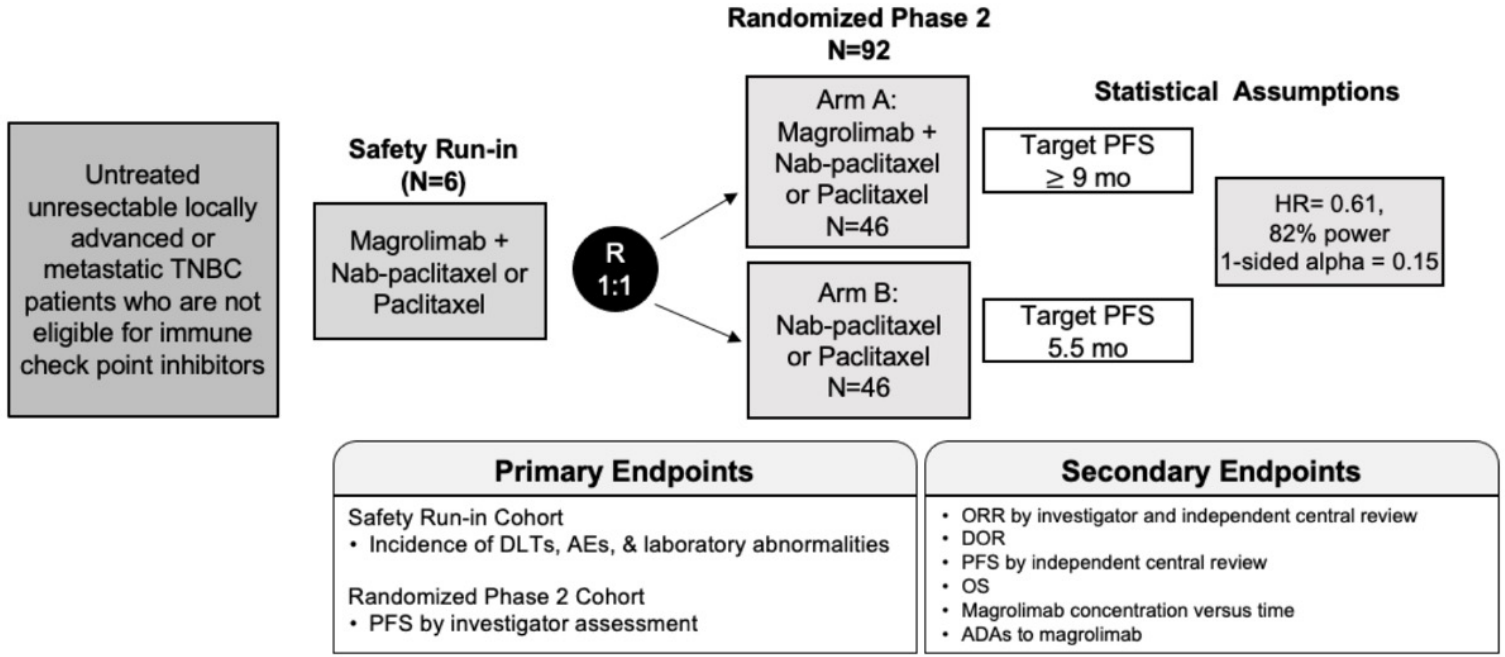
Anti-CD47 Antibody Significantly Reduces TNBC PDXs *in vivo* → Clinical Translation: Randomized Phase II





Willingham et al., PNAS 109 (42) E2842.

Study Schema



Primary Endpoints	Secondary Endpoints
Safety Run-in Cohort • Incidence of DLTs, AEs, & laboratory abnormalities Randomized Phase 2 Cohort • PFS by investigator assessment	• ORR by investigator and independent central review • DOR • PFS by independent central review • OS • Magrolimab concentration versus time • ADAs to magrolimab

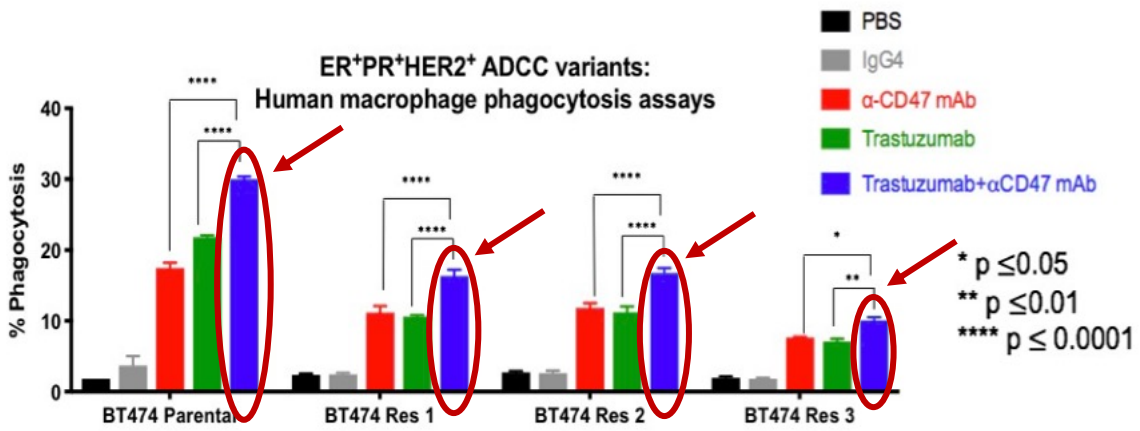
ADA = anti-drug antibodies; AE = adverse event; DOR = duration of response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = ratio; TNBC = triple-negative breast cancer

- CD47 is expressed on TNBC-derived cell lines
- CD47 blockade enhances TNBC phagocytosis
- Anti-CD47 dependent phagocytosis is further augmented by Paclitaxel
- 2nd cohort - Sacituzumab govitecan ± magrolimab

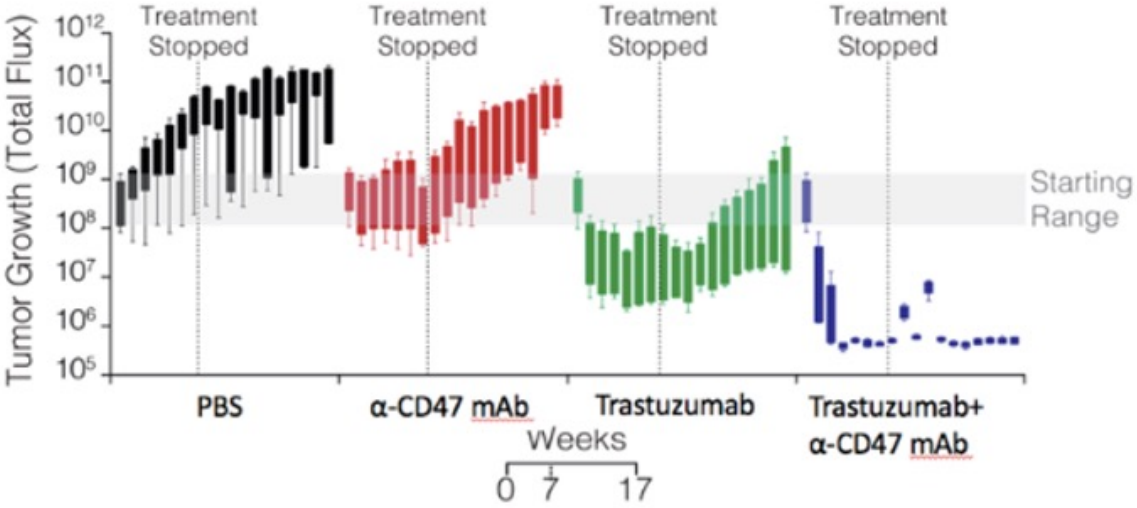
PNAS
Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

MOA – ADCP: Combining CD47 blockade with trastuzumab eliminates HER2-positive breast cancer cells to overcome trastuzumab ADCC tolerance

In vitro:
The circled blue bars (red arrows) indicate HER2+ ADCC-tolerant breast cancer cells being phagocytosed by human macrophages



In vivo:
Greater combined efficacy of anti-CD47 antibody magrolimab plus trastuzumab against HER2+ human GFP-luciferase BT474 breast cancer xenografts



Tumor burden was measured using *in vivo* bioluminescence imaging

Rosalynd Upton,…Mark D. Pegram[1], and Irving L. Weissman[1]. Proceedings of the National Academy of Sciences Jul 2021, 118 (29) e2026849118. [1]M.D.P. and I.L.W. contributed equally to this work.

Future Direction: HER2 ADCs with Immunologic Payloads

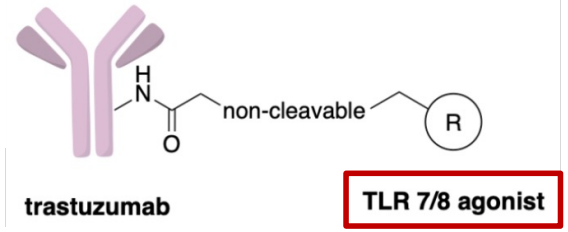
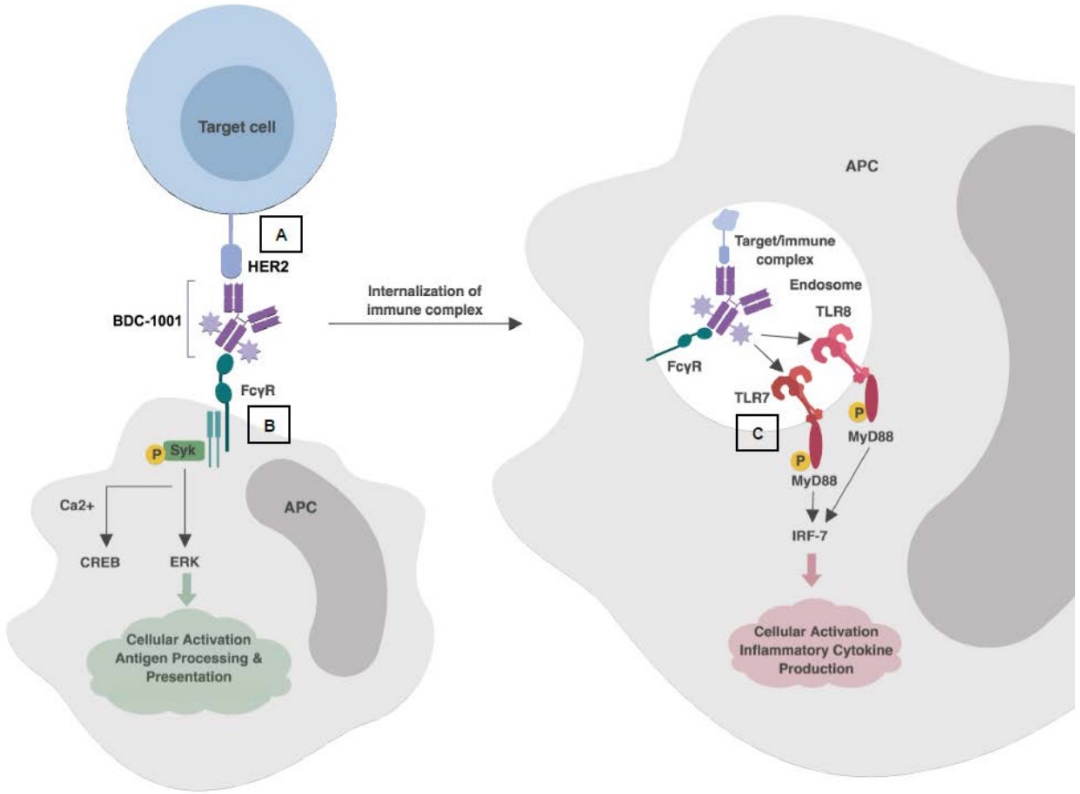


Figure 2: Proposed Mechanism of Action for BDC-1001

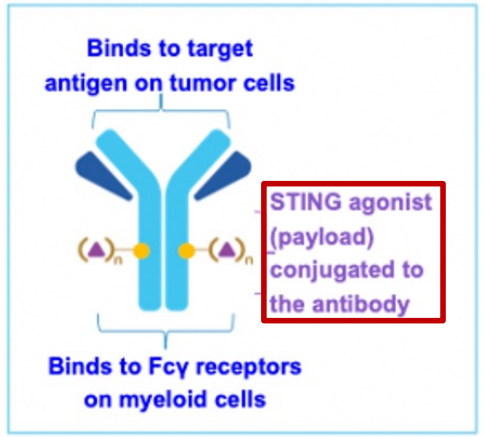


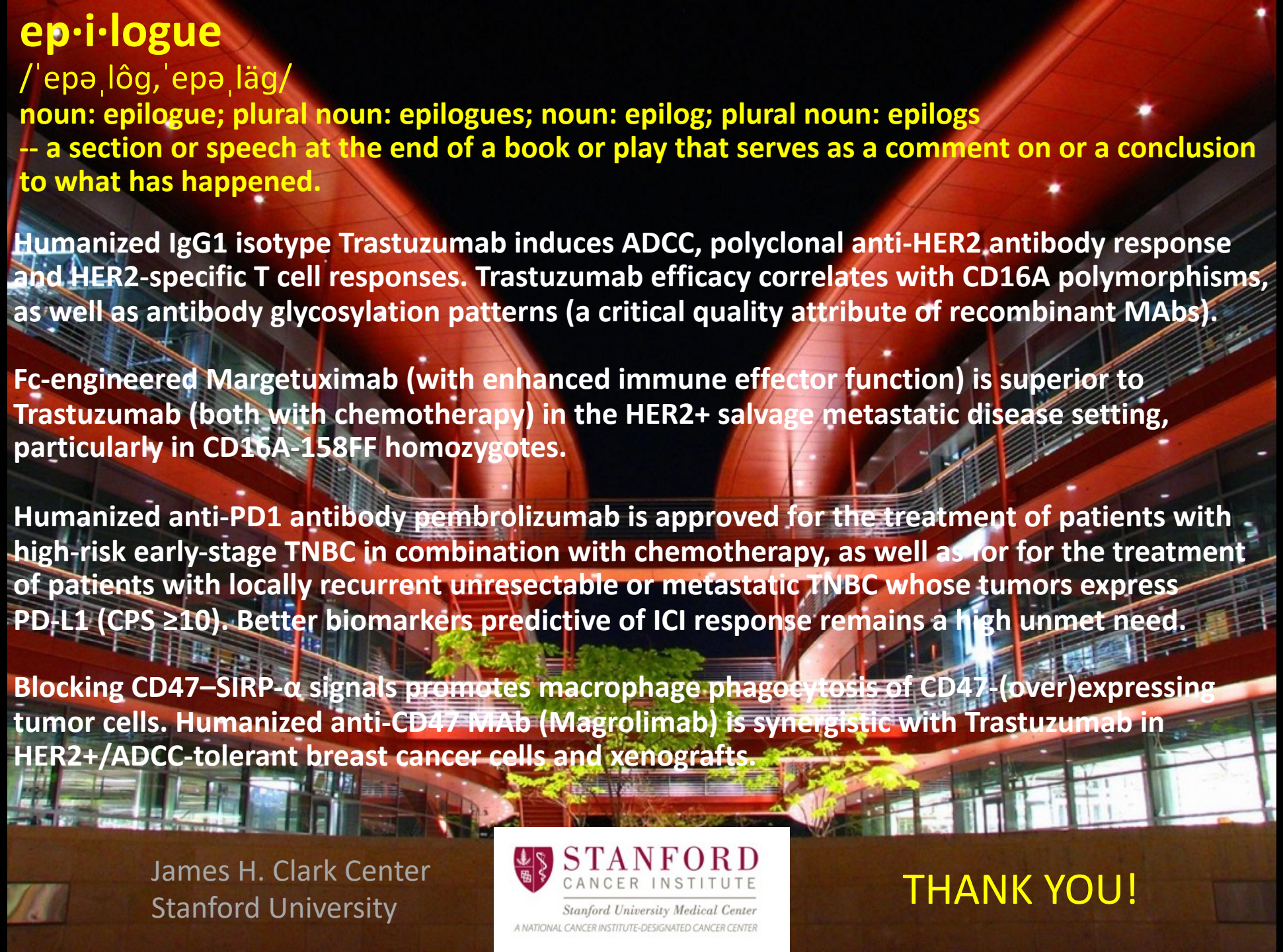
The proposed mechanism of action is tripartite, involving the antibody variable domain, the antibody Fc region and the TLR7/8 binding domain. (A) Fv portion of antibody recognizes HER2 expressing cancer cells; (B) APCs recognize antibody bound to HER2 expressing cancer cells via their Fc gamma receptors (FcγRs) and internalize tumor-immune complex following FcR clustering; (C) Once internalized, the TLR7/8 agonist attached to BDC-1001 gains access to the phagolysosome and mediates downstream events associated with TLR activation. Note that the number of HER2 molecules and bound BDC-1001 have been reduced to 1 each for schematic purpose.

Background

Tumor cell-targeted Immunosynthen STING agonist ADCs

- Systemically administered
- Tumor targeted delivery of STING agonist
- Efficacious at a single dose across multiple tumor models
- Well-tolerated at multiple doses in multiple non-clinical species
- Minimal systemic induction of inflammatory cytokines
- Dramatically greater efficacy compared to a systemically administered free STING agonist





ep·i·logue

/ˈepəˌlôg,ˈepəˌläg/

noun: epilogue; plural noun: epilogues; noun: epilog; plural noun: epilogs
-- a section or speech at the end of a book or play that serves as a comment on or a conclusion to what has happened.

Humanized IgG1 isotype Trastuzumab induces ADCC, polyclonal anti-HER2 antibody response and HER2-specific T cell responses. Trastuzumab efficacy correlates with CD16A polymorphisms, as well as antibody glycosylation patterns (a critical quality attribute of recombinant MAbs).

Fc-engineered Margetuximab (with enhanced immune effector function) is superior to Trastuzumab (both with chemotherapy) in the HER2+ salvage metastatic disease setting, particularly in CD16A-158FF homozygotes.

Humanized anti-PD1 antibody pembrolizumab is approved for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy, as well as for for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10). Better biomarkers predictive of ICI response remains a high unmet need.

Blocking CD47–SIRP-α signals promotes macrophage phagocytosis of CD47-(over)expressing tumor cells. Humanized anti-CD47 MAb (Magrolimab) is synergistic with Trastuzumab in HER2+/ADCC-tolerant breast cancer cells and xenografts.

James H. Clark Center
Stanford University

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THANK YOU!

Pegram Lab Support:
BCRF;
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Jill and John Freidenrich