Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Spotlight on Ongoing Clinical Trials
UPMC Hillman Cancer Center

Leisha A. Emens, MD, PhD
Professor of Medicine
Director of Translational Immunotherapy
For the Women's Cancer Research Center
Co-Leader, Hillman Cancer
Immunology/Immunotherapy Program
University of Pittsburg School of Medicine

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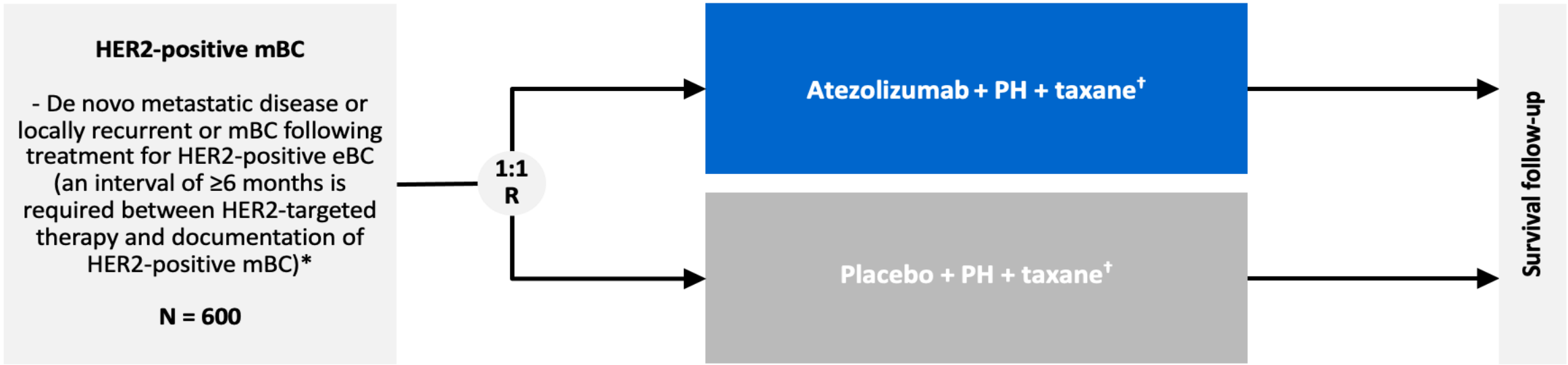
Conflict of Interest

Consulting Fees: Genentech, F Hoffman La Roche, Chugai, GCPR, Gilead, Immune Onc, Shionogi, Mersana

Contracted Research: Abbvie, Astrazeneca, Bolt Therapeutics, Bristol Myers Squibb, Compugen, Corvus, CytomX, EMD Serono, Genentech, F Hoffman La Roche, Immune Onc, Maxcyte, Merck, Next Cure, Silverback, Takeda, Tempest

Other (Grants): HeritX Incorporated, NSABP Foundation, Translational Breast Cancer Research Consortium, Breast Cancer Research Foundation, National Cancer Institute, Department of Defense, Johns Hopkins University, University of California San Francisco, Cornell University, Dana Farber Cancer Institute

NRG-BR004 study design (Phase III)

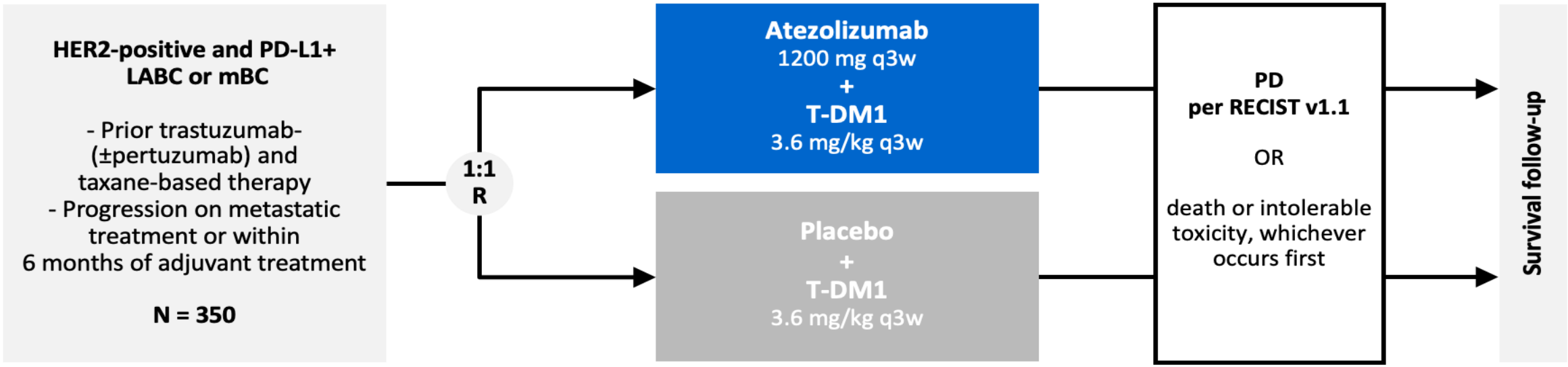


- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR, DoR, cumulative incidence of brain metastases, safety

* Patients with CNS metastases are eligible. Criteria are outlined on ClinicalTrials.gov here.
† Doses used in this study are as follows: atezolizumab 1200 mg IV; trastuzumab 8 mg/kg loading dose followed by 6 mg/kg thereafter; pertuzumab 840 mg loading dose followed by 420 mg thereafter; taxane 80 mg/m^2 IV.
CNS, central nervous system; DoR, duration of response; eBC, early breast cancer; H, trastuzumab; mBC, metastatic breast cancer, ORR, objective response rate; OS, overall survival; P, pertuzumab; PFS, progression-free survival.

https://clinicaltrials.gov/ct2/show/NCT03199885 (accessed August 2021).

KATE3 study design (Phase III)



- **Multiple primary endpoint:** PFS by investigator assessment using RECIST v1.1 and OS
- **Secondary endpoints:** ORR, DoR, PFS by independent central review, PFS and OS in patients with baseline brain metastases, CNS PFS, QoL

CNS, central nervous system; DoR, duration of response; LABC, locally advanced breast cancer; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, Programmed death-ligand 1; PFS, progression-free survival; q3w, every 3 weeks; QoL, quality of life; RECIST, response evaluation criteria in solid tumours; T-DM1, trastuzumab emtansine.

https://clinicaltrials.gov/ct2/show/NCT04740918 (accessed August 2021).

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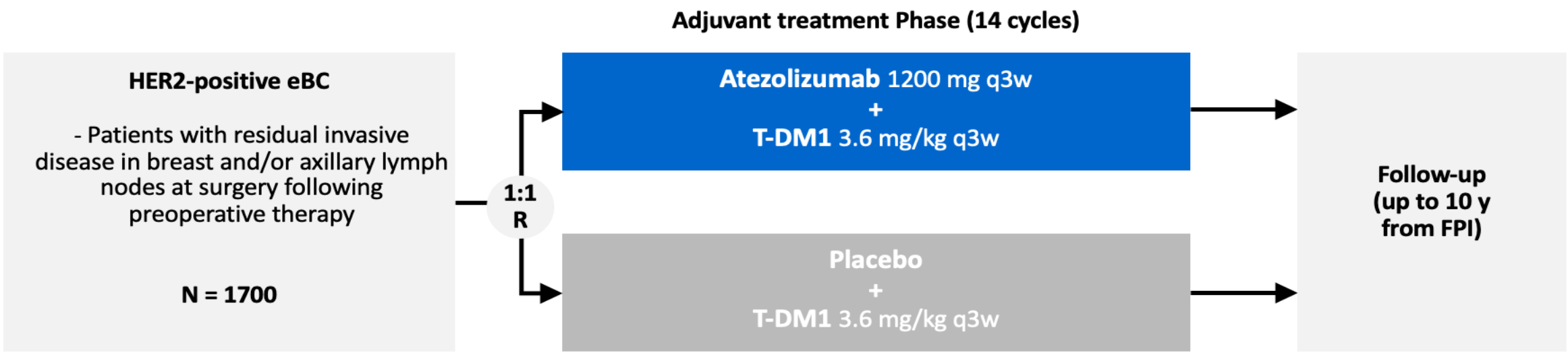
Astefania study design (Phase III)

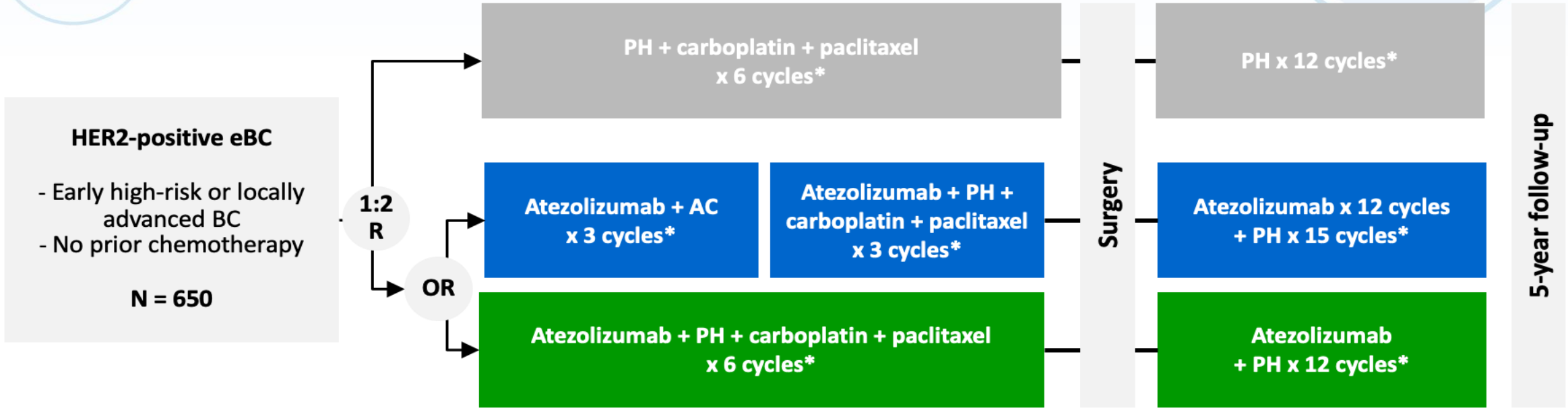


- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS including secondary primary non-breast invasive cancer, DFS, OS, DRFI, QoL, PRO, safety, pharmacokinetics

DFS, disease-free survival; DRFI, distant recurrence-free survival; eBC, early breast cancer; FPI, first patient in; IDFS, invasive disease-free survival; OS, overall survival; PRO, patient-reported outcome; q3w, every 3 weeks; QoL, quality of life; T-DM1, trastuzumab emtansine; y, years.

https://clinicaltrials.gov/ct2/show/NCT04873362 (accessed August 2021).

APTneo study design (Phase III)



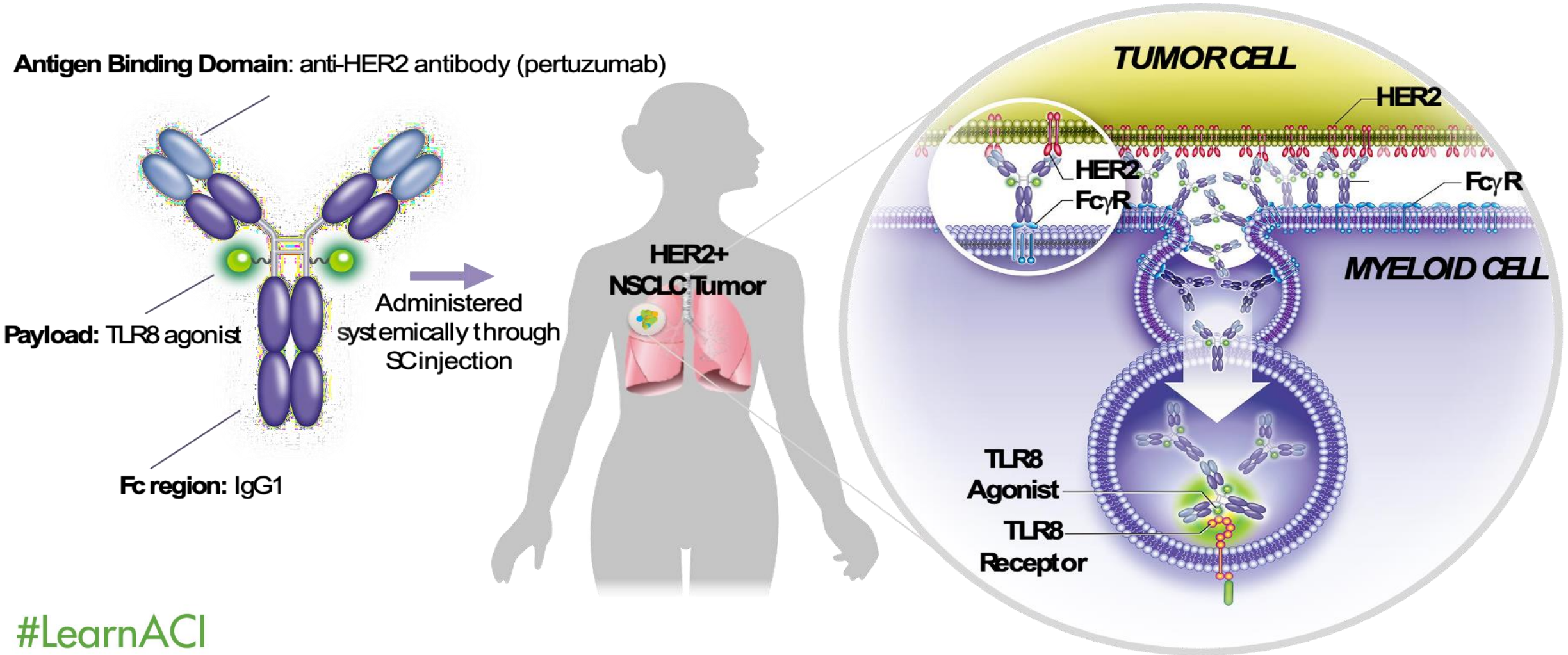
- **Primary endpoint:** EFS
- **Secondary endpoints:** pCR, cOR, DEFS, OS, safety

* Doses used in this study are as follows: atezolizumab 1200 mg IV q3w; doxorubicin 60 mg/m^2 q3w + cyclophosphamide 600 mg/m^2 q3w; carboplatin AUC2 D1 & D8 q3w; paclitaxel 90 mg/m^2 D1 & D8 q3w; pertuzumab 840 mg loading dose followed by 420 mg thereafter; trastuzumab 8 mg/kg loading dose followed by 6 mg/kg thereafter.

AC, doxorubicin + cyclophosphamide; BC, breast cancer; cOR, clinical objective response; DEFS, distant event-free survival; D, day; eBC, early breast cancer; EFS, event-free survival; IV, intravenous; OS, overall survival; pCR, pathological complete response; PH, pertuzumab–trastuzumab.

https://clinicaltrials.gov/ct2/show/NCT03595592 (accessed August 2021).

SBT6050: a HER2-targeted TLR8 agonist, designed activate myeloid cells in the tumor microenvironment



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SBT6050-101: Phase 1/1b study demonstrates tolerable safety profile, pharmacodynamic effects and signs of antitumor activity

Monotherapy SBT6050

SBT6050 SCinjection Q2W

Dose escalation

- 0.3 mg/kg
- 0.6 mg/kg
- 0.9 mg/kg
- 1.2 mg/kg

Expansion cohorts

- HER2+ and low BC
- HER2+ gastric/GEJ
- HER2exp NSCLC
- HER2exp basket

Checkpoint inhibitor combinations

SBT6050 SCinjection Q2-3W; pembrolizumab 400 mg IV Q6W; cemiplimab 350 mg/kg IV Q3W

Pembrolizumab dose escalation

- 0.15 mg/kg
- 0.3 mg/kg
- 0.45 mg/kg
- 0.6 mg/kg

Pembrolizumab combination cohort

- HER2+ basket (n=30)

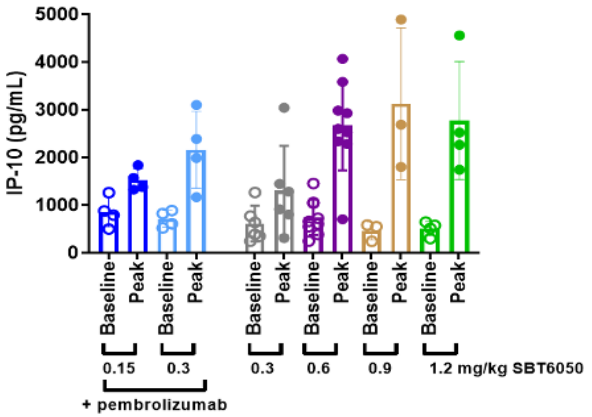
Cemiplimab combination cohorts

- HER2+ Gastric/GEJ (n=40)
- HER2exp NSCLC (n=40)

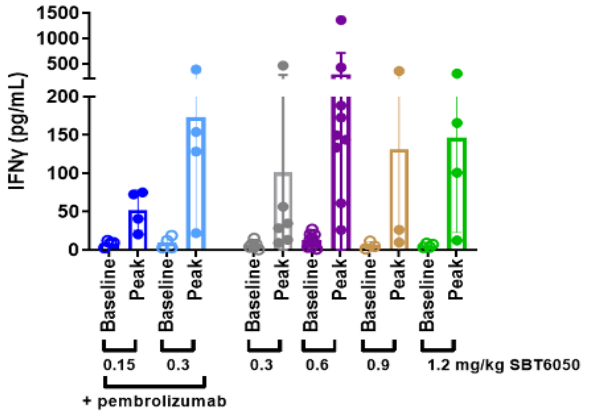
Preliminary Results *(presented at ESMO 2021, Klempner et al)*

- 40 subjects enrolled with HER2-expressing solid tumors, median 4.5 prior therapies
- Manageable safety profile consistent with an immune activator: common AEs include injection site reactions, pyrexia, chills, hypotension, nausea, vomiting, fatigue
- Serum PK suggests HER2 target saturation at 0.6 mg/kg dose
- Induction of myeloid and T/NK cell activation observed at all dose levels
- Payload is detected in intratumoral macrophages and on tumor cells
- Signals of anti-tumor activity, including a confirmed partial response and multiple patients with durable or decreasing volume stable disease

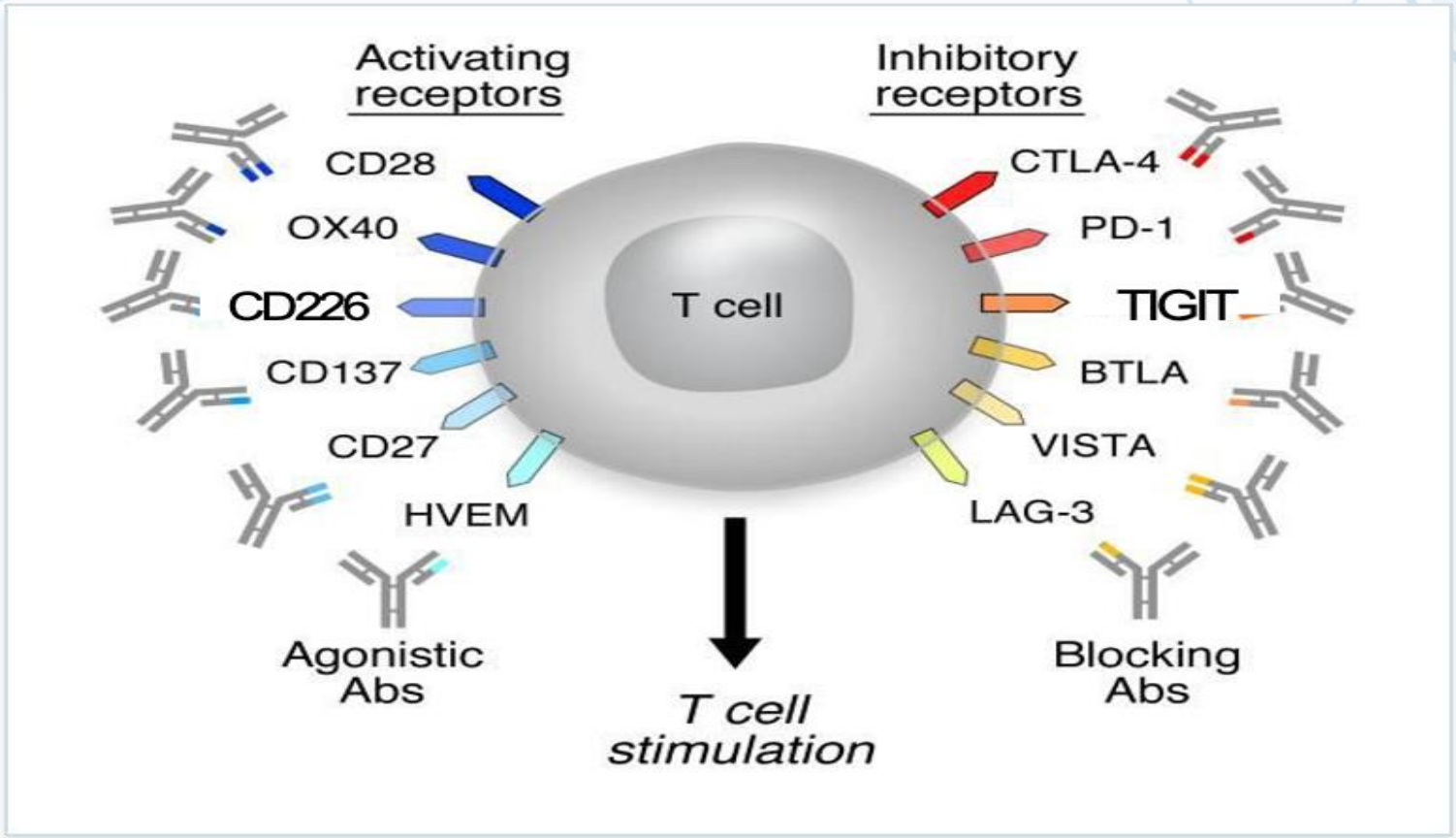
IP-10: myeloid cell activation



IFNγ : T/NK cell activation



#LearnAACI



Co-activating and inhibitory receptors are critical regulators of adaptive immune cell function

Adapted from Mellman I et al. Nature 2011

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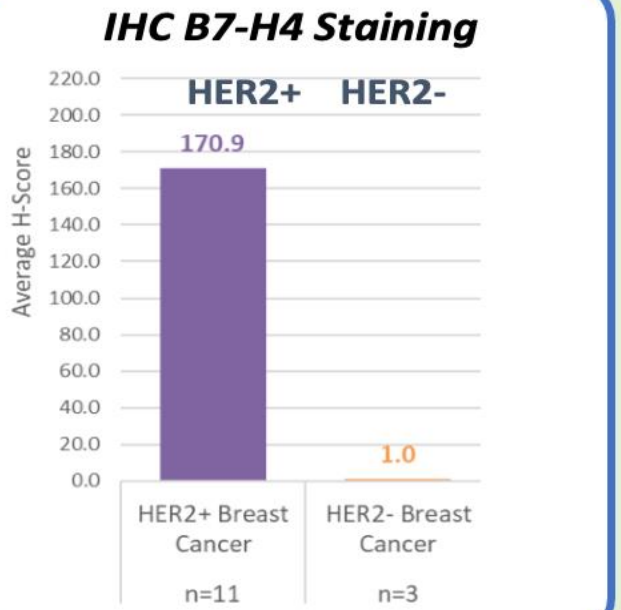
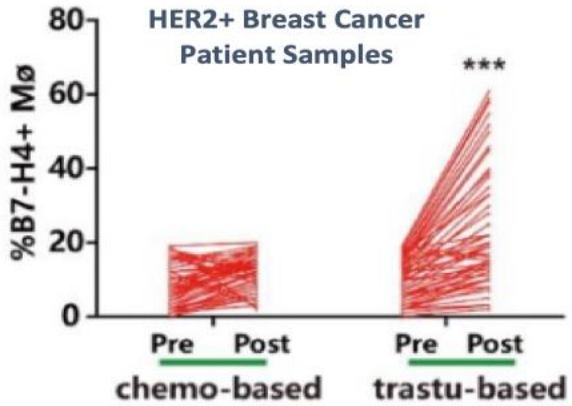
B7-H4 and HER2 Clinical Relationship in Breast Cancer

B7-H4 Overexpression in HER2+ Breast Tumors

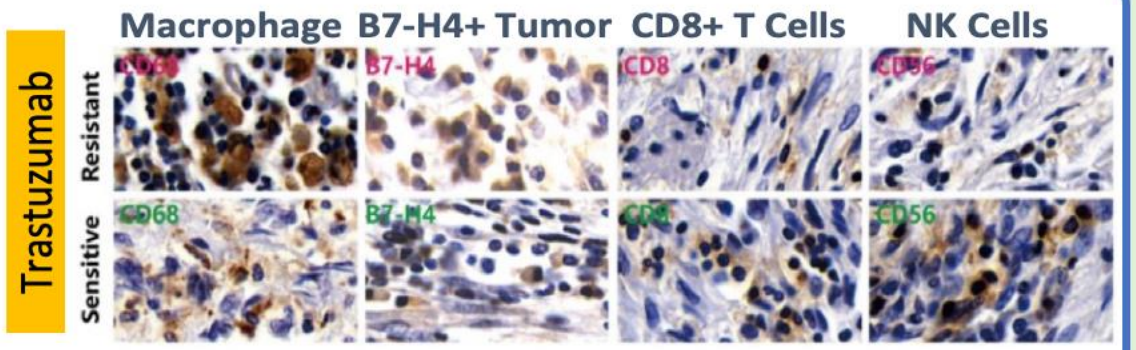


B7-H4 Expression Increase in Trastuzumab Resistance



Xiaochen Hu et al, Neoplasia, 2020

B7-H4 Expression and Trastuzumab Resistance Leads to Immunosuppression

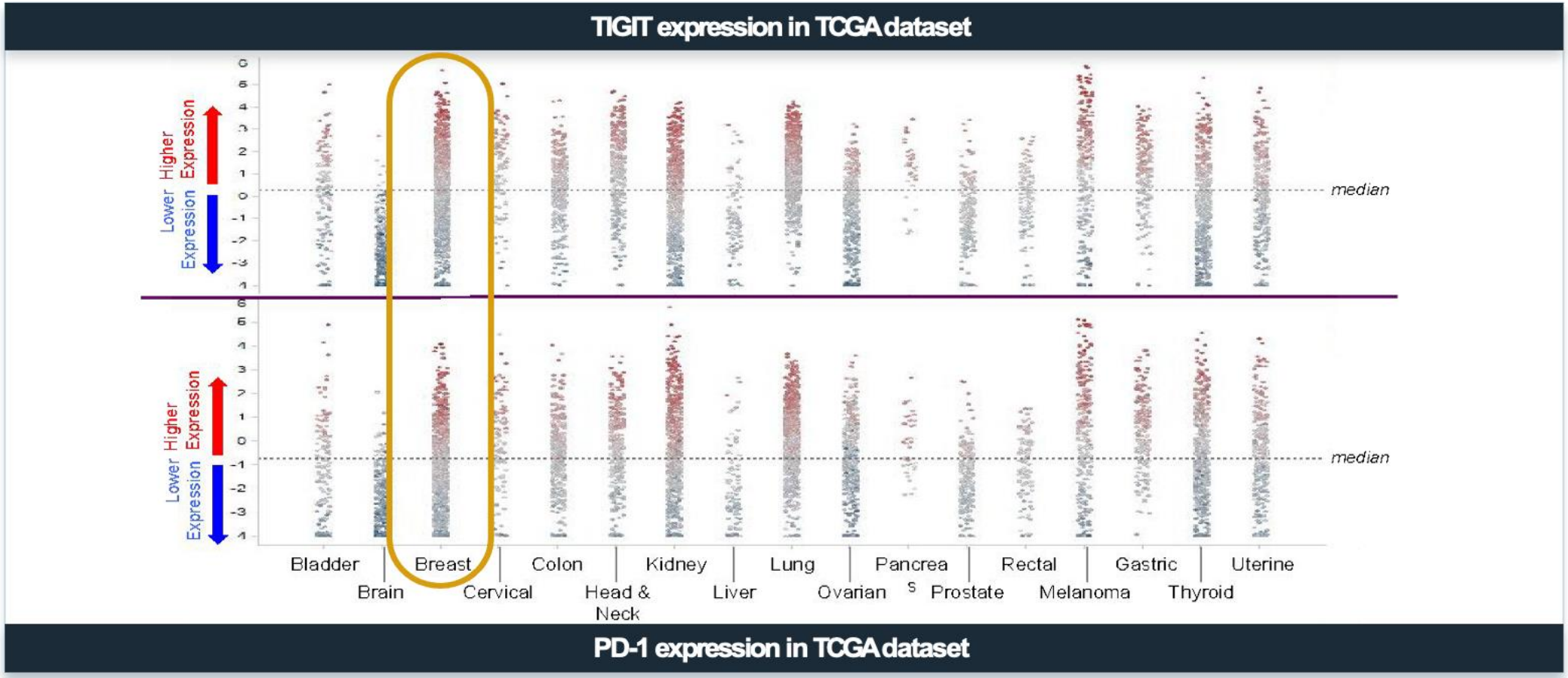


Trastuzumab resistance markers:

- B7-H4 expression
- Reduction of CD8 T and NK cells
- Increased macrophages

Xiaochen Hu et al, Neoplasia, 2020

TIGIT and PD-1 Expression are Similar Across Solid Tumors



Unpublished data courtesy of Mahesh Yadav, PhD
Biomarker, Scientist, TIGIT Team, Genentech

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Study Design | Overview

CO42177: Ph1b, open-label, multicohort study of tiragolumab in combination with atezolizumab and chemotherapy in TNBC patients

Cohort A
1LmTNBC (40 patients)

- **PD–L1-positive patients** with unresectable locally advanced or metastatic TNBC who have not received prior systemic therapy for metastatic BC

→ Tiragolumab + atezolizumab (**Q4Wk**) + nab-paclitaxel (3 weeks on/ 1 week off)

Cohort B
Early TNBC (20 patients)

- **PD-L1 all-comer population**, patients who are eligible for surgery with initially clinically assessed T2–4d TNBC

→ R 1:1

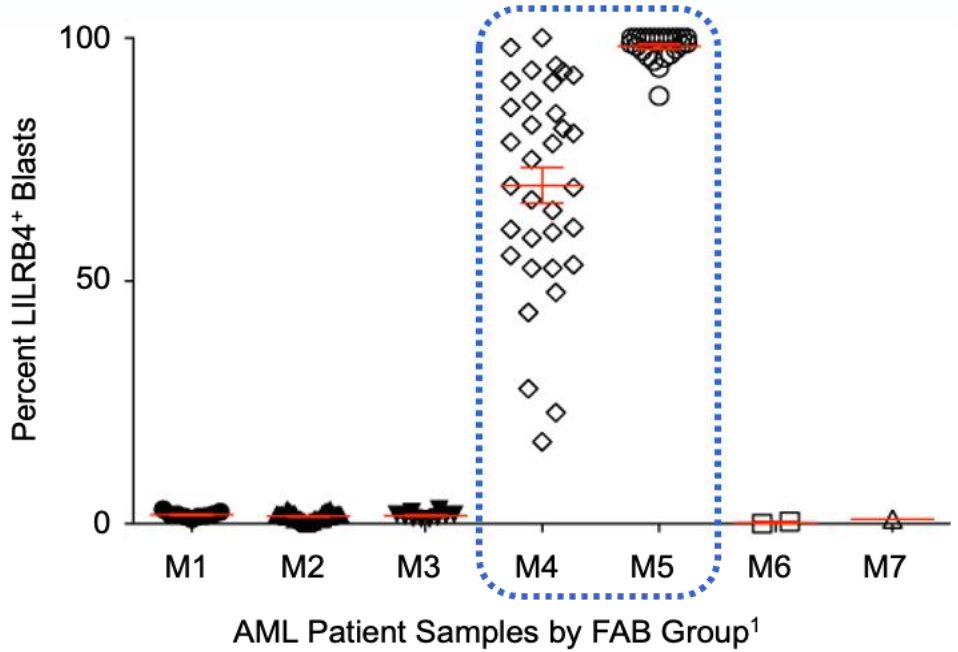
→ Tiragolumab + atezolizumab (**Q2Wk**) + Nab-paclitaxel (weekly) + **Carboplatin**, followed by Doxorubicin and Cyclophosphamide (AC)

→ Tiragolumab + Atezolizumab (**Q2Wk**) + Nab-paclitaxel (weekly), followed by Doxorubicin and Cyclophosphamide (AC)

End of study

- Completion of the 90-day AE reporting period after study treatment discontinuation for the last patient in both cohorts, expected to occur approximately 12 months after the last patient has been enrolled

LILRB4 is Expressed in Hematologic Cancers and Solid Tumor Microenvironment

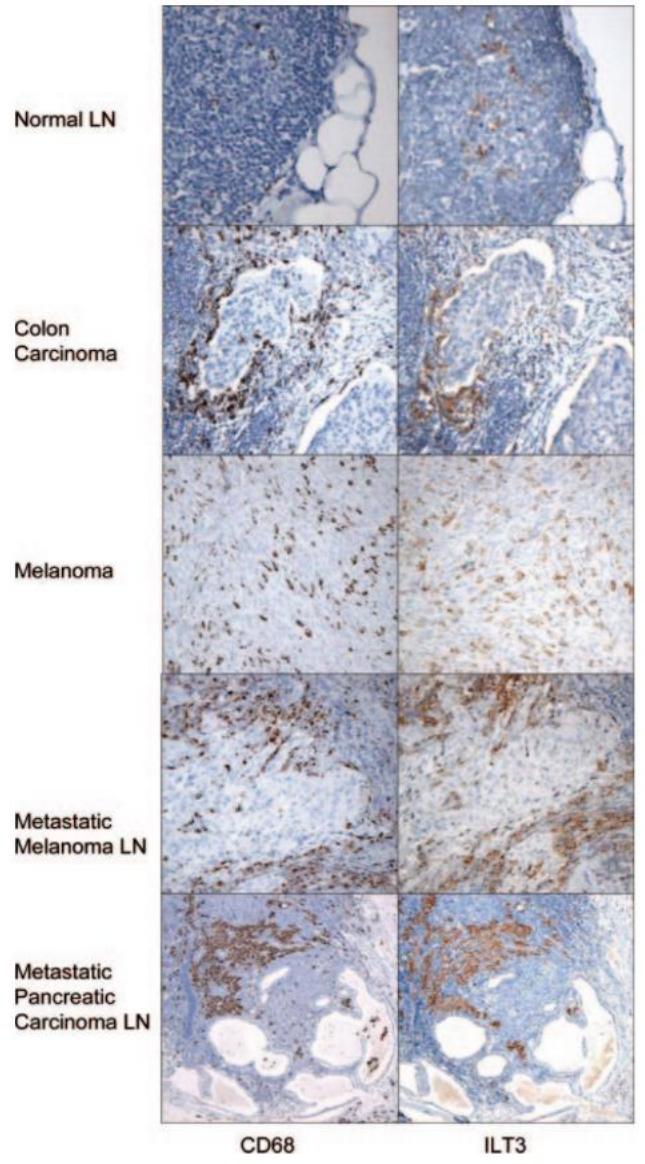


LILRB4 expression is also found in **CMML** and **MDS**[2] and **CLL**[3] patients and on **multiple myeloma** cell line OPM2 and **pre-B ALL** cell line KOPN8[4]

[1]Nature 562:605-609 (2018); [2]Leuk Lymphoma. 61:1493-1499 (2020); [3]Cytometry B Clin Cytom. 72:354-62 (2007); [4]Immune-Onc data. FAB = French–American–British classification; In WHO 2016 classification, M4 = acute myelomonocytic leukemia, M5 = acute monocytic/monoblastic leukemia

Immunohistochemistry showing co-staining of CD68 and LILRB4/ILT3

Suciu-Foca et al., J. Immunol. 178:7432-41 (2007)



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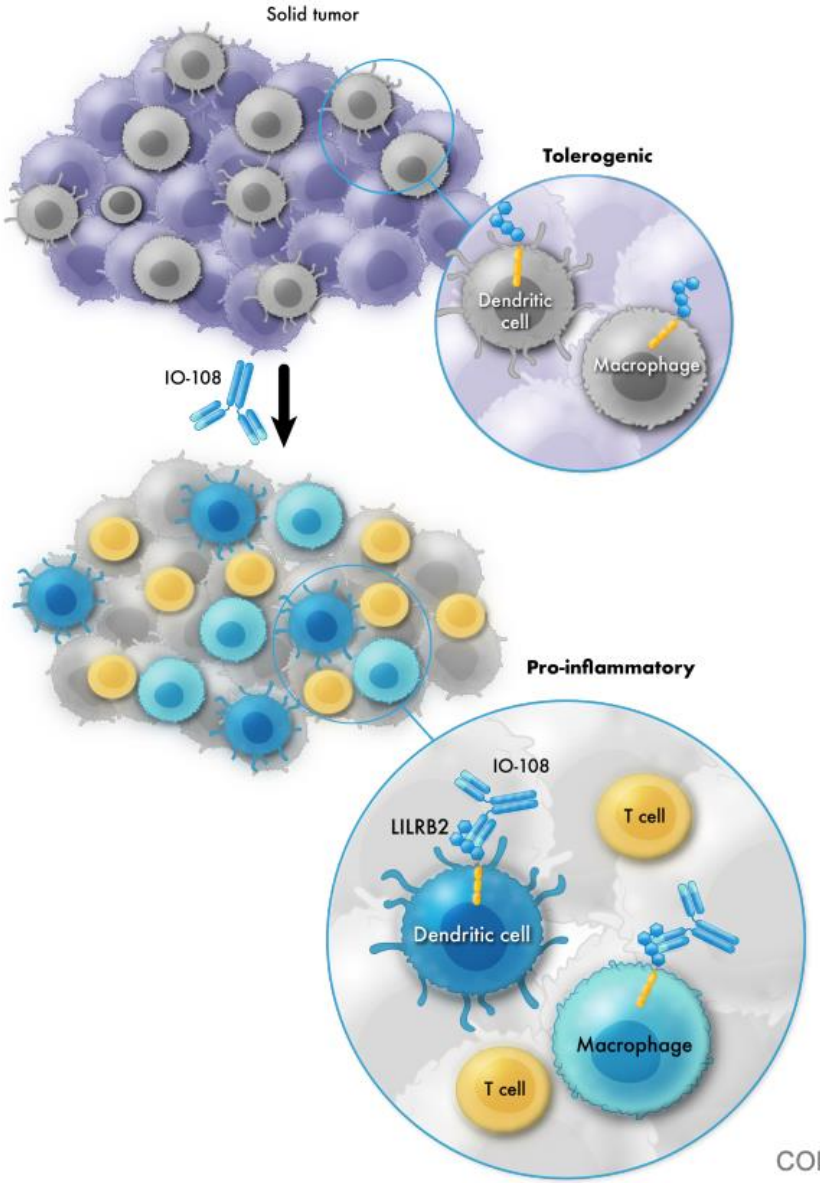
IO-108 (Anti-LILRB2 Blocking IgG4): **Re-Programs Myeloid Cells** to Activate T Cells



Therapeutic Mechanism of Action

LILRB2 blockade causes re-programming

of immune suppressive myeloid cells to pro-inflammatory in the tumor microenvironment, leading to activation of T cells.

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Spotlight on Ongoing Clinical Trials: The Ohio State University

Margaret E. Gatti-Mays, MD MPH FACP

Pelotonia Institute for Immuno-Oncology, Div. of Medical Oncology

The Ohio State University Comprehensive Cancer Center

@DrGattiMays

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Disclosures

- No relevant financial relationships to disclose

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OSU Clinical Trials

ER+/HER2- | HER2- | HER2+ | TNBC | Opening Soon

Early Stage Breast Cancer

Neoadjuvant

NSABP FB-12
Taxol plus
Herceptin/Pertuzumab

Decitabine + Pembro
prior to AC-T

ISPY2:
various combinations with
chemotherapy +/-
immunotherapy

Mammoglobin-A Vaccine
+ chemo

Residual Cancer

HER2 DC or WOKVAC
Vaccine

Cryotherapy plus Ipi/Nivo

Metastatic Triple Negative Breast Cancer

1-2L, BRCA+:
Olaparib plus
Atezolizumab

1L (BR004): THP
+ Atezolizumab

BRACELET-1:
2L+ Avelumab +
pelareorep vaccine

2-4L: Pelareorep
vaccine + PD1

Metastatic Solid Tumors

HER2 B Cell Peptide
Vaccine

REGN7075 + Cemiplimab

ONCR-177 +/-
Pembrolizumab

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ISPY2

Anatomic Stage 2 or 3

≥ 2.5cm biopsy confirmed breast cancer

ER/PR/HER2 testing
Mammaprint

HER2(-)

- Cemiplimab/Paclitaxel followed by AC
- Cemiplimab/REGN3767/Paclitaxel followed by AC
- Oral Paclitaxel/Encequidar/Dostarlimab followed by AC
- Oral Paclitaxel/Encequidar/Dostarlimab/Carboplatin followed by AC

HER(+)

- Paclitaxel/Trastuzumab/Pertuzumab (THP) followed by AC (control arm)
- Oral Paclitaxel/Encequidar/Dostarlimab/Trastuzumab followed by AC
- Oral Paclitaxel/Encequidar/Dostarlimab/Carboplatin/Trastuzumab followed by AC

PI: L. Esserman
OSU Co-I: N. Williams

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Encequidar = oral P-glycoprotein inhibitor; REGN3767 = anti-LAG3 mAB

A Multicenter Phase II Study of Vaccines to Prevent Recurrence in patients with HER-2 Positive Breast Cancer HER2 DC1/WOKVAC Vaccines

Residual Disease after neoadjuvant HER2-directed therapy for Stage 1-3 HER2+ Breast Cancer
AND
≤ 6 months completion of adjuvant HER2 therapy

WOKVAC: DNA plasmid Vaccine + GM-CSF

Week 1, 4, 7 | **Months 6, 9, 12**

DC1: Autologous HER2 pulsed DC vaccine

Week 1, 2, 3, 4, 5, 6 | **Months 6, 9, 12**

2 year Follow-Up

Primary:

- To evaluate the safety and tolerability of each vaccine therapy.
- To evaluate the immunogenicity following each vaccine therapy.

Secondary:

- To determine disease free survival (DFS) of patients with HER2 positive breast cancer after treatment with each vaccine.

Moffitt PI: H.Han
Univ Wash PI: N. Disis
OSU PI: R.Wesolowski

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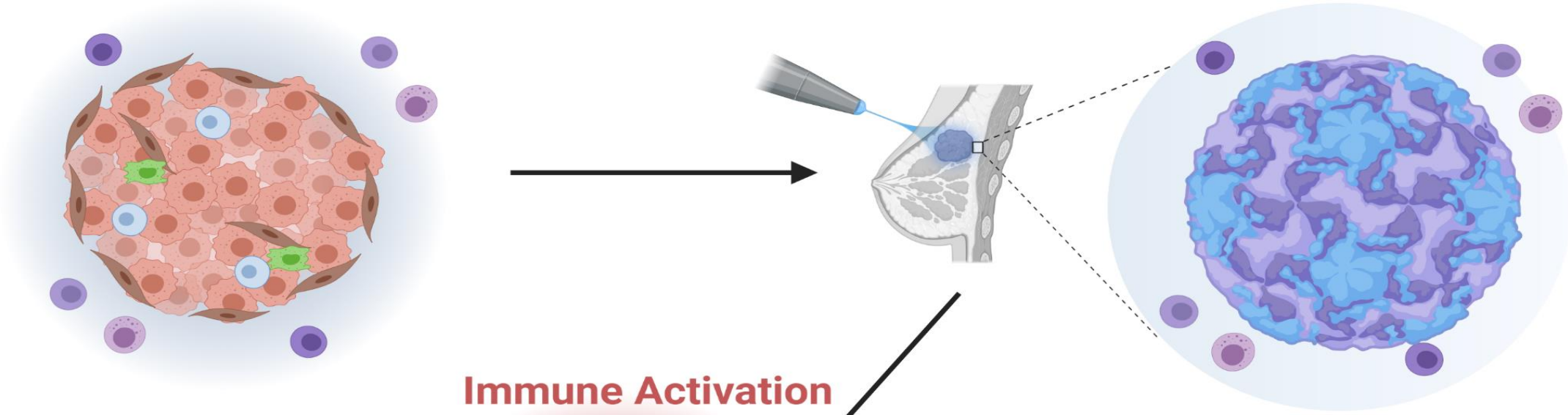
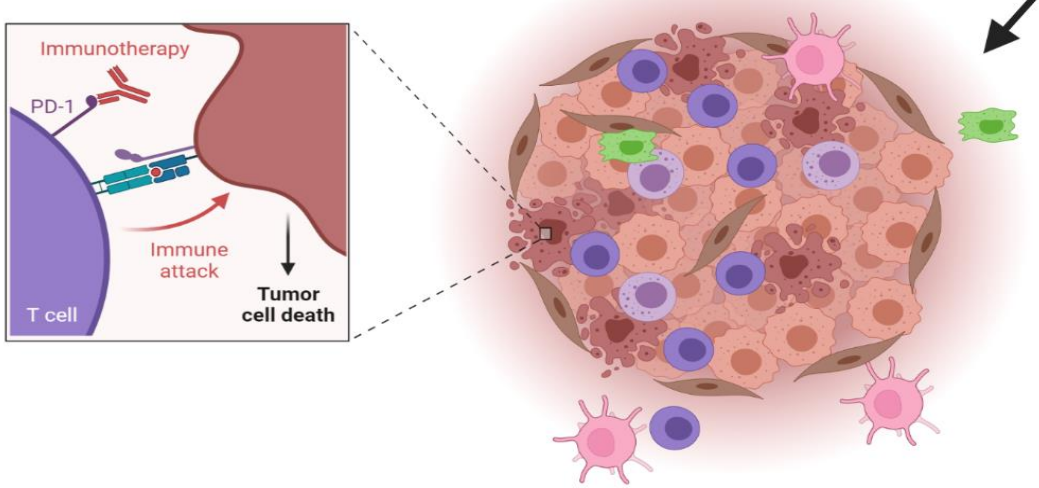
Breast Cancer

Cryoablation



Immune Activation



- Cryoablation uses short intervals of extremely cold temperatures to freeze-thaw the tumor and surrounding tissues.

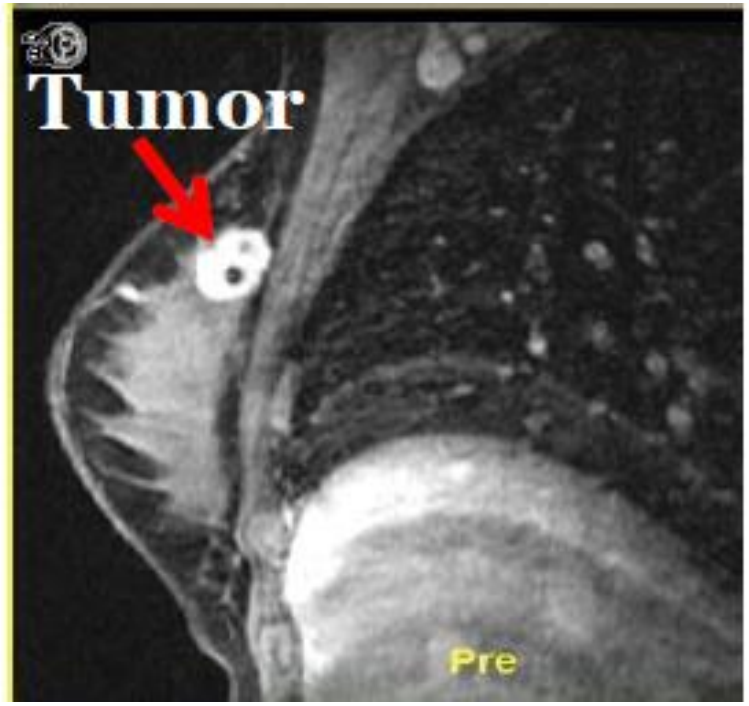
- Freezing causes tumor death (necrosis) AND results in a local inflammatory response

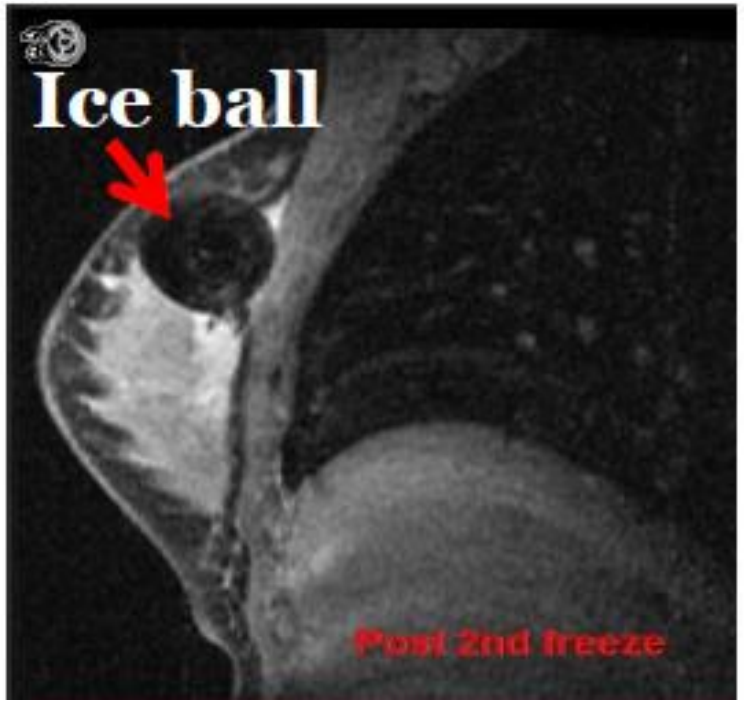
---- Release of intact tumor antigens
---- Release of cellular stress signals
---- Release of immunocytokines

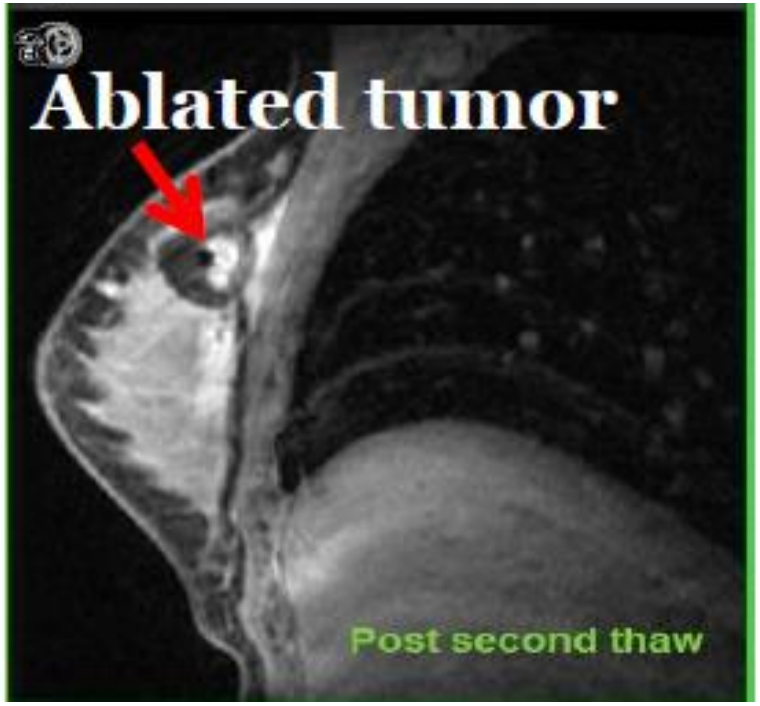
Cancer cell
Dying cancer cell
Treg
Macrophage
CD8+ T cell
NK cell
Dendritic Cells

Created by MGM with BioRender.com

Cryoablation





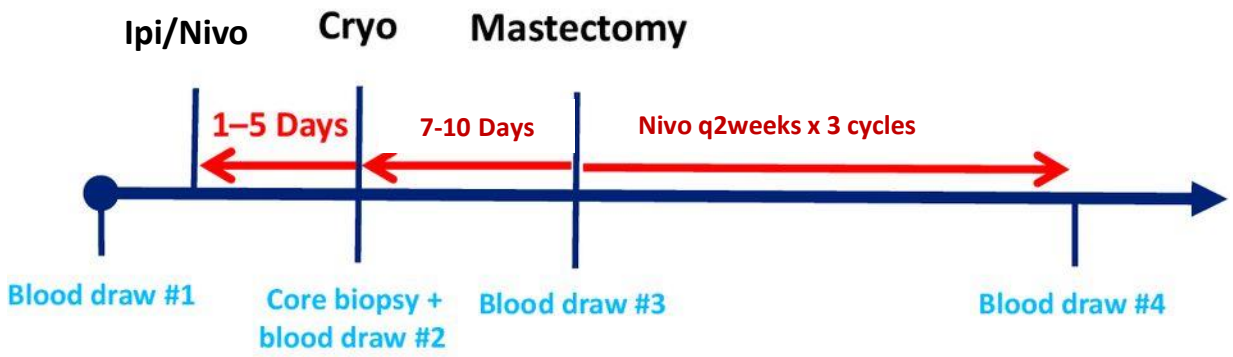


Slide provided by Dr H. McArthur

McArthur et al, CCR 2016

Peri-Operative Ipilimumab+Nivolumab and Cryoablation in Women With Triple-Negative Breast Cancer

Study Schema



Trial Eligibility and Design

- Residual lesion ≥1.0 cm identified on imaging or exam AND Surgical Resection Planned
- Receive preoperative ipilimumab, nivolumab and cryoablation
- Planned n = 80

Major Findings to Date

- **Clinical:**
  - No delays to surgery in first 6 patients
  - Clinical evaluation ongoing
- **Exploratory/Immune:**
  - Increase in activated CD4+ and CD8+ T cells that peaked at week 2 post ipi/nivo with the majority of activated CD 8+ T cell expressing PD1.
- Opened at Cedars-Sinai Medical Center, Providence Portland Medical Center, UT Southwestern
- **Anticipated Opening at OSU Summer 2022**

Study PI: H. McArthur. OSU site PI: M.Gatti-Mays

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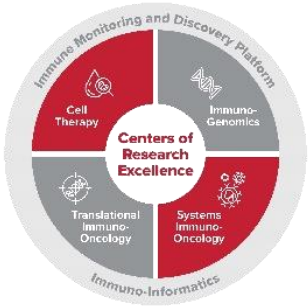
The Pelotonia Institute for Immuno-Oncology

Founding Director: Zihai Li, MD, PhD

cancer.osu.edu/PIIO

A comprehensive bench-to-bedside research initiative focused on harnessing the body's immune system to fight cancer *at all levels* — from **prevention** to **treatment** and **survivorship**

100+ Researchers focused on **Systems** and **Translational IO** and supported by **Immune Monitoring and Discovery** as well as **Immuno-Informatics**



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Work being Performed by PIIO Members in the Breast Cancer Space

Projects (PIIO Members Involved)

- RAGE: A novel therapeutic target against metastatic and triple negative breast cancer (Ramesh K. Ganju, PhD)
- PDGFB in breast cancer initiation, progression and metastasis (Gina Sizemore, PhD)
- Sociodemographic Factors Associated With Rapid Relapse in Triple-Negative Breast Cancer: A Multi-Institution Study (Daniel Stover, MD)
- Interruption of squalene epoxidase and DNA damage response proteins in treatment of breast cancer (Junran Zhang, MD)
- Harnessing innate immunity to improve metastatic breast cancer therapy (Anna Vilgelm, MD, PhD)
- Targeting tissue factor as a novel oncotarget for immunotherapy of triple negative breast cancer (Zhiwei Hu, MD, PhD)
- Gemcitabine, TGFβ imprinted Natural Killer cells and anti-GD2 antibody in advanced breast cancers (Margaret E. Gatti-Mays, MD, MPH)

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