A Phase 2 Single-Arm Open-Label Trial Evaluating Zanidatamab in Patients with Early Stage HER2-positive Breast Cancer: The NeoZanHER Study

Vicente Valero; Paula R. Pohlmann; Jason Mouabbi; Xuelin Huang; Wei Qiao; Heather Alonzo; Rashmi K. Murthy; Gaiane M. Rauch; Taiwo Adesoye; Cristina Checka; Fraser W. Symmans; Dmitri Grachev; Flora Alajajyan; Adaeze Nwosu-Iheme; Amy Hassan; Miral Patel; Sharon H. Giordano; Kelly Hunt; Debasish Tripathy, **Funda Meric-Bernstam**

The University of Texas MD Anderson Cancer Center, Houston, TX, USA; BostonGene Corporation, Waltham, MA, USA,

Cancer
UT MD Anderson

Disclosure Information

Funda Meric-Bernstam, MD

I have the following relevant financial relationships to disclose:

Employee of: UT MD Anderson

Consultant for: AstraZeneca Pharmaceuticals, Becton Dickinson, Biocartis NV, Boehringer Ingelheim International GmbH, Calibr (a division of Scripps Research), Crossbridge Bio, Daiichi Sankyo, Dava Oncology, Debiopharm International, DEM BioPharma Inc, EcoR1 Capital, eFFECTOR Therapeutics, Elevation Oncology, Exelixis, GT Aperion, Incyte Corporation, Jazz Pharmaceuticals, LigaChem Biosciences (formally LegoChem), Menarini Group, ModeX Therapeutics, Inc., Molecular Templates, Precede Biosciences Inc, Protai Bio, Ribometrix, SystImmune, Tacalyx GmbH, TEMPUS, TORL BioTherapeutics, Vir Biotechnology, Zymeworks

Speaker's Bureau for: Cybrexa Therapeutics, go Therapeutics, Guardant Health, Harbinger Health, Illumen Therapeutics, Kivu Biosciences, LOXO-Oncology, OnCusp Therapeutics, Sanofi Pharmaceuticals, Seagen (formerly Seattle Genetics), Sutro Biopharma, Inc., Theratechnologies Inc., Zentalis Pharmaceuticals.

Grant/Research support from AstraZeneca, Daiichi Sankyo Co. Ltd., Debiopharm International, eFFECTOR Therapeutics, Guardant Health Inc., Jazz Pharmaceuticals, Zymeworks.

Honoraria from Dava Oncology and Physician Education Resource (PER).

My additional financial relationship disclosures are Travel-related support has been provided by Cholangiocarcinoma Foundation, Dava Oncology, European Organisation for Research and Treatment of Cancer (EORTC), European Society for Medical Oncology (ESMO), and Physician Education Resource (PER).

Background

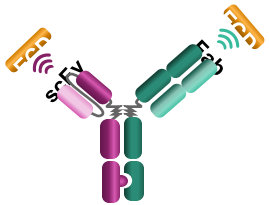
- Treatment of HER2+ breast cancer (BC) is rapidly evolving with routine use of neoadjuvant therapy with high-risk breast cancer and emerging role for ADCs
- The APT trial demonstrated that patients with stage I, lymph node-negative HER2+ BC treated with paclitaxel+trastuzumab for 1 year achieved a 96% 10-year recurrence-free survival
- TBCRC-026, PHERGain and NeoSphere have suggested dual targeted therapy with pertuzumab/trastuzumab may be able to achieve complete pathologic responses
- Effective rescue therapy with HER2 ADCs for non-pCR
- **As HER2-targeted therapy evolves, interest is growing in omitting chemotherapy for early-stage HER2+BC**

Gianni et al, Lancet Oncology, 2012, Connolly et al, JCO, 2019; Connolly et al, JCO, 2021; Tolaney et al, Lancet Oncology 2023; Pérez-García et al The Lancet, 2024; von Minckwitz et al, NEJM, 2019; Loibl et al, NEJM, 2026

Zanidatamab: HER2 Bispecific Ab

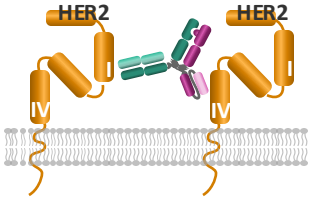
AACR American Association for Cancer Research Annual Meeting April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26

Zanidatamab (ZW25) is a novel HER2-targeted, bispecific antibody that simultaneously binds two distinct sites on HER2: the ECD4 (same target as that of trastuzumab) and the ECD2 (same target as that of pertuzumab)



Fc region

Biparatopic antibody binding in *trans*



- Biparatopic - targets two distinct HER2 epitopes
- Increased tumor cell binding
- Inhibition of both cell signaling and tumor growth,
- Blocks ligand-dependent and -independent tumor growth
- Enhanced HER2 internalization and down-regulation
- Potent complement-dependent cytotoxicity
- Antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP)

On November 20, 2024, the FDA granted accelerated approval to zanidatamab for previously treated, unresectable or metastatic HER2 IHC 3+ biliary tract cancer (BTC)

Weisser et al, Nat Communications, 2023

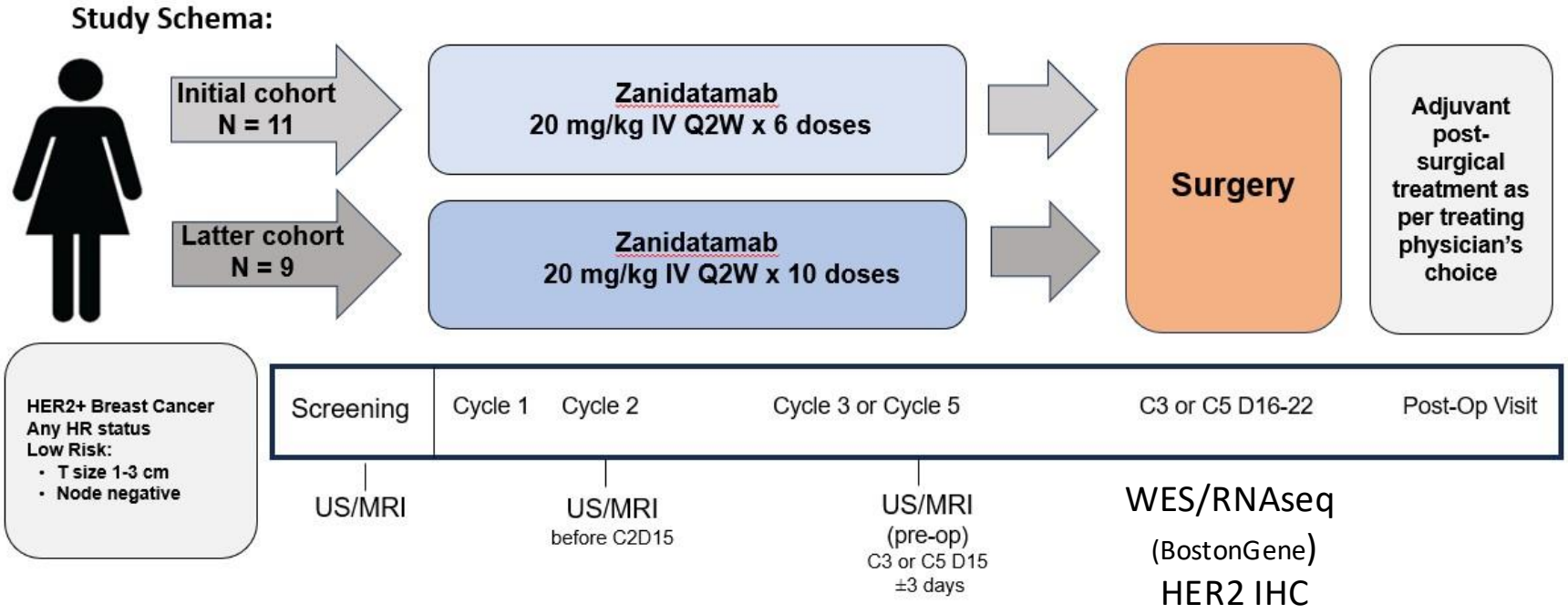
Study Objectives

- **Primary Objective:**
- To determine the efficacy of zanidatamab for patients with early stage HER2/neu positive (HER2+) breast cancer (BC) as determined by pathologic complete response (pCR)

- **Secondary Objective(s):**
- To determine pathologic response by residual cancer burden (RCB) [1]
- To evaluate the radiographic response and volumetric change in tumor size by ultrasound (US) and MRI
- To evaluate tolerability and safety of zanidatamab for treatment-naïve early stage HER2+ breast cancer
- To evaluate the rate of adverse events and treatment-emergent adverse events with zanidatamab alone (for patients with hormone receptor negative tumors) or with endocrine therapy tamoxifen or letrozole (in hormone receptor positive tumors)
- To evaluate the feasibility of treating patients with early stage HER2+ breast cancer with monotherapy zanidatamab
- To determine tumor-based predictive biomarkers of response

[1] Symmans WF, JCO, 2017

Study Schema



Patients that were HR+ also received endocrine therapy at physician discretion.

Patient and Tumor Characteristics

AACR American Association for Cancer Research Annual Meeting April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26

Characteristic, n (%)	N = 20
Age, years	
<60	9 (45%)
≥60	11 (55%)
Menopausal status	
Post	13 (65%)
Pre	7 (35%)
Pretreatment tumor size	
≤2 cm	**11 (55%)**
>2 cm	**9 (45%)**
HER2 status	
IHC 3+	15 (75%)
IHC 2+/FISH+	**5 (25%)**
ER/PR status	
ER+/PR+	13 (65%)
ER+/PR−	3 (15%)
ER−/PR−	4 (20%)
Endocrine therapy	
None	6 (30%)
Letrozole	**8 (40%)**
Tamoxifen	**6 (30%)**

45% with tumors >2 cm

75% pts HER2 3+
80% ER+ HER2+

87.5% ER+HER2+ pts also got endocrine therapy

Treatment-Related Adverse Events

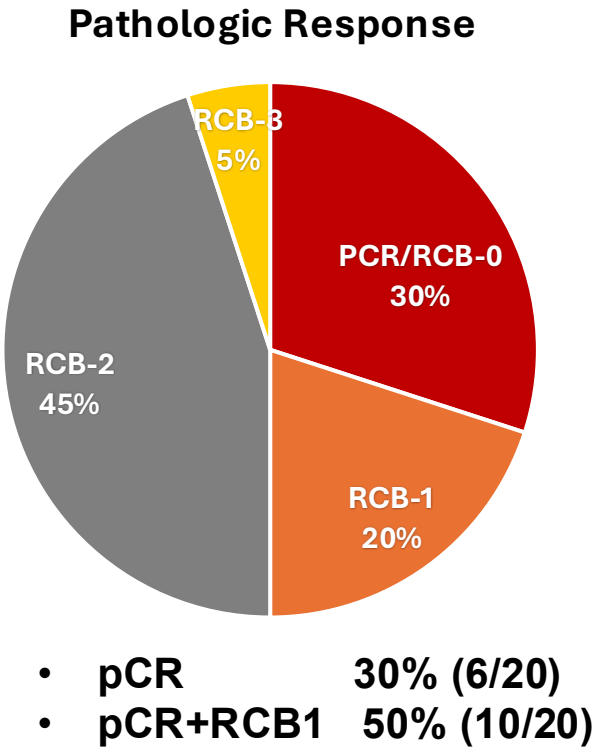
Adverse event			
AE term	Grade 1 n (%)	Grade 2 n (%)	Total N (%)
Diarrhea	15 (75%)	3 (15%)	18 (90%)
Fatigue	11 (55%)	0	11(55%)
Hyperglycemia	11 (55%)	0	11(55%)
Anemia	9 (45%)	0	9 (45%)
Alanine aminotransferase increased	4 (20%)	2	6 (30%)
Alkaline phosphatase increased	6 (30%)	0	6 (30%)
Nausea	6 (30%)	0	6 (30%)
Headache	4 (20%)	0	4 (20%)
Aspartate aminotransferase increased	4 (20%)	0	4 (20%)
Rash acneiform	2 (10%)	1(5%)	3 (15%)
Pruritus	3 (15%)	0	3 (15%)
Gastroesophageal reflux disease	3 (15%)	0	3 (15%)
Hypokalemia	3 (15%)	0	3 (15%)
Hypertension	0	3 (15%)	3 (15%)
Rash maculo-papular	2 (10%)	0	2 (10%
Dysgeusia	2 (10%)	0	2 (10%)
Anorexia	2 (10%)	0	2 (10%)
Infusion related reaction	0	1 (5%)	1 (5%)
Chills	1 (5%)	0	1 (5%)

- Zanidatamab was well tolerated
- Low grade diarrhea as most common TRAE
- No grade 3 or higher TRAE

Results: Pathologic Response

AACR American Association for Cancer Research
Annual Meeting
April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26

Residual cancer	Number (%)
pCR/RCB-0	6 (30%)
RCB-1	4 (20%)
RCB-2	9 (45%)
RCB-3	1 (5%)
Pathological stage	
pT0N0	5 (25%)
pTisN0	1 (5%)
pT1cN1	1 (5%)
pT1aN0	2 (10%)
pT1bN0	1 (5%)
pT1cN0	3 (15%)
pT1cN1a	1 (5%)
pT1cN1mi	2 (10%)
pT2N0	4 (20%)



- pCR 30% (6/20)
- pCR+RCB1 50% (10/20)

Associations of clinical characteristics with pathologic response and residual cancer burden

AACR American Association for Cancer Research Annual Meeting April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26

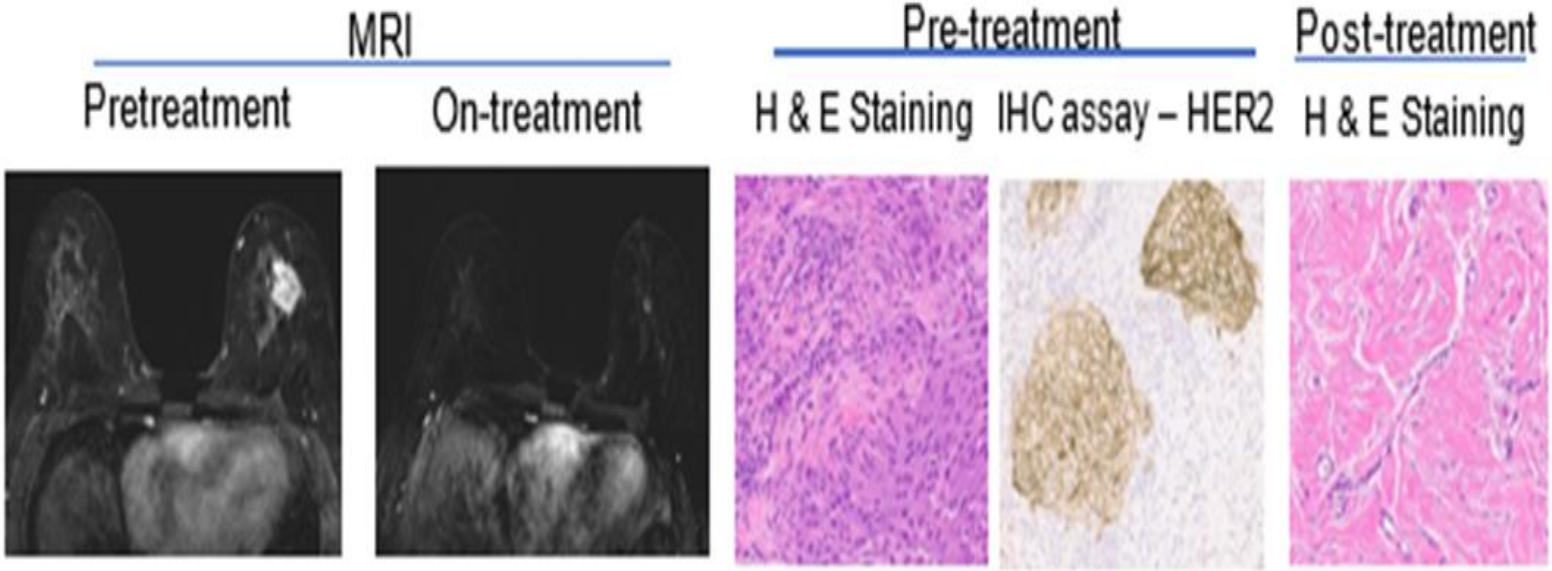
Covariate	pCR	No pCR	P-value	RCB-0/1	RCB-2/3	P-value
Age						
<60	4 (66.7%)	5 (35.7%)	0.336	5 (50%)	4 (40%)	1.000
≥60	2 (33.3%)	9 (64.3%)	.	5 (50%)	6 (60%)	.
Menopausal Status						
Post	3 (50%)	10 (71.4%)	0.613	6 (60%)	7 (70%)	1.000
Pre	3 (50%)	4 (28.6%)	.	4 (40%)	3 (30%)	.
Pretreatment tumor size						
≤2 cm	2 (33.3%)	9 (64.3%)	0.336	4 (40%)	7 (70%)	0.370
>2 cm	4 (66.7%)	5 (35.7%)	.	6 (60%)	3 (30%)	.
HER2 status						
IHC 2+	0 (0%)	5 (35.7%)	0.260	2 (20%)	3 (30%)	1.000
IHC 3+	6 (100%)	9 (64.3%)	.	8 (80%)	7 (70%)	.
Endocrine Therapy						
Letrozole	1 (16.7%)	7 (50%)	0.339	4 (40%)	4 (40%)	1.000
NA	2 (33.3%)	4 (28.6%)	.	3 (30%)	3 (30%)	.
Tamoxifen	3 (50%)	3 (21.4%)	.	3 (30%)	3 (30%)	.

No clinical variables were associated with pCR

Limited sample size

All pts with pCR had IHC 3+

Pathologic Response and Example of Responder

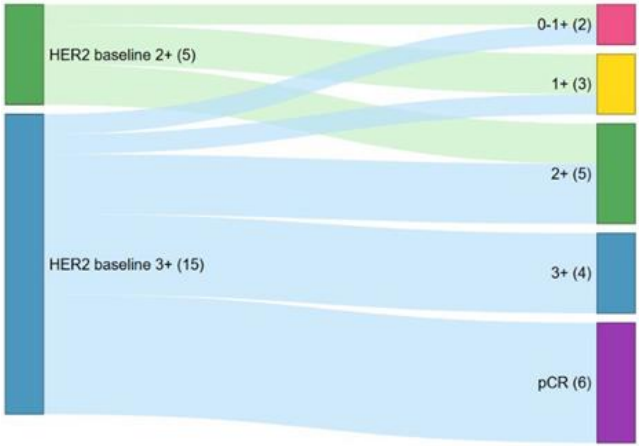


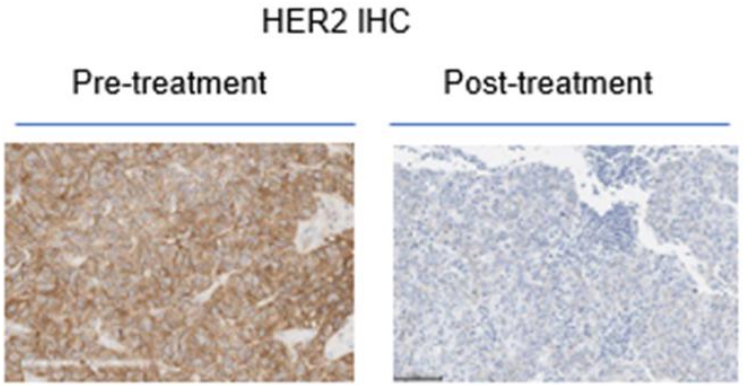
Radiographic Changes

- 20 patients with pre (baseline) and on-treatment (C2D15) US
  - Significant decrease in tumor size ($p=0.0005$) and tumor volume (TV; $p<0.0001$) with treatment by US
- 17 patients with pre and on-treatment MRIs
  - Significant decrease in tumor size ($p=0.009$) and TV ($p=0.0001$)
- 17 patients had tumor metrics assessable at third, preoperative US
  - **Patients with pCR (n=5) showed a greater preop reduction in US tumor size than those without pCR (p=0.31 Wilcoxon rank sum test, p=0.008 t-test)**
  - 5 patients had a complete radiological response on preop US
    - 3 had pCR, one had RCB-1, and another RCB-2

Changes in HER2 Testing and Loss of HER2 Expression

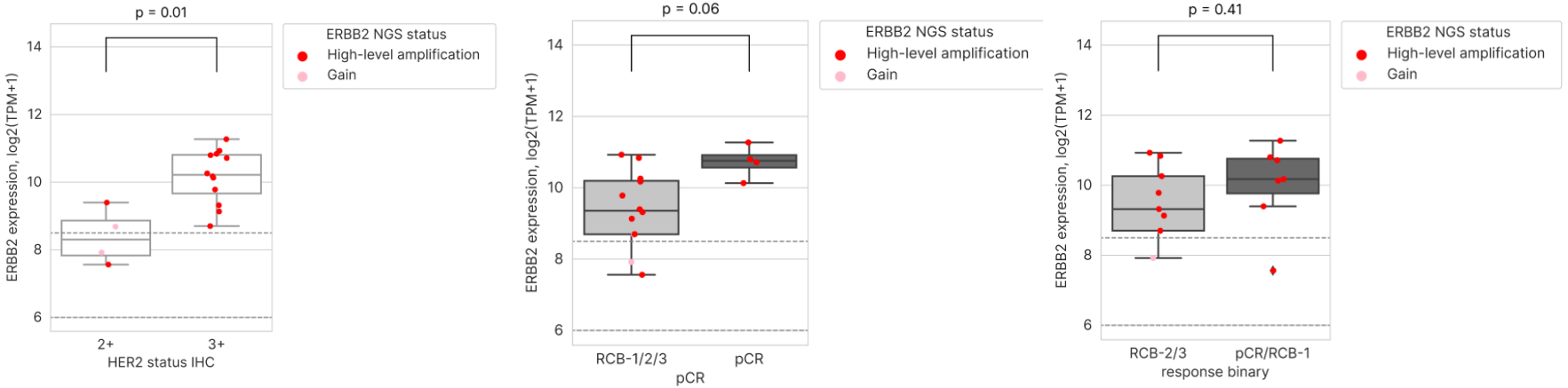
AACR American Association for Cancer Research
Annual Meeting
April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26





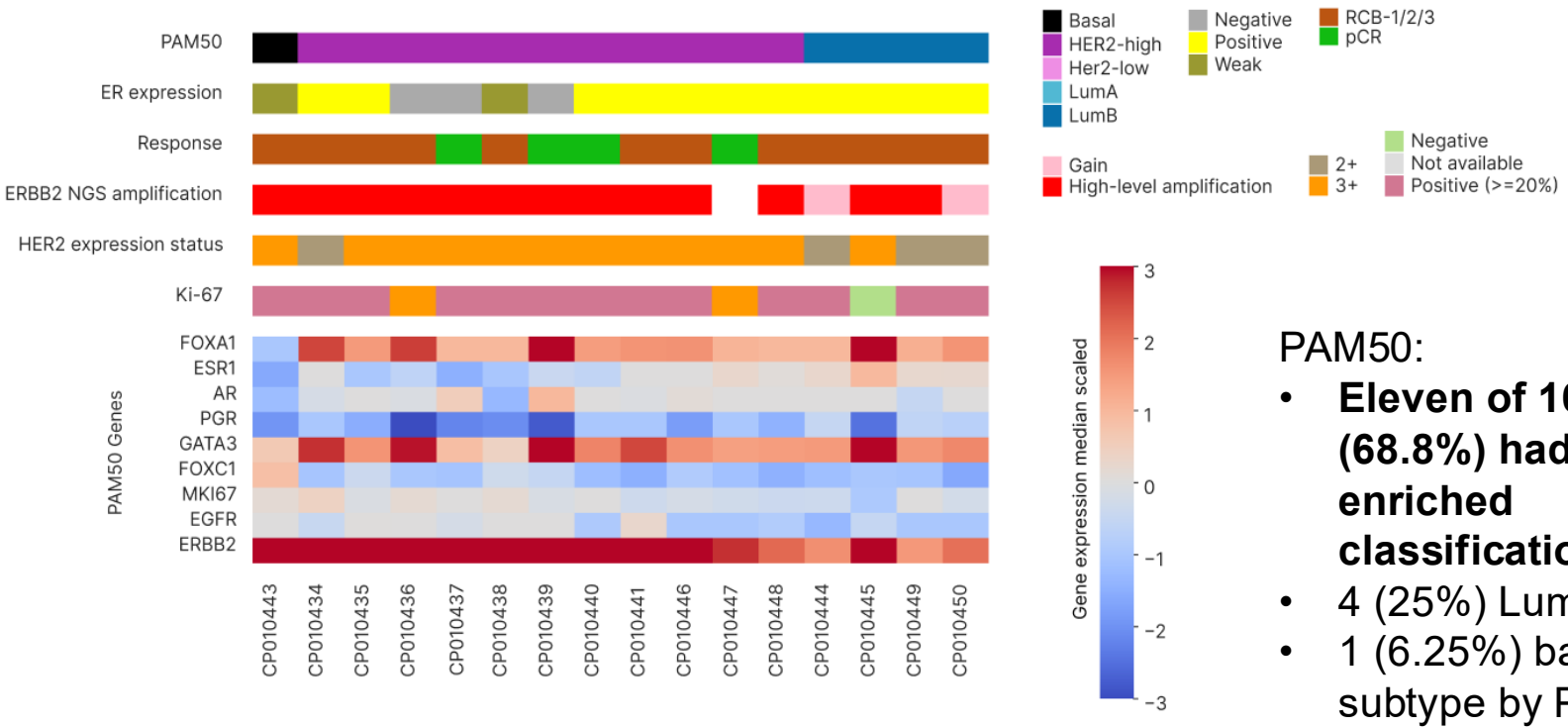
- Residual tumor was characterized in 14 patients without pCR.
- Among HER2 3+ baseline (n=9), 56% (5/9) demonstrated HER2 downregulation :
  - HER2 3+ (N=4), HER2 2+ (n=3), HER2 1+ (n=1), HER2 0-1+ (n=1)

ERBB2 RNA expression and copy number by response



- WES and RNAseq on 17 and 16 pre-treatment samples respectively.
- **All 4 responders (pCR) with WES had *ERBB2* amp.**
- *ERBB2* RNA expression was significantly higher in the 12 patients with HER2 IHC 3+ compared with patients with HER2 IHC 2+/ISH+ (p=0.01)
- *ERBB2* RNA expression was numerically higher in patients with pCR compared with patients without pCR (p=0.06)

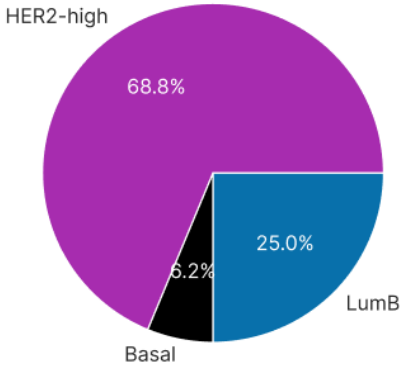
PAM50 subtypes

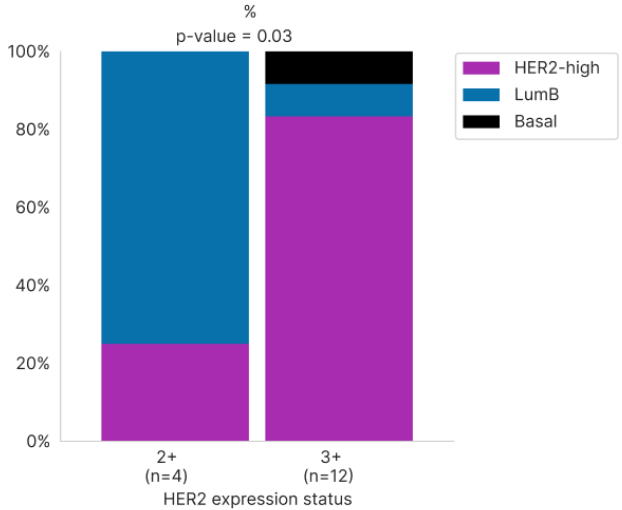


PAM50:

- **Eleven of 16 patients (68.8%) had HER2 enriched classification**
- 4 (25%) Luminal B
- 1 (6.25%) basal subtype by PAM50 classification

Distribution of PAM50 subtypes

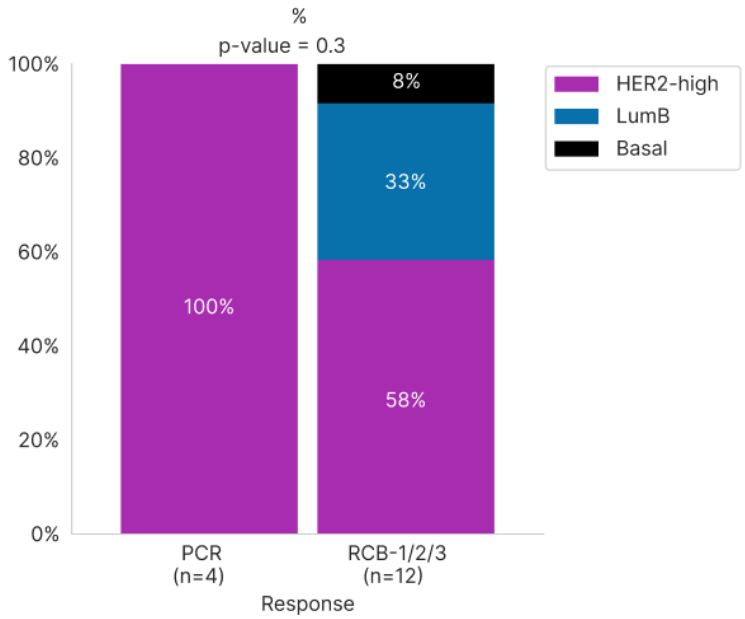


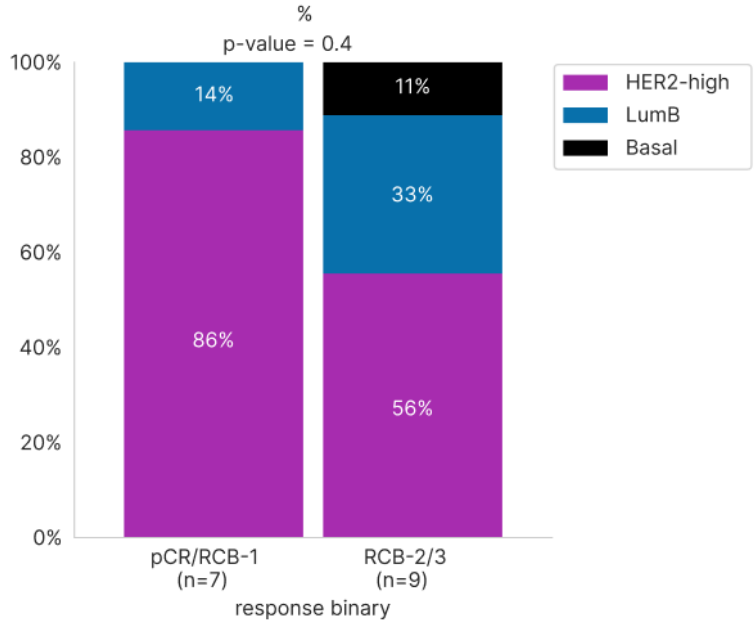


- **Patients with HER2 IHC 3+ were more likely to have HER2-high classification compared to patients with HER2 IHC 2+ cancers (p=0.03)**
- Only one patient with HER2 IHC 2+ was HER2-high classification
- 3 of 4 patients with luminal B classification had HER2 IHC 2+ tumors

PAM50 subtypes by response

AACR American Association for Cancer Research
Annual Meeting
April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26

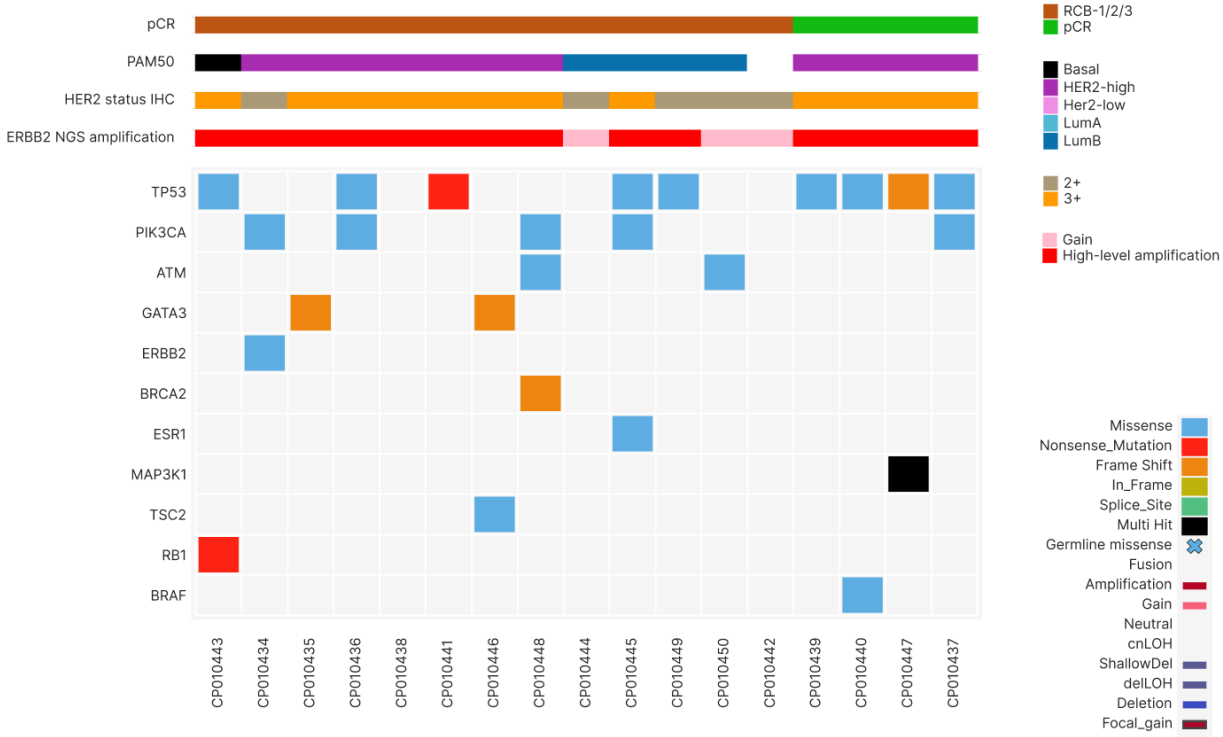




All patients with pCR, and 6 of 7 patients with RCB-0/1 had PAM50 HER2-high tumors.

Genomic features of patients on whole exome sequencing

AACR American Association for Cancer Research
Annual Meeting
April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26



Patients without pCR had more genomically diverse tumors.

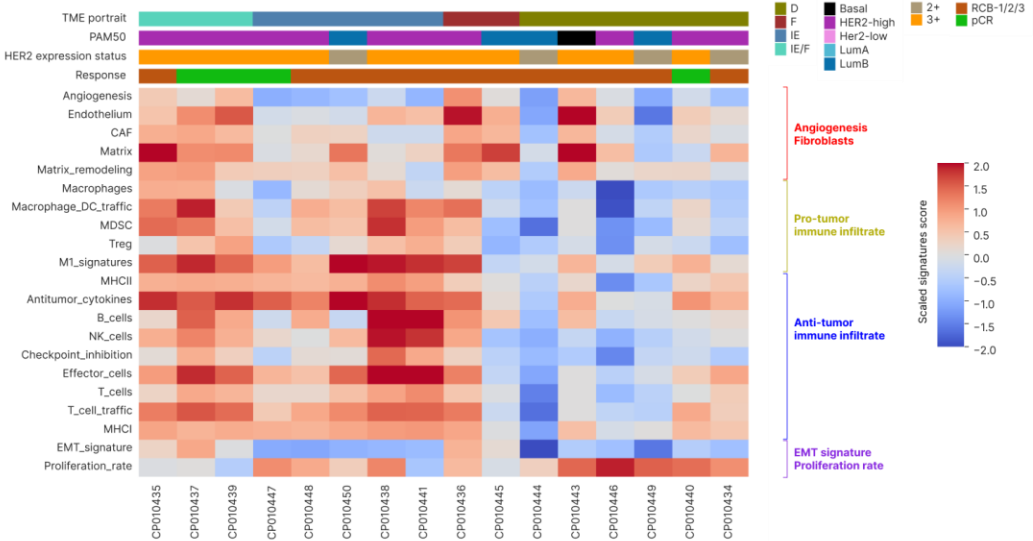
All 4 patients with pCR had *ERRB2* amplification and a *TP53* mutation.

One of the patients with pCR had a PIK3CA H1047R mutation while another had *MAP3K1* mutations.

One of 5 patients with a *PIK3CA* alteration had a pCR.

Immune classifications of tumors based on gene expression profiling

AACR American Association for Cancer Research
Annual Meeting
April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26



Tumor microenvironment (TME) was classified into 4 previously described subtypes:

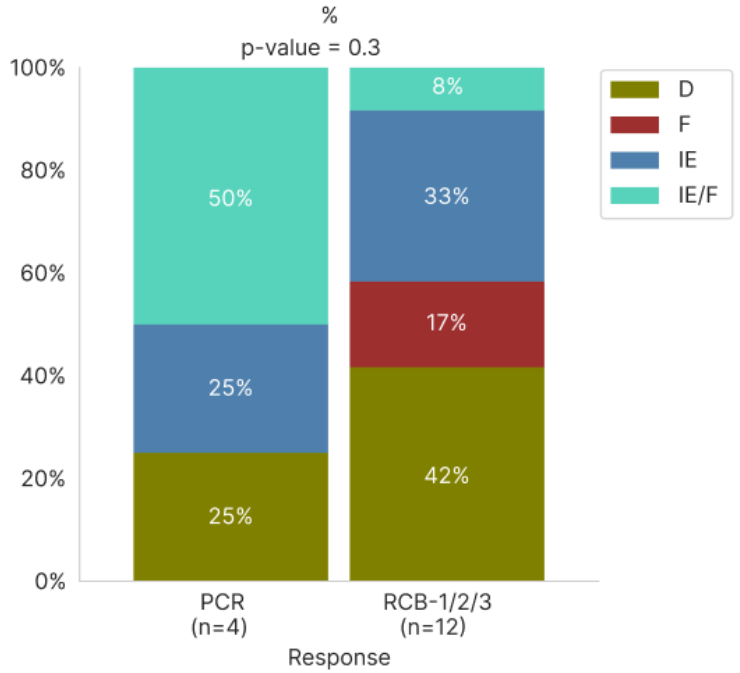
- Immune enriched/fibrotic (IE/F)
- Immune enriched (IE)
- Fibrotic (F)
- Immune desert (D)

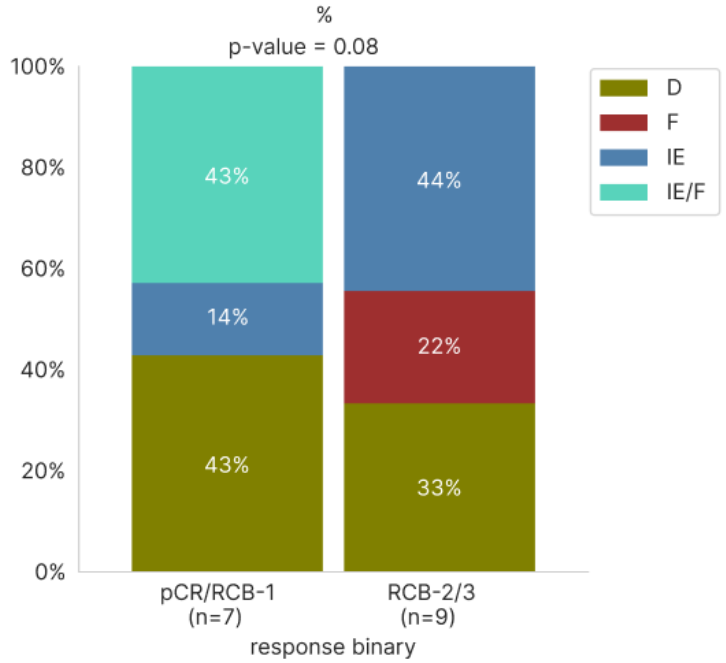
Non- fibrotic subtypes dominated the cohort.

Bagaev A, et al, Cancer Cell, 2021

Distribution of immune profiles based on response

AACR American Association for Cancer Research
Annual Meeting
April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26





3 of 4 patients with HER2 IHC 2+ disease had tumors of immune desert subtype.
Patients with better responses more frequently had immune-enriched tumors, but not statistically significant.

Conclusions

- Zanidatamab and endocrine therapy if ER+ tumor in patients with node negative, 1-3 cm HER2+ BC was associated with robust antitumor activity and manageable safety profile.
- Omitting chemotherapy and using targeted therapy alone in patients with early- stage HER2+BC is feasible
- All patients with pCR had HER2 IHC 3+ tumors, *ERBB2* amplification on WES, PAM50 HER2-high subtype, and a trend towards higher HER2 RNA expression. pCR was not dependent on ER status.
- Evaluating translational strategies for early response assessment to facilitate an adaptive design to de-escalate or escalate chemotherapy are urgently needed.

Acknowledgements

Multidisciplinary Breast Team at UT MD Anderson Cancer Center

Funding:

- **Investigator-initiated trial funded by Zymeworks and Jazz Pharmaceuticals**
  - Nellie B Connally Research funds
  - NCATS grant UM1 TR0045906,
  - P30 CA016672 (University of Texas MD Anderson Cancer Center).

We thank our patients and their families and caregivers

THANK YOU!

Questions/comments/collaborations/concepts:

fmeric@mdanderson.org