Utilizing Neoadjuvant Clinical Trials to Individualize Breast Cancer Treatment and Optimize Outcomes

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Disclosures

- Clinical Trial Support
  - Takeda Pharmaceuticals

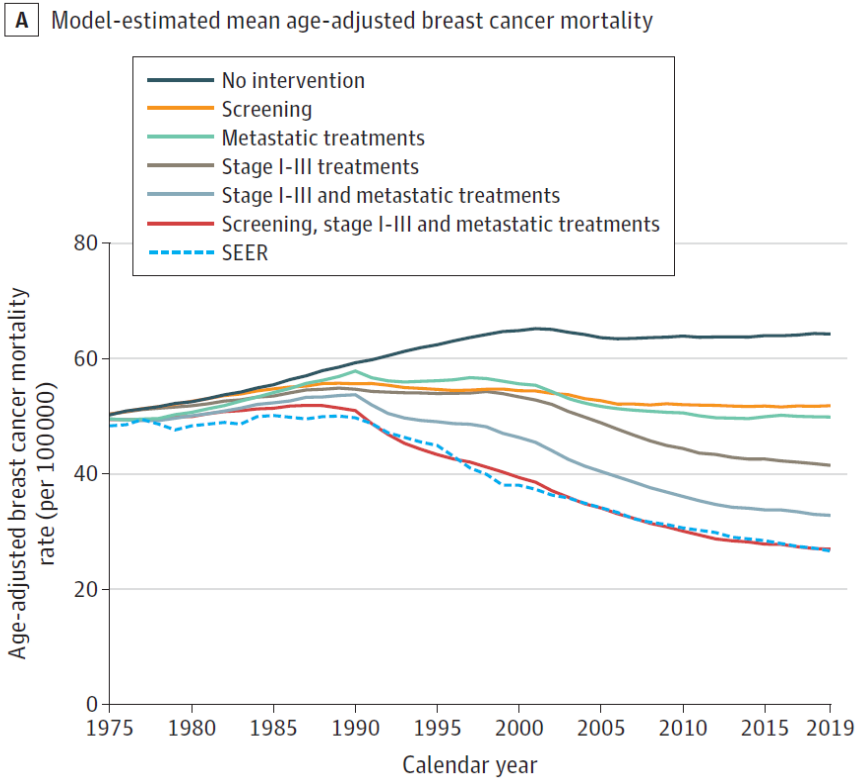
- Pending Clinical Trial Support

- Puma Biotechnology
- Eikon Therapeutics
- Scripps Research

Modeling Reduction In Breast Cancer Mortality

Despite a 1% annual increase in breast cancer incidence, breast cancer mortality rates have dropped by 44% since 1989.

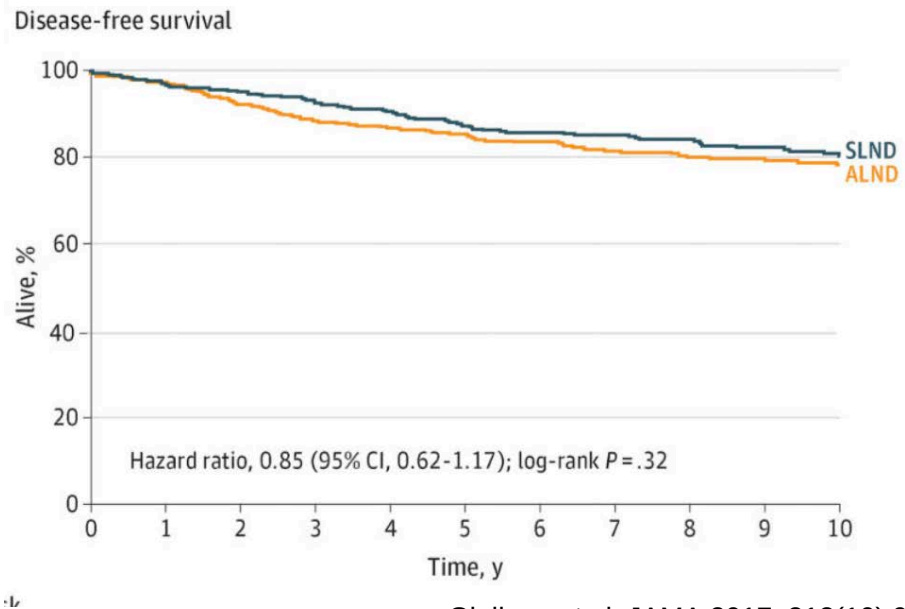
American Cancer Society Breast Cancer Statistics. Oct 1, 2024



Caswell-Jin, et al. JAMA 331:233 2024 PMID: 38227031

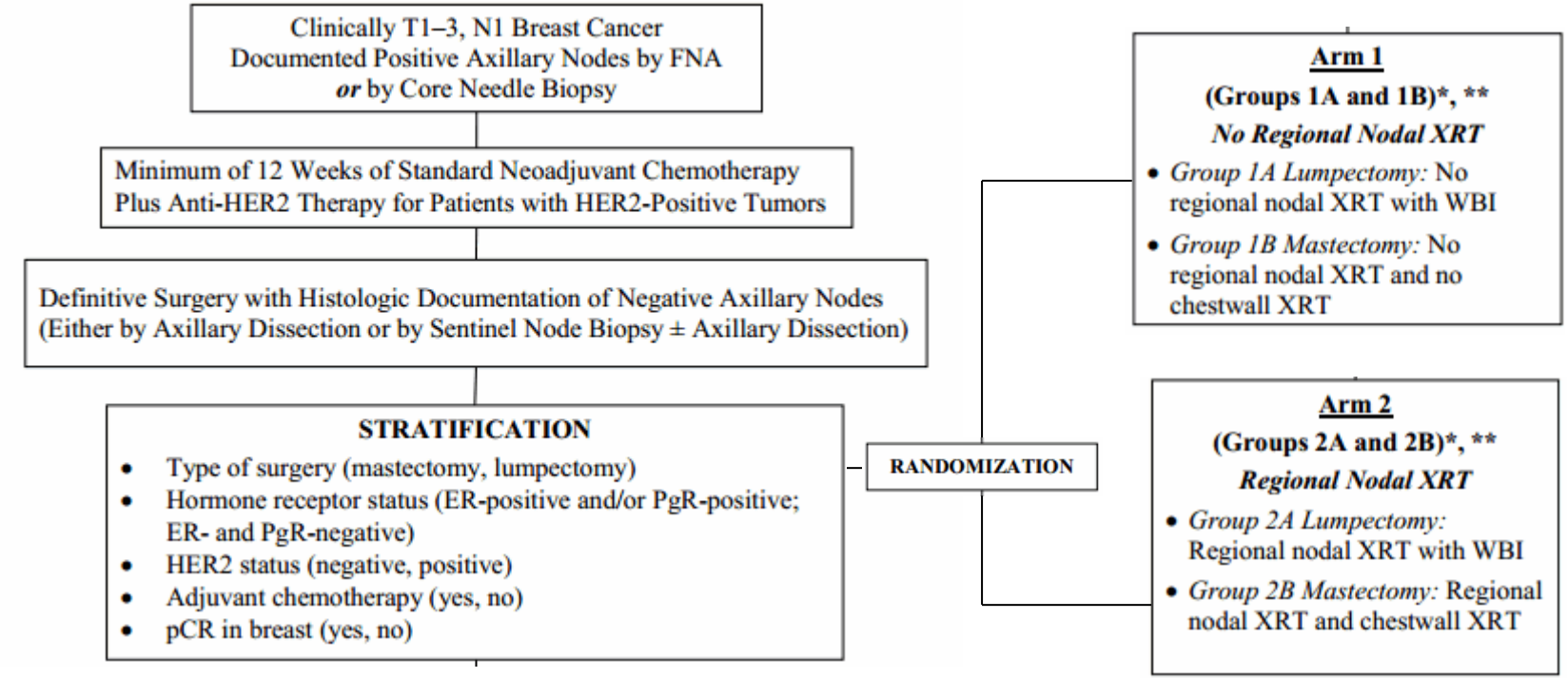
ACOSOG Z0011 – Sentinel lymph node biopsy as SOC in patients with nonpalpable lymph nodes prior to surgery

Women with T1 or T2 invasive breast cancer, no palpable axillary adenopathy, and 1 or 2 positive sentinel lymph nodes were randomized to sentinel lymph node biopsy vs axillary lymph node dissection



Giuliano et al. JAMA 2017; 318(10):918-926.

Omission of Nodal Radiotherapy after Nodal pCR to Neoadjuvant Chemotherapy: NSABP B51 Preliminary Results



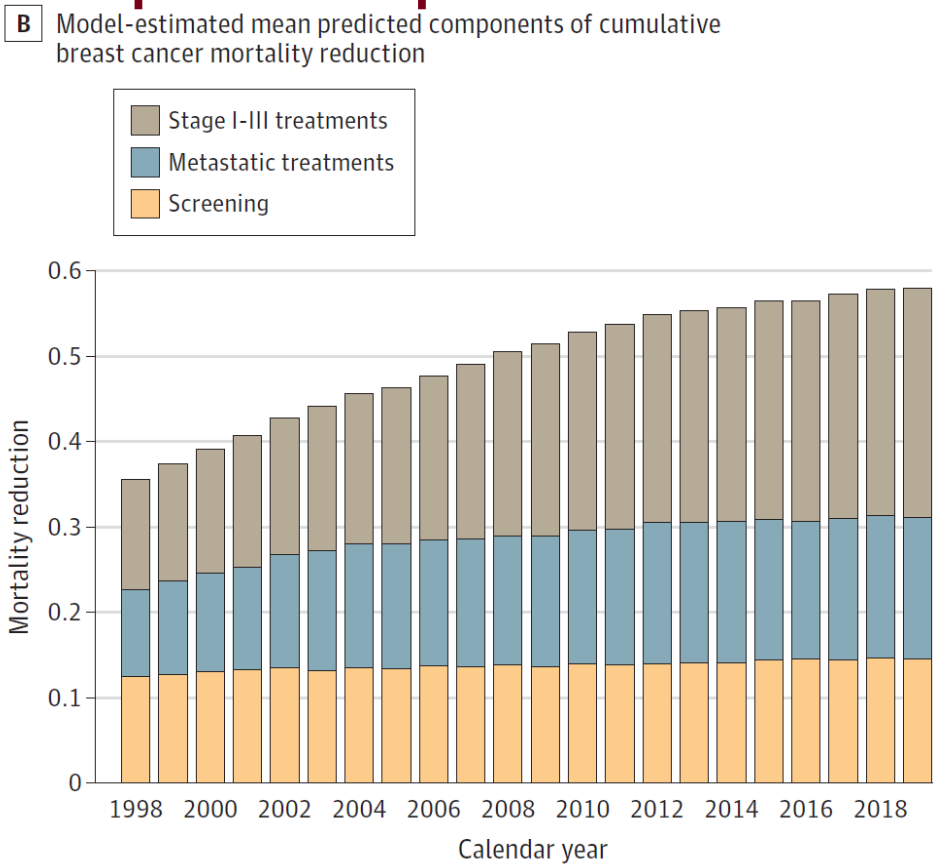
http://www.nsabp.pitt.edu/B-51.asp

NSABP B-51: Preliminary Results

- No significant difference in 5-year:
  - Invasive breast cancer recurrence-free interval (91.8% no RNI vs. 92.7% RNI, p=0.51)
  - Isolated locoregional recurrence-free interval (98.4% no RNI vs. 99.3% RNI, p=0.088)
  - Disease-free survival or overall survival
  - Subgroup differences show that HR+/HER2- may favor RNI

Mamounas et al., SABCS 2023

New Therapies Improve Outcomes



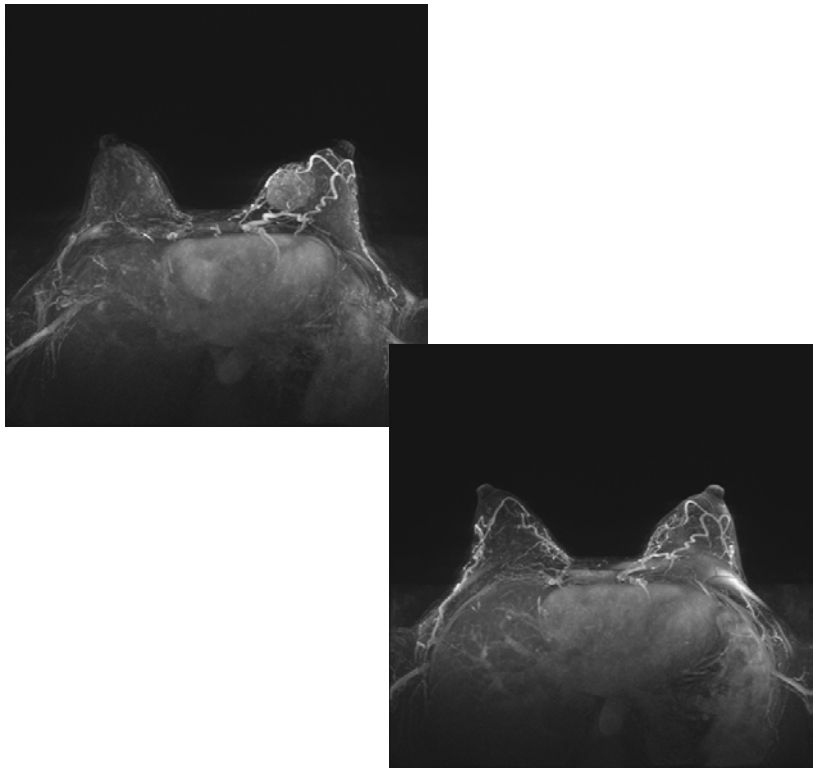
Caswell-Jin, et al. JAMA 331:233 2024 PMID: 38227031

Evolution of Neoadjuvant Therapy Use

Historically for inoperable or locally advanced breast cancer to downstage breast and axilla for breast conservation

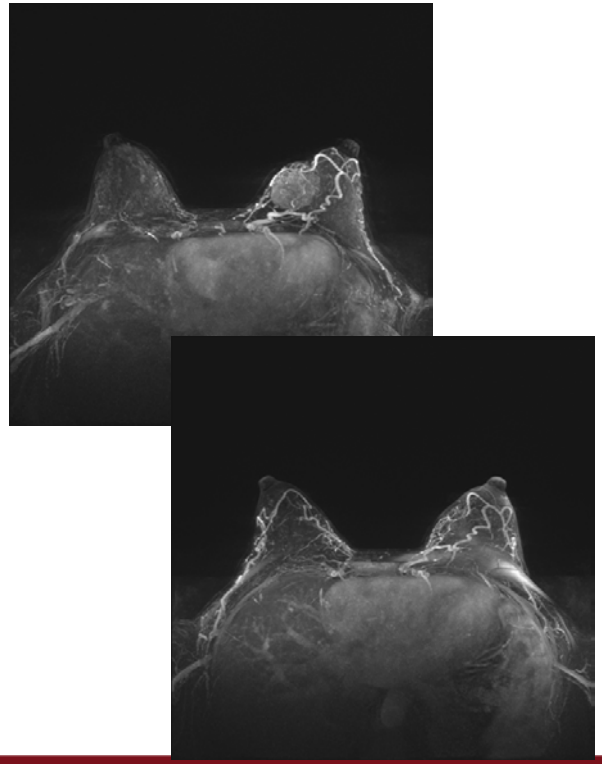
Current Uses:

- All unresectable breast cancer
- All triple-negative and HER2+ tumors >2 cm in size
- High-risk and or high-grade tumors HR+/HER2- patients
- Any patient who desires breast conservation and improved cosmesis

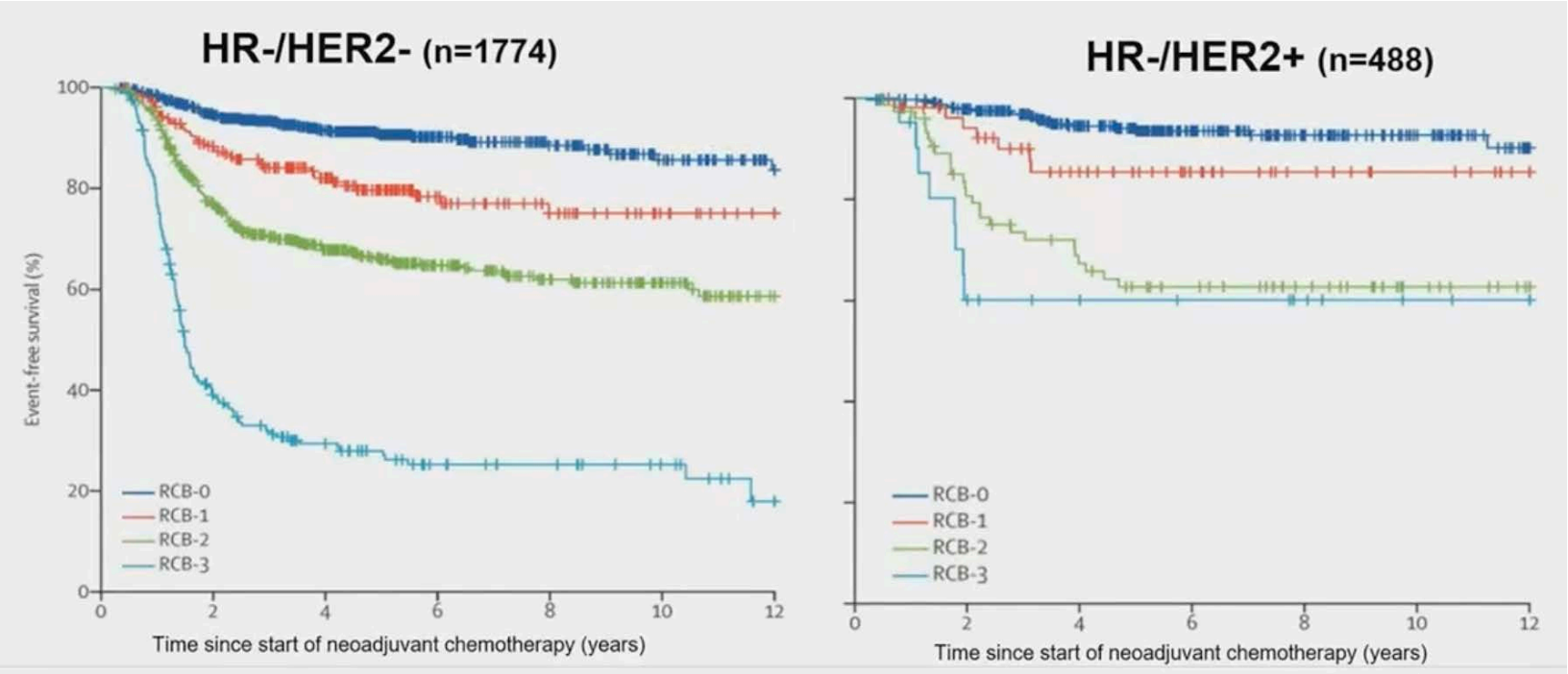


Neoadjuvant therapy, imparting the knowledge of who needs more treatment and who needs less

- Ability to monitor response to treatment
- Ability to predict prognosis based on response
  - pCR predicts improved outcomes
- Ability to choose adjuvant therapies based on response.

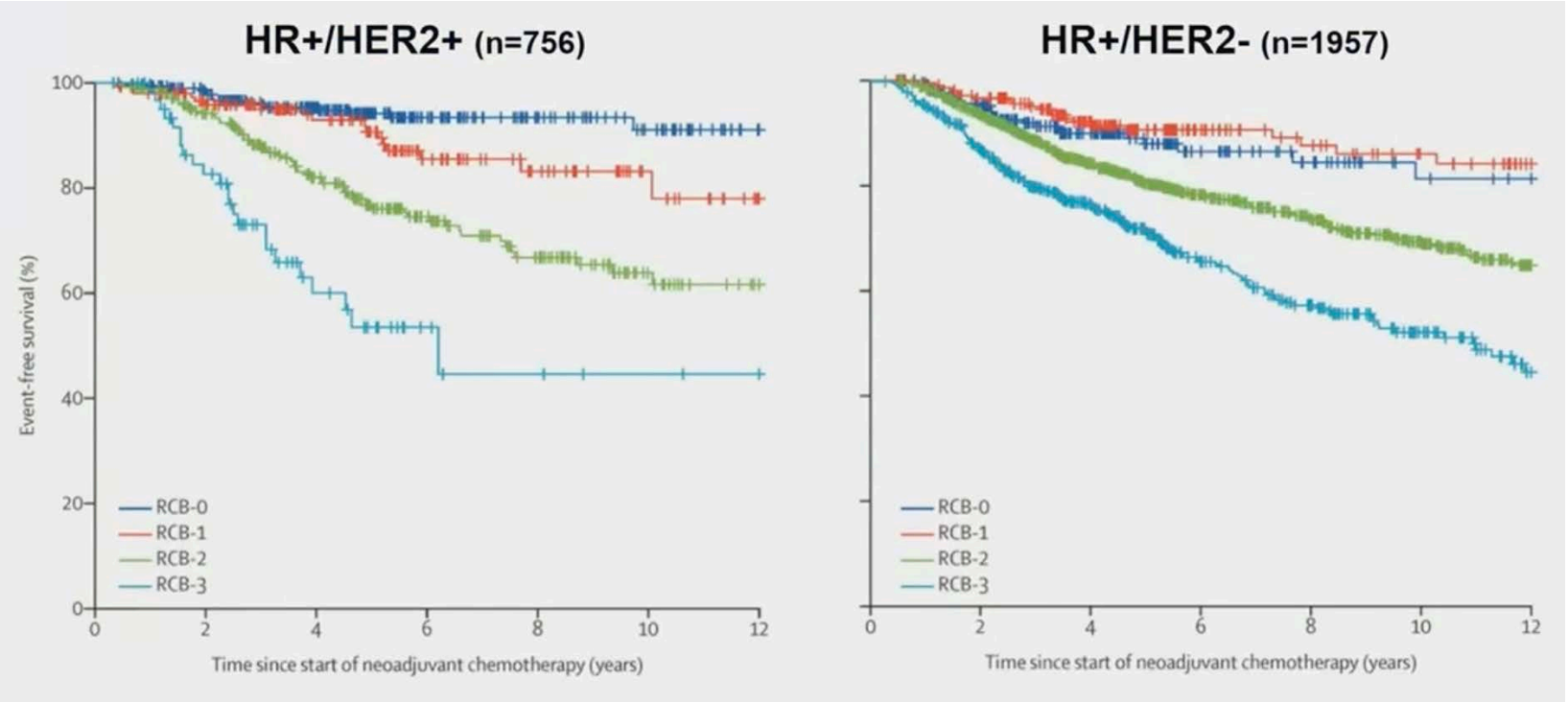


Why give neoadjuvant v adjuvant



Yau et al. Lancet Onc 2022

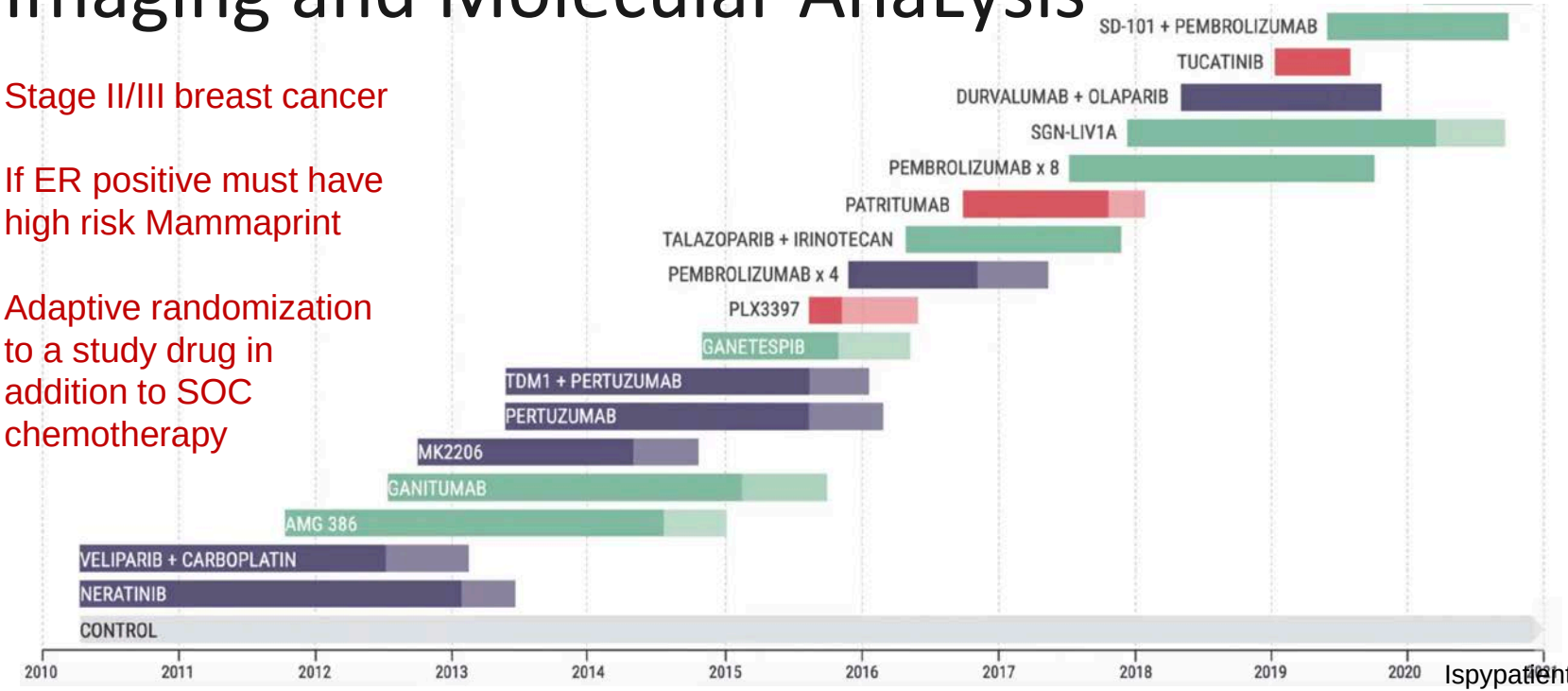
Prognostic significance of RCB



Yau et al. Lancet Onc 2022

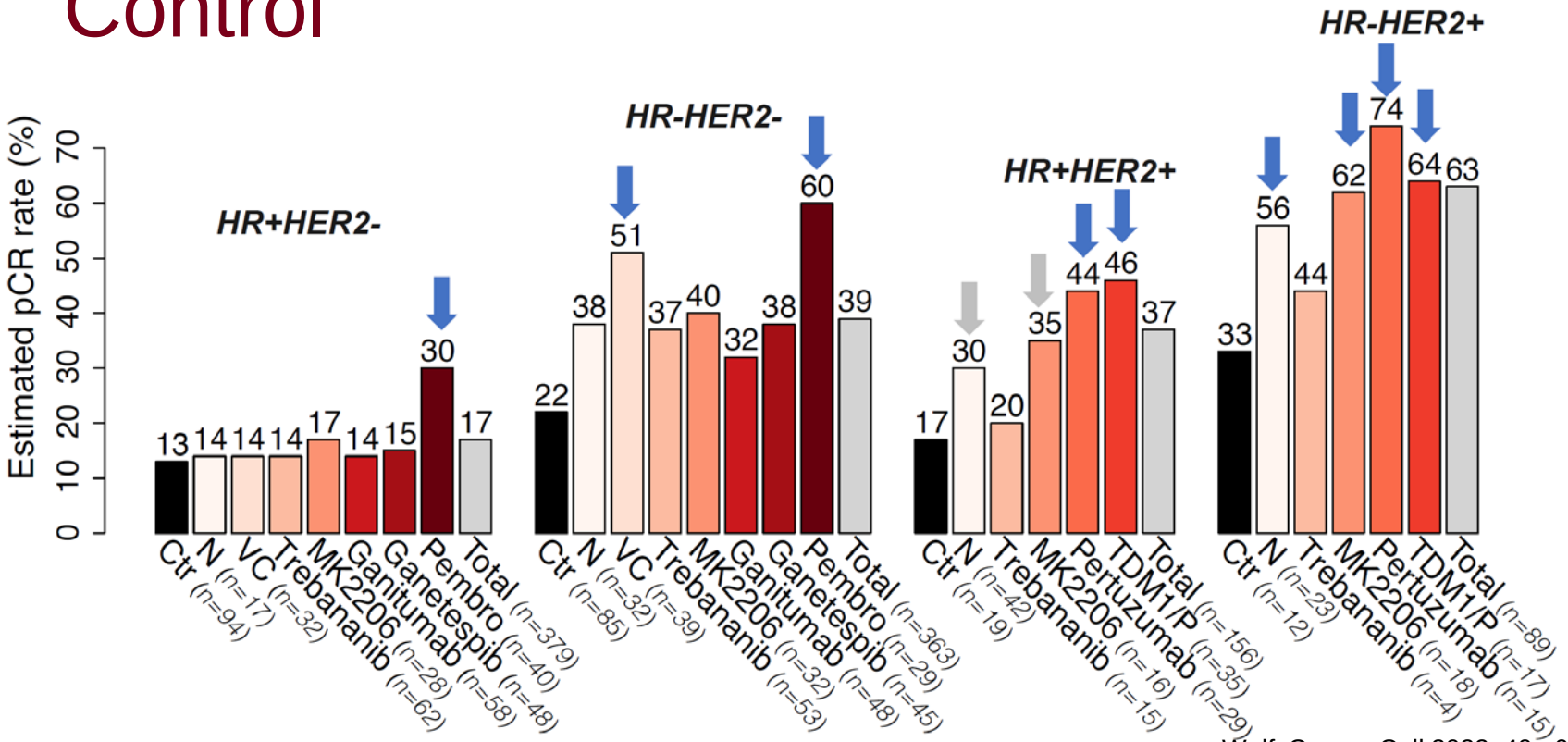
ISPY 2: Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and Molecular AnaLysis

- Stage II/III breast cancer
- If ER positive must have high risk Mammaprint
- Adaptive randomization to a study drug in addition to SOC chemotherapy



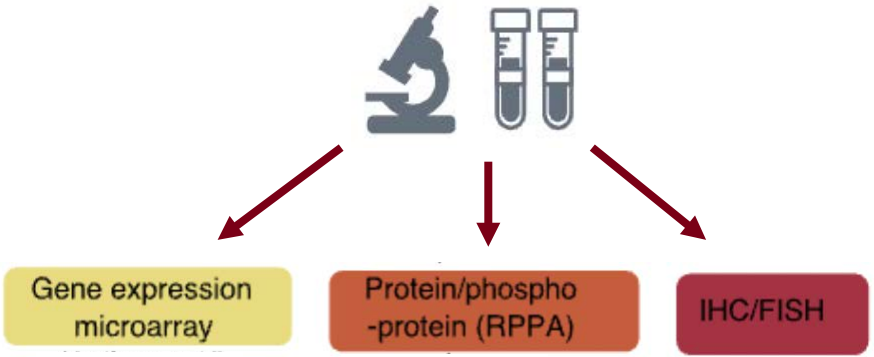
Ispypatient.org

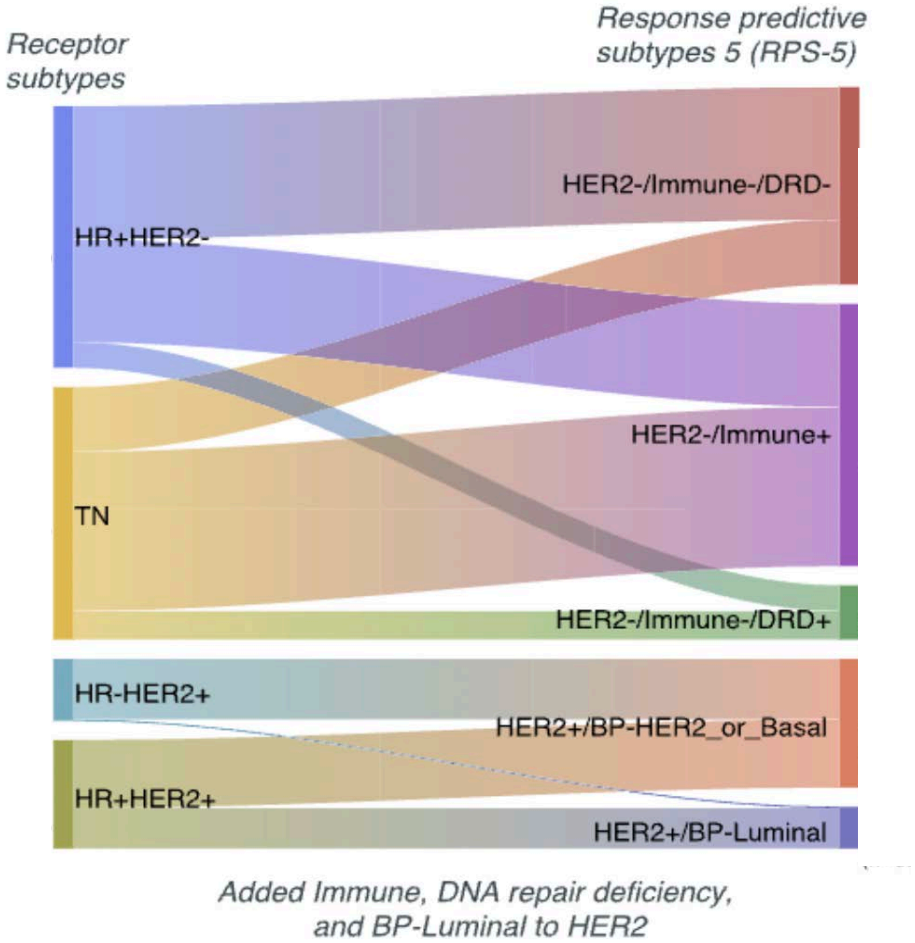
Most New Drugs Are Superior To Control



Wolf, Cancer Cell 2022; 40: 609-623

Response predictive subtypes (RPS) defined by the ISPY2 clinical trial

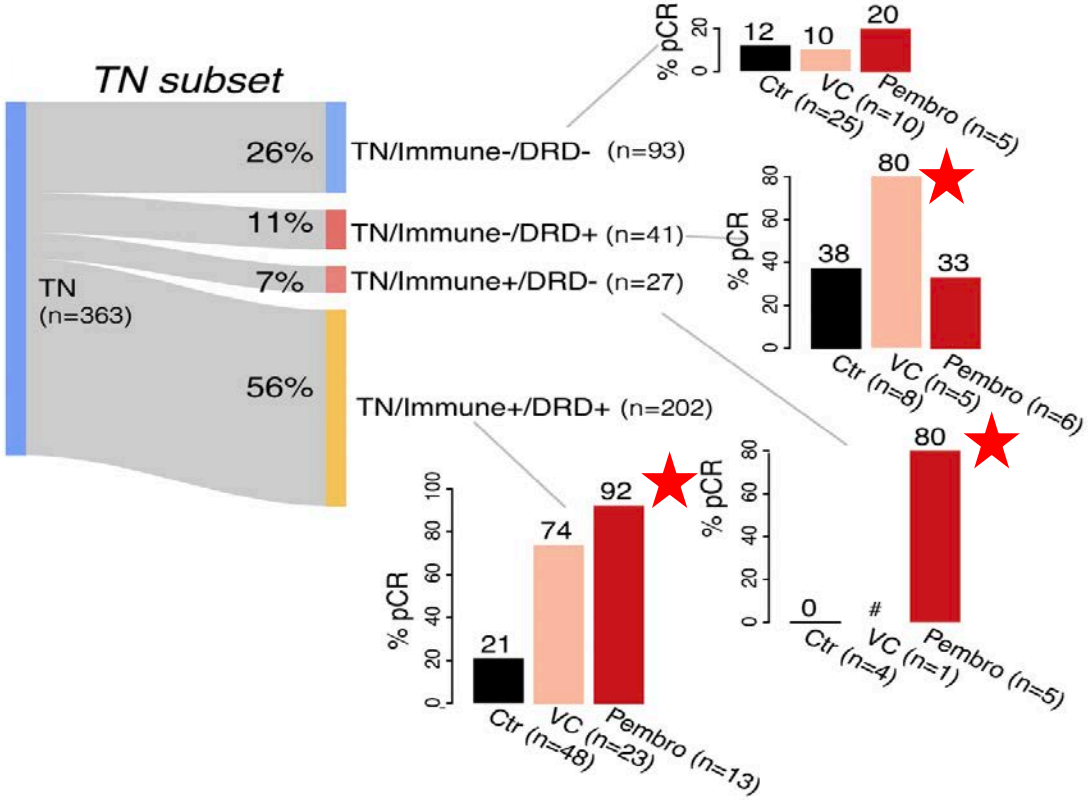




Added Immune, DNA repair deficiency, and BP-Luminal to HER2

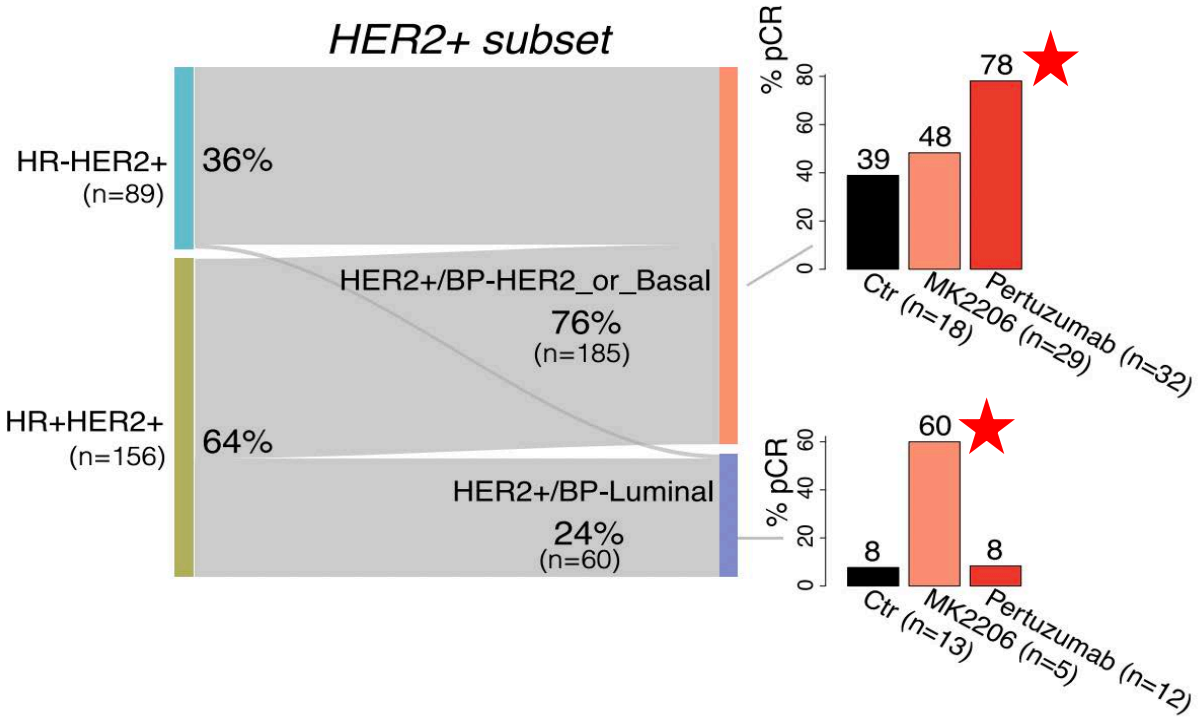
Wolf, Cancer Cell 2022; 40: 609-623

TNBC pCR and RPS



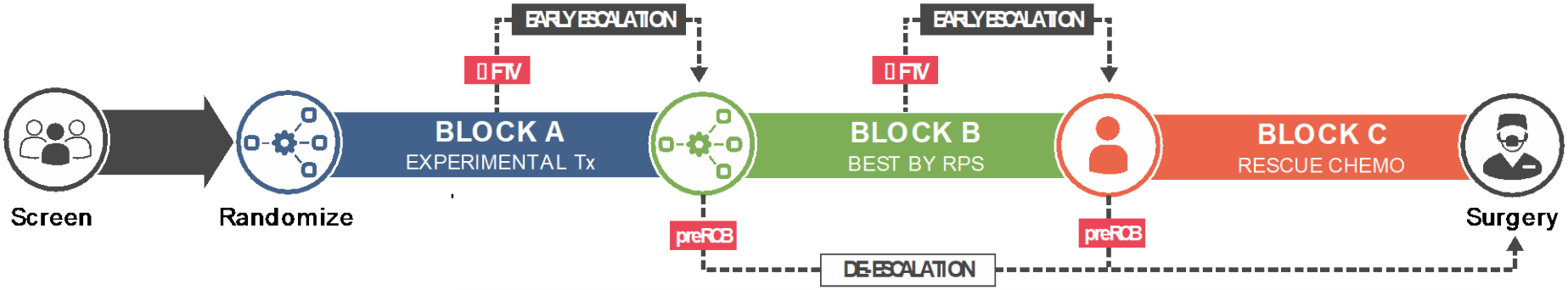
Wolf, Cancer Cell 2022; 40: 609-623

HER2+ pCR and RPS



Wolf, Cancer Cell 2022; 40: 609-623

I-SPY 2.2 Design Features: Multiple Sequential Regimens



Treatment Assignments/Randomization ***based on Response Predictive Subtype (RPS)***

HR+ HER2- Immune- DRD-	Taxol	AC
HR- HER2- Immune- DRD-:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune+:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+:	Taxol + Carbo	AC + Pembro

Comparator arm: Dynamic control

Specific to each subtype identified from previously tested I-SPY2 agents between March 2010 and April 2022 (e.g. paclitaxel -> AC ; paclitaxel + pembrolizumab -> AC ; paclitaxel + veliparib + carboplatin -> AC)

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LBA15: Rates of Pathologic Complete Response (pCR) after Datopotamab Deruxtecan (Dato) plus Durvalumab (Durva) Treatment Strategy in the Neoadjuvant Setting

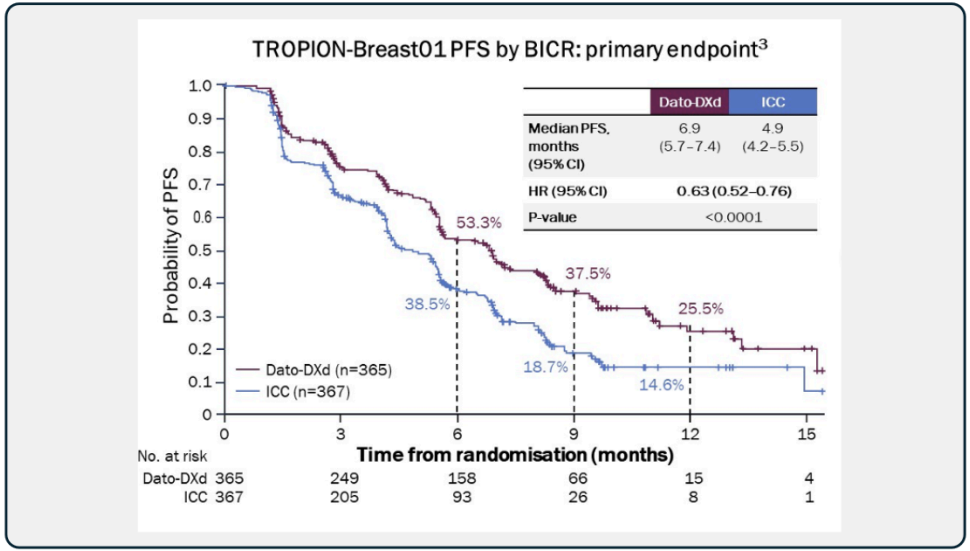
Results from the I-SPY 2.2 Trial

Meghna S. Trivedi, MD, MS
Herbert Irving Assistant Professor of Medicine
Columbia University Irving Medical Center

Barcelona, Spain
September 14, 2024

Rationale: Dato-DXd

- Dato-DXd is a TROP2-directed ADC that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells[1]
- Phase I TROPION-PanTumor01 showed promising results in patients with heavily pretreated HR+/HER2- and TNBC[2]
- In the phase 3 TROPION-Breast01 study, Dato-DXd demonstrated statistically significant and clinically meaningful improvement in PFS by BICR compared with ICC in patients with previously treated, inoperable or metastatic HR+/HER2- breast cancer[3,4]
- **In I-SPY 2.2, patients received monotherapy with Dato-DXd IV q3 weeks x 4 cycles as their Block A assignment**



1. Okajima D, et al. Mol Cancer Ther 2021; 20:2329_40
2. Bardia A, et al. J Clin Oncol. 2024; 42 (19): 2281-2294
3. Bardia A, et al. Ann Oncol 2023; 34 (suppl_2): S1264_5
4. Bardia A, et al. Future Oncol. 2024; 20 (8): 423-436

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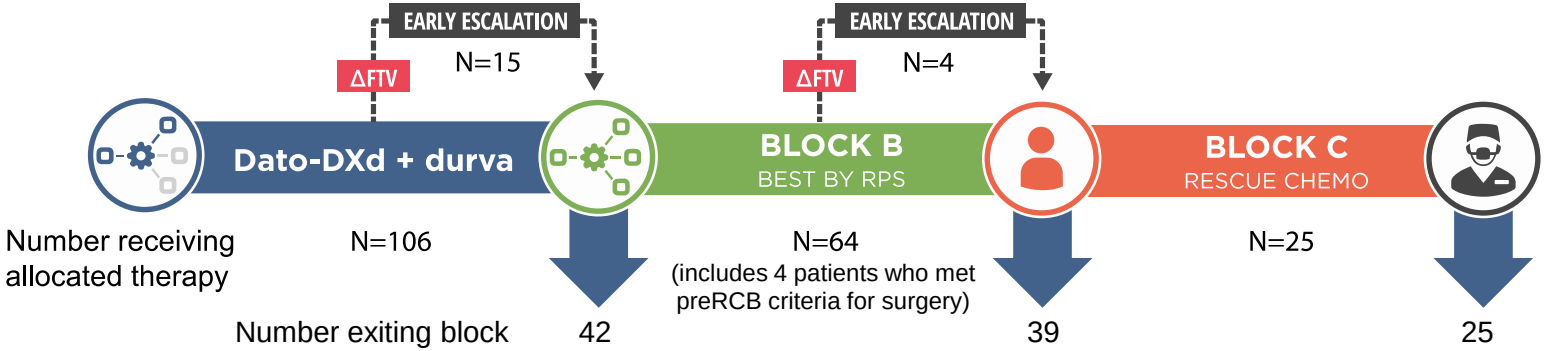
Timing of observed pCR



					Total achieving pCR
All patients (N=106)	N achieving pCR	25	22	6	53
	Cumulative % of total observed pCR	**47%** (25/53)	**89%** (47/53)	**100%** (53/53)	**50%** (53/106)

Eligibility for Dato-DXd arm:

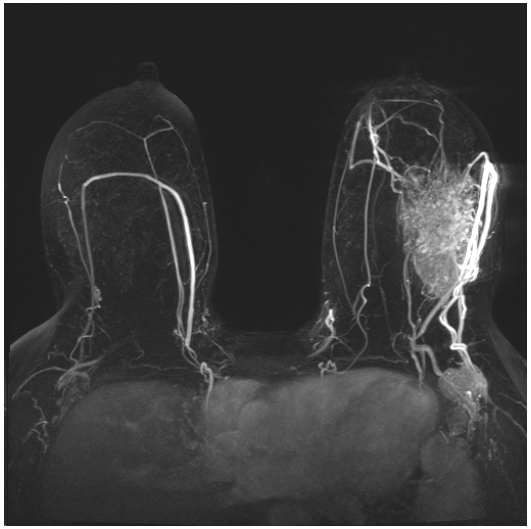
Anatomic Stage II/III

MammaPrint® High risk

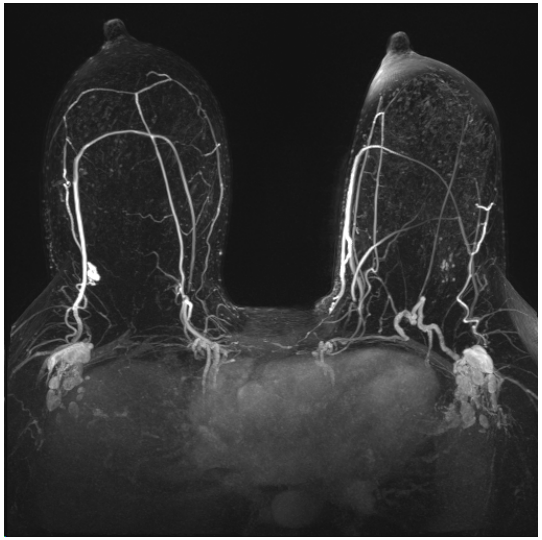
HER2 negative

44 yo female w/ T3N3, G3, ER positive, PR negative, HER-2 negative left breast cancer

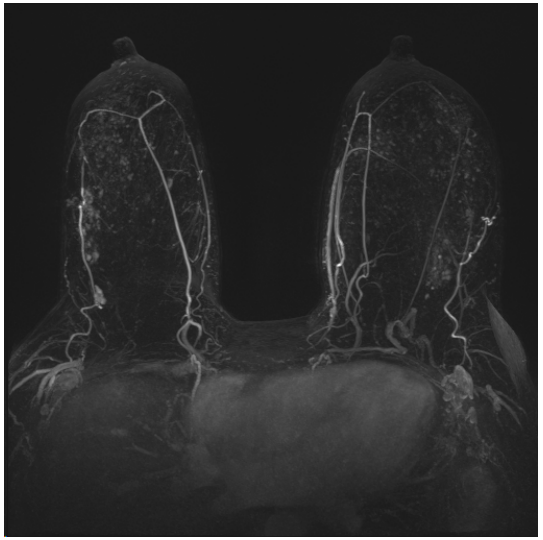
Pretreatment



s/p 4 cycles Dato-DXd + Durva



s/p 6 weeks Taxol, carbo, + pembro



Patient underwent left breast mastectomy and targeted lymph node dissection w/ pCR

Conclusions from Dato + Durva on ISPY2.2

- The ISPY 2.2 Dato + Durva treatment strategy resulted in an overall observed pCR rate of 50%
  - Highest pCR rate observed in Immune+ (79%) followed by TNBC (61%) subtypes
    - > 50% of pCRs achieved by Block A alone and >90% achieved by Block B
    - Ability to avoid taxane (Block B) and/or anthracycline (Block C) treatment
  - In HR-/Immune-/DRD-, the modeled pCR rate for the treatment strategy outperformed the dynamic control
- Further investigation in the randomized controlled trial setting in the Immune+ and HR-/Immune-/DRD- subtypes is warranted

Testing other agents with activity in the metastatic breast cancer in the neoadjuvant setting

2024 ASCO ANNUAL MEETING

DESTINY BREAST06

Trastuzumab deruxtecan vs physician's choice of chemotherapy in patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–low or HER2-ultralow metastatic breast cancer with prior endocrine therapy: primary results from DESTINY-Breast06

Giuseppe Curigliano
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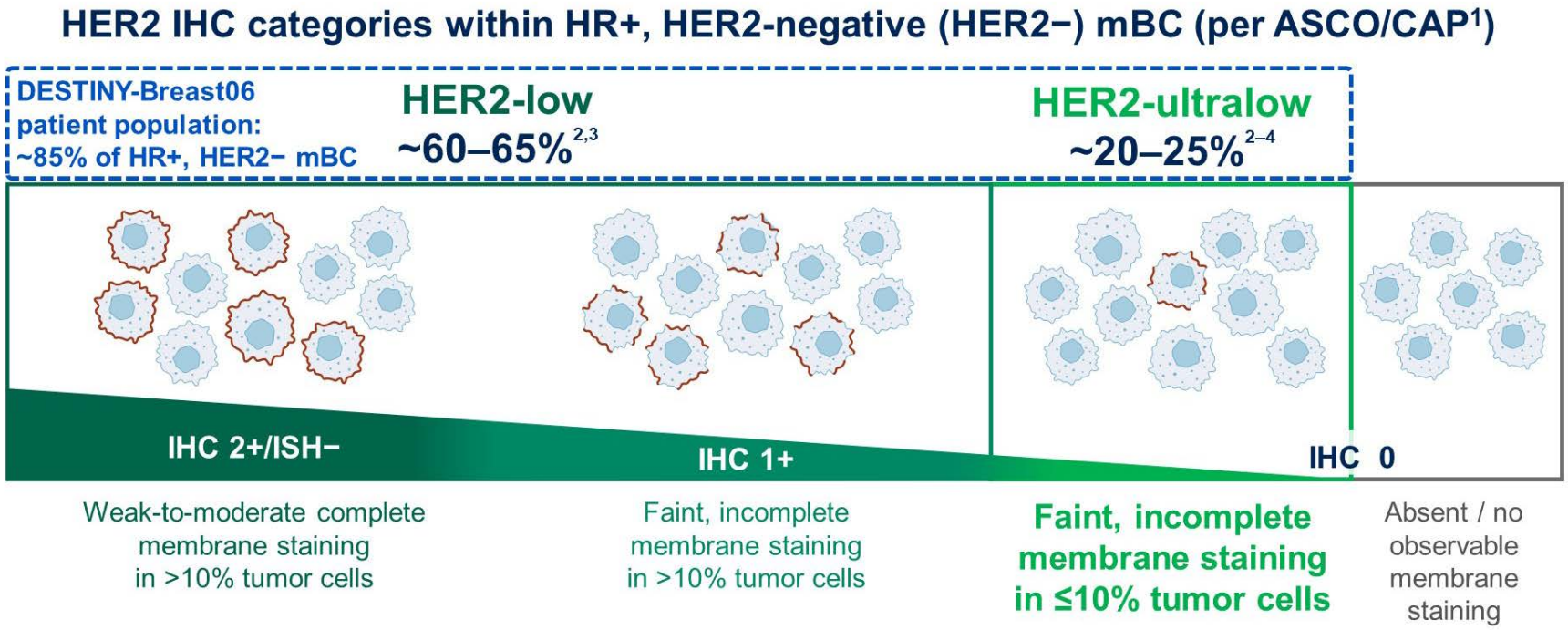
Department of Oncology and Hematology-Oncology, University of Milan, Italy

Sunday, June 2, 2024

Additional authors: Xichun Hu, Rebecca Dent, Kan Yonemori, Carlos H Barrios, Joyce A O'Shaughnessy, Hans Wildiers, Qingyuan Zhang, Seock-Ah Im, Cristina Saura, Laura Biganzoli, Joohyuk Sohn, Christelle Lévy, William Jacot, Natasha Begbie, Jun Ke, Gargi Patel, Aditya Bardia

On behalf of the DESTINY-Breast06 investigators

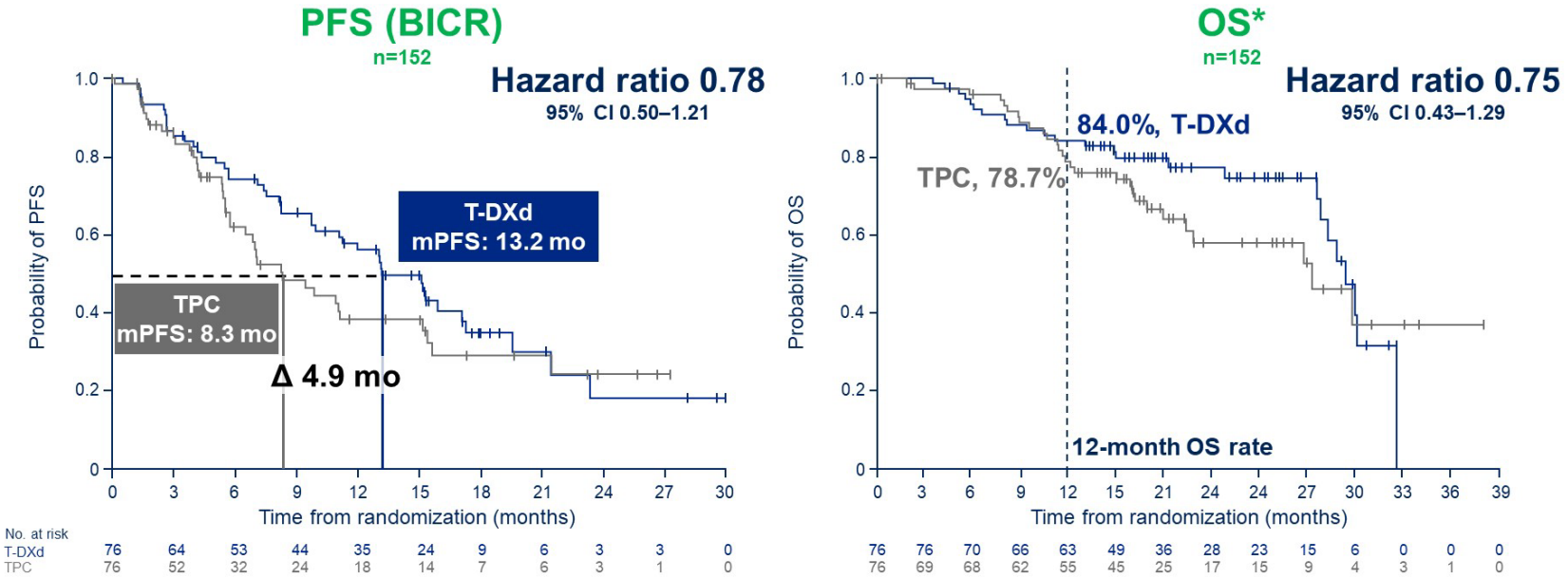
Targeting ”low” and “ultralow” HER2 expressing tumors in MBC



ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

1. Wolff AC, et al. *J Clin Oncol*. 2023;41:3867–3872; 2. Denkert C, et al. *Lancet Oncol*. 2021;22:1151–1161; 3. Chen Z, et al. *Breast Cancer Res Treat*. 2023;202:313–323; 4. Mehta S, et al. *J Clin Oncol*. 2024;42(Suppl. 16):Abstract e13156

PFS and OS in HER2 ultralow



PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Bardia et al. NEJM 2024, publ online Sept 14.

I-SPY 2 Block A Regimens

HER2 Positive

Appendix AD: ARX788

Appendix AI: Zanidatamab

HER2 Negative

Appendix AJ: Rilvegostomig + TDXD

Appendix AK: DAN222 + Niraparib

Note:

Regimens in dark blue are open to accrual

Regimen in Orange is temporarily paused to accrual

2024 ASCO® ANNUAL MEETING

ACE-Breast-02: a pivotal phase II/III trial of ARX788, a novel anti-HER2 ADC, vs lapatinib plus capecitabine for HER2+ advanced breast cancer

Xichun Hu, Leiping Wang, Jian Zhang, Qingyuan Zhang, Quchang Ouyang, Xiaojia Wang, Wei Li, Weimin Xie, Xiuqing Nie, Yuan Lei, ACE-Breast-02 group

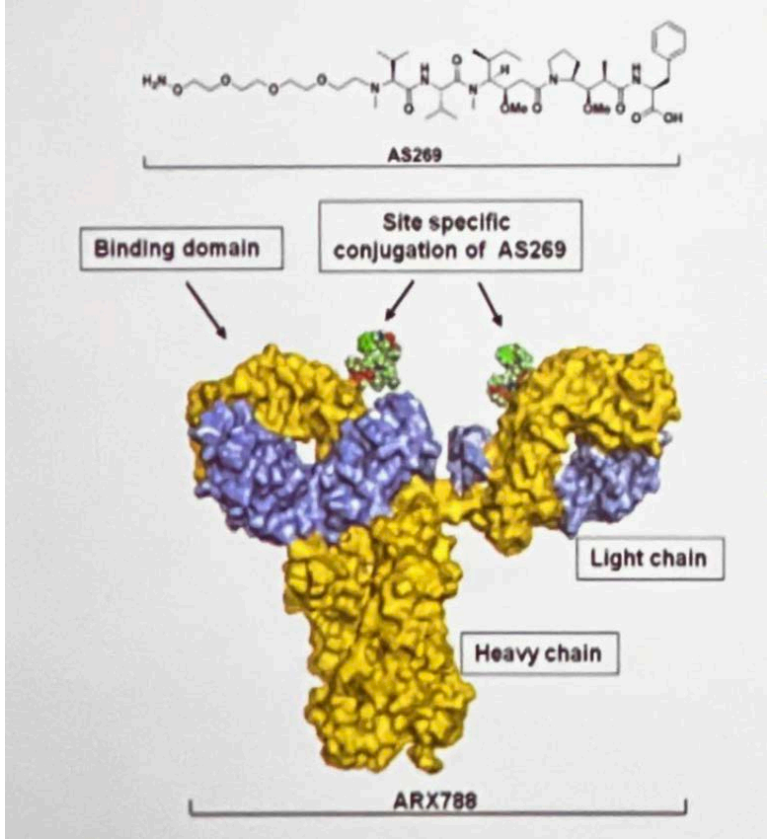
Leading Principal Investigator: Xichun Hu

Department of Medical Oncology, Fudan University Shanghai Cancer Center;

Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, 200032, P. R. China

ARX-788 – Novel ADC

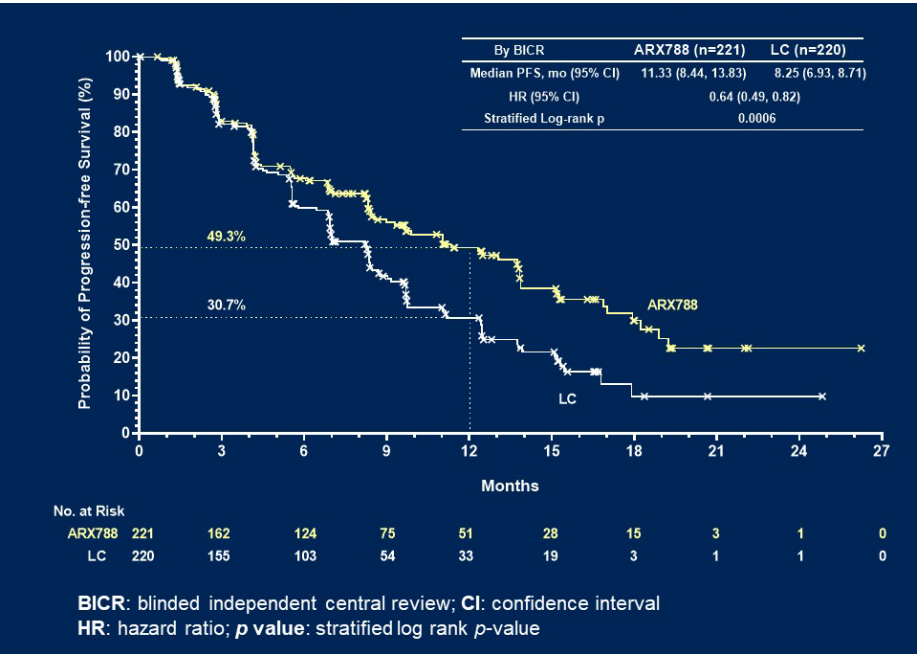
- Antibody: Fully humanized anti-HER2 mAb
- Payload: AS269 - A potent microtubule inhibitor

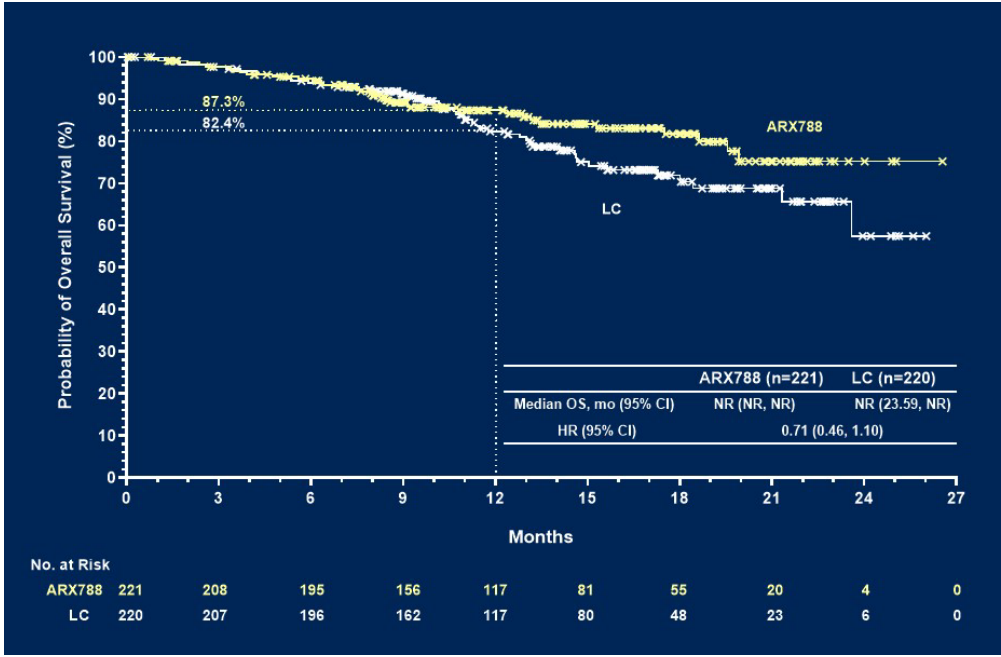


HR+ 53% vs 49%
Visceral mets 76% vs 77%
CNS mets 13% vs 12%
Prior lines of therapy <1 80%

Results: PFS and OS

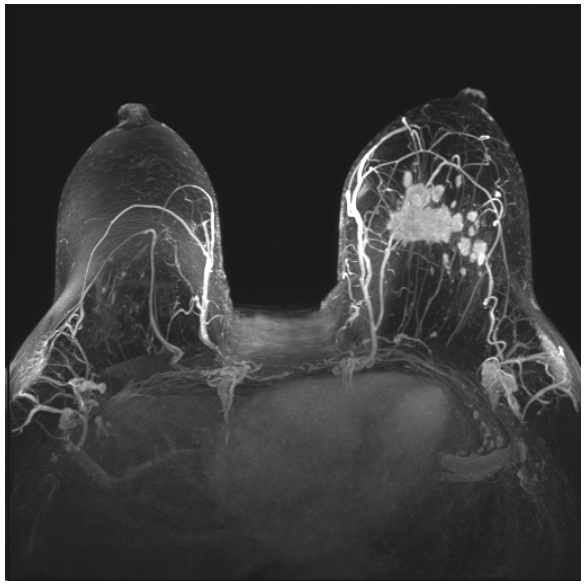
HR+ 53% vs 49%
Visceral mets 76% vs 77%
CNS mets 13% vs 12%
Prior lines of therapy <1 80%



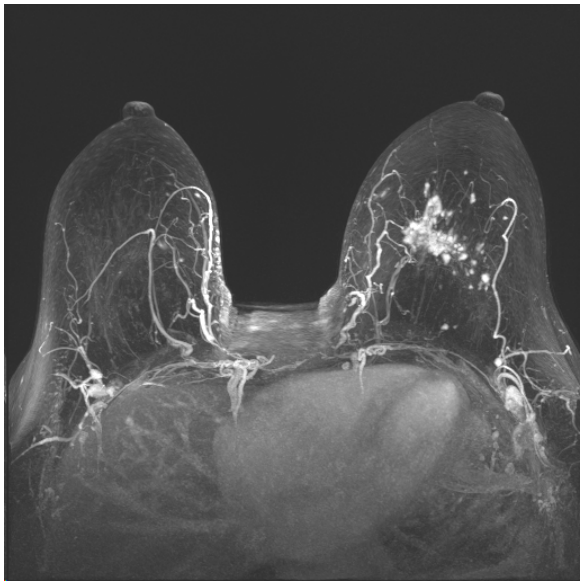


51 yo female with T3N3, ER positive, PR low, HER-2 positive left breast cancer

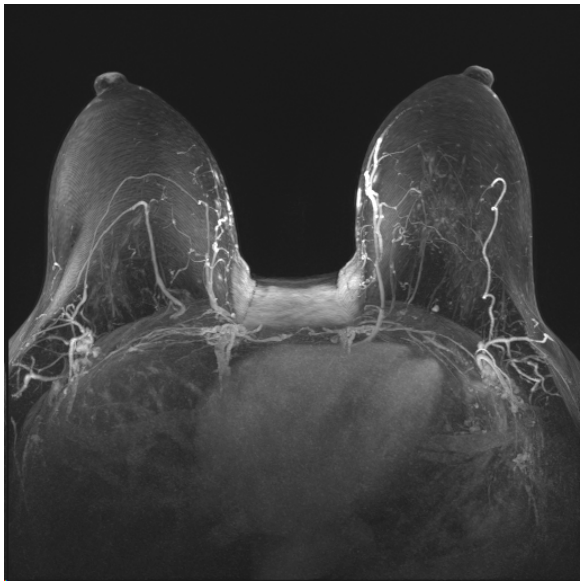
Pretreatment



s/p 2 cycles ARX-788



s/p 4 cycles ARX-788



Patient underwent left breast mastectomy and targeted lymph node dissection w/ pCR

Adjuvant Therapies for Non-PCR

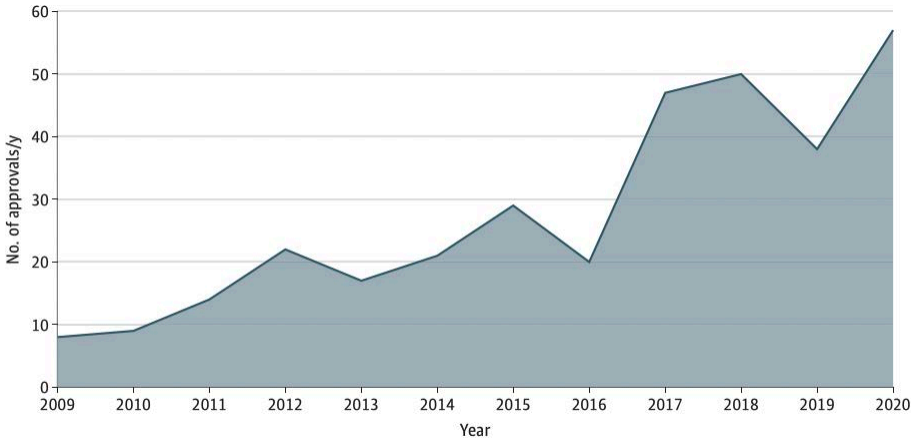
- ER positive
  - Adjuvant endocrine therapy +/- CDK 4/6 inhibitor
    - Abemaciclib
    - Ribociclib

Triple negative

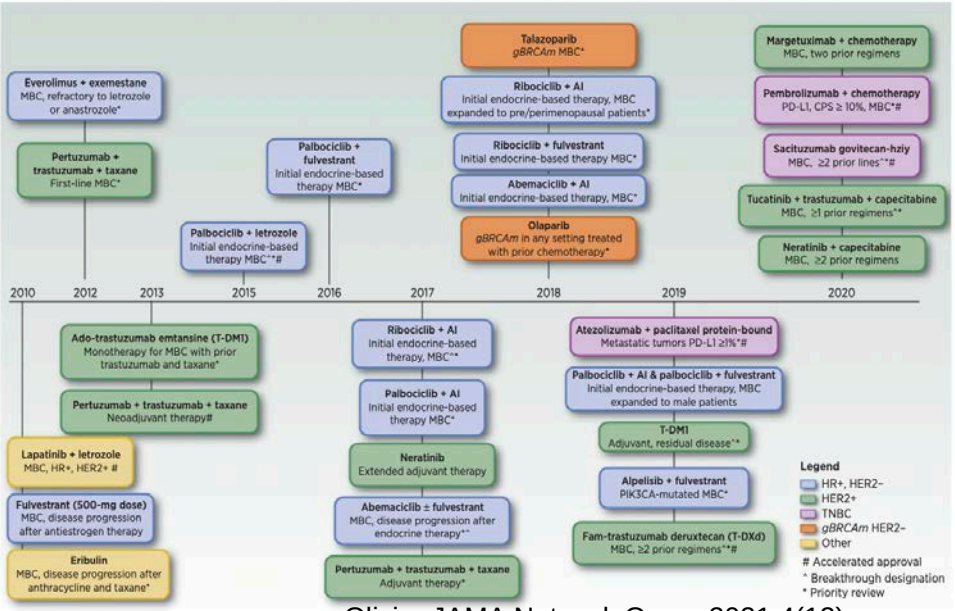
- Capecitabine
- Pembrolizumab
- ASCENT-05, Sacituzumab

- HER-2 positive
  - Trastuzumab
  - Trastuzumab + pertuzumab
  - Neratinib
  - Trastuzumab emtansine
  - DESTINY Breast-05, Trastuzumab deruxtecan

FDA approved drugs for cancer 2010 - 2020



Number of FDA approved cancer drugs per year



Olivier JAMA Network Open. 2021;4(12)
Arora Clin Cancer Res. 2022;28(6): 1072-1086

Individualizing Treatment Leads to Improved Outcomes and Raises Additional Questions

- Incorporating tumor biology beyond clinical receptor subtypes into breast cancer treatment decisions leads to improved outcomes.
- We need to continue to redefine the existing classification of breast cancer in order to:
  - Optimize the use of approved regimens
    - Who can avoid anthracycline?
    - Do all TNBC patients need both pembrolizumab and carboplatin?
    - Do some HR+ high risk breast cancer patients need immune checkpoint inhibitors?
    - Do patients who achieve a pCR need any further adjuvant therapy? Surgery?
  - Incorporate new agents – e.g. antibody drug conjugates, targeted therapies, new immunotherapies
  - Choose regimens that optimize outcomes with less toxicity
    - Given effective adjuvant therapies that may be less toxic than additional cytoxic chemotherapy, is RCB-I good enough?

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