Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of HER2-Low and HER2-Ultralow Breast Cancer

Part 1 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

Tuesday, December 10, 2024

7:15 PM – 8:45 PM CT (8:15 PM – 9:45 PM ET)

Faculty

Aditya Bardia, MD, MPH

Professor Giuseppe Curigliano, MD, PhD

Hope S Rugo, MD

Antonio C Wolff, MD, FACP, FASCO

Moderator

Neil Love, MD

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Faculty

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Miami, Florida

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Dr Bardia — Disclosures
Faculty

Consulting Agreements and Contracted Research	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Menarini Group, Merck, Novartis, Pfizer Inc, Sanofi

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Prof Curigliano — Disclosures
Faculty

Advisory Committees and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Bristol Myers Squibb, Daiichi Sankyo Inc, Lilly, Menarini Group, Merck, Novartis, Seagen Inc
Contracted Research	Merck
Data and Safety Monitoring Board/Committee	Roche Laboratories Inc
Scientific Board	Ellipses Pharma
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Lilly, Merck, Novartis, Pfizer Inc

Dr Rugo — Disclosures
Faculty

Consulting Agreements	Chugai Pharmaceutical Co Ltd, Napo Pharmaceuticals Inc, Puma Biotechnology Inc, Sanofi, Viatris
Contracted Research	Ambrx, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, F Hoffmann-La Roche Ltd, Genentech, a member of the Roche Group, Gilead Sciences Inc, Greenwich LifeSciences Inc, Lilly, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Stemline Therapeutics Inc

Dr Rugo — Disclosures
Faculty

Consulting Agreements	Chugai Pharmaceutical Co Ltd, Napo Pharmaceuticals Inc, Puma Biotechnology Inc, Sanofi, Viatris
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Dr Wolff — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Black Diamond Therapeutics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Geron Corporation, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, Hologic Inc, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Nuvalent, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

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Commercial Support

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Rounds with the Investigators: Compelling Teaching Cases Focused on the Role of Endocrine-Based Therapy in the Management of Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Komal Jhaveri, MD, FACP
Virginia Kaklamani, MD, DSc
Seth Wander, MD, PhD

Moderator

Neil Love, MD

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Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Metastatic Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

Thursday, December 12, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Ian E Krop, MD, PhD
Joyce O'Shaughnessy, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Save The Date

Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

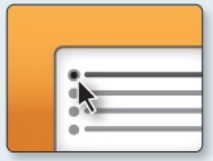
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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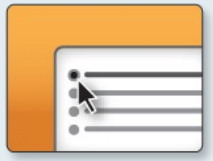
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Neil Love, MD

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Agenda

Module 1: Optimizing the Identification of HER2-Low and HER2-Ultralow Breast Cancer – Dr Wolff

Module 2: Available Data with HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease – Dr Bardia

Module 3: Practical Applications of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Metastatic Breast Cancer – Prof Curigliano

Module 4: Future Directions for HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Breast Cancer – Dr Rugo

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2018 and 2024 Surveys of Clinical Investigator (CI) Use of Postoperative Systemic Therapy After Prior Neoadjuvant Treatment of HER2-Positive Breast Cancer (HER2+ BC)

Abstract: P3-11-20

Thursday, December 12, 2024
12:00 PM – 2:00 PM

Second-Line, Post-CDKi Treatment of Metastatic ER+ HER2-Negative Breast Cancer (ER+ mBC): The Impact of a 30-Minute CME Video on Treatment Choices of Community-Based General Medical Oncologists (GMOs)

Abstract: P4-08-12

Thursday, December 12, 2024
5:30 PM – 7:00 PM

Key Factors Affecting Clinical Investigators' Use of Oral SERDs in Current Management of ER-Positive, HER2-Negative, ESR1-Mutated (ER+/HER2-/ESR1+) Metastatic Breast Cancer That Has Relapsed After Treatment with a CDK4/6 Inhibitor/Endocrine Therapy

Abstract: P4-12-15

Thursday, December 12, 2024
5:30 PM – 7:00 PM

Agenda

Module 1: Optimizing the Identification of HER2-Low and HER2-Ultralow Breast Cancer – Dr Wolff

Module 2: Available Data with HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease – Dr Bardia

Module 3: Practical Applications of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Metastatic Breast Cancer – Prof Curigliano

Module 4: Future Directions for HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Breast Cancer – Dr Rugo

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Research To Practice, SABCS 2024
Tue 10 Dec 2024

Optimizing the Identification of HER2-Low and HER2-Ultralow Breast Cancer

Antonio C. Wolff, MD, FACP, FASCO

Interim Director, Johns Hopkins Breast & Gyn Malignancies Group
COO, Translational Breast Cancer Research Consortium (TBCRC)
Co-Chair, NCI Breast Cancer Steering Committee

@awolff @HopkinsKimmel @JHBreastGyn

JOHNS HOPKINS MEDICINE | THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

Why Did ASCO and CAP Join Forces in 2005?

- Historically, IHC assays used as adjuncts to H&E in anatomic pathology
- LDTs (Lab Developed Tests) and further modifications were excessively common
- HER2 became a predictive biomarker used as the sole determinant of therapy selection; test accuracy became a "must"
- A general statement that "*assay was developed and performed in a CLIA-certified setting*" was no longer enough
  - analytical validation: standardization, robustness, and reproducibility
  - clinical validation: measures what it says it measures; is a defined clinical entity

Targeted agent

+

Companion diagnostic test

=

Potential for a big mess …

HER2 Testing (Dis)Concordance in 1st Generation of Adjuvant Trastuzumab Trials

Concordance Local & Central Lab (circa 2006)			
N9831	JNCI 2002 (total n=119)	ASCO 2004 (total n=976)	JCO 2006 (total n=2535)
IHC 3+ (HercepTest™)	74% *(false pos 26%)* →	79.5% →	82% *(false pos 18%)*
FISH + (PathVysion)	67% *(false pos 33%)* →	85% →	88% *(false pos 12%)*

Magnitude of false-neg HER2 testing unclear but also real …

Lessons we keep forgetting about HER2 …

- c-erbB-2 (HER2) – 185 kDa transmembrane glycoprotein tyrosine kinase, structurally similar to EGFR
- Normal tissues express HER2 protein & mRNA, but without amplification
  - GI, UAD, reproductive, GU, skin, breast, and placenta (including fetal tissue)
  - levels similar to those in non-amplified, non-overexpressing breast cancers
  - HER2 protein is a normal membrane constituent of a variety of epithelial cells
- PATHWAY anti-HER-2/neu (HER2) rabbit MoAb
  - Clone 4B5 targets internal domain of the HER2
  - Reacts w/ lysates (Western) of SKBR3 cells (128x overexpression HER2 mRNA)

Akiyama, Science 1986 PMID 3012781
Press, Oncogene 1990 PMID 1973830

Rationale for ASCO/CAP HER2 Effort (circa 2005)

- 1998: Trastuzumab FDA-approved as palliative therapy (improve PFS & OS)
  - Rush to develop commercial companion assay (HercepTest® ≠ Clinical Trial Assay)
- 2001: Poor concordance local vs central labs (adjuvant registration trials)
  - Concerns about false positive local test results (implies central testing is correct)
- 2005: Trastuzumab FDA-approved as adjuvant therapy (improve DFS & OS)
  - Focus no longer just palliation of MBC, but cure of early stage disease
- HER2 testing not just a companion prognostic marker, but a determinant of therapy selection

Give the right treatment to the right patient …

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

2007

Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, Karen L. Hagerty, D. Craig Allred, Richard J. Cote, Mitchell Dowsett, Patrick L. Fitzgibbons, Wedad M. Hanna, Amy Langer, Lisa M. McShane, Soonmyung Paik, Mark D. Pegram, Edith A. Perez, Michael F. Press, Anthony Rhodes, Catharine Sturgeon, Sheila E. Taube, Raymond Tubbs, Gail H. Vance, Marc van de Vijver, Thomas M. Wheeler and Daniel F. Hayes

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

JCO 2007 PMID 17159189
APLM 2007, PMID 19548375

Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

2013

Antonio C. Wolff, M. Elizabeth H. Hammond,* David G. Hicks,* Mitch Dowsett,* Lisa M. McShane,* Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes**

JCO 2013 PMID 24101045
APLM 2014, PMID 24099077

ARCHIVES of Pathology & Laboratory Medicine

COLLEGE of AMERICAN PATHOLOGISTS

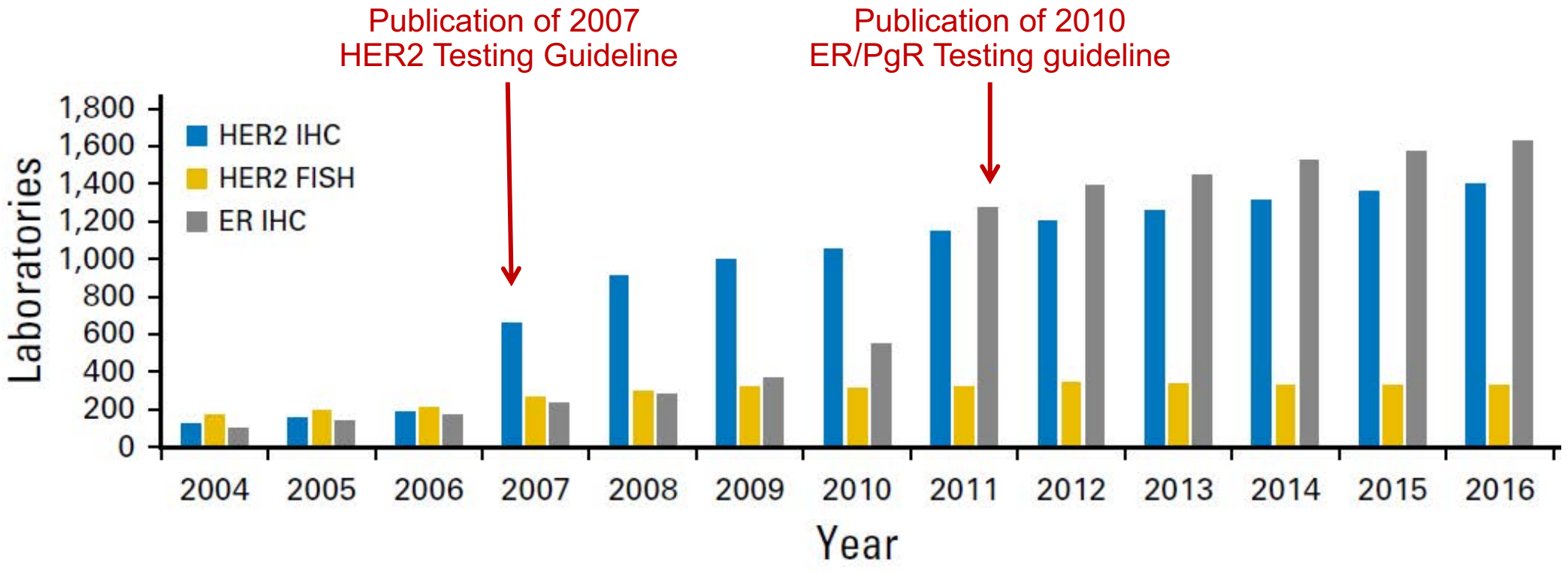
Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update

2018

Antonio C. Wolff, M. Elizabeth Hale Hammond, Kimberly H. Allison, Brittany E. Harvey, Pamela B. Mangu, John M.S. Bartlett, Michael Bilous, Ian O. Ellis, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, Lisa M. McShane, and Mitchell Dowsett

JCO 2018 PMID 29846122
APLM 2018 PMID 29846104

CAP Laboratory Accreditation Program

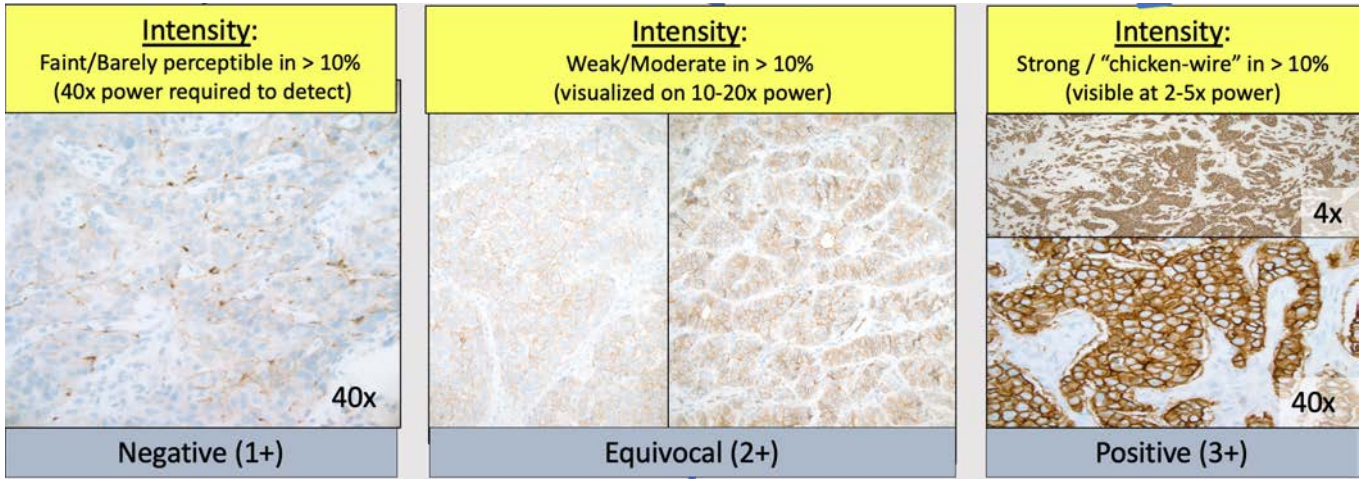


	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
HER2 IHC	125	156	188	659	907	1,000	1,050	1,150	1,202	1,260	1,311	1,357	1,399
HER2 FISH	174	191	210	263	295	320	315	317	345	337	331	330	330
ER IHC	97	139	168	233	283	370	550	1,276	1,393	1,449	1,526	1,570	1,625

J Clin Oncol 36:2015, 2018 (PMID 29846104)
https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/9751

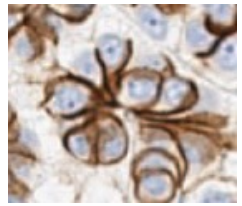
HER2 IHC Interpretation Complexities

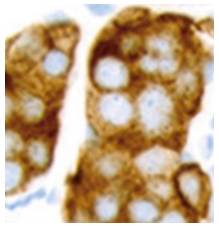
2018

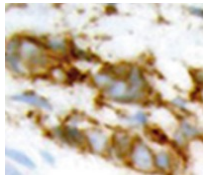


- **Intensity** of staining is key:
- Not about percentages unless obviously heterogeneous (3+ areas vs not)
- Compare with your 3+ control if considering calling 3+ (may be a strong 2+); "*when in doubt FISH it out!*"
- Use fresh cut slides, appropriate pre-analytic tissue handling

- Be aware of **unusual staining patterns**:
  - Micropapillary "u-shaped" incomplete staining = 2+
  - Apocrine can have strong cytoplasmic staining = 2+
  - Crush artifact = insufficient, send for reflex ISH







- Be aware if **discordant with histology** and do double checks
  - Grade 1, favorable histologic types → VERY unusual to be HER2 3+

Stanford MEDICINE School of Medicine Department of Pathology

Courtesy of Kim Allison, MD

The 2018 Focused Update

Bigger picture …

- Goal is to improve the analytic validity of HER2 testing and the clinical utility of HER2 as a predictive biomarker for potential responsiveness to therapies targeting the HER2 protein in tumors that are “HER2 addicted”

- *HER2* amplification (ISH) or HER2 overexpression (IHC) remains the primary predictor of responsiveness to HER2-targeted Rx

… and then comes T-DXd …

JCO 2018 PMID 29846122

Do HER2 antibodies work if HER2 is "negative"?

Beware of unplanned subset analyses …

Table 1. Relative Risks of Disease Progression and Death among Patients in the ACTH Group as Compared with the ACT Group.*

End Point and Central HER2 Assay†	ACT	ACTH	Relative Risk (95% CI)	P Value	P Value for the Interaction
	no. of events/total no. of events		NSABP-B-31		
Disease progression					
HER2-positive	163/875	85/804	0.47 (0.37–0.62)	<0.001	0.47
HER2-negative	20/92	7/82	0.34 (0.14–0.80)	0.014	
Death					
HER2-positive	55/875	38/804	0.66 (0.43–0.99)	0.047	0.08
HER2-negative	10/92	1/82	0.08 (0.01–0.64)	0.017	

Paik, NSABP-B-31, NEJM 2008 PMID 18367751

- NSABP-B-47: no benefit from adjuvant trastuzumab in non-amplified, non-overexpressed tumors (IHC 1+ or IHC2 2+ but FISH-neg)

Fehrenbacher, JCO 2020 PMID 31821109

Phase Ib T-DXd in HER2-low Breast Ca (n=54)

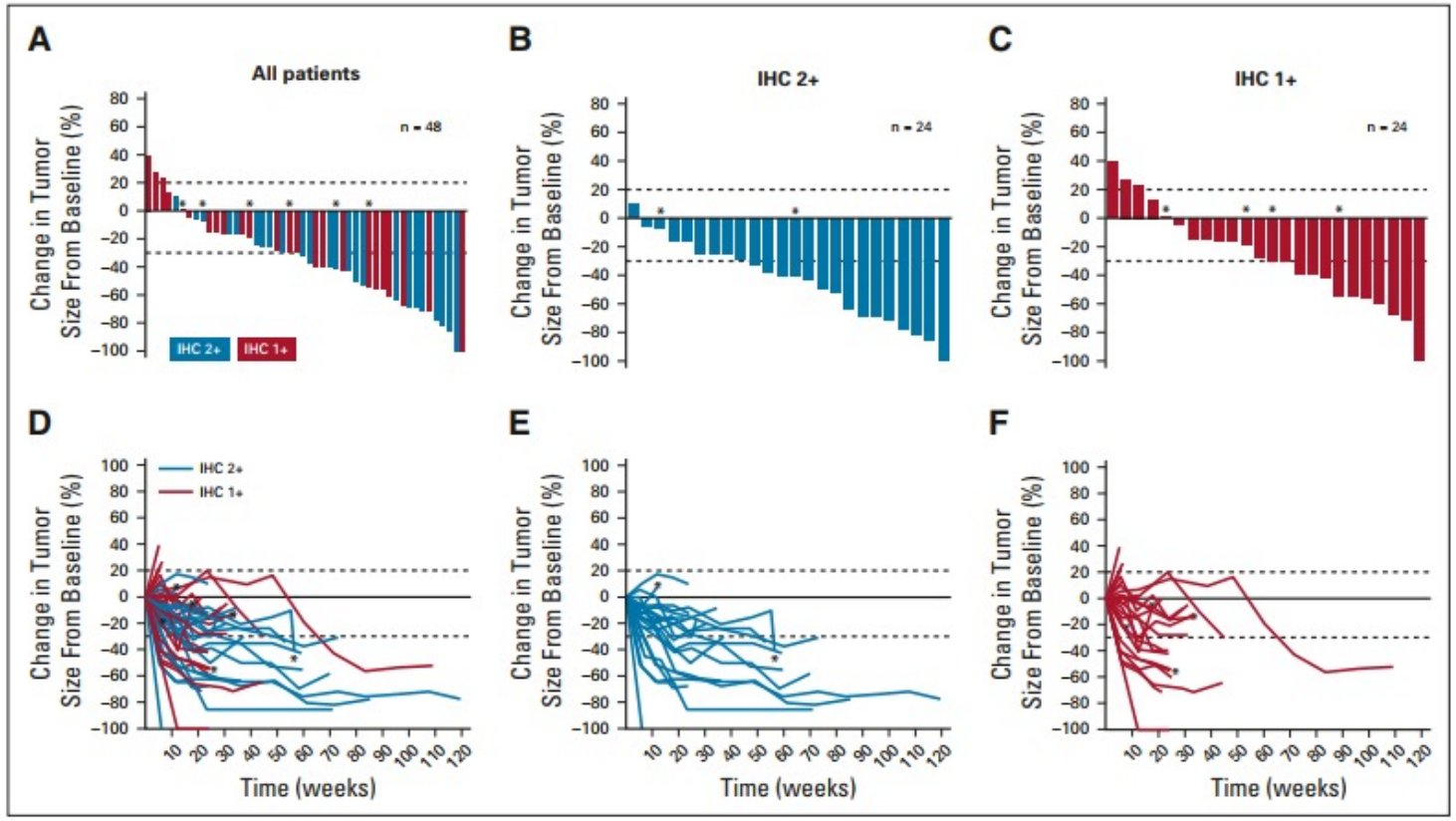


FIG 1. Best percent change in tumor size and percent change in tumor size, respectively, over time for individual patients in (A, D) the entire human epidermal growth factor receptor 2 (HER2)-low population, (B, E) the HER2 immunohistochemistry (IHC) 2+ group, and (C, F) the HER2 IHC 1+ group. Data cutoff was February 1, 2019. Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively. Tumor responses shown are per independent central review. The IHC status subgroups represent the IHC status as determined by local assessment. (*) HR negative. HR, hormone receptor.

Dose Expansion subset *(NCT02564900)*

- n=54 (2016-2018), local testing
- Immediate questions

  a) Agnostic of HER2 expression? Is HER2-addiction needed for activity of this ADC?

  or

  b) If HER2-addiction not needed, do measurements of low levels of expression matter? If so, how to measure them?

Active in mutHER2

- Phase II refractory NSCLC w/ mutHER2 *(ESMO 2021 NCT03505710)*

Modi, JCO 2020 PMID 32058843

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

Modi et al, NEJM 2022 PMID 35665782

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

DESTINY-Changing Results for Advanced Breast Cancer

Sara A. Hurvitz, M.D.

"The implications of the results of DESTINY-Breast04 trial are difficult to overstate"
"Immediately practice-changing"

Hurvitz, NEJM 2022 PMID 35793210

FDA NEWS RELEASE

FDA Approves First Targeted Therapy for HER2-Low Breast Cancer

For Immediate Release: August 05, 2022

What about the HER2 guidelines?!?
Do they need to change?!?

Is there such a thing as “HER2-low” or “-ultralow”?

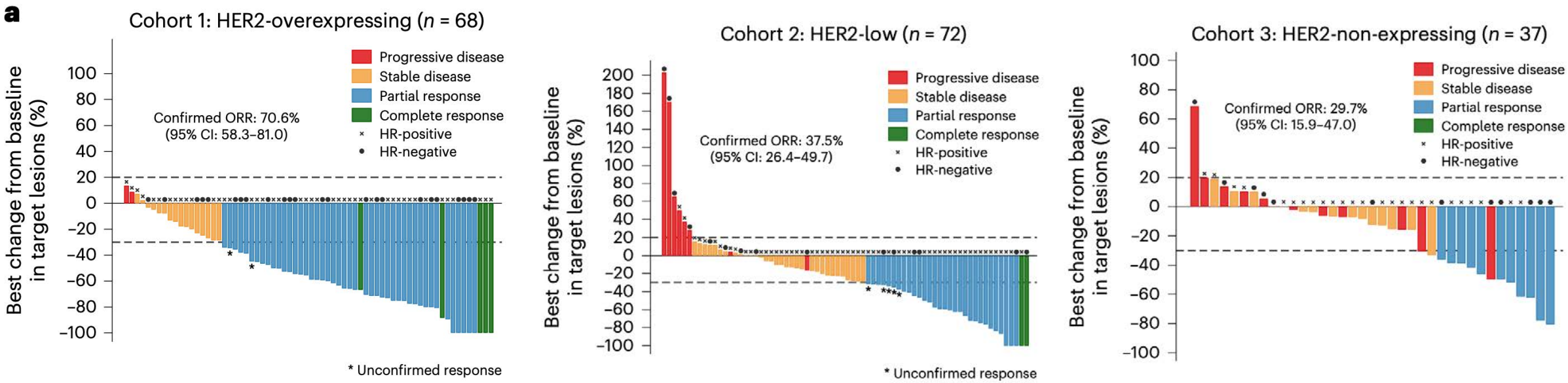
“In God we trust, all others must bring data …”

- Activation mutations in HER2 TK and ECD are rare but are targetable
- All breast tumors and tissues express low levels of HER2 protein
  - IHC 0 in FFPE tissues implies a fixation artifact (frozen specimens are not IHC 0)
- IHC is not a quantitative assay, was optimized for upper end of the expression spectrum, and lacks dynamic range for lower end
- If the “localizing target” for drug delivery is the HER2 protein, “HER2-low” detected by IHC may clinically behave no different than “HER2 0”
  - HER2-neg means “*HER2-neg for overexpression or amplification*”
  - Call it instead, HER2 normal versus HER2 overexpressed (IHC 3+) or amplified (by FISH)?
- Is “HER2-low” a biological entity? An artifact imposed by trial eligibility choices? Does it matter?
  - DB-04 excluded “IHC 1+” and DB-06 excluded “IHC 0/no staining”

Why did pharmaceutical company choose to create these untested terminologies?

Phase II trial of T-DXd regardless of HER2 status

DAISY trial



Are these tumors "HER2-low" or are they simply "HER2-normal" (i.e., HER2 "not positive")?

Mosele, Nat Med 2023 PMID 37488289

ASCO Special Articles

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update

2023

Antonio C. Wolff, MD[1]; Mark R. Somerfield, PhD[2]; Mitchell Dowsett, PhD[3]; M. Elizabeth H. Hammond, MD[4]; Daniel F. Hayes, MD[5]; Lisa M. McShane, PhD[6]; Thomas J. Saphner, MD[7]; Patricia A. Spears, BS[8]; and Kimberly H. Allison, MD[9]

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

American Society of Clinical Oncology–College of American Pathologists Guideline Update

Antonio C. Wolff, MD; Mark R. Somerfield, PhD; Mitchell Dowsett, PhD; M. Elizabeth H. Hammond, MD; Daniel F. Hayes, MD; Lisa M. McShane, PhD; Thomas J. Saphner, MD; Patricia A. Spears, BS; Kimberly H. Allison, MD

Recommendations

The 2018 ASCO-CAP recommendations for HER2 testing are affirmed.

Abstract

HER2 testing guidelines have focused on identifying HER2 protein overexpression or gene amplification in breast cancer to identify patients for therapies that disrupt HER2 signaling. This update acknowledges a new indication for trastuzumab deruxtecan when HER2 is not overexpressed or amplified but is immunohistochemistry (IHC) 1+ or 2+ without amplification by in situ hybridization. Clinical trial data on tumors that tested IHC 0 are limited (excluded from DESTINY-Breast04), and evidence is lacking that these cancers behave differently or do not respond similarly to newer HER2 ADCs. Although current data do not support a new IHC 0 versus 1+ prognostic or predictive threshold for response to trastuzumab deruxtecan, this threshold is now relevant because of the trial entry criteria that supported its new regulatory approval. Therefore, while it is premature to create new result categories of HER2 expression (eg, HER2-Low, HER2-Ultra-Low), best practices to distinguish IHC 0 from 1+ are now clinically relevant. This Update affirms prior HER2 reporting recommendations and offers a new HER2 testing reporting comment to highlight the current relevance of IHC 0 versus 1+ results and best practice recommendations to distinguish these often subtle differences.

JCO 2023 PMID 37303228
APLM 2023 PMID 37284804

FDA Approved Expansion of indications for Pathway 4B5 HER2 IHC assay

Table 1: PATHWAY anti-HER-2/neu Rabbit Monoclonal Antibody Scoring Algorithm for Breast Cancer

HER2 (4B5) Score (Report to treating physician)	Staining Pattern
0[1]	No membrane staining is observed Or, Faint, partial staining of the membrane in 10% or less of the cancer cells
1+[1]	Faint, partial staining of the membrane in greater than 10% of the cells
2+[2]	Weak to moderate membrane in greater than 10% of the cancer cells
3+	Intense complete staining of the membrane in greater than 10% of the cancer cells

[1] Review at 40X to discern faint, partial staining is recommended

[2] Recommend reflex test to assess gene amplification per ASCO/CAP guidance

PATHWAY anti-HER-2/*neu* (4B5) Rabbit Monoclonal Primary Antibody Interpretation Guide for Breast Cancer

Same test, but now adds new indication for "HER2 low"

PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody

REF 790-2991

05278368001

IVD Σ 50

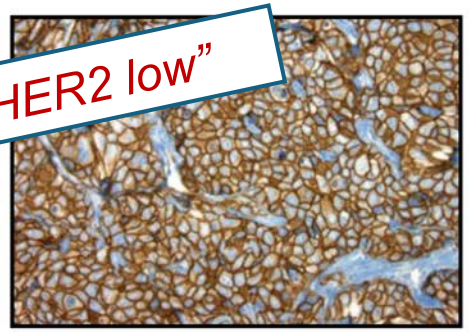


Figure 1. PATHWAY anti-HER2 (4B5) antibody staining in breast carcinoma.

INTENDED USE

PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody (PATHWAY anti-HER2 (4B5) antibody) is a rabbit monoclonal antibody intended for laboratory use for the semi-quantitative detection of HER2 antigen by immunohistochemistry (IHC) in sections of formalin-fixed, paraffin-embedded normal and neoplastic breast tissue using the *ultra*View Universal DAB Detection Kit on a BenchMark ULTRA instrument.

This IHC device is indicated for identifying breast cancer patients who are eligible for treatment with trastuzumab (IHC 3+ or IHC 2+/ISH amplified), T-DM1 (IHC 3+ or IHC 2+/ISH amplified) or trastuzumab deruxtecan (IHC 1+ or IHC 2+/ISH non-amplified). This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

This antibody is intended for in vitro diagnostic (IVD) use.

Adapted from Kim Allison, MD

HER2 IHC 0 vs 1+: A quandary for the pathologist …

- A clinically relevant to allow access to drug, but an untested threshold …
  - Issues with reproducibility (imaging analysis may help)
- The assay was never developed or standardized to discriminate IHC 0 from 1+
  - *IHC 0 is likely an issue of limit of detection or fixation*
  - No reflex assay available (or validated) to aid in discrimination
- No evidence that these are distinct biological entities …
- No evidence (yet) of an interaction between HER2 IHC levels and differential benefit from T-DXd

Invited Commentary

ERBB2-Low Breast Cancer—Is It a Fact or Fiction, and Do We Have the Right Assay?

Kimberly H. Allison, MD; Antonio C. Wolff, MD

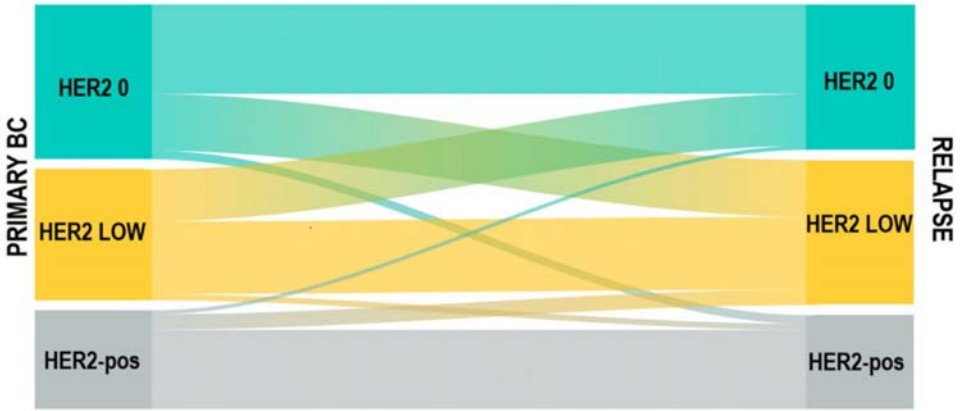
JAMA Oncol 2022 PMID 35113131

→ *Is all of this just an exercise in futility?*

Adapted from Kim Allison, MD

Best Practices for Clinical Care

- Medical oncologists may also **consider HER2 IHC results on prior or concurrent primary samples (or other metastatic sites)**
- A change in HER2 expression could be real (heterogeneity or biological change over time) or artifactual as metastatic cancer tissue samples may suffer from pre-analytic conditions that are not as well monitored as in primary breast tissue samples
- **Example**: Metastatic liver sample is IHC 0 but prior primary tested IHC 1+



		HER2 recurrence/metastasis N,%			Total
		0	Low	Positive	
HER2 primary BC N,%	0	132 (24.1)	83 (15.2)	13 (2.4)	228 (41.7)
	Low	77 (14.1)	101 (18.5)	9 (1.6)	187 (34.2)
	Positive	6 (1.1)	20 (3.7)	106 (19.4)	132 (24.1)
Total		215 (39.3)	204 (37.3)	128 (23.4)	547 (100)

Fig. 2 HER2 expression evolution from primary BC to relapse. Figure 2 shows the evolution of HER2 expression from primary to recurrent breast cancer. Absolute numbers and percentages are reported. BC breast cancer, N number.

Miglietta et al NPJ Breast 2021 PMID 34819500

Adapted from Kim Allison, MD

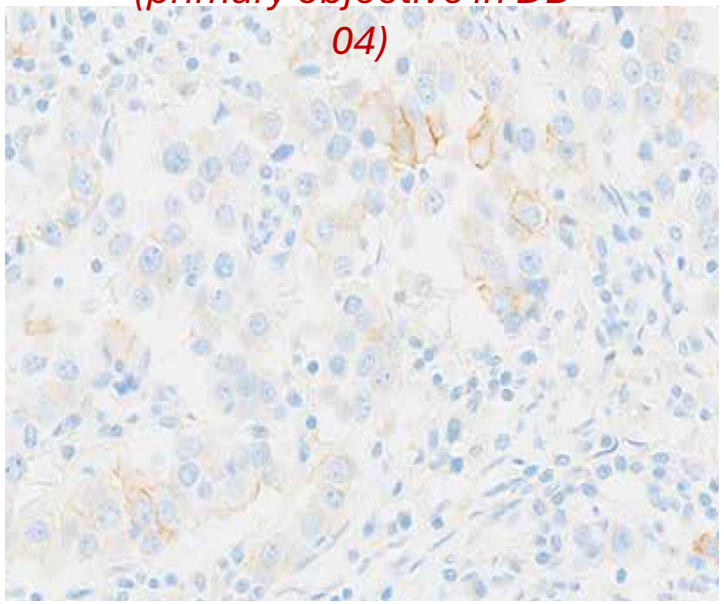
What Is HER2-Ultralow?

"Splitting the zero's …"

Faint, partial membrane staining in ≤10% of population (>0 but <1+)

IHC 1+

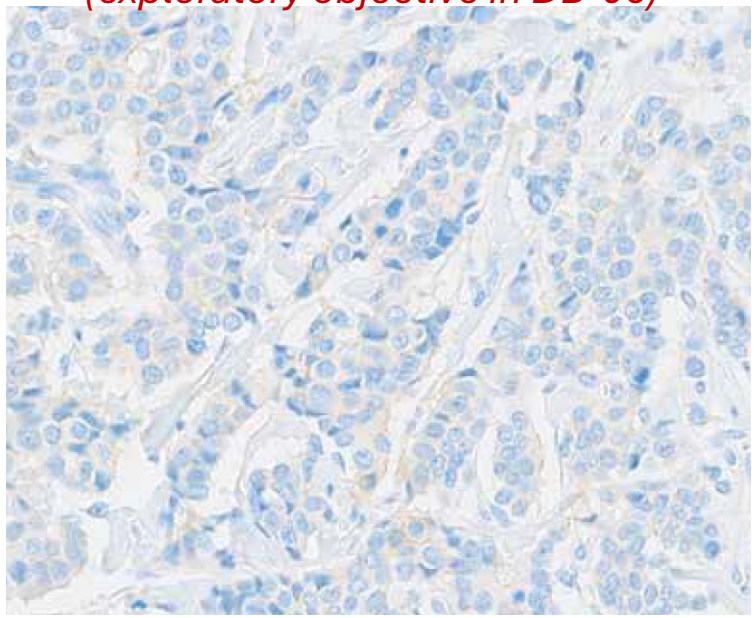
(primary objective in DB-04)



> 10% staining

IHC 0/some staining

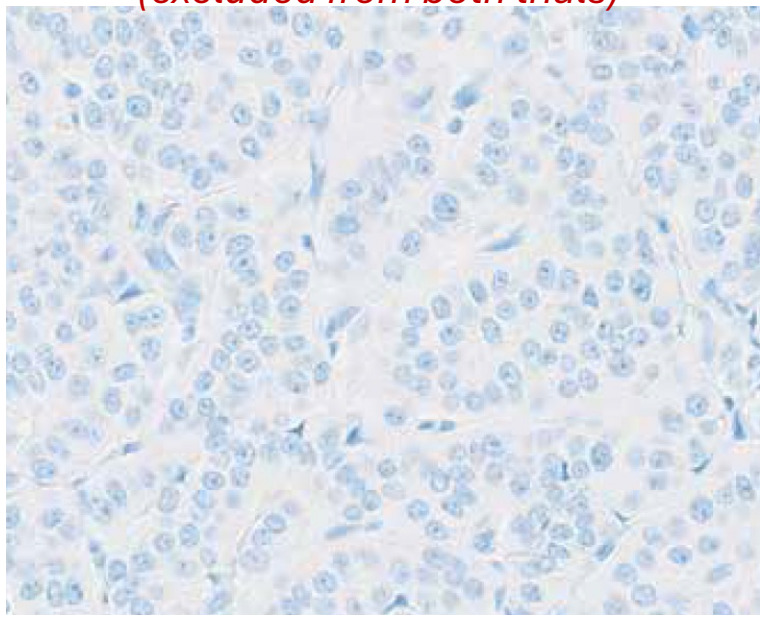
(exploratory objective in DB-06)



≤10% staining

IHC 0/no staining

(excluded from both trials)



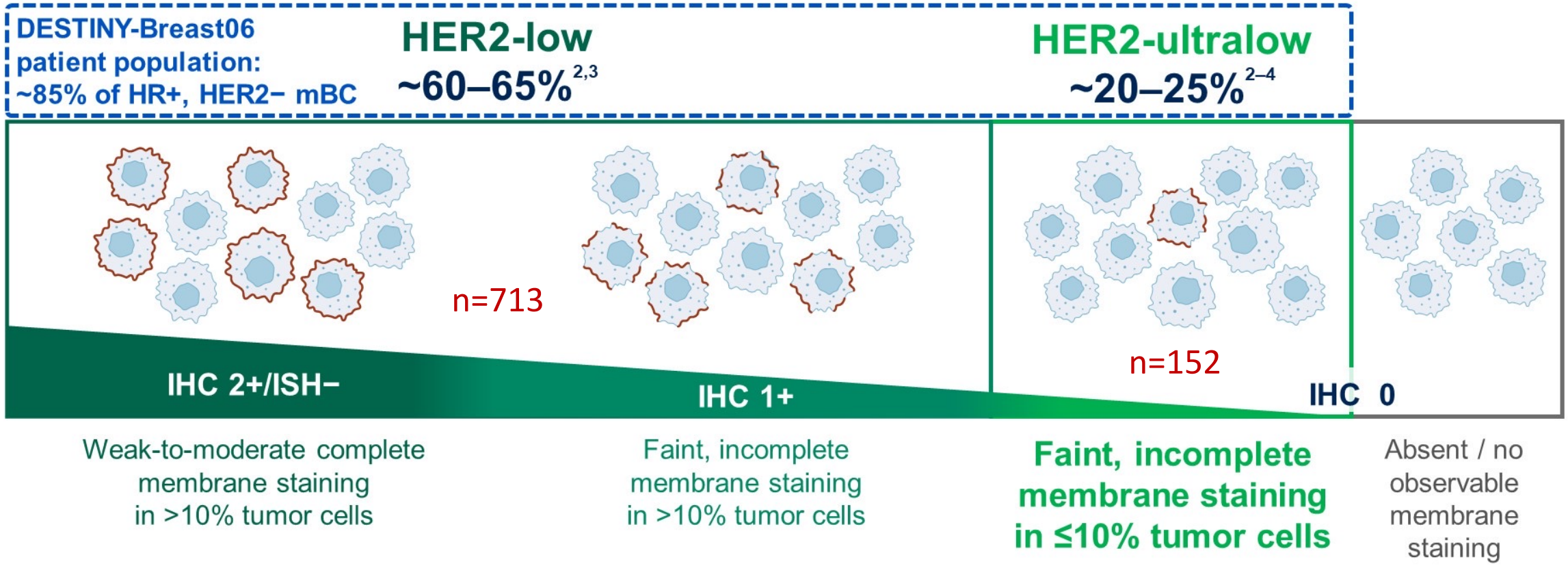
No staining

PATHWAY anti-HER-2/*neu* (4B5) Rabbit Monoclonal Primary Antibody Interpretation Guide for Breast Cancer

Adapted from Kim Allison, MD

Targeting 'low' and 'ultralow' HER2-expressing tumors in mBC

HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])

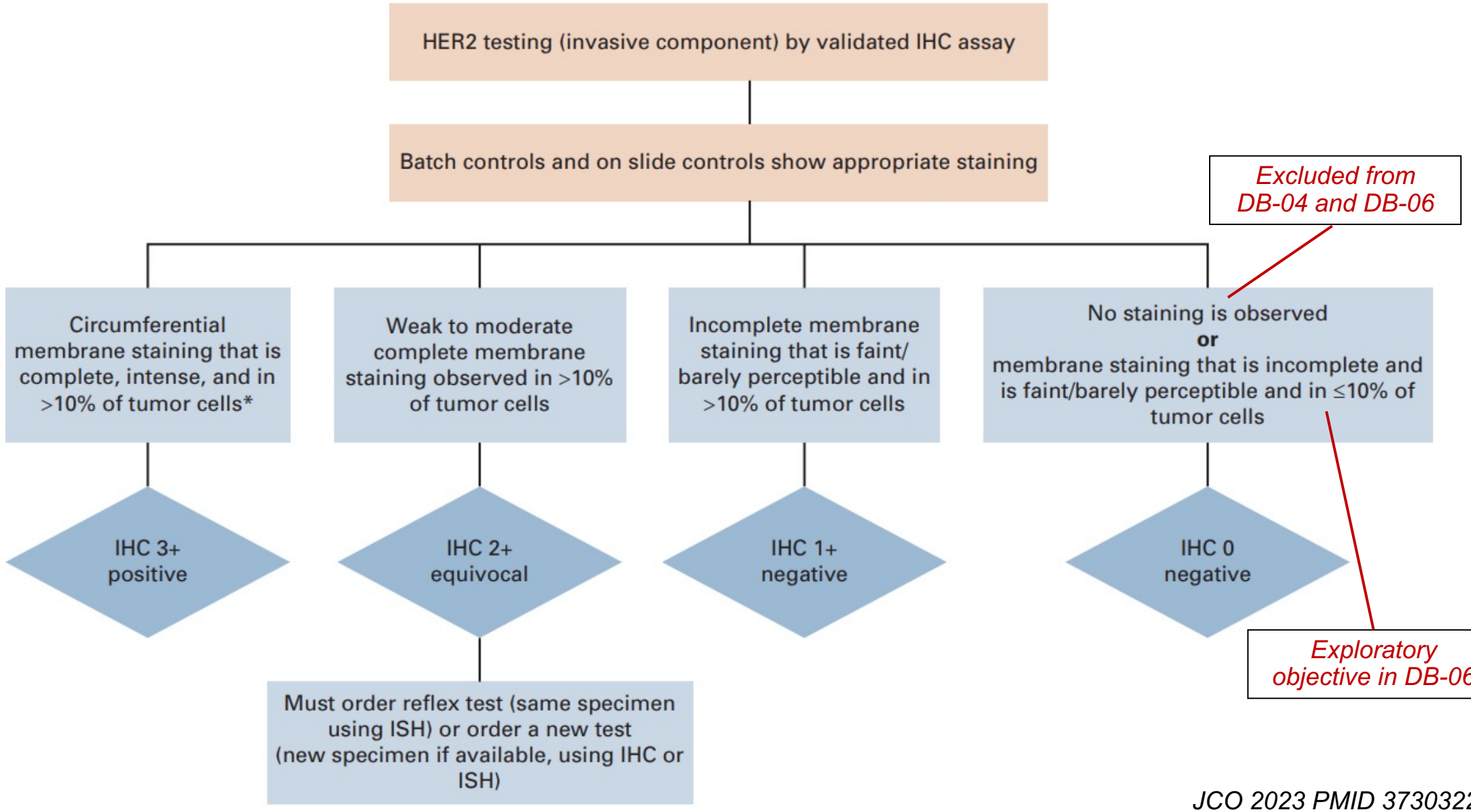


ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

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

Adapted from Curigliano ASCO 2024 LBA 1000
NEJM 2024 PMID 39282896

ASCO/CAP HER2 Testing 2018 – Figure 1



JCO 2023 PMID 37303228
APLM 2023 PMID 37284804

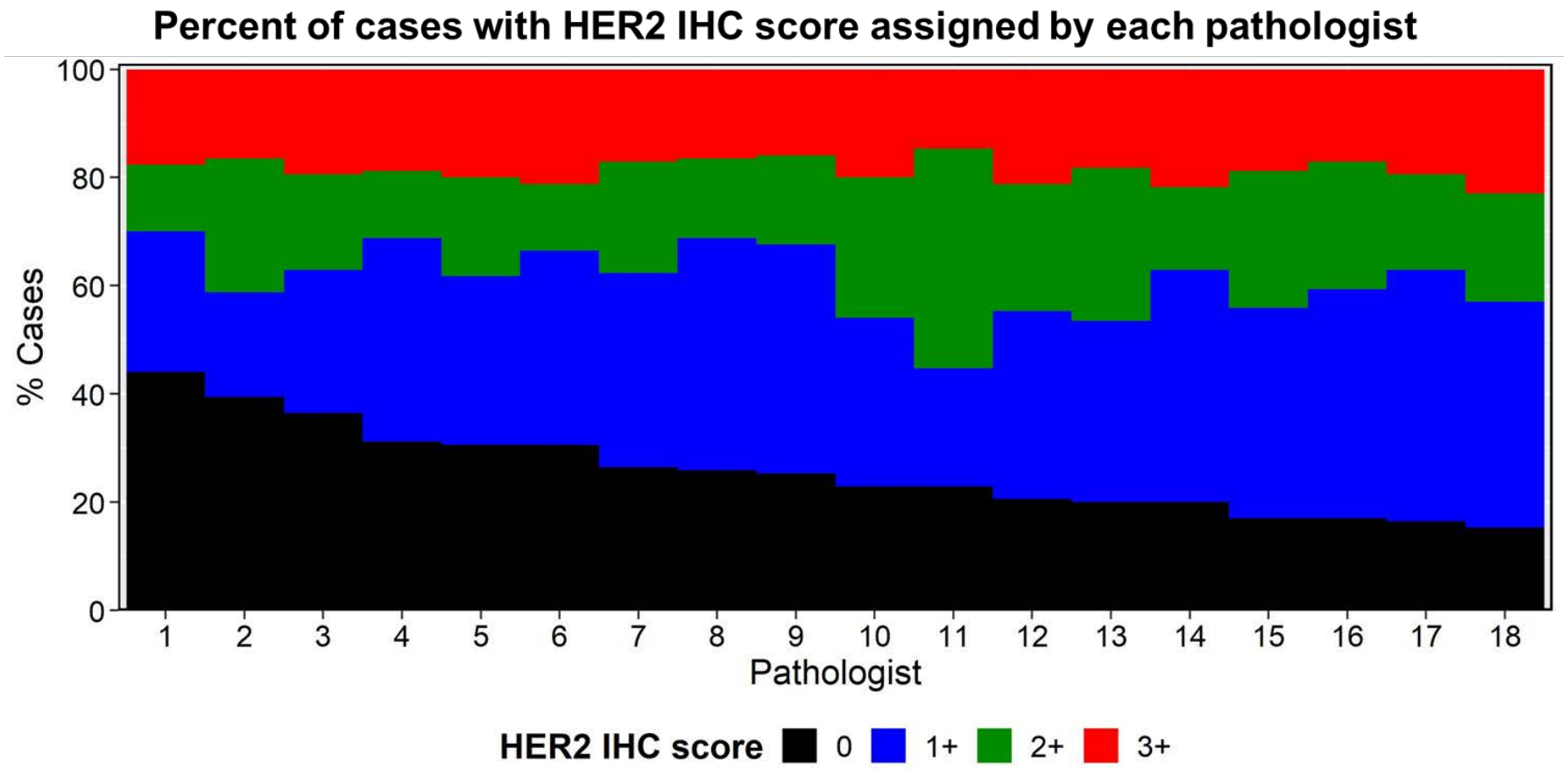
What to make of DESTINY-Breast06?

- ASCO/CAP Panel understood practical need after DB-04 to more clearly distinguish IHC 1+ from 0 results purely to ensure patient access to T-DXd
- But, absent evidence of new prognostic/predictive thresholds, creating new test result categories like "*HER2-Low*" and "*HER2-Ultralow*" was premature
- DB-06 data simplified things but added confusion ...
- We now understand that DB-06 used standard 2018 ASCO/CAP HER2 testing criteria, and exploratory data indicate that T-DXd is active in breast tumors with "IHC 0/some staining"
- But, excluding participants with ASCO/CAP "IHC 0/no staining" results was unnecessary and another missed opportunity …

What to make of DESTINY-Breast06?

- After DB-04, trial sponsors urged pathologists to "*more accurately differentiate between IHC 1+ and 0 cases*"
- Now, the new message is "*ignore that*", and pathologists are being asked to more accurately "*split the IHC 0 cases*" to fit patients to DB-06 trial criteria
- Instead, we encourage pathologists to continue to use the same 2018 ASCO/CAP HER2 testing criteria (Figure 1 of 2018 and 2023 guidelines) and report HER2 0 results as "IHC 0/no staining" or "IHC 0/some staining"
- CAP has no plans to institute proficiency testing for the low of the IHC spectrum
  - There are no tissue controls for low levels like there are for overexpression
  - Imaging analysis may help …
  - But, if it biologically does not matter (other than give patients access to drugs) and IHC is the wrong assay for this, then why bother?
- In the meantime, CAP is adjusting the reporting templates to fully conform with Fig 1

HER2 IHC 1+ scoring is not reliable with poor inter-reader concordance



Among 170 cases read by 18 pathologists at 15 institutions, pathologist #1 called >40% of cases IHC=0, while pathologist #18 called <20% IHC=0; there was similar discordance for IHC=1 (blue)

Adapted from David Rimm, MD
Robbins, Mod Pathol 2023 PMID 36788069

Let us pause and wonder …

- Will trial sponsors allow specimens from patients who volunteered for DB-04 and DB-06 to be available for prospective-retrospective studies using quantitative assays?
- Until then, we can only imagine how much simpler things could have been if trial sponsors (and trial leaders) had allowed all patients (including "IHC 0/no staining") to participate in these RCTs, even if in an exploratory manner as done in DB-06 for "IHC 0/some staining"

IHC 0 means no targetable HER2 protein or “below limit of detection/limit of quantification”?

- AQUA IF method standardized against cell line microarray quantified by mass spec
- 67% of “HER2 IHC 0” cases have some detectable HER2 protein expression

Quantitative measurement of HER2 expression to subclassify *ERBB2* unamplified breast cancer

Myrto Moutafi[1,2], Charles J. Robbins[1], Vesal Yaghoobi[1], Aileen I. Fernandez[1], Sandra Martinez-Morilla[1], Vasiliki Xirou[1], Yalai Bai[1], Yan Song[1], Patricia Gaule[1], Joseph Krueger[3], Kenneth Bloom[3], Salisha Hill[4], Daniel C. Liebler[4], Regan Fulton[5] and David L. Rimm[1,6]

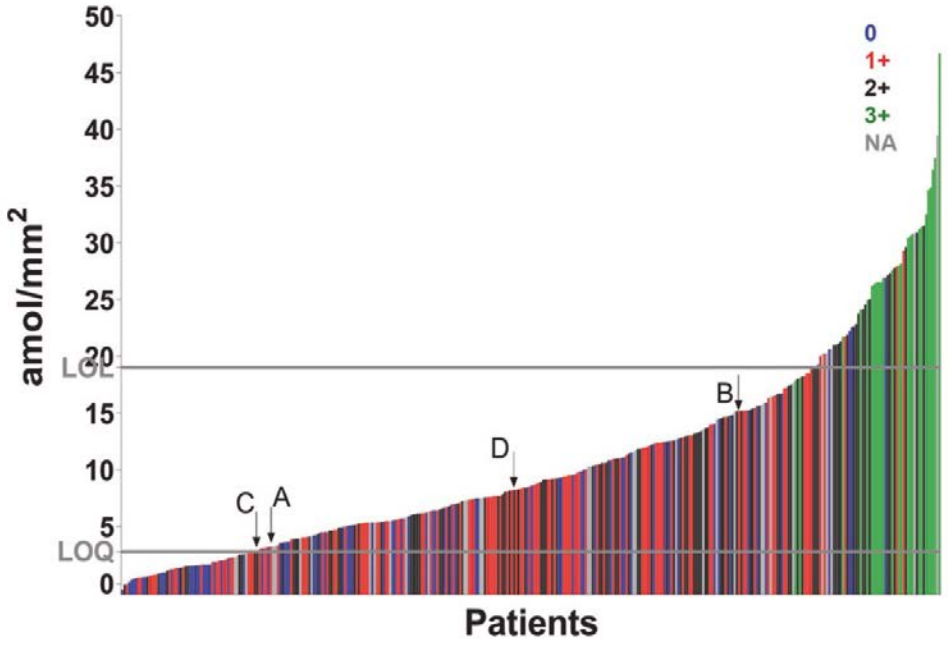


Fig. 5 The distribution of breast cancer cases in a serially collected population showing many cases above the LOQ that would be considered negative by the conventional assay. A histogram of the low HER2 assay in 364 breast cancer patients, measured in amol/mm^2. Color coding corresponds to the IHC HER2 scoring; green (3+), black (2+), red (1+), blue (0), grey (NA, Not Available). *LOQ* limit of quantification; *LOL* limit of linearity; *IHC* immunohistochemistry. Letters A through D are cases illustrated in Fig. 6.

PMID 35595825

Adapted from Kim Allison, MD

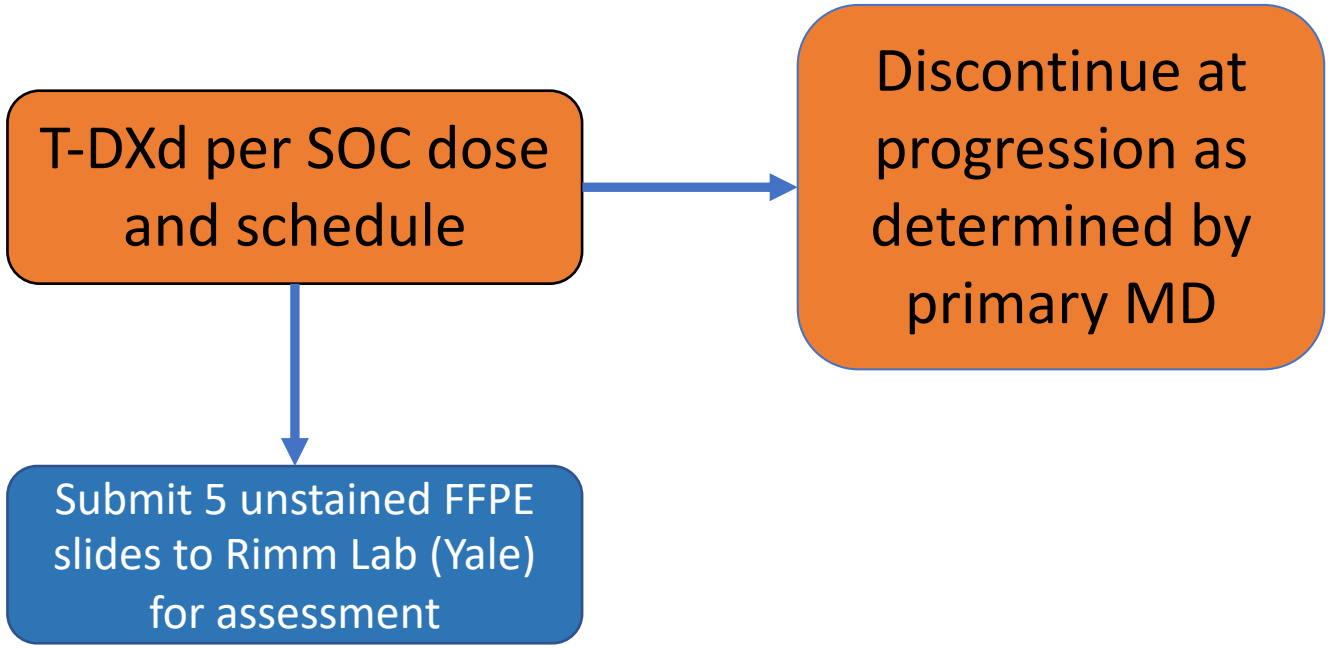
TBCRC 066 Schema

Longitudinal Cohort Study

n=200 participants

Eligibility:

- Metastatic Breast Cancer
- ER+ or ER-, HER2 IHC <2
- Measurable disease
- Available tissue for biomarker assessment
- Intention to initiate therapy with T-DXd



Follow for:

- **Real-world ORR**
- Real-world PFS
- Real-world OS

*per previously published methodologies

Bartlett et al. *PLoS One*. 2020;15(4):e0227256. doi:10.1371/JOURNAL.PONE.0227256
Ma X, et al. *Adv Ther*. 2021;38(4):1843-1859. doi:10.1007/S12325-021-01659-0/FIGURES/3
DeMichele et al. Breast Cancer Res. 2021;23(1):1-10.

OpenEvidence

Ask Feed About Announcements

New Question

is HER2-low a clinical entity?

Expanded question: Is ***human epidermal growth factor receptor 2-low*** a clinical entity?

Human epidermal growth factor receptor 2-low (HER2-low) is not currently recognized as a distinct clinical entity. The term "HER2-low" refers to breast cancers with an immunohistochemistry (IHC) score of 1+ or 2+ without gene amplification, distinguishing them from HER2-positive (IHC 3+) and HER2-negative (IHC 0) cancers. This classification emerged primarily from the DESTINY-Breast04 trial, which demonstrated the efficacy of trastuzumab deruxtecan in HER2-low breast cancer.[1-2]

However, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) have noted that HER2-low is not a new predictive or prognostic threshold but rather an artifact of trial eligibility criteria.[2] Studies have shown that HER2-low status is unstable, with significant variability between primary and metastatic tumors.[2] Additionally, there is no consistent evidence that HER2-low breast cancers have distinct biological or clinical characteristics compared to HER2-negative (IHC 0) cancers.[3-5]

In summary, while HER2-low breast cancer is a useful classification for identifying patients eligible for specific therapies, it is not considered a unique clinical entity with distinct prognostic or predictive implications. Further research is needed to clarify its biological and clinical significance.

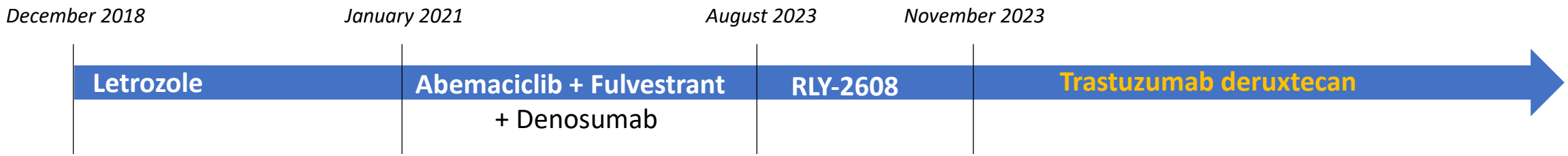
Share Helpful

https://www.openevidence.com/ask/cde95504-cb38-418c-96e0-4b7711961e4f
https://www.openevidence.com/ask/cde95504-cb38-418c-96e0-4b7711961e4f?utm_medium=referral&utm_source=share

Faculty Case Presentations

Case Presentation – Prof Curigliano

- **75 years old, ECOG PS 1**
- **Co-morbidities:** Hypertension
- **Concurrent medications:** Bisoprolol 1.25 mg, Amlodipine 5 mg



Diagnosis

Mastectomy + AND

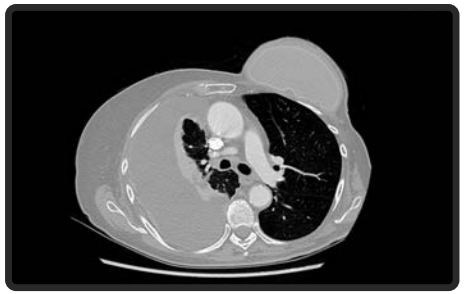
CDI G3 ER 90% PgR 90%
MIB1 25% HER2 0

pT2(22mm), pN1(3/11), M0

EC90 x4 -> Paclitaxel wk x12
RT + Letrozole

Recurrence

Bone and Pleural



Progressive disease
Liver

Liver biopsy:
IDC ER 70% PgR 0%
MIB1 35% HER20
PIK3CA mutant

PD
Liver

Liver biopsy
IDC ER 70% PgR
0% MIB1 35%
HER2 0 (<0%)
Ultralow

PR
Liver

Concordance central vs local testing

Results from central scoring

- Of samples scored as HER2-low locally, **94%** met DESTINY-Breast06 inclusion criteria (were either **HER2-low** or **HER2-ultralow** by central testing)
- **Overall percent agreement** was **77.8%** for HER2-low*
- Of samples scored as IHC 0 locally, central testing found
  - 35% were IHC 0 absent membrane staining
  - **40%** were **HER2-ultralow**
  - **24%** were **HER2-low**

64% with membrane staining

Central vs local HER2 scores in patients screened for DESTINY-Breast06†

HER2 status by central testing, n		HER2 status by local result, n				
		IHC 0†	HER2-low	IHC 2+/ISH+	IHC 3+	Total
IHC 0†	Absent membrane staining‡	123	65	0	1	189
	With membrane staining (HER2-ultralow)§	140	196	2	1	339
HER2-low		85	999	6	0	1090
IHC 2+/ISH+		1	7	0	0	8
IHC 3+		0	3	0	0	3
Total		349	1270	8	2	1629

Note: The sample used for central testing may not have been the same as that used for the local test result

*Agreement was assessed between central and local laboratories determining if samples were 'HER2-low' or 'not HER2-low' and overall percent agreement was calculated as the total number of samples that agreed divided by the total number of tests. Agreement was not calculated for HER2-ultralow because separating IHC 0 into 'absent membrane staining' and 'with membrane staining' at local sites was not part of standard practice; †per American Society of Clinical Oncology / College of American Pathologists 2018 guidelines; ‡no membrane staining is observed; §staining of the membrane in ≤10% of the cancer cells
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH+, in situ hybridization–positive

QUESTIONS FOR THE FACULTY

How, if at all, does response to T-DXd correlate with level of HER2 expression in mBC? Is it more effective in HER2-positive versus HER2-low versus HER2-ultralow disease?

How does the efficacy of T-DXd compare to that of chemotherapy in HER2-low and HER2-ultralow mBC?

Case Presentation – Dr Bardia

55F with metastatic HR+ MBC (HER2 IHC = 0). Disease progression on various endocrine based therapies, and recently capecitabine. PS = 1. No organ dysfunction. gBRCA = negative. What would you consider next?

1. Eribulin
2. Vinorelbine
3. Sacituzumab Govitecan (SG)
4. Trastuzumab Deruxtecan (T-DXd)
5. I don’t know

QUESTIONS FOR THE FACULTY

How would you think through subsequent treatment for this patient with HER2-negative (IHC 0) disease? What if the patient had HER2-low (IHC 1+ or 2+) disease? What about HER2-ultralow (IHC 0 with membrane staining) disease?

Would you use T-DXd in a patient with any history of low-level HER2 expression in their pathology report, even if it is not on the most recently acquired specimen?

Agenda

Module 1: Optimizing the Identification of HER2-Low and HER2-Ultralow Breast Cancer – Dr Wolff

Module 2: Available Data with HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease – Dr Bardia

Module 3: Practical Applications of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Metastatic Breast Cancer – Prof Curigliano

Module 4: Future Directions for HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Breast Cancer – Dr Rugo

RTP RESEARCH TO PRACTICE

Available Data With HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease

Aditya Bardia, MD, MPH

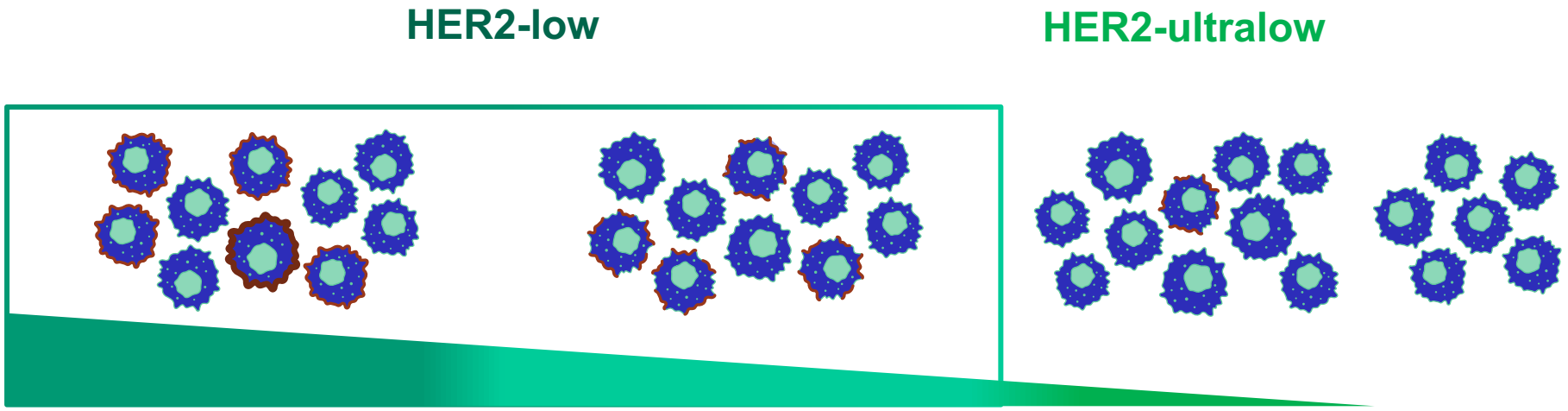
Program Director, Breast Medical Oncology, UCLA,
Assistant Chief, Hem Onc (Translational Research),
Director of Translational Research Integration,
Jonsson Comprehensive Cancer Center, Los Angeles

UCLA Health
Jonsson Comprehensive Cancer Center

David Geffen School of Medicine

What is HER2 low and ultra low?

HER2 IHC categories within HR+, HER2− mBC (per ASCO/CAP guidelines[1])

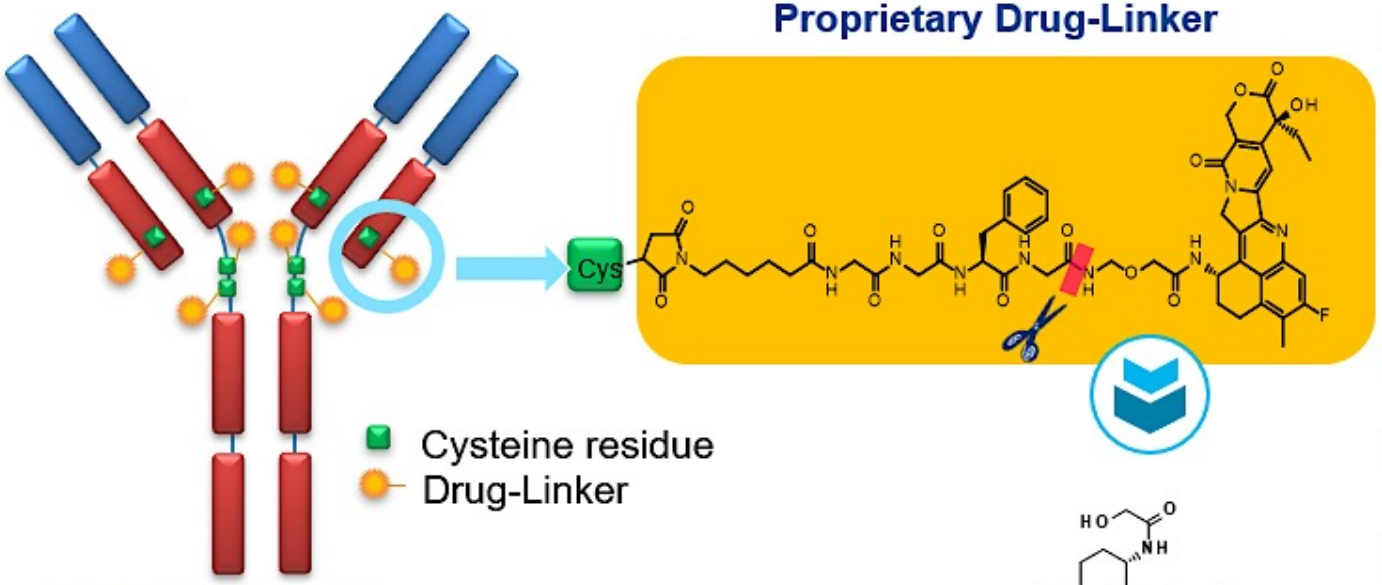


- HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022; 1. Wolff A, et al. *J Clin Oncol.* 2023;41:3867–3872

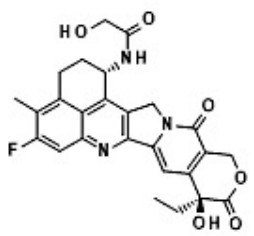
Trastuzumab Deruxtecan (T-DXd): HER2 ADC with bystander effect

Trastuzumab Deruxtecan is a HER2 targeted ADC with 7 key attributes



Conjugation chemistry
The tetrapeptide-based cleavable linker is connected to cysteine residues on the humanized anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab antibody

Proprietary Drug-Linker

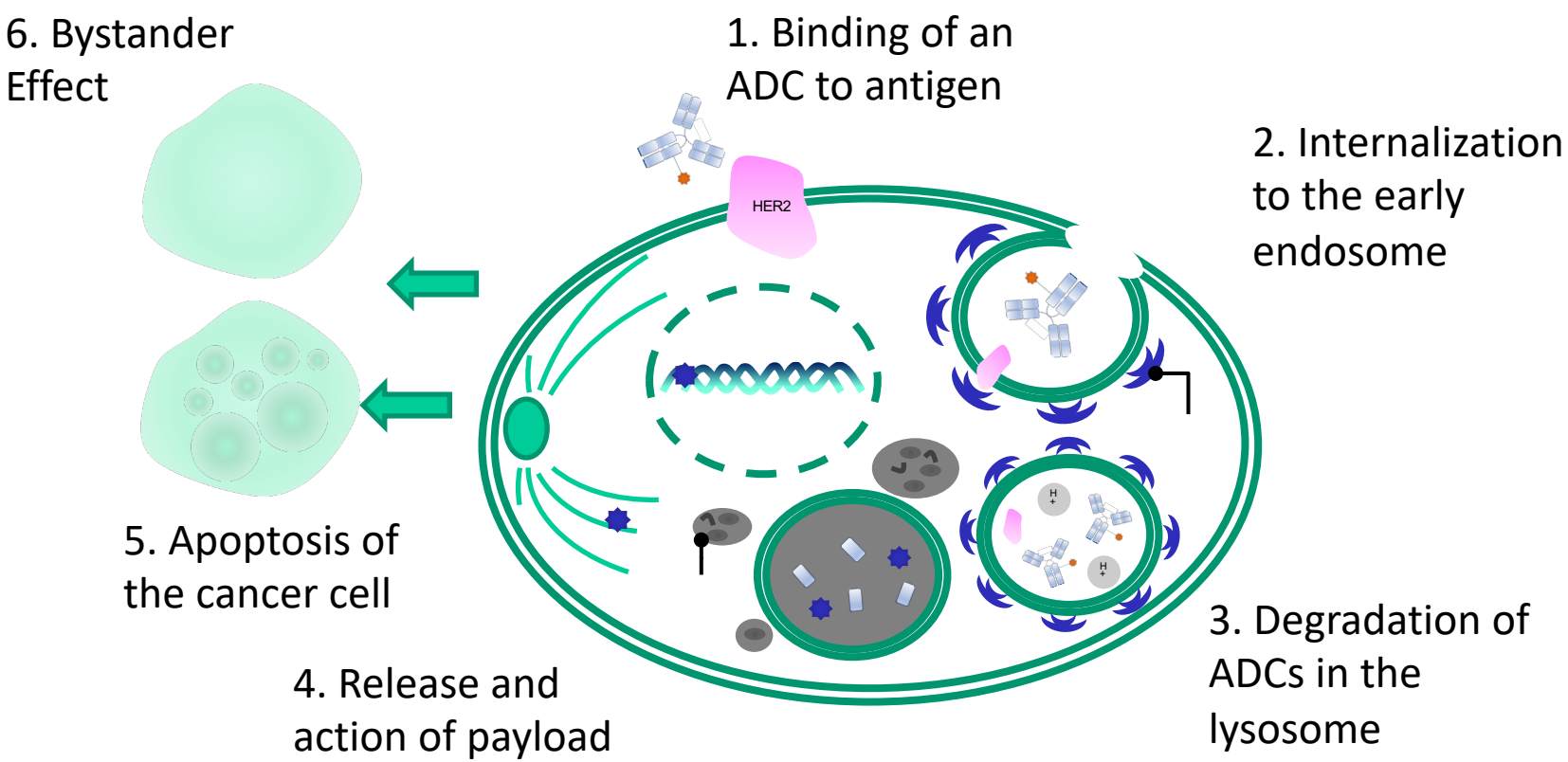


Proprietary Payload (DXd)
Exatecan derivative

1. Topoisomerase I inhibitor payload
2. High potency of payload based on a cell-free assay topoisomerase I-mediated DNA relaxation assay
3. Payload with a short systemic half-life
4. Highly membrane permeable, which may enable a bystander effect
5. Stable in plasma
6. Designed to be cleaved by lysosomal enzymes overexpressed in tumor cells
7. Drug-to-antibody ratio of 7-8

ADC=antibody-drug conjugate; HER2=human epidermal growth factor receptor 2

Selective delivery of toxic payload

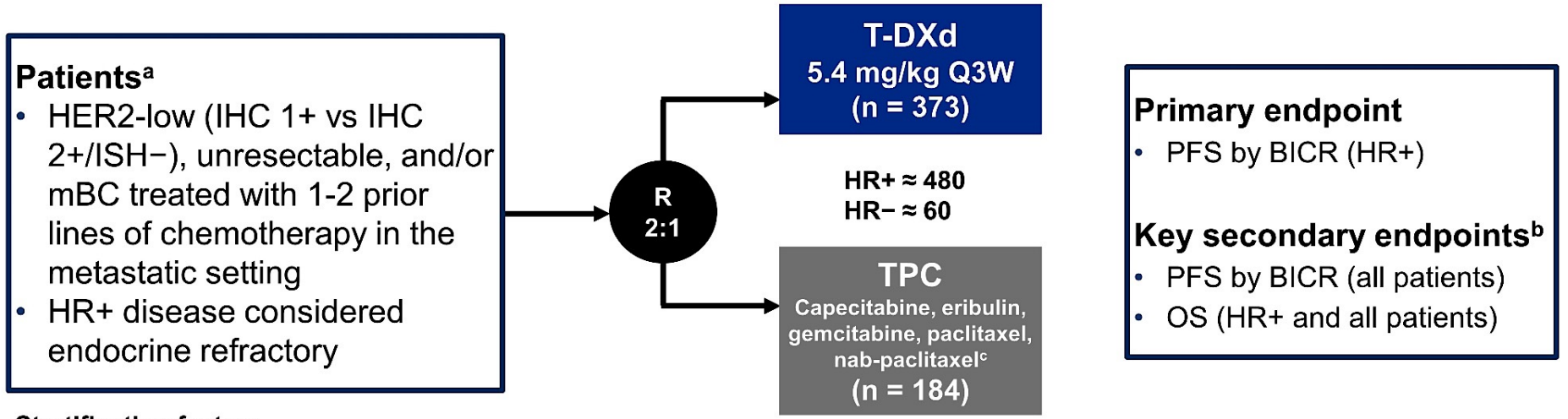


Nagayama A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

T-DXd vs TPC in HER2-low MBC: Study Design (DESTINY-Breast04)

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

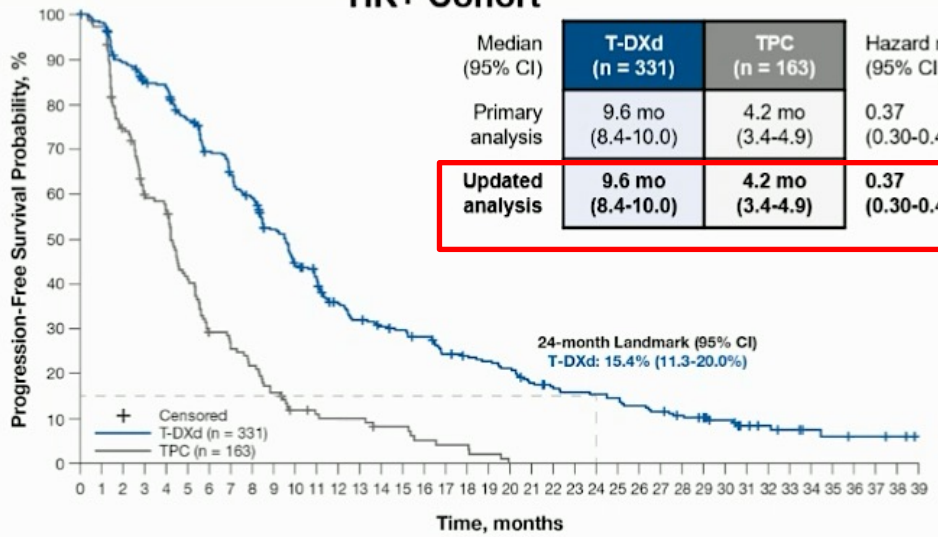
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

T-DXd vs TPC in HER2 low: Efficacy (DESTINY-Breast04)

Progression-Free Survival (by Investigator[a])

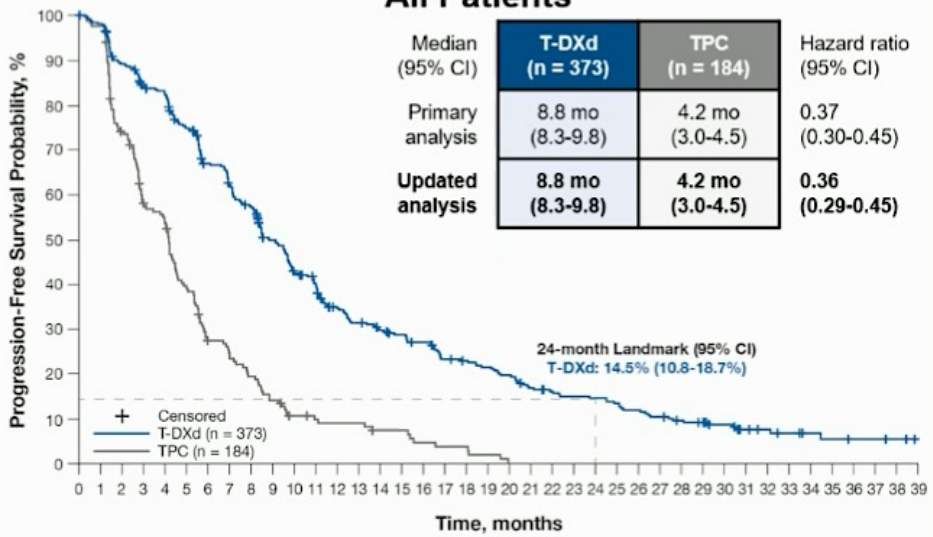
HR+ Cohort

	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Median (95% CI)			
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**



All Patients

	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Median (95% CI)			
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

BICR, blinded independent central review; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

Efficacy seen across all pre-defined subgroups

Modi S et al. ESMO 2023

How about lower HER2 expression?

Trastuzumab Deruxtecan vs TPC: Study Design (DESTINY-Breast06)

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

Three important differences from DESTINY-Breast04:

- Included HER2 ultra-low breast cancer
- No prior chemotherapy required
- Pts with rapid progression on 1st line therapy eligible

*Determined based on the most recent evaluable HER2 IHC sample prior to randomization; HER2-ultralow defined as faint, partial staining of the membrane in ≤10% of the cancer cells (also known as IHC >0<1+); †as determined by IRT (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 by central laboratory testing); ‡to be presented separately

BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

NCT04494425. Updated April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

Curigliano G et al. ASCO 2024

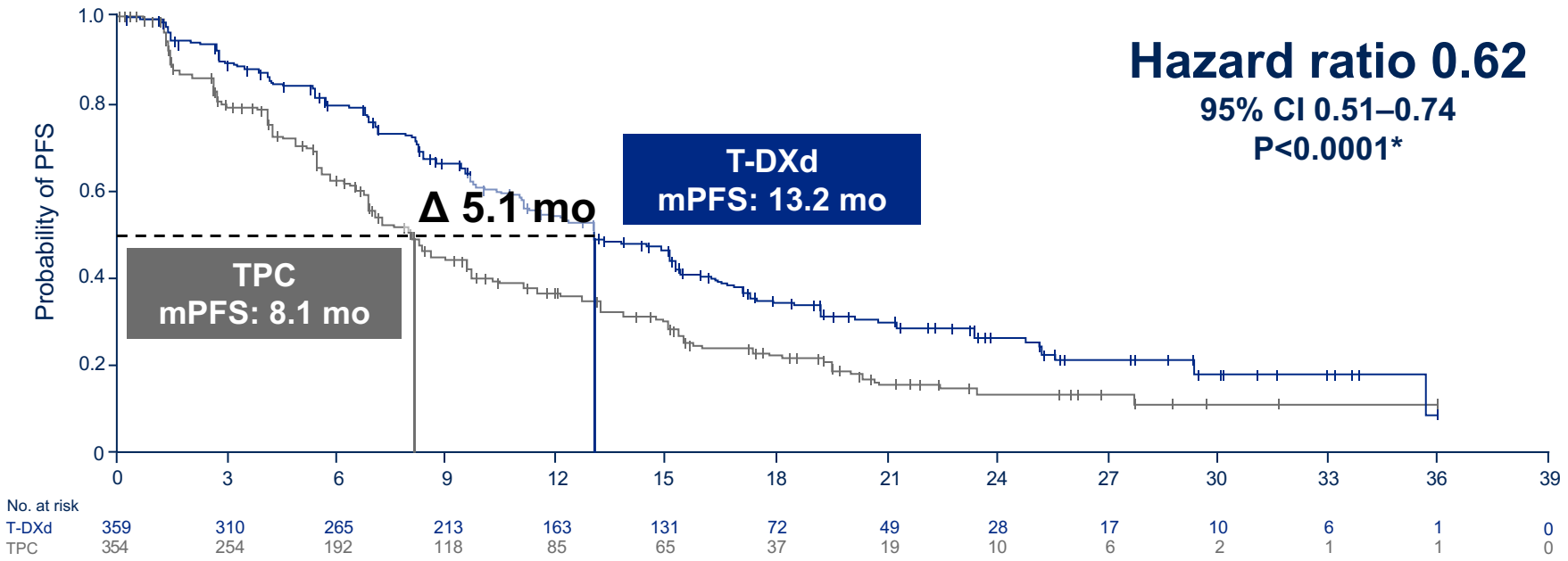
Patient demographics and baseline characteristics (DESTINY-Breast06)

	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Age, median (range), years	58.0 (28–87)	57.0 (32–83)	58.0 (28–87)	57.0 (32–83)	58.0 (33–85)	57.5 (34–82)
Female, n (%)	359 (100)	353 (99.7)	436 (100)	429 (99.8)	76 (100)	76 (100)
ECOG PS at screening, n (%)†						
0	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)	44 (57.9)	39 (51.3)
1	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)	30 (39.5)	35 (46.1)
HER2 status, n (%)						
IHC 0 with membrane staining (HER2-ultralow)	–	–	76 (17.4)	76 (17.7)	76 (100)	76 (100)
IHC 1+ (HER2-low)	238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)	–	–
IHC 2+/ISH− (HER2-low)	117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)	–	–
ER/PR status, n (%)‡						
ER+/PR+	206 (57.4)	193 (54.5)	253 (58.0)	237 (55.1)	46 (60.5)	44 (57.9)
ER+/PR−	141 (39.3)	152 (42.9)	167 (38.3)	181 (42.1)	26 (34.2)	29 (38.2)
ER−/PR+	3 (0.8)	2 (0.6)	3 (0.7)	2 (0.5)	–	–
De-novo disease at diagnosis, n (%)	111 (30.9)	104 (29.4)	133 (30.5)	132 (30.7)	22 (28.9)	28 (36.8)
Bone-only disease at baseline, n (%)	11 (3.1)	10 (2.8)	13 (3.0)	13 (3.0)	2 (2.6)	3 (3.9)
Liver metastases at baseline, n (%)	243 (67.7)	232 (65.5)	296 (67.9)	283 (65.8)	52 (68.4)	51 (67.1)

Curigliano G et al. ASCO 2024; Bardia A et al NEJM 2024

T-DXd vs TPC in HER2 low: Efficacy (DESTINY-Breast06)

PFS (BICR) in HER2-low: primary endpoint



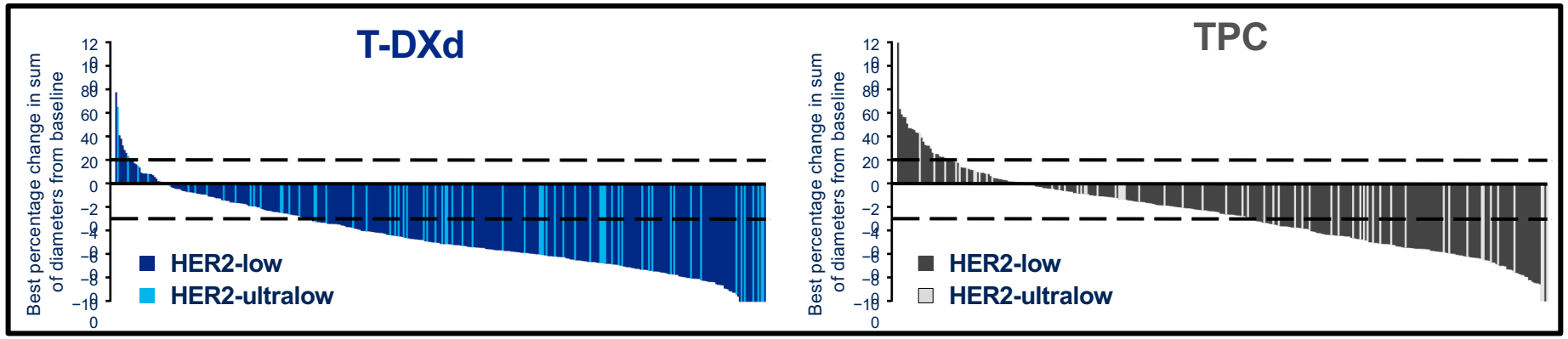
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Similar results in HER2 ultra-low MBC

Curigliano G et al. ASCO 2024; Bardia A et al NEJM 2024

ORR in HER2-low and ultralow: T-DXd vs TPC (DESTINY-Breast06)



	HER2-low*		ITT		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Confirmed ORR, n (%)	203 (56.5)	114 (32.2)	250 (57.3)	134 (31.2)	47 (61.8)	20 (26.3)
Best overall response, n (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Duration of response, median, mo	14.1	8.6	14.3	8.6	14.3	14.1

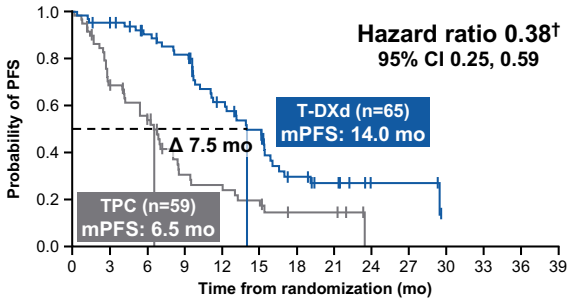
Activity seen in both HER2-low and ultra-low MBC

Curigliano G et al. ASCO 2024; Bardia A et al NEJM 2024

Results by TTP on prior ET+CDK4/6i: T-DXd vs TPC (DESTINY-Breast06)

PFS by time to progression on 1L ET + CDK4/6i and endocrine resistance

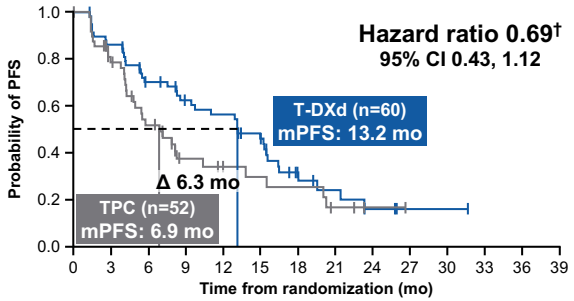
<6-mo 1L TTP*



Number at risk

T-DXd	65	61	53	47	32	25	12	8	3	3	0
TPC	59	38	30	14	12	9	4	4	0	0	0

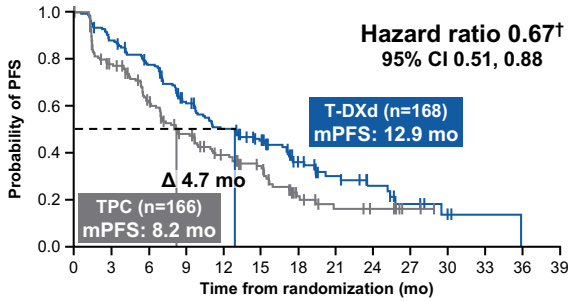
6–12-mo 1L TTP*



Number at risk

T-DXd	60	50	38	31	28	20	9	6	3	1	1	0
TPC	52	34	21	11	8	7	6	3	1	0	0	0

>12-mo 1L TTP*



Number at risk

T-DXd	168	146	125	94	74	59	28	17	11	6	2	1	0
TPC	166	114	86	62	44	33	14	8	6	2	0	0	0

	Primary endocrine resistance‡		Secondary endocrine resistance‡	
	T-DXd (n=128)	TPC (n=140)	T-DXd (n=308)	TPC (n=288)
mPFS, mo (95% CI)	12.4 (10.3, 15.2)	6.6 (5.4, 7.4)	13.2 (12.0, 15.5)	9.5 (8.0, 11.1)
PFS hazard ratio (95% CI)	0.57 (0.42, 0.77)†		0.68 (0.55, 0.84)†	

T-DXd improved PFS vs TPC regardless of time to progression on 1L ET + CDK4/6i or type of endocrine resistance

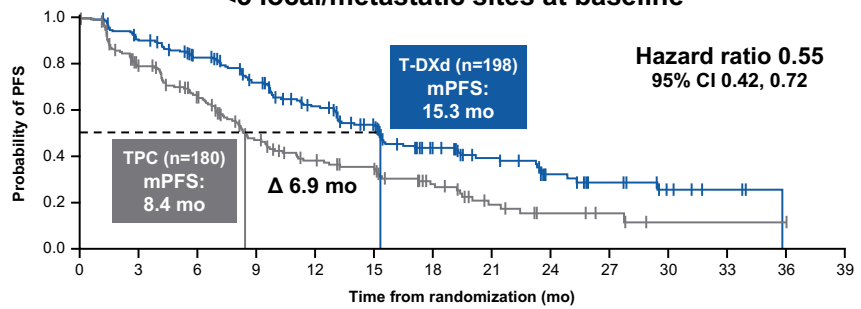
*TTP analysis included 570 patients with PD on prior 1L ET + CDK4/6i (65.8% of the ITT population); †the hazard ratio and its CI were estimated from an unstratified Cox proportional hazards model; ‡endocrine resistance assessed by investigators per 5th ESO-ESMO advanced breast cancer guidelines. Primary endocrine resistance was defined as relapse in the first 2 years of adjuvant ET, or PD <6 mo of 1L ET for mBC. Secondary (acquired) endocrine resistance was defined as relapse after the first 2 years on adjuvant ET, or relapse within 12 mo of completing adjuvant ET, or PD >6 mo after initiating ET for mBC[1]

1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ESO-ESMO, European School of Oncology-European Society for Medical Oncology; ET, endocrine therapy; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; (m)PFS, (median) progression-free survival; PD, progressive disease; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

Results by disease burden: T-DXd vs TPC (DESTINY-Breast06)

PFS by measures of disease burden

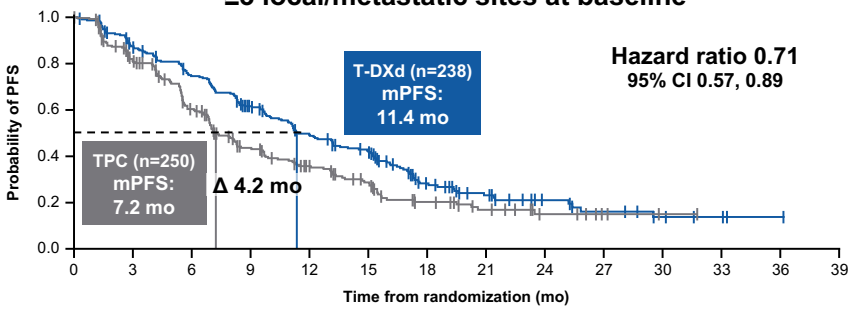
<3 local/metastatic sites at baseline



Number at risk

T-DXd	198	175	152	125	97	76	45	32	18	12	6	3	0	0
TPC	180	125	99	62	45	37	22	11	6	4	1	1	1	0

≥3 local/metastatic sites at baseline



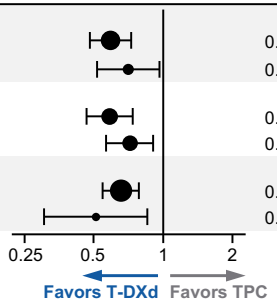
Number at risk

T-DXd	238	200	167	133	102	80	37	24	14	9	5	3	1	0
TPC	250	181	125	80	58	42	22	14	7	3	1	0	0	0

PFS benefit with T-DXd was observed regardless of disease burden, with efficacy noted in patients with lower disease burden

mPFS, mo (95% CI)

	T-DXd	TPC	Hazard ratio (95% CI)
Liver metastases			
Yes (n=579)	12.2 (10.4, 13.5)	7.0 (6.4, 8.1)	0.59 (0.48, 0.72)
No (n=287)	16.5 (13.2, 19.4)	11.3 (8.3, 15.2)	0.70 (0.51, 0.96)
Baseline tumor size*			
>Median (n=432)	12.0 (9.9, 15.2)	7.1 (6.5, 8.3)	0.57 (0.45, 0.72)
≤Median (n=434)	15.0 (13.1, 16.1)	9.7 (7.5, 13.2)	0.71 (0.55, 0.90)
Visceral disease			
Yes (n=740)	13.1 (11.1, 15.1)	7.9 (6.9, 8.5)	0.65 (0.55, 0.78)
No (n=126)	23.3 (13.1, NE)	11.3 (6.9, 15.7)	0.51 (0.30, 0.85)



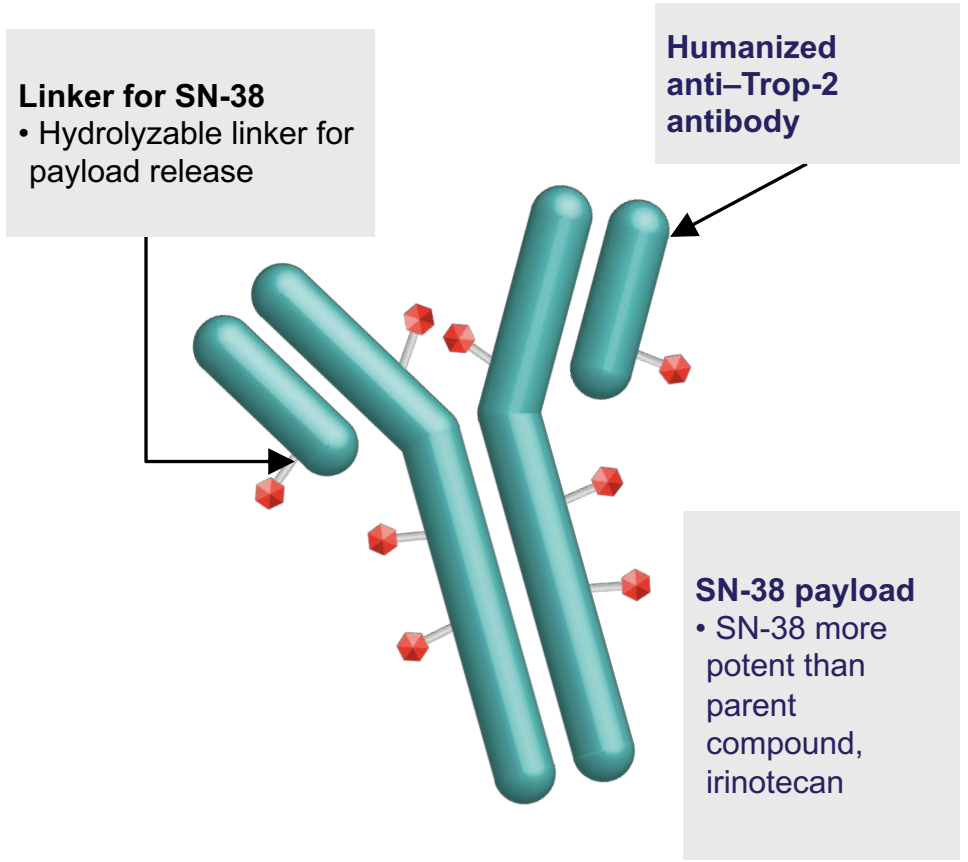
*Median baseline tumor size in the ITT population (per BICR) was 48.6 mm, considering '0' as baseline tumor size for patients without target lesion at baseline

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; ET, endocrine therapy; HR, hazard ratio; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; NE, not evaluable; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

Sacituzumab Govitecan: First-in-class trop2 ADC

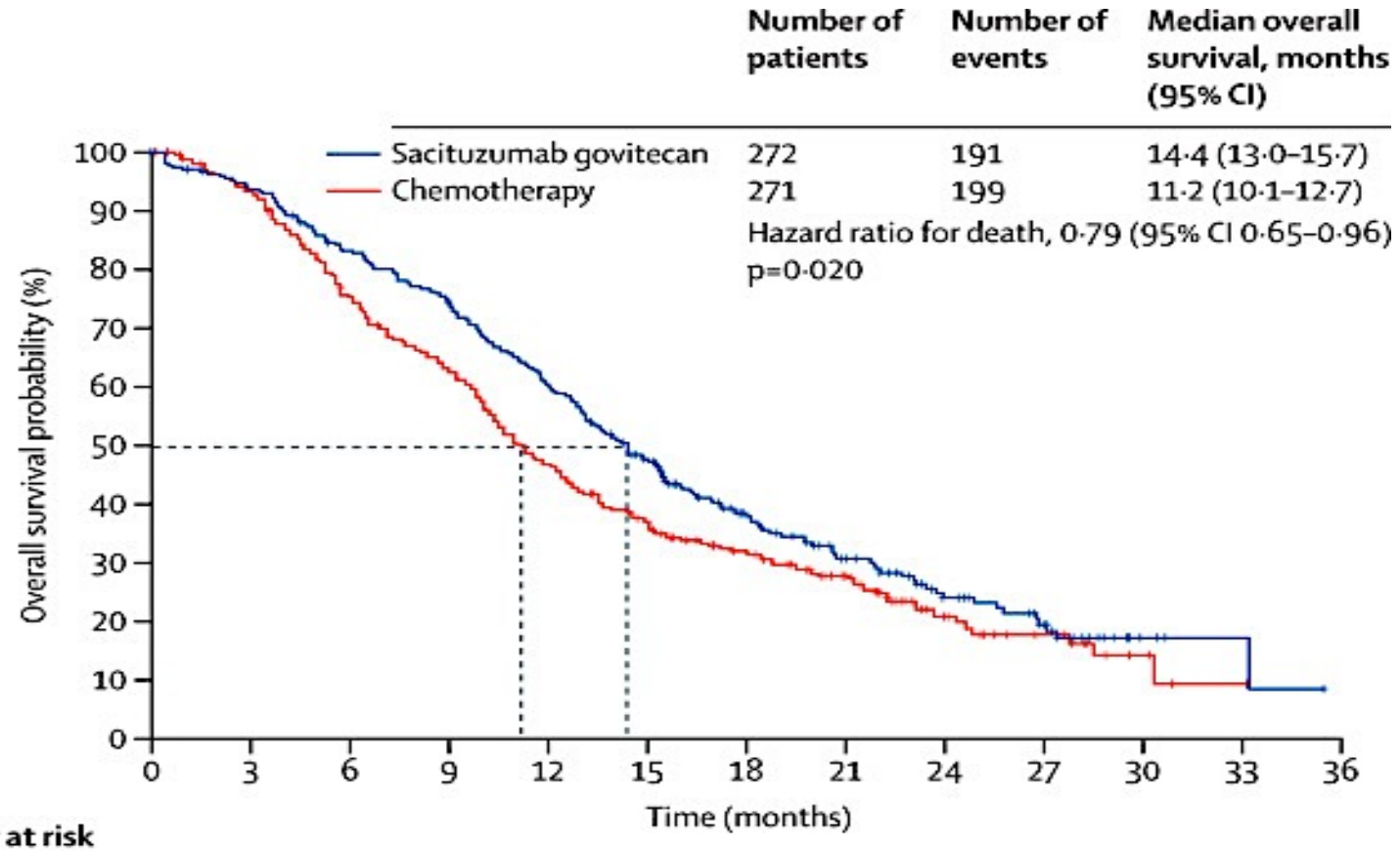
SG is distinct from other ADCs

- Antibody highly specific for Trop-2
- High drug-to-antibody ratio (7.6:1)
- Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
- Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect



Nagayama A et al. *Ther Adv Med Oncol*. 2020; Cardillo TM et al. *Bioconjugate Chem*. 2015.

Sacituzumab Govitecan vs TPC: Overall Survival (TROPiCs-02)



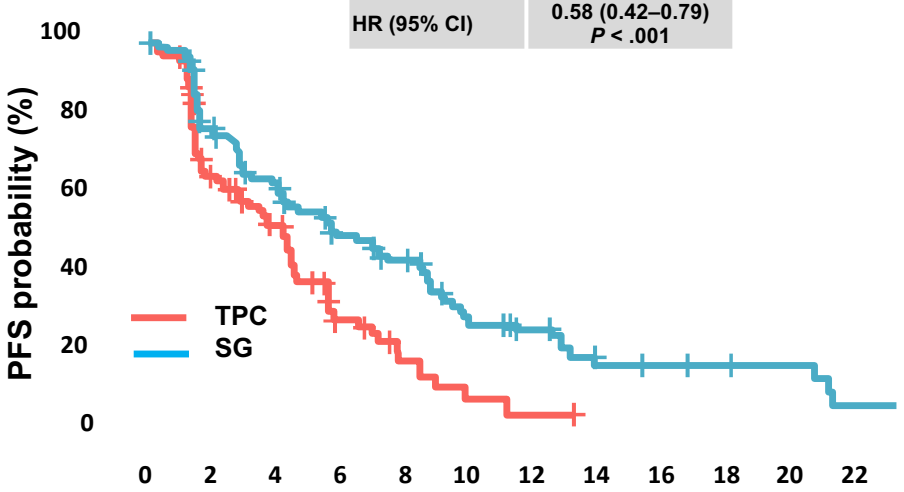
Number at risk (events)													
Sacituzumab govitecan	272	252	221	197	160	120	80	53	31	20	4	2	0
	(0)	(16)	(44)	(67)	(104)	(137)	(158)	(173)	(183)	(188)	(190)	(190)	(191)
Chemotherapy	271	246	196	164	122	92	70	49	23	13	5	1	0
	(0)	(16)	(64)	(95)	(137)	(163)	(174)	(183)	(193)	(196)	(198)	(199)	(199)

Rugo H and Bardia A et al. Lancet 2023

Sacituzumab Govitecan vs TPC: Efficacy by HER2 status (TROPiCs-02)

HER2-low

	SG (n = 149)	TPC (n = 134)
Median PFS, mo	6.4	4.2
HR (95% CI)	0.58 (0.42–0.79) *P* < .001	

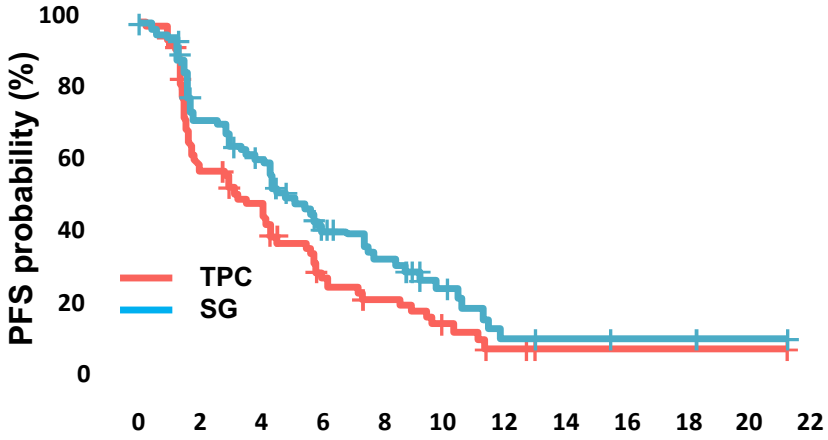


Number at risk

TPC	134	65	43	16	8	4	1	0	0	0	0	0
SG	149	99	77	50	38	22	16	8	7	5	5	2

HER2 IHC0

	SG (n = 101)	TPC (n = 116)
Median PFS, mo	5.0	3.4
HR (95% CI)	0.72 (0.51–1.00) *P* = .05	



Number at risk

TPC	116	53	39	20	14	7	3	1	1	1	1	0
SG	101	64	50	27	20	9	4	3	2	1	1	0

Similar results with Overall Survival

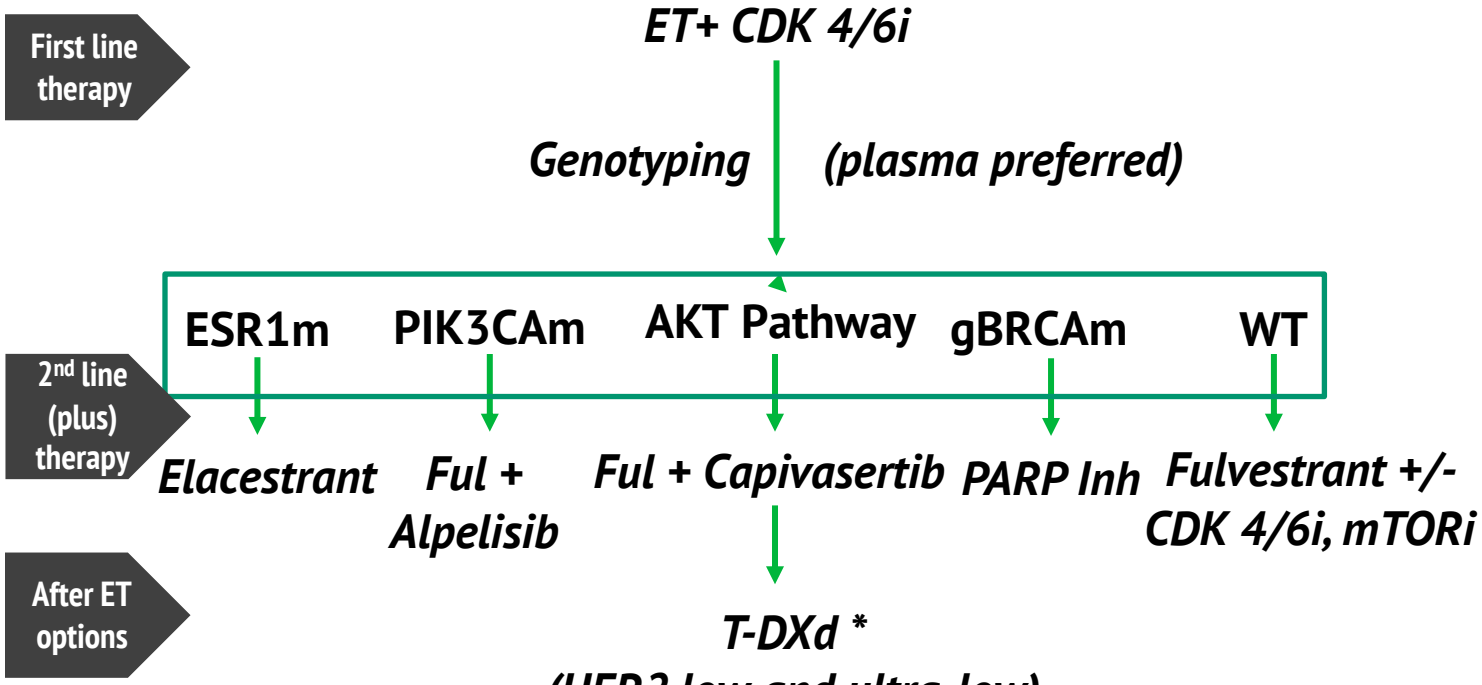
Marme F, et al. ESMO 2022

ADCs to target MBC: Multiple Agents in Development

Antibody Drug Conjugate	Target	Payload
Trastuzumab deruxtecan (DS-8201a)	HER2	Topo-1 inhibitor
Sacituzumab govitecan (IMMU-132)	Trop-2	Topo-1 inhibitor
Datopotamab deruxtecan (DS-1062)	Trop-2	Topo-1 inhibitor
Sacituzumab Tirumotecan (Sac-TMT)	Trop-2	Topo-1 inhibitor
Patritumab deruxtecan (U3-1402)	HER3	Topo-1 inhibitor
BB1701	HER2	Microtububle inhibitor
Disitamab Vedotin	HER2	Microtubule inhibitor

Besides target, type of payload might impact ADC success in advanced setting

Management of HR+/HER2- MBC: General Guideline



*For some patients, chemotherapy (cape) might be preferred before T-DXd. Patient-centered discussion

Summary

- Trastuzumab deruxtecan: currently approved for HER2 low MBC (both HR+ and TNBC) after 1 prior line of chemotherapy. Demonstrated activity in earlier lines as well as HER2 ultra-low MBC.
- Sacituzumab govitecan approved for metastatic HR+ breast cancer after 2 prior lines of systemic therapy.
- There are multiple other ADCs in development to target antigens overexpressed in MBC.

- Additional studies evaluating efficacy of ADCs alone and in combination as well as other indications in breast cancer could redefine the receptor classification of breast cancer.

Faculty Case Presentations

Case Presentation – Prof Curigliano

49 years old Previous Melanoma diagnosis (pT1bN0 2022).

February 2023:
- Imaging: **4,5 cm right breast nodule with axillary nodes**
- Biopsy IDC (G3, ER-, PR-, HER2: 0, Ki-67 60%).
- Stage: **cT2N1M0, IIIB. BRCA1/2 WT** -

March 2023 - September 2023: Neoadjuvant Pembrolizumab/Carboplatin/Paclitaxel followed by Epirubicin /Cyclophosphamide

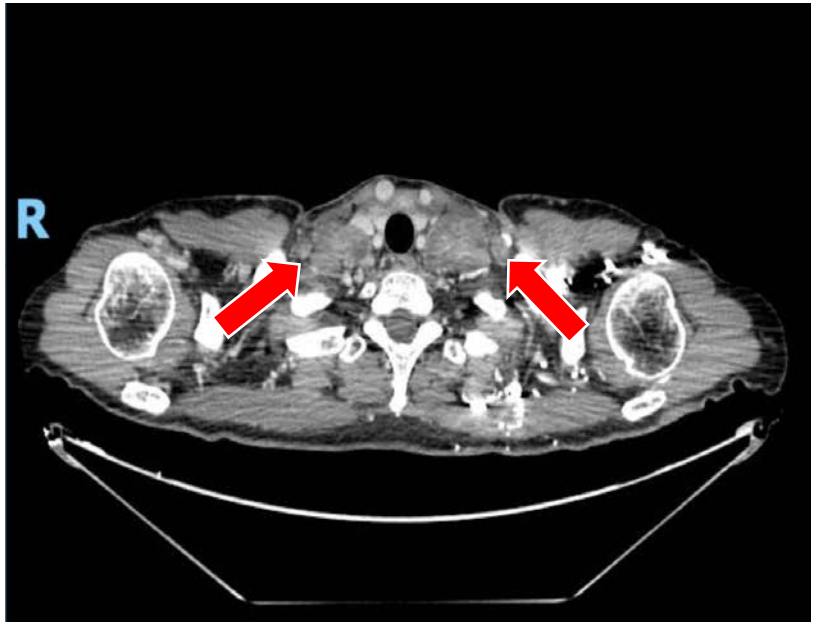
October 2023: Right mastectomy and axillary dissection
Stage **ypT1c (15 mm) N1a (2/18) (ER-, PR-, HER2: 0, Ki-67 30%)**-

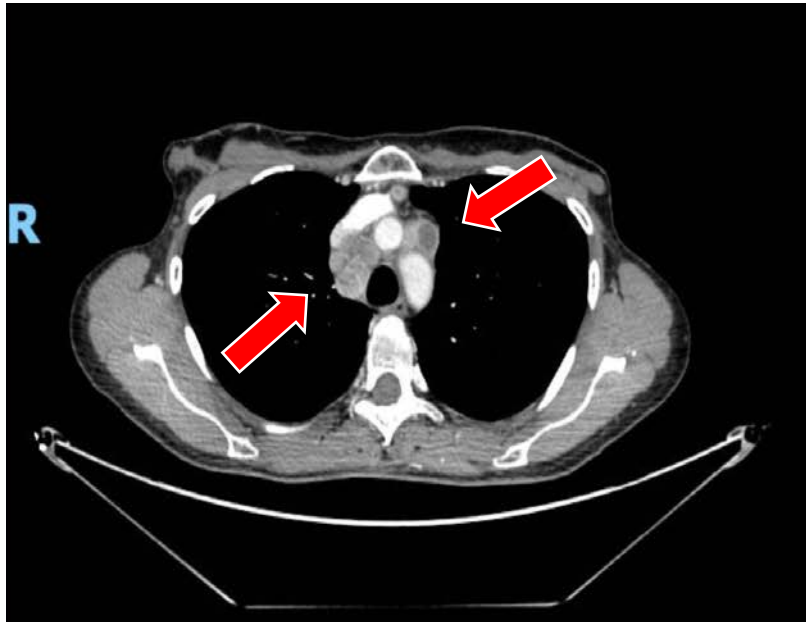
December 2023 to May 2024:
- **Radiotherapy and Pembrolizumab**

Case Presentation – Prof Curigliano (continued)

August 2024: Supraclavicular and mediastinal node progressive disease

- Biopsy: **IDC (ER-, PR-, HER2-low 1+, Ki-67 55%).**

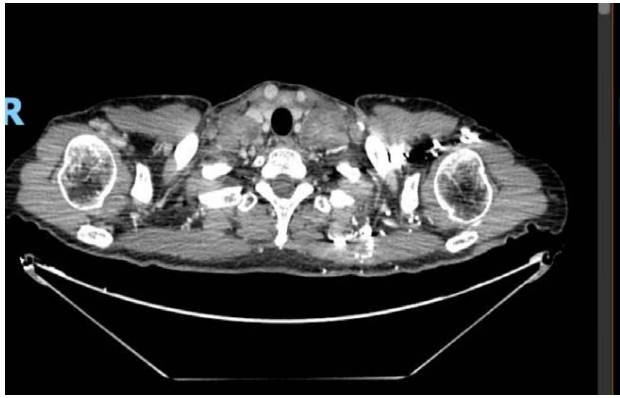




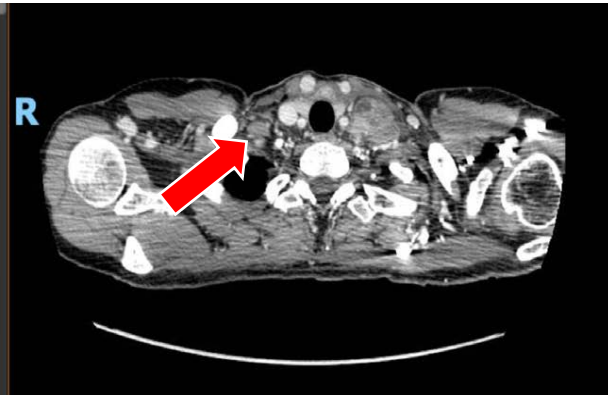
Case Presentation – Prof Curigliano (continued)

August 2024 to November 2024: Trastuzumab deruxtecan with partial response

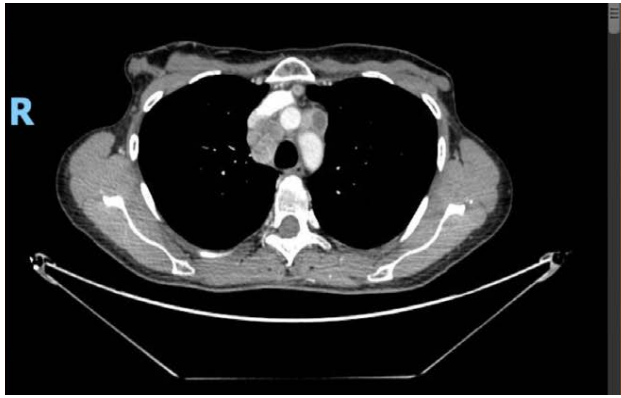
August ‘24



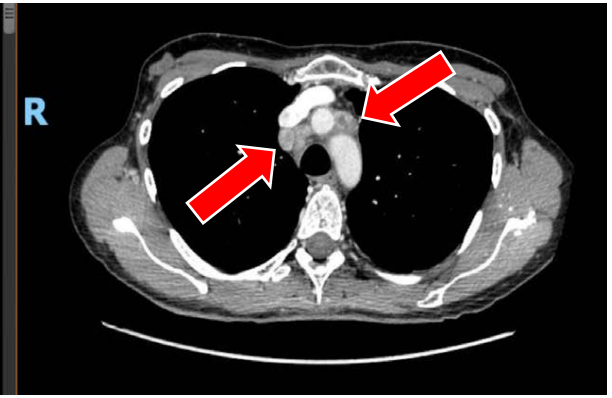
October ‘24



August ‘24



October ‘24



QUESTIONS FOR THE FACULTY

Do you routinely reassess HER2 status in patients who have recurrent disease? When a patient with mBC in your practice is found to have HER2-negative disease, do you ever ask the pathologist to reassess HER2 status?

Do you generally employ solid or liquid biopsy when reassessing HER2 status in patients with recurrent disease?

In patients with multiple disease sites (eg, breast primary, lung, liver), do you generally send multiple samples for HER2 testing?

Case Presentation – Dr Wolff

- 52 yo postmenopausal F previously diagnosed with Stage I (pT1c pN0) ER 0, HER2 IHC 1+ breast ca treated with breast conservation and 4 cycles of adjuvant docetaxel/cyclophosphamide
- 4y after initial diagnosis, she presents with new persistent cough, and imaging detects mediastinal and small volume lung disease
- EBUS-guided paratracheal node biopsy confirms breast cancer that tests ER 0, HER2 IHC 0, with tumor NGS that is unrevealing, and prior germline testing had been normal
- Her PS was 1 and she starts 1st line (1L) capecitabine with resolution of cough and partial response followed by stability on imaging
- She develops clear progression (imaging and markers) after 14 months but her PS remains 0
- What therapy would you consider next?
  - 2L chemotherapy with conventional single-agent or a combination regimen?
  - 2L chemotherapy with an ADC like sacituzumab govitecan?
  - 2L chemotherapy with an ADC like trastuzumab deruxtecan?

QUESTIONS FOR THE FACULTY

How are you generally sequencing T-DXd relative to other antibody-drug conjugates and chemotherapy for your patients with ER-negative, HER2-low mBC?

For patients eligible to receive T-DXd and sacituzumab govitecan, which agent do you generally recommend first? In which situations would you prioritize T-DXd over sacituzumab govitecan?

What is currently known about the effectiveness of T-DXd in patients who have previously received sacituzumab govitecan and vice versa? Is there any cross-resistance between the two drugs?

Case Presentation – Dr Rugo

- Presented at age 37 with left breast cancer (10/2008)
- Biopsy of breast mass: Grade 3 IDC, ER+ (90%), PR negative (<1%), HER2 negative (IHC 0)
  - FNA axillary node + for carcinoma
- 12/8/08 to 3/19/09: Neoadjuvant dose dense paclitaxel x 4 cycles followed by dose dense AC x 4 cycles
- 4/21/2009: Bilateral skin sparing mastectomy: left breast with 5.3 cm residual carcinoma with 5/24+ nodes; ypT3N2
  - Post surgery: radiation therapy
  - Endocrine therapy: 3 months of ovarian function suppression with goserelin with 2-3 months of tamoxifen, then took tamoxifen alone for 4 months, then restarted goserelin and tamoxifen for one year followed by 3 years of tamoxifen alone
- Germline testing pathologic variant in CFTR

Case Presentation – Dr Rugo (Continued)

- May-June 2020: Developed a persistent cough and fatigue.
- 9/5/2020: CXR by primary MD: Loculated right pleural effusion with adjacent consolidation.
- 10/6/2020 Chest CT: Multiple subcentimeter solid pulmonary nodules with irregular intralobular septal thickening, large right pleural effusion with thickening with near complete atelectasis of the right lower lobe. Extensive adenopathy and a large osteolytic sternal mass with soft tissue component, scattered osteolytic lesions within C7, T1, T6 vertebral bodies, subacute to chronic right 6 lateral rib fracture.
- 10/8/2020 Right thoracentesis (1500 cc): Malignant cells consistent with breast origin. GATA3 positive, ER+(60%), PR+(5%), HER2 neg(IHC 0).
- 10/8/2020 PET-CT: Lung, pleural and extensive bone metastases.
- 10/9/2020 Brain MR: Greater than 20 punctate foci of enhancement scattered throughout the supratentorial and infratentorial brain.
- 10/9/2020 Right anterior iliac bone CT-guided biopsy: Metastatic adenocarcinoma consistent with breast origin, ER+(90%), PR negative(0%), **HER2 negative(IHC 0 to 1)**.
- 10/13/20-12/2022: Letrozole with goserelin and palbociclib, changed to abemaciclib 1/22-11/23.
- 10/22/20-3/11/21 PleurX™ catheter.
- 11/6/20: Gamma knife to brain to 16 targets.

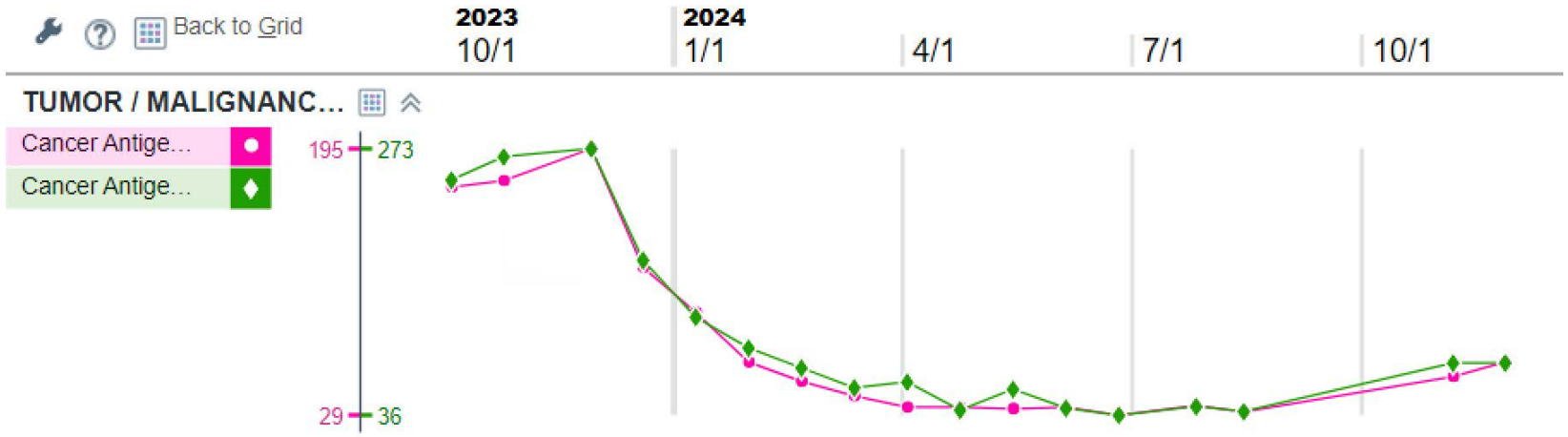
Case Presentation – Dr Rugo (Continued)

What Happened Next?

- 12/22/21 Guardant360®: ESR1 Y527N, ESR1 D528G, ESR1 E380Q, FGFR1
- Developed a single liver lesion, biopsy consistent with focal nodular hyperplasia
- Evidence of progressive disease in bone and pleura on imaging
- 3/30/23 - 6/13/23: Morpheus-2 clinical trial, randomized to giredestrant, abemaciclib, and atezolizumab
- Developed renal insufficiency and intractable nausea and vomiting with imaging consistent with bowel infiltration, required bilateral ureteral stent placement for bilateral hydronephrosis
- Resistant to starting chemotherapy, received one dose of fulvestrant
- 7/20/23 to 7/25/23: renal failure due to obstructive nephropathy, requiring bilateral nephrostomy, unable to tolerate oral meds due to refractory N/V
- 7/23 – 10/23: *nab*-paclitaxel
- 10/23 progression in brain, treated with stereotactic RT

Case Presentation – Dr Rugo (Continued)

- On *nab*-paclitaxel continued to have refractory N/V and abdominal pain, with nephrostomy tubes in place
- 11/23 started trastuzumab deruxtecan
- Dramatic response to therapy by cycle 3
  - N/V resolved as did abdominal pain
  - Ureteral stents placed and nephrostomy tubes removed
- 4/24 T-DXd held for one cycle due to grade 1 ILD
- 12/24 continues on T-DXd with the beginning of GI symptoms



QUESTIONS FOR THE FACULTY

How are you generally sequencing T-DXd relative to other available therapies for your patients with ER-positive, HER2-low and HER2-ultralow mBC?

How does this vary depending on the presence of other biomarkers (eg, ESR1 mutations, PIK3CA/AKT1/PTEN alterations) and the pace of disease progression on prior endocrine-based therapy?

Do you employ G-CSF prophylaxis for all patients receiving T-DXd or only under certain circumstances? How does the fact that this patient has ureteral stents affect your treatment strategy and your enthusiasm for using T-DXd?

Agenda

Module 1: Optimizing the Identification of HER2-Low and HER2-Ultralow Breast Cancer – Dr Wolff

Module 2: Available Data with HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease – Dr Bardia

Module 3: Practical Applications of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Metastatic Breast Cancer – Prof Curigliano

Module 4: Future Directions for HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Breast Cancer – Dr Rugo

RTP
RESEARCH
TO PRACTICE

UNIVERSITÀ DEGLI STUDI DI MILANO

IEO Istituto Europeo di Oncologia

Practical applications of HER2-targeted therapy for HER2 low and HER2 ultralow mBC

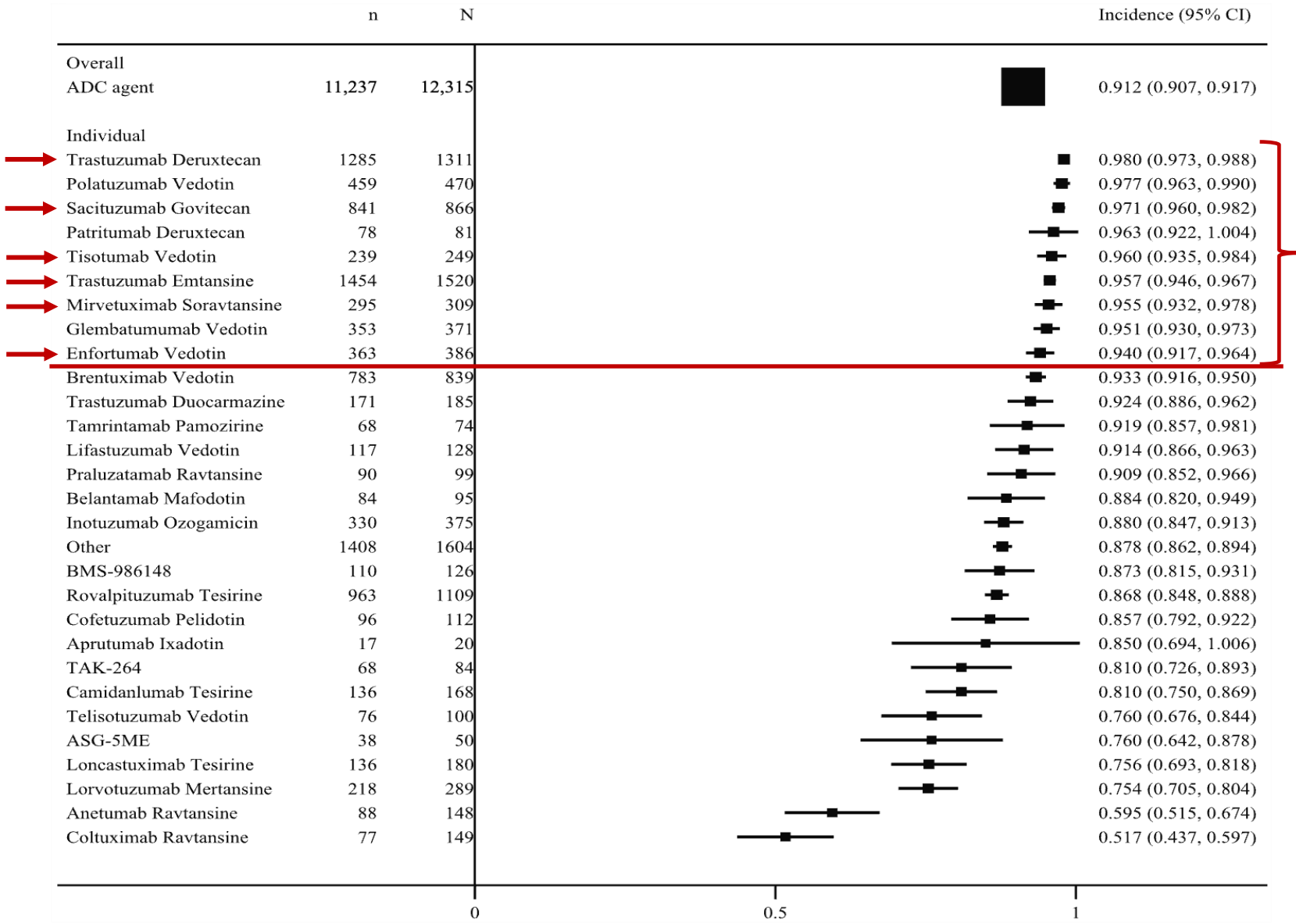
Giuseppe Curigliano, MD PhD

European Institute of Oncology, IRCCS

University of Milano

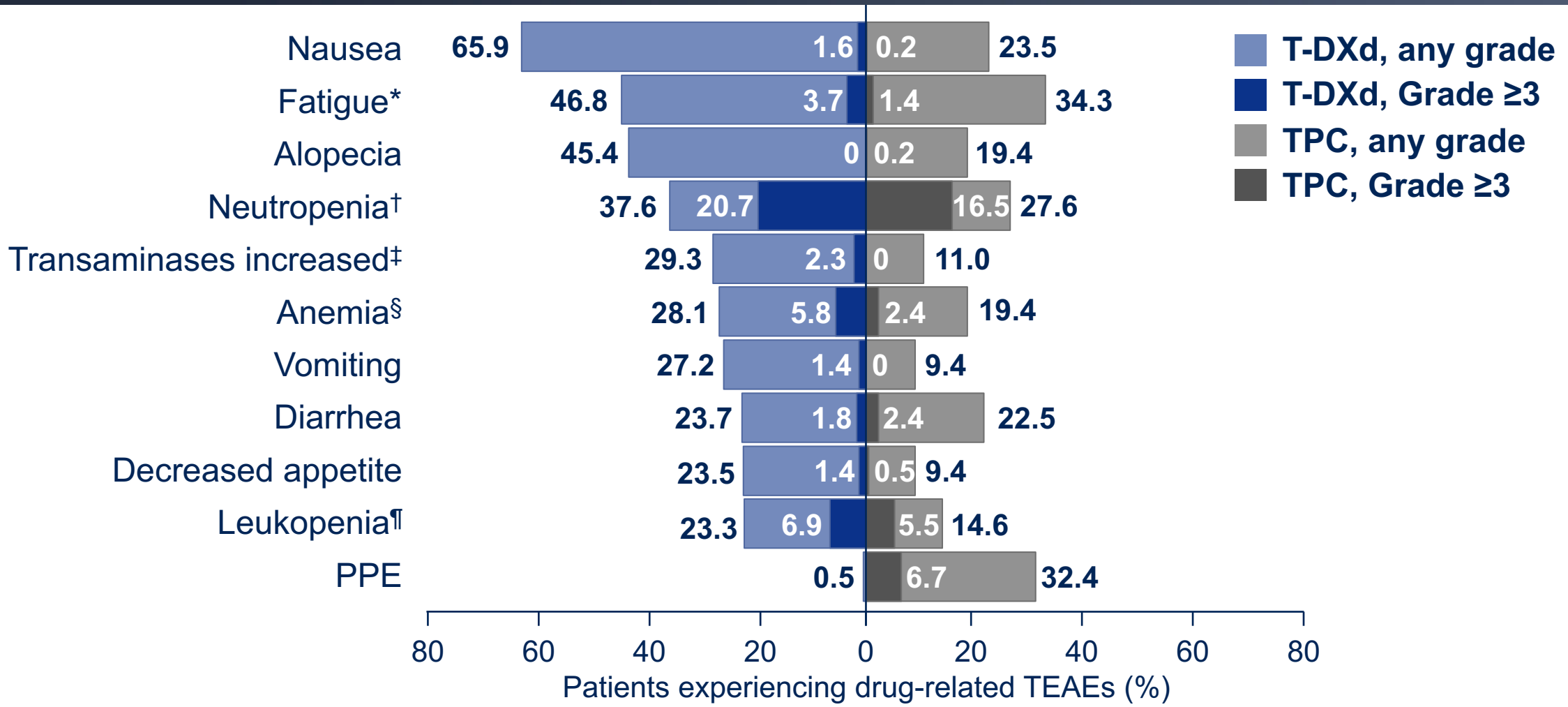
Treatment-related adverse events with ADCs

The rate of any-grade treatment-related adverse events is **>90%** with all the ADCs approved for solid tumors

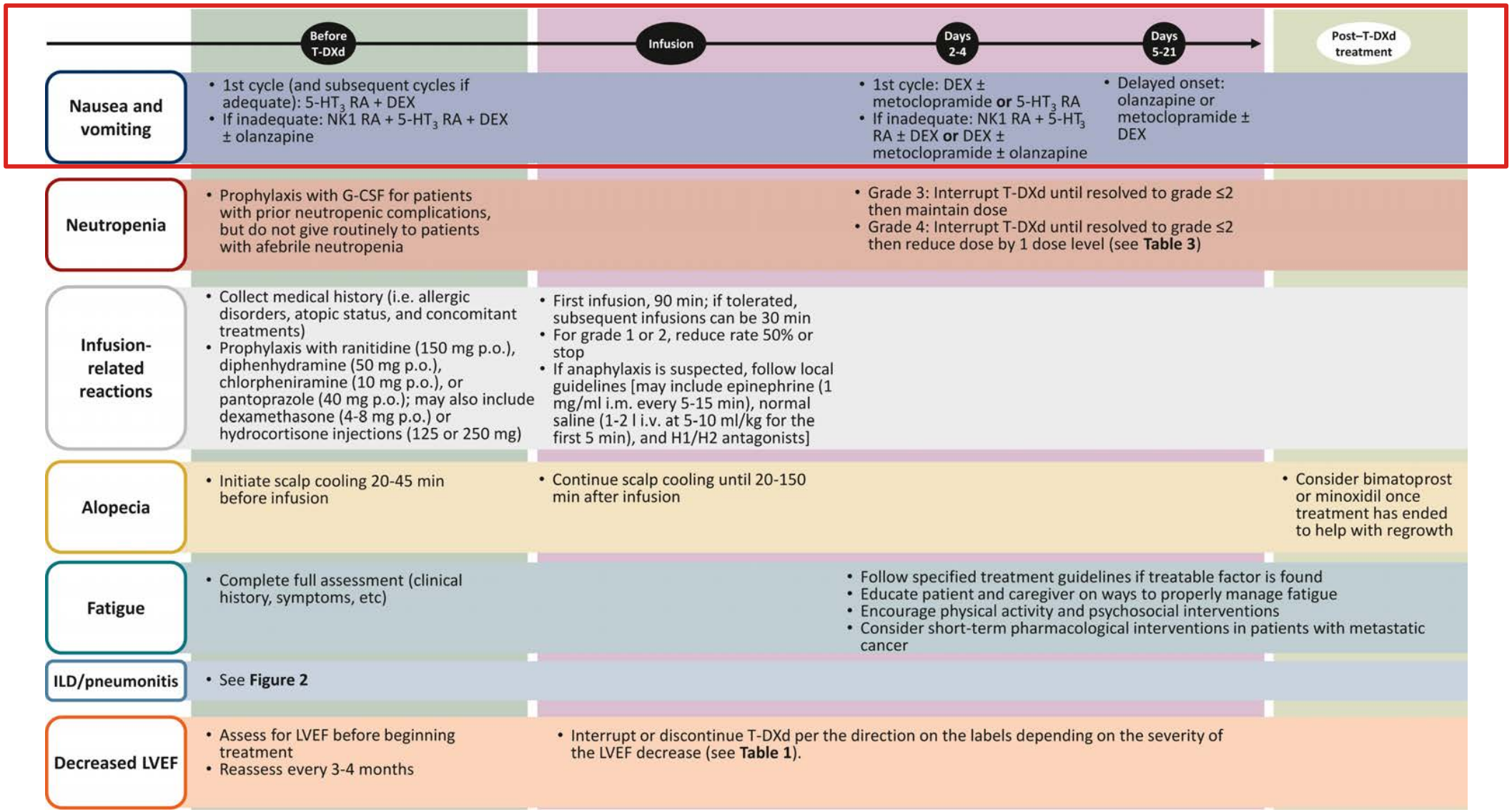


Zhu Y. et al. *Cancer 2022*

Drug-related TEAEs in ≥20% of patients (either treatment group)



Gastro-intestinal toxicities



Rugo HS, et al ESMO Open. 2022 Aug;7(4)

Nausea and vomiting

Nausea and vomiting	•DESTINY-Breast03, 72.8% (187/257) and 44.0% (113/257) [grade ≥3, 6.6% (17/257) and 1.6% (4/257)], respectively •DESTINY-Breast01, 77.7% (143/184) and 45.7% (84/184) [grade ≥3, 7.6% (14/184) and 4.3% (8/184)], respectively	•Pretreatment with a 5-HT_3 receptor antagonist and dexamethasone with or without a neurokinin-1 receptor antagonist •Delayed nausea prophylaxis: give dexamethasone on days 2-3 after infusion of T-DXd •Grade 3: delay dose until resolved to grade ≤1 •If resolved in ≤7 days, maintain dose •If resolved in >7 days, reduce dose 1 level

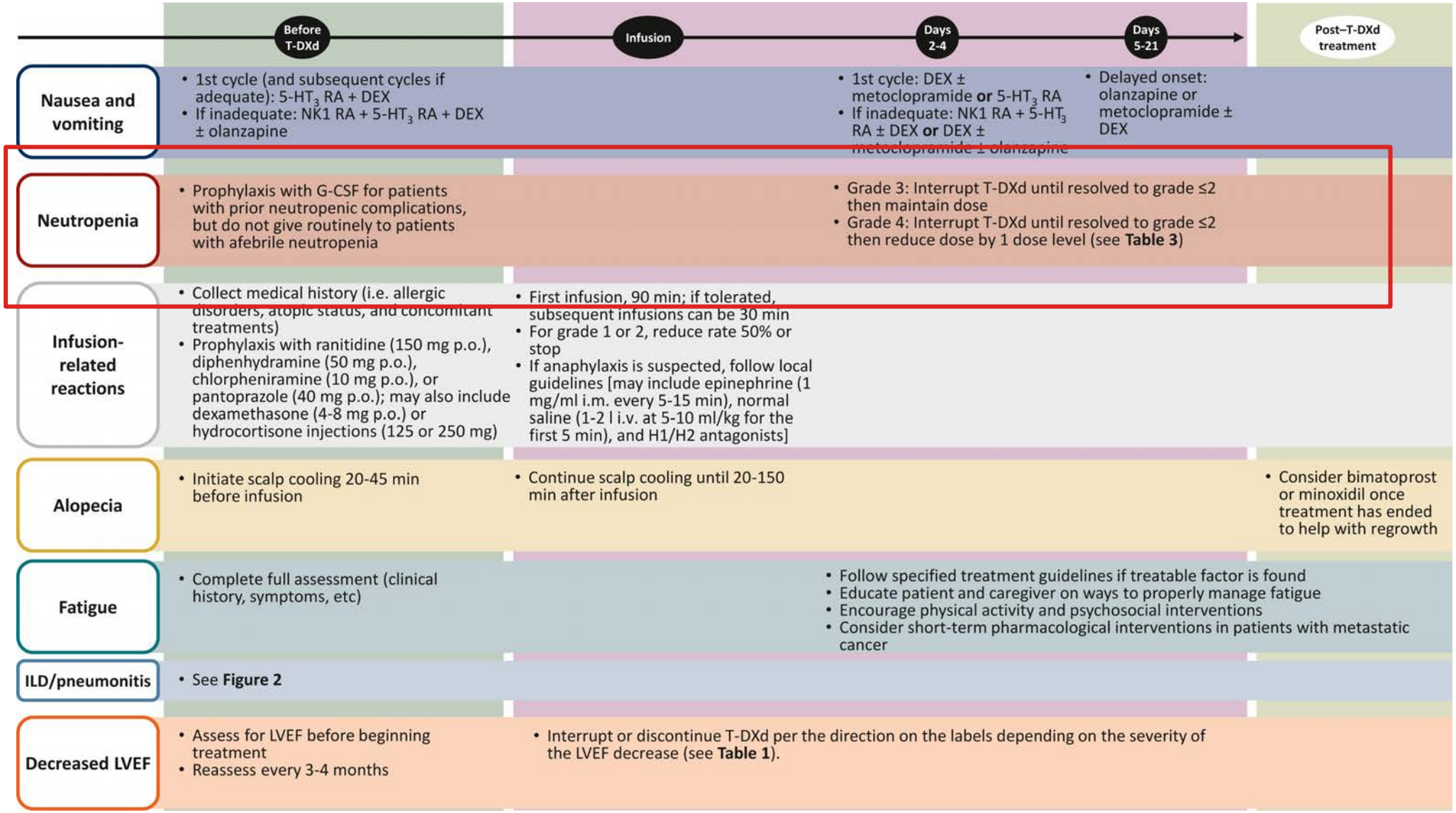
Rugo HS, et al ESMO Open. 2022 Aug;7(4)

Nausea and vomiting management protocol

Day	Medication protocols	Other considerations
Before infusion/day 1	•1st cycle: dexamethasone (8-12 mg p.o. or i.v.) + 5-HT_3 RA [e.g. palonosetron (0.25-0.5 mg i.v.), granisetron (10 mg s.c.), or ondansetron (8 mg i.v.)] •Subsequent cycles: if optimal control, repeat above. If not (e.g. grade ≥1 for ≥3 days), dexamethasone (12 mg i.v.) + NK1 RA [aprepitant (125 mg p.o.) or netupitant (300 mg p.o.)] + 5-HT_3 RA [e.g. palonosetron (0.25 mg i.v. or 0.5 mg p.o.) or granisetron (10 mg s.c.)]	•For patients with anticipatory N/V, consider anxiolytic therapy [e.g. lorazepam (0.5-1.0 mg p.o.)] the night before infusion and 1-2 h before infusion begins[28] •Behavioral therapy (e.g. relaxation exercises, hypnosis) and/or acupuncture/acupressure may also aid in anticipatory N/V prevention[38,39] •For subsequent infusions, estimate individual risk of emesis to determine whether past regimen was adequate or if escalation is necessary
After infusion/day 1	•Consider ondansetron (8 mg p.o. or i.v./i.m.) for 3 doses after infusion •1st cycle: dexamethasone (4 mg p.o. or 8 mg p.o. or i.v./i.m. daily) ± metoclopramide (10 mg p.o.) t.i.d. or 5-HT_3 RA [e.g. granisetron (1-2 mg p.o. qd or 0.1 mg/kg i.v. qd)]	•If N/V occur despite 3-drug regimen, offer olanzapine (2.5 mg p.o.; increase to 5-10 mg if needed) on days 1-4 or increase dexamethasone on days 2-4 on subsequent cycles
Days 2-4	•Subsequent cycles: If adequate, repeat above. If not (e.g. grade ≥1 for ≥3 days), give aprepitant (80 mg p.o.) + 5-HT_3 RA ± dexamethasone (8 mg p.o. or i.v.) or dexamethasone (8 mg p.o. or i.v./i.m. qd) ± metoclopramide (10 mg p.o. t.i.d.)	•For delayed nausea (after day 4), give olanzapine (5-10 mg p.o. at bedtime qd) or metoclopramide (10 mg p.o. t.i.d.) ± dexamethasone (4 mg p.o. qd) until resolution[38]

Rugo HS, et al ESMO Open. 2022 Aug;7(4)

Neutropenia



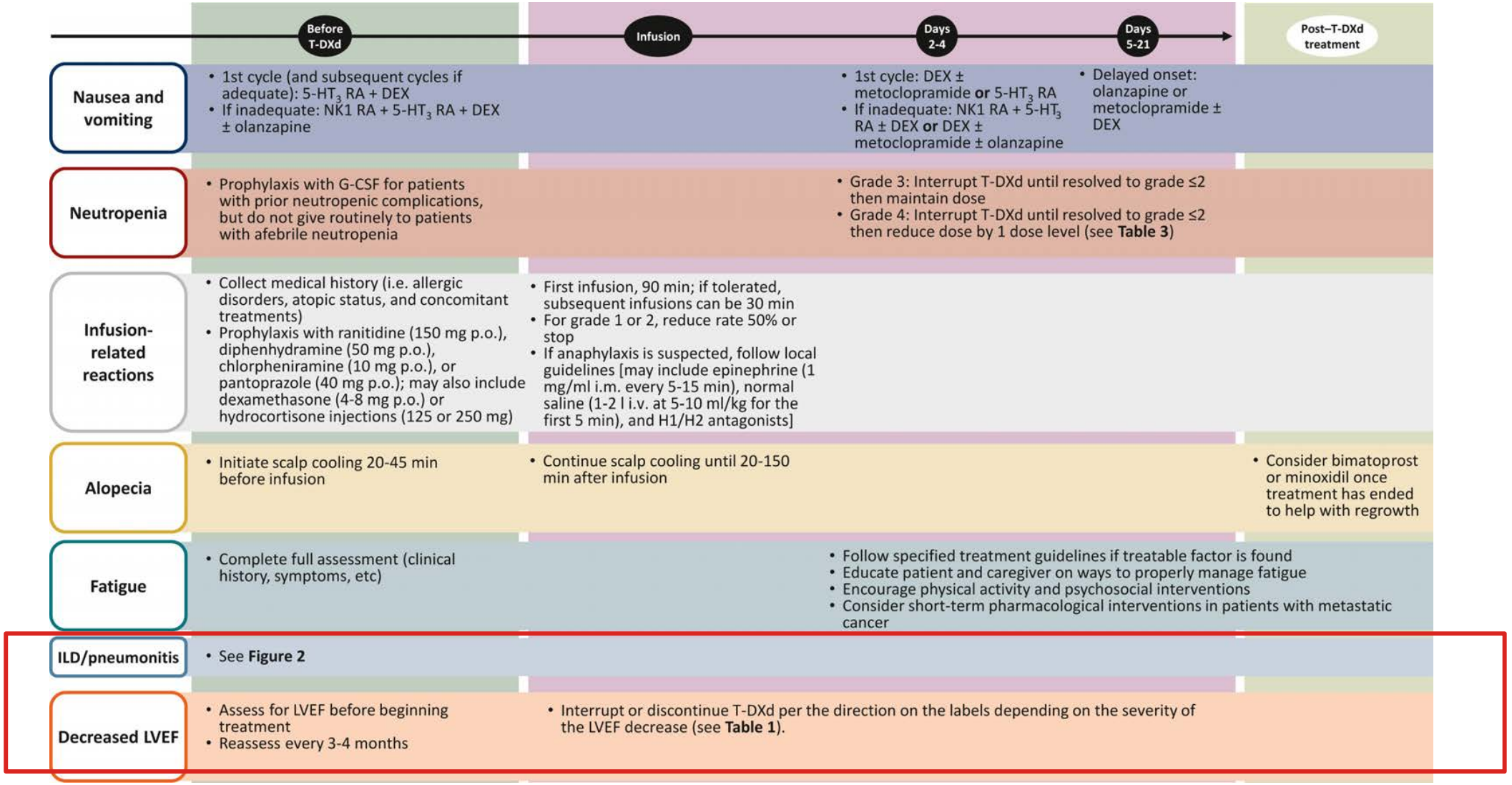
Rugo HS, et al ESMO Open. 2022 Aug;7(4)

Neutropenia

Neutropenia	•DESTINY-Breast03, 42.8% (110/257) [grade ≥3, 19.1% (49/257)] •DESTINY-Breast01, 34.8% (64/184) [grade ≥3, 20.7% (38/184)]	•Grade 3: hold T-DXd until resolved to grade ≤2, then maintain dose •Grade 4: hold T-DXd until resolved to grade ≤2, then reduce dose 1 level
Febrile neutropenia	•DESTINY-Breast01, 1.6% (3/184)	•Hold T-DXd until resolved, then reduce dose 1 level (Table 3)
Thrombocytopenia	•DESTINY-Breast03, 24.9% (64/257) [grade ≥3, 7.0% (18/257)] •DESTINY-Breast01, 21.2% (39/184) [grade ≥3, 4.3% (8/184)]	•Grade 3: hold T-DXd until resolved to grade ≤1, then reduce or maintain dose •Grade 4: hold T-DXd until resolved to grade ≤1, then reduce dose 1 level (Table 3)[10,11,14]

Rugo HS, et al ESMO Open. 2022 Aug;7(4)

Cardiac toxicity and ILD



Rugo HS, et al ESMO Open. 2022 Aug;7(4)

Adverse events of special interest

Adjudicated as drug-related interstitial lung disease / pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n=434)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)	49 (11.3)
TPC (n=417)	0	1 (0.2)	0	0	0	1 (0.2)

Left ventricular dysfunction

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased†						
T-DXd (n=434)	1 (0.2)	31 (7.1)	3 (0.7)	0	0	35 (8.1)
TPC (n=417)	0	11 (2.6)	1 (0.2)	0	0	12 (2.9)
Cardiac failure†						
T-DXd (n=434)	0	0	0	0	0	0
TPC (n=417)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.7)

Management of interstitial lung disease (ILD): the 5 S rules

1

Screen

- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on the baseline risk
- Screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD

2

Scan

- The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest
- A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks

3

Synergy

- Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected

4

Suspend Treatment

- T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves

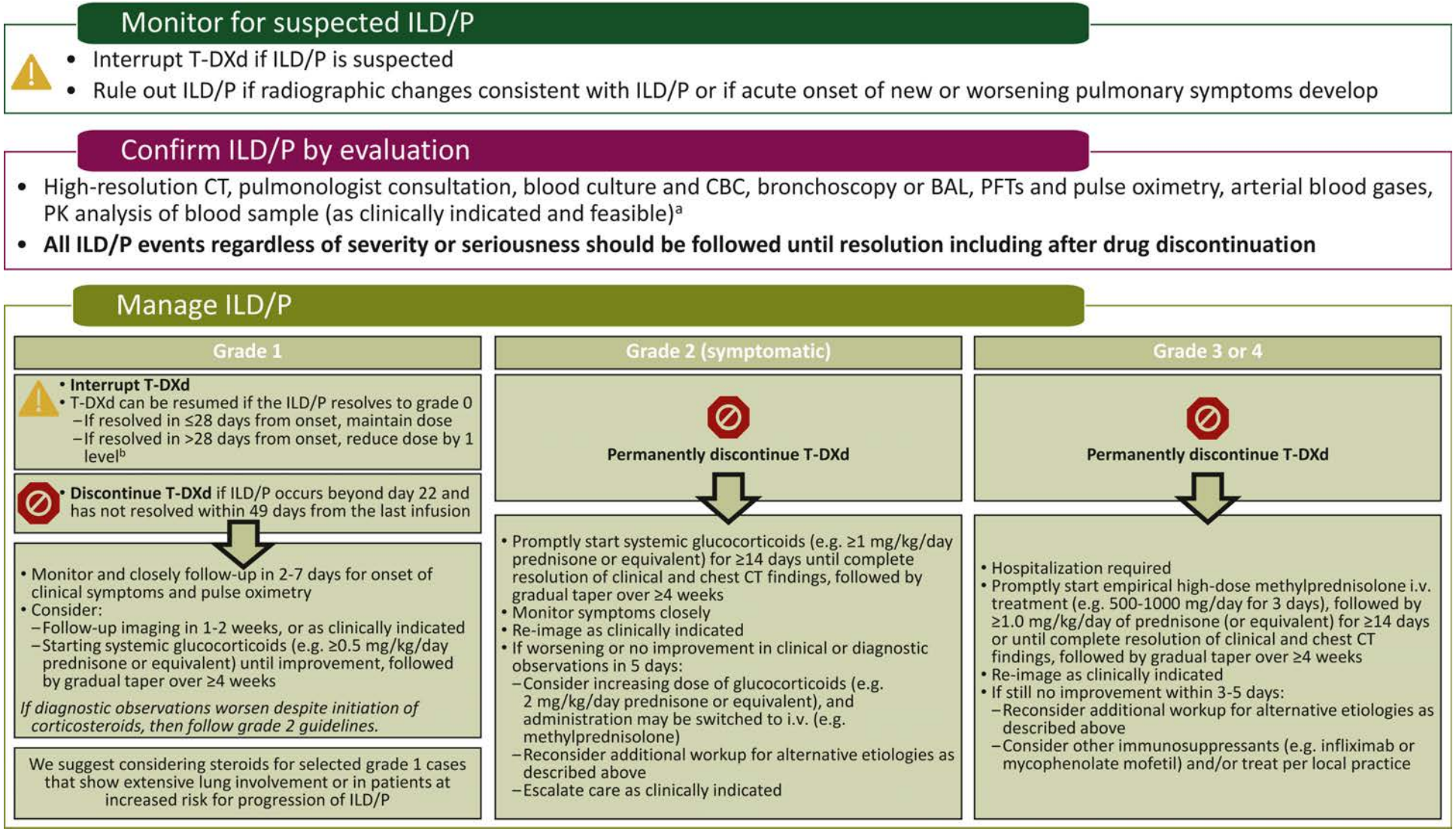
5

Steroids

- The mainstay for treating T-DXd–induced ILD remains corticosteroids, with the dose to be adapted to the toxicity grade

Tarantino P. et al, JCO Onc Prac 2023 Aug;19(8):526-527

Management of interstitial lung disease (ILD)



Rugo HS, et al ESMO Open. 2022 Aug;7(4)

T-DXd in elderly patients – Pooled Analysis

	T-DXd Pool		
	<65 (n = 673)	≥65 (n = 178)	≥75 (n = 34)
Age, median (range), years	51.5 (22.4-65.0)	69.9 (65.0-96.0)	79.0 (75.0-96.0)
Female, n (%)	670 (99.6)	177 (99.4)	34 (100.0)
Region, n (%)			
Asia	253 (37.6)	71 (39.9)	8 (23.5)
North America	82 (12.2)	29 (16.3)	8 (23.5)
Europe	220 (32.7)	54 (30.3)	14 (41.2)
Rest of world	118 (17.5)	24 (13.5)	4 (11.8)
Disease history, n (%)			
De novo mBC	183 (27.2)	49 (27.5)	9 (26.5)
Recurrent BC	348 (51.7)	84 (47.2)	15 (44.1)
Missing[b]	142 (21.1)	45 (25.3)	10 (29.4)
Time from the initial diagnosis of BC to randomization, median (range), mo	48.8 (1.5-318.1)	65.2 (6.0-431.4)	64.6 (6.2-431.4)
ECOG PS			
0	399 (59.3)	85 (47.8)	14 (41.2)
1	271 (40.3)	93 (52.2)	20 (58.8)

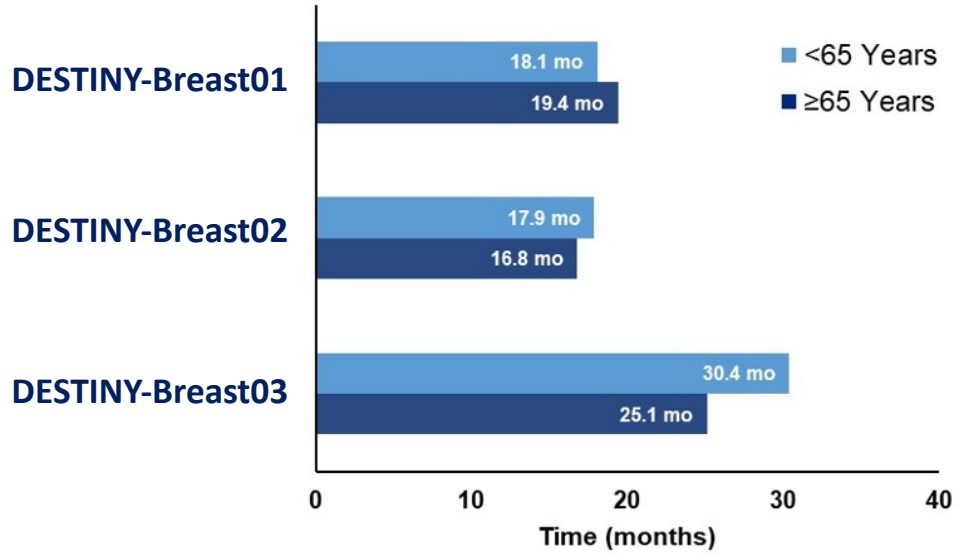
	T-DXd Pool		
	<65 (n = 673)	≥65 (n = 178)	≥75 (n = 34)
Disorders			
Blood and lymphatic system disorders (SOC)	73 (10.8)	26 (14.6)	5 (14.7)
Anemia	41 (6.1)	18 (10.1)	3 (8.8)
Cardiac disorders (SOC)	57 (8.5)	21 (11.8)	4 (11.8)
Diabetes mellitus	29 (4.3)	17 (9.6)	4 (11.8)
Renal and urinary disorders (SOC)	23 (3.4)	16 (9.0)	6 (17.6)
Vascular disorders (SOC)	174 (25.9)	109 (61.2)	28 (82.4)
Hypertension	123 (18.3)	93 (52.2)	26 (76.5)
Baseline renal function[b]			
Normal function	432 (64.2)	34 (19.1)	0
Mild renal impairment	205 (30.5)	91 (51.1)	14 (41.2)
Moderate renal impairment	35 (5.2)	53 (29.8)	20 (58.8)
Baseline hepatic function[c]			
Normal function	406 (60.3)	101 (56.7)	20 (58.8)
Mild hepatic impairment	260 (38.6)	75 (42.1)	14 (41.2)
Moderate hepatic impairment	2 (0.3)	2 (1.1)	0

Krop I, et al. ASCO 2023

T-DXd in elderly patients – Pooled Analysis

Outcome

Median Progression Free Survival



Median Overall Survival

	DESTINY-Breast01		DESTINY-Breast02		DESTINY-Breast03	
	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
mOS, months (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)

Safety

	T-DXd Pool		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)
Any grade[a] drug-related TEAEs, n (%)	**653 (97.8)**	**176 (99.4)**	**33 (100.0)**
Nausea	497 (74.4)	112 (63.3)	21 (63.6)
Fatigue[b]	344 (51.5)	98 (55.4)	21 (63.6)
Vomiting	268 (40.1)	59 (33.3)	10 (30.3)
Alopecia	265 (39.7)	63 (35.6)	10 (30.3)
Neutropenia[c]	240 (35.9)	72 (40.7)	9 (27.3)
Decreased appetite	181 (27.1)	53 (29.9)	9 (27.3)
Anemia[d]	180 (26.9)	61 (34.5)	12 (36.4)
Leukopenia[e]	156 (23.4)	49 (27.7)	6 (18.2)
Thrombocytopenia[f]	149 (22.3)	50 (28.2)	3 (9.1)
Constipation	148 (22.2)	36 (20.3)	4 (12.1)
Transaminases increased[g]	146 (21.9)	34 (19.2)	1 (3.0)
Diarrhea	142 (21.3)	48 (27.1)	6 (18.2)
Stomatitis[h]	82 (12.3)	35 (19.8)	2 (6.1)

ILD

	T-DXd Pool		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)
Any grade, n (%)	**79 (11.8)**	**31 (17.5)**	**5 (15.2)**
1	21 (3.1)	7 (4.0)	0
2	48 (7.2)	20 (11.3)	5 (15.2)
3	4 (0.6)	3 (1.7)	0
4	0	0	0
5	6 (0.9)	1 (0.6)	0

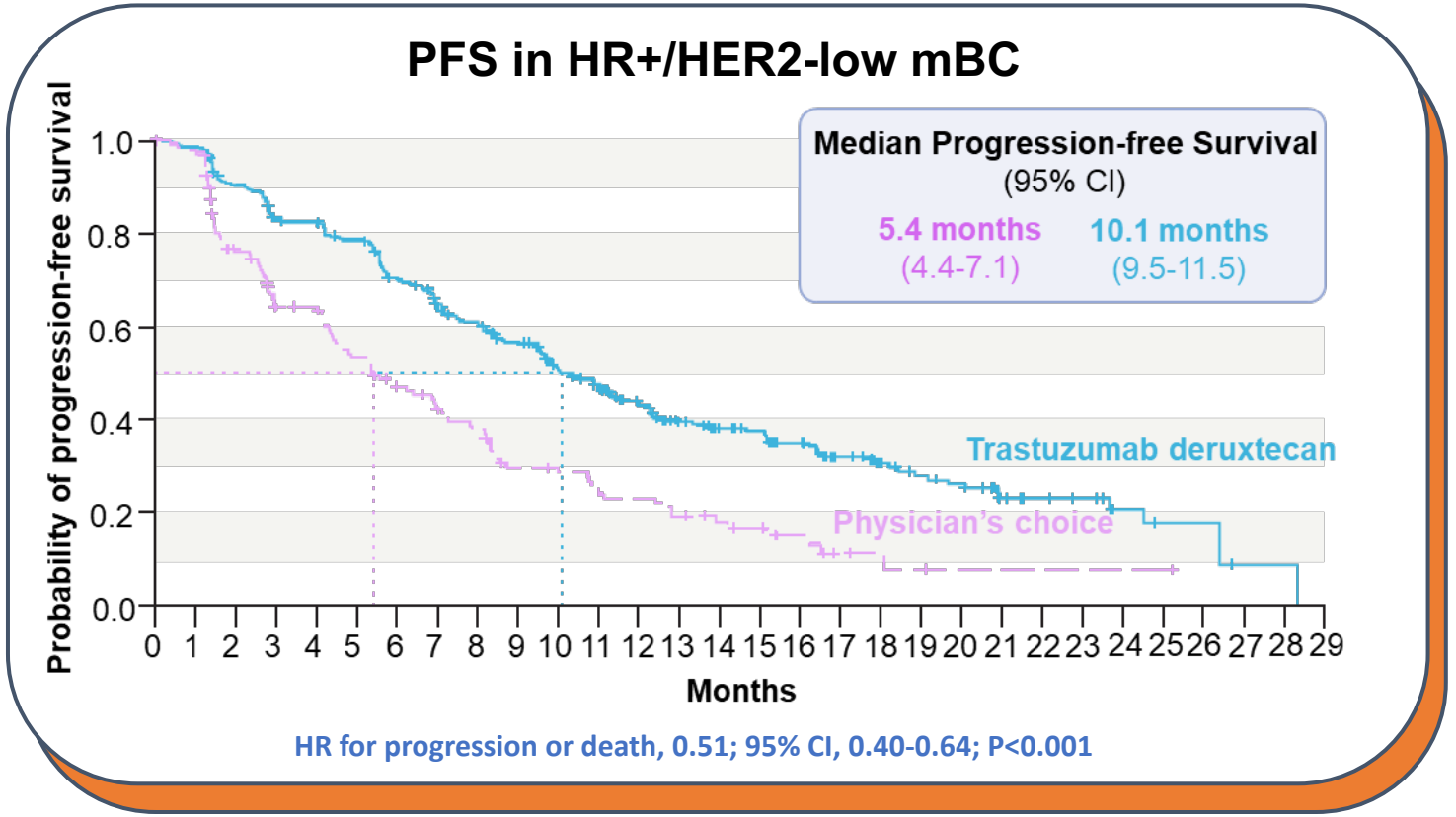
Krop I, et al. ASCO 2023

T-DXd in elderly patients – Pooled Analysis

	T-DXd (N=331)	TPC (N=163)
Median age, (range) years	56.8 (31.5-80.2)	55.7 (28.4-80.0)
<65 years, %	78.5	73.6
≥65 years, %	21.5	26.4

PFS in HR+/HER2-low by age mBC

	PFS mo (95%CI)	
	T-DXd	TPC
<65 years	9.8 (8.4–11.3)	5.4 (4.1–7.8)
≥65 years	12.0 (9.5–14.7)	5.6 (4.3–10.8)



Modi S, et al. NEJM. 2022

Brain Mets – HER2 low

A Multicenter, Open-Label, Single-Arm, Multicohort Phase II Clinical Trial of Trastuzumab Deruxtecan (DS-8201a) in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced Breast Cancer with Brain Metastases and/or Leptomeningeal Carcinomatosis

Trastuzumab-deruxtecan
(5.4 mg/kg) every 3 weeks until disease progression or unacceptable toxicity

Step 1: Single cohort

HER2-positive MBC pts with stable CNS Disease

8 patients

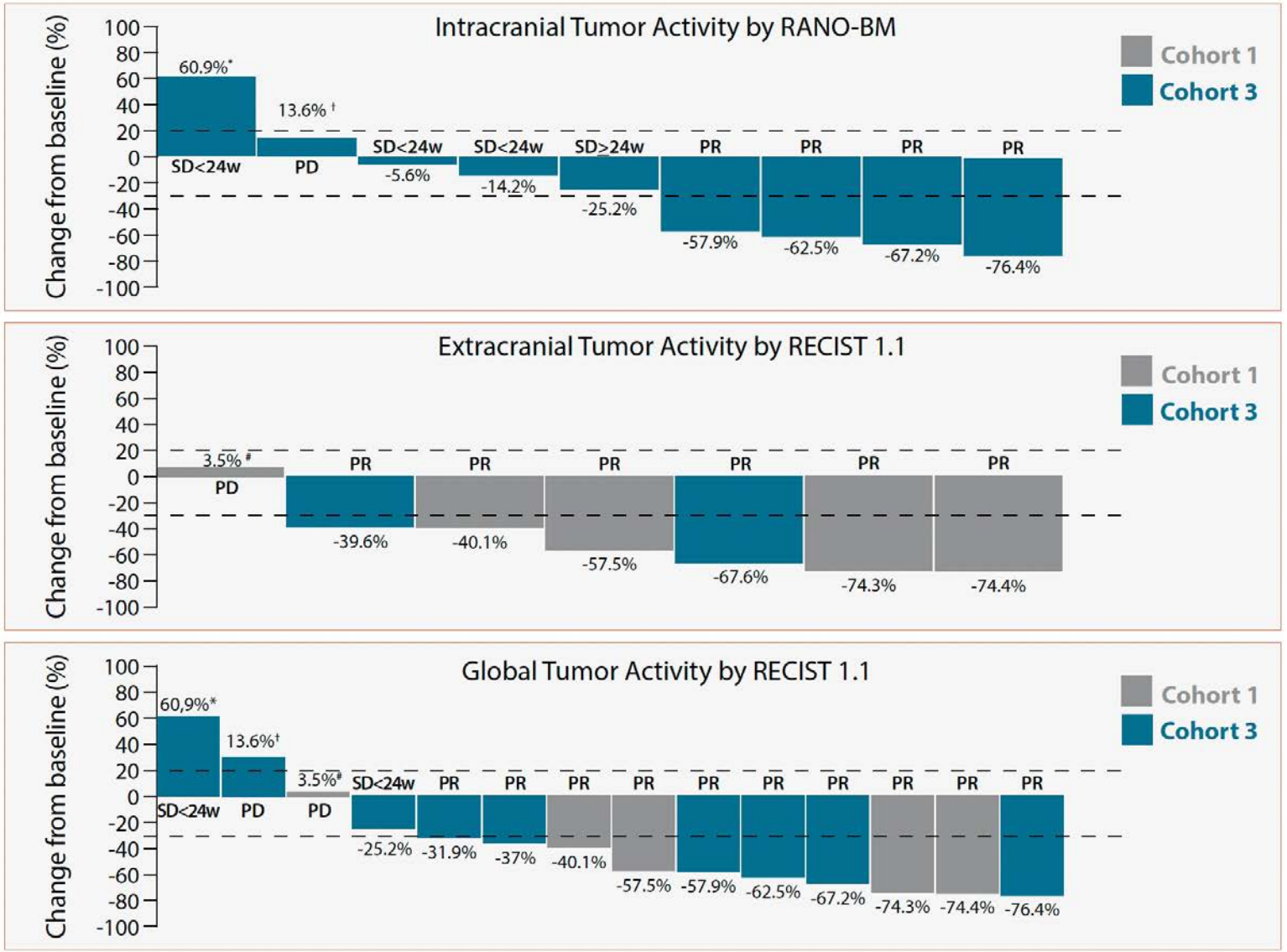
Step 2: 4 Cohorts

- *Cohort 2: HER2[3+] or [+low] with untreated BM* — 10 pts
- *Cohort 3: HER2[3+] & BM progression after local treatment* — 7 pts
- *Cohort 4: HER2[+low] & BM progression after local treatment* — 7 pts
- *Cohort 5: HER2[3+] or [+low] & meningeal carcinomatosis.* — 7 pts

Primary Objective: 16 weeks CNS PFS

Braga S, et al. SABCS 2021

T-DXd Brain Mets – HER2 low



Braga S, et al. SABCS 2021

Take-Home Messages

- Advances in the ADC field have led to **meaningful prognostic improvements** across cancer types
- Despite being more active than prior generations, the current generation of ADCs has proven more toxic, with **higher incidence of most chemotherapy-related side effects**
- Optimizing the toxicity of ADCs starts from **identifying the dose and schedule that maximize the benefit/risk ratio**.
- **Pharmacogenetic testing** may identify patients more vulnerable to side effects of certain ADCs, while **wearable devices** may enable an early detection of toxicities

Faculty Case Presentations

Case Presentation – Dr Wolff

- 52 yo postmenopausal F previously diagnosed with Stage II (N1) ER+ breast ca (Onco*type* DX® RS 20) treated with 5y of adjuvant tamoxifen and ovarian suppression
- 2y after end of TAM, she presents w/ bone and mediastinal/retroperitoneal node recurrence
- EBUS-guided paratracheal biopsy confirms ER+, HER2 IHC 1+ breast cancer, and tumor NGS is unrevealing
- She starts 1st line (1L) letrozole and palbociclib with initial response (bone pain resolves, tumor markers normalize) followed by prolonged stability
- She develops clear progression (imaging and markers) after 30 months on 1L therapy and her PS is 0
- Germline testing was normal and liquid bx does not identify any somatic mutations in ESR1, PIK3CA, or AKT
- She begins 2L endocrine therapy with exemestane and everolimus with stable disease as best response
- After 6 mo on both drugs, she develops a dry cough with diffuse pulmonary infiltrates and everolimus is stopped
- Cough and infiltrates resolve within 30 days, but after another 2 months she develops progressive disease
- Her PS is 0 and a repeat liquid bx is unrevealing
- What therapy would you consider next?
  - 3L endocrine therapy like fulvestrant plus a different CDK4/6i?
  - 1L chemo with an oral agent like capecitabine?
  - 1L chemo with an ADC like saci-govi or T-DXd?

QUESTIONS FOR THE FACULTY

How do you approach the use of T-DXd in patients who developed pneumonitis on previous therapies? What about patients with COPD or other noncancer-related lung issues?

Do you order chest imaging in patients receiving T-DXd any more frequently than you would to monitor the course of their disease?

Is your threshold for holding or discontinuing therapy with T-DXd in patients with HER2-low/HER2-ultralow mBC the same as it is for those with HER2-positive disease?

Case Presentation – Dr Rugo

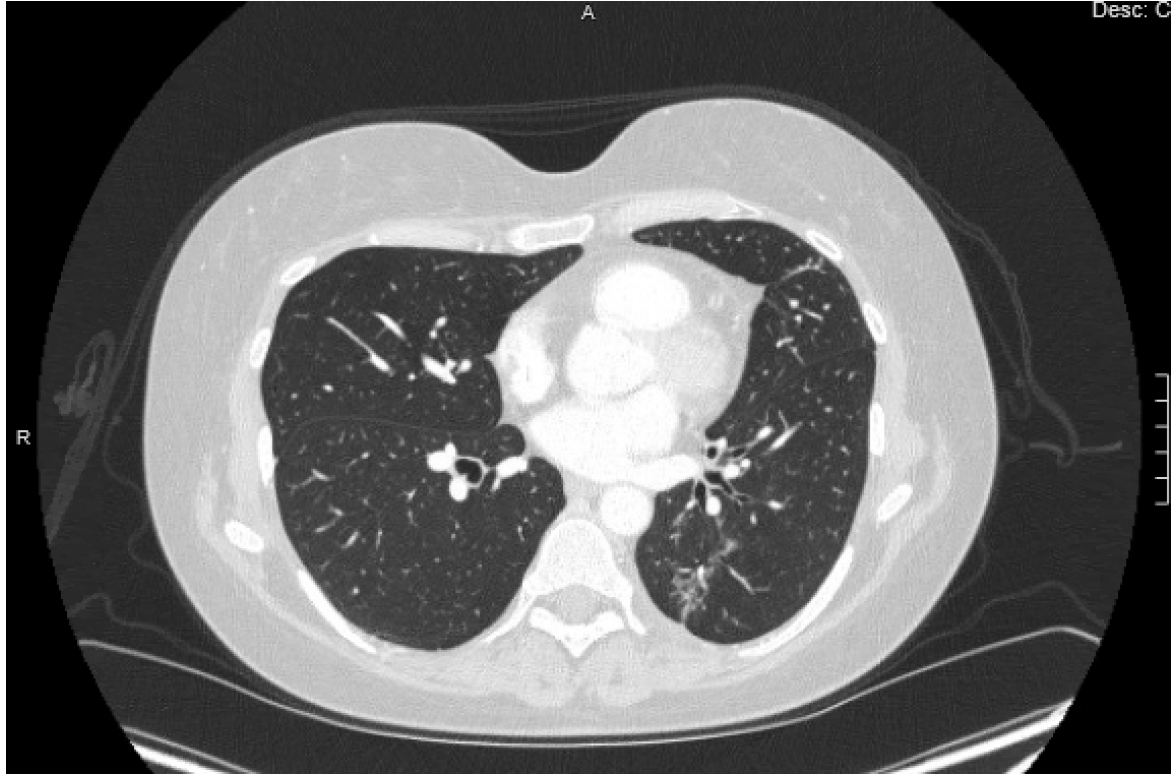
- Age 46 (2013): left breast cancer
  - L breast lumpectomy: 1.8 cm grade 2 IDC, 0/2 SLN; ER/PR+, HER2 1+
  - Ki67 50%, Oncotype DX® 26
  - Treatment: docetaxel/cyclophosphamide x 4, XRT, tamoxifen x 2 years
- Age 49 (2015): bone metastases
  - Iliac bone biopsy: metastatic adenocarcinoma, ER 50%, PR 0
  - 11/15-4/18 anastrozole
  - Radiation to sacrum and left iliac bone
  - 5/2018 - 5/5/19 fulvestrant and palbociclib
- 4/19 PET/CT: new metastases in liver, progression in bone and node
  - Liver biopsy: metastatic carcinoma, ER negative, PR 1+ in <10%, HER2 1+, FISH not amplified; PIK3CA E545K amplification; FGFR1 amplification
- 6/19 - 10/20 tesetaxel 50mg and capecitabine on the CONTESSA trial

Case Presentation – Dr Rugo (Continued)

- Discontinued capecitabine due to intolerance, continued tesetaxel alone
- 10/20: Enlarging small lung nodules, new and enlarging lytic lesions in bone
  - Biopsy L1 vertebra: ER 50%+/HER2 1+ metastatic adenocarcinoma
- 11/20 T-DXd on DESTINY-Breast04
  - Marked improvement in bone metastases, resolution of bone pain and all but one lung nodule
  - Nonocclusive pulmonary embolism with associated focal GGO, treated with anticoagulation with resolution of ground glass opacities (GGO)

Case Presentation – Dr Rugo (Continued)

- Management of toxicity
  - Significant nausea with delayed onset around day 5-7
  - Treated successfully with olanzapine at bedtime, CBD gummies
  - With aggressive management, able to continue to work
  - (Other options: dose reduction; other toxicity: diarrhea)
- Scans before cycle 7
  - Clustered centrilobular GG nodules in the left lower lobe, likely representing a mild infection; asymptomatic with normal oxygen saturation
  - Cycle 7 held for 3 weeks, started on prednisone 20 mg/day with slow taper
  - FU CT: resolution of GGO, restarted T-DXd
- 2/22 symptomatic shortness of breath with GGO consistent with grade 2 ILD
  - Permanently discontinued T-DXd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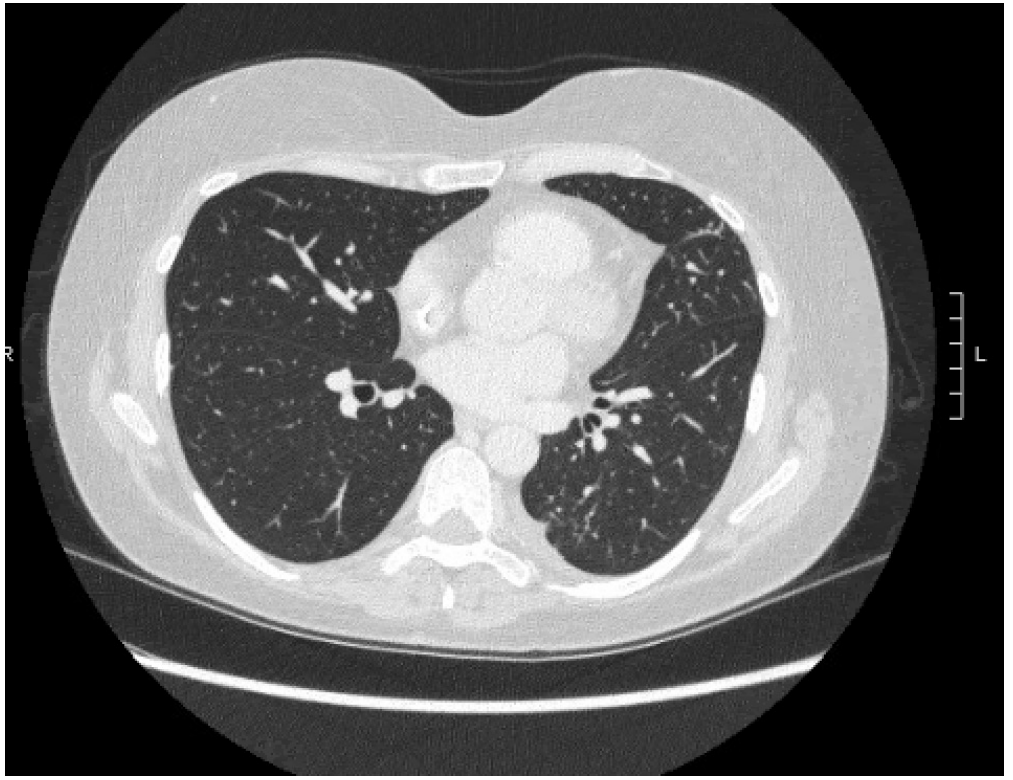
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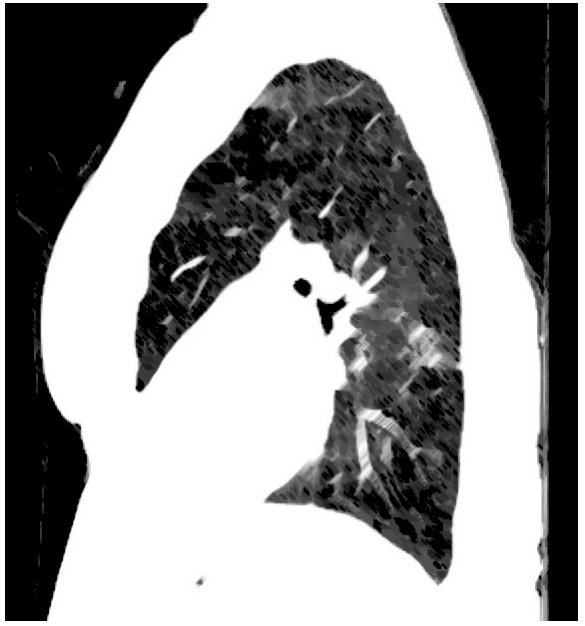
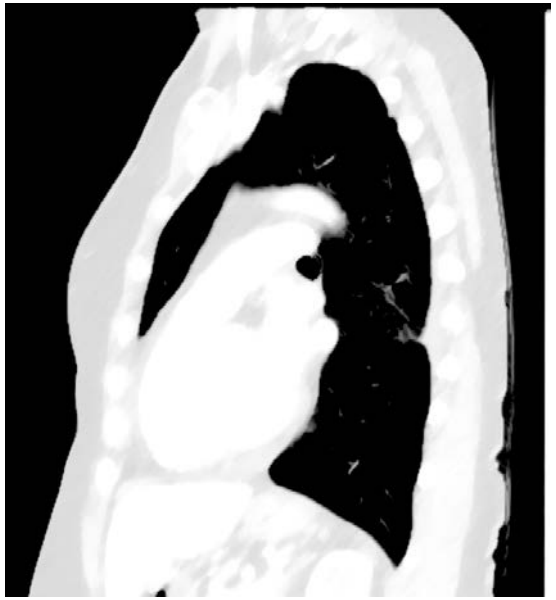




Case Presentation – Dr Rugo (Continued)

What Happened Next?

- 8/22 – 12/23 CAPItello-292 with fulvestrant, capivasertib (mPIK3CA) and palbociclib
- SBRT to one brain lesion
- Radiation to several bone lesions
- 12/23 – 5/24 liposomal doxorubicin
- 4/24 and 7/24 SBRT to limited brain mets
- 6-7/24 elacestrant (mESR1)
- 8-9/24 ADC trial x 6 weeks, stopped due to intolerable neuropathy
- 10/24 to present: gemcitabine and carboplatin

QUESTIONS FOR THE FACULTY

Do you routinely recommend GI prophylaxis for your patients receiving T-DXd? How do you intervene when GI toxicities occur?

How would you characterize the emetogenic potential of T-DXd relative to other later-line options for patients with HER2-low/ultralow mBC such as conventional chemotherapy or sacituzumab govitecan?

Beyond ILD, what other pulmonary issues would prompt you to hold or discontinue therapy with T-DXd?

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1: Optimizing the Identification of HER2-Low and HER2-Ultralow Breast Cancer – Dr Wolff

Module 2: Available Data with HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease – Dr Bardia

Module 3: Practical Applications of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Metastatic Breast Cancer – Prof Curigliano

Module 4: Future Directions for HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Breast Cancer – Dr Rugo

RTP RESEARCH TO PRACTICE

UCSF Helen Diller Family Comprehensive Cancer Center

Future Directions for HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Breast Cancer

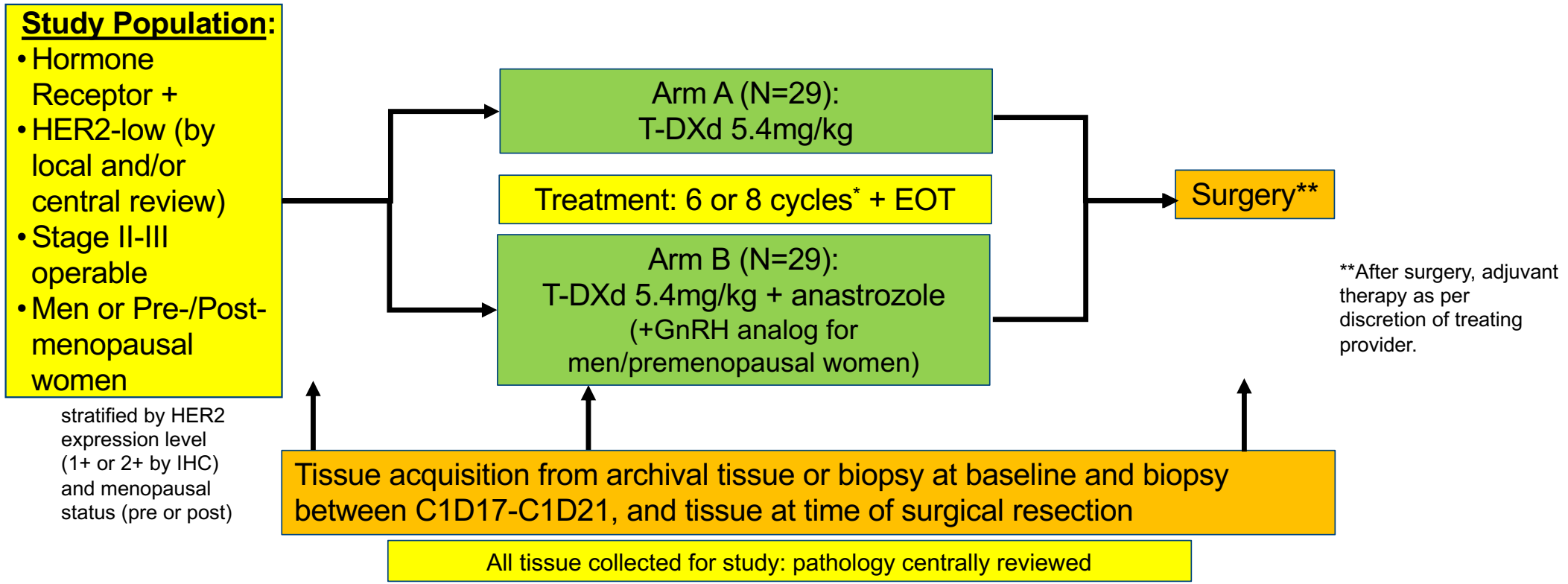
Hope S. Rugo, MD
Professor of Medicine and Winterhof Professor of Breast Oncology
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center

Topics

- T-DXd
  - Early stage HER2 low disease
- Can T-DXd be combined with other anti-cancer therapies?
- New antibody drug conjugates for HER2-low breast cancer
- HER2-targeted bispecific antibodies

T-DXd: Moving to Early-Stage Disease

TRIO-US B-12 TALENT

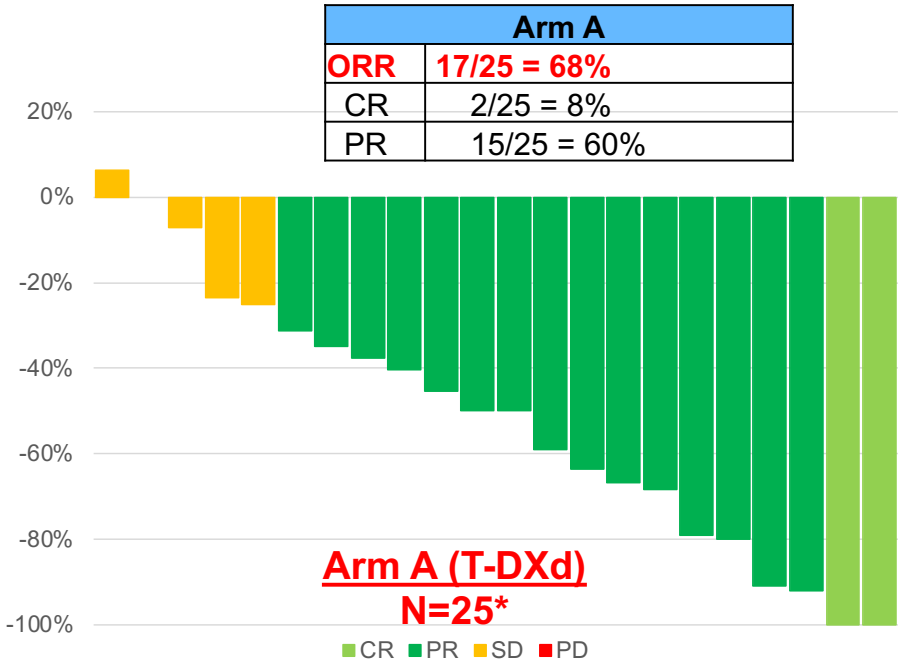


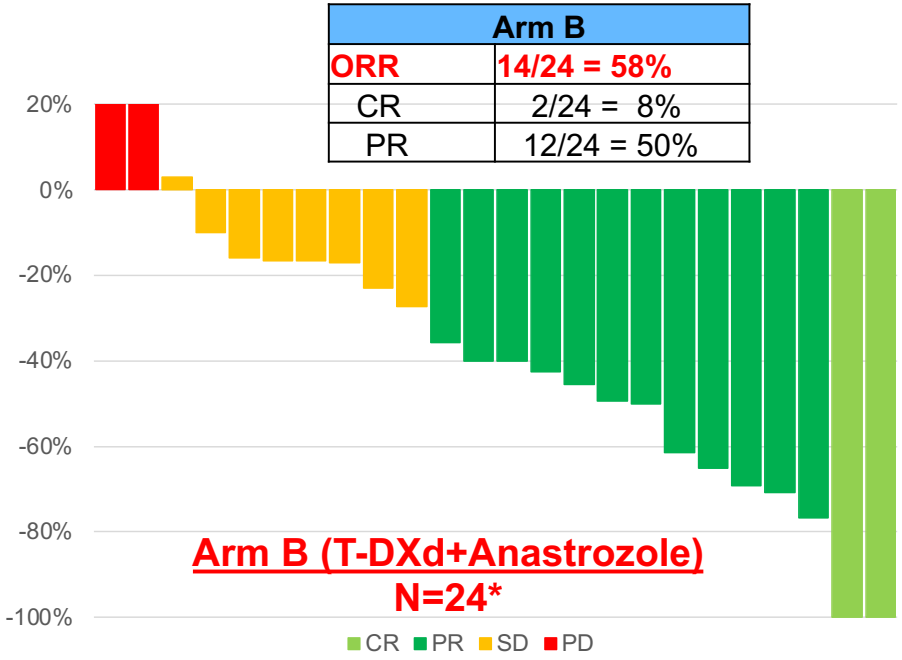
* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatment cycles from 6 to 8 cycles

Hurvitz et al, ASCO 2022

TALENT: Results

- 58 patients randomized, 29 to each arm
- Most patients had decreased HER2 IHC at surgery
- RCB 0/1 rate: 15% (both arms); surgical outcomes pending (24% in arm A; 31% in arm B)
- Nausea most common AE; 1 case of grade 2 pneumonitis; dose reductions due to AEs: 5%

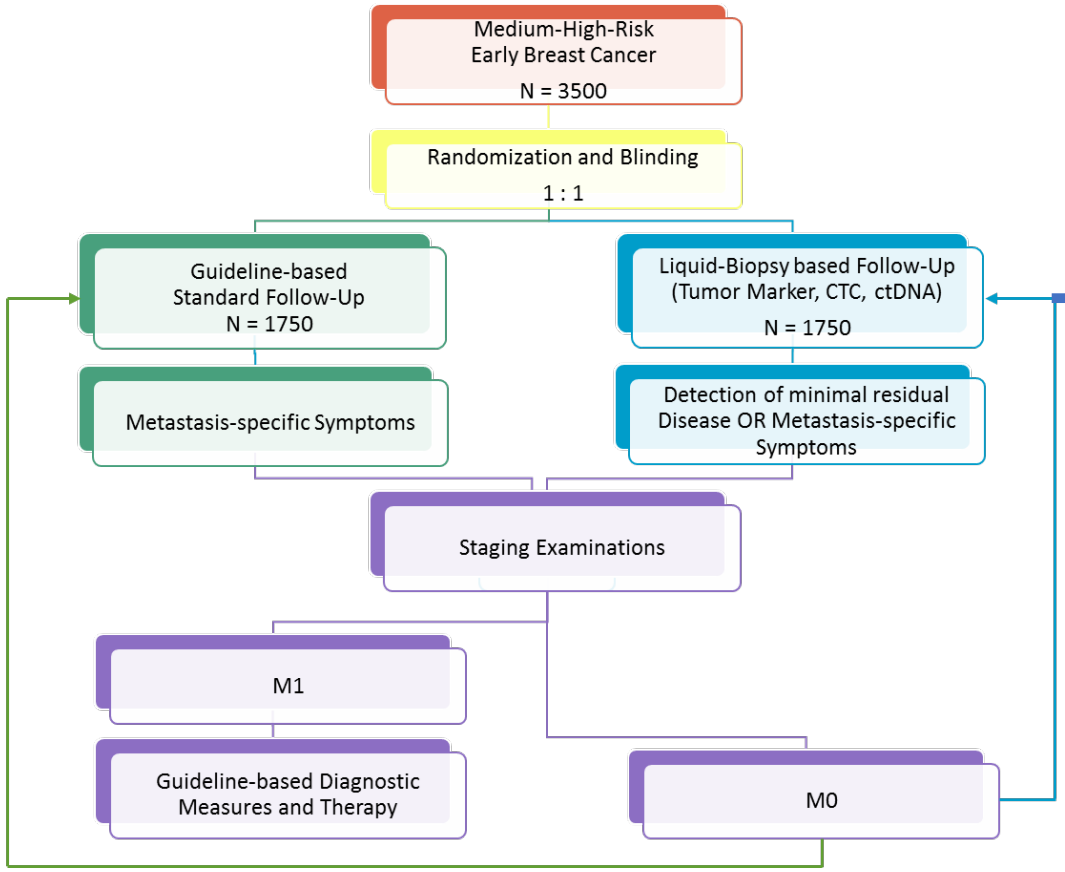




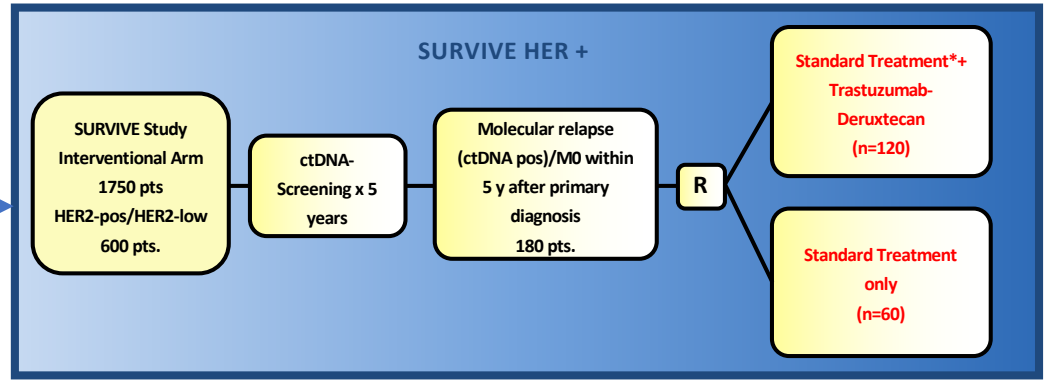
Hurvitz et al, ASCO 2022

SURVIVE-HERoes Trial

SURVIVE study (Diagnostic Part)



SURVIVE HERoes (Intervention Part) – Start Q3 2024



- 2:1 randomized, comparative Phase II study
- **Arm A**: Standard treatment + Trastuzumab-Deruxtecan for the duration of 12 months or until relapse, if earlier
- **Arm B**: Standard treatment only
- Primary outcome measure: ctDNA clearance rate after 6 months of treatment

Huesmann et al, SABCS 2023

Proposed Mechanism of ADC + IO Synergy

1: ADCs bind to the cancer cell

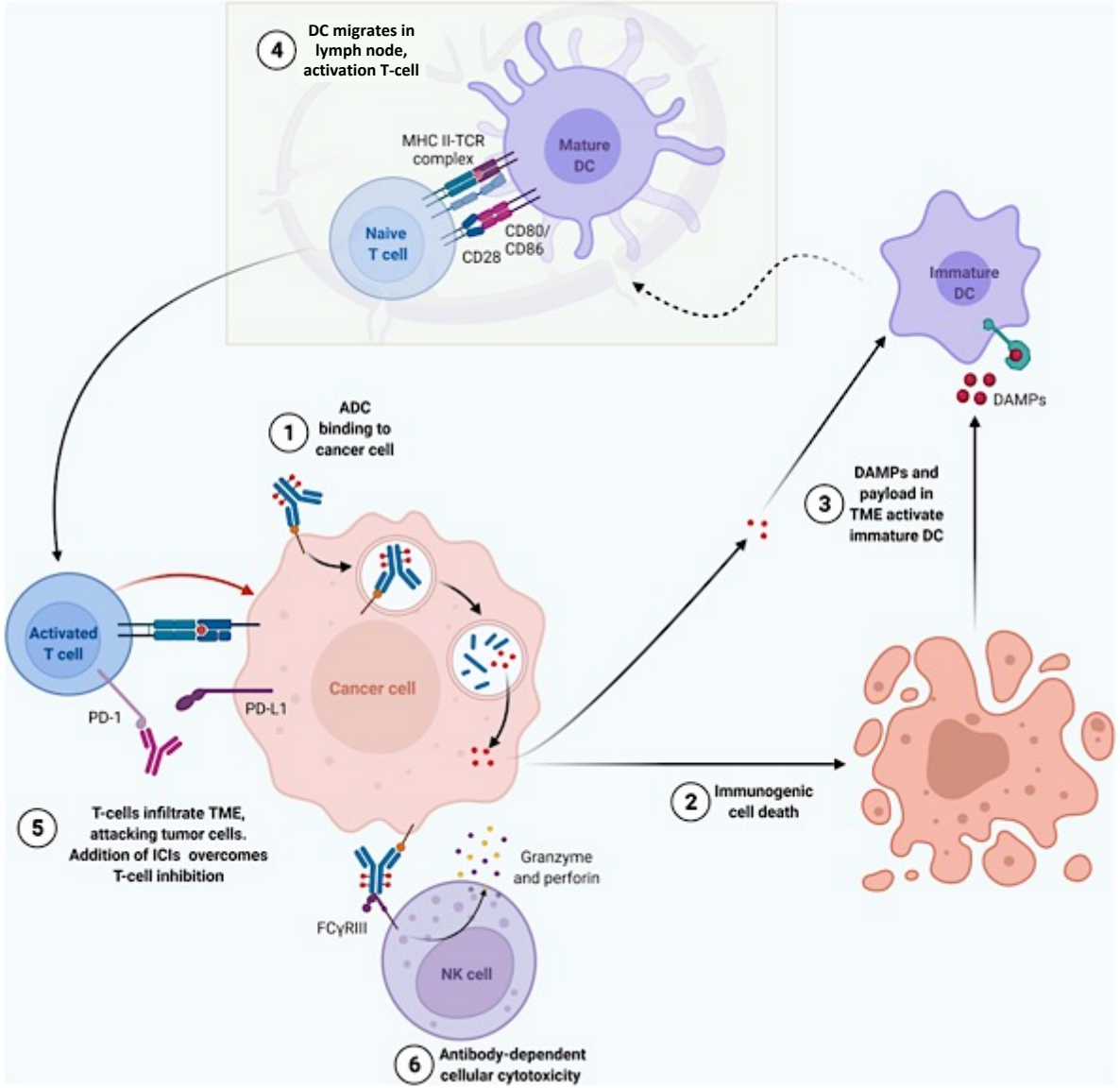
2: The ADC is internalized into the cancer cell, causing immunogenic cell death

3: Damage-associated molecular patterns (DAMPs) are released in the tumor microenvironment (TME), stimulating the maturation of dendritic cells

4: Dendritic cells (DCs) migrate into the lymph nodes, activating T cells

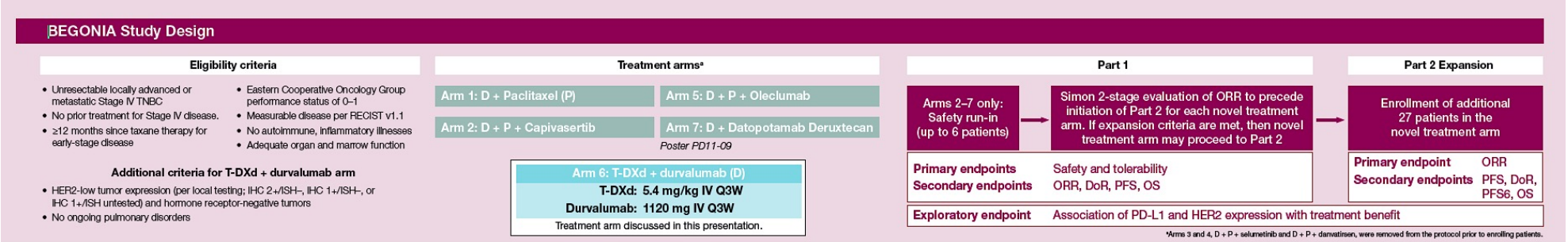
5: Activated T cells infiltrate the TME, attacking tumor cells. The addition of immune checkpoint inhibitors (ICIs) overcomes T cell inhibition

6: ADCs activate the immune system through antibody-dependent cellular cytotoxicity

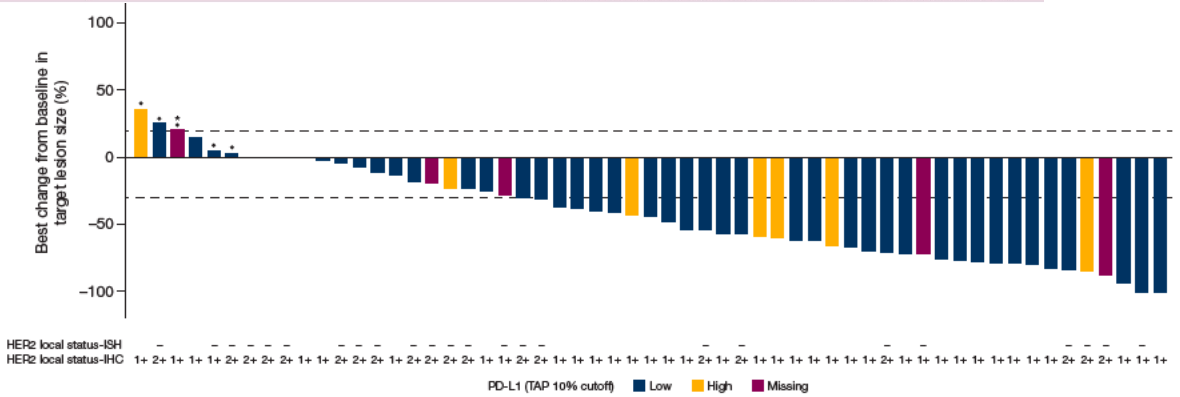


Nicolo et. al. *Cancer Treatment Reviews* 2022

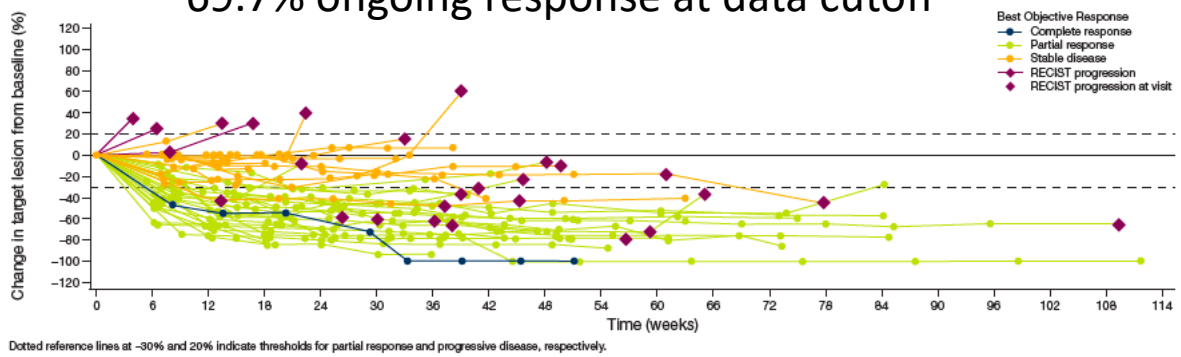
T-DXd + Durvalumab: The BEGONIA Trial



- First-line basket trial for HER2-low mTNBC
  - Arm 6 (n=58)
    - PD-L1 testing using SP263
    - ORR 56.9% (n=33)
    - PFS 12.6 mo (8.3-NC)
  - Safety
    - **8 cases of adjudicated ILD, 2 more pending review**
      - Grade 1 (3), grade 2 (2), grade 3 (1), grade 5 (1, Covid related)
      - 17% stopped rx due to AEs



69.7% ongoing response at data cutoff



Schmid et al, SABCS 2022; PD11-08

DESTINY-Breast08: Testing Combination Therapies

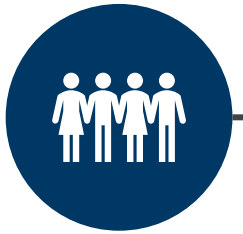
Phase 1b, multicenter, open-label, two-part, modular study (NCT04556773)

Part 1 dose-finding and Part 2 dose-expansion

Population for T-DXd-ET combination arms

- Locally assessed HER2-low (IHC 1+, IHC 2+/ISH−) HR+ advanced/mBC
- ≤1 prior treatment line of ET ± a targeted therapy (such as CDK4/6, mTOR, or PI3K inhibitors) for mBC allowed
- No prior chemotherapy in the metastatic setting allowed
- At least one measurable lesion per RECIST 1.1
- ECOG PS 0–1

Allocation



T-DXd + capecitabine, n=20 — HR+/HR−

T-DXd 5.4 mg/kg IV Q3W + capecitabine 750 mg/m2 PO BID on Days 1–14 Q3W

T-DXd + capivasertib, n=40 — HR−

T-DXd 5.4 mg/kg IV Q3W + capivasertib 400 mg PO BID Q1W on Days 1–4 within a 21-day treatment cycle

SABCS 2024
P3-09-17

HR+

T-DXd + ANA, n=21
(T-DXd 5.4 mg/kg IV Q3W + anastrozole 1 mg daily*)

HR+

T-DXd + FUL, n=20
(T-DXd 5.4 mg/kg IV Q3W + fulvestrant 500 mg IM Q4W, with a 500 mg loading dose on Cycle 1, Day 15*)

SABCS 2023

Endpoints for the dose-expansion phase

- **Primary:** Safety and tolerability, including AEs, AESIs, and SAEs
- **Secondary:** ORR, PFS, DOR (all evaluated by investigator per RECIST 1.1), and OS

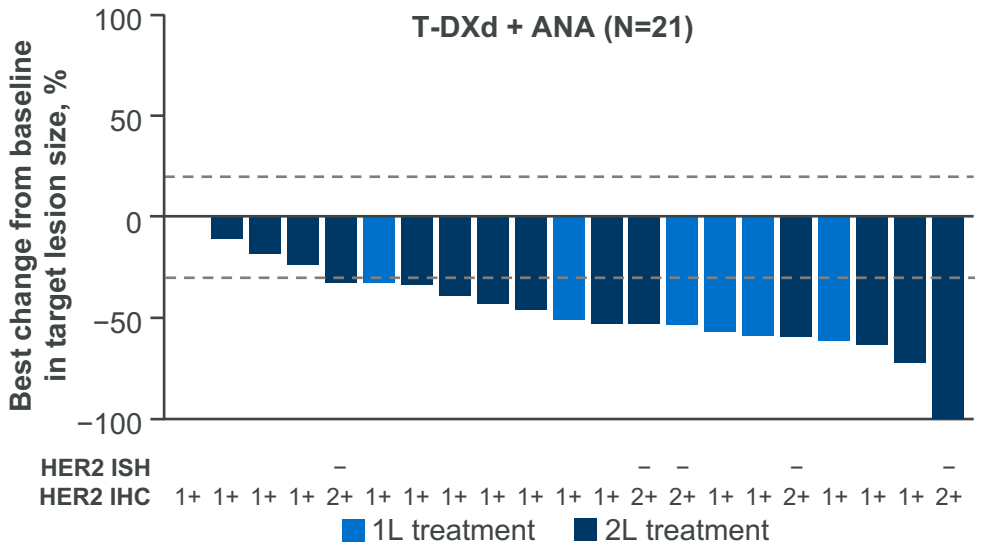
*Patients received the RP2D from the study's dose-finding phase

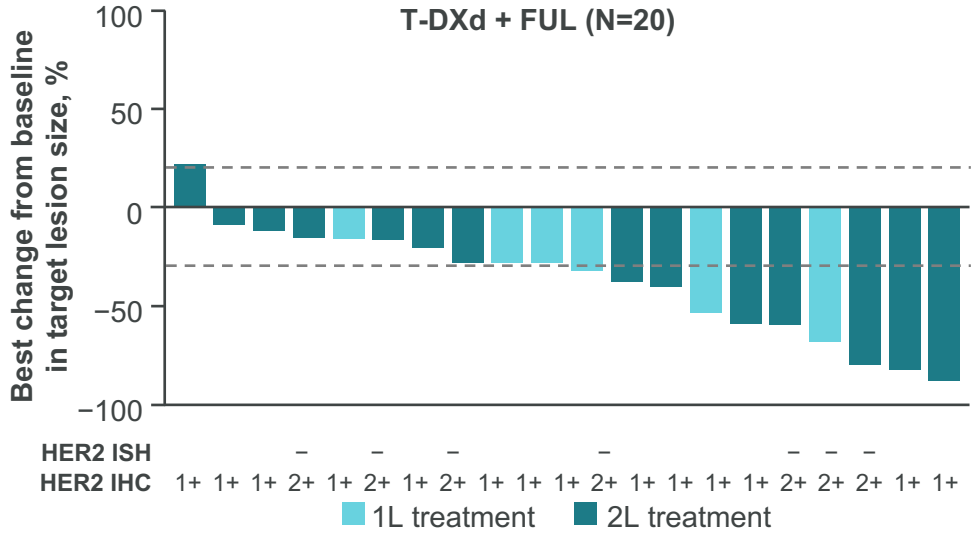
Jhaveri et al. SABCS 2023 and SABCS 2024; André F et al. ASCO 2022 (Abstract 3025)

Efficacy overview

	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Confirmed ORR, % (95% CI)	**71.4 (47.8, 88.7)**	**40.0 (19.1, 64.0)**
Unconfirmed ORR, % (95% CI)	**76.2 (52.8, 91.8)**	**50.0 (27.2, 72.8)**
Median DOR, months (95% CI)*	**9.8 (6.7, NE)**	**NE (4.1, NE)**
Total PFS events, n (%)	**14 (66.7)**	**7 (35.0)**
Median PFS, months (95% CI)*	**13.4 (8.5, 19.4)**	**NE (5.6, NE)**
PFS rate at 6 months, % (95% CI)	80.7 (56.3, 92.3)	75.3 (46.4, 90.0)
PFS rate at 12 months, % (95% CI)	50.4 (27.5, 69.5)	52.7 (25.0, 74.4)

- **Efficacy results need to be interpreted with caution owing to the small datasets**
  - **Of note, 15% of patients in the T-DXd + FUL arm withdrew consent and discontinued study treatment before disease progression**





*NE signifies that median DOR/PFS was not reached for these patients at the time of DCO
Median DOR calculated using Kaplan-Meier technique. Target lesion size is the sum of diameters of target lesions, assessed by investigator per RECIST 1.1.
Best change in target lesion is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively. PFS was assessed by investigator per RECIST 1.1
1L, first line; 2L, second line; CI, confidence interval

Jhaveri et al, SABCS 2023

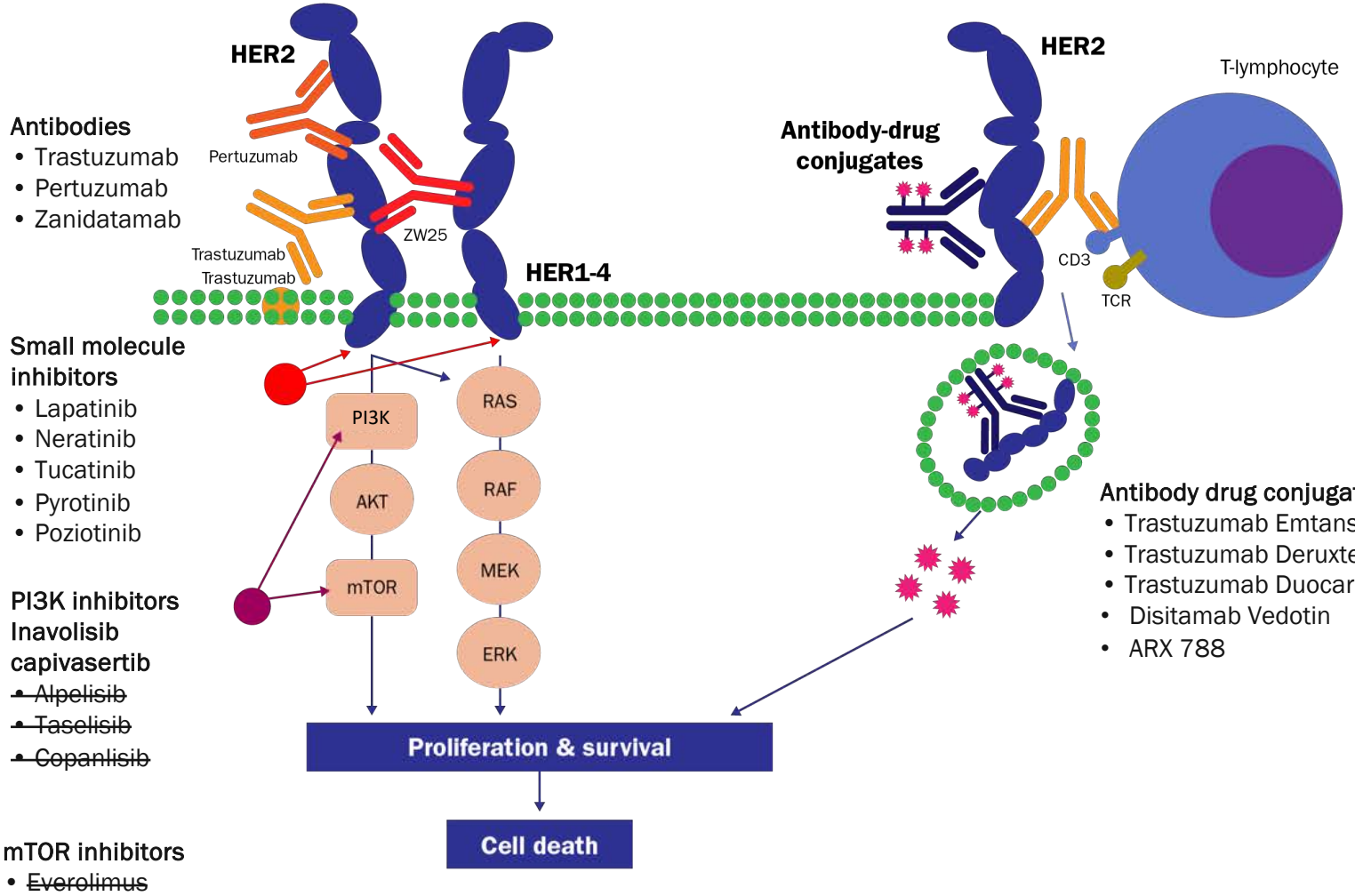
Safety and Conclusions

- Overall, there does not appear to be additive safety issues
  - Across both arms, 17 (41.5%) patients had an AE of Grade 3 or higher that was possibly related to study treatment
  - Five adjudicated drug-related ILD/pneumonitis events were reported
  - One death reported by investigator as related to disease ILD
    - The ILD was not considered to be drug-induced by adjudication
- A total of 10 patients had dose reductions of T-DXd and 10 patients discontinued T-DXd due to adverse events

- With this small data set it is impossible to know what the contribution of endocrine therapy is to the efficacy of T-DXd

- Await data from the second two cohorts on Friday!

Expanding the Armamentarium of Agents for HER2+ Breast Cancer: Expanding to HER2 Low



Antibodies
- Trastuzumab
- Pertuzumab
- Zanidatamab

Small molecule inhibitors
- Lapatinib
- Neratinib
- Tucatinib
- Pyrotinib
- Poziotinib

PI3K inhibitors
Inavolisib
capivasertib
- ~~Alpelisib~~
- ~~Taselisib~~
- ~~Copanlisib~~

mTOR inhibitors
- ~~Everolimus~~

Antibody drug conjugates
- Trastuzumab Emtansine
- Trastuzumab Deruxtecan
- Trastuzumab Duocarmazine
- Disitamab Vedotin
- ARX 788

Other drugs
- Margetuximab

Bispecific anitbodies & fusion protein
- Zenocutuzumab
- Azymetric™ (ZW25)
- PRS 343

Checkpoint inhibitors
CDK4-6 inhibitors

- Neratinib and neratinib-capecitabine therapy is FDA approved, not EMA approved in HER2+ MBC.

Margetuximab is FDA approved, not EMA approved in HER2+ MBC.

The following therapies are not FDA approved or EMA approved in HER2+ MBC: ZW25, pyrotinib, poziotinib, alpelisib, taselisib, copanlisib, everolimus, zenocutuzumab, azymetric (ZW25), PRS 343, trastuzumab duocarmazine.

- AKT, protein kinase B; CD, cluster of differentiation; ERK, extracellular signal-regulated kinase; HER, human epidermal growth factor receptor; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; TCR, T cell receptor.
- Angelis V, Okines AFC. *Cancers (Basel)*. 2023;16(1):23.

Novel HER2 Antibody Drug Conjugates in HER2 Low MBC

Agent	Disitamab vedotin	DB-1303	ARX788
Antibody	Hertuzumab	Trastuzumab biosimilar	Trastuzumab biosimilar
Linker	Cleavable valine-citrulline	Cleavable tetrapeptide-based	pAR, highly specific and stable oxime chemistry
Payload	MMAE, membrane permeable microtubule inhibitor	P1003, topoisomerase-1 inhibitor	MMAF analogue, non-cell permeable microtubule inhibitor
DAR	4:1	~8:1	2:1
Adverse events	Low grade liver enzyme elevation, 17% grade 3 neutropenia, peripheral neuropathy	Nausea, 3.5% EF drop, Rare ILD	Ocular toxicity, low grade liver enzyme elevation, rare ILD

Multiple other ADCs in early phase trials in HER2 low disease

- Ex: BB1701, eribulin ADC with DAR of 4. Phase Ib/II trial ongoing (George et al, SABCS 2024 TIP)

Wang et al, ASCO 2021; Moore et al, ASCO 2023; Hu et al, ASCO 2024

DB-1303: Encouraging Anti-Tumor Activity and a Manageable Safety Profile in a Phase I/II Trial in Patients with Advanced Solid Tumors Including HER2 Low BC[1,2]

Patients[1,2]
- Advanced/metastatic solid tumors
- ECOG PS 0–1
- Received prior therapies
  - Prior anti-HER2 ADC permitted

N=85 (HER2 low BC: n=21)

DB-1303 IV Q3W

Primary endpoints
- Safety
- ORR

Key secondary endpoints
- DOR, DCR, TTR, PFS, OS, PK, ADA

Efficacy in patients with HER2 low BC[1]	DB-1303 (n=13)
ORR, n (%)	5 (38.5)
DCR, n (%)	11 (84.6)

AEs occurring in ≥20% of all patients and AESIs[1]	DB-1303 (n=85)					
	TEAEs		TRAEs		AESI	
	All grades	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Nausea	44 (51.8%)	3 (3.5%)	42 (49.4%)	2 (2.4%)	-	-
Vomiting	37 (43.5%)	1 (1.2%)	32 (37.6%)	0	-	-
Platelet count decreased	30 (35.3%)	3 (3.5%)	30 (35.3%)	3 (3.5%)	-	-
Anemia	25 (29.4%)	5 (5.9%)	23 (27.1%)	5 (5.9%)	-	-
AST increased	22 (25.9%)	0	21 (24.7%)	0	-	-
Decreased appetite	22 (25.9%)	0	21 (24.7%)	0	-	-
Fatigue	18 (21.2%)	1 (1.2%)	15 (17.6%)	0	-	-
ALT increased	17 (20.0%)	0	17 (20.0%)	0	-	-
Ejection fraction decreased	-	-	-	-	3 (3.5%)	0
IRR	-	-	-	-	2 (2.4%)	0
ILD	-	-	-	-	2 (2.4%)	0
Electrocardiogram QT prolonged	-	-	-	-	1 (1.2%)	0

ADA, anti-drug antibody; ADC, antibody drug conjugate; AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BC, breast cancer; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Clinical Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; IRR, infusion related reaction; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; R, randomized; TEAE, treatment emergent adverse event; TRAE, treatment related adverse event; TTR, time to response.

1. Moore K, et al. Presented at ASCO 2023. June 2–6. Chicago, IL. Abstract #3023;
2. NCT05150691. Available at: https://clinicaltrials.gov/study/NCT05150691 (Accessed April 2024).

Disitamab Vedotin: Promising Anti-Tumor Activity and a Consistent Safety Profile in Advanced BC in a Pooled Analysis of Phase I/II Studies in China*

Patients
- aBC
- HER2 positive (IHC 3+ or 2+/FISH+) or HER2 low (IHC 1+ or 2+/FISH–)
- ECOG PS 0–1

N=118

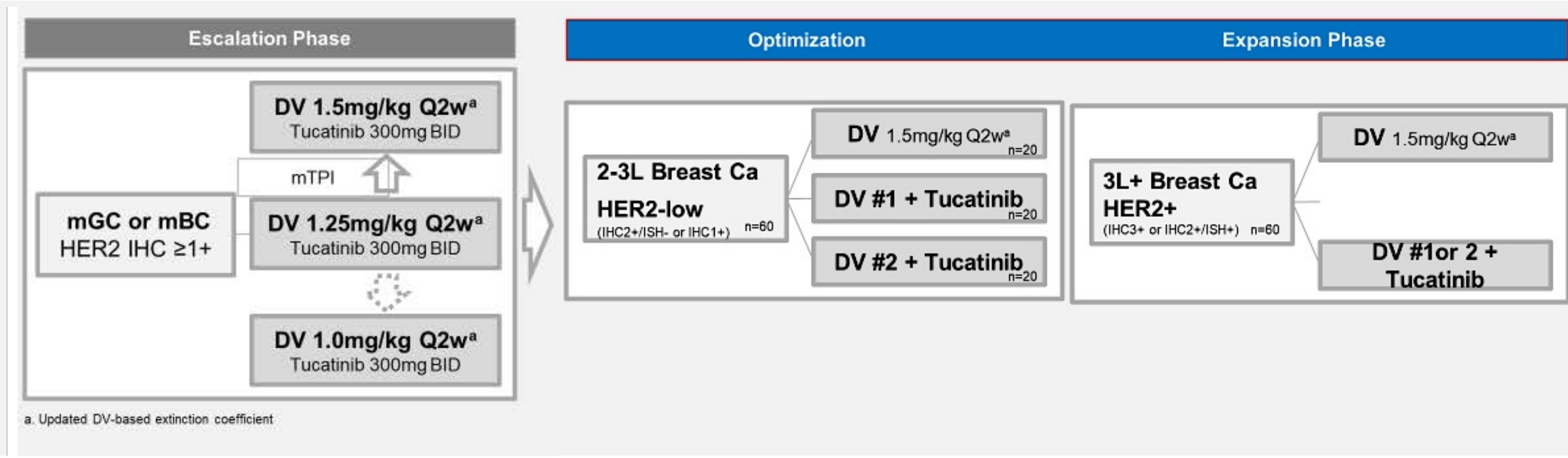
Disitamab vedotin
Dose escalation

Efficacy in patients with HER2 low aBC	Disitamab vedotin (n=48)
BOR, n (%)	
CR	0 (0)
PR	19 (39.6)
SD	25 (52.1)
PD	4 (8.3)
NE	0 (0)
Confirmed ORR, n (%; 95% CI)	19 (39.6; 25.8–54.7)
Confirmed DCR, n (%; 95% CI)	43 (89.6; 25.8–54.7)
CBR, n (%; 95% CI)	23 (47.9; 33.3–62.8)
Median PFS, months (95% CI)	5.7 (4.1–8.3)

Frequently reported TRAEs in all patients with aBC	Disitamab vedotin (N=118)	
	All	Grade ≥3
TRAE	112 (94.9)	54 (45.8)
AST increase	76 (64.4)	2 (1.7)
ALT increase	70 (59.3)	2 (1.7)
Hypoesthesia	69 (58.5)	7 (5.9)
Leukopenia	57 (48.3)	11 (9.3)
Neutrophil count decrease	56 (47.5)	20 (16.9)
Fatigue	51 (43.2)	14 (11.9)
Nausea	49 (41.5)	1 (0.8)
γ-GT increase	33 (28.0)	15 (12.7)

DCO: December 31, 2020.
*Pooled analysis of RC48-C001 (NCT02881138) and RC48-C003 (NCT03052634).
aBC, advanced breast cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOR, best overall response; CBR, clinical control rate; CI, confidence interval; CR, complete response; DCO, data cutoff; DCR, disease control rate; ECOG PS, Eastern Clinical Oncology Group performance status; FISH, fluorescence in situ hybridization; γ-GT, gamma-glutamyl transferase; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TRAE, treatment related adverse event.
Wang J, et al. Presented at ASCO 2021; June 4–8. Chicago, IL. Abstract #330883

DV004: A Phase 1b/2 Study of Disitamab Vedotin Plus Tucatinib in Post-Trastuzumab Deruxtecan HER2-Positive and HER2-Low mBC



a. Updated DV-based extinction coefficient

Phase III Trials

DYNASTY-Breast02

Patients
- HR positive HER2 low mBC
- Disease progression on ET + CDK4/6i within 6 months of starting 1L treatment for mBC, OR disease progression on ≥2 prior lines of ET ± targeted therapy
- ECOG PS 0–1

R
N=532

DB-1303
8 mg/kg IV Q3W

TPC
Capecitabine, paclitaxel, or nab-paclitaxel

Primary endpoint
- PFS (BICR, RECIST v1.1)

Key secondary endpoints
- OS, ORR, PFS (IA), DOR
- Safety, QoL, PROs

RC48-C012

Patients
- Locally advanced or metastatic HER2 low BC
- Prior anthracyclines
- 1–2 prior lines of chemotherapy
- For HR positive disease: prior ET
- No prior anti-HER2 therapy
- ECOG PS 0–1

R
N=366

Disitamab vedotin
2.0 mg/kg IV Q2W

TPC
Paclitaxel, docetaxel, vinorelbine or capecitabine

Primary endpoint
- PFS (BICR)

Key secondary endpoints
- PFS (IA), ORR, DOR, DCR, TTP, OS

Rosy

Patients
- HR positive HER2 low mBC
- Prior ET
- Stable or asymptomatic brain metastasis
- ECOG PS ≤2

R
N=288

Disitamab vedotin
2.0 mg/kg injection Q2W

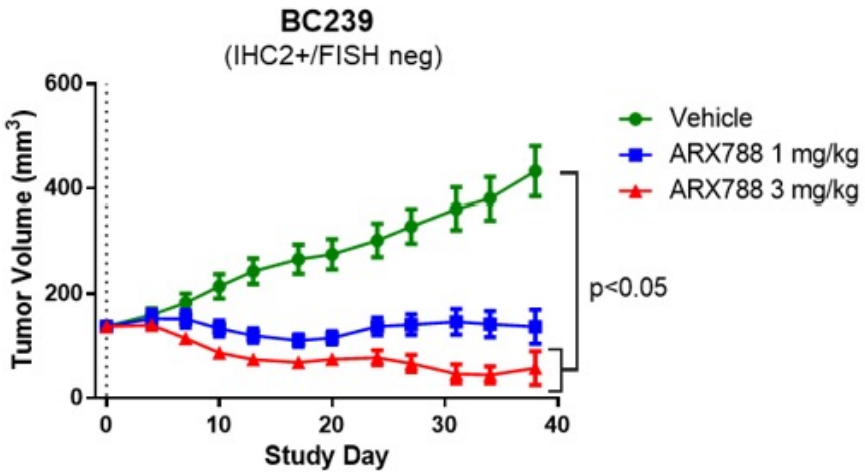
ET
Physician's choice

Primary endpoint
- PFS

Key secondary endpoints
- OS, ORR, DCR, CBR
- Safety, QoL, psychological condition, PSS
- Biomarkers & treatment sensitivity

ARX788 in HER2-Low MBC

Activity of ARX788 in HER2-Low Breast Cancer (BC239) PDX Model



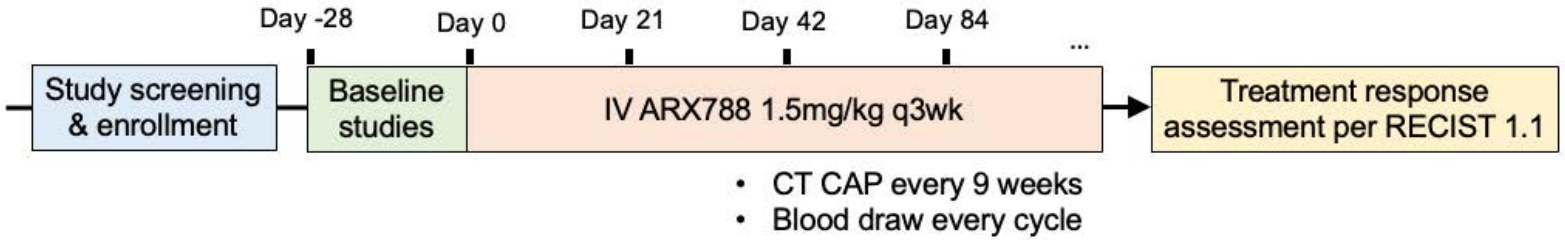
Phase 2 trial of ARX788 in HER2-low MBC

Key inclusion criteria:
- Pathologically documented HER2-low (immunohistochemistry 1+ or 2+ and no evidence of HER2 gene amplification by FISH) locally advanced unresectable or metastatic breast cancer
- Presence of at least one measurable lesion or bone lesion
- At least 1 prior line of chemotherapy or antibody-drug conjugate therapy for advanced/metastatic breast cancer

Patients (N=~30-36)

Cohort 1: HR+/HER2-, HER2-low MBC
N=~20-24

Cohort 2: HR-/HER2-low MBC
N=~10-12



- CT CAP every 9 weeks
- Blood draw every cycle

Primary Endpoint
- ORR

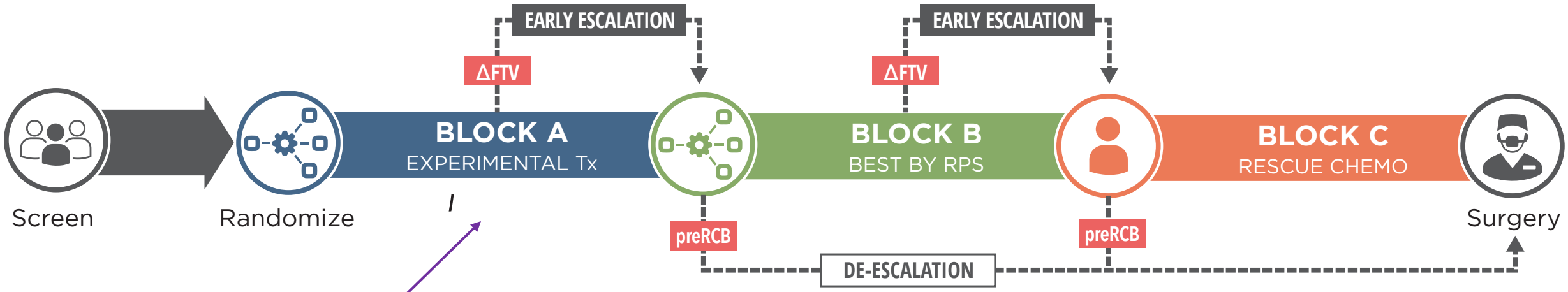
Secondary Endpoints:
- DOR, BOR, DCR, PFS, OS
- Safety

Exploratory Endpoints
- Correlative analysis to evaluate potential predictive/prognostic biomarkers
- Patient reported outcomes
- Eye toxicity prevention sub-study: Safety and efficacy of eye toxicity prevention plan

NCT06224673
PI: Laura Huppert (UCSF)

I-SPY 2.2

AZD2936 (Rilvegostomig) PD-1/TIGIT bispecific plus T-DXd
Every 3 weeks x 4 doses in Block A



Eligibility for Rilve/T-DXd:
Anatomic Stage II/III
MammaPrint® High risk
HER2 negative

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

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

Comparator arm: Dynamic control

Specific to each subtype identified from previously tested I-SPY 2 agents between March 2010 and April 2022 (e.g. paclitaxel -> AC; paclitaxel + pembrolizumab -> AC; paclitaxel + veliparib + carboplatin -> AC)

Novel HER2 Antibodies

- Both recently U.S. FDA approved for non-breast cancer indications!
  - Zenocutuzumab
    - Bispecific antibody to HER2 and HER3
  - Zanidatamab
    - Biparatopic antibody binding to 2 extracellular domains on HER2
    - ADC also in early phase trials

On December 4, 2024, the U.S. FDA granted accelerated approval to zenocutuzumab-zbco for adults with advanced non-small cell lung cancer or pancreatic adenocarcinoma progressing on prior systemic therapy and harboring a neuregulin 1 (NRG1) gene fusion.

The eNRGy study (NCT02912949) was a single arm trial that enrolled 64 adults with advanced *NRG1* fusion-positive NSCLC and 30 adults with advanced *NRG1* fusion-positive pancreatic adenoCA with progression after SOC treatment.

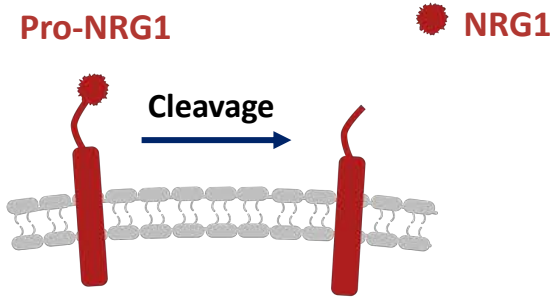
For NSCLC, ORR was 33% (95% CI: 22%, 46%); median DOR was 7.4 months (95% CI: 4.0, 16.6). For pancreatic adenocarcinoma, ORR was 40% (95% CI: 23%, 59%); the DOR range was 3.7 months -16.6 months.

The most common adverse reactions (≥10%) were diarrhea, pain, fatigue, nausea, infusion-related reactions, dyspnea, rash, constipation, vomiting, abdominal pain, and edema. The most common ≥Grade 3 laboratory abnormalities (≥10%) were increased GGT, anemia, hyponatremia and thrombocytopenia.

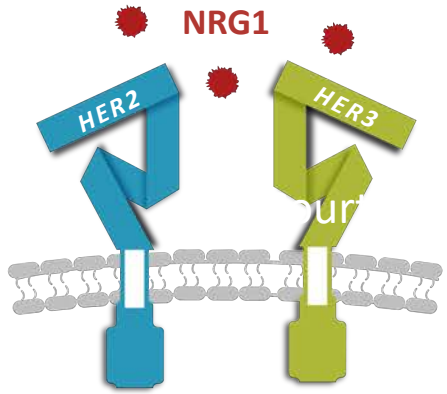
Neuregulin 1 (NRG1)/Heregulin Promotes Cellular Growth

Wild Type NRG1 Formation and Signaling

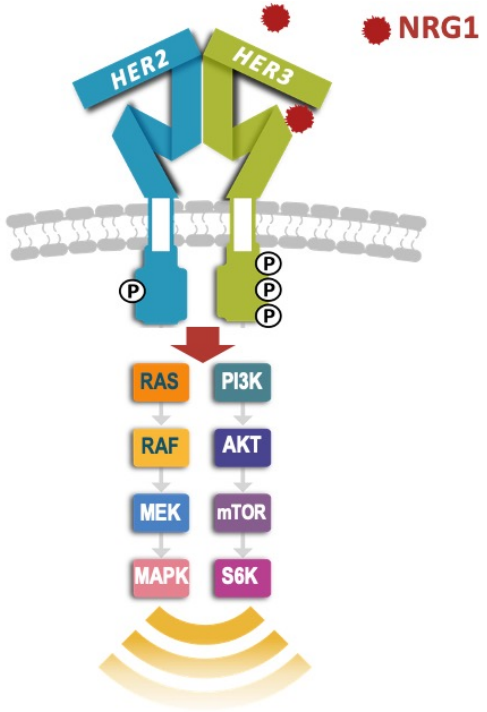
WT Pro-NRG1 cleavage to active NRG1



WT NRG1 unbound (extracellular)



WT NRG1-HER3 binding and receptor dimerization



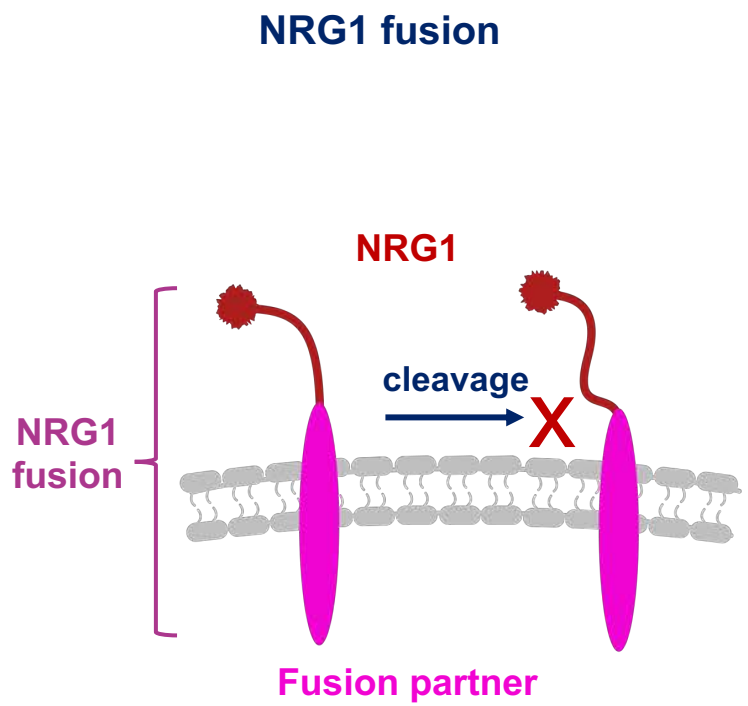
Pro-NRG1 is cleaved to active NRG1, allowing it to bind to HER3 and promote receptor dimerization and signaling.[3]

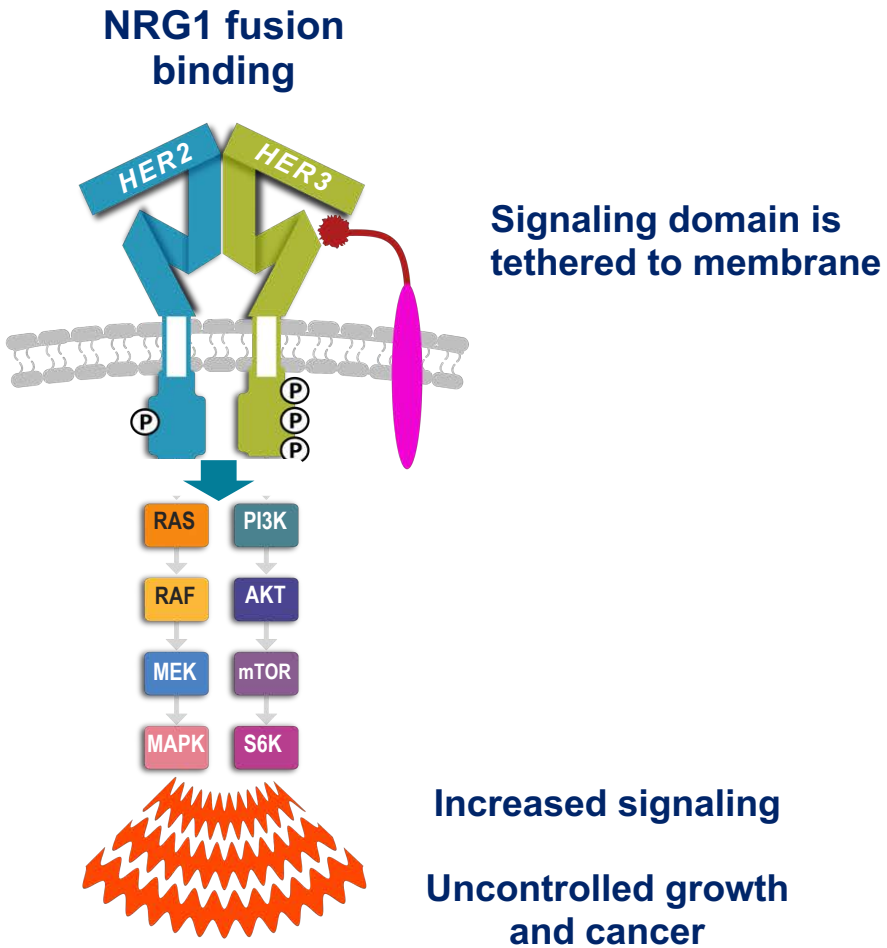
Courtesy of Schram

Mujoo et al., Oncotarget 2014; Teo et al., Academic Press 2016; Laskin et al., Ann Oncol 2020; Zhang et al., Acta Rev Cancer 2022

NRG1 Fusions Are a Novel Cancer Driver

NRG1 Fusion Signaling





Signaling domain is tethered to membrane

Increased signaling

Uncontrolled growth and cancer

NRG1 fusions remain anchored in the cell membrane where they bind to and activate HER3, leading to dimerization with HER2 and downstream oncogenic signaling.

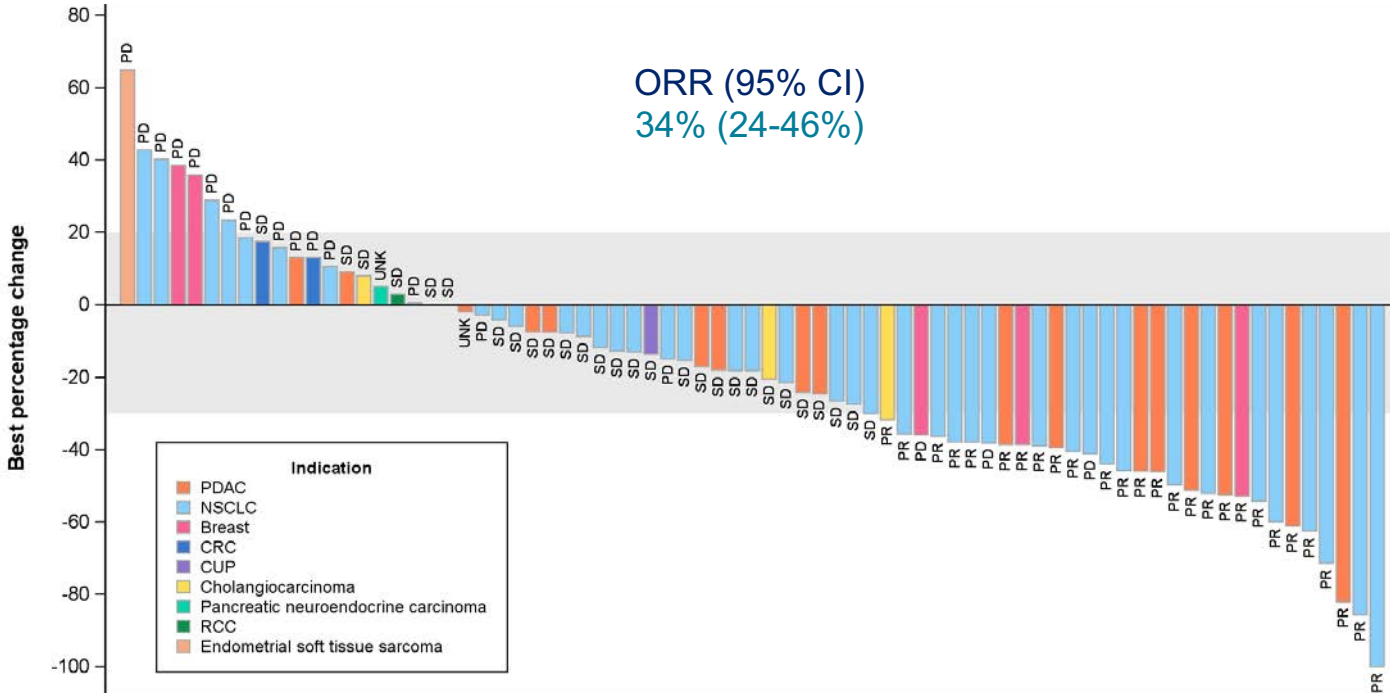
NRG1 fusions are found in 0.2-5% of breast cancers; multiple fusion partners

Revised from Schram

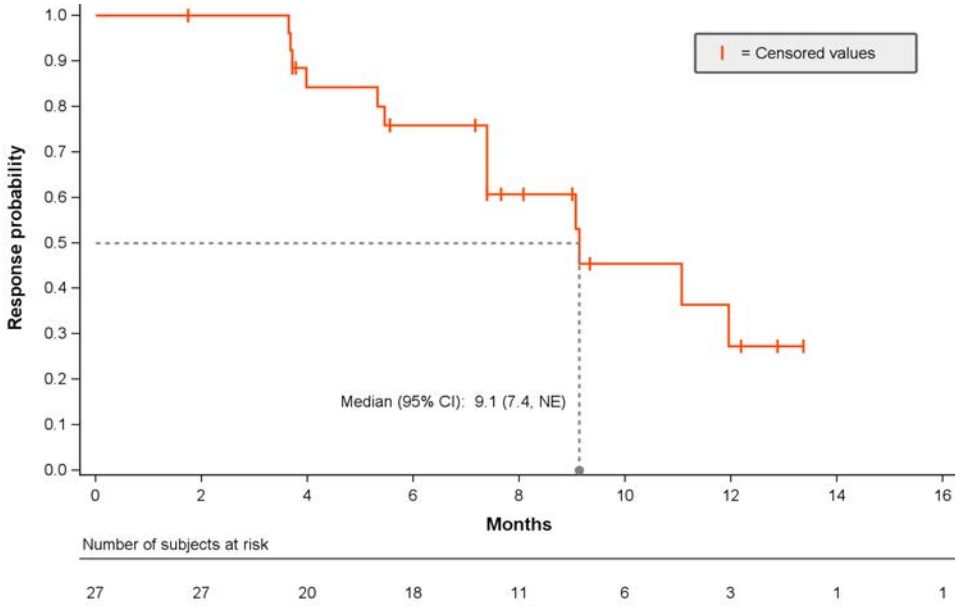
Mujoo et al., Oncotarget 2014; Teo et al., Academic Press 2016; Laskin et al., Ann Oncol 2020; Zhang et al., Acta Rev Cancer 2022

Zenocutuzumab Activity in NRG1+ Solid Tumors

Best percent change in target lesions from baseline



ORR (95% CI)
34% (24-46%)



Median follow-up: 6.3 months
Median DOR: 9.1 months (95% CI 7.4-NR)
6-month rate: 76%; 12-month rate: 27%

- 189 NRG1+ patients treated with zenocutuzumab 750 mg Q2W monotherapy
- Low incidence of grade 3 or 4 treatment-related TEAEs
- No patient discontinued treatment due to treatment-related TEAEs
- No grade 5 treatment-related TEAEs
- Infusion-related reactions in 23 of 189 (12%) patients, with no ≥grade 3 events

Schram et al., ASCO Annual Meeting 2022
Update soon: Schram et al., NEJM (in press)

On November 20, 2024, the U.S. FDA granted accelerated approval to zanidatamab-hrii, a bispecific HER2-directed antibody, for previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test.

HERIZON-BTC-01 (NCT04466891) was a single-arm trial in 62 patients with gemcitabine pre-treated advanced HER2+ (IHC3+) BTC. ORR was 52% (95% CI: 39, 65); median DOR was 14.9 months (95% CI: 7.4, not estimable).

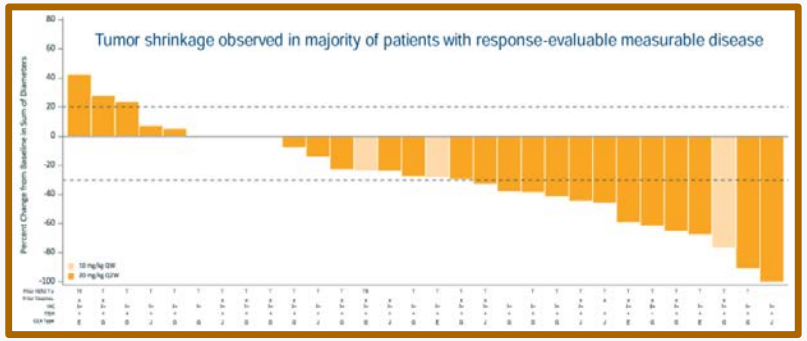
The most common adverse reactions in at least 20% of patients were diarrhea, infusion-related reactions, abdominal pain, and fatigue.

Zanidatamab Is Effective as Monotherapy in Patients with Advanced Tumors

Zanidatamab has shown monotherapy activity across a broad range of **HER2-expressing tumor types after multiple lines of therapy**

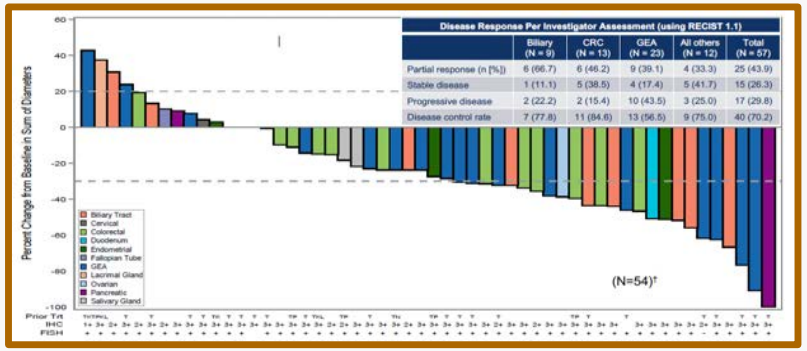
ORR 33%

3L+ GE Adenocarcinoma: Phase 1 Monotherapy[1]

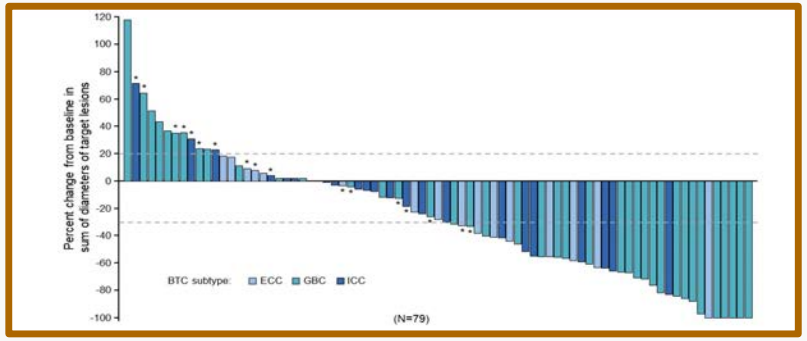


ORR 40%

4L+ Basket: Phase 1 Monotherapy[2]



2L+ Biliary Tract Cancer Pivotal: Phase 2 Monotherapy[3]



ORR 41%

2/3/4L+ = second/third/fourth line or greater; BTC = biliary tract cancer; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2. [1]Meric-Bernstam et. al. ASCO GI 2021; [2] Oh et. al. ESMO-Asia 2019; [3]Pant et. al. ASCO 2023.

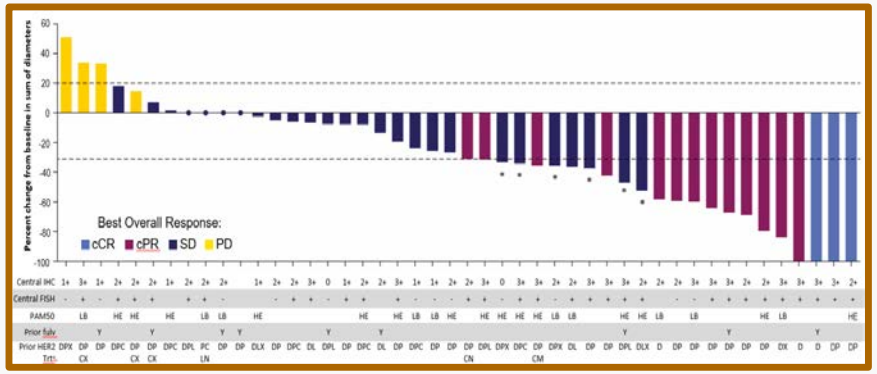
Zanidatamab Has Activity After Progression on Other HER2 Therapies

Zanidatamab has shown activity after treatment with HER2-targeted therapies:

- T-DXd
- T-DM1
- Trastuzumab
- Pertuzumab
- Tucatinib
- Lapatinib
- Neratinib
- Margetuximab

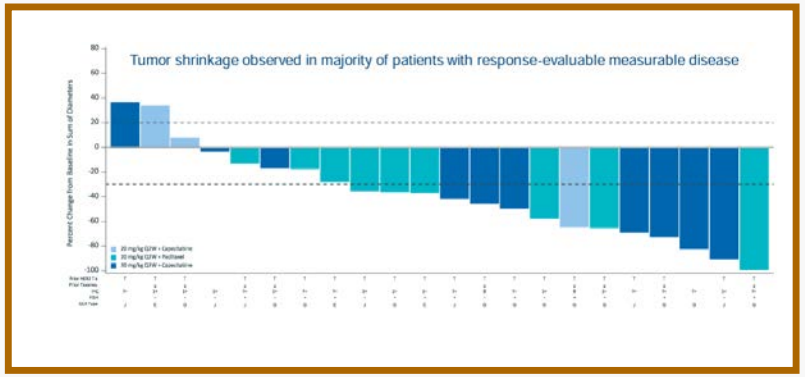
ORR 35 %

Late-Line HR+/HER2+ BC: Phase 2 Zanidatamab + Palbociclib + Fulvestrant[1]



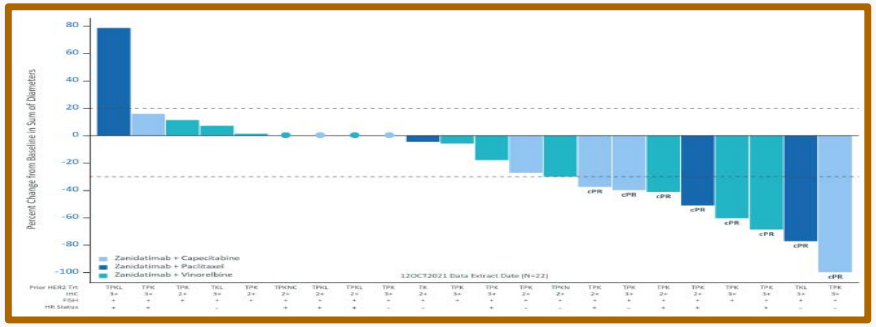
ORR 57 %

3L+ GEA: Phase 1 Chemo Combination[2]



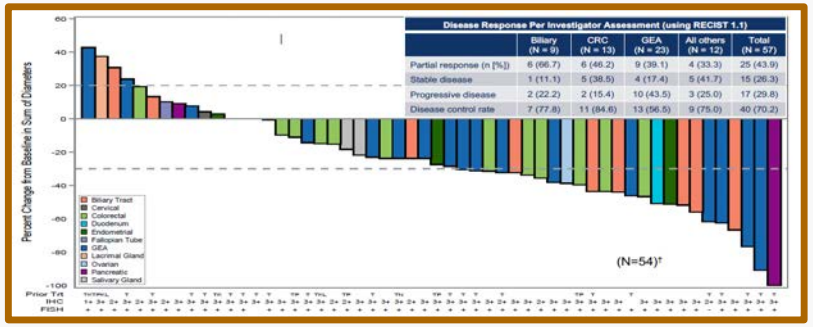
ORR 36 %

Late-Line BC: Phase 1 Chemo Combination[3]



ORR 40%

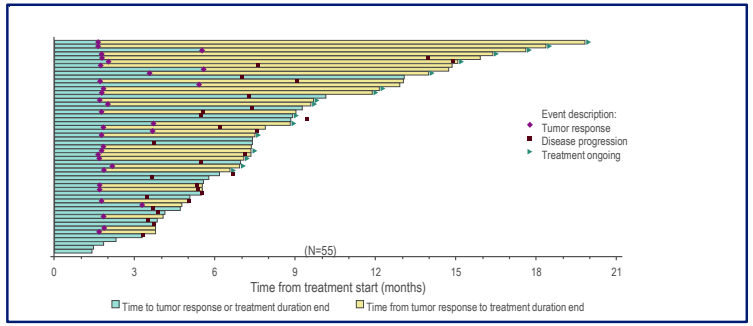
4L+ Basket: Phase 1 Monotherapy[4]



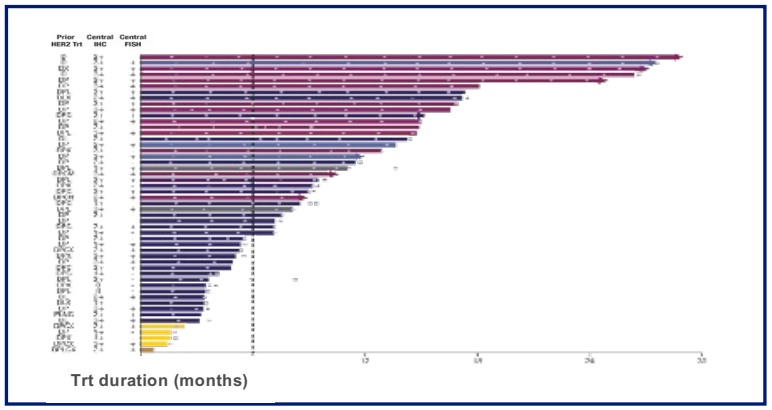
3/4L = third / fourth line; BC = breast cancer; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; T-DM1: trastuzumab emtansine; T-DXd = trastuzumab deruxtecan;[1]Escriva-de-Romani et. al. SABCS 2023; [2]Meric-Bernstam et. al. ASCO-GI 2021; [3]Bedard et. al. SABCS 2021; [4]Oh et. al. ESMO-Asia 2019.

Zanidatamab: Durable Activity in Multiple Indications and as Neoadjuvant Therapy for HER2+ Breast Cancer

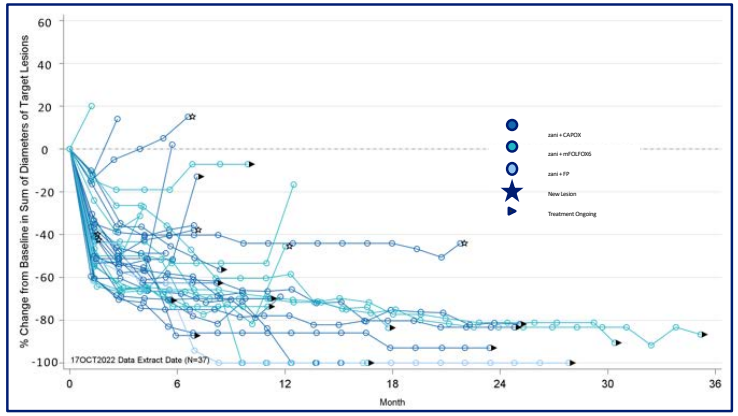
2L+ BTC Pivotal: Phase 2 Zanidatamab Monotherapy[1]



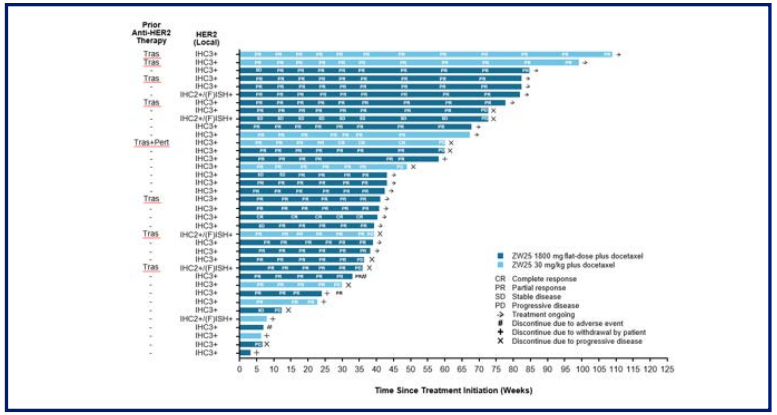
Late-Line HR+/HER2+ BC: Phase 2 Zanidatamab + Palbociclib + Fulvestrant [2]



1L GEA: Phase 2 Zanidatamab + Chemo[3]



1L BC: Phase 2 Zanidatamab + Chemo[4]



MDACC Neoadjuvant Study

- Neoadjuvant zanidatamab for 3 cycles (6-10 doses) showed **significant efficacy** in patients with stage I node negative HER2+ BC
- **No Grade 3 or Grade 4 TRAEs**
- Trial ongoing, cohort 2 combined with chemotherapy

Pathologic Response and Residual Cancer Burden

	# Patients	%
pCR/RCB-0	6	30
RCB-1	4	20
RCB-2	9	45
RCB-3	1	5

RCB0/1

1/2L = first / second line; BC = breast cancer; BTC = biliary tract cancer; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

[1]Pant et. al., ASCO 2023; [2]Escriva-de-Romani et. al., SABCS 2023; [3]Elimova et. al., ASCO GI 2023; [4]Wang et. al., ASCO 2023.

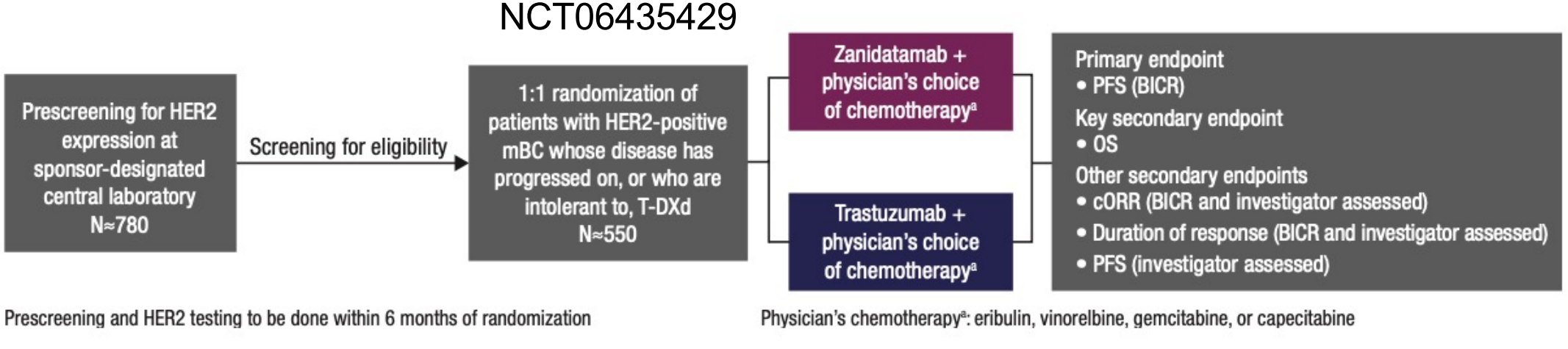
Zanidatamab + Evorpacept in HER2+ and Low MBC: New Data at SABCS 2024!

- Evorpacept: CD47 inhibitor (ALX 148)
- 3 cohorts
  - HER2+ with PD after T-DXd: 19 patients with a median of 6 lines of prior therapy
    - ORR 56%
    - Median DOR not reached (CI 2-22 months)
  - HER2 low MBC with PD after T-DXd
  - 15 patients with a median of 5 lines of prior therapy
    - ORR 20%
    - DOR 6 months (CI 4-7 months)
  - PFS on these two cohorts will be reported at the poster
  - Solid tumors: to be reported at a later date
  - 2 patients in each cohort discontinued due to reported adverse events

Montero et al, SABCS 2024, poster session December 12

EmpowHER-BC-303: A Phase 3 Study to Evaluate the Efficacy and Safety of Zanidatamab vs Trastuzumab With Chemotherapy in Patients With Metastatic HER2+ Breast Cancer Whose Disease Has Progressed on T-DXd

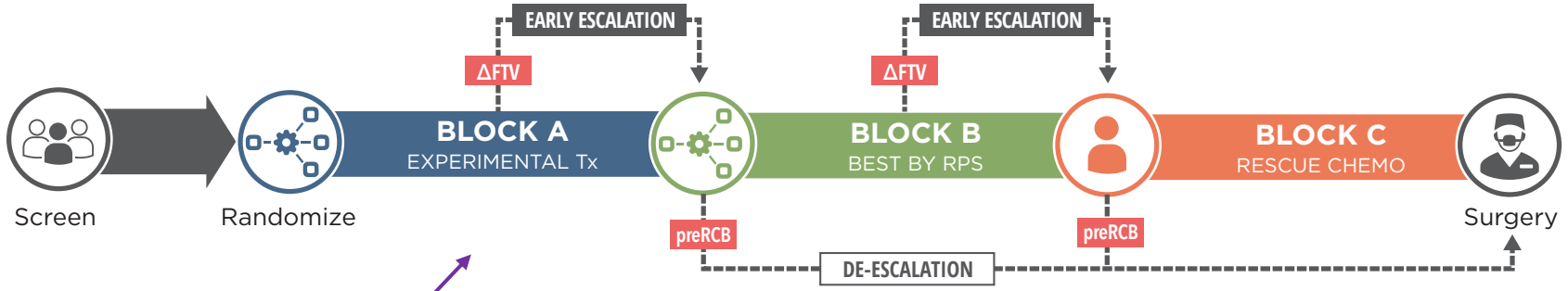
NCT06435429



Tolaney et al, SABCS 2024 TIP

I-SPY 2.2: Zanidatamab

Every 2 weeks x 6 doses in Block A



Eligibility for Zanidatamab:
Anatomic Stage II/III
HER2 positive
All have MammaPrint®/BluePrint®

Treatment Assignments/Randomization

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

Summary

- Expanded role for T-DXd for HER2 low disease under evaluation!
  - Early phase disease
  - Combination therapy
- Novel HER2 ADCs show promise
- New approaches to targeting HER2 with bispecific antibodies
  - Low toxicity with marked efficacy in HER2+ disease
    - Early approvals in highly resistant diseases
  - Expanding to HER2 low disease!
  - Suspect efficacy as well in HER2 mutant disease – no data to date

Faculty Case Presentation

Case Presentation – Dr Bardia

55F with metastatic HR+ MBC (HER2 IHC = 1+). Disease progression on various endocrine based therapies, and recently capecitabine. PS = 1. No organ dysfunction. gBRCA = negative. Patient has history of pneumonitis treated with everolimus. What would you consider next?

1. Eribulin
2. Vinorelbine
3. Sacituzumab Govitecan (SG)
4. Trastuzumab Deruxtecan (T-DXd)
5. Clinical Trial with novel HER2 ADC

QUESTIONS FOR THE FACULTY

In the future, do you anticipate that T-DXd will be combined with endocrine therapy for patients with HR-positive, HER2-low or HER2-ultralow mBC?

What about immune checkpoint inhibitors for patients with HR-negative, HER2-low disease?

Beyond T-DXd, what other novel strategies being investigated for patients with HER2-low mBC, if any, are you excited about?

Rounds with the Investigators: Compelling Teaching Cases Focused on the Role of Endocrine-Based Therapy in the Management of Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Komal Jhaveri, MD, FACP
Virginia Kaklamani, MD, DSc
Seth Wander, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Metastatic Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

Thursday, December 12, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Ian E Krop, MD, PhD
Joyce O'Shaughnessy, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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RTP
RESEARCH TO PRACTICE