Beyond the Guidelines: Clinical Investigator Perspectives on the Management of HER2-Low Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Thursday, December 7, 2023

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

Faculty

Aditya Bardia, MD, MPH

Lisa A Carey, MD, ScM, FASCO

Shanu Modi, MD

Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

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Faculty

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Director
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Lineberger Comprehensive Cancer Center
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Shanu Modi, MD
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Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

Professor Peter Schmid, FRCP, MD, PhD
Lead, Centre of Experimental
Cancer Medicine
Barts Cancer Institute
London, United Kingdom

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Dr Bardia — Disclosures

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, Radius Health Inc, Sanofi

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Dr Carey — Disclosures

No relevant conflicts of interest to disclose

Dr Modi — Disclosures

Advisory Committee and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Seagen Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Seagen Inc

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Prof Schmid — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Daiichi Sankyo Inc, Eisai Inc, Gilead Sciences Inc, Lilly, Merck, Novartis, Pfizer Inc, Puma Biotechnology Inc, Roche Laboratories Inc
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Medivation Inc, a Pfizer Company, Novartis, OncoGenex Pharmaceuticals Inc, Roche Laboratories Inc

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hematologic Cancers

A 4-Part CME Friday Satellite Symposium Series Preceding the 65th ASH Annual Meeting and Exposition

Friday, December 8, 2023

Follicular, Mantle Cell and Hodgkin Lymphoma
7:30 AM – 10:00 AM PT

Chronic Lymphocytic Leukemia
3:15 PM – 5:15 PM PT

Diffuse Large B-Cell Lymphoma
11:30 AM – 1:30 PM PT

Multiple Myeloma
7:00 PM – 9:00 PM PT

Moderator
Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Follicular, Mantle Cell and Hodgkin Lymphoma (Part 1 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:30 AM – 10:00 AM PT (10:30 AM – 1:00 PM ET)

Faculty

Jeremy S Abramson, MD, MMSc
Stephen M Ansell, MD, PhD
Nancy L Bartlett, MD
Jonathon B Cohen, MD
Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Diffuse Large B-Cell Lymphoma (Part 2 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Michael Dickinson, MD
Grzegorz S Nowakowski, MD
Gilles Salles, MD, PhD
Laurie H Sehn, MD, MPH
Jason Westin, MD, MS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Farrukh T Awan, MD
Matthew S Davids, MD, MMSc
Stephen J Schuster, MD
William G Wierda, MD, PhD
Jennifer Woyach, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Amrita Krishnan, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Neil Love, MD

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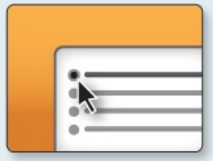
www.ResearchToPractice.com/Meetings/GMO2024

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 premeeting survey.

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.

Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

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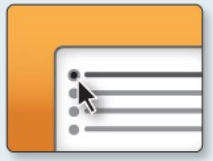
Clinicians Attending via Zoom

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 premeeting survey at the beginning of each module.

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

Get CME/NCPD Credit: CME and NCPD credit links will be provided in the chat room at the conclusion of the program. MOC and ONCC credit information will be emailed to attendees within the next 2-3 business days.

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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.
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Moderator

Neil Love, MD

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Agenda

Module 1: Optimal Approaches to HER2 Testing for the Identification of HER2-Low Breast Cancer — Dr Carey

Module 2: Available Data with and Current Role of HER2-Targeted Therapy for HER2-Low Disease — Dr Modi

Module 3: Identification and Management of Toxicities with Trastuzumab Deruxtecan — Prof Schmid

Module 4: Future Directions in the Management of HER2-Low Breast Cancer — Dr Bardia

Breast Cancer Survey Respondents

Aditya Bardia, MD, MPH
François-Clément Bidard, MD, PhD
Adam Brufsky, MD, PhD
Harold J Burstein, MD, PhD
Lisa A Carey, MD, ScM, FASCO
Matthew P Goetz, MD
Erika Hamilton, MD
Sara A Hurvitz, MD, FACP
Komal Jhaveri, MD, FACP
Virginia Kaklamani, MD, DSc
Jane Lowe Meisel, MD
Shanu Modi, MD
Joyce O'Shaughnessy, MD
Mark Pegram, MD
Lajos Pusztai, MD, DPhil, FASCO
Hope S Rugo, MD
Paolo Tarantino, MD
Prof Peter Schmid, FRCP, MD, PhD
Priyanka Sharma, MD
Eric P Winer, MD

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Consulting Faculty

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Associate Director for Clinical Research
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Stanford, California

Eric P Winer, MD
Alfred Gilman Professor of Medicine and Pharmacology
Director, Yale Cancer Center
President and Physician-in-Chief
Smilow Cancer Hospital
New Haven, Connecticut

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Agenda

Module 1: Optimal Approaches to HER2 Testing for the Identification of HER2-Low Breast Cancer — Dr Carey

Module 2: Available Data with and Current Role of HER2-Targeted Therapy for HER2-Low Disease — Dr Modi

Module 3: Identification and Management of Toxicities with Trastuzumab Deruxtecan — Prof Schmid

Module 4: Future Directions in the Management of HER2-Low Breast Cancer — Dr Bardia

Approximately what proportion of patients with metastatic breast cancer have tumors that are HER2-negative or HER2-low based on ER status? (Median; range)

	ER-positive	ER-negative
HER2 IHC 0	30% (20% - 50%)	58% (20% - 80%)
HER2 IHC 1+ or 2+	67% (50% - 80%)	35% (20% - 70%

Survey of 20 US-based clinical investigators November 2023

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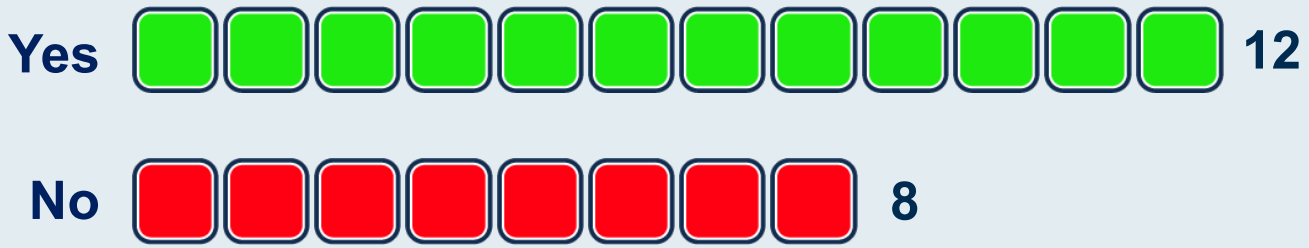
Based on available data, do you believe that trastuzumab deruxtecan has shown efficacy in HER2-low tumors other than breast cancer?



Survey of 20 US-based clinical investigators November 2023

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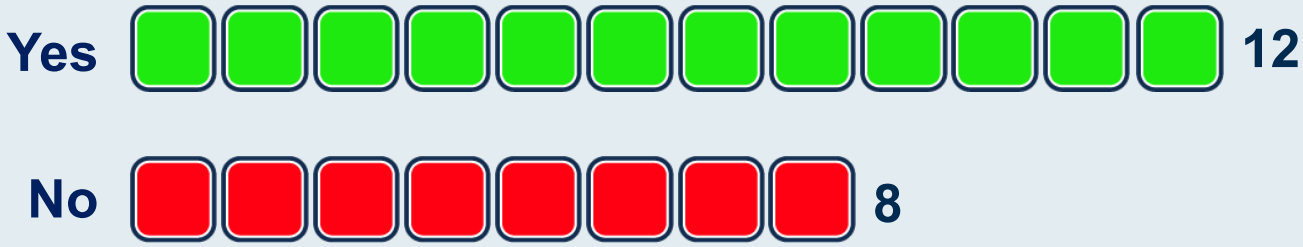
Do you believe that trastuzumab deruxtecan (T-DXd) should receive a tumor-agnostic FDA approval?



- HER2 gene amplification occurs in many tumor types (salivary, endometrial, ovarian, biliary, gastric, etc.). It is likely that T-DXd will have activity in all these HER2+ diseases.
- It seems to work for almost all HER2+ cancers and better to give people the option given its excellent efficacy compared to most chemo and very quick (most of the time) impact.
- T-DXd is clearly effective in many settings but I don't think there is enough data to use HER2-low in any tumor. I suspect there will be more data soon that might support this approach.
- For HER2 amplified tumors, I would be supportive of a tumor-agnostic label.
  But, for HER2 low tumors, the MoA is different and the concept of a universal sensitivity of tumors to vectorized TOPO1 inhibitor is not proven. Thresholds may also be different across tumor types.

Survey of 20 US-based clinical investigators November 2023

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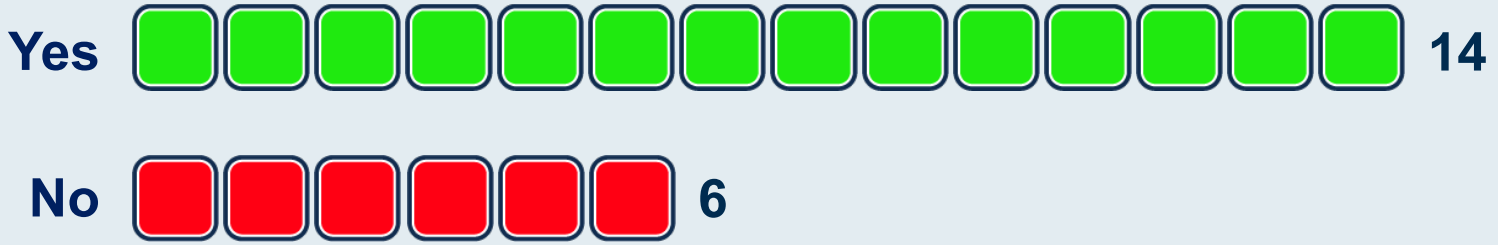
Regulatory and reimbursement issues aside, would you offer trastuzumab deruxtecan to a patient with HER2 IHC 0 metastatic breast cancer with a HER2 mutation?



Survey of 20 US-based clinical investigators November 2023

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HER2 IHC levels and selection of patients for treatment with trastuzumab deruxtecan

Adam M Brufsky, MD, PhD

Jane Lowe Meisel, MD

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HER2 IHC 0 breast cancer and potential role for trastuzumab deruxtecan

Paolo Tarantino, MD

Eric P Winer, MD

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UNC | LINEBERGER COMPREHENSIVE CANCER CENTER

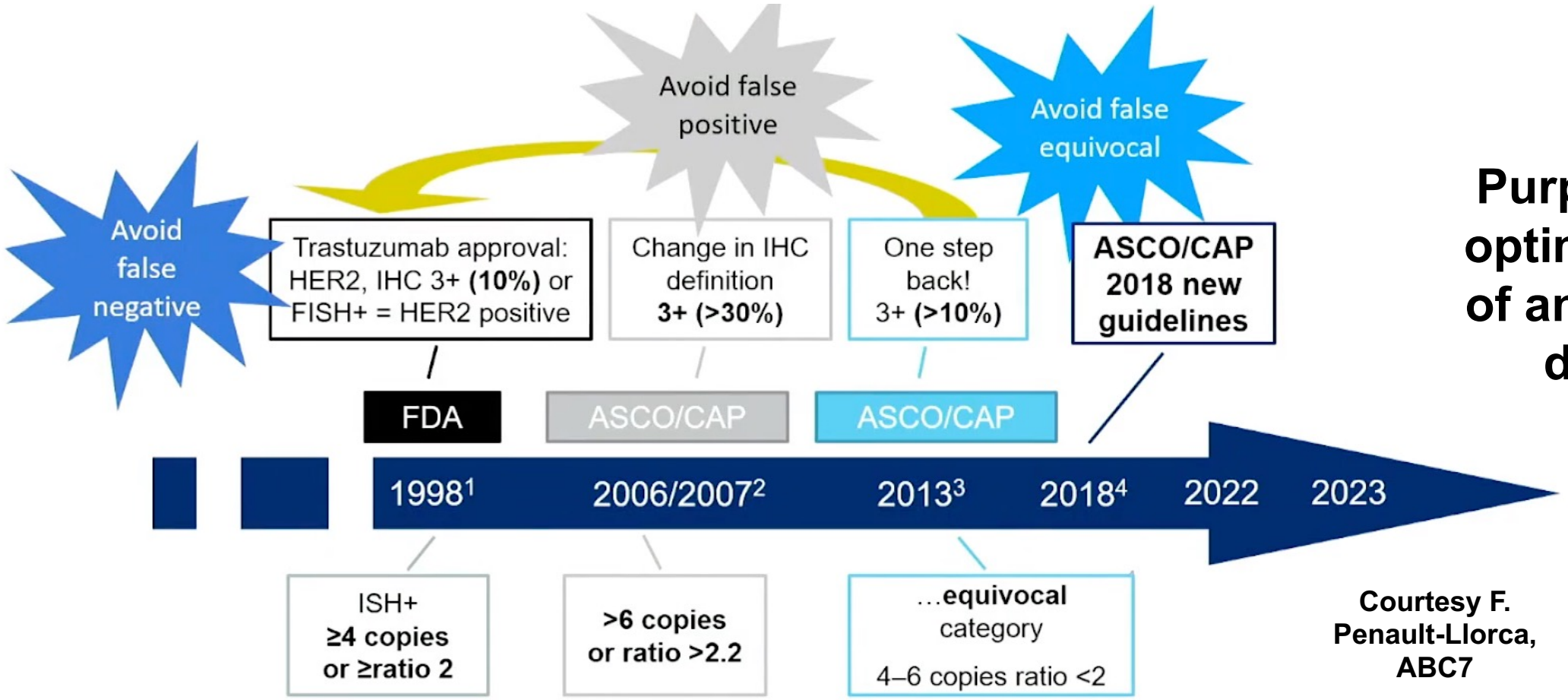
UNC CANCER CARE

Optimal Approaches to HER2 Testing to Identify HER2-Low Breast Cancer (BC)

Lisa A. Carey MD, ScM

December, 2023

History of HER2 Testing



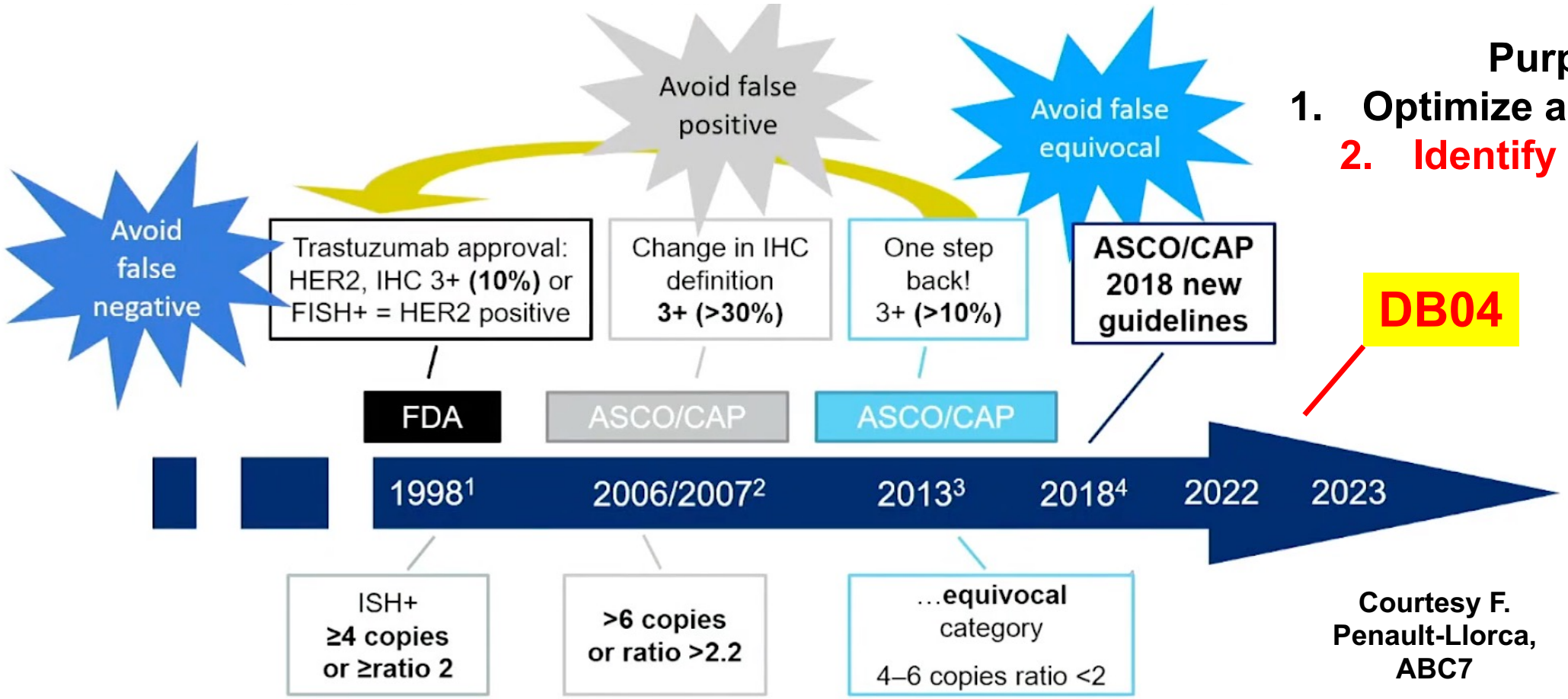
Purpose: to optimize use of anti-HER2 drugs

Courtesy F. Penault-Llorca, ABC7

Jorgensen JT et al, Front Oncol 2021; Wolff AC et al, JCO 2007; Wolff AC et al, JCO 2013; Wolff AC et al, JCO 2018

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

History of HER2 Testing



Purpose:

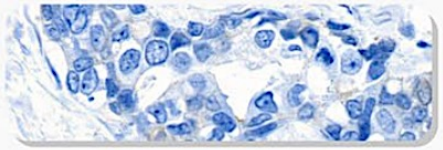
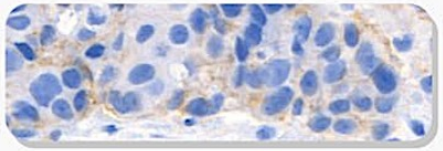
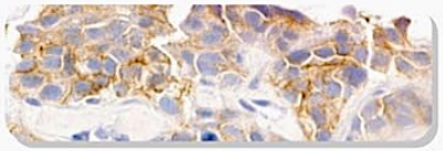
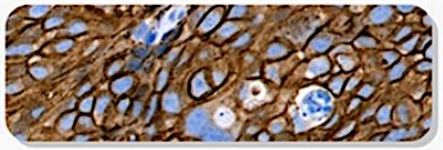
1. **Optimize anti-HER2 drugs**
2. **Identify "HER2-Low"**

DB04

Courtesy F. Penault-Llorca, ABC7

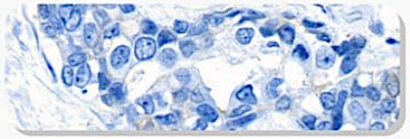
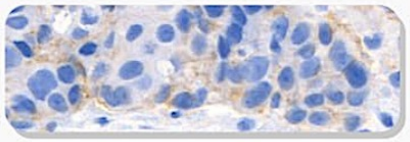
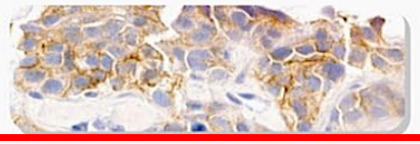
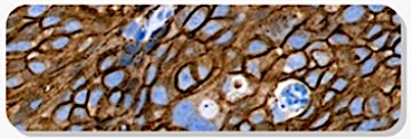
Jorgensen JT et al, Front Oncol 2021; Wolff AC et al, JCO 2007; Wolff AC et al, JCO 2013; Wolff AC et al, JCO 2018

Immunostains (IHC) for HER2

	IHC score	HER2 test intepretation	HER2 status	
	0	No staining or incomplete and faint/barely perceptible membrane staining in ≤10% of tumor cells	Negative	
	1+	Incomplete and faint/barely perceptible membrane staining in >10% of tumor cells	Low	Spectrum of HER2 positivity
	2+	Weak-moderate complete membrane staining in >10% of tumor cells OR intense membrane staining in ≤10% of tumor cells	NO ISH amplification? YES	
	3+	Complete and intense membrane staining in >10% of tumor cells	Positive	

Wolff A et al, Arch Path Lab Med 2023

Immunostains (IHC) for HER2: Focus was on ”HER2-Positive”

	IHC score	HER2 test intepretation	HER2 status	
	0	No staining or incomplete and faint/barely perceptible membrane staining in ≤10% of tumor cells	Negative	
	1+	Incomplete and faint/barely perceptible membrane staining in >10% of tumor cells	Low	Spectrum of HER2 positivity
	2+	Weak-moderate complete membrane staining in >10% of tumor cells OR intense membrane staining in ≤10% of tumor cells	NO ISH amplification? YES	
	3+	Complete and intense membrane staining in >10% of tumor cells	Positive	

HER2+

Focus 1998-2020
Defining where inhibitory antibodies would work

Wolff A et al, Arch Path Lab Med 2023

Then Came The Anti-HER2 ADCs…

original reports

Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study

Shanu Modi, MD[1]; Haeseong Park, MD, MPH[2]; Rashmi K. Murthy, MD
Junji Tsurutani, MD, PhD[6]; Alvaro Moreno-Aspitia, PhD[7]; Toshihiko Do
Ian E. Krop, MD, PhD[11]; Caleb Lee, MD, PhD[12]; Yoshihiko Fujisaki, M
Javad Shahidi, MD[12]; and Shunji Takahashi, MD[14]

Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study

Udai Banerji, Carla M L van Herpen, Cristina Saura, Fiona Thistlethwaite, Simon Lord, Victor Moreno, Iain R Macpherson, Valentina Boni, Christian Rolfo, Elisabeth G E de Vries, Sylvie Rottey, Jill Geenen, Ferry Eskens, Marta Gil-Martin, Ellen C Mommers, Norbert P Koper,

Meeting Abstract | 2021 ASCO Annual Meeting I

BREAST CANCER—METASTATIC

RC48-ADC, a HER2-targeting antibody-drug conjugate, in patients with HER2-positive and HER2-low expressing advanced or metastatic breast cancer: A pooled analysis of two studies.

Meeting Abstract | 2021 ASCO Annual Meeting I

BREAST CANCER—METASTATIC

BEGONIA: Phase 1b/2 study of durvalumab (D) combinations in locally advanced/metastatic triple-negative breast cancer (TNBC)—Initial results from arm 1, d+paclitaxel (P), and arm 6, d+trastuzumab deruxtecan (T-DXd).

Check for updates

ımin Fang, Xuelian Chen, …

Peter Schmid, Seock-Ah Im, Anne Armstrong, Yeon Hee Park, Wei-Pang Chung, Zbigniew Nowecki, …

Meeting Abstract | 2022 ASCO Annual Meeting I

BREAST CANCER—METASTATIC

A multiple center, open-label, single-arm, phase II clinical trial of MRG002, an HER2-targeted antibody-drug conjugate, in patients with HER2-low expressing advanced or metastatic breast cancer.

Check for updates

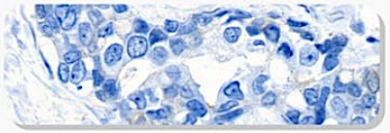
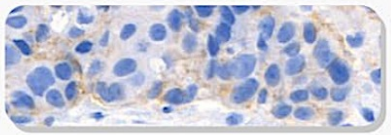
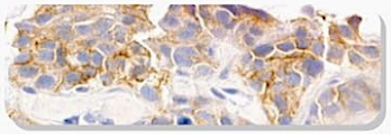
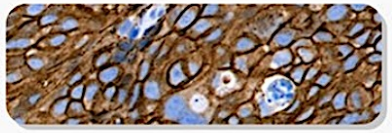
Zefei Jiang, Tao Sun, Xiaojia Wang, Qiang Liu, Min Yan, Zhongsheng Tong, …

POSTER PRESENTATIONS - PROFFERED ABSTRACTS | APRIL 14 2023

Abstract LB031: SHR-A1811, a novel anti-HER2 ADC with superior bystander effect, optimal DAR and favorable safety profiles FREE

Ting Zhang; Lingfeng You; Jianyan Xu; Junzhao Yin; Bolei Qu; Yuchang Mao; Beibei Fu; Dan Cao; Linda Zhao; Jun Feng; Min Hu; Feng He

Immunostains (IHC) for HER2: “HER2-Low”

	IHC score	HER2 test intepretation	HER2 status	
	0	No staining or incomplete and faint/barely perceptible membrane staining in ≤10% of tumor cells	Negative	
	1+	Incomplete and faint/barely perceptible membrane staining in >10% of tumor cells	Low	Spectrum of HER2 positivity
			NO	
	2+	Weak-moderate complete membrane staining in >10% of tumor cells OR intense membrane staining in ≤10% of tumor cells	ISH amplification?	
			YES	
	3+	Complete and intense membrane staining in >10% of tumor cells	Positive	

HER2-low

New focus!
Defined in NSABP B-47, used in ADC trials
(Below threshold where “naked” HER2 Ab alone would work)

Wolff A et al, Arch Path Lab Med 2023

HER2-Low: Defining Immunostains in the Lower Register

Table 1. Interpretation by the ASCO/CAP 2018 Guidelines and by the 2023 ESMO Consensus on HER2-low breast cancer regarding each pattern of HER2 staining

Description of staining	Denomination by 2018 ASCO/CAP Guidelines	Conclusion by 2018 ASCO/CAP Guidelines	Conclusion by 2023 ESMO clinical practice recommendations
- No staining	HER2-0	HER2-negative	**HER2-0** *HER2-null*[a]
- Incomplete or faint staining in ≤10% of invasive tumor cells	HER2-0	HER2-negative	*HER2-ultralow (or >no staining <1+)*[a]
- Incomplete or faint staining in >10% of invasive tumor cells	HER2 1+	HER2-negative	**HER2-low**
- Weak to moderate complete membrane staining in >10% of invasive tumor cells (ISH-negative)	HER2 2+ nonamplified	HER2-negative	**HER2-low**
- Weak to moderate complete membrane staining in >10% of invasive tumor cells (ISH-positive)	HER2 2+ amplified	HER2-positive	**HER2-positive**
- Intense complete membrane staining in >10% of invasive tumor cells	HER2 3+	HER2-positive	**HER2-positive**

How low do you go?
"HER2-ultralow" (vs "-null")
Included in DB06
(T-DXd vs TPC chemo in HR+ HER2-low)

Unknown if clinically valid

Tarantino et al, Ann Oncol 2023

Testing Biomarkers for Clinical Use

"I think you should be more explicit here in step two."

Key elements of assay development:

1. **Analytical validity (reproducible and accurate?)**
2. **Clinical validity (differentiate cancers?)**
3. **Clinical utility (assay = better decisions?)**

Adapted from Simon R, JNCI 2009

College of American Pathologists Is Not Happy…

HER2 Testing in Breast Cancer - 2023 Guideline Update

The 2023 **"Human Epidermal Growth Factor Receptor 2 (HER2) Breast Testing Guideline Update"** reaffirms the 2018 "HER2 Breast Testing Guideline Focused Update."

This reaffirmation was propelled by results of the 2022 DESTINY-Breast04 trial, which prompted the United States Food and Drug Administration (FDA) to expand the approval of the HER2 antibody-drug conjugate, trastuzumab deruxtecan, from metastatic breast cancer patients with HER2 protein over-expression/amplification to also include metastatic patients with HER2 IHC 1+ or 2+/ISH negative results.

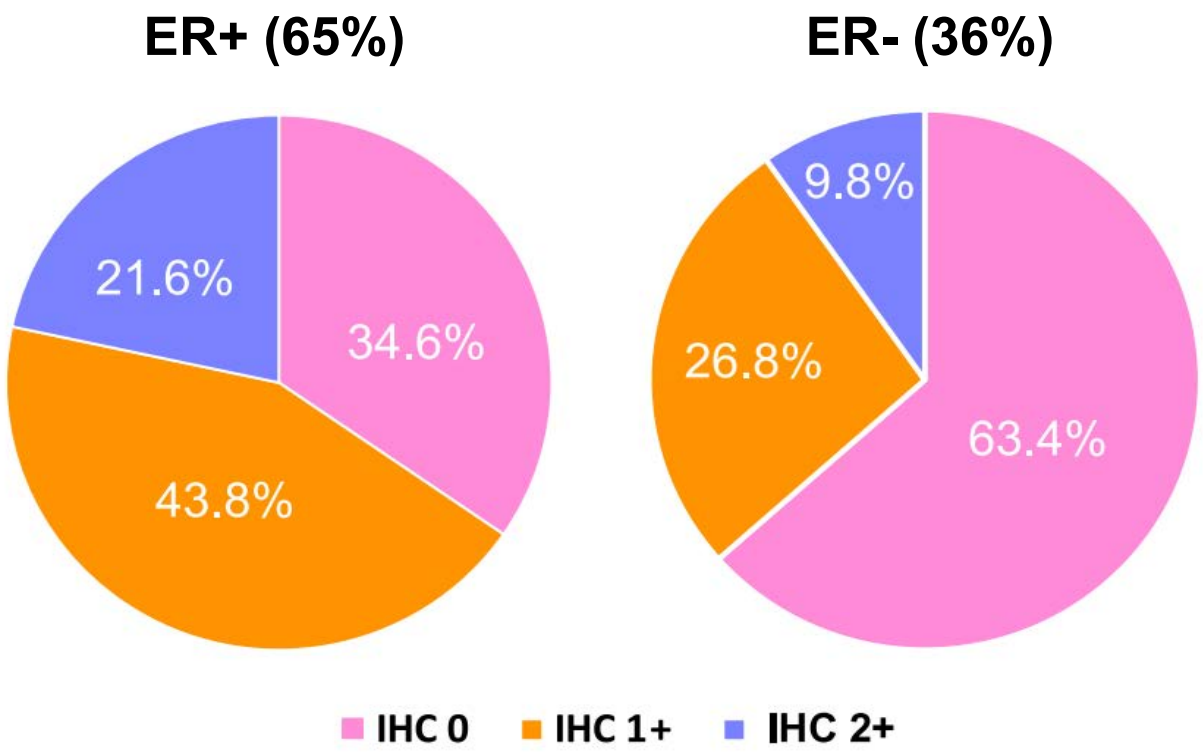
This guideline update does not support the use of a HER2-Low interpretive category because the DESTINY-Breast04 trial did not include patients with HER2 IHC 0 results, there is no evidence to support that IHC 1+ or 2+/ISH negative results are predictive of trastuzumab deruxtecan treatment response when compared to IHC 0 results. Therefore, the FDA expansion of approval to this group was only based on clinical trial eligibly criteria rather than a new predictive indication for HER2 testing.

https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/recommendations-for-human-epidermal-growth-factor-2-testing-in-breast-cancer

General Comments about Defining HER2-Low

1. **HER2 testing was designed to differentiate HER2+ (HER2-driven, HER2-addicted, etc) from not-that. They were not validated for score 0 vs 1+.**
2. **HER2-low was not a priori defined as a biologically distinct entity (it was a byproduct of the DESTINY-Breast04 and similar ADC trials).**
3. **It is biologically plausible that some HER2 expression is needed for the ”T” part of T-DXd and other HER2-directed ADCs to work.**
4. **How much HER2 expression is needed is unclear.**

Clinical Characteristics of HER2-Low



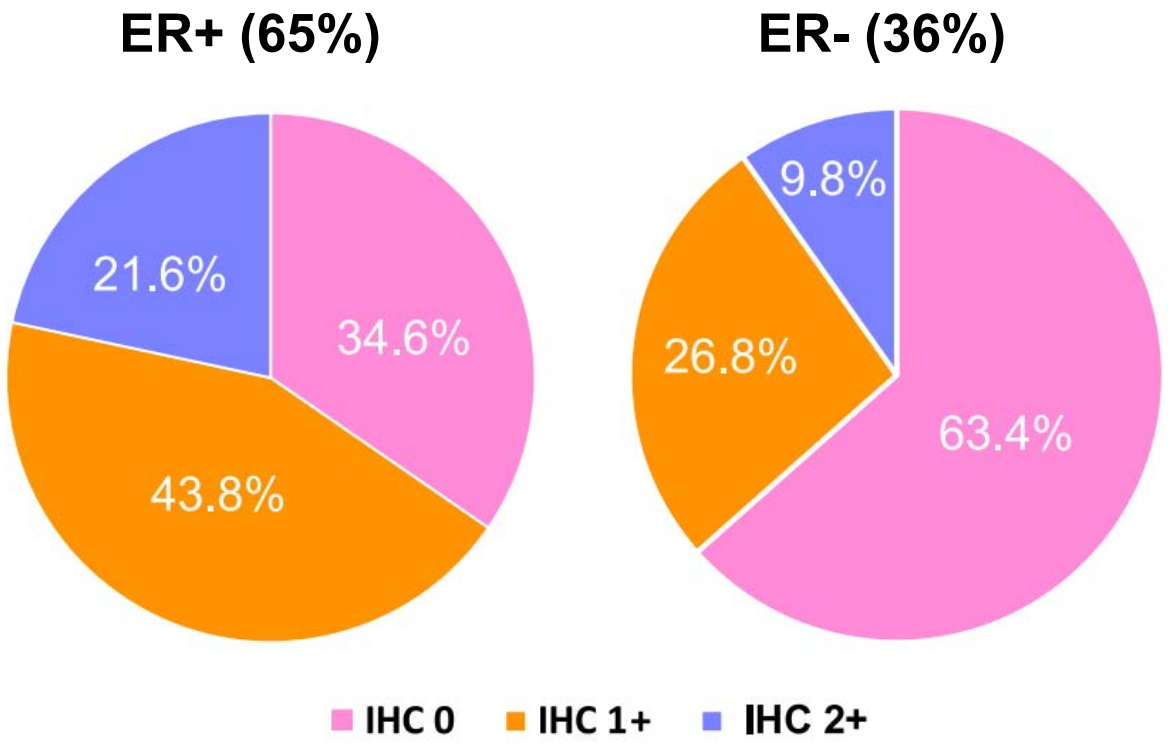
From 3700 incident BC (70% primary) Mixed MBC/EBC

1.1M patients, NCDB 2010-2019

All P<0.001:	HER2-0	HER2-Low
ER+ PR+	69%	79%
TNBC	20%	10%
< 50	23%	18%
Male	0.7%	1.0%
Black	12%	11%
Grade 3	31%	24%
T1	64%	66%
N0	73%	72%
Ductal	75%	79%
Lobular	12%	11%
Metaplastic	1.0%	0.3%
Mucinous	2.7%	1.6%

Schettini et al, NPJ Breast 2021; Peiffer DS et al, JAMA Oncol 2023

Clinical Characteristics of HER2-Low



From 3700 incident BC (70% primary) Mixed MBC/EBC

Beyond HR, other clinical differences are subtle

All P<0.001:	HER2-0	HER2-Low
ER+ PR+	69%	79%
TNBC	20%	10%
< 50	23%	18%
Male	0.7%	1.0%
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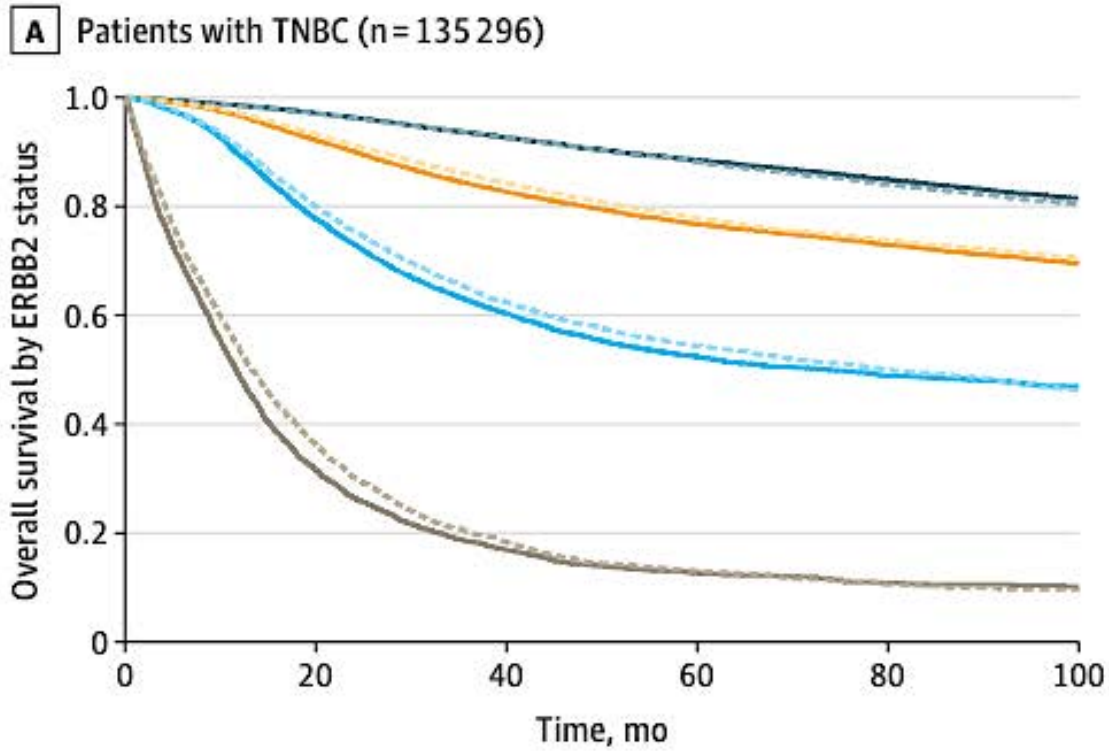
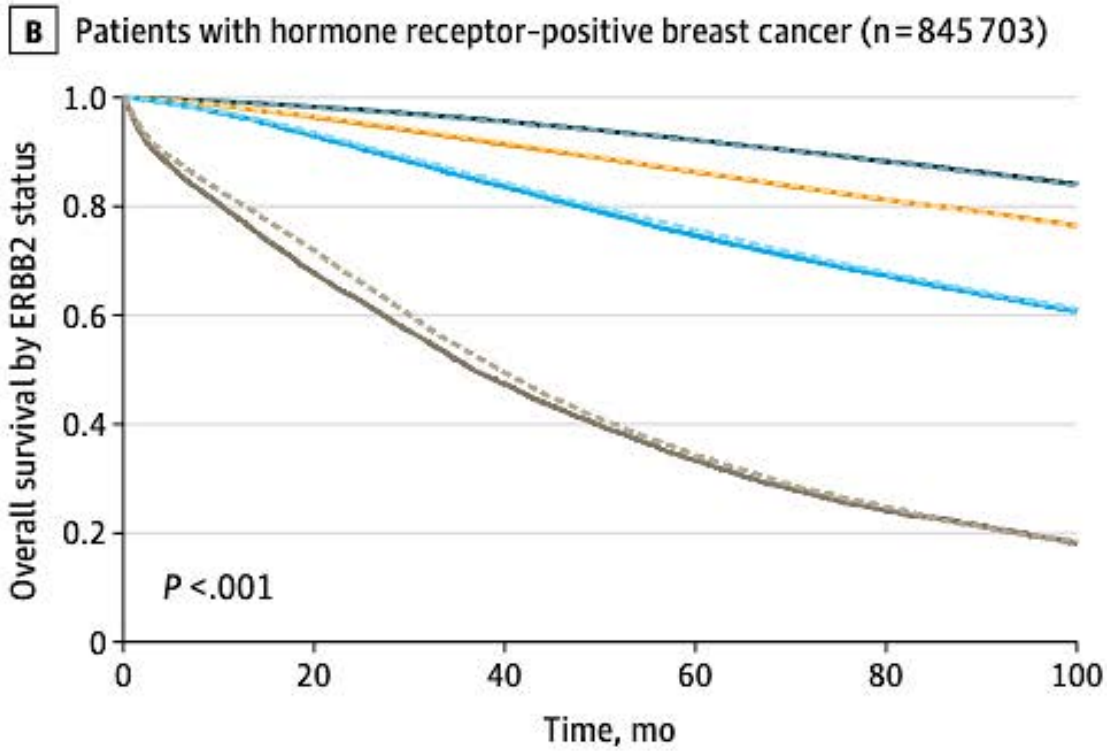
Mucinous	2.7%	1.6%

Schettini et al, NPJ Breast 2021; Peiffer DS et al, JAMA Oncol 2023

Prognosis by HER2-Low Status

After correcting for HR status, similar outcomes





With conventional therapies….
HER2-based Rx not represented

Peiffer DS et al, JAMA Oncol 2023

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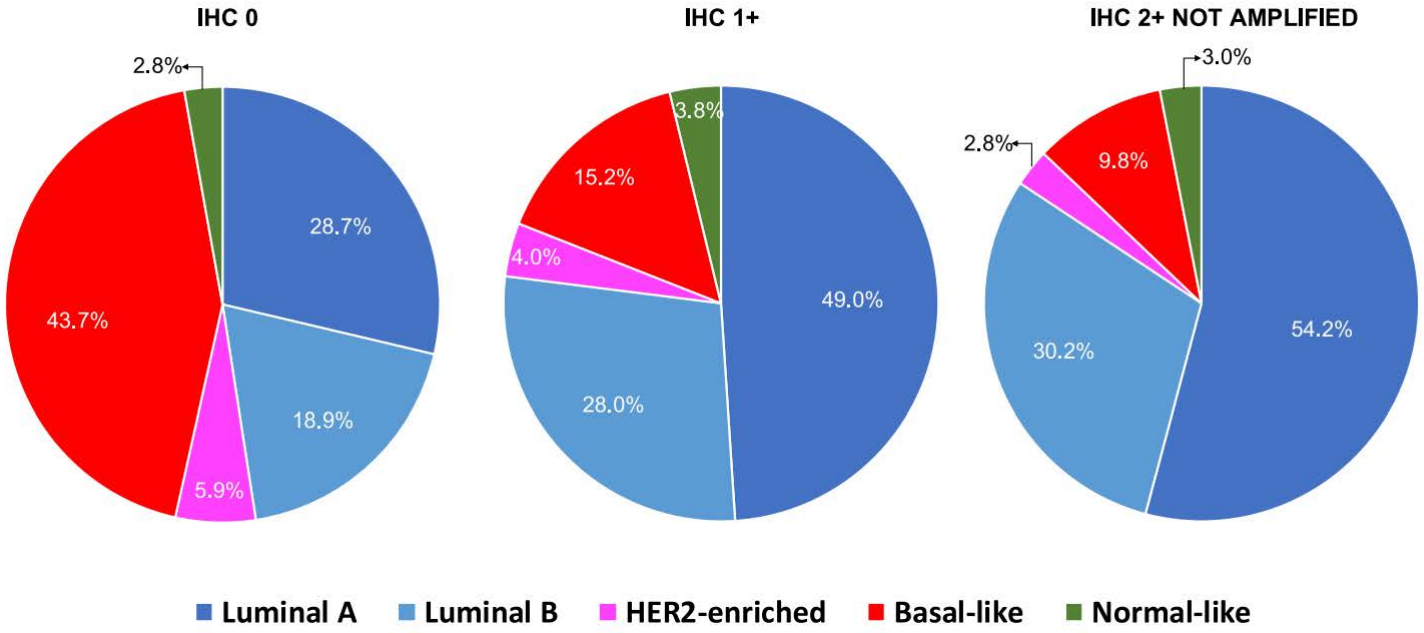
Molecular Subtypes

From 3700 incident BC (70% primary) Mixed MBC/EBC

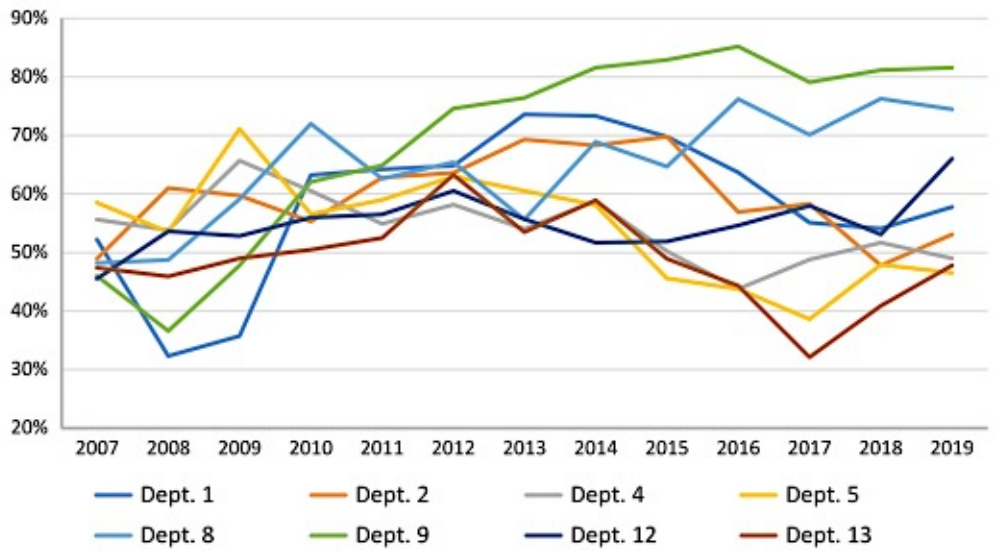


	ER+		TNBC	
Intrinsic Subtype	HER2-0	HER2-Low	HER2-0	HER2-Low
Luminal A	52%	59%	2%	2%
Luminal B	35%	33%	0	0
HER2-Enriched	3%	3%	9%	7%
Basal-like	8%	2%	85%	83%
Normal-like	2%	3%	4%	8%

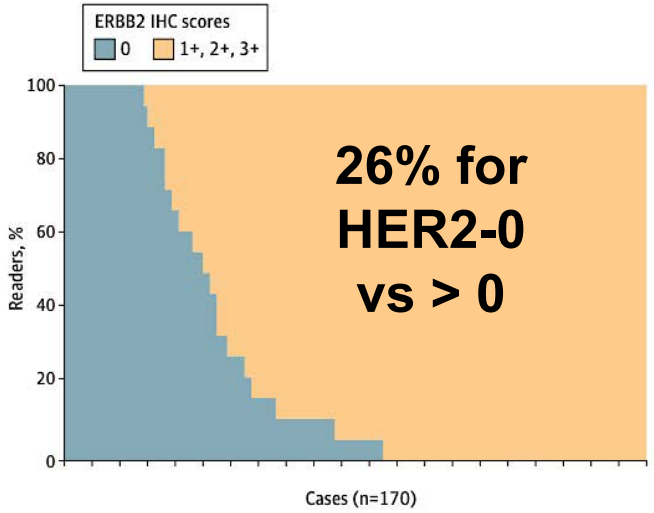
Schettini et al, NPJ Breast 2021

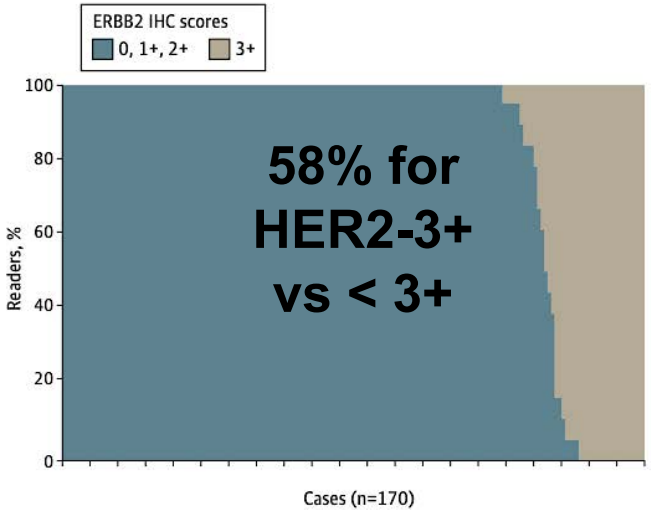
Precision of HER2-Low Testing

"HER2-Low" by IHC
8 Danish Pathology Depts
with > 3000 BC patients



Agreement among 18 board-certified pathologists



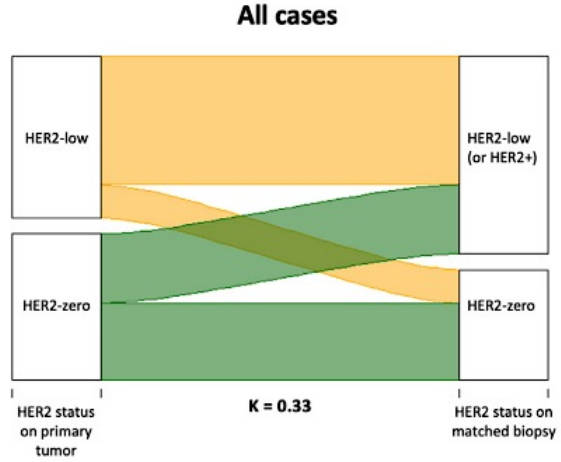


High inter-observer variability in calling HER2-Low.
Not seen in calling HER2 3+

Nielsen K et al, Breast Cancer Res 2023; Fernandez A et al, JAMA Oncol 2022

HER2-Low as a Biomarker: Sources of Heterogeneity

- **Analytic (fixation, Ag retrieval…)**
- **Histologic and spatial heterogeneity**
- **Primary / metastasis variation (38%)**
- **Others…**



Given these considerations, HER2-low disease, as currently defined, should not be considered a distinct molecular entity, but rather a heterogeneous group of tumors, with biology primarily driven by hormone receptor expression.

Level of consensus: 94% (n = 30) agree, 6% (n = 2) disagree, (n = 0) abstain.

2023 ESMO Expert Consensus Statement

Miglietta F et al, NPJ Breast 2021; Tarantino P et al, Eur J Cancer 2022; Tarantino et al, Ann Oncol 2023

Training for HER2-Low Interpretation

787 tumors from MBC patients rescored locally <u>after formal retraining in reading low-level HER2 immunostains (2018 ASCO/CAP).</u>

- **13 labs, 10 countries, multiple Abs (Ventana 4B5, HercepTest, Bond Oracle HER2,…)**

= 67% HER2-Low (no difference among IHC antibodies)

- ***71% HR+, 53% HR-***
- ***68% primary, 67% metastasis***

~ 80% concordance between original and rescore.

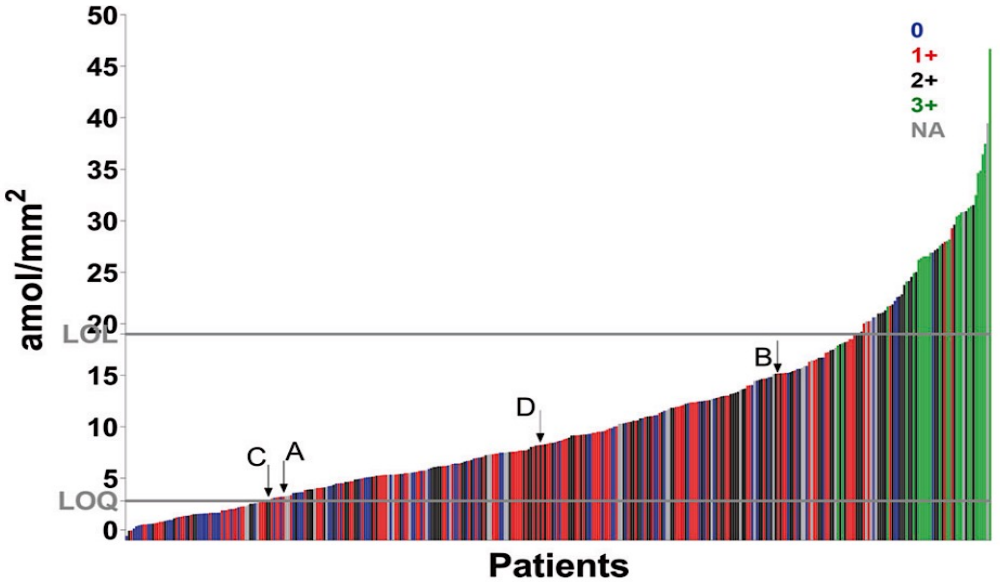
30% rescored from HER2-0 to -low (< 10% rescored from HER2-Low to -0)

Among 74 pathologists across the globe

HER2-0 concordance ↑ from 75% to 89% after 4h training

Viale G et al, JCO 2023; Ruschoff J et al, AACR 2023

Novel Quantitative Approaches Are Coming…



HER2 grade	Concordance of all pathologists	
	without AI	with AI
0	48.0% (12/25)	77.8% (21/27)
1+	25.7% (9/35)	68.9% (42/61)
2+	45.8% (44/96)	68.8% (55/80)
3+	71.7% (38/53)	92.7% (38/41)
All	49.3% (103/209)	74.6% (156/209)

Newer methods
e.g. AQUA – quantitative fluorescence
↑ discrimination in lower HER2 expression

And/Or: Machine learning-based image analysis to reduce interobserver variability

Moutafi M et al, Lab Invest 2022; Jung M et al, ASCO 2022

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Summary

- **Little evidence that HER2-Low represents a biologically distinct entity, but (despite CAP skepticism) it is clinically actionable**
- ***Any HER2-Low test result counts!***
- **Conventional IHC definition is improving but may be suboptimal for technical and biologic reasons.**
- **Newer methodologies may provide more clinical validity and utility; HER2 threshold for clinical activity of HER2-directed ADCs currently unknown.**

Agenda

Module 1: Optimal Approaches to HER2 Testing for the Identification of HER2-Low Breast Cancer — Dr Carey

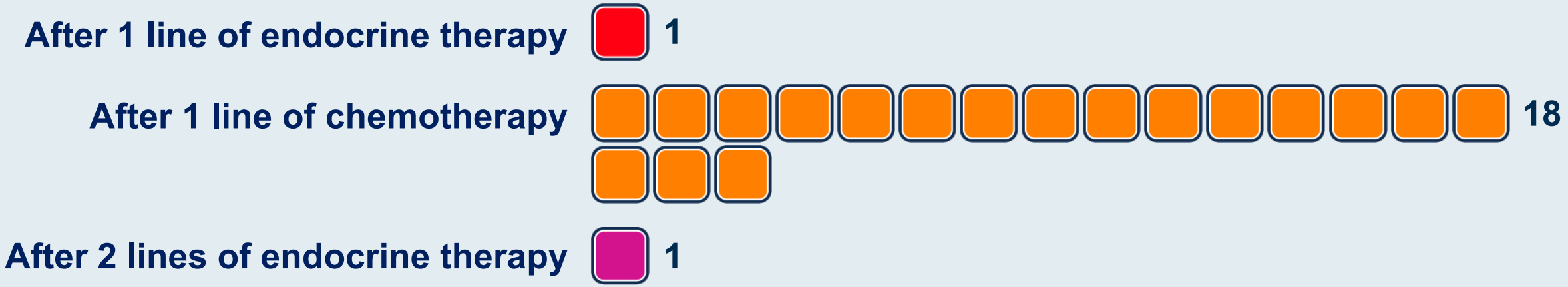
Module 2: Available Data with and Current Role of HER2-Targeted Therapy for HER2-Low Disease — Dr Modi

Module 3: Identification and Management of Toxicities with Trastuzumab Deruxtecan — Prof Schmid

Module 4: Future Directions in the Management of HER2-Low Breast Cancer — Dr Bardia

Regulatory and reimbursement issues aside, for a patient with metastatic breast cancer, at what point would you like to use trastuzumab deruxtecan?

ER-Positive **HER2-Low**

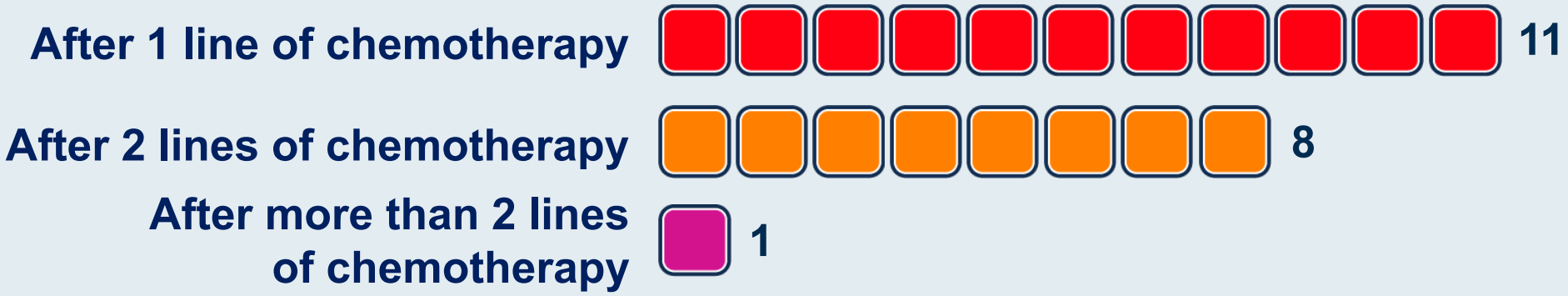


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, for a patient with metastatic breast cancer, at what point would you like to use trastuzumab deruxtecan?

ER-Negative **HER2-Low**



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

How do you generally sequence the following agents for a patient with HER2-low metastatic breast cancer who is eligible to receive both?

ER-Positive

Trastuzumab deruxtecan → sacituzumab govitecan

19

Sacituzumab govitecan → trastuzumab deruxtecan

1

ER-Negative

Sacituzumab govitecan → trastuzumab deruxtecan

18

Trastuzumab deruxtecan → sacituzumab govitecan

2

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

What is your global view on the antitumor efficacy of trastuzumab deruxtecan in patients with HER2-low breast cancer? (Eg, approximate proportion of patients who experience a clinical response; general duration of response)

- 75% respond; duration 6-12 months (in my practice)
- 3/4 of patients will either have a response or a PFS >6 months
- Most pts respond -- probably around two-thirds -- but duration is relatively short at 5-6 months (all pts would be pretreated with 1-2 lines of chemotherapy for MBC)
- 60% response rate, 10-12 month PFS
- Approximately half of the patients respond, duration is generally short (4-5 months)
- 40% response, duration of response 5-6 months
- 30-40% with partial/complete response; duration 8-10 months
- About 30-40% experience a response. In clinic I am not seeing the very long duration of responses in many patients
- Much better than chemotherapy, duration longer than just 2 months
- Hard to know, I usually give sacituzumab first and most rapid relapsing patients with TNBC are HER2 IHC 0
- Depends on prior lines of chemotherapy but response rate in 2L setting would be around 35% with median duration 4-6 months

Survey of 20 US-based clinical investigators November 2023

Integration of antibody-drug conjugates in the management of recurrent metastatic HER2-low breast cancer

Priyanka Sharma, MD

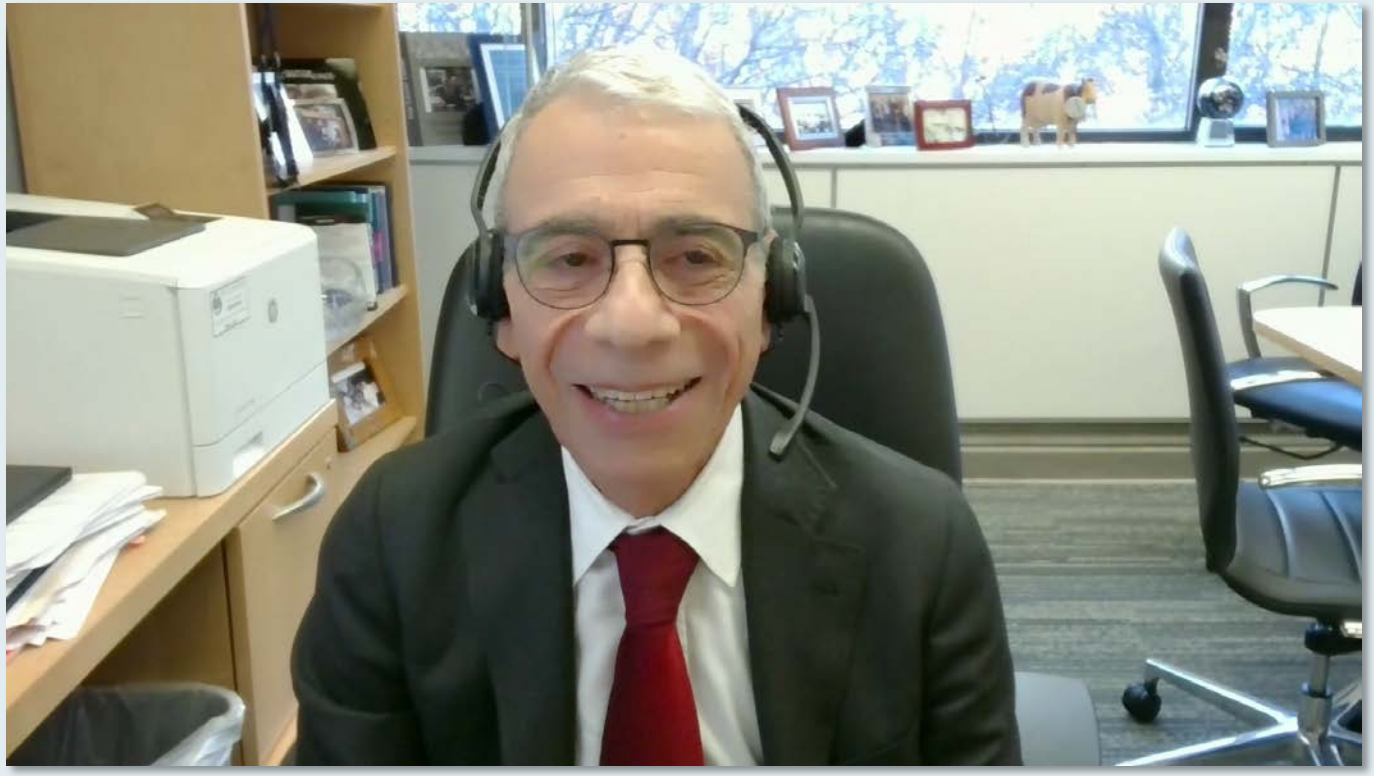
RTP
RESEARCH
TO PRACTICE

Sequencing therapy for recurrent metastatic triple-negative breast cancer

Adam M Brufsky, MD, PhD

RTP
RESEARCH
TO PRACTICE

Therapy options for patients with HER2-low metastatic breast cancer after capecitabine



Eric P Winer, MD

RTP
RESEARCH
TO PRACTICE

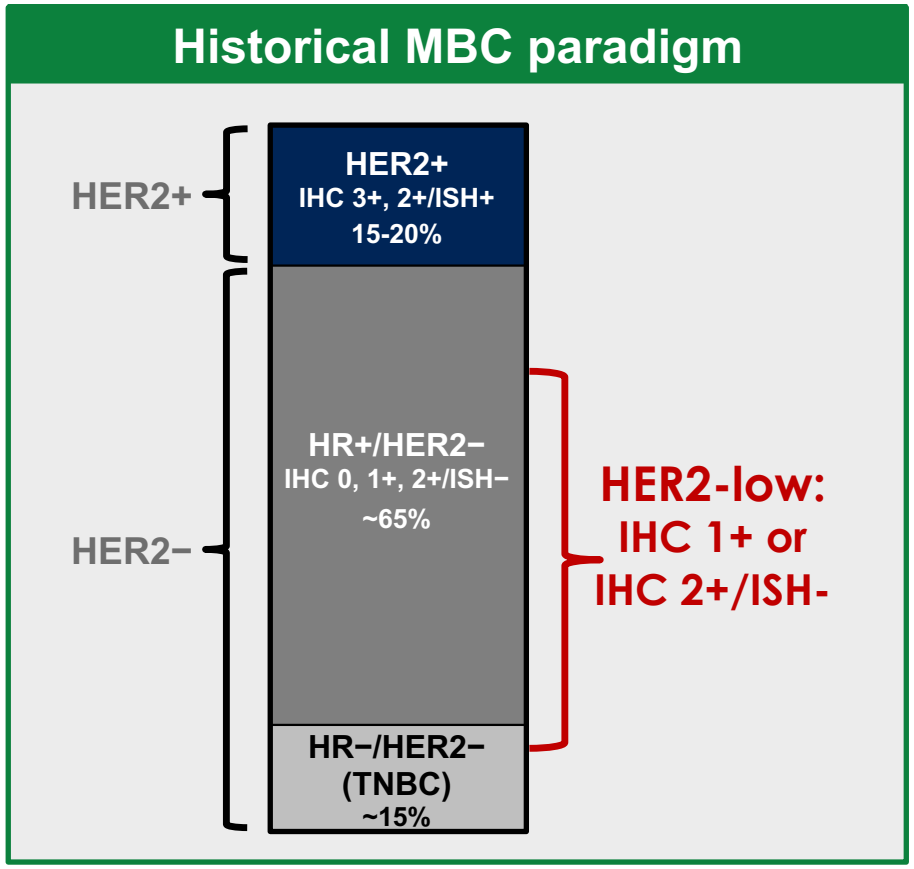
HER2 Targeted Therapy for HER2 LOW MBC

Shanu Modi, MD
Attending, Section Head HER2 Breast Program

Memorial Sloan Kettering Cancer Center

Dec 7, 2023

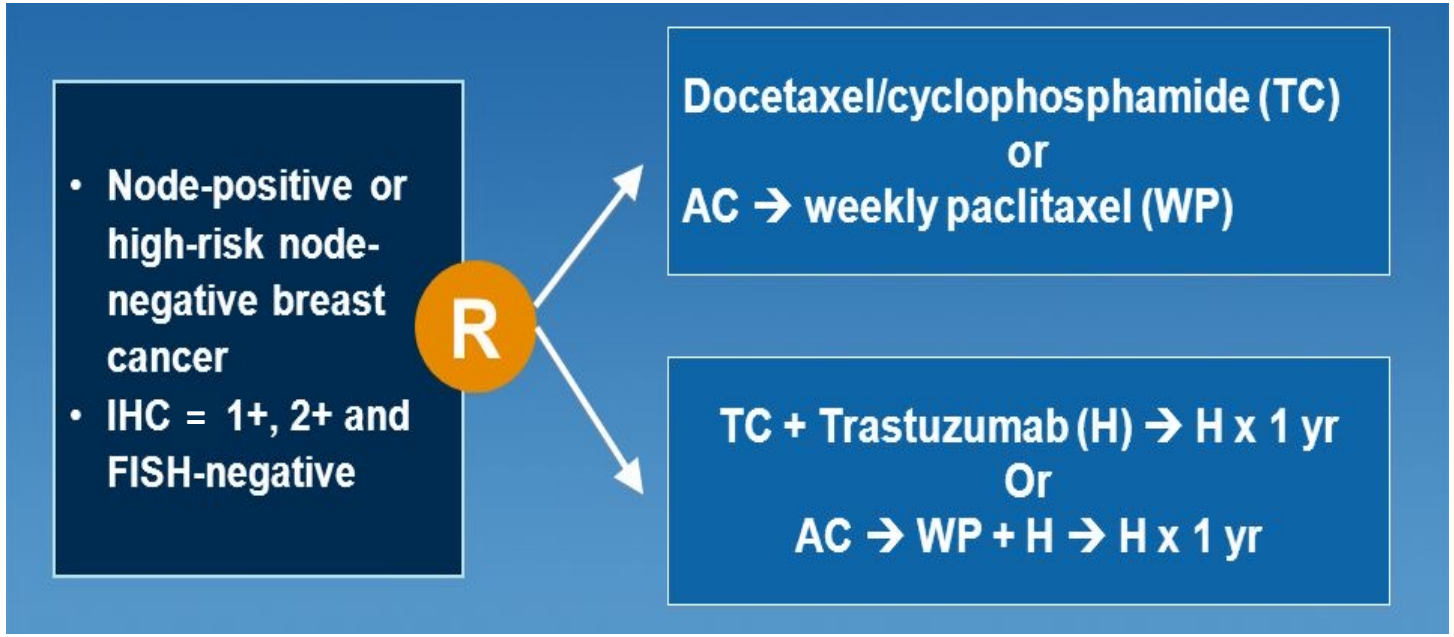
HER2 Expressing Breast Cancer: Positive, Negative, and HER2-Low



Aogi K, et al. *Ann Oncol*. 2012;23:1441-8.; Eiger D, et al. *Cancers (Basel)*. 2021;13(5):1015. ; Fehrenbacher L, et al. *J Clin Oncol*. 2019;38(5):444-453.; Mo H, et al. *Clin Breast Cancer*. 2022;22:143-8. ; Kaufman et al. *J Clin Oncol*. 2015;33:594-601.; Schettini F, et al. *NPJ Breast Cancer*. 2021;4;7(1):1.; Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-19622.;

NSABP B-47

A phase 3 trial was conducted to understand if adjuvant trastuzumab was beneficial for patients with HER2-low breast cancer

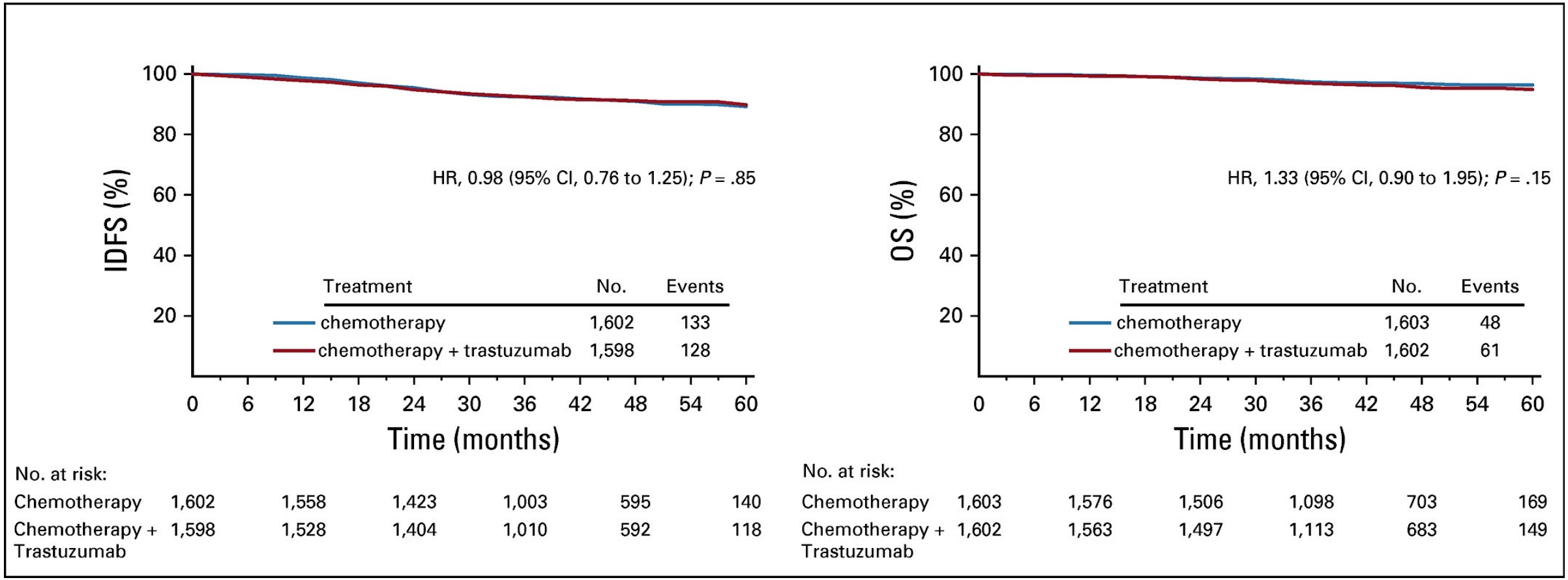


3,270 HER2-low EBC patients randomized

- 57% HER2 1+, 43% HER2 2+
- 20% N-, 80% N+
- 17% TNBC, 83% HR+
- 56% received AC-T, 44% received TC

Fehrenbacher L, et al. *J Clin Oncol.* 2020;38(5):444-453.

NSABP B-47: Efficacy Results



NO BENEFIT of adjuvant trastuzumab for HER2-low Breast Cancer

Fehrenbacher L, et al. *J Clin Oncol.* 2020;38(5):444-453.

Pertuzumab for HER2-low MBC

Similar results were observed in the metastatic setting

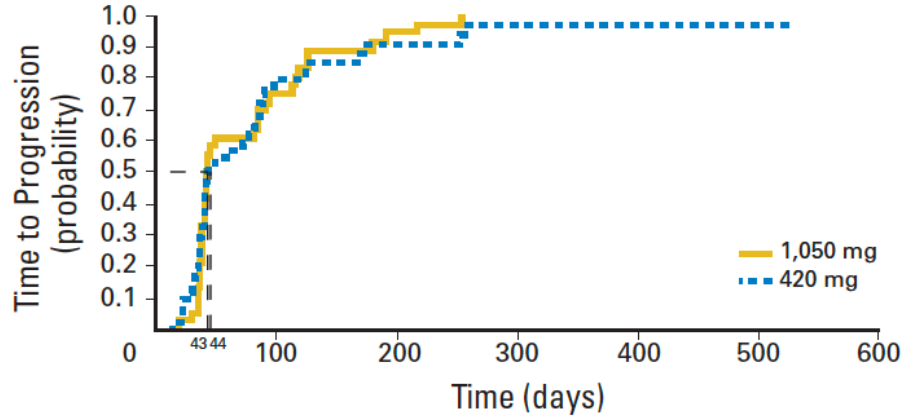
In a population of largely (90%) **HER2-low MBC** patients, treatment with **pertuzumab** led to an ORR of 4.9% and a median time to progression of 1.5 months

NO CLINICAL BENEFIT WITH THE BLOCKADE OF THE HER2 PATHWAY IN HER2-LOW BREAST CANCER

Table 2. Efficacy End Points (N = 78)

Variable	Arm A (n = 41) No.	Arm A (n = 41) %	Arm B (n = 37) No.	Arm B (n = 37) %
PR	2	4.9	0	
SD ≥ 12 weeks	18	43.9	14	37.8
SD ≥ 24 weeks	2	4.9	2	5.4
Progressive disease	21	51.2	22	59.5
Missing	0		1	2.7
Clinical benefit (CR + PR + SD ≥ 24 weeks)	4	9.8	2	5.4
Duration of clinical benefit, weeks				
Median	36.5		33.6	
Range	22.1-74.9		31.0-36.3	
Time to progression, weeks				
Median	6.1		6.1	
Range	2.0-37.0		2.7-36.3	

Abbreviations: PR, partial response; SD, stable disease; CR, complete response.



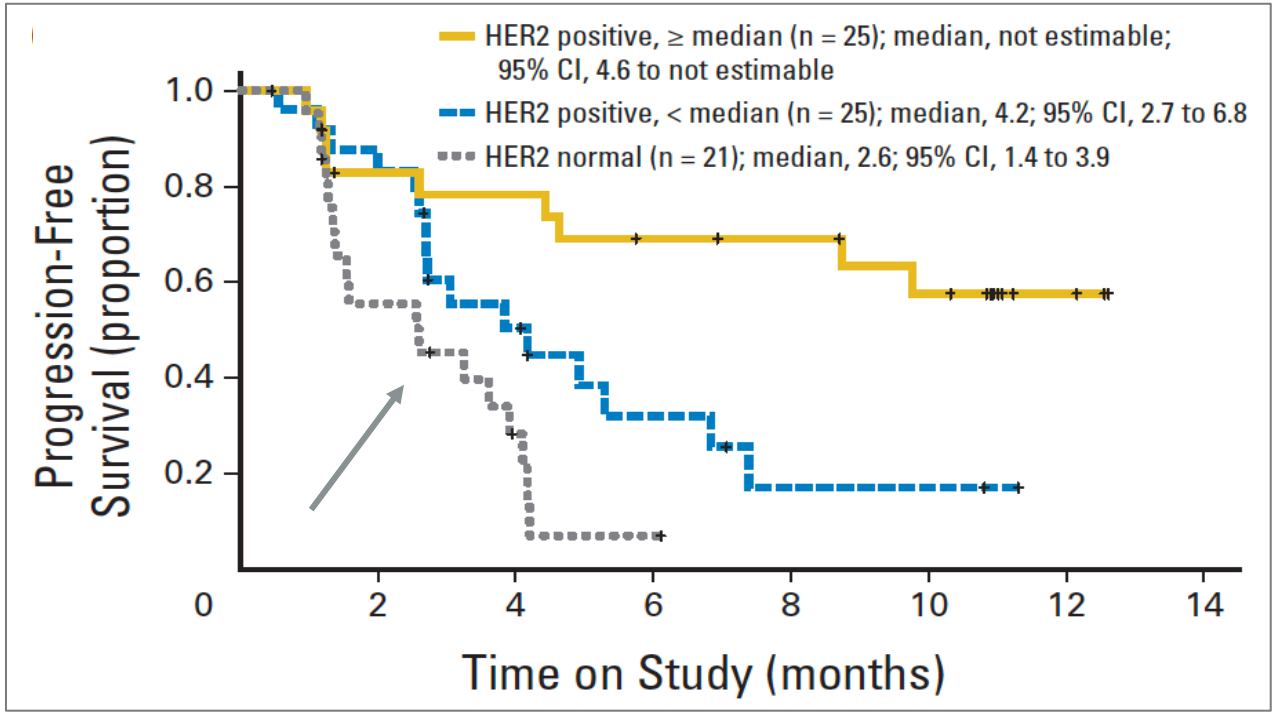
Gianni L et al. *J Clin Oncol.* 2010;28(7):1131-1137.

T-DM1 for HER2-low MBC

Retrospective evaluation of T-DM1 in 21 cases of HER2-non-amplified MBC

Only 1 response (ORR 4.8%) and mPFS 2.6 months

LITTLE ACTIVITY OF T-DM1 IN HER2-NEGATIVE mBC



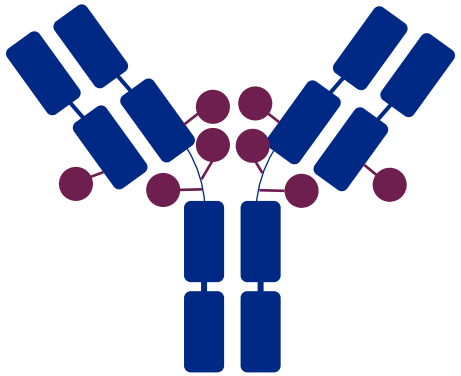
Burris HA, et al. *J Clin Oncol.* 2011;29(4):398–405.

Trastuzumab Deruxtecan (T-DXd): Next Generation HER2 ADC

Characteristic Differences Between T-DXd and T-DM1

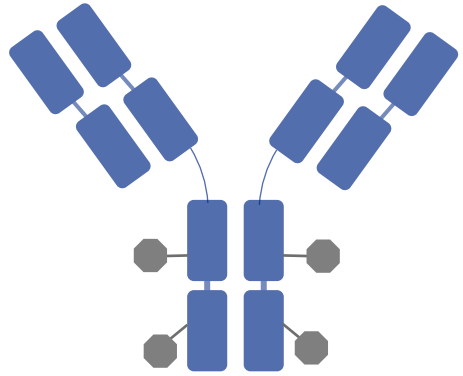
HER2 Targeting ADCs with similar mAB Backbone

Trastuzumab deruxtecan (T-DXd)



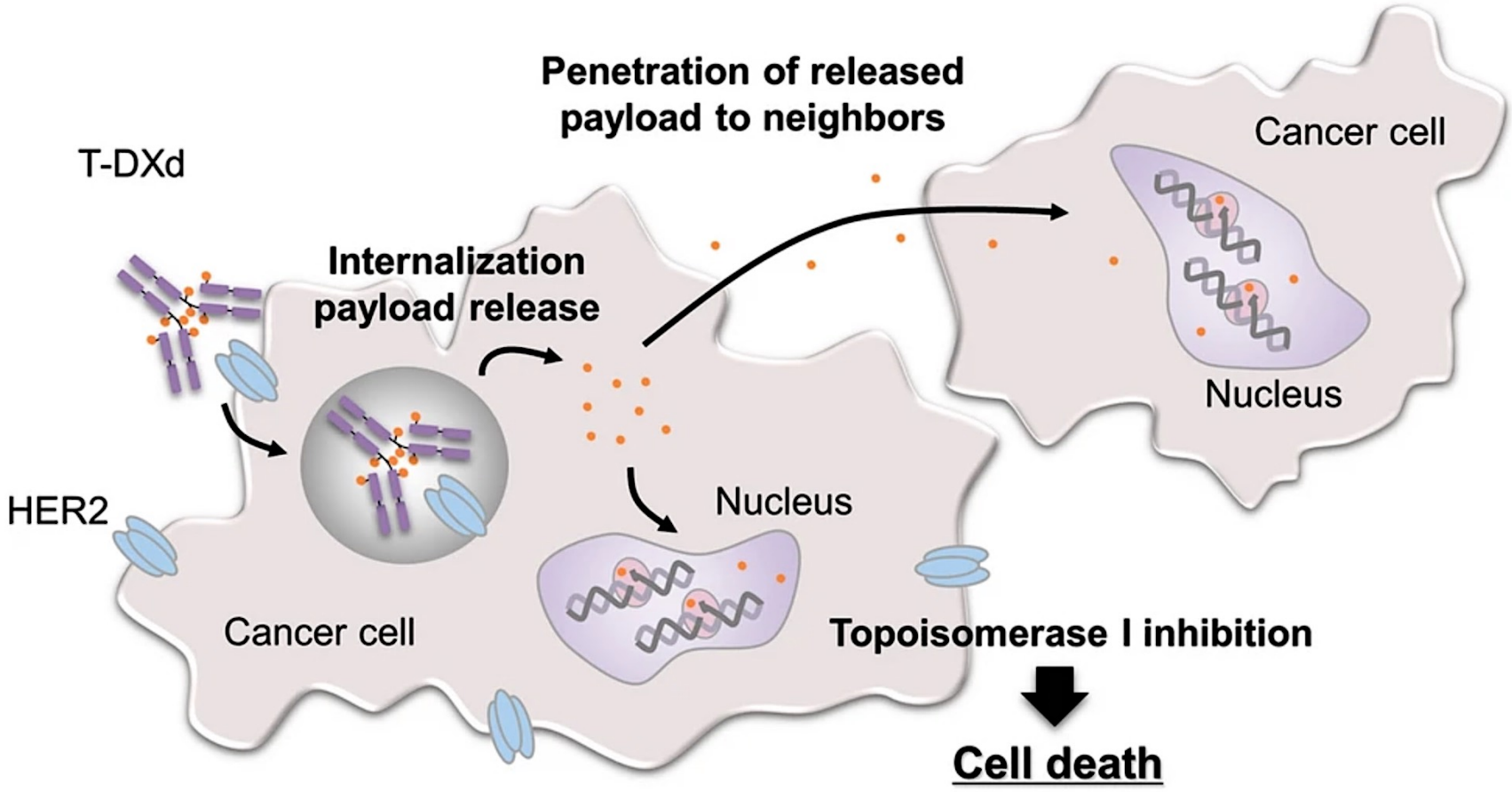
T-DXd	ADC Attributes	T-DM1
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)



1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42.
4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

T-DXd: Bystander Effect and Rationale for Targeting HER2 Heterogeneity

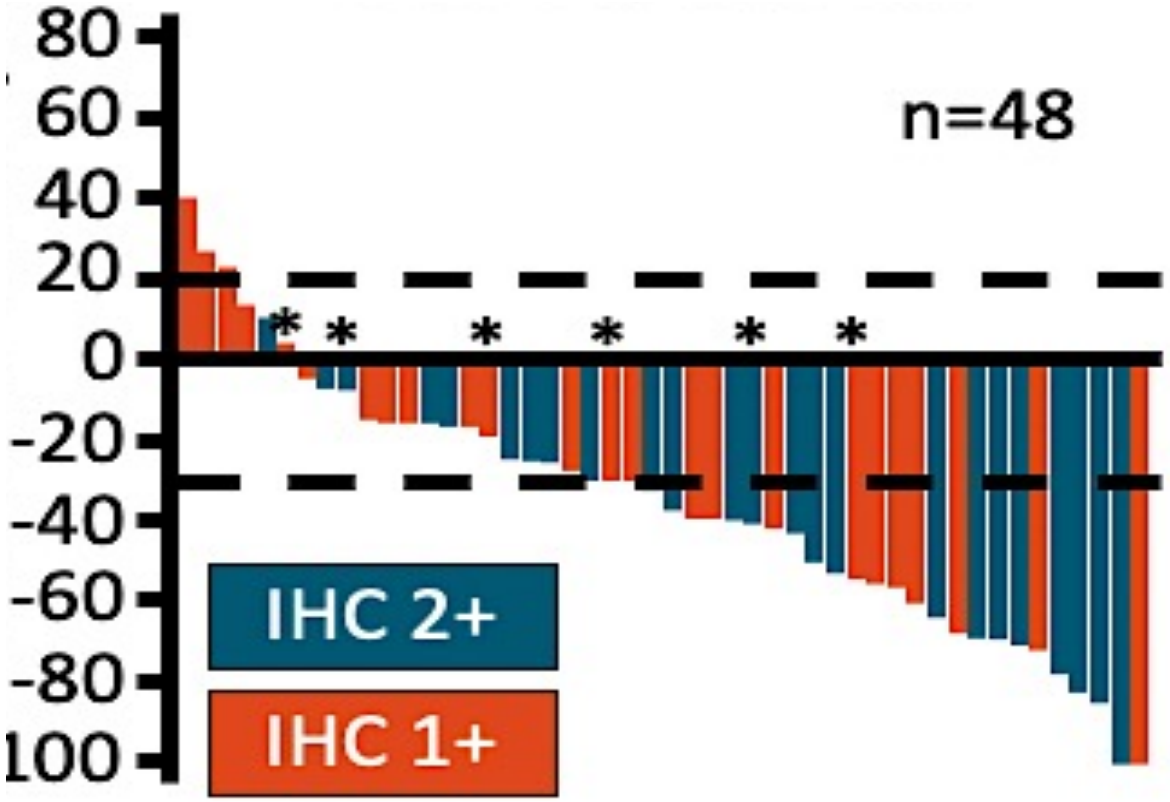


Antibody–drug conjugate functional mechanism and bystander antitumor effect of trastuzumab deruxtecan. *T-DXd* trastuzumab deruxtecan; *HER2* human epidermal growth factor receptor 2

Shitara K et al. *Gastric Cancer* 2021;24(4):780-89.

T-DXd in HER2-Low MBC: Robust and Durable Antitumor Activity

Phase 1 Trial



- Heavily pretreated HER2 Low MBC
- Median prior lines: 7.5
- ORR = 37%
- mDOR = 10.4 mo
- mPFS = 11 mo

Modi S, JCO. 2020;38:1887.

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

An open-label, multicenter study (NCT03734029)

- Centrally HER2 Low MBC (IHC 1+ or IHC 2+/ISH−)
- 1-2 prior lines of chemo or relapse <6mo of adj CTx
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

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

BICR, blinded independent central review; CDK, cyclin-dependent kinase; 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 three weeks; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system. [c]TPC was administered accordingly to the label. [d]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint.

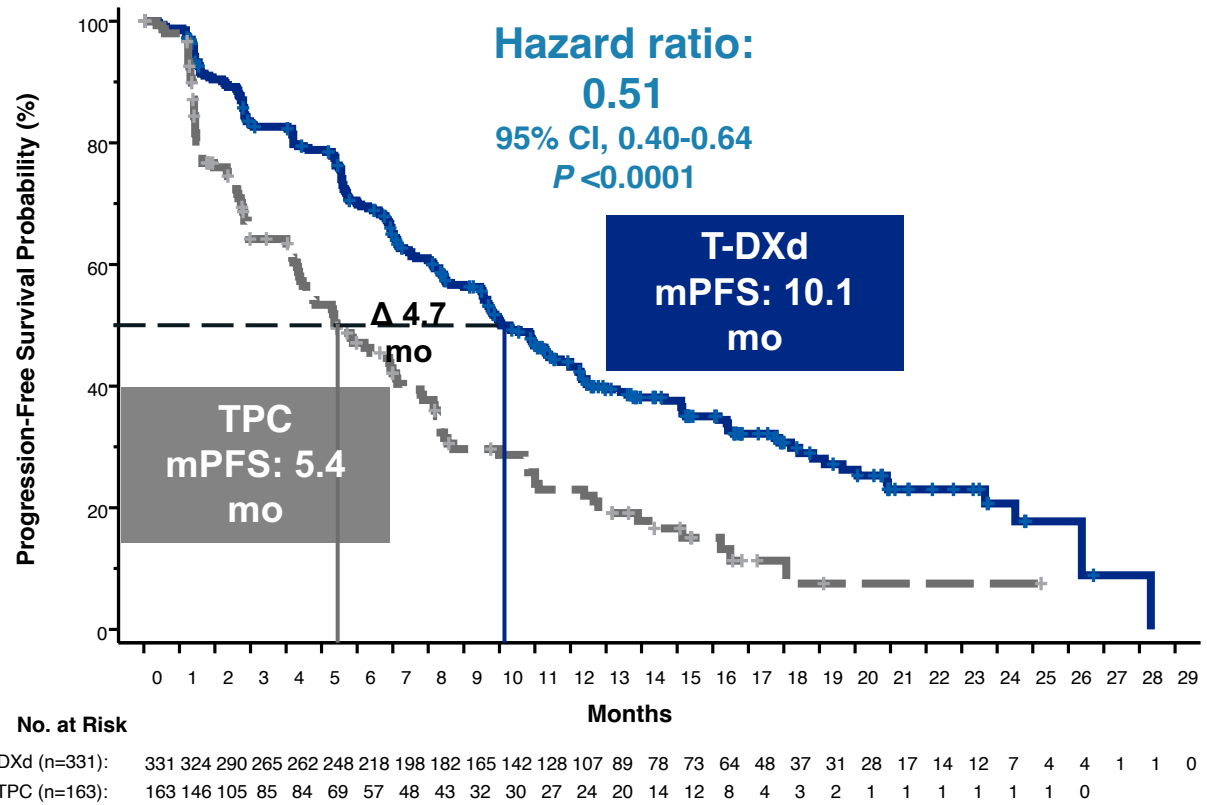
Modi S, et al. N Engl J Med. 2022 Jul 7;387(1):9-20.

DB-04: Prior Therapies

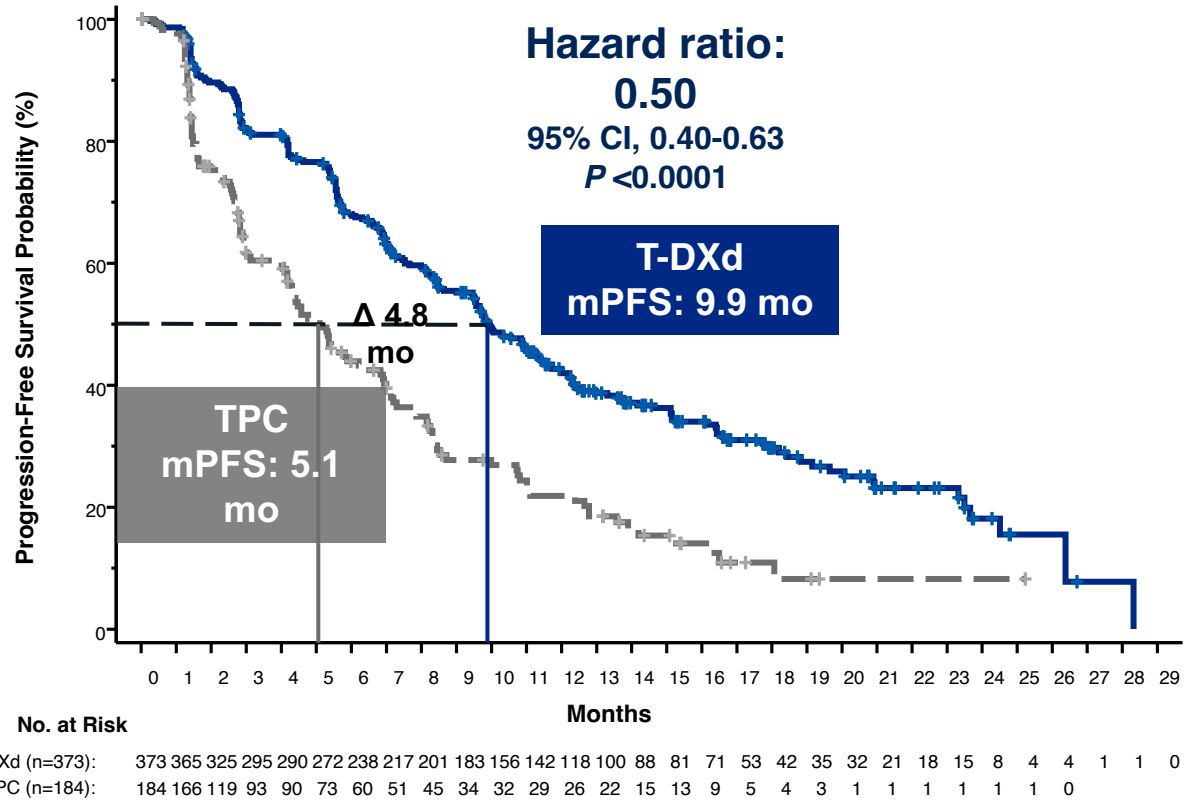
	Hormone receptor-positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Median number of lines (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Median number of lines (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Median number of lines (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)

DB-04 Primary Analysis: PFS in HR+ and All Patients

Hormone receptor-positive



All patients

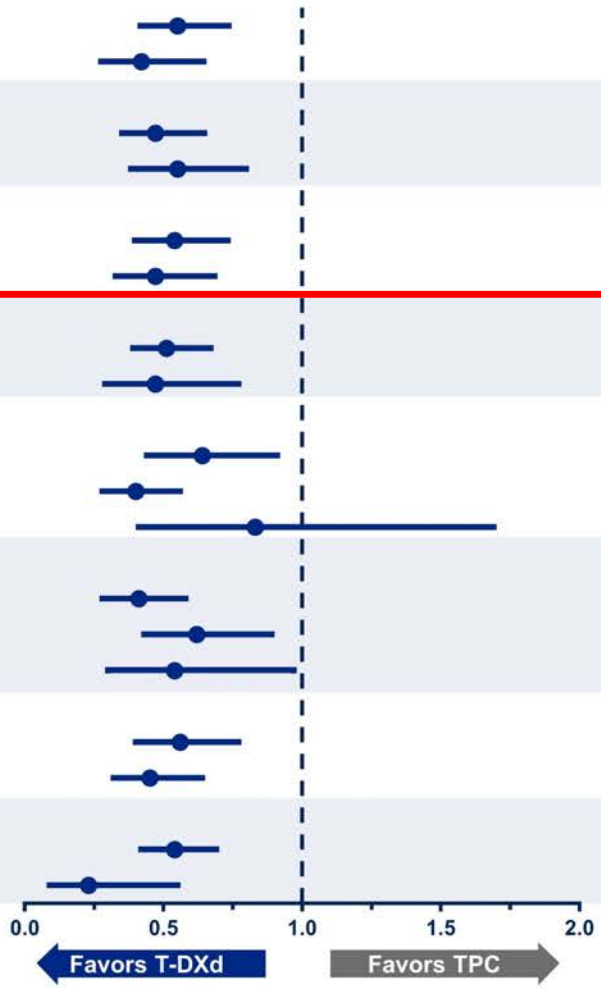


PFS by blinded independent central review.
HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi S, et al. N Engl J Med. 2022 Jul 7;387(1):9-20.

DB-04 Subgroup Analysis: PFS in HR+ HER2-low MBC

	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)



PFS by blinded independent central review. Based on derived data, which include protocol deviations.

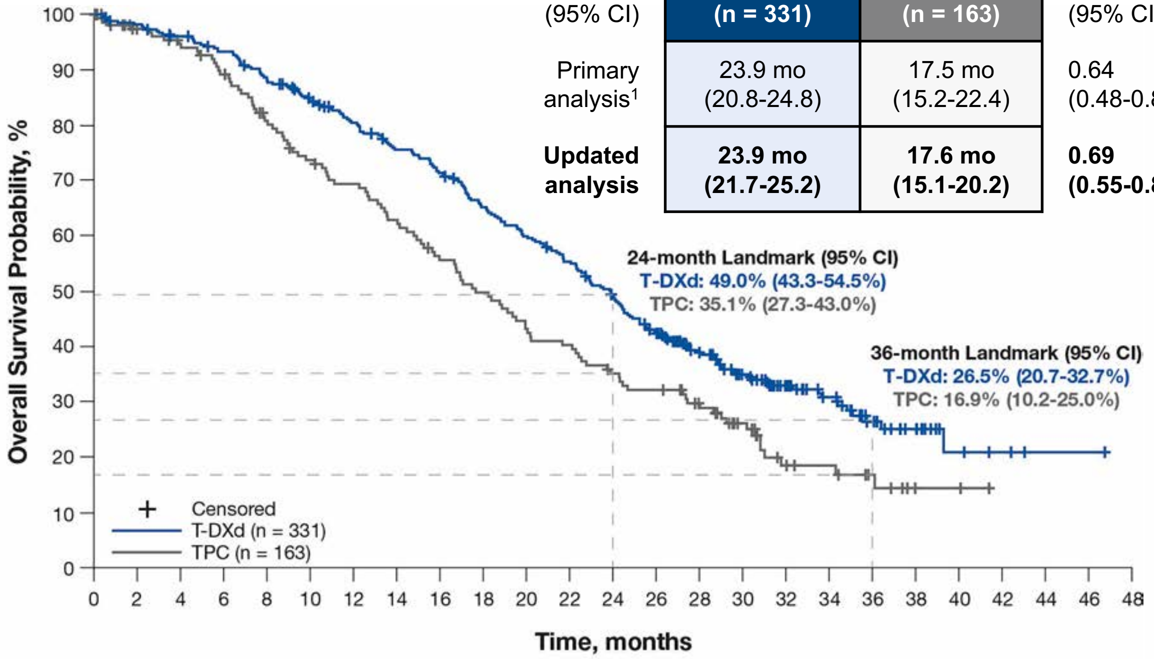
CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi S et al., N Engl J Med 2022; 387:9-20, DOI: 10.1056/NEJMoa2203690

DB-04: Updated Overall Survival (med 32 mo f/u)

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



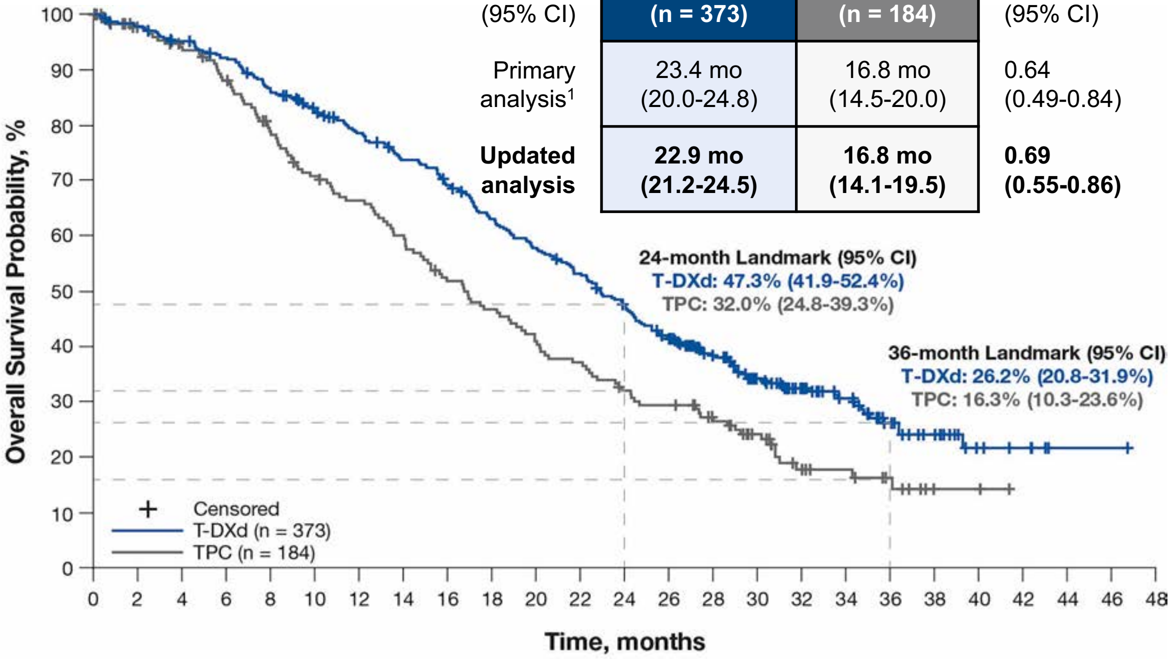
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

HR, hormone receptor; mo, month; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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

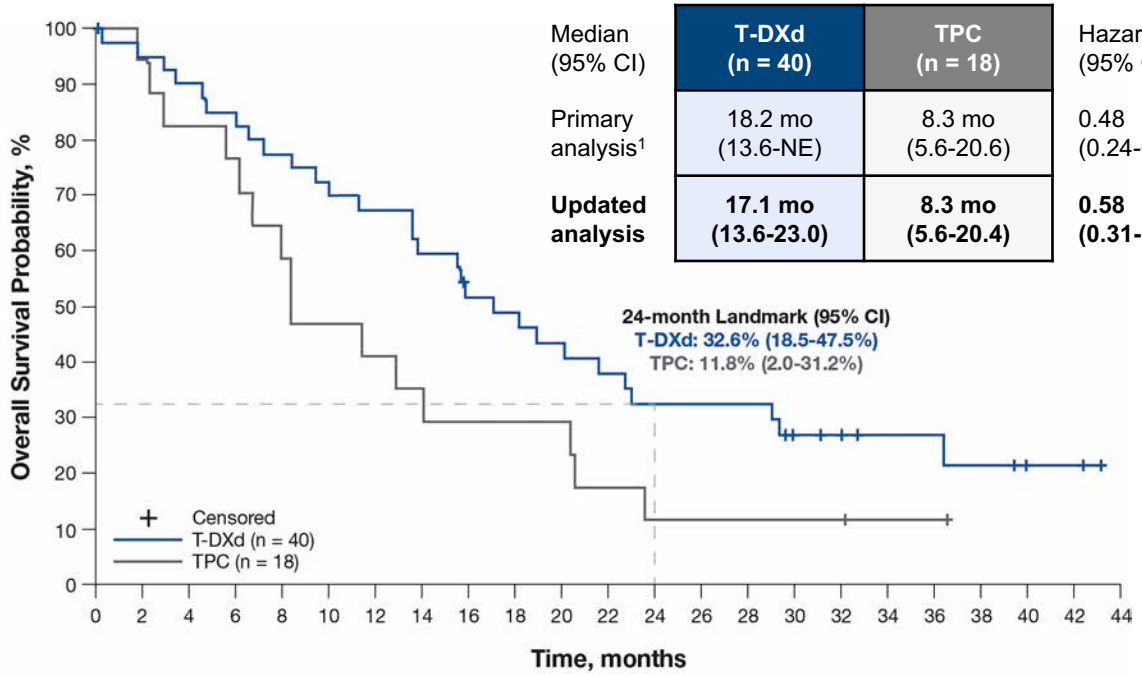
Modi S, ESMO 2023

Updated Efficacy in the HR− Cohort (Exploratory Analyses)

Med 32 mo followup

Overall Survival

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**



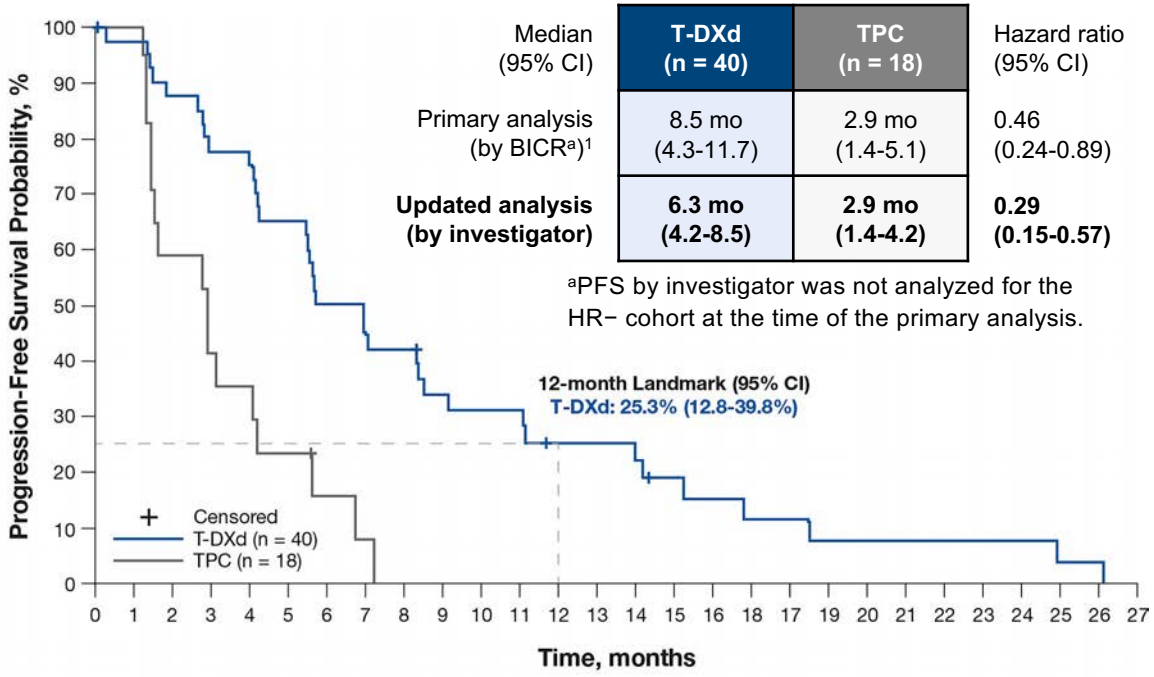
Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.



Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

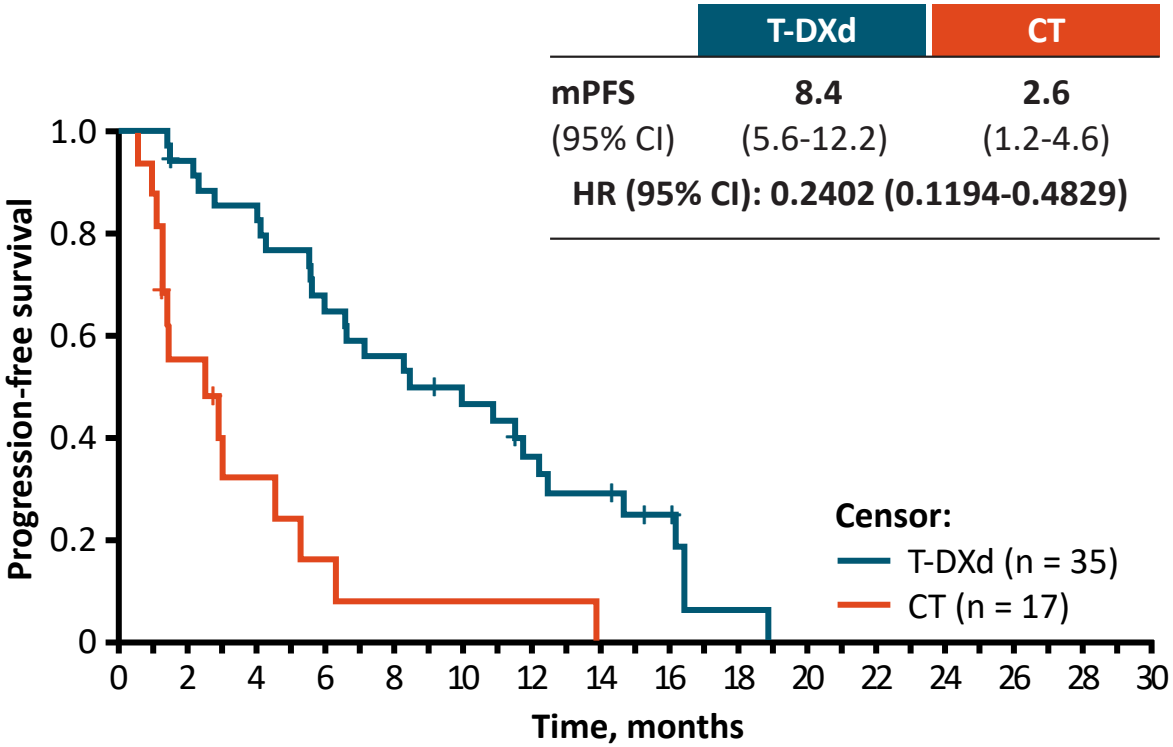
- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

BICR, blinded independent central review; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

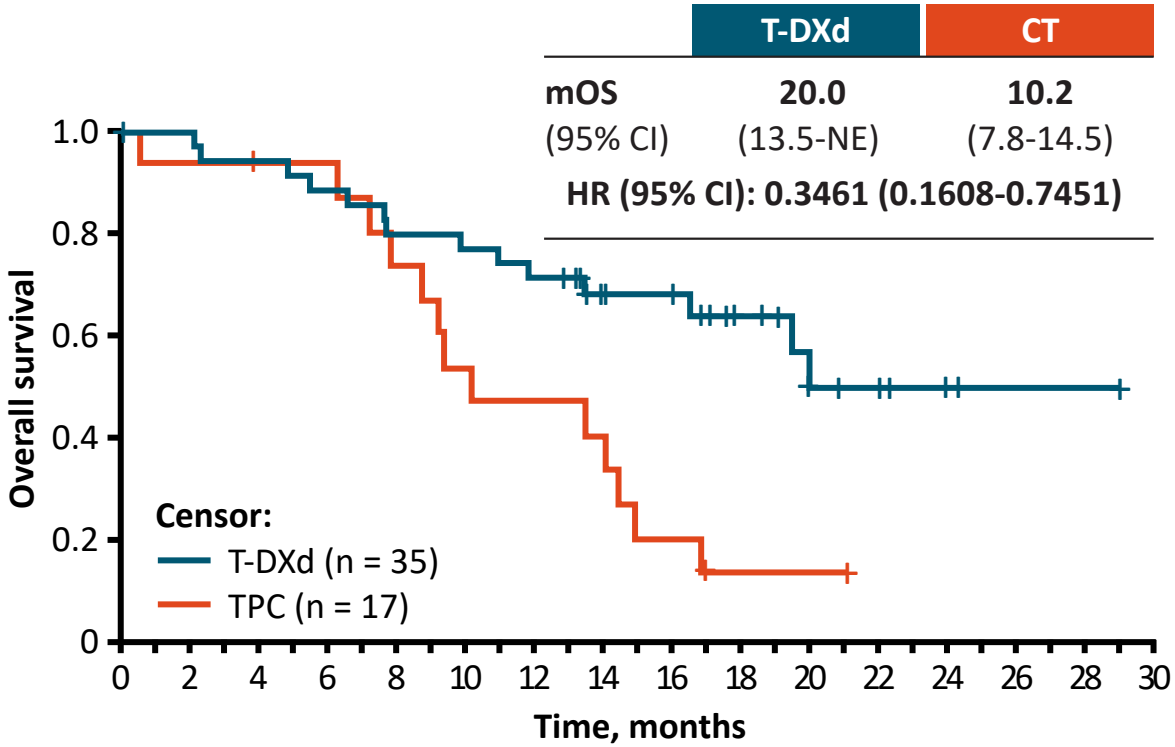
1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

DB-04: Exploratory Efficacy in ER-Low Cohort (IHC: 1-10%)

Progression Free Survival



Overall Survival



T-DXd significantly improved PFS and OS compared with CT in patients with ER-low advanced BC

Cameron. ESMO 2023. Abstr 192MO.

DB-04: PFS2 and Post-Study Anticancer Therapies

	HR+ Cohort		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median PFS2 by investigator, mo (95% CI)	15.5 (13.8-17.2)	10.5 (8.3-11.4)	15.4 (13.6-16.5)	9.7 (8.3-10.8)
Hazard ratio (95% CI)	0.51 (0.40-0.64)		0.51 (0.41-0.64)	
Post-study anticancer therapies				
Systemic treatment, n (%)	247 (74.6)	126 (77.3)	282 (75.6)	144 (78.3)
Targeted therapy[c]	119 (36.0)	70 (42.9)	134 (35.9)	75 (40.8)
CDK4/6 inhibitors	47 (14.2)	27 (16.6)	48 (12.9)	27 (14.7)
ADC	**16 (4.8)**	**15 (9.2)**	**18 (4.8)**	**15 (8.2)**
T-DXd	2 (0.6)	4 (2.5)	2 (0.5)	4 (2.2)
Sacituzumab govitecan	9 (2.7)	5 (3.1)	11 (2.9)	5 (2.7)
Endocrine therapy	102 (30.8)	56 (34.4)	103 (27.6)	57 (31.0)
Chemotherapy	222 (67.1)	109 (66.9)	257 (68.9)	126 (68.5)
Radiation, n (%)	32 (9.7)	25 (15.3)	37 (9.9)	29 (15.8)
Surgery, n (%)	3 (0.9)	1 (0.6)	5 (1.3)	1 (0.5)

ADC, antibody drug conjugate; CDK, cyclin-dependent kinase; HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Defined as the time from date of randomization to the first documented progression per investigator assessment on next-line of systemic therapy or death due to any cause, whichever occurs first.
[b]Participants may have been treated with more than 1 type of post-study anticancer therapy. [c]Class includes CDK4/6 inhibitor, immunotherapy, antibody drug conjugates, or no subclass specified.

Modi S, ESMO 2023

DESTINY-Breast04: Summary and Impact

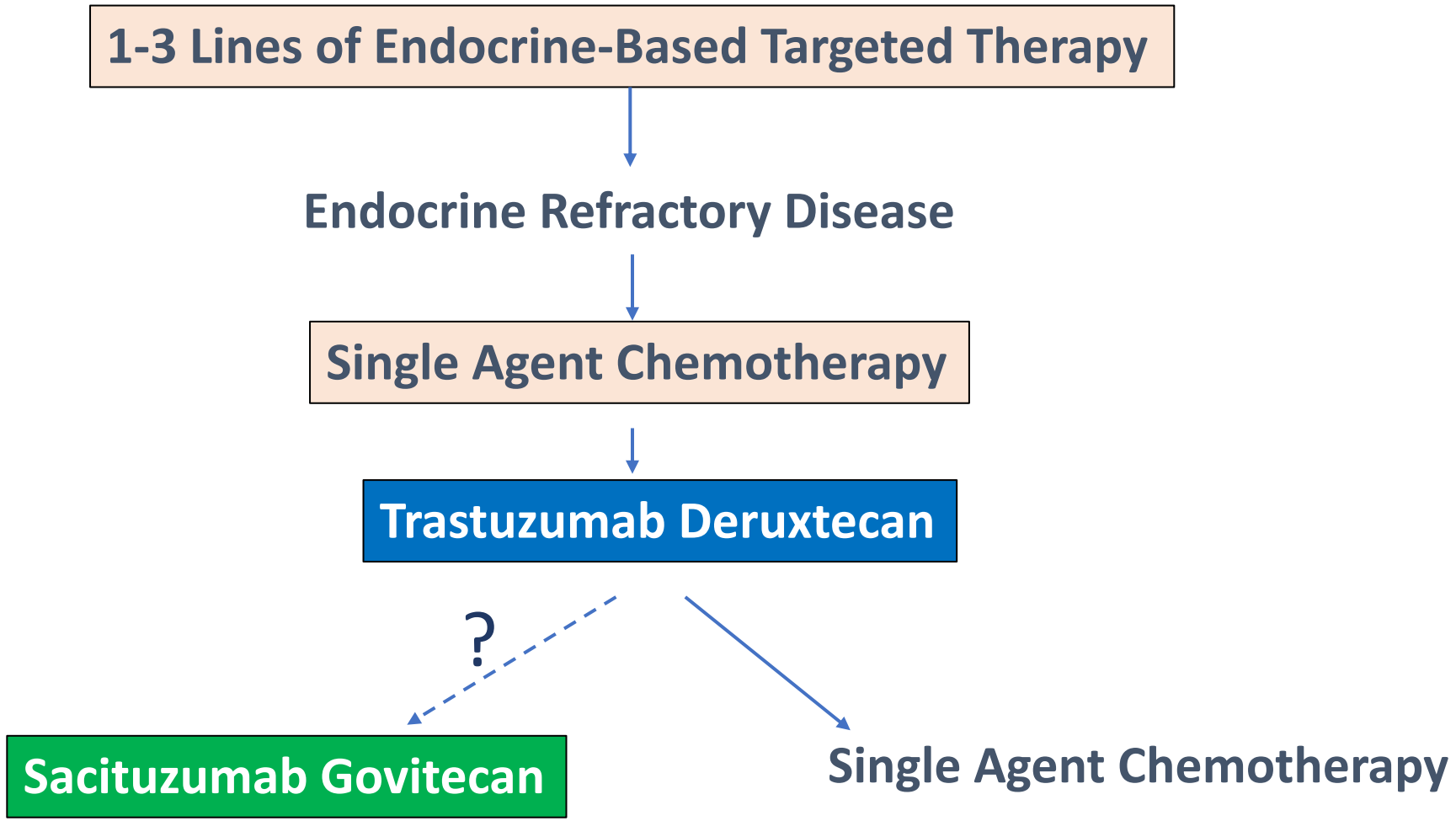
The new mBC paradigm

- T-DXd is the first HER2-targeted therapy to demonstrate improved efficacy in HER2-low MBC
- DESTINY-Breast04 establishes T-DXd as the new standard of care for HER2-low MBC
- Potential improvement for ~50% of all patients with MBC in this setting

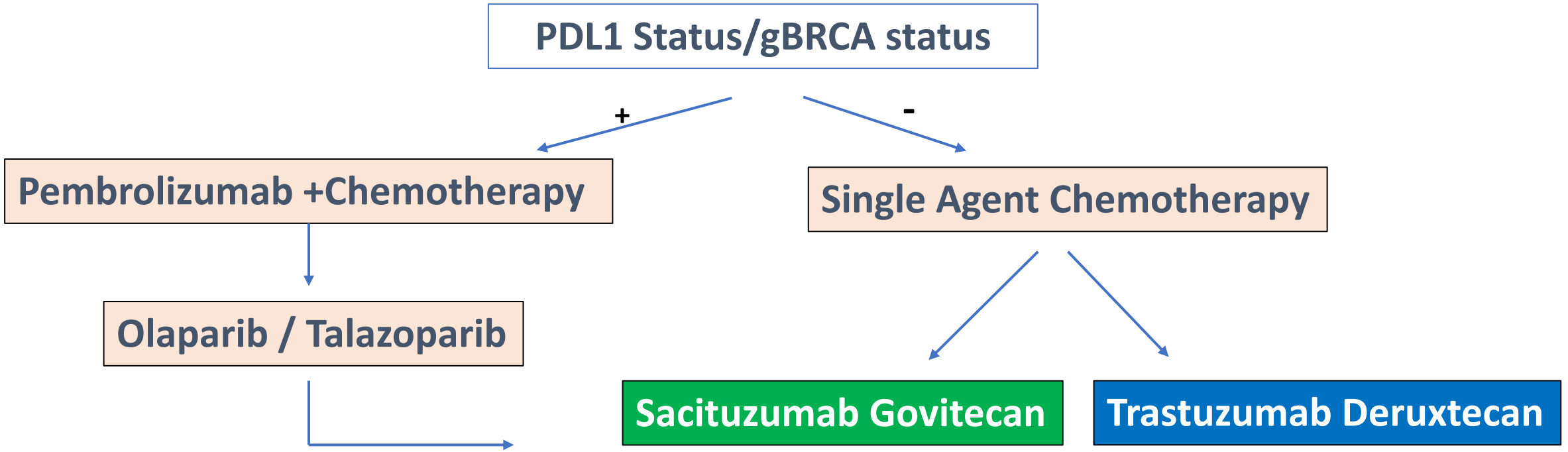
- **The FDA approved T-DXd for patients with unresectable or metastatic HER2-low BC who have received a prior CT in the metastatic setting or developed disease recurrence ≤6 mo of completing adjuvant CT.**
- **Endorsed by the International and NCCN Guidelines**

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022;387:9.

Approach to Sequencing Therapy in HR+ HER2 Low MBC



Approach to Sequencing Therapy in HR- HER2 Low MBC



- Both OS benefit
- T-DXd smaller cohort experience
- Toxicity profile & Patient characteristics to individualize Rx

Agenda

Module 1: Optimal Approaches to HER2 Testing for the Identification of HER2-Low Breast Cancer — Dr Carey

Module 2: Available Data with and Current Role of HER2-Targeted Therapy for HER2-Low Disease — Dr Modi

Module 3: Identification and Management of Toxicities with Trastuzumab Deruxtecan — Prof Schmid

Module 4: Future Directions in the Management of HER2-Low Breast Cancer — Dr Bardia

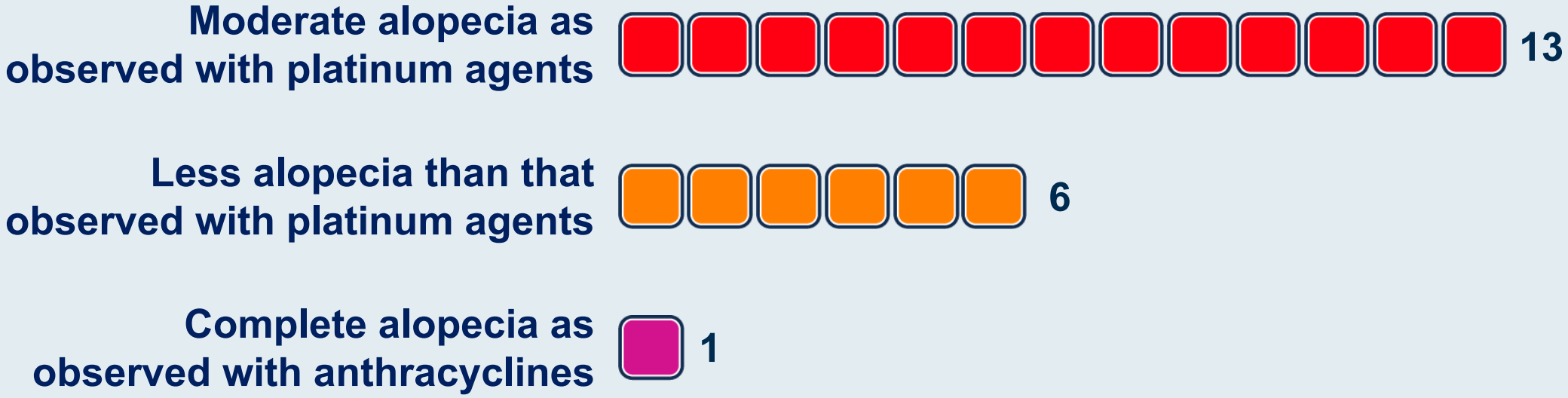
Have you readministered or would you readminister trastuzumab deruxtecan to a patient who developed Grade 2 interstitial lung disease (ILD)?

What grade of ILD would lead you to permanently discontinue treatment with trastuzumab deruxtecan?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

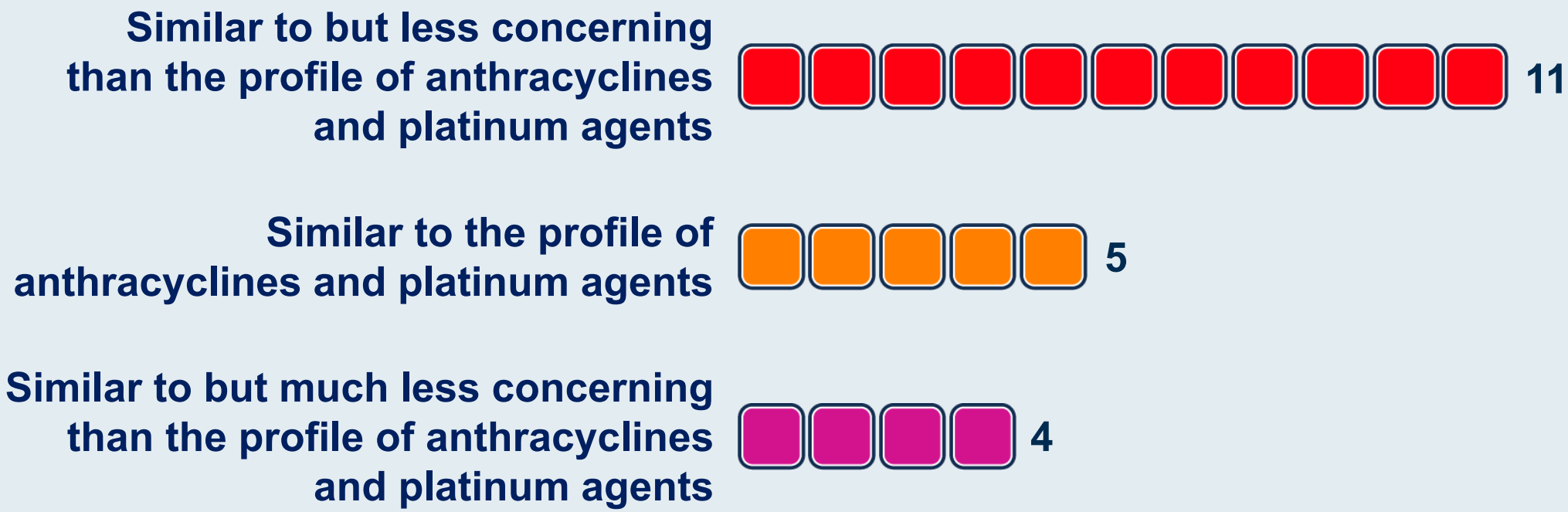
How would you characterize the degree of alopecia observed with trastuzumab deruxtecan?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

How would you describe the “chemotherapy-like” side-effect profile (fatigue, GI symptoms) of trastuzumab deruxtecan?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

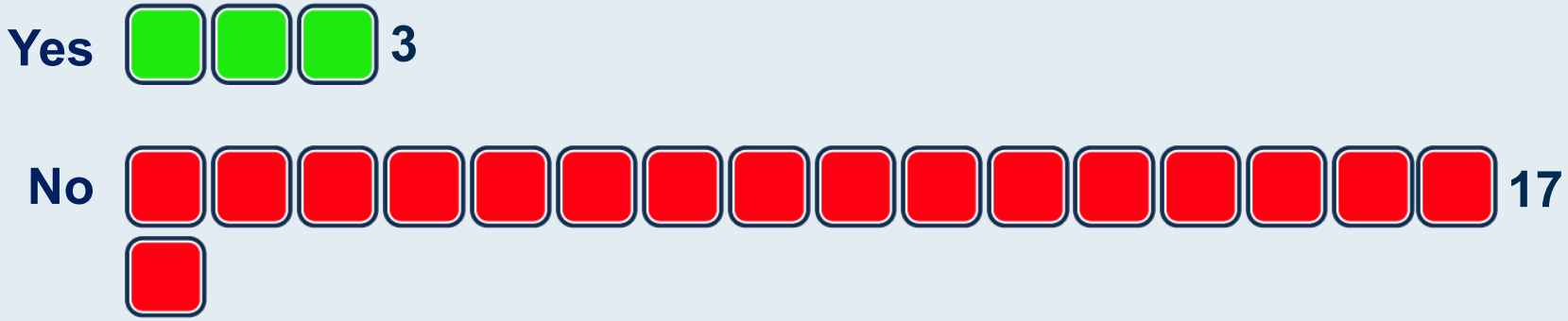
Do you use chest imaging to monitor a patient receiving trastuzumab deruxtecan who otherwise does not require chest imaging?

How often would you order imaging if the patient remained asymptomatic?

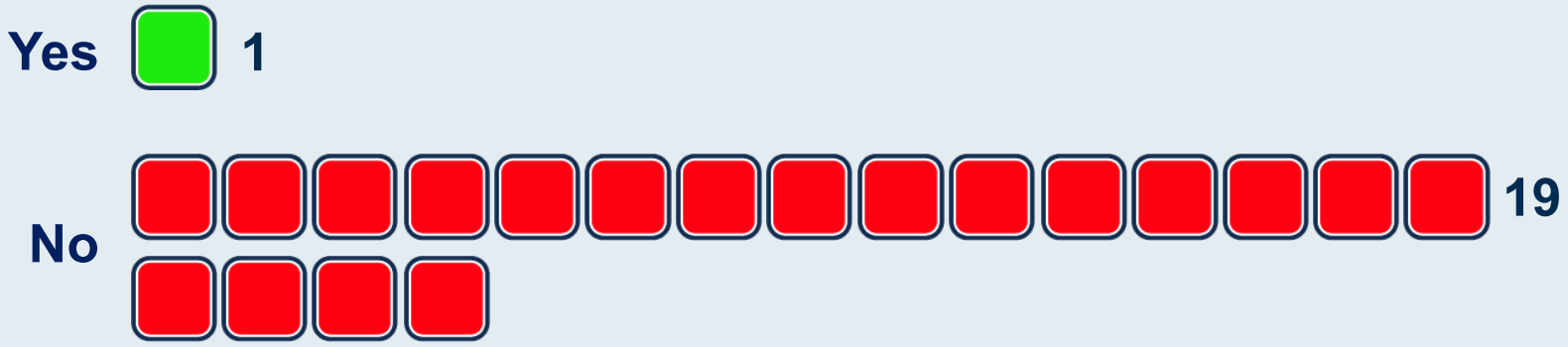
Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Do you perform pulmonary function tests?



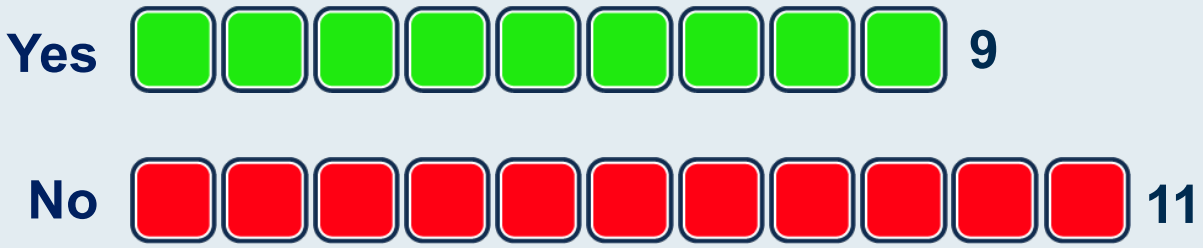
Do you use self-reporting apps, at-home oxygen saturation devices or other electronic means to pick up pulmonary symptoms particularly related to exercise?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Do you believe that the incidence of ILD is higher among Asian people who have immigrated to the United States than in non-Asian US populations?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Strategies to manage chemotherapy-related side effects associated with trastuzumab deruxtecan

Paolo Tarantino, MD

Approach to patients responding to trastuzumab deruxtecan who have abnormal chest imaging

Adam M Brufsky, MD, PhD

RTP
RESEARCH
TO PRACTICE

Monitoring for trastuzumab deruxtecan-associated ILD/pneumonitis; trastuzumab deruxtecan in patients with prior ILD

Jane Lowe Meisel, MD

Priyanka Sharma, MD

RTP
RESEARCH
TO PRACTICE

Identification and Management of Toxicities with T-DXd

Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine

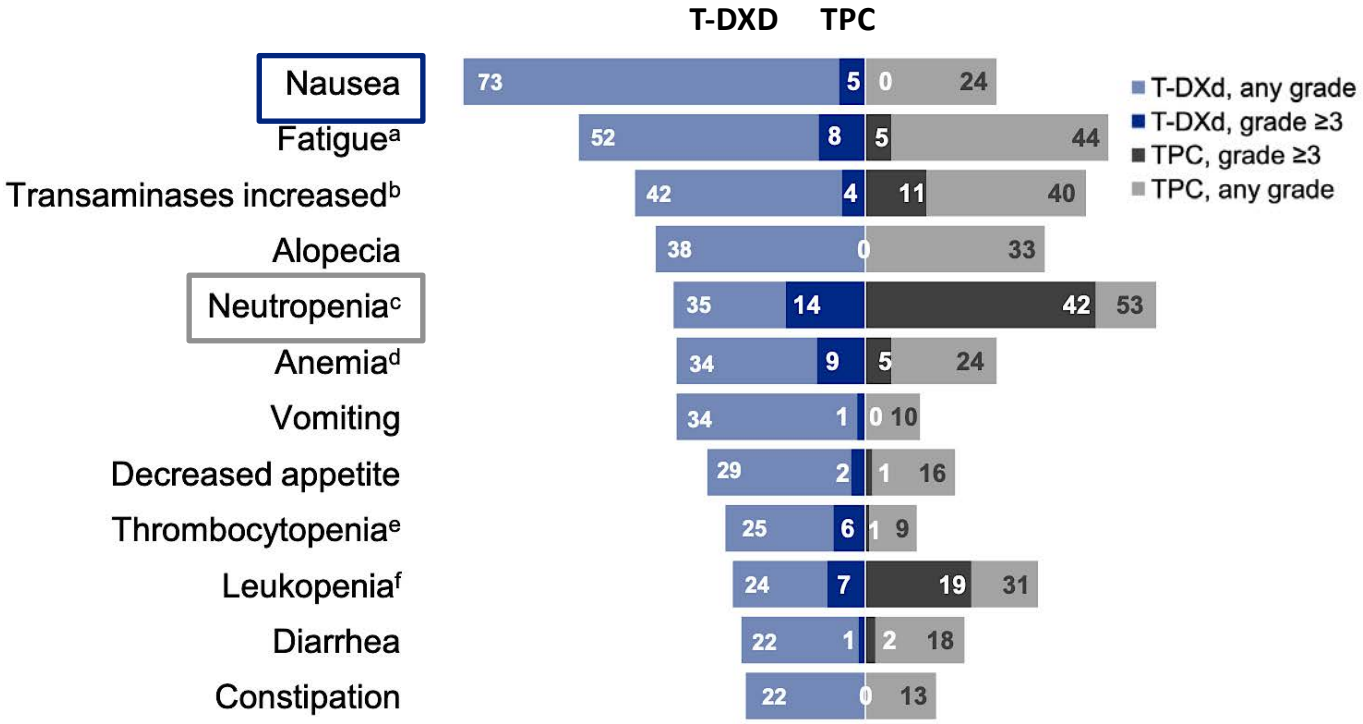
Barts Cancer Institute, St Bartholomew's Hospital
Queen Mary University of London

Queen Mary University of London

Barts Health NHS
NHS Trust

Trastuzumab Deruxtecan (T-DXd) in $HER2_{low}$ MBC

Drug related TEAEs in ≥20% of patients



Most common TEAEs associated with:

	T-DXd	TPC
Treatment discontinuation	10.2% ILD/pneumonitis	2.3% peripheral sensory neuropathy
Dose reduction	4.6% nausea and 3% decreased platelets	10.5% neutropenia
Total on-treatment deaths[§]	3.8%	4.7%

AEs of special interest

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Any Grade	
	T-DXd (n=371)	TPC (n=172)	T-DXd (n=371)	TPC (n=172)	T-DXd (n=371)	TPC (n=172)	T-DXd (n=371)	TPC (n=172)	T-DXd (n=371)	TPC (n=172)	T-DXd (n=371)	TPC (n=172)
ILD/pneumonitis*	13 (3.5)	1 (0.6)	24 (6.5)	0	4 (1.1)	0	0	0	4 (1.1)	0	45 (12.1)	1 (0.6)
Left ventricular dysfunction†												
LVEF decreased	2 (0.5)	0	15 (4.0)	0	1 (0.3)	0	0	0	0	0	18 (4.9)	0
Cardiac failure‡	0	0	1 (0.3)	0	1 (0.3)	0	0	0	0	0	2 (0.5)	0

Modi S, et al. *ESMO 2023; Abstract 376O.*

Side effects of ADCs

T-DM1

Fatigue 22-35%

Interstitial lung disease 0.5%

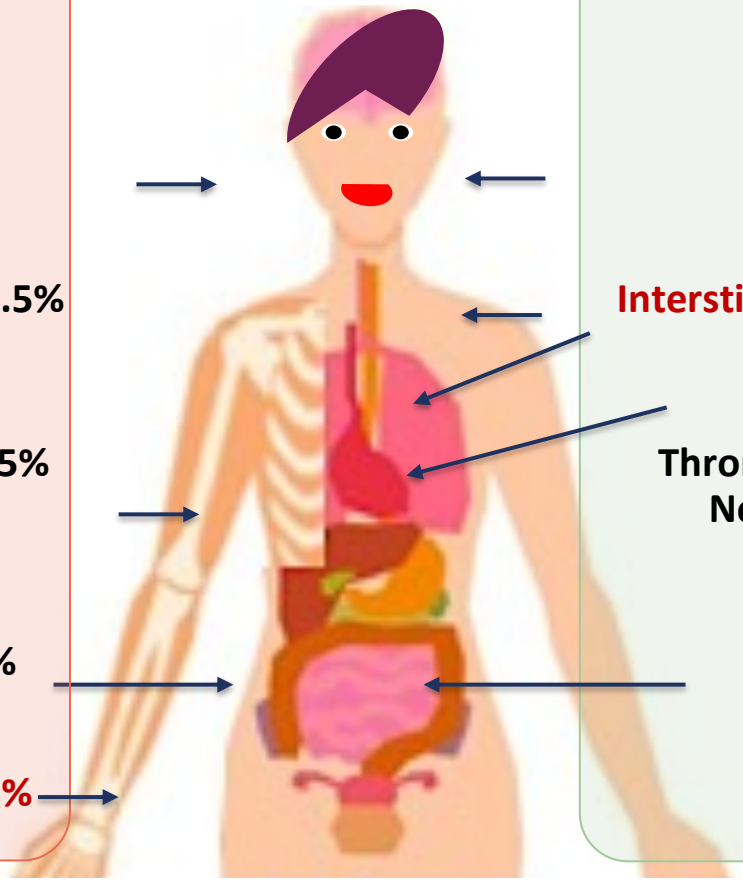
LVEF 2.2%

Thrombocytopenia 25%
Haemorrhage 35%

LFTs 24%

Diarrhoea 10-25%
Nausea 39-47%

Peripheral Neuropathy 32%



T-DXd

Fatigue 48%

Interstitial lung disease 12%

LVEF 4%

Thrombocytopenia 24%
Neutropenia 33%

LFTs 24%

Diarrhoea 22%
Nausea 73%

Determinants of ADC Toxicity

- Target (tissue distribution)
- Payload
- Linker
- Antibody effects (on target or immune)
- Patient factors

Modi, et al NEJM 2022; Hackshaw BCRT 2022; Powell, ESMO Open 2022; Abuhelwa, Drugs 2022

T-DXd: Management of Nausea and Vomiting

- **T-DXd is moderately emetogenic**
- **Nausea can be effectively managed with appropriate anti-emetic prophylaxis and treatment**
- **Consider slightly longer breakthrough medication compared to standard chemotherapy**

Prophylactic/Acute N/V	Delayed N/V (d2 & 3)	Breakthrough N/V
▪ **Moderately emetogenic** • **5-HT3 + Dexamethasone** ▪ **Highly emetogenic** • **5-HT3 + Dexamethasone** • **NK1R Antagonist**	• **5-HT3** • **Dexamethasone (8mg BD)** • **Olanzapine**	• **Ondansetron** • **Prochlorperazine** • **Cyclizine** • **Olanzapine** • **Dexamethasone**

5-HT3 receptor antagonist
- Dolasetron 100 mg PO once.
- Granisetron 10 mg SC or 2 mg PO or 0.01 mg/kg (max. 1 mg) IV once.
- Ondansetron 16 mg to 24 mg PO once or 8 mg to 16 mg IV once.
- Palonosetron 0.25 mg IV once.

NK1R antagonist
- Aprepitant 125 mg PO once or emulsion 130 mg IV.
- Fosaprepitant 150 mg IV once.
- Netupitant 300 mg/palonosetron 0.5 mg PO once.
- Fosnetupitant 235 mg/palonosetron 0.25 mg once.
- Rolapitant 180 mg PO once on days 2 and 3.

Breakthrough
- Ondansetron 8 mg PO BD or TDS.
- Prochlorperazine 10 mg IV/PO Q6H PRN for N/V.
- Cyclizine 50 mg PD BD or TDS.
- Dexamethasone 4 mg to 8 mg BID.
- Olanzapine 2.5 mg to 10 mg PO daily.

T-DXd: Management of Neutro- and Thrombocytopenia

Routine Monitoring

1. Prior to D1 of each cycle ANC ≥1 and Plt ≥75
2. Nadir control not required
3. Primary G-CSF prophylaxis only in risk groups
4. Secondary G-CSF as indicated

	T-DXd dose
Starting dose	5.4 mg/kg
1st reduction	4.4 mg/kg
2nd reduction	3.2 mg/kg
Further reduction required	Discontinue

Neutropenia	Grade 1	Grade 2	Grade 3	Grade 4	Febrile Neutropenia
Description	ANC 1.5 - <2	ANC 1 - <1.5	ANC 0.5 - <1	ANC <0.5	ANC <1 & T >38.3
T-DXd	Continue	Continue	Hold until ≥1	Hold until ≥1	Hold until resolved
Dose reduction	N/A	N/A	N/A	Reduce by 1 level	Reduce by 1 level
G-CSF	No primary prophylaxis (unless risk group)		Consider G-CSF	Consider G-CSF	Consider G-CSF

Thrombocytopenia:

1. **Hold if Platelets <50, until ≥75**
2. **Reduce by 1 level if Platelet nadir <25**

T-DXd: Management of LVEF changes

Routine Monitoring

1. LVEF assessment at baseline
2. Repeat LVEF every 3 months

	LVEF >45%	LVEF 40-45%	LVEF <40%
Decrease from BL <10%	Continue.	Continue. Repeat LVEF after 3 weeks.	• Hold T-DXd. • Repeat LVEF after 3 weeks. • If confirmed, discontinue.
Decrease from BL 10-20%	Continue.	• Hold T-DXd. • Repeat LVEF after 3 weeks. • If not recovered to within 10% from BL, discontinue. • If recovered, resume at same dose.	
Decrease from BL >20%	• Hold T-DXd. • Repeat LVEF after 3 weeks. • If confirmed, discontinue.		

Discontinue if symptomatic congestive heart failure

What is ILD?

ILD (Interstitial Lung Disease) is a broad term for a group of diffuse, parenchymal lung disorders including some types of pneumonitits

Symptoms

- Nonspecific cough[1,2]
- Fever[3]
- Shortness of breath (dyspnoea)[2]
- Pneumonitis and idiopathic pulmonary fibrosis[4]

Clinical signs

- Inflammation or scarring of the lung interstitium[2]
- Chest radiographic abnormalities[1]
- Changes in pulmonary function tests reflecting decreased lung volume[1]
- Microscopic patterns of inflammation and fibrosis[2]

Risk factors

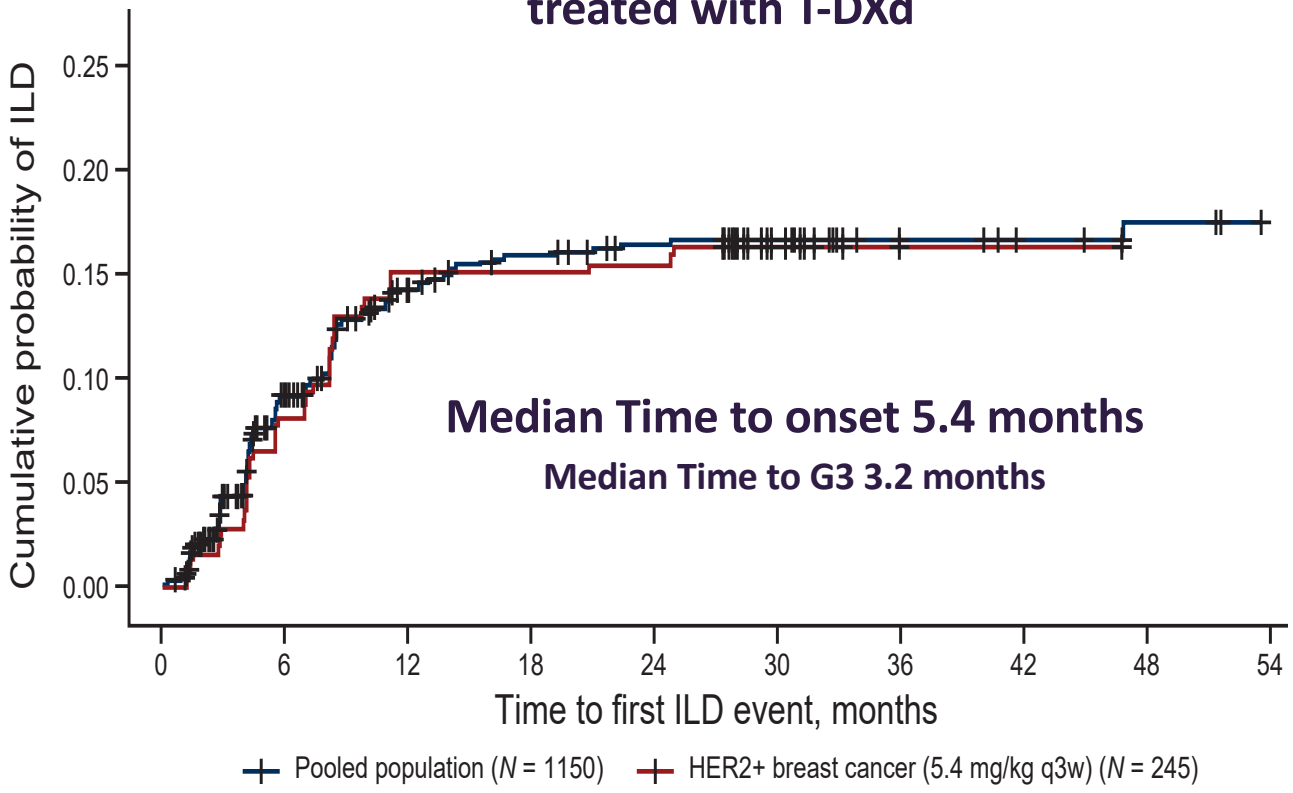
- Patient history of ILD/pneumonitis or lung disease[4,5]
- Smoking status[4,5]
- Age >70 years[5]
- Male[5]
- Use of anticancer agents

ILD, interstitial lung disease.

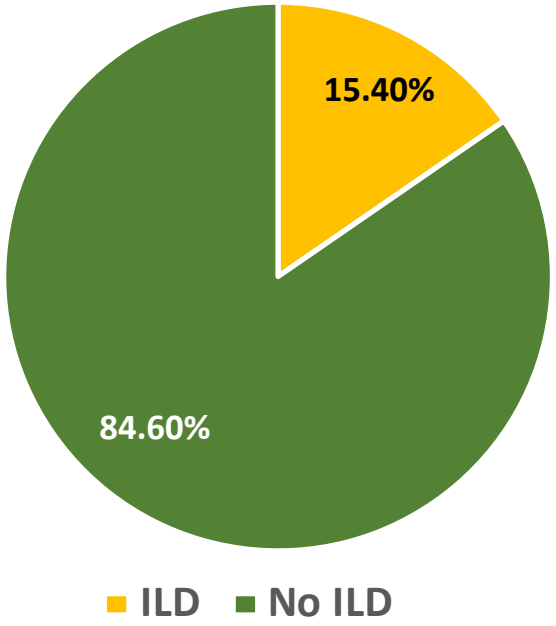
1. Wells AU et al. *Thorax* 2008;63:Sv1–Sv58; 2. Meyer KC. *Transl Respir Med* 2014;2:4; 3. Modi S et al. *N Engl J Med* 2020;382:610–621; 4. Kreuter M et al. *Biomed Res Int* 2015;2015:123876; 5. Choi W et al. *BMC Pulm Med* 2018;18:96

Incidence and time course of ILD with T-DXd

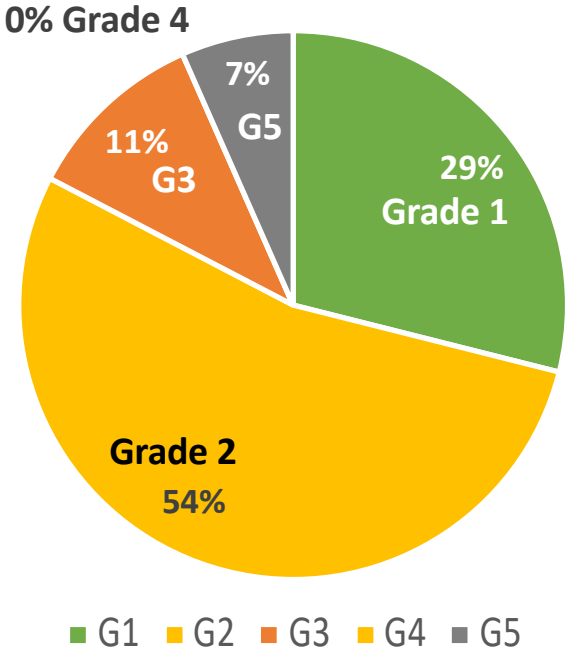
Cumulative probability of developing ILD for patients treated with T-DXd



Incidence of ILD



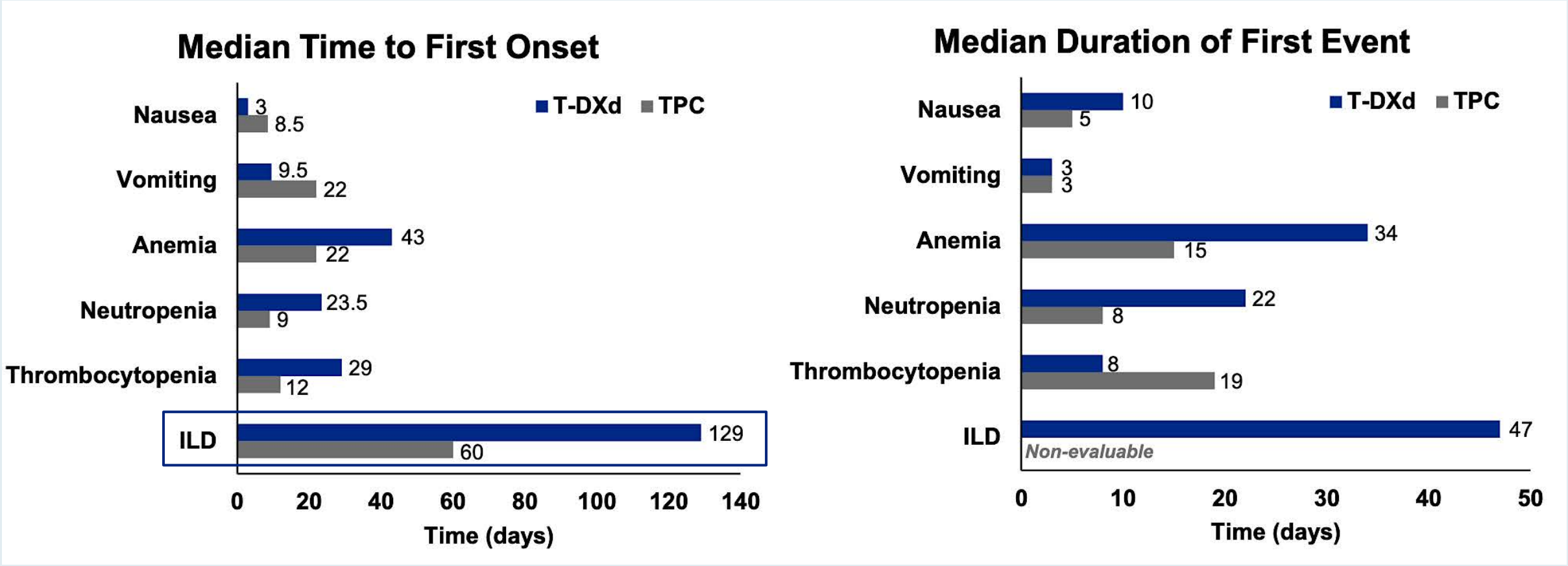
Severity of ILD



ILD does not appear to be directly associated with cumulative exposure to T-DXd

Powell, et al. ESMO OPEN 2022; Modi S, et al. *N Engl J Med*. 2022;387(1):9–20

DESTINY-Breast04: Detailed Safety Summary



Rugo HS et al. ESMO Breast 2023;Abstract 185O.

T-DXd: Management of ILD

Routine Monitoring

1. Monitor for symptoms (cough, dyspnea, pyrexia)
2. Review every 4-6 weeks
3. Monitor SpO2 (examine if drops by 2-4% for 1-3d)
4. CT scans every 9-12 weeks

Diagnostic if ILD suspected

1. Lung function test
2. CT chest scan (ideally high-resolution CT)
3. Possibly Bronchoscopy
4. Bloods, blood and sputum cultures

	Grade 1	Grade 2	Grade 3/4
Description	Asymptomatic (diagnostic observations only)	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen (G3); Life-threatening (G4)
T-DXd	Hold (restart if resolved within 49 days, otherwise discontinue)	Discontinue	Discontinue
Dose reduction	Same dose if ≤28d, lower dose if > 28d	N/A	N/A
Steroids	0.5 mg/kg/day	≥1 mg/kg/day	Methylprednisolone i.v. 500-1000 mg/d for 3d, followed by ≥1 mg/kg/d prednisolone for 14d
Escalation	If worsens despite initiation of steroids, follow Grade 2 guidelines	If not better within 5d: Increase dose or switch to IV	If not better within 5d: Infliximab, IVIG or MMF
Duration	Until improvement, followed by gradual taper over ≥4 weeks	For at least 14d or until complete resolution of clinical and chest CT findings then gradually taper (for at least 4wks)	

Agenda

Module 1: Optimal Approaches to HER2 Testing for the Identification of HER2-Low Breast Cancer — Dr Carey

Module 2: Available Data with and Current Role of HER2-Targeted Therapy for HER2-Low Disease — Dr Modi

Module 3: Identification and Management of Toxicities with Trastuzumab Deruxtecan — Prof Schmid

Module 4: Future Directions in the Management of HER2-Low Breast Cancer — Dr Bardia

RTP RESEARCH TO PRACTICE

Please describe the last patient with HER2-low metastatic breast cancer in your practice who received trastuzumab deruxtecan.

Patient age: 57 (median; range 30-77)

ER status:

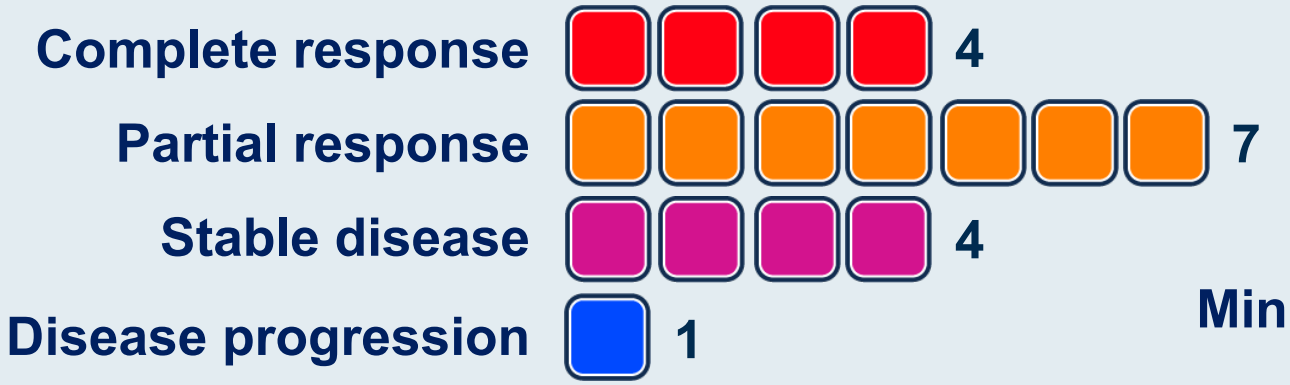
HER2 IHC:

Survey of 20 US-based clinical investigators November 2023

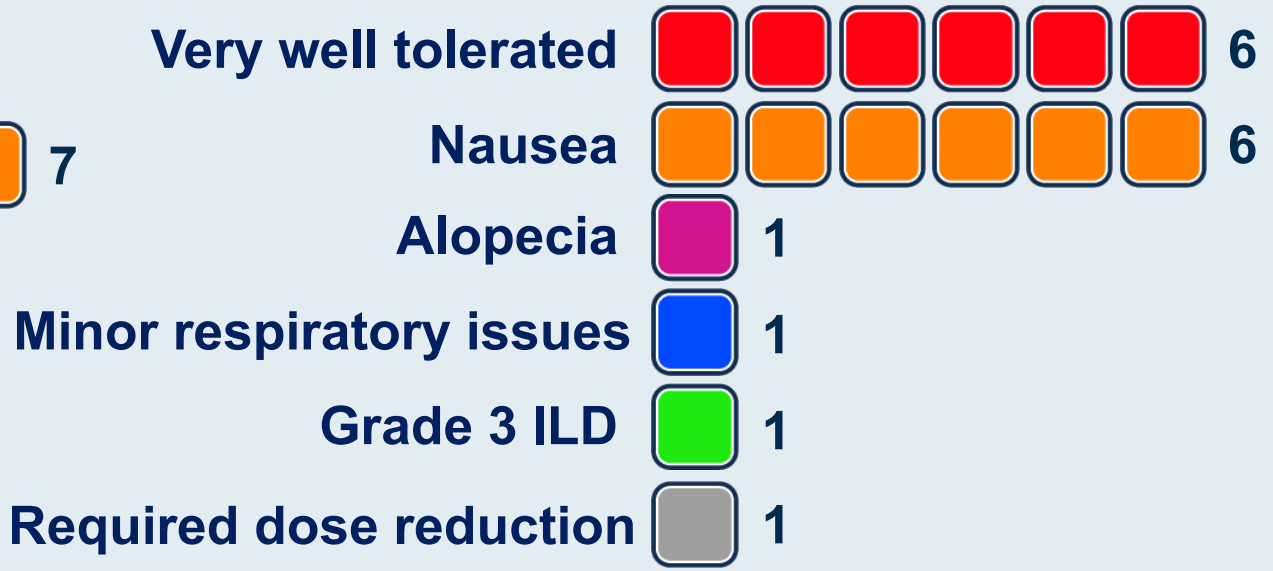
RTP RESEARCH TO PRACTICE

Please describe the last patient with HER2-low metastatic breast cancer in your practice who received trastuzumab deruxtecan.

Patient's response to therapy:



Patient's tolerance of therapy:



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Antibody-drug conjugate technology and novel cytotoxic payloads

Mark D Pegram, MD

RTP
RESEARCH
TO PRACTICE

Perspectives on the future management of HER2-positive breast cancer

Mark D Pegram, MD

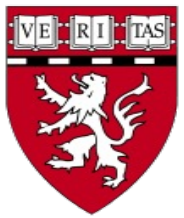
RTP RESEARCH TO PRACTICE

Future Directions in the Management of HER2-Low BC

Aditya Bardia, MD, MPH, FASCO

Director, Breast Cancer Research

Massachusetts General Hospital, Harvard Medical School

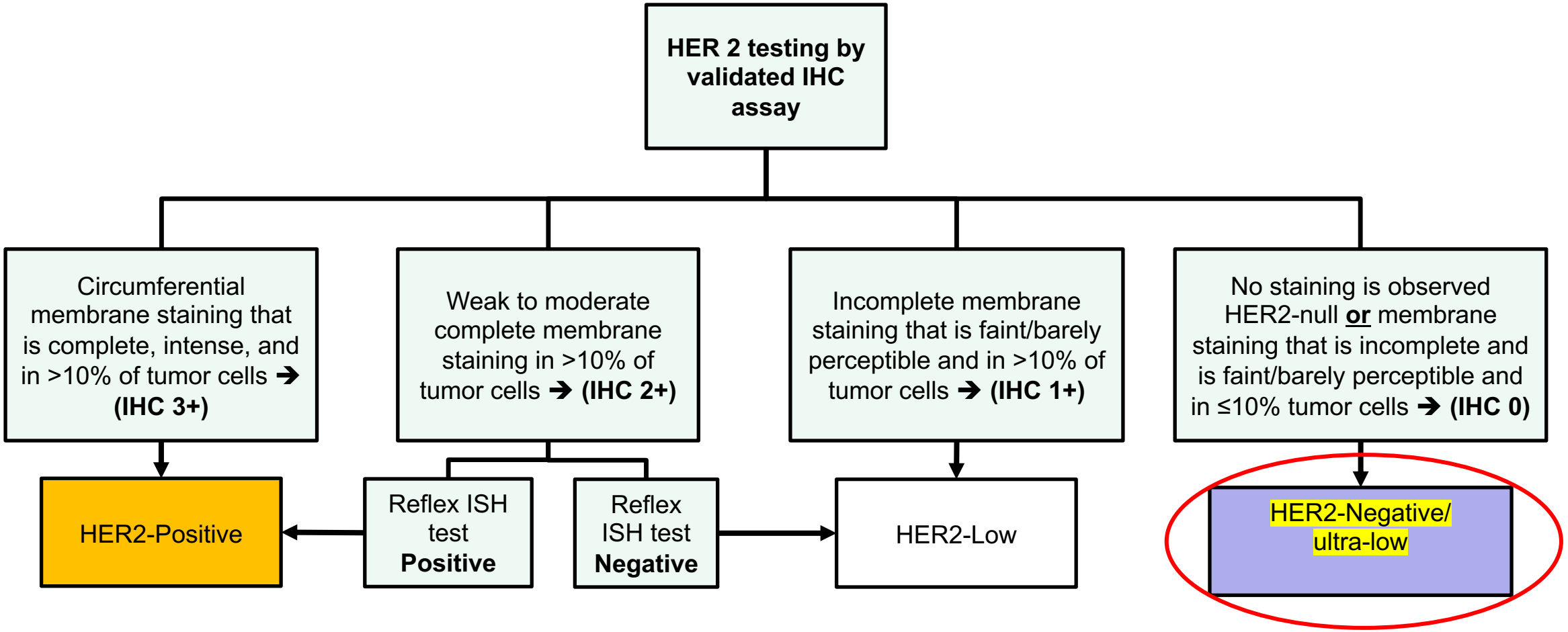


MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Objectives

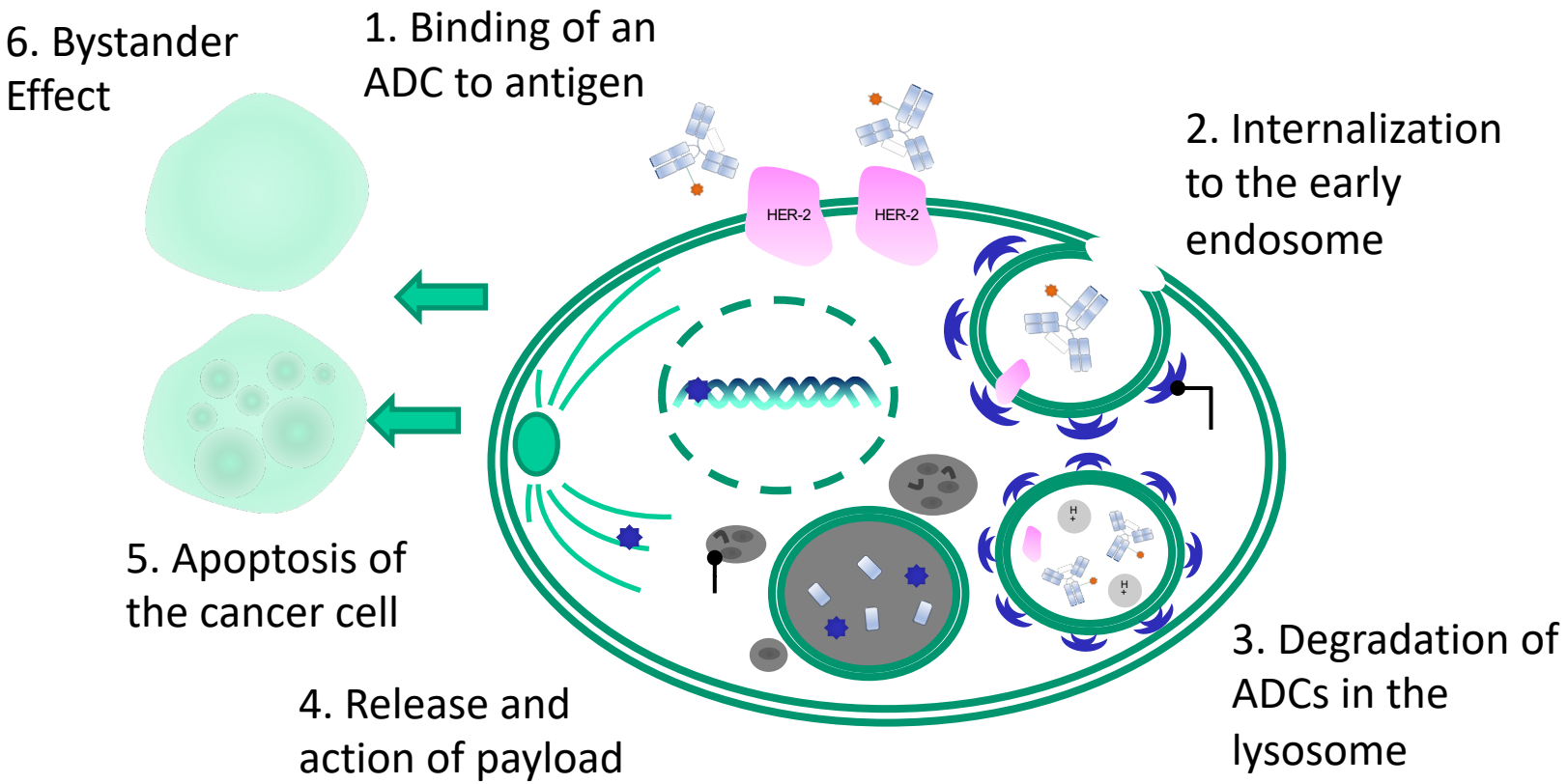
- Understand HER2 ultra-low breast cancer and biologic rationale for T-DXd
- Review clinical data of activity of T-DXd in HER2 ultra-low breast cancer
- Review ongoing and upcoming clinical trials in metastatic and localized breast cancer
- Understand research efforts combining T-DXd with other systemic therapies
- Review other novel HER2-targeted agents in HER2-low breast cancer

HER2-Low and Ultra-low Breast Cancer



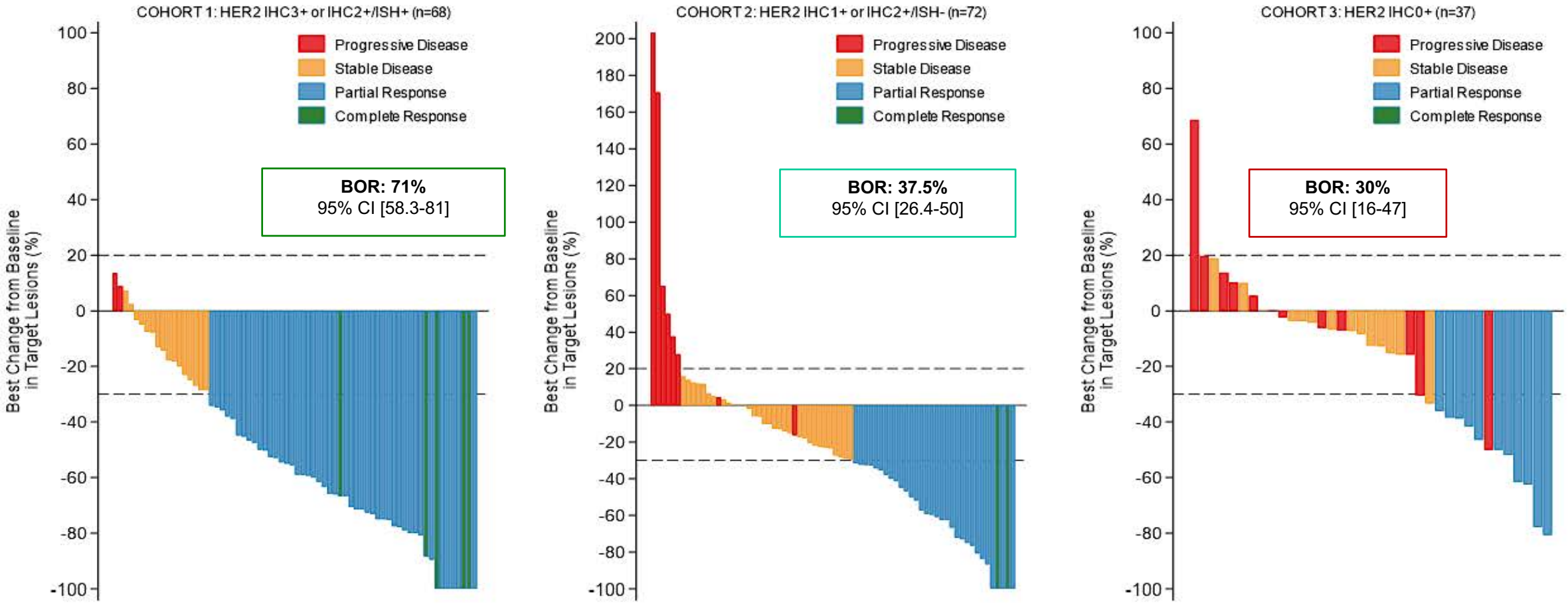
IHC, immunohistochemistry; ISH, in-situ hybridisation. Wolff AC, et al. *Arch Pathol Lab Med.* 2018.

ADC:
Selective delivery of toxic payload



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

DAISY: Response Rate according to HER2 expression

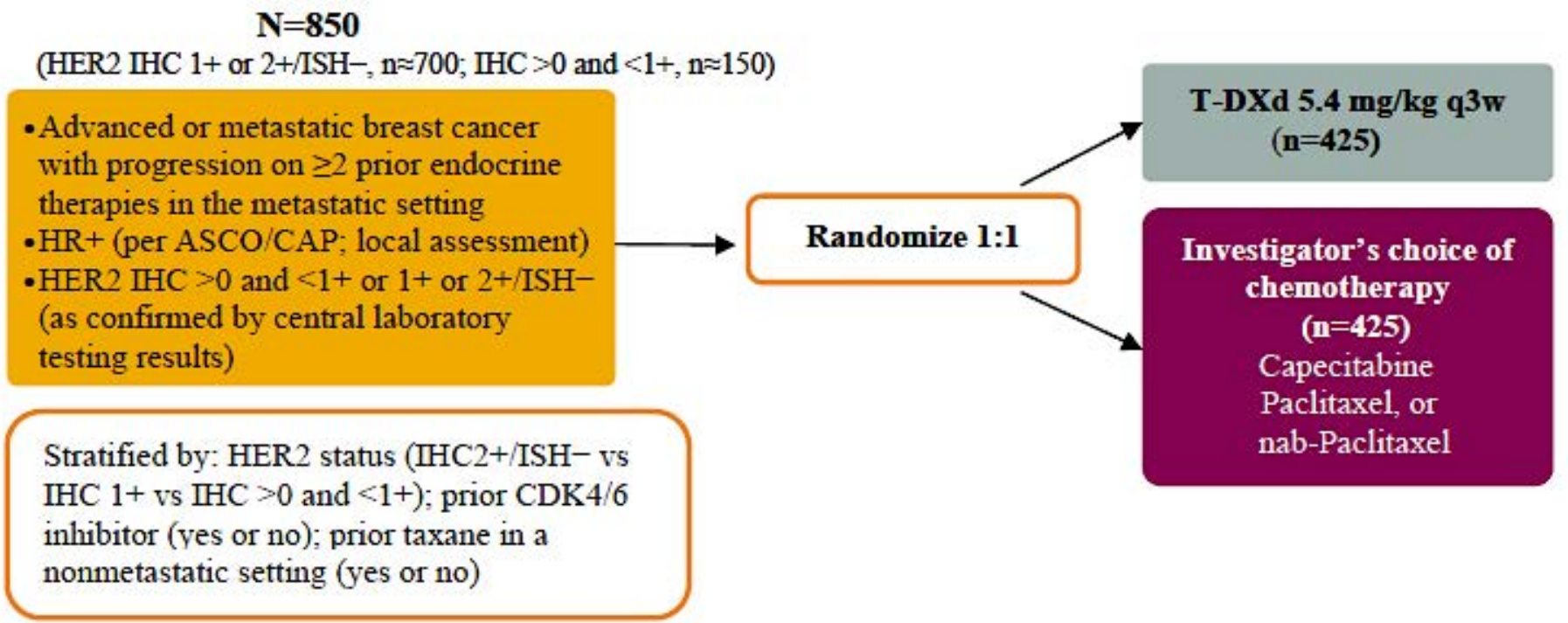


Data cut-off: Oct 19, 2021

Mosele F et al. Nature Medicine 2023

DESTINY-Breast06:
T-DXd vs ICC for HER2 low and ultra-low BC

FIGURE I: DESTINY-Breast06 Study Design.[2]

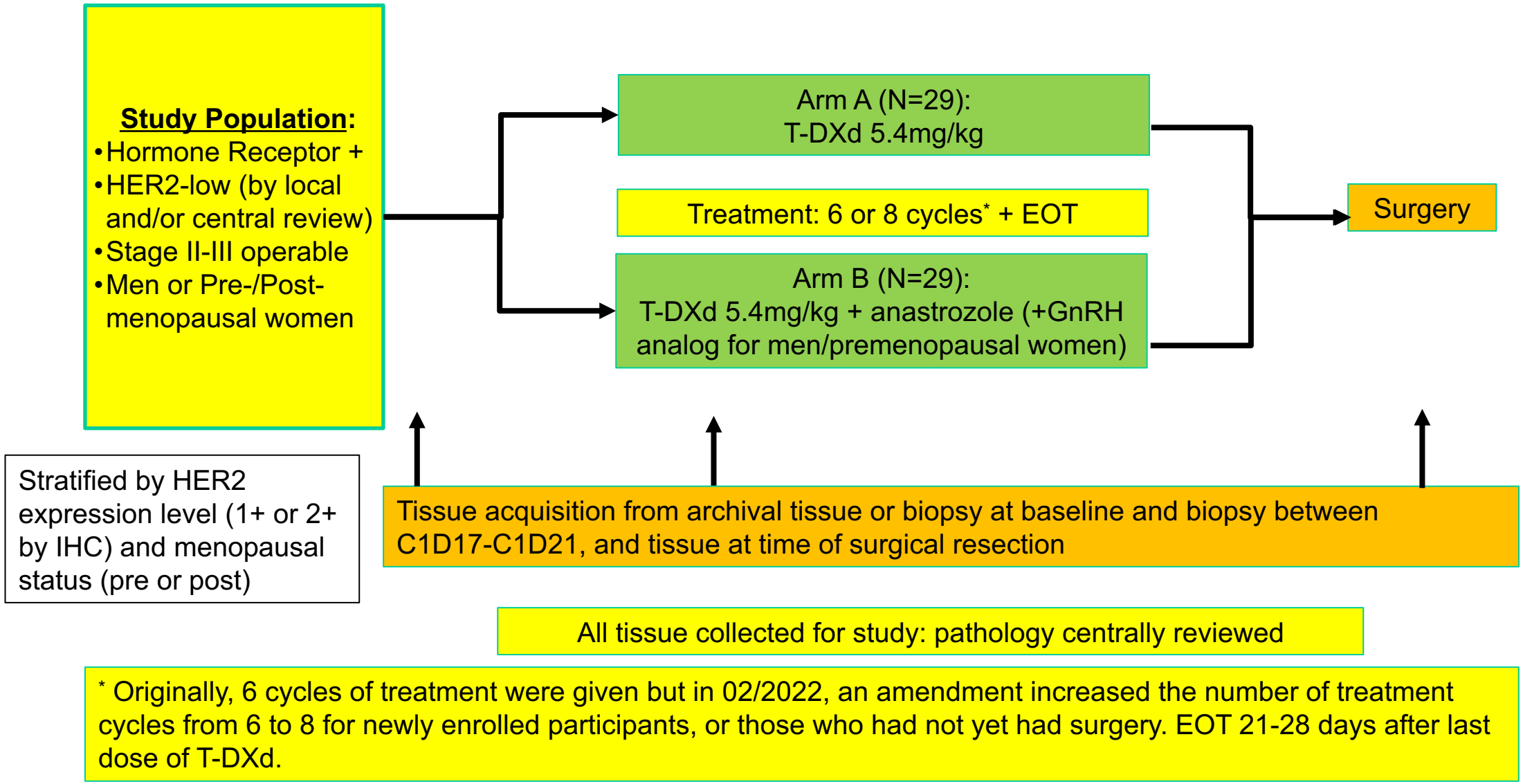


ASCO = American Society of Clinical Oncology; CAP = College of American Pathologists; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IHC = immunohistochemistry; ISH = in situ hybridization; q3w = every 3 weeks; T-DXd = fam-trastuzumab deruxtecan-nxki

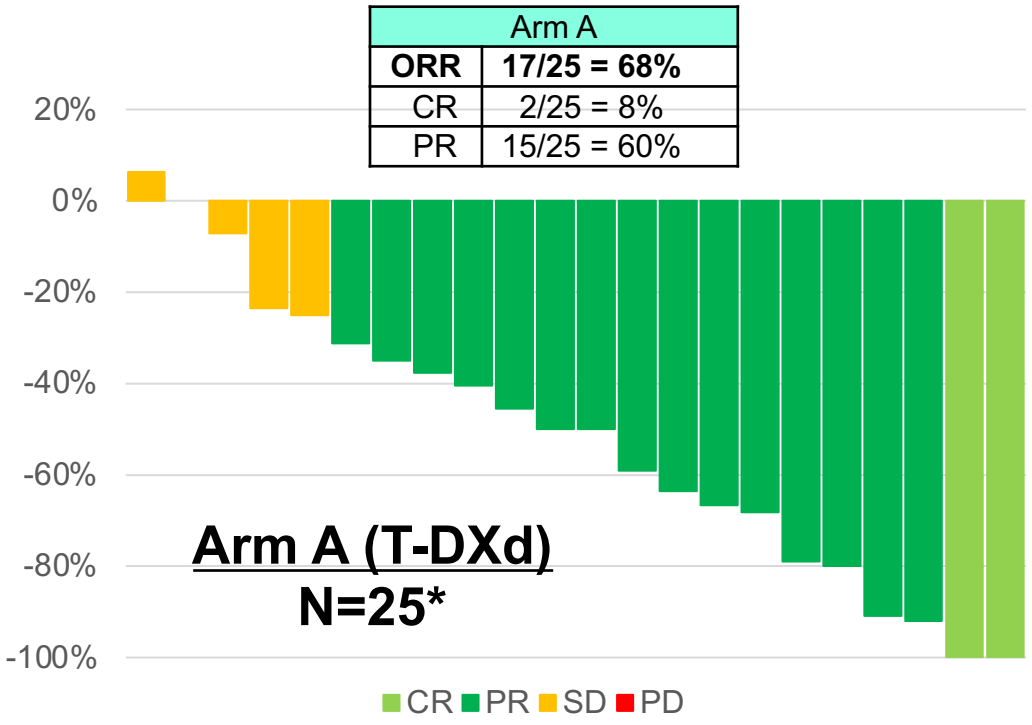
[2]Bardia A et al. SABCS 2020

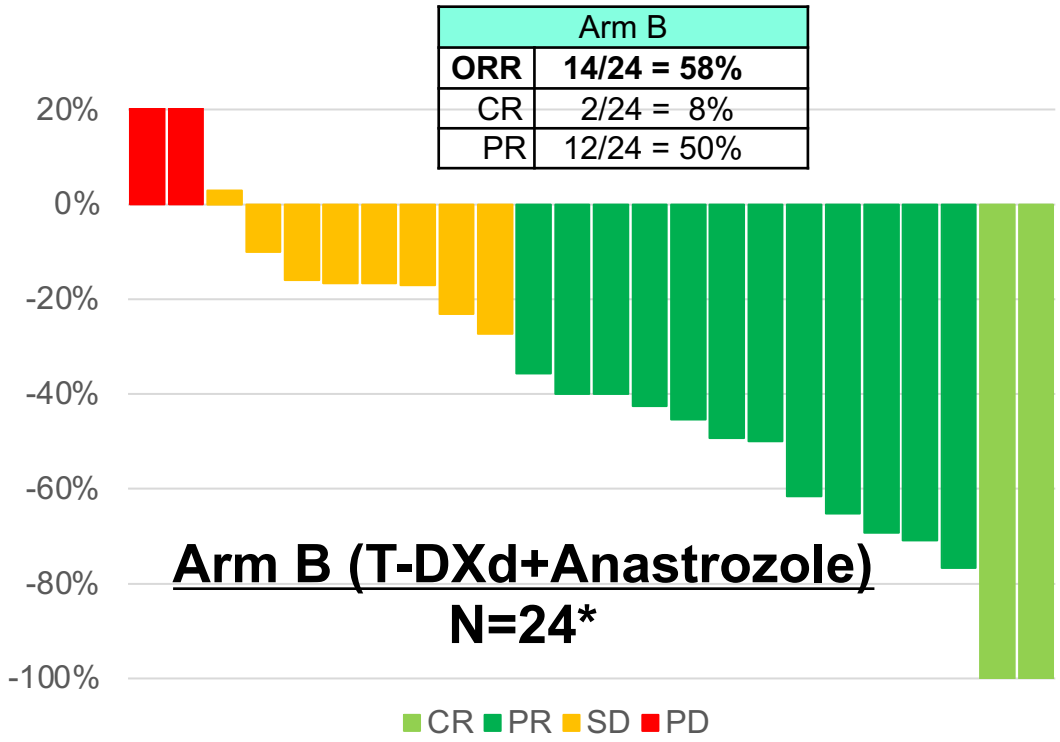
How about early breast cancer?

TRIO-US B-12 TALENT: Study Design



Objective Response Rate with T-DXd (based on imaging)



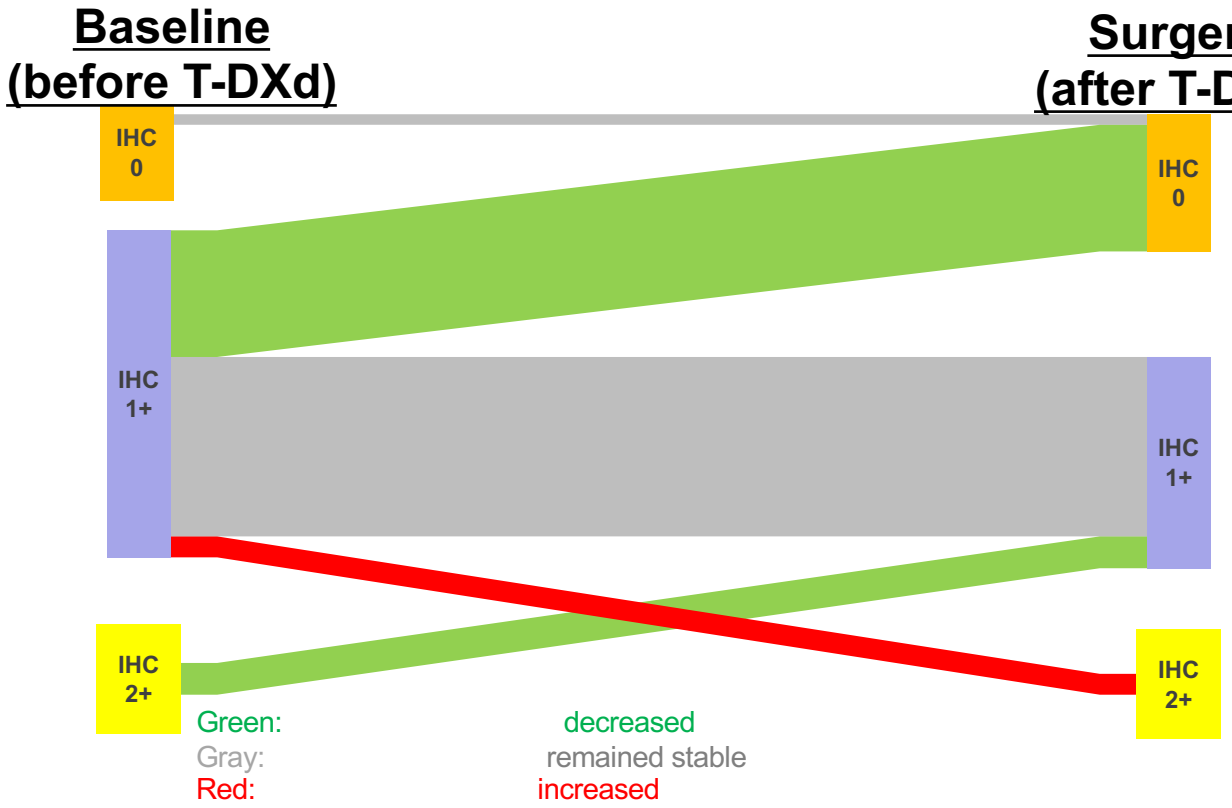


Waterfall plot with bars representing change in tumor size after treatment with T-DXd, compared to baseline, as per RECIST v1.1. Intention to treat population for ORR includes all who received at least 1 cycle of protocol therapy, data cutoff 11/25/2022.

* 4 patients still on treatment; 3 patients did have imaging (treatment discontinued prematurely), but included in intention to treat (ITT) denominator for ORR analysis per protocol

* 5 patients still on treatment

HER2 IHC Change from Baseline to Surgery with T-DXd (central review)

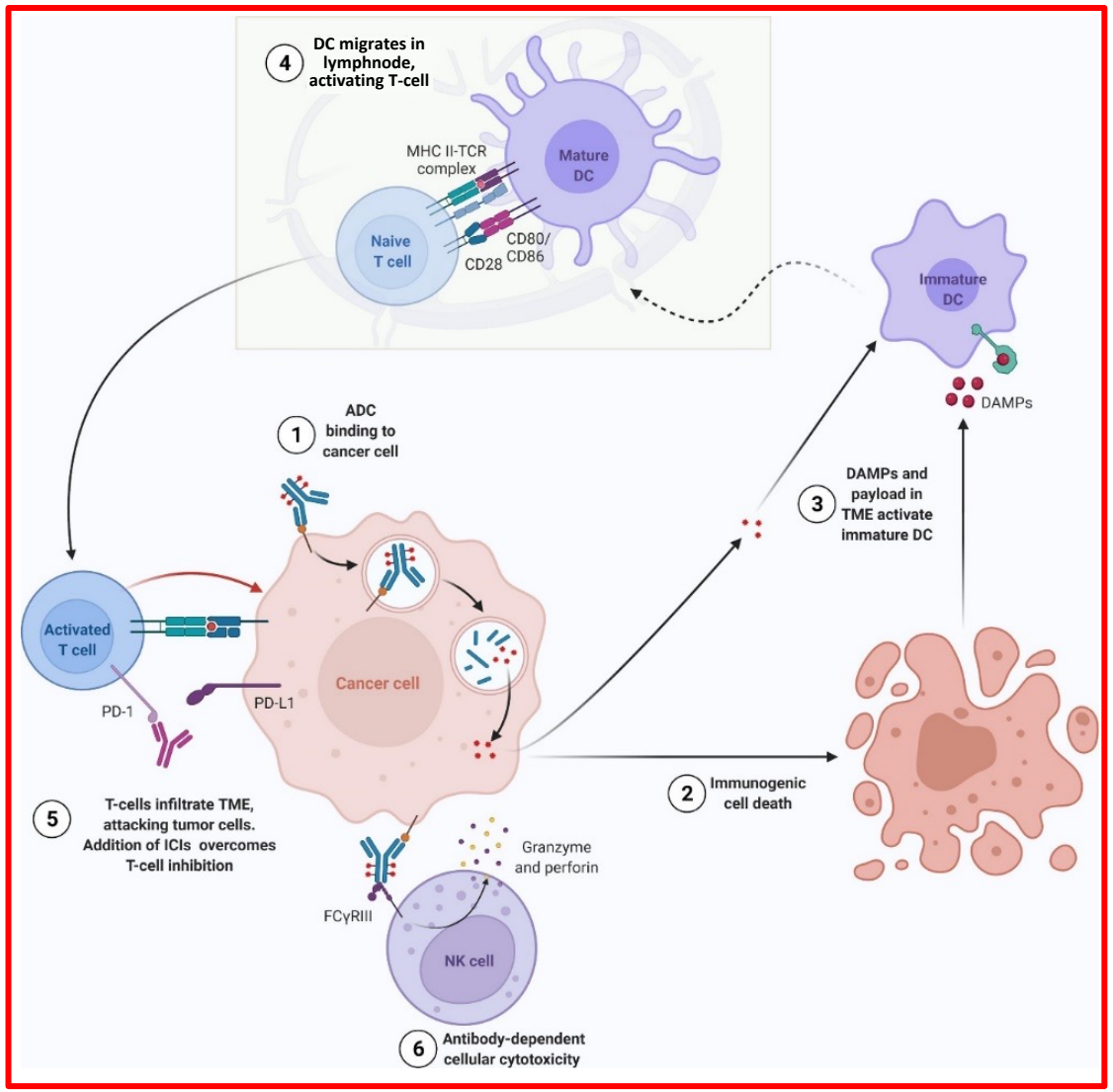


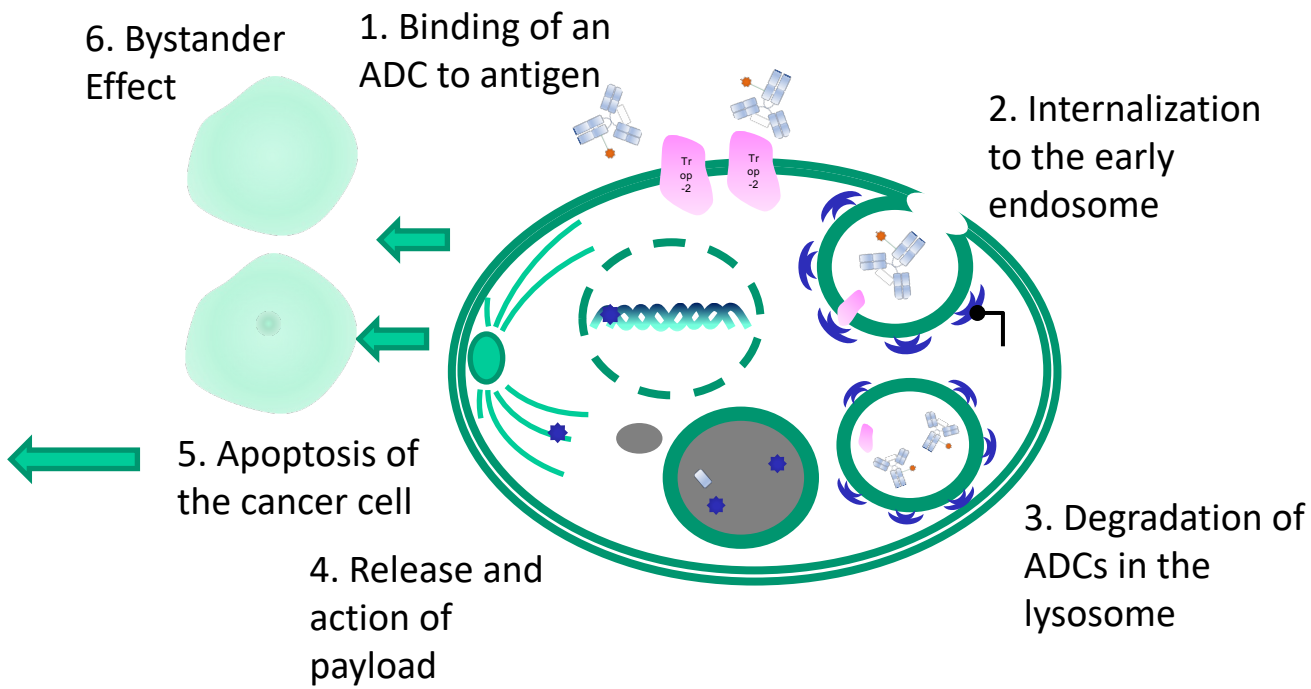
48.6% (17/35) had change in HER2 IHC expression after T-DXd treatment

Of those who had change, majority (88.2%) had decrease in HER2 expression

Note: The observed change in IHC immunostaining may not accurately reflect changes in HER2 protein expression in carcinoma cells

Antibody-Drug Conjugates: Combination with immunotherapy

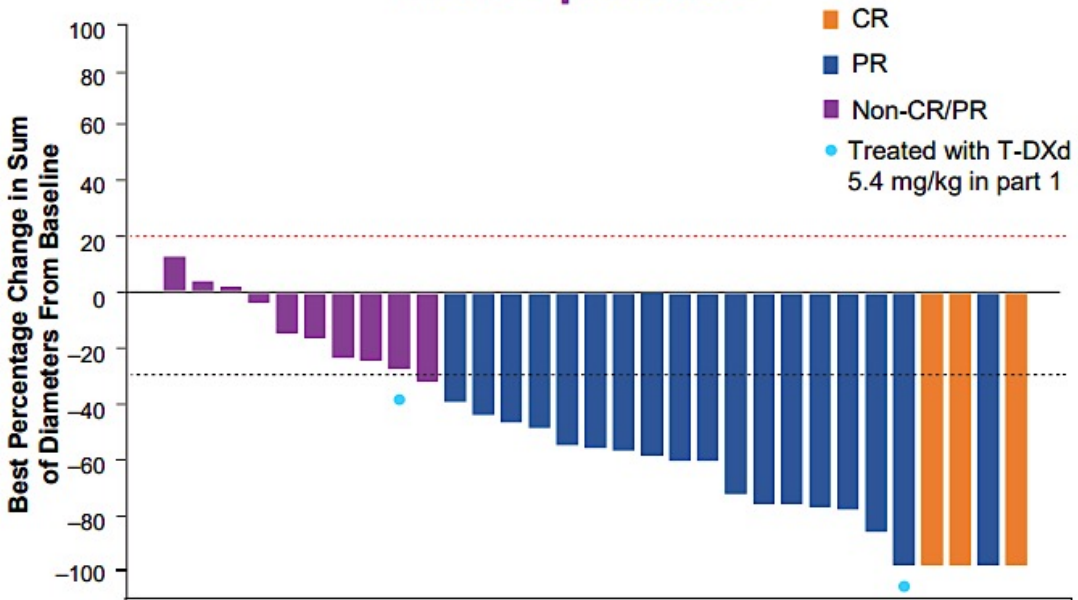




Nicolo et al. *CTR*. 2022

Combination with immunotherapy: T-DXd and Nivolumab (U105)

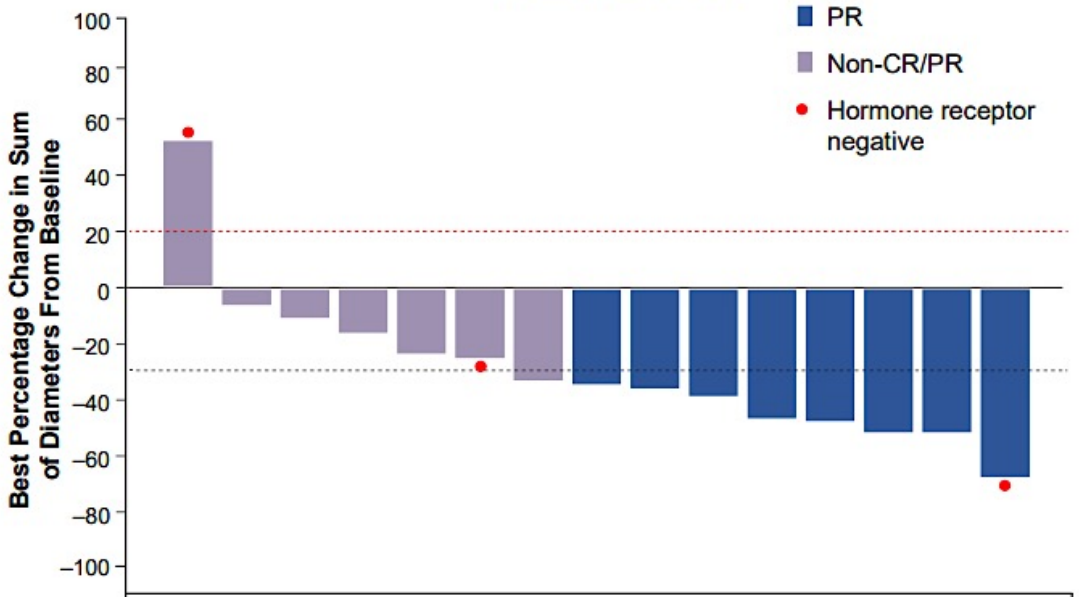
HER2-positive



Cohort 1 HER2-positive BC (n = 32)
Parts 1/2: T-DXd 5.4 mg/kg and Nivolumab 360 mg
Best (minimum) Percentage Change

n	Mean	SD	Median	Min	Max
31	–53.0	33.82	–57.0	–100	13

HER2-low



Cohort 2 HER2-low BC (n = 16)
Part 2: T-DXd 5.4 mg/kg and Nivolumab 360 mg
Best (minimum) Percentage Change

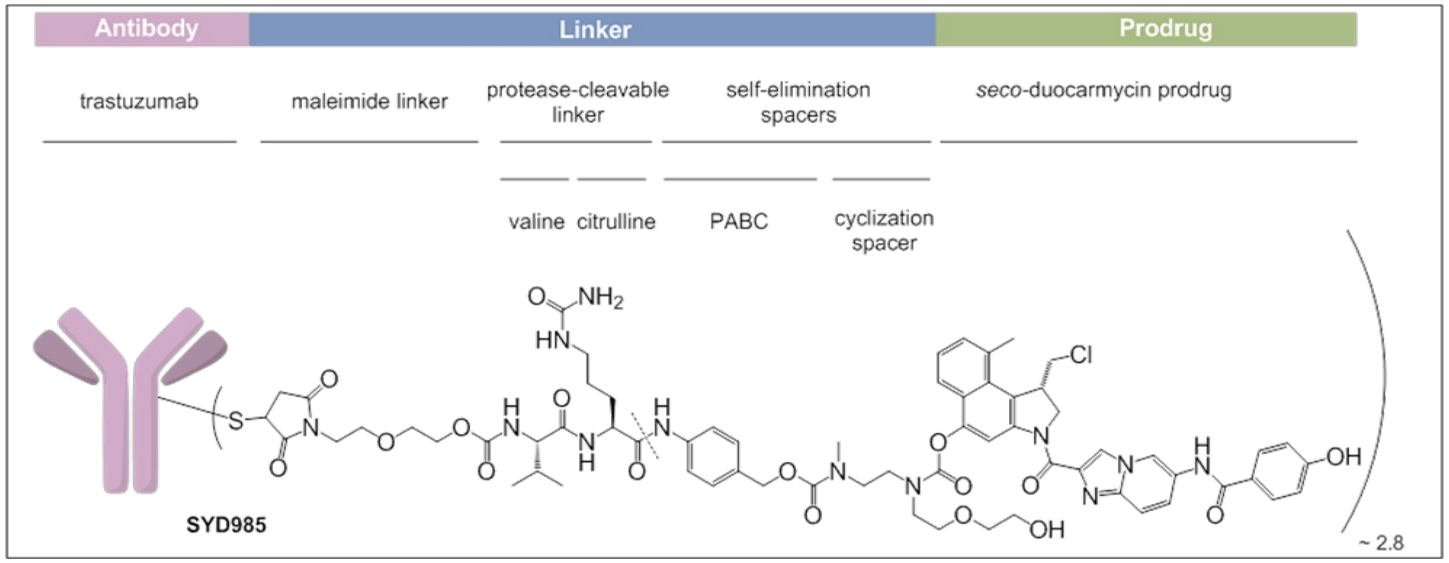
n	Mean	SD	Median	Min	Max
15	–29.2	28.56	–35.0	–68	54

Does immunotherapy add to efficacy of ADC?
Setting might matter.

Hamilton E. et al. ESMO Breast. 2022.

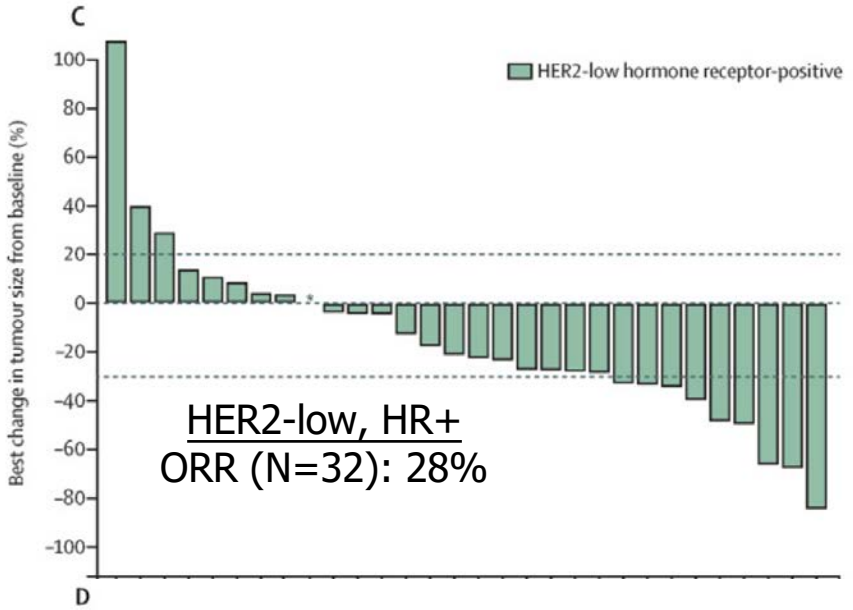
What about other ADCs?

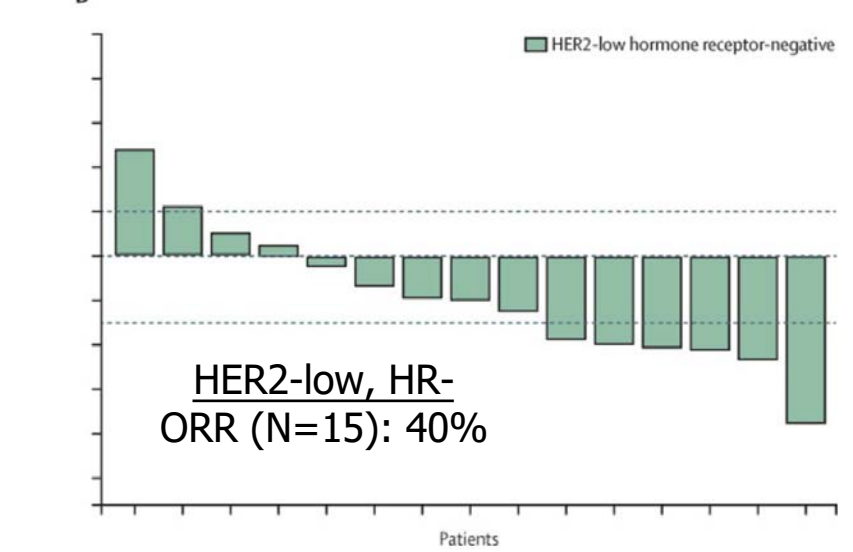
SYD985: HER2-targeting ADC
Trastuzumab duocarmazine



Antibody-drug conjugate

- HER2 antibody
- Cleavage of linker in tumor environment by proteases leads to activation
- Active toxin (DUBA) alkylates DNA, kills dividing and non-dividing cells

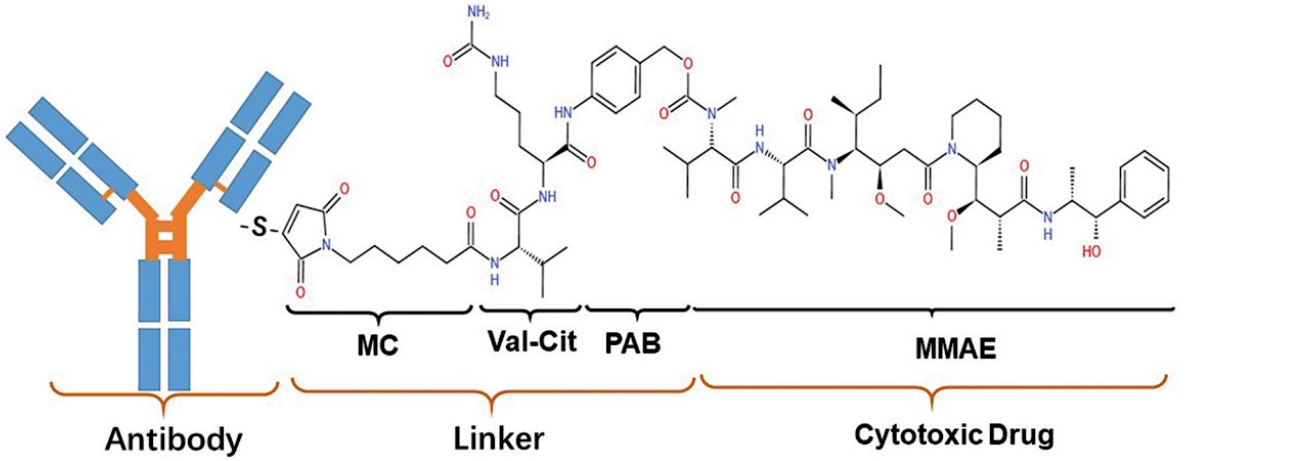


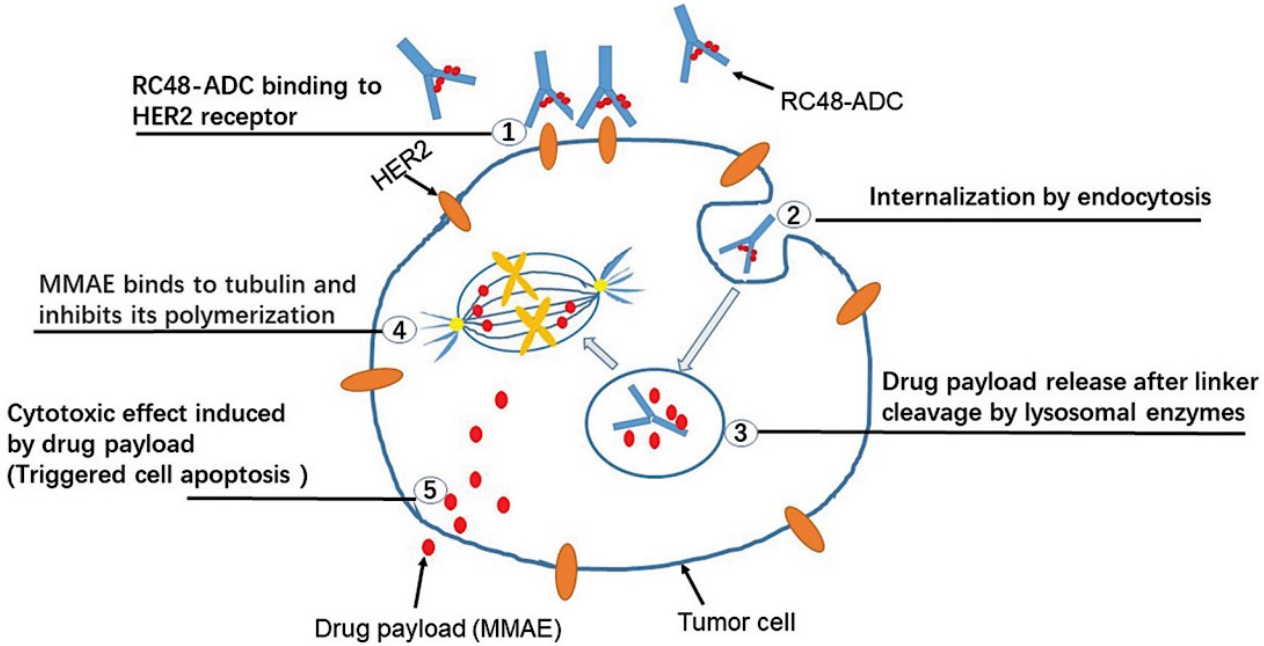


Dokter W et al. *Mol Cancer Ther.* 2014;13(11):2618-2629.

Banjeri U et al. *Lancet Oncol.* 2019;20(8):1124-1135

RC48-ADC: HER2-targeting ADC
Disitamab vedotin

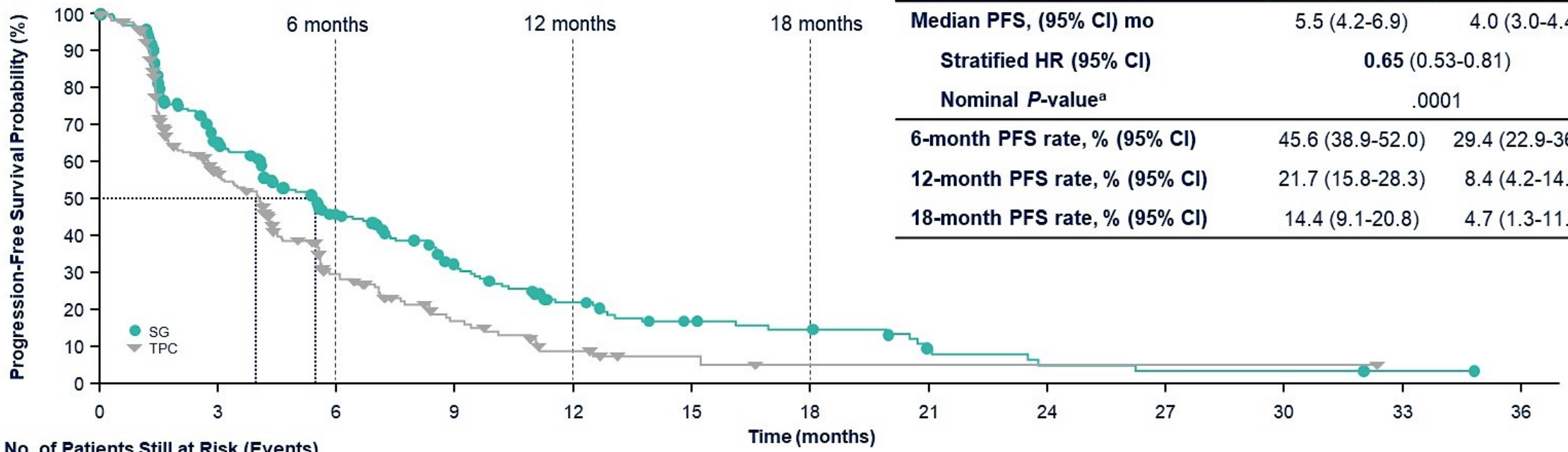




Shi F et al. *Drug Deliv*. 2022;29(1):1335-1344.

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

ITT Population



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65** (0.53-0.81)	
Nominal *P*-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

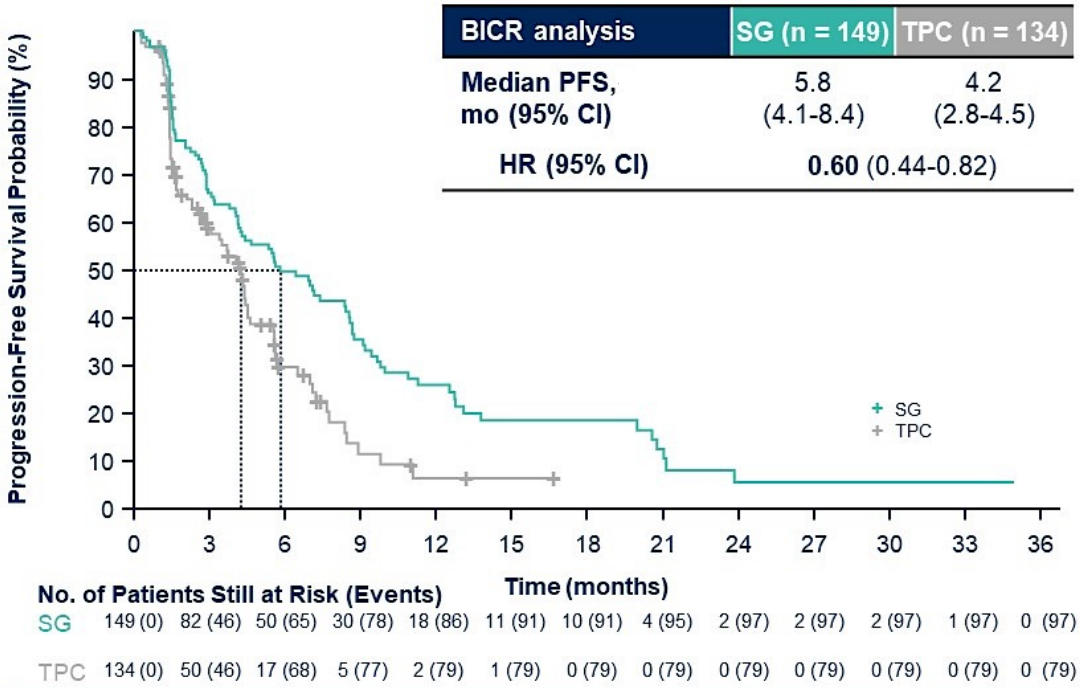
No. of Patients Still at Risk (Events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

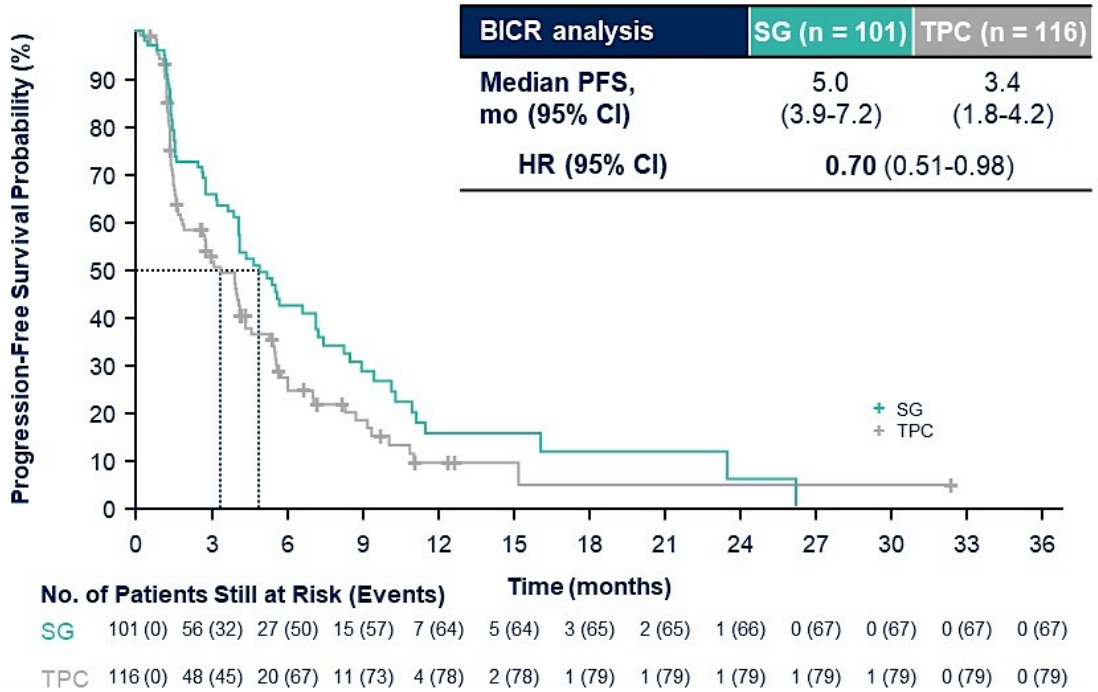
Tolaney SM et al. ASCO 2023; Abstract 1003.

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

HER2-low (IHC1+, IHC2+/ISH-)



HER2 IHC0



- Within the HER2-Low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- The hazard ratio for median PFS in a sensitivity analysis of the HER2-Low subgroup (excluding ISH-unverified) was similar (HR, 0.53)

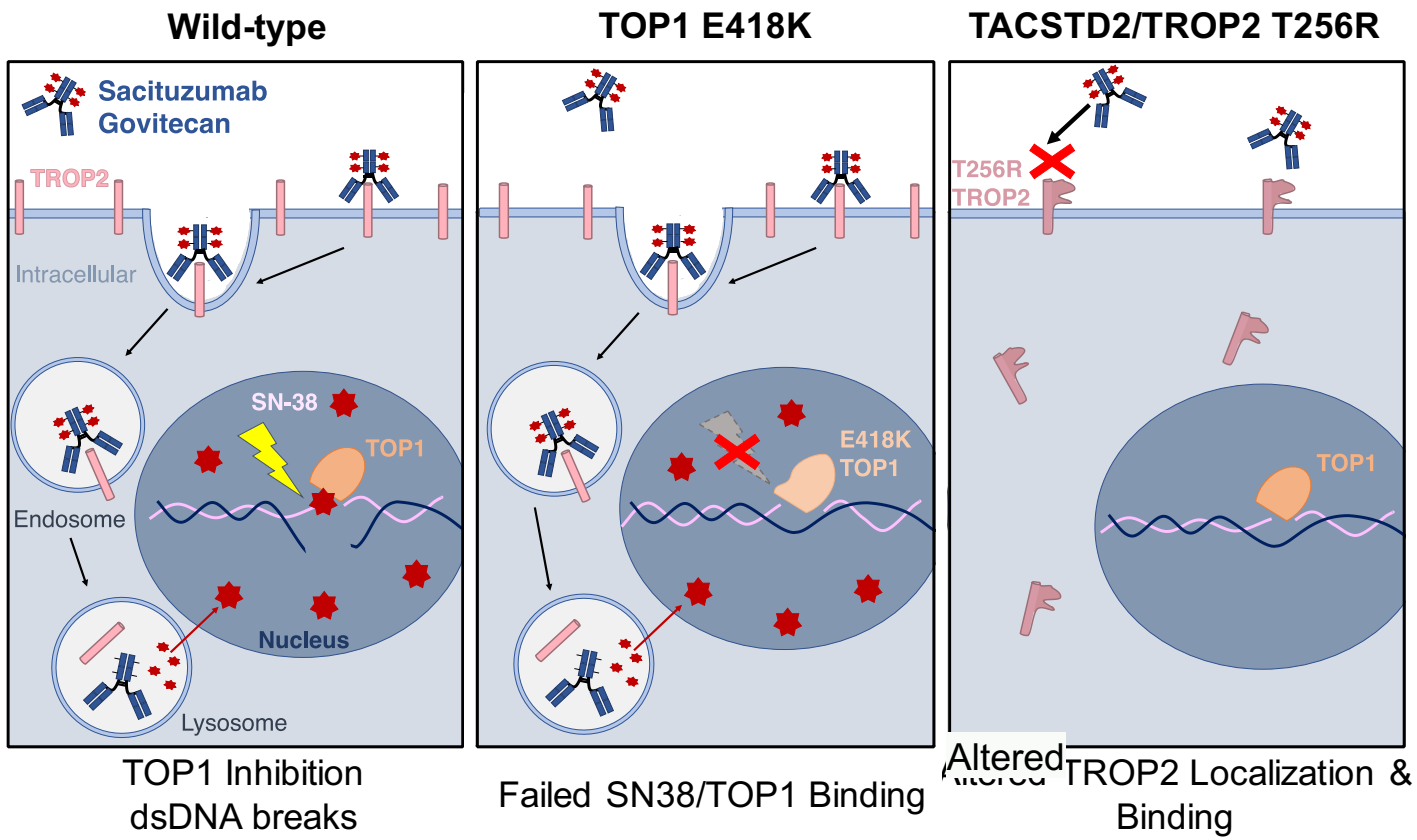
Schmid P et al. ESMO 2022; Abstract 214MO. Tolaney SM et al. ASCO 2023; Abstract 1003.

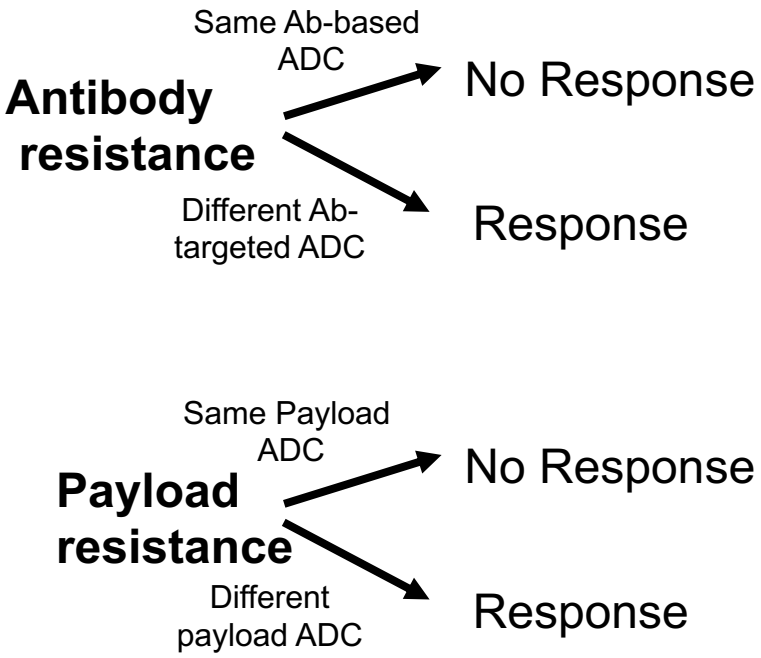
ADCs to target MBC: Multiple Agents in Development

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
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1	Microtubule inhibitor
Patritumab deruxtecan (U3-1402)	HER3	Topo-1 inhibitor
Trastuzumab duocarmazine	HER2	Alkylating agent
Disitamab vedotin	HER2	Microtubule inhibitor

Both target and payload important considerations for efficacy/toxicity profile and ADC sequencing

Implications of resistance mechanisms for ADC sequencing





Coates, Sun et al Cancer Discovery 2021.

Summary

- Even HER2 IHC 0 has some HER2 expression which can be leveraged as target for ADCs with bystander effect.
- Trastuzumab deruxtecan: approved for HER2 low MBC (both HR+ and TNBC). Ongoing studies in HER2 ultra-low breast cancer as well as early breast cancer.
- ADC combination with immunotherapy has demonstrated impressive clinical activity in mTNBC. However, additional contribution of immunotherapy currently remains undefined and will be clarified in various ongoing studies.
- There are multiple other HER2 ADCs in development for HER2 low breast cancer. Understanding mechanism of resistance, antibody vs payload, could help guide therapeutic sequencing and optimal therapeutic management of patients with breast cancer.

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of HER2-Low Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Thursday, December 7, 2023

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

Faculty

Aditya Bardia, MD, MPH

Lisa A Carey, MD, ScM, FASCO

Shanu Modi, MD

Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hematologic Cancers

A 4-Part CME Friday Satellite Symposium Series Preceding the 65th ASH Annual Meeting and Exposition

Friday, December 8, 2023

Follicular, Mantle Cell and Hodgkin Lymphoma
7:30 AM – 10:00 AM PT

Chronic Lymphocytic Leukemia
3:15 PM – 5:15 PM PT

Diffuse Large B-Cell Lymphoma
11:30 AM – 1:30 PM PT

Multiple Myeloma
7:00 PM – 9:00 PM PT

Moderator
Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. You may also use the iPads available in the meeting room to complete the course evaluation.

Online/Zoom attendees: The CME credit link is posted in the chat room.

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RESEARCH
TO PRACTICE