# Cases from the Community: Investigators Discuss the Optimal Clinical Care of Patients with HER2-Positive Gynecologic Cancers

*An Independent CME Symposium During the 2025 SGO Annual Meeting on Women's Cancer®*

**Saturday, March 15, 2025**

**12:30 PM – 2:00 PM PT (3:30 PM – 5:00 PM ET)**

## Faculty

**Kathleen N Moore, MD, MS**

**Alessandro D Santin, MD**

## Moderator

**David M O'Malley, MD**

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# Faculty

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Stephenson Cancer Center at the University of Oklahoma HSC
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Board of Directors, ASCO
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# Dr Moore — Disclosures
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# Dr Santin — Disclosures
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# Dr O'Malley — Disclosures
# Moderator

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# What Clinicians Want to Know: Addressing Current Questions and Controversies in the Care of Patients with Ovarian Cancer

*An Independent CME Symposium During*
*the 2025 SGO Annual Meeting on Women's Cancer®*

**Sunday, March 16, 2025**
**12:30 PM – 2:00 PM PT (3:30 PM – 5:00 PM ET)**

## Faculty

**Kathleen N Moore, MD, MS**
**Ritu Salani, MD, MBA**
**Shannon N Westin, MD, MPH, FASCO, FACOG**

## Moderator

**Angeles Alvarez Secord, MD, MHSc**

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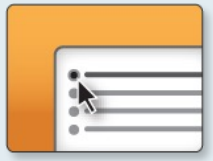
# Clinicians in the Meeting Room

**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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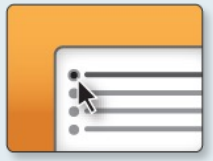
# Clinicians Attending via Zoom

**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 program. An email will be sent to all attendees when the activity is available.
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# Cases from the Community: Investigators Discuss the Optimal Clinical Care of Patients with HER2-Positive Gynecologic Cancers

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**David M O'Malley, MD**

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# Consulting Faculty

**Thomas P Morrissey, MD**
Director of Gynecologic Oncology
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Baptist Health South Florida
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**Lyndsay J Willmott, MD**
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Creighton University School of Medicine at Dignity Health St Joseph's Hospital and Medical Center
Assistant Professor
University of Arizona
Arizona Center for Cancer Care
Virginia G Piper
Cancer Care Network
Phoenix, Arizona

**Kellie E Schneider, MD**
Gynecologic Oncology
Novant Health Cancer Institute
Elizabeth (Gynecologic Oncology)
Charlotte, North Carolina

**Neil Love, MD**
Research To Practice
Miami, Florida

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# Agenda

**Module 1:** Strategies to Identify Patients with HER2-Positive Gynecologic Cancers — Dr Santin

**Module 2:** Available Data with and Practical Application of HER2-Targeted Therapy in Advanced Gynecologic Cancers — Dr O'Malley

**Module 3:** Identification and Management of Adverse Events with T-DXd — Dr Moore

# Agenda

**Module 1: Strategies to Identify Patients with HER2-Positive Gynecologic Cancers — Dr Santin**

**Module 2: Available Data with and Practical Application of HER2-Targeted Therapy in Advanced Gynecologic Cancers — Dr O'Malley**

**Module 3: Identification and Management of Adverse Events with T-DXd — Dr Moore**

# Strategies to Identify Patients with HER2-Positive Gynecologic Cancers

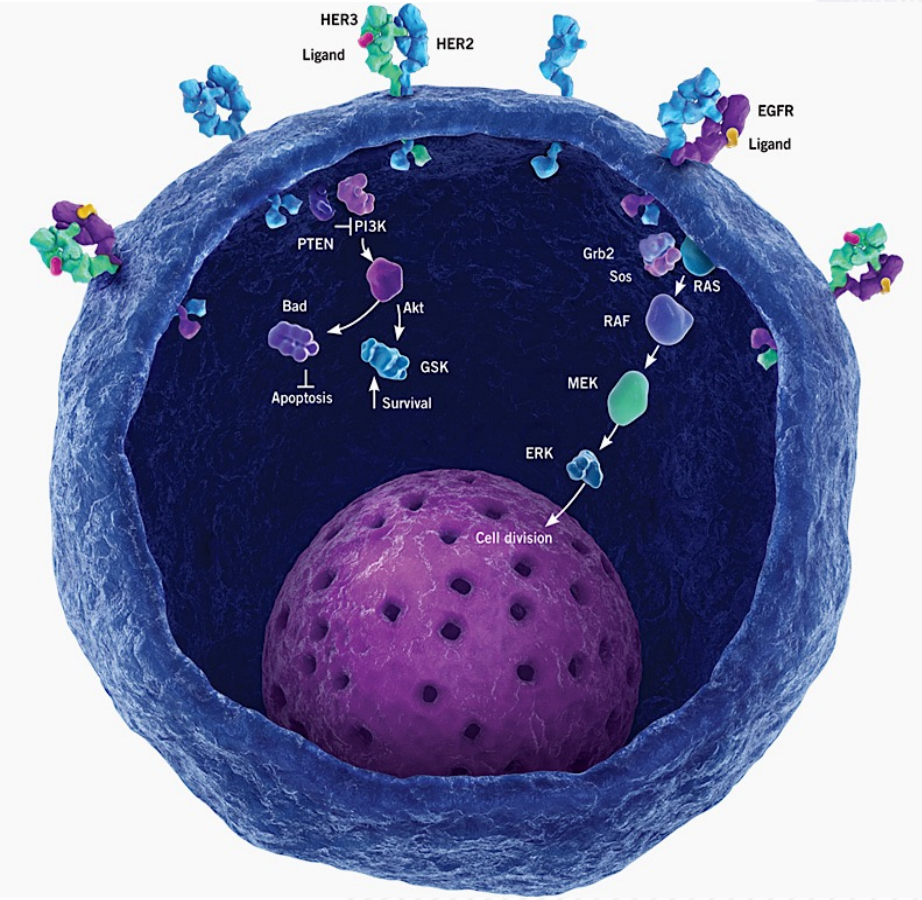
**Alessandro D. Santin, MD**
Professor of Gynecologic Oncology
Department of Obstetrics, Gynecology & Reproductive Sciences
Yale University School of Medicine
New Haven, CT

# HER2/neu in Gynecologic Cancers

- The Human Epidermal Growth Factor Type II receptor (i.e., HER2/neu, encoded by the c-ErbB2 gene) is a transmembrane RECEPTOR protein including an **extracellular** ligand-binding domain, **a membrane spanning region** and an **intracellular** TYROSINE KINASE domain.

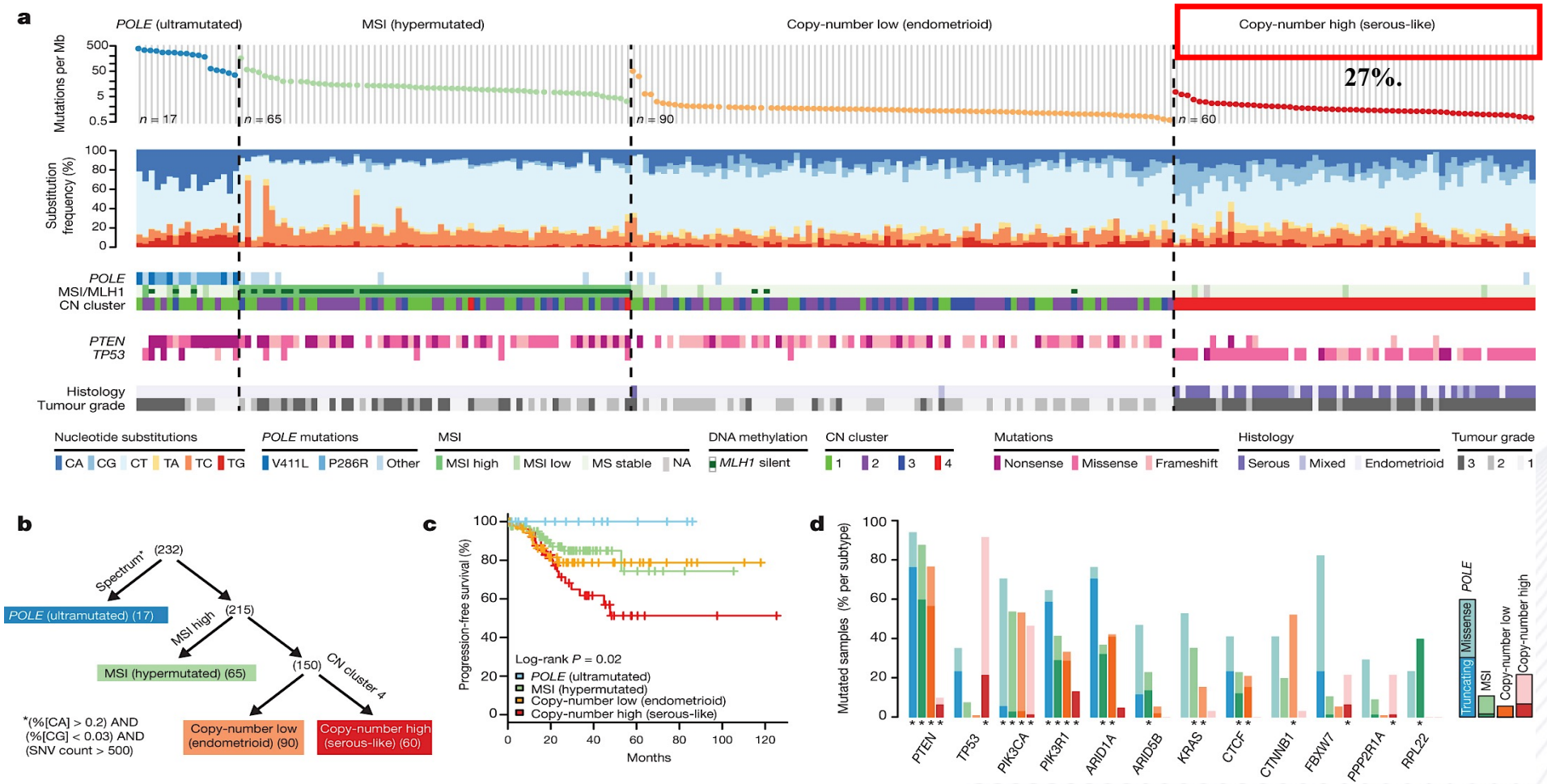
- HER2/neu functions as a **preferred partner for heterodimerisation** with any of the other members of the EGF receptor family (HER1, HER3 and HER4) and thus plays an important role in coordination of the complex c-ErbB2 signaling network that is responsible for regulating cell growth and differentiation.

- HER2/neu overexpression is thought to result in the **tyrosine kinase becoming constitutively activated** causing dysregulated gene transcription through activation of downstream protein pathways such as the PIK3CA/AKT/mTOR and RAS/RAF/MAPK.



# Incidence of HER2 expression/amplification/mutations documented among various gynecologic cancer subtypes

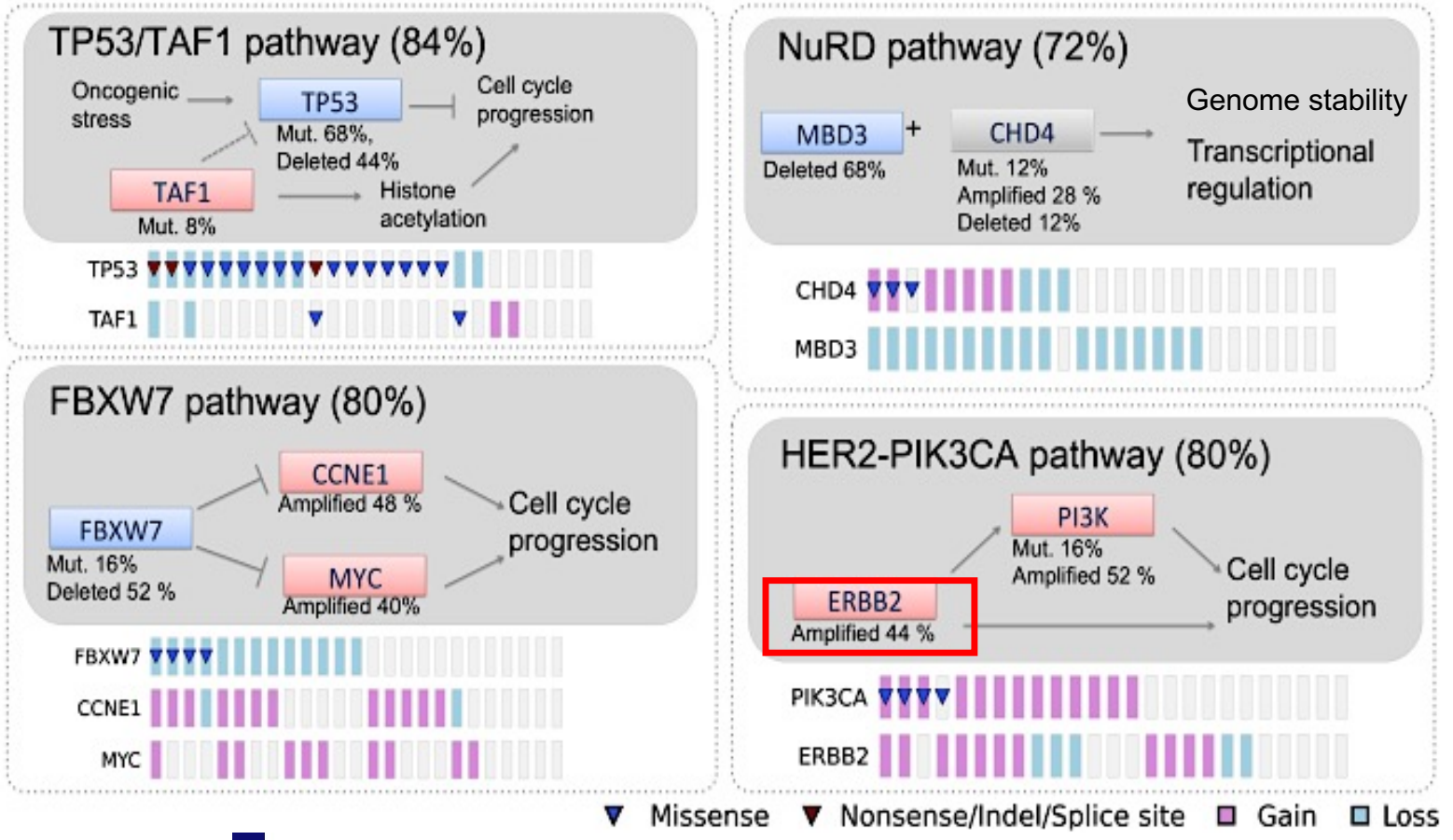
# Incidence of HER2 expression amplification/mutations among Uterine Cancers






Cancer Genome Atlas Network. *Nature* 2013;497(7447):67-73.

# Incidence of HER2 amplification in USC



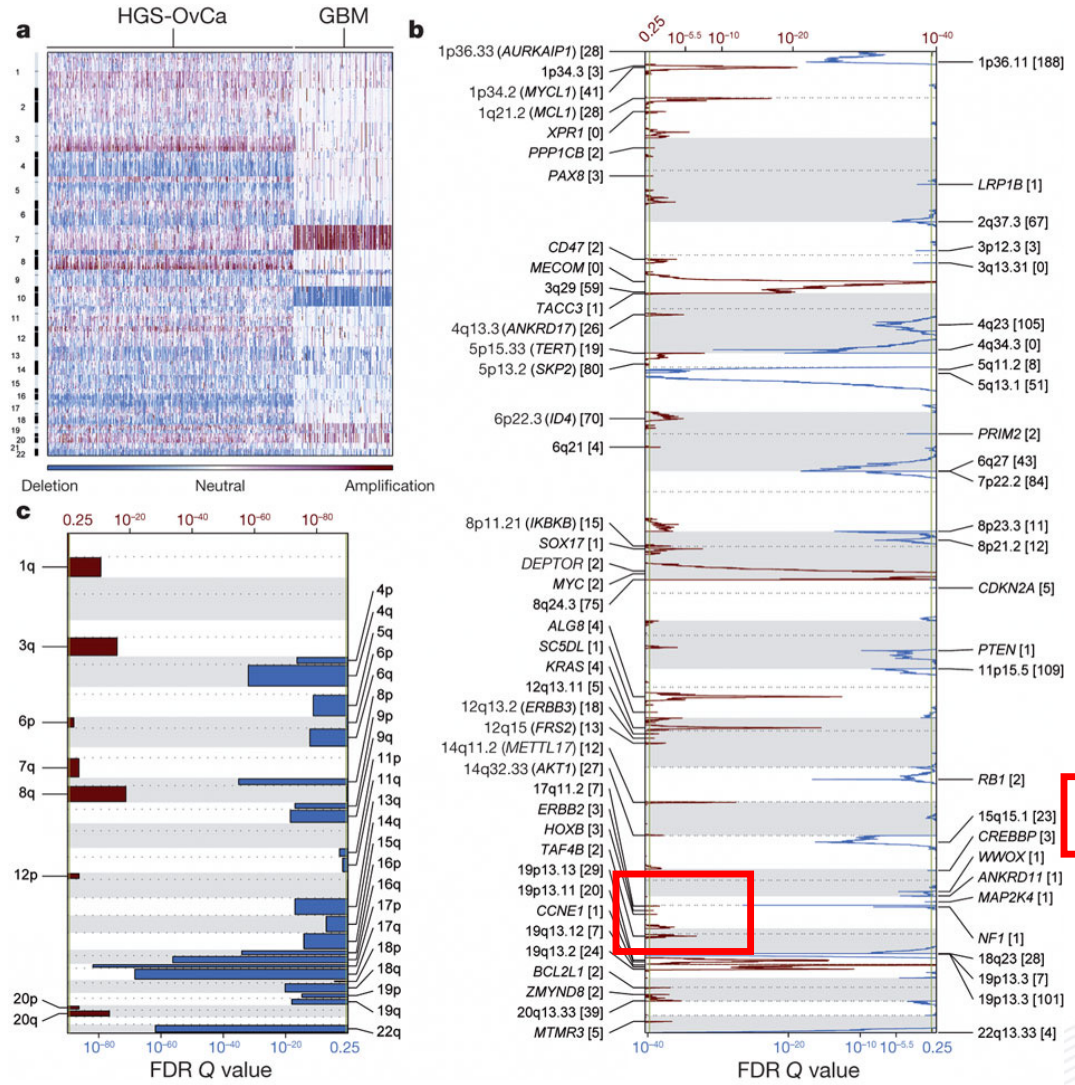

PNAS

## Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma


Siming Zhao[a], Murim Choi[a], John D. Overton[a], Stefania Bellone[b], Dana M. Roque[b], Emiliano Cocco[b], Federica Guzzo[b], Diana P. English[b], Joyce Varughese[b], Sara Gasparrini[b], Ileana Bortolomai[b], Natalia Buza[c], Pei Hui[c], Maysa Abu-Khalaf[d], Antonella Ravaggi[e], Eliana Bignotti[e], Elisabetta Bandiera[e], Chiara Romani[e], Paola Todeschini[e], Renata Tassi[e], Laura Zanotti[e], Luisa Carrara[e], Sergio Pecorelli[e], Dan-Arin Silasi[b], Elena Ratner[b], Masoud Azodi[b], Peter E. Schwartz[b], Thomas J. Rutherford[b], Amy L. Stiegler[f], Shrikant Mane[a], Titus J. Boggon[f], Joseph Schlessinger[f], Richard P. Lifton[a,1], and Alessandro D. Santin[b]

[a]Department of Genetics, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06510; [b]Departments of Obstetrics, Gynecology, and Reproductive Sciences, [c]Pathology, [d]Internal Medicine and Oncology, and [f]Pharmacology, Yale University School of Medicine, New Haven, CT 06510; and [e]Department of Obstetrics, and Gynecology, "Angelo Nocivelli" Institute of Molecular Medicine, University of Brescia, 25123 Brescia, Italy

# HER2 amplification in Ovarian Cancer



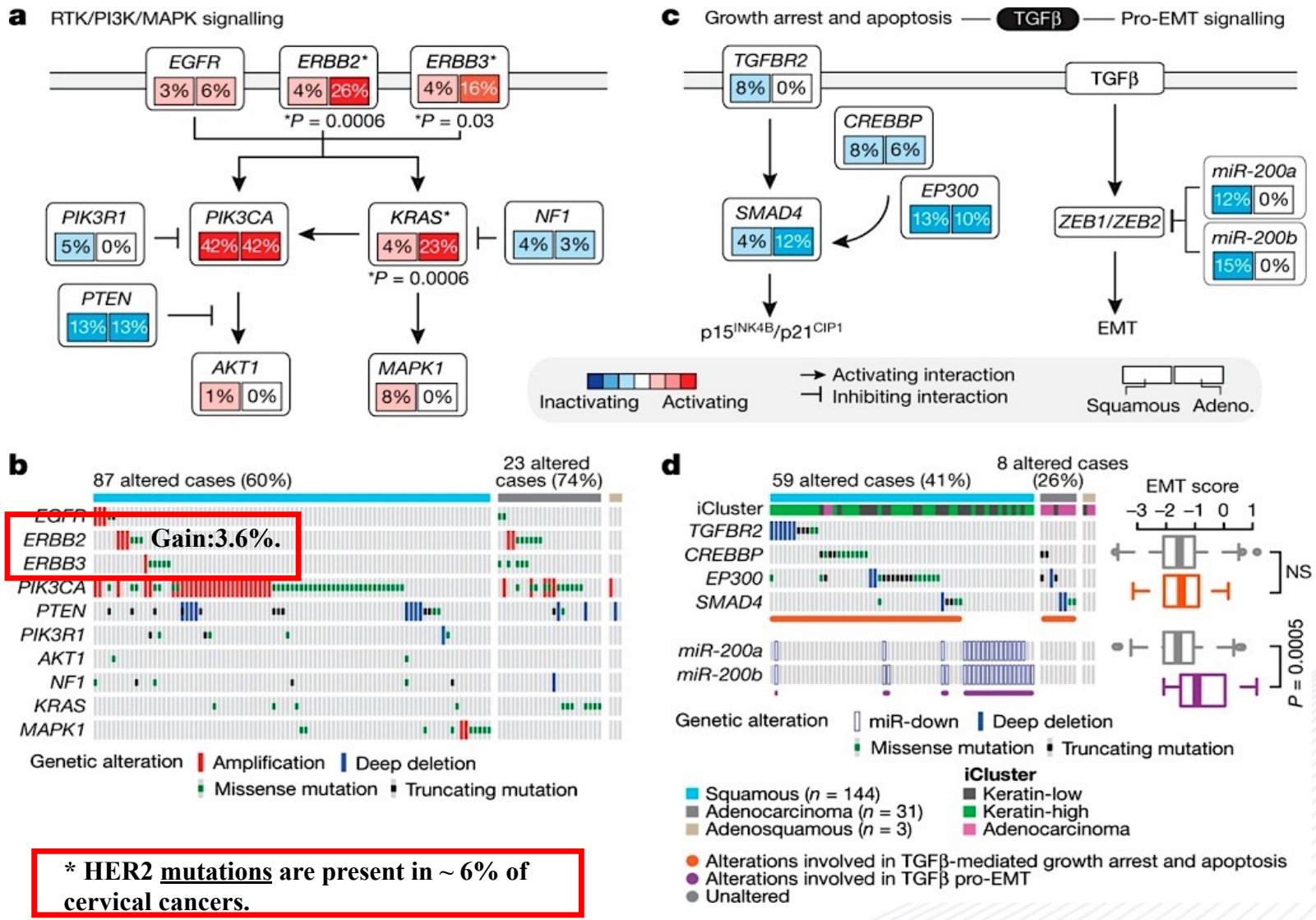

Genome copy number abnormalities

**c-erbB2 CNV gains: ~5%**

D Bell *et al. Nature* **474**, 609-615 (2011) doi:10.1038/nature10166

nature

# HER2 amplification in Cervical Cancer




*** HER2 <u>mutations</u> are present in ~ 6% of cervical cancers.**



R D Burk *et al. Nature* **543,** 378–384 (2017) doi:10.1038/nature21386

# Clinical and Molecular characteristics associated with HER2-positive gynecologic malignancies

# HER2 is a therapeutic target and poor prognostic biomarker in gynecologic cancers

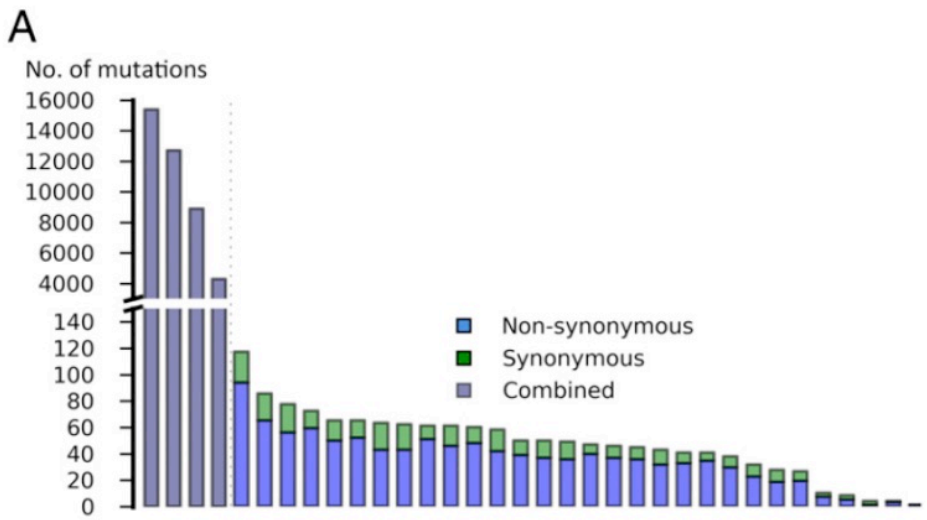
**Berchuck at al.,** Overexpression of HER-2/neu Is Associated with Poor Survival in Advanced Epithelial **Ovarian Cancer.** [CANCER RESEARCH 50, 4087-4091. July I, 1990]

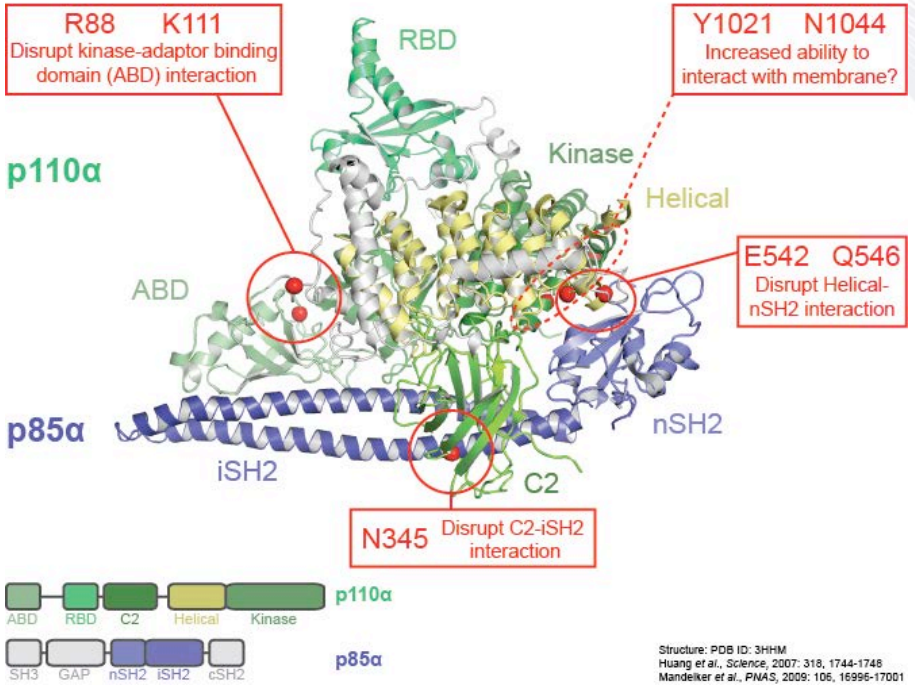
**AD. Santin et al.,** Racial differences in the overexpression of epidermal growth factor type II receptor (HER2/neu): a major prognostic indicator in **uterine serous papillary cancer.** AJOG, 2005 Mar;192(3):813-8.

**BK. Erickson et al.,*** Human epidermal growth factor 2 (HER2) in **early-stage uterine serous carcinoma**: A multi-institutional cohort study. Gynecol Oncol. 2020 Oct;159(1):17-22: **169 patients with stage I USC** were tested for HER2; 26% were HER2-positive. After a median follow-up of 50 months, there were 43 (25.4%) recurrences.
There were significantly more recurrences in the HER2-positive cohort **(50.0% vs 16.8%, p < .001).** HER2 positive tumors were associated with worse progression-free (PFS) and overall survival (OS) (p < .001 and p = .024).

***NRG-GY026:** Phase II/III study of paclitaxel/carboplatin combined with either trastuzumab and hyaluronidase-oysk (Herceptin HYLECTA) or pertuzumab, trastuzumab, and hyaluronidase-zzxf (PHESGO) in HER2 positive, stage I-IV **endometrial serous carcinoma or carcinosarcoma**

# Molecular characteristics associated with HER2-positivity in USC




**~ 95% of USC are MSI Stable and TMB low**

PNAS

## Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma


Siming Zhao[a], Murim Choi[a], John D. Overton[a], Stefania Bellone[b], Dana M. Roque[b], Emiliano Cocco[b], Federica Guzzo[b], Diana P. English[b], Joyce Varughese[b], Sara Gasparrini[b], Ileana Bortolomai[b], Natalia Buza[c], Pei Hui[c], Maysa Abu-Khalaf[d], Antonella Ravaggi[e], Eliana Bignotti[e], Elisabetta Bandiera[e], Chiara Romani[e], Paola Todeschini[e], Renata Tassi[e], Laura Zanotti[e], Luisa Carrara[e], Sergio Pecorelli[e], Dan-Arin Silasi[b], Elena Ratner[b], Masoud Azodi[b], Peter E. Schwartz[b], Thomas J. Rutherford[b], Amy L. Stiegler[f], Shrikant Mane[a], Titus J. Boggon[f], Joseph Schlessinger[f], Richard P. Lifton[a,1], and Alessandro D. Santin[b]

[a]Department of Genetics, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06510; [b]Departments of Obstetrics, Gynecology, and Reproductive Sciences, [c]Pathology, [d]Internal Medicine and Oncology, and [f]Pharmacology, Yale University School of Medicine, New Haven, CT 06510; and [e]Department of Obstetrics, and Gynecology, "Angelo Nocivelli" Institute of Molecular Medicine, University of Brescia, 25123 Brescia, Italy

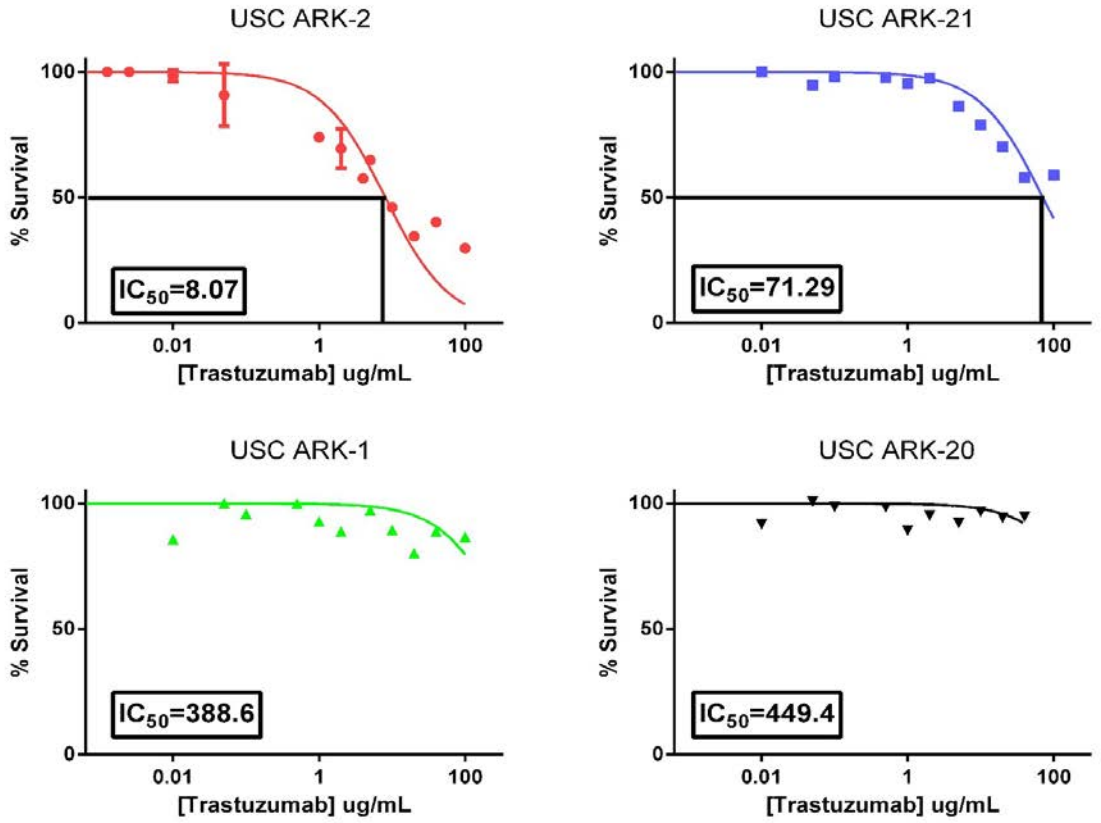

| 17 CELL LINES (%) | PIK3CA MUTATION (%) |
|---|---|
| **7 FISH+** (41%) | **4 (57%)** |
| 10 FISH- (59%) | 2 (20%) |

# Mutations in PIK3CA are a major determinant of resistance to trastuzumab in USC

**DOSE RESPONSE TO TRASTUZUMAB IN HER2 FISH+ USC CELL LINES**

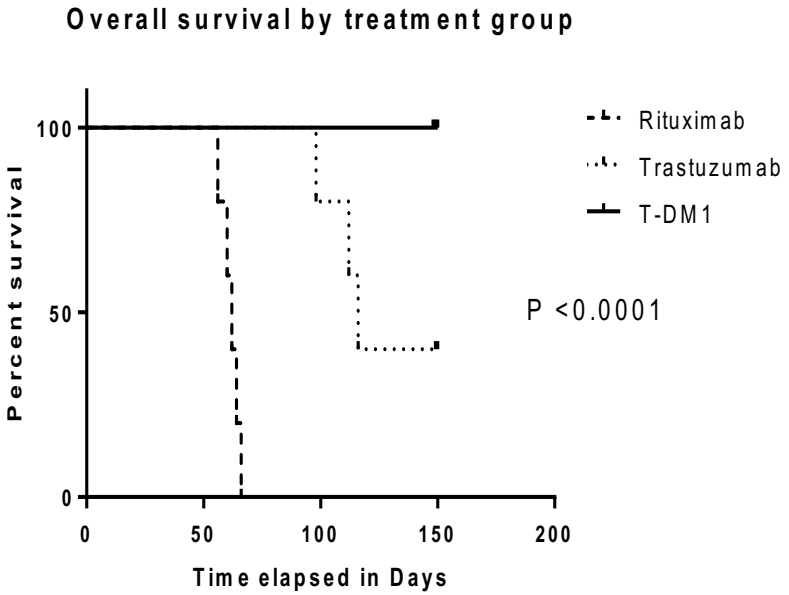
PIK3CA WILD TYPE

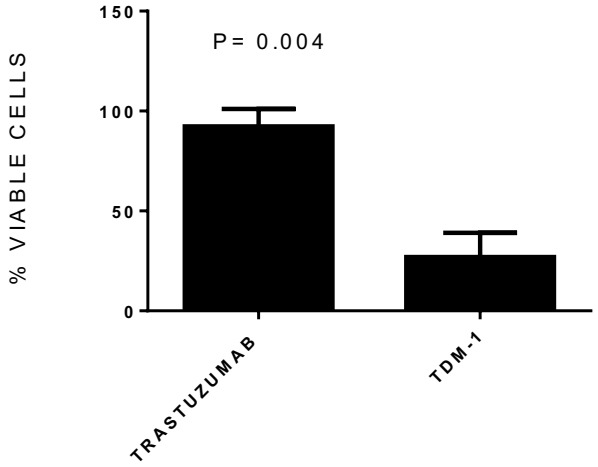
PIK3CA MUTATED

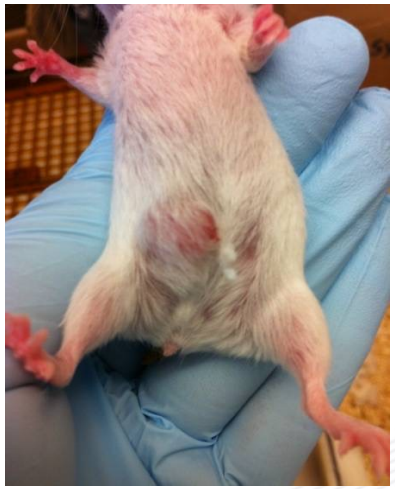


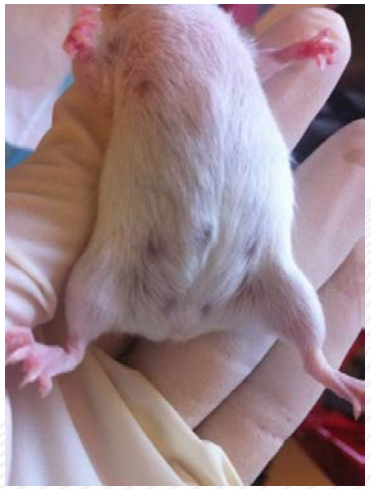

Black J. & Santin AD., British. J. Cancer. 2015 Sep 29;113(7):1020-6. doi: 10.1038/bjc.2015.306

# Trastuzumab (T) versus ADC (T-DM1) in HER2/NEU Amplified USC





*English D. et al. Cancer Medicine 3(5):1256–1265; 2014.*

# Molecular characteristics associated with HER2-positivity in OC

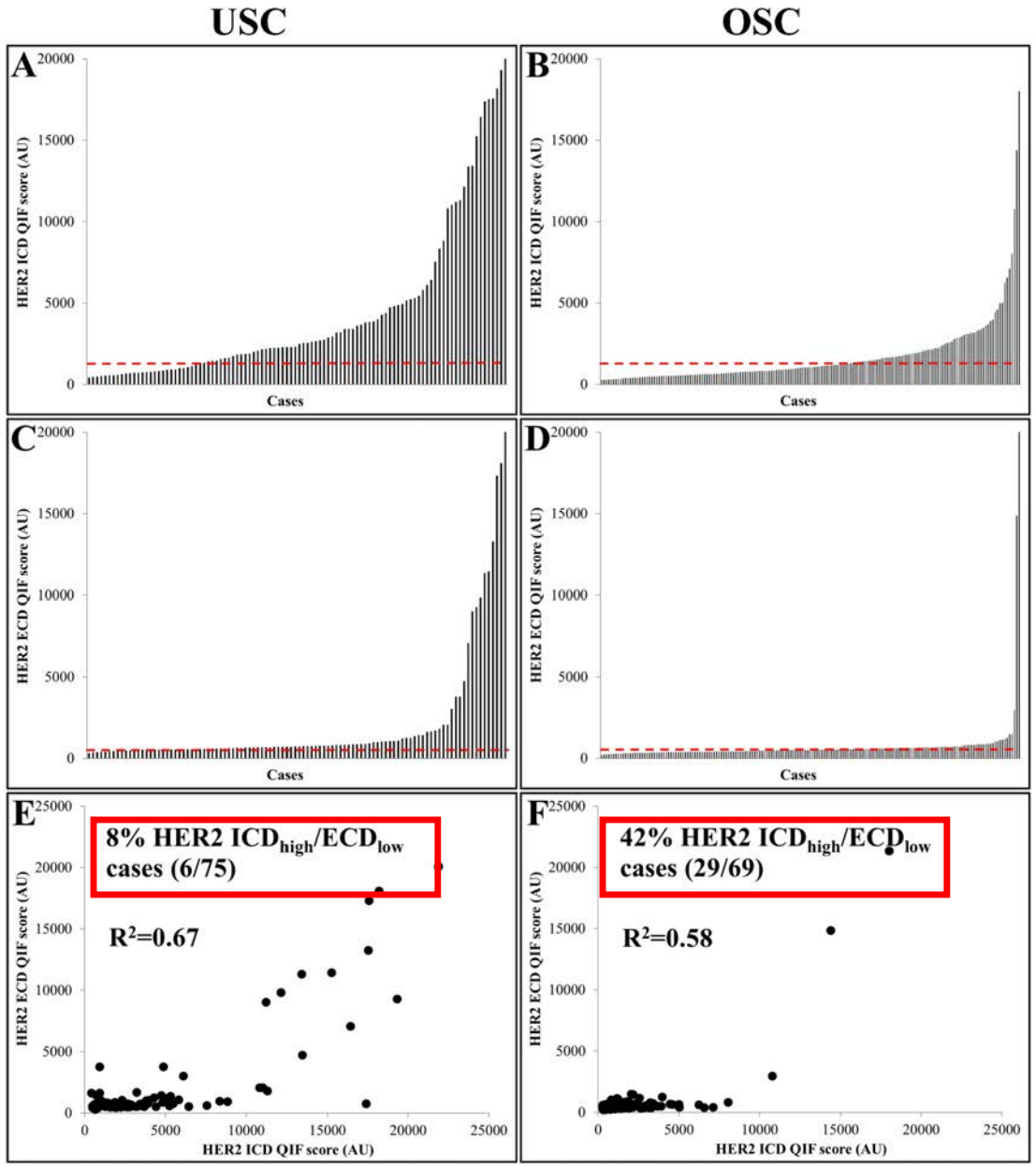



**Fig. 1**. HER2 **intracellular** (ICD) and **extracellular** (ECD) domain measurement in uterine (USC) and ovarian serous carcinomas (OSC). Bar plots show the distribution of scores for HER2 ICD/ECD in USC (A, C) and in OSC (B, D). Panels E and F depict ECD vs ICD scatterplots in USC and OSC, respectively. Red dotted line: median. QIF: quantitative immunofluorescence. AU: arbitrary units of fluorescence.

**Carvajal-Hausdorf D. & Santin AD.** Objective, domain-specific HER2 measurement in uterine and ovarian serous carcinomas and its clinical significance. **Gynecologic Oncology, 145, 154-158, 2017.**

# Integration of HER2 testing using IHC and ISH/FISH into routine gynecologic oncology practice

**CLINICAL CANCER RESERACH**

**Randomized Phase II Trial of Carboplatin-Paclitaxel Compared with Carboplatin-Paclitaxel-Trastuzumab in Advanced (Stage III-IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis**

Amanda N Fader[1], Dana M Roque[2], Eric Siegel[3], Natalia Buza[4], Pei Hui[4], Osama Abdelghany[4], Setsuko Chambers[5], Angeles Alvarez Secord[6], Laura Havrilesky[6], David M O'Malley[7], Floor J Backes[7], Nicole Nevadunsky[8], Babak Edraki[9], Dirk Pikaart[10], William Lowery[11], Karim ElSahwi[12], Paul Celano[13], Stefania Bellone[4], Masoud Azodi[4], Babak Litkouhi[14], Elena Ratner[4], Dan-Arin Silasi[4], Peter E Schwartz[4], **Alessandro D Santin**[15]

PMID: 32601075 PMCID: PMC8792803 DOI: 10.1158/1078-0432.CCR-20-0953 2020 Aug 1;26(15):3928-3935.

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

*Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin*

**Revision of the National Comprehensive Cancer Network (NCCN) guidelines,** which are widely recognized and used as the standard for clinical policy in oncology by clinicians and payers, adding carboplatin/paclitaxel trastuzumab (**2A category recommendation**) as the **preferred regimen** for women with **HER2+, advanced or recurrent USC** (http://www.jnccn.org).

# What is the optimal testing algorithm for the assessment of HER2 status in patients with Uterine Cancer?

| | Breast (ASCO/CAP 2018)[23] | Gastric (ASCO/CAP 2016)[36] | Colorectal (HERACLES Trial)[39] | Endometrial Serous (Fader et al Clinical Trial)[21] |
|---|---|---|---|---|
| HER2 IHC 3+ | >10% circumferential, strong, complete | ≥10%, strong complete, or basolateral/lateral | ≥50% strong complete, or basolateral/lateral | >30% strong complete or basolateral/lateral |
| *HER2* FISH amplification | *HER2*/CEP17 ratio ≥2.0 and *HER2* signal ≥4.0 per nucleus OR ratio <2.0 and *HER2* signal ≥6.0 per nucleus (if IHC score 2+ or 3+) | *HER2*/CEP17 ratio ≥2.0 OR ratio <2.0 and *HER2* signal >6.0 per nucleus | *HER2*/CEP17 ratio ≥2.0 in ≥50% of cells | *HER2*/CEP17 ratio ≥2.0 |

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists.

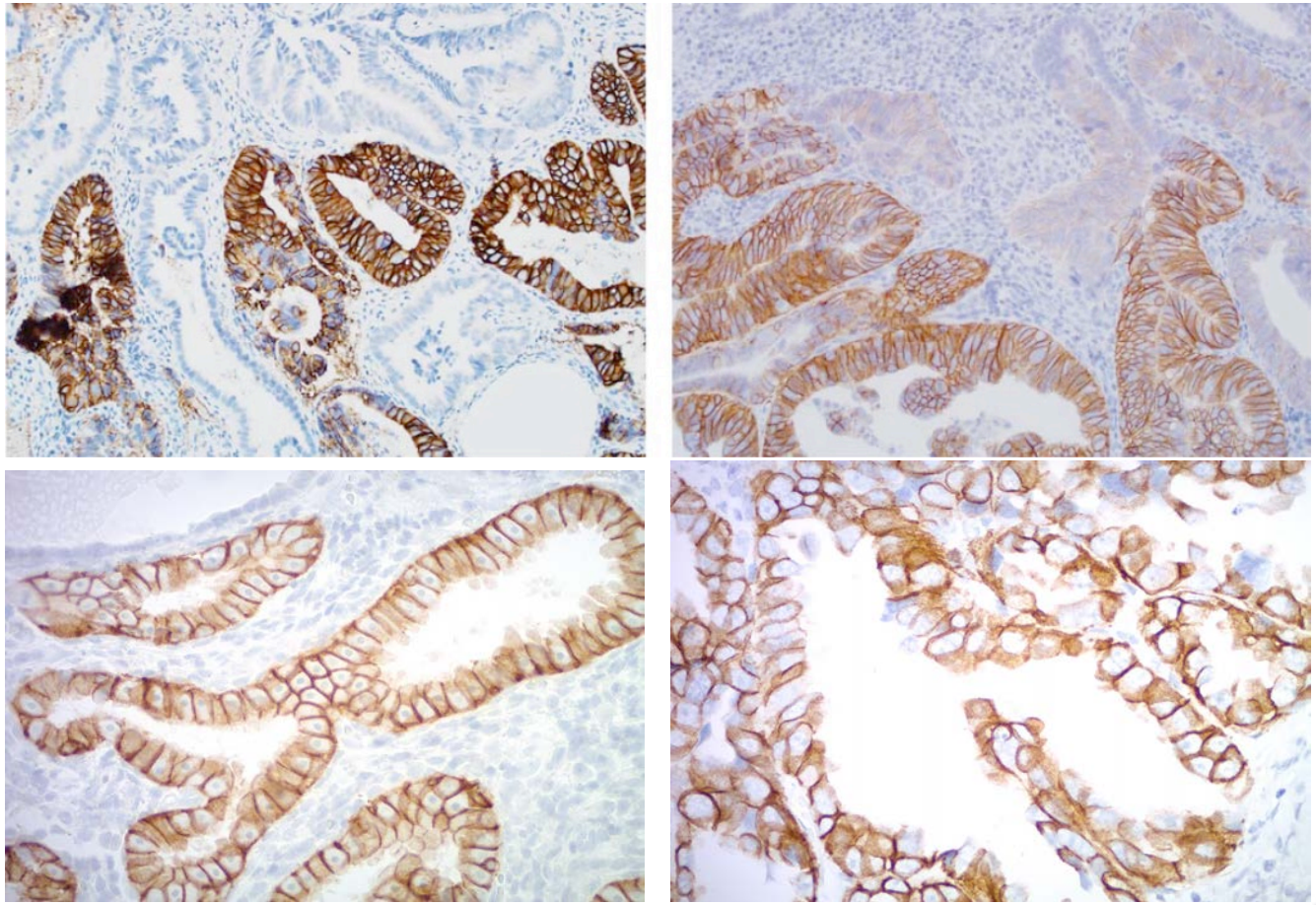
Solid tumors from different organs **have unique characteristics of HER2 protein expression and gene amplification**. Accordingly, different/specific HER2 scoring criteria should apply.

**Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice**

Natalia Buza[1], Diana P English[2], Alessandro D Santin[2] and Pei Hui[1]

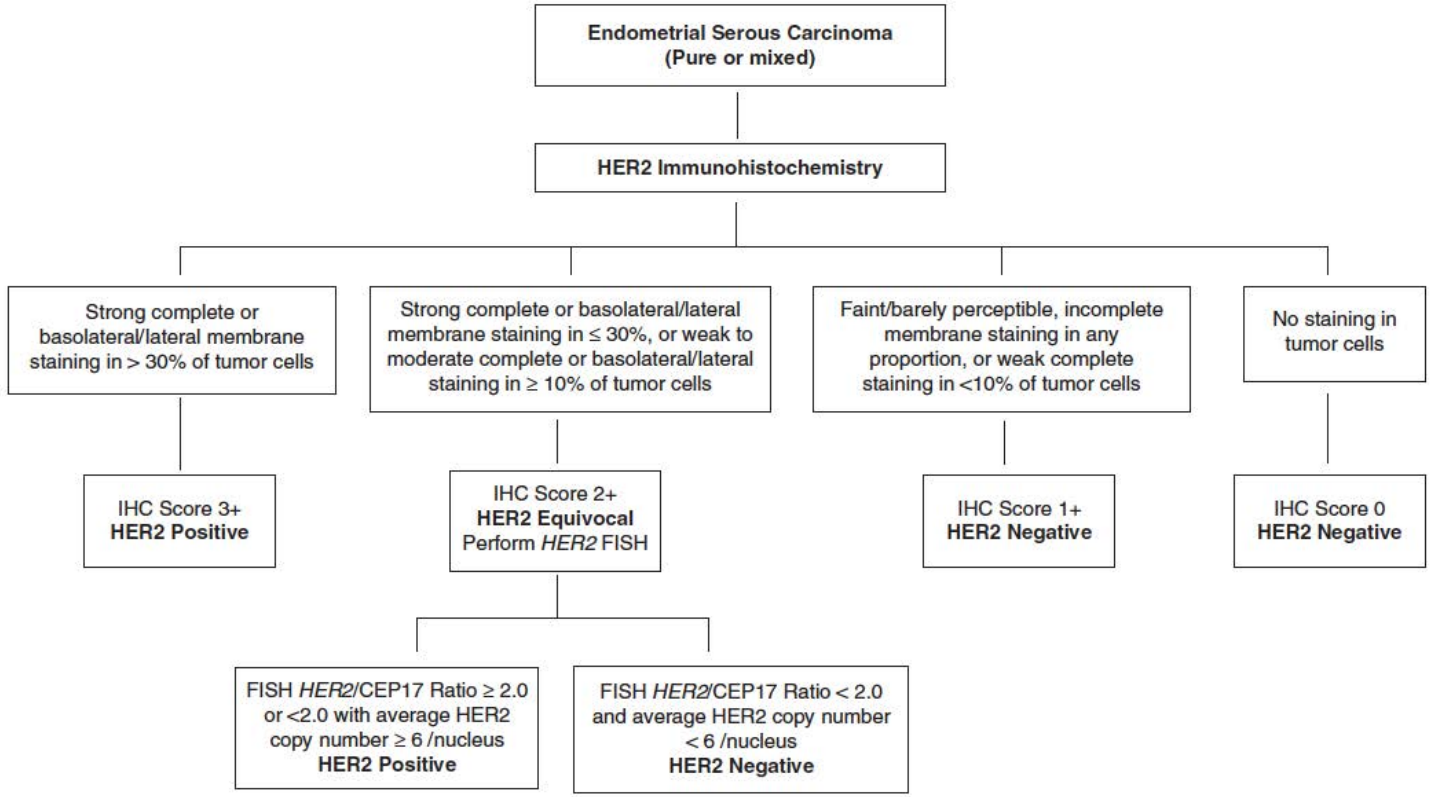
Natalia Buza, MD.
HER2 Testing in Endometrial Serous Carcinoma
Time for Standardized Pathology Practice to Meet the Clinical Demand
Arch Pathol Lab Med. 2021;145:687–691

# Molecular characteristics of HER2 protein expression and gene amplification in USC



Unlike breast cancer, **USC is highly heterogeneous in HER2/neu expression** with up **53%** of HER2/neu 3+ by IHC demonstrating at least two-degree difference in staining intensity in tumor cells.
**Lack of Apical Her2 Staining: ~75% of Her2 positive cases.**

# HER2 testing algorithm for Endometrial Serous Carcinoma



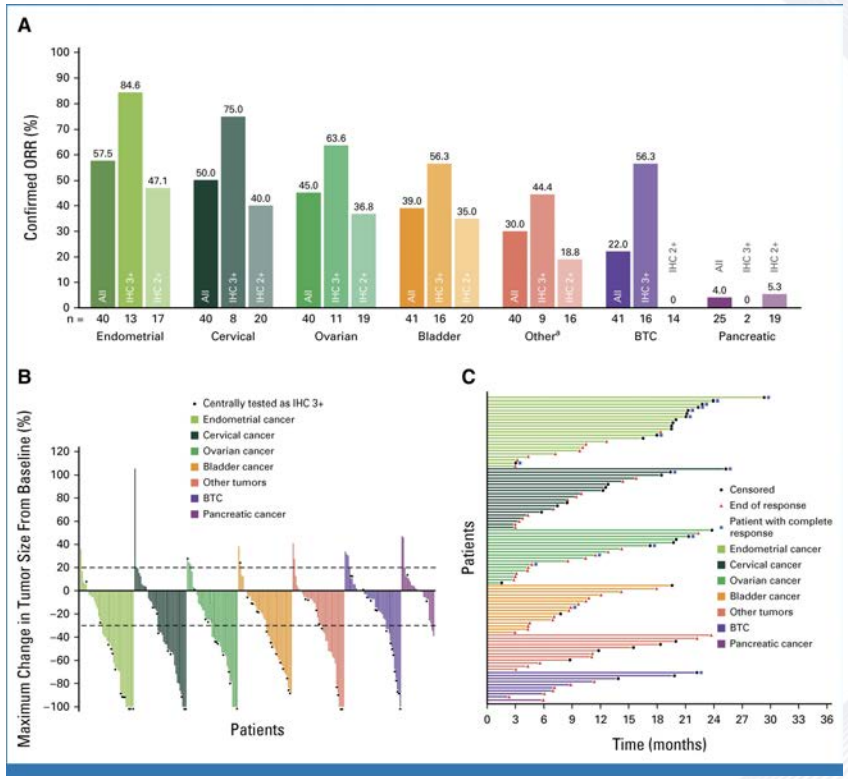

- **2007 ASCO/CAP breast with specific modifications:**
  - **30% staining cut-off for a 3+ positive score**
  - **Complete circumferential staining was not required, U-shaped/basolateral/lateral staining pattern (lack of apical staining) was also accepted**
  - **Heterogeneity was recognized, large tumor section(s) selected for IHC testing**
  - **Reflex FISH on 2+ IHC cases, in correlation with the IHC stained slide**
    - **Larger tumor area selected for FISH**

# HER2/neu as Target Unconjugated Antibody vs ADC

- **Main Mechanisms of action of Trastuzumab (unconjugated Ab)** include:
- 1) Inhibition of tumor cell proliferation/induction of apoptosis (secondary to **decreased** HER2/neu receptor **dimerization**).
- 2) **ADCC** secondary to engagement of Fc receptors on effector cells (NK) (Dominant component of in vivo activity).

- **Main Mechanisms of action of ADC (T-DXd, T-DM1)** include:
- 1) tumor cell killing directly related to its **"toxic payload,"** which is a highly potent cytotoxic drug specifically delivered to cancer cells by the attached antibody.
- 2) **Bystander effect:** Once processed by the Tumor HER2/neu + cells, ADCs can release cytotoxic drug molecules that can diffuse out of Ag+ cells into the neighboring antigen-negative (Ag−) cells to induce their cytotoxicity.

- **DESTINY TRIAL**: New category of targetable patients: **HER2/neu 2+ FISH- patients**.




Meric-Bernstam F., et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the **DESTINY-PanTumor02 Phase II Trial**. J Clin Oncol. 2024 Jan 1;42(1):47-58.

*HER2 IHC status was assessed centrally using HER2 HercepTest (DAKO) and scored according to gastric-specific criteria

# Optimal source material for and timing of HER2 testing in advanced gynecologic cancers

# HER2/neu testing Guidelines for Gynecologic tumors

**Clinicians** should request **HER2 testing** on tumor tissue in the biopsy or resection specimens (primary or metastasis) prior to the initiation of trastuzumab/ADC therapy.

When HER2 status is being evaluated, laboratories/pathologists should perform/order IHC testing first, followed by ISH/FISH when IHC result is 2+ (equivocal). **Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH/FISH testing**.

**Pathologists** should identify and **mark areas with strongest intensity** of HER2 expression by IHC in the specimen for subsequent ISH/FISH scoring when required.

The prevalence of HER2 status may be discordant between the primary tumor and metastases in **approximately 25% of cases**, especially after treatment.

Per **NCCN guidelines** treating clinicians should offer **combination chemotherapy and HER2-targeted therapy** as the initial treatment for appropriate patients harboring HER2 positive advanced USC and as treatment for recurrent USC. For any gynecologic cancer patient with recurrent tumors demonstrating HER2 2+/3+ expression by IHC, trastuzumab deruxtecan is recommended.

# Utility of other testing methods (eg, NGS, liquid biopsy) to identify patients with advanced gynecologic cancers who might benefit from HER2-targeted therapy

# NGS to identify patients with advanced gynecologic cancers who might benefit from HER2-targeted therapy

The accuracy of NGS in detecting **HER2 gene amplifications** remains uncertain due to conflicting reports in the scientific literature.

In breast and gastric cancer patients NGS assay has good concordance with conventional testing methods for gene amplifications (**with clinical positivity defined as 3+ IHC staining or 2+ IHC staining with reflex gene amplification utilizing fluorescent in-situ hybridization (FISH**) but is less sensitive in detecting low level gene amplification.

In endometrial cancer NGS assay **may potentially increase eligibility for targeted therapy** for patients with advanced and recurrent endometrial cancers. However, in the few pilot studies so far published the NGS platforms concordance vs the Gold Standard IHC/FISH testing vary from 50% to 100% HER2-positive cases (attributed to intra-tumoral heterogeneity, tumor cellularity, a small number of amplified cells, and the HER2/CEP17 ratio near the cut-off.)
**Yale University data for 139 USC tested at FM demonstrated 81% concordance**.

**Clinical HER2 testing remains the GOLD STANDARD and should not be abandoned**

# Video Cases and Questions for the Faculty

# Case Presentation: 72-year-old woman s/p surgery with newly diagnosed metastatic HER2-positive (IHC 2+, ISH amplified) uterine papillary serous carcinoma (UPSC)

Lyndsay J Willmott, MD (Phoenix, Arizona)

RTP RESEARCH TO PRACTICE

# QUESTIONS FOR THE FACULTY

**How long would you continue the trastuzumab maintenance for this patient with HER2-positive (IHC 2+, ISH amplified) UPSC who received carboplatin/paclitaxel/trastuzumab and now has no evidence of disease on imaging?**

**Should all patients with gynecologic cancers undergo HER2 testing regardless of tumor type or histology?**

**What is your preferred method of HER2 testing? For patients who are IHC 2+ do you reflexively order ISH? Should gynecologic tumors that are IHC 2+ and ISH-positive be classified as HER2-positive?**

Kellie E Schneider, MD
(Charlotte, North Carolina)

**Case Presentation: 77-year-old woman with newly diagnosed dMMR, TP53-mutated, HER2-positive (IHC 3+) UPSC, lymph node-positive**

Thomas P Morrissey, MD
(Boca Raton, Florida)

**Case Presentation: 65-year-old woman with newly diagnosed HER2-positive, node-positive UPSC with a somatic BRCA2 mutation (pMMR)**

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# QUESTIONS FOR THE FACULTY

**What initial systemic treatment would you recommend for a patient with dMMR, TP53-mutated and HER2-positive (IHC 3+) newly diagnosed UPSC? What maintenance would you recommend? What if the HER2 was IHC 2+ and ISH-positive?**

**How would you approach a patient with newly diagnosed HER2-positive and BRCA-positive endometrial cancer?**

**In what situations, if any, would you combine anti-HER2 therapy and immunotherapy? What about combining anti-HER2 therapy with a PARP inhibitor? If so, what specific regimens would you recommend for each setting?**

# Agenda

**Module 1:** Strategies to Identify Patients with HER2-Positive Gynecologic Cancers — Dr Santin

**Module 2: Available Data with and Practical Application of HER2-Targeted Therapy in Advanced Gynecologic Cancers — Dr O'Malley**

**Module 3:** Identification and Management of Adverse Events with T-DXd — Dr Moore

# Available Data with and Practical Application of HER2-Targeted Therapy in Advanced Gynecologic Cancers

**David M O'Malley, MD**

**The Ohio State University and**
**The James Comprehensive Cancer Center**

**Columbus, Ohio**

VOLUME 36 · NUMBER 20 · JULY 10, 2018

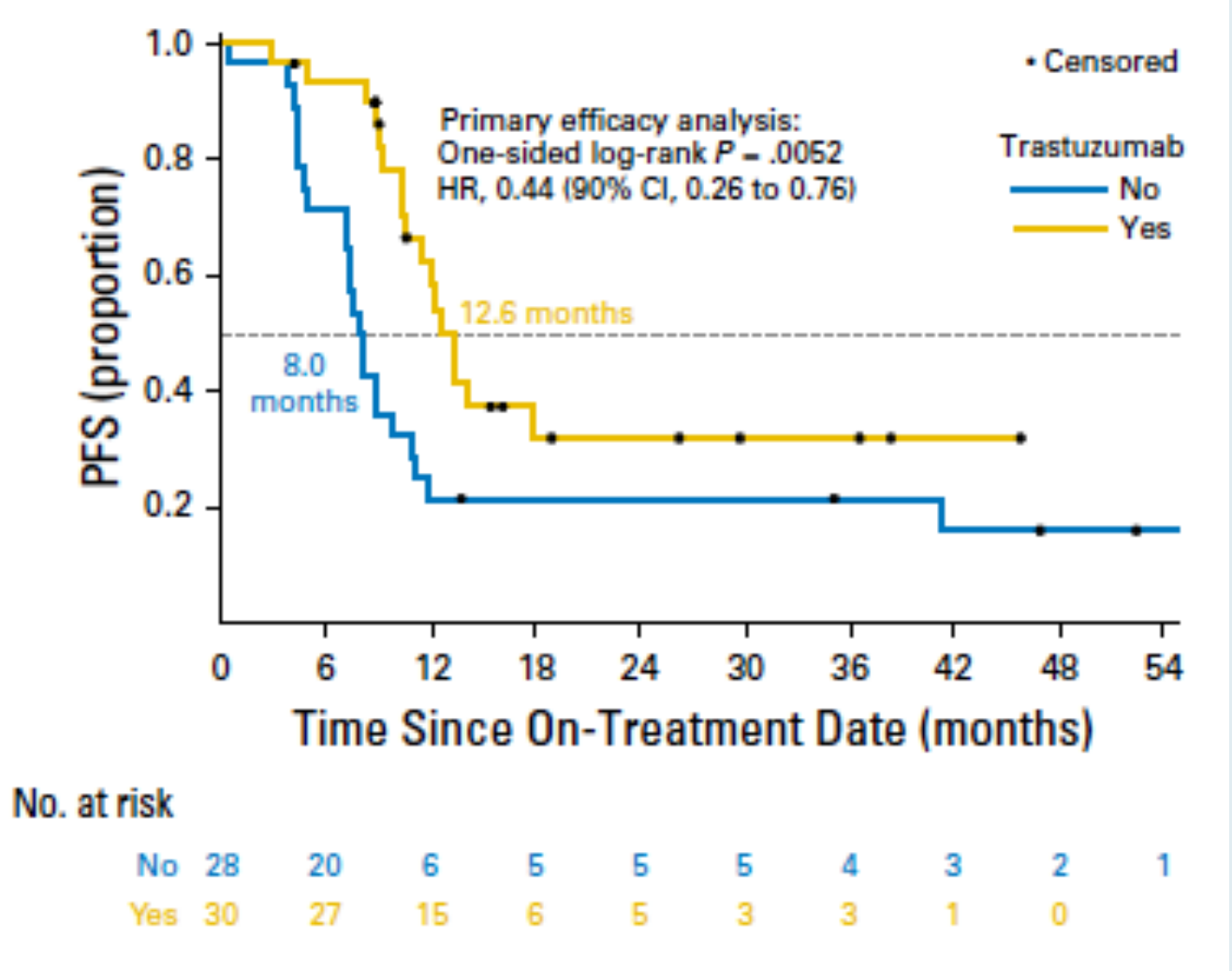
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

*Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin*

# Phase II Trial of Carboplatin/Paclitaxel with and without Trastuzumab for HER2-Positive Uterine Serous Carcinomas: Primary Efficacy Analysis

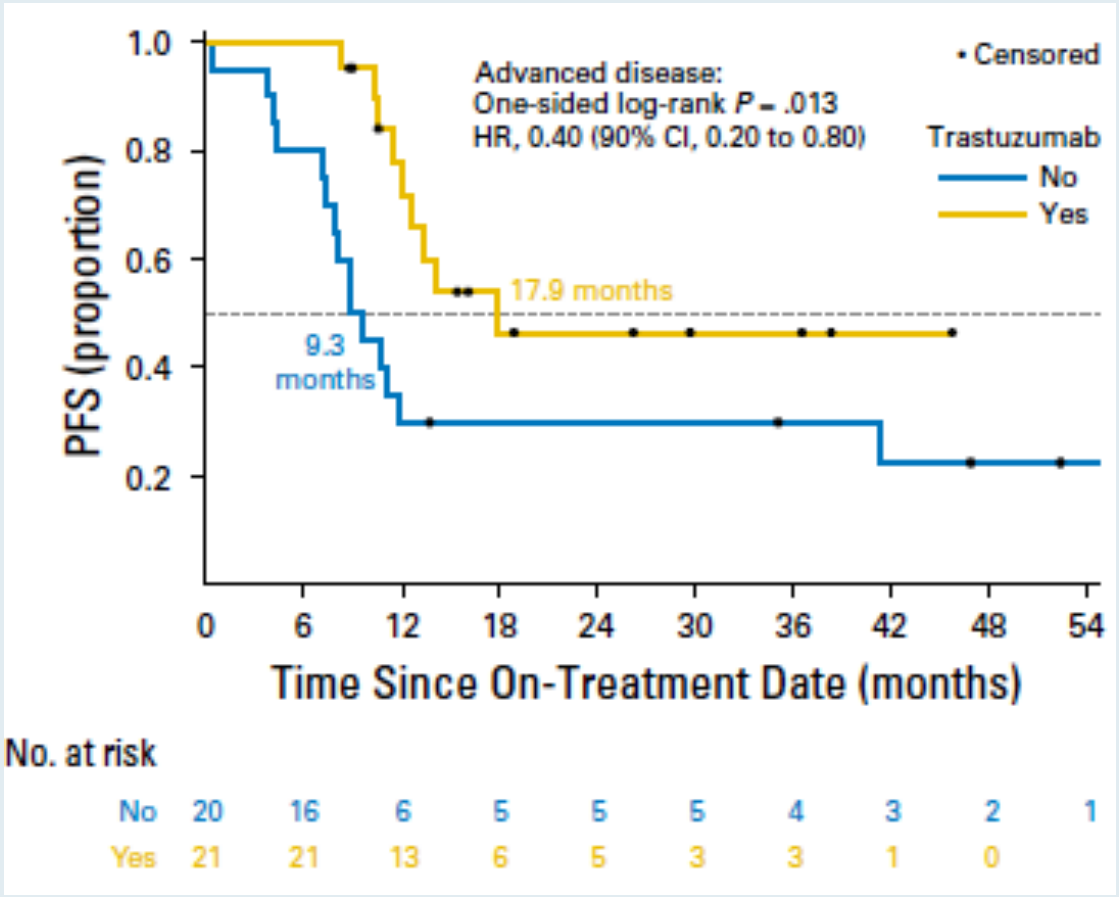


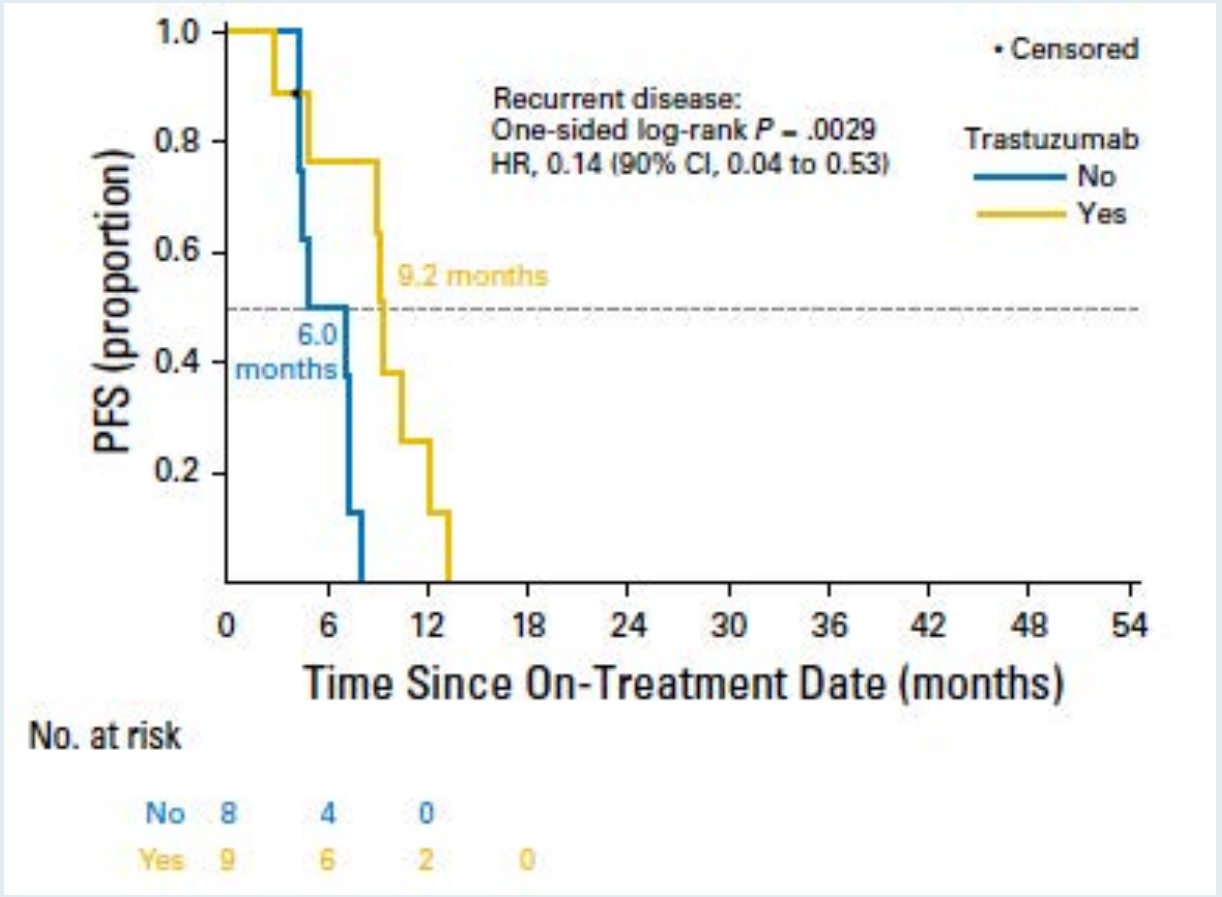

Fader AN et al. *J Clin Oncol* 2018;36(20):2044-51.

PFS = progression-free survival

RTP RESEARCH TO PRACTICE

# Phase II Trial of Carboplatin/Paclitaxel with and without Trastuzumab for HER2-Positive Uterine Serous Carcinomas: Advanced and Recurrent Disease

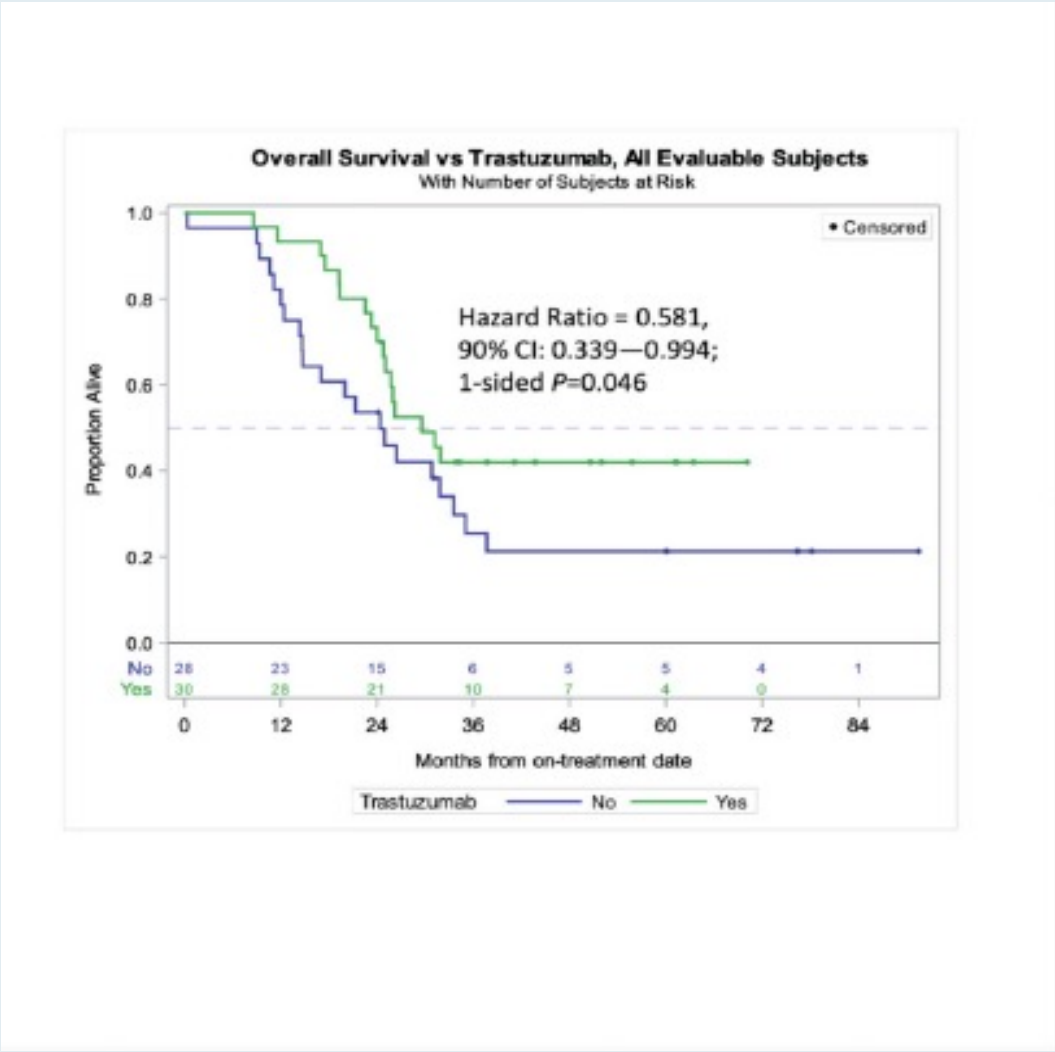


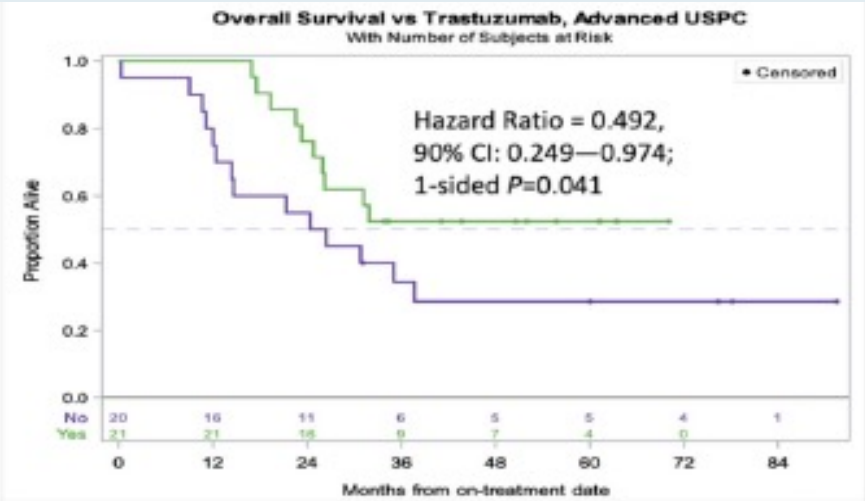



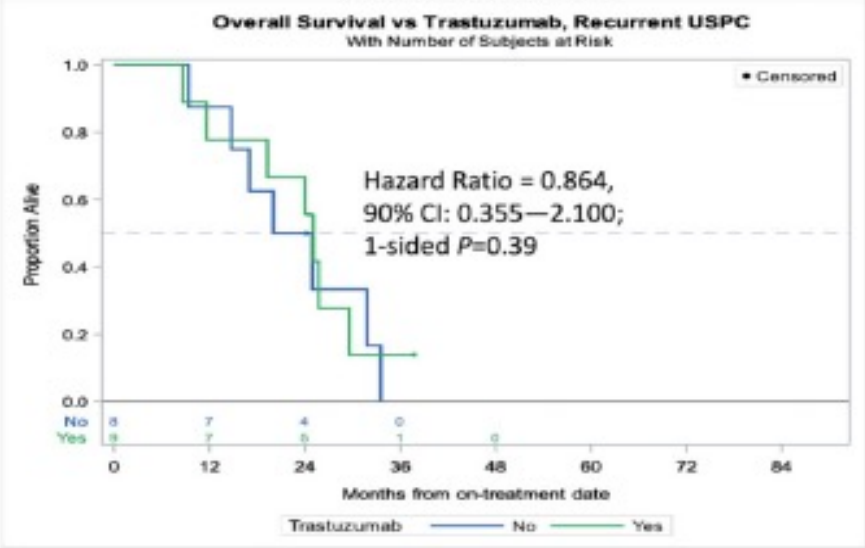

Fader AN et al. *J Clin Oncol* 2018;36(20):2044-51.

RTP RESEARCH TO PRACTICE

# Phase II Trial of Carboplatin/Paclitaxel with and without Trastuzumab for HER2-Positive Uterine Serous Carcinomas: Updated Overall Survival Analysis




Fader AN et al. *Clin Cancer Res* 2020;26(15):3928-35.

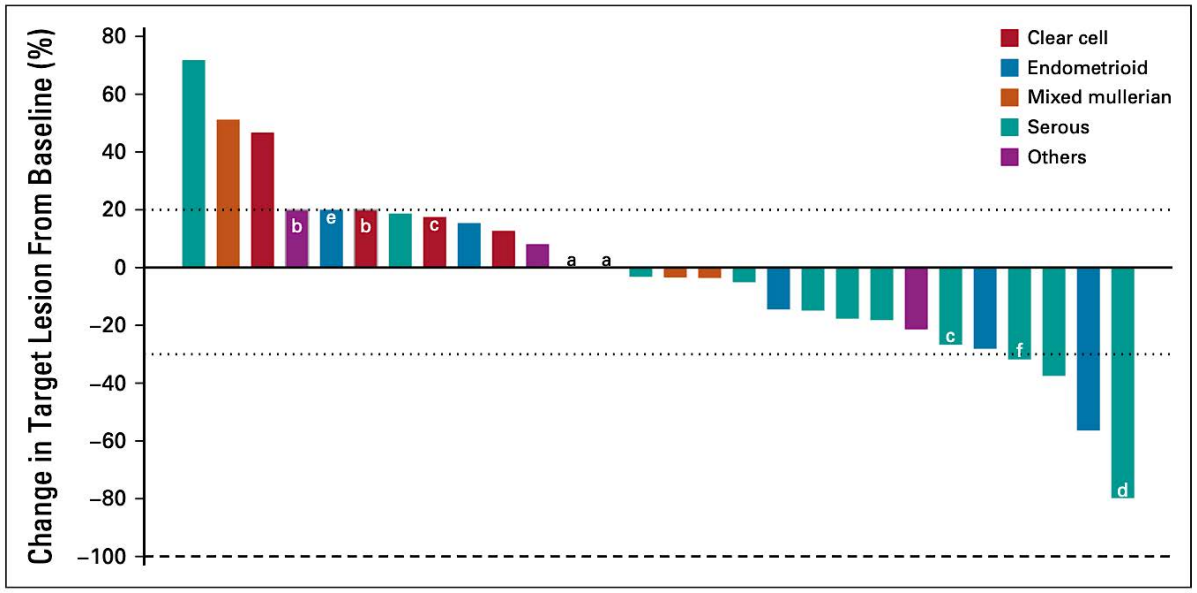
RTP RESEARCH TO PRACTICE

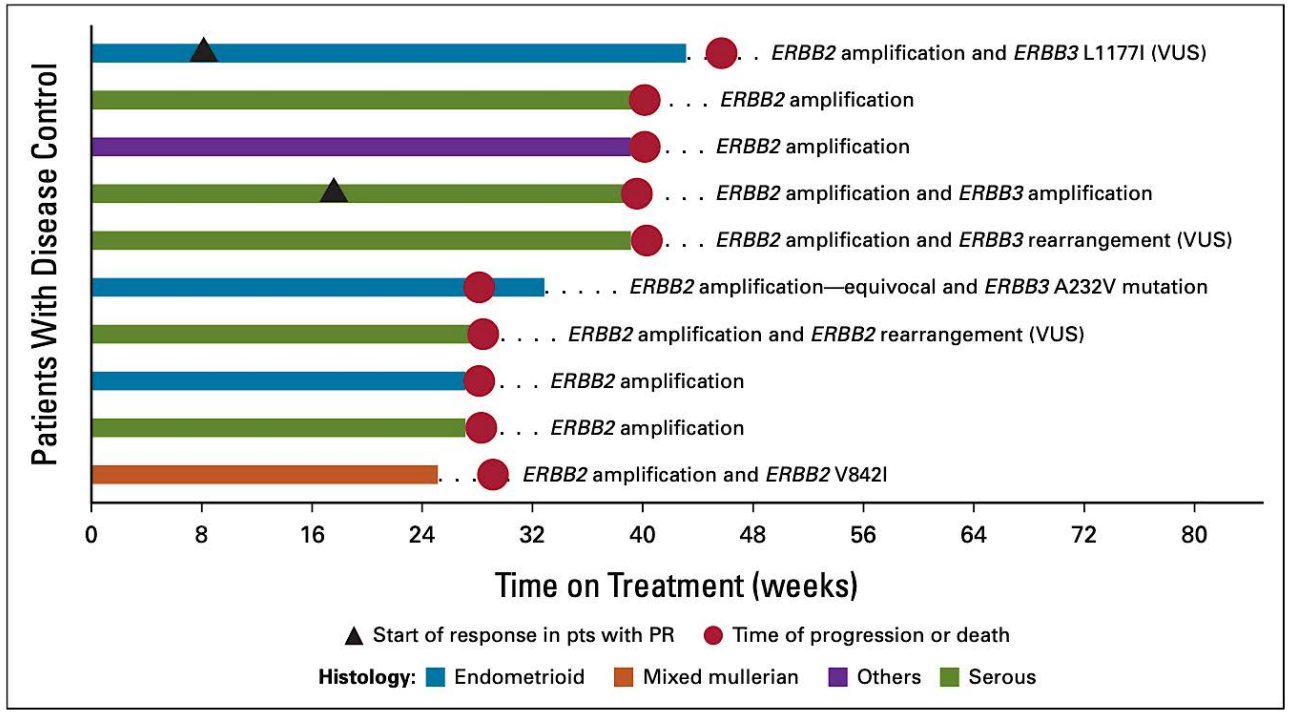
# Pertuzumab Plus Trastuzumab in Patients With Endometrial Cancer With *ERBB2/3* Amplification, Overexpression, or Mutation: Results From the TAPUR Study

Eugene R. Ahn, MD[1]; Michael Rothe, MS[2]; Pam K. Mangat, MS[2]; Elizabeth Garrett-Mayer, PhD[2]; Hussein M. Ali-Ahmad, MD[3]; John Chan, MD[4]; Michael L. Maitland, MD, PhD[5,6]; Sapna R. Patel, MD[7]; Zachary Reese, MD[8]; Ani S. Balmanoukian, MD[9]; Charles W. Drescher, MD[10]; Rui Li, MD, PhD[11]; Apostolia M. Tsimberidou, MD, PhD[12]; Charles A. Leath III, MD, MSPH[13]; Raegan O'Lone, PhD[2]; Gina N. Grantham, BS[2]; Susan Halabi, PhD[14]; and Richard L. Schilsky, MD[2]

*JCO Precis Oncol* 2023 April:7:e2200609.

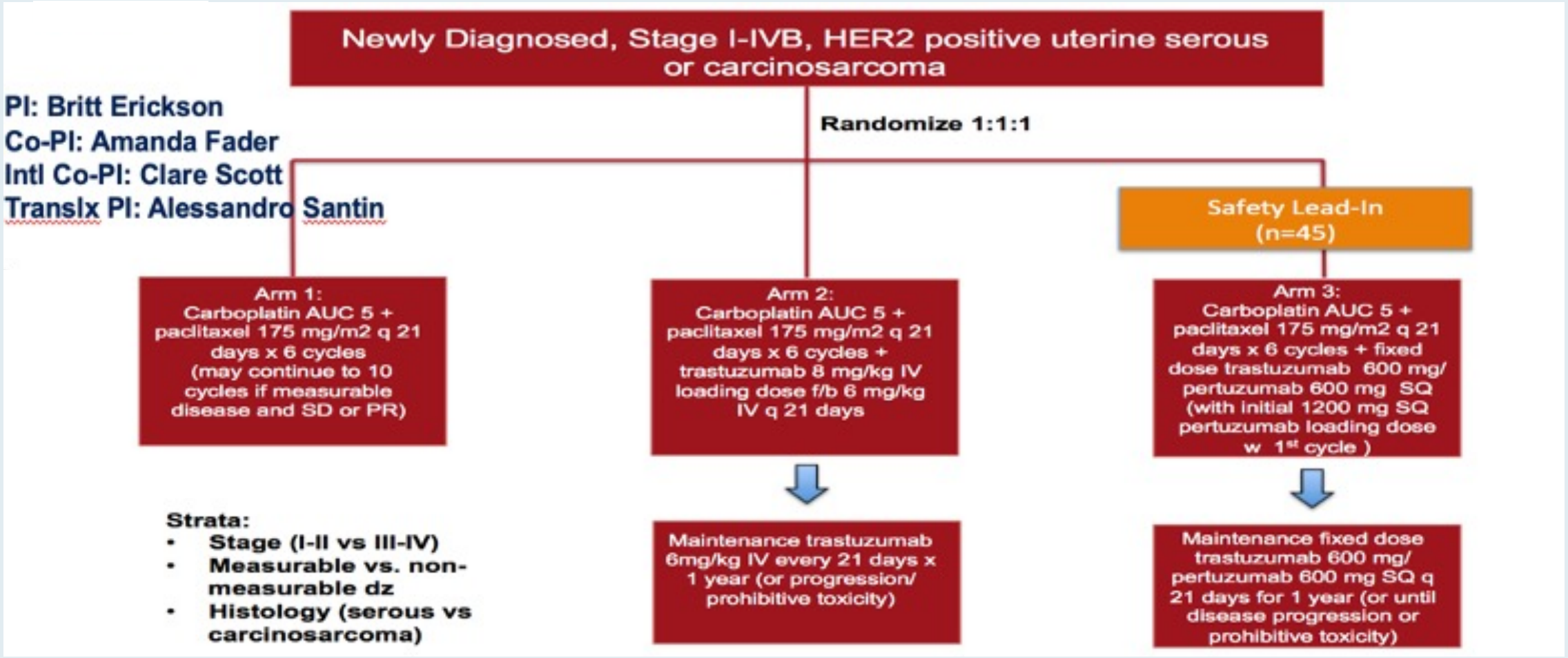
# TAPUR: Activity of Pertuzumab with Trastuzumab in Endometrial Cancer with HER2 or HER3 Alterations




Ahn ER et al. *JCO Precis Oncol* 2023 April:7:e2200609.

# NRG-GY026: An Ongoing Phase II/III Trial of Paclitaxel/Carboplatin Alone or with Either Trastuzumab or Trastuzumab/Pertuzumab for HER2-Positive Endometrial Cancer




Courtesy of Matthew A Powell, MD

# SGNTUC-019, Phase 2 Basket Study: Tucatinib + Trastuzumab for HER2+ Solid Tumors — Metastatic Biliary Tract Cancer Cohort

**Patients received tucatinib 300 mg PO BID and trastuzumab 8 mg/kg IV, then 6 mg/kg Q3W (21-day cycle).**

- HER2 overexpression, amplification, or mutation (IHC/ISH or NGS local test)
- Unresectable LA or met cancer
- Baseline measurable disease
- ≥1 prior systemic therapy for LA or met disease
- No prior HER2-directed therapy

**Tucatinib + Trastuzumab**

**Planned for 30/cohort**

**Cohorts:**

1. **Cervical**
2. **Uterine**
3. **Biliary tract cancer**
4. **Urothelial**
5. **Nonsq NSCLC**
6. **Other**
7. **Nonsq NSCLC HER2m**
8. **Breast HER2m**
9. **Other HER2m**

**Primary endpoint**

- Confirmed ORR (investigator)

**Secondary endpoints**

- Safety
- DCR
- DOR
- PFS
- OS

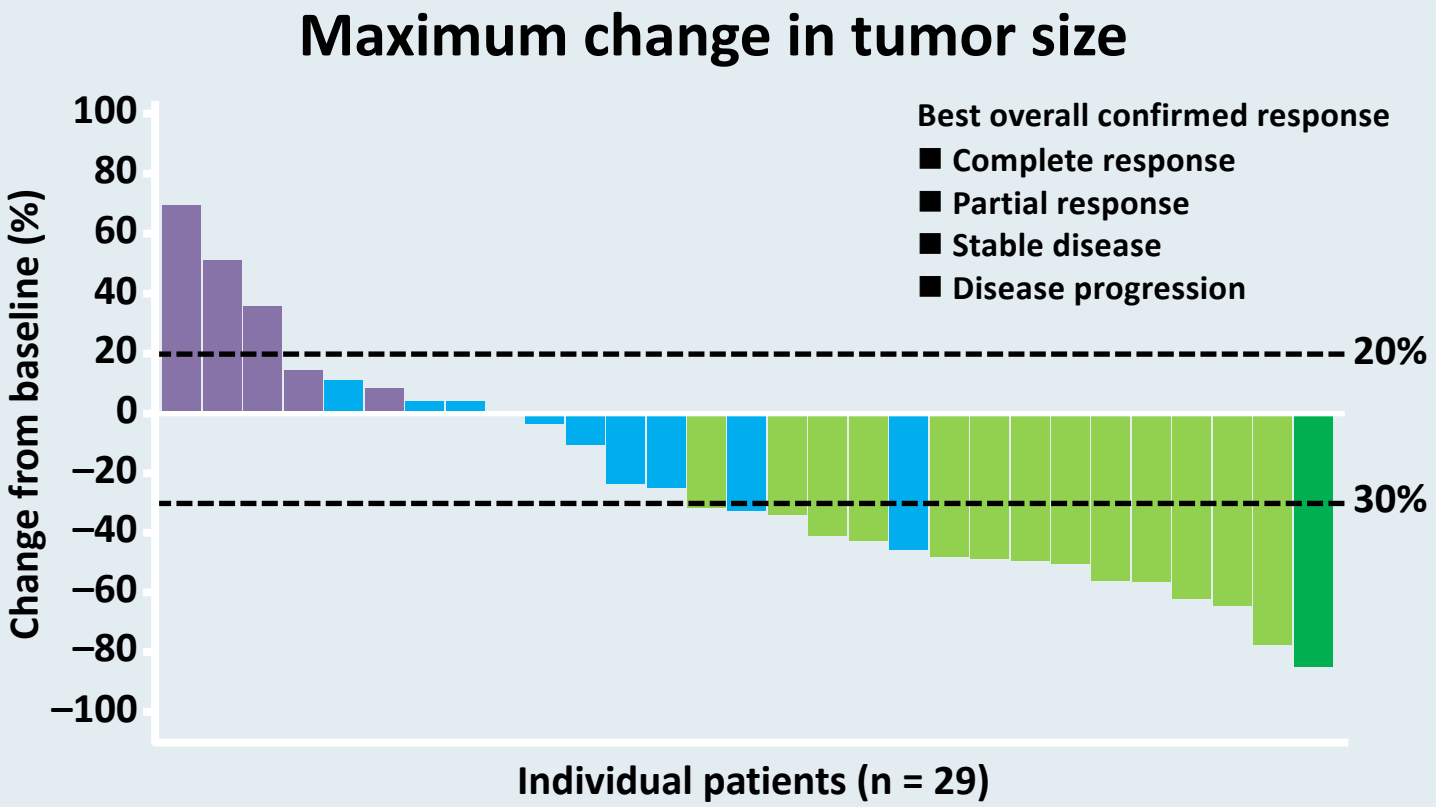
BID = 2 times a day; HER2m = HER2 mutated; LA = locally advanced; mBTC = metastatic biliary tract cancer; nonsq = nonsquamous; PO = by mouth; Q3W = every 3 weeks.

Nakamura Y et al. *J Clin Oncol* 2023;41:5569-78.

Tucatinib + trastuzumab is not approved by the FDA for this indication.

# SGNTUC-019 Phase 2 Basket Study: Tucatinib + Trastuzumab for HER2+ Solid Tumors — Metastatic Biliary Tract Cancer Cohort

## *Results*

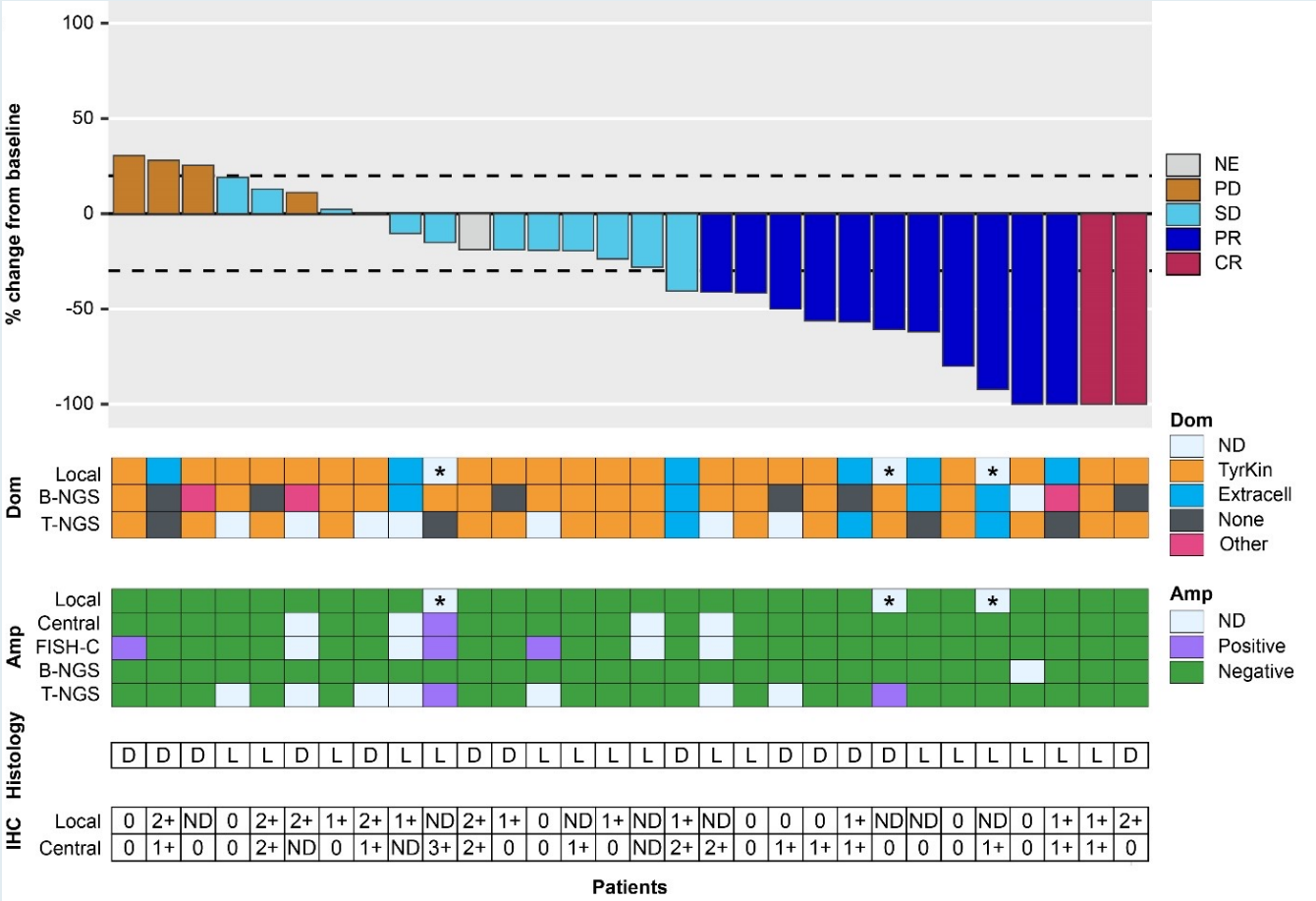



| | BTC (n = 30) |
|---|---|
| Median duration of follow-up, months | 10.8 |
| Median time to first response, months | 2.1 (1.2-4.3) |
| ORR, % | 14 (46.7) |
| CR | 1 (3.3) |
| PR | 13 (43.3) |
| SD | 9 (30.0) |
| PD | 6 (20.0) |
| Median DOR, months | 6.0 |
| Median PFS, months | 5.5 |
| Median OS, months | 15.5 |

- AEs were consistent with previously reported safety profile of this regimen

Nakamura Y et al. *J Clin Oncol* 2023;41:5569-78.

# SGNTUC-019 Phase 2 Basket Study: Tucatinib + Trastuzumab for HER2+ Solid Tumors — *HER2*-Mutated Metastatic Breast Cancer



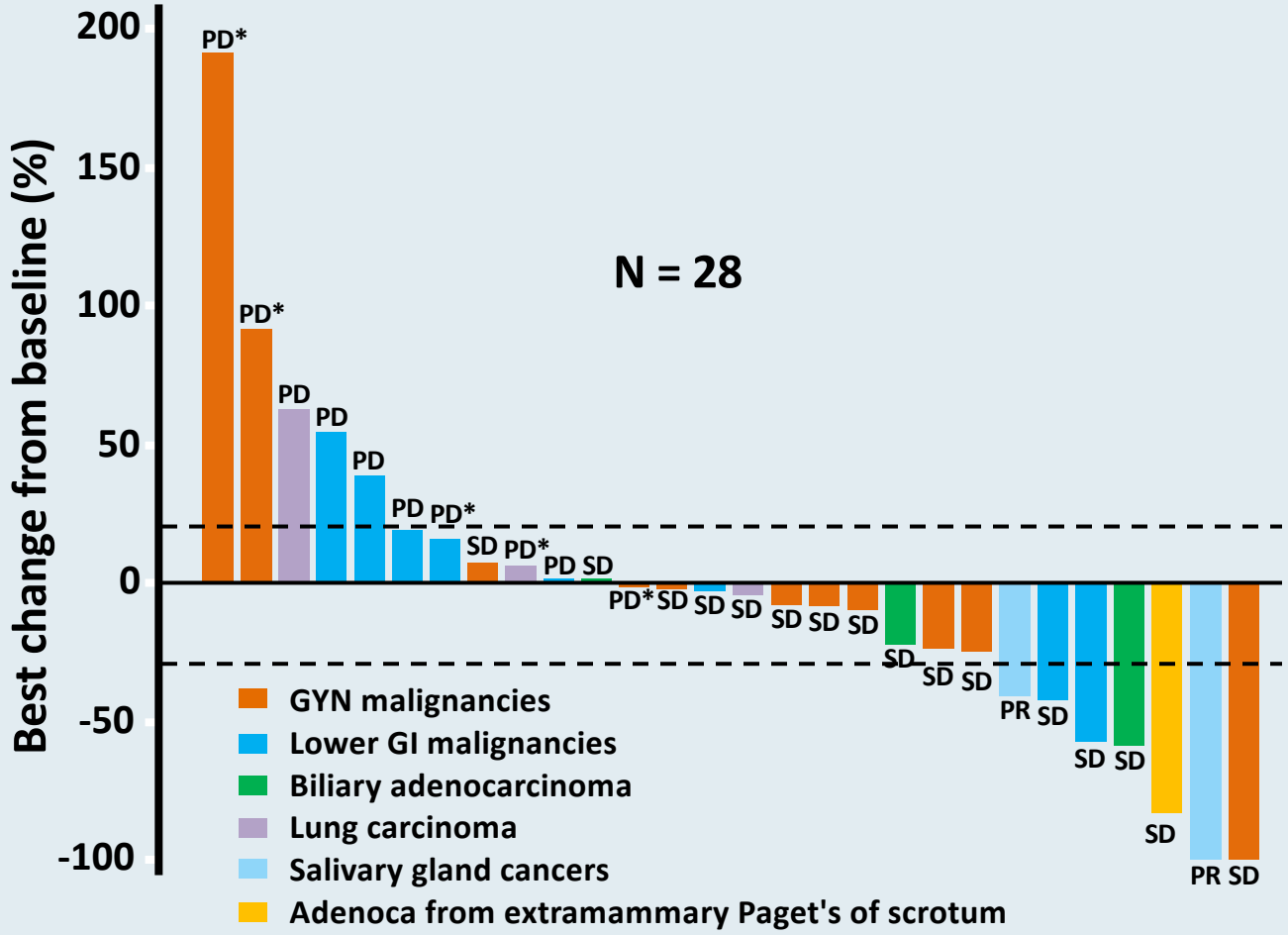

| | Total (N = 31) |
|---|---|
| Best overall response[a], n (%) | |
| Complete response | 2 (6.5) |
| Partial response | 11 (35.5) |
| Stable disease | 12 (38.7) |
| Progressive disease | 4 (12.9) |
| Not available[b] | 2 (6.5) |
| Confirmed objective response rate, n (%) | 13 (41.9) |
| 90% CI[c] for confirmed objective response rate | (26.9, 58.2) |
| Median duration of objective response[d] (months) (90% CI)[c] | 12.6 (4.7, -) |
| Disease control rate,[e] n (%) | 25 (80.6) |
| 90% CI[c] for disease control rate | (65.3, 91.2) |
| Median progression-free survival (months) (90% CI)[f] | 9.5 (5.4, 13.8) |
| Median overall survival (months) (90% CI)[f] | 20.1 (15.9, -) |

Amp, amplification; B-NGS, blood-based NGS testing by central lab assay; CR, complete response; D, ductal; Dom, domain; Extracell, extracellular domain of HER2; FISH-C, fluorescence in situ hybridization result from central testing; *HER2*, human epidermal growth factor receptor 2; IHC, immunohistochemistry; L, lobular; Local, local testing results; ND, not determined; NE, non-evaluable; NGS, next-generation sequencing; PD, progressive disease; PR, partial response; SD, stable disease; T-NGS, tissue-based NGS testing by central lab assay; TyrKin; tyrosine kinase domain of *HER2*

Okines AFC et al. *Nature Medicine* 2025

# NCI-MATCH Trial: T-DM1 in HER2+ Tumors Excluding Breast and Gastric/GEJ Adenocarcinomas

- Prior trastuzumab, pertuzumab or T-DM1 not permitted
- T-DM1 3.6 mg/kg Q3W to PD or toxicity
- Eligible patients had HER2 amplification
  - Copy number >7 based on targeted NGS
- Primary endpoint: ORR
- PR: 2 (5.6%; both parotid gland)
- SD: 17 (47%)
  - Ovarian/uterine: 8/10 (80%)
- 6-month PFS: 23.6%
- No new safety signals




* New lesions.

GI = gastrointestinal; NGS = next-generation sequencing.

Jhaveri KL et al. *Ann Oncol* 2019;30:1821-30.

original reports

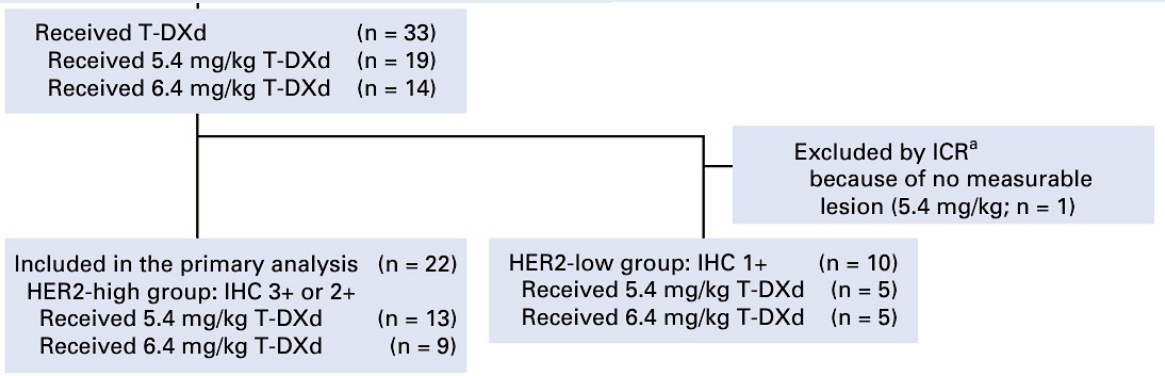
# Trastuzumab Deruxtecan for Human Epidermal Growth Factor Receptor 2–Expressing Advanced or Recurrent Uterine Carcinosarcoma (NCCH1615): The STATICE Trial

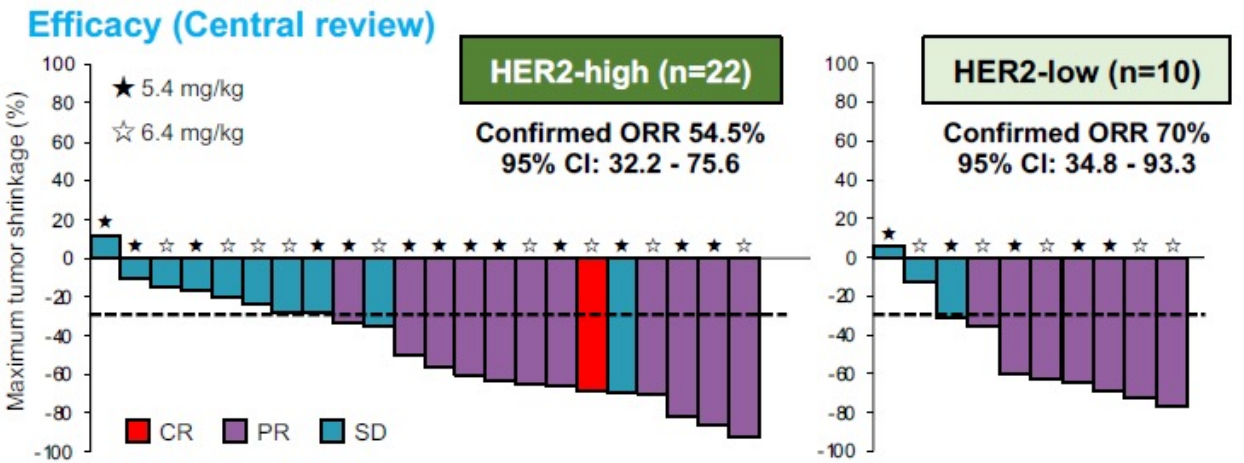
Tadaaki Nishikawa, MD, PhD[1]; Kosei Hasegawa, MD, PhD[2]; Koji Matsumoto, MD[3]; Masahiko Mori, MD, PhD[4]; Yasuyuki Hirashima, MD, PhD[5]; Kazuhiro Takehara, MD, PhD[6]; Kazuya Ariyoshi, MD, PhD[7]; Tomoyasu Kato, MD, PhD[8]; Shigehiro Yagishita, MD, PhD[9]; Akinobu Hamada, PhD[9]; Mamiko Kawasaki, MS[10]; Satoshi Kawashima, PhD[10]; Sawako Tomatsuri, MS[10]; Yukari Nagasaka, BS[10]; Hiroshi Yoshida, MD, PhD[11]; Ryunosuke Machida, ME[12]; Akihiro Hirakawa, PhD[13]; Kenichi Nakamura, MD, PhD[10]; and Kan Yonemori, MD, PhD[1]

*J Clin Oncol* 2023;41(15):2789-99.

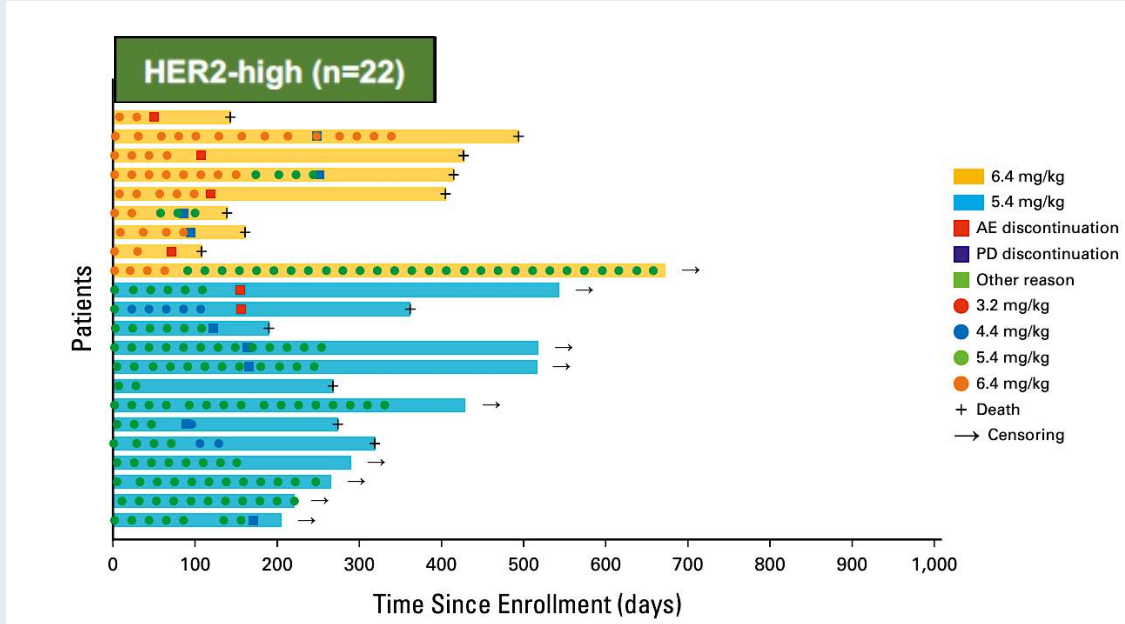
RTP RESEARCH TO PRACTICE

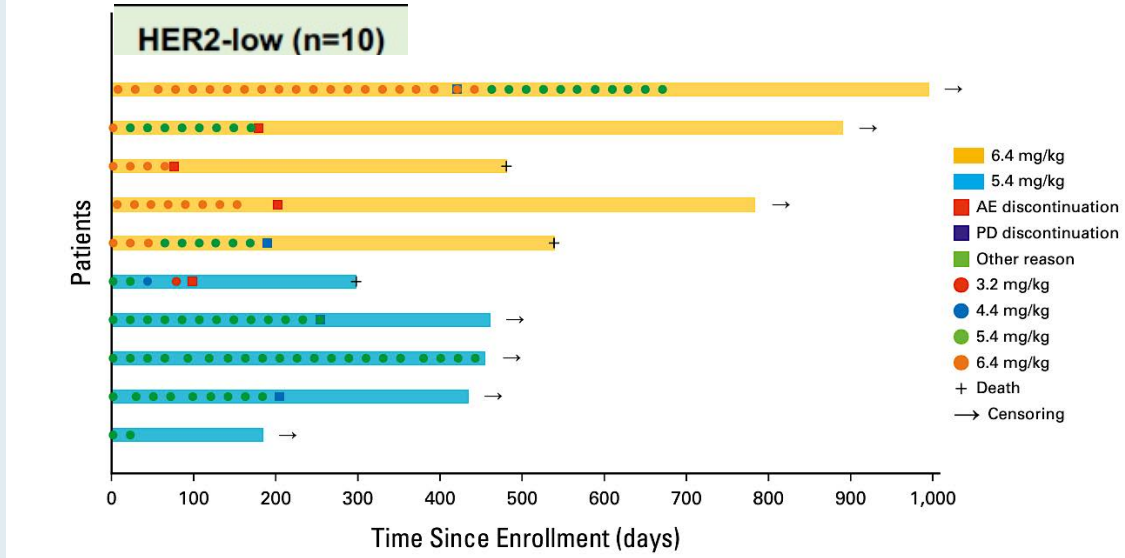
# Trastuzumab Deruxtecan in HER2+ UCS – STATICE TRIAL




| Confirmed Response Rate | CR (n, %) | | PR (n, %) | | SD (n, %) | | PD (n, %) | | ORR (%) |
|---|---|---|---|---|---|---|---|---|---|
| HER2-high (n=22) | 1 | (4.5) | 11 | (50) | 10 | (45.5) | 0 | (0) | 54.5 |
| HER2-low (n=10) | 0 | (0) | 7 | (70) | 3 | (30) | 0 | (0) | 70 |




Nishikawa T et al. *J Clin Oncol* 2023.

Hasegawa K et al. ESMO 2021 poster 813p.

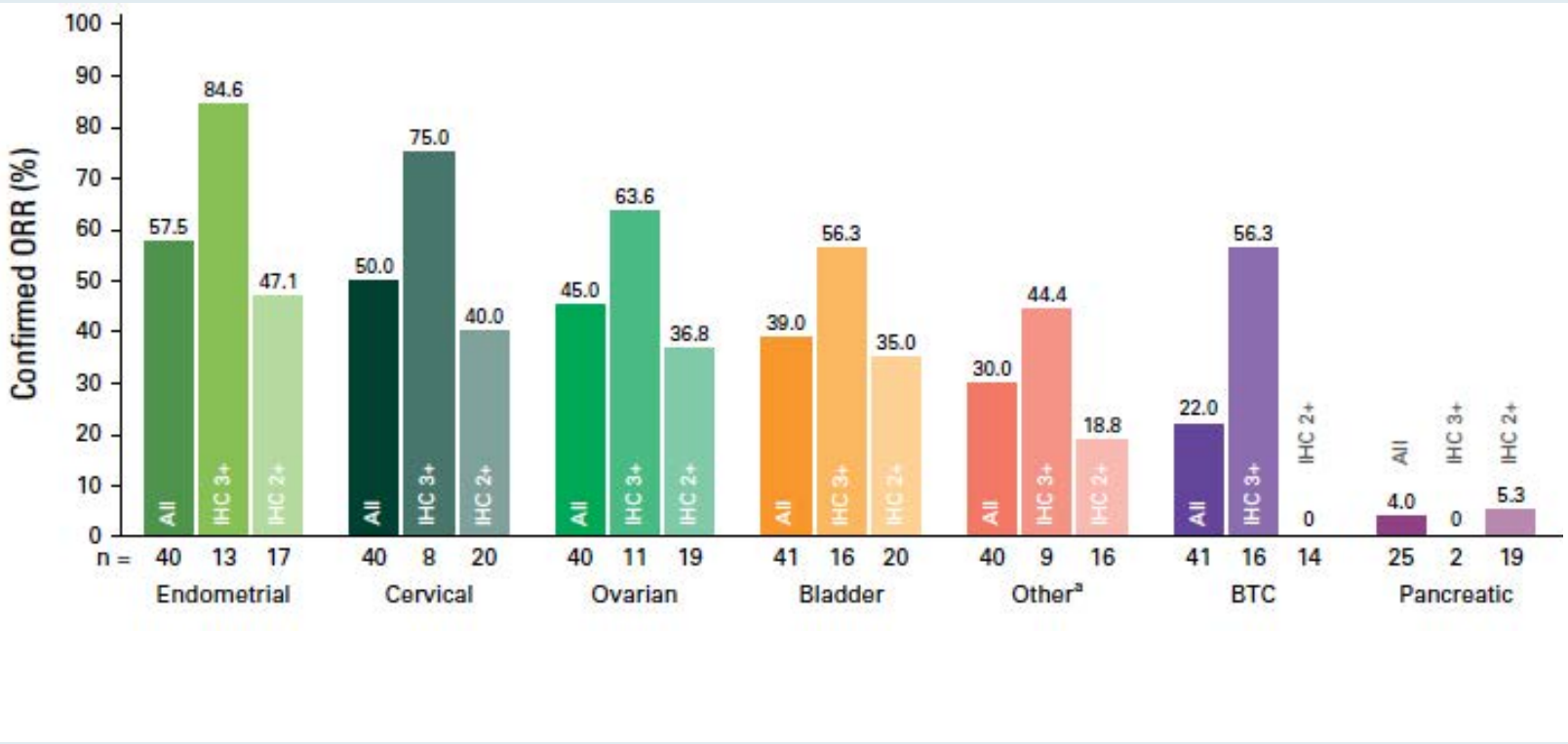
Original Reports | Gynecologic Cancer

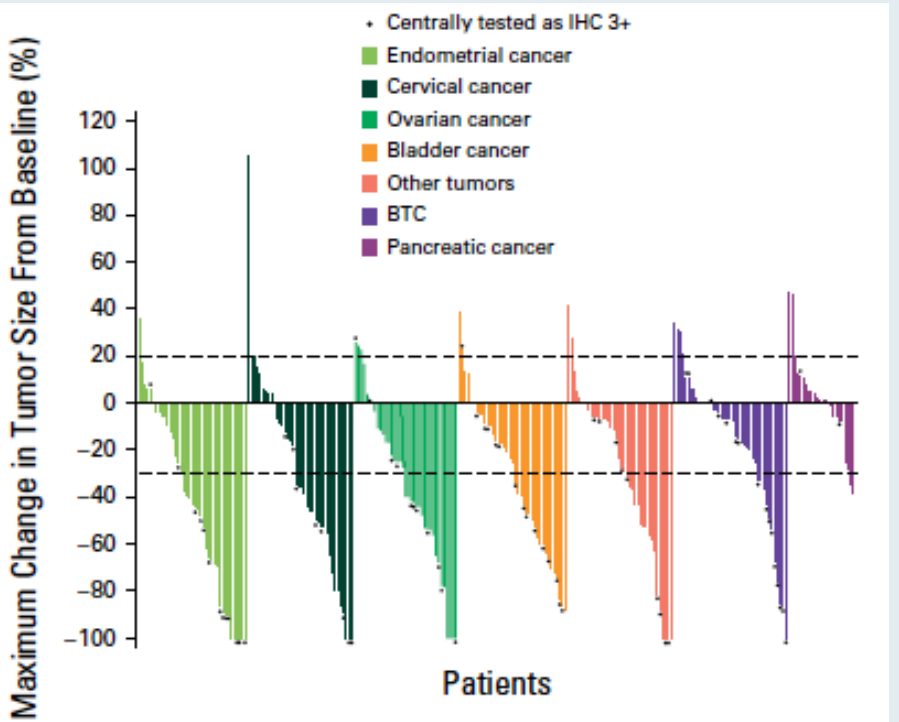
# Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

Funda Meric-Bernstam, MD[1]; Vicky Makker, MD[2,3]; Ana Oaknin, MD[4]; Do-Youn Oh, MD[5]; Susana Banerjee, PhD[6]; Antonio González-Martín, MD[7]; Kyung Hae Jung, MD[8]; Iwona Ługowska, MD[9]; Luis Manso, MD[10]; Aránzazu Manzano, MD[11]; Bohuslav Melichar, MD[12]; Salvatore Siena, MD[13]; Daniil Stroyakovskiy, MD[14]; Anitra Fielding, MBChB[15]; Yan Ma, MSc[16]; Soham Puvvada, MD[15]; Norah Shire, PhD[15]; and Jung-Yun Lee, MD[17]

*J Clin Oncol* 2024;42(1):47-58.

# DESTINY-PanTumor02: A Phase II Trial of Trastuzumab Deruxtecan for Patients with HER2-Expressing Solid Tumors

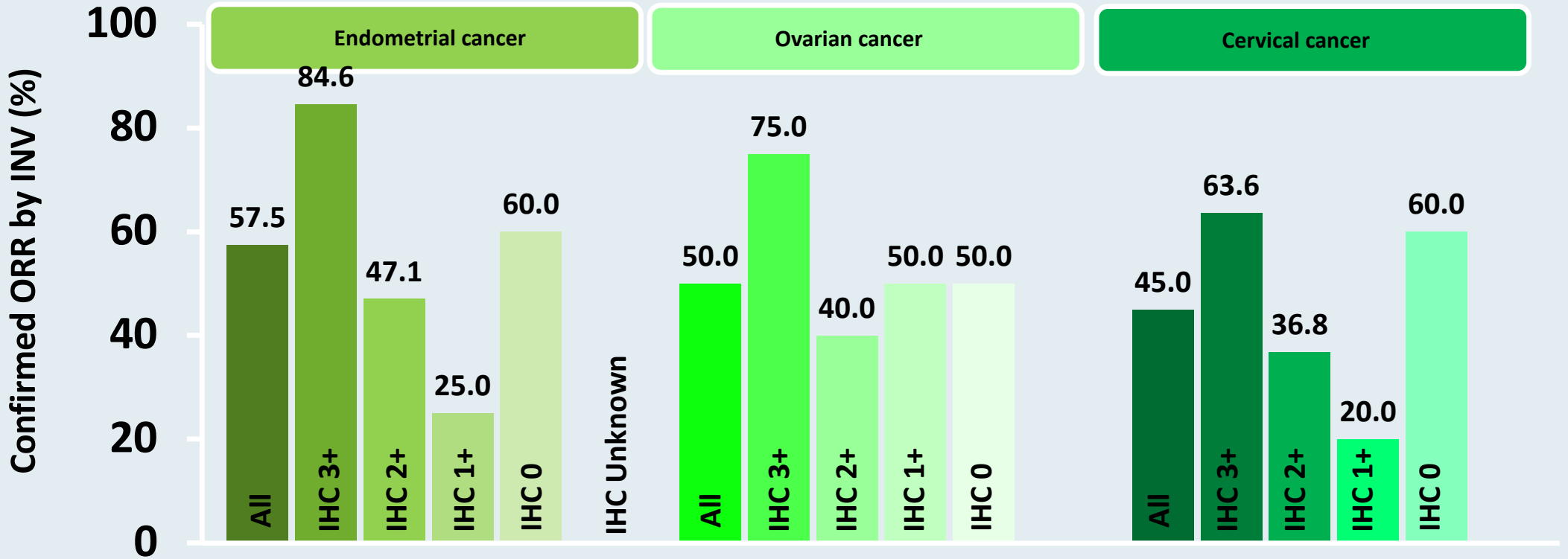



Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

RTP RESEARCH TO PRACTICE

# DESTINY-PanTumor02: Response by HER2 Expression Level (Central)



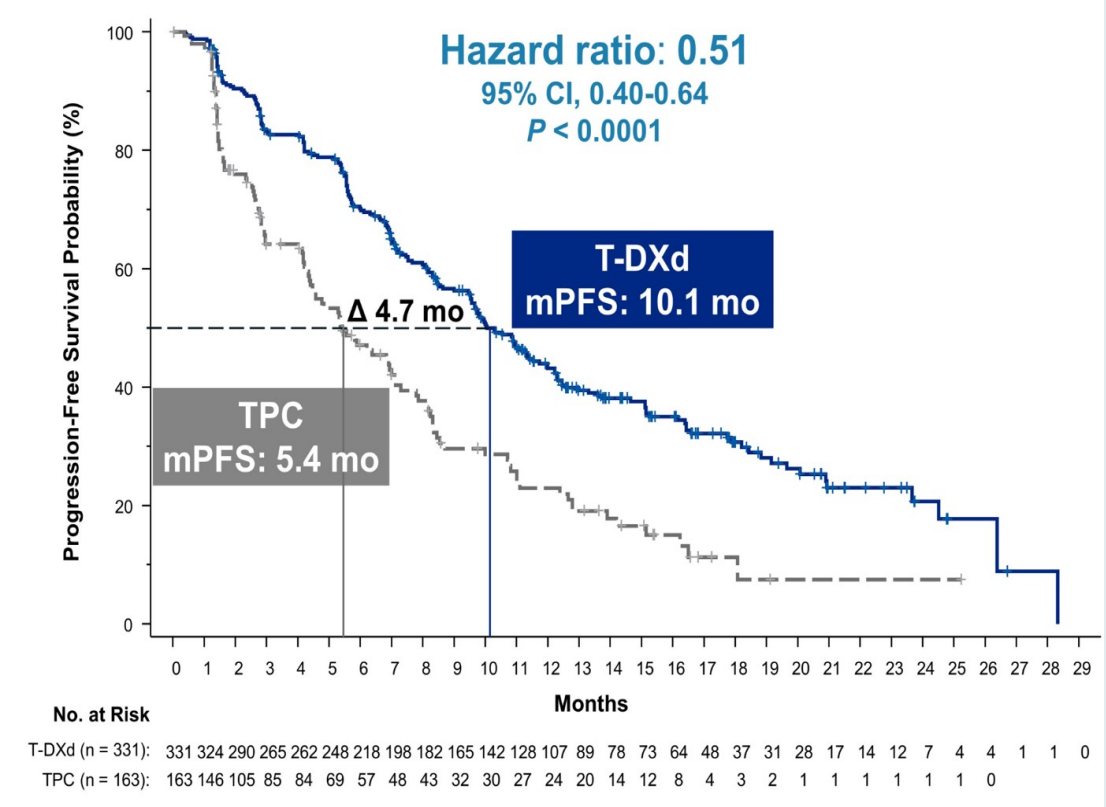

| | Endometrial cancer | | | | | | Ovarian cancer | | | | | Cervical cancer | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | IHC 3+ | IHC 2+ | IHC 1+ | IHC 0 | IHC Unknown | All | IHC 3+ | IHC 2+ | IHC 1+ | IHC 0 | All | IHC 3+ | IHC 2+ | IHC 1+ | IHC 0 |
| Total n in subgroup | 40 | 13 | 7 | 4 | 5 | 1 | 40 | 8 | 20 | 8 | 4 | 40 | 11 | 19 | 5 | 5 |
| n of responders | 23 | 11 | 8 | 1 | 3 | 0 | 20 | 6 | 8 | 4 | 2 | 18 | 7 | 7 | 1 | 3 |
| Median DOR, months | NR | NR | 18.2 | NR | 9.9 | – | 14.2 | NR | 3.8 | 14.2 | NR | | 11.3 | 22.1 | 11.3 | 8.3 | 4.5 |
| 95% CR | 9.9, NE | 9.6, NE | 3.0, NE | – | 2.8, NE | – | | 4.1, NE | 9.3, NE | 2.8, NE | 8.3, NE | 6.8, NE | 4.4, 22.1 | 4.2, NE | 2.8, NE | – | 2.6, NE |

GYN = gynecological; NE = not estimable; NR = not reached.

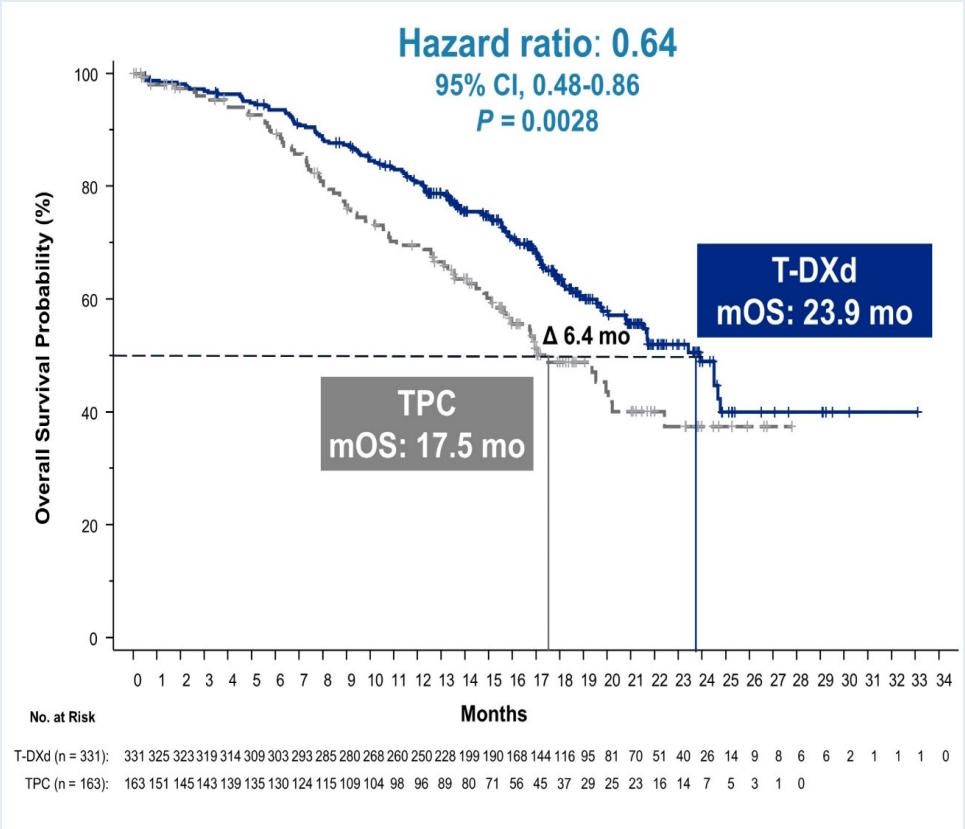
Lee J-Y, et al. International Gynecological Cancer Society (IGCS) 2023; Makker V et al. SGO 2024.

# DESTINY-Breast04: PFS (BICR) and OS in HR+ MBC

**PFS in HR+**
**Primary endpoint**




**OS in HR+**
**Secondary endpoint**

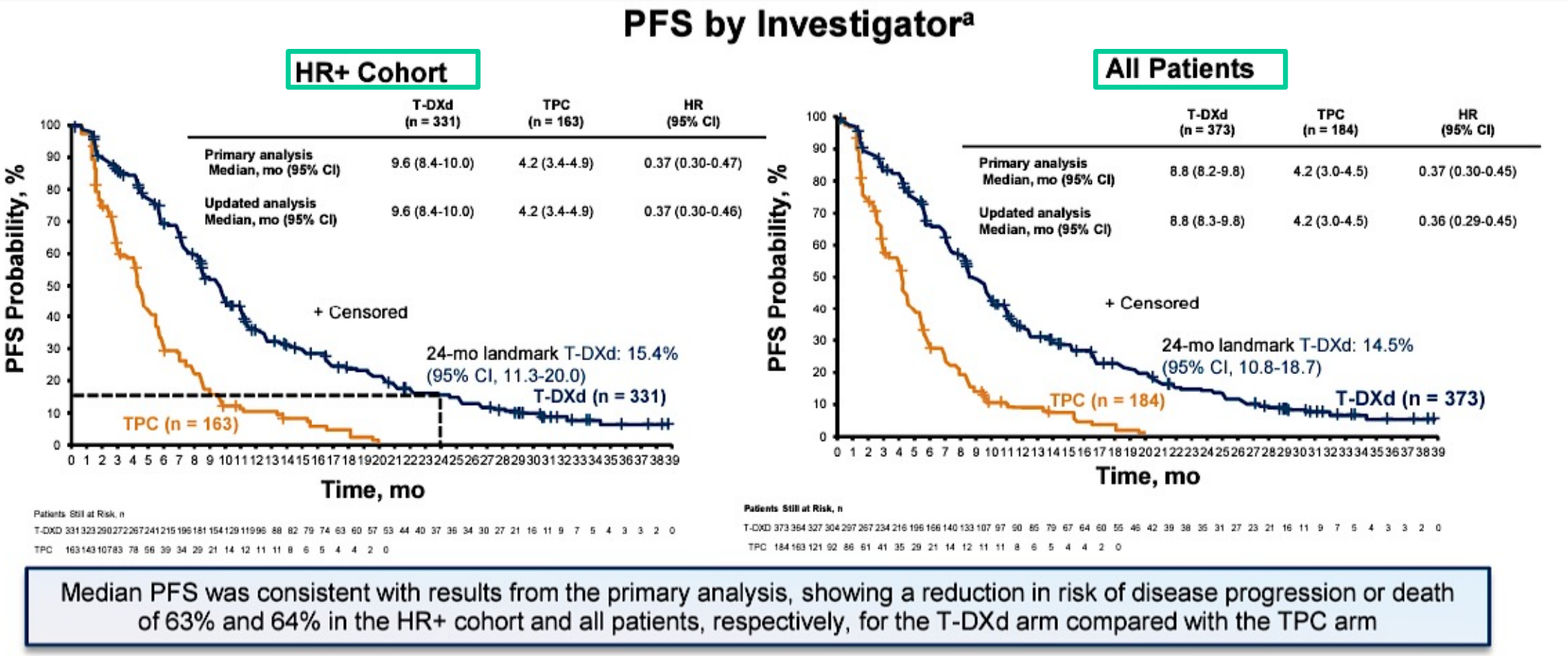



**Median duration of follow-up: 18.4 months**

T-DXd = Fam-trastuzumab deruxtecan-nxki; TPC = treatment of physician's choice

Modi S, et al. *N Engl J Med* 2022;387:9-20. Modi S, et al. ASCO 2022;Abstract LBA3.

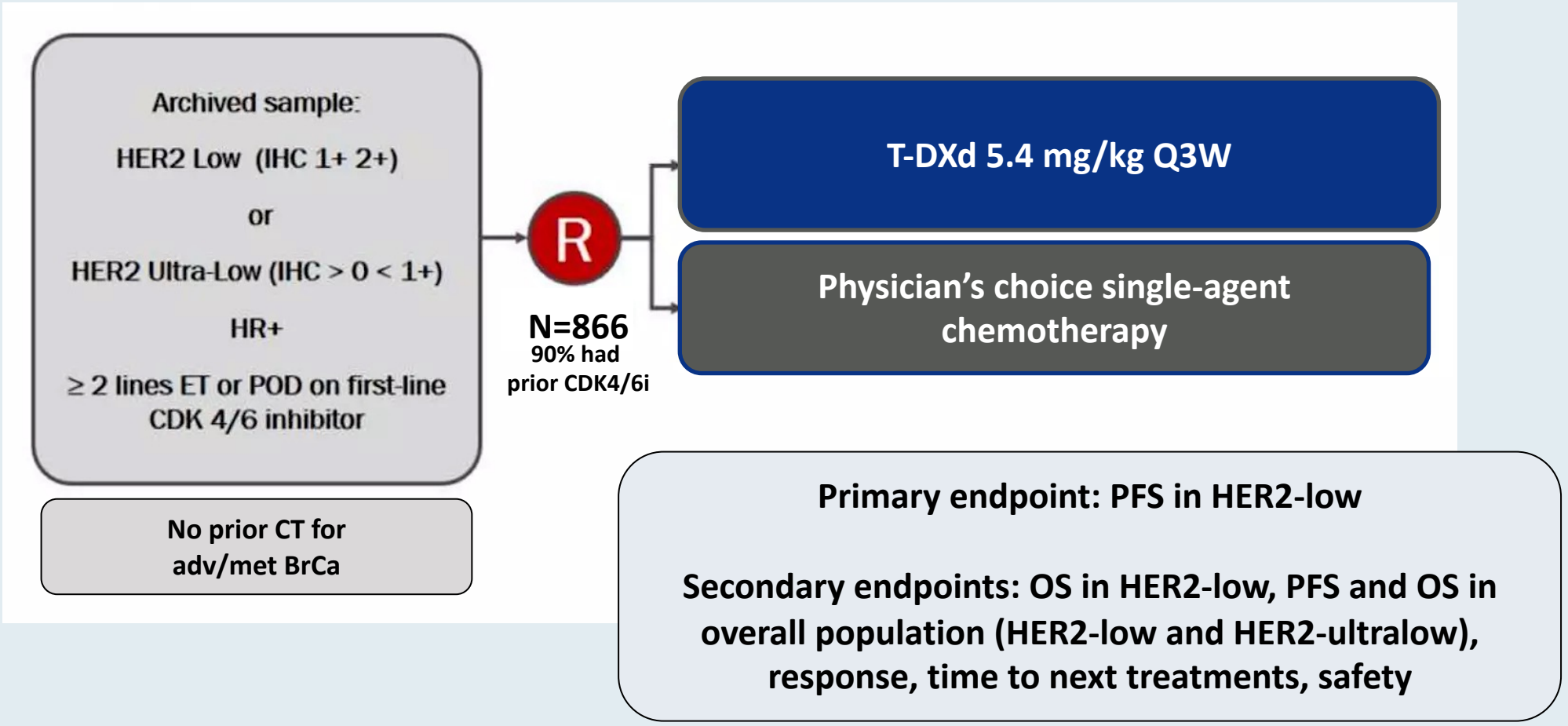
# DESTINY-Breast04: Updated Analysis PFS (by INV[a])
## *Median duration of follow-up: 32 months*




Median PFS was consistent with results from the primary analysis, 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

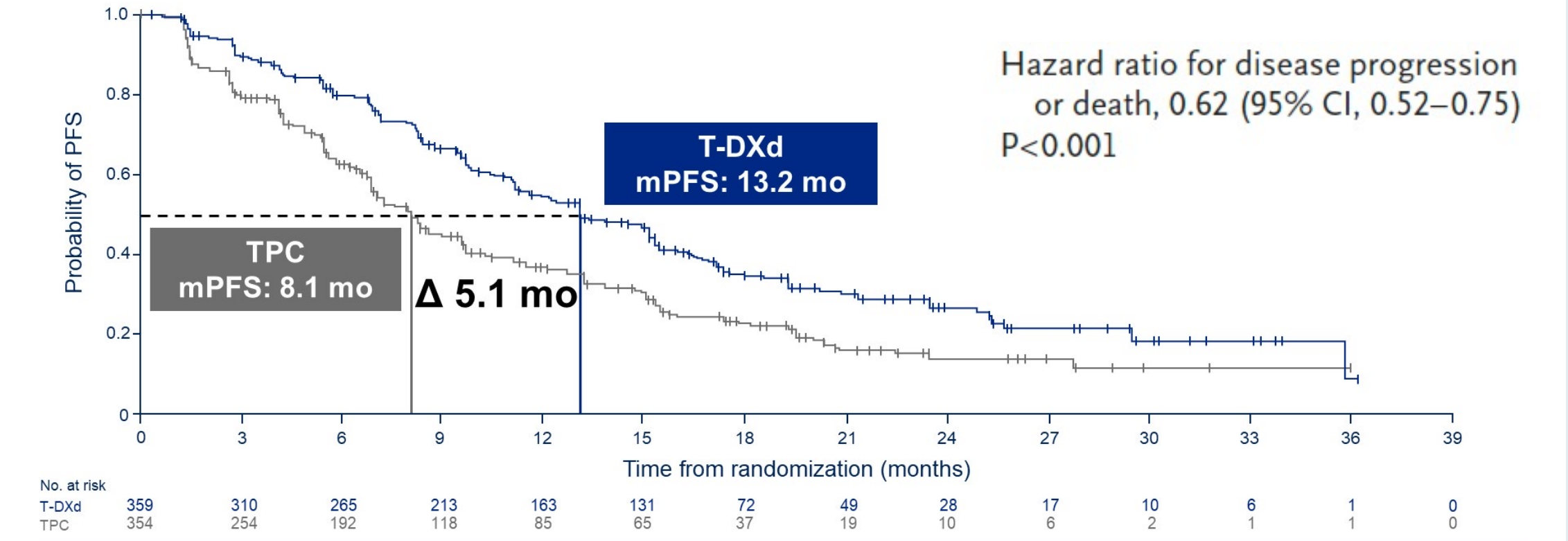
[a] PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved.
For all pts, PFS by BICR: 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (HR = 0.50).
Modi S, et al. ESMO 2023. Abstract 376O.

# Phase 3 DESTINY-Breast06: T-DXd for HER2-Low (IHC 1+ 2+) or Ultralow (IHC >0<1+), HR+ MBC




[a] Capecitabine (59.8%), *nab*-paclitaxel (24.4%) or paclitaxel (15.8%).
Prespecified analysis of the HER2-ultralow subgroup was not powered to demonstrate statistical significance.
POD, progression of disease (≤24 mo of adjuvant ET or ≤6 mo of ET + CDK4/6i for MBC).
Median follow up, 18.6 mo; data cutoff: Mar 18, 2024.
Curigliano G, et al. ASCO 2024;LBA1000.

# Phase 3 DESTINY-Breast06: PFS (BICR) in HER2-Low — Primary Endpoint

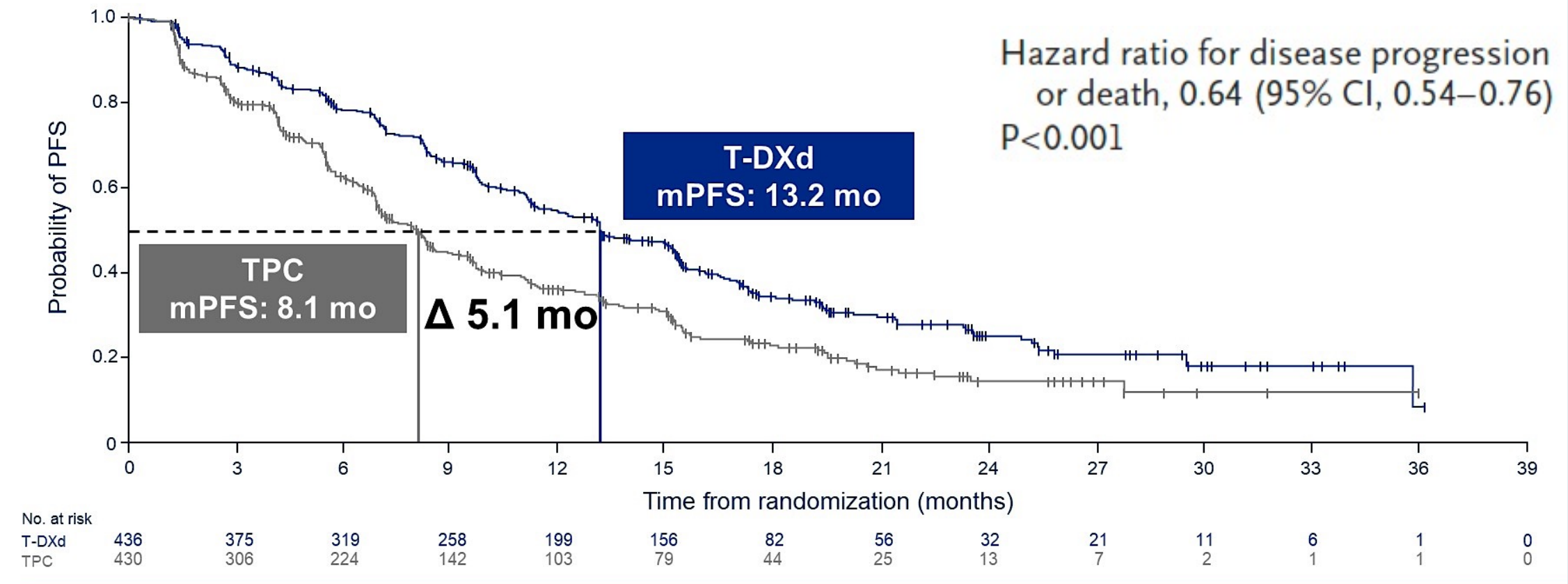



**PFS benefit maintained across subgroups**

Median follow up, 18.2 mo; data cutoff: Mar 18, 2024.

Curigliano G et al. ASCO 2024. LBA1000; Bardia A et al. *N Engl J Med* 2024;391(22):2110-22.

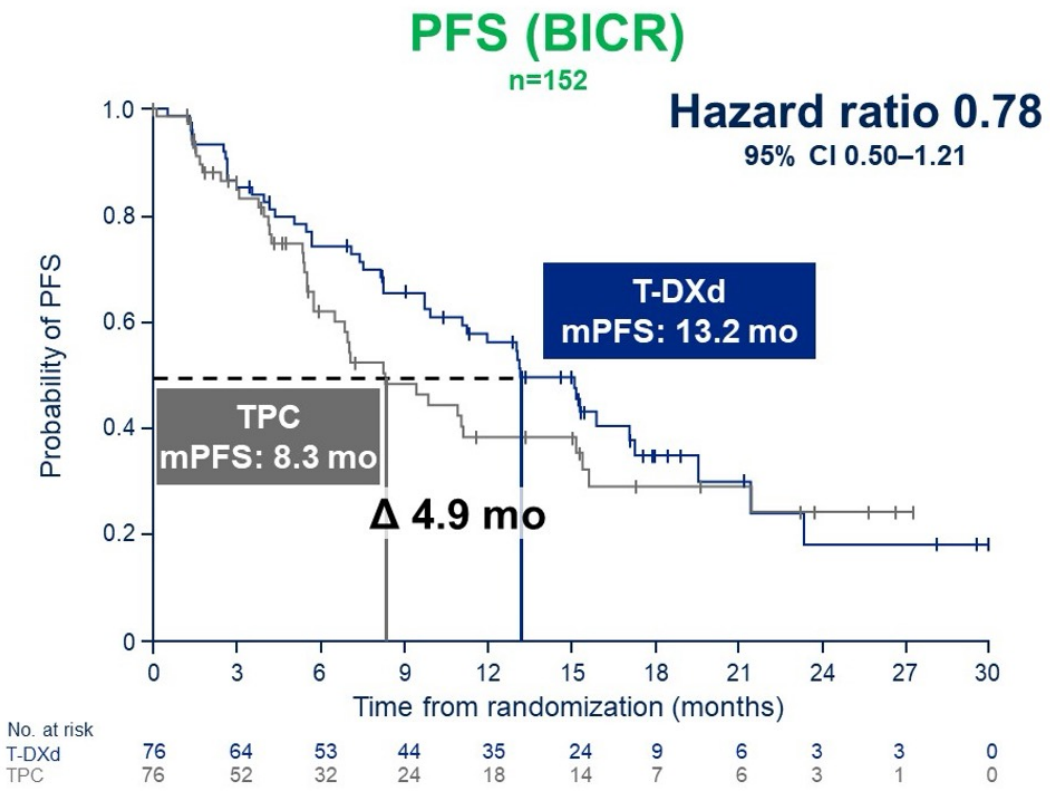
# Phase 3 DESTINY-Breast06: PFS (BICR) in ITT — Key Secondary Endpoint

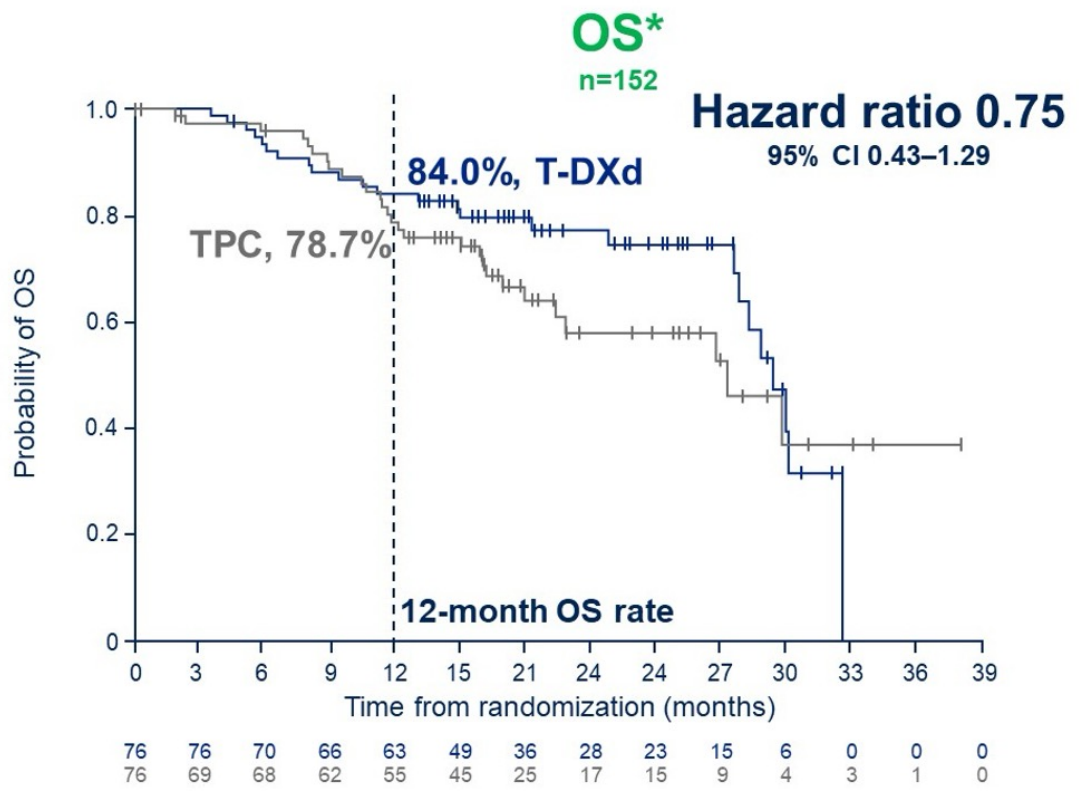



Median follow up, 18.2 mo; data cutoff: Mar 18, 2024.

Curigliano G et al. ASCO 2024. LBA1000; Bardia A et al. *N Engl J Med* 2024;391(22):2110-22.

# Phase 3 DESTINY-Breast06: PFS and OS in HER2-Ultralow — Prespecified Exploratory Analyses




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

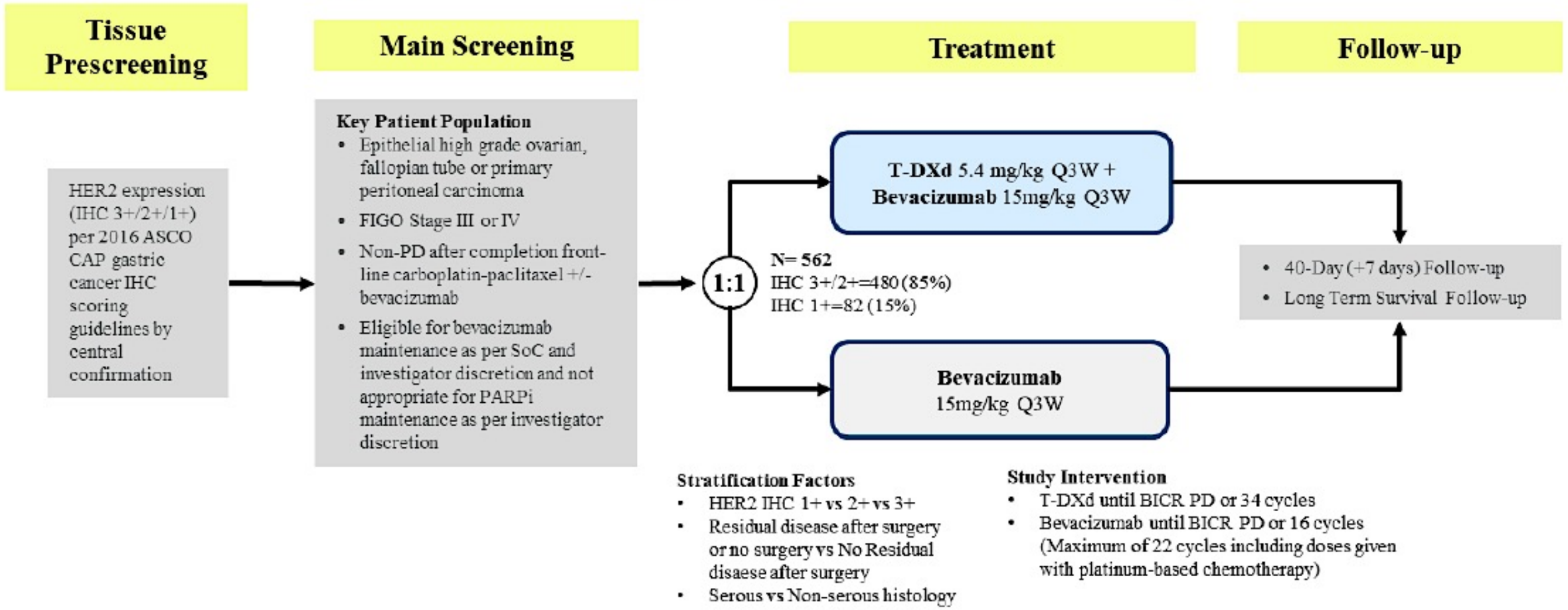
*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free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

Median follow up: 16.8 mo.

Curigliano G et al. ASCO 2024. LBA1000; Bardia A et al. *N Engl J Med* 2024;391(22):2110-22.

# GOG-3112/ENGOT-OV89/DESTINY-Ovarian01: Phase III Trial of T-DXd + Bevacizumab as 1L Maintenance Therapy in HER2-Expressing Ovarian Cancer

**PI: Joyce Liu**

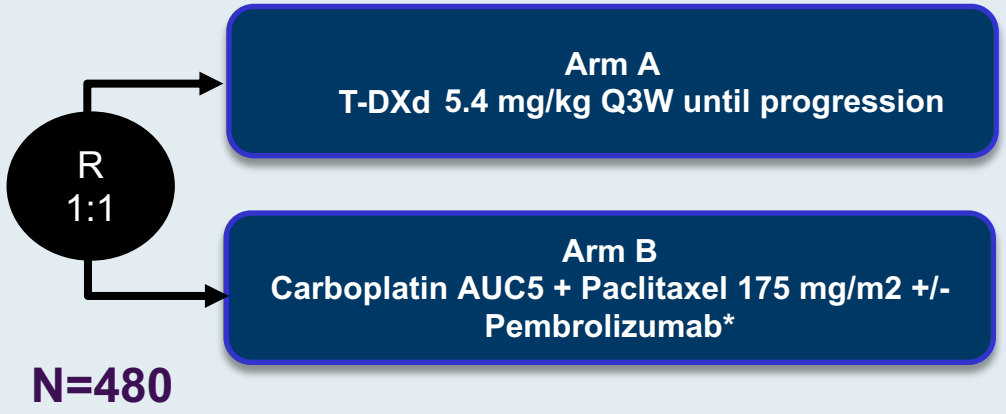



NCT06819007

# DESTINY-Endometrial01/GOG-3098/ENGOT-EN24-NSGO-CTU: A Phase III Study of Trastuzumab Deruxtecan (T-DXd) as First-Line Treatment of HER2-Expressing (IHC 3+/IHC 2+) Mismatch Repair Proficient (pMMR) Endometrial Cancer

## Patient Population

- Primary Stage III or Stage IV disease or recurrent (first-recurrence) histologically confirmed endometrial cancer
- pMMR by central IHC testing
- HER2 IHC expression per ASCO CAP gastric guidelines of IHC 3+ or IHC 2+ by prospective central testing. Local testing will be allowed until validated central testing is available.
  - IHC 3+ estimated n~192 (40%)
  - IHC 2+ capped at n=288 (60%)
- Any histological subtype except for sarcomas (carcinosarcomas are allowed)
- Subjects with recurrent disease may have received 1 prior line of adjuvant/neoadjuvant chemotherapy with curative intent (chemotherapy and/ or chemoradiation) if recurrence ≥ 6 months after last dose of therapy. Prior trastuzumab in adjuvant/ neoadjuvant setting is allowed.
- ECOG PS 0 or 1




**N=480**

**Stratification factors:**

- HER2 IHC 3+ vs 2+
- Recurrent vs Primary Stage III vs Primary Stage IV

Carboplatin AUC5 and Paclitaxel 175 mg/m2 IV +/- pembrolizumab 200 mg Q3W x 6 cycles (up to 10 cycles allowed).

In non-US countries, use of Pembrolizumab in Arm B will depend on local regulatory approval in the proposed setting.

IO: Pembrolizumab 200 mg Q3W x 6 cycles (combination phase) → Pembrolizumab 400 mg Q6W x 14 cycles (maintenance phase).

## Endpoints

**Primary:**

- PFS by BICR

**Secondary:**

- OS
- PFS by Investigator
- PFS2
- ORR and DoR in patients with measurable disease at baseline
- PROs

Shared with permission from AZ correspondence dated 13 March 2025 from Pia Herbolsheimer MD, PhD

# Phase I/IIa Study of BNT323/DB-1303 in Advanced/Metastatic Solid Tumors

| Response [a] | Dose Escalation | | Dose Expansion | Pooled 8 mg/kg (n=13) | Total (n=17) [b] |
|---|---|---|---|---|---|
| | 7 mg/kg (n=4) [b] | 8 mg/kg (n=4) [b] | 8 mg/kg (n=9) [b] | | |
| **Best overall response, n (%)** | | | | | |
| PR | 2 (50.0) | 4 (100) | 4 (44.4) | 8 (61.5) | 10 (58.8) |
| SD | 2 (50.0) | 0 | 4 (44.4) | 4 (30.8) | 6 (35.3) |
| PD | 0 | 0 | 1 (11.1) | 1 (7.7) | 1 (5.9) |
| **Unconfirmed ORR, n (%)** | 2 (50.0) | 4 (100) | 4 (44.4) | **8 (61.5)** | **10 (58.8)** |
| Confirmed ORR, n (%) | 1 (25.0) | 3 (75.0) | 0 | 3 (23.1) | 4 (23.5) |
| Pending confirmation ORR, n (%) | 1 (25.0) | 1 (25.0) | 4 (44.4) | 5 (38.5) | 6 (35.3) * |
| **Unconfirmed ORR by histology, n/N (%)** | | | | | |
| Serous carcinoma | 1/1 (100) | 4/4 (100) | 2/3 (66.7) | 6/7 (85.7) | **7/8 (87.5)** |
| Adenocarcinoma | 1/2 (50.0) | -- [c] | 0/1 | 0/1 | 1/3 (33.3) |
| Carcinosarcoma | -- [c] | -- [c] | 1/2 (50.0) | 1/2 (50.0) | 1/2 (50.0) |
| Mixed adenocarcinoma | -- [c] | -- [c] | 1/2 (50.0) | 1/2 (50.0) | 1/2 (50.0) |
| **Unconfirmed DCR, n (%)** | 4 (100) | 4 (100) | 8 (88.9) | 12 (92.3) | **16 (94.1)** |

Data cutoff: May 8, 2023.
* Up to now, of these 6 pending confirmation PRs, all were confirmed.
DCR=Disease control rate; ORR=Objective response rate; PD=Progressive disease; PR=Partial response; SD=Stable disease.
[a] By investigator. [b] Response-evaluable participants, which includes participants with ≥1 postbaseline overall response. [c] No efficacy-evaluable participants.

- Phase 1/2a, global, open-label, first in human study evaluating DB-1303 (IV, Q3W) in previously treated patients with solid tumors (NCT05150691)
- Humanized anti-HER2 IgG1 mAb
- Proprietary DNA topoisomerase I inhibitor

K Moore, ESGO 2023

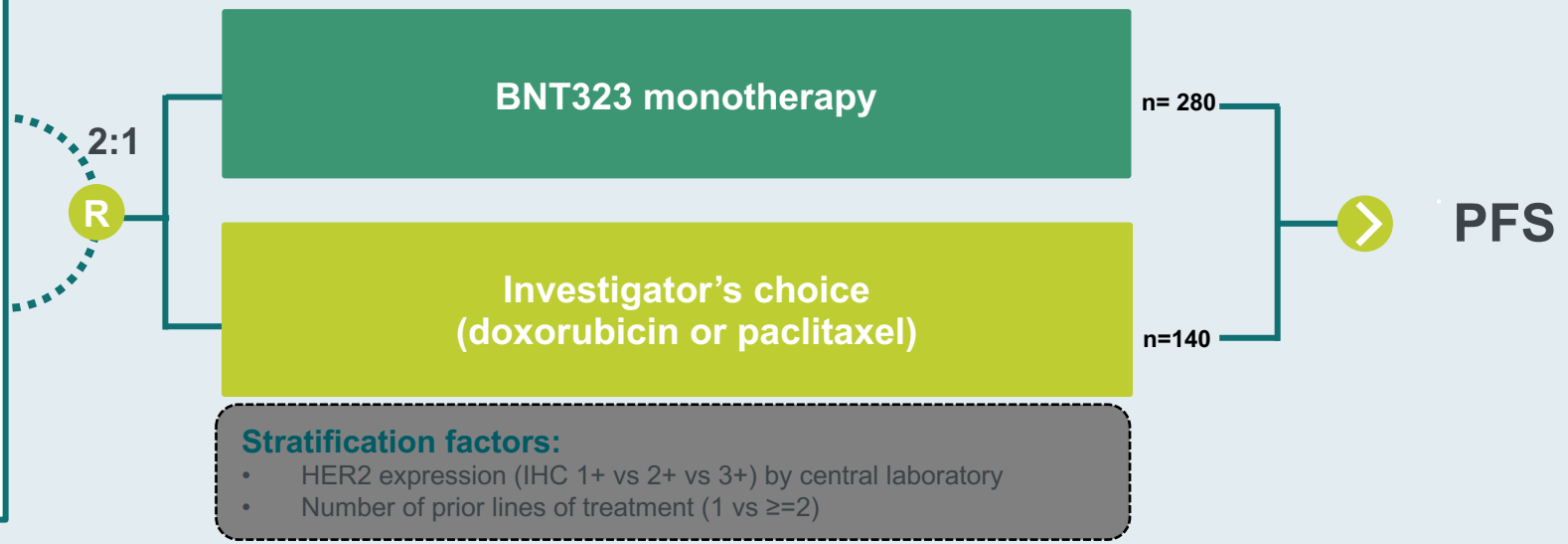
# BNT323-01/GOG-3105/ENGOT-EN25: Trial Design

- **A Phase III, Randomized, Multi-site, Open-label Trial of BNT323/DB-1303* Versus Investigator's Choice of Chemotherapy in Previously Treated Patients With HER2- Expressing Recurrent Endometrial Cancer (NCT06340568)**

- **PI: Dr. Floor Backes**

## KEY INCLUSION CRITERIA

- Recurrent, metastatic endometrial cancer (including HER2 1+, 2+, or 3+ score on IHC by central testing)
- At least 1 prior line of platinum-based therapy (in any setting) and prior immune checkpoint inhibitor (in any setting), up to three lines of prior therapy (excluding endocrine therapies)
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1




**Primary Endpoints**
- **PFS (BICR assessed)**

**Secondary Endpoints**
- **OS (Key)**
- PFS (Investigator assessed)
- ORR, DoR
- Safety

*Partnered with DualityBio; BICR = blinded independent central review; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; ICI = immune checkpoint inhibitor; IHC = immunohistochemistry; N = number of patients; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors; Accessed May 2024; BNT323 / DB-1303 is an unapproved investigational product; its safety and efficacy have not been established. Future commercially availability is not guaranteed.

# Key Takeaways

- Phase 2 DESTINY-PanTumor02 led to tumor-agnostic indication for T-DXd
  - April 5, 2024: FDA granted accelerated approval to T-DXd for unresectable/HER2+ (IHC3+) solid tumors after prior systemic treatment and no satisfactory alternative treatment options
  - Greatest benefit in IHC 3+ population
- Further exploration of T-DXd in HER2 IHC 1+/HER2-low is warranted
- Multiple trials are being initiated for HER2-expressing gynecologic cancers

# Video Cases and Questions for the Faculty

# Case Presentation: 38-year-old woman with metastatic PD-L1-positive squamous cell carcinoma of the cervix found to be HER2-positive (IHC 3+) after cisplatin/EBRT/ vaginal brachytherapy → PD on tisotumab vedotin

Lyndsay J Willmott, MD (Phoenix, Arizona)

# QUESTIONS FOR THE FACULTY

**If this patient had undergone HER2 testing and HER2 IHC 3+ was confirmed prior to the initiation of tisotumab vedotin, would you have opted for trastuzumab deruxtecan (T-DXd) first?**

**In general, how do you sequence these agents? What if the HER2 was IHC 2+ and ISH-positive? What if the patient was symptomatic and needed a rapid response?**

**What has been your clinical experience with tisotumab vedotin in terms of efficacy and tolerability? How do you monitor and mitigate ocular toxicity?**

Kellie E Schneider, MD
(Charlotte, North Carolina)

**Case Presentation: 73-year-old woman with metastatic platinum-resistant high-grade serous ovarian cancer (HRD-negative, HER2 IHC 2+, FR-alpha-positive) and residual treatment-related PN**

Thomas P Morrissey, MD
(Boca Raton, Florida)

**Case Presentation: 76-year-old woman with metastatic high-grade serous ovarian cancer (HER2 IHC 3+, FR-alpha-positive) who experiences PD on mirvetuximab soravtansine and receives trastuzumab deruxtecan**

RTP
RESEARCH
TO PRACTICE

# QUESTIONS FOR THE FACULTY

**In general, for a patient with folate-receptor-alpha positive and HER2-positive (IHC 3+) recurrent ovarian cancer, would you recommend mirvetuximab soravtansine or T-DXd first? What if the HER2 was IHC 2+ and ISH-positive? What if the patient has peripheral neuropathy? Are there other clinical factors that would influence your decision?**

**What has been your clinical experience with mirvetuximab soravtansine in terms of efficacy and tolerability?**

# Case Presentation: 81-year-old woman with UPSC and vulvar recurrence that is HER2-positive (IHC 3+) begins treatment with trastuzumab deruxtecan

Lyndsay J Willmott, MD (Phoenix, Arizona)

RTP
RESEARCH
TO PRACTICE

# QUESTIONS FOR THE FACULTY

**If this patient's disease recurrence were diagnosed today, what second-line treatment would you recommend, T-DXd or pembrolizumab/lenvatinib?**

**Do you foresee T-DXd moving up to earlier lines of therapy? Do you believe it will ultimately replace cytotoxic therapy for patients with HER2-positive disease?**

# Agenda

**Module 1:** Strategies to Identify Patients with HER2-Positive Gynecologic Cancers — Dr Santin

**Module 2:** Available Data with and Practical Application of HER2-Targeted Therapy in Advanced Gynecologic Cancers — Dr O'Malley

**Module 3: Identification and Management of Adverse Events with T-DXd — Dr Moore**

# Identification and Management of Adverse Events with T-DXd

**Kathleen N. Moore, MD, MS, FASCO**
Deputy Director, Stephenson Cancer Center at OU Health
Co-Lead, Cancer Therapeutics Program
Professor, Gynecologic Oncology
ASCO BOD
GOG F BOD

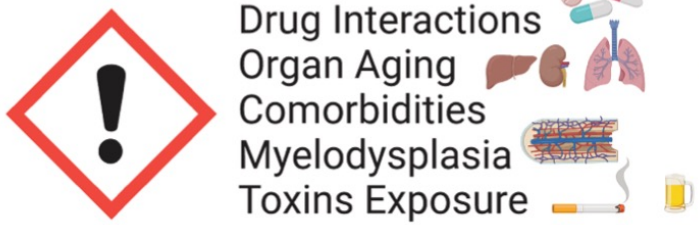
# Common ADC Treatment Related Side Effects

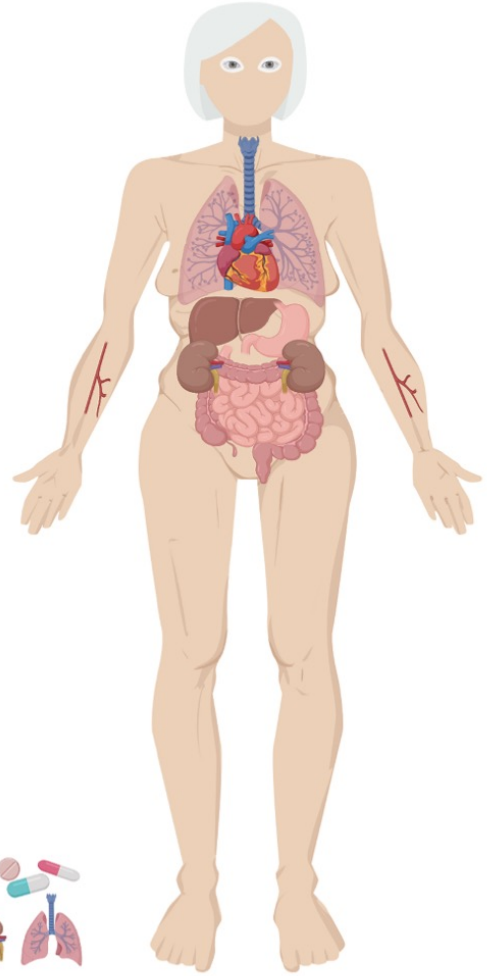
**Interstitial Lung Disease:**
Trastuzumab Deruxtecan
Trastuzumab Emtansine
Mirvetuximab Soravtansine

**Hepatic:**
Trastuzumab Emtansine
Loncastuximab Tesirine

**Renal:**
Moxetumomab Pasudotox
Loncastuximab Tesirine

**Peripheral Neuropathy:**
Brentuximab Vedotin
Polatuzumab Vedotin
Enfortumab Vedotin
Tisotumab Vedotin



**Occular:**
Mirvetuximab Soravtansine

**Cardiac:**
Trastuzumab Emtansine

**Vascular Leak Syndrom:**
Loncastuximab Tesirine

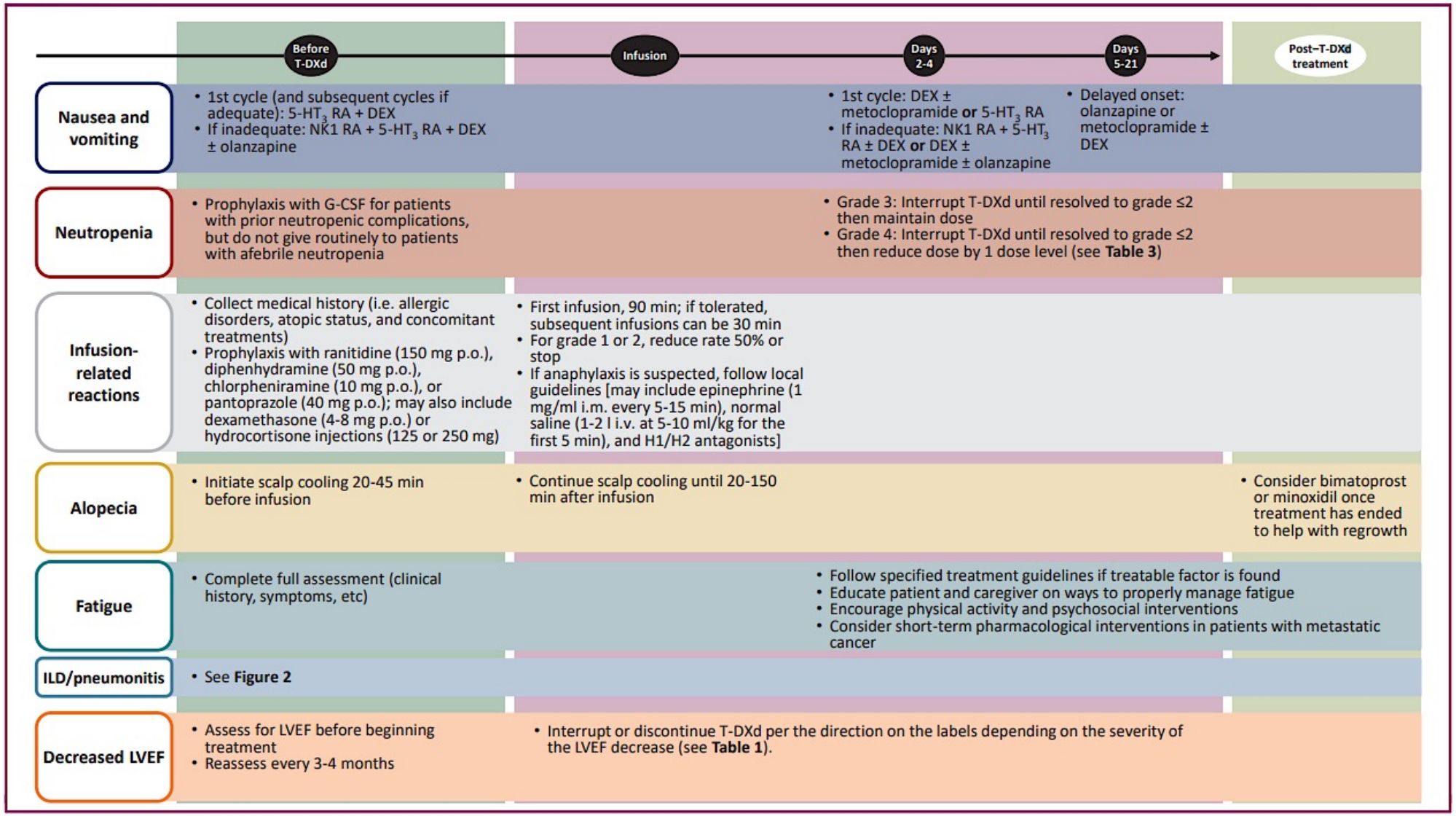
**Diarrhea:**
Loncastuximab Tesirine
Sacituzumab Govitecan

**Hematologic:**
Brentuximab Vedotin
Gemtuzumab Ozogamicin
Polatuzumab Vedotin
Enfortumab Vedotin
Tisotumab Vedotin
Loncastuximab Tesirine
Sacituzumab Govitecan
Trastuzumab Emtansine
Trastuzumab Deruxtecan

Rached et al. Critical Reviews in Oncology 2024

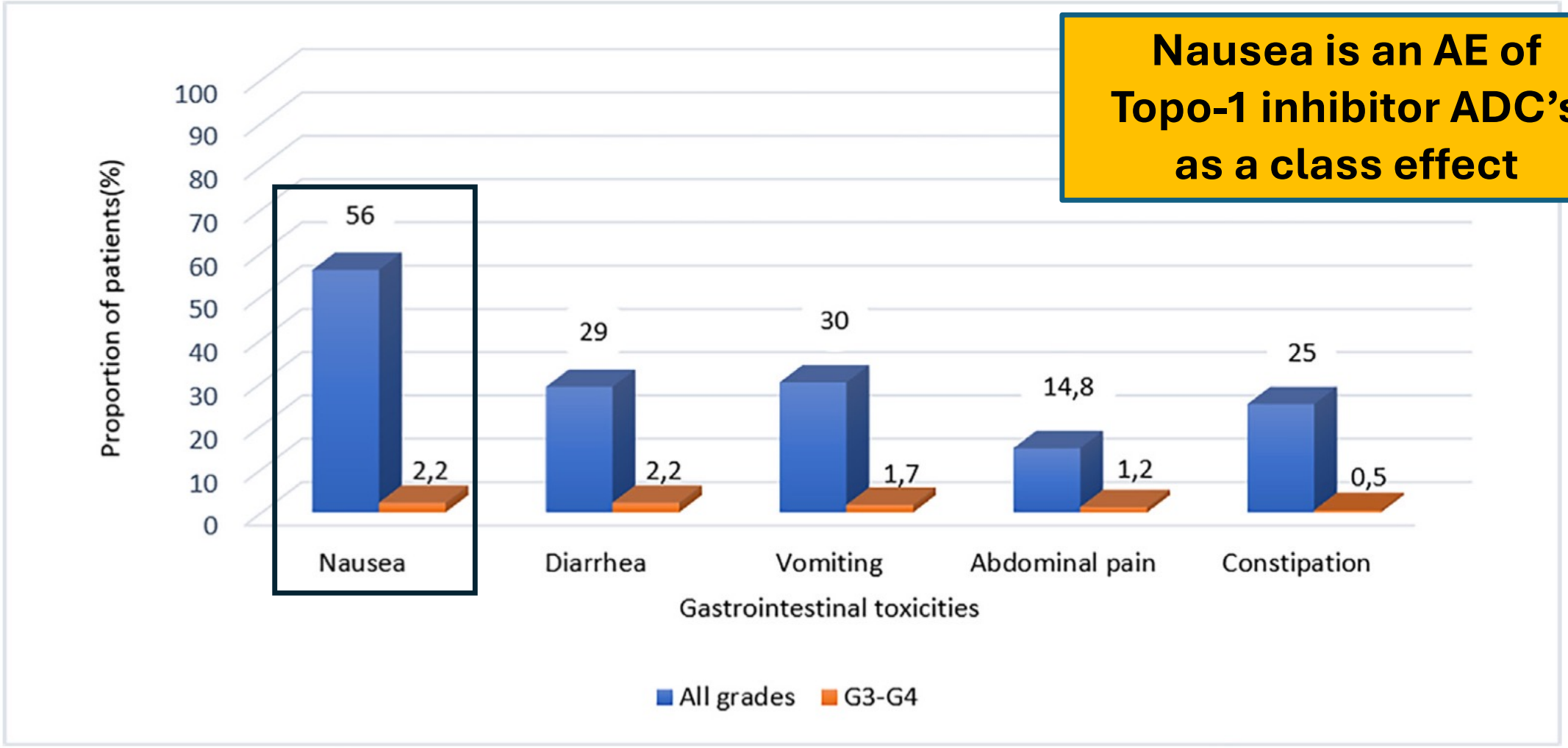
Slide courtesy of Dr. Ramez Eskander

# Overview of management of T-DXd related adverse events




Rugo H et al. ESMO Open 7(4) 2022

# ADC Related GI Toxicities




Pedersini et al. Clinical Breast Cancer 2024

Slide courtesy of Dr. Ramez Eskander

# T-DXd related nausea & emesis

## Incidence

**Nausea** with T-DXd is very common:
All grades: > 70%
Grade ≥ 3 ~7%

**Emesis** is also common
All grades ~45%
Grade ≥ 3 is < 5%

## Prevention

**Pre treatment:**
- 5-HT3 + DEX

If inadequate:
- NK1 + 5HT3 + DEX +/- olanzapine

**Days 2-4:**
- DEX +/- metoclopramide or 5HT3

If inadequate:
- NK1 + 5HT3 +/- DEX or DEX +/- metoclopramide +/- olanzapine

**Days 5-21**
**Delayed onset:**
- Olanzapine or metoclopramide +/- DEX

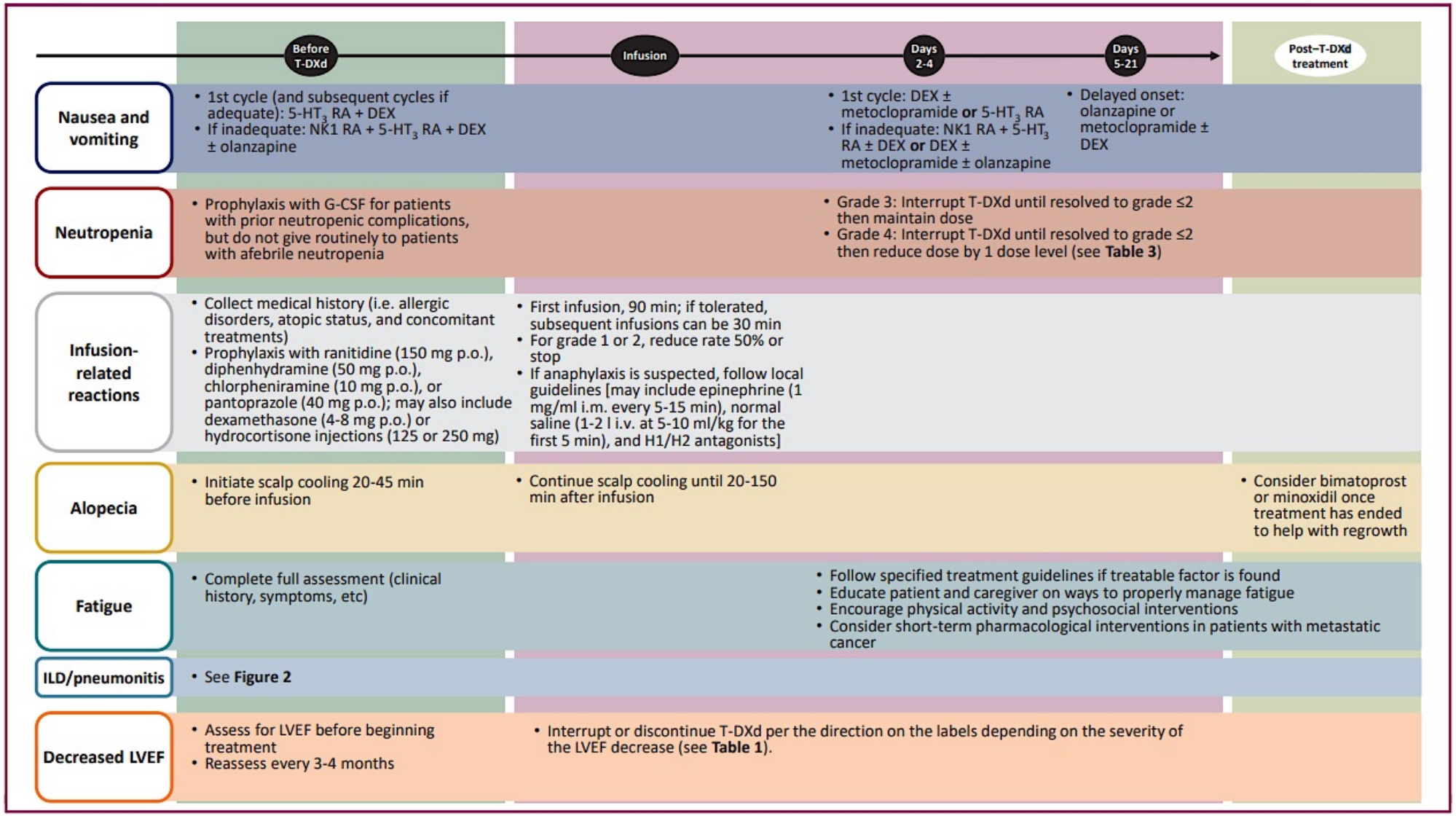
## Mitigation

**Prophylaxis for both pre treatment and delayed nausea is recommended**

**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 H et al. ESMO Open 7(4) 2022

# Overview of management of T-DXd related adverse events




Rugo H et al. ESMO Open 7(4) 2022

# ADC related Neutropenia

- ADC related AEs principally **driven by the payload** (Off-target, Off-site toxicity)[1]
- In a meta-analysis of 169 clinical trials inclusive of 22,492 patients, the **most common grade ≥3 treatment related adverse event was neutropenia (31%)**[2]
- ADC associated neutropenia correlates with cumulative plasma exposure of the payload
- T-DXd neutropenia (all grades) 35-43% and ≥ Grade 3 ~20% based on studies in breast cancer
  - 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 1 dose level[3]

[1]Zhu et al. Cancer 2023; [2]Nguyen et al. Cancers 2023; [3]Rugo et al. ESMO Open 2022

Slide courtesy of Dr. Ramez Eskander

# ADC related Neutropenia – Management

- **ASCO Guidelines**

| Patient Risk Factors for Febrile Neutropenia | |
|---|---|
| • Age > 65 years | • Poor performance status |
| • Advanced Stage Disease | • Poor nutritional status |
| • Previous chemotherapy or Radiation | • Poor renal/liver function |
| • Preexisting neutropenia or Bone Marrow involvement with tumor | • Cardiovascular disease |
| • Infections, or open wounds | • HIV infection |
| • Recent Surgery | • Multiple comorbid conditions |

Smith et al. J Clin Oncol 2015

Slide courtesy of Dr. Ramez Eskander

# ADC related Neutropenia – Management

- **ASCO Guidelines**

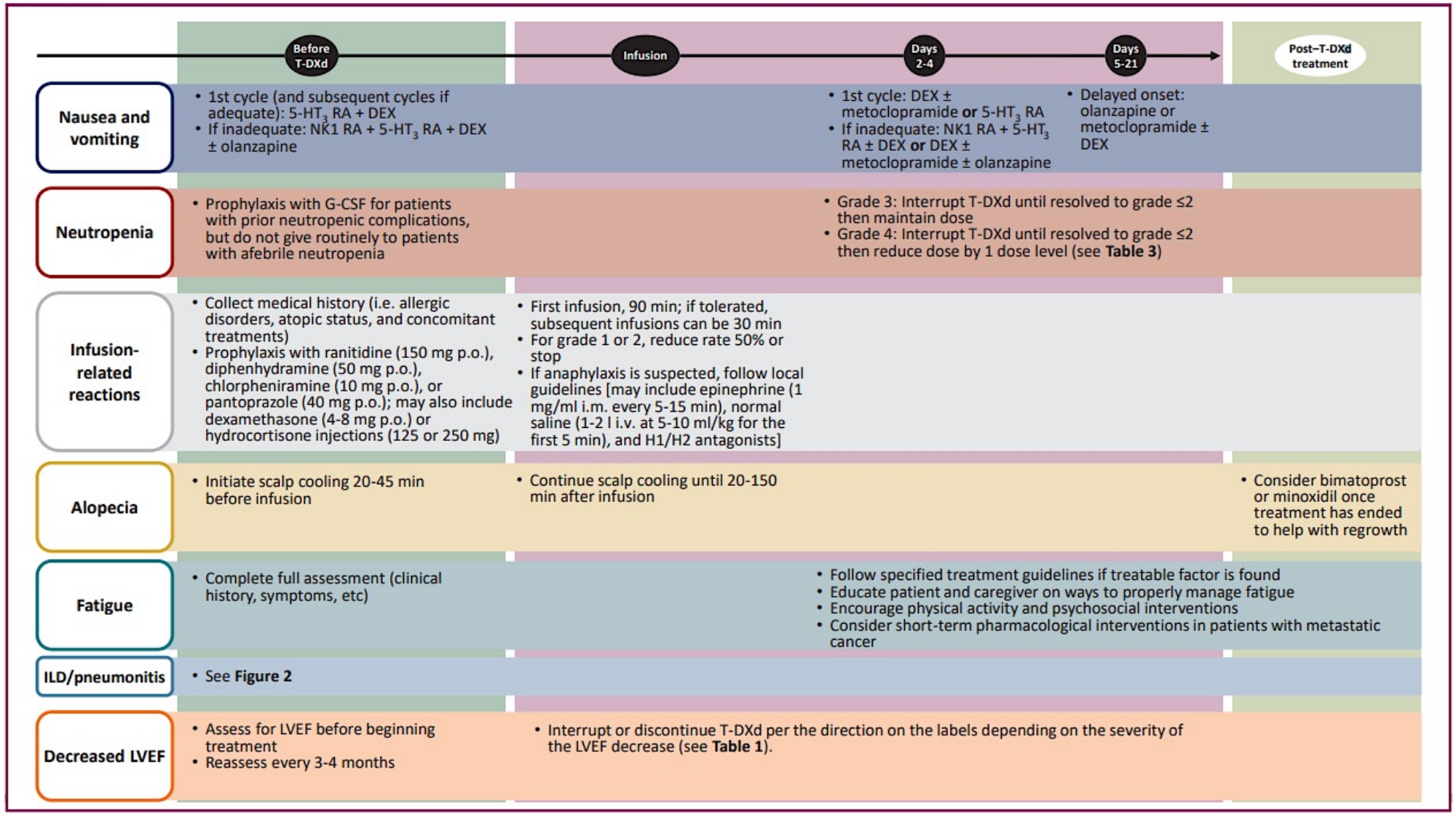
| Patient Risk Factors for Febrile Neutropenia | |
|---|---|
| • Age > 65 years | • Poor performance status |
| • Advanced Sta | |
| • Previous cher | |
| • Preexisting ne involvement with tumor | |
| • Infections, or open wounds | • HIV infection |
| • Recent Surgery | • Multiple comorbid conditions |

**Use of prophylactic growth factors should be strongly considered (in context of clinical trial requirements)**

Smith et al. J Clin Oncol 2015

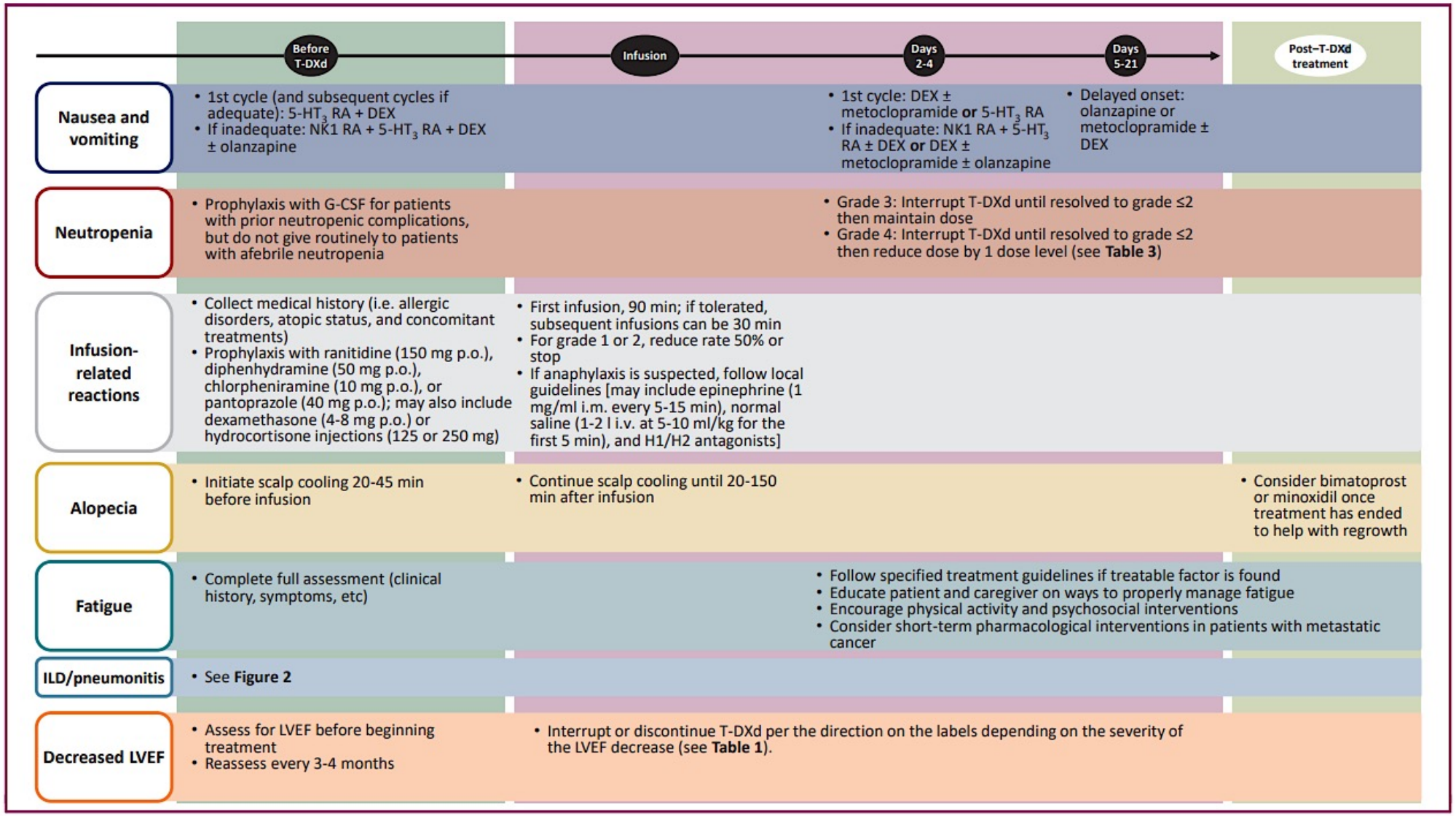
Slide courtesy of Dr. Ramez Eskander

# Overview of management of T-DXd related adverse events




Rugo H et al. ESMO Open 7(4) 2022

# Overview of management of T-DXd related adverse events



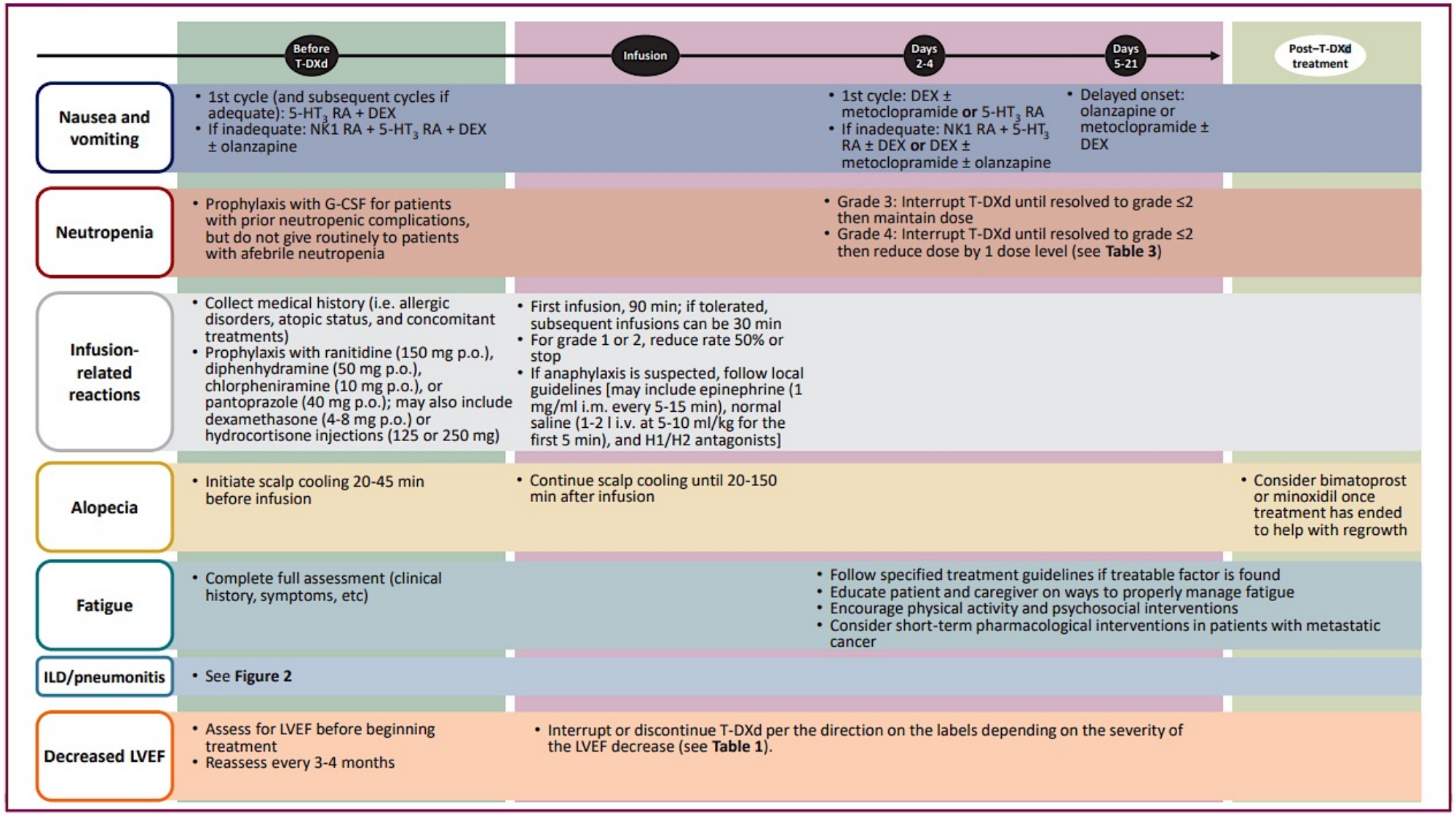

Rugo H et al. ESMO Open 7(4) 2022

# Overview of management of T-DXd related adverse events

| LVEF decrease | Incidence | LVEF change | Intervention |
|---|---|---|---|
| | All Grade: < 3% | > 45% and absolute decrease from BL 10-20% | Continue treatment |
| | Grade ≥ 3 < 1% | 40-45% and absolute decrease from BL < 10% | Continue treatment and repeat LVEF within 3 weeks |
| | | 40-45% and absolute decrease from BL 10-20% | Hold<br>Repeat LVEF within 3 weeks.<br>If not recovered to within 10% of BL – permanently discontinue |
| | | < 40% or absolute decrease from BL > 20% | Hold<br>Repeat LVEF within 3 weeks<br>If LVEF < 40% or absolute change from baseline> 20% confirmed, permanently discontinue |
| | | Symptomatic CHF | discontinue |

Rugo H et al. ESMO Open 7(4) 2022

# Overview of management of T-DXd related adverse events




Rugo H et al. ESMO Open 7(4) 2022

# ILD/Pneumonitis is a class effect of several – mainly deruxtecan payloads

| Study | N | Disease type | Grade1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Total |
|---|---|---|---|---|---|---|---|---|
| DESTINY-Breast02[1] | 404 (TDXd)<br>195 (PC) | Breast | 2.7%<br> | 6.4%<br> | 0.7%<br>0.5% | 0<br> | 0.5%<br> | 10.3%<br>0.5% |
| DESTINY-Breast03[2] | 257 (TDXd)<br>261 (TDM1) | Breast | 4.3%<br>1.5% | 10.1%<br>1.1% | 0.8%<br>0.5% | 0<br>0 | 0<br>0 | 15.2%<br>3.1% |
| DESTINY-Breast04[3] | 371 (TDXd)<br>172 (PC) | Breast | 3.5%<br>0.6% | 6.5%<br>0 | 1.3%<br>0 | 0<br>0 | 0.8%<br>0 | 12.1%<br>0.6% |
| DESTINY-PanTumor[4] | 267 | All Solid | 2.2% | 4.5% | 0.4% | 0 | 0.4% | 7.5% |
| Raludotatug deruxtecan[5] | 60 | Ovarian | 0 | 6.7% | 0 | 0 | 3.3%* | 10% |
| Datopotamab deruxtecan[6] | 75 | Ovarian Endo | 0 | 0 | 3% | 0 | 0 | 3% |

*Grade 5 events at 8mg/kg which was discontinued

- 1. Krop I, SABCS 2022. 2. Hurvitz SA, SABCS 2022. 3. Modi S, ASCO 2022.4. Meric Berstam J Clin Oncol. 2024 . 5. Moore et al. ESMO Annual Meeting 2023. 6. Oaknin et al. ESMO Annual Meeting 2024

# Detecting and Managing T-DXd–Related ILD: The Five "S" Rules[1]

## 1 Screen

- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on 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 adapted to the toxicity grade

1. Tarantino P, Tolaney SM. *JCO Oncol Pract*. 2023;19:526-527

# Careful pre-treatment and ongoing assessment for ILD is critical - but also tricky……

**Screen**

| | |
|---|---|
| Total number of patients<br>HR+/HER2-low<br>HER2+<br>TNBC/HER2-low | 68<br>24 (35.3%)<br>30 (44.1%)<br>14 (20.6%) |
| Median age | 57.4 years |
| Median time to pneumonitis | 83 days (range 35-266) |
| Baseline CT scan abnormalities<br>Interstitial lung abnormalities (ILA)<br>Radiation changes<br>Bronchial wall thickening<br>Emphysema<br>Infectious/inflammatory GGOs<br>Pleural effusion<br>Lung metastases | 62 (91.2%)<br>16 (23.5%)<br>48 (70.5%)<br>55 (80.1%)<br>9 (13.2%)<br>15 (22.1%)<br>24 (35.3%)<br>33 (48.5%) |

92% of patients had some sort of baseline radiographic abnormality

Do all of these patients need PFTs, High Res CTs, Pulm consults before starting a deruxtecan linked ADC?

Abelman et al. J Clin Oncol 41, 2023 (suppl 16; abstr 1106)

# Careful pre-treatment and ongoing assessment for ILD is critical - but also tricky……

**Screen**

| | |
|---|---|
| Total number of patients<br>HR+/HER2-low<br>HER2+<br>TNBC/HER2-low | 68<br>24 (35.3%)<br>30 (44.1%)<br>14 (20.6%) |
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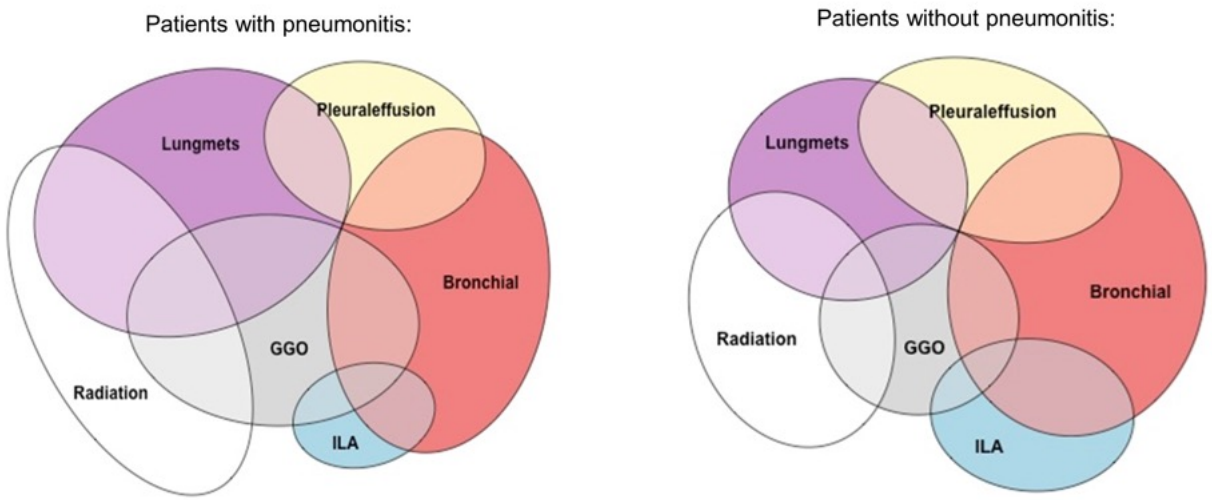
There was no association between presence of baseline abnormalities and development of ILD/pneumonitis……




Abelman et al. J Clin Oncol 41, 2023 (suppl 16; abstr 1106)

2

Scan

# Radiographic scans are fundamental diagnostic tool with repeat scans every 6-12 weeks. But even this can be tricky…..

| | |
|---|---|
| Total number of patients | 68 |
| HR+/HER2-low | 24 (35.3%) |
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| Infectious/inflammatory GGOs | 15 (22.1%) |
| Pleural effusion | 24 (35.3%) |
| Lung metastases | 33 (48.5%) |
| Independent assessment of pneumonitis | |
| Grade 1 | 16 (23.5%) |
| Grade 2 | 3 (4.4%) |
| None | 49 (72.1%) |
| Treating physician assessment of pneumonitis | |
| Grade 1 | 5 (7.4%) |
| Grade 2 | 3 (4.4%) |
| None | 60 (88.2%) |

3

Synergy

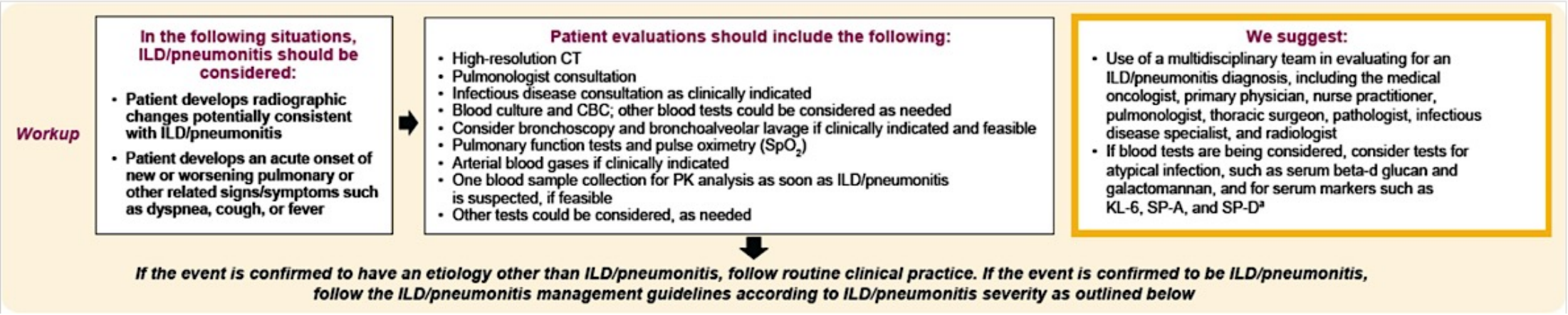

The rate of independently assessed pneumonitis was higher than that assessed by the treating physician – **but this was mainly an increase in grade 1**

**So what do we do now?**

Abelman et al. J Clin Oncol 41, 2023 (suppl 16; abstr 1106)

# Multi-disciplinary management is key once ILD/pneumonitis is suspected

Synergy




Direct communication with the pulmonology specialist is recommended. A referral for asymptomatic GGO will not be treated with urgency without context

Swain et al. Cancer Treat Rev 2022

4

**S**uspend Treatment

# Summary Guidelines: DXd–Induced ILD

5

**S**teroids

| | Grade 1 | Grade 2 | Grade 3/4 |
|---|---|---|---|
| **Defs.** | **Asymptomatic**: clinical or diagnostic | **Symptomatic**: limiting ADLs | ▪ Grade 3: **Severe symptoms:** limiting self-care; need O2<br>▪ Grade 4: **Life-threatening** |
| **Workup** | **Imaging** c/w ILD/pneumonitis or develops an acute pulmonary s/s dyspnea, cough, or fever, then rule out with<br>High-resolution CT<br>Pulmonologist with bronch or BAL +/- ID consult; PFT; pulse ox; ABG<br>Blood Cx | | |
| **Mods** | ▪ **Interrupt T-DXd until grade 0.**<br><28d = same dose; >28d, reduce | ▪ **<u>Permanently d/c T-DXd</u>**<br>▪ **Promptly corticosteroid treatment as soon as ILD suspected** | |
| **Management** | ▪ Monitor and closely follow up in 2-7 days **Consider follow-up imaging in 1-2 weeks (or as clinically indicated)**<br>▪ Consider steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, taper >= 4 weeks<br>▪ **If worsening despite corticosteroids, then follow grade 2 guidelines.** | ▪ **Steroids (>1 mg/kg/day prednisone or equivalent)** until improvement, followed by gradual taper >= 4 weeks<br>▪ If worsening or no improvement @ 5 days:<br>– Consider increasing dose (eg, 2 mg/kg/day prednisone or equivalent)<br>– Reconsider additional workup for alternative etiologies as described above<br>– Escalate care? | ▪ **Hospitalization required**<br>▪ **H**igh-dose methylprednisolone IV treatment (eg, **500-1000 mg/day for 3 days**), followed by at least 1 mg/kg/day of prednisone (or equivalent). Gradual taper over >= 4 weeks<br>▪ If still no improvement within 3-5 days:<br>▪ Reconsider additional workup for alternative etiologies as described above<br>▪ Consider other immunosuppressants and/or treat per local practice |

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# DXd–Induced ILD: Controversial Topics: If my patient is responding and recovers from grade 1 or 2 ILD, Can I re-treat?

| | Grade 1 | Grade 2 | Grade 3/4 |
|---|---|---|---|
| **Defs.** | **Asymptomatic**: clinical or diagnostic | **Symptomatic**: limiting ADLs | ▪ Grade 3: **Severe symptoms:** limiting self-care; need O2<br>▪ Grade 4: **Life-threatening** |
| **Workup** | **Imaging** c/w ILD/pneumonitis or develops an acute pulmonary s/s dyspnea, cough, or fever, then rule out with<br>High-resolution CT<br>Pulmonologist with bronch or BAL +/- ID consult; PFT; pulse ox; ABG<br>Blood Cx | | |
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# DXd–Induced ILD: Controversial Topics:
# If my patient is responding and recovers from grade 1 ILD, Can I re-treat?

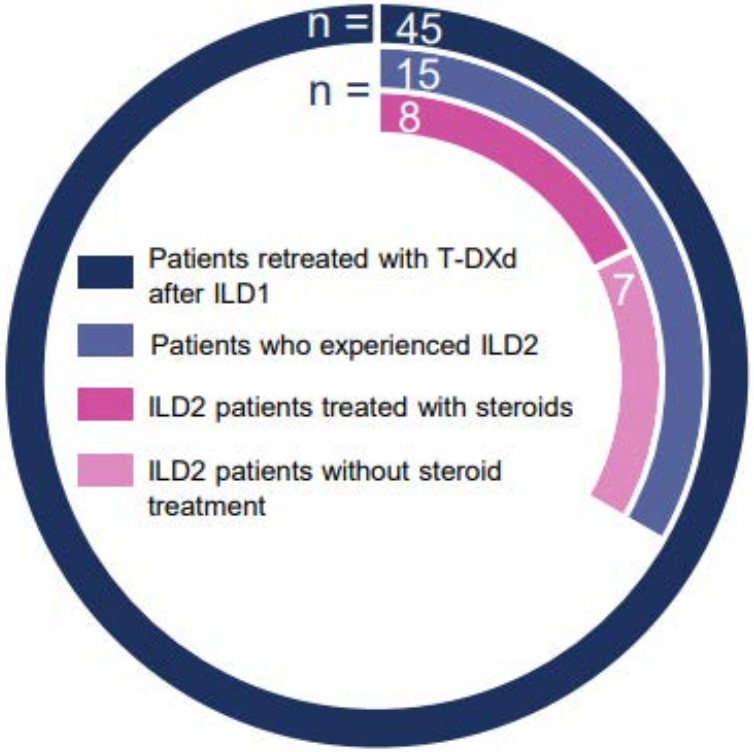
For Grade 1- With Care – the answer appears to be yes

**Patients in this analysis**
(N = 2145)

**Patients with adjudicated drug-related ILD of investigator-assessed Gr 1 (ILD1)[a]**
(N = 193)
Steroid for ILD1: 97 (50.3%)

**Patients not receiving T-DXd retreatment[b]: 148**
- Patients who recovered from ILD1: 61 (41.2%)
  - Recovered in >49 days: 53 (35.8%)
  - Recovered in <49 days[c]: 8 (5.4%)
- Patients recovering from ILD1: 12 (8.1%)
- Patients noted as not recovered from ILD1[d,e]: 65 (43.9%)
- Patients with unknown/missing ILD1 outcome: 10 (6.8%)

**Patients with T-DXd retreatment after recovery of ILD1**
(N = 45)
Steroid for ILD1: 31 (68.9%)




23% of patients were re-treated (68% without dose mod)

66.7% re-treated w/o recurrence of ILD
All recurrences that did occur were low grade
Note: ILD recovery period for re-treatment eligibility was modified from 49 – 126 days

Rugo H et al. ESMO Breast Cancer 2024

# DXd–Induced ILD: Controversial Topics:
# If my patient is responding and recovers from grade 2 ILD, Can I re-treat?

**Patients in this analysis**
(N = 2145)

**Patients with adjudicated drug-related ILD of investigator-assessed Gr 1 (ILD1)[a]**
(N = 193)
Steroid for ILD1: 97 (50.3%)

**Patients with T-DXd retreatment after recovery of ILD1**
(N = 45)
Steroid for ILD1: 31 (68.9%)

**Patients n**
- Patients w
  - Recov
  - Recov
- Patients r
- Patients n
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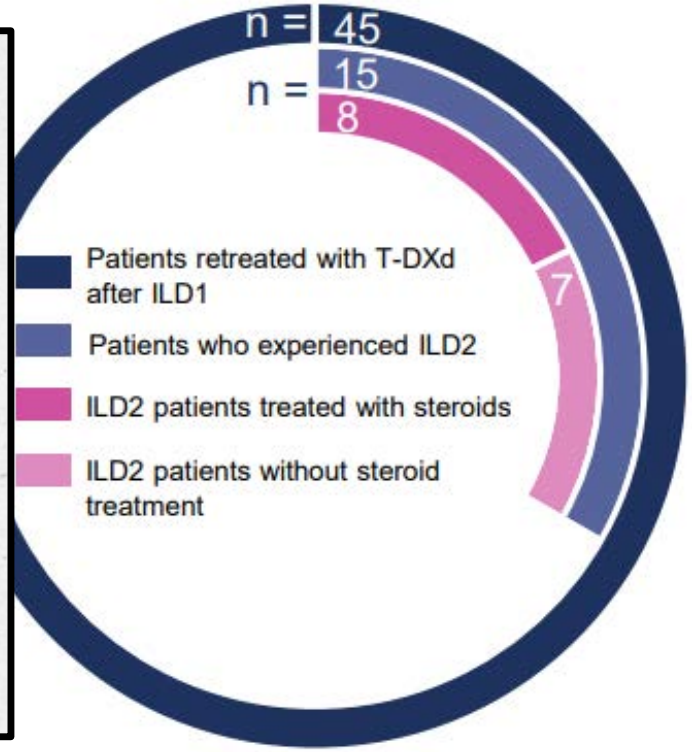


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Rugo H et al. ESMO Breast Cancer 2024


# DXd–Induced ILD: Controversial Topics
# What if my hospitalized patient is getting worse despite 2mg/kg/day of steroids?

| | Grade 1 | Grade 2 | Grade 3/4 |
|---|---|---|---|
| **Defs.** | **Asymptomatic**: clinical or diagnostic | **Symptomatic**: limiting ADLs | ▪ Grade 3: **Severe symptoms:** limiting self-care; need O2<br>▪ Grade 4: **Life-threatening** |
| **Workup** | **Imaging** c/w ILD/pneumonitis or develops an acute pulmonary s/s dyspnea, cough, or fever, then rule out with<br>High-resolution CT<br>Pulmonologist with bronch or BAL +/- ID consult; PFT; pulse ox; ABG<br>Blood Cx | | |
| **Mods** | ▪ **Interrupt T-DXd until grade 0.**<br><28d = same dose; >28d, reduce | ▪ **<u>Permanently d/c T-DXd</u>**<br>▪ **Promptly corticosteroid treatment as soon as ILD suspected** | |
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# DXd–Induced ILD: Controversial Topics
# What if my hospitalized patient is getting worse despite 2mg/kg/day of steroids?

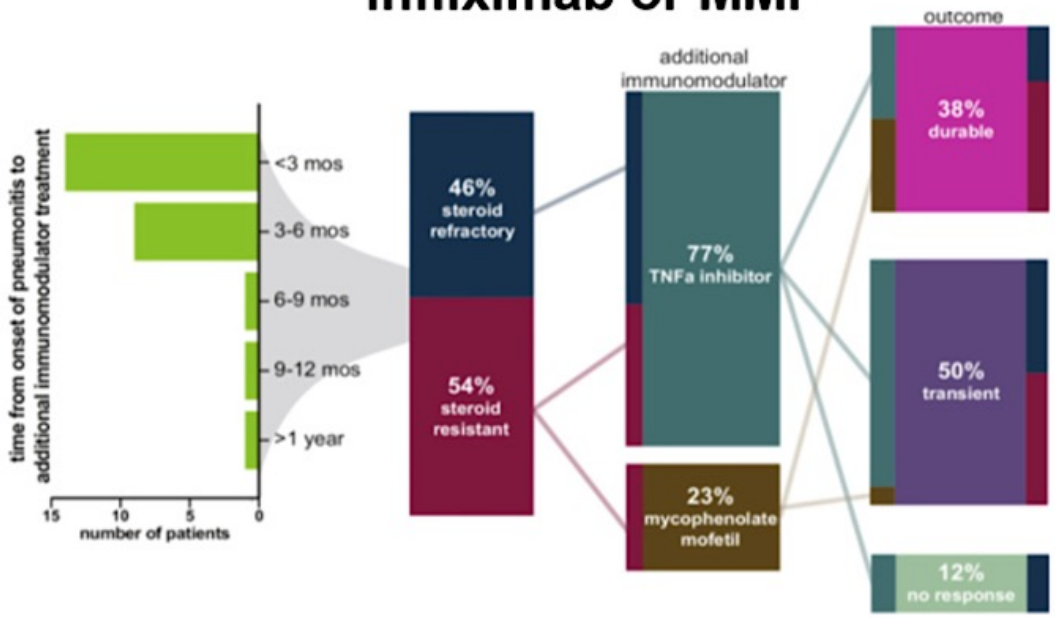
**Definitions from the ICI Literature:**
**Steroid-refractory**: Patients with no improvement or worsening of pneumonitis with initial treatment with systemic steroids. **Steroid-resistant**: Patients who initially responded to steroids but subsequently developed recurrent pneumonitis in the context of steroid tapering, in the absence of immune checkpoint rechallenge

| | Onset of Action | Evidence for use | Benefits | Risks |
|---|---|---|---|---|
| Mycophenolate | Slow (months) | From ILD and hepatic iRAE, case series for pneumonitis | Familiar to pulmonologists | Immunosuppression and cancer risk |
| IVIG | Fast (days to weeks) | Rheumatologic data, possibly superior to infliximab in one small study | No increased risk of infection | Prothrombotic, expensive, time consuming |
| Tocilizumab | Fast (days-weeks) | Gr 3-4 iRAEs including pneumonitis | Onset of action, relatively inexpensive | Immunosuppression |
| Infliximab | Fast (days –weeks) | From hepatic iRAE and small case series with cyclophosphamide | Familiarity | Immunosuppression long duration of action |

Table adapted from Dr. Maida Hafiz, Pulmonology SCC

# DXd–Induced ILD: Controversial Topics
# What if my hospitalized patient is getting worse despite 2mg/kg/day of steroids?

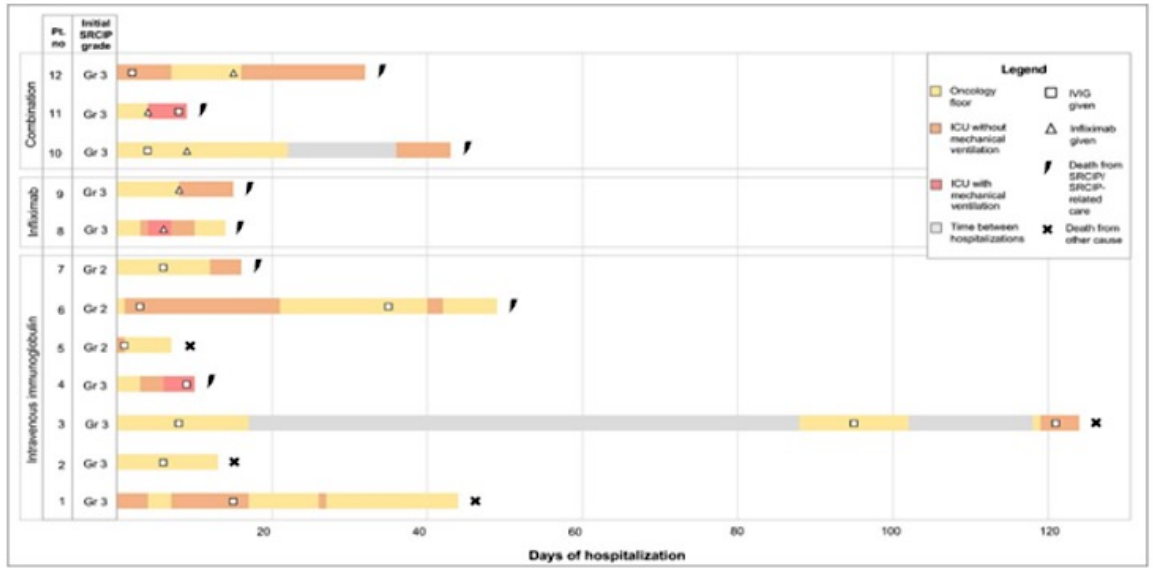
## Infliximab or MMF




10/26 (38%) response

Beattie et al, JITC 2021

## IVIG




4/12 (33%) response

Balaji et al, JITC 2021

Slides courtesy of Dr. Maida Hafiz, Pulmonology SCC

# Video Cases and Questions for the Faculty

# Case Presentation: 61-year-old woman with metastatic HER2-positive (IHC 3+) UPSC and PD on multiple lines of therapy receives trastuzumab deruxtecan

Kellie E Schneider, MD (Charlotte, North Carolina)

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# QUESTIONS FOR THE FACULTY

**What is your approach to the management of the acute nausea and vomiting associated with T-DXd? How do you manage breakthrough nausea and vomiting despite guideline-directed antiemetic prophylaxis?**

**How, specifically, are you monitoring for interstitial lung disease (ILD) in your patients receiving T-DXd?**

**Can you continue T-DXd if a patients develops asymptomatic Grade 1 ILD? Symptomatic? At what level of ILD are you permanently discontinuing treatment even after resolution of symptoms?**

# Case Presentation: 62-year-old woman with multiregimen-recurrent metastatic HER2-positive (IHC 3+) UPSC s/p chemotherapy/trastuzumab is a candidate for trastuzumab deruxtecan but with reduced cardiac EF (41%)

Kellie E Schneider, MD (Charlotte, North Carolina)

# QUESTIONS FOR THE FACULTY

**What is your approach to the use of T-DXd in patients with a history of cardiac disease? What baseline ejection fraction would you consider to be a contraindication to T-DXd?**

**Is T-DXd associated with the same level of cardiac toxicity as trastuzumab? What is your approach to cardiac monitoring in patients receiving T-DXd with no prior history of cardiac disease?**

# What Clinicians Want to Know: Addressing Current Questions and Controversies in the Care of Patients with Ovarian Cancer

*An Independent CME Symposium During*
*the 2025 SGO Annual Meeting on Women's Cancer®*

**Sunday, March 16, 2025**
**12:30 PM – 2:00 PM PT (3:30 PM – 5:00 PM ET)**

## Faculty

**Kathleen N Moore, MD, MS**
**Ritu Salani, MD, MBA**
**Shannon N Westin, MD, MPH, FASCO, FACOG**

## Moderator

**Angeles Alvarez Secord, MD, MHSc**

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