Expert Second Opinion: Investigators Provide Perspectives on the Management of HER2-Positive Gynecologic Cancers

An Independent CME Symposium During the SGO 2026 Annual Meeting on Women's Cancer®

Saturday, April 11, 2026

12:45 PM – 2:15 PM AST

Faculty

Joyce F Liu, MD, MPH

Brian M Slomovitz, MD

Moderator

David M O'Malley, MD

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Faculty

Joyce F Liu, MD, MPH
Associate Chief and Director of Clinical Research
Division of Gynecologic Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Moderator

David M O'Malley, MD
Director and Professor
Division of Gynecologic Oncology in Obstetrics and Gynecology
John G Boutselis Chair in Gynecologic Oncology
The Ohio State University and The James Comprehensive Cancer Center
Columbus, Ohio

Brian M Slomovitz, MD
Professor, OB-GYN, Florida International University
Director, Gynecologic Oncology
Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Miami, Florida

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Dr Liu — Disclosures
Faculty

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Dr Slomovitz — Disclosures
Faculty

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Prof Ledermann — Disclosures
Consulting Clinical Investigator

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Expert Second Opinion: Investigators Provide Perspectives on the Best-Practice Management of Ovarian Cancer

An Independent CME Symposium During the SGO 2026 Annual Meeting on Women's Cancer®

Sunday, April 12, 2026

1:30 PM – 3:00 PM AST

Faculty

Nicoletta Colombo, MD

Gottfried E Konecny, MD

Alexander B Olawaiye, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

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Data + Perspectives: The Potential Role of TROP2- and CDH6-Directed Antibody-Drug Conjugates in Gynecologic Cancers

An Independent CME Symposium During the SGO 2026 Annual Meeting on Women's Cancer®

Sunday, April 12, 2026

1:30 PM – 3:00 PM AST

Faculty

Ramez N Eskander, MD

Bradley J Monk, MD

Moderator

Kathleen N Moore, MD, MS

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

Friday to Sunday, April 24 to 26, 2026

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Please refer to the printed handout provided with your meeting syllabus, and scan the corresponding QR code to

Review and Download Program Slides.

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Ask a Question: We will aim to address as many questions as possible during the program.

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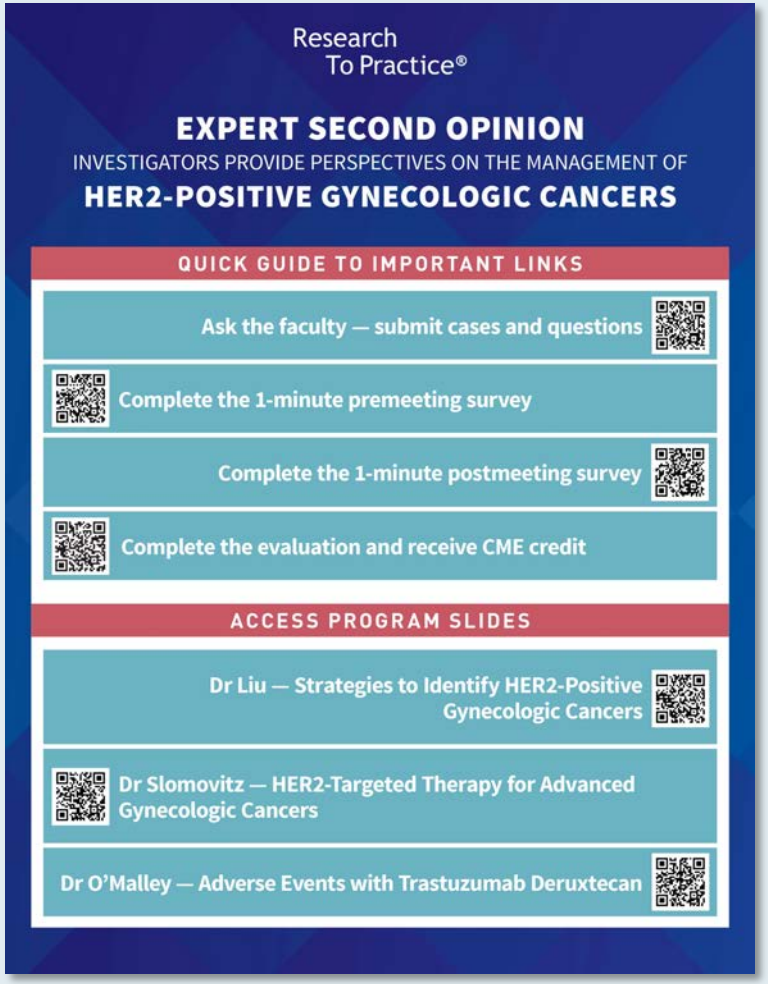

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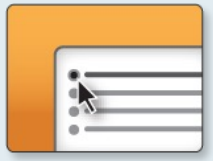
Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



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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.
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Second Opinion

Professor Jonathan A Ledermann
Professor of Medical Oncology
UCL Cancer Institute
London, United Kingdom

Angeles Alvarez Secord, MD, MHSc
Director of Gynecologic Oncology Clinical Trials
Associate Director, Clinical Research, Gynecologic Oncology Program
Duke Cancer Institute
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
Duke University School of Medicine
Durham, North Carolina

Ursula Matulonis, MD
Chief, Division of Gynecologic Oncology
Brock-Wilson Family Chair
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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 Liu

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

Module 3: Identification and Management of Adverse Events with T-DXd — Dr O'Malley

Agenda

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

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

Module 3: Identification and Management of Adverse Events with T-DXd — Dr O'Malley

Identifying Patients with HER2-“Positive” Gynecologic Cancers

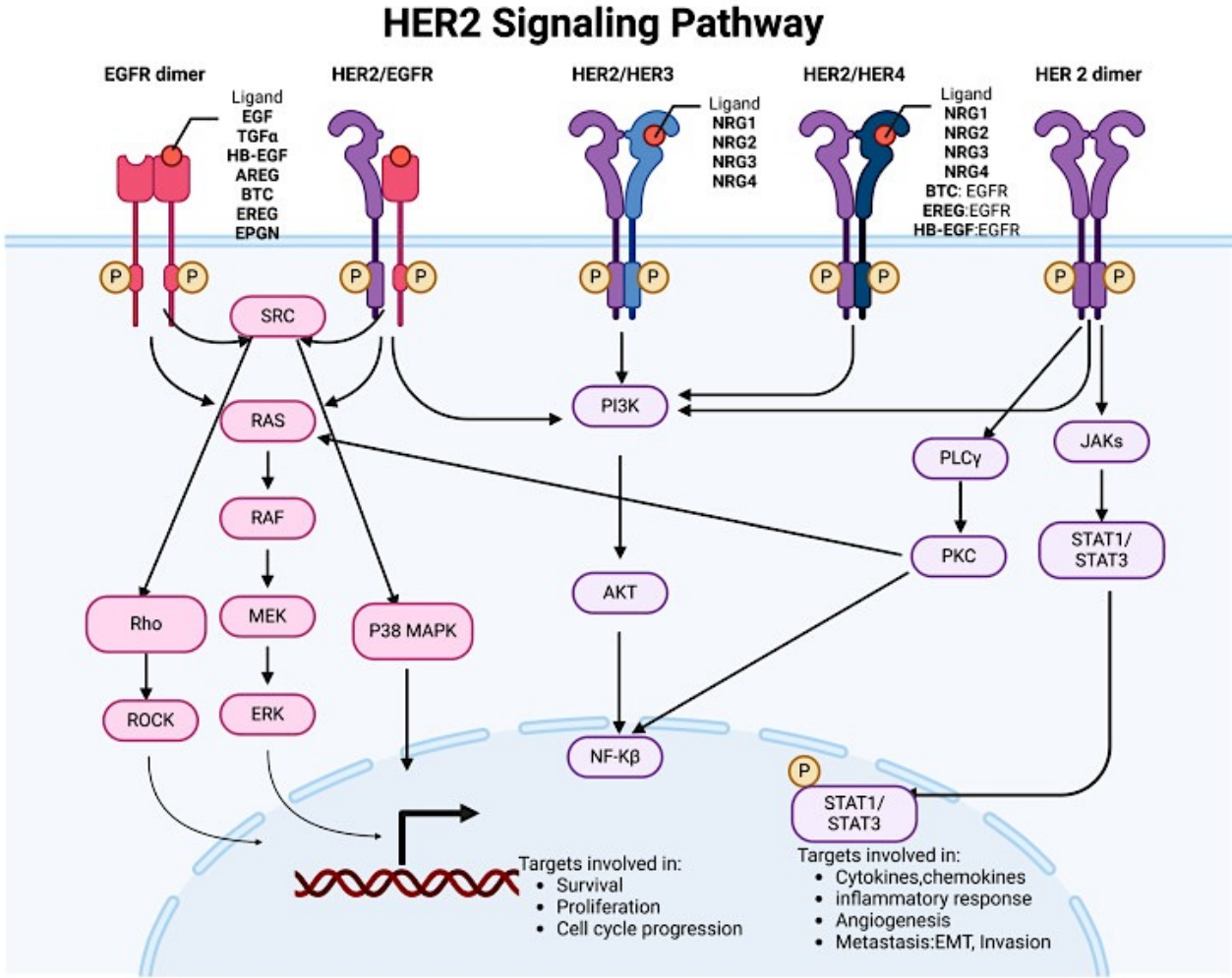
Joyce Liu, MD, MPH
Associate Chief and Director of Clinical Research
Division of Gynecologic Oncology
Dana-Farber Cancer Institute, Boston, MA

Agenda

- HER2 biology and the significance of HER2 addiction
- What does it mean to be HER2-“positive”?
- HER2 expression in gynecologic cancers
- Considerations for HER2 testing in gynecologic cancers in the ADC era

Biology of HER2

- Encoded by gene *ERBB2*
- Member of the EGFR family
- Does not have a known direct ligand
- Activates through dimerization and cross-phosphorylation
  - With other EGFR family members in presence of their ligands
  - With self or other EGFR family members in setting of high receptor density

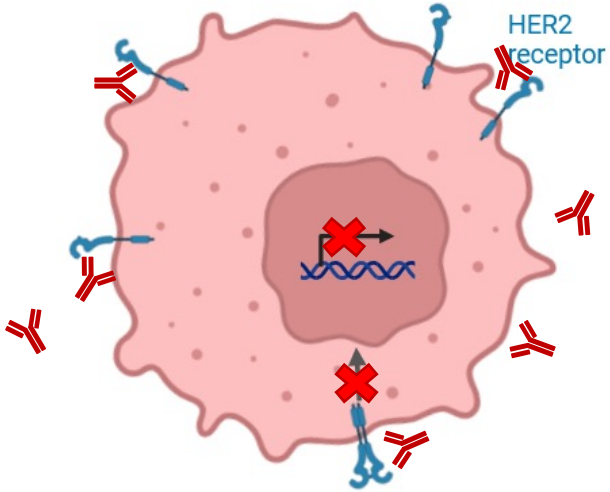


Cheng in *Genes (Basel)* 2024

HER2 amplification and the concept of HER2 addiction

HER2-directed monoclonal antibody

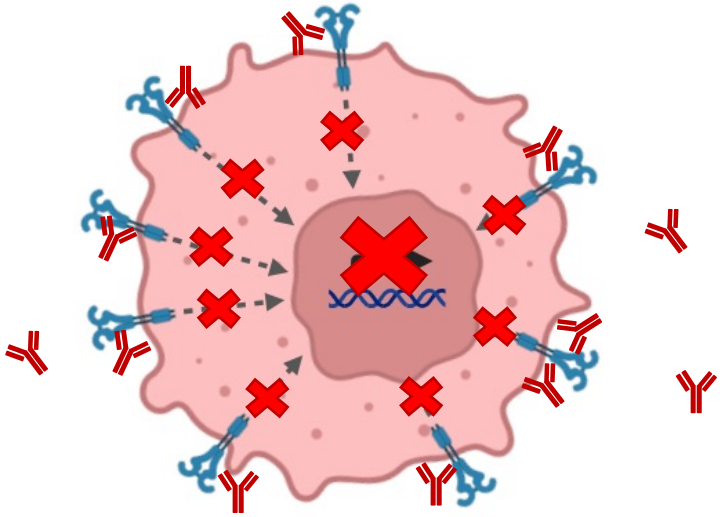
HER2-non-amplified cancer cell



HER2-non-addicted

Cell growth and survival are **independent** of HER2 signaling

HER2-amplified cancer cell



HER2-addicted

Cell growth and survival are **dependent** on HER2 signaling

Dana-Farber Cancer Institute

Images created with BioRender.com

Trastuzumab inactive in HER2-non-amplified tumors

- Trastuzumab monotherapy with limited to no activity in HER2 non-amplified breast cancer
- Trastuzumab + chemotherapy with no PFS or OS benefit in adjuvant setting for HER2 IHC 1+ or 2+ breast cancer (NSABP-47)
- **Conclusion**: HER2 non-amplified breast cancers not "addicted" to HER2 signaling and therefore insensitive to HER2-directed therapies

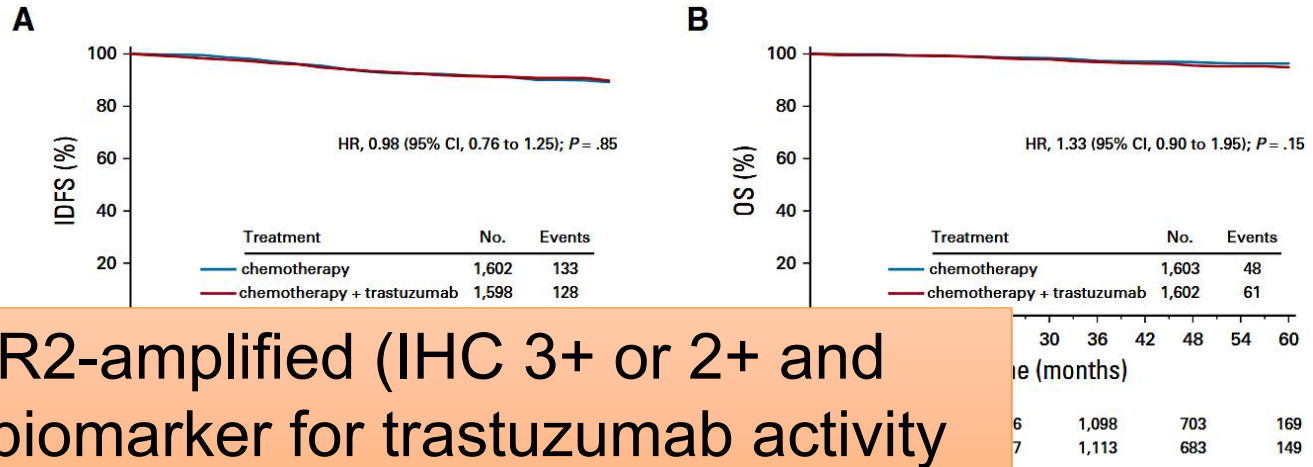
Table 4 Clinical Outcomes by HER2 Amplification Status in Patients Treated with Trastuzumab Alone

Study	HER2 Amplification	Evaluable Patients	Objective Response (CR plus PR)	Median Time to Progression, Months (Range)
H0649g	FISH-Positive	173	33 (19%)	3.2 (2.6-3.5*)
	FISH-Negative	36	0	1.9 (1.5-2.8)
H0650g	FISH-Positive	82	28 (34%)	4.9 (3.5-6.3)
	FISH-Negative	29	2 (7%)	1.7 (1.5-3.3*)

*Censored result.

Mass et al., *Clin Breast Cancer* 2005

PFS and OS for chemotherapy + trastuzumab in NSABP-47



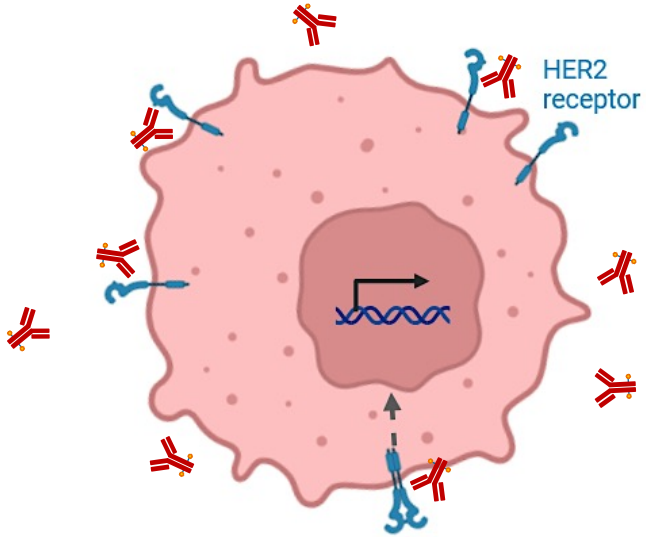
HER2-"positive" as HER2-amplified (IHC 3+ or 2+ and positive by FISH) as the biomarker for trastuzumab activity

Fehrenbacher et al., *J Clin Oncol* 2019

HER2 expression as a vulnerability for antibody-drug conjugates, independent of HER2 addiction/amplification

HER2-directed ADC

HER2-non-amplified cancer cell



HER2-non-addicted

Cell growth and survival are **independent** of HER2 signaling

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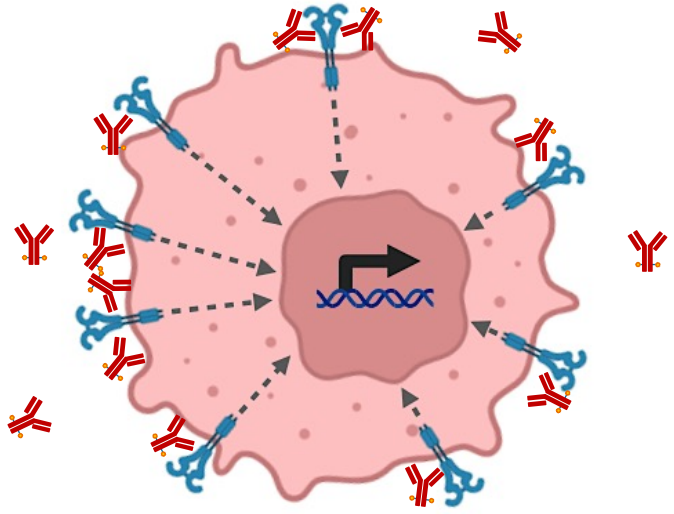

HER2-addicted

Cell growth and survival are **dependent** on HER2 signaling

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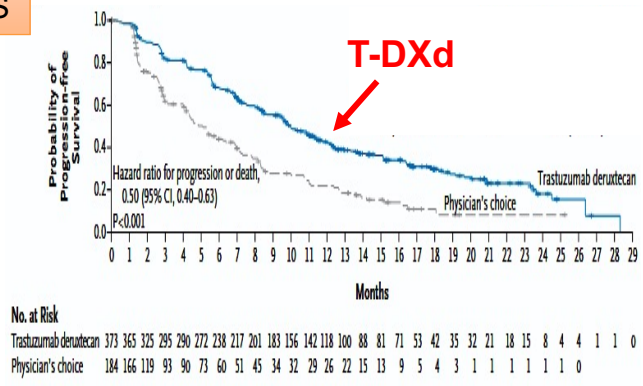
Images adapted from BioRender.com

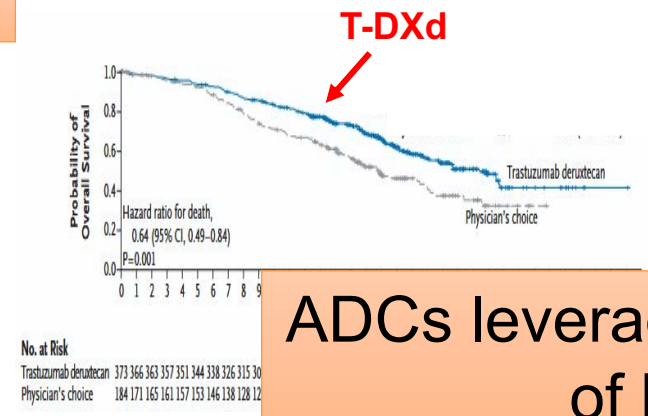
Re-visiting HER2 as a biomarker: Trastuzumab deruxtecan

DESTINY-Breast04
2/3L HER2 low met breast cancer

PFS



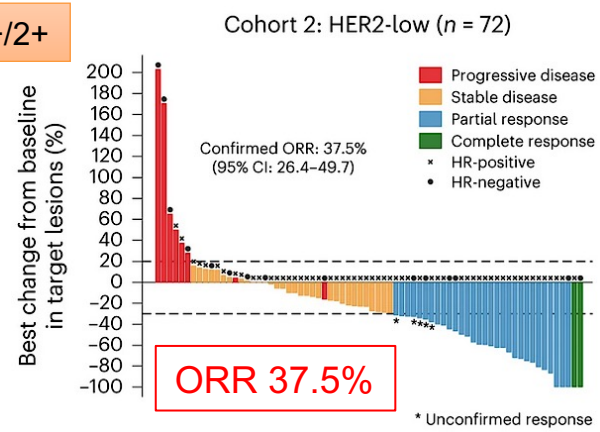
OS



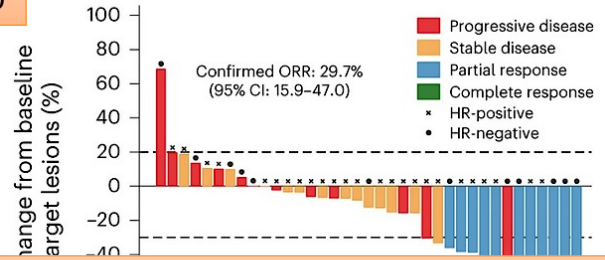
Modi et al., *N Engl J Med* 2022

DAISY
2L+ met breast cancer

IHC 1+/2+



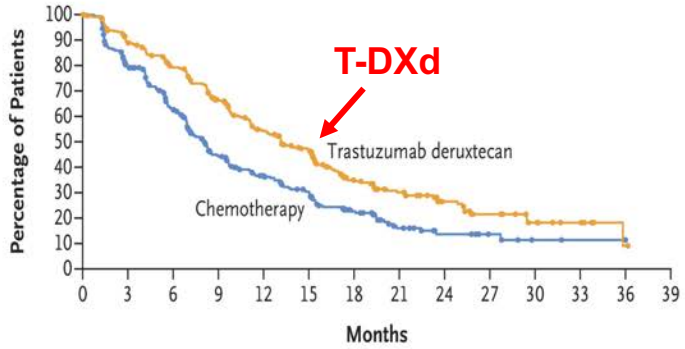
IHC 0



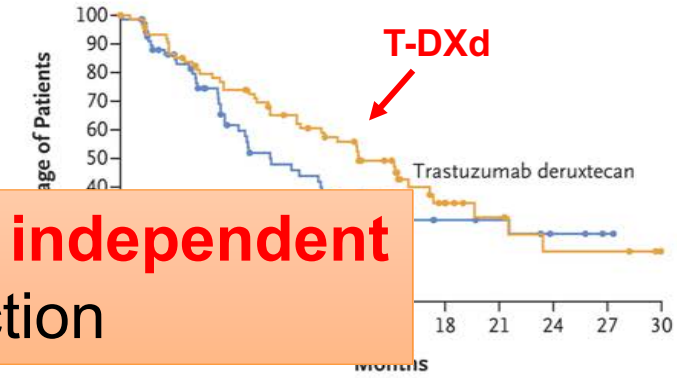
Mosele et al., *Nat Med* 2023

DESTINY-Breast06
1L HER2 low met breast cancer

HER2 low



HER2 ultralow

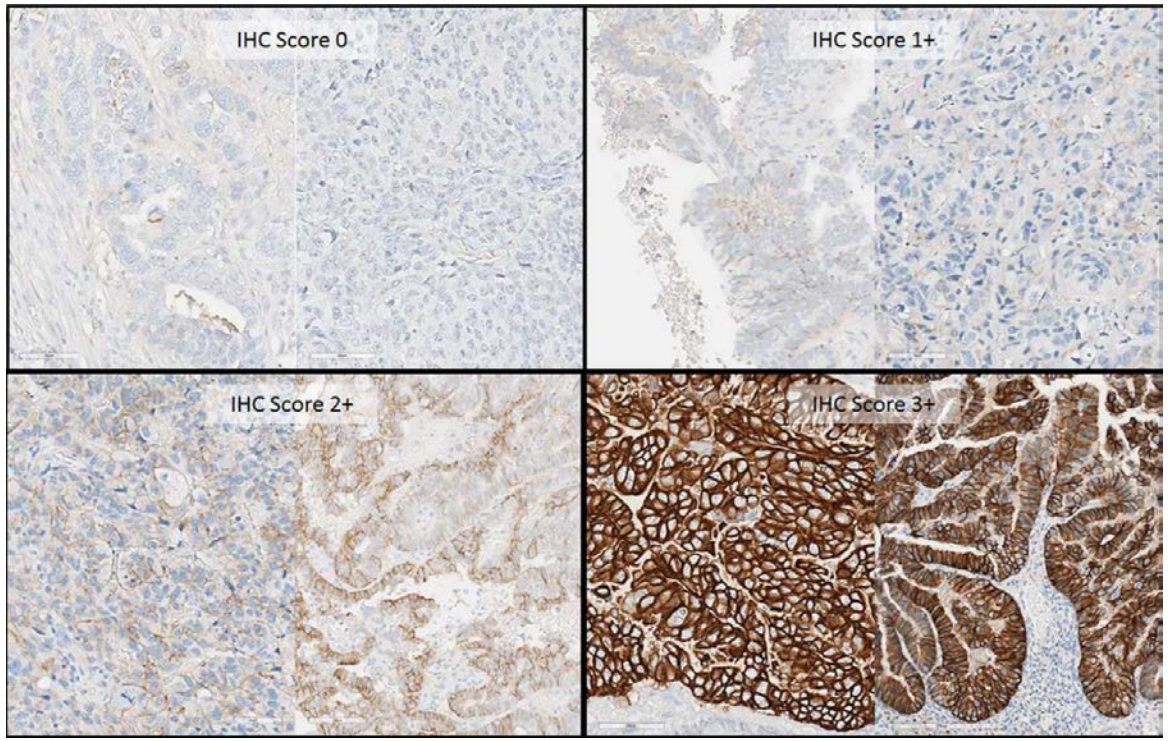


Bardia et al., *N Engl J Med* 2024

ADCs leverage HER2 as a delivery mechanism **independent** of biological HER2-dependency/addiction

HER2 expression evaluation by ASCO/CAP guidelines: two components

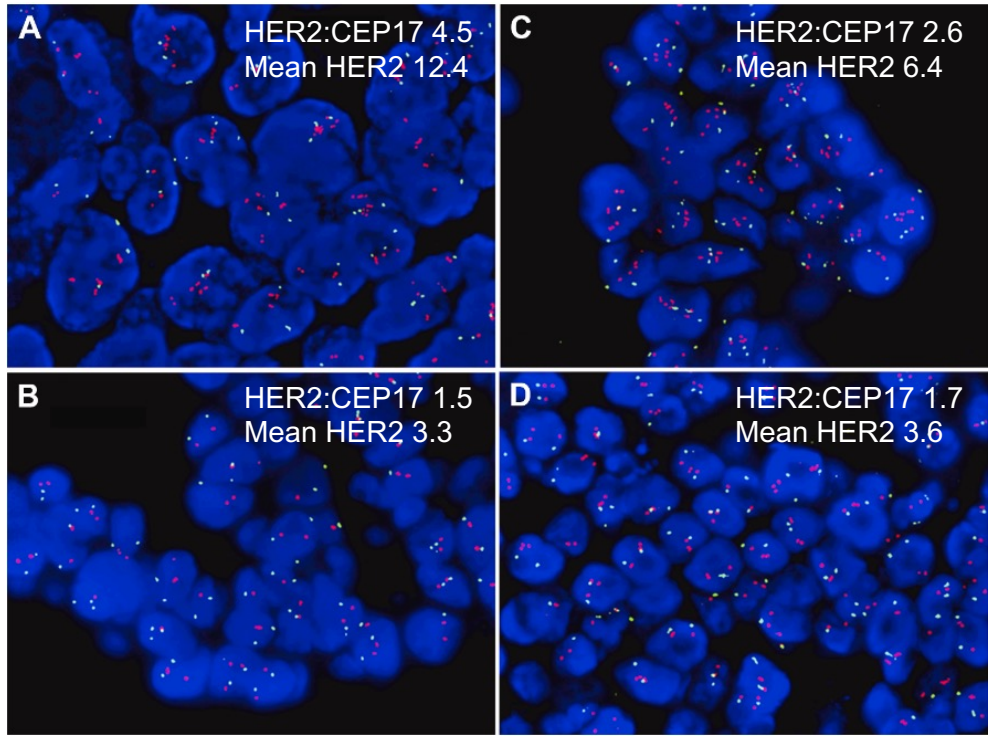
Immunohistochemistry (IHC)



Definitions for 0, 1+, 2+, and 3+ scoring differ based upon tumor type

Plotkin et al., *Cancers* 2024

In situ hybridization (ISH)



Green: CEP17
Red: HER2

Definitions for ISH amplification differ based upon tumor type

Menshikova et al., *Lab Invest* 2025

Current HER2 scoring guidelines

Criteria	Endometrial-specific	Breast ASCO/CAP (2018/2023)	Gastric ASCO/CAP
IHC 3+	Strong, complete circumferential or basolateral membranous staining in ≥30% of tumor cells	Intense, complete circumferential staining in ≥10% of tumor cells	Strong basolateral or complete membranous staining in ≥10% of tumor cells (resections) or in clusters of ≥5 cells (biopsies)
IHC 2+	Incomplete or weak-to-moderate membranous staining in ≥10% but ≤30% of tumor cells	Weak-to-moderate staining in ≥10% of tumor cells	Weak-to-moderate basolateral or complete staining in ≥10% of tumor cells (resections) or in clusters of ≥5 cells (biopsies)
IHC 1+	Faint/incomplete membranous staining in any proportion of tumor cells	Faint membranous staining in ≤10% of tumor cells	Faint or barely perceptible membranous reactivity in ≥10% of tumor cells (resections) or in clusters of ≥5 cells (biopsies)
IHC 0	No staining	No staining	No reactivity or membranous staining in <10 % of tumor cells (resections) or no reactivity in any tumor cell (biopsies)
ISH amplification	HER2/CEP17 signal ratio ≥2.0 or HER2 copy number ≥6 per nucleus	5-tier system; all HER2/CEP ratio ≥2.0 with average HER2 copy number ≥4.0 positive. Other categories require additional evaluation	HER2/CEP17 signal ratio ≥2.0

Adapted from Zannoni *Crit Rev in Oncol/Hem* 2026; Wolff et al. *Arch Pathol Lab Med* 2023; Bartley et al., *J Clin Oncol* 2016

Current HER2 scoring guidelines

NRG-GY026 **2018 ASCO CAP Breast Criteria**

DESTINY-PanTumor02 **IHC only**

Fader et al. **2007 ASCO CAP Breast Criteria**

Criteria	Endometrial-specific	Breast ASCO/CAP (2018/2023)	Gastric ASCO/CAP
IHC 3+	Strong, complete circumferential or basolateral membranous staining in **≥30%** of tumor cells	Intense, complete circumferential staining in **≥10%** of tumor cells	Strong basolateral or complete membranous staining in **≥10%** of tumor cells (resections) or in clusters of ≥5 cells (biopsies)
	Incomplete or weak-to-moderate membranous staining in **≥10% but ≤30%** of tumor cells	Weak-to-moderate staining in **≥10%** of tumor cells	Weak-to-moderate basolateral or complete staining in **≥10% of tumor** cells (resections) or in clusters of ≥5 cells (biopsies)
IHC 1+	Faint/incomplete membranous staining in **any proportion of tumor cells**	Faint membranous staining in **≤10%** of tumor cells	Faint or barely perceptible membranous reactivity in **≥10%** of tumor cells (resections) or in clusters of ≥5 cells (biopsies)
IHC 0	**No staining**	**No staining**	No reactivity or membranous staining in **<10%** of tumor cells (resections) or no reactivity in any tumor cell (biopsies)
ISH amplification	HER2/CEP17 signal ratio ≥2.0 or HER2 copy number ≥6 per nucleus	5-tier system; all HER2/CEP ratio ≥2.0 with average HER2 copy number ≥4.0 positive. Other categories require additional evaluation	HER2/CEP17 signal ratio ≥2.0

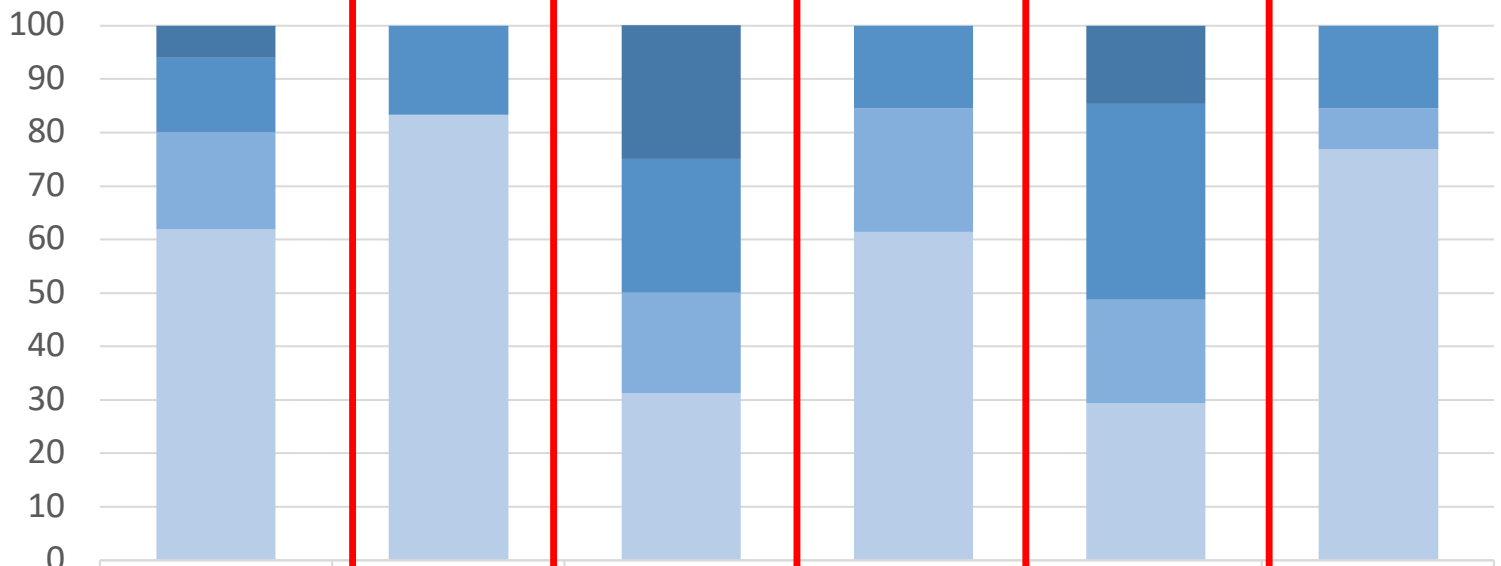
Adapted from Zannoni *Crit Rev in Oncol/Hem* 2026; Wolff et al. *Arch Pathol Lab Med* 2023; Bartley et al., *J Clin Oncol* 2016

HER2 “positive” is context-dependent

- Historically, referred to HER2-amplified tumors by IHC and ISH criteria
- Sometimes now used interchangeably to mean HER2 2+/3+ IHC expression (DESTINY PanTumor02 definition)
- HER2 status (positive vs negative) can vary depending upon the definition used
  - Tumor that is HER2-“positive” for trastuzumab deruxtecan per PanTumor02 criteria might have been HER2-“negative” when evaluated as candidate for 1L therapy with carboplatin/paclitaxel/trastuzumab

HER2 expression in gyn cancers: ovarian cancer

- Most historical series do not distinguish between HER2 IHC 0 and 1+ cancers
- HER2 amplification rare in high-grade serous ovarian cancer
  - Single-digit percentage range
- Highest levels of HER2 expression in mucinous and clear cell histologies

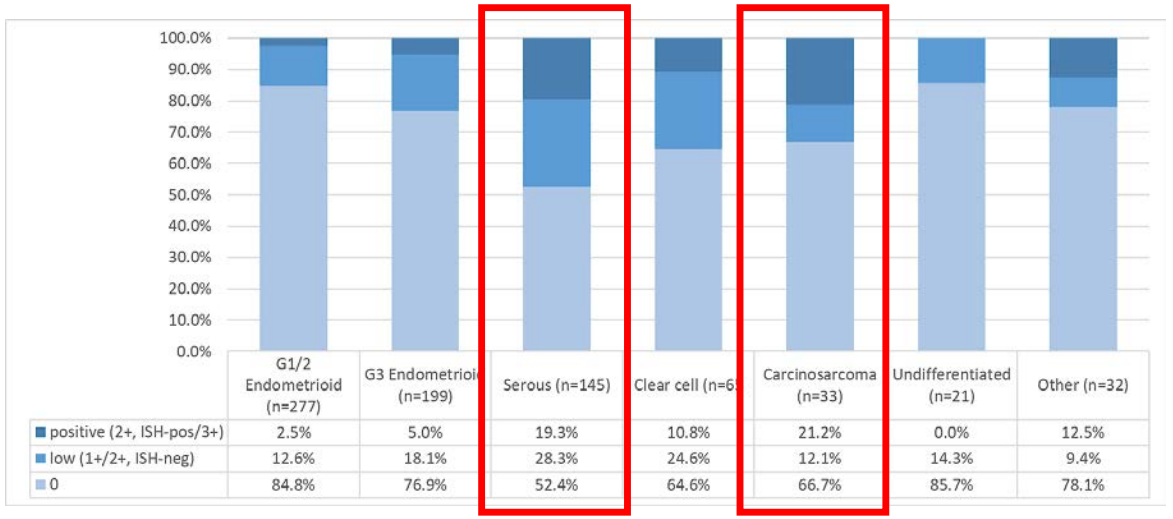


	HGSC (n=352)	LGSC (n=6)	Mucinous (n=16)	Endometrioid (n=13)	Clear cell (n=41)	Others (n=13)
3+	6	0	25	0	14.6	0
2+	13.9	16.7	25	15.4	36.6	15.4
1+	18.2	0	18.8	23.1	19.5	7.7
0	61.9	83.3	31.3	61.5	29.3	76.9

Adapted from Park et al., *Gynecol Oncol* 2025

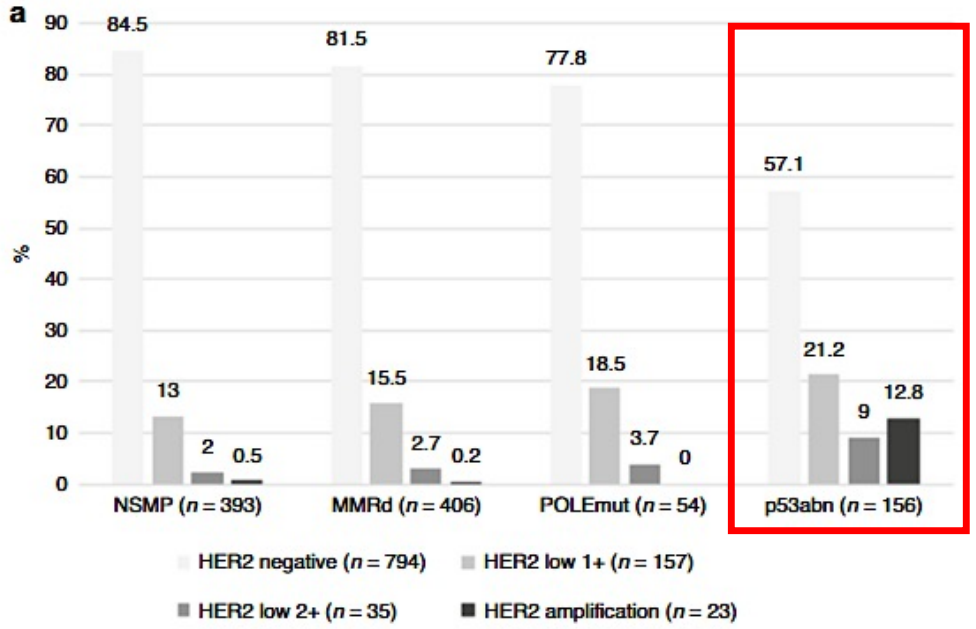
HER2 expression in gyn cancers: endometrial cancer

- HER2 amplification and expression rate highest in uterine serous carcinomas
- HER2-low expression seen across histologies and molecular subtypes
- HER2 amplification reported to be associated with poorer prognosis



	G1/2 Endometrioid (n=277)	G3 Endometrioid (n=199)	Serous (n=145)	Clear cell (n=6	Carcinosarcoma (n=33)	Undifferentiated (n=21)	Other (n=32)
positive (2+, ISH-pos/3+)	2.5%	5.0%	19.3%	10.8%	21.2%	0.0%	12.5%
low (1+/2+, ISH-neg)	12.6%	18.1%	28.3%	24.6%	12.1%	14.3%	9.4%
0	84.8%	76.9%	52.4%	64.6%	66.7%	85.7%	78.1%

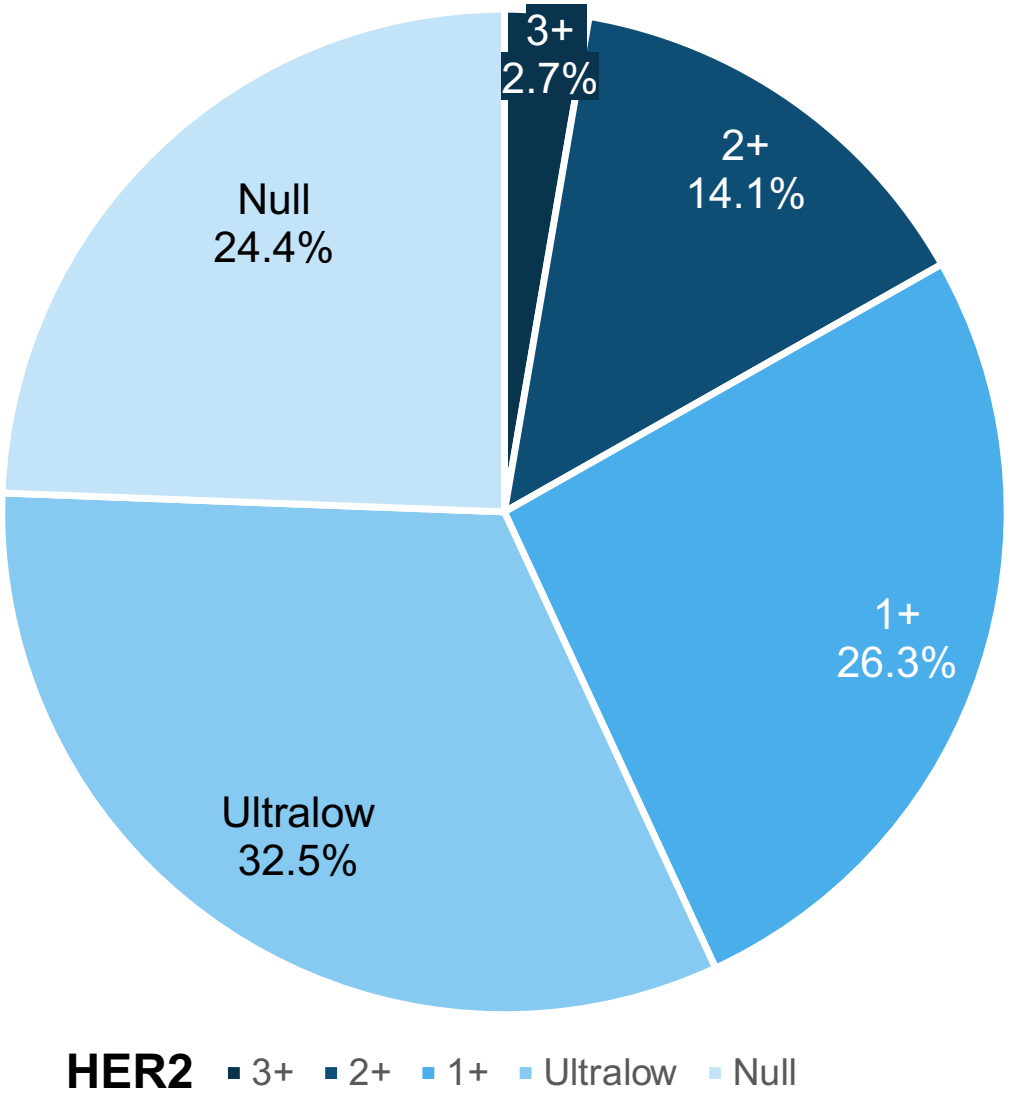
Adapted from van Dijk et al., *J Clin Oncol* 2024



Aro et al., *BJC Reports* 2025

HER2 expression in gyn cancers: cervical cancer

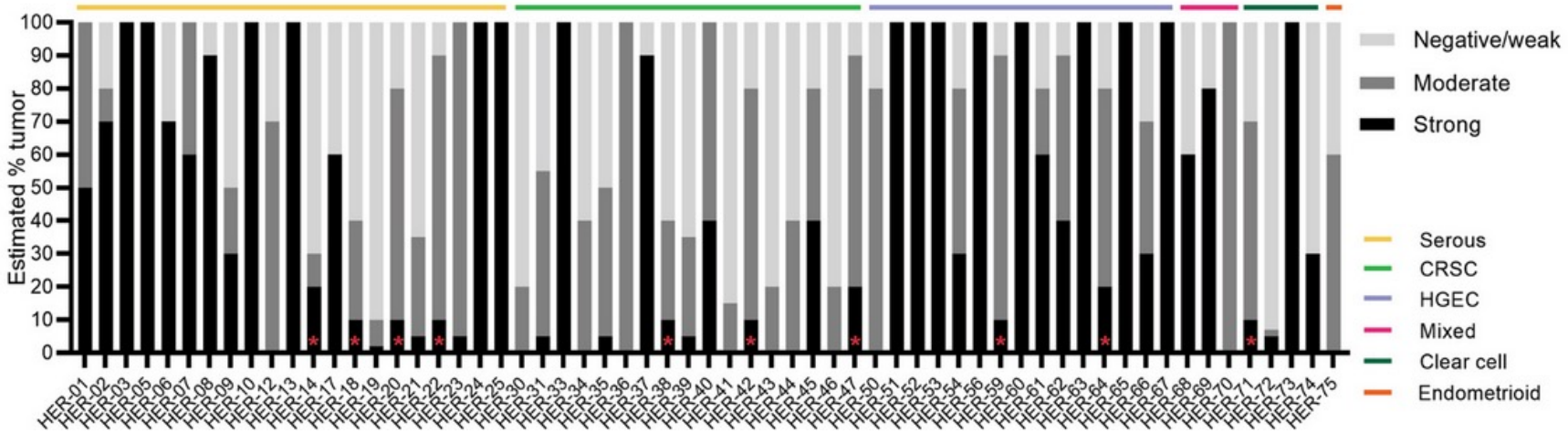
- Limited data currently available on prevalence of HER2 expression by IHC
- HER2 overexpression in ~4-12%, with higher rates in certain histological subtypes
  - HER2 amplification most common in gastric-type cervical cancer



Dana-Farber Cancer Institute

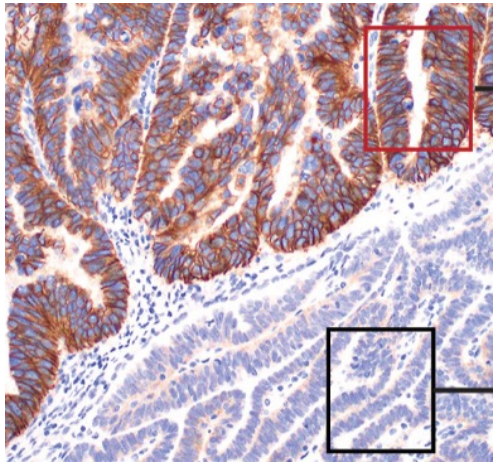
Liu W et al. NPJ *Precis Oncol* 2025

Challenges in HER2 testing in gyn cancers: Intratumoral heterogeneity



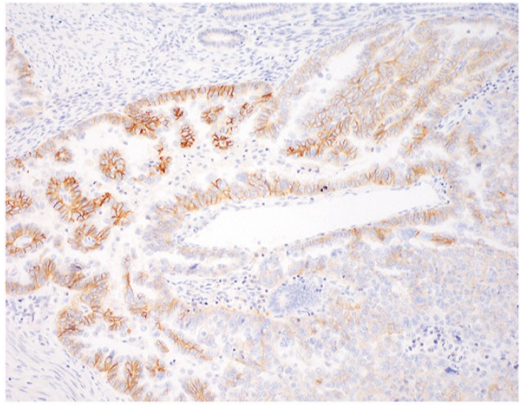
Ross et al., *Modern Pathology* 2022

"Cluster" pattern



Shen et al., *Modern Pathology* 2023

"Mosaic" pattern



FISH: HER2/CEP17 ratio: 2.1

Shen et al., *Modern Pathology* 2023

Challenges in HER2 testing in gyn cancers: Intra-test variability

Significant variability between central and local HER2 testing in DESTINY-Breast06 samples

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

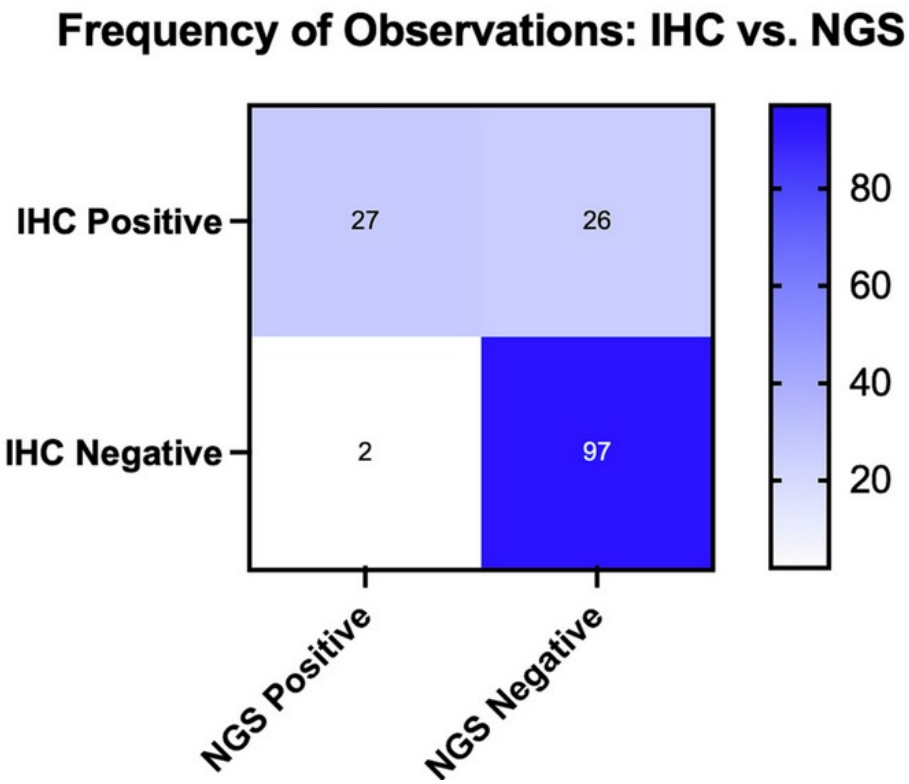
HER2 status by central testing, n		HER2 status by local result, n				
		IHC 0†	HER2-low	IHC 2+/ISH+	IHC 3+	Total
IHC 0†	Absent membrane staining‡	123	65	0	1	189
	With membrane staining (HER2-ultralow)§	140	196	2	1	339
HER2-low		85	999	6	0	1090
IHC 2+/ISH+		1	7	0	0	8
IHC 3+		0	3	0	0	3
Total		349	1270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

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

Viale et al., 2024 ESMO Congress

Alternative testing approaches: Next generation sequencing

- NGS can identify copy number amplifications or mutations in *ERBB2*
- Almost all *ERBB2*-amplified tumors demonstrate high HER2 expression by IHC
- HER2 high-expressing cancers may not have detectable amplification by NGS
- NGS cannot detect low/moderate IHC 1+/2+ HER2 expression levels



Ettorre et al., *Gyn Oncol* 2025

Considerations for clinical HER2 testing in Gyn cancers: current state

- Consider HER2 testing for all recurrent gynecologic cancers, given T-DXd FDA approval in HER2 IHC 3+ solid tumors and NCCN listing in HER2 IHC 2+/3+ gyn cancers
  - For potential T-DXd use, DESTINY-PanTumor02 utilized gastric HER2 IHC criteria
- Test for HER2 in newly diagnosed advanced/recurrent p53-mutated endometrial cancer
  - Addition of trastuzumab to chemotherapy in HER2-positive cancers by modified ASCO CAP 2007 breast guidelines
  - Eligibility for NRG-GY026 in HER2-positive tumors by ASCO CAP 2018 breast guidelines
- Consider HER2 re-testing for recurrent disease if feasible, recognizing intratumoral heterogeneity and intra-test variability.

Second Opinion

Professor Jonathan A Ledermann

Angeles Alvarez Secord, MD, MHSc

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

In which situations do you conduct HER2 testing for patients with gynecologic cancers? Do you test all patients regardless of tumor type, histology or stage? Or only patients with metastatic disease, certain histologies, etc? What criteria do you use to decide whether to test?

To what extent do you believe HER2 testing is being done in the "real-world" community-based setting?

What type of HER2 testing do you employ? Do you recommend HER2 testing using IHC staining in all cases? Do your pathologists employ the IHC scoring criteria for breast cancer or gastric cancer?

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

For a patient like Prof Ledermann's with an IHC score of 1+ (or 2+), would you order ISH or NGS testing and treat as if HER2-positive if amplification were seen? What is the correlation between IHC, ISH and NGS when determining HER2 status?

How, if at all, does the benefit of T-DXd vary based on level of HER2 expression in gynecologic cancers? Would you anticipate an antitumor effect in HER2-ultralow disease (ie, with incomplete, faint membrane staining in <10% of tumor cells), as is seen in breast cancer?

QUESTIONS FOR THE FACULTY

Where does liquid biopsy fit into HER2 assessment? Can HER2 status be accurately assessed using liquid biopsy?

How important is having recent versus archival tissue for the purposes of HER2 testing? Does HER2 testing need to be repeated after disease progression?

How often do you see HER2 mutations in gynecologic cancers? For a patient with a HER2 mutation, are there any specific TKIs or other targeted therapies you would recommend? Is there any experience with sevabertinib or zongertinib — TKIs targeting HER2 TKD mutations, including exon 20 insertion mutations, in non-small cell lung cancer — in patients with gynecologic cancers?

Agenda

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

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

Module 3: Identification and Management of Adverse Events with T-DXd — Dr O'Malley

Practical Application of HER2-Targeted Therapy in Advanced Gynecologic Cancers

Brian M. Slomovitz, MD, FACOG

Director, Gynecologic Oncology, Mount Sinai Medical Center

Professor, Obstetrics and Gynecology, Florida International University

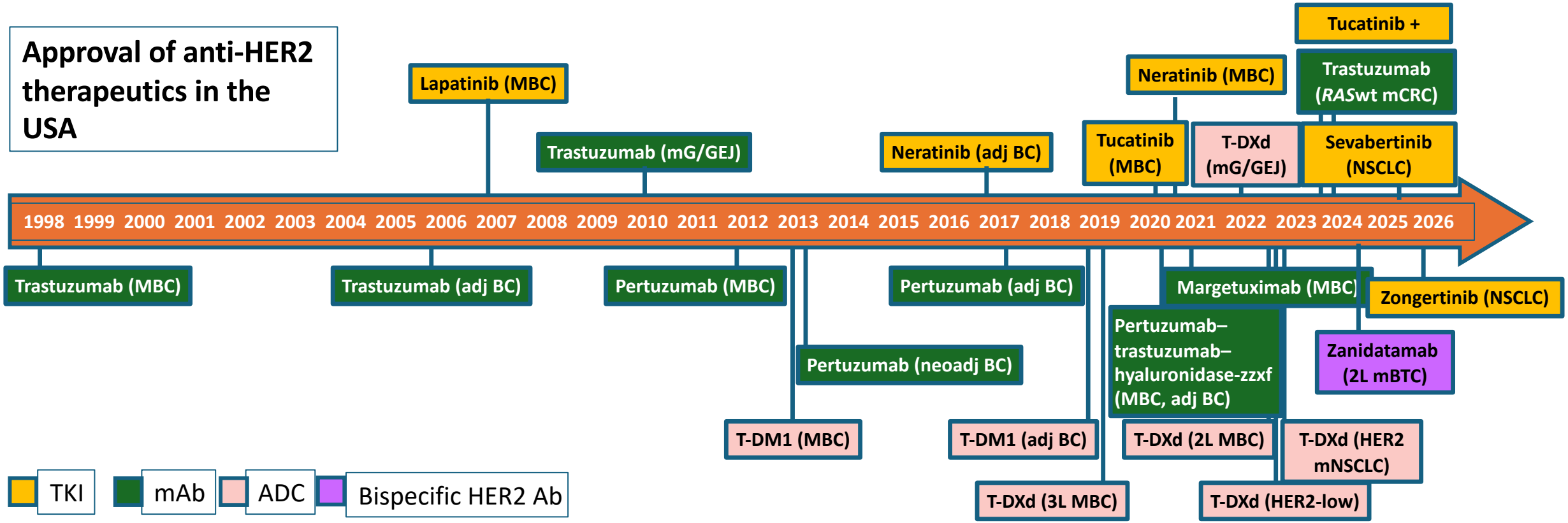
Member, Board of Directors, GOG Foundation

Uterine Cancer Clinical Trial Lead, GOG Partners

Miami Beach, FL

History of Approvals for HER2-Targeted Therapies for Cancer

- HER2 protein expression, gene amplification, and gene mutation are therapeutic targets in several types of tumors
- HER2-directed therapy is the standard of care for HER2-expressing unresectable or metastatic breast cancer, HER2-positive locally advanced or metastatic gastric cancers, CRC and GEJ adenocarcinomas, and *HER2*-mutant NSCLC

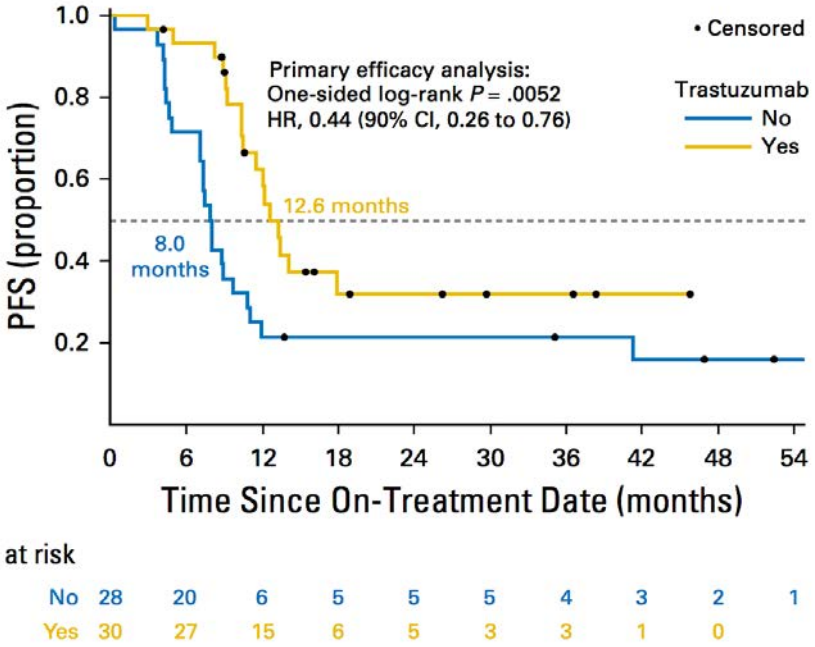


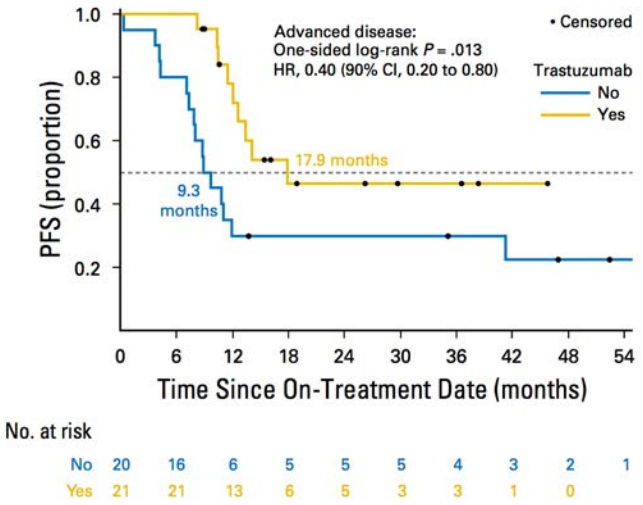
2L = second line; 3L = third line; ADC = antibody-drug conjugate; adj = adjuvant; BC = breast cancer; BTC = biliary tract cancer; MBC = metastatic breast cancer; mG/GEJ = metastatic gastric/gastroesophageal junction cancer; mAb = monoclonal antibody; mCRC = metastatic colorectal cancer; neoadj = neoadjuvant; mNSCLC = metastatic non-small cell lung cancer; *RAS*wt = *RAS* wild type; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.

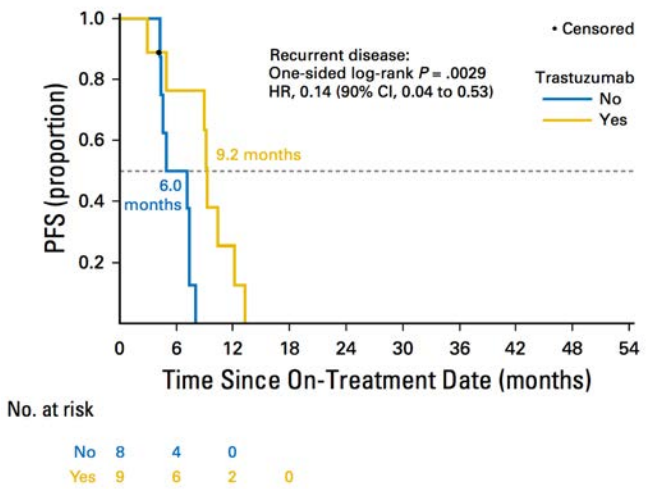
Incorporation of anti-HER2 treatment: Trastuzumab with Chemotherapy in Uterine Serous Carcinomas

Key eligibility criteria

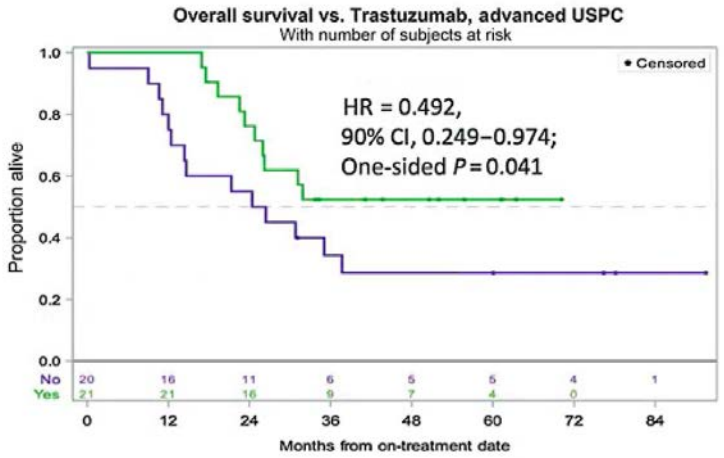
- Primary stage III or IV or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- “platinum sensitive” recurrence (6 mo)

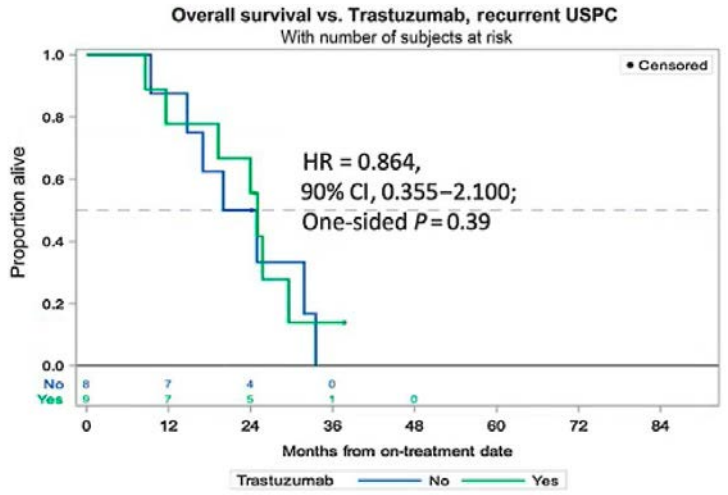






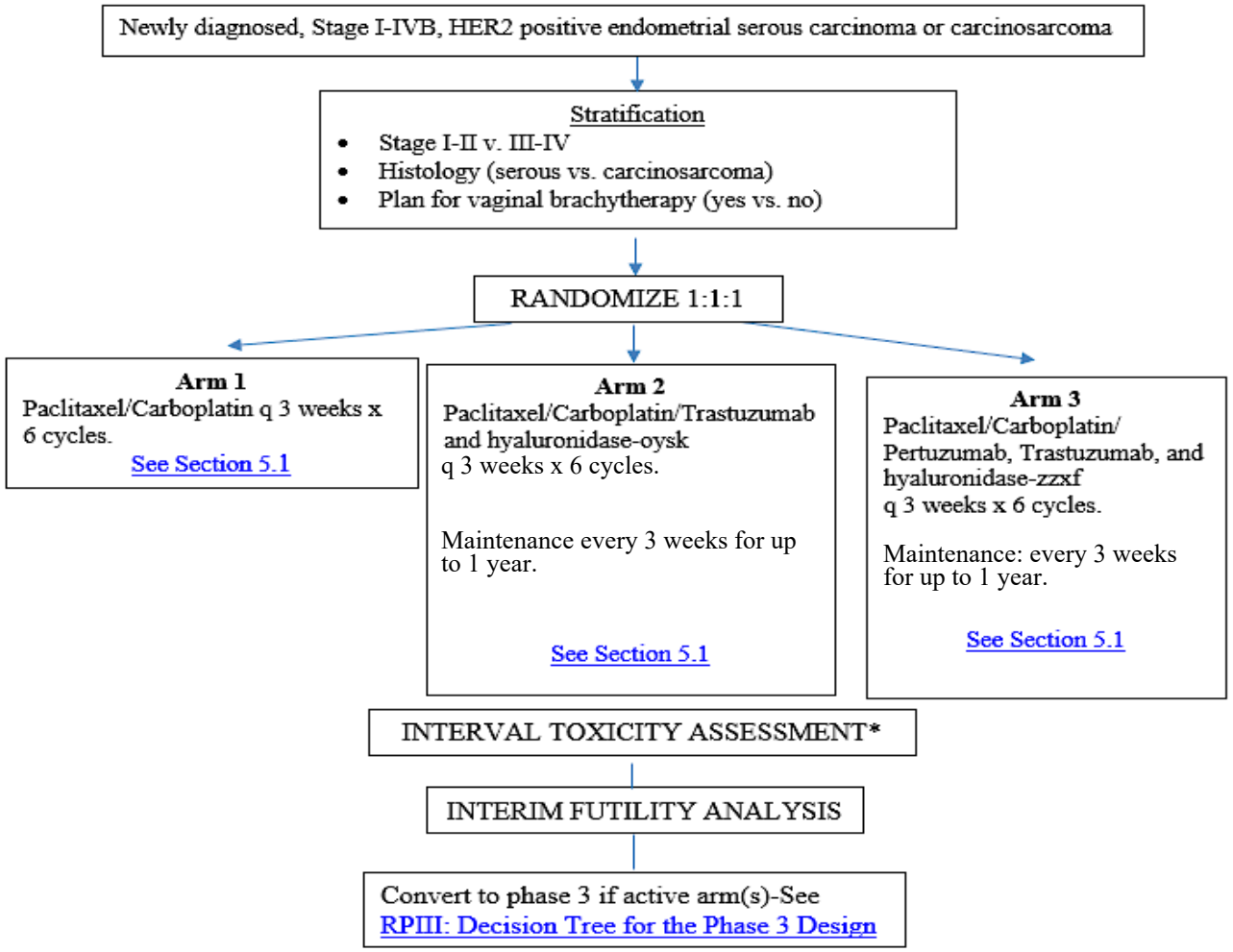
<u>OS benefit particularly striking in stage III–IV patients, OS median of 25.4 months (control) versus NR (p = 0.041, HR = 0.49, 90% CI 0.25–0.97).</u>





Fader J Clin Oncol 2018; Fader Clin Cancer Res 2020.

NRG-GY026



*An Interval Toxicity Assessment (ITA) is included to evaluate the safety and tolerability of Arm 3. The first 12 eligible patients who receive any protocol therapy will be monitored for the specified cardiac events for at least 12 weeks from the start of treatment. See Section 14.4.2.

Activation Date: 8/12/22
Accrual goal 326
N= 259

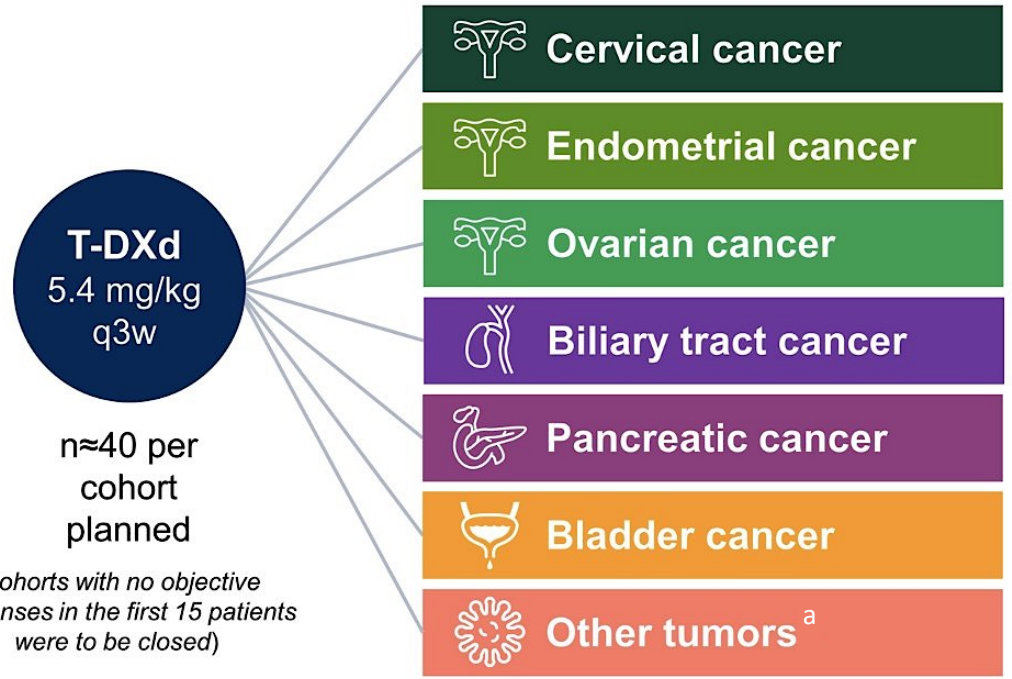
Issues:
Fear of PC alone
New TDxD

Study Chair: Britt Erickson, MD

Phase 2 DESTINY-PanTumor02 Study of T-DXd for HER2-Expressing Solid Tumors: Design

Tumor types were selected based on epidemiological frequency, prevalence of HER2 expression, and unmet medical need

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR
- DCR
- PFS
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

[a]Other tumors cohort: salivary gland cancer (n = 19), malignant neoplasm of unknown primary site (n = 5), extramammary Paget disease (n = 3), cutaneous melanoma (n = 2), oropharyngeal neoplasm (n = 2), adenoid cystic carcinoma, head and neck cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, intestinal adenocarcinoma, appendiceal adenocarcinoma, esophageal squamous cell carcinoma, testicular cancer, and vulvar carcinoma (all n = 1).

2L+ = second-line or beyond; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; PS = performance status; WHO = World Health Organization.

Meric-Bernstam F, et al. *J Clin Oncol*. October 23, 2023. DOI: 10.1200/JCO.23.02005. NCTID: NCT04482309.

DESTINY-PanTumor02 – Design and Analysis

- **Patient Group**
  - Advanced solid tumors not eligible for curative therapy
  - 2L+ patient population[a]
  - HER2 expression (by ASCO/CAP gastric cancer guidelines)
    - **Part 1**: IHC 3+ or IHC 2+ Local test or central test[b]
    - **Part 2**: IHC and ISH (cohort B only) results by central assessment as pre-defined for each cohort
  - Prior HER2-targeting therapy allowed
  - ECOG/WHO PS 0–1
- **Primary analysis** (DCO June 08, 2023) has been published (Meric-Bernstein F, et al. J Clin Oncol. 2024; 42: 47-48)
- **Final analysis**– DCO October 10, 2024

Phase 2, open label multi-center study (NCT04482309)

HER2-expressing solid tumors[c]

T-DXd 5.4 mg/kg Q3w

n = 267[d] (75 IHC3+)

Note: HER2 subgroup analyses by central testing

Part 1	Part 2[g]
Cohort 1 (n = 41) Biliary tract cancer	**Cohort A** HER2 IHC 3+ Metastatic Solid Tumors[h]
Cohort 2 (n = 41) Bladder cancer	**Cohort B** HER2 IHC 2+/ISH+ Metastatic Solid Tumors[h]
Cohort 3 (n = 40) Cervical cancer[e]	**Cohort C** HER2 IHC 2+ or 1+ Endometrial cancer
Cohort 4 (n = 40) Endometrial cancer	**Cohort D** HER2 IHC 2+ or 1+ Ovarian cancer
Cohort 5 (n = 40) Ovarian cancer	**Cohort E** HER2 IHC 2+ or 1+ Cervical cancer
Cohort 6 (n = 25) Pancreatic cancer	
Cohort 7 (n = 40) Other tumors[f]	

Primary endpoint
- Confirmed ORR (investigator)*

Secondary endpoints
- DoR[i]
- DCR[i]
- PFS[i]
- OS
- Safety

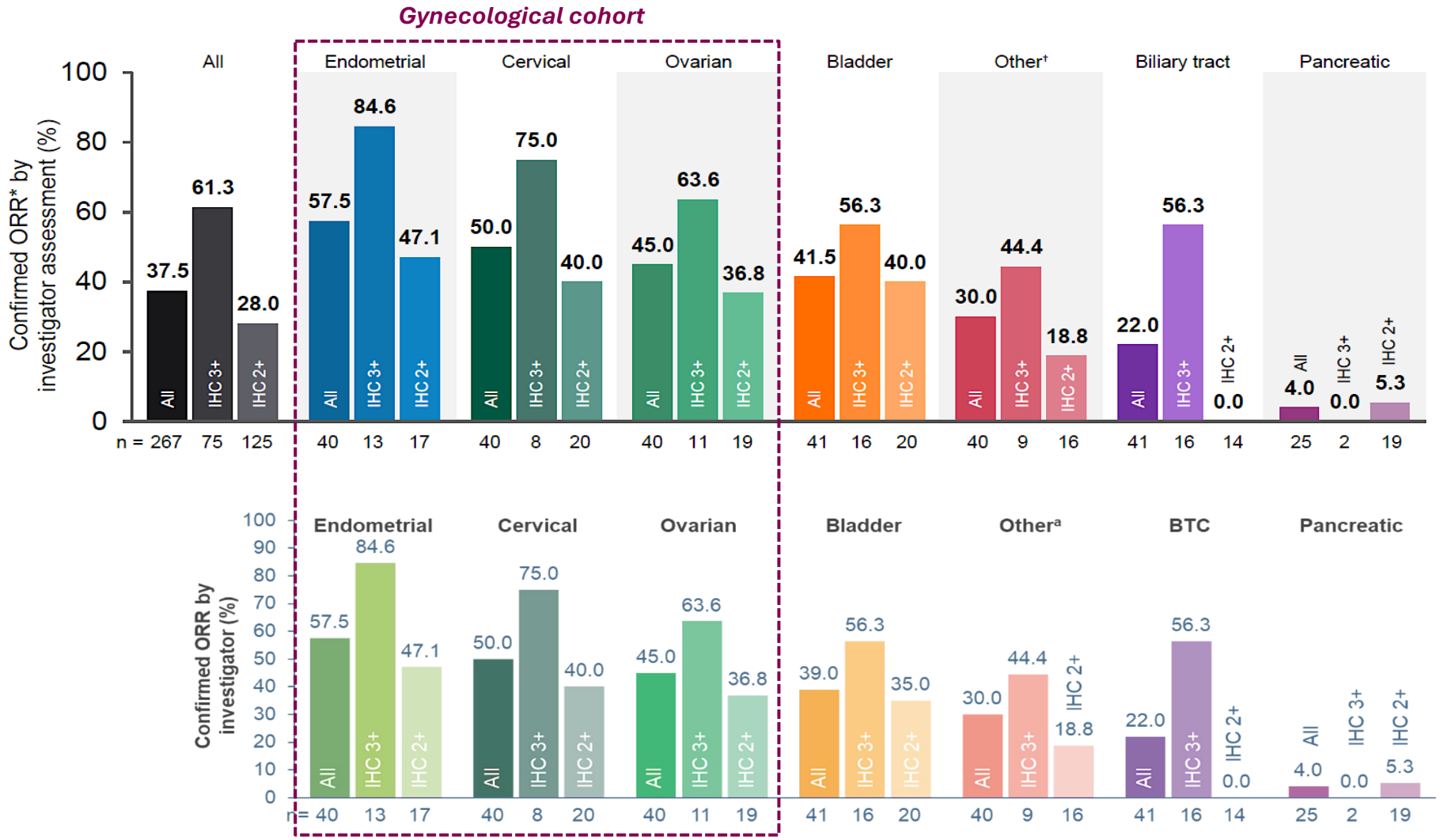
Exploratory endpoint
- Subgroup analyses by HER2 status[j]
- Subgroup analyses by biomarkers[j]

**Confirmed ORR per RECIST 1.1 is the percentage of patients with CR or PR that is subsequently confirmed*

[a]Patients with no satisfactory treatment options were also included; [b]Patients were eligible for either test. All patients were centrally confirmed; [c]Excluding breast, gastric, colorectal cancer; [d]Cohorts with no objective response in the first 15 patients were closed; [e]Cervical cohort was expanded to include five IHC1+ patients; [f]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer; [g]Enrollment started in 2024; [h]Excluding breast, gastric cancer, and colorectal cancer. Patients with non-small cell lung cancer can be included; [i]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1; j Subgroup analyses were based on central HER2 testing.

ASCO/CAP, American Society of Clinical Oncology and the College of American Pathologists; DCO, data cut off; DCR, duration of complete response; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance score; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

DESTINY-PanTumor02 – Final Analysis (confirmed ORR)



*Confirmed ORR per RECIST 1.1

FINAL ANALYSIS

Median (range) follow up (all cohorts) – 12.98 (0.4–47.4) months

PRIMARY ANALYSIS

Median (range) follow up (all cohorts) – 12.75 (0.4–31.6) months

Meric-Bernstam F, et al. *J Clin Oncol*. October 23, 2023; Makker V, et al. ESMO 2025;Abstract 957P.

DESTINY-PanTumor02 – Final Analysis (PFS & OS)

Progression-free survival

Gynecological cohorts	Median PFS, months (95% CI)	All patients	HER2 status by central testing: IHC 3+	HER2 status by central testing: IHC 2+
	Endometrial	**11.1 (7.1, 25.8)** *11.1 (7.1, NE)*	**28.1 (7.3, NE)** *NE (7.3, NE)*	**8.5 (4.6, 15.1)** *8.5 (4.6, 15.1)*
	Cervical	**7.0 (4.2, 11.1)** *7.0 (4.2, 11.1)*	**NE (3.9, NE)** *NE (3.9, NE)*	**4.8 (2.7, 5.7)** *4.8 (2.7, 5.7)*
	Ovarian	**5.9 (4.0, 8.3)** *5.9 (4.0, 8.3)*	**12.5 (3.1, NE)** *12.5 (3.1, NE)*	**4.1 (2.3, 12.6)** *4.1 (2.3, 12.6)*

Final analysis

Primary analysis

Overall survival

Median OS, months (95% CI)	All patients	HER2 status by central testing: IHC 3+	HER2 status by central testing: IHC 2+
Endometrial	**24.2 (12.8, 33.7)** *26.0 (12.8, NE)*	**33.7 (18.9, NE)** *26.0 (18.9, NE)*	**16.4 (8.0, 34.7)** *16.4 (8.0, NE)*
Cervical	**13.6 (11.1, 19.7)** *13.6 (11.1, NE)*	**35.8 (3.9, NE)** *NE (3.9, NE)*	**11.6 (5.1, 18.0)** *11.5 (5,1, NE)*
Ovarian	**13.2 (8.0, 17.7)** *13.2 (8.0, 17.7)*	**20.0 (3.8, NE)** *20.0 (3.8, NE)*	**13.0 (4.7, 21.9)** *13.0 (4.7, 21.9)*

- PFS and OS data were consistent across **primary** and **final** analyses
- PFS and OS data were consistent regardless of how HER2 testing was performed (**whether central testing was applied or not**)

Meric-Bernstam F, et al. *J Clin Oncol*. October 23, 2023; Makker V, et al. ESMO 2025;Abstract 957P.

DESTINY-PanTumor02 – Design and Analysis

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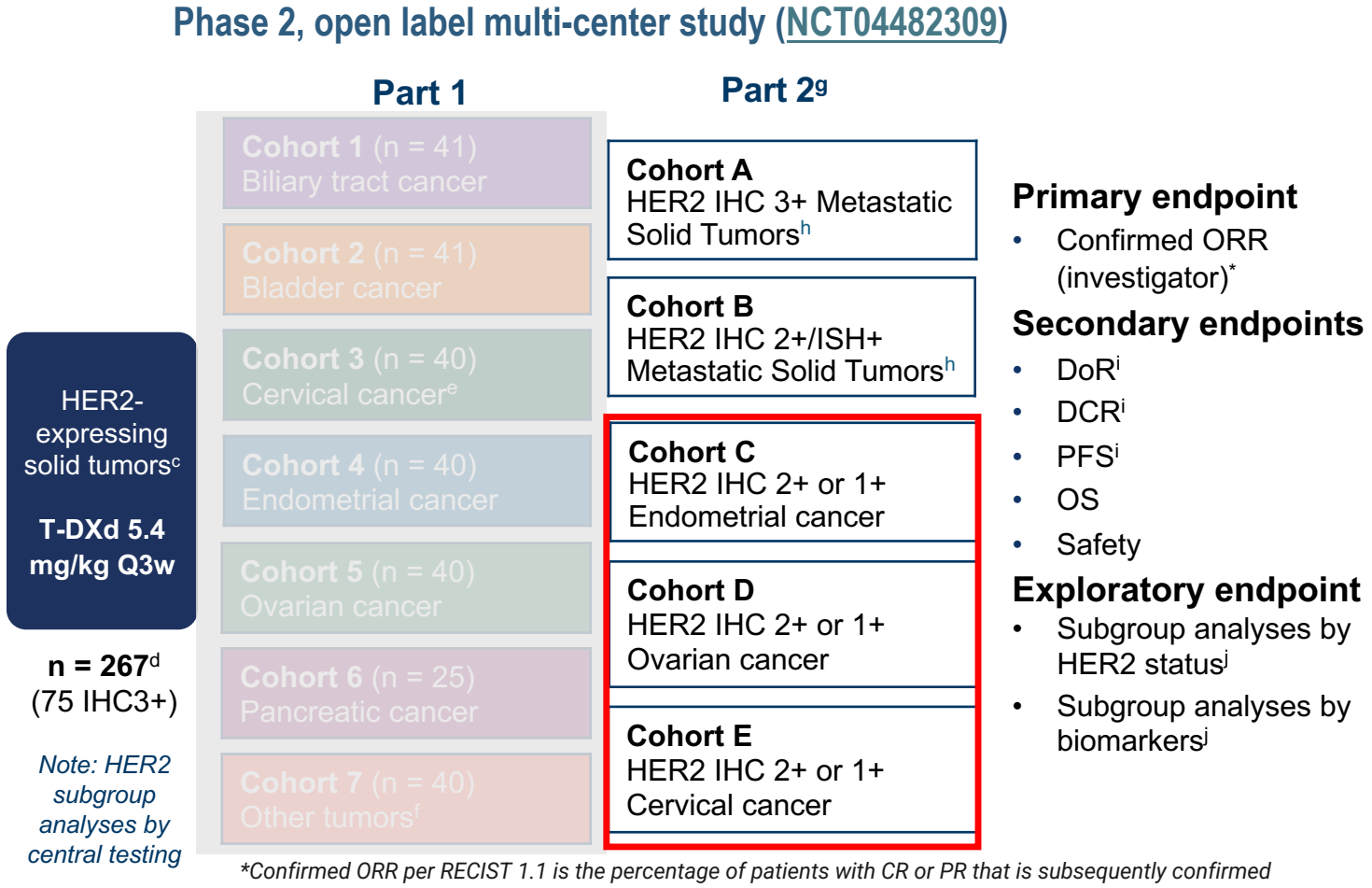


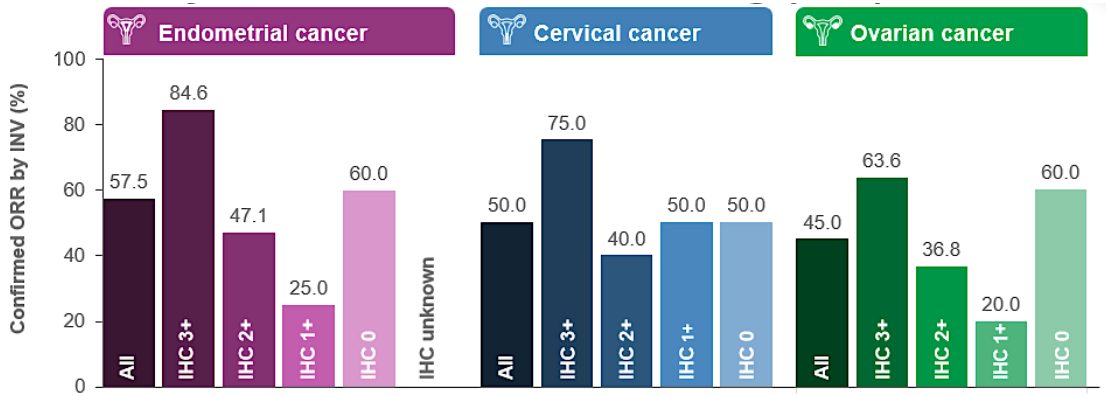
[a]Patients with no satisfactory treatment options were also included; [b]Patients were eligible for either test. All patients were centrally confirmed; [c]Excluding breast, gastric, colorectal cancer; [d]Cohorts with no objective response in the first 15 patients were closed; [e]Cervical cohort was expanded to include five IHC1+ patients; [f]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer; [g]Enrollment started in 2024; [h]Excluding breast, gastric cancer, and colorectal cancer. Patients with non-small cell lung cancer can be included; [i]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1; j Subgroup analyses were based on central HER2 testing.

ASCO/CAP, American Society of Clinical Oncology and the College of American Pathologists; DCO, data cut off; DCR, duration of complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PS, performance score; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

Destiny-PanTumor02 – IHC 2+ and IHC 1+ cohorts

DESTINY-PanTumor02[1]

(primary analysis of gynecological cancer cohorts)

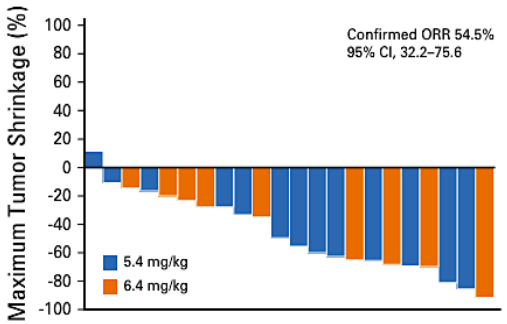


	Endometrial cancer						Cervical cancer					Ovarian cancer				
	All	IHC 3+	IHC 2+	IHC 1+	IHC 0	IHC unknown	All	IHC 3+	IHC 2+	IHC 1+	IHC 0	All	IHC 3+	IHC 2+	IHC 1+	IHC 0
Total n in subgroup	40	13	17	4	5	1	40	8	20	8	4	40	11	19	5	5
n of responders	23	11	8	1	3	0	20	6	8	4	2	18	7	7	1	3
Median DOR, months[b]	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% CI[c]	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	4.1, 22.1	4.2, NE	2.8, NE	-	2.6, NE

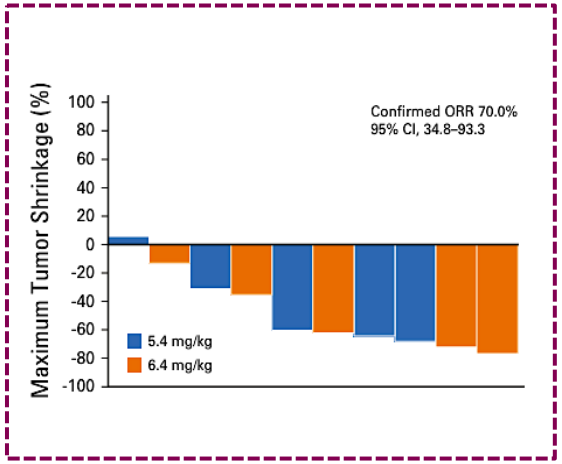
STATICE[2]

(Phase 2 T-DXd vs historical chemo in advanced/recurrent uterine carcinosarcoma)

HER2 high (IHC 2+/3+) n = 22



HER2 low (IHC1+) n = 10



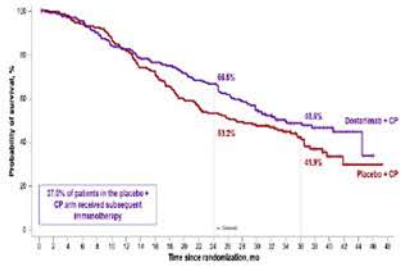
1. Meric-Bernstam, F, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol; 2024; 47-58; 2. Nishikawa T, et al. Trastuzumab Deruxtecan for Human Epidermal Growth Factor Receptor 2–Expressing Advanced or Recurrent Uterine Carcinosarcoma (NCCH1615): The STATICE Trial. J Clin Oncol 2023 41(15):2789-2799.

CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; INV, investigator; NR, not reached; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

Adding to the Marginal Benefit of Immunotherapy in Advanced and Recurrent EC

MMRp EC patients
Clinically meaningful PFS and OS benefit from ICI + Chemotherapy

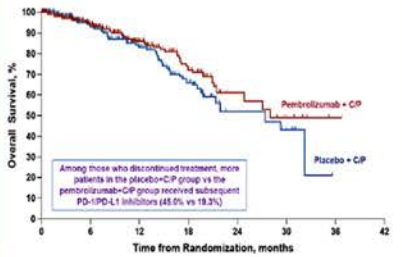
EN6-RUBY[1,2,5,6]
Part 1



OS Data	Events, %	Median (95% CI), mo
Dostarlimab + C/P	50.5	34.0 (28.6-NE)
Placebo + C/P	59.2	27.0 (21.5-35.6)
OS data maturity	54.8%	
Median follow-up, mo	37.5	

PFS	HR 0.76 (95% CI, 0.59-0.98);
OS	**HR 0.79** (95% CI, 0.60-1.04); *Nominal p*=0.0493

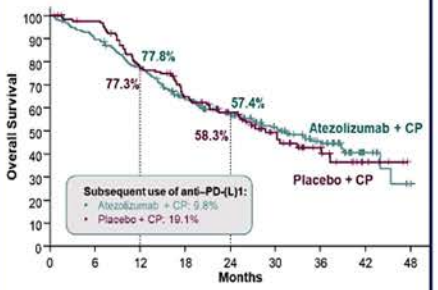
NRG018



OS Data	Events, %	Median (95% CI), mo
Pembrolizumab + C/P	15.3	27.9 (21.4-NR)
Placebo + C/P	18.3	27.4 (19.5-NR)
OS data maturity	27.2%	
Median follow-up, mo	8.4-8.8	

PFS	HR 0.54 (95% CI, 0.41-0.71); *P*<0.001
OS	**HR 0.79** (95% CI, 0.53-1.17) *Nominal p=0.1157*

EN7-AtTEnd



OS Data	Events, %	Median (95% CI), mo
Atezolizumab + C/P	47.2	31.5 (25.0-38.9)
Placebo + C/P	46.4	28.6 (22.4-37.2)
OS data maturity	–	
Median follow-up, mo	–	

PFS	HR 0.92 (95% CI, 0.73-1.16);
OS	**HR 1.00** (95% CI, 0.74-1.35)

DUO-E

OS Data	Events, %	Median (95% CI), mo
Durvalumab + C/P	30.2	NR (NR-NR)
Placebo + C/P	33.3	25.9 (25.1-NR)
OS data maturity	29.2%	
Median follow-up, mo	–	

PFS	HR 0.77 (95% CI, 0.60-0.97); *Durva + C/P arm*
OS	**HR 0.91** (95% CI, 0.64-1.30) *Durva + C/P arm*

The data presented are not intended to make comparisons and are used merely for didactic purposes. Direct or indirect comparisons between drugs should be based on head-to-head/comparative trials with level I or II of evidence. In the absence of comparative studies, efficacy and safety cannot be compared and are not intended.

MSS = microsatellite stable; pMMR = mismatch repair proficient; OS = overall survival.

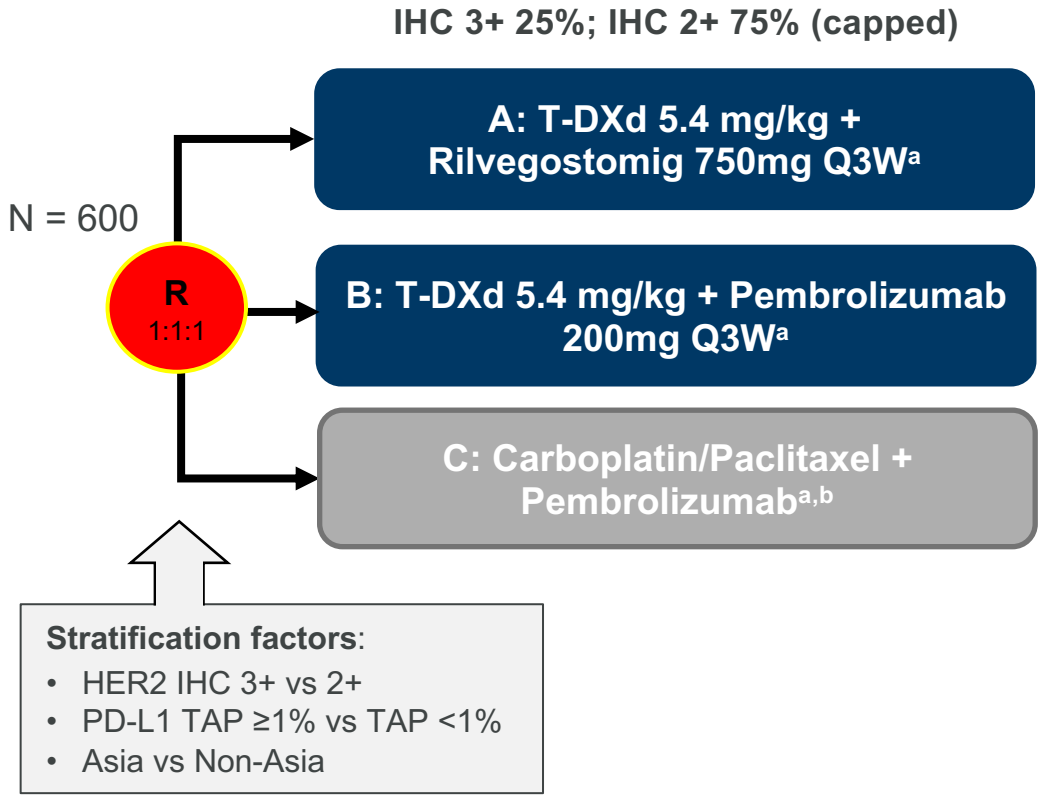
1. Mirza MR, et al. N Engl J Med. 2023;388:2145-2158. 2. Mirza MR, et al. Ann Oncol. 2023;34:500-501; 3. Eskander RN, et al. N Engl J Med. 2023;388:2159-2170. 4. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 5. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA.; 6. Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.; 7. Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132.; 6. Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1; 7. Eskander RN, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2; 8. Baurain JF, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Scientific Plenary V

DESTINY-Endometrial01 – Study Design

Patient Population

- Stage III (with m.d.), Stage IV, or first recurrent, histologically-confirmed epithelial endometrial cancer
- HER2 expressing (IHC 3+/2+) EC by central test
- pMMR EC by central test
- Stage III must have measurable disease
- Any histological subtype except for sarcomas
- ≤ 1 prior line of adjuvant/ neoadjuvant chemotherapy (chemotherapy and/ or chemoradiation) if recurrence ≥ 6 months after last dose of chemo
- No prior exposure to ADCs or ICIs
- ECOG PS 0 or 1

Inclusion/exclusion criteria



Endpoints

Primary:
- PFS (BICR) in ITT

Secondary:
- OS
- PFS (INV)
- PFS2
- ORR by BICR and INV
- DoR
- HRQoL (PRO)
- Safety and tolerability
- Pharmacokinetics and immunogenicity

Futility analysis at 40% IF

NCT06989112

[a] Treatment will continue until objective disease progression according to RECIST v1.1 as assessed by the Investigator and confirmed by BICR or until other discontinuation criteria is met, whichever occurs first.
[b] Carboplatin AUC5, paclitaxel 175 mg/m^2, and pembrolizumab 200 mg IV once Q3W x 6 cycles*, followed by maintenance with pembrolizumab 400 mg IV Q6W. Treatment with pembrolizumab will continue for up to 20 total cycles (approximately 24 months, accounting for combination and maintenance phases) or until other discontinuation criteria is met, whichever occurs first.
*At the discretion of the treating Investigator, participants may continue to receive carboplatin, paclitaxel and pembrolizumab Q3W for up to 10 cycles.
ADC, antibody-drug conjugate; DoR, duration of response; ICI, immune checkpoint inhibitor; IF, information fraction (of planned); IHC, immunohistochemistry; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRQoL, health-related quality of life; ITT, intention-to-treat; m.d., measurable disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, time from randomization to progression on second line therapy; pMMR, proficient mismatch repair; PRO, patient reported outcome; Q3W, every three weeks; Q6W, every six weeks; TAP, tumor area positivity; T-DXd, Trastuzumab deruxtecan; OS, overall survival.

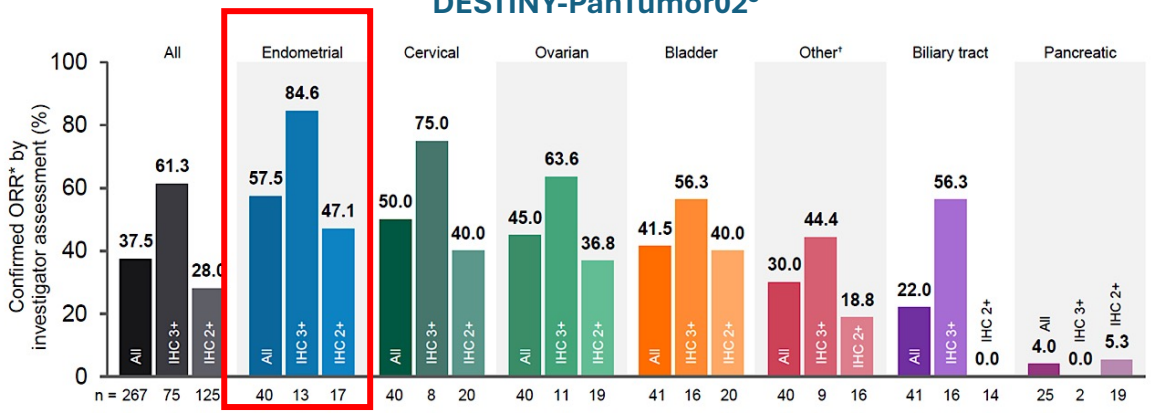
Slomovitz B, et al. ESMO 2025;Abstract 1223TiP.

Rationale for adjuvant trial using T-Dxd

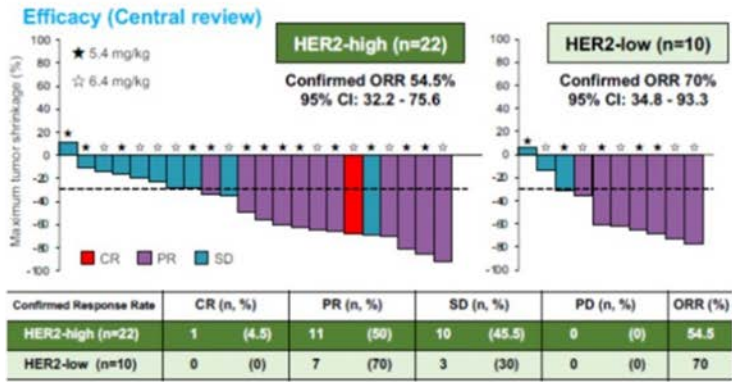
High-risk early endometrial cancer has a high rate of relapse.[1-3]

- The addition of pembrolizumab to adjuvant chemotherapy in KEYNOTE-B21 did not improve patient outcomes (for the majority pMMR disease)[4]
- The efficacy of T-DXd in the advanced setting,[5,6] *and* data on HER2 prevalence,[7,8] together support studying T-DXd in the high risk HER2-expressing adjuvant setting

DESTINY-PanTumor02[5]

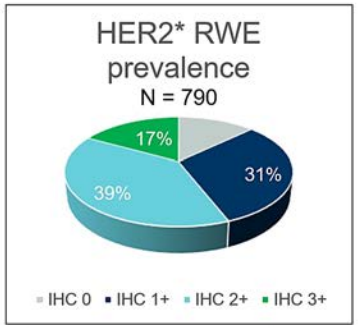


STATICE[6]



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

HER2 – RWE[7]



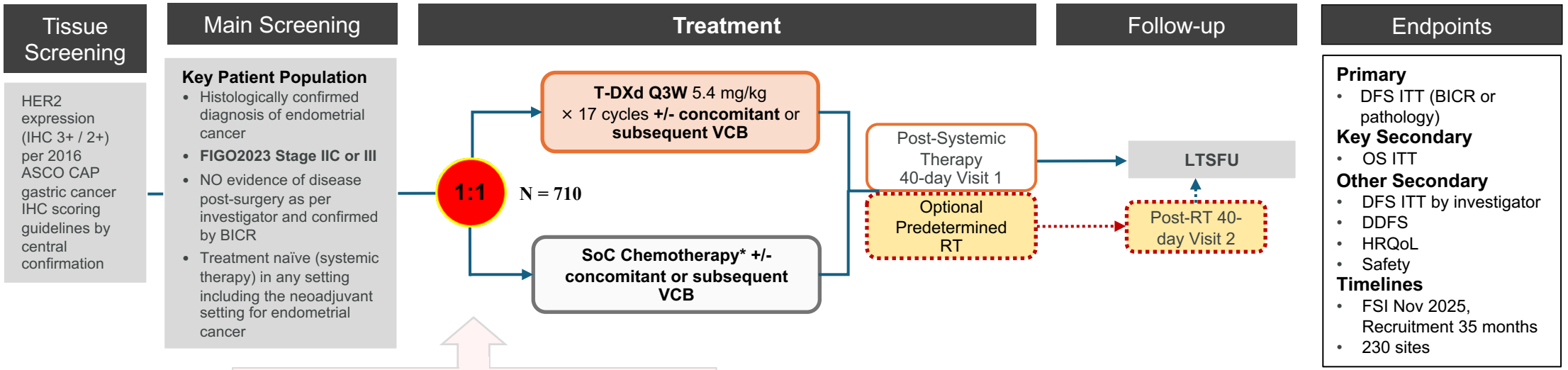
RWE data in endometrial cancer showed that majority of analyzed samples (87%) expressed HER2, notably 56% expressed IHC 3+ and 2+. Among HER2 IHC 2+/3+(n=443), 30 % were HER2 IHC3+

DESTINY-PanTumor02 and **STATICE** trials provide substantial evidence of the activity of T-DXd in HER2 expressing endometrial cancer. Notably, STATICE showed significant efficacy in carcinosarcomas, a histology subtype with a poor prognosis.

1. de Boer SM, et al. Lancet Oncol 2019; 20: 1273-1285; 2. Post CCB, et al. Lancet Oncol 2025; online first; 3. Matei E, et al. J Clin Oncol 2025; 43: 1055-1060; 4. Van Gorp T *et al. Ann Oncol* 2024;35(11):968–980; 5. Makker A, et al. Poster 957P, ESMO 2025; 6. Nishikawa T, et al. J Clin Oncol 2023 41(15):2789-2799; 7. Krakstad C, et al. JAMA Oncol 2024; 10: 1587-1588; 8. Halle MK, et al. BJC 2018; 118: 378-387.

CI, confidence interval; CR, complete response; IHC, immunohistochemistry; ORR, objective response rate; pMMR, proficient mismatch repair; PD, progressive disease; PR, partial response; RWE, real world evidence; SD, stable disease; T-DXd, trastuzumab deruxtecan.

DESTINY-Endometrial02 – Study Design



Full inclusion/exclusion criteria

Stratification Factors

- MMR status by local IHC status: pMMR vs dMMR

Within the pMMR stratum, patients will be further stratified by:

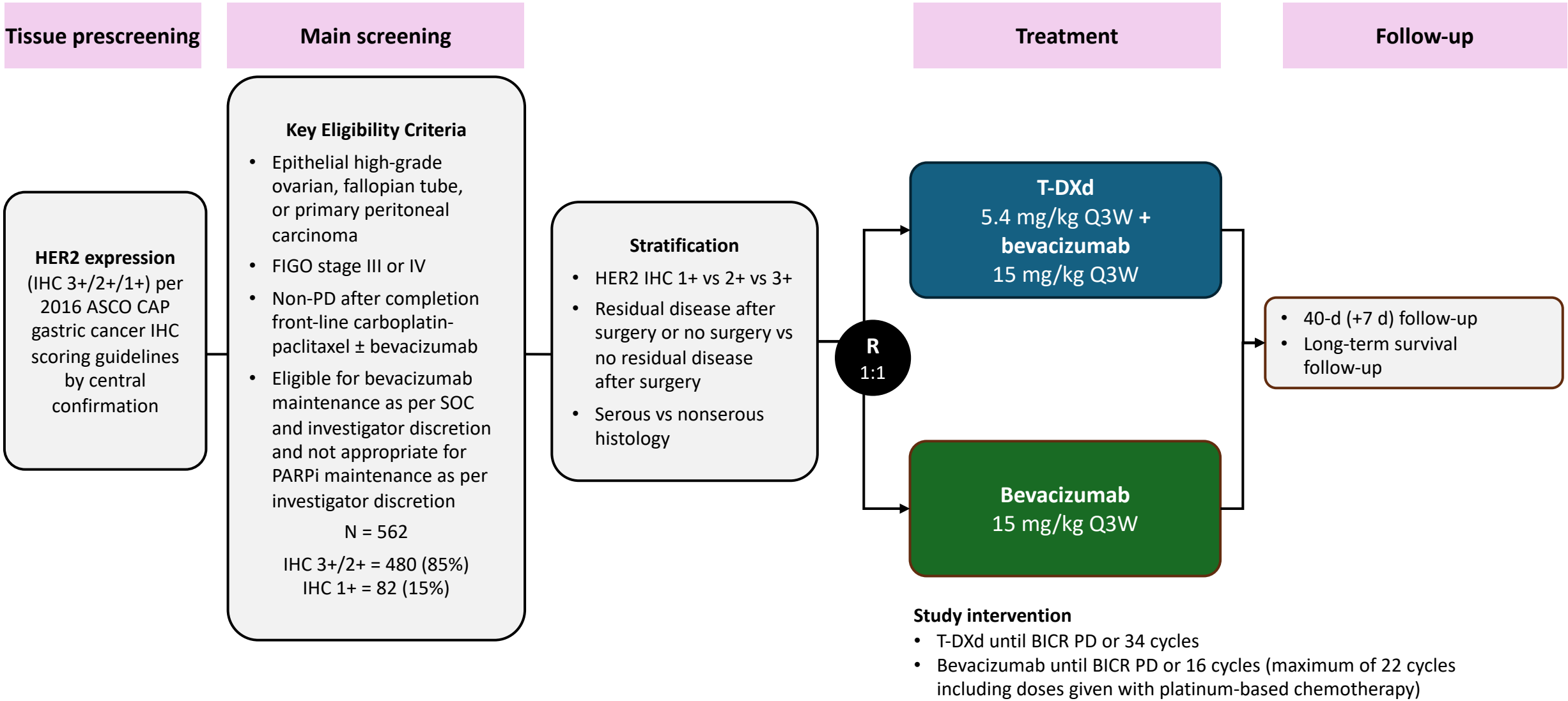
- **HER2 expression by central testing**: IHC 3+ vs 2+
- **FIGO 2023 stage**: IIC vs III
- **Region:** Region 1 vs Region 2 vs Region 3
  - Region 1: North America, Western EU, Australia
  - Region 2: Asia
  - Region 3: Rest of the World

***SoC Chemotherapy +/- EBRT Options**

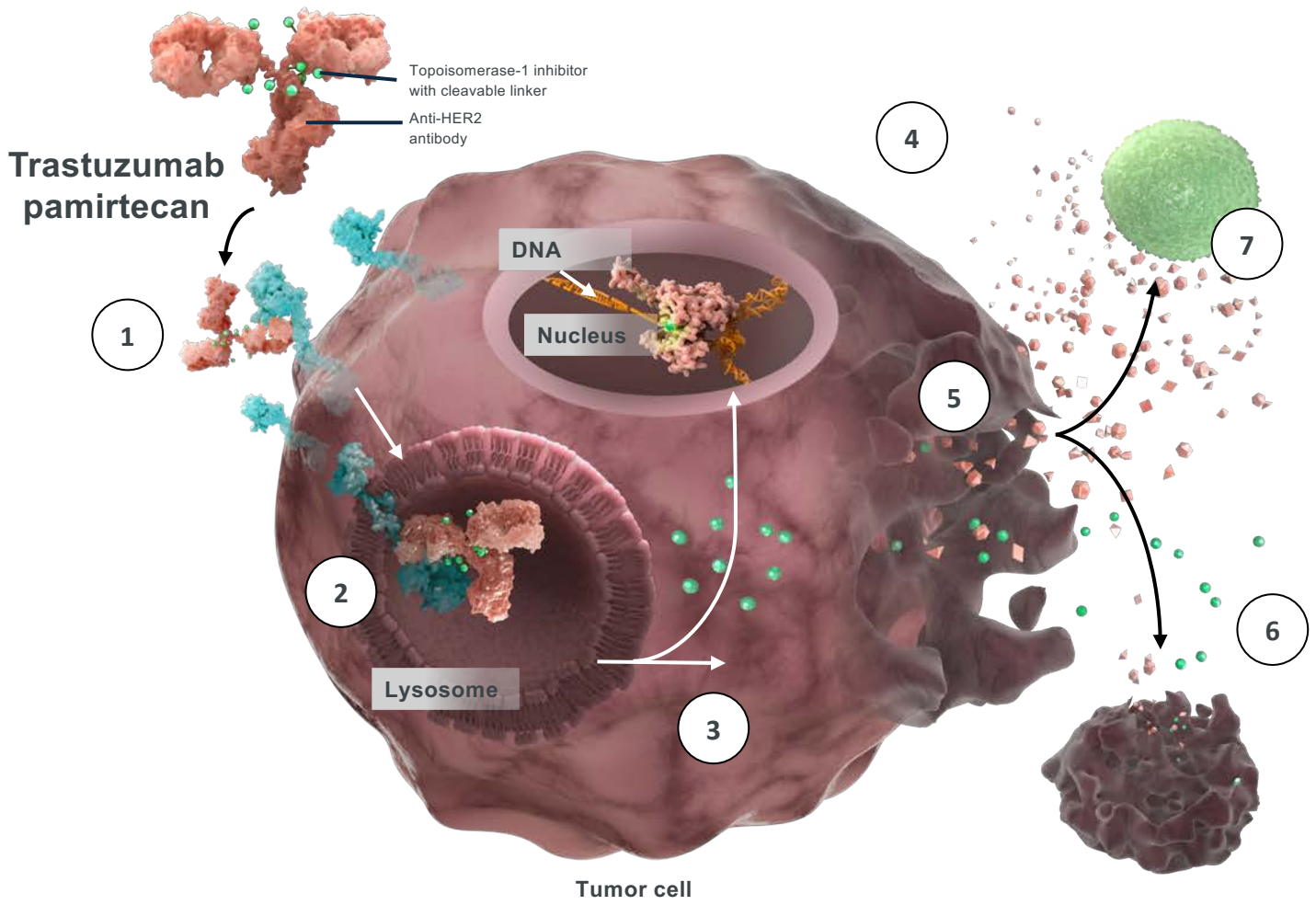
- 6 cycles of carboplatin AUC 5 or 6 and paclitaxel 175 mg/m^2 Q3W followed by EBRT
- 4 cycles carboplatin AUC 5 or 6 and paclitaxel 175 mg/m2 Q3W followed by chemoradiotherapy (EBRT plus cisplatin 50 mg/m^2 on days 1 and 29
- 6 cycles of carboplatin AUC 5 or 6 and paclitaxel 175 mg/m2 Q3W

Stage IIC includes the following aggressive histotypes: high-grade endometrioid (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.
ASCO-CAP, American Society of Clinical Oncology and College of American Pathologists; AUC, area under curve; BICR, blinded independent central review; DDFS, Distant disease-free survival; DFS, disease-free survival; dMMR, deficient mismatch repair; EBRT, external beam radiotherapy; EU, European Union; FIGO, International Federation of Gynecology and Obstetrics; FSI, first subject in; IHC, immunohistochemistry; ITT, intention-to-treat; LTSFU, long-term safety follow up; OS, overall survival; pMMR, proficient mismatch repair; Q3W, every 3 weeks; RT, radiotherapy; SoC, standard of care; T-DXd, Trastuzumab deruxtecan; VCB: vaginal cuff brachytherapy.

DESTINY Ovarian-01

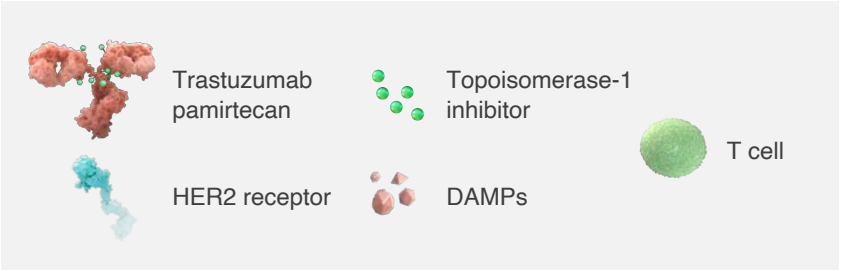


Trastuzumab Pamirtecan (BNT323/DB-1303): MoA



MoA:

1. Trastuzumab pamirtecan binds to HER2-expressing tumor cell[1]
2. Internalization into lysosome and cleavage of linkers[1,2]
3. Release of proprietary topoisomerase-1 inhibitors into the cell[1]
4. Topoisomerase-1 inhibitors travel to nucleus preventing resealing of replicating DNA[2]
5. Tumor cell death releases both topoisomerase-1 inhibitors and DAMPs into the TME[1]
6. Topoisomerase-1 inhibitors exhibit a bystander effect on neighboring tumor cells[1]
7. DAMPs may activate innate immune response[3]



- **Jointly developed by BioNTech and DualityBio.**
- **Trastuzumab pamirtecan (BNT323/DB-1303) is an investigational drug and has not been approved for marketed use by any regulatory agency.**
- For a comprehensive list of all clinical trials investigating trastuzumab pamirtecan (BNT323/DB-1303), please refer to ClinicalTrials.gov.
- 1. Lin S, et al. *Eur J Cancer*. 2022;174(suppl 1):S91. 2. Li TK, Liu LF. *Annu Rev Pharmacol Toxicol*. 2001;41:53-77. 3. Garg AD, et al. *Front Immunol*. 2015;6:588.

Phase 1/2a, global, open-label, first in human study evaluating Trastuzumab Pamirtecan (IV, Q3W) in previously treated patients with solid tumors (NCT05150691)

- Dose escalation part adopts an accelerated titration at first dose followed with classic “3+3” design

Phase 1 (Dose Escalation)
(HER2 IHC 3+, IHC 2+, IHC 1+ or ISH +, or HER2 amplification by NGS, or HER2 mutation by NGS)

12.0 mg/kg, n=3-6
10.0 mg/kg, n=3-6
8.0 mg/kg, n=3-6
7.0 mg/kg, n=3-6
6.0 mg/kg, n=3-6
4.4 mg/kg, n=3-6
2.2 mg/kg, n=1

Additional dose finding cohorts
(A total of up to 20 participants)

RP2D/MTD
(RP2D=8 mg/kg)

Dose extension
If a dose is confirmed to have a tolerable safety profile by the SMC, the cohort size may be backfilled to a maximum of 15-21 at any dose level ≥4.4mg/kg. Up to 57 additional participants (HER2 low BC, HER2+ BC, HER2+/low endometrial carcinoma, and HER2 activation mutation NSCLC) will be enrolled.

Phase 2a (Dose Expansion)

Cohort 2a Trastuzumab-treated HER2+ (IHC3+, IHC2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma (N=30), HER2+ esophageal carcinoma (N=10), and HER2+ CRC (N=15)

Cohort 2b Both HER2 overexpression and HER2 low (IHC3+,2+,1+ or ISH positive) endometrial carcinoma, including UC and USC (N=30-60)

Cohort 2c HR+/HER2 Low (IHC2+ /ISH negative, or IHC1+) BC (N=30-50)

Cohort 2d HER2+ (IHC3+, IHC2+/ISH positive) BC (N=20-40)

Cohort 2e NSCLC with activating HER2 mutation (N=15-30)

Cohort 2f HER2+ or HR+/HER2-low BC with treatment failure of trastuzumab deruxtecan (N=10, HER2+ BC; N=10, HR+/HER2-low BC)

Objectives

Dose Escalation
- **Primary:** safety and tolerability, MTD or RP2D
- **Secondary:** efficacy, PK, and immunogenicity
- **Exploratory:** biomarker and ER relationship

Dose Expansion
- **Primary:** safety and tolerability, efficacy
- **Secondary:** PK, antidrug antibodies, efficacy
- **Exploratory:** biomarker, ER relationship, population PK, neutralizing antibody, efficacy

Moore K, et al. ESGO 2023;Abstract 430.

Data cutoff: May 8, 2023.
ATD=Accelerated titration design; BC=Breast cancer; CRC=Colorectal cancer; ER=Exposure response; HER2=Human epidermal growth factor receptor 2; HR=Hormone receptor; IHC=Immunohistochemistry; ISH=*In situ* hybridization; IV=Intravenous; MTD=Maximum tolerated dose; NGS=Next generation sequencing; NSCLC=Non-small cell lung cancer; PK=Pharmacokinetic; Q3W=Once every 3 weeks; RP2D=Recommended phase 2 dose; SMC=Safety monitoring committee; UC=Uterine carcinosarcoma; USC=Uterine serous carcinoma.

Trastuzumab Pamirtecan - Antitumor Activity

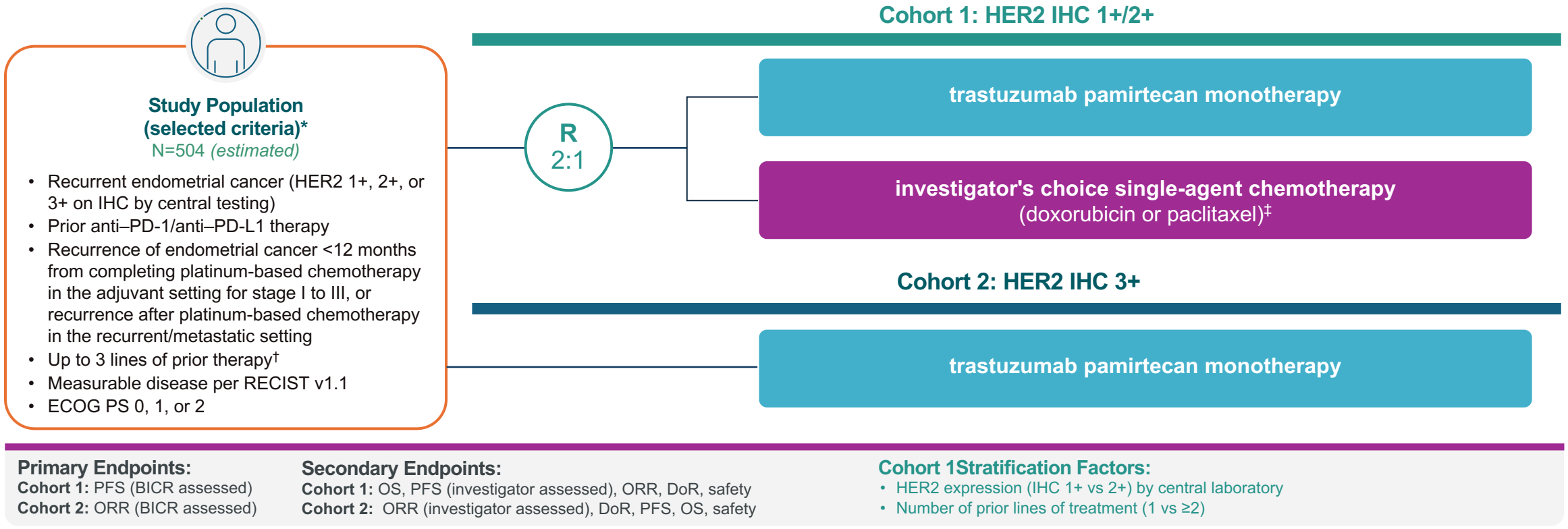
Response [a]	Dose Escalation		Dose Expansion	Pooled 8 mg/kg (n=13)	Total (n=17) [b]
	7 mg/kg (n=4) [b]	8 mg/kg (n=4) [b]	8 mg/kg (n=9) [b]		
Best overall response, n (%)					
PR	2 (50.0)	4 (100)	4 (44.4)	8 (61.5)	10 (58.8)
SD	2 (50.0)	0	4 (44.4)	4 (30.8)	6 (35.3)
PD	0	0	1 (11.1)	1 (7.7)	1 (5.9)
Unconfirmed 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)**

- Among all participants, the unconfirmed ORR was 58.8%, including 23.5% confirmed and 35.3% pending confirmation
- The unconfirmed ORR was 61.5% (8/13) in 8 mg/kg group and 50.0% (2/4) in 7 mg/kg group
- The unconfirmed DCR was 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.

Moore K, et al. ESGO 2023;Abstract 430.

FERN-EC-01 (BNT323-01): Phase 3 Study of Trastuzumab Pamirtecan in HER2-Expressing Recurrent Endometrial Cancer



Primary Endpoints:
Cohort 1: PFS (BICR assessed)
Cohort 2: ORR (BICR assessed)

Secondary Endpoints:
Cohort 1: OS, PFS (investigator assessed), ORR, DoR, safety
Cohort 2: ORR (investigator assessed), DoR, PFS, OS, safety

Cohort 1Stratification Factors:
- HER2 expression (IHC 1+ vs 2+) by central laboratory
- Number of prior lines of treatment (1 vs ≥2)

- Note: Unless specific treatment discontinuation criteria are met or the participant withdraws consent, all participants will continue to receive treatment until PD defined by RECIST 1.1. Long-term survival follow-up will be performed every 3 months (±14 days).
- ClinicalTrials.gov identifier: NCT06340568. Accessed January 26, 2026. https://clinicaltrials.gov/study/NCT06340568

Trastuzumab Pamirtecan (DB-1303/BNT323) in Patients with Previously Treated HER2-Expressing Advanced/Metastatic Endometrial Cancer: First Global Clinical Phase 2 Data

Pothuri B et al.

SGO 2026.

SCIENTIFIC PLENARY II

SATURDAY, APRIL 11, 2026

EXHIBIT HALL A

7:47 AM – 7:54 AM CDT

Trastuzumab Deruxtecan (T-DXd) for Pretreated Patients (pts) with HER2-Expressing Solid Tumors: DESTINY-PanTumor02 (DP-02) Part 1 Final Analysis

Makker V et al.

SGO 2026.

FOCUSED FORUM IX: PRECISION STRIKE, THE RISE OF ADCS

MONDAY, APRIL 13, 2026

BALLROOM B

8:52 AM – 8:58 AM CDT

Second Opinion

Ursula Matulonis, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you think through first-line therapy for patients with HER2-positive advanced endometrial cancer? How do you decide whether to add trastuzumab or an anti-PD-1/PD-L1 antibody to up-front chemotherapy? Do you ever add both?

What is your usual second-line therapy for a patient with HER2-positive advanced endometrial cancer who received chemotherapy/trastuzumab in the first-line setting? What about chemotherapy in combination with an anti-PD-1/PD-L1 antibody? Do you have any hesitation about using T-DXd for a patient who has experienced disease progression on a trastuzumab-containing regimen?

QUESTIONS FOR THE FACULTY

Where in the treatment course are you employing T-DXd for patients with HER2-positive advanced ovarian cancer? How does the presence of biomarkers beyond HER2 (eg, folate receptor alpha or PD-L1 expression) affect this decision? What about comorbidities and patient preferences/the desire to avoid certain side effects (eg, peripheral neuropathy)?

Where in the treatment course are you employing T-DXd for patients with HER2-positive advanced cervical cancer? How do response rates with T-DXd and tisotumab vedotin compare for patients who are eligible to receive both strategies, and which would you prefer in the second-line setting?

QUESTIONS FOR THE FACULTY

If a patient with a HER2-positive advanced gynecologic cancer were to ask you the likelihood that they would experience a significant response, including relief of cancer-related symptoms, with T-DXd, how would you reply? Would this differ at all for endometrial versus ovarian versus cervical cancer?

What would you recommend next for Dr Matulonis's patient? What future role do you see for WEE1 inhibitors for advanced endometrial cancer?

Second Opinion

Professor Jonathan A Ledermann

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you currently approach first-line maintenance therapy for patients with BRCA wild-type, HRD-negative advanced ovarian cancer? For a patient with HER2-positive (IHC 3+) disease, would you consider any type of anti-HER2 therapy in this space? How enthusiastic are you about clinical trials addressing the use of anti-HER2 therapy in that setting?

If T-DXd were to become available in the up-front maintenance setting for patients with HER2-positive advanced ovarian cancer, how long do you envision continuing it?

QUESTIONS FOR THE FACULTY

How enthusiastic are you about clinical trials evaluating T-DXd earlier in the treatment course in endometrial cancer? Do you think it will eventually be available in the first-line setting? What about as a component of adjuvant therapy? Are there any situations in which you would use adjuvant anti-HER2 treatment for a patient with endometrial cancer today?

Have you learned any clinical pearls from breast cancer investigators or general medical oncologists about the prevention and management of side effects with T-DXd? What, if anything, do you think gynecologic oncologists could learn about the optimal use of this agent from these other clinicians?

QUESTIONS FOR THE FACULTY

What other novel agents/strategies are you excited about for patients with HER2-positive gynecologic cancers? Do you see a future for the HER2-targeted bispecific antibody zanidatamab, which has proven effective in gastroesophageal and biliary tract cancers, in these diseases?

Agenda

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

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

Module 3: Identification and Management of Adverse Events with T-DXd — Dr O'Malley

Identification and Management of Adverse Events with T-DXd

David O'Malley, M.D.
Professor & Division Director, Gynecologic Oncology
John G. Boutselis Chair in Gynecologic Oncology
Co-Director, Gyn Oncology Phase I Program
James Cancer Center, Ohio State University
Columbus, Ohio US

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Member, Board of Directors, GOG Foundation
Ovarian Cancer Clinical Trial Lead, GOG Partners

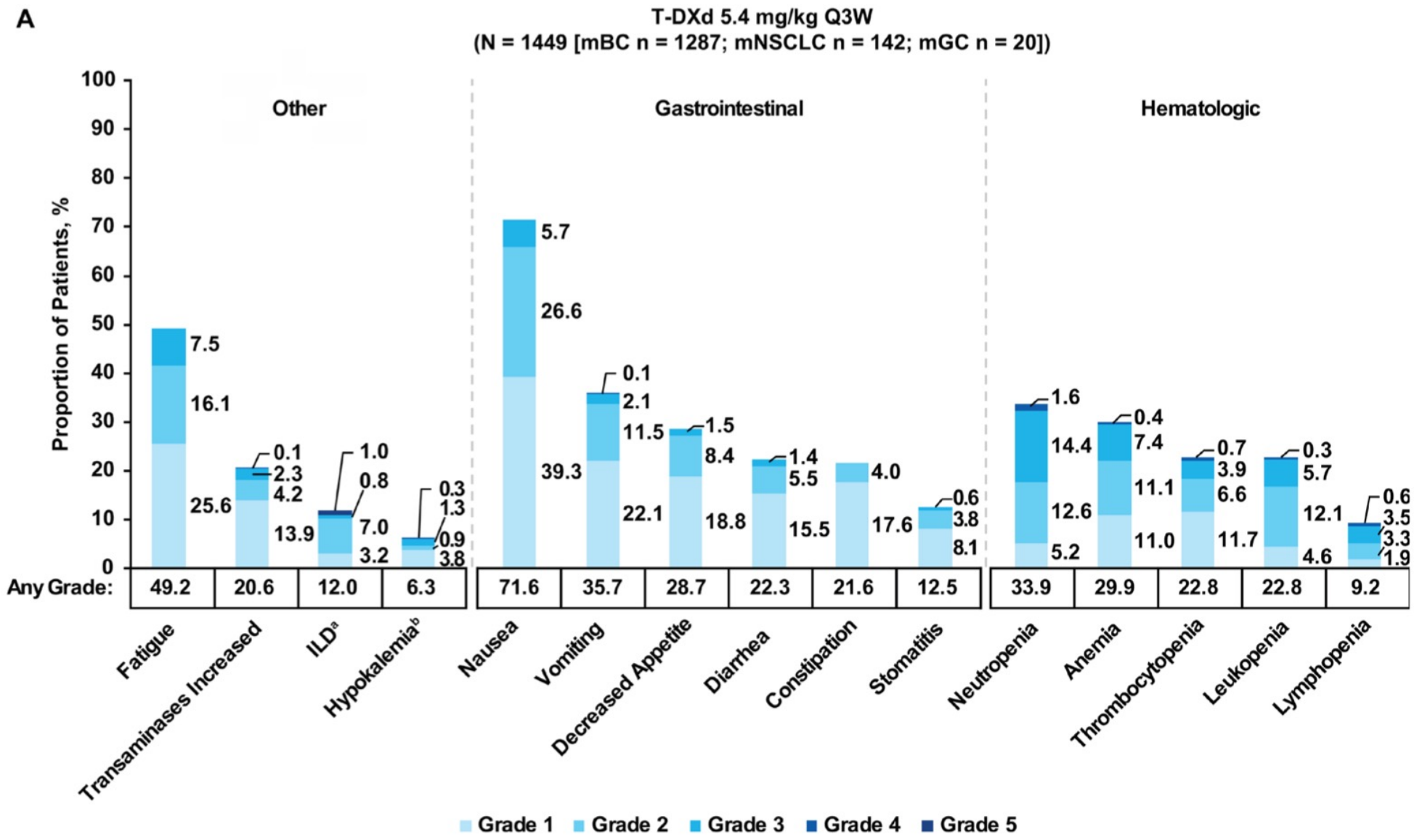
Creating a cancer-free world. One person, one discovery at a time.




Objectives

- Spectrum and incidence of common (eg, GI toxicities, myelosuppression) and more serious (eg, ILD, cardiac toxicities) treatment-emergent AEs observed with T-DXd
- Recommendations for monitoring and immediate reporting of symptoms of ILD and cardiac toxicities with T-DXd
- Strategies to manage T-DXd-associated ILD and cardiac toxicities; indications for restarting T-DXd after resolution of symptoms
- Recommended algorithms for mitigating and managing cytopenias, GI side effects and other complications of T-DXd

Drug-Related TEAEs Reported in a Pooled Analysis

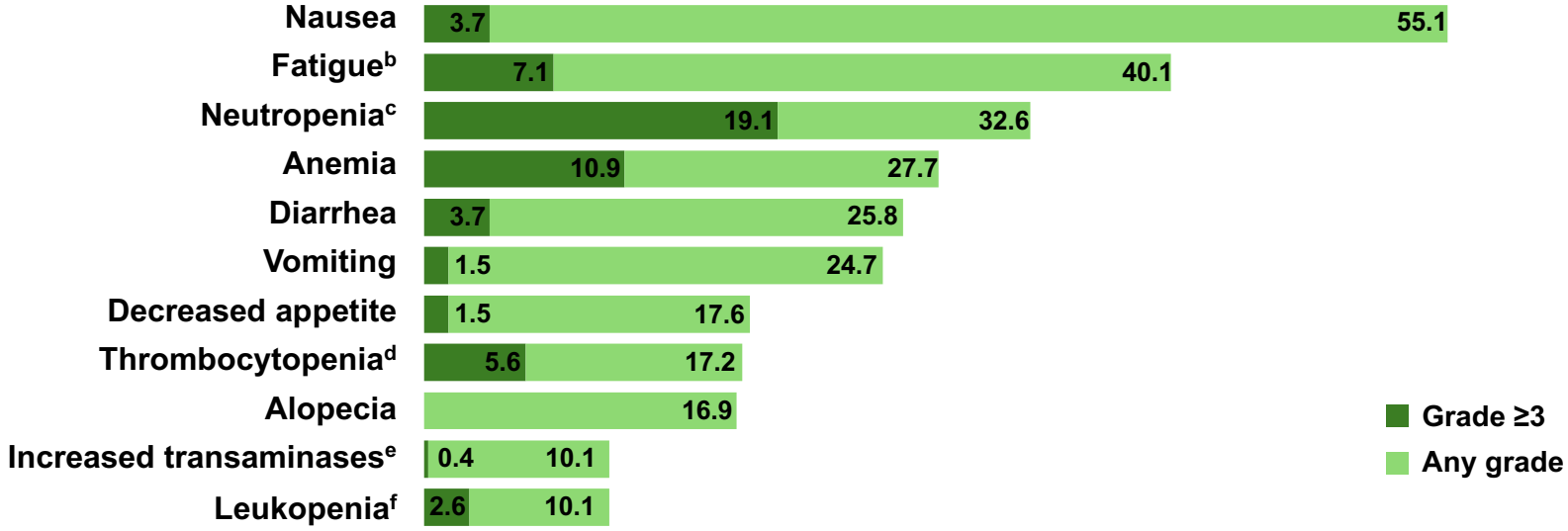


Park YH, Cortes J, Modi S, Hurvitz SA, Bianchini G, Iwata H, Shitara K, Siena S, Goto Y, Ku GY, Powell CA, Swain SM, Arunachalam M, Janek M, Cheng Y, Chu C, Verma P, Kuptsova-Clarkson N, Mathias E, Goodman E, Rugo HS. Characterization of the safety profile of trastuzumab deruxtecan by dose: a pooled analysis across DESTINY studies. Oncologist. 2025 Dec 27;31(1):oyaf396. doi: 10.1093/oncolo/oyaf396. PMID: 41330717; PMCID: PMC12743619.

Phase 2 DESTINY-PanTumor02 Study: Safety Summary

n (%)	All patients (N = 267)
Any drug-related TEAEs	226 (84.6)
Drug-related TEAEs Grade ≥3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with deaths	4 (1.5)[a]

Most common drug-related TEAEs (>10%)



Patients experiencing drug-related TEAEs (%)

ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N = 267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

Analyses were performed in patients who received ≥1 dose of T-DXd (N = 267); median total treatment duration 5.6 months (range 0.4–31.1).
[a]Included pneumonia (n = 1), organizing pneumonia (n = 1), pneumonitis (n = 1), and neutropenic sepsis (n = 1). [b]Category includes the preferred terms fatigue, asthenia, and malaise. [c]Category includes the preferred terms neutrophil count decreased and neutropenia. [d]Category includes the preferred terms platelet count decreased and thrombocytopenia. [e]Category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, hypertransaminasemia. [f]Category includes the preferred terms white blood cell count decreased and leukopenia.
ILD = interstitial lung disease; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event.

Meric-Bernstam F, et al. European Society for Medical Oncology (ESMO) 2023; Abstract LBA34.

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

Use of prophylactic growth factors should be strongly considered

Smith et al. J Clin Oncol 2015

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]

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

Cardio-Pulmonary Toxicity

Decreased Left Ventricular Dysfunction Management on PanTumor Study of T-DXd

- LVEF measurements via echocardiogram (ECHO) or multigated acquisition (MUGA) scan
- Baseline troponin-T and as needed
- Standard management for abnormal 12-lead electrocardiogram (ECG), perform ECG in triplicate
- Standard ECG parameters (including RR, PR, QT intervals, and QRS duration)

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58 including supplementary materials.

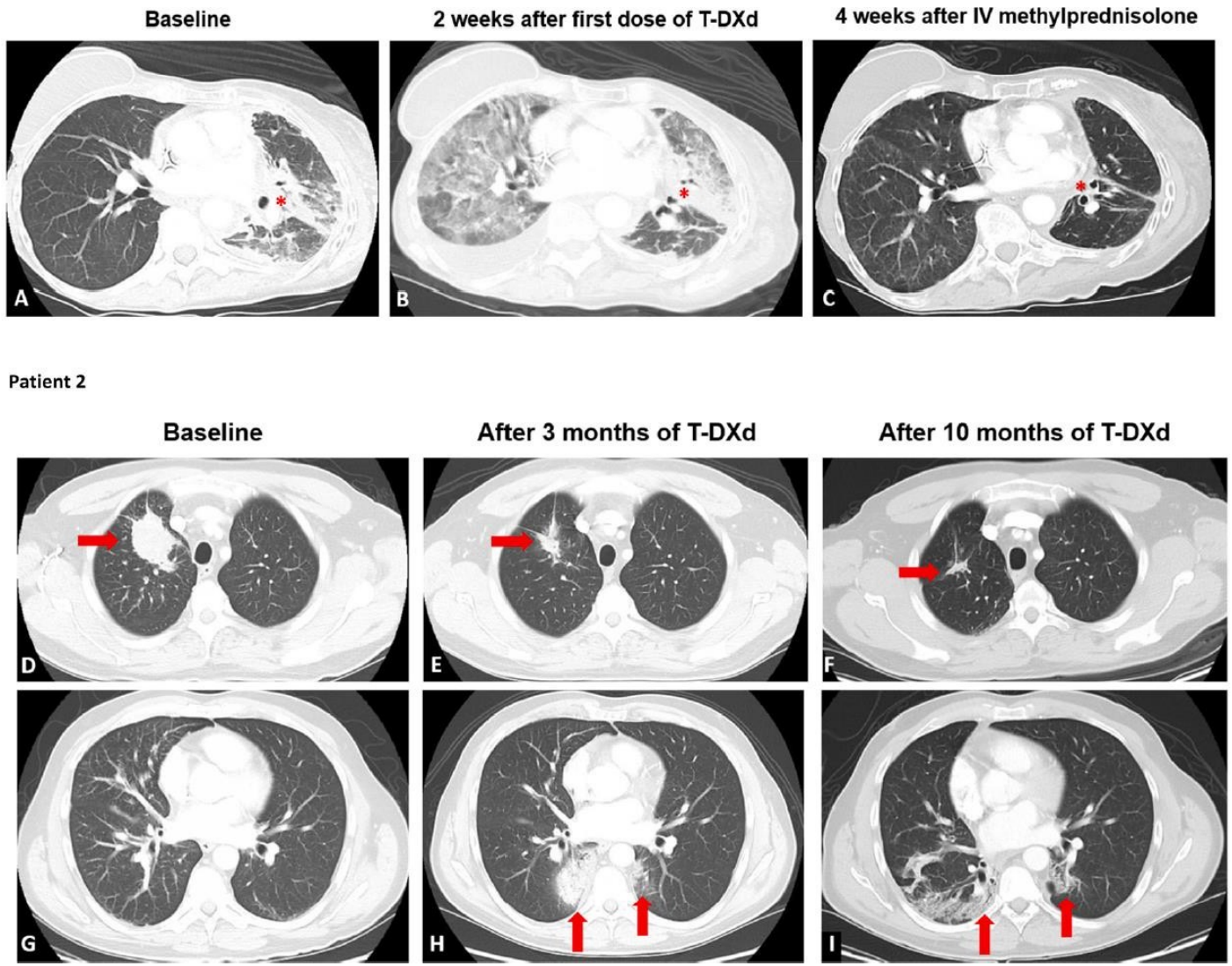
Cardiac Toxicity

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 Repeat LVEF within 3 weeks. If not recovered to within 10% of BL – permanently discontinue
		< 40% or absolute decrease from BL > 20%	Hold Repeat LVEF within 3 weeks If LVEF < 40% or absolute change from baseline> 20% confirmed, permanently discontinue
		Symptomatic CHF	discontinue

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

Interstitial Lung Disease (ILD)

- T-DXd was localized primarily in alveolar macrophages and not pulmonary epithelial cells, suggesting target-independent T-DXd uptake by alveolar macrophages and release of payload as a mechanism of off-target toxicity
- T-DXd–related ILD/pneumonitis may result from cytotoxic lung injury
- Diffuse alveolar damage (DAD) is a pulmonary damage pattern associated with poor prognosis that can result from ILD
- Can be fulminant from the outset, resulting in life-threatening DAD and acute respiratory distress syndrome



Swain, CTR 2022

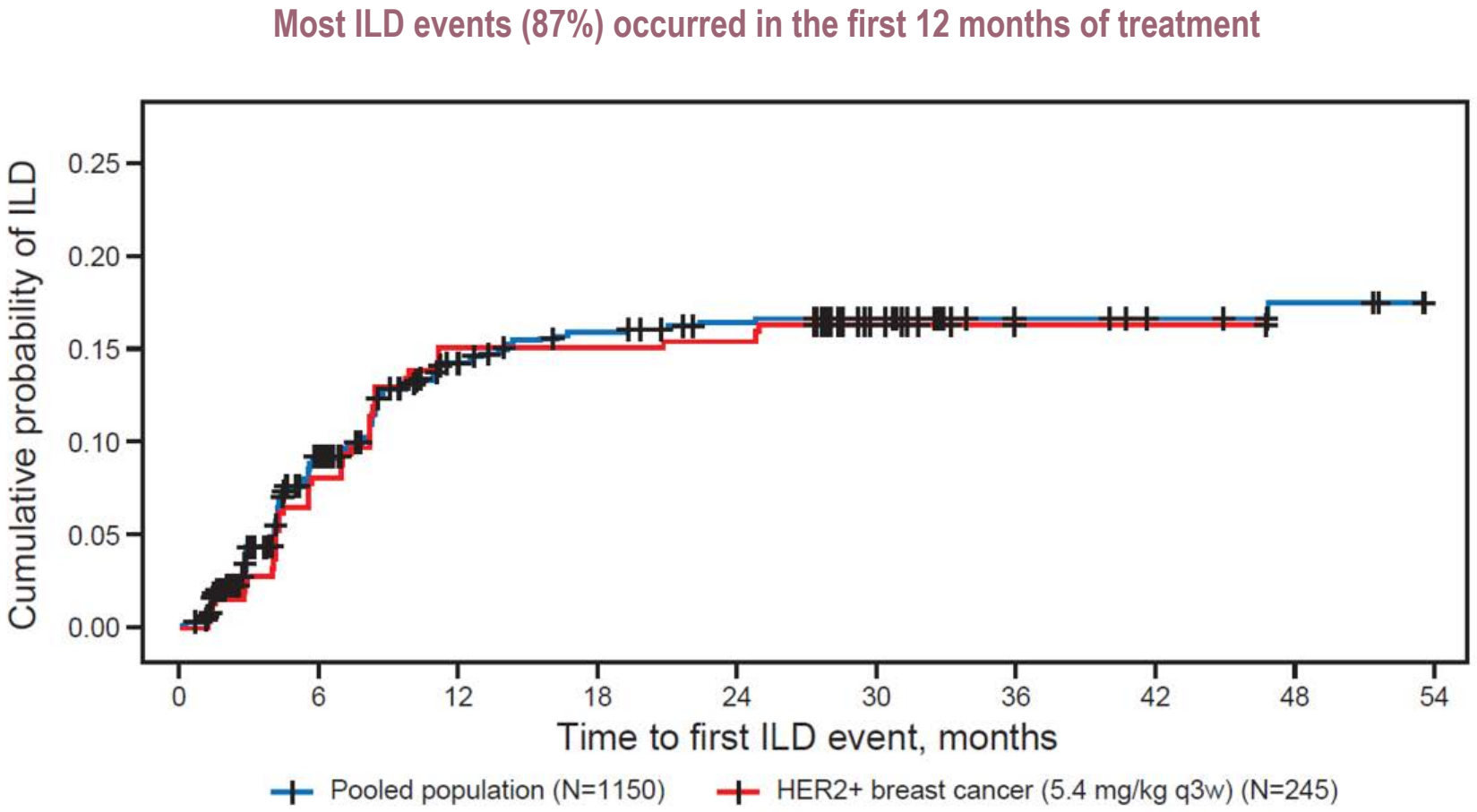
Pneumonitis/ILD

- Patients who received T-DXd across nine studies were included (1150 patients)
- Adjudicated drug-related ILD/pneumonitis was found to be 15.4% patients receiving T-DXd
- 87.0% had their first event within 12 months
  - median, 5.4 months (7-8 cycles)
  - Range: <0.1- 46.8 months
- Median time to onset of 5-6 months
- Most patients with ILD/pneumonitis experienced low-grade events (grade 1 or 2, 77.4%)
- Overall rate of fatal events of 2.2%

Powell CA, Modi S, Iwata H, etal: Pooled analysis of drug related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open7:100554,2022

Time to first ILD event

- The risk of all-grade ILD decreased after 12 months, as the cumulative probability of adjudicated drug-related ILD began to plateau at this point.



Powell CA, et al. ESMO Open 2022; 7:4.

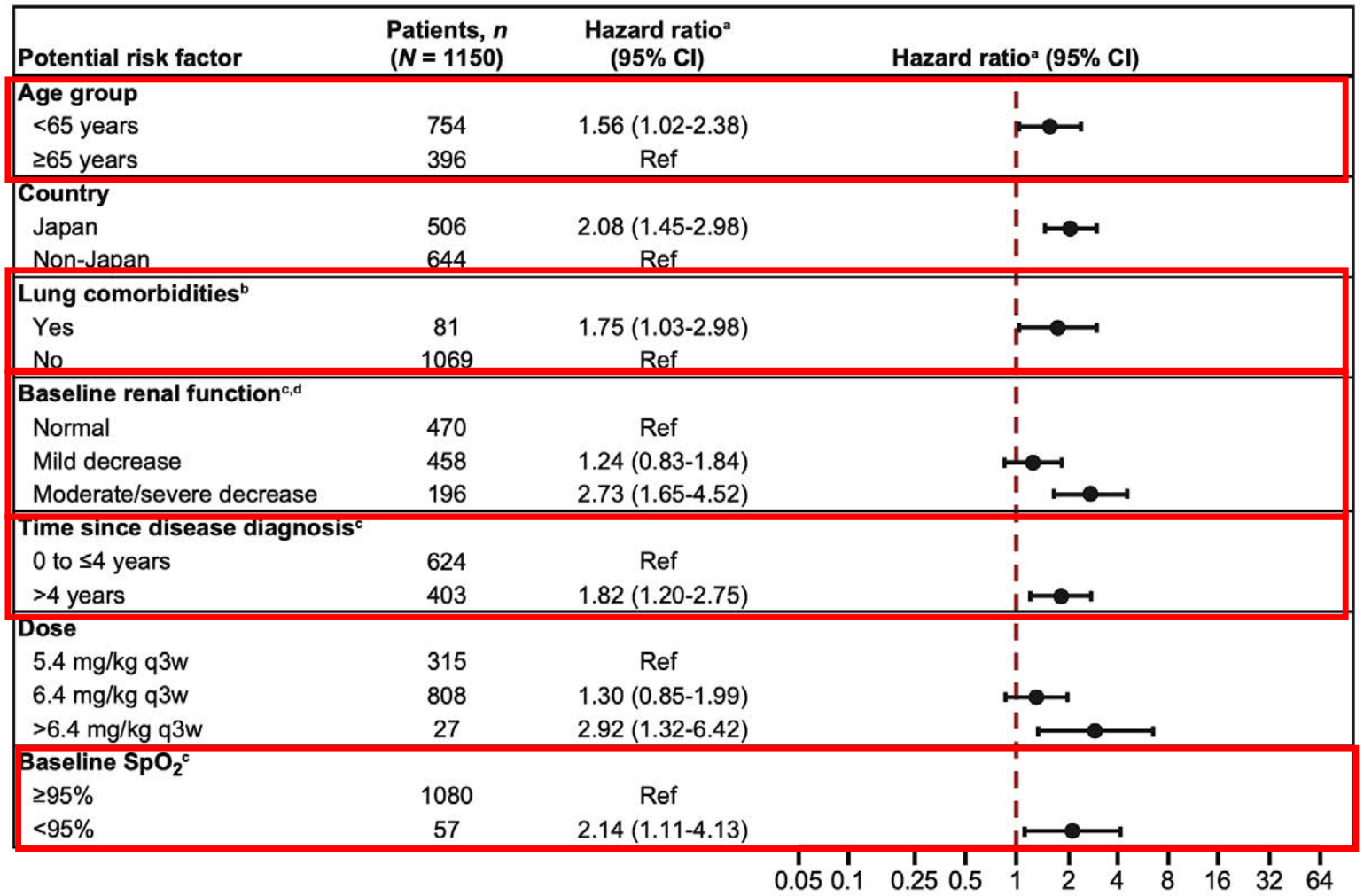
Adjudicated Drug Related in a Pooled Analysis

	T-DXd 5.4-mg/kg Pool *n*=1449
Adjudicated as drug-related ILD, *n* (%)	174 (12.0)
Grade 1	46 (3.2)
Grade 2	102 (7.0)
Grade 3	12 (0.8)
Grade 4	0
Grade 5	14 (1.0)
ILD associated with discontinuation of study drug, *n* (%)	127 (8.8)
ILD associated with dose reduction, *n* (%)	12 (0.8)
ILD associated with study drug interruption, *n* (%)	35 (2.4)
ILD associated with outcome of death, *n* (%)	14 (1.0)

Park YH, Cortes J, Modi S, Hurvitz SA, Bianchini G, Iwata H, Shitara K, Siena S, Goto Y, Ku GY, Powell CA, Swain SM, Arunachalam M, Janek M, Cheng Y, Chu C, Verma P, Kuptsova-Clarkson N, Mathias E, Goodman E, Rugo HS. Characterization of the safety profile of trastuzumab deruxtecan by dose: a pooled analysis across DESTINY studies. Oncologist. 2025 Dec 27;31(1):oyaf396. doi: 10.1093/oncolo/oyaf396. PMID: 41330717; PMCID: PMC12743619.

Pneumonitis/ILD – Who's Highest Risk of Trouble?

- Stepwise Cox regression identified several baseline factors potentially associated with increased risk of adjudicated drug-related ILD/pneumonitis:
  - age <65 years
  - enrollment in Japan
  - T-DXd dose >6.4 mg/kg
  - oxygen saturation <95%
  - moderate/severe renal impairment
  - presence of lung comorbidities
  - time since initial diagnosis >4 years.



Powell CA, Modi S, Iwata H, et al: Pooled analysis of drug related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open7:100554,2022

- Retrospective Metastatic breast cancer treated with T-DXd as SOC
- 2020 and 2024
- 19/203 patients (9.4%)

Variable (*N* = 203)	Univariable HR (95% CI)	*p*-value
Age	1.02 (0.99–1.06)	0.216
Asian ethnicity	0.67 (0.09–4.99)	0.692
People who formerly smoked	2.08 (0.82–5.29)	0.123
Cough*	1.79 (0.41–7.74)	0.438
Shortness of Breath*	3.89 (1.40–10.83)	0.009
Respiratory Infection*	1.51 (0.20–11.34)	0.686
History of Lung Disease	0.72 (0.17–3.12)	0.662
History of Autoimmune Disease	3.36 (1.32–8.54)	0.011
Baseline Interstitial Lung Abnormalities	17.28 (6.54–45.65)	< 0.0001
HER2/neu Receptor Positive (2+FISH/3+)	0.25 (0.09–0.70)	0.009

*prior to Trastuzumab deruxtecan

Azhar et al, Breast Cancer Res. 2025

Variable (*N* = 203)	Univariable HR (95% CI)	*p*-value
Lung Metastasis at Baseline	1.45 (0.58–3.67)	0.428
Prior Lines of Treatment	1.20 (1.03–1.40)	0.023
Use of ICI*	3.86 (1.28–11.65)	0.016
ICI within 6 months of T-DXd	3.01 (0.4–22)	0.28
ICI within 3 months of T-DXd	4.57 (0.6–34)	0.14
Chest Radiation Prior to T-DXd-All	1.71 (0.61–4.74)	0.306
Total Lung V20 (%)-All	1.05 (1.00–1.10)	0.073
Mean Lung Dose (Gy)-All	1.03 (0.98–1.07)	0.284
Lung Metastasis at Baseline	1.45 (0.58–3.67)	0.428

*prior to Trastuzumab deruxtecan

Azhar et al, Breast Cancer Res. 2025

Multivariable predictors for pneumonitis

Variable (*N* = 203)	Hazard Ratio (HR)	95% Confidence Interval	*p*-value
HER2 positive	0.30	0.09–0.96	0.042
Interstitial Lung Abnormalities (ILA)	10.56	3.80–29.31	< 0.0001
V20 (lung volume receiving ≥ 20 G)	1.04	0.99–1.09	0.081

Who needs extra caution?

- Pretreatment ILAs
- Poor Kidney Function
- Underlying Lung Disease
- Prior IO/Immune Disease?
- Long Treatment History?
- Older Age?

HR, hazard ratio; CI, confidence interval; IQR, interquartile range; HER2, human epidermal growth factor receptor 2;ILA, interstitial lung abnormalities; V20, lung volume receiving ≥ 20 G

Azhar et al, Breast Cancer Res. 2025

Strategies to Manage ILD/Pneumonitis

Monitor

Suspected ILD

Urge patients to immediately report cough, dyspnea, fever, and/or new or worsening pulmonary symptoms

- Monitor patients for signs/symptoms of ILD
- Promptly investigate evidence of ILD
- Evaluate patients with suspected ILD by radiographic imaging and assess as follows

Confirm

Assessments should include

- High-resolution CT
- Pulmonologist consult; if indicated, ID consult
- Blood culture and CBC; other blood tests as needed
- Consider bronchoscopy and BAL if indicated and feasible
- PFTs and pulse oximetry
- Arterial blood gases, if indicated
- As soon as ILD suspected, collect 1 blood sample for PK assessment, if feasible
- Rule out other causes of ILD (eg, progression, infection, other drugs, radiotherapy)
- All ILD events should be followed until resolution and after drug discontinuation

Manage

- **Grade 1 T-DXd:** Hold until resolved to grade 0; consider corticosteroids (0.5 mg/kg/day prednisolone), then
  - *If resolved ≤28 days from onset:* Maintain dose
  - *If resolved >28 days after onset:* Reduce dose by 1 level
  - *-Taper steroid over at least 4 weeks*
- **Grades 2–4:** Permanently discontinue treatment and promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) for ≥14 days followed by taper for ≥4 weeks

BAL = bronchoalveolar lavage; ID = infectious disease; PFTs = pulmonary function tests; PK = pharmcokinetics.

Ado-trastuzumab emtansine (Kadcyla®) PI 2022 (https://www.kadcyla.com/). Fam-trastuzumab deruxtecan-nxki (Enhertu®) PI 2024 (https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Enhertu& inline=true). URLs accessed 11/8/2024. Tarantino P, et al. *JAMA Oncol*. 2021;7:1873-1881.

Strategies to Manage Grade 2 to 4 ILD/Pneumonitis

Grade 2

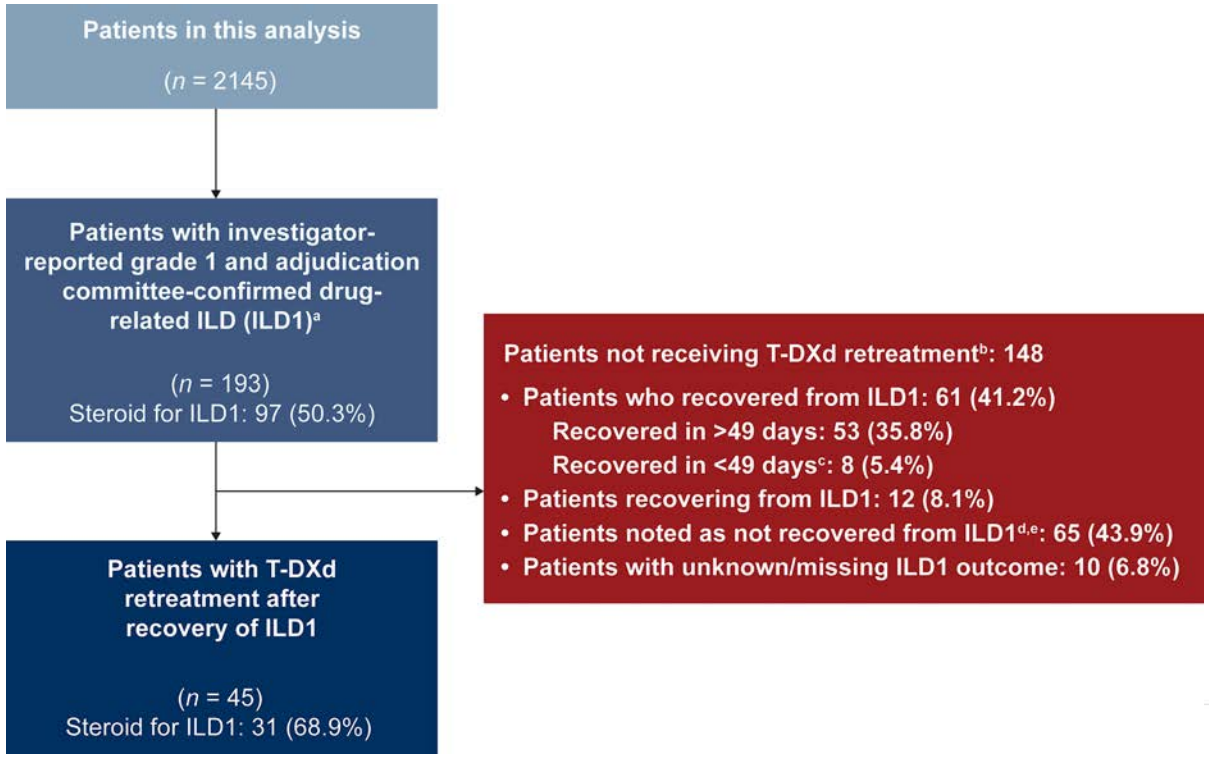
- Promptly start systemic glucocorticoids (eg, ≥1 mg/kg/d prednisone or equivalent) for ≥2 weeks or to complete resolution of clinical and chest CT findings, then gradual taper over ≥4 weeks
- Monitor symptoms closely
- Re-image as indicated
- If clinical or diagnostic observations worsen or do not improve in 5 days
  - Consider increase in steroid dose (eg, 2 mg/kg/day prednisone or equivalent) or switch to intravenous (IV)
  - Reconsider additional workup for alternative etiologies
  - Escalate care as needed

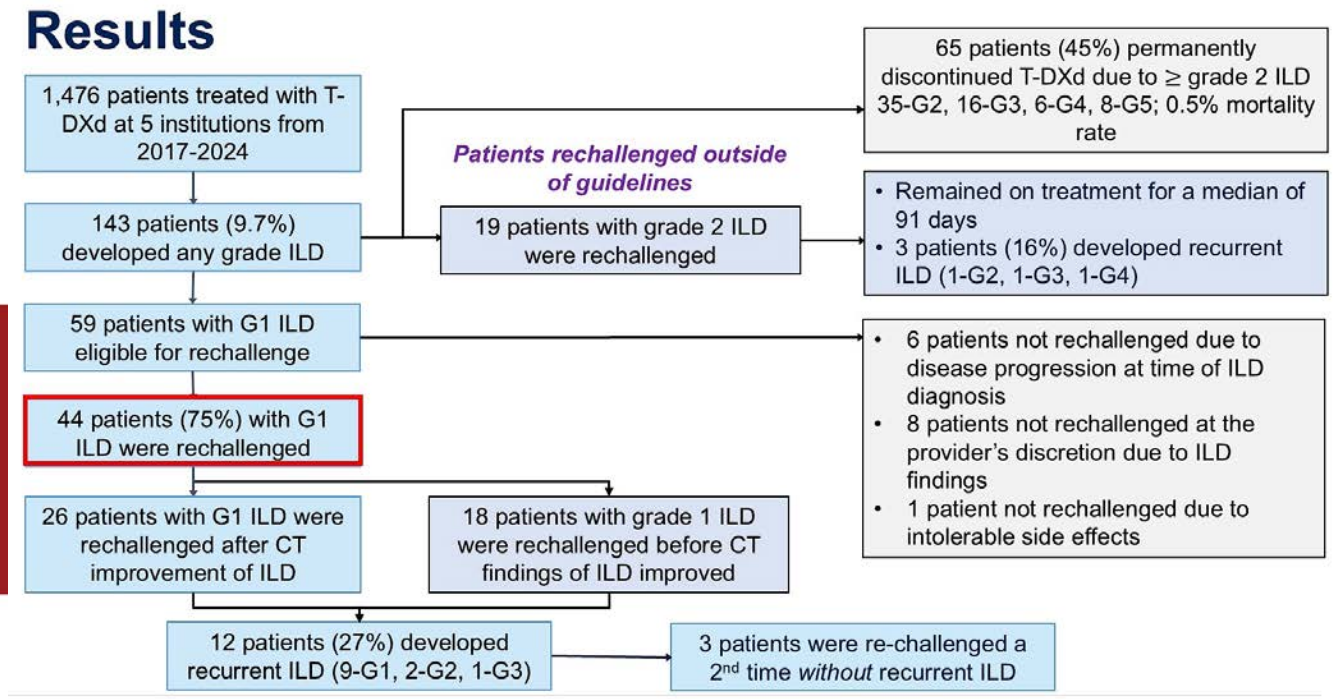
Grade 3 or 4

- Hospitalization required
- Promptly initiate empirical high-dose methylprednisolone IV (eg, 500–1000 mg/day for 3 days), followed by ≥1 mg/kg/ day prednisone (or equivalent) for ≥2 weeks until resolution of clinical and chest CT findings, then gradual taper over ≥4 weeks
- Re-image as clinically indicated
- If still no improvement with 3 to 5 days
  - Reconsider additional workup for alternative etiologies
  - Consider other immunosuppressants and/or treat per local practice

Li BT, et al. *N Engl J Med*. 2022;386:241-251 (Protocol).

How About Re-Treatment after ILD? 2 Recent Reports





H.S. Rugo, ...C.A. Powell, et al. Pooled analysis of trastuzumab deruxtecan retreatment after recovery from grade 1 interstitial lung disease/pneumonitis, Annals of Oncology (36 (11); 2025

Natsuhara K, Blum K, LeVee A,....Rugo et al. Treatment rechallenge after trastuzumab-deruxtecan–related interstitial lung disease: A multi-institution cohort study. ASCO. 2025.

How About Re-Treatment after ILD? Pooled Analysis

Table 1. T-DXd retreatment

	T-DXd retreatment (*N* = 45)
Median time to onset of ILD1[a] (range), days	210.0 (37-750)
Dose level of T-DXd retreatment	
Same dose, *n* (%)	31 (68.9)
Reduced dose, *n* (%)	14 (31.1)
Median time to retreatment after ILD1 onset (range), days	28 (8-48)
Median retreatment cycles (range)	5.0 (1-37)
Patients with ILD2 (*n* = 15)	5.0 (2-23)
Patients without ILD2 (*n* = 30)	4.5 (1-37)
Median retreatment duration (range), days	85.0 (1-848)
Patients with ILD2 (*n* = 15)	85.0 (22-648)
Patients without ILD2 (*n* = 30)	82.5 (1-848)

AC, adjudication committee; ILD, interstitial lung disease/pneumonitis; ILD1, first investigator-assessed grade 1 and AC-confirmed drug-related ILD event; ILD2, investigator-assessed AC-confirmed any-grade recurrent ILD event; T-DXd, trastuzumab deruxtecan.
[a]Time from initial T-DXd treatment start date to onset of first grade 1 ILD1.

Table 2. Grade and outcome of ILD2

n (%)	With steroid treatment for ILD2 (*n* = 8)	Without steroid treatment for ILD2 (*n* = 7)	Total with ILD2 (*n* = 15)
Adjudicated worst grade of ILD2			
1	2 (25.0)	4 (57.1)	6 (40.0)
2	6 (75.0)	3 (42.9)	9 (60.0)
≥3	0	0	0
Adjudicated outcome of ILD2[a]			
Recovered/ recovered with sequelae	6 (75.0)	3 (42.9)	9 (60.0)
No outcome recorded in CRF[b]	2 (25.0)	1 (14.3)	3 (20.0)
Ongoing[c]	0	3 (42.9)	3 (20.0)
Fatal	0	0	0

AC, adjudication committee; CRF, clinical reporting form; DCO, data cut-off; ILD, interstitial lung disease/pneumonitis; ILD2, investigator-assessed AC-confirmed any-grade recurrent ILD event.
[a]Outcome of the first recurrent ILD event as assessed by investigators and confirmed by the AC.
[b]Patients were lost to follow-up.
[c]Cases ongoing at the DCO of this analysis.

Patients with ILD who showed improvement on CT scans but had residual fibrosis were noted as recovered with sequelae

H.S. Rugo, …..C.A. Powell, et al. Pooled analysis of trastuzumab deruxtecan retreatment after recovery from grade 1 interstitial lung disease/pneumonitis, Annals of Oncology (36 (11); 2025

How About Re-Treatment after ILD? Multi-Institution Cohort Study

	Rechallenged (n=44)	Not Rechallenged (n=15)	Overall (n=59)
	n (%) or median (interquartile range)		
ILD onset from 1st T-DXd dose (days)	144 (77-216)	198 (123-334)	146 (81-246)
Cancer Diagnosis			
Breast	38 (86)	14 (93)	52 (88)
Other (GI, Gyn, Lung)	6 (14)	1 (7)	7 (12)
Age at 1st T-DXd dose (years)	60 (52-68)	63 (48-72)	60 (52-69)
Prior # treatment lines in the advanced/metastatic setting	3 (1-4)	2 (2-5)	3 (1-4)
Renal impairment (CrCl < 60 mL/min)	10 (23)	3 (20)	13 (22)
Treated with steroids	29 (66)	6 (40)	35 (59)
Duration of steroid treatment (days)	36 (21-76)	35 (25-49)	36 (21-75)
Radiographic ILD improvement (days)	39 (22-84)	80 (64-99)	55 (24-84)*

- **Radiographic ILD improvement was seen at a median of 29 days (IQR 20-70) for patients treate with steroids vs 82 days (IQR 50-108) without (p<0.001**)**

Median time to rechallenge was 42 days (IQR 34-64) from last dose before ILD

- 3 patients (7%) received intervening therapy prior to rechallenge
- 27 patients (61%) were rechallenged with a dose-reduction
- 17 patients (38%) were rechallenged while completing steroid taper

After rechallenge, patients remained on T-DXd for a median of 215 days (IQR 74-319)*

12 patients (27%) developed recurrent ILD (9-G1, 2-G2, 1-G3)

- Median time to recurrent ILD was 211 days (IQR 72-295)
- No statistically significant differences were seen in demographic or clinical characteristics between patients who developed recurrent ILD vs not treated

Natsuhara K, Blum K, LeVee A,....Rugo et al. Treatment rechallenge after trastuzumab-deruxtecan–related interstitial lung disease: A multi-institution cohort study. ASCO. 2025.

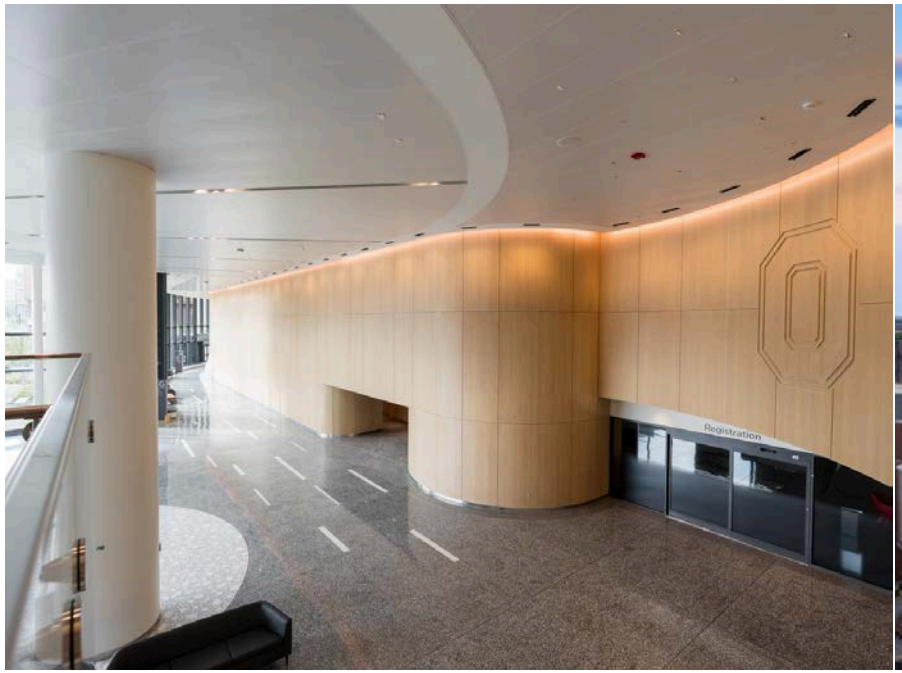
How About Re-Treatment after ILD? Even in Grade 2?

- **19 patients with grade 2 ILD were re-challenged with T-DXd**, outside of the guidelines
  - Median time to rechallenge was 49 days (IQR 42-126 days)
  - Patients remained on T-DXd after rechallenge for a median of 91 days (IQR 27-162)
  - 3 patients (16%) developed recurrent ILD (1-G2, 1-G3, 1-G4)

This is outside of guideline therapy and this limited data should be interpreted with caution

Natsuhara K, Blum K, LeVee A,….Rugo et al. Treatment rechallenge after trastuzumab-deruxtecan–related interstitial lung disease: A multi-institution cohort study. ASCO. 2025.

GI Toxicities



The James

The Ohio State University
Wexner Medical Center

Example of Nausea/Vomiting Management Strategy
NCCN guidelines now classify T-DXd as highly emetogenic

Day	Medication protocols
Day 1 **Before infusion**	**Cycle 1:** Dexamethasone (8–12 mg PO or IV) + 5-HT_3 RA **Subsequent cycles** **For optimal control:** Repeat above **For suboptimal control (eg, grade ≥1 for ≥3 days):** Dexamethasone (12 mg IV) + NK1 RA + 5-HT_3 RA
Day 1 **After infusion**	Consider ondansetron (8 mg PO or IV/IM) for 3 doses after infusion
Days 2 to 4	**Cycle 1:** Dexamethasone (4 mg PO or 8 mg PO or IV/IM QD) ± metoclopramide (10 mg PO) TID or 5-HT_3 RA **Subsequent cycles** **Adequate control:** Repeat above Inadequate control (eg, grade ≥1 for ≥3 days): Aprepitant (80 mg PO) + 5-HT_3 RA ± dexamethasone (8 mg PO or IV) or dexamethasone (8 mg PO or IV/IM QD) ± metoclopramide (10 mg PO TID)

Other considerations

Anticipatory N/V

- Consider anxiolytic therapy [eg, lorazepam (0.5–1.0 mg PO)] the night before infusion and 1 to 2 hours before infusion begins
- Behavioral therapy (eg, relaxation exercises, hypnosis) and/or acupuncture/acupressure may help with prevention

- **For subsequent infusions**
  - Estimate individual risk of emesis to determine whether past regimen was adequate or if escalation is necessary
- **If N/V occurs despite 3-drug regimen**
  - Days 1 to 4: Olanzapine (2.5 mg PO; increase to 5-10 mg if needed) OR
  - Days 2 to 4: Increase dexamethasone on subsequent cycles
- For delayed nausea (after Day 4) give 1 of the following to resolution
  - Olanzapine (5–10 mg PO at bedtime QD) OR
  - Metoclopramide (10 mg PO TID) ± dexamethasone (4 mg PO QD)

5-HT3 = serotonin type 3; IM = intramuscular; IV = intravenous; NK1 = neurokinin-1; N/V = nausea and/or vomiting; PO = by mouth; QD = once daily; RA = receptor antagonist; SC = subcutaneously; TID = 3 times daily.

Rugo HS, et al. *ESMO Open*. 2022;7:100553.

T-DXd and R-DXd Dose Modifications

- Toxicities treated maximum supportive care (including withholding agent as needed)
- At resolution of toxicity with supportive care, consider continuing the same dose with appropriate supportive care
- Dose modifications as needed

Starting dose	First reduction	Second reduction
T- DXd 5.4 mg/kg	4.4 mg/kg	3.2 mg/kg

- After dose reduction, subsequent cycles should be given at lower dose level unless further dose reduction is required
- Discontinue therapy if unacceptable toxicity occurs after 2 dose reductions

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58 including supplementary materials.

T-DXd Pneumonitis: What Matters – when it happens, who is at risk, and what you do next.

- Incidence 10–15%; fatal 1–2%
- Median onset: 5–6 months (~cycle 7–8)
- Most events occur within 12 months
- High risk: ILAs, prior IO, renal dysfunction
- Early steroids change outcomes
- Rechallenge only after Grade 1 and with caution
- Grade ≥2 → permanently discontinue

T-DXd Toxicities: Supportive Care Still Matters

- Highly emetogenic → use full prophylaxis
- Consider growth factor support in high-risk patients

Second Opinion

Angeles Alvarez Secord, MD, MHSc

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What screening techniques do you employ for early detection of ILD in patients receiving T-DXd? How frequently should patients receiving T-DXd undergo radiographic scans to monitor for ILD? How do you manage Grade 1 (asymptomatic) ILD, and what are your criteria for restarting the drug after radiographic evidence of ILD has resolved? How do you manage Grade 2 (symptomatic) ILD? Are there any situations in which you would rechallenge after resolution of symptoms?

QUESTIONS FOR THE FACULTY

What preemptive antiemetic strategies do you use for patients about to start T-DXd? What has been your experience with acute GI toxicity with the drug? What would you most likely recommend for a patient experiencing breakthrough nausea and vomiting with T-DXd despite antiemetic prophylaxis?

What screening techniques do you use to monitor cardiac function in patients receiving T-DXd? How often do you monitor LVEF?

QUESTIONS FOR THE FACULTY

What other side effects of interest (eg, cytopenias) have you observed in patients receiving T-DXd? Do you employ G-CSF prophylaxis for any patients receiving this agent?

Are there any patients for whom you preemptively start at a lower dose of T-DXd?

What experience do you have with strategies targeting both PD-1/PD-1 and VEGF — like the atezolizumab/bevacizumab regimen used for Dr Secord's patient — in advanced endometrial cancer? Is the PD-1 x VEGF-A bispecific antibody ivonescimab being looked at in gynecologic cancers?

Second Opinion

Ursula Matulonis, MD

Neil Love, MD

RTP
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QUESTIONS FOR THE FACULTY

In what situations would you use T-DXd for a patient with a history of cardiomyopathy? Is there a minimum LVEF that you require?

How do you approach patients with drops in LVEF on T-DXd? In patients for whom treatment has been withheld, are there any circumstances in which you would reintroduce T-DXd after normalization of LVEF?

Would you have any qualms about employing T-DXd before or after another antibody-drug conjugate, such as mirvetuximab soravtansine in ovarian cancer or tisotumab vedotin in cervical cancer? How do you generally sequence these strategies?

Second Opinion

Professor Jonathan A Ledermann
Professor of Medical Oncology
UCL Cancer Institute
London, United Kingdom

Angeles Alvarez Secord, MD, MHSc
Director of Gynecologic Oncology Clinical Trials
Associate Director, Clinical Research, Gynecologic Oncology Program
Duke Cancer Institute
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
Duke University School of Medicine
Durham, North Carolina

Ursula Matulonis, MD
Chief, Division of Gynecologic Oncology
Brock-Wilson Family Chair
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Neil Love, MD
Research To Practice
Miami, Florida

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An Independent CME Symposium During the SGO 2026 Annual Meeting on Women's Cancer®

Sunday, April 12, 2026

1:30 PM – 3:00 PM AST

Faculty

Nicoletta Colombo, MD

Gottfried E Konecny, MD

Alexander B Olawaiye, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

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Faculty

Ramez N Eskander, MD

Bradley J Monk, MD

Moderator

Kathleen N Moore, MD, MS

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