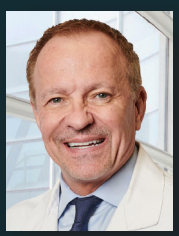
Comprehensive Care *with* HER2 ADCs ACROSS SOLID TUMORS:

Strategies *to* Enhance Efficacy *and* Minimize Toxicity



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Comprehensive Care with HER2 ADCs Across Solid Tumors: Strategies to Enhance Efficacy and Minimize Toxicity

Agenda

Introduction

I. Updates in Clinical Management of HER2-Positive Solid Tumors

II. Clinical Trial Data on Use of Other HER2-Targeted Therapies: HER2-Expressing Gynecological, Bladder, Biliary Tract, and Other Tumors

III. Adverse Event Monitoring and Management Best Practices with HER2-Targeted Therapies Across HER2-Positive Tumors

IV. Interpreting HER2: Integrating with Pathology Across HER2-Positive Malignancies

V. Case Studies

VI. Conclusions and Q&A

Comprehensive Care with HER2 ADCs Across Solid Tumors: Strategies to Enhance Efficacy and Minimize Toxicity

Virtual Symposium

PROGRAM CHAIR

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PROGRAM OVERVIEW

The goal of this program is to increase the healthcare professional's (HCP) ability to: analyze clinical data with use of HER2-targeted antibody-drug conjugates in HER2-expressing solid tumors; identify potential adverse events associated with HER2-targeted antibody-drug conjugates; and evaluate the need to accurately assess HER2 status in HER2-expressing solid tumors to facilitate use of HER2-targeted antibody-drug conjugates when appropriate.

TARGET AUDIENCE

This activity is intended for US-based community oncology teams, including oncologists and multidisciplinary HCPs involved in the treatment of patients with HER2-positive solid tumors, including gynecological, bladder, and biliary tract cancers.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Analyze clinical data with use of HER2-targeted antibody-drug conjugates in HER2-expressing solid tumors
- Identify potential adverse events associated with HER2-targeted antibody-drug conjugates
- Evaluate the need to accurately assess HER2 status in HER2-expressing solid tumors to facilitate use of HER2-targeted antibody-drug conjugates when appropriate

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Comprehensive Care With HER2 ADCs Across Solid Tumors: Strategies to Enhance Efficacy and Minimize Toxicity

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Disclosures

- **Dr. Monk** serves as speaker for AstraZeneca, DSI, Eisai, GSK, ImmunoGen/AbbVie, and Merck and receives consulting fees from AstraZeneca, BioNtech, Corcept, DSI, Eisai, Eli Lilly, Genmab/Seagen/Pfizer, GOG Foundation, GSK, ImmunoGen/AbbVie, Incyte, Karyopharm, Merck, Mersana, Mural/Alkermes, Myriad, Natera, Novartis, Novocure, OncoC4, Panavance Pharma & Profound Bio/Genmab, Regeneron, Roche/Genentech, Sutro, Tubulis, Verastem, Zentalis, and Zymeworks
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Learning Objectives

- Analyze clinical data with use of HER2-targeted antibody-drug conjugates in HER2-expressing solid tumors
- Identify potential adverse events associated with HER2-targeted antibody-drug conjugates
- Evaluate the need to accurately assess HER2 status in HER2-expressing solid tumors to facilitate use of HER2-targeted antibody-drug conjugates when appropriate

Updates in Clinical Management of HER2+ Solid Tumors

NCCN: Biomarker-Directed Therapy for Selected Hard-to-Treat Solid Tumors

	Cervical	Endometrial	Ovarian	Biliary tract carcinoma	Pancreatic	Bladder
MMR-proficient		✓				
TMB-H	✓	✓	✓	✓	✓	✓
MSI-H/dMMR	✓	✓	✓	✓	✓	
HER2+	✓*	✓*	✓*	✓†	✓*	✓*
NTRK fusion	✓	✓	✓	✓	✓	
PD-L1+	✓					
RET fusion	✓		✓	✓	✓	
BRAF V600E+			✓	✓	✓	
FGFR3 alteration						✓
FGFR alteration				✓ (for CCA)	✓	
FR alpha			✓			
IDH1 mutation				✓ (for CCA)		
BRCA1/2		✓ (for LMS)	✓		✓	
PALB2					✓	
KRAS			✓	✓	✓	

* T-DXd for IHC 2+ or 3+. † Trastuzumab + pertuzumab or tucatinib + trastuzumab. Note: Use of tucatinib/pertuzumab and trastuzumab/pertuzumab for this indication is included in NCCN clinical practice guidelines but is not approved by the FDA.

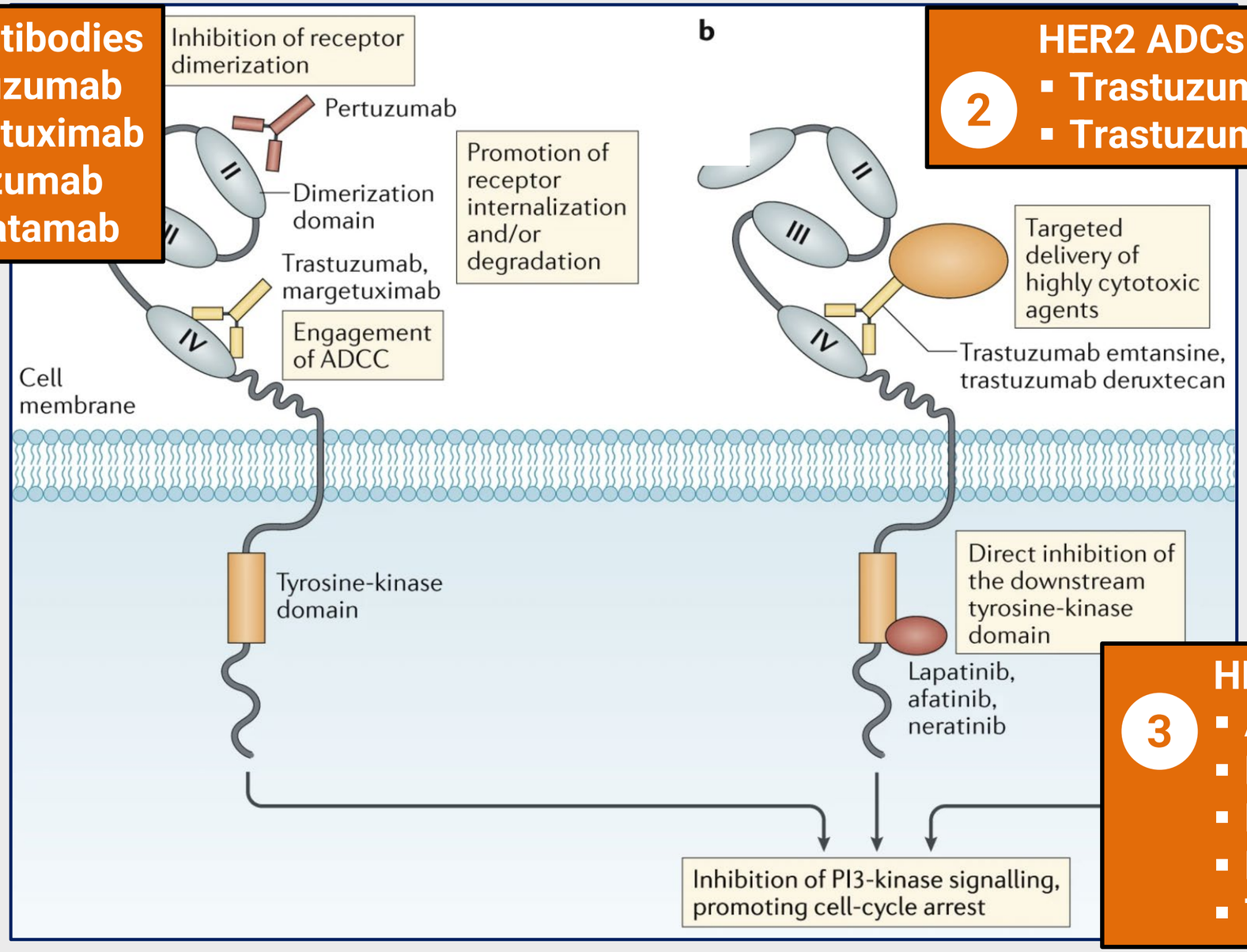
CCA = cholangiocarcinoma; dMMR = mismatch repair deficient; FR = folate receptor; IHC = immunohistochemistry; LMS = leiomyosarcoma; MMR = mismatch repair; MSI-H = microsatellite instability-high; NCCN = National Comprehensive Cancer Network; PD-L1 = programmed cell death ligand 1; T-DXd = trastuzumab deruxtecan; TMB-H = tumor mutational burden-high.

NCCN Guidelines. Treatment by cancer type (https://www.nccn.org/guidelines/category_1). FDA. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-combination-avutometinib-and-defactinib-kras-mutated-recurrent-low. Pembrolizumab. Prescribing information. 4/2025. Accessed 11/8/2024.

Strategies to Target HER2 Alterations

1 HER2 antibodies
- Trastuzumab
- Margetuximab
- Pertuzumab
- Zanidatamab

2 HER2 ADCs
- Trastuzumab emtansine
- Trastuzumab deruxtecan



3 HER2 TKIs
- Afatinib*
- Lapatinib
- Neratinib
- Pyrotinib
- Tucatinib

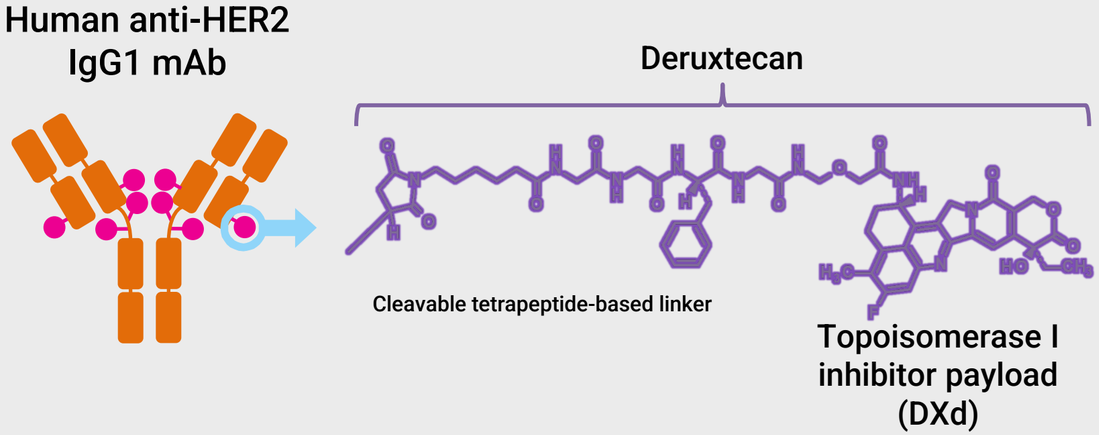
ADC = antibody-drug conjugate; ADCC = antibody-dependent cellular cytotoxicity; PI = phosphatidylinositol; TKI = tyrosine kinase inhibitor.
Adapted from Oh DY, Bang YJ. *Nat Rev Clin Oncol*. 2020;17:33-48.

*Afatinib is not approved by the FDA to treat HER2+ solid tumors.

Trastuzumab Deruxtecan (T-DXd): Pan-Tumor Approval

- April 2024: FDA granted accelerated approval to T-DXd for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options[1]

T-DXd[2,3]



Drug:antibody ratio = 7-8

The FDA-approved pantumor indication for T-DXd is specific to IHC 3+ solid tumors.

IgG1 = immunoglobulin 1; mAb = monoclonal antibody.

1. FDA. 4/5/24 (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2). Accessed 4/29/25.
2. Jerusalem G, *Cancer Discov.* 2022;12:2754-2762. 3. Habara H, et al. *Biopharm Drug Dispos.* 2023;44:380-384

T-DXd Pan-Tumor Use as Subsequent-Line Therapy for HER2+ Advanced/Metastatic Disease Now Included in NCCN Guidelines

—Examples—

Ovarian, Endometrial, and Cervical Cancer)	▪ HER2 IHC 3+ or 2+ (category 2A for endometrial, platinum-resistant ovarian, and cervical; 2B for platinum-sensitive ovarian)
Biliary Tract Cancers	▪ As subsequent-line systemic therapy for HER2 positive [IHC 3+] tumors (category 2A)
Pancreatic Cancer	▪ As subsequent-line systemic therapy for HER2 positive [IHC 3+ or IHC 2+ with FISH HER2 amplified] disease (category 2A)
Bladder Cancer	▪ As subsequent-line therapy HER2 positive [IHC 3+] disease (category 2A)

FISH = fluorescence in situ hybridization.

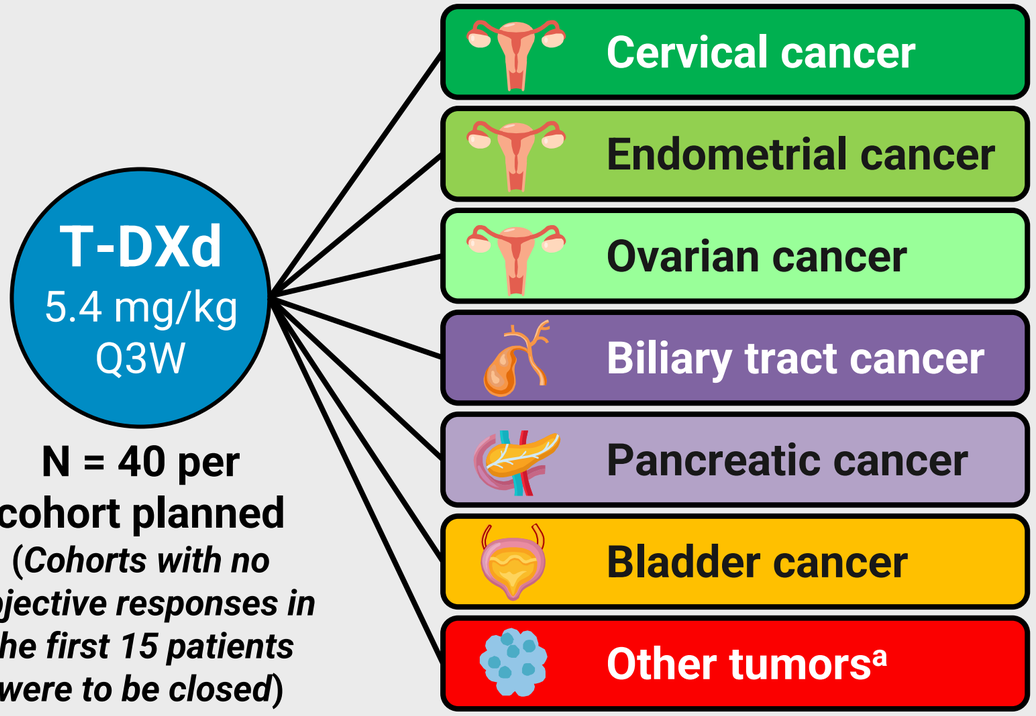
NCCN Guidelines. Treatment by cancer type (https://www.nccn.org/guidelines/category_1). Accessed 4/22/2025.

*T-DXd FDA-approved indication is limited to IHC 3+ solid tumors, except for breast and gastric cancers.

Open-Label, Phase 2 DESTINY-PanTumor02 Study of T-DXd for HER2-Expressing Solid Tumors

Tumor types 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 Hercep Test if local test not feasible (ASCO/CAP gastric cancer guidelines)
- Prior HER2-targeting therapy permitted
- ECOG/WHO PS 0–1 restricted in strenuous activity



N = 40 per cohort planned
(***Cohorts with no objective responses in the first 15 patients were to be closed***)

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR
- DCR
- PFS
- OS
- Safety

Data cutoff for analysis

- June 8, 2023

[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; ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; Q3W = every 3 weeks; WHO = World Health Organization.

Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42:47-58. Clinicaltrials.gov. NCT04482309 (https://clinicaltrials.gov/study/NCT04482309). Accessed 04/30/25.

*T-DXd FDA-approved indication is limited to IHC 3+ solid tumors, except for breast and gastric cancers.

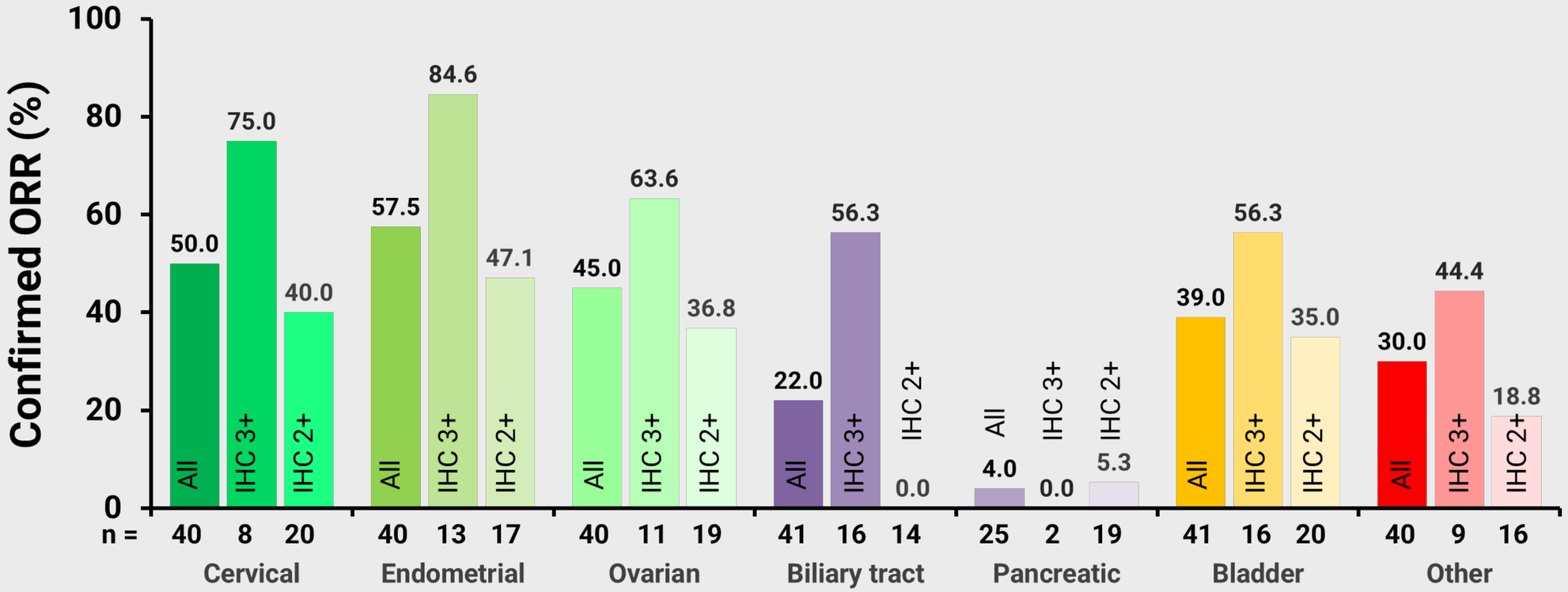
Phase 2 DESTINY-PanTumor02 Study: Baseline Characteristics

Baseline characteristics	Cervical cancer (n = 40)	Endometrial cancer (n = 40)	Ovarian cancer (n = 40)	Biliary tract cancer (n = 41)	Pancreatic cancer (n = 25)	Bladder cancer (n = 41)	Other tumors (n = 40)
Age, years, median	49	67	56	64	62	67	61
Female, %	100	100	100.0	51.2	40.0	34.1	32.5
Race, %							
White	72.5	57.5	55.0	48.8	68.0	61.0	67.5
Black or African American	0	10.0	2.5	0	4.0	0	0
Asian	17.5	25.0	42.5	51.2	24.0	39.0	25.0
ECOG performance status, %							
0	55.0	57.5	65.0	31.7	32.0	46.3	37.5
1	45.0	42.5	32.5	68.3	68.0	53.7	62.5
2	0	0	2.5	0	0	0	0
Prior therapy lines							
Median (range)	2 (1–6)	2 (0–7)	3 (1–12)	2 (1–5)	2 (1–4)	2 (0–9)	2 (0–8)
0, %	0	2.5	0	0	0	2.4	2.5
1, %	15.0	20.0	20.0	34.1	28.0	31.7	37.5
2, %	37.5	45.0	20.0	36.6	44.0	19.5	22.5
3, %	22.5	15.0	12.5	22.0	24.0	24.4	25.0
4, %	15.0	7.5	12.5	4.9	4.0	9.8	0
≥ 5, %	10.0	10.0	35.0	2.4	0	12.2	12.5
Prior HER2 therapy, % of patients	2.5	22.5	5.0	17.1	8.0	7.3	35.0
Trastuzumab	2.5	12.5	5.0	14.6	8.0	7.3	35.0
Pertuzumab	2.5	0	0	2.4	0	2.4	5.0
Zanidatamab	0	5.0	0	2.4	0	0	2.5
Trastuzumab emtansine	2.5	2.5	0	0	0	2.4	0
Trastuzumab duocarmazine	0	2.5	0	0	0	0	0
Tucatinib	0	0	0	0	4.0	0	0

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

*T-DXd FDA-approved indication is limited to IHC 3+ solid tumors, except for breast and gastric cancers.

Phase 2 DESTINY-PanTumor02 Study: Objective Response Rate by HER2 Status — Primary Analysis (N = 267)



	All patients	IHC 3+
Median DOR	11.3 months (range, 5.7–22.1)	22.1 months

Median follow-up: 12.75 months.

CI = confidence interval; NR = not reached.

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

*T-DXd FDA-approved indication is limited to IHC 3+ solid tumors, except for breast and gastric cancers.

Phase 2 DESTINY-PanTumor02 Study: Baseline Characteristics — HER2 Testing/Expression

Baseline characteristics	Cervical cancer (n = 40)	Endometrial cancer (n = 40)	Ovarian cancer (n = 40)	Biliary tract cancer (n = 41)	Pancreatic cancer (n = 25)	Bladder cancer (n = 41)	Other tumors (n = 40)
HER2 testing for eligibility,[a] %							
Local	57.5	77.5	92.5	82.9	60.0	80.5	72.5
Central	42.5	22.5	7.5	17.1	40.0	19.5	27.5
HER2 IHC status (eligibility), %							
IHC 3+	25.0	40.0	37.5	53.7	20.0	65.9	40.0
IHC 2+	62.5	60.0	62.5	46.3	80.0	34.1	60.0
IHC 1+	12.5	0	0	0	0	0	0
Centrally confirmed HER2 IHC status, %							
IHC 3+	20.0	32.5	27.5	39.0	8.0	39.0	22.5
IHC 2+	50.0	42.5	47.5	34.1	76.0	48.8	40.0
IHC 1+	20.0	10.0	12.5	7.3	4.0	4.9	5.0
IHC 0	10.0	12.5	12.5	17.1	12.0	4.9	10.0

[a]HER2 expression for eligibility based on local assessment/testing.

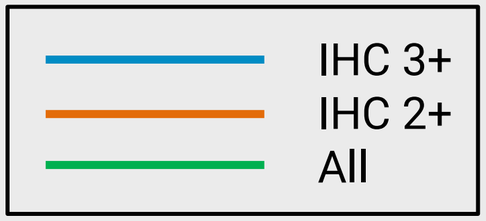
Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42:47-58.

*T-DXd FDA-approved indication is limited to IHC 3+ solid tumors, except for breast and gastric cancers.

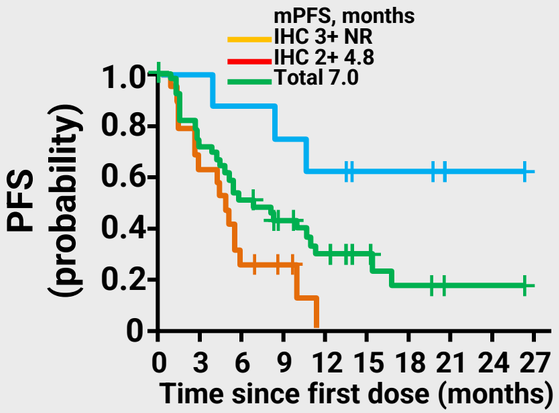
Phase 2 DESTINY-PanTumor02 Study: Progression-Free Survival (INV) by Tumor Type and HER2 Expression Level

mPFS (INV) across all cohorts: 6.9 months

- Longest mPFS by cohort
  - 11.1 months, endometrial cohort
- Longest mPFS in all HER2 subgroups
  - 11.9 months, IHC 3+



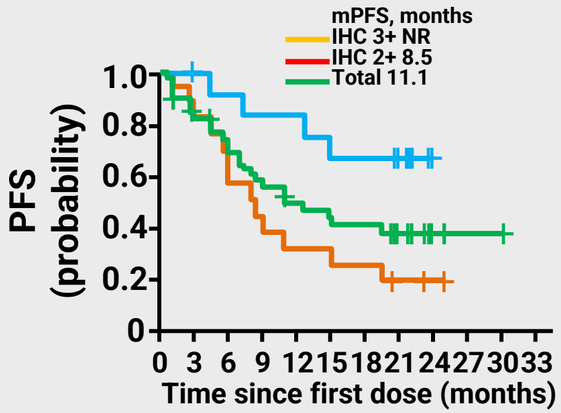
Cervical



No. at risk for cervical cancer

IHC 3+	8	8	7	6	5	3	3	1	1	0
IHC 2+	20	12	5	3	0					
Total	40	28	20	14	9	6	3	1	1	0

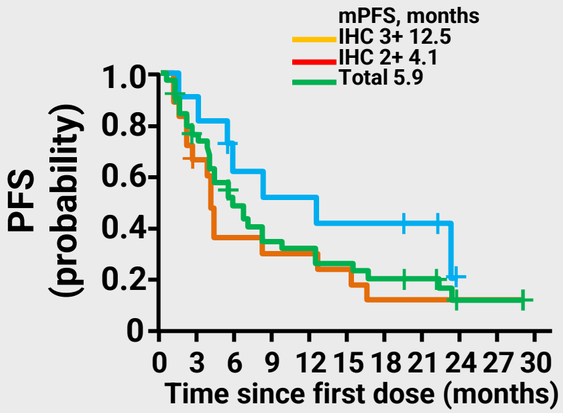
Endometrial



No. at risk for endometrial cancer

IHC 3+	13	12	11	10	10	9	8	5	0			
IHC 2+	17	14	11	7	5	5	4	2	1	0		
Total	40	31	27	21	17	16	14	8	2	1	1	0

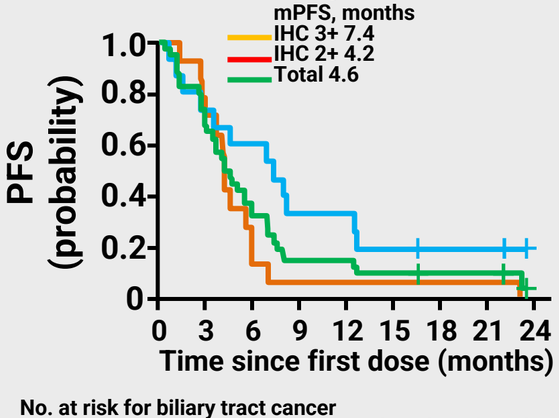
Ovarian



No. at risk for ovarian cancer

IHC 3+	11	10	6	5	5	4	4	3	0		
IHC 2+	19	11	6	5	5	4	2	2	1	1	0
Total	40	28	17	12	11	9	7	6	1	1	0

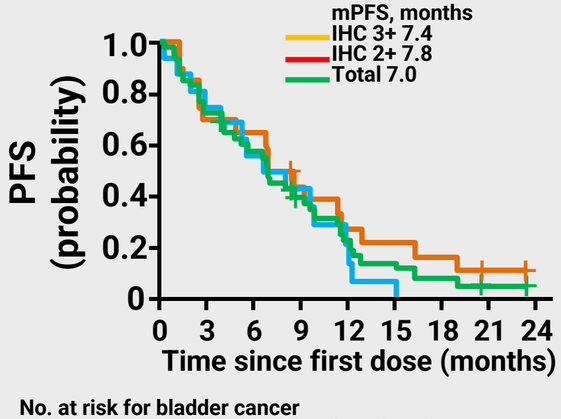
Biliary tract



No. at risk for biliary tract cancer

IHC 3+	16	11	9	5	5	3	2	2	0
IHC 2+	14	10	3	1	1	1	1	1	0
Total	41	27	14	6	6	4	3	3	0

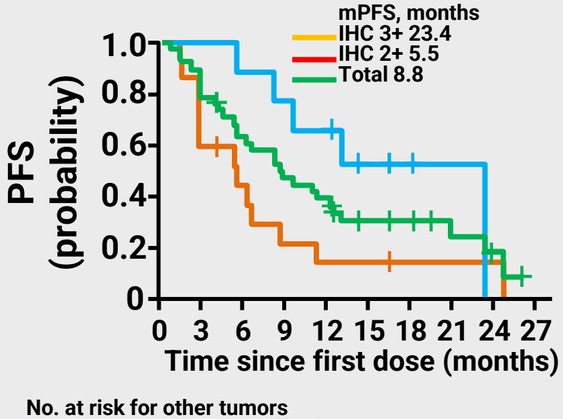
Bladder



No. at risk for bladder cancer

IHC 3+	16	12	9	6	3	1	0		
IHC 2+	20	14	13	8	5	4	3	1	0
Total	41	29	23	14	8	5	3	1	0

Other



No. at risk for other tumors

IHC 3+	9	9	8	7	6	3	2	1	0	
IHC 2+	16	9	6	3	2	2	1	1	1	0
Total	40	31	24	18	15	9	7	4	2	0

INV = investigator assessed; m = median.

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

*T-DXd FDA-approved indication does not include IHC 2+ solid tumors other than breast and gastric cancers.

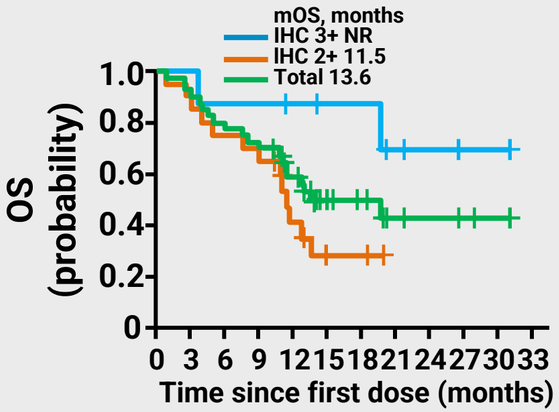
Phase 2 DESTINY-PanTumor02 Study: Overall Survival by Tumor Type and HER2 Expression Level

mOS across all cohorts: 13.4 months

- Longest mOS by cohort
  - 26.0 months, endometrial cohort
- Longest mOS in all HER2 subgroups
  - 21.1 months, IHC 3+

IHC 3+
IHC 2+
All

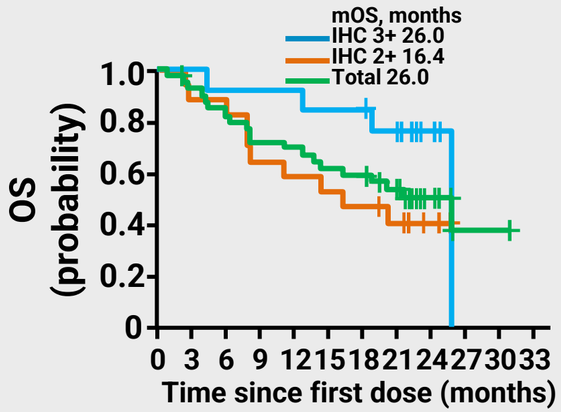
Cervical



No. at risk for cervical cancer

IHC 3+	8	8	7	7	6	5	5	3	2	1	1	0
IHC 2+	20	18	15	14	7	3	3	0				
Total	40	37	32	29	21	11	9	4	3	2	1	0

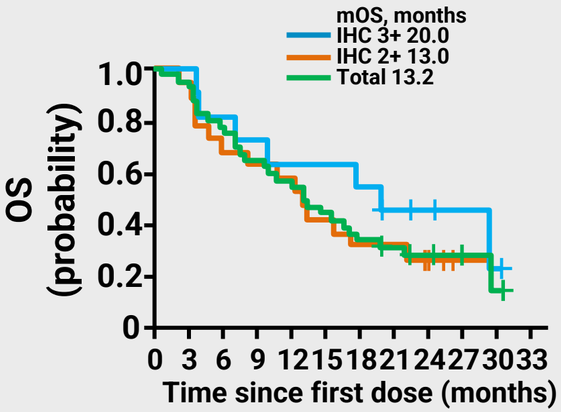
Endometrial



No. at risk for endometrial cancer

IHC 3+	13	13	12	12	12	11	11	9	4	0		
IHC 2+	17	15	15	11	10	9	8	6	3	0		
Total	40	36	33	28	27	24	23	19	9	1	1	0

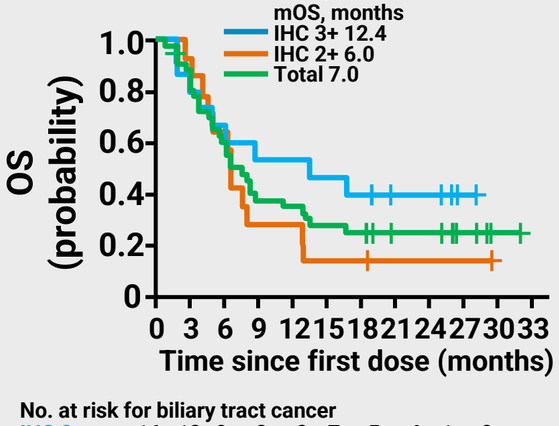
Ovarian



No. at risk for ovarian cancer

IHC 3+	11	11	9	8	7	7	6	4	3	2	1	0
IHC 2+	19	18	13	12	11	8	6	6	4	1	0	
Total	40	38	30	25	22	17	13	11	8	3	1	0

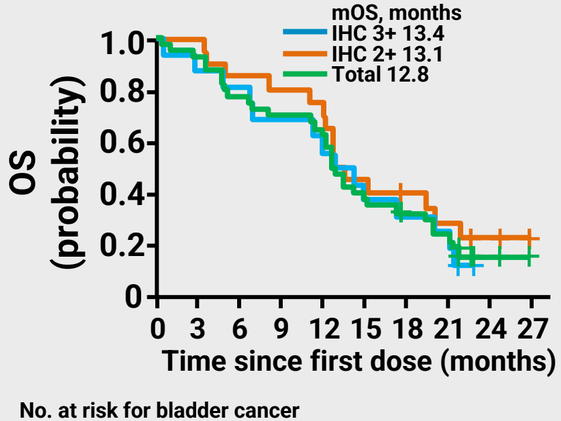
Biliary Tract



No. at risk for biliary tract cancer

IHC 3+	16	12	9	8	8	7	5	4	1	0		
IHC 2+	14	12	7	4	2	2	1	1	1	0		
Total	41	32	21	16	12	11	8	7	4	1	0	

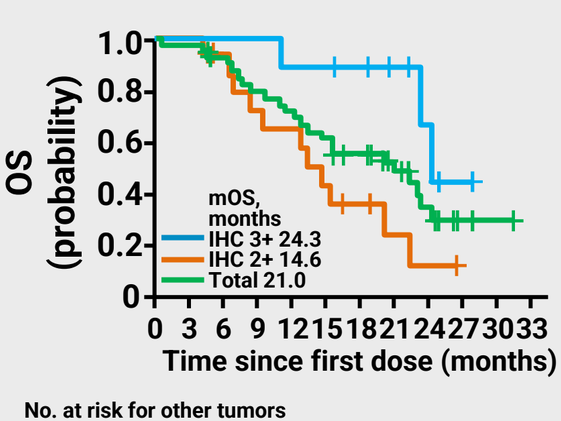
Bladder



No. at risk for bladder cancer

IHC 3+	16	14	13	11	9	6	5	4	0	
IHC 2+	20	20	17	16	15	9	7	5	2	0
Total	41	37	31	28	25	15	12	9	2	0

Other



No. at risk for other tumors

IHC 3+	9	9	9	9	8	8	7	5	3	1	0	
IHC 2+	16	16	13	10	9	6	4	2	1	0		
Total	40	39	35	30	27	23	19	13	7	2	1	0

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

*T-DXd FDA-approved indication does not include IHC 2+ solid tumors other than breast and gastric cancers.

Phase 2 DESTINY-PanTumor02 Study: Drug-Related Adverse Events

Adverse event	Cervical cancer (n = 40)	Endometrial cancer (n = 40)	Ovarian cancer (n = 40)	Biliary tract cancer (n = 41)	Pancreatic cancer (n = 25)	Bladder cancer (n = 41)	Other tumors (n = 40)
Drug-related AE, %	90.0	90.0	85.0	80.5	60.0	92.7	85.0
Grade ≥ 3	47.5	35.0	52.5	39.0	28.0	41.5	37.5
Serious AEs	7.5	10.0	27.5	12.2	12.0	9.8	15.0
Leading to discontinuation	7.5	7.5	2.5	12.2	4.0	9.8	15.0
Leading to dose modification*	32.5	32.5	45.0	31.7	0	36.6	32.5
Associated with death	0	5.0	0	0	0	2.4	2.5
Most common drug-related AEs (> 10% of total patients), % of patients							
Nausea	65.0	72.5	55.0	46.3	28.0	51.2	57.5
Anemia	37.5	17.5	37.5	24.4	16.0	29.3	27.5
Diarrhea	37.5	40.0	20.0	19.5	12.0	31.7	15.0
Fatigue	22.5	25.0	27.5	22.0	16.0	26.8	30.0
Vomiting	25.0	40.0	17.5	22.0	12.0	14.6	37.5
Neutropenia	20.0	10.0	12.5	22.0	16.0	26.8	22.5
Decreased appetite	17.5	20.0	20.0	17.1	8.0	19.5	17.5
Asthenia	22.5	27.5	15.0	14.6	12.0	7.3	20.0
Alopecia	20.0	22.5	12.5	22.0	8.0	12.2	17.5
Thrombocytopenia	5.0	5.0	12.5	12.2	12.0	14.6	17.5

- Drug-related AEs led to discontinuation in 8.6% of patients and to dose reduction in 20.2% of patients

*Dose modification includes AEs with action taken of dose reduced or drug interrupted. AEs associated with death included pneumonia (n = 1), organizing pneumonia (n = 1), pneumonitis (n = 1), and neutropenic sepsis (n = 1).

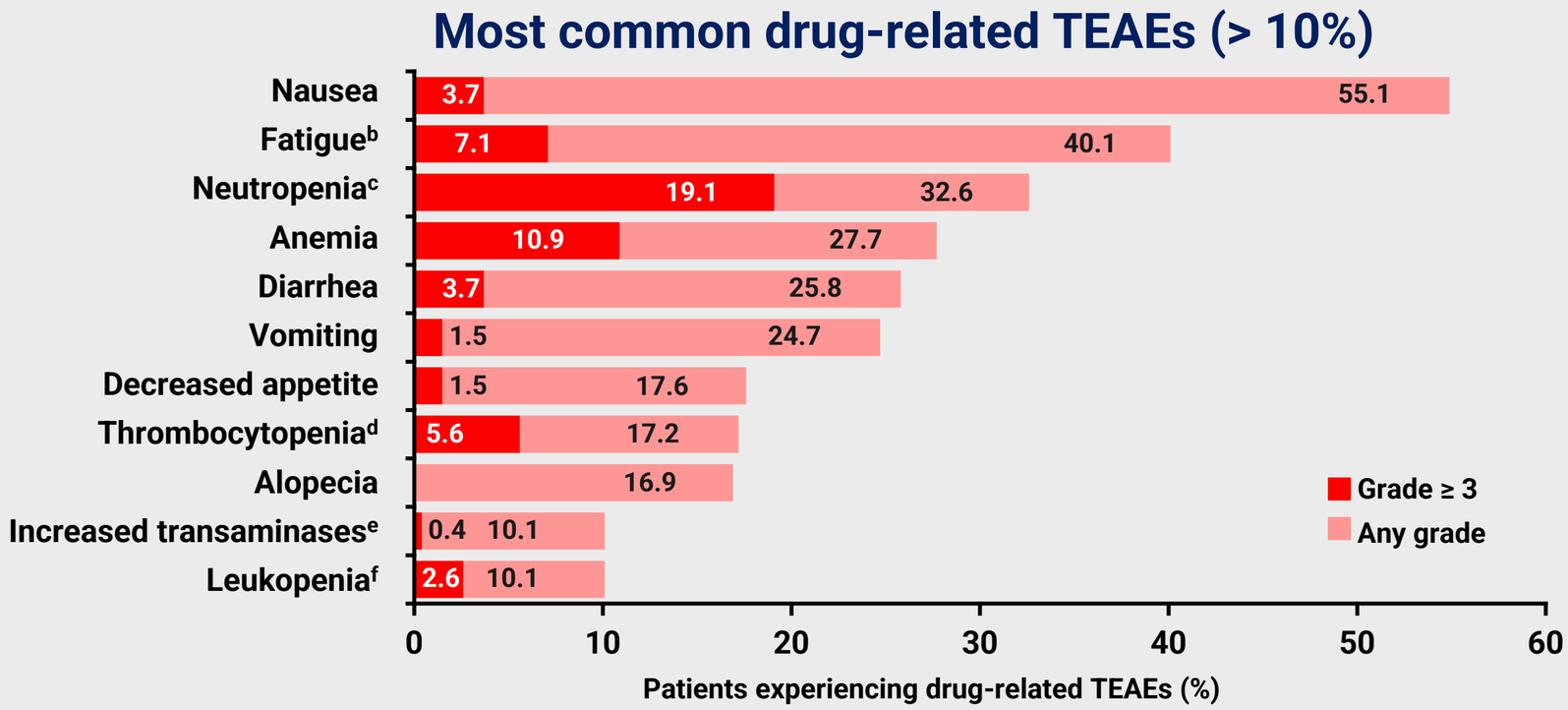
AE = adverse event.

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

*T-DXd FDA-approved indication is limited to IHC 3+ solid tumors, except for breast and gastric cancers.

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]



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; TEAE = treatment-emergent adverse event.

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

*T-DXd FDA-approved indication is limited to IHC 3+ solid tumors, except for breast and gastric cancers.

Now, let’s go to a question…

Question 1

How often are you using T-DXd to treat HER2-overexpressing solid tumors other than breast or gastric/GEJ cancers?

a) Frequently

b) Sometimes

c) Rarely

d) Never

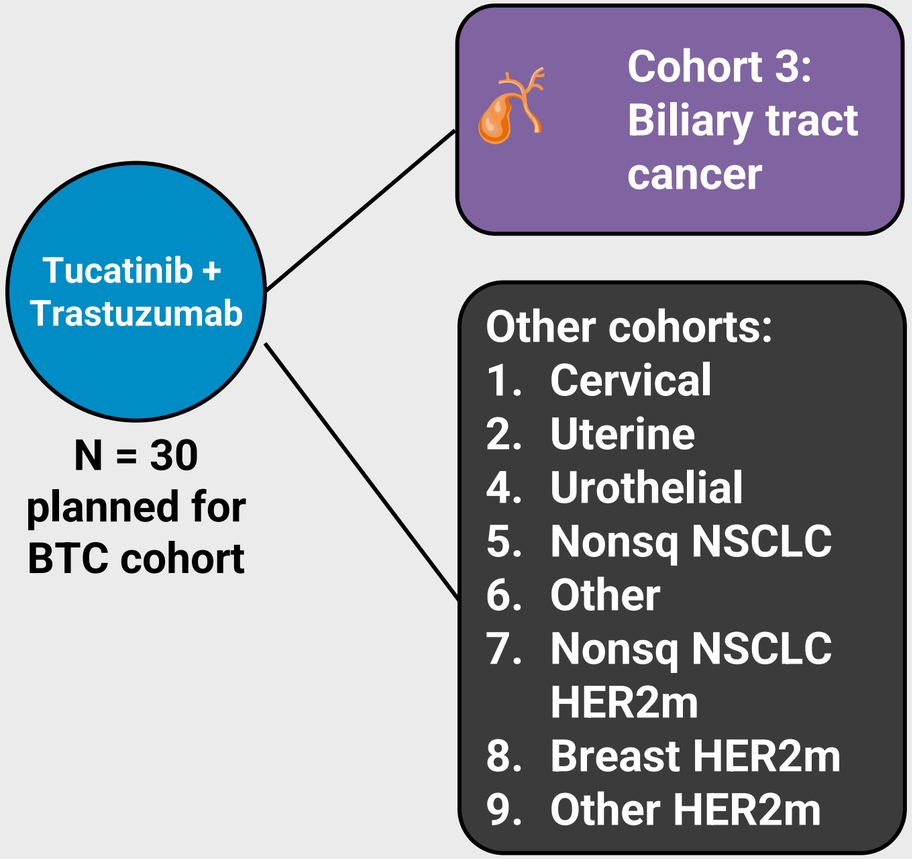
Clinical Trial Data on Use of Other HER2-Targeted Therapies

HER2-Expressing Gynecological, Bladder, Biliary Tract, and Other Tumors

SGNTUC-019, Phase 2 Basket Study: Tucatinib + Trastuzumab for HER2+ Solid Tumors — mBTC 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 metastatic disease
- No prior HER2-directed therapy



Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- Safety
- DCR
- DOR
- PFS
- OS

Data cutoff for analysis

- January 30, 2023

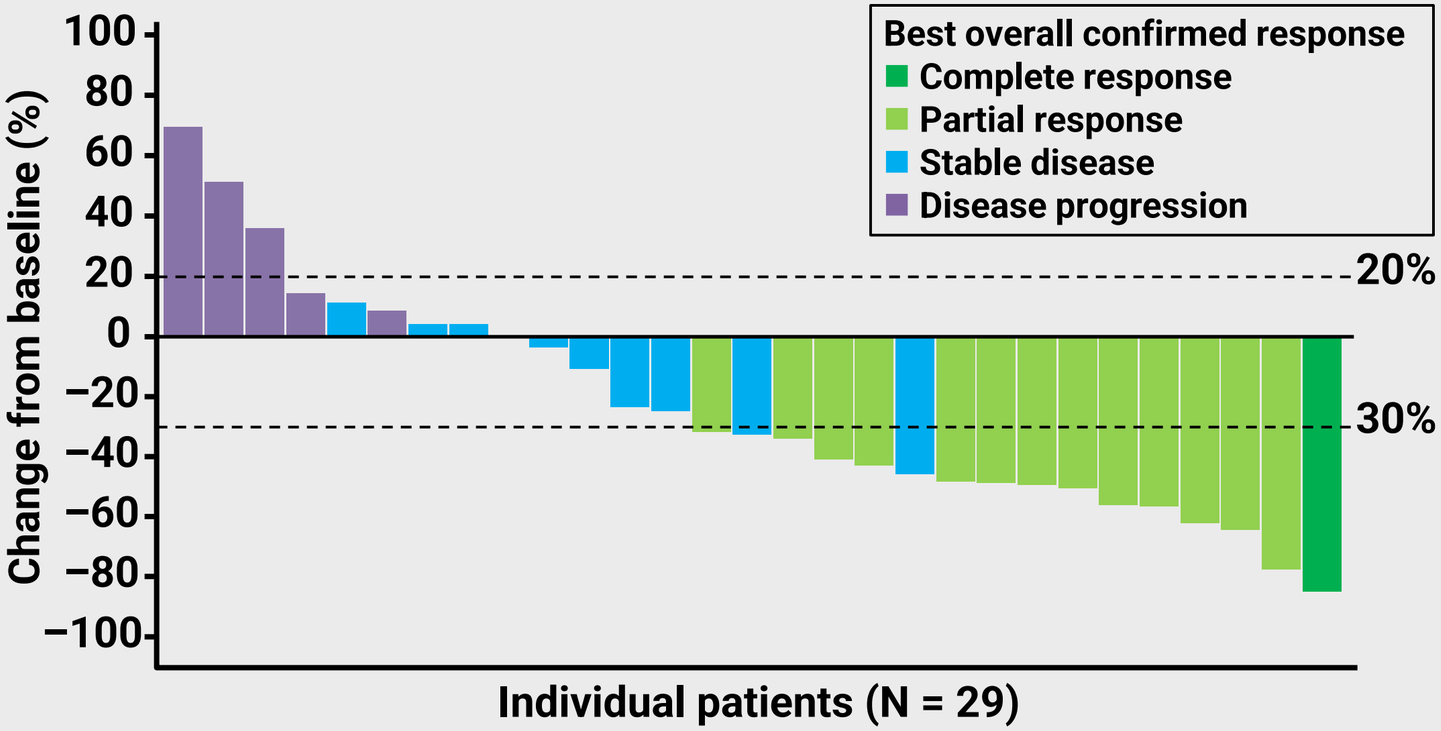
BID = 2 times a day; HER2m = HER2 mutated; ISH = in situ hybridization; IV = intravenously; LA = locally advanced; mBTC = metastatic biliary tract cancer; NGS = next-generation sequencing; nonsq = nonsquamous; PO = by mouth.

Nakamura Y, et al. *J Clin Oncol.* 2023;41:5569-5578. Stinchcombe T, et al. *J Clin Oncol.* 2021;39(15_suppl):TPS3151.

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

SGNTUC-019, Phase 2 Basket Study:
Tucatinib + Trastuzumab for HER2+ Solid Tumors — mBTC Cohort

Maximum change in tumor size



	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

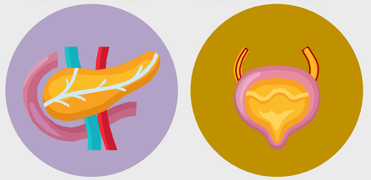
Data cutoff: January 30, 2023.

CR = complete response; PR = partial response; SD = stable disease.

Nakamura Y, et al. *J Clin Oncol.* 2023;41:5569-5578.

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

Phase 2 KAMELEON Study: T-DM1 for HER2+ Advanced UC or Pancreatic Cancer/Cholangiocarcinoma



Target population:

- HER2+ 2L+ without treatment options
- Locally advanced/ metastatic IHC 3+, non-focal (≥ 30% stained cells)
- ECOG PS: 0–2
- Stratification by tumor cell heterogeneity: 30%–70% and ≥ 71% of HER2 IHC 3+ stained tumor cells

Regimen A

Trastuzumab emtansine 2.4 mg/kg, QW (n = 6 per cohort[a])

Dose decision (tolerability)

Stopping Rule: Check for response after 13 patients enrolled in a cohort

Trastuzumab emtansine 2.4 mg/kg, QW (N = 26 per cohort[a])

Regimen B

Trastuzumab emtansine 3.6 mg/kg, Q3W (N = 32 per cohort[a])

PD Toxicity Withdrawal

Endpoints

Primary:
Best overall response (INV)

Secondary:
PFS (INV)
OS
Safety

- **Due to recruitment difficulty, the sponsor terminated KAMELEON prematurely and is unable to address primary and secondary objectives fully.**

[a]Planned.

PD= progressive disease; QW = weekly; T-DM1 = trastuzumab emtansine; UC = urothelial carcinoma.

de Vries EGE, et al. *Cancer Med.* 2023;12:12071-12083 and supplement. Clinicaltrials.gov. NCT02999672 (https://clinicaltrials.gov/study/NCT02999672). Accessed 4/30/2025.

T-DM1 is not approved by the FDA for these indications.

Phase 2 KAMELEON Study: T-DM1 for HER2+ Advanced UC or Pancreatic Cancer/Cholangiocarcinoma — Results

	Urothelial bladder cancer (n = 13)	Pancreatic cancer/cholangiocarcinoma (n = 7)
Median duration of follow-up, months	7.39	9.23
Median duration of exposure to T-DM1, weeks (range)	7.14 (0.1–27.0)	16.14 (4.1–41.4)
ORR, %	38.5	14.3
CR	0	0
PR	5 (38.5)	1 (14.3)
SD	1 (7.7)	3 (42.9)
PD	6 (46.2)	2 (28.6)
Median DOR, months	3.38	—*
PFS		
Events, n (%)	13 (100.0)	6 (85.7)
Median PFS, months	2.20	2.58
OS		
Events, n (%)	7 (53.8)	1 (14.3)
Median OS, months (95% CI)[a]	7.03	NE

- AEs observed were generally consistent with T-DM1's known safety profile

[a] Duration of response in patient in pancreatic cancer/cholangiocarcinoma cohort with a PR (n = 1) was 8.6 months.

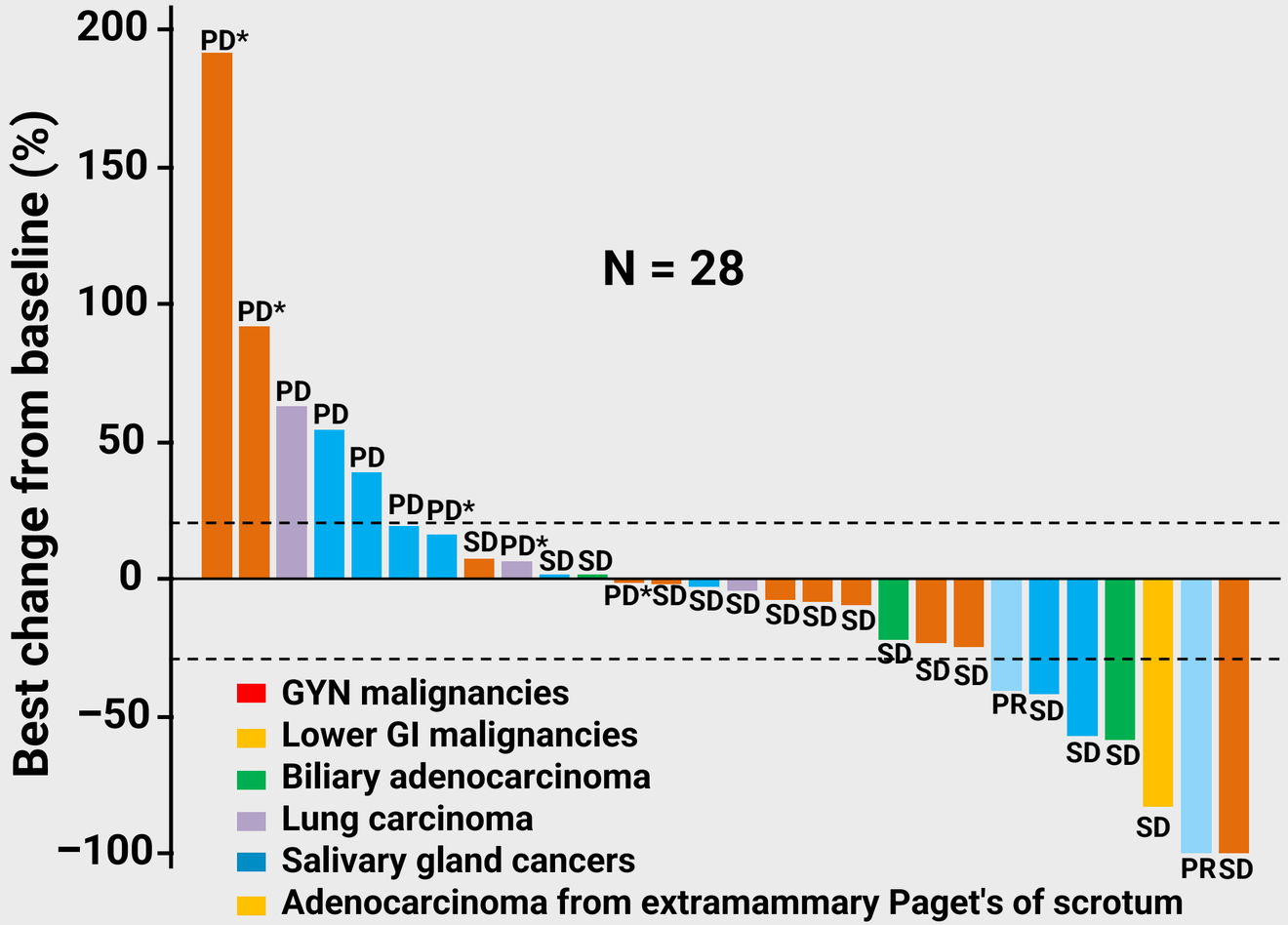
de Vries EGE, et al. *Cancer Med.* 2023;12:12071-12083.

T-DM1 is not approved by the FDA for these indications.

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
- 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.

Eligible patients had *HER2* amplification at a copy number > 7 based on targeted NGS with a custom Oncomine AmpliSeq™ (ThermoFisher Scientific) panel.

GEJ = gastroesophageal junction; GI = gastrointestinal; GYN = gynecologic.

Jhaveri KL, et al. *Ann Oncol.* 2019;30:1821-1830.

T-DM1 is not approved by the FDA for these indications.

Now let’s go to a question…

Question 2

Have you had an opportunity to use zanidatamab?

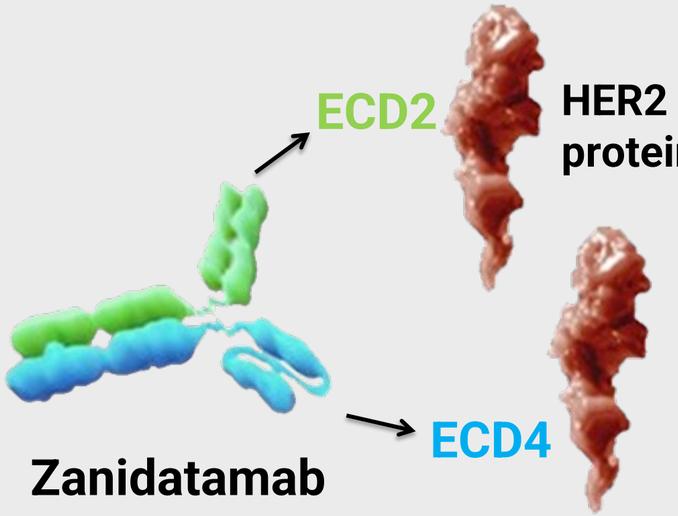
a) Yes, under its approved indication for BTC

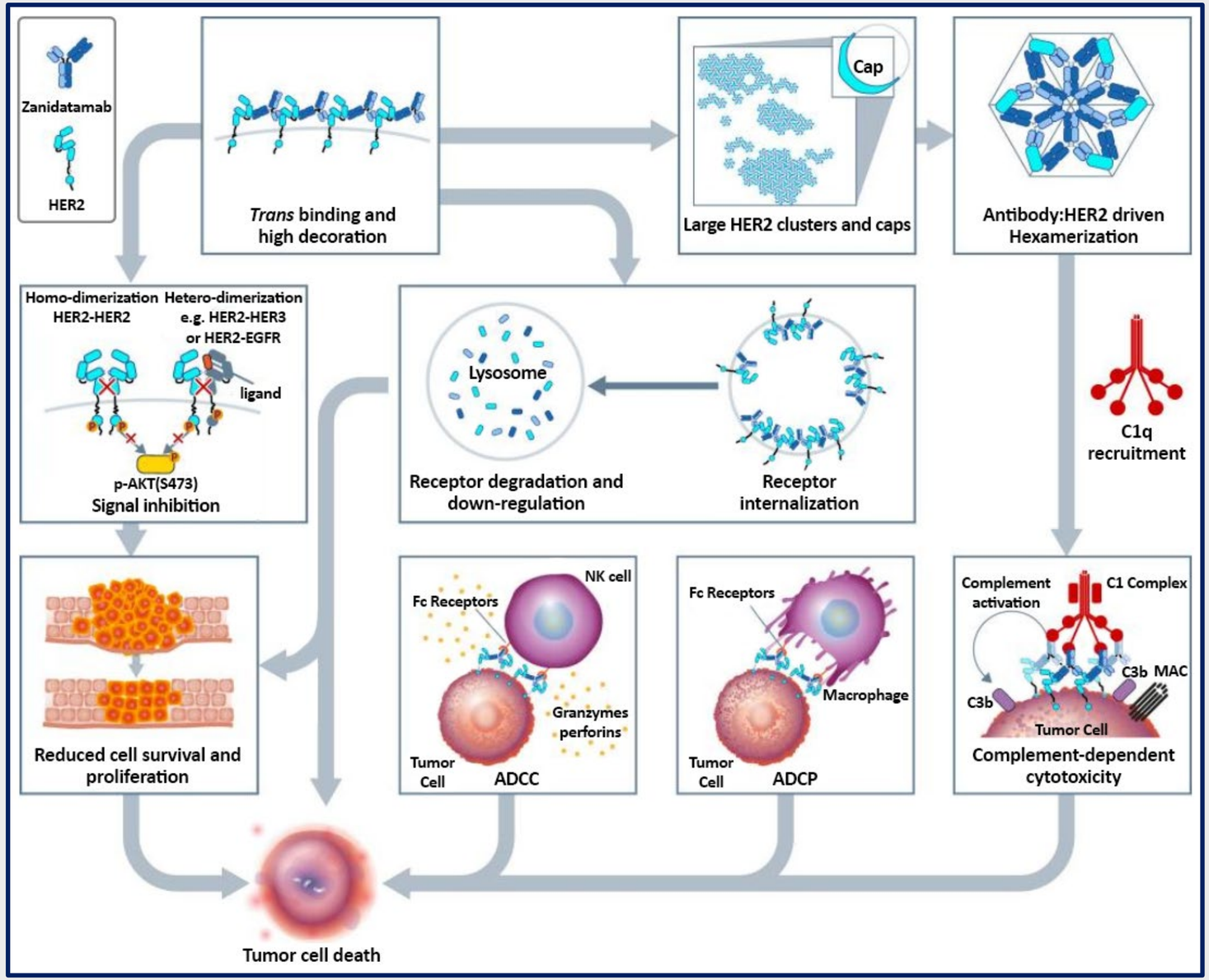
b) Yes, on a clinical trial

c) No

Novel HER2-Directed Bispecific, Biparatopic Therapeutic Antibody: Multiple Mechanisms of Action Contribute to Antitumor Activity

Zanidatamab binds two HER2 molecules simultaneously and in *trans*





ADCP = antibody-dependent cellular phagocytosis; ECD = extracellular domain; Fc = fragment crystallizable region; NK = natural killer.

Weisser N, et al. *Nat Commun*. 2023;14:1394.

Phase 2b HERIZON-BTC-01 Study: ASCO 2024 – Updated Efficacy With Additional Follow-Up

Median follow up: 21.9 mo[1]

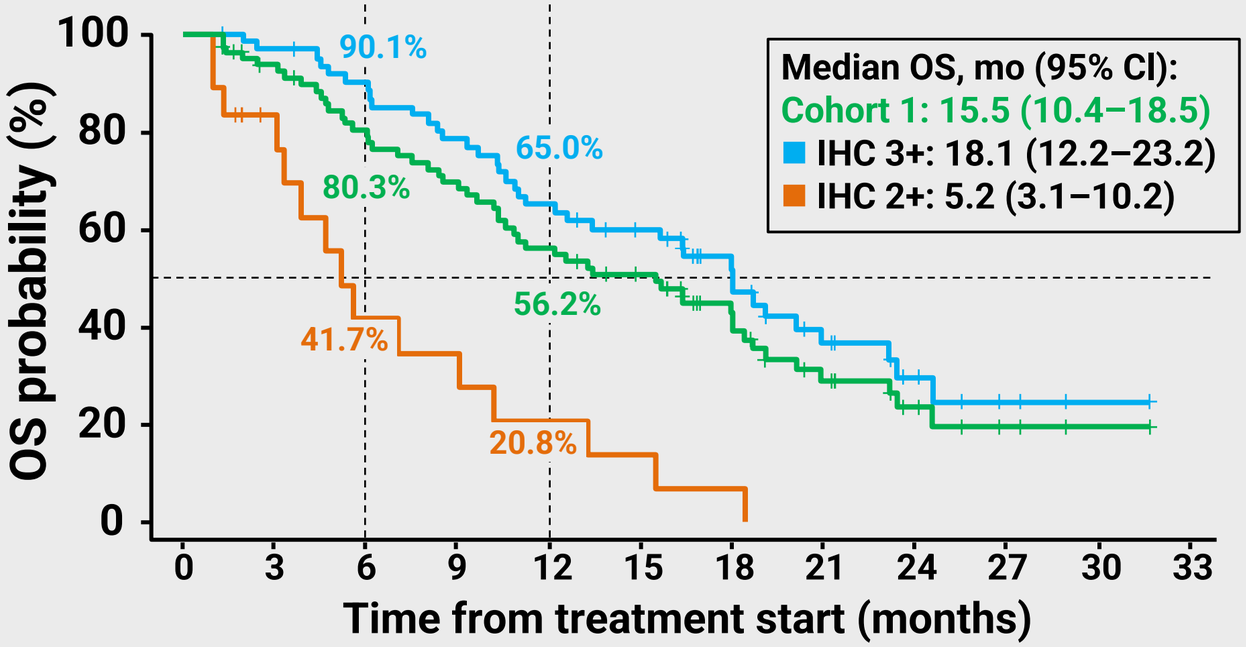
cORR = 41% (unchanged from prior analysis[2])

- 1 additional patient achieved a CR
- Preplanned analysis by HER2 expression
  - IHC 3+, cORR = 52%
  - IHC 2+, cORR = 6%

mDOR = 15 mo (from 13 months)

- IHC 3+ tumors, 15 mo
- IHC 2+ (n = 1), 8 mo

Overall Survival



No. at risk												
IHC 3+	62	59	54	47	39	33	23	13	7	3	1	0
IHC 2+	18	12	6	5	3	2	1	0	0	0	0	0
Overall	80	71	60	52	42	35	24	13	7	3	1	0

c = confirmed; mo = months.

1. Pant S, et al. ASCO 2024; Abstract 4091. 2. Harding JJ, et al. *Lancet Oncol.* 2023;24:772-782.

*Zanidatamab FDA-approved indication is limited to BTC IHC 3+ tumors.

Phase 2b HERIZON-BTC-01 Clinical Trial: Zanidatamab for HER2+, Unresectable, Locally Advanced or Metastatic BTC – Safety

	Cohort 1 (N = 80)	
	Any Grade	Grade ≥ 3
Any TEAE, %	97.5	57.5
Any TRAE, %	76.3	18.8
Serious TRAE, %	8.8	8.8
TRAEs leading to treatment discontinuation, %	2.5	1.3
TRAEs leading to death, %	0	0
TRAEs, any Grade occurring in ≥ 10% of patients or Grade ≥ 3 in ≥ 2 patients, (%)		
Diarrhea	40.0	5.0
Infusion-related reaction	35.0	1.3
Ejection fraction decreased	10.0	3.8
Nausea	10.0	1.3
Anemia	5.0	2.5

2 TRAEs led to zanidatamab discontinuation

- 1 Grade 2 ejection fraction decreased
- 1 Grade 3 pneumonitis

3 patients had TRAES that led to dose reductions

- 1 Grade 3 diarrhea
- 1 Grade 3 diarrhea and Grade 3 nausea
- 1 Grade 2 weight decreased

No serious TRAEs occurred in more than 1 patient

No Grade 4 TRAEs; no treatment-related deaths

Phase 3 study of first-line SOC ± zanidatamab is now recruiting.

SOC = standard of care; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event.

Pant S, et al. ASCO 2023; Abstract 4008. Harding JJ, et al. *Lancet Oncol.* 2023;24:772-782. Harding JJ, et al. ASCO 2025; Abstract TPS648.

*Zanidatamab FDA-approved indication is limited to BTC IHC 3+ tumors.

ASCO 2025 Preview

Phase 3 DESTINY-Gastric04 Primary Analysis: T-DXd vs ramucirumab + paclitaxel in second-line treatment of patients with HER2+ unresectable/metastatic gastric cancer or GEJ adenocarcinoma. Shitara K, et al. Abstract LBA4002.

TROPION-Lung02: Dato-DXd + pembrolizumab ± platinum chemotherapy as first-line therapy for advanced NSCLC. Levy BP, et al. Abstract 8501.

DESTINY-Breast09 Interim Results: T-DXd + pertuzumab vs taxane + trastuzumab + pertuzumab for first-line treatment of patients with HER2+ advanced/metastatic breast cancer. Tolaney SM, et al. Abstract #LBA1008.

Adverse Event Monitoring and Management Best Practices With HER2-Targeted Therapies Across HER2-Positive Tumors

Now let’s watch a video that provides an overview of adverse events associated with use of ADCs

Now let’s watch a video that provides an overview of adverse events associated with use of ADCs

Insert animation: *Differences in the AE profiles of ADCs used for the treatment of HER2-positive solid tumors*

AE Profiles of ADCs Used for the Treatment of HER2-Positive Solid Tumors

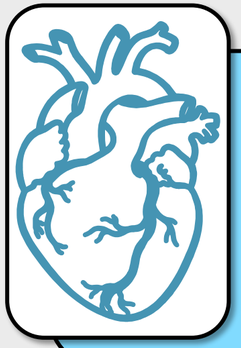
Approved HER2-directed ADC	Common AEs (any Grades)	Common Grade ≥ 3 AEs
Trastuzumab emtansine	Thrombocytopenia Elevated transaminases Fatigue Anemia Nausea	Thrombocytopenia Increased aspartate aminotransferase levels Anemia
Trastuzumab deruxtecan	GI (nausea, vomiting, diarrhea, constipation) Cytopenia (neutropenia, anemia, leukopenia, thrombocytopenia) Fatigue Alopecia Decreased appetite	Neutropenia Anemia Nausea Leukopenia Lymphopenia Fatigue

Adapted from Nguyen TD, et al. *Cancers (Basel).* 2023;15:713.

T-DXd: Adverse Event Management

Anemia/neutropenia/thrombocytopenia

- Dose reductions or delays
- Transfusion
- G-CSF for prevention and/or management of neutropenia

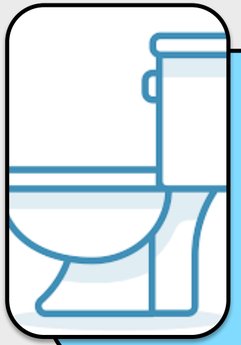


Left ventricular dysfunction

- Baseline LVEF and regular monitoring (every 3–4 months)
- Dose delay/discontinuations

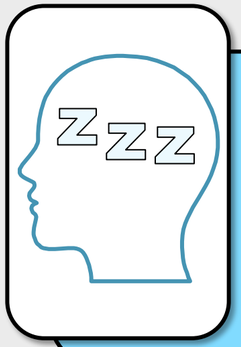
Nausea/vomiting

- High emetic risk
- Initiate tailored prophylactic antiemetic regimens (3 agents) before T-DXd infusion



Diarrhea

- Infectious workup
- Loperamide/fluid/electrolyte
- Atropine for severe diarrhea with cholinergic syndrome



Fatigue

- Listen/ask/counsel
- Consider holds/reductions
- Rule out other causes
- Encourage exercise/staying active

Alopecia

- Patient counseling/education
- Wig prescription
- Scalp cooling clinical trials ongoing (eg, NCT04986579)

G-CSF = granulocyte colony-stimulating factor; LVEF = left ventricular ejection fraction.

Rugo HS, et al. *ESMO Open.* 2022;7:100553. Ciruelos E, et al. *Clin Translat Oncol.* 2024;26:1539-1548. NCCN Guidelines. Antiemesis v1.2025 (https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf). Accessed 5/5/2025.

ASCO 2025 Preview

Assessing the impact of scalp cooling in patients receiving T-DXd for metastatic breast cancer. Salehi E, et al. Abstract 1095.

Now let’s go to a question….

Question 3

What is your perception/prediction of the efficacy of scalp cooling to prevent alopecia in patients receiving T-DXd or other ADCs?

a) Very effective

b) Somewhat effective

c) Not effective

d) Unsure/not applicable to me

T-DXd Dose Modification on Pan-Tumor Study

- Toxicities treated with 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
5.4 mg/kg	4.4 mg/kg	3.2 mg/kg

- After T-DXd dose reduction (due to toxicity), subsequent cycles should be given at that 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.

Interstitial Lung Disease: Recognition and Management

- **Advise** patients of risks of ILD prior to start of treatment, as well as signs/symptoms of ILD
- **Monitor** for new or worsening cough, dyspnea, or fever

- **Incidental findings on routine scan**
- **Symptomatic findings**

If ILD is suspected…

- Exclude other etiologies, including infectious etiologies
- Initiate evaluation without delay, which may include:
  - High-resolution CT
  - Consultation with pulmonologist
  - Blood culture and CBC
  - Additional tests, as clinically indicated

Grade 1 (asymptomatic)

- Hold T-DXd until resolved
- May resume treatment once fully resolved
- Consider starting systemic steroids (eg, ≥ 0.5 mg/kg/day of prednisone or equivalent) until improvement, followed by gradual taper over 4 weeks
- If > 28 days to resolve, reduce dose by 1 dose level

Grade 2+ (symptomatic)

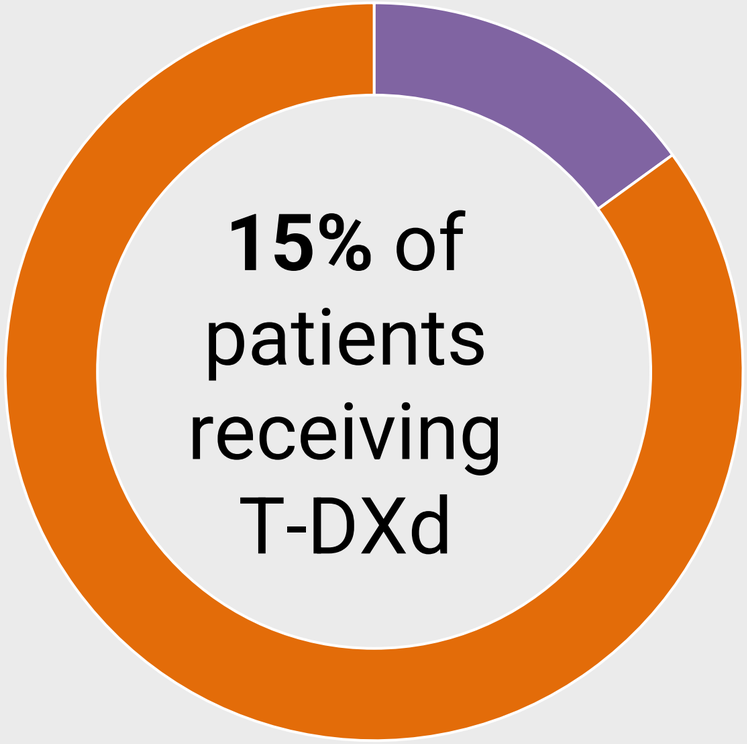
- Discontinue T-DXd permanently
- Begin steroid treatment (eg, prednisone ≥ 1 mg/kg daily) with gradual taper

CBC = complete blood (cell) count; CT = computed tomography; ILD = interstitial lung disease.

Fam-trastuzumab deruxtecan-nxki (Enhertu®) prescribing information (PI) 2024 (https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true). Accessed 5/5/2025.
Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378.

ILD/Pneumonitis Associated With T-DXd

Adjudicated drug-related ILD/pneumonitis



- 87.0% had their first event within 12 months
  - Median: 5.4 months
  - Range: < 0.1–46.8 months
- Median time to onset

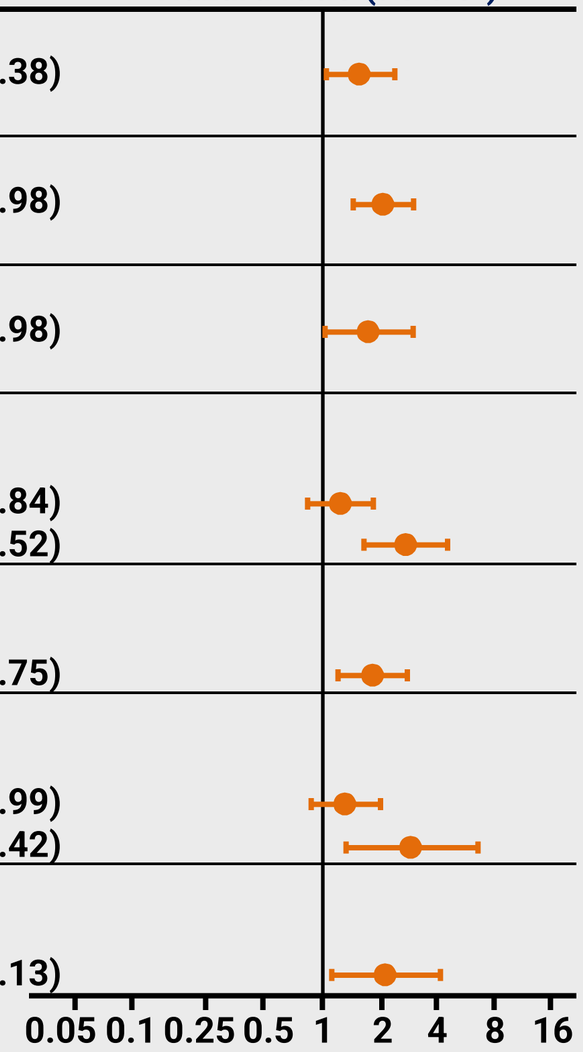
- Most patients with ILD/pneumonitis experienced low-grade events (Grade 1 or 2, 77.4%)
- Overall rate of fatal events: 2.2%

Powell CA, et al. *ESMO Open*. 2022;7:100554.

Pneumonitis

- 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 (SpO_2) < 95%
  - Moderate/severe renal impairment
  - Presence of lung comorbidities
  - Time since initial diagnosis > 4 years

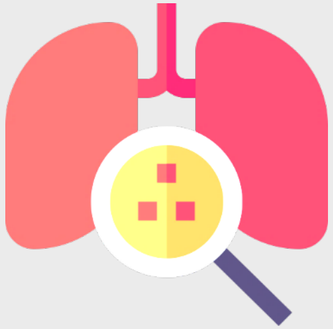
Potential risk factor	Patients, n (N = 1150)	Hazard ratio (95% CI)
Age group		
< 65 years	754	1.56 (1.02–2.38)
≥ 65 years	396	Ref
Country		
Japan	506	2.08 (1.45–2.98)
Non-Japan	644	Ref
Lung comorbidities		
Yes	81	1.75 (1.03–2.98)
No	1069	Ref
Baseline renal function		
Normal	470	Ref
Mild decrease	458	1.24 (0.83–1.84)
Moderate/severe decrease	196	2.73 (1.65–4.52)
Time since disease diagnosis		
0 to ≤ 4 years	624	Ref
> 4 years	403	1.82 (1.20–2.75)
Dose		
5.4 mg/kg q3w	315	Ref
6.4 mg/kg q3w	808	1.30 (0.85–1.99)
> 6.4 mg/kg q3w	27	2.92 (1.32–6.42)
Baseline SpO_2		
≥ 95%	1080	Ref
< 95%	57	2.14 (1.11–4.13)



Powell CA, et al. *ESMO Open*. 2022;7:100554.

5 “S” Rules

Screen

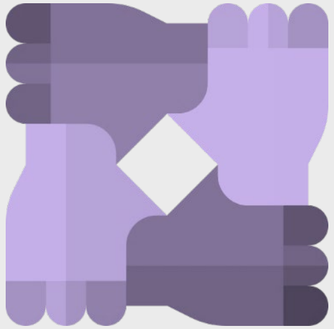


- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on the baseline risk; screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD
- Increased knowledge is needed on the impact of prior ILD with other treatments (eg, everolimus, CDK4/6 inhibitors) on future risk of ILD with T-DXd

Scan

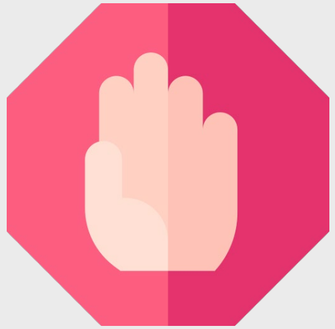
- The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest; a baseline scan is recommended, with repeat scans to be performed every 6 to 12 weeks

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
  - Improved synergy with pulmonologists during T-DXd treatment is being explored in several studies
  - Evaluate the predictive/prognostic role of monitoring pulmonary function tests

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

Steroids

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

CDK = cyclin-dependent kinase.

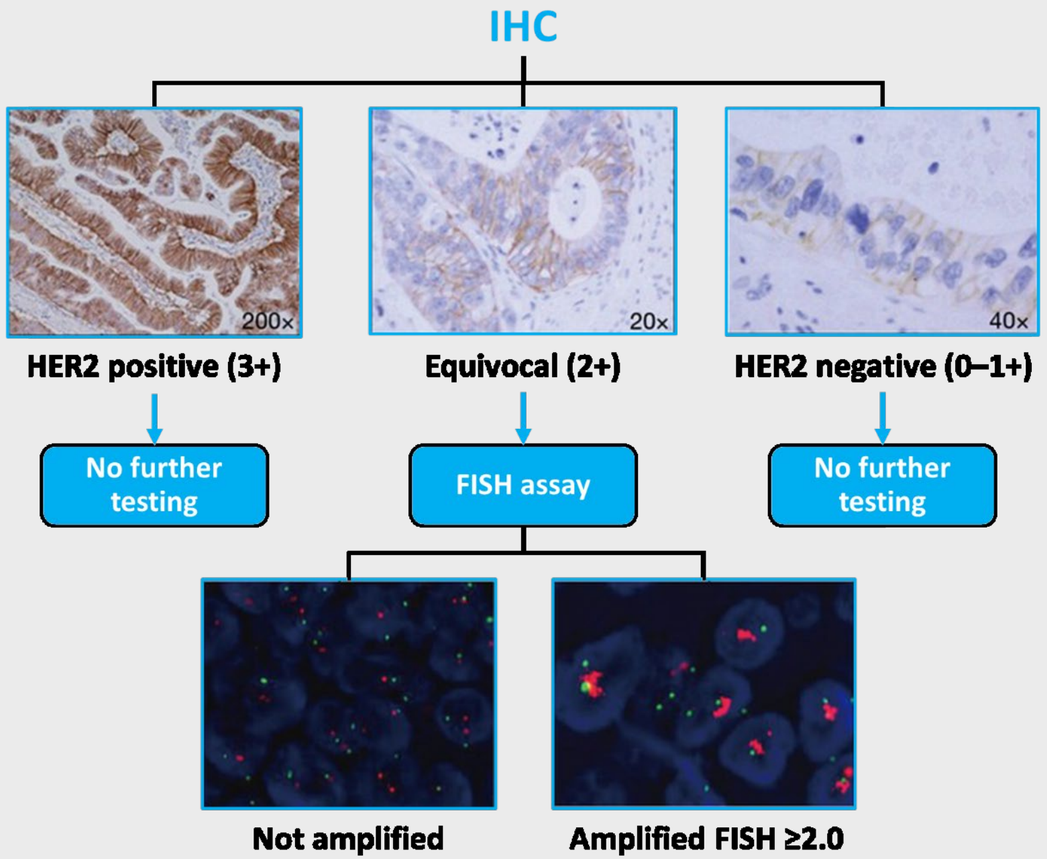
Tarantino P, Tolaney SM. *J Oncol Practice*. 2023;19:526-527.

Interpreting HER2: Integrating With Pathology Across HER2-Positive Malignancies

HER2 Testing: Protein Expression, HER2 Amplification, and HER2 Gene Mutations

- **HER2 testing**[1,2]
- HER2 protein expression: IHC
- *HER2/neu* amplification: FISH
- ***HER2*** mutation
  - Guardant360 CDx (blood)
  - Oncomine Dx Target Test (tissue)

Example of a HER2 testing algorithm[3,a]



[a]Gastric cancer.

1. Jaber N. Enhertu marks first targeted therapy for HER2-mutant lung cancer. 9/13/2022 (https://www.cancer.gov/news-events/cancer-currents-blog/2022/fda-lung-cancer-enhertu-her2). Accessed 5/6/2025.
2. Imyanitov EN, et al. *Crit Rev Oncol Hematol.* 2021;157:103194. 3. Kelly CM, Janjigian YY. *J Gastrointest Oncol.* 2016;7:750-762.

HER2 Testing

	Breast Cancer (ASCO/CAP 2007)	Breast Cancer (ASCO/ CAP 2013)	Breast Cancer (ASCO/ CAP 2018)	Gastric Cancer (ASCO/ CAP 2016)	Colorectal Cancer (HERACLES trial)	UPSC (Fader et al)
HER2 IHC 3+	> 30% strong, uniform, complete	> 10% circumferential, strong, complete	> 10% circumferential, strong, complete	≥ 10%, strong complete or basolateral/lateral	> 50% strong, complete or basolateral/ lateral	> 30% strong complete or basolateral/ lateral
***HER2/ERBB2* FISH amplification**	*HER2*/CEPT17 ratio > 2.2 Patients with *HER2*/CEPT17 ratio 2–2.2 eligible	*HER2*/CEPT17 ratio ≥ 2.0 OR ratio < 2.0 and *HER2* signal ≥ 6.0/nucleus	*HER2*/CEPT17 ratio ≥ 2.0 OR ratio < 2.0 and *HER2* signal ≥ 6.0/nucleus (if IHC 2+ or 3+)	HER2/CEPT17 ratio ≥ 2.0 OR ratio < 2.0 and HER2 signal ≥ 6.0/nucleus	HER2/CEPT17 ratio ≥ 2.0 in ≥ 50% of cells	HER2/CEPT17 ratio ≥ 2.0

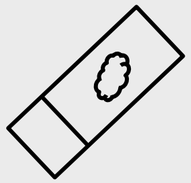
UPSC = uterine papillary serous carcinoma.

Adapted from Buza N, et al, *Arch Pathol Lab Med*. 2022;146(5):0. Slide courtesy of U. Matulonis.

What Do We Know About HER2 Testing Methods for Non-Breast/Gastric Cancers?

- Routine HER2 testing has been limited to a few tumor types (eg, breast, gastric)
- No validated HER2 assay available across all solid tumors
- Testing blood samples: Less invasive, quicker than testing tissue samples
- Blood testing vs tissue testing in the DESTINY-PanTumor02 Study
  - Low number of false readings (specific)
  - Failed to detect some positive samples (lacked sensitivity)

In the event of a negative result on blood testing



Utilize complementary tissue-based IHC and/or ISH methods

DESTINY-PanTumorO2: Integration of IHC3+ or ISH or plasma *HER2*amp captures most responders.

All patient cohort, N = 267					
Central IHC cohort		**Central ISH cohort**		**Plasma ctDNA cohort**	
IHC status	**N**	**ISH status**	**N**	**HER2*amp***	**N**
3+	75	Positive	78	Detected	48
2+	125				
1+	25	Negative	145	Not detected	212
0	30				
Unknown	12	Unknown	44	Unknown	7

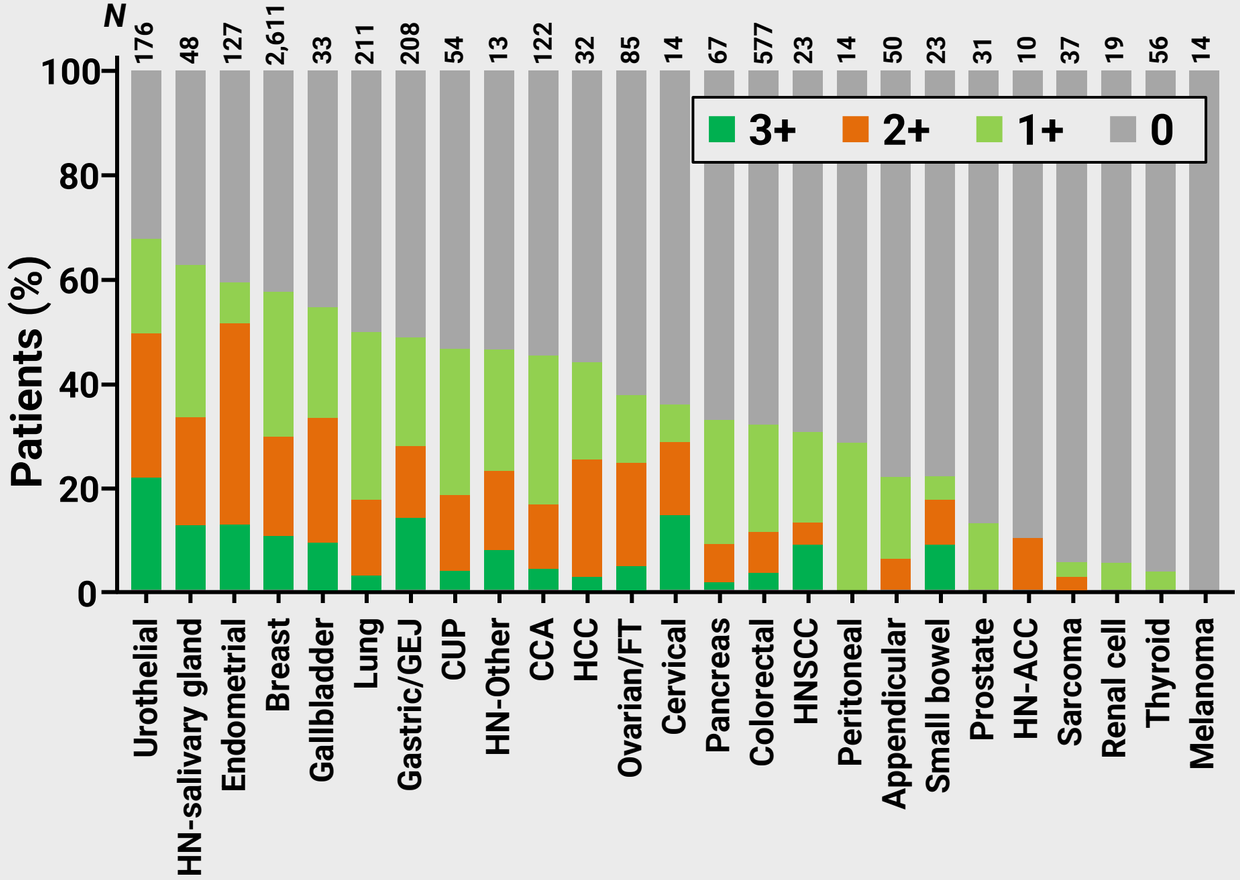
All testing methods identify responders;
IHC 3+ captures the greatest number of responders.

amp = amplification; ct = circulating tumor; ISH = in situ hybridization; ND = not detected.

Makker V, et al. ESMO 2023; Poster 148P.

What Is the Incidence of HER2 Expression Across Solid Tumors?

- **Distribution of HER2 IHC expression levels across cancers**
  - **Histologies with > 10 patients included in graph**



ACC = head and neck-adenoid cystic carcinoma; CNS, central nervous system; CUP = cancer of unknown primary; FT = fallopian tube; HCC = hepatocellular carcinoma; HN = head and neck; SCC = squamous cell carcinoma.

*Row percentages were used in the construction of this table.

Uzunparmak, B. et al. *Ann Oncol*, 2023;34:1035-1046.

HER2 expression across solid tumors

Cancer types		Distribution of HER2 IHC scores across cancers*				
		HER2 IHC expression levels, %				
		0	1+	2+	3+	Total, N
Breast		43	28	19	10	2611
Gastric/GEJ		51	21	14	14	208
Biliary tract	CCA	55	29	12	4	122
	Gallbladder	46	21	24	9	33
	Ampullary	50	33	17	0	6
GI—lower	Colorectal	68	21	8	3	577
	Appendiceal	78	16	6	0	50
	Small bowel	78	4	9	9	23
	Anal	100	0	0	0	5
GI—other	Pancreas	67	24	8	2	67
	HCC	56	19	25	0	32
	Mixed CCA and HCC	67	33	0	0	6
Gynecological	Endometrial	41	8	39	13	127
	Ovarian/FT	62	13	20	5	85
	Peritoneal	71	29	0	0	14
	Cervical	64	7	14	14	14
	Vaginal	100	0	0	0	2
	Vulvar	29	14	43	14	7
Head and neck	HN-ACC	90	0	10	0	10
	HN-Other	54	23	15	8	13
	HN-salivary gland	38	29	21	13	48
	HNSCC	70	17	4	9	23
Genitourinary	Urothelial	32	18	28	21	176
	Prostate	87	13	0	0	31
	Renal cell	95	5	0	0	19
	Germ cell/testicular	100	0	0	0	3
	Penile	100	0	0	0	1
Thoracic	Lung	50	32	15	3	211
	Thymic	100	0	0	0	4
Skin	Melanoma	100	0	0	0	14
	Non-melanoma skin	71	14	14	0	7
Other	Adrenal	67	0	33	0	3
	CUP	54	28	15	4	54
	CNS	50	50	0	0	2
	Sarcoma	95	3	3	0	37
	Thyroid	96	4	0	0	56
Total		2361 (50)	1137 (24)	796 (17)	407 (9)	4701

Tumor-Agnostic HER2-Directed Therapy: Unanswered Questions

- IHC 1+ (low enrollment on pan-tumor study)
- HER2-low
- What is the difference between IHC 1+ and HER2-low?
- Validated HER2 test
- When and where should we be tissue testing?

- ASCO 2025 Preview
  - Concordance analysis between tumor tissue HER2 status by IHC and ISH and a translational analysis of plasma ctDNA in patients with BTC: Exploratory analysis from the phase 2 HERIZON-BTC-01 trial. Harding J, et al. Abstract 4102.

Case Study

Case: Erin

Second-Line Recurrent Endometrial Cancer, IO-Exposed, IHC HER2 3+

A 67-year-old Haitian Black American with a stage 3C1 uterine serous cancer diagnosed 2 years ago

- Her tumor is pMMR (non-MSI), p53 mutated, ER-negative, and HER2 3+ using gastric scoring

Initially treated with 6 cycles of carboplatin and paclitaxel plus dostarlimab on the RUBY trial and progressed during the maintenance phase

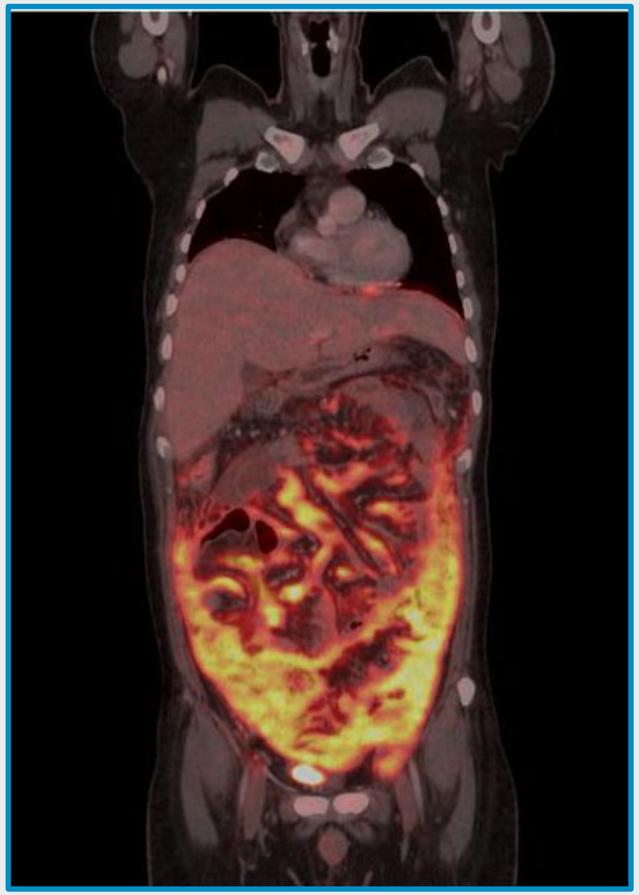
- BMI = 36.2
- Controlled essential HTN
- Prior surgery: Hyst BSO, nodes, cholecystectomy

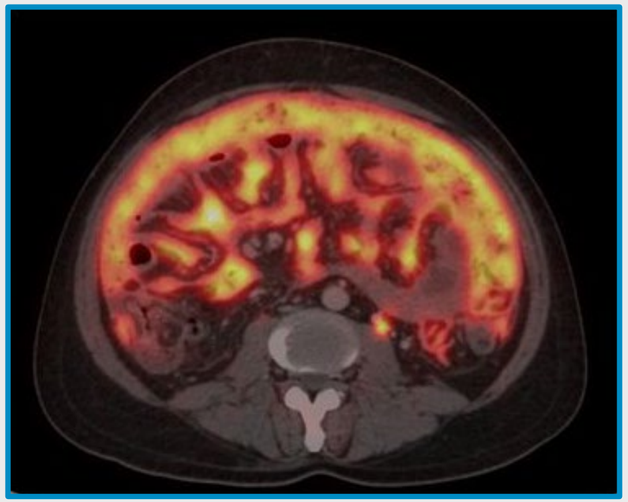
She now has small volume carcinomatosis and mild bloating

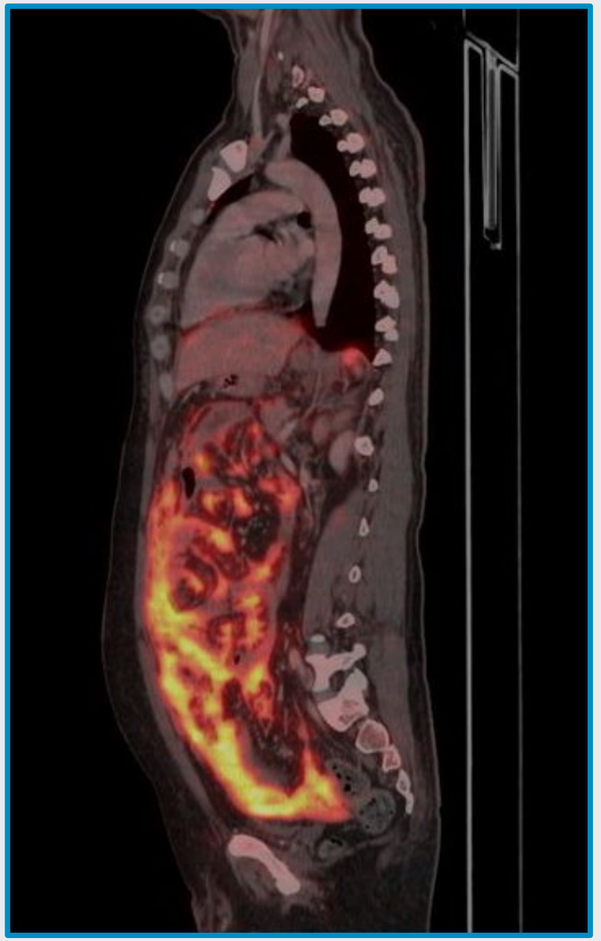
BMI = body mass index; ER = estrogen receptor; HTN = hypertensions; hyst BSO = hysterectomy with bilateral salpingo-oophorectomy; IO = immunotherapy; p = proficient

Case: Erin (cont)

Second-Line Recurrent Endometrial Cancer, IO-Exposed, IHC HER2 3+





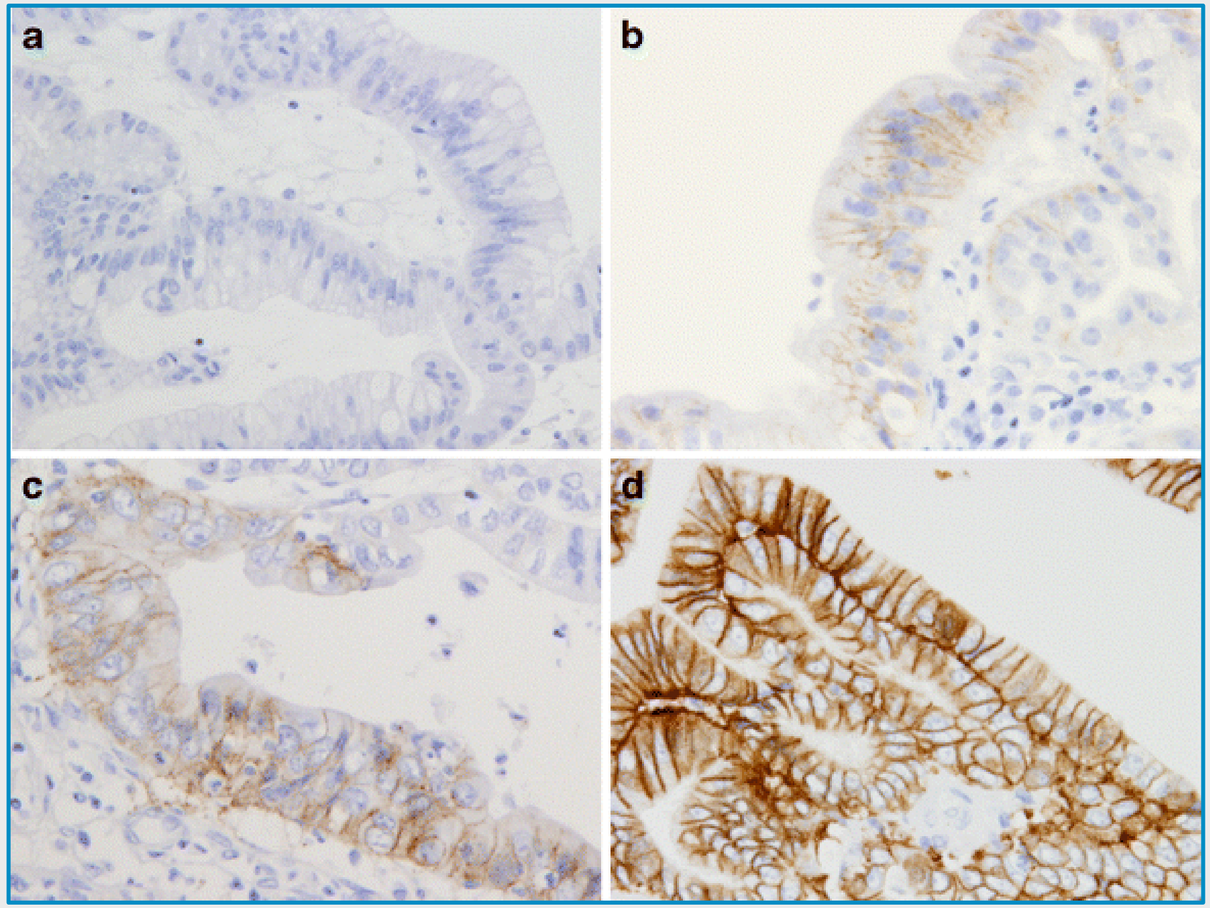


Goyal H, et al. *J Nuclear Med*. 2022;63(suppl 2):2697.

Case: Erin (cont)

Second-Line Recurrent Endometrial Cancer, IO-Exposed, IHC HER2 3+

- Representative microphotographs of HER2 IHC; scoring was performed in accordance with the modified criteria used for gastric cancer; scores of 0 (a) or 1+ (b) were considered negative, 2+ (c) were equivocal/2+, and 3+ (d) were positive for HER2 overexpression
- In cases with scores of 2+ or 3+, a basolateral membranous staining pattern was observed frequently (c, d)



Yoshida H, et al. *Virchows Archiv.* 2016;468:431-439.

Case: Erin—Polling Question

Second-Line Recurrent Endometrial Cancer, IO-Exposed, IHC HER2 3+

You recommend (no clinical trial is available):

a) Carboplatin and paclitaxel

b) Carboplatin and paclitaxel plus bevacizumab

c) T-DXd

d) Pembrolizumab and lenvatinib

e) Other

Case Study

Case: Jill

Platinum-Resistant Recurrent Ovarian Cancer, Bevacizumab-Exposed, IHC HER2 2+, FRα-negative

A 53-year-old Jewish American with a germline *BRCA1* mutation (HRD positive) diagnosed with a stage IVA high-grade serous tubal cancer treated with IV carboplatin and paclitaxel plus bevacizumab and olaparib added in the maintenance phase

- Her sister died of breast cancer
- She has no comorbidities and plays tennis every day

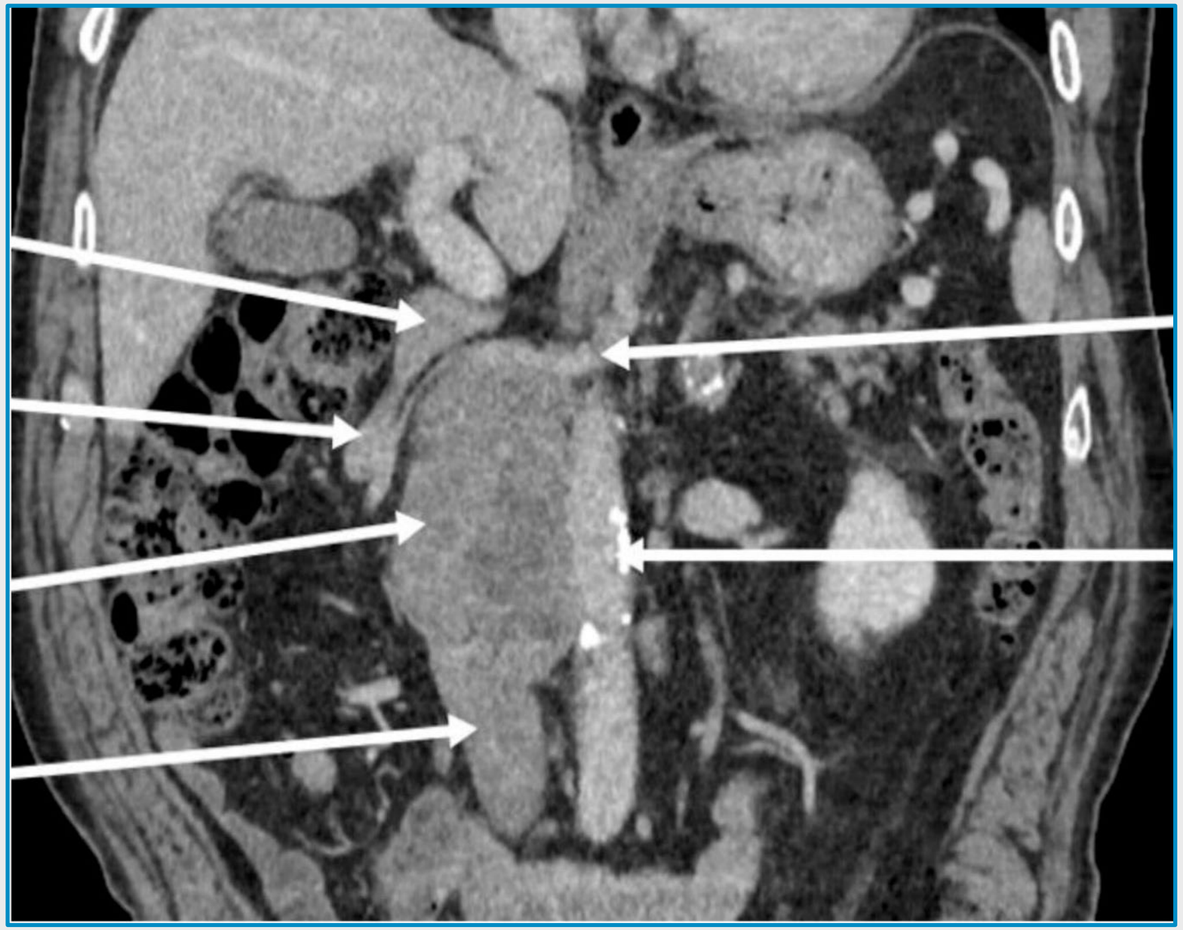
She has a 3-year, platinum-sensitive recurrence and is treated with carboplatin and liposomal doxorubicin plus bevacizumab continued in maintenance

She recurs 18 months later (5 years after diagnosis) and progresses on carboplatin and gemcitabine (secondary platinum refractory) in the retroperitoneum

HRD = homologous recombination deficiency.

Case: Jill (cont)

Platinum-Resistant Recurrent Ovarian Cancer, Bevacizumab-Exposed, IHC HER2 2+, FRα-negative



IVC = inferior vena cava.

Case: Jill—Polling Question

Platinum-Resistant Recurrent Ovarian Cancer, Bevacizumab-exposed, IHC HER2 2+, FRα-negative

You recommended (no clinical trial is available):

a) Surgical resection

b) Weekly paclitaxel ± bevacizumab

c) Mirvetuximab soravtansine ± bevacizumab

d) T-DXd

e) Radiation

f) Other

Case: Jill

- Next-line therapy with T-DXd is initiated. Jill does well for 7 months, then reports dyspnea and cough
- Vitals: Temperature: 99 F, heart rate 90 beats per minute, blood pressure (155/78 mm Hg), oxygen saturation 95%
- PE: she is breathing comfortably on room air, with bilateral crackles on pulmonary exam and no edema
- Laboratories: Sodium (Na) 142 mmol/L, creatinine level 1.3 (baseline 1.2–1.4), hemoglobin 12.5, absolute neutrophil count (ANC) 2100, platelets 215
- CT chest shows bilateral new ground glass opacities

PE = physical examination.

Case: Jill (poll)

What would you do next?

a) Hold treatment, initiate steroids, and resume at a reduced dose level if symptoms resolve

b) Hold treatment and monitor closely off steroids; consider resuming if symptoms resolve without need for steroid therapy

c) Initiate steroids and permanently discontinue treatment

d) Continue treatment with close monitoring of PFTs

PFTs = pulmonary function tests.

Key Takeaways and Conclusions

Key Takeaways

HER2-targeted therapy approved for breast, gastric, colorectal, lung, and biliary tract cancers

- Recent FDA accelerated approvals:
  - April 5, 2024: T-DXd for unresectable/HER2+ (IHC 3+) solid tumors after prior systemic treatment and no satisfactory alternative treatment options[1]
  - November 20, 2024: Zanidatamab for previously treated, unresectable or metastatic HER2+ (IHC 3+) BTC

Pan-tumor HER2-directed therapy

- Phase 2 DESTINY-PanTumor02, tumor-agnostic, biomarker-driven clinical trial of HER2-targeted ADC, T-DXd, for pretreated, HER2-expressing solid tumors[3]
  - Durable responses and clinical improvements in PFS and OS across endometrial, cervical, ovarian, bladder, and biliary tract cancers
  - Greatest benefit in IHC 3+ population
  - Safety results were consistent with known profile of T-DXd
    - Guidelines available to aid adverse event management[4,5]

Further exploration of T-DXd in HER2 IHC 1+/HER2-low is warranted

- ILD is a rare but serious AE associated with ADCs
  - Proactive, multidisciplinary monitoring, evaluation, and management of ADC-associated ILD are critical

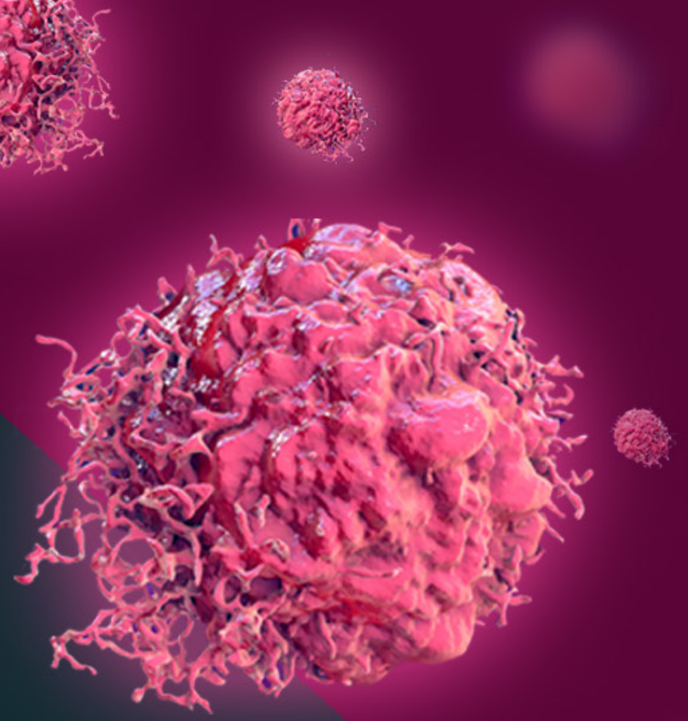
1. FDA. (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2). 2. FDA. (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanidatamab-hrii-previously-treated-unresectable-or-metastatic-her2). 3. Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58. 4. NCCN Guidelines. Treatment by cancer type (https://www.nccn.org/guidelines/category_1). 5. Rugo HS, et al. *ESMO Open*. 2022;7:100553. All URLs accessed 5/15/2025.

Questions?

Thank you!

Comprehensive Care *with* HER2 ADCs ACROSS SOLID TUMORS:

Strategies *to* Enhance Efficacy *and* Minimize Toxicity



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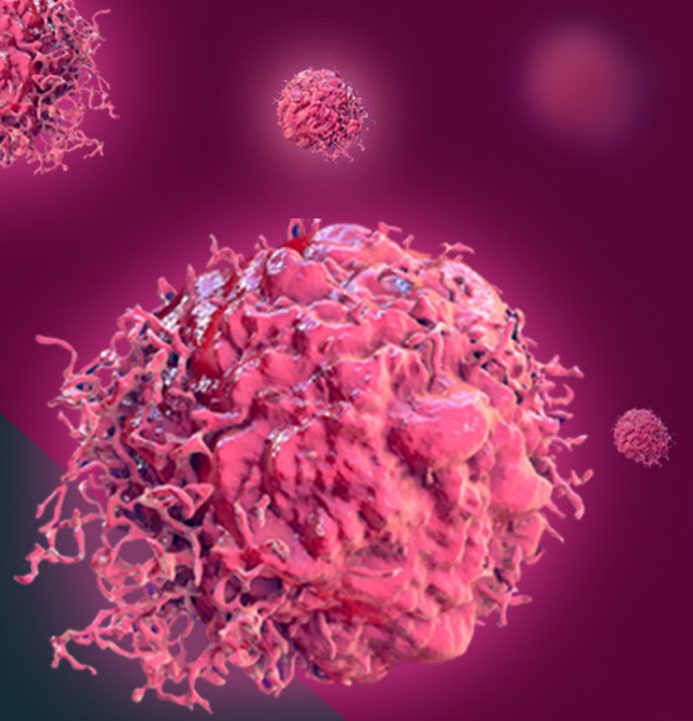
Strategies *to* Enhance Efficacy *and* Minimize Toxicity



FOR MORE INFORMATION AND ADDITIONAL RESOURCES, PLEASE VISIT

https://linktr.ee/HER2ADCs

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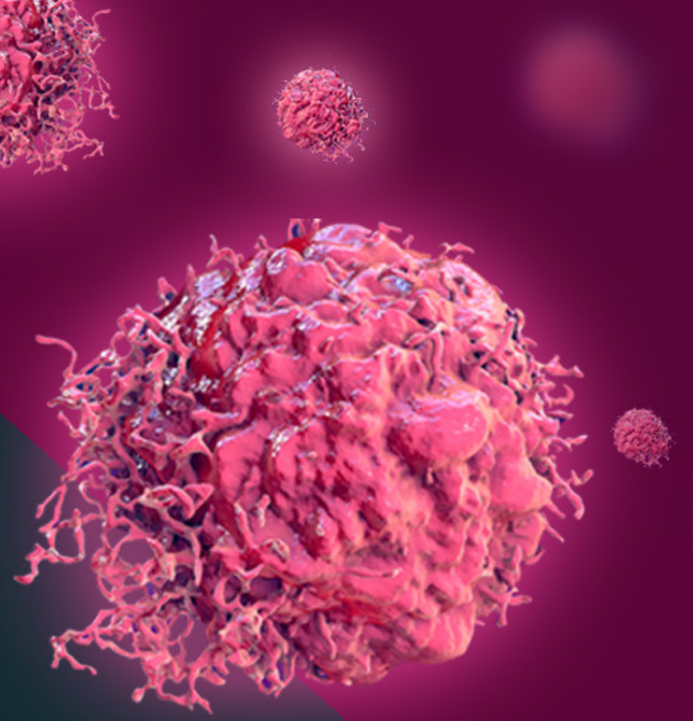
Strategies *to* Enhance Efficacy *and* Minimize Toxicity



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Comprehensive Care with HER2 ADCs Across Solid Tumors: Strategies to Enhance Efficacy and Minimize Toxicity

Updates in Clinical Management of HER2+ Solid Tumors

Resource	Address
de Vries EGE, Rüschoff J, Lolkema M, et al. Phase II study (KAMELEON) of single-agent T-DM1 in patients with HER2-positive advanced urothelial bladder cancer or pancreatic cancer/cholangiocarcinoma. *Cancer Med*. 2023;12:12071-12083.	https://doi.org/10.1002/cam4.5893
Harding JJ, Fan J, Oh DY, et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. *Lancet Oncol*. 2023;24:772-782.	https://doi.org/10.1016/S1470-2045(23)00242-5
Jaber N. Enhertu Marks First Targeted Therapy for HER2-Mutant Lung Cancer. National Cancer Institute. September 13, 2022.	https://www.cancer.gov/news-events/cancer-currents-blog/2022/fda-lung-cancer-enhertu-her2
Jerusalem G, Park YH, Yamashita T, et al. Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: A subgroup analysis of the DESTINY-Breast01 trial. *J Clin Oncol*. 2021;39(suppl 15):526.	https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.526
Jhaveri KL, Wang XV, Makker V, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: Results from the NCI-MATCH trial (EAY131) subprotocol Q. *Ann Oncol*. 2019;30:1821-1830.	https://doi.org/10.1093/annonc/mdz291
Meric-Bernstam F, Makker V, Oaknin A, 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;42:47-58.	https://ascopubs.org/doi/10.1200/JCO.23.02005
Nakamura Y, Mizuno N, Sunakawa Y, et al. Tucatinib and trastuzumab for previously treated human epidermal growth factor receptor 2-positive metastatic biliary tract cancer (SGNTUC-019): A phase II basket study. *J Clin Oncol*. 2023;41:5569-5578.	https://ascopubs.org/doi/10.1200/JCO.23.00606
National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology.	https://www.nccn.org/guidelines/category_1
Oh DY, Bang YJ. HER2-targeted therapies - a role beyond breast cancer. *Nat Rev Clin Oncol*. 2020;17:33-48.	https://doi.org/10.1038/s41571-019-0268-3
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