# Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

*A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress*

# Antibody-Drug Conjugates

**Wednesday, April 9, 2025**

**11:15 AM – 12:45 PM**

## Faculty

**Marianne J Davies, DNP, ACNP, AOCNP, FAAN**
**Edward B Garon, MD, MS**
**Marissa Marti-Smith, DNP, APRN, AGNP-C, AOCNP**
**Tiffany A Traina, MD, FASCO**

## Moderator

**Neil Love, MD**

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# Ms Davies — Disclosures

No relevant conflicts of interest to disclose

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# Dr Garon — Disclosures

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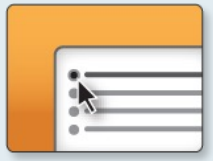
**Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.**



**Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.**

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

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

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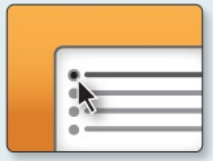

**Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.**

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

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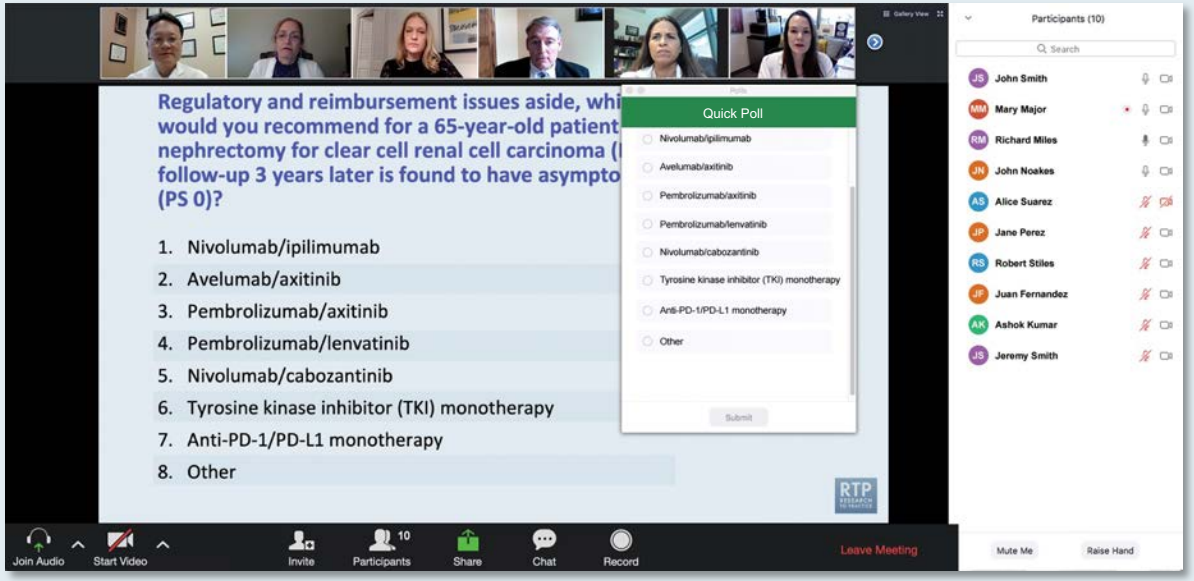


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# About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
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# ONCOLOGY NURSING UPDATE WITH DR NEIL LOVE

## Bispecific Antibodies in Lymphoma Part 1 — An Interview with Ms Robin Klebig for Oncology Nurses

MS ROBIN KLEBIG
MAYO CLINIC

Listen on Apple Podcasts

Spotify

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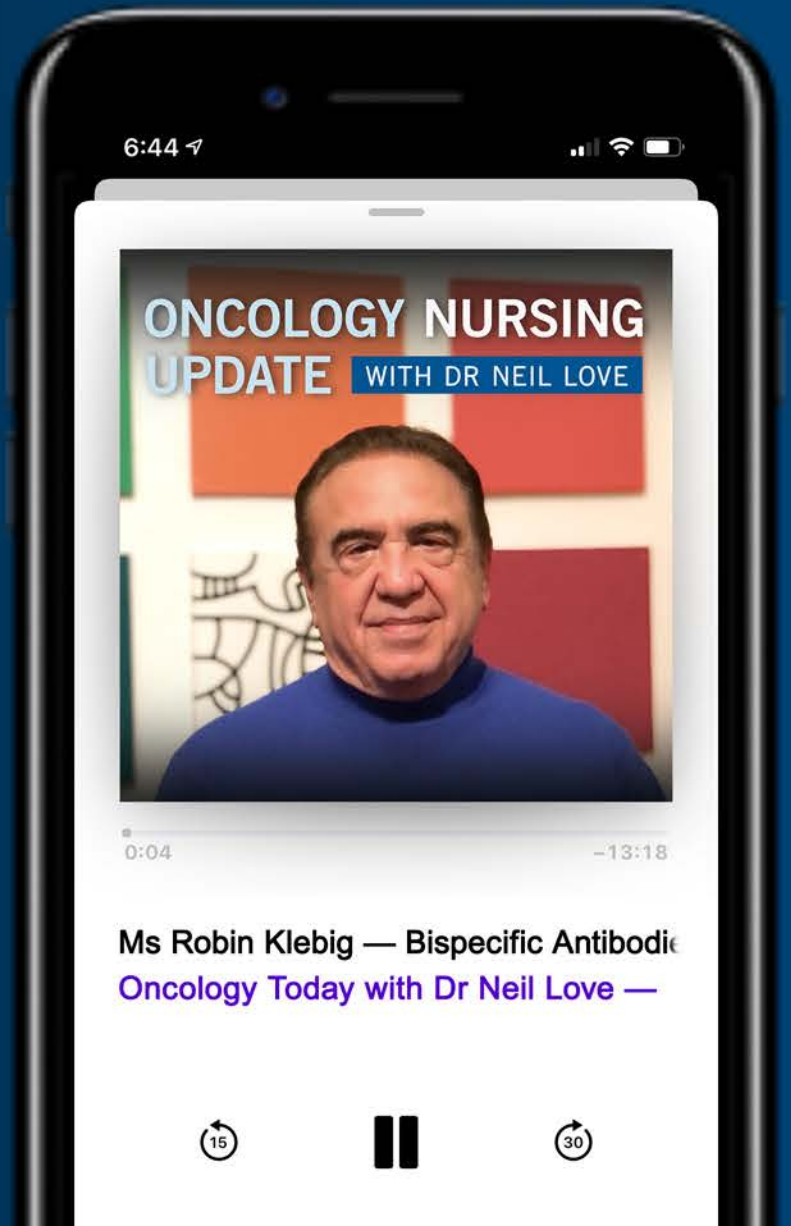

50TH ANNUAL ONS™ Congress

CELEBRATING YESTERDAY TRANSFORMING TOMORROW

CELEBRATING 50 YEARS

# *Welcome ONS Members!*

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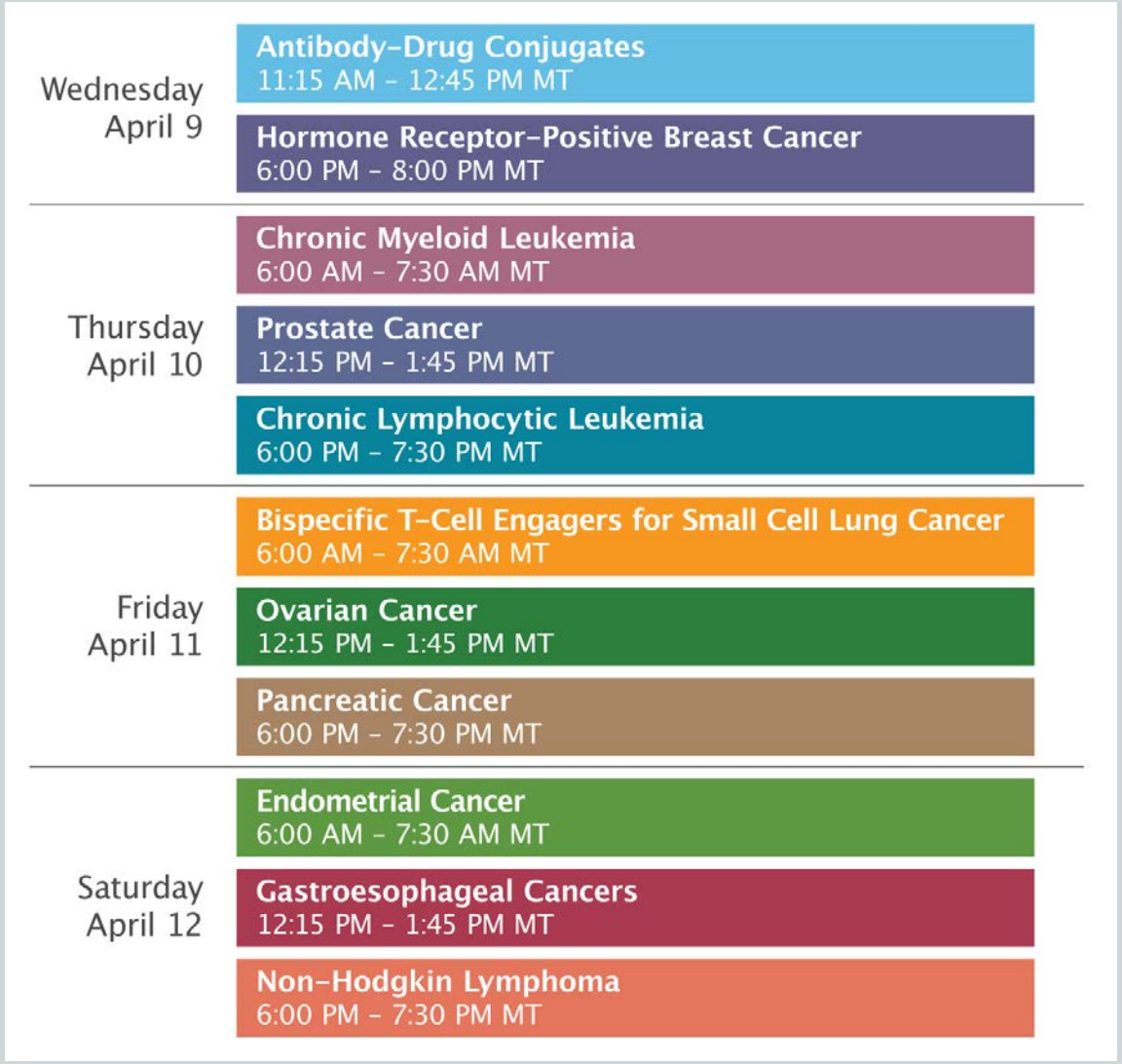
# “Understanding the Current Paradigm and New Approaches”
# Seventeenth Annual RTP-ONS NCPD Symposium Series

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# RTP Faculty at ONS 2025

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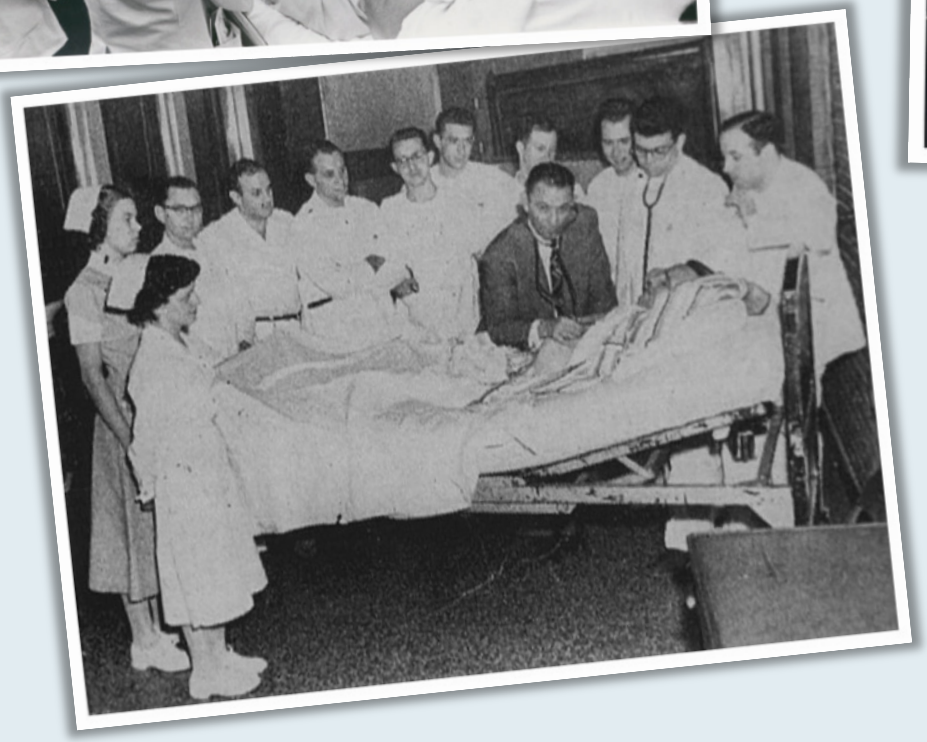

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# The Core Oncology Triad
# Developing an Individualized Oncology Strategy


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# Understanding the Current Paradigm and New Approaches
# Denver, Colorado

## Symposia Themes

### Personalized oncology: Implementing an individualized oncologic strategy

- Tumor factors (eg, biomarkers, numeracy)
- Biopsychosocial factors (eg, adherence, available family support, comorbidities, mood)

### Novel agents and treatment strategies

- The new-agents revolution (beginning of the end?)

### The bond that heals (both ways)

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**How was it different to take care of this patient versus another patient in the same oncologic setting?**

**What unique biopsychosocial factors (eg, attitude, comorbidities, social support) were considered in the overall management of this case?**

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# Agenda

**Module 1:** Overview of Antibody-Drug Conjugates (ADCs)

**Module 2:** Trastuzumab Deruxtecan (T-DXd) in Patients with HER2-Positive Metastatic Breast Cancer (mBC) with and without Brain Metastases

**Module 3:** Role of ADCs for Patients with ER-Positive mBC

**Module 4:** T-DXd in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) with HER2 Alterations

**Module 5:** Emerging Role of ADCs for Patients with Progressive EGFR-Mutant NSCLC

# Agenda

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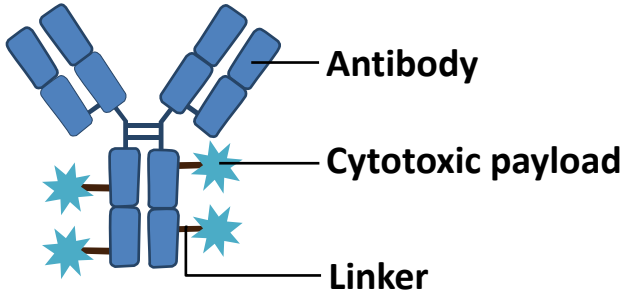
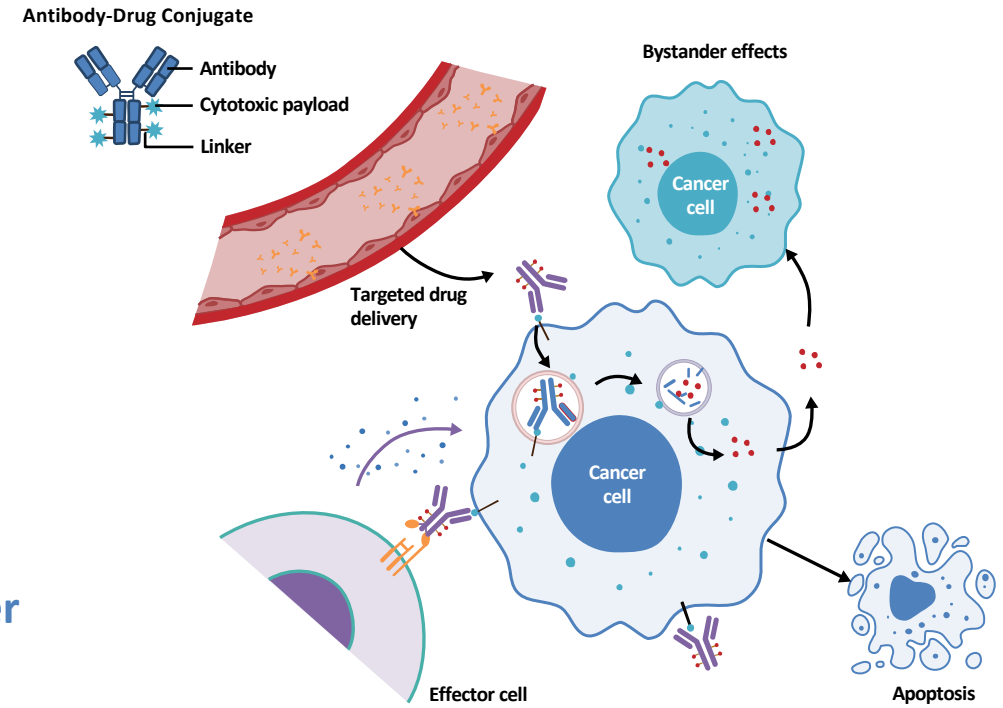
# Mechanism of ADCs: Multi-step Process Teaching Point




## ADC Components

- **Antibody** specific for target antigen on cancer cells
- High-potency **cytotoxic payload**
- Cleavable or non-cleavable **linker** between antibody and payload




Courtesy of Marianne J Davies, DNP, ACNP, AOCNP, FAAN

# Current Approved ADCs in Oncology

| Name | Year approved | Tumor type |
|---|---|---|
| Trastuzumab emtansine (T-DM1) | Adjuvant: 2019<br>Metastatic: 2013 | Breast |
| Sacituzumab govitecan | HR-positive: 2023<br>Triple-negative: 2021 (Traditional)<br>Triple-negative: 2020 (Accelerated) | Breast |
| Datopotamab deruxtecan | 2025 | Breast |
| Trastuzumab deruxtecan | 2025<br>2024<br>2022<br>2022<br>2021<br>2019 (Accelerated) 2022 (Traditional) | HER2-low/ultralow breast<br>HER2-positive solid tumors<br>HER2-mutant lung<br>HER2-low breast<br>HER2-positive gastric<br>HER2-positive mBC |

https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications

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# Current Approved ADCs in Oncology (Continued)

| Name | Year approved | Tumor type |
|---|---|---|
| Mirvetuximab soravtansine | 2024 (Traditional)<br>2022 (Accelerated) | Ovarian |
| Tisotumab vedotin | 2021 | Cervical |
| Enfortumab vedotin (monotherapy) | 2021 (Traditional)<br>2019 (Accelerated) | Urothelial |
| Enfortumab vedotin (with pembrolizumab) | 2023 (Accelerated/Traditional) | Urothelial |
| Gemtuzumab ozogamicin | 2017 (Traditional)<br>2000 (Accelerated) | AML |
| Brentuximab vedotin | 2025 (Traditional)<br>2015 (Traditional)<br>2011 (Accelerated) | DLBCL<br>Hodgkin lymphoma |
| Inotuzumab ozogamicin | 2017 | ALL |
| Polatuzumab vedotin | 2023 (Traditional)<br>2019 (Accelerated) | DLBCL |
| Loncastuximab tesirine | 2021 | LBCL |

https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications

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# Select Promising Investigational ADCs in Oncology

| Name | Biological target | Tumor types under investigation |
|---|---|---|
| Ifinatamab Deruxtecan | B7-H3 | SCLC, ESCC, CRPC, NSCLC |
| Raludotatug Deruxtecan | CDH6 | Ovarian, RCC |
| Patritumab Deruxtecan | HER3 | Breast, NSCLC, melanoma, SCCHN, gastric |
| Sacituzumab Tirumotecan | TROP2 | Breast, NSCLC, cervical, endometrial, gastric, BTCs, CRC, pancreatic, malignant neoplasms |
| Telisotuzumab Vedotin | c-Met | NSCLC |
| Disitamab Vedotin | HER2 | Bladder, breast, GI cancers |

# Agenda

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# Clinical Scenario

**A patient with HER2-positive mBC experiences disease progression, including new brain metastases, on first-line THP (docetaxel/trastuzumab/pertuzumab) and is about to begin treatment with T-DXd**

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# ADCs @ ONS

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Vice Chair, Department of Medicine
Section Head, TNBC Clinical Research Program
Memorial Sloan Kettering Cancer Center
Associate Professor, Weill Cornell Medicine

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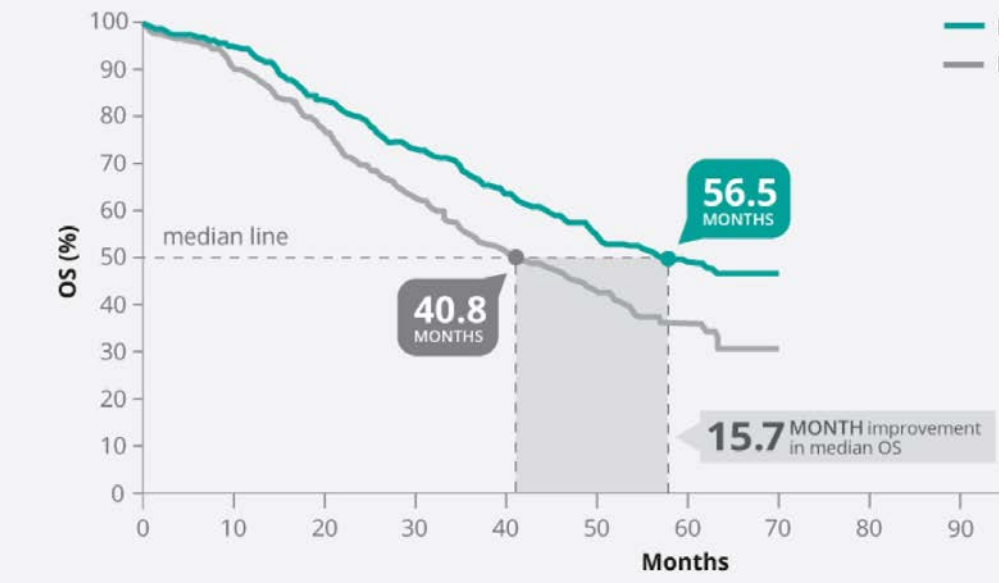
# 1L HER2+ MBC

## THP is Standard of Care




Significant ~16% absolute benefit in overall survival with docetaxel, trastuzumab and pertuzumab ("THP")

Median OS 56.5mo vs. 40.8mo (HR 0.68, p=0.0002)

## Lingering Considerations

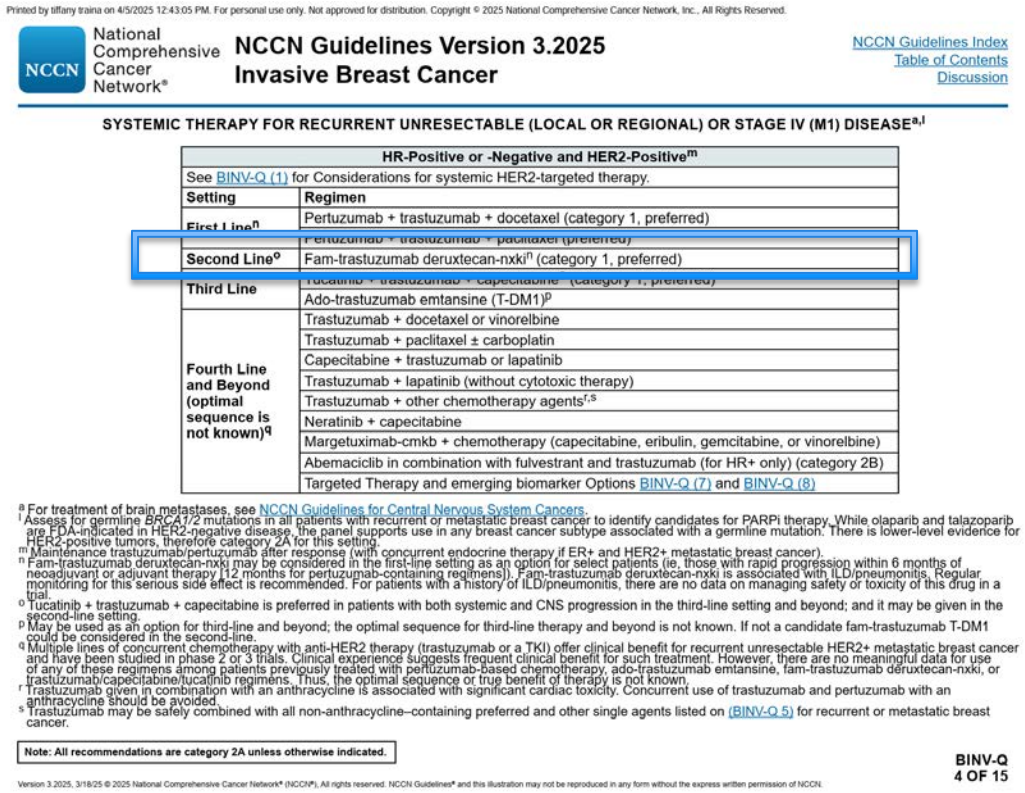
- Often discontinue chemotherapy and continue maintenance HP
  - Residual neuropathy from prolonged taxane
  - High QoL with dual antibodies alone
- Median Duration of Response ~ 2 years on 1L therapy

Swain et al 2020

Memorial Sloan Kettering Cancer Center

# Guidelines support 2L T-DXd in HER2+ MBC

## NCCN 3.2025





National Comprehensive Cancer Network®

**NCCN Guidelines Version 3.2025**
**Invasive Breast Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

**SYSTEMIC THERAPY FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,l]**

| HR-Positive or -Negative and HER2-Positive[m] | |
|---|---|
| See BINV-Q (1) for Considerations for systemic HER2-targeted therapy. | |
| **Setting** | **Regimen** |
| **First Line[n]** | Pertuzumab + trastuzumab + docetaxel (category 1, preferred) |
| | Pertuzumab + trastuzumab + paclitaxel (preferred) |
| **Second Line[o]** | Fam-trastuzumab deruxtecan-nxki[n] (category 1, preferred) |
| **Third Line** | Tucatinib + trastuzumab + capecitabine (category 1, preferred) |
| | Ado-trastuzumab emtansine (T-DM1)[p] |
| **Fourth Line and Beyond (optimal sequence is not known)[q]** | Trastuzumab + docetaxel or vinorelbine |
| | Trastuzumab + paclitaxel ± carboplatin |
| | Capecitabine + trastuzumab or lapatinib |
| | Trastuzumab + lapatinib (without cytotoxic therapy) |
| | Trastuzumab + other chemotherapy agents[r,s] |
| | Neratinib + capecitabine |
| | Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) |
| | Abemaciclib in combination with fulvestrant and trastuzumab (for HR+ only) (category 2B) |
| | Targeted Therapy and emerging biomarker Options BINV-Q (7) and BINV-Q (8) |

[a] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[l] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARPi therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline mutation. There is lower-level evidence for HER2-positive tumors, therefore category 2A for this setting.
[m] Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+ metastatic breast cancer).
[n] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]). Fam-trastuzumab deruxtecan-nxki is associated with ILD/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.
[o] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.
[p] May be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known. If not a candidate fam-trastuzumab T-DM1 could be considered in the second-line.
[q] Multiple lines of concurrent chemotherapy with anti-HER2 therapy (trastuzumab or a TKI) offer clinical benefit for recurrent unresectable HER2+ metastatic breast cancer and have been studied in phase 2 or 3 trials. Clinical experience suggests frequent clinical benefit for such treatment. However, there are no meaningful data for use of any of these regimens among patients previously treated with pertuzumab-based chemotherapy, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, or trastuzumab/capecitabine/tucatinib regimens. Thus, the optimal sequence or true benefit of therapy is not known.
[r] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[s] Trastuzumab may be safely combined with all non-anthracycline–containing preferred and other single agents listed on (BINV-Q 5) for recurrent or metastatic breast cancer.

**Note: All recommendations are category 2A unless otherwise indicated.**





## ASCO

***Second-line.***

**Recommendation 2.1.**

If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy (and the patient has not received trastuzumab deruxtecan [T-Dxd]), clinicians should recommend T-Dxd as a second-line treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong). *New/changed.*

NCCN Guidelines 3.2025; Giordano et al JCO 2022

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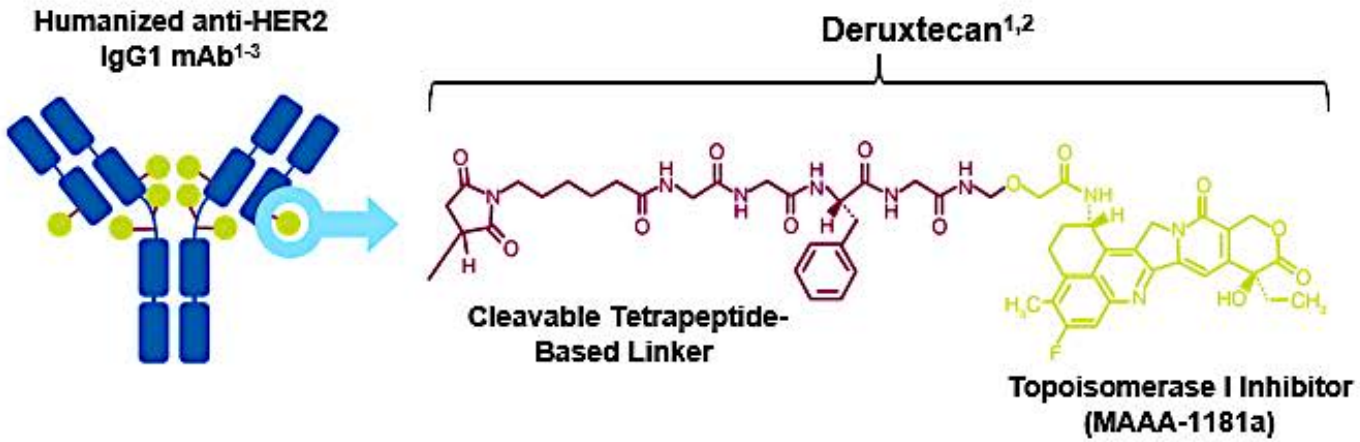
# Trastuzumab Deruxtecan

**An ADC composed of 3 components[1,2]:**

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:
  - A topoisomerase I inhibitor, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker




| | T-DM1 Attributes |
|---|---|
| 1 Payload MOA: topoisomerase I inhibitor[1,2,a] | Microtubule inhibitor[5] |
| 2 High potency of payload[1,2,a] | |
| 3 High DAR≈8[1,2,a] | DAR≈3.5[3,6] |
| 4 Payload with short systemic half-life[1,2,a] | |
| 5 Stable linker-payload[1,2,a] | |
| 6 Tumor-selective cleavable linker[1,2,a] | Non-cleavable linker[6] |
| 7 Membrane permeable payload[1,4,a] | Less membrane permeable[4] |

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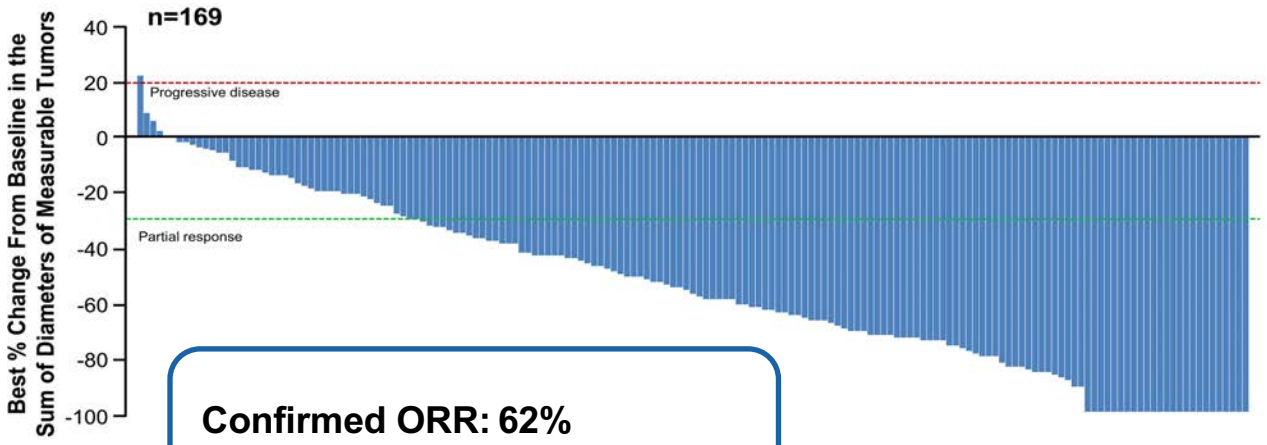
# DESTINY-Breast01:

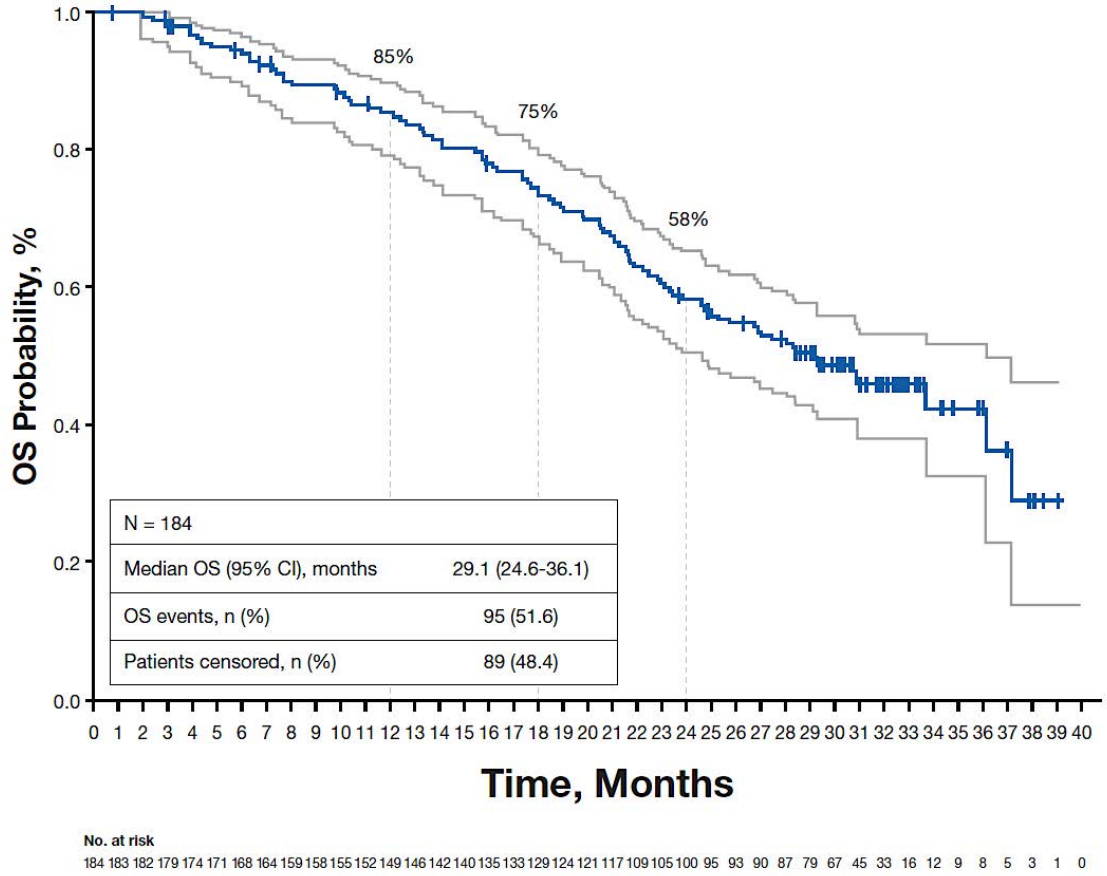
## T-DXd is Highly Active in HER2+ MBC

**Best Percentage Change From Baseline in Tumor Size (by ICR)**




**Confirmed ORR: 62%**
(95% CI, 54.5%–69.0%)

**Median Overall Survival = 29 months!**




Modi et al Destiny Breast01; Saura C, et al. ESMO 2021. Abstract 279P; Saura C, et al. Ann Oncol 2024 35(3):302-307.

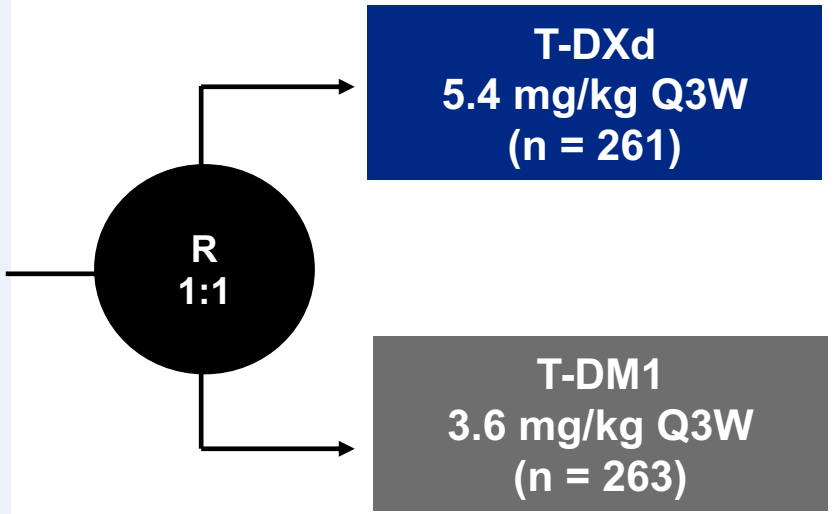
# DESTINY-Breast03: Phase 3 RCT

## Patients

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

## Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease




## Primary endpoint

- PFS (BICR)

## Key secondary endpoint

- OS

## Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

**Key Characteristics:**

- 100% received prior trastuzumab
- 60% received prior pertuzumab
- 16% received HER2 TKI
- 50% were treated in the 2L setting, ~50% were 3L+
- 22% had brain metastases

Cortes, J et al. ESMO 2021

[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

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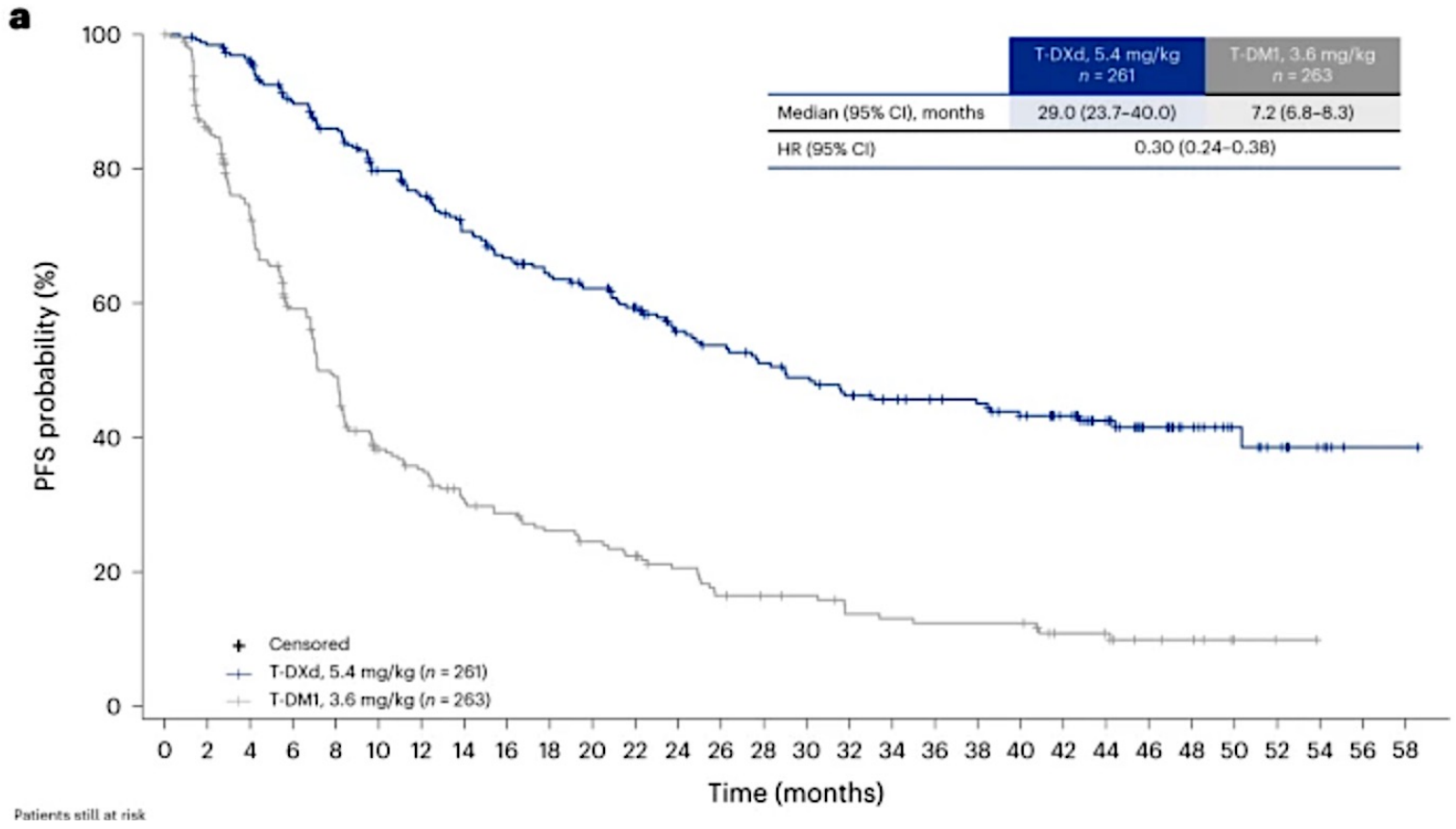
# DESTINY-Breast03: Primary Endpoint - PFS

**Fig. 2: Kaplan–Meier estimates.**




| | T-DXd, 5.4 mg/kg n = 261 | T-DM1, 3.6 mg/kg n = 263 |
|---|---|---|
| Median (95% CI), months | 29.0 (23.7–40.0) | 7.2 (6.8–8.3) |
| HR (95% CI) | 0.30 (0.24–0.38) | |

**Median OS was 52.6 months (95% CI, 48.7 months to NE) with T-DXd vs. 42.7 months (95% CI, 35.4 months to NE) with T-DM1**

**(HR, 0.73; 95% CI, 0.56–0.94)**

Cortes et al Nature Medicine June 2024; Hamilton et al. ASCO 2024;Abstract 1025.

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Cortes, J et al. ESMO 2021

# T-DXd Toxicity Considerations

**≥Gr 3**

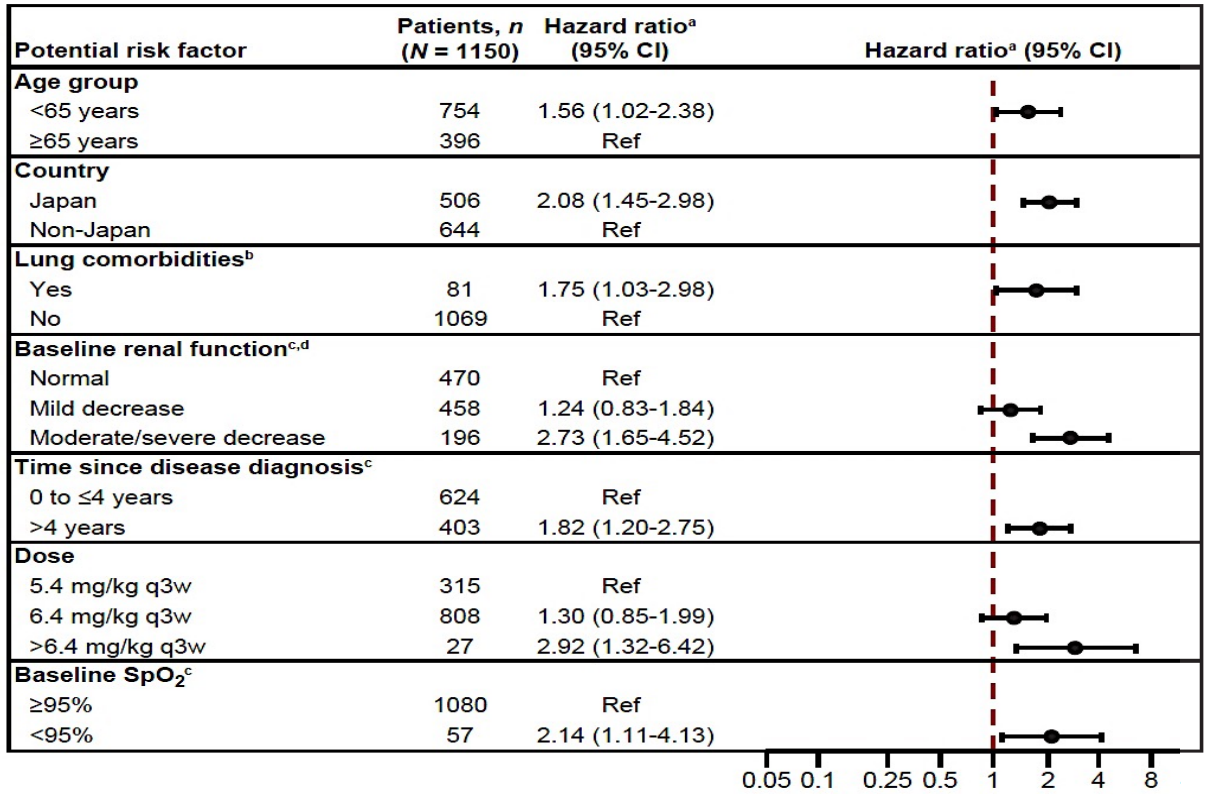
- Nausea: 7% (all grade 77%)
- Vomiting 2% (all grade 52%)
- Thrombocytopenia 8% (25%)
- Alopecia <1% (40%)

**Don't forget cardiac monitoring**

Treatment related discontinuation for
T-DXd 20% vs T-DM1 6.5%
Median duration of treatment was
18.2 mo. vs. 6.9 mo

**Adjudicated drug-related ILD/pneumonitis events for the entire study period through November 20, 2023 (DCO)**

| n (%)[a] | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any grade |
|---|---|---|---|---|---|---|
| T-DXd (n = 257)[b] | 11 (4.3) | 30 (11.7) | 2 (0.8) | 0 | 0 | 43 (16.7) |
| T-DM1 (n = 261)[b] | 5 (1.9) | 3 (1.1) | 1 (0.4) | 0 | 0 | 9 (3.4) |




Hurvitz et al Lancet 2023; Powell et al ESMO Open 2022; Hamilton et al. ASCO 2024;Abstract 1025.

# Brain metastases: unmet need

- 17 studies with 5,971 patients reported a pooled cumulative incidence of brain metastases of 31% over a median follow-up of approximately 31 months.

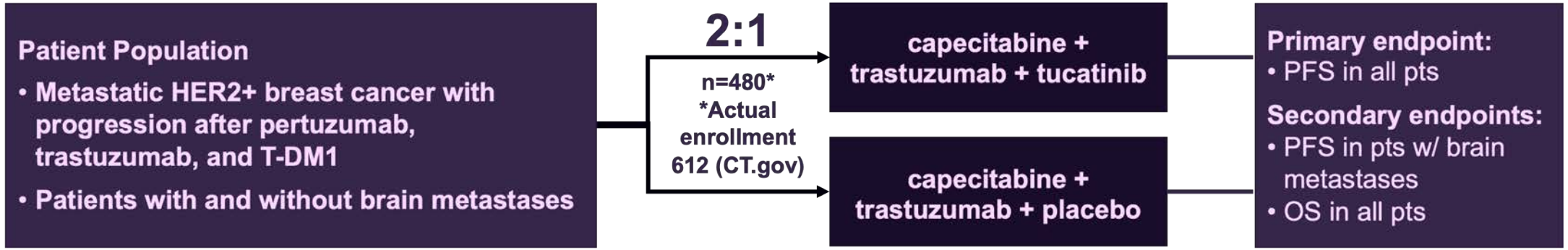
- Flatiron Health database ~17,000 patients:  by 4L therapy the incidence of brain metastases is:
  - **HR-/HER2+:** 37.1%
  - **HR+/HER2+:** 26.1%

- Median Overall Survival when diagnosed with breast cancer brain metastases (BCBM) ~ 6-15 mo

- Important considerations include symptom management, palliative goals, loss of function and independence, impact of local therapies (ie, RT), social supports, proxy designation

Kuksis et al Neuro Oncol 2020; Sammons et al SABCS 2023;
Raghavendra et al JCO OP May 2024

# HER2CLIMB: Tucatinib, Trastuzumab and Capecitabine



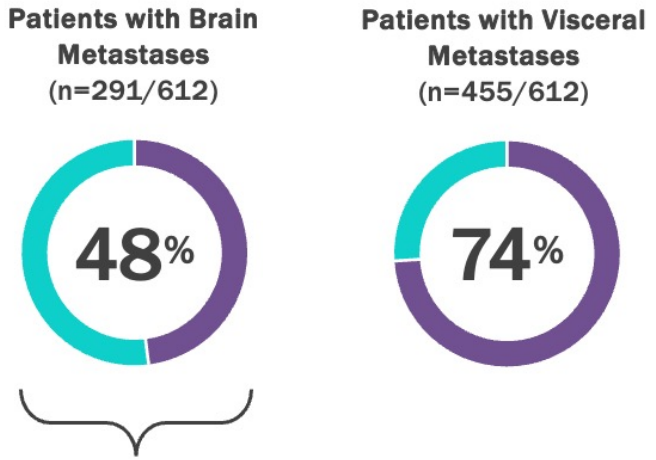

Tucatinib is an oral, HER2 selective kinase inhibitor

Key characteristics:

All had prior trastuzumab, pertuzumab, T-DM1

75% had visceral disease

Brain metastases enrollment robust…




- 40% had stable BM
- 60% had active BM
  - 23% had untreated progressing BM
  - 37% had treated but progressing BM

Murthy RK, et al. *N Engl J Med.* 2020;382:597-609.

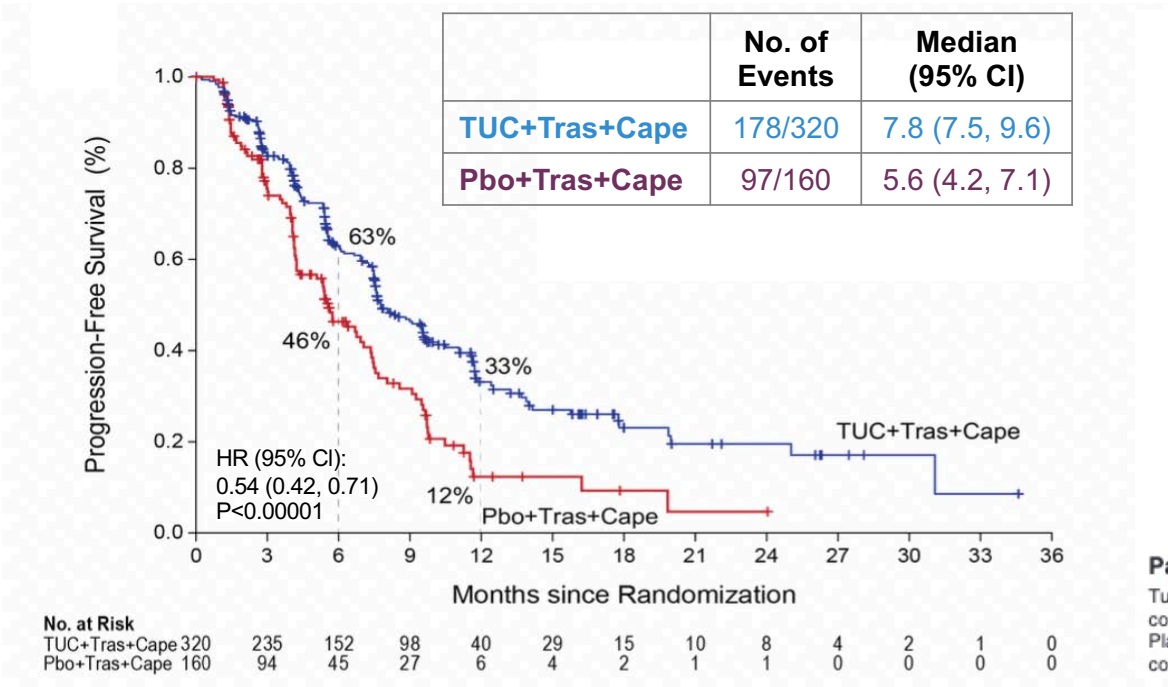
# HER2CLIMB:

## PFS and OS in Overall Population

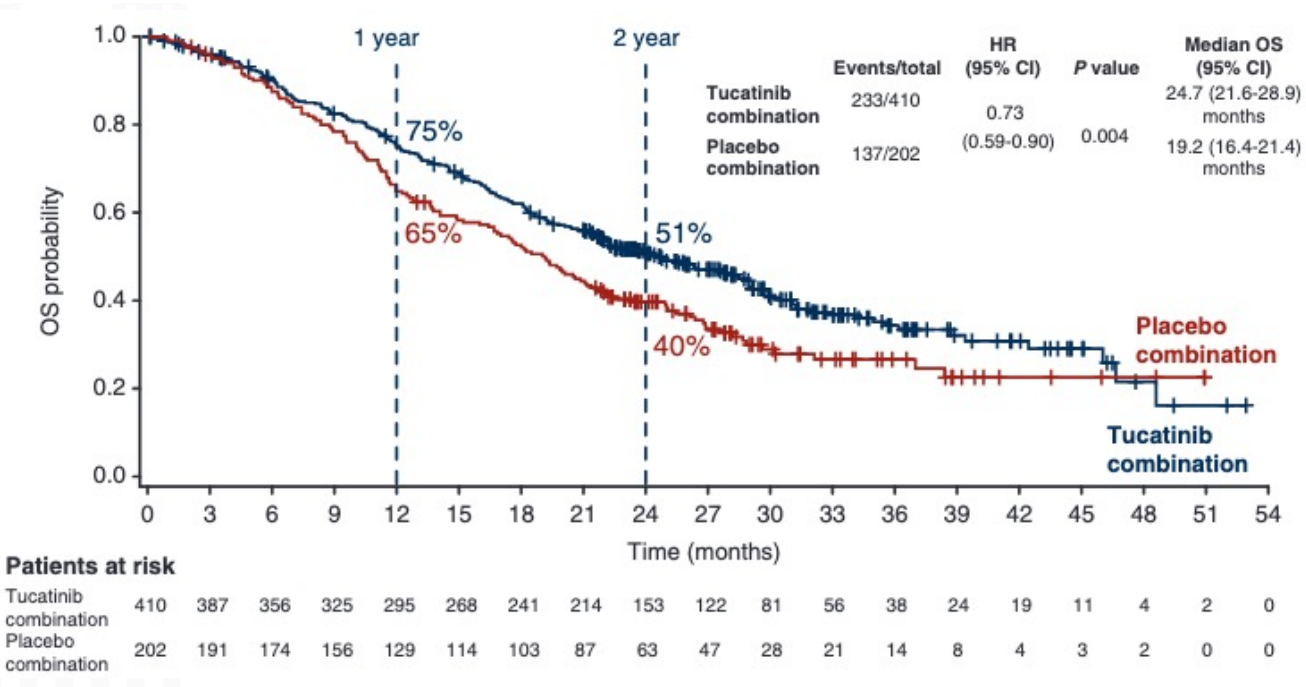
Indication - "...metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting".

### Progression-Free Survival by BICR (N=480)

| | No. of Events | Median (95% CI) |
|---|---|---|
| TUC+Tras+Cape | 178/320 | 7.8 (7.5, 9.6) |
| Pbo+Tras+Cape | 97/160 | 5.6 (4.2, 7.1) |




### Overall Survival (N=612)




| | Events/total | HR (95% CI) | P value | Median OS (95% CI) |
|---|---|---|---|---|
| Tucatinib combination | 233/410 | 0.73 (0.59-0.90) | 0.004 | 24.7 (21.6-28.9) months |
| Placebo combination | 137/202 | | | 19.2 (16.4-21.4) months |

Murthy RK, et al. N Engl J Med. 2020;382:597-609; Curigliano G et al. Ann Oncol 2022;33(3):321-29.

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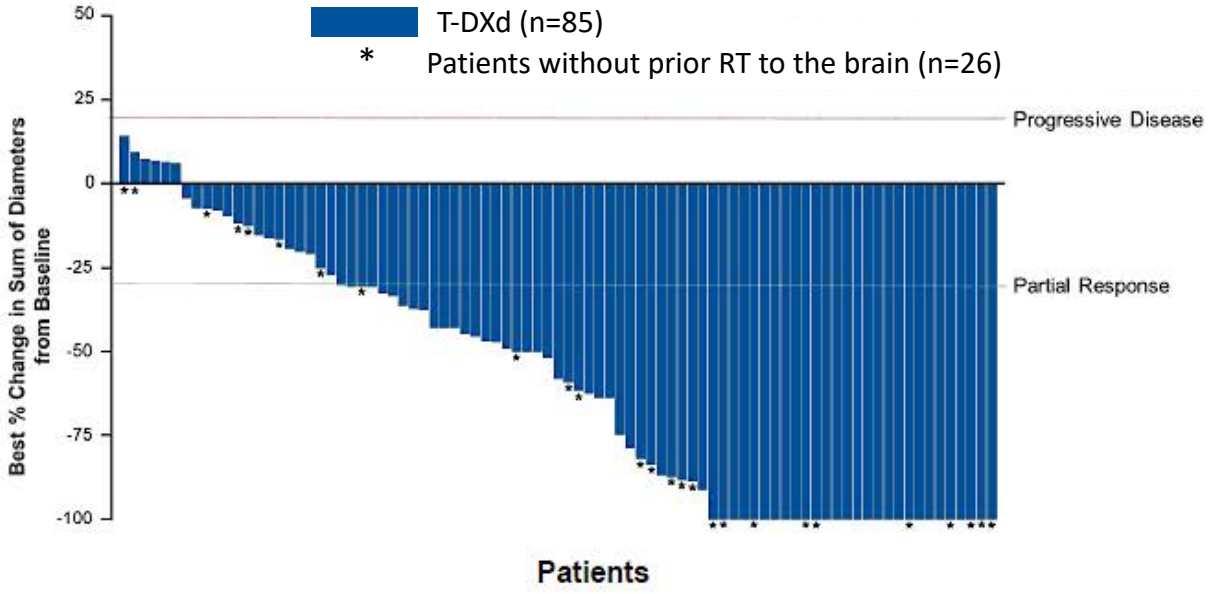
# HER2CLIMB:

## Key Safety Event is Diarrhea

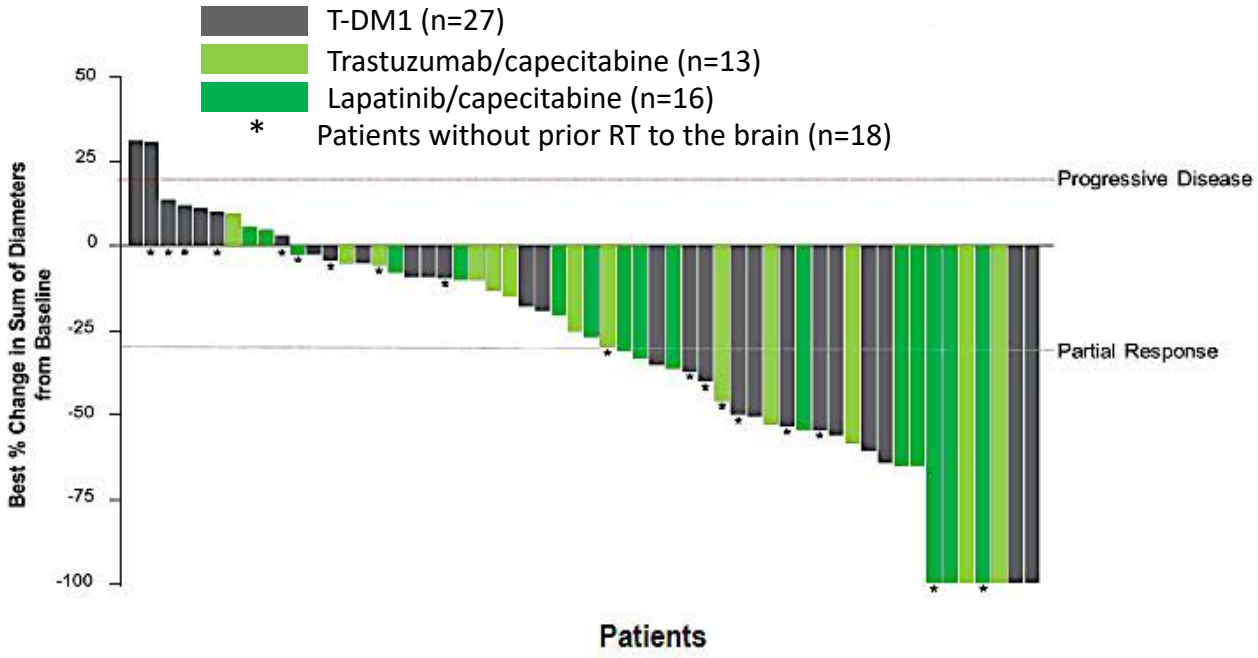
- Most common AE in both arms (82% tucatinib arm vs 54% control arm); Grade ≥3: 13% vs 9%
- The median time to onset of any grade diarrhea was 12 days, and the median time to resolution was 8 days
- Treatment discontinuation of tucatinib due to diarrhea occurred in 1% of patients
- Antidiarrheal prophylaxis:
  - Antidiarrheals used in less than half of all cycles where diarrhea was reported
  - When used, duration of antidiarrheal treatment was short (median of 3 days/cycle) and the same in both arms

# DESTINY-Breast01, -02, and -03 Pooled Analysis: T-DXd in HER2+ MBC With Brain Metastases

T-DXd




Comparator




For patients with measurable brain lesion(s) at baseline and at least 1 postbaseline assessment.

Hurvitz SA, et al. ESMO 2023. Abstract 377O; Andes F Ann Oncol 2024;35(12):1169-80.

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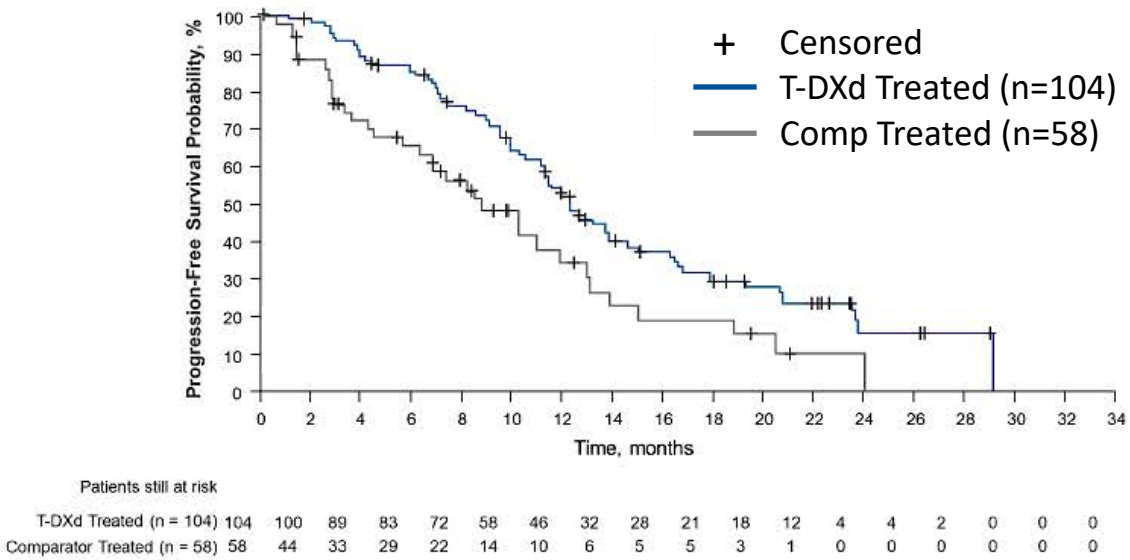
# DESTINY-Breast01, -02, and -03 Pooled Analysis Exploratory CNS-PFS

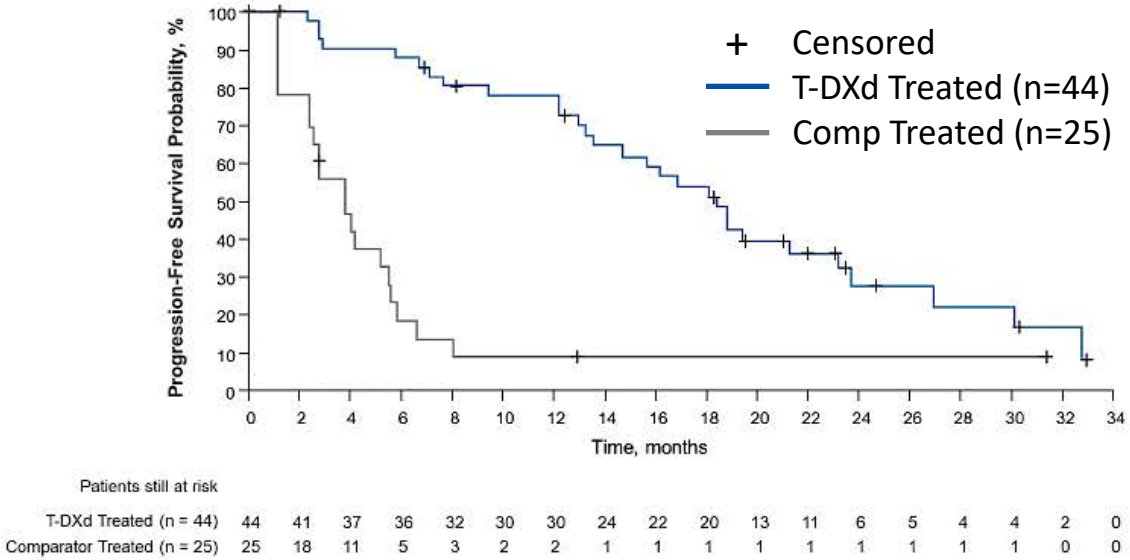
## CNS-PFS in Treated/Stable BMs




| Treated/Stable BMs | T-DXd (n=104) | Comparator (n=58) |
|---|---|---|
| Median CNS-PFS, mo (95% CI) | 12.3 (11.1-13.8) | 8.7 (6.3-11.8) |
| HR (95% CI) | 0.59 (0.39-0.89) | |

Treated/stable BMs: Patients have received prior CNS-directed therapy for their BMs, and their CNS disease is stable

## CNS-PFS in Untreated/Active BMs




| Untreated/Active BMs | T-DXd (n=44) | Comparator (n=25) |
|---|---|---|
| Median CNS-PFS, mo (95% CI) | 18.5 (13.6-23.3) | 4.0 (2.7-5.7) |
| HR (95% CI) | 0.19 (0.11-0.35) | |

Untreated/active BMs: Patients have new BMs or progressive BMs that have not been subjected to CNS-directed therapy since documented progression

Hurvitz SA, et al. ESMO 2023. Abstract 377O; Andes F Ann Oncol 2024;35(12):1169-80.

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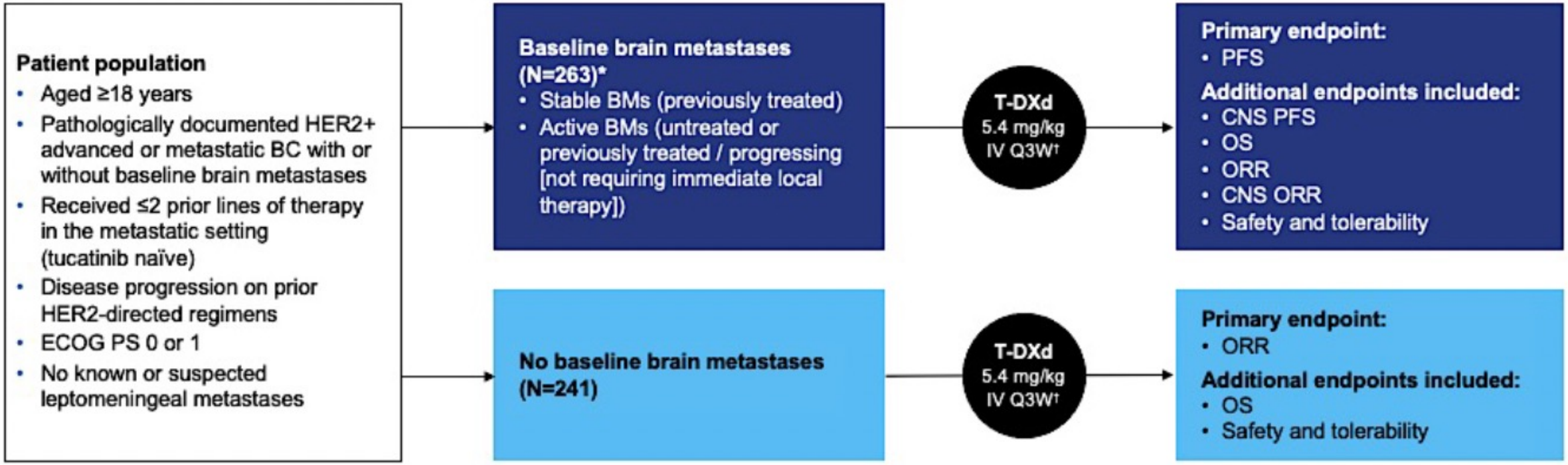
# DESTINY-Breast12: T-DXd for HER2+ Brain Mets

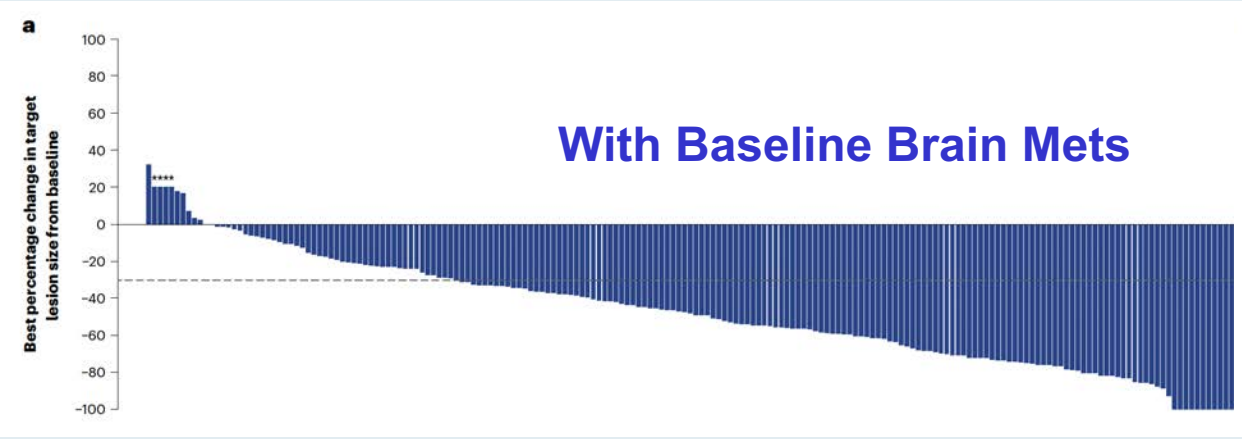
Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs




Harbeck N et al. *Nat Med* 2024;30(12):3717-3727.

RTP RESEARCH TO PRACTICE

# DESTINY-Breast12: T-DXd for HER2+ Brain Mets





| | Patients with baseline BMs (*N*=263) | | | Patients with no baseline BMs (*N*=241) |
|---|---|---|---|---|
| | Overall (*N*=263) | Stable BMs (*n*=157) | Active BMs (*n*=106) | Overall (*N*=241) |
| 12-month PFS, % (95% CI)[a] | 61.6 (54.9–67.6) | 62.9 (54.0–70.5) | 59.6 (49.0–68.7) | – |
| 12-month CNS PFS, % (95% CI)[a] | 58.9 (51.9–65.3) | 57.8 (48.2–66.1) | 60.1 (49.2–69.4) | – |
| Median PFS, months (95% CI)[b] | 17.3 (13.7–22.1) | NR | NR | – |
| 12-month OS, % (95% CI) | 90.3 (85.9–93.4) | 93.2 (87.7–96.3) | 86.1 (77.6–91.5) | 90.6 (86.0–93.8) |
| Confirmed ORR, % (95% CI)[a,c] | 51.7 (45.7–57.8) | 49.7 (41.9–57.5) | 54.7 (45.2–64.2) | 62.7 (56.5–68.8) |

Harbeck N et al. *Nat Med* 2024;30(12):3717-3727.

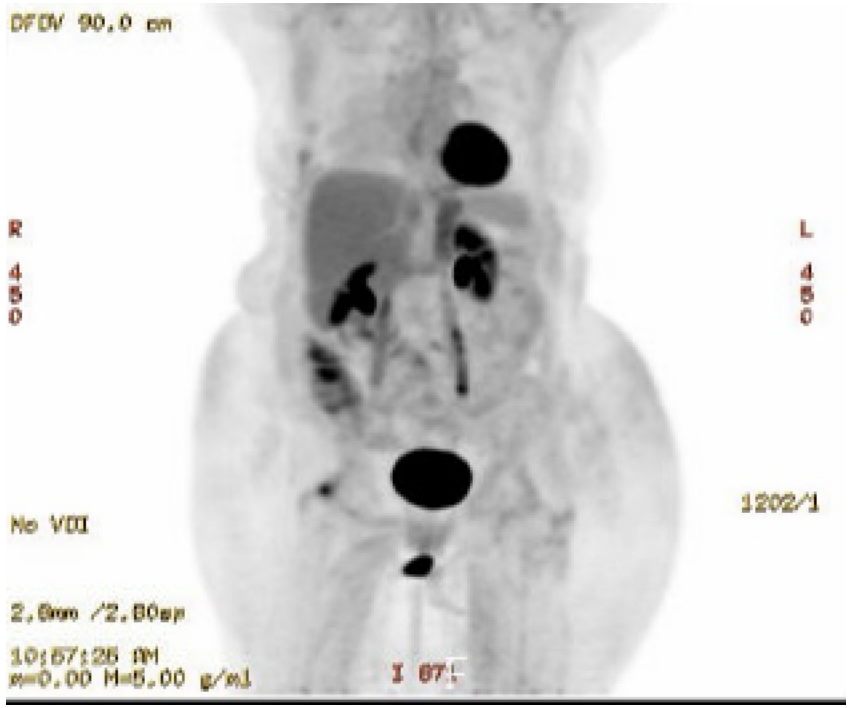
# How do I choose in 2L?

## Shared decision making

| | T-DXd | HER2Climb Regimen |
|---|---|---|
| **PRO** | • Superiority in PFS/OS compared to prior 2L Standard of care<br>• Does have non-Ph 3 signs of activity in BCBM<br>• Convenient q3 week schedule | • Impressive OS and activity in patients with BCBM and ITT<br>• All oral regimen<br>• No alopecia |
| **CON** | • ILD risk is rare but non-trivial including Gr 5 events<br>• ~40% all grade alopecia with uncertain scalp cooling benefit<br>• IV therapy<br>• No randomized data for sequencing | • Control arm not typical 2L SOC<br>• All oral regimen may be complicated for some<br>• Large pill burden<br>• Overlapping GI toxicity with cape and tucatinib<br>• Diarrhea<br>• No randomized data for sequencing |

# ER(-) HER2+ MBC

- 69 yo woman diagnosed with de novo MBC ER(-) HER2 3+ to brain, bone, liver in 3/2015
- 1L: weekly paclitaxel + HP x 6 mo with near CR → HP alone
- 3/2016 new brain lesions s/p WBXRT; continued HP
- 4/2024 LE weakness, spinal uptake on imaging, MRI concerning for LMD, LP cytology +
  - T-DXd → improved MRI, cleared cytology, improved function but increasing fatigue/nausea
  - Dose reduced x2 since




PET Feb 2025 NED

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# ER(-) HER2+ MBC

- 56 yo woman diagnosed with pT1No ER"+" HER2? in 2006. Declined therapy.
- 2008 Local recurrence s/p TM for ER+ HER2 3+ BC s/p ddAC-TH → Tam until self d/c in 2011
- 2012 Local rec s/p excision → OS/letrozole/H → pt self d/c'd 2012
- Reestablished care 2013 and resumed letrozole
- 2019 Diagnosed with cervical cancer s/p Cis/RT
- 3/2022 CT CAP for cervical ca = liver & bone lesions
  - Liver Bx metastatic breast ca ER+ HER2 3+

THP x4mo → HP + denosumab maintenance
NED by 8/2022

6/2023 POD in oligo bone
RT to humerus

8/2023 POD in bone and liver
Started T-DXd

8/2023 POD in bone and liver
Started T-DXd

**Excellent response**
1/2025 Inc SOB/dry cough
GGO, Pulm, Steroids
Holding T-DXd for ?ILD

# Roundtable Discussion

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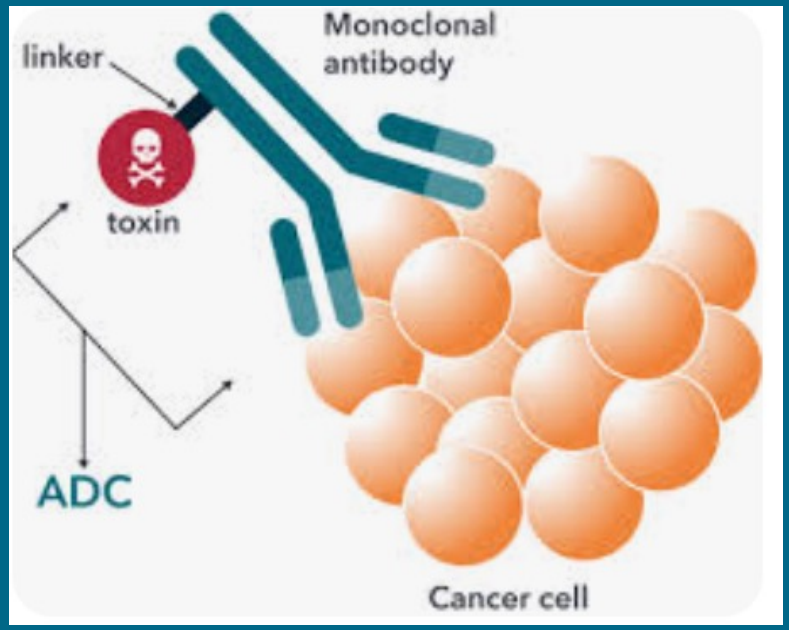
# Antibody-Drug Conjugates

**Marissa Marti-Smith**
DNP, APRN, AGNP-C, AOCNP

Breast Oncology
Nurse Practitioner

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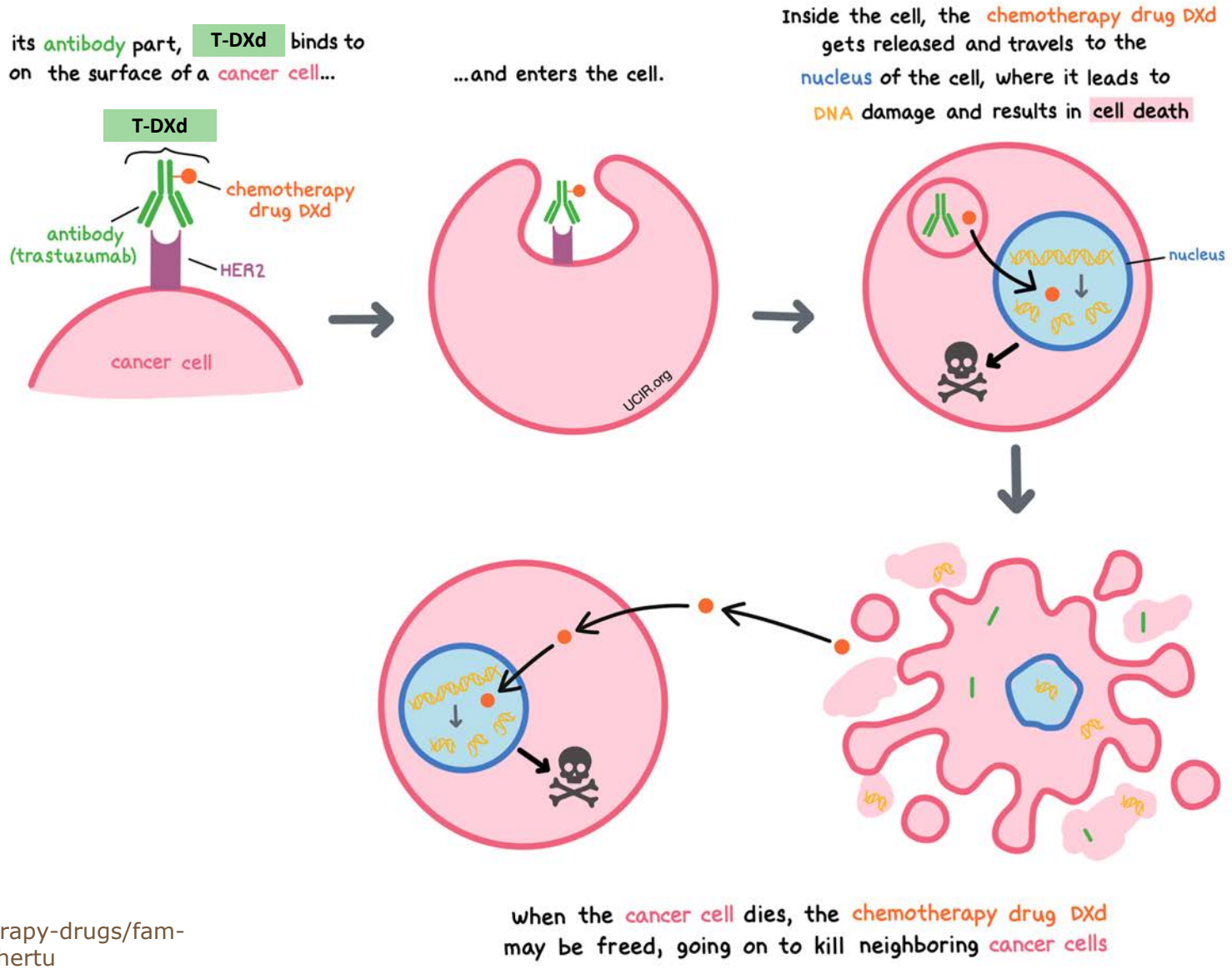
# T-DXd (Trastuzumab deruxtecan)




https://www.ucir.org/immunotherapy-drugs/fam-trastuzumab-deruxtecan-nxki-enhertu

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# Patient Education

1. Her2+ target
2. **Guided missile analogy**
   - Target > deliver > destroy
   - Her2 antibody > linker > Deruxtecan
   - Bystander antitumor effect
3. Positive data on longer PFS

(Rugo et al, 2023)

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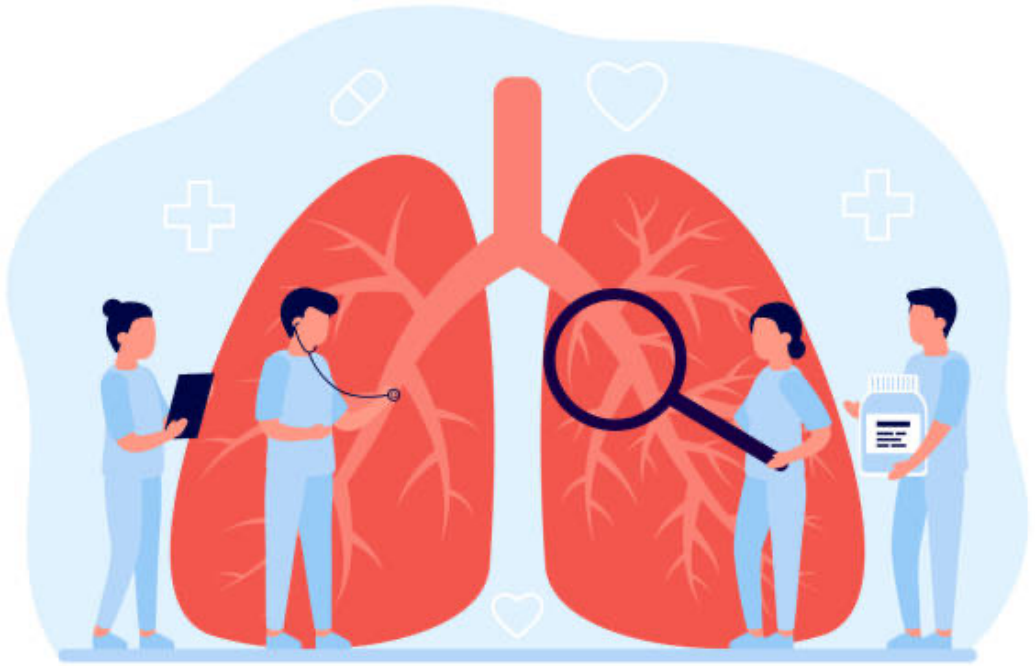
# T-DXd toxicity monitoring



**ILD**

- ✓ Baseline O2 sats
- ✓ HRCT every 12 weeks (if higher risk q6-9 weeks)
- ✓ Consider PFTs
- ✓ Higher risk pts
  - *Pts with lower O2 levels*
  - *Japanese ancestry*
  - *Poor renal function*
  - *Decreased lung function as baseline*

(Rugo et al, 2023)

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# Management of ILD

**TABLE 1.** T-DXd Prescribing Information and DESTINY-Breast03 and DESTINY-Breast04 Protocol-Recommended Dose Modifications for Pneumonitis/ILD[4,7,9]

| Severity | Treatment | |
|---|---|---|
| Asymptomatic pneumonitis/ILD (grade 1) | Interrupt T-DXd until resolved to grade 0, then<br>If resolved in 28 days or less from date of onset, maintain dose<br>If resolved in >28 days from date of onset, reduce dose 1 level per the recommendations below<br>However, if the grade 1 pneumonitis/ILD event occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued<br>Consider corticosteroid treatment (eg, ≥0.5 mg/kg/d prednisolone or equivalent) as soon as pneumonitis/ILD is suspected | |
| | Dose reduction schedule | Breast cancer |
| | Recommended starting dose | 5.4 mg/kg |
| | First dose reduction | 4.4 mg/kg |
| | Second dose reduction | 3.2 mg/kg |
| | Requirement for further dose reduction | Discontinue treatment |
| Symptomatic pneumonitis/ILD (grade 2 or greater) | Permanently discontinue T-DXd<br>Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg/d prednisolone or equivalent and continue for ≥14 days, followed by gradual taper for ≥4 weeks) as soon as pneumonitis/ILD is suspected | |

Abbreviations: ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

(Rugo et al, 2023)

**TABLE 2.** Recommended Guidance for Toxicity Management of T-DXd–Induced Pneumonitis/ILD From the DESTINY-Breast03 and DESTINY-Breast04 Protocols[7,9]

| Clinical Approach | Grade 1 | Grade 2 | Grades 3 and 4 |
|---|---|---|---|
| Monitoring | Monitor and closely follow up in 2-7 days for onset of clinical symptoms and pulse oximetry | Monitor symptoms closely | Hospitalization required |
| Corticosteroid treatment | Consider starting systemic corticosteroids (eg, ≥0.5 mg/kg/d prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks | Promptly start systemic corticosteroids (eg, ≥1 mg/kg/d prednisone or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks | Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1,000 mg/d for 3 days), followed by ≥1 mg/kg/d of prednisone or equivalent for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks |
| Imaging | Consider follow-up imaging in 1-2 weeks (or as clinically indicated) | Reimage as clinically indicated | |
| Worsening of or no improvement in pneumonitis/ILD | If worsening of diagnostic observations despite initiation of corticosteroids, then follow grade 2 guidelines (if the patient is asymptomatic, then they should still be considered as grade 1, even if corticosteroid treatment is given) | If worsening or no improvement in clinical or diagnostic observations in 5 days:<br>Consider increasing dose of corticosteroids (eg, 2 mg/kg/d prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone)<br>Reconsider additional workup for alternative etiologies, as described above<br>Escalate care as clinically indicated | If still no improvement within 3-5 days:<br>Reconsider additional workup for alternative etiologies, as described above<br>Consider other immunosuppressants and/or treat per local practice |

(Rugo et al, 2023)

# T-DXd Patient Case Study

| |
|---|
| 74-year-old female |
| 4th line, mBC (bone), hx renal insufficiency |
| Cycle 4 (full dose 5.4 mg/kg) |
| AE: fatigue, nausea (x 8 days) |
| Routine CT chest showed ground glass changes upper lobes, pt asymptomatic |
| Prednisone taper, held treatment x 3-4 weeks, reimaged |
| Restarted, dose reduction 4.4 mg/kg |
| Continued until Cycle 21 (d/c'ed due to progressive disease) |

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# Roundtable Discussion

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# Agenda

**Module 1:** Overview of Antibody-Drug Conjugates (ADCs)

**Module 2:** Trastuzumab Deruxtecan (T-DXd) in Patients with HER2-Positive Metastatic Breast Cancer (mBC) with and without Brain Metastases

**Module 3: Role of ADCs for Patients with ER-Positive mBC**

**Module 4:** T-DXd in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) with HER2 Alterations

**Module 5:** Emerging Role of ADCs for Patients with Progressive EGFR-Mutant NSCLC

# Clinical Scenario

**A patient with ER-positive, HER2-low mBC who has received multiple lines of standard treatment, including endocrine therapy, capecitabine, T-DXd and sacituzumab govitecan, is about to start therapy with datopotamab deruxtecan**

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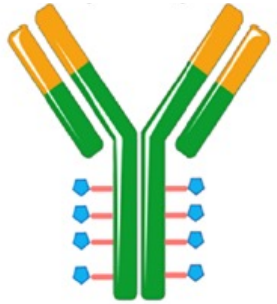
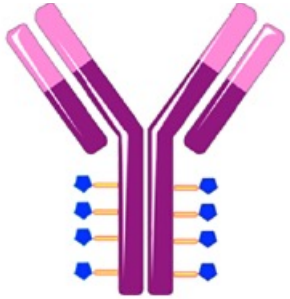
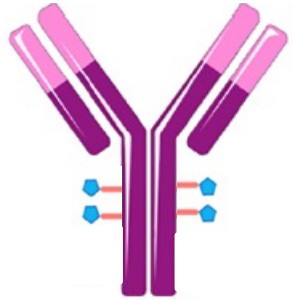
# ADCs @ ONS

Tiffany A. Traina, MD FASCO
Associate Attending, Breast Medicine Service
Vice Chair, Department of Medicine
Section Head, TNBC Clinical Research Program
Memorial Sloan Kettering Cancer Center
Associate Professor, Weill Cornell Medicine

Memorial Sloan Kettering Cancer Center

# ADCs in ER+ MBC

| | T-DXd | Sacituzumab Govitecan | Dato-DXd |
|---|---|---|---|
| |  |  |  |
| **Monoclonal antibody** | Trastuzumab | Sacituzumab | Datopotamab |
| **Target antigen** | HER2 | Trop2 | Trop2 |
| **Payload** | Deruxtecan | SN-38 (irinotecan metabolite) | Deruxtecan |
| **Payload class** | Topo-I inhibitor | Topo-I inhibitor | Topo-I inhibitor |
| **Bystander effect** | Yes | Yes | Yes |
| **Linker subtype** | Cleavable | Cleavable | Cleavable |
| **Drug:Antibody Ratio** | ~8:1 | ~8:1 | 4:1 |
| **Half-life** | ~7 days | ~15 hours | ~5 days |

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# ADCs in ER+ MBC

| | T-DXd | Sacituzumab Govitecan | Dato-DXd |
|---|---|---|---|
| | DB04, DB06 | Tropics02 | TROPION Breast01 |
| Need testing for target expression? | Yes, HER2 low (1+, 2+) or Ultralow | No | No |
| FDA indication | • HER2 low or UL after 1 or more endocrine tx<br>• HER2 low after 1 prior chemo | • Endocrine tx and at least two additional systemic therapies in the metastatic setting | • Endocrine tx and chemotherapy for metastatic disease |
| Main toxicity | Nausea, alopecia, ILD, LVEF | Diarrhea, neutropenia | Stomatitis, rare ocular events, rare ILD |
| Sequencing data | There are no prospective randomized sequencing data to guide decision-making | | |

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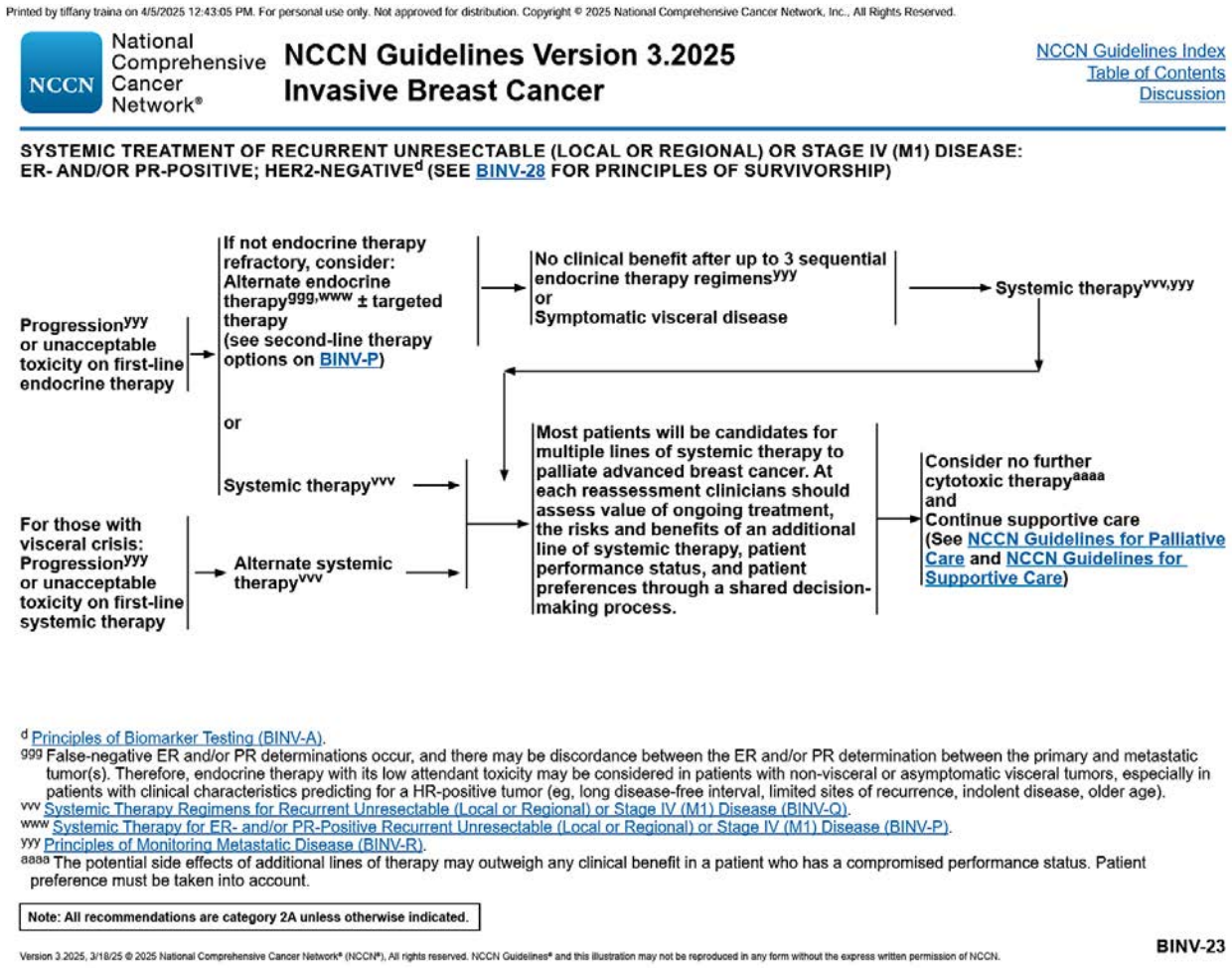
# Approach to ER+ MBC before ADCs





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**NCCN Guidelines Version 3.2025**
**Invasive Breast Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

**SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-POSITIVE; HER2-NEGATIVE[d] (SEE BINV-28 FOR PRINCIPLES OF SURVIVORSHIP)**

**Progression[yyy] or unacceptable toxicity on first-line endocrine therapy**

→ **If not endocrine therapy refractory, consider: Alternate endocrine therapy[ggg,www] ± targeted therapy (see second-line therapy options on BINV-P)**

→ **No clinical benefit after up to 3 sequential endocrine therapy regimens[yyy] or Symptomatic visceral disease**

→ **Systemic therapy[vvv,yyy]**

**or**

**Systemic therapy[vvv]**

**For those with visceral crisis: Progression[yyy] or unacceptable toxicity on first-line systemic therapy**

→ **Alternate systemic therapy[vvv]**

→ **Most patients will be candidates for multiple lines of systemic therapy to palliate advanced breast cancer. At each reassessment clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared decision-making process.**

→ **Consider no further cytotoxic therapy[aaaa] and Continue supportive care (See NCCN Guidelines for Palliative Care and NCCN Guidelines for Supportive Care)**

[d] Principles of Biomarker Testing (BINV-A).
[ggg] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a HR-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).
[vvv] Systemic Therapy Regimens for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-Q).
[www] Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-P).
[yyy] Principles of Monitoring Metastatic Disease (BINV-R).
[aaaa] The potential side effects of additional lines of therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

**Note: All recommendations are category 2A unless otherwise indicated.**

BINV-23



Serial sequential endocrine therapies beginning with CDK4/6i

Biomarker driven targeted options to overcome endocrine resistance:

- PI3K } alpelisib
- AKT
- PTEN } capivasertib
- ESR1 } elacestrant
- BRCA1 or BRCA2 } olaparib, talazoparib

**Generally exhaust endocrine options and transition to ADCs or chemotherapy upon endocrine resistance**

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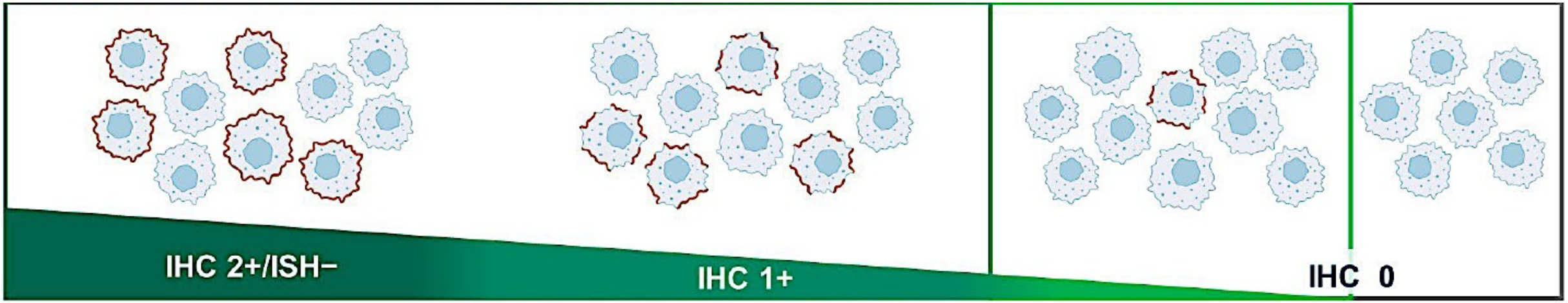
# HER2 IHC Categories Within HR+/HER2– MBC

**HER2-low**
~60% to 65% of HR+/HER2– MBC

**HER2-ultralow**
~20% to 25% of HR+/HER2– MBC




| IHC 2+/ISH– | IHC 1+ | IHC 0 | |
|---|---|---|---|
| Weak-to-moderate complete membrane staining in >10% cells | Faint, incomplete membrane staining in >10% tumor cells | Faint, incomplete membrane staining in ≤10% tumor cells | Absent/no observable membrane staining |

Curigliano G, et al. ASCO 2024. Abstract LBA1000.

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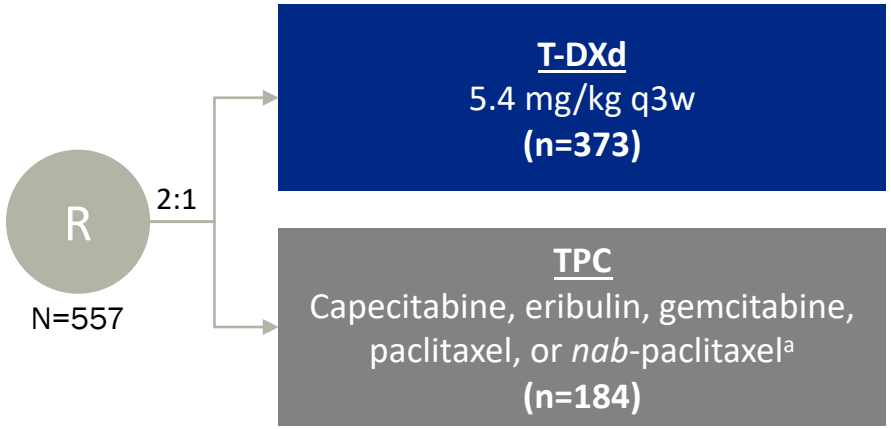
# DESTINY-Breast04: T-DXd in HER2 low MBC

## 30% improvement in OS!

### Key Eligibility Criteria

- HER2-low (IHC 1+ or IHC 2+/ISH–) unresectable and/or MBC
- ≥1 prior line of chemotherapy in the metastatic setting
- ≥1 line of ET if HR+ MBC




**Primary endpoint:**
PFS by BICR (HR+)

**Key characteristics:**
~90% of population had HR+ disease
Median 1 prior line of chemo
2% had 3 or more lines of chemo
Median 2 prior ET

| | PFS in HR+ Patients (by INV) | | OS in HR+ Patients | |
|---|---|---|---|---|
| | T-DXd (n=331) | TPC (n=163) | T-DXd (n=331) | TPC (n=163) |
| Median, months | 9.6 (8.4-10.0) | 4.2 (3.4-4.9) | 23.9 (21.7-25.2) | 17.6 (15.1-20.2) |
| HR (95% CI) | 0.37 (0.30-0.46) | | 0.69 (0.55-0.87) | |

Modi et al ESMO 2023

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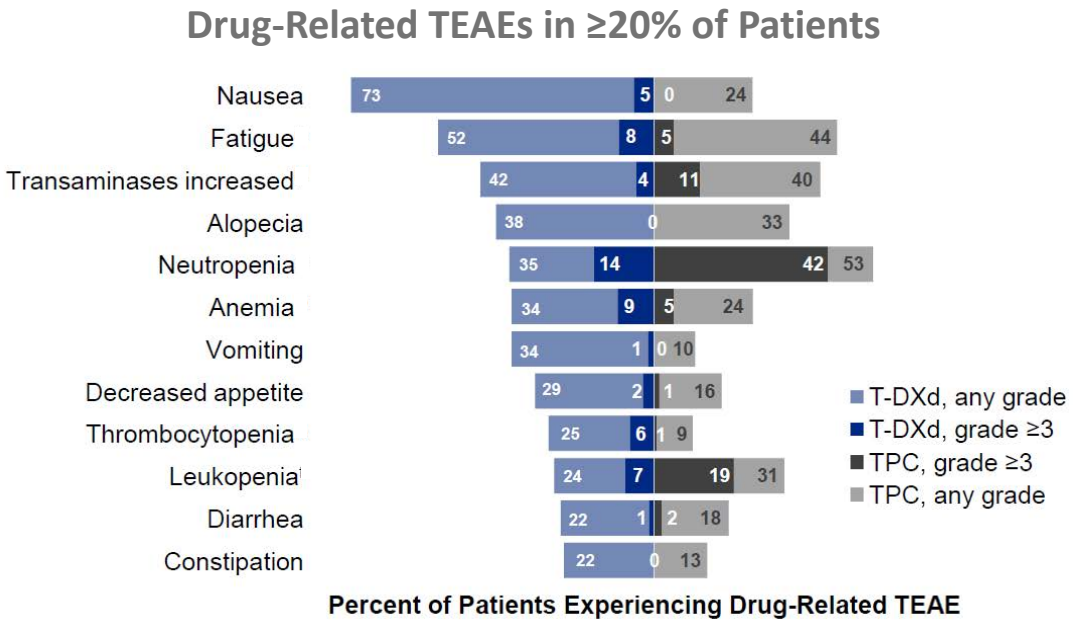
# DESTINY-Breast04: Safety

## Is the risk/benefit balance different in ER+ MBC?




Tx discontinuation 17%
54% Gr 3 or greater TEAEs
4% treatment related deaths (ILD)

| AEs of Special Interest, n (%) | | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any Grade |
|---|---|---|---|---|---|---|---|
| Adjudicated as drug-related ILD/pneumonitis | T-DXd (n=371) | 13 (3.5) | 24 (6.5) | 4 (1.1)[a] | 0 | 4 (1.1)[a] | 45 (12.1) |
| | TPC (n=172) | 1 (0.6) | 0 | 0 | 0 | 0 | 1 (0.6) |

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

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# DESTINY-Breast06: T-DXd in HER2-Low/Ultralow MBC and in earlier line of therapy

Key Eligibility Criteria

- HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) or HR+/HER2-ultralow (IHC 0 with membrane staining) MBC
- Chemotherapy-naive in the MBC setting
- ≥2 lines of ET ± targeted therapy for MBC OR
- 1 line for MBC AND
  - Progression ≤6 mo of starting 1L ET + CDK4/6i OR recurrence ≤24 mo of starting adjuvant ET

R 1:1

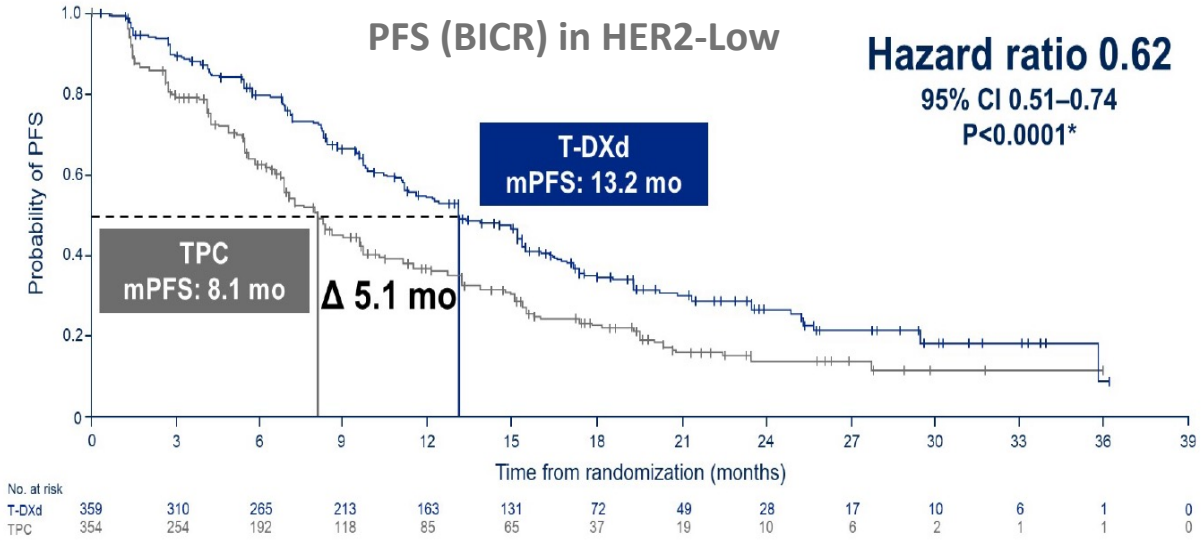
- T-DXd (n=436) 5.4 mg/kg q3w
- TPC (n=430) Capecitabine, *nab*-paclitaxel, paclitaxel

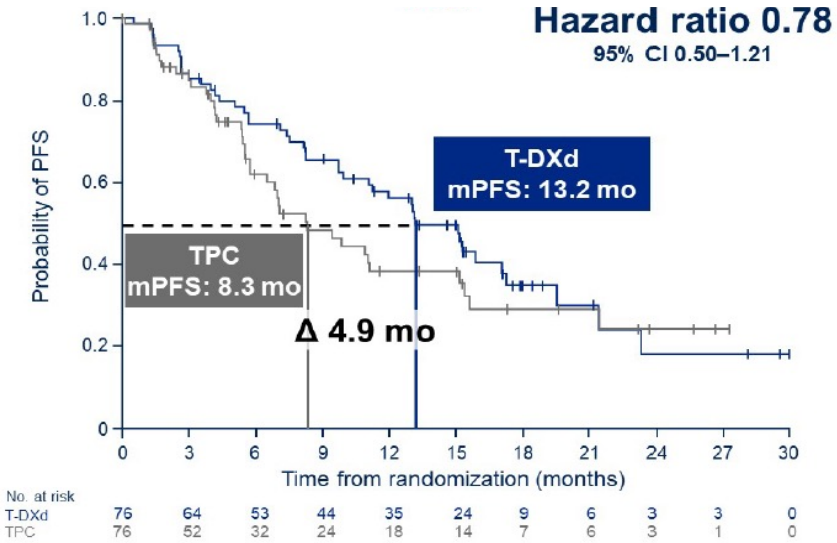
Stratification Factors

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

**ITT (N=866)**
**HER2-low (n=713)**
**HER2-ultralow (n=153)[b]**

**Primary endpoint:** PFS (BICR) in HER2-low




Curigliano G, et al. ASCO 2024. Abstract LBA1000; Bardia A et al. N Engl J Med 2024

# How do you weigh safety & efficacy?

| AESI Adjudicated as Drug-Related ILD/Pneumonitis[b] | | | | | | |
|---|---|---|---|---|---|---|
| n (%) | Any grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
| T-DXd (n=434) | 49 (11.3) | 7 (1.6) | 36 (8.3) | 3 (0.7) | 0 | 3 (0.7) |
| TPC (n=417) | 1 (0.2) | 0 | 1 (0.2) | 0 | 0 | 0 |

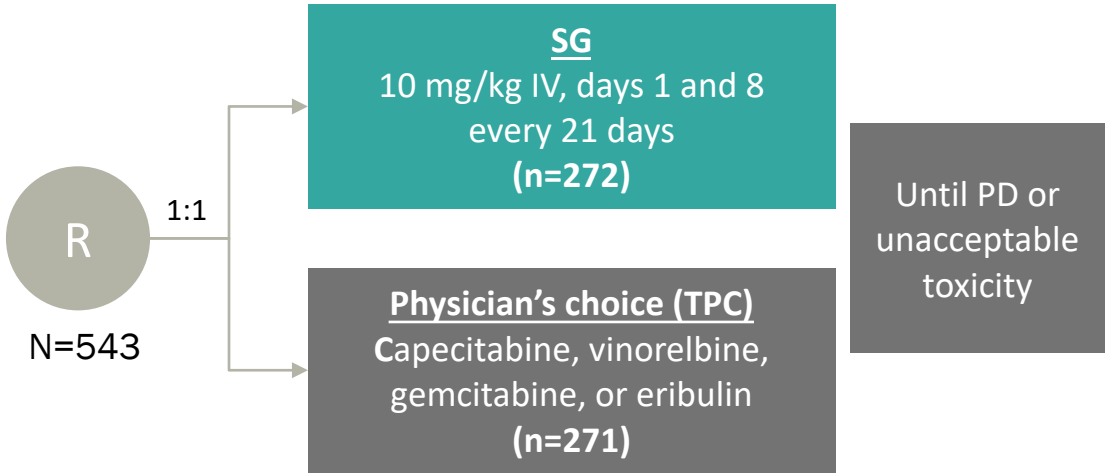
- In the T-DXd vs TPC arms, 35 (8.1%) vs 12 (2.9%) patients experienced any grade ejection fraction decreased, and 0 vs 3 (0.7%) patients experienced any grade cardiac failure

- Sites of disease
- Burden of disease
- Underlying risks for ILD?
- KPS, frailty
- Cardiac comorbidities?
- Psychosocial factors: IV vs oral, alopecia, q3 week travel to infusion
- DB04 as salvage

# TROPiCS-02: Sacituzumab in ER+ MBC

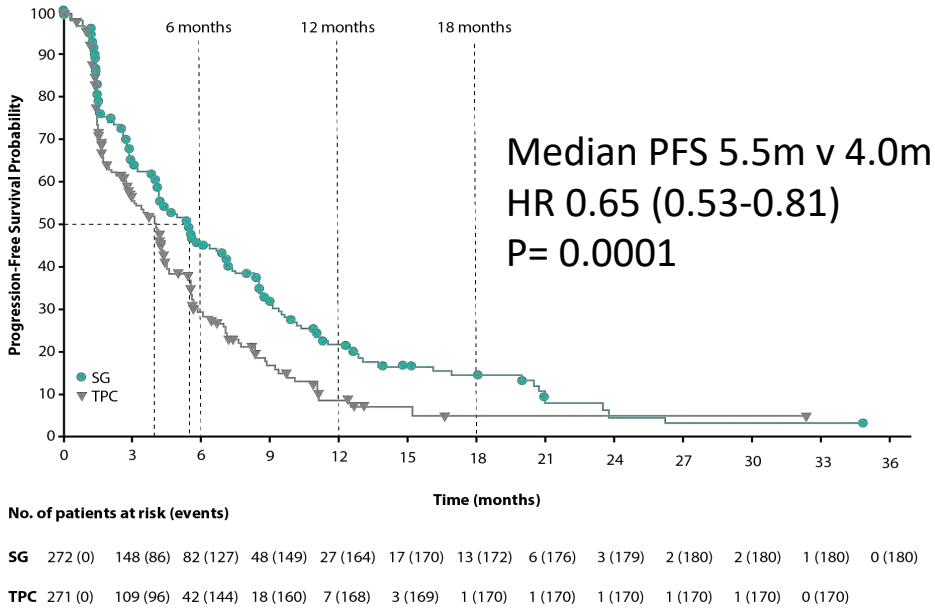
## Key Eligibility Criteria

- HR+/HER2– MBC (or locally recurrent inoperable) with PD after:
  - ≥1 ET, taxane, and CDK4/6i in any setting
  - ≥2 to ≤4 lines of chemotherapy for metastatic disease
  - Measurable disease by RECIST v1:1



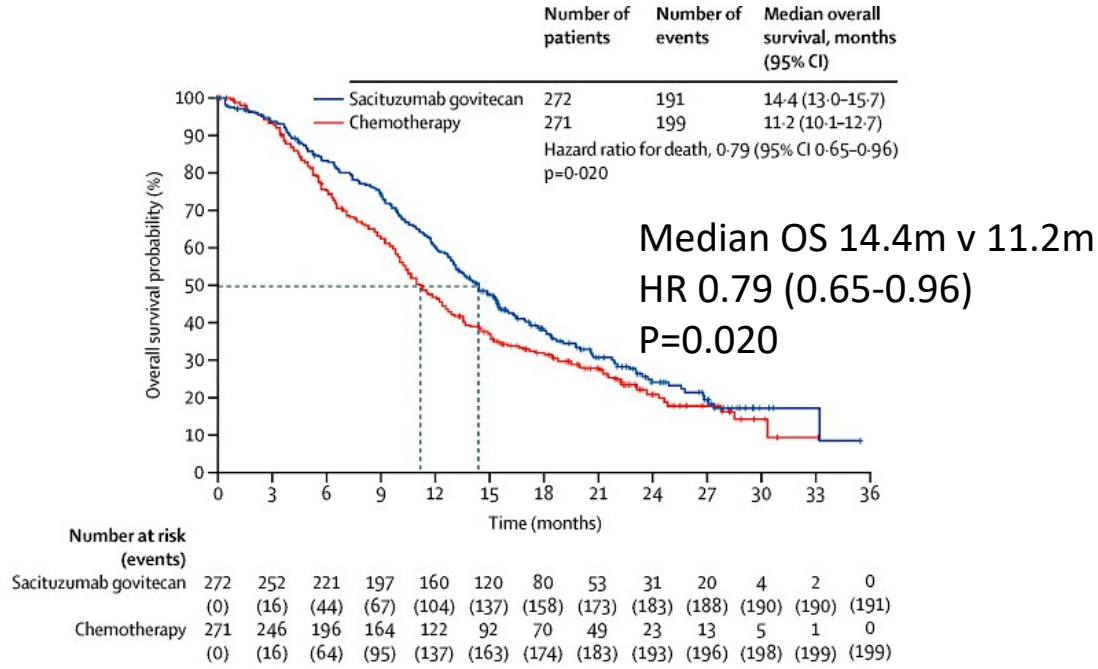

**Primary endpoint:** PFS by BICR

### BICR-Assessed PFS in the ITT Population




Median PFS 5.5m v 4.0m
HR 0.65 (0.53-0.81)
P= 0.0001

### OS in the ITT Population




Median OS 14.4m v 11.2m
HR 0.79 (0.65-0.96)
P=0.020

Rugo H, et al. ASCO 2022. Abstract LBA1001.; Tolaney S, et al. ASCO 2023. Abstract 1003. Rugo H, et al. Lancet 2023

# TROPiCS-02: Safety

| TEAEs (All Grade >20%), n (%) | | SG (n=268) | | TPC (n=249) | |
|---|---|---|---|---|---|
| | | All grade | Grade ≥3 | All grade | Grade ≥3 |
| Hematologic | Neutropenia | 189 (71) | 140 (52) | 136 (55) | 97 (39) |
| | Anemia | 98 (37) | 20 (7) | 69 (28) | 8 (3) |
| GI | Diarrhea | 166 (62) | 27 (10) | 57 (23) | 3 (1) |
| | Nausea | 157 (59) | 3 (1) | 87 (35) | 7 (3) |
| | Constipation | 93 (35) | 1 (<1) | 61 (24) | 0 |
| | Vomiting | 64 (24) | 3 (1) | 39 (16) | 4 (2) |
| | Abdominal pain | 53 (20) | 10 (4) | 34 (14) | 2 (1) |
| Other | Alopecia | 128 (48) | 0 | 46 (18) | 0 |
| | Fatigue | 105 (39) | 16 (6) | 82 (33) | 9 (4) |
| | Asthenia | 62 (23) | 6 (2) | 50 (20) | 5 (2) |
| | Decreased appetite | 57 (21) | 4 (1) | 52 (21) | 2 (1) |

Treatment discontinuations due to AEs occurred in **17 patients (6%)** receiving SG and **11 patients (4%)** receiving TPC

Tolaney S, et al. ASCO 2023. Abstract 1003.

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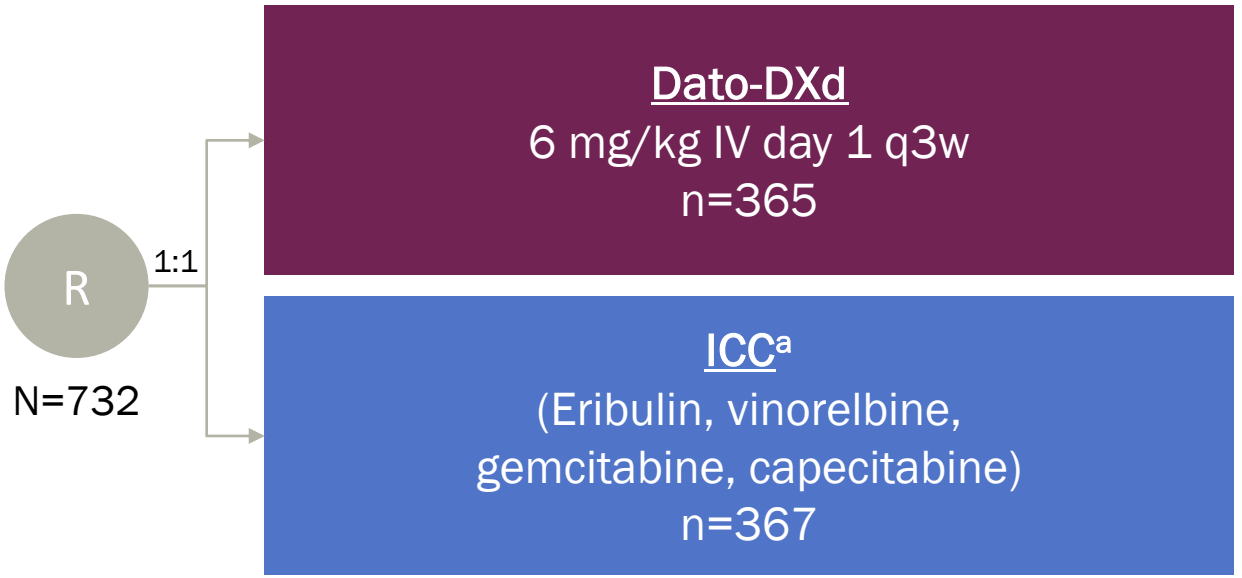
# TROPION-Breast01: Dato-DXd in ER+ MBC

**Key Eligibility Criteria**

- HR+/HER2– MBC (HER2 IHC 0/1+/2+; ISH–)
- Progressed on and not suitable for ET
- 1-2 prior lines of Chemo in inoperable/metastatic setting
- ECOG PS 0-1




**Dual primary endpoints:** PFS by BICR per RECIST v1.1, OS

Bardia A, et al. ESMO 2023. Abstract LBA11.; Bardia A, et al. SABCS 2023. Abstract GS02-01.

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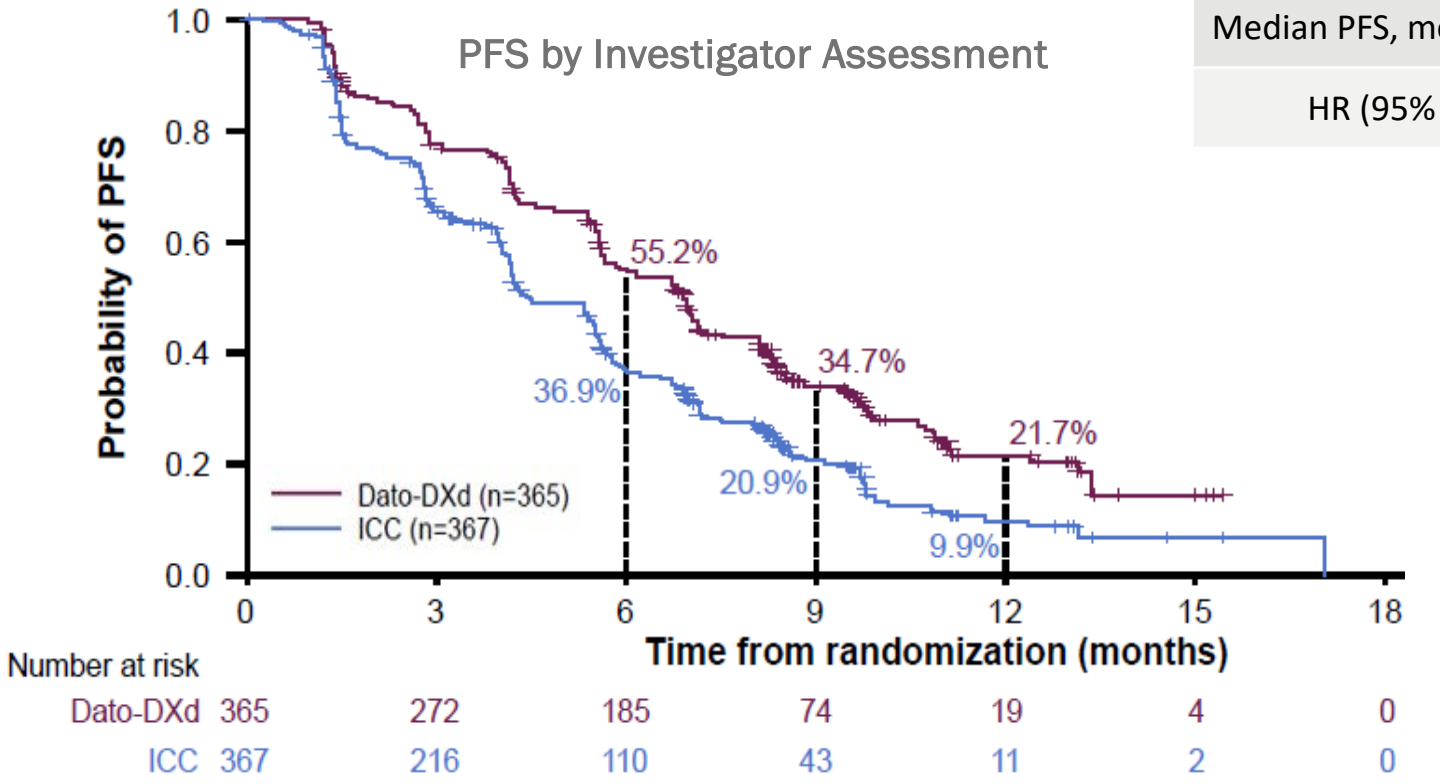
# TROPION-Breast01: Dato-DXd Efficacy




| PFS by Investigator | Dato-DXd (n=365) | ICC (n=367) |
|---|---|---|
| Median PFS, mo (95% CI) | 6.9 (5.9-7.1) | 4.5 (4.2-5.5) |
| HR (95% CI) | 0.64 (0.53-0.76) | |

Median PFS by BICR (primary endpoint):
6.9 vs 4.9 mo;
HR=0.63 (95% CI: 0.52-0.76); *P*<0.0001

Bardia A, et al. ESMO 2023. Abstract LBA11.; Bardia A, et al. SABCS 2023. Abstract GS02-01.

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# TROPION-Breast01: Dato-DXd Safety

| TRAEs (in ≥15%), n (%) | Dato-DXd (n=360) | | ICC (n=351) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Anemia | 40 (11) | 4 (1) | 69 (20) | 7 (2) |
| Neutropenia | 39 (11) | 4 (1) | 149 (42) | 108 (31) |
| Dry eye | 78 (22) | 2 (1) | 27 (8) | 0 |
| Nausea | 184 (51) | 5 (1) | 83 (24) | 2 (1) |
| Stomatitis | 180 (50) | 23 (6) | 46 (13) | 9 (3) |
| Vomiting | 71 (20) | 4 (1) | 27 (8) | 2 (1) |
| Constipation | 65 (18) | 0 | 32 (9) | 0 |
| Fatigue | 85 (24) | 6 (2) | 64 (18) | 7 (2) |
| Alopecia | 131 (36) | 0 | 72 (21) | 0 |

Favorable toxicity profile, unlike T-DXd

Stomatitis prophylaxis successful with steroid rinse

- Only 1 patient d/c Dato due to stomatitis

Most ocular events were dry eye and low grade

- Only 1 patient d/c Dato due to ocular AE

ILD rare: 3% all grade

Bardia A, et al. ESMO 2023. Abstract LBA11.

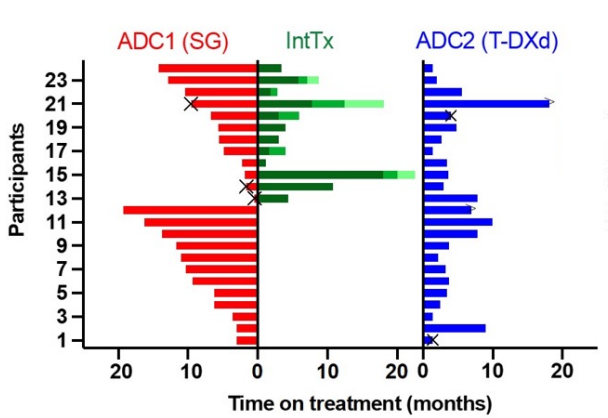
# Sequential ADC Use?

## No prospective data

- 1st ADC generally has longer time on tx
- Intervening cytotoxic chemotherapy “sandwich” approach does not appear to be an advantage
- What drives resistance?
  - Target?
  - Payload?
- Where does Dato-DXd fit in?

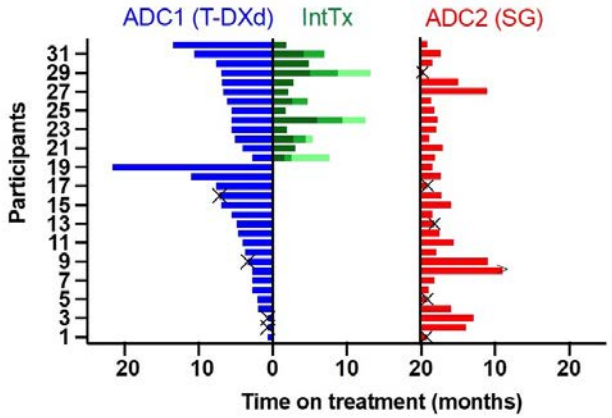
HR+/HER2-Low (n=56)

SG→T-DXd (n=24)




| n=24 | ADC1 (SG) | ADC2 (T-DXd) |
|---|---|---|
| mrwPFS, mo | 6.5 | 3.6 |
| mrwOS, mo | 20.1 | 7.7 |

T-DXd→SG (n=32)




| n=32 | ADC1 (T-DXd) | ADC2 (SG) |
|---|---|---|
| mrwPFS, mo | 5.3 | 2.1 |
| mrwOS, mo | 15.1 | 5.6 |

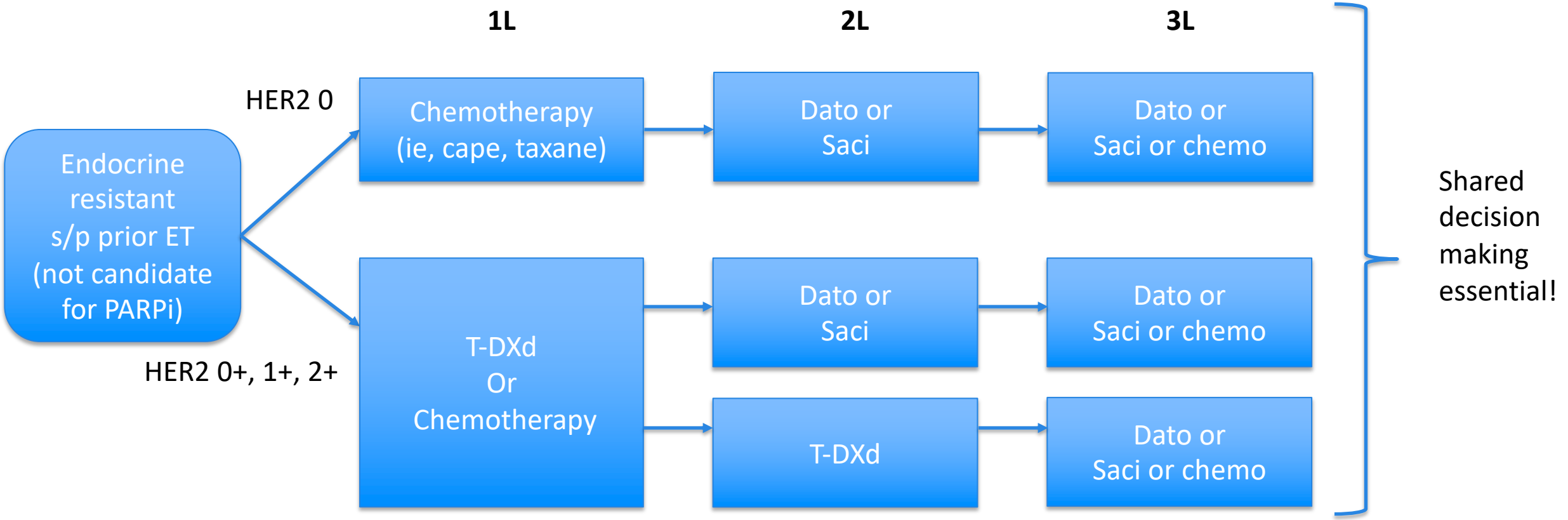
Huppert L, et al. ASCO 2024. Abstract 1083.

Memorial Sloan Kettering Cancer Center

# ADCs in ER+ MBC

## Bringing it together

| | T-DXd | Sacituzumab Govitecan | Dato-DXd |
|---|---|---|---|
| FDA indication | • HER2 low or UL after 1 or more endocrine tx<br>• HER2 low after 1 prior chemo | • Prior Endocrine tx and at least two additional systemic therapies in the metastatic setting | • Prior Endocrine tx and chemotherapy for metastatic disease |



# ER(+) HER2 low MBC

- 71 yo pT1N2 ER >95% HER2 2+ FISH NA →PET/CT negative for MBC
  - ddAC started but c/b anemia (hgb 4.6)
  - Bone marrow bx = MBC ER+ HER2 3+ FISH amplified *and* low grade B cell lymphoma
- 1L anastrozole (9/2022) → added Palbociclib (11/2022) and HP w/ excellent clinical response and NED on scans
- 11/2024 Altered MS and seizure → MR w/ CNS metastases and LMD
- s/p WBXRT, pCSI → 1/2025 Began T-DXd

**MRI Brain & Spine 3/24/25: Numerous subcm brain mets have contracted with a few resolved. Dominant parietal lesion decreased from ~2cm to 0.9cm. No new lesions. Decreased conspicuity of cauda equina lesions**

**PET 3/2025: No new lesions. Stable treated bone lesions.**

# ER low HER2 low MBC

- 70 yo pT2No ER low HER2 0 →ddAC-T; no ET (2014)
- 2018 Ipsilateral Ax recurrence ER 40% HER2 1+ s/p neo Gem/Carbo → AxD → RT → Anastrozole
- 2020 Unresectable Axillary and chest wall recurrence cw MBC ER 5-10% HER2 0 PDL1 1% → Capecitabine
- 2022 POD in chest wall, LN, ?lung → eribulin
- 3/2023 POD in lung; Bx MBC ER 5% HER2 0
  - Started sacituzumab govitecan

**PET 11/2024:**
**Stable subcm pulm nodules. Reactive marrow. No new sites of disease**

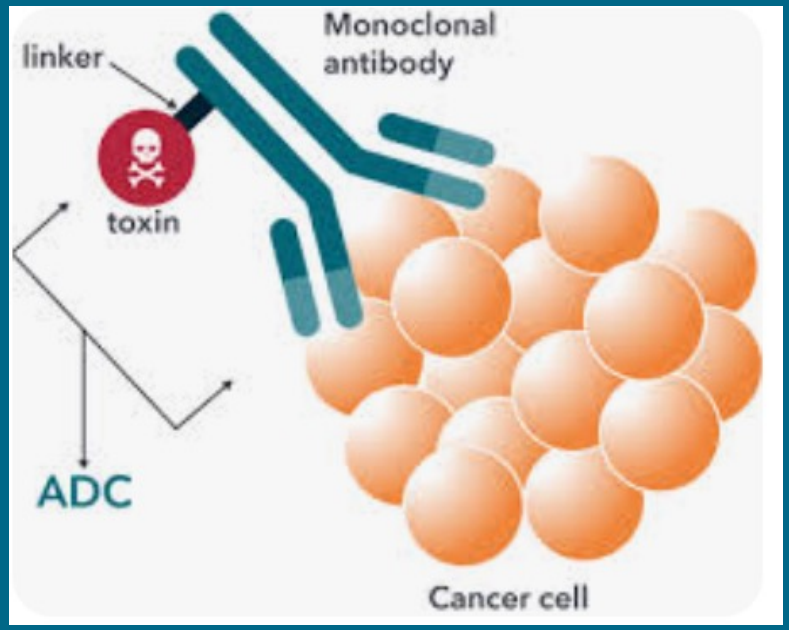
# Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

# Antibody-Drug Conjugates

**Marissa Marti-Smith**
DNP, APRN, AGNP-C, AOCNP

Breast Oncology
Nurse Practitioner

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# Dato DXd (Datopotamab Deruxtecan)

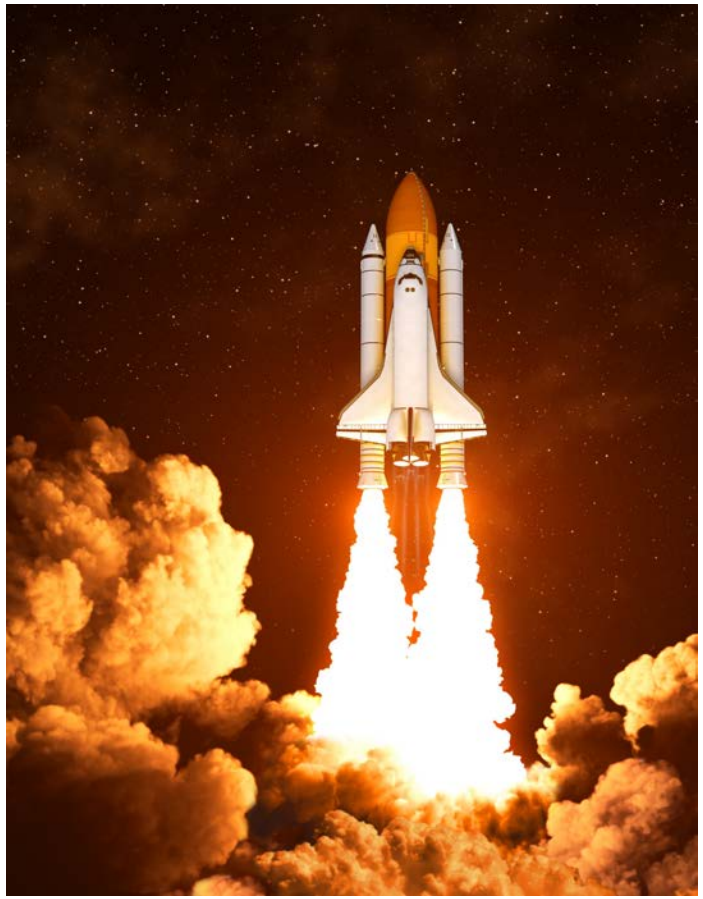
- **TROP2-directed** ADC comprising a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody covalently linked to a highly potent topoisomerase I (topo I) inhibitor, a derivative of exatecan, via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker, resulting in reduced systemic exposure and off-target adverse effects.

(Bardia et al, 2024)

# Patient Education

- Internalization of Dato-DXd **into TROP2-expressing** cells leads to death of target tumor cells and bystander killing of neighboring cells in the tumor microenvironment.

- **Guided missile analogy**
- **Approved for mBC ER+ Her2-**



(Bardia et al, 2024)

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# Dato DXd side effects

- **Stomatitis** (59%; grades 3/4 7%)
- **Dry eyes** (27%), **Keratitis** (24%)
- Low blood counts (hgb, ANC, leukopenia)
- **Fatigue** (44%)
- Cough (15%)
- GI (poor appetite, constipation, diarrhea, **nausea** (56%), vomiting
- Decreased Ca+ (39%)
- Alopecia (38%)
- Rash (19%)
- ILD/pneumonitis
- Elevated LFTS (23%)

(UptoDate)


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# Dato-DXd Patient Case Study

| |
|---|
| 68-year-old female |
| 1st line, mBC (liver x 4 lesions, lymphatics, breast), Triple negative |
| On Trial: Durvalumab + Dato-DXd IV Q21D initiated 5/17/2022 |
| AE: fatigue, mouth sores & dry mouth, poor appetite, watery eyes |
| C7: dose reduction 4 mg/kg (Dato-DXd) due to mucositis |
| C18: worsening inflammatory arthritis (HELD durvalumab) |
| Recently received C50: stability > almost 3 years |
| NED, other than new inflammatory lung nodule seen on scan |

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# Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

# Sacituzumab Govitecan: TROP2-Targeting ADC

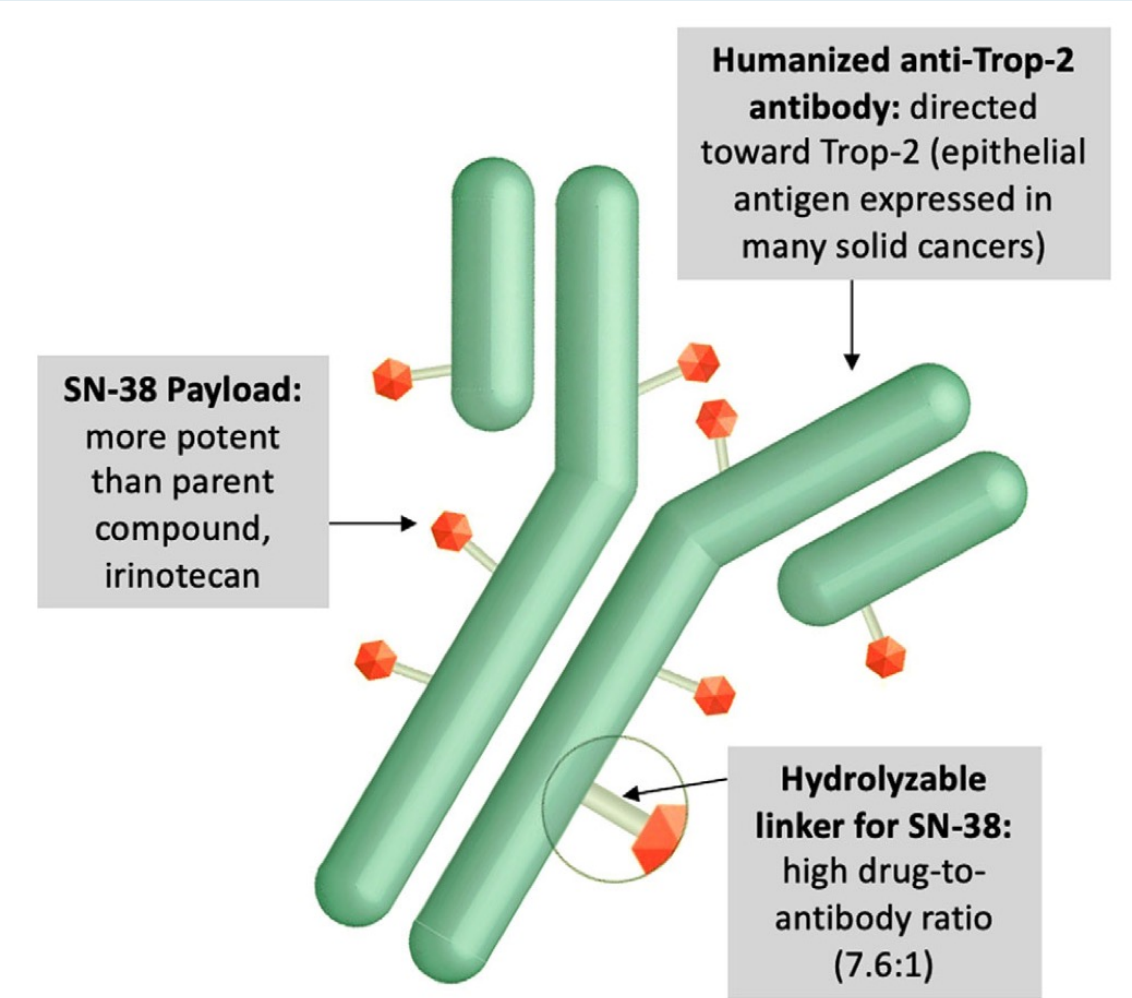
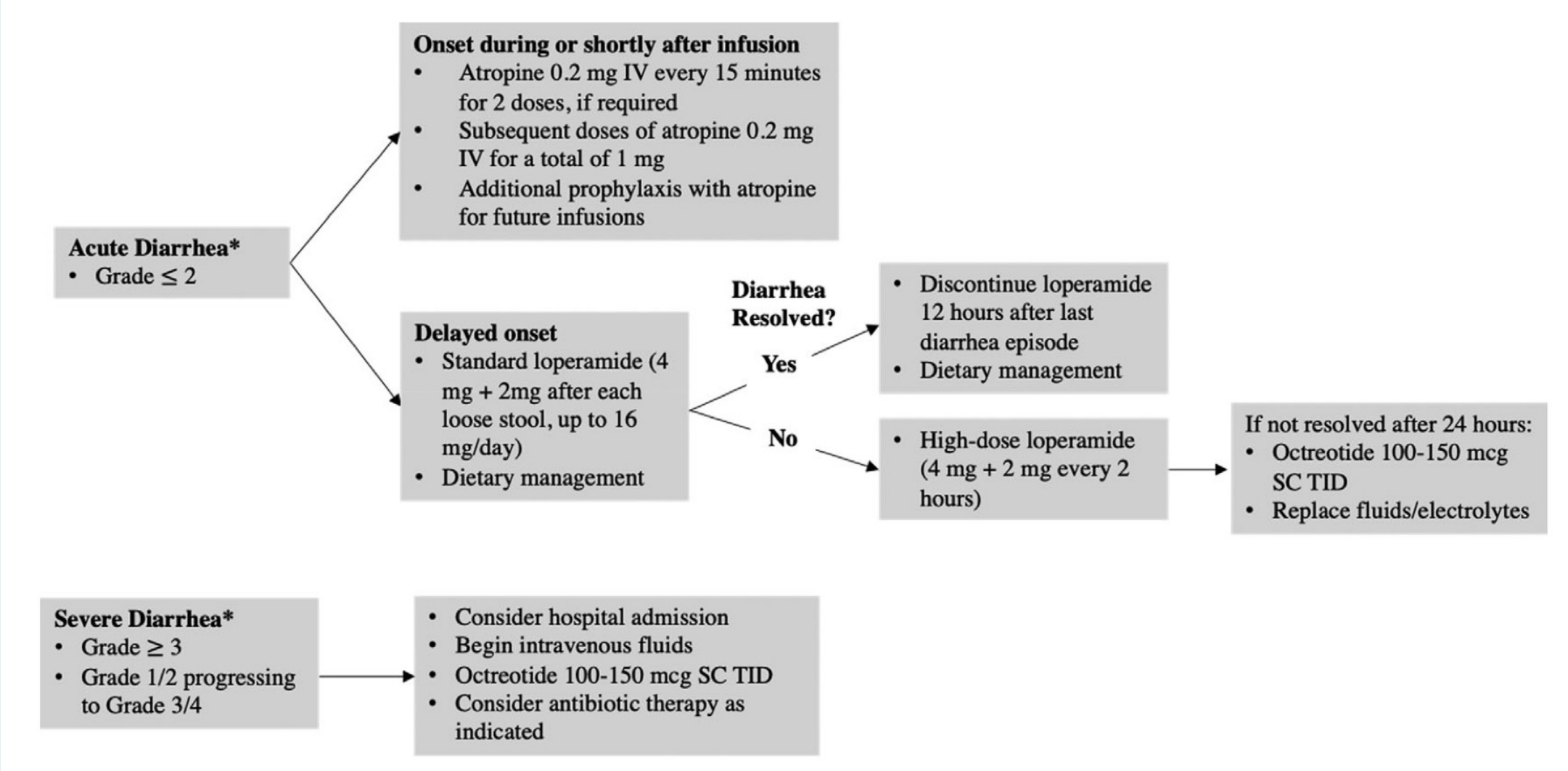



**Figure 1.** Sacituzumab govitecan.
Abbreviation: Trop-2, trophoblast cell surface antigen 2.

Spring LM et al. *Oncologist* 2021;26(10):827-834.

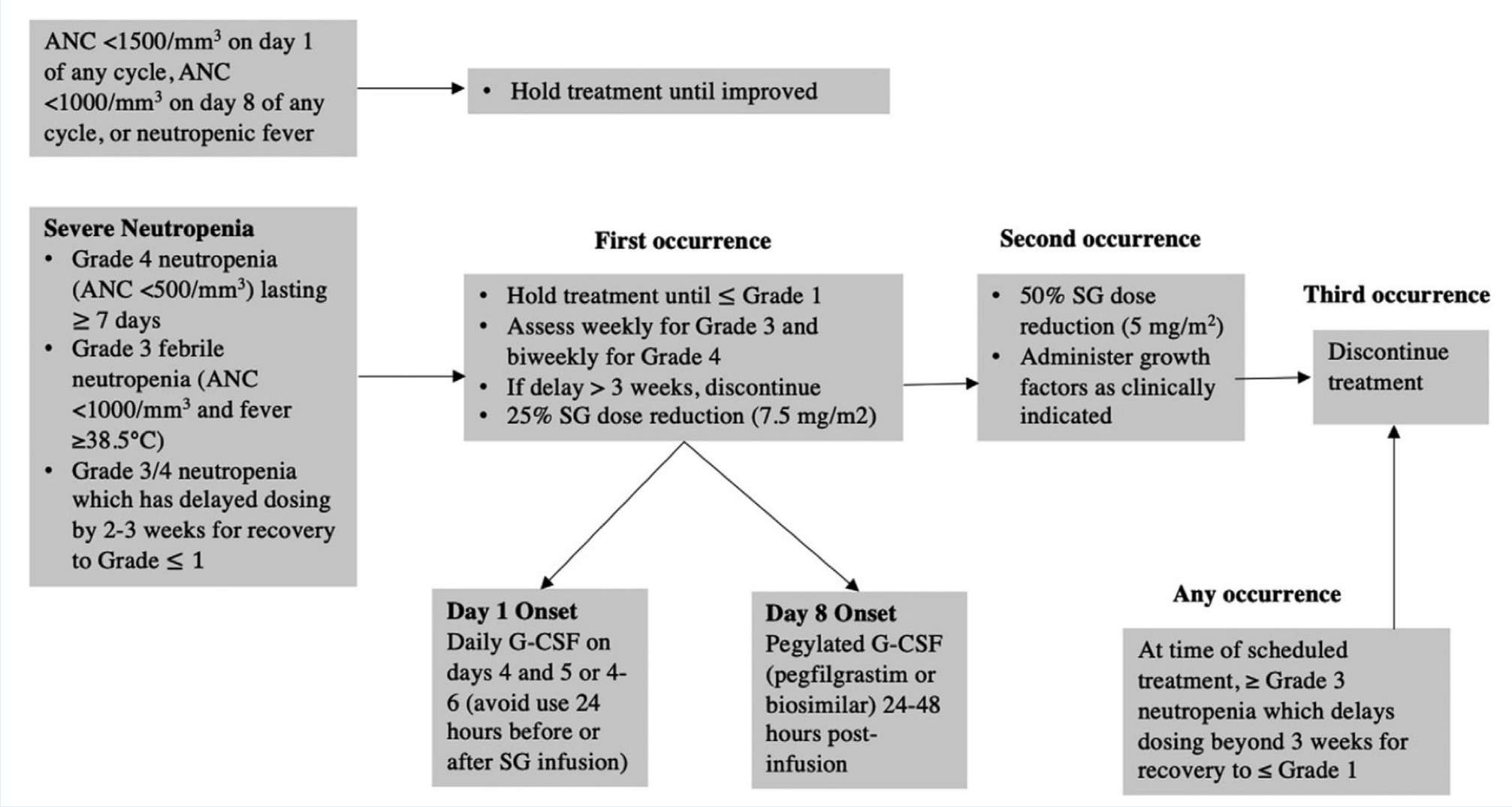
# Management of Sacituzumab Govitecan–Induced Diarrhea




Spring LM et al. *Oncologist* 2021;26(10):827-834.

RTP RESEARCH TO PRACTICE

# Management of Sacituzumab Govitecan–Induced Neutropenia




Spring LM et al. *Oncologist* 2021;26(10):827-834.

# Agenda

**Module 1:** Overview of Antibody-Drug Conjugates (ADCs)

**Module 2:** Trastuzumab Deruxtecan (T-DXd) in Patients with HER2-Positive Metastatic Breast Cancer (mBC) with and without Brain Metastases

**Module 3:** Role of ADCs for Patients with ER-Positive mBC

**Module 4: T-DXd in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) with HER2 Alterations**

**Module 5:** Emerging Role of ADCs for Patients with Progressive EGFR-Mutant NSCLC

# Clinical Scenario

**A patient with metastatic HER2-mutant NSCLC is about to start first-line therapy with T-DXd**

# Role of T-DXd in Patients with Metastatic NSCLC with HER2 Alterations

**Edward B. Garon, MD, MS**

Professor

David Geffen School of Medicine at UCLA

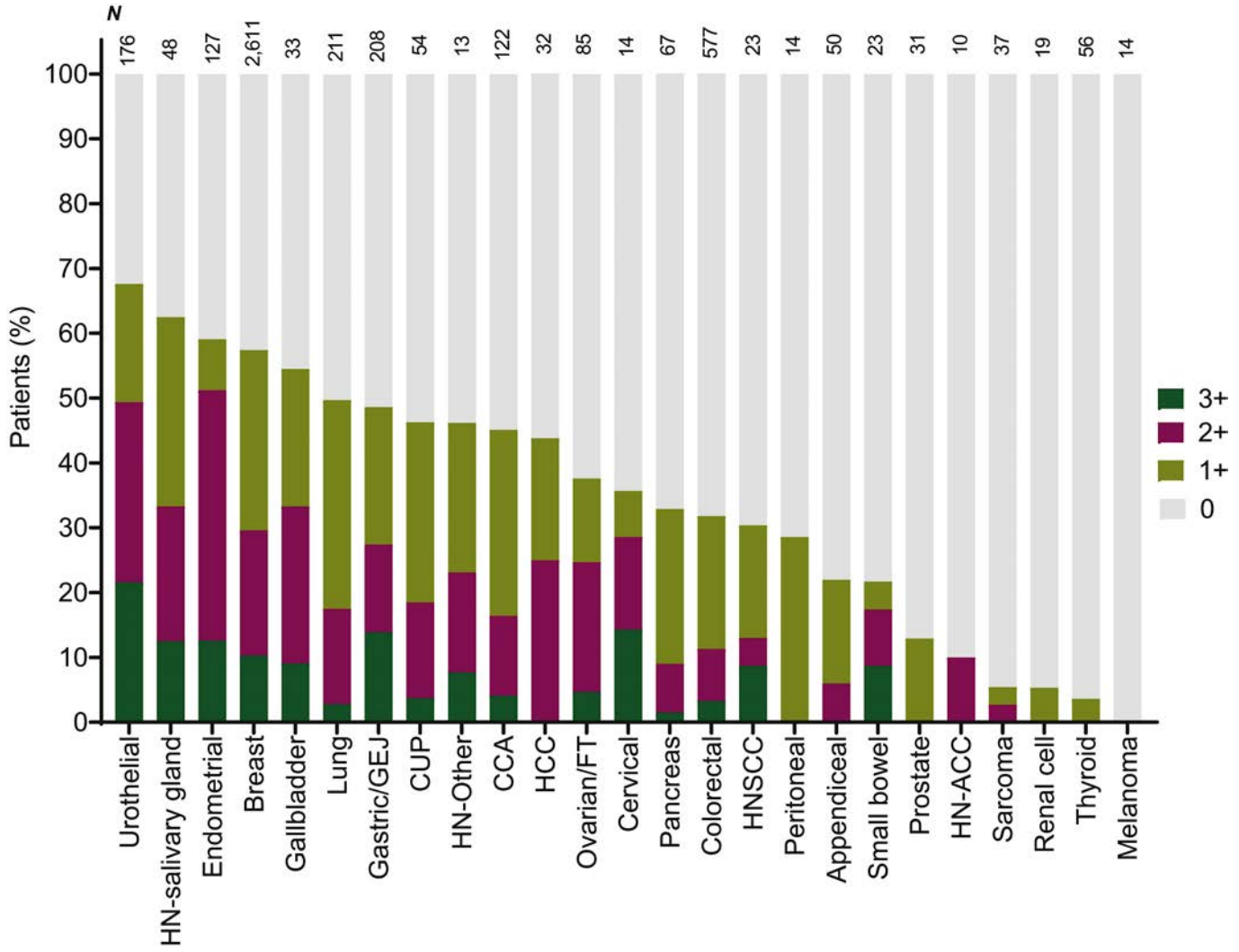
Los Angeles, CA

# Case

- 63 year old woman with no smoking history presented when a chest X-ray obtained for work showed masses
- Scans demonstrated bilateral lung lesions including three masses over 4 cm
- Patient was without complaint
- Biopsy demonstrated adenocarcinoma
- Molecular studies showed ERBB2 (Her2/Neu) Exon 20 p.G778_P780dup

# HER2 Abnormalities in NSCLC

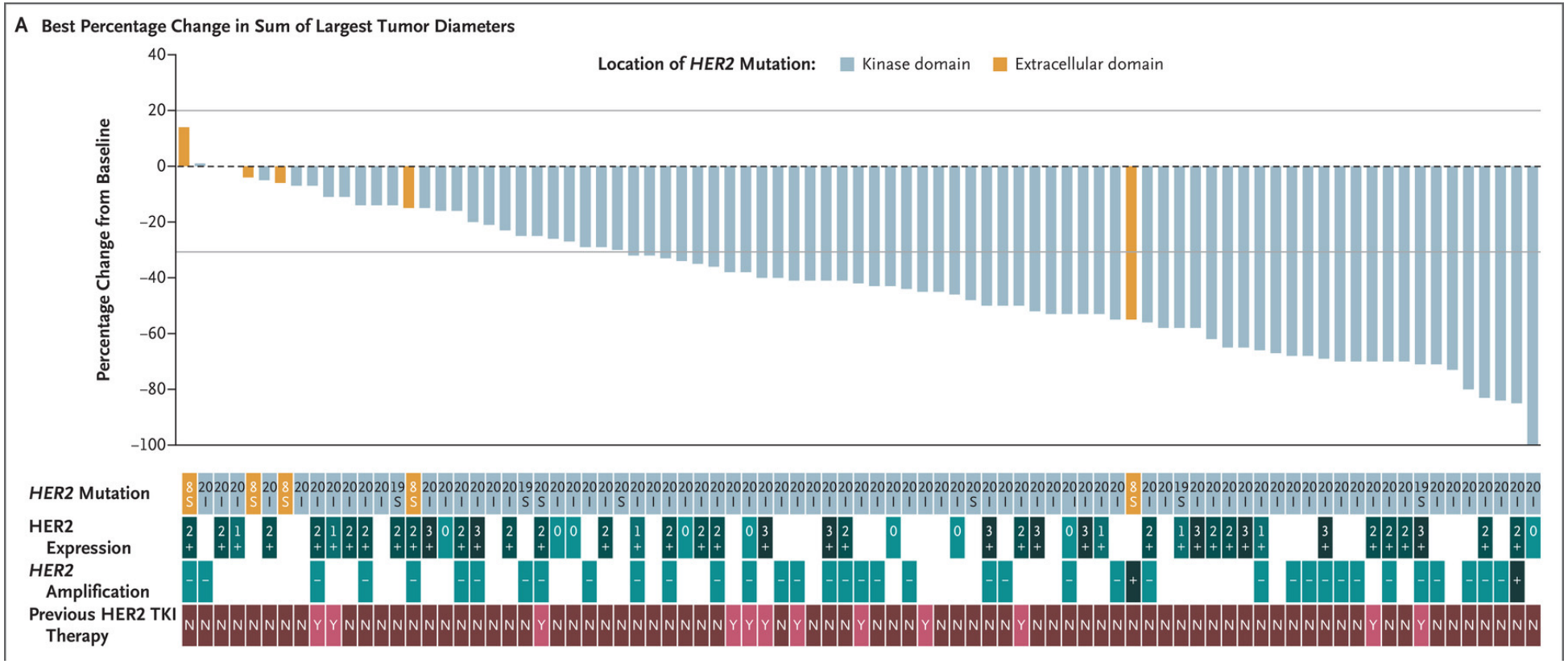
- HER2 mutations are seen in nearly 2% of NSCLC cases in US
- HER2 3+ is seen in nearly 3% of NSCLC
- High level HER2 amplification is seen in nearly 1% of NSCLC





Uzunparnak B. Annals of Oncology 2023
Waliany S. Cancer Med 2024
Odintsov I. Journal of Thoracic Oncology 2024

# Trastuzumab Deruxtecan in HER2 Mutation Positive NSCLC




Li BT et al. N Engl J Med. 2022 Jan 20;386(3):241-251.

# DESTINY-Lung02

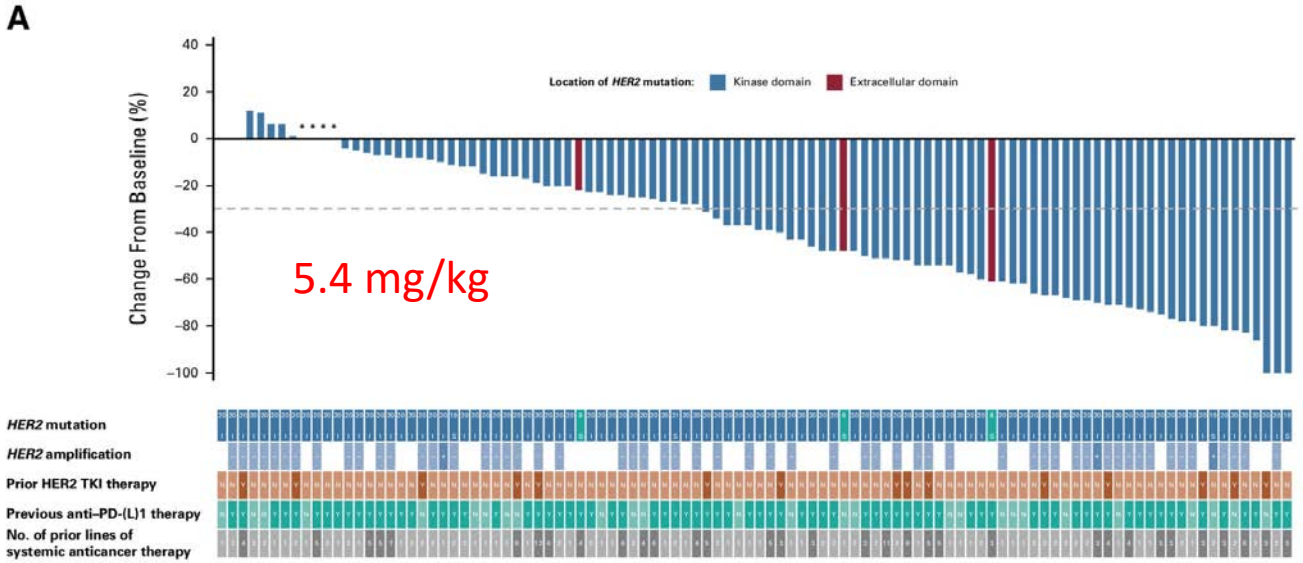
## Baseline characteristics and patient disposition

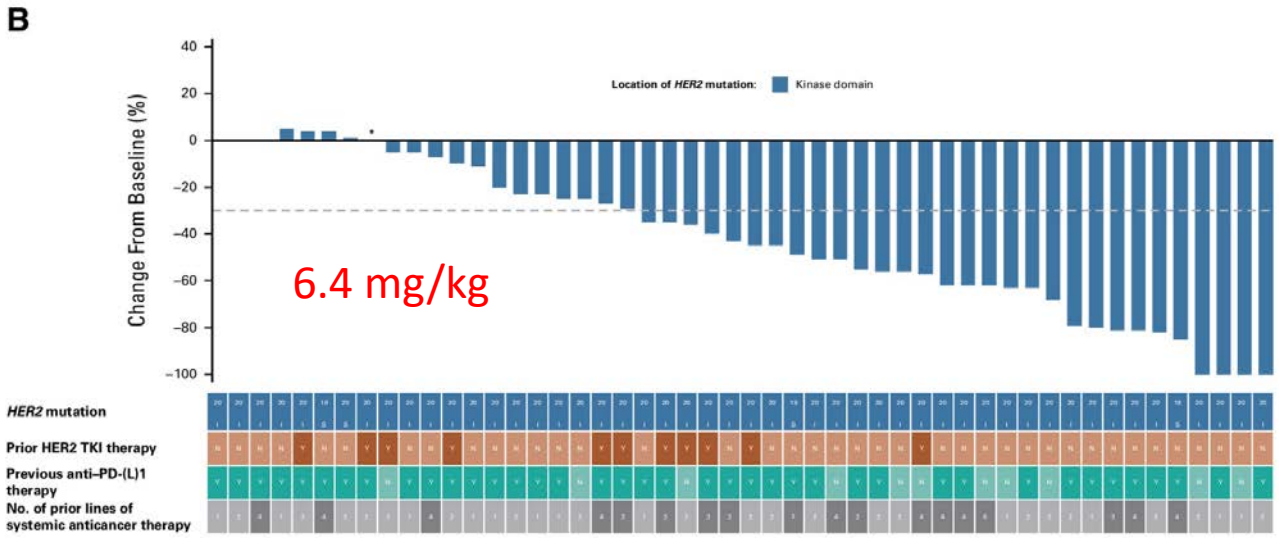
- Baseline demographics and clinical characteristics were similar across the T-DXd 5.4 mg/kg and 6.4 mg/kg arms
- In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:
  - Most patients received **prior anti–PD-(L)1 therapy** (73.5% and 78.0%)
  - Most patients had **never smoked** (53.9% and 58.0%)
  - ***HER2* mutations** were primarily in the **kinase domain** (97.1% and 100%)
  - Baseline CNS metastasis was present in 34.3% and 44.0% of patients
- At final analysis data cutoff, 12.9% of patients (13/101) in the T-DXd 5.4 mg/kg arm and 12.0% of patients (6/50) in the T-DXd 6.4 mg/kg arm were continuing on study treatment

## Efficacy

| Efficacy summary | T-DXd 5.4 mg/kg n = 102 | T-DXd 6.4 mg/kg n = 50 |
|---|---|---|
| **cORR,[a,b] n (% [95% CI])** | 51 (50.0 [39.9-60.1]) | 28 (56.0 [41.3-70.0]) |
| CR \| PR | 3 (2.9) \| 48 (47.1) | 4 (8.0) \| 24 (48.0) |
| SD \| PD | 44 (43.1) \| 4 (3.9) | 18 (36.0) \| 2 (4.0) |
| Non-evaluable | 3 (2.9) | 2 (4.0) |
| **DCR,[c] n (% [95% CI])** | 95 (93.1 [86.4-97.2]) | 46 (92.0 [80.8-97.8]) |
| **DoR,[b] median (95%CI), months** | 12.6 (6.4 to NE) | 12.2 (7.0 to NE) |
| **PFS, median (95% CI), months** | 10.0 (7.7-15.2) | 12.9 (7.2-16.7) |
| **OS, median (95% CI), months** | 19.0 (14.7 to NE) | 17.3 (13.8 to NE) |
| **Follow-up, median (range), months** | 15.8 (1.1-28.6) | 16.5 (0.6-28.7) |

Data cutoff: August 25, 2023.

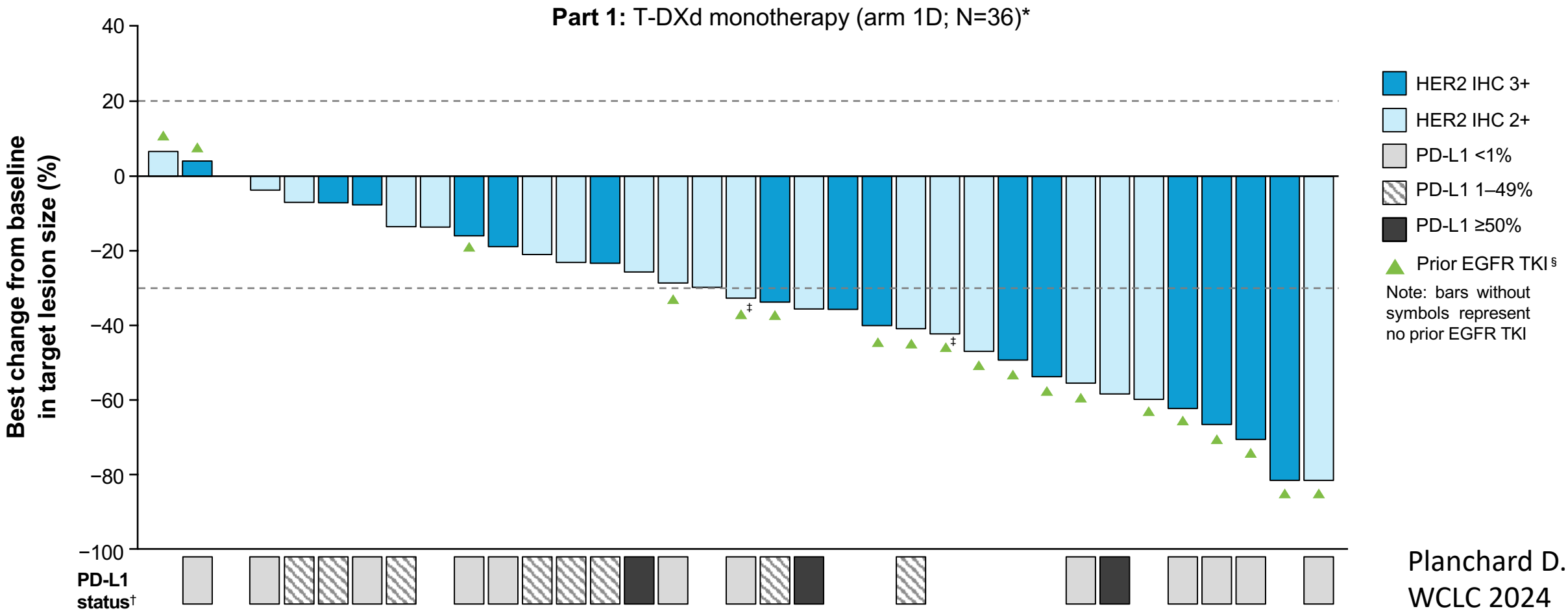



Goto K et al. *J Clin Oncol* 2024;42(30):3635. Janne P et al. ASCO 2024;Abstract 8543.

# T-DXd in HER2-overexpressing NSCLC: Best percentage change from baseline in target lesion size

DESTINY-Lung03




Planchard D. WCLC 2024

Investigator assessed per RECIST v1.1. Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size; the dashed lines at −30% and 20% change in target lesion size indicate the thresholds for partial response and progressive disease, respectively. The study was not designed/powered to compare efficacy between subgroups.
*One patient was not evaluable; †patients with unknown PD-L1 status (n=12) are represented by white spaces; ‡unconfirmed response; §patients had HER2-OE (IHC 3+/2+) NSCLC
EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

# Trastuzumab Deruxtecan in HER2 3+

- On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki 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.
- ORR exceeded 50% and DOR exceeded a year (n = 16)

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grantsaccelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2

Planchard D et al. WCLC 2024;Abstract OA16.05.

# Case 1 Continued

- Patient initially was treated with carboplatin/pemetrexed and pembrolizumab
- She responded and tolerated it well, but progressed after approximately a year and a half
- She switched to trastuzumab deruxtecan, and again responded but progressed after approximately a year and a half
- She recently initiated therapy on a trial of zongertinib

# Conclusions

- Although there is no HER2 molecular abnormality with high prevalence, when combining HER2 mutant NSCLC and HER2 3+, HER2 is one of the more common molecular drivers
- Trastuzumab deruxtecan is the only agent approved for treating HER2 driven NSCLC, although oral inhibitors are in development
- HER2 amplification is rare in NSCLC, and the role of targeted agents in this context is not clear

# Roundtable Discussion

RTP
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# Understanding the Current Paradigm and New Approaches: The Optimal Implementation of Antibody-Drug Conjugates in the Care of Patients with Cancer

Yale NewHaven Health
Smilow Cancer Hospital

Yale CANCER CENTER

Yale SCHOOL OF NURSING

Research To Practice
Oncology Nursing Society Congress 2025

Marianne Davies, DNP, CNS-BC, ACNP-BC, AOCNP-BC, FAAN
Program Manager, Care Signature: Oncology Service Line
Thoracic Oncology Nurse Practitioner, Smilow Cancer Hospital
Associate Professor, Yale University School of Nursing

# Scenario 3: Nursing Considerations for Patients with NSCLC Receiving T-DXd

62 yo male, married with two adult children and grandchildren; remote smoking history; works in sales; pizza aficionado; domestic bird owner.

- Diagnosed with HER2-mutant (Exon 20 insertion) NSCLC

HER-2 mutant NSCLC:

- More common in females, never smokers and younger age
- 2%-4% of NSCLC
- Can also have HER-2 amplification +/or overexpression

Yale NewHaven Health Smilow Cancer Hospital

Yale CANCER CENTER

# Interstitial Lung Disease

## Screen (History and Physical)

- Baseline $SpO_2$
- Educate patients about signs & symptoms to report
- Rule out other causes of ILD (other drugs or RT tox)
- Rule out infection, progression of disease, or pulmonary embolism

## Scan (Evaluation)

- High-resolution CT scan, every 6-9 wks if s/s
- Bronchoscopy and BAL +/- biopsy
- Pulmonary function test

## Synergy: Patient-MDT-Staff Triad

- Pulmonary consult
- Radiology

## Suspend Treatment

- Hold treatment during evaluation
- GRADE Toxicity
- May consider dose reduction
- Permanent discontinuation for unresolving ILD

## Steroids

- Based on severity or grade of toxicity
- Taper steroid based on response

Rule out: Bird Fancier's Lung (Avian Hypersensitivity Pneumonitis)

Tarantino P. *JAMA Oncol*. 2021;7(12):1873-1881. doi:10.1001/jamaoncol.2021.3595
Tarantino P. *JCO Oncol Pract*. 2023;19(8):526-527. doi:10.1200/OP.23.00097

# T-DXd MOA & Approval

Trastuzumab Deruxtecan (T-DXd)

Trastuzumab: antibody that binds to HER2

Deruxtecan: chemotherapy

Irinotecan derivative: Topoisomerase 1 inhibitor

DESTINY-Lung01, DESTINY-Lung02

- Approved for treatment of patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations and who have received **a prior line of therapy**
- Approved for treatment of patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

**Patient enrolled on a First-Line Clinical Trial with T-DXd**

# Potential Toxicities & Monitoring

- Factors influencing the side effects:  T-DXd:  has to do with the chemotherapy
  - Diarrhea
  - Neutropenia
  - Thrombocytopenia

- Rash
- Interstitial Lung Disease (ILD)
- Cardiac/ myocarditis:  Left Ventricular Dysfunction: monitor LVEF at regular intervals; if decreased by >10%;
  - Need baseline Echocardiogram;  If 40-45% and if decreased by 10-20%, hold tx and repeat ECHO at 3 weeks;  if it does not recover to within 10%, then need to discontinue

- Reproductive Considerations in those of child bearing years.
- Embryo-Fetal toxicity

# Cardiac Toxicity- Left Ventricular Dysfunction

- Overall Incidence - 4.6% --- Grade 3 or worse - 0.6%
- Assess LVEF prior to initiation of therapy and then every 3 months
- Interrupt and consult Cardiology if
  - IF LVEF 40%-45% and absolute decrease from 10-20%
  - LVEF <40%
  - Absolute decrease from baseline >20%

Courtesy of Jaclyn Shaver, MS, APRN, CNP, WHNP

Trastuzumab deruxtecan package insert.

# Nausea and Vomiting Management

- NCCN -Highly Emetogenic and includes delayed nausea and or vomiting. Administer prophylactic anti-emetics medications per institutional guidelines
- At least D1-D4
- NK1
- 5-HT3 antagonist
- Olanzapine
- Dexamethasone

Courtesy of Jaclyn Shaver, MS, APRN, CNP, WHNP

# Nausea and Vomiting

- Nonpharmacological Interventions
  - Eat small frequent meals
  - Avoid foods that cause nausea such as food with strong smells
  - Sit upright or lie with head raised for 1 hour after eating
  - Drink plenty of water throughout day – small sips
  - Consult dietician
  - Alternative Therapies – Relaxation Techniques, Acupuncture, hypnosis, music therapy

Courtesy of Jaclyn Shaver, MS, APRN, CNP, WHNP

# Neutropenia Management

- Monitor Complete Blood Counts prior to each infusion
- Delay/Dose reduce for grade 3 / 4
- Add G-CSF as needed based on patient risk factors
- Patient education
  - Reduce risk of infection by washing hands frequently, avoid being in contact with people who are sick. Avoid dental work while white count is low
  - Immediately contact provider if fever occurs

Courtesy of Jaclyn Shaver, MS, APRN, CNP, WHNP

# Fatigue Management

- No Reliable laboratory test or objective measurements for cancer related fatigue
- Rule out other causes – medication side effects, pain, anemia, emotional distress, sleep disturbances, nutritional deficiencies
- Risk factors for cancer related fatigue- Pain, Nausea, pre-existing mental health disorders or stressors
- Treatments- Physical Activity/Exercise, Cognitive Behavioral Therapy, mindfulness-based programs, Tai chi, Qigong, American Ginseng 2,000mg daily may also be recommended

Courtesy of Jaclyn Shaver, MS, APRN, CNP, WHNP

# Alopecia

- Typically manifests as thinning, rather than hair loss- best to be upfront with patients
  - Consider scalp cooling
  - Rule out other cause – can check TSH, Vit D, Zinc, and ferritin/iron levels
- Patient counseling
  - Can use wigs, caps, or head covering
  - Protect scalp from heat, cold, and the sun
  - Sleep on satin pillowcase, wrap hair at night
  - Avoid excessive brushing, styling, or washing

Courtesy of Jaclyn Shaver, MS, APRN, CNP, WHNP

# Roundtable Discussion

RTP
RESEARCH
TO PRACTICE

# Agenda

**Module 1:** Overview of Antibody-Drug Conjugates (ADCs)

**Module 2:** Trastuzumab Deruxtecan (T-DXd) in Patients with HER2-Positive Metastatic Breast Cancer (mBC) with and without Brain Metastases

**Module 3:** Role of ADCs for Patients with ER-Positive mBC

**Module 4:** T-DXd in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) with HER2 Alterations

**Module 5: Emerging Role of ADCs for Patients with Progressive EGFR-Mutant NSCLC**

RTP RESEARCH TO PRACTICE

# Clinical Scenario

**A patient with metastatic EGFR-mutant NSCLC has experienced disease progression on standard targeted therapy and is about to start treatment with Dato-DXd**

# Emerging Role of ADCs in Patients with Progressive EGFR-Mutant NSCLC

**Edward B. Garon, MD, MS**

Professor

David Geffen School of Medicine at UCLA

Los Angeles, CA

# Case

- 77 year old woman presents after relocating to be closer to family
- She was originally diagnosed 8 years earlier with Stage IB NSCLC with an *EGFR* L858R mutation for which resection was performed
- First scan after 4 cycles of cisplatin/pemetrexed showed liver metastasis
- Treated with gefitinib for 6 years
- At progression, she initiated treatment with osimertinib
- Symptomatically, she is a little worse, and there is evidence of progression on scans

# TROPION-Lung01 Study Design

## Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

### Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

**Without actionable genomic alterations[a]**

- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

**With actionable genomic alterations**

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

**Dato-DXd**
**6 mg/kg Q3W**
**(N=299)**

**Docetaxel**
**75 mg/m² Q3W**
**(N=305)**

### Dual Primary Endpoints

- PFS by BICR
- OS

### Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

**Stratified by:** histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

Enrollment period: 19 February 2021 to 7 November 2022.

BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.

[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs non-squamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.



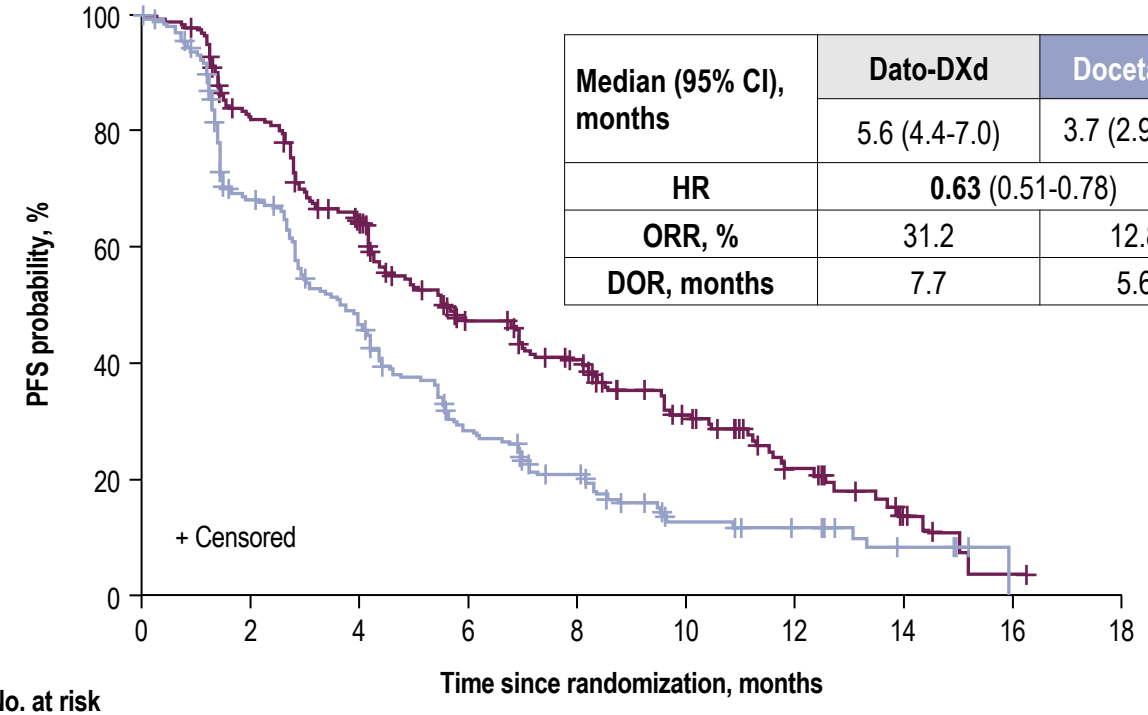
Lisberg A et al. ESMO 2023;Abstract LBA12.

# PFS by Histology

## Non-squamous

(with and without AGAs)

| Median (95% CI), months | Dato-DXd | Docetaxel |
|---|---|---|
| | 5.6 (4.4-7.0) | 3.7 (2.9-4.2) |
| HR | **0.63** (0.51-0.78) | |
| ORR, % | 31.2 | 12.8 |
| DOR, months | 7.7 | 5.6 |

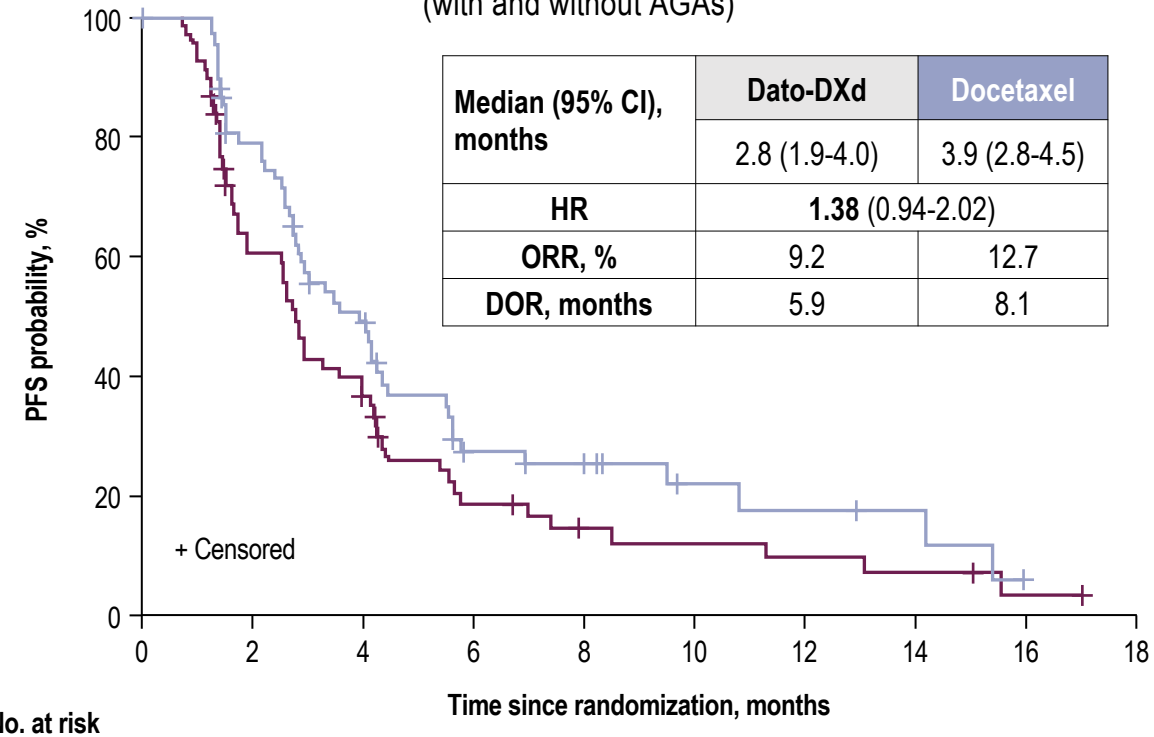



| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 229 | 178 | 134 | 86 | 68 | 41 | 20 | 7 | 1 | 0 |
| Docetaxel | 232 | 135 | 90 | 50 | 32 | 14 | 10 | 4 | 0 | 0 |

## Squamous

(with and without AGAs)

| Median (95% CI), months | Dato-DXd | Docetaxel |
|---|---|---|
| | 2.8 (1.9-4.0) | 3.9 (2.8-4.5) |
| HR | **1.38** (0.94-2.02) | |
| ORR, % | 9.2 | 12.7 |
| DOR, months | 5.9 | 8.1 |




| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 70 | 38 | 22 | 10 | 6 | 5 | 4 | 3 | 1 | 0 |
| Docetaxel | 73 | 51 | 30 | 13 | 10 | 5 | 4 | 3 | 0 | 0 |

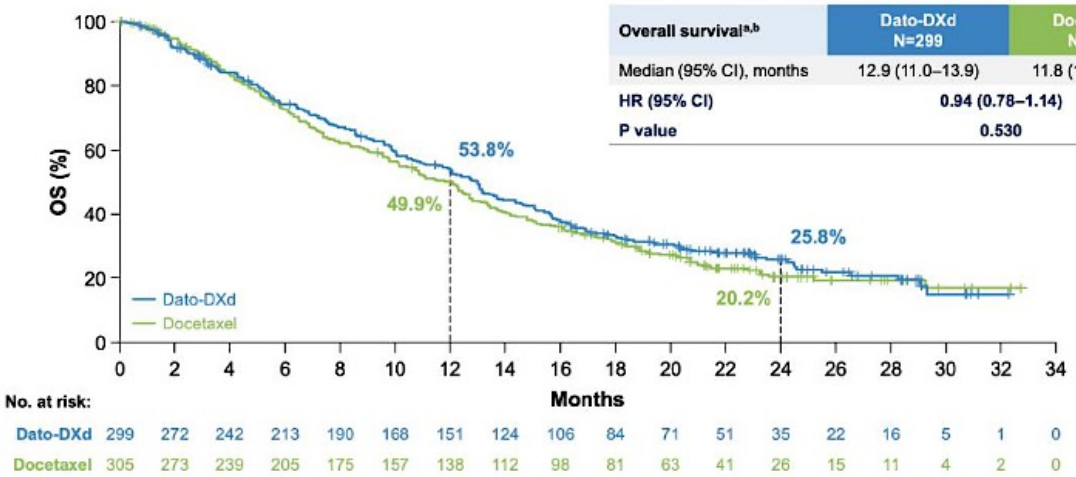
**PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)**

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival.
Squamous subset included 3 patients with AGAs



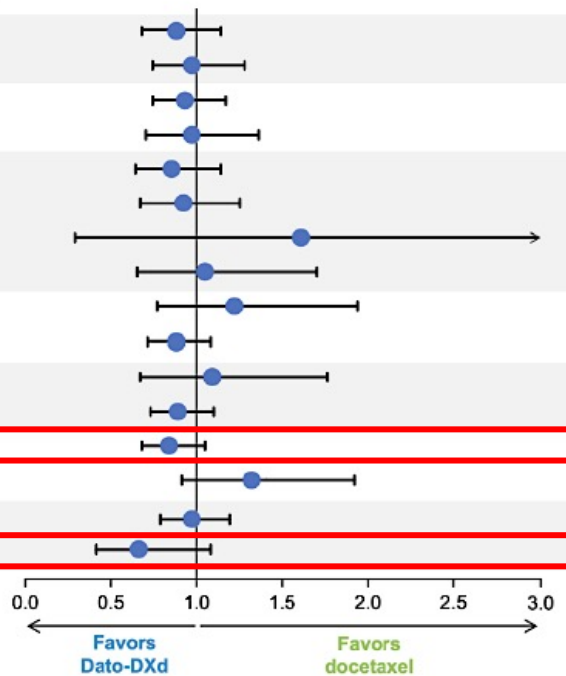
Lisberg A et al. ESMO 2023;Abstract LBA12.

# Final Overall Survival from TROPION-Lung01




| Overall survival[a,b] | Dato-DXd N=299 | Docetaxel N=305 |
|---|---|---|
| Median (95% CI), months | 12.9 (11.0–13.9) | 11.8 (10.0–12.8) |
| HR (95% CI) | 0.94 (0.78–1.14) | |
| P value | 0.530 | |

| | | No. of events/No. of patients Dato-DXd | Docetaxel | HR |
|---|---|---|---|---|
| Age at randomization | <65 years | 117/162 | 112/155 | 0.88 |
| | ≥65 years | 98/137 | 106/150 | 0.97 |
| Sex | Male | 136/183 | 156/210 | 0.93 |
| | Female | 79/116 | 62/95 | 0.97 |
| Race | White | 90/123 | 95/126 | 0.85 |
| | Asian | 83/121 | 79/120 | 0.92 |
| | Black/African American | 4/6 | 2/4 | 1.61 |
| | Other | 33/43 | 35/47 | 1.05 |
| Smoking status | Never | 43/60 | 31/52 | 1.22 |
| | Former/current | 172/239 | 186/251 | 0.88 |
| Brain metastases at baseline | With | 37/50 | 31/47 | 1.09 |
| | Without | 178/249 | 187/258 | 0.89 |
| Histology | Nonsquamous | 160/234 | 163/234 | 0.84 |
| | Squamous | 55/65 | 55/71 | 1.32 |
| Actionable genomic alterations[a] | Absent | 182/249 | 185/254 | 0.97 |
| | Present | 33/50 | 33/51 | 0.66 |




The dual primary endpoint of OS showed a numerical improvement but was not statistically significant

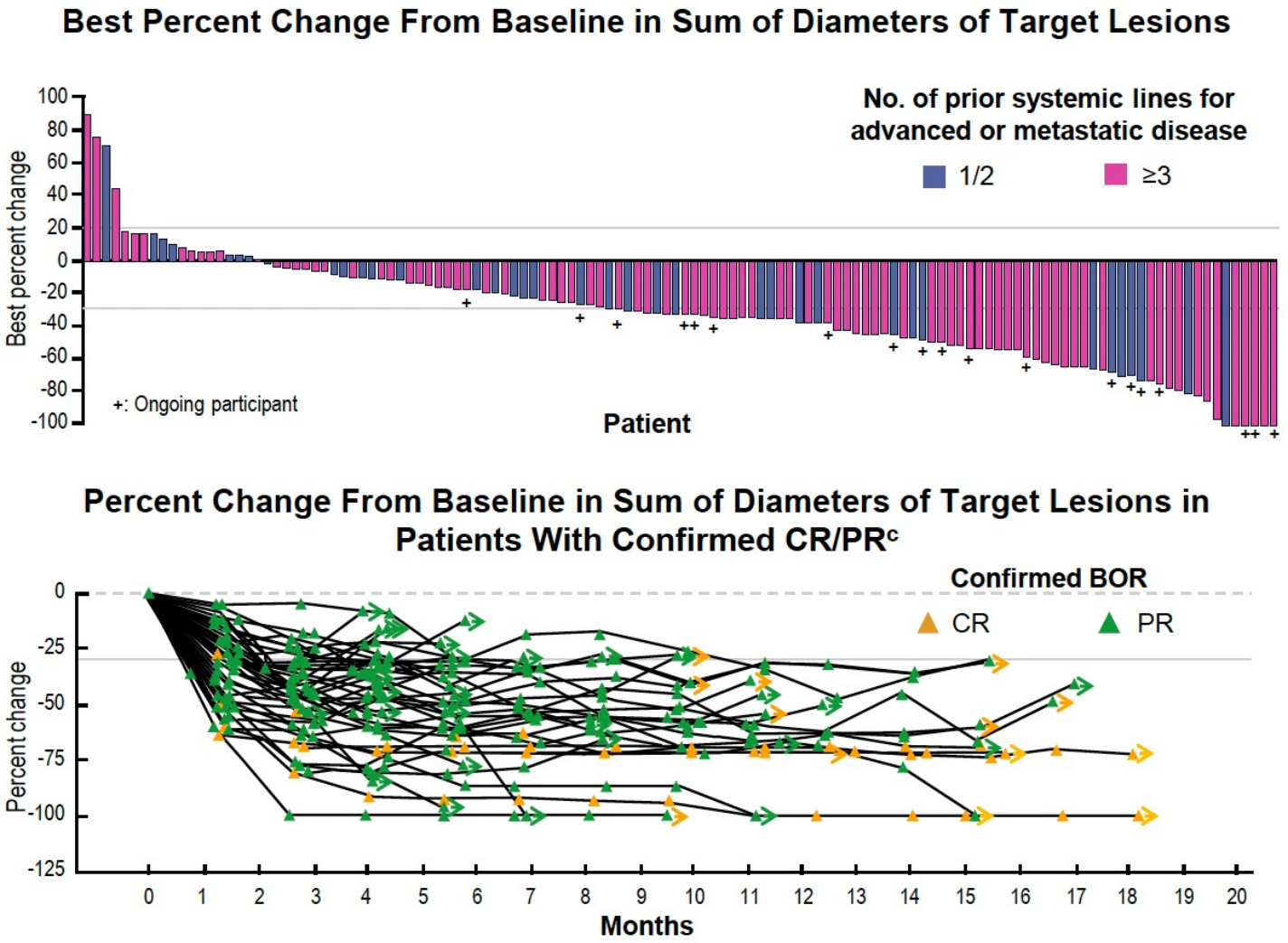
Sands et al, WCLC 2024

# Phase II TROPION-Lung05: Dato-DXd in Previously Treated Advanced NSCLC With Actionable Genomic Alterations (AGAs)

| Outcome | All Patients (N = 137) | *EGFR*m (n = 78) | *ALK*+ (n = 34) |
|---|---|---|---|
| Confirmed ORR, n (%) | 49 (35.8) | 34 (43.6) | 8 (23.5) |
| mDoR, mo (95% CI) | 7.0 (4.2-9.8) | 7.0 (4.2-10.2) | 7.0 (2.8-8.4) |
| Confirmed DCR, n (%) | 108 (78.8) | 64 (82.1) | 25 (73.5) |
| mPFS, mo (95% CI) | 5.4 (4.7-7.0) | 5.8 (5.4-8.3) | 4.3 (2.6-6.9) |

Paz-Ares. ESMO 2023. Abstr 1314MO.

# Phase II TROPION-Lung05: Dato-DXd in Previously Treated Advanced NSCLC With AGAs




Paz-Ares. ESMO 2023. Abstr 1314MO.

# Datopotamab deruxtecan granted Priority Review in the US for patients with previously treated advanced EGFR-mutated NSCLC

## Press Release: January 13, 2025

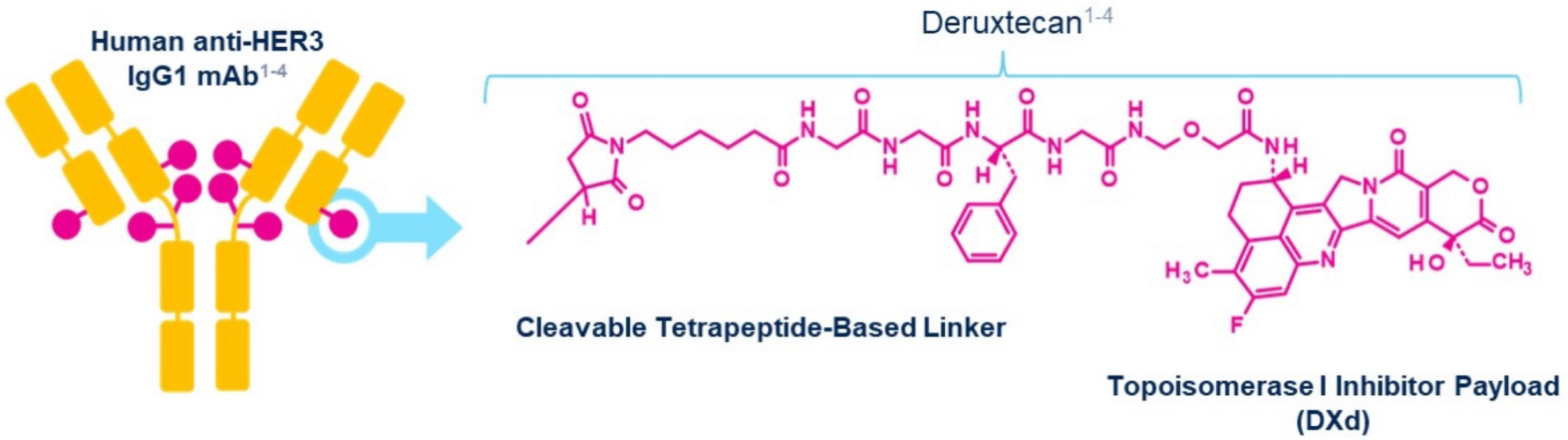
The Biologics License Application (BLA) for datopotamab deruxtecan (Dato-DXd) has been accepted and granted Priority Review in the US for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) who have received prior systemic therapies, including an EGFR-directed therapy.

In a pooled analysis of patients with previously treated advanced or metastatic EGFRm NSCLC in the TROPION-Lung05 and TROPION-Lung01 trials presented at the European Society for Medical Oncology (ESMO) Asia 2024 Congress, datopotamab deruxtecan demonstrated a confirmed objective response rate (ORR) of 42.7% (95% confidence interval [CI] 33.6-52.2) as assessed by blinded independent central review (BICR) and a median duration of response (DoR) of 7.0 months (95% CI 4.2-9.8). The safety profile of datopotamab deruxtecan was consistent with previous reports from the TROPION-Lung05 and TROPION-Lung01 trials, with no new safety concerns identified.

https://www.astrazeneca.com/media-centre/press-releases/2025/datopotamab-deruxtecan-granted-priority-review-in-the-us-for-patients-with-previously-treated-advanced-egfr-mutated-non-small-cell-lung-cancer.html#:~:text=AstraZeneca%20and%20Daiichi%20Sankyo's%20Biologics,small%20cell%20lung%20cancer%20(NSCLC)

# Patritumab Deruxtecan (HER3-DXd)

- HER3-DXd is an ADC with 3 components[1-6]:
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker

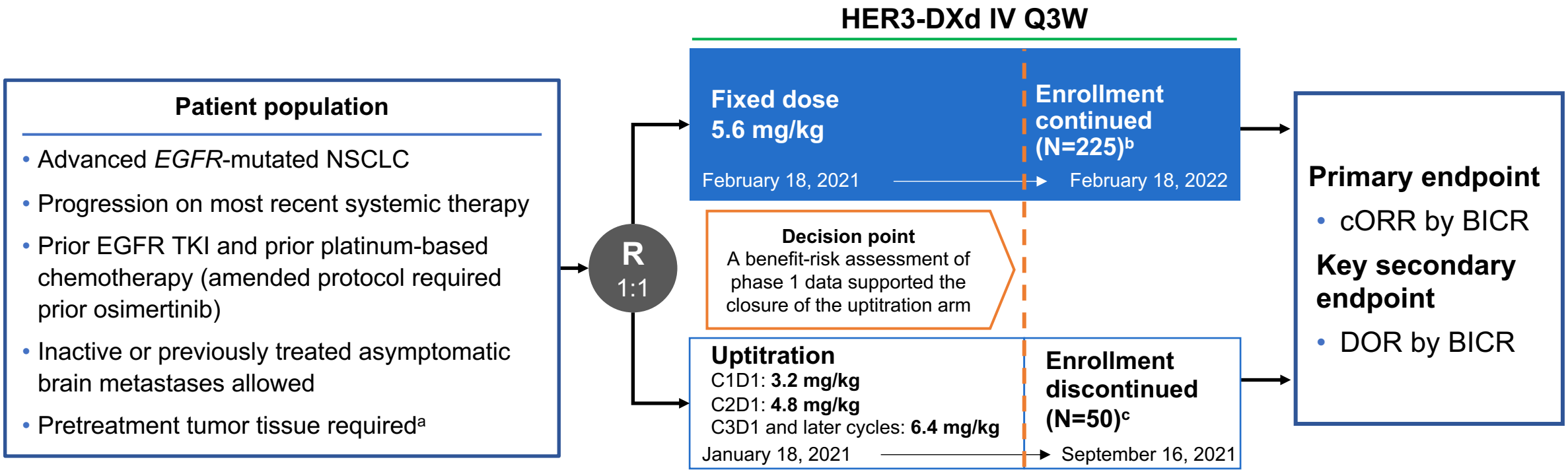



**7 Key Attributes of HER3-DXd**

| |
|---|
| Payload mechanism of action: topoisomerase I inhibitor [a,1-4] |
| High potency of payload [a,1-4] |
| High drug to antibody ratio ≈ 8 [a,1,2] |
| Payload with short systemic half-life [a,b,2,3] |
| Stable linker-payload [a,2-4] |
| Tumor-selective cleavable linker [a,1-5] |
| Bystander antitumor effect [a,2,6] |

Krop IE et al. ASCO 2022;Abstract 1002.

# HERTHENA-Lung01 Study Design[1]

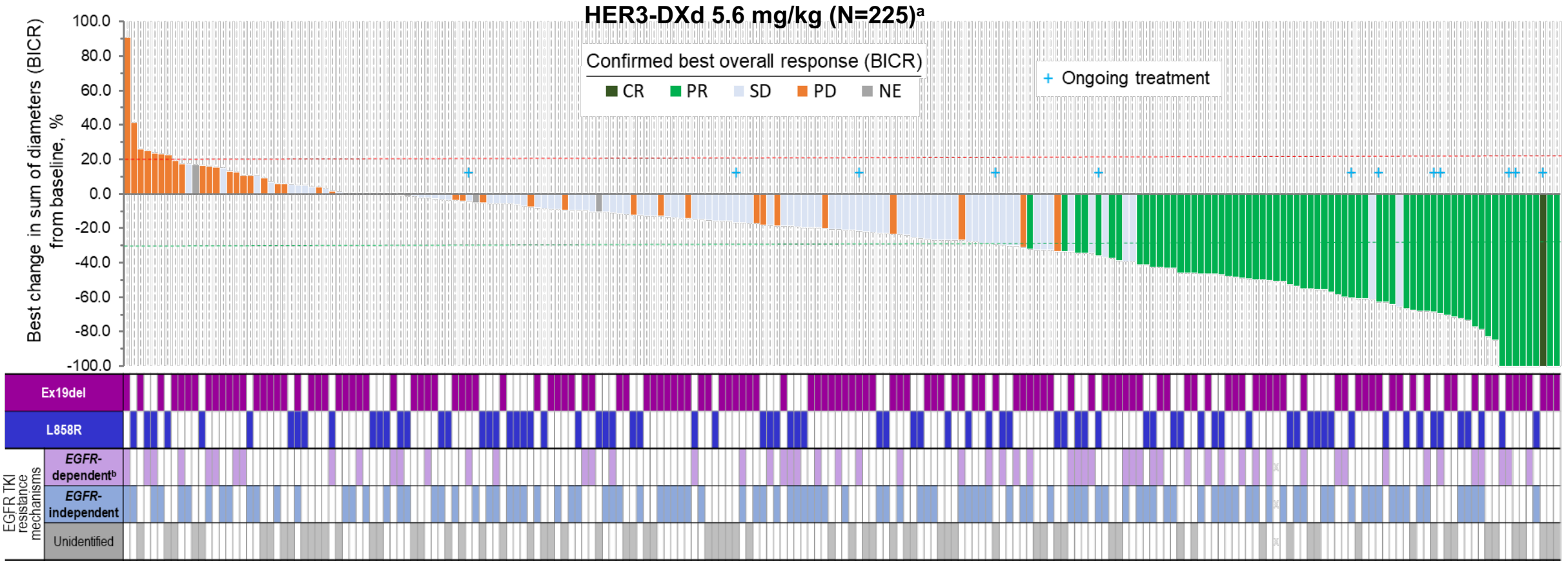



Primary data cutoff, 21 Nov 2022[d]
Snapshot data cutoff, 18 May 2023 (additional 6 months follow-up)
Data are presented for the 5.6-mg/kg fixed-dose arm

- Efficacy from snapshot data cutoff—median study follow-up, 18.9 (range, 14.9-27.5) months
- Safety from primary data cutoff—median treatment duration, 5.5 (range, 0.7-18.2) months

BICR, blinded independent central review; C, cycle; cORR, confirmed objective response rate (complete or partial response confirmed ≥4 weeks after initial response [RECIST version 1.1]); D, day; DOR, duration of response; HER, human epidermal growth factor receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.
[a] Inclusion not based on detection of HER3 expression. [b] 226 patients were enrolled; 225 received ≥1 dose. [c] 51 patients were enrolled; 50 received ≥1 dose. [d] Data cutoff for the primary analysis occurred when all enrolled patients had either ≥9 months of follow-up or had discontinued from the study earlier.
1. Yu HA, et al. *Future Oncol*. 2023;19:1319-1329.

# Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance



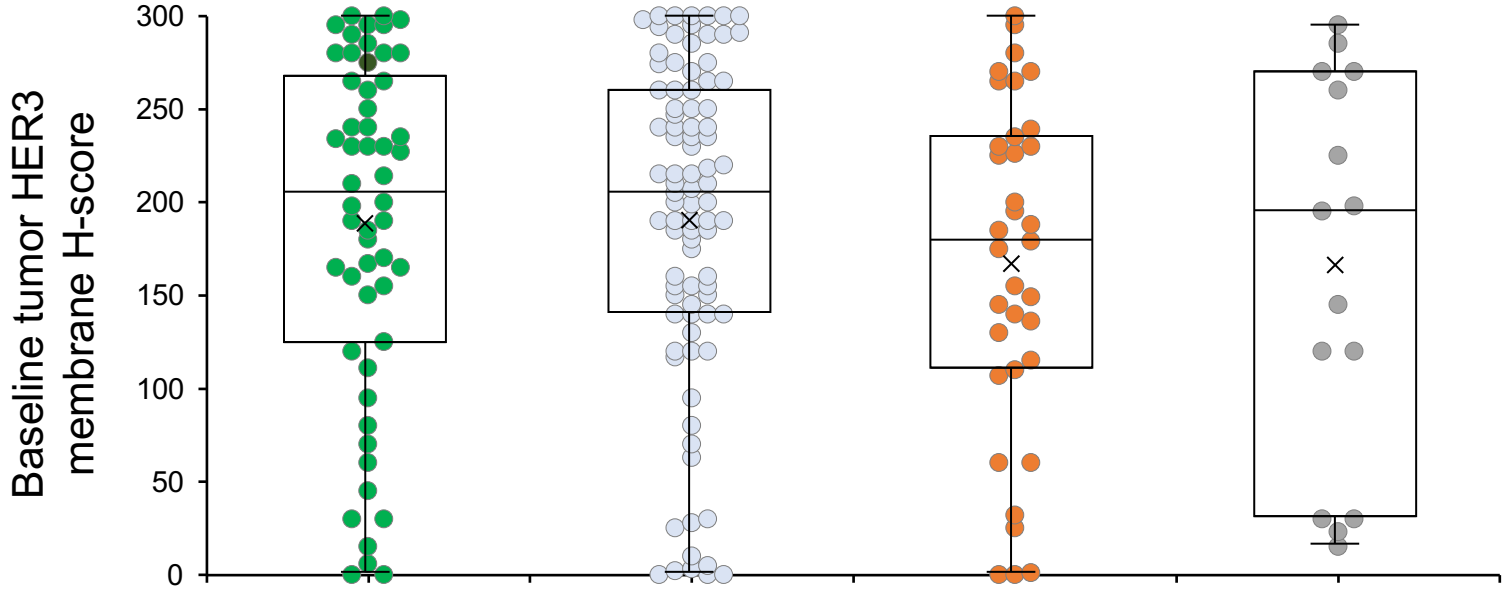

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

BICR, blinded independent central review; CR, complete response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] 210 patients had evaluable target lesion measurements at both baseline and post baseline and are included. [b] T790M was not included as an *EGFR*-dependent mechanism of EGFR TKI resistance.

Yu HA et al. *J Clin Oncol* 2023;41(35):5363-5375.

# Efficacy Observed Across a Broad Range of Pretreatment Tumor HER3 Membrane Expression Levels

**Association of Baseline Tumor HER3 Membrane H-Score With Confirmed BOR by BICR Following Treatment With HER3-DXd 5.6 mg/kg (N=225)[a]**




| Confirmed BOR (BICR) | CR/PR | SD | PD | NE |
|---|---|---|---|---|
| Biomarker-evaluable patients, n/n | 54/67 | 89/99 | 35/43 | 15/16 |
| H-score, median | 205 | 205 | 179 | 195 |
| (range) | (0-300) | (0-300) | (0-300) | (15-295) |

Response data are for the snapshot data cutoff, 18 May 2023.
Medians are indicated by horizontal lines; means are indicated by X.

BICR, blinded independent central review; BOR, best overall response; CR, complete response; HER, human epidermal growth factor receptor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a] 193 patients had tumor tissue evaluable for H-score. Baseline was the sample on or before the first dose date and not earlier than 90 days before the first dose date. Highest HER3 membrane H-score value was used if multiple records were available.

Yu HA et al. *J Clin Oncol* 2023;41(35):5363-5375.

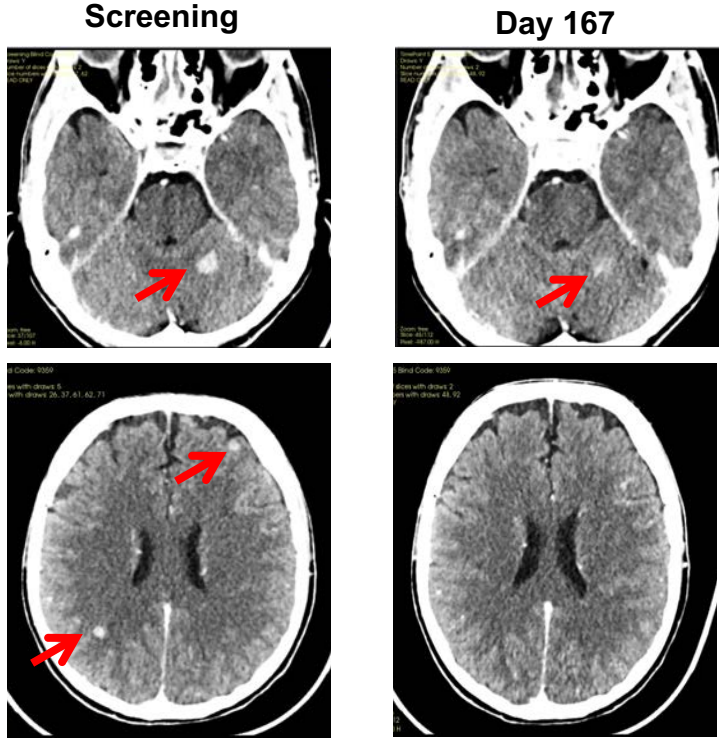
# Intracranial Responses (by CNS BICR) Observed With HER3-DXd

## Intracranial Efficacy of HER3-DXd in Patients With Brain Metastases at Baseline

| Intracranial response by CNS BICR per CNS RECIST | Patients with brain metastasis at baseline and no prior radiotherapy (N=30)[a] |
|---|---|
| Confirmed ORR (95% CI), % | 33.3 (17.3-52.8) |
| CR, n (%) | 9 (30.0)[b] |
| PR, n (%) | 1 (3.3) |
| SD, n (%)[c] | 13 (43.3) |
| PD, n (%) | 4 (13.3) |
| NE, n (%) | 3 (10.0) |
| DCR (95% CI), % | 76.7 (57.7-90.1) |
| DOR, median (95% CI), mo | 8.4 (5.8-9.2) |

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

### Partial CNS Response in a Patient With a Measurable CNS BICR Target Lesion




BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCR, disease control rate (CR+PR+SD); DOR, duration of response; MRI, magnetic resonance imaging; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] 7 patients had measurable target lesions; 23 patients had only nontarget lesions. [b] 8 patients had only nontarget lesions. [c] Includes non-CR/non-PD.

Yu HA et al. *J Clin Oncol* 2023;41(35):5363-5375.

# HERTHENA-Lung02

- Patritumab deruxtecan demonstrated statistically significant improvement in progression-free survival versus doublet chemotherapy in patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer in HERTHENA-Lung02 phase 3 trial. News Release. September 17, 2024.

# Conclusions

- The greatest efficacy for datopotamab deruxtecan is among EGFR mutation positive patients
- Patritumab deruxtecan has demonstrated efficacy among patients with EGFR mutations
- The toxicity profile of the agents are somewhat unique
- To date, we have not seen clear association of the target of the antibody and efficacy, although evaluation is ongoing

# Roundtable Discussion

RTP
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TO PRACTICE

# Understanding the Current Paradigm and New Approaches: The Optimal Implementation of Antibody-Drug Conjugates in the Care of Patients with Cancer

Yale NewHaven Health
Smilow Cancer Hospital

Yale CANCER CENTER

Yale SCHOOL OF NURSING

Research To Practice
Oncology Nursing Society Congress 2025

Marianne Davies, DNP, CNS-BC, ACNP-BC, AOCNP-BC, FAAN
Program Manager, Care Signature: Oncology Service Line
Thoracic Oncology Nurse Practitioner, Smilow Cancer Hospital
Associate Professor, Yale University School of Nursing

# Scenario 4: EGFR-mutant NSCLC

- 55 yo woman, never smoker
  - Married, Adult children & young grandchild
  - Husband is ophthalmologist
  - Volunteers in NICU, Community Dining Hall, Church
- Diagnosed 2023 with EGFR-mutant NSCLC, L858R point mutation exon 21
- Treated with 18 months on EGFR inhibitor therapy
- Progression of disease on recent scans
- About to start Datopotamab Deruxtecan (Dato-DXd)

Yale NewHaven Health
Smilow Cancer Hospital

Yale CANCER CENTER

# Dato-DXd: Side Effect Reports on TROPION-Lung01

- Nausea
- Stomatitis/mucositis inflammation 55% all grade; 6% ≥ grade 3
  - $TROP_2$ expressed on mucosal surfaces
- Ocular:  21% overall; Dry eye (7%) increased lacrimation (7%)
  - Conjunctivitis, keratitis
- ILD (9% all grade; 4% ≥ grade 3; 2% death)
- Hematologic toxicities: neutropenia, fever

# Management of Ocular Surface Toxicities Associated With Datopotamab Deruxtecan

| Grade and Description | Protocol Management Recommendations |
|---|---|
| **Grade 1:** Asymptomatic; Nonconfluent superficial keratitis | Consider ophthalmology assessment<br>Maintain dose |
| **Grade 2:** Symptomatic with moderate decrease in visual acuity; Confluent keratitis, cornea defect or 3-line or more loss of best corrected distance visual acuity. | Obtain ophthalmology assessment<br>Delay dose until resolved to grade ≤1 |
| **Grade 3:** Symptomatic limiting self-care ADLs; Corneal ulcer or stromal opacity or best corrected visual acuity <20/200 | Obtain ophthalmology assessment<br>Delay dose until resolved to grade ≤1, then reduce by one dose level |
| **Grade 4:** Corneal Perforation | Obtain ophthalmology assessment<br>Discontinue drug |

Heist RS, et al. *Cancer Treat Rev*. 2024;125:102720.

# Ocular Surface Events (OSE)

**Prophylaxis**

- Avoid contact lens use
- Lubricating artificial tears

**Management**

- Ophthalmologic eye exam
  - Other ADCs use prophylactic steroid, lubricant, vasoconstrictive drops. This has not so far been recommended for Dato-DXd given lower incidence
- Use of eye cooling packs during infusion?

# Management of Stomatitis/Mucositis Associated With Datopotamab Deruxtecan

| Grade | Protocol Management Recommendations |
|---|---|
| **1** | Maintain dose |
| **2** | Consider dose delay or reduction |
| **3** | Delay dose until resolved to grade ≤1 or baseline<br>Consider dose reduction by one level if supportive medications are already optimized |
| **4** | Discontinue drug |

Heist RS, et al. *Cancer Treat Rev*. 2024;125:102720.

# Stomatitis

## Prophylactic

- Educate patients on importance of oral hygiene, hydration and lubrication of oral mucosa
- Gentle teeth brushing, soft toothbrush, bland fluoride-containing toothpaste
- Daily flossing (stop if bleeding or painful)
- Education about oral hygiene, hydration, lubrication
  - What not to do or use
- Steroid-containing mouthwash
  - 4 times a day, swish and spit 1 to 2 minutes
  - Example is dexamethasone 0.1 mg/mL

## Management

- Use bland mouthwashes every hour if needed
- Pain management topical or systemic
  - (doxepin 0.5%, viscous lidocaine 2%)
- Referral to dentist or oral surgeon for further evaluation
- Use of ice chips (cryotherapy) during infusions
  - Held in mouth during the infusion

Heist RS, et al. *Cancer Treat Rev*. 2024;125:102720.

# ILD Risk factors

- Smoking
- Previous ILD
- ECOG PS >2
- Preexisting lung disease

- Patients with NSCLC are at higher risk due to underlying preexisting lung pathology and higher rates of smoking

- EGFR-TKI, osimertinib, in first line setting (incidence of grade >3 ILD ranges from 0.9-3%)

# Management of ILD Associated With Datopotamab Deruxtecan

**Monitor**

HOLD Dato-DXd for concerning new symptoms; Rule out other causes

**Confirm**

Evaluation with CT scan, Pulse oximetry, Pulmonology

**Manage**

| Grade | Protocol Management Recommendations in Addition to Holding or Discontinuing Agent |
|---|---|
| **1** | Monitor symptoms and closely follow up in 2-7 days for clinical onset of symptoms and $SpO_2$<br>Consider follow-up imaging in 1-2 weeks<br>Consider starting systemic steroids (prednisone 0.5 mg/kg/day)<br>Hold Dato-DXd until fully resolved<br>---If resolved in <28 days, maintain dose<br>---If resolved >28 days, reduce by one dose level<br>---If grade 1 ILD/pneumonitis does not resolve within 84 days, permanently discontinue Dato-DXd |
| **2** | Permanently discontinue Dato-DXd<br>Monitor and re-image<br>Start systemic steroids (prednisone 1.0 mg/kg/day); increase steroid dose if worsening or no improvement in ≤5 days; duration until grade 1, then taper over ≥ 4 weeks |
| **3/4** | Permanently discontinue Dato-DXd<br>Hospitalization<br>Initiate high-dose systemic steroids (Methylprednisolone 500-1000 mg/day x 3 days)<br>Re-image as clinically indicated<br>If no improvement within 3-5 days, reconsider workup for alternative etiologies and consider other immunosuppressants and/or treat per local practice |

$SpO_2$, oxygen saturation.

Heist RS, et al. *Cancer Treat Rev*. 2024;125:102720.

# Roundtable Discussion

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# Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

*A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress*

# Antibody-Drug Conjugates

**Wednesday, April 9, 2025**

**11:15 AM – 12:45 PM**

## Faculty

**Marianne J Davies, DNP, ACNP, AOCNP, FAAN**
**Edward B Garon, MD, MS**
**Marissa Marti-Smith, DNP, APRN, AGNP-C, AOCNP**
**Tiffany A Traina, MD, FASCO**

## Moderator

**Neil Love, MD**

RTP RESEARCH TO PRACTICE

# Understanding the Current Paradigm and New Approaches in the Care of Patients with Cancer

*A Complimentary NCPD Hybrid Symposium Series Held During the 50th Annual ONS Congress*

# Hormone Receptor-Positive Breast Cancer

**Wednesday, April 9, 2025**

**6:00 PM – 8:00 PM**

## Faculty

**Virginia F Borges, MD, MMSc**
**Jamie Carroll, APRN, MSN, CNP**
**Ronald Stein, JD, MSN, NP-C, AOCNP**
**Seth Wander, MD, PhD**

## Moderator

**Neil Love, MD**

RTP RESEARCH TO PRACTICE

*Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.*

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*Virtual attendees: The NCPD credit link is posted in the chat room.*

*NCPD/ONCC credit information will be emailed to each participant within 1 to 2 business days.*

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