Harnessing the Power of **Antibody-Drug Conjugates** for the **Treatment of Hematologic and Solid Cancers**

# Leveraging Antibody-Drug Conjugates in Breast Cancer Care

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# Introductions

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# Disclosures

## Sara Hurvitz, MD, FACP

Contracted Research: Ambrx, Amgen, Astra Zeneca, Arvinas, Bayer, Cytomx, Daiichi-Sankyo, Dignitana, Genentech/Roche, Gilead, GSK, Immunomedics, Eli Lilly, Macrogenics, Novartis, Pfizer, OBI Pharma, Orinove, Pieris, UMA, Radius, Sanofi, Seattle Genetics/Seagen, Zymeworks, Phoenix Molecular Designs, Ltd.

## Hope S. Rugo, MD, FASCO

Research support for clinical trials through the University of California: Pfizer, Merck, Novartis, Lilly, Roche, Odonate, Daiichi, Seattle Genetics, Sermonix, Polyphor, Astra Zeneca, OBI, Gilead, Ayala, Astellas.

Honoraria: Puma, Samsung, Napo.

## Planning Committee

The following planning committee members have nothing to disclose:
**UNMC:** Brenda Ram, CMP, CHCP

**Bio Ascend:** Patti Bunyasaranand, MS; Jessica Davis; Tisheeka Graham-Steed, PhD; Kraig Steubing

# Learning Objectives

- Describe the mechanism of action of ADCs and their rationale for use in patients with cancer
- Evaluate the safety and efficacy of current and emerging ADCs for patients with solid tumors
- Assess clinical trial results of approved and investigational ADCs that are being examined in patients with hematologic malignancies
- Review adverse events associated with the use of ADCs in patients with cancer and strategies to mitigate these adverse events

# Reminders

Visit www.bioascend.com/antibody-drug-conjugates to register for upcoming webinars and view past webinars

# Antibody Drug Conjugates

*Advances in chemotherapy delivery and efficacy*

# ADCs consist of numerous elements, including the monoclonal antibody, conjugated drug, and stable linker

**Monoclonal antibody**

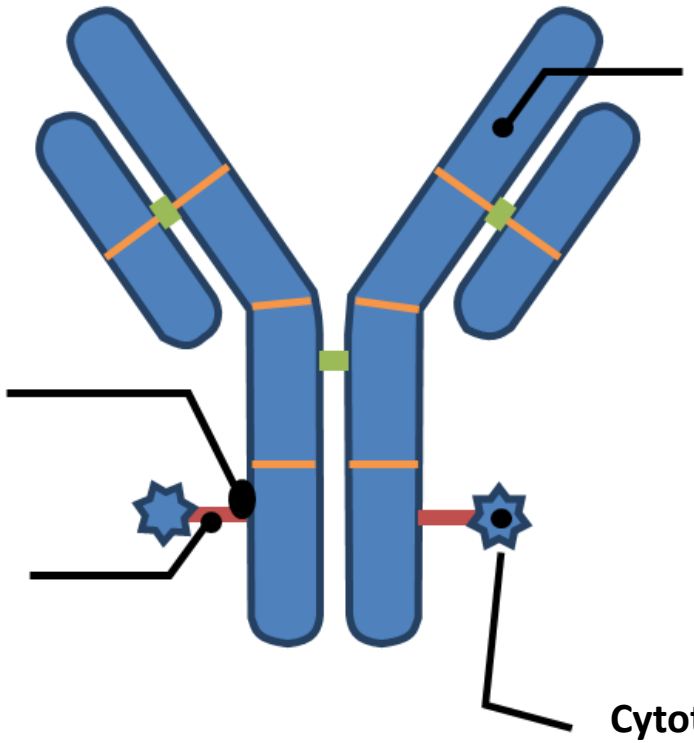
- Selective for an antigen with high copy numbers on the target tumour cell
- Internalises in target cell
- Minimal immunogenic response

**Conjugation chemistry**

- Lys or Cys residue of the mAb; controls drug distribution and DAR

**Stable linker**

- Selectively releases drug in target cell
- Long term stability



**Cytotoxic drug**

- Highly potent subnanomolar activity
- Functional groups for linking
- Lower hydrophobicity

ADC=antibody-drug conjugate; Cys=cysteine; DAR=drug:antibody ratio; Lys=lysine; mAb=monoclonal antibody.

Nakada T, et al. *Chem Pharm Bull*. 2019;67:173–185.

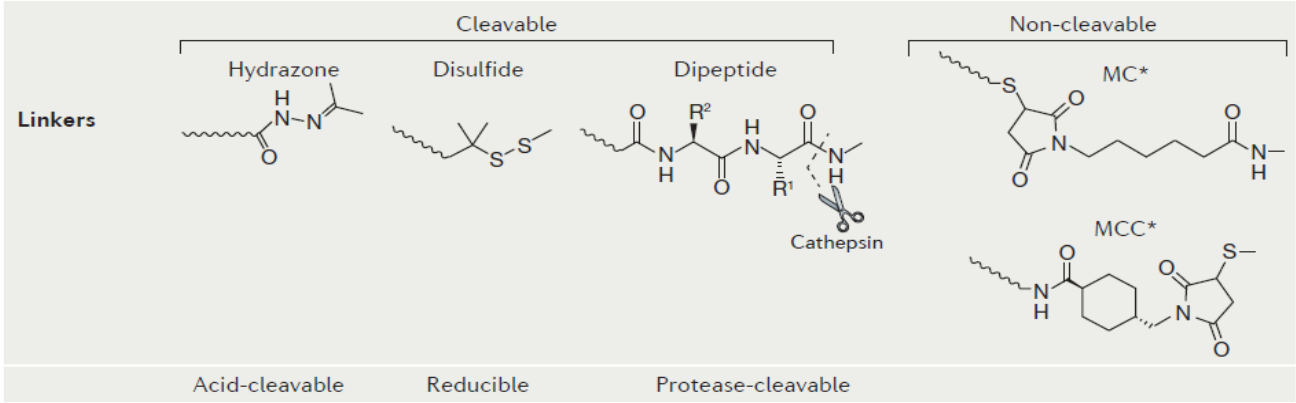
Linker Payload Disulphide bonds

# ADC Design and Construction

**mAb**

| Antibodies | IgG1 | IgG2 | IgG3 | IgG4 |
|---|---|---|---|---|
| Serum half-life | 21 days | 21 days | 7–21 days | 21 days |
| C1q binding | Yes | Yes | Yes | No |
| Fcγ avidity | High | Low | High | Moderate |

**Linker**

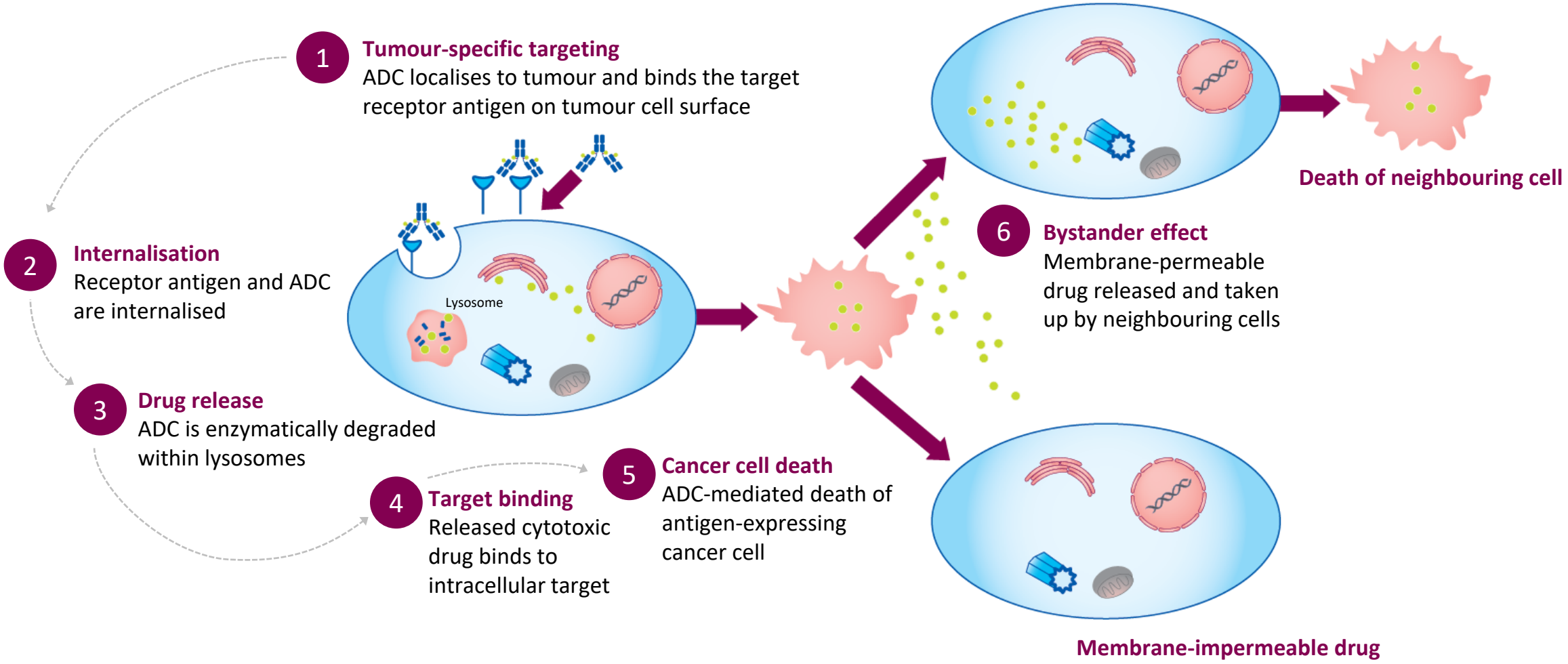



**Payload (chemotherapy)**

| Payloads | Auristatins | Maytansinoids | Calicheamicins | Camptothecins |
|---|---|---|---|---|
| | Anti-microtubule | Anti-microtubule | DNA cleavage | Topoisomerase 1 inhibition |
| Examples: | MMAE<br>MMAF | DM1<br>DM4 | Ozogamicin | DXd<br>SN-38 |

Drago, Modi, and Chandarlapaty; Nat Rev. Clin Onc. 2021

# ADC technology enables tumour-specific targeting




ADC=antibody-drug conjugate

1. Adapted from: Trail PA, et al. *Pharmacol Ther.* 2018;181:126–142.

# Overview of ADCs in Development for Breast Cancer

| ADC | Target | Antibody | Payload | DAR | Clinical programme | Company |
|---|---|---|---|---|---|---|
| **Trastuzumab emtansine (T-DM1)** | HER2 | Trastuzumab | DM1 | 3.5 | Approved in mBC with prior therapy, multiple trials in mBC | Roche Holding AG |
| **Trastuzumab deruxtecan (T-DXd, DS-8201)** | HER2 | Trastuzumab | DXd | 8 | Approved in mBC with two prior therapies, multiple trials in mBC | AstraZeneca and Daiichi Sankyo |
| **(vic-)trastuzumab duocarmazine (SYD985)** | HER2 | Trastuzumab | Seco-DUBA | 2.8 | Phase 1 BC, Phase 3 mBC | Synthon Biopharmaceuticals BV |
| **Sacituzumab govitecan** | TROP2 | RS7 | SN-38 | 7.6 | Approved in TNBC with two prior therapies, multiple trials in mTNBC, mBC | Gilead Sciences, Inc. |
| **Datopotamab deruxtecan (Dato-DXd, DS-1062)** | TROP2 | Datopotamab | DXd | 4 | Phase 1 TNBC and HR+/HER2- | AstraZeneca and Daiichi Sankyo |
| **Ladiratuzumab vedotin (SGN-LIV1A)** | LIV1 | hLIV22 | Vc-MMAE | 4 | Phase 1 mBC, Phase 1/2 mTNBC | Seagen |
| **RC48-ADC** | HER2 | Hertuzumab | MMAE | 4 | Phase 1 BC | RemeGen Co |
| **Patritumab deruxtecan (U3-1402)** | HER3 | Patritumab | DXd | 8 | Phase 1/2 mBC | Daiichi Sankyo |
| A166 | HER2 | Trastuzumab | ND | ND | Phase 1/2 BC | Klus Pharma, Inc. |
| ALT-P7 (HM2-MMAE) | HER2 | HM2 | MMAE | ND | Phase 1 mBC | Alteogen, Inc. |
| ARX788 | HER2 | ND | Amberstatin269 | 1.9 | Phase 1 mBC | Ambrx Biopharma |
| DHES0815A (anti-HER2/PBC-MA) | HER2 | ND | PBD-MA | ND | Phase 1 mBC | Genentech and Roche Holding AG |
| MEDI4276 | HER2 | Trastuzumab scFv | AZI13599185 | 4 | Phase 1 BC | MedImmune, LLC |
| XMT-1522 (TAK-522) | HER2 | HT-18 | AF-HPA | 12 | Phase 1 BC | Mersana Therapeutics, Inc. |
| AVID100 | EGFR | MAB100 | DM1 | ND | Phase 1/2 TNBC | Formation Biologics, Inc. |
| CAB-ROR2-ADC | Ror2 | CAB | ND | ND | Phase 1/2 TNBC | BioAtla |
| Anti-CA6-DM4 immunoconjugate (SAR566658) | CA6 | DS6 | SPDB-DM4 | 1 | Phase 2 TNBC | Sanofi |

ADC=antibody-drug conjugate; AF-HPA=auristatin F-hydroxypropylamide; DM1=mertansine; DXd=trastuzumab deruxtecan; mBC=metastatic breast cancer; HER2/3=human epidermal growth factor receptor 2/3; MMAE=monomethyl auristatin E; ND=not defined; PBD-MA=pyrrolo benzodiazepine monoamide; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan; (m)TNBC=(metastatic) triple-negative breast cancer; TROP-2=trophoblast cell surface antigen 2.

1. Nagayama A, et al. Ther Adv Med Oncol. 2020; 2. Rinnerthaler G, et al. Int J Mol Sci. 2019

# EMILIA: T-DM1: Historic Standard 2nd Line Therapy

*But times have changed!*

**HER2+ LABC or MBC (N=980)**

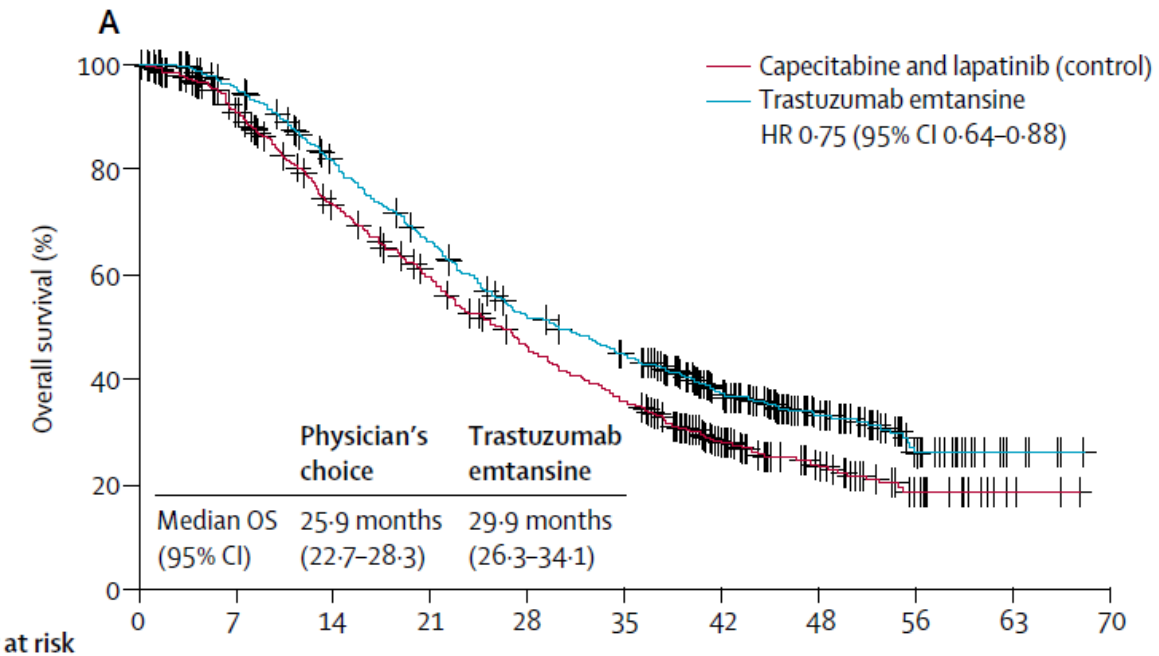
- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 mos of adjuvant tx

1:1

**T-DM1**

**Capecitabine + Lapatinib**

## Overall

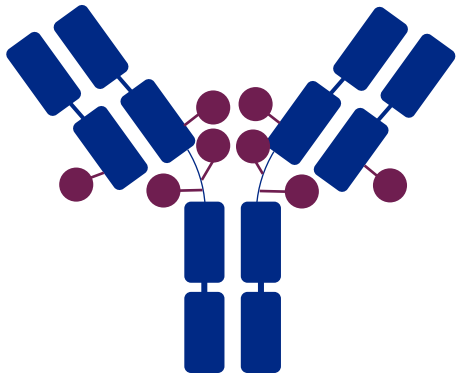



| Number at risk (number censored) | 0 | 7 | 14 | 21 | 28 | 35 | 42 | 48 | 56 | 63 | 70 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Capecitabine and lapatinib | 496 (0) | 418 (35) | 326 (47) | 258 (53) | 195 (58) | 153 (58) | 82 (99) | 48 (122) | 19 (144) | 3 (160) | 0 (163) |
| Trastuzumab emtansine | 495 (0) | 451 (21) | 374 (34) | 302 (36) | 231 (42) | 194 (47) | 127 (85) | 68 (133) | 23 (169) | 5 (187) | 0 (191) |

Dieras V et al, *Lancet Oncology;* 2017.

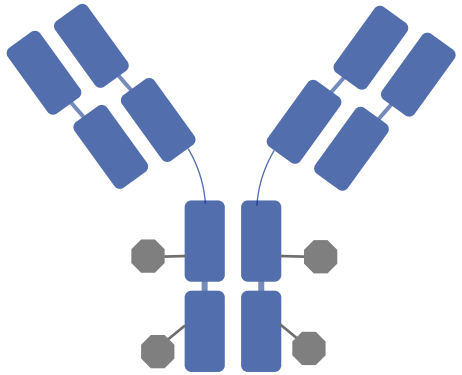
# ADC Characteristic Differences Between T-DXd and T-DM1

**Trastuzumab deruxtecan (T-DXd)[1]**



| T-DXd[1-4,a] | ADC Attributes | T-DM1[3-5] |
|---|---|---|
| Topoisomerase I inhibitor | **Payload MoA** | Anti-microtubule |
| ~8:1 | **Drug-to-antibody ratio** | ~3.5:1 |
| Yes | **Tumor-selective cleavable linker?** | No |
| Yes | **Evidence of bystander anti-tumor effect?** | No |

**Trastuzumab emtansine (T-DM1)[5]**



Destiny Breast01

**Confirmed ORR: 60.9%[a]**
(95% CI, 53.4%-68.0%)
**Updated ORR: 61.4%**
**12 CRs** (n=169)

**CBR x 6 months: 76.1%**
(95% CI, 69.3%-82.1%)

**Median duration of response: 14.8 months**
**Updated DOR: 20.8 mo**
(95% CI, 15.0 months-NE)

**Median time to response: 1.6 months**
(95% CI, 1.4-2.6 months)

Modi. NEJM. 2020;382:610

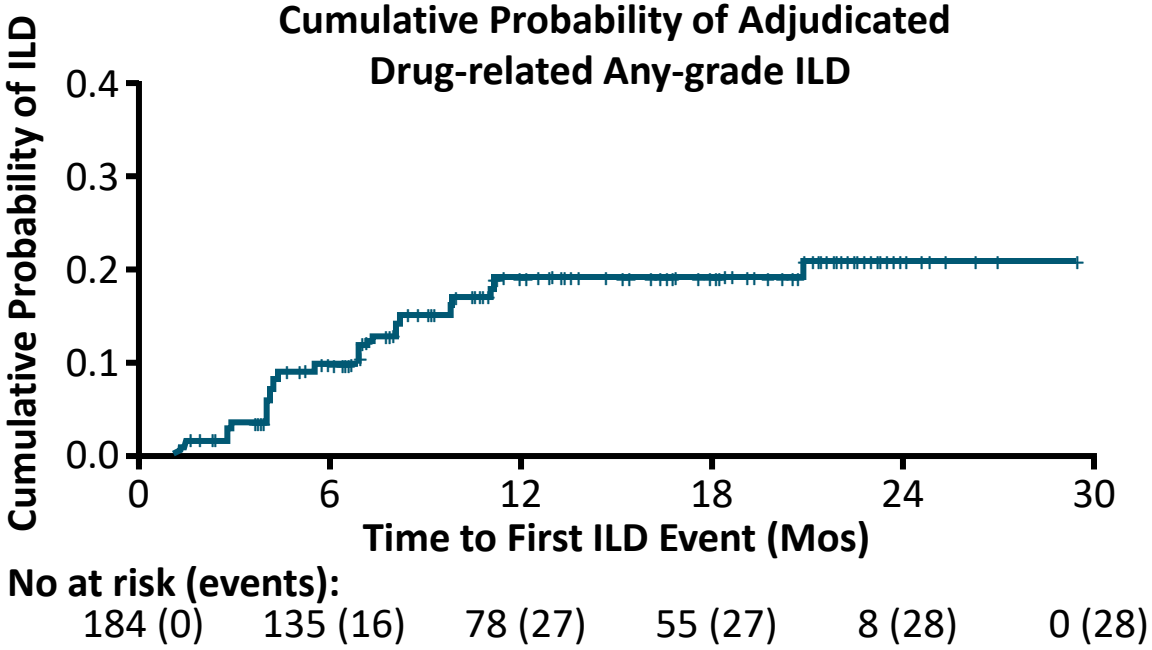
1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42.
4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

# Warnings and Precautions: ILD/Pneumonitis Monitoring and Management

| Interstitial lung disease, n (%) | T-Dxd 5.4 mg/kg (N = 184) | | | | | |
|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any grade/Total |
| **Aug 2019 data cutoff** | 5 (2.7) | 15 (8.2) | 1 (0.5) | 0 | 4 (2.2) | **25 (13.6)** |
| **June 2020 data cutoff** | 6 (3.3) | 16 (8.7) | 1 (0.5) | 0 | 5 (2.7) | **28 (15.2)** |

As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

**Cumulative Probability of Adjudicated Drug-related Any-grade ILD**




**Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected**

**Promptly Investigate Evidence of ILD**

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

**For Asymptomatic ILD (Grade 1)**

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

**For Symptomatic ILD (Grade ≥ 2)**

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan

Modi et al, SABCS 2020

Trastuzumab deruxtecan [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo Inc and Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.

# Incidence of ILD after implementation of toxicity management guidelines

Updated toxicity management guidelines implemented (December 2019)

## Incidence of ILD over time

| | 2016 (n=74) | 2017 (n=168) | 2018 (n=569) | 2019 (n=179) | 2020 (n=160) |
|---|---|---|---|---|---|
| **Any Grade ILD, n (%)** | 18 (24.3) | 33 (19.6) | 87 (15.3) | 28 (15.6) | 11 (6.9) |
| **Grade ≥3 ILD, n (%)** | 2 (2.7) | 6 (3.6) | 21 (3.7) | 8 (4.5) | 3 (1.9) |
| **Grade 5 ILD, n (%)** | 1 (1.4) | 5 (3.0) | 12 (2.1) | 5 (2.8) | 2 (1.3) |

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**.

- Patients enrolled in 2020 (after implementation of toxicity management guidelines) appear to have had lower rates of all grade (6.9%), grade ≥3 (1.9%) and grade 5 ILD (1.3%) compared with those enrolled in previous years based on a December 2020 snapshot; however, this may be partly due to the shorter treatment duration

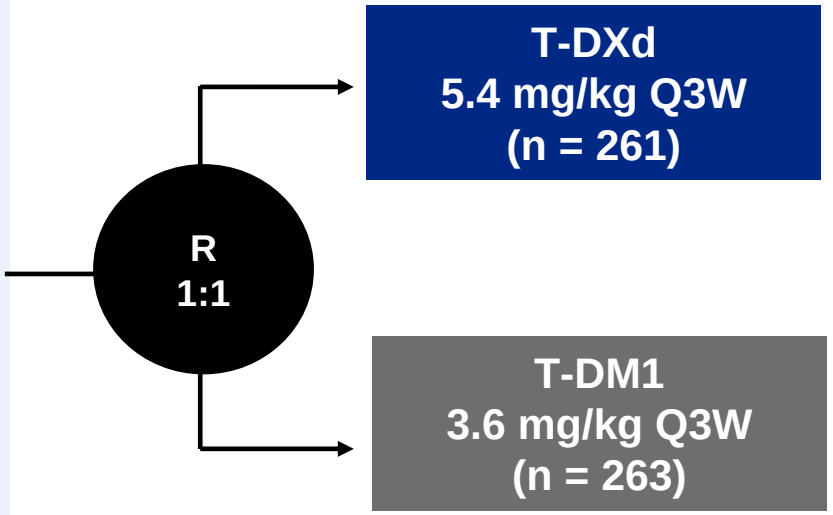
Powell, et al AACR 2021

# DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

## An open-label, multicenter study (NCT03529110)

**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

**Interim analysis for PFS (data cutoff: May 21, 2021)**
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

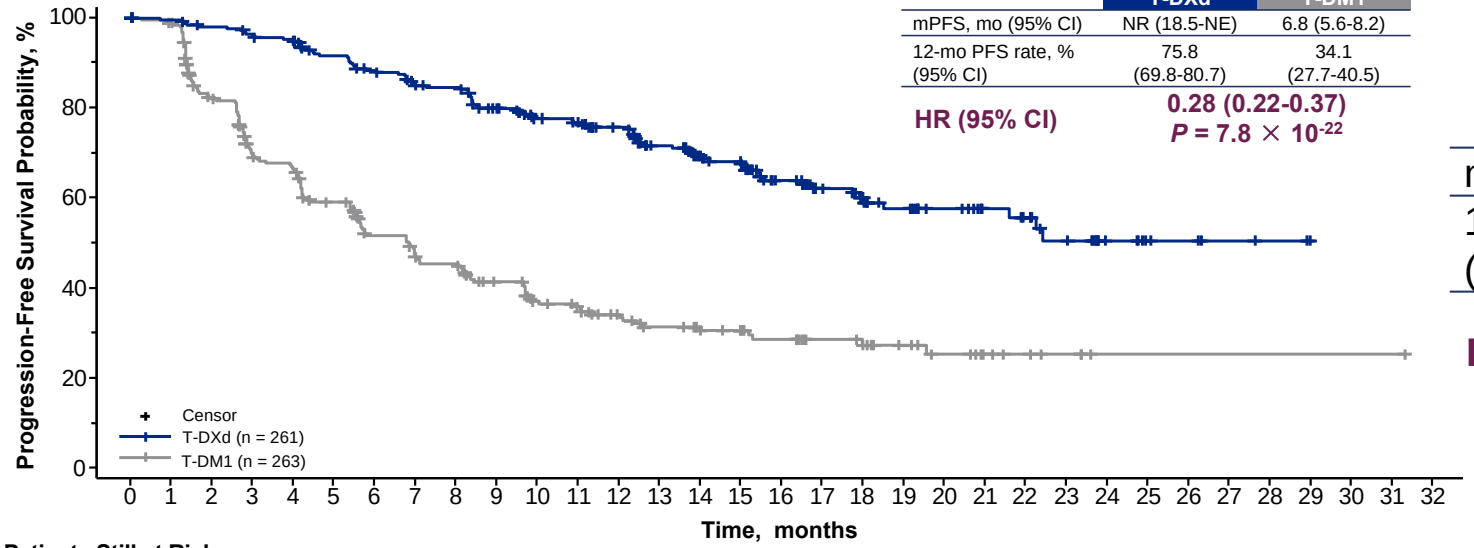
**Key secondary endpoint, OS:** boundary for efficacy: $P < 0.000265$ (based on 86 events)

Details:
- HR+: 50%
- Brain mets: 24 vs 20%
- Prior pertuzumab: 61%
- One line of prior rx: 50 vs 47%

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Cortes et al, NEJM 2022

# Primary Endpoint: PFS by BICR




| | T-DXd | T-DM1 |
|---|---|---|
| mPFS, mo (95% CI) | NR (18.5-NE) | 6.8 (5.6-8.2) |
| 12-mo PFS rate, % (95% CI) | 75.8 (69.8-80.7) | 34.1 (27.7-40.5) |
| HR (95% CI) | 0.28 (0.22-0.37) $P = 7.8 \times 10^{-22}$ | |

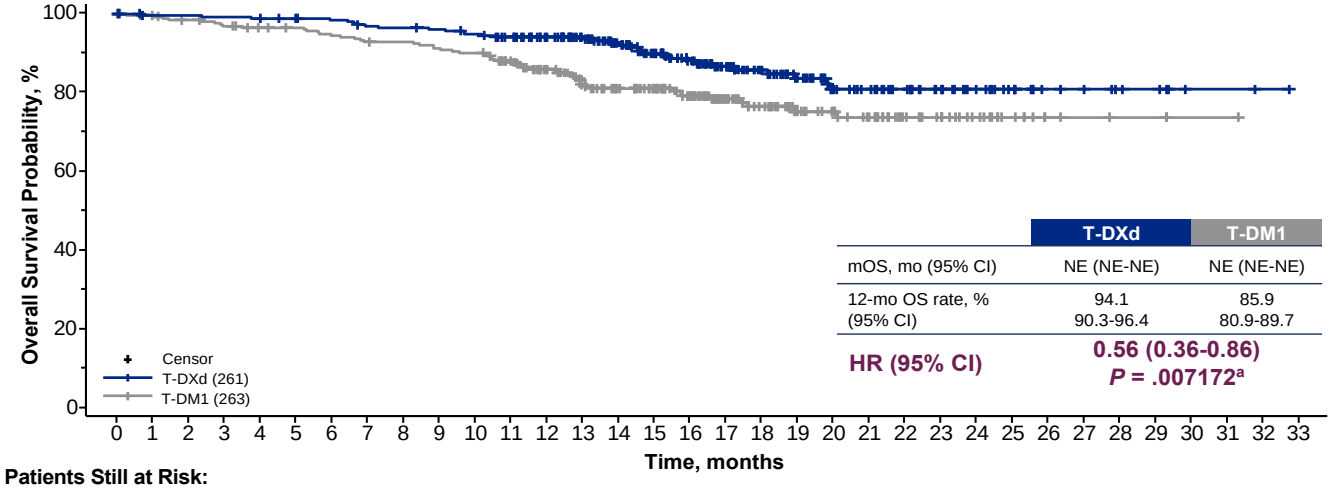
**Patients Still at Risk:**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **T-DXd (261)** | 261 | 256 | 250 | 244 | 240 | 224 | 214 | 202 | 200 | 183 | 168 | 164 | 150 | 132 | 112 | 105 | 79 | 64 | 53 | 45 | 36 | 29 | 25 | 19 | 10 | 6 | 5 | 3 | 2 | 0 | | | |
| **T-DM1 (263)** | 263 | 252 | 200 | 163 | 155 | 132 | 108 | 96 | 93 | 78 | 65 | 60 | 51 | 43 | 37 | 34 | 29 | 23 | 21 | 16 | 12 | 8 | 6 | 4 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |

## PFS by Investigator Assessment

| | T-DXd | T-DM1 |
|---|---|---|
| mPFS, mo (95% CI) | 25.1 (22.1-NE) | 7.2 (6.8-8.3) |
| 12-mo PFS rate, % (95% CI) | 76.3 (70.4-81.2) | 34.9 (28.8-41.2) |
| HR (95% CI) | 0.26 (0.20-0.35) $P = 6.5 \times 10^{-24}$ | |

# Key Secondary Endpoint: OS




| | T-DXd | T-DM1 |
|---|---|---|
| mOS, mo (95% CI) | NE (NE-NE) | NE (NE-NE) |
| 12-mo OS rate, % (95% CI) | 94.1 90.3-96.4 | 85.9 80.9-89.7 |
| HR (95% CI) | 0.56 (0.36-0.86) $P = .007172^{a}$ | |

**Patients Still at Risk:**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **T-DXd (261)** | 261 | 256 | 256 | 255 | 254 | 251 | 249 | 244 | 243 | 241 | 237 | 230 | 218 | 202 | 180 | 158 | 133 | 108 | 86 | 71 | 56 | 50 | 42 | 33 | 24 | 18 | 11 | 10 | 7 | 6 | 2 | 2 | 1 | 0 |
| **T-DM1 (263)** | 263 | 258 | 253 | 248 | 243 | 241 | 236 | 232 | 231 | 227 | 224 | 210 | 188 | 165 | 151 | 140 | 120 | 91 | 75 | 58 | 52 | 44 | 32 | 27 | 18 | 11 | 5 | 4 | 3 | 3 | 1 | 1 | 0 | |

**Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)**

[a]$P = .007172$, but does not cross pre-specified boundary of $P < .000265$

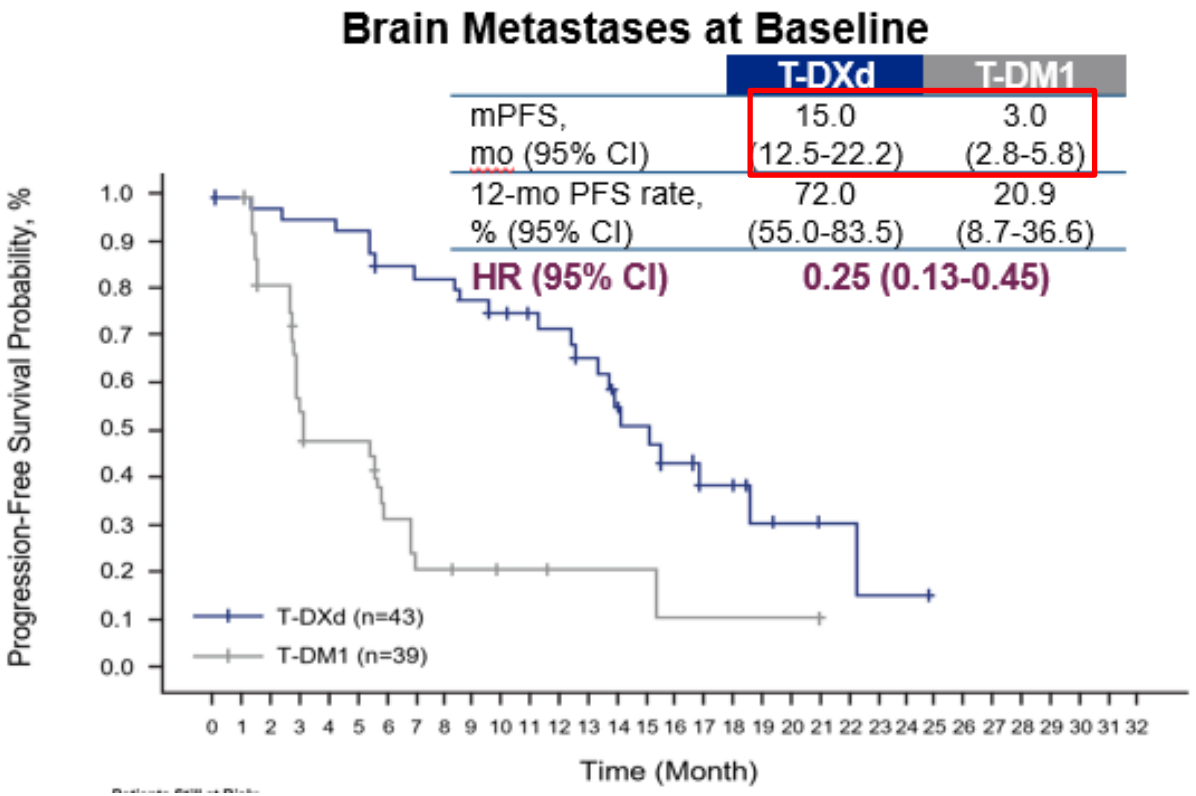
## PFS in Key Subgroups

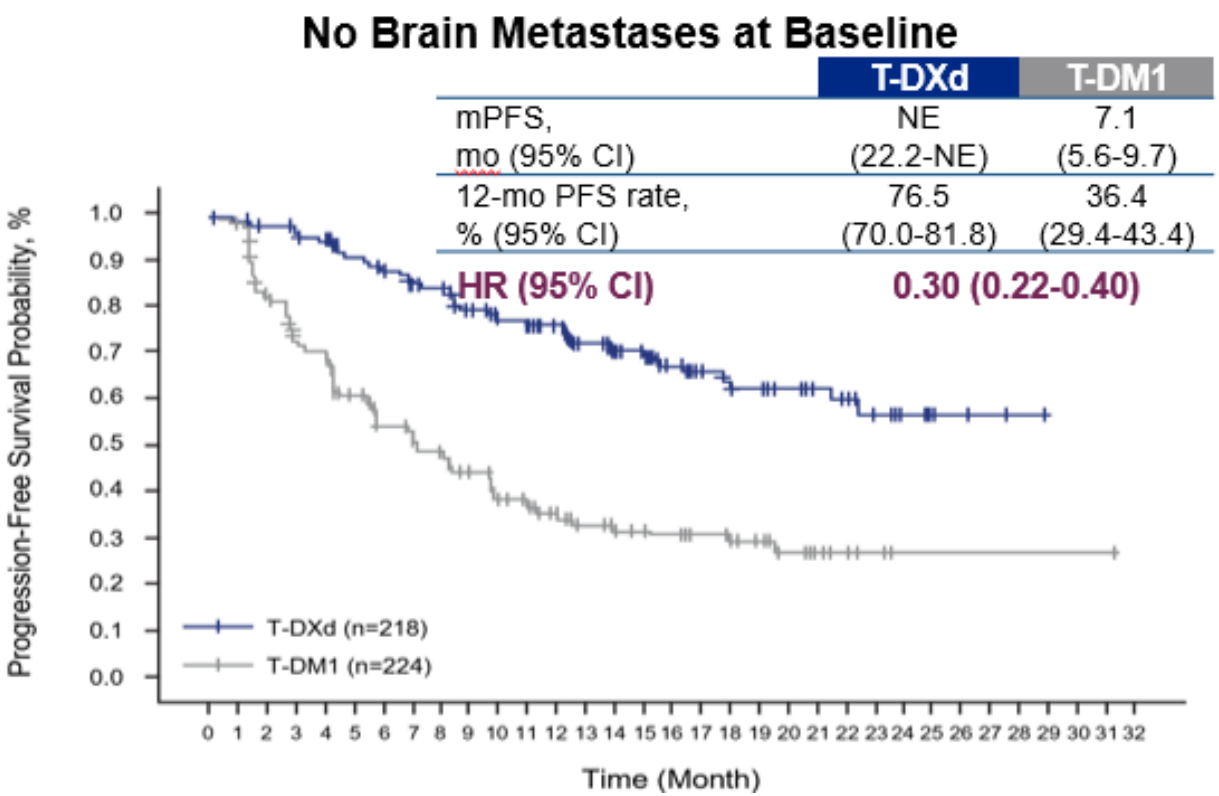
| | | Number of Events | | Median PFS (mo, 95% CI) | | HR (95% CI) |
|---|---|---|---|---|---|---|
| | | T-DXd | T-DM1 | T-DXd | T-DM1 | |
| **All patients** | | 87/261 | 158/263 | NE (18.5-NE) | 6.8 (5.6-8.2) | 0.2840 (0.2165-0.3727) |
| **Hormone Receptor Status** | Positive (n = 272) | 46/133 | 84/139 | 22.4 (17.7-NE) | 6.9 (4.2-9.8) | 0.3191 (0.2217-0.4594) |
| | Negative (n = 248) | 41/126 | 73/122 | NE (18.0-NE) | 6.8 (5.4-8.3) | 0.2965 (0.2008-0.4378) |
| **Prior Pertuzumab Treatment** | Yes (n = 320) | 57/162 | 98/158 | NE (18.5-NE) | 6.8 (5.4-8.3) | 0.3050 (0.2185-0.4257) |
| | No (n = 204) | 30/99 | 60/105 | NE (16.5-NE) | 7.0 (4.2-9.7) | 0.2999 (0.1924-0.4675) |
| **Visceral Disease** | Yes (n = 384) | 72/195 | 123/189 | 22.2 (16.5-NE) | 5.7 (4.2-7.0) | 0.2806 (0.2083-0.3779) |
| | No (n = 140) | 15/66 | 35/74 | NE (NE-NE) | 11.3 (6.8-NE) | 0.3157 (0.1718-0.5804) |
| **Prior Lines of Therapy[a]** | 0-1 (n = 258) | 46/132 | 75/126 | 22.4 (17.9-NE) | 8.0 (5.7-9.7) | 0.3302 (0.2275-0.4794) |
| | ≥2 (n = 266) | 41/129 | 83/137 | NE (16.8-NE) | 5.6 (4.2-7.1) | 0.2828 (0.1933-0.4136) |
| **Brain Metastases** | Yes (n = 114) | 31/62 | 31/52 | 15.0 (12.6-22.2) | 5.7 (2.9-7.1) | 0.3796 (0.2267-0.6357) |
| | No (n = 410) | 56/199 | 127/211 | NE (22.4-NE) | 7.0 (5.5-9.7) | 0.2665 (0.1939-0.3665) |


Cortes et al, NEJM 2022

# DESTINY Breast03

## PFS curves for patients w/ and w/o brain mets



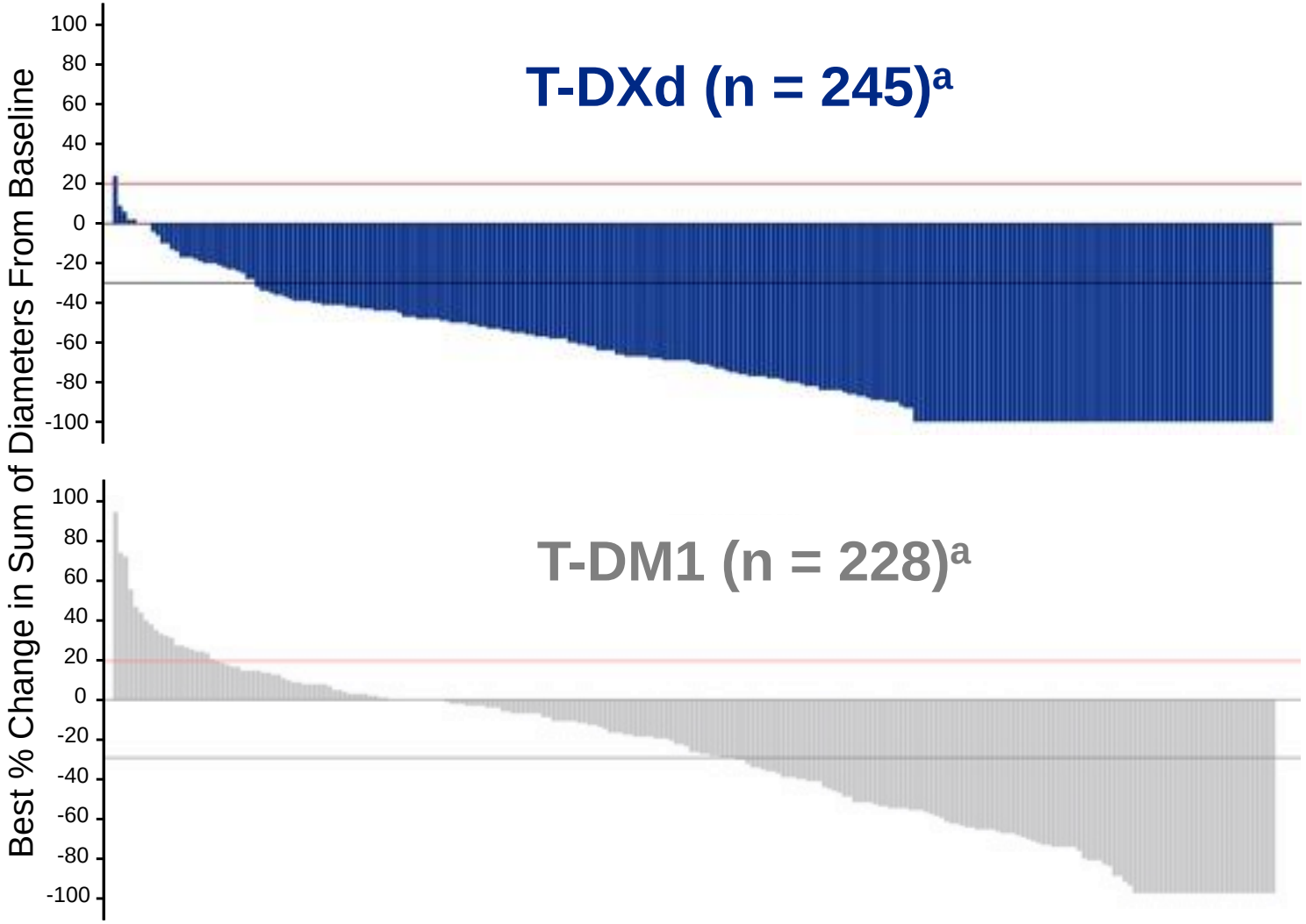




Intracranial response rates in pts with brain mets:
63.9% with T-DXd vs 33.4% with T-DM1

| | | |
|---|---|---|
| **History of BM, n (%)** | | |
| Yes \| No | 62 (23.8) \| 199 (76.2) | 52 (19.8) \| 211 (80.2) |
| **BM at baseline,[b] n (%)** | | |
| Yes \| No | 43 (16.5) \| 218 (83.5) | 39 (14.8) \| 224 (85.2) |

Hurvitz S et al. SABCS 2021

# Confirmed ORR and Best Overall Response

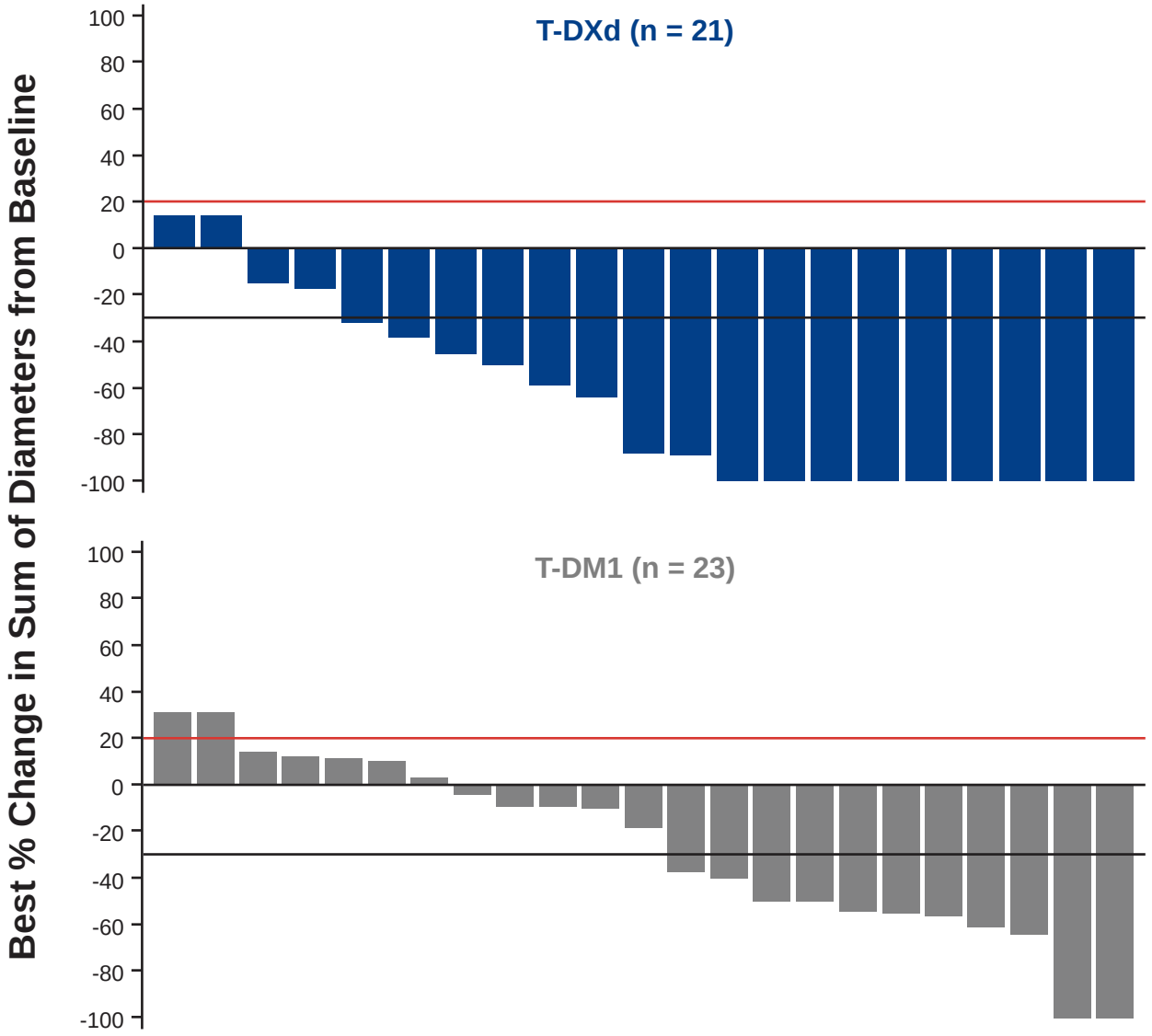



| | T-DXd (n = 261) | T-DM1 (n = 263) |
|---|---|---|
| **Confirmed ORR** | | |
| n (%)[b] | 208 **(79.7)** | 90 **(34.2)** |
| [95% CI] | [74.3-84.4] | [28.5-40.3] |
| | *P* < .0001 | |
| **CR** | 42 **(16.1)** | 23 **(8.7)** |
| **PR** | 166 **(63.6)** | 67 **(25.5)** |
| SD | 44 (16.9) | 112 (42.6) |
| PD | 3 (1.1) | 46 (17.5) |
| Not evaluable | 6 (2.3) | 15 (5.7) |
| CR + PR + SD (DCR) | 252 (96.6) | 202 (76.8) |

CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. [b]Based on BICR.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.

Cortes et al, ESMO 2021

# Intracranial Response per BICR using RECIST 1.1




| | T-DXd (n = 36) | T-DM1 (n = 36) |
|---|---|---|
| **Best Overall Response, n (%)[a]** | | |
| CR | 10 (27.8) | 1 (2.8) |
| PR | 13 (36.1) | 11 (30.6) |
| Non-CR/non-PD | 6 (16.7) | 7 (19.4) |
| SD | 4 (11.1) | 7 (19.4) |
| PD | 1 (2.8) | 8 (22.2) |
| Not evaluable | 0 | 1 (2.8) |
| Missing | 2 (5.6) | 1 (2.8) |

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

Hurvitz S et al. SABCS 2021

# Adverse Events of Special Interest

| Adjudicated as drug-related ILD/pneumonitis[a], n (%) | | | | | | |
|---|---|---|---|---|---|---|
| **n (%)** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** | **Any Grade** |
| T-DXd (n = 257) | 7 (2.7) | 18 (7.0) | 2 (0.8) | 0 | 0 | 27 (10.5) |
| T-DM1 (n = 261) | 4 (1.5) | 1 (0.4) | 0 | 0 | 0 | 5 (1.9) |

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

| LVEF decrease, n (%) | | | | | | |
|---|---|---|---|---|---|---|
| **n (%)** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** | **Any Grade** |
| T-DXd (n = 257) | 1 (0.4)[b] | 6 (2.3)[c] | 0 | 0 | 0 | 7 (2.7) |
| T-DM1 (n = 261) | 0 | 1 (0.4)[c] | 0 | 0 | 0 | 1 (0.4) |

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

Cortes et al, ESMO 2021

Drug-Related TEAEs in ≥20% of Patients

| **Gastrointestinal disorders** | T-DXd All grade | T-DXd grade >3 | T-DM1 All grade | T-DM1 grade >3 |
|---|---|---|---|---|
| Nausea | 195 (75.9) | 17 (6.6) | 79 (30.3) | 1 (0.4) |
| Vomiting | 126 (49.0) | 4 (1.6) | 26 (10.0) | 1 (0.4) |
| Diarrhea | 75 (29.2) | 1 (0.4) | 18 (6.9) | 1 (0.4) |

[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction.

Hurvitz S et al. SABCS 2021

# TUXEDO-1 Phase 2 Trial of T-DXd for HER2+ BCBM

**HER2+ MBC with newly diagnosed or progressive brain metastases N=15**

→ **Trastuzumab Deruxtecan 5.4mg/kg IV q3wk**

**Primary endpoint: CNS Response Rate**

- Simon 2 Stage Design
- Stage 1: Intracranial Response in 5/6 patients **(ICRR: 83.3%)**
- Stage 2 is fully enrolled

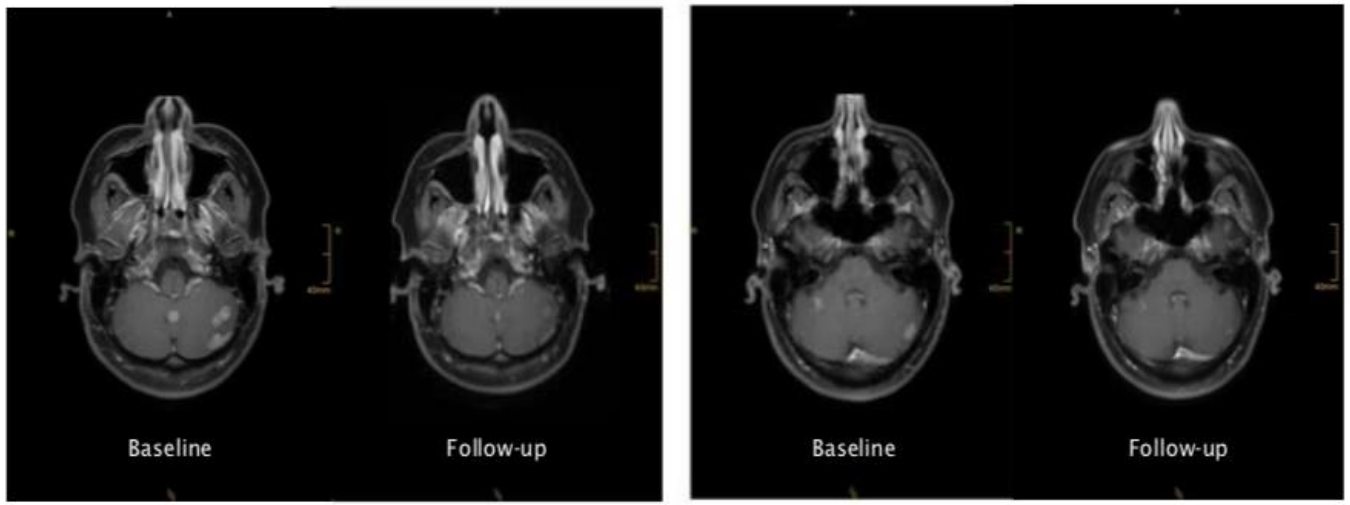


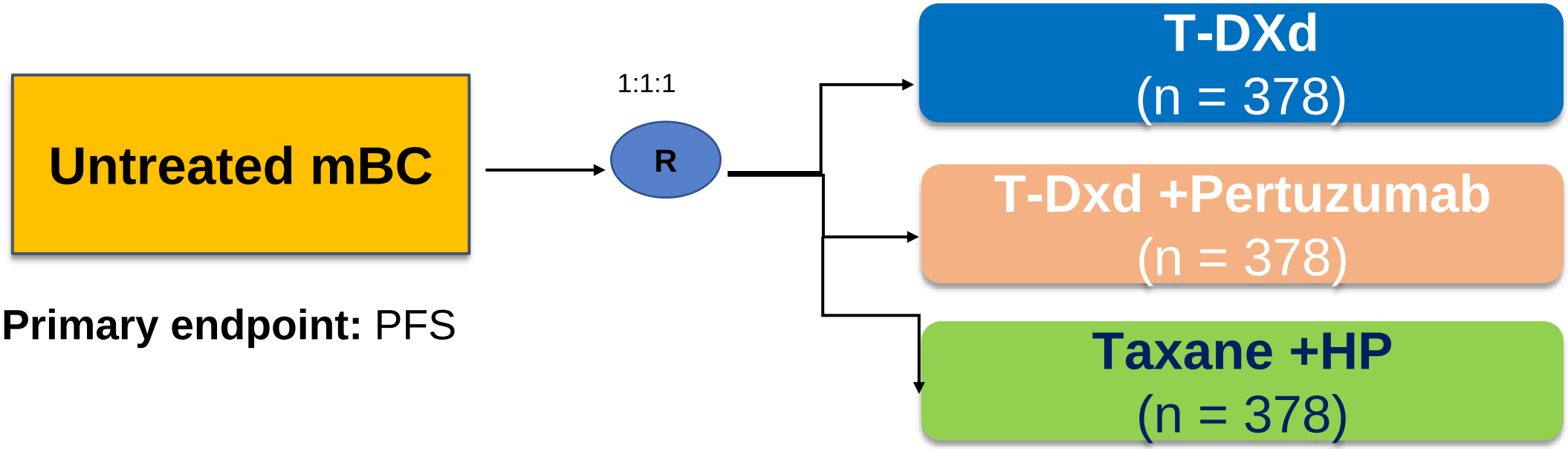

**Figure 2 – Intracerebral response on cerebral MRI**

A 37-year-old woman with bilateral cerebellar breast cancer brain metastases. T1-weighted contrast enhanced cerebral magnetic resonance images (MRI) at baseline (left) and follow-up (right) after 10 applications of therapy with T-DXd showing an ongoing partial response according to RANO criteria.

Bartsch R et al, ESMO 2021

# Next Steps with T-DXd

## Destiny Breast-09 (NCT04784715): 1st Line Trial in HER2+ MBC




**Primary endpoint:** PFS

## DESTINY Breast05: T-DXd vs T-DM1 (NCT03742102)

# Trastuzumab Duocarmazine (SYD985) in HER2+ MBC
# TULIP - Phase III Trial Design

**HER2-positive LABC or MBC**
≥2 therapies for metastatic disease, or T-DM1 for metastatic disease
Treated brain mets are allowed
N=437

R 2:1

**SYD985 treatment**
**1.2 mg/kg IV every 21 days**
**N=291**

**Physician's choice treatment (PC)**
**N=146**

**Continue treatment until progression or unacceptable toxicity**

**Primary Endpoint**
- Centrally assessed PFS

**Secondary Endpoints**
- Investigator assessed PFS
- OS
- ORR
- HRQOL

**Physician's choice**
- Lapatinib + Capecitabine; Trastuzumab + Capecitabine; Trastuzumab + Vinorelbine; Trastuzumab + Eribulin

- SYD985 is a HER2-targeting ADC based on trastuzumab and a cleavable linker-duocarmycin (vc-*seco*-DUBA) payload:
  - Active toxin (DUBA) alkylates DNA
  - Drug to Antibody Ratio (DAR) ranges from 2.4 to 2.8

**3-Way Mechanism of Action**

**A** Uptake of ADC by internalization and **intracellular release** of payload

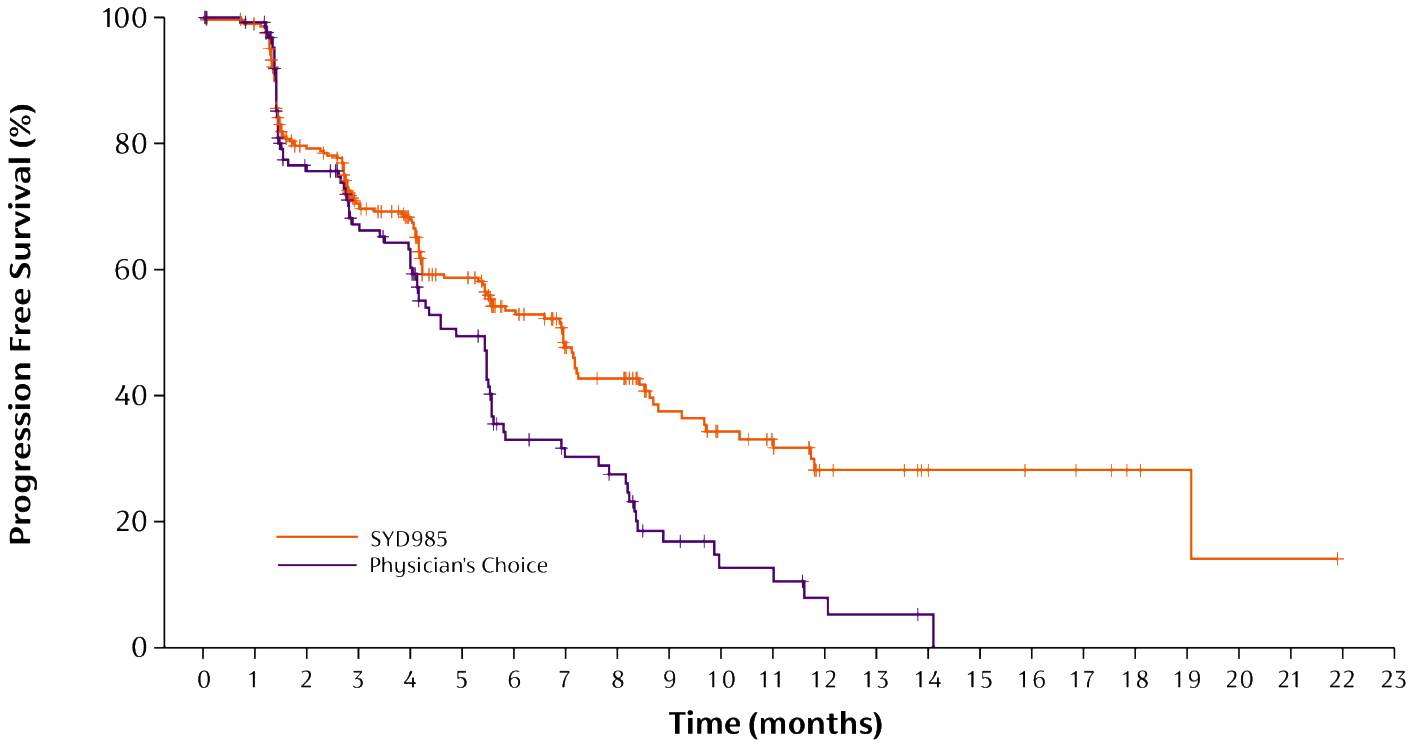
**B** Proteolytic cleavage and subsequent release of payload in **tumor microenvironment** (bystander effect)

**C** **Diffusion of active payload** to neighboring tumor cells (bystander effect)

Saura et al, ESMO 2021.

Van der Lee et al. Mol Cancer Ther 14(3); 692-703, 2015

# TULIP – Centrally Reviewed PFS




| No. Patients at Risk | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SYD985 | 291 | 278 | 208 | 167 | 150 | 109 | 83 | 59 | 51 | 35 | 28 | 24 | 13 | 12 | 9 | 8 | 6 | 5 | 3 | 2 | 1 | 1 | 0 |
| Physician's Choice | 146 | 125 | 86 | 69 | 64 | 44 | 26 | 22 | 19 | 10 | 6 | 6 | 3 | 2 | 1 | 0 | | | | | | | |

| Full Analysis Set (FAS) | SYD985 (N=291) | Physician's choice (N=146) |
|---|---|---|
| Median PFS (95% CI) months | 7.0 (5.4 – 7.2) | 4.9 (4.0 – 5.5) |
| Events | 140 (48.1%) | 86 (58.9%) |
| HR (95% CI) | **0.64 (0.49 – 0.84); p=0.002** | |

## AEs of Special Interest

**Eye toxicity: 78.1%** SYD985, 29.2% physician's choice

- Grade≥ 3: 21.2% SYD985
- Rx discontinued due to eye toxicity : 20.8%
- Dose mods due to eye toxicity: 22.9%

Risk mitigation strategy in trial: Pts with prior keratitis excluded, prophylactic lubricating eye drops, regular eye exams by ophthalmologist, ≥grade 3 keratitis stop treatment, grade 3 conjunctivitis delay treatment until grade 2

**ILD/pneumonitis: 7.6%** (N=22/288) SYD985, NR physician's choice

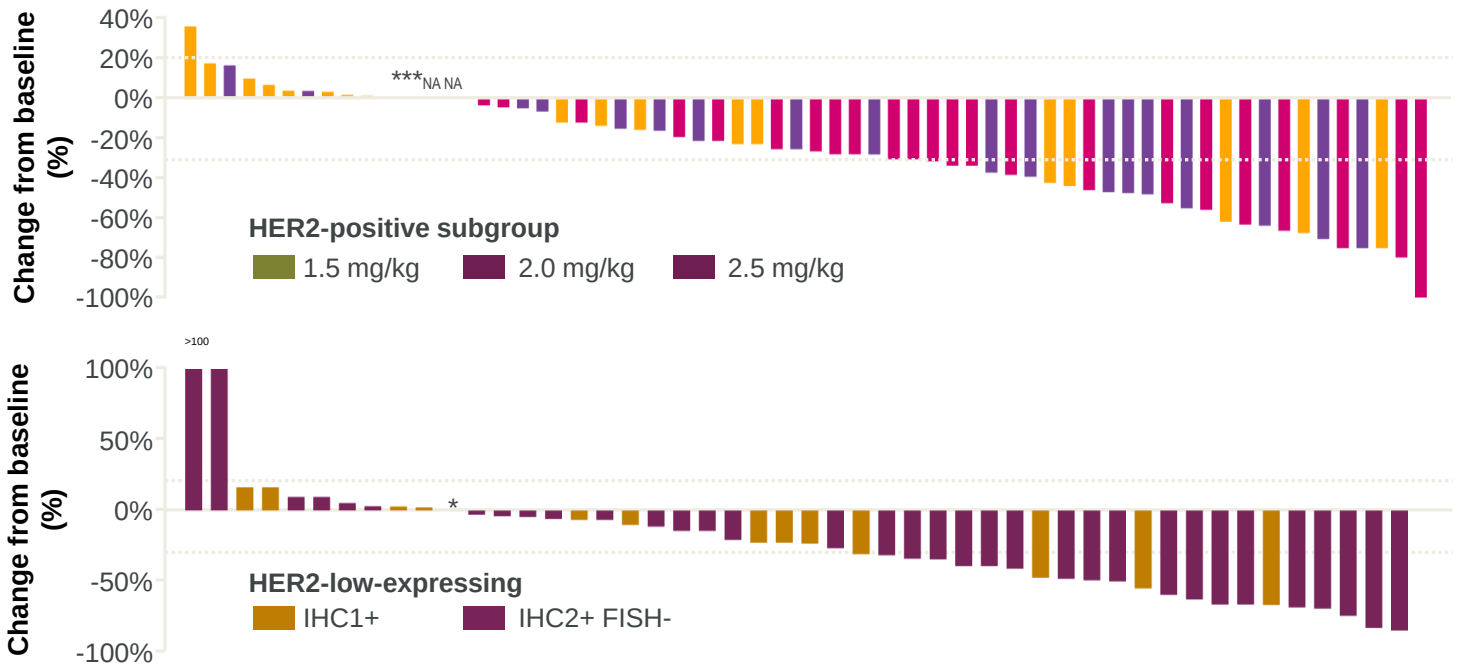
- Grade ≥3: 2.4% SYD985 patients
- Rx discontinued due to ILD/Pneumonitis in 15 (5.2%)
- Dose mods due to ILD/Pneumonitis in 6 (2.1%)
- Fatal: 4 related, 2 unrelated

Risk mitigation strategy in trial: Pts with prior pneumonitis excluded, evaluate CT scans for lung changes, full diagnostic work-up for new or worsening respiratory symptoms, ≥grade 2 pneumonitis stop treatment, grade 1 pneumonitis delay treatment until resolution

# Other Novel ADC: RC48

## Phase Ib: NCT03052634
RC48-ADC

**Best percentage change from baseline of target lesion**




**RC-48**
Antibody: Hertuzumab
Payload: MMAE
DAR: 4

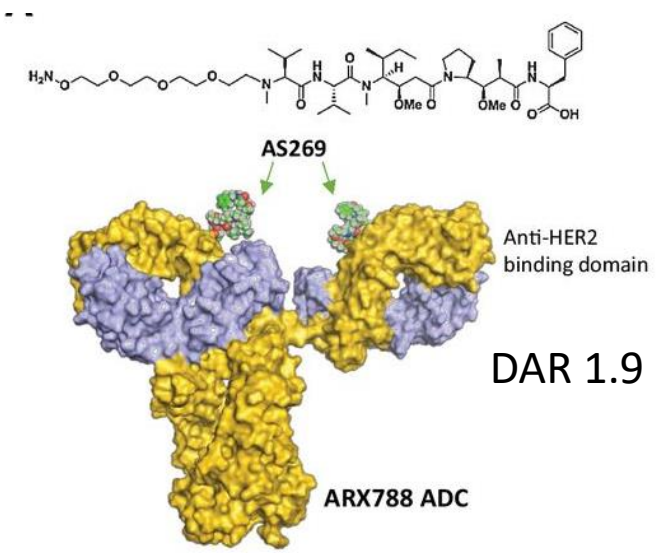
| Clinical activity in 2.0 mg/kg cohorts | HER2-positive BC (2.0 mg/kg) (N=70) | HER2-low BC (2.0 mg/kg) (N=48) |
|---|---|---|
| ORR, n (%) | 23 (32.9) | 19 (39.6) |
| DCR, n (%) | 60 (85.7) | 43 (89.6) |
| mPFS, months (95% CI) | 5.5 (4.6–6.5) | 5.7 (4.1–8.3) |

- *percent change from baseline of target lesion is 0%
- ADC=antibody-drug conjugate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BC=breast cancer; CI=confidence interval; DCR=disease control rate; γ–GT=gamma-glutamyl transferase; HER2=human epidermal growth factor receptor 2; mPFS=median progression-free survival; ORR=objective response rate; T-DM1=trastuzumab emtansine; TRAE=treatment-related adverse event.

**Wang J et al. Presented at ASCO 2021, Chicago US. Abstract #1022**

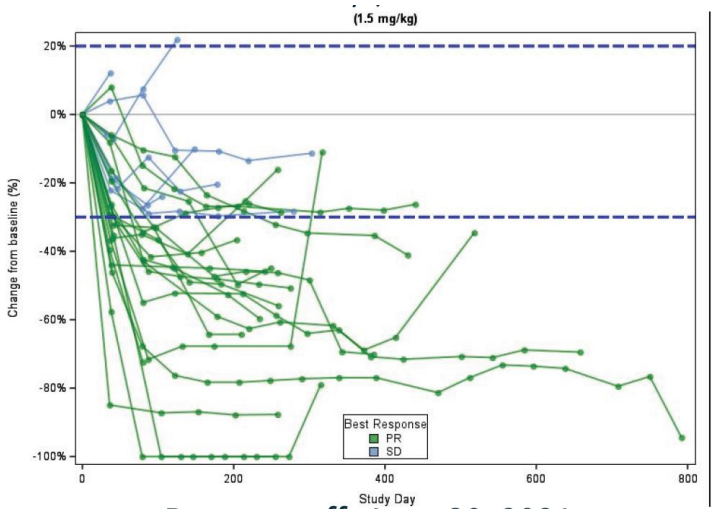
# ARX788

- Site-specific conjugated ADC
  - HER2 targeting mAb and a highly potent tubulin inhibitor payload, AS269
  - Conjugated via the incorporated non-natural AA paraacetylphenylalanine (pAF)
- Heavily pre-treated HER2+ BC
  - ORR 66% in the 1.5 mg/kg cohort (n=29)
  - DCR: 100%
  - Median PFS: 17 months
- Low toxicity: 12-15% rate of ≥grade 3 drug related AEs
  - Ocular toxicity managed by eye drops, dose reduction




DAR 1.9

| Prior anti-HER2 Therapy | Confirmed ORR |
|---|---|
| Trastuzumab containing regimens* | 19/29 (66%) |
| HER2 ADCs (T-DM1, DX126-262, A166, BAT8001, and HS630) regimens** | 4/5 (80%) |
| HER2 TKIs (lapatinib, pyrotinib, neratinib, AST-1306, and Hemay-022) regimens | 15/23 (65%) |
| Both HER2 ADC and HER2 TKI regimens | 3/4 (75%) |
| Bispecific antibodies (KN026 and M802) containing regimens | 3/4 (75%) |



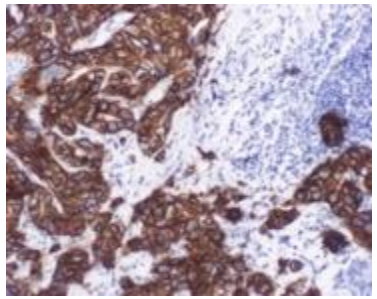

ACE-Breast 03: Phase 2 trial of AR788 in HER2+ MBC tx with prior T-DM1/T-DXd /Tucatinib (NCT04829604)

Hurvitz et al, ASCO 2021; Zhang J et al. SABCS 2021

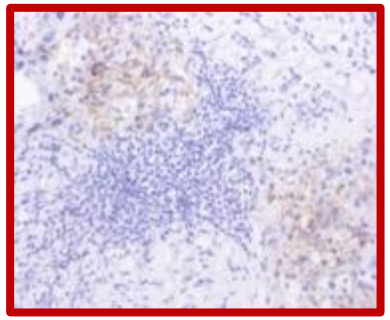
# Prevalence of HER2 Low

**HER2 IHC examples**

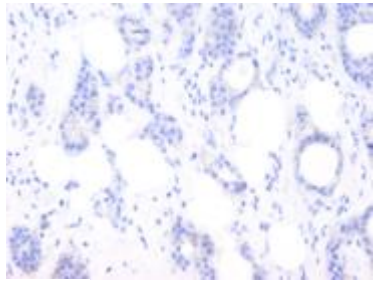
**HER2+**

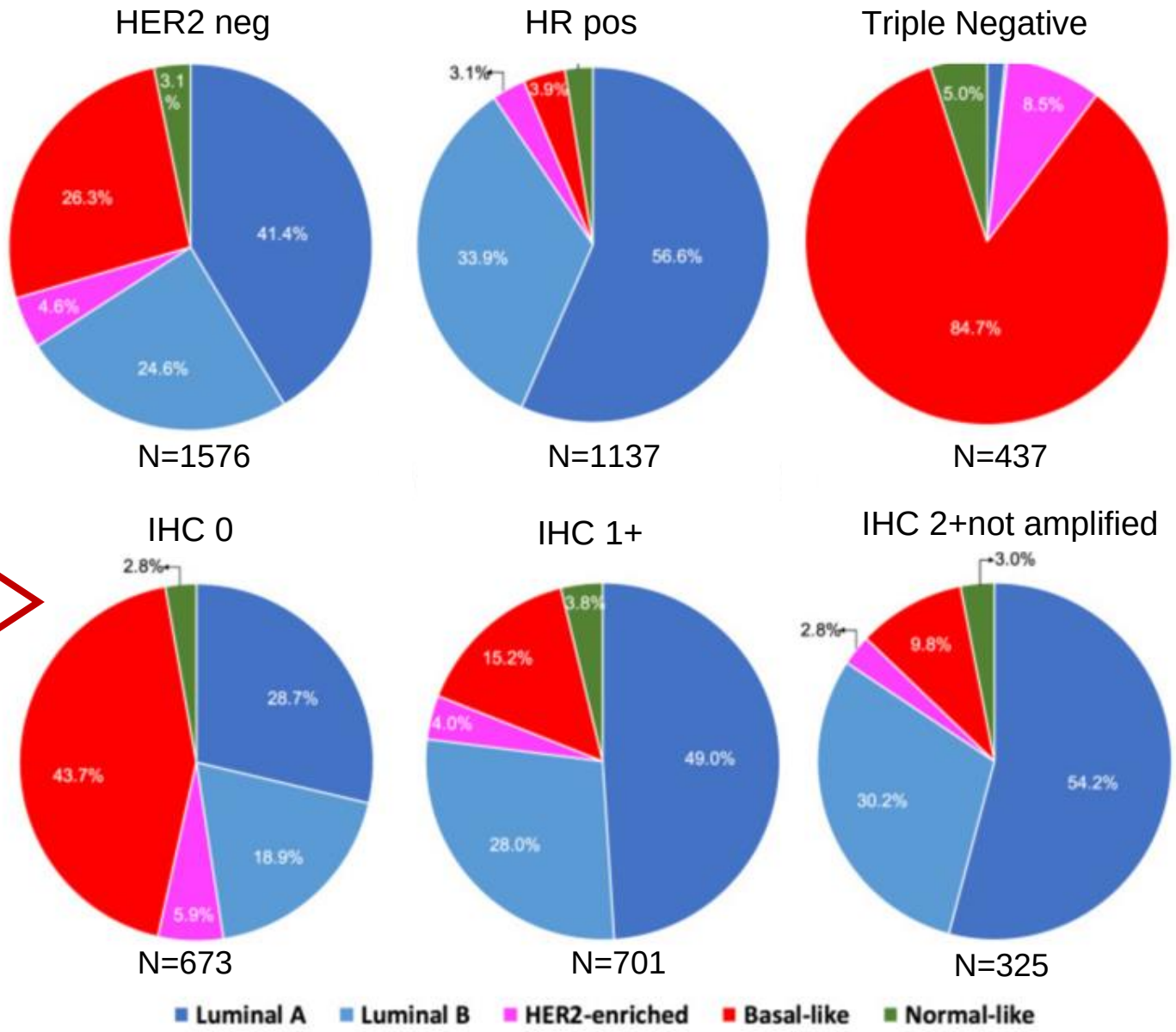


**HER2-low**



**HER2-**

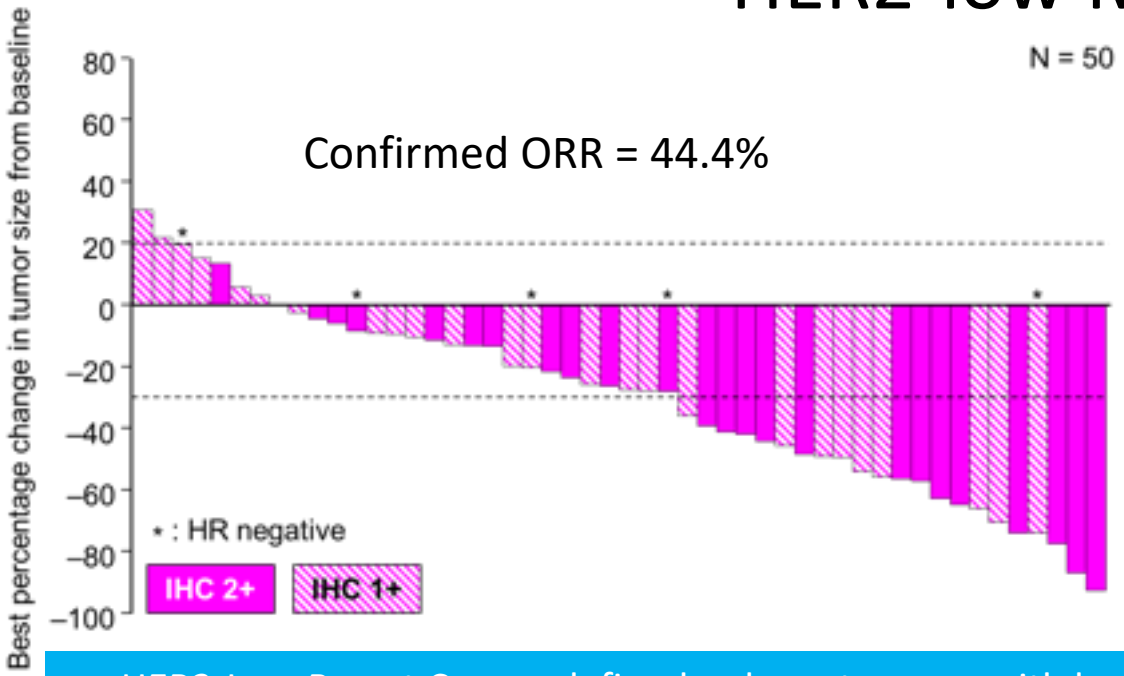


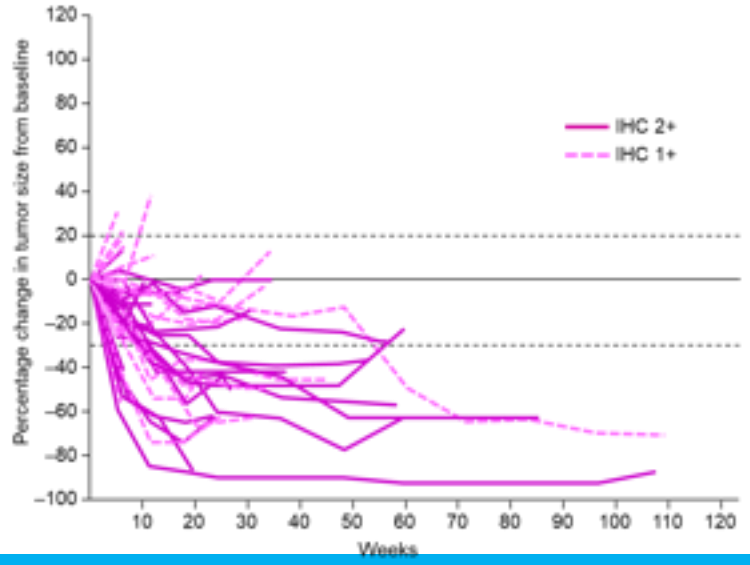



**Proportion of HER2-low higher in HR+ BC (65%) compared to TNBC (37%)**

Schettini et al, NPJ Breast Cancer 2021

# Trastuzumab Deruxtecan Has Clinical Activity in HER2-low MBC




HER2-Low Breast Cancer defined as breast cancer with low levels of HER2 expression (ie, IHC 1+ or 2+/ISH-negative)

| | Confirmed ORR | mDoR | mPFS |
|---|---|---|---|
| All (N = 51) | 44.2% (N=43) | 9.4m | 7.6m |
| IHC 2+ (n = 24) | 54.5% (N=22) | 11.0m | 13.6m |
| IHC 1+ (n = 27) | 33.3% (N=21) | 7.9m | 5.7m |
| HR+ (n = 45) | 47.4% (N=38) | 11.0m | 7.9m |
| Prior CDK4/6 inhibitor (n = 15) | 33.3% (N=12) | NR | 7.1m |

Modi S et al. J Clin Oncol. 2020.

# DAISY Trial

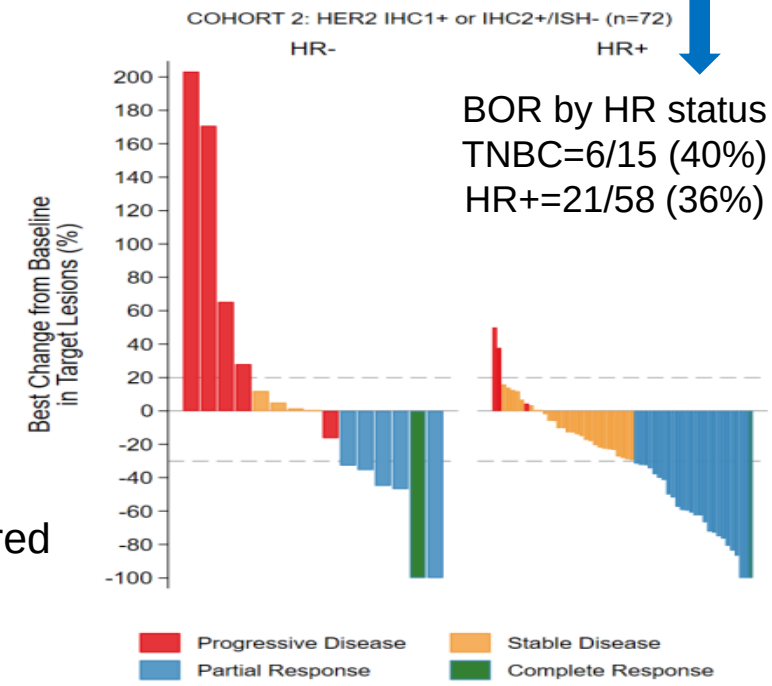
Median follow-up 15.6 mo

| | Total | Cohort 1 (HER2 over-expressing) | Cohort 2 (HER2 low-expressing) | Cohort 3 (HER2 non-detected) |
|---|---|---|---|---|
| **BOR confirmed n/N [95%CI]** | 86 / 177 (48.6%) [41.0; 56.2] | 48 / 68 **(70.6%)** [58.3; 81.0] | 27 / 72 **(37.5%)** [26.4; 49.7] | 11 / 37 **(29.7%)** [15.9; 47.0] |
| **Median DOR (months)** | 8.5 [6.5; 9.8] | 9.7 [6.8; 13] | 7.6 [4.2; 9.2] | 6.8[2.8; NR] |
| **Median PFS (months) [95%CI]** | 7.0 [6.0; 8.7] | **11.1** [8.5; 14.4] HR+=11 TNBC =12.2 | **6.7** [4.4; 8.3] **HR+=6.9 TNBC=3.5** | **4.2** [2.0; 5.7] **HR+=4.5 TNBC=2.1** |

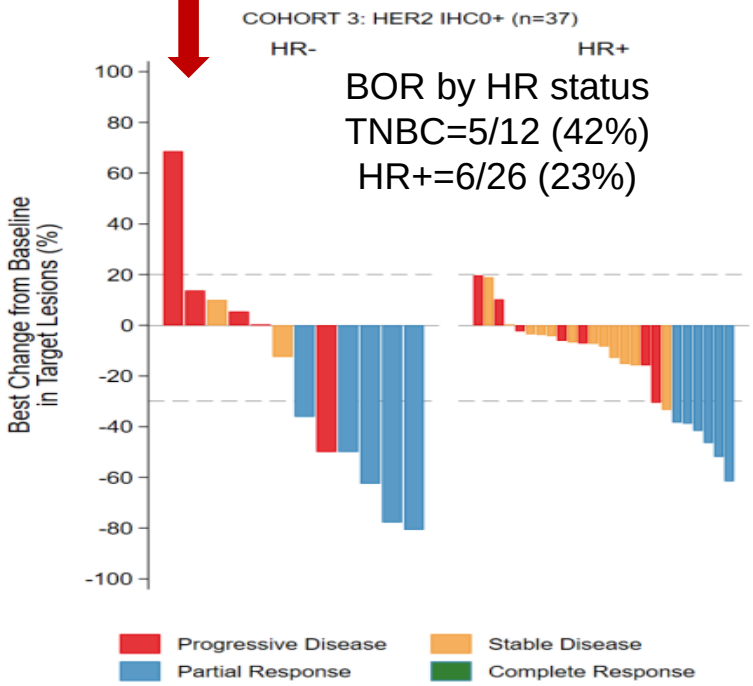
**Cohort 3**
≥13/40 confirmed BOR needed to declare success

## Toxicity

- ILD : 5/179 (2.8%)
  - Grade 1=4, Grade 2=1
- 13 patients discontinued treatment due to treatment-related adverse events
  - 5 for ILD
- No drug-related deaths occurred




BOR by HR status
TNBC=6/15 (40%)
HR+=21/58 (36%)




BOR by HR status
TNBC=5/12 (42%)
HR+=6/26 (23%)

Dieras et al, SABCS 2021

# Ongoing Phase III Trials of ADCs in HER2-low Breast Cancer

***21 FEB 2022: Astra Zeneca Press Release:** Positive high-level results from the pivotal DESTINY-Breast04 Phase III trial showed trastuzumab deruxtecan demonstrated a statistically significant and clinically meaningful improvement in both PFS and OS in pts with HER2-low MBC regardless of hormone receptor (HR) status versus physician's choice of chemotherapy.

## DESTINY-Breast06

Phase 3

Trastuzumab deruxtecan vs TPC

**HR+, HER2-negative or low (IHC >0 <1+ or IHC 1+ or IHC2+/ISH-) advanced or metastatic BC**

- **No prior chemotherapy for metastatic disease**
- **Progression after ≥2 prior lines of endocrine +/- targeted therapy or within 6 months of 1st line endocrine therapy + CDK4/6i**

Randomization stratified by:

- HER2 IHC status
- Prior CDK4/6i
- Prior taxane in non-metastatic setting

1 → **Trastuzumab deruxtecan**
5.4 mg/kg IV Q3W
N=425

1 → **Chemotherapy of physician's choice**:
Capecitabine, paclitaxel, or nab-paclitaxel
N=425

**Primary endpoint:**
**PFS**

**Secondary endpoints:**
**OS, ORR, DOR, QoL**

## RC48-C012

Phase 3

Disitamab vedotin vs TPC

**HER2-low (IHC2+/FISH-) advanced or metastatic BC**

- **1-2 prior lines of chemotherapy**
- **Prior anthracycline therapy**
- **Prior endocrine therapy if HR+**

1 → **Disitamab vedotin**
2 mg/kg IV Q2W
N=183

1 → **Chemotherapy of physician's choice**:
Capecitabine, vinorelbine, paclitaxel, or docetaxel
N=183

**Primary endpoint:**
**PFS**

**Secondary endpoints:**
**OS, ORR, CBR, DOR, TTP**

# BEGONIA study design:
# T-Dxd + Durvalumab for HER2 low TNBC

- Metastatic TNBC
- No prior treatment for stage IV disease
- ECOG PS 0 -1
- RECIST evaluable
- Patients may have relapsed from earlier stage disease but must be ≥ 12 months since prior taxane treatment
- **Arm 6: Locally confirmed HER2 IHC 1-2+ ( ISH-)**

## Part 1

1: Durva + Paclitaxel (n = 20)

2: Durva + Pac + Capivasertib (AKT) (n = 30)

5:Durva + Pac + Oleclumab (CD73) (n = 30)

6: Durva + DS-8201a (T-DXd) (n = 30)

7:Durva + Novel ADC (n=30)

**ORR ≥ 57% (17/30)**

## Part 2 Expansion (TBD)

Durva Combination (n = 27)

Durva Combination (n = 27)

Arms 2-6:
Safety run-in:
6 DLT evaluable patients for 28 days (Arms 2-5) or 21 days (Arms 6 and 7) with ≤ 1 DLT

Part 1:
Primary Endpoint: Safety and tolerability
Secondary Endpoint: ORR, PFS, DoR, OS, PK/ADA

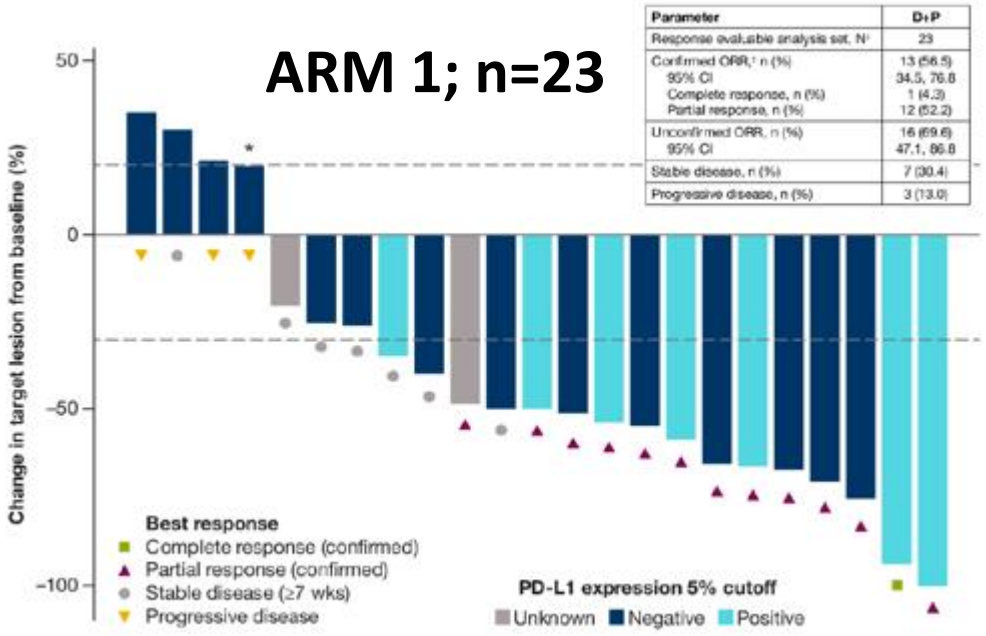
Part 2:
Primary Endpoint: ORR
Secondary Endpoint: Safety and tolerability, PFS, DoR, OS, PFS6m

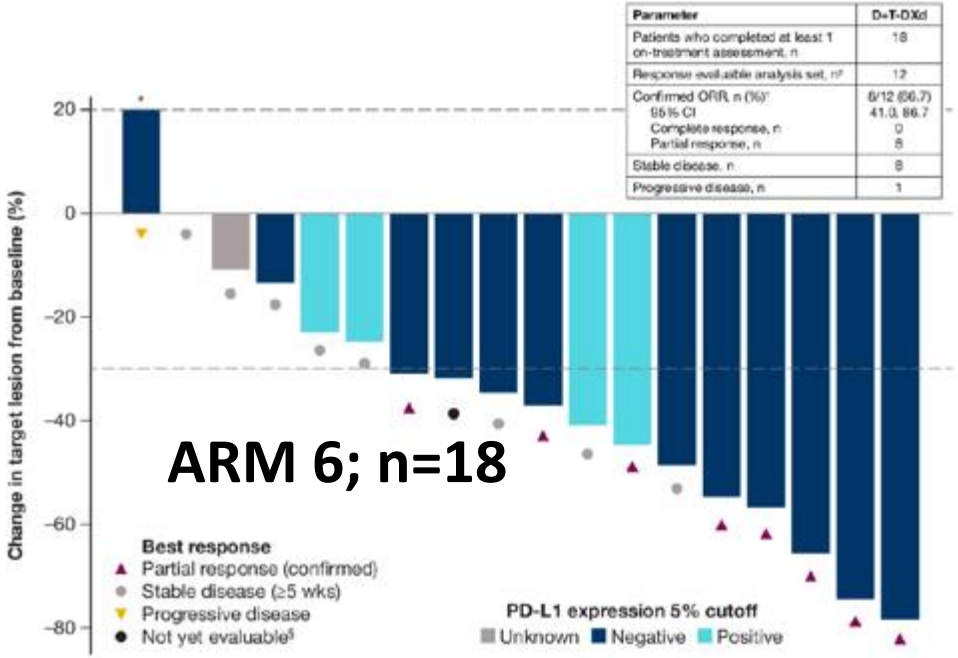
Note:
- Arms 3 (Durva + selumetinib + pac) and Arms 4 (Durva + AZD9150 + pac) were removed before patient enrollment
- Part 1 of this study is considered Stage 1 of the Simon 2-Stage design, and Part 2 of this study is considered Stage 2
- Amendment for a new arm (Arm 7) to include a novel combination of durvalumab + a novel ADC (will include HER2-0 patients)

= Enrollment complete: only Arm 6 is open at this time

# BEGONIA Trial

- First-line therapy for metastatic TNBC
- Basket trial
  - Arm 1: Durvalumab and weekly paclitaxel
  - Arm 6: Durvalumab and T-DXd (also had to be HER2 low)
- PD-L1 testing using SP263
- Safety
  - Arm 6: 2 cases of ILD
    - Grade 2 and 3
    - Both discontinued T-DXd



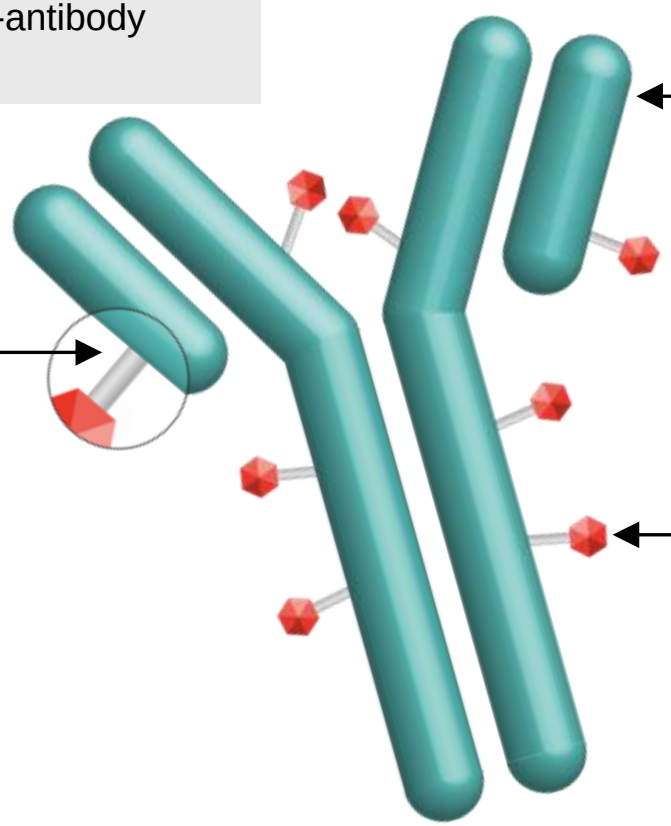




Schmid et al, Abstract 1023 ASCO 2021

# Sacituzumab Govitecan (SG): First-in-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- Distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Accelerated FDA approval for metastatic TNBC in 2020 and fast-track designation in metastatic urothelial cancer[7]

**Linker for SN-38**
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)[6]



**Humanized anti–Trop-2 antibody**
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

**SN-38 payload**
- SN-38 more potent than parent compound, irinotecan

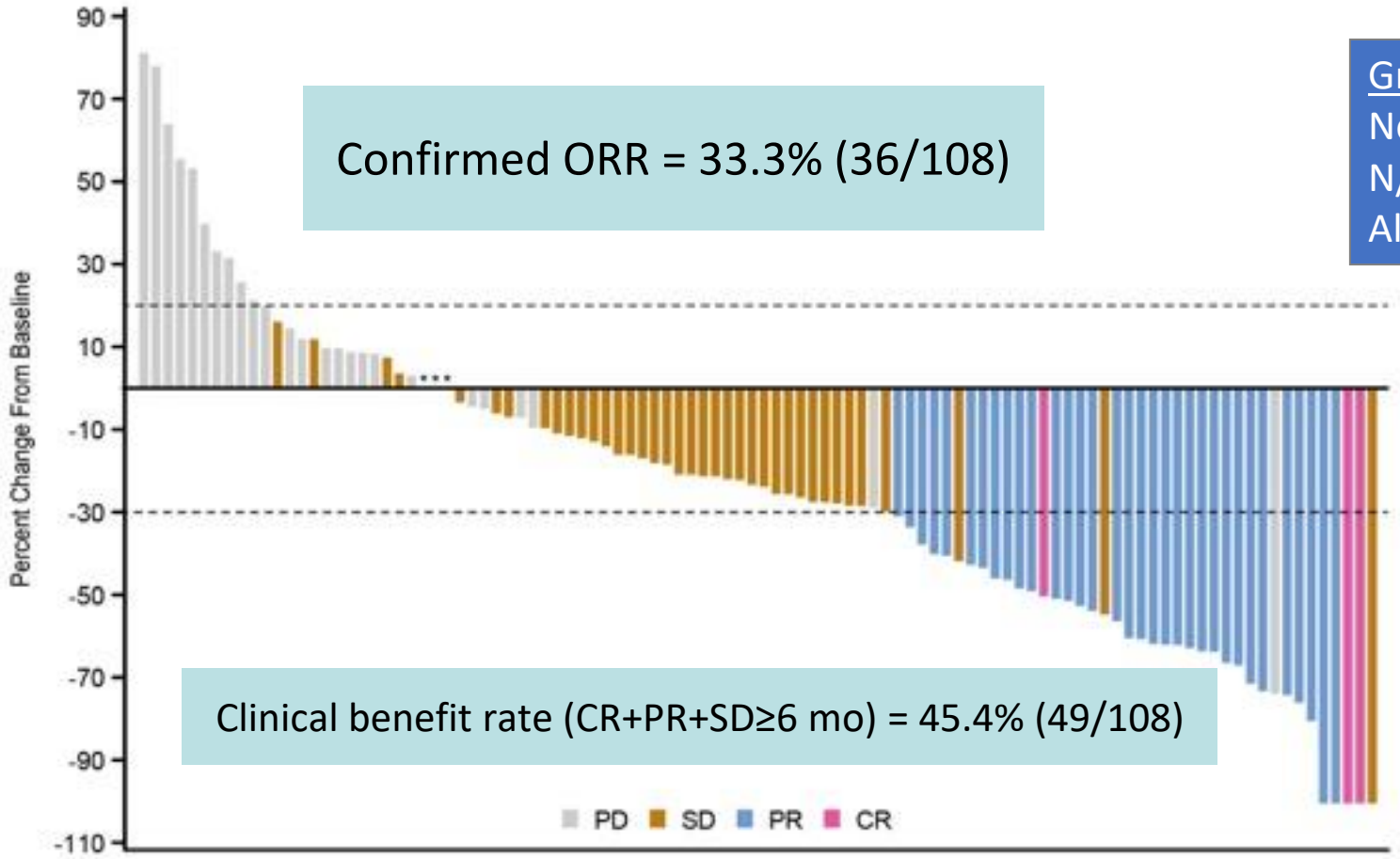
ADC, antibody−drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula N et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem.* 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget.* 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

# Sacituzumab Govitecan: Phase I/II Trial in mTNBC

108 patients with refractory mTNBC

Median of 3 prior lines of therapy (range 2-10) in the advanced setting




Confirmed ORR = 33.3% (36/108)

Clinical benefit rate (CR+PR+SD≥6 mo) = 45.4% (49/108)

Grade 3/4 toxicity:
Neutropenia: 41%; FN 8%
N/V/D: 5/5/8%
Alopecia: 36%

Bardia et al. *NEJM*. 2019.

# ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC

**Metastatic TNBC (per ASCO/CAP)**

≥2 chemotherapies for advanced disease

[no upper limit; 1 of the required prior regimens could be progression occurred within a 12-month period after completion of (neo)adjuvant therapy)]

**N=529**

R 1:1

**Sacituzumab Govitecan (SG)**
**10 mg/kg IV**
**days 1 & 8, every 21-day cycle**
(n=267)

**Treatment of Physician's Choice (TPC)***
(n=262)

**Continue treatment until progression or unacceptable toxicity**

**Endpoints**

**Primary**
- PFS†

**Secondary**
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

**Stratification factors**
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

**Data cutoff:** March 11, 2020

NCT02574455

Demographics:

TPC: 53% eribulin, 20% vinorelbine, 15% gemcitabine, 13% capecitabine; 70% TN at initial diagnosis

Median prior regimens 4 (2-17); ~88% with visceral disease

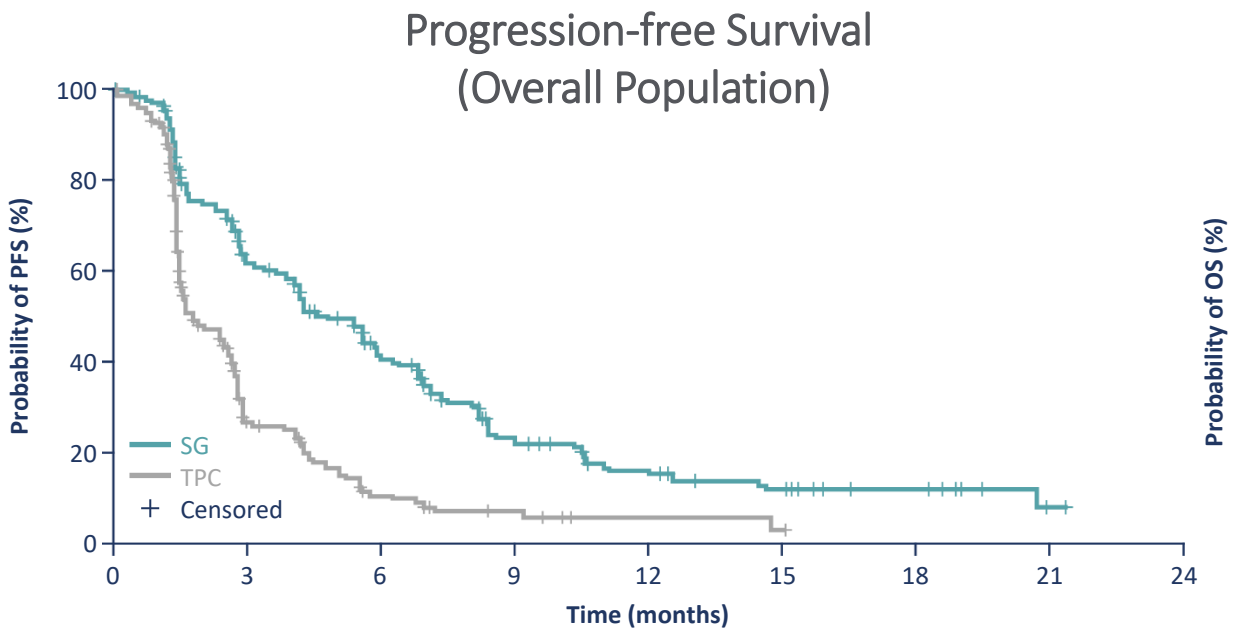
**ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.**

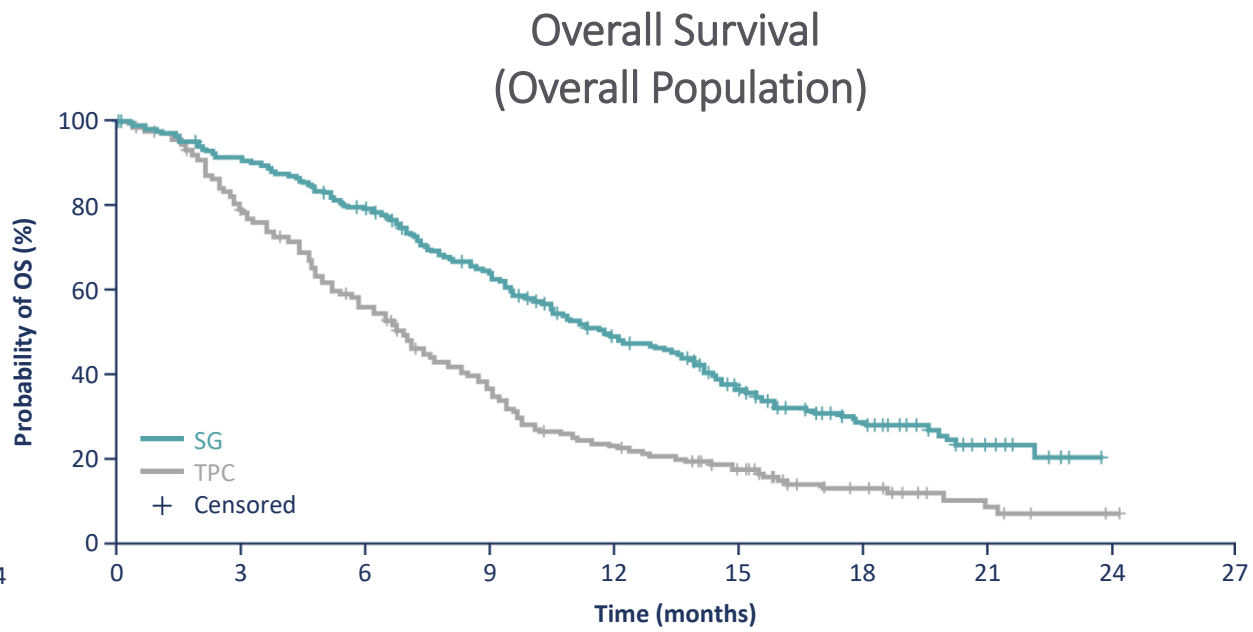
*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Bardia et al, NEJM 2021

# ASCENT: PFS and OS in the ITT Population



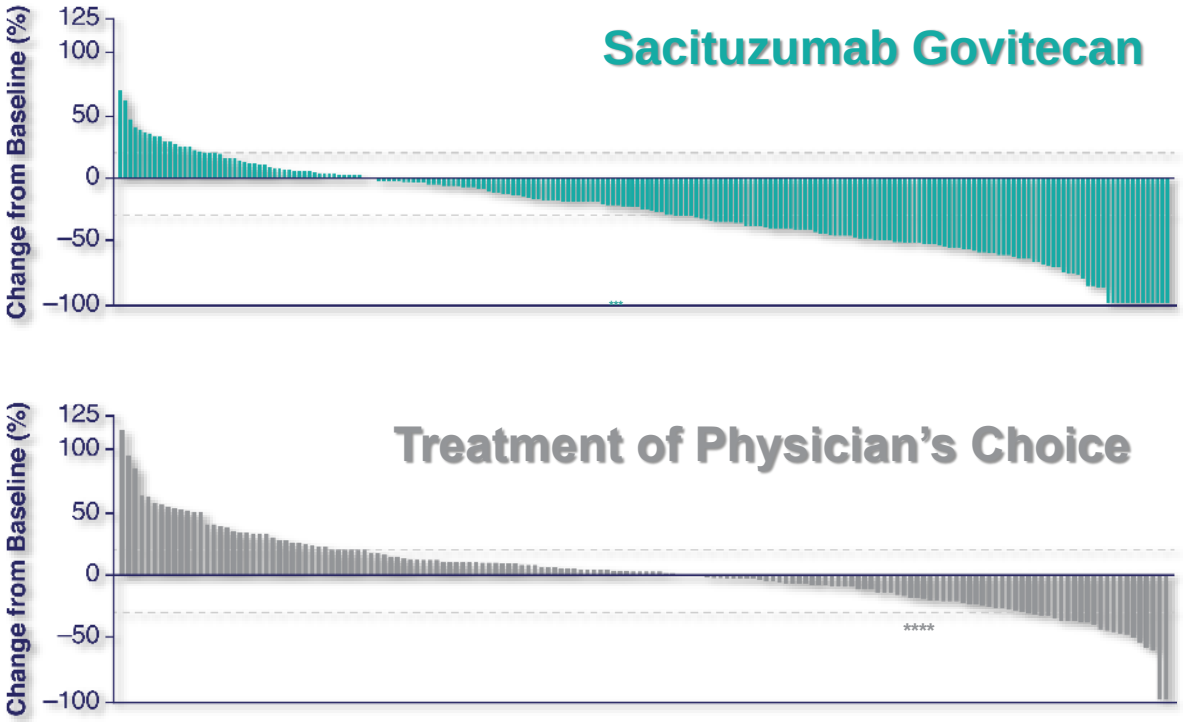

| | SG (n=267) | TPC (n=262) |
|---|---|---|
| **Median PFS, mo** (95% CI) | **4.8** (4.1-5.8) | **1.7** (1.5-2.5) |
| **HR (95% CI), *P* value** | **0.43** (0.35-0.54), ***P*<0.0001** | |

| | SG (n=267) | TPC (n=262) |
|---|---|---|
| **Median OS, mo** (95% CI) | **11.8** (10.5-13.8) | **6.9** (5.9-7.7) |
| **HR (95% CI), *P* value** | **0.51** (0.41-0.62), ***P*<0.0001** | |

HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice. Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541.

**Bardia A, et al. N Engl J Med. 2021**

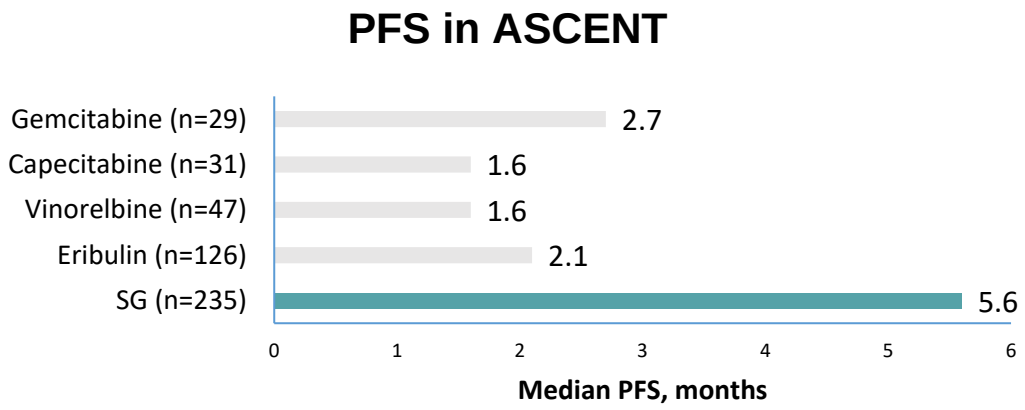
# ASCENT Study: Overall Response Rate

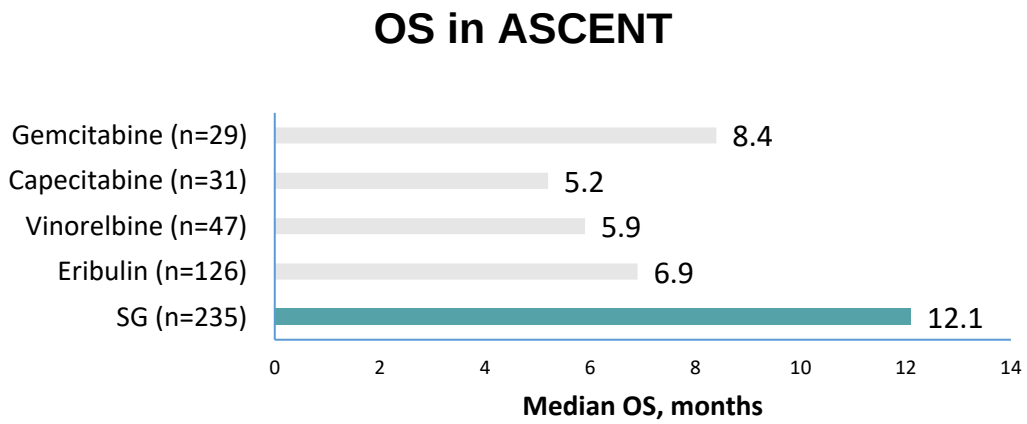



| | Patients without Brain Metastases | |
|---|---|---|
| | SG (N=235) | TPC (N=233) |
| Median PFS (95% CI) — mo | 5.6 (4.3–6.3) | 1.7 (1.5–2.6) |
| HR (95% CI) | 0.41 (0.32–0.52)‡ | |
| Median OS (95% CI) — mo | 12.1 (10.7–14.0) | 6.7 (5.8–7.7) |
| HR (95% CI) | 0.48 (0.38–0.59)‡ | |
| Objective response — n (%)§ | 82 (35) | 11 (5) |
| CR | 10 (4) | 2 (1) |
| PR | 72 (31) | 9 (4) |
| Clinical benefit — n (%)¶ | 105 (45) | 20 (9) |
| SD — n (%) | 81 (34) | 62 (27) |
| SD for ≥6 mo | 23 (10) | 9 (4) |
| PD — n (%) | 54 (23) | 89 (38) |
| Response NE — n (%)‖ | 18 (8) | 71 (30) |
| Median TTR (95% CI) — mo | 1.5 (0.7–10.6) | 1.5 (1.3–4.2) |
| Median DOR (95% CI) — mo | 6.3 (5.5–9.0) | 3.6 (2.8–NE) |
| HR (95% CI) | 0.39 (0.14–1.07) | |

Assessed by independent central review in brain met-neg population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo).
Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541; Bardia et al. ESMO 2020. Abstract LBA17.

# ASCENT: Assessment of SG vs TPC by Agent



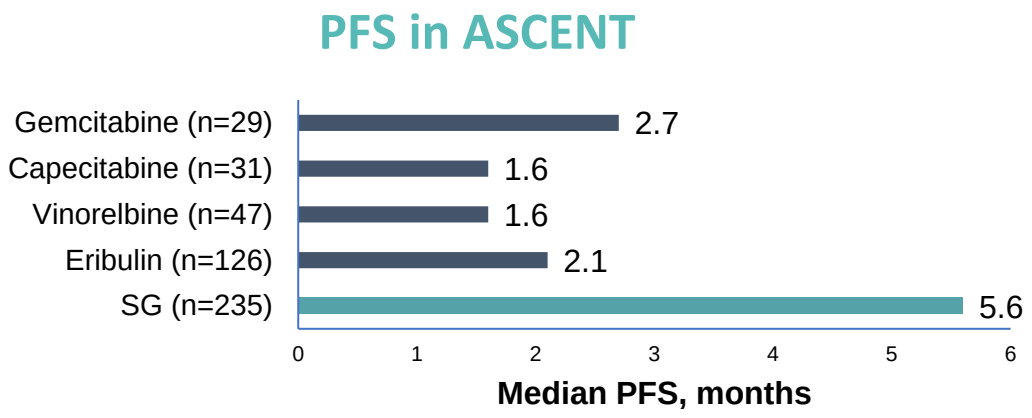

| | Sacituzumab Govitecan (n=235) | TPC (n=233) | | | |
|---|---|---|---|---|---|
| | | Eribulin (n=126) | Vinorelbine (n=47) | Gemcitabine (n=29) | Capecitabine (n=31) |
| **ORR** | **35%** | **5%** | **4%** | **3%** | **6%** |
| **CBR** | **45%** | **8%** | **6%** | **14%** | **10%** |

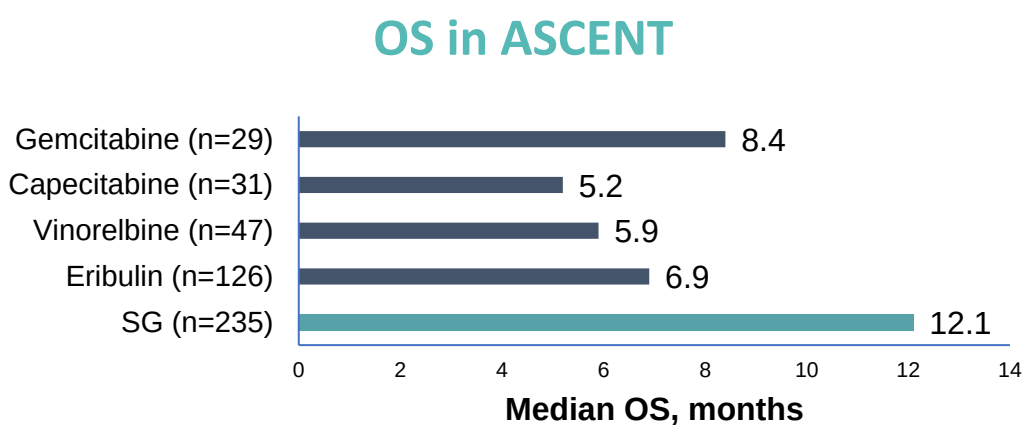
The efficacy benefit observed with SG was retained when evaluating each TPC chemotherapy agent individually

CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

**O'Shaughnessy J, et al. ASCO 2021 (Poster 1077)**

# ASCENT: Assessment of SG vs TPC by Agent




| | Sacituzumab Govitecan (n=235) | TPC (n=233) | | | |
|---|---|---|---|---|---|
| | | Eribulin (n=126) | Vinorelbine (n=47) | Gemcitabine (n=29) | Capecitabine (n=31) |
| **ORR** | **35%** | **5%** | **4%** | **3%** | **6%** |
| **CBR** | **45%** | **8%** | **6%** | **14%** | **10%** |

**The efficacy benefit observed with SG was retained when evaluating each TPC chemotherapy agent individually**

CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

**O'Shaughnessy J, et al. ASCO 2021 (Poster 1077)**

# ASCENT: Exploratory analysis of TROP2 and gBRCA

- Trop-2 expression assessed by IHC
  - H-score <100 (including H-score 0): Trop-2 Low
  - H-score 100-200: Trop-2 Medium
  - H-score 200-300: Trop-2 High
- Clinical benefit with SG versus TPC in previously treated mTNBC is irrespective of level of Trop-2 expression

| | SG (n=235) | TPC (n=233) |
|---|---|---|
| *BRCA1/2* mutational status—no. (%) | 149 (63) | 143 (61) |
| Positive | 16 (7) | 18 (8) |
| Negative | 133 (57) | 125 (54) |
| Trop-2 expression—no. (%) | 151 (64) | 139 (60) |
| (High) H-score 200-300 | 85 (56) | 72 (52) |
| (Medium) H-score 100-200 | 39 (26) | 35 (25) |
| (Low) H-score <100 | 27 (18) | 32 (23) |

| | Trop-2 High \| H-score: 200-300 | | Trop-2 Medium \| H-score: 100-200 | | Trop-2 Low \| H-score: <100 | |
|---|---|---|---|---|---|---|
| | SG (n=85) | TPC (n=72) | SG (n=39) | TPC (n=35) | SG (n=27) | TPC (n=32) |
| **Median PFS—mo (95% CI)** | 6.9 (5.8-7.4) | 2.5 (1.5-2.9) | 5.6 (2.9-8.2) | 2.2 (1.4-4.3) | 2.7 (1.4-5.8) | 1.6 (1.4-2.7) |

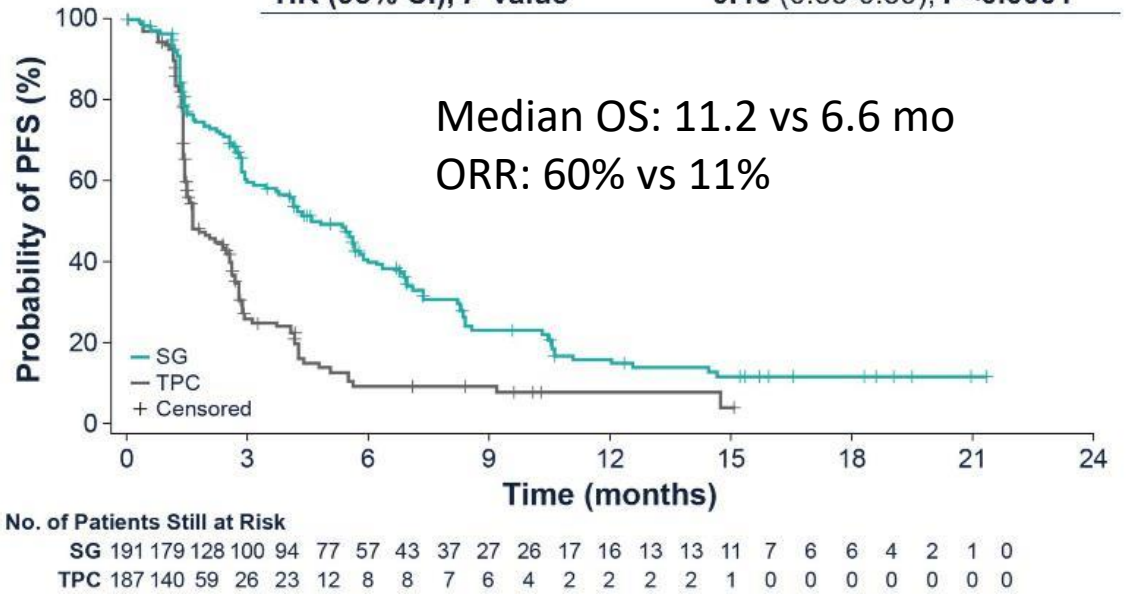
| | Trop-2 High \| H-score: 200-300 | | Trop-2 Medium \| H-score: 100-200 | | Trop-2 Low \| H-score: <100 | |
|---|---|---|---|---|---|---|
| | SG (n=85) | TPC (n=72) | SG (n=39) | TPC (n=35) | SG (n=27) | TPC (n=32) |
| **Median OS—mo (95% CI)** | 14.2 (11.3-17.5) | 6.9 (5.3-8.9) | 14.9 (6.9-NE) | 6.9 (4.6-10.1) | 9.3 (7.5-17.8) | 7.6 (5.0-9.6) |

| | Trop-2 High H-score: 200-300 (n=157) | | Trop-2 Medium H-score: 100-200 (n=74) | | Trop-2 Low H-score: <100 (n=59) | |
|---|---|---|---|---|---|---|
| | SG (n=85) | TPC (n=72) | SG (n=39) | TPC (n=35) | SG (n=27) | TPC (n=32) |
| ORR—% (no.) | 44% (37) | 1% (1) | 38% (15) | 11% (4) | 22% (6) | 6% (2) |
| 95% CI | 33-55 | 0-8 | 23-55 | 3-27 | 9-42 | 1-21 |

Hurvitz et al, SABCS 2020; Bardia et al, Ann Oncol 2021

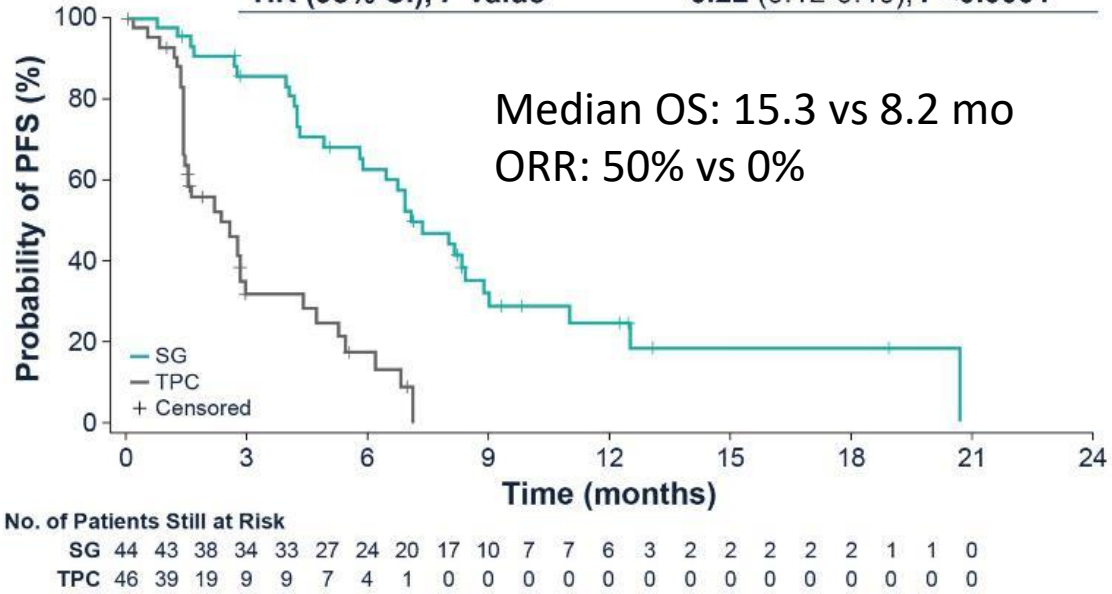
# Phase 3 ASCENT: Outcomes by Age—<65 Versus ≥65 Years

| PFS BICR Analysis | <65 y | |
|---|---|---|
| | SG (n=191) | TPC (n=187) |
| No. of events | 136 | 117 |
| Median PFS—mo (95% CI) | 4.6 (3.7-5.7) | 1.7 (1.5-2.5) |
| HR (95% CI), *P* value | **0.46** (0.35-0.59), ***P*<0.0001** | |




Median OS: 11.2 vs 6.6 mo
ORR: 60% vs 11%

| PFS BICR Analysis | ≥65 y | |
|---|---|---|
| | SG (n=44) | TPC (n=46) |
| No. of events | 30 | 33 |
| Median PFS—mo (95% CI) | 7.1 (5.8-8.9) | 2.4 (1.4-2.9) |
| HR (95% CI), *P* value | **0.22** (0.12-0.40), ***P*<0.0001** | |




Median OS: 15.3 vs 8.2 mo
ORR: 50% vs 0%

- Dose reductions: more frequent in patients ≥ 65 versus < 65 years; similar between SG and TPC treatment arms in all age groups, with no considerable impact on efficacy
- Treatment discontinuation due to TRAE: 2% each for ≥65-year versus < 65-year groups
- No treatment-related deaths
- Rates of AEs were similar for patients aged ≥ 75 years as observed in patients aged ≥ 65 years

Kalinsky K, et al. ASCO 2021. Abstract 1011.

# TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

| | | SG (n=258) | | | TPC (n=224) | | |
|---|---|---|---|---|---|---|---|
| | TRAE* | All grade % | Grade 3, % | Grade 4, % | All grade, % | Grade 3, % | Grade 4, % |
| Haematologic | **Neutropenia†** | **63** | **46** | **17** | **43** | **27** | **13** |
| | **Anemia‡** | **34** | **8** | **0** | **24** | **5** | **0** |
| | Leukopenia§ | 16 | 10 | 1 | 11 | 5 | 1 |
| | Febrile neutropenia | 6 | 5 | 1 | 2 | 2 | <1 |
| Gastrointestinal | **Diarrhoea** | **59** | **10** | **0** | 12 | <1 | 0 |
| | **Nausea** | **57** | **2** | **<1** | **26** | **<1** | **0** |
| | Vomiting | 29 | 1 | <1 | 10 | <1 | 0 |
| Other | **Fatigue** | **45** | **3** | **0** | **30** | **5** | **0** |
| | **Alopecia** | **46** | **0** | **0** | **16** | **0** | **0** |

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhoea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
  - **G-CSF usage was 49% in the SG arm vs 23% in the TPC arm**
  - **Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)**
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG
- No treatment-related deaths with SG; 1 treatment-related death (neutropenic sepsis) with TPC
- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%
- Patients received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months (range, 0.03-22.9)

*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‡Combined preferred terms of 'anemia' and 'decreased hemoglobin'. §Combined preferred terms of 'leukopenia' and 'decreased white blood cell count'.

G-CSF, granulocyte-colony stimulating factor; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE.

1. Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541.



Bardia A, et al. ESMO 2020. Oral LBA17.

# ASCENT
# Exploratory Safety Analyses By UGT1A1 Allele Status

| | | SG (n=250)[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | *1/*1 Wild-Type (n=113) | | *1/*28 Heterozygous (n=96) | | *28/*28 Homozygous (n=34) | |
| | TRAE[b] | All Grade, % | Grade ≥3, % | All Grade, % | Grade ≥3, % | All Grade, % | Grade ≥3, % |
| Haematologic | Neutropenia[c] | 76 (67) | 60 (53) | 55 (57) | 45 (47) | 24 (71) | 20 (59) |
| | **Anemia[d]** | **37 (33)** | **5 (4)** | **29 (30)** | **6 (6)** | **16 (47)** | **5 (15)** |
| | Leukopenia[e] | 18 (16) | 10 (9) | 13 (14) | 9 (9) | 8 (24) | 5 (15) |
| | Lymphopenia[f] | 10 (9) | 1 (1) | 5 (5) | 1 (1) | 4 (12) | 2 (6) |
| | **Febrile neutropenia** | **3 (3)** | **3 (3)** | **5 (5)** | **5 (5)** | **6 (18)** | **6 (18)** |
| | Thrombocytopenia[f] | 3 (3) | 0 | 6 (6) | 0 | 4 (12) | 4 (12) |
| Gastrointestinal | Diarrhoea | 65 (58) | 11 (10) | 57 (59) | 9 (9) | 21 (62) | 5 (15) |

***UGT1A1* *28/*28 had higher rates of:**

**Grade ≥3 treatment-related AESIs (*28/*28 vs *1/*1 vs *1/*28)**
- Anemia: 15% vs 4% vs 6%
- Febrile neutropenia: 18% vs 3% vs 6%
- Diarrhoea: 15% vs 10% vs 9%

**Treatment Discontinuations (*28/*28 vs *1/*1 vs *1/*28)**
- 6% vs 2% vs 1%

**Conclusions:** Individuals with *UGT1A1* *28/*28 genotype were at modestly higher risk for anemia and febrile neutropenia with SG and should be monitored closely. These data suggest that *UGT1A1* status does not alter recommendations for treatment or management. Note: The frequency of *28/*28 mutation was low, so this limited the ability to discern additional differences.

Assessed in the safety population of patients with *UGT1A1* genotype. Shown are key TRAEs significantly impacted by the *UGT1A1* *28/*28 genotype. Other TRAEs like nausea, vomiting, constipation, fatigue, alopecia, and decrease appetite were not significantly impacted. [a]Seven patients had *UGT1A1* genotypes not listed in the table. [b]Patients may report more than 1 event per preferred term. Adverse events were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. [c]Combined preferred terms of "Neutropenia" and "Decreased neutrophil count." [d]Combined preferred terms of "Anemia" and "Decreased hemoglobin." [e]Combined preferred terms of "Leukopenia" and "Decreased white blood cell count." [f]Combined preferred terms of "Lymphopenia" and "Decreased lymphocyte count." [f]Combined preferred terms of "Thrombocytopenia" and "Decreased platelet count."
SG, sacituzumab govitecan; TRAE, treatment-related adverse event; UGT1A1, UDP glucuronosyltransferase family 1 member A1.



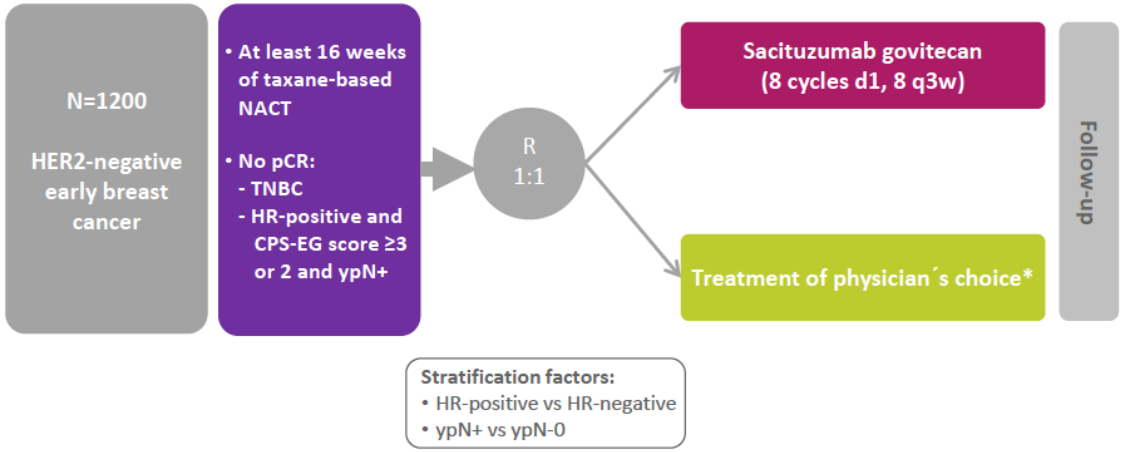
Rugo H, et al. Poster. SABCS [virtual meeting]. 2020 (abstr PS11-09); submitted

# Sacituzumab in ER+ MBC

3/7/22 Press release: results from the Phase 3 TROPiCS-02 study evaluating sacituzumab govitecan-hziy in patients with HR+/HER2- MBC who received prior endocrine therapy, CDK4/6 inhibitors and 2 to 4 lines of chemotherapy. **The study met its primary endpoint with a statistically significant improvement in PFS** vs physician's choice of chemotherapy. The trial targeted a 30% reduction in the risk of disease progression or death. The 1st interim analysis of the key secondary endpoint of OS in the TROPiCS-02 study demonstrated a trend in improvement for OS. Patients will be followed for a subsequent OS analysis. Safety for sacituzumab govitecan was consistent with prior studies, with no new safety concerns.

# GBG: SASCIA Post-Neoadjuvant Trial

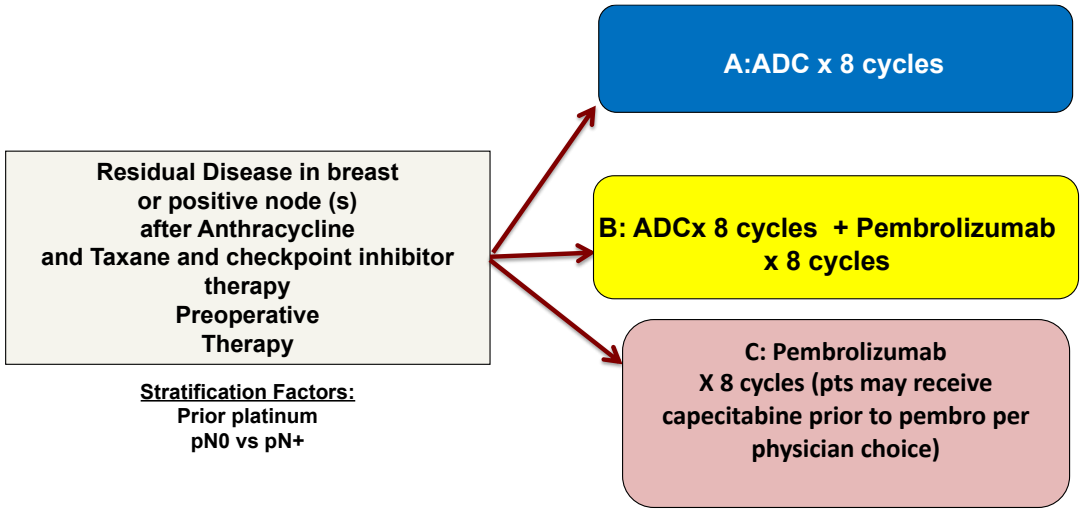
NCT04595565




*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation.
Background therapy: in patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

**Challenge combining ER+ and TNBC pts**

# Potential Future Trial




Courtesy of Sara Tolaney; Alliance for Clinical Trials in Oncology

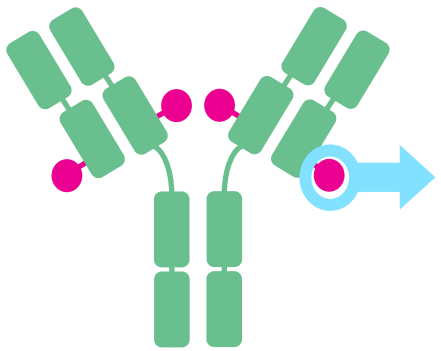
ASPRIA Trial: +ctDNA post NAC/RT with RD
Treat with Sacituzumab and atezolizumab (n=40)
Primary endpoint: clearance of ctDNA
PIs: Mittendorf, DeMichele
SU2C funded consortium

# Datopotamab Deruxtecan (Dato-DXd)

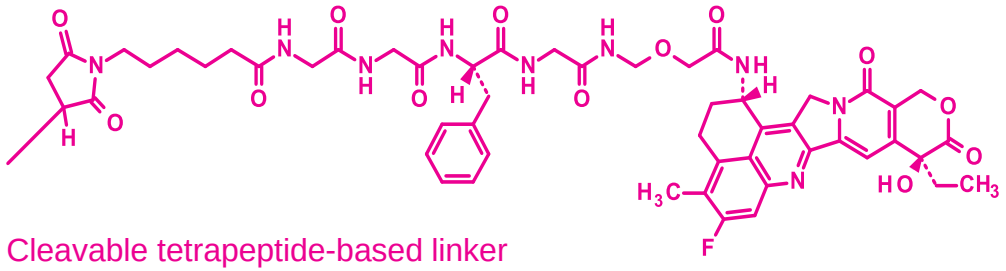
## Dato-DXd is an ADC with 3 components[1,2]:

- A humanized anti-TROP2 IgG1[3] monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker

**Humanized anti-TROP2 IgG1 mAb**



Deruxtecan[a,4]



Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)

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

[a] Image is for illustrative purposes only; actual drug positions may vary. [b] The clinical relevance of these features is under investigation. [c] Based on animal data.

1. Okajima D, et al. AACR-NCI-EORTC 2019; [abstract C026]; 2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173-185; 3. Daiichi Sankyo Co. Ltd. DS-1062. Daiichi Sankyo.com. Accessed October 6, 2020. https://www.daiichisankyo.com/media_investors/investor_relations/ir_calendar/files/005438/DS-1062%20Seminar%20Slides_EN.pdf; 4. Krop I, et al. SABCS 2019; [abstract GS1-03]; 5. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

Krop et al, SABCS 2021

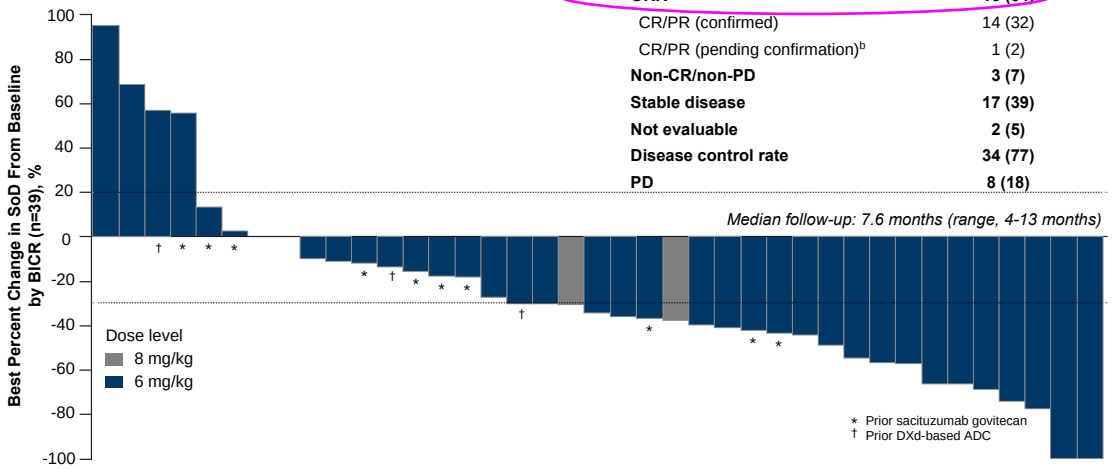
# TROPION-PanTumor01 Dato-DXd TNBC Cohort: Results

- Two breast cancer cohorts; HR+ and TNBC. TNBC presented at SABCS
- 13/44 (30%) with prior Trop-1 inhibitor-based ADC treatment

## Antitumor Responses by BICR

*All patients with TNBC*

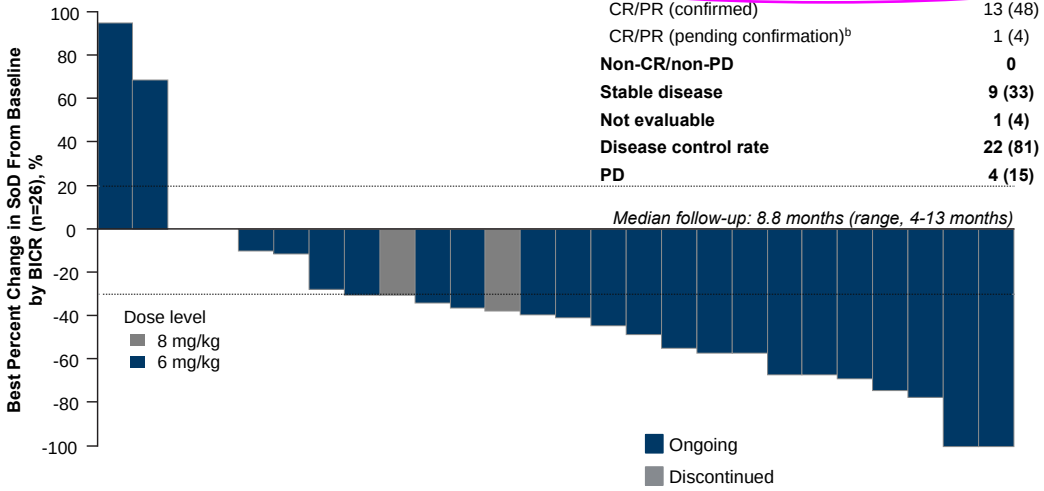
| Patients, n (%)[a] | All Patients (n=44) |
|---|---|
| **ORR** | **15 (34)** |
| CR/PR (confirmed) | 14 (32) |
| CR/PR (pending confirmation)[b] | 1 (2) |
| **Non-CR/non-PD** | **3 (7)** |
| **Stable disease** | **17 (39)** |
| **Not evaluable** | **2 (5)** |
| **Disease control rate** | **34 (77)** |
| **PD** | **8 (18)** |

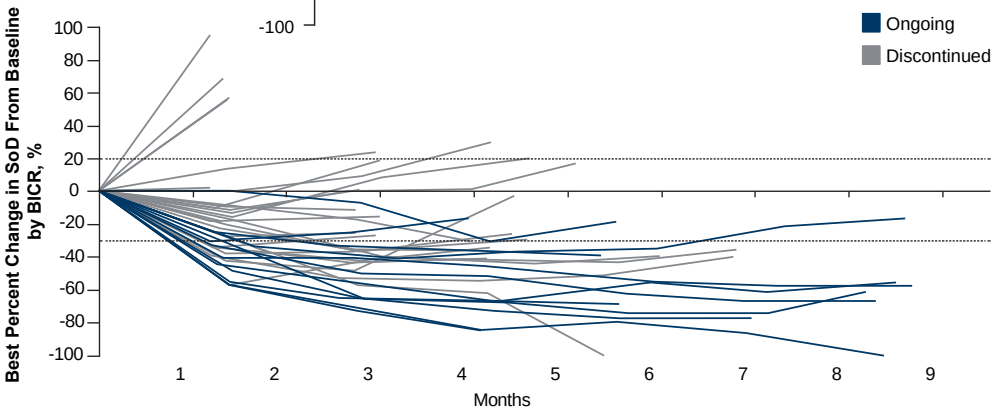



## Antitumor Responses by BICR

*Patients with TNBC without prior Topo I inhibitor-based ADC*

| Patients, n (%)[a] | SG/DXd Naïve Patients with Measurable Disease at BL (n=27) |
|---|---|
| **ORR** | **14 (52)** |
| CR/PR (confirmed) | 13 (48) |
| CR/PR (pending confirmation)[b] | 1 (4) |
| **Non-CR/non-PD** | **0** |
| **Stable disease** | **9 (33)** |
| **Not evaluable** | **1 (4)** |
| **Disease control rate** | **22 (81)** |
| **PD** | **4 (15)** |



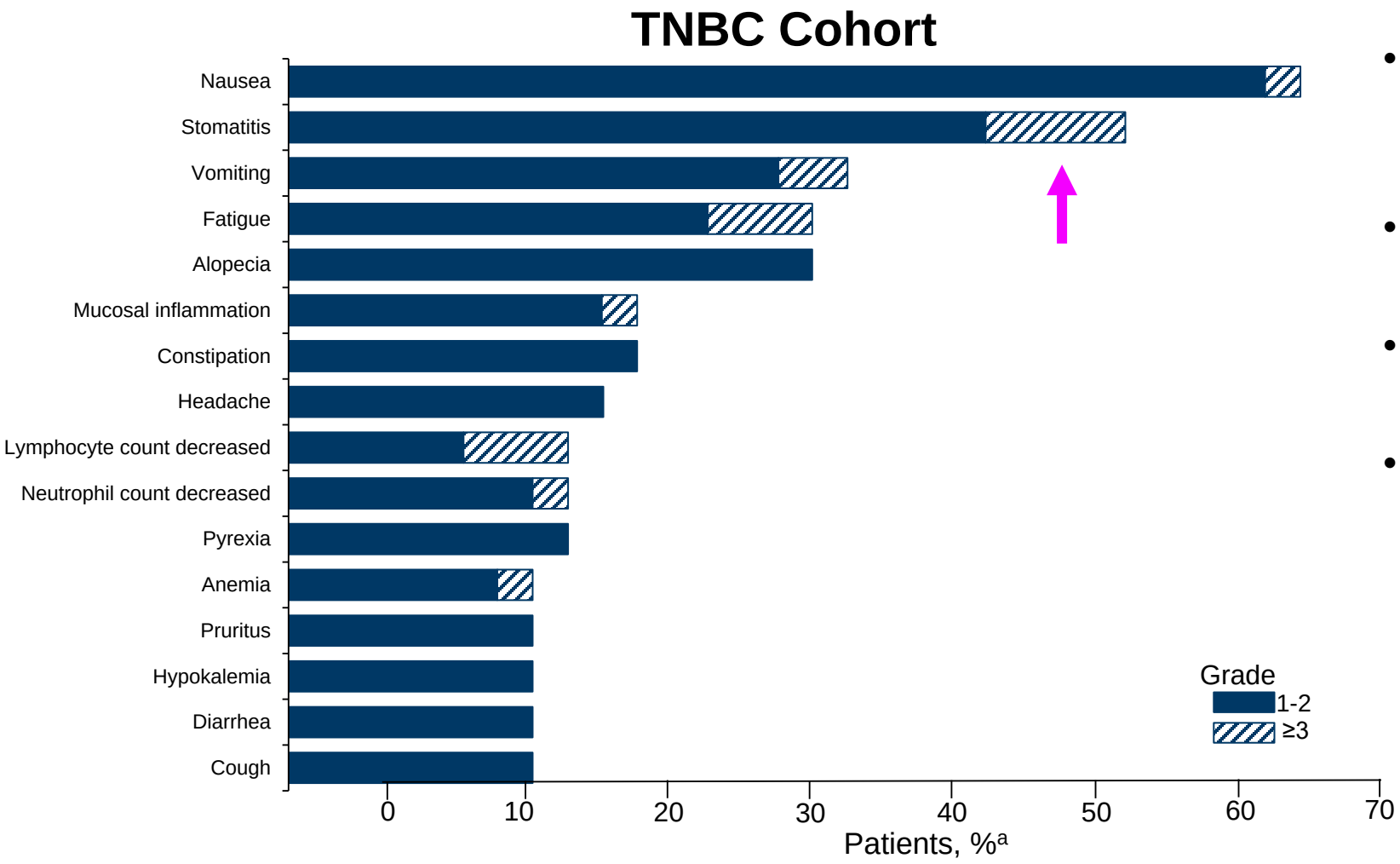

<u>Duration of disease control</u>

Median DOR not reached (range, 2.7-7.4+ mos)

Majority of responses ongoing at the data cutoff

Krop et al, SABCS 2021

# Treatment-Emergent Adverse Events in ≥ 15% of Patients

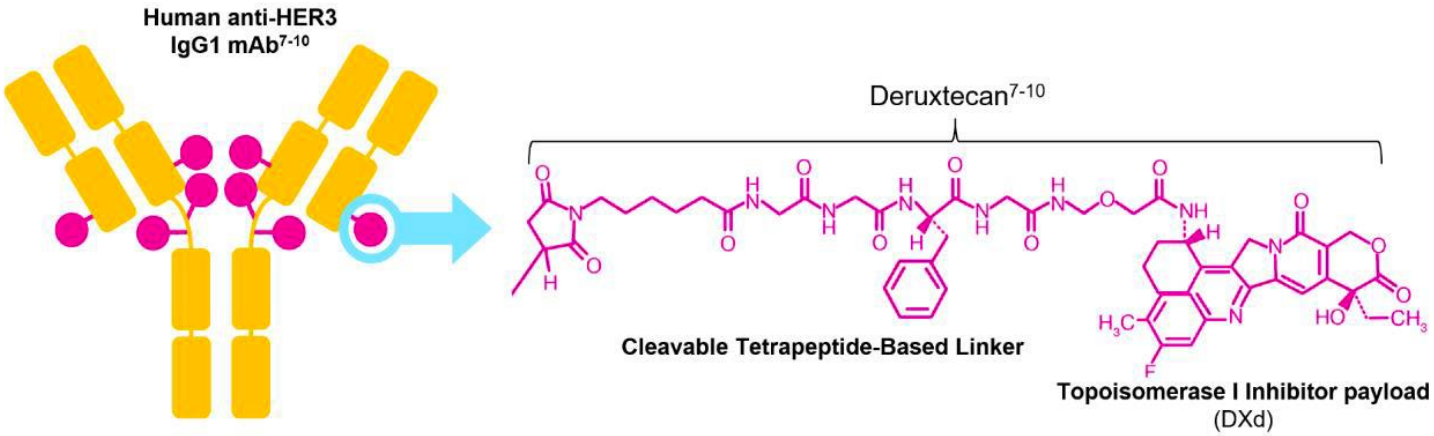



ILD, interstitial lung disease.
[a] n=44 patients.

Data cutoff: July 30, 2021

- Most common adverse events observed were nausea and stomatitis (predominantly grade 1-2)
- Low frequency of hematologic toxicity and diarrhea
- No cases adjudicated as drug-related ILD
- Next steps
  - Phase 3 trial in TNBC is planned
  - BEGONIA, an ongoing trial in TNBC evaluating efficacy and safety of Dato-DXd plus durvalumab
  - The HR+ cohort is fully accrued, data is expected this year
  - TROPION-Breast01, a phase 3 trial in HR+/HER2- BC, has been initiated (NCT05104866)

# U3-1402: Novel Anti-HER3 ADC in HER3+ MBC




HER3-expression found in multiple tumor types

- Breast, melanoma, ovarian, bladder, prostate cancer, NSCLC, etc.

| Patient Cohorts | HER3-DXd Dose |
|---|---|
| HER3-high, HR+/HER2− MBC (N≈60) • Prior chemotherapy regimens: ≥2 to ≤6[b] | 4.8 mg/kg IV Q3W |
| | 6.4 mg/kg IV Q3W |
| HER3-low, HR+/HER2− MBC (N≈20) • Prior chemotherapy regimens: ≥2 to ≤6[b] | 6.4 mg/kg IV Q3W |
| HER3-high TNBC (N≈30) • Prior chemotherapy regimens: 1 to 2[c] | 6.4 mg/kg IV Q3W |

Median prior cytotoxic regimens: 3-4 (2-6)
For TNBC: 1 (0-2)

Response evaluated by BICR

| | HER3-high, HR+/HER2− MBC | | HER3 low, HR+/HER2− MBC 6.4 mg/kg (n=21) | HER3-high TNBC 6.4 mg/kg (n=31) |
|---|---|---|---|---|
| | 4.8 mg/kg (n=33) | 6.4 mg/kg (n=31) | | |
| Follow-up, median (range), months | 16.8 (8.4-23.5) | 20.4 (8.1-26.5) | 18.7 (11.0-25.7) | 7.4 (3.2-14.5) |
| Confirmed ORR (95% CI) | 30.3% (15.6-48.7) | 12.9% (3.6-29.8) | 33.3% (14.6-57.0) | 16.1% (5.5-33.7) |
| PR | 30.3% | 12.9% | 33.3% | 16.1% |
| SD | 60.6% | 61.3% | 33.3% | 67.7% |
| PD | 6.1% | 22.6% | 14.3% | 9.7% |
| NE | 3.0% | 3.2% | 19.0% | 6.5% |
| DCR (95% CI) | 90.9% (75.7-98.1) | 74.2% (55.4-88.1) | 66.7% (43.0-85.4) | 83.9% (66.3-94.5) |
| Median DOR (95% CI), months | 5.0 (2.8-NE) | 7.2 (5.5-7.2) | 5.3 (3.0-NE) | Not reached (4.2-NE) |
| Median PFS (95% CI), months | 8.4 (5.6-9.9) | 2.8 (1.9-8.2) | 5.8 (1.4-11.0) | 5.5 (3.9-NE) |
| Median OS (95% CI), months | 14.3 (10.9-NE) | 9.7 (6.6-19.5) | 9.2 (4.7-21.9) | Not reached (6.4-NE) |

Toxicity (grade >3)

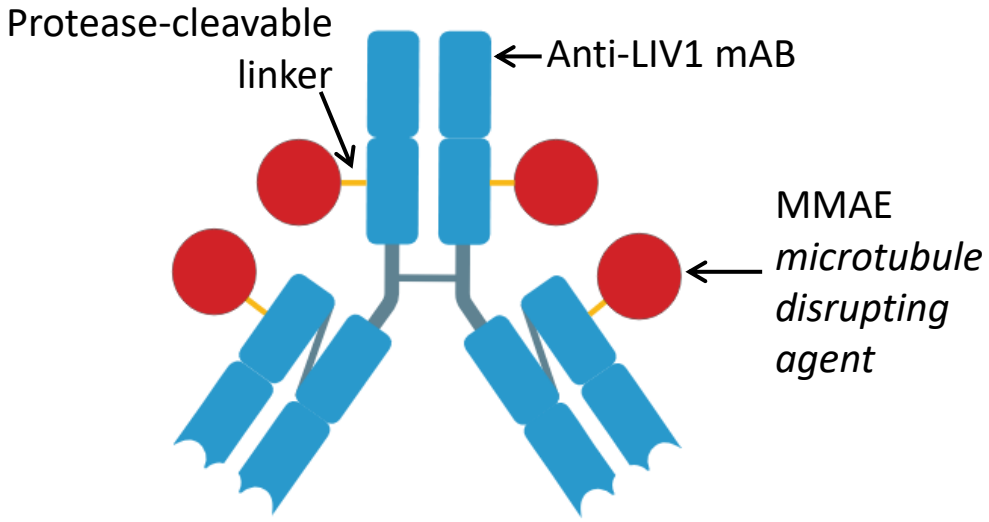
- Platelet decrease: 33%
- Neutrophil decrease: 42%
- ALT/AST increase: ~4%
- Nausea: ~4%

ILD

- 5.2% all grade
- 1.7% ≥grade 3
- 1 ILD related death

Krop et al, SABCS 2020; Yonemori et al, ESMO Breast Cancer 2019; Hashimoto et al, CCR 2019

# Ladiratuzumab Vedotin: ADC Targeting LIV1



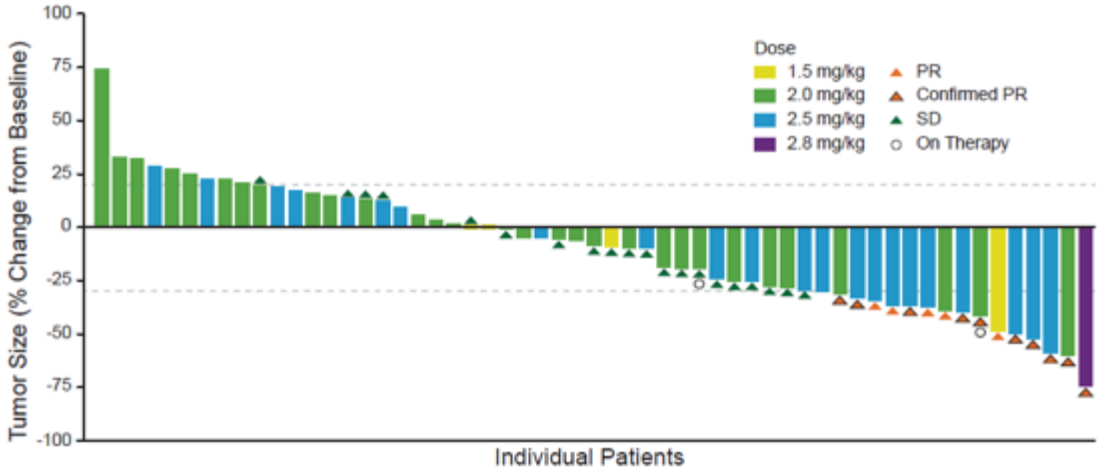

LIV1 is a transmembrane cell adhesion molecule highly expressed in metastatic breast cancer

<u>Mech. of Action:</u>

1. Binds to antigen
2. Complex internalized and trafficked to lysosome
3. Release of MMAE payload
4. Microtubule disruption
5. Cell cycle arrest/disruption

**Phase I Study of Ladiratuzumab Vedotin**

Confirmed ORR = 25% (15/60)

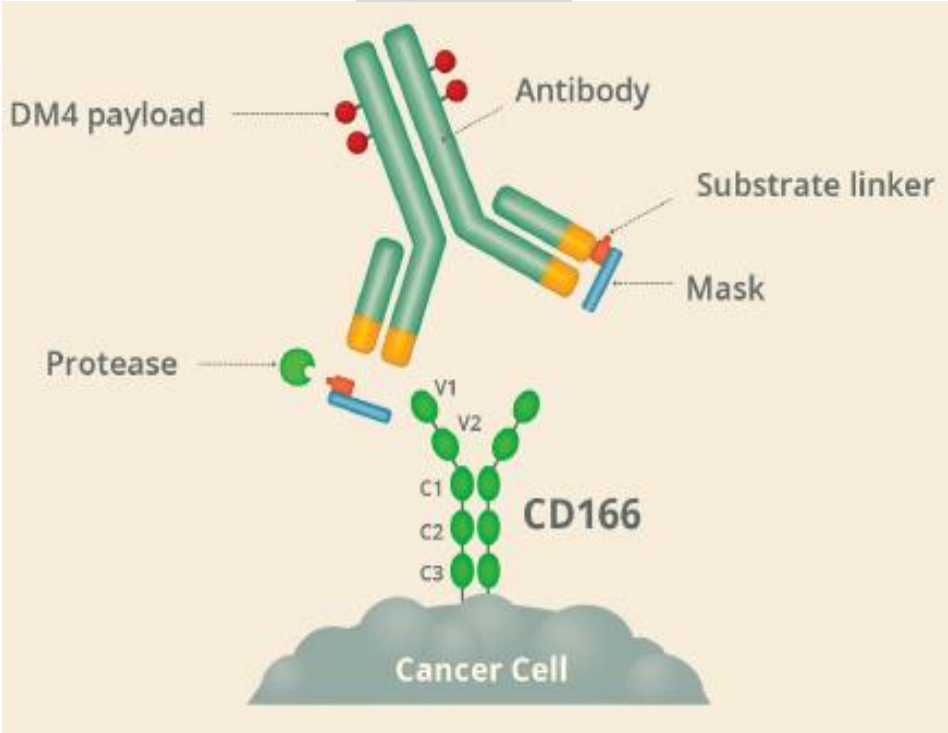



Next steps:
Weekly therapy to reduce toxicity

Modi S, et al. SABCS. 2017.

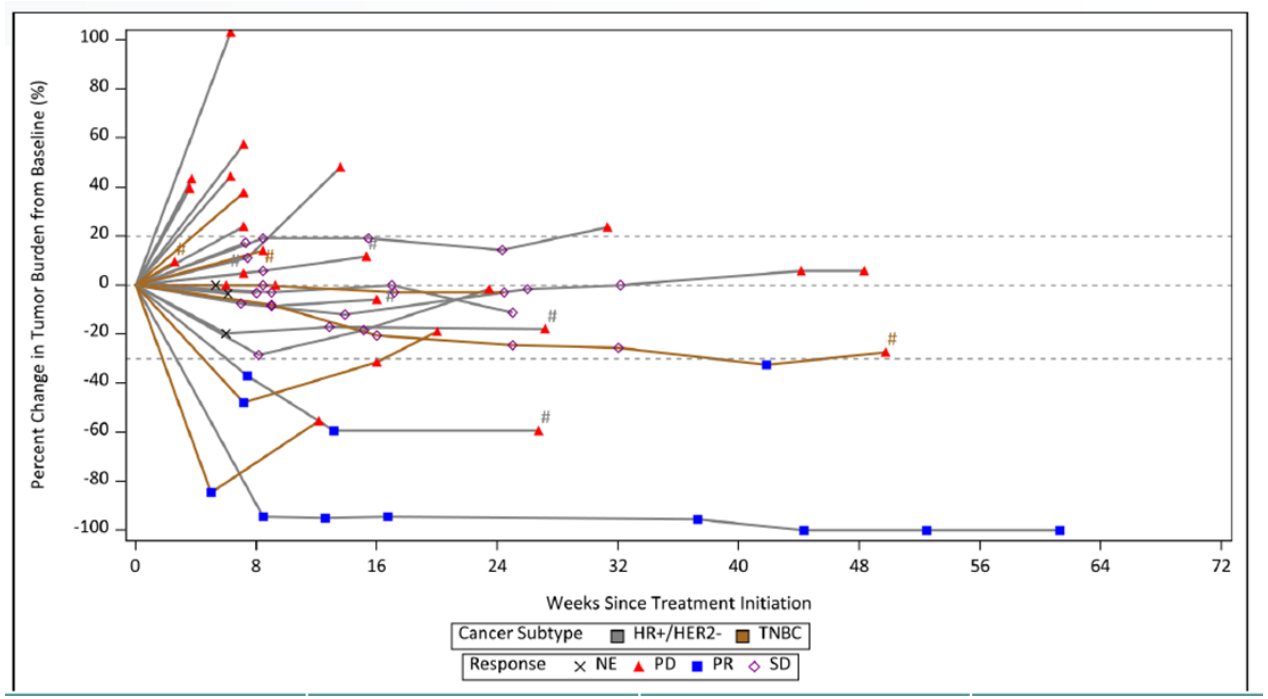
# CX-2009 : Probody drug conjugate targeting CD166

## CX-2009



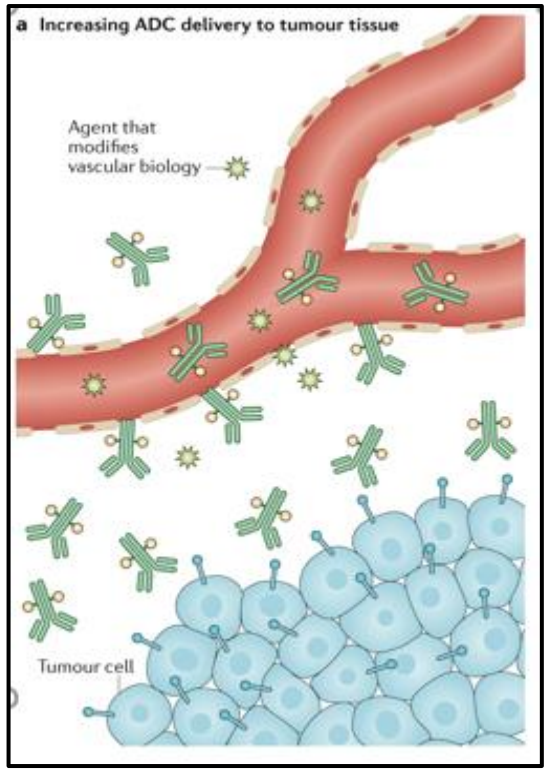

- CD166 is a transmembrane protein that facilitates cell migration, differentiation and hematopoiesis
- CD166 is a broadly and highly expressed tumor antigen
- ~80% expression in HR+/HER2- BC and 50% in TNBC

## Anti tumor activity (ph 1)

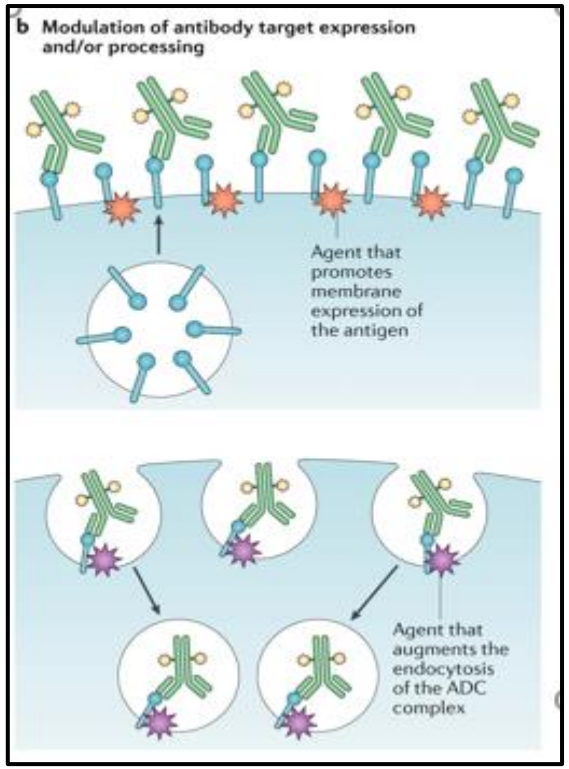



Boni et al ASCO 2020

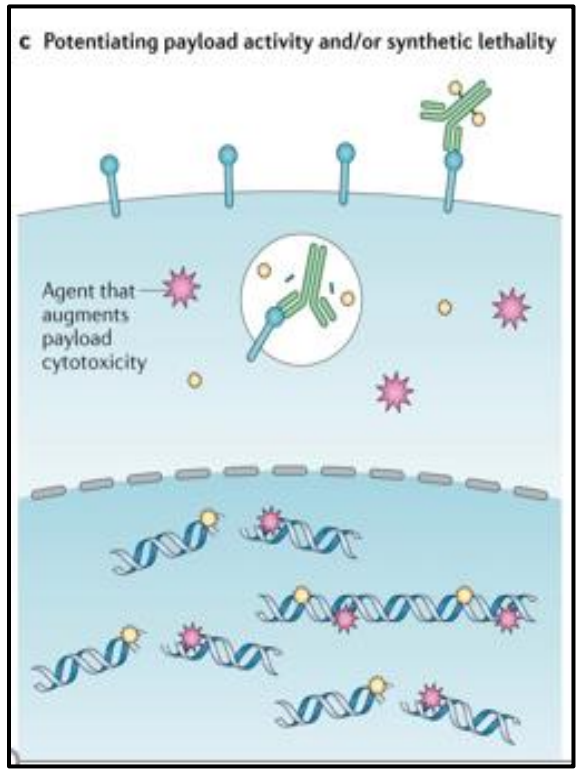
# Future Directions: Strategies to Enhance Efficacy of ADCs



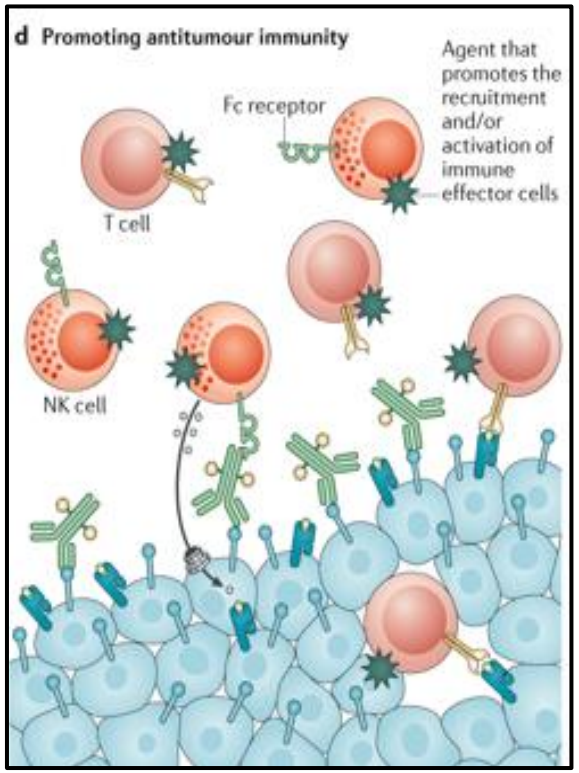

ADC + Bevacizumab
(NCT02606305)




ADC + PI3K/Akt Inhibitors




T-Dxd + PARPi
(NCT04644068)




T-Dxd + IO
(NCT03742102)

Adapted from Drago, Modi, and Chandarlapaty; Nat Rev. Clin Onc. 2021

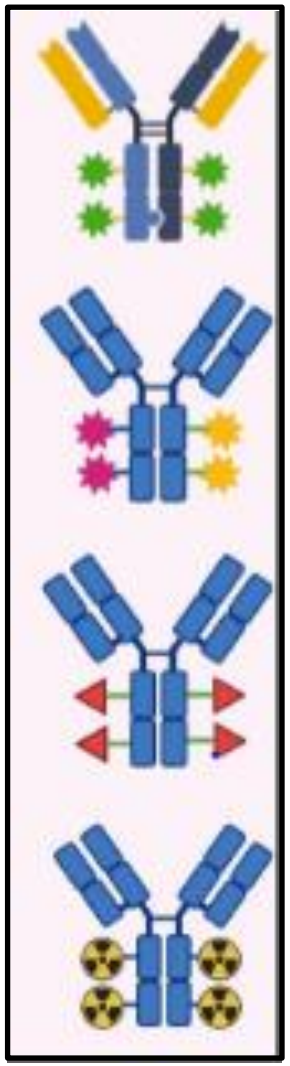
# Newer Strategies for ADC Constructs

**Bispecific ADCs**
**e.x. ZW-49 (NCT03821233)**

**Dual Payload ADCs**
**Overcome HER2 heterogeneity and resistance**

**ADCs with immune stimulating Payloads**
**e.x. TLR7/8 agonist- BDC-1001**
**(NCT04278144)**

**Radionuclide ADCs**
**e.x. Yttrium-90–conjugated,**
**P-cadherin–targeting antibody, 90Y-FF-21101**



Tarantino et al CA A Cancer J Clinicians, First published: 12 November 2021

# Conclusions

- Antibody Drug Conjugates!
  - An exciting and effective new therapy for mBC with evolving studies
- Established role in TNBC
  - SG is a new standard of care for mTNBC
    - Post-neoadjuvant SASCIA trial, expected Alliance trial
- Established role in HER2+ disease
  - T-DXd is a new standard of care for mHER2+ BC
    - Multiple trials in mHER2+ disease, CNS mets, post-neoadjuvant in HER2+
  - New data with SYD985 for mHER2+ BC
  - Newer agents in development: ARX788, RC-48, ZW-49
- Evolving role in HER2 low and HR+ disease
  - Destiny Breast04
  - TROPICS-02
- New ADCs in phase III trials
  - Dato-DXd (anti-TROP2 ADC): Phase III studies in HR+ (enrolling), TNBC (planned)
  - ARX788 (anti-HER2 ADC): Phase III studies in HER2+, phase Ib in HER2 low

# Thank You!

Visit **www.bioascend.com/antibody-drug-conjugates** to register for upcoming presentations in this series.

Next presentation:

**Antibody-Drug Conjugates in Lung Cancer**

Presented by Benjamin Levy, MD

Monday, May 2, 2022