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# Advancements and Applications of Antibody-Drug Conjugates in HER2-Negative Breast Cancer

Presented by Creative Educational Concepts

Supported by an independent educational grant from Gilead Sciences, Inc.


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# Disclosures

**Faculty**

**Sara M. Tolaney, MD, MPH,** reports the following financial relationships:

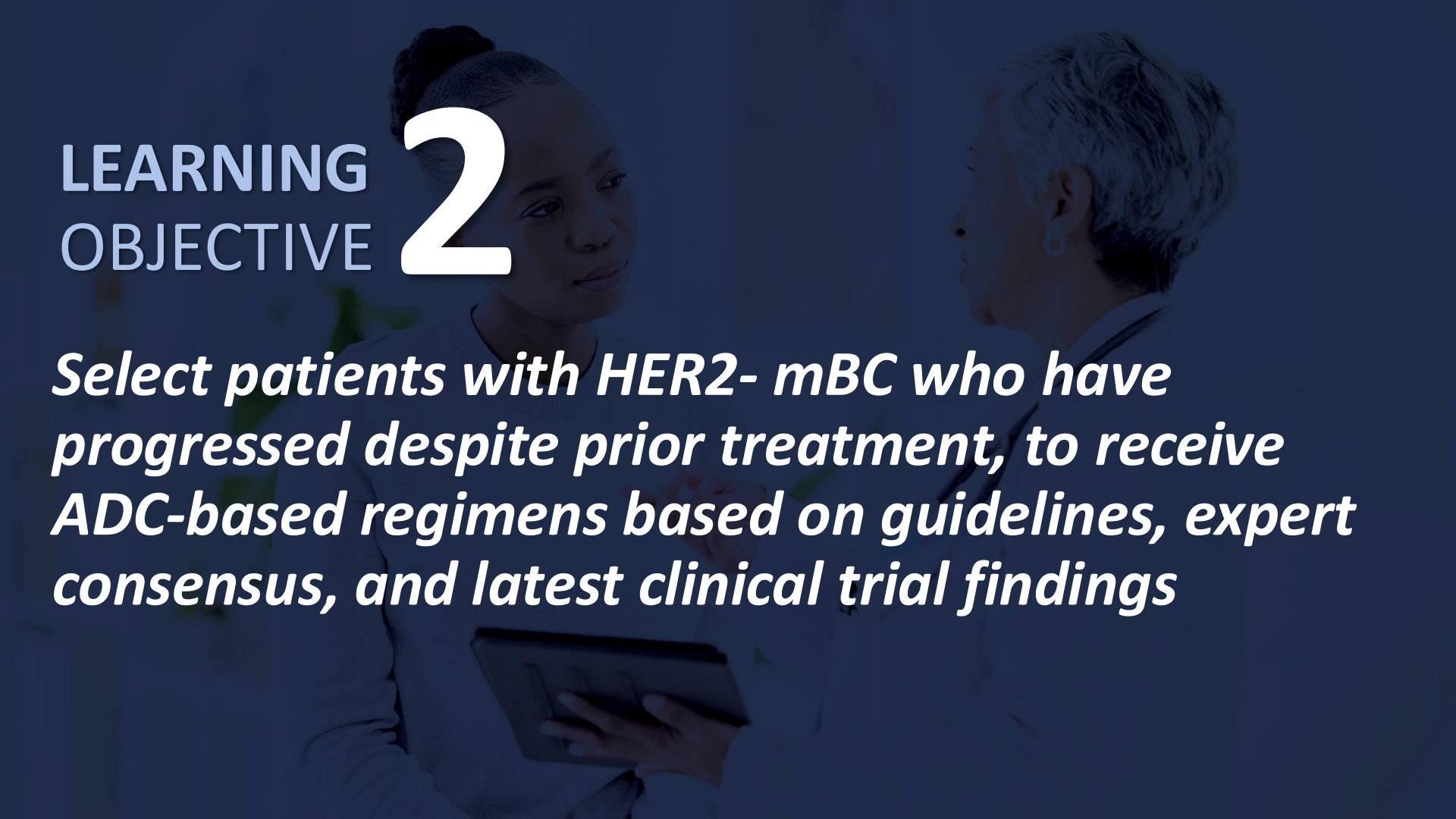
- *Consultant/Advisory Board (not leadership)*—Aadi Biosciences; ARC Therapeutics; Artios Pharma; AstraZeneca; Bayer; Blueprint Medicines Corporation; Bristol Myers Squibb Company; CytomX Therapeutics, Inc.; Daiichi Sankyo, Inc.; eFFECTOR; Eisai Inc.; Eli Lilly and Company; Genentech, Inc./Roche; Gilead Sciences, Inc.; Hengrui USA; Incyte; Infinity Therapeutics; Jazz Pharmaceuticals, Inc.; Menarini/Stemline Therapeutics, Inc.; Merck & Co., Inc.; Natera, Inc.; Novartis Pharmaceuticals Corporation; OncXerna Therapeutics, Inc.; Pfizer Inc.; Reveal Genomics; Sanofi; Seattle Genetics; Inc.; Sumitovant Biopharma, Inc.; SystImmune, Inc.; Tango Therapeutics; Umoja Biopharma; Zentalis Pharmaceuticals; and Zymeworks Inc.
- *Research Support (paid to institution)*—AstraZeneca; Bristol Myers Squibb Company; Daiichi Sankyo, Inc.; Eisai Inc.; Exelixis, Inc.; Genentech, Inc./Roche; Gilead Sciences, Inc.; Lilly; Merck & Co., Inc.; NanoString; Novartis Pharmaceuticals Corporation; OncoPep, Inc.; Pfizer Inc.; and Seattle Genetics, Inc.
- *Other financial or material support (travel support)*—Eli Lilly and Company; Sanofi; Gilead Sciences, Inc.; and Jazz Pharmaceuticals, Inc.

**Disclosures were obtained from the peer reviewer and Creative Educational Concepts staff**—no disclosures to report.

- Alaa Bawaneh, MD, PhD (peer reviewer)
- Albert Eubanks, Jr., RN (peer reviewer)
- David Modrak, PhD (planning committee)
- Mary Gleason, PhD (planning committee)
- Ashley C. Lilly, MHA (planning committee)
- Sandra Caballero, PharmD (planning committee)
- Sharon Tordoff (planning committee)

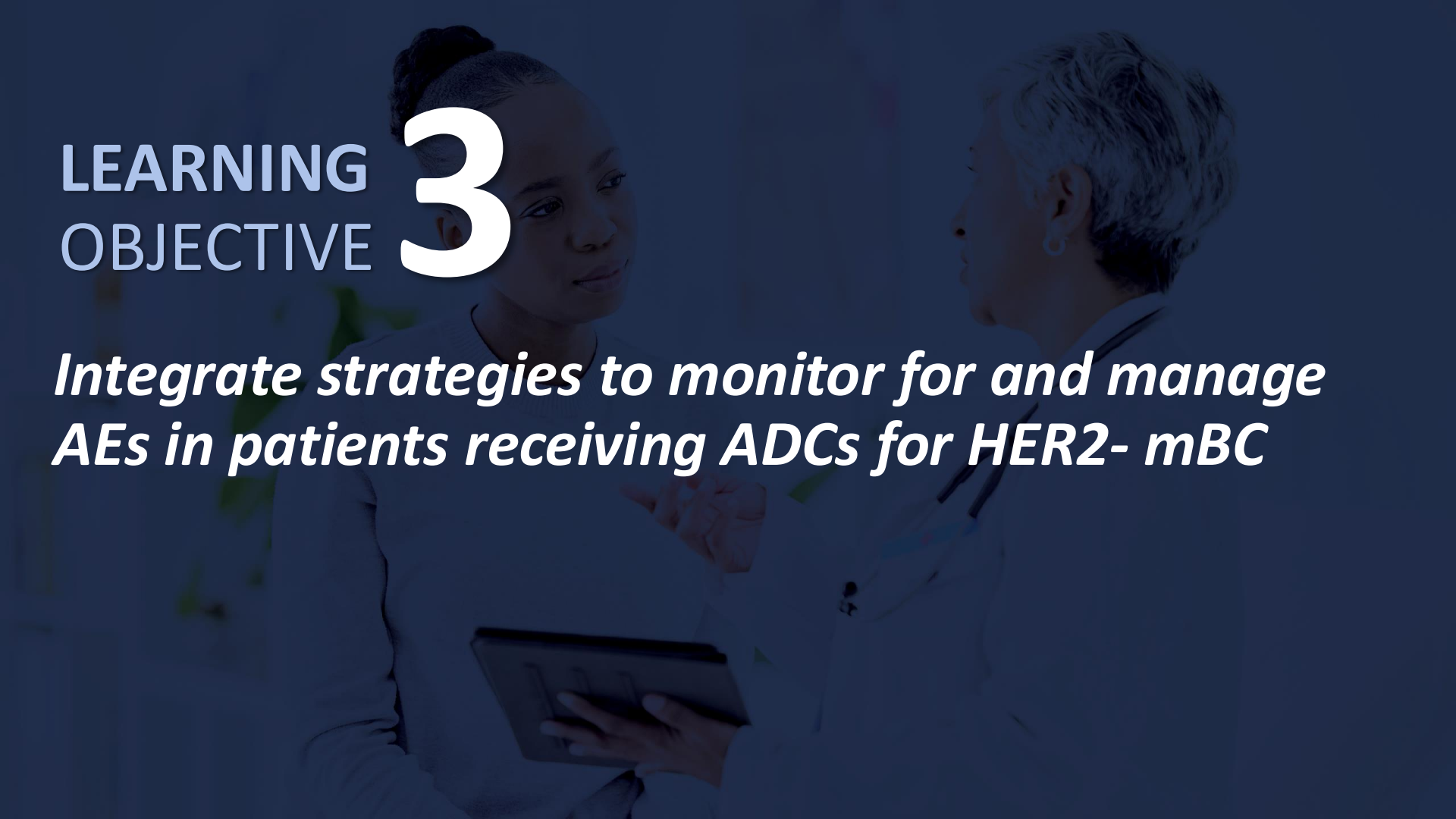
# LEARNING OBJECTIVE 1

***Evaluate unmet needs in the management of HER2- mBC including expanding treatment options for those who have progressive disease and the implementation of policies to promote equitable care***



# LEARNING OBJECTIVE 2

***Select patients with HER2- mBC who have progressed despite prior treatment, to receive ADC-based regimens based on guidelines, expert consensus, and latest clinical trial findings***



# LEARNING OBJECTIVE 3

***Integrate strategies to monitor for and manage AEs in patients receiving ADCs for HER2- mBC***

# Health Disparities in the Management of mBC

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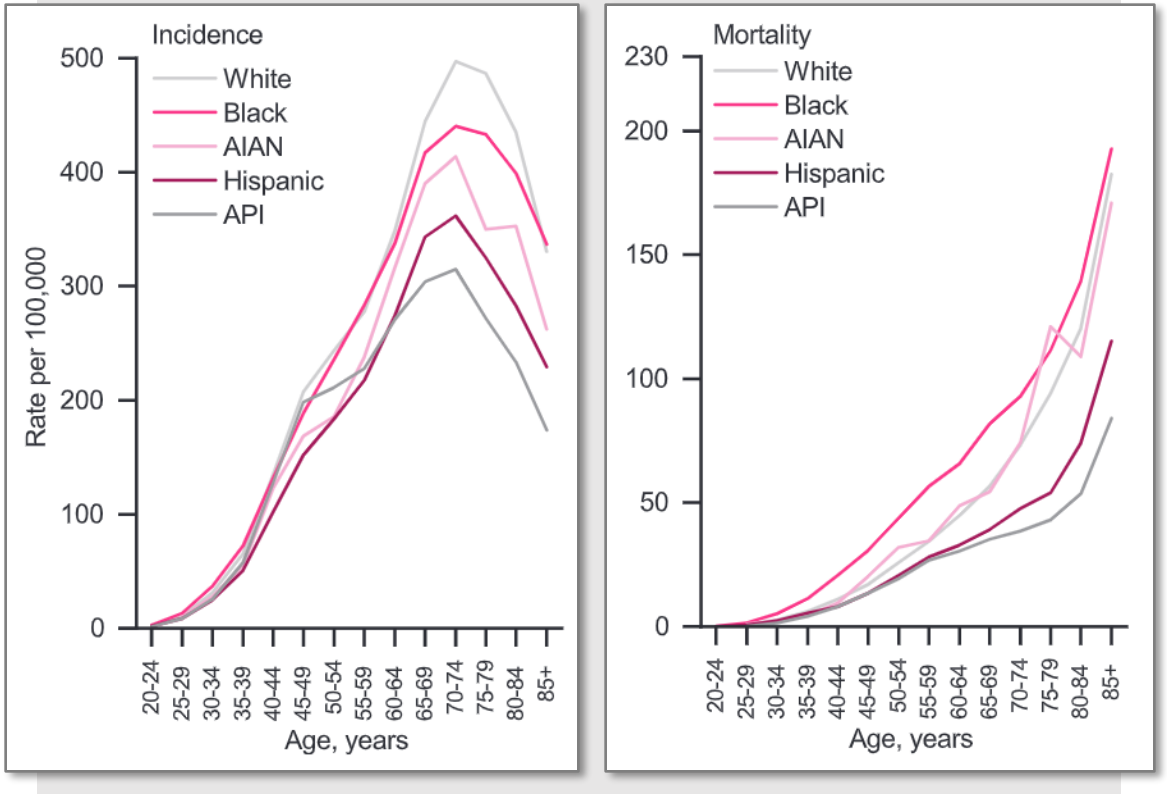
# Breast Cancer Incidence and Mortality by Age

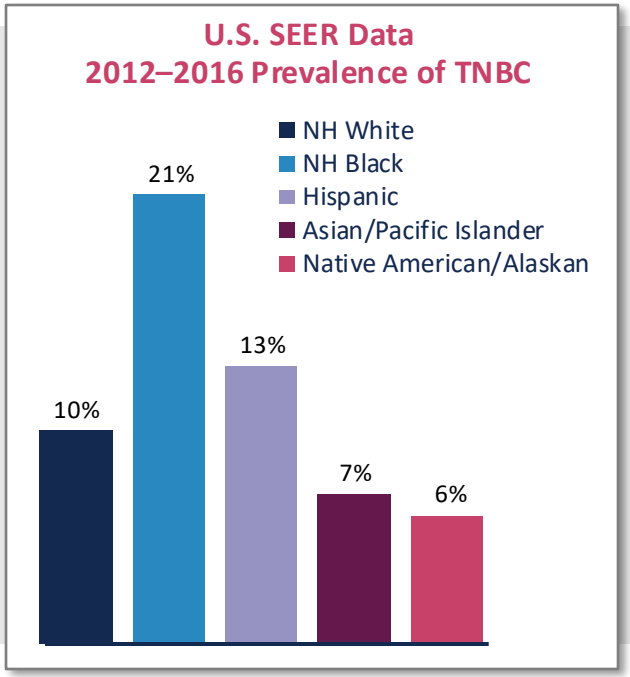
- Five-year BC-specific survival rates are significantly lower in Black (80%) vs White (91%) women
- Median age at death due to breast cancer
  - 68 yrs all women
  - 70 yrs White women
  - 63 yrs Black women




Giaquinto AN, et al. *CA Cancer J Clin.* 2022;72:524-541. Prakash O, et al. *Front Public Health.* 2020;8:576964. Rebner M, et al. *J Breast Imaging.* 2020;2(5):416-421.

# Prevalence of TNBC by Race and Ethnicity

- TNBC is more prevalent in Black women than other races and/or ethnicities
  - Worldwide, highest rates found in Black women from the United States and West Africa (~24%)
  - Contributes to excess BC-related mortality among Black women, but not sole explanation
- Incidence of TNBC is 2-fold higher for Black women compared to White women
- TNBC disproportionately affects younger, premenopausal women
- Pathogenic variant frequency in 21 cancer-associated genes
  - White: 7.8% BRCA1/BRCA2, 6.2% non-BRCA
  - Black: 9.0% BRCA1/BRCA2, 5.6% non-BRCA




American Cancer Society [ACS]. ACS Website. 2017. https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html. Dietze EC, et al. *Am J Pathol.* 2018;188(2):280-290. Foulkes WD, et al. *N Engl J Med.* 2010;363(20):1938-1948. Howard FM, et al. *Cancer J.* 2021;27(1):8-16. National Cancer Institute [NCI]. NCI website. 2024. https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#_2723_toc. Prakash O, et al. *Front Public Health*. 2020;8:576964. Sharma P. *Oncologist*. 2016;21(9):1050-1062.

BC = breast cancer;
BRCA = breast cancer gene; NH = non-Hispanic;
SEER = surveillance, epidemiology, and end results;
TNBC = triple-negative breast cancer.

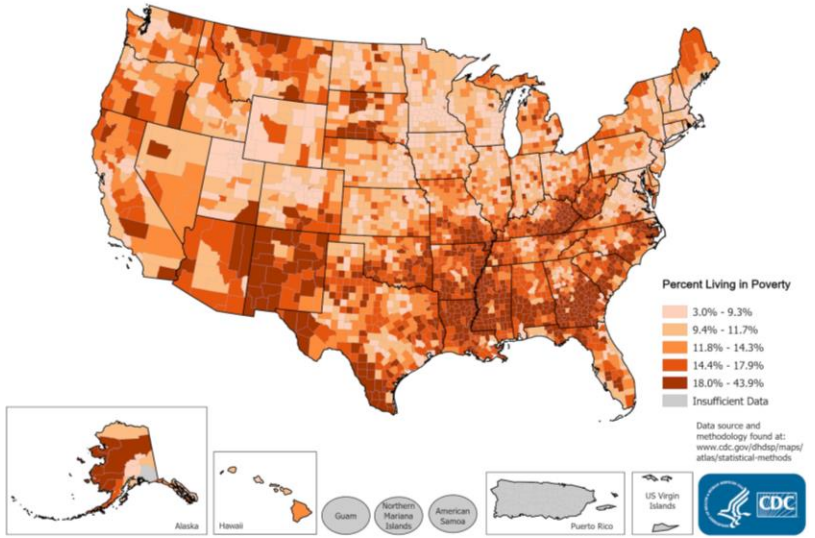
# Social Determinants of Health Risk Factors

- Socioeconomic disparities
  - Poverty: lower rates of screening, higher likelihood of diagnosis at a later stage, inadequate or inequitable care—all leading to higher mortality rate
  - Lack of insurance or under-insured
  - Inability to take time off work to attend medical appointments due to financial limitations
- Structural disadvantages: neighborhood segregation, lack of or significant distance to health care providers and facilities, lack of transportation, lack of childcare/ support, geographic barriers to care
- Lifestyle
  - Higher rates of tobacco and alcohol use, obesity, physical inactivity, lower socioeconomic status (SES)
  - Limited/no access to healthy nutrition

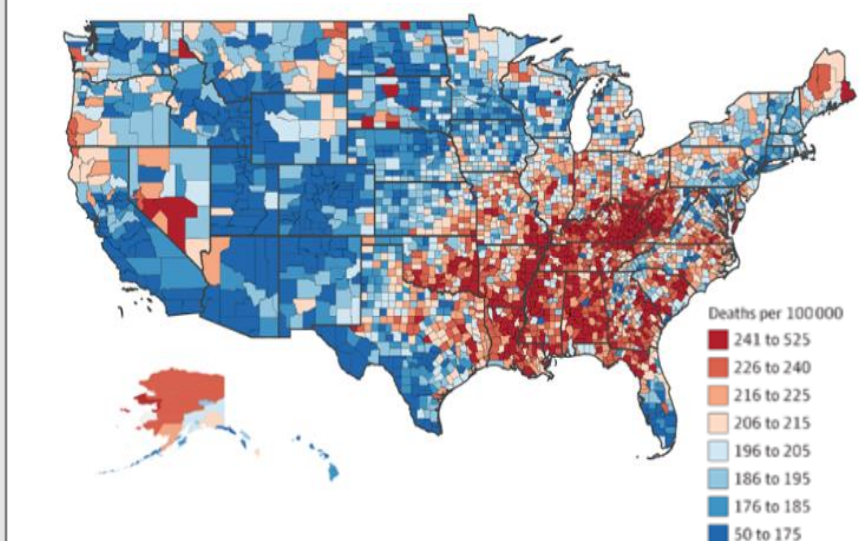
Chen L, et al. *Cancer Epidemiol Biomarkers Prev.* 2015;24(11):1666-1672. Giaquinto AN, et al. *CA A Cancer J Clin*. 2022;72(6):524-541.
Yedjou CG, et al. *Adv Exp Med Biol*. 2019;1152:31-49.

# Geographical Disparities

## Percent of Population Living in Poverty, 2020 by County




## Cancer Death Rate, 2018




Centers for Disease Control and Prevention [CDC]. CDC website. 2022. https://www.cdc.gov/dhdsp/maps/sd_poverty.htm.
O'Connor JM, et al. *JAMA Netw Open.* 2018;1(6):e183146.

# Health Inequity

- Under-representation of racial and ethnic minority groups in clinical trials
- Lack of understanding of the etiology of suboptimal treatment response often seen in patients from racial and ethnic underserved populations
- Lack of understanding of biological and hereditary factors leading to poorer breast cancer outcomes and higher risk disease
- Health insurance coverage increases the likelihood of services across the cancer care continuum
    - Medicaid expansion: cancer outcomes improved in Medicaid expansion states and worsened in states choosing not to expand

Beyer KMM, et al. *J Clin Oncol.* 2021;39(25):2749-2757. Levit LA, et al. *JCO Oncol Pract*. 2020;16(7):422-430.
Weinstein JN, et al (eds). *Communities in Action: Pathways to Health Equity*. 2017. https://www.ncbi.nlm.nih.gov/books/NBK425848/pdf/Bookshelf_NBK425848.pdf.

# What Are the Major Barriers to Effective Care?

- System and providers
  - Systemic barriers
  - Not always easily accessible
  - Personal biases
- Patients
  - Lack of trust
    - Personal beliefs related to healthcare
    - Trust that clinicians are acting in their best interest
  - Not challenging clinicians to provide the care they need
  - Not receiving all information needed to make informed treatment choices (e.g., clinical trials)

# What Is Ideal Care?

- Patient-centric care
  - Gives the patient their undivided attention
  - Communicates clearly and ensures the patient understands their treatment plan
  - Gets to know the patient as a person and understands their needs beyond just treatment
  - Ensures patient is aware of and has access to the entire care team
  - Facilitates patient's connection to the community, within the cancer center (e.g., support groups) and beyond

James D. Interview by Creative Educational Concepts. May 2, 2024.

# How Should Oncologists Approach Their Patients?

- Assess socioeconomic and healthcare access factors
- Assess quality of health insurance
- Be mindful of provider and patient communication and interactions, due to unconscious bias
- Acknowledge discrimination and bias within the healthcare system, such as inadequate screening and longer time to initial therapy

James D. Interview by Creative Educational Concepts. May 2, 2024.

# Addressing Disparities in Access to Care

- Ensure equitable access to research and clinical trial participation
  - Improve recruitment strategies to ensure adequate representation of diverse populations
- Address structural barriers
  - Promote access to socially, culturally, and linguistically appropriate, respectful, and high-quality cancer care
  - Address implicit and explicit institutional biases
  - Diversify workforce
  - Address social determinants of health (SDoH)
  - Integrate genetic counselors into oncology community practices
- Implement patient navigation programs

Adamson BJS, et al. *J Clin Oncol*. 2019;37(18_suppl):LBA1. Crown A, et al. *J Am Coll Surgeons* website. 2023. https://www.facs.org/for-medical-professionals/news-publications/news-and-articles/press-releases/2023/significant-disparities-in-breast-cancer-care-persist-but-surgeons-can-drive-change/. Patel MI, et al. *J Clin Oncol*. 2020;38(29):3439–3448.

# Multidisciplinary Oncology Care Team

- Assesses individual social risk factors in healthcare settings
  - Patient's personal challenges affect access and adherence to care
  - Socioeconomic position; race, ethnicity, and cultural context; gender; social relationships; residential and community context; other barriers to care
- Improves patient understanding and literacy on
  - The patient's cancer
  - The healthcare system, financial navigators
  - Treatment options, importance of treatment adherence, potential adverse effects
- Connects patients to resources
  - Navigation services
  - Support services
    - Social, mental health, transportation, financial

**Get to know your patient!**

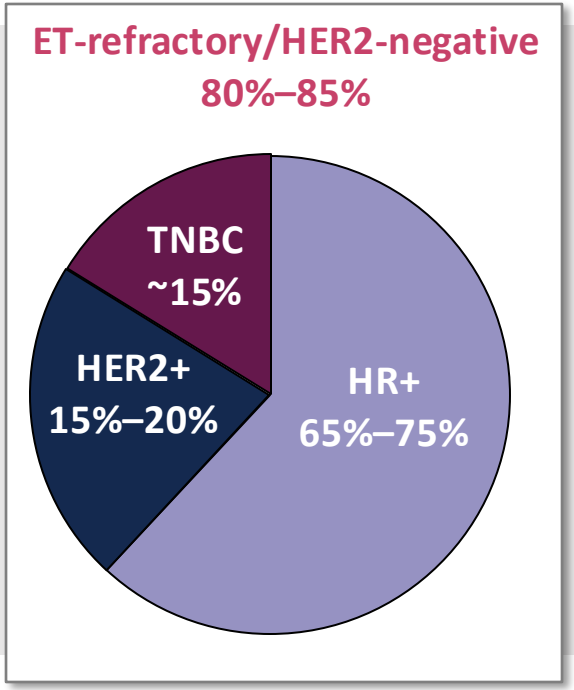
The Joint Commission. The Joint Commission website. 2024.
https://www.jointcommission.org/our-priorities/health-care-equity/accreditation-resource-center/assess-health-related-social-needs/#t=_StrategiesTab&sort=%40created%20descending.

# The Evolving Treatment Landscape of Metastatic Breast Cancer

# Unmet Needs in mBC

- Endocrine therapies are effective in HR+/HER2- disease with smaller effects on QoL than chemotherapies
- Chemotherapies for endocrine therapy–refractory HR+/HER2- and TNBC are associated with diminished QoL

| Real-world Outcomes in Patients with HR+/HER2- mBC Initiating Treatment or Previously Treated with CT | | | | |
|---|---|---|---|---|
| | 1st CT | 2nd CT | 3rd CT | 4th CT |
| **Median rwOS,** months (95% CI) | 23.3 (21.3–25.4) | 16.5 (14.8–18.3) | 11.8 (10.4–13.1) | 9.1 (7.3–11.2) |
| **Median rwPFS,** months (95% CI) | 6.9 (6.4–7.6) | 5.5 (5.0–6.2) | 4.5 (4.1–5.1) | 3.7 (3.2–4.6) |




CI = confidence interval; CT = chemotherapy; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; mBC = metastatic breast cancer; QoL = quality of life; rwOS = real-world overall survival; rwPFS = real-world progression-free survival.

Waks AG, et al. *JAMA*. 2019;321(3):288-300.

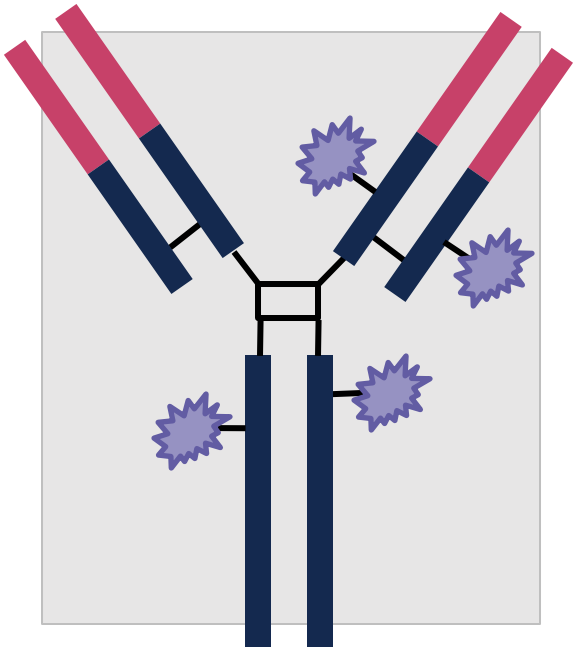
# Antibody-Drug Conjugates (ADCs)

**Target/MAb**

- Exploitable selectivity
  - High expression on tumor
  - Limited normal tissue expression
- Limited heterogenicity
- Internalizes following binding
- Conjugation sites (cysteine or lysine) should not impact stability, binding, internalization, pharmacokinetics

**Linker**

- Stable in circulation
- Selective intracellular release of biologically active drug
  - Enzymatic cleavage
  - MAb degradation
- Limited heterogenicity of drug product



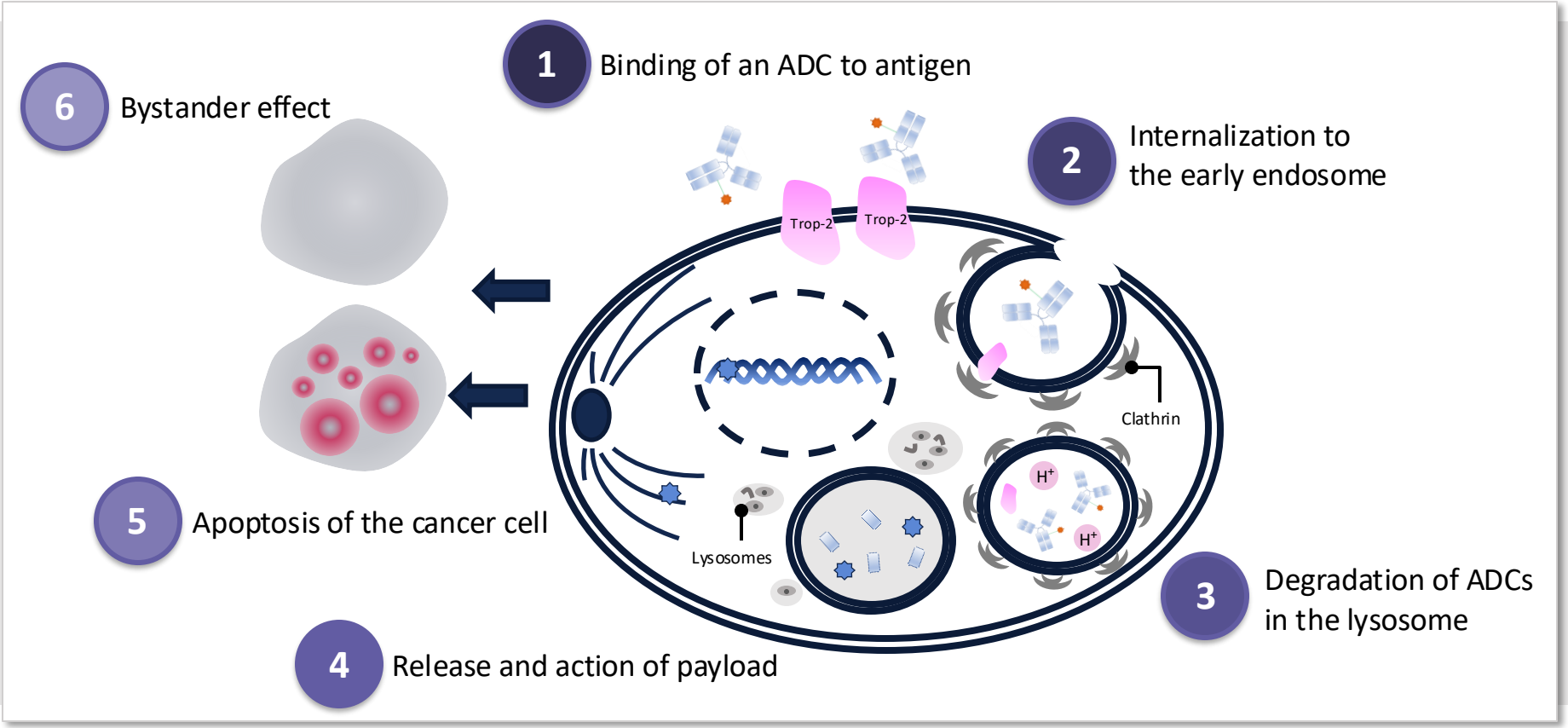
**Drug**

- Highly potent
- Amenable to modifications that allow linker attachment
- Stable
  - In circulation
  - In lysosomes
- Defined mechanisms of action
- Local bystander effect?

Koster KL, et al. *Explor Target Antitumor Ther*. 2022;3(1):27-36. Trail PA. *Antibodies.* 2013;2(1):113-129.

MAb = monoclonal antibodies.

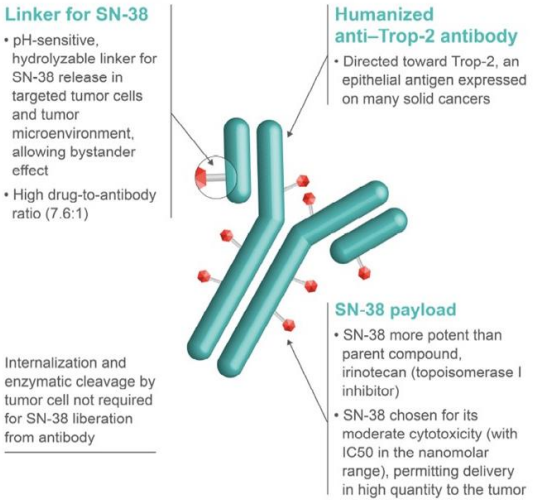
# ADC Mechanism of Action



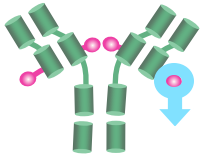
# Anti-Trop2 ADCs

| | Sacituzumab-gov. (N = 272) | Datopotamab-DXd (N = 365) | SKB264 (MK-2870) (N = 38) |
|---|---|---|---|
| Payload | Anti-TOPO1 | Anti-TOPO1 | Anti-TOPO1 |
| DAR | 7.6 | 4 | 7.8 |
| Trial | Ph3 RCT (TROPiCS-02) | Ph3 RCT (TROPION-Breast01) | Single arm Ph1-2 |

## Sacituzumab govitecan

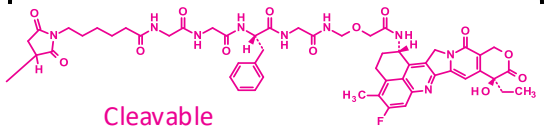



## Datopotamab deruxtecan



- Payload mechanism of action: Topo-I inhibitor
- High potency payload
- Optimised drug to antibody ratio ≈**4**
- Payload with short systemic half-life
- Stable linker-payload
- Tumour-selective cleavable linker
- Bystander antitumour effect

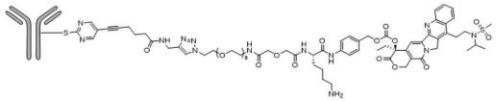
**Deruxtecan**



Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

## SKB264 (MK-2870)



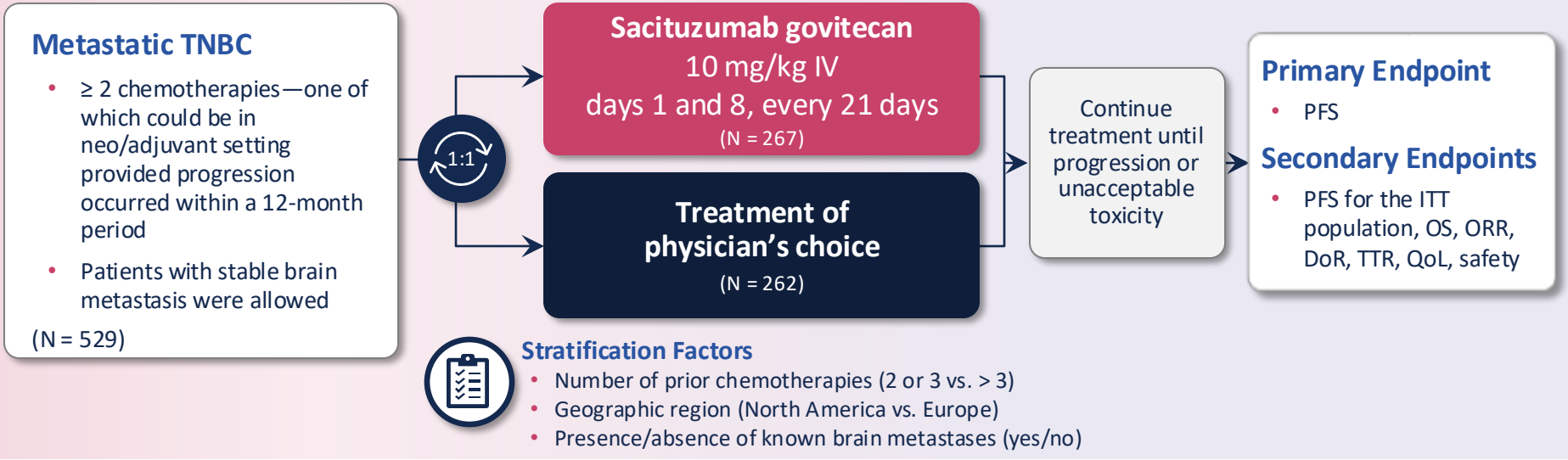
- anti-TROP2 ADC
- Sulfonyl pyrimidine-CL2A-carbonate linker
- **Payload**: belotecan-derivative topoisomerase I inhibitor
- **DAR**: 7.4



DAR = drug to antibody ratio; DXd = datopotamab deruxtecan; Ig = immunoglobulin; TM = transmembrane.

# ASCENT

## *A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Second Line and Later mTNBC[1–3]*



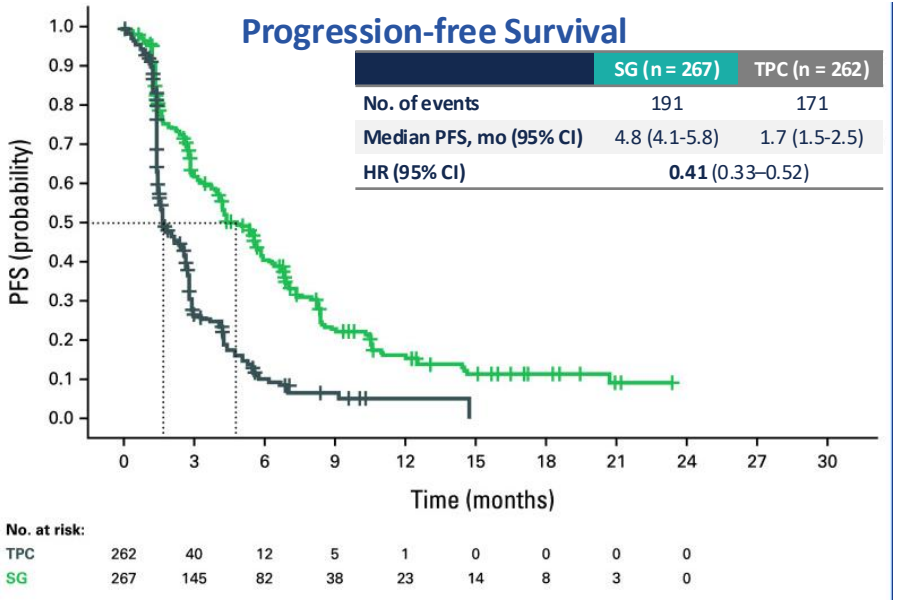

DoR = duration of response; IV = intravenous; ITT = intention to treat; mTNBC = metastatic triple-negative breast cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours; TTR = time to response.

[1]Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541. [2]Bardia A, et al. ESMO Virtual Congress; 2020. Abstract No. LBA17. https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/ascent-a-randomized-phase-iii-study-of-sacituzumab-govitecan-sg-vs-treatment-of-physician-s-choice-tpc-in-patients-pts-with-previously-treat. [3]Gilead Sciences. Trial of Sacituzumab Govitecan in Participants With Refractory/Relapsed Metastatic Triple-Negative Breast Cancer (TNBC) (ASCENT). ClinicalTrials.gov. Identifier: NCT02574455. First Received 2015.

# ASCENT

## *Statistically Significant and Clinically Meaningful Improvement in PFS and OS*

### Progression-free Survival

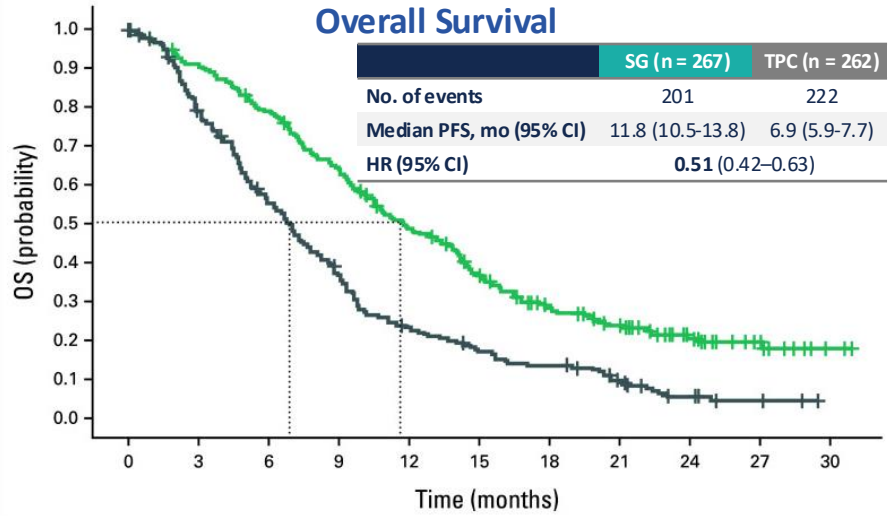



| | SG (n = 267) | TPC (n = 262) |
|---|---|---|
| No. of events | 191 | 171 |
| Median PFS, mo (95% CI) | 4.8 (4.1-5.8) | 1.7 (1.5-2.5) |
| HR (95% CI) | **0.41** (0.33–0.52) | |

No. at risk:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TPC | 262 | 40 | 12 | 5 | 1 | 0 | 0 | 0 | 0 |
| SG | 267 | 145 | 82 | 38 | 23 | 14 | 8 | 3 | 0 |

### Overall Survival




| | SG (n = 267) | TPC (n = 262) |
|---|---|---|
| No. of events | 201 | 222 |
| Median PFS, mo (95% CI) | 11.8 (10.5-13.8) | 6.9 (5.9-7.7) |
| HR (95% CI) | **0.51** (0.42–0.63) | |

No. at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TPC | 262 | 192 | 132 | 87 | 54 | 39 | 31 | 16 | 7 | 3 | 0 |
| SG | 267 | 242 | 209 | 169 | 125 | 92 | 62 | 42 | 25 | 11 | 2 |

The ASCENT trial demonstrated statistically significant improvement in PFS and OS over single-agent chemotherapy in the primary study population.

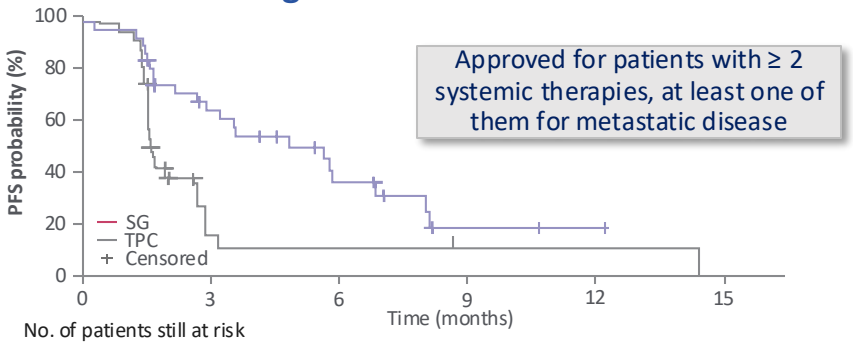
Bardia A, et al. J Clin Oncol. 2024;42(15):1738-1744.

HR = hazard ratio; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

# ASCENT

## *In Patients with Second Line mTNBC, PFS and OS Improvement Was Consistent with the Overall Study Population*

### Progression-free Survival



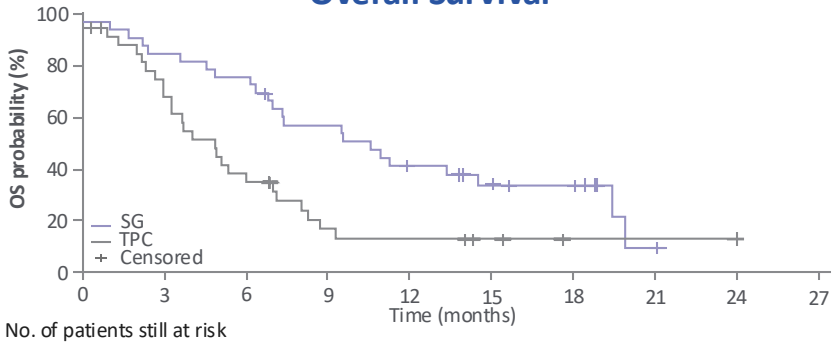

Approved for patients with ≥ 2 systemic therapies, at least one of them for metastatic disease

No. of patients still at risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SG | 33 | 32 | 23 | 19 | 16 | 12 | 8 | 6 | 5 | 2 | 2 | 1 | 1 | 1 | 0 | 0 |
| TCP | 32 | 28 | 8 | 3 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |

| BICR Analysis | SG (N = 33) | TPC (N = 32) |
|---|---|---|
| No. of events | 21 | 23 |
| Median PFS, mo (95% CI) | 5.7 (2.6–8.1) | 1.5 (1.4–2.6) |
| HR (95% CI) | 0.41 (0.22–0.76) | |

### Overall Survival




No. of patients still at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SG | 33 | 32 | 31 | 29 | 28 | 26 | 26 | 21 | 19 | 19 | 17 | 15 | 13 | 13 | 11 | 9 | 7 | 7 | 7 | 4 | 2 | 1 | 0 | 0 | 0 | 0 |
| TCP | 32 | 29 | 27 | 22 | 17 | 14 | 12 | 10 | 8 | 6 | 5 | 5 | 5 | 5 | 5 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |

| BICR Analysis | SG (N = 33) | TPC (N = 32) |
|---|---|---|
| No. of events | 22 | 24 |
| Median OS, mo (95% CI) | 10.9 (6.9–19.5) | 4.9 (3.1–7.1) |
| HR (95% CI) | **0.51** (0.28–0.91) | |

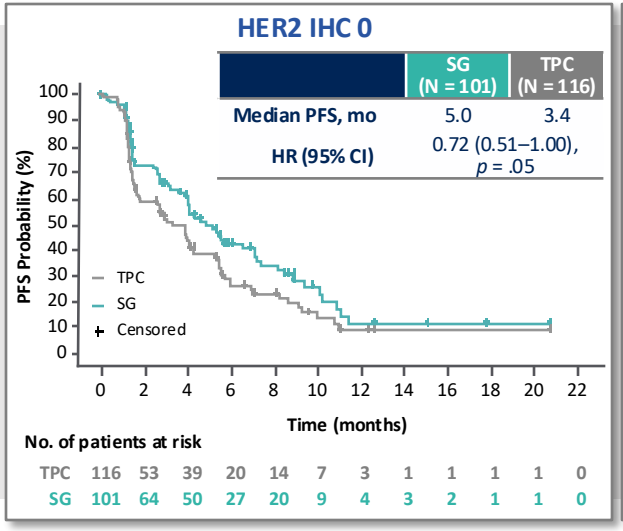

Carey LA, et al. *NPJ Breast Cancer*. 2022;8(1):72. Committee for Medicinal Products for Human Use [CHMP]. European Medicines Agency (EMA) Website. 2023. https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf.

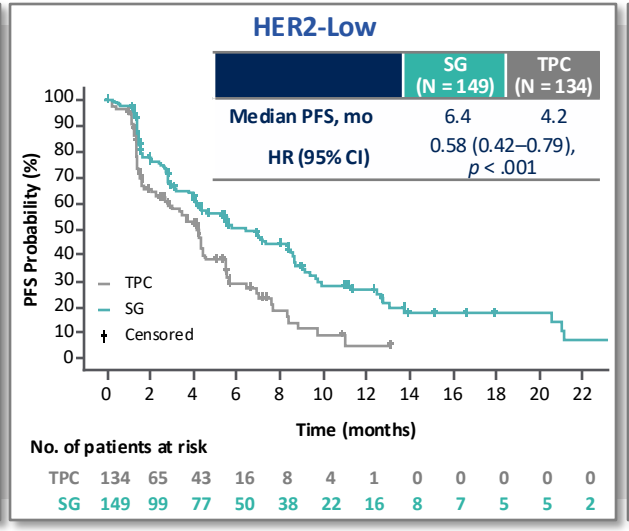
# Clinical Benefit with SG vs. TPC is Irrespective of Level of Trop-2 Expression, in Previously Treated mTNBC

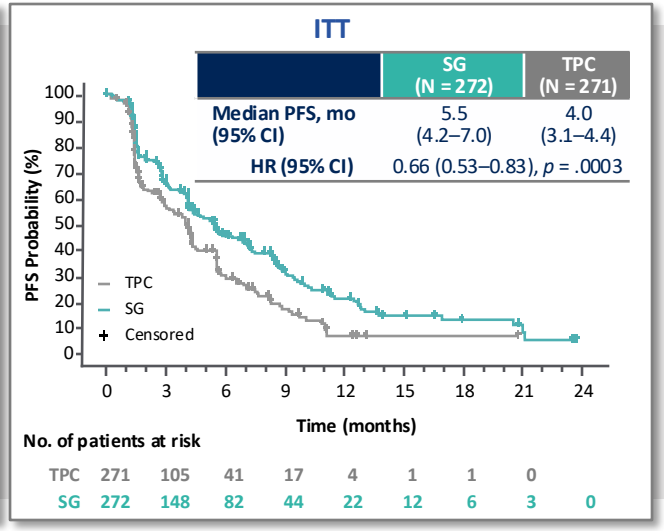
| | Trop-2 Low H-score: 0-129 | | Trop-2 Medium H-score: 130–219 | | Trop-2 High H-score: 220-275 | | Trop-2 Very high H-score: >275 | |
|---|---|---|---|---|---|---|---|---|
| | SG (n=35) | TPC (n=45) | SG (n=47) | TPC (n=33) | SG (n=39) | TPC (n=40) | SG (n=47) | TPC (n=32) |
| Median PFS (95% CI) | 2.7 (1.4-5.7) | 1.5 (1.4-2.2) | 4.8 (2.9-7.1) | 2.8 (1.7-4.3) | 6.8 (4.3-8.3) | 1.6 (1.4-2.7) | 6.9 (5.6-8.1) | 2.8 (1.4-3.1) |
| HR for disease progression (95% CI) | 0.58 (0.34-1.00) | | 0.52 (0.29-0.92) | | 0.20 (0.11-0.36) | | 0.31 (0.17-0.59) | |
| Median OS (95% CI) | 8.7 (6.9-12.9) | 7.0 (4.9-9.6) | 13.4 (7.8-16.5) | 8.8 (4.8-10.2) | 15.2 (11.8-17.5) | 6.5 (4.1-8.2) | 14.5 (10.6-18.3) | 7.1 (4.9-9.8) |
| HR for death (95% CI) | 0.74 (0.46-1.20) | | 0.69 (0.41-1.17) | | 0.34 (0.21-0.57) | | 0.36 (0.22-0.59) | |

H-score = histochemical score; NE = not estimable.

# SG Improved PFS vs. TPC in HER2 IHC 0 and HER2-low Groups, Consistent with Outcomes in the ITT Population




- Within the HER2-low population, median PFS with SG vs. TPC for the IHC 1+ and IHC 2+ subgroups was 7.0 vs. 4.3 (HR, 0.57) and 5.6 vs. 4.0 (HR, 0.58) months, respectively
- Median PFS in a sensitivity analysis of the HER2-low subgroup did not show any differences compared with the ITT population

Rugo H, et al. *J Clin Oncol*. 2022;40(29):3365-3376.

# ASCENT 03

## *Sacituzumab Govitecan vs TPC (Gem + Carbo, Paclitaxel, Nab-Paclitaxel) in First-line PD-L1-neg mTNBC, NCT05382299*

### First-line mTNBC PD-L1–

- Previously untreated, inoperable, locally advanced, or metastatic TNBC
- PD-L1– tumors (CPS < 10, IHC 22C3 assay) **or** PD-L1+ tumors (CPS ≥ 10, IHC 22C3 assay) if treated with anti–PD-(L)1 agent in the curative setting
- ≥ 6 months since treatment in curative setting
- Prior anti–PD-(L)1 agent allowed in the curative setting
- PD-L1 and TNBC status centrally confirmed

1:1

N = 540
(≤ 25% *de novo*)

**Sacituzumab govitecan**
10 mg/kg IV on
days 1 and 8 of 21-day cycles

**TPC chemotherapy**
**Gem + carbo:** gem 1,000 mg/m$^2$ with carbo AUC 2 IV on days 1 and 8 of 21-day cycles
**Paclitaxel:** 90 mg/m$^2$ IV on days 1, 8, and 15 of 28-day cycles
**Nab-paclitaxel:** 100 mg/m$^2$ IV on days 1, 8, and 15 of 28-day cycles

Treated until BICR-confirmed progression or unacceptable toxicity

*Crossover to SG allowed after BICR-verified disease progression*

**Long-term follow-up**

### Stratification Factors

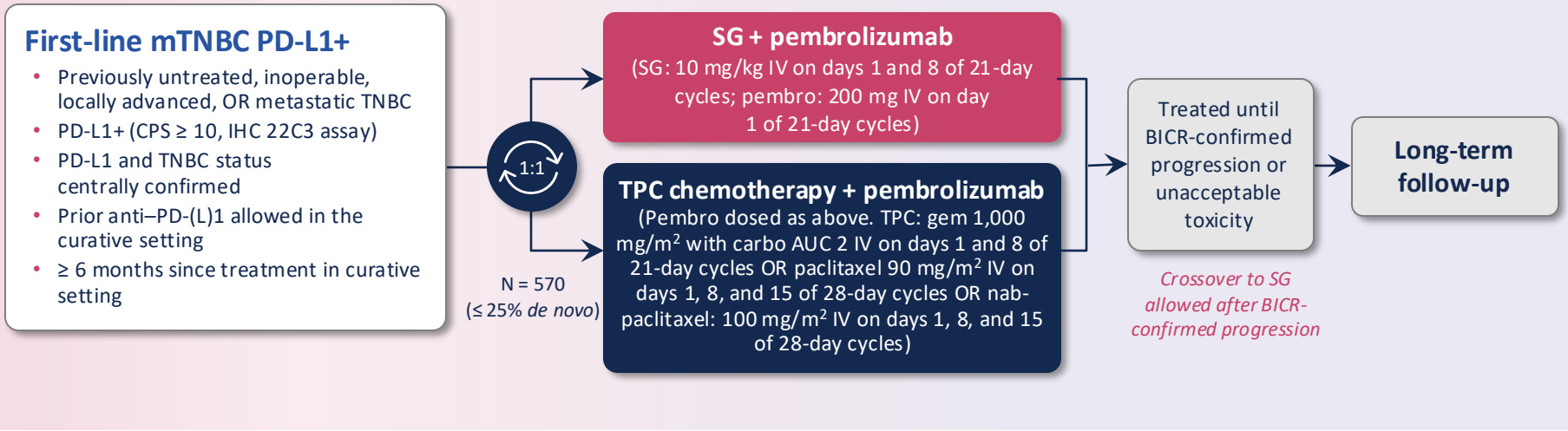
- *De novo* vs. recurrent disease within 6–12 months of treatment in the curative setting vs. recurrent disease > 12 months after treatment in the curative setting
- Geographic region

Carbo = carboplatin; Gem = gemcitabine.

EU Clinical Trials Register. *A Randomized, Open-label, Phase 3 Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Patients with Previously Untreated, Locally Advanced, Inoperable or Metastatic Triple-negative Breast Cancer.* Identifier: 2021-005743-79. First Received 2022.

# ASCENT 04

## *Sacituzumab Govitecan + Pembrolizumab vs. TPC + Pembrolizumab in First-line PD-L1+ mTNBC, NCT05382286*




### Stratification Factors

- *De novo* vs. recurrent disease within 6–12 months of treatment in the curative setting vs. recurrent disease > 12 months after treatment in the curative setting
- Geographic region (US/Canada vs. rest of world)
- Prior exposure to anti–PD-(L)1 therapy

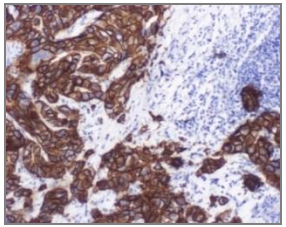
AUC = area under the curve.

EU Clinical Trials Register. *A Randomized, Open-label, Phase 3 Study of Sacituzumab Govitecan and Pembrolizumab Versus Treatment of Physician's Choice and Pembrolizumab in Patients with Previously Untreated, Locally Advanced, Inoperable or Metastatic Triple-negative Breast Cancer.* Identifier: 2021-005743-79. First Received 2022.

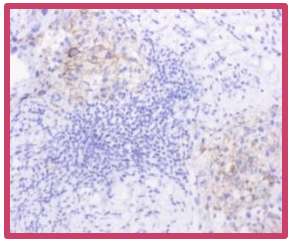
# Prevalence of HER2-low by HR Status

## HER2 IHC Examples

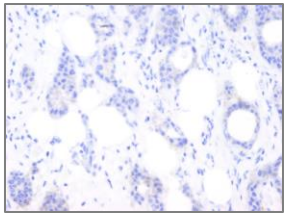
HER2+



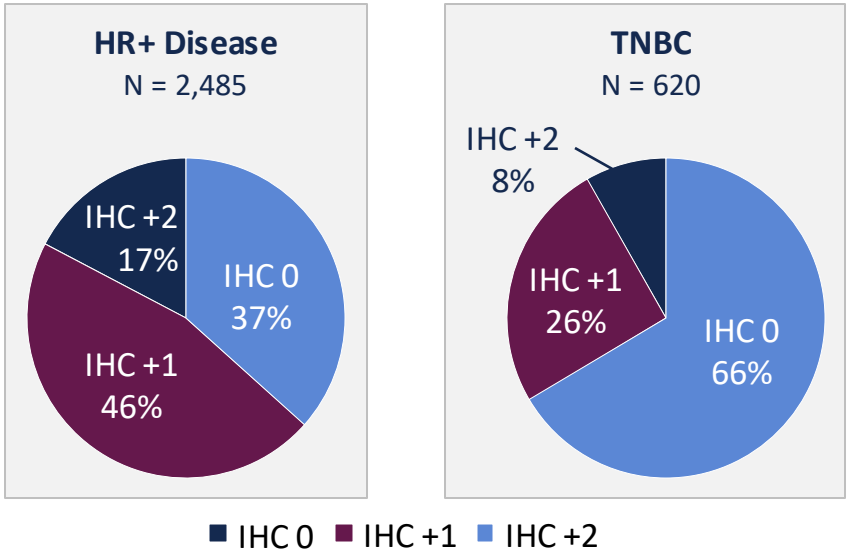
HER2-low



HER2-



## HER2-negative




34%–63% of breast cancer patients considered HER2-negative under current guidelines express low levels of HER2

Schettini F, et al. ESMO Virtual Congress; 2020. Abstract No. 23P.
https://cslide.ctimeetingtech.com/global_storage/media/content/breast2020/ANNONC_31_S2_Breast_2020_Final.pdf.Slide courtesy of Aleix Prat.

# DESTINY-Breast04

## *First Randomized Phase 3 Study of T-DXd for HER2-low mBC*

**An open-label, multicenter study (NCT03734029)**

### Patients

- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1–2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

**T-DXd**
5.4 mg/kg Q3W
(N = 373)

**HR+ ≈ 480**
**HR− ≈ 60**

**TPC**
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel
(N = 184)

### Primary Endpoint

- PFS by BICR (HR+)

### Key secondary Endpoints

- PFS by BICR (all patients)
- OS (HR+ and all patients)

### Stratification Factors

- Centrally assessed HER2 status (IHC 1+ vs. IHC 2+/ISH−)
- 1 vs. 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) vs. HR-

Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

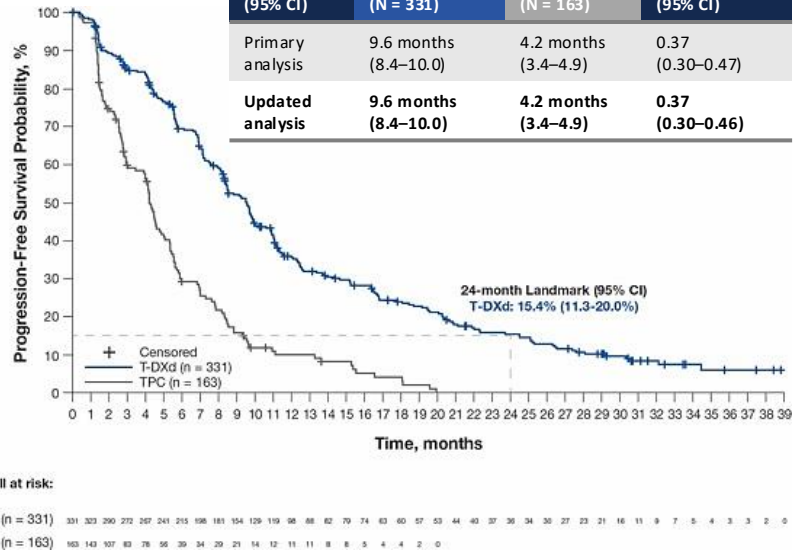
ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; CDK = cyclin-dependent kinase; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan.

# DESTINY-Breast04

## Updated Progression-free Survival: *Investigator Assessed*

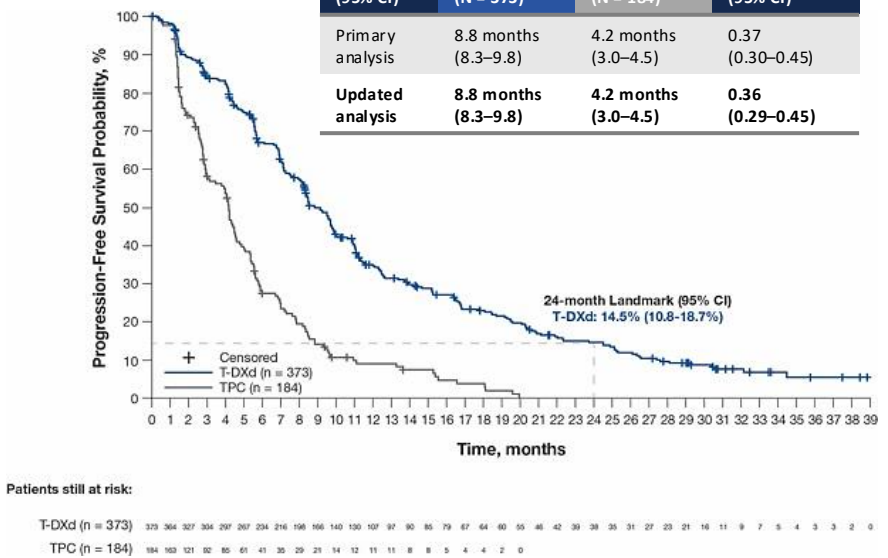
### HR+ Cohort

| Median (95% CI) | T-DXd (N = 331) | TPC (N = 163) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Primary analysis | 9.6 months (8.4–10.0) | 4.2 months (3.4–4.9) | 0.37 (0.30–0.47) |
| **Updated analysis** | **9.6 months (8.4–10.0)** | **4.2 months (3.4–4.9)** | **0.37 (0.30–0.46)** |




### All Patients

| Median (95% CI) | T-DXd (N = 373) | TPC (N = 184) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Primary analysis | 8.8 months (8.3–9.8) | 4.2 months (3.0–4.5) | 0.37 (0.30–0.45) |
| **Updated analysis** | **8.8 months (8.3–9.8)** | **4.2 months (3.0–4.5)** | **0.36 (0.29–0.45)** |




### Primary Analysis (BICR)

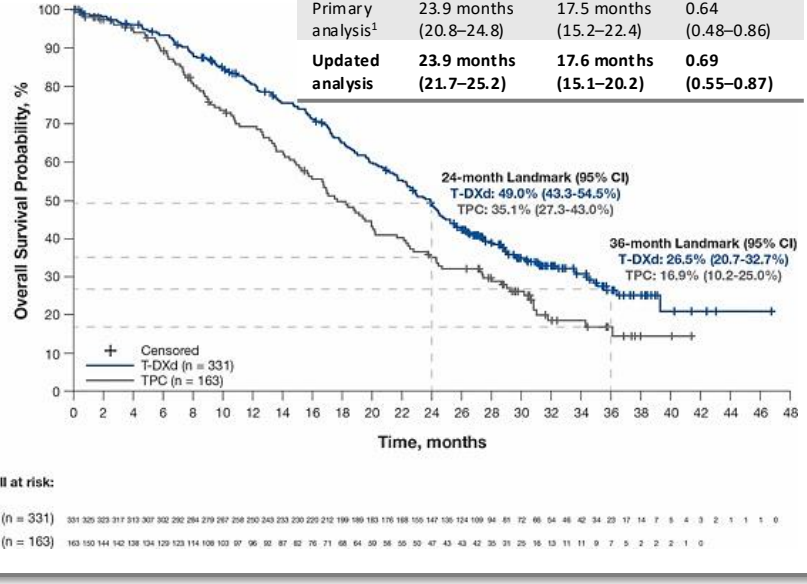
| PFS | HR+ | | HR-negative | | All Patients | |
|---|---|---|---|---|---|---|
| | T-DXd (N = 331) | TPC (N = 163) | T-DXd (N = 40) | TPC (N = 18) | T-DXd (N = 373) | TPC (N = 184) |
| Median PFS, months | 10.1 | 5.4 | 8.5 | 2.9 | 9.9 | 5.1 |
| HR (95% CI); *p* value | 0.51 (0.40–0.64); $p < .0001$ | | 0.46 (0.24–0.89) | | HR, 0.50 (0.40–0.63); $p < .0001$ | |

Modi S, et al. *N Engl J Med.* 2022;387(1):9–20. Modi S, et al. ESMO Congress 2023. Abstract 3760.

# DESTINY-Breast04
# Updated Overall Survival

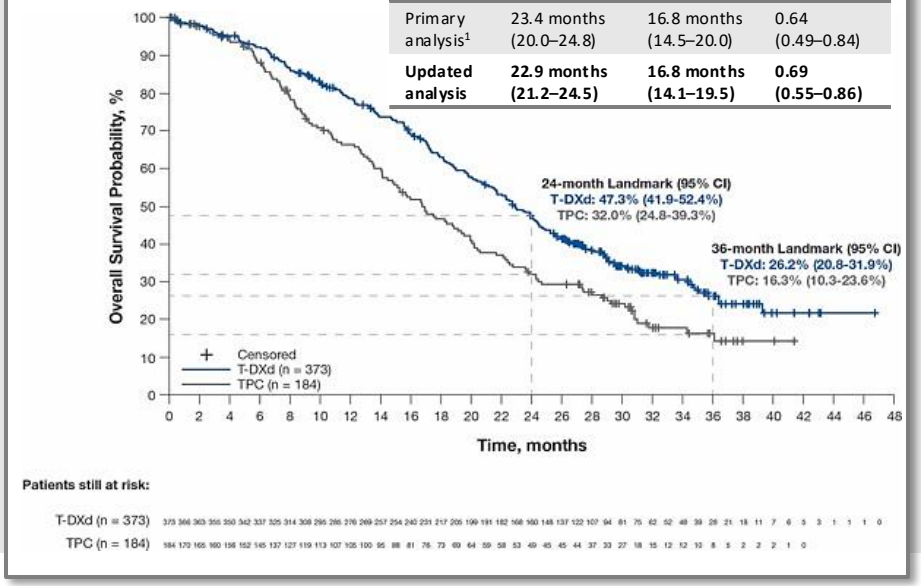
## HR+ Cohort

| Median (95% CI) | T-DXd (N = 331) | TPC (N = 163) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Primary analysis[1] | 23.9 months (20.8–24.8) | 17.5 months (15.2–22.4) | 0.64 (0.48–0.86) |
| **Updated analysis** | **23.9 months (21.7–25.2)** | **17.6 months (15.1–20.2)** | **0.69 (0.55–0.87)** |




## All Patients

| Median (95% CI) | T-DXd (N = 373) | TPC (N = 184) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Primary analysis[1] | 23.4 months (20.0–24.8) | 16.8 months (14.5–20.0) | 0.64 (0.49–0.84) |
| **Updated analysis** | **22.9 months (21.2–24.5)** | **16.8 months (14.1–19.5)** | **0.69 (0.55–0.86)** |

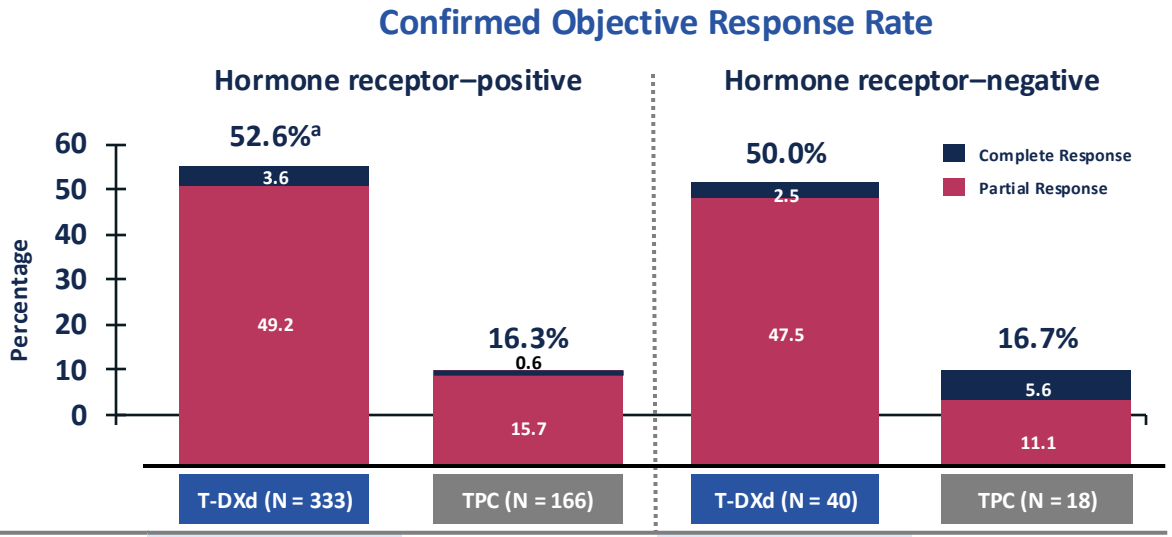



## Primary Analysis (BICR)

| OS | HR+ | | HR- | | All Patients | |
|---|---|---|---|---|---|---|
| | T-DXd (N = 331) | TPC (N = 163) | T-DXd (N = 40) | TPC (N = 18) | T-DXd (N = 373) | TPC (N = 184) |
| Median OS, months | 23.9 | 17.5 | 18.2 | 8.3 | 23.4 | 16.8 |
| HR (95% CI); *p* value | HR, 0.64 (0.48–0.86); *p* = .0028 | | 0.48 (0.24–0.95) | | HR, 0.64 (0.49–0.84); *p* = .0010 | |

Modi S, et al. *N Engl J Med.* 2022; 387(1):9–20. Modi S, et al. ESMO Congress 2023. Abstract 3760.

# Confirmed ORR




| | T-DXd (N = 333) | TPC (N = 166) | T-DXd (N = 40) | TPC (N = 18) |
|---|---|---|---|---|
| Progressive disease, % | 7.8 | 21.1 | 12.5 | 33.3 |
| Not evaluable, % | 4.2 | 12.7 | 7.5 | 5.6 |
| **Clinical benefit rate,[b] %** | 71.2 | 34.3 | 62.5 | 27.8 |
| **Duration of response, months** | 10.7 | 6.8 | 8.6 | 4.9 |

**Hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.**

[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate (CRR), partial response rate (PRR), and more than 6 months' stable disease rate, based on blinded independent central review.

# Updated NCCN guidelines for TNBC

**Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease**

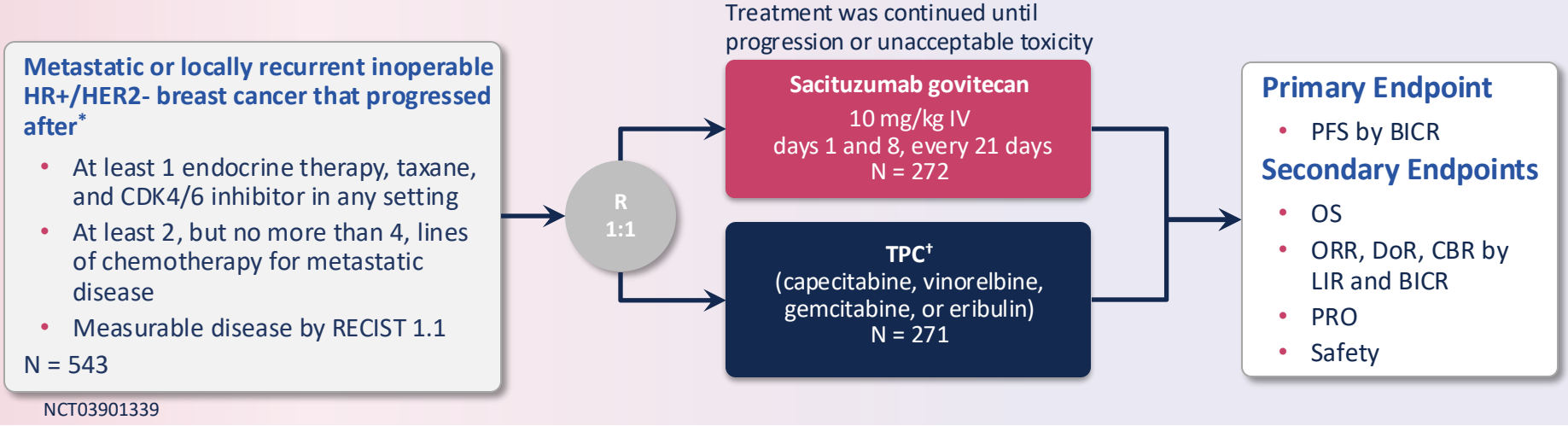
| HR-Negative and HER2-Negative (TNBC) | | |
|---|---|---|
| Setting | Subtype/Biomarker | Regimen |
| First-line | PD-L1 CPS ≥ 10 regardless of germline *BRCA* mutation status | Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin) (Category 1, preferred) |
| | PD-L1 CPS < 10 and no germline *BRCA 1/2* mutation | Systemic chemotherapy see BINV-Q (5) |
| | PD-L1 CPS < 10 and germline *BRCA 1/2* mutation | PARPI (olaparib, talazoparib) (Category 1, preferred)<br>Platinum (cisplatin or carboplatin) (Category 1, preferred) |
| Second-line | Germline *BRCA 1/2* mutation | PARPI (olaparib, talazoparib) (Category 1, preferred) |
| | Any | Sacituzumab govitecan (Category 1, preferred)<br>Systemic chemotherapy see BINV-Q (5) |
| | No germline *BRCA 1/2* mutation and HER2 IHC 1+ or 2+/ISH negative | Fam-trastuzumab deruxtecan-nxki (Category 1, preferred) |
| Third-line and beyond | Biomarker positive (i.e., MSI-H, NTRK, RET, TMB-H) | Targeted agents see BINV-Q (6) |
| | Any | Systemic chemotherapy see BINV-Q (5) |

BINV = invasive breast cancer recommendations; CPS = Combined positive score; ISH = in-situ hybridization; MSI-H = microsatellite instability-high; NTRK = neurotrophic tyrosine receptor kinase; PARPi = poly (ADP-ribose) poly merase inhibitor; RET = rearranged during transfection; TMB-H = tumor mutation burden-high.

National Comprehensive Cancer Network [NCCN]. NCCN website. 2024. https://www.nccn.org/professionals/physician_gls/pdf/breastpdf.

# TROPiCS-02

## *A Phase 3 Study of SG in Pre-treated HR+/HER2- (IHC 0, IHC 1+, IHC 2+/ISH-) Locally Recurrent Inoperable or Metastatic Breast Cancer*




### Stratification Factors

- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥ 6 months (yes/no)
- Prior lines of chemotherapies (2 vs. 3/4)

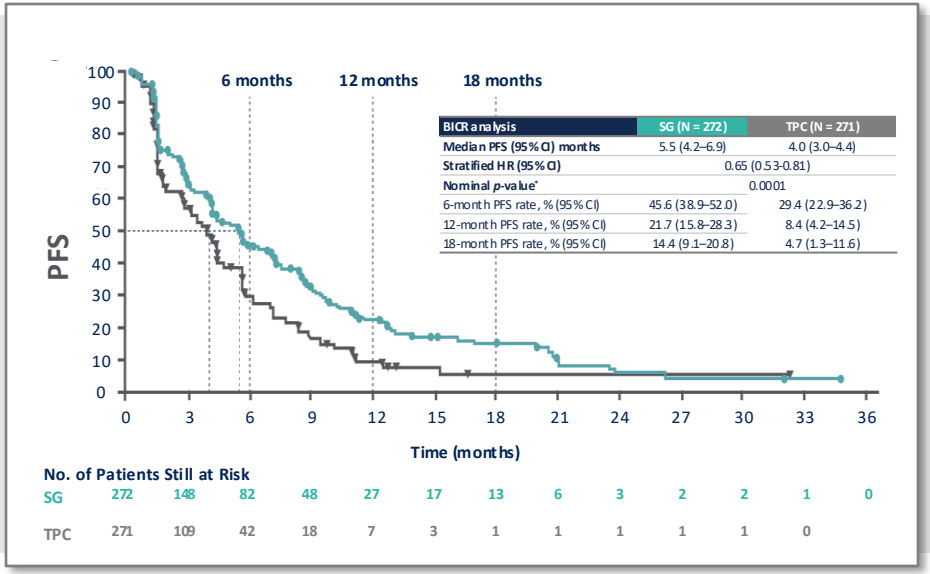
*Disease histology based on the ASCO/CAP criteria. †Single-agent SoC TPC was specified prior to randomization by the investigator.

CBR = clinical benefit rate; LIR = local investigator review; PRO = patient reported outcomes; SoC = standard of care.

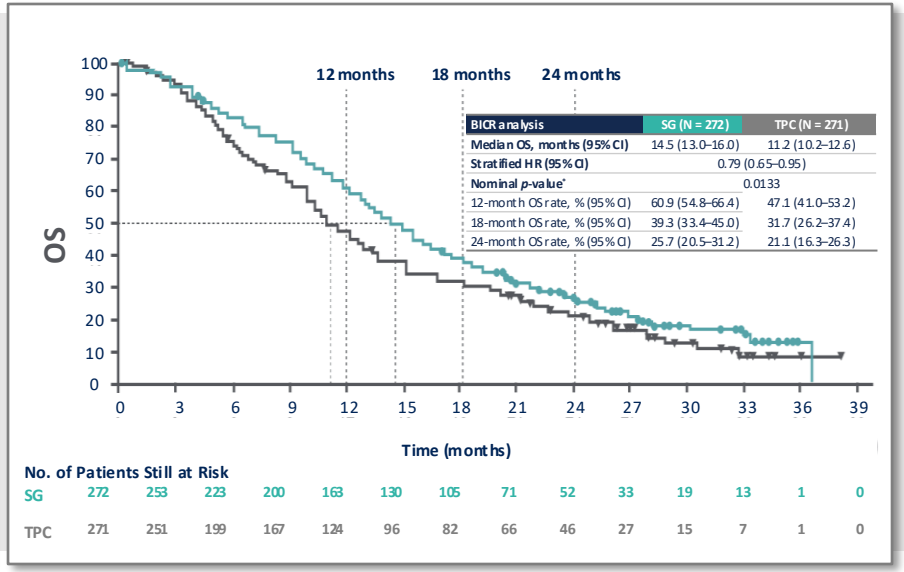
Adapted from Rugo H, et al. ESMO Congress; 2022. Abstract No. LBA76. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2022/overall-survival-os-results-from-the-phase-iii-tropics-02-study-of-sacituzumab-govitecan-sg-vs-treatment-of-physician-s-choice-tpc-in-patient. Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365-3376.

# TROPiCS-02

## *Sacituzumab Govitecan Demonstrated a Statistically Significant and Clinically Meaningful Improvement in PFS and OS vs Chemotherapy, with Continued Improvement Confirmed with Longer Follow-up[1–4]*




| BICR analysis | SG (N = 272) | TPC (N = 271) |
|---|---|---|
| Median PFS (95% CI) months | 5.5 (4.2–6.9) | 4.0 (3.0–4.4) |
| Stratified HR (95% CI) | 0.65 (0.53-0.81) | |
| Nominal *p*-value* | 0.0001 | |
| 6-month PFS rate, % (95% CI) | 45.6 (38.9–52.0) | 29.4 (22.9–36.2) |
| 12-month PFS rate, % (95% CI) | 21.7 (15.8–28.3) | 8.4 (4.2–14.5) |
| 18-month PFS rate, % (95% CI) | 14.4 (9.1–20.8) | 4.7 (1.3–11.6) |

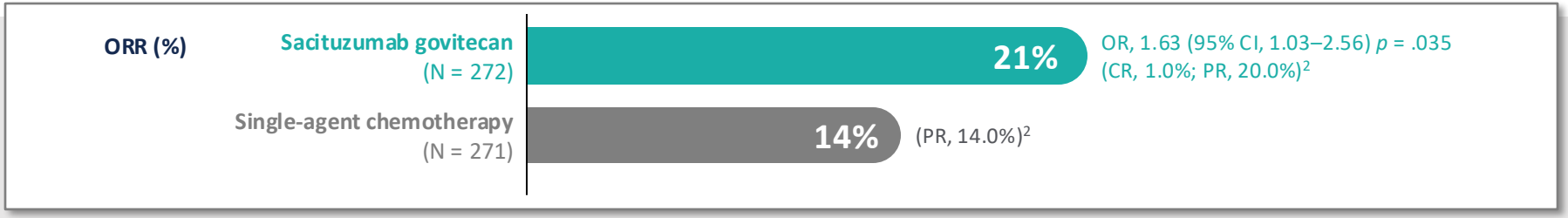



| BICR analysis | SG (N = 272) | TPC (N = 271) |
|---|---|---|
| Median OS, months (95% CI) | 14.5 (13.0–16.0) | 11.2 (10.2–12.6) |
| Stratified HR (95% CI) | 0.79 (0.65–0.95) | |
| Nominal *p*-value* | 0.0133 | |
| 12-month OS rate, % (95% CI) | 60.9 (54.8–66.4) | 47.1 (41.0–53.2) |
| 18-month OS rate, % (95% CI) | 39.3 (33.4–45.0) | 31.7 (26.2–37.4) |
| 24-month OS rate, % (95% CI) | 25.7 (20.5–31.2) | 21.1 (16.3–26.3) |

[1]Adapted from Rugo HS, et al. *J Clin Oncol*. 2022;40:3365–3376. [2]Adapted from Rugo H, et al. ESMO Congress 2022. Abstract LBA76.
[3]Adapted from Rugo H, et al. *Lancet.* 2023;402(10411):1423–1433. [4]Tolaney S, et al. 2023 ASCO Annual Meeting. Abstract 1003.

# TROPiCS-02

## *Sacituzumab Govitecan Significantly Improved ORR[1] and Significantly Extended TTD of Global Health Status and Fatigue vs. TPC[2]*




| TTD | Patients SG/TPC, n/n | SG Median TTD, Months (95% CI) | TPC Median TTD, Months (95% CI) | Stratified HR (95% CI) | Stratified Log Rank *p*-value |
|---|---|---|---|---|---|
| **Global health status QoL** | 234/207 | 4.3 (3.1–5.7) | 3.0 (2.2–3.9) | 0.75 (0.61–0.92) | .006 |
| **Fatigue** | 234/205 | 2.2 (1.6–2.8) | 1.4 (1.1–1.9) | 0.73 (0.60–0.89) | .002 |
| **Pain** | 229/202 | 3.8 (2.8–5.0) | 3.5 (2.8–5.0) | 0.92 (0.75–1.13) | .415 |

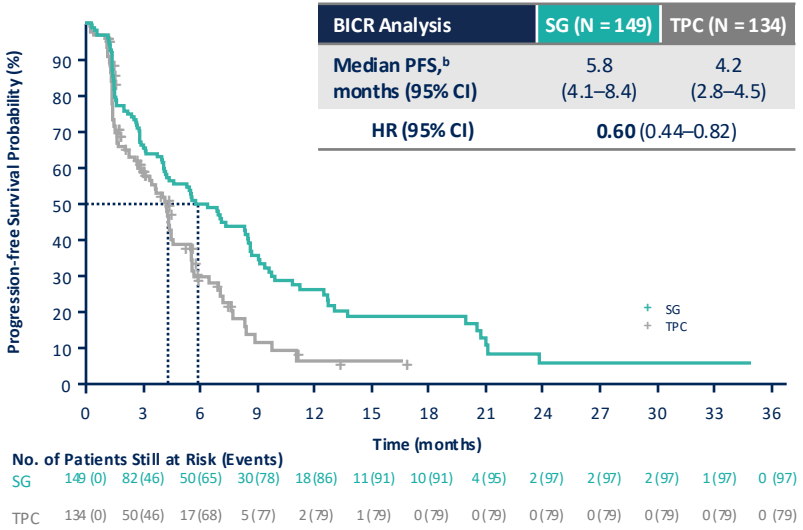
[1]Adapted from Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376. [2]Adapted from Rugo H, et al. *ESMO Open*. 2022;7(4):100553.

CR = complete response; PR = partial response.

# TROPiCS-02

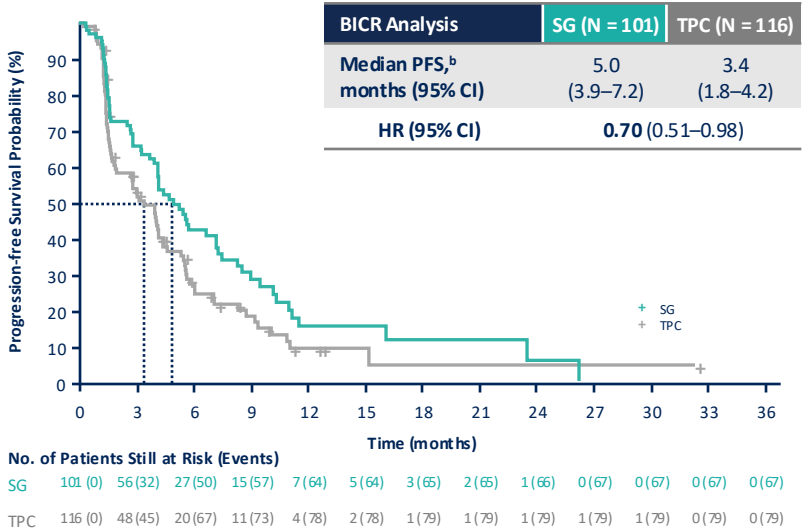
# Progression-free Survival by HER2 IHC Status

## HER2-low (IHC 1+, IHC 2+/ISH negative)[a]




| BICR Analysis | SG (N = 149) | TPC (N = 134) |
|---|---|---|
| Median PFS,[b] months (95% CI) | 5.8 (4.1–8.4) | 4.2 (2.8–4.5) |
| HR (95% CI) | **0.60** (0.44–0.82) | |

## HER2 IHC 0[a]




| BICR Analysis | SG (N = 101) | TPC (N = 116) |
|---|---|---|
| Median PFS,[b] months (95% CI) | 5.0 (3.9–7.2) | 3.4 (1.8–4.2) |
| HR (95% CI) | **0.70** (0.51–0.98) | |

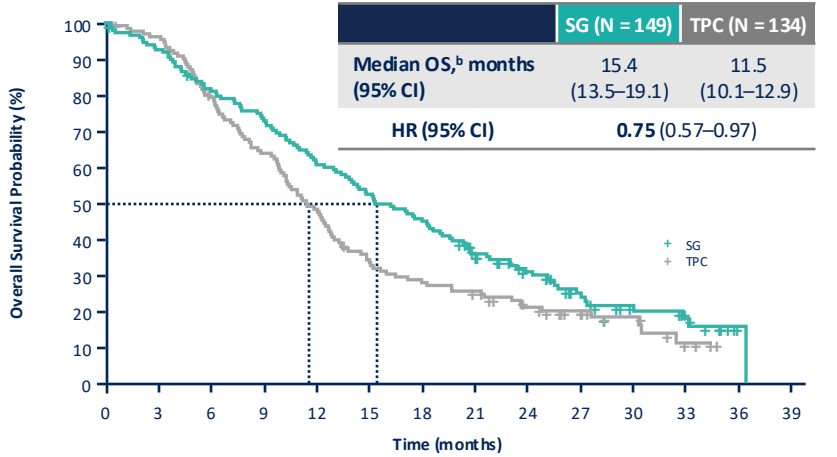
**SG consistently improved PFS vs TPC in the HER2-low (IHC 1+, IHC 2+/ISH negative) and the HER2 IHC 0 groups with longer follow-up, consistent with a previous analysis**

[a]HER2 IHC was determined by local assessment on last available pathology sample; 57% of patients were HER2-low (IHC 1+, IHC 2+/ISH negative) and 43% were HER2 IHC 0. [b]PFS probability was estimated using an unstratified Cox model using treatment (SG vs TPC) as the only predictor.

Schmid P, et al. ESMO Congress 2022. Abstract 214MO. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2022/sacituzumab-govitecan-sg-efficacy-in-hormone-receptor-positive-human-epidermal-growth-factor-receptor-2-negative-hr-her2-metastatic-breast-ca.

# TROPiCS-02
# Overall Survival by HER2 IHC Status

## HER2-low (IHC 1+, IHC 2+/ISH negative)[a]

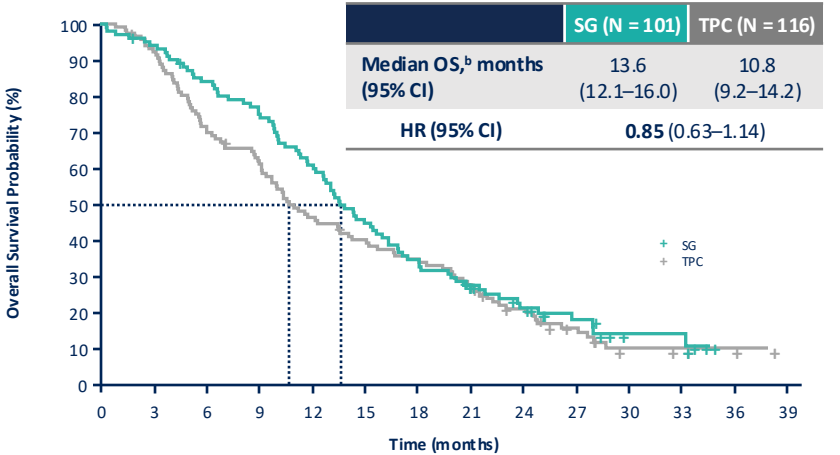



| | SG (N = 149) | TPC (N = 134) |
|---|---|---|
| Median OS,[b] months (95% CI) | 15.4 (13.5–19.1) | 11.5 (10.1–12.9) |
| HR (95% CI) | **0.75** (0.57–0.97) | |

No. of Patients Still at Risk (Events)

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SG | 149 (0) | 137 (11) | 120 (27) | 108 (39) | 91 (56) | 77 (70) | 67 (80) | 46 (94) | 35 (100) | 22 (106) | 14 (109) | 9 (111) | 1 (112) | 0 (113) |
| TPC | 134 (0) | 126 (5) | 102 (27) | 82 (47) | 62 (67) | 43 (85) | 36 (92) | 31 (96) | 22 (101) | 13 (102) | 9 (103) | 3 (106) | 0 (106) | 0 (106) |

## HER2 IHC 0[a]




| | SG (N = 101) | TPC (N = 116) |
|---|---|---|
| Median OS,[b] months (95% CI) | 13.6 (12.1–16.0) | 10.8 (9.2–14.2) |
| HR (95% CI) | **0.85** (0.63–1.14) | |

No. of Patients Still at Risk (Events)

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SG | 101 (0) | 94 (6) | 83 (16) | 76 (23) | 60 (39) | 45 (54) | 34 (65) | 22 (72) | 15 (77) | 10 (79) | 4 (81) | 4 (81) | 0 (82) | 0 (82) |
| TPC | 116 (0) | 107 (8) | 82 (33) | 71 (43) | 52 (62) | 44 (69) | 38 (75) | 29 (83) | 20 (90) | 12 (95) | 5 (99) | 4 (99) | 1 (99) | 0 (99) |

**SG consistently improved OS vs TPC in the HER2-low (IHC 1+, IHC 2+/ISH negative) and the HER2 IHC 0 groups**

[a]HER2 IHC was determined by local assessment on last available pathology sample; 57% of patients were HER2-low (IHC 1+, IHC 2+/ISH negative) and 43% were HER2 IHC 0. [b]OS probability was estimated using an unstratified Cox model using treatment (SG vs TPC) as the only predictor.

Schmid P, et al. ESMO Congress 2022. Abstract 214MO. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2022/sacituzumab-govitecan-sg-efficacy-in-hormone-receptor-positive-human-epidermal-growth-factor-receptor-2-negative-hr-her2-metastatic-breast-ca.

# ASCENT-07

## *A Phase 3, Randomized, Open-label Study of Sacituzumab Govitecan vs. TPC in Patients with HR+/HER2- (IHC 0, IHC 1+, IHC 2+/ISH-) Inoperable, Locally Advanced, or Metastatic BC and Have Received ET*

### Key Eligibility Criteria

- HR+/HER2-, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced or metastatic breast cancer
- No prior treatment with topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Patients must have one of the following
  - Disease progression on ≥ 2 previous lines of ET with or without a targeted therapy in the metastatic setting
    - Disease recurrence while on the first 24 months of starting adjuvant ET will be considered a line of therapy; these patients will only require 1 line of ET in the metastatic setting
  - Disease progression within 6 months of starting first-line ET with or without a CDK4/6i in the metastatic setting
  - Disease recurrence while on the first 24 months of starting adjuvant ET with CDK4/6i and if the patient is no longer a candidate for additional ET in the metastatic setting as determined by the investigator

R

N ~ 654

**SG**
10 mg/kg IV
Days 1 and 8, every 21 days

**TPC**
(capecitabine, paclitaxel, nab-paclitaxel)

### Primary Endpoint

- PFS by BICR

### Key Secondary Endpoints

- OS
- ORR by BICR
- Change from baseline in physical functioning and TTD of Global Health Status

### Secondary Endpoints

- PFS by investigator
- ORR by investigator
- DoR
- Safety

NCT05840211—full participation criteria available at ClinicalTrials.gov

### Stratification Factors

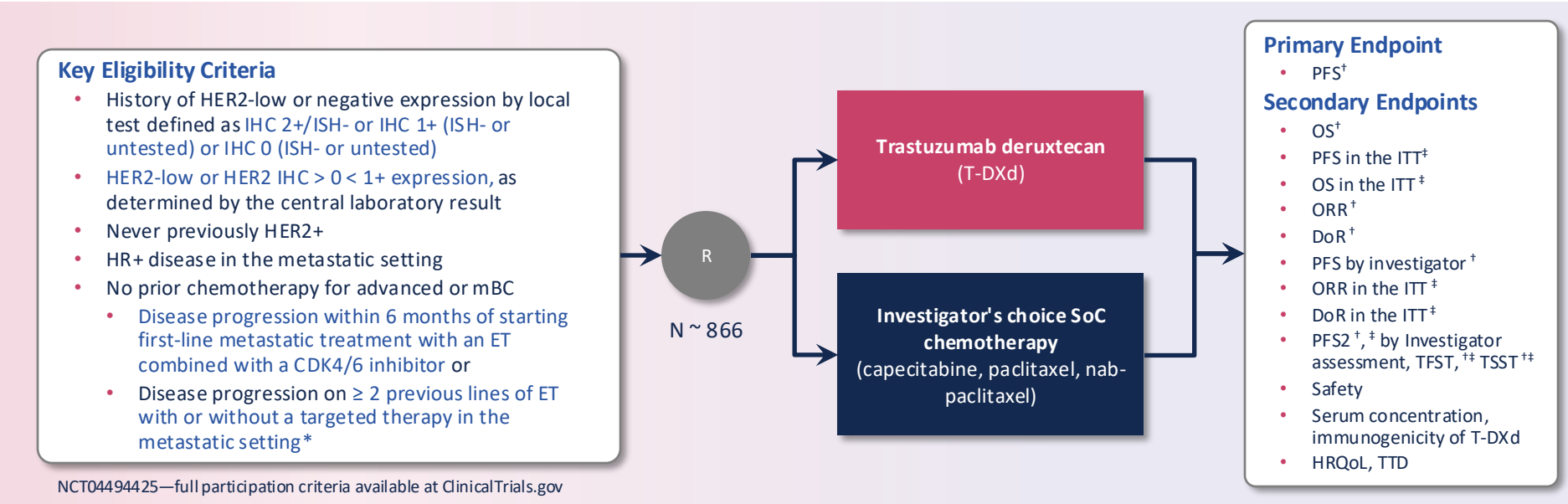
- Duration of prior CDK 4/6i in the metastatic setting (none vs. ≤ 12 months vs. > 12 months)
- HER2 (HER2 IHC 0 vs. HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/UK/EU vs. ROW)

Gilead Sciences. Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Patients With Hormone Receptor-positive/Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2-) Metastatic Breast Cancer Who Have Received Endocrine Therapy (ASCENT-07). Clinical Trials.gov. Identifier: NCT05840211. https://classic.clinicaltrials.gov/ct2/show/NCT05840211.

ROW = rest of world.

# DESTINY-BREAST06 (Phase 3)

## *Trastuzumab Deruxtecan vs. TPC in HR+/HER2-low (IHC 1+, IHC 2+/ISH-) or HER2 IHC > 0 < 1+ mBC*




*Of note with regards to the ≥ 2 lines of previous ET requirement: disease recurrence while on the first 24 months of starting adjuvant ET, will be considered a line of therapy; these patients will only require first line of ET in the metastatic setting.

†In HR+/HER2-low (IHC 2+/ISH- or IHC 1+ [ISH- or untested]).

‡HER2-low (IHC 2+/ISH- or IHC 1+ [ISH- or untested] or HER2 IHC >0 <1+).

HRQoL = health-related quality of life; TFST = time to first subsequent therapy; TSST = time to second subsequent treatment or death; TTD = time to deterioration.

# DESTINY-BREAST06 (Phase 3) Ongoing

## *T-DXd vs TPC in HR+/HER2-low (IHC 1+, IHC 2+/ISH Negative) or HER2 IHC > 0 <1+ mBC*

| | T-DXd, HER2-low (N = 359) | TPC, HER2-low (N = 354) | T-DXd, ITT (N = 436) | TPC, ITT (N = 430) | T-DXd, HER2-ultralow (N = 76) | TPC, HER2-ultralow (N = 76) |
|---|---|---|---|---|---|---|
| mPFS (95% CI), mo | 13.2 (11.4, 15.2) | 8.1 (7.0, 9.0) | 13.2 (12.0, 15.2) | 8.1 (7.0, 9.0) | 13.2 (9.8, 17.3) | 8.3 (5.8, 15.2) |
| HR (95% CI), *p* value | 0.62 (0.51, 0.74), < .0001 | | 0.63 (0.53, 0.75), < .0001 | | 0.78 (0.50, 1.21) | |
| 12-mo OS rate, % | 87.6 | 81.7 | 87 | 81.1 | 84 | 78.7 |
| HR (95% CI), *p* value | 0.83 (0.66, 1.05), 0.1181 | | 0.81 (0.65, 1.00) | | 0.75 (0.43, 1.29) | |
| Confirmed ORR, % | 56.5 (51.2, 61.7) | 32.2 (27.4, 37.3) | 57.3 (52.5, 62.0) | 31.2 (26.8, 35.8) | 61.8 (50.0, 72.8) | 26.3 (16.9, 37.7) |

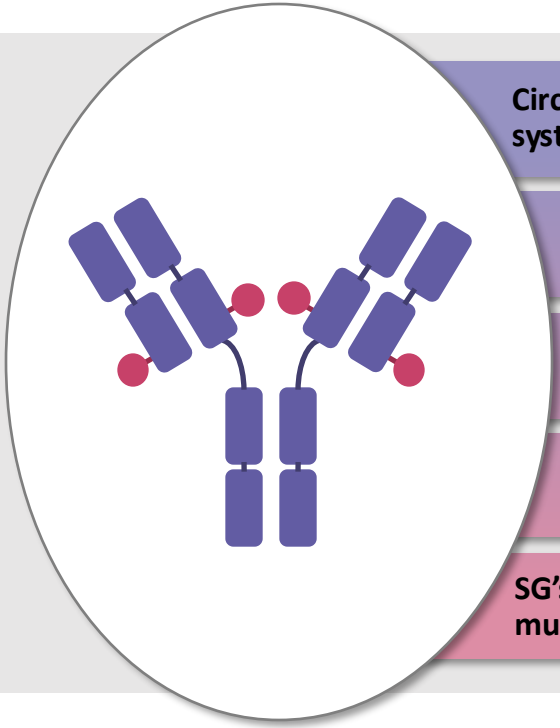
# Updated NCCN guidelines HR+HER2-neg

**Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease**

| HR-Positive and HER2-Negative With Visceral Crisis or Endocrine Refractory | | |
|---|---|---|
| Setting | Subtype/Biomarker | Regimen |
| First-line | No germline *BRCA 1/2* mutation | Systemic chemotherapy see BINV-Q (5) |
| | Germline *BRCA 1/2* mutation | PARPI (olaparib, talazoparib) (Category 1, preferred) |
| Second-line | HER2 IHC 1+ or 2+/ISH negative | Fam-trastuzumab deruxtecan-nxki (Category 1, preferred) |
| | Not a candidate for fam-trastuzumab deruxtecan-nxki | Sacituzumab govitecan (Category 1, preferred)<br>Systemic chemotherapy see BINV-Q (5) |
| Third-line and beyond | Any | Systemic chemotherapy see BINV-Q (5) |
| | Biomarker positive (i.e., MSI-H, NTRK, RET, TMB-H) | Targeted agents see BINV-Q (6) |

National Comprehensive Cancer Network [NCCN]. NCCN website. 2024. https://www.nccn.org/professionals/physician_gls/pdf/breastpdf.

# Datopotamab Deruxtecan (Dato-DXd)
## *TROP2 ADC in Development*



- Circulating free payload is negligible due to high stability of the linker, thereby limiting systemic exposure or nontargeted delivery of the payload
- High-potency membrane-permeable payload (DXd) that requires TROP2-mediated internalization for release
- DS-1062 has a DAR of 4 for optimized therapeutic index
- DS-1062 has a substantially longer half-life than SG (≈ 5 days vs. 11–14 hours), enabling a more optimal dosing regimen
- SG's DLT is neutropenia, while DS-1062's DLTs are maculopapular rash and stomatitis/ mucosal inflammation

DLT= dose limiting toxicities.

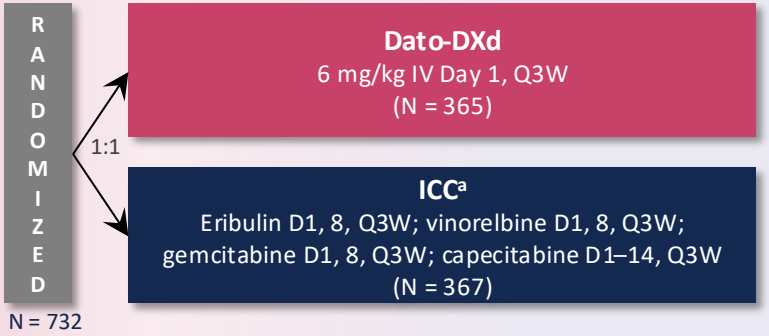
Bardia A, et al. *J Clin Oncol.* 2017;35(19):2141-2148. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-22512. Lisberg AE, et al. ASCO Virtual Scientific Program. 2020. Abstract No. 9619. https://meetings.asco.org/abstracts-presentations/184866. Ocean AJ, et al. *Cancer*. 2017;123:3843-3854. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108.

# TROPION-Breast01 Phase 3 Trial of Dato-DXd vs. CT in HR+/HER2- Metastatic BC

## *Study Design and Patients*

**Key Eligibility Criteria**

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




**Dual primary endpoints:** PFS by BICR per RECIST v1.1, and OS
**Secondary endpoints:** ORR, PFS by investigator, safety

| Patient Characteristics, n (%) | | Dato-DXd (N = 365)[b] | ICC (N = 367)[c] |
|---|---|---|---|
| Median age (range), years | | 56 (29–86) | 54 (28–86) |
| Race | Black or African American | 4 (1) | 7 (2) |
| | Asian | 146 (40) | 152 (41) |
| | White | 180 (49) | 170 (46) |
| | Other | 35 (10) | 38 (10) |
| Ethnicity | Hispanic or Latino | 40 (11) | 43 (12) |
| | Not Hispanic or Latino | 322 (88) | 318 (87) |
| Prior lines of CT | 1 | 229 (63) | 225 (61) |
| | 2 | 135 (37) | 141 (38) |
| Prior CDK4/6i | | 288 (82) | 286 (78) |
| Prior taxane and/or anthracycline | | 330 (90) | 339 (92) |

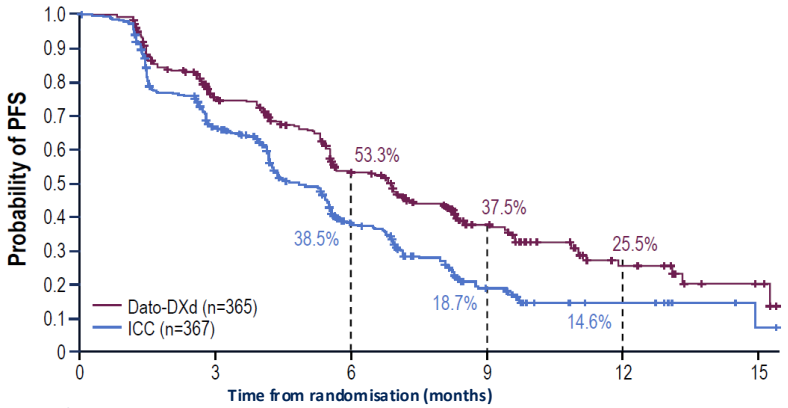
[a]Investigator's choice of chemotherapy (ICC) was administered as follows: eribulin, 1.4 mg/kg IV on D1, 8, Q3W; vinorelbine, 25 mg/m$^2$ IV on D1, 8, Q3W; gemcitabine 1,000 mg/m$^2$ IV on D1, 8, Q3W; capecitabine 1,000 or 1,250 mg/m$^2$ (dose per standard institutional practice) orally twice daily D1–14, Q3W.
[b]360 patients received treatment with Dato-DXd. [c] 351 received treatment with ICC: eribulin (N = 220); vinorelbine (N = 38); capecitabine (N = 76); gemcitabine (N = 33).

Bardia A, et al. ESMO Congress 2023. Abstract No. LBA11. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2023/datopotamab-deruxtecan-dato-dxd-vs-chemotherapy-in-previously-treated-inoperable-or-metastatic-hormone-receptor-positive-her2-negative-hr-her2.

# TROPION-Breast01 Phase 3 Trial of Dato-DXd vs. CT in HR+/HER2- Metastatic BC

## *PFS by BICR*

### PFS by BICR: Primary Endpoint

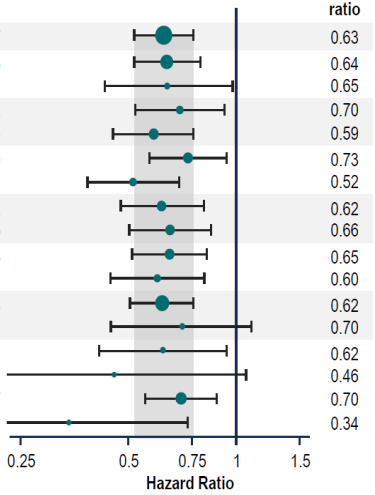



Number at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Dato-DXd | 365 | 249 | 158 | 66 | 15 | 4 |
| ICC | 367 | 205 | 93 | 26 | 8 | 1 |

### PFS by BICR across Subgroups

| | | Events/n Dato-DXd | Events/n ICC | Hazard ratio |
|---|---|---|---|---|
| All patients | | 212/365 | 235/367 | 0.63 |
| Age at randomisation | <65 years | 163/274 | 190/295 | 0.64 |
| | ≥65 years | 49/91 | 45/72 | 0.65 |
| Race | Asian | 88/146 | 101/152 | 0.70 |
| | Non-Asian | 109/187 | 119/183 | 0.59 |
| ECOG performance status | 0 | 119/197 | 136/220 | 0.73 |
| | 1 | 91/165 | 98/145 | 0.52 |
| Geographic region | US, Canada, Europe | 110/186 | 112/182 | 0.62 |
| | Rest of World* | 102/179 | 123/185 | 0.66 |
| Number of previous lines of chemotherapy | 1 | 128/229 | 145/225 | 0.65 |
| | 2 | 84/135 | 90/141 | 0.60 |
| Prior use of CDK4/6 inhibitor | Yes | 177/299 | 190/286 | 0.62 |
| | No | 35/66 | 45/81 | 0.70 |
| Prior use of taxane and/or anthracycline | Taxane alone | 48/80 | 47/71 | 0.62 |
| | Anthracycline alone | 9/14 | 16/21 | 0.46 |
| | Both taxane and anthracycline | 141/236 | 155/247 | 0.70 |
| | Neither taxane nor anthracycline | 14/35 | 17/28 | 0.34 |




| PFS by BICR | Dato-DXd (N = 365) | ICC (N = 367) |
|---|---|---|
| Median PFS, months (95% CI) | 6.9 (5.7–7.4) | 4.9 (4.2–5.5) |
| HR (95% CI) | 0.63 (0.52–0.76) | |
| *p* | < .0001 | |

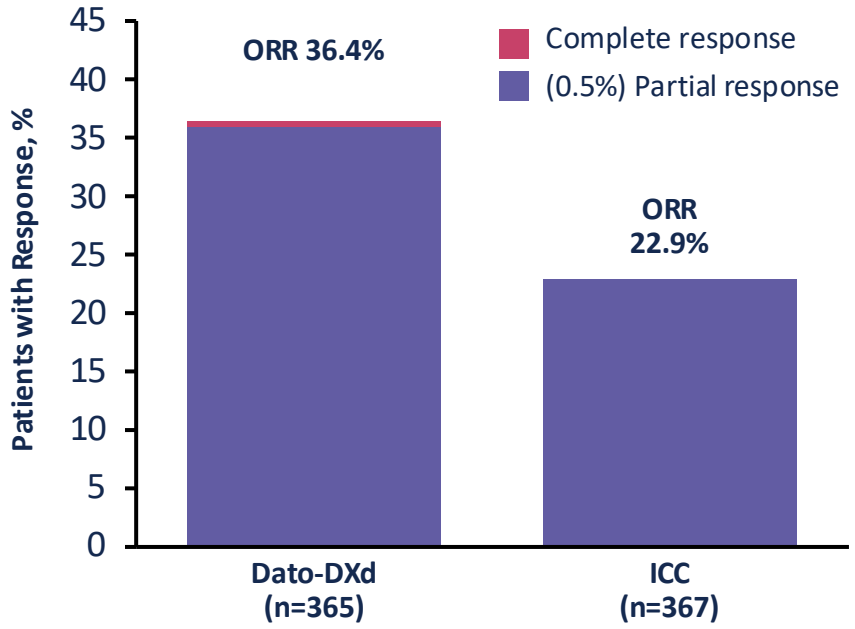
- Median study follow-up: 10.8 months
- Median PFS by investigator: 6.9 vs. 4.5 months; HR, 0.64 (95% CI, 0.53–0.76)

Bardia A, et al. ESMO Congress 2023. Abstract No. LBA11. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2023/datopotamab-deruxtecan-dato-dxd-vs-chemotherapy-in-previously-treated-inoperable-or-metastatic-hormone-receptor-positive-her2-negative-hr-her2.

# TROPION-Breast01

## Response and Interim OS

### Response Rate




### OS: Dual Primary Endpoint

- OS data not mature*
  - Median follow-up 9.7 months
- A trend favoring Dato-DXd was observed
  - HR, 0.84 (95% CI, 0.62–1.14)
- However, a September 23, 2024 press release indicated that the trial, "did not achieve statistical significance in the final OS analysis"

*Information fraction: 39%

ORR = confirmed objective response rate by BICR.


Bardia A, et al. ESMO Congress 2023. Abstract LBA11. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2023/datopotamab-deruxtecan-dato-dxd-vs-chemotherapy-in-previously-treated-inoperable-or-metastatic-hormone-receptor-positive-her2-negative-hr-her2.

AstraZeneca. AstraZeneca Website. 2024. https://www.astrazeneca.com/media-centre/press-releases/2024/datopotamab-deruxtecan-final-overall-survival-results-reported-in-patients-with-metastatic-hr-positive-her2-low-or-negative-breast-cancer-in-tropion-breast01-phase-iii-trial.html.

# TROPION-Breast01

## TRAEs Occurring in ≥ 15% of Patients and AESIs

| System Organ Class<br>Preferred term, n (%) | Dato-DXd (N = 360) | | ICC (N = 351) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥ 3 | Any Grade | Grade ≥ 3 |
| **Blood and lymphatic system** | | | | |
| Anaemia | 40 (11) | 4 (1) | 69 (20) | 7 (2) |
| Neutropenia | 39 (11) | 4 (1) | 149 (42) | 108 (31) |
| **Eye** | | | | |
| Dry eye | 78 (22) | 2 (1) | 27 (8) | 0 |
| **Gastrointestinal** | | | | |
| 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 |
| **General** | | | | |
| Fatigue | 85 (24) | 6 (2) | 64 (18) | 7 (2) |
| **Skin and subcutaneous** | | | | |
| Alopecia | 131 (36) | 0 | 72 (21) | 0 |

- Most TRAEs were grade 1–2 and manageable

**AESIs**

- Oral mucositis/stomatitis[†]: led to treatment discontinuation in one patient in the Dato-DXd group
- Ocular events[‡]: most were dry eye; one patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD[§]: rate was low; mainly grade 1/2

| Adjudicated Drug-related ILD | Dato-DXd | ICC |
|---|---|---|
| All grades, n (%) | 9 (3) | 0 |
| Grade ≥ 3, n (%) | 2 (1)[¶] | 0 |

[†]Oral mucositis/stomatitis events included PTs of aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis, tongue ulceration; all grade: 59% with Dato-DXd, 17% with ICC; grade 3: 7% with Dato-DXd, 3% with ICC.
[‡]Ophthalmologic assessments were required at screening, and then every 3 cycles from C1D1 and at end of therapy; ocular events included selected PTs from Corneal Disorder SMQ and select relevant PTs from Eye Disorder SOC; all grade: 49% with Dato-DXd, 23% with ICC; grade 3: 1% with Dato-DXd (one patient with dry eye, one patient with punctate keratitis, and one patient with dry eye and ulcerative keratitis), 0% with ICC. [§]ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or ICC (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure).
[¶]One adjudicated drug-related grade 5 ILD event: attributed to disease progression by investigator.

AESIs = adverse events of special interest; ILD = interstitial lung disease; PTs = preferred terms; SMQ = standard MedDRA query; SOC = system organ class; TRAEs = treatment-related adverse events.

Bardia A, et al. ESMO Congress 2023. Abstract LBA11. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2023/datopotamab-deruxtecan-dato-dxd-vs-chemotherapy-in-previously-treated-inoperable-or-metastatic-hormone-receptor-positive-her2-negative-hr-her2.

# Dato-DXd vs. Chemo in First-line Metastatic TNBC Not Candidate for Anti–PD-(L)1 Therapy

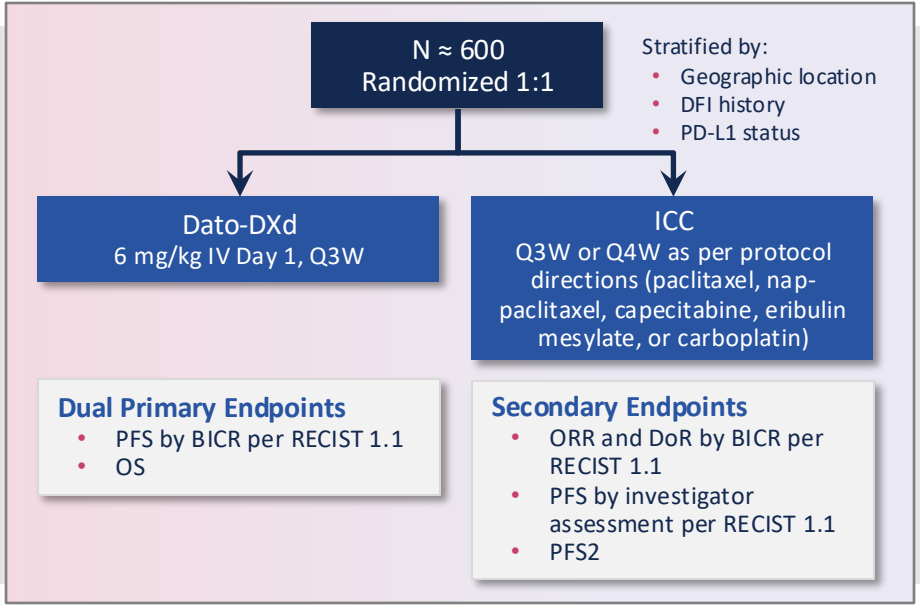
## *TROPION-Breast02 Study*

**Study Design**

TROPION-Breast02 is a phase 3, open-label, randomized study of first-line Dato-DXd vs. chemotherapy in patients with locally recurrent inoperable or metastatic TNBC who are not candidates for anti–PD-(L)1 therapy

### Key Inclusion Criteria

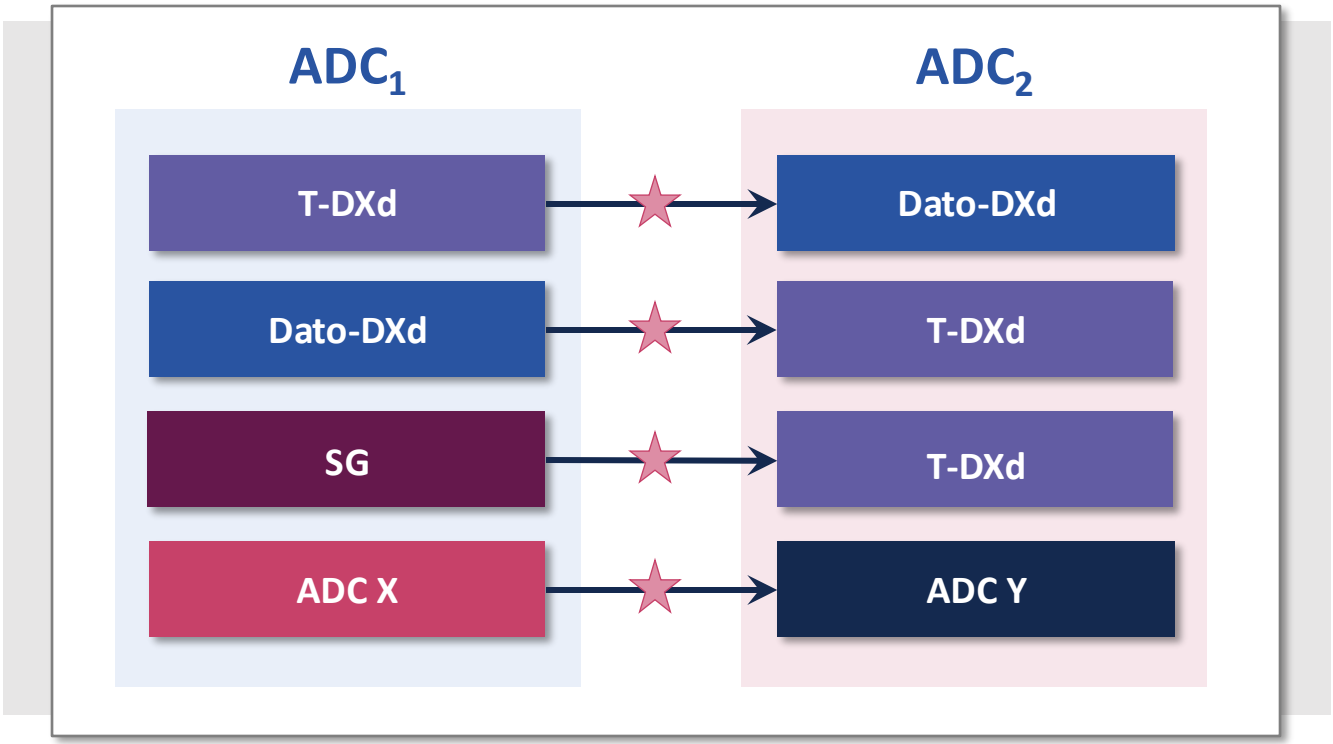
- Adults with histologically or cytologically documented **locally recurrent inoperable or metastatic TNBC**
- **No prior chemotherapy or targeted systemic therapy for locally recurrent inoperable or mBC**
- At least one measurable lesion (≥ 10 mm) per RECIST 1.1 that has not been previously irradiated
- **ECOG PS of 0 or 1**
- A recent (≤ 3 months prior to screening) formalin-fixed, paraffin-embedded metastatic (excluding bone) or locally recurrent inoperable tumor sample
- **Not a candidate for PD-(L)1 inhibitor therapy,** defined as
  - Patients whose tumors are PD-L1–negative, or
  - Patients whose tumors are PD-L1–positive, but have
    - Relapsed after prior PD-(L)1 inhibitor therapy for early-stage BC
    - Comorbidities precluding PD-(L)1 inhibitor therapy, or
    - No regulatory access to PD-(L)1 inhibitor therapy
- Eligible for one of the listed ICCs (i.e., paclitaxel, nab-paclitaxel, capecitabine, carboplatin, or eribulin mesylate)




Dent R, et al. San Antonio Breast Cancer Symposium. 2022. Abstract No. OT1-03-05.
https://www.sabcs.org/Portals/SABCS2016/2022%20SABCS/SABCS%202022%20Abstract%20Report.pdf?ver=2022-12-08-111637-860.

# Critical Question

## *How will ADCs work in sequence?*



# TReatment of ADC-refractory Breast CancEr with Dato-DXd or T-DXd (TRADE-DXd)

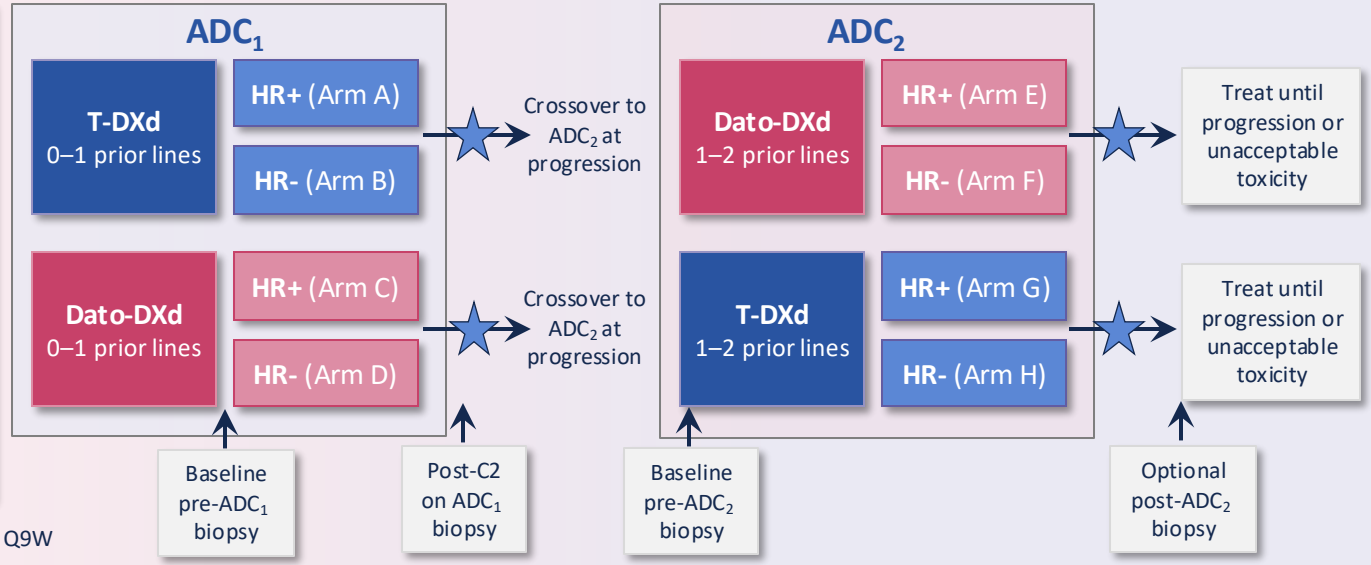
Same payload, different MAb target

**Primary Endpoint ($ADC_1$, $ADC_2$):** ORR
**Secondary Endpoints:** PFS, OS, CBR, TTOR, DoR

## Eligibility

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low breast cancer (any prior primary or metastatic tumor) defined as IHC 1+ or 2+/ISH non-amplified
- Most recent pathology: HER2 IHC 0 or HER2-low
- Measurable disease
- No prior topo-I inhibitor-based therapy

★ Tumor assessments + blood collection Q9W




*Patients who received T-DXd/Dato-DXd as $ADC_1$ off-study allowed to enroll on $ADC_2$ cohorts

Allocation 1:1 to T-DXd **or** Dato-DXd as $ADC_1$

# Management of AEs in ADC Therapy

# Safety of Sacituzumab Govitecan

- ASCENT: safety of sacituzumab govitecan in second line and later mTNBC
  - Most common grade 3/4 adverse events (AEs) with SG
    - Neutropenia (51%)
    - Leukopenia (10%)
    - Diarrhea (10%)
    - Anemia (8%)
    - Febrile neutropenia (6%)
  - There were 3 deaths related to AEs in each group; no deaths were considered a result of SG
- TROPiCS-02: safety of SG in HR+, HER2-low mBC
  - Most common grade 3/4 AEs with SG
    - Neutropenia (51%)
    - Diarrhea (9%)
  - There was 1 treatment-related death in the SG arm

Chemotherapy comparators: eribulin (54%), vinorelbine (20%), capecitabine (13%), and gemcitabine (12%).

Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541. Rugo HS, et al. *NPJ Breast Cancer*. 2022;8(1):98. Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376.

# Sacituzumab Govitecan for Breast Cancer

## BOXED WARNINGS

- Neutropenia: severe, possibly life-threatening
- Diarrhea: may be severe and lead to dehydration

### AEs of Special Concern

- Hypersensitivity and infusion-related reactions
- Nausea and vomiting
- Increased risk of adverse reactions in patients with reduced UGT1A1 activity
- Embryo-fetal harm

### Hematologic

- Neutropenia (63%)
- Anemia (34%)

### Other

- Fatigue (45%)
- Alopecia (46%)

### Gastrointestinal

- Diarrhea (59%)
- Nausea (57%)
- Vomiting (29%)
- Constipation (17%)
- Abdominal pain (11%)

Trodelvy® (sacituzumab govitecan-hziy)[package insert]. Foster City, CA: Gilead Sciences, Inc. Revised 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761115s035lbl.pdf.

# ASCENT and TROPiCS-02
## *Safety Outcomes by UGT1A1 Status*

### UGT1A1

- Variants affect enzymatic function, causing reduced metabolic capacity
- Over 50% of individuals may harbor a UGT1A1 polymorphism dependent on genetic ancestry

| Grade ≥3 TEAEs Overall (%) | SG (n=268) |
|---|---|
| **Neutropenia** | 52 |
| **Diarrhea** | 10 |
| **Anemia** | 8 |
| **Febrile neutropenia** | 6 |

| | ASCENT | | TROPiCS-02 | |
|---|---|---|---|---|
| SG patients (n=250) | UGT1A1 Status n(%) | Dose Intensity (%) | UGT1A1 Status n(%) | Dose Intensity (%) |
| ***1/*1 (wt)** | 113 (44) | 99.8 | 104 (38) | 99 |
| ***1/*28** | 96 (37) | 99.5 | 119 (44) | 98 |
| ***28/*28** | 34 (13) | 99.8 | 25 (9) | 94 |

| | ASCENT | | | TROPiCS-02 | | |
|---|---|---|---|---|---|---|
| Grade ≥3 TEAEs By UGT1A1 Status (%) | *1/*1 (wt) | *1/*28 | *28/*28 | *1/*1 (wt) | *1/*28 | *28/*28 |
| **Neutropenia** | 53 | 47 | 59 | 45 | 57 | 64 |
| **Diarrhea** | 10 | 9 | 15 | 6 | 13 | 24 |
| **Anemia** | 4 | 6 | 15 | 6 | 8 | 8 |
| **Febrile neutropenia** | 3 | 5 | 18 | 6 | 7 | 4 |
| **Growth factor for neutropenia (initiated on/after first dose) overall 54%** | | | | | | |
| | | | | 33 | 49 | 11 |

ASCENT: Treatment discontinuation due to TRAEs more common in *28 homozygous genotype

Nelson RS, et al. *Cancers (Basel).* 2021;13(7):1566. Rugo, HS, et al. *NPJ Breast Cancer.* 2022;8(1):98.
Marmé, F, et al. *Ann Oncol.* 2023;8(1suppl_4):101223–101223. Rugo HS, et al. *Lancet.* 2023;402(10411):1423–1433.

# Management of Neutropenia

## Sacituzumab Govitecan in Breast Cancer

- Primary prophylaxis with G-CSF was not used in clinical trials
- Monitor complete blood counts prior to each treatment (Days 1 and 8)
- Hold treatment for ANC < 1,500/µL on Day 1 of any cycle or ANC < 1,000/µL on Day 8; or with neutropenic fever; resume when recovered
- Dose reductions are indicated for severe neutropenia

**First occurrence:** 75% original dose (7.5 mg/kg)

**Second occurrence:** 50% original dose (5 mg/kg)

**Third occurrence:** discontinue

Spring LM, et al. *Ann Oncol.* 2024;35(3):293-301. Trodelvy® (sacituzumab govitecan-hziy) [package insert]. Foster City, CA: Gilead Sciences, Inc. Revised 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761115s035lbl.pdf.

ANC = absolute neutrophil count;
G-CSF = granulocyte colony-stimulating factor.

# Assessing and Grading GI Toxicities

| GI disorder | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Nausea | Loss of appetite without changes in eating habits | Decreased oral intake without weight loss, dehydration, or malnutrition | Inadequate calorie or fluid intake, or tube feeding, TPN, or hospitalization indicated | — | — |
| Vomiting | No intervention indicated | Intervention needed: outpatient IV hydration or antiemetics | Tube feeding, TPN, or hospitalization needed | Life-threatening | Death |
| Diarrhea | Increase of 4 stools/day above baseline, or mild increase in ostomy output | Increase of 4-6 stools/day above baseline, or moderate ostomy output, or limiting instrumental ADLs | Increase of ≥ 7 stools/day above baseline, or severe increase in ostomy output, or limiting self-care ADLs, or hospitalization indicated | Life-threatening, or urgent intervention needed | Death |
| Constipation | Occasional or intermittent, or occasional/intermittent use of laxatives, stool softeners, diet modification, or enema | Persistent symptoms, or regular use of laxatives or enema, or limiting instrumental ADLs | Obstipation with manual evacuation indicated, or limiting self-care ADL | Life-threatening, or urgent intervention required | Death |

National Cancer Institute. National Cancer Institute Website. 2023. https://www.cancer.gov/about-cancer/treatment/side-effects/constipation/gi-complications-hp-pdq# 119.

# Management of Diarrhea

## Sacituzumab Govitecan in Breast Cancer

*Acute or early cholinergic syndrome*

- During or shortly after infusion
- Signs/symptoms: abdominal cramping, sweating, diarrhea, excess salivation
- Give atropine 0.4 mg IV every 15 minutes ×2 doses, if needed; then 0.2 mg IV for total of 1 mg
- Use atropine prophylactically in future cycles

*Delayed (effect of SN-38)*

- Rule out infection
- If negative, start loperamide 4 mg PO after first loose stool, followed by 2 mg PO after each subsequent loose stool (total daily dose 16 mg); discontinue 12 hours after last loose stool
- High dose: 4 mg PO ×1, followed by 2 mg PO every 2 hours
- Octreotide or oral atropine if needed
- Replace fluid and electrolytes as needed

Benson AB, et al. *J Clin Oncol*. 2004;22(14):2918–2926. Spring LM, et al. *Ann Oncol.* 2024;35(3):293–301.

PO = by mouth.

# Management of Severe Diarrhea

## Sacituzumab Govitecan in Breast Cancer

- Grade ≥ 3 OR grade 1/2 progressing to grade 3/4
  - Consider hospital admission
  - Intravenous fluids
  - Octreotide 100–150 μg TID
  - Consider antibiotics as appropriate
- Hold treatment until symptoms resolve to grade ≤ 1, then resume with 1 level dose reduction

Adams, E. et al. *ESMO Open*. 2021;6(4):100204. Spring LM, et al. *Ann Oncol*. 2024;35(3):293-301.

TID = three times daily.

# Nausea and Alopecia

## Sacituzumab Govitecan in Breast Cancer

*Nausea—moderately emetogenic (30%–90% risk of emesis)*

- Often occurs > 3 weeks after treatment started
- Follow NCCN guidelines for CINV
- 5-HT3 antagonist + dexamethasone on Day 1
- Consider adding NK-1 antagonist for high-risk or refractory CINV
- Provide patients with antiemetics for home

*Alopecia*

- Educate patients
- Scalp cooling has not been studied; may not be financially feasible given SG dosing schedule

National Comprehensive Cancer Network [NCCN]. NCCN website. 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
Spring LM, et al. *Ann Oncol*. 2024;35(3):293-301.

CINV = chemotherapy-induced nausea and vomiting; NK-1 = neurokinin 1.

# Trastuzumab Deruxtecan for Breast Cancer

## BOXED WARNINGS

- Interstitial lung disease/pneumonitis: severe, possibly life-threatening
- Embryo-fetal harm

### AEs of Special Concern

- Neutropenia/febrile neutropenia
- Left ventricular dysfunction

### Hematologic

- Neutropenia (70%)
- Anemia (33%)

### Other

- Fatigue (49%)
- Alopecia (37%)

### Gastrointestinal

- Nausea (76%)
- Vomiting (49%)
- Constipation (34%)
- Diarrhea (29%)
- Abdominal pain (21%)

Trodelvy® (sacituzumab govitecan-hziy) [package insert]. Foster City, CA: Gilead Sciences, Inc.; Revised 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761115s035lbl.pdf.

# Interstitial Lung Disease/Pneumonitis

- T-DXd is approved for the treatment of HER2+ and HER2-low[a] mBC, HER2+ mGC/GEJA, HER2 (ERBB2)-mutant NSCLC, and HER2+ (IHC 3+) solid tumors[b,1]
- ILD has been identified as an AE of special interest with T-DXd treatment[2–4]
- Incidence of ILD with T-DXd treatment is reported at ~15% across all indications; most of these ILD events are low-grade, being reported as either Grade 1 (27%) or Grade 2 (50%),[4] but ILD can be fatal if not appropriately managed
  - Current toxicity management guidelines require T-DXd be withheld upon development of suspected Grade 1 ILD and treatment with T-DXd can be resumed following full recovery from ILD[c]; systemic steroid therapy for Grade 1 ILD can be initiated per investigator judgement[d,4]
  - Upon development of Grade ≥2 ILD T-DXd must be discontinued, and systemic steroid therapy is indicated[4]

[a]Defined as IHC 1+/2+ with ISH not-amplified. [b]For patients who have received systemic treatment and have no satisfactory alternative treatment options. [c]If ILD has not resolved within 18 weeks (126 days) of the last T-DXd dose then T-DXd should be discontinued; if ILD resolves in ≤28 days from onset T-DXd dose can be maintained. [d]Asymptomatic ILD should still be considered Gr 1 even if steroid therapy is administered.

[1]Enhertu® (fam-trastuzumab deruxtecan-nxki) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf. [2]Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378. [3]Powell CA, et al. *ESMO Open*. 2022;7(4):100554. [4]Rugo HS, et al. *ESMO Open*. 2022;7(4):100553.

mGC/GEJA = metastatic gastric cancer/gastroesophageal junction adenocarcinoma; NSCLC = non–small cell lung cancer.

# Trastuzumab Deruxtecan Can Only Be Restarted following a Confirmed and Resolved (Grade 0) Case of Grade 1 ILD/Pneumonitis

| Severity | Grade 1 | Grade 2-4 |
|---|---|---|
| | **Guidelines suggest:** manage and treat the ILD/pneumonitis jointly with an MDT and involve a pulmonologist early | |
| T-DXd dosing modification | **Interrupt T-DXd**<br>T-DXd can be resumed if the ILD/pneumonitis fully resolved to Grade 0<br>• If resolved in ≤ 28 days from day of onset, maintain dose<br>• If resolved in > 28 days from day of onset, reduce dose by one level*<br>• Swain SM, et al. recommend that if ILD/pneumonitis occurs beyond Day 22 and has not resolved within 49 days from the last infusion, discontinue T-DXd<br>• Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected | • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected<br>• Permanently discontinue T-DXd |
| | **Retreatment can be safe and effective** | |

*In the event a dose reduction is needed, per the US, EU, and Canada prescribing information, dose reductions from the indicated dose of 5.4 mg/kg for patients with breast cancer are 4.4 and 3.2 mg/kg for the first and second dose-level reductions, respectively. Per the US and EU prescribing information, dose reductions from the indicated dose of 6.4 mg/kg for patients with gastric cancer are 5.4 and 4.4 mg/kg for the first and second dose-level reductions, respectively. If further dose reductions are required, treatment should be discontinued.[2]

Enhertu® (fam-trastuzumab deruxtecan-nxki) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf. Rugo HS, et al. ESMO Open. 2024;9. Swain SM, et al. *Cancer Treat Rev.* 2022;106:102378.

MDT = multidisciplinary team.

# Chemotherapy Induced Nausea and Vomiting
## *Prevention and Management*

### T-DXd for Breast Cancer is Highly Emetogenic

| Before T-DXd | Days 2–4 | Days 5–21 | Dose Delays/ Modifications |
|---|---|---|---|
| NK1 receptor antagonist ± 5-HT3 RA + DEX ± olanzapine | DEX ± 5-HT3 RA **OR** metoclopramide | Olanzapine or metoclopramide ± DEX | Grade 3: delay dose until resolved to grade ≤ 1<br><br>If > 7 days until resolution, reduce dose by 1 level |

Rugo HS, et al. *ESMO Open*. 2022;7(4):100553.

DEX = dexamethasone.

# Decline in LVEF
## *Assessment and Management*

### T-DXd for Breast Cancer

- 2.3% of patients on T-DXd in DB-03 had decline in EF; most cases were grade 1/2 and asymptomatic
- 4.6% of patients on T-DXd in DB-04 had decline in EF; 1.5% grade 3 events
- Monitor LVEF at baseline and every 3–4 months during therapy

| LVEF > 45% and Decrease from Baseline 10%–20% | LVEF 40%–45% and Decrease from Baseline < 10% | LVEF 40%–45% and Decrease from Baseline 10%–20% | LVEF < 40% OR Decrease from Baseline > 20% | Symptomatic CHF |
|---|---|---|---|---|
| Continue treatment | Continue treatment, repeat LVEF assessment in 3 weeks | Hold treatment and repeat LVEF assessment in 3 weeks; if LVEF has not recovered to within 10% baseline, permanently stop T-DXd | Hold treatment and repeat LVEF assessment in 3 weeks; if LVEF < 40% or > 20% decline from baseline persists, permanently stop T-DXd | Permanently stop T-DXd |

Cortés J, et al. *N Engl J Med*. 2022;386(12):1143-1154. Enhertu® (fam-trastuzumab deruxtecan-nxki) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf. Modi S, et al. *N Engl J Med*. 2022;387(1):9-20. Rugo HS, et al. *ESMO Open*. 2022;7(4):100553.

CHF = congestive heart failure; DB-03 = DESTINY-Breast03; DB-04 = DESTINY-Breast04; EF = ejection fraction; LVEF = left ventricular ejection fraction.

# Case Studies

# Case Study 1: JA


JA is a 48-year-old female with a history of stage III left breast cancer (ER/PR/HER2-), diagnosed in 2020. She received neoadjuvant AC plus T followed by left mastectomy and axillary dissection.


She had residual disease at surgery with a 0.8 cm breast mass and 3/14 axillary lymph nodes with metastatic deposits, for which she received adjuvant capecitabine and radiation.

In February 2023, she developed metastases to the lungs and thoracic lymph nodes, for which she received first-line pembrolizumab, gemcitabine, and carboplatin.

Her cancer recently progressed, and her physician recommends second-line sacituzumab govitecan per the ASCENT trial.

AC+T = doxorubicin/cyclophosphamide + paclitaxel.

# Case Study 1: JA (…continued)

You educate JA about the risks of neutropenia and diarrhea associated with sacituzumab, and she tolerates the first 2 cycles without significant events.

However, while she is receiving her infusion on Cycle 3 Day 1, she reports abdominal cramping and diarrhea. By Day 8, she reports worsening diarrhea in the last 4 days, with 5–6 loose stools per day. Her baseline bowel pattern was 1 formed stool daily.

# What is the most appropriate next step for managing for abdominal cramping and diarrhea during SG administration?

A. Continue the infusion at its current rate; this is an expected side effect
B. Stop the infusion and notify the physician/nurse practitioner of possible hypersensitivity reaction
C. Slow the infusion rate
D. Administer atropine 0.4 mg IV every 15 minute for 2 doses; then 0.2 mg IV as needed, up to 1 mg total

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C. Slow the infusion rate
D. Administer atropine 0.4 mg IV every 15 minute for 2 doses; then 0.2 mg IV as needed, up to 1 mg total

JA is able to control her diarrhea at home with loperamide and diet modifications as needed. She presents for Cycle 5 Day 1 of sacituzumab govitecan (SG) with an ANC of 1,100/µL. Her vital signs are stable, and she is afebrile. You contact the physician with the lab results.

**Which of the following is the most appropriate next step?**

A. Continue SG infusion as planned, but order pegfilgrastim to be administered within 24–48 hours post-dose
B. Hold SG until her ANC recovers to >1,500/µL
C. Continue SG infusion as planned, but reduce the dose 1 level
D. Continue SG infusion as planned without dose reductions

JA is able to control her diarrhea at home with loperamide and diet modifications as needed. She presents for Cycle 5 Day 1 of sacituzumab govitecan (SG) with an ANC of 1,100/µL. Her vital signs are stable, and she is afebrile. You contact the physician with the lab results.

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# Case Study 2: AM


AM is a 65-year-old female with a history of de novo metastatic breast cancer to the bone, diagnosed in 2017.


Biopsy of metastases to left iliac revealed IDC (ER-positive, PR-negative, HER2 1+ by IHC).

Her prior therapies include palbociclib + anastrozole, everolimus + fulvestrant, and capecitabine.

Her most recent CT chest/abdomen/pelvis shows disease progression with new liver metastases.

She is scheduled to begin T-DXd for HER2-low, progressive disease after endocrine and first-line chemotherapy

IDC, invasive ductal carcinoma.

AM starts trastuzumab deruxtecan (T-DXd) and receives palonosetron, fosaprepitant, dexamethasone as pre-medications for nausea on Day 1 of each cycle. She has completed 2 cycles and reports significant fatigue, dyspnea, and dry cough associated with deep inspiration. A high-resolution CT scan of the chest shows patchy interstitial infiltrates in the left and right upper lobes. The oxygen saturation is 85% on room air.

**Which of the following actions do you recommend?**

A. Continue T-DXd therapy without modification

B. Discontinue T-DXd, start supplemental oxygen, consult pulmonary, and initiate prednisone 2 mg/kg daily

C. Hold T-DXd, start supplemental oxygen, consult pulmonary, and initiate prednisone 2 mg/kg daily; if infiltrates and symptoms resolved in greater than 28 days from date of onset, reduce dose one level

D. Hold T-DXd, start supplemental oxygen, consult pulmonary, and initiate prednisone 1 mg/kg daily; if infiltrates and symptoms resolved in less than 28 days from date of onset, reduce dose one level

IVPB = IV piggyback.

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# SMART Goals

- Take time to talk to your patient about their unique needs while they receive therapy.
- Incorporate latest clinical trial data regarding ADCs into the care of your patients with HER2- mBC, as documented by treatment selection in electronic health record (EHR) patient charts.
- Manage AEs in patients receiving ADCs for HER2- mBC according to updated guidelines and expert consensus, as documented by increased use of AE assessment tools and mitigation strategies in electronic health record (EHR) patient charts.

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# Advancements and Applications of Antibody-Drug Conjugates in HER2-Negative Breast Cancer

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Supported by an independent educational grant from Gilead Sciences, Inc.