Transforming Metastatic Breast Cancer Management

Harnessing the Power of Antibody-Drug Conjugate Therapies

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LEARNING OBJECTIVE 1

Implement strategies to mitigate breast cancer (BC) health disparities based on specific drivers of inequity

LEARNING OBJECTIVE 2

Integrate the latest data on antibody-drug conjugates (ADCs) to individualize treatment for metastatic breast cancer (mBC) based on recent clinical evidence and updated guidelines

LEARNING OBJECTIVE 3

Develop strategies for the management of adverse events (AEs) associated with ADCs used to treat patients with mBC

Health Disparities in the Management of mBC

Deltra James

Patient/Patient Advocate

MBC Advocate and Death Doula

Deltra James
Patient/Patient Advocate

What Is Ideal Care?

Deltra James in interview with Creative Educational Concepts. May 2024.

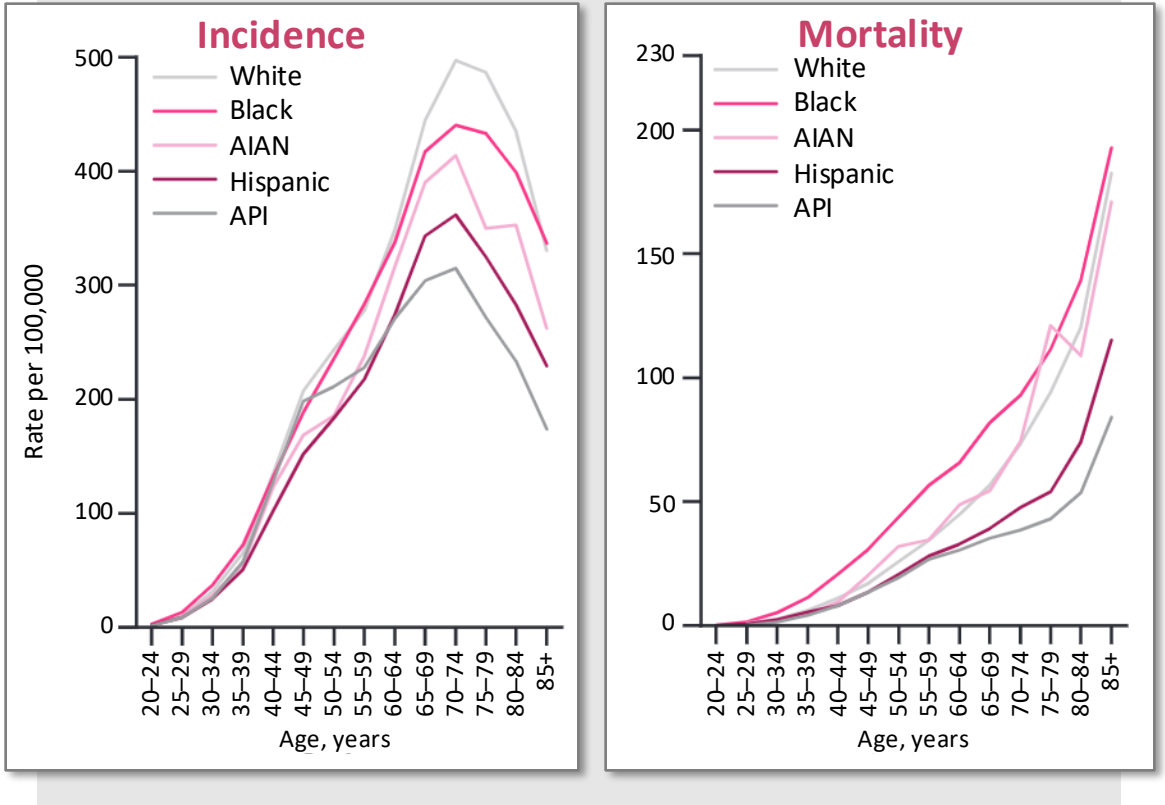
What Is Ideal Care?

- 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

Deltra James in interview with Creative Educational Concepts. May 2024.

Breast Cancer Incidence and Mortality by Age

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

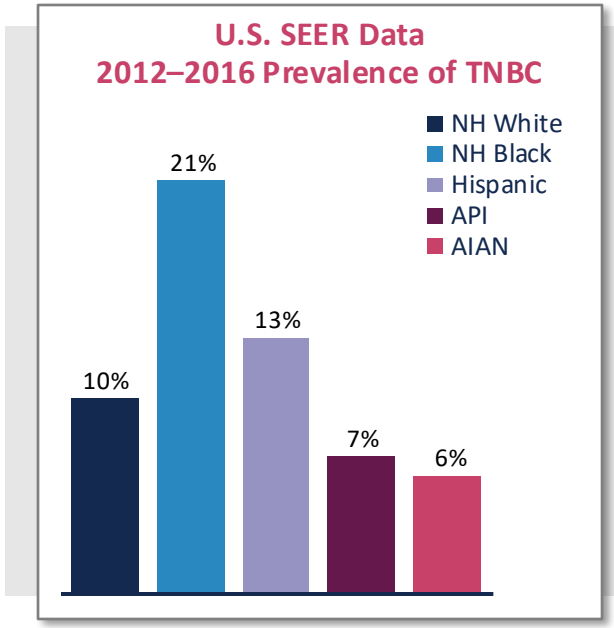


AIAN, American Indian and Alaska Native; API, Asian Pacific Islander.

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

Incidence and Mortality of TNBC by Race and Ethnicity

- Triple-negative breast cancer (TNBC) is more prevalent in Black women than other races 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



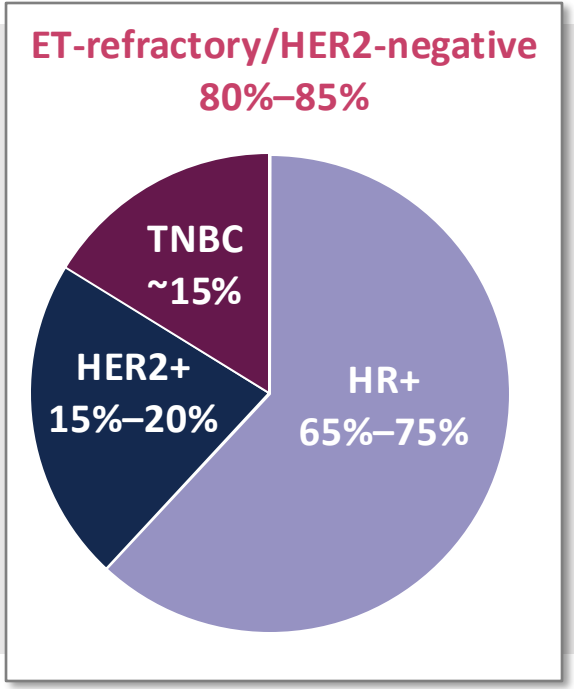
American Cancer Society (ACS). ACS website. https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html. Dietze EC, et al. *Am J Pathol.* 2018;188:280–290. Foulkes WD, et al. *N Engl J Med.* 2010;363:1938–1948. Howard FM, et al. *Cancer J.* 2021;27(1):8–16. Prakash O, et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

NH, non-Hispanic.

Unmet Needs in mBC

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

Real-world Outcomes in Patients with HR+/HER2-negative 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)



Waks AG, Winer EP. *JAMA*. 2019;321(3):288–300.

CT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HER2-neg, HER2-negative; HR, hormone receptor; QoL, quality of life; rwOS, real-world overall survival; rwPFS, real-world progression-free survival.

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.
Yedjou CG, et al. *Adv Exp Med Biol*. 2019;1152:31–49. Giaquinto AN, et al. *CA Cancer J Clin*. 2022;72(6):524–541.

Deltra James
Patient/Patient Advocate

What Are the Major Barriers to Effective Care?

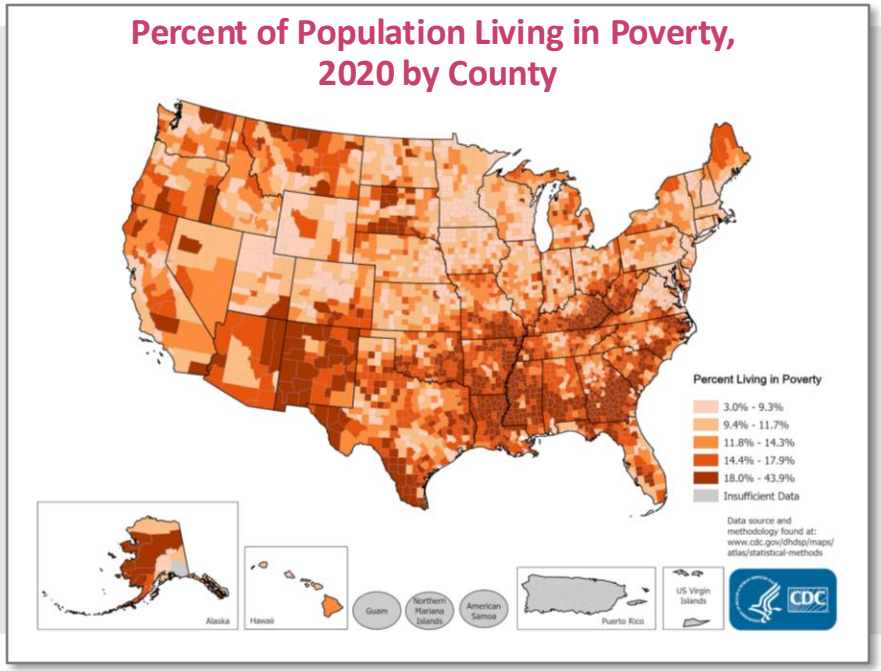
Deltra James in interview with Creative Educational Concepts. May 2024.

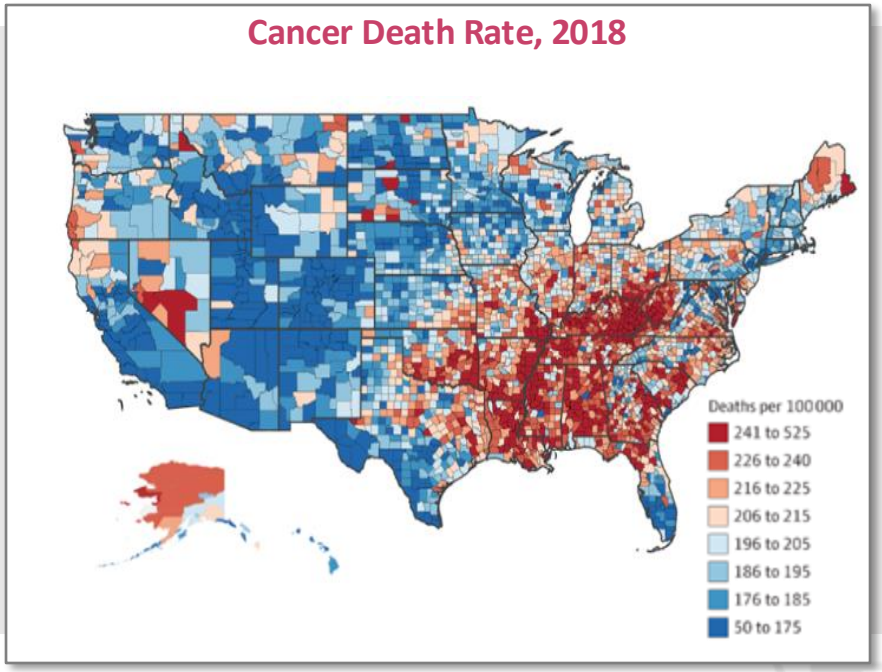
What Are the Major Barriers to Effective Care?

- 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)

Deltra James in interview with Creative Educational Concepts. May 2024.

Geographical Disparities





Centers for Disease Control and Prevention (CDC). CDC website. 2021. https://www.cdc.gov/dhdsp/maps/sd_poverty.htm.
O'Connor JM, et al. *JAMA Network Open.* 2018;1(6):e183146–e183146.

Deltra James
Patient/Patient Advocate

How Do Race/ Ethnicity and Other Socioeconomic Factors Affect Care?

Deltra James in interview with Creative Educational Concepts. May 2024.

How Do Race/Ethnicity and Other Socioeconomic Factors Affect Care?

- Patient-provider racial and ethnic concordance increases likelihood of
  - Seeking preventative care
  - Visiting their provider for
    - New health problems
    - Ongoing medical problems
- Patient-provider language concordance improves
  - Behaviors of both patients and providers
  - Interpersonal processes of care
  - Clinical outcomes

Deltra James in interview with Creative Educational Concepts. May 2024.

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

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.

Deltra James
Patient/Patient Advocate

How Should Oncologists Approach Their Patients?

Deltra James in interview with Creative Educational Concepts. May 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

Deltra James in interview with Creative Educational Concepts. May 2024. Patel MI, et al.*J Clin Oncol*. 2020;38(29):3439–3448. 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/.

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

The Joint Commission. The Joint Commission website. 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 mBC

Focus on Antibody-Drug Conjugates

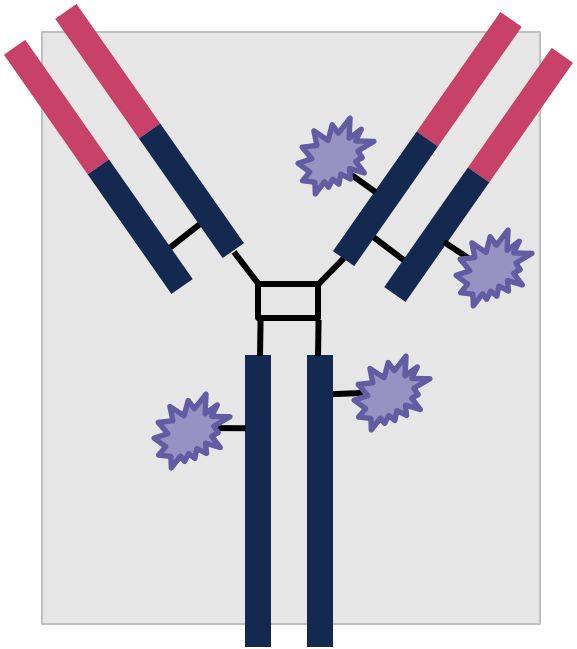
Antibody-Drug Conjugates (ADCs)

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

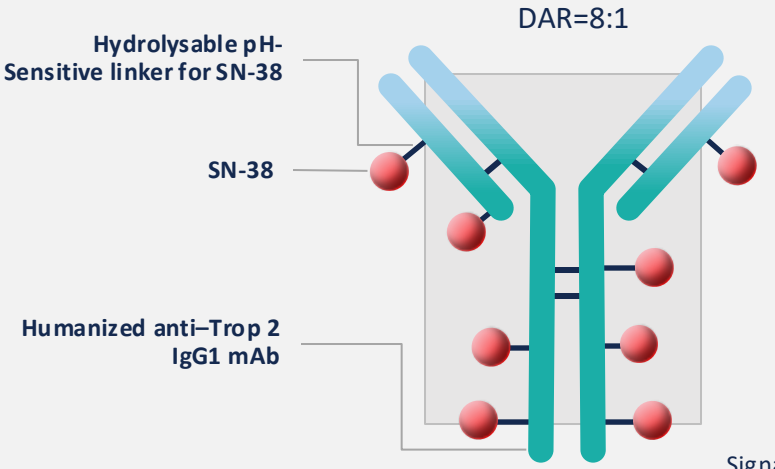
- Highly potent
- Amenable to modifications that allow linker attachment
- Stable
  - In circulation
  - In lysosomes
- Defined mechanisms of action
- Local bystander effect?

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

mAb, monoclonal antibody.

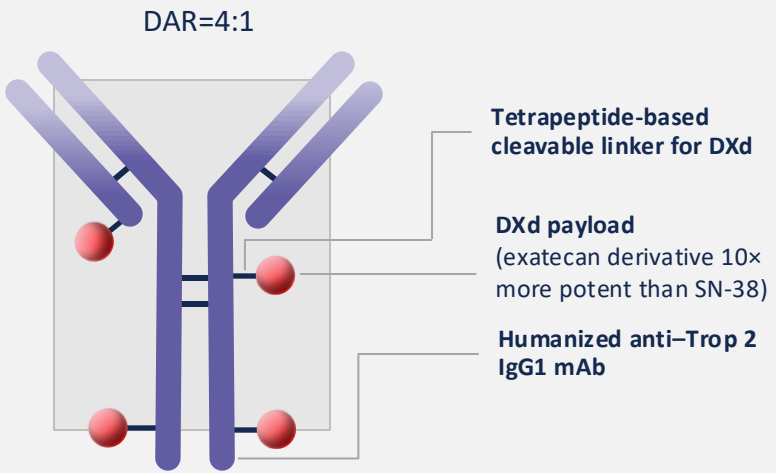
Comparison of Trop-2 ADCs

Sacituzumab govitecan

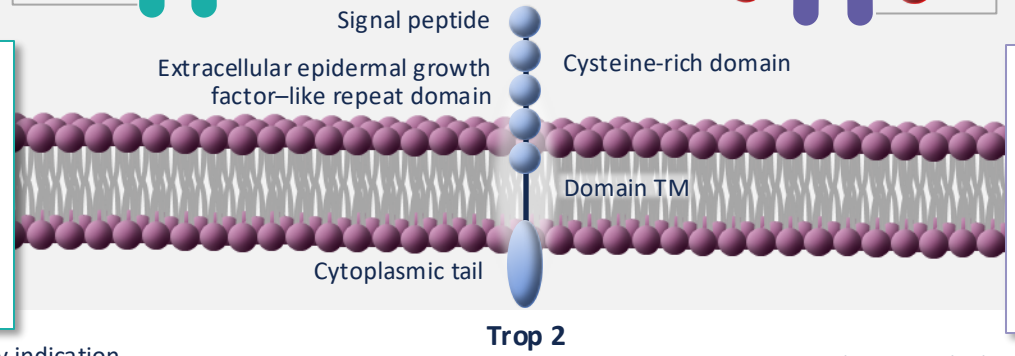


- Payload mechanism of action: topoisomerase I inhibitor
- Payload with **long** systemic half-life
- Bystander antitumor effect

Datopotamab deruxtecan*



- Payload mechanism of action: topoisomerase I inhibitor
- Payload with **short** systemic half-life
- Bystander antitumor effect



*Dato-DXd is not yet approved for any indication.

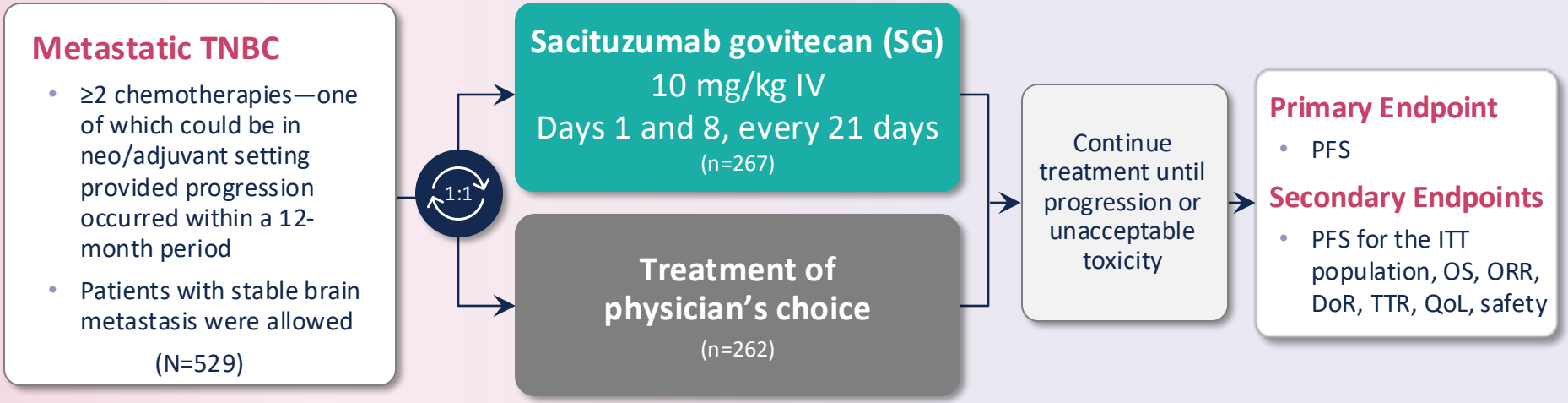
Parisi C, et al. *Cancer Treat Rev*. 2023;118:102572.

DAR, drug to antibody ratio; Dato-DXd, datopotamab deruxtecan; Ig, immunoglobulin; TM, transmembrane.

Triple-negative Breast Cancer (TNBC)

ASCENT

A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Second-line and Later mTNBC



Stratification Factors

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

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.

Bardia A, et al. *N Engl J Med*. 2021;384(16):1529–1541; Bardia A, et al. ESMO Virtual Congress 2020. Abstract LBA17; ClinicalTrials.gov. Identifier: NCT02574455.

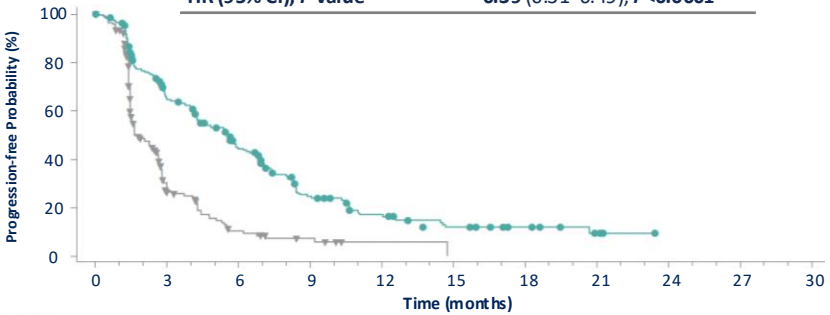
ASCENT

Statistically Significant and Clinically Meaningful Improvement in PFS and OS (BMneg Population)

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

Progression-free Survival (BICR Analysis)

BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	167	150
Median PFS, mo (95% CI)	5.6 (4.3–6.3)	1.7 (1.5–2.6)
HR (95% CI), *P* value	**0.39** (0.31–0.49), ***P*<0.0001**	

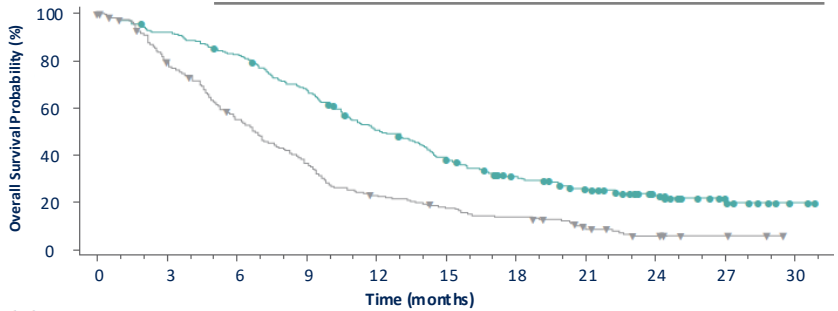


No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
IMMU-132	235	222	166	134	127	104	81	63	54	37	33	24	22	17	16	13	11	10	8	6	5	3	1	1	0

Overall Survival

	SG (n=235)	TPC (n=233)
No. of events	173	199
Median OS, mo (95% CI)	12.1 (10.7–14.0)	6.7 (5.8–7.7)
HR (95% CI), *P* value	**0.48** (0.39–0.59), ***P*<0.0001**	



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
IMMU-132	235	228	220	214	206	197	191	177	164	156	140	122	113	105	97	85	74	65	59	56	46	40	35	30	25	17	14	11	7	4	2
TPC	233	214	200	173	156	134	117	101	90	77	58	53	47	44	40	35	30	28	27	24	22	13	11	7	6	4	3	3	2	1	0

Analysis based on final database lock confirmed the improvement in clinical outcomes over TPC:

- Median PFS of 5.6 vs 1.7 months (HR, 0.39, *P*<0.0001)
- Median OS of 12.1 vs 6.7 months (HR, 0.48, *P*<0.0001)
- **OS rate at 24 months of 22.4% (95% CI, 16.8–28.5) vs 5.2% (95% CI, 2.5–9.4)**

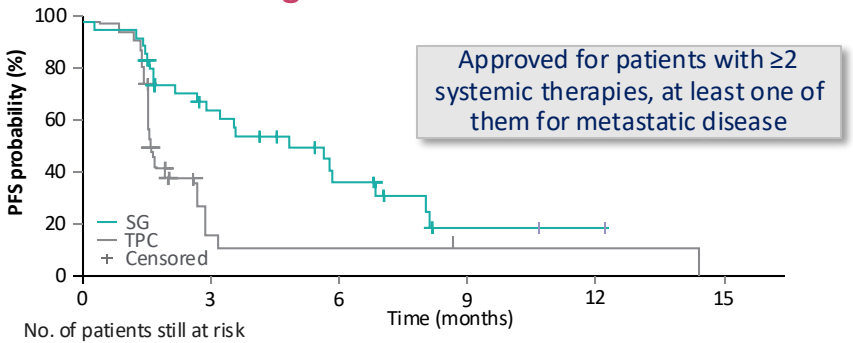
Bardia A, et al. *J Clin Oncol*. 2022;40(suppl 16):1071.

BICR, blinded independent central review; BMneg, brain metastases negative; CI, confidence interval; HR, hazard ratio; 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



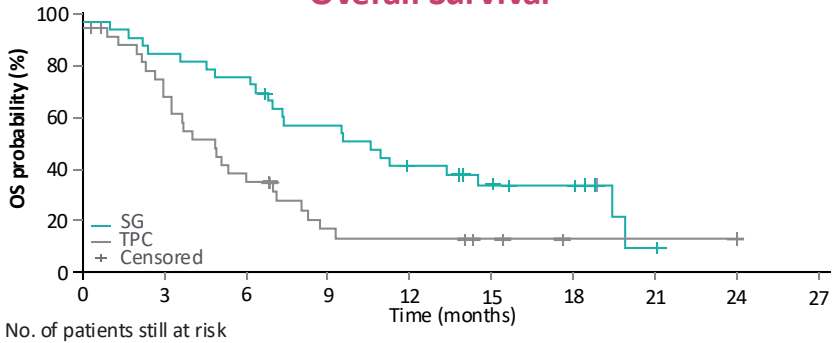
Approved for patients with ≥2 systemic therapies, at least one of them for metastatic disease

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, months (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, months (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.
European Medicines Agency (EMA). EMA website. 2021. https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf.

ASCENT 03 Ongoing

SG vs TPC (Gem + Carbo, Paclitaxel, Nab-Paclitaxel) in First-line PD-L1–negative mTNBC

First-line mTNBC PD-L1–

- Previously untreated, inoperable, locally advanced, or metastatic TNBC
- PD-L1–negative 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
OR paclitaxel: 90 mg/m^2 IV on Days 1, 8, and 15 of 28-day cycles OR
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

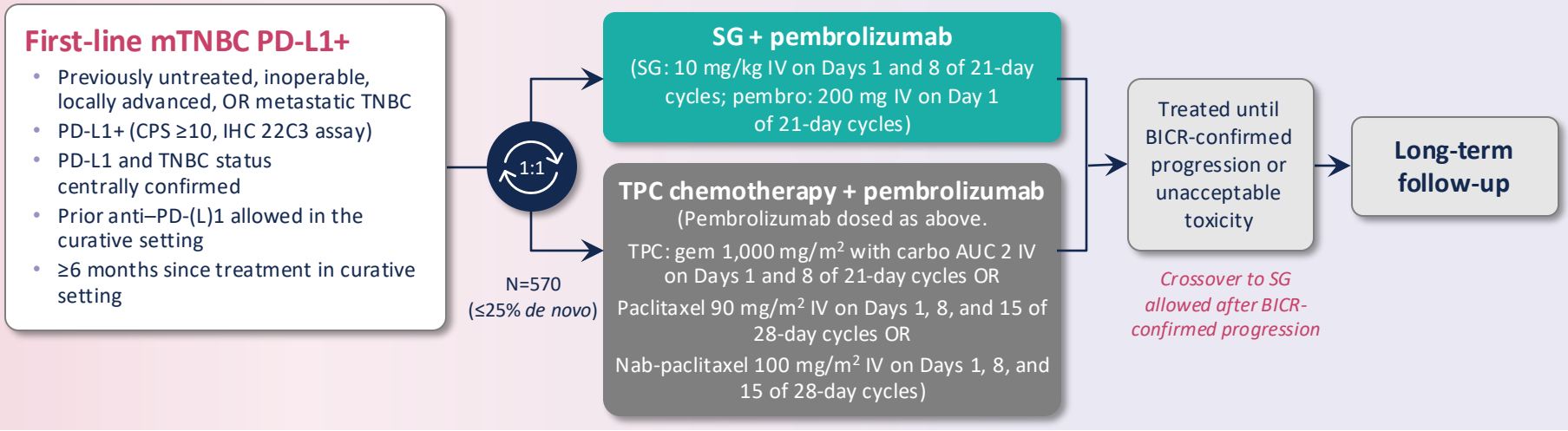
Stratification Factors

- *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

EU Clinical Trials Register. Identifier: 2021-005743-79. ClinicalTrials.gov. Identifier: NCT05382299.

Carbo, carboplatin; CPS, combined positive score; Gem, gemcitabine.

ASCENT 04 Ongoing
SG + Pembrolizumab vs TPC + Pembrolizumab in First-line PD-L1+ mTNBC



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

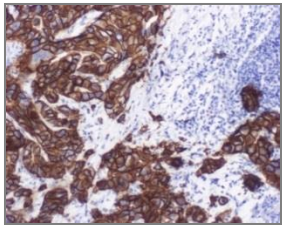
EU Clinical Trials Register. Identifier: 2021-005742-14. ClinicalTrials.gov. Identifier: NCT05382286.

AUC, area under the curve;
PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

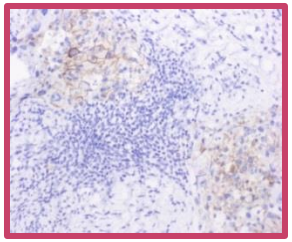
Prevalence of HER2-low by HR Status

HER2 IHC Examples

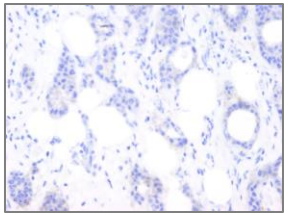
HER2+



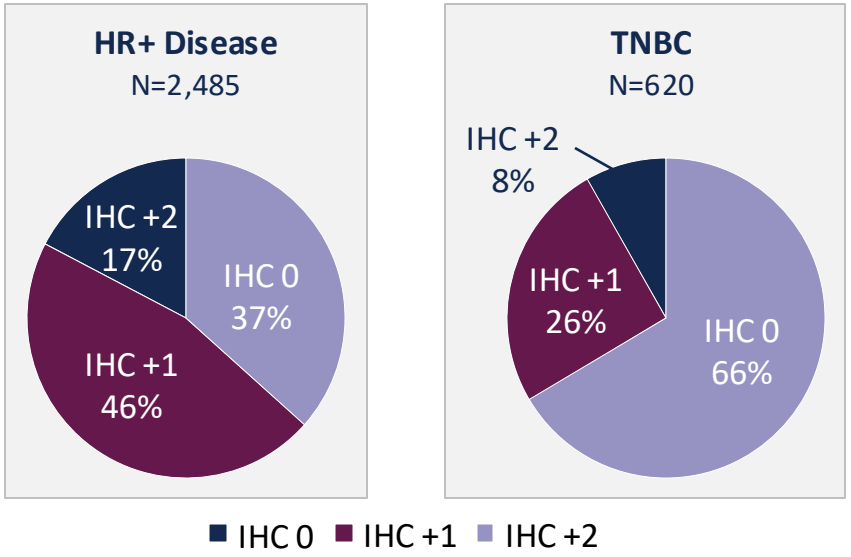
HER2-low



HER2-neg



HER2-negative

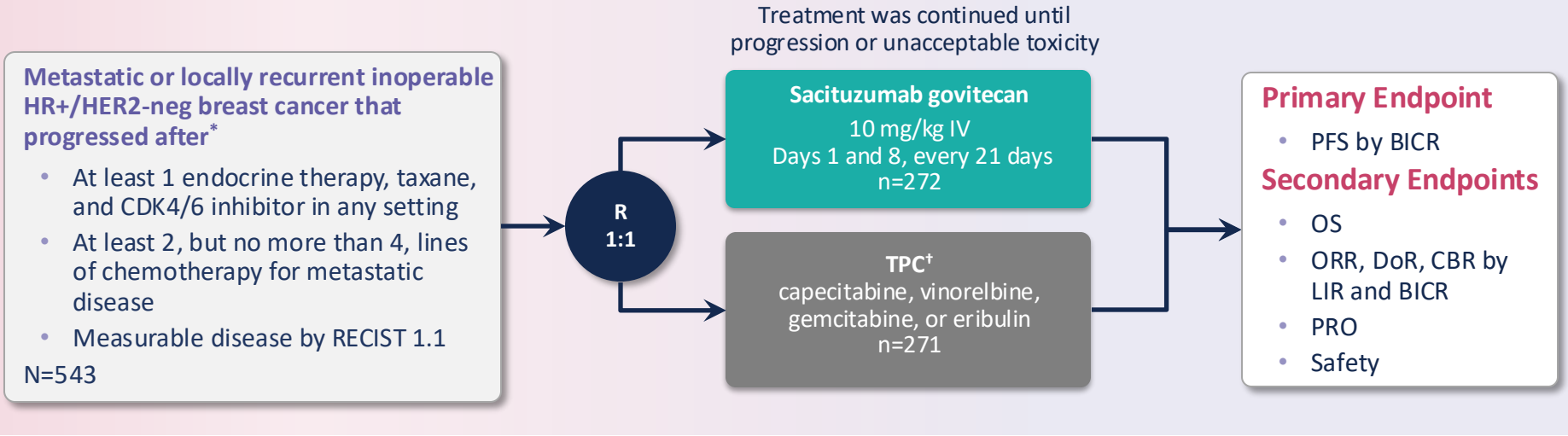


34%–63% of breast cancer patients considered HER2-neg under current guidelines express low levels of HER2

HR+/HER2-negative mBC

TROPiCS-02

A Phase 3 Study of SG in Pre-treated HR+/HER2-negative (IHC 0, IHC 1+, IHC 2+/ISH Negative) 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)

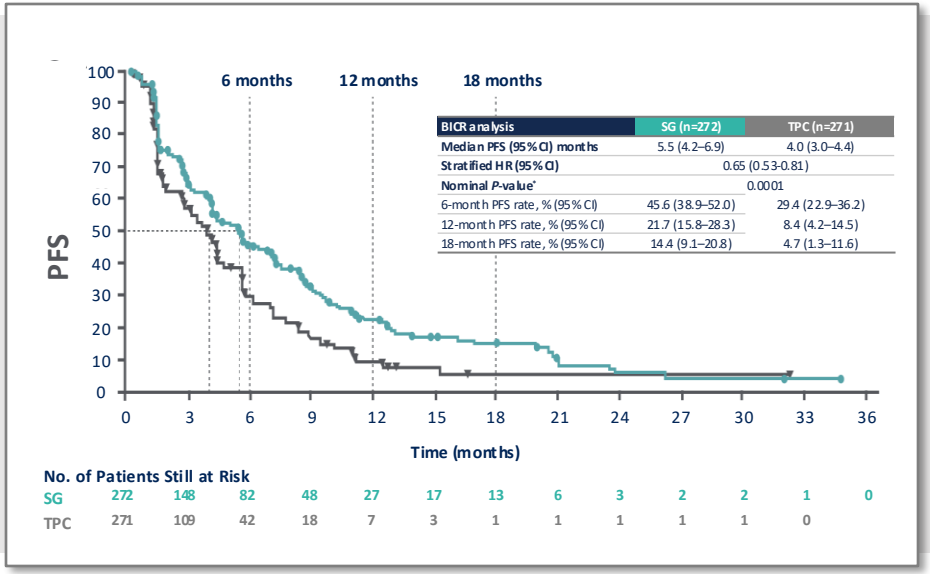
*Disease histology based on the ASCO/CAP criteria. †Single-agent SoC TPC was specified prior to randomization by the investigator.

Adapted from Rugo H, et al. ESMO Congress 2022. Abstract LBA76.
Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365–3376. ClinicalTrials.gov. Identifier: NCT03901339.

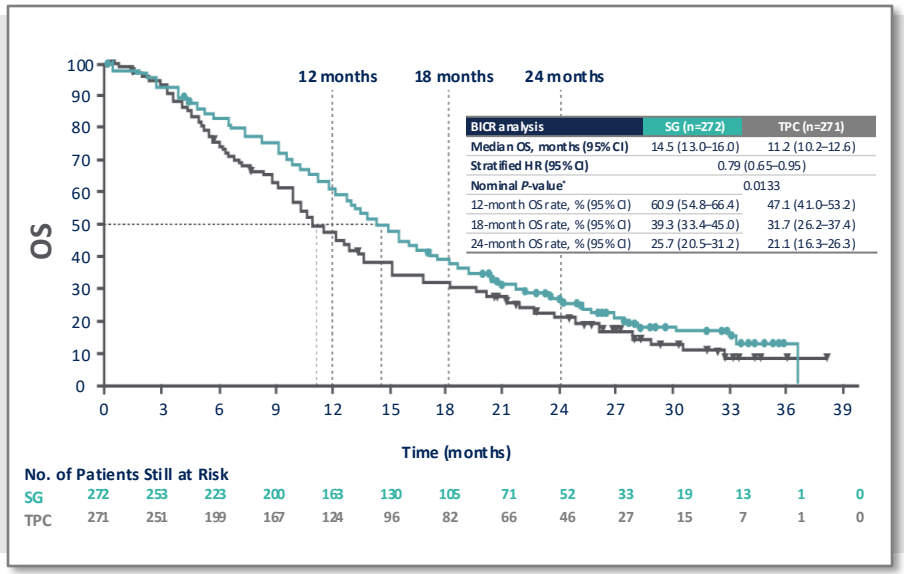
CBR, clinical benefit rate; LIR, local investigator review; PRO, patient reported outcomes; SoC, standard of care.

TROPiCS-02

SG 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)

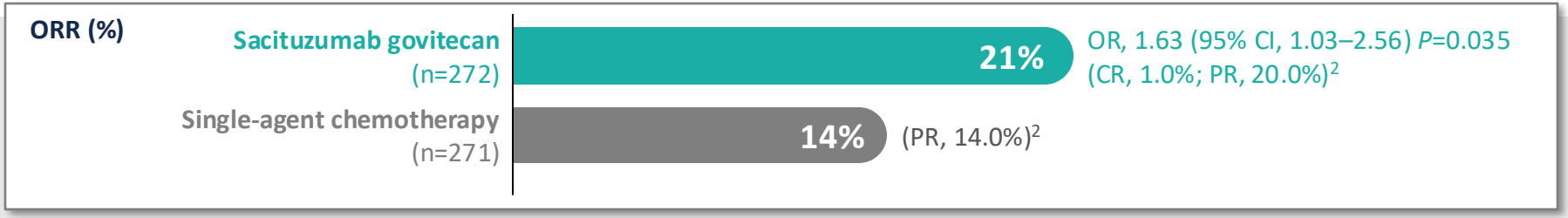


BICR analysis	SG (n=272)	TPC (n=271)
Median OS, months (95% CI)	14.5 (13.0–16.0)	11.2 (10.2–12.6)
Stratified HR (95% CI)	0.79 (0.65–0.95)	
Nominal *P*-value*	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8–66.4)	47.1 (41.0–53.2)
18-month OS rate, % (95% CI)	39.3 (33.4–45.0)	31.7 (26.2–37.4)
24-month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

SG 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)	0.006
Fatigue	234/205	2.2 (1.6–2.8)	1.4 (1.1–1.9)	0.73 (0.60–0.89)	0.002
Pain	229/202	3.8 (2.8–5.0)	3.5 (2.8–5.0)	0.92 (0.75–1.13)	0.415

[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.

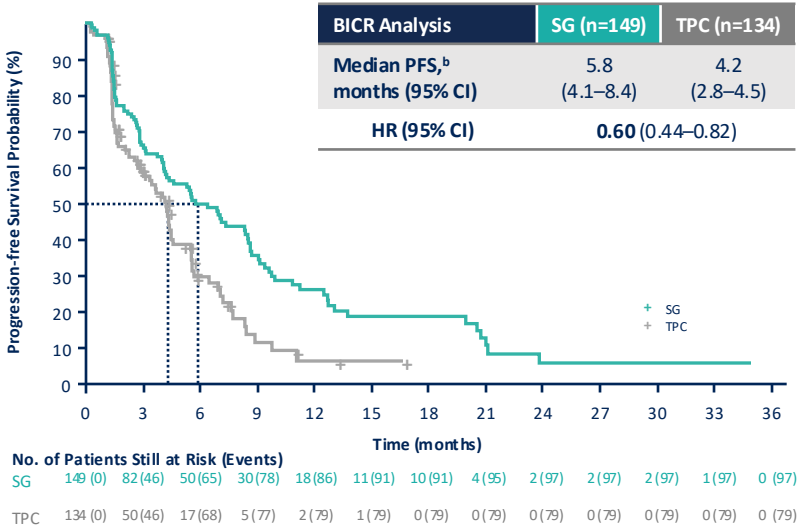
CR, complete response; PR, partial response; TTD, time to treatment deterioration.

TROPiCS-02

Progression-free Survival by HER2 IHC Status

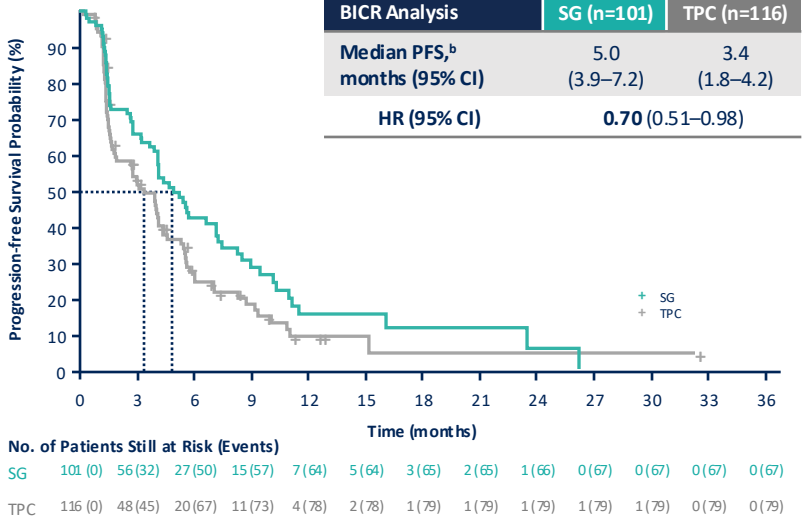
HER2-low (IHC 1+, IHC 2+/ISH negative)[a]

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)	



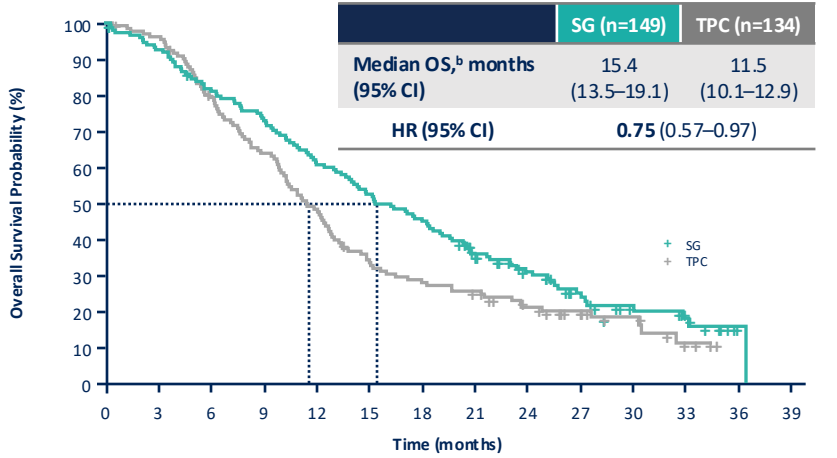
SG consistently improved PFS vs TPC in the HER2-low (IHC 1+, IHC 2+/ISH negative) and the HER2 IHC 0 groups with longer follow-up, consistent with a previous analysis

[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.

TROPiCS-02

Overall Survival by HER2 IHC Status

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

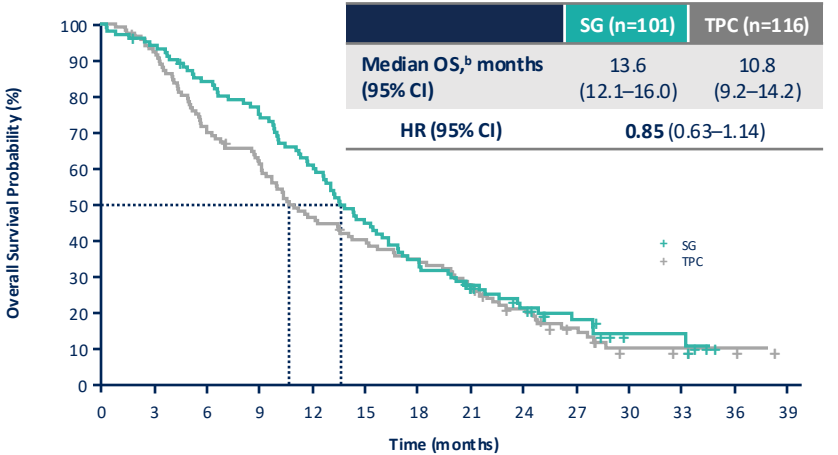


	SG (n=149)	TPC (n=134)
Median OS,[b] months (95% CI)	15.4 (13.5–19.1)	11.5 (10.1–12.9)
HR (95% CI)	**0.75** (0.57–0.97)	

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.

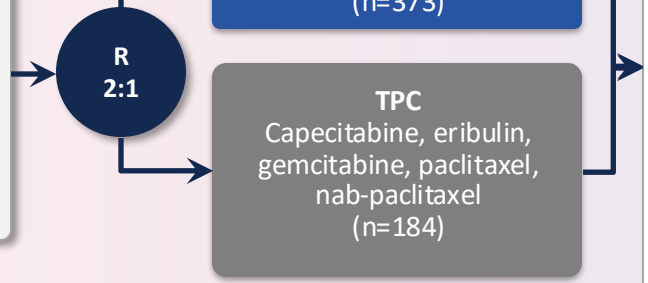
DESTINY-Breast04

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

An open-label, multicenter study (NCT03734029)

Patients

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



Primary Endpoint

- PFS by BICR (HR+)

Key Secondary Endpoints

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

Secondary Endpoints

- *PFS by investigator*
- ORR by BICR and investigator
- DOR by BICR
- *Safety*
- Patient-reported outcomes (HR+)
- OS (HR+ and all patients)

Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

Stratification Factors

- Centrally assessed HER2 status (IHC 1+ vs IHC 2+/ISH negative)
- 1 vs 2 prior lines of CT
- HR+ (with vs without prior treatment with CDK4/6i) vs HR negative

- At the primary analysis (data cutoff, January 11, 2022), median follow-up was 18.4 months
- The primary analysis of PFS was by BICR; this is comparing investigator assessment
- Patient population: median one line of chemotherapy for mBC, 65%–70% prior CDKi, 70% liver mets

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0–32.8 months)

Modi S, et al. *N Engl J Med.* 2022;387(1):9–20. Modi S, et al. ESMO Congress 2023. Abstract 3760.
ClinicalTrials.gov. Identifier: NCT03734029.

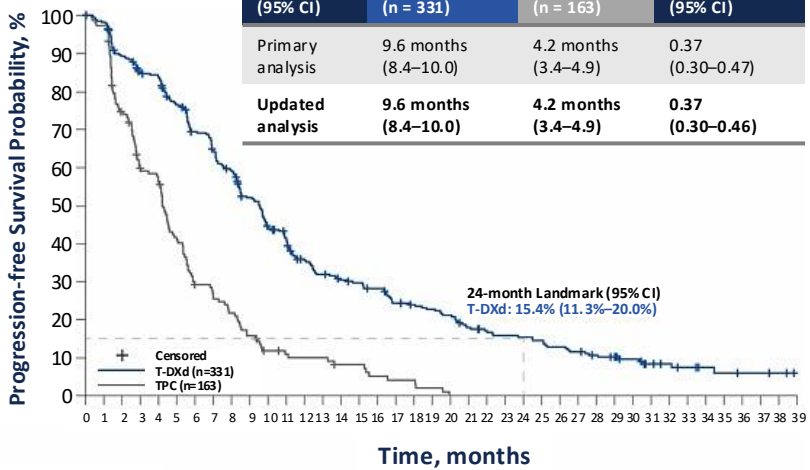
CBR, clinical benefit rate; LIR, local investigator review; PRO, patient reported outcomes; SoC, standard of care.

DESTINY-Breast04

Updated Progression-free Survival (Investigator Assessed)

HR+ Cohort

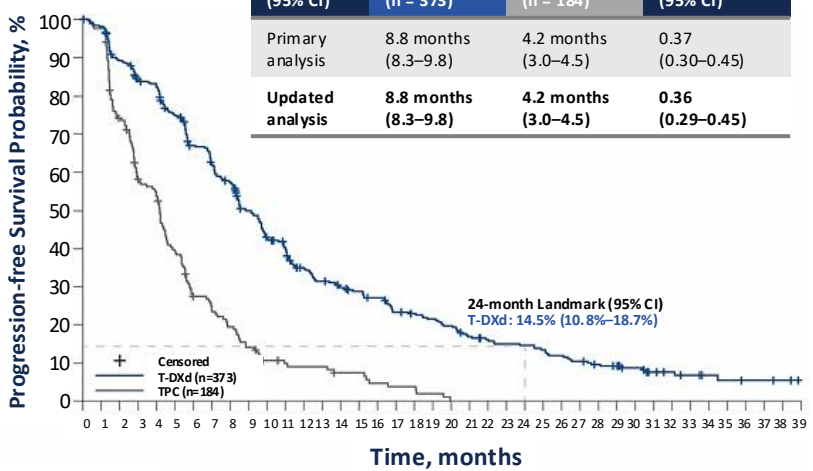
Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard Ratio (95% CI)
Primary analysis	9.6 months (8.4–10.0)	4.2 months (3.4–4.9)	0.37 (0.30–0.47)
Updated analysis	**9.6 months (8.4–10.0)**	**4.2 months (3.4–4.9)**	**0.37 (0.30–0.46)**



Patients still at risk

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)**



Patients still at risk

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*<0.0001		0.46 (0.24–0.89)		HR, 0.50 (0.40–0.63); *P*<0.0001	

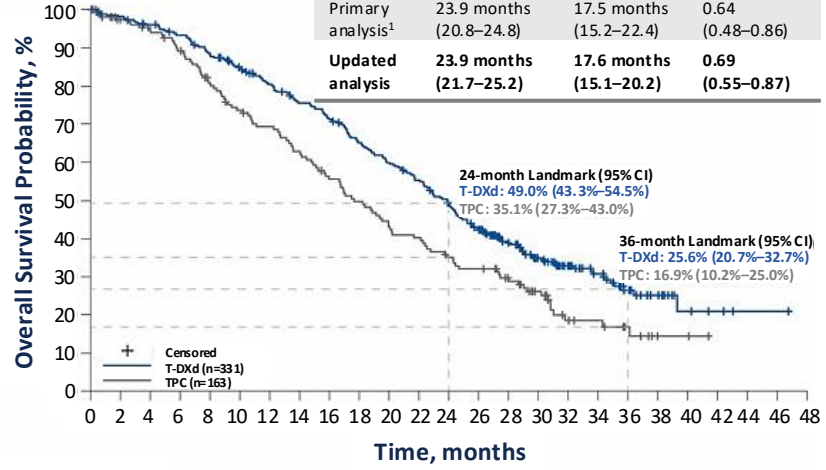
Modi S, et al. *N Engl J Med.* 2022;387(1):9–20. Modi S, et al. ESMO Congress 2023. Abstract 3760.

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)**



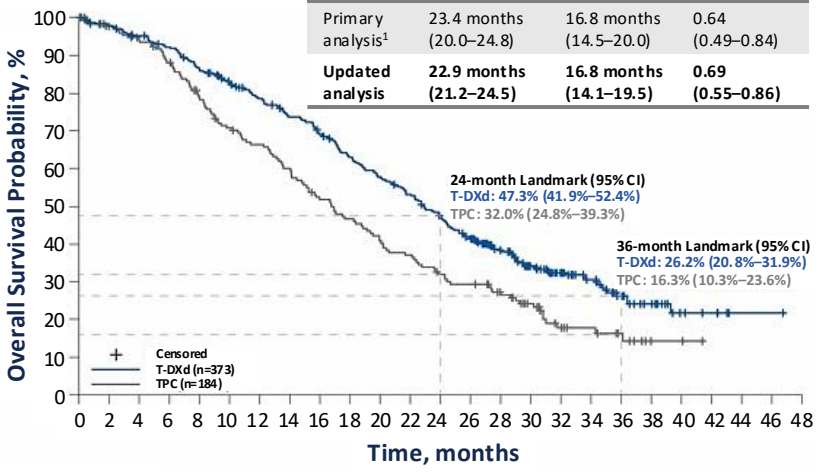
Patients still at risk

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

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)**



Patients still at risk

T-DXd (n = 373) 373 366 363 356 350 342 337 325 314 308 296 286 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

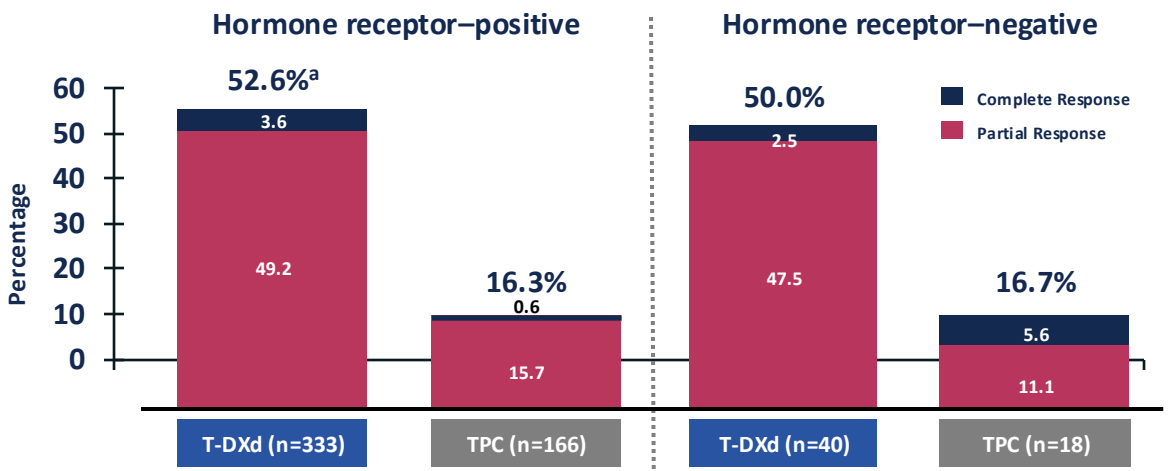
Primary Analysis (BICR)

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*=0.0028		0.48 (0.24–0.95)		HR, 0.64 (0.49–0.84); *P*=0.0010	

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

DESTINY-Breast04
Confirmed ORR

Confirmed Objective Response Rate



	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

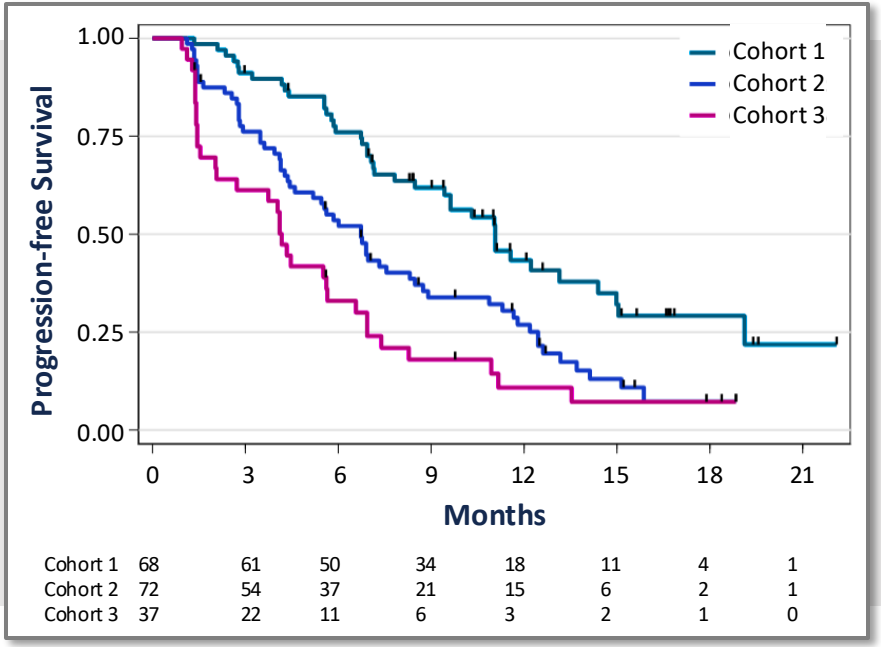
Hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.

[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.

DAISY: PFS According to HER2 Expression

Data cut-off: Oct 19, 2021	Cohort 1 HER2 IHC 3+ or IHC 2+/ISH+ (n=68)	Cohort 2 HER2 IHC 2+/ISH- or IHC 1+ (n=72)	Cohort 3 HER2 IHC 0 (n=37)
Median PFS (months) (95% CI)	11.1 (8.5–14.4)	6.7 (4.4–8.3)	4.2 (2–5.7)
HR (95% CI)	0.53 (0.34–0.84)	1.00	1.96 (1.21–3.15)
***P*-value**		***P*<0.0001**	

	Median PFS	Median OS
(HR+)	4.5 months	11.6 months
(HR-)	2.1 months	10.3 months



Median follow up: 15.6 months

The PFS is different between the three cohorts *P*<0.0001

ASCENT-07 Ongoing

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

Key Eligibility Criteria

- HR+/HER2-negative, 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

Sacituzumab govitecan
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[1]

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 negative])
- Geographic region (US/CAN/UK/EU vs ROW)

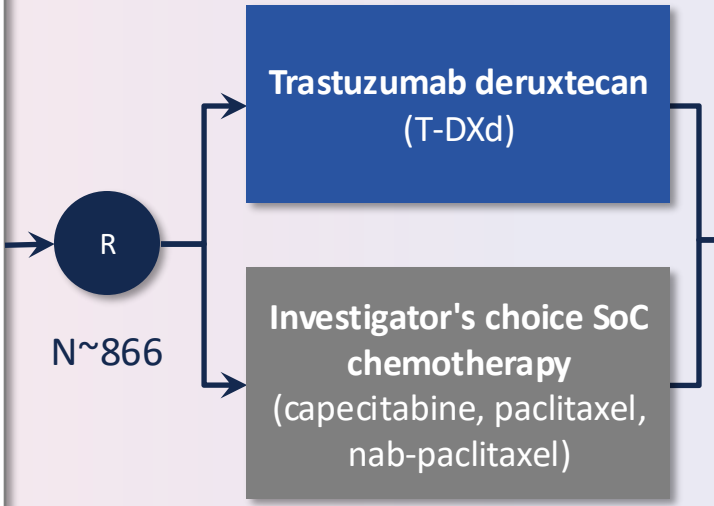
Clinical Trials.gov. Identifier: NCT05840211.

ROW, rest of world.

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

Key Eligibility Criteria

- History of HER2-low or negative expression by local test defined as IHC 2+/ISH negative or IHC 1+ (ISH negative or untested) or IHC 0 (ISH negative or untested)
- HER2-low or HER2 IHC >0 <1+ expression, as determined by the central laboratory result
- Never previously HER2+
- HR+ disease in the metastatic setting
- No prior chemotherapy for advanced or metastatic BC
  - Disease progression within 6 months of starting first-line metastatic treatment with an ET combined with a CDK4/6 inhibitor or
  - Disease progression on ≥2 previous lines of ET with or without a targeted therapy in the metastatic setting



Primary Endpoint

- PFS

Secondary Endpoints

- OS
- PFS in the ITT
- OS in the ITT
- ORR
- DoR
- PFS by investigator
- ORR in the ITT
- DoR in the ITT
- PFS-2, by investigator assessment, TFST, TSST
- Safety
- Serum concentration, immunogenicity of T-DXd
- HRQoL, TTD

NCT04494425—full participation criteria available at ClinicalTrials.gov.

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), months	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), *P*<0.0001		0.63 (0.53–0.75), *P*<0.0001		0.78 (0.50–1.21)	
12-month OS rate, %	87.6	81.7	87	81.1	84	78.7
HR (95% CI), *P* value	0.83 (0.66–1.05), *P*=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)

Antibody-Drug Conjugates

Does Expression of the Target Receptor Matter?

TROPiCS-02

SG in HR+/HER2-negative mBC

PFS

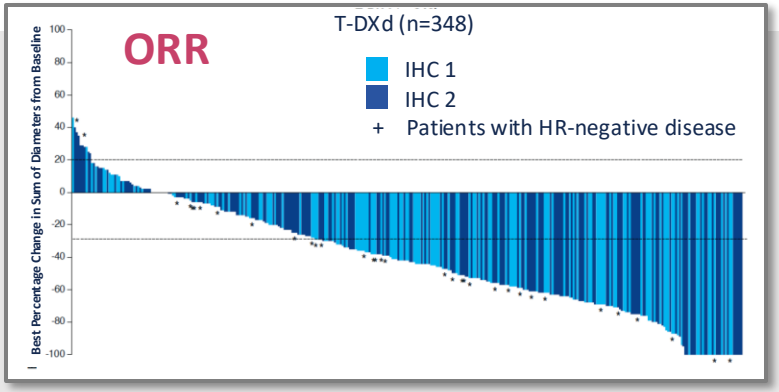
	Status	Median PFS, months (95% CI)		HR (95% CI)
		SG	TPC	
Trop-2	H-score <100	5.0 (4.1–6.0) n=96	4.0 (2.7–5.6) n=96	**0.79** (0.56–1.12)
	H-score ≥100	5.8 (4.0–8.3) n=142	4.1 (2.3–4.5) n=128	**0.61** (0.45–0.83)

OS

	Status	Median OS, months (95% CI)		HR (95% CI)
		SG	TPC	
Trop-2	H-score <100	14.9 (12.7–18.1) n=96	11.3 (10.0–13.3) n=96	**0.78** (0.57–1.06)
	H-score ≥100	14.4 (12.7–17.0) n=142	11.2 (9.9–12.7) n=128	**0.82** (0.63–1.08)

DESTINY BREAST-04

T-DXd in HR+ HER2-low mBC



Hazard Ratio for Disease Progression or Death (95% CI)	
IHC status	
IHC 1+	0.48 (0.35–0.65)
IHC 2+/ISH negative	0.55 (0.38–0.80)

Figure modified from supplemental material

Tolaney SM, et al. ASCO Annual Meeting 2023. Abstract 1003. Updated from Rugo HS, et al. ESMO Congress 2022. Abstract LBA76; and Rugo HS, et al. SABCS 2022. Abstract GS1-11.
Rugo HS, et al. *Lancet.* 2023;402(10411):1423–1433. Modi S, et al. *N Engl J Med.* 2022;387(1):9–20. Harbeck N, et al. SABCS 2022. Abstract P1-11-01.

National Comprehensive Cancer Network (NCCN) Updated 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) 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) Systemic chemotherapy see BINV-Q (5)
	No germline BRCA 1/2 mutation and HER2 IHC 1+ or 2+/ISH negative	Fam-trastuzumab deruxtecan (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)

NCCN Guidelines. Breast Cancer. NCCN website. v2.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

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.

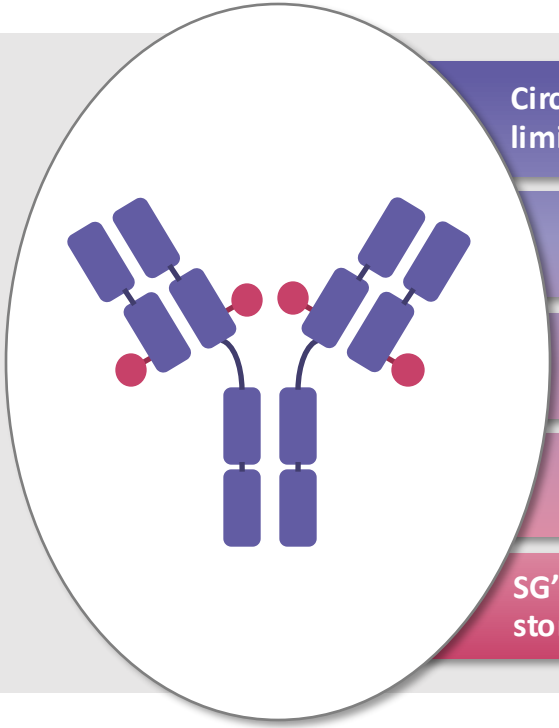
NCCN Updated Guidelines for HR+/HER2-negative

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 (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan	Sacituzumab govitecan (Category 1, preferred) 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)

NCCN Guidelines. Breast Cancer. NCCN website. v2.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

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 toxicity.

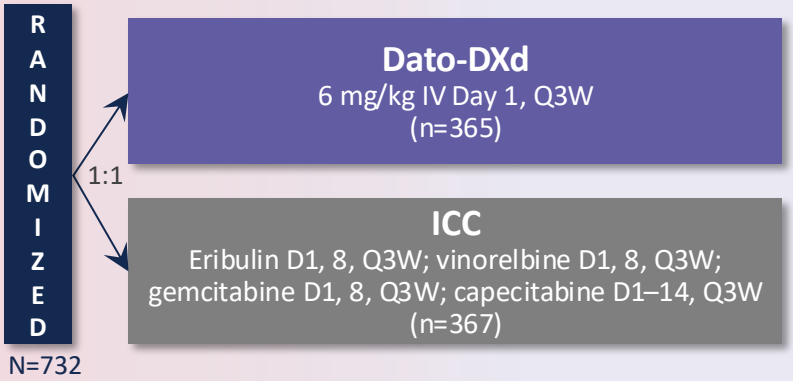
Goldenberg DM, et al. *Oncotarget.* 2015;6:22496–22512. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097–5108. Ocean AJ, et al. *Cancer*. 2017;123:3843–3854.
Bardia A, et al. *J Clin Oncol.* 2017;35:2141–2148. Lisberg AE, et al. 2020 ASCO Virtual Scientific Program. Abstract 9619.

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

Study Design and Patients

Key Eligibility Criteria

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

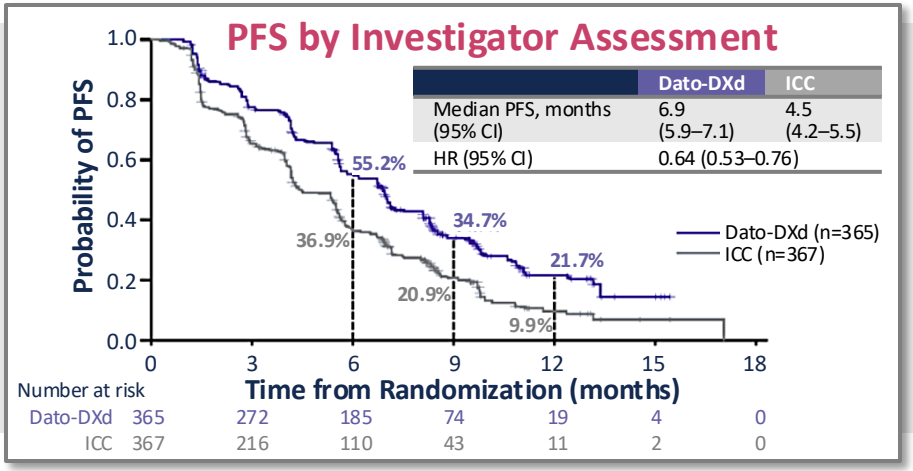


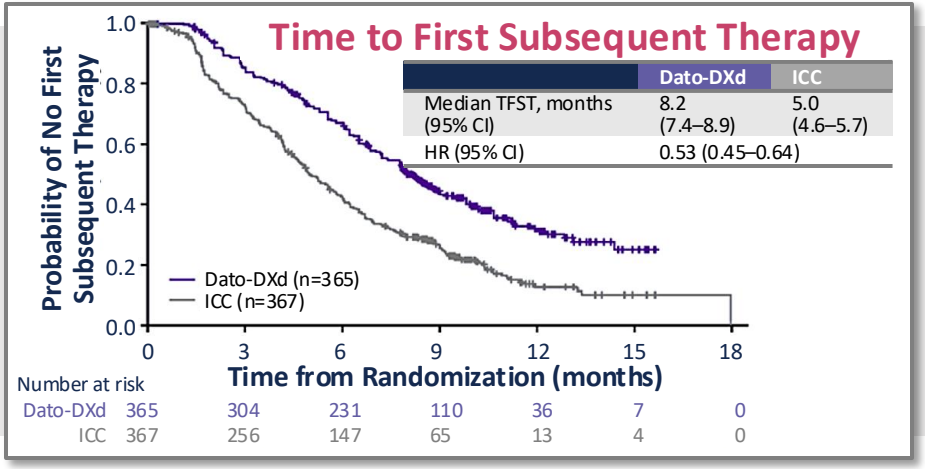
Dual primary endpoints: PFS by BICR per RECIST v1.1, and OS
Secondary endpoints: ORR, PFS by investigator, safety

Patient Characteristics, n (%)		Dato-DXd (n=365)	ICC (n=367)
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)

ICC, investigator's choice of CT.

TROPION-Breast01
Dato-DXd vs TPC in HR+ MBC
PFS and Time to Subsequent Therapy





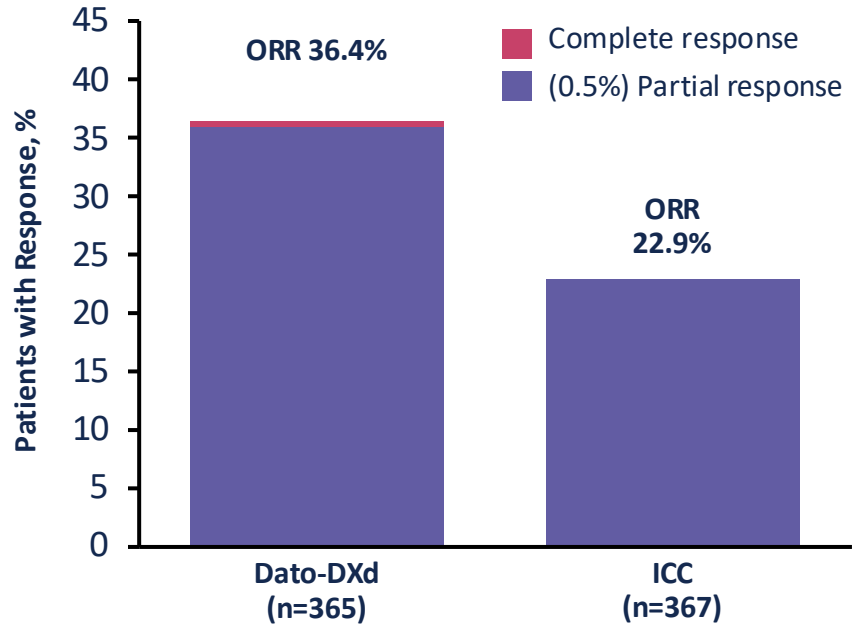
Median 1 line of prior chemotherapy

PFS by BICR (primary endpoint)

- Median 6.9 vs 4.9 months
- HR 0.63 (95% CI: 0.52, 0)

TROPION-Breast01
Response and Interim OS

Response Rate



OS: Dual Primary Endpoint

- OS data not mature*
  - Median follow-up 9.7 months
- A trend favouring Dato-DXd was observed
  - HR, 0.84 (95% CI, 0.62–1.14)
- The study is continuing to the next planned analysis for OS

*Information fraction: 39%.

ORR, confirmed objective response rate by BICR.

TROPION-Breast01

TRAEs Occurring in ≥15% of Patients and AESIs

System Organ Class 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

AE of special interest

- 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.

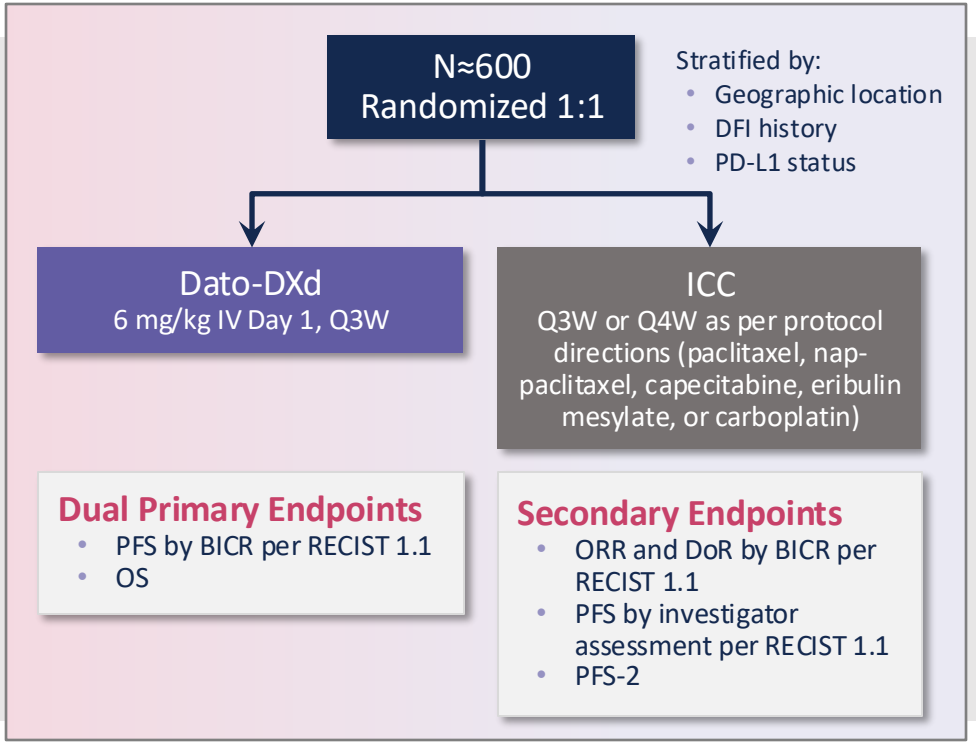
AESIs, adverse events of special interest; ILD, interstitial lung disease; PTs, preferred terms; SMQ, standard MedDRA query; SOC, system organ class; TRAEs, treatment-related adverse events

TROPION-Breast02 Study Ongoing

Dato-DXd vs Chemo in First-line Metastatic TNBC Not Candidate for Anti–PD-(L)1 Therapy, NCT05374512

Key Inclusion Criteria

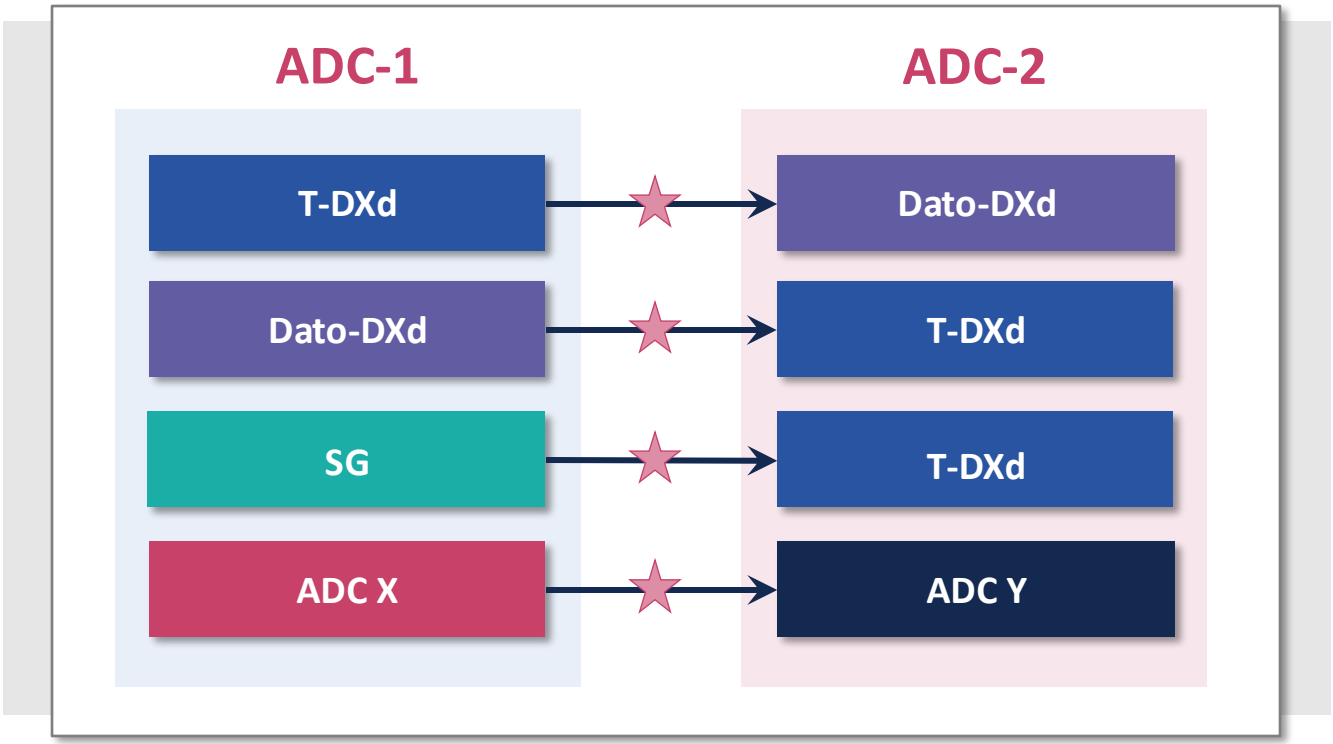
- Adults with histologically or cytologically documented **locally recurrent inoperable or metastatic TNBC**
- **No prior chemotherapy or targeted systemic therapy for locally recurrent inoperable or metastatic BC**
- **ECOG PS of 0 or 1**
- **Not a candidate for PD-(L)1 inhibitor therapy**
- Eligible for one of the listed ICCs (i.e., paclitaxel, nab-paclitaxel, capecitabine, carboplatin, or eribulin mesylate)



DFI, disease-free interval; PFS-2, progression-free survival on second-line therapy.

Critical Question

How will ADCs work in sequence?



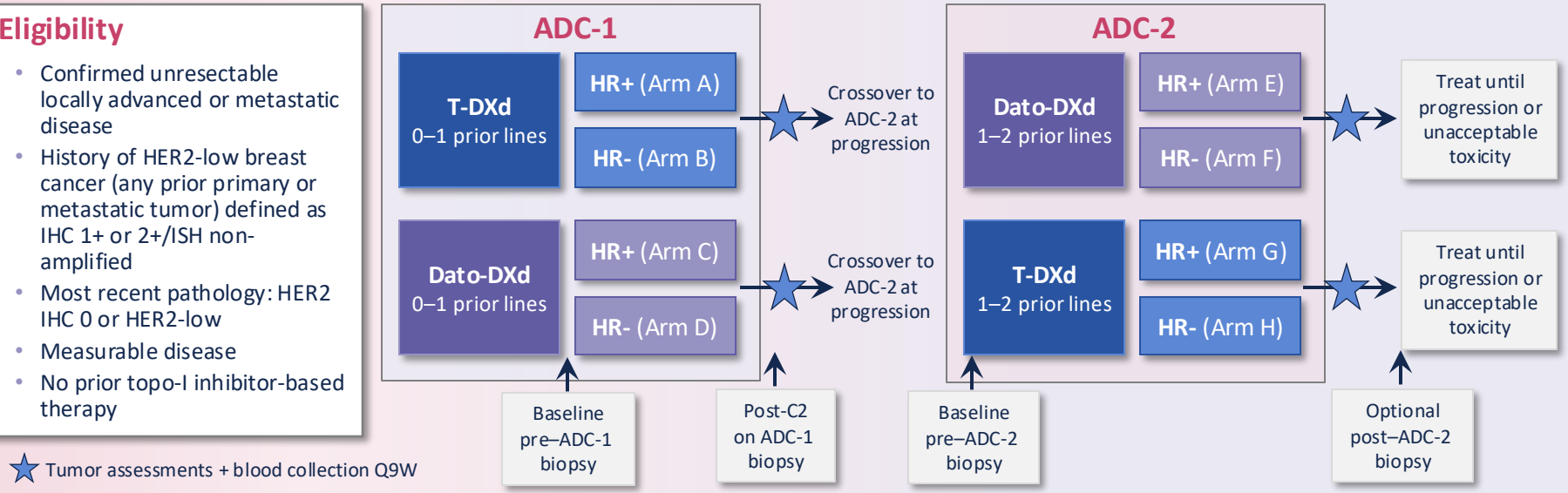
TReatment of ADC-refractory Breast CancEr with Dato-DXd or T-DXd (TRADE-DXd)

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



*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

Fenton MA, et al. *Curr Oncol.* 2023;30(12):10211–10223.

TTOR , time to objective response

Management of AEs in ADC Therapy

Sacituzumab Govitecan (SG)

Safety of Sacituzumab Govitecan

- ASCENT: safety of SG in second-line and later mTNBC
  - Most common grade 3/4 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

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%)

FDA-approved drug: sacituzumab govitecan-hziy. Revised February 2023. FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761115s035lbl.pdf.

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	Second Occurrence	Third Occurrence
75% original dose (7.5 mg/kg)	50% original dose (5 mg/kg)	Discontinue

Spring LM, et al. *Ann Oncol.* 2024;35(3):293–301. FDA-approved drug: sacituzumab govitecan-hziy. FDA website. Revised February 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 iADLs	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 iADLs	Obstipation with manual evacuation indicated, or limiting self-care ADL	Life-threatening, or urgent intervention required	Death

National Cancer Institute (NCI). Updated August 2023. NCI website. https://www.cancer.gov/about-cancer/treatment/side-effects/constipation/gi-complications-hp-pdq#_119.

iADLs, instrumental activities of daily living; TPN, total parenteral nutrition.

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

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

PO, by mouth.

Management of Severe Diarrhea

- 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

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

TID, three times daily.

Diarrhea
Nursing Interventions and Patient Education

Sacituzumab Govitecan in Breast Cancer

- Counsel patients on risks of severe diarrhea
- Monitor for signs/symptoms of cholinergic syndrome
- Advise patients to promptly start antidiarrheals at symptom onset
- Encourage bland diet until gastrointestinal (GI) symptoms improve
- Replace fluids and electrolytes (orally; IV if indicated)
- Monitor and assess for signs of dehydration
- Encourage patients to call if black or bloody stool, inability to drink oral fluids, or nausea/vomiting/diarrhea not responding to supportive medications

Spring LM, et al. *Ann Oncol*. 2024;35(3):293–301. Skay A, Kardashian A. *Proceedings of UCLA Health*. 2020;24.

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

Spring LM, et al. *Ann Oncol*. 2024;35(3):293–301. NCCN Guidelines. Breast Cancer. NCCN website. v2.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

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

Promoting Patient Adherence

Sacituzumab Govitecan in Breast Cancer

- Dose reductions or treatment interruptions in ASCENT trial did not appear to reduce efficacy
- PFS in those who received a dose reduction was similar to the overall study population
- Encourage patients to discuss symptoms and side effect management challenges with the health care team

Rugo HS, et al. *NPJ Breast Cancer*. 2022;8(1):98.

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

	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

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

	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.

Understanding UGT1A1 Polymorphisms

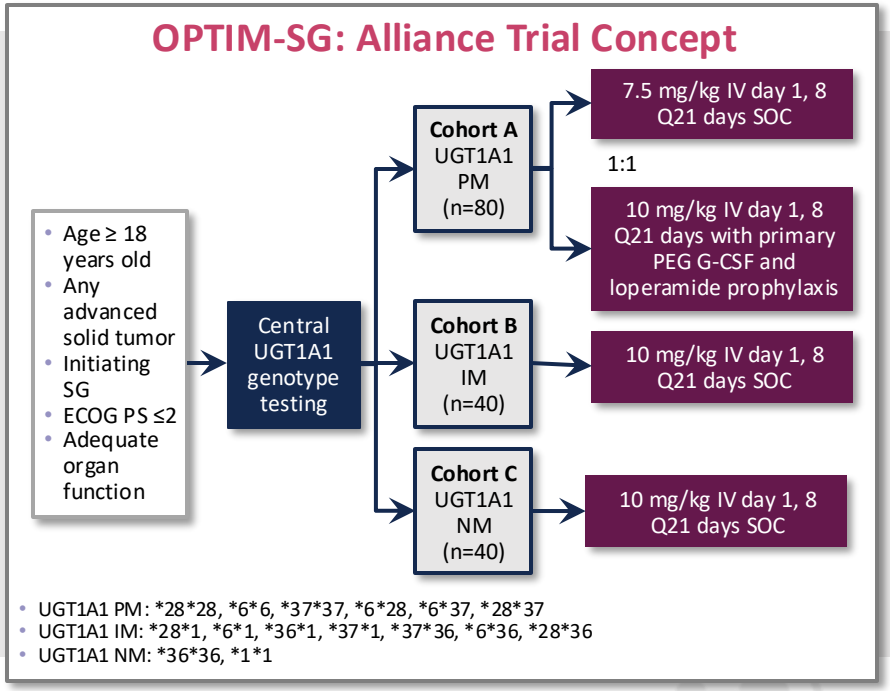
An Opportunity to Maximize Efficacy and Minimize Toxicity

Predicted UGT1A1 Phenotypes Based on Commonly Observed Diplotypes

Predicted UGT1A1 Phenotype	Frequently Reported Diplotypes (less commonly investigated diplotypes)
Normal metabolizer (NM)	*1/*1 (*1/*36, *36/*36)
Intermediate metabolizer (IM)	*1/*28, *1/*6 (*1/*37, *6/*36, *28/*36, *36/*37)
Poor metabolizer (PM)	*6/*6, *6/*28, *28/*28 (*6/*37, *28/*37, *37/*37)

UGT1A1 Phenotype Frequencies among Racial/Ethnic Groups

UGT1A1 Phenotype	African American/ Afro-Caribbean	Central/ South Asian	East Asian	European	Latino	Sub-Saharan African
NM	2%	29%	50%	13%	4%	32%
IM	20%	50%	42%	46%	33%	49%
PM	78%	21%	8%	41%	63%	19%



Trastuzumab Deruxtecan (T-DXd)

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%)

FDA-approved drug: fam-trastuzumab deruxtecan-nxki. Revised April 2024. FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf.

Interstitial Lung Disease/Pneumonitis

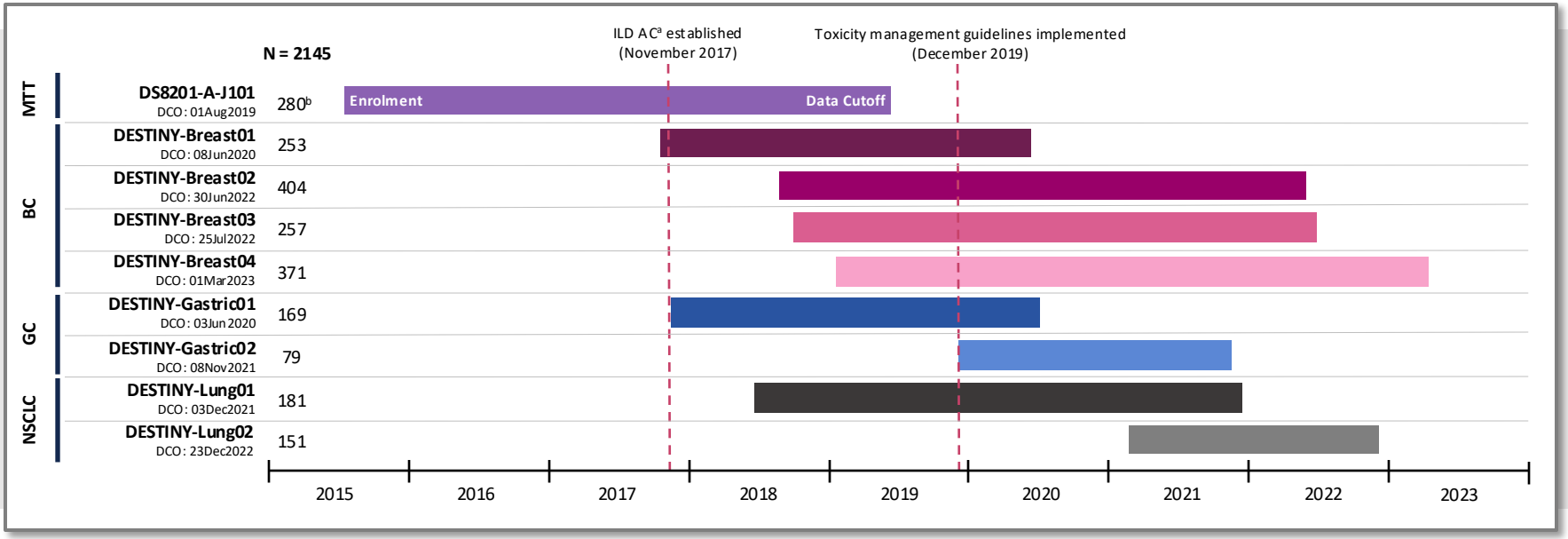
- T-DXd is approved for the treatment of HER2+ and HER2-low[a] mBC, HER2+ mGC/GEJA, HER2 (ERBB2)-mutant NSCLC, and HER2+ (IHC 3+) solid tumors[b,1]
- ILD has been identified as an AE of special interest with T-DXd treatment[2–4]
- Incidence of ILD with T-DXd treatment is reported at ~15% across all indications; 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]FDA-approved drug: fam-trastuzumab deruxtecan-nxki. Revised April 2024. FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.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.

ILD across T-DXd Studies



- Data were pooled from 9 clinical trials to identify patients with Gr 1 ILD as assessed by the investigators and confirmed by the adjudication committee (AC) who were retreated with T-DXd
  - All patients received at least 1 dose of T-DXd (5.4-8.0 mg/kg) monotherapy
- *T-DXd toxicity management guidelines recommend a dose reduction for retreatment if ILD takes longer than 28 days to resolve. At the time of study inclusions, guidelines recommended discontinuation of T-DXd if ILD had not resolved within 49 days from the last T-DXd dose*[c]

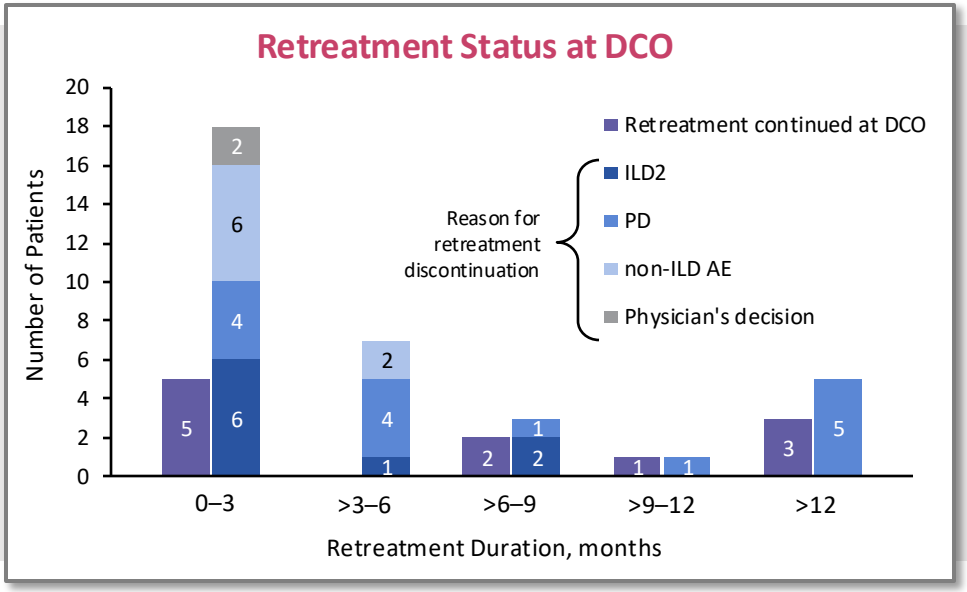
[a]Each AC session included an oncologist, a radiologist, and a pulmonologist. [b]Only patients who received at least 1 dose of T-DXd 5.4-8.0 mg/kg are included. The color bar for each study indicates the time from patient enrollment to data cut-off. [c]Guidelines have subsequently been updated to recommend discontinuation of T-DXd if ILD has not resolved within 126 days from the date of last drug dose.

Rugo HS, et al. *ESMO Open*. 2024;9:103326.

AC, adjudication committee; DCO, data cutoff; GC, gastric cancer; MTT, multiple tumor types.

T-DXd Retreatment Characteristics

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



- 68.9% (31/45) of patients were retreated without any dose reductions
- 24.4% (11/45) of patients were still receiving T-DXd retreatment at the DCOs of each respective study
- Progressive disease was the main reason for T-DXd retreatment discontinuation (33.3% [15/45] of patients)
  - 20.0% (9/45) of patients discontinued retreatment due to recurrent ILD (ILD2)
- **33.3% (15/45) of patients were retreated for >6 months and 17.8% (8/45) of patients were retreated for >12 months**

ILD1; first Gr 1 ILD event; ILD2, any-grade recurrent ILD event; PD, progressive disease.

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** T-DXd can be resumed if the ILD/pneumonitis fully resolved to Grade 0 • If resolved in ≤28 days from day of onset, maintain dose • If resolved in >28 days from day of onset, reduce dose by one level* • 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 • Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected	• Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected • 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]

Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378. FDA-approved drug: fam-trastuzumab deruxtecan-nxki. Revised April 2024. FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf. Rugo HS, et al. ESMO Open. 2024;9.

MDT, multidisciplinary team.

DESTINY-Breast04

Nausea and Vomiting

- 189/371 patients (50.9%) in the T-DXd arm and 64/172 patients (37.2%) in the TPC arm received antiemetic prophylaxis[a]
- Prophylaxis was not mandatory per study protocol, but was recommended

n (%)	Nausea		Vomiting	
	T-DXd (n=371)	TPC (n=172)	T-DXd (n=371)	TPC (n=172)
Dose reduction associated with N/V	17 (4.6)	4 (2.3)	3 (0.8)	1 (0.6)
Drug interruption associated with N/V	5 (1.3)	4 (2.3)	0	0
Drug discontinuation associated with N/V	1 (0.3)	0	1 (0.3)	0

Three Classes of Anti-emetic Premedication is Recommended—*this can be individualized to patient symptoms*

[a]Prophylaxis included antiemetics and antinauseants, corticosteroids for systemic use, drugs for functional gastrointestinal disorders, or other.

Rugo HS, et al. ESMO Breast Cancer Congress 2023. Abstract 1850.
NCCN Guidelines. Breast Cancer. NCCN website. v2.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

BID, twice daily; N/V, nausea or vomiting.

Questions & Answers

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-negative), diagnosed in 2020. She received neoadjuvant AC-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 followed by paclitaxel.

Case Study 1: JA (…continued)

You discuss the risks of neutropenia and diarrhea associated with sacituzumab govitecan with JA, 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 sacituzumab govitecan (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 minutes for 2 doses; then 0.2 mg IV as needed, up to 1 mg total

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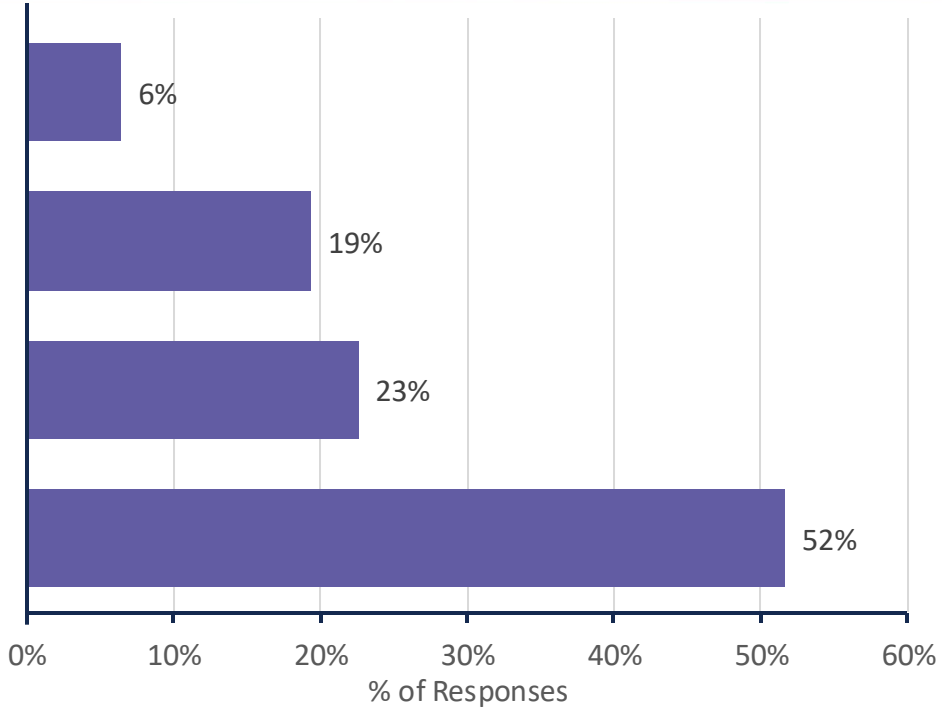

JA is able to control her diarrhea at home with loperamide and diet modifications as needed. She presents for Cycle 5 Day 1 of sacituzumab govitecan (SG) with an ANC of 1,100/µL. Her vital signs are stable, and she is afebrile. You contact the physician with the lab results.
Which of the following is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

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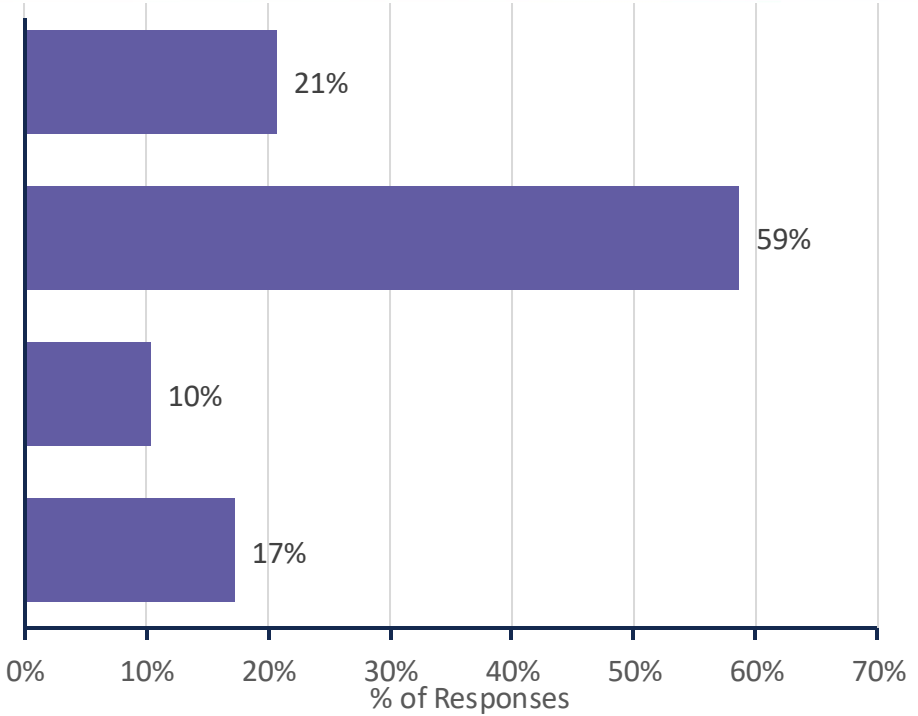

Case Study 2: AM

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

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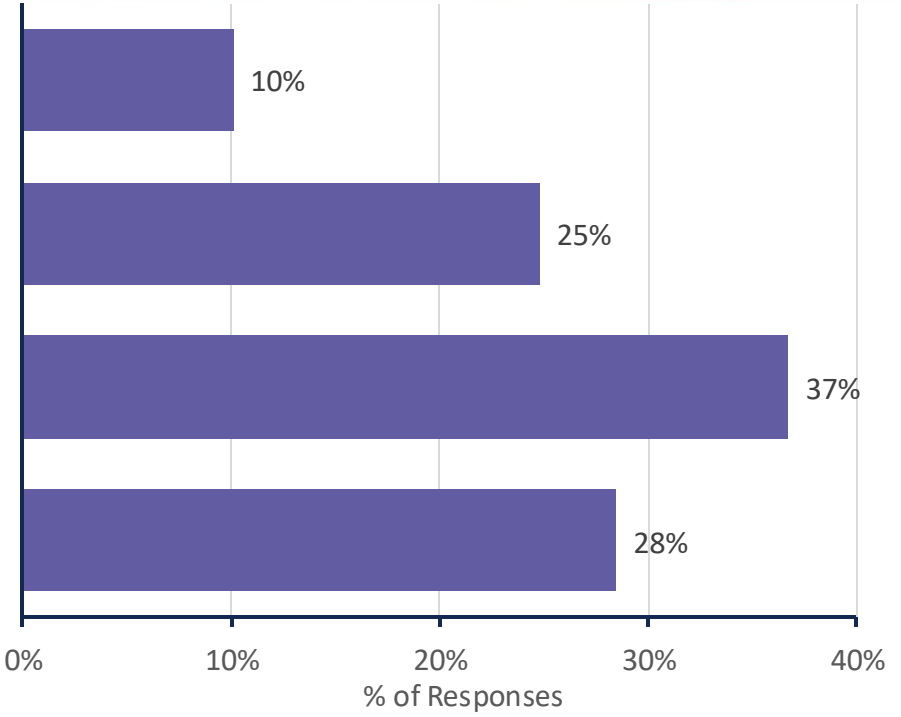

Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- *Provide ideal patient care* by taking time focus on your patients to get to know them as a person and understand their unique needs while they receive therapy.
- *Incorporate latest clinical trial data* regarding ADCs into the care of your patients with HER2-neg mBC, as documented by treatment selection in electronic health record (EHR) patient charts.
- *Manage AEs* in patients receiving ADCs for HER2-neg mBC according to updated guidelines and expert consensus, as documented by increased use of AE assessment tools and mitigation strategies in EHR patient charts.

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