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# Antibody–Drug Conjugates in Development for Breast Cancer

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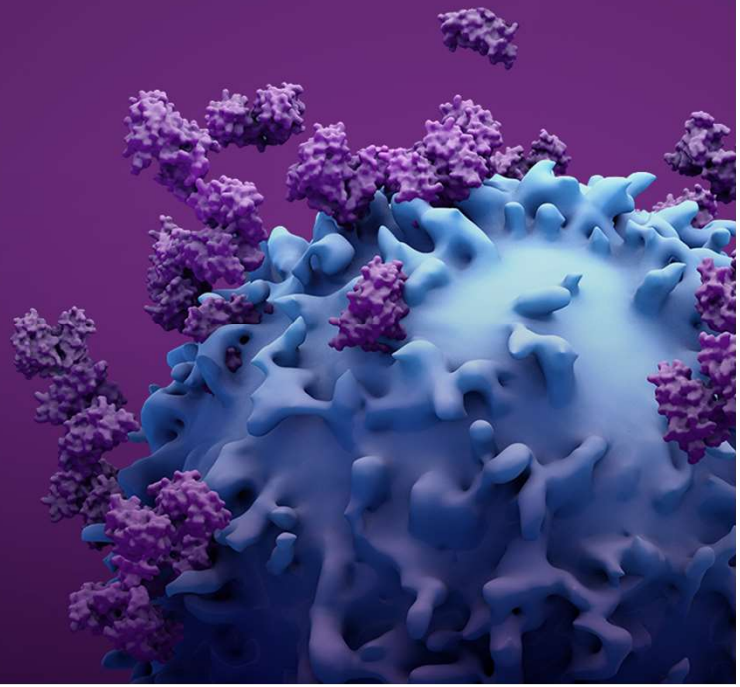

# Learning Objectives

**Review 3 FDA-approved ADCs and ADCs in clinical development for breast cancer**

- Analyze the unmet need in patients with breast cancer
- Discuss their mechanisms of action
- Analyze available clinical data and discuss ongoing clinical trials

ADC, antibody–drug conjugate; BC, breast cancer; FDA, US Food and Drug Administration.

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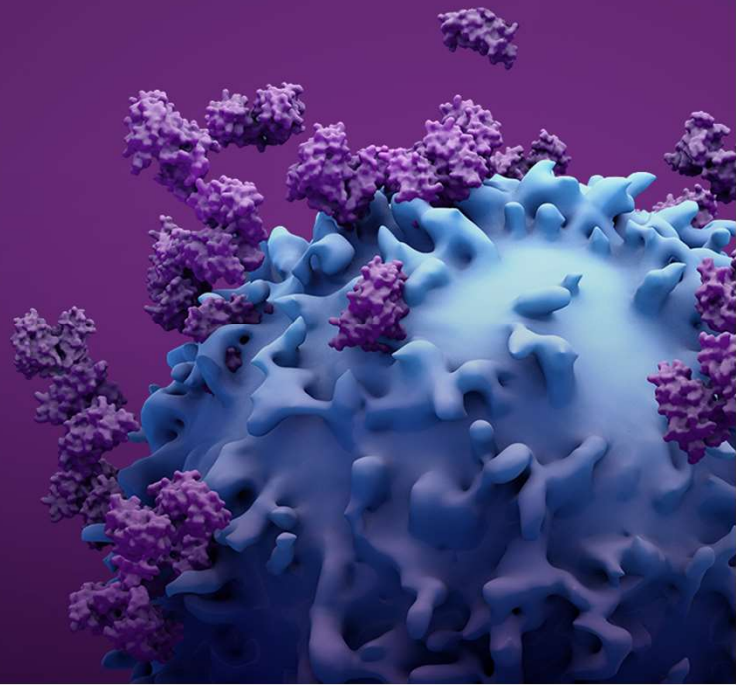
# FDA-Approved ADCs in Breast Cancer



# The Majority of Breast Cancer Cases Are Diagnosed in Early Stages, When the Disease Is Curable

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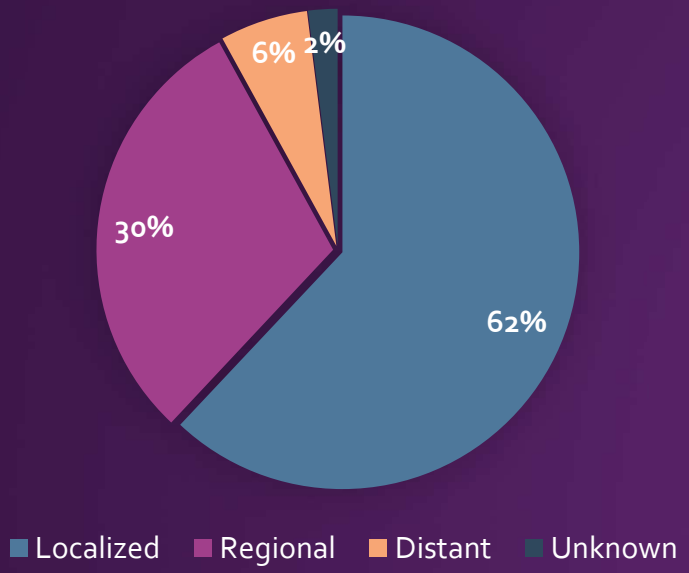


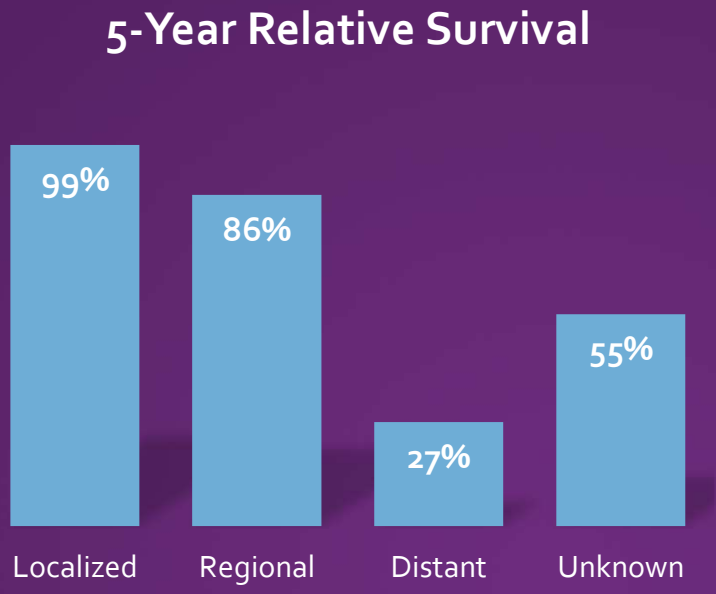


Breast Cancer Stage Distribution of SEER Incidence Cases, 2008-2017. URL: https://seer.cancer.gov/explorer/application.php?site=55&data_type=1&graph_type=4&compareBy=sex&chk_sex_3=3&chk_race_1=1&chk_age_range_1=1&advopt_precision=1&showDataFor=race_1_and_age_range_1. Accessed: November 8, 2020.

# Breast Cancer Subtypes Guide Treatment Decisions

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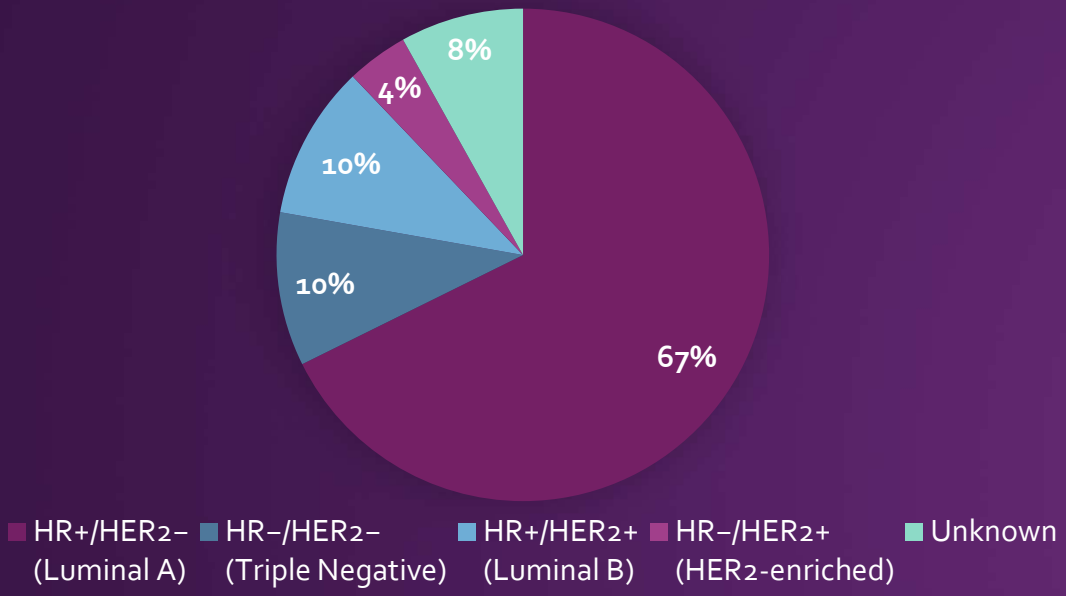
## Female Breast Cancer Cases by Subtype (%) SEER 21 2012-2016




## Rate of New Breast Cases per 100,000 Women, SEER 21 2012-2016

| Subtype | New Cases |
|---|---|
| HR+/HER2− | 85.8 |
| HR−/HER2− | 13.0 |
| HR+/HER2+ | 12.9 |
| HR−/HER2+ | 5.4 |
| Unknown | 10.4 |
| Total | 127.5 |

HER, human epidermal growth factor receptor; HR, hormone receptor.
Cancer Stat Facts: Female Breast Cancer Subtypes. URL: https://seer.cancer.gov/statfacts/html/breast-subtypes.html.

# FDA-Approved ADCs in Breast Cancer (BC)

| Drug name | Target | Indication | FDA Approval |
|---|---|---|---|
| KADCYLA® (trastuzumab emtansine)[1] | HER2 | **Early Breast Cancer**: as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. **Metastatic Breast Cancer**: as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination | 02/2013 |
| ENHERTU ® (trastuzumab deruxtecan)[2] | HER2 | Adults with unresectable or metastatic HER2+ breast cancer who have received ≥2 prior anti-HER2 based regimens | 12/2019 |
| TRODELVY ® (sacituzumab govitecan)[3] | TROP-2 | Adult patients with metastatic triple-negative breast cancer (TNBC) who have received ≥ 2 prior therapies for metastatic disease | 06/2020 |

1. KADCYLA (trastuzumab emtansine) [package insert]. San Francisco, CA: Genentech, Inc; 2019.
2. ENHERTU (trastuzumab deruxtecan) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2019.
3. TRODELVY (sacituzumab govitecan-hziy) [package insert]. Morris Plains, NJ: Immunomedics, Inc; 2020.

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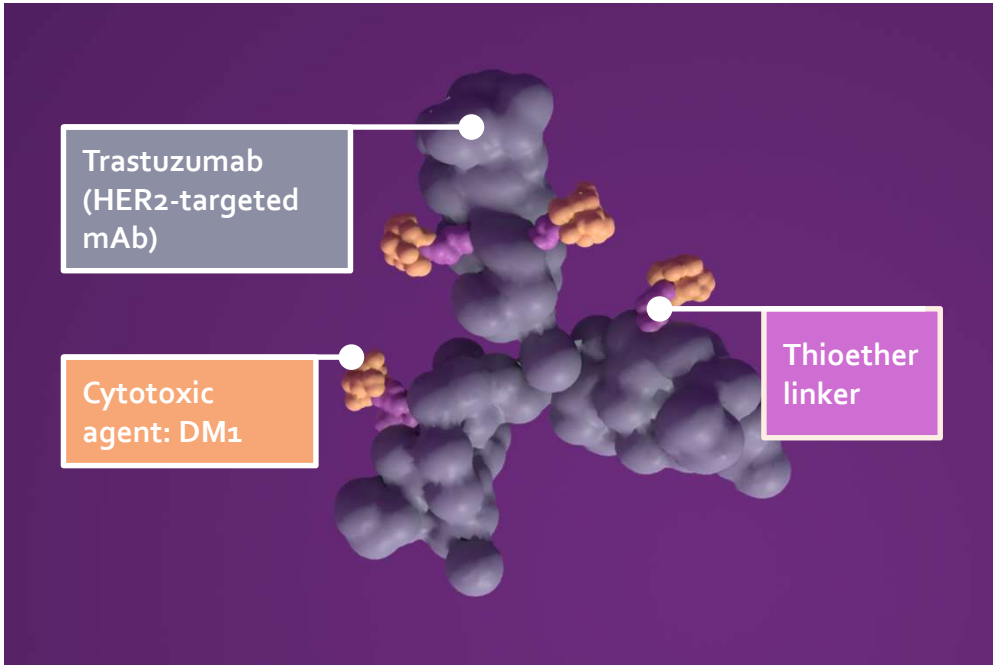


- HER2+ antitumor and DM1 cytotoxic activity[1]
- DM1 payload
- DM1, a maytansinoid, is approximately 20 to 200 times more potent than taxanes and vinca alkaloids[2,3]
- MCC linker was designed to provide a more stable bond between[1-3] trastuzumab and the active cytotoxic agent, with the goal of minimizing systemic exposure in circulation

DM1, myotonic dystrophy type 1; mAB, monoclonal antibody; MCC, N-succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate; T-DM1, trastuzumab emtansine.

1. KADCYLA Prescribing Information. Genentech, Inc. 2019; 2. Lewis Phillips GD, Li G, Dugger DL, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res. 2008;68(22):9280-9290; 3. Staudacher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? Br J Cancer. 2017;117(12):1736-1742; 4. Brufsky AM. HER2-Positive Metastatic Breast Cancer: Current Status and Promising Agents. https://www.clinicaloptions.com/sitecore/content/clinicaloptions/cco/oncology/programs/her2-positive-mbc-care/module/text-module/page-5#. Published April 13, 2020. Accessed October 22, 2020.

Breast Cancer | T-DXd

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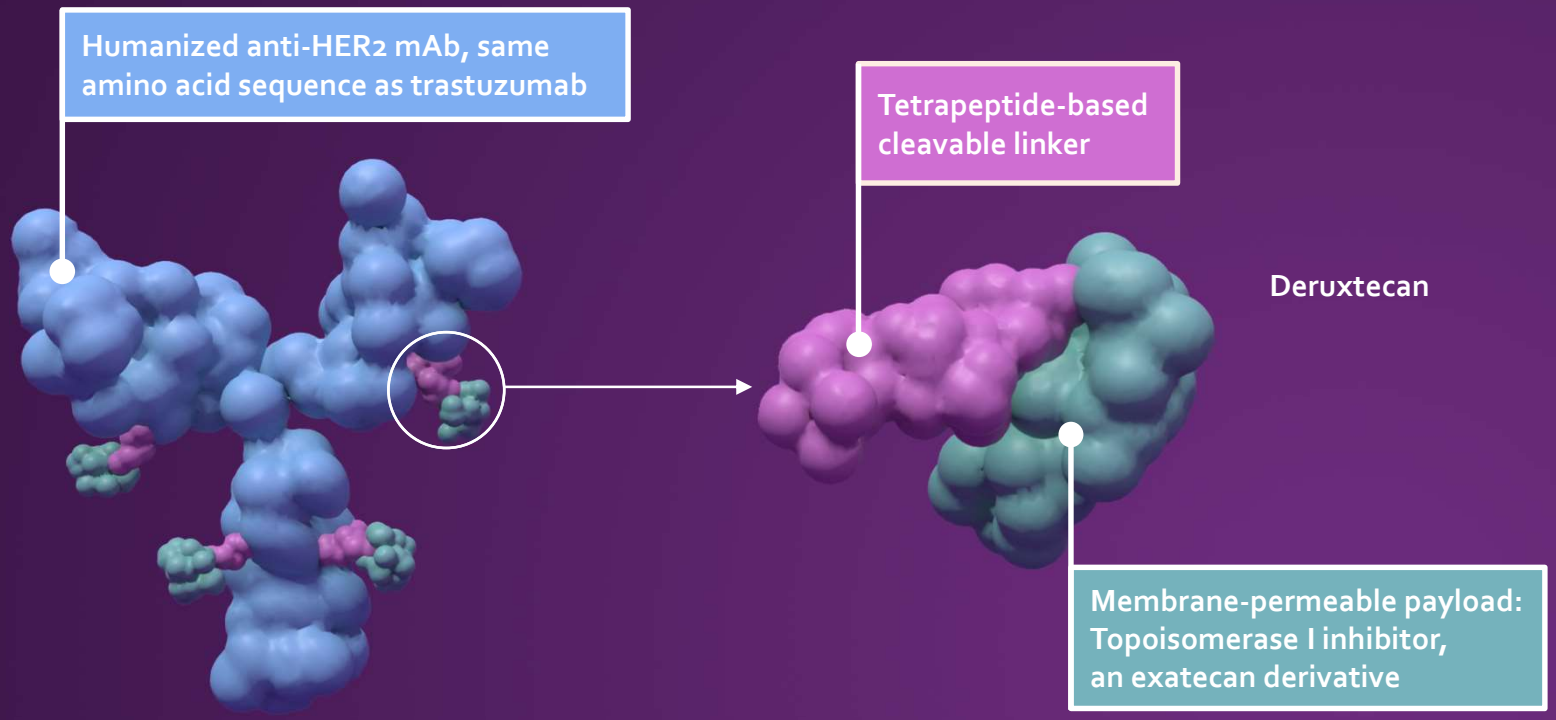
# Trastuzumab Deruxtecan (T-DXd)




Smit EF et al. Trastuzumab Deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer: interim results of DESTINY-Lung01. Presented at: American Society for Clinical Oncology 2020 Virtual Scientific Program; May 29 – 31. Accessed November 6, 2020. https://meetinglibrary.asco.org/session/12667

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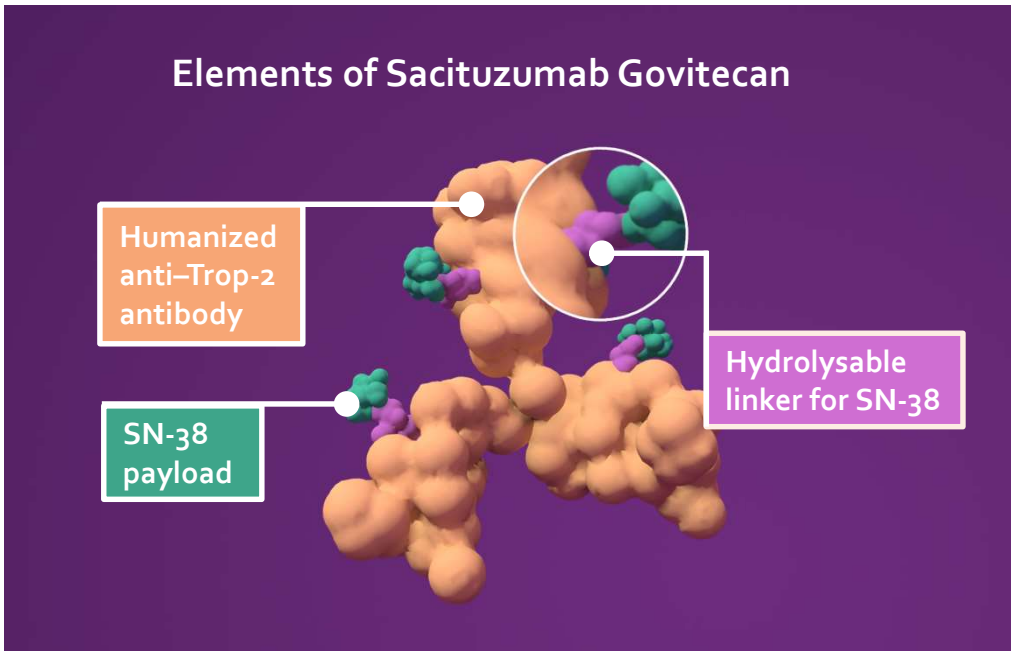


- SN-38 is the active metabolite of irinotecan, a topoisomerase I inhibitor that interferes with cell growth and spread[1]
- Sacituzumab govitecan delivers up to 136x more SN-38 than irinotecan[2]
- Inhibition of topoisomerase I by SN-38 leads to apoptosis[1]

# Mechanism of Sacituzumab Govitecan (IMMU-132)

1. Bardia A et al. J Clin Oncol. 2017;35(19):2141-2148; 2. Goldenberg DM et al. Oncotarget. 2015;6(26):22496–22512.

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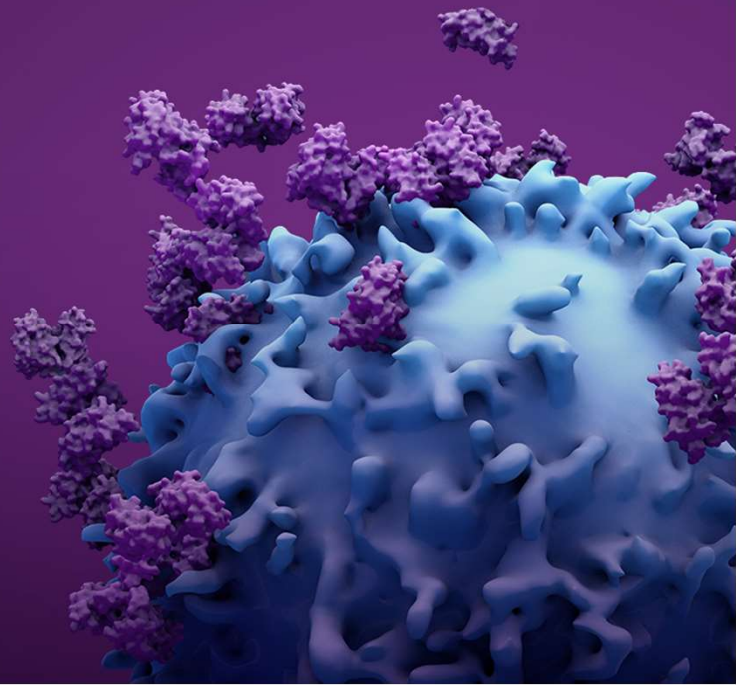
# ADCs Targeting HER2



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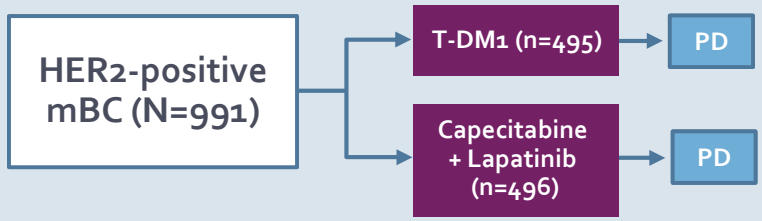
# EMILIA: Improved OS With T-DM1 vs Capecitabine + Lapatinib in Pts With HER2+ Locally Advanced or mBC

## PATIENTS

- HER2-positive locally advanced or mBC
- Previously treated with trastuzumab and taxane

## STUDY DESIGN




## ENDPOINTS

**1°**

- PFS
- OS
- Safety

**Select 2°**

- ORR
- DOR
- CBR
- TTF

CBR, clinical benefit rate; DOR, duration of response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Pts, patients; ORR, overall response rate; TTF, time to treatment failure.
U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT00829166. Accessed November 8, 2020. Last updated: October 31, 2016.

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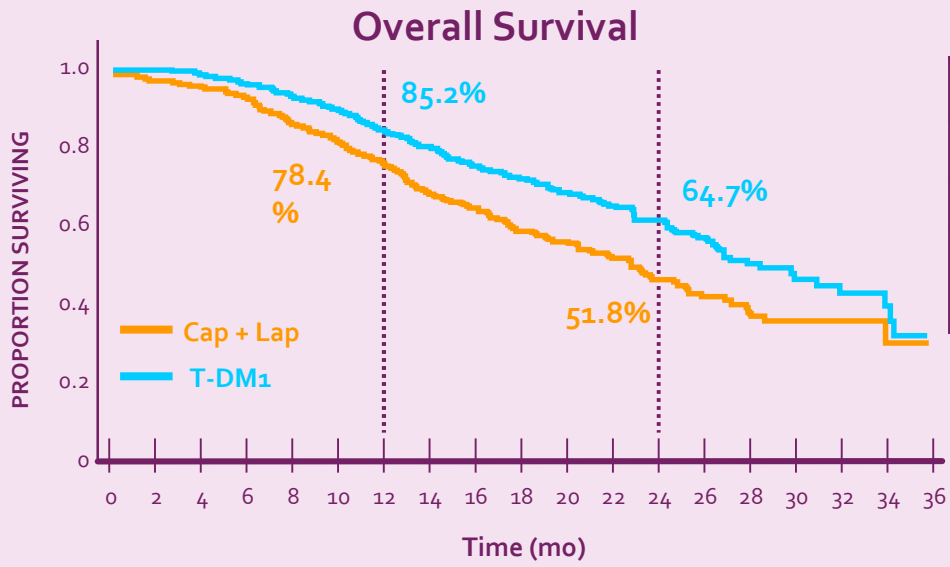
# EMILIA Led to Kadcyla Approval in Patients With HER2+ Locally Advanced or mBC in Feb 2013[1,2]

## ANTITUMOR ACTIVITY




| | Median (mo) | No. of events |
|---|---|---|
| Cap + Lap | 25.1 | 182 |
| T-DM1 | 30.9 | 149 |

Stratified HR=0.682 (95% CI, 0.55-0.85); *P* = 0.0006

*Efficacy stopping boundary* P = *0.0037 or HR=0.727*

Data cut-off July 31, 2012;
Unstratified HR=0.70 (*P* = 0.0012)

Cap, capecitabine; CI, confidence interval; HR, hazard ratio; Lap, lapatinib; mo, month.

1. CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 125427Orig1s000. fda.gov.URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000SumR.pdf. Published February 21, 2013. Accessed May 11, 2020; 2. Verma S et al. *N Engl J Med*. 2012;367:1783-1791.

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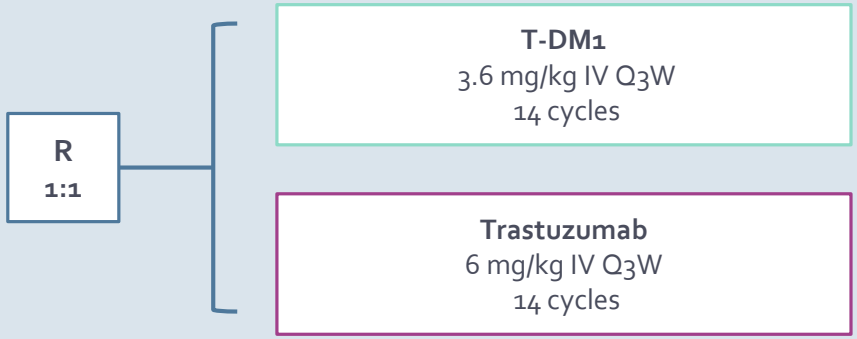
# KATHERINE: Ph 3, Open-Label Study of Adjuvant T-DM1 vs Trastuzumab for Residual Invasive HER2-Positive BC

## PATIENTS

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
  - Minimum of 9 weeks of taxane
  - Anthracyclines and alkylating agents allowed
  - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
  - Second HER2-targeted agent allowed
  - Residual invasive tumor in breast or axillary nodes
  - Randomization within 12 weeks of surgery

## STUDY DESIGN




Radiation and endocrine therapy per protocol and local guidelines

## ENDPOINTS

**1°**

- iDFS

**Select 2°**

- DFS
- OS
- Distant recurrence-free survival
- safety

Presented by Charles E. Geyer at the San Antonio Breast Cancer Symposium 2018 Dec 4-8
Von Minckwitz G et al. *N Engl J Med.* 2019;380(7):617-628.

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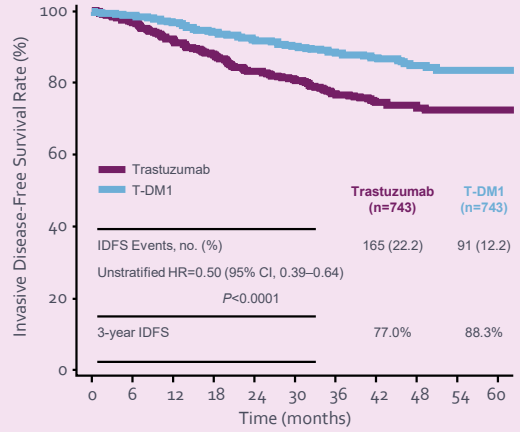
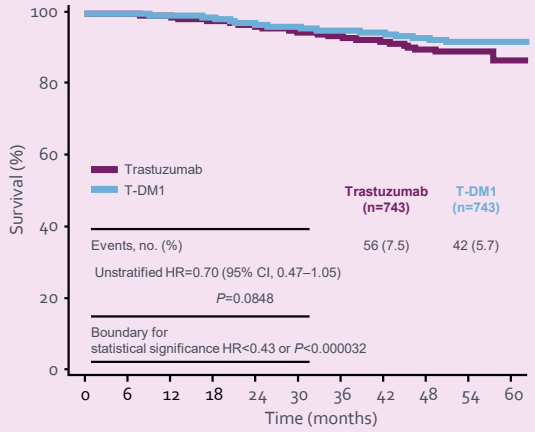
# KATHERINE: iDFS and OS

## ANTITUMOR ACTIVITY




## SAFETY RESULTS

- The most common AEs of gr ≥3 with T-DM1: decreased platelet count (in 5.7% of pts) and hypertension (2.0%); with trasuzumab: hypertension (1.2%), radiation-related skin injury (1.0%)
- SAEs occurred in 94 patients who received T-DM1 (12.7%) and 58 patients who received trastuzumab (8.1%)
- AEs leading to discontinuation occurred in 133 patients in the T-DM1 group (18.0%) and 15 patients in the trastuzumab group (2.1%)
- 1 pt in the T-DM1 group with a decreased platelet count died from an intracranial hemorrhage that occurred after a fall. The % of patients with hemorrhage of gr ≥3 were similar in the T-DM1 group and the trastuzumab group (0.4% and 0.3%)

Presented by Charles E. Geyer at the San Antonio Breast Cancer Symposium 2018 Dec 4-8

# T-DM1 Approved Based Upon Results From KATHERINE

**As of May 6, 2019, the FDA has approved ado-trastuzumab emtansine (T-DM1; KADCYLA) for use as an adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease following neoadjuvant trastuzumab (Herceptin) and chemotherapy[1]**

NCCN Guidelines Recommend T-DM1 for HER2-positive Breast Cancer Residual Disease :

- If HER2-positive with presence of residual disease[2]
- T-DM1 alone for 14 cycles (KATHERINE[3])

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# Selected Ongoing Studies With T-DM1

| Study | Ph | Patients | N | Arms | 1° EP | Est Study Completion |
|---|---|---|---|---|---|---|
| ATOP TRIAL[1] | 2 | • ≥60 years of age<br>• HER2-positive breast cancer<br>• Standard chemotherapy/trastuzumab declined by pt or pt is not deemed an eligible candidate for therapy | 82 | Experimental: T-DM1 | 5-year iDFS rate | 01/2022 |

**Several clinical studies of combinations with T-DM1 are ongoing and not represented in this list.**

EST, estimated; ET, endocrine therapy; EP< endpoint; iDFS, invasive disease-free survival; pCR, pathological compete response rate; ph, phase; pt, patient.

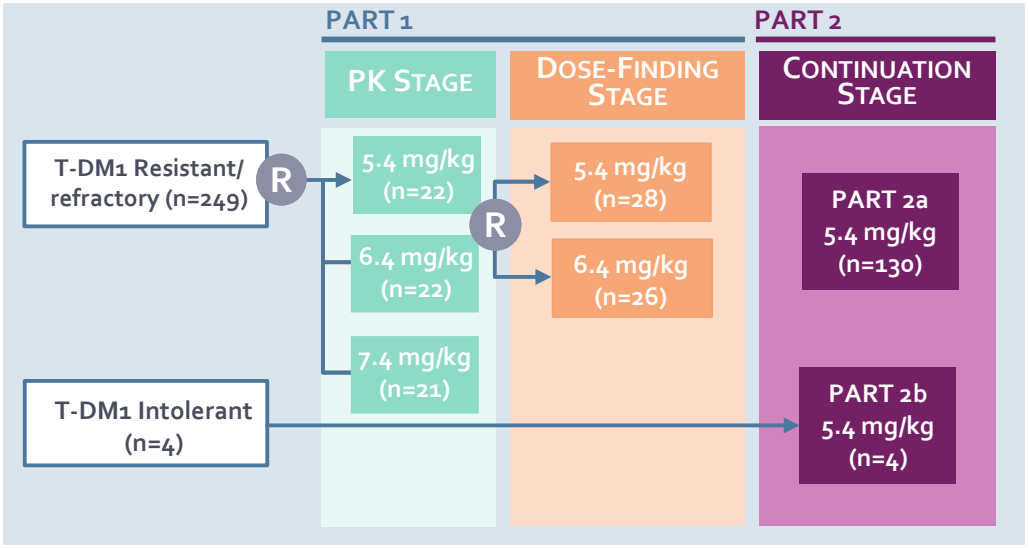
1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03587740. Published July 16, 2018. Accessed November 7, 2020. Last updated: October 5, 2020;
2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT01745965. Published December 10, 2012. Accessed November 7, 2020. Last updated: July 23, 2020.

# DESTINY-BREAST01 Study Schema[1,2]

## PATIENTS

- ≥18 years of age
- Unresectable and/or mBC
- HER2-positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed

## STUDY DESIGN




## ENDPOINTS

**1°**

Confirmed ORR

**Select 2°**

- Investigator-assessed ORR
- DCR
- DOR
- CBR
- PFS
- OS
- PK

DCR, disease control rate; ILD, interstitial lung disease, PK, pharmacokinetics.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03248492. Accessed November 7, 2020. Last updated: August 18, 2020;
2. Modi S et al. *N Engl J Med*. 2020;382(7):610-621.

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# DESTINY-BREAST01 (NCT03248492), Phase 2, Showed Positive Outcomes in OS, PFS, ORR, and Change in Baseline Tumor Size, Leading to Accelerated Approval of Trastuzumab Deruxtecan in 2019[1,2]

## ANTITUMOR ACTIVITY

| Endpoint | Result (N = 184) |
|---|---|
| OS, % (95% CI) at 6 mo | 93.9 (89.3, 96.6) |
| OS, % (95% CI) at 12 mo | 86.2 (79.8, 90.7) |
| PFS, mo (95% CI) for all patients | 16.4 (12.7, NR) |
| PFS, mo (95% CI) for patients with asymptomatic brain metastases | 18.1 (6.7, 18.1) |
| CBR | 76.1 (69.3, 82.1) |
| Confirmed ORR | 60.9 (53.4, 68) |

## SAFETY RESULTS

- Most common AEs of gr ≥3 were decreased neutrophil count (20.7% of patients), anemia (8.7%), and nausea (7.6%)
- T-DXd was associated with ILD in 13.6% of patients (gr 1 or 2, 10.9%; gr 3 or 4, 0.5%; and gr 5, 2.2%)

AE, adverse event; gr, grade; NR, not reached.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03248492. Accessed November 7, 2020. Last updated: August 18, 2020;
2. Modi S et al. *N Engl J Med*. 2020;382(7):610-621.

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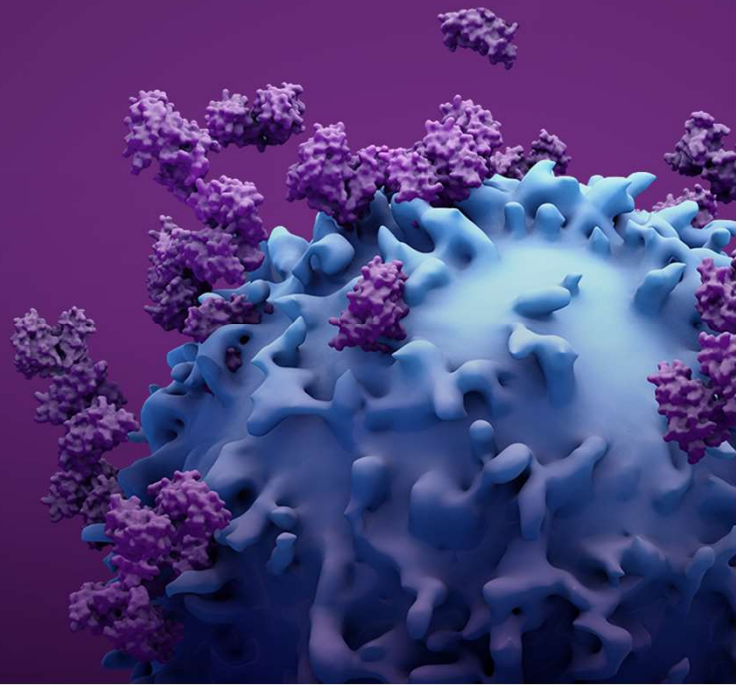
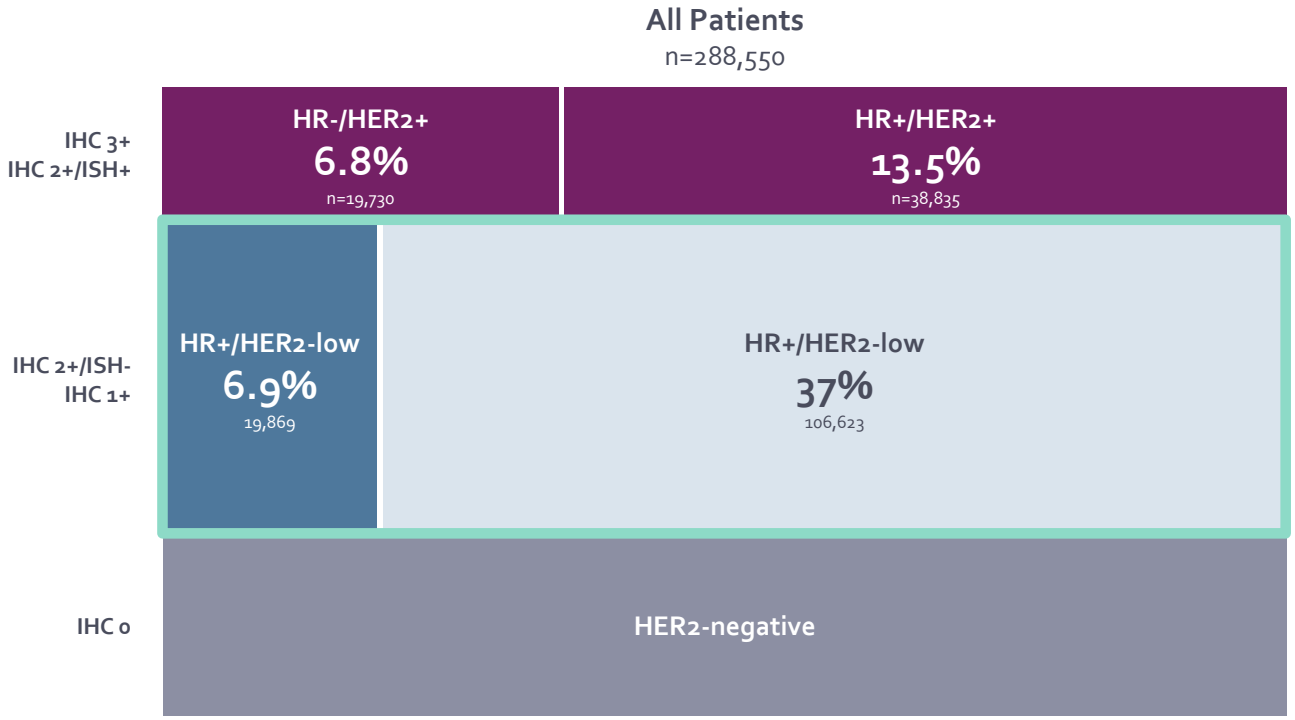
# T-DXd in HER2-Low



# Ongoing Clinical Trials Have Defined Tumors With HER2-Low Expression as IHC 1+ or IHC 2+ and in-Situ Hybridization (ISH)-Negative




*Source: Decision Resources, inclusive of US, Europe, and Japan (Breast Cancer, Last updated, December 2017, CAncerMPACT (2017))

# NSABP B-47: HER2-Negative Patients Derived Similar Benefits From Trastuzumab as Demonstrated in HER2-Positive Patients

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## STUDY DESIGN

**NSABP B-47**

- Randomized phase 3 study of 3,270 patients tested the hypothesis that trastuzumab can be effective in patients with node-positive or high-risk node-negative breast cancer who are "HER2-low" (1+ or 2+ by immunohistochemistry, not amplified by fluorescence in situ hybridization)
- **Patients were randomized to chemotherapy with or without trastuzumab for 1 year to determine if the addition of trastuzumab improves DFS**

## ANTITUMOR ACTIVITY

- Study demonstrated feasibility of identifying and accruing these patients to trials
- The randomized trial showed no improvement in invasive disease–free survival, overall survival, or other endpoints when women received 1 year of trastuzumab in addition to standard chemotherapy vs chemotherapy alone

1. https://www.ascopost.com/issues/january-25-2018/nsabp-b-47-no-benefit-for-adjuvant-trastuzumab-in-her2-low-breast-cancer/; 2. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673-1684,2005; 3. Fehrenbacher L, Cecchini RS, Geyer CE, et al: NSABP B-47 (NRG Oncology): Phase III randomized controlled trial comparing adjuvant chemotherapy with adriamycin and cyclophosphamide followed by weekly paclitaxel, or docetaxel and cyclophosphamide with or without a year of trastuzumab in women with node-positive or high-risk node-negative invasive breast cancer expressing HER2 staining intensity of IHC 1+ or 2+ with negative FISH. 2017 San Antonio Breast Cancer Symposium. Abstract GS1-02. Presented December 6, 2017.

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# J101 Ongoing Phase 1 Trial With T-DXd Demonstrated Positive Results in Patients With Heavily Pretreated, Advanced, HER2-Low BC

## PATIENTS

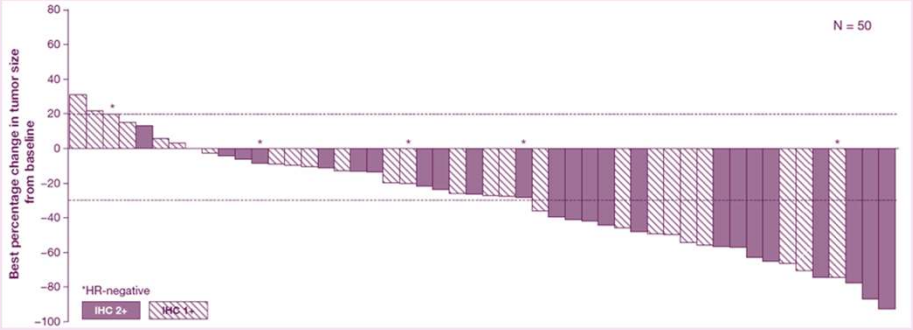
Patients with breast cancer or gastric/GEJ adenocarcinoma

mCRM with EWOC

Two-part dose escalation and dose expansion phase

## ANTITUMOR ACTIVITY

**T-DXd Demonstrated a 44.2% ORR (19/43) with a Manageable Safety Profile**




## SAFETY RESULTS

- 99.4% of patients experienced a TEAE regardless of causality
- 22.9% of patients experienced a serious TEAE
- 50.0% of patients experienced grade ≥3 TEAE
- 4 fatal cases of ILD/pneumonitis

| N = 51 | Confirmed ORR n/N (%) | Confirmed DCR n/N (%) | DOR Median (range), mo | PFS Median (95% CI), mo |
|---|---|---|---|---|
| HER2-low BC (IHC 2+ / ISH– or IHC 1+) | 44.4% | 83.3% | 11 (4.5, 12.8) | 8 (5.6, 13.9) |

EWOC, escalation with overdose control; GEJ, gastroesophageal junction; IHC, immunohistochemistry; ISH, in situ hybridization; mCRM, modified Continuous Reassessment Method; TEAE, treatment-emergent adverse event.

Modi S et al. *J Clin Oncol*. 2020;38(17):1887-1896.

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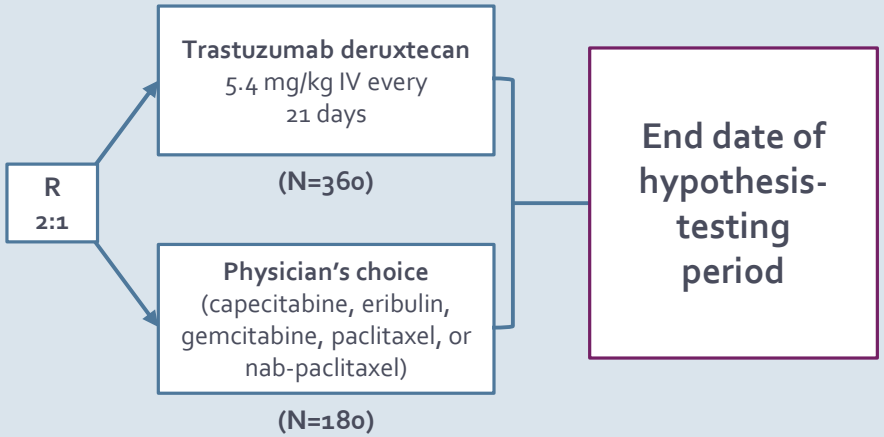
# DESTINY-Breast04: Multicenter, Int'l, Randomized, Open-Label Phase 3 Study of T-DXd vs Investigators Choice in HER2-Low BC

## PATIENTS

- Unresectable and/or metastatic HER2-low BC
- (IHC 2+/ISH- or IHC 1+)

## STUDY DESIGN




## ENDPOINTS

**1°**

PFS

**Select 2°**

- OS
- ORR
- Safety

**Estimated study completion: January 2023**

U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed November 7, 2020. Last updated: October 20, 2020.

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# Ongoing Studies With T-DXd

| Study | Ph | Patients | N | Arms | 1° EP | ''''''''''''' |
|---|---|---|---|---|---|---|
| DESTINY-Breast02 (NCT03523585)[1] | 3 | Previously treated unresectable and/or metastatic HER2-positive BC | 600 | • Experimental: T-DXd<br>• Comparator: trastuzumab + capecitabine<br>• Comparator: lapatinib + capecitabine | PFS based on BICR (2° EP: OS, ORR, DOR, PFS based on investigator's assessment) | 09/2024 |
| DESTINY-Breast03 (NCT03529110)[2] | 3 | Unresectable and/or metastatic HER2-positive BC previously treated with trastuzumab and taxane | 500 | • Experimental: T-DXd<br>• Comparator: T-DM1 | PFS based on BICR (2° EP: OS, ORR, DOR, PFS based on investigator's assessment) | 04/2023 |
| DESTINY-Breast04 (NCT03734029)[3] | 3 | Previously treated unresectable and/or metastatic HER2-low BC | 540 | • Experimental: T-DXd<br>• Comparator: PC (capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel) | PFS based on BICR (2° EP: PFS based on investigator's assessment, OS, ORR, DOR) | 01/2023 |
| DESTINY-Breast05 (NCT04622319) | 3 | Patients with HER2-positive primary BC with residual invasive disease in breast or axillary lymph nodes with higher risk of recurrence | 1600 | • Head-to-head comparison of T-DXd vs T-DM1 | iDFS (2° EP: OS, DFS) | 09/2027 |
| DESTINY-Breast06 (NCT04494425)[4] | 3 | HER2-Low, HR+ adv or metastatic BC who have had disease progression on ≥2 lines of ET | 850 | • Experimental: T-DXd<br>• Comparator: SOC (capecitabine, paclitaxel, nab-paclitaxel) | PFS in HR+, HER2-low (2° EP: PFS in ITT, OS, ORR, DOR, PFS, safety, TTD, HRQoL) | 12/2022 |

BICR, blinded independent central review ; HRQoL, health-related quality of life; ITT, intention-to-treat; PC, physician's choice SOC, standard of care.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03523585. Accessed November 7, 2020. Last updated: September 30, 2020; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03529110. Accessed November 7, 2020. Last updated: September 25, 2020; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03529110; 3. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed November 7, 2020. Last updated: October 20, 2020; 4. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04494425. Accessed: November 7, 2020. Last updated: November 5, 2020.

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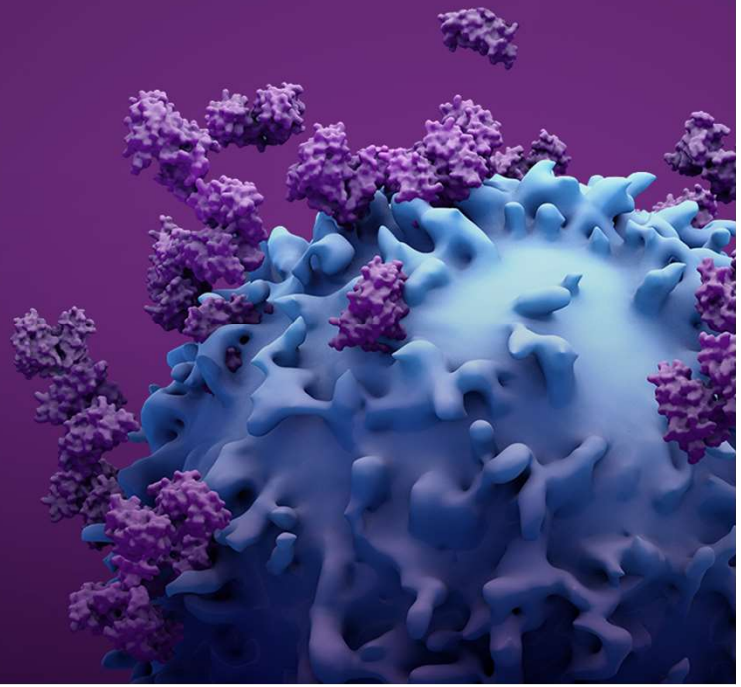
# ADCs IN TRIPLE-NEGATIVE BREAST CANCER (TNBC)



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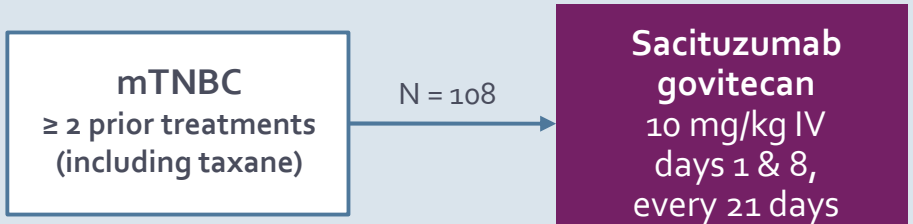
# IMMU-132-01: Ph 1/2 Study of Sacituzumab Govitecan (IMMU-132) in Pts With Epithelial Cancers[1,2]

## PATIENTS

- ≥18 years of age
- Stage IV mTNBC
- Refractory to or relapsed after 2 standard therapeutic regimens (for TNBC)

## STUDY DESIGN




## ENDPOINTS

**1°**

ORR

**Select 2°**

- Time to response
- DOR
- CBR
- PFS
- OS

TNBC, triple-negative breast cancer.

1. Bardia A et al. *N Engl J Med*. 2019; 380(8):741-751; 2. Goldenberg DM et al. Oncotarget. 2015;6(26):22496–22512; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT01631552. Accessed November 7, 2020. Last updated: September 9, 2020.

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# Sacituzumab Govitecan Was Associated With Durable Objective Responses in Patients With Heavily Pretreated mTNBC

## ANTITUMOR ACTIVITY

- **ORR = 33.3% (36/108)**
- CBR = 45.4% (49/108)

| Endpoint | Result (N = 108) |
|---|---|
| Median PFS, mo (95% CI) | 5.5 (4.1, 6.3) |
| Median OS, mo (95% CI) | 13.0 (11.2, 13.7) |
| Median time to onset of response, mo (range) | 2.0 (1.6, 13.5) |
| Median DOR, mo (95% CI) | 7.7 (4.9, 10.8) |

## SAFETY RESULTS

- 4 deaths (3.7%) occurred during treatment
- 3 pts (2.8%) discontinued treatment because of AEs
- Gr 3 or 4 AEs occurred in ≥10% of pts, including anemia and neutropenia
  - Gr 3 or 4 neutropenia occurred in 45 pts (41.7%)
  - Gr 3 anemia occurred in 12 pts (11%)
- 10 pts (9.3%) had febrile neutropenia

Bardia A et al. *N Engl J Med*. 2019; 380(8):741-751.

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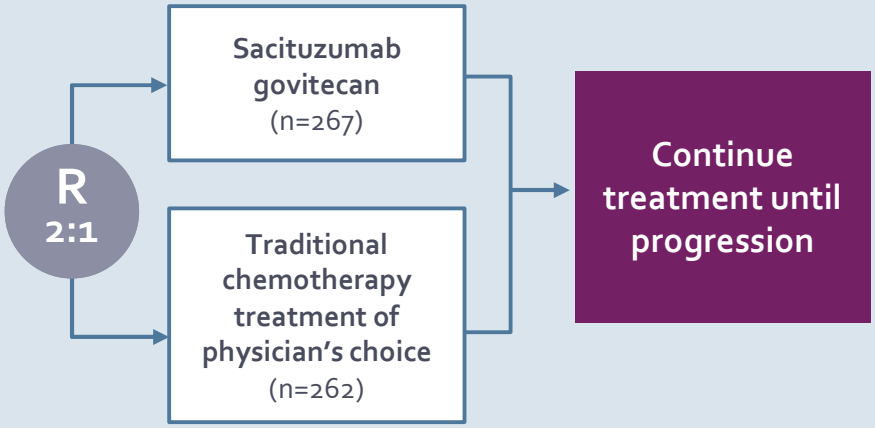
# ASCENT: Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Previously Treated TNBC[1,2]

## PATIENTS

- ≥18 years of age
- mTNBC
- ≥2 prior treatments or >1 therapy for advanced disease

## STUDY DESIGN




## ENDPOINTS

**1°**

PFS

**Select 2°**

OS

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT02574455. Accessed November 7, 2020. Last updated: October 8, 2020;
2. Bardia A. ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Presented at: European Society for Medical Oncology Virtual 2020 Scientific Sessions. September 19, 2020. 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.

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# ASCENT: Results Confirm Sacituzumab Govitecan Should Be Considered as a New SOC in Pts With Pretreated mTNBC

## ANTITUMOR ACTIVITY

| BCIR Analysis | SG (n=235) | TPC (n=233) |
|---|---|---|
| No. of events | 166 | 150 |
| mPFS – mo (95% CI) | 5.6 (4.3-6.3) | 1.7 (1.5-2.6) |
| HR (95% CI), *P* value | **0.41** (0.32-0.52) ***P* < 0.0001** | |

| OS | SG (n=235) | TPC (n=233) |
|---|---|---|
| No. of events | 155 | 185 |
| mOS – mo (95% CI) | 12.1 (10.7-14.0) | 6.7 (5.8-7.7) |
| HR (95% CI), *P* value | **0.48** (0.38-0.59) ***P* < 0.0001** | |

| | SG (n=235) | TPC (n=233) |
|---|---|---|
| ORR – no. (%) | 82 (35) | 11 (%) |
| *P* value | < 0.0001 | |
| CR | 10 (4) | 2 (1) |
| PR | 72 (31) | 9 (4) |

## SAFETY RESULTS

- Key gr ≥3 TRAEs (SG): neutropenia (51%), diarrhea (10%), leukopenia (10%) anemia (8%), and febrile neutropenia (6%)
- No severe cardiovascular toxicity, no gr >2 neuropathy or gr >3 ILD with SG
- No treatment-related deaths with SG
- AEs leading to treatment discontinuations were low for SG (4.7%)

mOS, median overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Bardia A. ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Presented at: European Society for Medical Oncology Virtual 2020 Scientific Sessions. September 19, 2020. 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.

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# TROPiCS-02: Ph 3 Study of Sacituzumab Govitecan (IMMU-132) in Patients With HR+/HER2–Negative mBC

## PATIENTS

- ≥18 years of age
- HR+/HER2– mBC
- ≥1 prior anticancer hormonal treatment
- ≥1 prior CDK4/6 inhibitor treatment in the metastatic setting

## STUDY DESIGN

**HR+/HER2– mBC**

≥2 prior treatment failures
AND
<4 prior chemotherapy regimens
N=108

→ **Sacituzumab govitecan**
10 mg/kg IV
days 1 & 8, every 21 days

→ **Traditional chemotherapy treatment of PC**
(eribulin, gemcitabine, capecitabine & vinorelbine)

## ENDPOINTS

**1°**

- PFS
- ORR

**Select 2°**

- OS
- DOR

## Estimated study completion: May 2023

CDK4/6, cyclin-dependent kinase 4/6 inhibitor.

U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03901339. Accessed November 7, 2020. Last updated: September 29, 2020.

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# Ongoing Studies With Sacituzumab Govitecan in Breast Cancer

| Study | Ph | Patients | N | Arms | 1° EP | Est Study Completion |
|---|---|---|---|---|---|---|
| NCT04230109 **(NeoSTAR)**[1] | 2 | Pts with localized TNBC | ~50 | Safety and efficacy of sacituzumab govitecan in localized TNBC | DFS, OS | August 31, 2023 |
| NCT03992131 **(SEASTAR)**[2] | 1b/2 | Pts with TNBC and other cancers | 329 | Safety, tolerability, PK, and preliminary efficacy of sacituzumab govitecan + rucaparib in patients an advanced/metastatic solid malignancy | Safety, ORR | March 2024 |
| NCT04039230[3] | 1/2 | Pts with mTNBC | 65 | Effects of sacituzumab govitecan + talazoparib | Safety | August 31, 2024 |

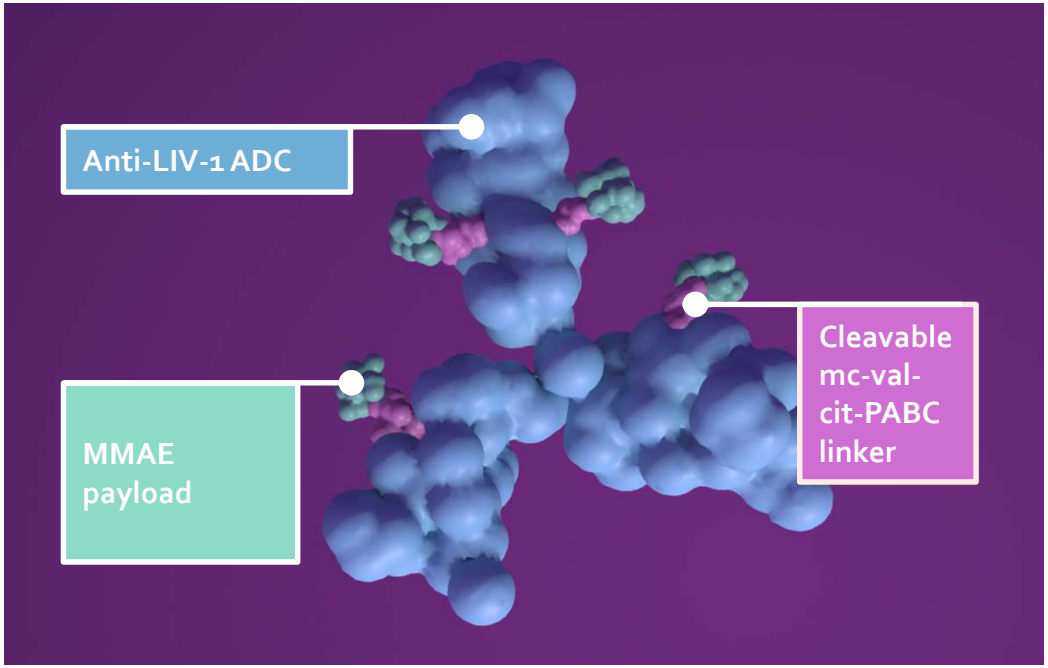
DFS, disease-free survival.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04230109. Accessed November 7, 2020. Last updated: July 16, 2020; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03992131. Accessed November 7, 2020. Last updated: August 26, 2019; 3. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://www.clinicaltrials.gov/ct2/show/NCT04039230. Accessed November 7, 2020. Last updated: May 5, 2020

# Select Investigational ADCs in Breast Cancer

| Trial | Drug name | Target | Ph | Brief Summary |
|---|---|---|---|---|
| NCT01969643[1] | Ladiratuzumab vedotin | Anti–LIV-1 | 1 | Safety/tolerability in patients with mTNBC |
| NCT03262935[2] | Trastuzumab duocarmazine (SYD985) | HER2-targeting | 3 | Patients with HER2+ mBC pretreated with T-DM1 |
| NCT02980341[2] | U3-1402 | HER3-targeting | 1/2 | Trial in patients with HER3+ mBC |

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT01969643. Accessed November 7, 2020. Last updated: October 22, 2020;
2. Rinnerthaler G et al. *Int J Mol Sci*. 2019;20(5):1115.




# Ladiratuzumab vedotin (SGN-LIV1A)

- Ladiratuzumab vedotin delivers a potent microtubule-disrupting agent called MMAE via a protease-cleavable linker, to cancer cells expressing LIV-1[1,2]
- LIV1 is a transmembrane cell adhesion molecule highly expressed in metastatic breast cancer
- The disruption of microtubules leads to targeted tumor cell cycle arrest/disruption[2]

MMAE, monomethyl auristatin E; mc-val-cit-PABC, Maleimidocaproyl-L-valine-L-citrulline-p-aminobenzyl alcohol.

1. Goldenberg DM et al. Oncotarget. 2018;9(48):28989–29006; 2. Sussman DM et al. *Mol Cancer Ther.* 2014;13(12):2991-3000.

# SGNLVA-001: A Phase 1 Safety Study of Ladiratuzumab Vedotin (SGN-LIV1A) in Patients With Heavily Pretreated mBC[1,2]

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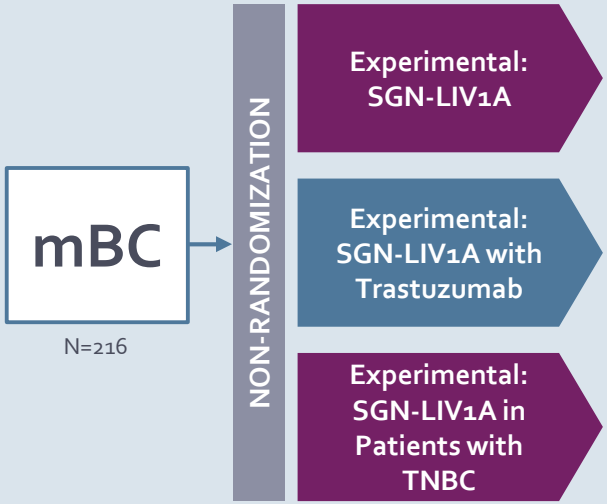
## STUDY DESIGN




## ANTITUMOR ACTIVITY

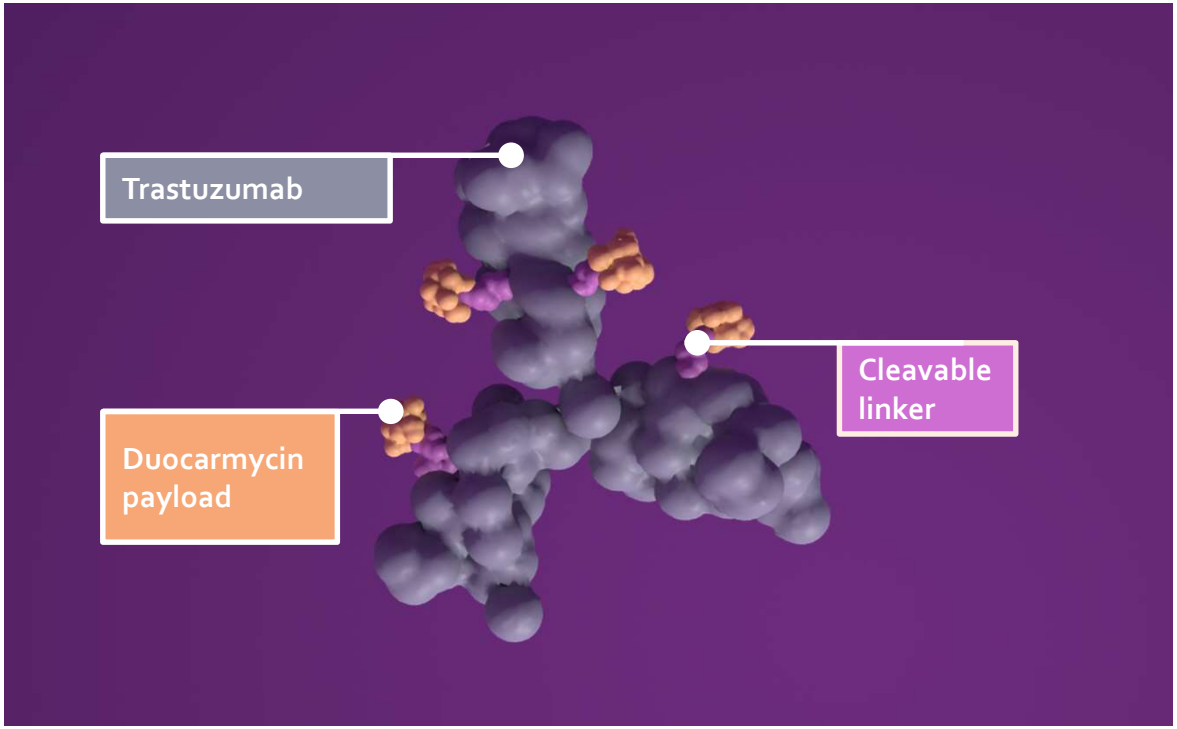
- All patients (n=60)
  - ORR = 25%
- RP2D of 2.5 mg/kg IV q3w (n = 26)
  - ORR = 34.6%
  - PFS = 2.9 months

## SAFETY RESULTS

- At the recommended dose, ladiratuzumab vedotin was generally well tolerated, and most AEs were grade 1/2
- Toxicities: alopecia, nausea, neutropenia, transaminitis, neuropathy

q3w, every 3 weeks.

1. U.S. National Library of Medicine ClinicalTrials.gov. URL: https://www.clinicaltrials.gov/ct2/show/NCT01969643. Accessed November 8, 2020. Last updated: October 22, 2020; 2. Modi S, et al. Cancer Res.2018;78(4 Suppl): Abstract PD3-14.




# Trastuzumab Duocarmazine (SYD985)[1,2]

- HER2-targeting ADC[1]
- Duocarmycins are DNA-alkylating agents composed of a DNA-alkylating and a DNA-binding moiety[2]

1. Banerji U et al. *Lancet Oncol*. 2019;20(8):1124-1135; 2. Rinnerthaler G et al. *Int J Mol Sci*. 2019;20(5):1115.

# SYD985 Shows Promising Efficacy in Heavily Pretreated Patients With HER2-Positive Breast Cancer

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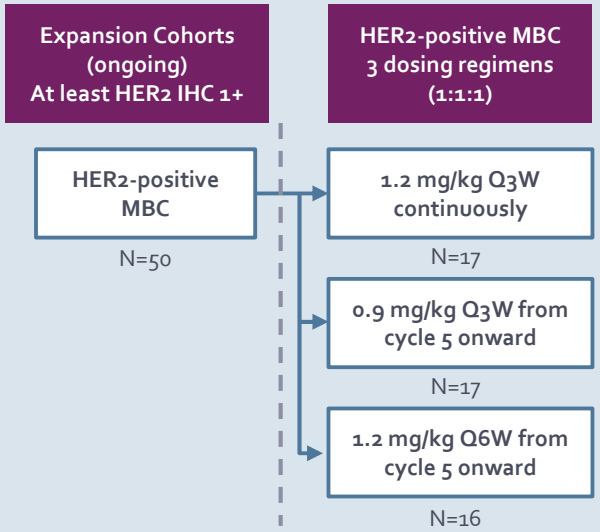
## STUDY DESIGN

- Patients with any solid tumor and at least HER2 IHC 1+ status




## ANTITUMOR ACTIVITY

| Patients with BC | N | ORR (%) | Median PFS (95% CI) |
|---|---|---|---|
| HER2-positive T-DM1 pretreated | 50<br>40 | 14 (29)<br>9 (24) | 9.4 (4.5-12.4)<br>8.3 (4.1-15.0) |
| HR+/HER2-low | 32 | 6 (20) | 4.1 (2.4-5.4) |
| TNBC | 17 | 4 (27) | 4.4. (1.0-7.1) |

## SAFETY RESULTS

- Majority of ADRs were gr 1 or 2 in intensity, with 6% of all ADRs gr ≥3
- Ocular toxicity and fatigue were most commonly reported
- No treatment-related deaths

ADR, adverse drug reaction; Q6W; every 6 weeks.

Saura C et al. A phase I expansion cohorts study of SYD985 in heavily pretreated patients with HER2-positive or HER2-low metastatic breast cancer. Poster presented at: American Society of Clinical Oncology Annual Meeting. June 1-5, 2018

# TULIP: Ph 3 Randomized, Active-Controlled, Superiority Study of SYD985 vs PC in Patients With HER2-Positive Locally Advanced or mBC

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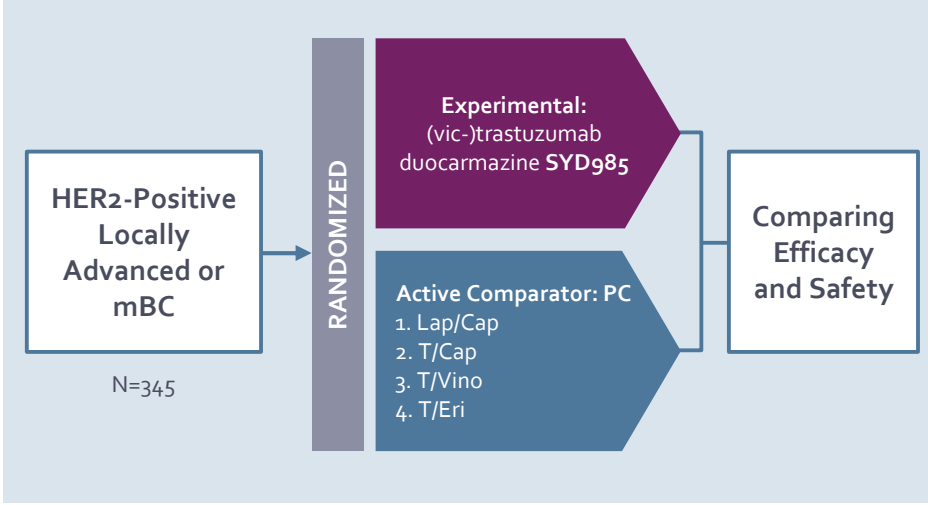
## PATIENTS

- Female pts with unresectable HER2-positive locally advanced or mBC
- Progression during or after at least 2 HER2-targeting treatment regimens

## STUDY DESIGN




## ENDPOINTS

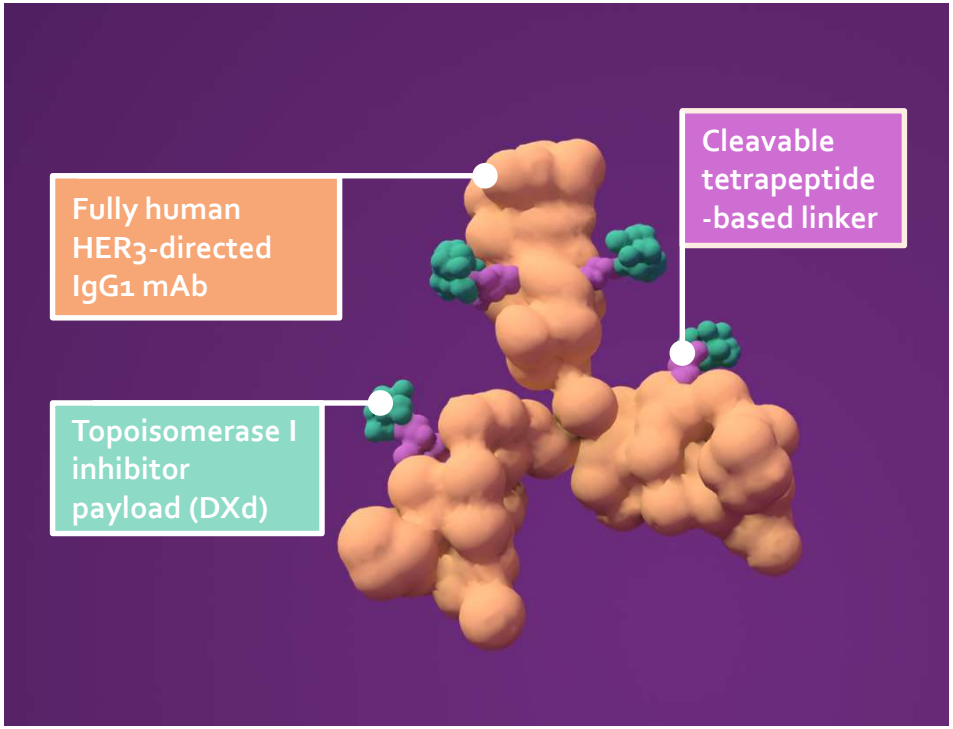
**1°**

PFS

**Select 2°**

- OS
- ORR
- Investigator-assessed PFS
- PROs for HRQoL

Eri, eribulin, Pc, physician's choice; PROS, patient-reported outcomes; T, trastuzumab; Vino, vinorelbine.
U.S. National Library of Medicine ClinicalTrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03262935. Accessed November 8, 2020. Last updated: October 5, 2020.




# Patritumab Deruxtecan (U3-1402)

- HER3-targeting IgG1 ADC
- Cleavable tetrapeptide-based linker
- Topoisomerase I inhibitor payload (DXd)
- U3-1402 shows HER3-specific binding with highly efficient internalization into tumor cells
- After linker cleavage, U3-1402 induces tumor cells to undergo apoptosis through DNA damage via released DXd

IgG1, immunoglobulin G1.
Hashimoto et al. Clin Cancer Res. 2019;25(23):7151-7161.

# Phase 1/2, Multicenter, Open-Label, Multiple-Dose Study of U3-1402, in Pts With HER3-Positive mBC

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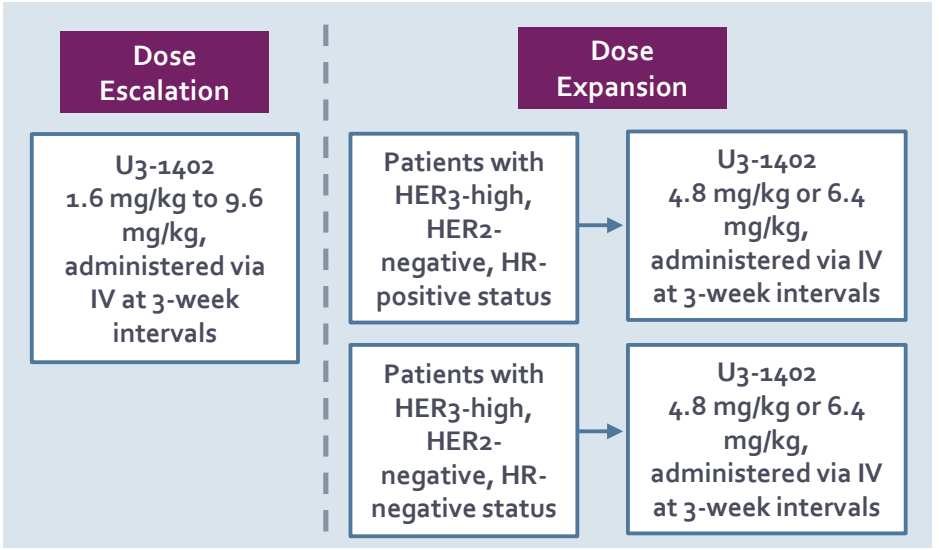
## PATIENTS

- Advanced/unresectable or metastatic HER3-positive BC
- Disease refractory to intolerable with standard treatment
- Received 2-6 prior chemotherapy regimens for BC, of which ≥2 were administered for advanced/unresectable or metastatic disease

## STUDY DESIGN




## ENDPOINTS

### 1°

- Safety
- No. of patients with tumor response

### Select 2°

- AUC of U3-1402
- Cmax
- Tmax

AUC, area under curve; Cmax, maximum concentration; Tmax, time to maximum.

U.S. National Library of Medicine ClinicalTrials.gov. URL:https://clinicaltrials.gov/ct2/show/NCT02980341. Accessed November 8, 2020. Last updated: April 6, 2020.

# Key Learnings

- There are 2 ADCs FDA approved in HER2+ BC
- Sacituzumab govitecan gained FDA approval for adults with mTNBC who received ≥2 prior therapies for metastatic disease
- Clinical trials are ongoing for several agents for the treatment of patients with HER2-low, HER3-positive, and TNBC

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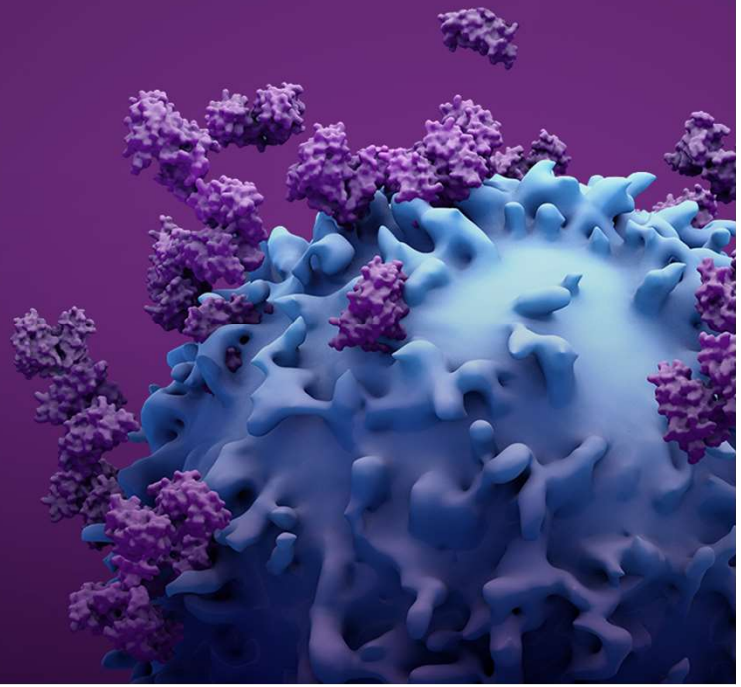
# Thank You!



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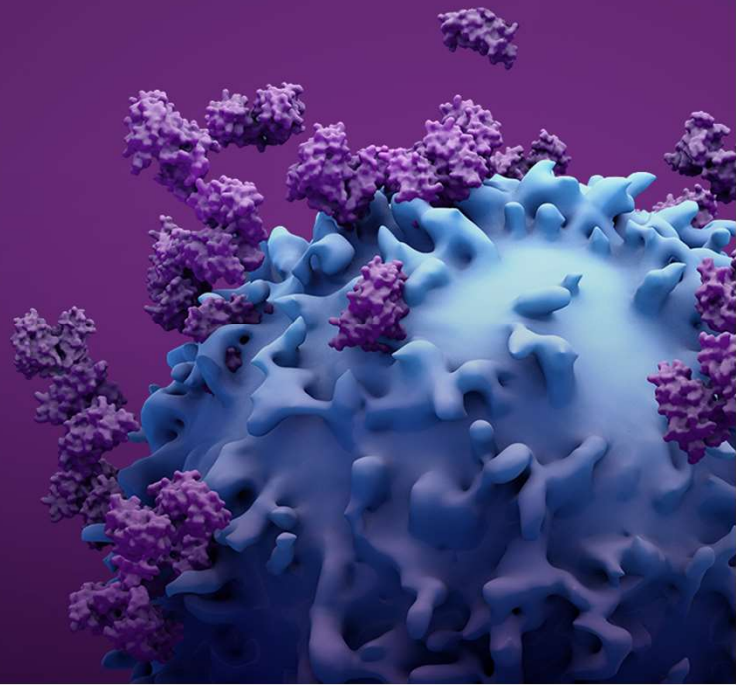
# Clinical Applications of ADCs



# 2 ADCs Currently Approved for HER2+ BC[1,2]

| | |
|---|---|
| **Trastuzumab emtansine (T-DM1; Kadcyla)** | indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:<br>• Received prior therapy for metastatic disease, or<br>• Developed disease recurrence during or within 6 months of completing adjuvant therapy. |
| **Trastuzumab deruxtecan (DS8201a; T-DXd; Enhertu)** | indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting.<br>This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. |

mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; TROP-2, tumor-associated calcium signal transducer 2.

1. KADCYLA (trastuzumab emtansine) [package insert]. San Francisco, CA: Genentech, Inc; 2019; 2. ENHERTU (trastuzumab deruxtecan) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2019.

# ADCs in HER2+ BC: NCCN Guidelines

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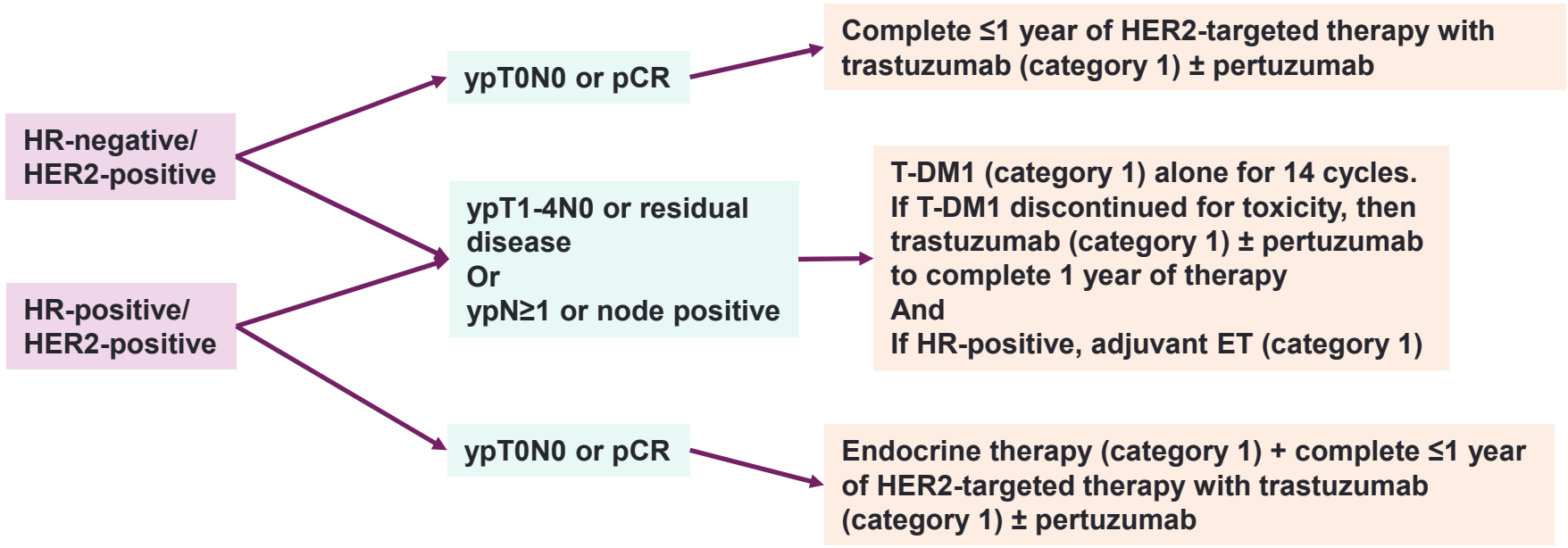
## PREOPERATIVE/ADJUVANT THERAPY REGIMENS

| HER2-Positive |
| --- |
| **Preferred Regimens**:<br>• AC followed by T + trastuzumab<br>AC followed by T + trastuzumab + pertuzumab<br>• Paclitaxel + trastuzumab<br>• TCH<br>• TCHP<br>• If no residual disease after preoperative therapy or no preoperative therapy: complete ≤ 1 year of HER2-targeted therapy with trastuzumab ± pertuzumab<br>• If residual disease after preoperative therapy: T-DM1 (cat 1) alone. If T-DM1 is discontinued for toxicity, then trastuzumab (cat 1) ± pertuzumab to complete 1 year of therapy |
| **Useful in Certain Circumstances**:<br>• Docetaxel + cyclophosphamide + trastuzumab |
| **Other recommended Regimens**:<br>• AC followed by docetaxel + trastuzumab<br>• AC followed by docetaxel + trastuzumab + pertuzumab |

AC, doxorubicin/cyclophosphamide; TCH, docetaxel/carboplatin/trastuzumab; TCHP, docetaxel/carboplatin/trastuzumab/pertuzumab; T, paclitaxel.
NCCN, National Comprehensive Cancer Network.

# ADCs in HER2+ BC: NCCN Guidelines (Continued)

## ADJUVANT SYSTEMIC THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY




NCCN, National Comprehensive Cancer Network.

# ADCs in HER2+ BC: NCCN Guidelines (Continued)

## SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE: ER- AND/OR PR-NEGATIVE; HER2-POSITIVE

**Systemic therapy + HER2-targeted therapy with:**

- **Pertuzumab + trastuzumab + taxane**
- **T-DM1**
- **T-DXd**
- **Trastuzumab + chemotherapy**
- **Other HER2-targeted therapies**

→ **Continue therapy until progression or unacceptable toxicity** → **Progression** → **Another line of systemic therapy + HER2-targeted therapy** → **Most patients will be candidates for multiple lines of systemic therapy to palliate advanced BC. At each reassessment, clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared-decision making process**

## SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE: ER- AND/OR PR-POSITIVE; HER2-POSITIVE

**Systemic therapy + HER2-targeted therapy with:**

- **Pertuzumab + trastuzumab + taxane**
- **T-DM1**
- **T-DXd**
- **Trastuzumab + chemotherapy**

- **Endocrine therapy +/- HER2-targeted therapy (if premenopausal, consider ovarian ablation or suppression)**
- **Other HER2-targeted therapies**

→ **Continue therapy until progression or unacceptable toxicity**

NCCN, National Comprehensive Cancer Network.

# 1 ADC Currently Approved for TNBC[1]

**Sacituzumab govitecan (Trodelvy)**

indicated for the treatment of adult patients with mTNBC who have received at least 2 prior therapies for metastatic disease. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1. TRODELVY (sacituzumab govitecan-hziy) [package insert]. Morris Plains, NJ: Immunomedics, Inc; 2020.

# NCCN Guidelines—Systemic Therapy For Recurrent TNBC

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## SYSTEMIC THERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE

| HER2-Negative | | |
|---|---|---|
| **Preferred Regimens**:<br>• Anthracyclines: doxorubicine, liposomal doxorubicin<br>• Taxanes: paclitaxel<br>• Anti-metabolites: capecitabine, gemcitabine<br>• Microtubule inhibitors: vinorelbine, eribulin<br>• For germline BRCA1/2 mutations, see additional targeted therapy options<br>• Platinum (for TNBC and germline BRCA1/2 mutation): carboplatin, cisplatin<br>• For PD-1L-positive TNBC see additional targeted therapy options | **Other Recommended Regimens**:<br>• Cyclophosphamide<br>• Docetaxel<br>• Albumin-bound paclitaxel<br>• Epirubicine<br>• Ixabepilone<br>• Sacituzumab govitecan-hziy (for TNBC) | **Useful in Certain Circumstances**:<br>• AC (doxorubicin/cyclophosphamide)<br>• ED (epirubicin/cyclophosphamide)<br>• CMF (cyclophosphamide/ methotrexate/uorouracil)<br>• Docetaxel/capecitabine<br>• GT (gemcitabine/paclitaxel)<br>• Gemcitabine/carboplatin<br>• Paclitaxel/becacizumab<br>• Carboplatin + paclitaxel or albumin-bound paclitaxel |

BRCA, BReast CAncer gene; PD-L1, programmed death-ligand 1.
NCCN, National Comprehensive Cancer Network.

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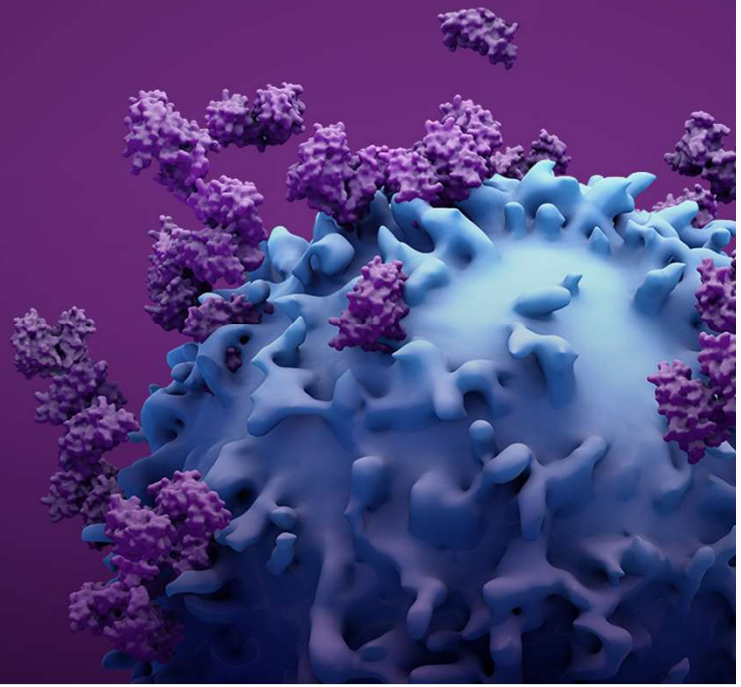
# Combinations With Immunotherapy



# ADC and Immunotherapy Combinations: Rationale[1,2]

- Preclinical data suggests ADCs result in TIL expansion and effector T cell activation, which may help overcome anti-CTLA4 and anti-PD-1 resistance[1]
- Proposed synergy: ADCs increase T-cell infiltration and immunotherapy revives exhausted T-cells[1]
- Sacituzumab govitecan: Response rate of 44% (8 of 18) among patients who had received previous checkpoint inhibitors[2]
  - Suggests a lack of cross-resistance with immune checkpoint inhibitors and the potential of combination therapy

1. Tray N et al. *Future Oncol*. 2018;14(25):2651-2661; 2. Bardia A et al. *N Engl J Med*. 2019:380;741-751.

# ADCs and Immunotherapy Combinations

| Trial | Regimen | Ph | N | Brief Summary | Study Completion |
|---|---|---|---|---|---|
| NCT04042701[1] | Trastuzumab deruxtecan + Pembrolizumab | 1b | ~115 | 1. Dose escalation to determine recommended dose of combination<br>2. Dose expansion to evaluate efficacy, safety, and tolerability of combination in patients with metastatic HER2+ or HER2-low BC | 4/2022 |
| NCT03424005 **(Morpheus-TNBC)**[6] | Ladiratuzumab vedotin/sacituzumab govitecan + Atezolizumab | 1b/2 | ~280 | Safety and efficacy of multiple immunotherapy-based combinations in metastatic or inoperable TNBC | 6/2022 |
| NCT03310957 **(KEYNOTE-721)**[5] | Ladiratuzumab vedotin + Pembrolizumab (1L) | 1b/2 | ~122 | Safety and efficacy of ADC + immunotherapy combination in locally-advanced or metastatic TNBC | 3/2023 |
| NCT03032107[2] | Trastuzumab emtansine + Pembrolizumab | 1 | ~27 | Tests safety of intervention in patients with metastatic HER2+ BC and attempts to define the appropriate dosage for future studies | 7/2024 |

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04042701. Published August 2, 2019. Accessed April 21, 2020; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03032107. Published January 26, 2017. Accessed April 21, 2020; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02924883. Published October 5, 2016. Accessed April 24, 2020; 4. Emens LA, Esteva F, Beresford M, et al. In: Proceedings of the 2018 San Antonio Breast Cancer Symposium; 2018 Dec 4-8; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2019;79(4 Suppl):Abstract nr PD3-01. doi: 10.1158/1538-7445.SABCS18-PD3 01; 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03310957. Published October 16, 2017. Accessed April 21, 2020; 6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03424005. Published February 6, 2018. Accessed April 21, 2020.

# KATE2: Randomized, Phase 2 Study of Atezolizumab + T-DM1 vs Placebo + T-DM1 In Previously Treated HER2+ aBC

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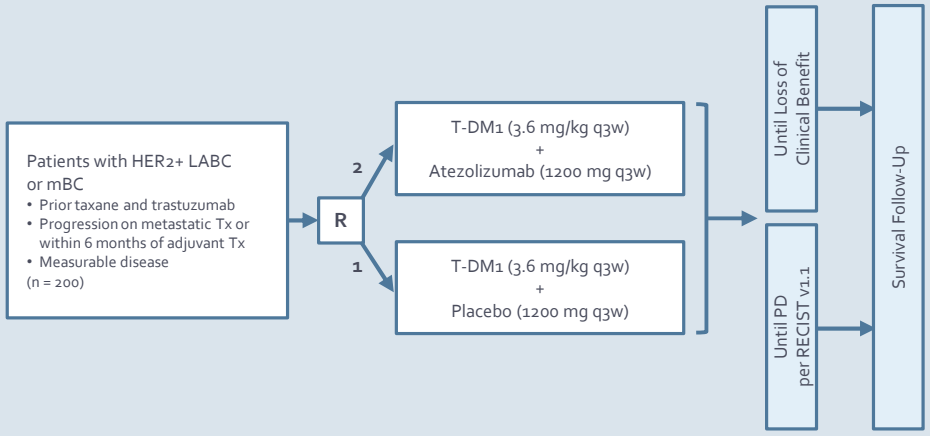
## PATIENTS

Patients with HER2-positive, locally-advanced or mBC who had received prior tratuzumab and taxane-based therapy

## STUDY DESIGN




## ENDPOINTS

**1°**

PFS (ITT)

**Select 2°**

- OS (ITT)
- ORR (ITT)
- DOR (ITT)

Presented at: SABCS 2018.

# KATE2 Did Not Demonstrate Meaningful PFS Benefit in the ITT Population

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## ANTITUMOR ACTIVITY

Median PFS (95% CI):
T-DM1 + atezolizumab: 8.5 mo (5.7 to NE)
T-DM1 + placebo: 4.1 mo (2.7 to 11.1)
Stratified HR, 0.60 (95% CI: 0.32, 1.11)

| Secondary EP: ORR in ITT Population | | |
|---|---|---|
| | T-DM1 + Atezolizumab | T-DM1 + Placebo |
| ORR% | 45.5 | 43.5 |
| CR% | 6.1 | 7.2 |
| PR% | 39.4 | 36.2 |
| SD% | 37.9 | 29.0 |
| PD% | 16.7 | 26.1 |

## SAFETY RESULTS

| Incidence, n (%) | T-DM1 + Atezo (N=132) | T-DM1 + Placebo (N=68) |
|---|---|---|
| Pts with ≥1 AE | 131 (99.2) | 65 (95.6) |
| Gr ≥3 | 58 (43.9) | 28 (41.2) |
| Gr 5 | 1 (0.8) | 0 |
| Pts with ≥1 SAE | 43 (32.6) | 13 (19.1) |
| AE leading to atezolizumab/placebo discontinuation | 33 (25.0) | 10 (14.7) |
| AE leading to T-DM1 discontinuation | 20 (15.2) | 9 (13.2) |
| AE leading to T-DM1 dose reduction | 22 (16.7) | 6 (8.8) |

Emens LA et al. Poster Presented at SABCS December 4-8, 2018
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30465-4/fulltext

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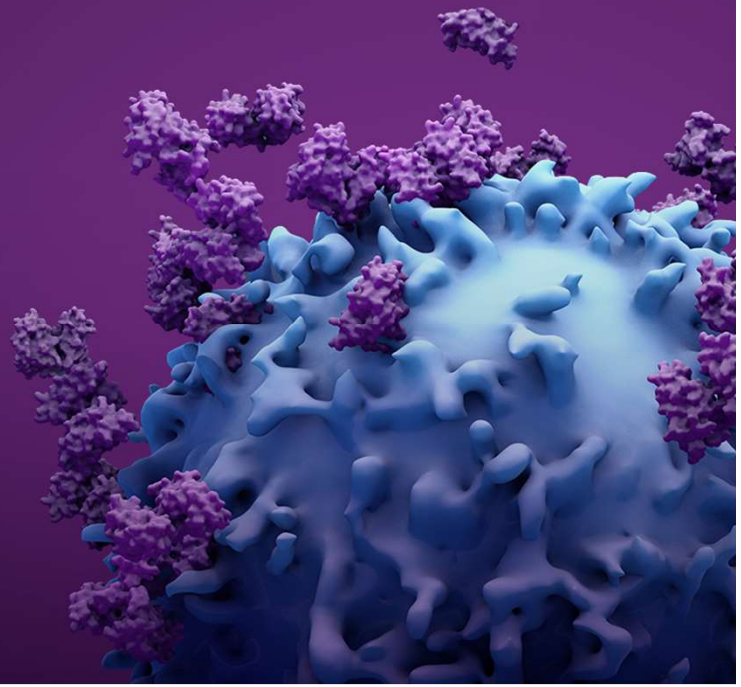
# Thank You!



# Presentation Breakdown

- Hurvitz: Slides 1-18, 42-48
- Gradishar: Slides 19-41, 49-54