PrimO
Practical Recommendations in Immuno & Molecular Oncology
ADC Summit

Antibody–Drug Conjugates: Practical Considerations and Applications in Clinical Use

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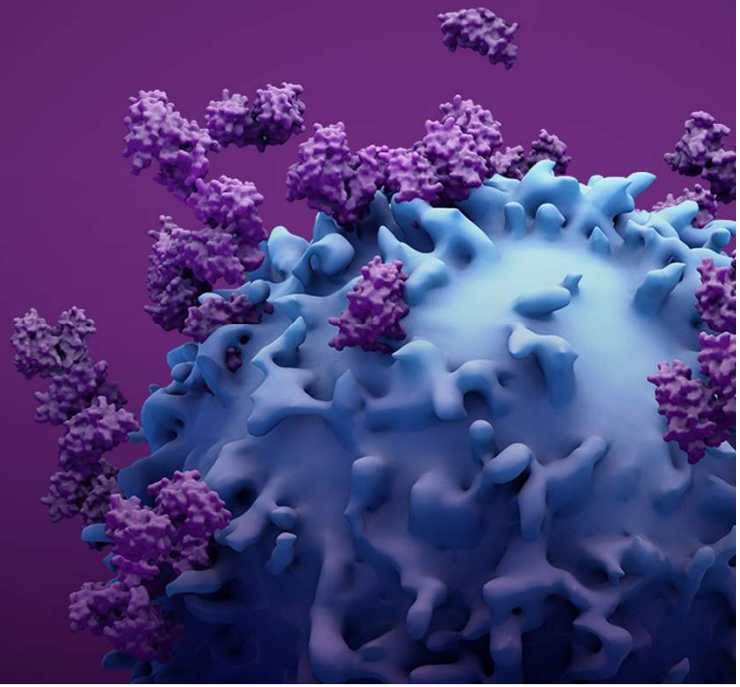

Learning Objectives

Identify current thinking and rationale around patient selection and sequencing of ADCs in breast cancer

FDA-Approved ADCs in BC

Drug name	Target	Indication	FDA Approval
KADCYLA® (ado-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® (fam-trastuzumab deruxtecan-nxki)[2]	HER2	Adults with unresectable or metastatic HER2+ breast cancer who have received ≥2 prior anti–HER2-based regimens	12/2019
TRODELVY® (sacituzumab govitecan-hziy)[3]	TROP-2	Adult patients with metastatic triple-negative BC (TNBC) who have received ≥2 prior therapies for metastatic disease	06/2020

BC, breast cancer; FDA, US Food and Drug Administration; HER, human epidermal growth factor receptor; TROP-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.
3. TRODELVY (sacituzumab govitecan-hziy) [package insert]. Morris Plains, NJ: Immunomedics, Inc; 2020.

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

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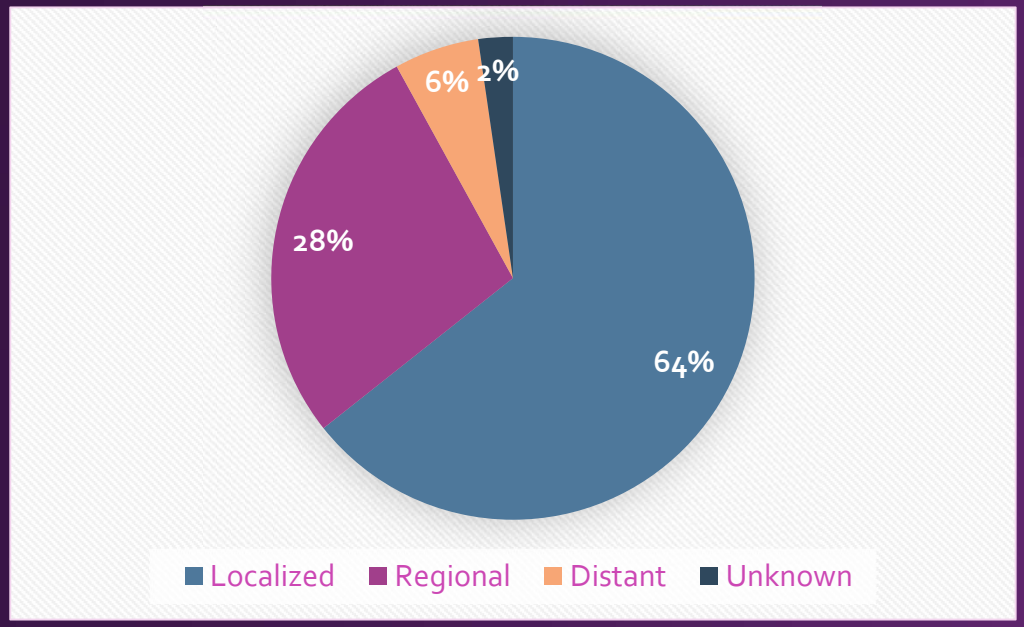
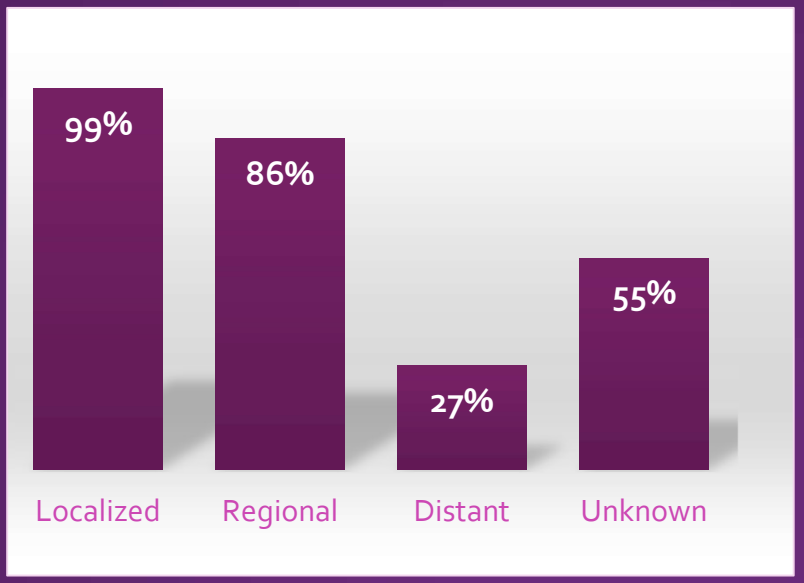


5-Year Relative Survival



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.

Neoadjuvant and Adjuvant Therapies Are Administered in Early-Stage BC With Curative Intent

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Most BC presents in early stages where the prognosis is favorable[1]

of BC are not metastatic at the time of diagnosis[2,3]

The main goals of therapy at this stage are **eliminating** the tumor from the breast (tumor eradication) and regional lymph nodes and **preventing** recurrence or metastasis

Stages I and II are often referred to as early BC; it is in these early stages that the disease is highly curable

1. Barnett CM, et al. *Breast Cancer*. In: DiPiro JT et al. 10th ed. 2017, Accessed February 18, 201; 2. Waks AG, Winer EP. Breast Cancer Treatment: A Review. *JAMA*. 2019;321(3):288–300. doi:10.1001/jama.2018.19323;
3.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

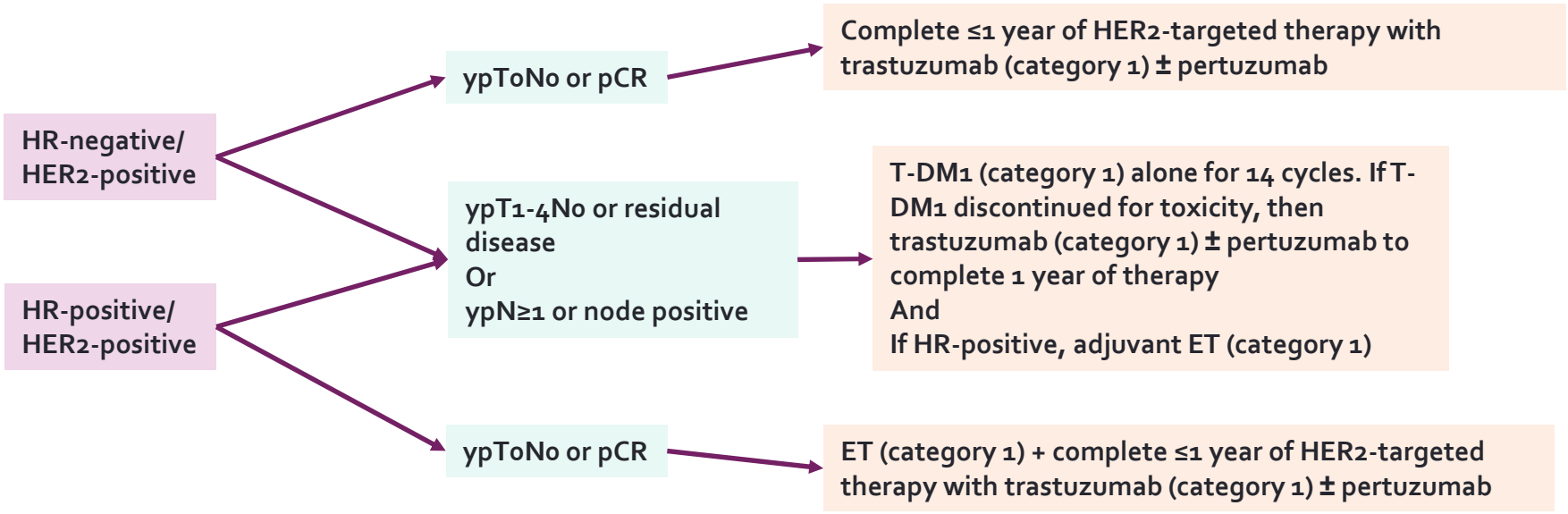
Patient Case - 48 Y/O Woman

- Diagnosed with 3-cm high-grade ER+ PR– HER2+ (3+ by IHC and FISH positive) left breast cancer with a large palpable left axillary lymph node; biopsy proven to be involved with breast cancer
- She received 6 cycles of neoadjuvant TCHP with a complete clinical response
- At the time of surgery, there was 5 mm residual intermediate-grade invasive breast cancer, ER+ PR– HER2 2+ by IHC, FISH positive; 0/3 SLN

ER, estrogen receptor; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PR, progesterone receptor; SLN, sentinel lymph node; TCHP, docetaxel/carboplatin/trastuzumab/pertuzumab; Y/O, year-old.

ADCs in HER2+ BC: NCCN Guidelines

ADJUVANT SYSTEMIC THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY



ET, endocrine therapy; HR, hormone receptor; NCCN, National Comprehensive Cancer Network; pCR, pathologic complete response; T-DM1, ado-trastuzumab emtansine.

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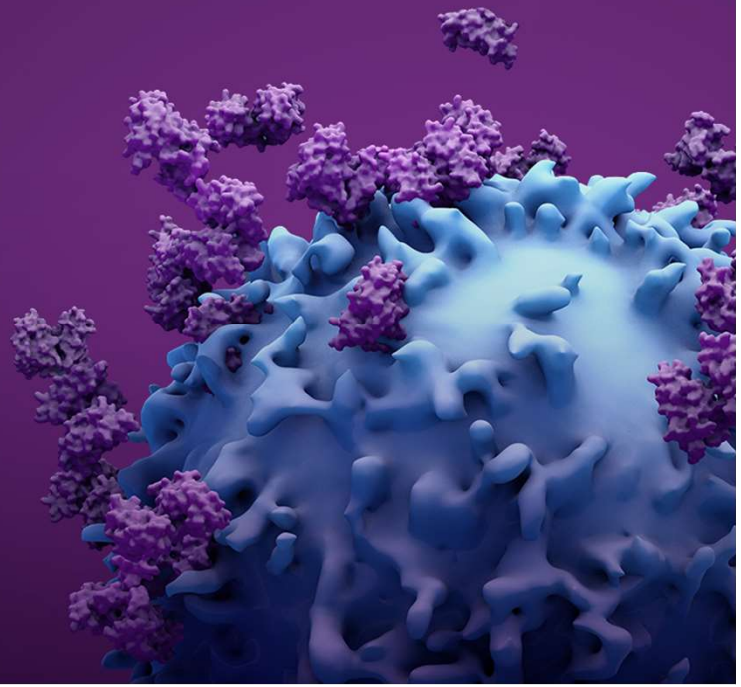
Clinical Data With ADCs in Early HER2+ Breast Cancer



Measuring Outcomes in Neoadjuvant and Adjuvant Breast Cancer Clinical Trials[1,2]

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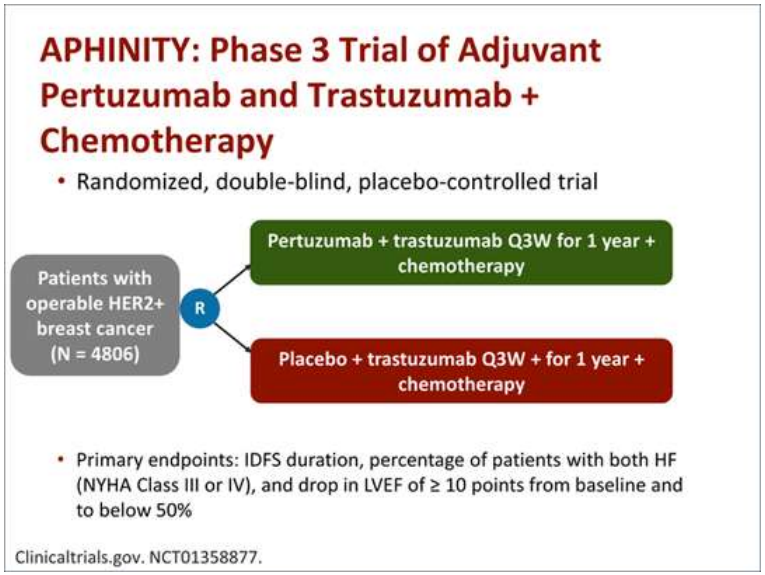
Pathological Outcomes	Clinical Outcomes	Pathological and Clinical outcomes
• Pathological complete response (**pCR**) – Surrogate outcome measure (endpoint) that assesses treatment efficacy – Associated with highly significant improved rates of disease-free survival and overall survival in patients with HER2-positive disease	• Overall Survival (**OS**; time from randomization to death from any cause) – Gold standard primary EP, **but takes a long time** before improvements can be observed and reliably confirmed due to the relatively long expected survival time for BC patients • Event-free survival (**EFS**) → more rapid, surrogate endpoint for OS – Used in **neoadjuvant** clinical trials • Disease-free survival (**DFS**) → surrogate EP for OS – More rapid surrogate EP used in adjuvant clinical trials	• Invasive Disease-Free Survival (**iDFS**) → surrogate endpoint for OS – iDFS is used in place of DFS in BC adjuvant trials – iDFS definition excludes all in situ cancer events

1. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol*. 2007 May 20;25(15):2127-32; 2. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. *N Engl J Med*. 2012;366(26):2438–2441. doi:10.1056/NEJMp1205737. PubMed PMID: 22646508.

APHINITY Trial Supports Adjuvant Pertuzumab and Trastuzumab + Chemotherapy



- Randomized, double-blind, placebo-controlled phase 3 trial assessing the safety and efficacy of pertuzumab in addition to chemotherapy plus trastuzumab as adjuvant therapy in participants with operable HER2-positive primary BC
- 171 patients (7.1%) in the pertuzumab group and 210 patients (8.7%) in the placebo group had disease recurrence (HR, 0.81; 95% CI, 0.66-1.00; *P* = 0.045)
- Estimates of the 3-year rates of iDFS were 94.1% in the pertuzumab group and 93.2% in the placebo group
- Diarrhea of grade 3 or higher occurred almost exclusively during chemotherapy, more frequently with pertuzumab than with placebo

When added to chemotherapy and trastuzumab, pertuzumab significantly improved the rates of iDFS among patients with HER2-positive early breast cancer (APHINITY)

CI, confidence interval; HR, hazard ratio.

von Minckwitz G, Procter M, de Azambuja, E. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017;377:122-31. DOI: 10.1056/NEJMoa1703643.

ExteNET Supports Neratinib After Trastuzumab-Based Adjuvant Therapy in HER2-Positive Early Breast Cancer

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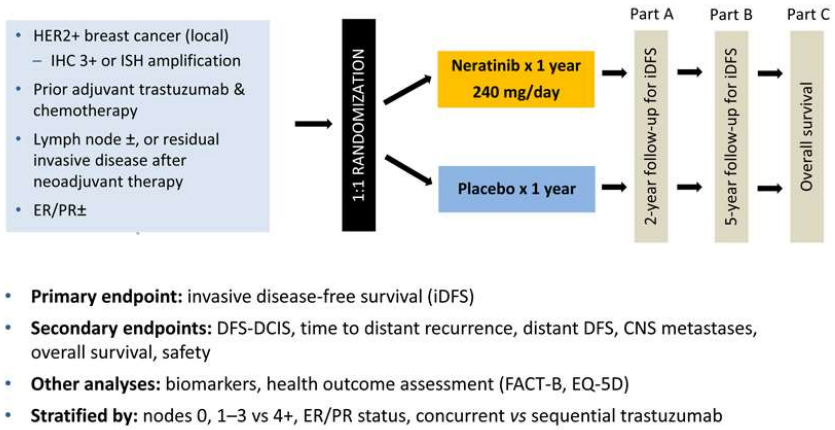
ExteNET: Study Design



- **Primary endpoint:** invasive disease-free survival (iDFS)
- **Secondary endpoints:** DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- **Other analyses:** biomarkers, health outcome assessment (FACT-B, EQ-5D)
- **Stratified by:** nodes 0, 1–3 vs 4+, ER/PR status, concurrent *vs* sequential trastuzumab

Neratinib After Trastuzumab (ExteNET)

- Randomized, double-blind, phase 3, placebo-controlled trial of neratinib after trastuzumab-based adjuvant therapy in women with early-stage HER-2/Neu overexpressed/amplified BC
- At 2-year follow-up, 70 iDFS events occurred in the neratinib group vs 109 events in the placebo group (stratified HR, 0.67; 95% CI, 0.50-0.91; *P* = 0.0091)
- 93.9% 2-year iDFS rate in the neratinib group vs 91.6% in the placebo group
- Most common grade 3–4 AEs in patients in the neratinib group were diarrhea, vomiting, and nausea
- Benefit maintained after a median of 5 years of follow-up

Neratinib for 12 months significantly improved 2-year iDFS when given after chemotherapy and trastuzumab-based adjuvant therapy to women with HER2-positive BC

Neratinib was approved in 2017 for adjuvant use, but there are significant GI toxicities

AE, adverse event; GI, gastrointestinal.

https://www.sec.gov/Archives/edgar/data/1401667/000119312516653895/d349535dex991.htm

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

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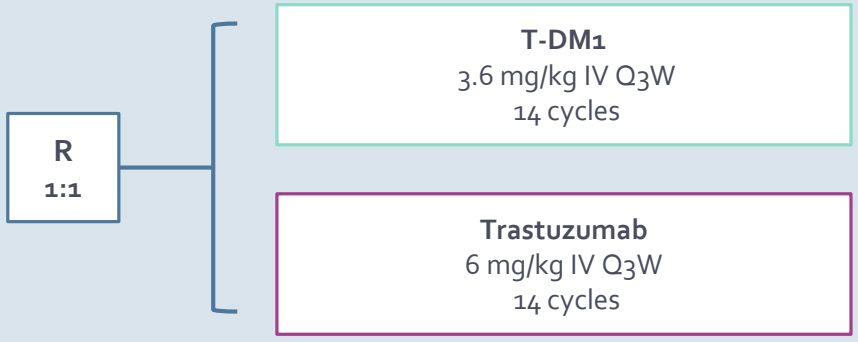
PATIENTS

- 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 ET per protocol and local guidelines

ENDPOINTS

1°

- iDFS

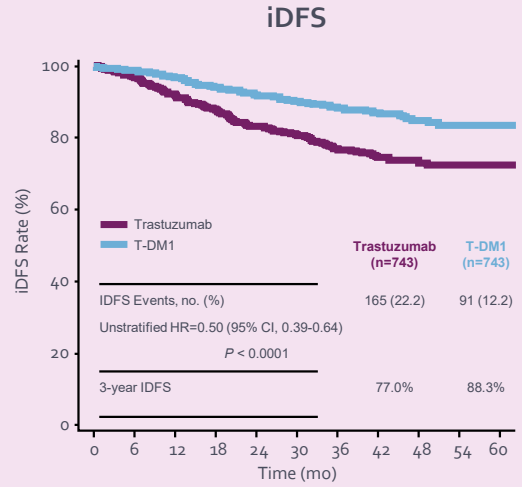
Select 2°

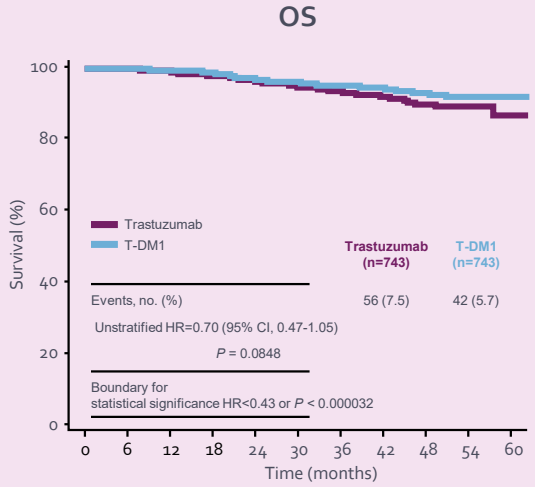
- DFS
- OS
- Distant recurrence-free survival
- Safety

IV, intravenous; Ph, phase; R, randomization; Q3W, every 3 weeks.
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.

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 trastuzumab: 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 percentages of patients with hemorrhage of gr ≥3 were similar in the T-DM1 group and the trastuzumab group (0.4% and 0.3%)

gr, grade; pt, patient; SAE, serious adverse event.
Presented by Charles E. Geyer at the San Antonio Breast Cancer Symposium 2018 Dec 4-8

T-DM1 Approved Based Upon Results From KATHERINE

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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])

https://www.roche.com/media/releases/med-cor-2019-05-06.htm
[NCCN Guidelines, Clinical Practice Guidelines in Oncology Breast Cancer v1 2019; Treatment Approach BINV-L 2 of 6 and BINV-14]
von Minckwitz G, Huang C, Mano M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019;380:617-628.

NCCN Recommended Options for T-DM1 Toxicity in the Adjuvant Setting

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If T-DM1 is discontinued due to toxicity:

NCCN RECOMMENDATIONS

- Trastuzumab ± pertuzumab to complete 1 year of therapy
- HER2-targeted therapy may be administered concurrently with radiation and with ET, if indicated
- Consider extended adjuvant **neratinib** following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence (ExteNET)
- Benefit/toxicity associated with extended neratinib in patients who have received pertuzumab or T-DM1 is unknown

[NCCN Guidelines, Clinical Practice Guidelines in Oncology Breast Cancer v1 2019; Treatment Approach BINV-L 2 of 6 and BINV-14]
von Minckwitz G, Huang C, Mano M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019;380:617-628.

Patient Case - 48 Y/O Woman

What adjuvant HER2-targeted therapy would you discuss with her and which would you recommend?

Patient Case - 48 Y/O Woman

Are there situations where you would use adjuvant T-DM1 followed by extended adjuvant neratinib? What factors would lead you to recommend this?

Patient Case - 48 Y/O Woman

In which situations would you use adjuvant pertuzumab/trastuzumab (after neoadjuvant HP-based therapy)?

Patient Case - 48 Y/O Woman

Are there patients with residual HER2+ breast cancer after standard neoadjuvant therapy who are unlikely to benefit from adjuvant T-DM1 (Small size? HER2 status change? Hormone receptor status?)

Patient Case - 65 Y/O Woman

- Diagnosed with de novo ER–, PR– HER2+ mBC in liver, bones
- Received first-line THP with PR. Continued maintenance HP for 24 months when she has PD in liver and lungs and receives second-line T-DM1
- Achieved PR again, lasting 18 months
- Progression in liver, lungs, bones, lymph nodes. Patient is moderately symptomatic with abdominal pain, bone pain, and mild shortness of breath

mBC, metastatic breast cancer; PD, progressive disease; THP, trastuzumab/pertuzumab/docetaxel.

ADCs in HER2+ BC: NCCN Guidelines

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 the 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

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

→ Continue therapy until progression or unacceptable toxicity

T-DXd, trastuzumab deruxtecan.

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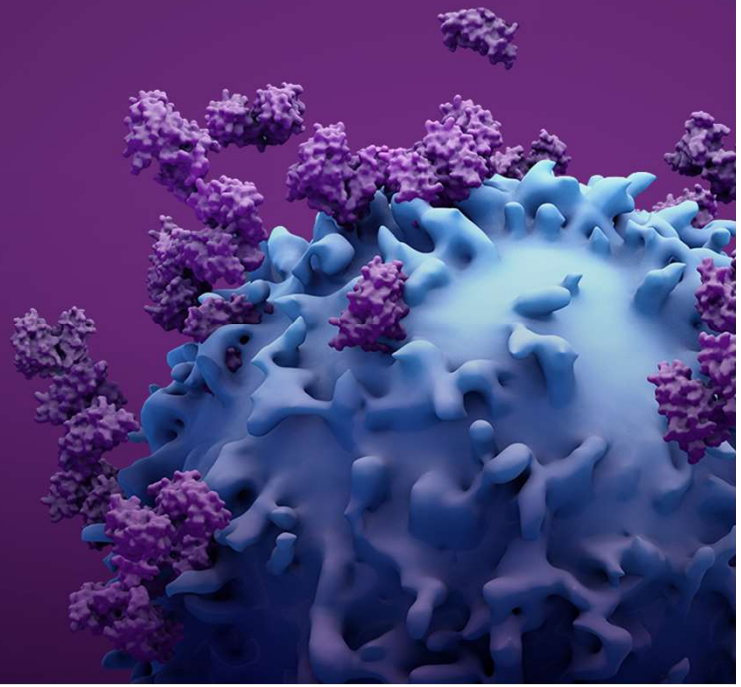
Clinical Data With ADCs in Metastatic HER2+ Breast Cancer



Efficacy Outcomes in Patients With HER2+ BC

	N + CAPE[1,a] NALA	DS-8201[2] DESTINY-Breast01	T-DM1[3,a] EMILIA	Tucatinib + H + CAPE[4,b] HER2CLIMB
Study type	Ph 3	Ph 2	Ph 3	Ph 2
Total population (E vs C)	621 (307 vs 314)	184	991 (495 vs 496)	612 (410 vs 202)
ORR (% [95% CI]); E vs C	**33** vs **27** *P* = 0.1201	**60.9** [53.4-68.0]	**43.6** [38.6-48.6] vs **30.8** [26.3-35.7] *P* < 0.001	**40.6** [35.3-46.0] vs **22.8** [16.7-29.8] *P* < 0.001
CBR (% [95% CI]); E vs C	**45** vs **36** *P* = 0.0328	**76.1** [69.3-82.1]	--	--
mPFS (mo [95% CI]); E vs C	**8.8** vs **6.6**[c] *P* = 0.0003	**16.4** [12.7-NR]	**9.6** vs **6.4** HR 0.65 [0.55-0.77], *P* < 0.001	**7.8** [7.5-9.6] vs **5.6** [4.2-7.1][d] HR 0.54 [0.42-0.71], *P* < 0.001
mOS (mo [95% CI]); E vs C	**24.0** vs **22.2** HR 0.88 [0.72-1.07], *P* = 0.2086	NR	**30.9** vs **25.1** HR 0.68 [0.55-0.85], *P* < 0.001	**21.9** [18.3-31.0] vs **17.4** [13.6-19.9] HR 0.66 [0.50-0.88], *P* = 0.005
mDOR (mo [95% CI]); E vs C	**8.5** vs **5.6** HR 0.50 [0.33-0.74], *P* = 0.0004	**14.8** [13.8-16.9]	**12.6** [8.4-20.8] vs **6.5** [5.5-7.2]	--

C, control; CAPE, capecitabine; CBR, clinical benefit rate; E, experimental; H, trastuzumab; mDOR, median duration of response; mo, month; mOS, median overall survival; mPFS, median progression-free survival; N, neratinib; NR, not reached; ORR, objective response rate; P, phase.

Note: Direct cross-study comparisons must be interpreted with caution.

[a]Control arm: lapatinib + CAPE.
[b]Control arm: H + CAPE.
[c]Prespecified restricted means analysis.
[d]mPFS in the primary endpoint population (n=480).

1. Saura C, et al. *J Clin Oncol*. 2019;37(15_suppl):1002-1002. 2. Modi S, et al. *N Engl J Med*. 2019. 3. Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791. 4. Murthy RK, et al. *N Engl J Med*. 2019.

Efficacy Outcomes in Patients With HER2+ BC With Brain Metastases

	N + CAPE[1,a] TBCRC 022	N + CAPE[2] NALA		DS-8201[3] DESTINY-Breast01	T-DM1[4]	T-DM1[5] EMILIA	Tucatinib + H + CAPE[6] HER2CLIMB	
		N + CAPE	L + CAPE				Tuc + H + CAPE	H + CAPE
Study type	P2	P3		P2	Retrospective	Retrospective	P2	
Patients with BM	37	19	13	24	87	45	198	93
Brain/CNS ORR (%) [95% CI]	49 [32-66]	26.3	15.4	--	24.5	--	47	20
mPFS (mo) [95% CI]	5.5	--	--	18.1 [6.7-18.1]	7.0 [5.4-8.6]	5.9	9.9[b]	4.2
mOS (mo)	13.3	--	--	--	--	26.8	--	--
CNS incidence (%)	--	22.8[7,c]	29.2[7,c]	--	--	2[d]; 22.2[e]	--	--

BM, brain metastases; CNS, central nervous system; H, trastuzumab; L, lapatinib; mets, metastases; N, neratinib; Tuc, tucatinib.

Note: Direct cross-study comparisons must be interpreted with caution.

[a]Efficacy from cohort 3A (lapatinib naïve).
[b]HR=0.32 [95% CI, 0.22-0.48]; *P* < 0.0001.
[c]Patient population N + CAPE (N=307) and L + CAPE (N=314); statistically significant reduction (*P* = 0.043).
[d]In patients with no CNS mets at baseline (N=450).
[e]In patients with stable CNS mets at baseline.

1. Freedman RA, et al. *J Clin Oncol*. 2019;37(13):1081-1089. 2. Awada A, et al. Poster presented at: San Antonio Breast Cancer Symposium. December 10-14, 2019; San Antonio, TX. Poster P2-20-01. 3. Modi S, et al. *N Engl J Med*. 2019. 4. Fabi A, et al. Breast. 2018;41:137-143. 5. Krop IE, et al. *Ann Oncol*. 2015;26(1):113-119. 6. Presented at: ASCO 2020. 7. Saura C, et al. *J Clin Oncol*. 2019;37(15_suppl):1002-1002.

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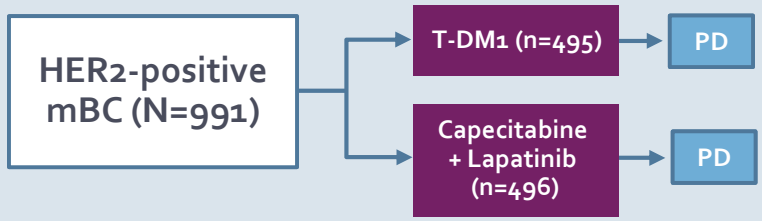
EMILIA: Improved OS With T-DM1 vs Capecitabine + Lapatinib in Pts With HER2+ Locally Advanced or mBC

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

DOR, duration of response; PFS, progression-free survival; 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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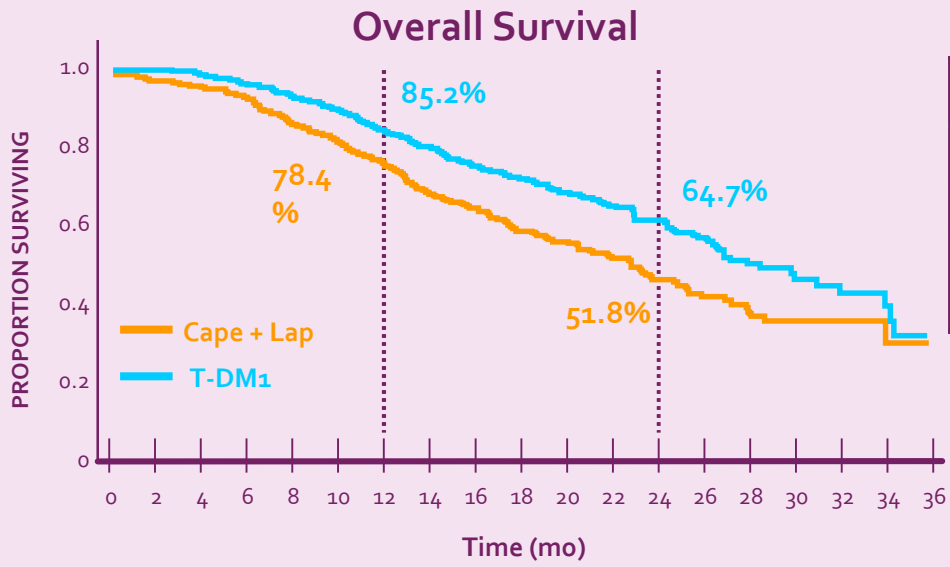
EMILIA Led to KADCYLA Approval in Patients With HER2+ Locally Advanced or mBC in Feb 2013[1,2]

ANTITUMOR ACTIVITY



	Median (mo)	No. of events
Cape + 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)

Cape, capecitabine.

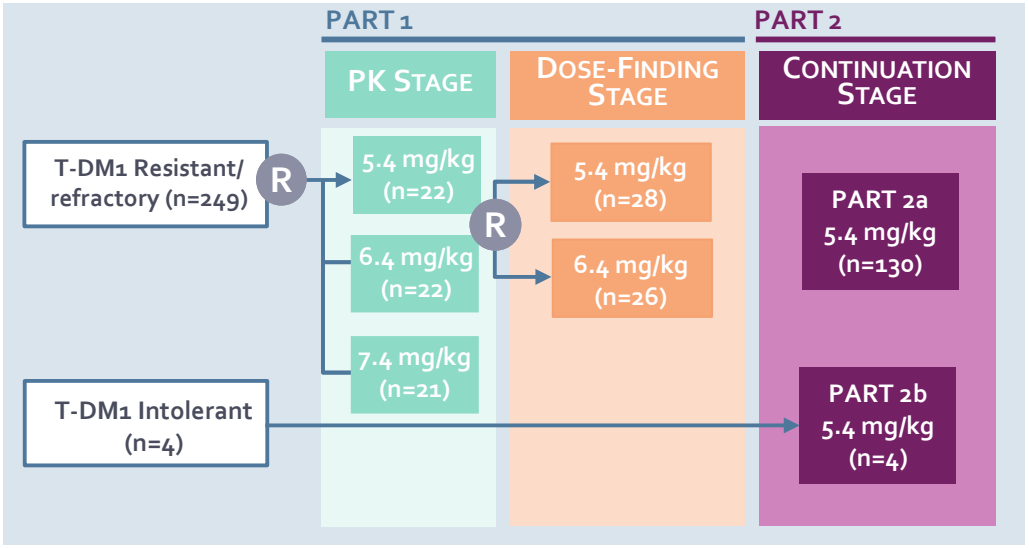
1. CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 125427Orig1s000. fda.gov.URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000SumR.pdf. Published February 21, 2013. Accessed May 11, 2020; 2. Verma S et al. *N Engl J Med*. 2012;367:1783-1791.

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%)

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.

Safety Results With HER2-Targeting ADCs

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T-DXd[1]

The most common gr 3 or 4 TEAEs included **decreased neutrophil count, nausea, and anemia**

Patients who received T-DXd (N = 184)

TEAE (≥ 15%), n (%)	All Grades	Grade 3	Grade 4
Patients with any TEAE	183 (99.5)	89 (48.4)	7 (3.8)
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Neutropenia	**64 (34.8)**	**36 (19.6)**	**2 (1.1)**
Decreased appetite	57 (31.0)	3 (1.6)	0
Anemia	**55 (29.9)**	**15 (8.2)**	**1 (0.5)**
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased WBC count	**39 (21.2)**	**11 (6.0)**	**1 (0.5)**
Thrombocytopenia	**39 (21.2)**	**7 (3.8)**	**1 (0.5)**
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain	31 (16.8)	2 (1.1)	0

T-DM1[2]

The most commonly reported gr 3 or 4 events were **thrombocytopenia (12.9%)** and **elevated serum concentrations of AST (4.3%)** and **ALT (2.9%)**

Patients who received T-DM1 (N = 490)

TEAE (≥ 2%), n (%)	All Grades	Grade ≥3
Patients with any TEAE	470 (95.9)	200 (40.8)
Diarrhea	114 (23.3)	8 (1.6)
Palmar-plantar erythrodysesthesia	6 (1.2)	0
Vomiting	93 (19.0)	4 (0.8)
Neutropenia	29 (5.9)	10 (2.0)
Hypokalemia	42 (8.6)	11 (2.2)
Fatigue	172 (35.1)	12 (2.4)
Nausea	192 (39.2)	4 (0.8)
Mucosal inflammation	33 (6.7)	1 (0.2)
Anemia	51 (10.4)	13 (2.7)
Elevated ALT	**83 (16.9)**	14 (2.9)
Elevated AST	**110 (22.4)**	**21 (4.3)**
Thrombocytopenia	**137 (28.0)**	**63 (12.9)**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-related adverse events; WBC, white blood cell.

1. Modi S, et al. *N Engl J Med*. 2019;382(7):610-621; 2. Verma S et al. *N Engl J Med*. 2012. 367:1783-1791.

AEs of Interest With T-DXd: ILD[1-3]

- Identified across clinical development programs with T-DXd
- Protocol recommendation: monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade/total
DESTINY-Breast01	184	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)
DESTINY-CRC01	78	0	2 (2.6)	1 (1.3)	0	2 (2.6)	5 (6.4)
DESTINY-Lung01	42	0	5 (11.9)	0	0	0	5 (11.9)

1. Modi S. Poster presented at the San Antonio Breast Cancer Symposium; December 4-7, 2018; San Antonio, TX [poster P6-17-02]; 2. 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; 3. Siena S et al. A phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01. Presented at: American Society of Clinical Oncology 2020 Virtual Scientific Sessions; May 29 – 31. Accessed November 6, 2020. https://meetinglibrary.asco.org/record/185482/abstract;

Patient Case - 65 Y/O Woman

How do you prioritize and select among the available treatment options in the third-line setting (neratinib/capecitabine; lapatinib/cape; T-DxD; tucatinib/tras/cape; tras-lapat; tras-chemo)?

chemo, chemotherapy; tras, trastuzumab.

Patient Case - 65 Y/O Woman

Are you obtaining brain imaging in patients without CNS symptoms to help choose among the available options (TKI vs ADC)?

TKI, tyrosine kinase inhibitor.

Patient Case - 65 Y/O Woman

How do you monitor for ILD with T-DxD? Are there patients you would not treat with T-DxD given the ILD risk (eg, lung mets, symptomatic, Japanese ancestry, h/o ILD)?

h/o, history of.

Key Learnings

- T-DM1 is an SOC in early HER2-positive BC with residual disease after neoadjuvant therapy
- However, there is more to learn about the benefit of ADCs for patients with BC
  - Clinical trials are ongoing for patients with HER2-low BC and in combination with PD-(L)1 inhibitors
- ILD is an AE of interest with T-DXd; it is suggested that patients are monitored for symptoms related to ILD

PD-L1, programmed death-ligand 1; SOC, standard of care.

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Thank You