2024 Breast Cancer Congress

with Updates from the 2023 SABCS

Friday, February 2, 2024
10:15 AM – 10:40 AM CST

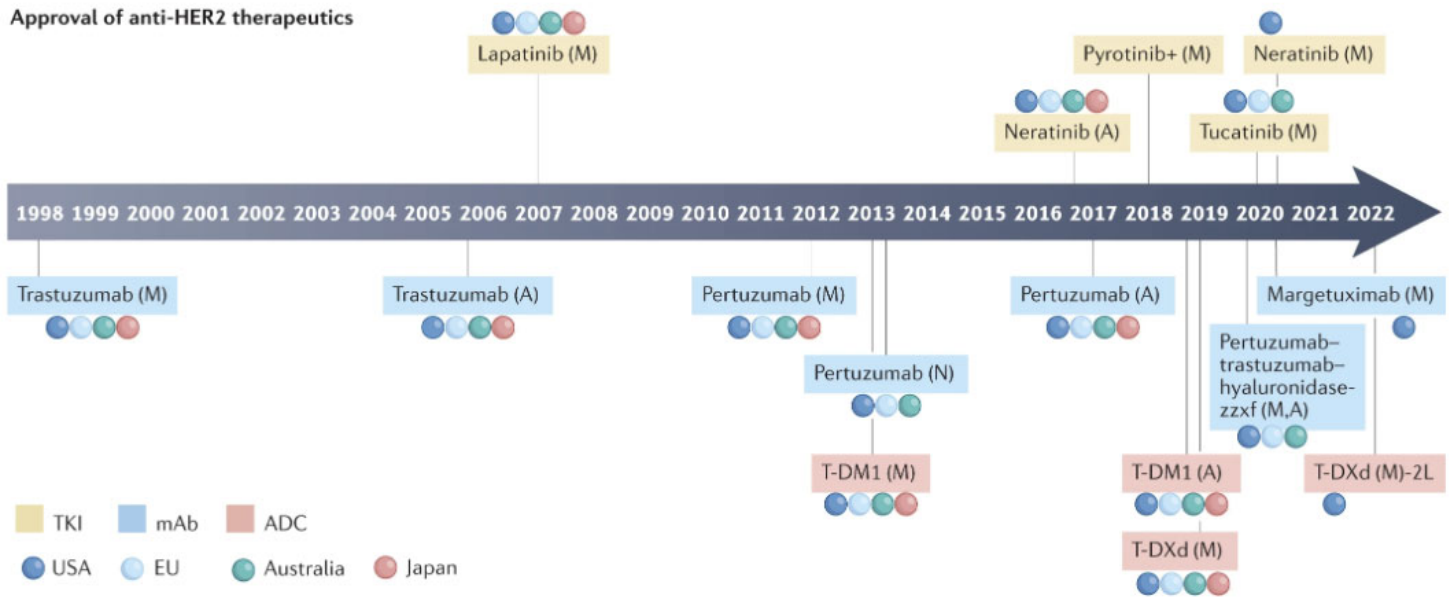
Neoadjuvant/Adjuvant Treatment for HER2-Positive Breast Cancer with SABCS Updates

Patricia Robinson, MD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

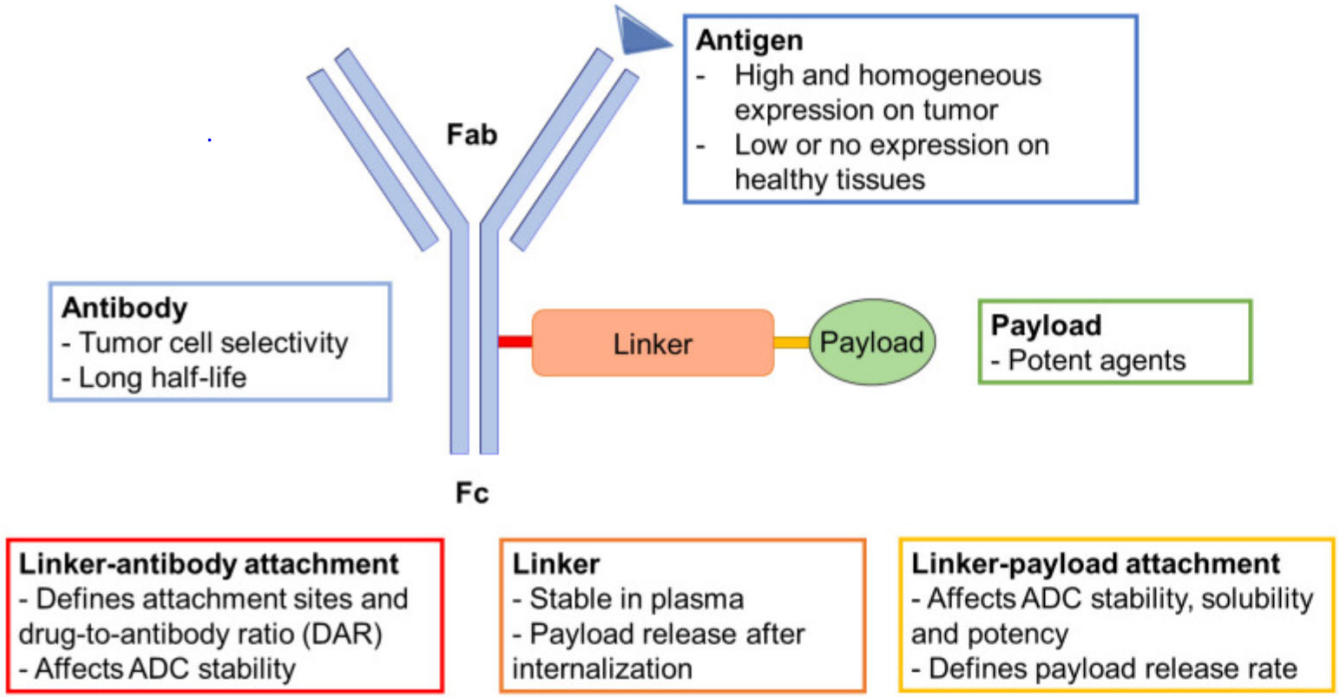
NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal

HER2 drug therapy timeline



Swain, S.M., Shastry, M. & Hamilton, E. Targeting HER2-positive breast cancer: advances and future directions. *Nat Rev Drug Discov* **22**, 101–126 (2023)

ADCs



Esnault C, Schrama D, Houben R, et al. Antibody-Drug Conjugates as an Emerging Therapy in Oncodermatology. *Cancers (Basel)*. 2022;14(3):778. Published 2022 Feb 2. doi:10.3390/cancers14030778

KATHERINE: phase III, open label study of adjuvant T-DM1 vs trastuzumab for residual invasive HER2 positive breast cancer

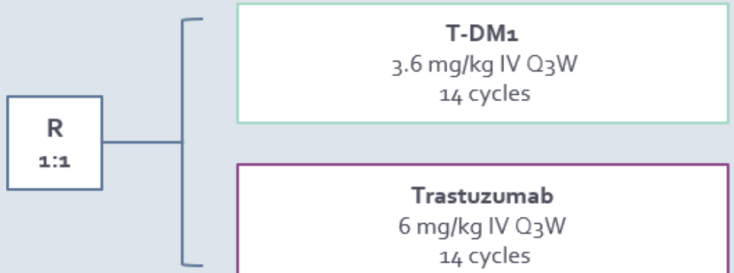
- Rationale: Approximately 40-60% of patients do not achieve pathologic complete response in the neo-adjuvant setting.
- These patients have poor outcomes.
- KATHERINE study assessed the value of switching from current HER2-directed therapy to single-agent T-DM1 in the adjuvant setting.

KATHERINE: study design

PATIENTS

- cT1-4/No-3/Mo at presentation (cT1a-b/No 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°

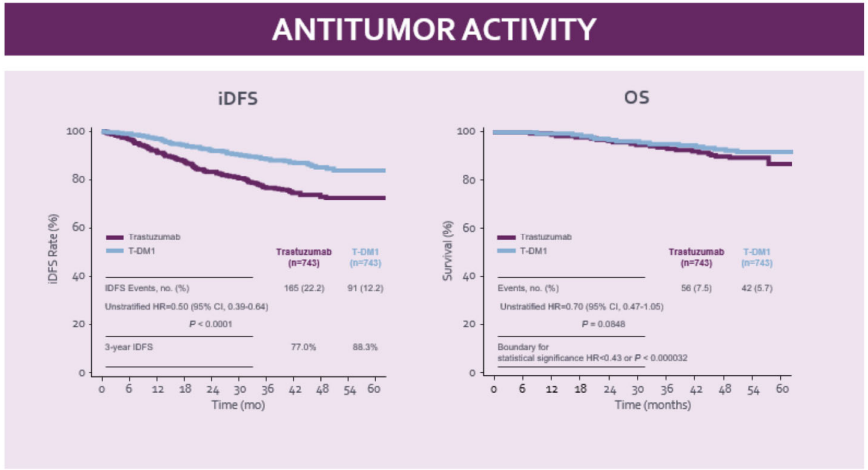
- iDFS

Select 2°

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

Initial results

- Primary analysis, conducted in 2018, showed significant improvement in 3-year IDFS with T-DM1, compared with trastuzumab (88.3% vs 77% trastuzumab). An absolute difference of 11%.
- OS data were immature.



Approvals and recommendations

- May 2019, the FDA approved TDM-1 for use as an adjuvant treatment of patients with HER2 positive early breast cancer who have residual invasive disease following neoadjuvant trastuzumab and chemotherapy.

- NCCN Guidelines recommend adjuvant T-DM1 for HER2 positive residual breast cancer for 14 cycles (category 1).

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer (Version 1.2024). © 2024 National Comprehensive Cancer Network, Inc. Available at: NCCN.org.

8.4-year follow-up:

- 70.1% (n=521) and 62.0% (n=461) in the T-DM1 and trastuzumab arms, respectively, were still alive.

	• TDM1	trastuzumab	
• iDFS	19.7% (n=239)	32.2% (n=146)	(HR, 0.54; 95% CI, 0.44-0.66; p<0.0001)

- There was a 13.7% absolute iDFS benefit at 7 years.

Loibl S, Mano M, Untch M, et al: Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy. 2023 San Antonio Breast Cancer Symposium. Abstract GS03-12. Presented December 8, 2023.

First iDFS events:

	T-DM1	trastuzumab
Distant recurrence	14.7%	21.5%
CNS met	7.0%	5.1%
Locoregional recurrence	2.2%	6.2%
Contralateral breast cancer	0.9%	2.6%
Death without prior event	1.9%	1.9%

T-DM1 led to an absolute OS benefit of 4.7% at 7 years, with a 34% significant reduction in the risk of death.

12% (n=89) experiencing an OS event in the T-DM1 arm
17% (n=126) in the trastuzumab arm (HR, 0.66; 95% CI, 0.51-0.87; p=0.0027).

The causes of death were breast cancer (9.5% in the T-DM1 cohort, vs 15% in the trastuzumab cohort); adverse event (0.1% vs 0%); and other (2.4% vs 2.5%).

Loibl S, Mano M, Untch M, et al., 2023 San Antonio Breast Cancer Symposium. Abstract GS03-12. Presented December 8, 2023.

Safety

- No new safety signals emerged with longer follow-ups from the KATHERINE trial.
- Twenty-four patients (3.2%) in the T-DM1 group and 12 patients (1.7%) in the T-DM1 and trastuzumab cohorts, respectively, experienced any-grade adverse events (AEs).
  - cardiac disorders (0.7% in each arm)
  - nervous system disorders (0.5% vs 0% in the T-DM1 and trastuzumab arms, respectively)
  - hepatobiliary disorders (0.3% vs 0%)
  - metabolism and nutrition disorders (0.3% vs 0%)
  - skin and subcutaneous tissue disorders (0.3% vs 0%).

Loibl S, Mano M, Untch M, et al,. 2023 San Antonio Breast Cancer Symposium. Abstract GS03-12. Presented December 8, 2023.

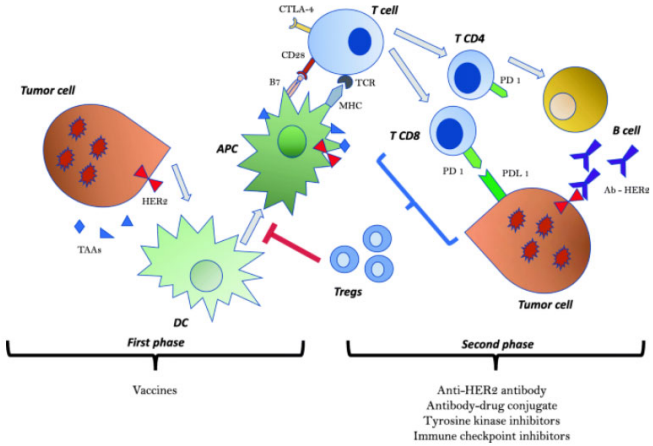
Safety

- Serious AEs occurred in 0.3% (n=2) and 0.6% (n=4) of patients in the T-DM1 and trastuzumab groups, respectively.
  - cardiac disorders (0 vs 0.4%)
  - hepatobiliary disorders (0.3% vs 0%)
  - vascular disorders (0 vs 0.1%)
- Regarding patients discontinuing the study, 14.1% (n=105) and 21.4% (n=159) in the T-DM1 and trastuzumab arms, respectively, stopped treatment with an iDFS event reported.
- 15.7% and 16.6% (n=123), respectively, discontinued before an iDFS event.

Loibl S, Mano M, Untch M, et al, 2023 San Antonio Breast Cancer Symposium. Abstract GS03-12. Presented December 8, 2023.

Immunotherapy

- Clinical data in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies.
- Many human tumors have been found to overexpress PD L1 which acts to suppress anti tumor immunity.



- While innate immune responses appear to be important for tumor antigen-targeted monoclonal antibody therapies, recent studies in mice and correlative clinical evidence suggest that trastuzumab may also stimulate adaptive antitumor immunity. These studies raise the possibility that combination strategies may be used to capitalize on the adaptive tumor-specific immunity generated by anti-HER2 monoclonal antibodies.

Hodi FS and Dranoff G, J Cutan Pathol 2010; Kantoff PW et al, New Engl J Med 2010; Chen DS et al, Clin Cancer Res 2012
Krasniqi, E., Barchiesi, G., Pizzuti, L. et al. Immunotherapy in HER2-positive breast cancer: state of the art and future perspectives. J Hematol Oncol 12, 111 (2019).

Immunotherapy interaction

- In addition to being involved in the natural progression of cancer, immunity can affect the activity of various anticancer agents.
- Accordingly, recent evidence suggests that some chemotherapeutic drugs, such as anthracyclines and oxaliplatin, rely on the induction of anticancer immune responses.
- Immune responses also play a major role in the efficacy of targeted therapies with monoclonal antibodies.

Stagg J et al, Breast Care 2012

APTneo

- The APTneo trial was a randomized neoadjuvant study of the combination of trastuzumab, pertuzumab, carboplatin and paclitaxel (HPCT) with or without atezolizumab in women with early high-risk and locally advanced HER2-positive suitable for neoadjuvant therapy.
- One study arm included anthracycline and cyclophosphamide.

Gianni L, Munzone E, Mansutti M, et al. Pathologic complete response (pCR) of neoadjuvant therapy with or without atezolizumab in HER2-positive, early high-risk and locally advanced breast cancer: APTneo Michelangelo randomized trial. Presented at SABCS 2023. December 5-9, 2023. San Antonio, TX. Abstract LBO1-02.

APTneo

- The open-label phase III APTneo trial enrolled 661 patients with operable or locally advanced HER2-positive breast cancer who had not previously been exposed to chemotherapy.

- **Arm A)** (n=223) received neoadjuvant Q3 week trastuzumab / pertuzumab / carboplatin AUC 2 and paclitaxel 90 mg/m on days 1 and 8 every 21 days for 6 cycles. Adjuvant HP for another 12 cycles.
- **Arm B1)** (n=218) received neoadjuvant doxorubicin /cyclophosphamide Q3 weeks for 3 cycles followed by HPCT for 3 cycles plus atezolizumab at 1200 mg every 3 weeks. Adjuvant HP and atezolizumab for an additional 12 cycles.
- **Arm B2)** (n=220) were given HPCT plus atezolizumab for 6 cycles followed by surgery and adjuvant HP and atezolizumab for an additional 12 cycles.

Gianni L, Munzone E, Mansutti M, et al. Presented at SABCS 2023. December 5-9, 2023. San Antonio, TX. Abstract LBO1-02.

Characteristics

- The median patient age:
  - Arm A was 50 years (range, 29-79)
  - Arm B1 was 50 years (range, 21-81)
  - Arm B2 was 49 years (range, 24-78)

- 44% of patients across arms A, B1, and B2 had locally advanced disease (45.3%; 45.0%; 44.1% respectively)
- Approximately 30% were PD-L1 positive (30.5%; 29.8%; 30.9% respectively)
- Approximately 1/3rd were estrogen receptor negative (39.0%, 34.9%, and 30.9% respectively)

Gianni L, Munzone E, Mansutti M, et al. Presented at SABCS 2023. December 5-9, 2023. San Antonio, TX. Abstract LBO1-02

pCR results

- pCR achieved with Atezolizumab plus HPCT with or without anthracyclines vs those given HPCT alone, 57.8% vs 52.0%, respectively (P = .526).
- The pCR achieved with AC and atezolizumab followed by HPCT was significantly higher vs HPCT alone, 61.9% vs 52% (p=.022)
- No significant difference in pCR between who received atezolizumab + HPCT without anthracyclines vs HPCT alone.(p=.091)
- In a multivariate analysis, treatment with anthracyclines, PD-L1-positivity, estrogen receptor negativity, and the presence of ≥30% stromal tumor-infiltrating lymphocytes were associated with a higher probability of pCR.

In the intention-to-treat population, the pCR defined as the absence of invasive cells in the breast and lymph nodes achieved:

	pCR
Arm A HPCT (n=223)	52%
Arm B1 atezo + AC followed by HPCT (n=218)	61.9%
Arm B2 atezo + HPCT (n=220)	53.6%

P=.022

P=0.91

P=0.89

Gianni L, Munzone E, Mansutti M, et al. Presented at SABCS 2023. December 5-9, 2023. San Antonio, TX. Abstract LBO1-02.

The most common grade 3 or higher TRAEs reported

Arm A:

- decreased neutrophil count (12.3%)
- neutropenia (11.9%)
- diarrhea (3.2%)
- anemia (1.4%)
- asthenia (0.9%)
- fatigue (0.5%)
- mucosal inflammation (0.5%)

Arm B1

- neutropenia (16.2%)
- decreased neutrophil count (10.6%)
- diarrhea (6.9%)
- anemia (3.7%)
- asthenia (3.7%)
- vomiting (0.9%)
- fatigue (0.9%)
- mucosal inflammation (0.5%)
- nausea (0.5%)

Arm B2:

- neutropenia (14.8%)
- decreased neutrophil count (10.6%)
- diarrhea (6.4%)
- anemia (2.3%)
- asthenia (2.3%)
- vomiting (1.9%)
- mucosal inflammation (0.9%)
- rash (0.6%)
- fatigue (0.5%)

Gianni L, Munzone E, Mansutti M, et al. Presented at SABCS 2023. December 5-9, 2023. San Antonio, TX. Abstract LBO1-02

Summary

- The initial results of the KATHERINE study demonstrated the magnitude of benefit from T-DM1 on residual HER2 positive breast cancer that led to the NCCN recommendation.
- The 8 year follow up reported at SABCS 2023 demonstrated the durability of those results and sustained benefit.

Summary

- The APTneo study demonstrated the influence and benefit of immunotherapy and HER2 therapy in the neoadjuvant setting in a select patient population.
- The role of immunotherapy in a HER2 positive breast cancer in the neoadjuvant setting remains to be defined.

Conclusion

- We look forward to the results of:
- **DESTINY breast 11**: neo-adjuvant phase III trial of TDXd initiated in patients with high risk HER2 positive early stage cancer
- **DESTINY breast 05**: TDXd versus T-DM1 initiated in patients with HER2 positive early breast cancer at high risk after neo-adjuvant therapy
- **Astefania**: adjuvant T-DM1 and atezolizumab for high risk, HER2 positive breast cancer in patients with residual disease following neoadjuvant HER2 targeted therapy.
- Ongoing analysis of studies that included de-escalation, elimination of chemotherapy in HER2 positive tumors, HER2 targeted drug resistance and biomarkers.

National Comprehensive Cancer Network®

NCCN Member Institutions

Who We Are

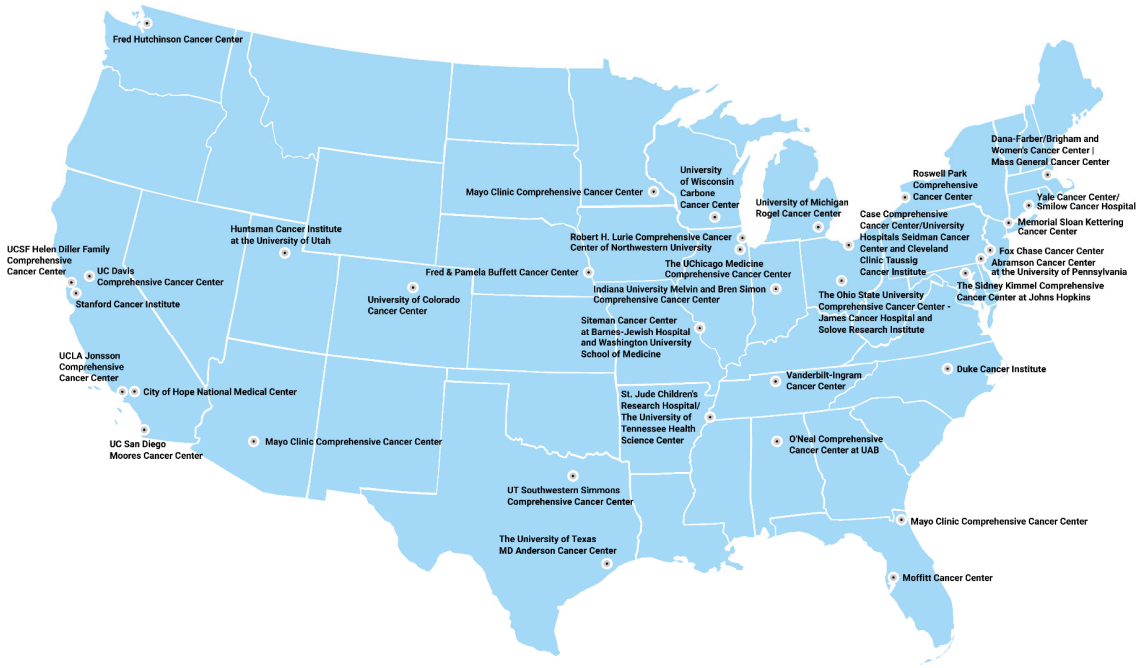
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal