Targeted delivery. Measured benefit.

T-DM1 (ado-trastuzumab emtansine) | HER2-positive metastatic breast cancer

The clinical problem

HER2-positive advanced breast cancer can progress despite trastuzumab and a taxane. EMILIA tested whether linking HER2 recognition to a cytotoxic payload could improve outcomes compared with lapatinib plus capecitabine. [2]

The mechanism

T-DM1 couples trastuzumab to DM1 through a stable linker. HER2 binding precedes uptake and lysosomal processing; DM1-containing material acts on microtubules. The six-panel figure follows this sequence. [1; Figure 1]

What changed - and what changed again

EMILIA established a survival benefit for T-DM1 against its comparator. Later, DESTINY-Breast03 favored T-DXd over T-DM1. The clinical story therefore includes both the original advance and evidence for a newer conjugate. These are separate randomized trials. [2,3]

The delivery mechanism explains how T-DM1 acts. Randomized comparisons establish where it improved outcomes, and where another therapy performed better.

Continue the story

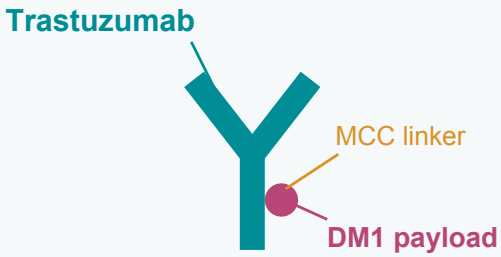
Watch the film and explore the mechanism

The animation explains biology. The following pages examine measured patient outcomes.

Figure 1. T-DM1: HER2 binding to payload action

Follow the mechanism from left to right, then down each row.

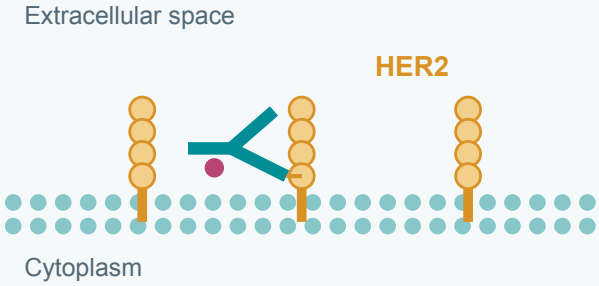
A Targeted conjugate



Anti-HER2 antibody + stable linker + DM1

Average drug-to-antibody ratio: 3.5 [1]

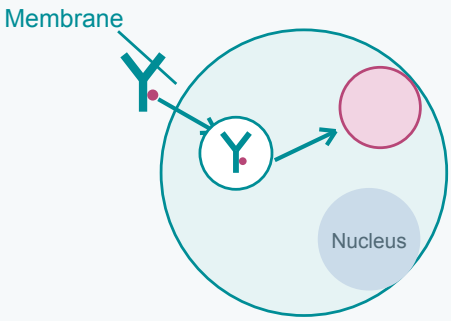
B HER2 binding



Antibody binds HER2 domain IV. [1,2]

Binding precedes receptor-mediated uptake.

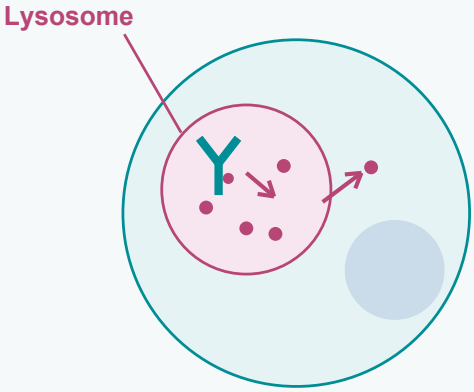
C Cellular uptake



The bound complex enters a vesicle. [1]

Trafficking carries it toward the lysosome.

D Lysosomal processing

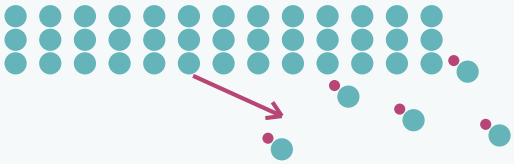


Proteolysis yields DM1-containing catabolites. [1]

The stable linker is not shown as freely cleaving.

E Payload action

Tubulin / microtubule network

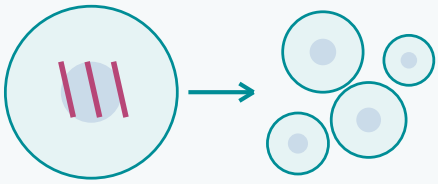


DM1 binds tubulin and disrupts microtubules. [1]

Payload action occurs within the cell.

F Cellular consequence

Arrest **Apoptotic changes**



Cell-cycle arrest can lead to apoptosis. [1]

This does not predict a patient-level response.

[1] KADCYLA prescribing information, sections 11–12.1.
[2] Cho et al., Nature (2003); PDB 1N8Z.

Schematic, not to scale. Mechanism does not predict an individual clinical response.

Two trials, two clinical questions.

Metastatic / unresectable HER2-positive breast cancer after trastuzumab and taxane therapy. Comparators and analysis dates remain separate.

EMILIA | T-DM1 vs lapatinib + capecitabine [2]

Median PFS	**9.6 vs 6.4 months** Independent review; HR 0.65 (95% CI 0.55-0.77)
Median overall survival	**30.9 vs 25.1 months** Second interim analysis; HR 0.68 (95% CI 0.55-0.85)

991 randomized: 495 vs 496. Published 2012. Survival at the second interim analysis crossed the prespecified efficacy boundary.

DESTINY-Breast03 | T-DXd vs T-DM1 [3]

Median PFS	**29.0 vs 7.2 months** Investigator assessment; HR 0.30 (95% CI 0.24-0.38)
Median overall survival	**52.6 vs 42.7 months** HR 0.73 (95% CI 0.56-0.94)

524 randomized: 261 vs 263. Cutoff 20 November 2023; published 2024. Updated exploratory analysis; the primary endpoint was centrally assessed PFS.

A later response snapshot [4]

At the 27 June 2025 cutoff, investigator-assessed CR / PR counts were 34 / 172 for T-DXd and 13 / 84 for T-DM1. CR + PR was 78.9% versus 36.9%, using all randomized patients. These figures come from an ESMO Breast 2026 poster, not the 2024 publication.

What the evidence means.

Benefit, uncertainty and safety belong in the same clinical story.

What supports the clinical claim

EMILIA supports benefit over lapatinib plus capecitabine in its enrolled population. DESTINY-Breast03 supports the superiority of T-DXd over T-DM1 on the reported outcomes. Neither comparison establishes a ranking across every breast cancer setting. [2,3]

Response is not survival

CR means complete response; PR means partial response. Neither means cure. The 2026 poster explores depth of response among responders; its subgroup survival curves are descriptive and should not be interpreted as a randomized test of achieving a deeper response. [4]

Safety changes the interpretation

T-DM1 carries boxed warnings for hepatotoxicity, cardiac toxicity and embryo-fetal toxicity. Thrombocytopenia and pulmonary toxicity also matter. [1] In the 2024 DESTINY-Breast03 analysis, adjudicated drug-related ILD / pneumonitis occurred in 16.7% with T-DXd and 3.4% with T-DM1; exposure duration differed. [3]

Keep the indication boundary visible

T-DM1 also has an adjuvant indication for residual invasive HER2-positive early breast cancer after neoadjuvant taxane and trastuzumab therapy. That setting asks a different question about recurrence and is not represented by the metastatic response chart. [1]

What the animation can establish

The sequence communicates a biological mechanism. It does not measure drug delivery in a patient, show the frequency of resistance, or convert a cellular event into a predicted response percentage.

Sources you can follow.

Numbered citations on pages 1, 3 and 4 refer to this list. Figure 1 retains its own source key.

[1] KADCYLA US prescribing information.

Genentech | Current US label

Regulatory source. Sections 1, 5 and 12.1 support indication, selected risks and mechanism.

[2] Verma S et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. NEJM (2012).

DOI: 10.1056/NEJMoa1209124

Peer-reviewed EMILIA primary report; efficacy and second interim overall survival.

[3] Cortes J et al. DESTINY-Breast03 long-term survival analysis. Nature Medicine (2024).

DOI: 10.1038/s41591-024-03021-7

Peer-reviewed update. Cutoff 20 November 2023; endpoint methods and safety accompany the results.

[4] Hamilton E et al. DESTINY-Breast03 depth-of-response analysis. ESMO Breast 2026, 453P.

Sponsor-hosted conference poster

Cutoff 27 June 2025. Later response counts; exploratory analysis, distinct from the journal report.

How this brief was prepared

Selected primary publications, prescribing information and clearly identified conference material were checked on 7 September 2026. Data are not pooled across trials or cutoffs. This is a focused evidence summary, not a systematic review, prescribing guide or health-economic analysis.