# Her2-positive breast cancer

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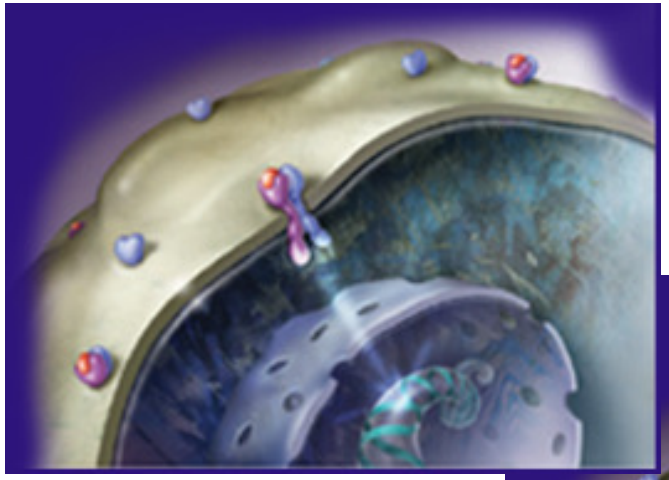
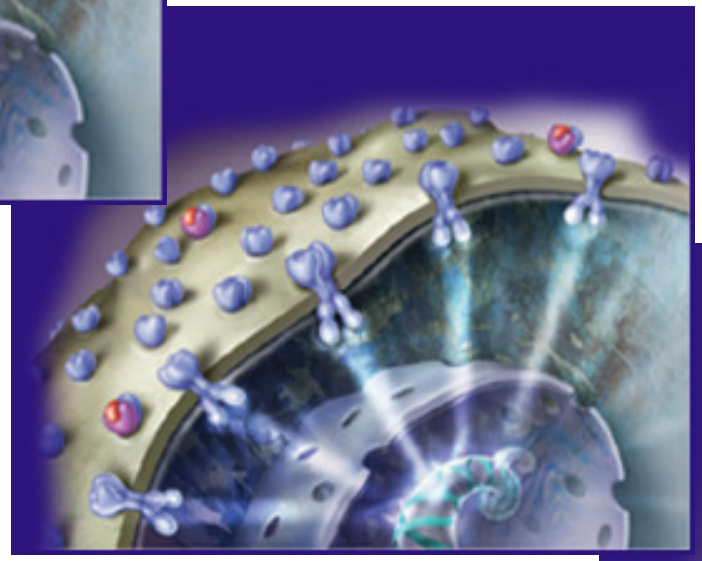
**University of Colorado Anschutz Medical Campus**

# HER2 Signals Cells to Divide

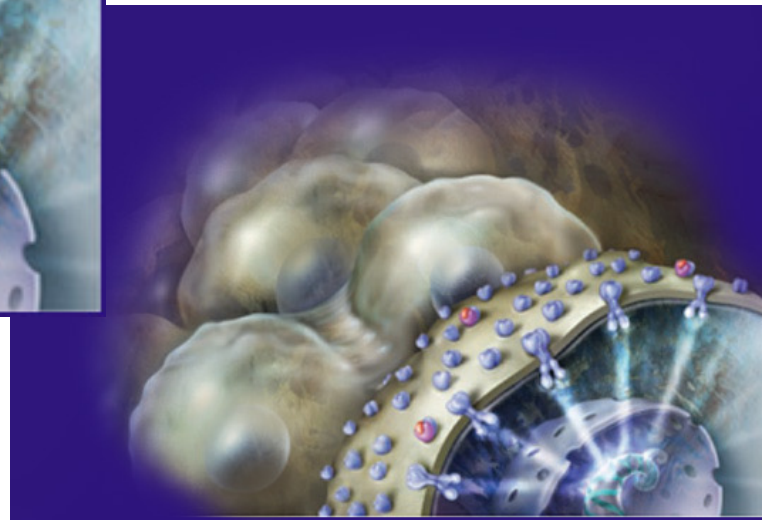


Normal

**HER2 is overexpressed in ~20%-30% of breast cancers**



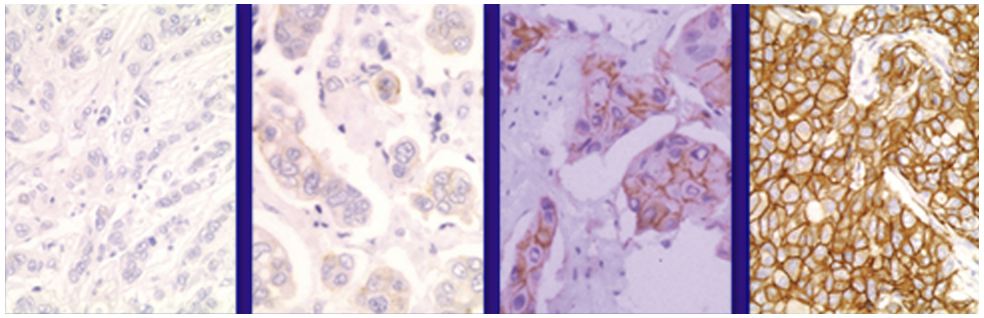
Overexpressed HER2



Excessive cellular division

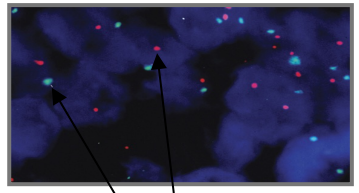

Berger et al. *Cancer Res.* 1988;48:1238.
Roskoski. *Biochem Biophys Res Commun*. 2004;319:1.
Rowinsky. *Annu Rev Med*. 2004;55:433.
Slamon et al. *Science*. 1987;235:177.

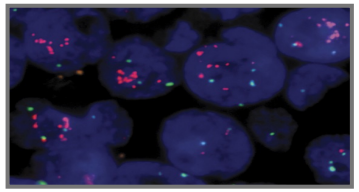
# HER2 Protein Overexpression Clinical Discrimination



IHC 0 IHC I+ IHC 2+ IHC 3+

**Her 2 negative**

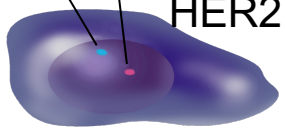


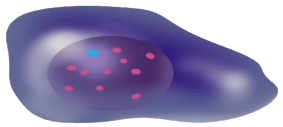


**Her 2 Positive**

Chromosome 17 centromere

HER2 gene





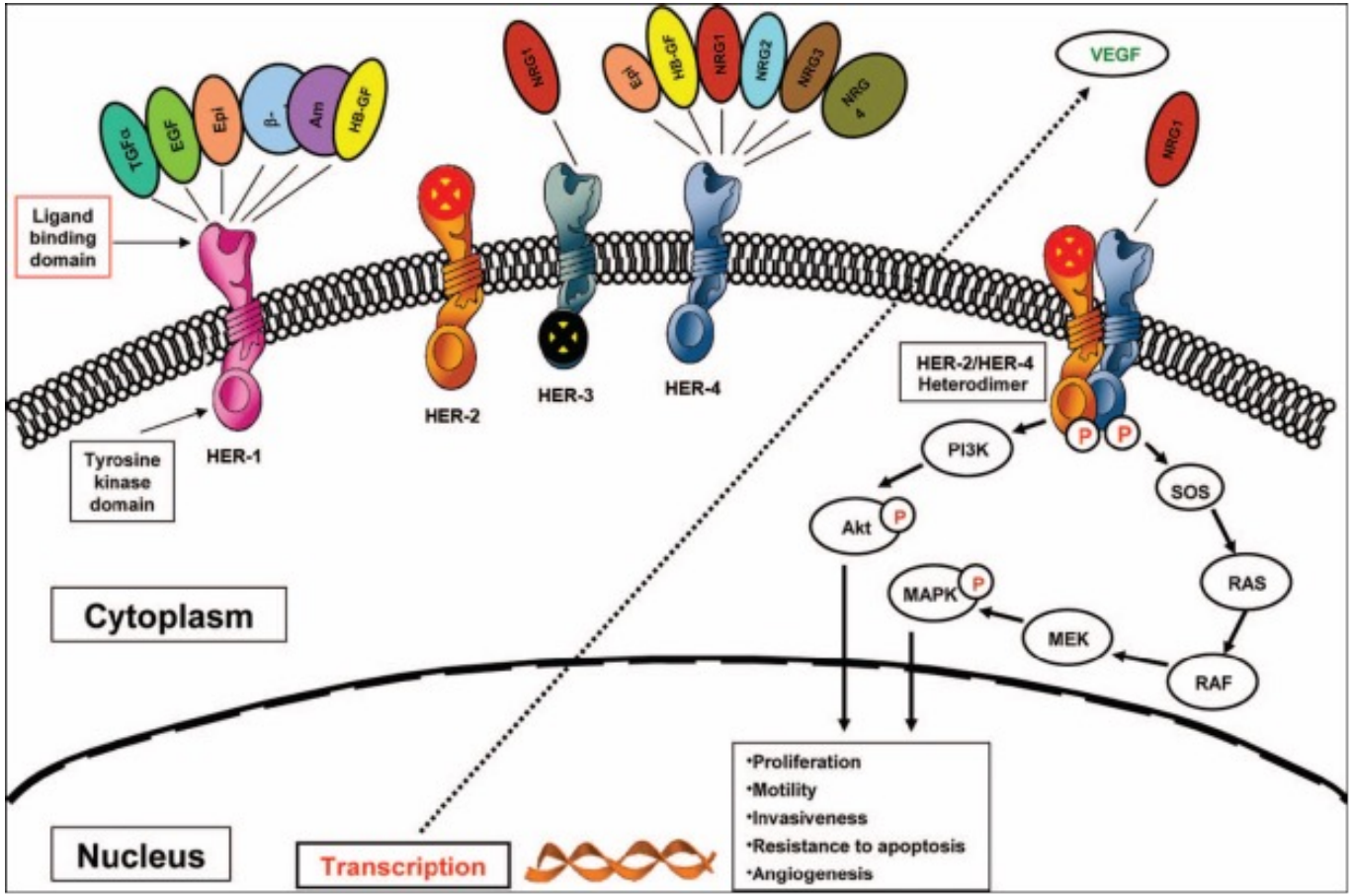
**HER2-normal Ratio <2.0**

**HER2-amplified Ratio ≥2.0**

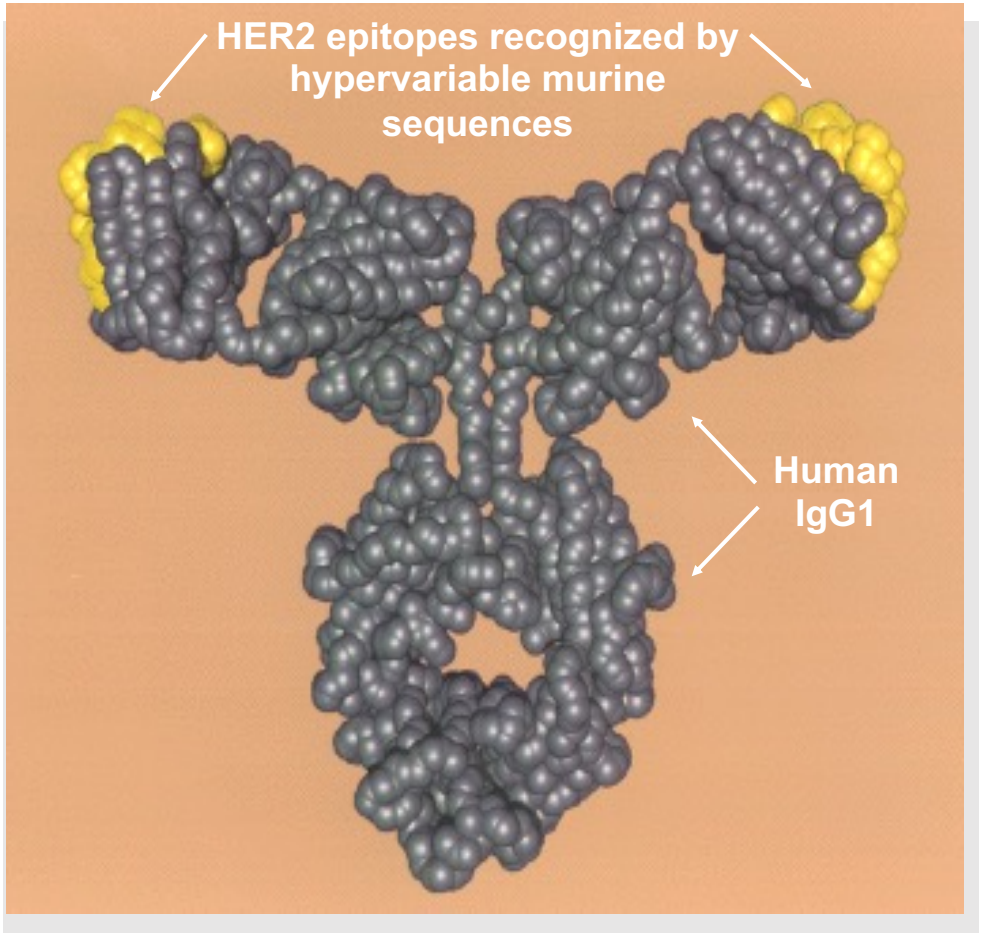
Treatment pathway follows the ER status

Treatment driven down the Her 2 pathway

# ErbB family of receptors

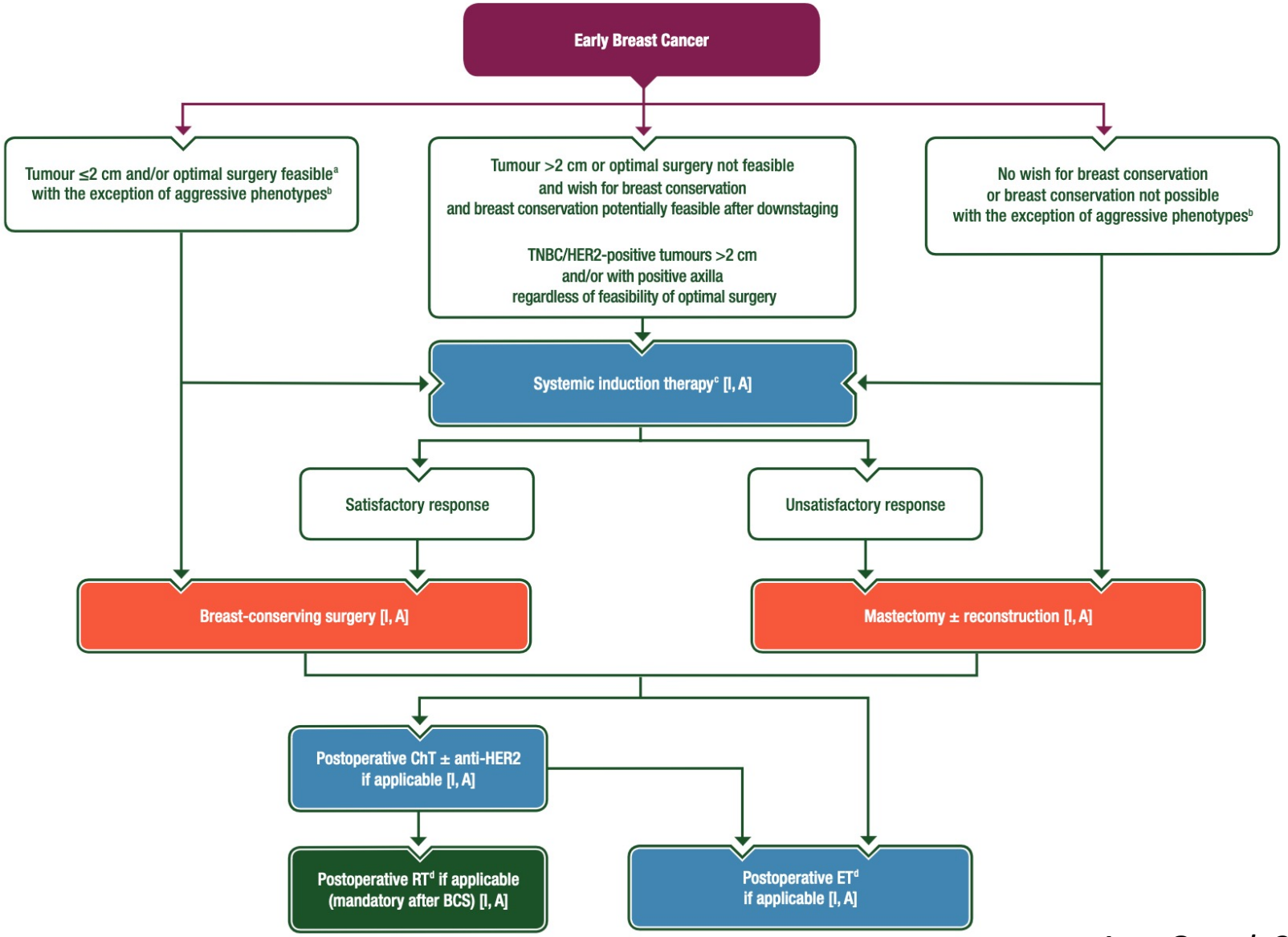


# Trastuzumab: Humanized Anti-HER2 MAb

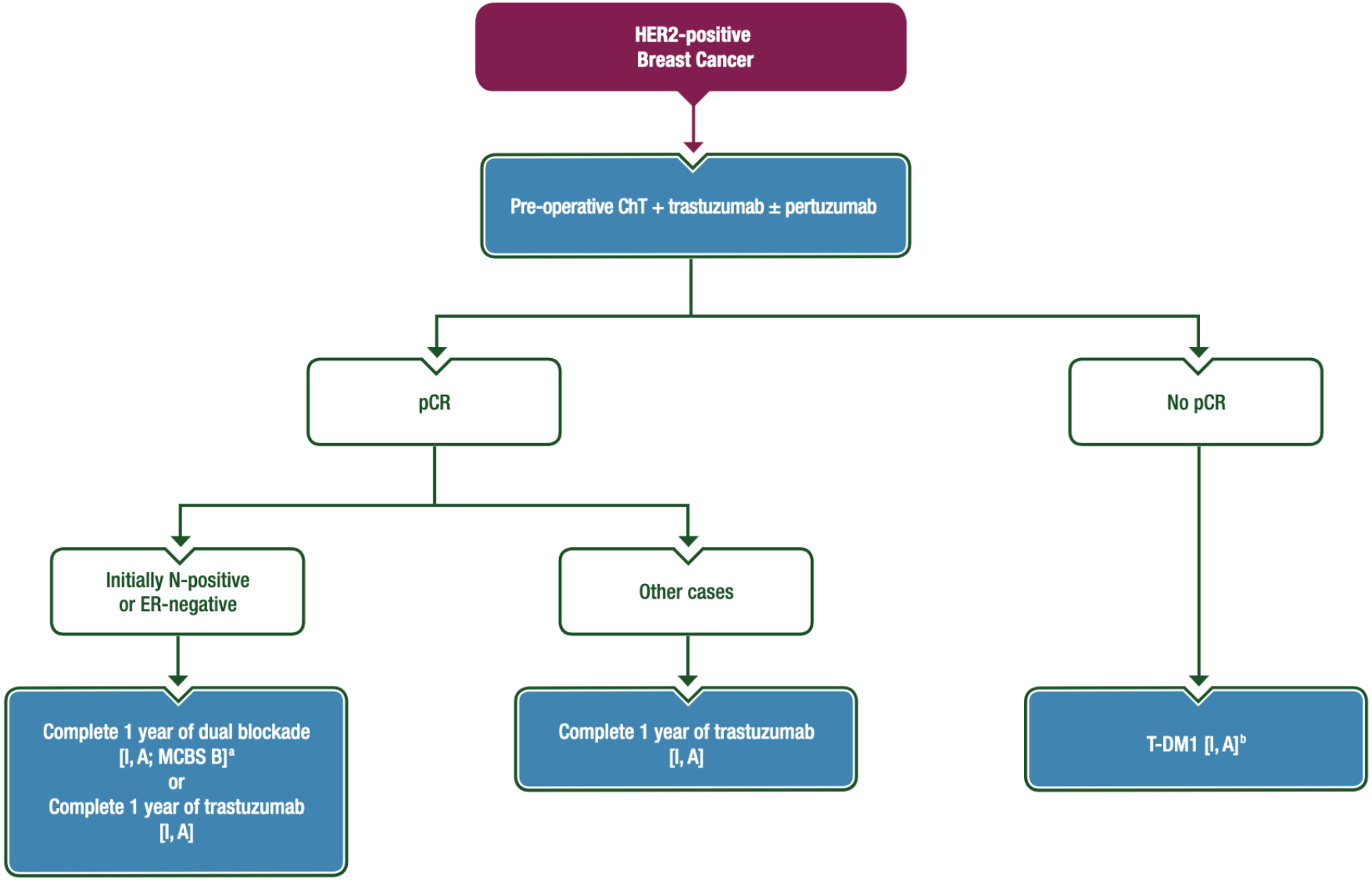



- Targets HER2 protein
- Selectively binds with high affinity ($K_d \leq 0.5$ nM)
- 95% human, 5% murine

# Early stage Her2+ breast cancer




*Ann Oncol*. 2019;30(8):1194-1220



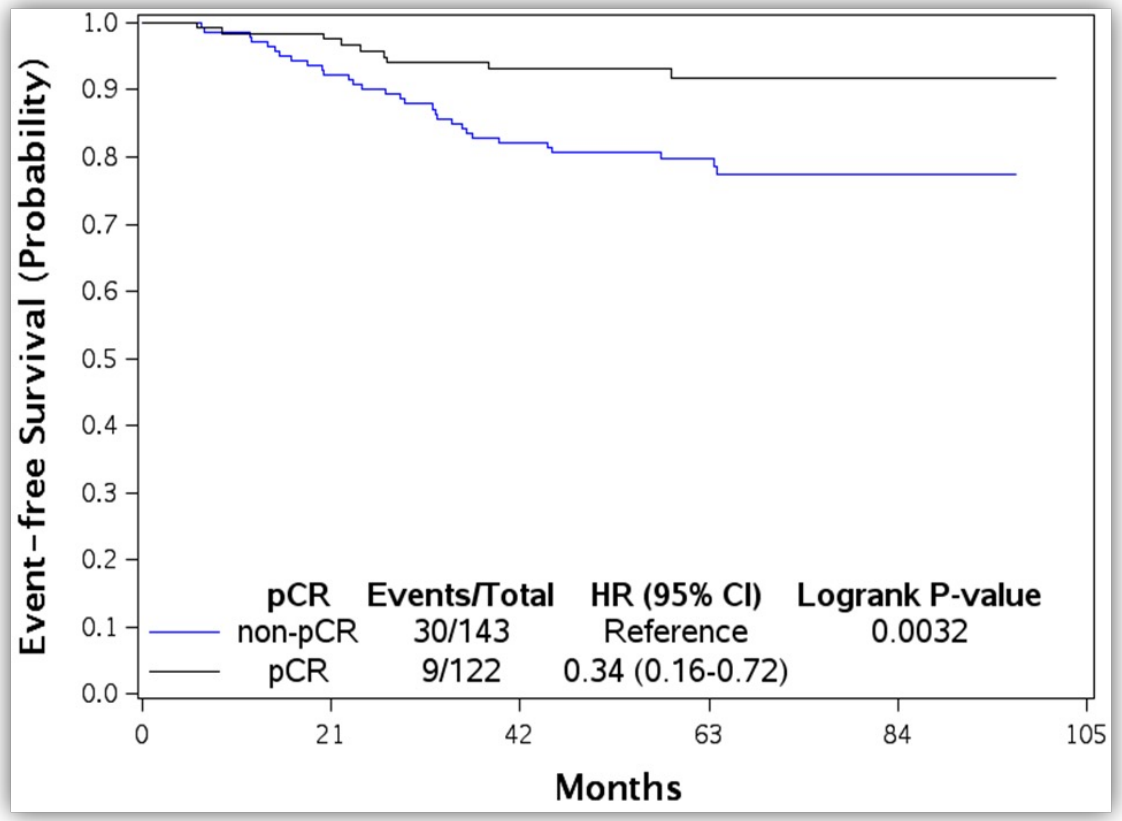

*Ann Oncol*. 2019;30(8):1194-1220

# The neoadjuvant era highlighted the role of pCR in survival for Her 2 + early breast cancer

Patients with residual invasive breast cancer after completion of preoperative HER2-directed therapy and chemotherapy have an inferior prognosis [2-6]

Investigation of additional treatment strategies warranted

CALGB 40601




*Krop et al, AACR-SABCS 2017*

**RD: ~80 % 5y EFS**

Untch et. al. JCO 2011[2]; Cortazar et al. Lancet 2014[3]; de Azambuja et. al Lancet Oncol 2014[4]; Gianni et al.,Lancet Oncol 2014[5]; Schneeweiss et al., Eur J Cancer 2018[6]

# Improvements in the Adjuvant Setting

## APHINITY TRIAL

6 year follow up data:

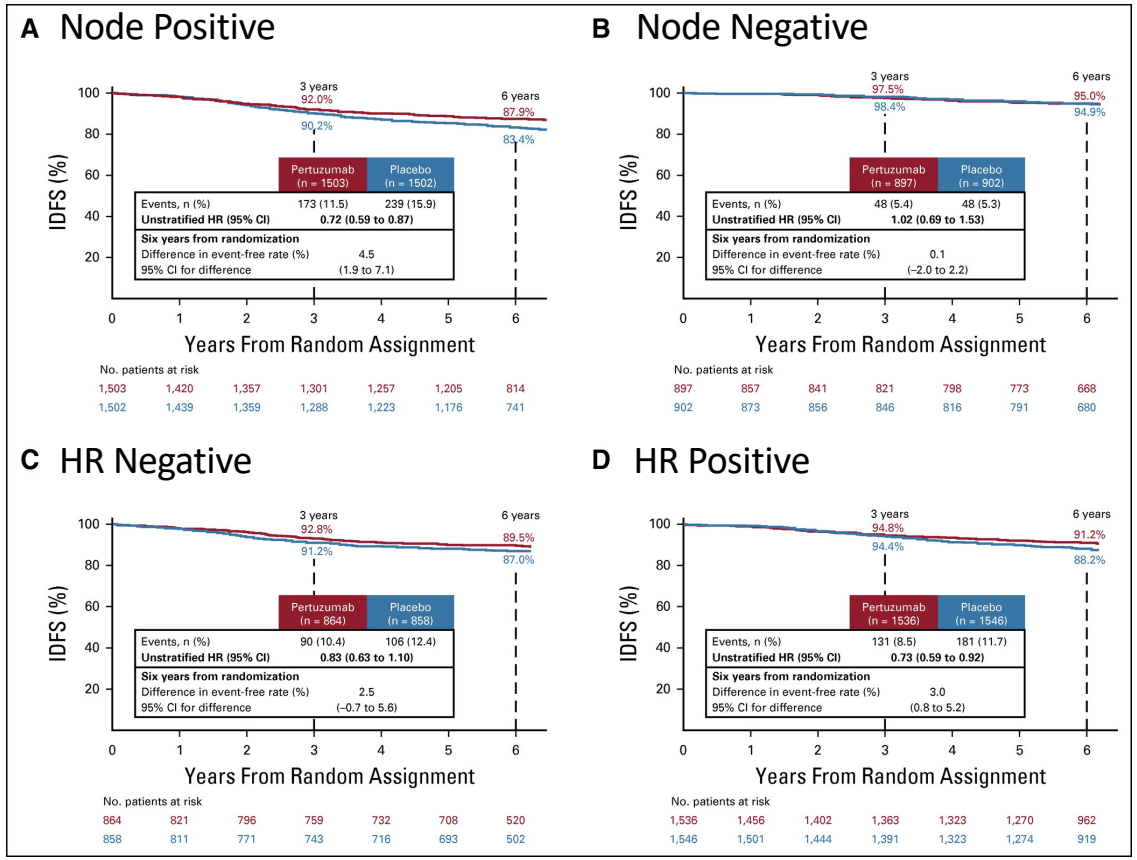
Overall IDFS 91% v 88%

Node pos IDFS 88% v 83%

Both HR+ and HR- benefit:

3% gain and 2.5% gain respectively

Cardiac event rate <1%



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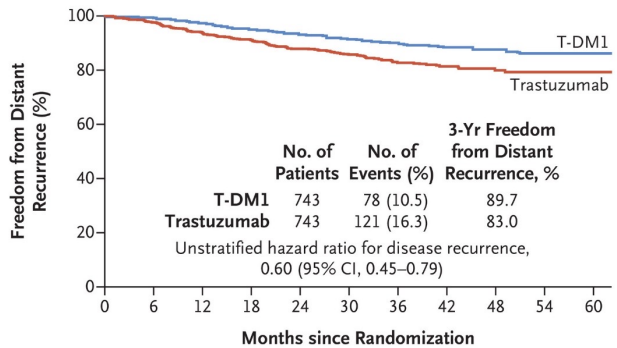
# Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

KATHERINE Trial, von Minckwitz, et al.

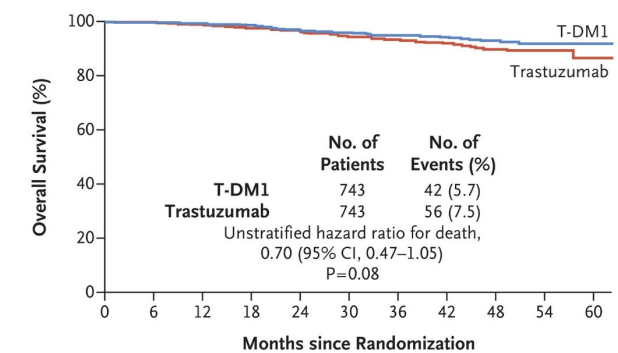
**B**




**No. at Risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DM1 | 743 | 707 | 682 | 661 | 636 | 564 | 412 | 254 | 143 | 45 | 4 |
| Trastuzumab | 743 | 679 | 643 | 609 | 577 | 520 | 359 | 233 | 126 | 41 | 4 |

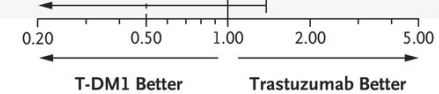
**C**



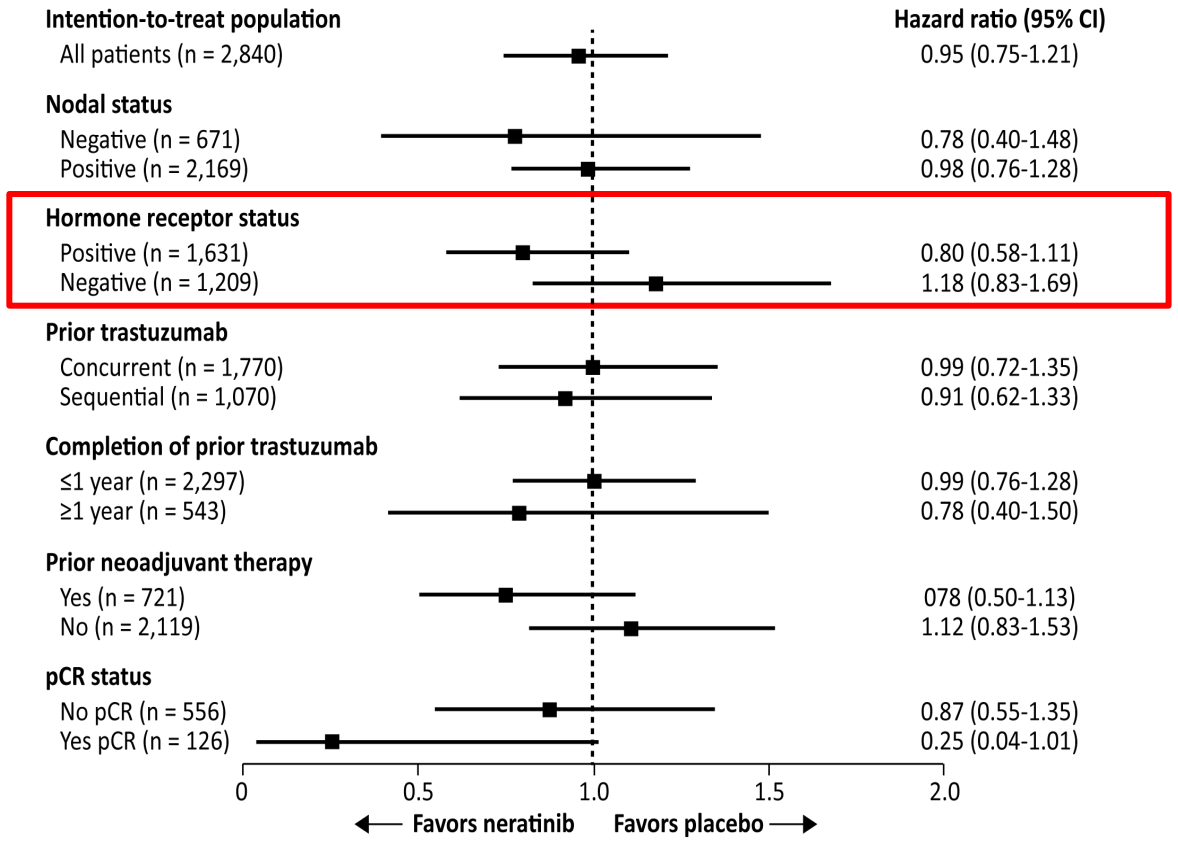

**No. at Risk**

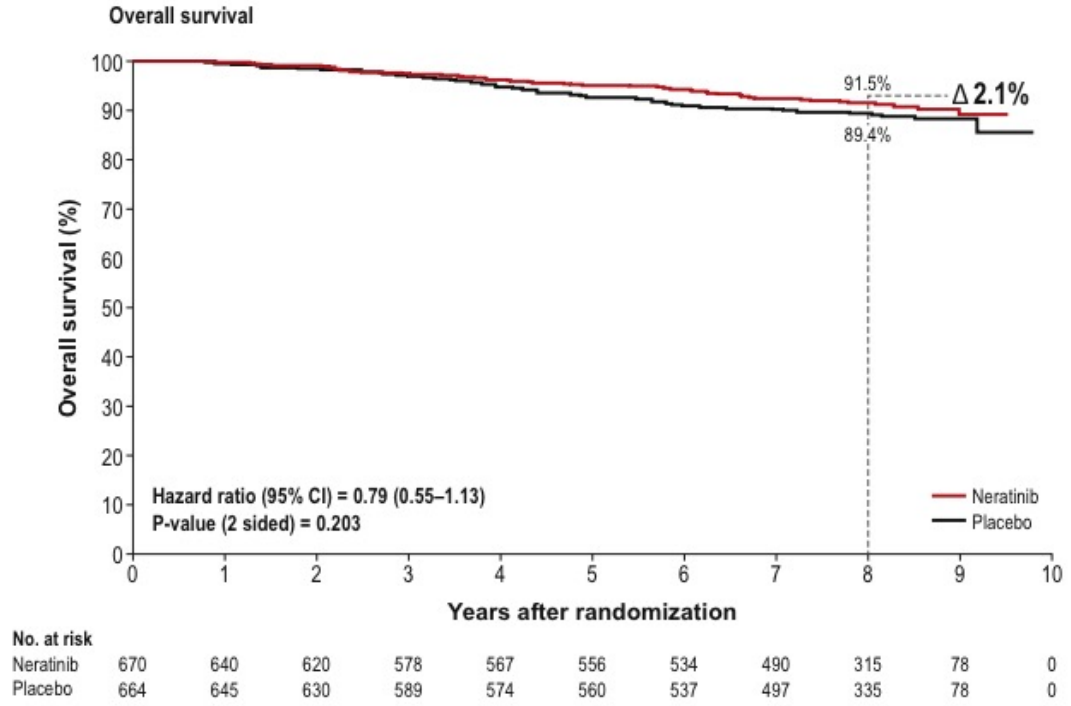
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DM1 | 743 | 719 | 702 | 693 | 668 | 648 | 508 | 345 | 195 | 76 | 12 |
| Trastuzumab | 743 | 695 | 677 | 657 | 635 | 608 | 471 | 312 | 175 | 71 | 8 |

| Subgroup | T-DM1 | Trastuzumab | Hazard Ratio for Invasive-Disease Event (95% CI) | 3-Yr Invasive Disease–free Survival Rate | |
|---|---|---|---|---|---|
| | *no. of patients with an invasive-disease event/total no.* | | | T-DM1 | Trastuzumab |
| | | | | % | |
| All patients | 91/743 | 165/743 | 0.50 (0.39–0.64) | 88.3 | 77.0 |
| Age group | | | | | |
| <40 yr | 20/143 | 37/153 | 0.50 (0.29–0.86) | 86.5 | 74.9 |
| 40–64 yr | 64/542 | 113/522 | 0.49 (0.36–0.67) | 88.8 | 77.1 |
| ≥65 yr | 7/58 | 15/68 | 0.55 (0.22–1.34) | 87.4 | 81.1 |
| Clinical stage at presentation | | | | | |
| Inoperable breast cancer | 42/185 | 70/190 | 0.54 (0.37–0.80) | 76.0 | 60.2 |
| Operable breast cancer | 49/558 | 95/553 | 0.47 (0.33–0.66) | 92.3 | 82.8 |
| Hormone-receptor status | | | | | |
| Negative (ER-negative and progesterone-receptor–negative or unknown) | 38/209 | 61/203 | 0.50 (0.33–0.74) | 82.1 | 66.6 |
| Positive (ER-positive, progesterone-receptor–positive, or both) | 53/534 | 104/540 | 0.48 (0.35–0.67) | 90.7 | 80.7 |
| Preoperative HER2-directed therapy | | | | | |
| Trastuzumab alone | 78/600 | 141/596 | 0.49 (0.37–0.65) | 87.7 | 75.9 |
| Trastuzumab plus additional HER2-directed agent or agents | 13/143 | 24/147 | 0.54 (0.27–1.06) | 90.9 | 81.8 |
| Pathological nodal status after preoperative therapy | | | | | |
| Node-positive | 62/343 | 103/346 | 0.52 (0.38–0.71) | 83.0 | 67.7 |
| Node-negative or NE | 29/400 | 62/397 | 0.44 (0.28–0.68) | 92.8 | 84.6 |
| Primary tumor stage at definitive surgery | | | | | |
| ypT0, ypT1a, ypT1b, ypT1mic, ypTis | 40/331 | 52/306 | 0.66 (0.44–1.00) | 88.3 | 83.6 |
| ypT1, ypT1c | 14/175 | 42/184 | 0.34 (0.19–0.62) | 91.9 | 75.9 |
| ypT2 | 25/174 | 44/185 | 0.50 (0.31–0.82) | 88.3 | 74.3 |
| ypT3 | 9/51 | 21/57 | 0.40 (0.18–0.88) | 79.8 | 61.1 |
| ypT4 | 3/12 | 6/11 | 0.29 (0.07–1.17) | 70.0 | 30.0 |
| Regional lymph-node stage at definitive surgery | | | | | |
| ypN0 | 28/344 | 56/335 | 0.46 (0.30–0.73) | 91.9 | 83.9 |
| ypN1 | 29/220 | 50/213 | 0.49 (0.31–0.78) | 88.9 | 75.8 |
| ypN2 | 16/86 | 38/103 | 0.43 (0.24–0.77) | 81.1 | 58.2 |
| ypN3 | 17/37 | 15/30 | 0.71 (0.35–1.42) | 52.0 | 40.6 |
| ypNX | 1/56 | 6/62 | 0.17 (0.02–1.38) | 98.1 | 88.7 |



# ExteNET: Final Overall Survival Analysis




Holmes FA et al. SABCS 2020;Abstract PD3-03.

Chan A et al, Clinical Breast Cancer, Feb 2021

# ExteNET: Cumulative Incidence of CNS Recurrences

| Population or subgroup | Events, n | | Cumulative incidence of CNS recurrences | |
|---|---|---|---|---|
| | Neratinib | Placebo | Neratinib | Placebo |
| **Intention-to-treat population** (n = 2,840) | 16 | 23 | 1.3% | 1.8% |
| **HR-positive/≤1-year population (EU indication)** (n = 1,334) | 4 | 12 | 0.7% | 2.1% |
| **Prior neoadjuvant therapy (n = 1,334)** | | | | |
| No (n = 980) | 3 | 6 | 0.7% | 1.5% |
| Yes (n = 354) | 1 | 6 | 0.7% | 3.7% |
| **pCR status** (n = 354) | | | | |
| No (n = 295) | 1 | 5 | 0.8% | 3.6% |
| Yes (n = 38) | 0 | 1 | 0 | 5.0% |

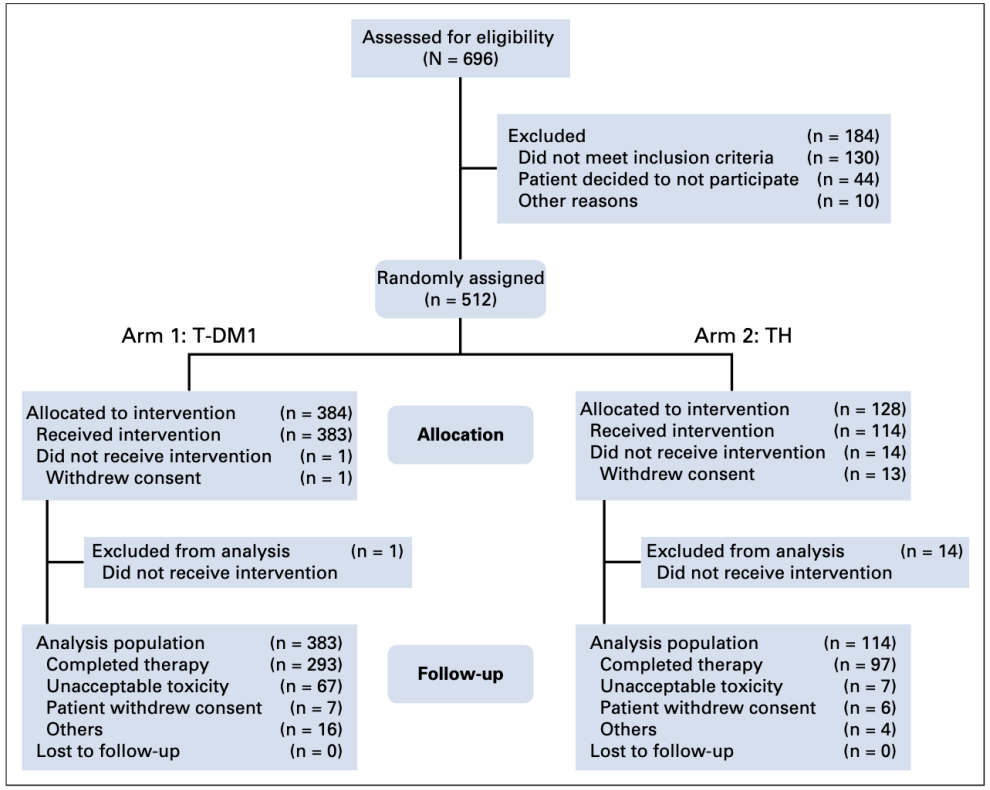
Holmes FA et al. SABCS 2020;Abstract PD3-03, update and further analysis Lin N et al, SABCS 2021, Abstract P2-13-05

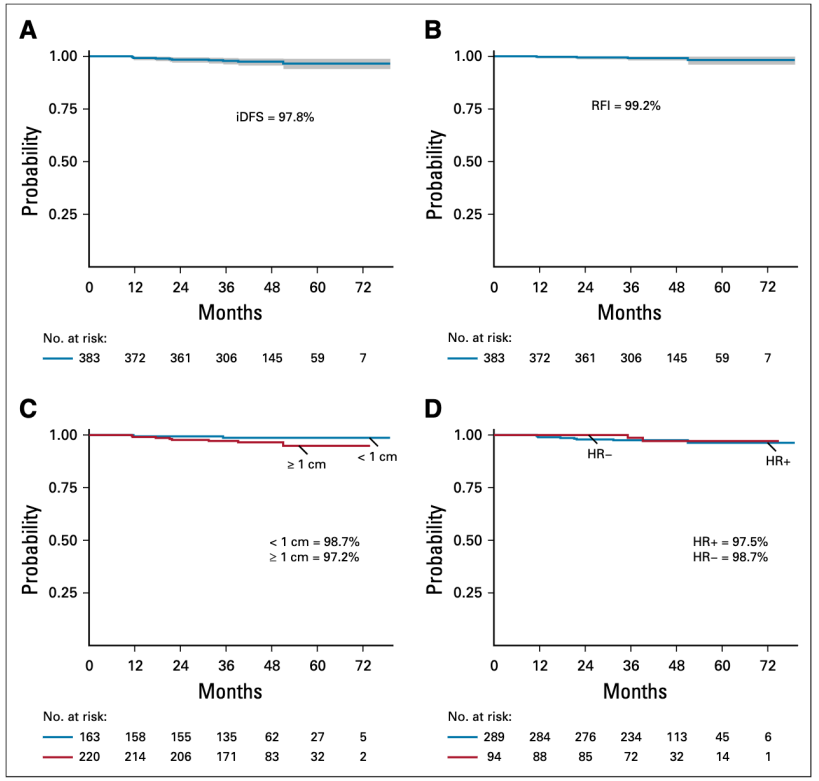
original reports

# Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial

Sara M. Tolaney, MD, MPH[1,2]; Nabihah Tayob, PhD[1]; Chau Dang, MD[3]; Denise A. Yardley, MD[4]; Steven J. Isakoff, MD, PhD[5]; Vicente Valero, MD[6]; Meredith Faggen, MD[1]; Therese Mulvey, MD[5]; Ron Bose, MD, PhD[7]; Jiani Hu, MSc[1]; Douglas Weckstein, MD[1]; Antonio C. Wolff, MD[8]; Katherine Reeder-Hayes, MD, MBA, MSc[9]; Hope S. Rugo, MD[10]; Bhuvaneswari Ramaswamy, MD[11]; Dan Zuckerman, MD[12]; Lowell Hart, MD[13]; Vijayakrishna K. Gadi, MD, PhD[14]; Michael Constantine, MD[1]; Kit Cheng, MD[15]; Frederick Briccetti, MD[1]; Bryan Schneider, MD[16]; Audrey Merrill Garrett, MD[17]; Kelly Marcom, MD[18]; Kathy Albain, MD[19]; Patricia DeFusco, MD[20]; Nadine Tung, MD[2,21]; Blair Ardman, MD[22]; Rita Nanda, MD[23]; Rachel C. Jankowitz, MD[24]; Mothaffar Rimawi, MD[25]; Vandana Abramson, MD[26]; Paula R. Pohlmann, MD, PhD, MSc[27]; Catherine Van Poznak, MD[28]; Andres Forero-Torres, MD[29]; Minetta Liu, MD[30]; Kathryn Ruddy, MD[30]; Yue Zheng, MSc[1]; Shoshana M. Rosenberg, ScD, MPH[1,2]; Richard D. Gelber, PhD[1,2]; Lorenzo Trippa, PhD[1,2]; William Barry, PhD[1]; Michelle DeMeo, BS[1]; Harold Burstein, MD, PhD[1,2]; Ann Partridge, MD, MPH[1,2]; Eric P. Winer, MD[1,2]; and Ian Krop, MD, PhD[1,2]

# 3 year iDFS in ATEMPT trial



# Summary of the Early Her2+ BC Field

## NODE NEGATIVE

Adjuvant :

TH-> H

TCH->H

? TDM-1

Larger tumor [>2cm]:

Neoadjuvant TCHP -> HP

## NODE POSITIVE

Neoadjuvant: TCHP or anthracycline based regimen

Adjuvant:

pCR yes: HP

pCR no: TDM-1

Option to add neratinib if ER+ and high risk

Pregnancy: AC x 4 during 2 or 3rd trimester (stop by 36-37 weeks) then TH or THP postpartum

# Metastatic Her2+ breast cancer, a rapidly moving field

## Approved treatments for HER2-positive metastatic breast cancer

1L **Trastuzumab + pertuzumab + taxane, CLEOPATRA:** mPFS = 18.7 months[1]

2L+ **T-DM1, EMILIA:** mPFS = 9.6 months[3]

- 1L standard of care was established in the CLEOPATRA trial[1,2]
- EMILIA trial established T-DM1 as 2L+ standard of care[3]

## T-DXd in HER2-positive metastatic breast cancer

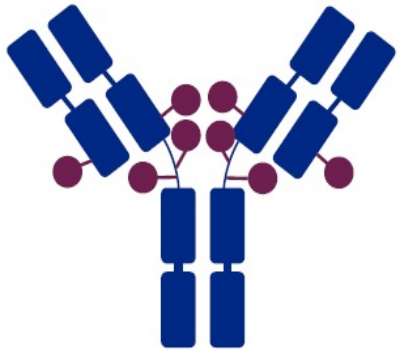
- Based on the strength of DESTINY-Breast03 efficacy and safety data, T-DXd is considered the **preferred 2L treatment** and T-DM1 is an alternative option[4,5]
  - At the previously reported DESTINY-Breast03 PFS interim analysis (data cutoff, May 21, 2021), in the T-DXd arm, the risk of disease progression or death was reduced by 72%[6]
    - mPFS by BICR was NR with T-DXd vs 6.8 months with T-DM1; HR, 0.28 (95% CI, 0.22-0.37); *P* < 0.001

1L, first-line; 2L, second-line; 2L+, second-line and beyond; BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mPFS, median progression-free survival; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Swain SM et al. *N Engl J Med.* 2015;372(8):724-734. 2. Perez J et al. *Expert Opin Biol Ther.* 2021;21:811-24. 3. Verma S et al. *N Engl J Med.* 2012;367:1783-91. 4. Gennari A et al. *Ann Oncol.* 2021;32:1475-1495. 5. FDA Press Release. FDA grants regular approval to fam-trastuzumab deruxtecan-nxki for breast cancer. May 4, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-fam-trastuzumab-deruxtecan-nxki-breast-cancer. 6. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

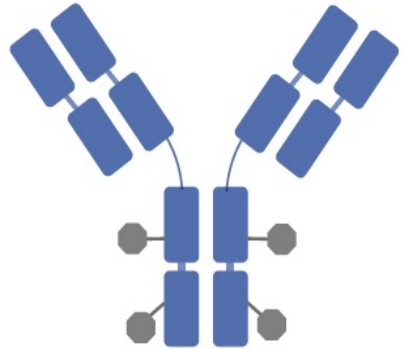
# ADC Characteristic Differences Between T-DXd and T-DM1

**Trastuzumab deruxtecan (T-DXd)[1]**



| T-DXd[1-4,a] | ADC Attributes | T-DM1[3-5] |
|---|---|---|
| Topoisomerase I inhibitor | **Payload MoA** | Anti-microtubule |
| ~8:1 | **Drug-to-antibody ratio** | ~3.5:1 |
| Yes | **Tumor-selective cleavable linker?** | No |
| Yes | **Evidence of bystander anti-tumor effect?** | No |

**Trastuzumab emtansine (T-DM1)[5]**



ADC, antibody-drug conjugate; MoA, mechanism of action.
[a]The clinical relevance of these features is under investigation.



1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther*. 2018;181:126-42. 4. Ogitani Y et al. *Cancer Sci*. 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

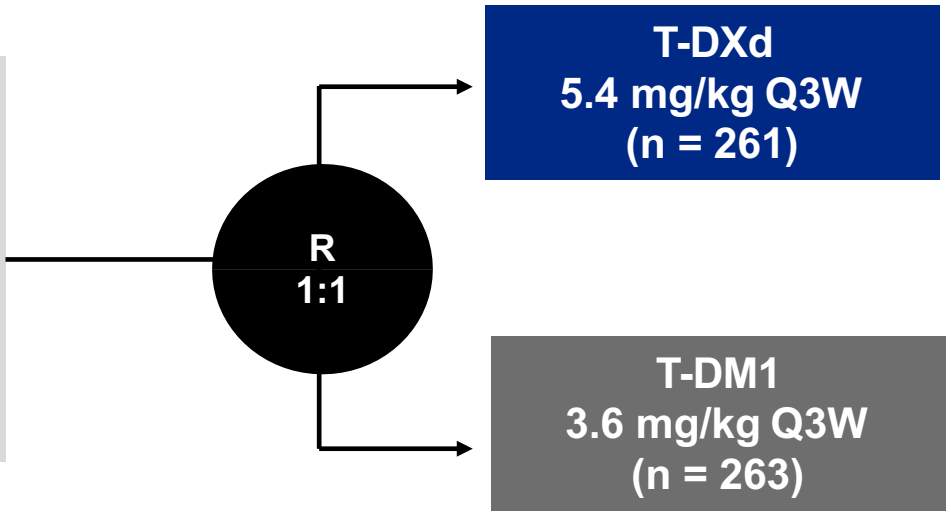
N Engl J Med 2022;386:1143-54.
DOI: 10.1056/NEJMoa2115022

# Updated OS Analysis of DESTINY-Breast03

## Randomized, open-label, multicenter study (NCT03529110)

### Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy[b]




### Primary endpoint

- PFS (BICR)

### Key secondary endpoint

- OS[c]

### Secondary endpoints

- ORR (BICR and investigator)
- DoR (BICR)
- Safety

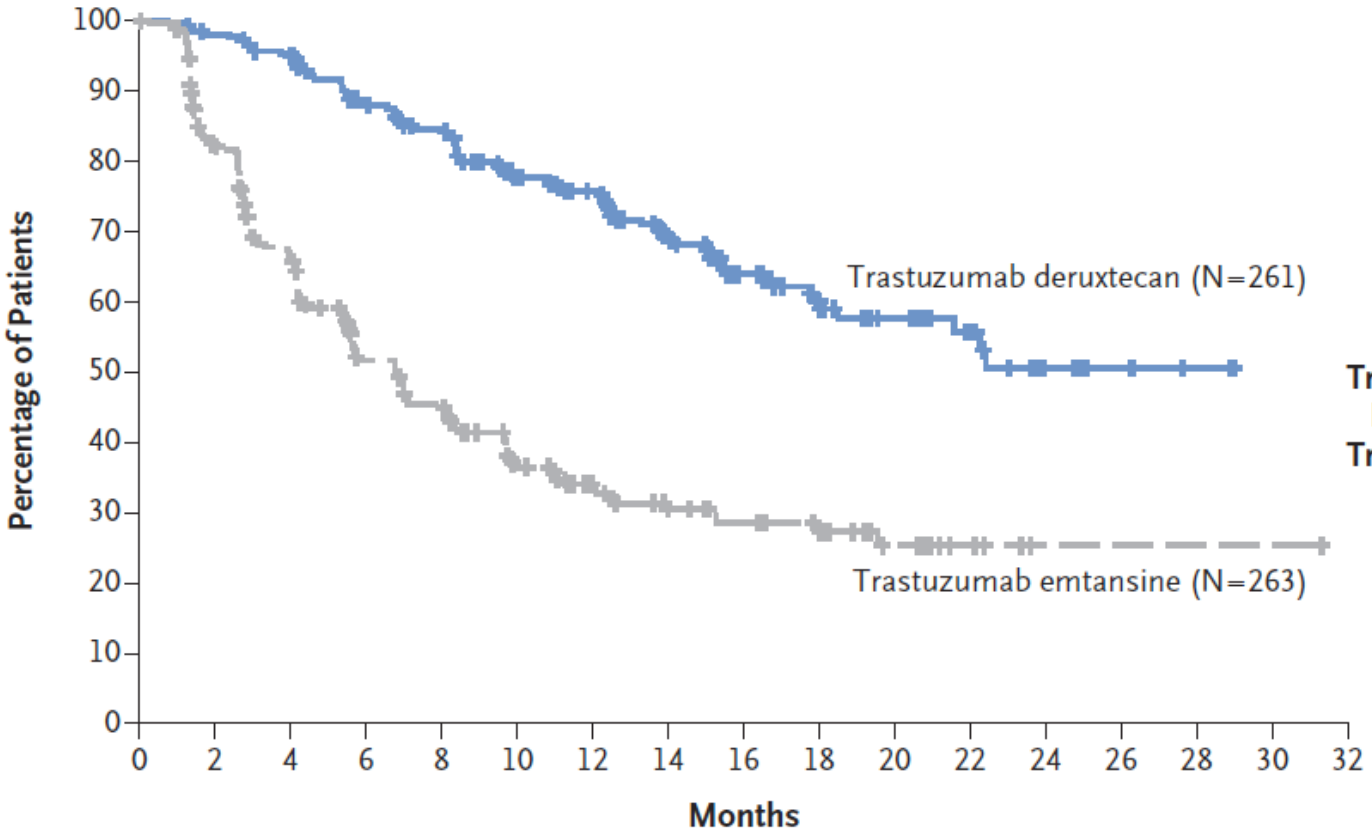
### Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

**The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013**

BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or within 6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]80% powered at 2-sided significance level of 5%. [d]Information fraction of 61%, with a *P* value boundary to reach statistical significance of 0.008. The *P* value was recalculated based on the actual OS events at the data cutoff.

# DESTINY-Breast03: Progression Free Survival




| | Median Progression-free Survival (95% CI) | 12-Mo Progression-free Survival (95% CI) |
|---|---|---|
| | *mo* | % |
| **Trastuzumab Deruxtecan** | NR (18.5–NE) | 75.8 (69.8–80.7) |
| **Trastuzumab Emtansine** | 6.8 (5.6–8.2) | 34.1 (27.7–40.5) |

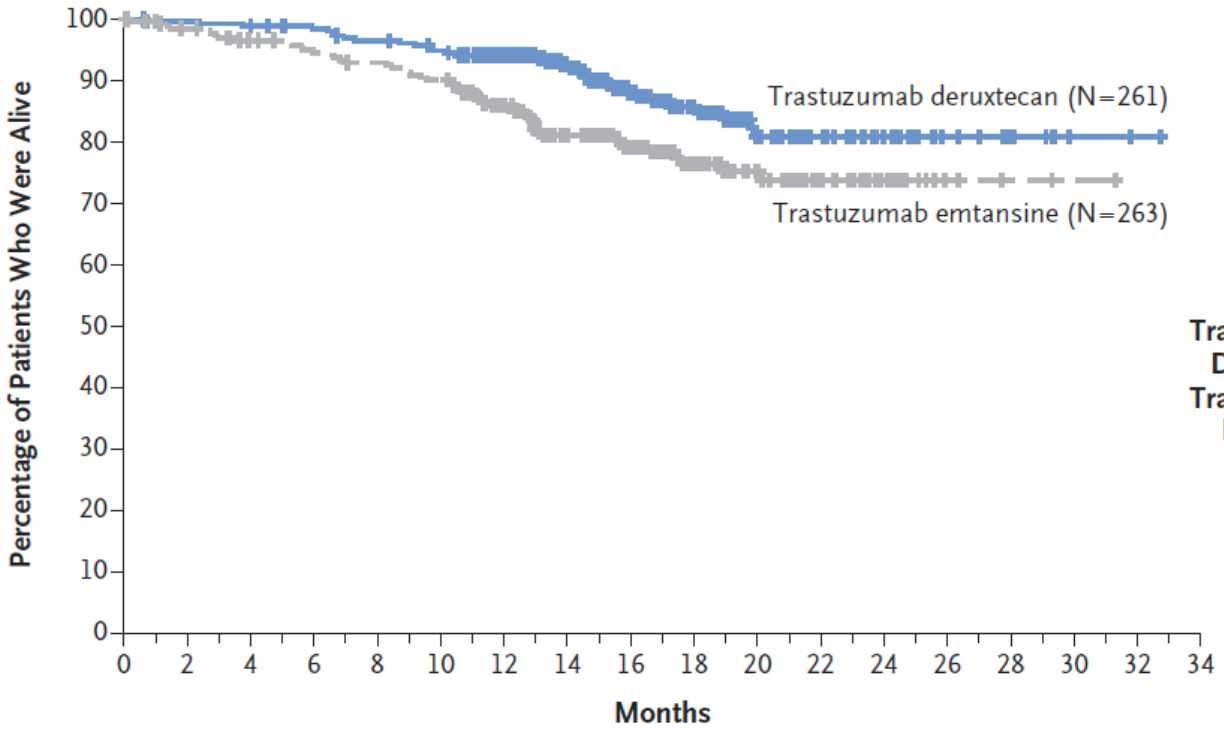
Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

**No. at Risk**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 261 | 250 | 240 | 214 | 200 | 168 | 150 | 112 | 79 | 53 | 36 | 25 | 10 | 5 | 2 | |
| Trastuzumab emtansine | 263 | 200 | 155 | 108 | 93 | 65 | 51 | 37 | 29 | 21 | 12 | 6 | 1 | 1 | 1 | 0 |

NEJM 2022; 386:1143-54

# DESTINY-Breast03: Overall Survival




| | Median Overall Survival (95% CI) | 12-Mo Overall Survival (95% CI) |
|---|---|---|
| | *mo* | % |
| **Trastuzumab Deruxtecan** | NE (NE–NE) | 94.1 (90.3–96.4) |
| **Trastuzumab Emtansine** | NE (NE–NE) | 85.9 (80.9–89.7) |

Hazard ratio for death, 0.55
(95% CI, 0.36–0.86)
P=0.007

**No. at Risk**

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 261 | 256 | 254 | 249 | 243 | 237 | 218 | 180 | 133 | 86 | 56 | 42 | 24 | 11 | 7 | 6 | 2 | 2 | 1 | 0 |
| Trastuzumab emtansine | 263 | 253 | 243 | 236 | 231 | 224 | 188 | 151 | 120 | 75 | 52 | 32 | 18 | 5 | 3 | 3 | 1 | 1 | 0 | |

NEJM 2022; 386:1143-54

# DESTINY-Breast03: Drug-Related Treatment-Emergent Adverse Events in ≥20% of Patients

| System Organ Class<br>Preferred term, n (%) | T-DXd (n = 257) | | T-DM1 (n = 261) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Blood and lymphatic system disorders** | | | | |
| Neutropenia[a] | 110 (42.8) | 49 (19.1) | 29 (11.1) | 8 (3.1) |
| Anemia[b] | 78 (30.4) | 15 (5.8) | 37 (14.2) | 11 (4.2) |
| Leukopenia[c] | 77 (30.0) | 17 (6.6) | 20 (7.7) | 1 (0.4) |
| Thrombocytopenia[d] | 64 (24.9) | 18 (7.0) | 135 (51.7) | 65 (24.9) |
| **Gastrointestinal disorders** | | | | |
| Nausea | 187 (72.8) | 17 (6.6) | 72 (27.6) | 1 (0.4) |
| Vomiting | 113 (44.0) | 4 (1.6) | 15 (5.7) | 1 (0.4) |
| Diarrhea | 61 (23.7) | 1 (0.4) | 10 (3.8) | 1 (0.4) |
| Constipation | 58 (22.6) | 0 | 25 (9.6) | 0 |
| **General disorders** | | | | |
| Fatigue[e] | 115 (44.7) | 13 (5.1) | 77 (29.5) | 2 (0.8) |
| **Investigations** | | | | |
| AST increased | 60 (23.3) | 2 (0.8) | 97 (37.2) | 13 (5.0) |
| ALT increased | 50 (19.5) | 4 (1.6) | 71 (27.2) | 12 (4.6) |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 67 (26.1) | 3 (1.2) | 33 (12.6) | 0 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia[f] | 93 (36.2) | 1 (0.4) | 6 (2.3) | 0 |

Cortés J et al. ESMO 2021;Abstract LBA1.

# DESTINY-Breast03: Adverse Events of Special Interest

| Adjudicated as drug-related ILD/pneumonitis[a], n (%) | | | | | | |
|---|---|---|---|---|---|---|
| n (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any Grade |
| T-DXd (n = 257) | 7 (2.7) | 18 (7.0) | 2 (0.8) | 0 | 0 | 27 (10.5) |
| T-DM1 (n = 261) | 4 (1.5) | 1 (0.4) | 0 | 0 | 0 | 5 (1.9) |

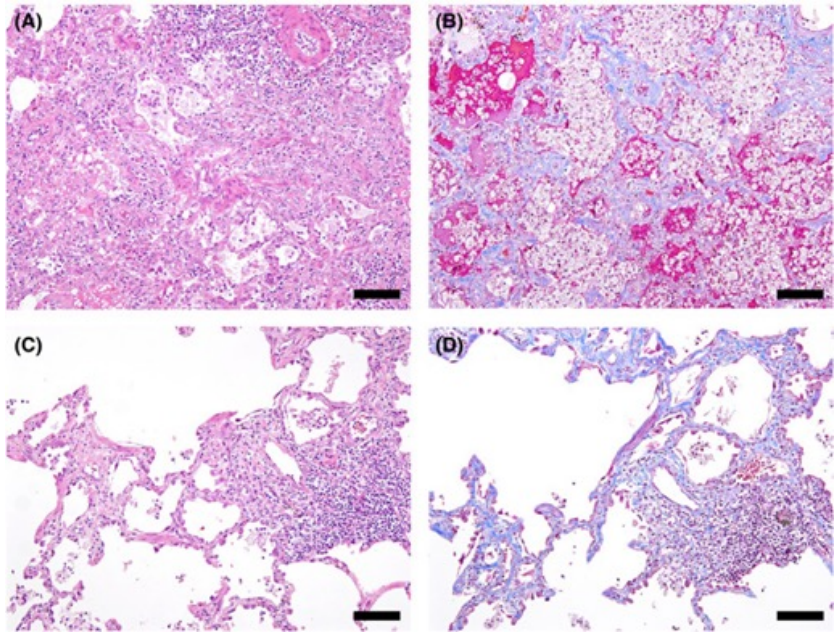
- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

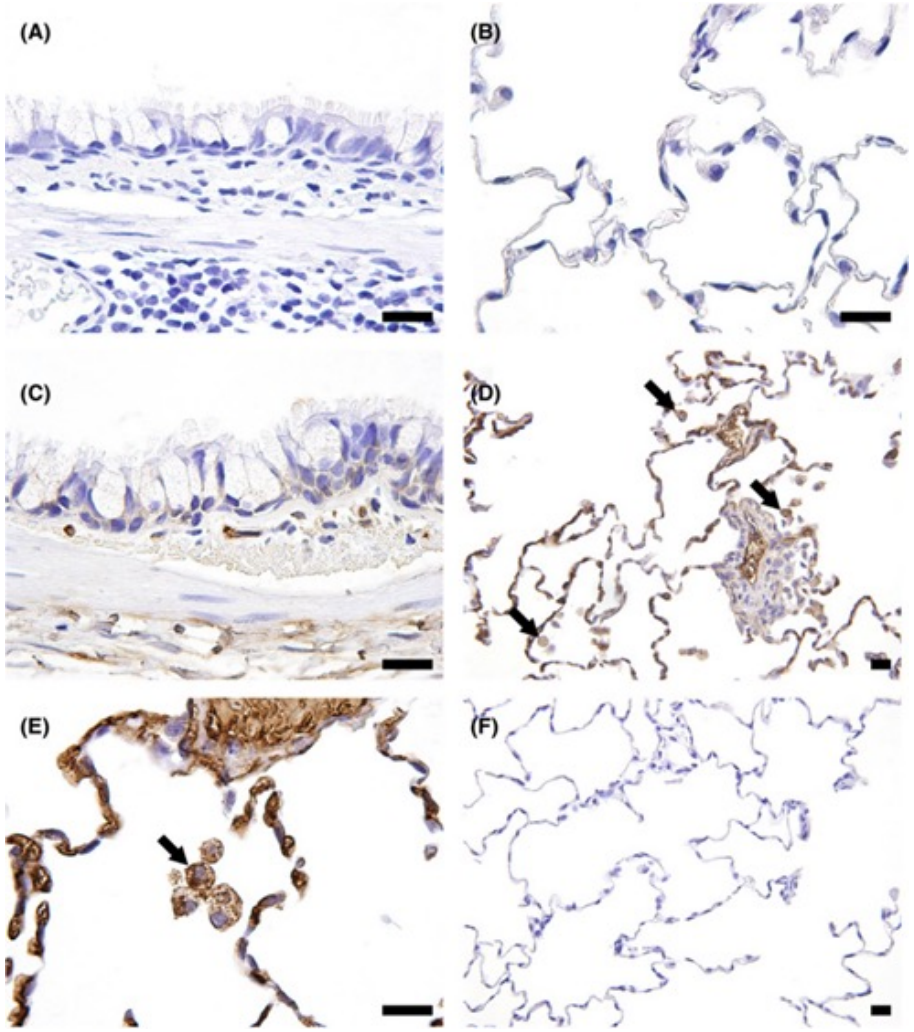
| LVEF decrease, n (%) | | | | | | |
|---|---|---|---|---|---|---|
| n (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any Grade |
| T-DXd (n = 257) | 1 (0.4)[b] | 6 (2.3)[c] | 0 | 0 | 0 | 7 (2.7) |
| T-DM1 (n = 261) | 0 | 1 (0.4)[c] | 0 | 0 | 0 | 1 (0.4) |

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

Cortés J et al. ESMO 2021;Abstract LBA1, NEJM 2022; 386:1143-54

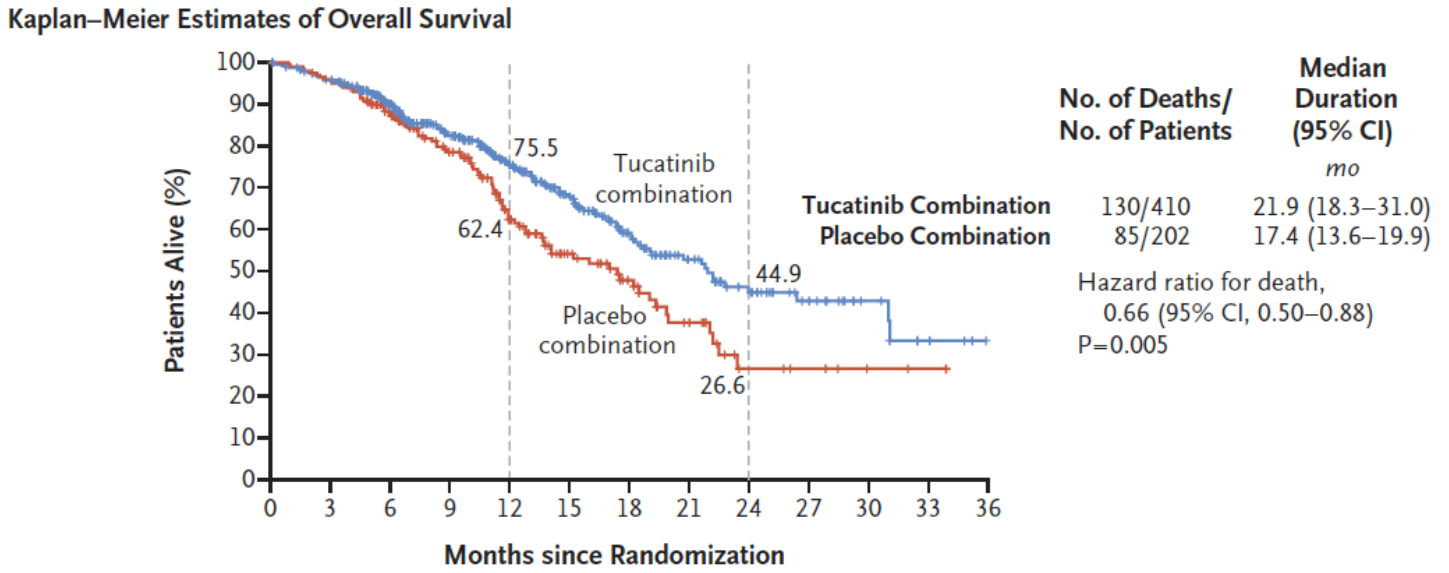
**T-DXd induces dose dependent and dose-frequency dependent interstitial pneumonitis**



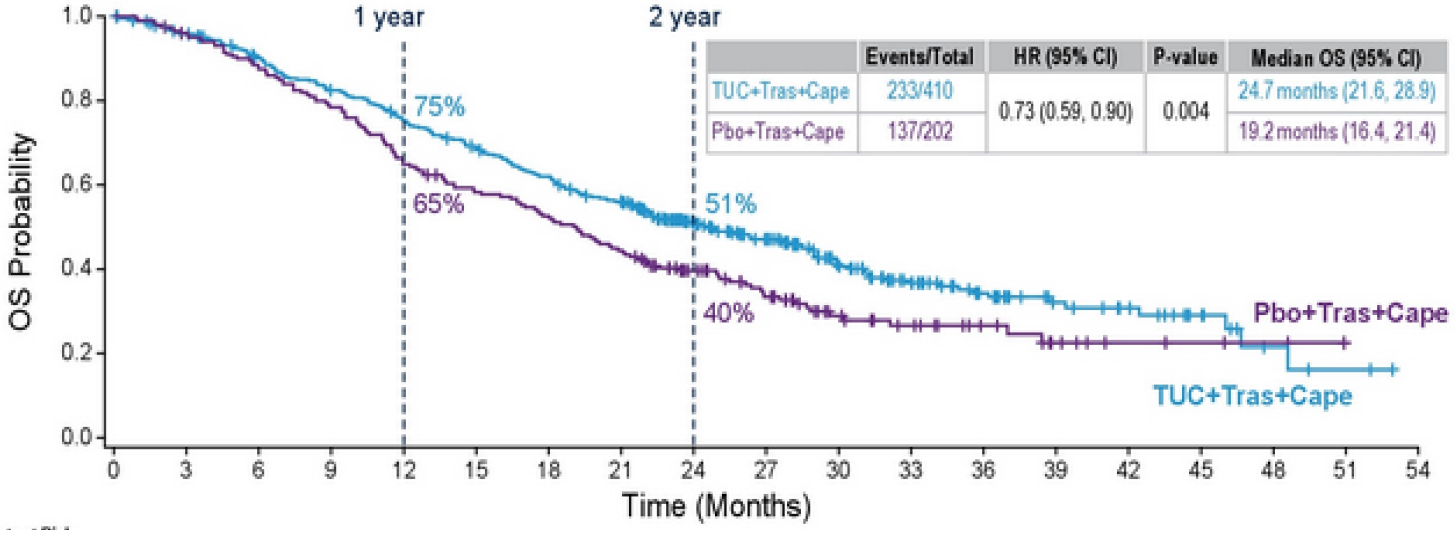




Kumagi, et al. *Cancer Sci.* 2020 doi: 10.1111/cas.14686

# HER2CLIMB: Overall Survival

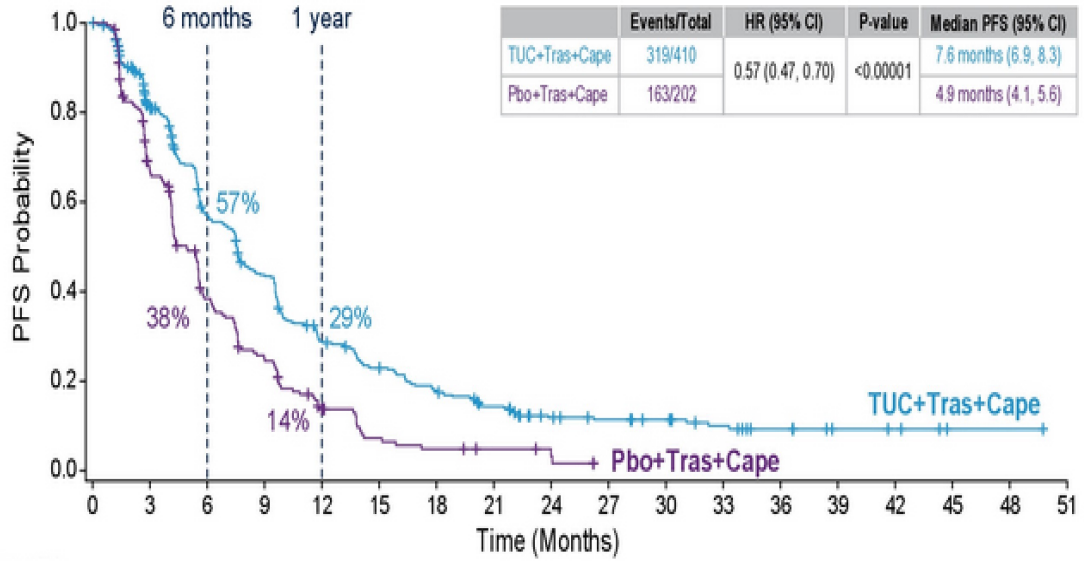



NEJM 2020;382:597-609




Curigliano G et al. ASCO 2021;Abstract 1043

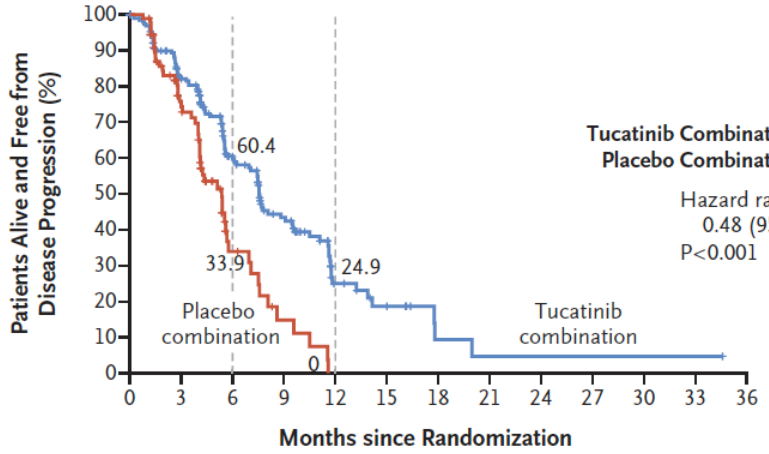
# HER2CLIMB: Progression-Free Survival (PFS)




| | Events/Total | HR (95% CI) | P-value | Median PFS (95% CI) |
|---|---|---|---|---|
| TUC+Tras+Cape | 319/410 | 0.57 (0.47, 0.70) | <0.00001 | 7.6 months (6.9, 8.3) |
| Pbo+Tras+Cape | 163/202 | | | 4.9 months (4.1, 5.6) |

Curigliano G et al. ASCO 2021;Abstract 1043

**Kaplan–Meier Estimates of Progression-free Survival among Patients with Brain Metastases**




| | No. of Events/ No. of Patients | Median Duration (95% CI) |
|---|---|---|
| | | *mo* |
| **Tucatinib Combination** | 106/198 | 7.6 (6.2–9.5) |
| **Placebo Combination** | 51/93 | 5.4 (4.1–5.7) |

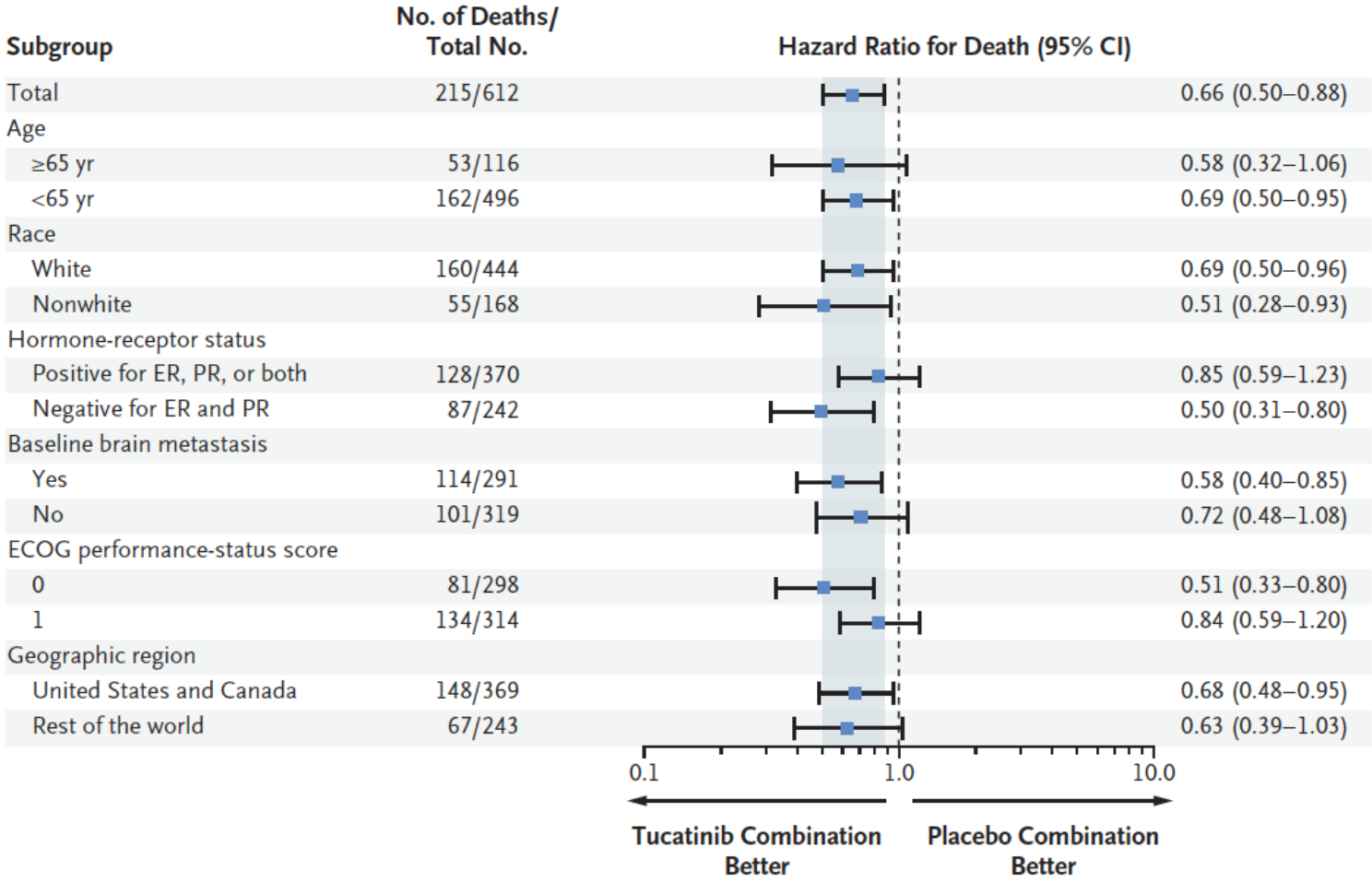
Hazard ratio for disease progression or death, 0.48 (95% CI, 0.34–0.69)
P<0.001

**No. at Risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tucatinib combination | 198 | 144 | 78 | 45 | 14 | 8 | 2 | 1 | 1 | 1 | 1 | 1 | 0 |
| Placebo combination | 93 | 49 | 12 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

NEJM 2020;382:597-609

# HER2CLIMB: Subgroup analysis of overall survival




NEJM 2020;382:597-609

# HER2CLIMB: Safety Outcomes

| Select adverse events | Tucatinib (n = 404) | | Placebo (n = 197) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any | 99.3% | 55.2% | 97.0% | 48.7% |
| Diarrhea | 80.9% | 12.9% | 53.3% | 8.6% |
| PPE syndrome | 63.4% | 13.1% | 52.8% | 9.1% |
| Nausea | 58.4% | 3.7% | 43.7% | 3.0% |
| Fatigue | 45.0% | 4.7% | 43.1% | 4.1% |
| Vomiting | 35.9% | 3.0% | 25.4% | 3.6% |
| Stomatitis | 25.5% | 2.5% | 14.2% | 0.5% |
| Increased AST | 21.3% | 4.5% | 11.2% | 0.5% |
| Increased ALT | 20.0% | 5.4% | 6.6% | 0.5% |

Murthy RK et al. SABCS 2019;Abstract GS1-01; Murthy RK et al. *N Engl J Med* 2020;382(7):597-609.

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# An Age-Specific Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Positive Metastatic Breast Cancer (mBC) From DESTINY-Breast01, -02, and -03


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June 5, 2023


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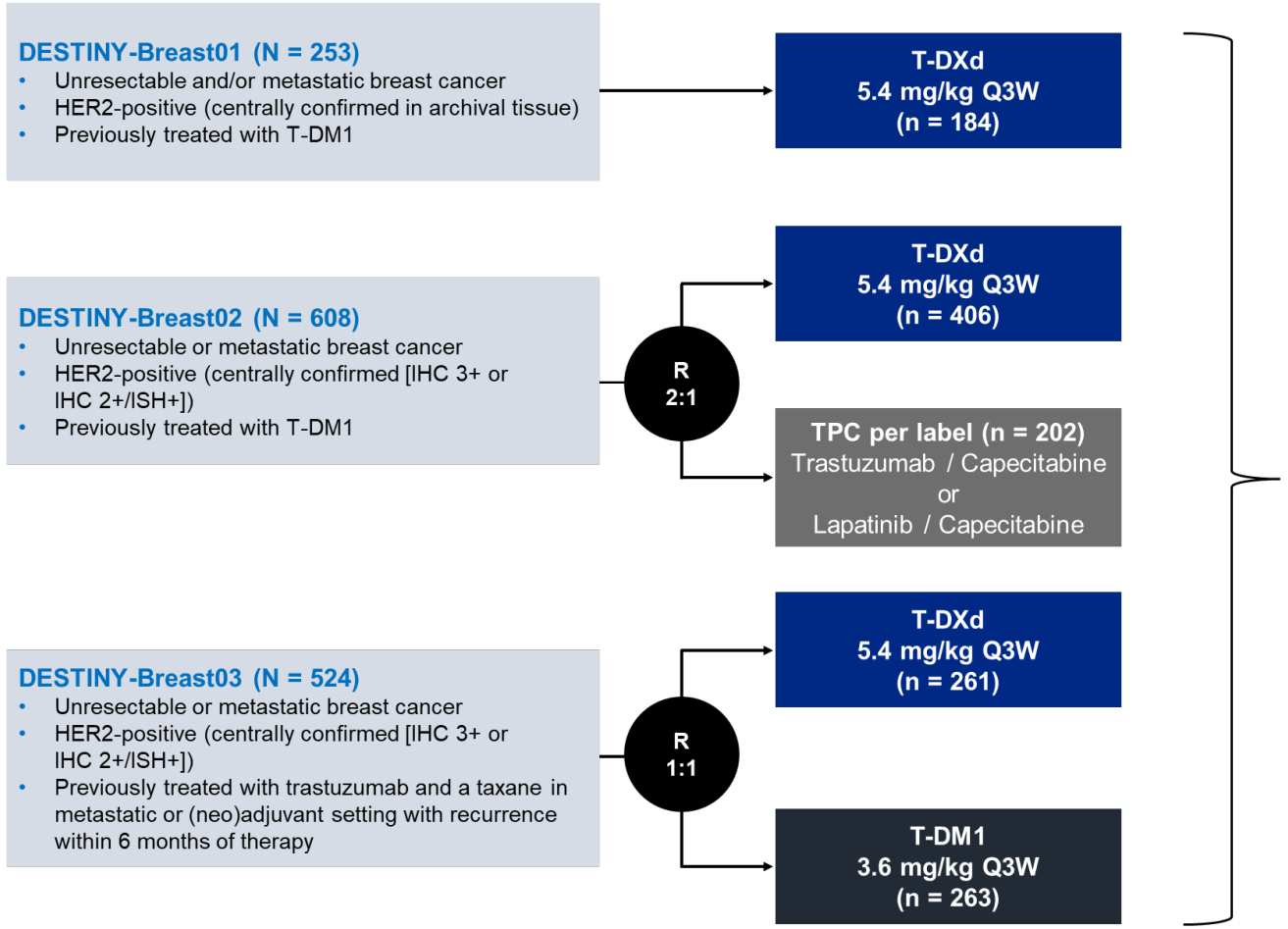
# Study Design[1-3]




[a]Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022.
DB, DESTINY-Breast; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi et al. *N Engl J Med.* 2020; 382:610-621. 2. André et al. *The Lancet.* 2023. https://doi.org/10.1016/S0140-6736(23)00725-0. 3. Cortés et al. *N Engl J Med*. 2022; 386(12):1143-1154.

# Medical History and Comorbidities[a]

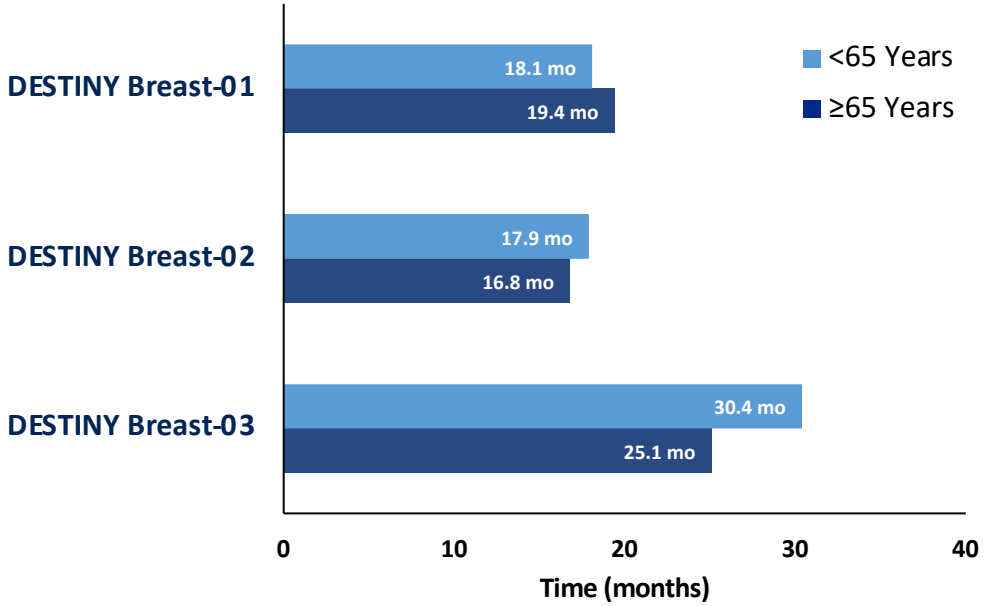
| | T-DXd Pool | | | TPC (DB-02) | | | T-DM1 (DB-03) | | |
|---|---|---|---|---|---|---|---|---|---|
| | <65 (n = 673) | ≥65 (n = 178) | ≥75 (n = 34) | <65 (n = 164) | ≥65 (n = 38) | ≥75 (n = 8) | <65 (n = 206) | ≥65 (n = 57) | ≥75 (n = 8) |
| **Disorders** | | | | | | | | | |
| Blood and lymphatic system disorders (SOC) | 73 (10.8) | 26 (14.6) | 5 (14.7) | 12 (7.3) | 6 (15.8) | 1 (12.5) | 14 (6.8) | 6 (10.5) | 1 (12.5) |
| Anemia | 41 (6.1) | 18 (10.1) | 3 (8.8) | 9 (5.5) | 4 (10.5) | 1 (12.5) | 6 (2.9) | 2 (3.5) | 1 (12.5) |
| Cardiac disorders (SOC) | 57 (8.5) | 21 (11.8) | 4 (11.8) | 7 (4.3) | 3 (7.9) | 0 | 8 (3.9) | 5 (8.8) | 0 |
| Diabetes mellitus | 29 (4.3) | 17 (9.6) | 4 (11.8) | 7 (4.3) | 3 (7.9) | 2 (25.0) | 6 (2.9) | 8 (14.0) | 1 (12.5) |
| Renal and urinary disorders (SOC) | 23 (3.4) | 16 (9.0) | 6 (17.6) | 3 (1.8) | 4 (10.5) | 1 (12.5) | 3 (1.5) | 11 (19.3) | 0 |
| Vascular disorders (SOC) | 174 (25.9) | 109 (61.2) | 28 (82.4) | 43 (26.2) | 24 (63.2) | 5 (62.5) | 52 (25.2) | 31 (54.4) | 6 (75.0) |
| Hypertension | 123 (18.3) | 93 (52.2) | 26 (76.5) | 30 (18.3) | 24 (63.2) | 5 (62.5) | 35 (17.0) | 28 (49.1) | 5 (62.5) |
| **Baseline renal function[b]** | | | | | | | | | |
| Normal function | 432 (64.2) | 34 (19.1) | 0 | 104 (63.4) | 8 (21.1) | 0 | 124 (60.2) | 8 (14.0) | 0 |
| Mild renal impairment | 205 (30.5) | 91 (51.1) | 14 (41.2) | 54 (32.9) | 22 (57.9) | 3 (37.5) | 77 (37.4) | 28 (49.1) | 3 (37.5) |
| Moderate renal impairment | 35 (5.2) | 53 (29.8) | 20 (58.8) | 6 (3.7) | 8 (21.1) | 5 (62.5) | 4 (1.9) | 21 (36.8) | 5 (62.5) |
| **Baseline hepatic function[c]** | | | | | | | | | |
| Normal function | 406 (60.3) | 101 (56.7) | 20 (58.8) | 78 (47.6) | 21 (55.3) | 2 (25.0) | 162 (78.6) | 50 (87.7) | 8 (100.0) |
| Mild hepatic impairment | 260 (38.6) | 75 (42.1) | 14 (41.2) | 86 (52.4) | 17 (44.7) | 6 (75.0) | 43 (20.9) | 7 (12.3) | 0 |
| Moderate hepatic impairment | 2 (0.3) | 2 (1.1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

- Comorbidities were generally low in the overall population due to selection criteria

[a]Medical history and comorbidities are on the pooled analysis of patients treated with T-DXd from all 3 trials (DB-01, DB-02, and DB-03). [b]Renal impairment status is determined by baseline creatine clearance as calculated using the Cockcroft-Gault equation. [c]Adequate hepatic function is defined as total bilirubin ≤ULN and AST≤ULN, mild hepatic dysfunction is defined as total bilirubin ≤ ULN and AST>ULN regardless of Gilbert Syndrome; moderate hepatic dysfunction is defined as total bilirubin >1.5 x ULN, ≤ 3.0 x ULN and any AST except for subjects with Gilbert syndrome.
AST, aspartate transaminase; DB, DESTINY-Breast; SOC, system organ class; T-DM1; trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; ULN, upper limit of normal.

# Descriptive Efficacy According to Age for T-DXd[a]

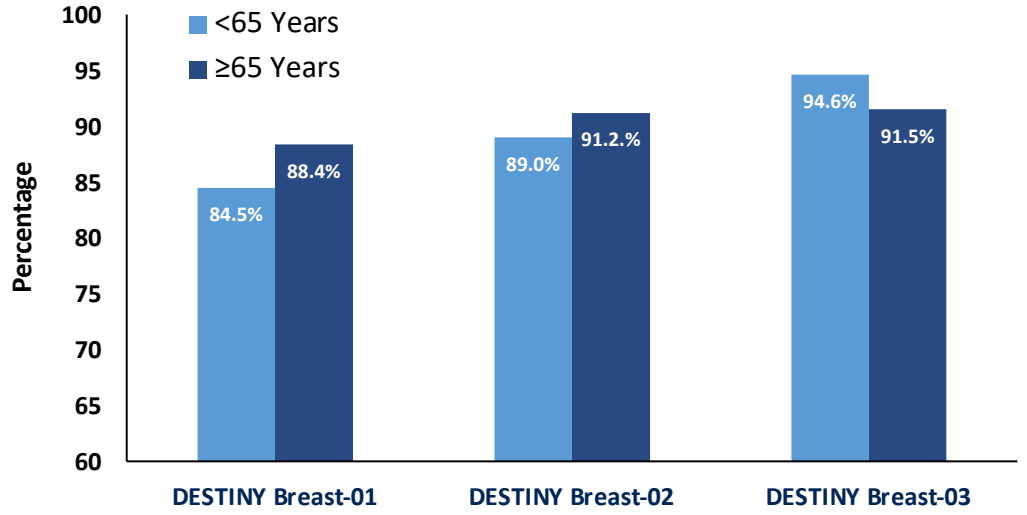
## Median Progression Free Survival




## Median Overall Survival

| | DESTINY-Breast01 | | DESTINY-Breast02 | | DESTINY-Breast03 | |
|---|---|---|---|---|---|---|
| | <65 (n = 140) | ≥65 (n = 44) | <65 (n = 321) | ≥65 (n = 85) | <65 (n = 212) | ≥65 (n = 49) |
| mOS, months (95% CI) | 28.1 (23.3-36.1) | 30.9 (21.9-NE) | NR (35.5-NE) | 30.2 (22.3-39.2) | NR (40.5-NE) | NR (26.3-NE) |

## 12-month Landmark Overall Survival




- Efficacy in patients aged <65 and ≥65 years treated with T-DXd was generally similar; however no formal comparison was made

[a]Efficacy data was not pooled due to bias induced by the heterogeneity of the study population. Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022.
mOS, median overall survival; NE, not estimable; NR, not reached; T-DXd, trastuzumab deruxtecan.

# Overall Safety Summary[a]

| | T-DXd Pool | | | TPC (DB-02) | | | T-DM1 (DB-03) | | |
|---|---|---|---|---|---|---|---|---|---|
| | <65 (n = 668) | ≥65 (n = 177) | ≥75 (n = 33) | <65 (n = 157) | ≥65 (n = 38) | ≥75 (n = 8) | <65 (n = 204) | ≥65 (n = 57) | ≥75 (n = 8) |
| **Median treatment duration, mo (range)** | **13.1 (0.7-44.0)** | **12.4 (0.7-45.1)** | **9.0 (0.7-35.6)** | **N/A[b]** | **N/A[b]** | **N/A[b]** | **6.9 (0.7-38.9)** | **8.2 (0.7-38.9)** | **7.7 (2.0-29.4)** |
| **TEAE, n (%)** | **665 (99.6)** | **177 (100.0)** | **33 (100.0)** | **148 (94.3)** | **37 (97.4)** | **8 (100.0)** | **194 (95.1)** | **55 (96.5)** | **8 (100.0)** |
| Drug-related | 653 (97.8) | 176 (99.4) | 33 (100.0) | 144 (91.7) | 36 (94.7) | 8 (100.0) | 178 (87.3) | 50 (87.7) | 8 (100.0) |
| **TEAEs grade ≥3, n (%)** | **358 (53.6)** | **116 (65.5)** | **17 (51.5)** | **68 (43.3)** | **18 (47.4)** | **6 (75.0)** | **100 (49.0)** | **35 (61.4)** | **4 (50.0)** |
| Drug-related | 291 (43.6) | 96 (54.2) | 13 (39.4) | 48 (30.6) | 12 (31.6) | 5 (62.5) | 82 (40.2) | 28 (49.1) | 3 (37.5) |
| **Serious TEAEs, n (%)** | **162 (24.3)** | **57 (32.2)** | **10 (30.3)** | **39 (24.8)** | **7 (18.4)** | **1 (12.5)** | **33 (16.2)** | **25 (43.9)** | **4 (50.0)** |
| Drug-related | 77 (11.5) | 29 (16.4) | 5 (15.2) | 13 (8.3) | 2 (5.3) | 1 (12.5) | 11 (5.4) | 9 (15.8) | 2 (25.0) |
| **TEAEs associated with drug discontinuation, n (%)** | **125 (18.7)** | **45 (25.4)** | **8 (24.2)** | **15 (9.6)** | **4 (10.5)** | **1 (12.5)** | **13 (6.4)** | **11 (19.3)** | **3 (37.5)** |
| Drug-related | 100 (15.0) | 42 (23.7) | 8 (24.2) | 8 (5.1) | 2 (5.3) | 1 (12.5) | 9 (4.4) | 8 (14.0) | 2 (25.0) |
| **TEAEs associated with dose reduction, n (%)** | **163 (24.4)** | **51 (28.8)** | **10 (30.3)** | **67 (42.7)** | **22 (57.9)** | **7 (87.5)** | **23 (11.3)** | **15 (26.3)** | **2 (25.0)** |
| Drug-related | 156 (23.4) | 47 (26.6) | 8 (24.2) | 67 (42.7) | 22 (57.9) | 7 (87.5) | 23 (11.3) | 15 (26.3) | 2 (25.0) |
| **TEAEs associated with dose interruption, n (%)** | **302 (45.2)** | **94 (53.1)** | **15 (45.5)** | **73 (46.5)** | **17 (44.7)** | **5 (62.5)** | **53 (26.0)** | **23 (40.4)** | **3 (37.5)** |
| Drug-related | 226 (33.8) | 74 (41.8) | 11 (33.3) | 61 (38.9) | 15 (39.5) | 5 (62.5) | 30 (14.7) | 15 (26.3) | 3 (37.5) |
| **TEAEs associated with death, n (%)** | **17 (2.5)** | **10 (5.6)** | **0** | **6 (3.8)** | **1 (2.6)** | **0** | **4 (2.0)** | **2 (3.5)** | **1 (12.5)** |
| Drug-related | 4 (0.6) | 3 (1.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[a]Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022. [b]Not reported for TPC as this was a combination regimen; median treatment duration, mo (range), for <65, ≥65, and ≥75 was 4.1 (0.1-43.0), 4.7 (1.4-22.7), and 13.3 (4.1-22.7) for trastuzumab; 4.5 (0.1-43.0), 4.9 (0.7-28.7), and 9.8 (2.6-22.7) for capecitabine; 4.6 (0.4-23.7), 5.2 (0.7-28.7), and 8.0 (2.6-11.5) for lapatinib.
mo, months; N/A, not applicable; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event; TPC, treatment of physician's choice.

# Most Common Drug-related TEAEs in ≥20% of Patients

| | T-DXd Pool | | | TPC (DB-02) | | | T-DM1 (DB-03) | | |
|---|---|---|---|---|---|---|---|---|---|
| | <65 (n = 668) | ≥65 (n = 177) | ≥75 (n = 33) | <65 (n = 157) | ≥65 (n = 38) | ≥75 (n = 8) | <65 (n = 204) | ≥65 (n = 57) | ≥75 (n = 8) |
| **Any grade[a] drug-related TEAEs, n (%)** | **653 (97.8)** | **176 (99.4)** | **33 (100.0)** | **144 (91.7)** | **36 (94.7)** | **8 (100.0)** | **178 (87.3)** | **50 (87.7)** | **8 (100)** |
| Nausea | 497 (74.4) | 112 (63.3) | 21 (63.6) | 50 (31.8) | 10 (26.3) | 3 (37.5) | 59 (28.9) | 13 (22.8) | 3 (37.5) |
| Fatigue[b] | 344 (51.5) | 98 (55.4) | 21 (63.6) | 45 (28.7) | 16 (42.1) | 7 (87.5) | 56 (27.5) | 20 (35.1) | 2 (25.0) |
| Vomiting | 268 (40.1) | 59 (33.3) | 10 (30.3) | 21 (13.4) | 2 (5.3) | 2 (25.0) | 13 (6.4) | 2 (3.5) | 0 |
| Alopecia | 265 (39.7) | 63 (35.6) | 10 (30.3) | 6 (3.8) | 2 (5.3) | 2 (25.0) | 4 (2.0) | 3 (5.3) | 0 |
| Neutropenia[c] | 240 (35.9) | 72 (40.7) | 9 (27.3) | 16 (10.2) | 4 (10.5) | 3 (37.5) | 25 (12.3) | 10 (17.5) | 2 (25.0) |
| Decreased appetite | 181 (27.1) | 53 (29.9) | 9 (27.3) | 22 (14.0) | 9 (23.7) | 4 (50.0) | 21 (10.3) | 13 (22.8) | 2 (25.0) |
| Anemia[d] | 180 (26.9) | 61 (34.5) | 12 (36.4) | 17 (10.8) | 3 (7.9) | 1 (12.5) | 31 (15.2) | 13 (22.8) | 1 (12.5) |
| Leukopenia[e] | 156 (23.4) | 49 (27.7) | 6 (18.2) | 10 (6.4) | 1 (2.6) | 0 | 18 (8.8) | 4 (7.0) | 0 |
| Thrombocytopenia[f] | 149 (22.3) | 50 (28.2) | 3 (9.1) | 18 (11.5) | 3 (7.9) | 1 (12.5) | 110 (53.9) | 31 (54.4) | 3 (37.5) |
| Constipation | 148 (22.2) | 36 (20.3) | 4 (12.1) | 4 (2.5) | 1 (2.6) | 0 | 18 (8.8) | 7 (12.3) | 2 (25.0) |
| Transaminases increased[g] | 146 (21.9) | 34 (19.2) | 1 (3.0) | 16 (10.2) | 5 (13.2) | 1 (12.5) | 88 (43.1) | 24 (42.1) | 5 (62.5) |
| Diarrhea | 142 (21.3) | 48 (27.1) | 6 (18.2) | 81 (51.6) | 18 (47.4) | 5 (62.5) | 9 (4.4) | 4 (7.0) | 1 (12.5) |
| Stomatitis[h] | 82 (12.3) | 35 (19.8) | 2 (6.1) | 28 (17.8) | 10 (26.3) | 1 (12.5) | 7 (3.4) | 5 (8.8) | 0 |

- Any grade drug-related TEAEs were similar across age groups

[a]Any grade drug-related TEAEs present in ≥20% of patients sorted in descending order of frequency in the T-DXd pooled arm for the <65 years age group. [b]Fatigue includes preferred terms fatigue, asthenia, malaise, and lethargy. [c]Neutropenia includes preferred terms neutrophil count decreased and neutropenia. [d]Anemia includes preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [e]Leukopenia includes preferred terms white blood cell count decrease and leukopenia. [f]Thrombocytopenia includes preferred terms platelet count decreased and thrombocytopenia. [g]Transaminases increased includes preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased. [h]Stomatitis includes preferred terms stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosa blistering, and oral mucosa eruption.
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event; TPC, treatment of physician's choice.

# Adjudicated Drug-related ILD/Pneumonitis[a]

| | T-DXd Pool | | | TPC (DB-02) | | | T-DM1 (DB-03) | | |
|---|---|---|---|---|---|---|---|---|---|
| | <65 (n = 668) | ≥65 (n = 177) | ≥75 (n = 33) | <65 (n = 157) | ≥65 (n = 38) | ≥75 (n = 8) | <65 (n = 204) | ≥65 (n = 57) | ≥75 (n = 8) |
| **Any grade, n (%)** | **79 (11.8)** | **31 (17.5)** | **5 (15.2)** | **0** | **1 (2.6)** | **0** | **6 (2.9)** | **2 (3.5)** | **1 (12.5)** |
| 1 | 21 (3.1) | 7 (4.0) | 0 | 0 | 0 | 0 | 3 (1.5) | 1 (1.8) | 0 |
| 2 | 48 (7.2) | 20 (11.3) | 5 (15.2) | 0 | 0 | 0 | 2 (1.0) | 1 (1.8) | 1 (12.5) |
| 3 | 4 (0.6) | 3 (1.7) | 0 | 0 | 1 (2.6) | 0 | 1 (0.5) | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 6 (0.9) | 1 (0.6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

- Rates of adjudicated ILD/pneumonitis were generally higher in patients ≥65 years of age across all trials compared to patients <65 years of age
- Most drug-related ILD/pneumonitis cases were of low grade

[a]No ILD/pneumonitis cases were pending adjudication at the respective data cutoff dates (DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022).
ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

# Impact on practice

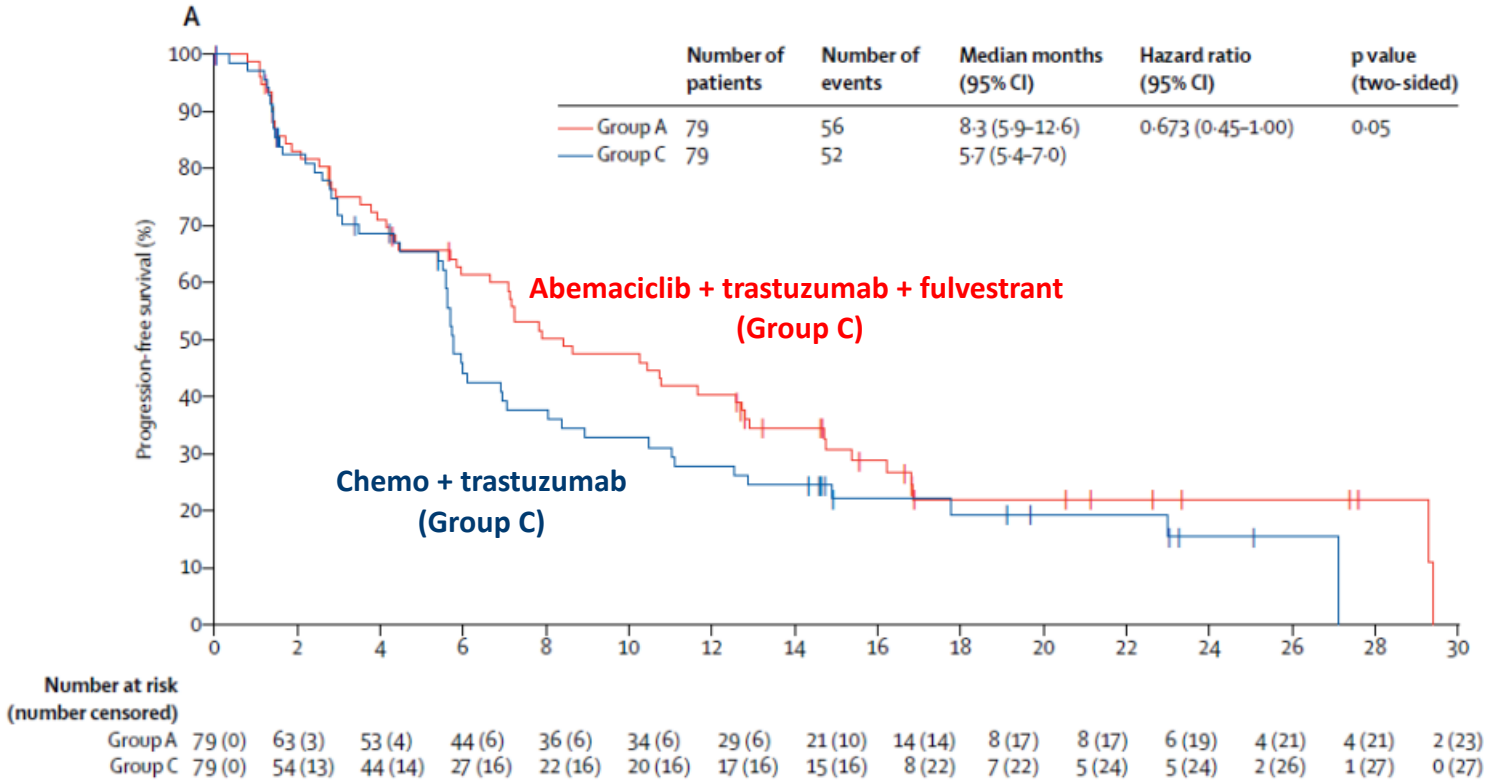
- T-DXd has similar efficacy in patients aged ≥ 65 years with somewhat higher risk of grade ≥ 3 events
- Overall, incidence of AEs is acceptable across all age groups
- **T-DXd is a reasonable treatment option in older adults, but as with all treatment, requires a careful risk-benefit discussion**

# Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial

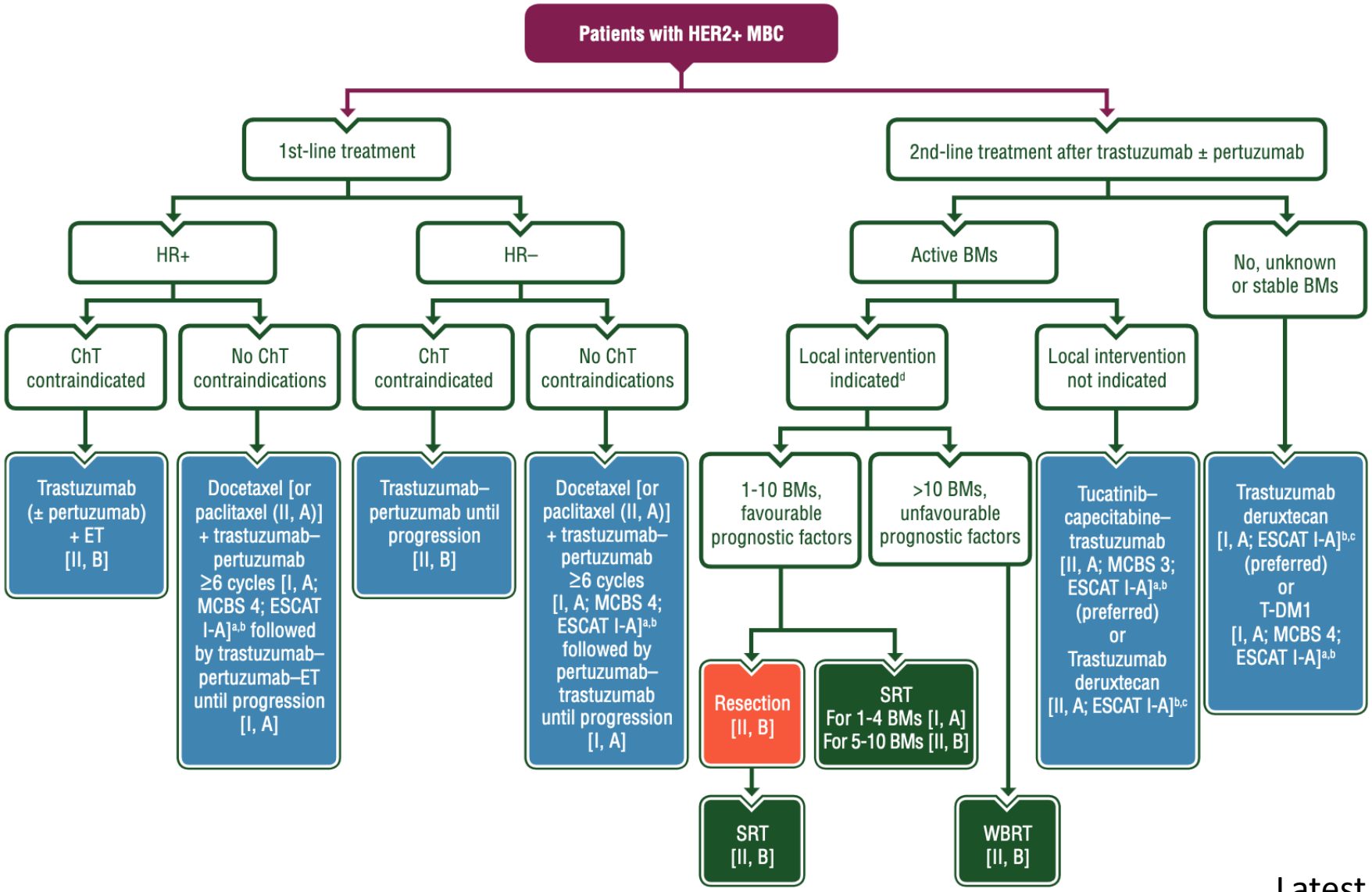
*Sara M Tolaney, Andrew M Wardley, Stefania Zambelli, John F Hilton, Tiffany A Troso-Sandoval, Francesco Ricci, Seock-Ah Im, Sung-Bae Kim, Stephen RD Johnston, Arlene Chan, Shom Goel*, Kristen Catron, Sonya C Chapman, Gregory L Price, Zhengyu Yang, M Corona Gainford, Fabrice André*

*Lancet Oncol* 2020; 21: 763–775

All patients had at least two prior lines of therapy in the metastatic setting



# Metastatic Her2+ breast cancer




Latest ESMO guidelines

Thank you

# KATHERINE: Central Nervous System Recurrence Events

| | T-DM1 (n = 743) | Trastuzumab (n = 743) |
|---|---|---|
| Patients with CNS recurrence | 45 (6.1%) | 40 (5.4%) |
| At first IDFS event[a] | 44 (5.9%) | 32 (4.3%) |
| After first IDFS event[b] | 1 (0.1%) | 8 (1.1%) |
| Patients with CNS as only event[c] | 36 (4.8%) | 21 (2.8%) |
| Median time to CNS recurrence | 17.5 months | 11.9 months |

T-DM1 = trastuzumab emtansine; CNS = central nervous system; IDFS = invasive disease-free survival
CNS recurrence [a]within or [b]after 61 days of first IDFS event or at [c]any time

Mamounas EP et al. *Ann Oncol* 2021;32(8):1005-14.