AT THE FOREFRONT
UChicago Medicine

# Improving and Optimizing Adjuvant Therapy for HER2-Positive Residual Breast Cancer

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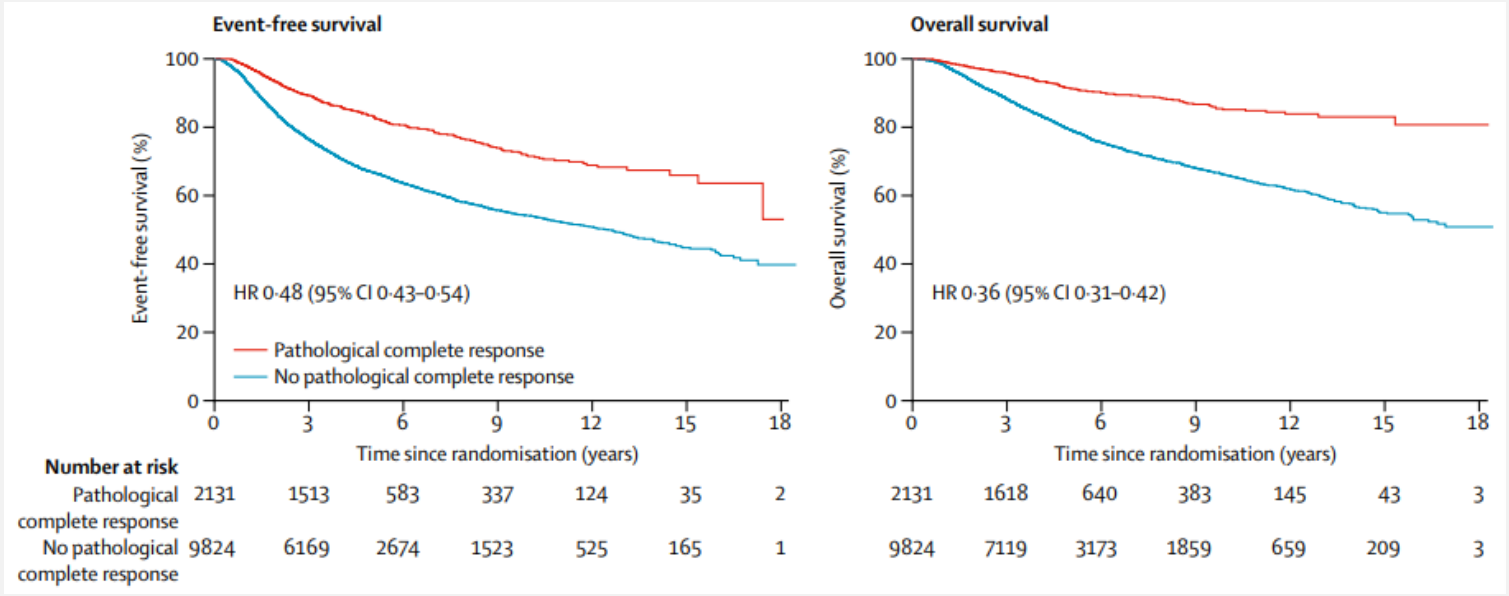
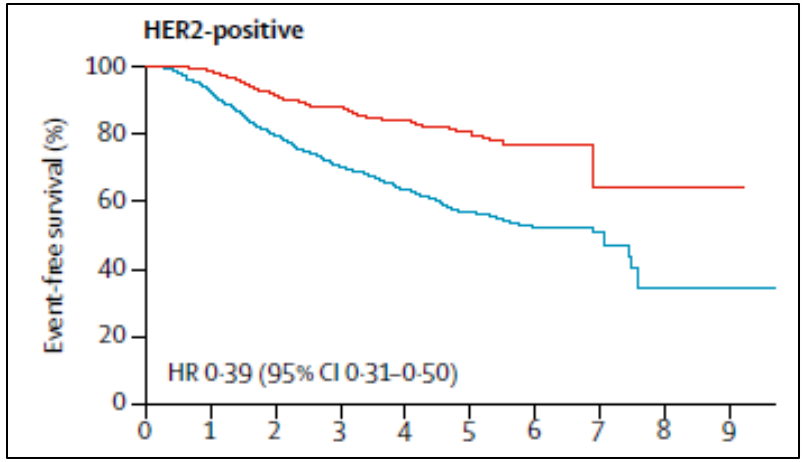
# Response to Neoadjuvant Therapy Predicts Outcomes for Early-Stage HER2-Positive Breast Cancer



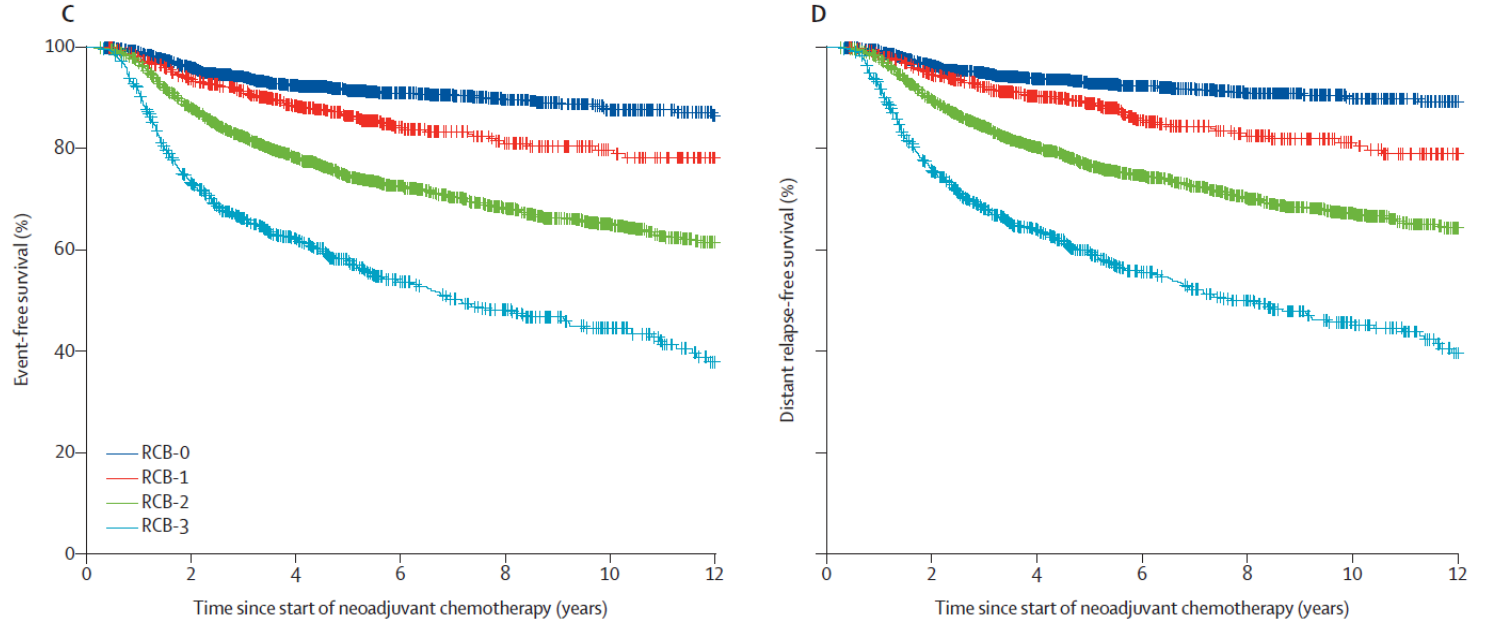




- Pathological response to NACT correlates with risk of recurrence and long-term prognosis
- Strongest prognostic value in TNBC and HER2-positive BC
- Hazard ratios for EFS for HER2+/HR-: 0.25;  HR for HER2+/HR+: 0.58

Cortazar et al, Lancet 2014

# Residual Cancer Burden Further Refines Outcomes

- In a pooled analysis of 5161 patients treated with NACT, RCB was strongly prognostic in each breast cancer subtype, with progressive worsening of prognosis with increasing RCB score
- The binary division between pCR and non-pCR disregards degree of residual disease
- RCB better captures prognosis depending on extent of residual disease

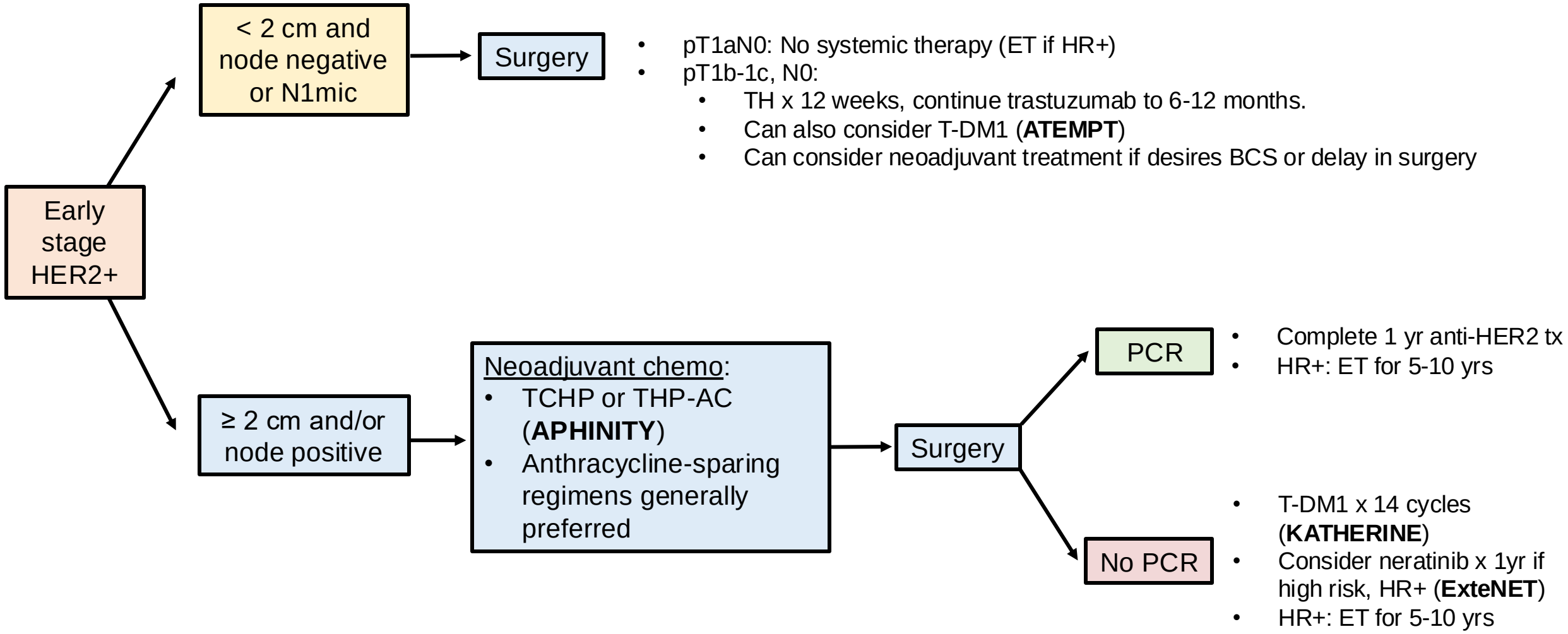



Number at risk (number censored)

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RCB-0 | 1676 (0) | 1434 (179) | 950 (618) | 527 (1029) | 353 (1195) | 227 (1314) | 135 (1404) | 1676 (0) | 1442 (179) | 960 (626) | 536 (1039) | 356 (1210) | 229 (1333) | 137 (1424) |
| RCB-1 | 662 (0) | 575 (46) | 396 (197) | 225 (353) | 161 (410) | 106 (463) | 67 (500) | 662 (0) | 580 (47) | 405 (199) | 227 (361) | 163 (418) | 108 (471) | 68 (508) |
| RCB-2 | 2017 (0) | 1638 (146) | 1084 (533) | 679 (872) | 485 (1031) | 308 (1188) | 168 (1314) | 2017 (0) | 1668 (148) | 1110 (547) | 695 (896) | 496 (1060) | 315 (1222) | 173 (1353) |
| RCB-3 | 806 (0) | 551 (45) | 344 (178) | 199 (282) | 146 (316) | 85 (368) | 38 (406) | 806 (0) | 567 (49) | 350 (188) | 204 (294) | 151 (328) | 87 (381) | 39 (421) |

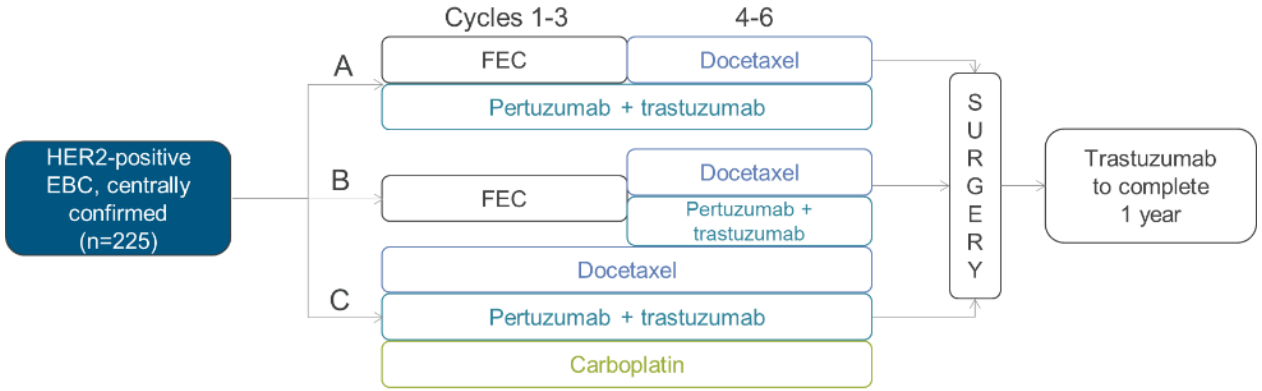
Yau et al, Lancet Oncology 2022

# Current Standard of Care for HER2+ EBC

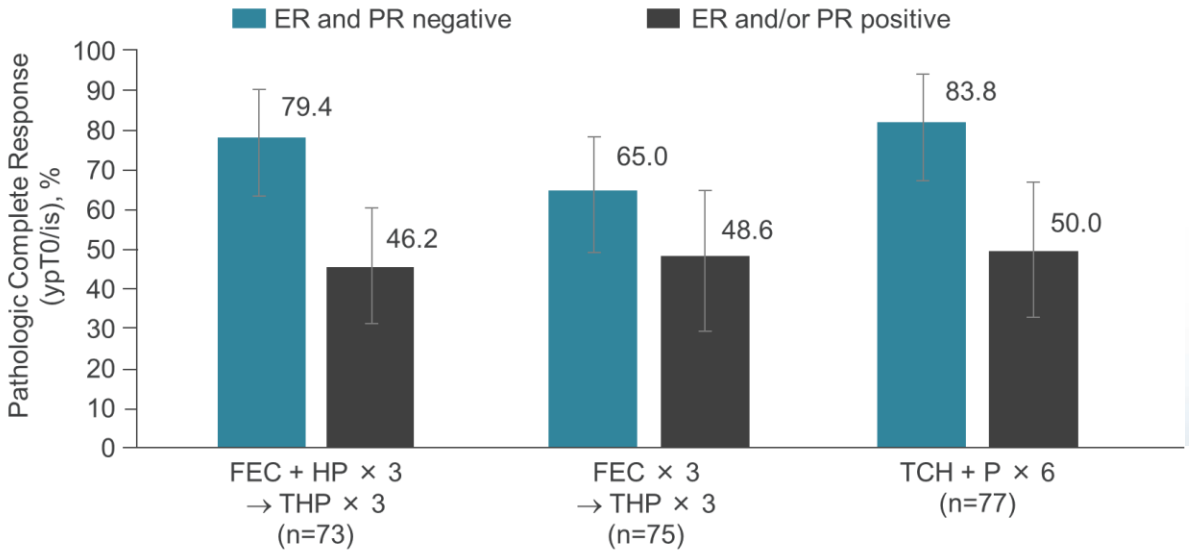


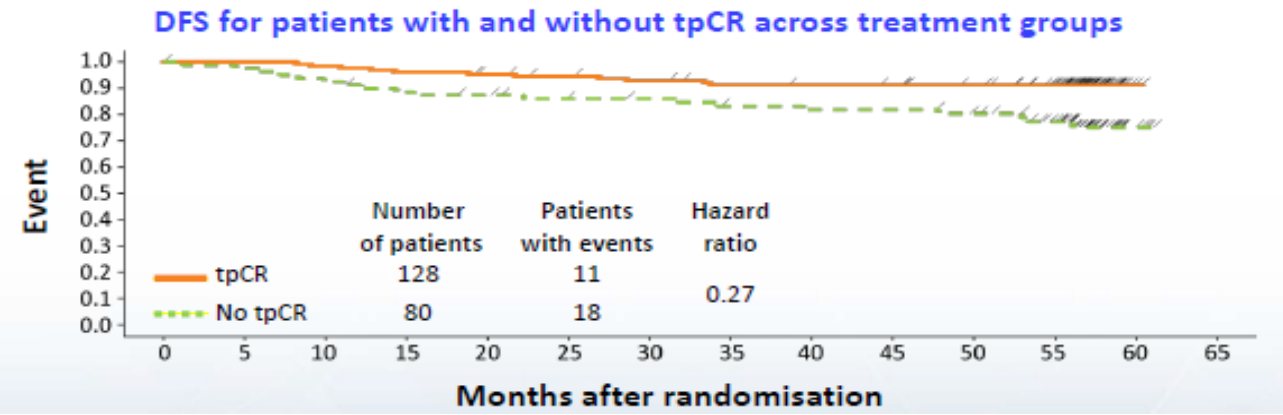

Slide courtesy of Laura Huppert, MD

# TRYPHAENA: Neoadjuvant Therapy for HER2+ EBC




| | T + P + FEC + D | FEC → T + P + D | T + P + D + C |
|---|---|---|---|
| 3-year DFS (n = 69, 67, 72) | 87% | 88% | 90% |
| 3-year PFS (n = 73, 75, 77) | 89% | 89% | 87% |
| 3-year OS (n = 73, 75, 77) | 94% | 94% | 93% |
| Any grade left ventricular systolic dysfunction* (n = 72, 75, 76) | 2.8% | 4% | 5.4% |
| LVEF declines ≥10% from baseline to <50% (n = 72, 75, 76) | 11.1% | 16% | 11.8% |




Schneeweiss A, et al. Eur J Cancer. 2018;89:27-35.

# KATHERINE: iDFS/OS with T-DM1 vs Trastuzumab for Residual Disease

- Centrally confirmed HER2+ breast cancer
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Received neoadjuvant therapy consisting of
  - Minimum of 6 cycles as neoadjuvant therapy
    - All chemotherapy as neoadjuvant therapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylators allowed
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Pathologic residual invasive tumor in breast or axilla
- Randomization within 12 weeks of surgery

R 1:1

*N*=1486

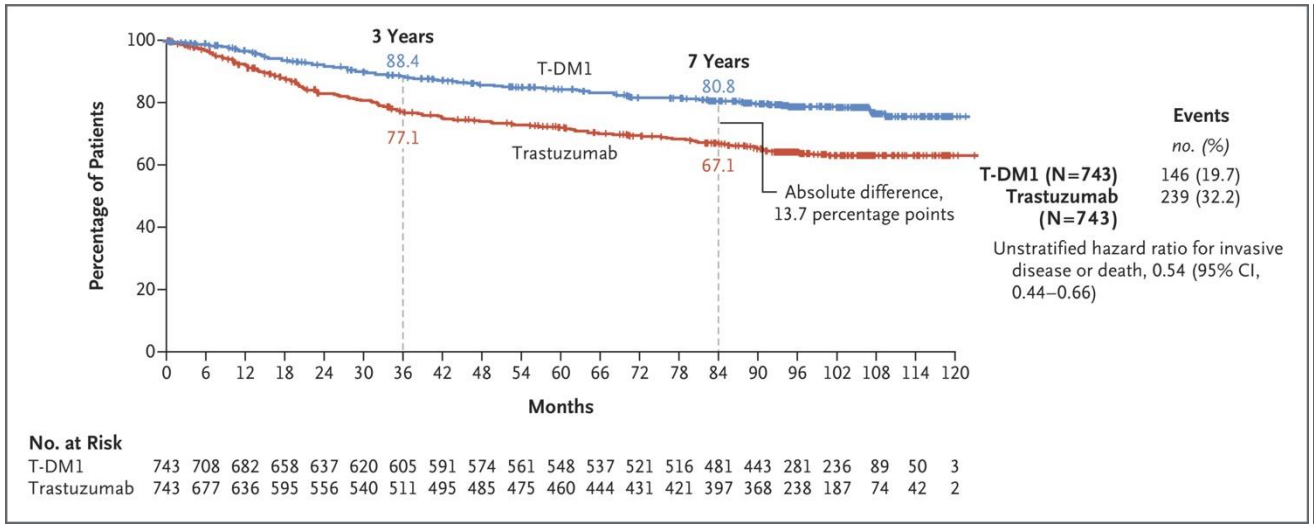
**T-DM1**
3.6 mg/kg IV q3w
14 cycles

**Trastuzumab**
6 mg/kg IV q3w
14 cycles

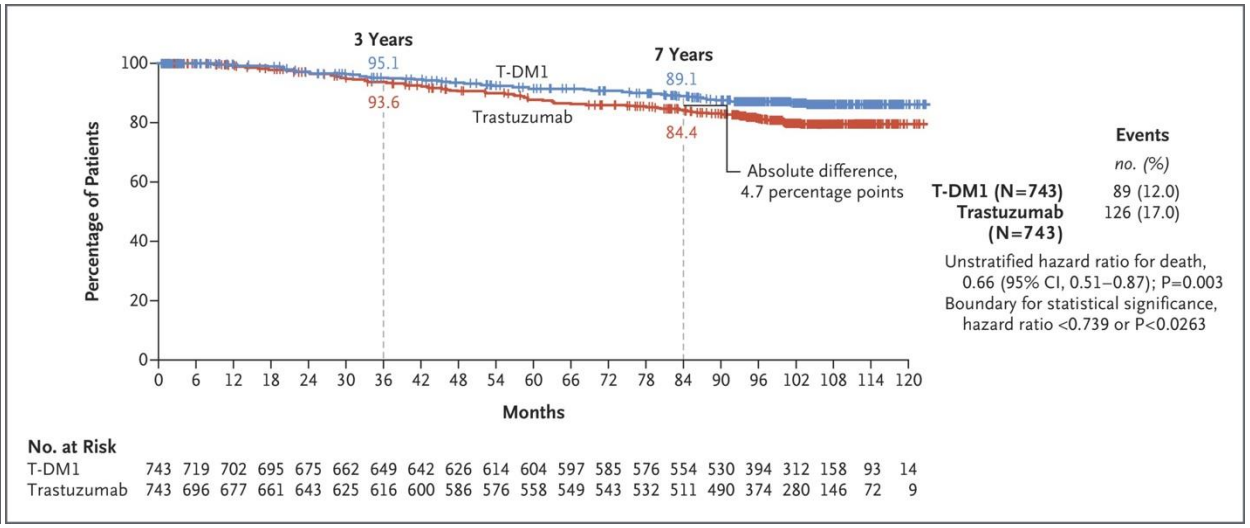
- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

**Primary endpoint:** IDFS*

## Invasive Disease-Free Survival



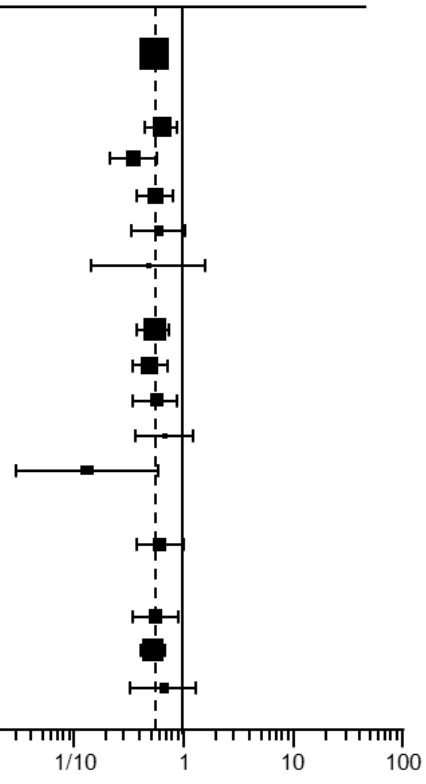

## Overall Survival




Geyer et al, NEJM 2025

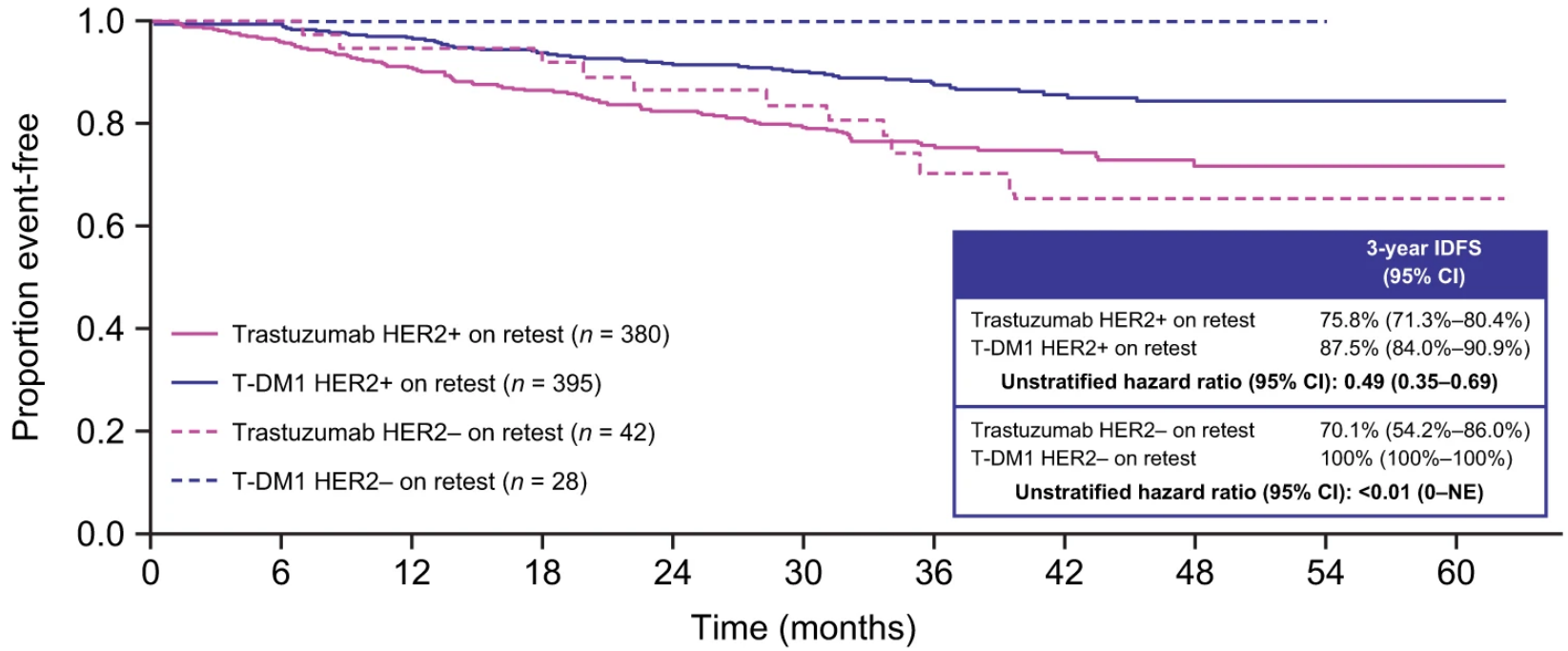
# KATHERINE Trial: Benefit of T-DM1 vs Trastuzumab by Subgroups

| Baseline risk factors | Total n | Trastuzumab (n = 743) Patients per group | Trastuzumab (n = 743) n events | Trastuzumab (n = 743) 7-year IDFS | T-DM1 (n = 743) Patients per group | T-DM1 (n = 743) n events | T-DM1 (n = 743) 7-year IDFS | Hazard ratio | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| **All** | 1486 | 743 | 239 | 67.1 | 743 | 146 | 80.8 | 0.54 | (0.44, 0.66) |
| **Primary tumor stage (at definitive surgery)** | | | | | | | | | |
| ypT0, ypT1a, ypT1b, ypT1mic, ypTis | 637 | 306 | 78 | 74.6 | 331 | 59 | 82.0 | 0.65 | (0.46, 0.90) |
| ypT1, ypT1c | 359 | 184 | 60 | 66.8 | 175 | 22 | 87.4 | 0.35 | (0.21, 0.56) |
| ypT2 | 359 | 185 | 67 | 62.9 | 174 | 41 | 78.4 | 0.55 | (0.37, 0.80) |
| ypT3 | 108 | 57 | 28 | 46.4 | 51 | 19 | 62.0 | 0.59 | (0.33, 1.06) |
| ypT4* | 23 | 11 | 6 | 33.8 | 12 | 5 | 70.0 | 0.49 | (0.15, 1.61) |
| **Regional lymph node stage (at definitive surgery)** | | | | | | | | | |
| ypN0 | 673 | 332 | 83 | 74.0 | 341 | 48 | 87.1 | 0.53 | (0.37,0.75) |
| ypN1 | 432 | 212 | 76 | 63.6 | 220 | 47 | 78.0 | 0.50 | (0.35, 0.72) |
| ypN2 | 189 | 103 | 47 | 52.4 | 86 | 28 | 69.5 | 0.56 | (0.35, 0.89) |
| ypN3 | 67 | 30 | 19 | 32.1 | 37 | 21 | 38.6 | 0.67 | (0.36, 1.24) |
| ypNX | 125 | 66 | 14 | 79.1 | 59 | 2 | 98.2 | 0.13 | (0.03, 0.59) |
| **Residual disease ≤1 cm with negative axillary lymph nodes** | | | | | | | | | |
| ypT1a, ypT1b or ypT1mic and ypN0 | 328 | 160 | 36 | 76.7 | 168 | 25 | 85.7 | 0.62 | (0.37, 1.03) |
| **Age group (years)** | | | | | | | | | |
| <40 | 296 | 153 | 46 | 67.2 | 143 | 28 | 81.2 | 0.56 | (0.35, 0.90) |
| 40–64 | 1064 | 522 | 170 | 66.7 | 542 | 104 | 80.9 | 0.52 | (0.41, 0.66) |
| ≥65 | 126 | 68 | 23 | 69.4 | 58 | 14 | 78.6 | 0.67 | (0.34, 1.30) |




Geyer et al, NEJM 2025

# KATHERINE: EFS for T-DM1 vs Trastuzumab for Residual Disease Based on HER2 Expression at Surgery

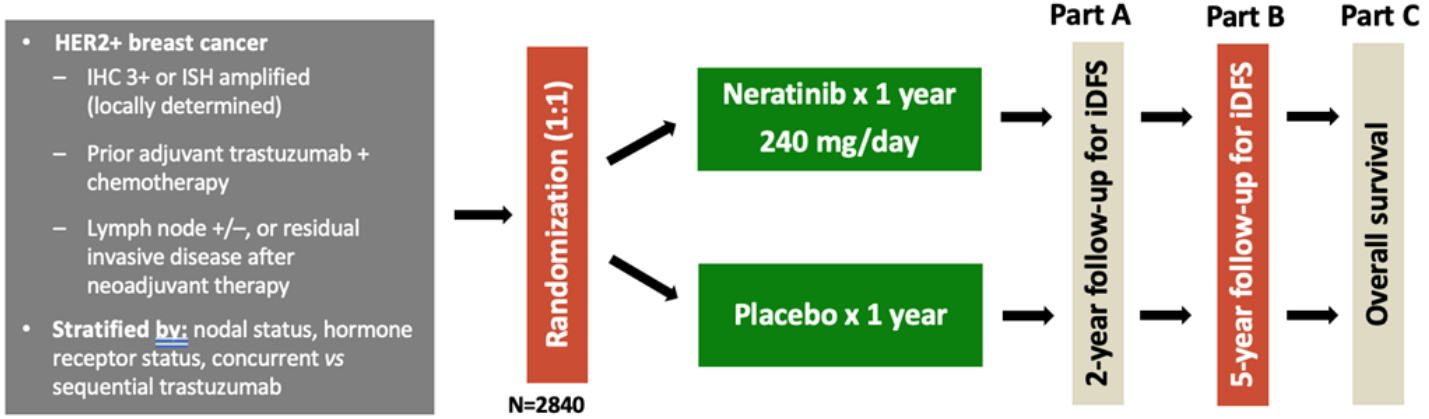



**Number at risk:**

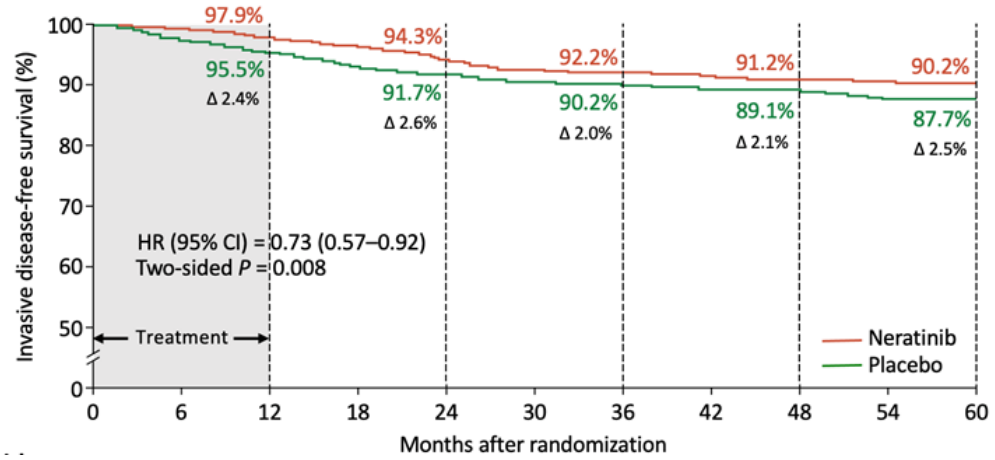
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab HER2+ on retest | 380 | 344 | 325 | 306 | 288 | 262 | 184 | 113 | 64 | 22 | 2 |
| T-DM1 HER2+ on retest | 395 | 377 | 365 | 352 | 340 | 309 | 224 | 138 | 79 | 30 | 3 |
| Trastuzumab HER2– on retest | 42 | 38 | 35 | 34 | 31 | 29 | 17 | 9 | 5 | 2 | 1 |
| T-DM1 HER2– on retest | 28 | 25 | 24 | 24 | 23 | 21 | 14 | 5 | 2 | 1 | 0 |

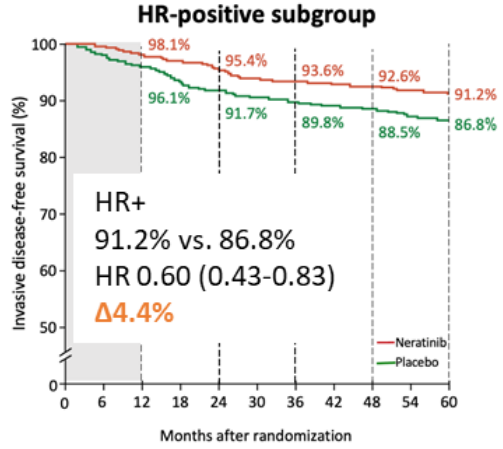
Geyer et al, NEJM 2025

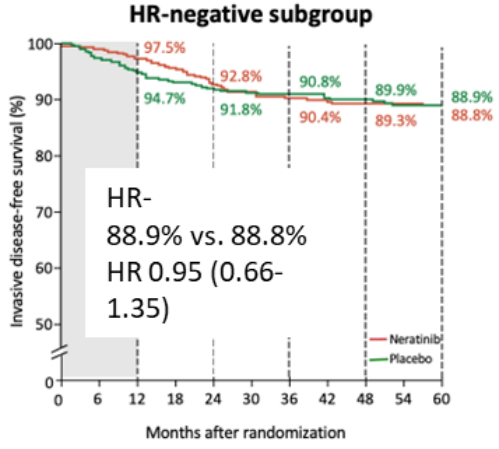
# ExteNET: Improvement in iDFS in HR+ Subgroup




2840 pts
77+ node+
57% HR+
81% started < 1 yr after H



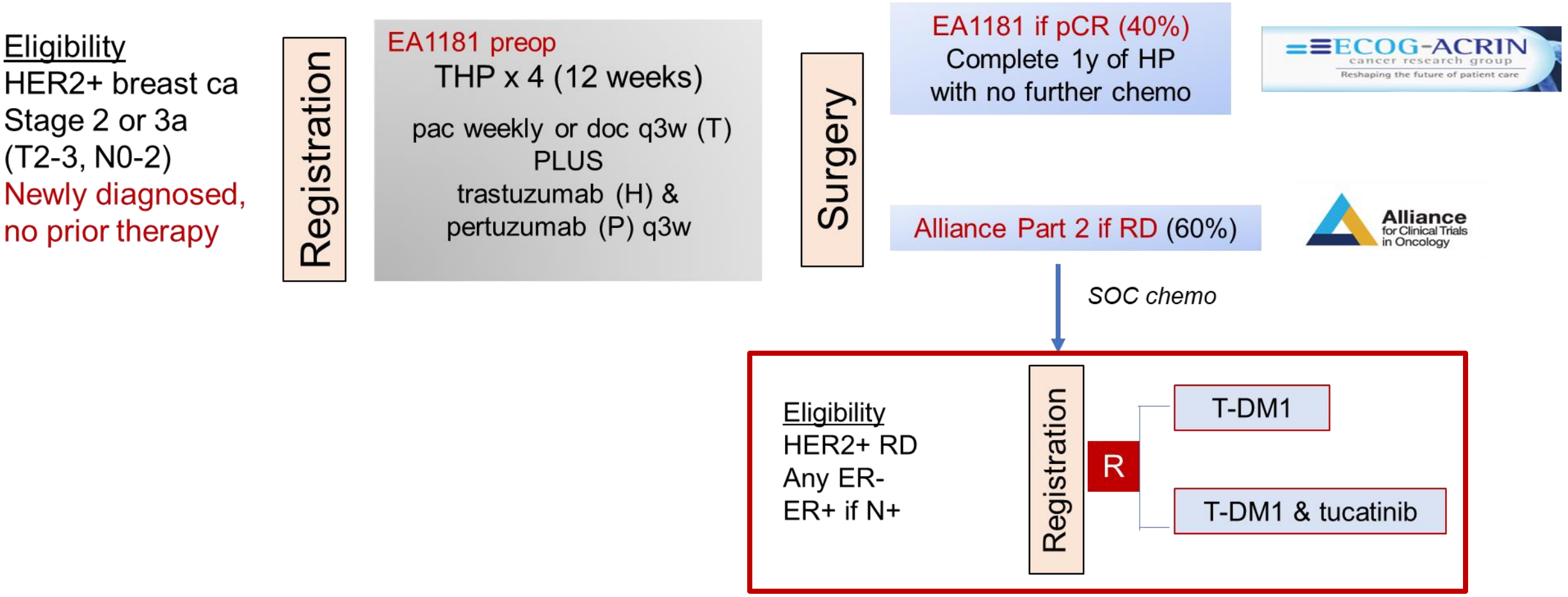




**Trial conducted prior to use of pertuzumab and T-DM1**

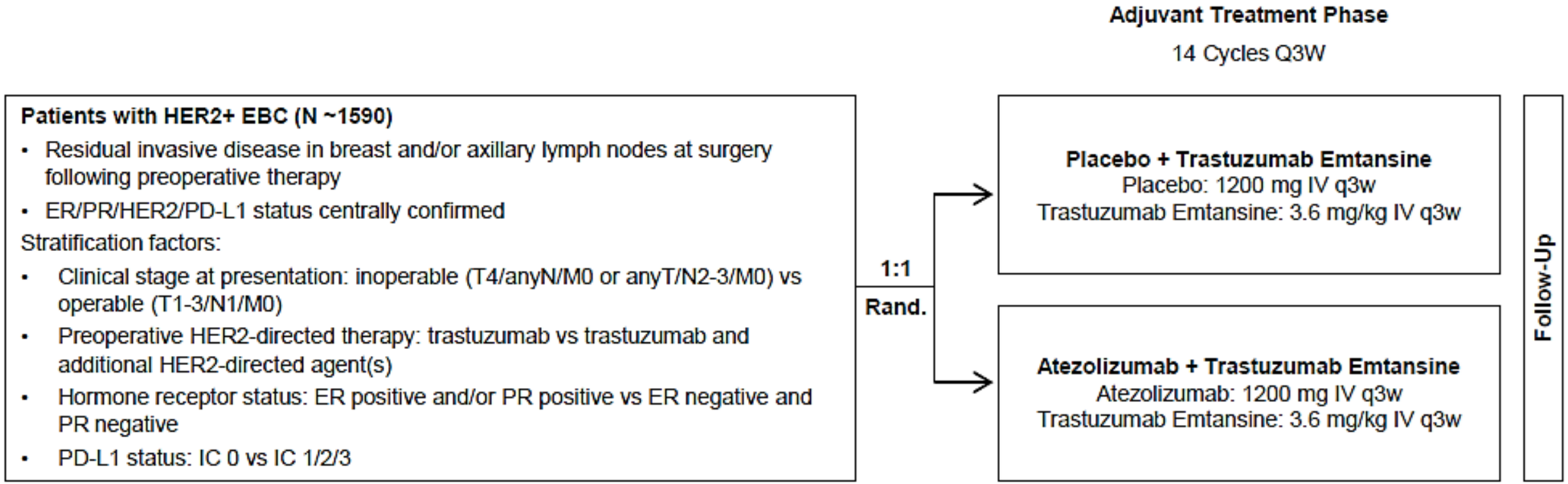
Martin et al, Lancet Oncology 2017

# Optimization of (Neo)adjuvant Therapy for HER2+ EBC: COMPASS and COMPASS-RD



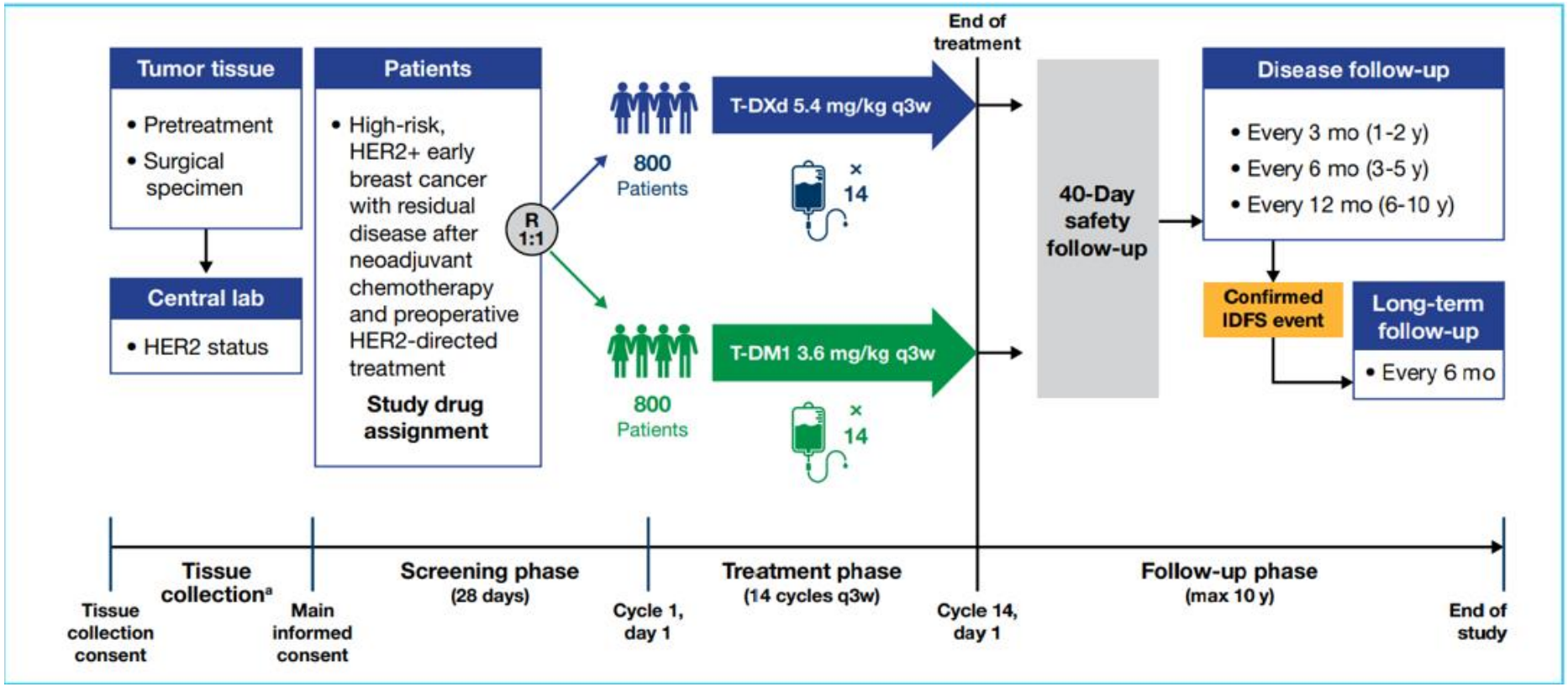

Slide courtesy of Nadine Tung, MD

# ASTEFANIA Trial: T-DM1 + Atezolizumab/Placebo for High-Risk RD




Slide courtesy of Ada Waks, MD

# DESTINY-Breast05: T-DXd vs T-DM1 for High-Risk RD




**Key Eligibility**

- Inoperable breast cancer at presentation
- Operable breast cancer at presentation with node–positive (ypN1-3) disease after neoadjuvant therapy

Geyer et al, SABCS 2020

# Summary: Early HER2+ Breast Cancer

- Adjuvant therapy SOC for stage 1 disease
- Neoadjuvant chemo+HP is SOC for stage 2/3 disease
- T-DM1 SOC in pts with residual disease
- Neratinib can be considered in pts with HR+ residual disease
- Optimization of neoadjuvant and adjuvant therapy ongoing
  - pCR: de-escalation of therapy
  - Residual disease: T-DM1 +/- tucatinib, T-DM1 +/- immunotherapy, T-DM1 vs T-DXd
  - T-DXd in neoadjuvant setting in high-risk disease
  - Role of predictive assays/ctDNA?

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Thank You!

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