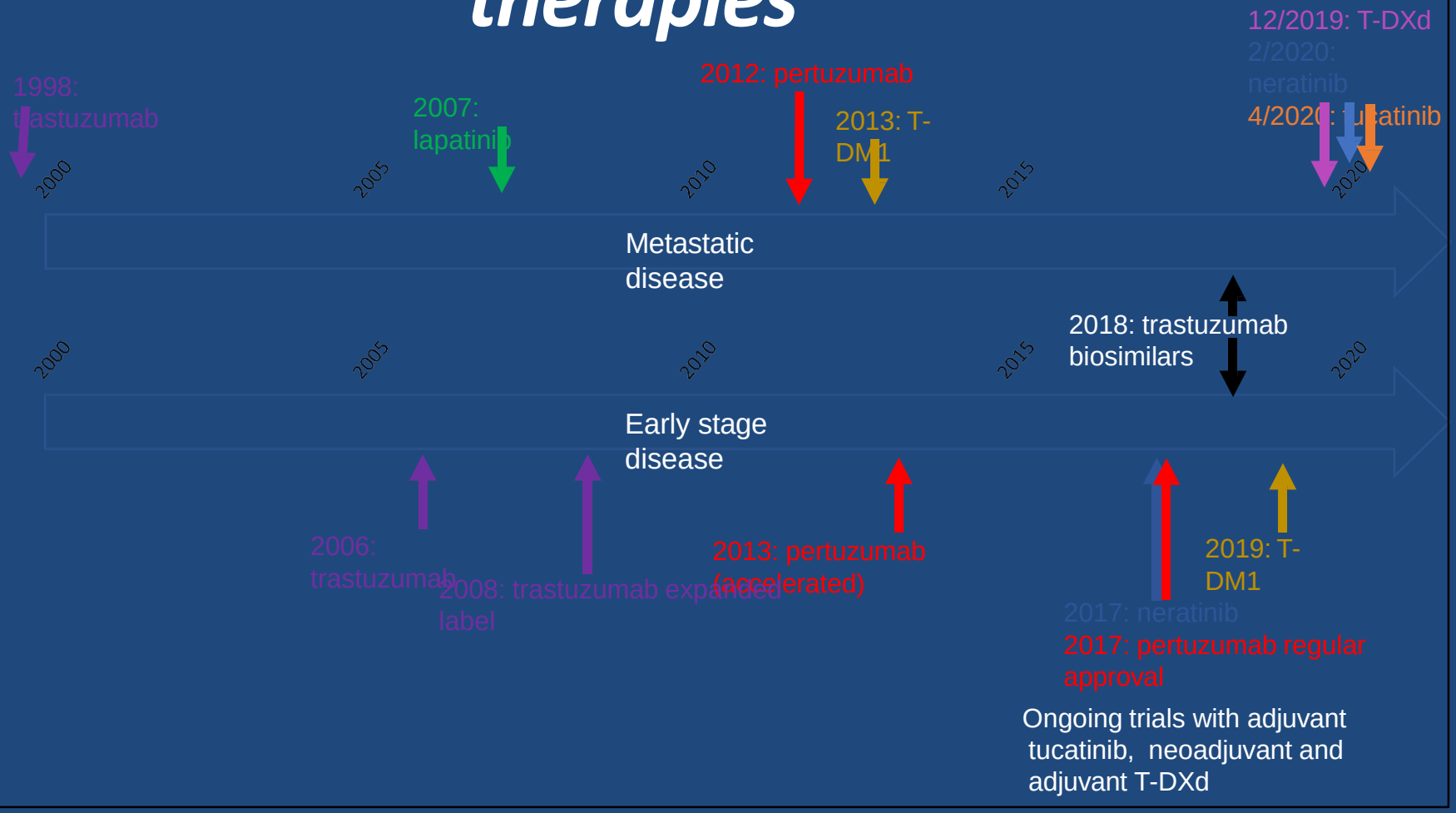
# What should we do for small HER2 positive BC in adjuvant

Safa najafi M.D

Associated professor

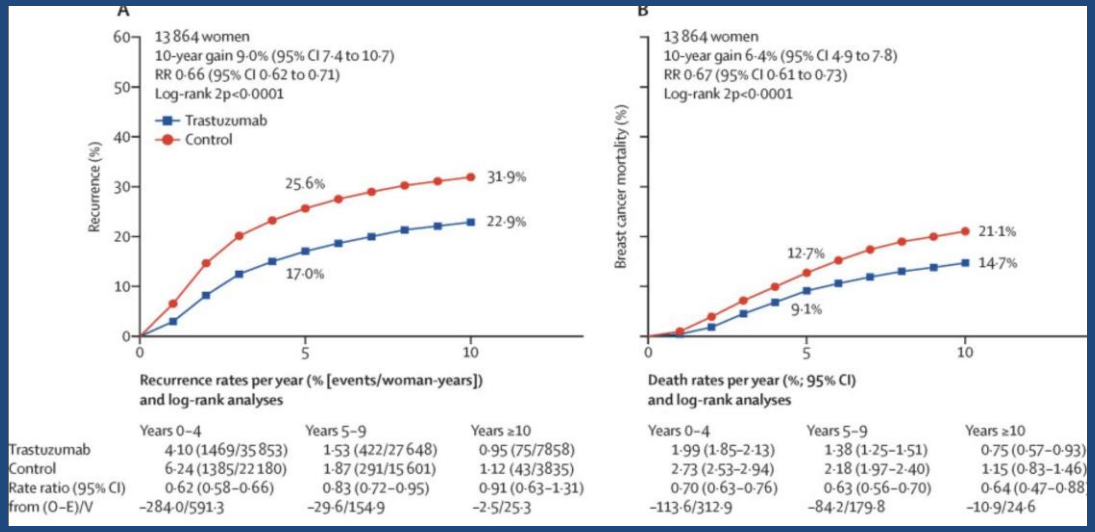
Motamed cancer institute

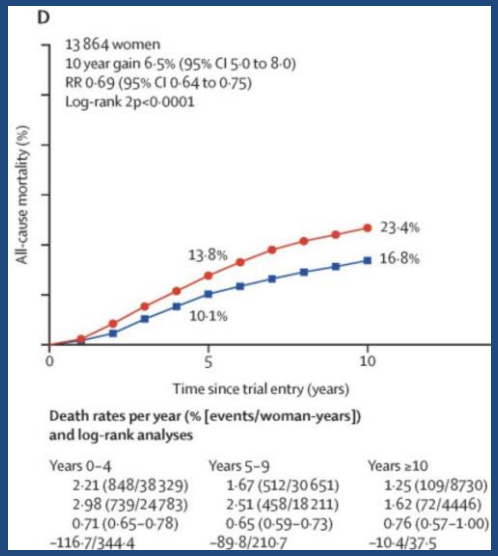
# Timeline of advances in HER2 therapies



# Meta-analysis with individual data from 13,864 patients demonstrating benefit of trastuzumab therapy

- Pooled from 7 RCTs




EBCTG. Lancet Oncol, 2021

# When several options present:

Listen

Be Aware

Be Calm

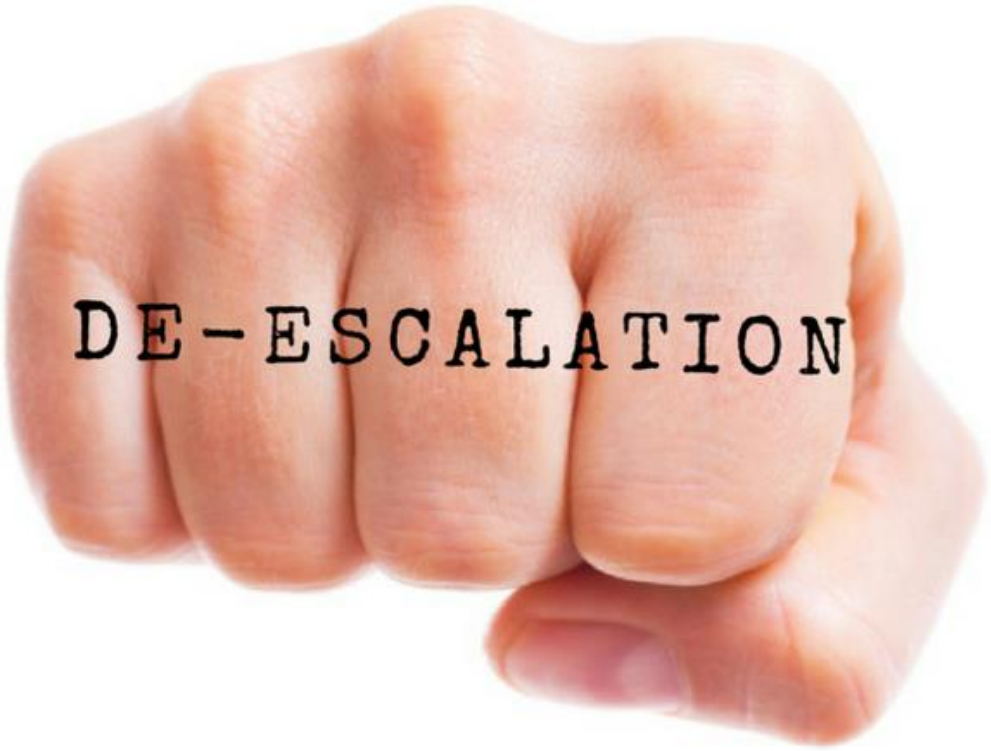
Offer

Plan

Ask For Help

Document

Reflect

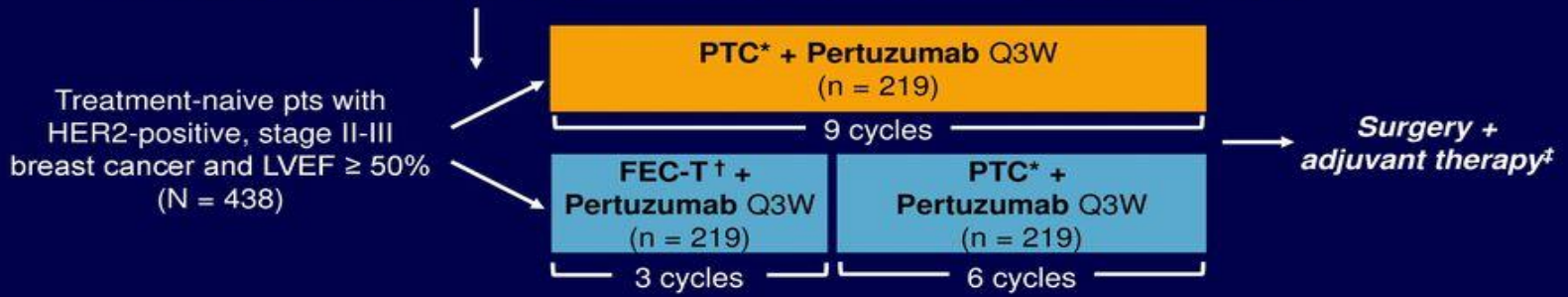


# ten-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual *ERBB2* Blockade in Patients With *ERBB2-Positive Breast Cancer*

## TRAIN-2: Study Design

- Multicenter, randomized phase III study in the Netherlands

*Stratified by cT (0-2 vs 3-4), cN (neg vs pos), ER (neg vs pos), and age (< 50 vs ≥ 50 yrs)*




*21-day cycles: PTC + pertuzumab Day 1, P Day 8; paclitaxel 80 mg/m², carboplatin AUC 6 mg·min/mL.
†21-day cycles. 5-fluorouracil 500 mg/m², epirubicin 90 mg/m², cyclophosphamide 500 mg/m².
Trastuzumab 6 mg/kg with 8-mg/kg loading dose, pertuzumab 420 mg with 840-mg loading dose.
‡To complete 1 yr of adjuvant trastuzumab; endocrine therapy for ER+ and/or PgR+ tumors.

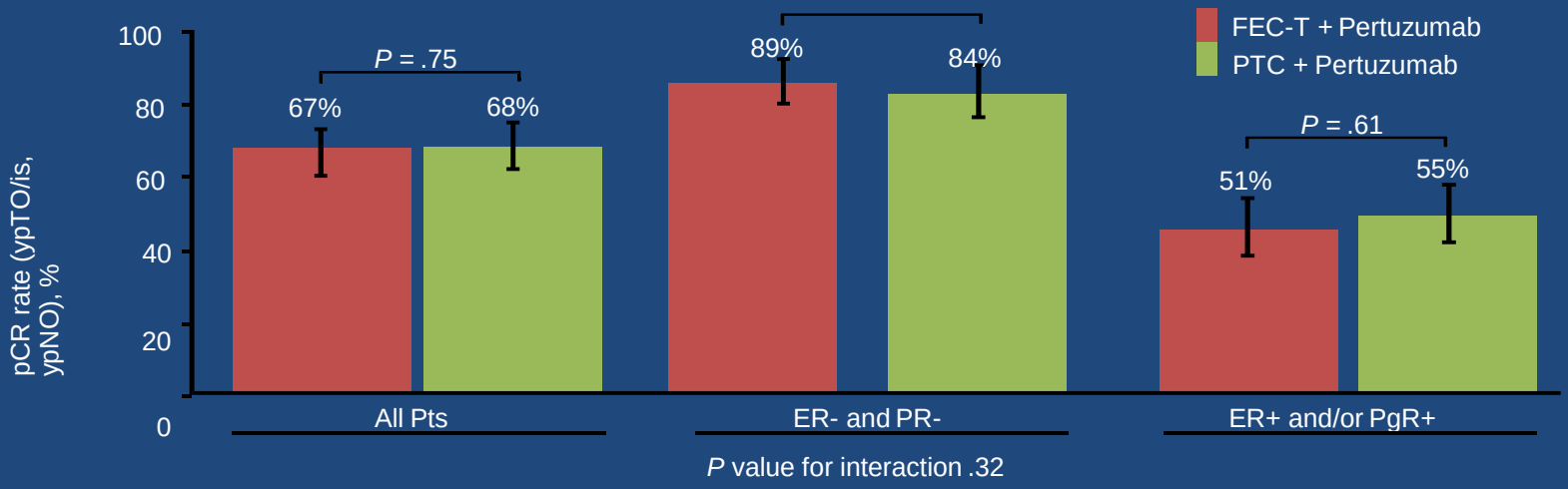
- Primary endpoint: pCR (ypT0/is, ypN0) by local assessment
- Secondary endpoints: RFS, BCSS, OS, toxicity

van Ramshorst MS, et al. ASCO 2017. Abstract 507.

Slide credit: clinicaloptions.com

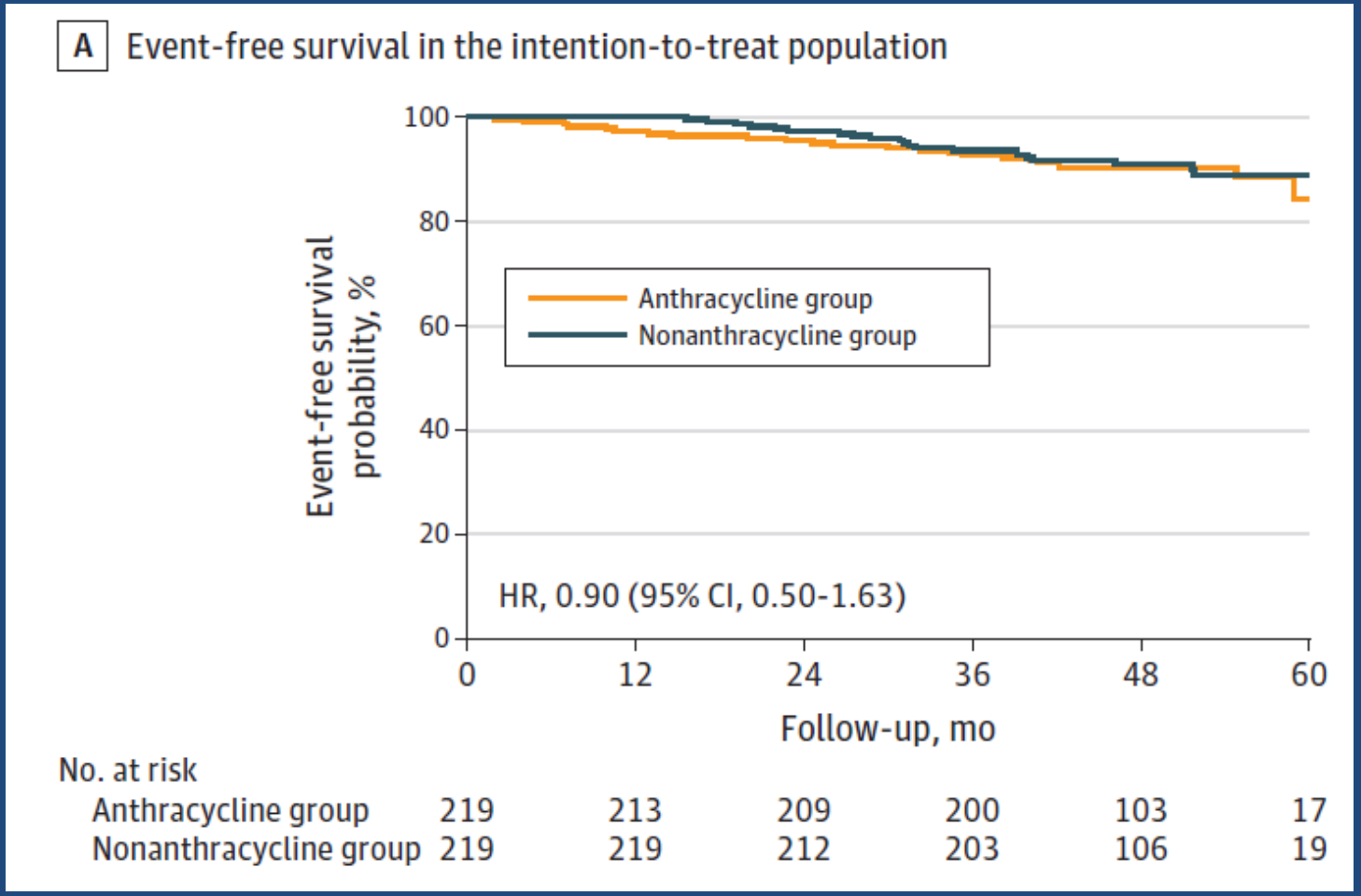
# TRAIN-2: pCR

*P* = .51

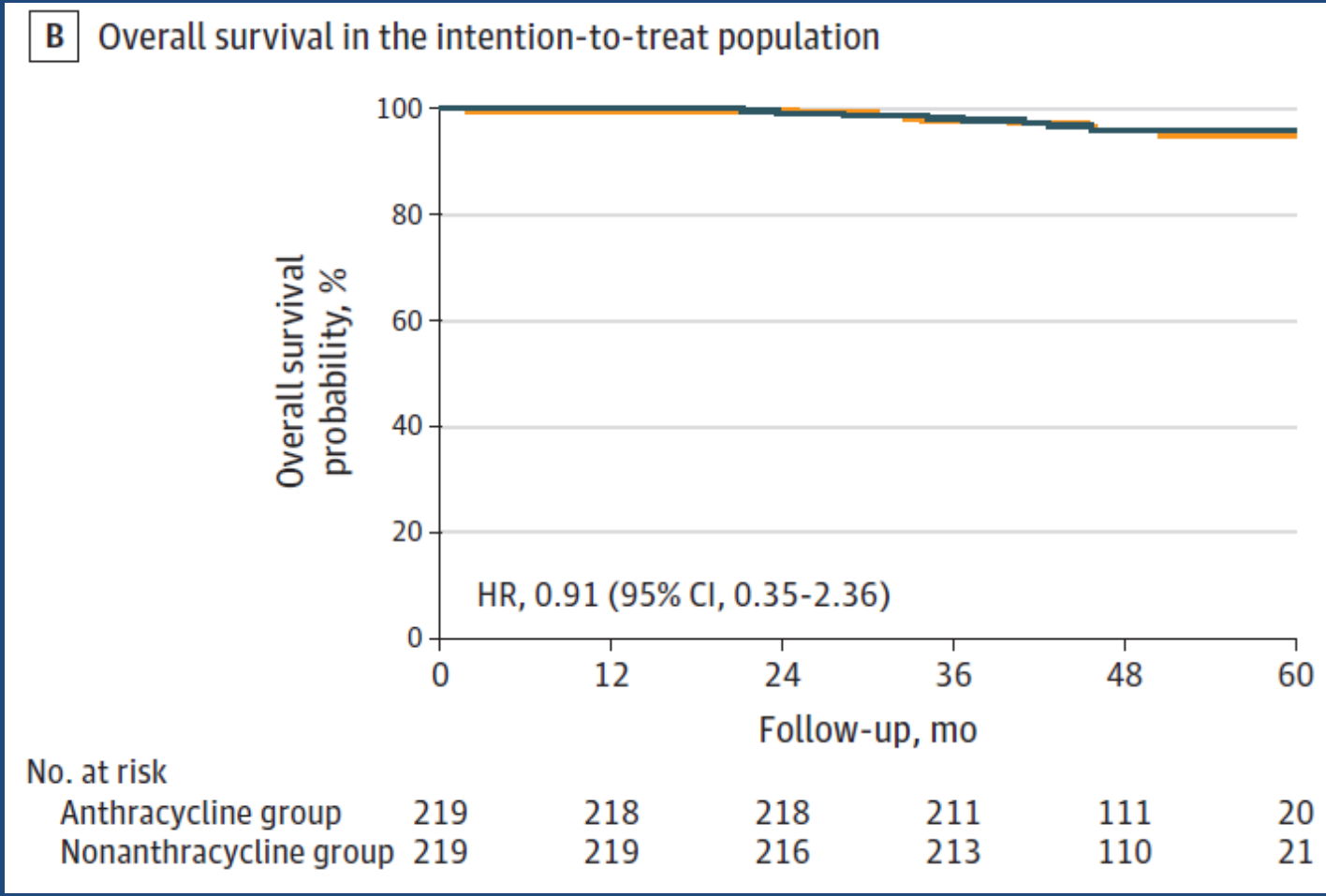



van Ramshorst MS, et al. Lancet Oncol 2018

# EFS in Train-2



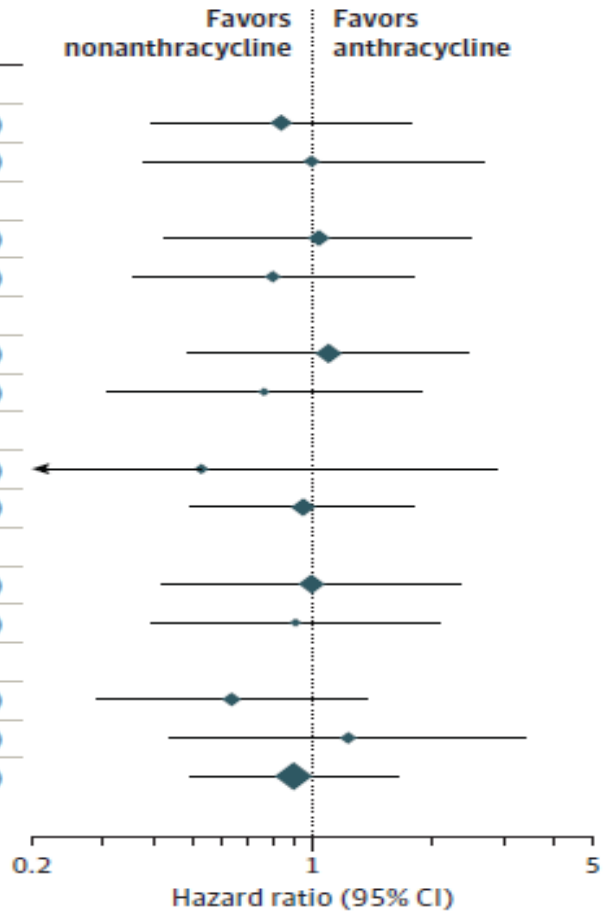
# OS in Train-2


B
Overall survival in the intention-to-treat population
Overall survival probability, %
100
80
60
40
20
0
HR, 0.91 (95% CI, 0.35-2.36)
0
12
24
36
48
60
Follow-up, mo
No. at risk
Anthracycline group 219 218 218 211 111 20
Nonanthracycline group 219 219 216 213 110 21

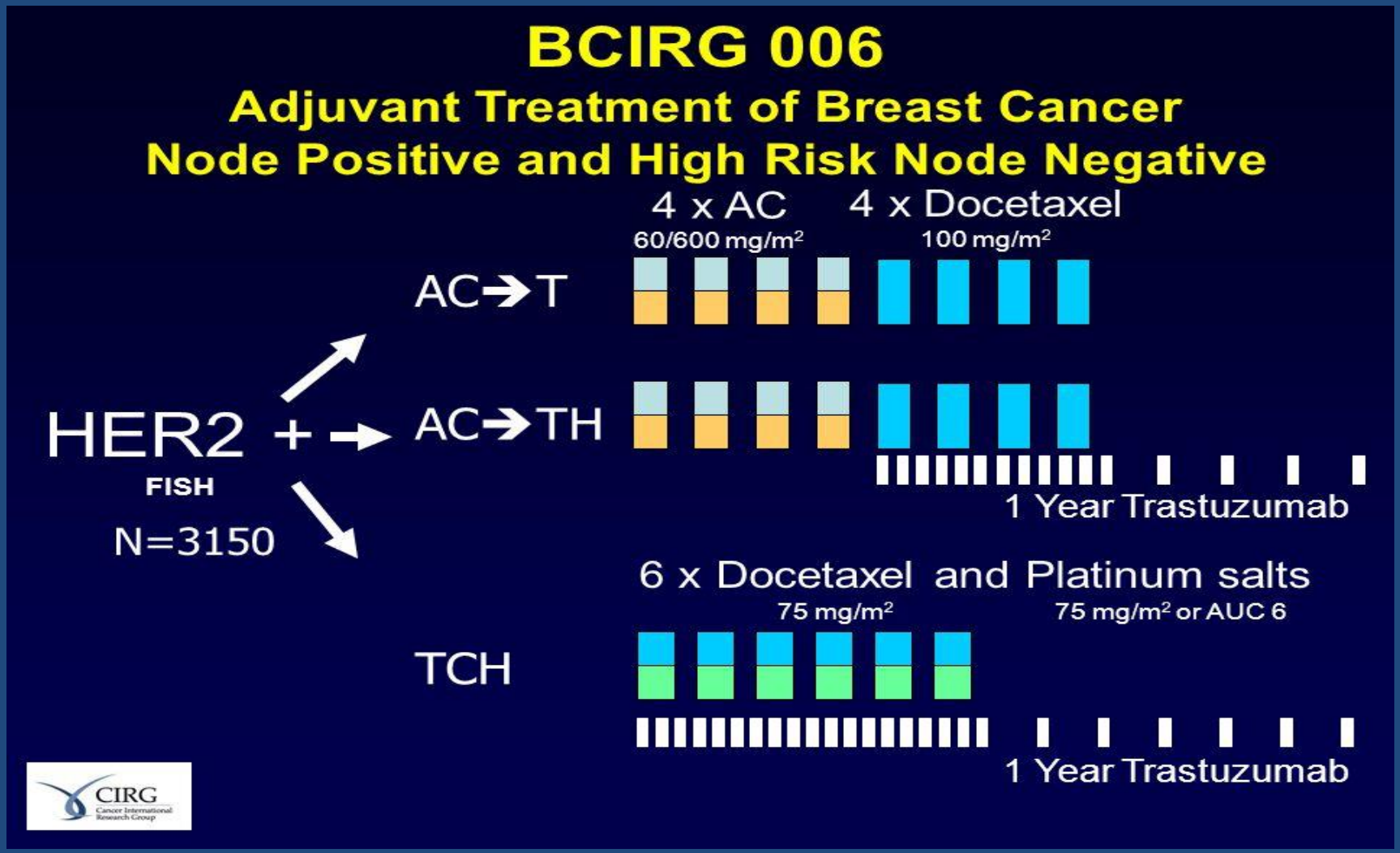
# Benefit in Even higher grades and stages

**Figure 2. Subgroup Analysis Event-Free Survival According to Treatment Arm**

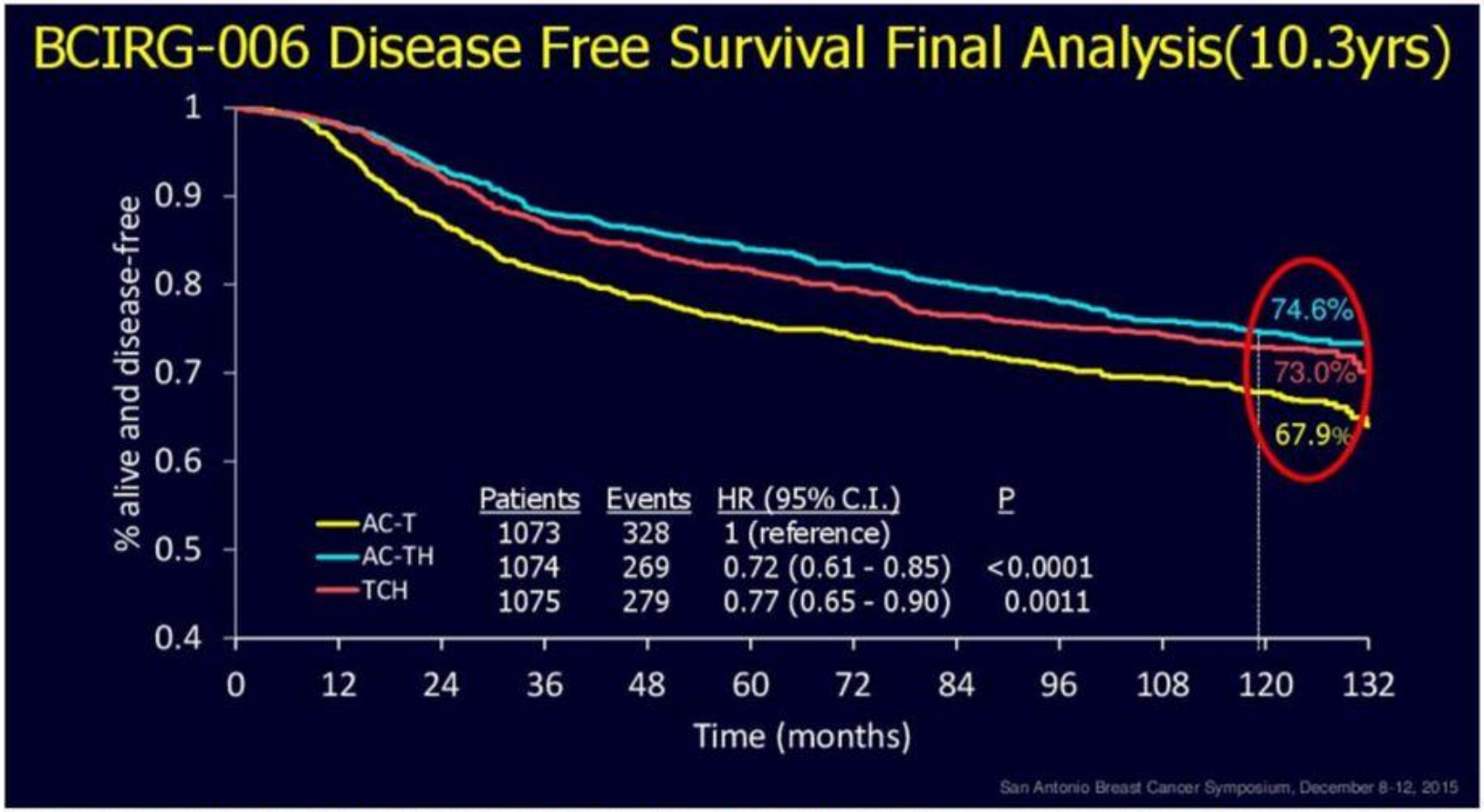
| Subgroup | Patients, No./total No. (%) Nonanthracycline (n=219) | Anthracycline (n=219) | Hazard ratio (95% CI)[a] |
|---|---|---|---|
| Hormone receptor | | | |
| Positive | 13/126 (10.3) | 15/129 (11.6) | 0.84 (0.40-1.77) |
| Negative | 8/93 (8.6) | 8/90 (8.9) | 1.00 (0.38-2.68) |
| Age, y | | | |
| <50 | 10/118 (8.5) | 10/119 (8.4) | 1.04 (0.43-2.50) |
| ≥50 | 11/101 (10.9) | 13/100 (13.0) | 0.80 (0.36-1.78) |
| Clinical tumor stage | | | |
| 0-2 | 13/154 (8.4) | 11/147 (7.5) | 1.10 (0.49-2.45) |
| 3-4 | 8/65 (12.3) | 12/72 (16.7) | 0.76 (0.31-1.87) |
| Clinical nodal status | | | |
| Negative | 2/76 (2.6) | 4/82 (4.9) | 0.53 (0.10-2.90) |
| Positive | 19/143 (13.3) | 19/137 (13.9) | 0.95 (0.50-1.79) |
| Disease stage | | | |
| II[b] | 11/151 (7.3) | 10/139 (7.2) | 1.00 (0.42-2.35) |
| III | 10/68 (14.7) | 13/80 (16.3) | 0.92 (0.40-2.09) |
| Tumor grade[c] | | | |
| 1-2 | 11/113 (9.7) | 16/107 (15.0) | 0.63 (0.29-1.37) |
| 3 | 8/95 (8.4) | 7/101 (6.9) | 1.23 (0.44-3.38) |
| All patients | 21/219 (9.6) | 23/219 (10.5) | 0.90 (0.50-1.63) |



# Non-antracyclins in adjuvant



# Disease-Free Survival (10.3 years)




**Same results in high-risk patients (ie, lymph node positive and lymph node ≥ 4)**

Slamon D, et al. SABCS 2015. Abstract S5-04.

# BCIRG 006 - > can we avoid anthracycline?

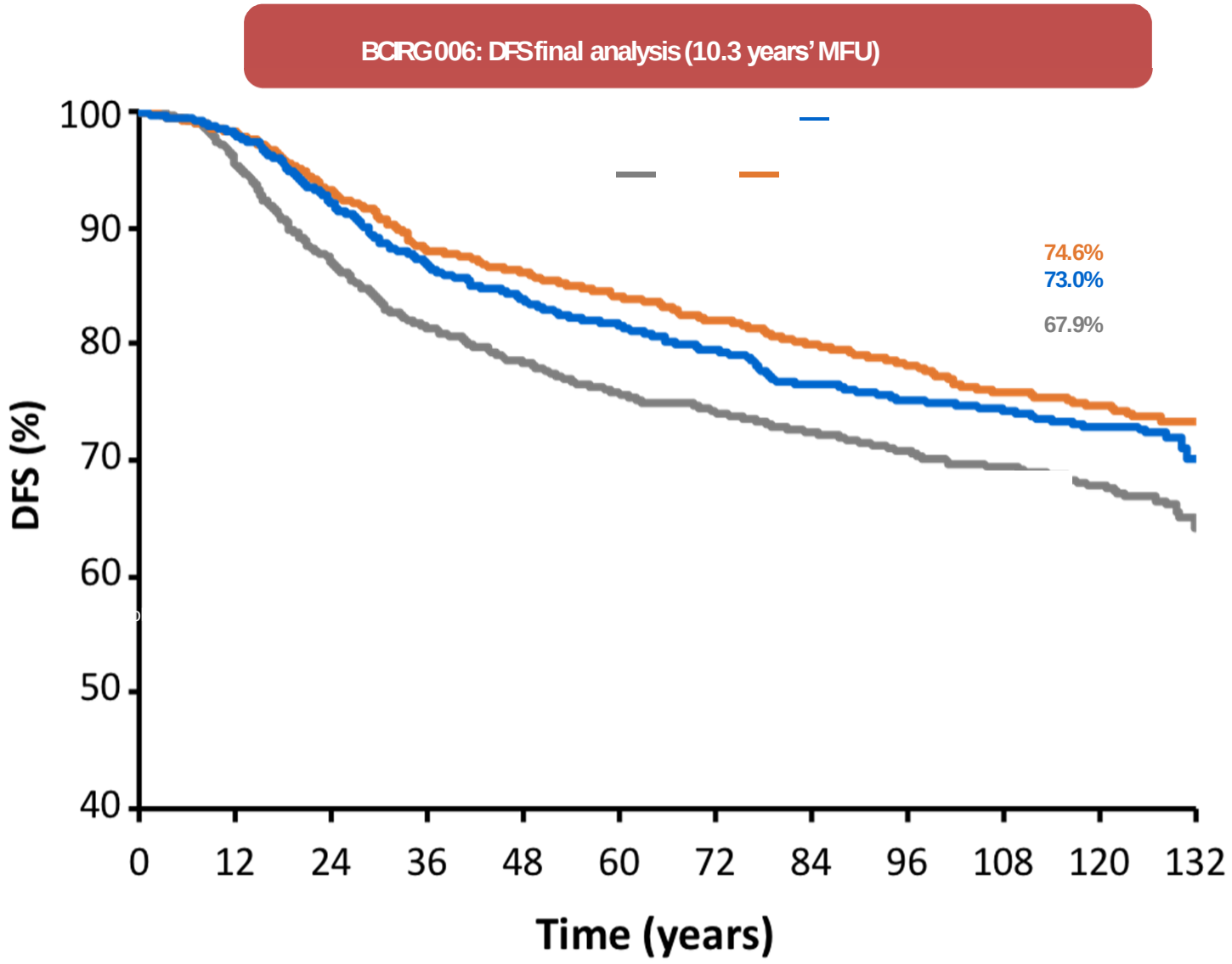


**Table 2. Therapeutic Index for Critical Clinical Events.***

| Clinical Event | AC-T | AC-T plus Trastuzumab | TCH |
|---|---|---|---|
| | | *number of events* | |
| Total events | 201 | 146 | 149 |
| Distant breast-cancer recurrence | 188 | 124 | 144 |
| Grade 3 or 4 congestive heart failure | 7 | 21 | 4 |
| Acute leukemia | 6 | 1 | 1† |

* This therapeutic index is a compilation of the numbers of distant breast-cancer recurrences, cases of congestive heart failure, and cases of acute leukemia. AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.

† This case of acute leukemia developed after the patient received an anthracycline as part of a combination chemotherapy regimen for a diffuse large B-cell lymphoma that occurred after she received treatment with TCH for breast cancer.

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2023
# Breast Cancer

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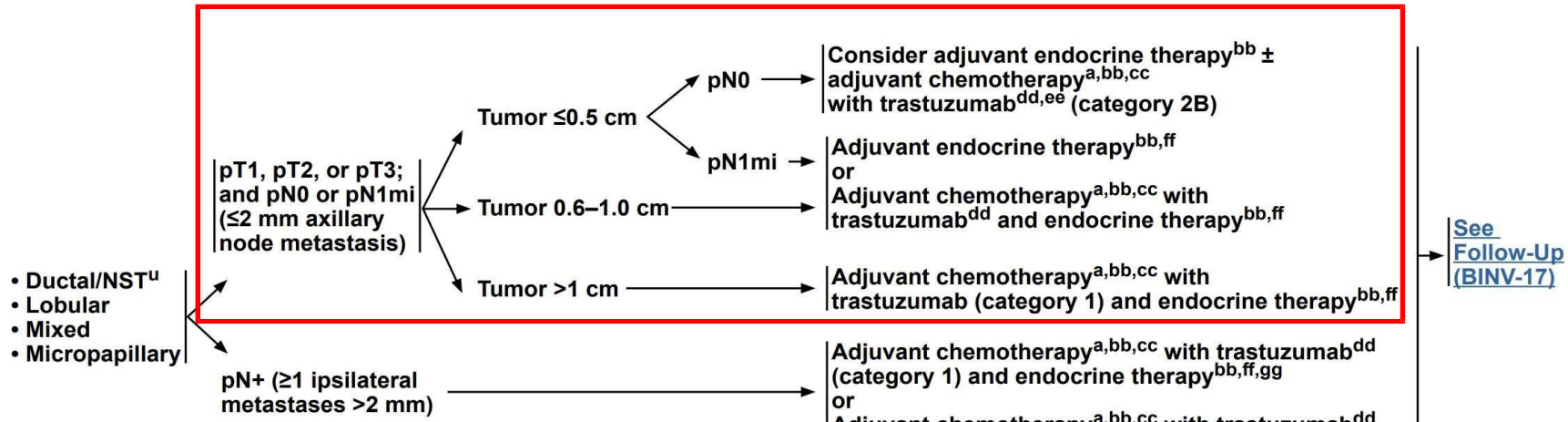
## SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-POSITIVE DISEASE[d,r,z]




[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[r] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).

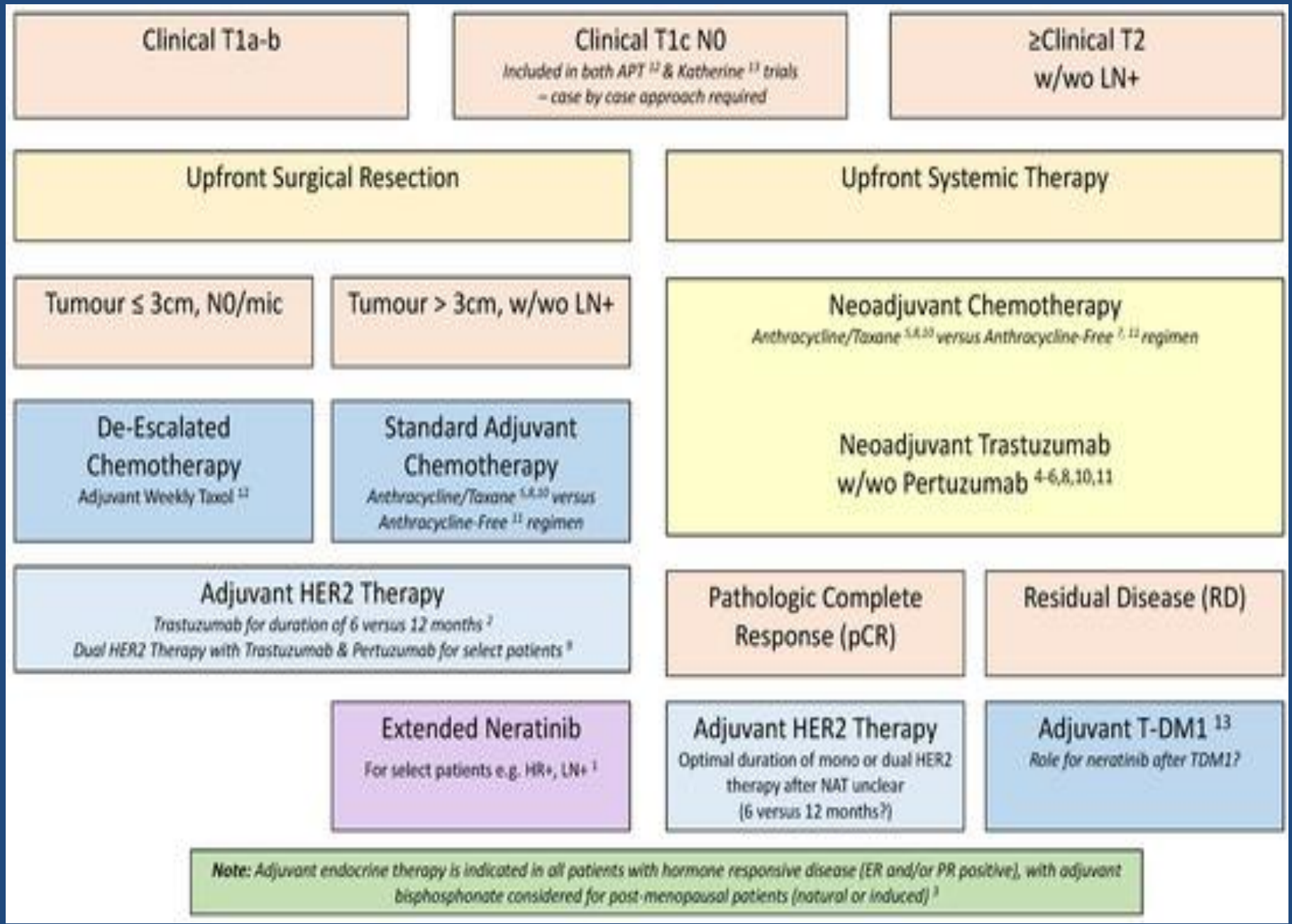
 

# *Risk of Disease Recurrence at 5 yrs*

- Definitions vary
- With these caveats, without treatment

| | |
|---|---|
| T1a | 2 – 10% |
| T1b | 5 – 20 % |
| T1c | 10 – 25% |

Tolaney ASCO 2017


Clinical T1a-b
Clinical T1c N0
Included in both APT [12] & Katherine [13] trials
– case by case approach required
≥Clinical T2
w/wo LN+
Upfront Surgical Resection
Upfront Systemic Therapy
Tumour ≤ 3cm, N0/mic
Tumour > 3cm, w/wo LN+
Neoadjuvant Chemotherapy
Anthracycline/Taxane [5,8,10] versus Anthracycline-Free [7, 11] regimen
Neoadjuvant Trastuzumab
w/wo Pertuzumab [4-6,8,10,11]
De-Escalated Chemotherapy
Adjuvant Weekly Taxol [12]
Standard Adjuvant Chemotherapy
Anthracycline/Taxane [5,8,10] versus Anthracycline-Free [11] regimen
Adjuvant HER2 Therapy
Trastuzumab for duration of 6 versus 12 months [2]
Dual HER2 Therapy with Trastuzumab & Pertuzumab for select patients [9]
Pathologic Complete Response (pCR)
Residual Disease (RD)
Extended Neratinib
For select patients e.g. HR+, LN+ [1]
Adjuvant HER2 Therapy
Optimal duration of mono or dual HER2 therapy after NAT unclear
(6 versus 12 months?)
Adjuvant T-DM1 [13]
Role for neratinib after TDM1?
Note: Adjuvant endocrine therapy is indicated in all patients with hormone responsive disease (ER and/or PR positive), with adjuvant bisphosphonate considered for post-menopausal patients (natural or induced) [3]

# Study Design (APT Trial)

HER2+
ER+ or ER-
node negative
≤3 cm

Planned N = 400

Enroll

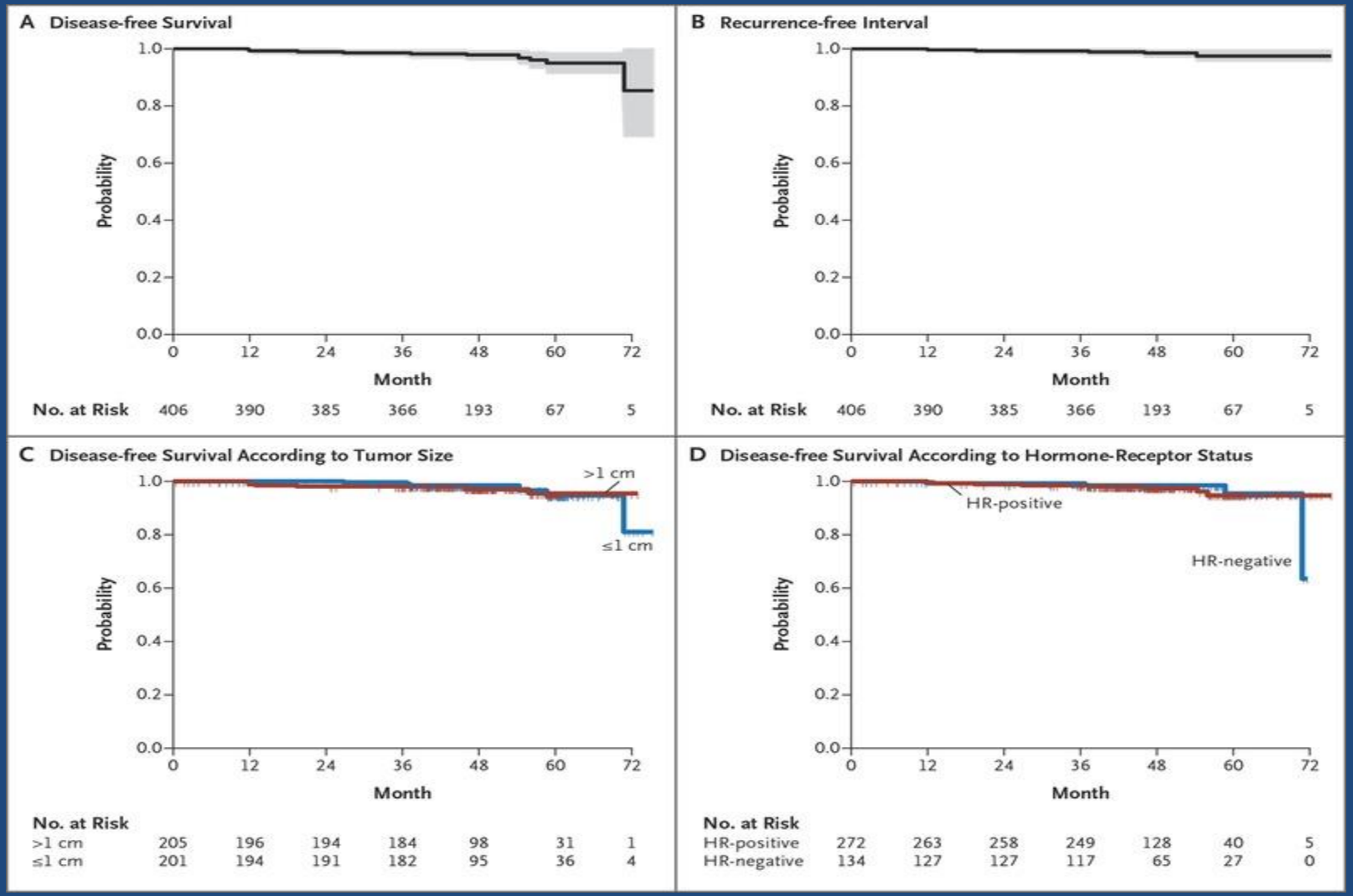

PACLITAXEL 80 mg/m$^2$ + TRASTUZUMAB 2 mg/kg x 12


FOLLOWED BY 13 EVERY 3 WEEK DOSES
OF TRASTUZUMAB (6 mg/kg)*

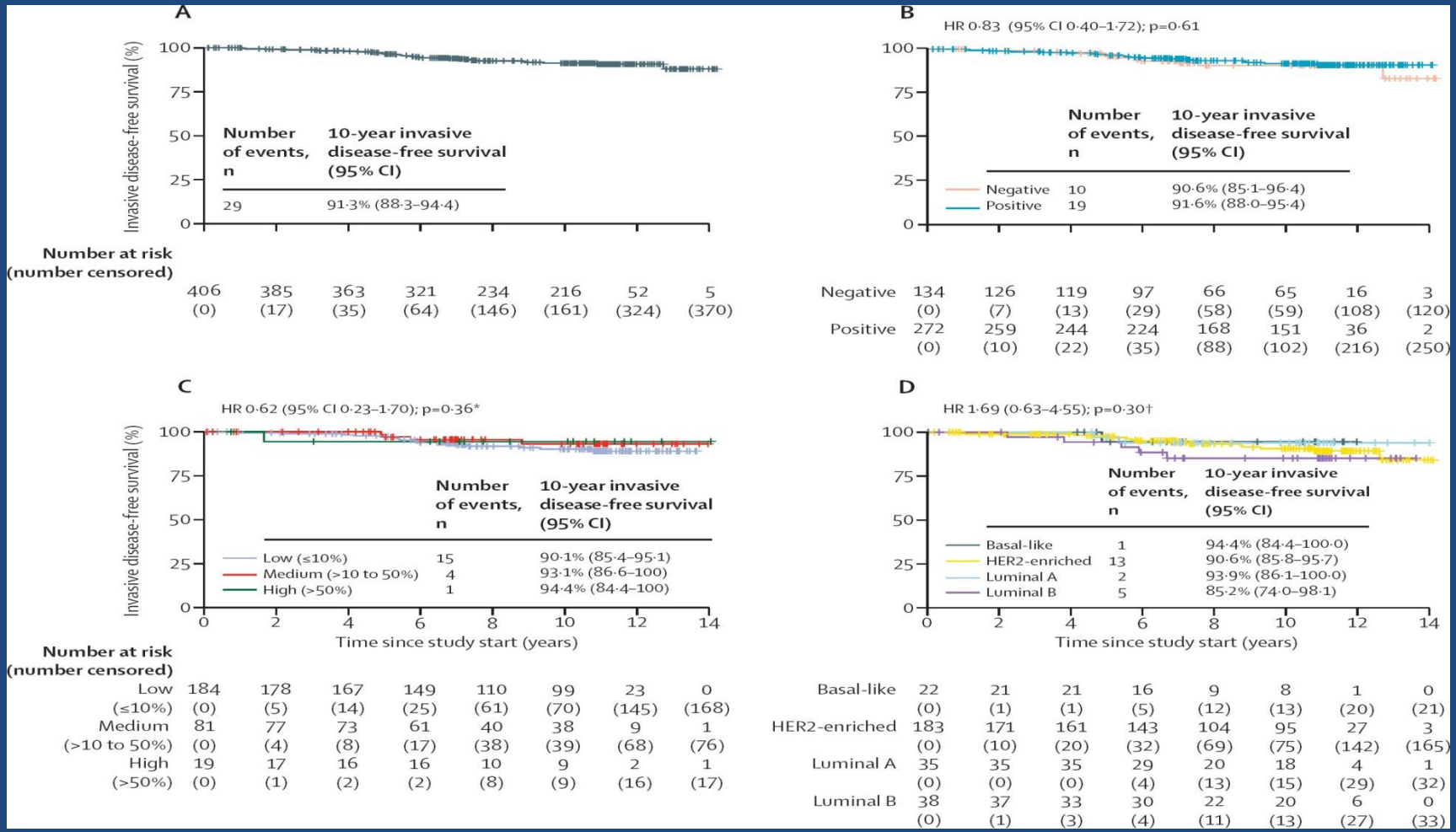
*Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks
**Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

# 5 years APT result NEJM



# 10 years result APT



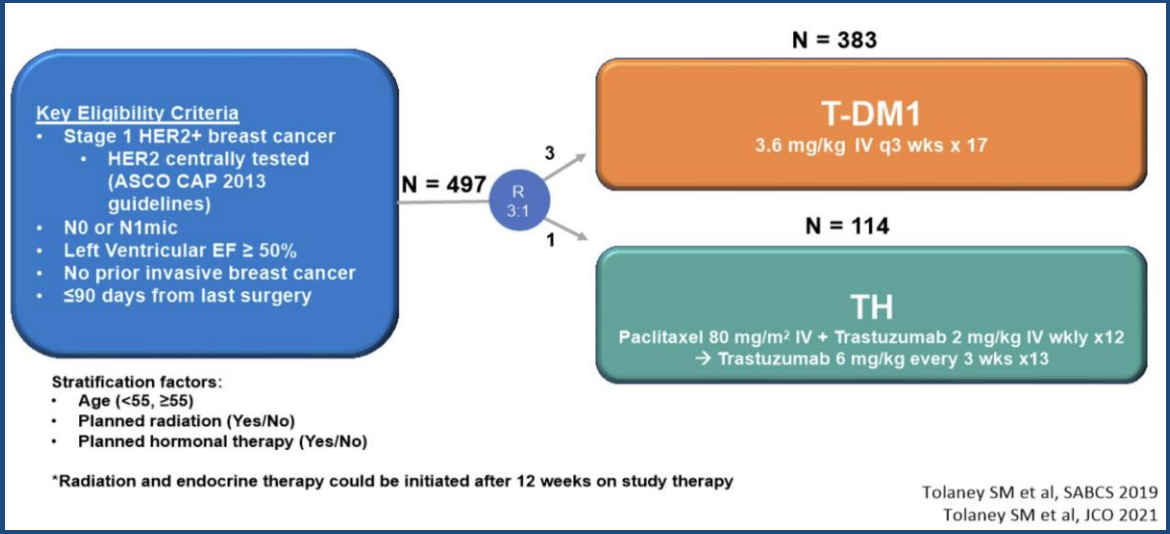
# Adjuvant TH– APT trial, 10 year results

- 406 patients, single arm study, tumor <3cm, node negative (except 6 N1mic)
- Adjuvant paclitaxel 80mg/m2 + trastuzumab 2mg/kg weekly x 12 weeks
  - trastuzumab 6mg/kg q3 weeks x 13
- 49% T1a/T1b, 42% T1c, 9% T2; 67% HR+
- 31 events
  - 6 distant recurrences (including occurrence years 5-10)
  - 6 ipsilateral recurrences
  - 9 contralateral new BC (1 HER2+)
  - 10 year relapse free interval 96.3% (95% CI 94.3-98.3%)
  - No different by HR status

Tolaney et al, SABCS 2022

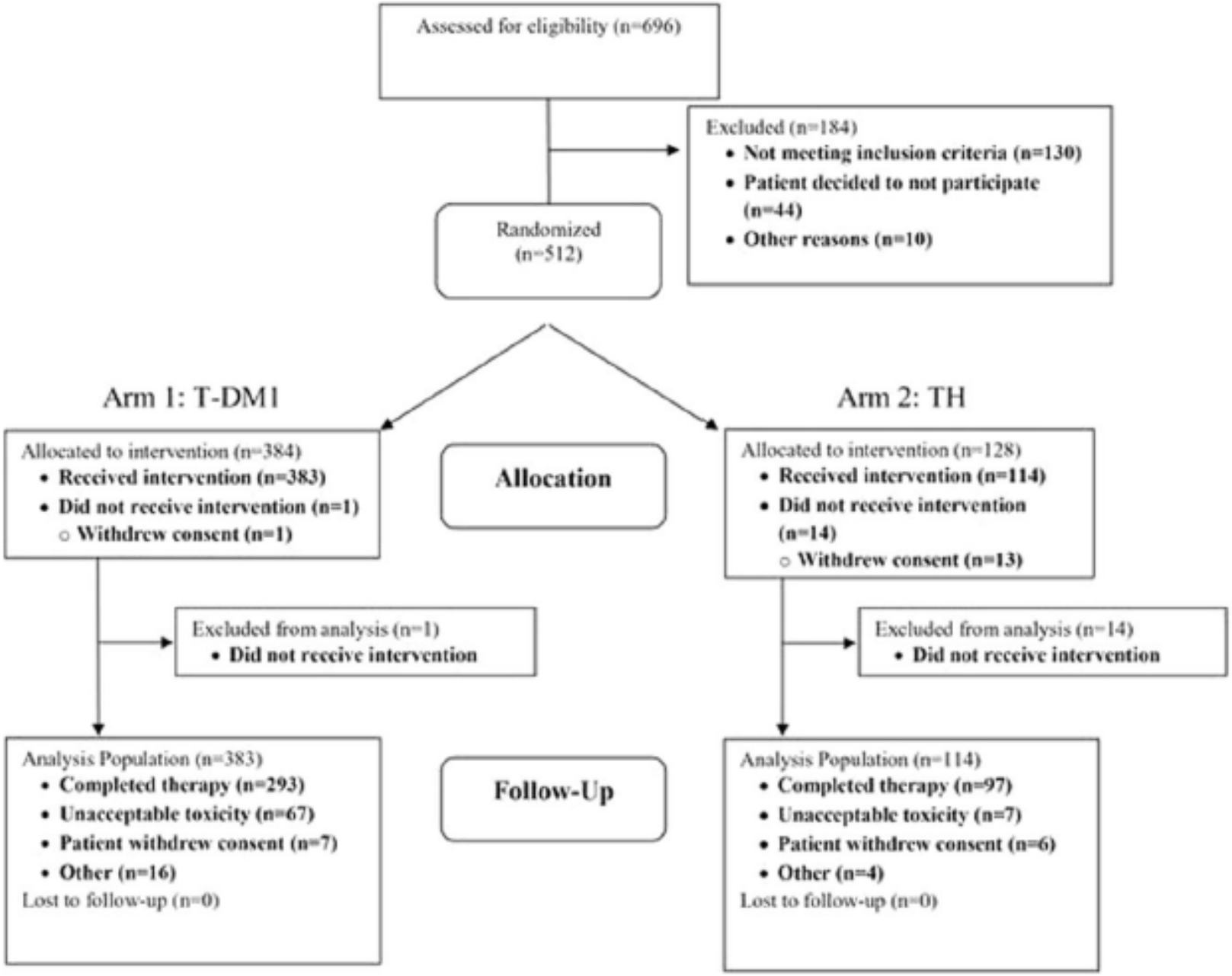

De-Escalation
Training

# ATEMPT: Stage 1 HER2+ BC: Adjuvant TH vs T-DM1




Tumor size:
-T1a 16%
-T1b 34%
-T1c 50%
Grade:
-G1 3%
-G2 39%
-G3 57%
HR+ 75%

Tolaney et al. J Clin Oncol 2019

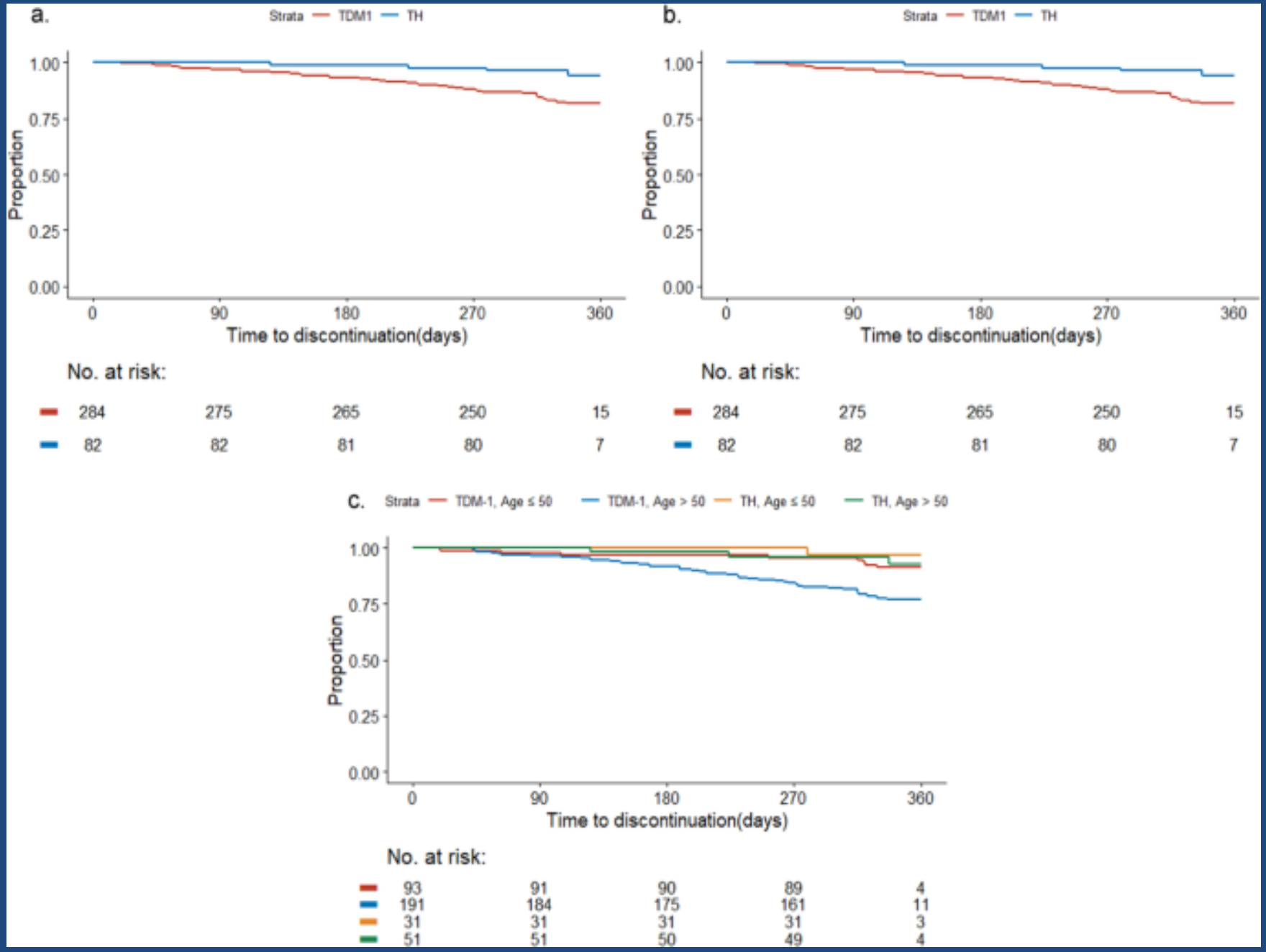

Assessed for eligibility (n=696)
Excluded (n=184)
• Not meeting inclusion criteria (n=130)
• Patient decided to not participate (n=44)
• Other reasons (n=10)
Randomized (n=512)
Arm 1: T-DM1
Arm 2: TH
Allocated to intervention (n=384)
• Received intervention (n=383)
• Did not receive intervention (n=1)
○ Withdrew consent (n=1)
Allocation
Allocated to intervention (n=128)
• Received intervention (n=114)
• Did not receive intervention (n=14)
○ Withdrew consent (n=13)
Excluded from analysis (n=1)
• Did not receive intervention
Excluded from analysis (n=14)
• Did not receive intervention
Analysis Population (n=383)
• Completed therapy (n=293)
• Unacceptable toxicity (n=67)
• Patient withdrew consent (n=7)
• Other (n=16)
Lost to follow-up (n=0)
Follow-Up
Analysis Population (n=114)
• Completed therapy (n=97)
• Unacceptable toxicity (n=7)
• Patient withdrew consent (n=6)
• Other (n=4)
Lost to follow-up (n=0)

# ATEMPT trial 5 year results and other updates

- 5.8 years follow up
  - T-DM1: 11 iDFS events; 3 distant recurrences, 3 non-related deaths, 3 contralateral HER2- breast cancers, 2 ipsilateral recurrences (1 HER2+)
    - Outcomes similar across HR and tumor size

| | T-DM1 (N=383) | TH (ATEMPT) (N=114) | TH (APT) (N=406) |
|---|---|---|---|
| 3-year iDFS | 97.8%<br>10 events | 93.4%<br>8 events | 98.5% |
| 5-year iDFS | 97.0%<br>11 events* | 91.1%<br>9 events | 96.3% |
| 5-year RFI | 98.3%<br>6 events | 93.2%<br>7 events | 98.1%<br>7 events |
| 5-year OS | 97.8%<br>3 events | 97.9% | 98.7%<br>5 events |
| 5-year BCSS | 99.4% | Not reported | 99.7%<br>1 event |

Table from Hurvitz SABCS 2022 Tarantino et al SABCS 2022 Tolaney et al. J Clin Oncol 2019


a.
Strata TDM1 TH
1.00
0.75
0.50
0.25
0.00
Proportion
0 90 180 270 360
Time to discontinuation(days)
No. at risk:
284 275 265 250 15
82 82 81 80 7
b.
Strata TDM1 TH
1.00
0.75
0.50
0.25
0.00
Proportion
0 90 180 270 360
Time to discontinuation(days)
No. at risk:
284 275 265 250 15
82 82 81 80 7
c.
Strata TDM-1, Age ≤ 50 TDM-1, Age > 50 TH, Age ≤ 50 TH, Age > 50
1.00
0.75
0.50
0.25
0.00
Proportion
0 90 180 270 360
Time to discontinuation(days)
No. at risk:
93 91 90 89 4
191 184 175 161 11
31 31 31 31 3
51 51 50 49 4

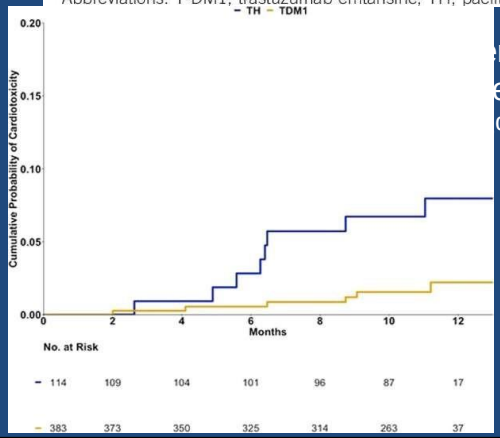
# Toxicities

**TABLE 2.** Clinically Relevant Toxicities

| Clinically Significant Toxicity | Arm 1: T-DM1 (n = 383), No. (%, 95% CI) | Arm 2: TH (n = 114), No. (%, 95% CI) | Overall (N = 497), No. (%, 95% CI) |
|---|---|---|---|
| Grade 3 or higher nonhematologic toxicity | 36 (9, 7 to 13) | 13 (11, 7 to 19) | 49 (10, 8 to 13) |
| Grade 2 or higher neurotoxicity | 42 (11, 8 to 14) | 26 (23, 16 to 31) | 68 (14, 11 to 17) |
| Grade 4 or higher hematologic toxicity | 4 (1, 0 to 3) | 0 (0, 0 to 3) | 4 (1, 0 to 2) |
| Febrile neutropenia | 0 (0, 0 to 1) | 2 (2, 0 to 6) | 2 (0, 0 to 1) |
| Any toxicity requiring dose delay | 106 (28, 23 to 32) | 30 (26, 19 to 35) | 136 (27, 24 to 31) |
| Any toxicity requiring early discontinuation of protocol therapy | 67 (17, 14 to 22) | 7 (6, 3 to 12) | 74 (15, 12 to 18) |
| Serious adverse event | 11 (3, 2 to 5) | 6 (5, 2 to 11) | 17 (3, 2 to 5) |
| Total | 177 (46, 41 to 51) | 54 (47, 38 to 56) | 231 (46, 42 to 51) |

Abbreviations: T-DM1, trastuzumab emtansine; TH, paclitaxel plus trastuzumab.

G2+ neurotox 11% vs 23% G4+ hematology tox 1% vs 0% Tox requiring early dc 17 vs 6% SAE 3% vs 5%




nt (G3-
eline &
%

18-month chemotherapy related amenorrhea rate among a subgroup of 76 premenopausal women without GnRH agonist, oophorectomy, or hysterectomy and with menstrual survey data:
50% after TH, 24% after T-DM1
p=0.045

Tolaney et al. J Clin Oncol 2021 Ruddy et al. BCRT 2021 Barroso-Sousa et al. NPJ 2022

# Cardiac toxicity

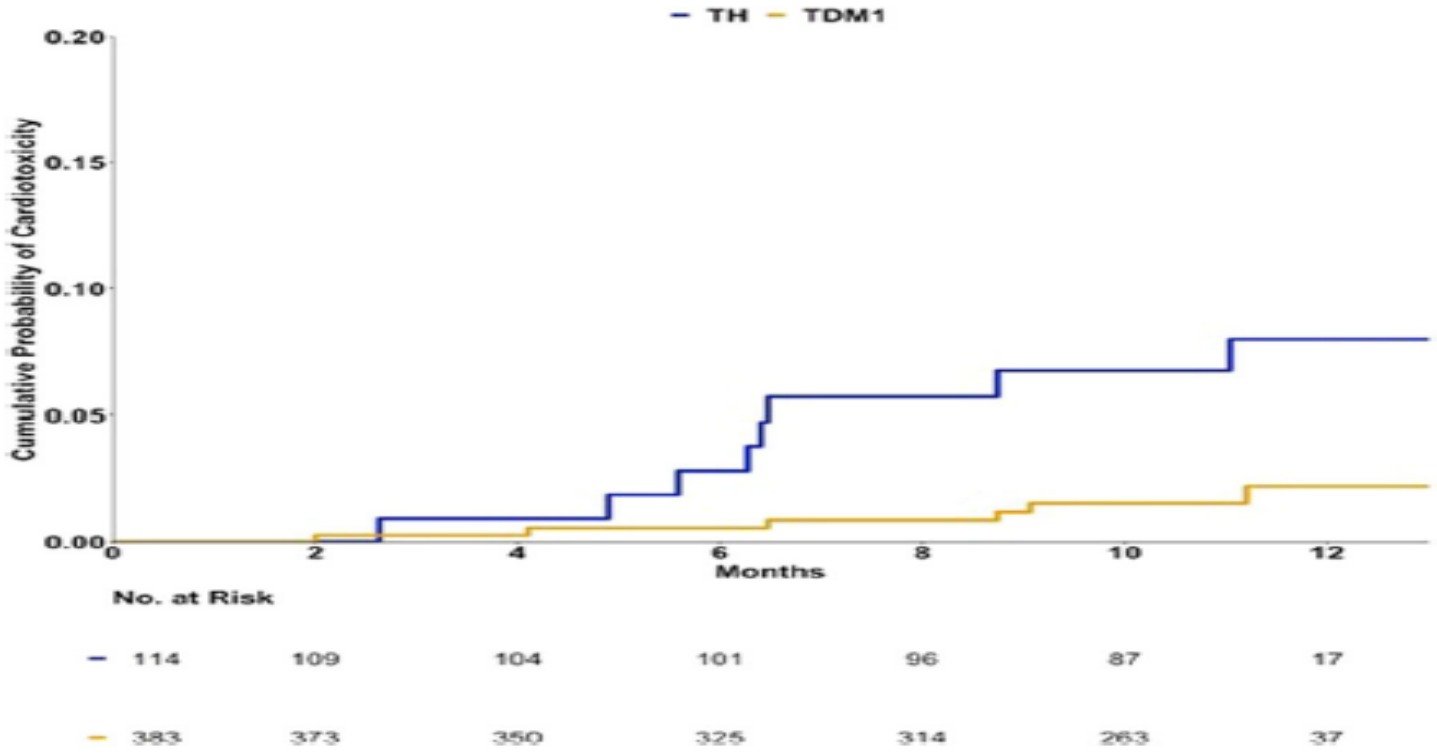
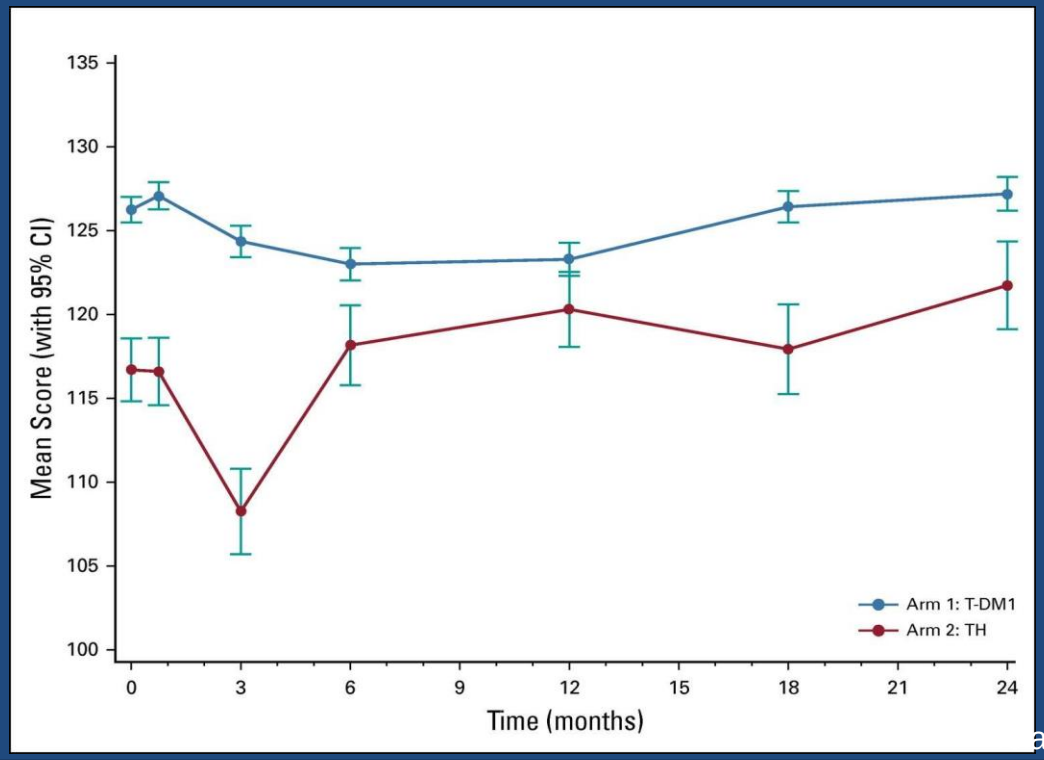



**Fig. 2 Kaplan–Meier estimate of the cumulative probability of a cardiotoxicity# event during the treatment period.** Probability of cardiotoxicity by 6 months: TH: 0.03 (95% CI: 0–0.06); T-DM1: 0.01 (95% CI: 0–0.01). Probability of cardiotoxicity by 12 months: TH: 0.08 (95% CI: 0.02–0.13); T-DM1: 0.02 (95% CI: 0–0.04). Cardiotoxicity here

# Patient reported outcomes




aney et al J Clin Oncol 2021

# Stage 1 HER2+ breast cancer

National Comprehensive Cancer Network®

## NCCN Guidelines Version 1.2023
## Breast Cancer

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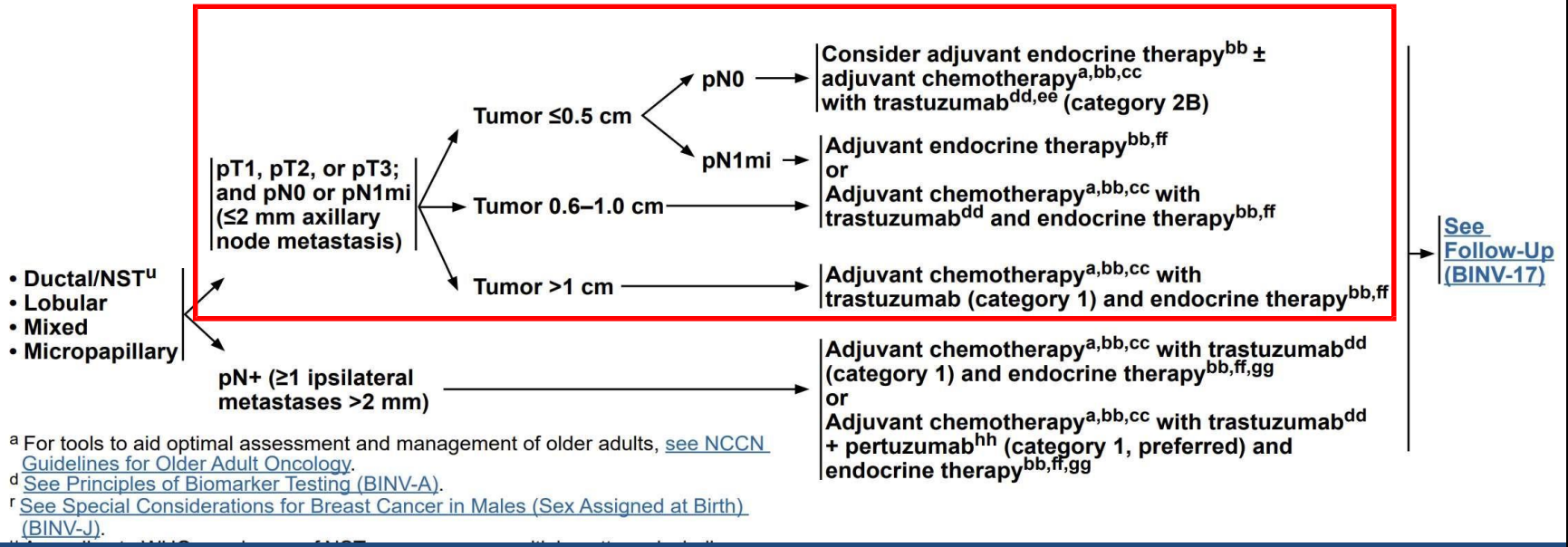
**SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-POSITIVE DISEASE[d,r,z]**




[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[r] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).

# T1aN0 tumors

- NCCN Guidelines:
  - The prognosis of patients with pT1a and pT1b tumors that are pN0 is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.
  - Adjuvant chemotherapy with weekly paclitaxel and trastuzumab can be considered for pT1,N0,M0, HER2-positive cancers, particularly if the primary cancer is HR-negative. The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with HR-positive cancers and tumor size bordering on T1mic (<1 mm), when the estimated recurrence risk is less than 5% and endocrine therapy remains a viable option for systemic treatment.

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# NCCN Guidelines Version 1.2023
# Breast Cancer

## PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

### HER2-Positive

**Preferred Regimens:**

- Paclitaxel + trastuzumab[h]
- TCH (docetaxel/carboplatin/trastuzumab)
- TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)
- If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab.
- If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j]

**Useful in Certain Circumstances:**

- Docetaxel + cyclophosphamide + trastuzumab
- AC followed by T[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- AC followed by T[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules)
- Neratinib[i] (adjuvant setting only)
- Paclitaxel + trastuzumab + pertuzumab[j]
- Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)

**Other Recommended Regimens:**

- AC followed by docetaxel[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab)
- AC followed by docetaxel[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)