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UNC CANCER CARE

Research To Practice Satellite Symposium
2019 AACR-SABCS

Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer Receiving Neoadjuvant Systemic Therapy

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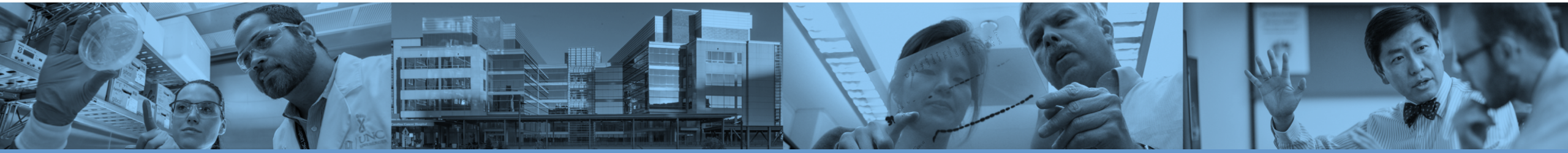


Disclosures

No relevant conflicts of interest to disclose.

Case Presentation: Dr Brufsky

A 36-year-old woman with no FHx of breast cancer who presented with a 4 cm palpable right breast mass. Ultrasound guided core biopsy was remarkable for IDC, ER 50% PR 0% HER2 3+ by IHC. There was no clinical evidence of distant metastases, and echo EF was 60%. Genetic testing (expanded panel) was negative.

She received TCHP x 6 cycles with clinical response of her cancer (1 cm of residual palpable mass). She had a bilateral mastectomy with 0.5 cm of residual IDC, ER 50% PR 0% HER2 3+ and 0/2 SLN positive.

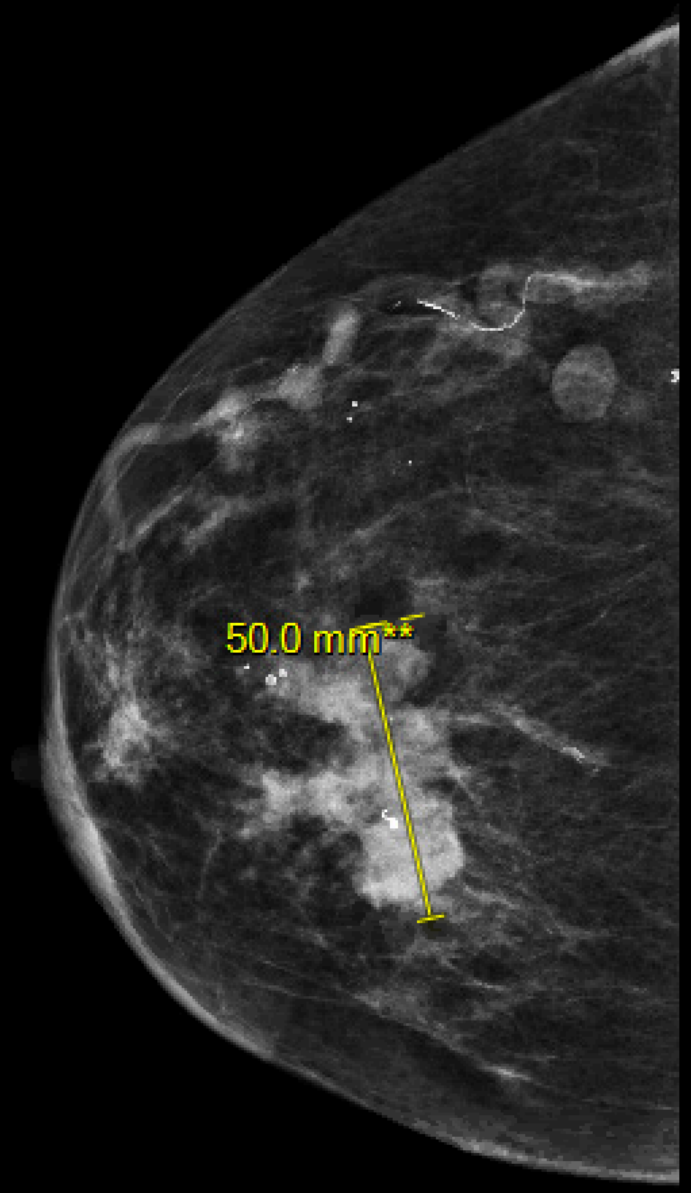
Questions:

1. Would you give her adjuvant T-DM1?
2. Would you give her adjuvant neratinib?

Case Presentation: Dr Carey

- 85 yo otherwise healthy retired teacher from NC mountains ~ 2.5h away. Transportation issues.
- Clinical T3N1 IDC right breast; ER40%, PR20%, HER2+. Erythema without peau d'orange, > 2cm axillary LN.
- *Nab*-paclitaxel denied, Rx dose-reduced docetaxel + HP x 4 cycles complicated by diarrhea despite prophylaxis and management, at breast conserving surgery had ypT1aN0 disease. Planning H + AI out back without pertuzumab and without T-DM1.

Questions for other faculty: What is your algorithm regarding pertuzumab in neoadjuvant setting for pCR purposes, adjuvant setting for EFS purposes? How do you approach older patient with aggressive but curable HER2+ disease?



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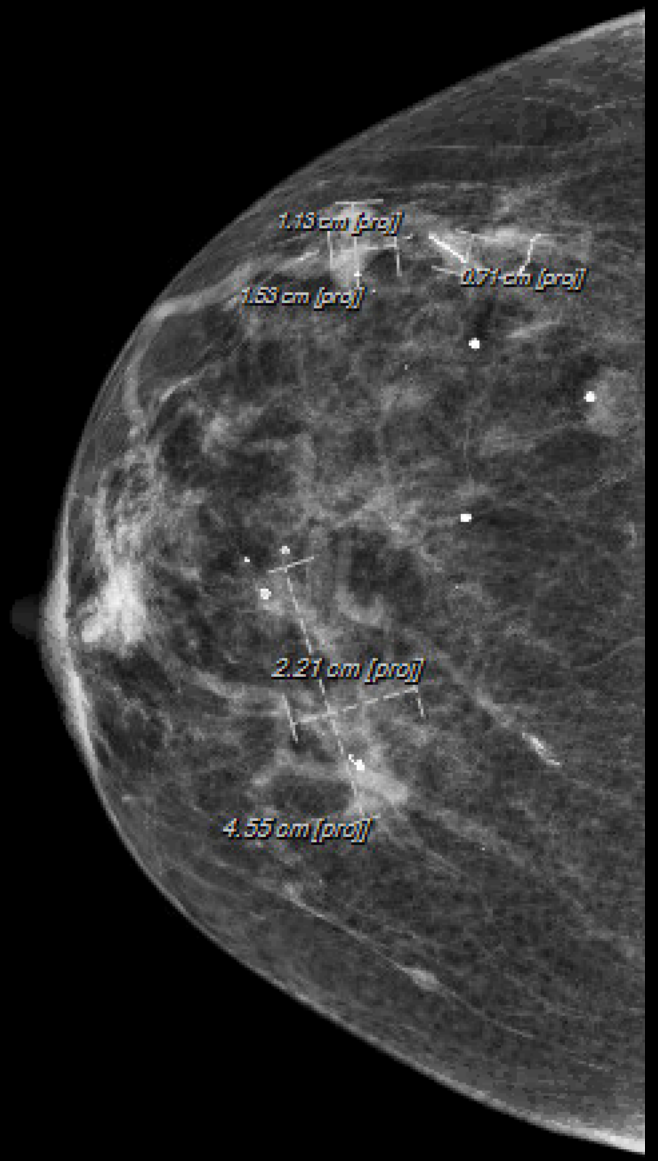

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Questions To Consider

- Optimal chemotherapy backbone?
- Implications of pCR
- Implications of RD
- De-escalation and escalation opportunities

Anthracycline or Non-Anthracycline-based Regimens

In pre-trastuzumab era, HER2+ breast cancers benefited particularly from anthracyclines.

Does this still matter in HER2-targeting era?

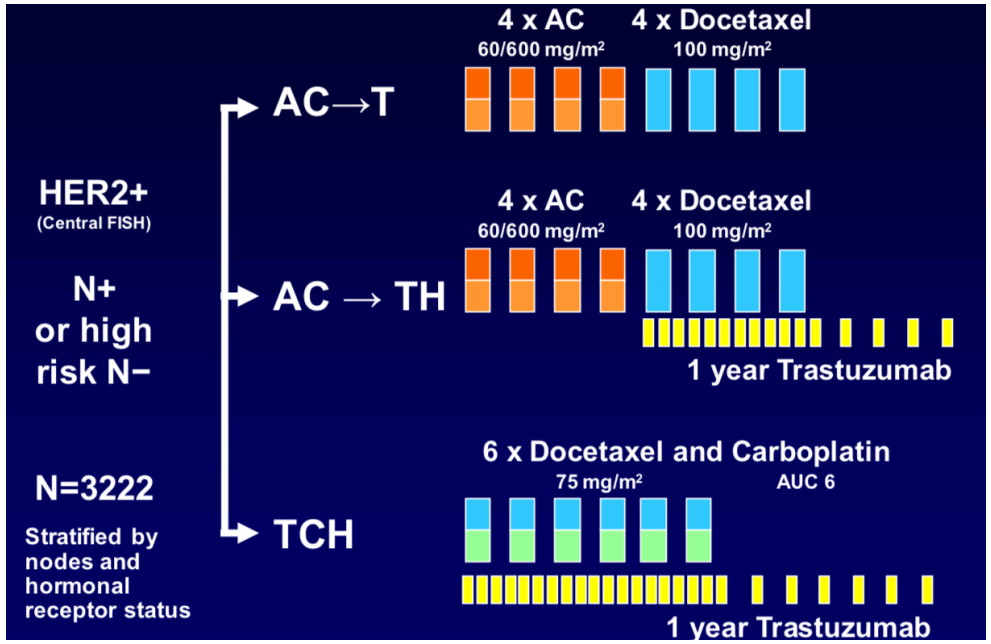
Anthracyclines have small but real risk of cardiotoxicity (and leukemia).

- ***EF ↓ below normal during AC: ~2%***
- ***Long-term:***
  - ***BCIRG006: 6% persistent EF decline, 2% CHF with ACTH***
  - ***N9831: 3% CHF in H arms, most recovered***
- ***Cardiac risk factors matter (age, antihypertensives, baseline EF, etc)***

Slamon D, NEJM 2011; Perez E, JCO 2008; Perez E, JCO 2016

Main Options and Implications

- **AC-TH(P) or TCH(P)**
  - ***Pertuzumab RFS benefit > 2% in ER-negative or N+***
- **Only trial with both = BCIRG 006:**



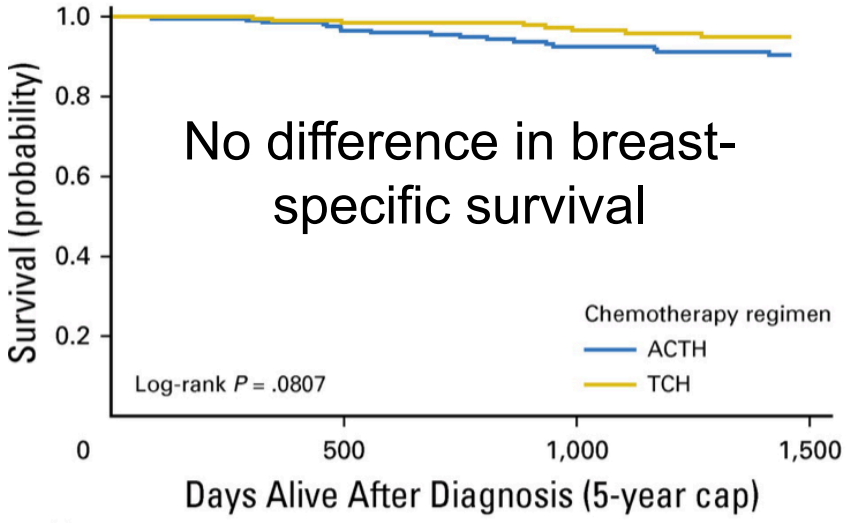
	AC-T (N=1073)	ACTH (N=1074)	TCH (N=1075)
Total events	201 (19%)	146 (14%)	149 (14%)
Distant mets	188 (18%)	124 (11.5%)	144 (13.4%)
CHF	7 (0.7%)	21 (2.0%)	4 (0.4%)
Acute leukemia	6 (0.6%)	1 (0.1%)*	1 (0.1%)

(*0.2% in B31/N9831)

Slamon et al, NEJM 2011

Real World Data

- **SEER/Medicare data (≥65yo), 2005-2013, including propensity-matched group**



ACTH used in higher risk,
TCH used in more comorbid patients

H completion better in TCH (89% vs 77%)
Hospitalization more in TCH (even with matching)

Did not include pertuzumab

APT for stage I, esp ER+ HER2+
If polychemo needed - Either AC-TH(P) or TCH(P) is reasonable

I tend to use TCH(P) except when concerned re HER2 status.

Reeder-Hayes, JCO 2017

Neoadjuvant Therapy

- Off-trial should mimic adjuvant choices

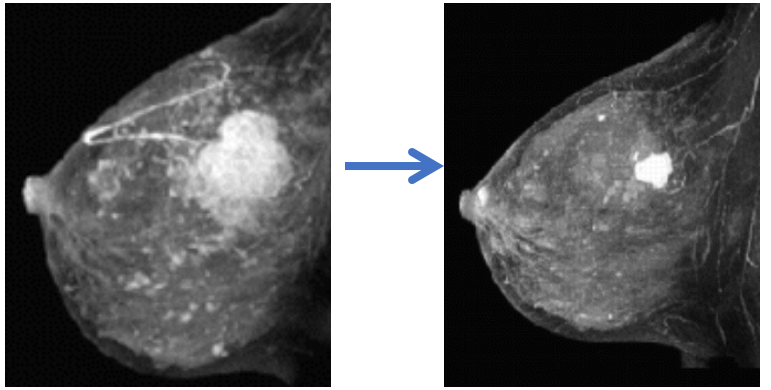
- Excellent arena for testing new regimens and drugs

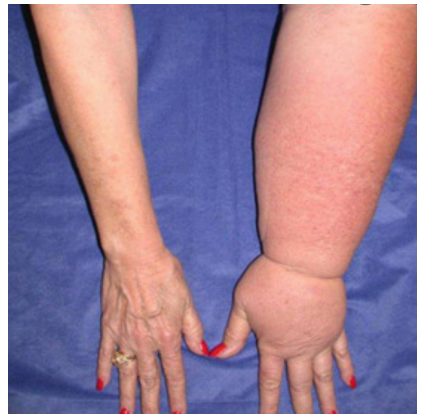
  De-escalating using pCR

  Escalating in RD

Leveraging Neoadjuvant Therapy 1: Surgical Endpoints

- Original indication = improved operability
- NSABP-B-18 (and others) confirmed no distant disease sacrifice
- Axillary management clearly improved
  - N+ changed to N- in 35-68%
  - ACOSOG Z1071: Post-NAC SN feasible and accurate (if careful - dual tracer, > 2 retrieved SN)





Lymphedema:

10-20%

with axillary dissection

Fisher B, JCO 1997; Boughey JC JAMA 2014; Pilewskie & Morrow JAMA Oncol 2017

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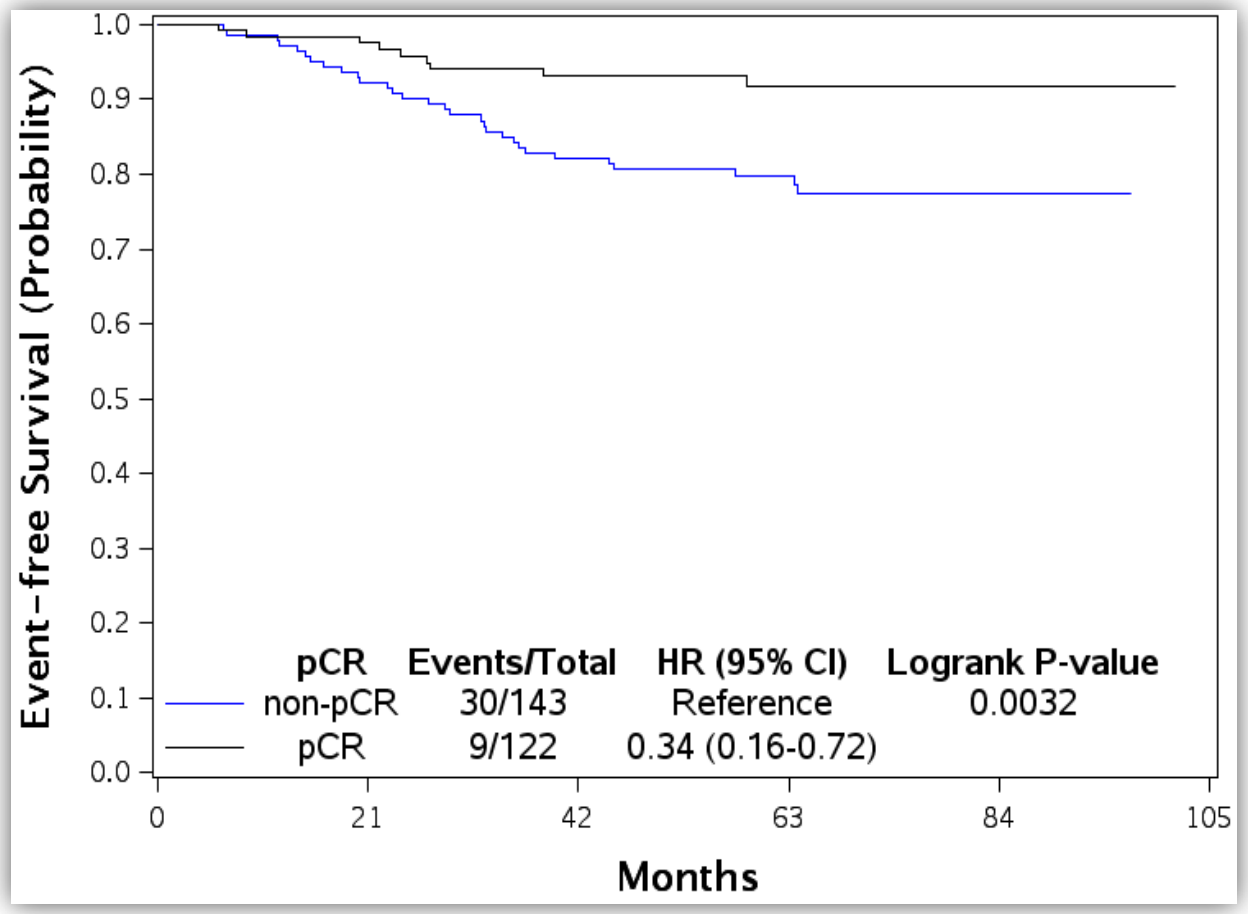
Leveraging Neoadjuvant Therapy 2: Risk Stratification



Pathologic complete response (pCR)

Residual disease (RD)

Strong consistent relationship between pCR and relapse/survival in multiple trials

Although…

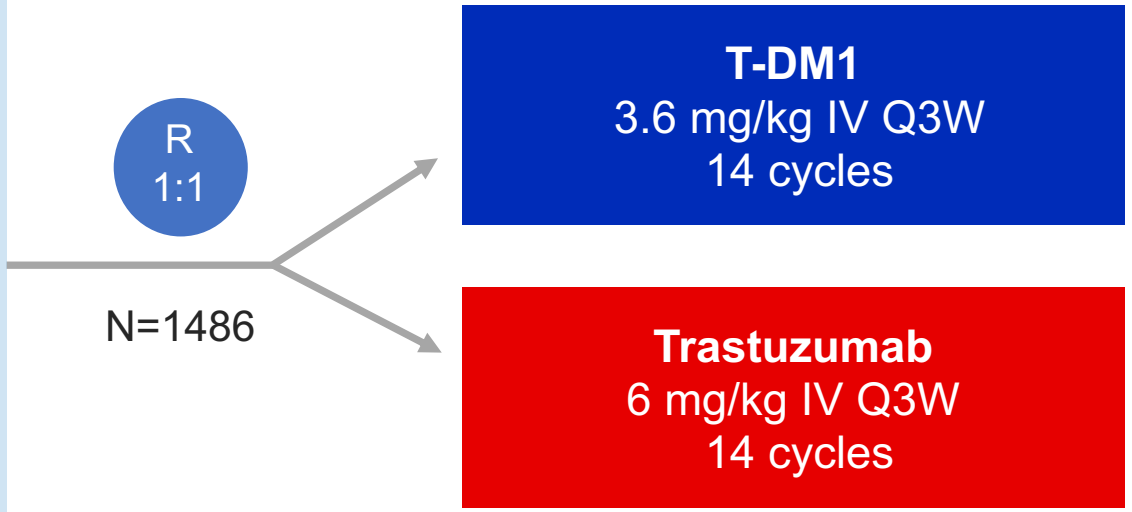
Some pCR relapse

Many RD don't relapse

Krop et al, AACR-SABCS 2017

Phase III Study of T-DM1 vs Trastuzumab as Adjuvant Therapy in Pts with HER2+ EBC with Residual Invasive Disease after NAC and HER2-Targeted Therapy Including Trastuzumab: Primary Results from KATHERINE (NSABP-B-50, GBG-77)

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 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



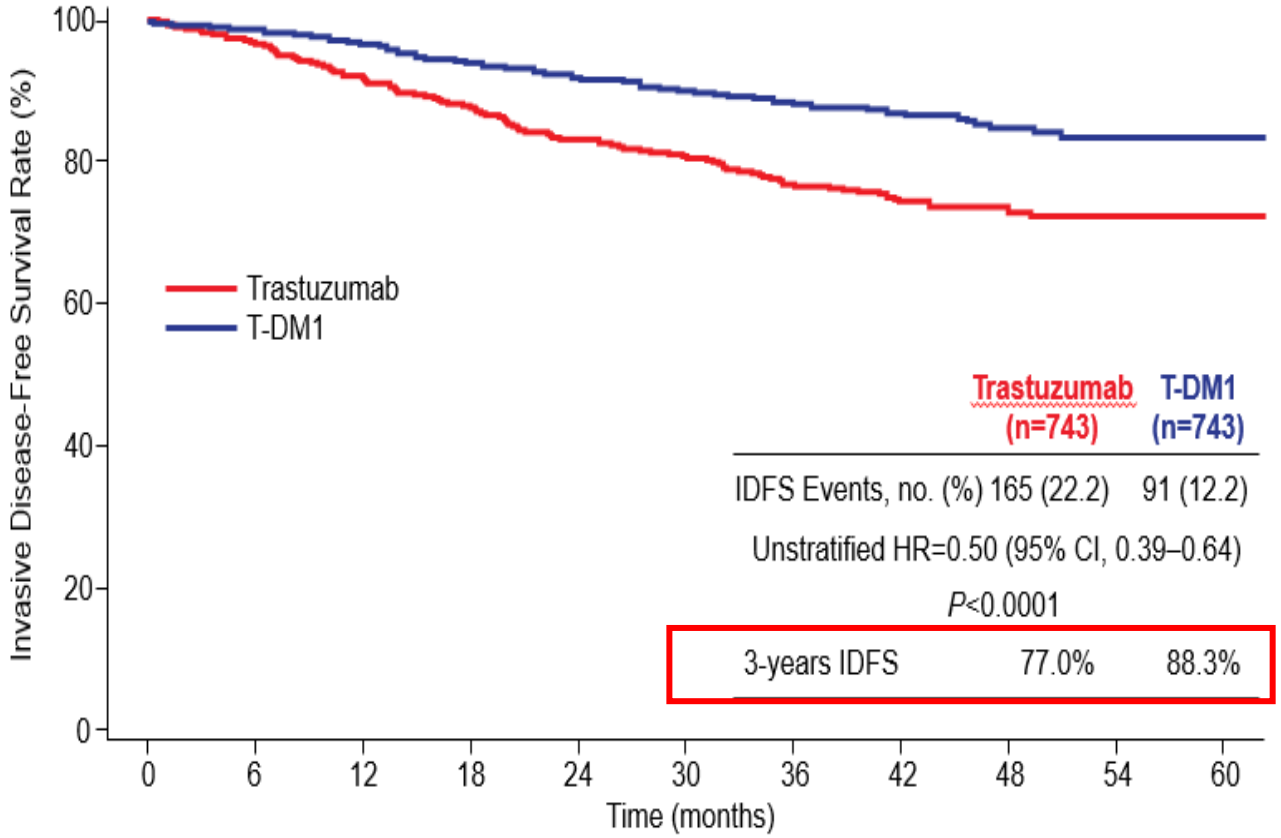
Radiation and endocrine therapy per protocol and local guidelines

Primary endpoint: IDFS (70 to 76.5%), boundary HR < 0.732, $p < 0.0124$
First interim OS analysis to be done at interim IDFS if boundary crossed

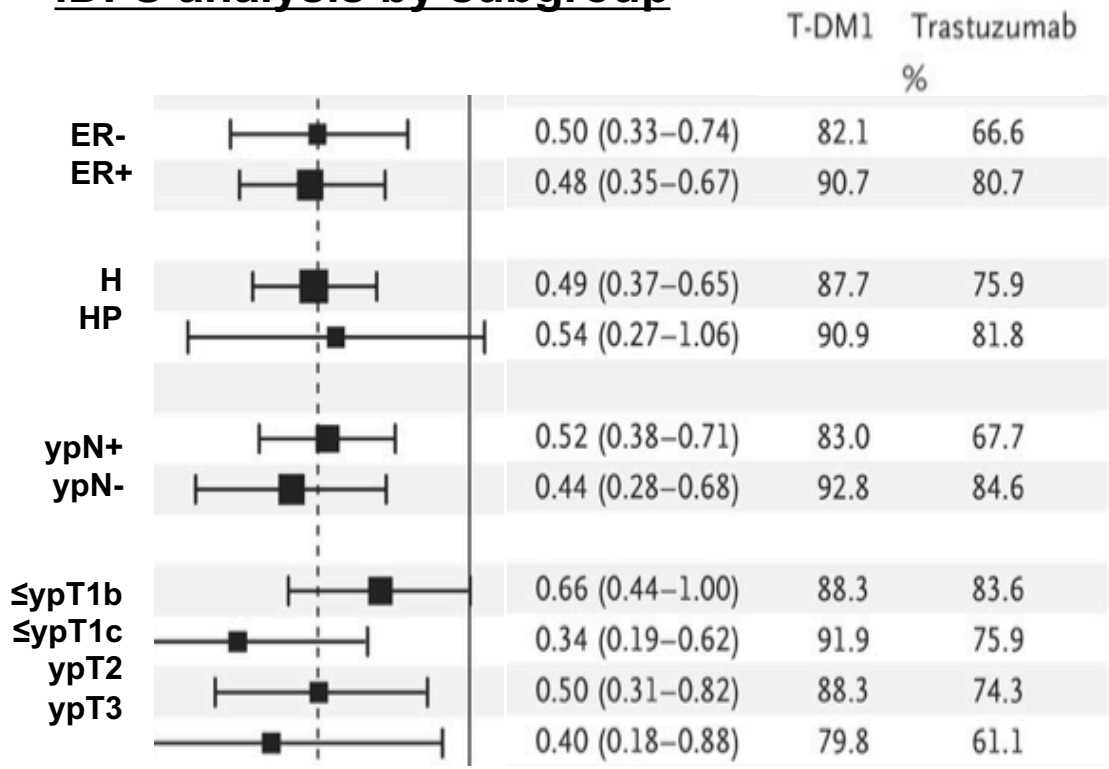
Stratification factors: clinical presentation, HR status, type of preoperative therapy and pathological nodal status after neoadjuvant therapy

Geyer CE Jr et al, SABCS 2018;Abstract GS1-10; von Minckwitz G et al, NEJM 2019;380(7):617-28.

KATHERINE: Escalating Rx in Residual Disease



iDFS analysis by subgroup

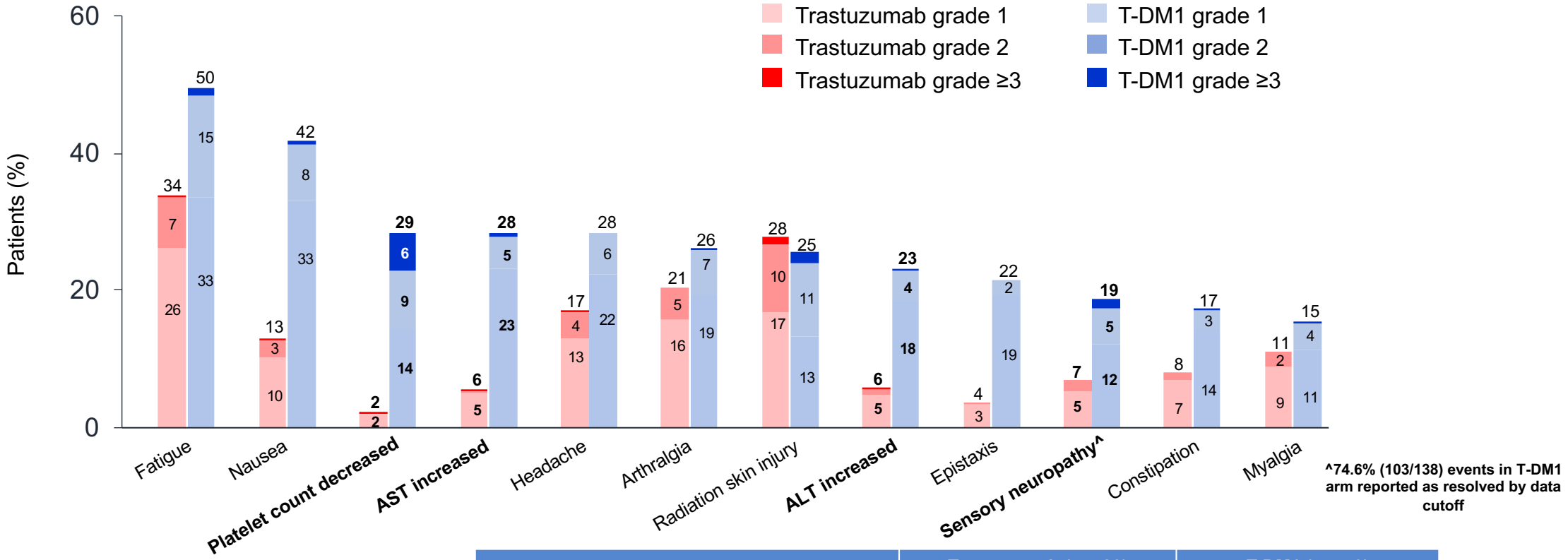


- **EFS ER-, LN+ still 82-83%**
- **Very few received pertuzumab**

- OS did not cross the early reporting boundary (HR 0.70)

Von Minkwitz et al, NEJM 2018

KATHERINE: All Grade AEs ≥15% Incidence in Either Arm



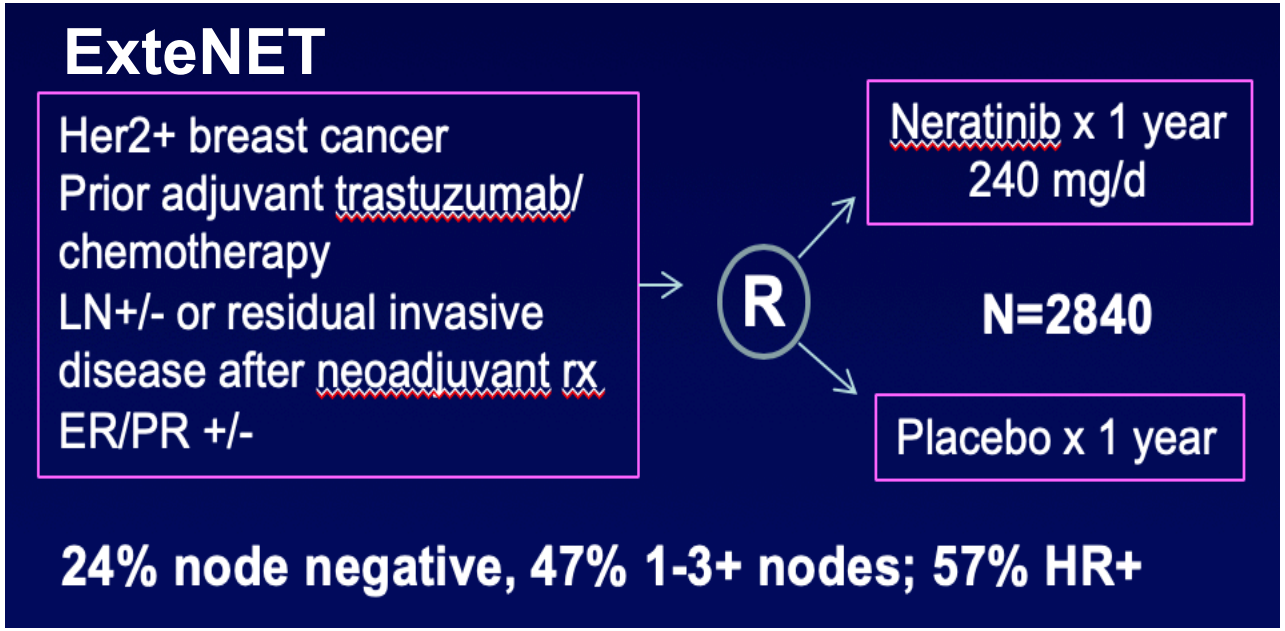
Exposure to Study Treatment

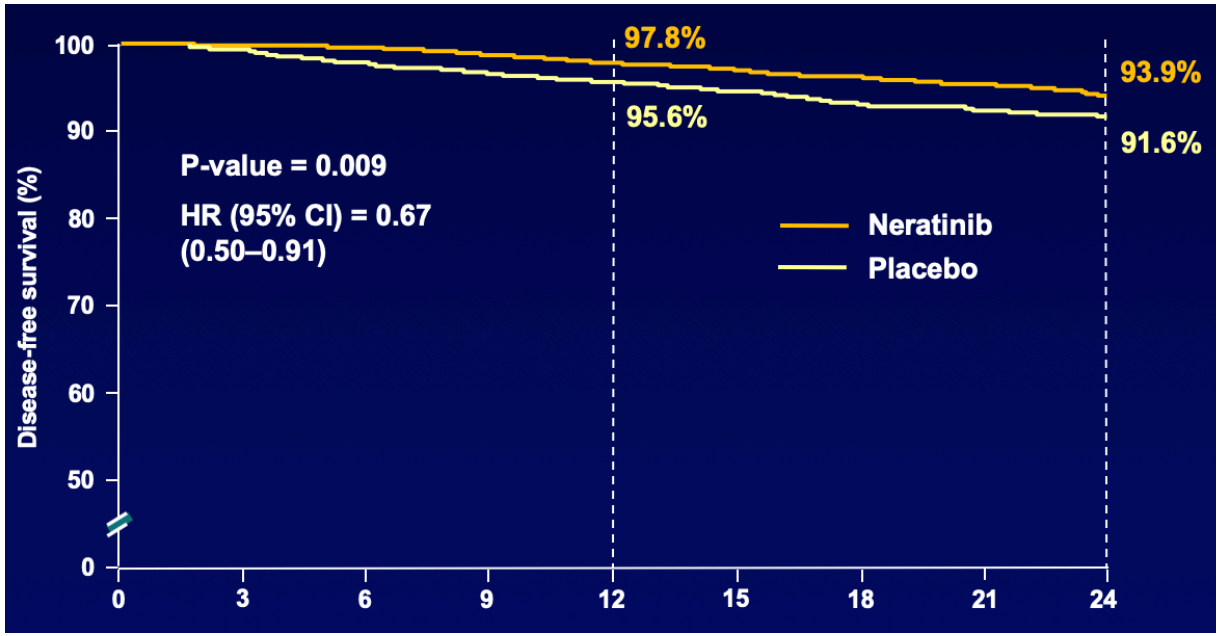
2% (trastuzumab) vs 18% (T-DM1) discontinued due to adverse events

	Trastuzumab (n=720)	T-DM1 (n=740)
Cycles of trastuzumab/T-DM1 completed, n (%)		
7 cycles	664 (92.2)	637 (86.1)
14 cycles	583 (81.0)	528 (71.4)
Patients with a dose reduction, n (%)		
No dose reduction	N/A	634 (85.7)
One dose level reduction (3.0 mg/kg)	N/A	77 (10.4)
Two dose level reductions (2.4 mg/kg)	N/A	29 (3.9)
Completed 14 cycles of any study treatment	583 (81.0)	593 (80.1)

Geyer CE Jr et al. SABCS 2018;Abstract GS1-10.

Other Escalation Options: Neratinib Year 1-2





- 2-3% Δ, 40% gr3+ diarrhea (better strategies now)
  - ~4% Δ in ER+

However:

- Few received pertuzumab
- Unclear role in tailored RD era

Chan A, Lancet Oncol 2016

De-Escalation and Escalation: COMPASS Trials

Eligibility
HER2+ BC
Stage 2 or 3a
(T2-3, N0-2)
Newly dx, no prior therapy

Registration

Part 1 preop
THP x 4 (12 wks)

Surgery

Part 1 pCR
(~40-45%)
No further chemo

Part 2 RD
(~55%)

ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA1181

SOC chemo

Eligibility
HER2+ RD
Any ER-
ER+ if N+
~ 50% Part 1, 50% outside enrollees

Registration

Alliance for Clinical Trials in Oncology

- T-DM1 + placebo x 14 cycles
- T-DM1 + tucatinib x 14 cycles

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Primary Objectives:
3y RFS
Secondary Objectives:
3y RFS by intrinsic subtype

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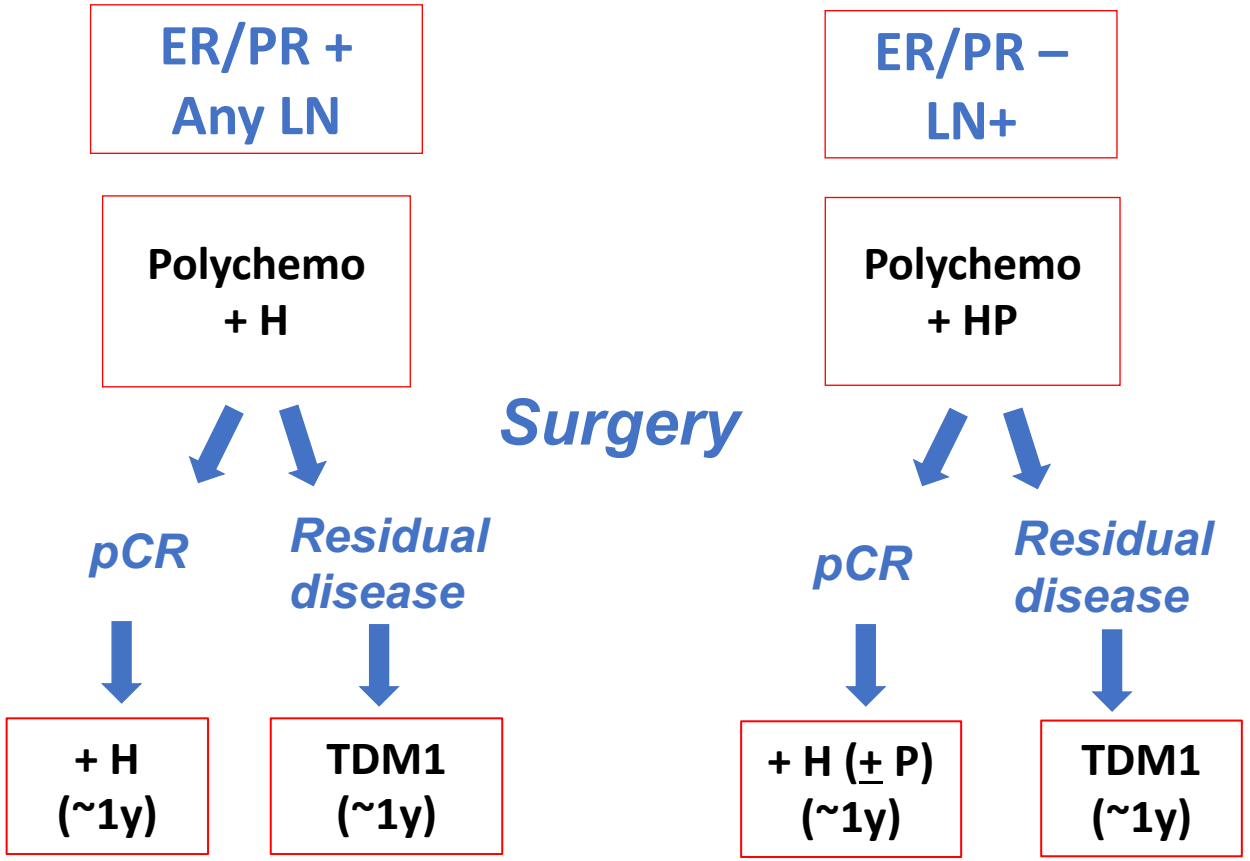
HER2-Directed Strategies in Early Breast Cancer

Neoadjuvant



H=trastuzumab, P=pertuzumab, N=neratinib