Improving Outcomes in HER2+ Breast Cancer: Analysis and Application of Evolving Data and Best Practices

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Welcome and Introductions

Financial Disclosures

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- Nothing to disclose

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Product Disclosure

This activity may include discussion of agents that have not yet been approved by the U.S. Food and Drug Administration and investigational uses of approved products. Please consult prescribing information and practice guidelines for detail regarding safe and effective use of therapeutic agents.

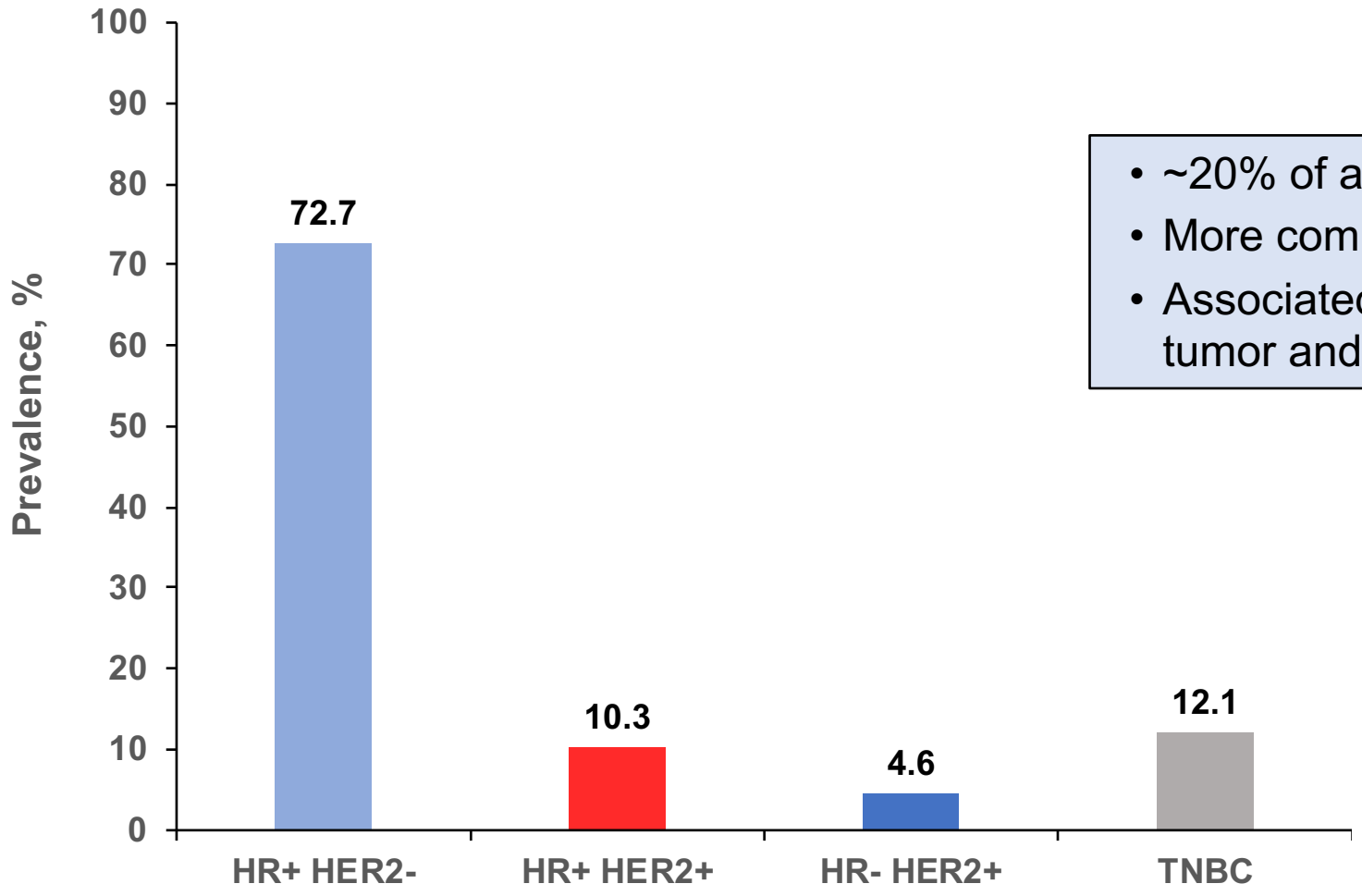
Learning Objectives

At the conclusion of this continuing education activity, the oncology advanced practice provider will be better able to:

1. Evaluate the clinical significance of existing and emerging data for current and investigational therapies for HER2+ breast cancer (BC).
2. Devise a plan for managing central nervous system (CNS) metastases in patients with HER2+ BC.
3. Manage adverse events associated with treatments for HER2+ BC.

Current Standards of Care

Incidence of HER2+ Breast Cancer



- ~20% of all breast cancers are HER2+
- More common in younger patients
- Associated with a more aggressive tumor and poorer prognosis

Howlader N, et al. *J Natl Cancer Inst.* 2014;106; Baselga J, et al. *N Engl J Med*. 2012;366:109-9.

HR, hormone receptor; TNBC, triple-negative breast cancer.

Current Standards of Care for HER2+ Breast Cancer

Early-Stage (Adjuvant and Neoadjuvant)

- Trastuzumab+ chemotherapy
- Trastuzumab + pertuzumab + chemotherapy

Post-Neoadjuvant Residual Disease

- T-DM1

MBC

- 1st-line: taxane + trastuzumab + pertuzumab
- 2nd-line: T-DM1 (trastuzumab emtansine)
- 3rd-line: lapatinib + capecitabine

Neoadjuvant Therapy

Case Study

- 54-year-old patient who presented with a 3-cm palpable mass 3 months after her last mammogram
- Biopsy-confirmed invasive ductal cancer, grade 3, ER/PR-, and HER2+ by IHC (3+)

Treatment options?

A. Refer the patient for surgery
B. Neoadjuvant chemotherapy with docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP)
C. Adjuvant chemotherapy with TCHP
D. All of the above

Tryphaena Phase II Trial

Pertuzumab + Trastuzumab for Inflammatory or Early-stage HER2+ Breast Cancer

- Multicenter study to evaluate safety of neoadjuvant pertuzumab + trastuzumab plus chemotherapy for HER2+ early-stage breast cancer
  - 6% of patients had inflammatory cancer, 25% locally advanced cancer, 69% operable cancer
  - Approximately half the patients in each treatment group had ER+ and/or PgR+ disease
- Patients with operable, locally advanced, or inflammatory breast cancer were randomized to receive 6 neoadjuvant cycles q3wk
  - Arm A: FEC + H + P ×3 → docetaxel [T] + H + P ×3
  - Arm B: FEC ×3 → T + H + P ×3
  - Arm C: T + carboplatin + H [TCH] + P ×6
- Adjuvant therapy administered to complete 1 year of H

Schneeweiss A, et al. *Ann Oncol*. 2013;24:2278-84.

Tryphaena Phase II Trial

Pertuzumab + Trastuzumab for Inflammatory or Early-stage HER2+ Breast Cancer

3-yr follow-up:

Regimen	3-yr DFS (95% CI)	3-yr PFS (95% CI)
Arm A (FEC + H + P ×3 → T + H + P ×3)	87% (79-95)	89% (81-96)
Arm B (FEC ×3 → T + H + P ×3)	88% (80-96)	89% (81-96)
Arm C (TCHP)	90% (82-97)	87% (80-95)

- Patients who achieved total pathCR had improved DFS vs none (HR 0.27; 95% CI 0.11-0.64)
- PathCR rates were significantly higher in patients with hormone receptor (HR)-negative tumors (eg, 73% vs 41% in Arm A)

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

DFS, disease-free survival; pathCR, pathologic complete response; PFS, progression-free survival.

Tryphaena Phase II Trial

Pertuzumab + Trastuzumab for Inflammatory or Early-stage HER2+ Breast Cancer

Cardiac Safety

Regimen	Left Ventricular Systolic Dysfunction (any grade)	Left Ventricular Ejection Fraction Declines*
Arm A (FEC + H + P ×3 → T + H + P ×3)	2/72 (2.8%)	8 (11.1%)
Arm B (FEC ×3 → T + H + P ×3)	3/75 (4.0%)	12 (16.0%)
Arm C (TCHP)	4/76 (5.4%)	9 (11.8%)

- During long-term post-treatment follow-up.

* ≥10% from baseline to <50%.

Schneeweiss A, et al. *Ann Oncol*. 2013;24:2278-84.

NeoSphere Phase II Trial

Pertuzumab + Trastuzumab for Inflammatory or Early-Stage HER2+ Breast Cancer

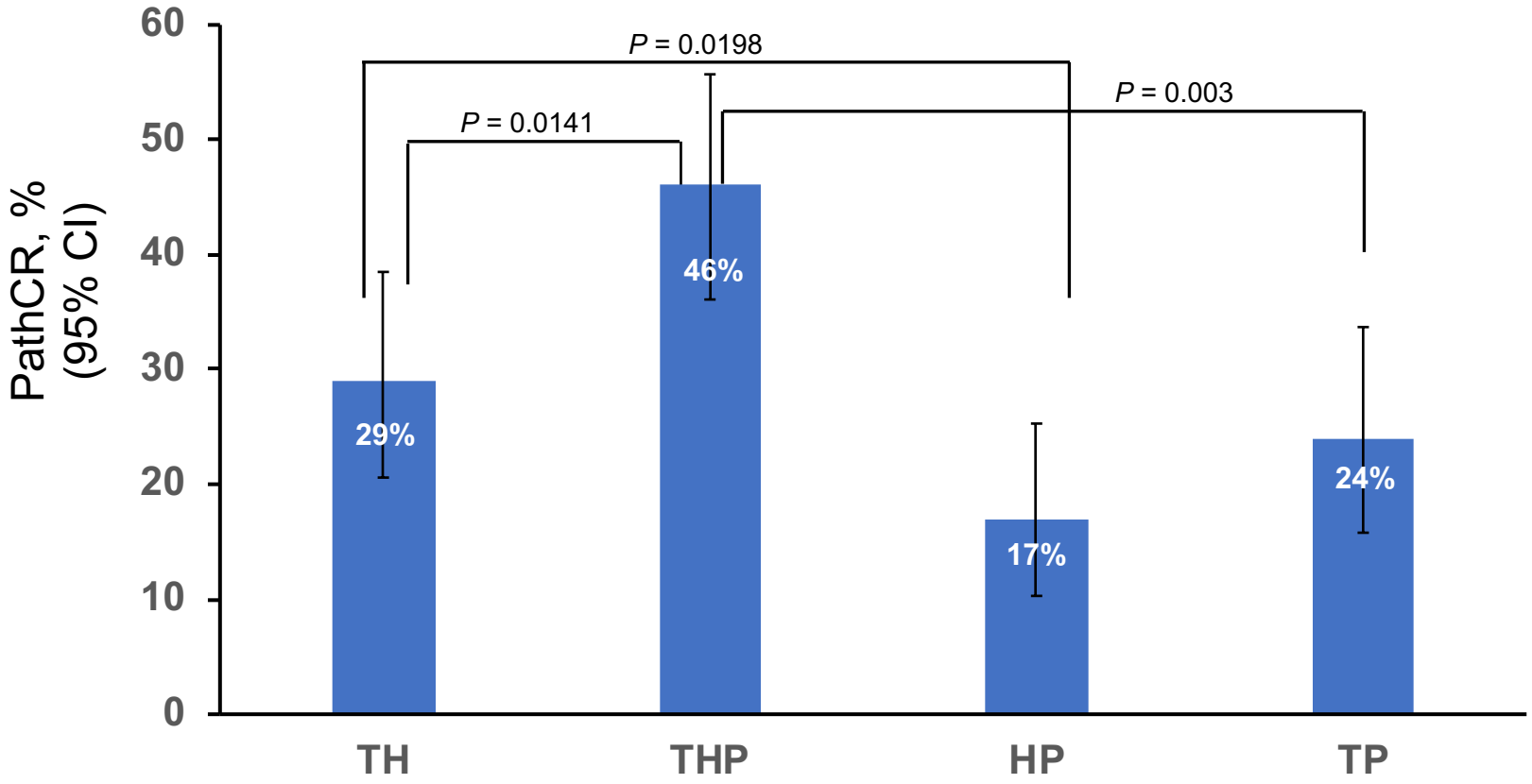
- Multicenter, open-label, randomized trial
- Treatment-naive adults with locally advanced, inflammatory, or early-stage HER2+ breast cancer
- Patients received four neoadjuvant cycles of:
  - Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg q3wk) plus docetaxel
  - Pertuzumab (840 mg loading dose, followed by 420 mg q3wk) and trastuzumab plus docetaxel
  - Pertuzumab and trastuzumab, *or*
  - Pertuzumab and docetaxel
- After surgery, patients received 3 cycles of FEC and trastuzumab for total of 1 year of therapy (17 cycles)

Gianni L, et al. *Lancet Oncol*. 2012;13:25-32.

NeoSphere Phase II Trial

Pertuzumab + Trastuzumab for Inflammatory or Early-Stage HER2+ Breast Cancer

Pathologic Complete Response (primary outcome measure)



Gianni L, et al. *Lancet Oncol*. 2012;13:25-32.

H, trastuzumab; P, pertuzumab; T, docetaxel for 4 cycles followed by surgery, then 3 cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) and H for 1 yr.

NeoSphere Phase II Trial

Pertuzumab + Trastuzumab for Inflammatory or Early-Stage HER2+ Breast Cancer

- Addition of pertuzumab to trastuzumab/docetaxel significantly improved pathCR (primary outcome measure) vs trastuzumab/docetaxel alone (45.8% vs 29.0%)
  - 5-yr follow-up data confirmed pathCR benefit of neoadjuvant pertuzumab + trastuzumab, which was supported by longer PFS (86% vs 81%) and DFS (84% vs 81%)
- Data resulted in pertuzumab/trastuzumab-based therapy becoming a standard treatment option for early-stage HER2+ breast cancer
  - Total pathCR may prove to be an early indicator of long-term outcome in this patient population

Gianni L, et al. *Lancet Oncol*. 2012;13:25-32; Gianni L, et al. *Lancet Oncol*. 2016;17:791-800.

Case Study

- 54-year-old patient who presented with a 3-cm palpable mass 3 months after her last mammogram
- Biopsy-confirmed invasive ductal cancer, grade 3, ER/PR-, and HER2+ by IHC (3+)

Treatment options?

A. Refer the patient for surgery
B. Neoadjuvant chemotherapy with docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP)
C. Adjuvant chemotherapy with TCHP
D. All of the above

Adjuvant Therapy

Case Study

- 61-year-old patient underwent a routine mammogram, which showed a 1.1-cm spiculated mass
- Biopsy confirmed an invasive ductal cancer, ER/PR 80% and 20%, and HER2+ by IHC 3+
- Clinical stage T1cN0

Treatment options?

A. Neoadjuvant chemotherapy with TCHP
B. Refer to surgery and adjuvant paclitaxel and trastuzumab
C. T-DM1
D. Not sure

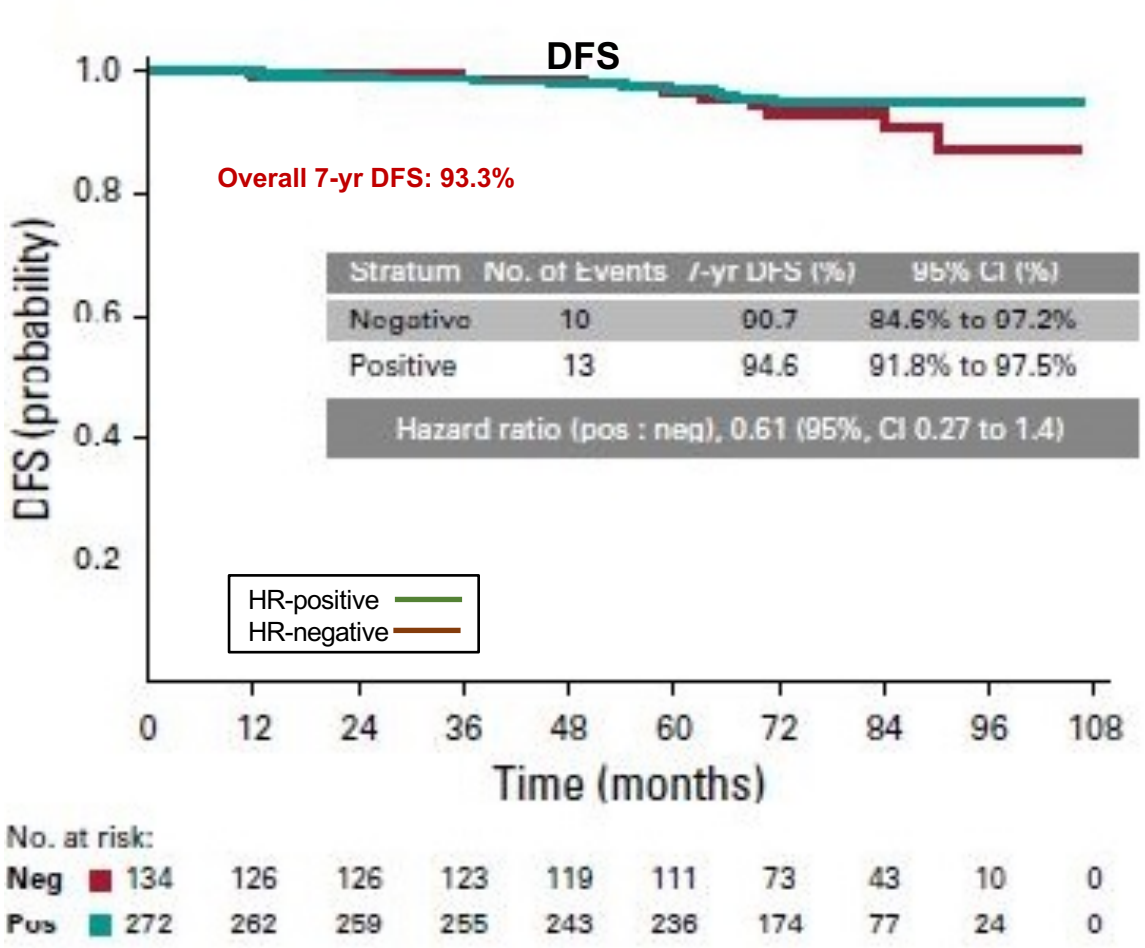
Adjuvant Paclitaxel + Trastuzumab (APT) for Node-negative, HER2+ Breast Cancer

- Patients (N = 406) with tumors ≤3 cm received weekly paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab monotherapy for 9 months
  - Median follow-up: 4.0 yr
- 3-yr iDFS: 98.7%
- 13 patients (3.2%) with ≥1 episode of Grade 3 neuropathy; 2 (0.5%) had symptomatic CHF
- 13 patients (3.2%) had significant asymptomatic declines in ejection fraction (11 could resume trastuzumab therapy after brief interruption)

Tolaney SM, et al. *N Engl J Med*. 2015;372:134-41.

CHF, congestive heart failure; iDFS, invasive disease-free survival.

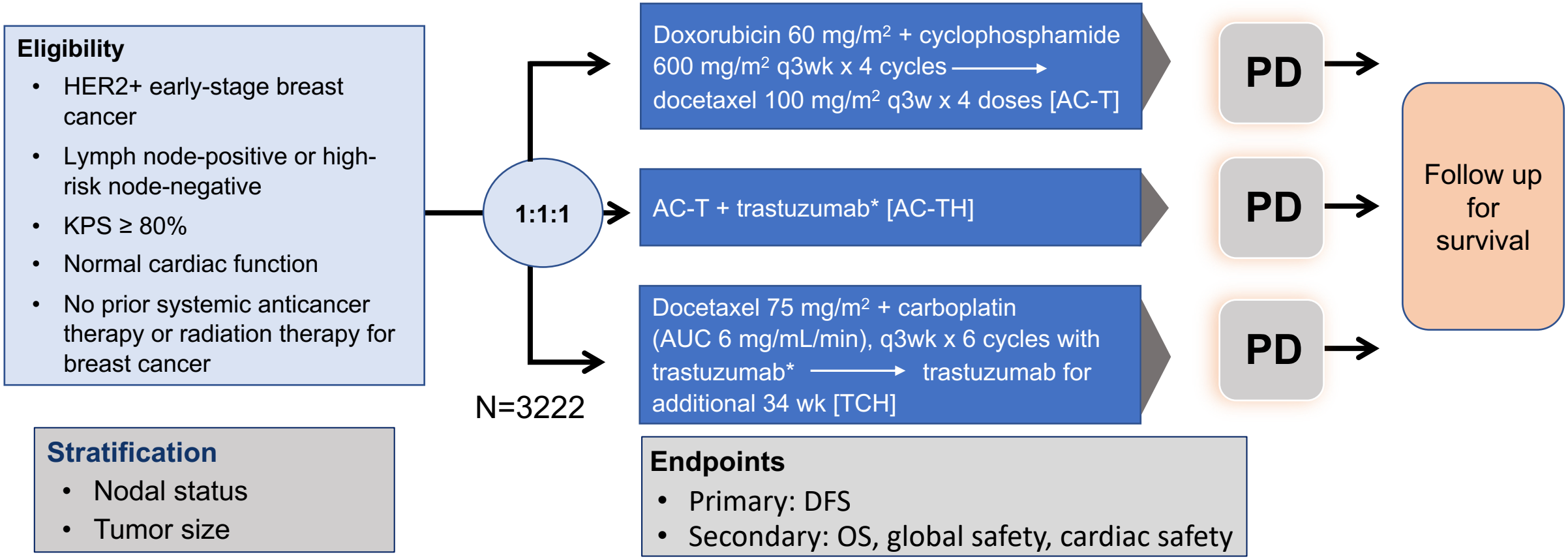
APT Trial: 7-Year Follow-up



Tumor Subtype	Overall Cohort (N = 278)	HR-Positive (n = 196)	HR-Negative (n = 82)
HER2-enriched	183 (66%)	114 (58%)	69 (82%)
Luminal A	38 (14%)	38 (19%)	2 (3%)
Luminal B	35 (12%)	33 (17%)	0
Basal-like	22 (8%)	11 (6%)	11 (15%)

Tolaney SM, et al. *J Clin Oncol.* 2019;37:1868-75.

BCIRG-006: Adjuvant Trastuzumab for HER2+ Early Breast Cancer

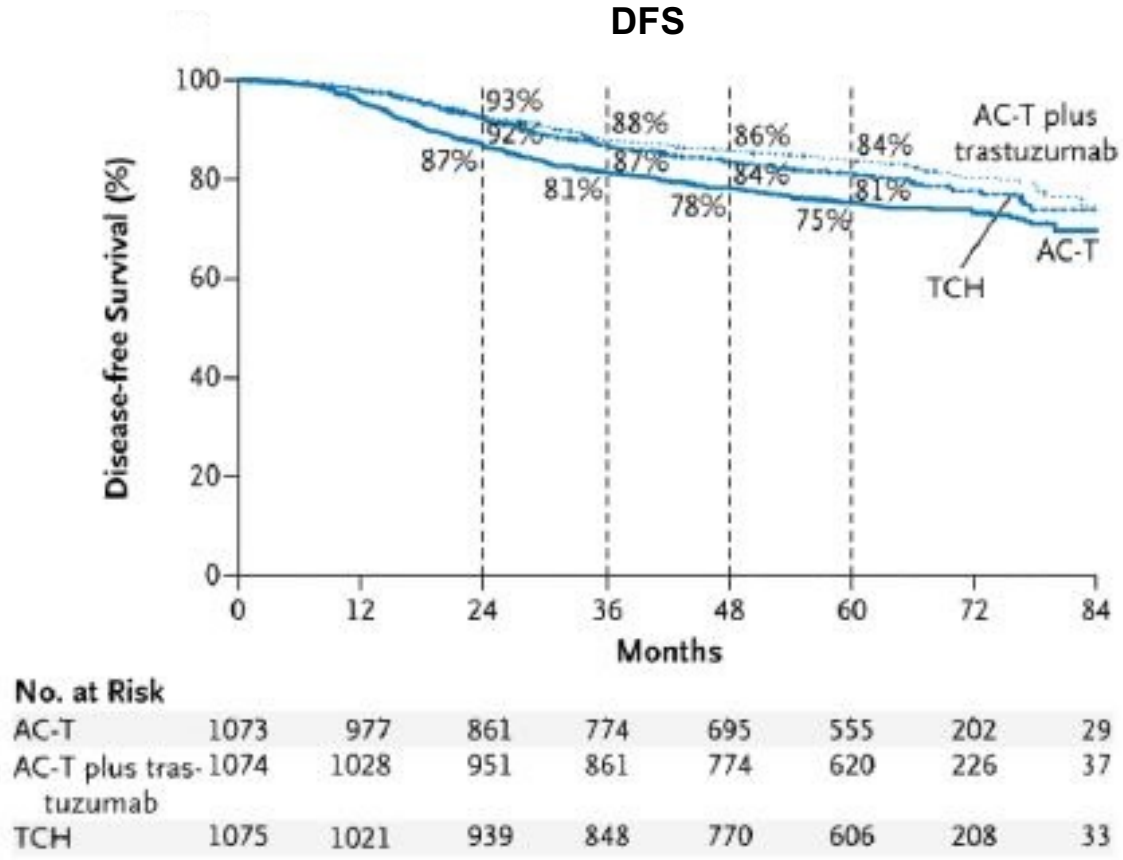


*Beginning with first dose of docetaxel and continuing for 1 yr.
†Trastuzumab initially administered at 4 mg/kg of body weight, followed by 2 mg/kg per week during chemotherapy, then 6 mg/kg q3w to complete 1 year of trastuzumab treatment.

Slamon D, et al. *N Engl J Med*. 2011;365:1273-83.

KPS, Karnofsky performance status; PD, progressive disease.

BCIRG-006: Adjuvant Trastuzumab in HER2+ Breast Cancer



Endpoint (5 yr)	AC-T (n = 1073)	AC-TH (n = 1074)	TCH (n = 1075)
DFS	75%	84%	81%
OS	87%	92%	91%

- For DFS and OS, both trastuzumab regimens were significantly different from AC-T regimen but not from one another
- Greater DFS benefit with trastuzumab in patients without *TOP2A* coamplification, which occurs in 35% of HER2+ cancers

Slamon D, et al. *N Engl J Med*. 2011;365:1273-83.

TOP2A, topoisomerase II alpha.

BCIRG-006: Adjuvant Trastuzumab in HER2+ Breast Cancer

- Significantly more CHF and cardiac dysfunction with AC-TH vs TCH
  - More Grade ≥3 AEs and secondary leukemias with anthracycline use
- Continued survival benefit in both trastuzumab arms vs AC-T at 10 yr
  - DFS: 67.9%, 74.6%, 73.0% for AC-T, AC-TH, and TCH, respectively
  - OS: 78.7%, 85.9%, 83.3%
- Conclusion: no survival advantage for AC-TH vs TCH, but 5x higher rate of CHF with AC-TH
  - Results support the use of trastuzumab-based, non–anthracycline-containing regimen as adjuvant therapy in this setting

Slamon D, et al. *N Engl J Med*. 2011;365:1273-83; Slamon DJ, et al. SABCS 2015. Abstract S5-04.

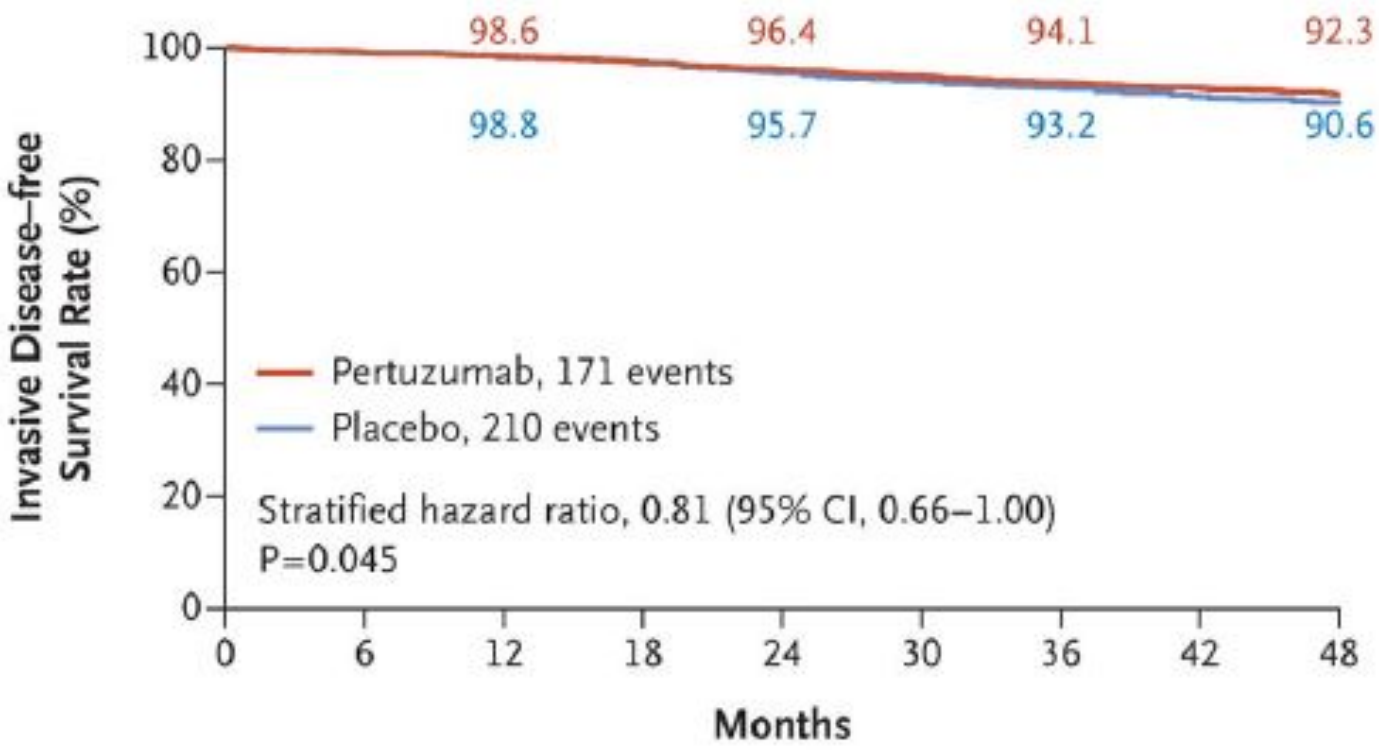
APHINITY: Adjuvant Pertuzumab and Trastuzumab in Early HER2+ Breast Cancer

- Phase III randomized trial to evaluate addition of pertuzumab to adjuvant trastuzumab and chemotherapy in patients with HER2+ early breast cancer
- Patients (N = 4805) had nonmetastatic, adequately excised, histologically confirmed invasive HER2+ breast cancer
  - Node-positive
  - Node-negative with T ≥1 cm tumors 0.5–1.0 cm in diameter and high-risk features*
- Pertuzumab (840 mg loading dose, followed by 420 mg q3wk) or placebo, plus trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg q3wk)
  - Both drugs were added to standard chemotherapy and continued for maximum of 18 cycles within 1 yr

von Minckwitz G, et al. *N Engl J Med*. 2017;377:122-31.

*Patients with node-negative tumors 0.5–1 cm initially eligible if ≥1 high-risk feature present (histologic or nuclear grade 3, ER/PR-negative, or age <35).

APHINITY: Invasive Disease-free Survival*



No. at Risk									
Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

- iDFS benefit of pertuzumab was seen across various patient subgroups, including those with HR+ and HR- breast cancer
- Survival benefit mainly in patients with node-positive disease

*Primary endpoint

von Minckwitz G, et al. *N Engl J Med*. 2017;377:122-31.

APHINITY: Adverse Events

Event	Pertuzumab Arm, n (%) (n = 2364)	Placebo Arm, n (%) (n = 2405)
Grade ≥3 Adverse Event	1518 (64.2)	1379 (57.3)
Neutropenia	385 (16.3)	377 (15.7)
Febrile neutropenia	287 (12.1)	266 (11.1)
Neutrophil count decreased	228 (9.6)	230 (9.6)
Diarrhea	232 (9.8)	90 (3.7)
Anemia	163 (6.9)	113 (4.7)
Primary cardiac event	17 (0.7)	8 (0.3)
NYHA Class III or IV heart failure and substantial decrease in LVEF	15 (0.6)	6 (0.2)

von Minckwitz G, et al. *N Engl J Med*. 2017;377:122-31.

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

Case Study: Adjuvant Therapy

- 45-year-old patient who is referred to your clinic after surgery
- Pathology showed a 3.9-cm tumor, invasive ductal, grade 3, ER/PR-negative, HER2-positive by FISH, with four positive nodes
- Metastatic workup was negative

Treatment options?

A. Adjuvant therapy with docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP)
B. Adjuvant therapy with T-DM1 since she is high risk
C. Adjuvant therapy with AC followed by weekly paclitaxel
D. Adjuvant therapy with TCH

AC, doxorubicin and cyclophosphamide.

Extended Adjuvant Therapy

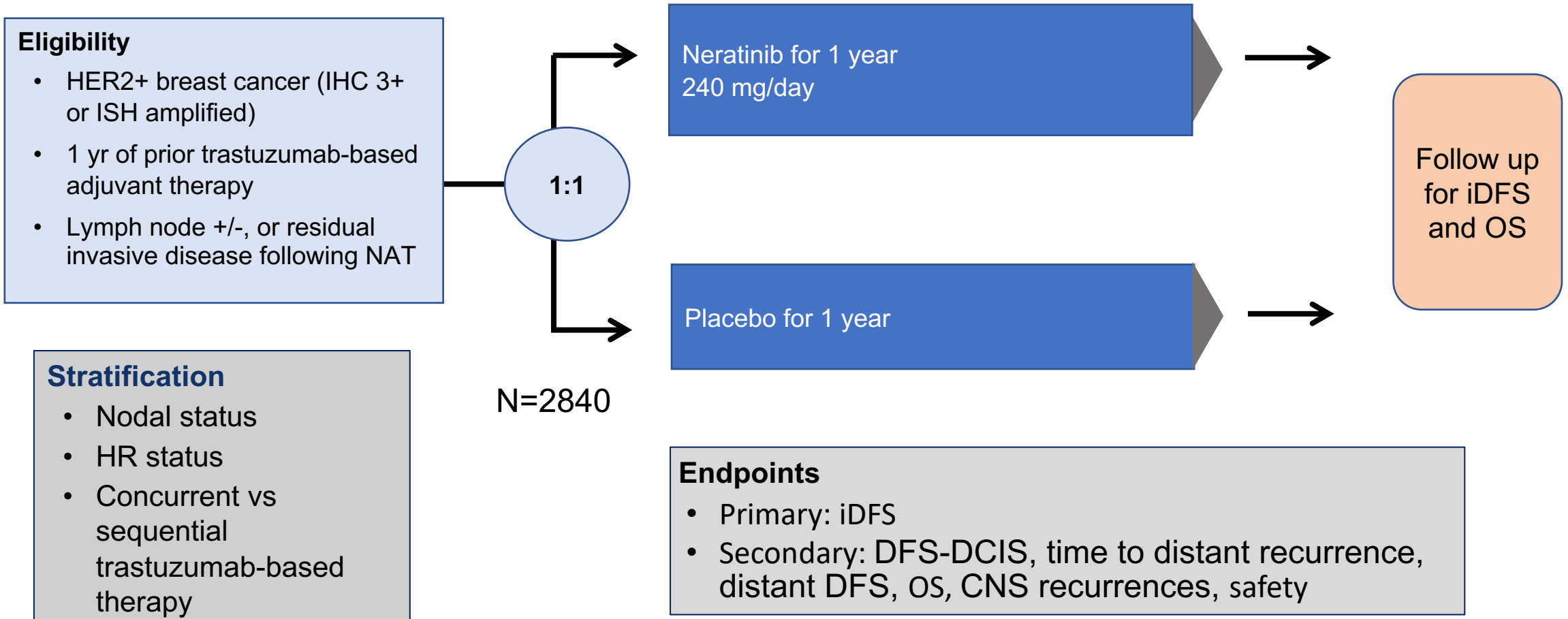
Case Study

- 45-year-old patient with a 4-cm invasive ductal cancer, ER 90% and PR 10%, HER2-positive, with two positive nodes
- She was treated with TCHP adjuvant chemotherapy and completed 1 year of trastuzumab and pertuzumab

Treatment options?

A. No further therapy
B. Extend trastuzumab for 2 years
C. Start neratinib 240 mg daily with diarrheal prophylaxis
D. Start T-DM1, based upon KATHERINE data

ExteNET: Extended Adjuvant Treatment with Neratinib for HER2+ Early Breast Cancer



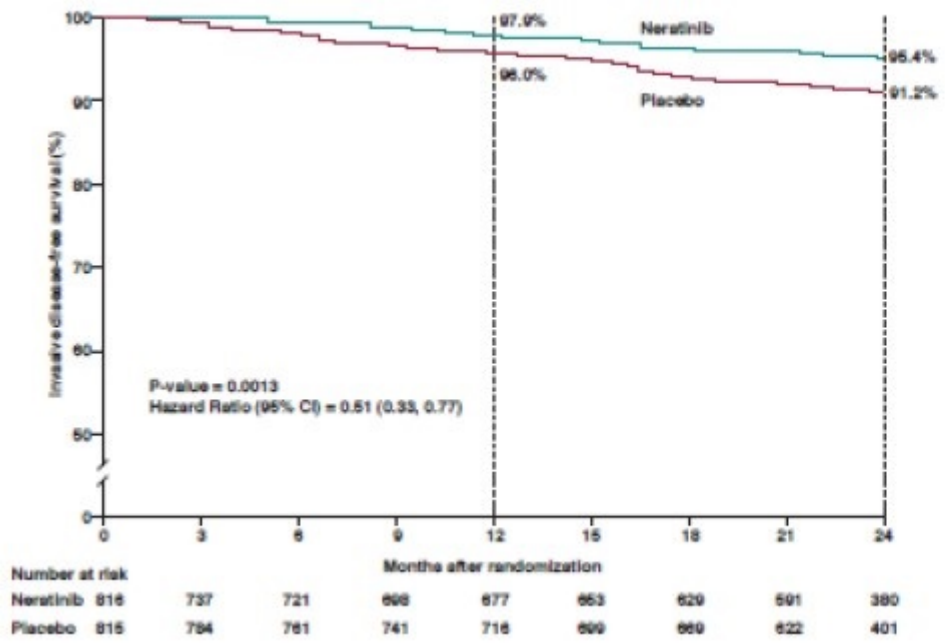
Chan A, et al. *Lancet Oncol*. 2016;17:e176-7; Singh H, et al. *Cancer Res.* 2018;24:3486-91.

DFS-DCIS, disease-free survival including ductal carcinoma in situ.

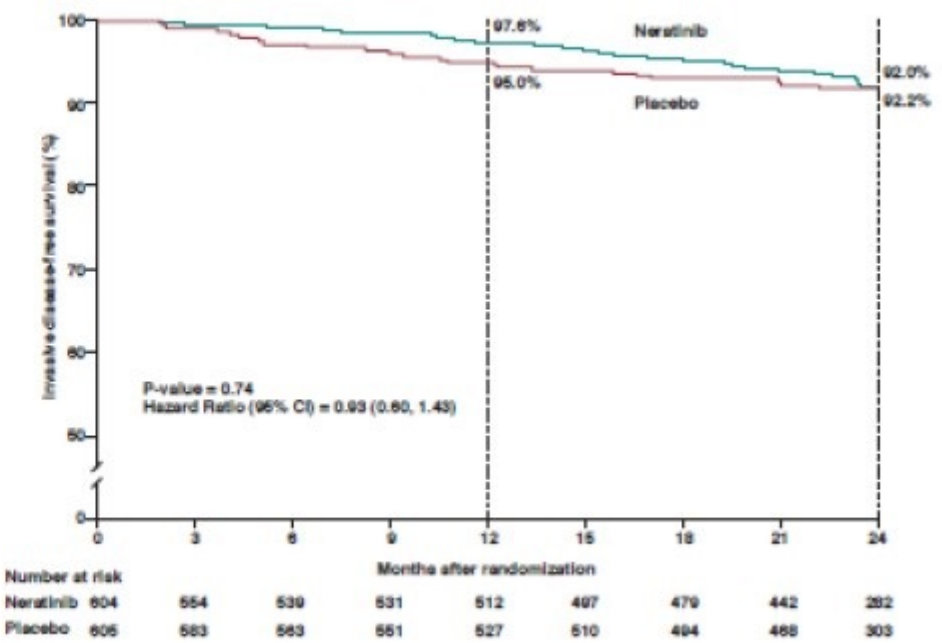
ExteNET: iDFS

- Overall 5-yr iDFS for neratinib vs placebo: 90.2% vs 87.7%; HR 0.73 (95% CI 0.57-0.92; *P* = 0.008)

HR-Positive



HR-Negative



- For overall analysis, neratinib resulted in 27% reduction in risk of recurrence vs placebo
- Largest reduction seen in HR+ subgroup

Chan A, et al. *Lancet Oncol*. 2016;17:e176-7; Singh H, et al. *Cancer Res.* 2018;24:3486-91.

ExteNET: Adverse Events

Adverse Event	Neratinib (n = 1408)		Placebo (n = 1408)	
	All Grades, ≥10% (%)	Grades ≥3, ≥1% (%)	All Grades, ≥10% (%)	Grades ≥3, ≥1% (%)
Diarrhea	95	40	35	2
Nausea	43	2	22	0.1
Abdominal pain	36	2	15	0.4
Fatigue	27	2	20	0.4
Vomiting	26	3	8	0.4
Rash	18	0.6	9	0
Stomatitis	14	0.6	6	0.1
Decreased appetite	12	0.2	3	0
Muscle spasms	11	0.1	3	0.1
Dyspepsia	10	0.4	4	0

- No evidence of hematologic, cardiac, or pulmonary toxicity, and no increased risk for secondary malignancy.

Chan A, et al. *Lancet Oncol*. 2016;17:e176-7.

Post-Neoadjuvant Therapy

Case Study

- 45-year-old patient with a cT3N1M0, ER/PR-positive, HER2-positive breast cancer was treated with TCHP
- Last week she opted for a bilateral mastectomy; pathology revealed a 1.9-cm tumor, with one node showing micrometastatic disease pT1CN1mic

Treatment options?

A. Adjuvant TH for 1 year
B. Adjuvant capecitabine
C. Adjuvant T-DM1
D. Adjuvant carboplatin

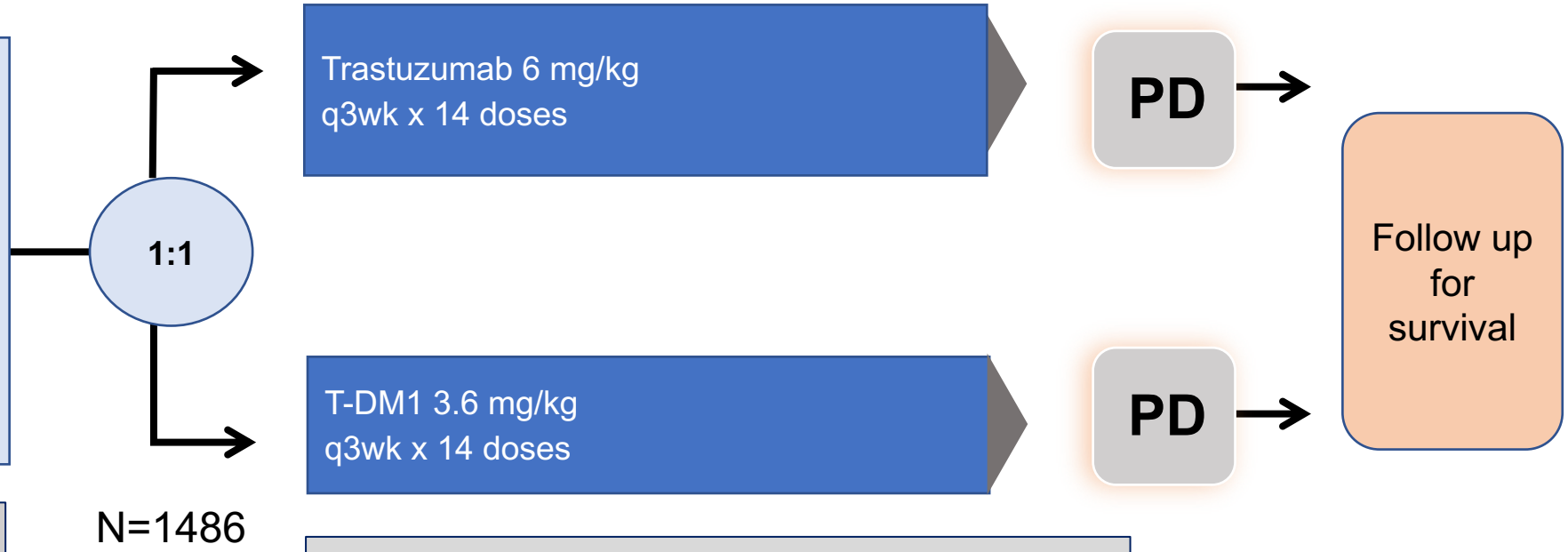
KATHERINE: Adjuvant Trastuzumab vs T-DM1 for HER2+ Early Breast Cancer

Eligibility

- Residual invasive HER2+ breast cancer in breast and/or axillary nodes after neoadjuvant chemotherapy + trastuzumab
- Adequate surgical excision
- ≥6 cycles of neoadjuvant therapy (≥9 wk of trastuzumab or taxane-based chemotherapy)

Stratification

- Clinical stage at presentation
- HR status
- HER2-directed neoadjuvant therapy
- Pathologic nodal status after neoadjuvant therapy



N=1486

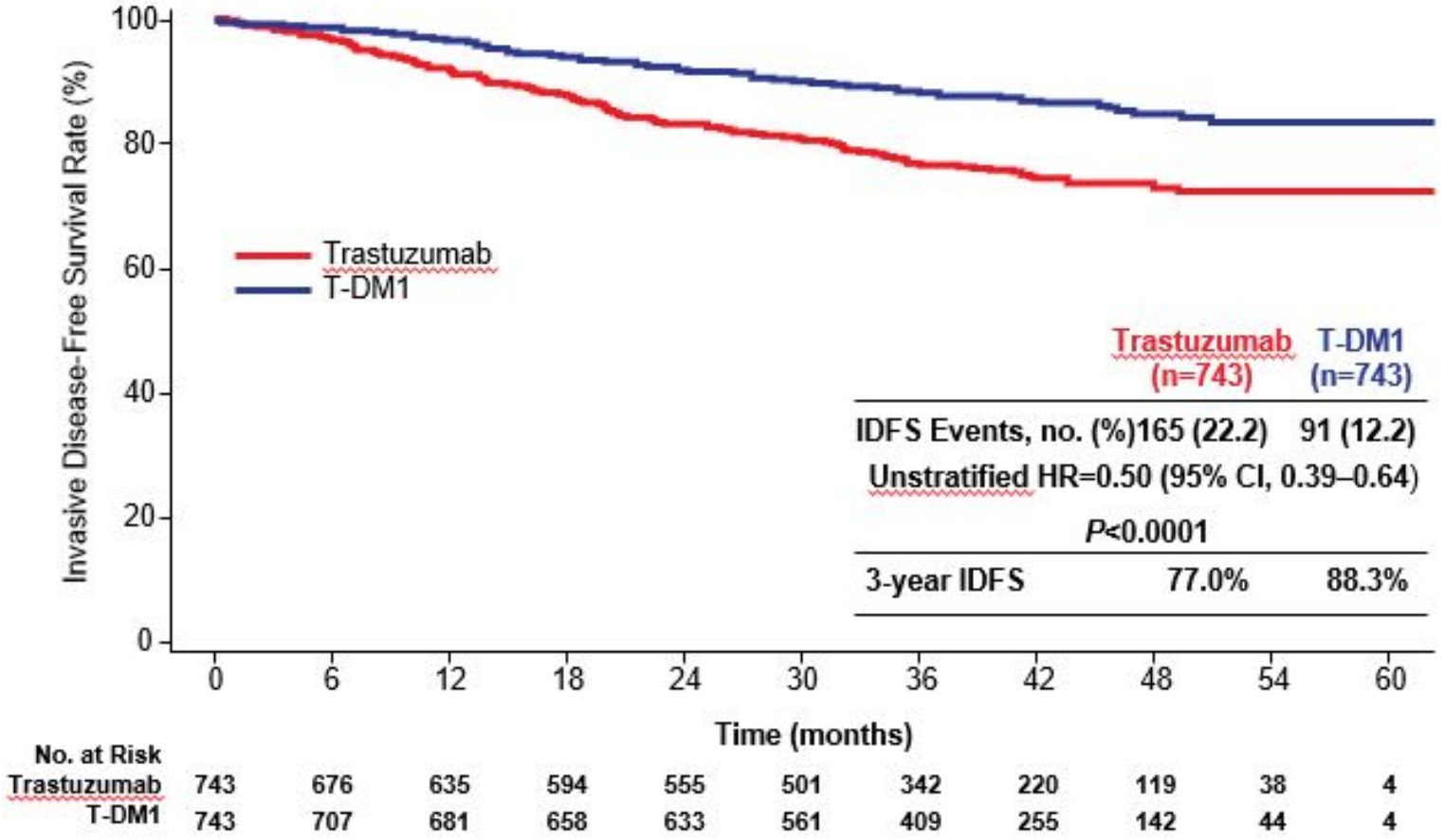
Endpoints

- Primary: iDFS
- Secondary: OS, DFS, relapse-free and distant–relapse-free interval, safety

Radiation administered according to standard guidance; hormonal therapy given if ER+ or PgR+.

von Minckwitz G, et al. *N Engl J Med.* 2019;380:617-28.

KATHERINE: Invasive Disease-free Survival

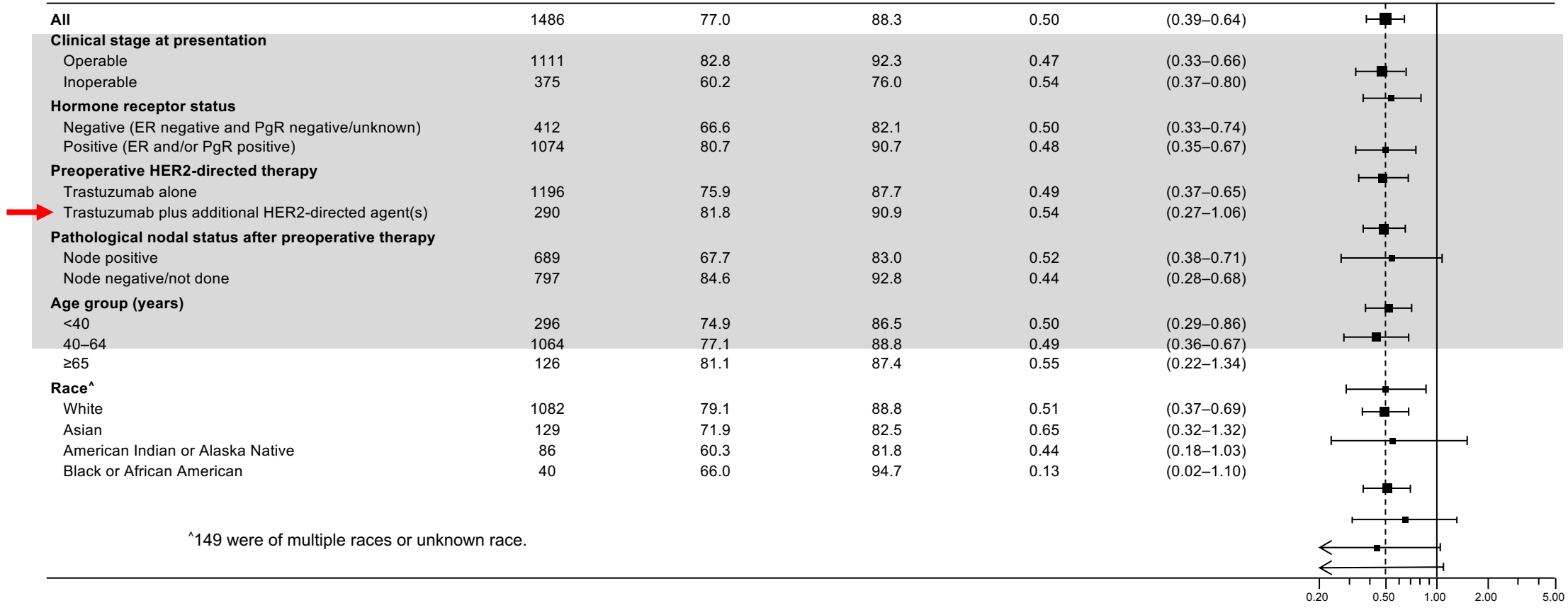


- iDFS benefit with T-DM1 observed:
  - Across all stratified subgroups
  - Greater benefit seen in patients with HER2 3+ tumors (by IHC) vs lower expression levels

Geyer CE, et al. SABCS 2018. Abstract GS1-10.

KATHERINE: iDFS Subgroup Analysis (1)

Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39–0.64)
Clinical stage at presentation					
Operable	1111	82.8	92.3	0.47	(0.33–0.66)
Inoperable	375	60.2	76.0	0.54	(0.37–0.80)
Hormone receptor status					
Negative (ER negative and PgR negative/unknown)	412	66.6	82.1	0.50	(0.33–0.74)
Positive (ER and/or PgR positive)	1074	80.7	90.7	0.48	(0.35–0.67)
Preoperative HER2-directed therapy					
Trastuzumab alone	1196	75.9	87.7	0.49	(0.37–0.65)
Trastuzumab plus additional HER2-directed agent(s)	290	81.8	90.9	0.54	(0.27–1.06)
Pathological nodal status after preoperative therapy					
Node positive	689	67.7	83.0	0.52	(0.38–0.71)
Node negative/not done	797	84.6	92.8	0.44	(0.28–0.68)
Age group (years)					
<40	296	74.9	86.5	0.50	(0.29–0.86)
40–64	1064	77.1	88.8	0.49	(0.36–0.67)
≥65	126	81.1	87.4	0.55	(0.22–1.34)
Race^					
White	1082	79.1	88.8	0.51	(0.37–0.69)
Asian	129	71.9	82.5	0.65	(0.32–1.32)
American Indian or Alaska Native	86	60.3	81.8	0.44	(0.18–1.03)
Black or African American	40	66.0	94.7	0.13	(0.02–1.10)

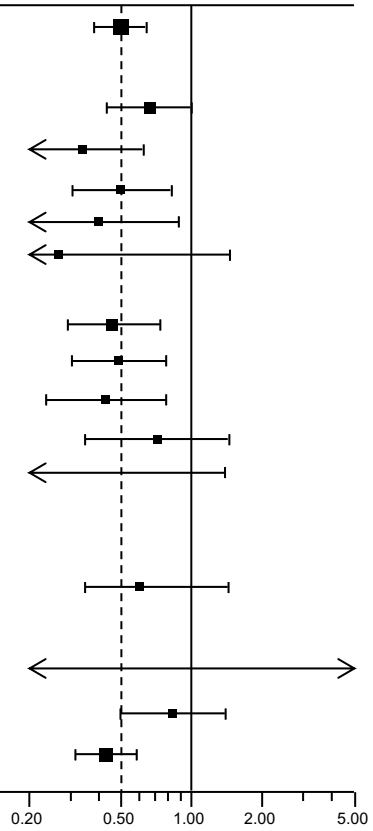


^149 were of multiple races or unknown race.

Geyer CE, et al. SABCS 2018. Abstract GS1-10.

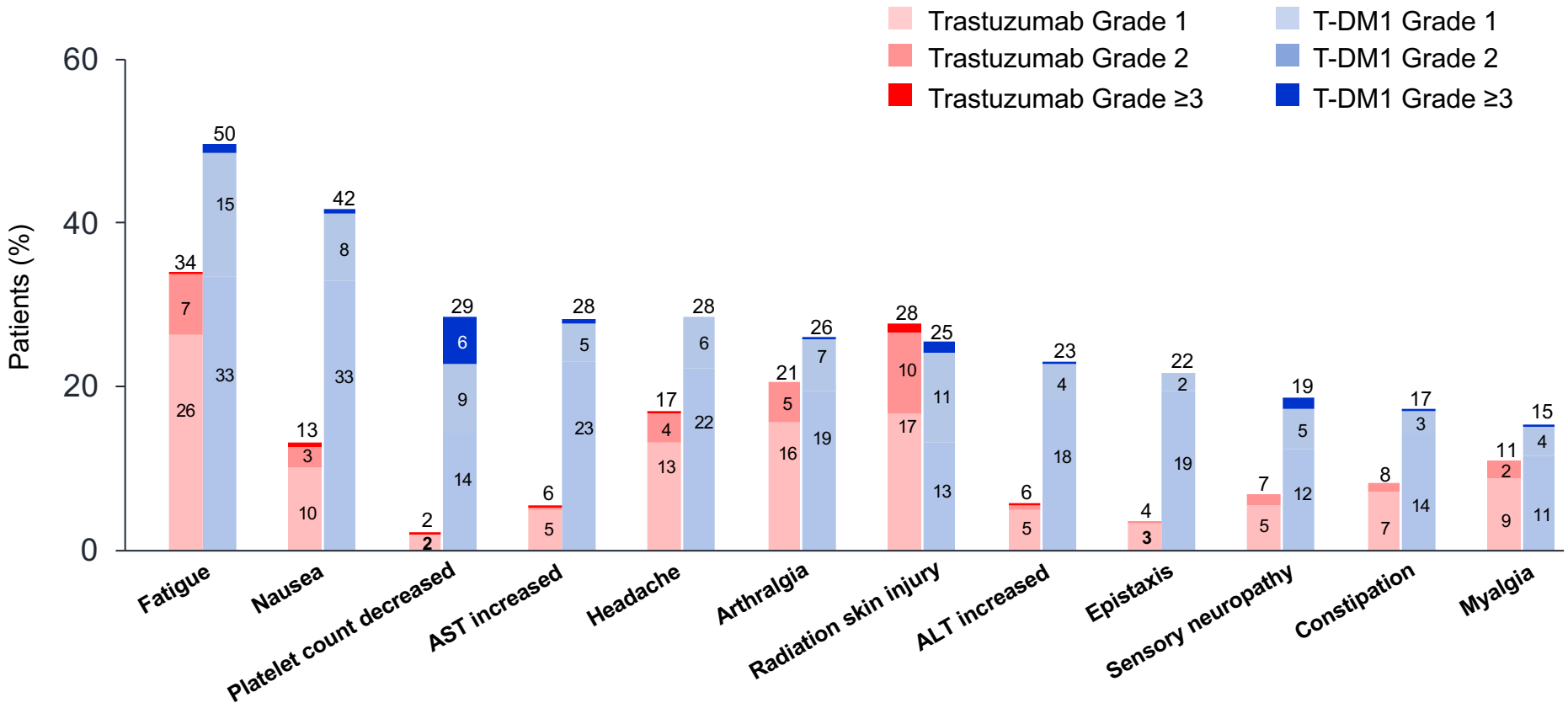
KATHERINE: iDFS Subgroup Analysis (2)

Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39–0.64)
Primary tumor stage (at definitive surgery)					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	83.6	88.3	0.66	(0.44–1.00)
ypT1, ypT1c	359	75.9	91.9	0.34	(0.19–0.62)
ypT2	359	74.3	88.3	0.50	(0.31–0.82)
ypT3	108	61.1	79.8	0.40	(0.18–0.88)
ypT4^	23	30.0	70.0	0.29	(0.07–1.17)
Regional lymph node stage (at definitive surgery)					
ypN0	679	83.9	91.9	0.46	(0.30–0.73)
ypN1	433	75.8	88.9	0.49	(0.31–0.78)
ypN2	189	58.2	81.1	0.43	(0.24–0.77)
ypN3	67	40.6	52.0	0.71	(0.35–1.42)
ypNX	118	88.7	98.1	0.17	(0.02–1.38)
Residual disease ≤1 cm with negative axillary lymph nodes					
ypT1a, ypT1b or ypT1mic and ypN0	331	85.3	90.0	0.60	(0.33–1.12)
Central HER2 status by IHC*					
0/1+	25	83.9	100.0	<0.01	(0.00–NE)
2+	326	80.9	84.7	0.83	(0.50–1.38)
3+	1132	75.7	89.0	0.43	(0.32–0.58)



^Includes all ypT4 and 1 patient with ypTX. *Three patients had "unknown" HER2 IHC status.

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



Geyer CE, et al. SABCS 2018. Abstract GS1-10.

HER2+ Metastatic Breast Cancer

Case Study

- 39-year-old patient diagnosed with a T2N1 breast cancer, ER/PR- and HER2+, who was treated with TCH in the adjuvant setting about 4 years ago
- Now presenting with biopsy-proven multiple liver lesions that are ER/PR+ and HER2+

Treatment options?

A. Palbociclib and endocrine therapy with ovarian suppression
B. Taxane, trastuzumab, and pertuzumab
C. T-DM1
D. All of the above

First-line Therapy for HER2+ MBC

- First-line treatment for HER2+ MBC often involves combining HER2-targeted agents with standard chemotherapy:
  - Pertuzumab + trastuzumab + docetaxel
  - Consider T-DM1 if patients are unsuitable for above regimen, or following fast progression on adjuvant trastuzumab and pertuzumab
- Combination of HER2 inhibitors and chemotherapy can prolong time to progression and increase survival

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V2.2019; Swain SM, et al. *N Engl J Med*. 2015;372:724-34; Larionov AA. *Front Oncol*. 2018;8:89.

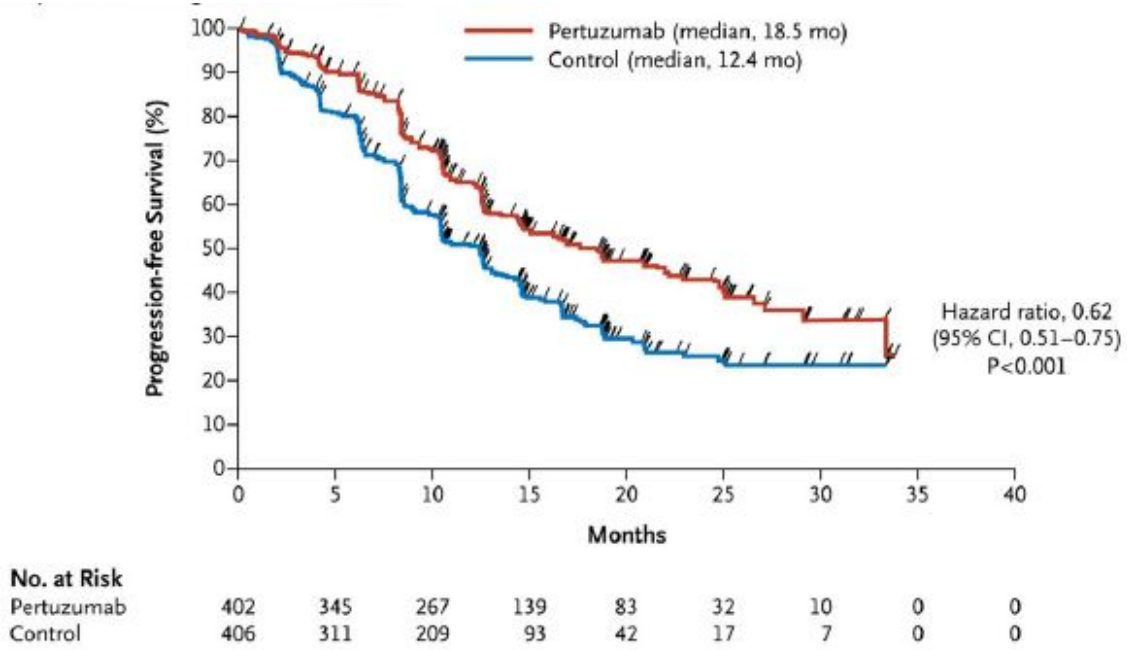
CLEOPATRA Trial: First-line Pertuzumab + Trastuzumab

- Phase III trial of trastuzumab + docetaxel combined with pertuzumab or placebo in patients with HER2+ MBC not previously treated with chemotherapy or anti-HER2 therapy for metastatic disease
  - Pertuzumab and trastuzumab have complementary MOAs so combination could have synergistic efficacy
- Combination of pertuzumab + trastuzumab has shown clinical activity in patients with HER2+ MBC in previous phase II studies

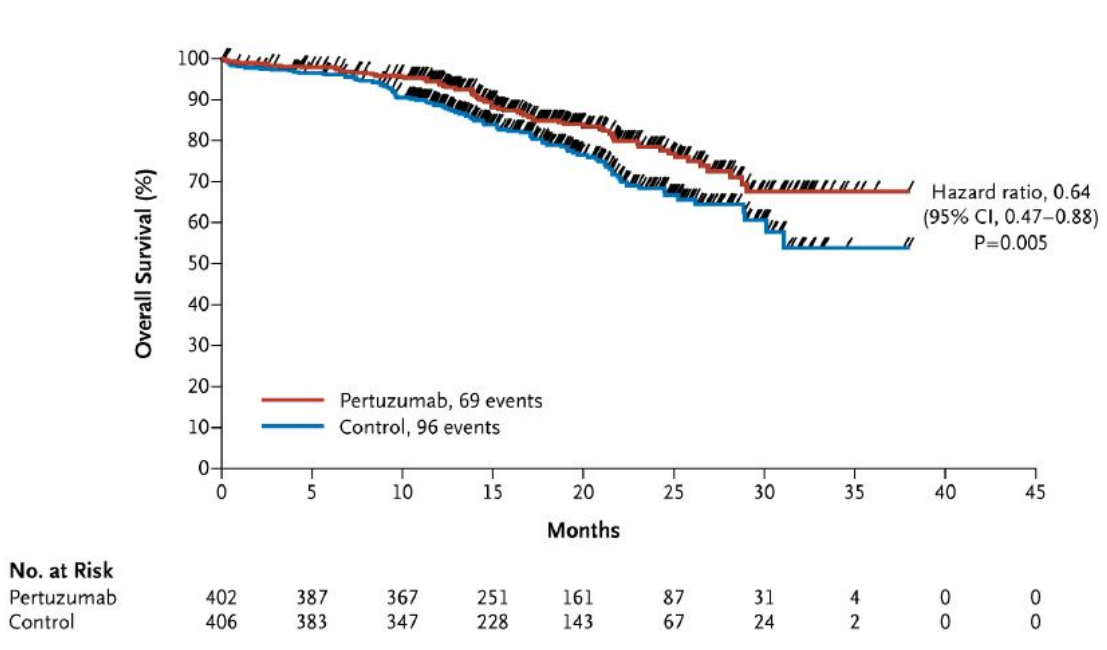
Baselga J, et al. *N Engl J Med*. 2012;366:109-9; Swain SM, et al. *N Engl J Med*. 2015;372:724-34;
Baselga J, et al. *J Clin Oncol*. 2010;28:1138-44; Portera CC, et al. *Clin Cancer Res*. 2008;4:2710-6.

CLEOPATRA: Survival

PFS



OS



Endpoint	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel	Hazard Ratio	*P* value
ORR	80.2%	69.3%		0.0001
PFS	18.7 mo	12.4 mo	0.69	<0.0001
OS	56.5 mo	40.8 mo	0.66	0.001

mOS was extended by >1 yr to a maximum of >4.5 yr

Baselga J, et al. *N Engl J Med*. 2012;366:109-9; Swain SM, et al. *N Engl J Med*. 2015;372:724-34.

CLEOPATRA: Most Common Grade ≥3 Adverse Events

Adverse Event (incidence >5%)	Placebo + Trastuzumab + Docetaxel (%) n = 397	Pertuzumab + Trastuzumab + Docetaxel (%) n = 407
Neutropenia	45.8	48.9
Febrile neutropenia	7.6	13.8
Leukopenia	14.6	12.3
Diarrhea	5.0	7.9

- Majority of adverse events occurred during docetaxel treatment.
- Addition of pertuzumab did not increase cardiotoxicity, nor was late cardiac toxicity observed.

Baselga J, et al. *N Engl J Med*. 2012;366:109-9.

CLEOPATRA: Conclusions

- Addition of pertuzumab led to a statistical and clinically meaningful increase in survival compared with trastuzumab + docetaxel alone
- Pertuzumab + trastuzumab + docetaxel now has replaced trastuzumab + taxane combination as first-line treatment of choice for HER2+ MBC
  - Optimal duration of pertuzumab regimen has yet to be determined
  - Biomarkers are needed to better predict responders

Case Study

- 39-year-old patient diagnosed with a T2N1 breast cancer, ER/PR- and HER2+, who was treated with TCH in the adjuvant setting about 4 years ago
- She has biopsy-proven multiple liver lesions, which are ER/PR+ and HER2+
- She was treated with THP and did well for 2 years
- Most recent scans show multiple new lesions in the lung

Treatment options?

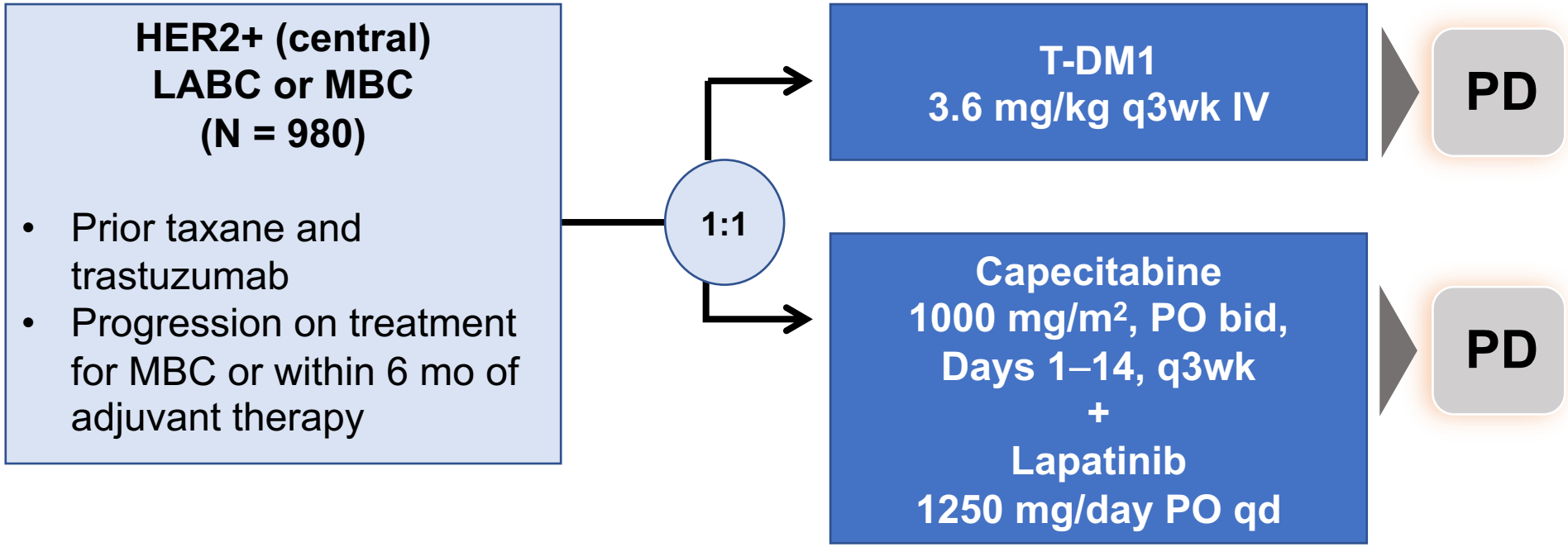
A. Palbociclib and endocrine therapy with ovarian suppression
B. Vinorelbine, trastuzumab, and pertuzumab
C. T-DM1
D. Capecitabine and lapatinib

Second-line Therapy for HER2+ MBC

- Preferred second-line treatment options for HER2+ MBC:
  - Trastuzumab emtansine (T-DM1)
  - Trastuzumab + pertuzumab + cytotoxic chemotherapy (taxanes, vinorelbine, or capecitabine are options if no prior pertuzumab exposure)

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V2.2019; Larionov AA. *Front Oncol*. 2018;8:89.

EMILIA: Study Design



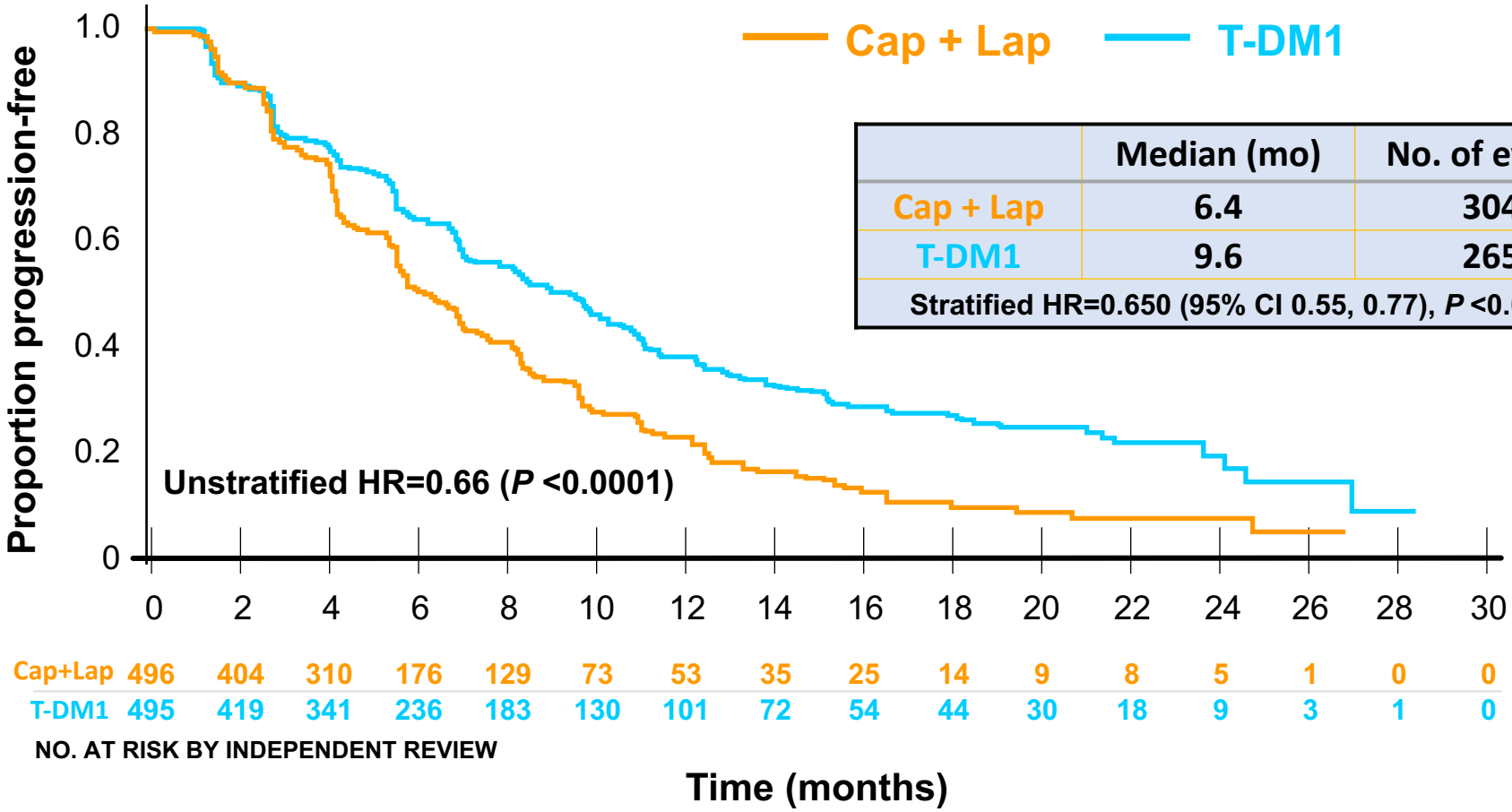
Primary Endpoints: PFS by independent review, OS, safety

Key Secondary Endpoints: PFS by investigator, ORR, duration of response, time to symptom progression

Blackwell KL, et al. ASCO 2012. Abstract LBA1; Verma S, et al. *N Engl J Med*. 2012;367:1783-91.

LABC, locally advanced breast cancer.

EMILIA: Progression-Free Survival*



	Median (mo)	No. of events
Cap + Lap	6.4	304
T-DM1	9.6	265
Stratified HR=0.650 (95% CI 0.55, 0.77), *P* <0.0001		

*By independent review

Blackwell KL, et al. ASCO 2012. Abstract LBA1; Verma S, et al. *N Engl J Med*. 2012;367:1783-91.

HR, hazard ratio.

EMILIA: Conclusions

- In patients with HER2+ advanced breast cancer previously treated with trastuzumab and a taxane, T-DM1 significantly prolonged survival vs lapatinib + capecitabine, with less toxicity
  - Benefit observed across multiple subgroups (less so among patients ≥75 yrs and those with nonvisceral or nonmeasurable disease)
  - Results led to approval of T-DM1 monotherapy in this setting
- Results of EMILIA, along with survival benefit in TH3RESA and MARIANNE trials, confirm that T-DM1 is an effective treatment option for this patient population

Larionov AA. *Front Oncol*. 2018;8:89.

NSABP FB-10: Trial Design

HER2+ MBC with Prior Trastuzumab and Pertuzumab Treatment*

Study Entry

Treatment Regimen for All Patients

T-DM1 3.6 mg/kg IV Day 1 q21d†

Neratinib PO daily beginning on Day 1 of T-DM1 and continuing until disease progression

†T-DM1 Dose level 1

Dose de-escalation based on dose-limiting toxicity during Cycle 1

Neratinib Dose Escalation

Dose level 1: 120 mg/day
Dose level 2: 160 mg/day
Dose level 3: 200 mg/day
Dose level 4: 240 mg/day

Loperamide 4 mg q6h initiated with first dose of neratinib.

Abraham J, et al. *J Clin Oncol*. 2019;37:2601-9.

*Patients must have had anti–HER2-based therapy with trastuzumab and pertuzumab as neoadjuvant, adjuvant, or for first-line metastatic disease.

NSABP FB-10: Responses

Best Response	N
Evaluable patients	19
Responses (CR + PR) Complete Partial Stable disease Progressive disease	12 (63%) 3 9 2 5
Non-evaluable DLT Withdrew	8 5 3
Patients with brain metastases PR (duration 330 days) PD (outside CNS)	6 1 5

Abraham J, et al. *J Clin Oncol*. 2019;37:2601-9.

CNS, central nervous system; CR, complete response; DLT, dose-limiting toxicity; PR, partial response.

NSABP FB-10: Grade 2-4 Treatment-emergent Adverse Events (>10%)

CTCAE v. 4.0	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Diarrhea	14 (52)	6 (22)	0
Nausea	10 (37)	3 (11)	0
Vomiting	4 (15)	0	0
Dehydration	6 (22)	3 (11)	0
Electrolyte imbalance	2 (7)	6 (22)	1 (4)
Elevated transaminases	6 (22)	3 (11)	0
Thrombocytopenia	1 (4)	4 (15)	0
Fatigue	9 (33)	2 (7)	0

Abraham J, et al. *J Clin Oncol*. 2019;37:2601-9.

CTCAE, Common Terminology Criteria for Adverse Events (ver. 4.0).

NSABP FB-10: Conclusions

- Neratinib RP2D is 160 mg/day, with T-DM1 3.6 mg/kg q3wk
- At RP2D, diarrhea is well managed in most patients
- Objective responses seen at all doses of neratinib
- Loss of *HER2* amplification in blood pretreatment may influence depth and duration of response to anti-HER2 therapy
  - ORR significantly higher in patients with baseline *HER2* cell-free DNA amplification vs no amplification (70% vs 29%)
  - Loss of *HER2* amplification on treatment associates with response

Abraham J, et al. *J Clin Oncol*. 2019;37:2601-9.

RP2D, recommended Phase II dose.

Case Study

- 39-year-old patient who was diagnosed with a T2N1M1 breast cancer, ER/PR-, and HER2+, treated with THP in the metastatic setting
- After 3 years she developed new lung lesions and was treated with T-DM1, but is now progressing with new liver lesions
- Potential options in approaches in third-line HER2+ metastatic breast cancer

Treatment options?

A. Palbociclib and endocrine therapy with ovarian suppression
B. Vinorelbine, trastuzumab, and pertuzumab
C. T-DM1
D. Capecitabine and lapatinib or neratinib and capecitabine

Third-line Therapy for HER2+ MBC

- Third-line treatment options for HER2+ MBC:
  - Regimens currently recommended for use in first or second line should be considered for later lines, if not used previously
  - Trastuzumab or lapatinib + cytotoxic chemotherapy (including vinorelbine, capecitabine, gemcitabine, eribulin, and others, if not used previously)
  - Trastuzumab + lapatinib if patients are not suitable for cytotoxic chemotherapy

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V2.2019; Larionov AA. *Front Oncol*. 2018;8:89;
Geyer CE, et al. *N Engl J Med*. 2006;355:2733-43.

Lapatinib + Capecitabine in Pretreated HER2+ MBC

- Phase III randomized trial of lapatinib + capecitabine vs capecitabine monotherapy for pretreated HER2+ MBC
  - Patients with locally advanced or metastatic breast cancer with disease progression after an anthracycline, a taxane, and trastuzumab
- Median TTP: 8.4 mo with combination vs 4.4 mo with capecitabine (51% reduction in risk of disease progression)
  - TTP HR: 0.49 (95% CI 0.34-0.71; $P < 0.001$)
  - No significant increase in serious toxicities or symptomatic cardiac events

Geyer CE, et al. *N Engl J Med*. 2006;355:2733-43.

TTP, time to progression.

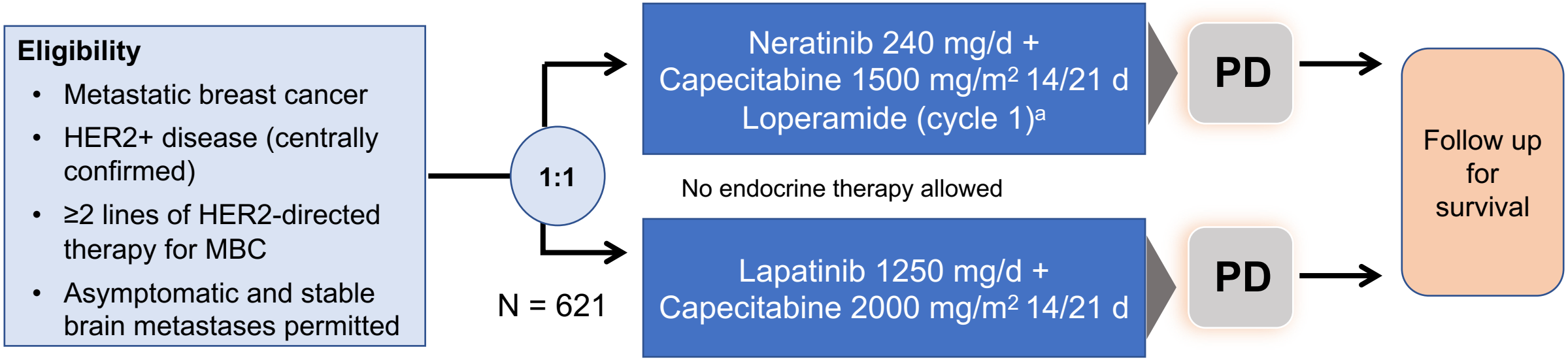
Neratinib/Capecitabine vs Lapatinib/ Capecitabine for HER2+ MBC (NALA)

- Phase III multinational, randomized trial of neratinib + capecitabine vs lapatinib + capecitabine in patients with HER2+ MBC previously treated with ≥2 HER2-directed regimens
  - Neratinib is a pan-HER TKI that binds irreversibly (vs reversible binding with lapatinib)
- Neratinib previously shown to be efficacious in HER2+ MBC:
  - Study 2206: neratinib + capecitabine in trastuzumab-pretreated patients
  - NSABP FB-10: neratinib + T-DM1 in patients previously treated with trastuzumab + pertuzumab
  - NEfERT-T and TBCRC 022: neratinib + paclitaxel or capecitabine in patients with HER2+ brain metastases

Saura C, et al. ASCO 2019. Abstract 1002; Abraham J, et al. ASCO 2018. Abstract 1027; Awada A, et al. *JAMA Oncol*. 2016;2:1557-64; Freedman RA, et al. *J Clin Oncol*. 2019;37:1081-9.

TKI, tyrosine kinase inhibitor.

NALA: Study Design



Stratification

- Number of prior HER2 therapies for MBC
- HR status
- Disease location
- Geographic location

Endpoints

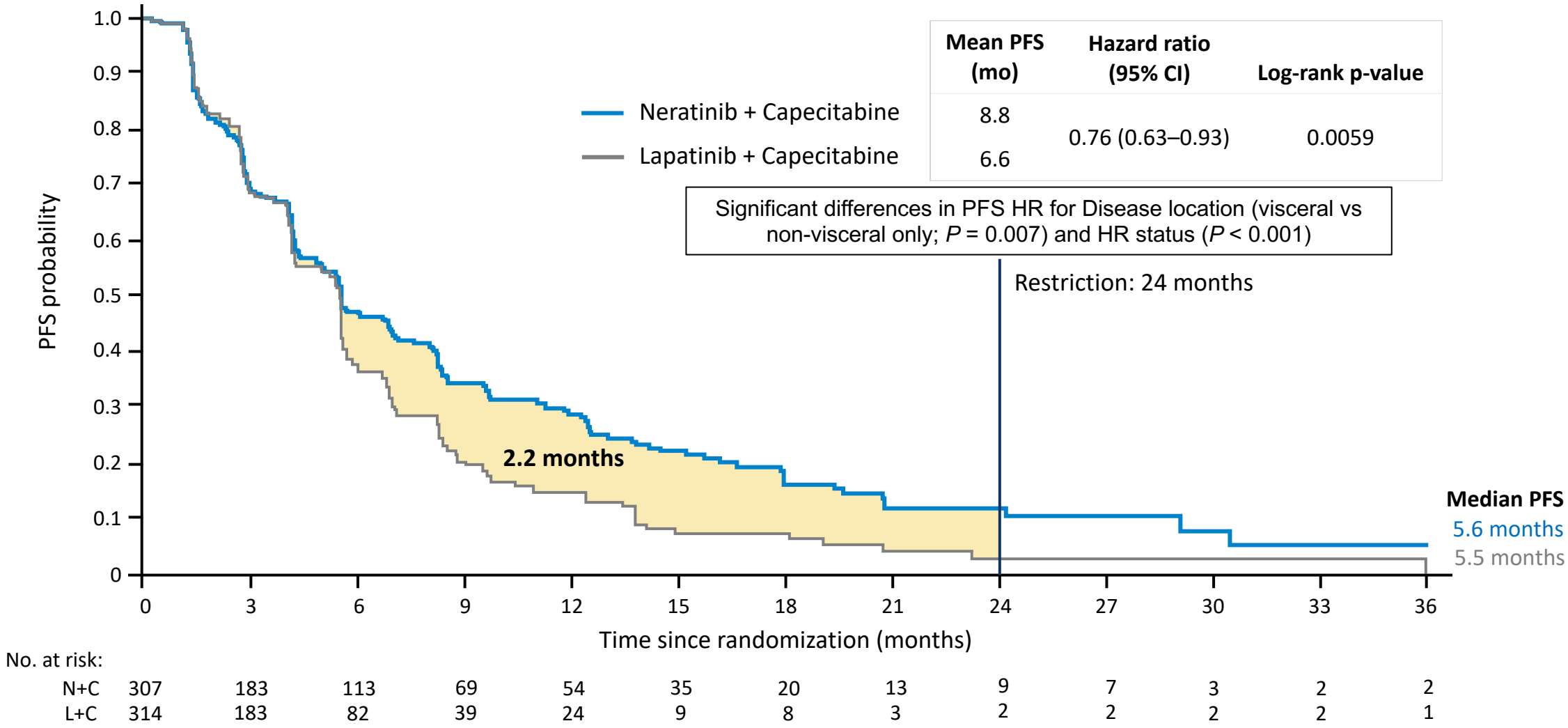
- Co-primary: PFS (centrally confirmed), OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

[a]Loperamide 4 mg with first neratinib dose, followed by 2 mg every 4 hr for first 3 d, then loperamide 2 mg every 6-8 hr until end of Cycle 1 (thereafter as needed).

Saura C, et al. ASCO 2019. Abstract 1002.

CBR, clinical benefit rate.

NALA: PFS (co-primary endpoint)



Mean PFS (mo)	Hazard ratio (95% CI)	Log-rank p-value
8.8 6.6	0.76 (0.63–0.93)	0.0059

Significant differences in PFS HR for Disease location (visceral vs non-visceral only; $P = 0.007$) and HR status ($P < 0.001$)

Saura C, et al. ASCO 2019. Abstract 1002.

NALA: Most Frequent Grade 3/4 Adverse Events

	Neratinib + Capecitabine (n = 303)		Lapatinib + Capecitabine (n = 311)	
	All grade	Grade 3/4	All grade	Grade 3/4
Treatment-emergent AEs, %	100	61	99	60
Diarrhea	83	24	66	13
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2

- Treatment discontinuation due to treatment-emergent AEs: N+C, 10.9% vs L+C, 14.5% (due to diarrhea: N+C, 2.6%; L+C, 2.3%).

Saura C, et al. ASCO 2019. Abstract 1002.

NALA: Conclusions

- NALA met its primary objective, with N+C regimen superior to L+C as third-line MBC therapy
  - Significant PFS benefit: HR = 0.76 (*P* = 0.0059); mean improvement 2.2 months
  - Trend toward OS benefit: HR = 0.88 (*P* = 0.2086); mean improvement 1.7 months
- All secondary endpoints favored N+C regimen
  - Increased duration of response
  - Lower cumulative incidence of CNS intervention (*P* = 0.043), similar to CNS findings from other neratinib MBC studies
- No new safety signals observed with neratinib, with similar tolerability, adherence, and QoL among the two treatment arms

QoL, quality of life.

Selected Emerging Therapies

Tucatinib

- Tucatinib is a small-molecule TKI highly selective for HER2
- Phase I trial of tucatinib in HER2+ MBC suggested promising efficacy and an acceptable safety profile
- Tucatinib combined with T-DM1 also showed efficacy in some patients with brain metastases who were previously treated with trastuzumab and a taxane

Moulder SL, et al. *Clin Cancer Res*. 2017;23:3529-36; Borges VF, et al. *JAMA Oncol*. 2018;4:1214-20.

Tucatinib Phase Ib Trial

- Patients with HER2+ MBC (+/- brain metastases) previously treated with trastuzumab, pertuzumab, and T-DM1 were eligible
  - Tucatinib 300 mg BID given with capecitabine 1000 mg/m^2 orally BID for 14 of 21 days, and trastuzumab 6 mg/kg IV q21d, or both
- Treatment-related grade ≥3 AEs (all patients): fatigue, diarrhea, palmar-plantar erythrodysesthesia

	Tucatinib + Capecitabine (n = 6)	Tucatinib + Trastuzumab (n = 15)	Tucatinib + Capecitabine + Trastuzumab (n = 23)
ORR, n (%)	5 (83%)	6 (40%)	14 (61%)
CR	0	0	1 (4%)
PR	5 (83%)	6 (40%)	13 (57%)
Stable disease	1 (17%)	6 (40%)	6 (26%)

Murthy R, et al. *Lancet Oncol*. 2018;19:880-8.

Phase Ib Trial of Tucatinib + T-DM1

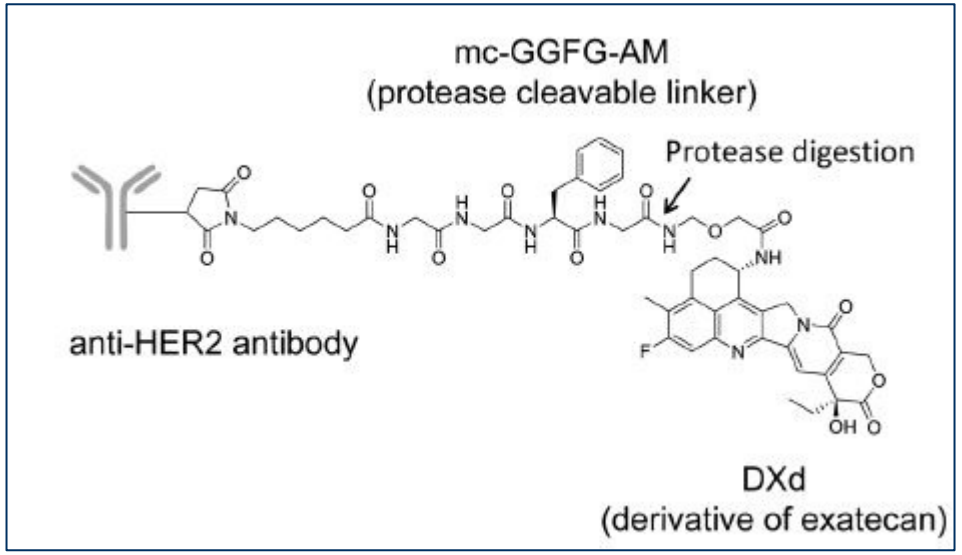
- Patients with advanced/metastatic HER2+ MBC previously treated with trastuzumab and a taxane were eligible
  - Tucatinib (300-350 mg) administered BID for 21 days
  - T-DM1 3.6 mg/kg administered once every 21 days
- mPFS: 8.2 mo (95% CI 4.8-10.3)
  - Clinical benefit rate*: 58%
- Tucatinib-related grade ≥3 adverse events (≥10% of patients): thrombocytopenia, increased ALT levels, increased AST levels

*Clinical benefit rate = CR + PR + stable disease >6 months.

Borges VF, et al. *JAMA Oncol.* 2018;4:1214-20.

Trastuzumab Deruxtecan (DS-8201a)

- Humanized anti-HER2 antibody conjugated with highly potent topoisomerase I inhibitor payload and cleavable peptide-based linker
- High drug-to-antibody ratio, thus exerting greater antitumor activity
- Antitumor activity against breast cancer cell lines with low HER2 levels



Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-85.

Trastuzumab Deruxtecan Phase I Trial

- Evaluated in 115 patients with HER2+ MBC who had a median of 7 prior lines of therapy, including trastuzumab, trastuzumab emtansine, and pertuzumab
- Confirmed ORR 59.5%; disease control rate 93.7%
  - Median DoR: 20.7 mo (95% CI 0-21.8)
  - Median PFS 22.1 mo (95% CI 0.8-27.9)
- Most common adverse events (≥30%, any grade) included nausea, decreased appetite, vomiting, alopecia, fatigue, anemia, diarrhea, constipation
  - Half of patients experienced an AE grade ≥3; 19% serious AEs including 2 cases of grade 5 treatment-related pneumonitis

Tamura K, et al. *Lancet Oncol*. 2019;20:816-26.

CNS Metastasis in HER2+ Breast Cancer Overview

- Brain metastases (BM) develop in 10%-30% of patients with breast cancer
  - Associated with high mortality rate, increased neurologic symptoms, and lower QoL
- 30%-55% of patients with HER2+ MBC will ultimately develop BM, and approximately half will die from intracranial disease progression
  - CNS is most common first site of metastasis in HER2+ disease
- Until recently, few effective systemic therapies were available, especially for patients who progress after standard radiosurgery

O'Sullivan CC, et al. *Semin Oncol*. 2017;44:85-100; Sperduto PW, et al. *J Neurooncol*. 2013;112:467-72.

Risk Factors for CNS Metastasis in HER2+ Breast Cancer

Risk Factor	Data	
Young age	Significant impact of age by univariate and multivariate analysis	
ER- breast cancer	56% of patients had ER- disease; patients with TNBC had worse survival vs non-TNBC tumors	
Grade III tumors	Significant correlation between high histologic grade and incidence of CNS metastases	
Tumor size (≥5 cm)	Worse OS in patients with BM and tumors ≥5 cm vs those with smaller tumors	
HER2+ disease	Incidence of BM highest in ER-, HER2+ breast cancers	
Histologic subtype	Luminal A: 9% Luminal B: 11%	TNBC: 15% HER2+: 17%

O'Sullivan CC, et al. *Semin Oncol*. 2017;44:85-100.

Selected Novel Systemic Therapies Under Evaluation for Brain Metastases

Agent	Mechanism of Action
Neratinib	Pan-HER tyrosine kinase inhibitor
Abemaciclib, palbociclib	CDK4/6 inhibitors
Tucatinib	HER2 tyrosine kinase inhibitor
Etirinotecan pegol	Pegylated derivative of irinotecan
Veliparib, olaparib, talazoparib	PARP inhibitors
Atezolizumab, pembrolizumab	Immune checkpoint inhibitors
ANG1005, TPI-287	Taxane derivatives

CDK, cyclin-dependent kinases; PARP, poly (ADP-ribose) polymerase.

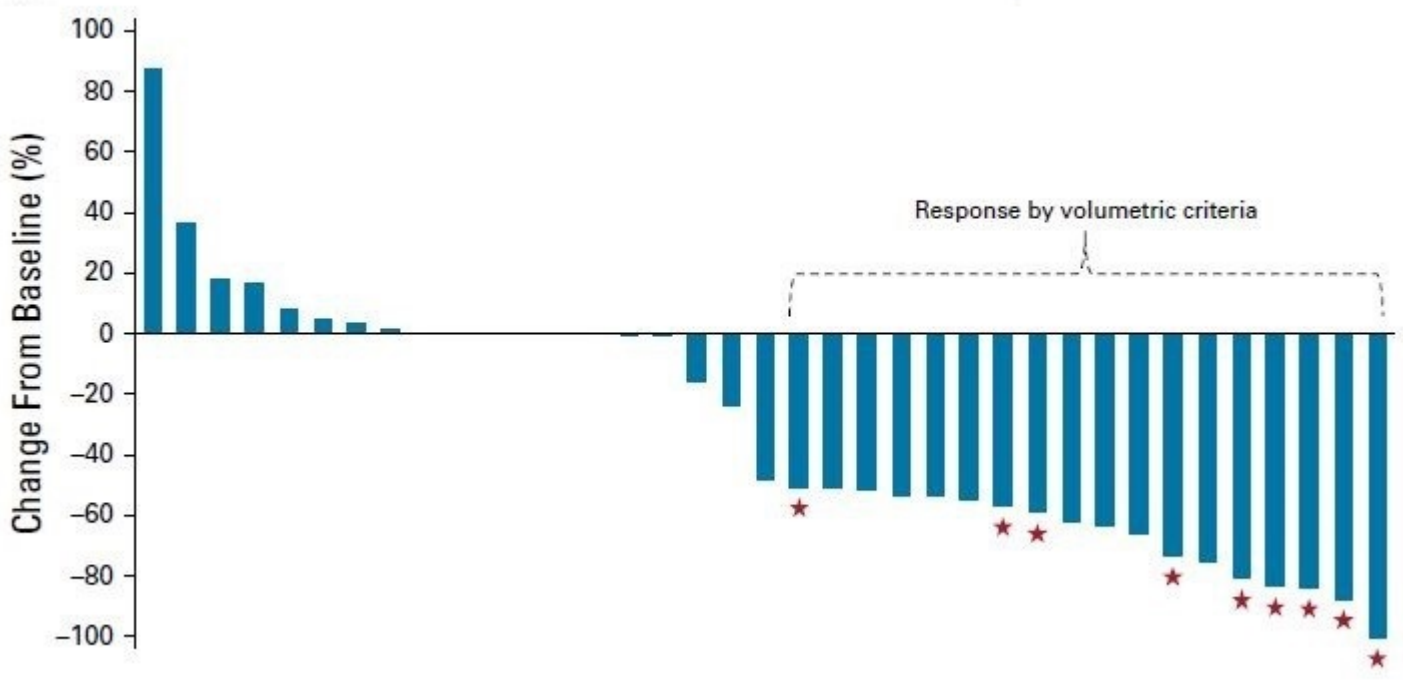
TBCRC 022 Phase II Trial: Neratinib + Capecitabine for BM in HER2+ MBC

- Combination of neratinib + capecitabine previously reported to be active in HER2+ MBC without BM
  - Neratinib monotherapy active against BM in HER2+ MBC
- TBCRC 022 Phase II trial: neratinib (240 mg/day) and capecitabine (750 mg/m^2 D1-14 of 3-wk cycle)
- Patients had ≥ 1 CNS lesion and CNS progression (new or previously treated site) after ≥1 line of local CNS therapy
  - Primary endpoint: composite CNS ORR*

*Requiring reduction of ≥50% in sum of target CNS lesion volumes without progression of nontarget lesions, new lesions, escalating steroids, progressive neurologic signs or symptoms, or non-CNS progression.

Saura C, et al. *J Clin Oncol*. 2014;32:3626-33; Freedman RA, et al. *J Clin Oncol*. 2019;37:1081-9.

TBCRC 022: Best CNS Volumetric Response



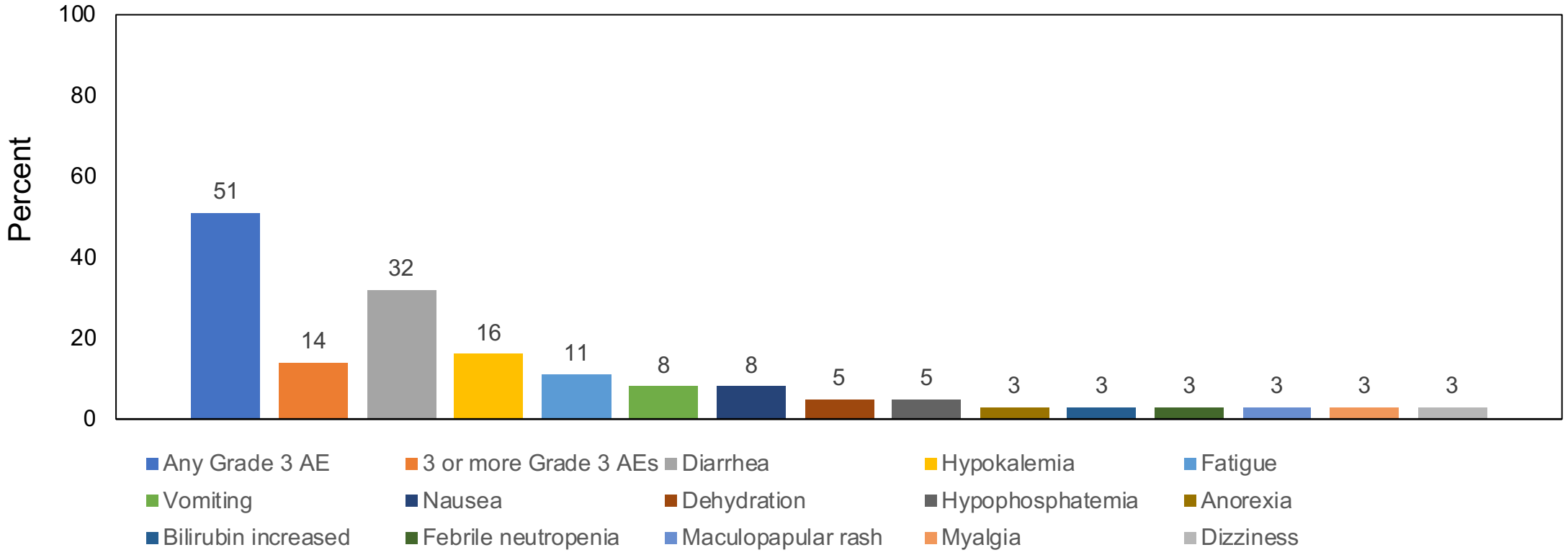
CNS ORR (by RANO-BM): 24% (95% CI 12-41%)

Best CNS Response (n = 37)	Composite Criteria, n (%)
Complete response	–
Partial response	18 (49)
Stable disease ≥6 cycles†	7 (19)
Stable disease <6 cycles†	5 (14)
Progressive disease	
Progressive disease in CNS only	1 (3)
Symptomatic deterioration or clinical progression before restaging	2 (5)
Progressive disease (CNS and non-CNS)	–
Off treatment before restaging due to toxicity (n = 3) or MD discretion (n = 1)	4 (11)

†Cycles initiated.

Freedman RA, et al. *J Clin Oncol*. 2019;37:1081-9.

TBCRC 022: Grade 3 Treatment-Related Adverse Events



Freedman RA, et al. *J Clin Oncol*. 2019;37:1081-9.

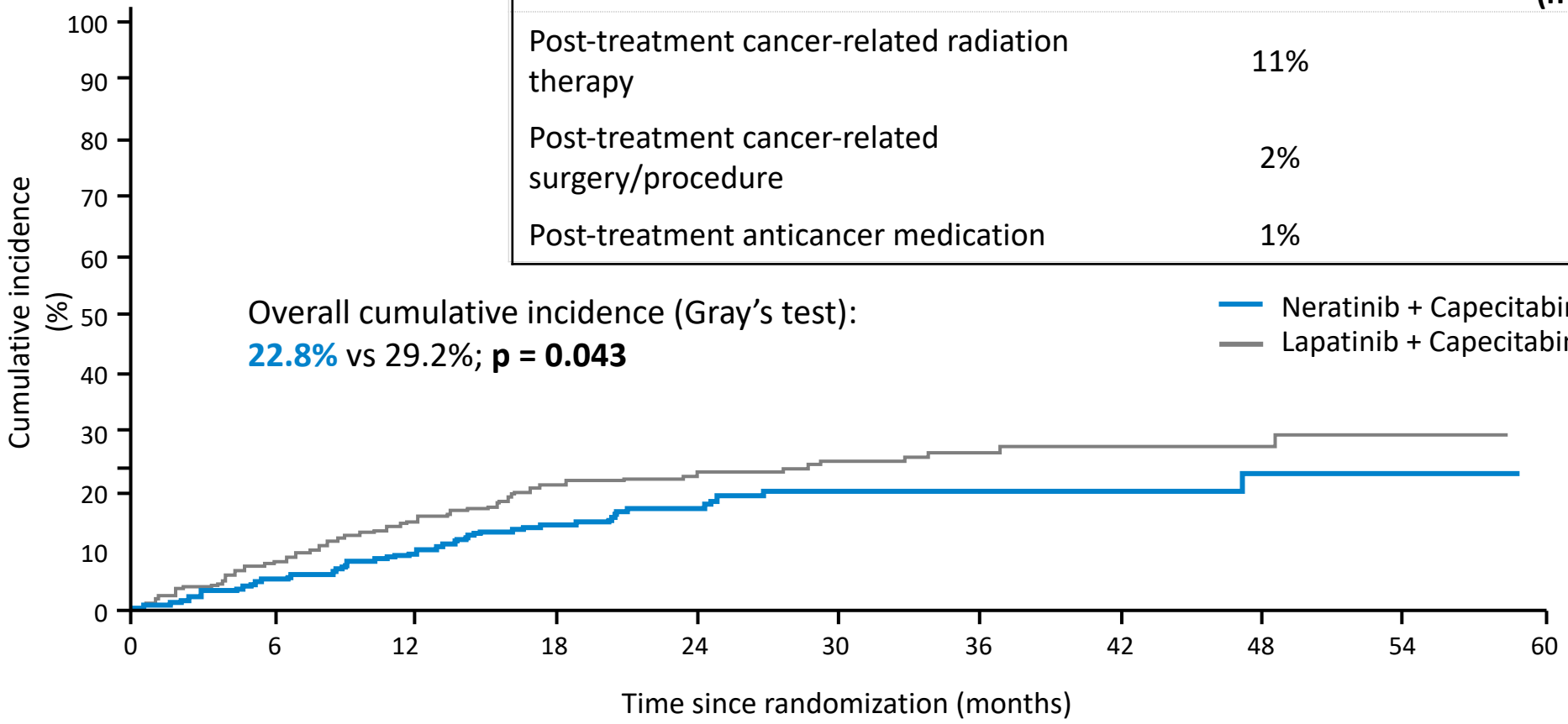
TBCRC 022: Conclusions

- Neratinib + capecitabine is an active regimen for pretreated patients with refractory HER2+ MBC and CNS metastases
  - 49% CNS ORR by composite criteria (33% in lapatinib-treated patients)
  - 24% CNS ORR by RANO-BM criteria
  - Reponses seen in patients with or without prior lapatinib exposure
- Median time to CNS progression: 5.5 months
  - Median OS: 13.5 months
- Prolonged disease control achieved in many patients (51% initiated 6+ cycles of therapy, 19% initiated 10+ cycles)

Freedman RA, et al. *J Clin Oncol*. 2019;37:1081-9.

NALA: Time to Intervention for CNS Metastases

Intervention	Neratinib + Capecitabine (n = 55/307)	Lapatinib + Capecitabine (n = 75/314)
Post-treatment cancer-related radiation therapy	11%	15%
Post-treatment cancer-related surgery/procedure	2%	3%
Post-treatment anticancer medication	1%	1%



Clinical Pearls: Management of CNS Metastases

- Management of BM is increasingly important given recent improvements in survival of patients with HER2+ breast cancer
- TBCRC 022 and NALA results support the use of chemotherapy to enhance HER2-directed therapy for BM
- NCCN now recommends neratinib + capecitabine regimen as a treatment option for CNS disease in HER2+ MBC
  - ASCO Clinical Practice Guideline (2018) states: ”For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer”

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V2.2019;
Ramakrishna N, et al. *J Clin Oncol*. 2018;36:2804-7.

ASCO, American Society of Clinical Oncology.

Trastuzumab Biosimilars for HER2+ Breast Cancer

Case Study

- 54-year-old woman with HER2+ MBC is to receive chemotherapy and a trastuzumab biosimilar
- She voices concerns about receiving a biosimilar

Which of the following is the most appropriate course of action?

A. Tell her it is OK since biosimilar trastuzumab is a generic of reference trastuzumab
B. Tell her you understand and withhold therapy
C. Explain the rigorous testing process for biosimilars and address any other concerns
D. Switch her to therapy to neratinib and capecitabine

Trastuzumab Biosimilars

- A biosimilar is “a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product”
- Unmet clinical need exists for trastuzumab biosimilars, given
  - Increasing use of/ indications for trastuzumab, and duration of therapy
  - High cost of parent drug and inadequate reimbursement, resulting in undertreatment
  - Lack of coverage for off-label use
- Adverse event profiles comparable to trastuzumab

Biological Product Definitions. Available at: www.fda.gov; Uifălean A, et al. *Pharmaceutics.* 2018;10:168; Blackwell K, et al. *Clin Breast Cancer.* 2018;18:95-113.

FDA-Approved Trastuzumab Biosimilars
(only one currently marketed in US)

Trade Name (Generic)	Manufacturer	Approval Date
Ogivri (trastuzumab-dkst)	Mylan	December 1, 2017
Herzuma (trastuzumab-pkrb)	Celltrion, Teva Pharmaceutical	December14, 2018
Ontruzant (trastuzumab-dttb)	Samsung Bioepis	January 20, 2019
Trazimera (trastuzumab-qyyp)	Pfizer	March 11, 2019
Kanjinti (trastuzumab-anns)*	Amgen, Allergan	June 13, 2019

*Now commercially available in the U.S.

Potential Issues with Biosimilars

- Practitioner and patient awareness/education
- Benefits (eg, increased drug access, lower cost)
- Comparability to parent drug (substitution)
  - Choosing between multiple trastuzumab biosimilars
- Extrapolation of indications to other settings
- Possible PK/PD differences
- Safety, including immunogenicity and long-term use (pharmacovigilance)
- Time lag between FDA approval and availability

Clinical Pearls: Trastuzumab Biosimilars for HER2+ Breast Cancer

- A significant need exists for trastuzumab biosimilars in order to increase patient access and affordability
- Trastuzumab biosimilars marketed abroad; now available in US
  - Efficacy and safety are comparable to trastuzumab in phase III trials
- Practitioners need to be informed about the production, approval process, and interchangeability of biosimilars for breast cancer therapy

Management of Common Adverse Events

Case Study

- 49-year-old woman with IDC of breast (ER-, PR-, HER2+) is continuing trastuzumab after mastectomy (neoadjuvant TCHP)
- Prior to the start of chemotherapy, LVEF was 65% with global longitudinal strain of -25.5 %
- At 3-month follow-up study, LVEF was 58% with global longitudinal strain -19%, representing a 25% reduction in strain from baseline
- No current symptoms

Treatment options?

A. Continue trastuzumab until a 16% drop in LVEF is noted
B. Hold therapy and repeat testing in 6 weeks
C. Continue therapy and consider cardioprotective measures
D. Change to biosimilar trastuzumab
E. Collaborate with cardio-oncology expert

IDC, invasive ductal carcinoma.

Common Toxicities with HER2-Targeted Therapies

- Fatigue
- Headache
- Rash
- Alopecia
- GI toxicities
- Hematologic toxicities
- Peripheral neuropathy
- Cardiotoxicity

- May occur with monotherapy and in combination regimens

Treatment-Associated Cardiotoxicity

Anthracyclines

HER2 antagonists

Radiation involving heart field

- Improved therapy → decreased mortality, more cancer survivors
- CV death is greatest among patients > age 65
- CV toxicity decreases survival and QoL
- Significant number of survivors are affected by treatment-induced permanent myocardial damage

Cardiotoxicity with HER2 Inhibitors

- Most frequent adverse event with trastuzumab treatment
  - Primarily asymptomatic decline in LVEF, especially when used with anthracyclines or in high-risk patients with pre-existing cardiac conditions
  - Secondary cardiac events* reported in 7% of patients with trastuzumab monotherapy and up to 19% with trastuzumab + chemotherapy
- Avoid concomitant use of trastuzumab and anthracyclines
- Cardiotoxicity usually reversible
- Can rechallenge after recovery

*Secondary cardiac endpoints classified as asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II).

Mazzotta M, et al. *J Clin Med*. 2019;18;8; Mantarro S, et al. *Intern Emerg Med*. 2016;11:123-40.

Risk Factors for Cardiotoxicity with Anthracyclines and Trastuzumab Therapy

Anthracyclines

- Cumulative dose
- Female sex
- Age >60 yr
- Concomitant or previous
- radiation therapy to the heart
- Concomitant chemotherapy with alkylating or antimicrotubule agents or immuno- and targeted therapies
- Selected pre-existing conditions (eg, cardiac diseases, CV risk factors, renal failure, genetic factors)

Trastuzumab

- Previous or concomitant anthracyclines
- Short interval between anthracycline and anti-HER2 treatment
- Age >65 yr
- Body mass index >30 kg/m^2
- Previous left ventricular dysfunction
- Arterial hypertension
- Prior radiation therapy

Niccolazzi MA, et al. *Eur Rev Med Pharmacol Sci.* 2018;22:2175-85; Armenian SH, et al. *J Oncol Pract*. 2017;13:270-5

Prevention and Management of Cardiotoxicity

- Ensure accurate analysis of pre-existing cardiovascular risk factors and any subclinical cardiovascular damage
  - LVEF recommended after treatment in high-risk patients or when using high doses of anthracyclines
- Global systolic longitudinal myocardial strain (GLS) is gold standard for predicting LV dysfunction with cardiotoxic chemotherapy
  - GLS reduction of 15% from baseline is considered abnormal
- Thorough assessment of optimal type and cumulative dose of planned therapy is essential
  - Consider holding or reducing dose*
  - Treat with ACE inhibitor, beta blocker, or cardioprotectant if indicated
  - Post-Rx echo in asymptomatic patients at increased risk of cardiac dysfunction

Niccolazzi MA, et al. *Eur Rev Med Pharmacol Sci.* 2018;22:2175-85;
Armenian SH, et al. *J Clin Oncol*. 2017;35:893-911.

*See prescribing information for individual products.
ACE, angiotensin-converting enzyme.

Cardiac Biomarkers
ABCDE Steps for Prevention

- Brain natriuretic peptide
- Troponin TnI
- N-terminal pro-BNP

- Awareness of risks
- Aspirin
- Blood pressure
- Cholesterol
- Cigarette cessation
- Diet and weight management
- Dose of chemo/XRT
- Diabetes prevention/Rx
- Exercise
- Echocardiogram

Montazeri K, et al. *Circulation*. 2014;30:e157-9.

Clinical Practice Guideline

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline Summary

Saro H. Armenian, Christina Lacchetti, and Daniel Lenihan

Armenian SH, et al. *J Oncol Pract*. 2017;13:270-5.

Case Study

- 42-year-old woman with stage IIIB ER+, PR+, HER2+ IDC received neoadjuvant TCHP but did not achieve a pathCR
- She received ado-trastuzumab following surgery, and was prescribed neratinib in the extended adjuvant setting

Which of the following should be prescribed in addition to neratinib?

A. Loperamide every 2 hr until no diarrhea for 12 hr x 2 cycles
B. Colestipol 2 g 2 x daily with loperamide as needed x 1 cycle
C. Budesonide 9 mg daily with scheduled loperamide
D. Escalate neratinib dose with loperamide as needed
E. Begin long-acting octreotide and loperamide

Diarrhea with HER2-Directed Therapy

- Common adverse effect with HER2 therapy (incidence varies with agent)
- Can result in
  - Dose reductions or delays
  - Reduced quality of life
  - Higher costs
  - Reduced treatment adherence
  - Potentially life-threatening

Swain SM, et al. *Annals Oncol*. 2017;28:761-8; Mortimer J, et al. *Breast Cancer Res*. 2019;21:32; Chan A, et al. *Lancet Oncol*. 2016;17:e176-7.

Neratinib-Associated Diarrhea

- Common on-target toxicity with EGFR and HER2 inhibitors
  - Inhibition of EGFR can induce secretory diarrhea
  - Possible inflammatory, secretory, and bile acid malabsorption etiologies, which supports therapies for treating the diarrhea
- Diarrhea most commonly observed adverse event with neratinib
  - Occurs in up to two-thirds of all treated patients (all grades)
  - Reported in 95% of patients in ExteNET trial (93% within first month); 40% Grade 3 severity
    - Higher-grade diarrhea occurs early and generally does not recur
    - Median time to first onset of grade ≥3 diarrhea: 8 days; median duration: 5 days

Dy GK, et al. *CA Cancer J Clin*. 2013;63:249; Mortimer J, et al. *Breast Cancer Res*. 2019;21:32;
Chan A, et al. *Lancet Oncol*. 2016;17:e176-7.

The CONTROL Study Was Designed to Investigate Management Strategies for Neratinib-Associated Diarrhea

Phase 2 Open-Label Study

OBJECTIVE:

to investigate the efficacy of

proactive diarrhea management with mandated prophylaxis or neratinib dose-escalation

for the prevention of neratinib-associated diarrhea in patients with HER2-positive early-stage breast cancer

Stage 1-3c HER2+ Breast Cancer

Neratinib
240 mg, 1x daily

Neratinib
Dose Escalation

Additional patient cohorts added to investigate adding **budesonide**, a locally acting corticosteroid used for inflammatory gastrointestinal conditions, **colestipol**, a bile acid sequestrant, or **neratinib dose-escalation** for neratinib-associated diarrhea.

Barcenas CH, et al. ASCO 2019. Abstract 548.

Management of Diarrhea with Neratinib

- Initiate antidiarrheal prophylaxis with loperamide, plus budesonide or colestipol with initial neratinib dose, and continue during first two cycles; dose escalation optional
- Aggressively manage with additional antidiarrheals, fluids, and electrolytes as indicated
  - Withhold neratinib for severe and/or persistent diarrhea, and reduce subsequent doses
  - Permanently discontinue in case of grade 4 diarrhea or grade ≥2 diarrhea that occurs following maximal dose reduction
- Need for patient and provider awareness of compliance monitoring

Barbee MS. *Oncology (Williston Park)*. 2019;33:232-4.

Role of Advanced Practitioners in Managing Patients on HER2 Therapy

- Knowledge of treatment options and patient selection
- Essential baseline assessments
  - Extent of disease
  - Cardiovascular history and assessments (eg, LVEF)
  - Gastrointestinal history and assessments as required
- Monitor for toxicities and patient adherence to oral medications
- Patient education
  - Disease
  - Therapy
  - Proactive self-management of potential toxicities
  - Report unexpected or serious side effects immediately

Conclusions

- Historical standards of care for HER2+ breast cancer have been impacted by emerging evidence over the last several years
- Data support the use of pertuzumab as combination therapy in the neoadjuvant, adjuvant, and metastatic settings
- PathCR is now predictive of outcome and directive of adjuvant therapy
- Advances in the extended adjuvant setting point to a new SOC
- Breast cancer patients are living longer, and therapy is being refined in the metastatic setting, with specific guidelines addressing CNS metastases

Improving Outcomes in HER2+ Breast Cancer: Analysis and Application of Evolving Data and Best Practices

Thank you for joining us!

Please complete your evaluation.