Optimal Treatment for Early Stage HER2-Positive Breast Cancer: Tailoring Treatment to Response

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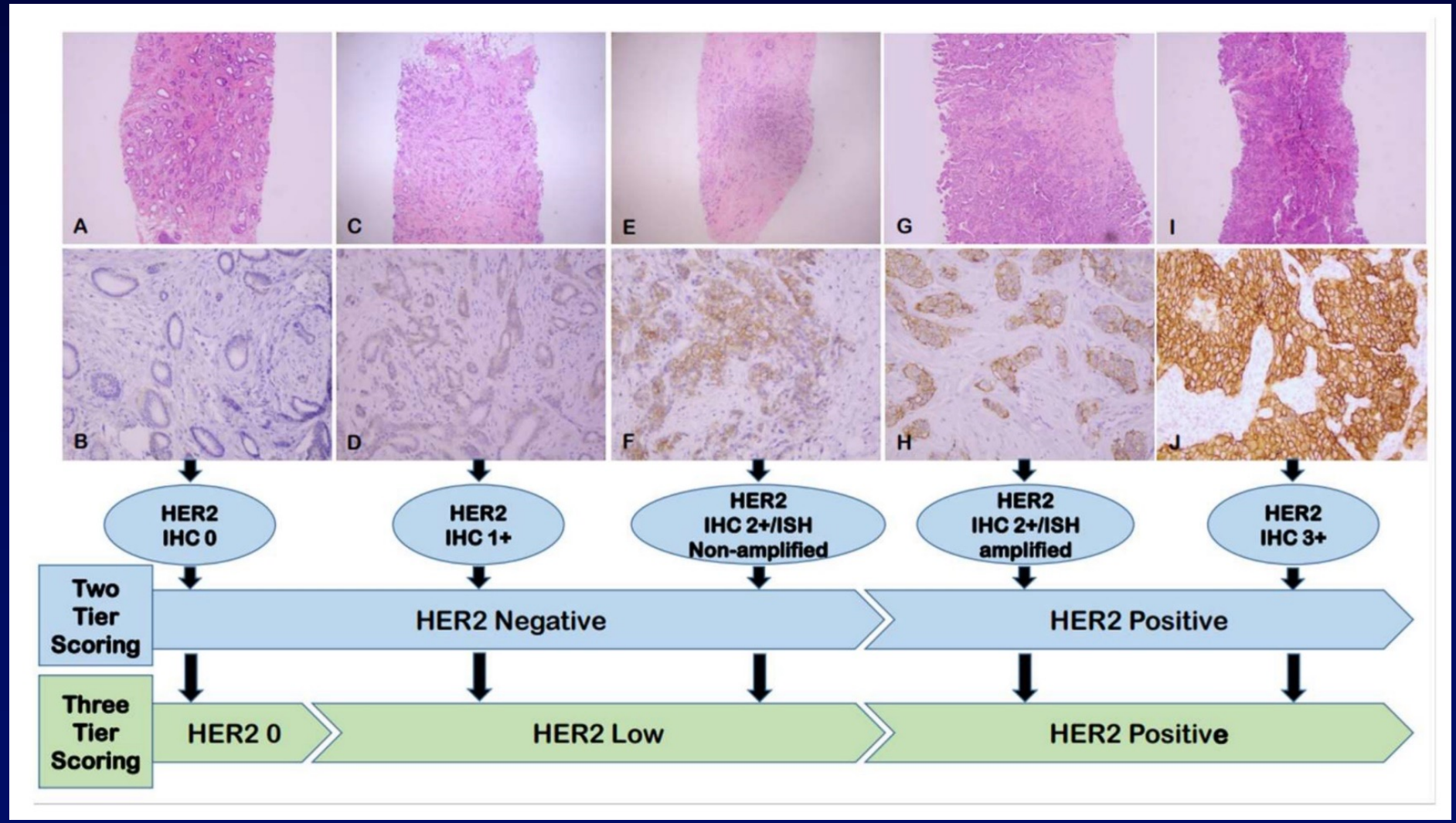
Overview

- HER2 Classification
- Neoadjuvant Approach
  - NeoSphere | TRYPHAENA | TRAIN-2 | ~~KRISTINE~~ | *APTneo*
- Adjuvant Therapy
  - APT | ATEMPT | APHINITY | ExteNET
- Post-Neoadjuvant:
  - Katherine | ExteNET | *COMPASSHER2 RD* | *Destiny-Breast 05 (NSABP B-60)*

Defining HER2 Status



NSABP B-47/NRG Oncology Phase III Randomized Trial Comparing Adjuvant Chemotherapy With or Without Trastuzumab in High-Risk Invasive Breast Cancer Negative for HER2 by FISH and With IHC 1+ or 2+

Louis Fehrenbacher, MD[1,2]; Reena S. Cecchini, PhD[1,3]; Charles E. Geyer Jr , MD[1,4]; Priya Rastogi, MD[1,5]; Joseph P. Costantino, DrPH[1,3]; James N. Atkins, MD[1,6]; John P. Crown, MD[1,7,8]; Jonathan Polikoff, MD[1,9]; Jean-Francois Boileau, MD[1,10]; Louise Provencher, MD[1,11]; Christopher Stokoe, MD[1,12]; Timothy D. Moore, MD[1,13]; André Robidoux, MD[1,14]; Patrick J. Flynn, MD[1,15]; Virginia F. Borges, MD[1,16]; Kathy S. Albain, MD[1,17]; Sandra M. Swain, MD[1,18]; Soonmyung Paik, MD[1,19]; Eleftherios P. Mamounas, MD[1,20]; and Norman Wolmark, MD[1]

J Clin Oncol 38:444-453. © 2019 by American Society of Clinical Oncology

N = 3,270

Dates:
2/8/2011 to
2/10/2015

Adjuvant HER2 Therapy Low HER2 Expression Tumors

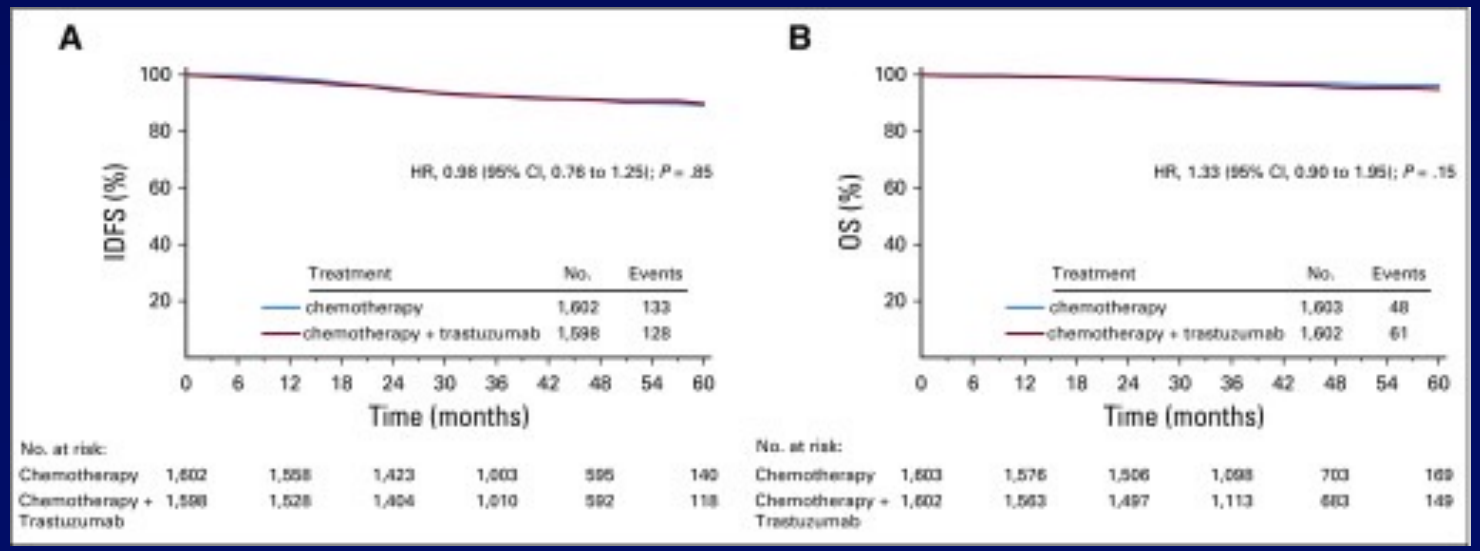
ONGOING NSABP B-47: Adjuvant Trastuzumab in Breast Cancer with Normal HER2 Expression

N= 3,260

Primary Breast Cancer
HER2 IHC 1+ or 2+
FISH Negative

Randomization

Docetaxel + Cyclophosphamide x 6 or AC x 4 + Paclitaxel x 12 (MD Choice)	Docetaxel + Cyclophosphamide x 6 or AC x 4 + Paclitaxel x 12 (MD Choice) + Trastuzumab x 1 yr



Destiny-Breast04

The NEW ENGLAND JOURNAL of MEDICINE

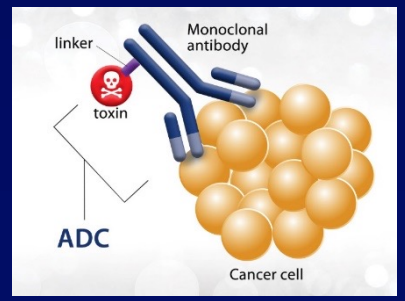
ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

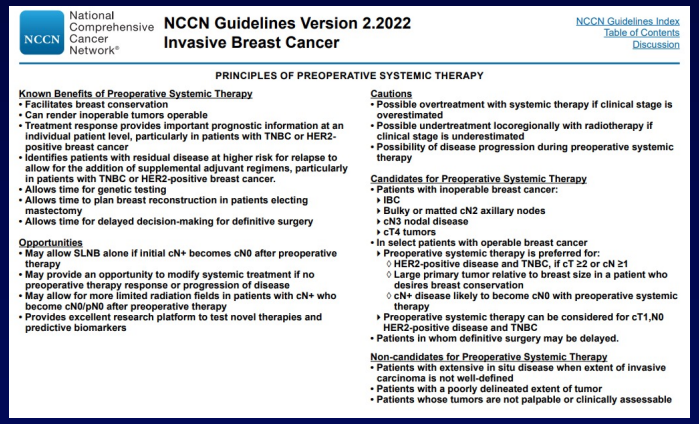
- New definition of breast cancer subtype
- FDA Approved on August 5, 2022
  - 2nd line M1 or within 6 months of adjuvant therapy

5-Aug-2022



Groundbreaking Plenary Session ASCO 2022

Rationale Neoadjuvant Systemic Therapy



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

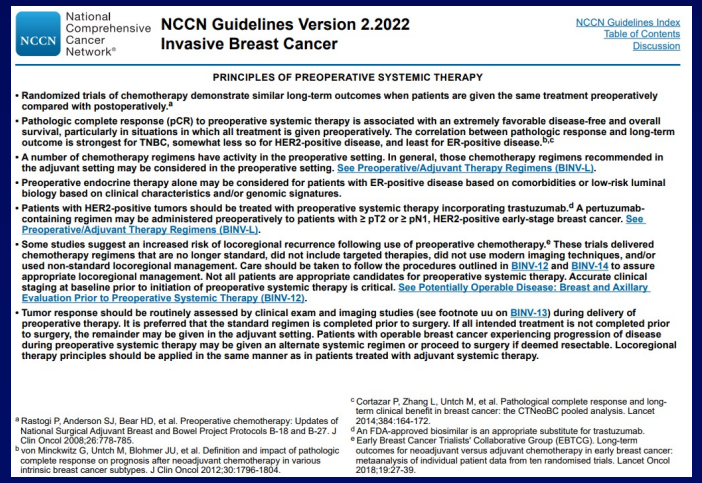
Known Benefits of Preoperative Systemic Therapy
- Facilitates breast conservation
- Can render inoperable tumors operable
- Treatment response provides important prognostic information at an individual patient level, particularly in patients with TNBC or HER2-positive breast cancer
- Identifies patients with residual disease at higher risk for relapse to allow for the addition of supplemental adjuvant regimens, particularly in patients with TNBC or HER2-positive breast cancer.
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy
- Allows time for delayed decision-making for definitive surgery

Opportunities
- May allow SLNB alone if initial cN+ becomes cN0 after preoperative therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease
- May allow for more limited radiation fields in patients with cN+ who become cN0/pN0 after preoperative therapy
- Provides excellent research platform to test novel therapies and predictive biomarkers

Cautions
- Possible overtreatment with systemic therapy if clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

Candidates for Preoperative Systemic Therapy
- Patients with inoperable breast cancer:
  - IBC
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - cT4 tumors
- In select patients with operable breast cancer
  - Preoperative systemic therapy is preferred for:
    - HER2-positive disease and TNBC, if cT ≥2 or cN ≥1
    - Large primary tumor relative to breast size in a patient who desires breast conservation
    - cN+ disease likely to become cN0 with preoperative systemic therapy
  - Preoperative systemic therapy can be considered for cT1,N0 HER2-positive disease and TNBC
- Patients in whom definitive surgery may be delayed.

Non-candidates for Preoperative Systemic Therapy
- Patients with extensive in situ disease when extent of invasive carcinoma is not well-defined
- Patients with a poorly delineated extent of tumor
- Patients whose tumors are not palpable or clinically assessable



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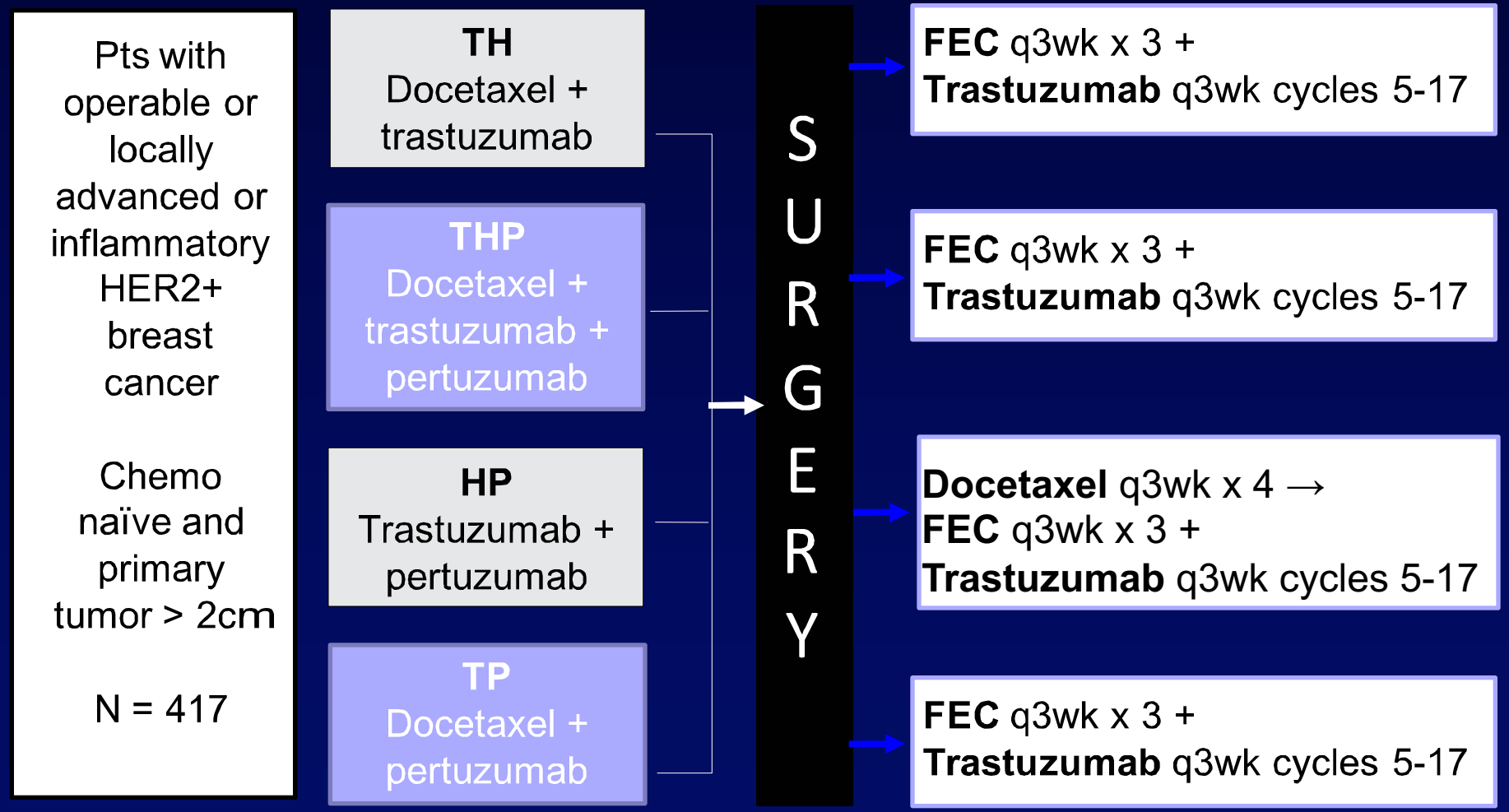
PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

- Randomized trials of chemotherapy demonstrate similar long-term outcomes when patients are given the same treatment preoperatively compared with postoperatively.[a]
- Pathologic complete response (pCR) to preoperative systemic therapy is associated with an extremely favorable disease-free and overall survival, particularly in situations in which all treatment is given preoperatively. The correlation between pathologic response and long-term outcome is strongest for TNBC, somewhat less so for HER2-positive disease, and least for ER-positive disease.[b,c]
- A number of chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. See Preoperative/Adjuvant Therapy Regimens (BINV-L).
- Preoperative endocrine therapy alone may be considered for patients with ER-positive disease based on comorbidities or low-risk luminal biology based on clinical characteristics and/or genomic signatures.
- Patients with HER2-positive tumors should be treated with preoperative systemic therapy incorporating trastuzumab.[d] A pertuzumab-containing regimen may be administered preoperatively to patients with ≥ pT2 or ≥ pN1, HER2-positive early-stage breast cancer. See Preoperative/Adjuvant Therapy Regimens (BINV-L).
- Some studies suggest an increased risk of locoregional recurrence following use of preoperative chemotherapy.[e] These trials delivered chemotherapy regimens that are no longer standard, did not include targeted therapies, did not use modern imaging techniques, and/or used non-standard locoregional management. Care should be taken to follow the procedures outlined in BINV-12 and BINV-14 to assure appropriate locoregional management. Not all patients are appropriate candidates for preoperative systemic therapy. Accurate clinical staging at baseline prior to initiation of preoperative systemic therapy is critical. See Potentially Operable Disease: Breast and Axillary Evaluation Prior to Preoperative Systemic Therapy (BINV-12).
- Tumor response should be routinely assessed by clinical exam and imaging studies (see footnote uu on BINV-13) during delivery of preoperative therapy. It is preferred that the standard regimen is completed prior to surgery. If all intended treatment is not completed prior to surgery, the remainder may be given in the adjuvant setting. Patients with operable breast cancer experiencing progression of disease during preoperative systemic therapy may be given an alternate systemic regimen or proceed to surgery if deemed resectable. Locoregional therapy principles should be applied in the same manner as in patients treated with adjuvant systemic therapy.

[a] Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26:778-785.
[b] von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30:1796-1804.
[c] Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-172.
[d] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[e] Early Breast Cancer Trialists' Collaborative Group (EBTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: metaanalysis of individual patient data from ten randomised trials. Lancet Oncol 2018;19:27-39.

- If systemic adjuvant therapy is indicated, then neoadjuvant use of the same regimen is also an appropriate option
  - COVID-19
  - Patient-centered care
- In-vivo assessment of response to systemic therapy
- Complete pathological response, pCR, is an early surrogate marker for long term outcome, DFS and OS specially in ER-HER-2+ and TNBC
- It potentially provides molecular and biological information of the mechanism of sensitivity and resistant to systemic therapy including predictive markers, and new targets
- Improved tumor down-staging, operability and BCS rates
- May expedite new drug development and FDA approval in EBC

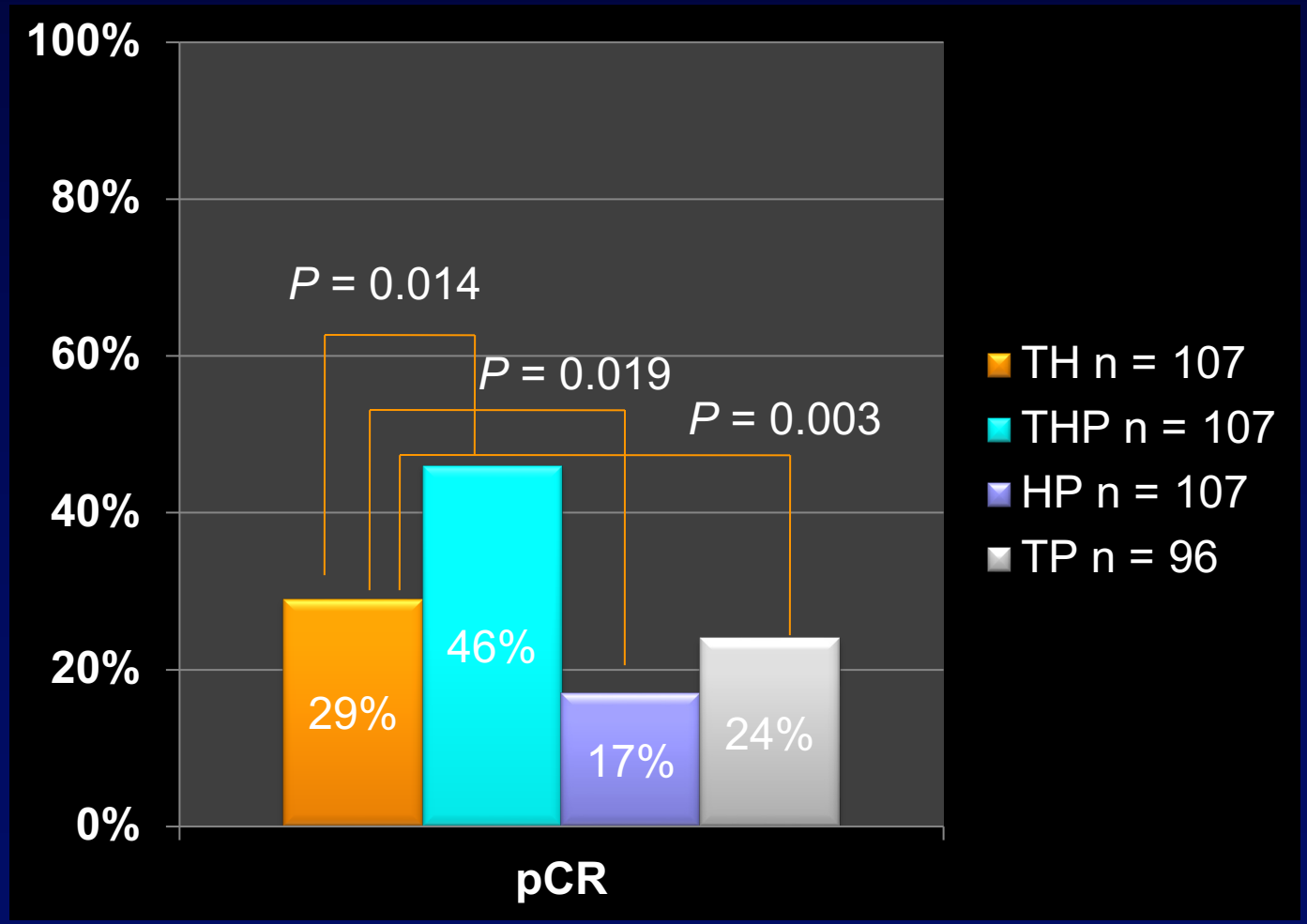
NAC HER2+: Phase II NeoSphere Study



FEC = 5-fluorouracil, epirubicin, and cyclophosphamide

Gianni L, et al. *Lancet Oncol.* 2012;13(1):25-32.

NeoSphere Primary Outcome Measure: pCR*



*Pathologic complete response (pCR) rate defined as the absence of invasive cancer in the breast at the time of surgery.
T = docetaxel; H = trastuzumab, P = pertuzumab.

Gianni L, et al. *Lancet Oncol.* 2012;13(1):25-32.

NAC HER2+: Phase II TRYPHAENA Study

Operable,
Locally
Advanced,
Inflammatory,
HER2+,
Chemo-naïve
T>2cm

N = 225

epirubi/cyclo x 3 // docetaxel x 3 plus

→

trastuzumab /pertuzumab

Epirubi/cyclo
X3

docetaxel x 3 plus

trastuzu/ pertuzu

Docetaxel / Carboplatin

Trastuzumab /pertuzumab

(TCHP) X 6

SURGERY / XRT

Trastuzumab
+ pertuzumab

to 1 year

Trastuzumab
+ pertuzumab

to 1 year

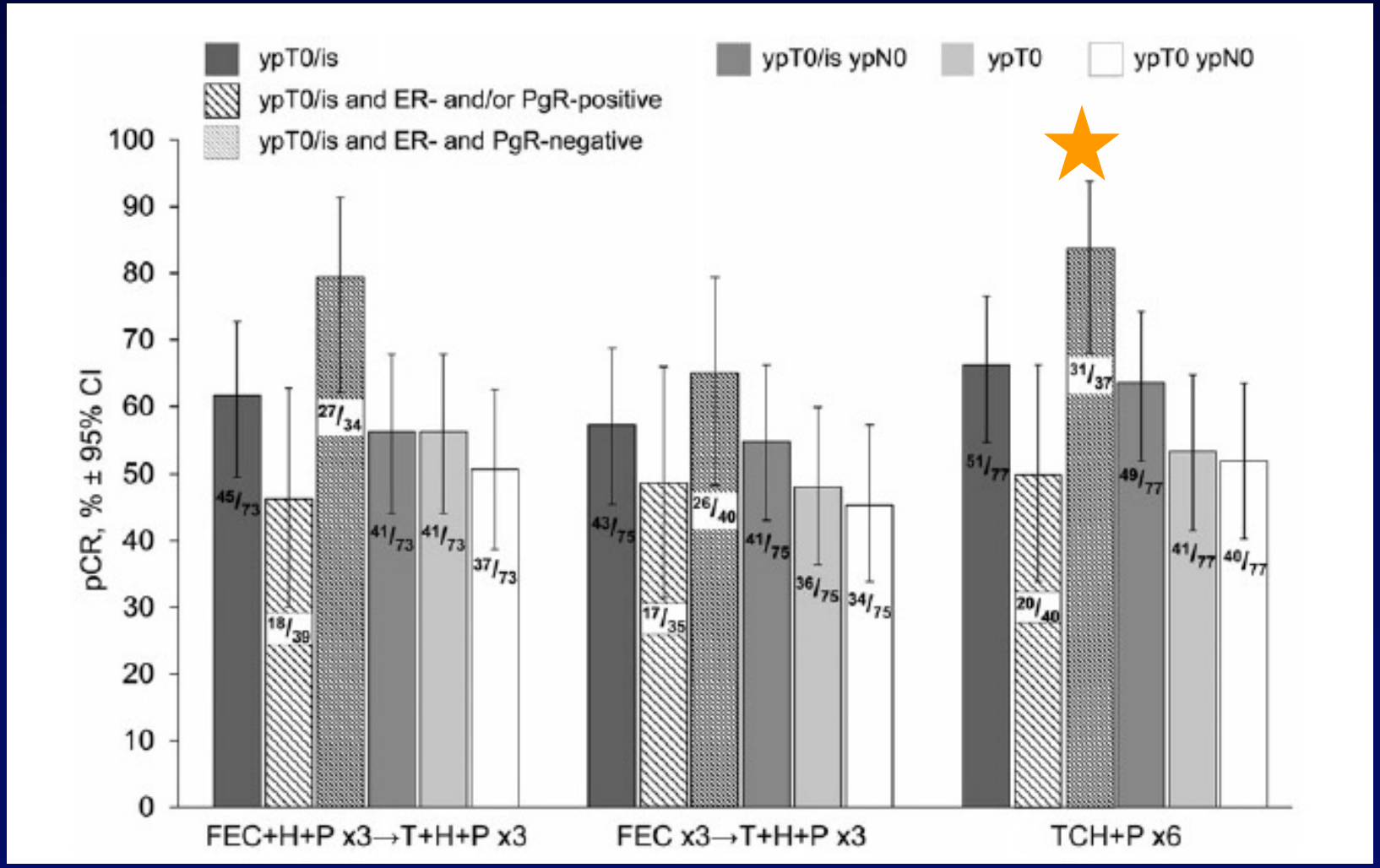
Trastuzumab
+ pertuzumab

to 1 year

Additional chemoRx
if required

Schneeweiss, et al. SABCS 2011

TRYPHAENA: pCR Rates by Hormone Receptor Status



Role of non-anthracycline therapy: TRAIN-2

Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial

Mette S van Ramshorst, Anna van der Voort, Erik D van Werkhoven, Ingrid A Mandjes, Inge Kemper, Vincent O Dezentjé, Irma M Oving, Aafke H Honkoop, Lidwine W Tick, Agnes J van de Wouw, Caroline M Mandigers, Laurence J van Warmerdam, Jelle Wesseling, Marie-Jeanne T Vrancken Peeters, Sabine C Linn, Gabe S Sonke, on behalf of the Dutch Breast Cancer Research Group (BOOG)

- Open-label, randomized, controlled, phase III trial

Stratified by cT (02- vs 3-4), cN (neg vs pos), ER status (neg vs pos), and age (<50 vs ≥50)

TCHP: 3-wk cycles, Day 1 TCHP, Day 8 T only. T, paclitaxel 80 mg/m^2; C, carboplatin AUC = 6 mg/min/mL; H, trastuzumab 6 mg/kg (loading dose 8 mg/kg); P, pertuzumab 420 mg (loading dose 840 mg).

FEC + HP: 3-wk cycles. F, 5-fluorouracil 500 mg/m^2; E, epirubicin 90 mg/m^2; C, cyclophosphamide 500 mg/m^2; H, trastuzumab 6 mg/kg (loading dose 8 mg/kg); P, pertuzumab 420 mg (loading dose 840 mg).

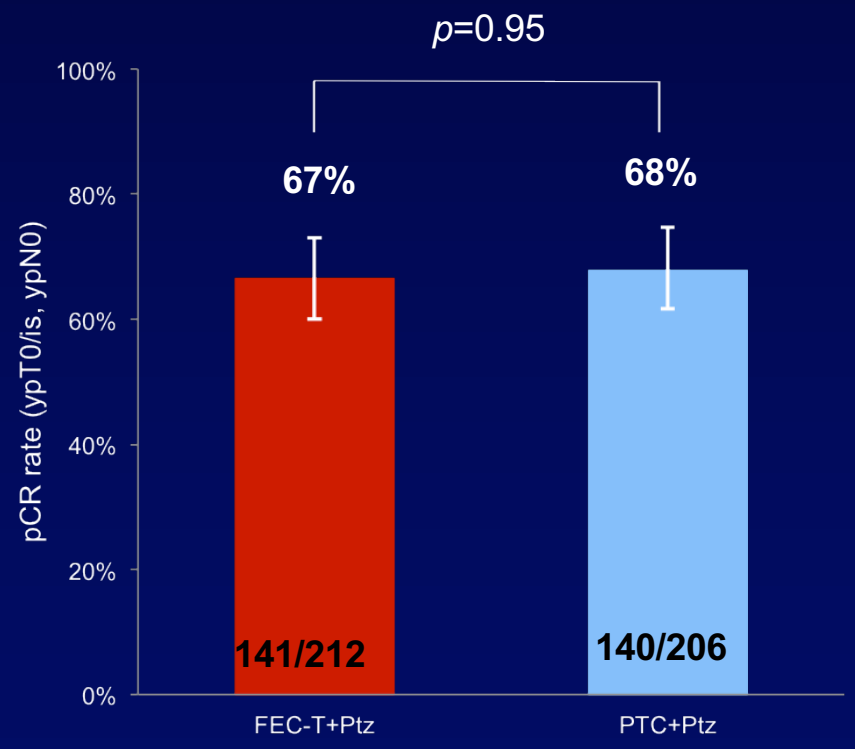
- Primary endpoint: pCR (ypT0/is, ypN0) by local assessment
- Secondary endpoints: safety, RFS, BCSS, OS

Van Ramshort. Lancet Oncol. 2018;19:1630. van der Voort. ASCO 2020. Abstr 501.

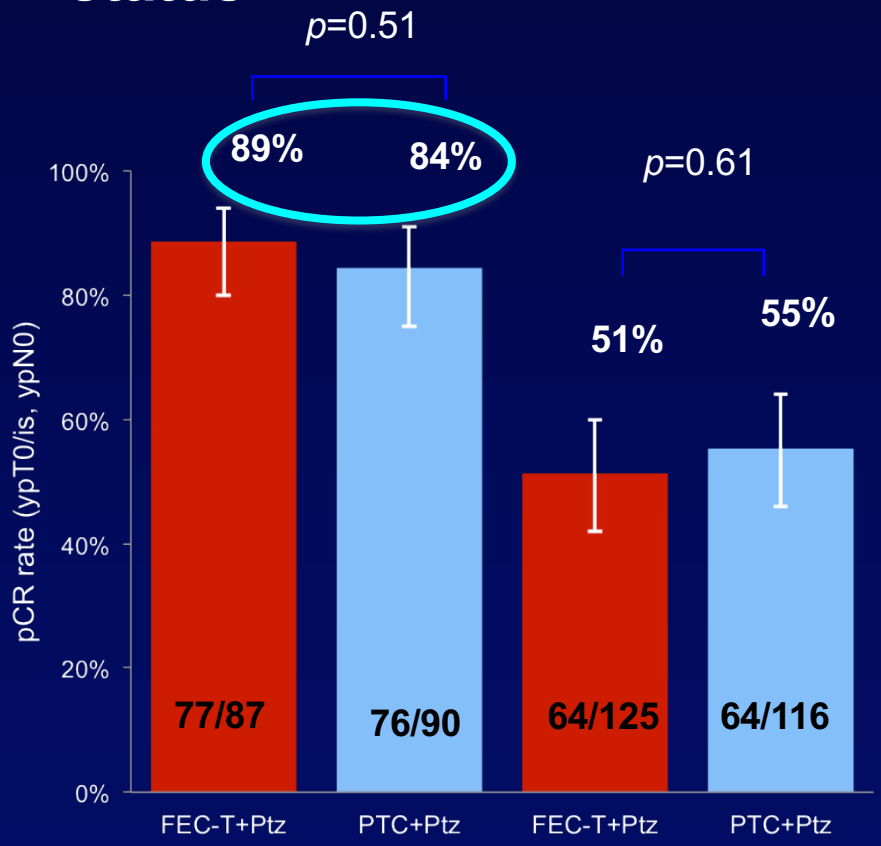
Lancet Oncol 2018; 19: 1630–40
Published Online
November 6, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30570-9

TRAIN-2: No difference with anthracyclines

Overall pCR



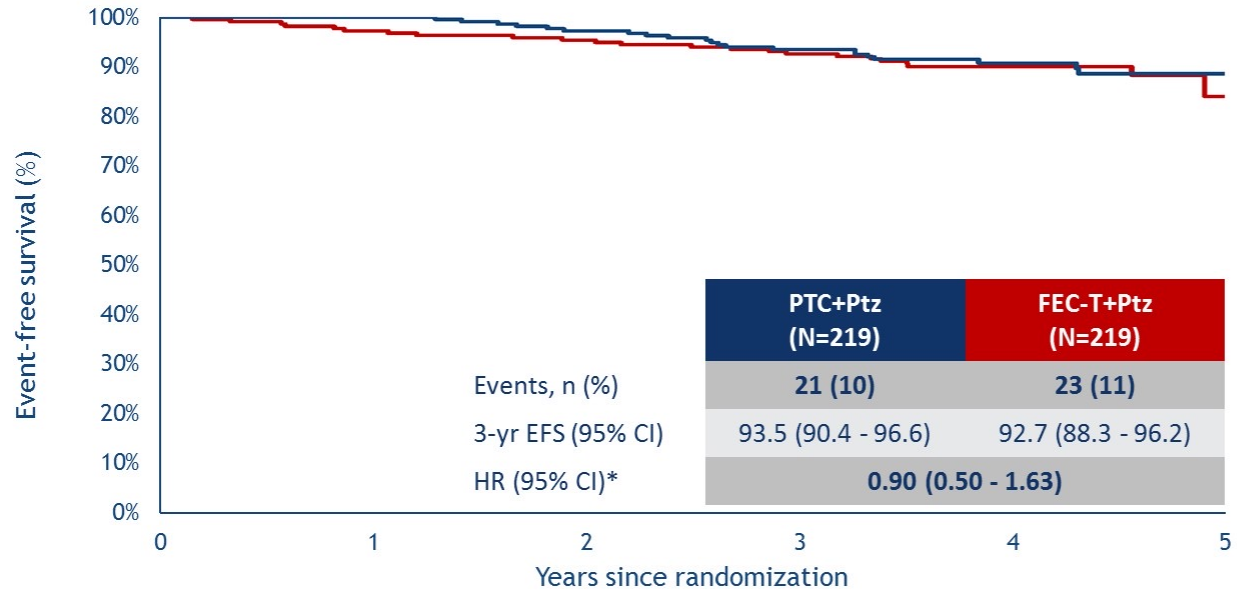
pCR by hormone receptor status



Preplanned subgroup analysis did not demonstrate superiority of FEC-T+Ptz > PTC+Ptz in any subgroups

TRAIN-2: No difference for including anthracycline

Event-free survival



	PTC+Ptz (N=219)	FEC-T+Ptz (N=219)
Events, n (%)	**21 (10)**	**23 (11)**
3-yr EFS (95% CI)	93.5 (90.4 - 96.6)	92.7 (88.3 - 96.2)
HR (95% CI)*	**0.90 (0.50 - 1.63)**	

No. at risk

PTC+Ptz	219	219	212	203	106	19
FEC-T+Ptz	219	213	209	200	103	17

*HR <1 favors PTC+Ptz

Presented By Anna van der Voort at TBD

Neoadjuvant Trastuzumab / Pertuzumab Review

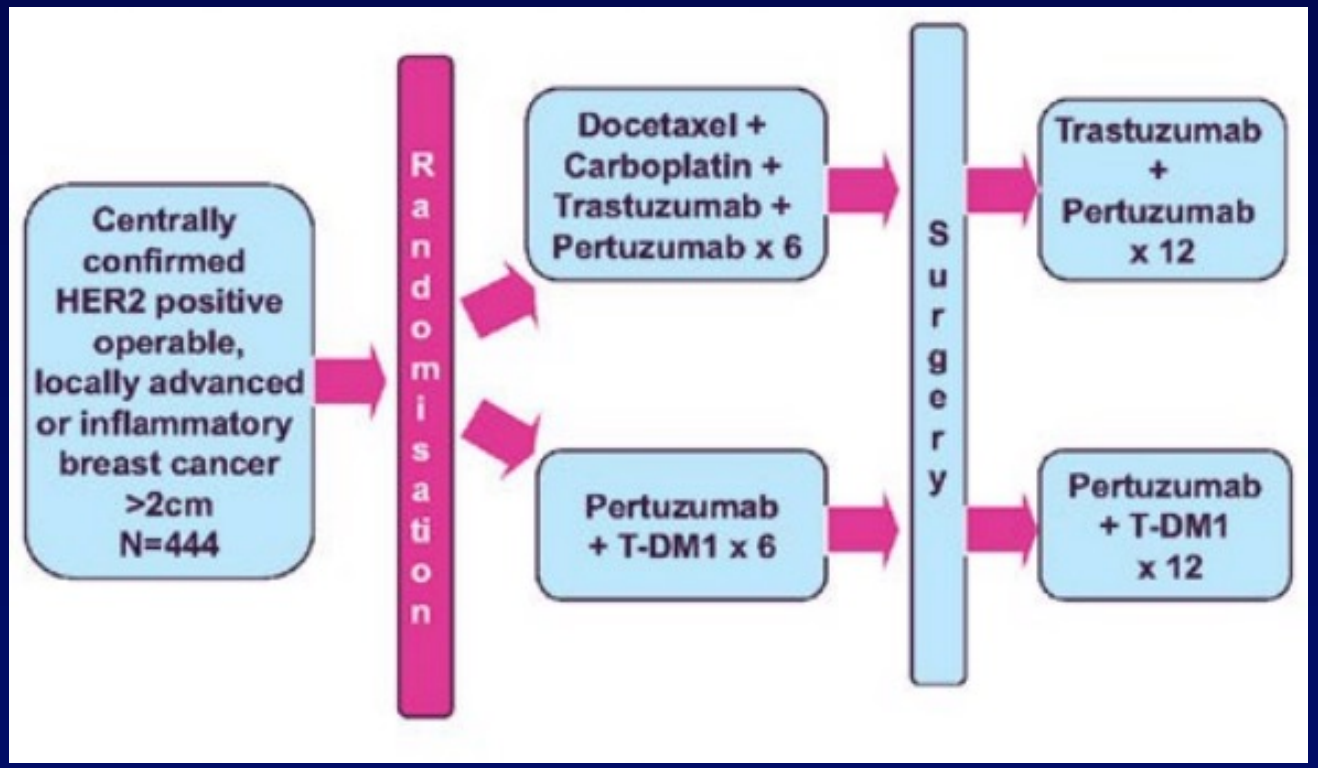
	NEOSPHERE[1]	TRYPHAENA[2]	TRYPHAENA[2]	TRAIN-2[3]	TRAIN-2[3]
Treatment	THP x 4 (FEC x 3 post-op)	TCHP x 6	FEC x 3 → THP x 3	TCHP x 9	FEC x 3 → TCHP x 6
N	107	77	75	206	212
ypT0/is ypN0 (%)	39	64	55	68	67
pCR (%) ER and PR neg	*63	84	65	84	89
pCR (%) ER and PR +	*26	50	49	55	51

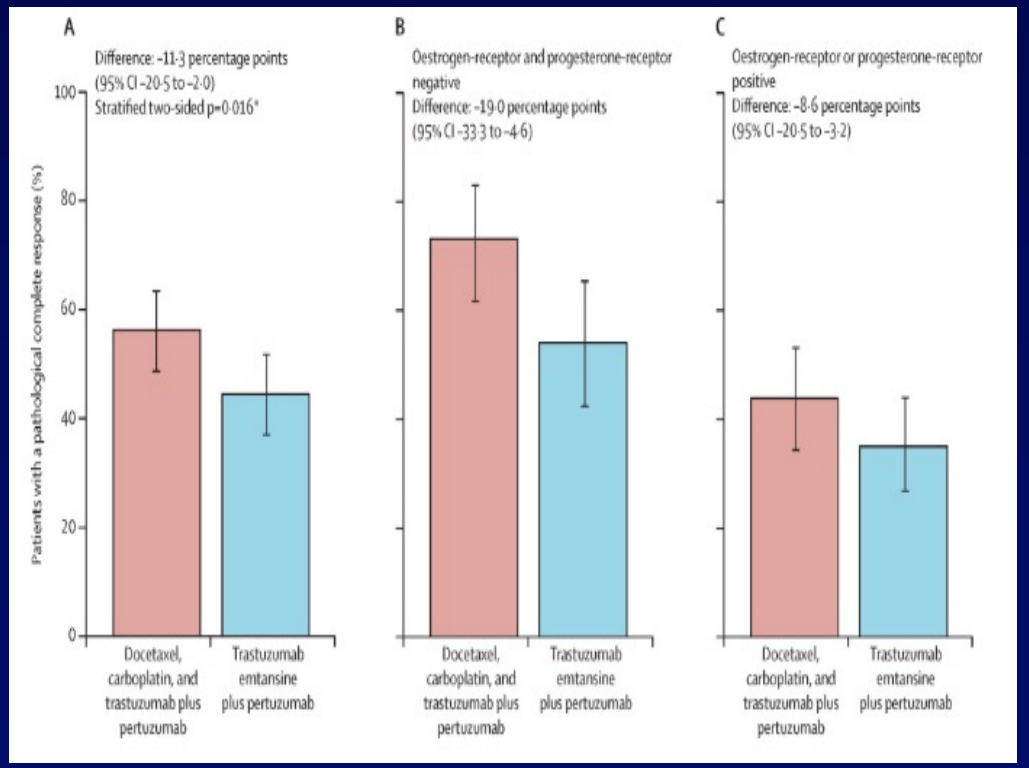
*pCR only in breast

1. Gianni L, et al. *Lancet Oncol*. 2012;13:25-32. 2. Schneeweiss A, et al. *Ann Oncol*. 2013;24:2278-2284. 3. van Ramshorst M, et al. *Lancet Oncol.* 2018;19(12):1630-1640; van der Voort A. *J Clin Oncol* 2020;38(15 suppl):501.

Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial

Sara A Hurvitz, Miguel Martin, W Fraser Symmans, Kyung Hae Jung, Chiun-Sheng Huang, Alastair M Thompson, Nadia Harbeck, Vicente Valero, Daniil Stroyakovskiy, Hans Wildiers, Mario Campone, Jean-François Boileau, Matthias W Beckmann, Karen Afenjar, Rodrigo Fresco, Hans-Joachim Helms, Jin Xu, Yvonne G Lin, Joseph Sparano, Dennis Slamon





Lancet Oncology January 1, 2018

SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM®

DECEMBER 5-9, 2023 | @SABCSSanAntonio

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Mays Cancer Center UT Health San Antonio MD Anderson Cancer Center

AACR American Association for Cancer Research

Pathologic complete response (pCR) of neoadjuvant therapy with or without atezolizumab in HER2 positive, early high risk and locally advanced breast cancer: APTneo Michelangelo randomized trial

Luca Gianni, MD
Chair, International Breast Cancer Research Committee
Fondazione Michelangelo
Milano, Italy

Gianni et al, SABCS 2023

Introduction

- Neoadjuvant dual targeting of HER2 with trastuzumab (H) and pertuzumab (P) plus chemotherapy is the standard of care for high-risk HER2+ breast cancer.
- Data show the contribution of the immune system in prognosis and response/resistance to HER2 directed therapies and support the combination of immune checkpoint inhibitors with anti HER2 antibodies.
- In the APTneo trial we test the role of adding atezolizumab to neoadjuvant HP and chemotherapy containing or not containing anthracyclines

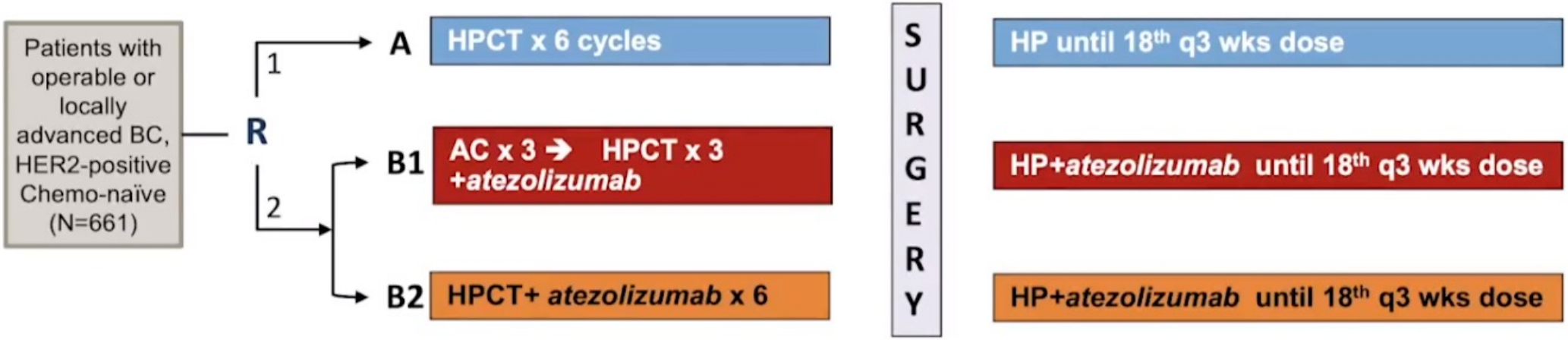
Gianni et al, SABCS 2023

Aims of Study

Open-label, randomized phase III trial

- ***The primary aim*** of the study is to compare event-free survival (**EFS, arm A v. arm B**) 5 years after randomization of the last patient
- ***Important secondary aim is the rate of pCR*** (defined as absence of invasive cells in breast and lymph nodes). The primary population for all efficacy endpoints is the ITT (intent-to-treat) population
- Other secondary aims are to evaluate tolerability of the regimens and to conduct molecular analyses to assess the presence of predictive markers of benefit and/or resistance to the study regimens

APTneo Study Schema



A = doxorubicin, 60 mg/m² q 21 days; Cy = Cyclophosphamide, 600 mg/m² q 21 days; C = Carboplatin, AUC 2 d1&8 q 21 days; T = paclitaxel, 90 mg/m² d1&8 q 21 days; H = Trastuzumab, 8 mg/kg on first dose, 6 mg/kg thereafter; P = Pertuzumab, 840 mg on first dose, 420 mg thereafter; Atezolizumab, 1200 mg i.v. infusion q 3 wks, S = surgery ; CBx = Core Biopsy; SN = Sentinel Node. As of May 2021, patients with RD at surgery could receive T-DM1

Gianni et al, SABCS 2023

APTneo

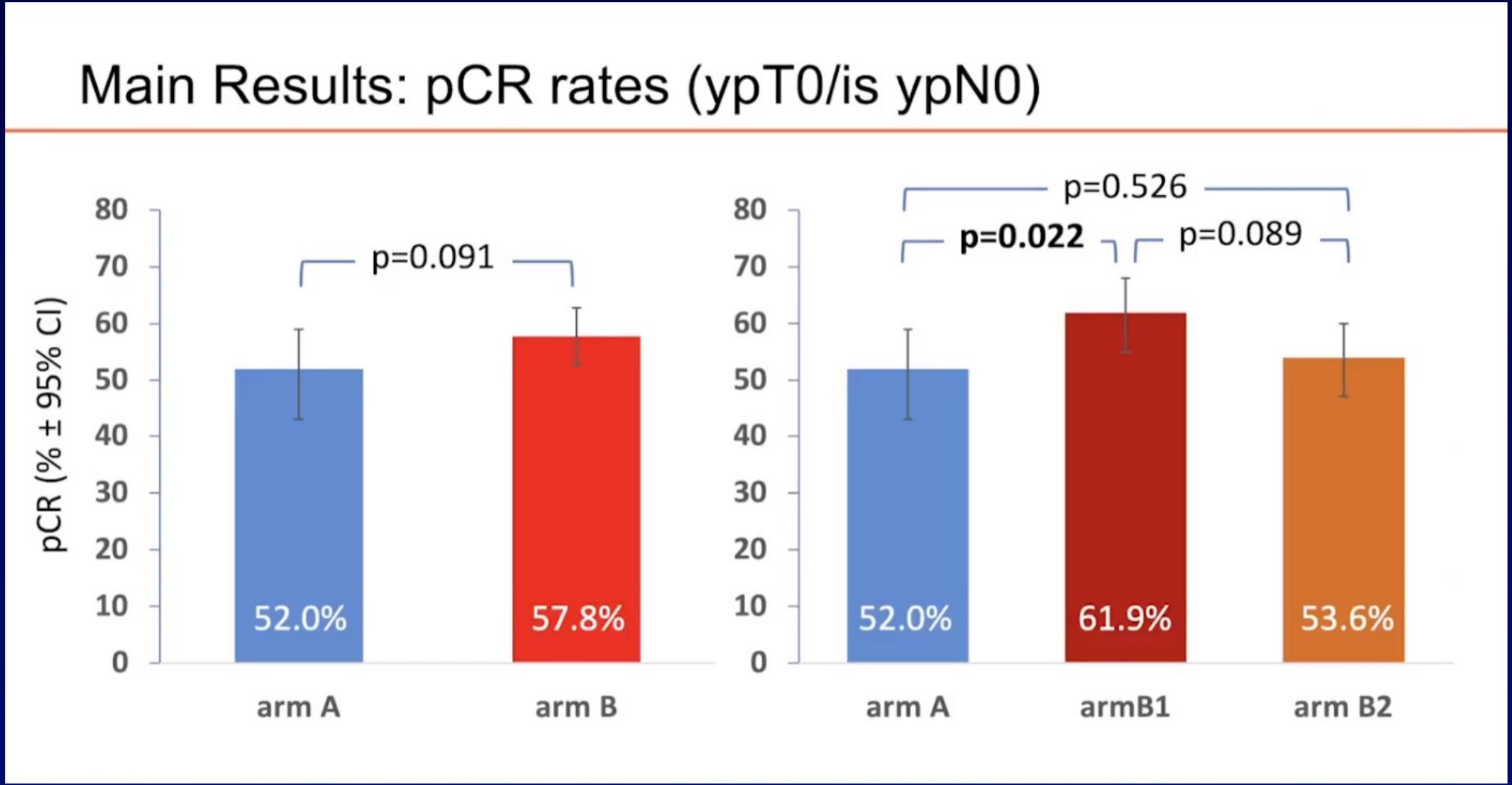
Main patient characteristics at randomization (ITT population)

		Arm A (223)		Arm B1 (218)		Arm B2 (220)	
		#	%	#	%	#	%
Disease stage	Early high-risk	122	54.7	120	55.0	123	55.9
	Locally advanced	101	45.3	98	45.0	97	44.1
PD-L1*	Positive	68	30.5	65	29.8	68	30.9
	Negative	155	69.5	153	70.2	152	69.1
ER and/or PR	Positive	136	61.0	142	65.1	152	69.1
	Negative	87	39.0	76	34.9	68	30.9
Median age (range)		50 (29-79)		50 (21-81)		49 (24-78)	

* SP142; pos ≥ 1% IC

Gianni et al, SABCS 2023

APTneo



Gianni et al, SABCS 2023

APTneo

Summary and Conclusions

- Addition of atezolizumab to chemotherapy and HP led to a 5.8% non statistically significant numerical increase of pCR in women with HER2+ operable breast cancer.
- An exploratory analysis shows a statistically significant higher rate of pCR (9.9%) with atezolizumab added to AC followed by HPTC compared to control HPCT, suggesting either a direct anthracycline's effect or a mechanistic enhancement of AC with atezolizumab
- Atezolizumab did not cause major tolerability issues
- The study continues follow up until analysis of the primary endpoint of EFS

Gianni et al, SABCS 2023

Adjuvant therapy for HER2+: APT Trial

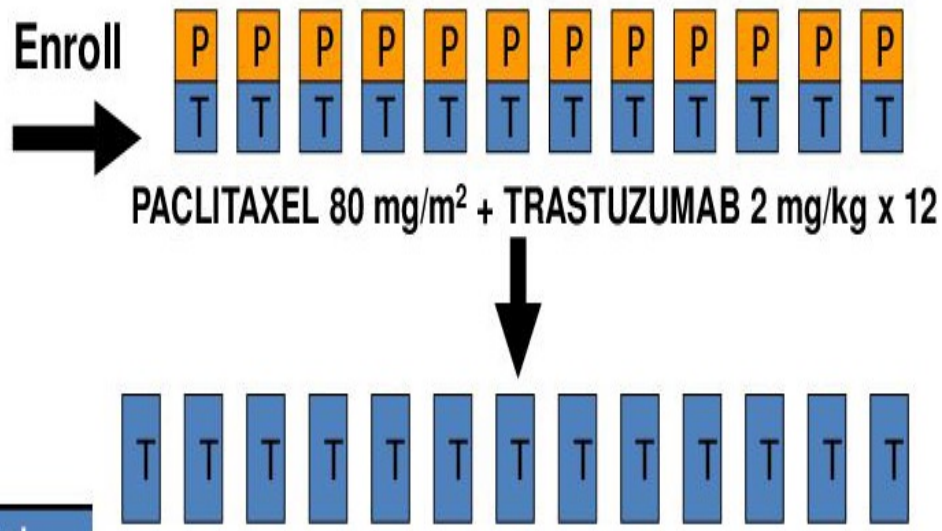
ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D., Denise A. Yardley, M.D., Beverly Moy, M.D., M.P.H., P. Kelly Marcom, M.D., Kathy S. Albain, M.D., Hope S. Rugo, M.D., Matthew Ellis, M.B., B.Chir., Ph.D., Iuliana Shapira, M.D., Antonio C. Wolff, M.D., Lisa A. Carey, M.D., Beth A. Overmoyer, M.D., Ann H. Partridge, M.D., M.P.H., Hao Guo, M.S., Clifford A. Hudis, M.D., Ian E. Krop, M.D., Ph.D., Harold J. Burstein, M.D., Ph.D., and Eric P. Winer, M.D.

N ENGL J MED 372;2 NEJM.ORG JANUARY 8, 2015

HER2+
Node Negative
≤ 3 cm
N=406

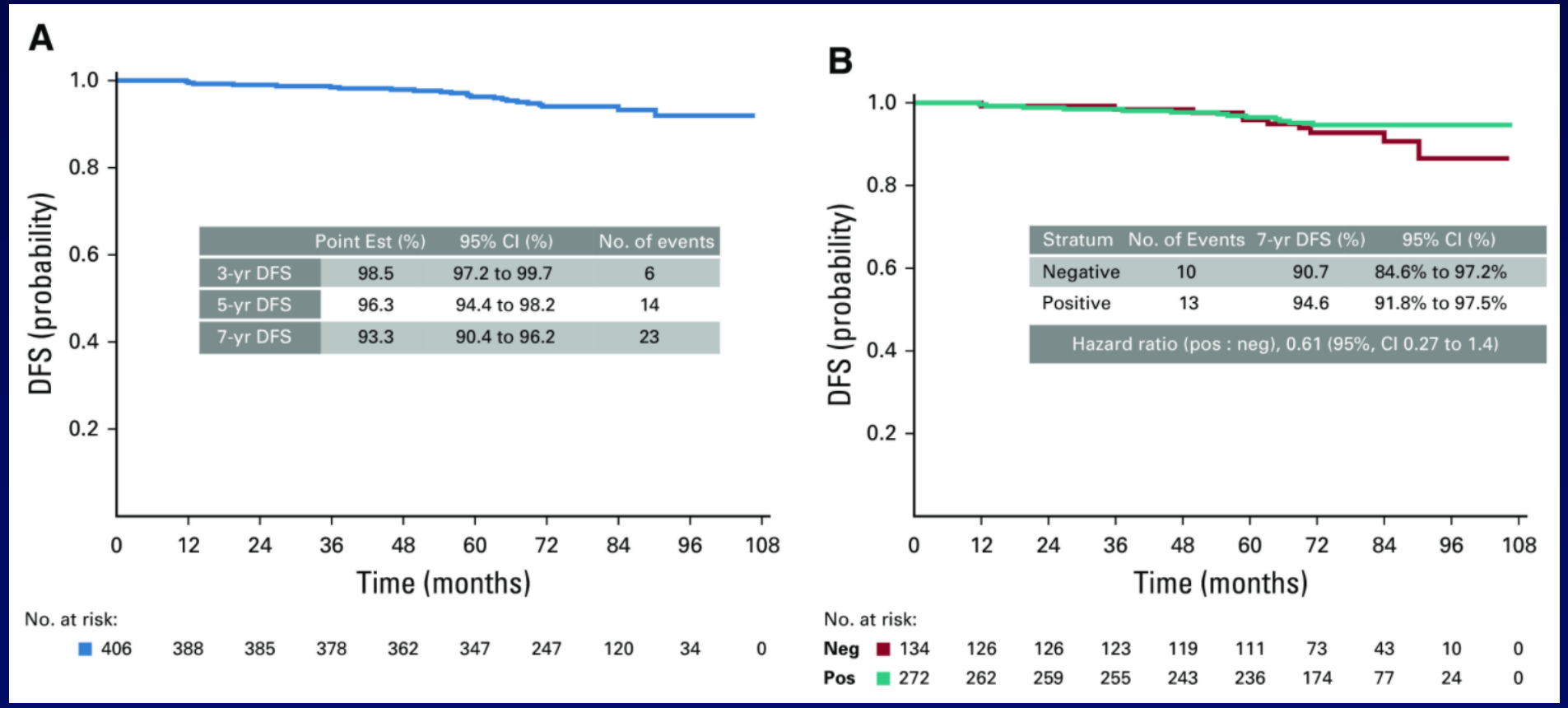


3-year DFS	95% Conf. Interval
98.7%	97.6% to 99.8%

Poisson p-value: <0.0001

Tolaney et al, NEJM 2015

APT Trial
7-year Follow-up Analysis



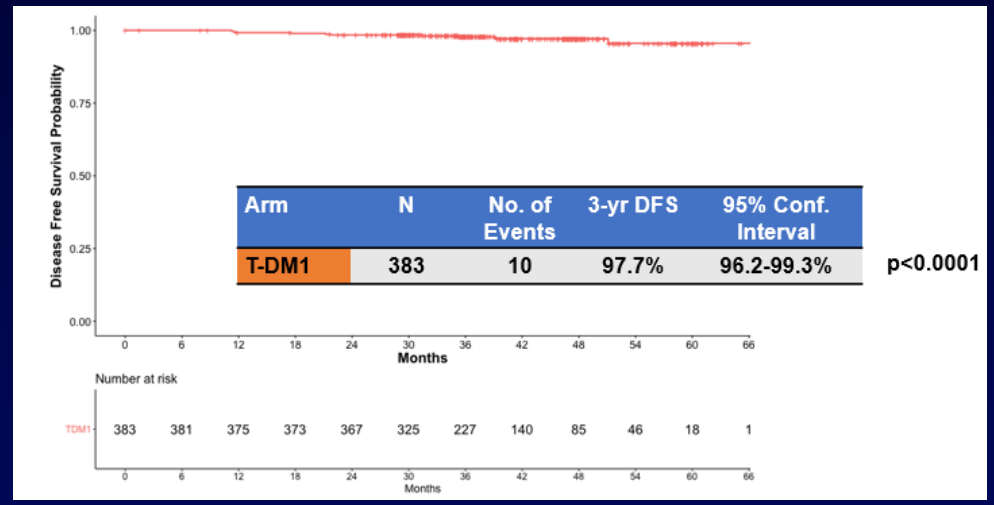
ATEMPT Trial

** Phase II - Closed to accrual and abstract published in SABCS 2019*

Stage I HER 2 +
n= 512

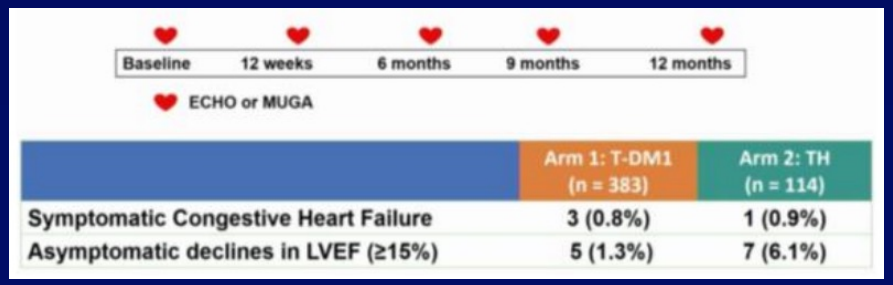
Trastuzumab-DM1
q 3 weeks x 17

Paclitaxel
Trastuzumab x 12
Trastuzumb q weeks x 13



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
T-DM1	383	10	97.7%	96.2-99.3%

p<0.0001



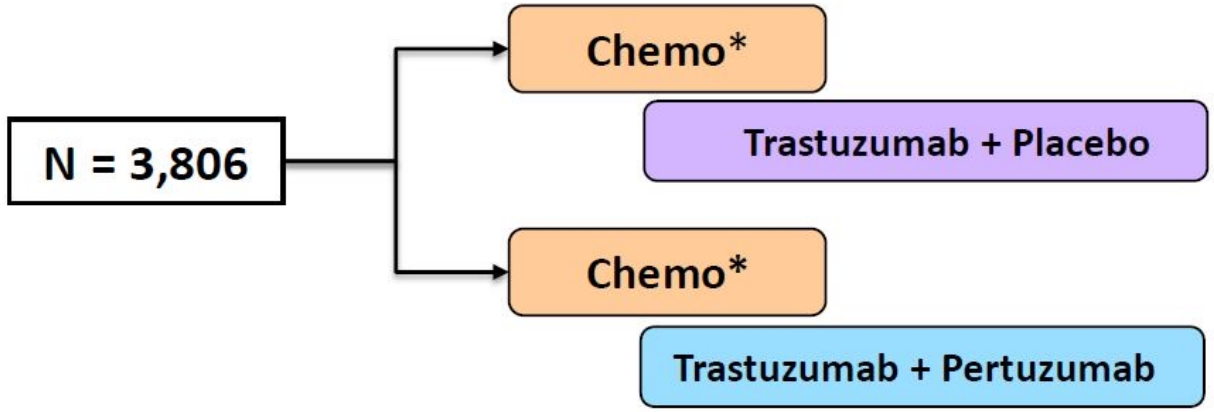
	Arm 1: T-DM1 (n = 383)	Arm 2: TH (n = 114)
Symptomatic Congestive Heart Failure	3 (0.8%)	1 (0.9%)
Asymptomatic declines in LVEF (≥15%)	5 (1.3%)	7 (6.1%)

Treatment Related Adverse Events: Grade ≥2 by Arm

	T-DM1 (n = 383)	TH (n = 114)
Fatigue	84 (22%)	26 (23%)
Neuropathy	44 (11%)	27 (24%)
Neutropenia	13 (3%)	15 (13%)
Thrombocytopenia	43 (11%)	1 (1%)
Nausea	39 (10%)	8 (7%)
Hypertension	35 (9%)	7 (6%)
ALT increase	33 (9%)	5 (4%)
Headache	24 (6%)	4 (4%)
Bilirubin increase	21 (5%)	1 (1%)
Infusion related reaction	19 (5%)	12 (11%)
Arthralgia	18 (5%)	2 (2%)
Anemia	18 (5%)	2 (2%)

Tolaney S, et al. Abstract GS1-05. SABCS 2019;

Phase III APHINITY: Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Primary Breast Cancer



Her2+ *centrally confirmed*
Node + or node – (tumor >1 cm or 0.5-1 cm with high risk feature)

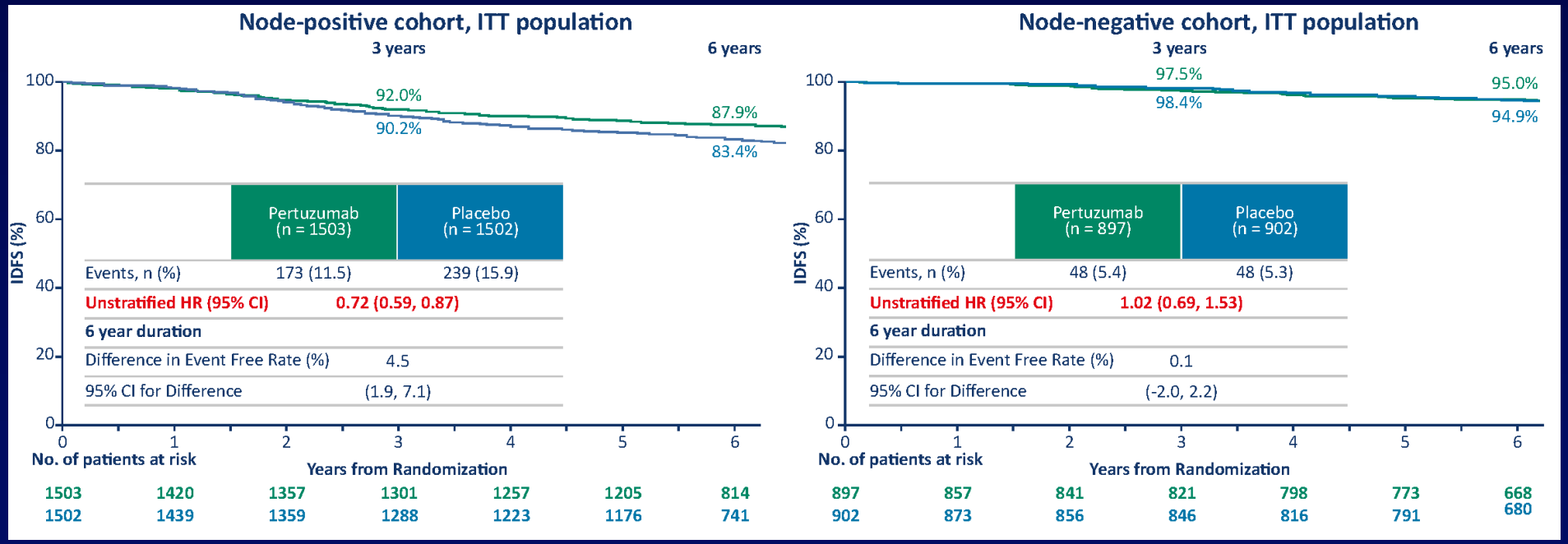
1ry EP: DFS

Stratification factors:
Nodal status, ER/PR +/ -; geographic region;
anthracyclines vs. non-anthracycline regimen

*Chemo: FEC or FAC x 3 or 4 →TH x 3-4 OR AC x 4 → TH x 4 OR TCH x 6

APHINITY
Time to first IDFS event by treatment regimen and nodal status

The node positive cohort continues to derive clear benefit from addition of pertuzumab.



APHINITY: Clinical benefit of adjuvant dual-HER2 blockade with chemotherapy

Hazard ratio (95% CI) for IDFS in the ITT population and subgroups based on lymph node & hormone receptor status			IDFS at 6 years from randomization (APHINITY Updated descriptive analysis)		
Population	**Primary Analysis** median FU 45.4 months; 2017	**Updated Analysis** median FU 74.1 months; 2019	**Pertuzumab arm**	**Placebo arm**	**Absolute benefit (95% CI)**
ITT	0.81 (0.66-1.00)	0.76 (0.64-0.91)	90.6%	87.8%	**2.8% (1.0, 4.6)**
LN-positive	0.77 (0.62-0.96)	0.72 (0.59-0.87)	87.9%	83.4%	**4.5% (1.9, 7.1)**
LN-negative	1.13 (0.68-1.86)	1.02 (0.69-1.53)	95.0%	94.9%	0.1% (-2.0, 2.2)
HR-positive	0.86 (0.66-1.13)	0.73 (0.59-0.92)	91.2%	88.2%	3.0% (0.8, 5.2)
HR-negative	0.76 (0.56-1.04)	0.83 (0.63-1.10)	89.5%	87.0%	2.5% (-0.7, 5.6)

OS difference after 74.1 months of median FU did not yet reach statistical significance.

LN = lymph-node; HR = hormone receptor

Post-Neoadjuvant Adjuvant Therapy: High Risk HER2+ Breast Cancer

- 10-30% of patients with HER-2+ EBC will relapse despite trastuzumab-chemotherapy-based adjuvant therapy
- 5-10% of patients with HER-2+ EBC will lack objective response to neoadjuvant trastuzumab-chemotherapy-based therapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 14, 2019 VOL. 380 NO. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

- Early HER2+ breast cancer patients
- Pertuzumab use was allowed
- Residual disease after neoadjuvant treatment with chemotherapy and trastuzumab

R 1:1

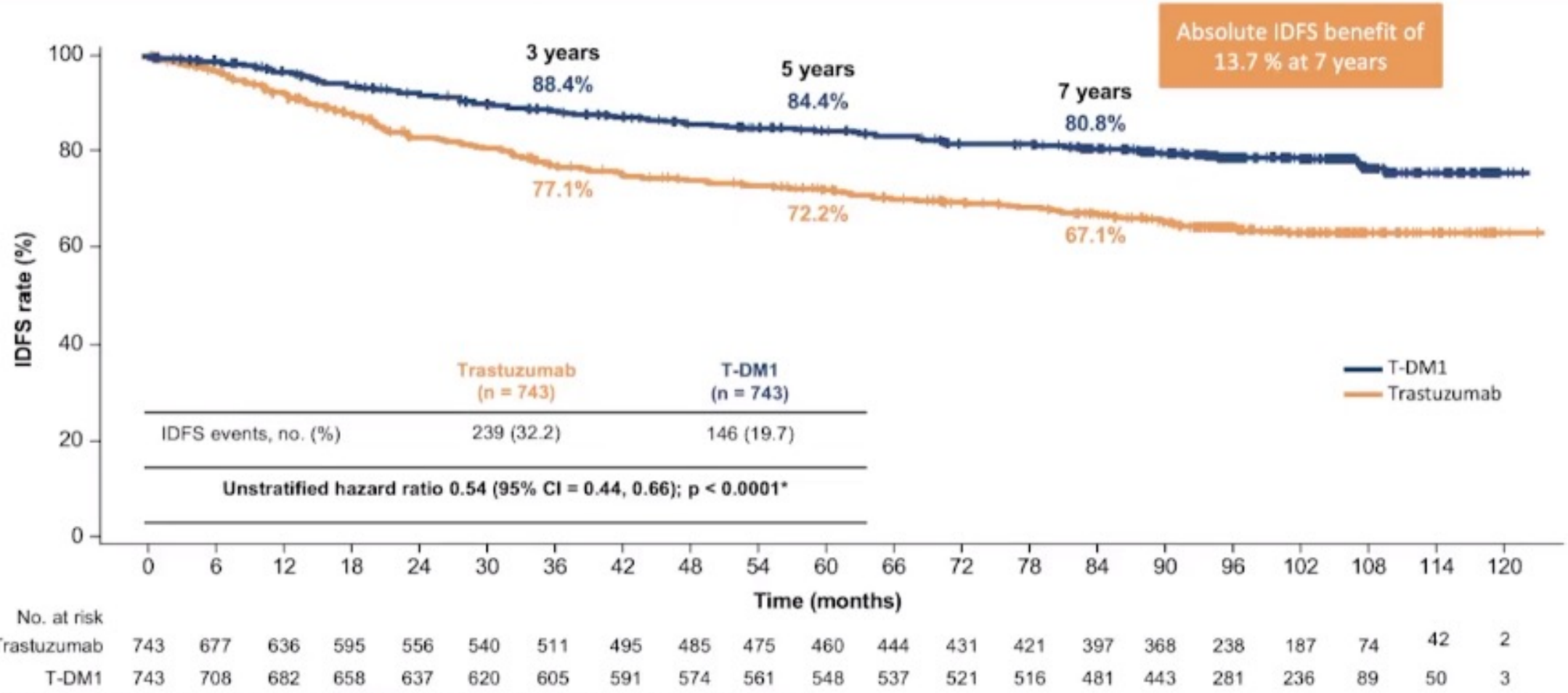
N=1,486

T-DM1
3.6mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

Radiation and endocrine treatment were administered according to local guidelines

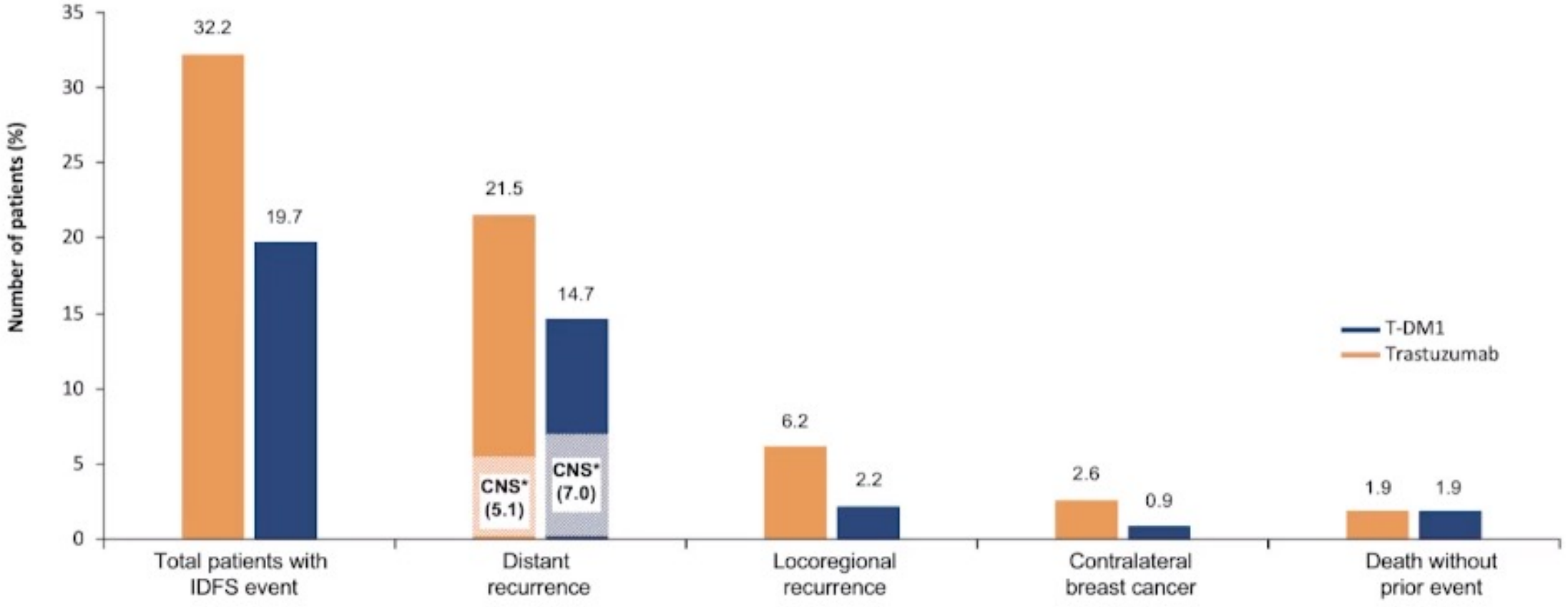
KATHERINE IDFS final analysis; median follow-up 8.4 years



* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Loibl et al, SABCS 2023

Site of first occurrence of an IDFS event

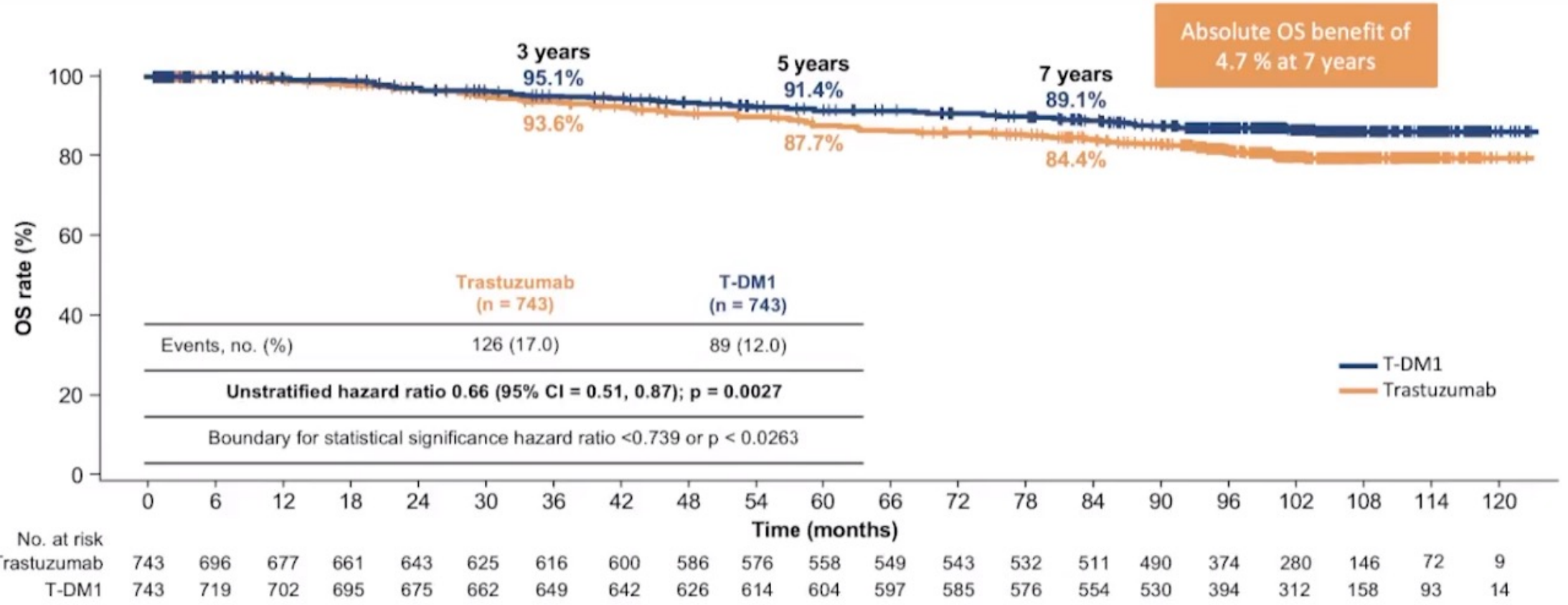


* **CNS metastases as component of distant recurrence (isolated or with other sites).** Trastuzumab T-DM1
CNS recurrence after first IDFS event: 19 patients (2.6%) in the trastuzumab arm and four patients (0.5%) in the T-DM1 arm.
CNS, central nervous system; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Loibl et al, SABCS 2023

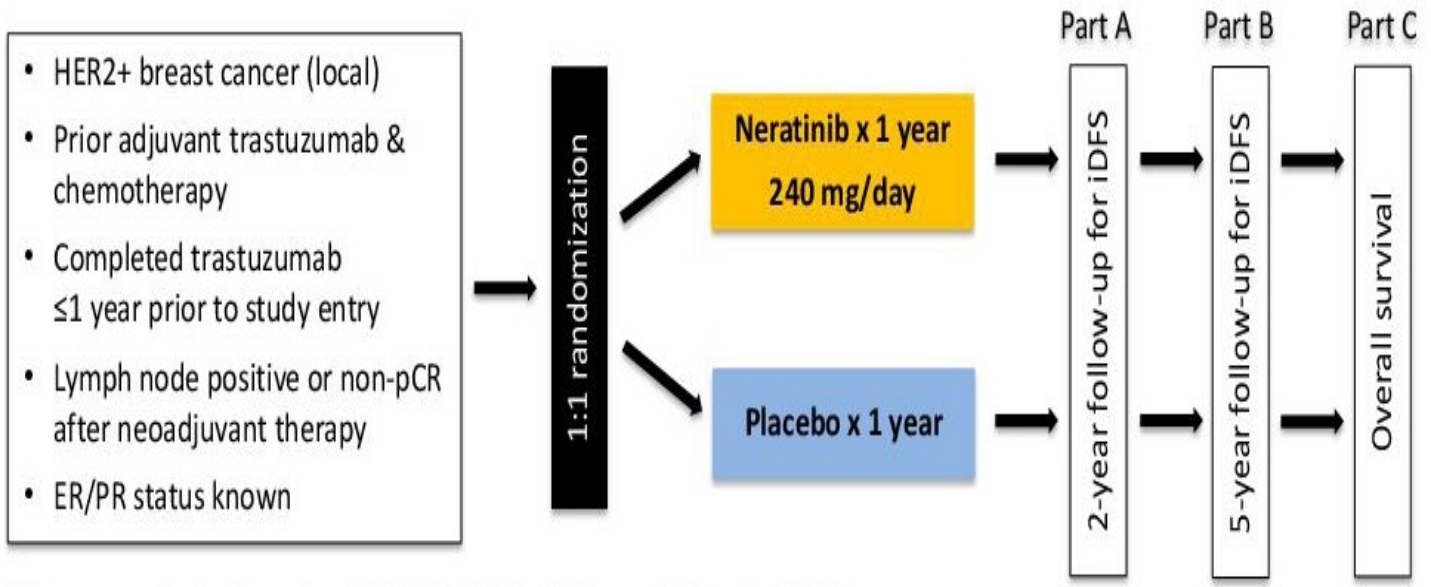
San Antonio Breast Cancer Symposium®, December 5–9, 2023

KATHERINE OS at median follow-up 8.4 years



Loibl e al, SABCS 2023

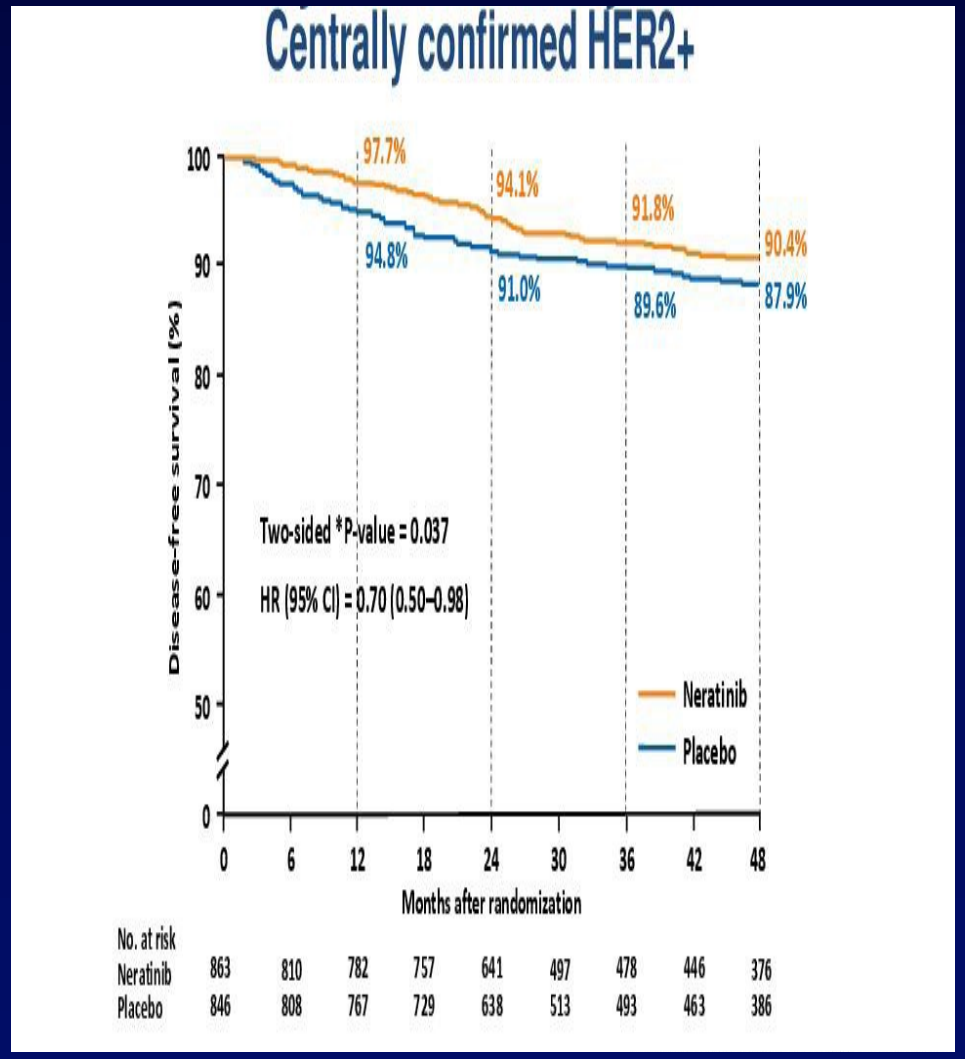
ExteNET : Final study design

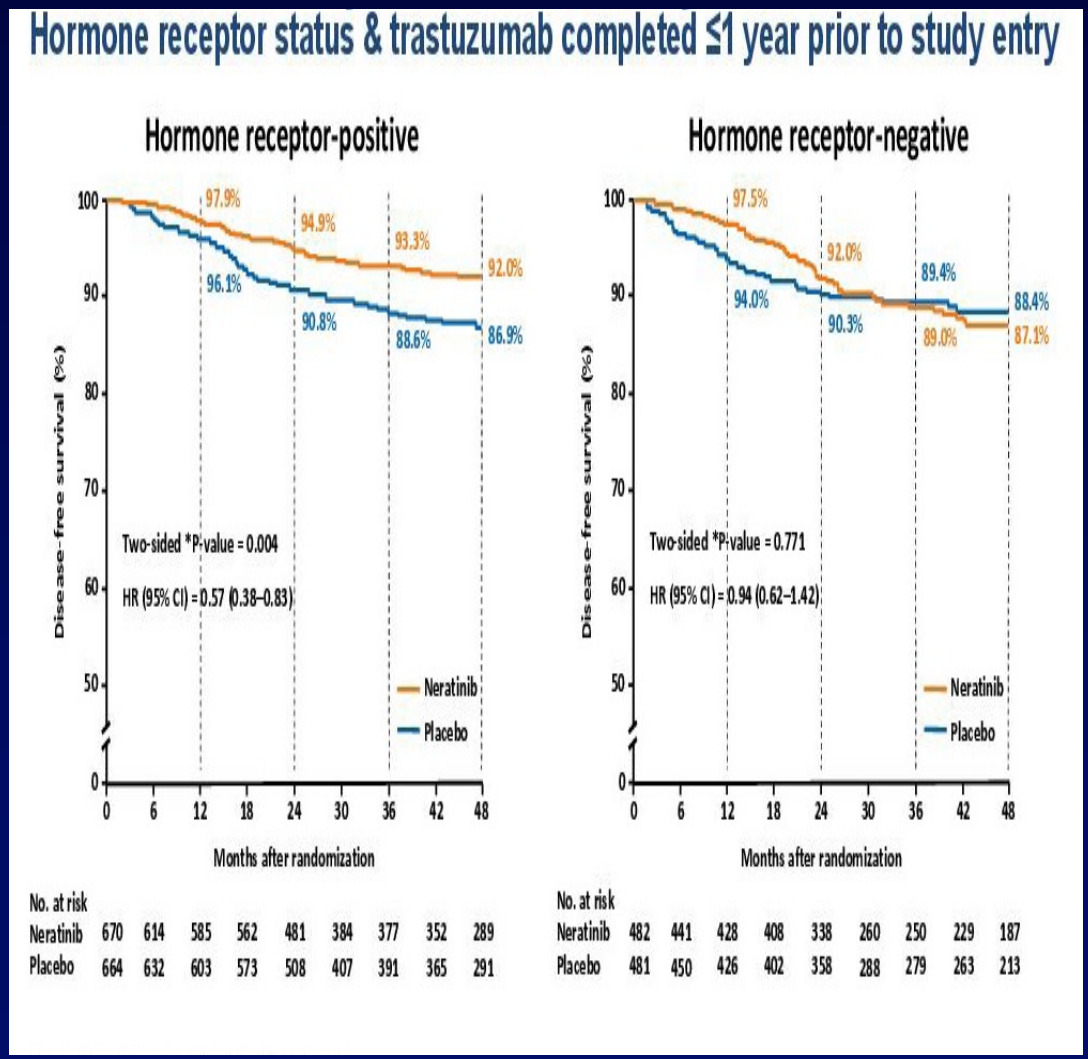


Primary analysis: invasive DFS (iDFS) in ITT population (n=2840)

- iDFS at 2 years: HR=0.67 (0.50–0.91); p=0.009
  - Hormone receptor-positive (n=1631; 57.4%); HR=0.51; p=0.001
  - Centrally-confirmed HER2-positive 60% (n=1463; 51%); HR=0.51; p=0.002

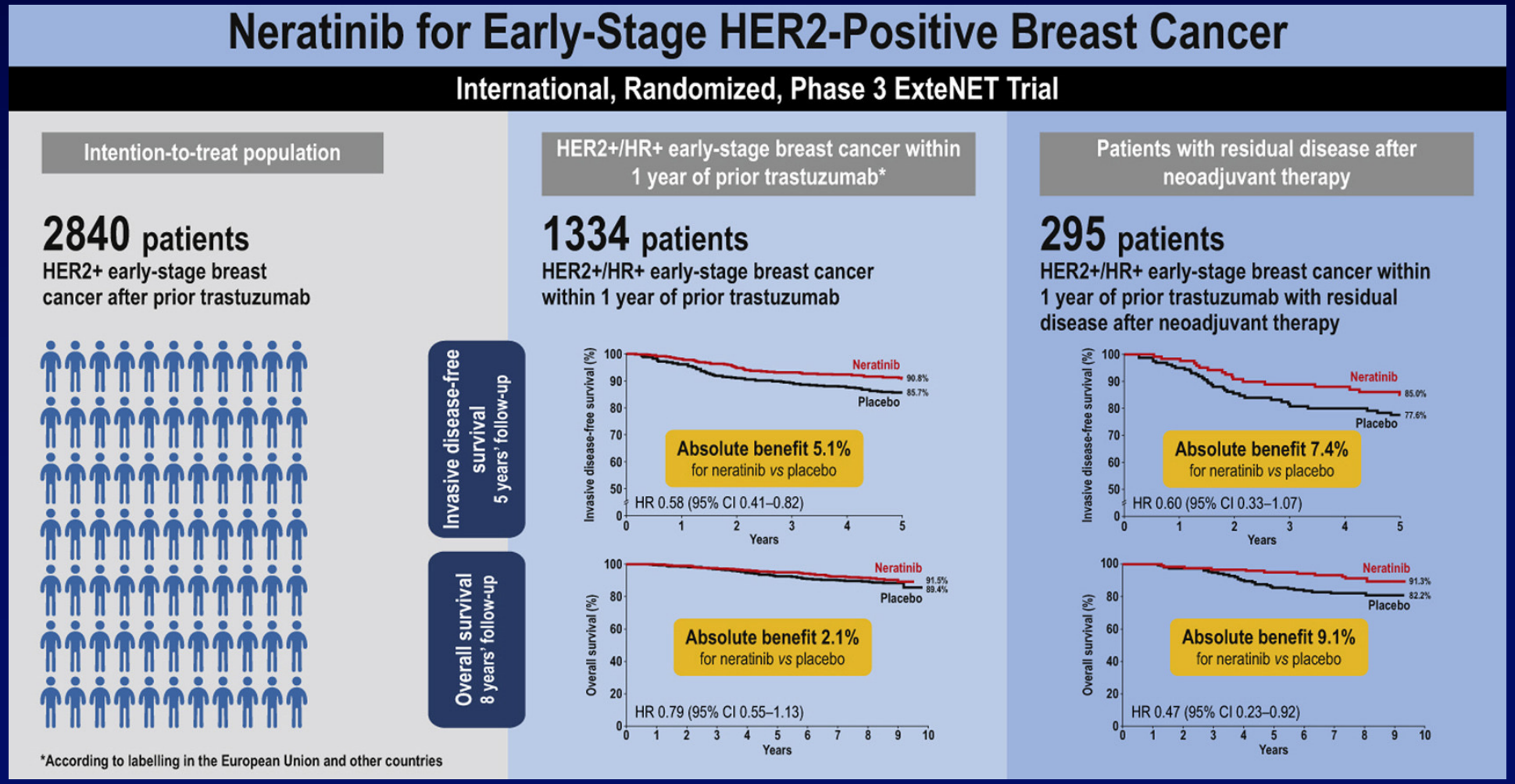
3-year iDFS analysis: Centrally confirmed HER2+ & According to Hormone receptor status





Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial

Clinical Breast Cancer
Volume 21 Issue 1 Pages 80-91.e7 (February 2021)
DOI: 10.1016/j.clbc.2020.09.014



Open to accrual in Puerto Rico NCORP – P.I. Luis Baez Vallecillo MD

CompassHER2 Trials
EA1181 and A011801

EA1181 CompassHER2 pCR

EA1181 Eligibility (n=1,250)
Stage II or IIIA HER2+ BC (T2-3, N0-2)
- cN0 eligible if ≥ 2.0 cm
- cN1-2 eligible ≥ 1.5cm
- **ER+ and ER- eligible**

REGISTRATION

Preoperative Phase: all patients

THP* x 4 cycles
paclitaxel weekly x12
(or
docetaxel q3w x4)
plus
trastuzumab (H)
& pertuzumab (P)
q3w x4

*nab-pacl and biosimilars allowed

SURGERY

pCR (ypT0/Tis ypN0) *40%*

EA1181 Arm A: pCR
continue EA1181
- complete 1 yr HP
- radiation and endocrine rx (as appropriate)

No pCR *60%*

EA1181 Arm B: Residual Disease
may join A011801 CompassHER2 RD

Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> post-op AC, more THP, or Cb/HP x 2-4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

EA1181 Primary Objective
3y RFS in patients w/ pCR after 12 weeks of THP
Stats: 1p= 0.025; 3y RFS H_0=92%, H_1≥95%

Eligibility A011801
HER2+ RD
ER- & ER+
(must have N+ if ER+)
(~30% of A011801 participants expected to come from EA1181)

Registration
R
- T-DM1 + placebo x 14 doses
- T-DM1+ tucatinib x 14 doses

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Opening soon in Puerto Rico NCORP – P.I. Luis Baez Vallecillo MD

NSABP B-60: DESTINY-Breast-05

Study Design

Key Eligibility

- **eBC with residual disease in breast and/or regional lymph nodes following neoadjuvant therapy**
- **Completion of neoadjuvant therapy[1] including trastuzumab followed by surgery**
- **High-risk[2] of recurrence (inoperable at presentation or node-positive)**
- **Centrally confirmed HER2+ status**
- **ECOG PS: 0-1**

Stratification

- Operative status at presentation (operable vs inoperable)[3]
- Post-neoadjuvant pathologic nodal status (positive [ypN1-3] vs negative [ypN0])
- Tumor hormone receptor (HR) status (positive vs negative)
- HER2-targeted neoadjuvant therapy (single vs dual)

R
1:1

N = 1,600

Investigational Arm

Trastuzumab deruxtecan (T-DXd; DS-8201)
Day 1 every 3 weeks for 14 cycles (N=800)

Control Arm

Trastuzumab emtansine (T-DM1)
Day 1 every 3 weeks for 14 cycles (N=800)

[1] **Neoadjuvant therapy** to include at least 16 weeks of total systemic treatment in the preoperative setting, including:

- At least 9 weeks of HER2-targeted therapy including **trastuzumab** and,
- At least 9 weeks of **taxane** therapy

[2] **High-risk definitions:**

- **Inoperable:** Inoperable breast cancer at presentation (prior to neoadjuvant therapy), defined as clinical stages T4, N0-3, M0 or T1-3, N2-3,M0
- **Node-positive:** Operable disease at presentation, defined as clinical stages T1-3, N0-1, M0 with axillary node positive disease (ypN1-3) following neoadjuvant therapy

[3] **Operative status at presentation** (prior to neoadjuvant therapy):

- **Operable:** clinical stages T1-3, N0-1, M0
- **Inoperable:** clinical stages T4, N0-3, M0 or T1-3, N2-3, M0

Endpoints

- **Primary:**
  - **IDFS** (Invasive disease-free survival)
- **Secondary:**
  - **DFS** (Disease-free survival)
  - **DRFI** (Distant recurrence-free interval)
  - **BMFI** (Brain metastases-free interval)
  - **OS** (Overall survival)
  - **Adverse events**
- **Exploratory:**
  - **PROs** (Patient reported outcomes; QoL)
  - **Biomarkers** associated with efficacy/safety
  - **PK** associated with efficacy/safety

NSABP

Summary

- HER2-positive breast cancer landscape is evolving swiftly as drug technology advances
- HER2-positive breast cancer is a systemic disease requiring systemic therapy
- **Neoadjuvant therapy yields a tailored treatment strategy based on response**
- Immunotherapy is expected to gain traction in combination with chemotherapy and HER2-directed therapy
- Antibody-drug conjugates and small molecule TKI's are expected to make their way into the early phases of treatment in the next months to years

Thank you!

Questions?

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787-919-7919 (office)
LBaez@PROncology.com