Optimal treatment for early stage HER2 positive breast cancer: Tailoring treatment to response

Virginia F Borges, MD, MMSc
Professor and Deputy Head, Medical Oncology
Director, Breast Cancer Research Program & Young Women's Breast Cancer Translational Program
University of Colorado Cancer Center
Denver, CO

Objectives

1. Summarize the key advances in early stage Her 2 positive breast cancer that led to today's standard of care.

2. Apply these latest advances in breast cancer research in clinical practice to how we currently optimize patient outcomes.

3. Understand the current clinical trials in progress through review of the background data and identify the key questions facing the management of patients with Her 2+ breast cancer.

HER2 Signals Cells to Divide

Normal

Overexpressed HER2

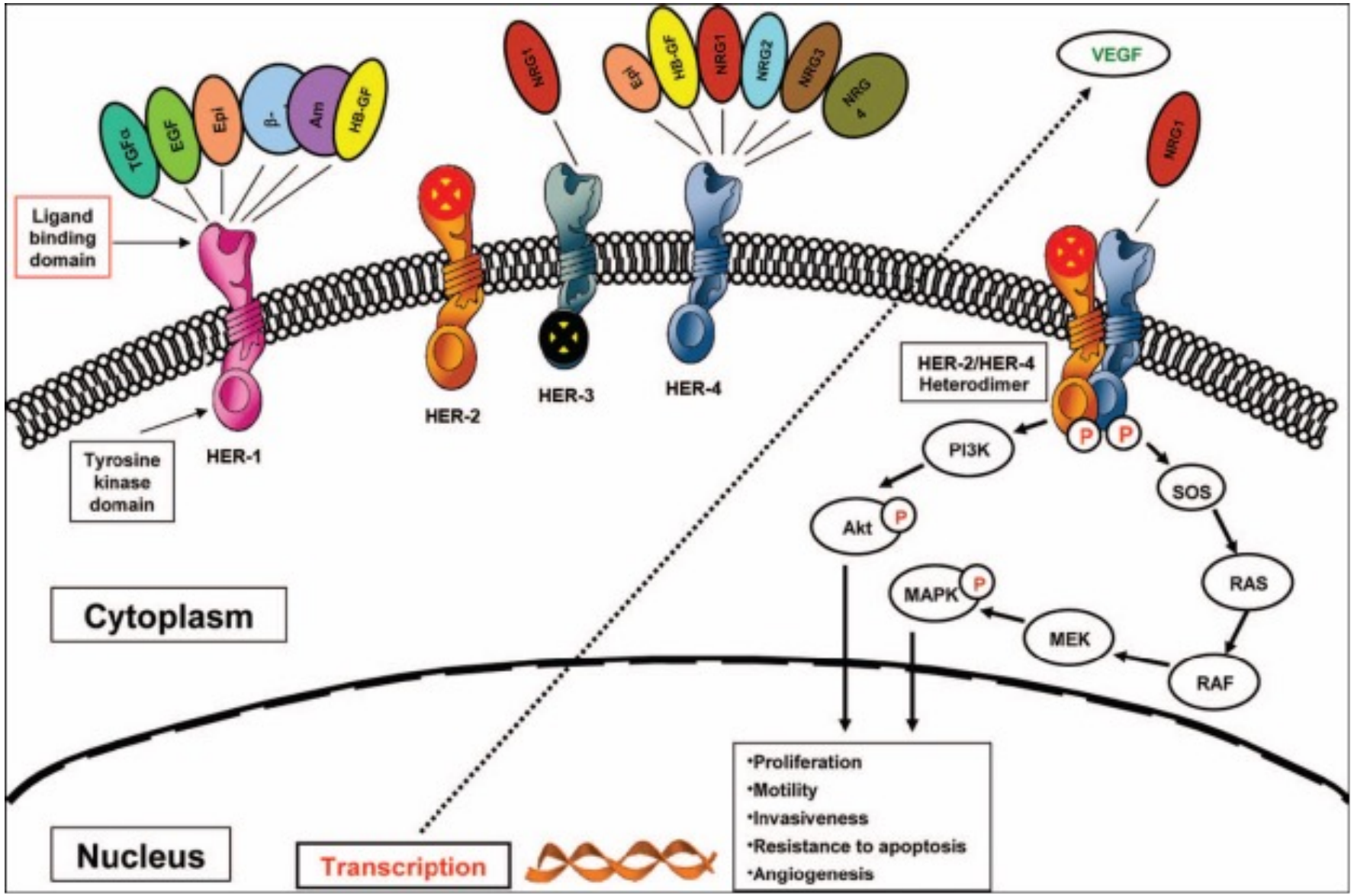
Excessive cellular division

Berger et al. *Cancer Res.* 1988;48:1238.

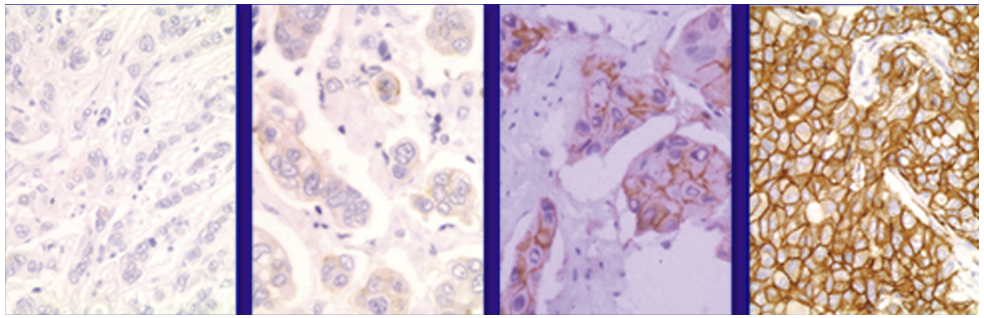
Roskoski. *Biochem Biophys Res Commun*. 2004;319:1.

Rowinsky. *Annu Rev Med*. 2004;55:433.

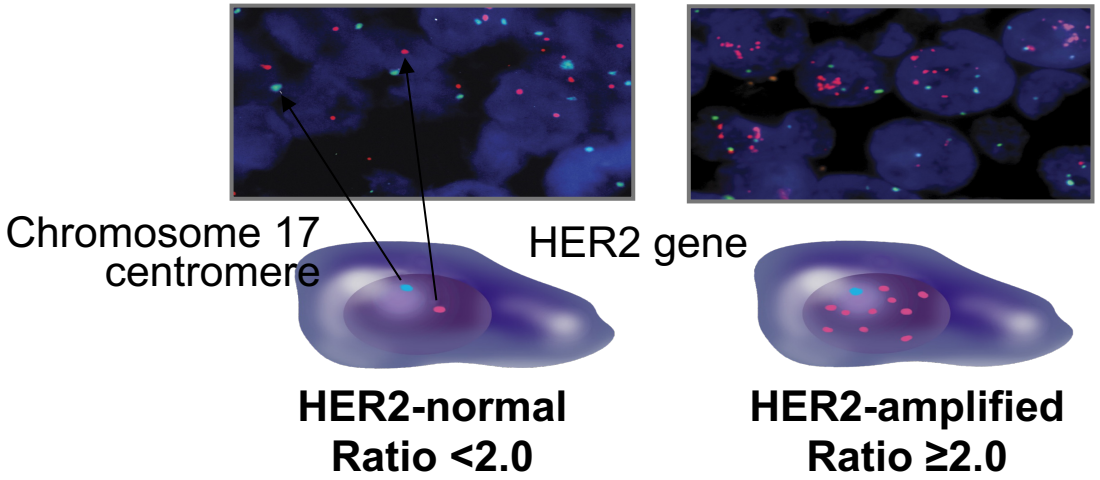
Slamon et al. *Science*. 1987;235:177.


TGFα
EGF
Epi
β-
Am
HB-GF
Ligand binding domain
Tyrosine kinase domain
HER-1
HER-2
NRG1
HER-3
Epi
HB-GF
NRG1
NRG2
NRG3
NRG 4
HER-4
VEGF
NRG1
HER-2/HER-4 Heterodimer
P
P
PI3K
SOS
Akt
P
RAS
MAPK
P
MEK
RAF
Cytoplasm
Nucleus
Transcription
•Proliferation
•Motility
•Invasiveness
•Resistance to apoptosis
•Angiogenesis

HER2 Protein Overexpression for Clinical Discrimination



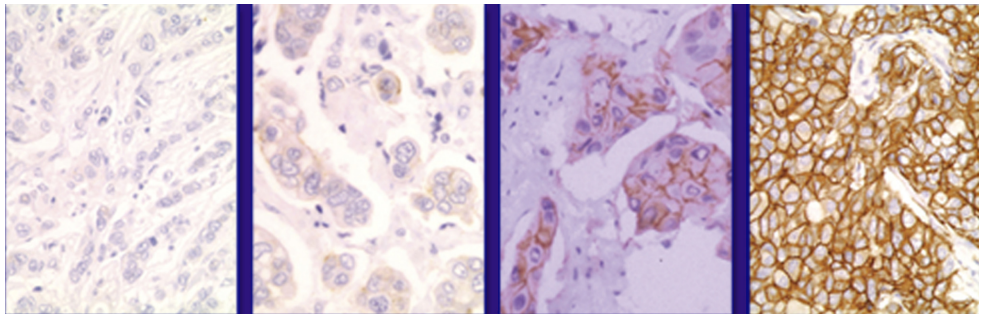
IHC 0 **IHC I+** **IHC 2+** **IHC 3+**



HER2-normal
Ratio <2.0

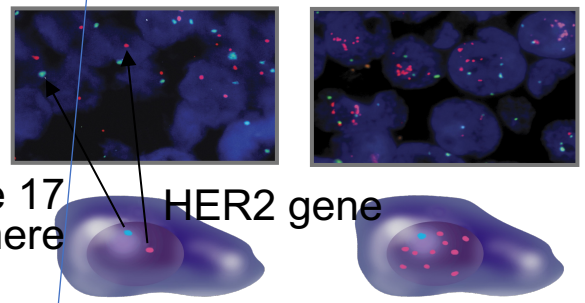
HER2-amplified
Ratio ≥2.0

HER2 Protein Overexpression for Clinical Discrimination



IHC 0 **IHC I+** **IHC 2+** **IHC 3+**

Her 2 negative



HER2-normal
Ratio <2.0

HER2-amplified
Ratio ≥2.0

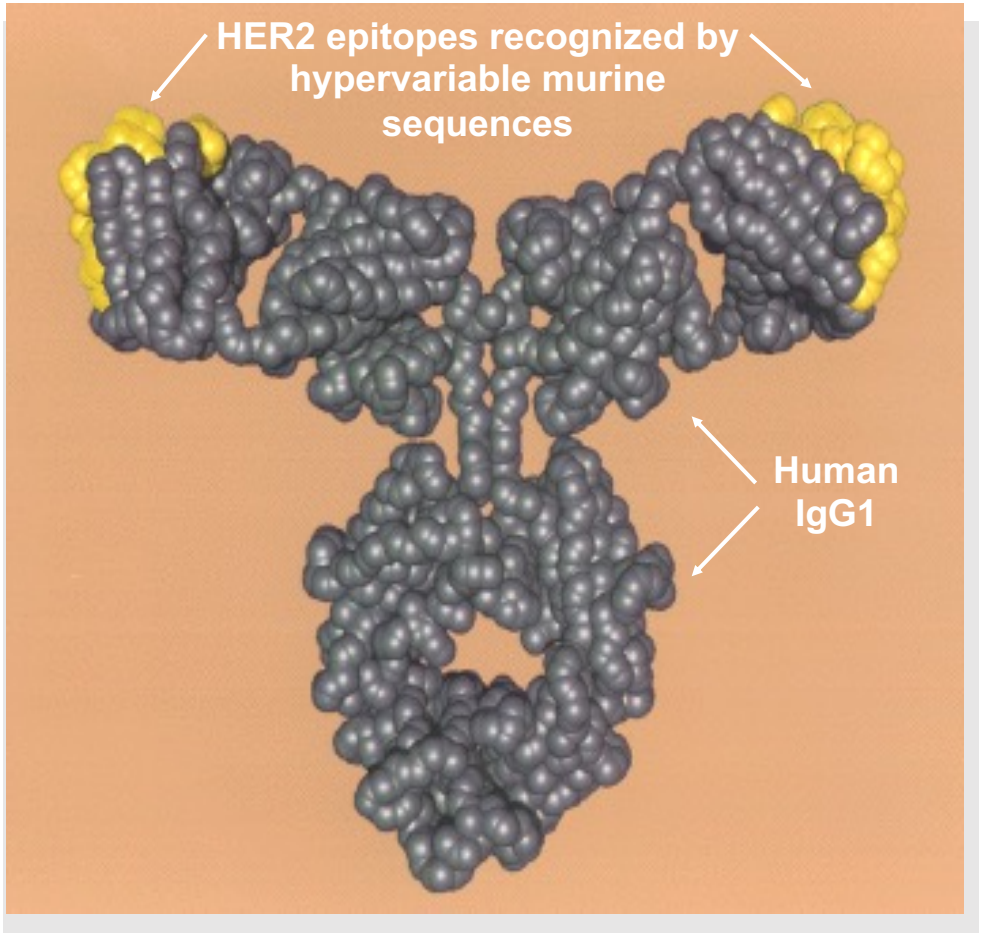
Her 2 Positive

Treatment pathway follows the ER status

Her 2 Low treatment pathway in MBC

Treatment driven down the Her 2 pathway

Trastuzumab: Humanized Anti-HER2 MAb



- Targets HER2 protein
- Selectively binds with high affinity ($K_d \leq 0.5$ nM)
- 95% human, 5% murine

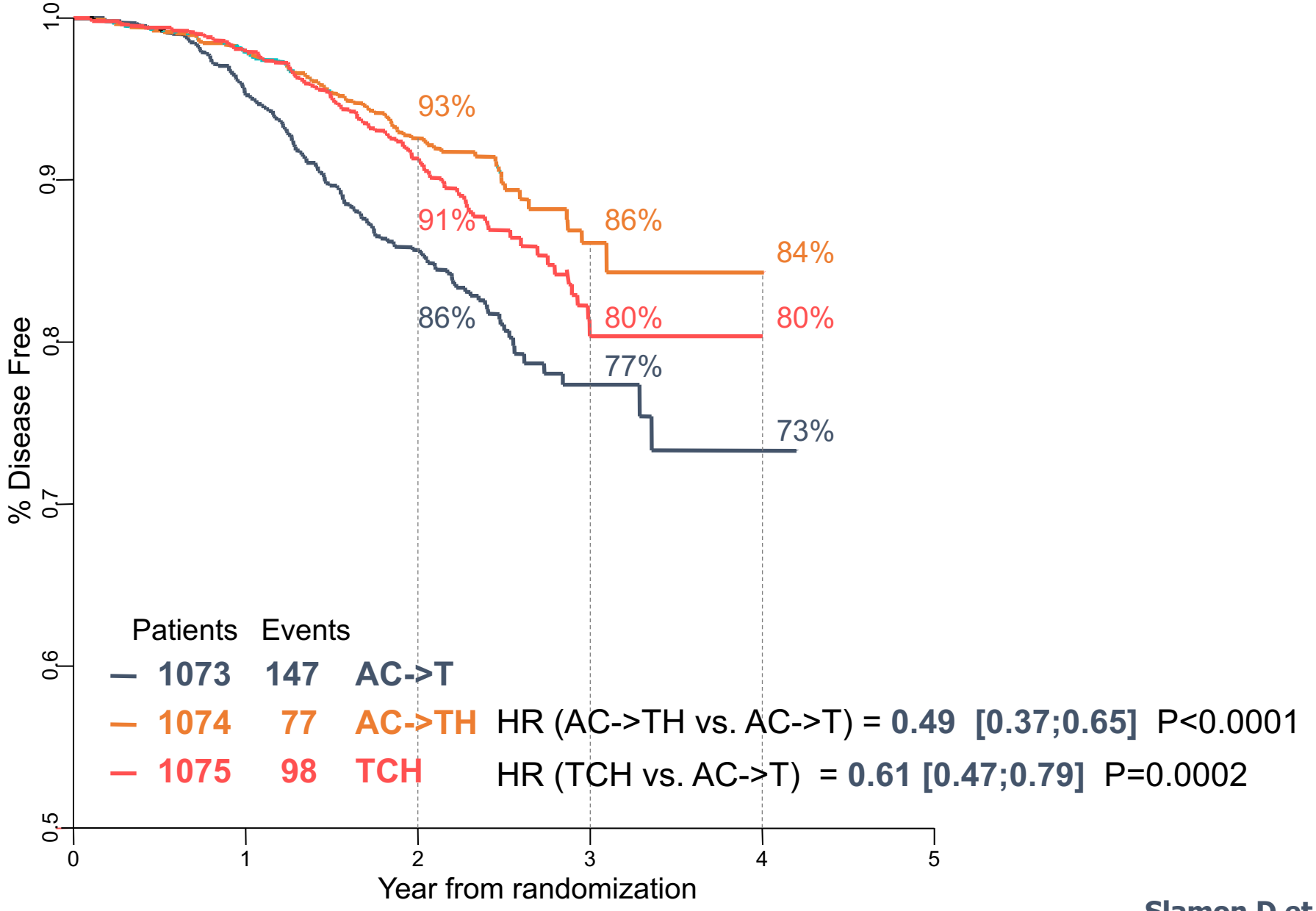
Trastuzumab Randomized Adjuvant Clinical Trials: 2006

Intergroup N9831 (2614 pts)	**AC → P** **AC → P → H** **AC → PH → H**	None vs Sequential vs Concurrent long
NSABP B-31 (2043 pts)	**AC → P** **AC → PH → H**	None vs Concurrent long
HERA (5081 pts)	**Chemo →** **none** **H x 1 year** **H x 2 years**	None vs Sequential For 1 or 2y
BCIRG 006 (3222 pts)	**AC → D** **AC → DH → H** **DCbH**	None vs Concurrent vs Non-A
FinHer (232 pts)	**D or V** **D or V plus H →** **FEC**	None vs Concurrent short

A = doxorubicin, C = cyclophosphamide, P = paclitaxel, H = trastuzumab, D = docetaxel, Cb = carboplatin, V = vinorelbine, E = epirubicin, F = 5-FU

Tam/AI for ER+

BCIRG 006: Disease Free Survival: 2005



Slamon D et al, SABCS 2005

The mABs trastuzumab and pertuzumab in the Neoadjuvant Space

Study	Regimen	Phase/Size	pCR	Disease outcomes
NOAH trial	SOC chemo +/- H	II/235	43% v 58%	HR 0.64
TRYPHAENA	FEC-THP FECHP-THP TCHP	II/150	55% 56% 64%	DFS 87-90%
TRAIN-2	FEC-TCHP TCHP		67% v 68%	EFS 93%, OS 98% both arms
KRISTINE	TDM-1P TCHP	III/444	44% 55.7%	
NeoSPhere	TH [FEC H adj.] THP HP TP	II/417	29% 45.8% 24% 17%	PFS 81% 86% 73% 73%

These significant studies paved the way for TCHP to become a standard neoadjuvant regimen moving forward.

Gianni, Lancet Oncol 2014.
Schneeweiss, Eur J Cancer 2018
Hurvitz Lancet Oncol 2018
Gianni, Lancet Oncol 2014
Sikov W. 2021 https://doi.org/10.1007/978-3-030-88020-0_6

Improvements in the Adjuvant Setting

APHINITY TRIAL

6 year follow up data:

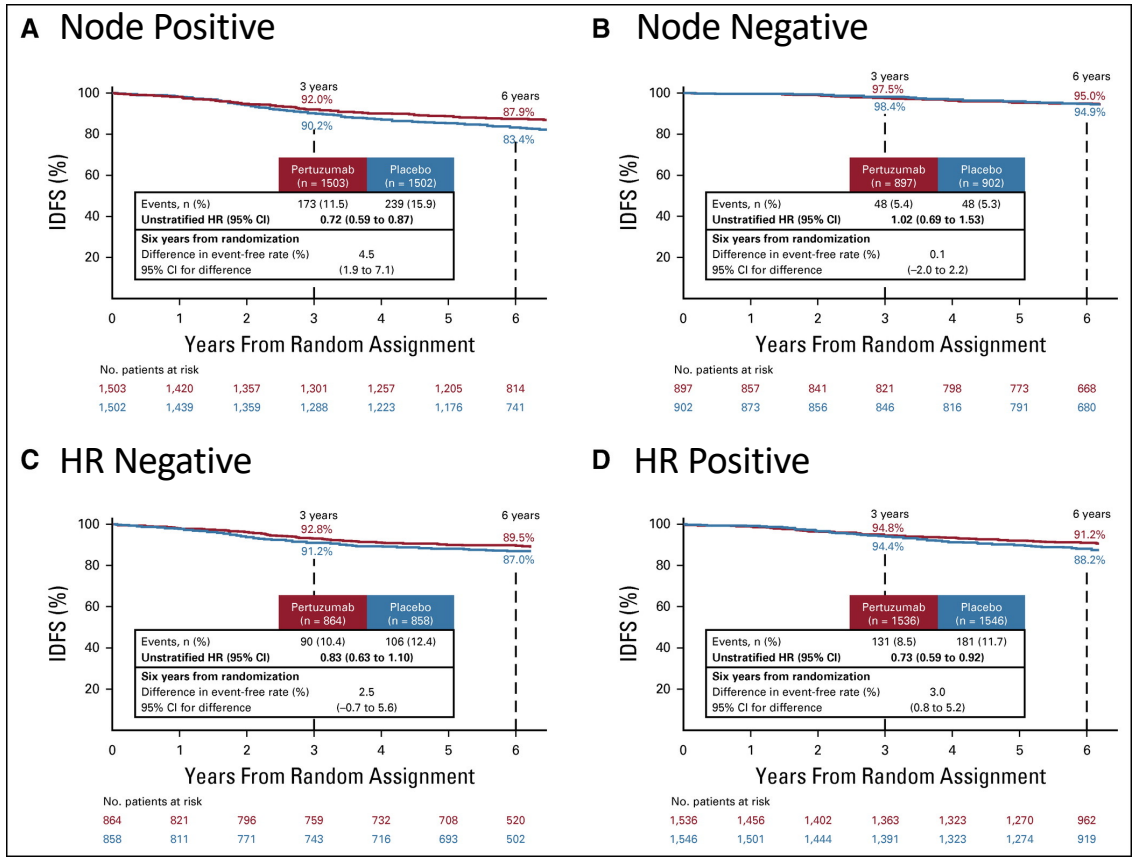
Overall IDFS 91% v 88%

Node pos IDFS 88% v 83%

Both HR+ and HR- benefit:

3% gain and 2.5% gain respectively

Cardiac event rate <1%



ExteNET

Neratinib for Early Stage Her 2+ BC

HR+/≤ 1-year population (n=1334)

Absolute improvements seen:

- iDFS 5.1%, dDFS 4.7% , OS 2.1%

- 4 versus 12 CNS events for neratinib v placebo

- neoadjuvant/non-pCR population (n=295)
  - iDFS 7.4%, dDFS 7.0%, OS 9.1%

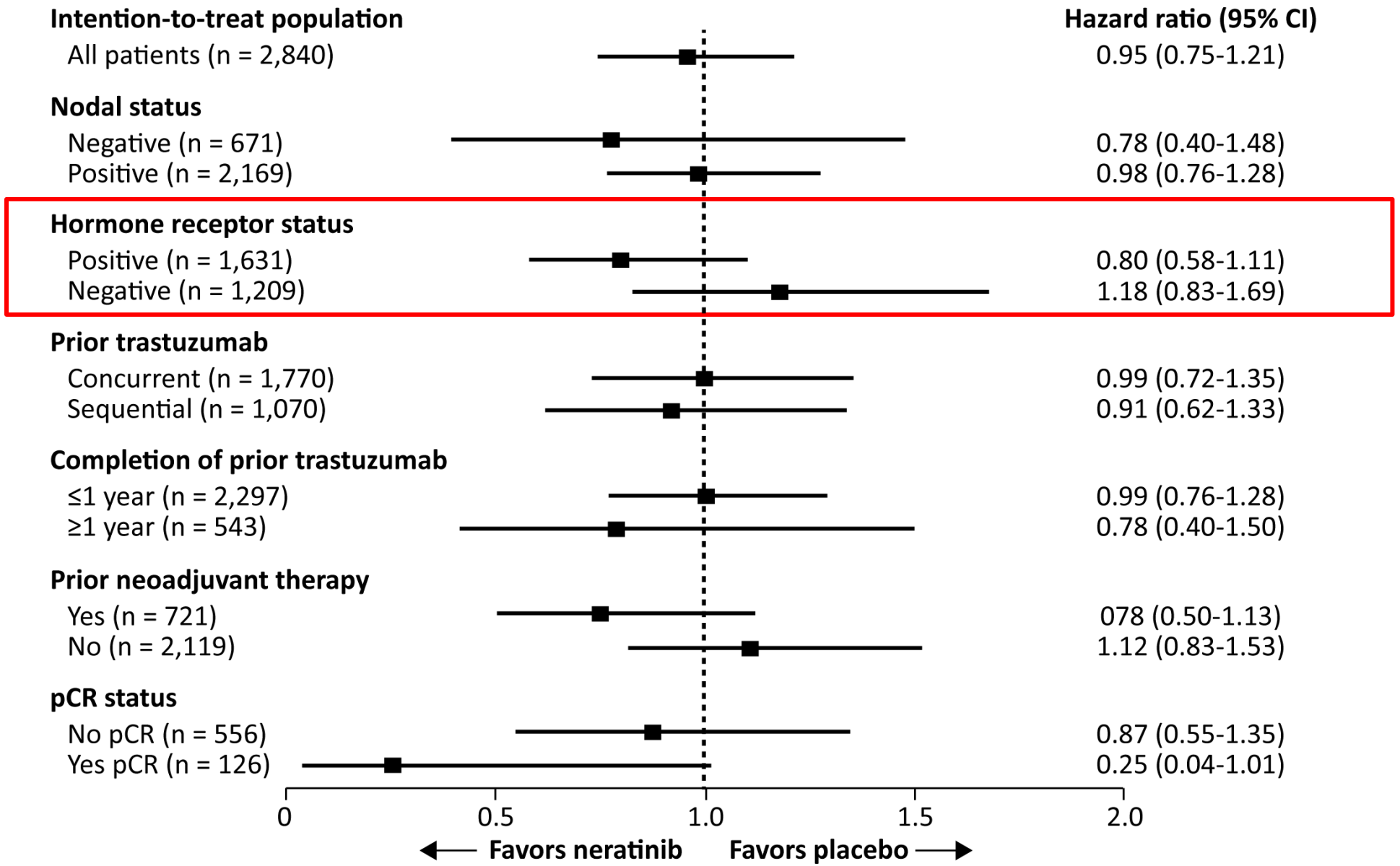
- neratinib is a pan-HER TKI

- unmitigated neratinib at recommended 240mg dosing has 40% incidence grade 3 diarrhea

- median onset 8 days
- majority occur in the first 2 months

Chan et al. Clin Breast Can 2021 doi.org/10.1016/j.dbc.2020.09.014

ExteNET: Final Overall Survival Analysis

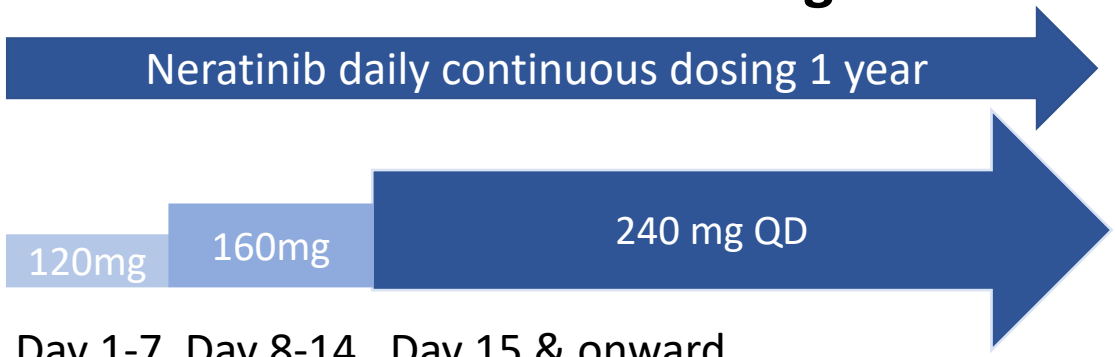


Holmes FA et al. SABCS 2020;Abstract PD3-03.

CONTROL Trial

NCT02400476

Dose Escalation Prevention regimens



Day 1-7 Day 8-14 Day 15 & onward

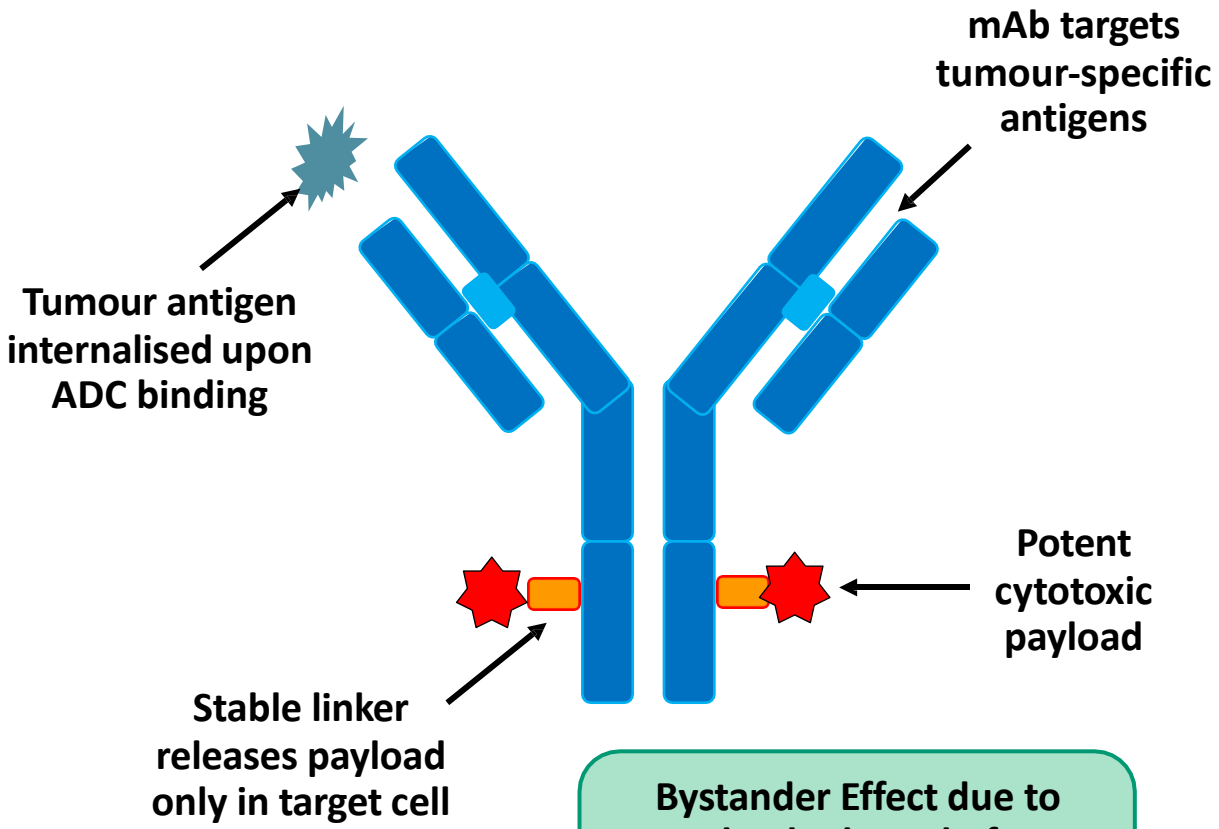
Loperamide given 2-16mg daily as needed

Results:

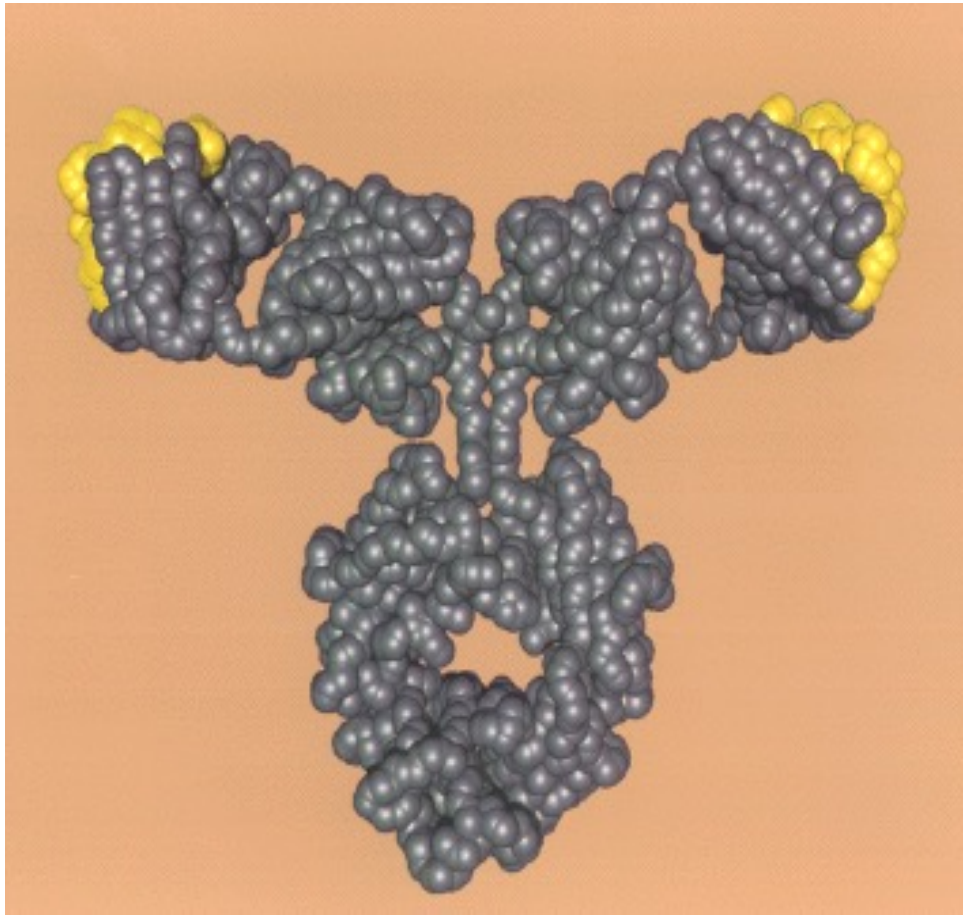
- Grade 3 diarrhea: 15%
- Improvement in constipation (33%)
- Diarrhea related drug discontinuation 3%

Barcenas, Hurvitz, et al. *Annal of Oncol*. 2020

HER2-Targeting Antibody-Drug Conjugates (ADCs)



Bystander Effect due to Payload release before internalisation or membrane permeability

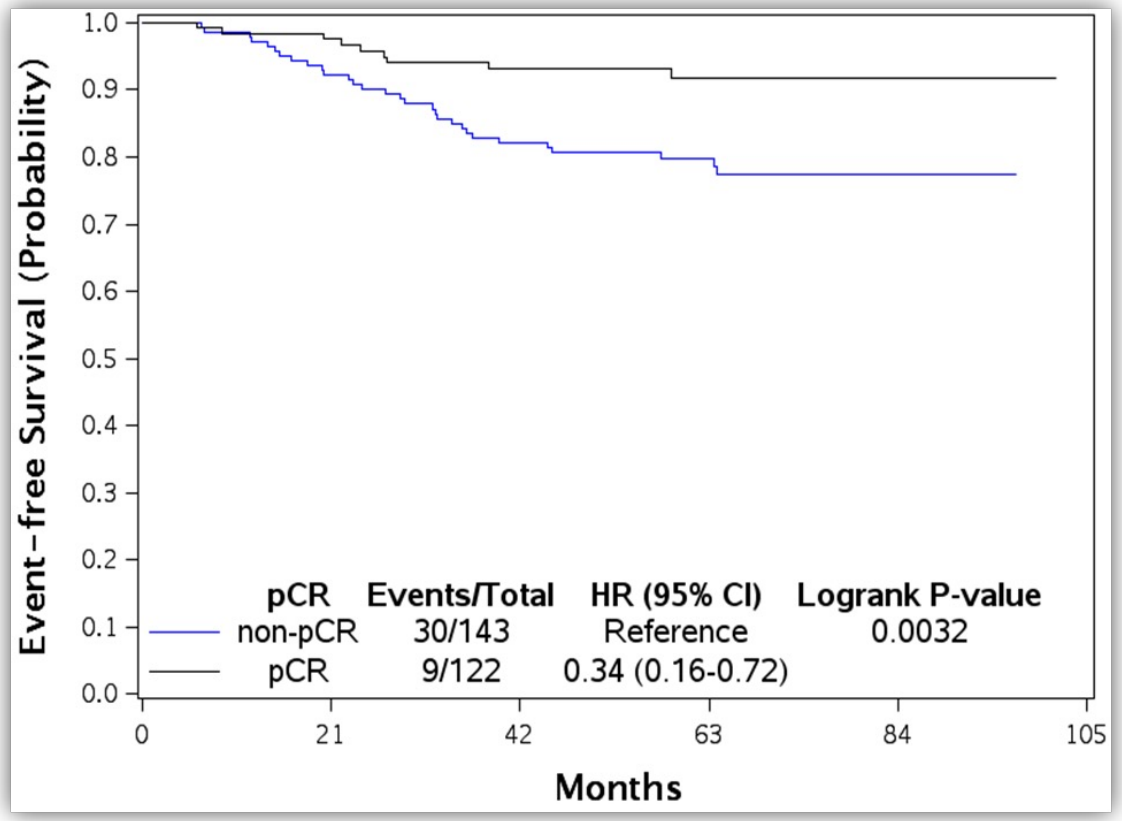


The neoadjuvant era highlighted the role of pCR in survival for Her 2 + early breast cancer

Patients with residual invasive breast cancer after completion of preoperative HER2-directed therapy and chemotherapy have an inferior prognosis [2-6]

Investigation of additional treatment strategies warranted

CALGB 40601



Krop et al, AACR-SABCS 2017

RD: ~80 % 5y EFS

Untch et. al. JCO 2011[2]; Cortazar et al. Lancet 2014[3]; de Azambuja et. al Lancet Oncol 2014[4]; Gianni et al.,Lancet Oncol 2014[5]; Schneeweiss et al., Eur J Cancer 2018[6]

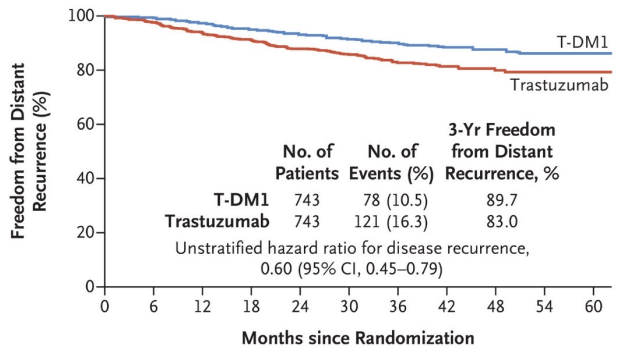
The NEW ENGLAND JOURNAL of MEDICINE

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

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

KATHERINE Trial, von Minckwitz, et al.

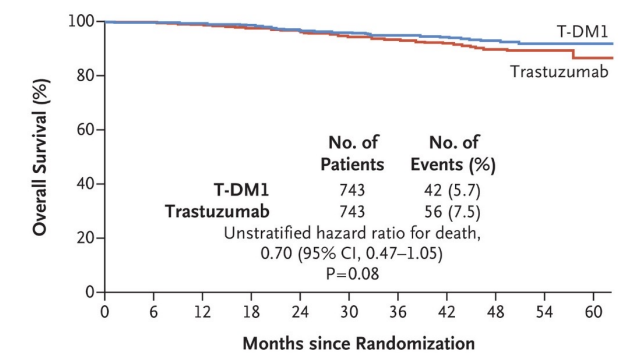
B



No. at Risk

T-DM1	743	707	682	661	636	564	412	254	143	45	4
Trastuzumab	743	679	643	609	577	520	359	233	126	41	4

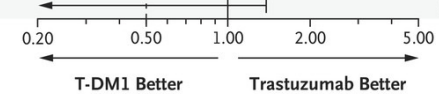
C



No. at Risk

T-DM1	743	719	702	693	668	648	508	345	195	76	12
Trastuzumab	743	695	677	657	635	608	471	312	175	71	8

Subgroup	T-DM1	Trastuzumab	Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate	
	no. of patients with an invasive-disease event/total no.			T-DM1	Trastuzumab
				%	
All patients	91/743	165/743	0.50 (0.39–0.64)	88.3	77.0
Age group					
<40 yr	20/143	37/153	0.50 (0.29–0.86)	86.5	74.9
40–64 yr	64/542	113/522	0.49 (0.36–0.67)	88.8	77.1
≥65 yr	7/58	15/68	0.55 (0.22–1.34)	87.4	81.1
Clinical stage at presentation					
Inoperable breast cancer	42/185	70/190	0.54 (0.37–0.80)	76.0	60.2
Operable breast cancer	49/558	95/553	0.47 (0.33–0.66)	92.3	82.8
Hormone-receptor status					
Negative (ER-negative and progesterone-receptor–negative or unknown)	38/209	61/203	0.50 (0.33–0.74)	82.1	66.6
Positive (ER-positive, progesterone-receptor–positive, or both)	53/534	104/540	0.48 (0.35–0.67)	90.7	80.7
Preoperative HER2-directed therapy					
Trastuzumab alone	78/600	141/596	0.49 (0.37–0.65)	87.7	75.9
Trastuzumab plus additional HER2-directed agent or agents	13/143	24/147	0.54 (0.27–1.06)	90.9	81.8
Pathological nodal status after preoperative therapy					
Node-positive	62/343	103/346	0.52 (0.38–0.71)	83.0	67.7
Node-negative or NE	29/400	62/397	0.44 (0.28–0.68)	92.8	84.6
Primary tumor stage at definitive surgery					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	40/331	52/306	0.66 (0.44–1.00)	88.3	83.6
ypT1, ypT1c	14/175	42/184	0.34 (0.19–0.62)	91.9	75.9
ypT2	25/174	44/185	0.50 (0.31–0.82)	88.3	74.3
ypT3	9/51	21/57	0.40 (0.18–0.88)	79.8	61.1
ypT4	3/12	6/11	0.29 (0.07–1.17)	70.0	30.0
Regional lymph-node stage at definitive surgery					
ypN0	28/344	56/335	0.46 (0.30–0.73)	91.9	83.9
ypN1	29/220	50/213	0.49 (0.31–0.78)	88.9	75.8
ypN2	16/86	38/103	0.43 (0.24–0.77)	81.1	58.2
ypN3	17/37	15/30	0.71 (0.35–1.42)	52.0	40.6
ypNX	1/56	6/62	0.17 (0.02–1.38)	98.1	88.7



Summary of the Early Her2+ BC Field

NODE NEGATIVE

Adjuvant :

TH-> H

TCH->H

? TDM-1

Larger tumor [>2cm]:

Neoadjuvant TCHP -> HP

NODE POSITIVE

Neoadjuvant: TCHP or anthracycline based regimen

Adjuvant:

pCR yes: HP

pCR no: TDM-1

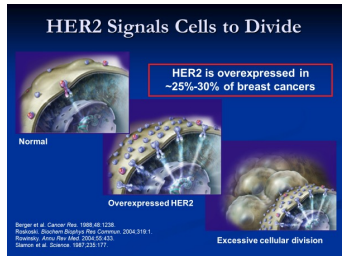
Option to add neratinib add if ER+ and high risk

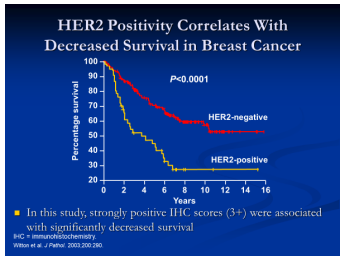
Pregnancy: AC x 4 during 2 or 3rd trimester (stop by 36-37 weeks) then TH or THP postpartum

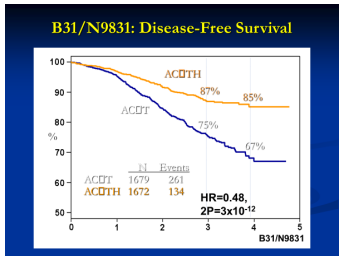
SUMMARY: IMPACT ON CLINICAL PRACTICE

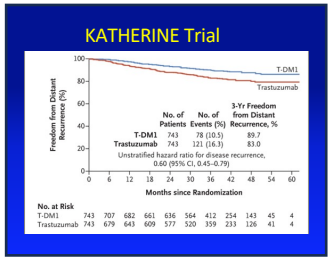
FROM EARLY SUCCESS WE LEARNED:

- Hitting the target => lives saved
- All stages of Her 2 + breast cancer need targeted therapy, but lower stages still lower risk, so minimally toxic regimens are a must!
- Less toxic options needed
- Success at systemic disease control has led to CNS outgrowth
- Future directions => better definition of risk and better targeted combination therapies tailored to the risk at hand

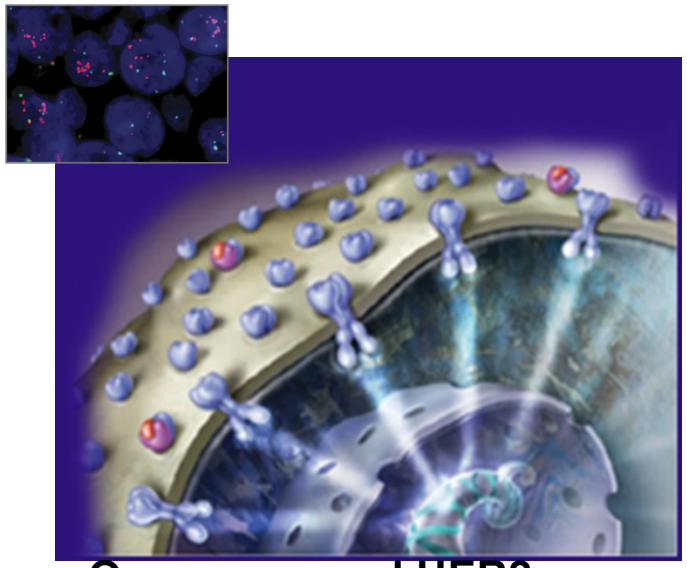








TODAY'S OPTIONS IN HER 2 TARGETED THERAPY FOR EARLY-STAGE DISEASE



Overexpressed HER2

1998-2023

trastuzumab

pertuzumab

ado-emtansine-trastuzumab [T-DM1]

neratinib

Contenders:

tucatinib

trastuzumab-deruxtecan [T-DXd]

COMPARATIVE SELECT TOXICITIES OVERVIEW

Drug	neuropathy	neutropenia	thrombocytopenia	Diarrhea	LFTs	Pulmonary
trastuzumab	-	-	-	+	-	+
pertuzumab	+	-	-	+	-	-
T-DM1	+	+	+	+	+	+
neratinib	-	-	-	+	+	-
tucatinib	-	-	-	+	+	-
T-DXd	-	+	+	+	+	+

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

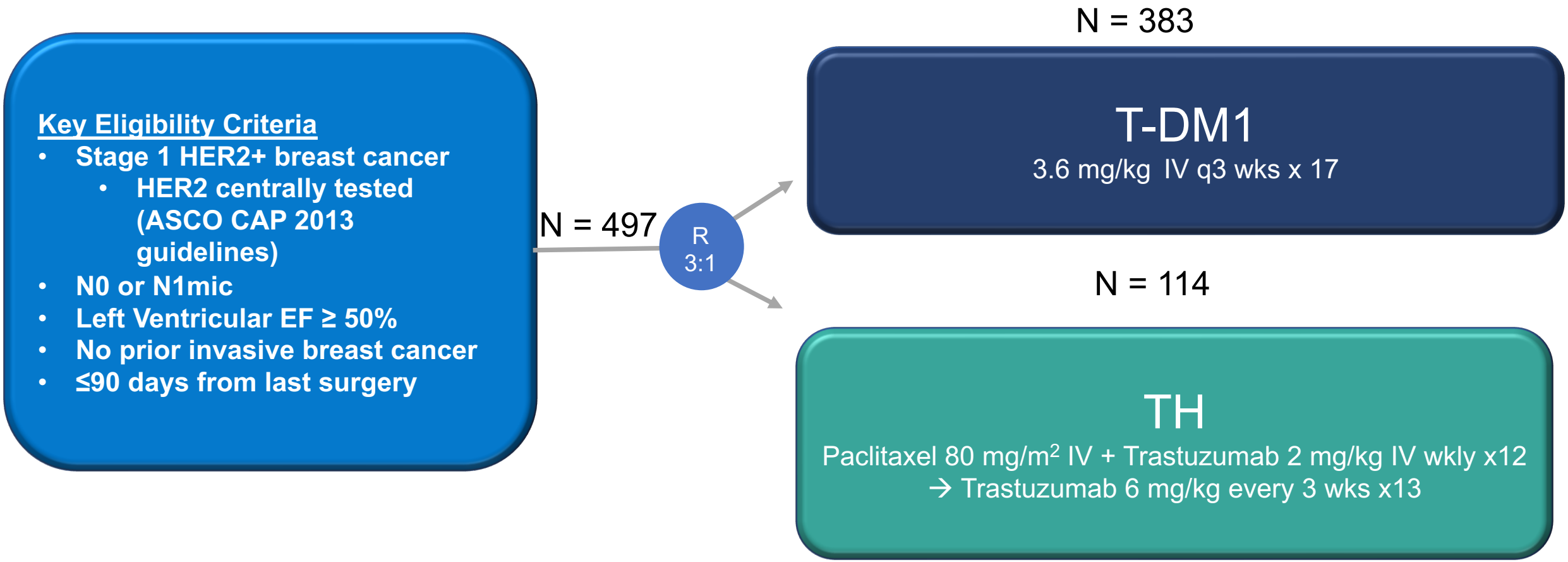
tbcrc

TBCRC 033: A Randomized Phase 2 Trial of Adjuvant Trastuzumab Emtansine (T-DM1) vs. Paclitaxel with Trastuzumab for Stage 1 HER2+ Breast Cancer (ATEMPT)

Sara M. Tolaney[1,2], Jiani Hu[1,2], Chau Dang[3], Denise Yardley[4], Steven J. Isakoff[5], Vicente Valero[6], Meredith Faggen[1], Therese Mulvey[5], Ron Bose[7], Nabihah Tayob[1,2], William Barry[1,2], Douglas Weckstein[1], Antonio C. Wolff[8], Katherine Reeder-Hayes[9], Hope S. Rugo[10], Bhuvaneswari Ramaswamy[11], Dan Zuckerman[12], Lowell Hart[13], Vijayakrishna K. Gadi[14], Michael Constantine[1], Kit Cheng[15], Frederick Briccetti[1], Bryan Schneider[16], Nadine Tung[1,2], Merrill Garrett[17], Kelly Marcom[18], Kathy Albain[19], Patricia DeFusco[20], Blair Ardman[21], Rita Nanda[22], Rachel Jankowitz[23], Mothaffar Rimawi[24], Vandana Abramson[25], Paula Pohlmann[26], Catherine Van Poznak[27], Andres Forero-Torres[28], Minetta Liu[29], Michelle DeMeo[1], Ann Partridge[1,2], Harold Burstein[1,2], Eric P. Winer[1,2], Ian Krop[1,2]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Memorial Sloan-Kettering Cancer Center, New York, NY; [4]Sarah Cannon Cancer Center, Nashville, TN; [5]Massachusetts General Hospital, Boston, MA; [6]MD Anderson Cancer Center, Houston, TX; [7]Washington University, St. Louis, MO; [8]Johns Hopkins Sidney Kimmel Cancer Center, Washington, DC; [9]UNC Chapel Hill, Chapel Hill, NC; [10]UCSF, San Francisco, CA; [11]OSU Comprehensive Cancer Center, Columbus, OH; [12]St. Luke's Mountain States Tumor Institute, Boise, ID; [13]Florida Cancer Specialists, Fort Myers, FL; [14]Seattle Cancer Care Alliance, Seattle, WA; [15]North Shore-LIJ Cancer Institute, Lake Success, NY; [16]IU School of Medicine, Indianapolis, Indiana; [17]Northern Light Cancer Care, Brewer, ME; [18]Duke University, Durham, NC; [19]Loyola University Medical Center, Maywood, IL; [20]Hartford Healthcare Cancer Institute, Hartford, CT; [21]Lowell General Hospital, Lowell, MA; [22]UChicago Medicine, Chicago, IL; [23]UPMC Hillman Cancer Center, Pittsburgh, PA; [24]Baylor College of Medicine, Houston, TX; [25]Vanderbilt Ingram Cancer Center, Nashville, TN; [26]Georgetown University Hospital, Washington DC; [27]University of Michigan, Ann Arbor, MI; [28]Birmingham Veterans Affairs Medical Center, Birmingham, AL; [29]Mayo Clinic Cancer Center, Rochester, MN

Study Design: ATEMPT Trial

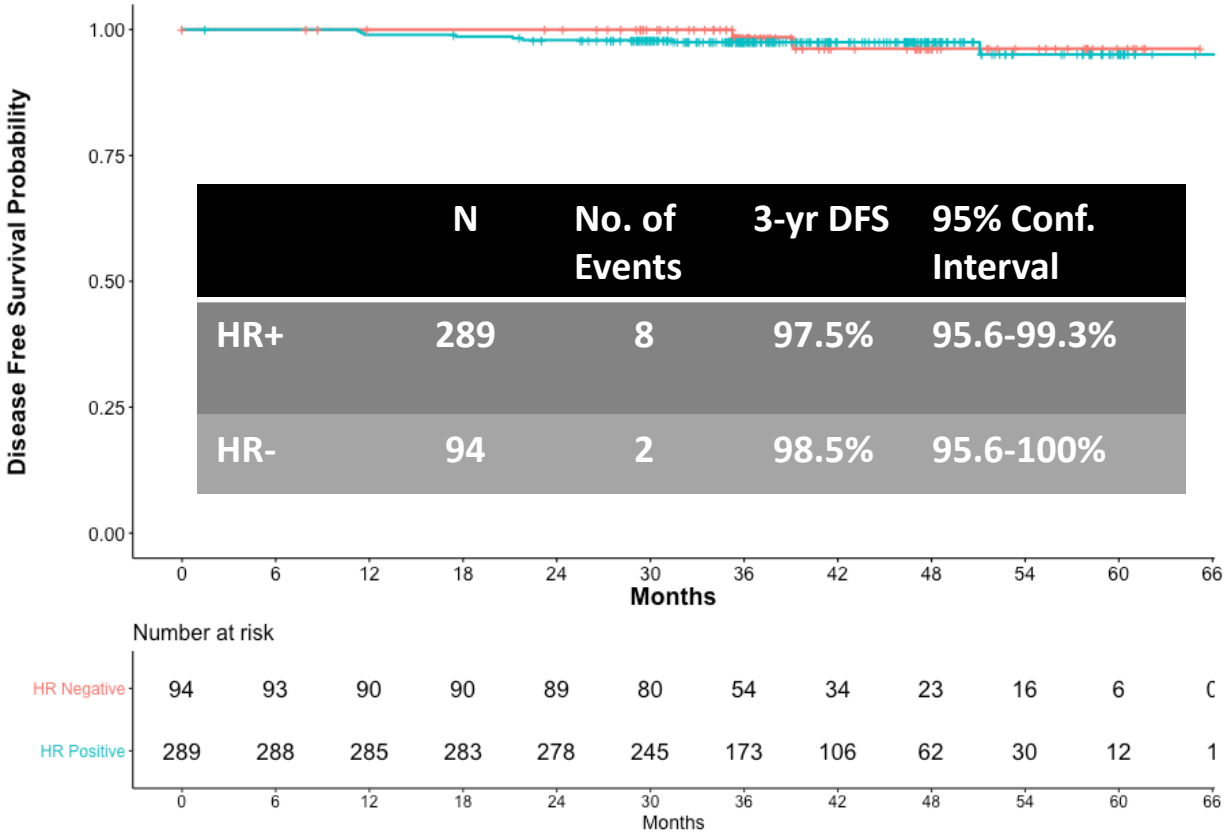


Study Population

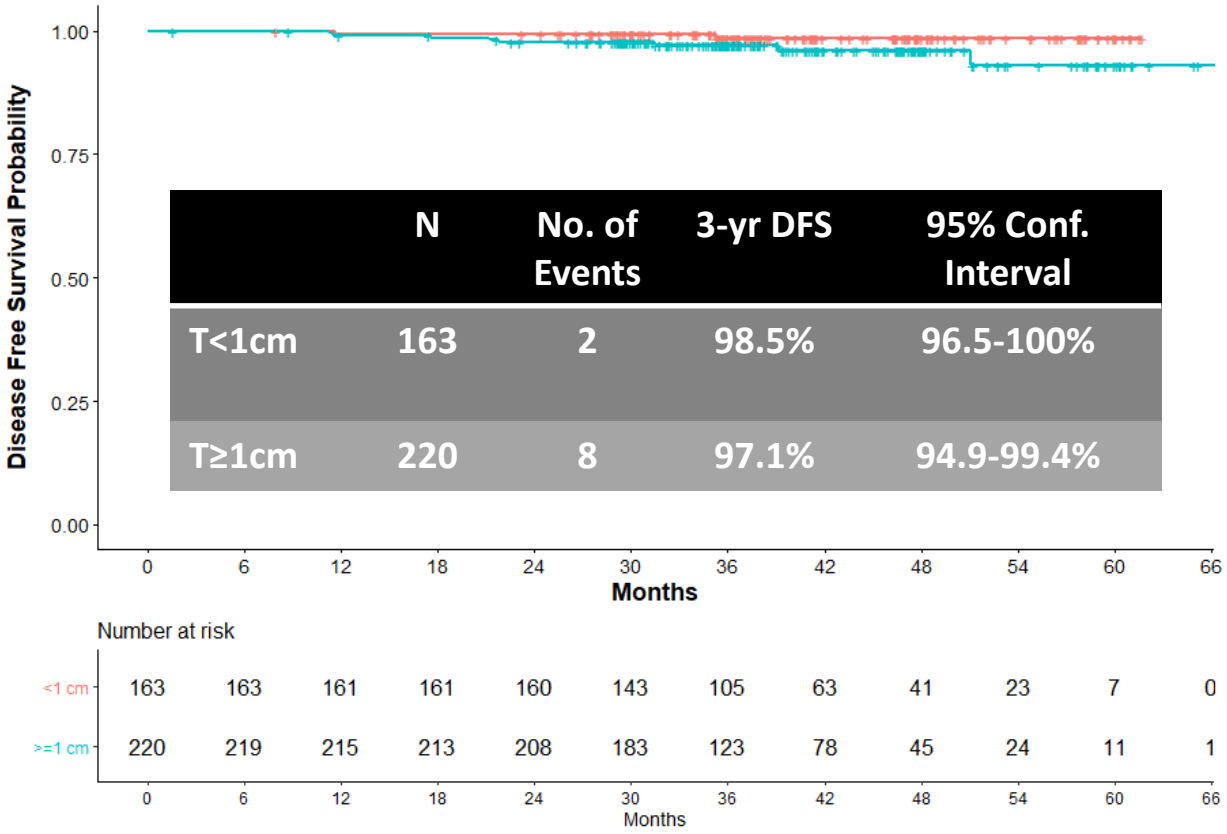
	T-DM1 (n = 383)	TH (n = 114)	All Patients (n = 497)
Median Age (Range)	56 (32-85)	55 (23-82)	56 (23-85)
Tumor Size			
<0.5 cm	42 (11%)	14 (12%)	56 (11%) } 43%
≥0.5-1.0 cm	121 (32%)	38 (33%)	159 (32%)
≥1.0-1.5 cm	118 (31%)	29 (25%)	147 (30%) } 57%
≥1.5-2.0 cm	102 (27%)	33 (29%)	135 (27%)
Histologic Grade			
Well Differentiated	11 (3%)	4 (4%)	15 (3%)
Moderately Differentiated	148 (39%)	46 (40%)	194 (39%)
Poorly Differentiated	219 (57%)	62 (54%)	281 (57%)
Unknown	5 (1%)	2 (2%)	7 (2%)
HR status			
Positive	289 (75%)	84 (74%)	373 (75%)
Negative	94 (25%)	30 (26%)	124 (25%)
HER2 Status (Central)			
1+	5 (1%)	1 (1%)	6 (1%)
2+	92 (24%)	25 (22%)	117 (24%)
3+	277 (72%)	87 (76%)	364 (73%)
Not done*	9 (2%)	1 (1%)	10 (2%)

*FISH performed centrally without IHC

Disease-Free Survival: T-DM1

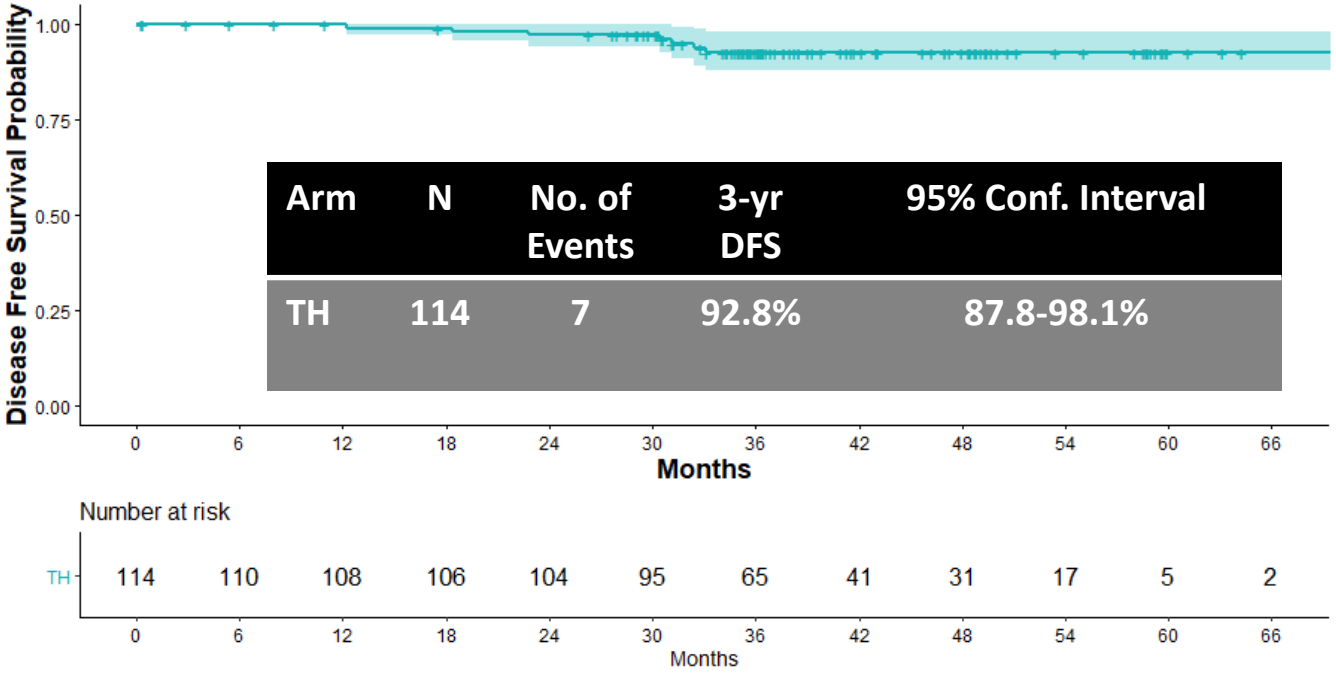


	N	No. of Events	3-yr DFS	95% Conf. Interval
HR+	289	8	97.5%	95.6-99.3%
HR-	94	2	98.5%	95.6-100%

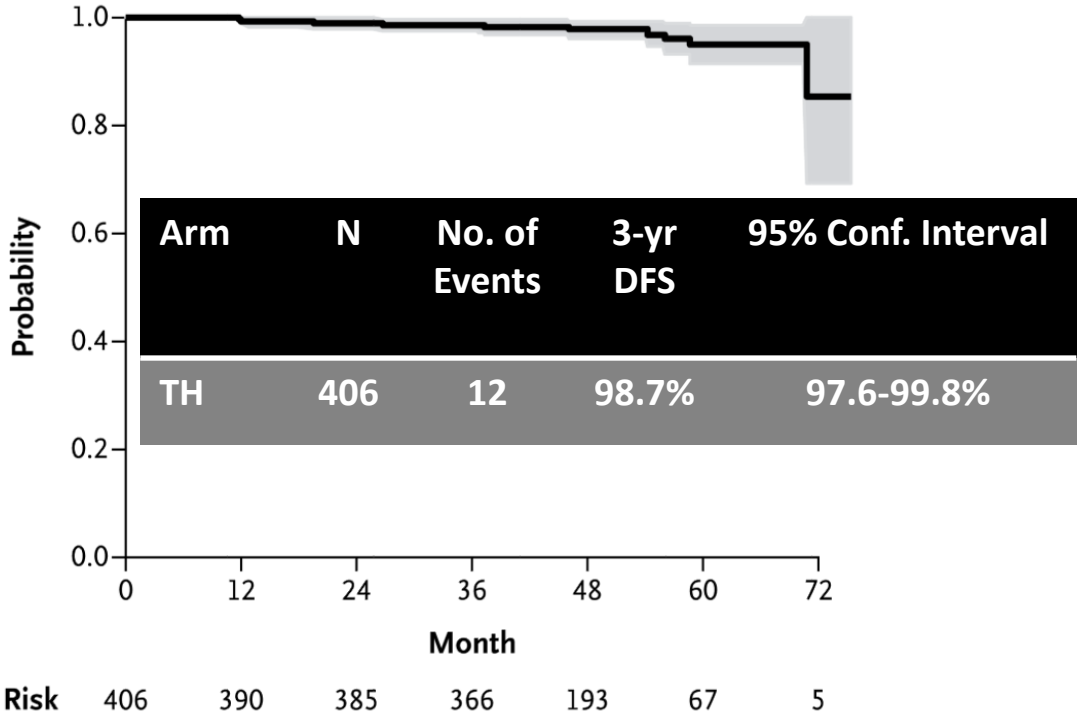


	N	No. of Events	3-yr DFS	95% Conf. Interval
T<1cm	163	2	98.5%	96.5-100%
T≥1cm	220	8	97.1%	94.9-99.4%

Disease-Free Survival: TH



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
TH	114	7	92.8%	87.8-98.1%



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
TH	406	12	98.7%	97.6-99.8%

Tolaney S et al, NEJM 2015

Clinically Relevant Toxicity

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

Suitability of Chemotherapy De-escalation Based on Response to Neoadjuvant Paclitaxel + Trastuzumab + Pertuzumab in HER2-Positive Breast Cancer: The DAPHNE Trial

- Feasibility study, single arm, dose de-escalation study -THP
- Stage II/III ER any Her 2 positive breast cancer
- “Infeasible if adherence is <80% in patients with pCR”
  - 81 subjects, 86% stage 2, 32% ER/PR-
  - 51 achieved pathCR – adherence endpoint was met in that 95% stayed on regimen
  - 30 without pCR 14 got chemo, 16 got non-chemo approach [TDM-1]

A011801 (CompassHER2 RD)
Postneoadjuvant T-DM1 + Tucatinib/Placebo in Patients With Residual Disease

The CompassHER2 Trials

COMprehensive use of Pathologic response ASSessment to optimize therapy in HER2-positive breast cancer

CompassHER2 pCR(EA1181): Patients with pCR after preoperative THP

CTSU active, Feb 11,2020

CompassHER2 RD (A011801): Patients with residual disease after THP

CTSU activation, January 6,2021

Virginia F. Borges, MD, MMSc
University of Colorado Cancer Center
NRG co-Chair RD trial

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 T ≥ 2.0 cm
- **cN1-2 eligible if T ≥ 1.0cm**
- ER+ and ER- eligible

REGISTRATION

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

- complete 1 yr HP
- radiation and endocrine rx (as appropriate)

No pCR
60%

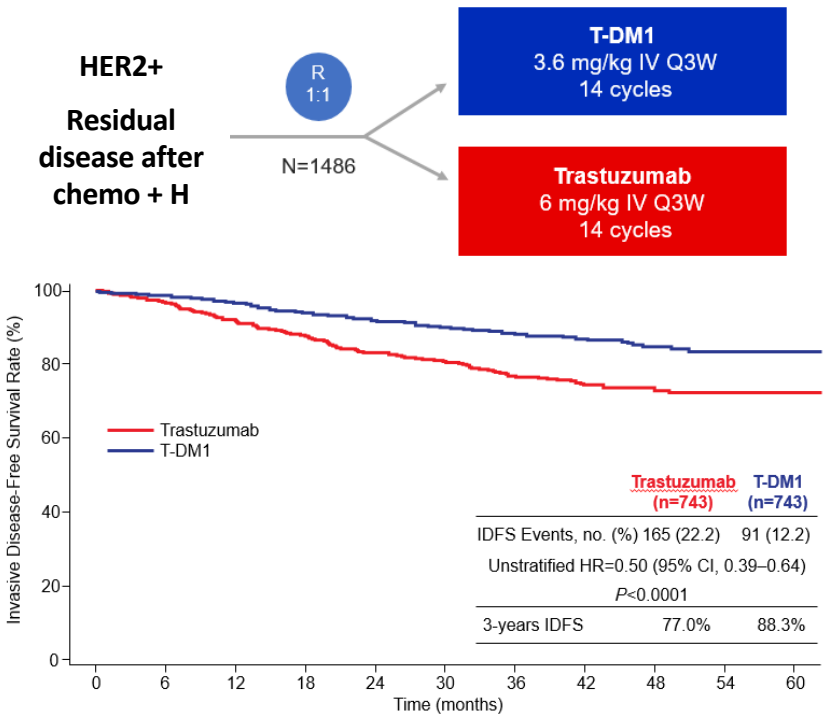
EA1181 Arm B: Residual Disease

- post-op AC
- THP x 2
- Cb/HP x 2-4

TDM-1
or clinical trial:
A011801 CompassHER2 RD BR009

Rationale for Escalation in Residual Disease

KATHERINE POSTNEOADJUVANT TRIAL



Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS
All	1486	77.0	88.3
Clinical stage at presentation			
Operable	1111	82.8	92.3
Inoperable	375	60.2	76.0
Hormone receptor status			
Negative (ER negative and PgR negative/unknown)	412	66.6	82.1
Positive (ER and/or PgR positive)	1074	80.7	90.7
Preoperative HER2-directed therapy			
Trastuzumab alone	1196	75.9	87.7
Trastuzumab plus additional HER2-directed agent(s)	290	81.8	90.9
Pathological nodal status after preoperative therapy			
Node positive	689	67.7	83.0
Node negative/not done	797	84.6	92.8
Age group (years)			
<40	296	74.9	86.5
40–64	1064	77.1	88.8
≥65	126	81.1	87.4
Race^			
White	1082	79.1	88.8
Asian	129	71.9	82.5
American Indian or Alaska Native	86	60.3	81.8
Black or African American	40	66.0	94.7

28% of pop'n

46% of pop'n

Even with T-DM1, ER-negative and any node+ have EFS ~ 82%

Incidence of brain metastases similar in both treatment arms

- **Appropriate subgroups for escalation: (ER-/HER2+ patients, high-risk ER+/HER2+ patients, e.g. N+ after preoperative systemic therapy)**

Geyer, NEJM 2018

KATHERINE: Central Nervous System Recurrence Events

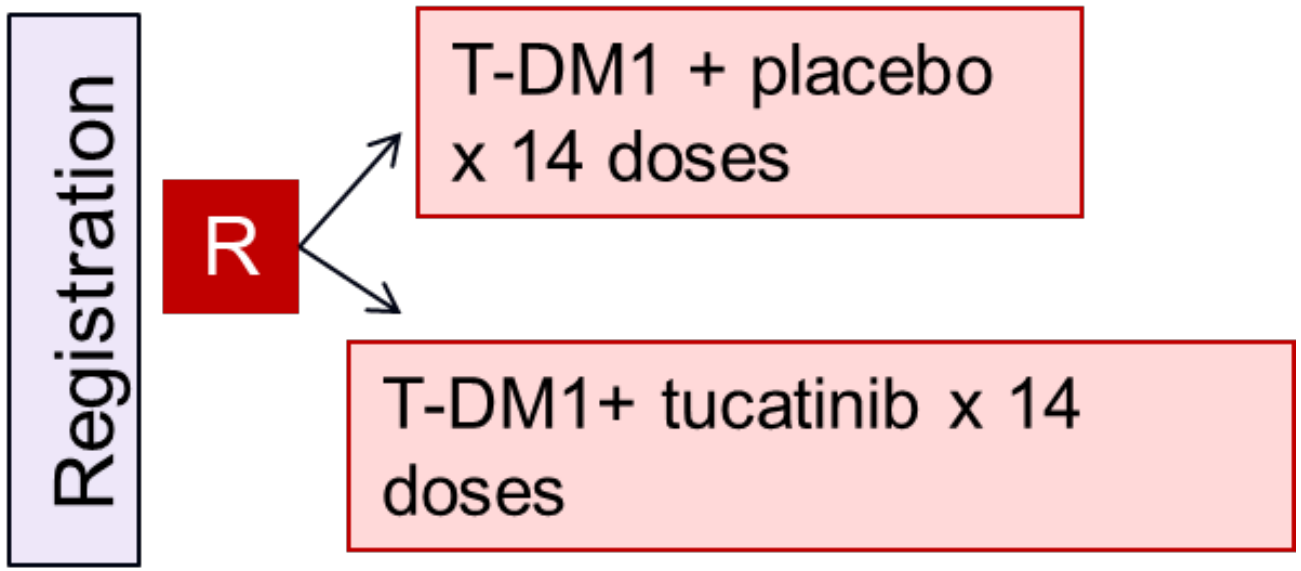
	T-DM1 (n = 743)	Trastuzumab (n = 743)
Patients with CNS recurrence	45 (6.1%)	40 (5.4%)
At first IDFS event[a]	44 (5.9%)	32 (4.3%)
After first IDFS event[b]	1 (0.1%)	8 (1.1%)
Patients with CNS as only event[c]	36 (4.8%)	21 (2.8%)
Median time to CNS recurrence	17.5 months	11.9 months

T-DM1 = trastuzumab emtansine; CNS = central nervous system; IDFS = invasive disease-free survival
CNS recurrence [a]within or [b]after 61 days of first IDFS event or at [c]any time

Mamounas EP et al. *Ann Oncol* 2021;32(8):1005-14.

A011801 (CompassHER2 RD)
Postneoadjuvant T-DM1 + Tucatinib/Placebo in Patients With Residual Disease

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

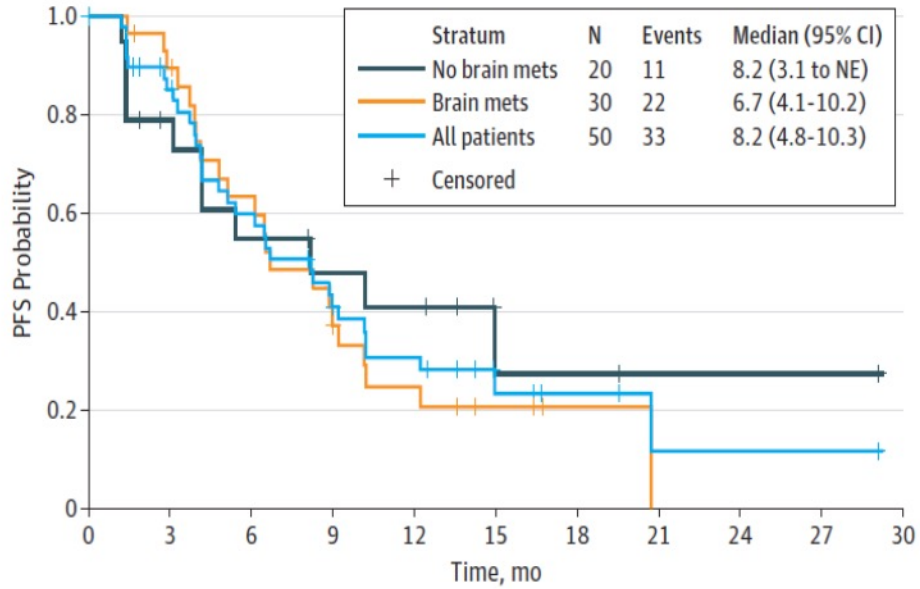


JAMA Oncology | Original Investigation

Tucatinib Combined With Ado-Trastuzumab Emtansine in Advanced *ERBB2/HER2*-Positive Metastatic Breast Cancer
A Phase 1b Clinical Trial

Virginia F. Borges, MD, MMSc; Cristiano Ferrario, MD; Nathalie Aucoin, MD; Carla Falkson, MD; Qamar Khan, MD; Ian Krop, MD, PhD; Stephen Welch, MD; Alison Conlin, MD; Jorge Chaves, MD; Philippe L. Bedard, MD; Marc Chamberlain, MD; Todd Gray, MD; Alex Vo, MD; Erika Hamilton, MD

Figure 2. Kaplan-Meier Plot of Progression-Free Survival (PFS) Among Patients Treated With the Maximum Tolerated Dosage of Tucatinib Combined With Ado-Trastuzumab Emtansine



Findings In this phase 1b study of 57 patients with metastatic or unresectable locally advanced *ERBB2/HER2*-positive breast cancer treated previously with trastuzumab and a taxane, the maximum tolerated dosage of tucatinib combined with ado-trastuzumab emtansine was determined to be 300 mg administered orally twice daily; the objective response rate was 48%; and median progression-free survival was 8.2 months.

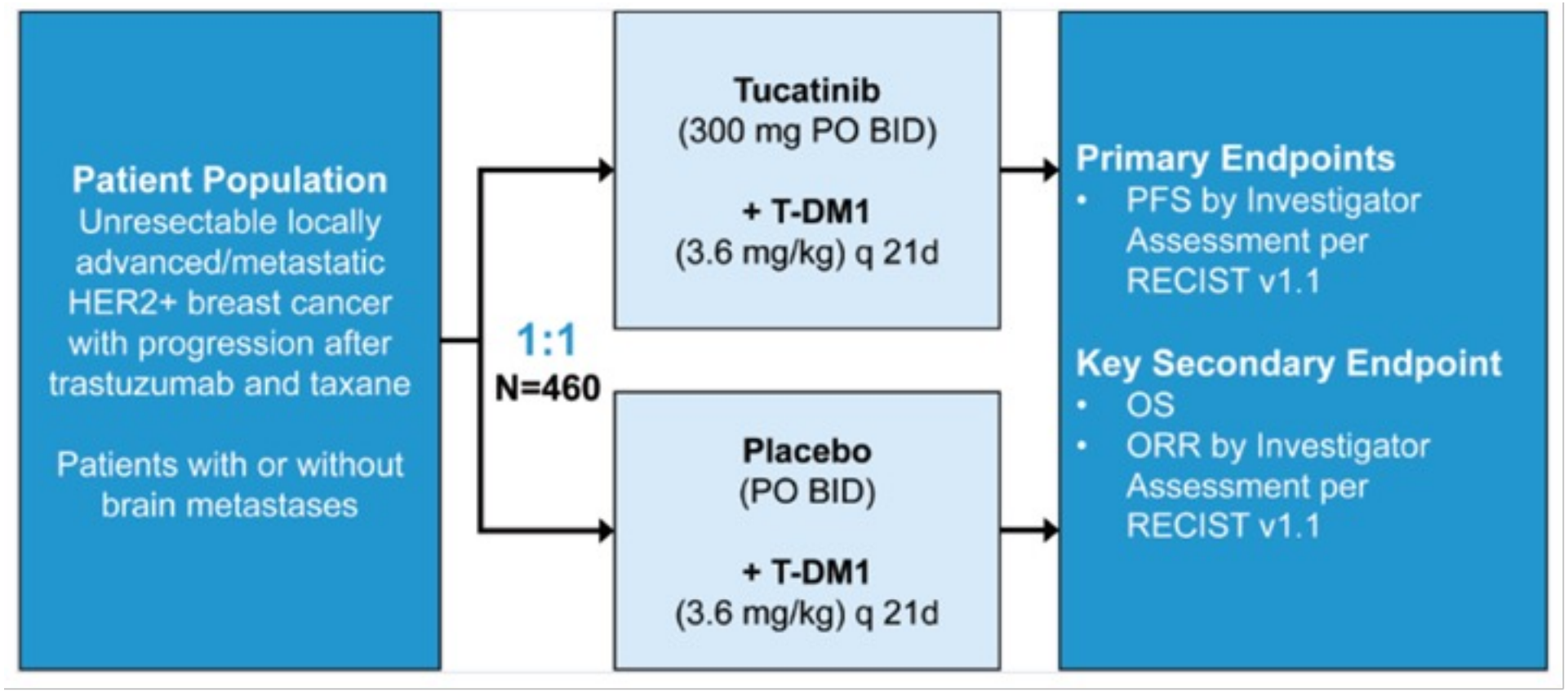
- **Adverse events**: nausea (72%), diarrhea (60%), fatigue (56%), epistaxis (44%), headache (44%), vomiting (42%), constipation (42%), decreased appetite (40%);

- Majority AEs grade 1 or 2.
- Tucatinib-related toxic reactions ≥ grade 3: thrombocytopenia (7 patients; 14%) and transaminitis (6 patients; 12%).

Acceptable safety profile and preliminary antitumor efficacy

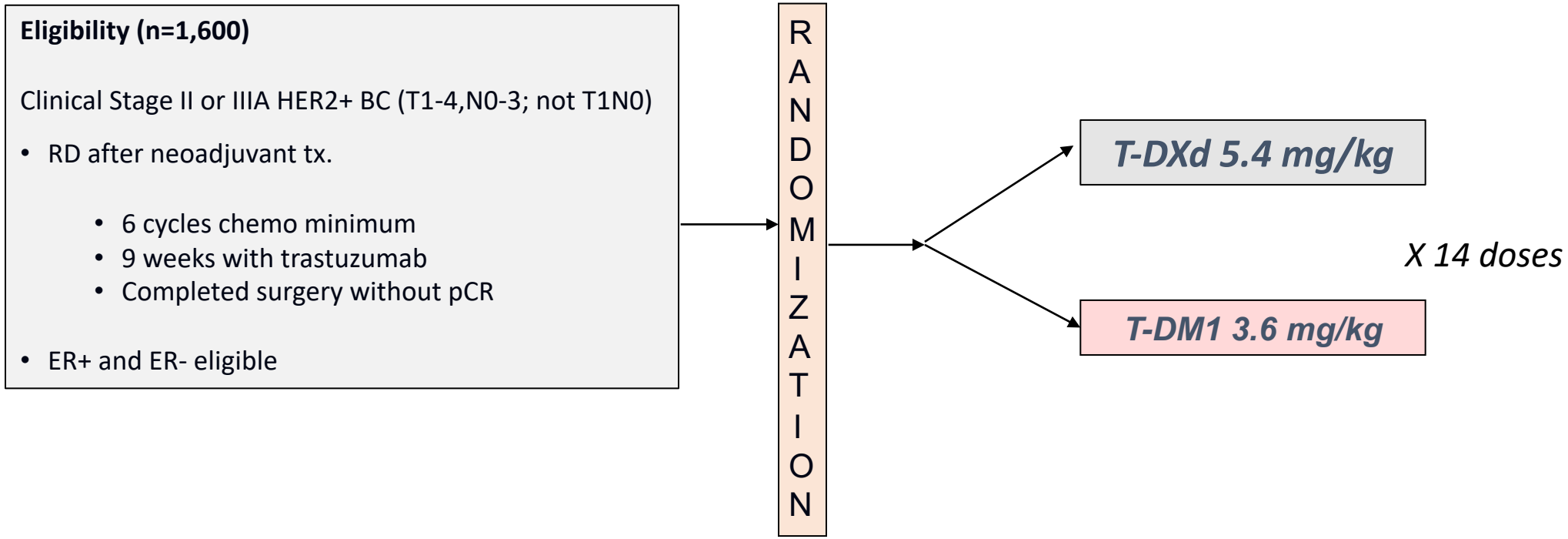
HER2CLIMB-02: A Randomized, Double-Blind, Phase 3 Study of Tucatinib or Placebo with T-DM1 for Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer (Trial in Progress)

Sara Hurvitz[1], Linda Vahdat[2], Nadia Harbeck[3], Antonio C. Wolff[4], Sara M. Tolaney[5], Sherene Loi[6], Norikazu Masuda[7], Joyce O'Shaughnessy[8], Cassie Dong[9], Luke Walker[9], Evelyn Rustia[9], Virginia F. Borges[10]
[1]University of California, Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, CA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Brustzentrum der Universität München (LMU), Munich, Germany; [4]The Johns Hopkins Kimmel Cancer Center, Baltimore, MD; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Peter MacCallum Cancer Center, Melbourne, Australia; [7]NHO Osaka National Hospital, Osaka, Japan; 8Baylor University Medical Center, Texas Oncology, US Oncology, Dallas;



DESTINY-Breast05

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in Participants With High-Risk HER2-Positive Primary Breast Cancer Who Have Residual Invasive Disease in Breast or Axillary Lymph Nodes Following Neoadjuvant Therapy [NCT04622319]



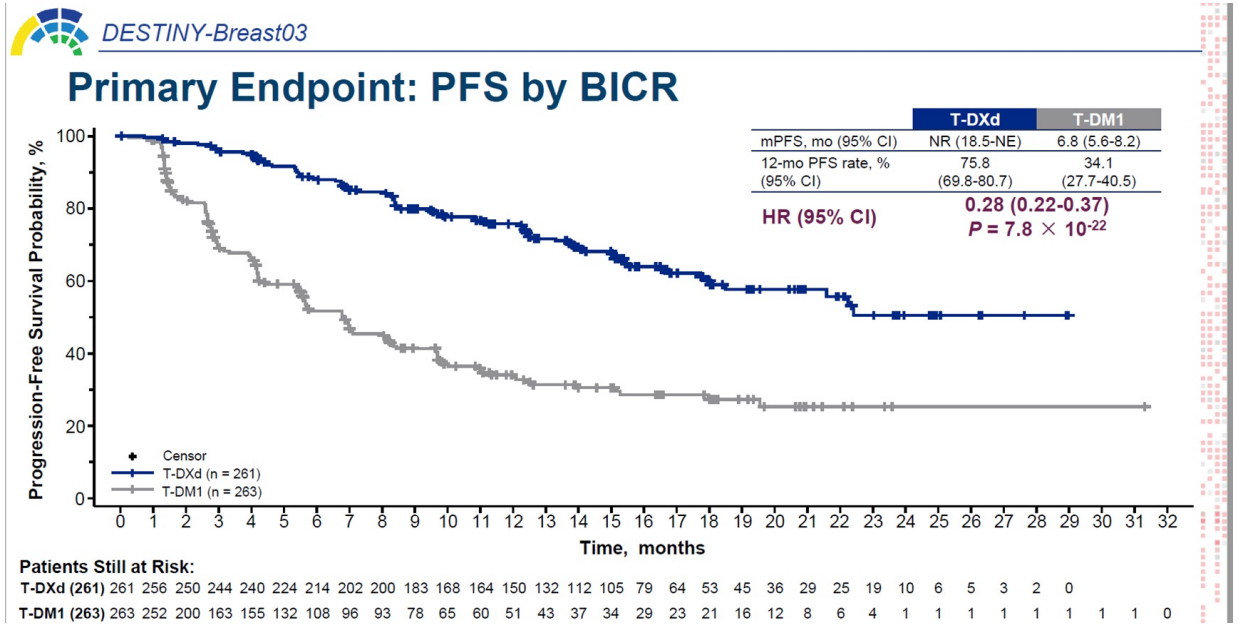
RATIONALE FOR ESCALATION TO T-DXD IN RD: DESTINY-03

T-DXD v. T-DM1 in Previously Treated HER2+ Positive Breast Cancer

Randomized Phase III (n=524)

mPFS T-DXD not yet reached
mPFS T-DM1 6.8 months

12-month PFS 75.8% T-DXD
12-months PFS 34.1% T-DM1



Cortes, et al. ESMO Congress 2021

DESTINY-Breast03

PFS in Key Subgroups

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)

HR (T-DXd vs T-DM1)

2021 ESMO congress

[a]Rapid progressors on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

Summary and future directions

- We are living in an era of opportunity to tailor therapy to the biology, the stage, the response, and the tolerability/patient preferences.
- These are long treatment pathways for patients, so PROs, QOL, clinical resources and support are of increased importance.
- Continuing to tweak options for the lower risk patients
- Ongoing HR+ Her 2+ concepts
- Understanding Low Her2+ in the adjuvant setting
- Additional pathways and outcome drivers – PIK3CA+, etc.

Thank you!