Challenges in HER2+ Breast Cancer

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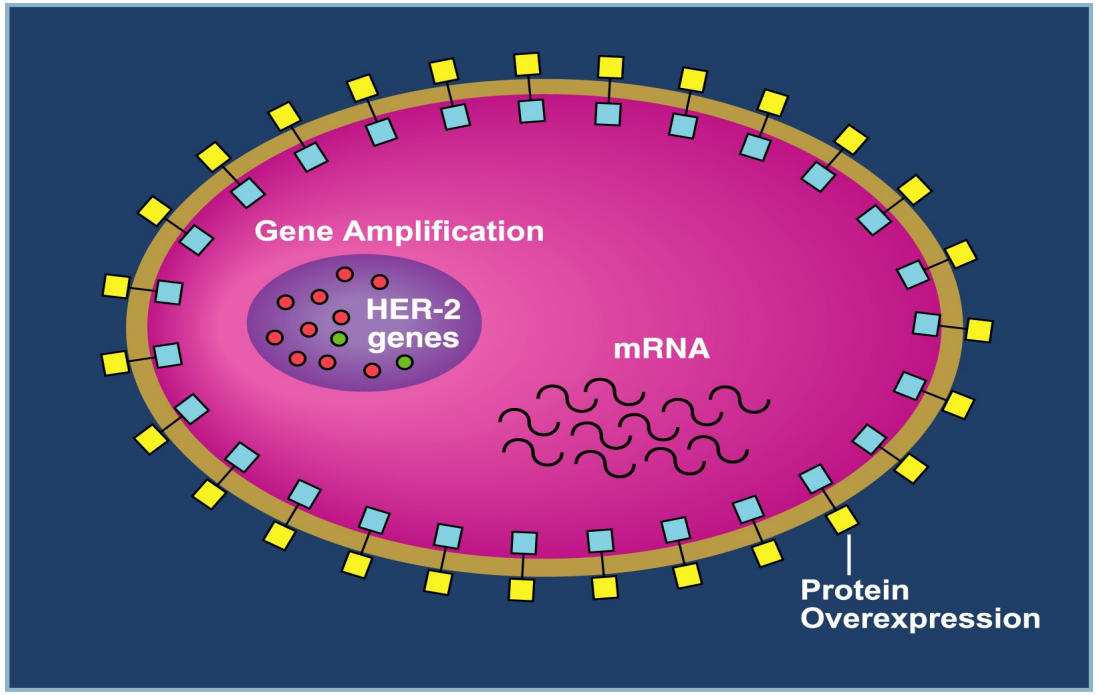
HER 2 + Breast Cancer

- 1980s HER2+ breast cancer denoted aggressive phenotype increased risk of recurrence and death, median survival 2-3 years, very difficult to treat
  - 1982-'84 HER2/neu oncogene discovered
  - '86 ErbB-2/HER2 cloned; mutated gene could stimulate excess cell growth and division
- Better understanding of molecular mechanisms underlying pathogenesis of HER2+ disease has generated targeted therapy options to combat this poor prognosis
- Deaths per year from breast cancer declining because of advances in HER2+ disease



Timeline of FDA Approvals for HER2+ Breast Cancer

1998	2007-08	2012	2013	2017	2019	2020
Trastuzumab (metastatic)	Lapatinib (metastatic)	Pertuzumab (metastatic)	T-DM1 (metastatic)	Neratinib (adjuvant)	T-DM1 (adjuvant)	Tucatinib (metastatic)
	Trastuzumab (adjuvant)		Pertuzumab (neoadjuvant)	Pertuzumab (adjuvant)	Trastuzumab deruxtecan (metastatic)	Neratinib (metastatic)
						Margetuximab (metastatic)

Drugs@FDA: FDA-approved drugs.
Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=reportsSearch.process. Accessed January 7, 2022.

OS for HER2+ Trastuzumab-Treated Early Disease Similar to or Better Than HER2-Normal

Study	Median F/U	HER2+/+tras	HER2+/-tras	HER2 –
BCIRG 005[1]/006[2]	10 years	(1841/2149) **86%**	(870/1073) 81%	(2647/3298) **80%**
NOAH[3]	5 years	(87/117) **74%**	(74/118) 63%	(75/99) **76%**
Italian Registry[4]	4.1 years	(52/53) **98%**	(140/161) 87%	(1108/1186) **93%**
GeparQuattro[5]	5.4 years	(392/446) **88%**		(889/1049) **85%**
FinHer[6]	5 years	(12/115) **91%**	(21/116) 82%	(61/778) **92%**

1. Mackey J, et al. *Ann Oncol.* 2016;27:1041-1047. 2. Slamon DJ, et al. SABCS 2015. Abstract S5-04. 3. Gianni L, et al. *Lancet Oncol.* 2014;15:640-647. 4. Musolino A, et al. *Cancer.* 2011;117:1837-1846. 5. Von Minckwitz G, et al. *Ann Oncol.* 2013;25:81-89. 6. Joensuu H, et al. *J Clin Oncol*. 2009;27:5685-5692.

For ~15% of HER2-positive at risk for relapse

- How do we do more/improve outcomes?

For the rest:

- For whom can we safely “do less” to decrease toxicity/overtreatment without compromising outcomes?

How to individualize therapy in Early Stage HER2+

- Stage I (T ≤ 2 cm, N0)
- Stage II to III (T > 2 cm, N+)
  - Role of neoadjuvant therapy
  - Role of anthracyclines and platinum therapy
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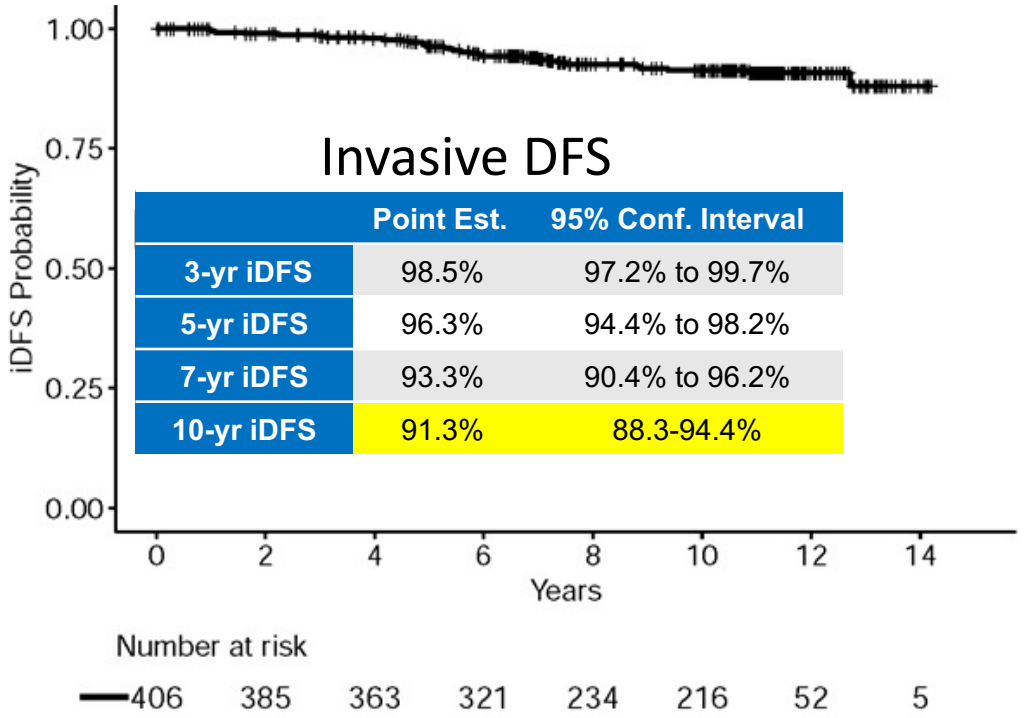
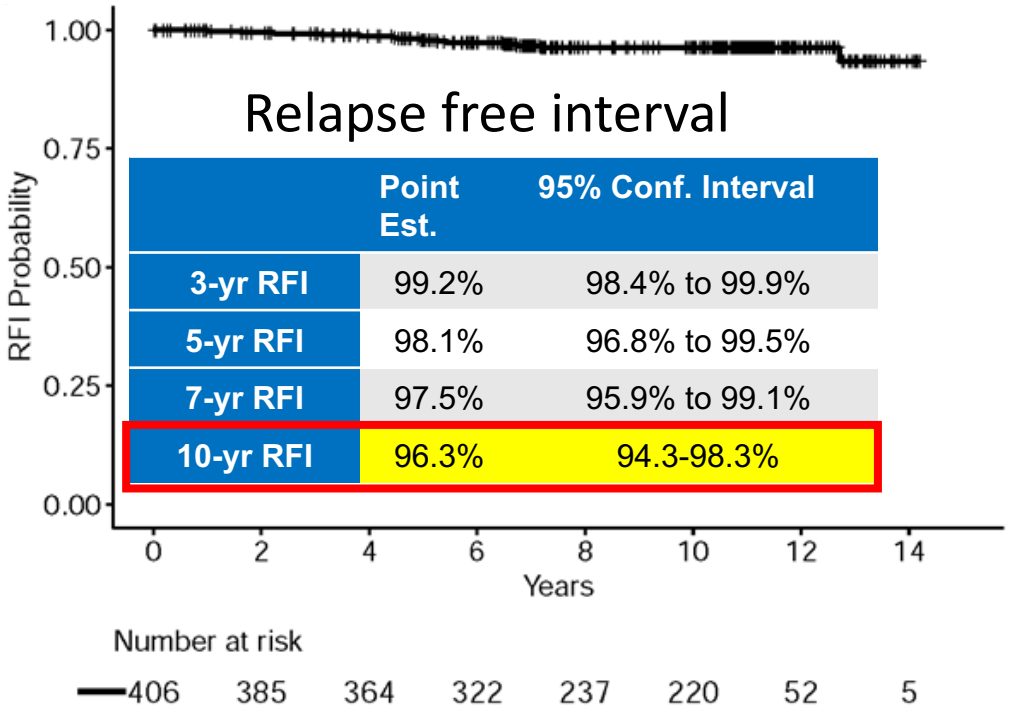
APT trial: Adjuvant TH for HER2+ tumors ≤3 cm Outcomes at 10 yrs – final study results



Invasive DFS

	Point Est.	95% Conf. Interval
3-yr iDFS	98.5%	97.2% to 99.7%
5-yr iDFS	96.3%	94.4% to 98.2%
7-yr iDFS	93.3%	90.4% to 96.2%
10-yr iDFS	91.3%	88.3-94.4%



Relapse free interval

	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to 99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%
10-yr RFI	96.3%	94.3-98.3%

iDFS events at 10 yrs: N=31

- 6 Distant recurrences, 10 Deaths
  - **Some distant recurrences detected 5+ years**

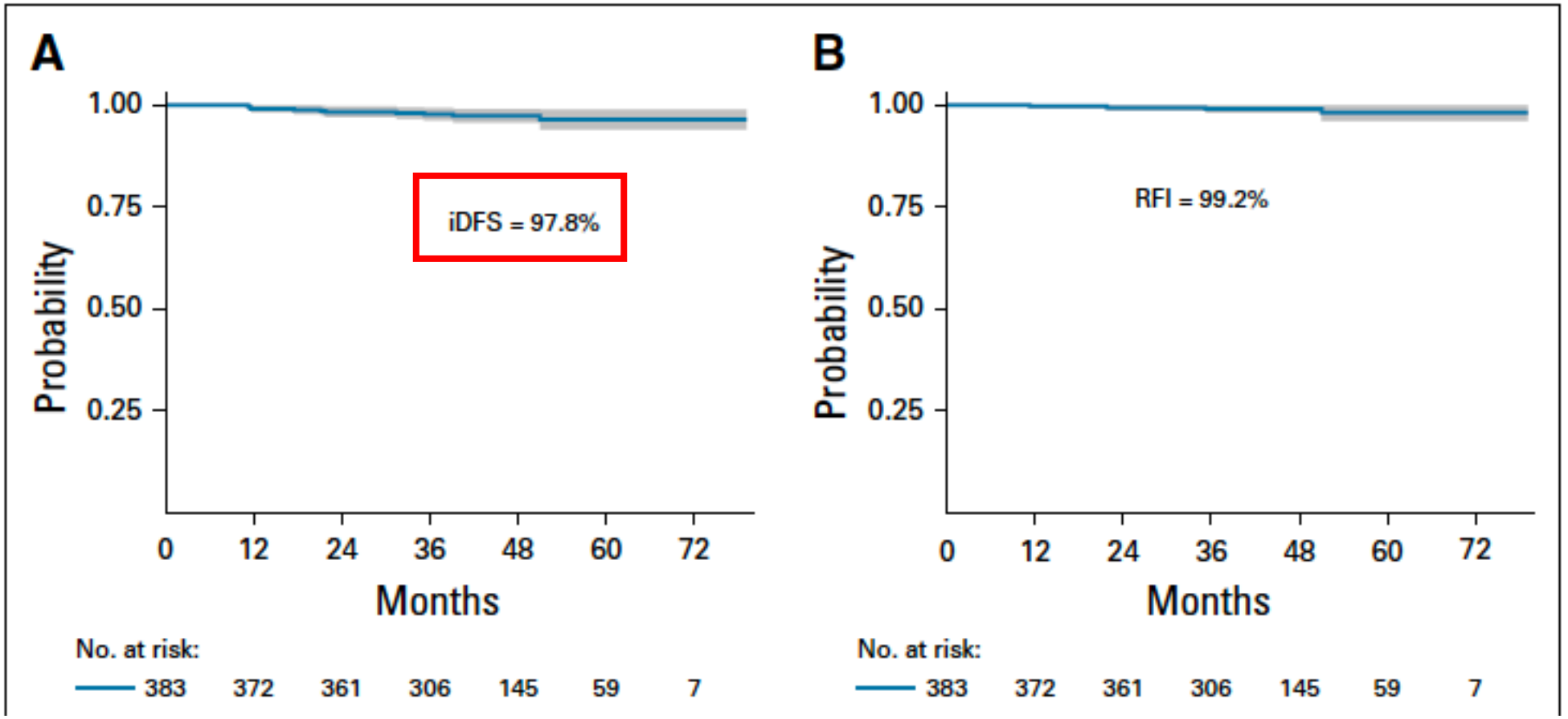
RFI Events:

- Invasive Local/Regional Recurrence
- Distant Recurrence
- Death from Breast Cancer

Tolaney SM et al SABCS 2022

ATEMPT trial: 1 yr of adjuvant T-DM1 for stage I HER2+

✓ Co-primary objective #1: 3 yr iDFS in pts receiving T-DM1



✗ Co-primary objective #2: Compare incidence of clinically relevant toxicities between arms

Tolaney SM et al. J Clin Oncol. 2021;39(21):2375-2385.

ATEMPT 2.0: Shorter Course of T-DM1

Enrolling since 06/2021

Key Eligibility Criteria

- Stage 1 HER-positive breast cancer
  - HER2 centrally tested (ASCO CAP 2013 guidelines): HER2 3+
- N0 or N1mic
- Left Ventricular EF ≥ 50%
- No prior invasive breast cancer
- ≤ 90 days from last surgery

N = 500

R 3:1

3

1

N = 375

T-DM1→ H

3.6 mg/kg IV q3 wks × 6 cycles→ SQ Trastuzumab every 3 wks × 11

N = 125

TH

Paclitaxel 80 mg/m^2 IV + Trastuzumab every 3 wks × 4 → SQ Trastuzumab every 3 wks × 13

Stratification factors:

- Age (< 55, ≥ 55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

*Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

ClinicalTrial.gov. Accessed October 7, 2022. https://clinicaltrials.gov/ct2/show/NCT04893109

What is The Optimal Approach for cT1cN0 HER-positive Tumors?

In favor of upfront surgery:

- Excellent long-term outcomes with adjuvant TH or T-DM1 alone:
  - 7-year RFI 97.5% (APT)
  - 3-year RFI 99.2% (ATEMPT)
  - Approx. 50% of pts in APT/ATEMPT had T size > 1.0 cm

In favor of upfront systemic therapy:

- cT1cN0 pts were eligible for KATHERINE
- cT1a-b/N0 pts were not
- Pathologic nodal disease is found at surgery in a significant proportion of cT1cN0 HER-positive pts
- Opportunity to explore biomarkers of response and resistance to therapy

Potential risk of <u>undertreatment</u> for:

- Pts who ultimately would be found to have pN+
- Few pts with recurrence post-TH/T-DM1

(unclear though if additional therapy would salvage)

Risk of <u>overtreatment</u> for pts who would otherwise do well with "de-escalated" adjuvant regimen, e.g. TH.

Modified slide courtesy Ada Waks, MD

How to individualize therapy in Early Stage HER2+

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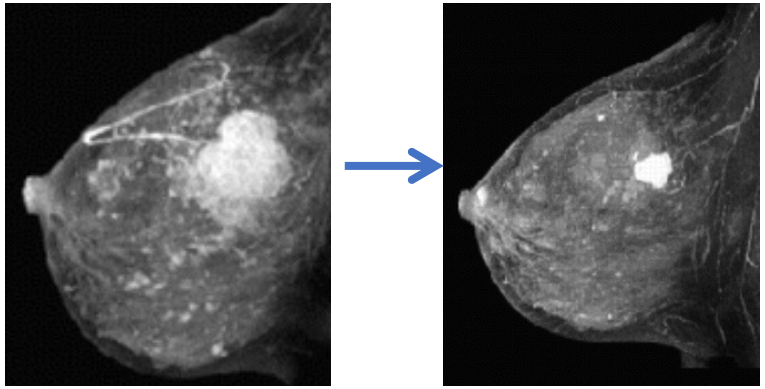
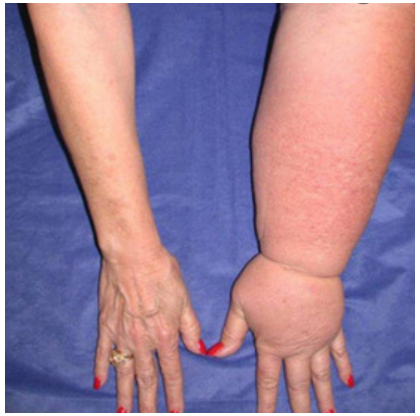
Leveraging Neoadjuvant Therapy 1: Surgical Endpoints

- Original indication = improved operability
- NSABP-B-18 (and others) confirmed no distant disease sacrifice[a, b]
- Axillary management clearly improved



- N-positive changed to N-negative in 35% to 68%
- ACOSOG Z1071: Post-NAC SN feasible and accurate (if careful - dual tracer, > 2 retrieved SN)[b, c]

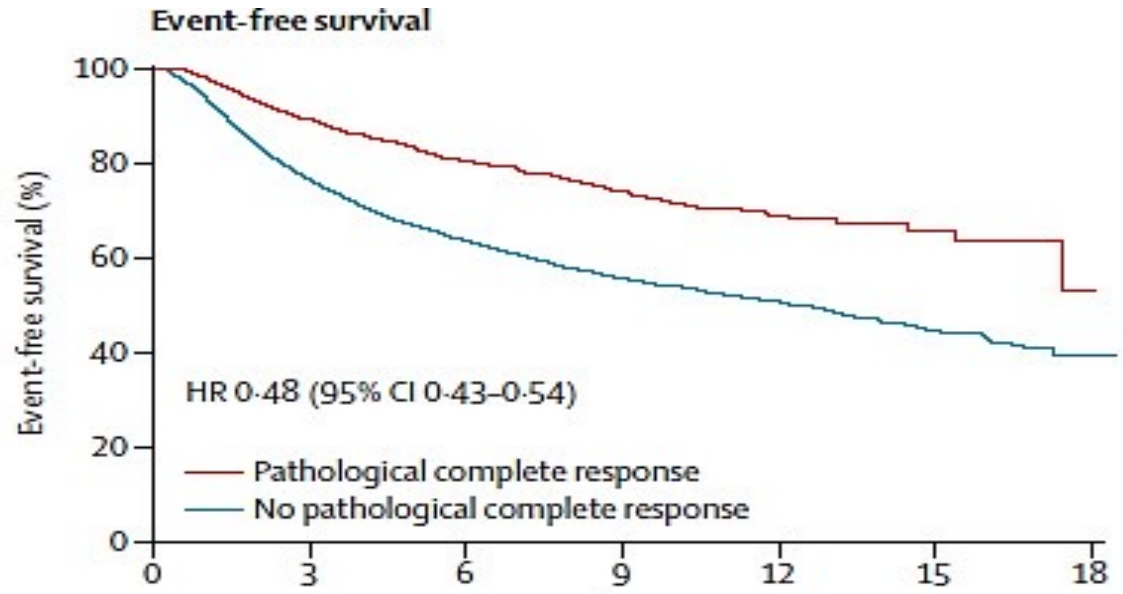


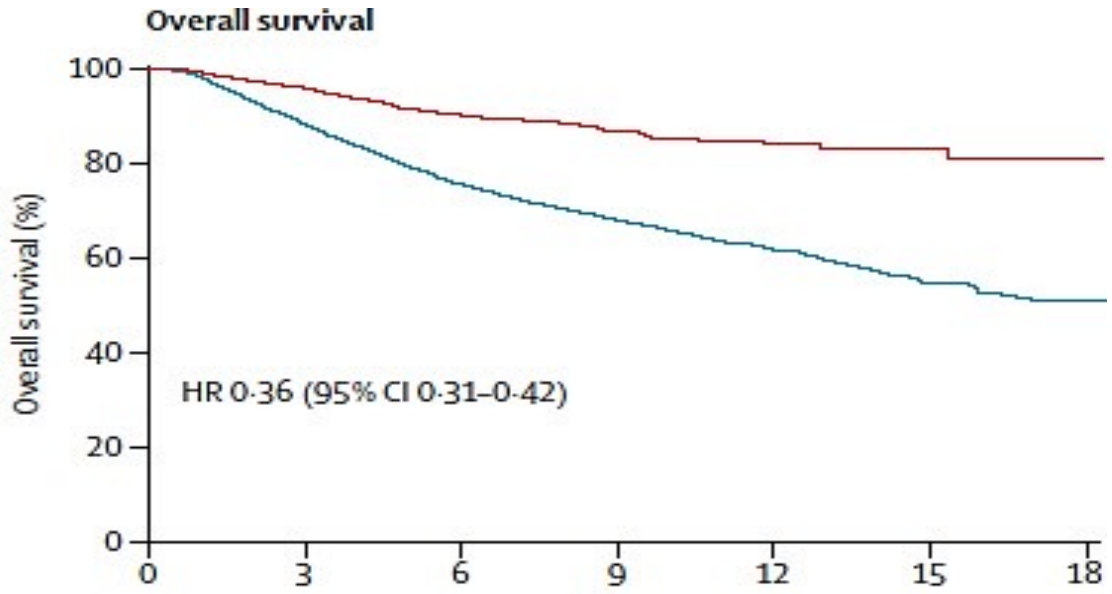
Lymphedema:
10-20% with axillary dissection

a. Fisher B, et al. J Clin Oncol. 1997;7:2483-93; b. Boughey JC, et al. JAMA 2013;310(14):1455–1461; c. Pilewskie M, Morrow M. JAMA Oncol 2017;4:549-555

Leveraging Neoadjuvant Therapy 2: Risk Stratification

- Association between pCR and EFS/OS





Number at risk							
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1

	2131	1618	640	383	145	43	3
	9824	7119	3173	1859	659	209	3

- Cortazar P, et al. Lancet. 2014;384:164-172.

Individualizing Therapy in Higher Risk HER2- Positive Breast Cancer

Use neoadjuvant setting: pCR

Use dual HER2-targeted therapy to increase pCR rate

- NeoSphere: addition of pertuzumab to TH (Doce) improved pCR[a]
  pCR breast: 29% → 45.8%; pCR breast + nodes: 21.5% → 39.3%[a]

Aphinity…disappointing (modest benefit in iDFS with addition of pertuzumab to AC-TH). But adding pertuzumab may allow *de-escalation* of chemo[b]

a. Gianni L, et al. Lancet Oncol. 2012;13:25-32; b. Von Minckwitz G, et al. N Engl J Med. 2017;377:122-131.

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Rationale for De-Escalating Chemotherapy:
Anthracycline and Platinum Toxicity

Anthracyclines[a]

- Toxicities: Cardiac dysfunction, MDS/AML

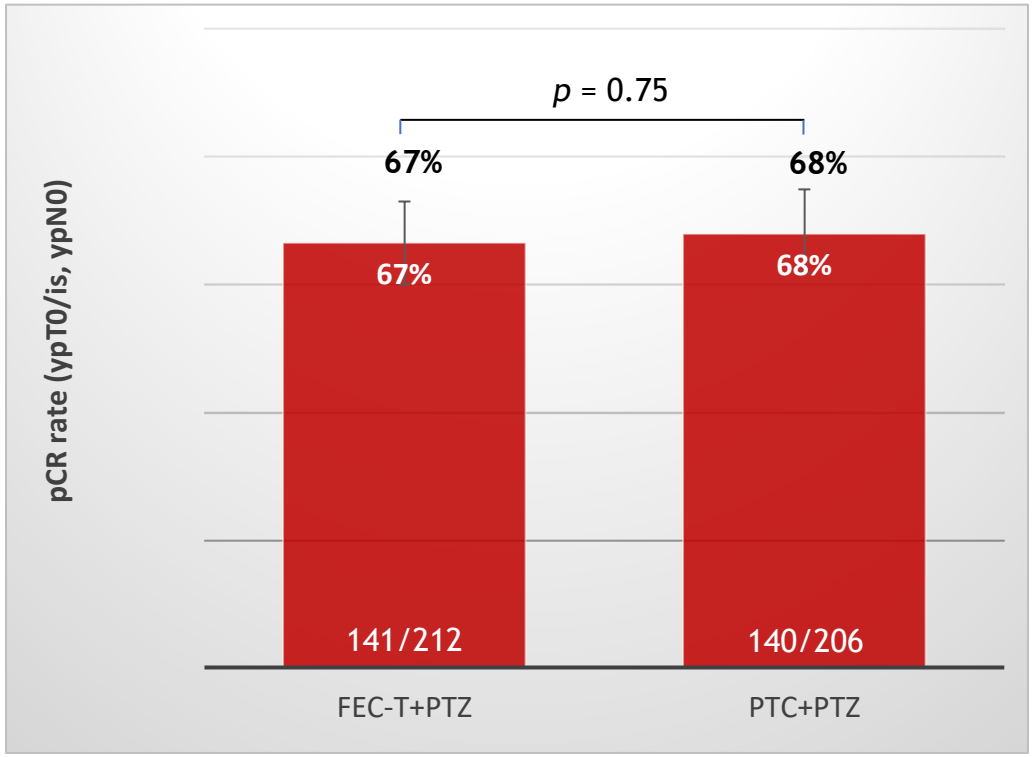
Carboplatin[b]

- Toxicities: Nephrotoxicity, ototoxicity, heme, GI toxicity
- Efficacy?[b]
  - pCR not significantly increased when carboplatin added to TH (paclitaxel)
  - No benefit (TTP, RR, survival) when carboplatin added to TH (docetaxel) in metastatic breast cancer (BCIRG 007)[c]

a. Slamon D, et al. N Engl J Med. 2011;365:1273-1283; b. von Minckwitz G, et al. Lancet Oncol. 2014;15:747-756; c. Valero V, et al. J Clin Oncol. 2011;29:149-56.

TRAIN-2: Primary Endpoint—pCR

- 9cy Paclitaxel-CHP vs 3 cy FECHP → 6 cy PacCHP
- 64% node positive, 33% stage III, 42% HR negative
- pCR was consistent across levels of prespecified subgroups (size, node status, HR status, age)
- More pts completed 1 year trastuzumab in PTC/Ptz arm (97% vs 89%)
- Significantly more grade 3/4 febrile neutropenia (10% vs 1%) in anthracycline arm



Median follow-up for all patients, 19 mo
van Ramshorst MS, et al. *Lancet Oncol*. 2018;19:1630-1640.

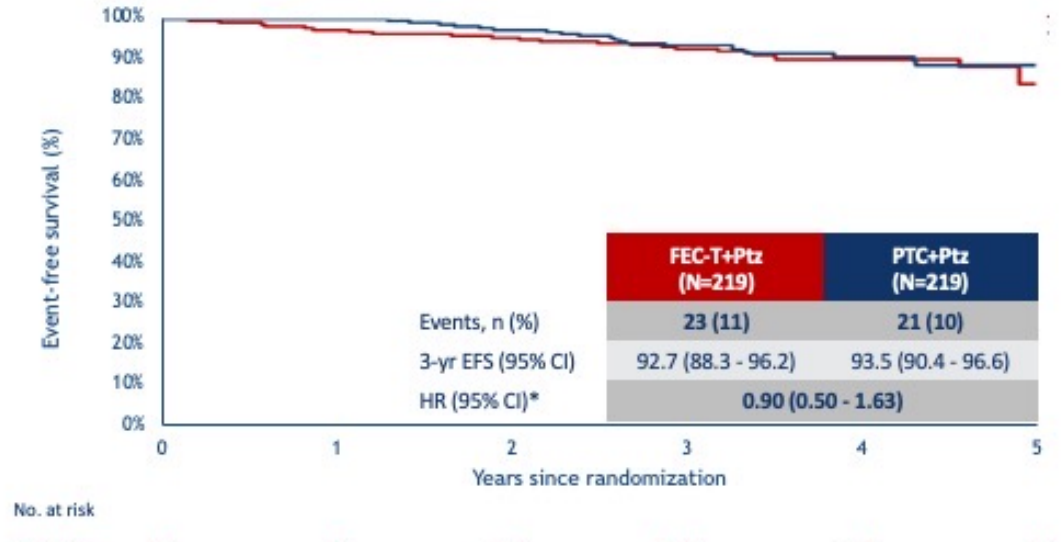
TRAIN-2: 3-Year Follow UP—EFS

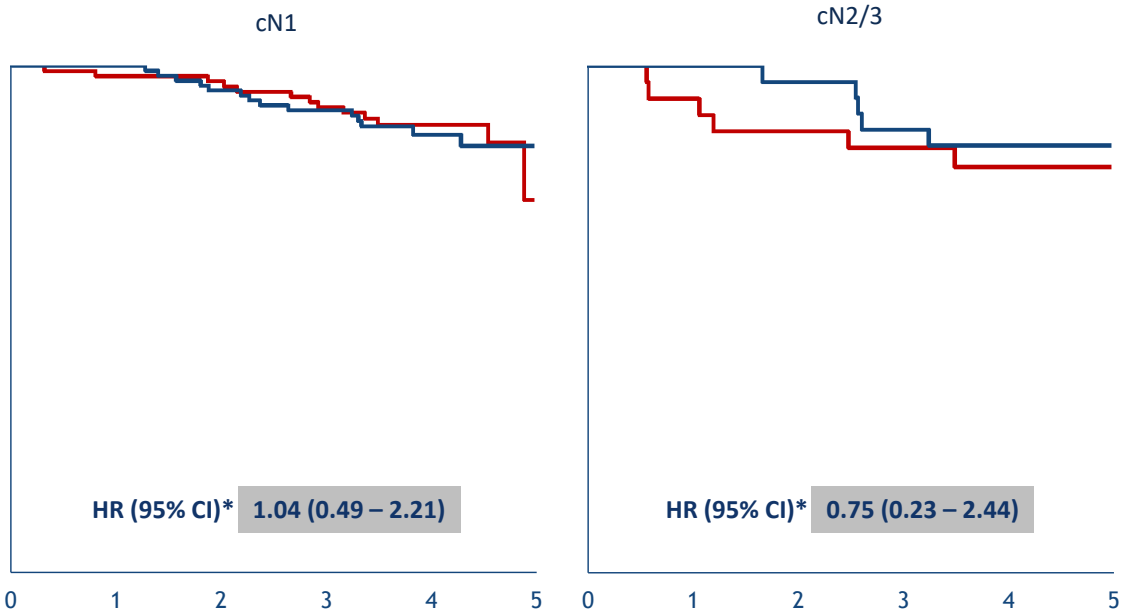
PTC + Ptz (21d):
Paclitaxel 80 mg/m2 d1/8
Trastuzumab/Pertuzumab and
Carbo (AUC 6) day 1

TOTAL OF 9 CYCLES!

LVEF decrease ≥10% and LVEF<50% 8% in FECHP-TCHP arm vs 3% in TCHP arm

2 leukemia with FECHP-TCHP





Median follow-up, 48.8 mo.
van der Voort A, et al. ASCO 2020. Abstract 501.

Summary Neoadjuvant Non-Anthracycline Taxane/Carbo-Based Regimens (N=895)

Regimen/ Study	N	tpCR
TCH x 6 **TRIO B07/Hurvitz, et al. Nature Comm 2020**	34	**47%**
TCHP x 6 **TRYPHAENA/Schneeweiss, et al. Ann Oncol 2013**	77	**64%**
TCHP x 6 **KRISTINE-TRIO-021/Hurvitz, et al. Lancet Oncol 2018**	221	**56%**
TCHP x 4 (in HR+ only) **NSABP B52/Rimawi, et al. Cancer Res 2016, SABCS S3-06**	155	***41%*** ***HR+ only***
Paclitaxel/Carbo/Trastuzumab/Pertuzumab x 9 **TRAIN-2/van Ramshorst et al. Lancet Oncol 2018**	206	**68%**
TCH x 6 **neoCARH/Gao, et al. ASCO 2020 Abs 585**	131	**56%**
TCHP x 6 **PHERGAIN/Perez-Garcia, et al. Lancet 2021**	71	**58%**

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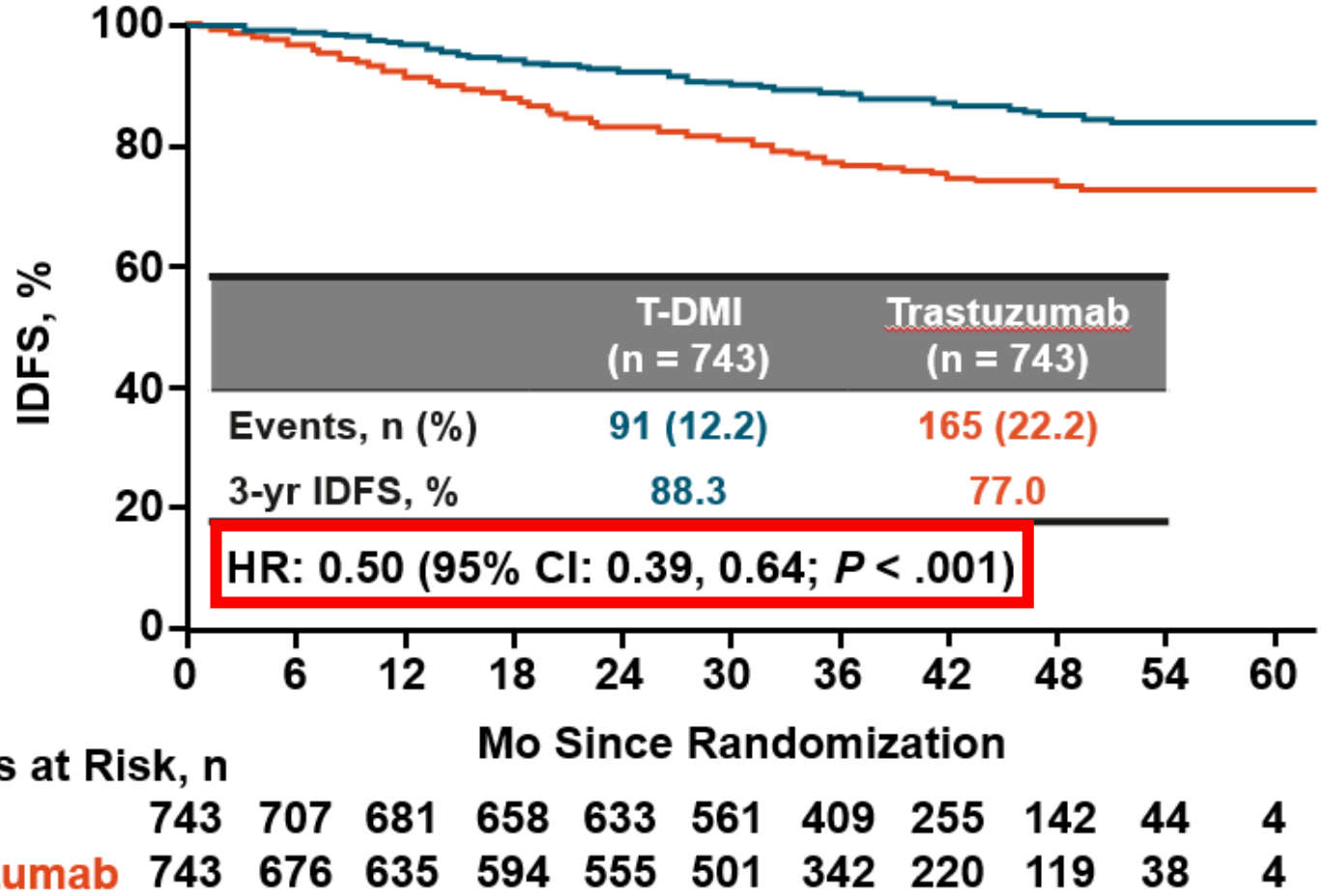
KATHERINE: 3 yr iDFS significantly improved with T-DM1

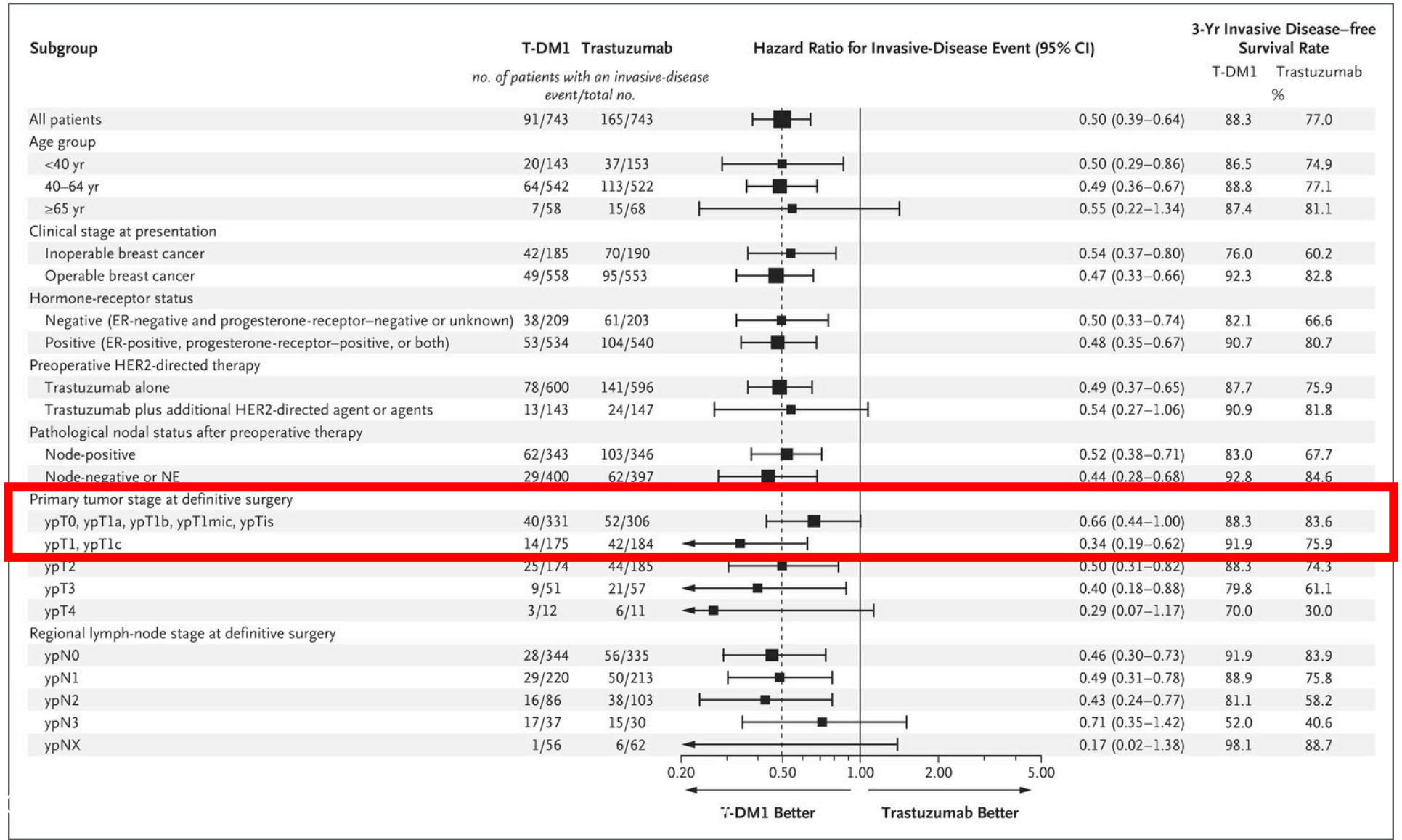


First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral breast cancer	0.4	1.3
Death without prior event	0.3	0.4

CNS events: *5.9% vs †4.3%.

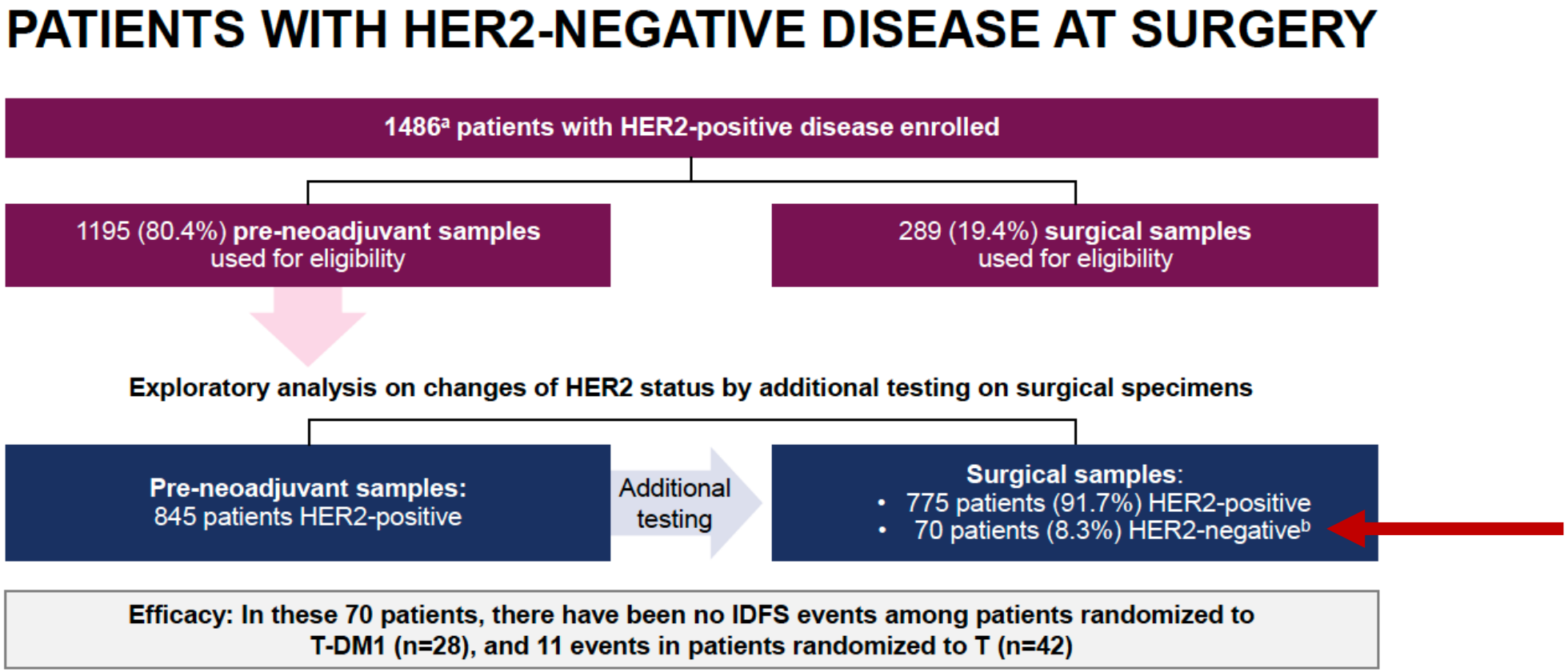
Geyer C et al. SABCS 2018. Abstract GS1-10;
von Minckwitz et al. N Engl J Med. 2019;380(7):617-628.

KATHERINE: even patients with small amounts of residual tumor benefit



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

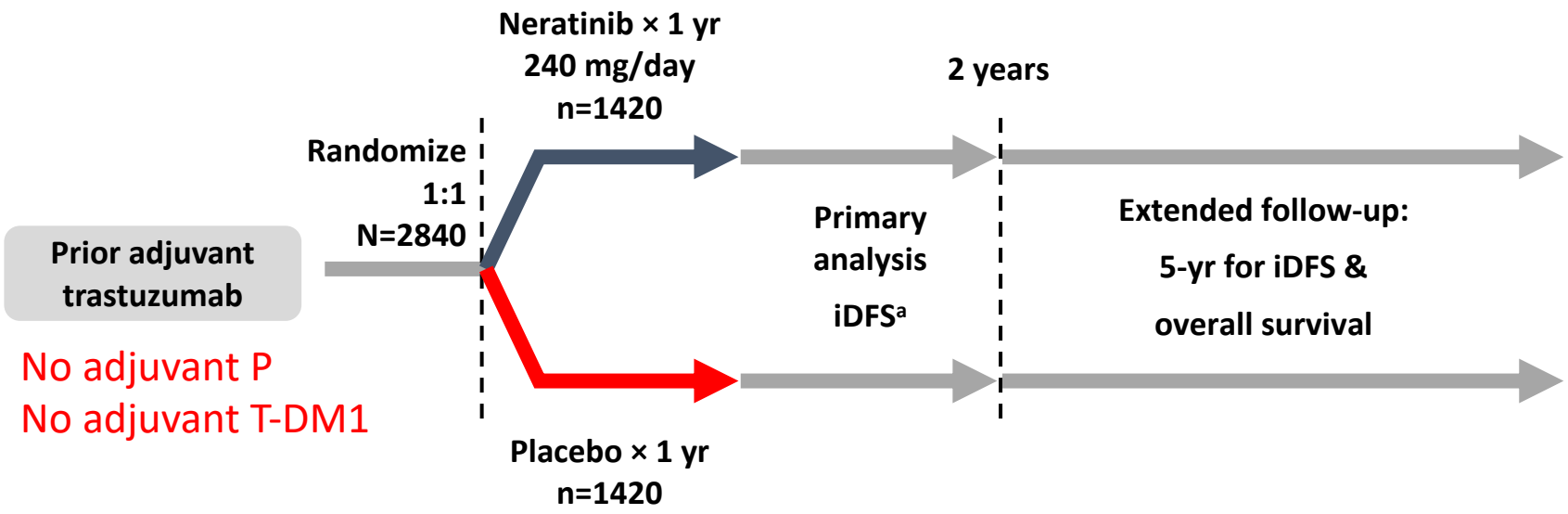
KATHERINE: even patients with HER2-negative residual tumor may benefit



SUPPORTS THE USE OF ADJUVANT T-DM1 EVEN IF RESIDUAL DISEASE IS HER2-NEGATIVE

Loibl S et al. ESMO Breast 2020. Abstract 960.

ExteNET study: Adding neratinib



Primary endpoint: invasive disease-free survival (iDFS)[a]

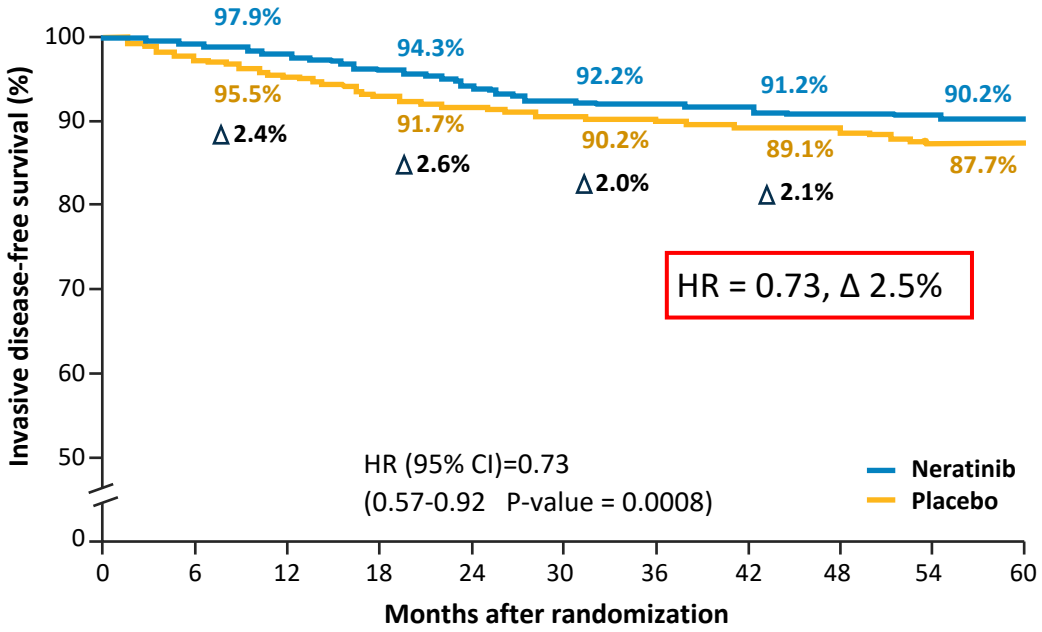
Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,

Stratification: nodes 0, 1-3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Study blinded: Until primary analysis; OS remains blinded

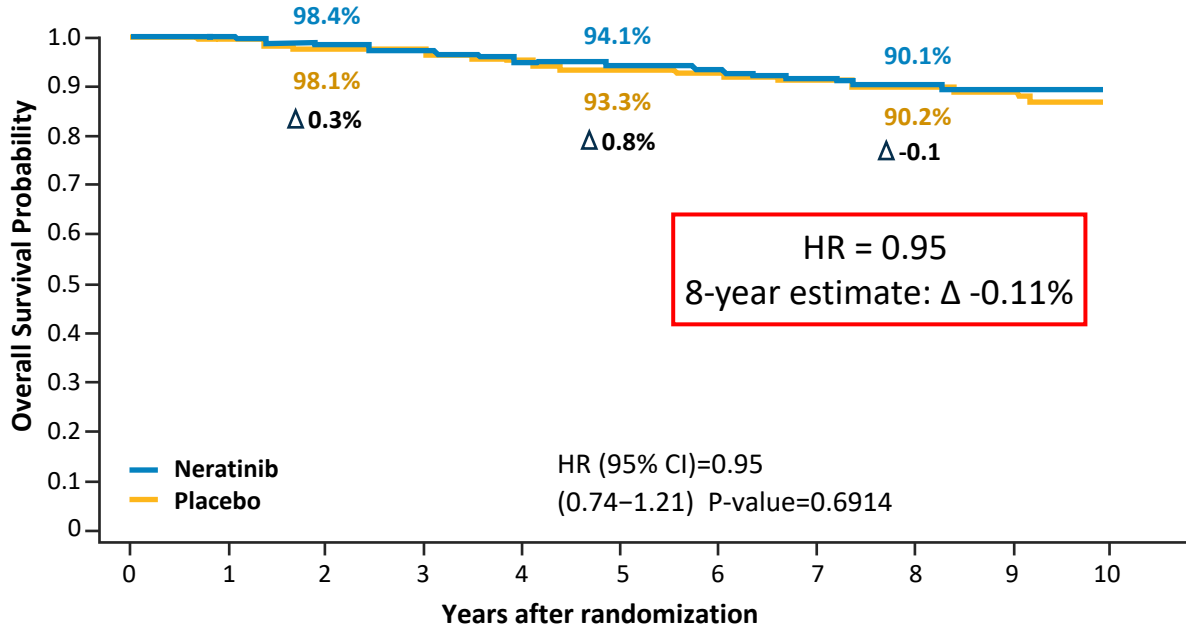
ExteNET: iDFS and OS for ITT Population (N=2,840)

ITT iDFS at 5 yrs



No. at risk											
Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

ITT OS (264 events)

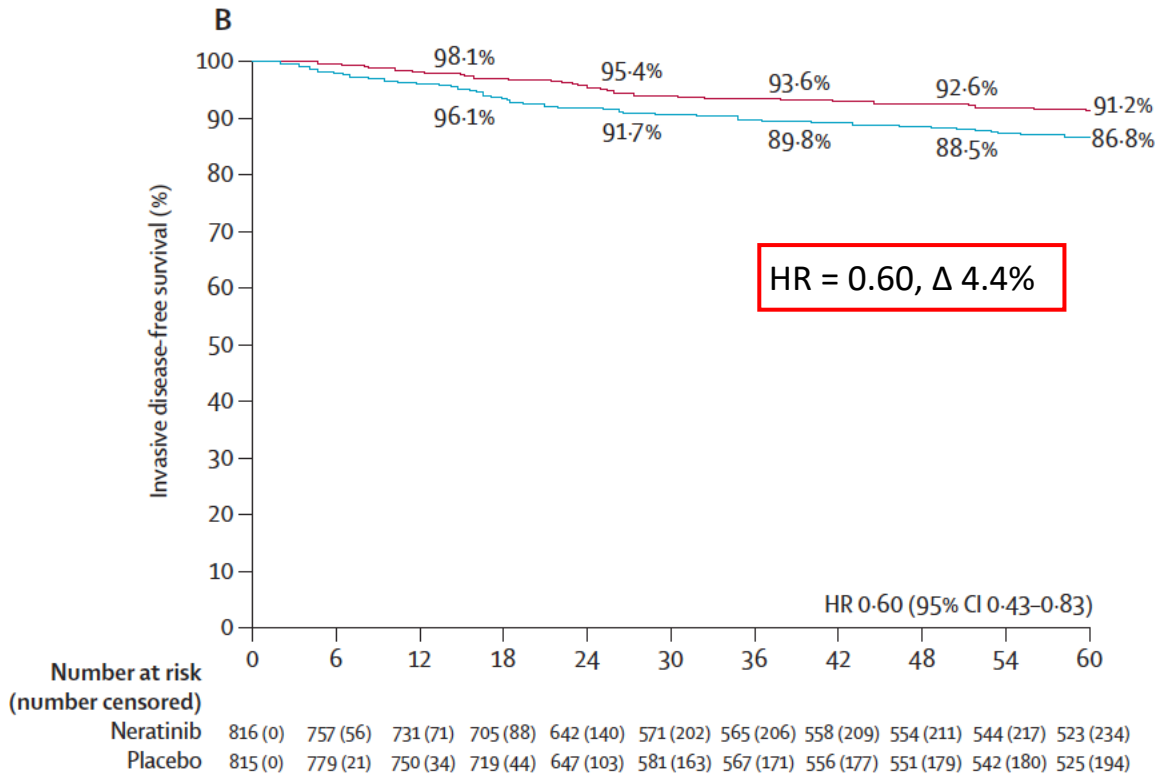


No. at risk											
Neratinib	1420	1364	1309	1213	1118	1168	1123	1041	746	218	0
Placebo	1420	1384	1341	1249	1223	1199	1166	1086	796	221	0

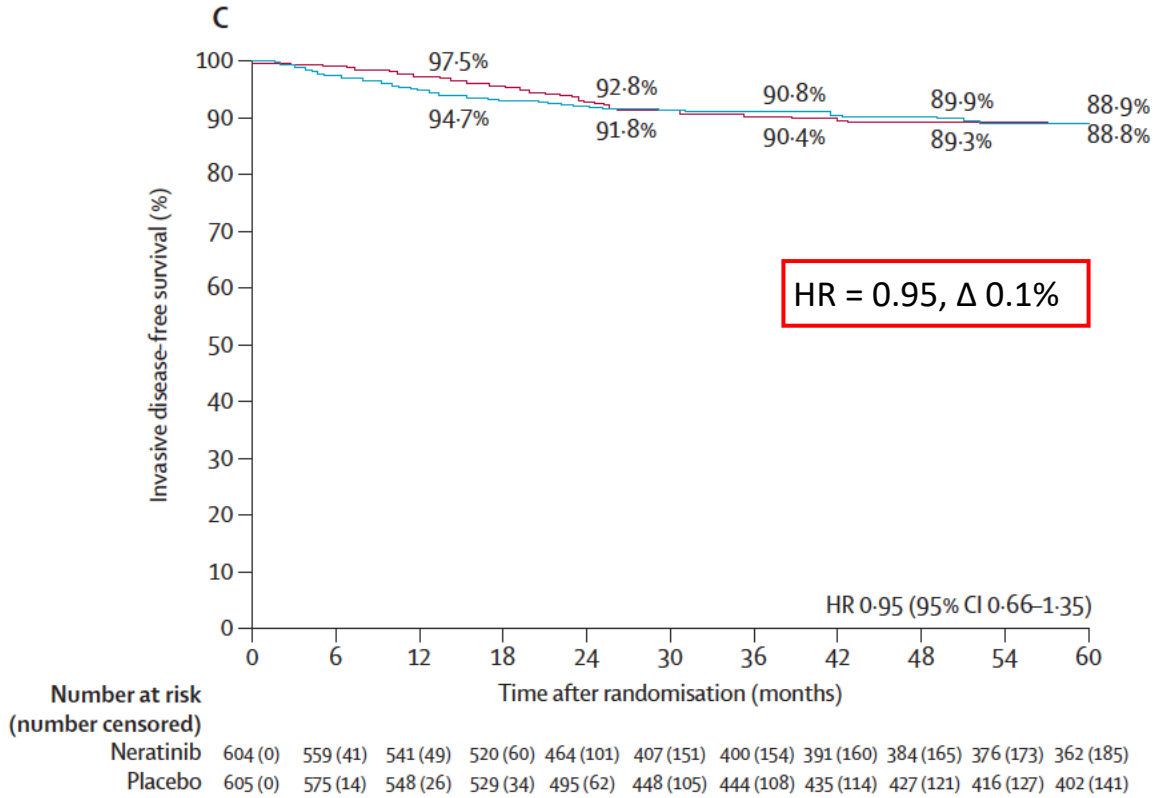
Martin et al. Lancet Oncol. 2017;18(12):1688-1700.

ExteNET: iDFS by HR status

HR+ iDFS at 5 yrs



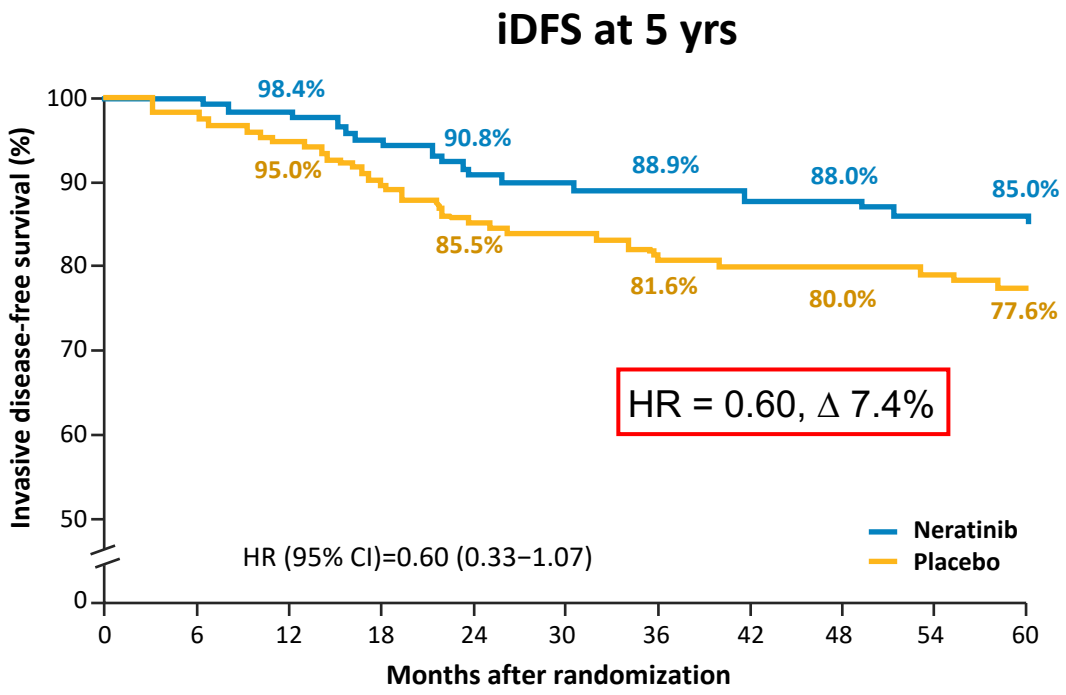
HR- iDFS at 5 yrs

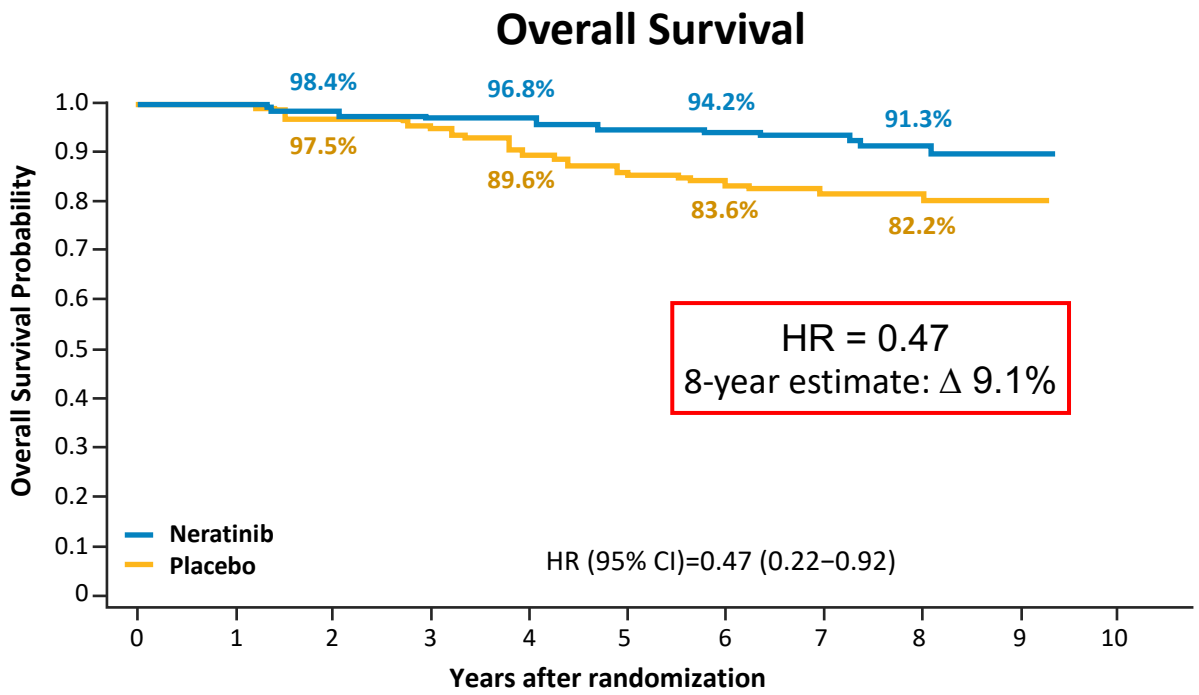


Martin et al. Lancet Oncol. 2017;18(12):1688-1700.

ExteNET: Greater benefit among non-pCR, HR+, <1 yr from adjuvant trastuzumab patients (N=295)

**subgroup analysis*





No. at risk

Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

No. at risk

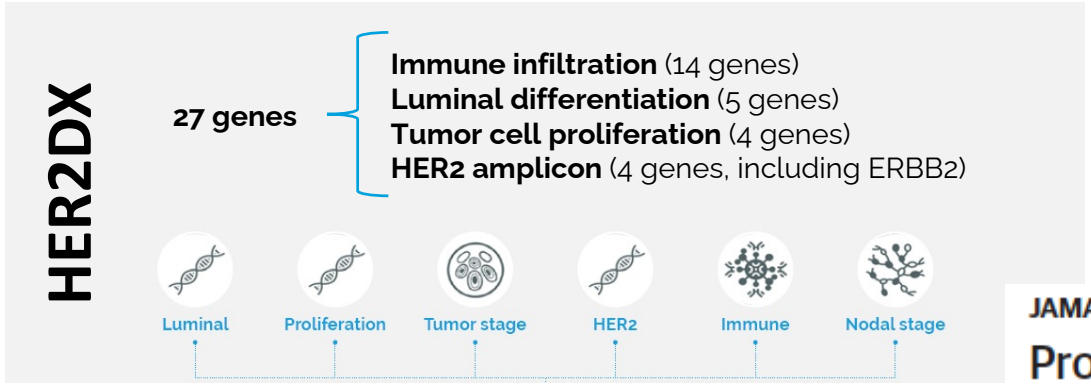
Neratinib	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

Chan A et al. Clin Breast Cancer. 2021;21(1):80-91.e7

How to individualize therapy in Early Stage HER2+

- Stage I (T ≤ 2 cm, N0)
- Stage II to III (T > 2 cm, N+)
  - Role of neoadjuvant therapy
  - Role of anthracyclines and platinum therapy
  - How should we escalate for those patients without pCR?
  - Biomarkers: which are promising and how should we use them?
  - Ongoing trials to watch

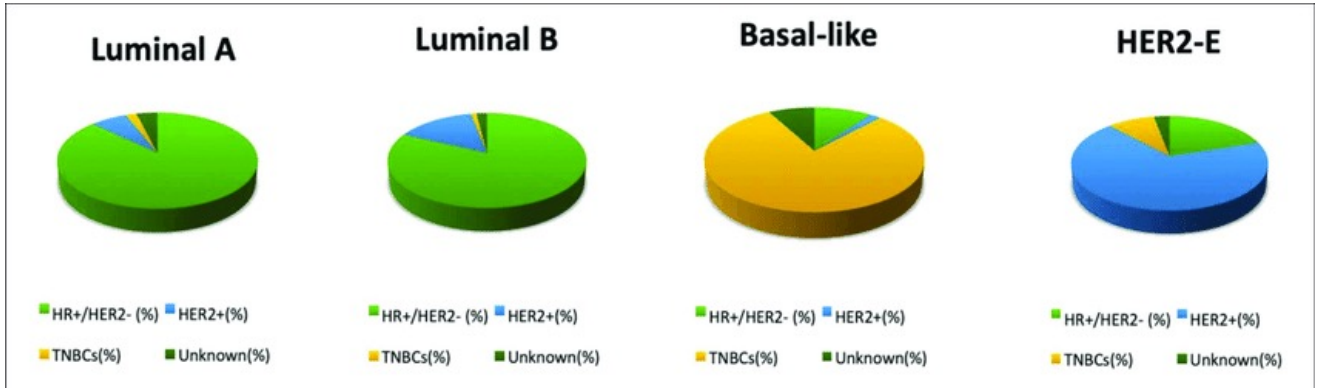
Biomarkers: many of interest



Immune gene expression signatures

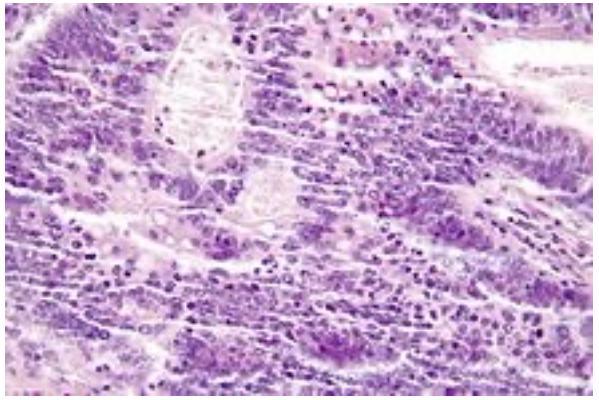
JAMA Oncology | Original Investigation

Prognostic and Predictive Value of Immune-Related Gene Expression Signatures vs Tumor-Infiltrating Lymphocytes in Early-Stage ERBB2/HER2-Positive Breast Cancer
A Correlative Analysis of the CALGB 40601 and PAMELA Trials



Intrinsic subtype

TILs



Role for biomarkers in the investigation of escalation and de-escalation

- Dictate best course of action for cT1cN0 tumors
- Identify the stage II-III patients for whom even THP will be too much therapy
  - Eg could achieve pCR with HP, or T-DM1/P, etc
- Identify the stage II-III patients who need more than THP (eg TCHP) to achieve pCR
- Identify the non-pCR patients who *don't* need escalation in the adjuvant setting
- Identify patients who will recur despite pCR
- Biomarkers should be prospectively incorporated into trials developing escalation and de-escalation paradigms

How to individualize therapy in Early Stage HER2+

- Stage I (T ≤ 2 cm, N0)
- Stage II to III (T > 2 cm, N+)
  - Role of neoadjuvant therapy
  - Role of anthracyclines and platinum therapy
  - How should we escalate for those patients without pCR?
  - Biomarkers: which are promising and how should we use them?
  - Ongoing trials to watch

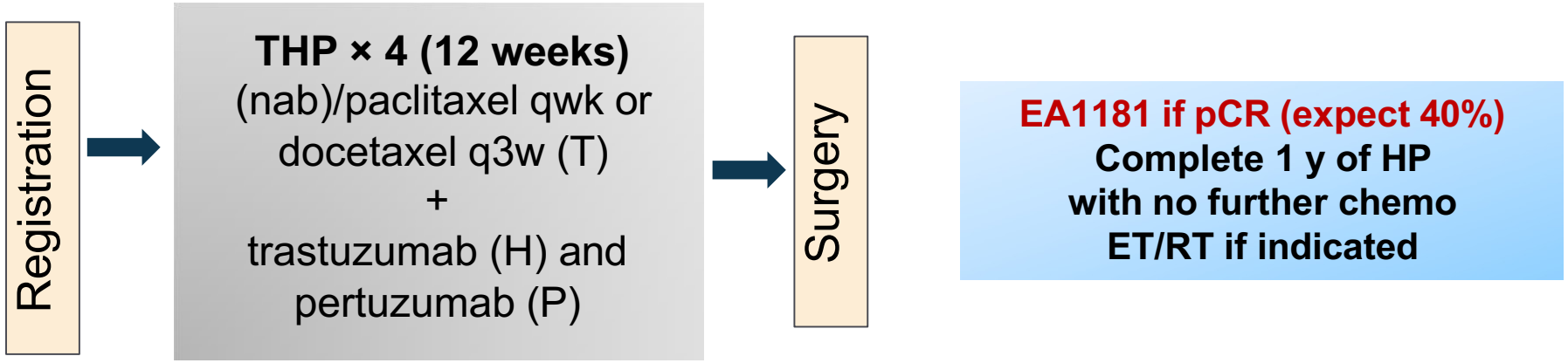
CompassHER2 Trials

EA1181: CompassHER2-pCR

Eligibility

- HER2+ BC
- T>2 cm or N+ (T2-3, N0-2)

N = 2152



EA1181 if pCR (expect 40%)
Complete 1 y of HP
with no further chemo
ET/RT if indicated

Tissue block collection
Blood collection for ctDNA, CTCs at several timepoints

Co-primary Objectives; in patients with pCR:

ER-positive HER2-positive: 3y RFS > 92% *(3y RFS H_0 = 92%, $H_1 \geq$ 95%)*
ER-negative HER2-positive: 3y RFS > 92% *(3y RFS H_0 = 92%, $H_1 \geq$ 95%)*

Clinicaltrials.gov. Accessed September 19, 2022. https://clinicaltrials.gov/ct2/show/results/NCT04266249?view=results.

A011801 (CompassHER2-RD) Trial: Post-Neoadjuvant T-DM1 + Tucatinib in Residual HER-Positive Invasive BC

- **HER-positive** invasive residual BC, ER+, and ER-
- cT1-4,N0-3 *at diagnosis*
- ER-: any amount of residual disease
- ER+: lymph node positive disease post op
- Received ≥ 6 cycles of chemotherapy (preop ± postop; including ≥ 9 weeks neoadjuvant taxane and trastuzumab) prior to registration

Residual invasive HER-positive breast cancer after neoadjuvant chemotherapy and HER2-directed treatment

REGISTRATION

R 1:1

T-DM1 and placebo x 14 cycles

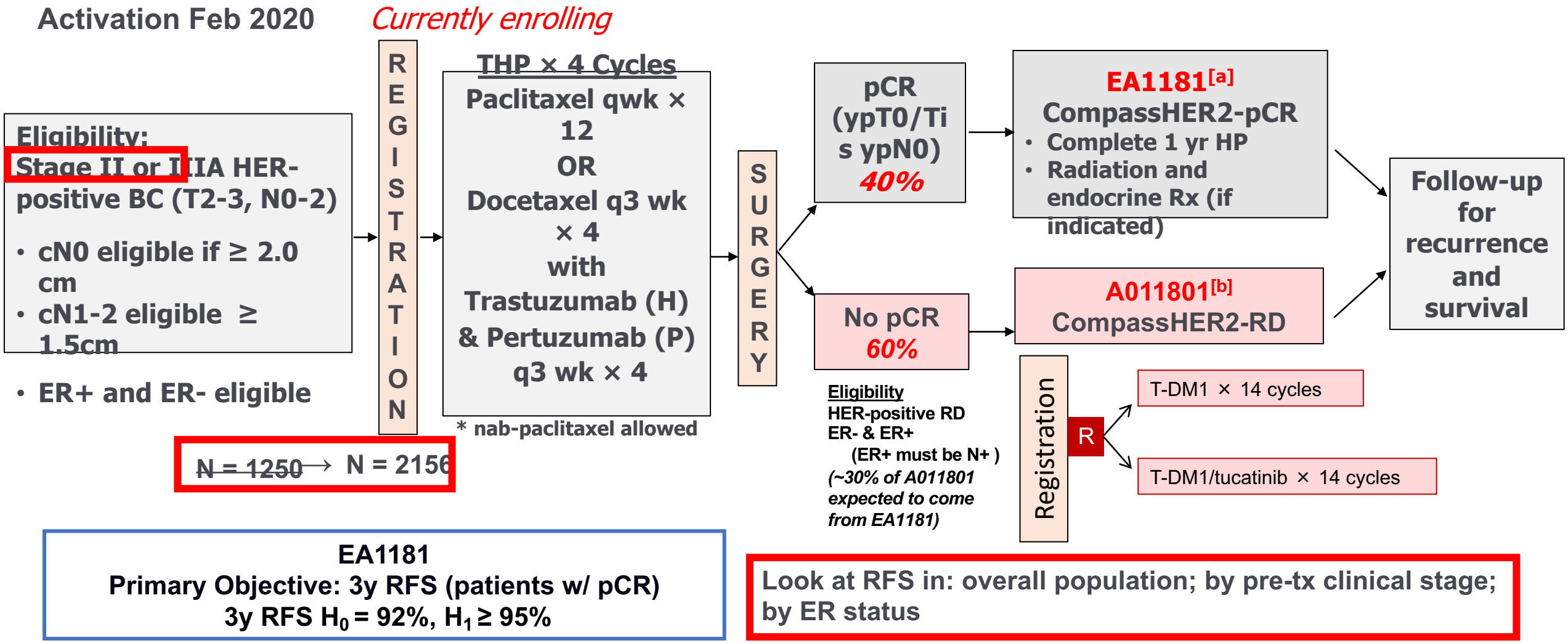
T-DM1 and tucatinib x 14 cycles

- Stratification factors
  - Receipt of postoperative chemotherapy (yes/no)
  - HR status: positive (ER and/or PgR positive) vs negative (ER negative and PgR negative)
  - Pathologic lymph node status (positive/negative)

Primary objective: IDFS *HER-positive* (all)

- O'Sullivan CC, et al. Future Oncol. 2021;17:4665-4676.

CompassHER2 trials



- ClinicalTrials.gov. Accessed October 7, 2022. https://clinicaltrials.gov/ct2/show/NCT04266249, ClinicalTrials.gov. Accessed October 7, 2022. https://clinicaltrials.gov/ct2/show/NCT04457596

ASTEFANIA Trial: Atezolizumab or Placebo with T-DM1 for HER-positive BC at High Risk of Recurrence Following Preoperative Therapy

Currently enrolling

Patients with HER2+ EBC (N ~1590)

- Residual invasive disease in breast and/or axillary lymph nodes at surgery following preoperative therapy
- ER/PR/HER2/PD-L1 status centrally confirmed

Stratification factors:

- Clinical stage at presentation: inoperable (T4/anyN/M0 or anyT/N2-3/M0) vs operable (T1-3/N1/M0)
- Preoperative HER2-directed therapy: trastuzumab vs trastuzumab and additional HER2-directed agent(s)
- Hormone receptor status: ER positive and/or PR positive vs ER negative and PR negative
- PD-L1 status: IC 0 vs IC 1/2/3

1:1 Rand.

Adjuvant Treatment Phase

14 Cycles Q3W

Placebo + Trastuzumab Emtansine
Placebo: 1200 mg IV q3w
Trastuzumab Emtansine: 3.6 mg/kg IV q3w

Atezolizumab + Trastuzumab Emtansine
Atezolizumab: 1200 mg IV q3w
Trastuzumab Emtansine: 3.6 mg/kg IV q3w

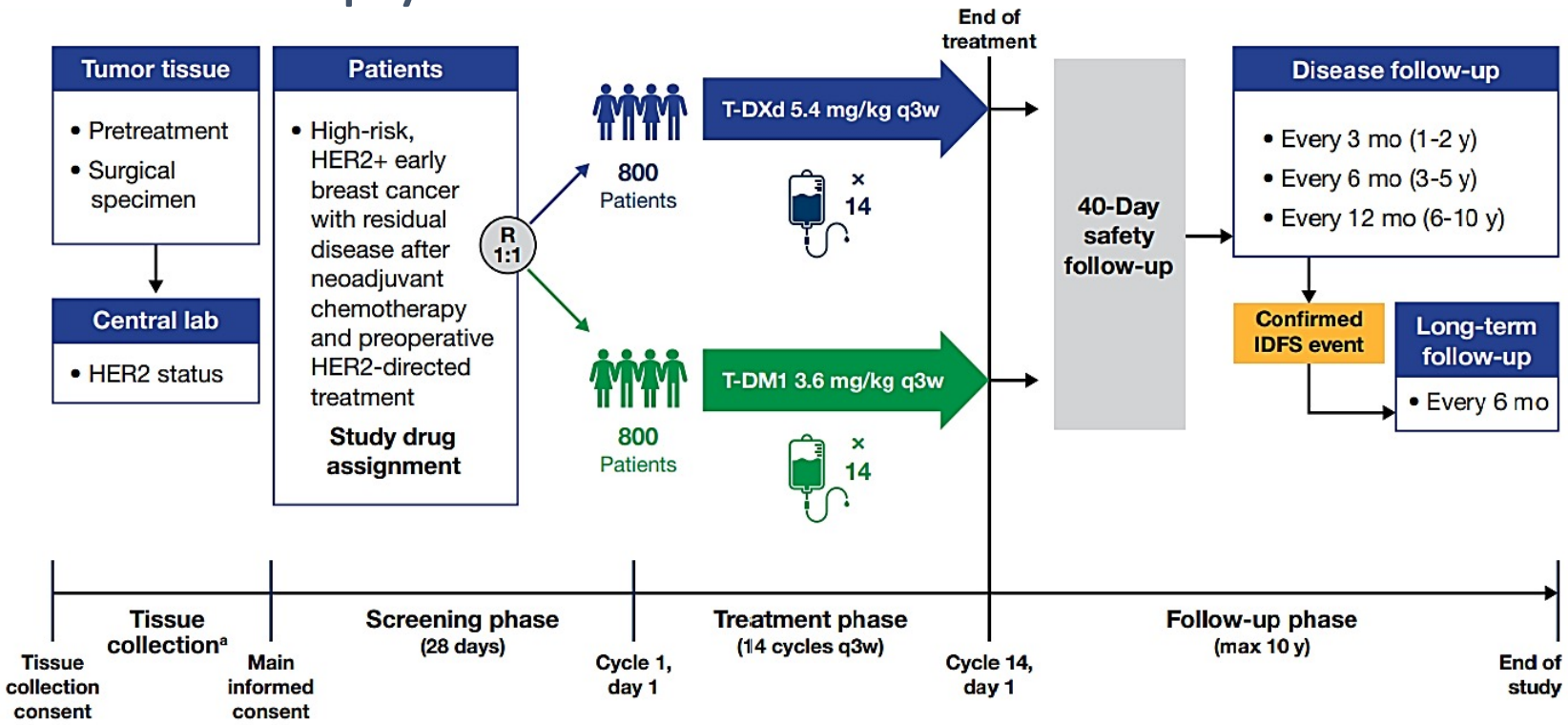
Follow-Up

- Slides courtesy Ada Waks, MD

- ClinicalTrials.gov. Accessed October 7, 2022. https://clinicaltrials.gov/ct2/show/NCT04873362.

DESTINY-Breast05: T-DXd vs. T-DM1 in High-risk Patients with Her-Positive Residual Invasive Disease after Neoadjuvant Therapy

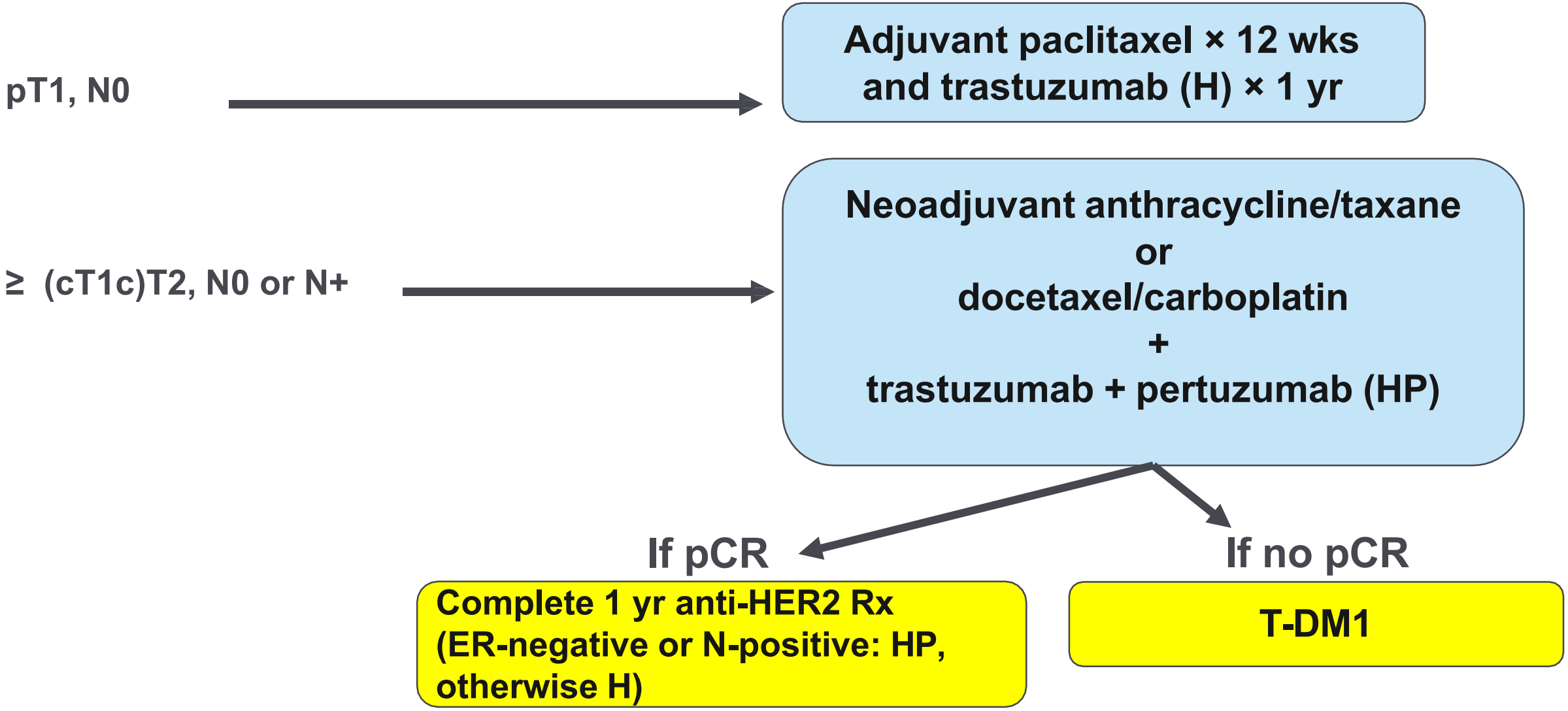
- Inoperable breast cancer at presentation
- Operable breast cancer at presentation with node-positive (ypN1-3) disease after neoadjuvant therapy



Currently enrolling

- Geyer C, et al. SABCS. 2020: Abstract OT-03-01.

Standard Approach: HER2-positive breast cancer



a. Pogue-Gelie K, et al. J Natl Cancer Inst. 2013;105:1782-1788; b. Hurvitz SA, et al. Lancet Oncol. 2018;19:115-126.

METASTATIC HER2 POSITIVE BREAST CANCER

The Journey Begins

- In the metastatic setting, this pivotal phase III trial compared first-line chemotherapy (doxorubicin/epirubicin and cyclophosphamide or paclitaxel) plus trastuzumab versus chemotherapy alone in HER2-positive patients.
- Trastuzumab plus chemotherapy was associated with a significant improvement in
  - time to disease progression (7.4 mo vs 4.6 mo),
  - objective response rate (50% vs 32%), and
  - 1-year survival (25.1 mo vs 20.3 mo) compared with chemotherapy alone.
- Evidence also suggested that in women with advanced HER2-positive breast cancer, survival is better with up-front use of trastuzumab plus chemotherapy than it is with sequential administration (ie, with trastuzumab reserved for the time of disease progression on an initial chemotherapy regimen).
- Based on these results, the FDA approved trastuzumab for first-line therapy in HER2-positive metastatic breast cancer.

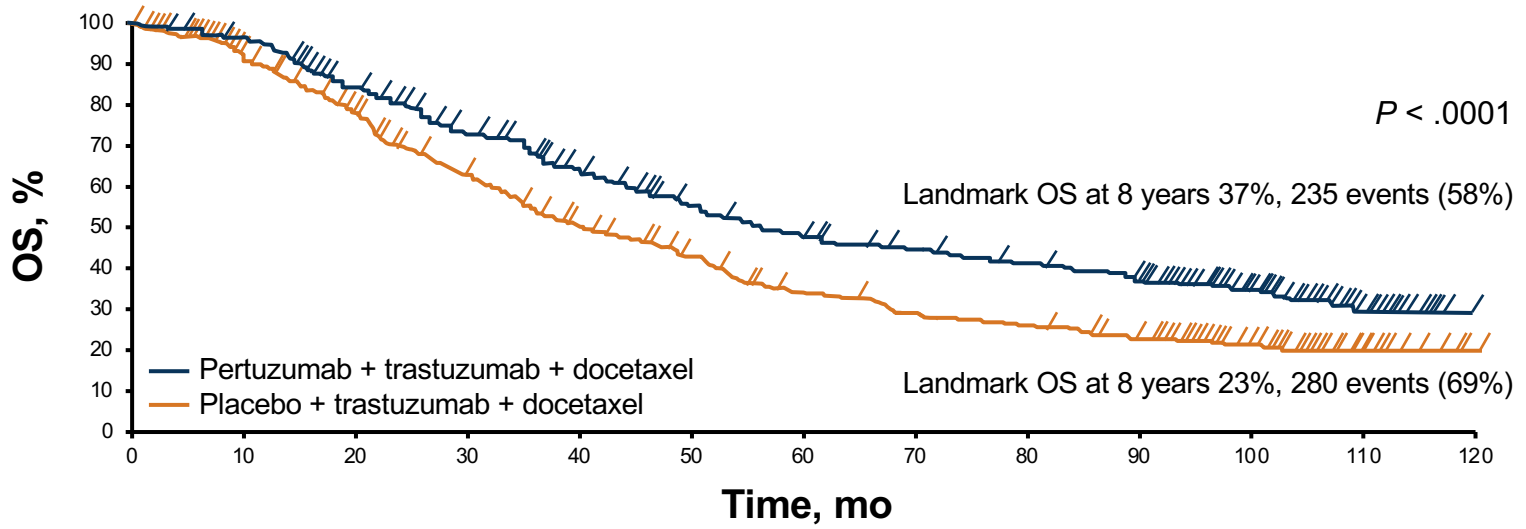
NCCN Guidelines®: HER2+ MBC

Setting	Regimen	NCCN Category of Preference (Category of Evidence)
First Line	Pertuzumab + trastuzumab + docetaxel	Preferred regimen (1)
	Pertuzumab + trastuzumab + paclitaxel	Preferred regimen (2A)
Second line	Fam-trastuzumab deruxtecan-nxki (T-DXd)	Preferred regimen (1) (May be considered in the first-line setting as an option for select patients, ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens])
	Ado-trastuzumab emtansine (T-DM1)	Other recommended regimen (2A)
Third line and beyond	Tucatinib + trastuzumab + capecitabine	Other recommended regimen (1) (May be used as a third- or fourth-line option; preferred in patients with both systemic and CNS progression in the third-line or beyond; and it may be given in the second-line setting)
	Trastuzumab + docetaxel or vinorelbine	Other recommended regimen (2A)
	Trastuzumab + paclitaxel ± carboplatin	
	Capecitabine + trastuzumab or lapatinib	
	Trastuzumab + lapatinib (without cytotoxic therapy)	
	Trastuzumab + other agents	
	Neratinib + capecitabine	
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)	

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.4.2022. Accessed June 22, 2022.

Overall Survival in Patients With Advanced HER2+ mBC[1]

CLEOPATRA End-of-Study Results
(Median Follow-Up: ~100 mo)



No. at Risk (number censored)

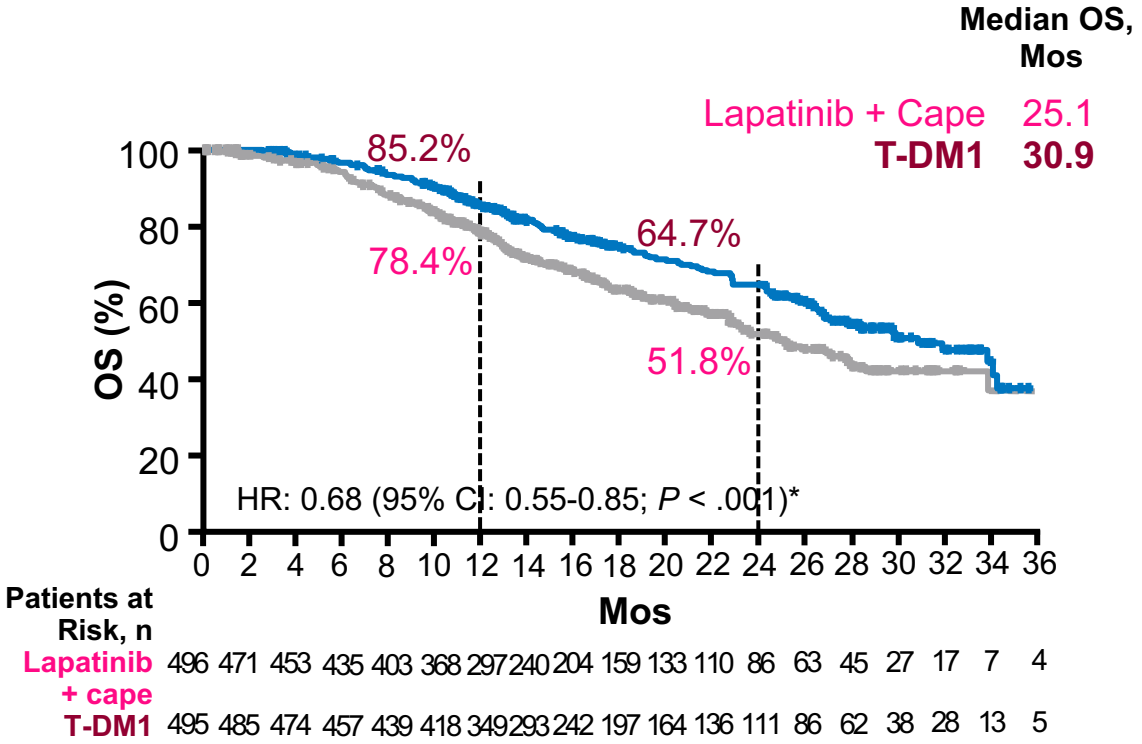
Pertuzumab	402 (0)	371 (14)	318 (23)	269 (32)	228 (41)	188 (48)	165 (50)	150 (54)	137 (56)	120 (59)	71 (102)	20 (147)	0 (167)
Placebo	406 (0)	350 (19)	289 (30)	230 (36)	181 (41)	149 (48)	115 (52)	96 (53)	88 (53)	75 (57)	44 (84)	11 (115)	1 (125)

Median OS
with TP-based initial therapy:
57.1 mo

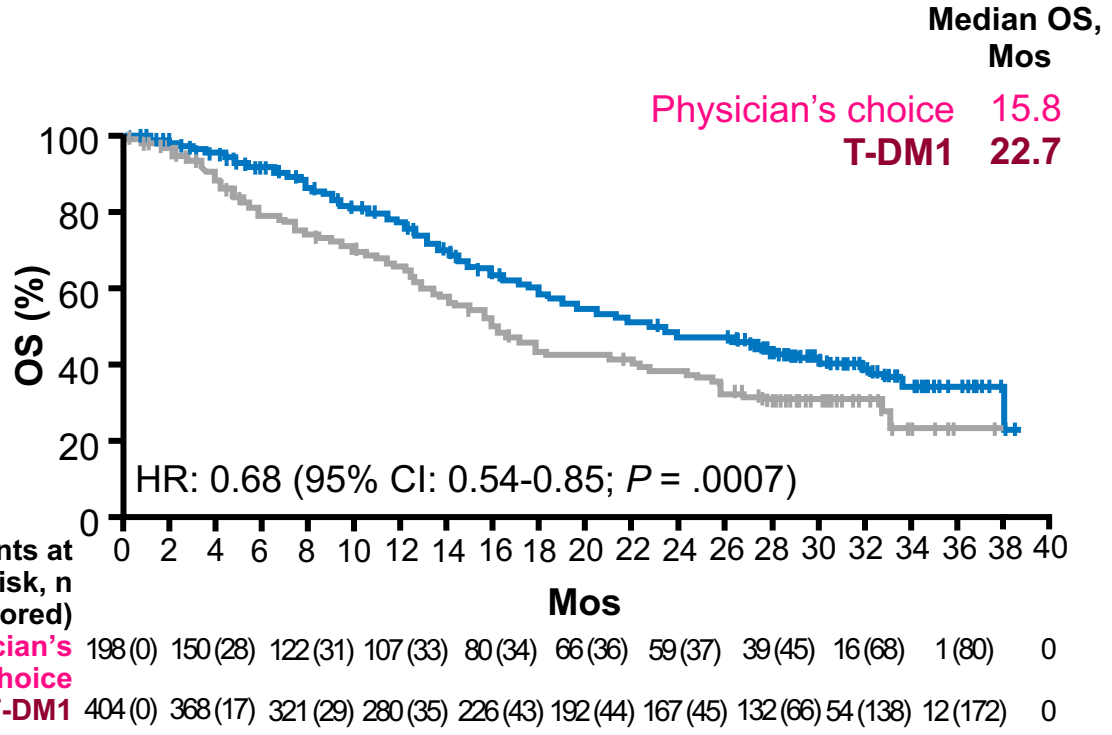
1. Swain SM et al. *Lancet Oncol*. 2020;21:519-530.

EMILIA and TH3RESA: 2nd line Therapy With T-DM1 After Progression on HER2-Targeted Agents

EMILIA: Randomized phase 3 study of lapatinib + capecitabine vs T-DM1 for HER2+ MBC with progression on trastuzumab + taxane (N = 991)[1]



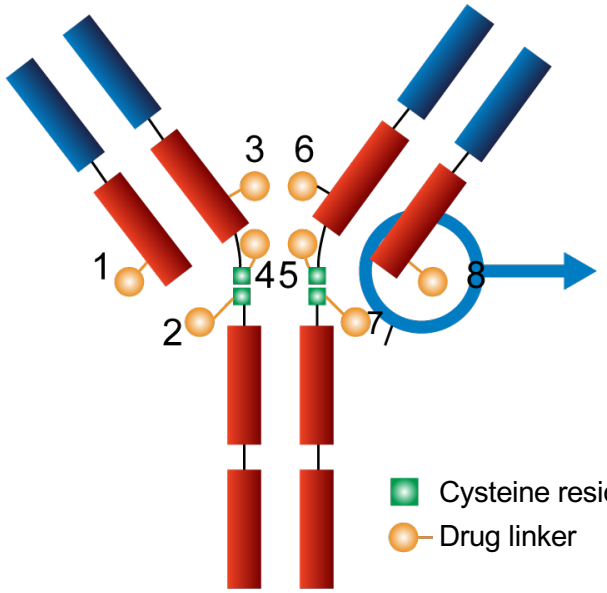
TH3RESA: Randomized phase 3 study of physician's choice vs T-DM1 for HER2+ MBC with progression on a taxane, lapatinib, and ≥ 2 HER2-targeted regimens including trastuzumab (N = 602)[2]

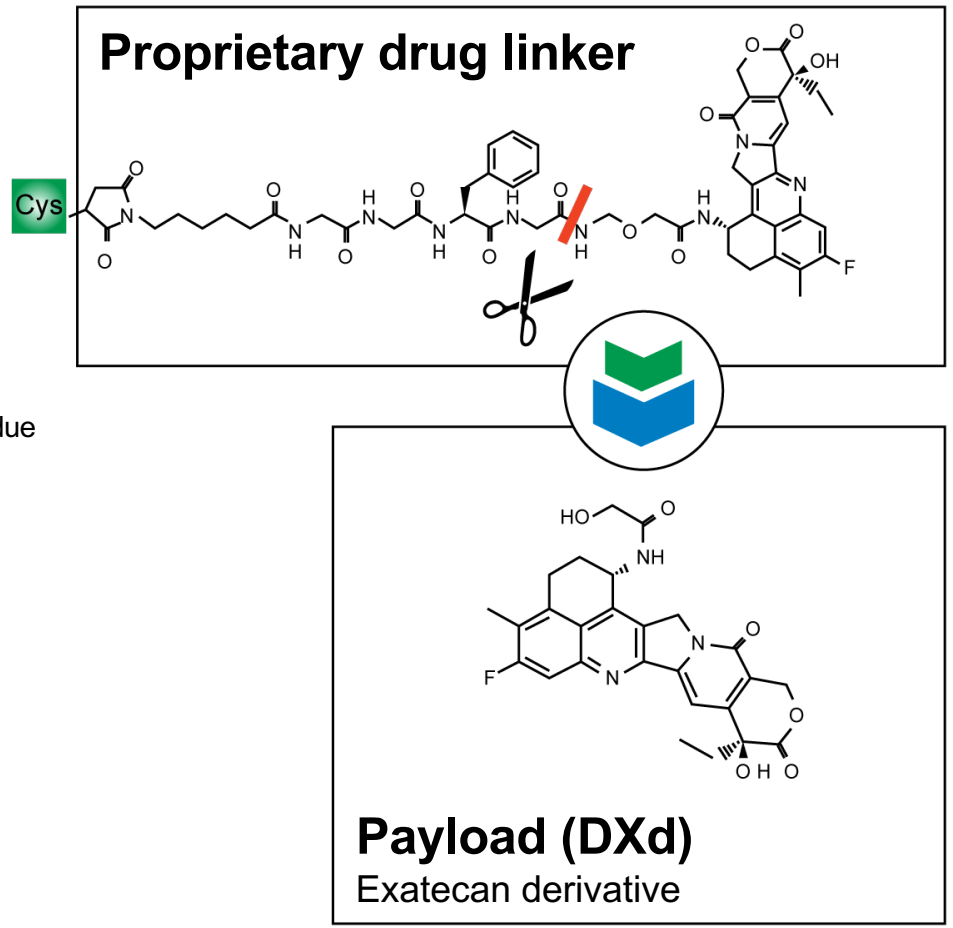


*Efficacy stopping boundary: HR of 0.73 or *P* = .0037. Cape, capecitabine; MBC, metastatic breast cancer; T-DM1, trastuzumab emtansine.

1. Verma S et al. *NEJM* 2012;367:1783-91; 2. Krop IE et al. *Lancet Oncol* 2017;18:743-54.

Trastuzumab Deruxtecan (T-DXd; DS8201a) Is a Novel HER2 ADC[1,2]





Conjugation chemistry

The linker is connected to cysteine residue of the antibody

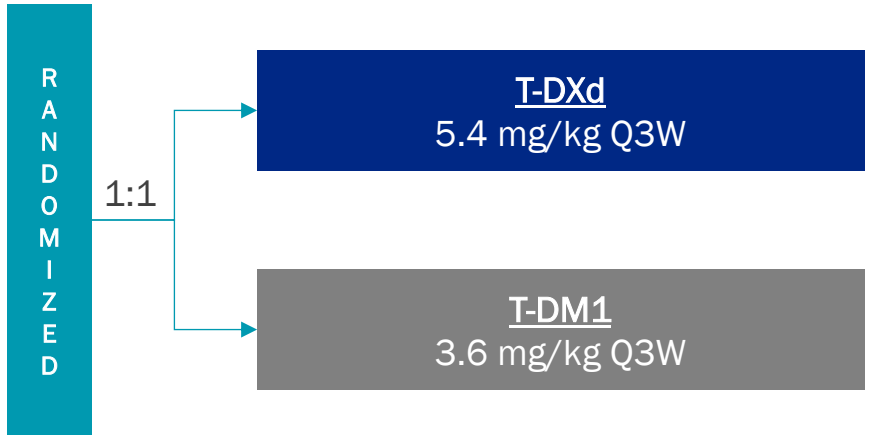
	T-DXd	T-DM1
Antibody	Anti-HER2 mAb	Trastuzumab
Payload	Topoisomerase I inhibitor	Tubulin inhibitor
DAR	7-8	3.5
Membrane Permeability	Yes (bystander effect)	No

1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 2. Pondé N et al. *Curr Treat Options Oncol*. 2019;20:37.

T-DXd vs T-DM1 in HER2+ MBC, Results From the Randomized Phase 3 DESTINY-Breast03 Study: Study Design and Patients

Key Eligibility Criteria

- HER2+ unresectable or MBC[a]
- Previous treatment with trastuzumab and taxane in advanced/metastatic setting[b]
- Clinically stable, treated brain metastases allowed



Primary endpoint: PFS by BICR
Secondary endpoints: OS, ORR (BICR and investigator), DOR (BICR), PFS (investigator), safety

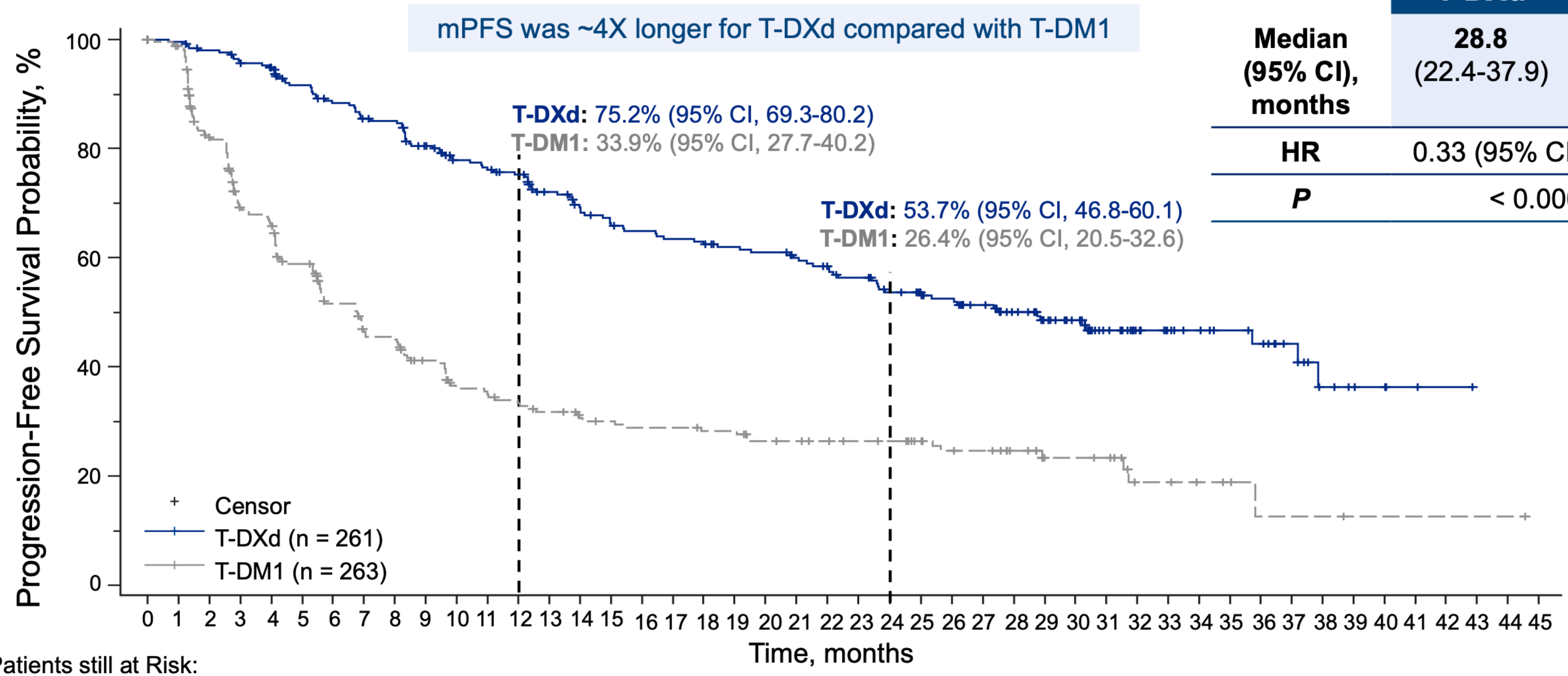
Patient Characteristics		T-DXd (n=261)	T-DM1 (n=263)
Median age, years (range)		54.3 (27.9-83.1)	54.2 (20.2-83.0)
Region, Asia		57.1	60.8
HER2 status (IHC,[c] %)	3+	89.7	88.2
	2+ (ISH amplified)	9.6	11.4
	1+/NE/not examined	0.4/0.4/0	0/0.4/0
ECOG PS, %	0/1/Missing	59.0/40.6/0.4	66.5/33.1/0.4
Brain metastases, %	Yes/No	23.8/76.2	19.8/80.2
Visceral disease, %	Yes/No	70.5/29.5	70.3/29.7
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment), n (%)	0	2 (0.8)	3 (1.1)
	1	130 (49.8)	123 (46.8)
	2	56 (21.5)	65 (24.7)
	3	35 (13.4)	35 (13.3)
	4	15 (5.7)	19 (7.2)
	≥5	23 (8.8)	18 (6.8)
Prior trastuzumab, %		99.6	99.6
Prior pertuzumab, %		62.1	60.1

[a] HER2+ is defined as IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b] Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane. [c] HER2 status as evaluated by central lab.

Cortes J, et al. ESMO 2021. Abstract LBA1.

Updated Primary Endpoint: PFS by BICR

	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	



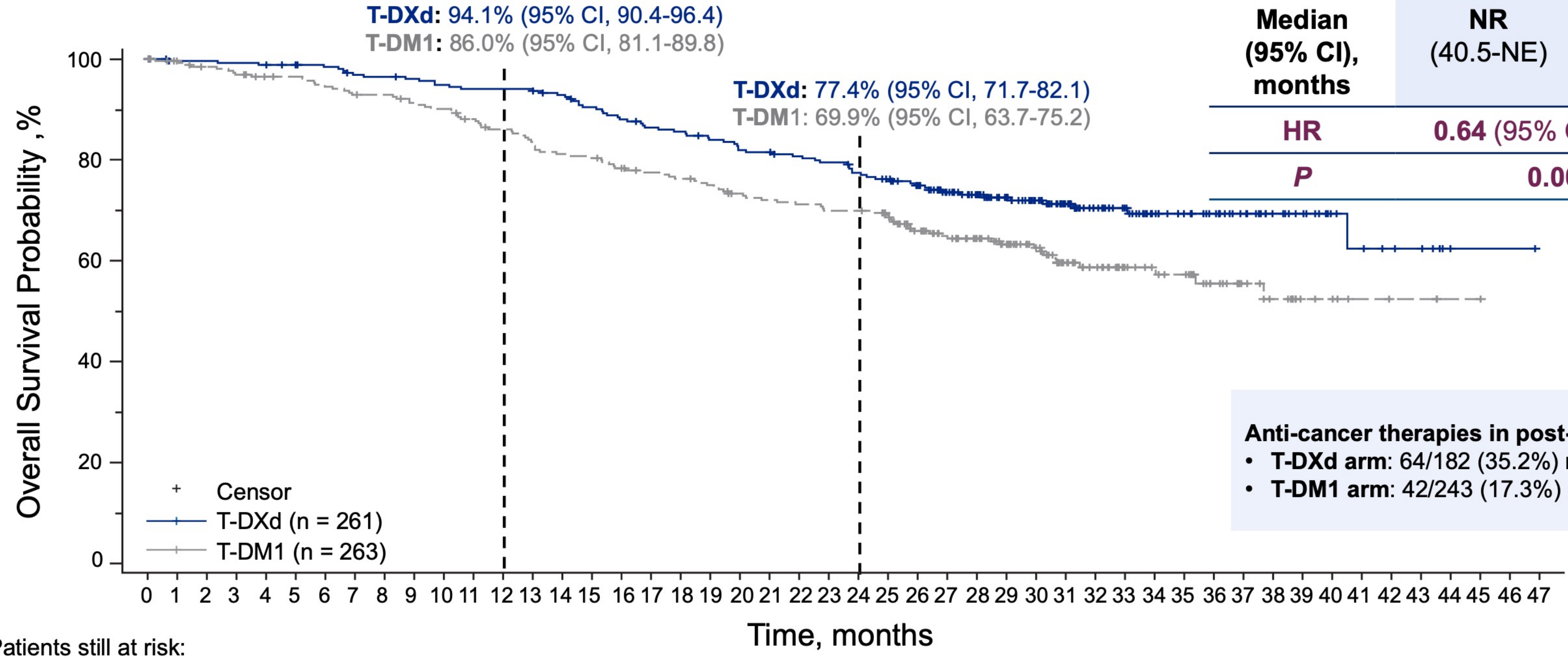
Patients still at Risk:

T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

Presented by Sara Hurvitz at SABCS 2022

Key Secondary Endpoint: Overall Survival

	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	



Patients still at risk:

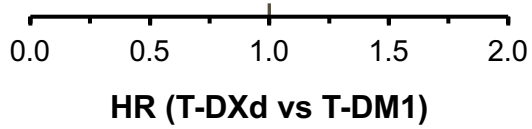
T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

Anti-cancer therapies in post-trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Presented by Sara Hurvitz at SABCS 2022

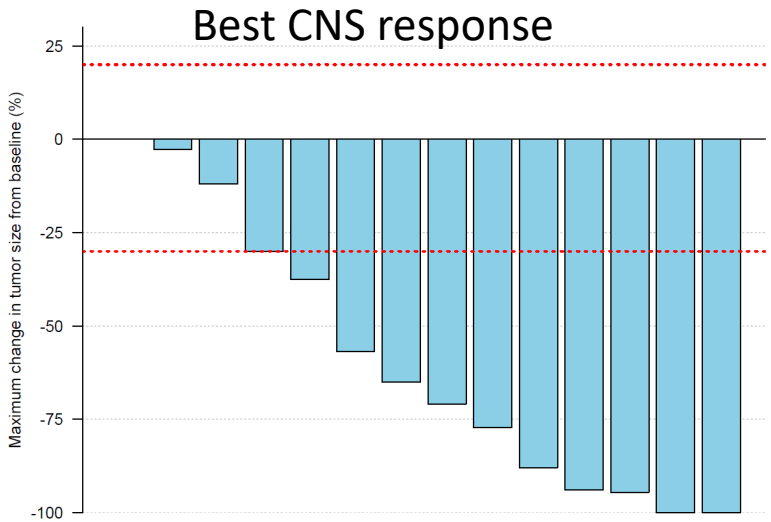
PFS in Key Subgroups

		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)
Patients with BM	Yes (n = 82)	22/43	27/39	15.0 (12.5-22.2)	3.0 (2.8-5.8)	0.2465 (0.1341-0.4529)
	No (n = 442)	65/218	131/224	NE (22.4-NE)	7.1 (5.6-9.7)	0.2971 (0.2199-0.4014)



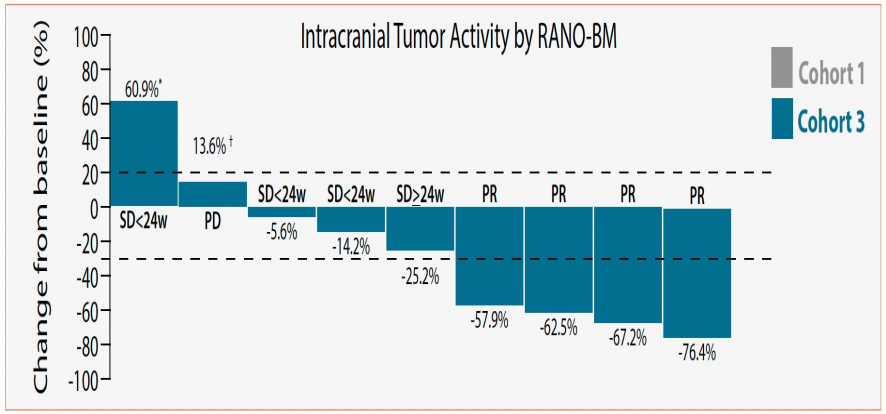
BM, brain metastasis; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Patients with rapid progression on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

CNS activity of T-DXd in pts with breast cancer and active brain metastases



TUXEDO-1 trial
Bartsch et al, ESMO Breast 2022

ORR-IC = **73%** in pts with Active BM



DEBBRAH trial
Vaz Batista et al, SABCS 2021

ORR-IC =**44%** in pts with Active BM

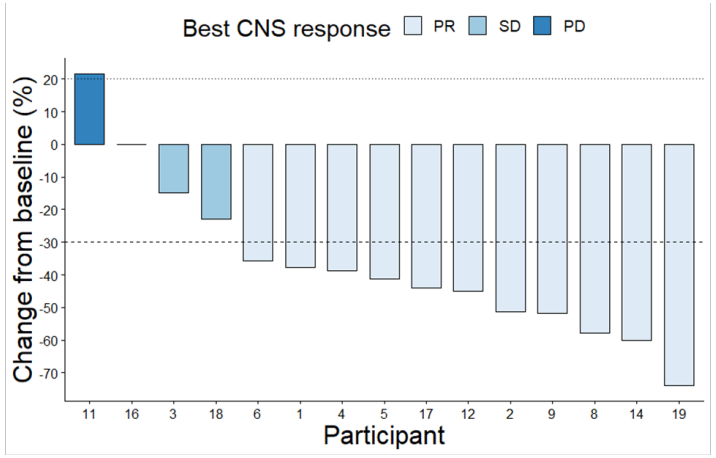


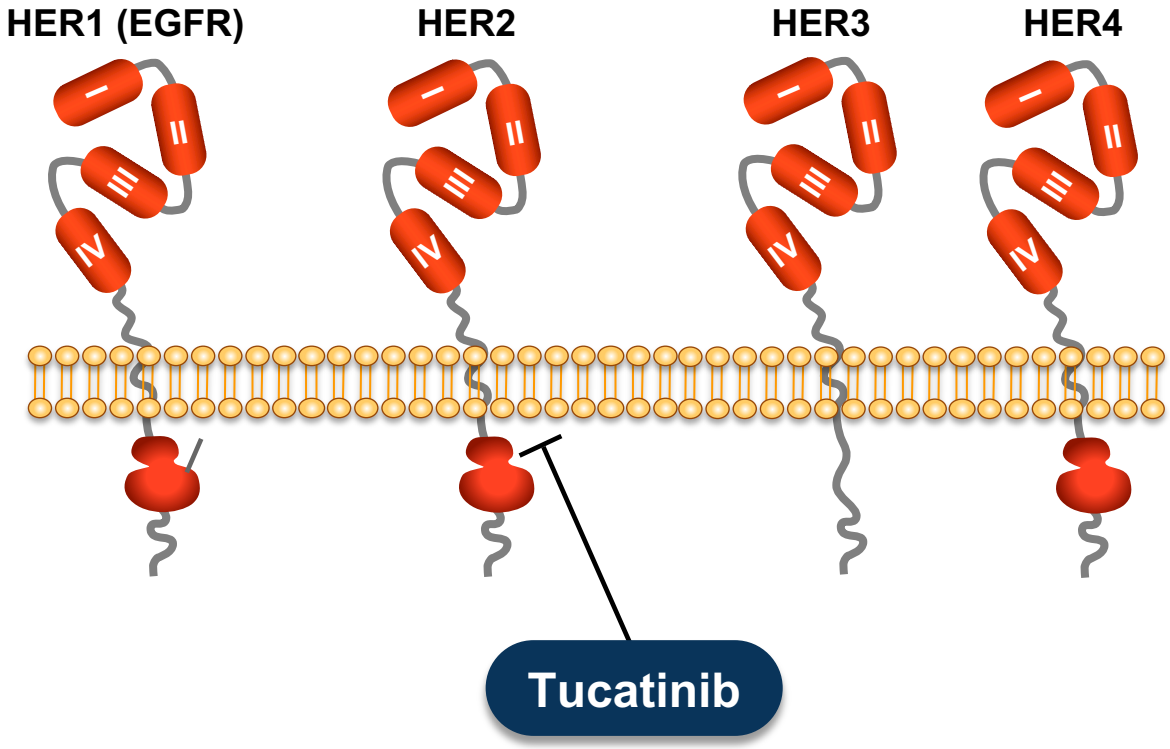
Figure 5 : Best CNS response to T-DXd. Waterfall plot of best CNS response in participants with measurable disease (n = 15). PR = partial response

DFCI/Duke/MDACCC series
Kabraji et al, SABCS 2021

ORR-IC =**73%**
(70% in pts with Active BM)

Slide courtesy of Nancy Lin/Sarah Sammons

Tucatinib: A HER2-Selective TKI[1]



Phase 1b tucatinib + capecitabine + trastuzumab (n = 60)[1]

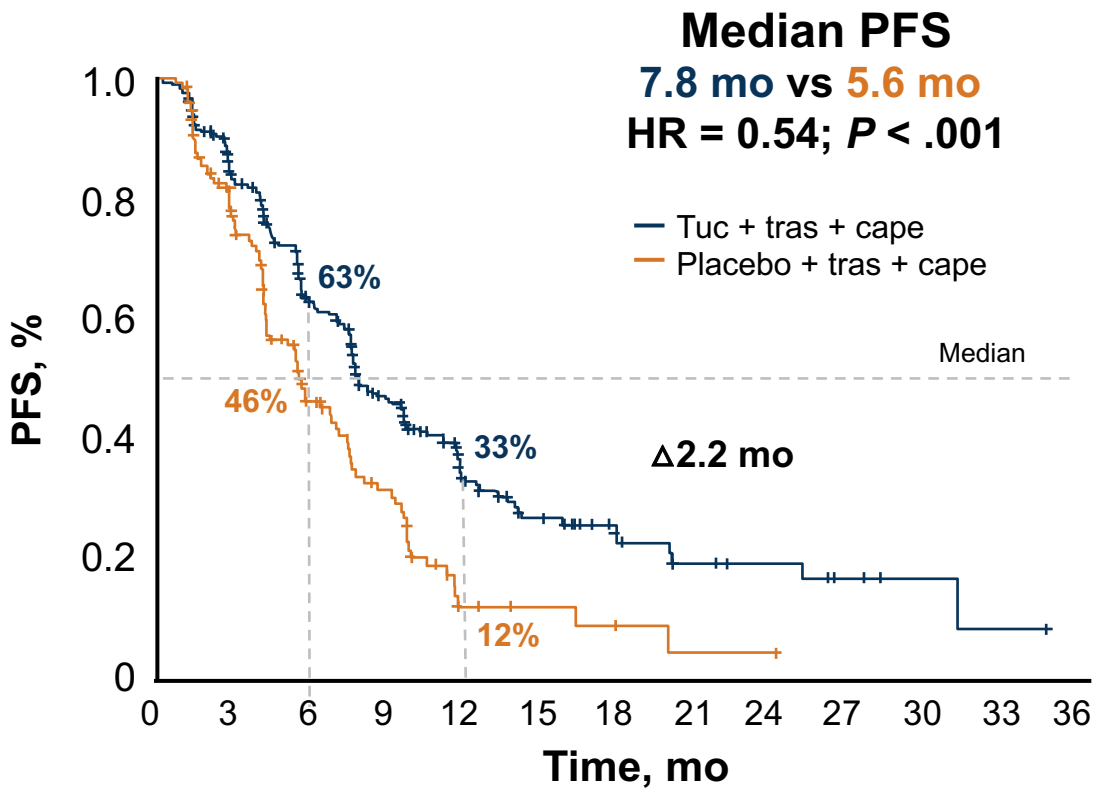
- **Prior treatment**
  - 100% trastuzumab
  - 65% pertuzumab
  - 97% T-DM1
  - 55% lapatinib
  - 56% with CNS metastasis
- **ORR**
  - 61% (14/23)
  - 42% (5/12) with CNS metastasis
- **PFS**
  - 7.8 months
  - 6.7 months with CNS metastasis
- **Diarrhea**
  - 33% grade 1-2
  - 0% grade 3-4

1. Murthy R et al. *Lancet Oncol*. 2018;19:880-888.

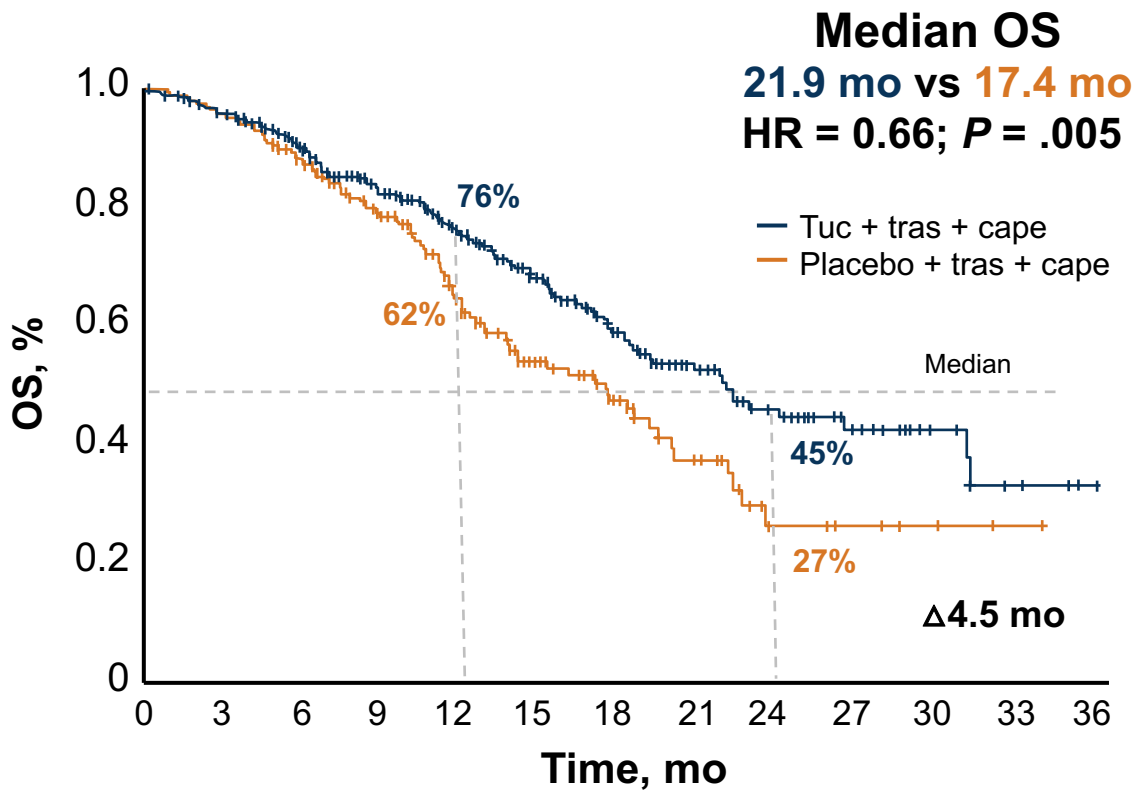
HER2CLIMB: Randomized Phase 2 Trial of Tucatinib[1]

Tucatinib + Capecitabine + Trastuzumab vs Capecitabine + Trastuzumab

Tucatinib Improves PFS and OS



No. at Risk													
Tuc + tras + cape	320	235	152	96	40	29	15	10	8	4	2	1	0
PBO + tras + cape	160	94	45	27	6	4	2	1	1	0	0	0	0

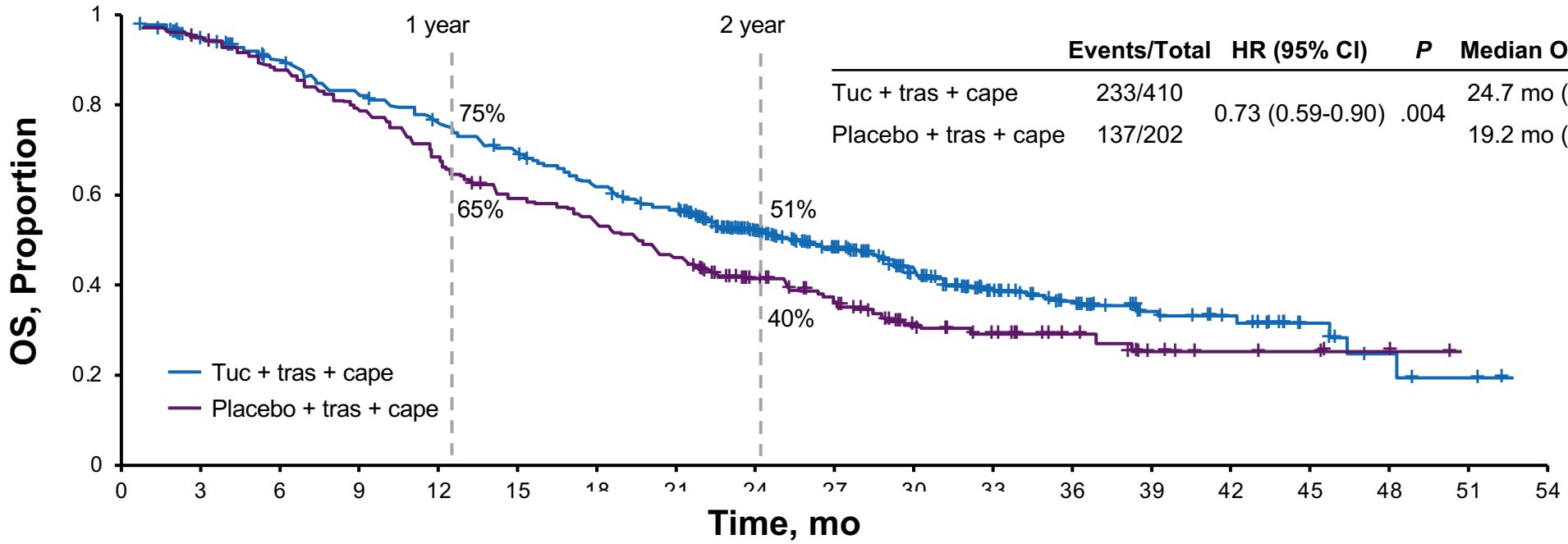


No. at Risk													
Tuc + tras + cape	410	388	322	245	178	123	80	51	34	20	10	4	0
PBO + tras + cape	202	191	160	119	77	48	32	19	7	5	2	1	0

1. Murthy R et al. *N Engl J Med*. 2020;382:597-609.

HER2CLIMB: Updated OS Results[1]

Overall Survival[a]



	Events/Total	HR (95% CI)	*P*	Median OS (95% CI)
Tuc + tras + cape	233/410	0.73 (0.59-0.90)	.004	24.7 mo (21.6-28.9)
Placebo + tras + cape	137/202			19.2 mo (16.4-21.4)

No. at Risk

Tuc + tras + cape	410	387	356	325	295	268	241	214	153	122	81	56	38	24	19	11	4	2	0
Placebo + tras + cape	202	191	174	155	129	114	103	87	63	47	28	21	14	8	4	3	2	0	0

- OS benefit with tucatinib was maintained with longer follow-up, with a 5.5-month improvement in median OS in the tucatinib arm compared with the placebo arm
- Sensitivity analyses accounting for crossover showed consistent results with ITT analysis

[a] Median overall study follow-up: 29.6 months.

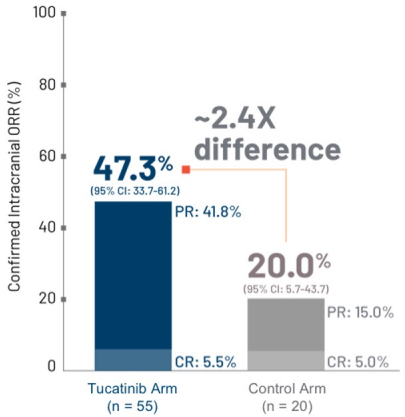
1. Gurigliano G et al. ASCO 2021. Abstract 1043.

CNS SUBGROUP ANALYSIS

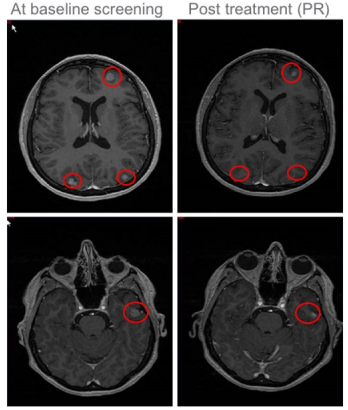
ASCO 2020 UPDATE: POST HOC EXPLORATORY ANALYSES

CONFIRMED INTRACRANIAL OBJECTIVE RESPONSE RATE[1*]

Confirmed intracranial ORR by RECIST 1.1 (n = 75) in patients with active brain metastases and measurable intracranial lesions at baseline per investigator assessment[1]



Brain CT scans of a patient in the tucatinib arm†



CT = computed tomography; RECIST = Response Evaluation Criteria in Solid Tumors.

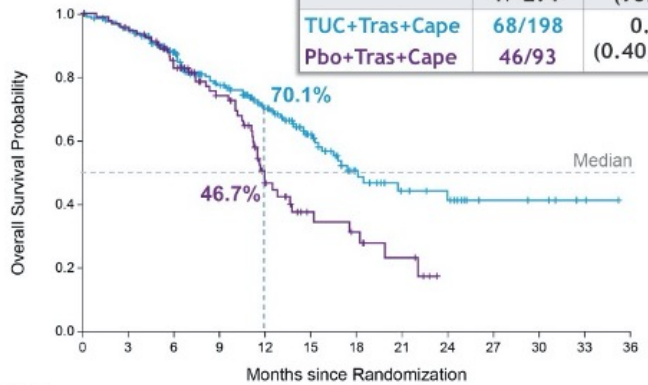
* Results of this exploratory analysis are descriptive, not in the approved labeling, and not controlled for type 1 error, as HER2CLIMB was not powered to test this analy results are estimates (not exact numbers). Due to a high rate of censoring of patients owing to extra-CNS progression (new or enlarging extracranial lesions) or death, r should be interpreted with caution. †Individual results may vary.

1. Lin NU et al. *J Clin Oncol*. 2020;38:2610-2619.

Please see Important Safety Information on slides 32-35 and refer to the full Prescribing Information available at this event.

OS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



No. at Risk

TUC+Tras+Cape	198	184	146	108	79	49	26	17	14	7	6	2	0
Pbo+Tras+Cape	93	87	67	49	23	12	9	5	0	0	0	0	0

Risk of death was reduced by 42% in patients with brain metastases

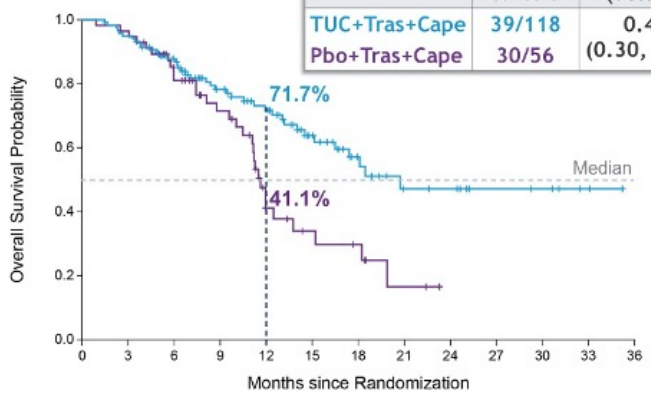
One-year OS (95% CI):	
TUC+Tras+Cape 70.1% (62.1, 76.7)	Pbo+Tras+Cape 46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		



No. at Risk

TUC+Tras+Cape	118	111	89	66	51	33	19	11	10	6	5	2	0
Pbo+Tras+Cape	56	54	39	29	12	8	6	2	0	0	0	0	0

Risk of death was reduced by 51% in patients with active brain metastases

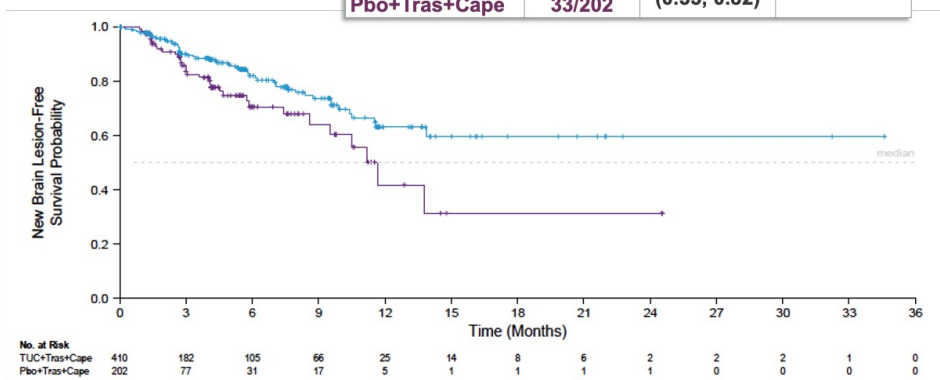
One-year OS (95% CI):	
TUC+Tras+Cape 71.7% (61.4, 79.7)	Pbo+Tras+Cape 41.1% (25.5, 56.1)
Median OS (95% CI):	
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)

NE: not estimable

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

HER2CLIMB: New Brain Lesion-Free Survival

	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	52/410	0.52 (0.33, 0.82)	0.005
Pbo+Tras+Cape	33/202		



No. at Risk

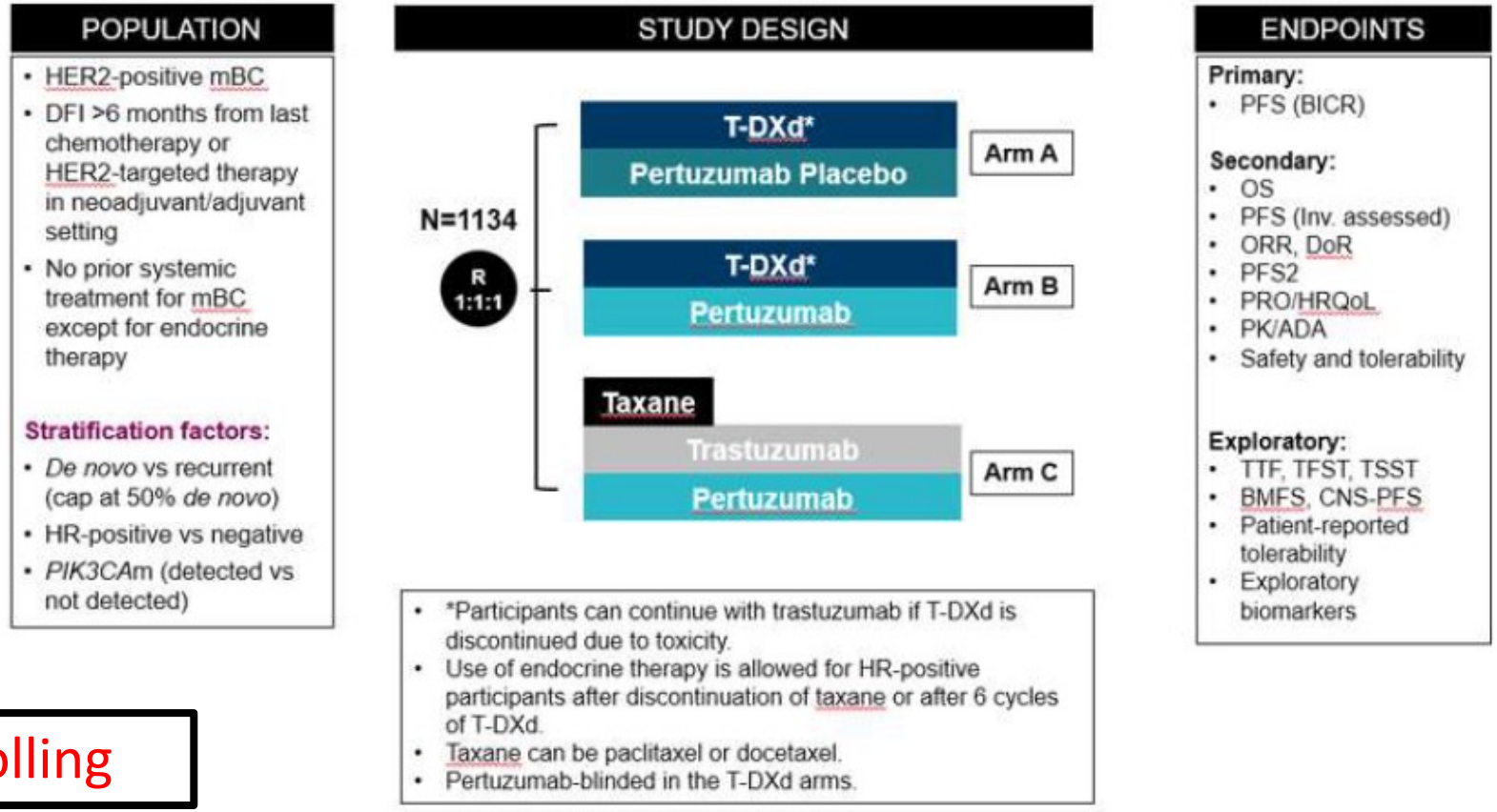
TUC+Tras+Cape	410	182	105	66	25	14	8	6	2	2	2	1	0
Pbo+Tras+Cape	202	77	31	17	5	1	1	1	1	0	0	0	0

Patients with HER2+ brain metastases in the second line setting

- Both T-DXd and the HER2CLIMB regimen (tucatinib/capecitabine/trastuzumab) are reasonable options
- For patients with intracranial-predominant disease and active CNS metastases (progressing after prior local tx, or not yet treated with local tx), HER2CLIMB regimen has a greater evidence basis
- Selected other patients of advanced age, with multiple comorbidities, or with history of ILD may not be T-DXd candidates…otherwise, T-DXd is the default choice in second line

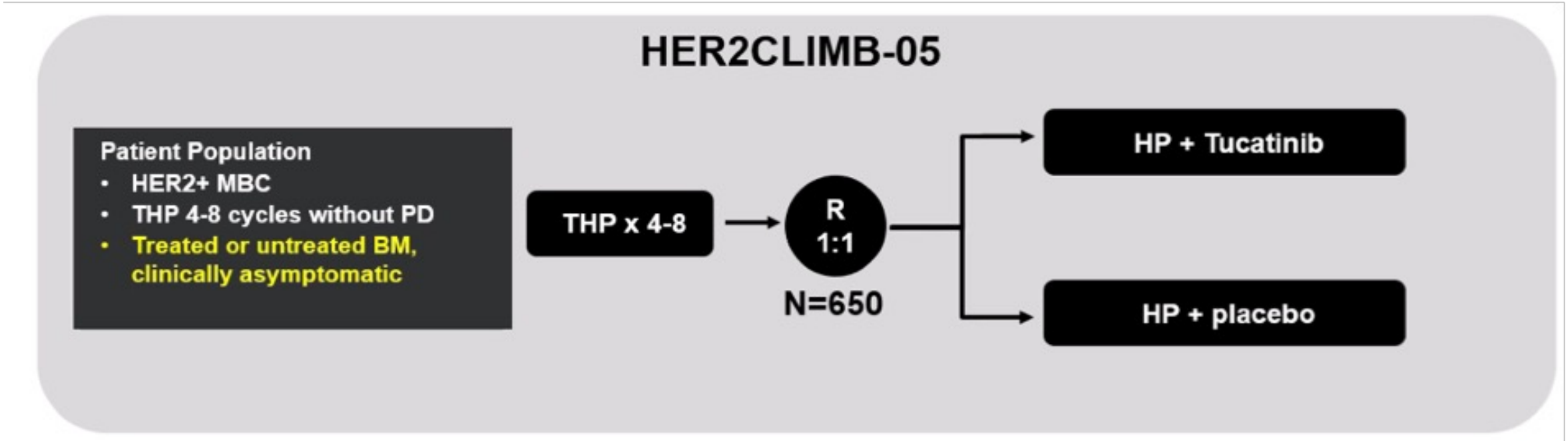
DESTINY-Breast09: A Phase III Study of Trastuzumab Deruxtecan (T-DXd) with or without Pertuzumab versus THP in **First-line** HER2-positive Breast Cancer

Study Design



Currently enrolling

HER2CLIMB-05: A Study of Tucatinib or Placebo With Trastuzumab and Pertuzumab for Metastatic HER2+ Breast Cancer

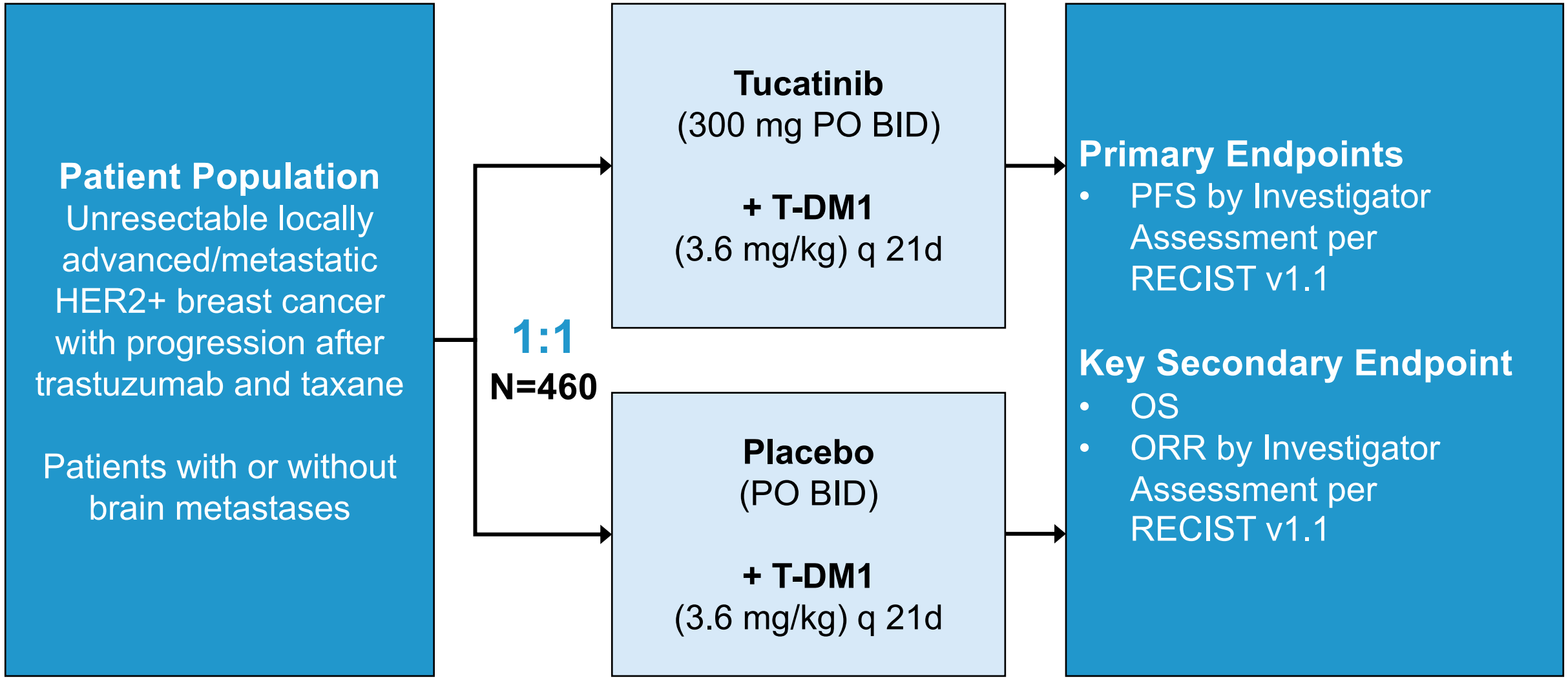


Currently enrolling

NRG BR004: First-line THP +/- atezolizumab

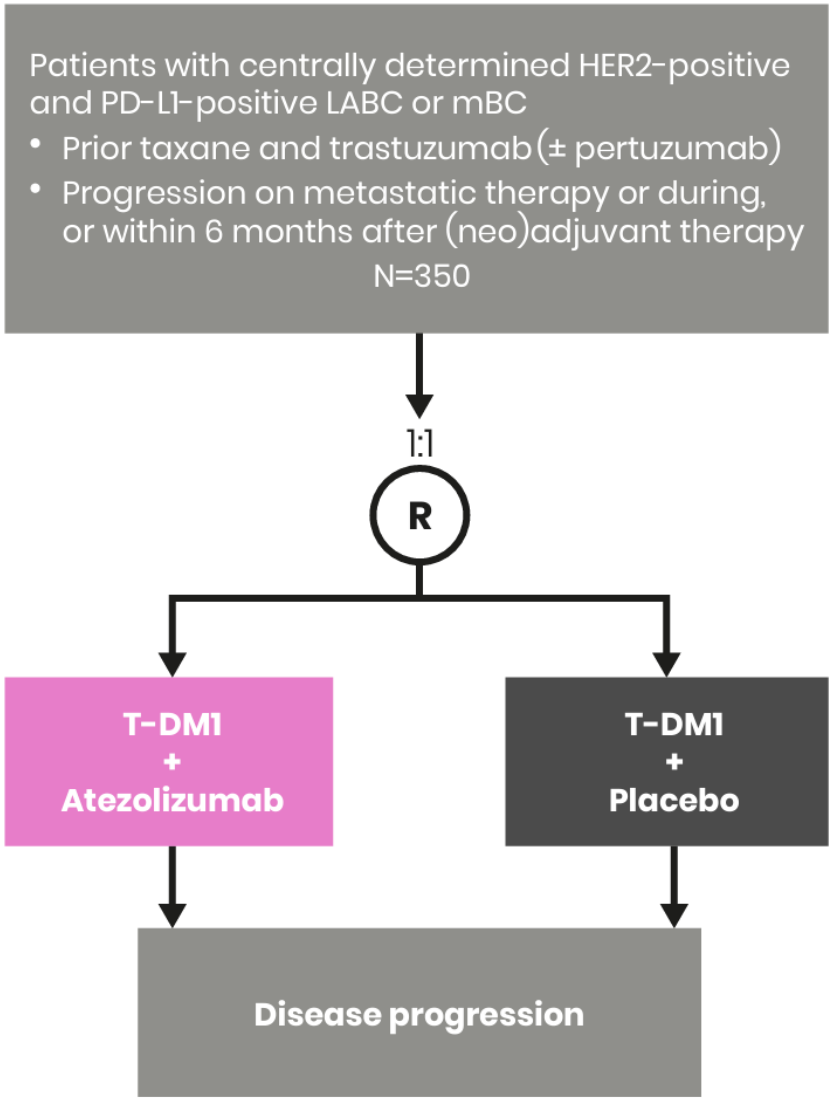
Closed early for toxicity – further details unknown

HER2CLIMB-02: Completed Accrual



Completed enrollment

KATE3: T-DM1 +/- atezolizumab in PD-L1+ HER2+ metastatic breast cancer



Currently enrolling

Current Standard of Care for HER2+ MBC

First Line

Trastuzumab + pertuzumab + taxane

CLEOPATRA

Second Line

Trastuzumab deruxtecan (T-DXd)

DB03

-or-

Tucatinib + Trastuzumab + Capecitabine

HER2CLIMB

Factors: extracranial dz burden, intracranial dz burden, co-morbidities, pt preference, etc

Third Line

Tucatinib + Trastuzumab + Capecitabine

HER2CLIMB

-or-

Trastuzumab deruxtecan

DB03

-or-

Trastuzumab emtansine (T-DM1)

EMILIA, TH3RESA

- Activity post TDxd?

Slide courtesy of Nancy Lin

Late Line Options for HER2+ MBC: "Dealer's Choice"

Fourth line +

- Trastuzumab emtansine (T-DM1) — TH3RESA
- Trastuzumab + chemo**
- Margetuximab + chemo — SOPHIA
- Trastuzumab + lapatinib — EGF104900
- Neratinib + capecitabine — NALA

**Many possible agents:
Vinorelbine
Eribulin
Gemcitabine
Doxorubicin
Carboplatin
Etc.

Special consideration in HR+/HER2+:
Fulvestrant/abema/trastuzumab

*or tucatinib/cape/trastuzumab, or T-DXd if not already received

Slide modified from Nancy Lin