Updates on HER2-positive breast cancers

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- Associate Professor
- Director, Translational Research, Breast Cancer Program
- Associate Director, Clinical Science, Lester and Sue Smith Breast Center
- Baylor College of Medicine

Escalation, De-Escalation
Choice of Genomics, Serial Monitoring, Extreme Responders

Baylor College of Medicine

HER2 adjuvant therapy: The Age of three kingdoms

Baylor College of Medicine

Agents:
T-DM1
Pertuzumab + Herceptin
Neratinib

Down-tailoring biomarkers being studied.

Duration continues to be an issue:
Herceptin – 9 weeks vs 6 mo vs 12 mo

ExteNET: Results

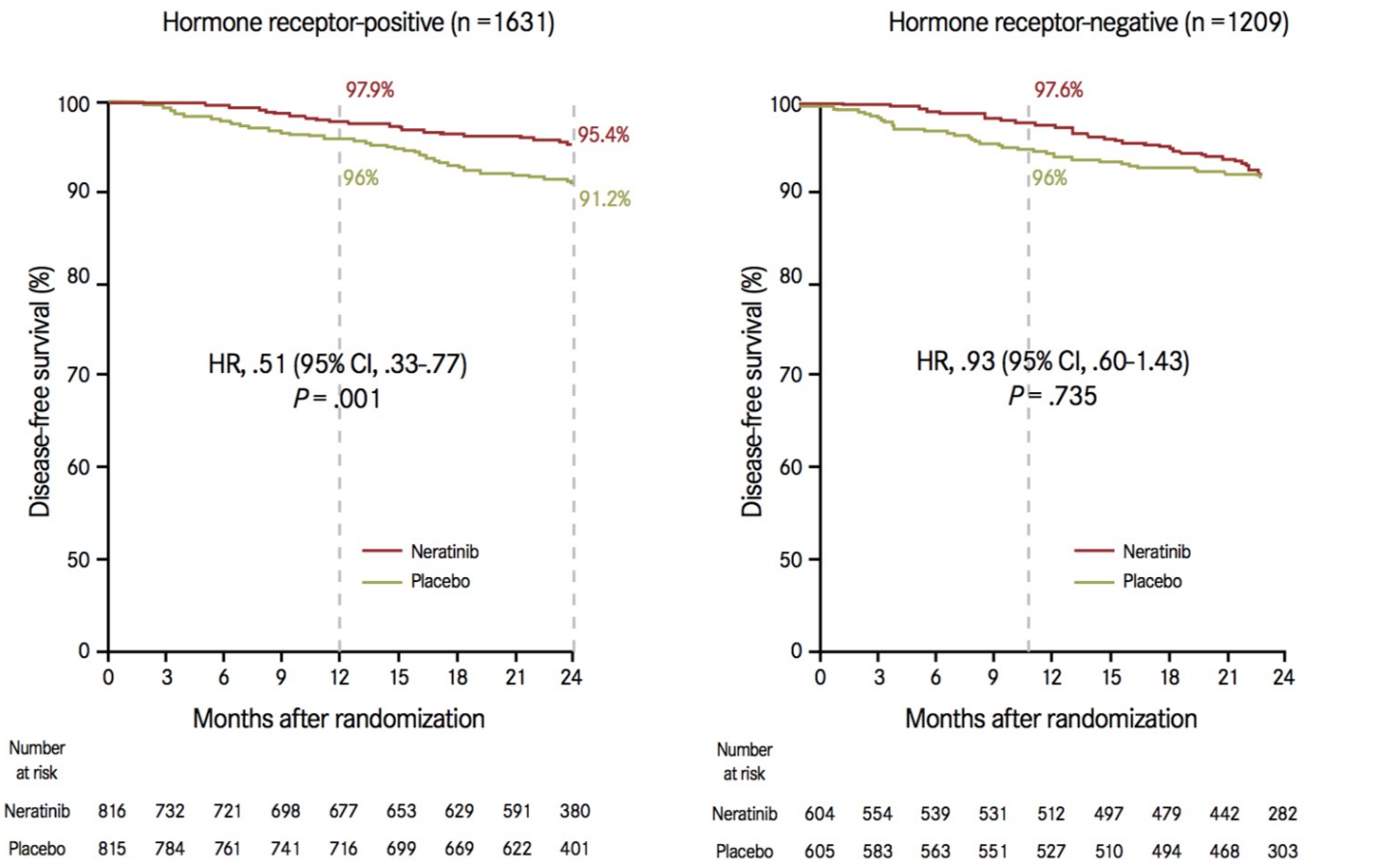

FIGURE 1. iDFS by Hormone Receptor–Status in Adjuvant Neratinib Trial

CI indicates confidence interval; HR, hazard ratio or hormone receptor; iDFS, invasive disease-free survival.
Chan A, Delaloge S, Holmes FA, et al. Neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer: primary analysis at 2 years of a phase III, randomized, placebo-controlled trial (ExteNET). *J Clin Oncol.* 2015;33(suppl; abstr 508). Used with permission from author.

APHINITY: Intent-to-Treat Primary Endpoint Analysis
Invasive Disease-free Survival

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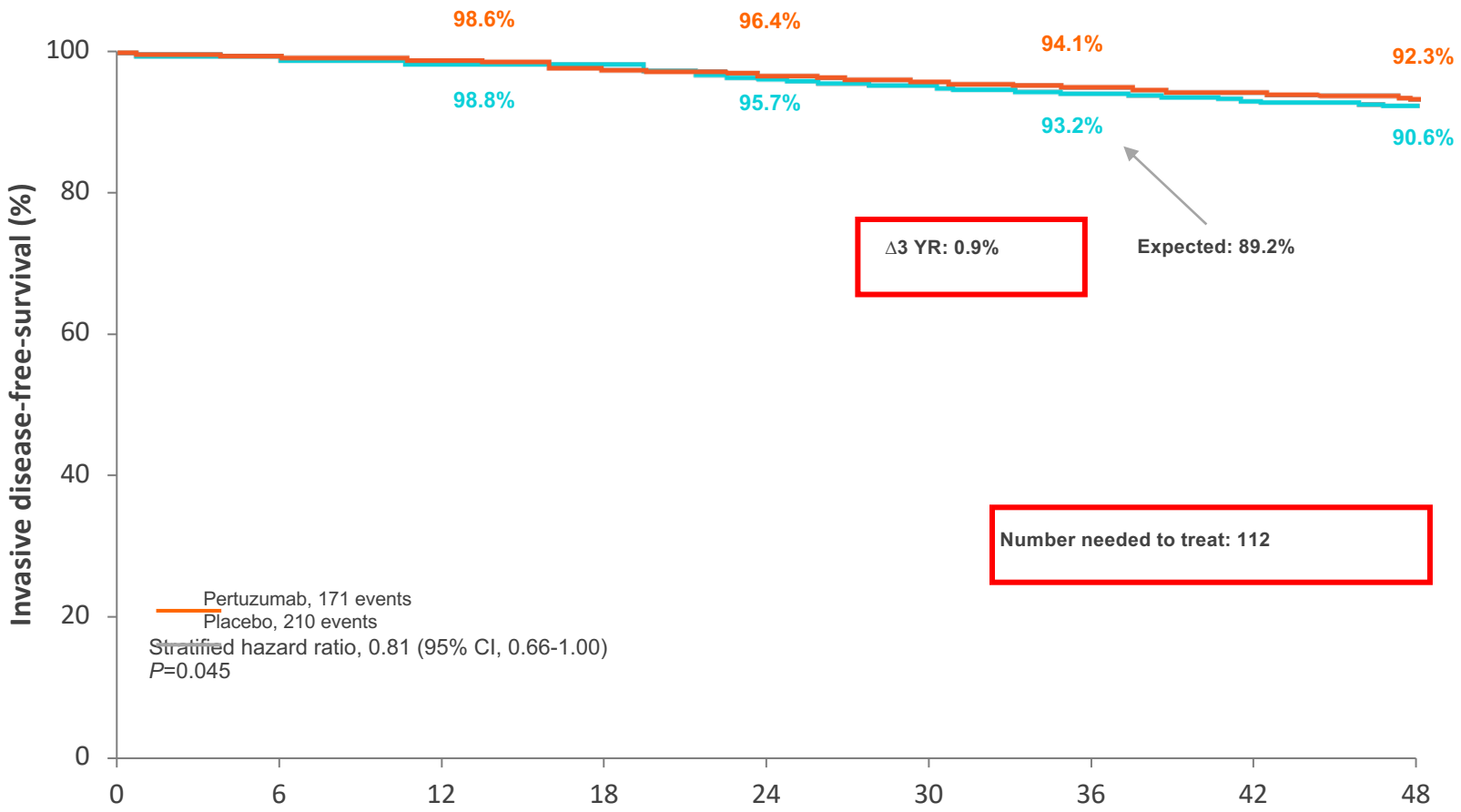

No. at Risk									
Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

von Minckwitz, G et al. *N Engl J Med.* 2017;377:122-131

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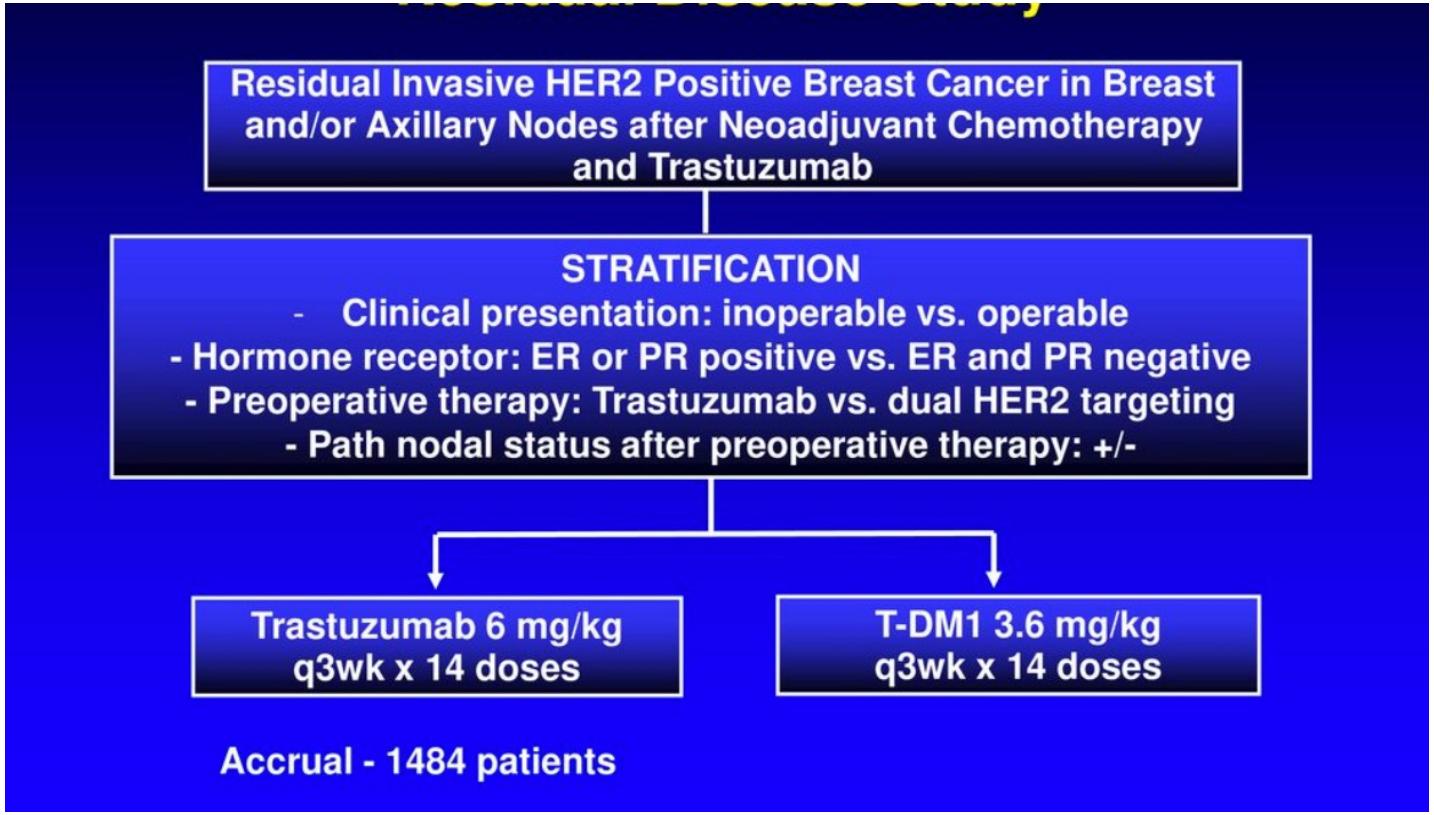
KATHERINE/NSABP B50 Study Schema

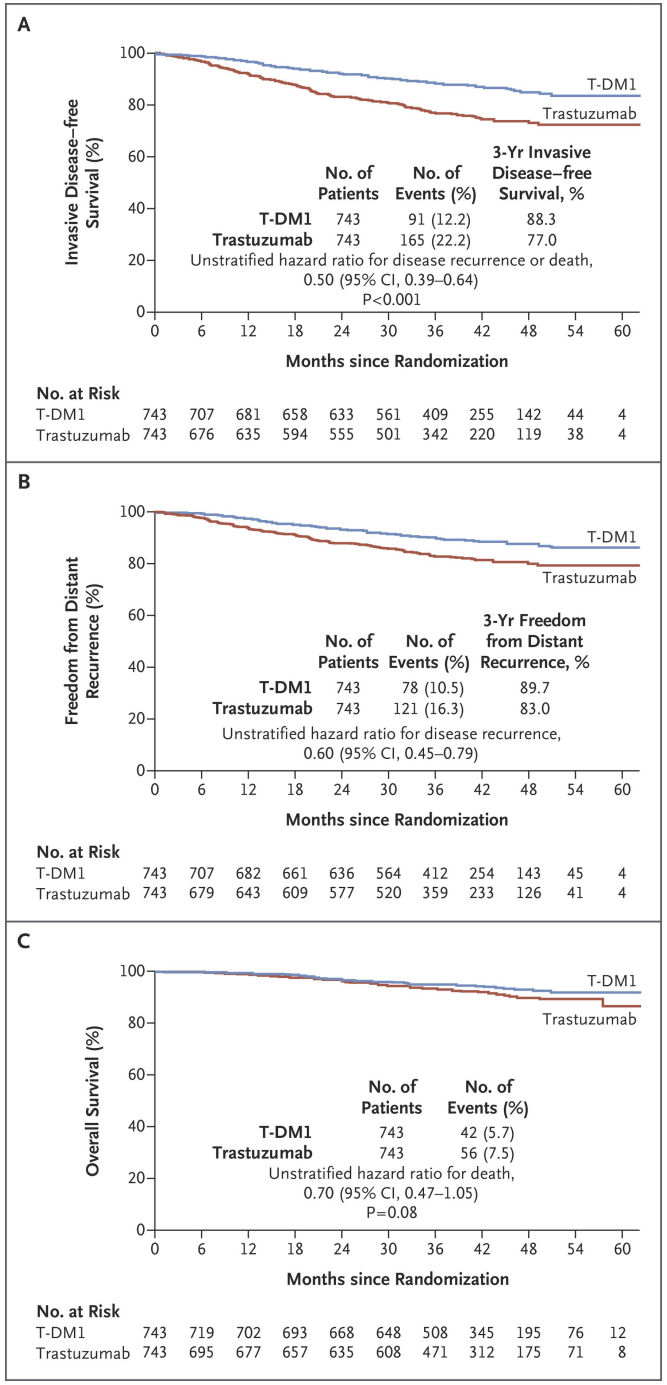


KATHERINE: Result

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Trastuzumab Group (N=743)	T-DM1 Group (N=743)
Median age (range) — yr	49 (23–80)	49 (24–79)
Race or ethnic group — no. of patients (%)†		
White	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
Black	19 (2.6)	21 (2.8)
American Indian or Alaska Native‡	50 (6.7)	36 (4.8)
Multiple or unknown	79 (10.6)	70 (9.4)
Clinical stage at presentation — no. of patients (%)		
Inoperable breast cancer§	190 (25.6)	185 (24.9)
Operable breast cancer¶	553 (74.4)	558 (75.1)
Hormone-receptor status — no. of patients (%)		
Estrogen-receptor–negative and progesterone-receptor–negative or status unknown	203 (27.3)	209 (28.1)
Estrogen-receptor–positive, progesterone-receptor–positive, or both	540 (72.7)	534 (71.9)
Previous use of anthracycline — no. of patients (%)	564 (75.9)	579 (77.9)
Neoadjuvant HER2-targeted therapy — no. of patients (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus pertuzumab	139 (18.7)	133 (17.9)
Trastuzumab plus other HER2-targeted therapy‖	8 (1.1)	10 (1.3)

* Additional baseline characteristics are listed in Table S1 in the Supplementary Appendix. Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor 2, and T-DM1 trastuzumab emtansine.
† Race or ethnic group was reported by the investigators.
‡ The American Indian category includes North, Central, and South American Indians.
§ Inoperable breast cancer was defined as tumor stage T4, nodal stage Nx, and metastasis stage M0 or tumor stage Tx, nodal stage N2 or N3, and metastasis stage M0.
¶ Operable breast cancer was defined as tumor stage T1 to T3, nodal stage N0 or N1, and metastasis stage M0.
‖ Other HER2-targeted agents were neratinib, dacomitinib, afatinib, and lapatinib.



G von Minckwitz et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1814017

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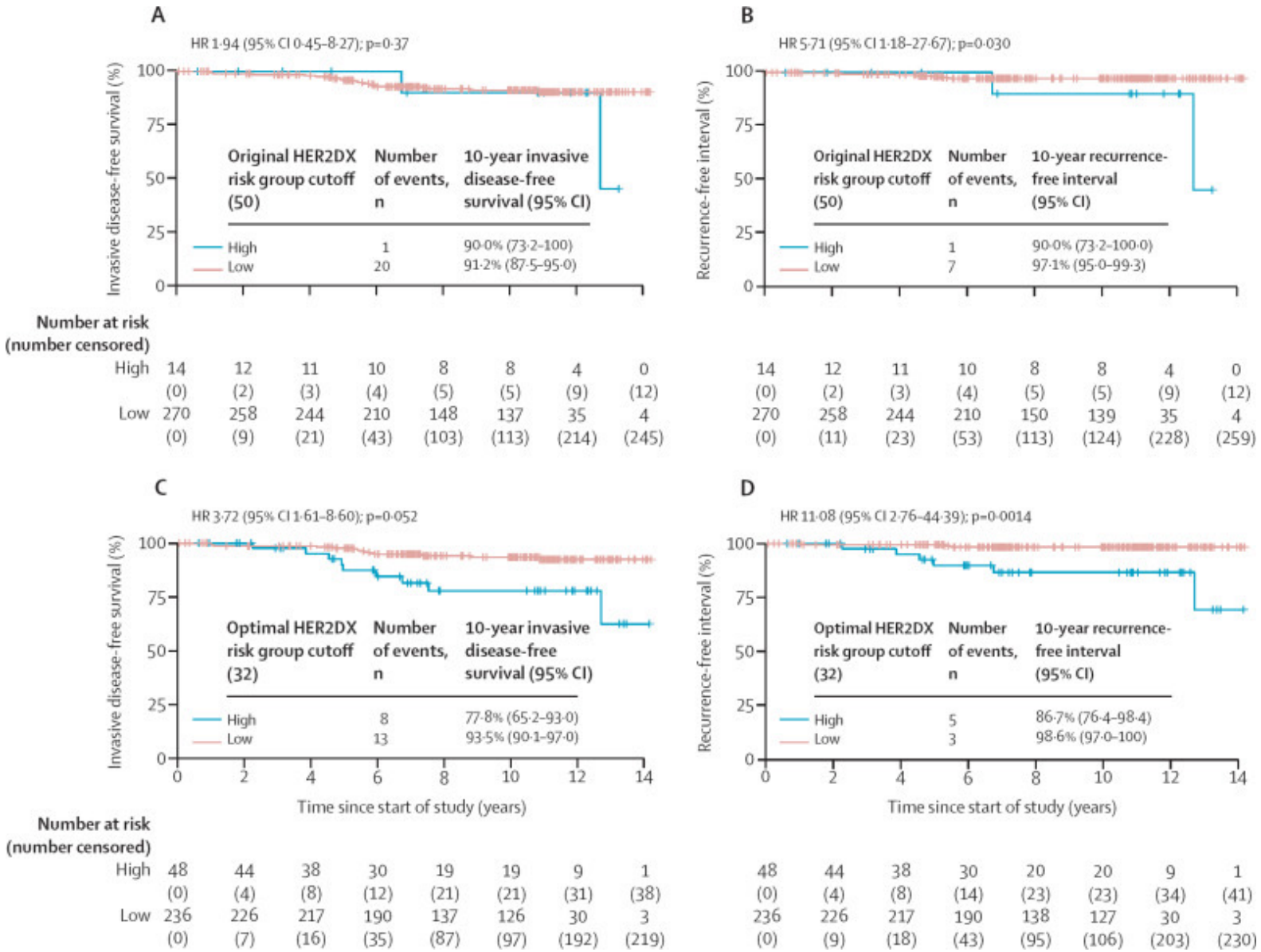
APT (NCT00542451)



HER2 adjuvant therapy: The New Age

Agents:

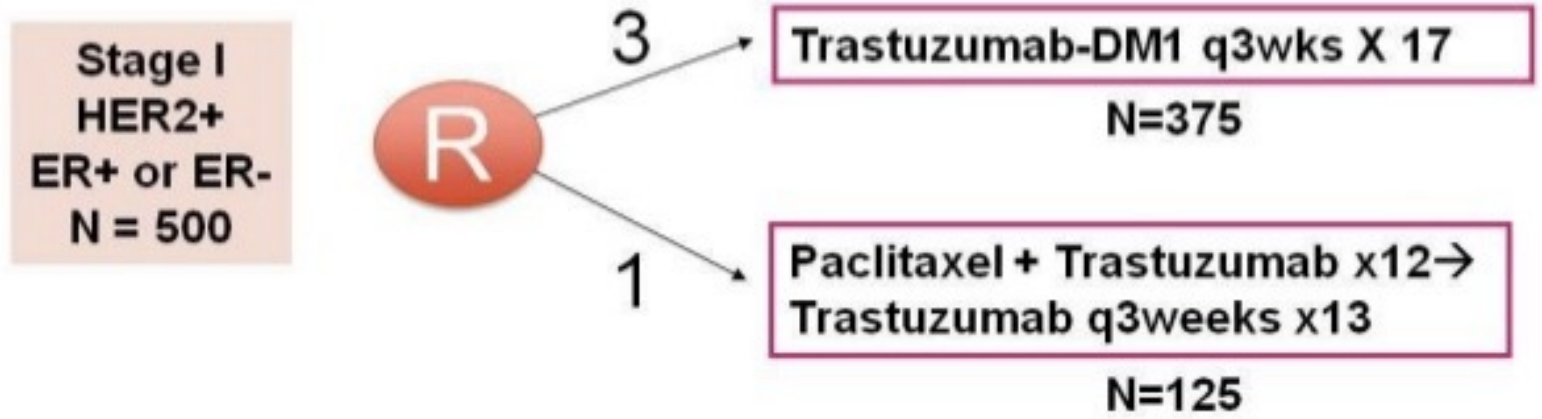
T-DxD

Other antibiody-drug-conjugates

ATEMPT

Baylor College of Medicine

(TBCRC 033)

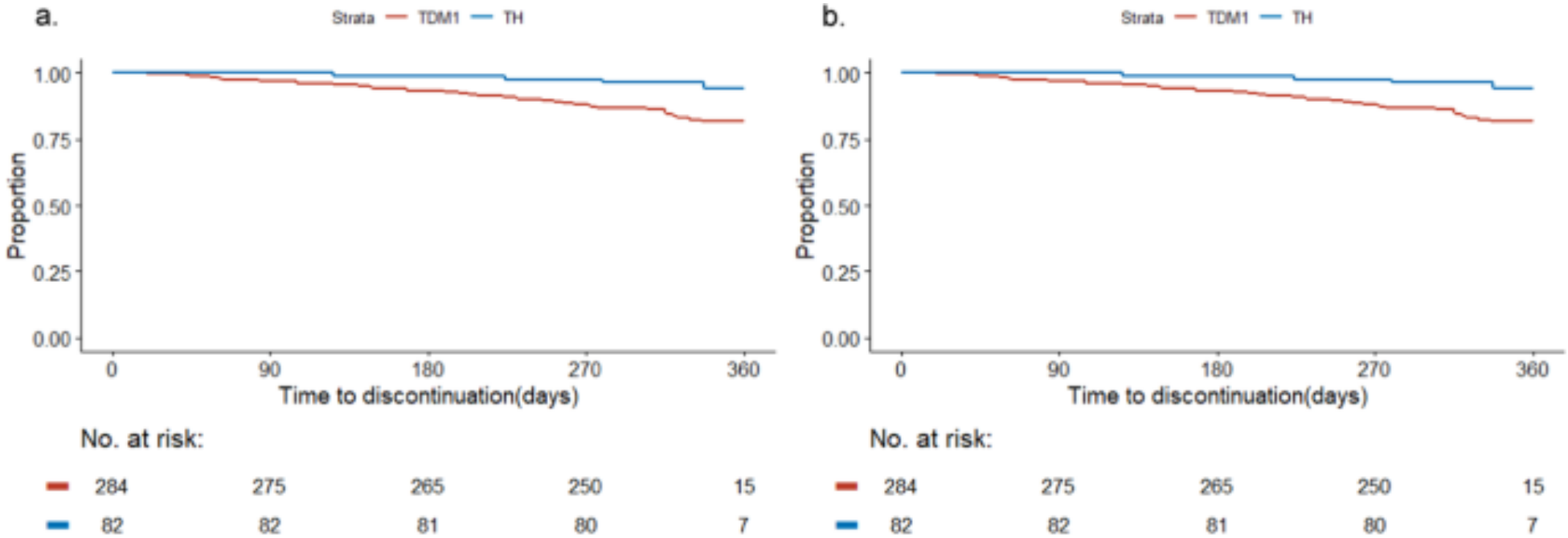


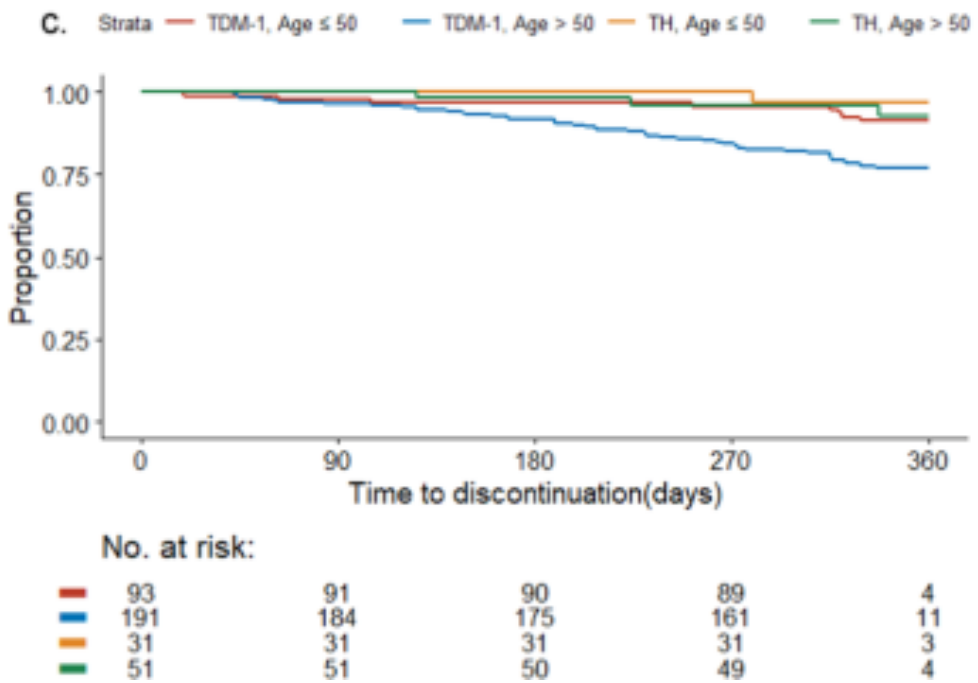
Primary endpoint to look for toxicity differences and a 3yr DFS of at least 95%

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Shanu Modi at 2015 ASCO Annual Meeting

Finished Accrual. Result to be seen.





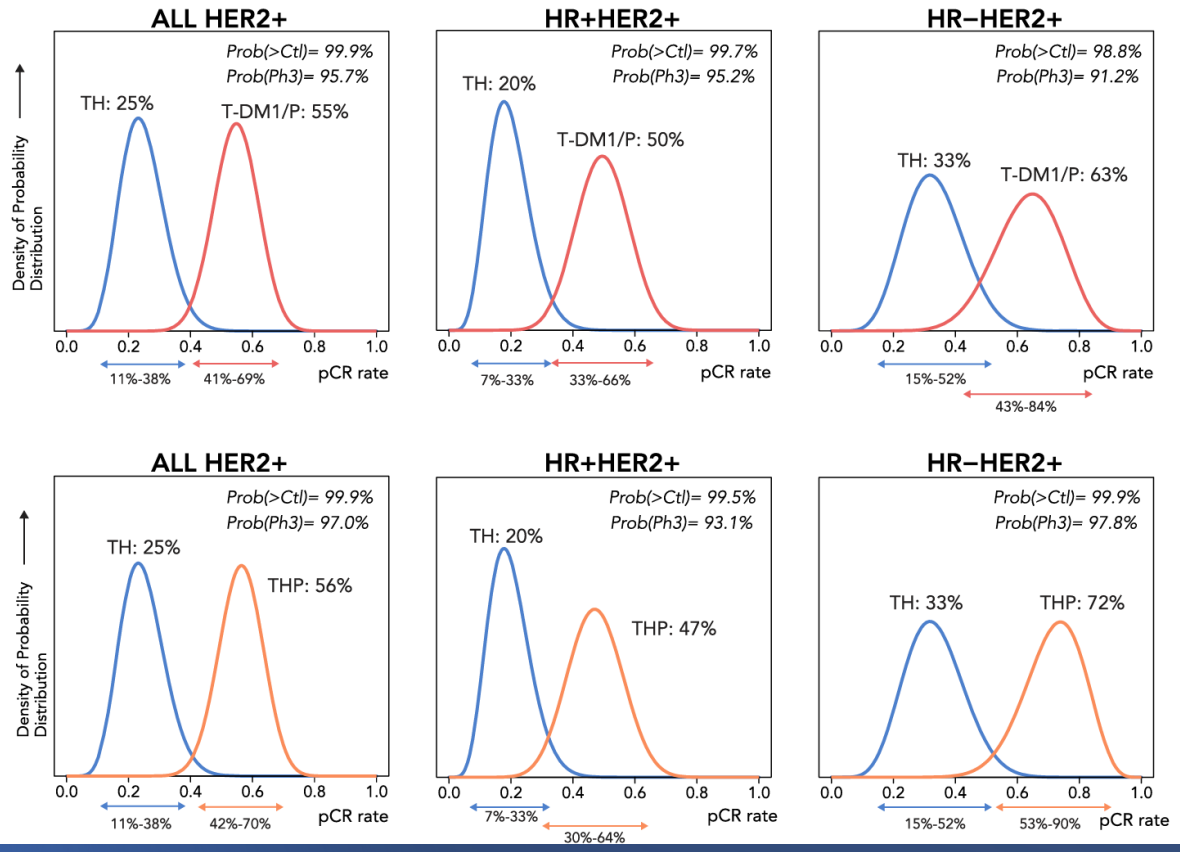
TH still the winner

ARTICLE

https://doi.org/10.1038/s41467-021-26019-y OPEN

Check for updates

Neoadjuvant T-DM1/pertuzumab and paclitaxel/trastuzumab/pertuzumab for HER2+ breast cancer in the adaptively randomized I-SPY2 trial



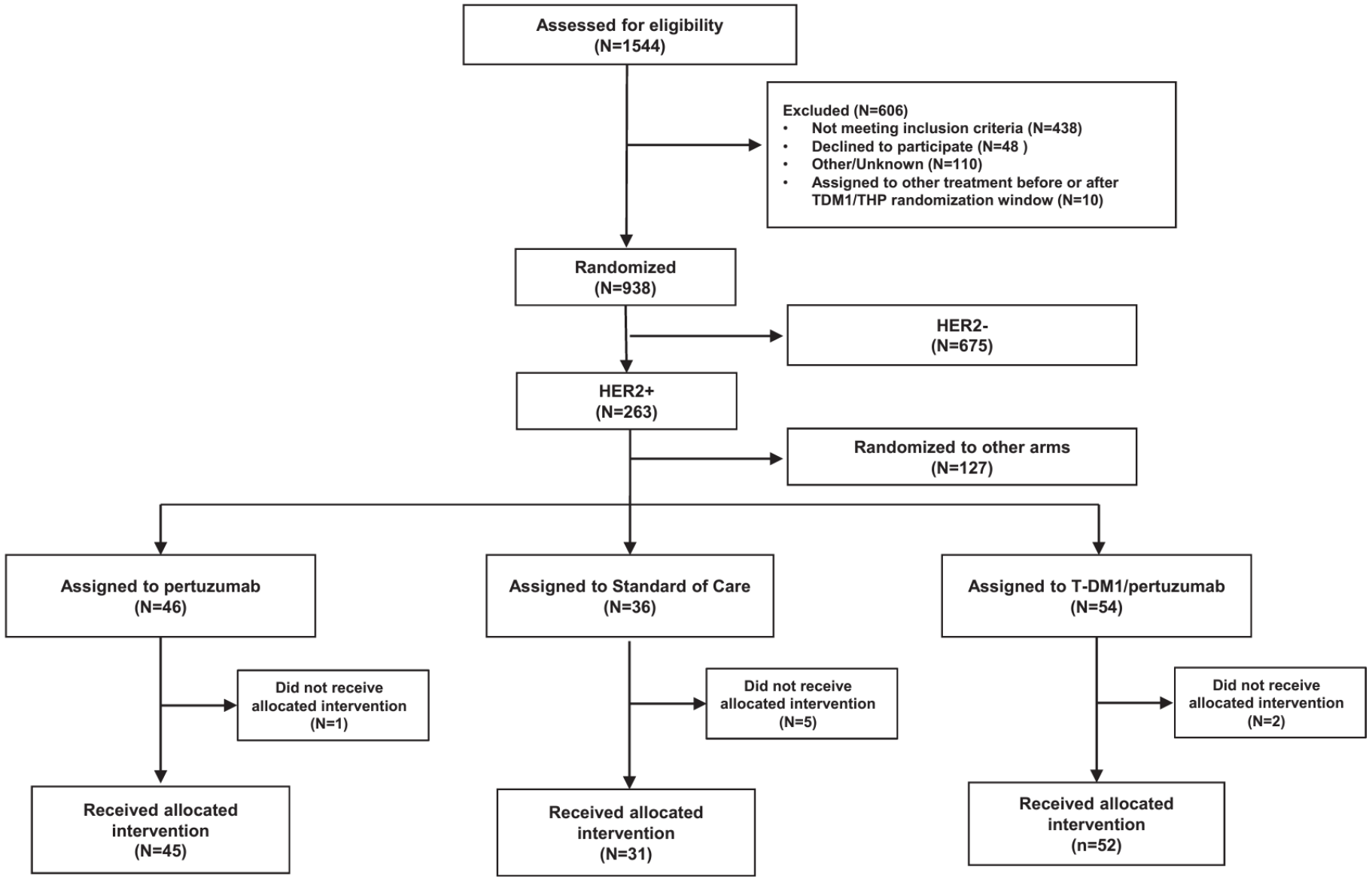
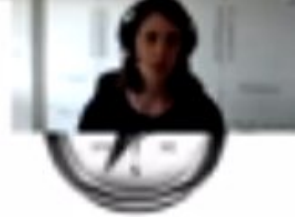


Fig. 1 Consort diagram for the T-DM1/Pertuzumab, THP, and control populations. Consort diagram shows the number of patients screening,

CompassHER2 trials



Preoperative Phase: all patients

Eligibility:
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

THP x 4 Cycles
Paclitaxel qwk x12
OR
Docetaxel q3 wk x4
with
Trastuzumab (H)
& Pertuzumab (P)
q3 wk x4

* nab-pacl allowed

SURGERY

pCR (ypT0/Tis ypN0) *40%*

Arm A: pCR (no invasive disease)

EA1181
CompassHER2-pCR
- Complete 1 yr HP
- Radiation and endocrine Rx (if appropriate)

ECOG-ACRIN

No pCR *60%*

A011801
CompassHER2-RD

Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> AC, CbHP x 4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

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

Registration

R

T-DM1 x 14 doses

T-DM1/tucatinib x 14 doses

EA1181, NCT04266249, PI Nadine Tung
AA11801,NCT04457596, PI Ciara O'Sullivan

San Antonio Breast Cancer Symposium – December 6-10,2022

endent validation of the HER2DX genomic test in HER2-positive breast cancer treated with neoadjuvant paclitaxel, trastuz and pertuzumab (THP): a correlative analysis from the DAPHNe phase II clinical trial

Adrienne G. Waks,[1] Esther R. Ogayo,[1] Laia Paré,[2] Mercedes Marín-Aguilera,[2] Fara Brasó-Maristany,[3] Patricia Galván,[3] Oleguer Castillo,[3] Olga Martínez-Sáez,[3] Ana Vivancos,[4] Patricia Villagrasa,[2] Paolo Tarantino,[1] Neelam Desai,[5] Otto Metzger,[1] Nadine M. Tung,[5] Ian E. Krop,[6] Joel S. Parker,[7] Charles M. Perou,[7] Aleix Prat,[3] Eric P. Winer,[6] Sara M. Tolaney,[1] Elizabeth A. Mittendorf[1,8]

r Cancer Institute, Boston, MA; 2. Reveal Genomics, Barcelona, Spain; 3. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain; 4. Cancer Genomics Group, Vall d'Hebr Oncology, Barcelona, Spain; 5. Beth Israel Deaconess Medical Center, Boston, MA; 6. Yale Cancer Center, New Haven, CT; 7. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; 8. Brigham and Women's Hospital, Boston, M

ND:

assay is a supervised learning algorithm that incorporates clinical information (tumor size, nodal four gene expression signatures (immune infiltration, tumor cell proliferation, luminal n, and expression of the HER2 amplicon) to provide two independent scores to predict the pCR (pCR score) and long-term prognosis (risk score) in patients with early-stage HER2+ breast *A et al EBioMedicine 2022 PMID: 34990895; Prat A et al Lancet Oncol 2020 PMID: 33152285*)

T03716180) was a single-arm investigator-initiated prospective phase II trial in which patients with ïve stage II-III HER2+ breast cancer received a de-escalated neoadjuvant regimen consisting of axel (T) for 12 cycles along with trastuzumab and pertuzumab (HP) every 3 weeks for 4 cycles. *al NPJ Breast Cancer 2022 PMID: 35538105*)

d the HER2DX assay centrally on pre-treatment tumor biopsy tissue from patients enrolled in

te the predictive value of the HER2DX pCR score in the setting of a modern, de-escalated systemic imen (THP).

the HER2DX pCR score assay in patient subpopulations according to hormone receptor status.

he relationship between the predictive HER2DX pCR score and the prognostic HER2DX risk score.

enrolled on the DAPHNe trial underwent pre-treatment research biopsy. RNA was extracted from tissue. HER2DX assay was evaluated centrally.

and multivariable logistic regression analyses were used to investigate the association of each nterest with pCR. Factors found to be significant in the univariable model were incorporated into riable model.

RESULTS-1: Description of the DAPHNe trial HER2DX cohort

gram: Patients enrolled in the overall DAPHNe who were evaluable for HER2DX testing (N=80).

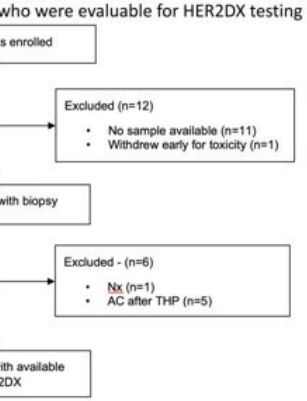


Table: Comparison of the HER2DX assay population to the overall trial population. The overall pCR rate among the HER2DX cohort was 60.0%.

	HER2DX sub-population		Original trial population	
	N	%	N	%
N	80	-	98	-
Age (mean and range)	50.3 (26-78)			49.5 (24-78)
Clinical tumor stage				
cT1	15	18.7%	18	18.4%
cT2-3	65	81.3%	80	81.6%
Clinical nodal stage				
cN0	52	65.0%	65	66.3%
cN1-3	28	35.0%	33	36.7%
Pathological response (breast and axilla)				
pCR	48	60.0%	55	56.7%
Residual disease	32	40.0%	42	43.3%
Hormone receptor status				
Positive	56	70.0%	65	66.3%
Negative	24	30.0%	33	33.7%

- HER2DX pCR score was predictive of pCR in HER2+ breast cancer patients treated with neoadjuvant THP.
- HER2DX pCR score predicted pCR with high accuracy in the overall population, HR+ sub-population, and HR- sub-population.
- In a multivariable model incorporating clinico-pathologic variables (eg HR status, HER2 IHC status) and established gene expression-based classifiers (eg HER2-enriched subtype by PAM50), HER2DX pCR score was the only significant predictor of pCR status.

Dana-Farber Cancer Institute

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Poster ID P1-04-05

HARVARD MEDICAL SCHOOL

RESULTS-2: HER2DX pCR score and risk score distribution in DAPHNe

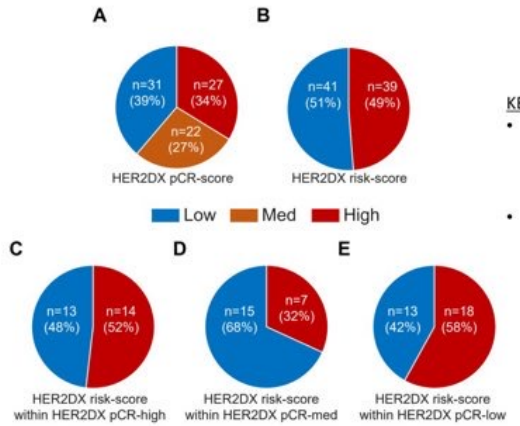


Figure: (A) HER2DX pCR score groups; **(B)** HER2DX risk score groups; **(C-E)** HER2DX risk score groups within each pCR score category.

KEY POINTS:

- Correlation between the HER2DX pCR score and risk score was weak (Pearson coefficient = -0.12).
- There have been no breast cancer recurrences in the DAPHNe trial cohort (with 19.1 mos median of follow-up), so HER2DX risk score performance could not be assessed.

RESULTS-3: Performance of the HER2DX pCR score for pCR pre

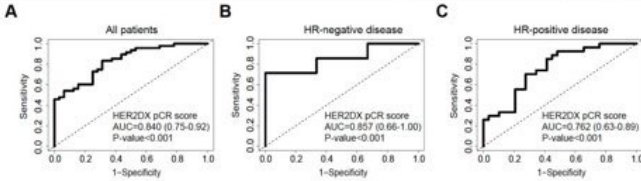


Figure: Receiver operating characteristic curve analysis of HER2DX pCR score among all patients **(A)**, HR-negative patients **(B)**, and HR-positive patients **(C)**.

KEY POINTS:

- The pCR rates in the HER2DX pCR score high, medium, and low groups were 92.6%, 63.6% respectively (OR 30.6 for comparison of high versus low groups, p<0.001).
- In univariable analysis there were multiple significant predictors of pCR status, including H score, HER2DX ERBB2 score, HER2-enriched status by PAM50, HER2 IHC status, and HR sta
- In multivariable analysis, HER2DX pCR score was the only significant predictor of pCR statu

			Univariable			Multivariable		
	N	pCR rate	OR	95% CI	p-value	OR	95% CI	p
HER2DX pCR score (continuous variable)	80	-	1.05	1.03-1.08	<0.001	1.03	1.00-1.07	
HER2DX pCR score groups								
Low	31	29.0%	1	-	-	-	-	
Med	22	63.6%	4.3	1.34	0.014			
High	27	92.6%	30.6	6.00-156.90	<0.001	-	-	
HER2DX ERBB2 score (continuous variable)	80	-	1.05	1.02-1.08	<0.001	1.03	0.99-1.06	
HER2DX ERBB2 mRNA score								
Low	9	44.4%	1	-	-	-	-	
Med	12	16.7%	0.25	0.03-1.86	0.176	-	-	
High	59	71.2%	3.09	0.74-12-91	0.122	-	-	
Clinical tumor stage								
cT1	15	80.0%	1	-	-	-	-	
cT2-3	65	55.4%	0.31	0.08-1.20	0.091	-	-	
Clinical nodal stage								
cN-negative	52	59.6%	1	-	-	-	-	
cN-positive	28	60.7%	1.05	0.41-2.68	0.924	-	-	
PAM50 HER2-enriched								
Non-HER2-enriched	34	35.3%	1	-	-	1	-	
HER2-enriched	46	78.3%	6.6	2.45-17.81	<0.001	1.96	0.53-7.17	
HER2 IHC status								
2+	10	30.0%	1	-	-	1	-	
3+	68	66.2%	4.57	1.08-19.32	0.0391	1.14	0.17-7.85	
Hormone receptor status								
Positive	56	48.2%	1	-	-	1	-	
Negative	24	87.5%	7.52	2.01-28.10	0.003	1.78	0.29-11.01	

Table: Univariable and multivariable predictors of pCR in DAPHNe.

FUNDING AND ACKNOWLEDGEMENTS

Funded by:

- Conquer Cancer/BCRF Career Development Award to A. Waks MD
- Breast Cancer Research Foundation grant to E. Winer MD
- Reveal Genomics
- Terri Brodeur Breast Cancer Foundation grant to A. Waks MD
- Susan G. Komen for the Cure grant to E. Mittendorf MD

We acknowledge and thank all the patients who participated in the DAPHNe trial

Current ASCO guideline

CLINICAL QUESTION 5

What neoadjuvant treatment is recommended for patients with HER2-positive disease?

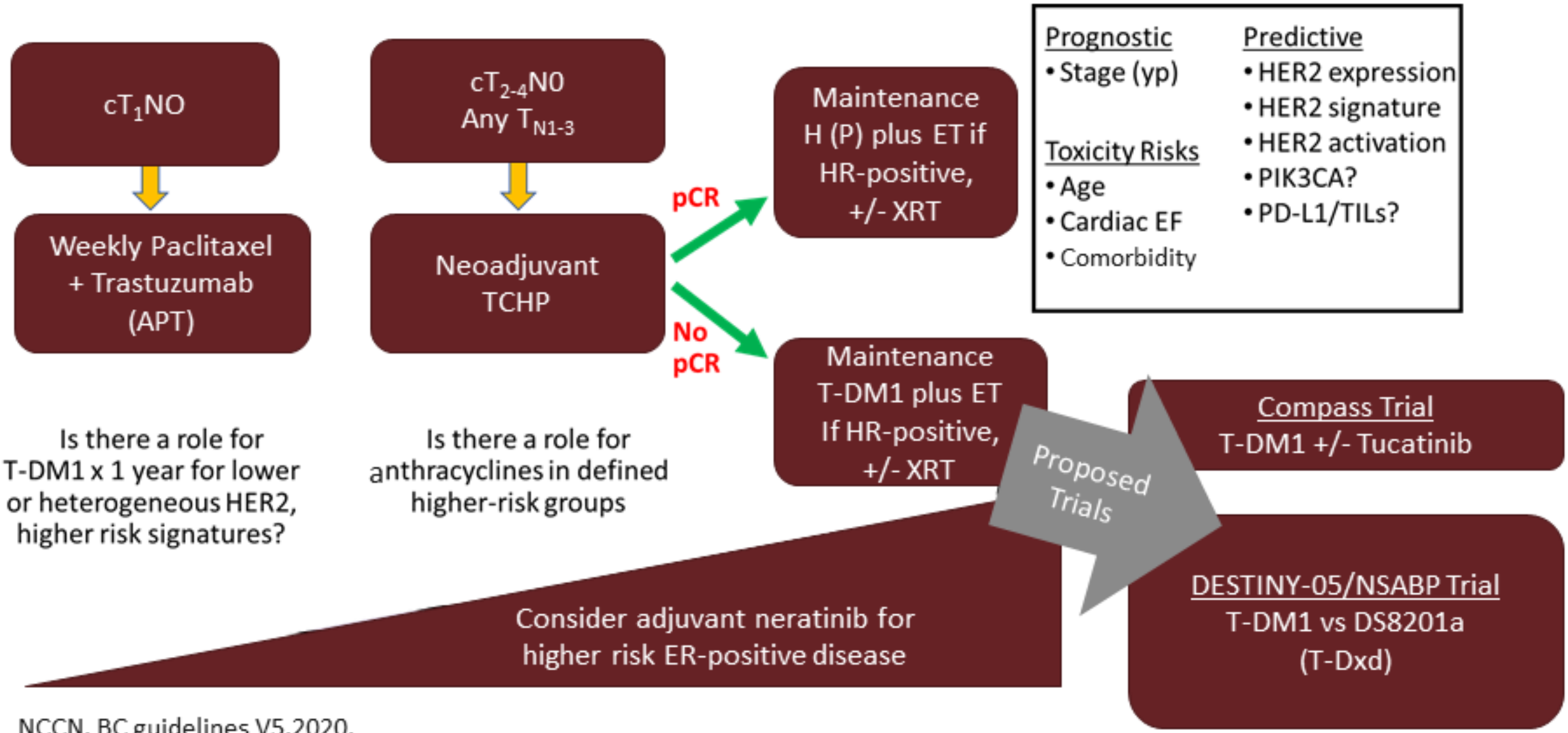
Recommendations

Recommendation 5.1. Patients with node-positive or high-risk node-negative, HER2-positive disease should be offered neoadjuvant therapy with an anthracycline and taxane or non–anthracycline-based regimen in combination with trastuzumab. Pertuzumab may be used with trastuzumab in the neoadjuvant setting (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 5.2. Patients with T1a N0 and T1b N0, HER2-positive disease should not be routinely offered neoadjuvant chemotherapy or anti-HER2 agents outside of a clinical trial (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

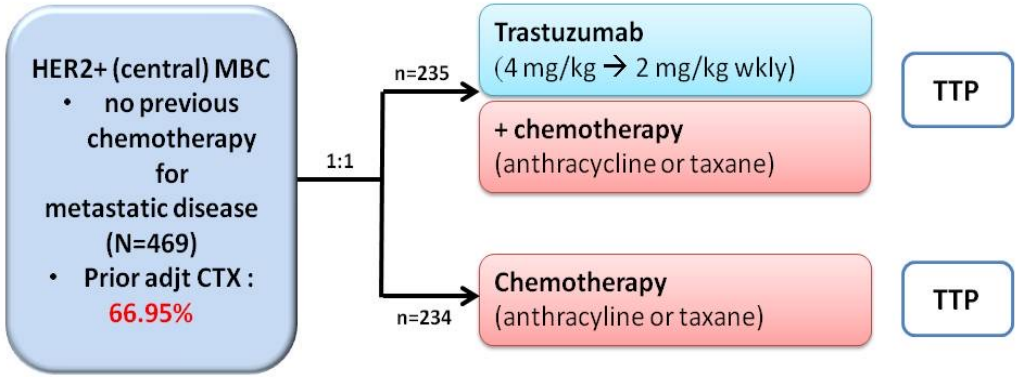
Strategies to Use Prognostic Outcomes in Real Time to Guide Therapy

Early Stage HER2-Positive BC



NCCN. BC guidelines V5.2020.

1st Line Trastuzumab for MBC (2000)



	Trastuzumab+chemotherapy	Chemotherapy	P-value
ORR	50%	32%	<0.001
TTP	7.4 months	4.6 months	<0.001
OS	25.1 months	20.3 months	0.046

TTP, time to disease progression; ORR, objective response rate; OS, overall survival; MBC, metastatic breast cancer; adjt CTX, adjuvant chemotherap

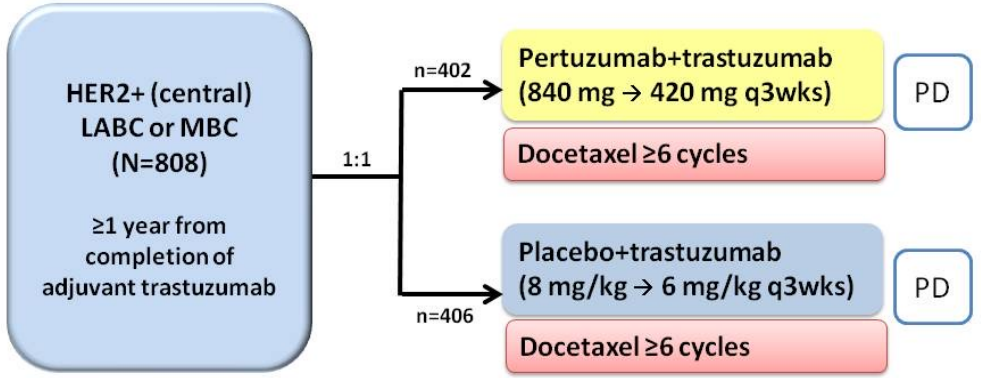
Most significant adverse events:

Trastuzumab+anthracycline: cardiac dysfunction (27%) compared to 13% in Anthracycline alone

2/3 patients assigned to chemotherapy alone crossed over upon disease progression

Slamon et al. NEJM 2001; 344(11):783-92.

1st line Pertuzumab + Trastuzumab (CLEOPATRA)



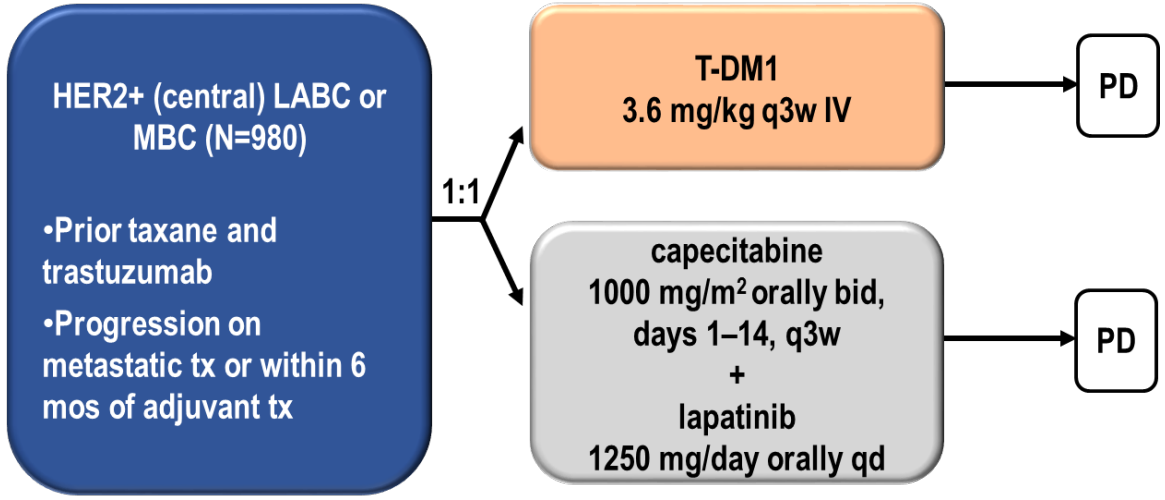
Important points:

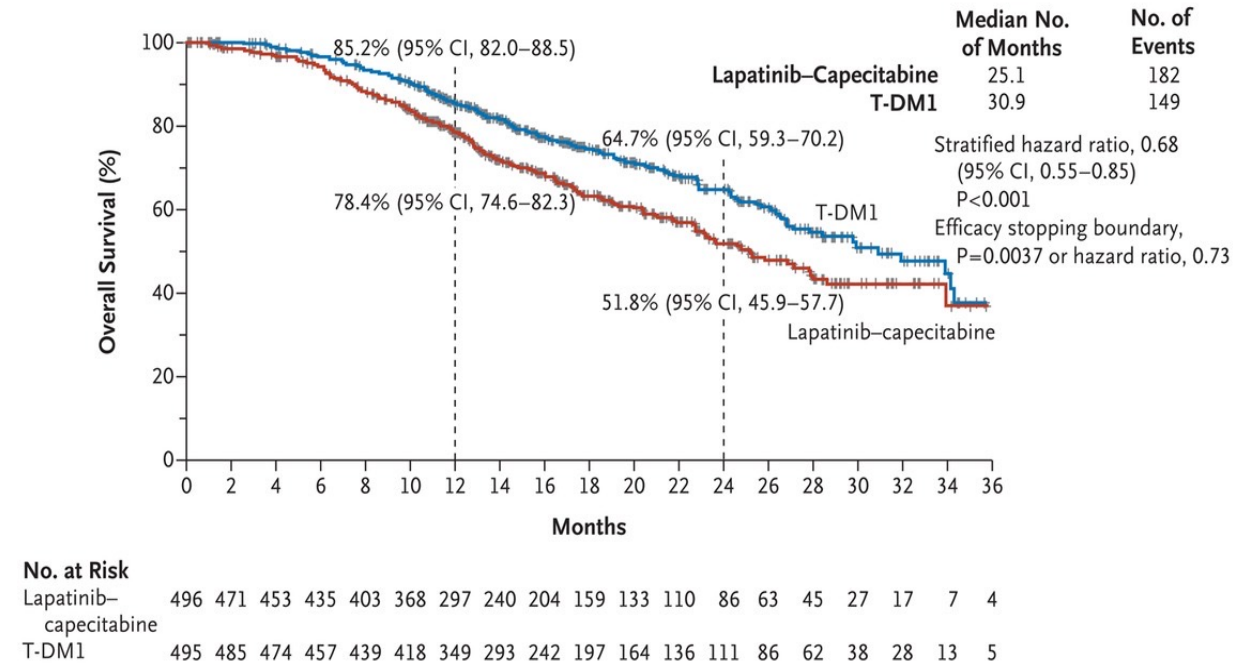
- ~ 90% of patients did not receive trastuzumab in (neo) adjuvant setting
- ~ 50% of patients did not receive any prior (neo) adjuvant chemotherapy
- Patients with CNS metastases were excluded

Baselga et al. N Engl J Med 2012;366:109.

1st Line Trastuzumab for MBC

EMILIA: T-DM1 vs lapatinib + capecitabine



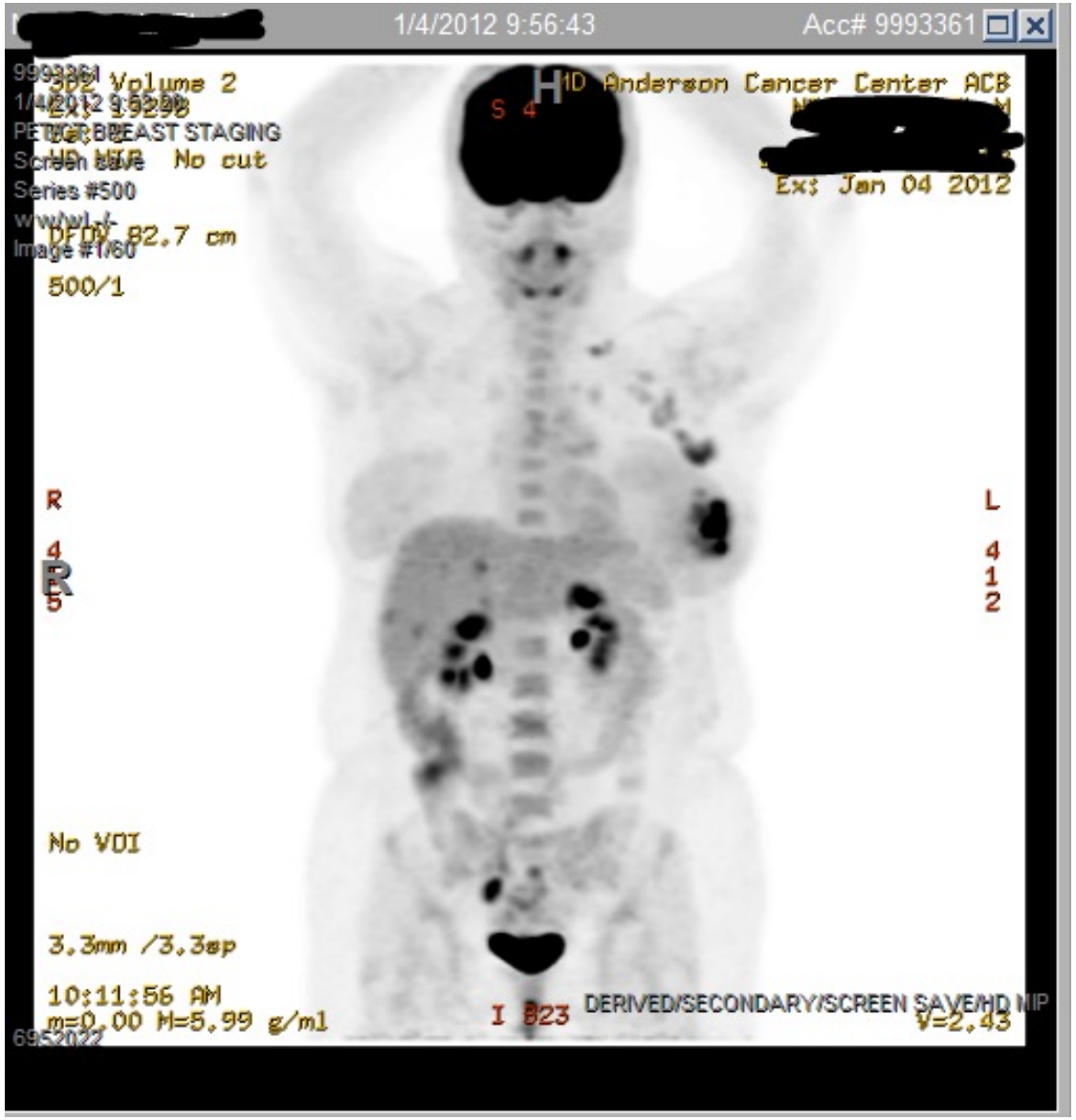


- **Better PFS** vs lapatinib plus capecitabine (median, 10 vs 6 months; HR 0.65, 95% CI 0.55-0.77);

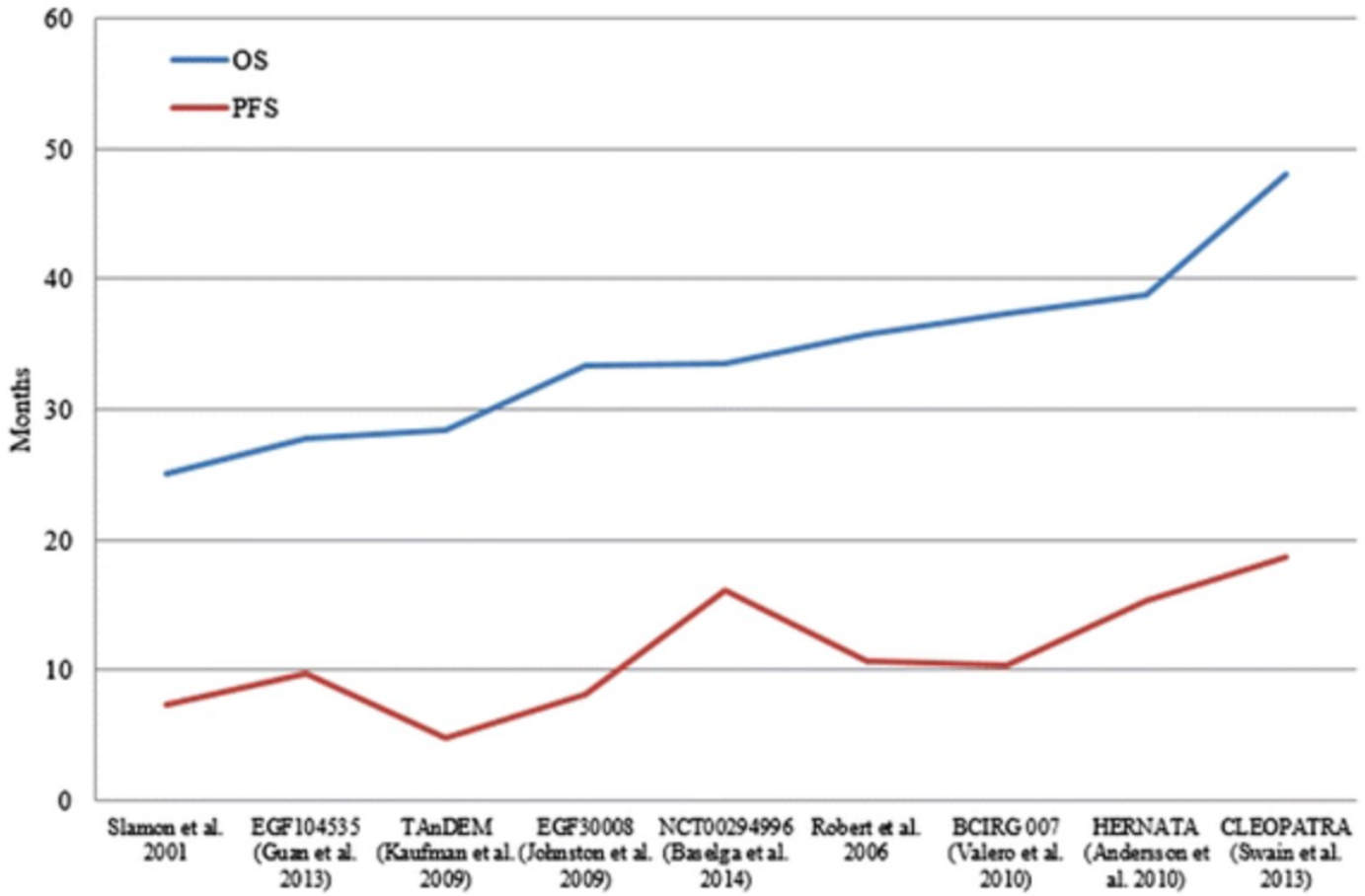
- **Better OS** (median, 31 vs 25 months; HR 0.68, 95% CI 0.55-0.85), maintained with longer follow-up (>40 months) (crossover allowed).

Verma et al. NEJM 2012

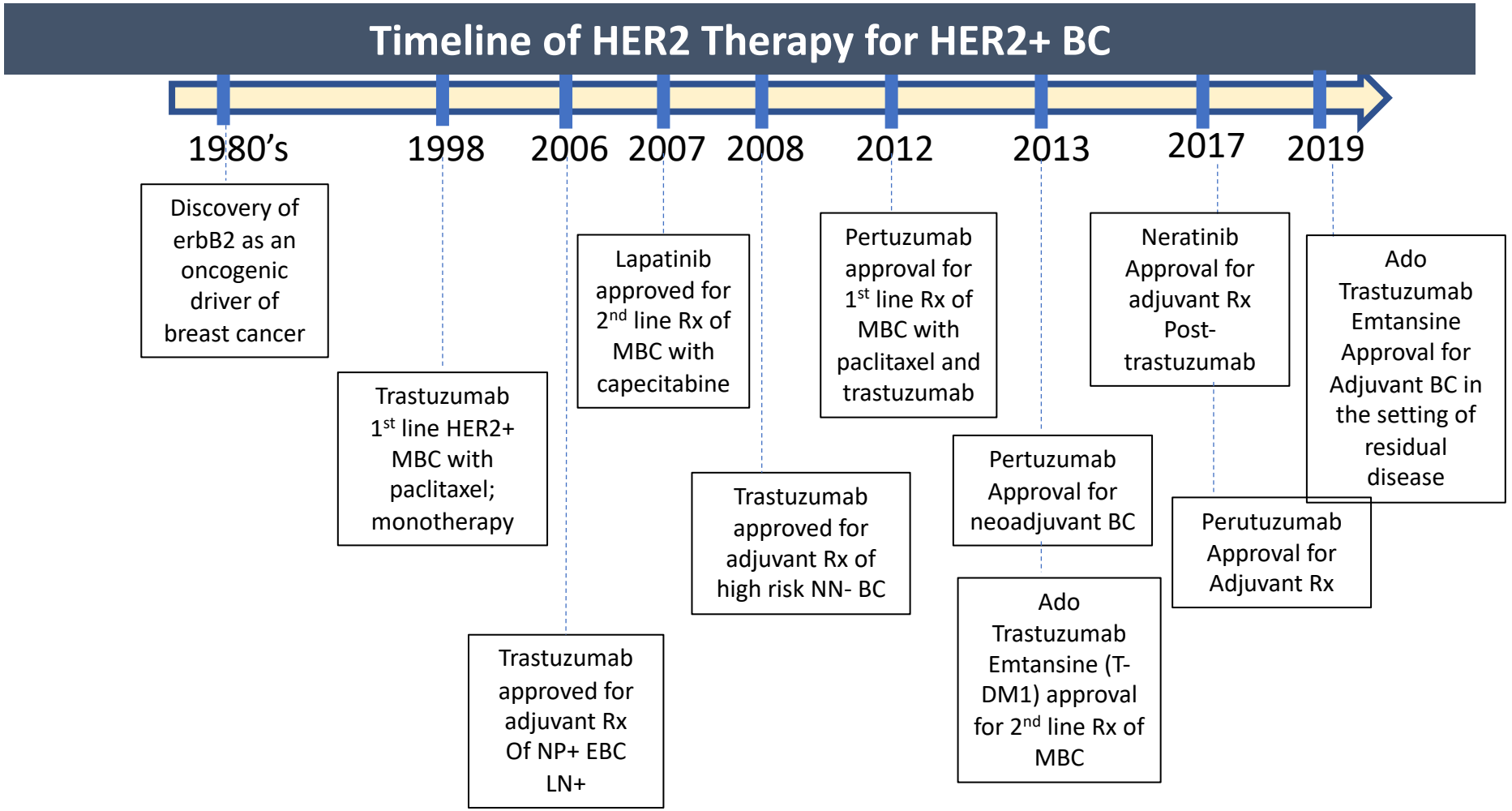
Stage IV triple + breast cancer
She received TDM-1 plus minus pertuzumab (2012)



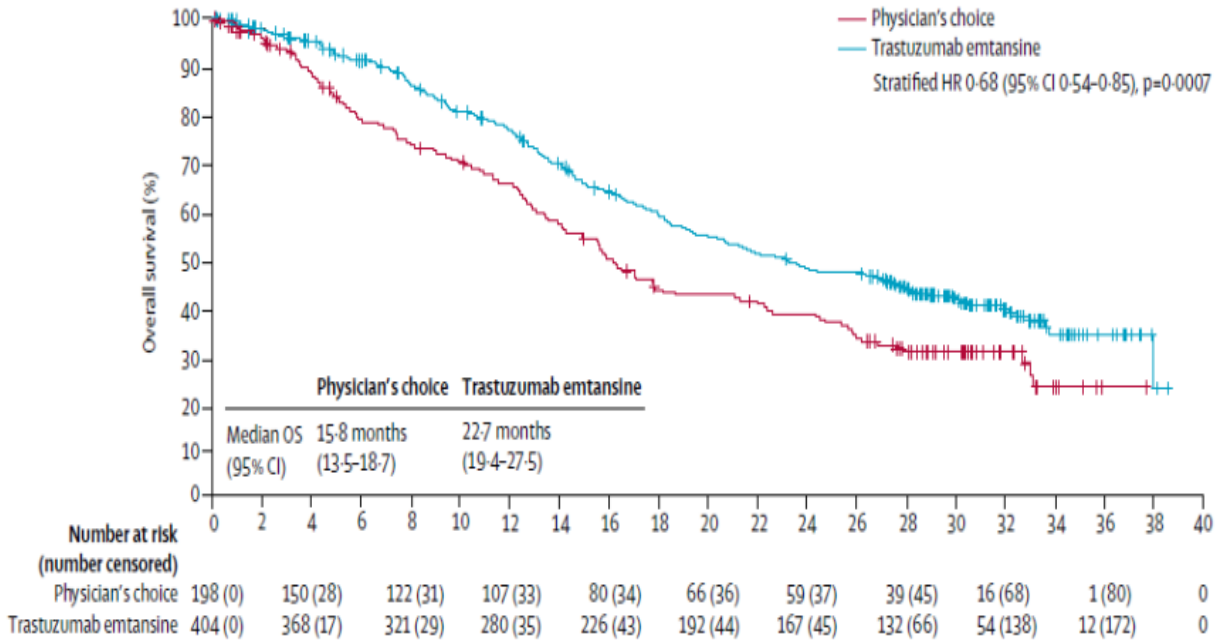
The benefit of HER2 targeted therapies on OS of patients with metastatic HER2+ BC

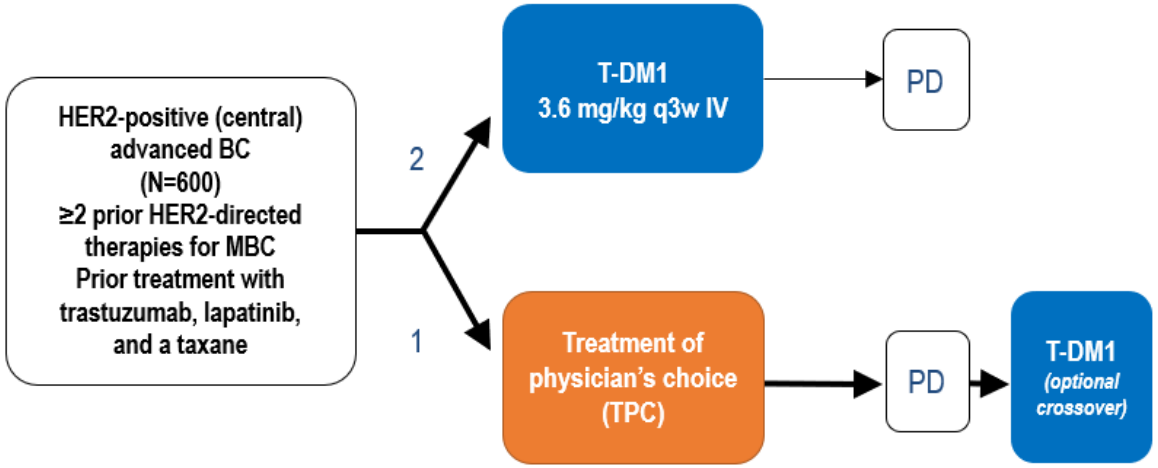


Mendes D. et al. Br Ca Res 2015


Timeline of HER2 Therapy for HER2+ BC
1980's
1998
2006
2007
2008
2012
2013
2017
2019
Discovery of erbB2 as an oncogenic driver of breast cancer
Trastuzumab 1st line HER2+ MBC with paclitaxel; monotherapy
Trastuzumab approved for adjuvant Rx Of NP+ EBC LN+
Lapatinib approved for 2nd line Rx of MBC with capecitabine
Trastuzumab approved for adjuvant Rx of high risk NN- BC
Pertuzumab approval for 1st line Rx of MBC with paclitaxel and trastuzumab
Pertuzumab Approval for neoadjuvant BC
Ado Trastuzumab Emtansine (T-DM1) approval for 2nd line Rx of MBC
Neratinib Approval for adjuvant Rx Post-trastuzumab
Perutuzumab Approval for Adjuvant Rx
Ado Trastuzumab Emtansine Approval for Adjuvant BC in the setting of residual disease

TH3RESA: T-DM1 vs clinician's choice





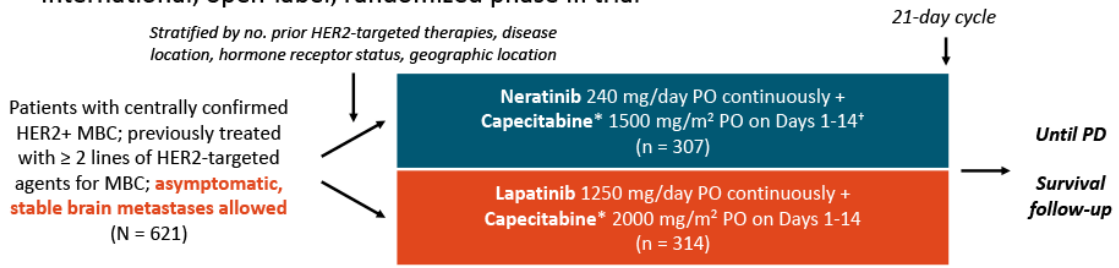
- **Better PFS**, (median, 6.2 vs 3.3 months; HR, 0.53, 95% CI 0.42-0.66).
- **Better OS**, (median, 22.7 vs 15.8 months; HR 0.68, 95% CI 0.54-0.85)

Krop IE et al, Lancet Oncol. 2017

NALA study

NALA: Neratinib/Cape vs Lapatinib/Cape in HER2+ MBC With ≥ 2 Prior Lines of HER2-Targeted Therapy

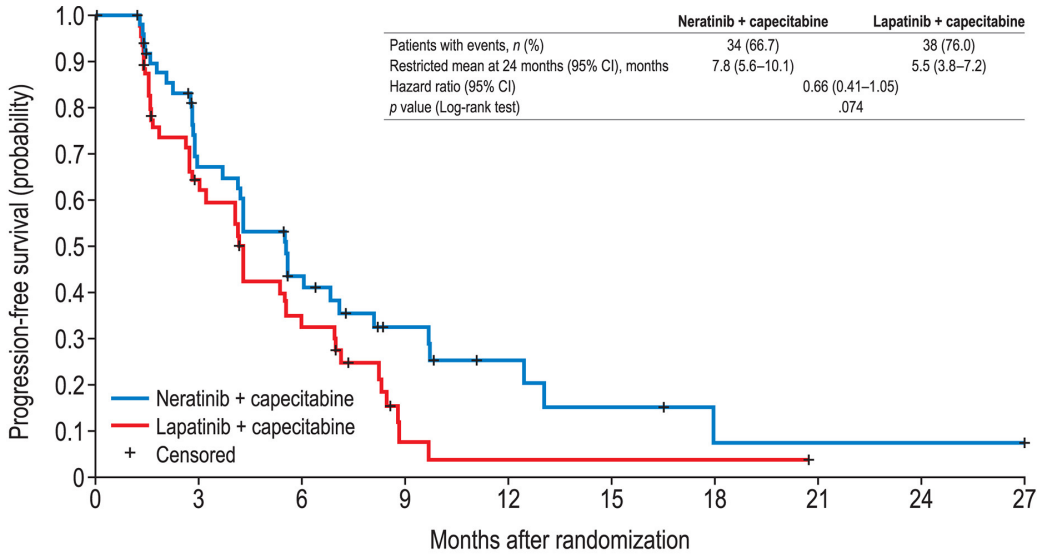
- International, open-label, randomized phase III trial



*BID in 2 evenly divided doses. †Loperamide administered at 4 mg with first neratinib dose followed by 2 mg Q4H for first 3 days, followed by 2 mg every 6-8 hrs through end of cycle 1; as needed thereafter. No ET permitted.

- Coprimary endpoints: OS, PFS (centrally confirmed)
  - Study positive if either endpoint statistically significant (OS, $P < .04$; PFS, $P < .01$)
- Secondary endpoints: PFS (locally determined), ORR, DoR, CBR, time to intervention for CNS mets, safety, PRO

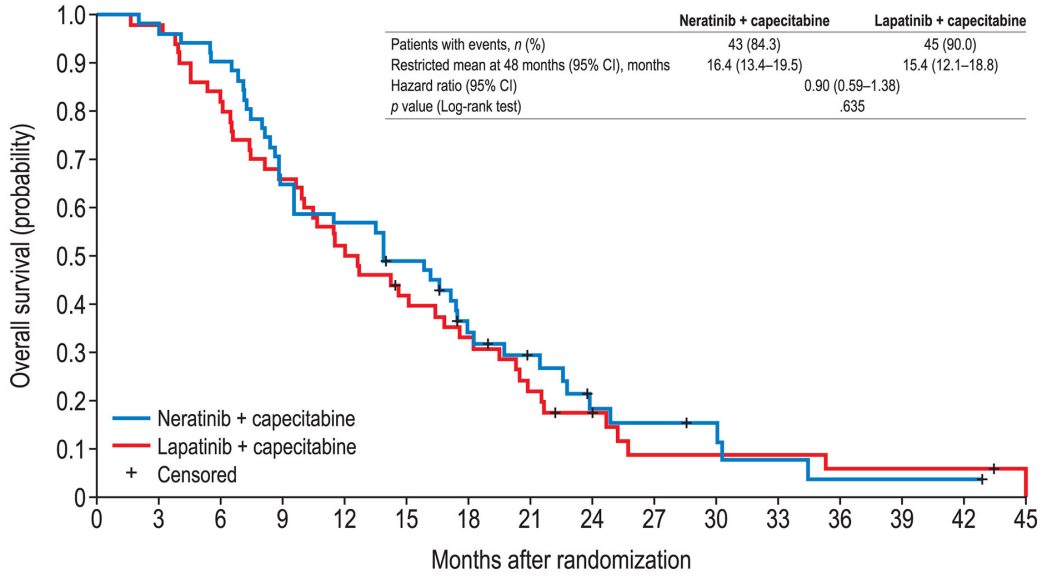
A



No. at risk

Neratinib + capecitabine	51	29	17	9	5	3	1	1	1	1
Lapatinib + capecitabine	50	27	13	2	1	1	1	0	0	0

B

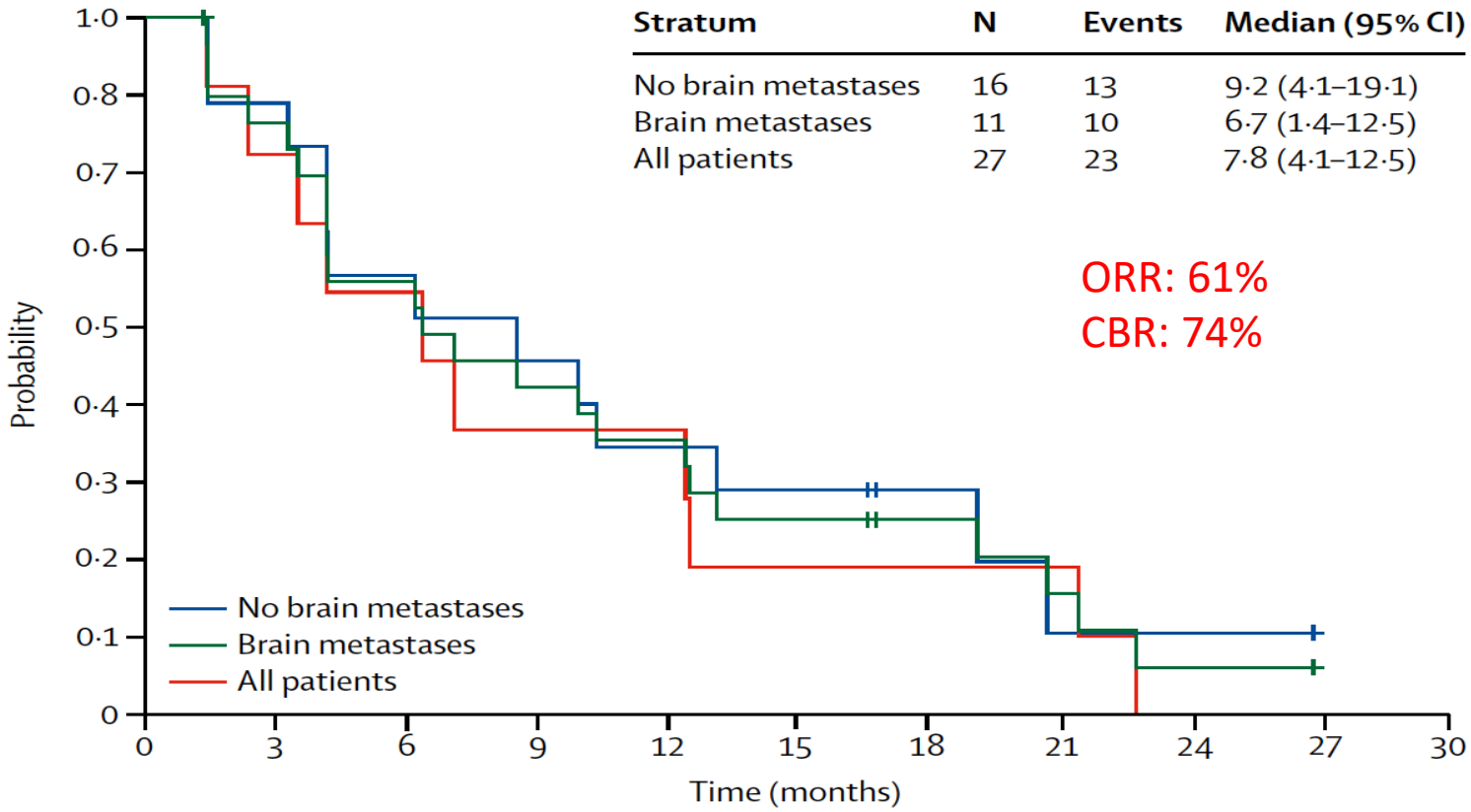


No. at risk

Neratinib + capecitabine	51	50	46	33	29	24	15	11	6	5	4	2	1	1	1	0
Lapatinib + capecitabine	50	49	42	33	26	19	15	10	7	3	3	3	2	2	2	1

Tucatinib (ONT-380) (Arry 380) Clinical Activity: Phase 1B combination trial with Trastuzumab and Capecitabine

Kaplan-Meier Plot of PFS in Tucatinib + Trastuzumab + Capecitabine Group



Stratum	N	Events	Median (95% CI)
No brain metastases	16	13	9·2 (4·1–19·1)
Brain metastases	11	10	6·7 (1·4–12·5)
All patients	27	23	7·8 (4·1–12·5)

ORR: 61%
CBR: 74%

Brain metastases	16	14	10	8	6	5	3	1	1	0	0
No brain metastases	11	8	6	4	4	2	2	2	0	0	0
All	27	22	16	12	10	7	5	3	1	0	0

Murthy RK. et al. Lancet Oncology 2018

HER2 CLIMB

Key Eligibility

- HER2+ breast carcinoma
- Previous treatment with a taxane, trastuzumab, pertuzumab, and T-DM1
- ECOG PS 0-1

Capecitabine + trastuzumab + tucatinib

Capecitabine + trastuzumab + placebo

Primary objectives

- PFS

Secondary objectives

- PFS (brain mets)
- OS
- ORR
- DOR
- CBR

Stratification

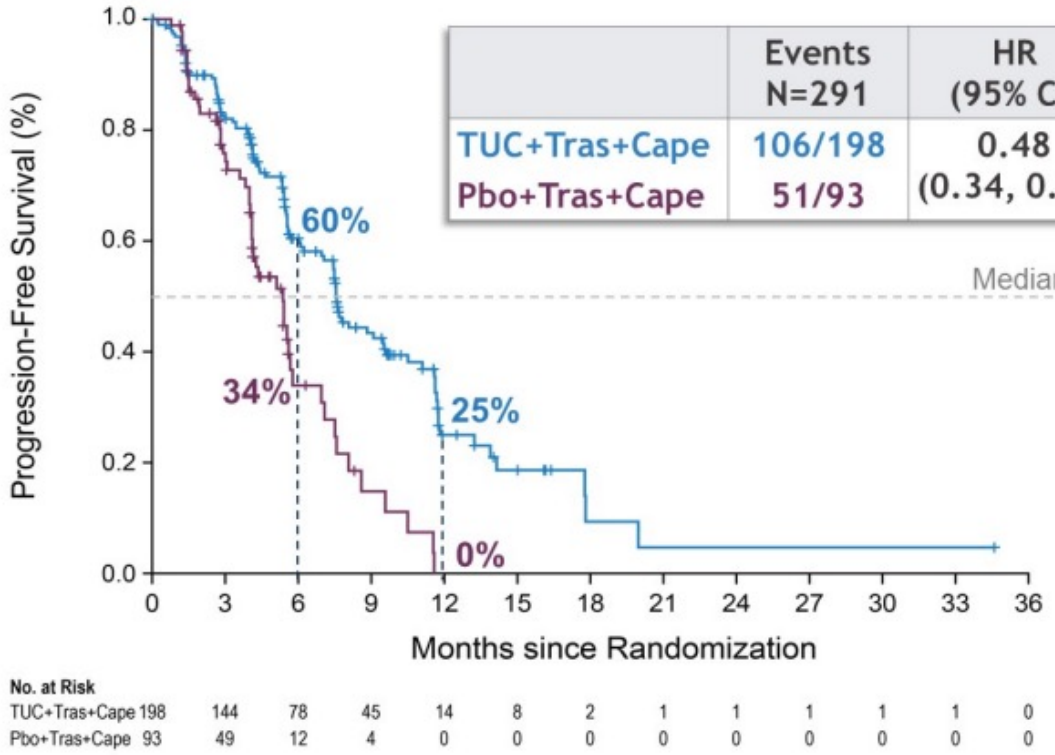
- History of brain metastases
- ECOG PS
- Region of the world

Study Drug	Dose	Treatment Period
Tucatinib	300 mg PO BID	Every 21 days
Capecitabine	1000 mg/m2 PO BID on Days 1–14	Every 21 days
Trastuzumab	C1 loading dose - 8 mg/kg IV C2+ 6 mg/kg IV	Every 21 days

HER2 Climb study

Progression-Free Survival* in Patients with Brain Metastases

Alpha-controlled secondary endpoint in the HER2CLIMB trial



	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	106/198	0.48 (0.34, 0.69)	<0.00001
Pbo+Tras+Cape	51/93		

Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

One-year PFS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
25% (17, 34)	0%

Median PFS (95% CI):	
7.6 months (6.2, 9.5)	5.4 months (4.1, 5.7)

Prespecified efficacy boundary for PFS-brain metastases (P=0.0080) was met at the first interim analysis.
Data cut off: Sep 4, 2019

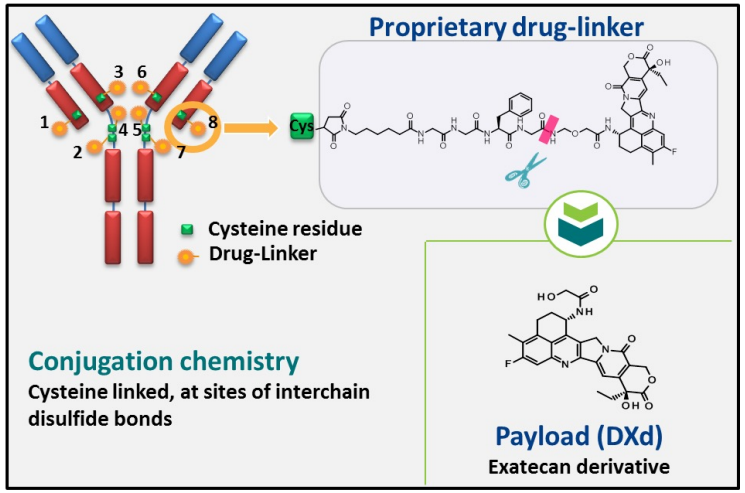
*PFS, defined as time from randomization to documented disease progression (assessed by blinded independent central review) or death from any cause. Analysis does not include patients with dural lesions only.

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

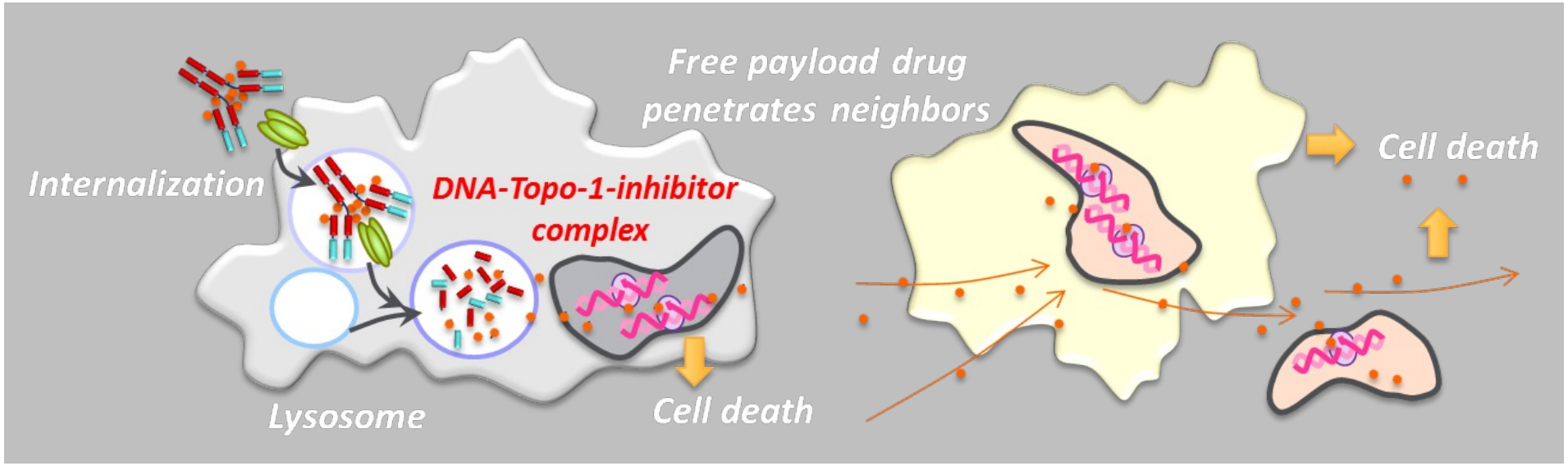
PRESENTED BY: Nancy Lin, nlin@partners.org

DS8201a: ADC (Topoisomerase 1 inhibitor)

Key features: Novel payload, high potency,, high DAR, short systemic half-life payload, bystander effect



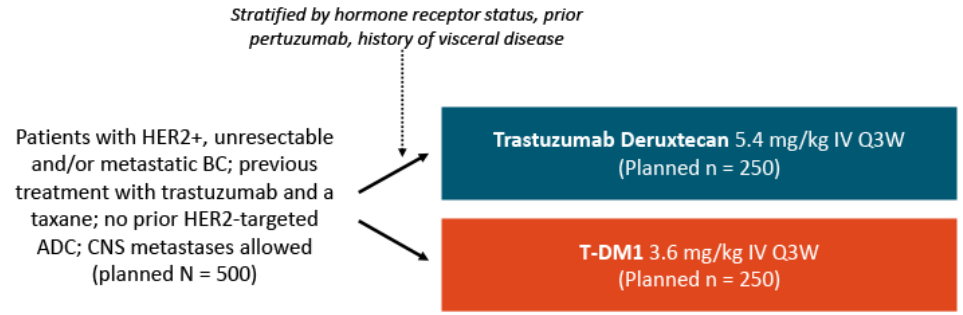
	DS-8201a	T-DM1
Antibody	Anti-HER2 Ab	Trastuzumab
MOA	Topoisomerase I Bystander effect*	Tubulin
Drug-to-antibody ratio	7-8	3.5**



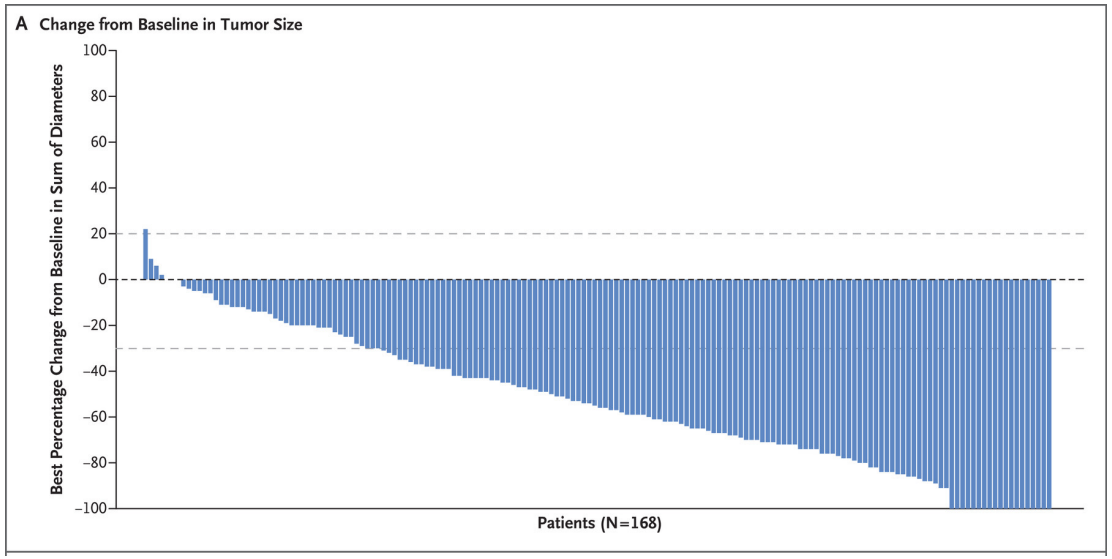
Takegawa N., et al. Int J Cancer 2017

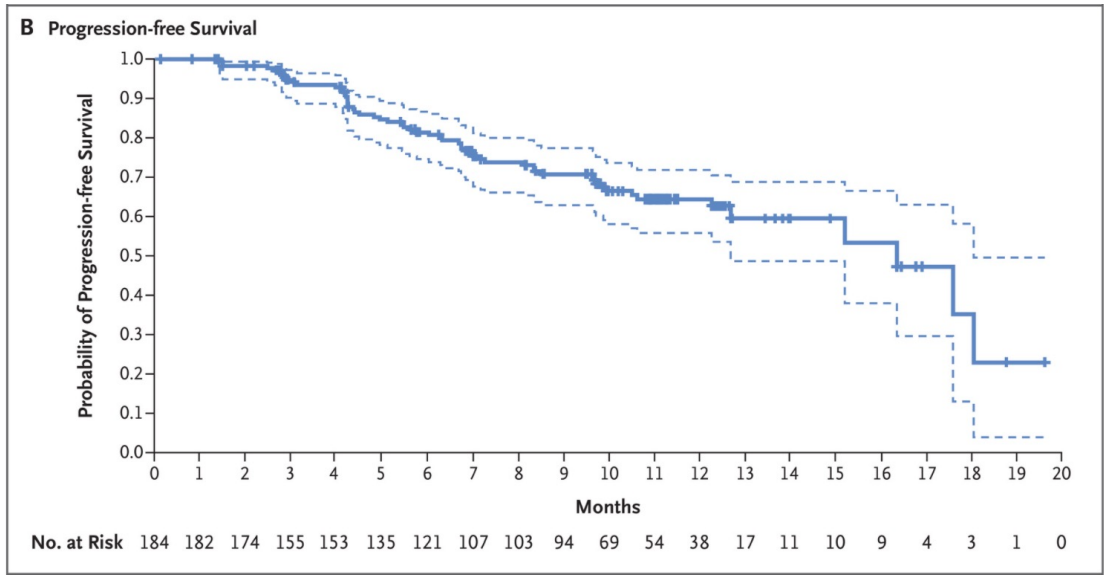
DESTINY Breast 01

trastuzumab deruxtecan (T-DXd) showed unprecedented response rate (61%) and median PFS (19 months) despite patients being heavily pretreated (median 6 lines) ->a randomized trial, DESTINY-Breast03 phase 3, comparing T-DXd to T-DM1 in patients progressing to trastuzumab and taxanes



- Primary endpoint: PFS (RECIST v 1.1 by BICR)
- Secondary endpoints: OS, ORR, DoR, CBR, PFS (investigator assessment)





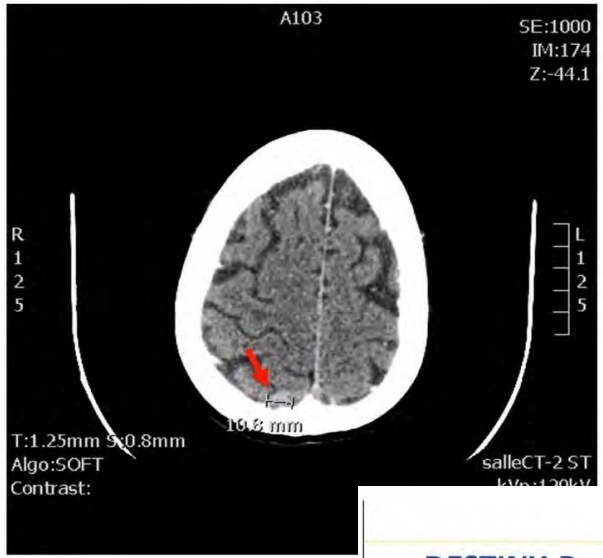
Modi S et al NEJM 2020

DESTINY-Breast01

Case Report: 55% Regression of a Metastatic Brain Lesion

Baseline scan

- 48-year-old woman with HER2-positive (IHC 3+)/HR-negative metastatic BC
- 17 prior lines of treatment, including T-DM1, pertuzumab, trastuzumab, and lapatinib
- Prior brain lesion treatment included:
  - WBRT 5 years prior to enrollment
  - Stereotactic radiosurgery 3 years prior to enrollment
- Target lesions at baseline in brain, lymph nodes, and retroperitoneum
- Nontarget lesions in lung, pancreas, bone, and axillary lymph node



WBRT, whole-brain radiotherapy.

DESTINY-Breast01

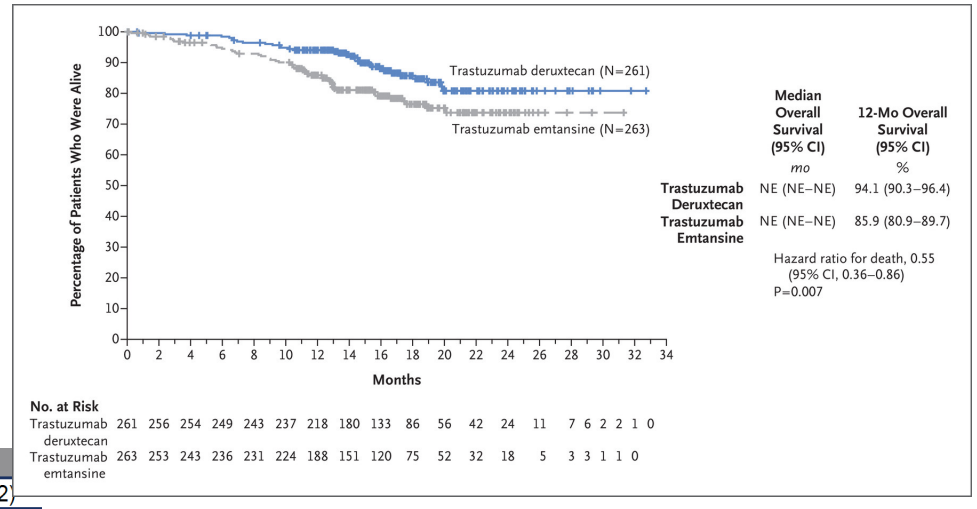
CNS Subgroup Conclusions

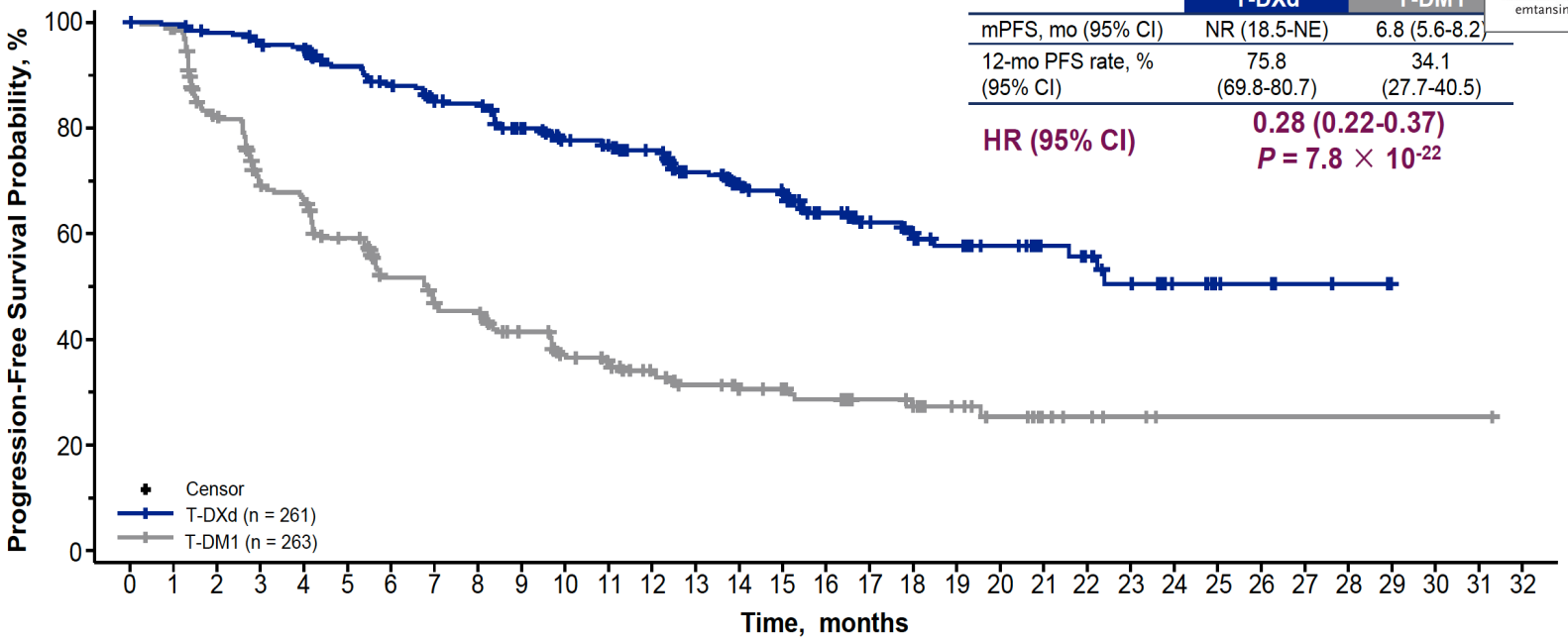
- T-DXd demonstrated efficacy in patients who had stable, treated brain metastases at baseline that was similar to its efficacy in the overall population
  - Median DOR, **16.9 months**
  - Median PFS, **18.1 months**
  - Progression in the brain was noted in only 8% of patients. Among 40 patients without brain lesions at baseline who had progressive disease, only 2 had new brain lesions and both were late events
- The safety profile in the CNS subgroup is consistent with the non-CNS subgroup and overall population
- Phase 3 studies in HER2-expressing BC are ongoing
  - DESTINY-Breast02: vs standard of care after T-DM1 (HER2 positive)
  - DESTINY-Breast03: vs T-DM1 (HER2 positive)
  - DESTINY-Breast04: vs chemotherapy (HER2 low[a])

[a] IHC 2+/ISH– or IHC 1+.

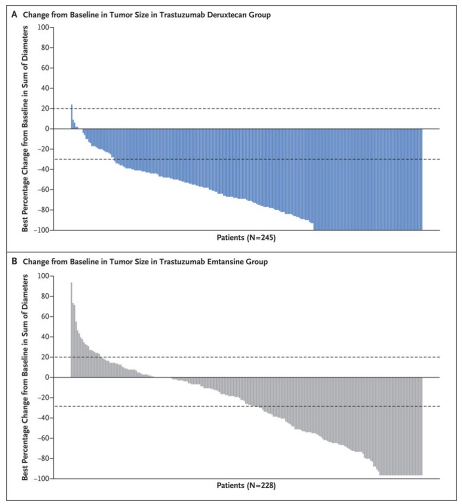
Destiny Breast 03-PFS

OS difference after 16mo





	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
P	7.8×10^{-22}	



ORR 79% vs 34%

Cortes J et al. ESMO Congress 2021

Destiny Breast 03 - toxicities

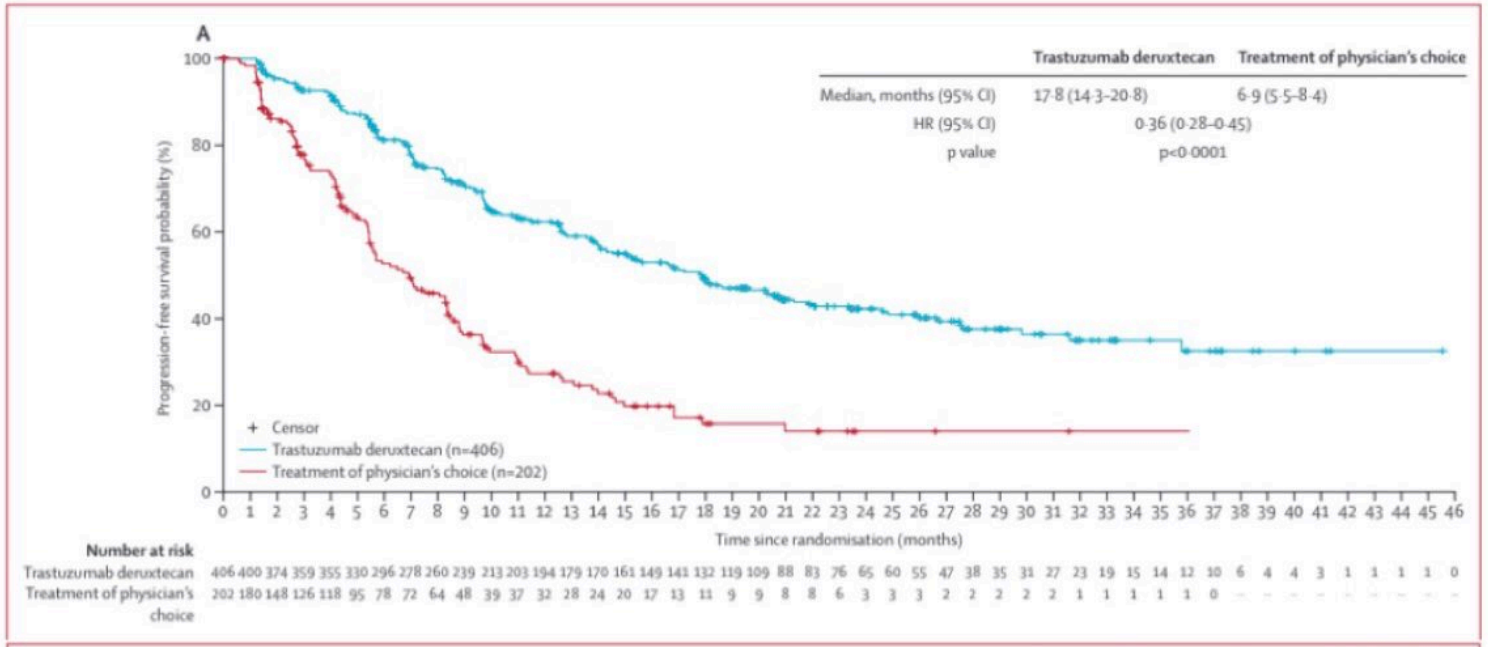
10.5% developed **interstitial lung disease**
Neutropenia
Alopecia
GI side effects (nausea, vomiting)
No grade 4/5 AE reported

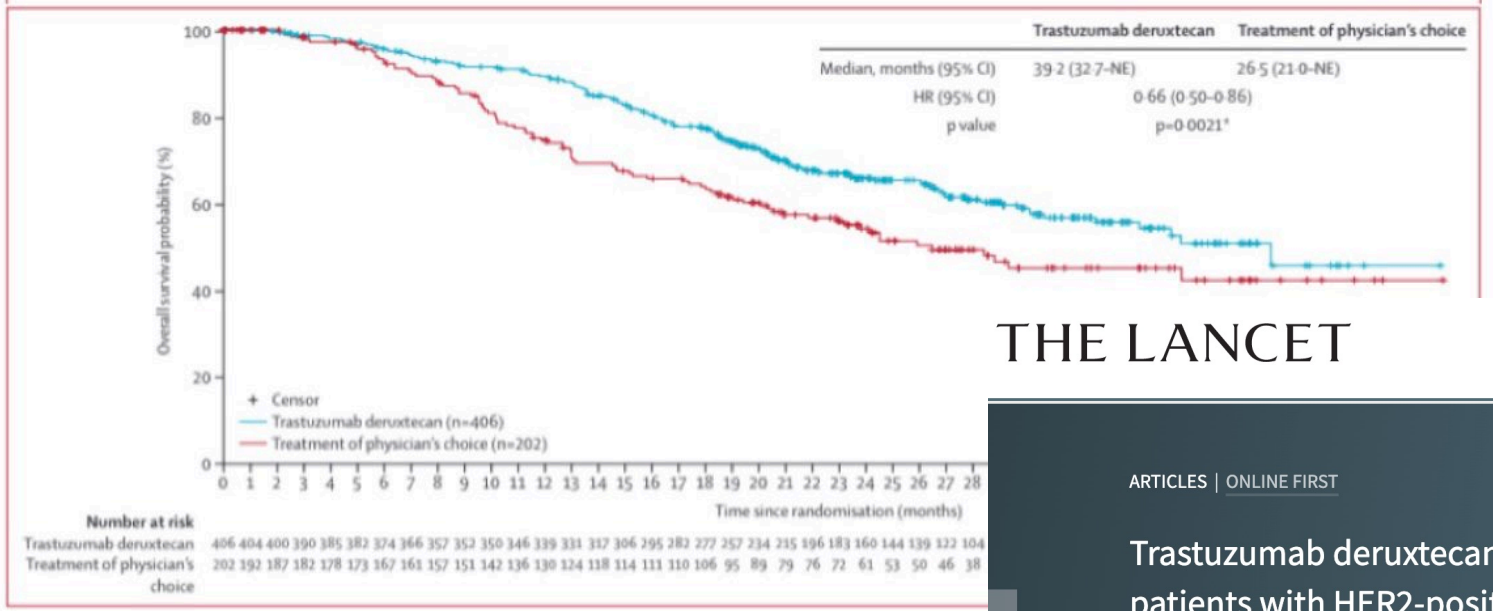
Thrombocytopenia, LFT abnormalities more common with T-DM1

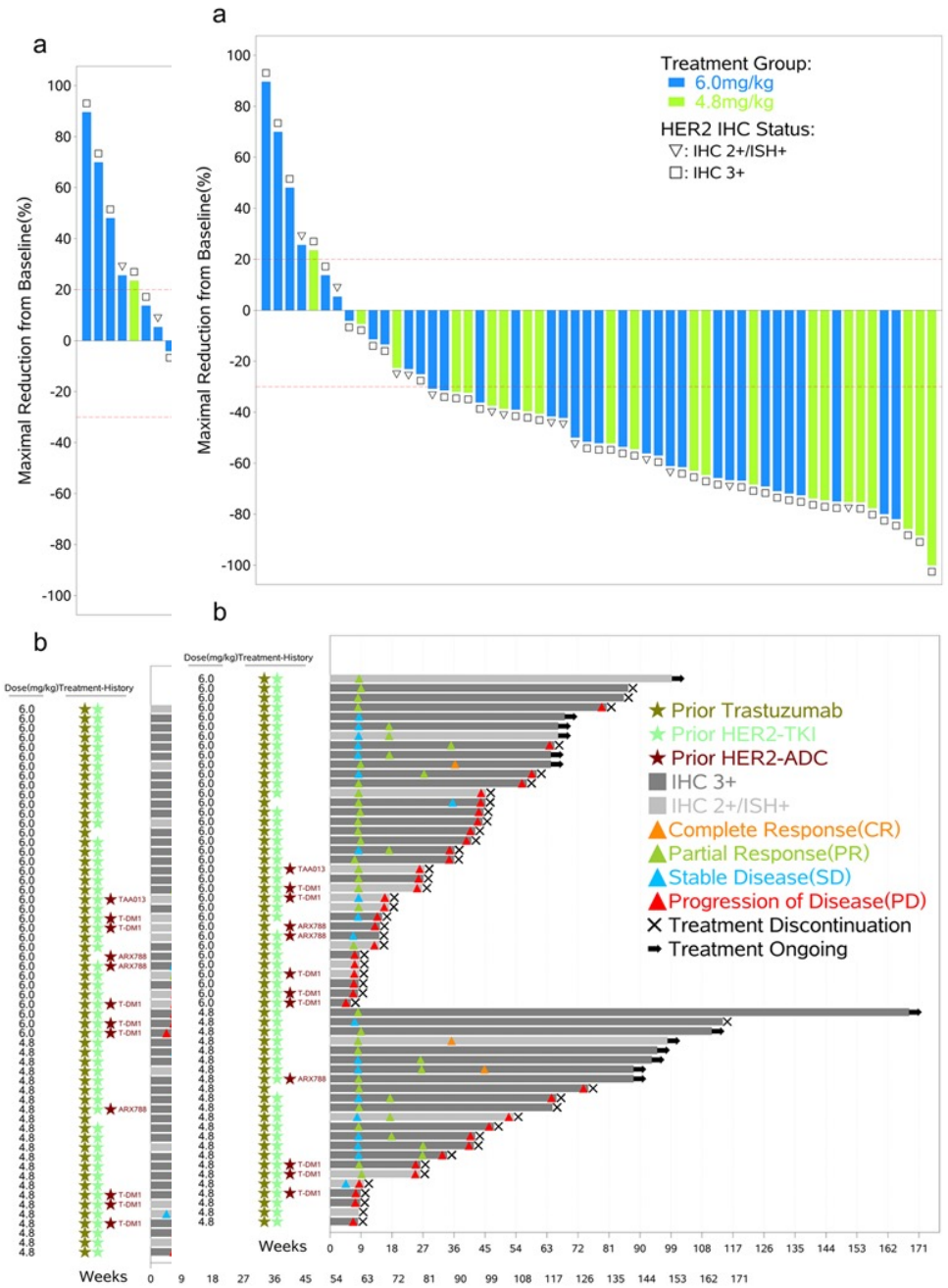
Table 2. Most Common Drug-Related Adverse Events and Adjudicated Drug-Related Interstitial Lung Disease or Pneumonitis.

Event	Trastuzumab Deruxtecan (N=257)		Trastuzumab Emtansine (N=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

Cortes J et al. NEJM 2022







More ADCs are coming

npj | breast cancer

www.nature.com/npjbcancer

ARTICLE OPEN

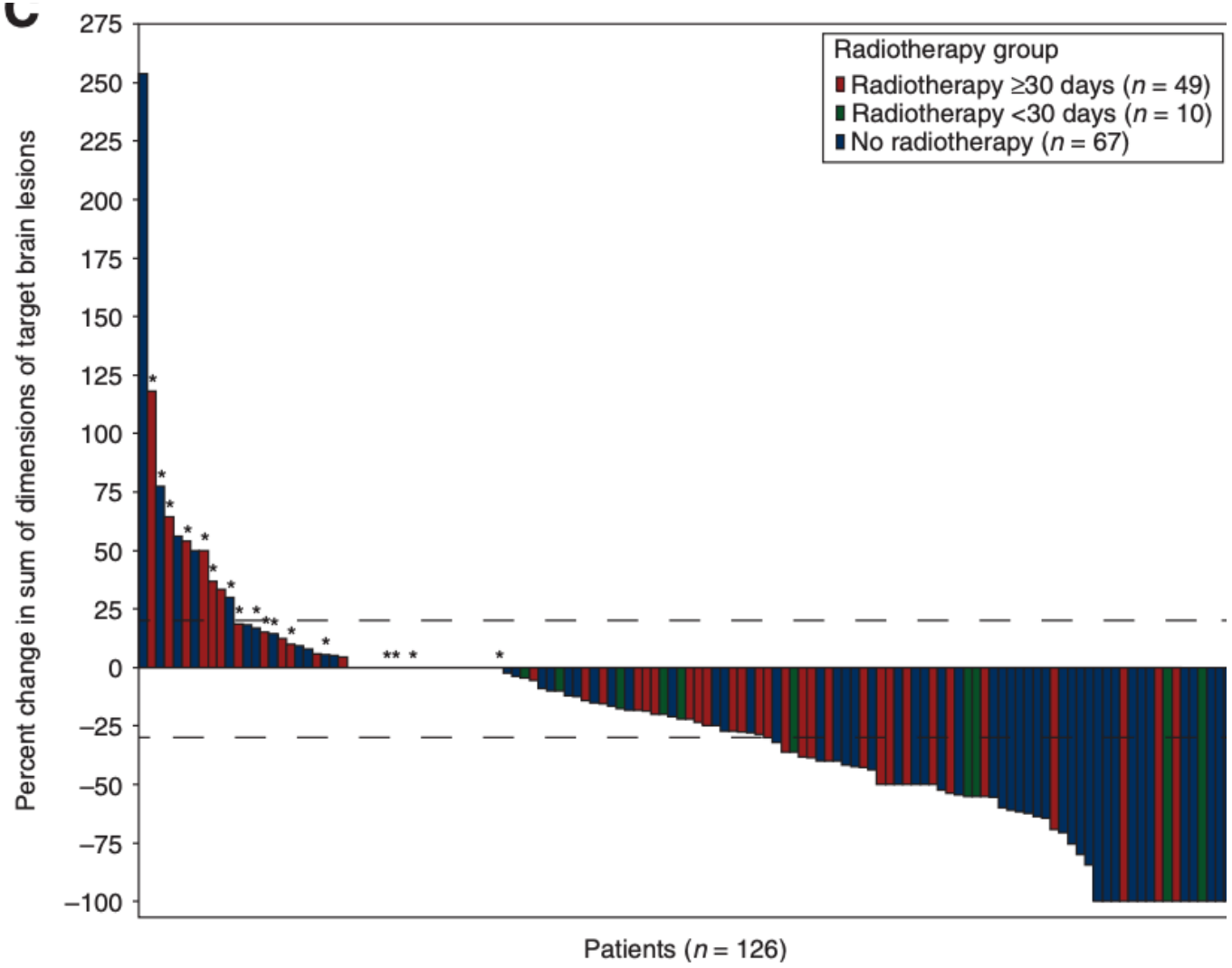
Check for updates

Phase I study of A166, an antibody–drug conjugate in advanced HER2-expressing solid tumours

Jian Zhang[1,2,8], Rujiao Liu[1,2,8], Shuiping Gao[1,2], Wenhua Li[1,3], Yang Chen[1,2], Yanchun Meng[1,2], Chang Liu[1], Wenyue Jin[1], Junyan Wu[4], Ying Wang[4], Yanrong Hao[5], Shuli Yi[6], Yan Qing[6], Junyou Ge[6] and Xichun Hu[1,7]✉

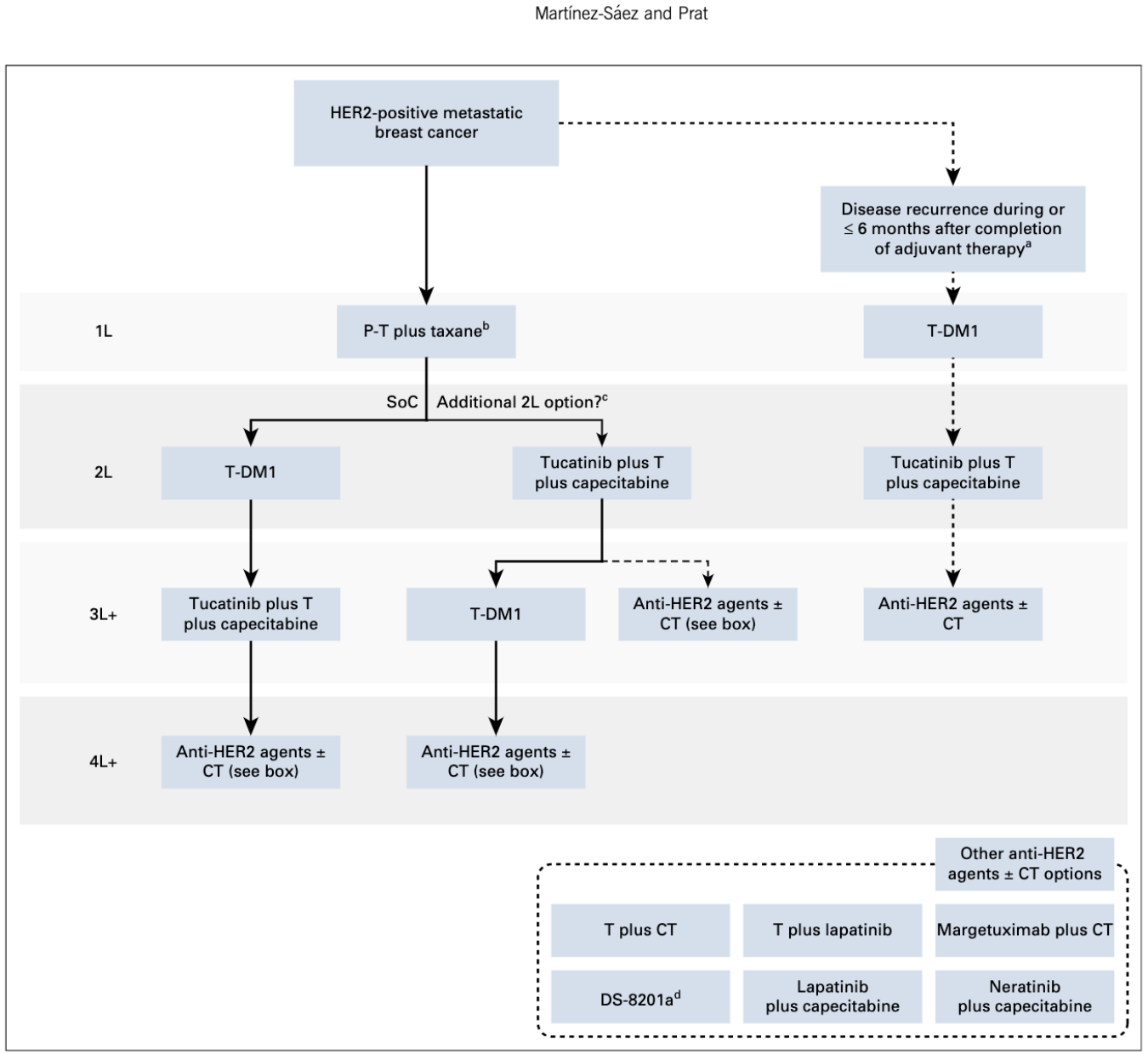
CNS mets and T-DxD (KAMILLA)

Among 126 patients,
ORR 21%
median PFS 5.5 months
median OS 18.9 months



Montemurro F et al. Ann Onc 2020

Current recommended mHER2 therapy – in 2022



- But, also dependent on the changes in NAT and AT
- Novel combination with other ADC
- ADC/Ab + TKI still in question
- Combination with immunotherapy has not shown clear benefit

O. Martínez-Sáez, A. Prat
JCO Oncology Practice (2021)

Strategies for Sequential Therapy
Advanced Stage/Metastatic HER2-Positive BC (cont)

Baylor College of Medicine

Later-line options

Clinical trials should be explored

- Trastuzumab + lapatinib
- Capecitabine + neratinib
- Capecitabine + lapatinib
- Trastuzumab (+/-P) + vinorelbine
- Trastuzumab + capecitabine

Trastuzumab with other cytotoxics (gemcitabine, eribulin, liposomal doxorubicin, nab-paclitaxel, ixabepilone)

Emerging Questions

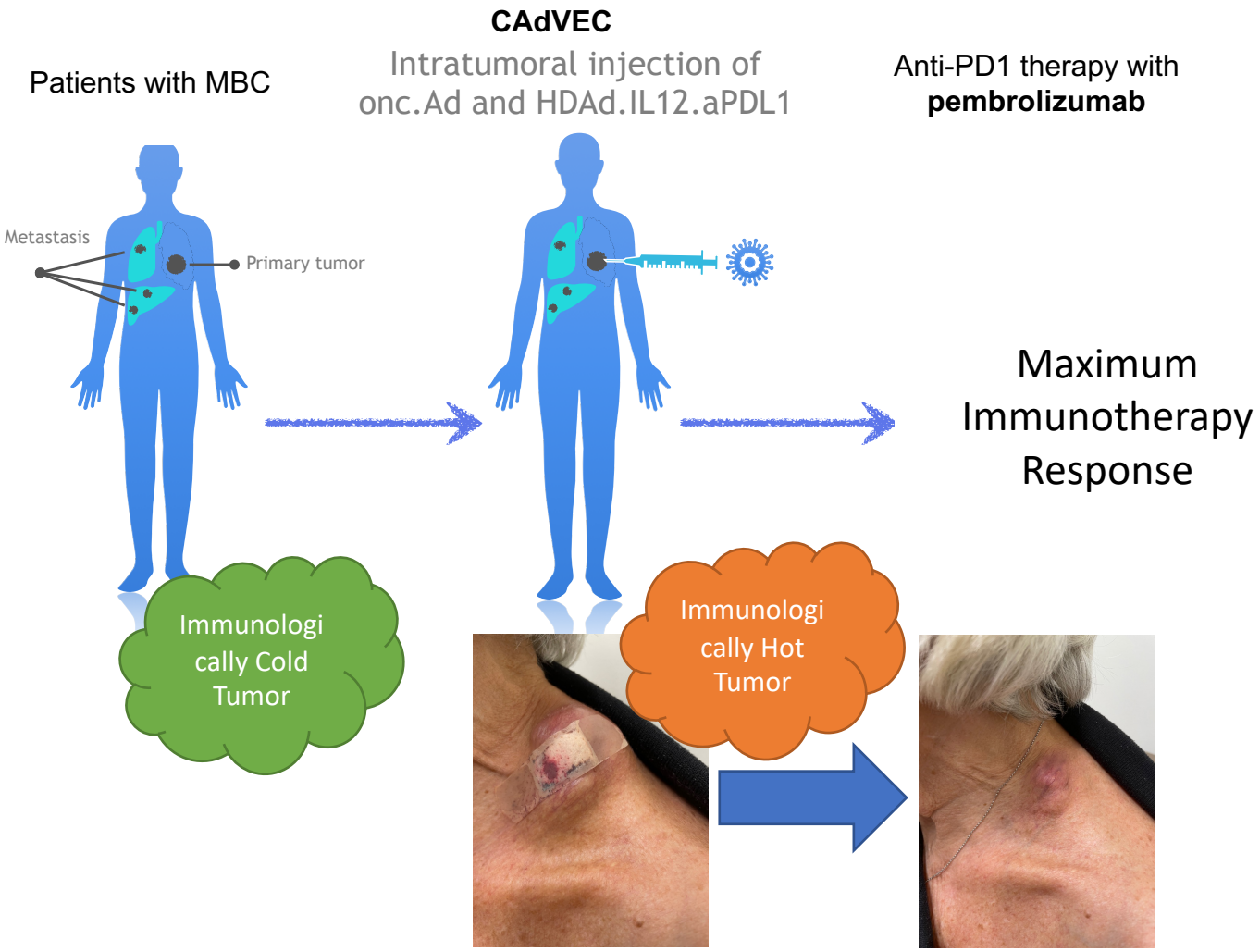
- **Immunotherapy for defined groups (eg. PD-L1+, TILs), immune-enhanced engineered antibody (FcR-gamma), vaccines**
- **Role of CDK inhibitors for HR+ disease during maintenance therapy**
- **PI3K inhibition for *PIK3CA* mutant cases**
- **PARPi with trastuzumab for gBRCA mutations**
- **Re-use of immunoconjugates and downregulation of HER2**

NCCN. BC guidelines V5.2020.

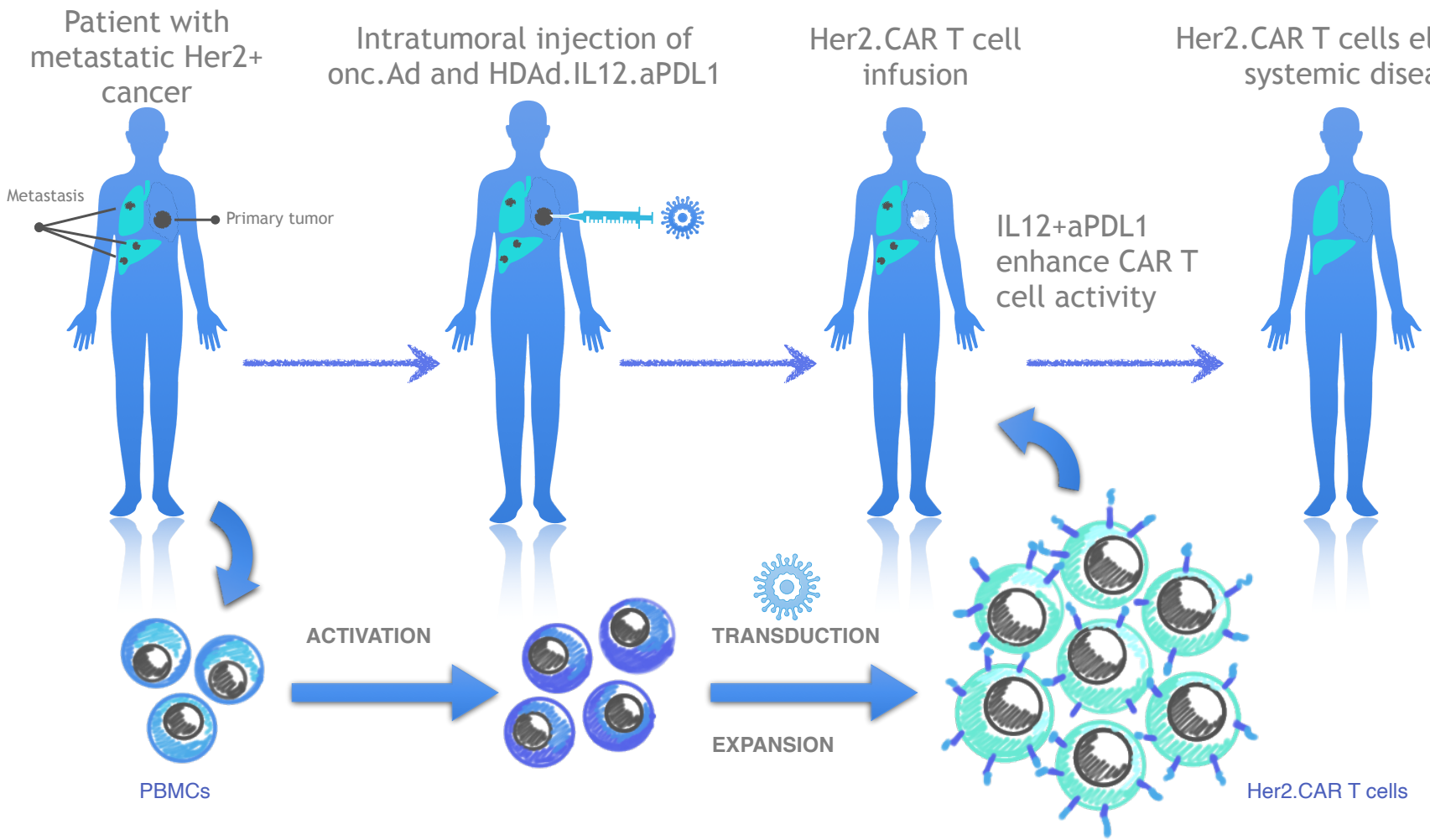
Newer agents in the horizon

Compound	MOA	Pt Population
Zw25	Biparatropic (ECD4 and ECD2) HER2 targeted antibody	HER2+ Breast and Gastric
PRS-343	Bispecific fusion protein targeting CD137 and HER2	HER2+ solid tumors
Pf-06804103	Site specific anti-HER2 ADC (NG-HER2 ADC)	HER2+ solid tumors
Neratinib w/ everolimus, palbociclib or trametinib	Pan-ERBB inhibitor + mTOR/CDK 4/6/MEK inhibitor	EGFR mut/amp, HER2 mut/amp, or HER3/4 mut solid tumors
Everolimus, Letrozole, and Trastuzumab	mTOR inhibitor + AI + Trastuzumab	HR+/HER2+ solid tumors
BTRC4017A	T cell dependent bispecific antibody	HER2+, TNBC, HR+/HER2-

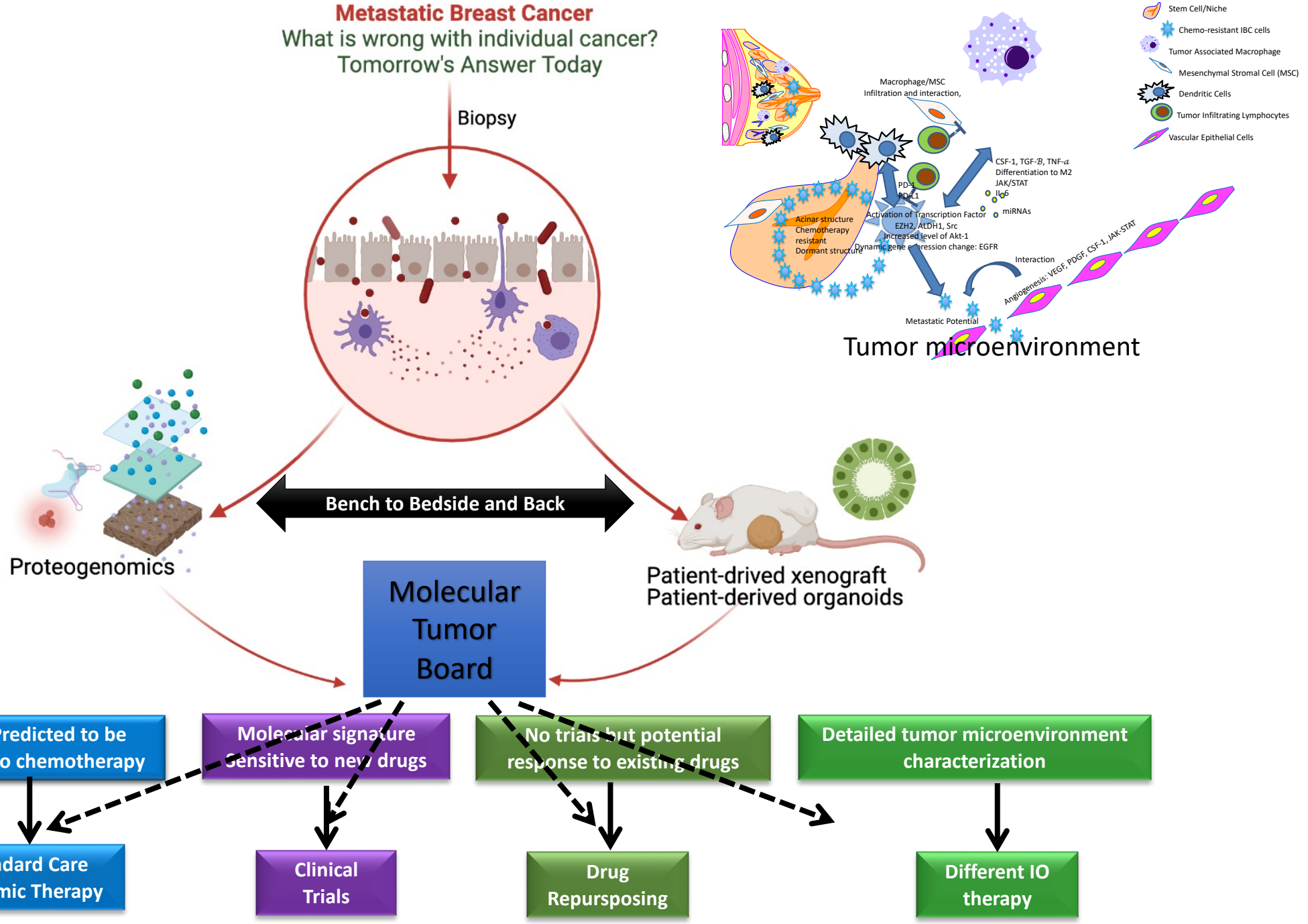
Biomodular oncolytic virus



CAR-T


Patient with metastatic Her2+ cancer
Metastasis
Primary tumor
Intratumoral injection of onc.Ad and HDAd.IL12.aPDL1
Her2.CAR T cell infusion
IL12+aPDL1 enhance CAR T cell activity
Her2.CAR T cells eliminate systemic disease
PBMCs
ACTIVATION
TRANSDUCTION
EXPANSION
Her2.CAR T cells

MBC prism


Metastatic Breast Cancer
What is wrong with individual cancer?
Tomorrow's Answer Today
Biopsy
Bench to Bedside and Back
Proteogenomics
Patient-drived xenograft
Patient-derived organoids
Molecular Tumor Board
Tumor Predicted to be sensitive to chemotherapy
Molecular signature Sensitive to new drugs
No trials but potential response to existing drugs
Detailed tumor microenvironment characterization
Standard Care Systemic Therapy
Clinical Trials
Drug Repursposing
Different IO therapy
Stem Cell/Niche
Chemo-resistant IBC cells
Tumor Associated Macrophage
Mesenchymal Stromal Cell (MSC)
Dendritic Cells
Tumor Infiltrating Lymphocytes
Vascular Epithelial Cells
Macrophage/MSC
Infiltration and interaction,
CSF-1, TGF-B, TNF-a
Differentiation to M2
JAK/STAT
Il-6
miRNAs
PD-1
PD-L1
Acinar structure
Chemotherapy
resistant
Dormant structure
Activation of Transcription Factor
EZH2, ALDH1, Src
Increased level of Akt-1
Dynamic gene expression change: EGFR
Interaction
Angiogenesis: VEGF, PDGF, CSF-1, JAK-STAT
Metastatic Potential
Tumor microenvironment

Thank you !!

Masataka Suzuki
Igor Bado
Evie Hobbs
Funda Meric
Angela Alexander
Angela Marx
Jie Willey
Huiming Sun
Elise Courtois
Santhosh Sivajothi
Bill Flynn
Nicholas Navin
Paul Robson
Ignatio Wistuba

And so many more

Patients
BCM Breast Cancer Team
MDACC Breast Medical Oncology/Phase I/TMP

THE HOPE FOUNDATION

Baylor College of Medicine

Lilly | ONCOLOGY

CHAN ZUCKERBERG INITIATIVE

Genentech
A Member of the Roche Group

MD Anderson
Morgan Welch Inflammatory Breast Cancer Research Program and Clinic

MERCK
INVENTING FOR LIFE

Next weekend in Houston