The management of HER2+ breast cancer: A rapidly changing frontier

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Goals for today

- **Early stage breast cancer**
  - Optimizing treatment for locally advanced disease
    - TRAIN-2, KATHERINE, APHINITY, EXTENET
  - Trials that may allow us to de-escalate therapy for patients who respond well to initial therapy or patients with the lowest burden of disease
    - APT, COMPASS-HER2, ADEPT

- **Metastatic breast cancer**
  - How to incorporate new agents into standard practice
    - Tucatinib, trastuzumab deruxtecan, margetuximab, neratinib
  - Future directions

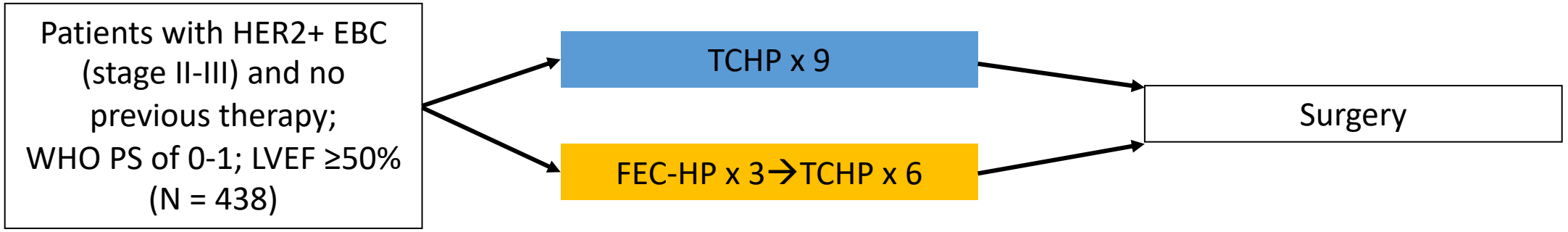
Early stage HER2+ Breast Cancer

Locally advanced HER2+ Breast Cancer

- Standard of care for patients with >T2 or node-positive HER2+ breast cancer has been AC-THP or TCHP, followed by a year of H+/-P
  - These are not easy treatments – and despite all of this treatment, there are still patients who recur
- Questions:
  - With dual HER2-directed antibody therapy, do we still really need an anthracycline? Does everyone need a year of HP?
  - For those who don’t get to pCR with neoadjuvant chemotherapy, can we do more in the adjuvant setting to improve their outcomes ultimately?
  - For those who have a robust response to upfront therapy, can we get away with less treatment?

TRAIN-2: Neoadjuvant CT with or without anthracyclines

- Randomized, phase 3 trial with pCR as primary endpoint



- Patients went on to complete one year of adjuvant trastuzumab, +/- endocrine therapy

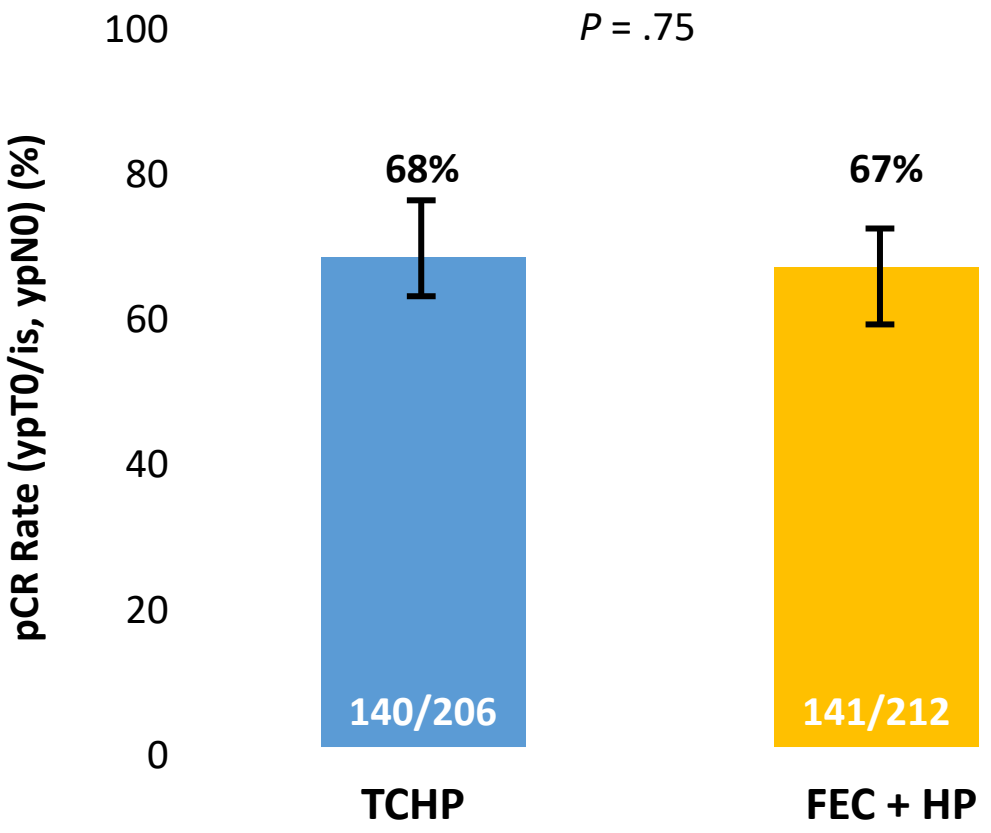
TCHP: 3-wk cycles, D1 TCHP, D8 T only. T, paclitaxel 80 mg/m^2; C, carboplatin AUC = 6 mg per min/mL; H, trastuzumab 6 mg/kg (loading dose 8 mg/kg); P, pertuzumab 420 mg (loading dose 840 mg).

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

van der Voort. JAMA Oncol. 2021;7:978.

TRAIN-2: primary results

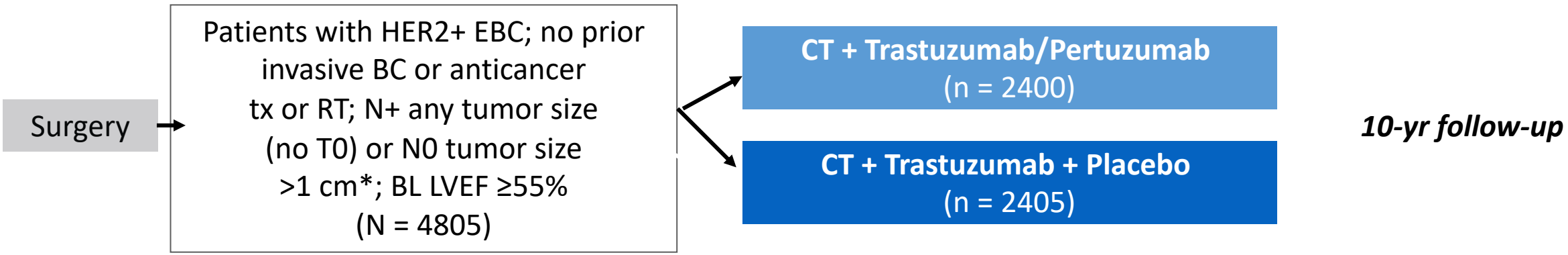
- High rate of pCR with or without anthracyclines (68% in TCHP groups, 67% in FEC-HP—>TCHP)
- pCR was consistent across prespecified subgroups
  - Clinical T stage (0-2 vs 3-4)
  - Nodal status (negative vs positive)
  - HR status (negative vs positive)
  - Age (<50 yr vs ≥50 yr)
- There was no difference in EFS or OS



van der Voort. JAMA Oncol. 2021;7:978.

APHINITY: evaluating adjuvant pertuzumab

Randomized, phase 3 adjuvant trial for HER2+ breast cancer patients



*Or node negative with tumors >0.5 to ≤1 cm + ≥1 of following: histologic/nuclear grade 3; ER negative and PgR negative; aged <35 yr. Node-negative enrollment capped after first 3655 patients randomized.

Primary endpoint: IDFS

Piccart. JCO. 2021;39:1448

APHINITY: 6-year follow-up data

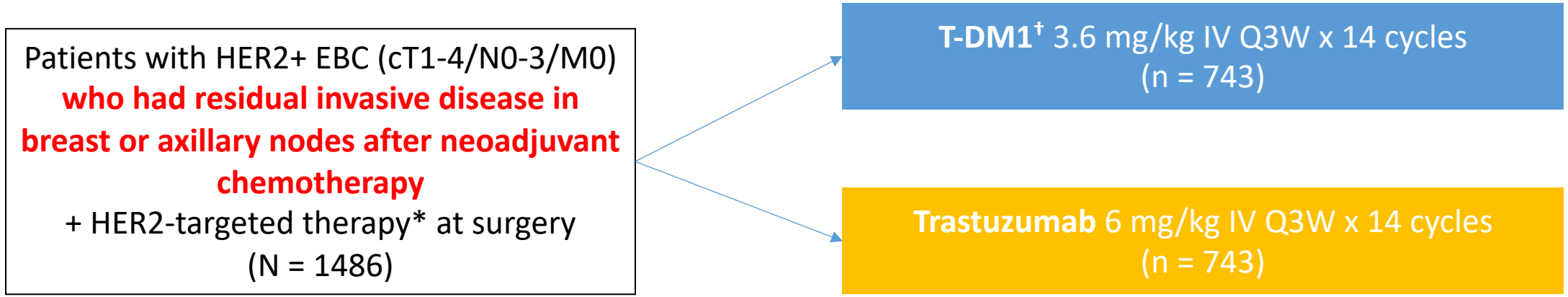
Hazard ratio (95% CI for IDFS in ITT and in subgroups based on LN/ HR)			IDFS at six years (median f/u 74.1 months)		
Population	Primary analysis (median f/u 45.4 months, 2017)	Updated analysis (median f/u 74.1 months, 2019)	Trastuzumab + chemo + pertuzumab	Trastuzumab + chemo + placebo	Absolute benefit
ITT	0.81 (0.66-1.00)	0.76 (0.64-0.91)	90.6%	87.8%	2.8%
LN+	0.77 (0.62-0.96)	0.72 (0.59-0.87)	87.9%	83.4%	4.5%
LN-	1.13 (0.68-1.86)	1.02 (0.69-1.53)	95.0%	94.9%	0.1%
HR+	0.73 (0.59-0.92)	0.73 (0.59-0.92)	91.2%	88.2%	3.0%
HR-	0.76 (0.56-1.04)	0.83 (0.63-1.10)	89.5%	87.0%	2.5%

- Improvement in iDFS driven by the node-positive patient population

Piccart. JCO. 2021;39:1448.

KATHERINE trial

- Phase III randomized controlled trial

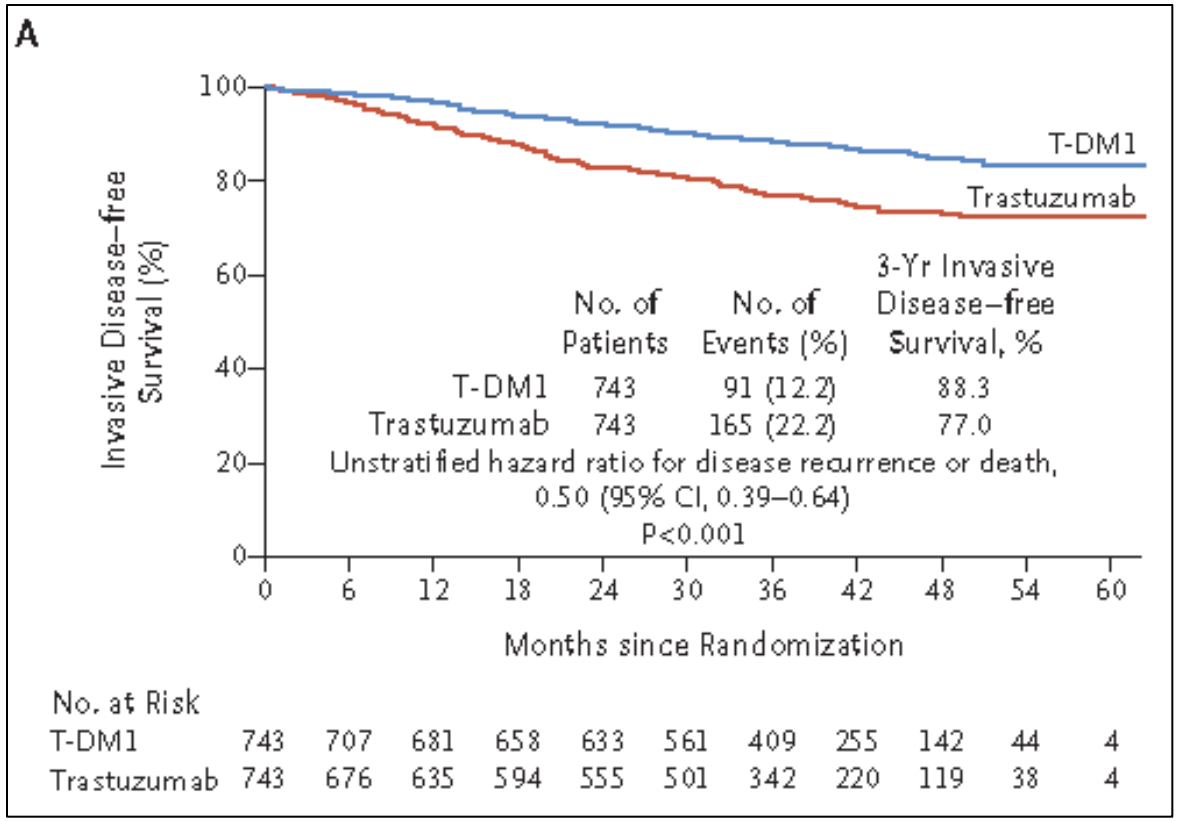


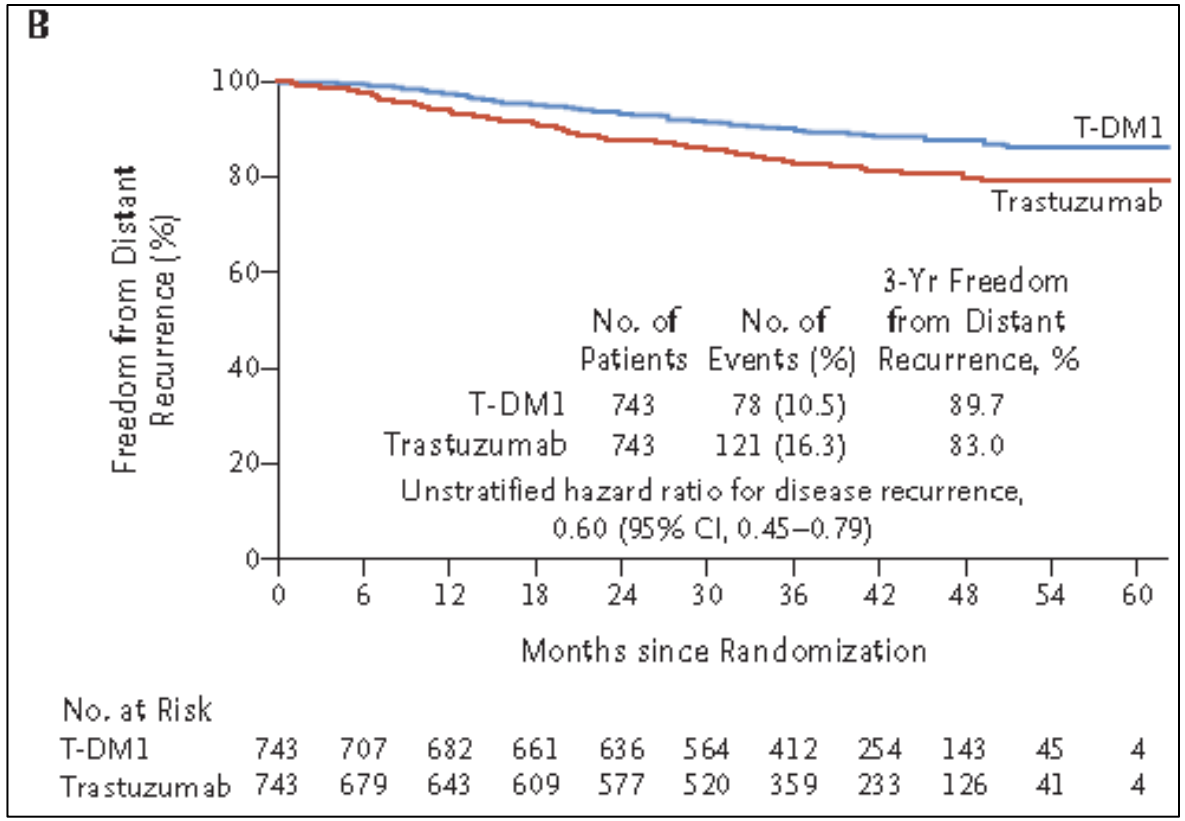
Randomization occurred within 12 wk of surgery; **radiotherapy and/or endocrine therapy given per local standards**.
*Minimum of 9 wk of taxane and trastuzumab. †Patients who d/c T-DM1 for toxicity allowed to switch to trastuzumab to complete 14 cycles.

- Primary endpoint: IDFS
- Secondary endpoints: distant recurrence-free survival, OS, safety

N Engl J Med. 2019;380(7):617.

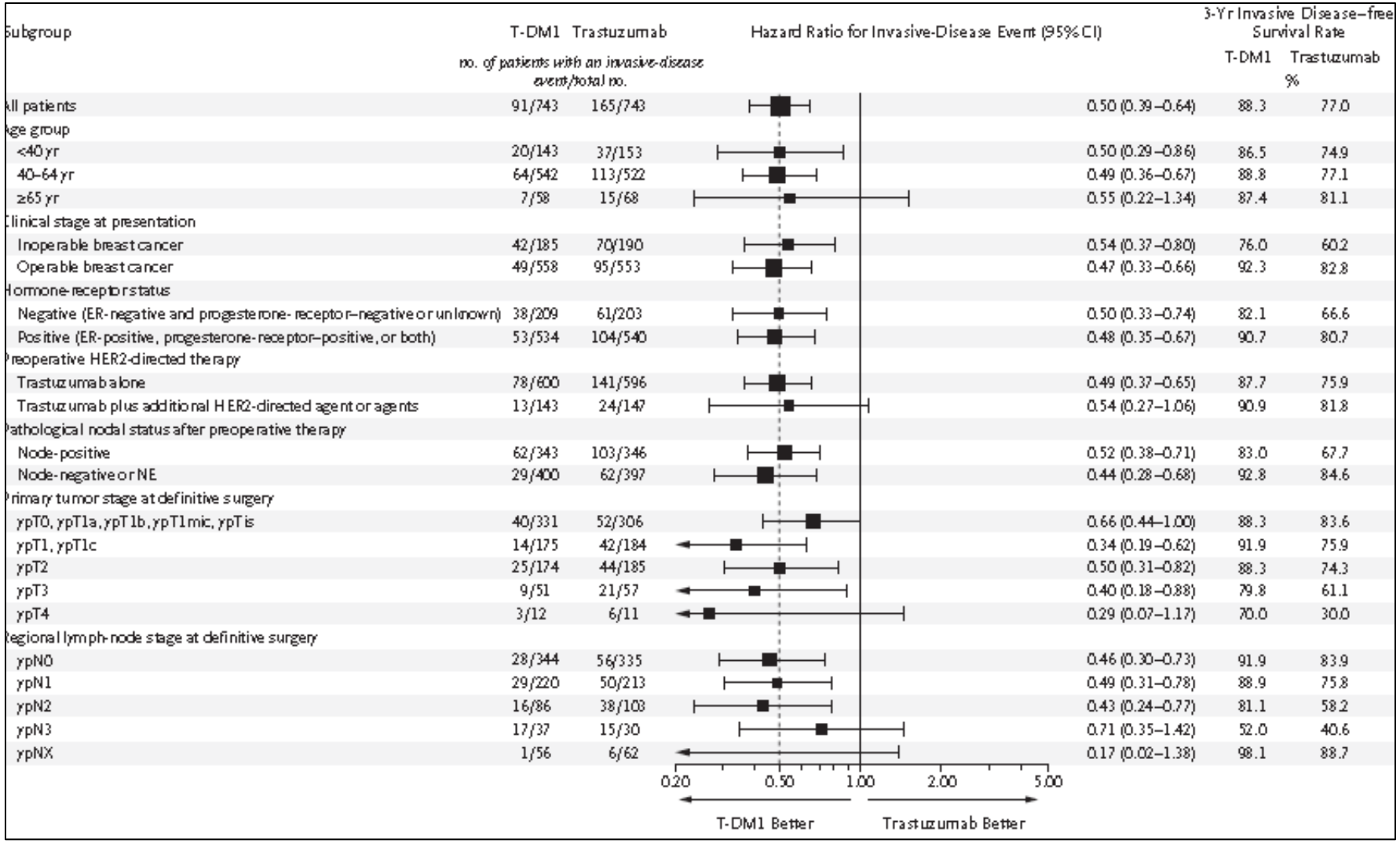
KATHERINE: Results





N Engl J Med. 2019;380(7):617.

KATHERINE Subgroup Analysis



N Engl J Med. 2019;380(7):617.

Using adjuvant T-DM1

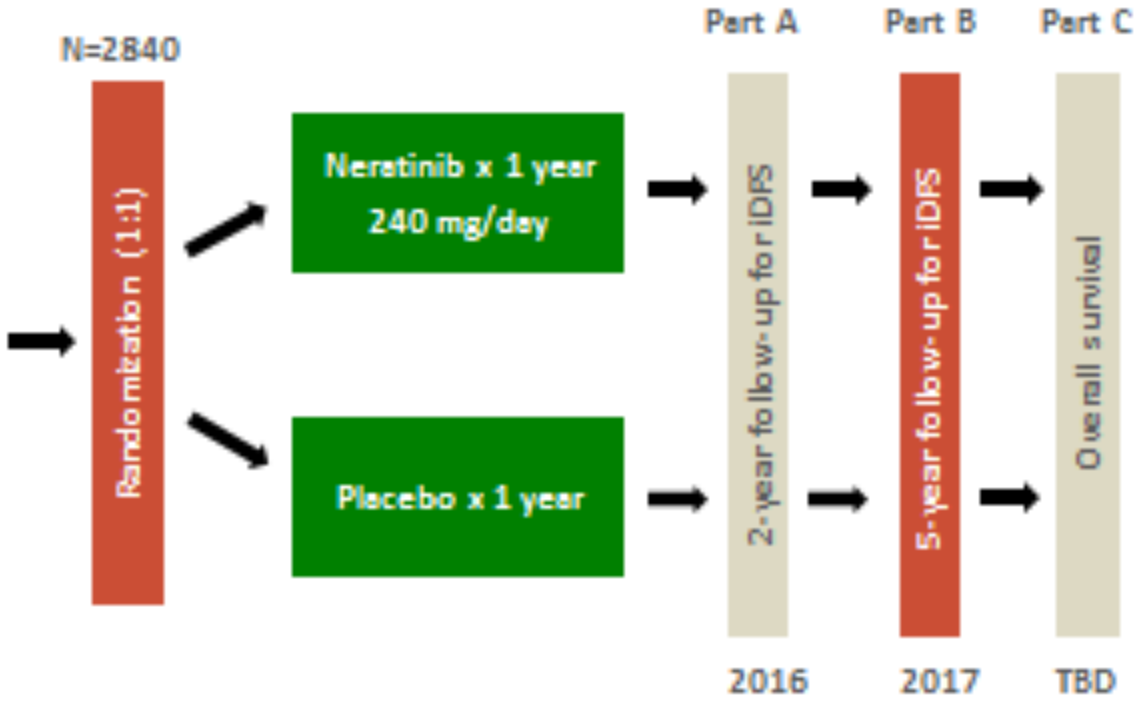
- KATHERINE showed a statistically and clinically significant benefit to adjuvant T-DM1 in HER2+ patients with residual disease after neoadjuvant therapy
- Definitely practice-changing

- A few small caveats:
- **Side effects** of adjuvant TDM1 on study were more significant than trastuzumab (fatigue, nausea, lab abnormalities – resulting in 18% treatment discontinuation in the study)
- **Financial toxicity** is a real issue (esp for underinsured, ex-US)

N Engl J Med. 2019;380(7):617.

ExteNET: Study Design

- HER2+ breast cancer
  - IHC 3+ or ISH amplified (locally determined)
  - Stage 2 to 3c node positive breast cancer
  - Prior adjuvant trastuzumab + chemotherapy
  - Post neoadjuvant therapy, either LN- or LN+ with residual invasive disease
- Stratified by: nodal status, hormone receptor status, concurrent *vs* sequential trastuzumab



Primary endpoint: invasive disease-free survival (iDFS)

Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS recurrences, OS, safety

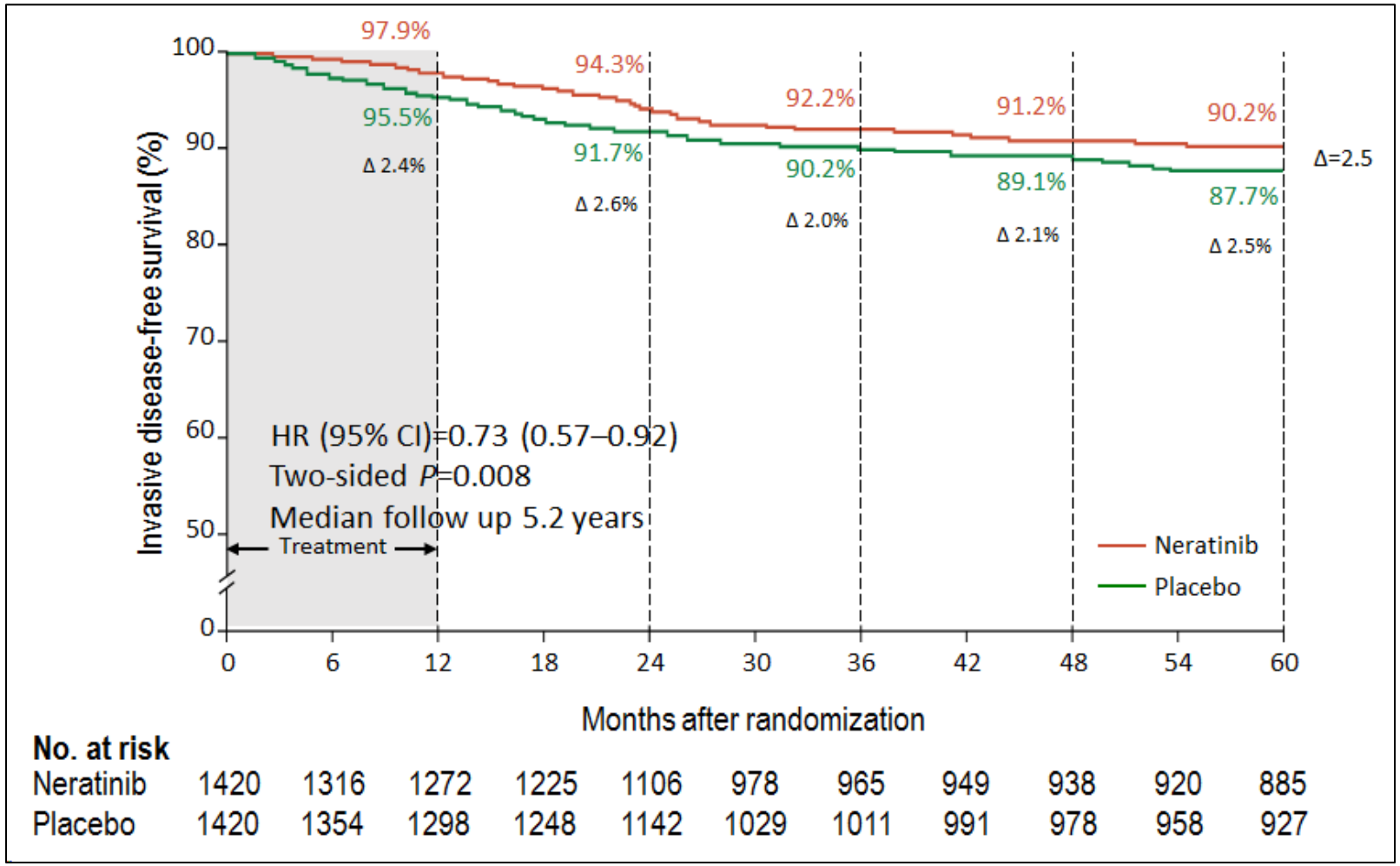
Other analyses: biomarkers, health outcome assessments (FACT-B, EQ-5D)

Endocrine adjuvant therapy given to patients with HR-positive tumors according to local practice

1. Chan et al. Lancet Oncol 2016.
2. Clinicaltrials.gov Identifier: NCT00878709
3. Martin M et al. Lancet Oncol. 2017;18(12):1688-1700.

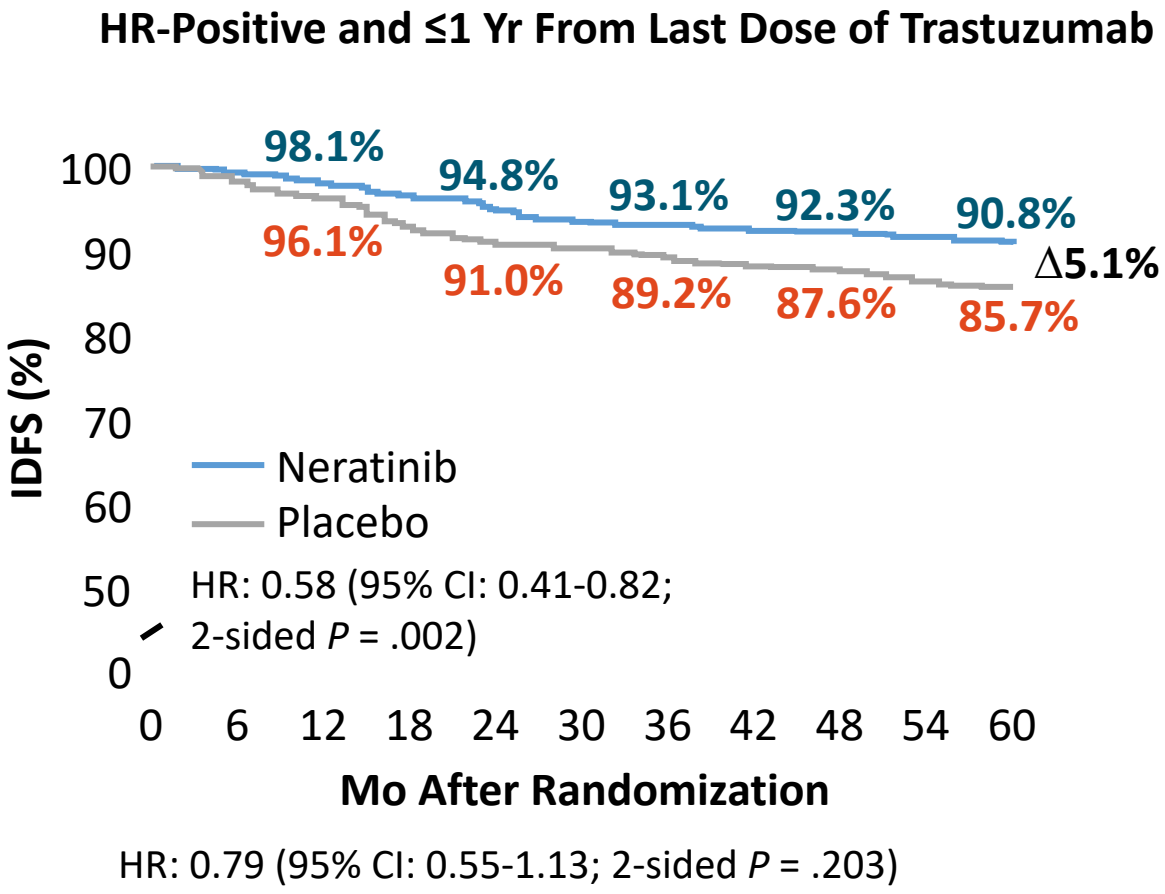
Adapted from Puma Biotechnology.

ExteNET 5-year iDFS analysis

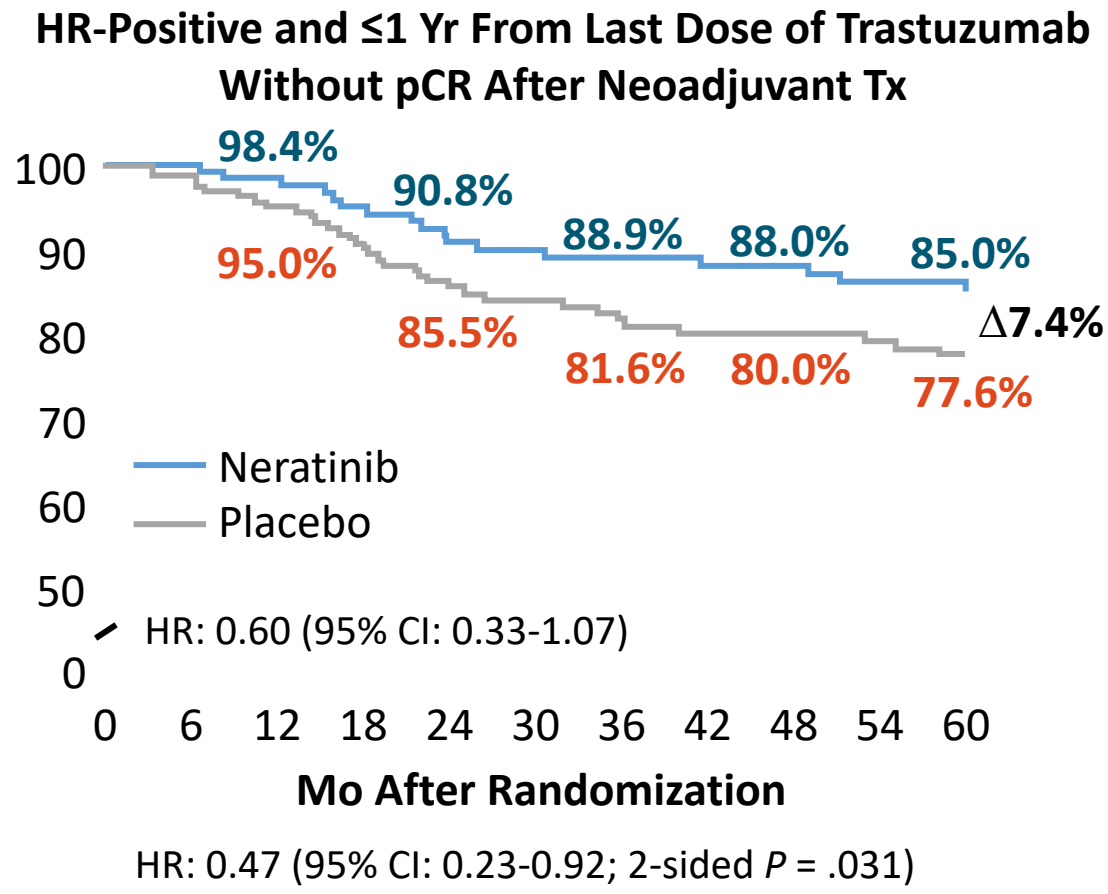


1. Martin et al. Lancet Oncol. 2017 Dec;18(12)

ExteNET: 5-Yr IDFS in HR+Positive Subgroups



HR: 0.79 (95% CI: 0.55-1.13; 2-sided *P* = .203)



HR: 0.47 (95% CI: 0.23-0.92; 2-sided *P* = .031)

Chan. Clin Breast Cancer. 2021;21:80. Slide adapted from Clinical Care Options

Using adjuvant neratinib

- We consider it for locally advanced patients with ER+ HER2+ disease, and try to start it right after the year of trastuzumab (+ pertuzumab) ends
- We try to bring it up early so patients aren't blindsided at the end of therapy by the idea of another year
  - Treatment fatigue is an issue
- Caveat: none of the EXTENET received pertuzumab, so hard to know how to apply in this population
  - But…if diarrhea can be controlled, for the right patient, not much of a down side

Conclusions: Locally advanced breast cancer

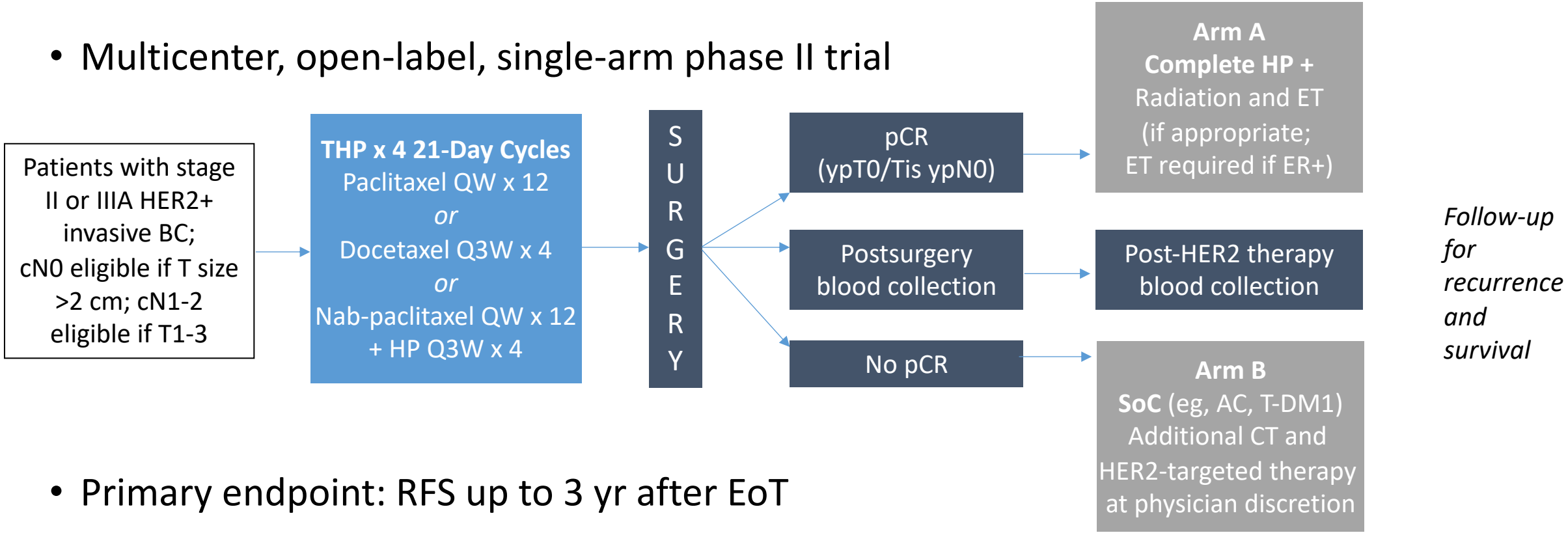
- Does everyone need anthracyclines?
  - Per TRAIN-2, probably not
- What about a year of HP?
  - Node-positive patients benefit; if node-negative, probably not
- What should we do with patients who have residual disease after neoadjuvant chemotherapy?
  - T-DM1 +/- neratinib (+/- endocrine therapy)

Future directions?

- Response-based treatment (COMPASS-HER2)
- Additional options post-neoadjuvant (T-DM1 vs T-Dxd, T-DM1 +/- tucatinib)

COMPASS-HER2

- Multicenter, open-label, single-arm phase II trial



- Primary endpoint: RFS up to 3 yr after EoT
- Secondary endpoints: IDFS, DDFS, DRFS, RFI, OS, EFS, safety

De-escalating therapy in HER2+ breast cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

APT trial: design and patient population

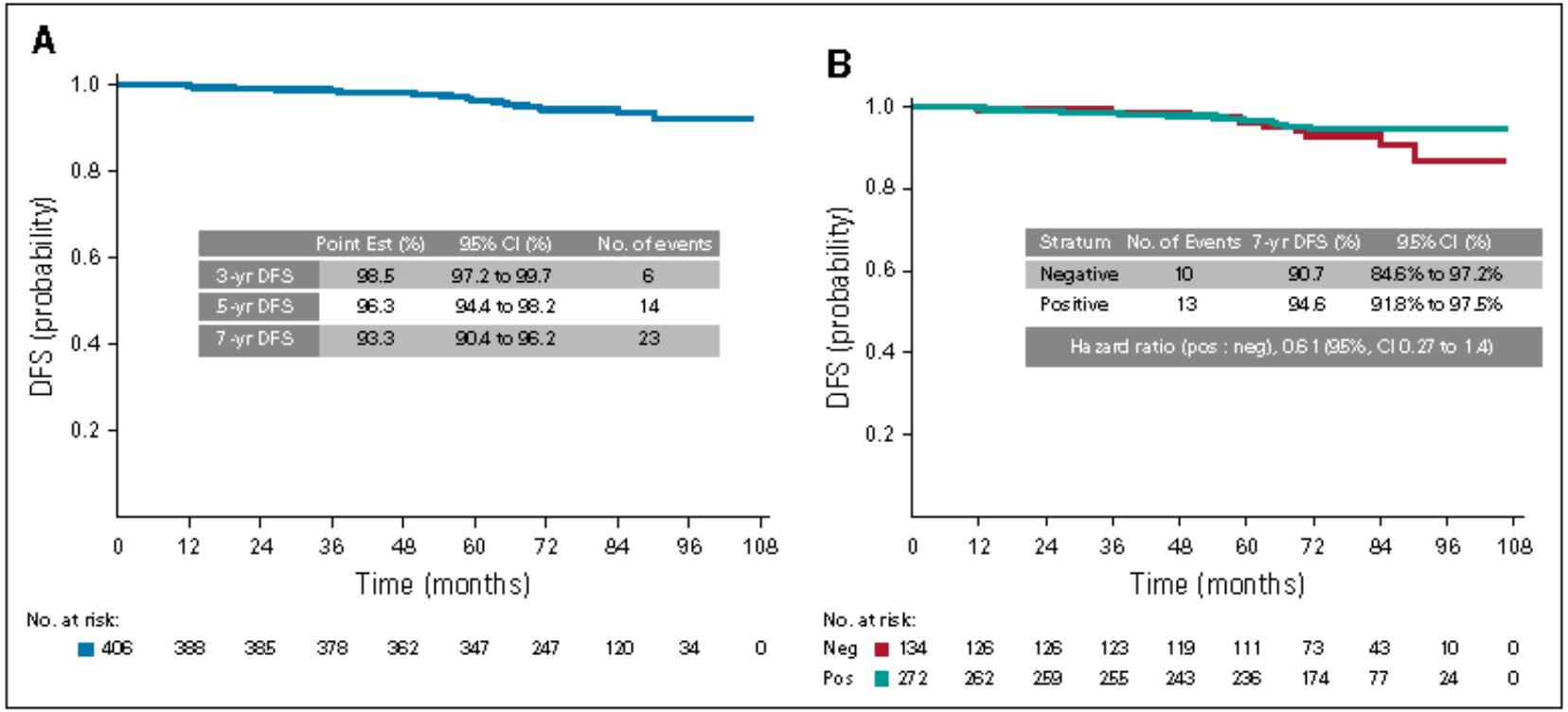
- Single-arm study of weekly paclitaxel x trastuzumab x 12 weeks followed by trastuzumab q3 weeks x 1 year
- Primary endpoint: DFS
- Secondary endpoints: recurrence-free survival, OS, breast-cancer specific survival

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients (N = 406)
	no. (%)
Age group	
<50 yr	132 (32.5)
50–59 yr	137 (33.7)
60–69 yr	96 (23.6)
≥70 yr	41 (10.1)
Sex	
Female	405 (99.8)
Male	1 (0.2)
Race†	
White	351 (86.5)
Black	28 (6.9)
Asian	11 (2.7)
Other	16 (3.9)
Primary tumor	
Size	
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0 cm	36 (8.9)
Nodal status	
N0	400 (98.5)
N1mic	6 (1.5)
Histologic grade	
I: well-differentiated	44 (10.8)
II: moderately differentiated	131 (32.3)
III: poorly differentiated	228 (56.2)
Unknown	3 (0.7)
HER2-positive status	406 (100)
Estrogen-receptor status	
Positive	260 (64.0)
Negative	141 (34.7)
Borderline	5 (1.2)
Progesterone-receptor status	
Positive	201 (49.9)
Negative	196 (48.3)
Borderline	8 (2.0)
Unknown	1 (0.2)
Hormone-receptor status	
Positive	272 (67.0)
Negative	134 (33.0)

N Engl J Med 2015: 372: 134-141. January 8, 2015.

APT trial: 7-year follow-up



- This has become a new standard-of-care for stage I patients

*3y-rate of survival free from invasive disease was 98.7%

*3y RFS was 99.2%

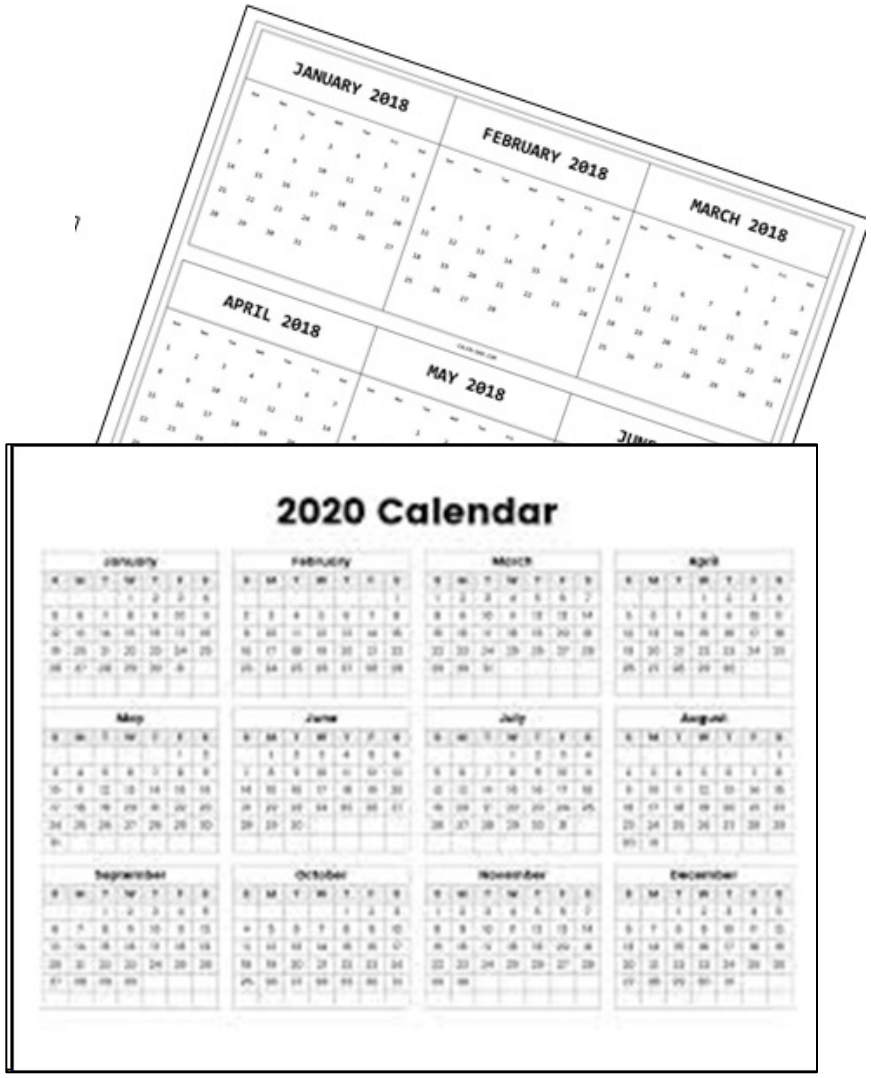
*There was no difference seen when patients were stratified by tumor size (≤1 versus >1 cm).

*7-year DFS of 93 percent and OS of 95 percent.

J Clin Oncol 2019; 37: 1868-1875.

Duration of trastuzumab

- HERA found no difference between 1 and 2 years of adjuvant trastuzumab
- What about 12 months vs 6 months?
- PERSEPHONE, HORG, and PHARE have examined this important question



6 months vs 12 months

- HORG (Hellenic Oncology Research Group)
  - 481 women with node + or high-risk node negative HER2+ breast cancer
  - 6 months failed to demonstrate non-inferiority compared to 12 months
  - 3y DFS 95.7 vs 93.3%, with HR 1.57 (noninferiority margin defined at 1.53)

- PERSEPHONE
  - 4089 women; 6 months of treatment demonstrated noninferior 4y DFS rates compared to those who received 12 months (89.4 vs 89.8%, HR 1.07)
  - In the subset of PERSEPHONE patients that most mirrors current practice, there *was* a benefit for 12 months over 6 months of trastuzumab (HR 1.53, 1.16-2.01)

- PHARE
  - 3380 women; treatment for 6 months resulted in a shorter DFS than 12 months (91% vs 94% with HR of 1.28)

Lancet Oncol. 2013;14(8):741. Ann Oncol. 2015; 26 (7): 1333.

Where are we now for our earliest-stage patients?

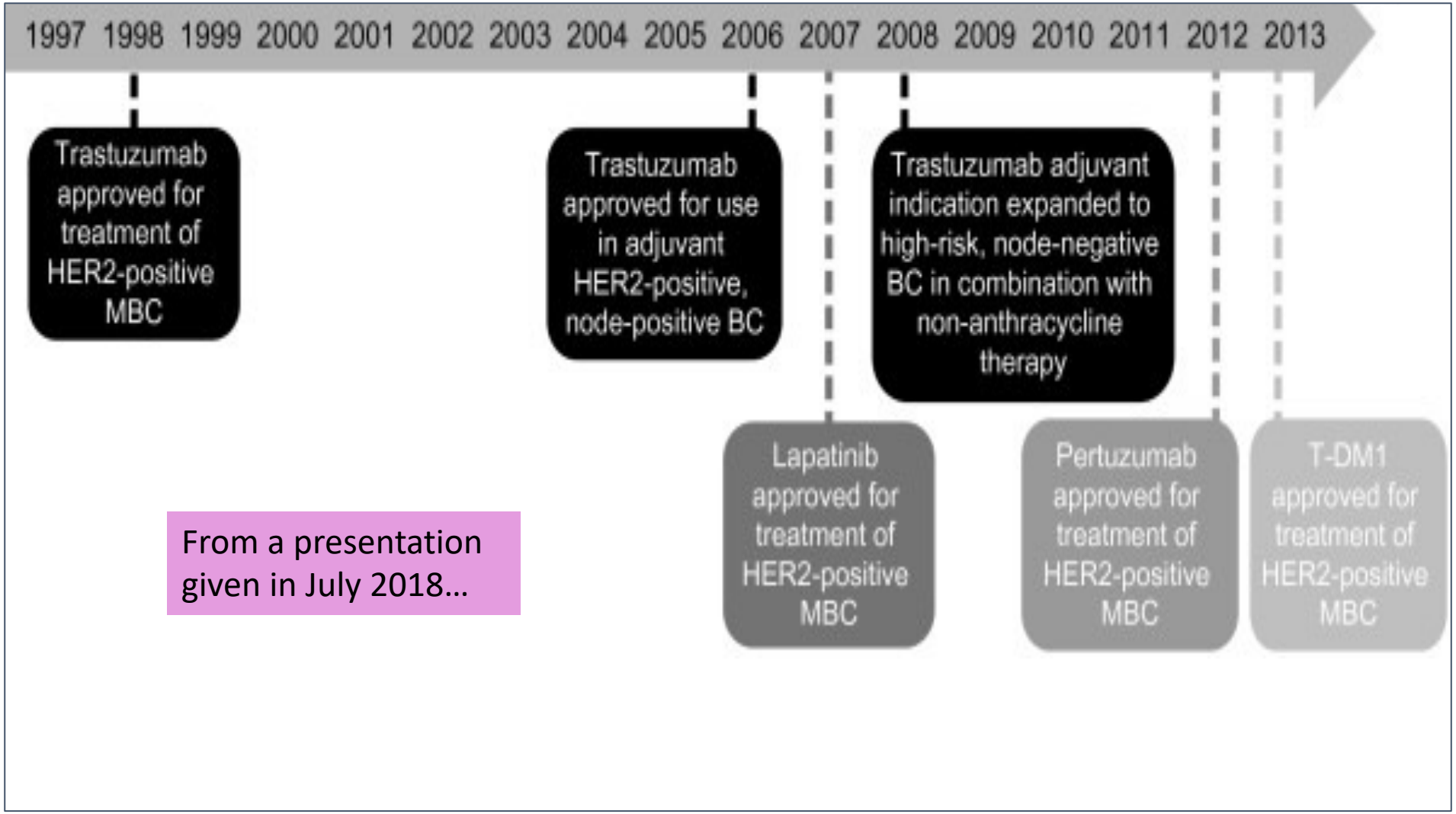
- Paclitaxel x trastuzumab x 12 weeks followed by trastuzumab q3 weeks x 1 year = standard of care for most stage 1 patients
  - Reasonable to also adopt this approach to early T2N0 patients, especially if they have other comorbidities

- 1 year of trastuzumab remains the standard, but reasonable to do less in certain clinical situations

- Future directions
  - ADEPT trial: chemotherapy-free regimen for our earliest ER+HER2+ patients?

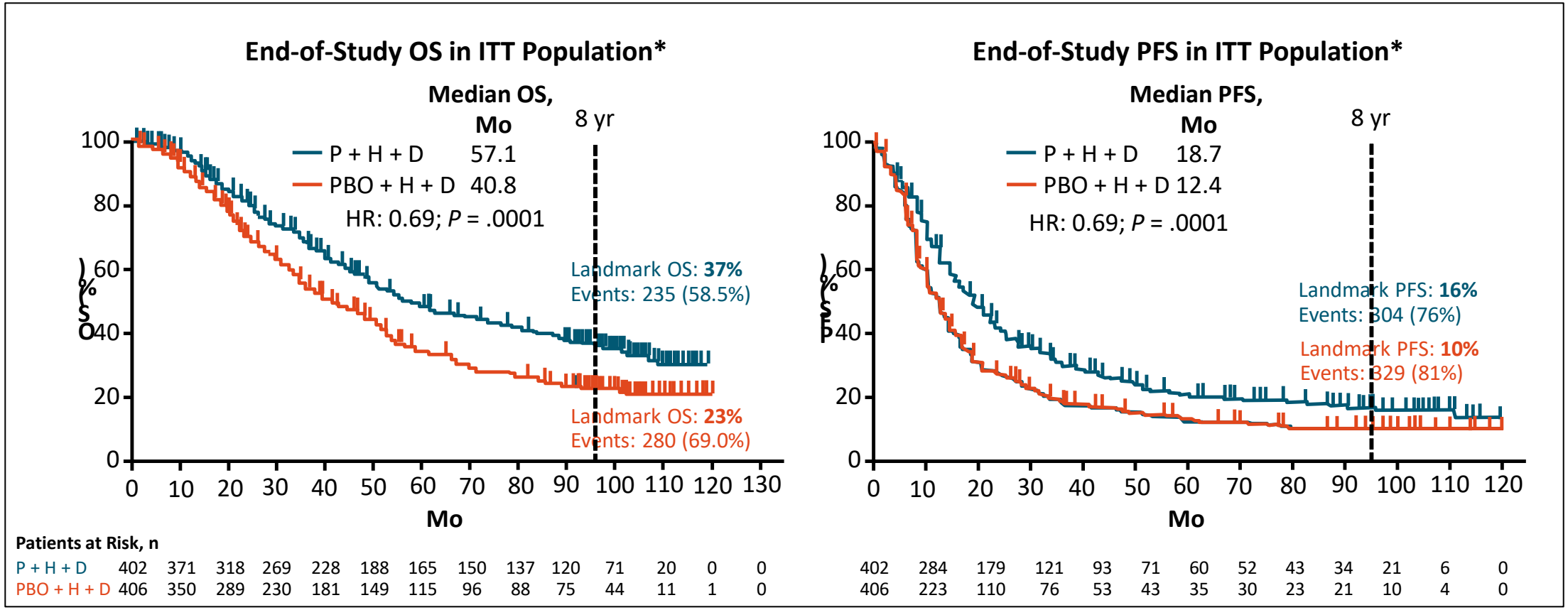
Metastatic HER2+ Breast Cancer

A “historical” look at metastatic HER2+ BC



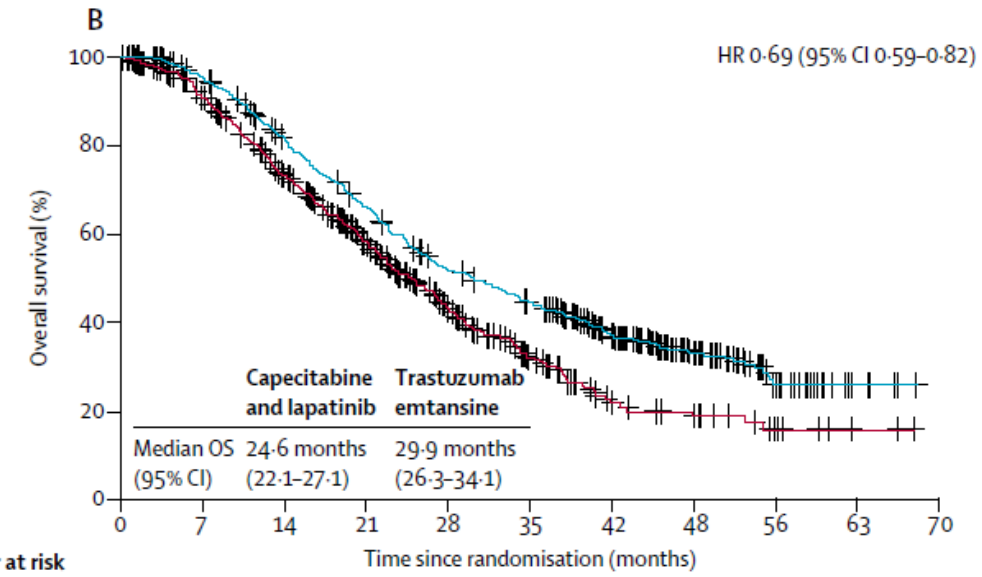
From a presentation given in July 2018…

CLEOPATRA: The addition of pertuzumab to trastuzumab/docetaxel in HER2+ MBC

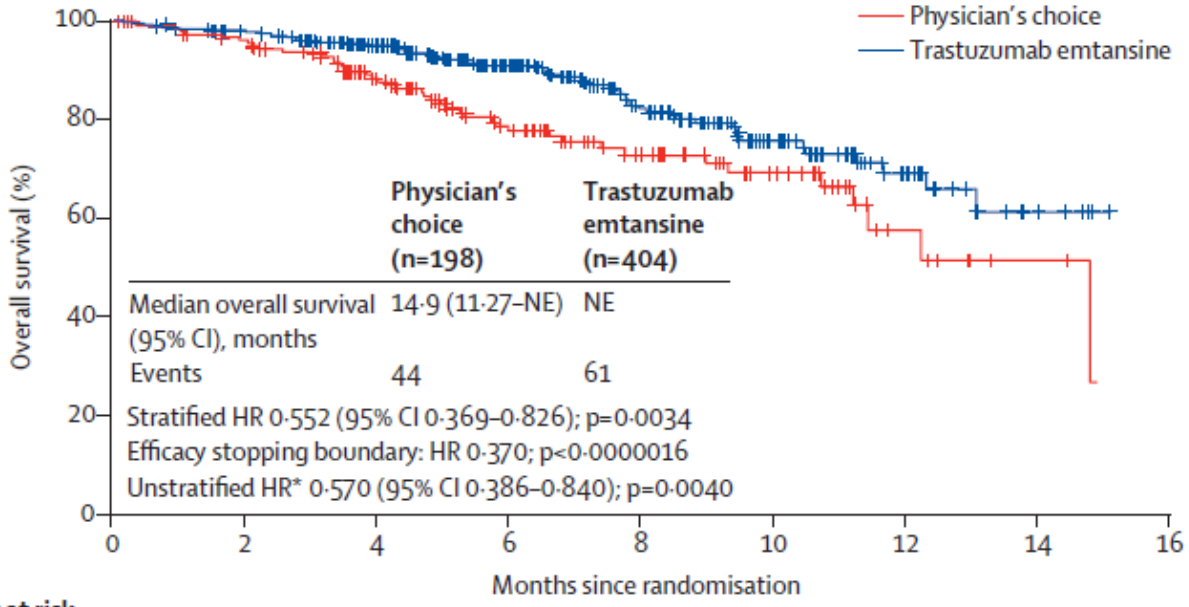


Swain, Lancet Oncol 2020; 21: 519.

EMILIA and TH3RESA: TDM1 as second-line therapy for HER2+ MBC



Number at risk (number censored)										
Capecitabine and lapatinib	496 (0)	418 (35)	312 (62)	208 (106)	119 (146)	64 (175)	24 (199)	17 (203)	8 (210)	2 (216)	0 (218)
Trastuzumab emtansine	495 (0)	451 (21)	374 (34)	302 (36)	231 (42)	194 (47)	127 (85)	68 (133)	23 (169)	5 (187)	0 (191)



Number at risk									
Physician's choice	198	169	125	80	51	30	9	3	0
Trastuzumab emtansine	404	381	316	207	127	65	30	7	0

EMILIA: TDM1 vs lapatinib+ capecitabine (after POD on trastuzumab + taxane)

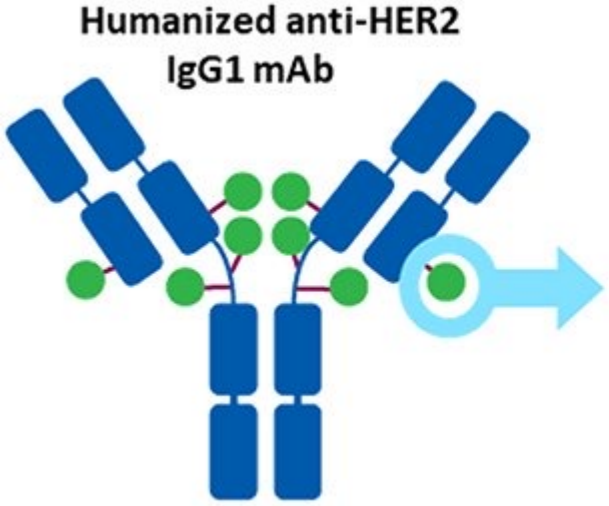
TH3RESA: TDM1 vs physician's choice (POD on ≥ 2 HER2-targeted regimens)

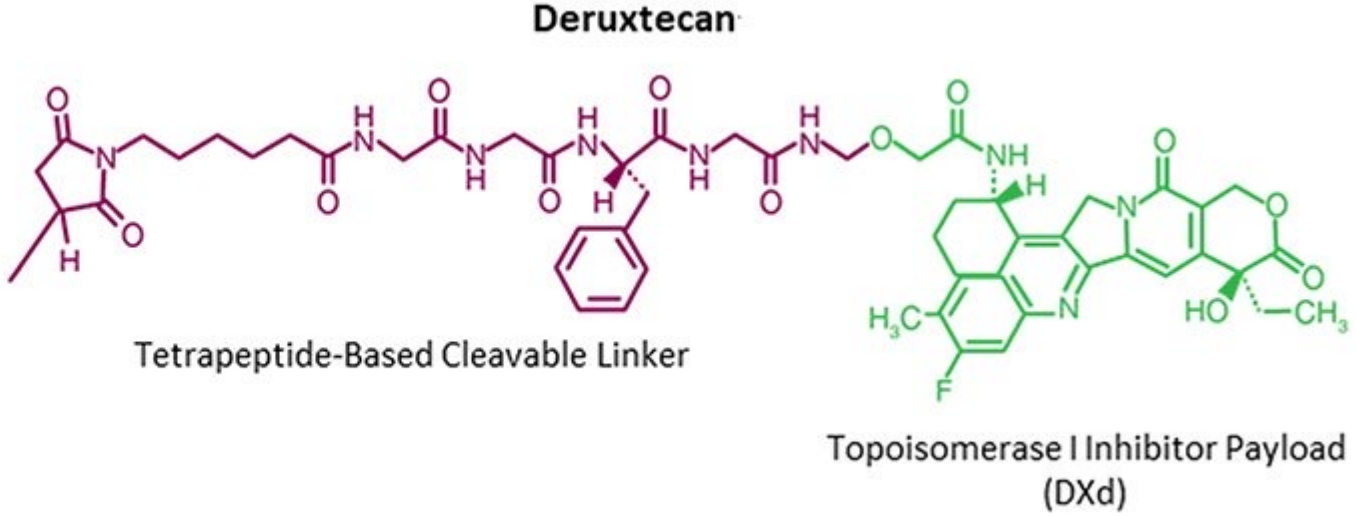
Lancet Oncol 2017; 18: 732-42. Lancet Oncol 2014; 15: 689-99

Extraordinary progress: multiple novel agents

Drug	Route	Mechanism of action	Partner drug	Special features
Trastuzumab deruxtecan	IV	Antibody drug conjugate targeting HER2	None	High membrane permeability and drug/antibody ratio
Tucatinib	PO	Reversible TKI targeting HER2	Capecitabine + trastuzumab	CNS penetration
Neratinib	PO	Irreversible TKI targeting HER1, HER2, HER4	Capecitabine	CNS penetration
Margetuximab	IV	Her2-directed antibody	Chemotherapy	Optimized Fc region to optimize antibody-dependent cellular toxicity

Trastuzumab deruxtecan





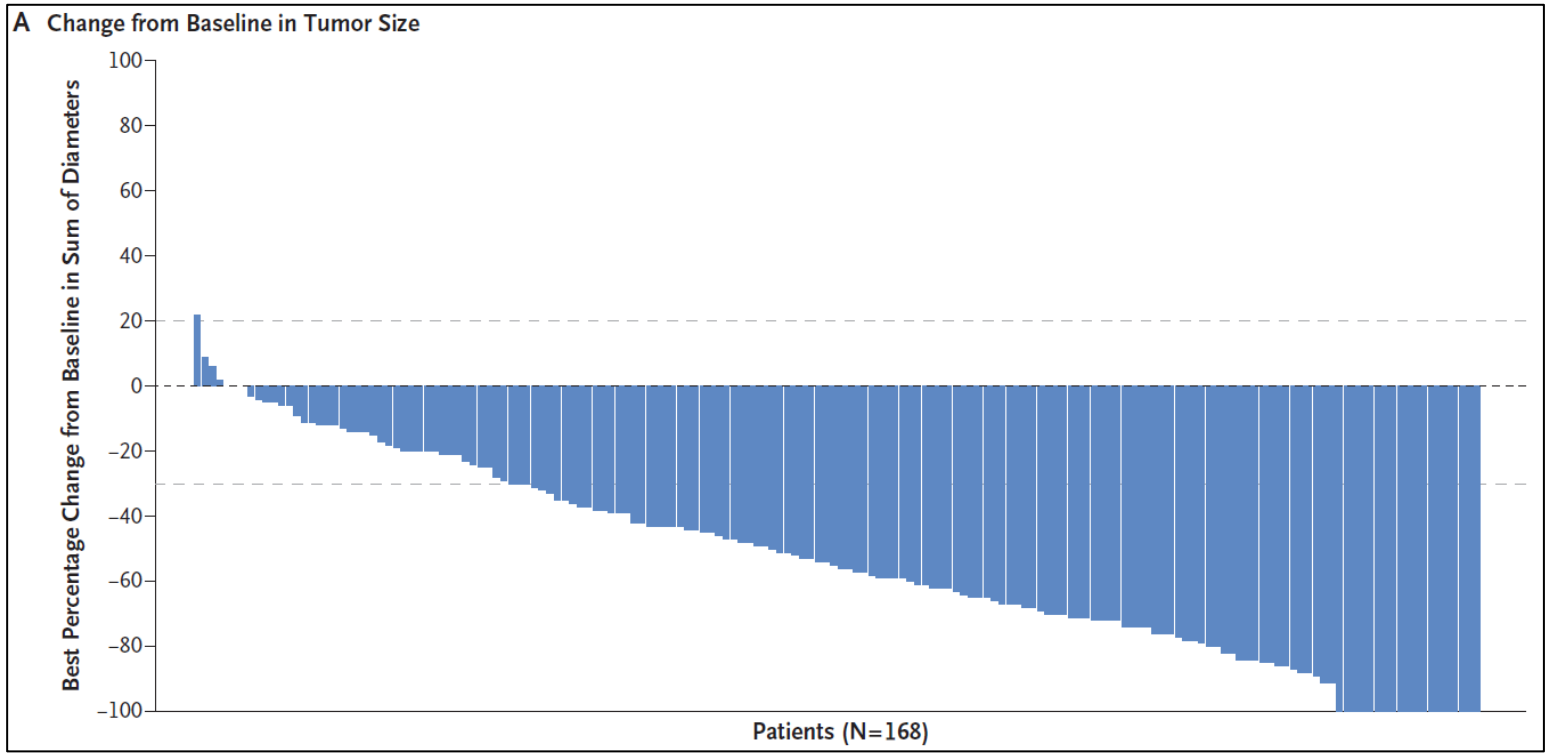
Unique features:

-High potency payload
-High drug to antibody ration (~8)
-Payload with short systemic half-life
-Tumor selective (cleavable linker)
-Membrane permeable payload

Chem Pharm Bull (Tokyo). 2019; 67 (3): 173-185. Clin Cancer Res 2016; 22 (20): 5097-5108. Pharmacol Ther. 2018; 181:126-142. Cancer Sci 2016; 107 (7): 1039-1046.

DESTINY-Breast01 (NCT03248492)

- Single-arm phase 2 study of trastuzumab deruxtecan for HER2+ metastatic breast cancer
- Median 6 prior lines of therapy
- ORR= 61% (58% in patients with brain metastases)
- Median PFS 16.4 months (18.1 months in patients with brain metastases



Modi S et al N Eng J Med. 2020; 382 (7): 610-21.

DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd

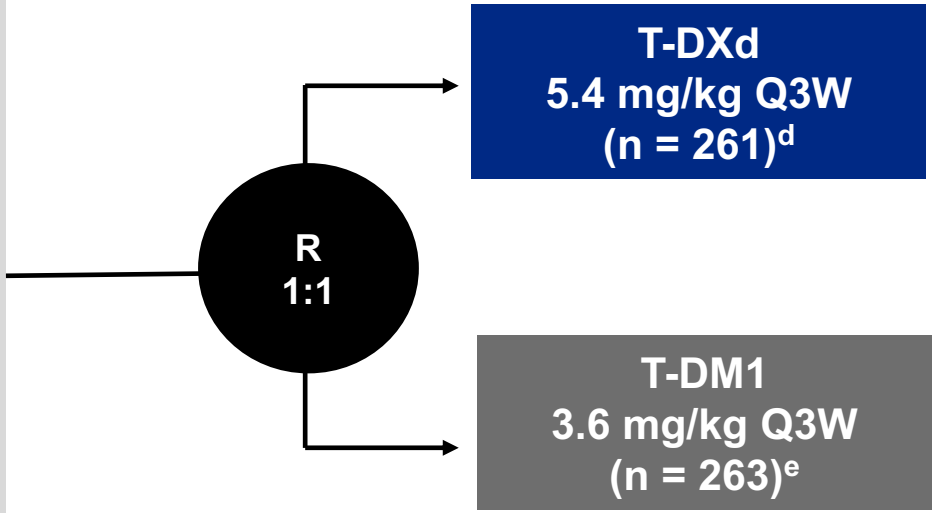
An open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer that has been previously treated with trastuzumab and a taxane[b]
- Could have clinically stable, treated brain metastases[c]
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

- At the time of data cutoff (May 21, 2021), 125 (48.6%) T-DXd patients and 214 (82.0%) T-DM1 patients had discontinued treatment
- Median follow up was 15.9 months
- BMs were measured at baseline by CT or MRI and lesions were monitored throughout the study

BICR, blinded independent central review; BM, brain metastasis; CT, computed tomography; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MRI, magnetic resonance imagining; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. [a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]Prior to protocol amendment, patients with stable, untreated BM were eligible. [d]4 patients were randomly assigned but not treated. [e]2patients were randomly assigned but not treated.

Baseline Characteristics and Prior Therapies

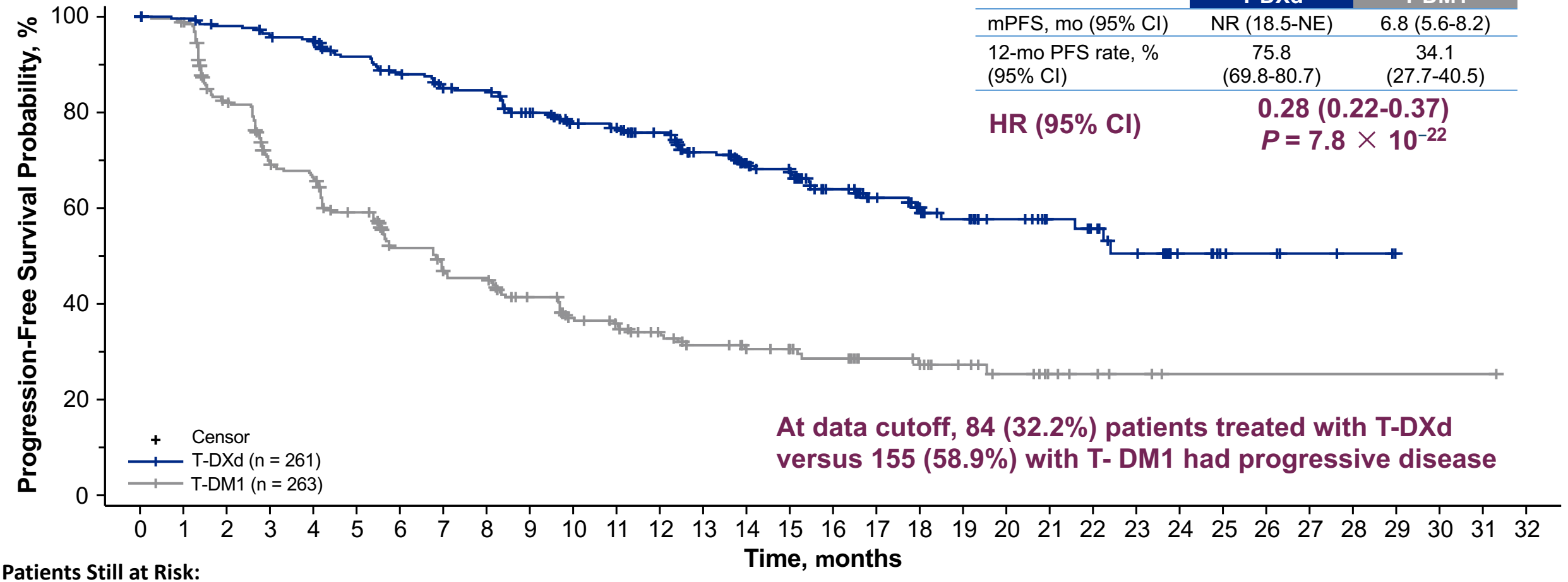
	T-DXd n = 261	T-DM1 n = 263
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, n (%)	260 (99.6)	262 (99.6)
Region, n (%)		
Europe	54 (20.7)	50 (19.0)
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Rest of world	41 (15.7)	36 (13.7)
HER2 status (IHC[a]), n (%)		
3+	234 (89.7)	232 (88.2)
2+ (ISH amplified)	25 (9.6)	30 (11.4)
1+ | Not evaluable	1 (0.4) | 1 (0.4)	0 | 1 (0.4)
ECOG PS, n (%)		
0 | 1	154 (59.0) | 106 (40.6)	175 (66.5) | 87 (33.1)
Hormone receptor, n (%)		
Positive | Negative	131 (50.2) | 130 (49.8)	134 (51.0) | 129 (49.0)
History of BM, n (%)		
Yes | No	62 (23.8) | 199 (76.2)	52 (19.8) | 211 (80.2)
BM at baseline,[b] n (%)		
Yes | No	43 (16.5) | 218 (83.5)	39 (14.8) | 224 (85.2)
Visceral disease, n (%)		
Yes | No	184 (70.5) | 77 (29.5)	185 (70.3) | 78 (29.7)
Prior treatment for mBC, n (%)	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting,[c] n (%)		
0-1 | ≥2	132 (50.6) | 129 (49.4)	126 (47.9) | 137 (52.1)
Prior cancer therapy,[d] n (%)		
Trastuzumab	260 (99.6)	262 (99.6)
Pertuzumab	162 (62.1)	158 (60.1)

BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; BC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]HER2-status as evaluated by central laboratory. [b]Patients with BM at baseline compose the patient population described in all subsequent slides. [c]Includes patients with rapid progression as 1 line of treatment. Rapid progression defined as progression within 6 months of (neo)adjuvant therapy or 12 months if regimen contained pertuzumab. Line of therapy does not include endocrine therapy. [d]All patients received at least 1 prior cancer therapy. One patient who underwent prior T-DM1 treatment was enrolled in error in the T-DXd arm.

Primary Endpoint: PFS by BICR

	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)	
	$P = 7.8 \times 10^{-22}$	



At data cutoff, 84 (32.2%) patients treated with T-DXd versus 155 (58.9%) with T- DM1 had progressive disease

Patients Still at Risk:

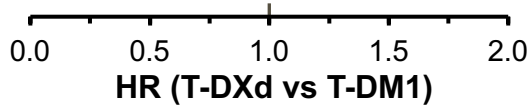
T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0			
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and was 13.9 months (range, 11.8-15.1) for T-DM1.

Cortés et al. *Ann Oncol*. 2021; 32(suppl_5):S1283-S1346. 10.1016/annonc/annonc741

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)

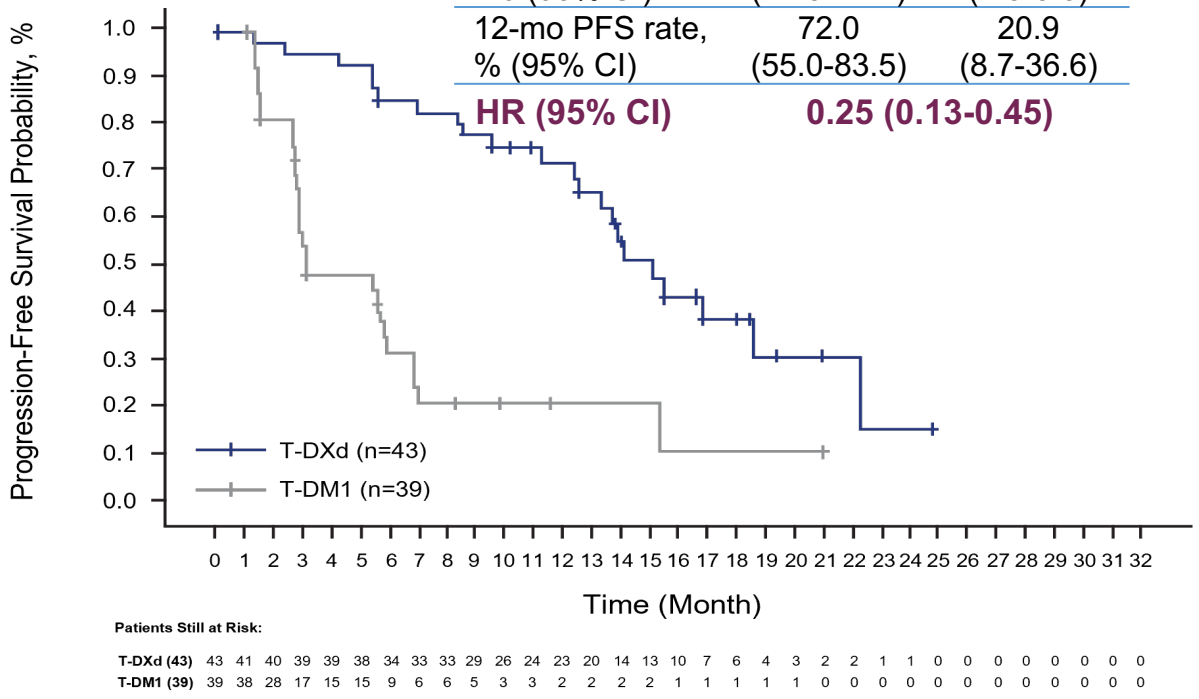


BM, brain metastasis; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Patients with rapid progression on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

PFS KM Curves for Patients With and Without BM

Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	**0.25 (0.13-0.45)**	

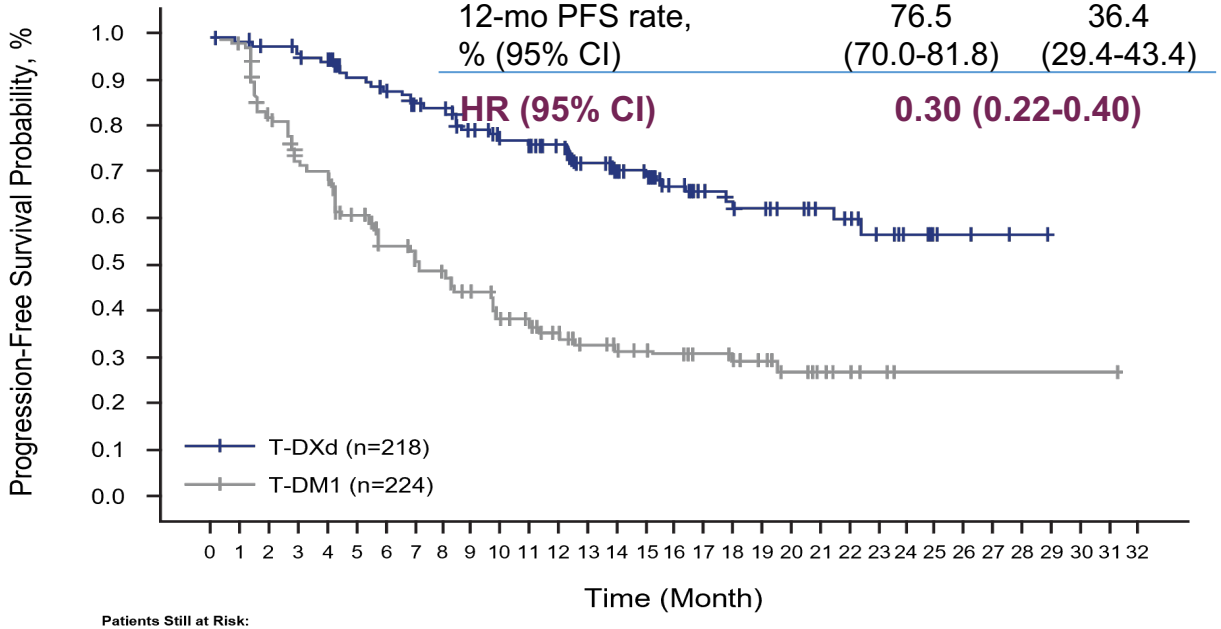


Patients Still at Risk:

T-DXd (43)	43	41	40	39	39	38	34	33	33	29	26	24	23	20	14	13	10	7	6	4	3	2	2	1	1	0	0	0	0	0	0	0	0
T-DM1 (39)	39	38	28	17	15	15	9	6	6	5	3	3	2	2	2	2	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0

No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	**0.30 (0.22-0.40)**	



Patients Still at Risk:

T-DXd (218)	218	215	210	205	201	186	180	169	167	154	142	140	127	112	98	92	69	57	47	41	33	27	23	18	9	6	5	3	2	0	0	0	0
T-DM1 (224)	224	214	172	146	140	117	99	90	87	73	62	57	49	41	35	32	28	22	20	15	11	8	6	4	1	1	1	1	1	1	1	1	0

At data cutoff, in patients with BM at baseline, PD was observed:

- In 21/43 treated with T-DXd versus 27/39 with T-DM1
  - In the brain in 9/21 treated with T-DXd versus 11/27 with T-DM1

At data cutoff, in patients without BM at baseline, PD was observed:

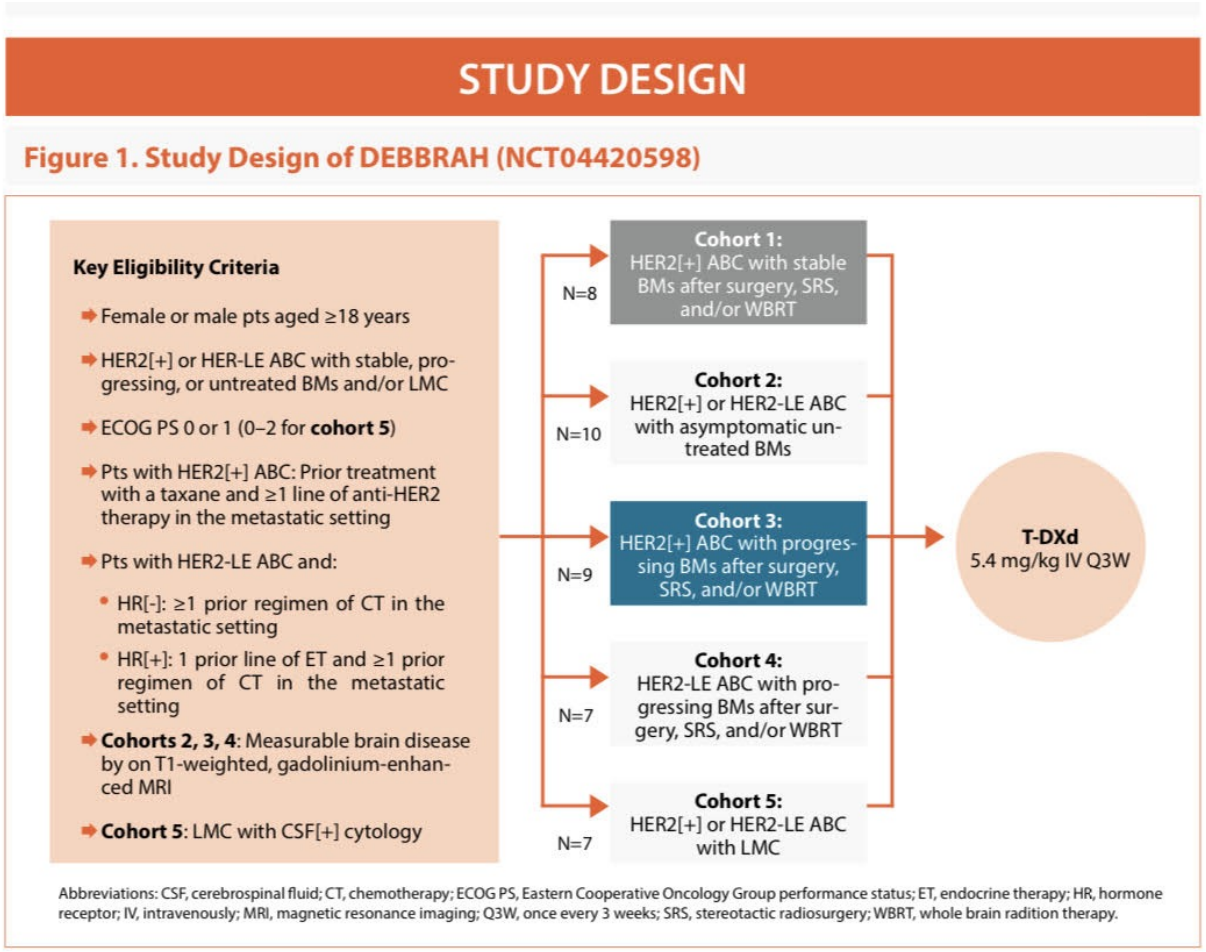
- In 63/218 treated with T-DXd versus 128/224 with T-DM1
  - In the brain in 4/63 treated with T-DXd versus 1/128 with T-DM1

mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

DEBBRAH: Trastuzumab deruxtecan in patients with Her2+ brain metastases (BM) and/or leptomeningeal carcinomatosis

- Among patients with non-progressing BM: 87.5% had stable BMs and were alive without progression at 16 weeks

- Among patients with progressive BM after local treatment, an intracranial objective response rate (ORR-IC) was reported in 44.4% of patients



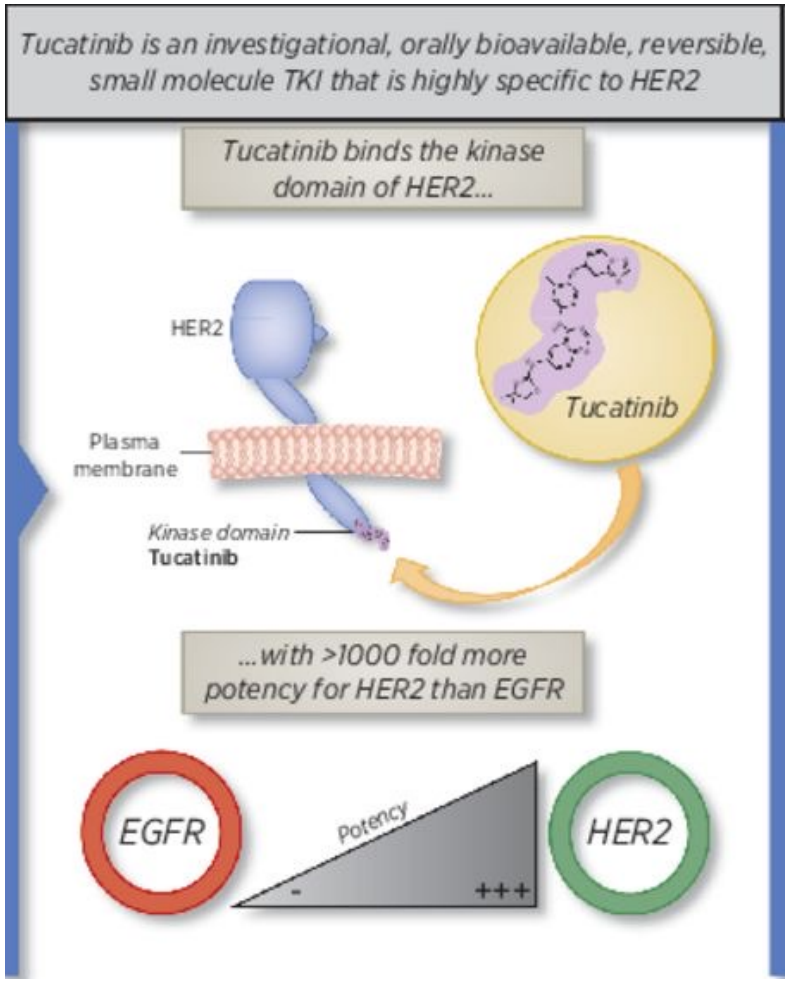
SABCS 2021

Trastuzumab deruxtecan

- Rapidly becoming a second-line standard of care
- Important to prepare patients for side effect profile that is different than T-DM1
  - Nausea, cytopenias, fatigue, alopecia
  - Have a low threshold to suspect ILD if symptoms develop
- In real-world practice, dose reductions and spacing out dosing can make the drug much more tolerable
- The every-three-week dosing and extremely short time to response make it a wonderful option for our patients

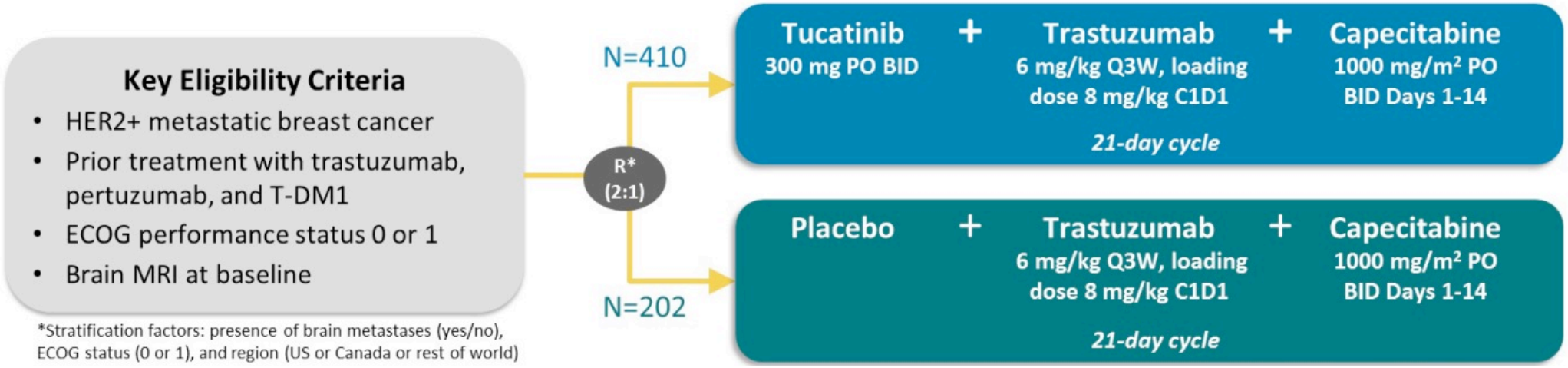
Tucatinib

- Orally bioavailable, highly potent
- Highly selective for HER>EGFR
  - Because of this, fewer EGFR-related toxicities (diarrhea, rash)
  - More favorable side effect profile may lead to better compliance, fewer dose reductions, and longer duration of treatment
- Superior activity compared with other TKIs in preclinical models of brain metastases



Dinkel V et al, AACR 2012, Abstract 852. Mol Cancer Ther. 2020; 19 (4): 976-987.

HER2CLIMB

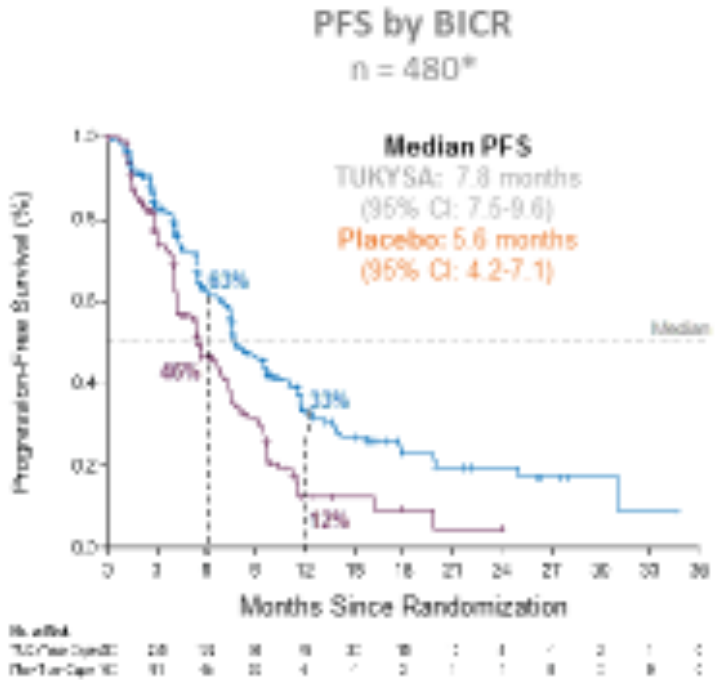


Brain Metastasis population included:

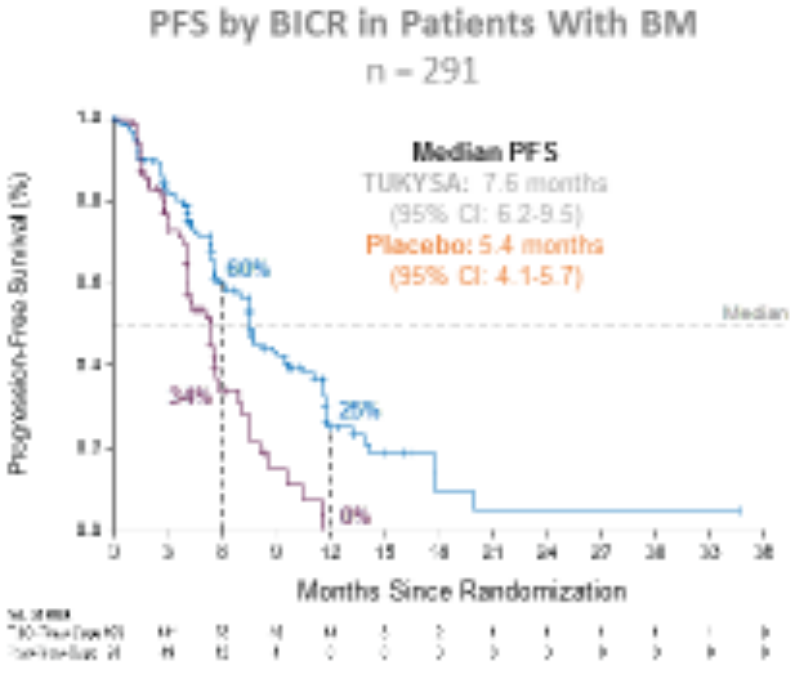
- Previously treated stable BM
- Untreated BM not needing immediate local therapy
- Previously treated progressing BM not needing immediate local therapy
- No evidence of BM

All Patients With BM, n	N = 291
Treated stable BM	**117**
Active BM	**174**
Treated progressing	108
Untreated	66

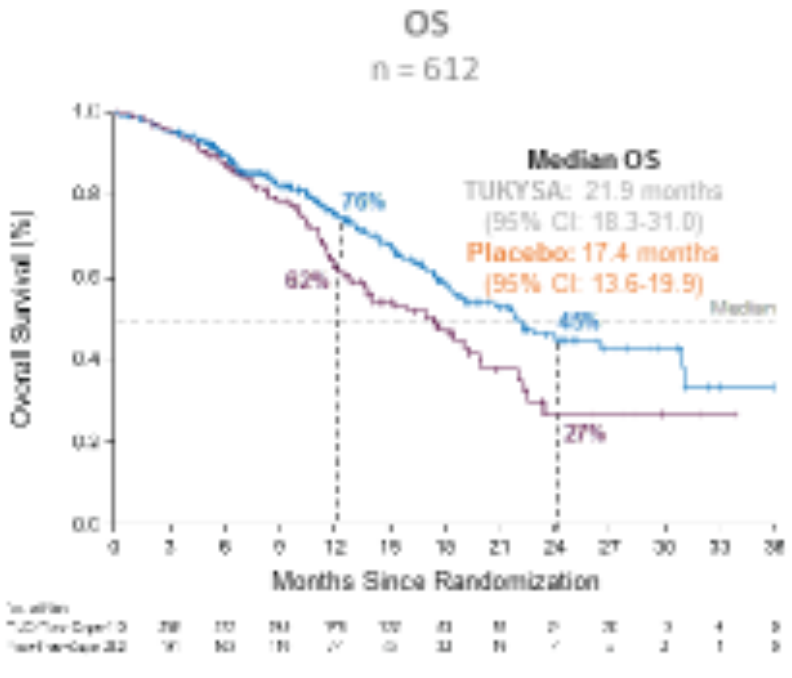
HER2CLIMB: Updated Results (primary interim analysis)



HR = 0.54 (95% CI: 0.42 to 0.71); *P* <0.001



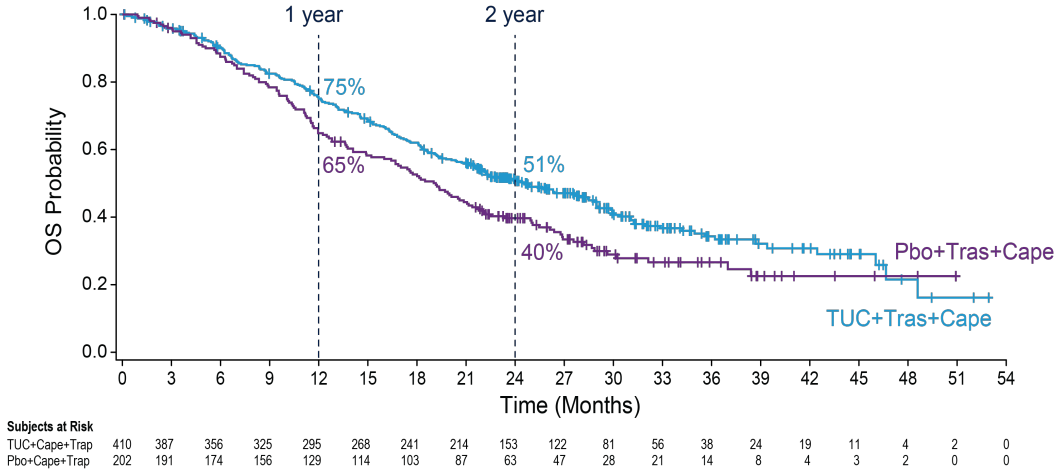
HR = 0.48 (95% CI: 0.34 to 0.69); *P* <0.001



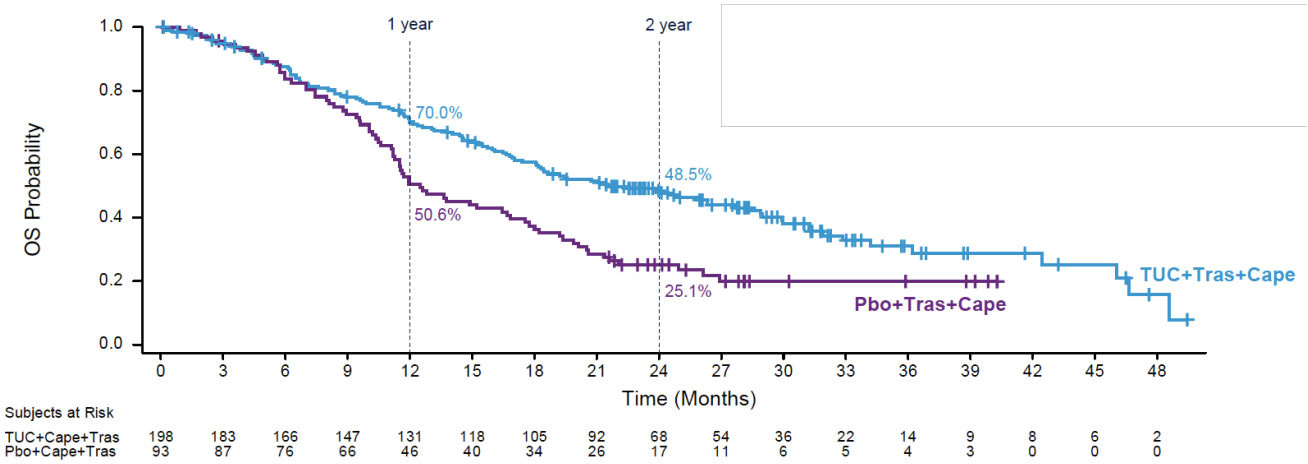
HR = 0.66 (95% CI: 0.50 to 0.87); *P* = 0.005

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

HER2CLIMB Updated Survival Analysis



OS for total population (n=612)



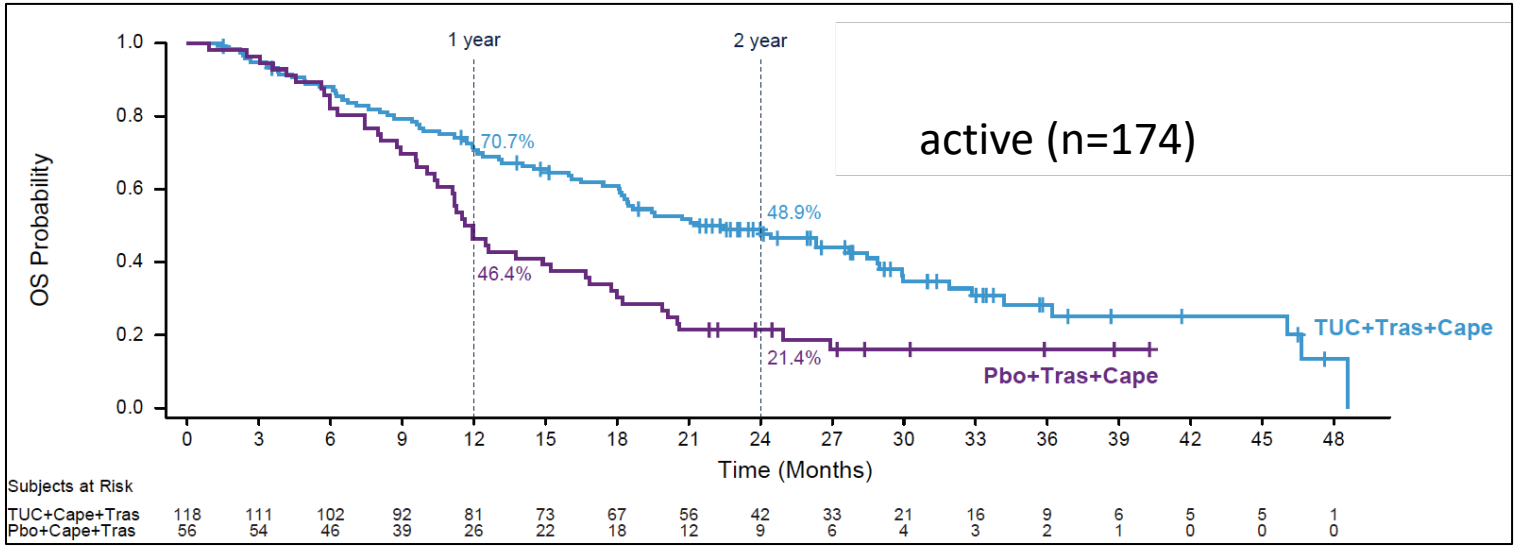
OS for all patients with brain mets (291)

	Events	HR (95% CI)	*P* Value	Median OS (95% CI)
TUC+Tras+Cape	**233/410**	0.73 (0.59, 0.90)	0.004	**24.7 months (21.6, 28.9)**
Pbo+Tras+Cape	**137/202**			**19.2 months (16.4, 21.4)**

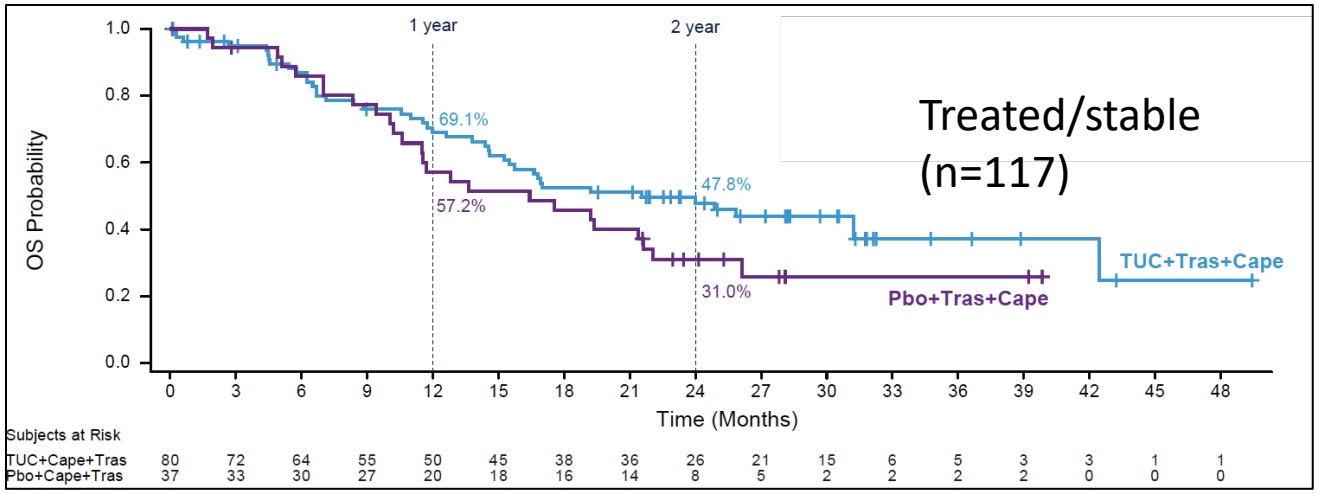
	Events	HR (95% CI)	*P* value	Median OS (95% CI)
TUC+Tras+Cape	**118/198**	0.600 (0.444, 0.811)	0.00078	**21.6 months (18.1, 28.5)**
Pbo+Tras+Cape	**71/93**			**12.5 months (11.2, 16.9)**

Curigliano G et al. Presented at American Society of Clinical Oncology Annual Meeting. June 4-8, 2021; Abstract 1043.
Lin NU et al. Presented at the San Antonio Breast Cancer Symposium. December 7-10, 2021. Abstract PD4-04.

OS in patients with stable vs active brain mets



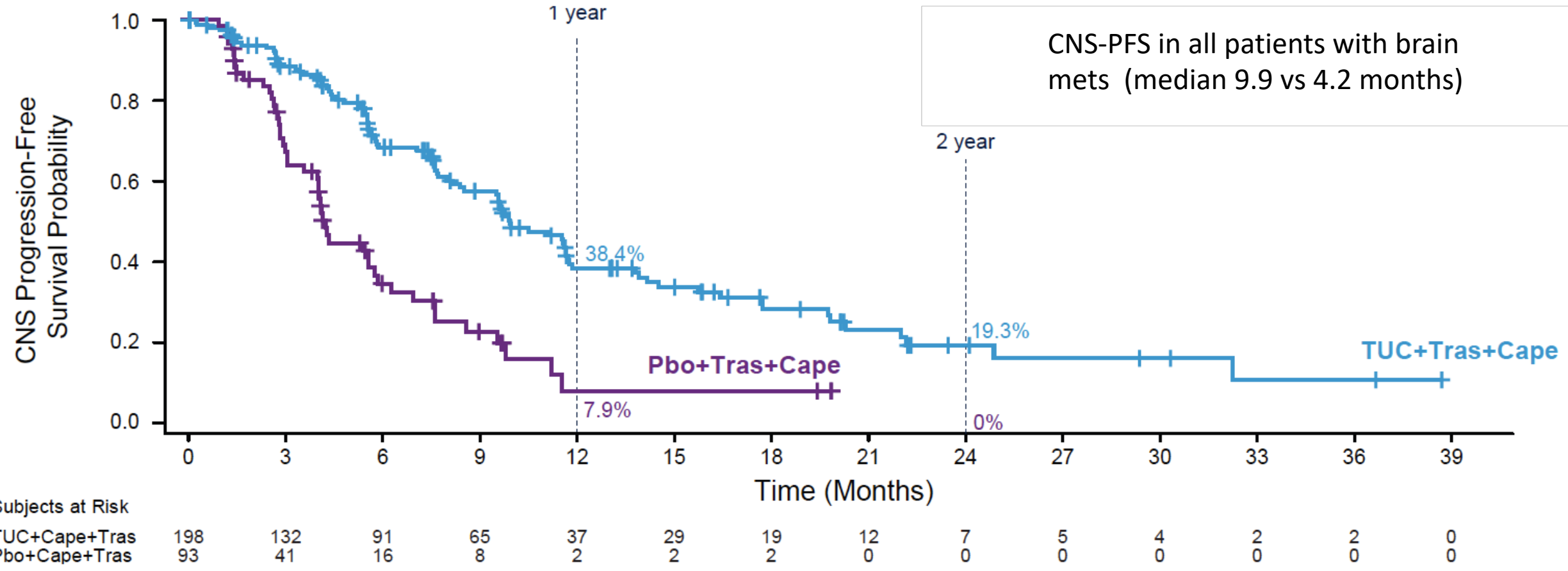
	Events	HR (95% CI)	*P* value	Median OS (95% CI)
TUC+Tras+Cape	**75/118**	0.524 (0.356, 0.771)	0.00087	**21.4 months (18.1, 28.9)**
Pbo+Tras+Cape	**46/56**			**11.8 months (10.3, 15.2)**



	Events	HR (95% CI)	*P* value	Median OS (95% CI)
TUC+Tras+Cape	**43/80**	0.695 (0.416, 1.160)	0.16223	**21.6 months (15.3, 42.4)**
Pbo+Tras+Cape	**25/37**			**16.4 months (10.6, 21.6)**

Lin NU et al. Presented at the San Antonio Breast Cancer Symposium. December 7-10, 2021. Abstract PD4-04.

Intracranial efficacy

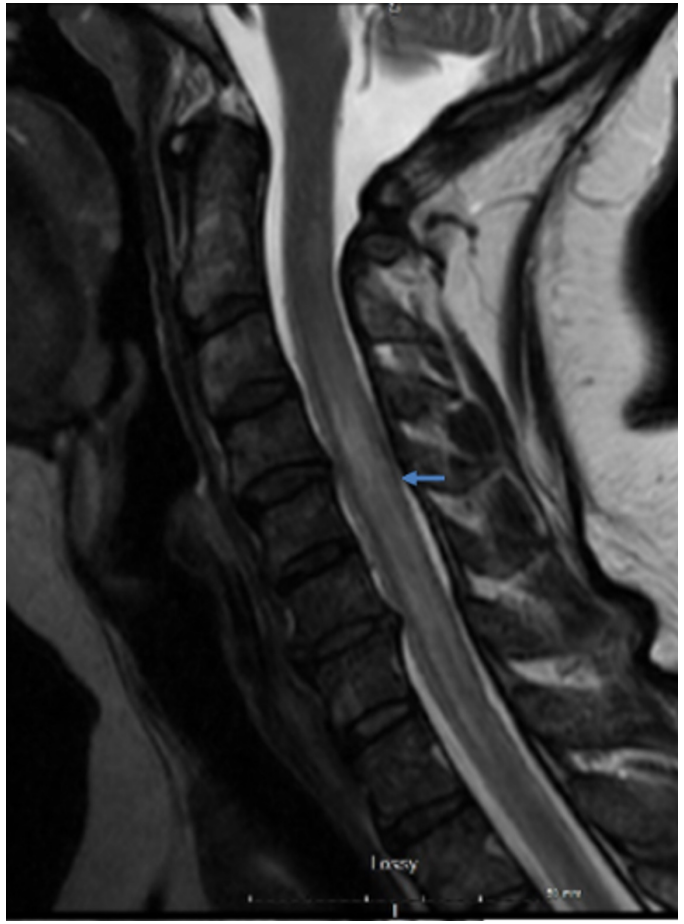


CNS-PFS in all patients with brain mets (median 9.9 vs 4.2 months)

Lin NU et al. Presented at the San Antonio Breast Cancer Symposium. December 7-10, 2021. Abstract PD4-04.

Tucatinib in Leptomeningeal disease: TBCRC 049

- Enrolled patients with HER2+ MBC and newly diagnosed, untreated LMD
- Primary endpoint: Overall survival (with parallel PK endpoints in plasma and CSF)
  - ASCO 2021: Tucatinib levels and levels of ONT-993, its predominant metabolite, were detectable in CSF of all patients at median levels similar to plasma tucatinib
  - SABCS 2021: Median OS was 10 months, compared to a 4-5 month OS for historical controls



J Clin Oncol 2021; 39 (suppl 15; absr 1044). SABCS 2021, PD4-02.

Tucatinib: real-world use

- HER2CLIMB regimen is a great option in second/third line and is approved in this setting
  - Toxicity is minimal due to its targeted nature

- Choice of this regimen vs trastuzumab deruxtecan has to take multiple features into account
  - Presence and level of activity of brain metastases
  - Disease burden of systemic disease
  - Timing of progression on initial therapy
  - Patient preferences regarding side effect profiles and schedules

Tucatinib: future possibilities

- Trials looking at tucatinib in other spaces:
  - T-DM1 + placebo or tucatinib (NCT03975647; actively recruiting)
  - Trastuzumab deruxtecan + placebo or tucatinib (NCT04539938, actively recruiting)
  - Trastuzumab/pertuzumab + tucatinib or placebo (NCT05132582; actively recruiting)
  - Tucatinib + palbociclib + letrozole (NCT03054363; fully enrolled)

OTHER PLANNED STUDIES

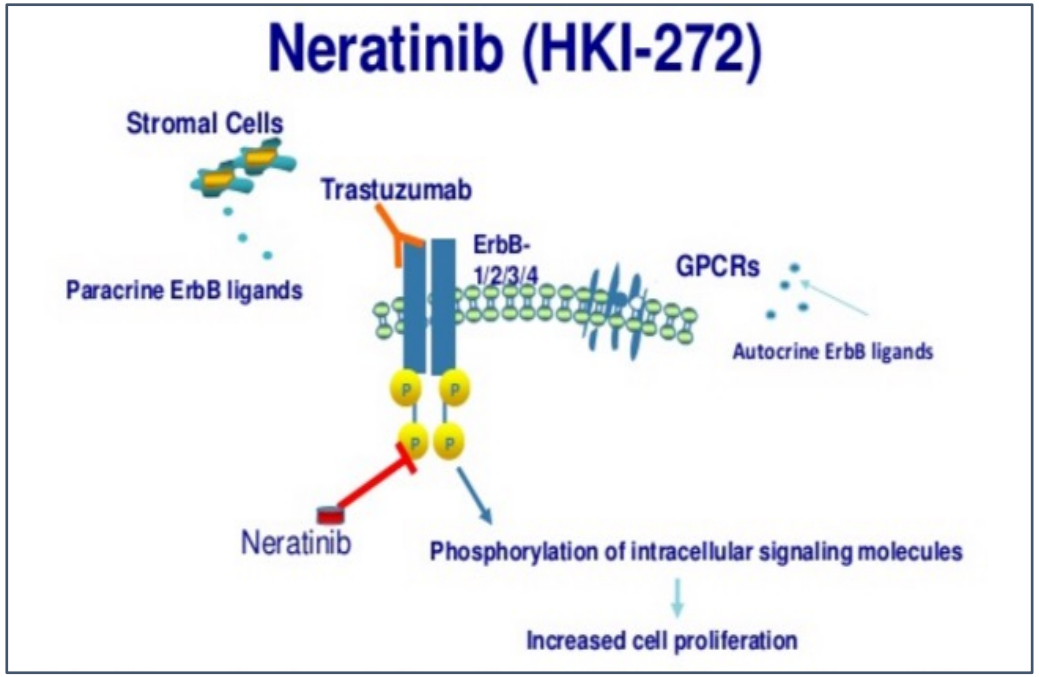
- Tucatinib + margetuximab + capecitabine
- Alpelisib + tucatinib in HER2+ PIK3CA mutant breast cancer

Neratinib

- Potent, low-molecular weight, irreversible pan-TKI with activity against HER1, HER2 and HER4

- Binds to intracellular tyrosine kinase domain to inhibit auto-phosphorylation and downstream signaling

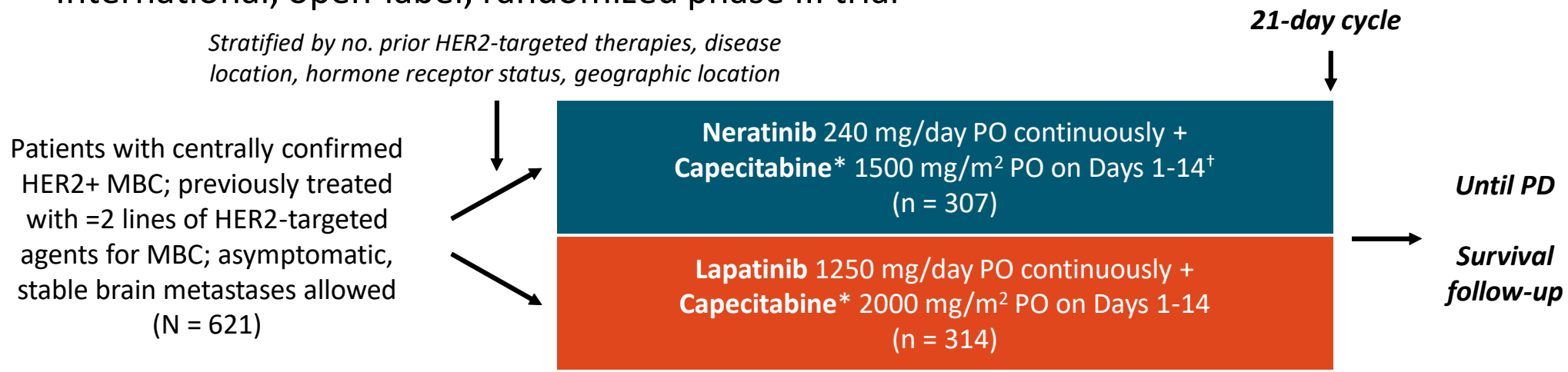
- Most common adverse effects: diarrhea, nausea, fatigue, vomiting



Breast Cancer Res 2009 Suppl 1: S19

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

- International, open-label, randomized phase III trial



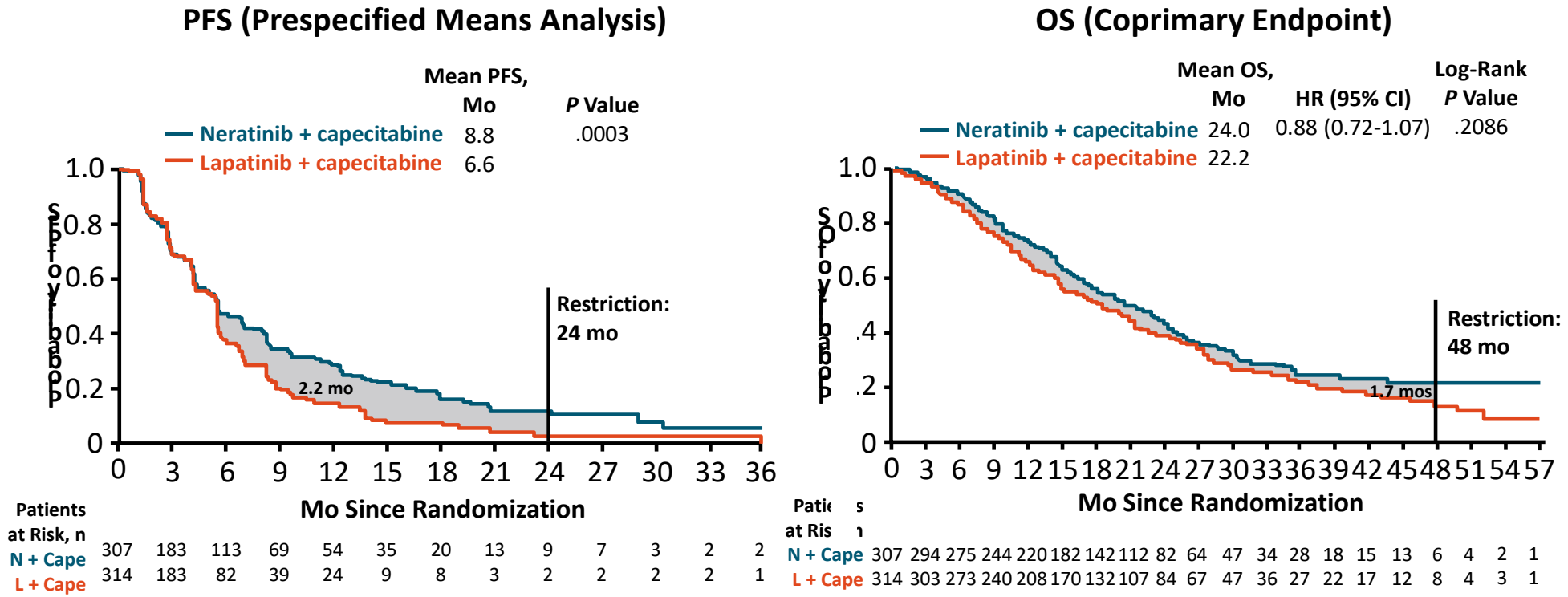
*BID in 2 evenly divided doses. †Loperamide administered at 4 mg with first neratinib dose followed by 2 mg Q4H for first 3 days, followed by 2 mg every 6-8 hr through end of cycle 1; as needed thereafter.

- 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, intervention for CNS metastases, safety, PROs
- No endocrine therapy permitted

Saura. JCO. 2020; 38:3138.

Slide credit: clinicaloptions.com

NALA results



	Neratinib	Lapatinib
ORR	33%	27%
18-month PFS	16%	7%
Mean OS	24 mo	22 mo

Saura . JCO. 2020; 38: 3138

Margetuximab

- Same specificity and affinity to HER2 as trastuzumab with similar ability to disrupt signaling

- However, due to increased affinity for Fc CD16A and decreased affinity for CD32B, it may enhance innate immunity and provide more potent ADCC stimulation

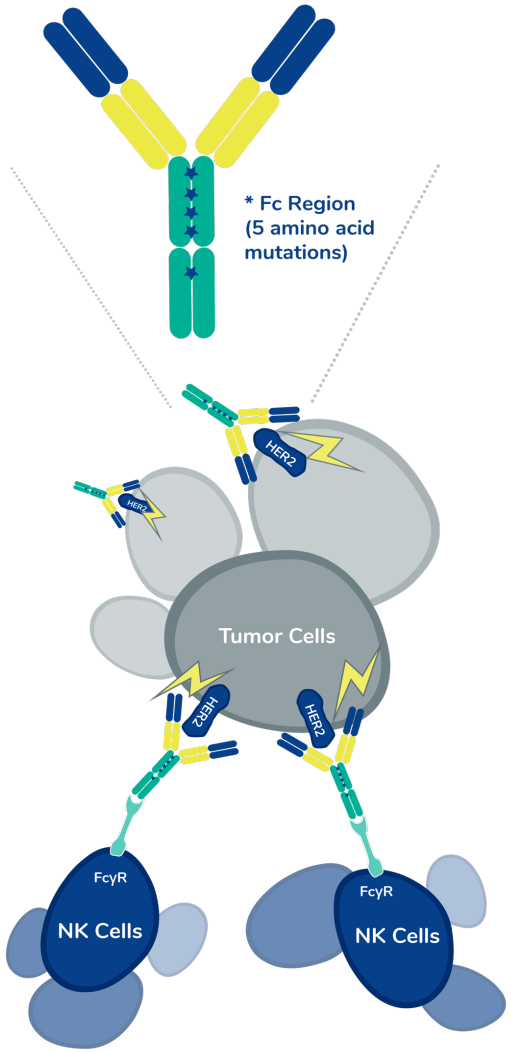
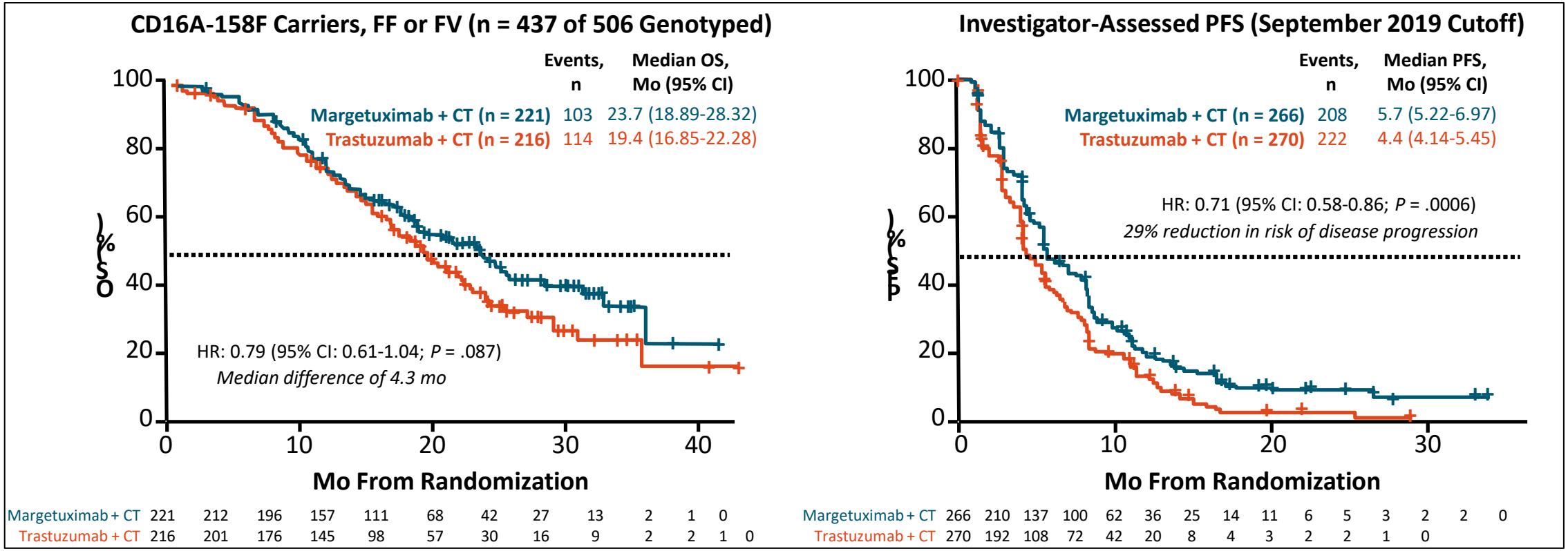


Photo courtesy of margetuximab prescribing information.

SOPHIA trial (margetuximab vs trastuzumab + chemotherapy): survival



Margetuximab: clinical practice

- Given cost and modest benefits over trastuzumab, this is generally reserved for later lines of treatment
- Most common reactions: fatigue, GI symptoms, headache, cough, dyspnea, and infusion reactions
- Trials
  - Ongoing: MARGOT study (margetuximab vs trastuzumab + pertuzumab/paclitaxel in stage 2-3 disease)
  - Upcoming: margetuximab + tucatinib + capecitabine

Possible future directions

- **Trastuzumab deruxtecan in HER2-low breast cancer**
  - DESTINY-Breast-04 met its primary endpoint
- **New antibody-drug conjugates**
  - After promising early results in ACE-Breast-01, ARX-788 being studied in ACE-Breast 03
- **Tucatinib in other spaces**
  - Tucatinib with HP as first line maintenance (HER2-CLIMB 05)
  - Trastuzumab deruxtecan and tucatinib (HER2CLIMB-04)
- **CDK 4/6 inhibitors in triple-positive disease**
  - PATINA: evaluating palbociclib + letrozole/trastuzumab/trastuzumab as first-line maintenance
  - MONARCHer: showed benefit of fulvestrant/abemaciclib/trastuzumab vs chemotherapy + trastuzumab in an RCT

Conclusions

- The management of HER2+ breast cancer has improved by leaps and bounds over the past 3 years
- Many new treatment options now, and more will be available as additional studies report conclusions
- Given all the options available, shared decision making and optimization of side effects becomes even more important

Thank you!