Advances in HER2 Positive Breast Cancer

The ESHOS Review of

San Antonio Breast Cancer Symposium

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Wilmot Cancer Institute

University of Rochester Medical Center

Medicine of the Highest Order

UR Medicine | Wilmot Cancer Institute

Disclosures

- Advisory Board: Gilead, AstraZeneca
- Honorarium: MJH Life Sciences (OncLive), WebMD

Slides from past conferences: Permission received from original presenters (Hurvitz, Modi, Lin, Krop)

HER2 Pathway

Monoclonal Antibodies:

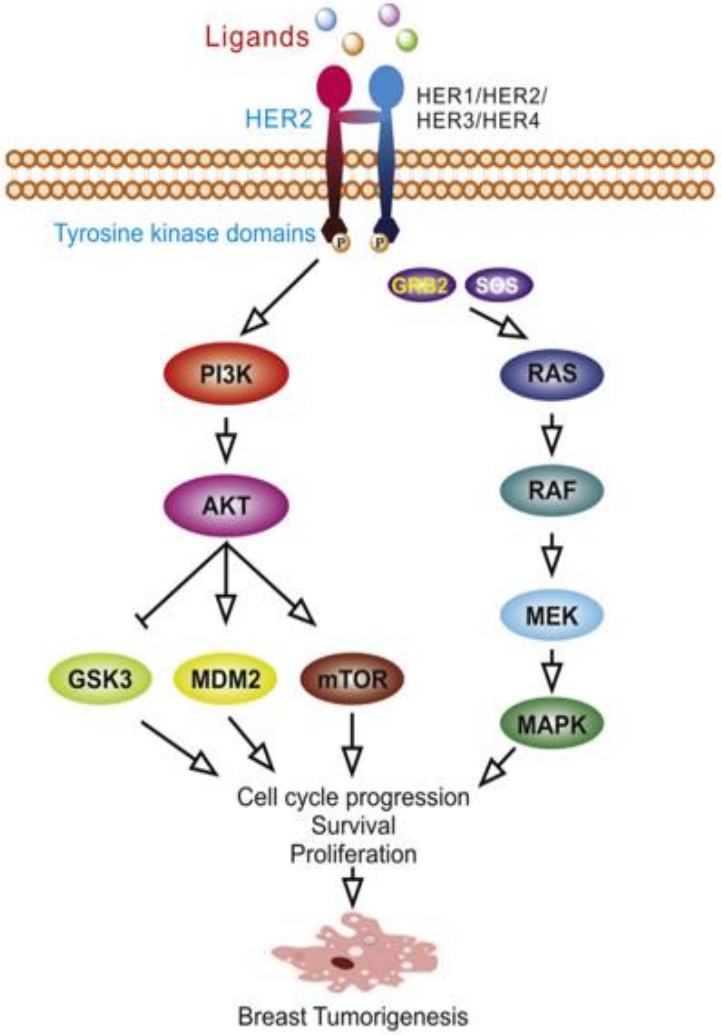
Trastuzumab

Pertuzumab

Margetuximab

Tyrosine Kinase Inhibitors:

1. Tucatinib
2. Neratinib
3. Lapatinib



Feng Y, Spezia M, et al. Genes Dis. 2018 May 12;5(2):77-106.

Antibody Drug Conjugates:

Trastuzumab deruxtecan

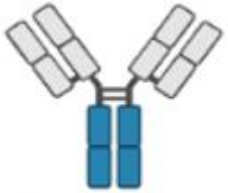
Trastuzumab emtansine

HER2 Pathway

Monoclonal Antibodies:

Trastuzumab

Pertuzumab



Margetuximab

Tyrosine Kinase Inhibitors:

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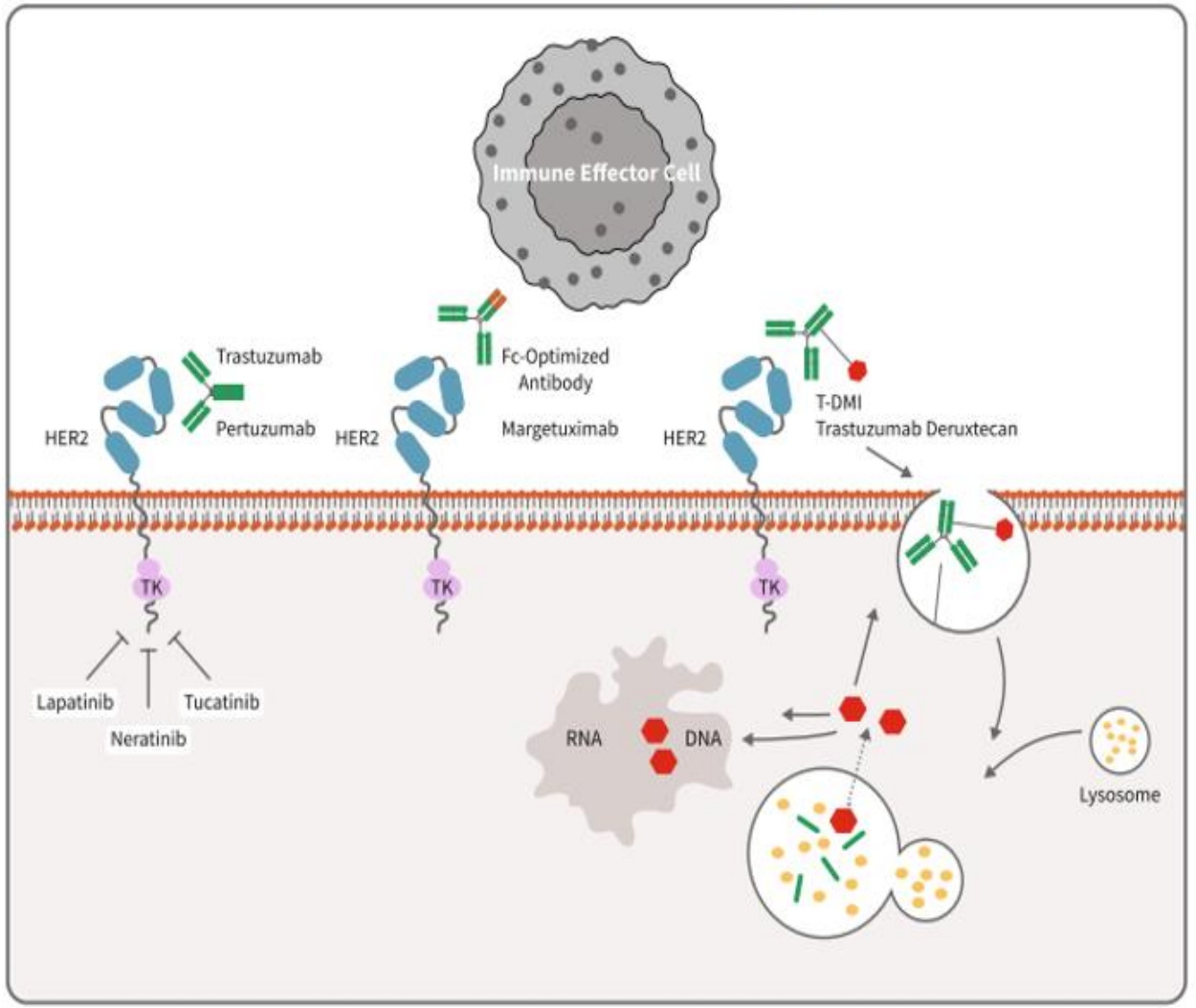
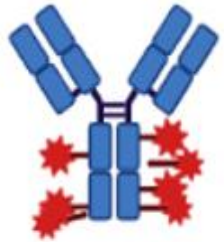


Antibody Drug Conjugates:



Trastuzumab deruxtecan

Trastuzumab emtansine

Wynn, C.S., Tang, SC. Anti-HER2 therapy in metastatic breast cancer: many choices and future directions. *Cancer Metastasis Rev* **41**, 193–209 (2022).

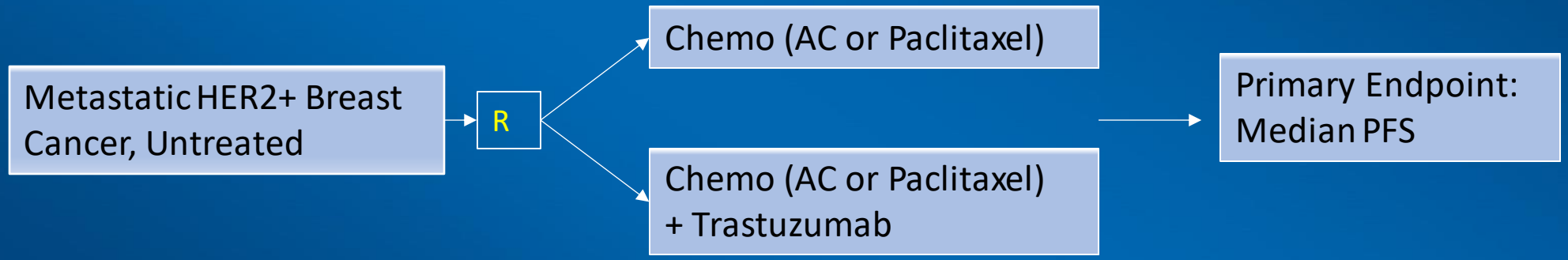
Metastatic Space

Trastuzumab

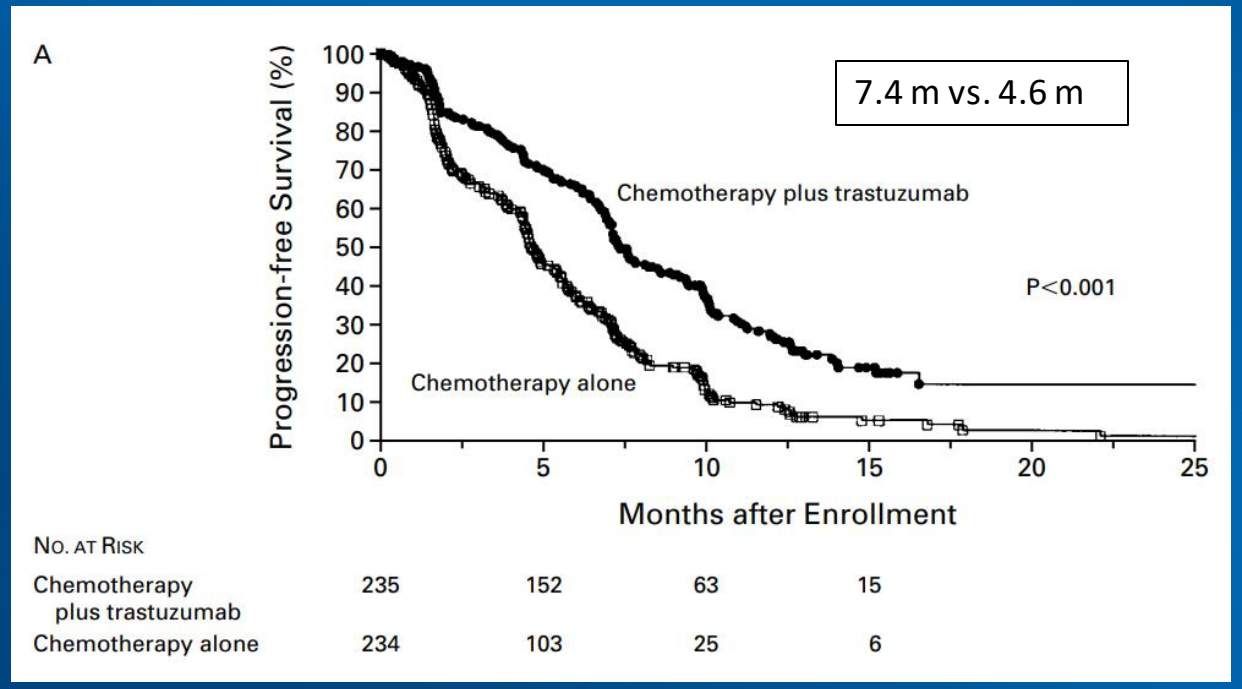
ORIGINAL ARTICLE

Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2

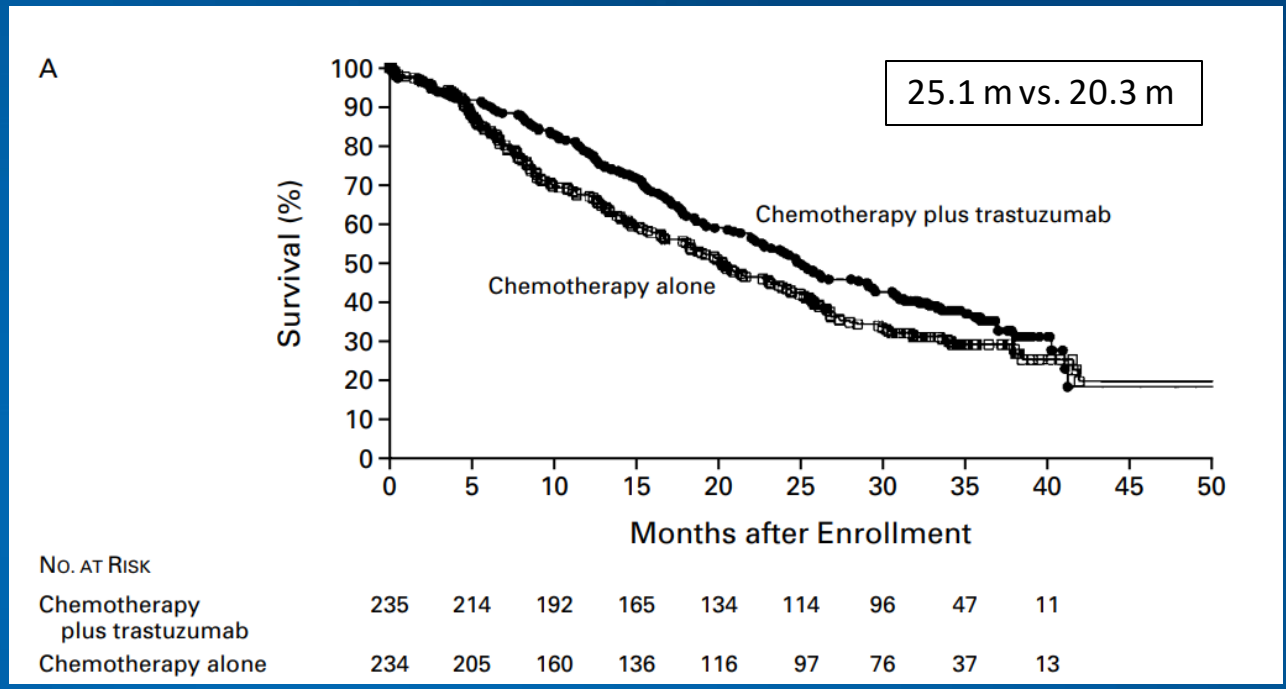
Dennis J. Slamon, M.D., Ph.D., Brian Leyland-Jones, M.D., Steven Shak, M.D., Hank Fuchs, M.D., Virginia Paton, Pharm.D., Alex Bajamonde, Ph.D., Thomas Fleming, Ph.D., Wolfgang Eiermann, M.D., Janet Wolter, M.D., Mark Pegram, M.D., Jose Baselga, M.D., and Larry Norton, M.D.*



Slamon et al. N Engl J Med 2001; 344:783-792



Progression Free Survival



Overall Survival

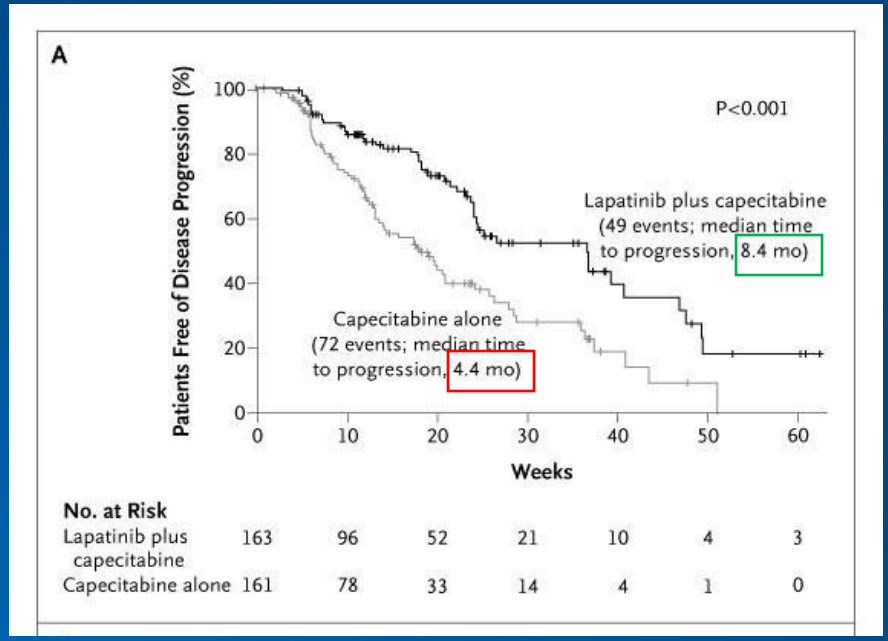
Slamon et al. N Engl J Med 2001; 344:783-792

Lapatinib

ORIGINAL ARTICLE

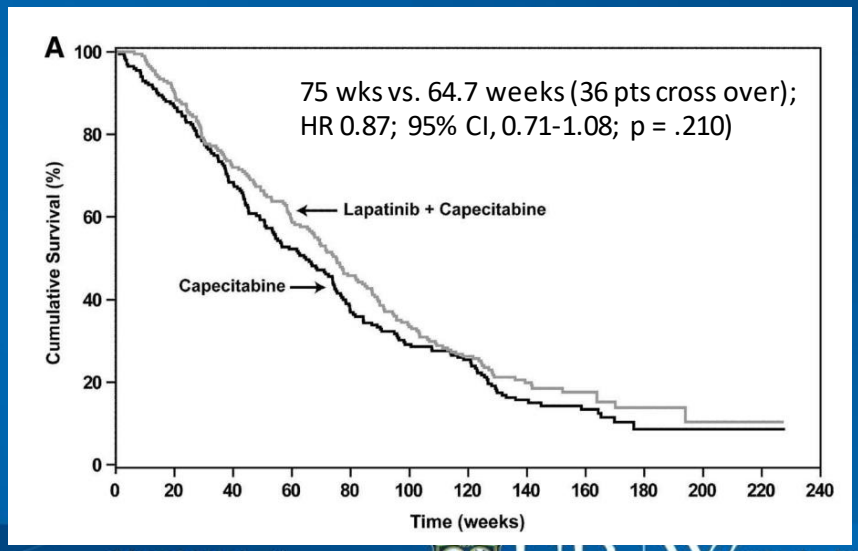
Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer

Charles E. Geyer, M.D., John Forster, M.Sc., Deborah Lindquist, M.D., Stephen Chan, M.D., C. Gilles Romieu, M.D., Tadeusz Pienkowski, M.D., Ph.D., Agnieszka Jagiello-Gruszfeld, M.D., John Crown, M.D., Arlene Chan, M.D., Bella Kaufman, M.D., Dimosthenis Skarlos, M.D., Mario Campone, M.D., et al.



Metastatic HER2+ BC after progression on chemo + trastuzumab

- Lapatinib 1250mg+ capecitabine 1000mg/m2/dose
- capecitabine 1250mg/m2/dose



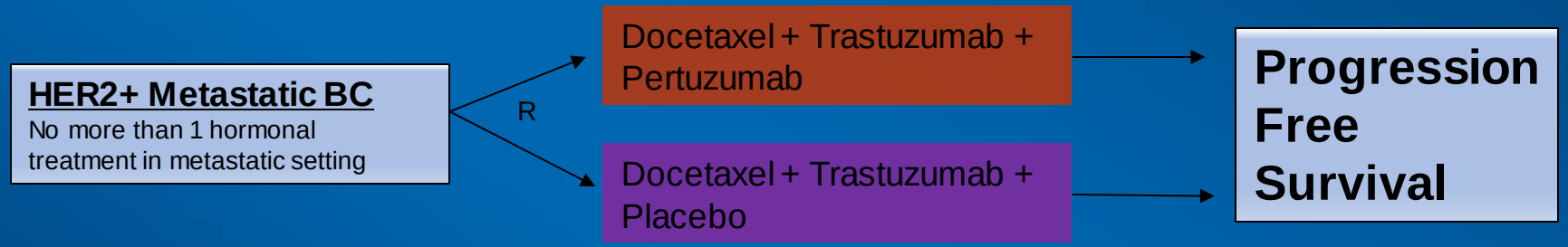
Geyer CE et al. N Engl J Med 2006;355:2733-2743.

Cameron D et al. Oncologist. 2010;15(9):924-34. doi: 10.1634/theoncologist.2009-0181.

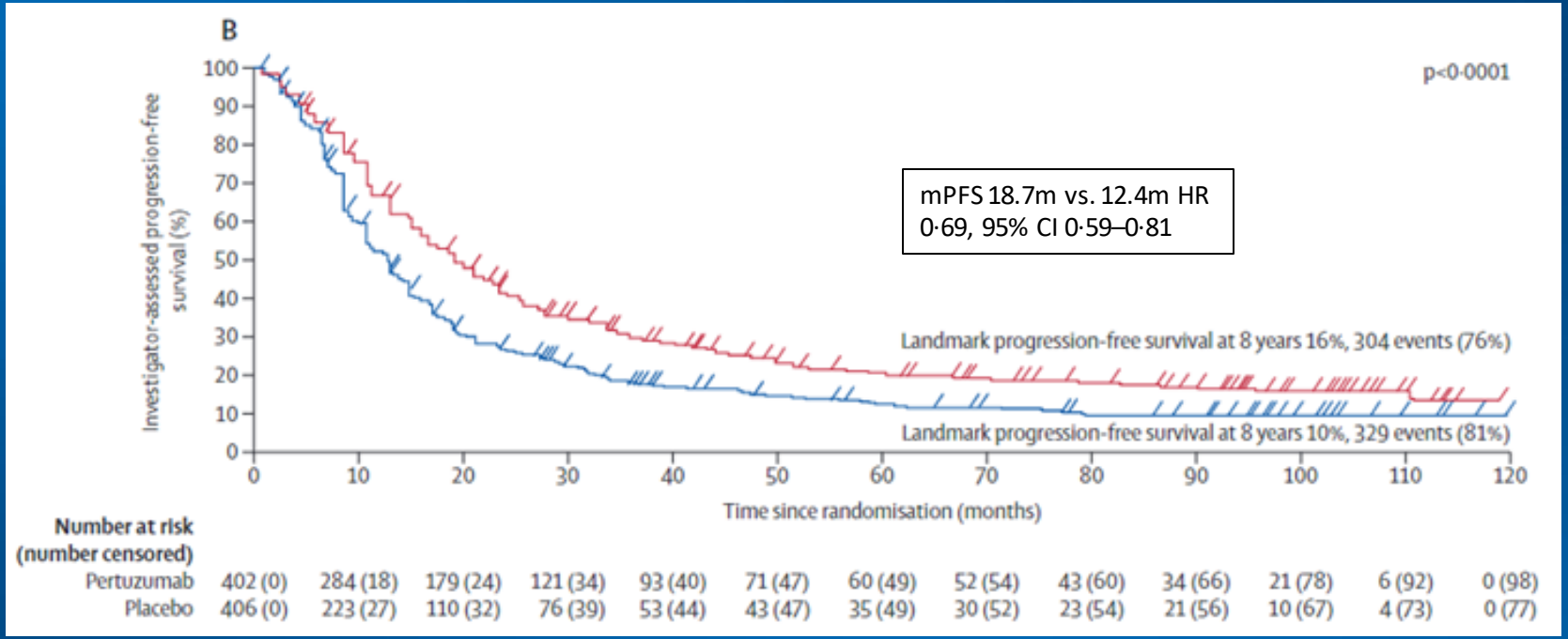
Pertuzumab

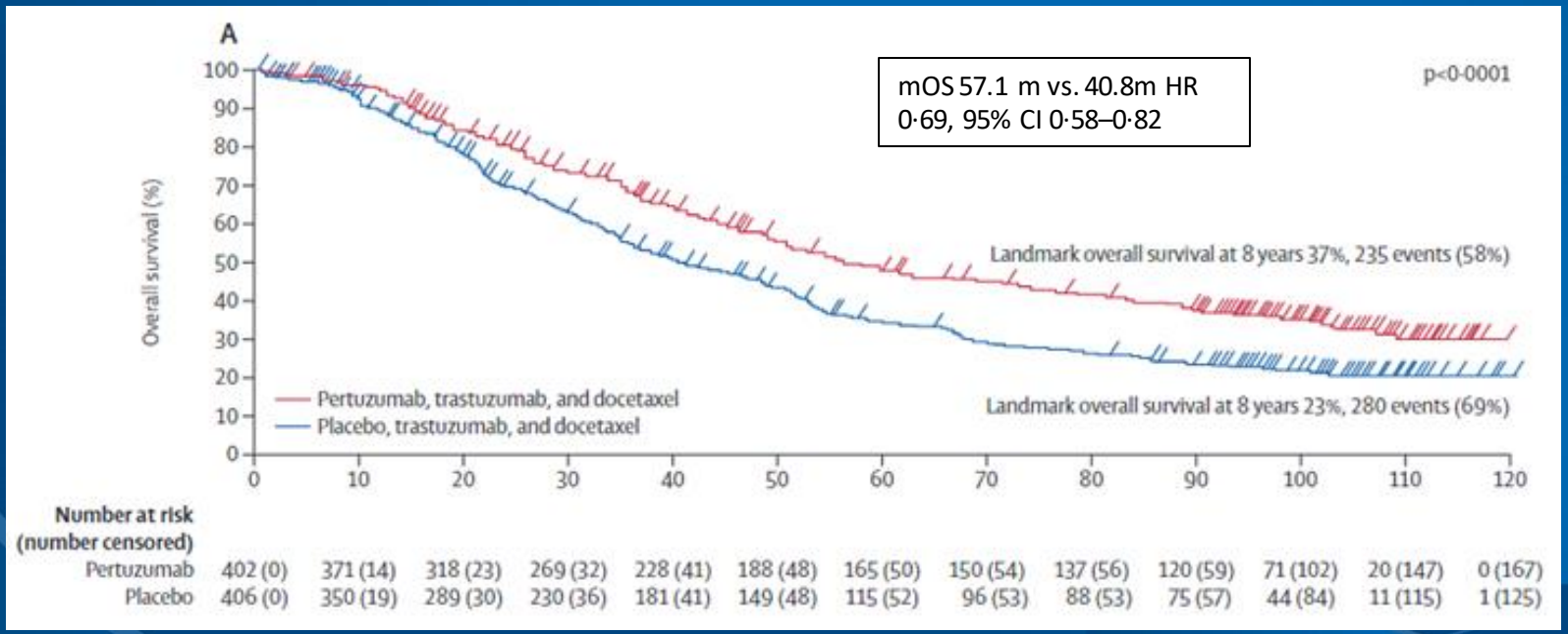
Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., et al., for the CLEOPATRA Study Group*



Baselga et al. NEJM 2012





G3 Diarrhea: 10% with pertuzumab vs. 5% with placebo

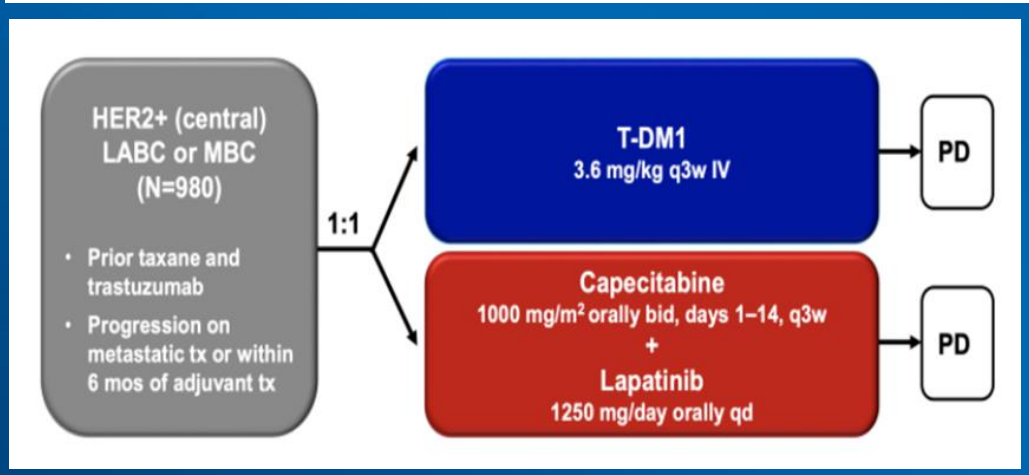
Swain et al. Lancet Oncology 2020

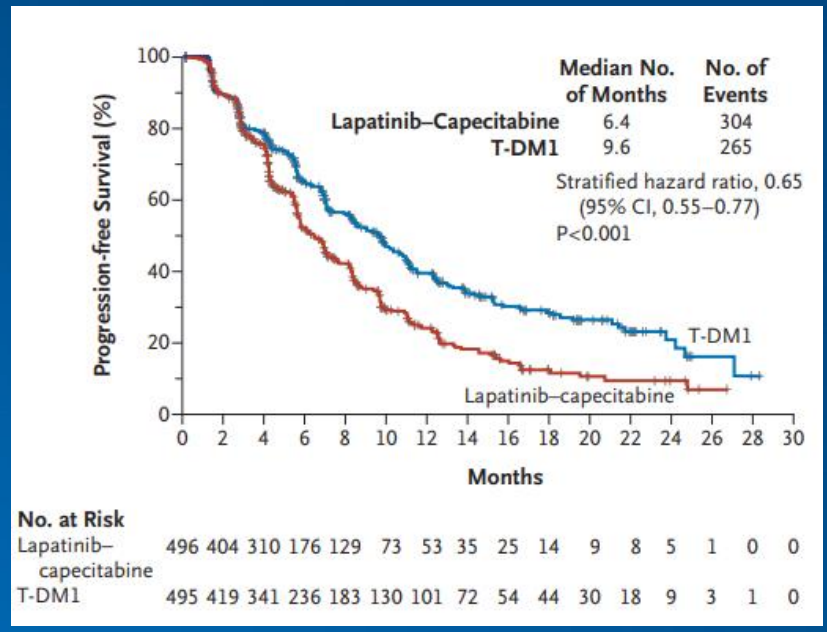
Trastuzumab emtansine

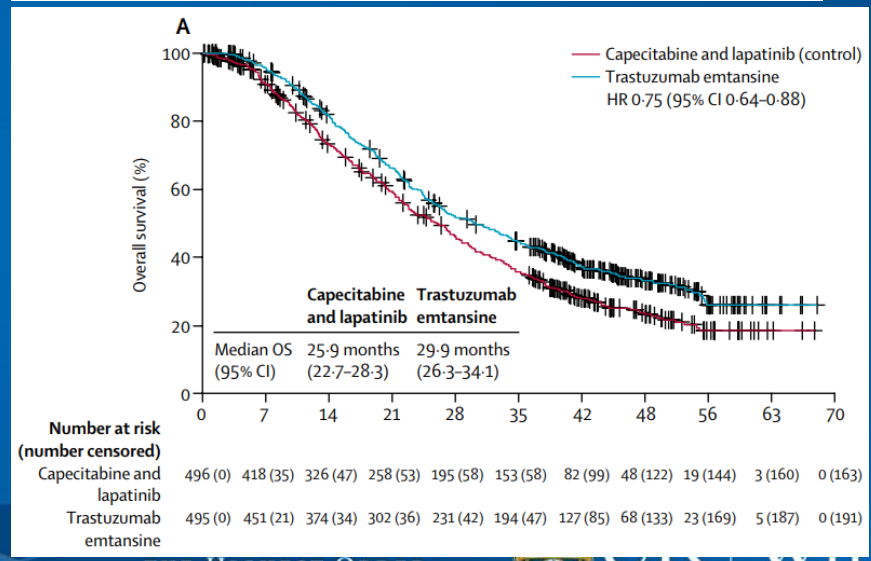
ORIGINAL ARTICLE

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., et al., for the EMILIA Study Group







Verma et al. NEJM 2012
Dieras et al. Lancet Onc 2017

Trastuzumab deruxtecan

Trastuzumab Deruxtecan (T-DXd): Next Generation HER2 ADC

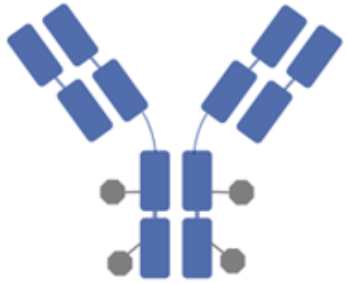
Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)

HER2 Targeting ADCs with similar mAB Backbone

T-DXd	ADC Attributes	T-DM1
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)



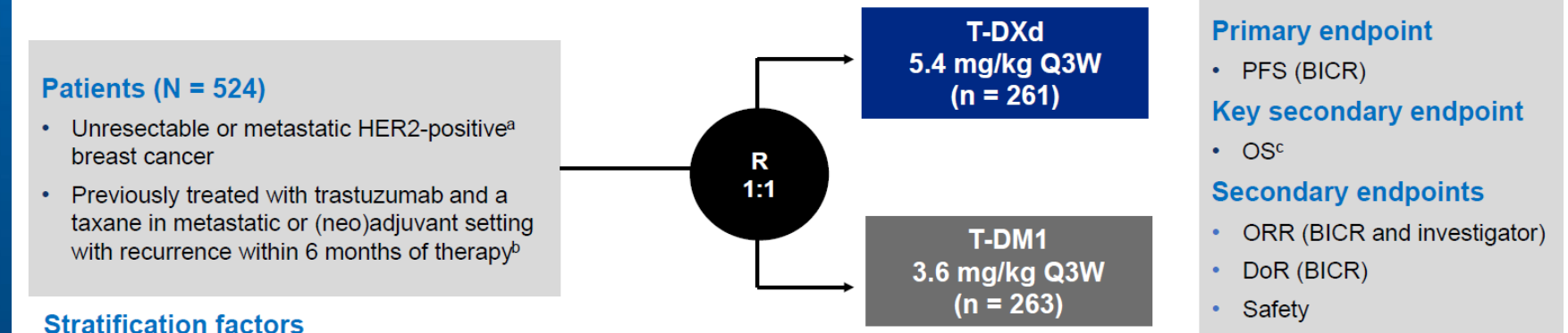
1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42.
4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res.* 2011;17:6437-47.

Cortes, J et al. ESMO 2021

ORIGINAL ARTICLE

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

Javier Cortés, M.D., Ph.D., Sung-Bae Kim, M.D., Ph.D., Wei-Pang Chung, M.D., Seock-Ah Im, M.D., Ph.D., Yeon Hee Park, M.D., Ph.D., Roberto Hegg, M.D., Ph.D., Min Hwan Kim, M.D., Ph.D., Ling-Ming Tseng, M.D., Vanessa Petry, M.D., Chi-Feng Chung, M.D., Hiroji Iwata, M.D., Ph.D., Erika Hamilton, M.D., et al., for the DESTINY-Breast03 Trial Investigators*



The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; 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 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or within 6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]80% powered at 2-sided significance level of 5%. [d]Information fraction of 61%, with a *P* value boundary to reach statistical significance of 0.008. The *P* value was recalculated based on the actual OS events at the data cutoff.

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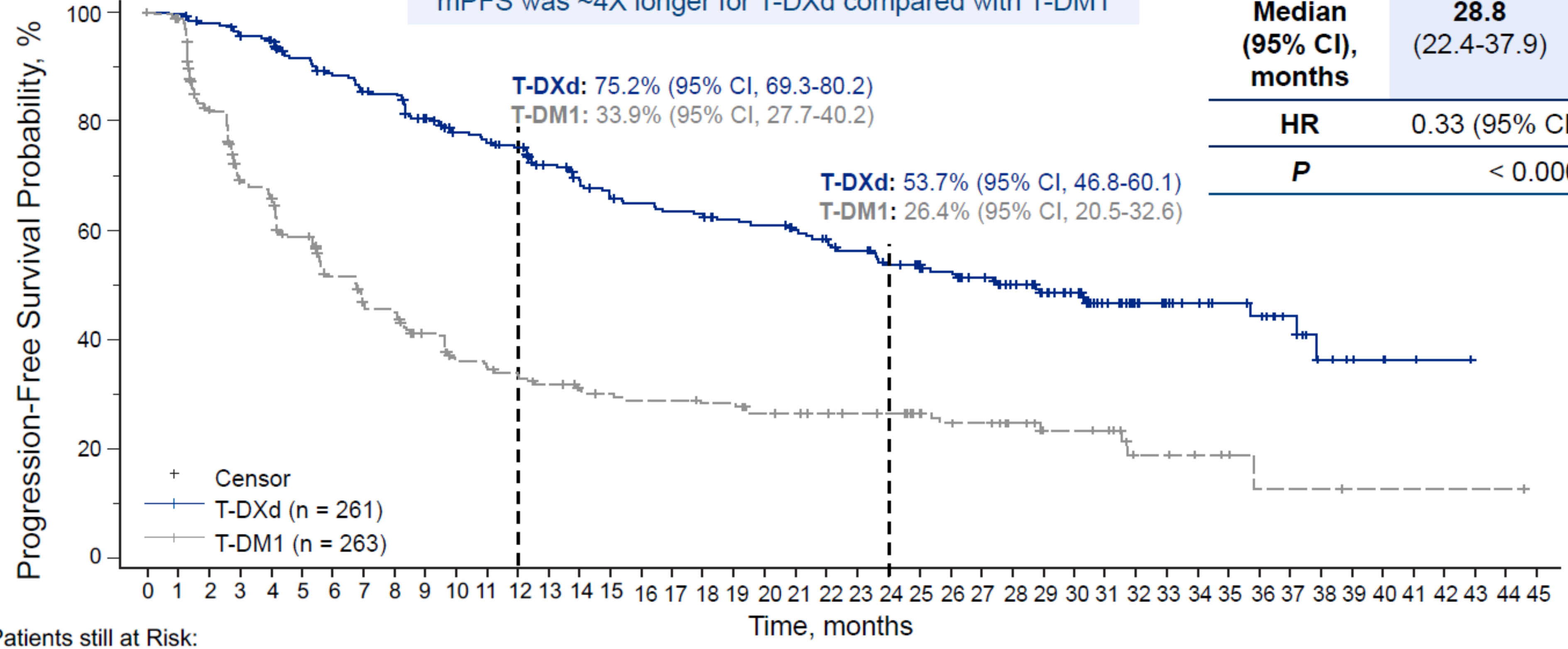
Cortes et al. NEJM 2022.
Hurvitz et al. SABCS 2022

Updated Primary Endpoint: PFS by BICR

mPFS was ~4X longer for T-DXd compared with T-DM1



	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:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
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

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

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Hurvitz et al. SABCS 2022

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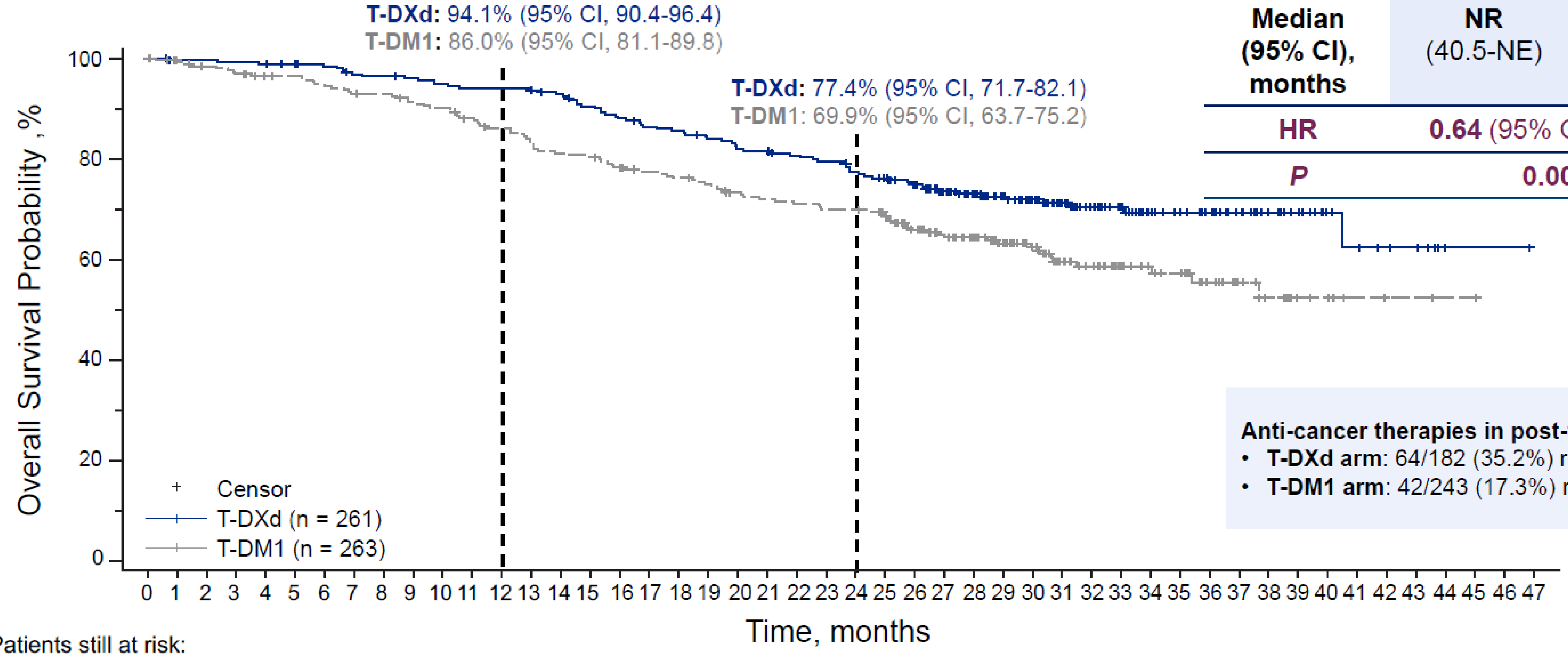
Key Secondary Endpoint: Overall Survival

	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]	



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

Patients still at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
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
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

	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
T-DXd	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	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

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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 et al, NEJM 2022

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

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

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
  or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

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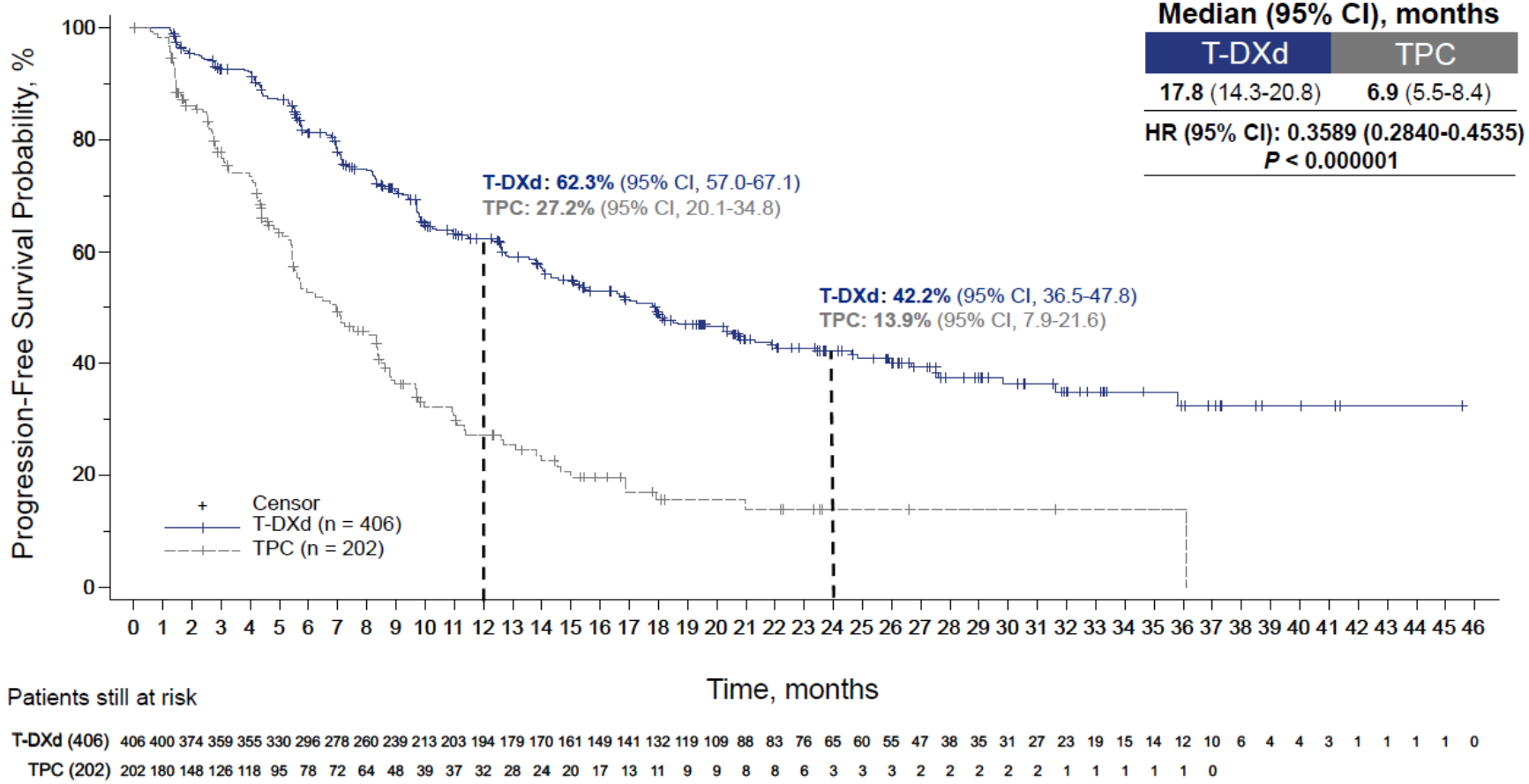
Krop et al, SABCS 2022

Primary Endpoint: PFS by BICR



Krop et al, SABCS 2022

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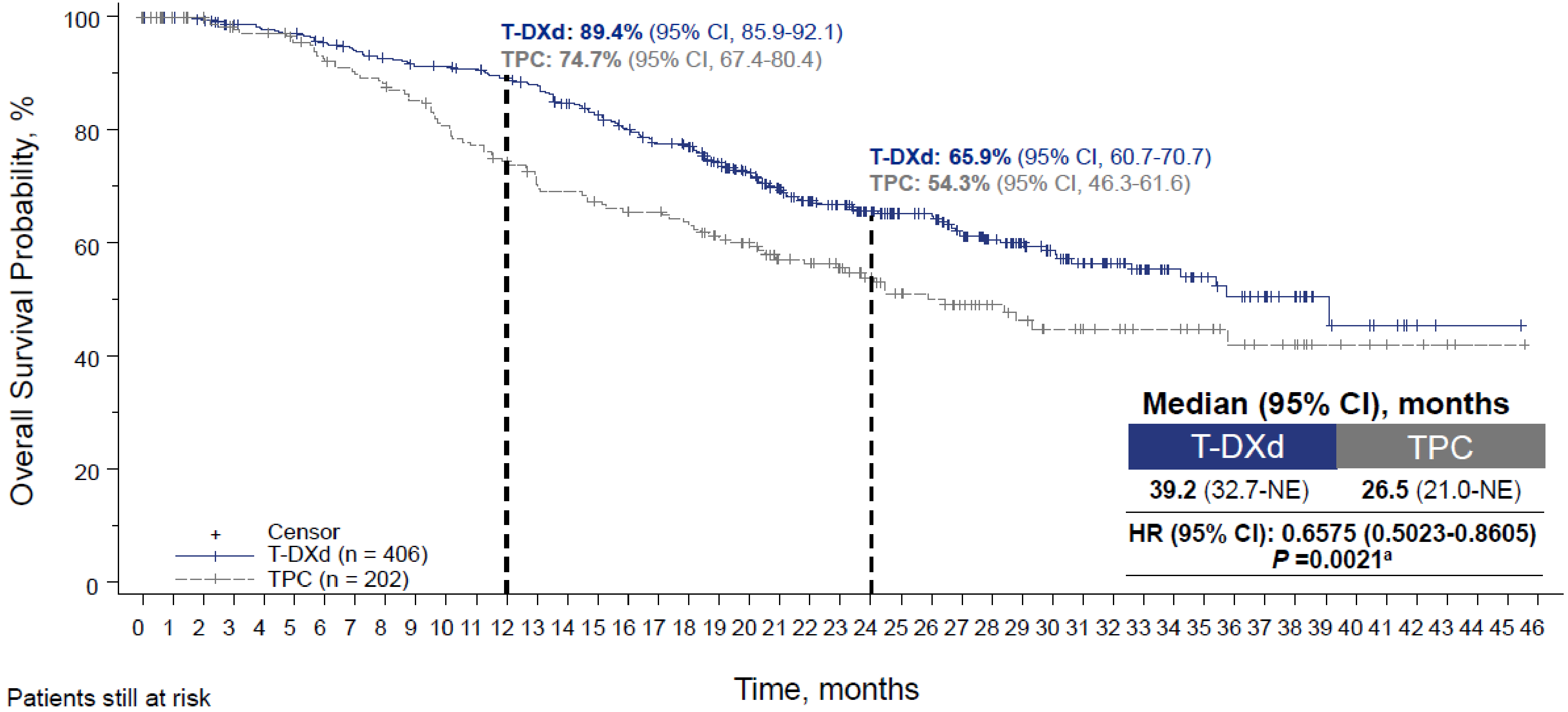
Key Secondary Endpoint: OS



Patients still at risk

T-DXd (406)	406	404	400	390	385	382	374	366	357	352	350	346	339	331	317	306	295	282	277	257	234	215	196
TPC (202)	202	192	187	182	178	173	167	161	157	151	142	136	130	124	118	114	111	110	106	95	89	79	76

T-DXd (406)	183	160	144	139	122	104	93	82	72	63	51	40	34	29	25	19	10	8	6	3	1	1	1	0
TPC (202)	72	61	53	50	46	38	33	29	28	25	22	22	18	15	13	12	7	6	5	4	3	1	1	0

In the TPC arm

- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

Krop et al, SABCS 2022

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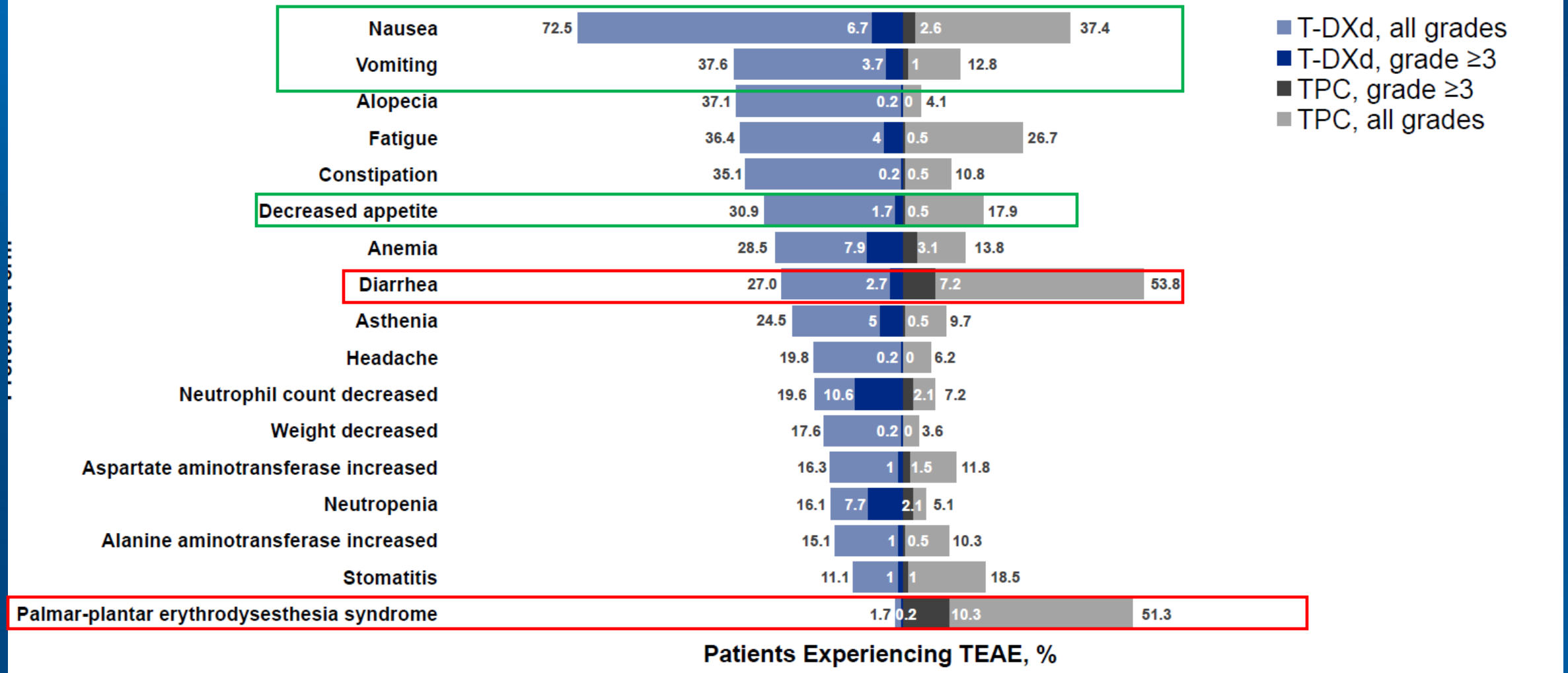
Most Common TEAEs (≥15% of Patients in Either Treatment Arm)



Krop et al, SABCS 2022

Adjudicated as Drug-related ILD[a]						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 404)	11 (2.7)	26 (6.4)	3 (0.7)	0	2 (0.5)	42 (10.4)
TPC (n = 195)	0	0	1 (0.5)	0	0	1 (0.5)

- Median time to onset of adjudicated drug-related ILD was 209.5 days (range, 41-638 days) with T-DXd

LV dysfunction[b]

- In the T-DXd arm, 18 (4.5%) patients experienced an LV dysfunction event[c]
  - 2 (0.5%) patients had a grade ≥3 event
- In the TPC arm, 3 (1.5%) patients experienced an LV dysfunction[d]
  - 1 (0.5%) patient had a grade ≥3 event

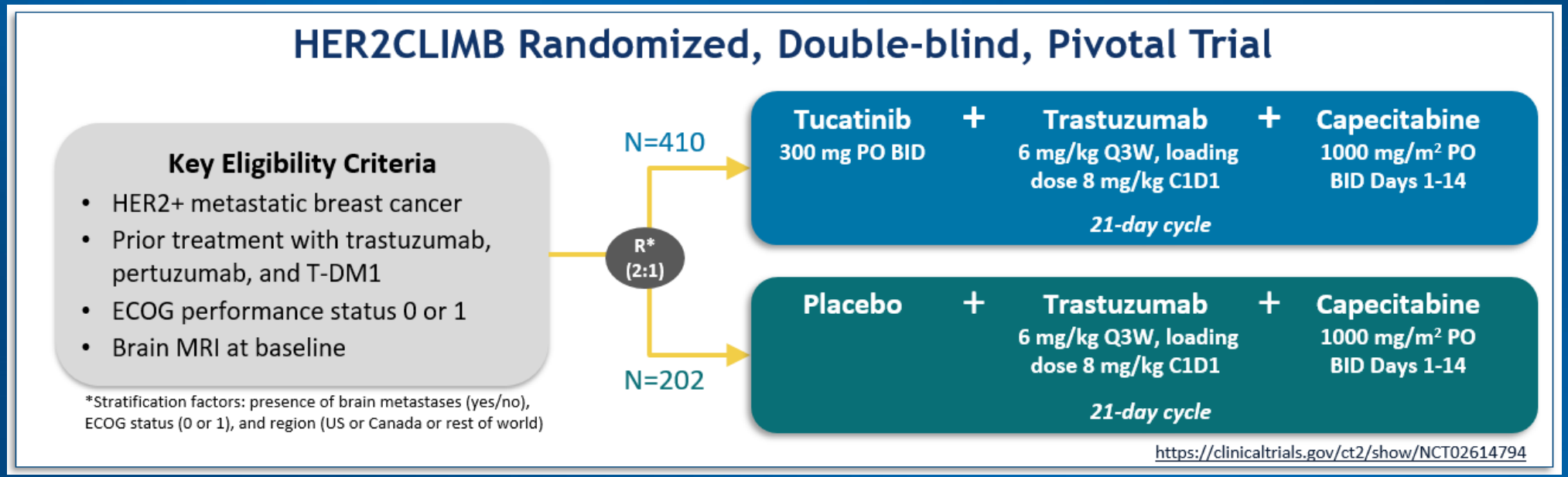
Krop et al, SABCS 2022

Tucatinib

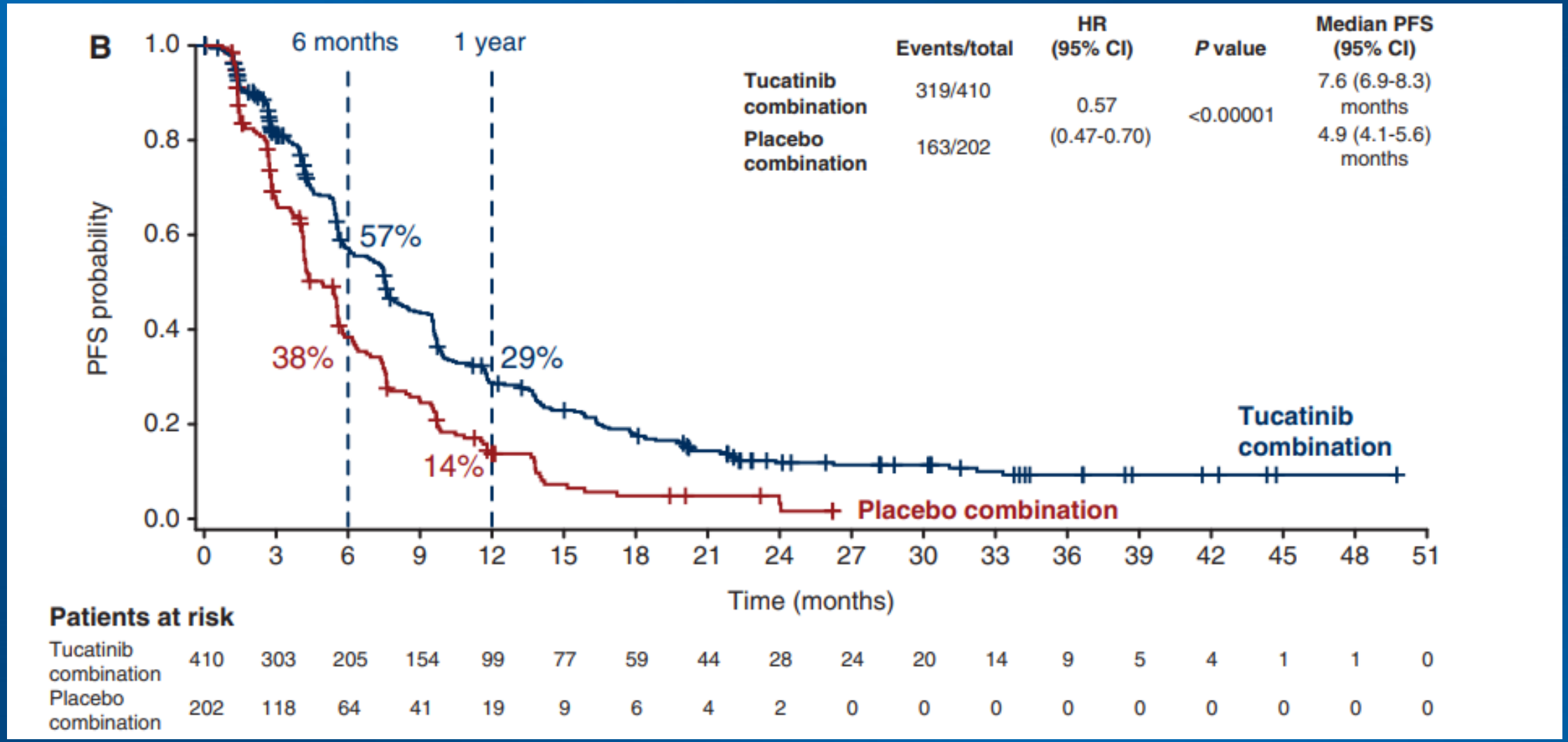
ORIGINAL ARTICLE

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

Rashmi K. Murthy, M.D., Sherene Loi, M.D., Alicia Okines, M.D., Elisavet Paplomata, M.D., Erika Hamilton, M.D., Sara A. Hurvitz, M.D., Nancy U. Lin, M.D., Virginia Borges, M.D., Vandana Abramson, M.D., Carey Anders, M.D., Philippe L. Bedard, M.D., Mafalda Oliveira, M.D., et al.

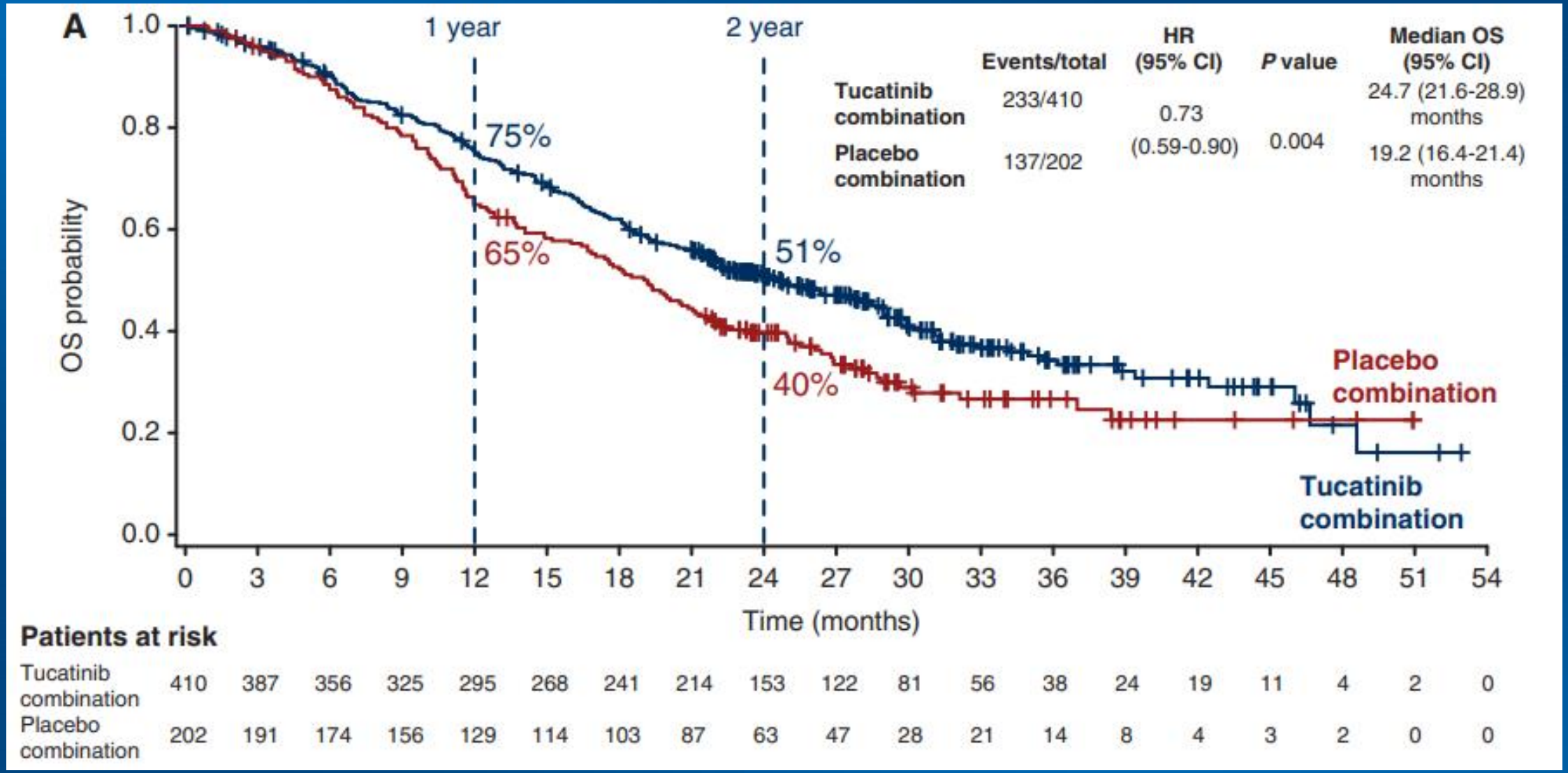


Murthy et al. NEJM 2020
Lin et al. ASCO 2020



Curigliano et al. Annals of Oncology 2021

MEDICINE of THE HIGHEST ORDER
UR MEDICINE | WILMOT CANCER INSTITUTE



Curigliano et al. Annals of Oncology 2021

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Table 2. Adverse events reported in ≥20% of patients in the tucatinib arm

Adverse event	Tucatinib combination (*N* = 404) *n* (%)		Placebo combination (*N* = 197) *n* (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	53 (13.1)	106 (53.8)	17 (8.6)
Palmar-plantar erythrodysesthesia syndrome	264 (65.3)	57 (14.1)	105 (53.3)	18 (9.1)
Nausea	243 (60.1)	16 (4.0)	88 (44.7)	7 (3.6)
Fatigue	193 (47.8)	22 (5.4)	87 (44.2)	8 (4.1)
Vomiting	152 (37.6)	13 (3.2)	51 (25.9)	8 (4.1)
Decreased appetite	105 (26.0)	3 (0.7)	41 (20.8)	0
Stomatitis	105 (26.0)	10 (2.5)	28 (14.2)	1 (0.5)
Headache	96 (23.8)	3 (0.7)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	89 (22.0)	19 (4.7)	22 (11.2)	1 (0.5)
Anemia	88 (21.8)	17 (4.2)	24 (12.2)	5 (2.5)
Alanine aminotransferase increased	85 (21.0)	23 (5.7)	13 (6.6)	1 (0.5)
Blood bilirubin increased	81 (20.0)	4 (1.0)	21 (10.7)	5 (2.5)

Tucatinib combination: tucatinib, trastuzumab, and capecitabine. Placebo combination: placebo, trastuzumab, and capecitabine.

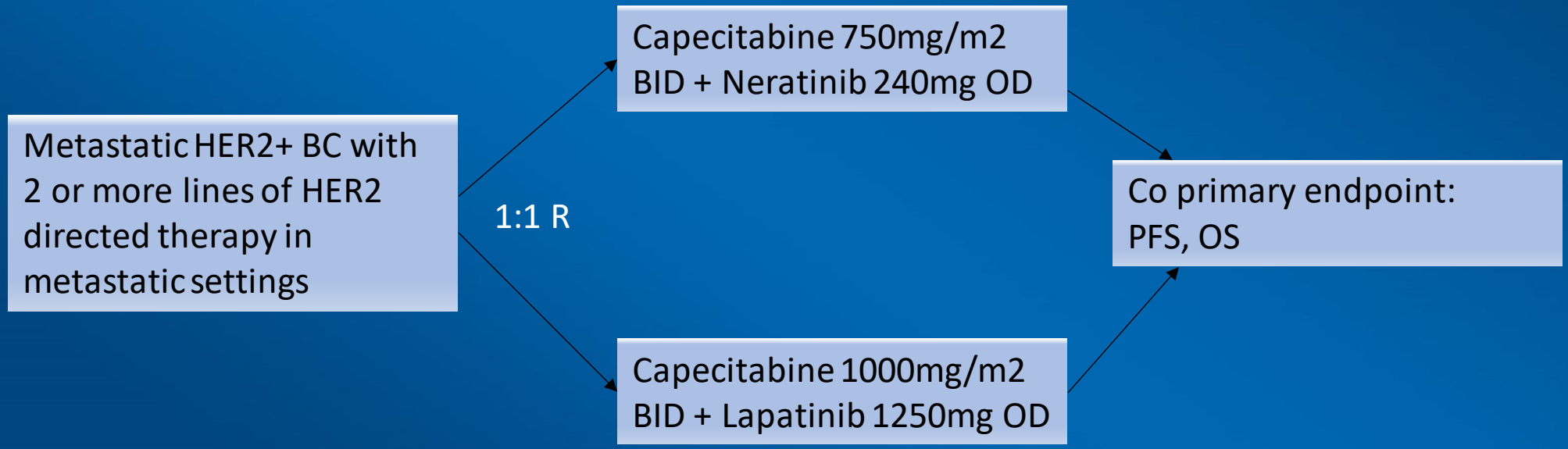
Curigliano et al. Annals of Oncology 2021

Neratinib

original reports

Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial

Cristina Saura, MD[1]; Mafalda Oliveira, MD, PhD[1]; Yin-Hsun Feng, MD, PhD[2]; Ming-Shen Dai, MD, PhD[2]; Shang-Wen Chen, MD[2]; Sara A. Hurvitz, MD[3]; Sung-Bae Kim, MD, PhD[4]; Beverly Moy, MD, PhD[5]; Suzette Delaloge, MD, MSc[6]; William Gradishar, MD[7]; Norikazu Masuda, MD, PhD[8]; Marketa Palacova, MD[9]; Maureen E. Trudeau, MD[10]; Johanna Mattson, MD, PhD[11]; Yoon Sim Yap, MBBS[12]; Ming-Feng Hou, MD[13]; Michelino De Laurentiis, MD, PhD[14]; Yu-Min Yeh, MD[15]; Hong-Tai Chang, MD[16]; Thomas Yau, MBBS, MD[17]; Hans Wildiers, MD, PhD[18,19]; Barbara Haley, MD[20]; Daniele Fagnani, MD[21]; Yen-Shen Lu, MD, PhD[22]; John Crown, MBBCh, MD[23]; Johnson Lin, MD[24]; Masato Takahashi, MD, PhD[25]; Toshimi Takano, MD[26]; Miki Yamaguchi, MD, PhD[27]; Takaaki Fujii, MD, PhD[28]; Bin Yao, MS[29]; Judith Bebchuk, ScD[29]; Kiana Keyvanjah, PharmD[29]; Richard Bryce, MBChB[29]; and Adam Brufsky, MD, PhD[30]; for the NALA Investigators



Saura et al. JCO 2020

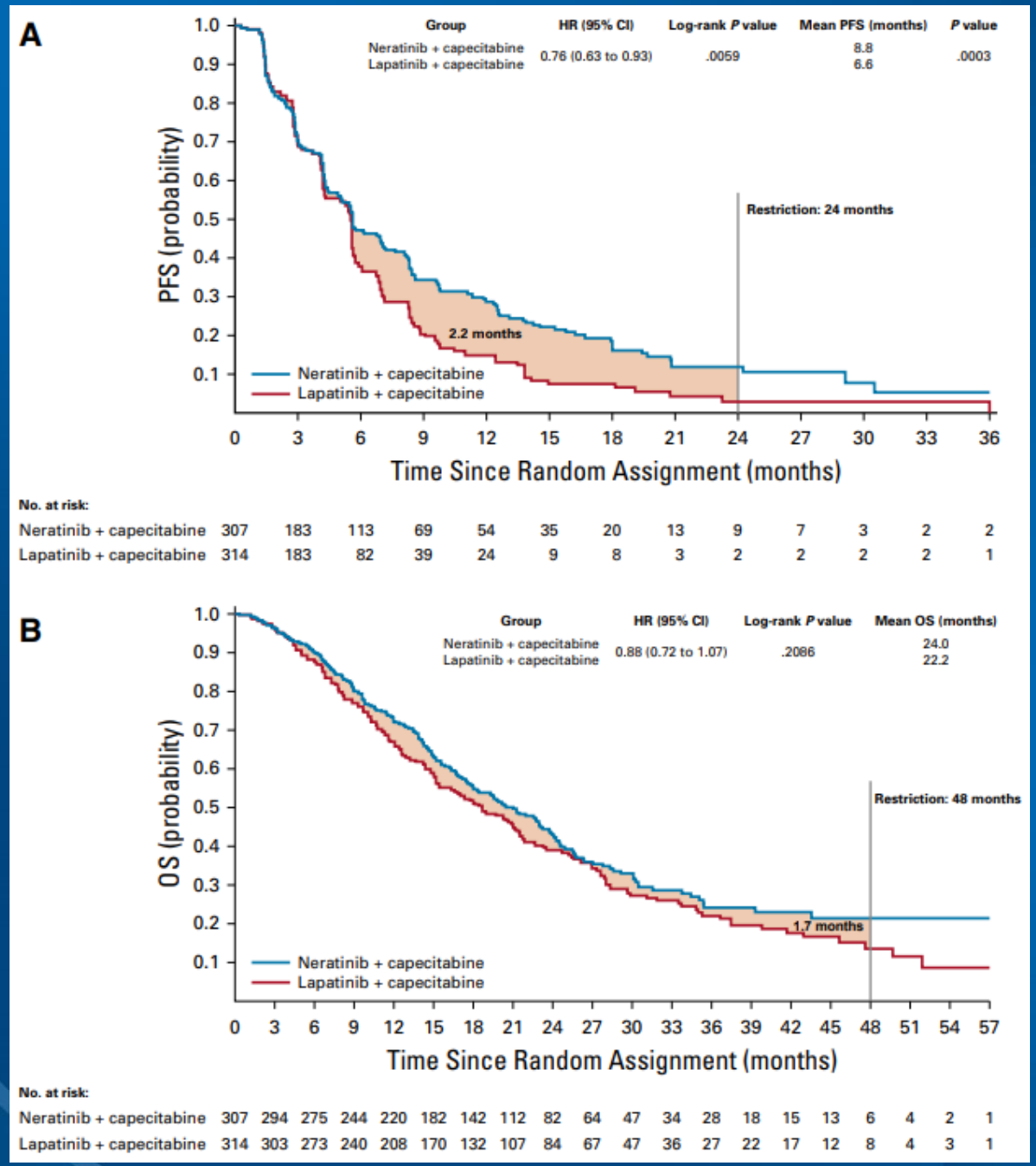


TABLE 3. Treatment-Emergent AEs Occurring in ≥ 10% of Patients in the Safety Population

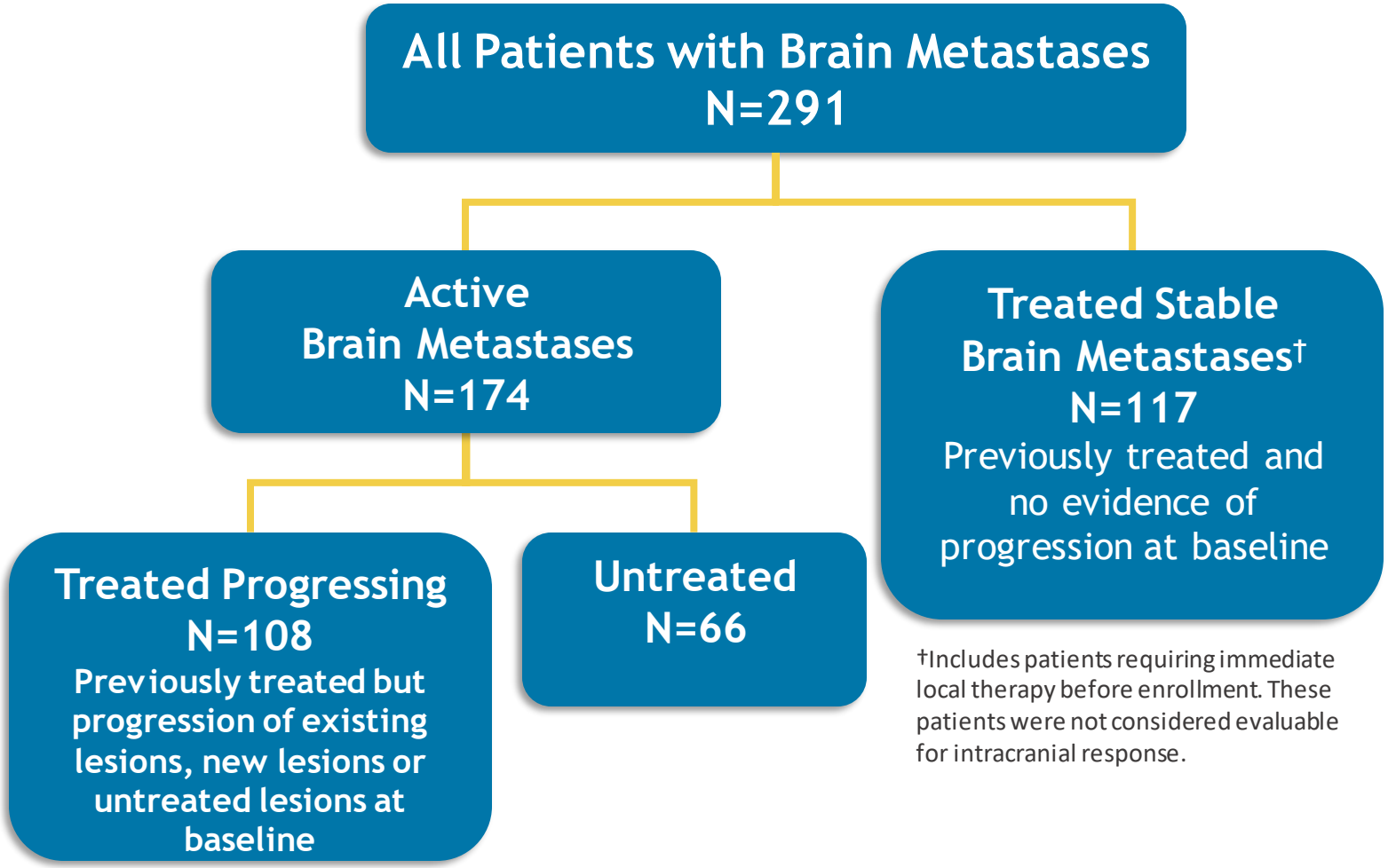
	N+C (n = 303)		L+C (n = 311)	
AE	**All Grade**	**Grade 3/4**	**All Grade**	**Grade 3/4**
Diarrhea	252 (83.2)	74 (24.4)	206 (66.2)	39 (12.5)
Nausea	161 (53.1)	13 (4.3)	132 (42.4)	9 (2.9)
PPE syndrome	139 (45.9)	29 (9.6)	175 (56.3)	35 (11.3)
Vomiting	138 (45.5)	12 (4.0)	97 (31.2)	6 (1.9)
Decreased appetite	107 (35.3)	8 (2.6)	67 (21.5)	7 (2.3)
Fatigue	104 (34.3)	9 (3.0)	97 (31.2)	10 (3.2)
Constipation	94 (31.0)	4 (1.3)	41 (13.2)	1 (0.3)
Stomatitis	62 (20.5)	6 (2.0)	83 (26.7)	8 (2.6)
Weight decreased	60 (19.8)	1 (0.3)	41 (13.2)	2 (0.6)
Rash	30 (9.9)	0	69 (22.2)	2 (0.6)
Anemia	45 (14.9)	6 (2.0)	51 (16.4)	11 (3.5)
Dizziness	43 (14.2)	1 (0.3)	31 (10.0)	2 (0.6)
Cough	37 (12.2)	0	34 (10.9)	0
Abdominal pain	36 (11.9)	3 (1.0)	45 (14.5)	6 (1.9)
Asthenia	36 (11.9)	8 (2.6)	36 (11.6)	5 (1.6)
Hypokalemia	35 (11.6)	14 (4.6)	44 (14.1)	20 (6.4)
Paronychia	35 (11.6)	2 (0.7)	49 (15.8)	3 (1.0)
Pyrexia	33 (10.9)	0	32 (10.3)	1 (0.3)
Headache	32 (10.6)	1 (0.3)	51 (16.4)	3 (1.0)

Saura et al. JCO 2020

Brain Metastasis Space

HER2CLIMB Analysis of Patients with Brain Metastases

- Brain MRI at baseline for all patients
- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout*



†Includes patients requiring immediate local therapy before enrollment. These patients were not considered evaluable for intracranial response.

*These patients were included in the Treated Stable group for analysis.

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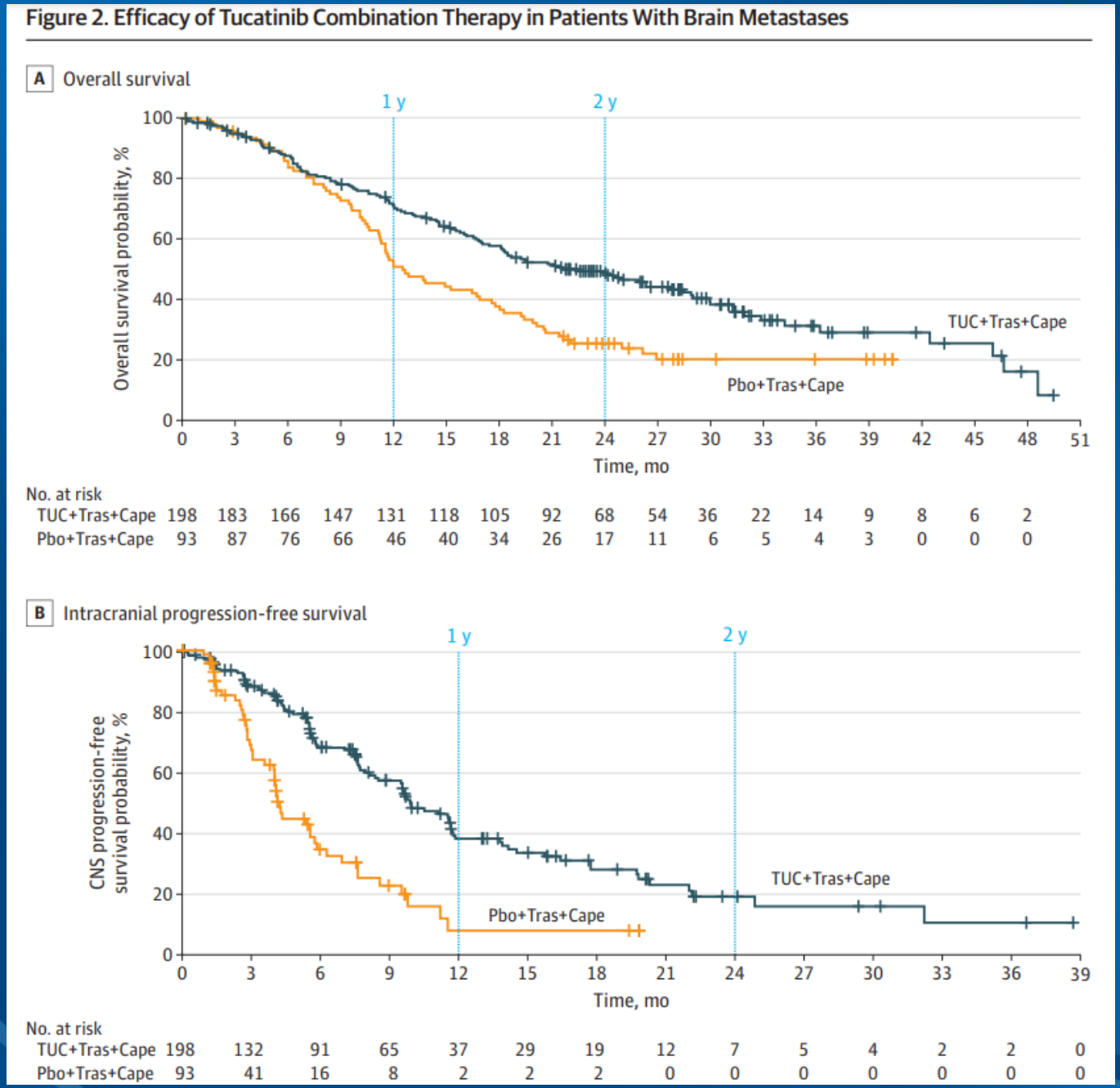
PRESENTED BY: Nancy Lin, nlin@partners.org

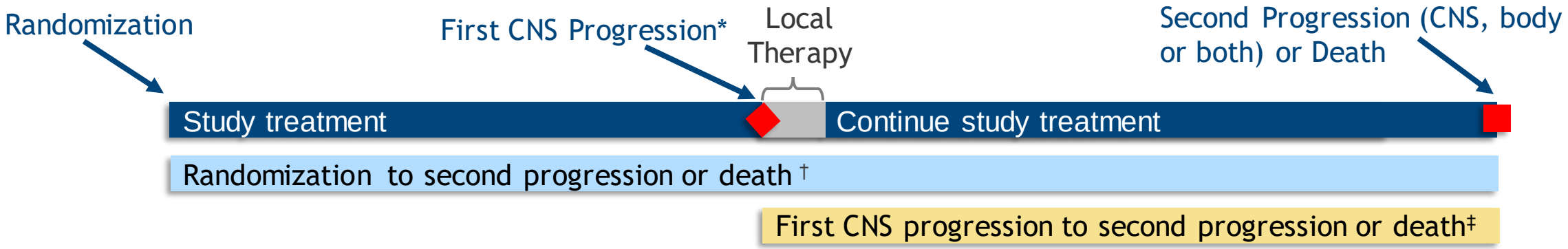


mOS: 21.6m (95% CI, 18.1-28.5 m) vs. 12.5 m (95% CI, 11.2-16.9 m)

iPFS: 9.9m (95% CI, 8.4-11.7 m) vs. 4.2 m (95% CI, 3.6-5.7 m)

Lin et al. Jama Oncology 2023

PFS in Patients with Isolated Progression in the Brain Who Continued with Assigned Study Treatment



	Median time from randomization to second progression or death	HR	Median time from first CNS progression to second progression or death	HR
TUC+Tras+Cap N=21	15.9 months (11.7, 28.2)	0.292 (0.11, 0.77) P=0.009	7.6 months (3.9, 11.3)	0.332 (0.13, 0.85) P=0.02
Pbo+Tras+Cap N=9	9.7 months (4.9, 12.0)		3.1 months (1.2, 4.1)	

*Note: First CNS progression was captured as a PFS event in the primary analysis.
†Time from randomization to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.
‡Time from first isolated CNS progression to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.

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PRESENTED BY: Nancy Lin, nlin@partners.org

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.

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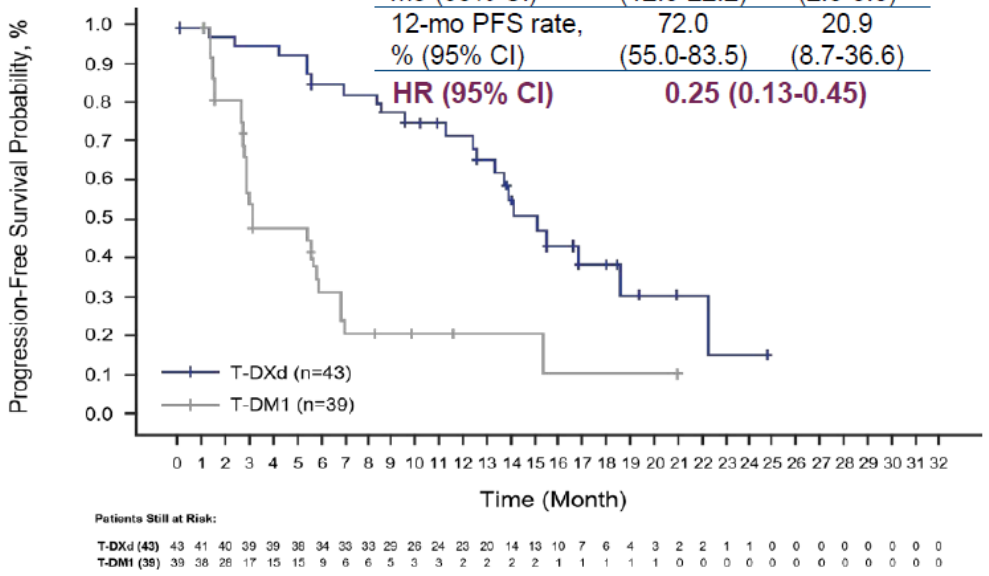
PFS KM Curves for Patients With and Without BM

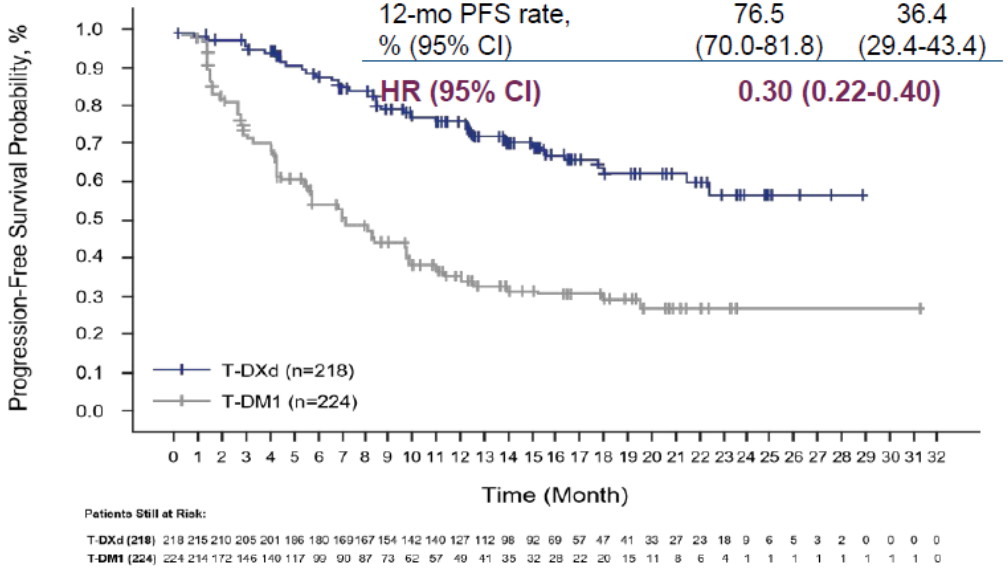
Brain Metastases at Baseline

	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)	



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)	



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

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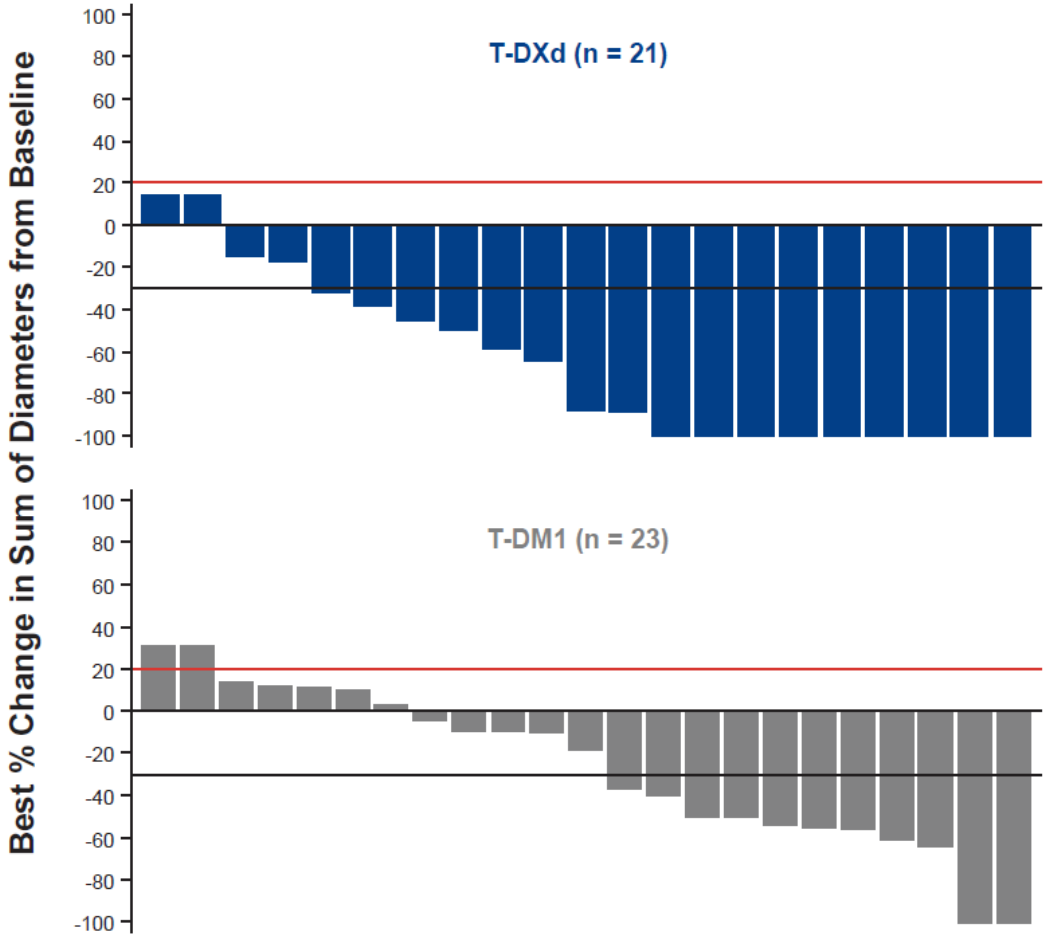
Intracranial Response per BICR using RECIST 1.1



	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

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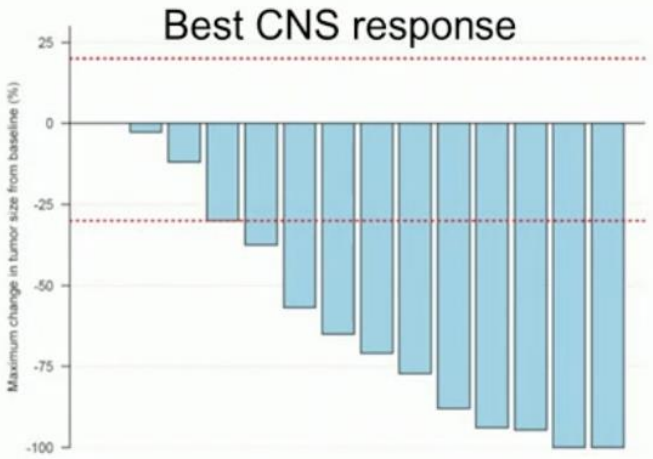
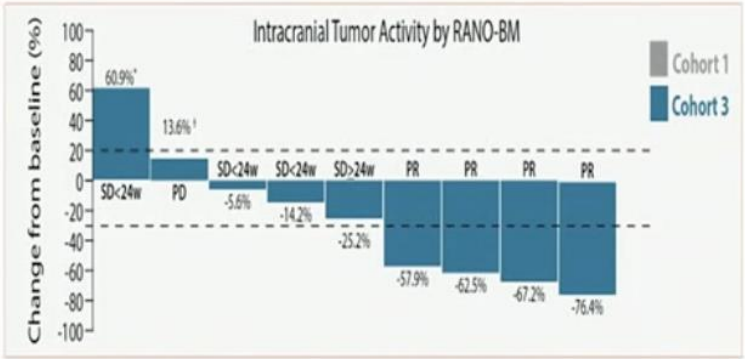
CNS Activity of TDXd in Pts with HER2+ Breast Cancer Brain Metastases





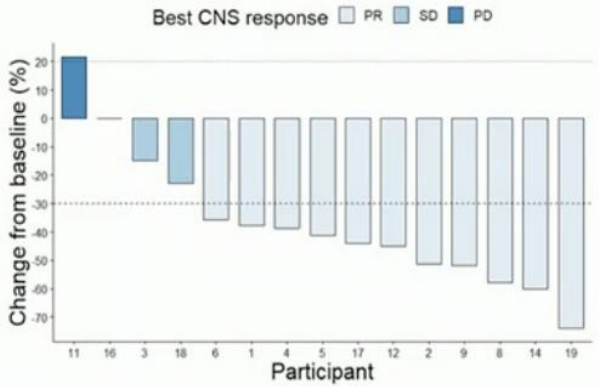


Figure 5 : Best CNS response to T-DXd. Waterfall plot of best CNS response in participants with measurable disease (n = 15). PR = partial response

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

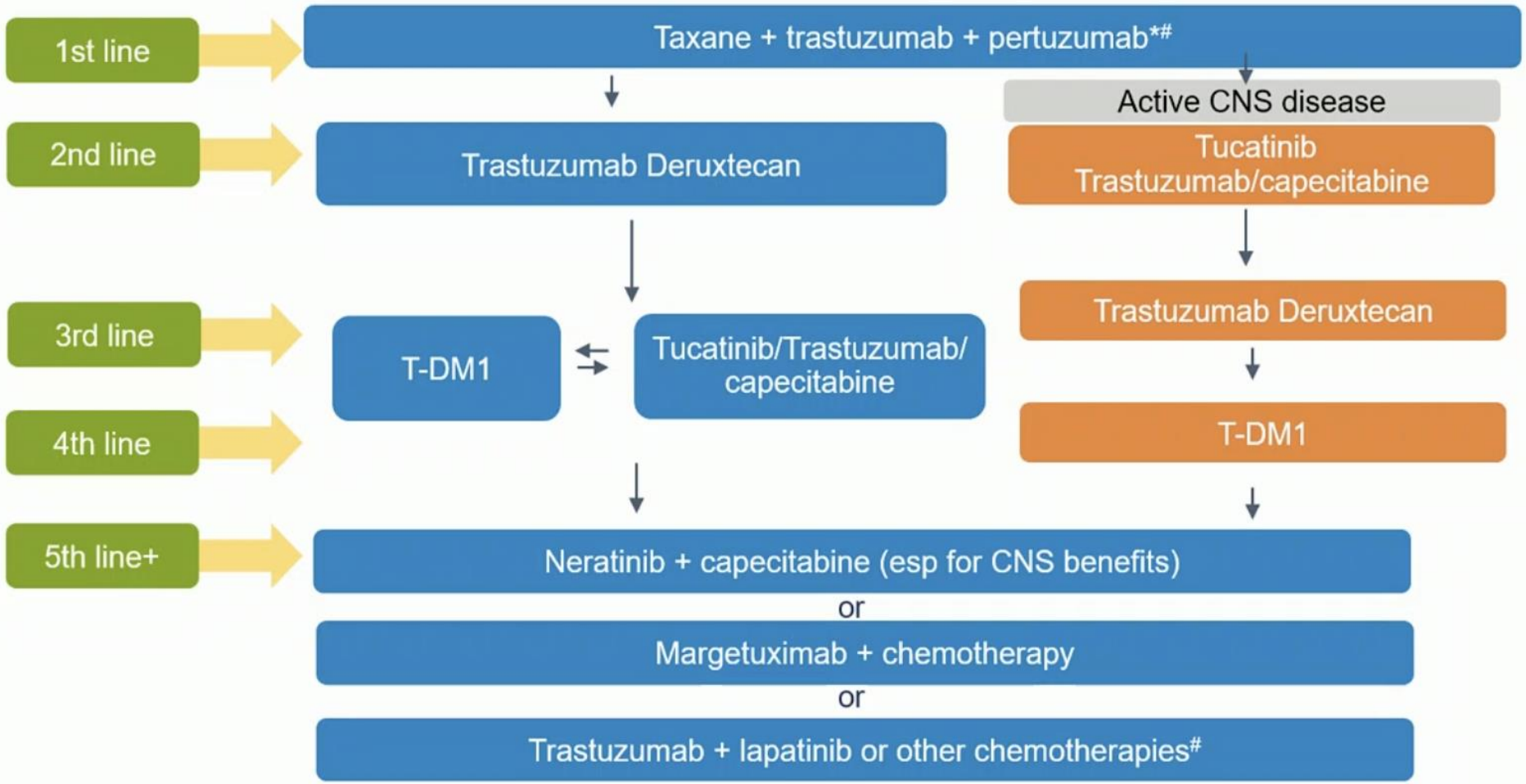
ORR-IC =**44%** in pts with Active BM

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

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

Lin N , ASCO 2022

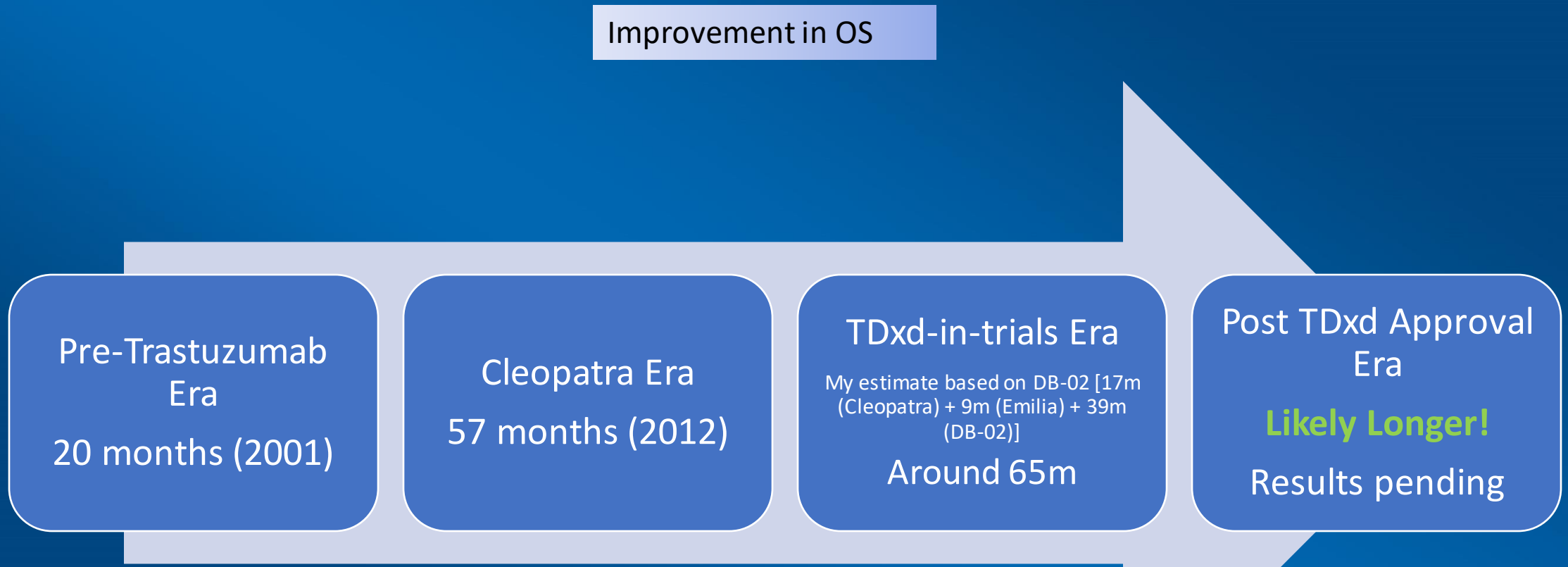
Current Approach to Therapy for Metastatic HER2+ BC:



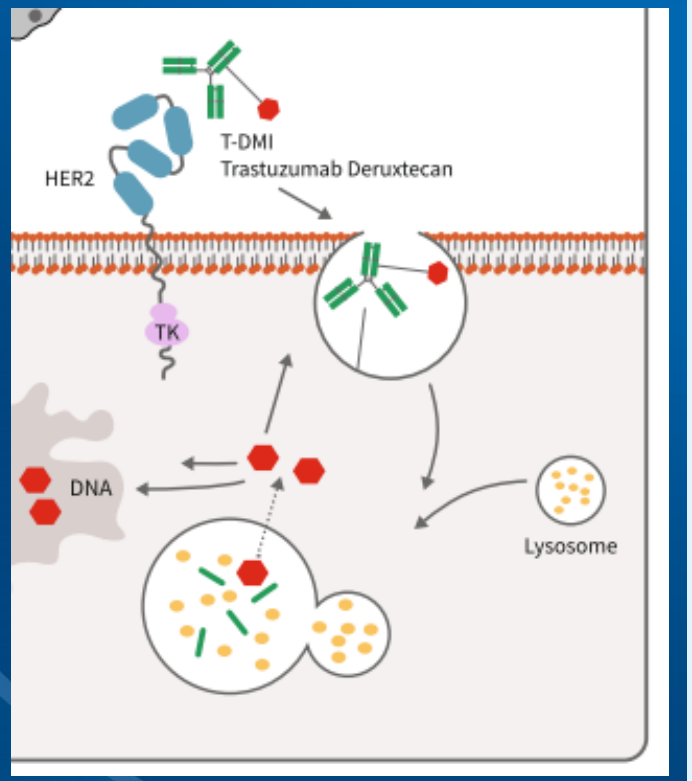
*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

Slide Courtesy: Dr. Gradishar

What we have achieved in the last 2 decades?



Trastuzumab Deruxtecan in "HER2 Low" Breast Cancer



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

HER2 expression in breast cancer – update 2022

	0	1+	2+		3+
HER2 IHC	≤10% weak, incomplete staining	>10% weak, incomplete staining	>10% weak to moderate, circular staining		>10% strong, circular staining
HER2 ISH			negative	positive	
traditional classification	HER2-negative			HER2-positive	
current classification	HER2-negative / HER2-zero	HER2-Low		HER2-positive	

HER2-positive HER2-Low HER2-negative

Denkert, Lebeau, Schildhaus, Jackisch, Rüschoff „Die Pathologie, 2022

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Curigliano et al. SABCS 2022

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

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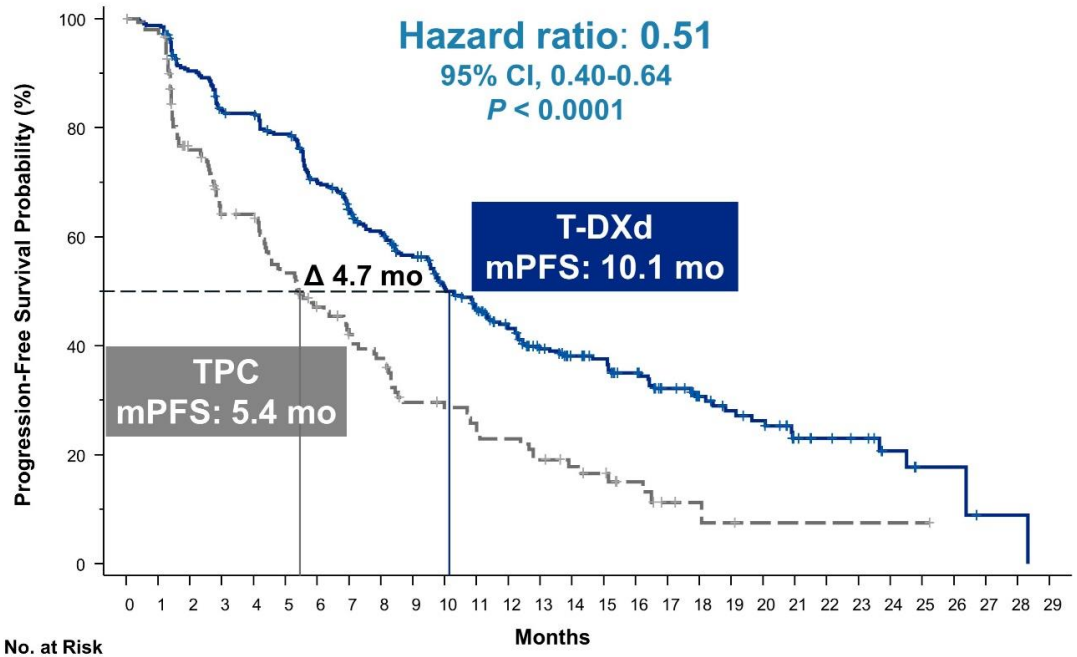
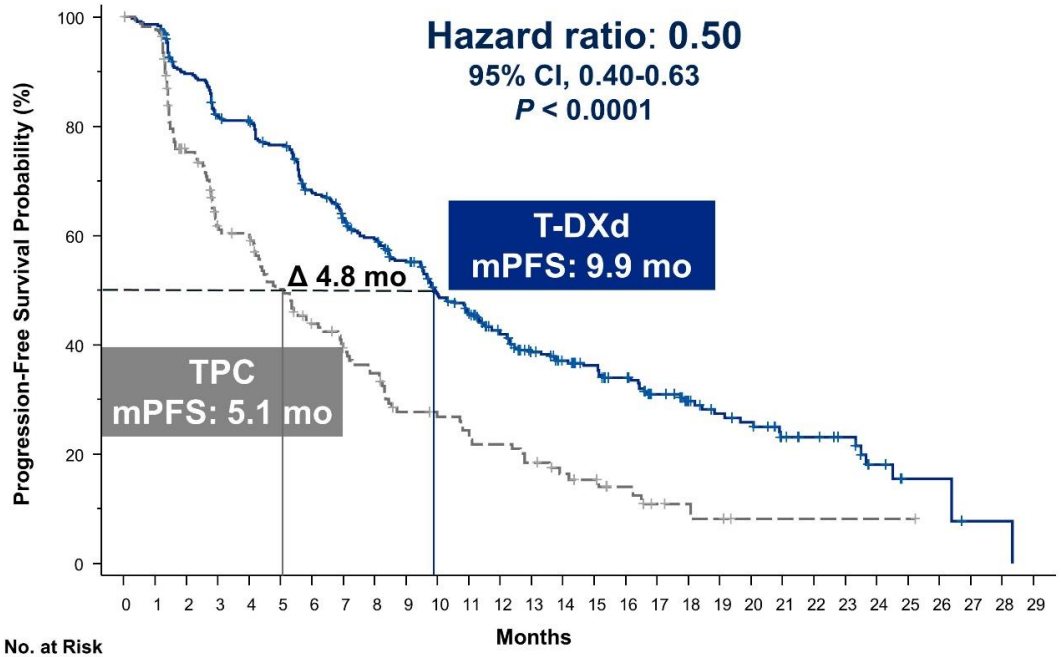
PFS in HR+ and All Patients

Hormone receptor–positive



All patients



PFS by blinded independent central review.

HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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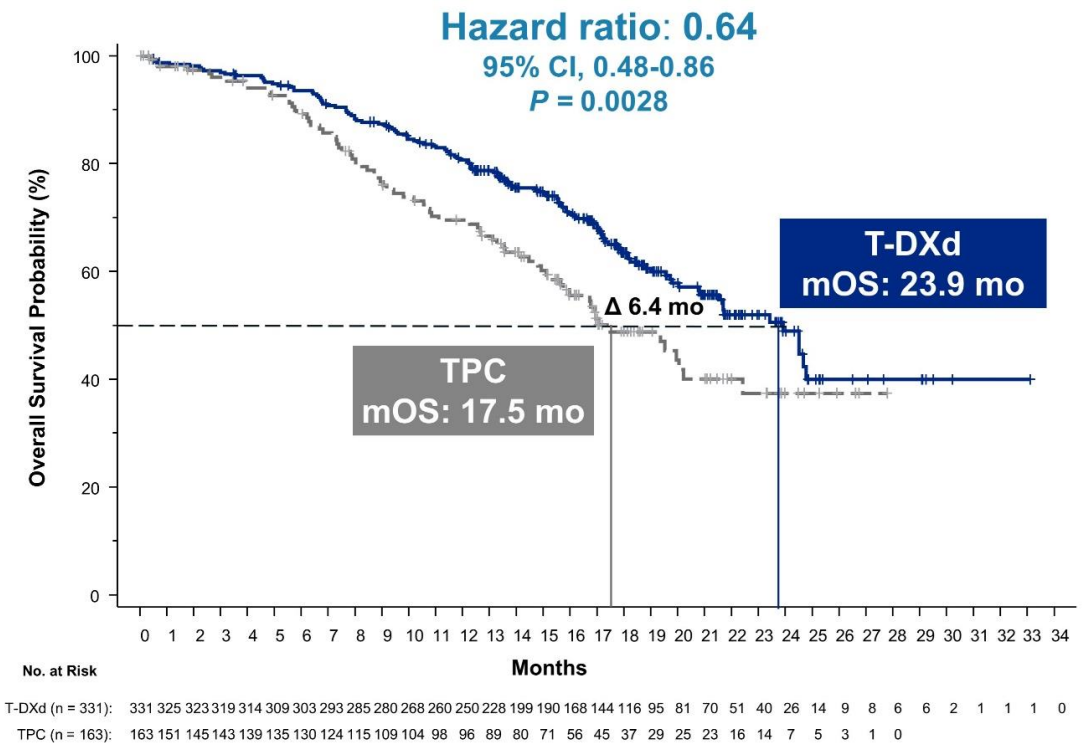
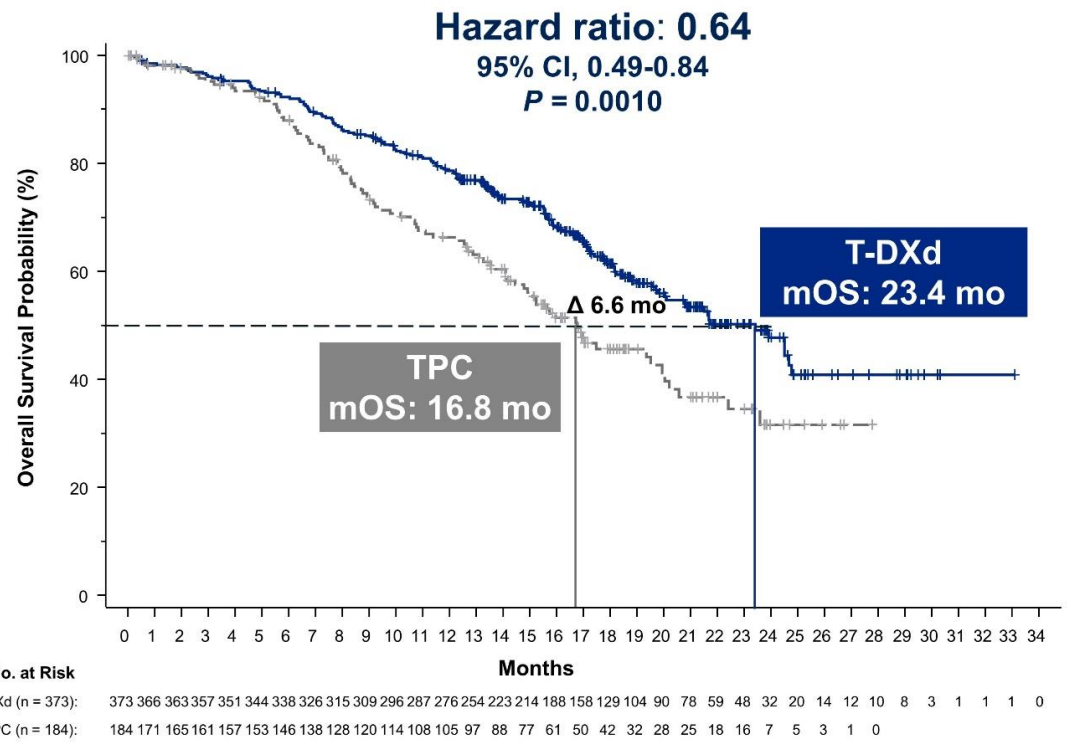
OS in HR+ and All Patients

Hormone receptor–positive



All patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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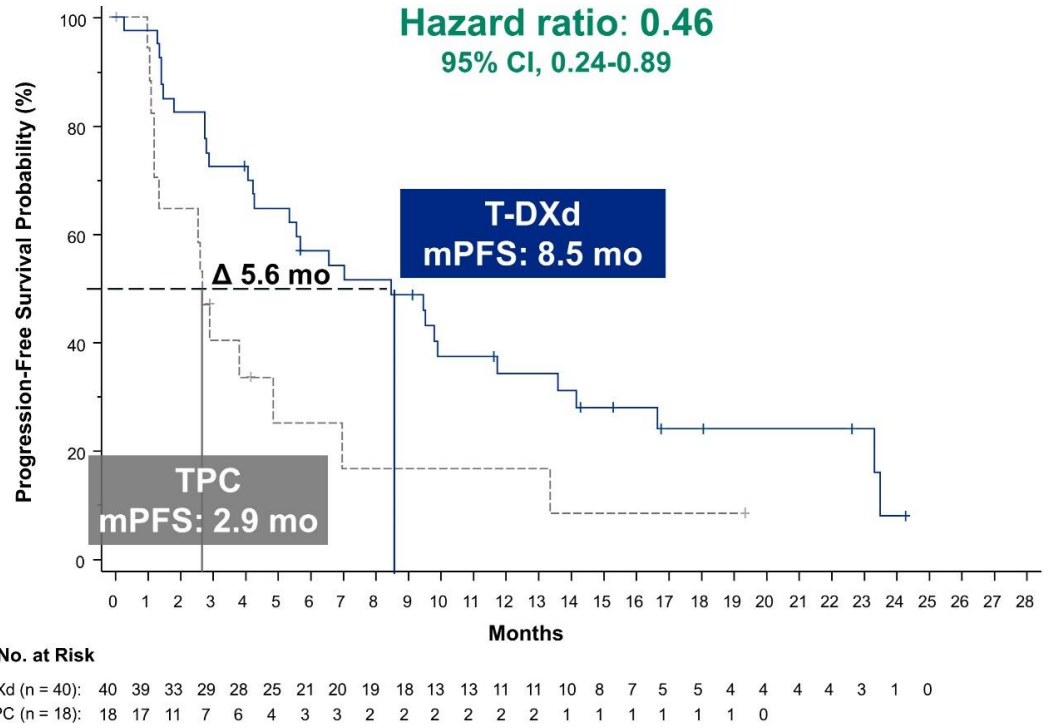
PFS and OS in HR− (Exploratory Endpoints)

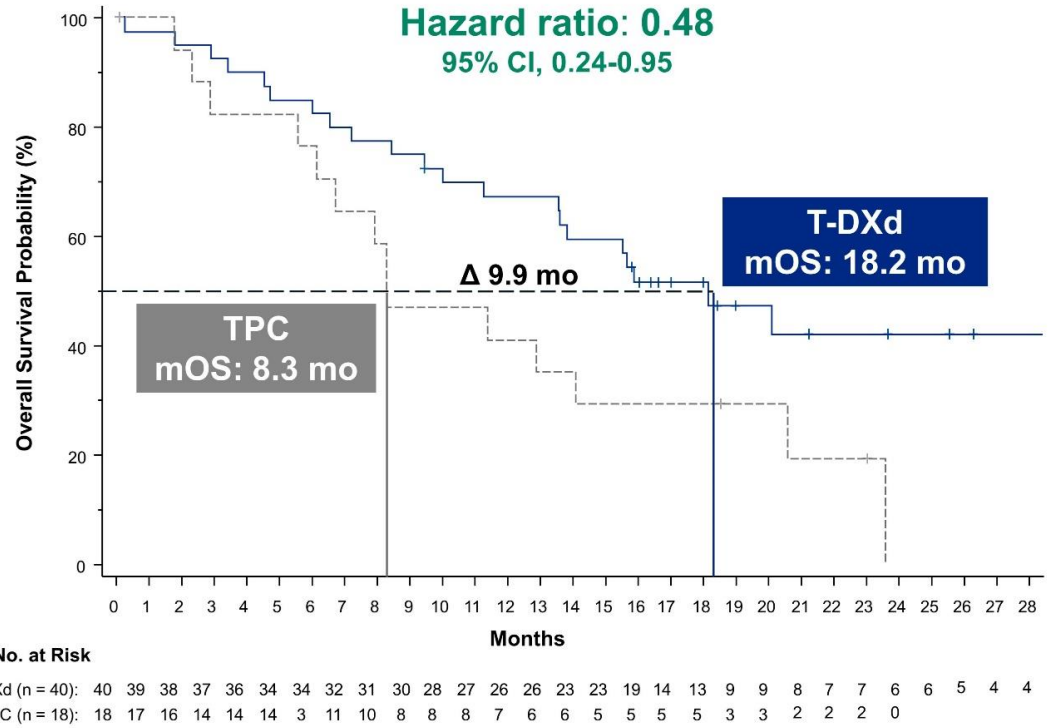
PFS



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0	
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0						

OS



No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

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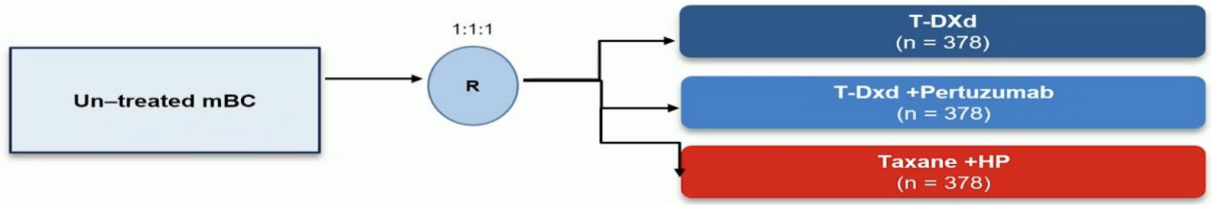
Important Ongoing Trials

DESTINY Breast-09 Trial : 1st Line HER2+ MBC



Primary endpoint: PFS

Destiny Breast 06

Archived sample

- HER2 low (IHC 1+ 2+)

  or
- **HER2 ultralow (IHC >0 <1+)**
- HR+
- ≥2 lines ET or POD on 1st line CDK4/6 inhibitor

R

N = 850

Trastuzumab deruxtecan (T-DXd)

Physician's choice of single-agent
capecitabine, paclitaxel, nab-paclitaxel

Primary endpoint: PFS

Early Stage HER2+ Breast Cancer:
Story of Escalations/De-escalations

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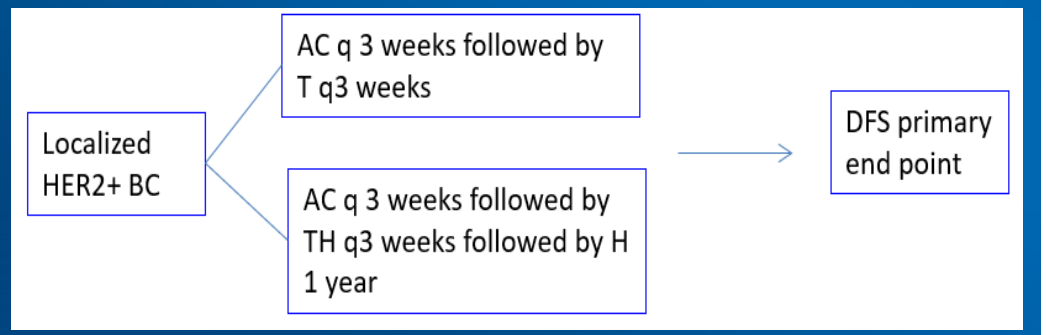
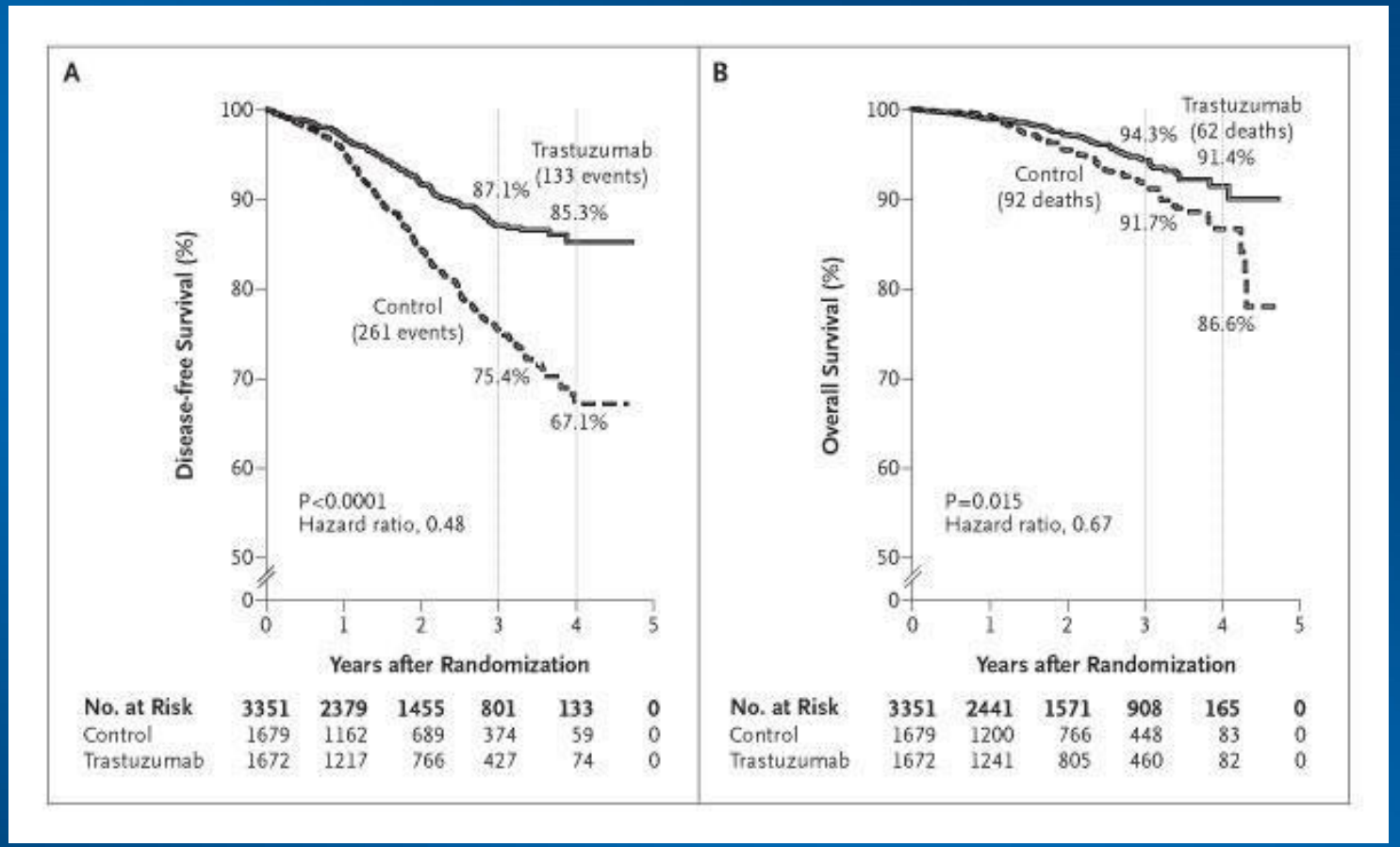
Trastuzumab in Adjuvant settings: With Chemo

NSABP B 31 plus N9831 combined analysis:





Romond EH et al. N Engl J Med 2005;353:1673-1684

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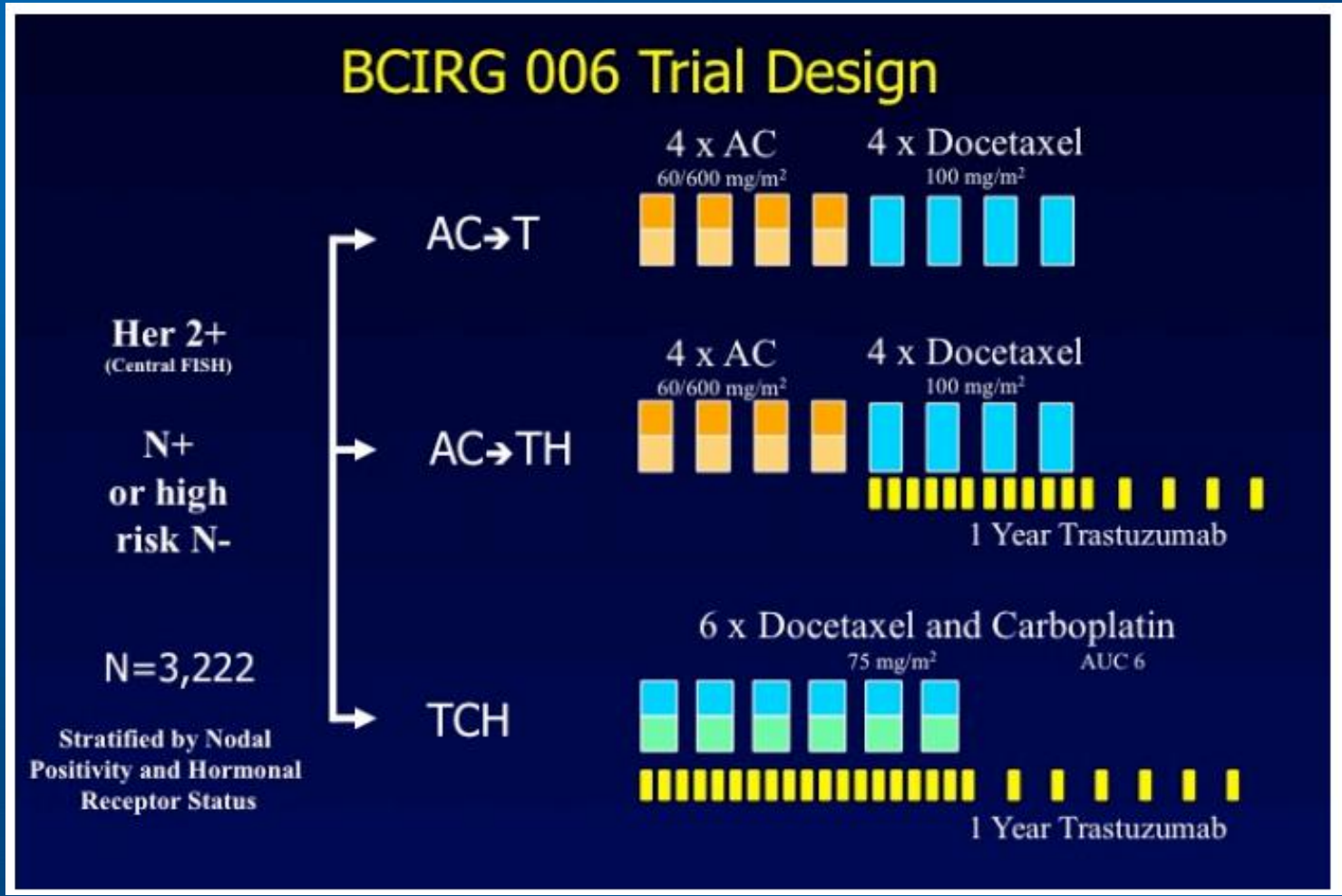
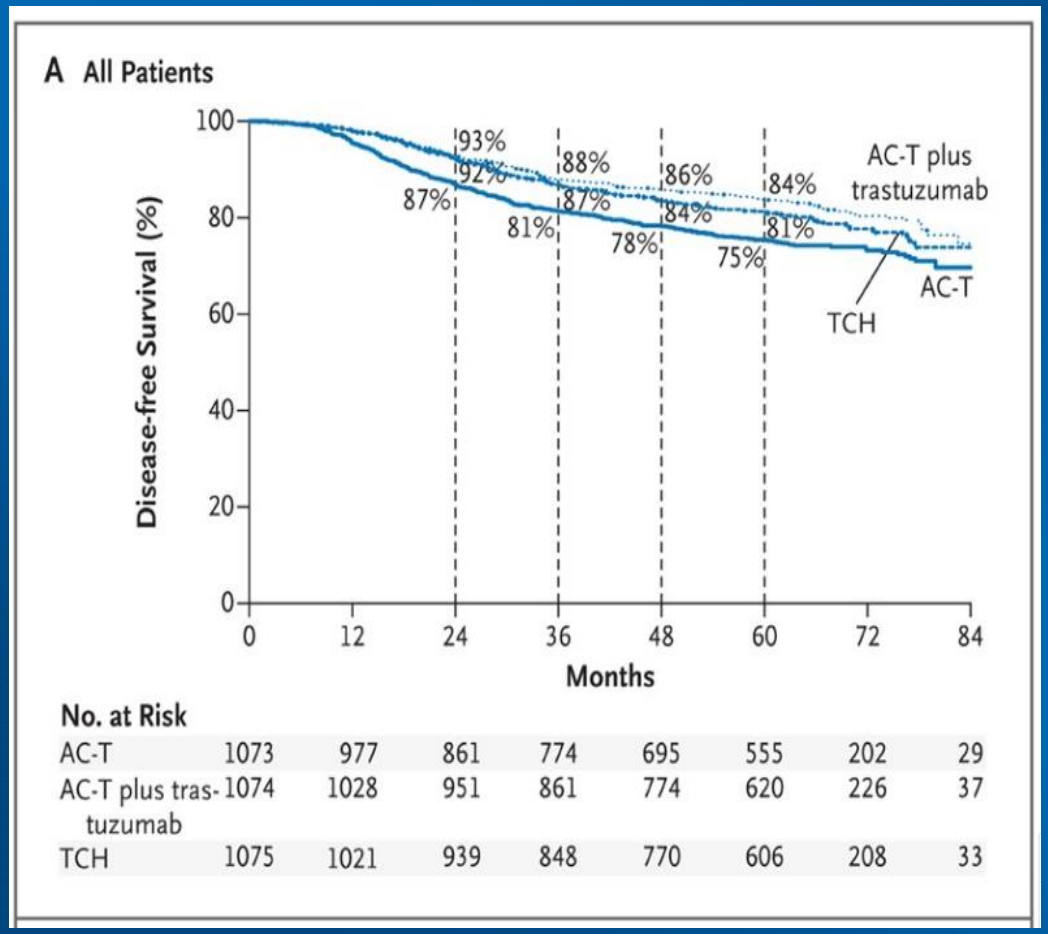
Trastuzumab with Chemo, (Platinum)

tumor size > 2 cm, ER and PR status is negative, histologic and/or nuclear grade 2-3, or age < 35 years



Slamon et al 2011, NEJM



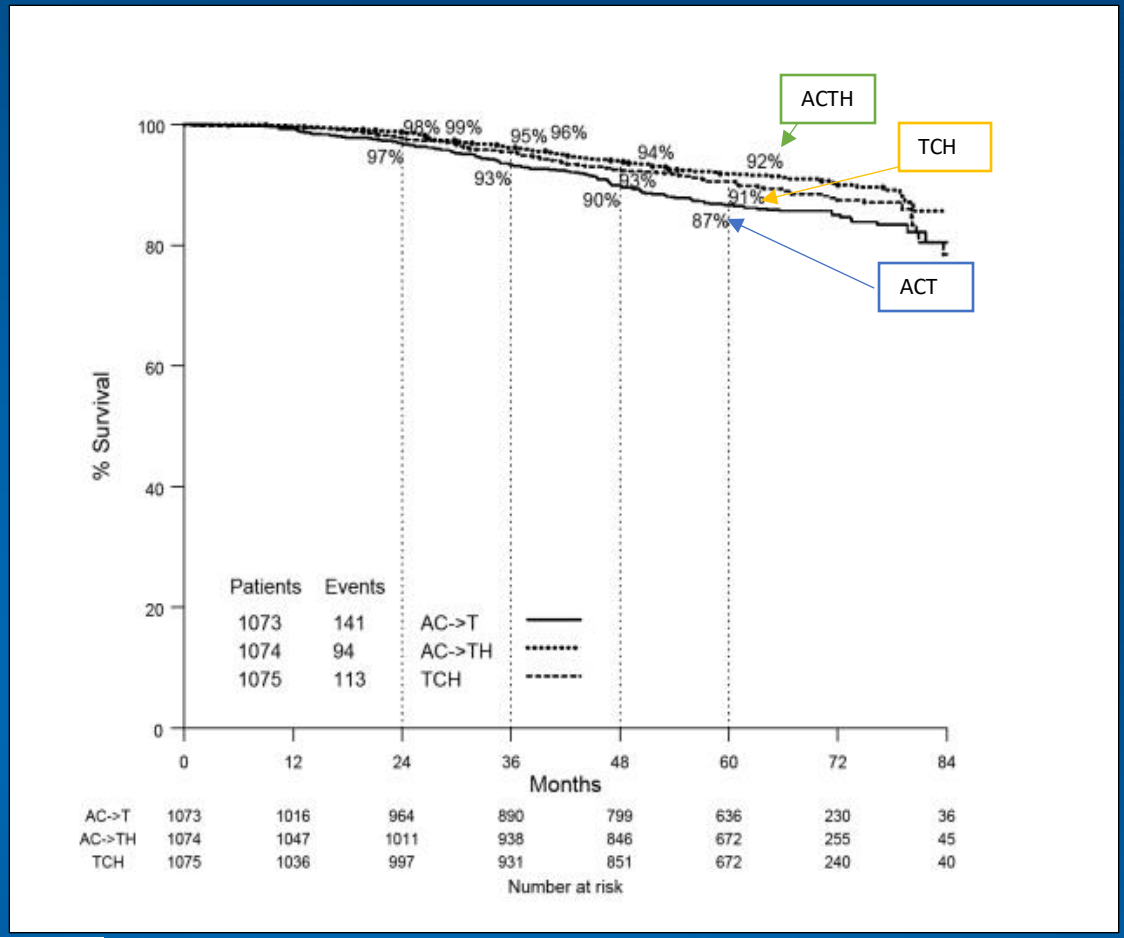


Table 2. Therapeutic Index for Critical Clinical Events.*

Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
	number of events		
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1†

Slamon et al 2011, NEJM

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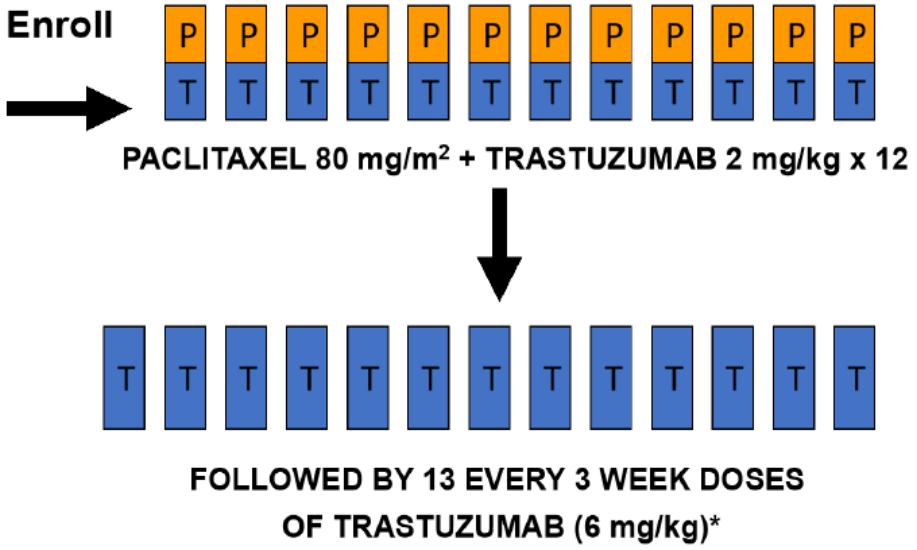
APT Trial

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400
Actual: 406

49% T1a/T1b
42% T1c
9% T2 (≤3 cm)
67% HR positive



Tolaney SM et al NEJM 2015 and JCO 2019
Tolaney SM, SABCS 2022

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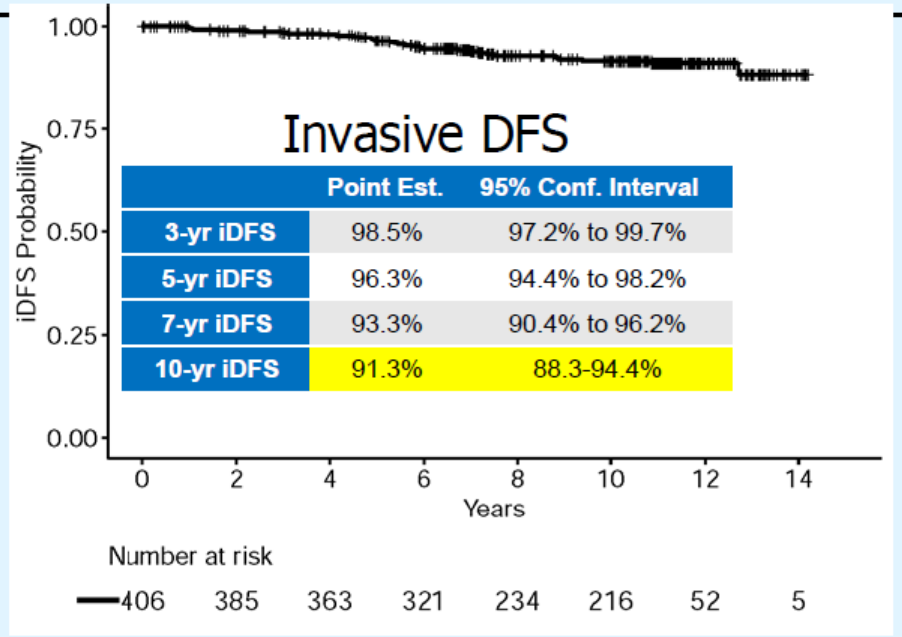
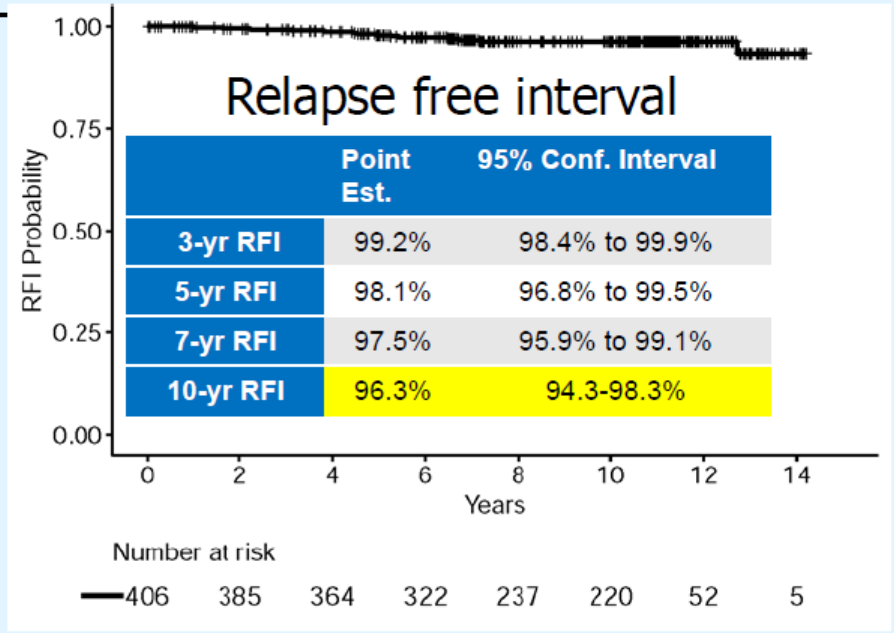
APT: 10-year RESULTS



	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%



	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%

Events: N=31

- 6 Ipsilateral recurrences, 9 contralateral new cancers (1 HER2+)
- 6 Distant recurrences, 10 Deaths
  - **Some distant recurrences detected 5+ years**

Ten-year OS for the ITT population: 94.3% (95% CI: 91.8% - 96.8%)

10-year BCSS was 98.8% (95% CI: 97.6% - 100.0%)

Tolaney SM, SABCS 202

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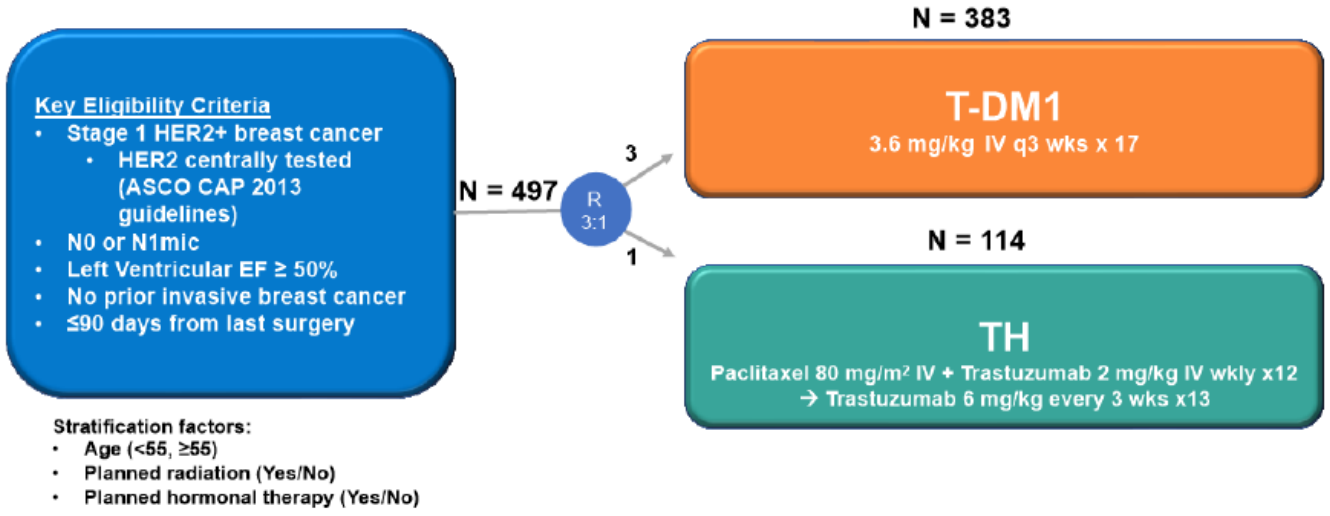
ATEMPT: 5 year results



Tolaney SM et al, SABCS 2019
Tolaney SM et al, JCO 2021

	All Patients (n = 497)	
Tumor Size		
<0.5 cm	56 (11%)	**43%**
≥0.5-1.0 cm	159 (32%)	
≥1.0-1.5 cm	147 (30%)	**57%**
≥1.5-2.0 cm	135 (27%)	
HR Positive	373 (75%)	
HER2 Status (Central) 3+	364 (73%)	

Tarantino P, SABCS 2022

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ATEMPT & APT 5-year outcomes

	T-DM1 (N=383)	TH (ATEMPT) (N=114)	TH (APT) (N=406)
3-year iDFS	97.8% 10 events	93.4% 8 events	98.5%
5-year iDFS	97.0% 11 events*	91.1% 9 events	96.3%
5-year RFI	98.3% 6 events	93.2% 7 events	98.1% 7 events
5-year OS	97.8% 3 events	97.9%	98.7% 5 events
5-year BCSS	99.4%	Not reported	99.7% 1 event

Tarantino P, SABCS 2022; Tolaney S J Clin Oncol 2019;37.

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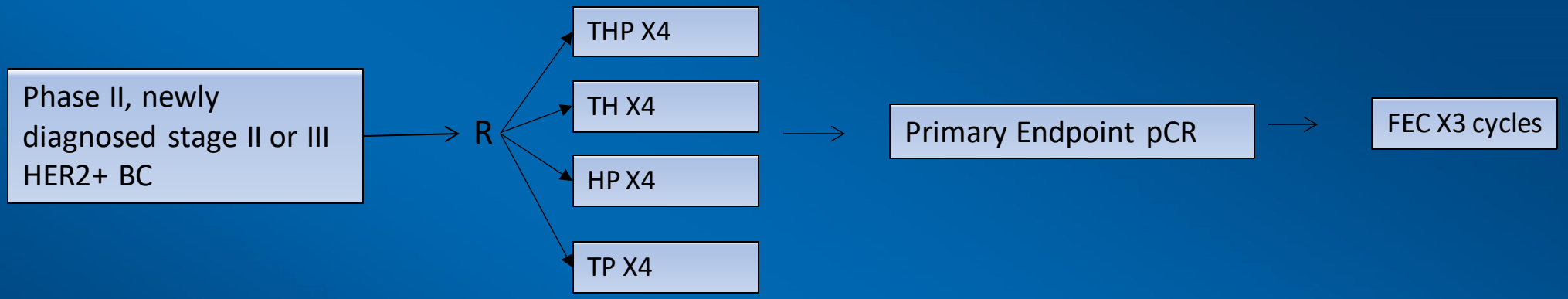
NeoSphere Trial



regimen	pCR
THP	45
TH	29
TP	24
HP	16

This trial supported addition of pertuzumab in the neoadjuvant treatment of stage II or III HER2+ BC

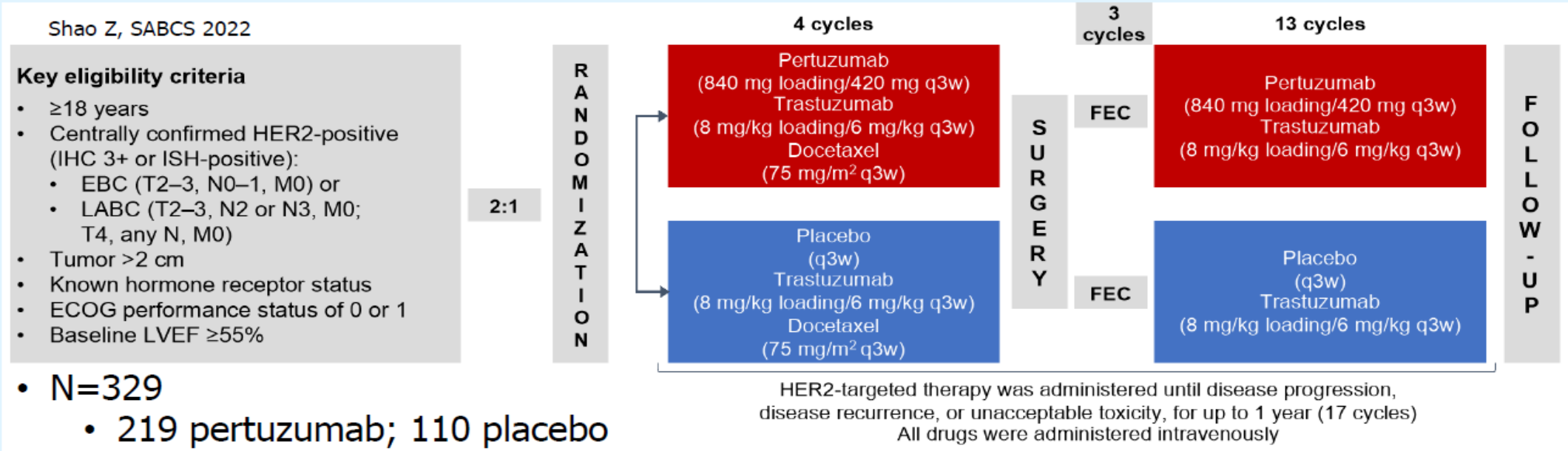
Gianni et al. Lancet Oncology 2012

Final Analysis of PEONY: THP in Asian Population

Shao Z, SABCS 2022

Key eligibility criteria

- ≥18 years
- Centrally confirmed HER2-positive (IHC 3+ or ISH-positive):
  - EBC (T2–3, N0–1, M0) or
  - LABC (T2–3, N2 or N3, M0; T4, any N, M0)
- Tumor >2 cm
- Known hormone receptor status
- ECOG performance status of 0 or 1
- Baseline LVEF ≥55%



- N=329
  - 219 pertuzumab; 110 placebo

Baseline Characteristics:

Hormone Receptor Positive:	52%
Premenopausal:	60%
Node:	76%
Locally advanced:	30%

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Final Analysis of PEONY: THP in Asian Population

Median Follow Up 62.9 months			
	Docetaxel/ Trastuzumab	Docetaxel/ Trastuzumab/ Pertuzumab	P-value
tpCR	21.8%	39.3%	0.001
3-year DFS	81%	90.1%	0.043
5-year DFS	75%	86%	0.028
3-year OS	91%	97%	0.053
5-year OS	90%	93.9%	0.26

Shao Z, SABCS 2022
Shao Z, JAMA Oncol 2020

Figure 2B: Kaplan–Meier plot of DFS in the ITT population

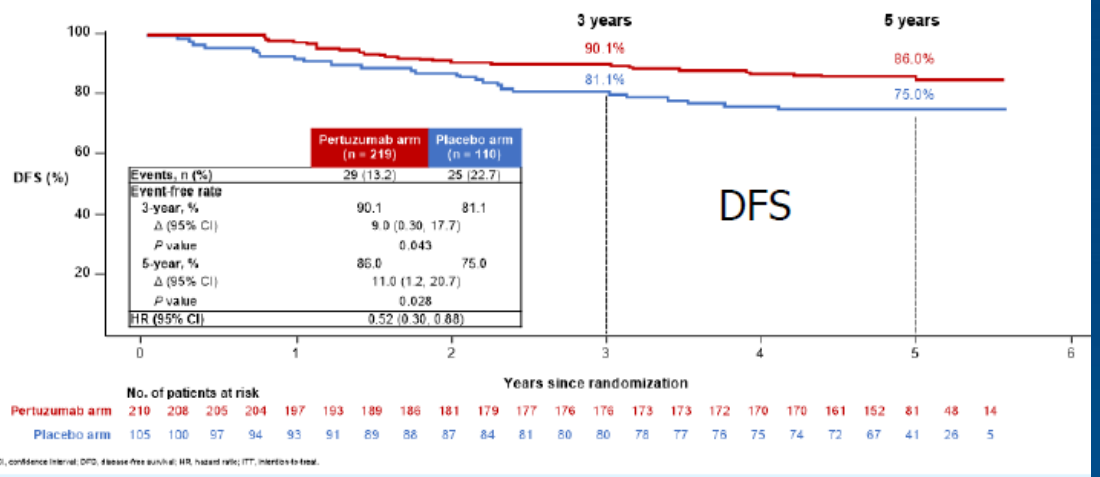
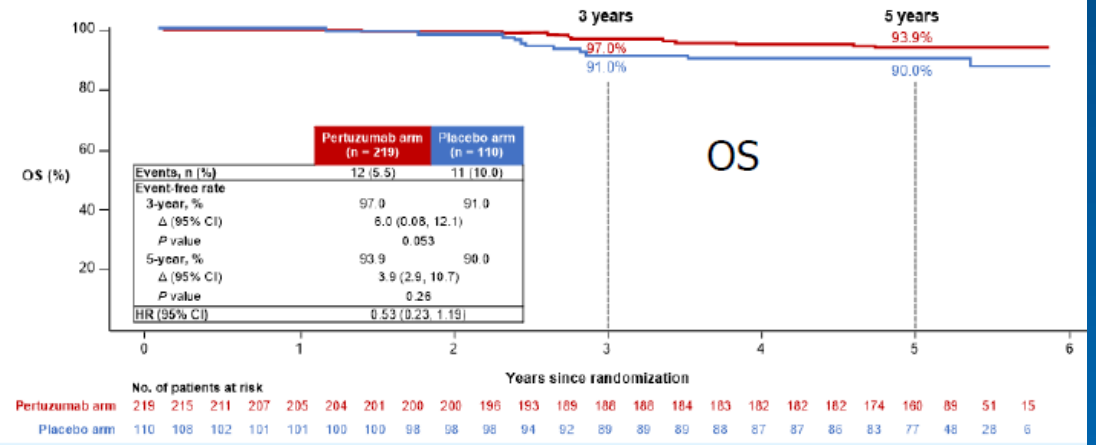


Figure 2C: Kaplan–Meier plot of OS in the ITT population



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Summary Neoadjuvant Taxane-plus HP

Regimen/ Study	N	tpCR	5-year DFS
Paclitaxel + HP x 12 weeks (in HR+ only) Triple Positive-II/Gluz et al. ASCO 2020 Abs 515	107	**57%**	**Not reported**
Paclitaxel + HP x 12 weeks (in HR- only) (FEC after surgery if non pCR) WGS-ADAPT HER2+/HR-/Nitz UA, et al. *Ann Oncol.* 2017;28:2768-2772, Nitz UA, et al. Lancet Oncol. 2022;23:625-635.	42	**91%**	**98% (iDFS)**
Docetaxel + HP x 4 cycles (FEC after surgery) NeoSphere/Gianni L *Lancet Oncol* 2012;13:25-32 & *Lancet Oncol.* 2016;17:791–800.	107	**39.3%**	**84%**
Docetaxel + HP x 6 cycles (FEC after surgery) PREDIX HER2/Hatschek T, et al. *JAMA Oncol.* 2021;7:1360-1367.	99	**45.5%**	**Not reported**
Docetaxel + HP x 4 cycles (FEC after surgery) Peony/Shao Z, et al. JAMA Oncol 2020;6; Shao Z et al. SABCS 2022	219	**39.3%**	**86%**

Patients treated with taxane/HP generally received adjuvant anthracycline.

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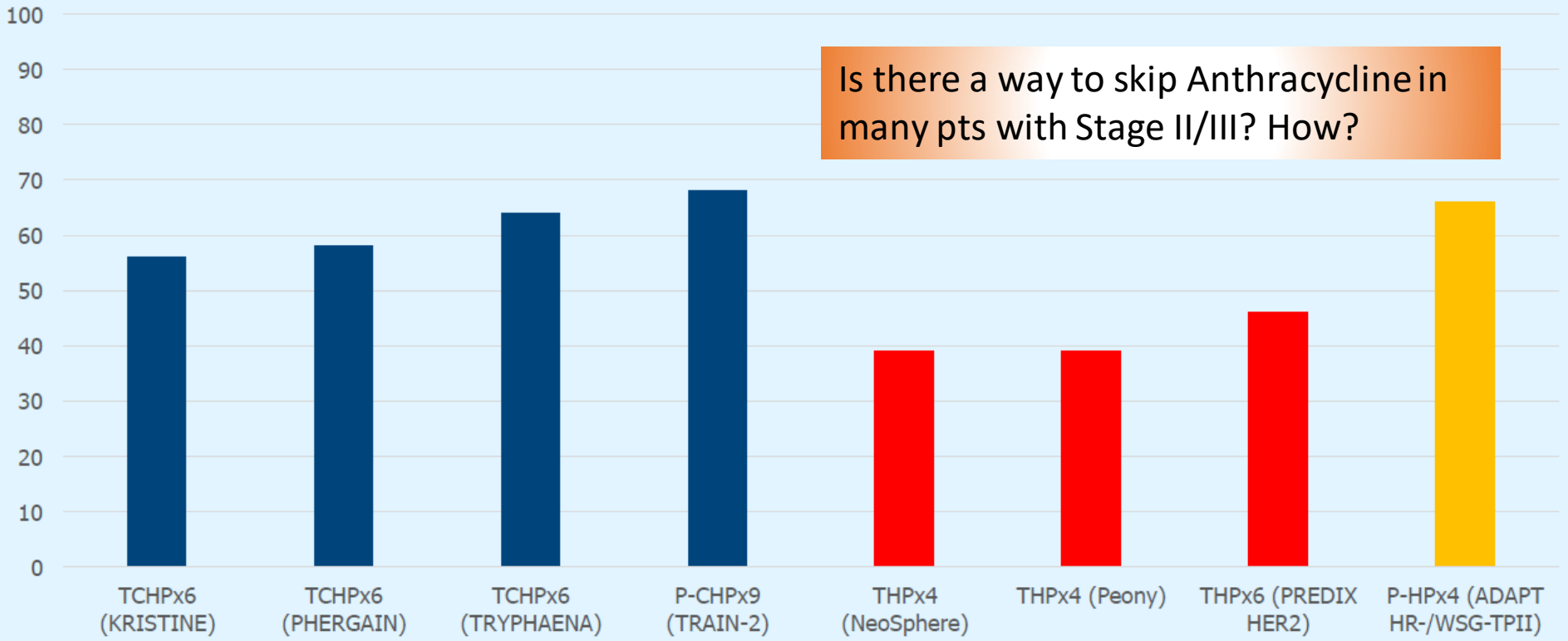
pCR rates with platinum and non platinum based treatment:



KRISTINE: Hurvitz, et al. J Clin Oncol 2016; PHERGAIN: Perez-Garcia, et al. Lancet 2021; TRYPHAENA: Schneeweiss, et al. Ann Oncol 2013; TRAIN-2: van Ramshorst et al. Lancet Oncol 2018; NeoSphere: Gianni et al. Lancet Oncol 2012; Peony: Shao et al JAMA Onc 2020; PREDIX HER2: Hatschek T, et al. *JAMA Oncol*. 2021; ADAPT HR- Nitz UA, et al. *Ann Oncol*. 2017; WSG-TPII Gluz et al. ASCO 2020

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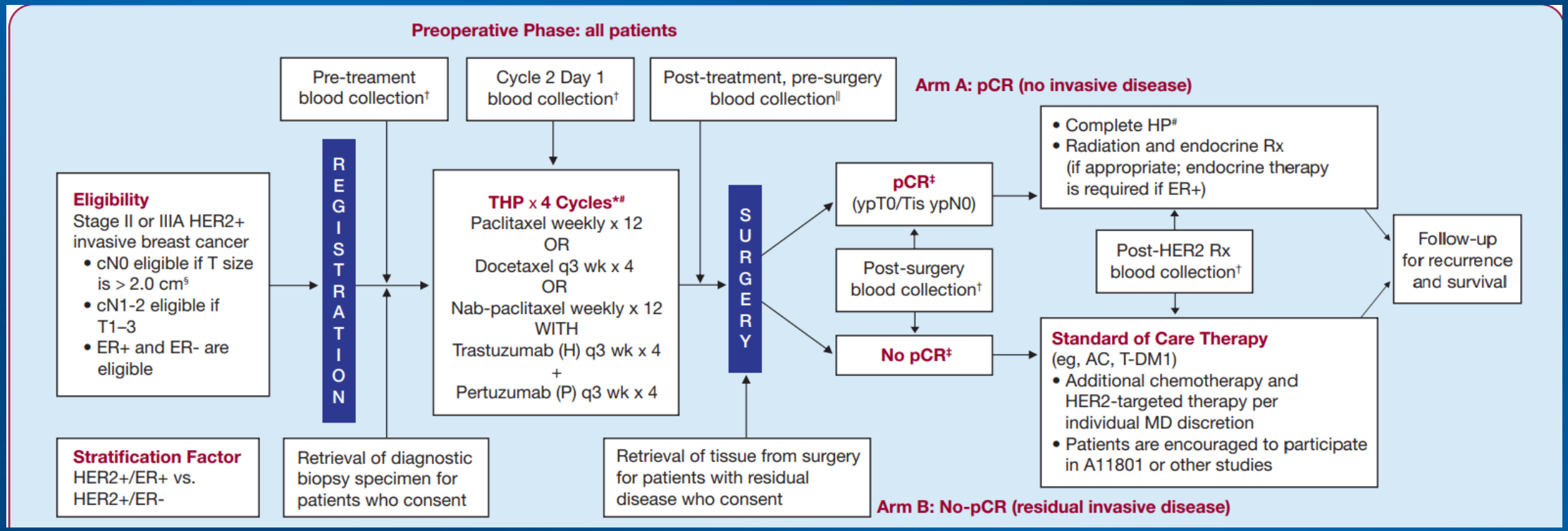
EA1181 (Compass pCR Study)



Primary Endpoint: 3 year RFI among pCR grp

Katherine Trial

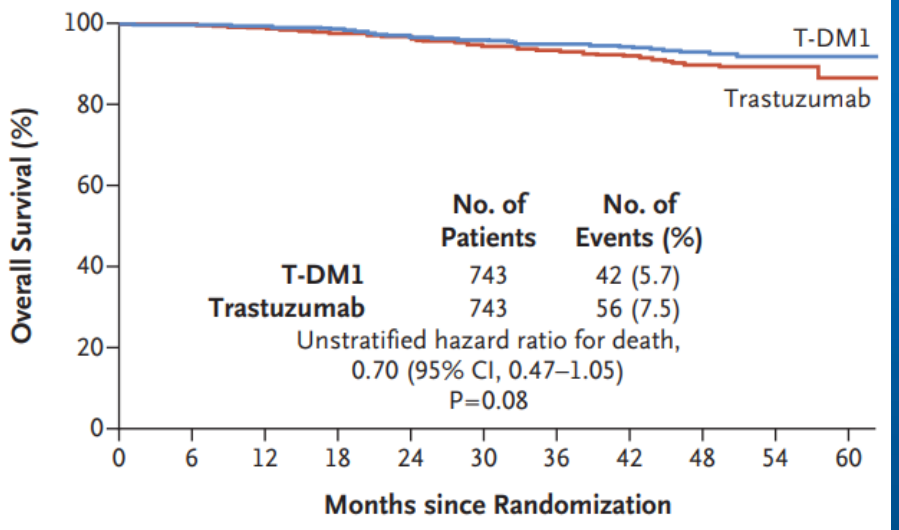
- Centrally confirmed HER2-positive breast cancer
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Received neoadjuvant therapy consisting of
  - Minimum of 6 cycles of chemotherapy
  - Minimum of 9 weeks of taxane+ trastuzumab
- Pathologic residual invasive tumor in breast or axilla

R 1:1

N=1486

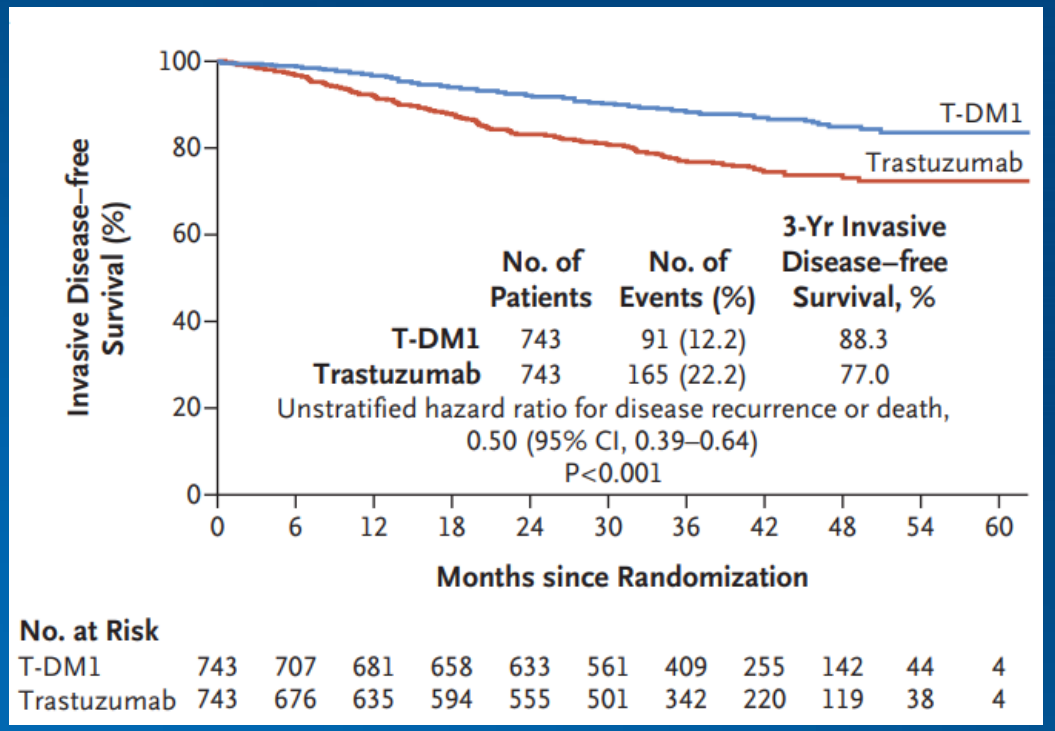
T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles



No. at Risk

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

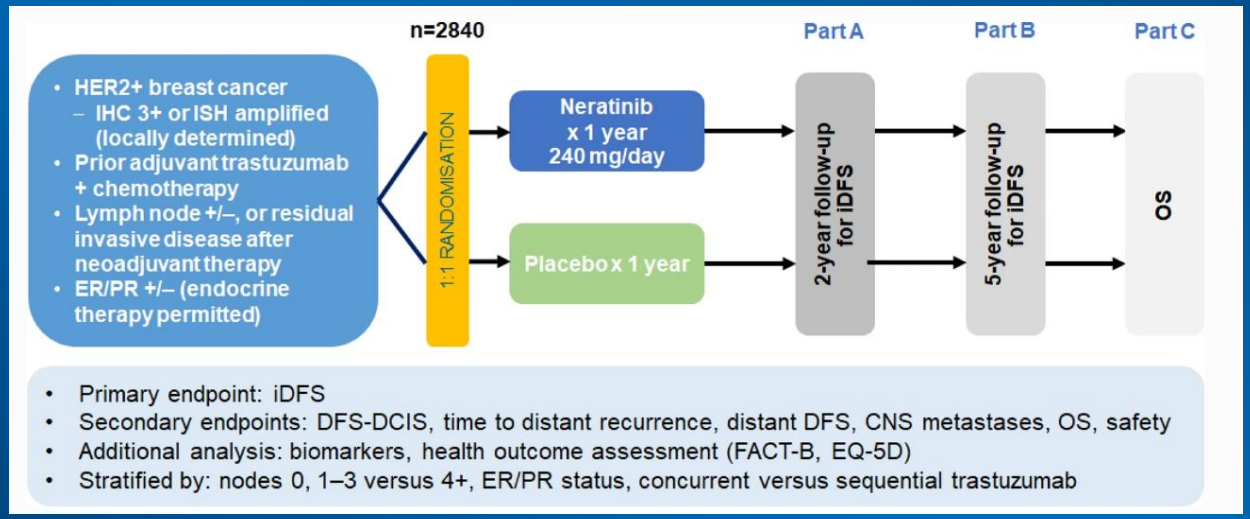


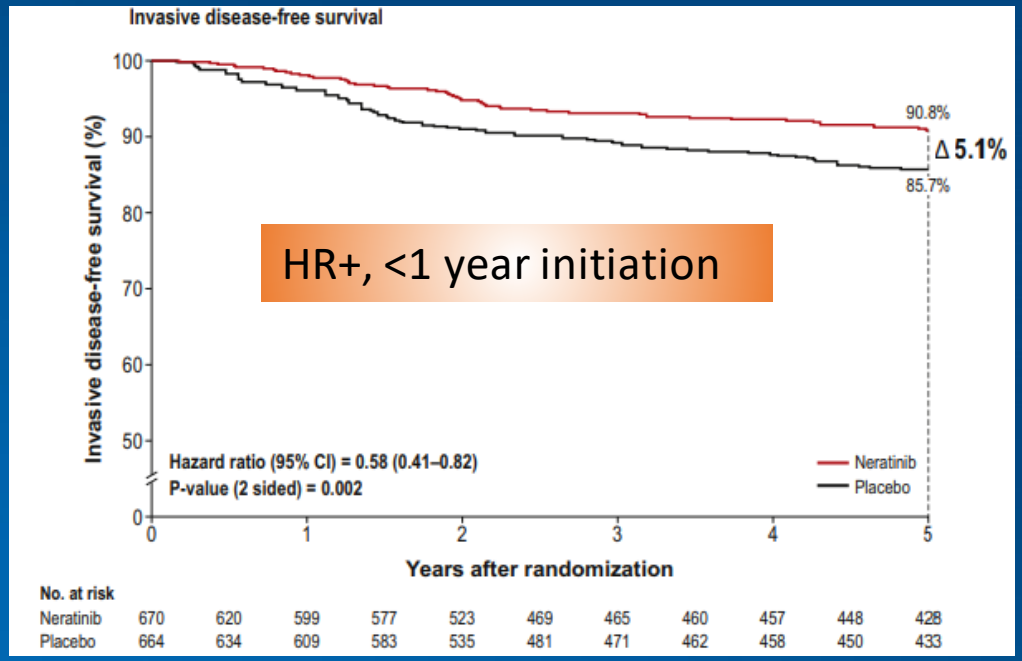
No. at Risk

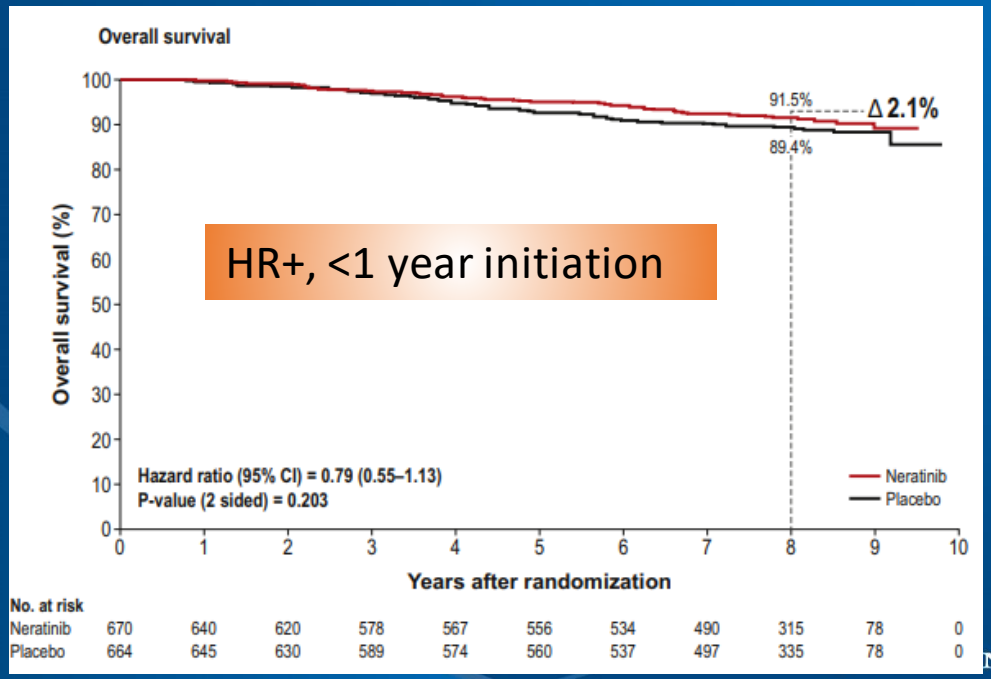
T-DM1	743	707	681	658	633	561	409	255	142	44	4
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4

von Minckwitz et al, NEJM 2019

ExteNET Trial







Untch M et al, Oncol Ther 2021

NE of
THE HIGHEST ORDER

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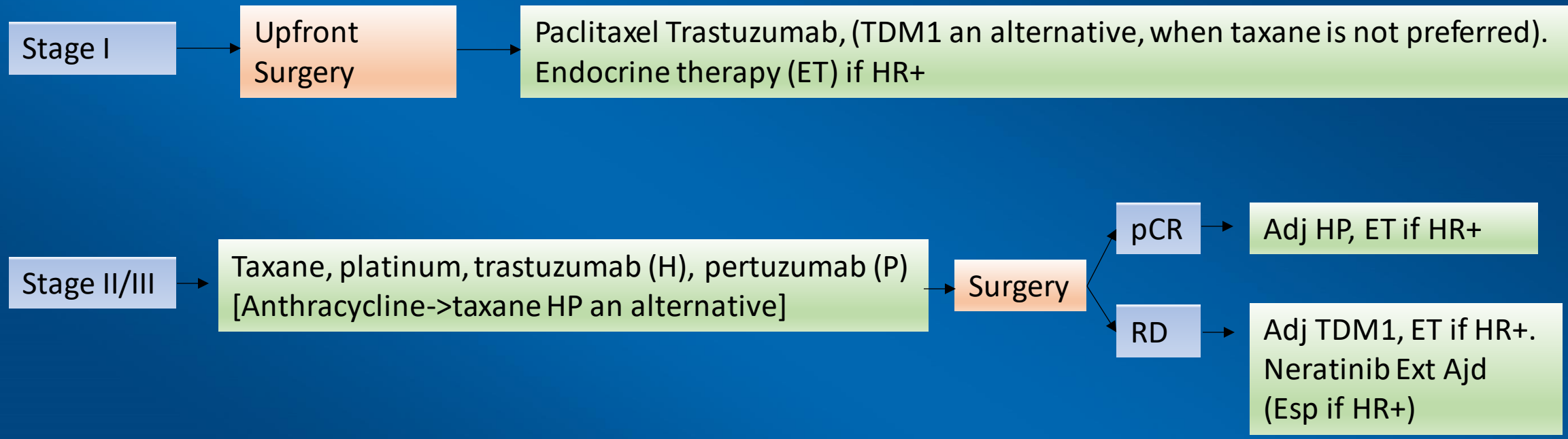
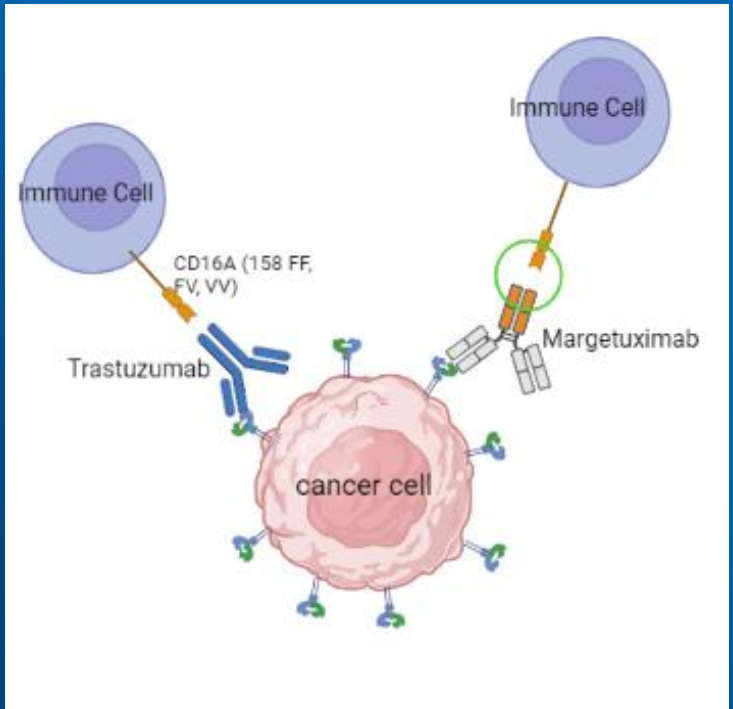
Current Treatment Paradigm for HER2+ Early Stage BC



Thank you for your attention!

- Slides not included due to Time Constraints:

Margetuximab



HER2+ Advanced Breast Cancer

- ≥2 prior anti-HER2 therapies, with pertuzumab
- 1-3 prior treatment lines in metastatic setting
- Prior brain metastasis ok, if treated and stable

Investigator's Choice of Chemotherapy
(capecitabine, eribulin, gemcitabine, or vinorelbine)

R

Margetuximab
(15 mg/kg for 2 hours Q3W)
+ chemotherapy

1:1 Randomization (N=536)

Trastuzumab
(8 mg/kg loading -> 6 mg/kg Q3W)
+ chemotherapy

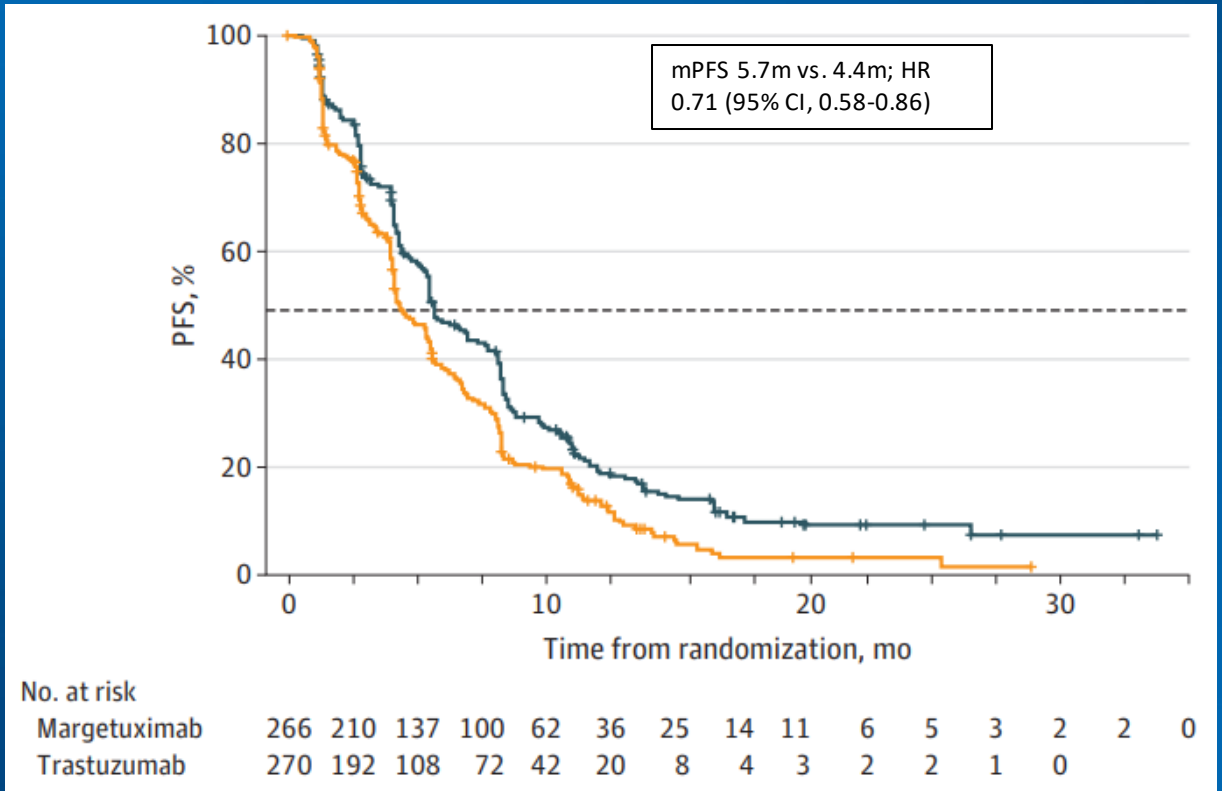
Sequential Primary End Points	• PFS (by CBA; n=257; HR=0.67; α=0.05; power=90%) • OS (n=385; HR=0.75; α=0.05; power=80%)
Secondary End Points	• PFS (Investigator assessed) • ORR (by CBA)
Tertiary/Exploratory End Points	• Clinical benefit rate • Duration of response • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy • ORR (Investigator assessed)

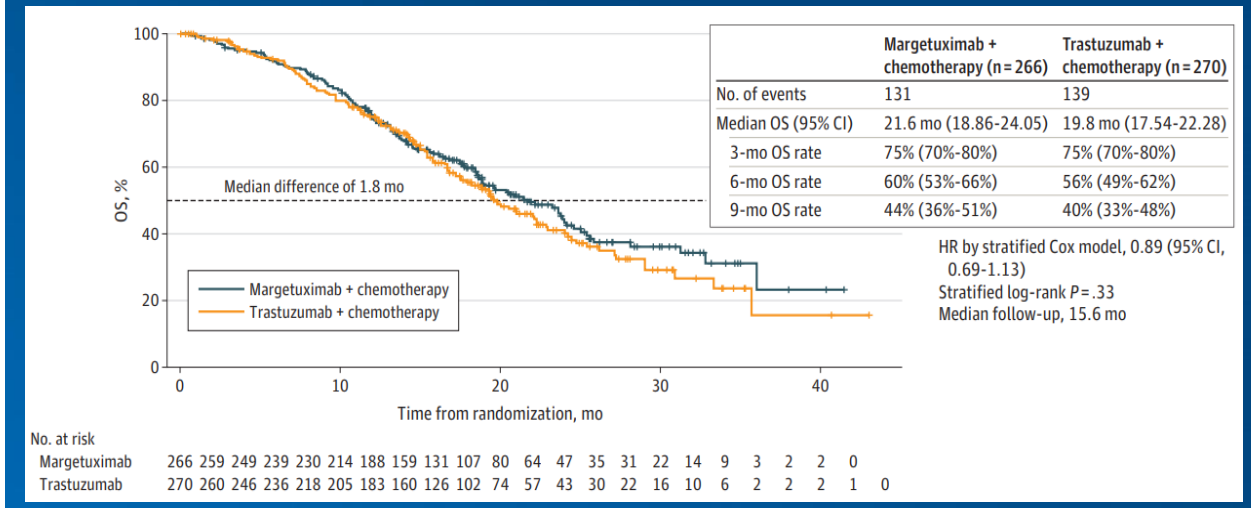
Stratification
- **Chemotherapy choice**
- **Prior therapies (≤2 vs >2)**
- **Metastatic sites (≤2 vs >2)**

CBA = centrally blinded analysis (also referred as BCIR); CD = cluster of differentiation; HER2 = human epidermal growth factor receptor 2; HER2+ = HER2-positive; HR = hazard ratio; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; Q3W = every 3 weeks; SOPHIA = Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of HER2+ Metastatic Breast Cancer.

1. NCT02492711. https://clinicaltrials.gov/ct2/show/NCT02492711?term=margetuximab&draw=2&rank=4. Accessed November 25, 2019. 2. Rugo HS, et al. *JAMA Oncol*. doi:10.1001/jamaoncol.2020.7932. Accessed March 11, 2021.

This Proprietary Information of MacroGenics is provided in response to HCP unsolicited request.

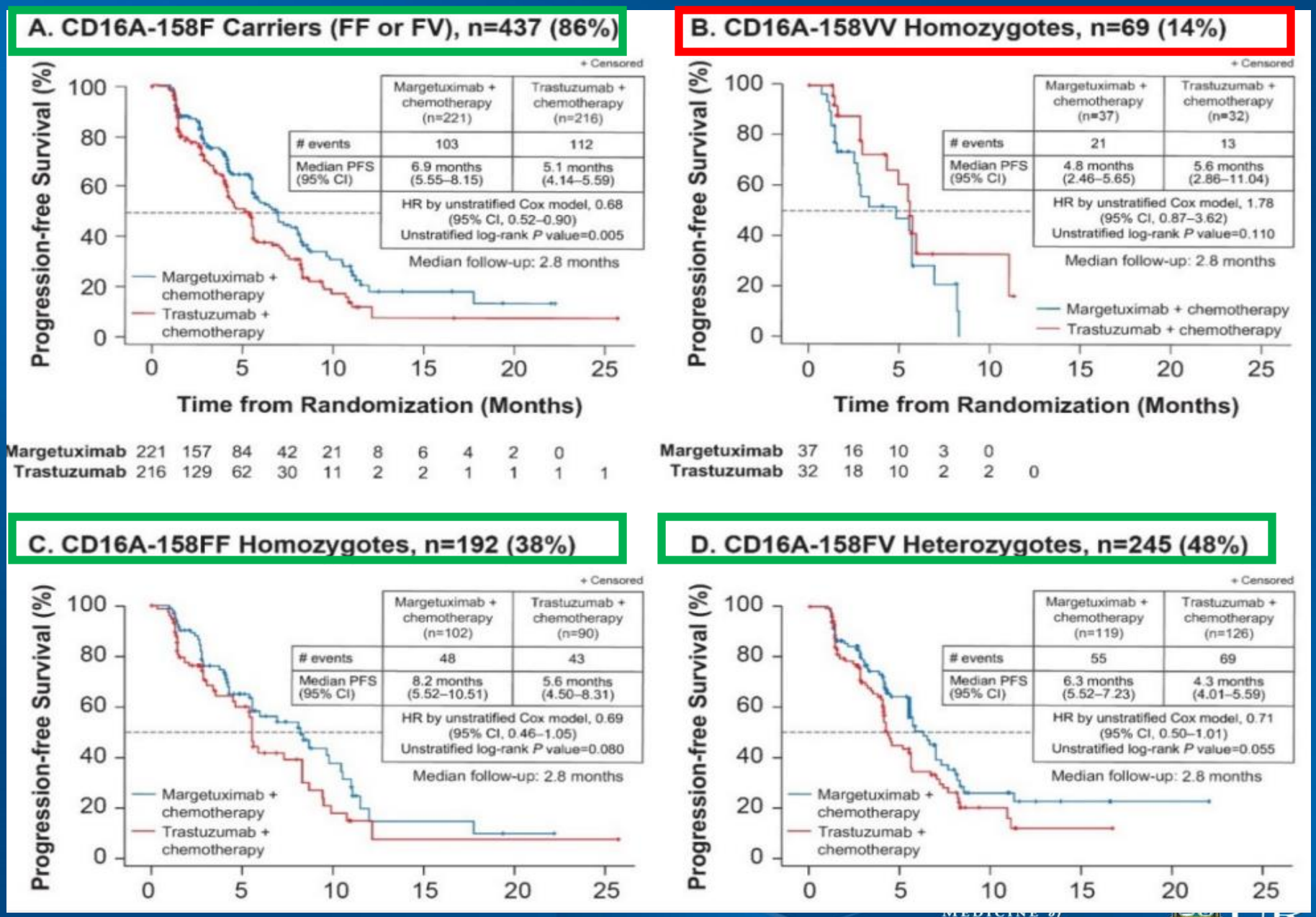




	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	131	139
Median OS (95% CI)	21.6 mo (18.86-24.05)	19.8 mo (17.54-22.28)
3-mo OS rate	75% (70%-80%)	75% (70%-80%)
6-mo OS rate	60% (53%-66%)	56% (49%-62%)
9-mo OS rate	44% (36%-51%)	40% (33%-48%)

HR by stratified Cox model, 0.89 (95% CI, 0.69-1.13)
Stratified log-rank $P = .33$
Median follow-up, 15.6 mo

Rugo et al. *JAMA Oncol.* 2021



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