Optimizing Management of HER2-Positive Advanced Breast Cancer

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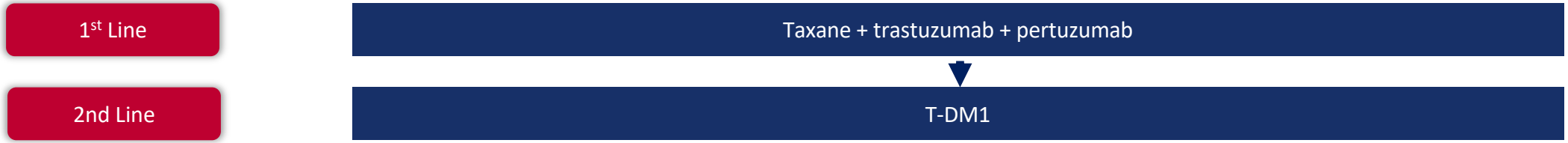
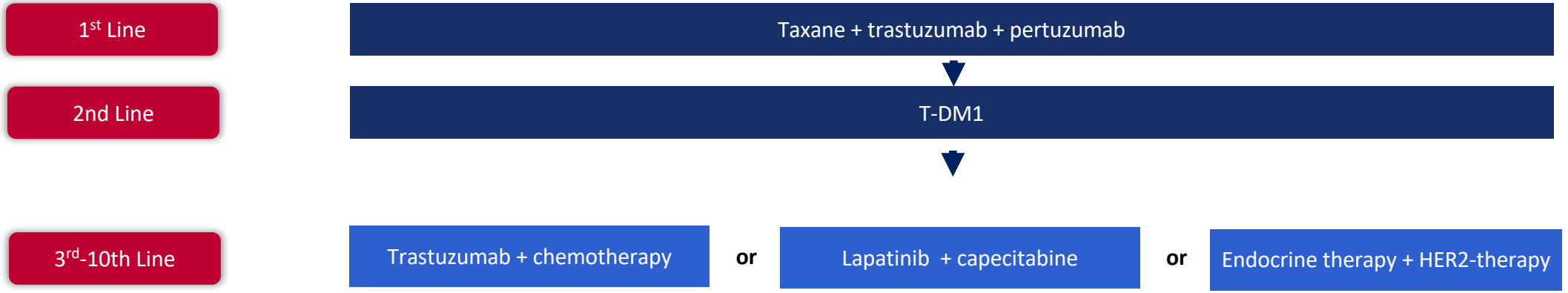
December 2022

Treatment Paradigm for Metastatic HER2+ Breast Cancer (Circa 2019)



Treatment Paradigm for Metastatic HER2+ Breast Cancer (Circa 2019)



Efficacy of Chemotherapy + Trastuzumab is limited in ≥3rd line*

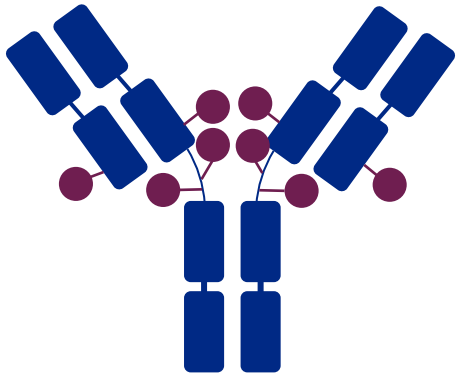
– PFS ≈ 5 months

– ORR ≈ 20%

* Ie control arms of SOPHIA and HER2CLIMB

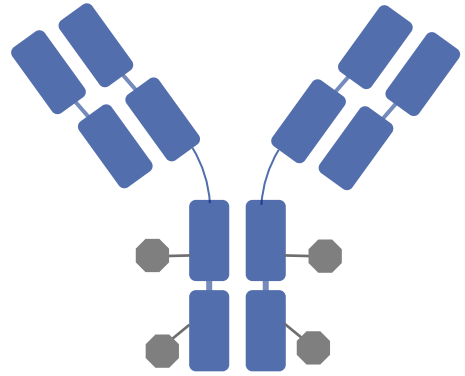
Trastuzumab deruxtecan: a 2nd generation HER2-targeted ADC

Trastuzumab deruxtecan (T-DXd)[1]



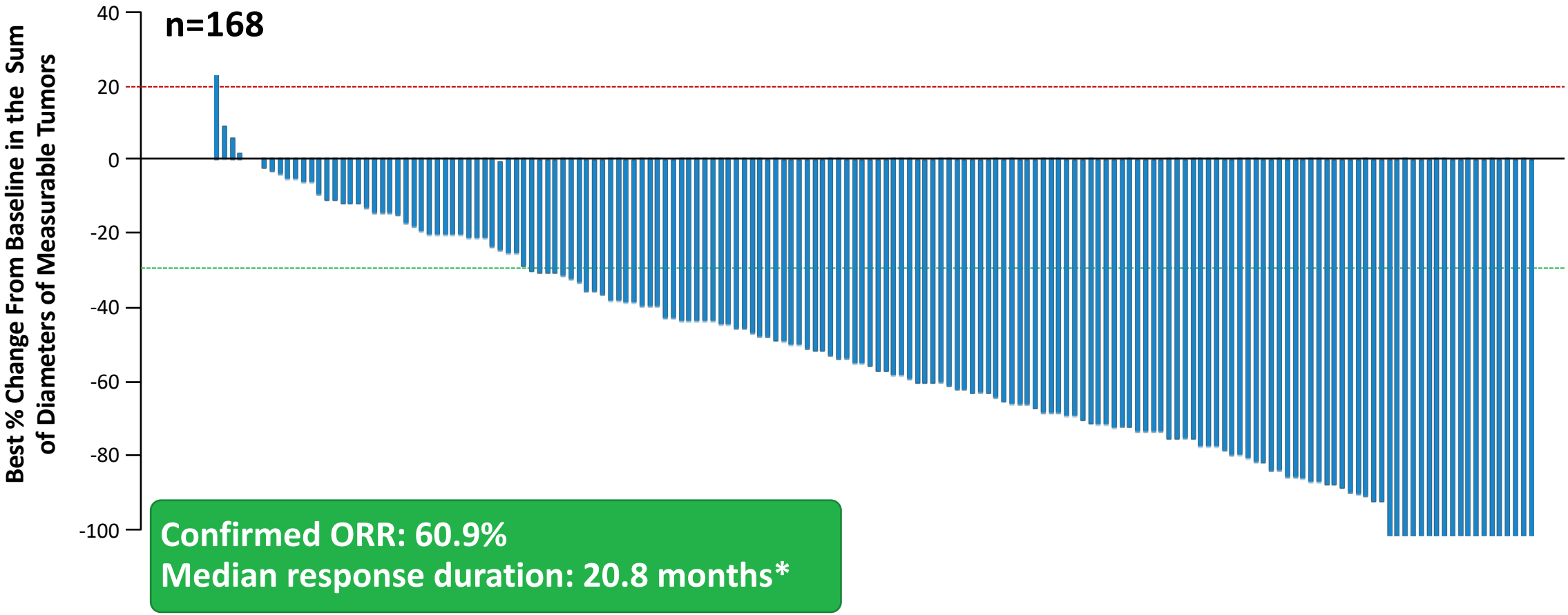
T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



Adapted from J Cortes et al, ESMO 2021

Destiny Breast-01: Phase 2 Efficacy of Trastuzumab Deruxtecan in heavily pretreated HER2+ metastatic breast cancer



By independent central review.
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
[a] Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

Adapted from Krop et al, SABCS 2019; *Modi S et al, SABCS 2020

Updated OS Analysis of DESTINY-Breast03

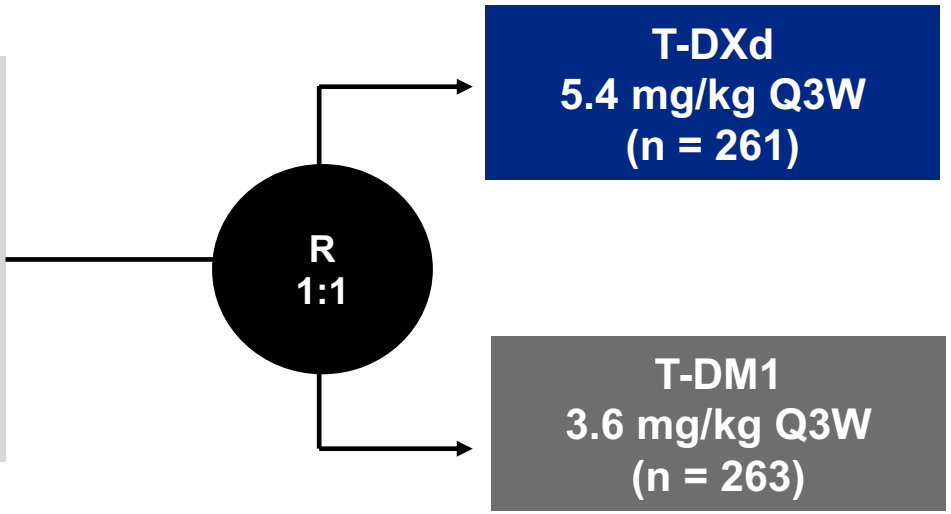
Randomized, open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy[b]

Stratification factors

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



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS[c]

Secondary endpoints

- ORR (BICR and investigator)
- DoR (BICR)
- Safety

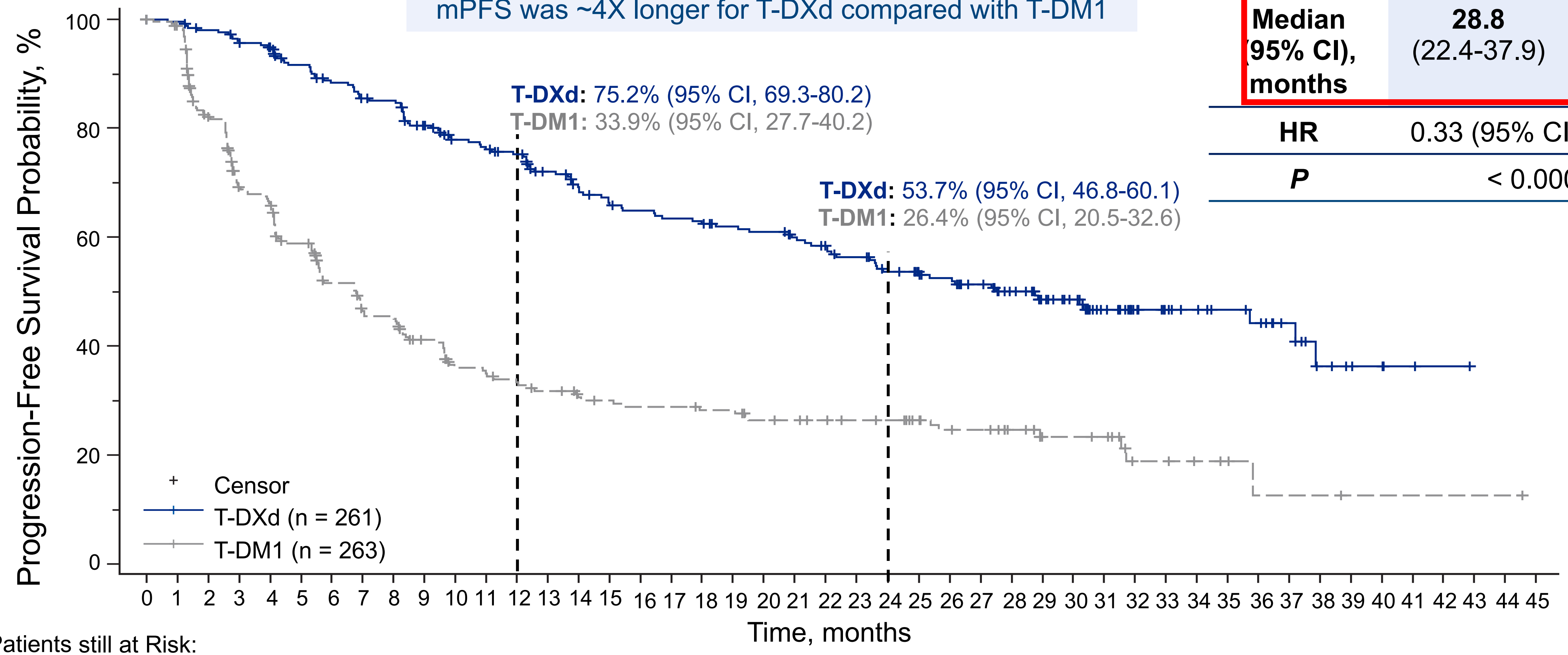
The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

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.

Updated Primary Endpoint: PFS by BICR

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



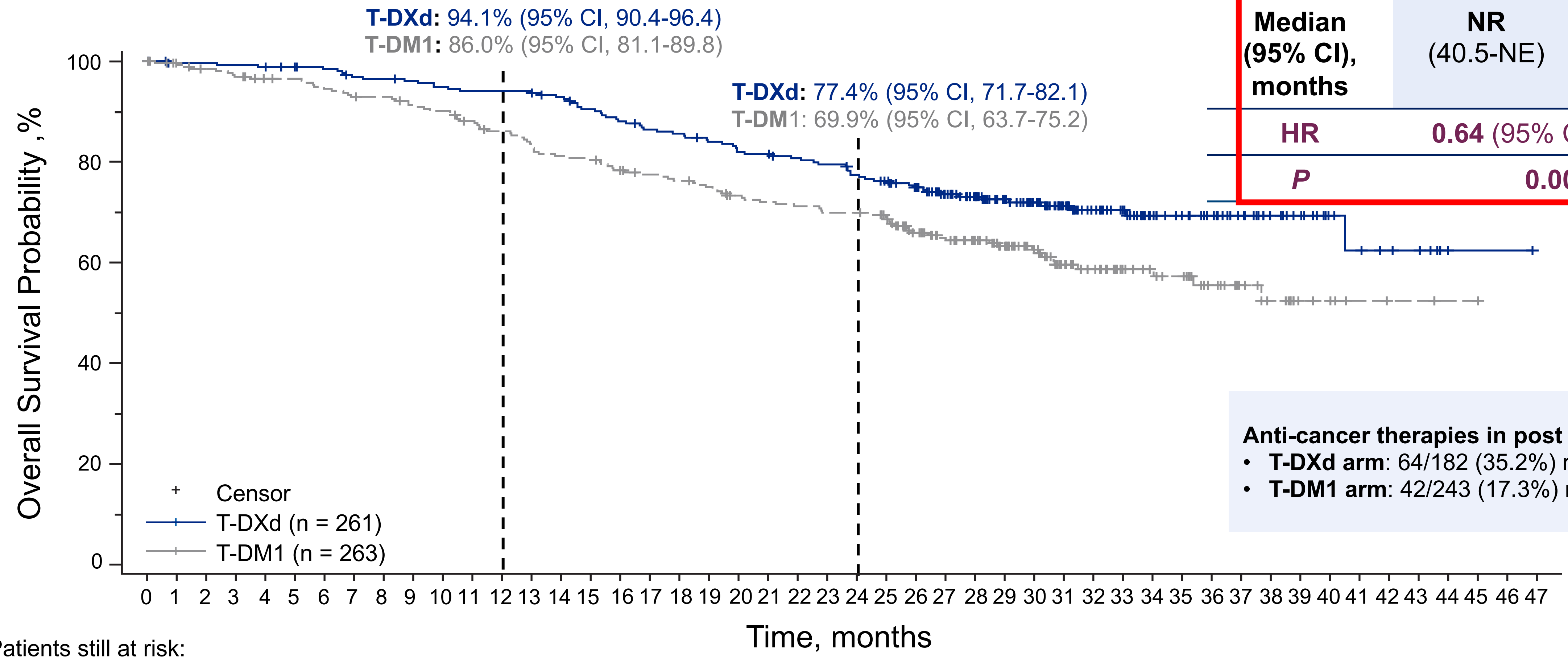
	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Patients still at Risk:

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.

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]	

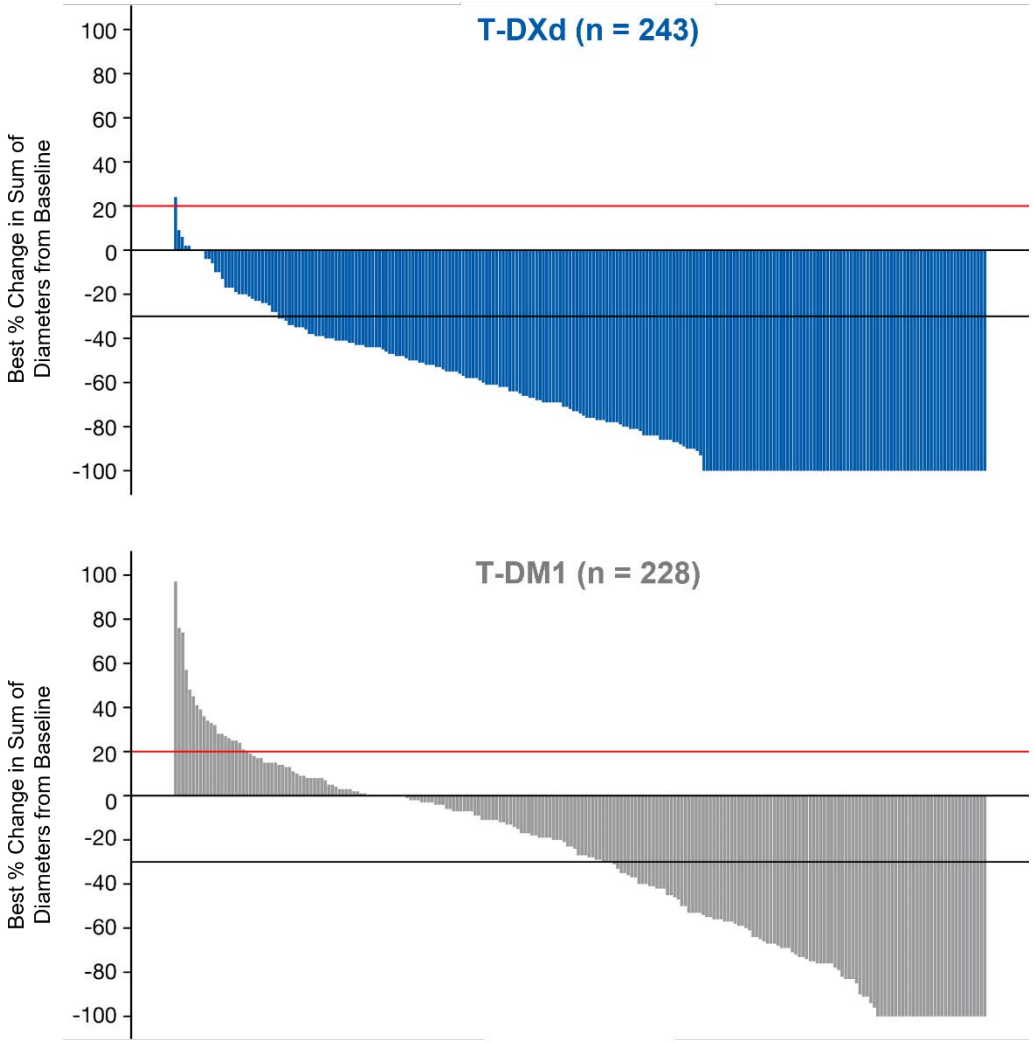
Anti-cancer therapies in post trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

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

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.

Confirmed ORR and Other Efficacy Endpoints



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	
mDoR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDoR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Red line at 20% indicates progressive disease; black line at −30% indicates partial response.

[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

Most Common TEAEs in ≥20% of Patients

System Organ Class Preferred Term, n (%)	T-DXd n = 257		T-DM1 n = 261	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system disorders				
Anemia	95 (37.0)	24 (9.3)	51 (19.5)	17 (6.5)
Platelet count decreased	64 (24.9)	20 (7.8)	114 (43.7)	52 (19.9)
White blood cell count decreased	60 (23.3)	16 (6.2)	16 (6.1)	2 (0.8)
Gastrointestinal disorders				
Nausea	198 (77.0)	18 (7.0)	79 (30.3)	1 (0.4)
Vomiting	133 (51.8)	4 (1.6)	28 (10.7)	2 (0.8)
Constipation	96 (37.4)	0	51 (19.5)	0
Diarrhea	83 (32.3)	3 (1.2)	21 (8.0)	2 (0.8)
General disorders				
Fatigue	79 (30.7)	15 (5.8)	53 (20.3)	2 (0.8)
Headache	61 (23.7)	1 (0.4)	40 (15.3)	0
Investigations				
Neutrophil count decreased	79 (30.7)	41 (16.0)	30 (11.5)	8 (3.1)
Aspartate aminotransferase increased	72 (28.0)	2 (0.8)	108 (41.4)	14 (5.4)
Alanine aminotransferase increased	59 (23.0)	4 (1.6)	83 (31.8)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	78 (30.4)	4 (1.6)	46 (17.6)	1 (0.4)
Weight decreased	58 (22.6)	6 (2.3)	23 (8.8)	2 (0.8)
Skin and subcutaneous tissue disorders				
Alopecia	102 (39.7)	1 (0.4)[a]	9 (3.4)	0

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Adverse events were managed according to the protocol. [a]Cases of alopecia reported during the study were graded based on the clinical judgement of the investigator. 1 case of alopecia was categorized as grade 3 by the investigator despite grade 3 alopecia not being recognized by the NCI Common Terminology criteria. The event outcome was reported as recovered by the investigator.

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Modi S et al. *N Engl J Med* 2020; 382(7): 610-21. 2. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

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

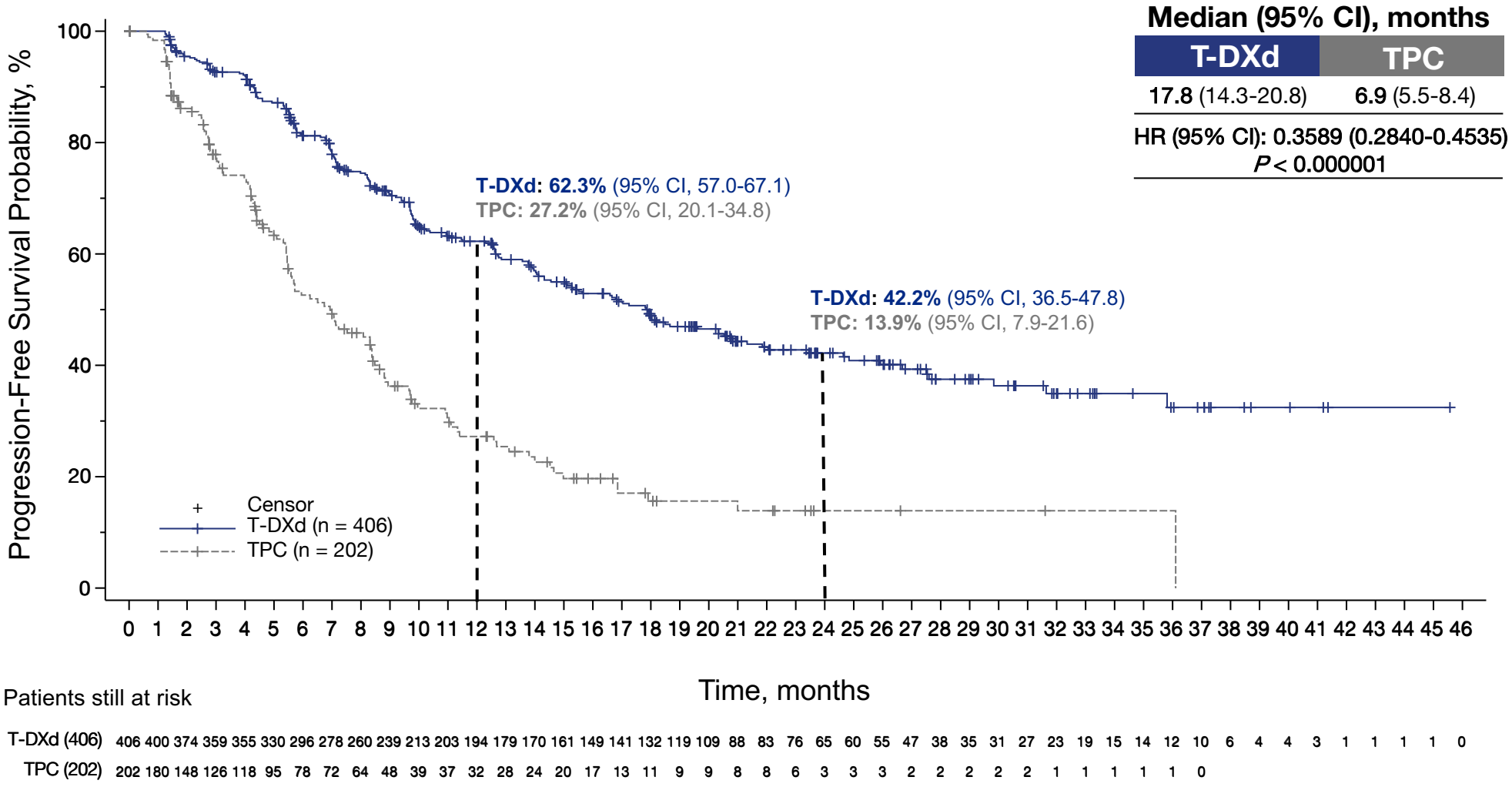
Protocol-prespecified statistical analysis plan

- 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.

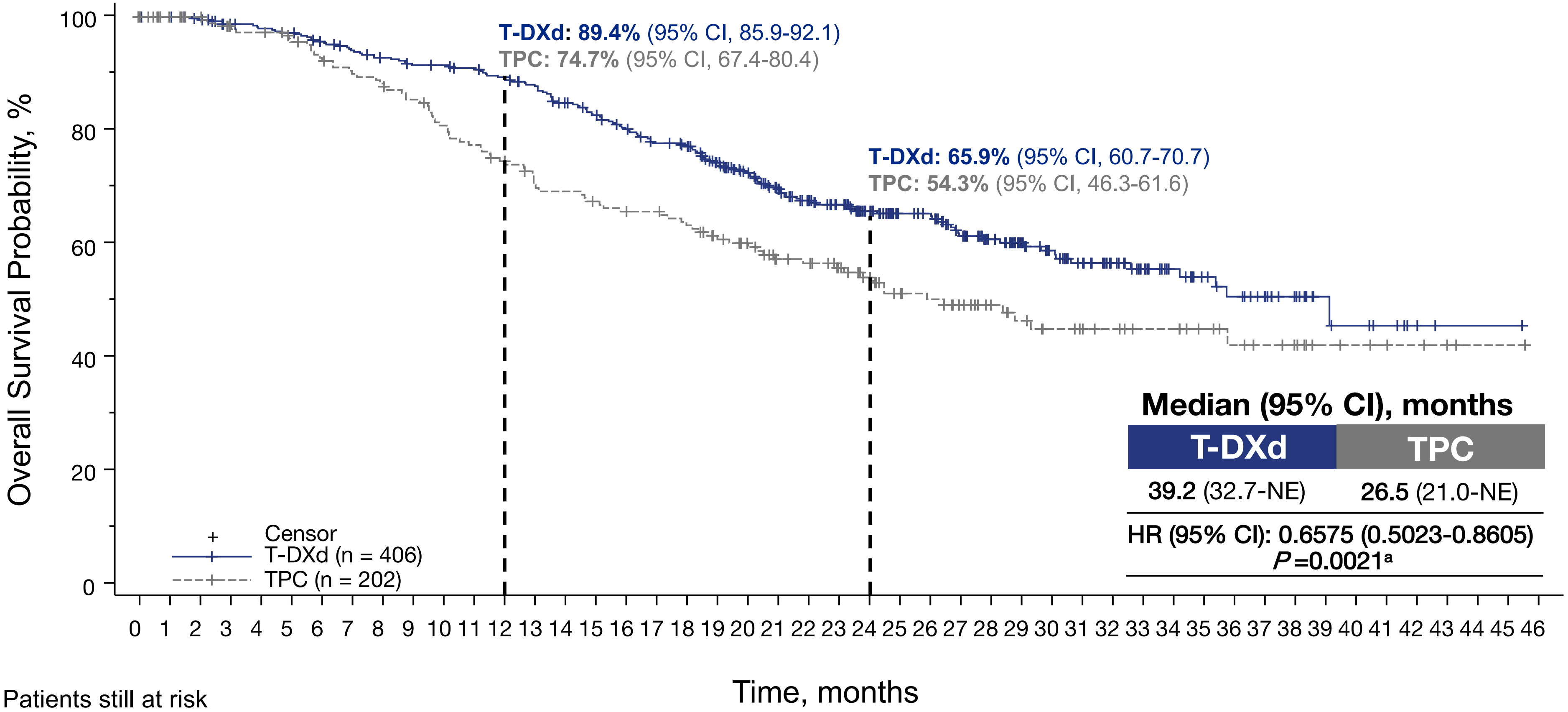
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization 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.

Primary Endpoint: PFS by BICR



BICR, blinded independent central review; HR, hazard ratio; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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	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)	202	192	187	182	178	173	167	161	157	151	142	136	130	124	118	114	111	110	106	95	89	79	76	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 who discontinued therapy received a new systemic anticancer**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Adverse Events of Special Interest: ILD and LV Dysfunction

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

ILD, interstitial lung disease; LV, left ventricular; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The safety analysis set includes all randomly assigned patients who received at least 1 dose of study treatment. [b]Left ventricular dysfunction included preferred terms of acute left ventricular failure, acute right ventricular failure, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, chronic left ventricular failure, chronic right ventricular failure, ejection fraction decreased, left ventricular failure, right ventricular failure, ventricular failure, and left ventricular dysfunction. [c]17 ejection fraction decreased (2 grade ≥3), 1 LV dysfunction (grade 1). [d]1 ejection fraction decreased (grade 1), 2 cardiac failure (1 grade ≥3).

Tucatinib – A Potent & Selective HER2 Inhibitor

- Selective small molecular tyrosine kinase inhibitor with nanomolar potency
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
  - Phase 1 single agent data had no treatment-related g3 diarrhea in heavily pretreated patients
- Penetrates CNS very well

Compound	Cellular Selectivity Data	
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)
Lapatinib	49	31
Neratinib	7	8
Tucatinib	**8**	**>10,000**

Moulder et al. AACR-NCI-EORTC 2011; Koch et al. AACR 2011

Slide adapted from S Tolaney ASCO 2018

HER2CLIMB Trial Design

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

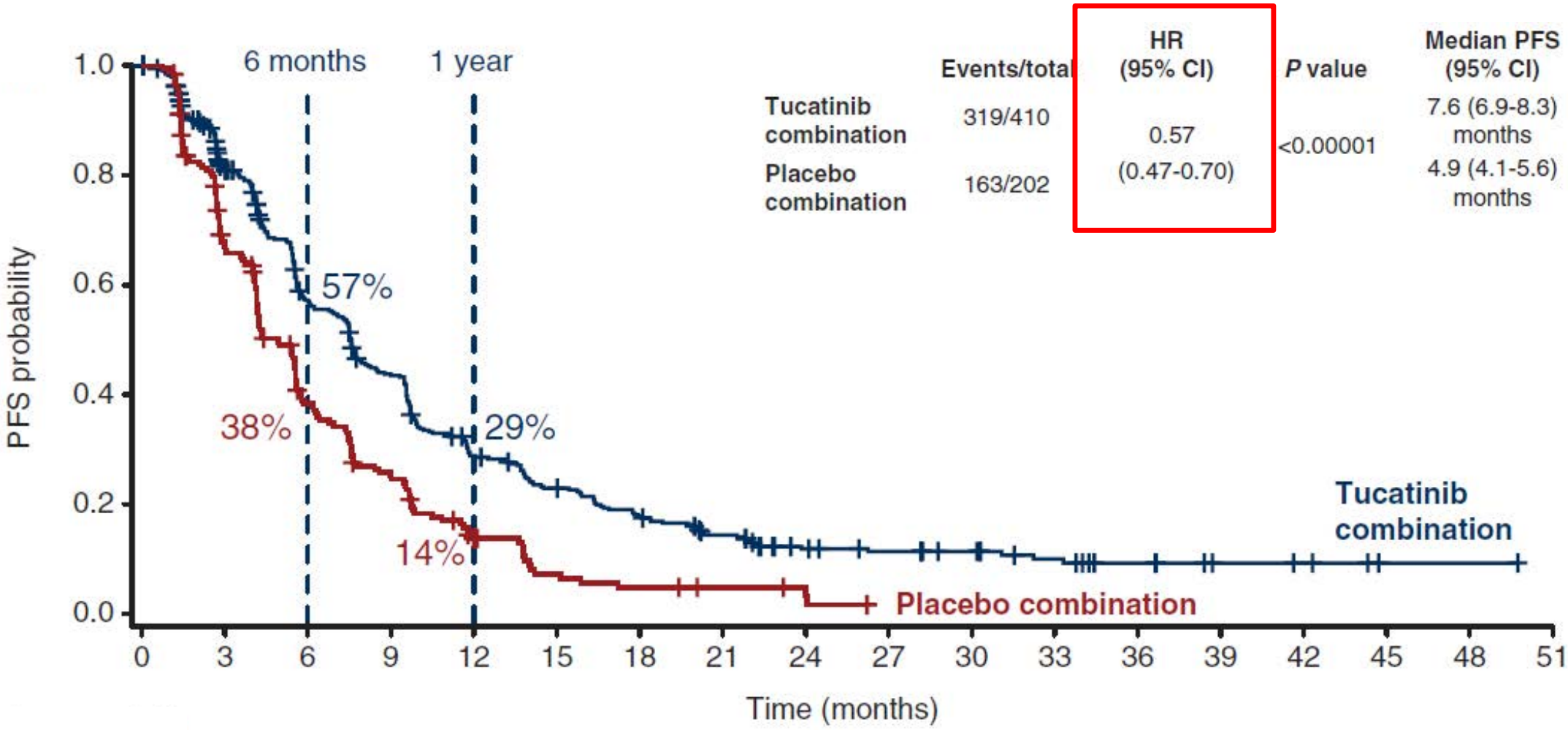
Placebo + Trastuzumab + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794

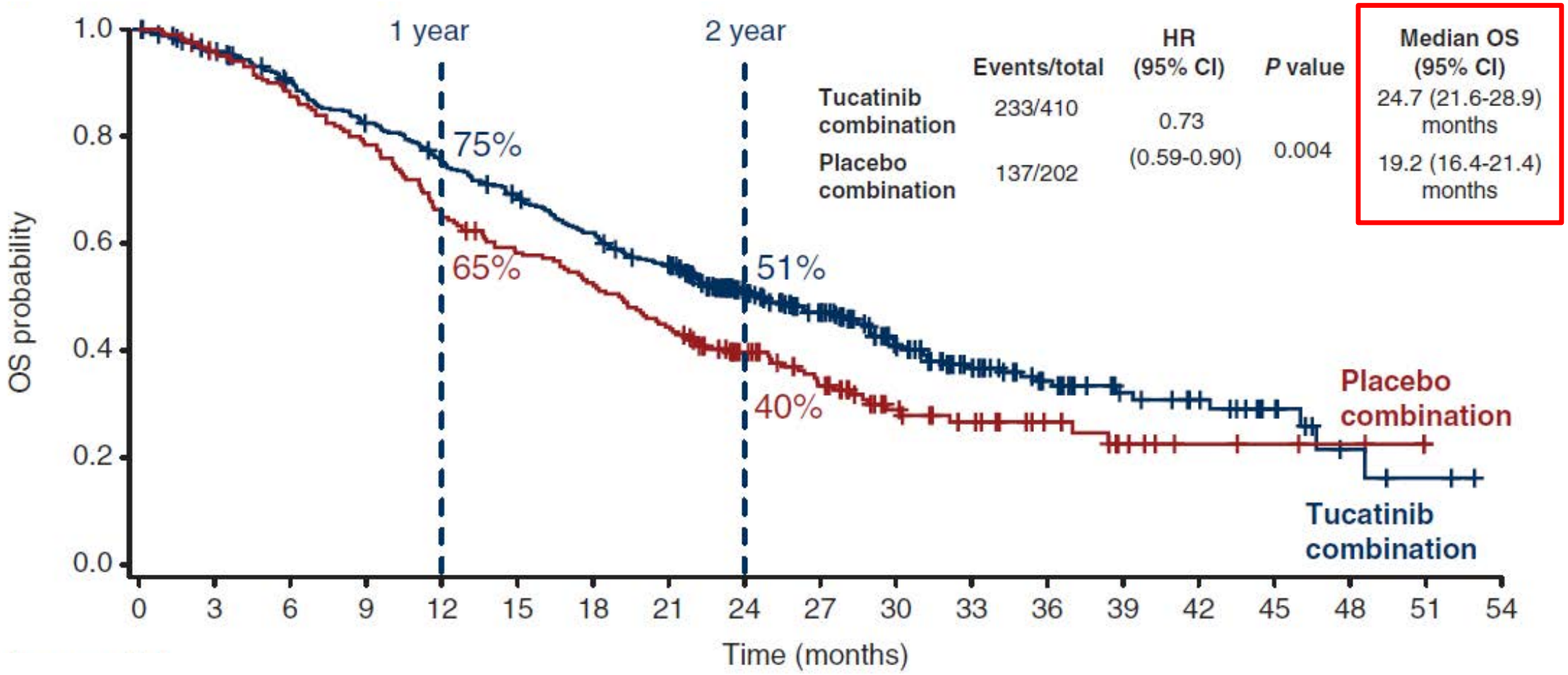
HER2CLIMB Updated PFS results



	Events/total	HR (95% CI)	*P* value	Median PFS (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<0.00001	7.6 (6.9-8.3) months
Placebo combination	163/202			4.9 (4.1-5.6) months

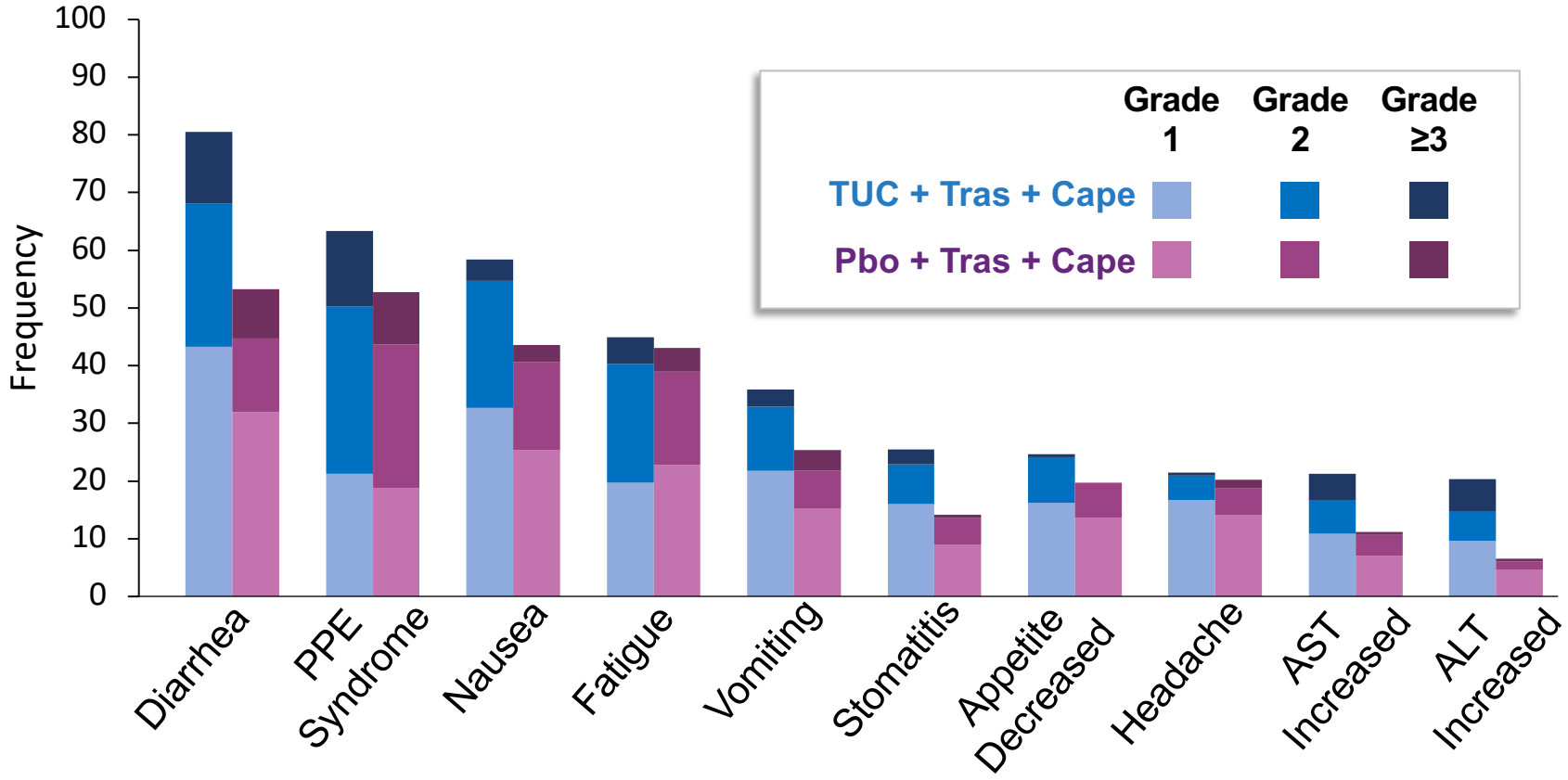
Curigliano et al, Annals Oncology 2022 33:321

HER2CLIMB Updated OS results



Curigliano et al, Annals Oncology 2022 33:321

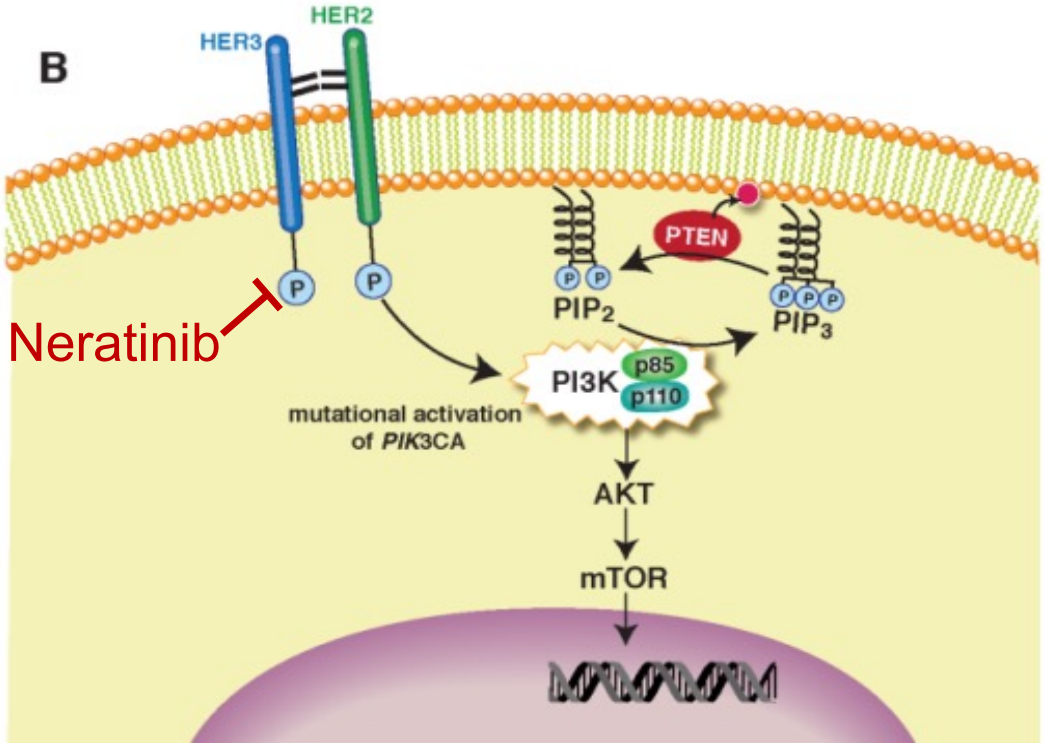
Most Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

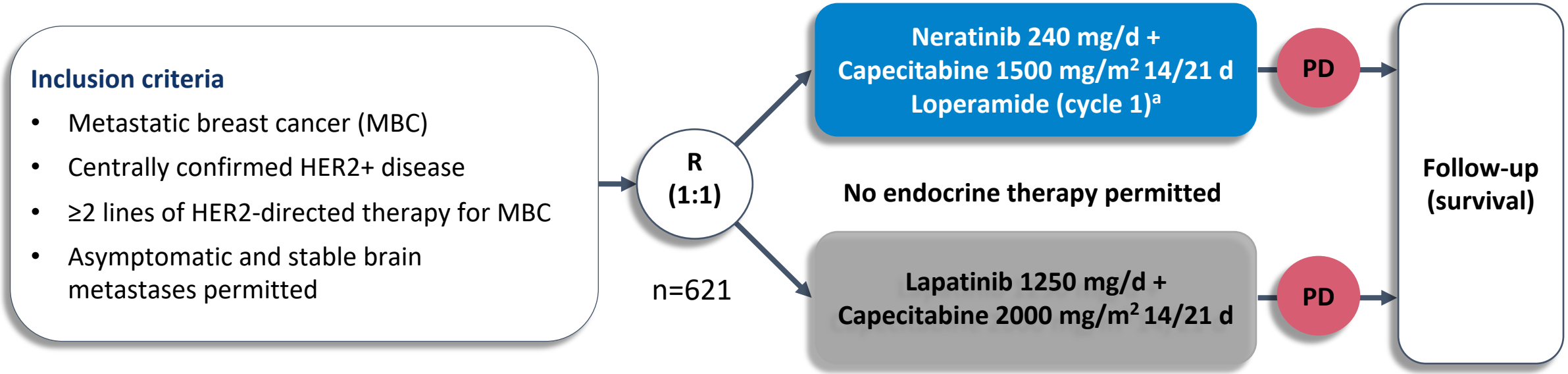
NERATINIB

- Low-molecular-weight, irreversible, pan-HER inhibitor (ErbB1,2,4)
- Significant toxicity: 21% Grade 3-4 diarrhea



Burstein et al
JCO. 2010. 28:1301

NALA study design



Stratification variables

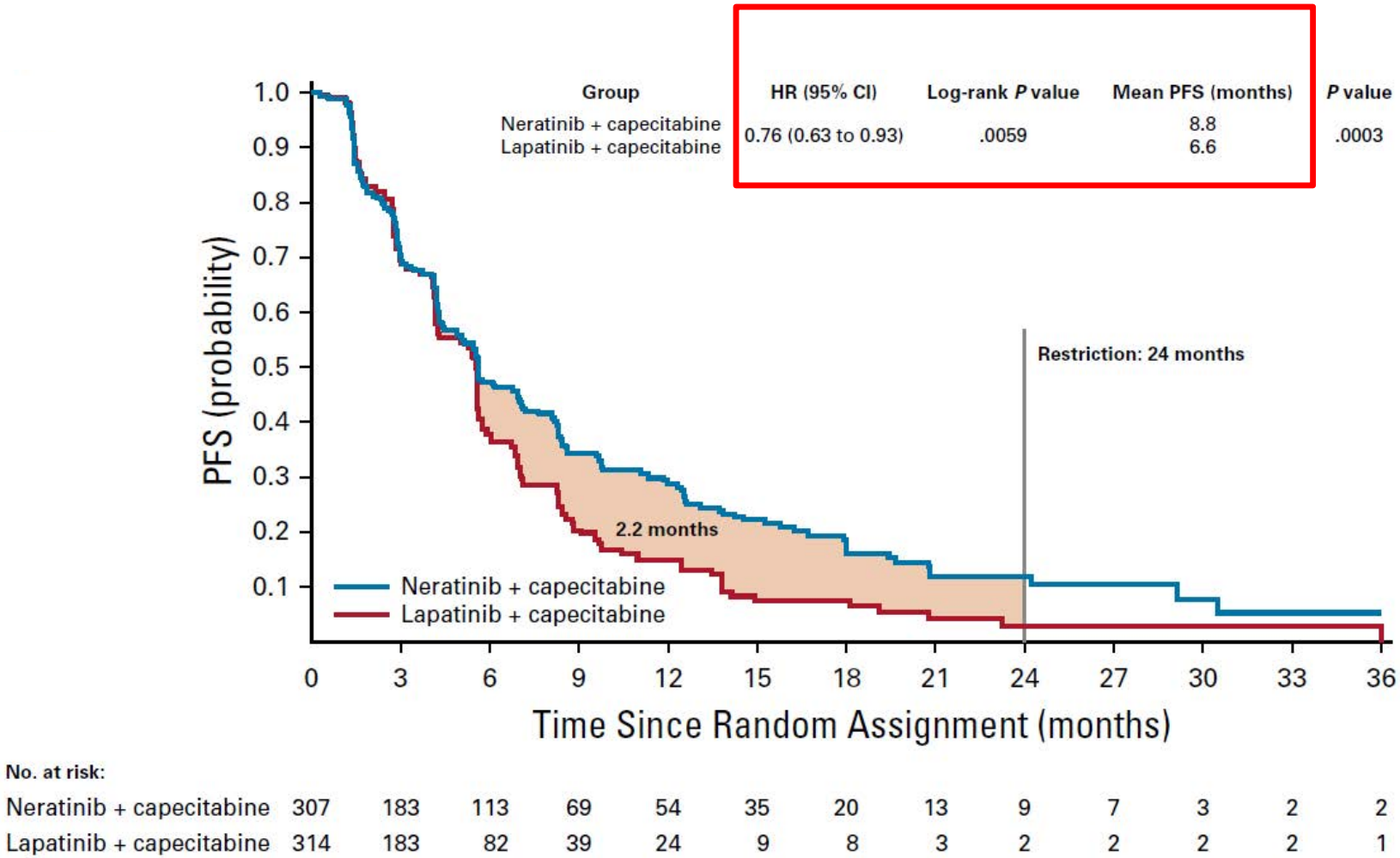
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

NALA Centrally Confirmed PFS

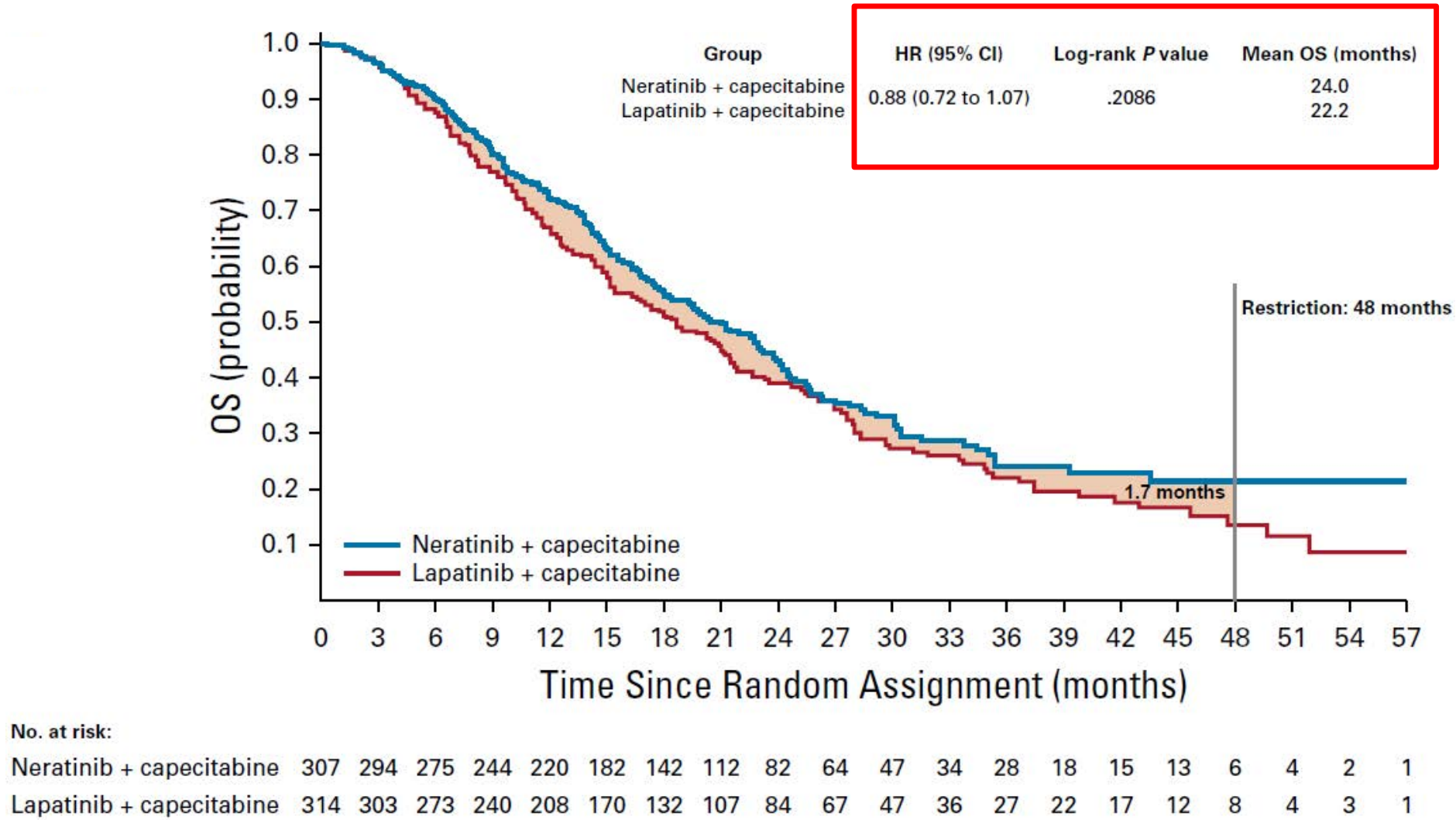


No. at risk:

Neratinib + capecitabine	307	183	113	69	54	35	20	13	9	7	3	2	2
Lapatinib + capecitabine	314	183	82	39	24	9	8	3	2	2	2	2	1

Saura et al, JCO 2020 38:3138

NALA Overall Survival Analysis



No. at risk:

Neratinib + capecitabine	307	294	275	244	220	182	142	112	82	64	47	34	28	18	15	13	6	4	2	1
Lapatinib + capecitabine	314	303	273	240	208	170	132	107	84	67	47	36	27	22	17	12	8	4	3	1

Saura et al, JCO 2020 38:3138

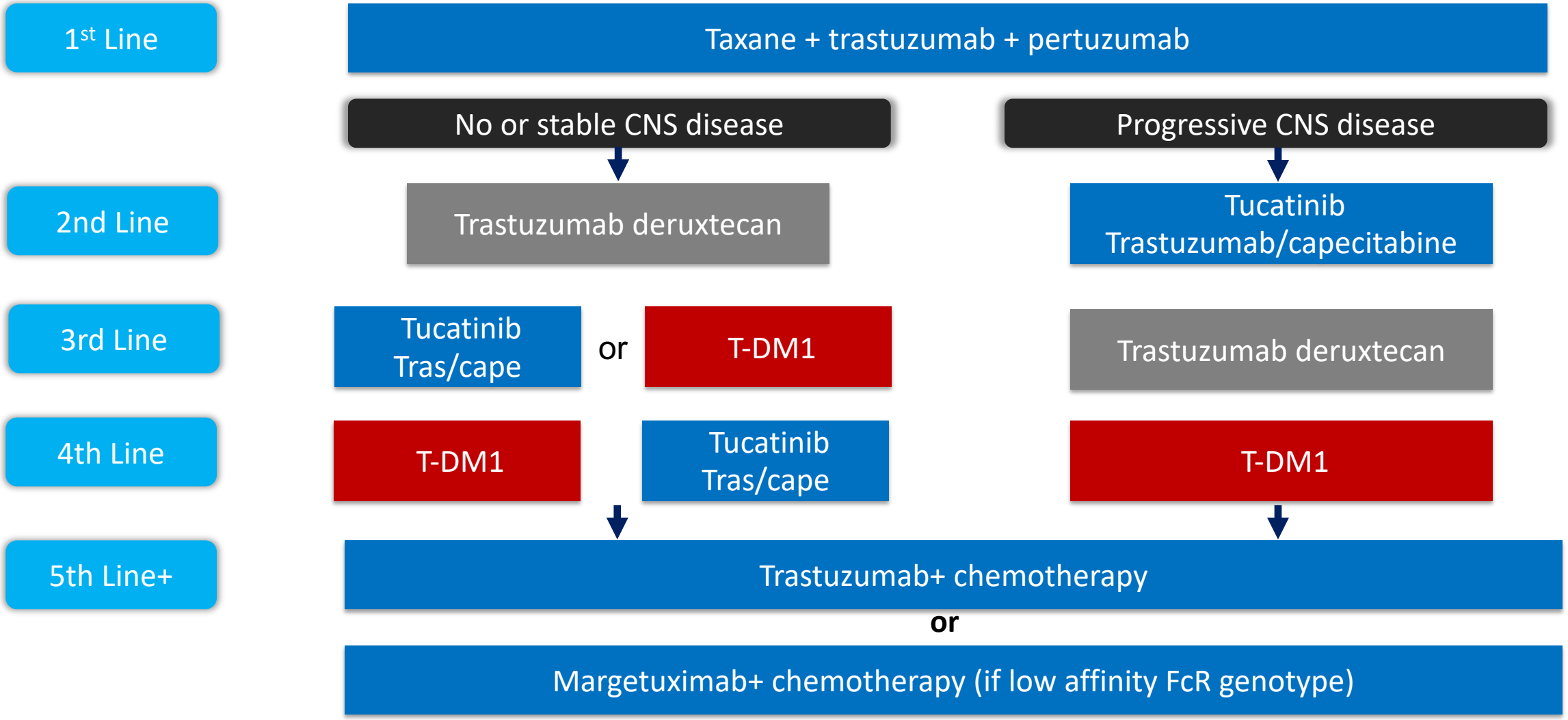
Most frequent grade 3/4 adverse events

	Neratinib + Capecitabine (n=303)		Lapatinib + Capecitabine (n=311)	
	All grade	Grade 3/4	All grade	Grade 3/4
Treatment-emergent AE, %	100	61	99	60
Diarrhea	83	24*	66	13*
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2

Treatment discontinuation due to treatment-emergent AEs: N+C: 10.9%; L+C: 14.5%

*No Grade 4 diarrhea

Approach to Therapy for Metastatic HER2+ disease



Adapted from Modi et al, ESMO 2021

Unanswered questions in HER2+ MBC

- What is the efficacy of T-DM1 after trastuzumab deruxtecan?
- Is there a role for neratinib or pyrotinib?
- What is comparative efficacy of T-DXd vs tucatinib in patients with active brain metastases?

APPENDIX

Total Slides: 27
Data Slides: 26

- Long-term results, including final overall survival data, from the HER2CLIMB study of tucatinib/trastuzumab/capecitabine for patients with HER2-positive mBC
  - Slides 16-20
- Key data, including updated survival results, from the Phase III DESTINY-Breast03 study evaluating trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine for patients with HER2-positive mBC
  - Slides 6-11
- Findings from key studies (eg, DESTINY-Breast01, DESTINY-Breast02) evaluating the use of T-DXd for multiple regimen-relapsed HER2-positive mBC
  - DESTINY-Breast01: Slide 5
  - DESTINY-Breast02: Slides 12-15
- Published data from the pivotal NALA study of neratinib/capecitabine for previously treated HER2-positive mBC
  - Slides 21-25

(Please do not focus extensively on CNS disease, as Dr Hamilton will be covering that topic)