Advances in Treatment of HER2+ BC

WAHO 2023

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Disclosure of Conflicts of Interest

- William Gradishar, MD, FASCO has no relevant financial relationships to disclose.

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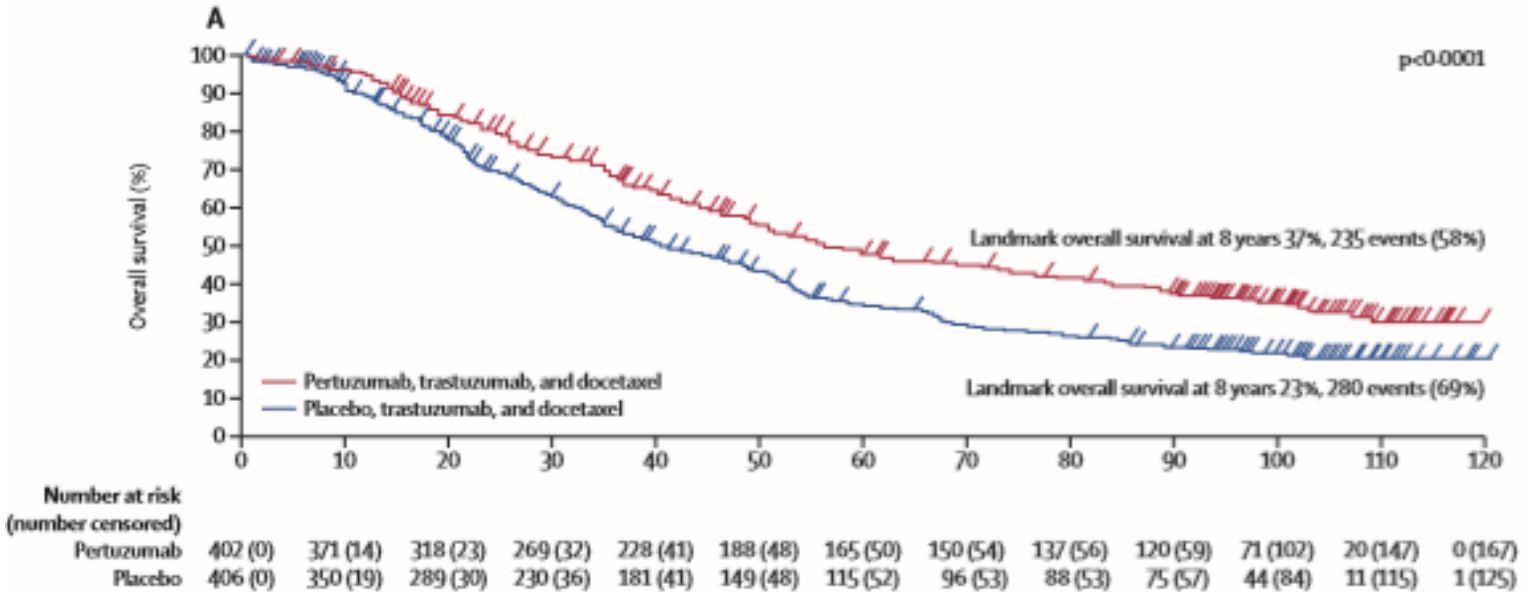
SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[j]

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[k]	Pertuzumab + trastuzumab + docetaxel[m]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[m]	Preferred Regimen	2A
Second line[l]	Fam-trastuzumab deruxtecan-nxki[l,n,o]	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)[l]	Other Recommended Regimen	2A
Third line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine[m,p]	Other Recommended Regimen[p]	1
	Trastuzumab + docetaxel or vinorelbine[m,q]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[m,q]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[m,q]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[m,q] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[m,q,r,s]	Other Recommended Regimen	2A
	Neratinib + capecitabine[q]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[q] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A
Additional targeted therapy options (See BINV-R)			

CLEOPATRA: End-of Study Results

Median follow-up was 99·9 months in the pertuzumab group (IQR 92·9–106·4) and 98·7 months (90·9–105·7) in the placebo group

End-of-Study OS in ITT Population*



*Crossover patients were analyzed in the placebo arm.

	Median OS, Mos (95% CI)
Pertuzumab + Trastuzumab/Doc	57.1
Placebo + Trastuzumab/Doc	40.8

Swain SM et al. *Lancet Oncol* 2020; 21: 519–30.

T-DM1: Standard Second-Line Therapy

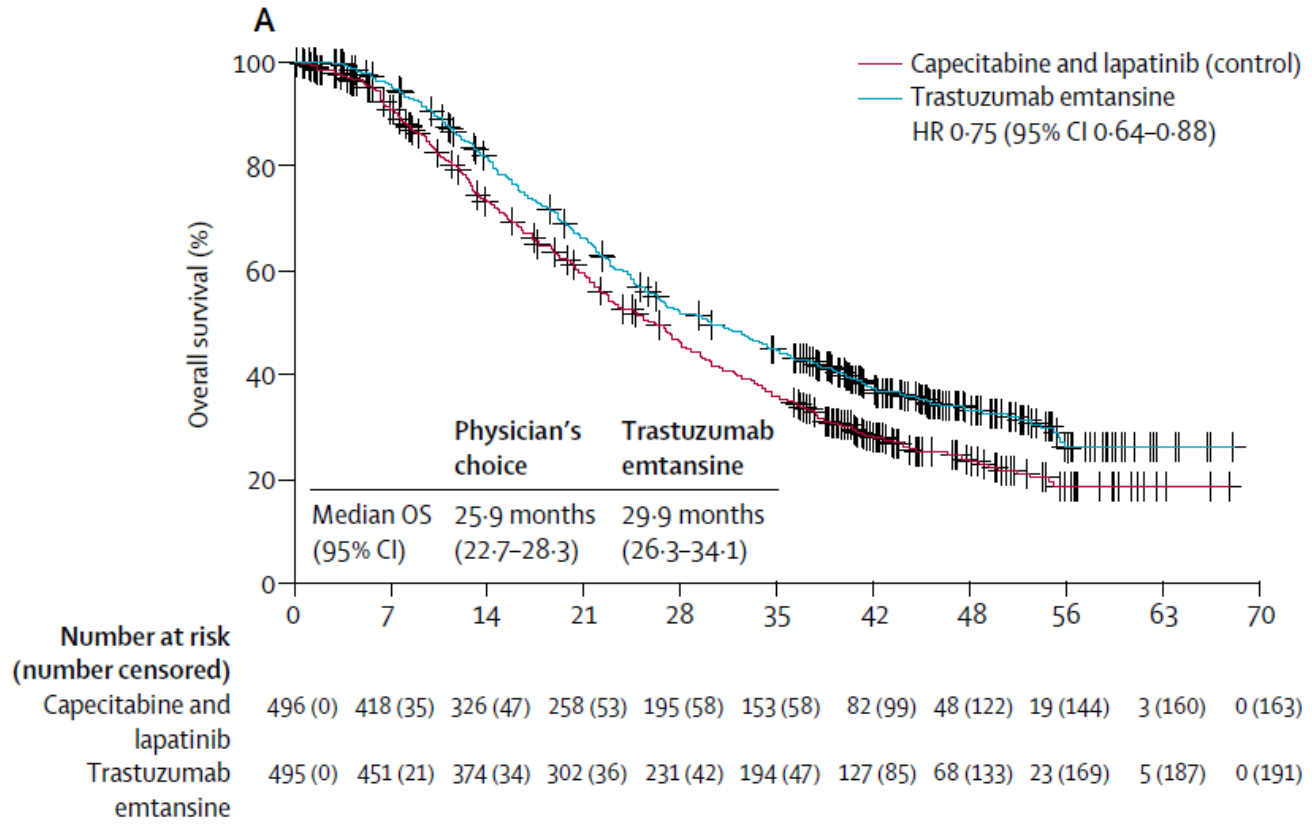
HER2+ (central) LABC or MBC (N = 980)

- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 mo of adjuvant tx

1:1

- **T-DM1**
- **Capecitabine + Lapatinib**

EMILIA

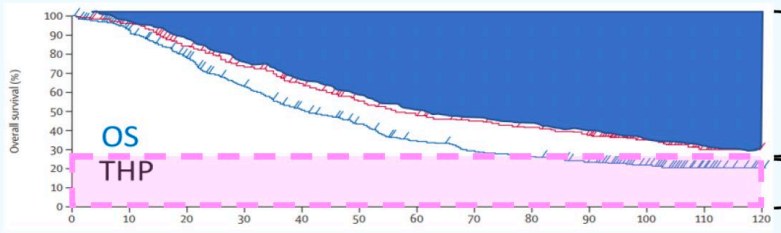


Overall Survival

Dieras V, et al. *Lancet Oncol*. 2017;18:732-742.

Why do we need more anti-HER2 treatment options?

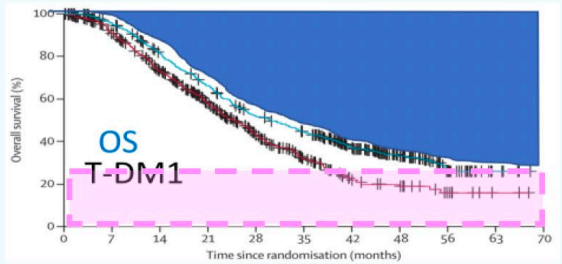
CLEOPATRA [1,2]



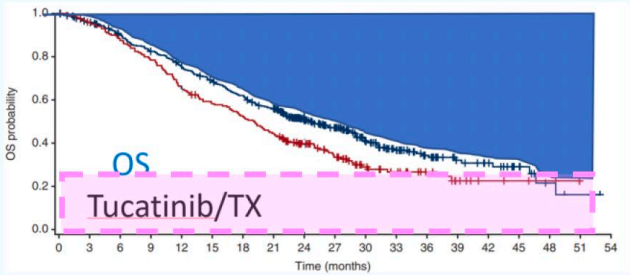
The losses we want to prevent

The plateau we want to expand and consolidate

EMILIA [3,4]



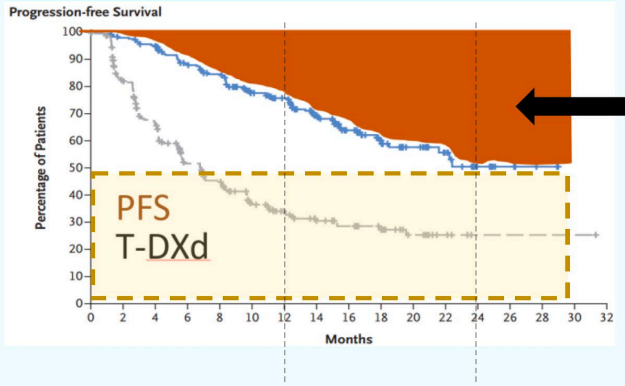
HER2Climb [5,6]



Adapted from: 1. Swain SM, et al. Lancet Oncol 2020; 2. Swain SM, et al. N Engl J Med 2015; 3. Dieras V, et al. Lancet Oncol 2017; 4. Verma S, et al. N Engl J Med 2012; 5. Murthy R, et al. N Engl J Med 2020; 6. Curigliano G, et al. Ann Oncol 2022

Why do we need more anti-HER2 treatment options?

DestinyBREAST-03 [1]



Estimate post-T-DXd treatment will be needed when T-DXd is used in second line:

- In 25% of patients after 1yr
- In 50% of patients after 2yr

1. Adapted from Cortes J, et al N Engl J Med 2022

Destiny-Breast 03 Study

Clinical Trial Design (Phase III- Destiny-Breast03)

Patients

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

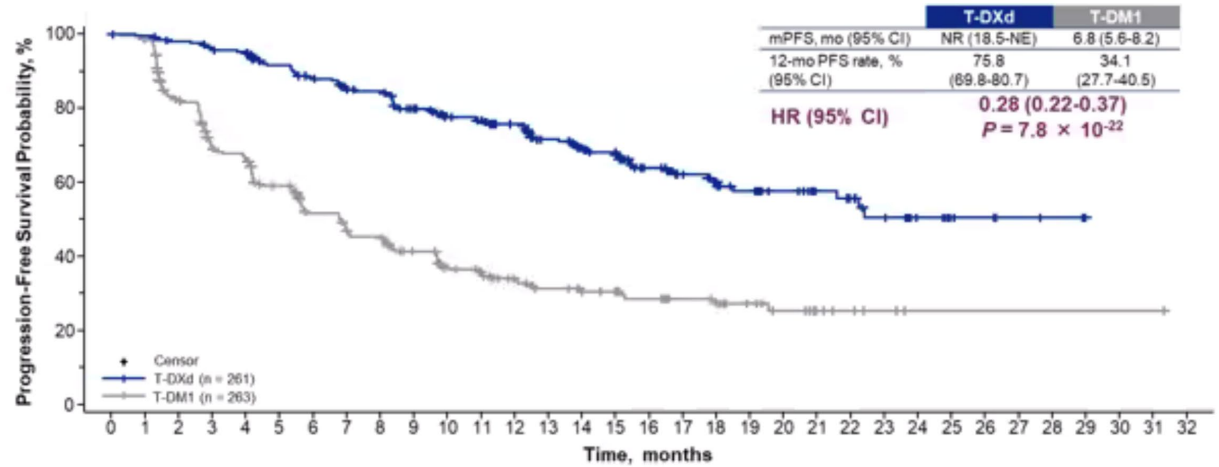
Stratification factors

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

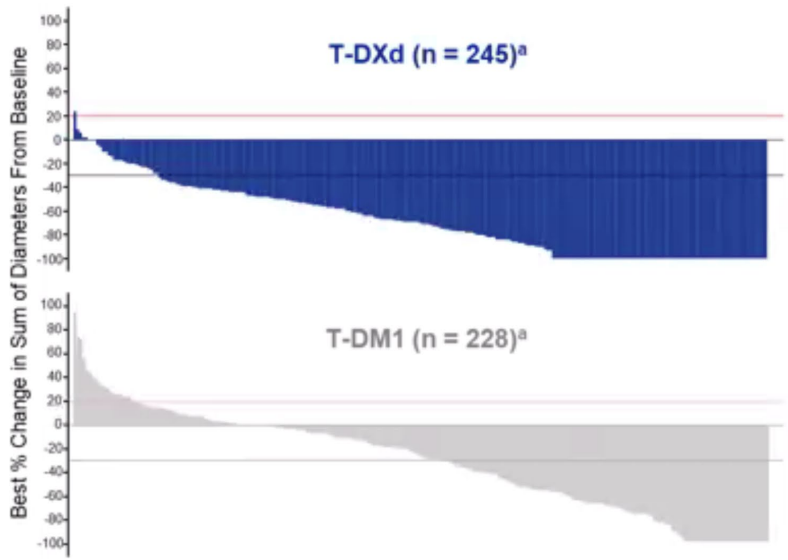
R 1:1

- T-DXd 5.4 mg/kg Q3W (n = 261)
- T-DM1 3.6 mg/kg Q3W (n = 263)

PFS

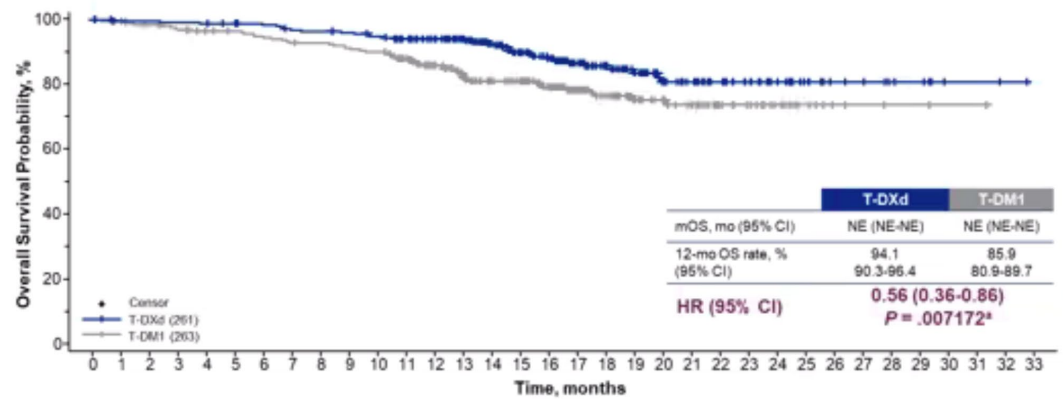


ORR



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b] [95% CI]	208 **(79.7)** [74.3-84.4]	90 **(34.2)** [28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

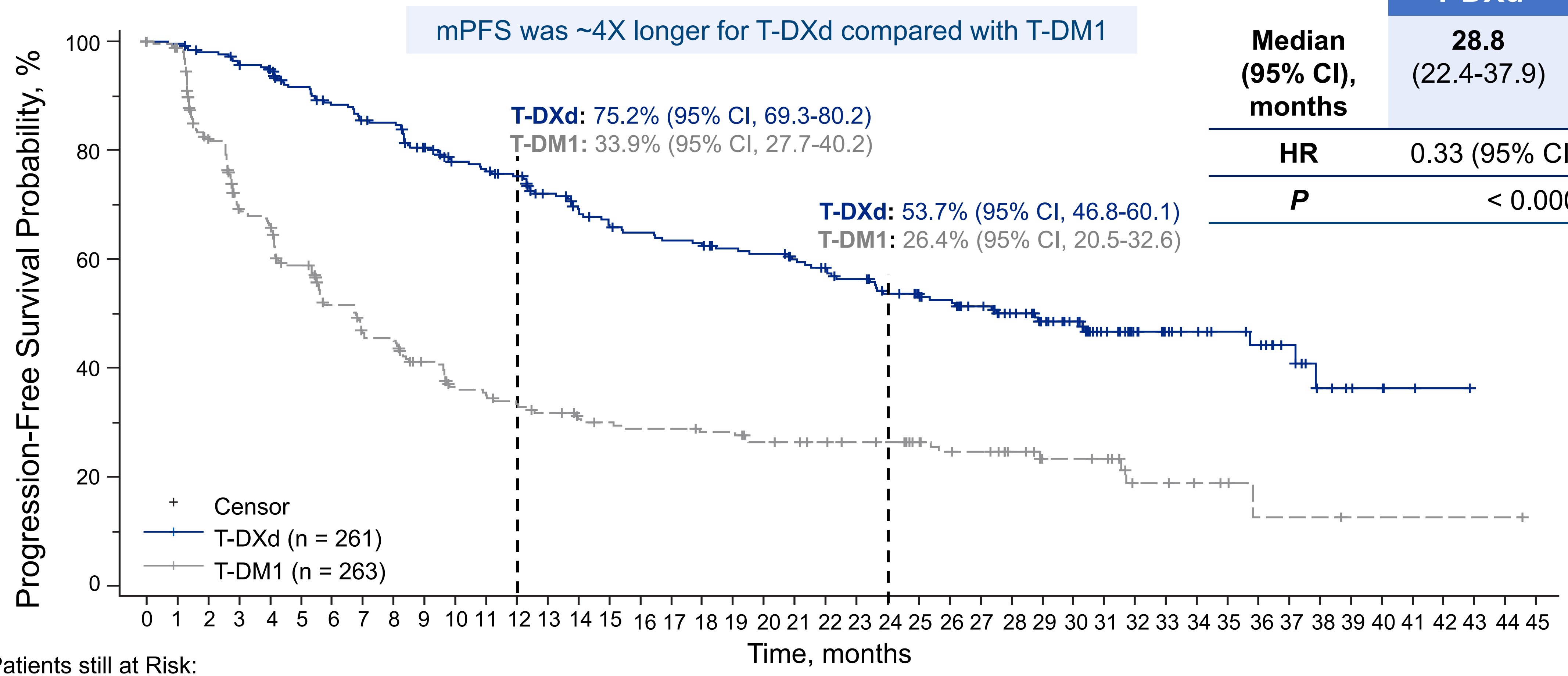
OS



Cortes J, et al. ESMO 2021

Updated Primary Endpoint: PFS by BICR

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



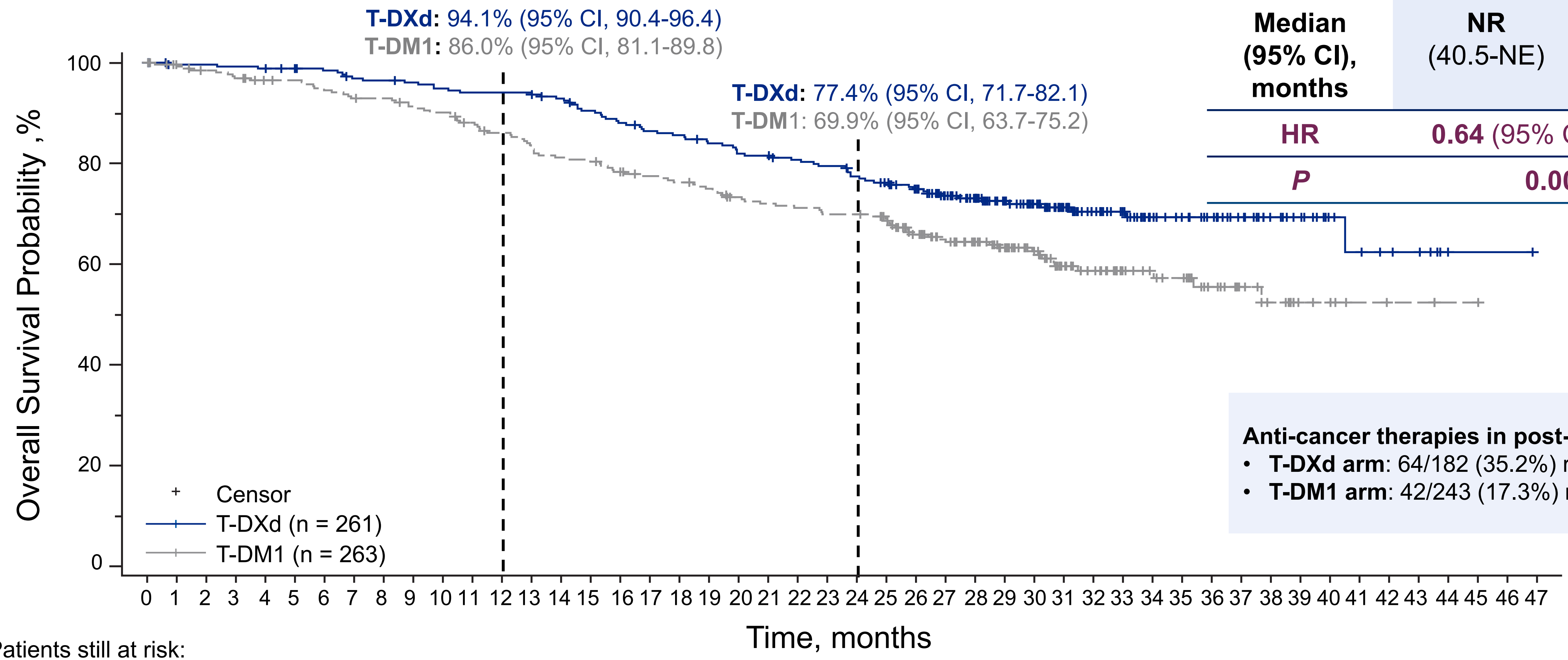
Patients still at Risk:

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

Hurvitz S, GS2-02, SABCS 2022

Key Secondary Endpoint: Overall Survival

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



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:

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

Hurvitz S, GS2-02, SABCS 2022

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

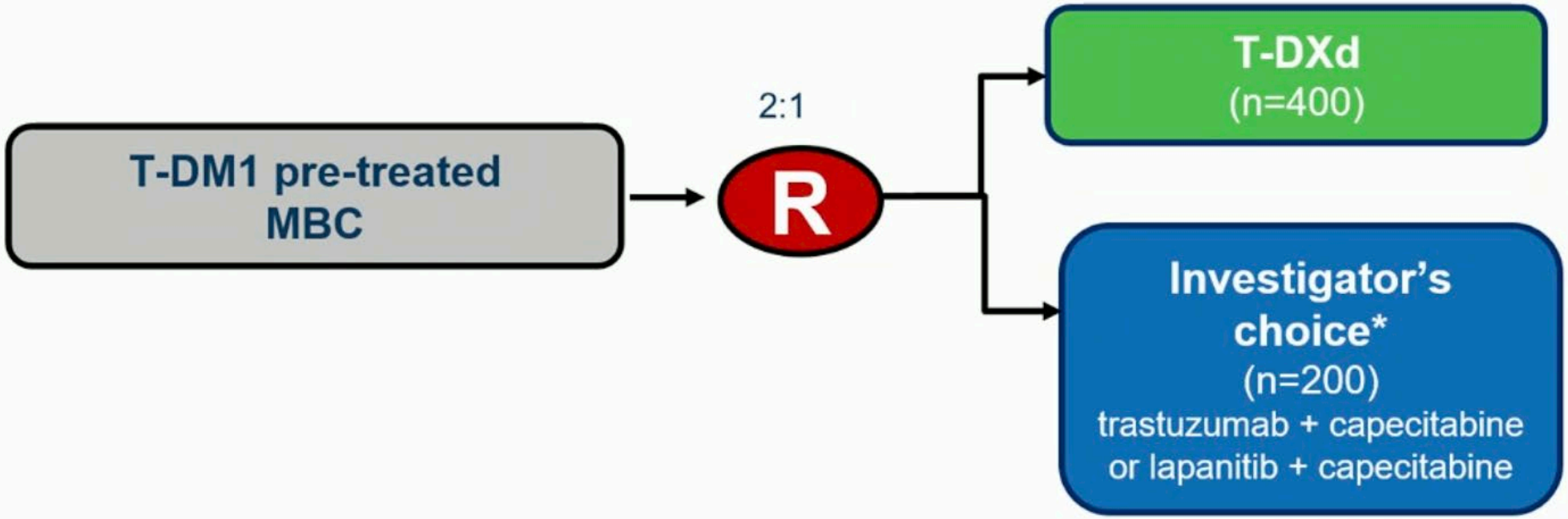
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- 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

Hurvitz S, GS2-02, SABCS 2022

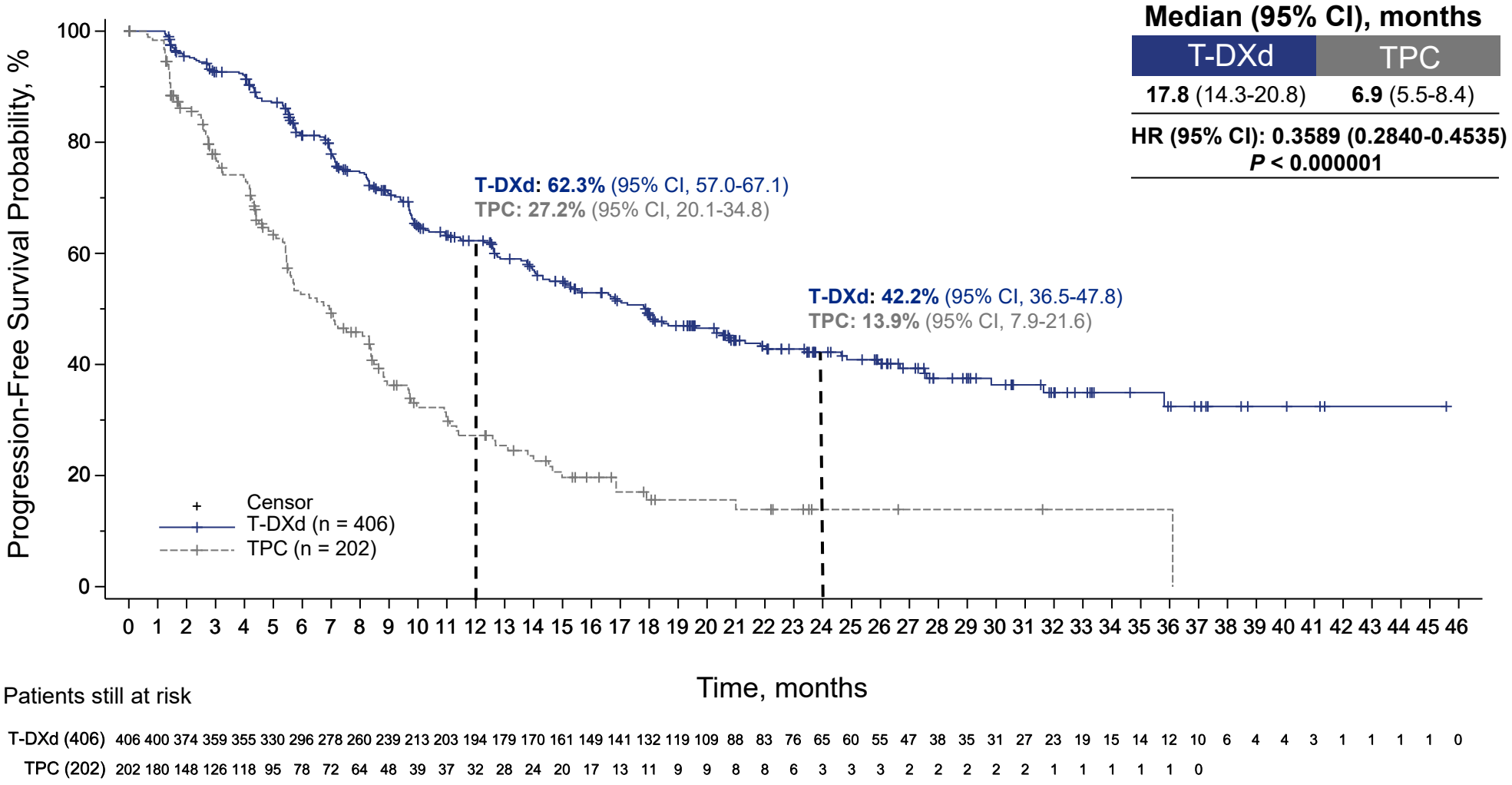
1. Modi S et al. *N Engl J Med* 2020; 382(7): 610-21. 2. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

DESTINY-Breast02 Trial for HER2+ MBC



Positive Trial for Dual Primary Endpoints of PFS and OS!

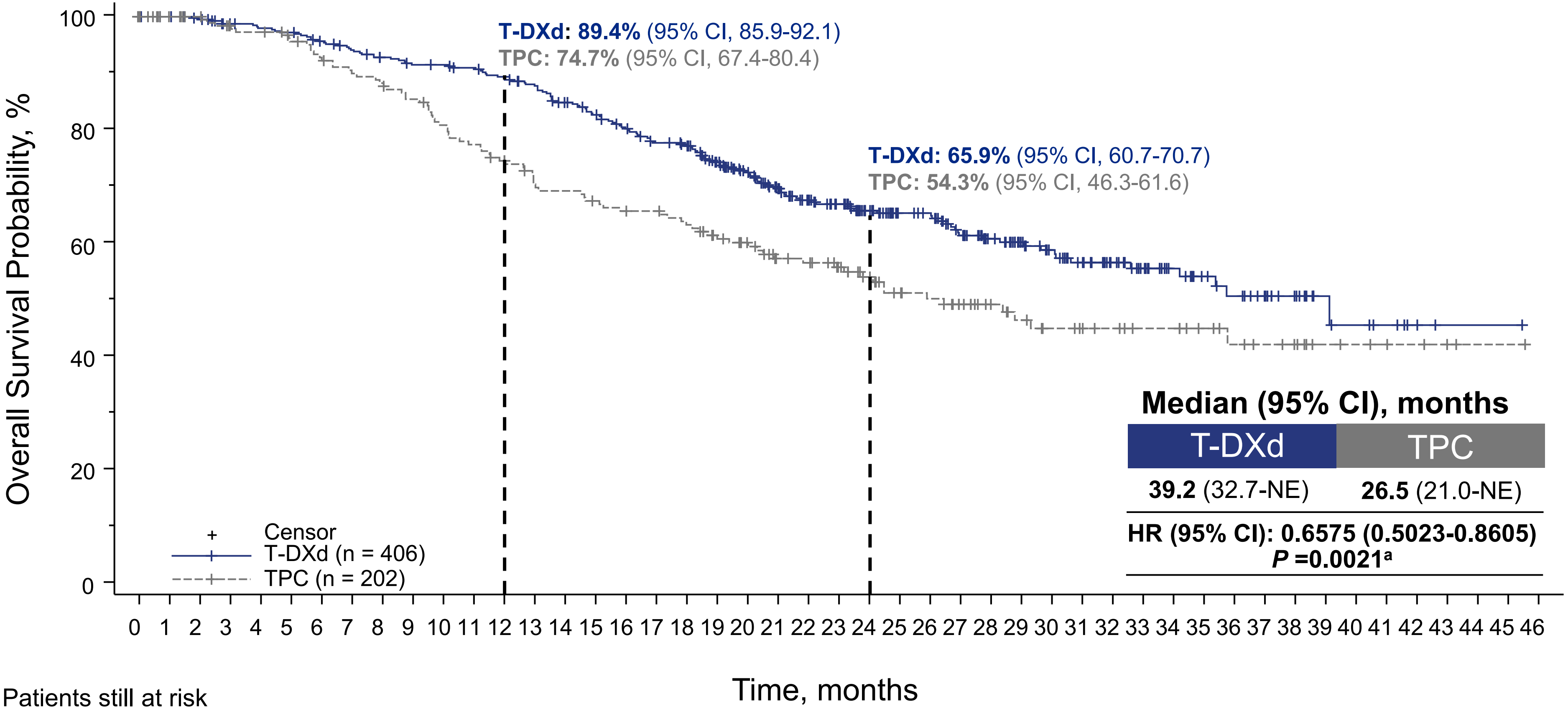
Primary Endpoint: PFS by BICR



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

Krop I, SABCS 2022. GS2-01

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

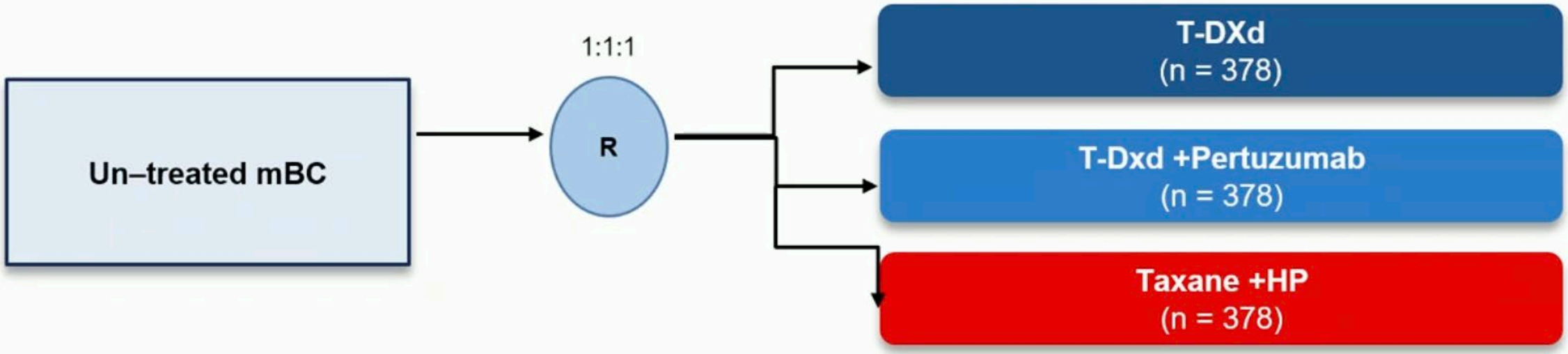
In the TPC arm

- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **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.

Krop I, SABCS 2022. GS2-01

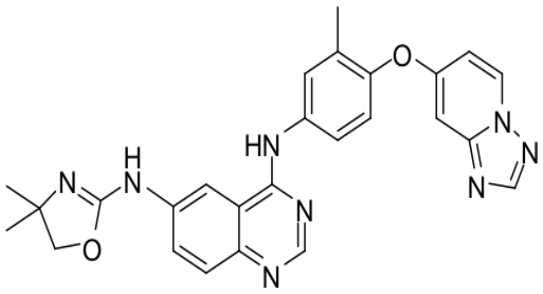
DESTINY Breast-09 Trial : 1st Line HER2+ MBC



Primary endpoint: PFS

HER2CLIMB Pivotal Trial Design: Capecitabine/Trastuzumab +/- Tucatinib

Tucatinib



Compound	Cellular Selectivity Data	
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)
tucatinib	8	>10,000
neratinib	7	8
lapatinib	49	31

Patient Population

- Metastatic HER2+ breast cancer with progression after pertuzumab, trastuzumab, and T-DM1
- Patients with and without brain metastases

2:1
n=480

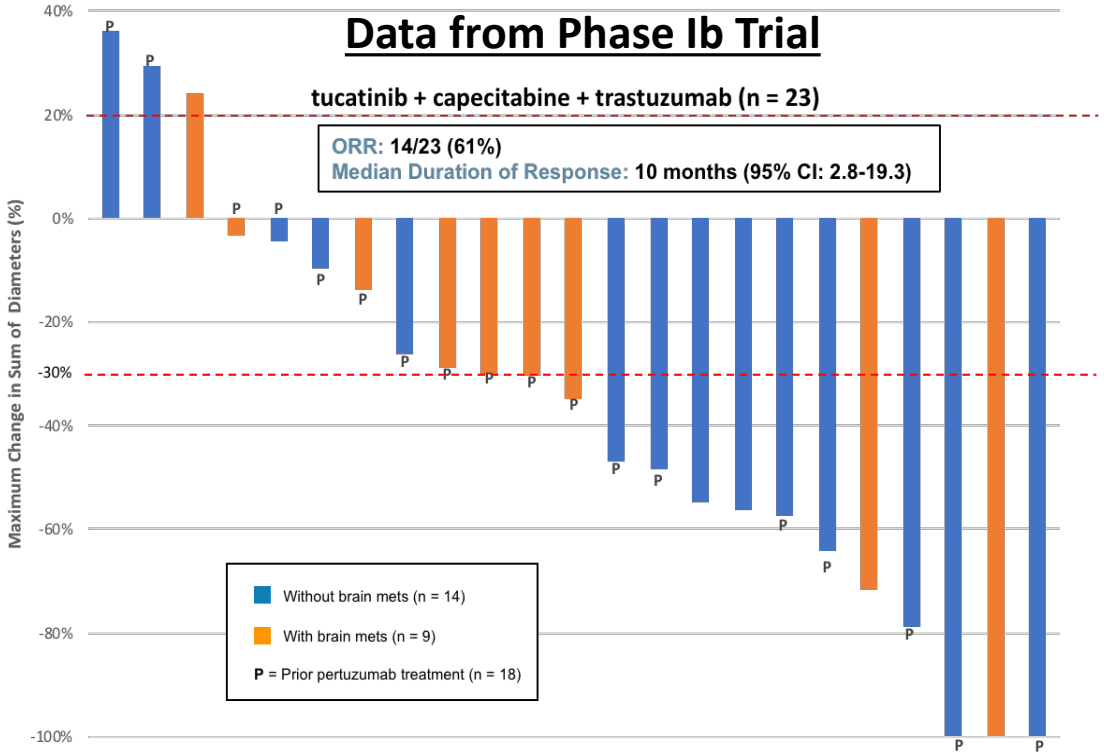
- **capecitabine + trastuzumab + tucatinib**
- **capecitabine + trastuzumab + placebo**

Primary endpoint:
- PFS in all pts

Secondary endpoints:
- PFS in pts w/ brain metastases
- OS in all pts

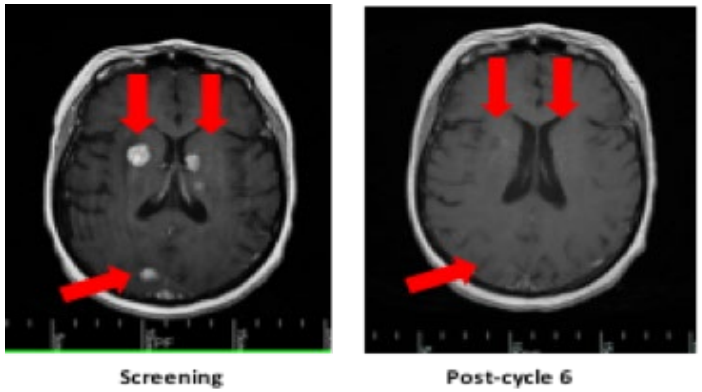
Sample size ↑'ed to N = 612 [NCT02614794]

Data from Phase Ib Trial



Note: Bars represent change in measurable lesions but some patients also have nonmeasurable lesions. In addition, 4 patients in the Triplet cohort had nonmeasurable lesions only and are therefore not able to be represented on the waterfall.

*CNS metastases = 48%
Untreated 22% and
Treated, progressing 18%



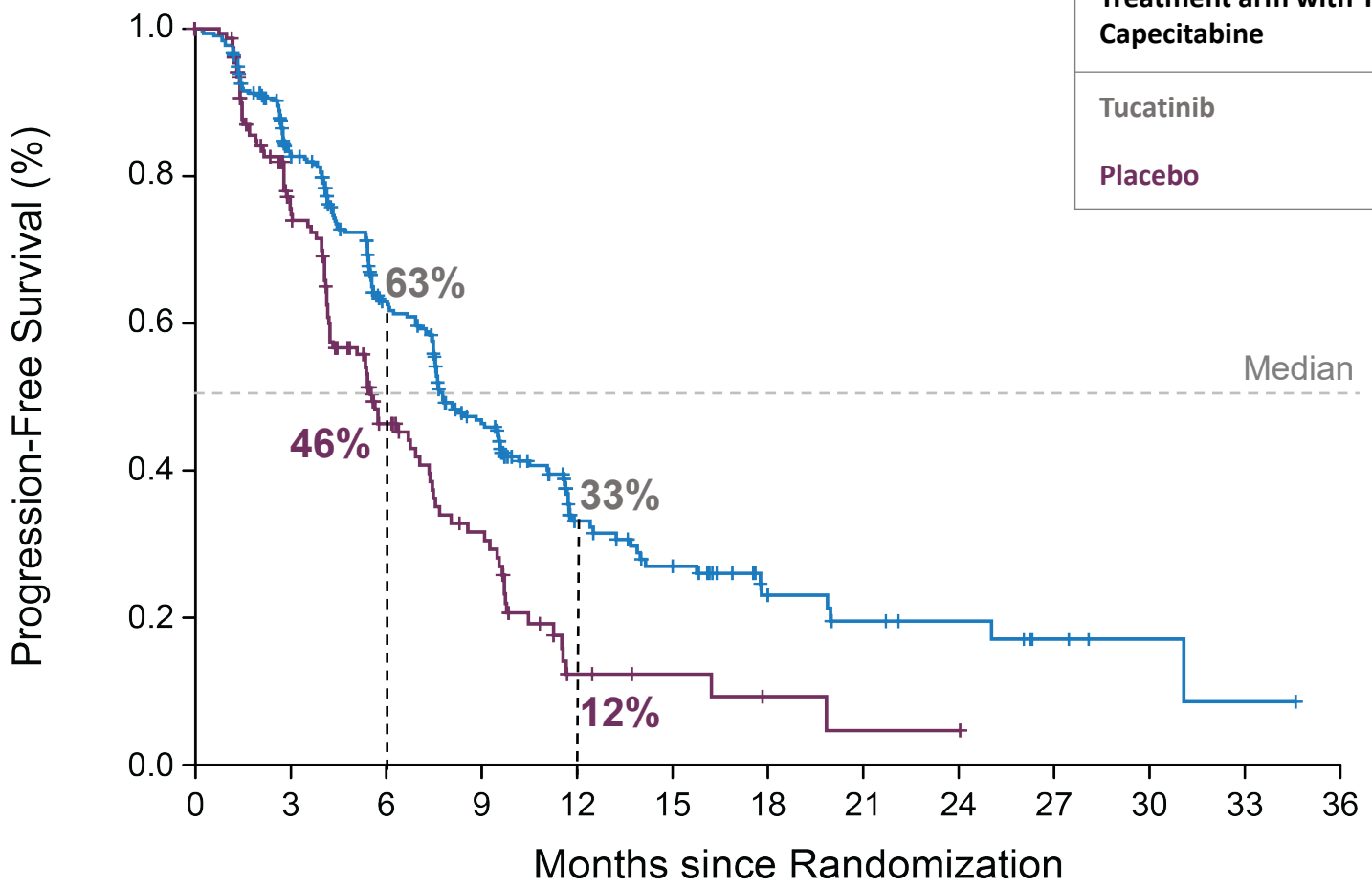
Screening Post-cycle 6

(Images selected to demonstrate longest axis of lesions)

Murthy R, et al. Lancet Oncology 2018

Progression-Free Survival with Tucatinib Added to Capecitabine and Trastuzumab in HER2+ MBC (Including with Brain Metastases): HER2CLIMB Study Results

Treatment arm with Trastuzumab + Capecitabine	Events, N=480	HR (95% CI)	P Value
Tucatinib	178/320	0.54 (0.42, 0.71)	<0.00001
Placebo	97/160		



No. at Risk												
TUC+Tras+Cape 320	235	152	98	40	29	15	10	8	4	2	1	0
Pbo+Tras+Cape 160	94	45	27	6	4	2	1	1	0	0	0	0

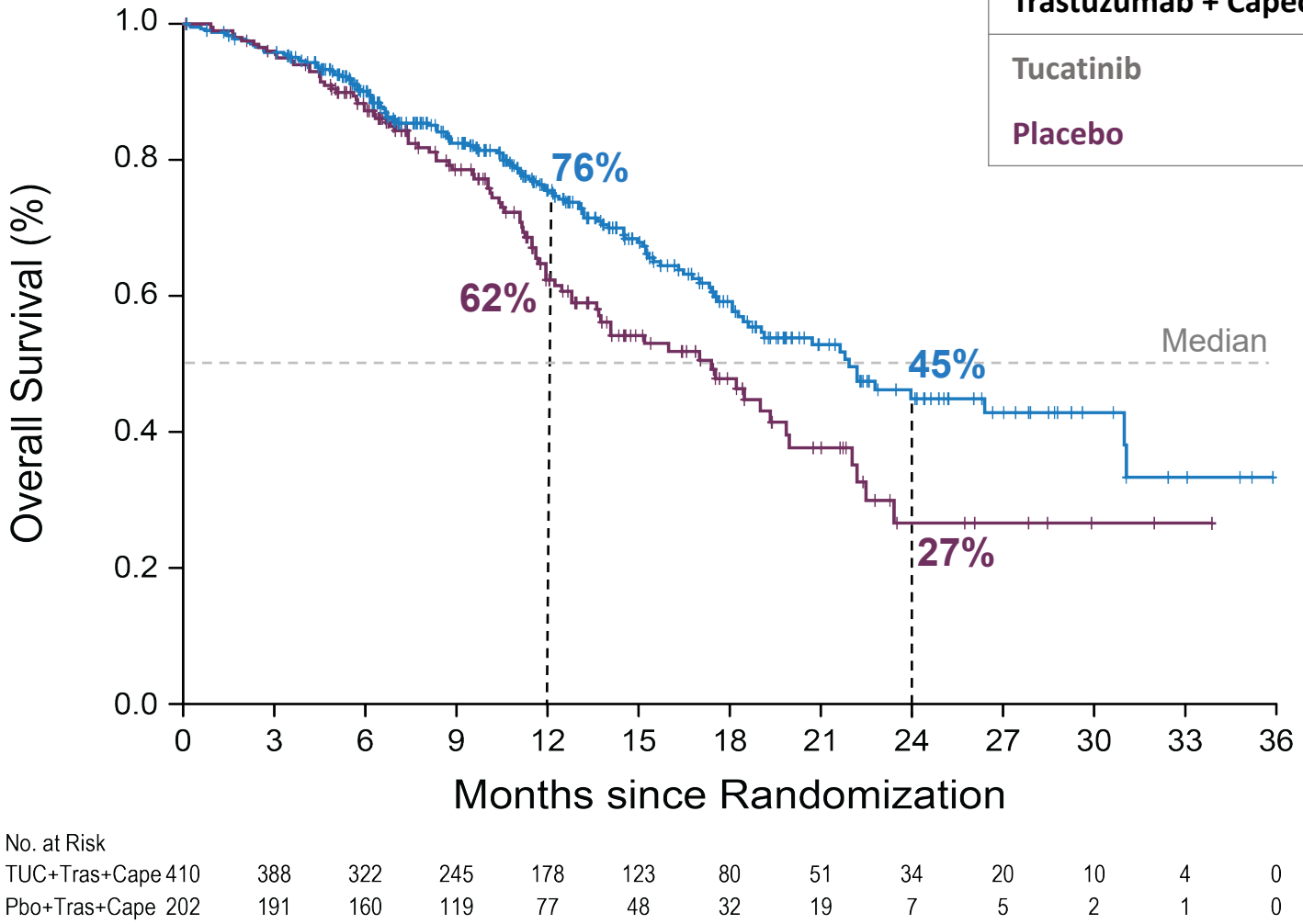
Risk of progression or death was reduced by 46% in the primary endpoint population

One-year PFS (95% CI):	
Tucatinib	**Placebo**
33%	**12%**
(27, 40)	**(6, 21)**
Median PFS (95% CI):	
7.8 months	**5.6 months**
(7.5, 9.6)	**(4.2, 7.1)**

Prespecified efficacy boundary for PFS: P=0.05
Data cut off: Sep 4, 2019

Murthy R, et al. NEJM 2019

Overall Survival with Tucatinib Added to Capecitabine and Trastuzumab in HER2+ MBC (Including with Brain Metastases): HER2CLIMB Study Results



Treatment arm with Trastuzumab + Capecitabine	Events N=612	HR (95% CI)	P Value
Tucatinib	130/410	0.66 (0.50, 0.88)	0.00480
Placebo	85/202		

Risk of death was reduced by 34% in the total population

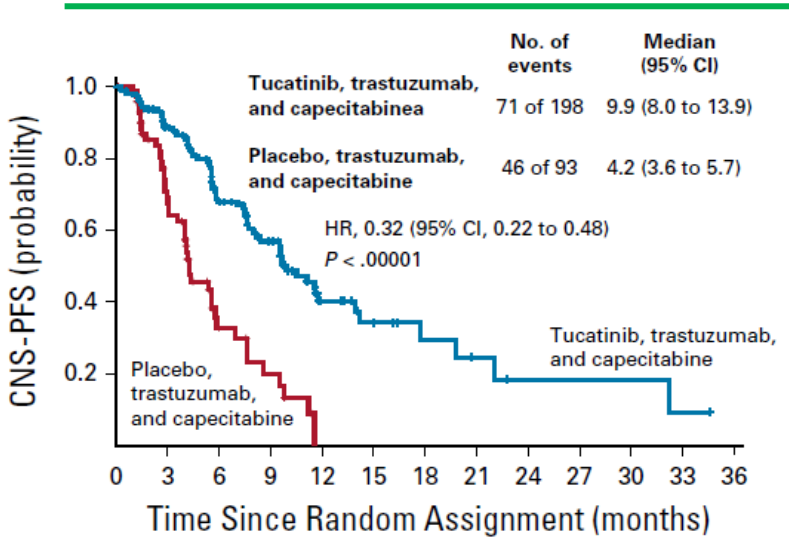
Two-year OS (95% CI):	
Capecitabine 45% (37, 53)	Placebo 27% (16, 39)
Median OS (95% CI):	
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

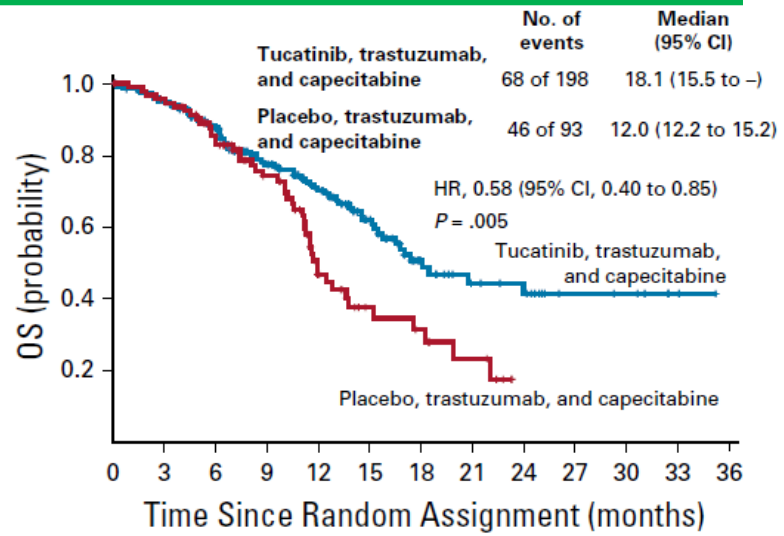
Prespecified efficacy boundary for OS (P=0.0074) was met at the first interim analysis.
Data cut off: Sep 4, 2019

Murthy R, et al. NEJM 2019

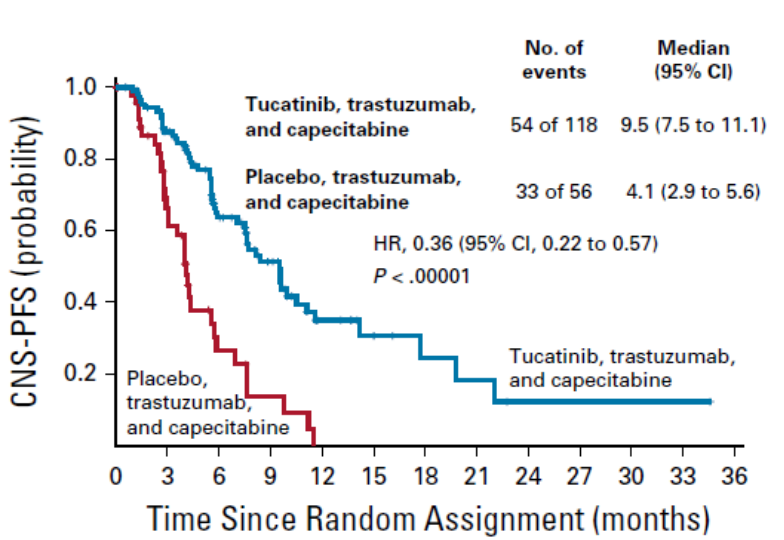
Intracranial CNS-Specific Outcomes: HER2CLIMB Study Results

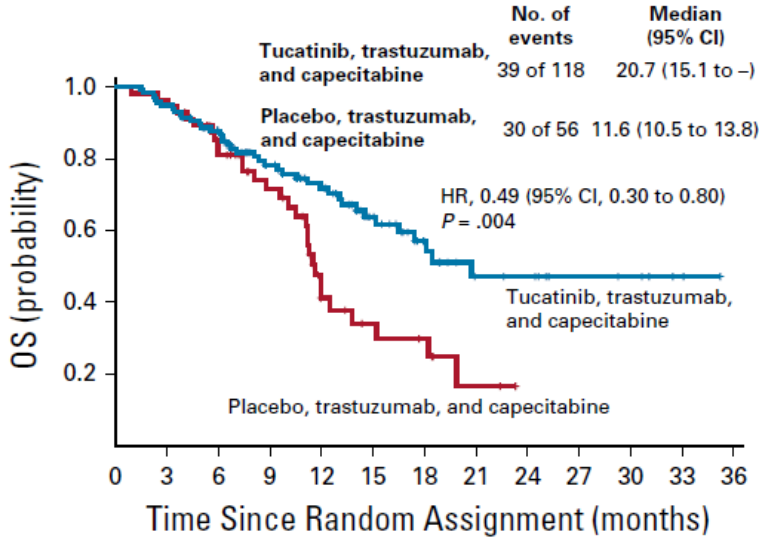
Patient with Brain Metastases (active or treated/stable)





Patient with Brain Metastases (active)





Intra-Cranial CNS Response (RECIST) N=75	Tucatinib N=55 N (%)	Placebo N=20 N (%)
CR	3 (5.5)	1 (5.0)
PR	23 (41.8)	3 (15.0)
SD	24 (43.6)	16 (80.0)
PD	2 (3.6)	0
Not Available	3 (5.5)	0
Confirmed ORR	26 (47.3)	4 (20.0)
95% CI	33.7-61.2%	5.7-43.7%
Stratified p-value	0.03	
DOR (months)	6.8	3.0

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; ORR=objective response rate (CR+PR); DOR=duration of intracranial response

Lin NU, et al. JCO 2020

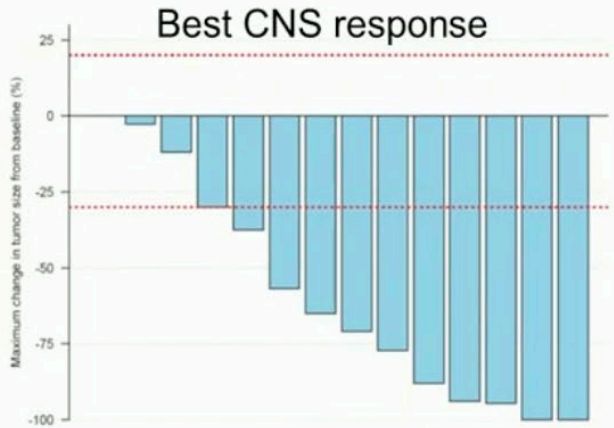
T-DXd in Breast cancer brain metastases

Table 1. Studies on T-DXd in brain metastases from advanced HER2-positive breast cancer.

Study	Type of study	Number of patients with BM	Intracranial response	Intracranial PFS
DESTINY-Breast 01 NCT03248492 (10)	Single-arm phase II	24 with asymptomatic BM	ORR: 58.3% CR: 4.2% PR: 54.2% SD: 33.3%	Median: 18.1 months
DESTINY-Breast 03 NCT03529110 (11)	Phase III randomized (T-DXd vs. T-DM1)	62 (T-DXd arm) and 52 (T-DM1) stable BM	T-DXd arm: • ORR: 63.9% • CR: 27.8% • PR: 36.1% T-DM1 arm: • ORR: 33.4% • CR: 2.8% • PR: 30.6%	T-DXd arm: median: 15.0 months T-DM1 arm: median: 5.7 months
TUXEDO-1 NCT04752059 (12)	Single-arm phase II	15: • 6 stable/untreated BM • 9 active/progressing BM after local therapy	ORR: 73.3% CR: 13.3% PR: 60.0% SD: 33.3% Per protocol population: ORR 78.6%	Median: 14.0 months
DEBBRAH NCT04420598 (13)	Single-arm phase II	21: • Cohort 1: 8 HER2 stable BM after surgery and/or RT • Cohort 2: 4 $HER2^{+}$ asymptomatic untreated BM • Cohort 3: 9 $HER2^{+}$ progressing BM after surgery and/or RT	Cohort 2: • ORR: 50.0% Cohort 3: • ORR: 44%	At 6 months: 78.7%
Kabraji et al. (1)	Retrospective	15 asymptomatic or active/progressing BM	ORR: 73.0% PR: 73.3% SD: 13.3%	Median: 7.0 to not reached 12 months: 74.7%

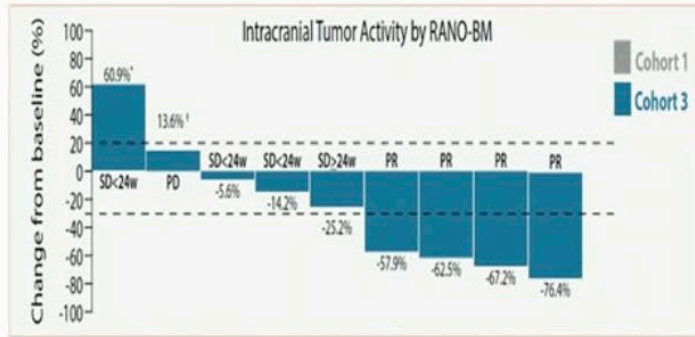
Modi S NEJM 2022; Cortes J NEJM 2022; Bartsch R Nature Med 2022; Perez-Garcia JM Neuro Oncol 2022; Kabraji S Clin Cancer Res 1;2023;

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



TUXEDO-1 trial
Bartsch et al, ESMO Breast 2022

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



DEBBRAH trial
Vaz Batista et al, SABCS 2021

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

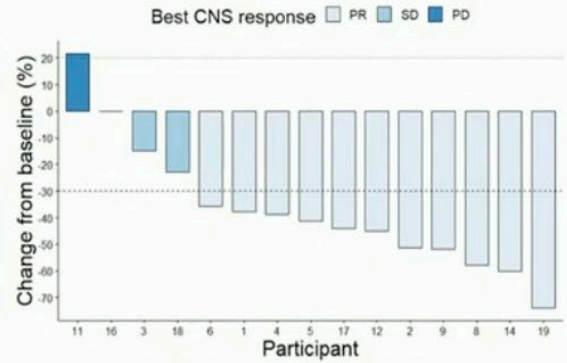


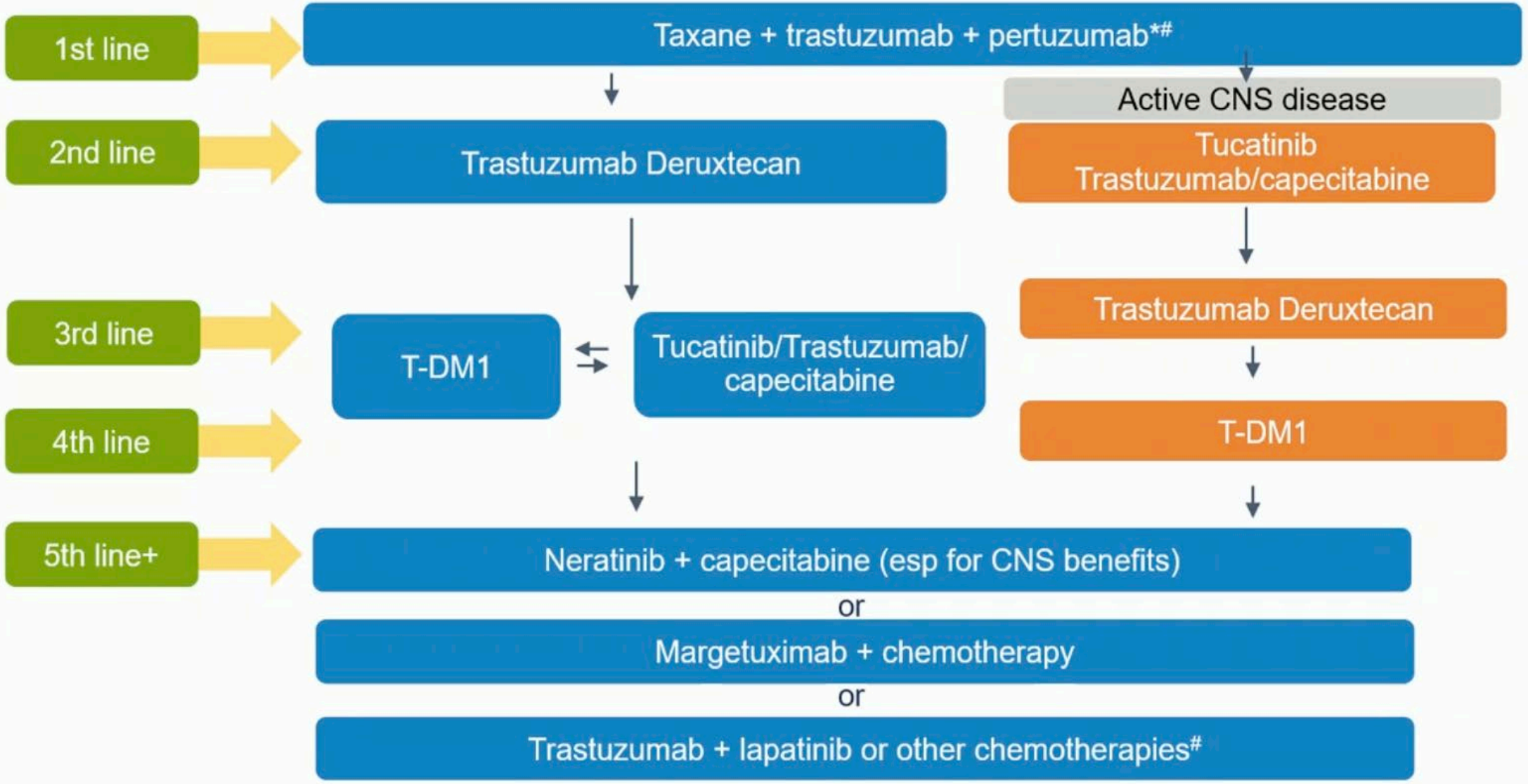
Figure 5 : Best CNS response to T-DXd. Waterfall plot of best CNS response in participants with measurable disease (n = 15). PR = partial response

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

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

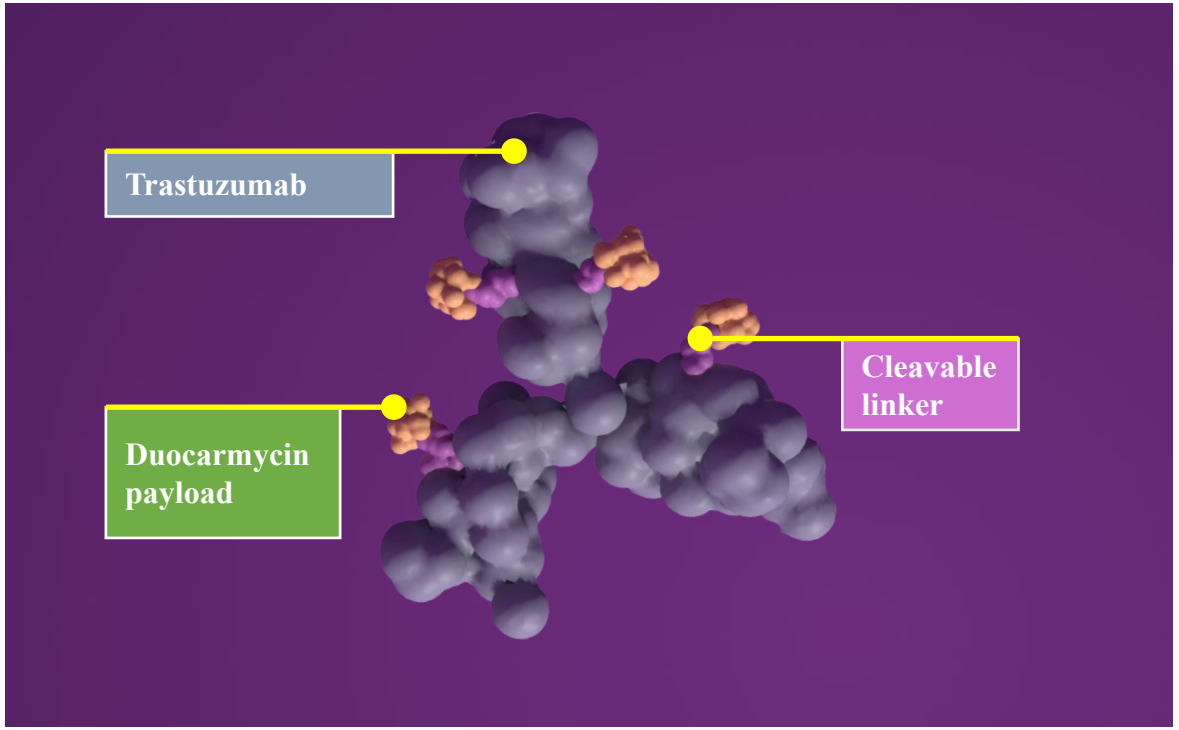
Lin N , ASCO 2022

2023 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

Trastuzumab Duocarmazine (SYD985)[1,2]

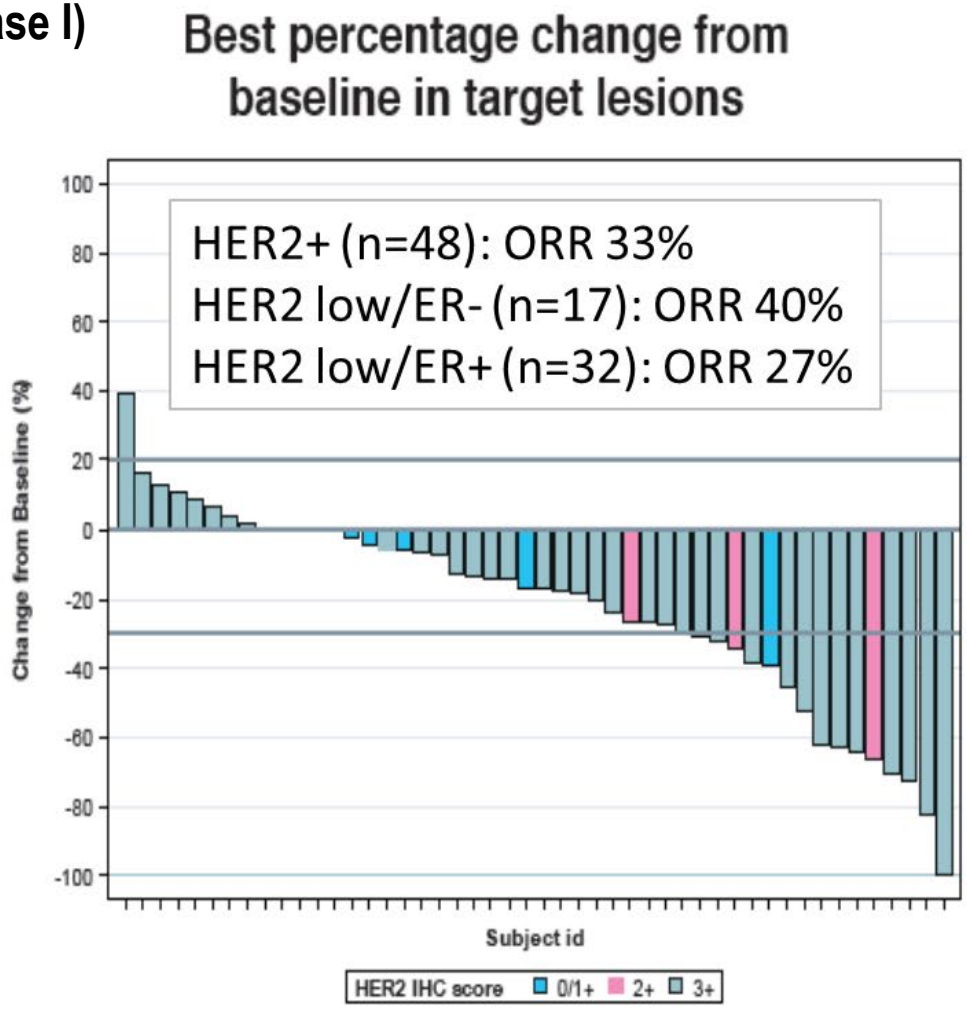


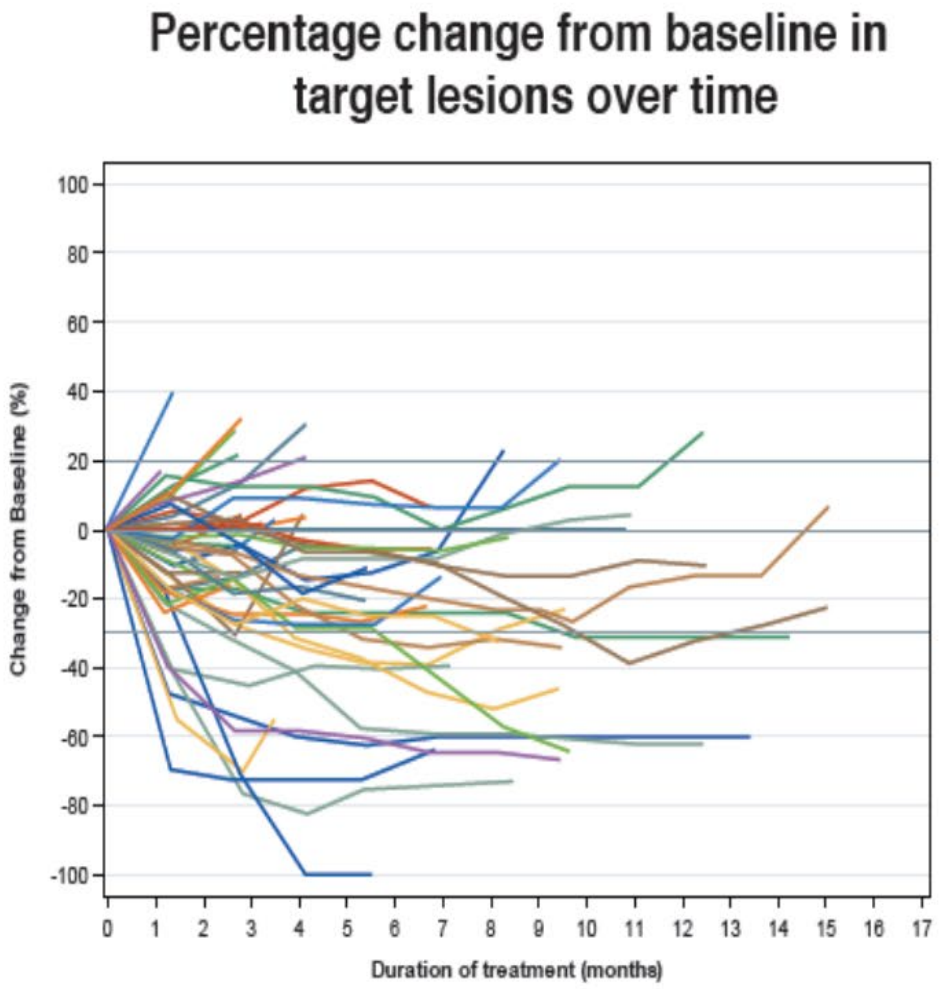
- HER2-targeting ADC[1]
- Duocarmycins are DNA-alkylating agents composed of a DNA-alkylating and a DNA-binding moiety[2]

1. Banerji U et al. *Lancet Oncol*. 2019;20(8):1124-1135; 2. Rinnerthaler G et al. *Int J Mol Sci*. 2019;20(5):1115.

Trastuzumab-Duocarmazine
SYD-985

Clinical Trial Design
(Phase I)





Saura C, et al. ASCO 2018

New Antibody-Drug Conjugates Trastuzumab-Duocarmazine

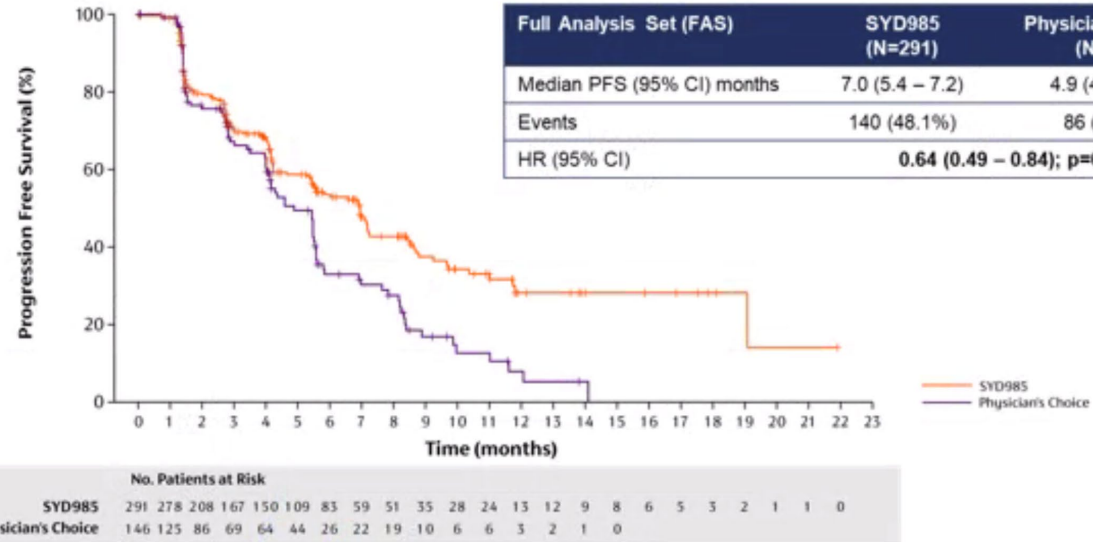
Clinical Trial Design (TULIP)

Patients with HER2+, unresectable, locally advanced and/or metastatic BC; progression on or after ≥ 2 HER2-targeted regimens or after T-DM1; ECOG PS 0-2 (Planned N = 345)

- Trastuzumab Duocarmazine Q3W (planned n = 230)
- Physician's Choice: Lapatinib/Capecitabine, Trastuzumab/Capecitabine, Trastuzumab/Vinorelbine, Trastuzumab/Eribulin (planned n = 115)

PFS

Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	0.64 (0.49 – 0.84); p=0.002	



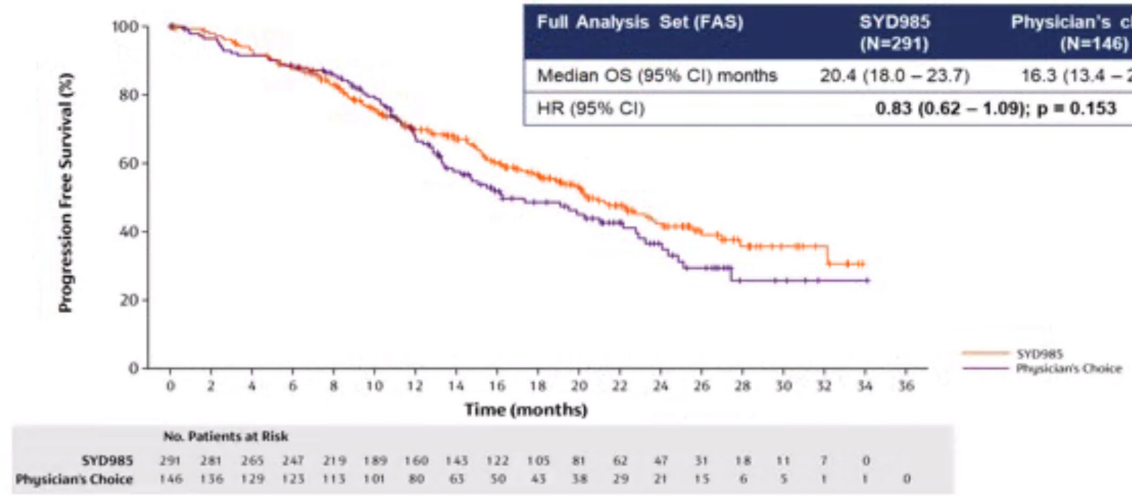
ORR

Number of patients with	SYD985 (N=291)	Physician's choice (N=146)
Measurable disease at baseline	252 (86.6%)	122 (83.6%)
Overall Response Rate# (PR or CR)	70 (27.8%)	36 (29.5%)
Reduction Target lesion measurement#	177 (70.2%)	71 (58.2%)
Clinical Benefit Rate	112 (38.5%)	47 (32.2%)

#pts with measurable disease used as denominator

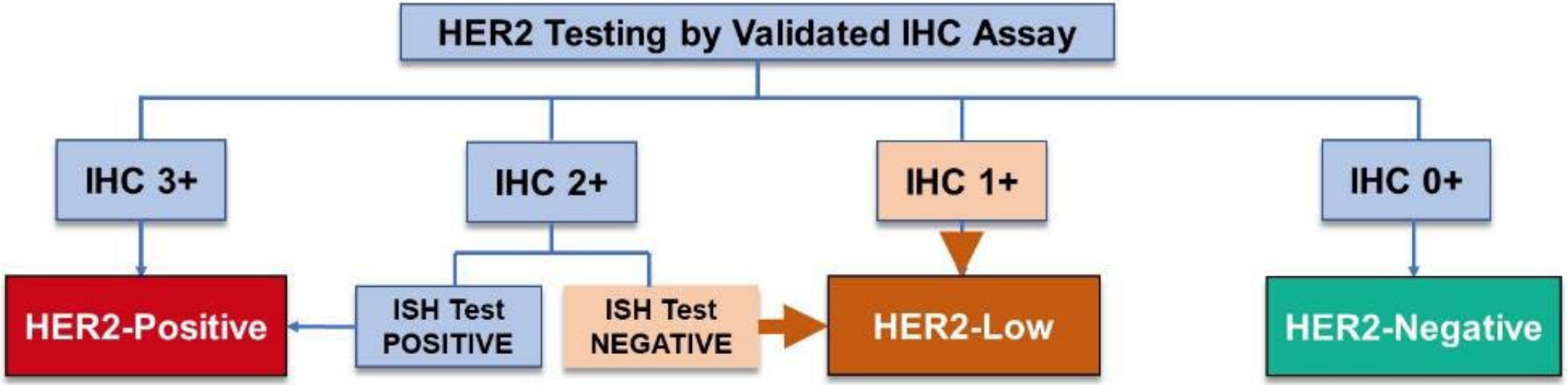
OS

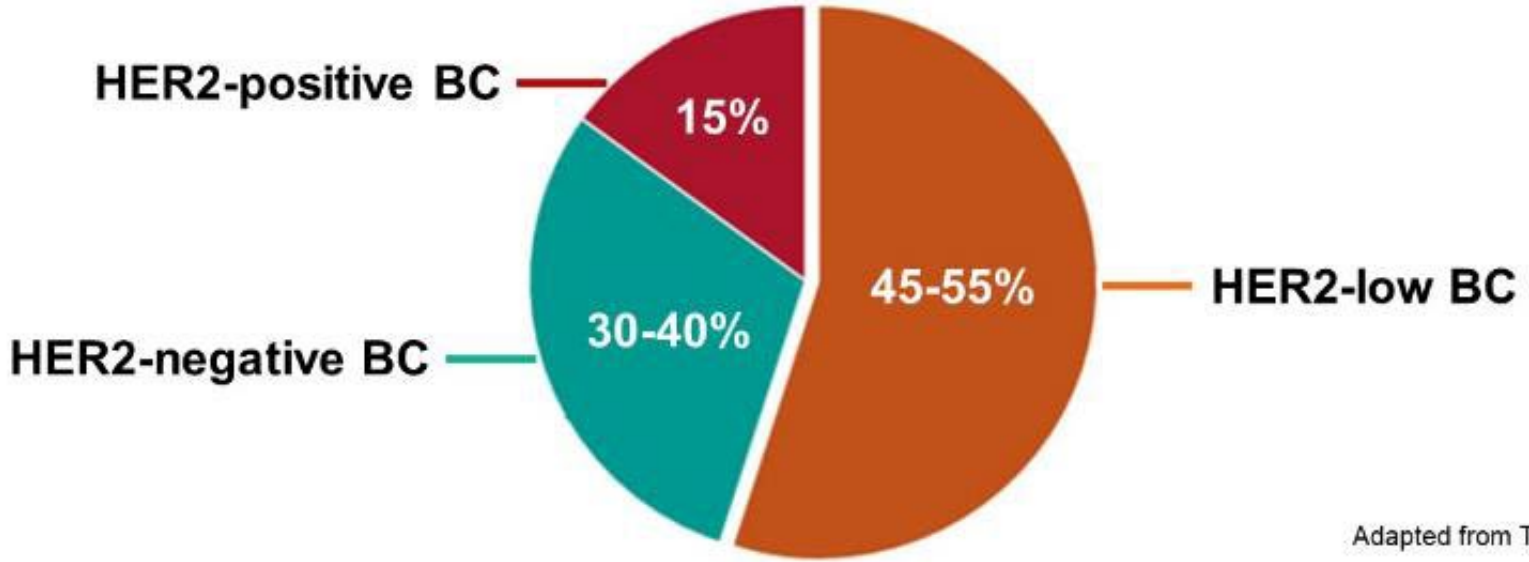
Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median OS (95% CI) months	20.4 (18.0 – 23.7)	16.3 (13.4 – 22.8)
HR (95% CI)	0.83 (0.62 – 1.09); p = 0.153	



Saura C, et al. ESMO 2021

Proposal of an algorithm for defining HER2-low BC





Adapted from Tarantino et al. J Clin Oncol. 2020 38(17)

Role for HER2-directed agents in HER2-low breast cancer? NSABP B-47

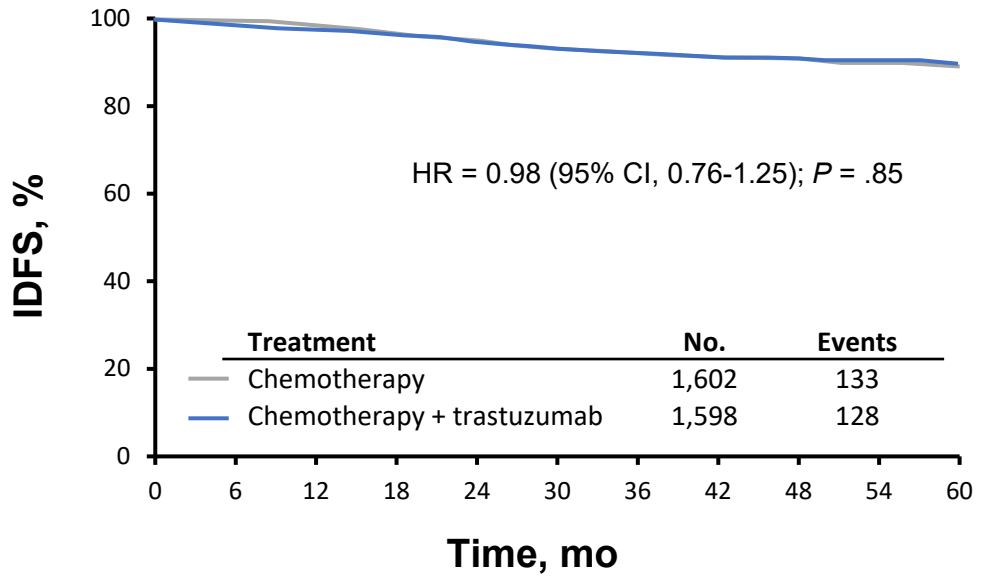
A phase 3 trial was conducted to understand if adjuvant trastuzumab was beneficial for HER2-low patients

- Node-positive or high-risk node-negative breast cancer
- IHC 1+, 2+ and FISH negative

R

Docetaxel/cyclophosphamide
or
AC → weekly paclitaxel (WP)

TC + trastuzumab → trastuzumab x 1 y
or
AC → **weekly paclitaxel + trastuzumab → trastuzumab x 1 y**



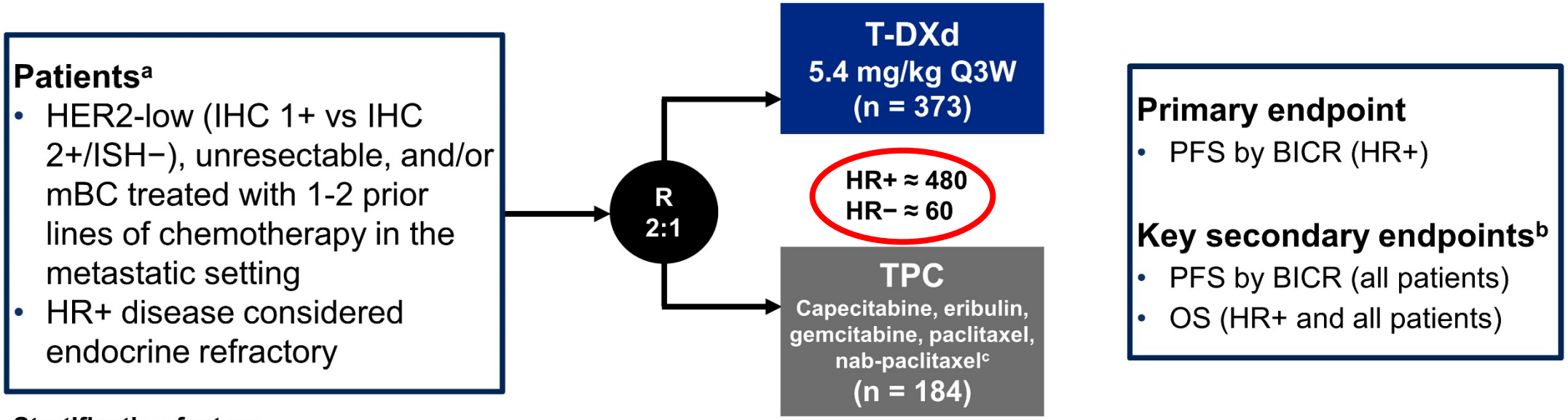
No. at Risk						
Chemotherapy	1,602	1,558	1,423	1,003	595	140
Chemotherapy + trastuzumab	1,598	1,528	1,404	1,010	592	118

No benefit of adjuvant trastuzumab for HER2-low patients

Fehrenbacher L et al. *J Clin Oncol*. 2020;38:444-453.

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

An open-label, multicenter study (NCT03734029)



Stratification factors

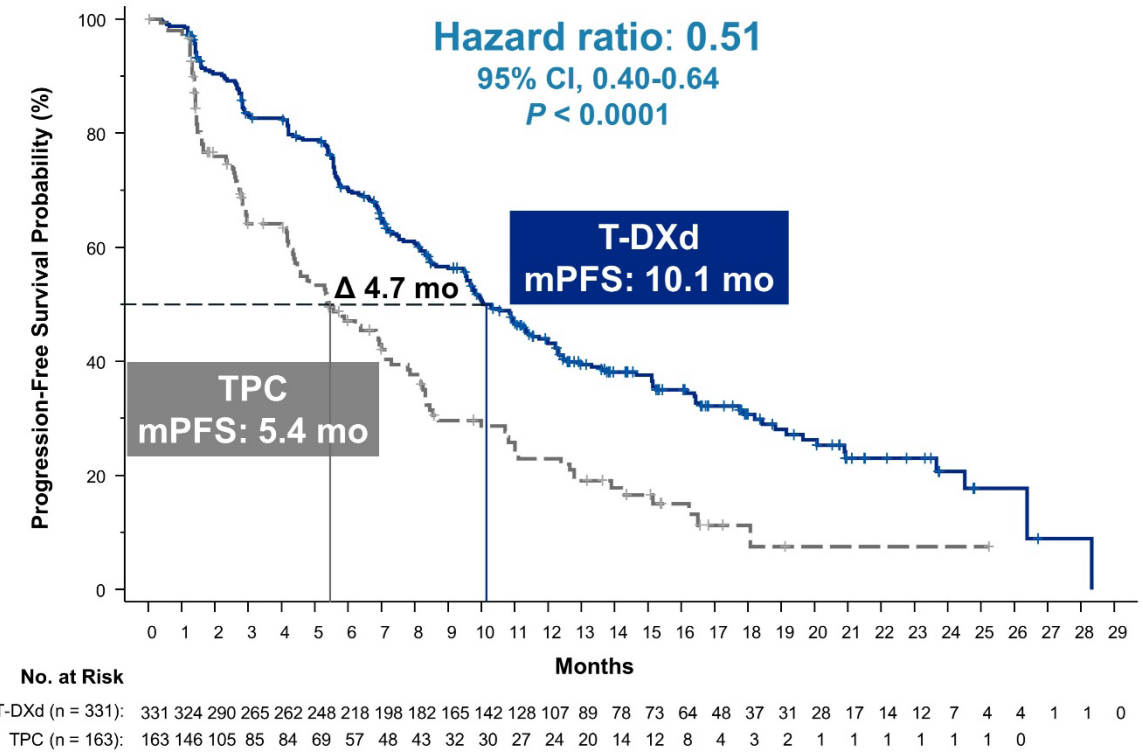
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

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.

PFS in HR+ and All Patients

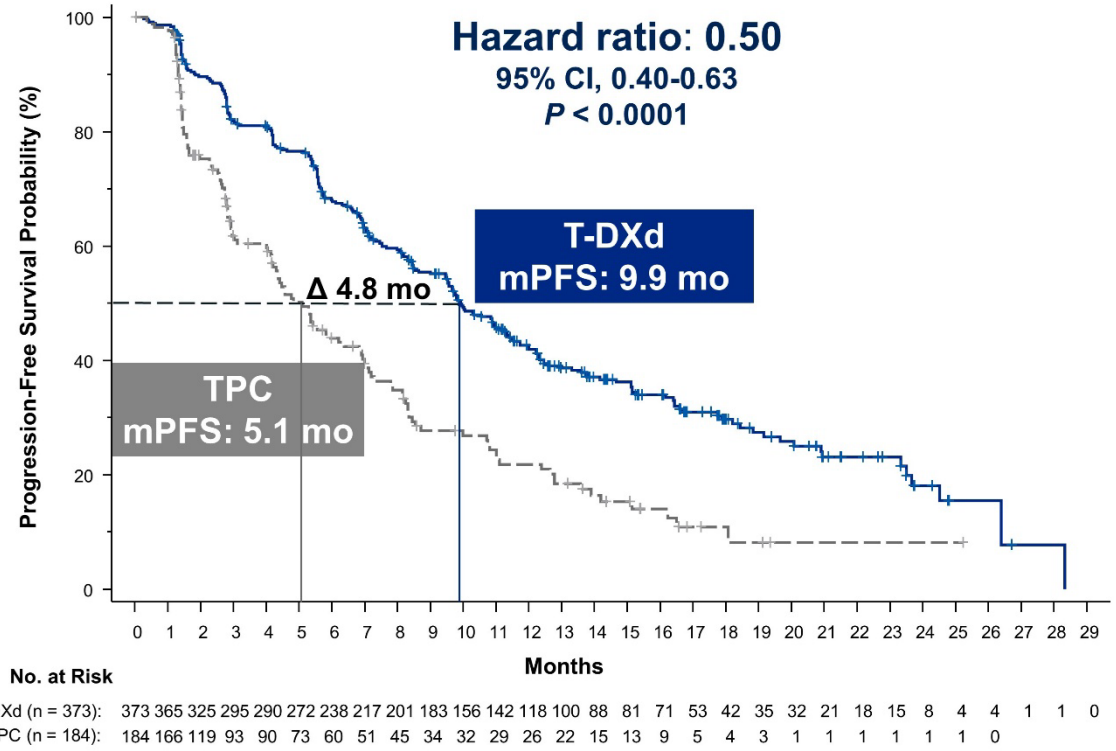
Hormone receptor–positive



No. at Risk

T-DXd (n = 331):	331	324	290	265	262	248	218	198	182	165	142	128	107	89	78	73	64	48	37	31	28	17	14	12	7	4	4	1	1	0
TPC (n = 163):	163	146	105	85	84	69	57	48	43	32	30	27	24	20	14	12	8	4	3	2	1	1	1	1	1	1	0			

All patients



No. at Risk

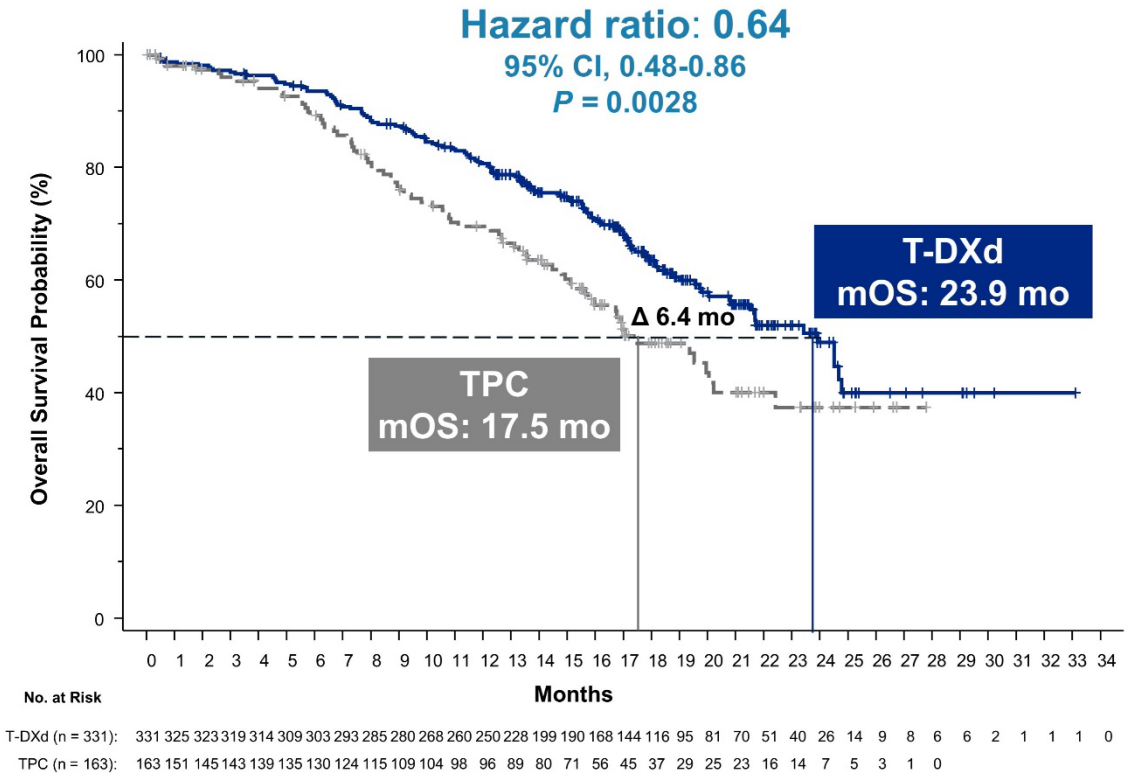
T-DXd (n = 373):	373	365	325	295	290	272	238	217	201	183	156	142	118	100	88	81	71	53	42	35	32	21	18	15	8	4	4	1	1	0
TPC (n = 184):	184	166	119	93	90	73	60	51	45	34	32	29	26	22	15	13	9	5	4	3	1	1	1	1	1	1	0			

PFS by blinded independent central review.

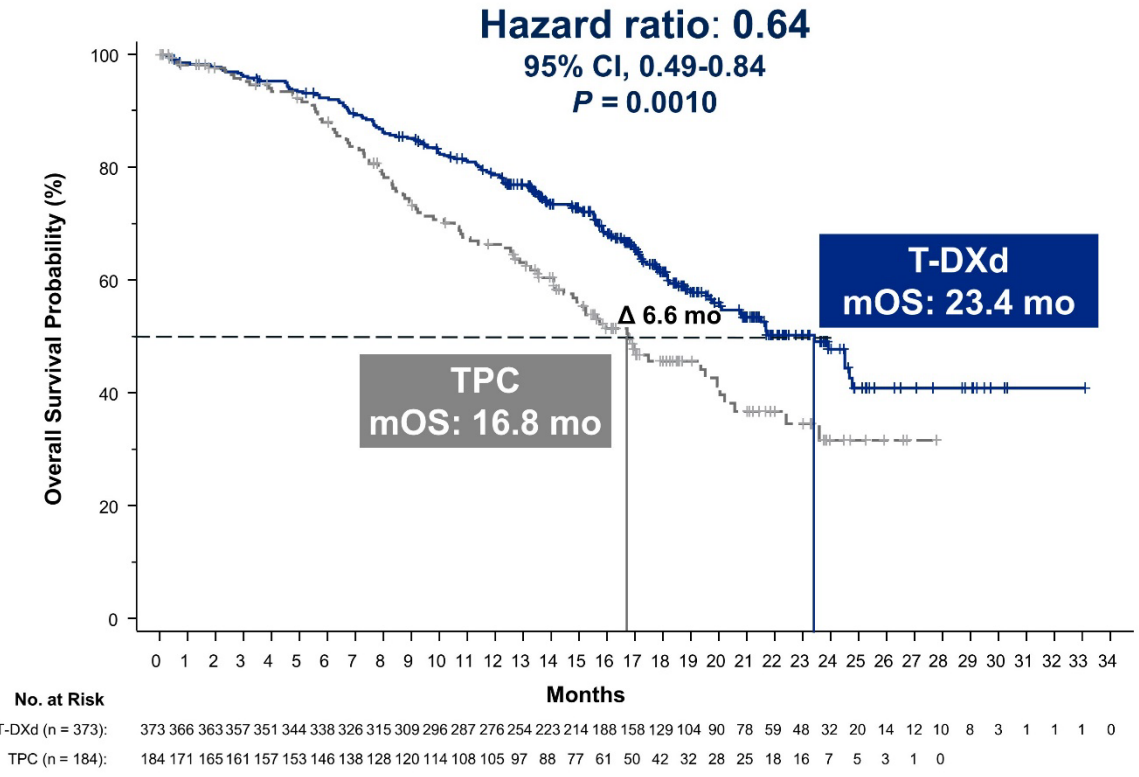
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



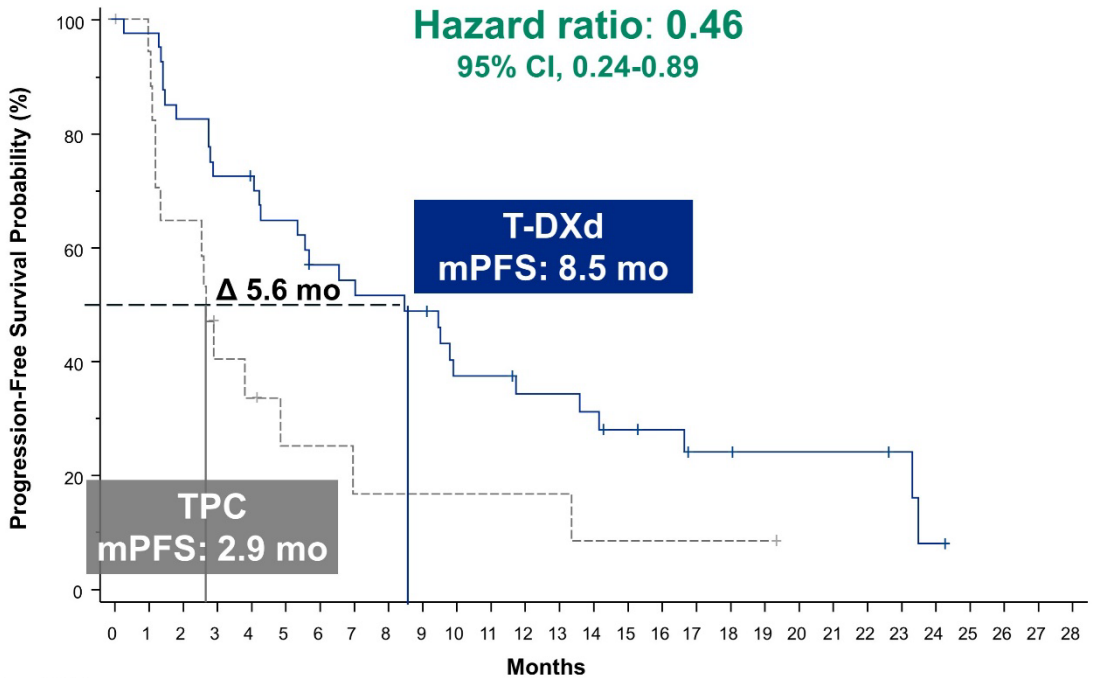
All patients



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

PFS and OS in HR− (Exploratory Endpoints)

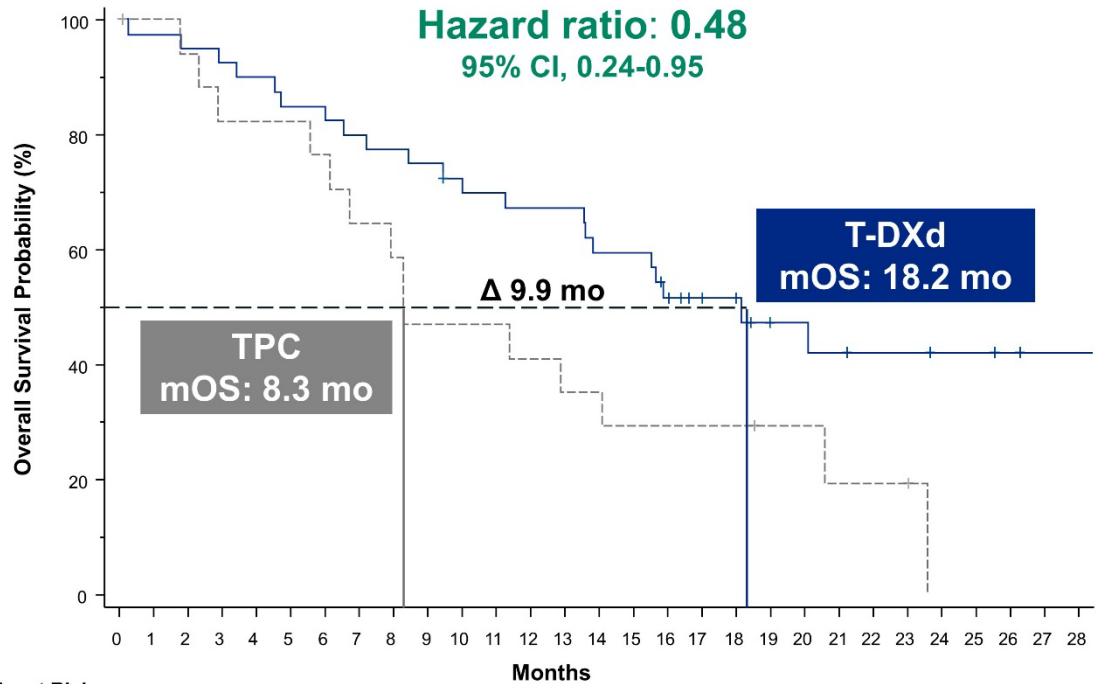
PFS



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



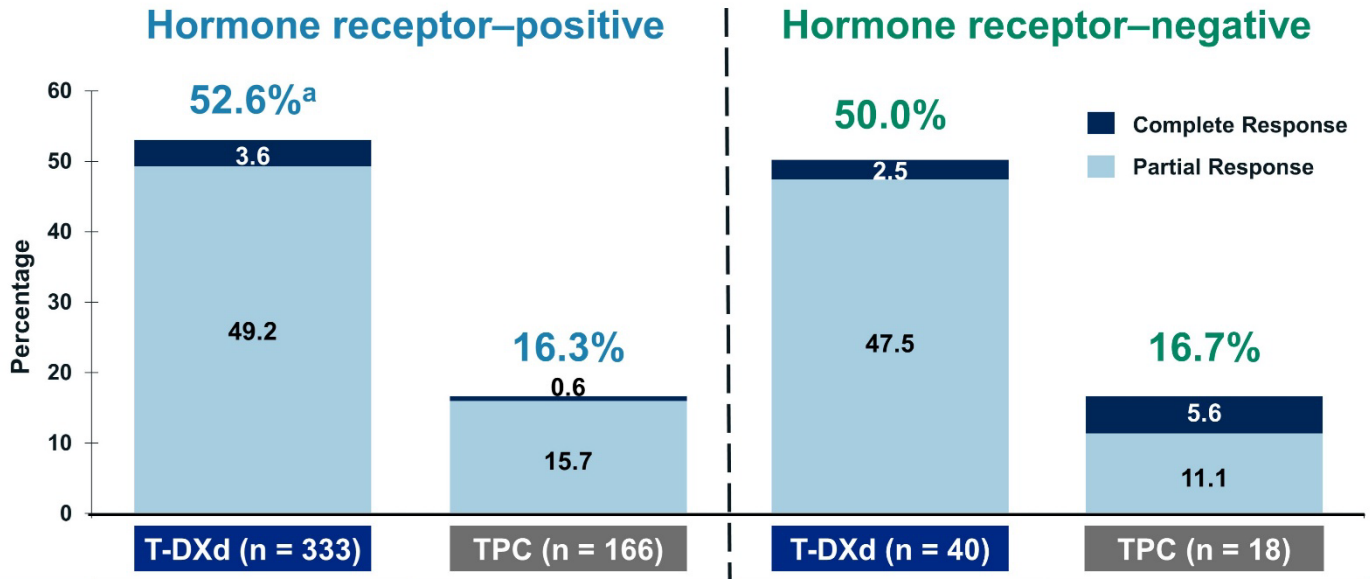
No. at Risk

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.

Confirmed ORR

Confirmed Objective Response Rate



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

Next Challenge: How LOW can we go?

DAISY

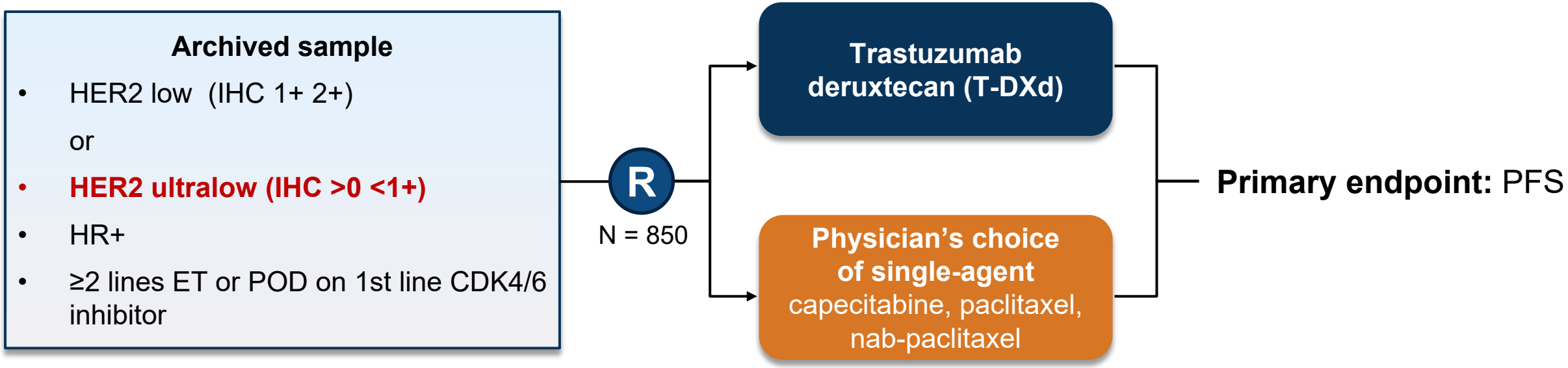
	Total	Cohort 1 (HER2 over-expressing)	Cohort 2 (HER2 low-expressing)	Cohort 3 (HER2 non-detected)
BOR confirmed n / N [95%CI]	86 / 177 (48.6%) [41.0; 56.2]	48 / 68 (70.6%) [58.3; 81.0]	27 / 72 (37.5%) [26.4; 49.7]	11 / 37 (29.7%) [15.9; 47.0]
Median DOR (months) [95%CI]	8.5 [6.5; 9.8]	9.7 [6.8; 13]	7.6 [4.2; 9.2]	6.8 [2.8; Not reached]
Median PFS (months) [95%CI]	7.0 [6.0; 8.7]	11.1 [8.5; 14.4]	6.7 [4.4; 8.3]	4.2 [2.0; 5.7]

Decreasing ORR by degree of HER2 expression

Dieras V et al, SABCS 2021

Potential Future Challenge: HER2 “Ultralow”

- DESTINY-Breast06 phase 3 includes IHC 0 with “ultralow” expression and may expand the population of patients deriving benefit from T-DXd



- **Key differences with DESTINY-Breast04:** includes IHC 0+ (“ultralow”), larger (N = 850), restricted to HR+ disease, and includes chemo-naïve patients

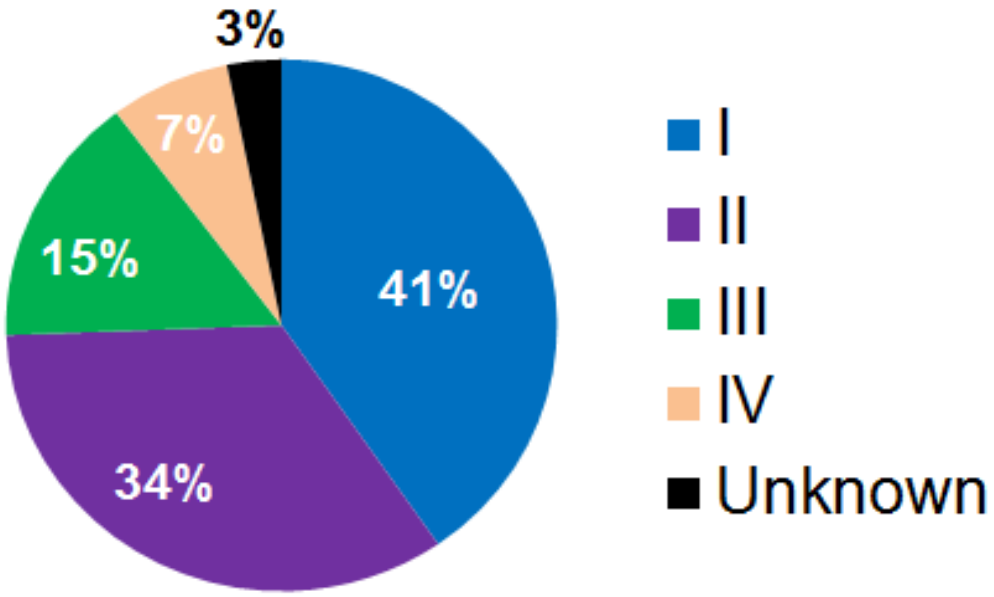
https://clinicaltrials.gov/ct2/show/NCT04494425.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive	
Preferred Regimens: • Paclitaxel + trastuzumab[h] • TCH (docetaxel/carboplatin/trastuzumab) • TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab) • If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab. • If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j]	
Useful in Certain Circumstances: • Docetaxel + cyclophosphamide + trastuzumab • AC followed by T[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules) • AC followed by T[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules) • Neratinib[i] (adjuvant setting only) • Paclitaxel + trastuzumab + pertuzumab[j] • Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)	**Other Recommended Regimens:** • AC followed by docetaxel[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab) • AC followed by docetaxel[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

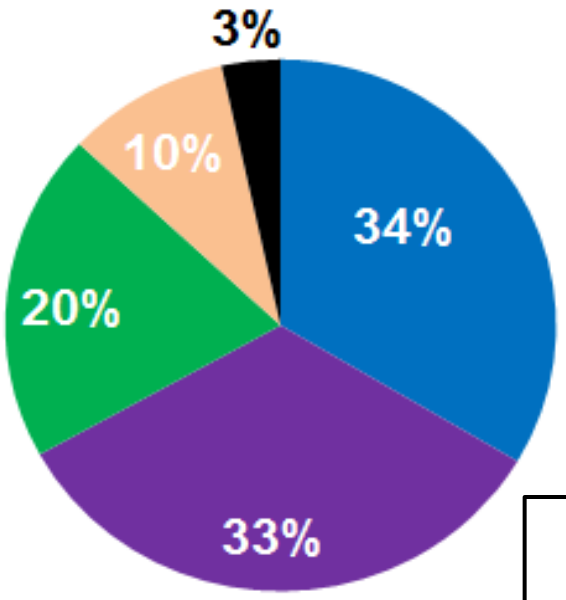
SEER Staging of HER2+ disease

HR+/HER2+



N=5,240

HR-/HER2+



N=2,328

Stage I: 34-41%

Contrary to initial impressions, early stage HER2+ cancers are not so very rare

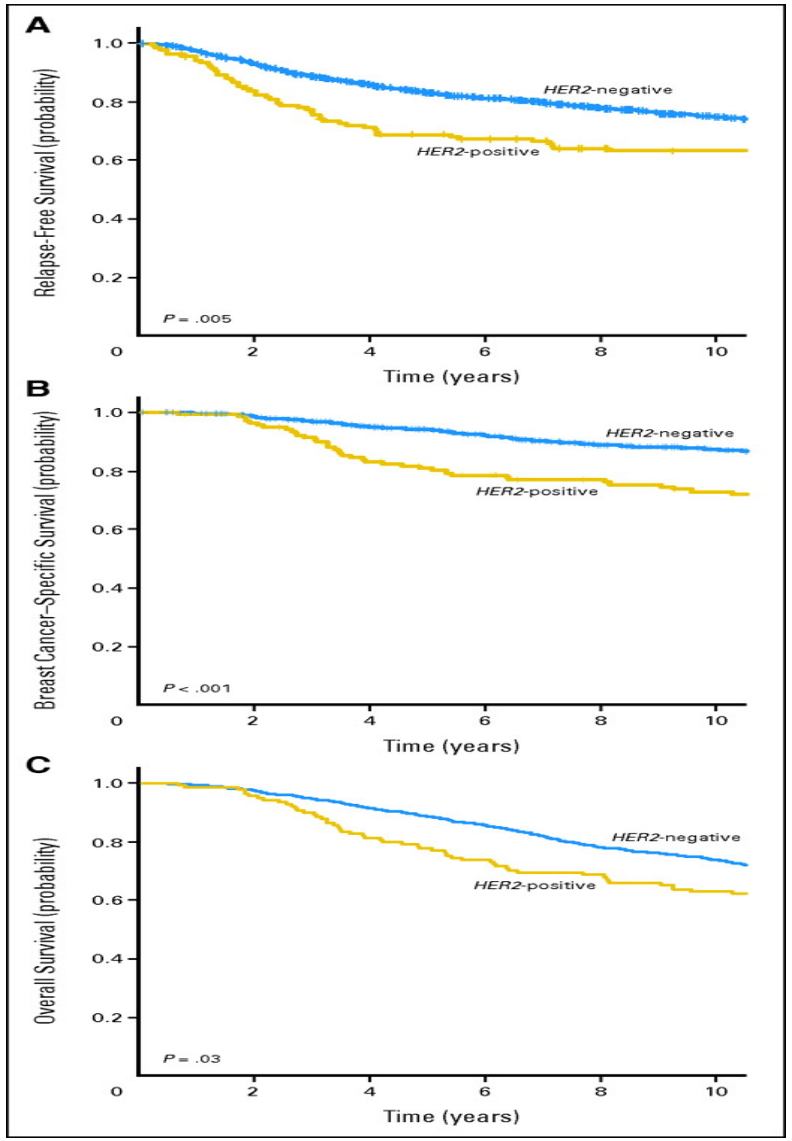
Howlader N. et al. JNCI 2014
Slide courtesy of Aleix Prat

British Columbia Tumor Registry

Stage I Only

HER2 status	n	10 yr RFS (%)
HER2-	1128	75.5
HER2+	117	65.9

P=0.01



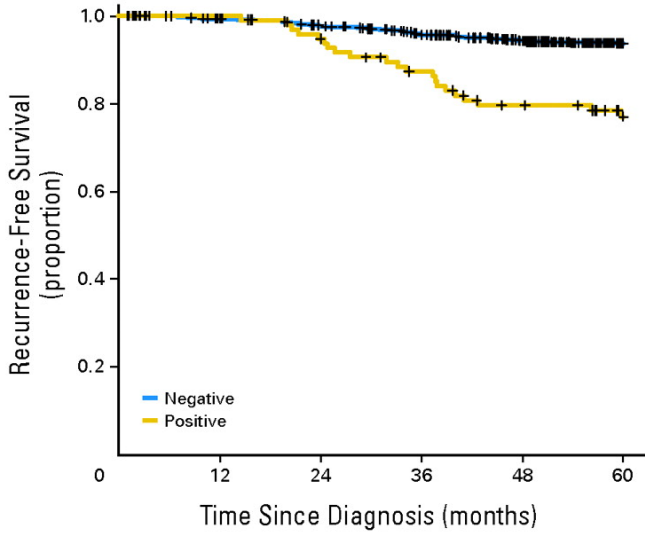
No Systemic Therapy, n=1420
Node Negative, Any Size

Chia S et al. J Clin Oncol 2008 26:5697-5704

Outcomes for T1a/bN0 HER2+ Tumors

MD Anderson Series

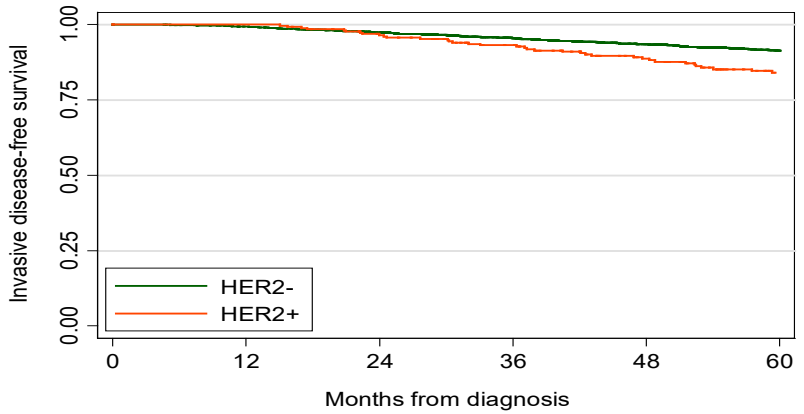
HER2 status	n	5 yr RFS
HER2+	98	77.1%
HER2-	867	93.7%



Gonzalez-Angulo A M et al. JCO 2009;27:5700-5706

NCCN Series

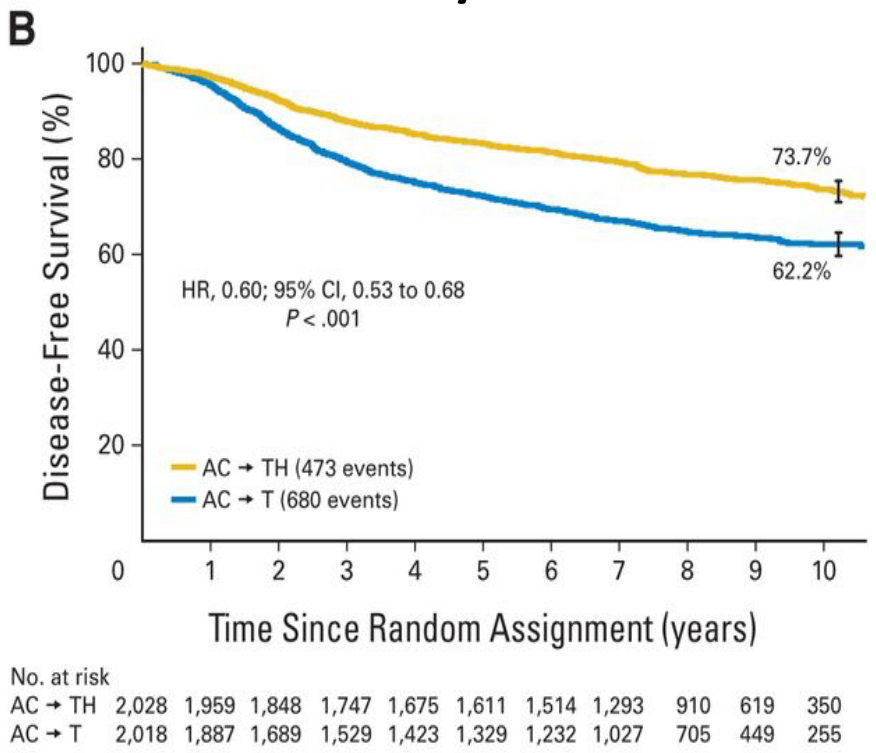
HER2 status	n	5 yr DFS
HER2+	255	83.3%
HER2-	3127	89.0%



Vaz-Luis, I et al. ASCO Meeting 2013, abstract 1006

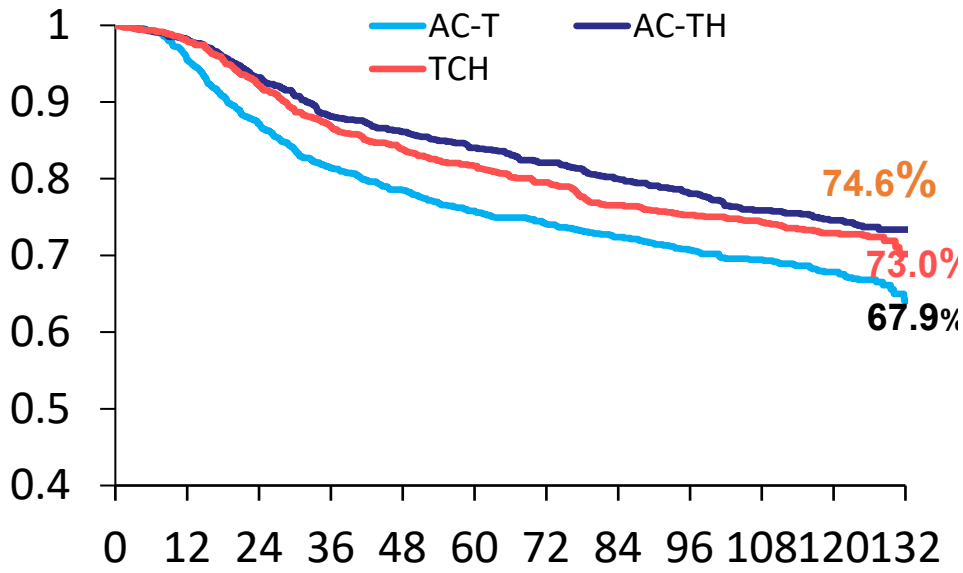
ADJUVANT TRASTUZUMAB: LONG TERM OUTCOMES

NSABP B-31/N9831: DFS



Perez E et al, J Clin Oncol 2014

BCIRG006: DFS



Slamon D et al, SABCS 2015

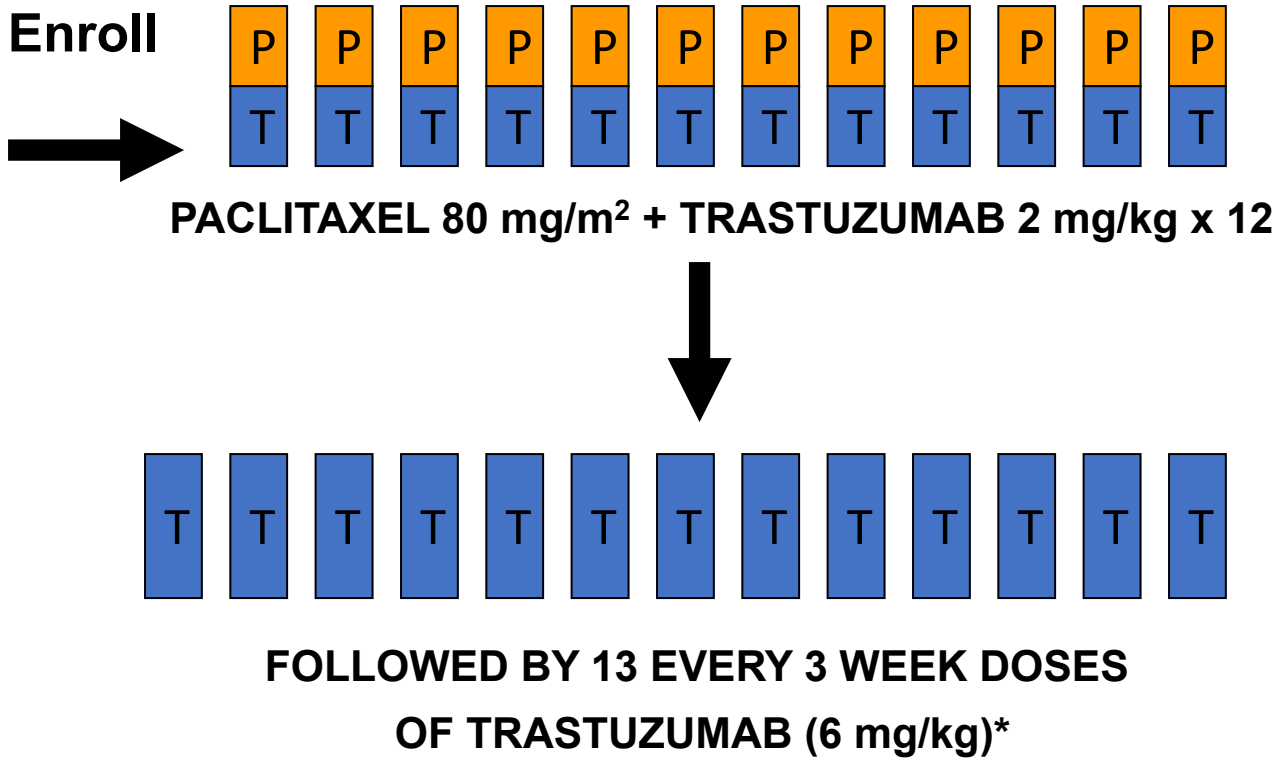
~25% of patients recur with 10 years of follow-up

APT TRIAL: STUDY DESIGN

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400

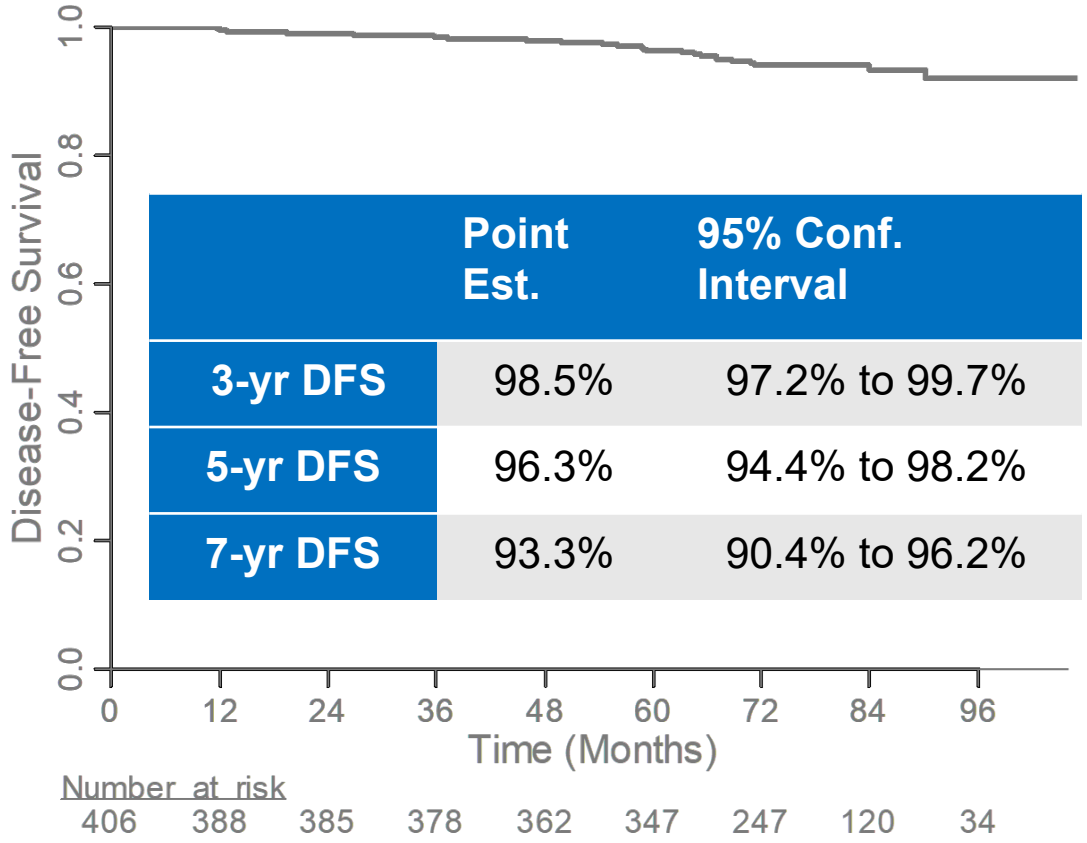
49% T1a/T1b
42% T1c
9% T2 (≤3 cm)
67% HR positive



Tolaney SM et al, NEJM 2015
Tolaney SM et al, JCO 2019

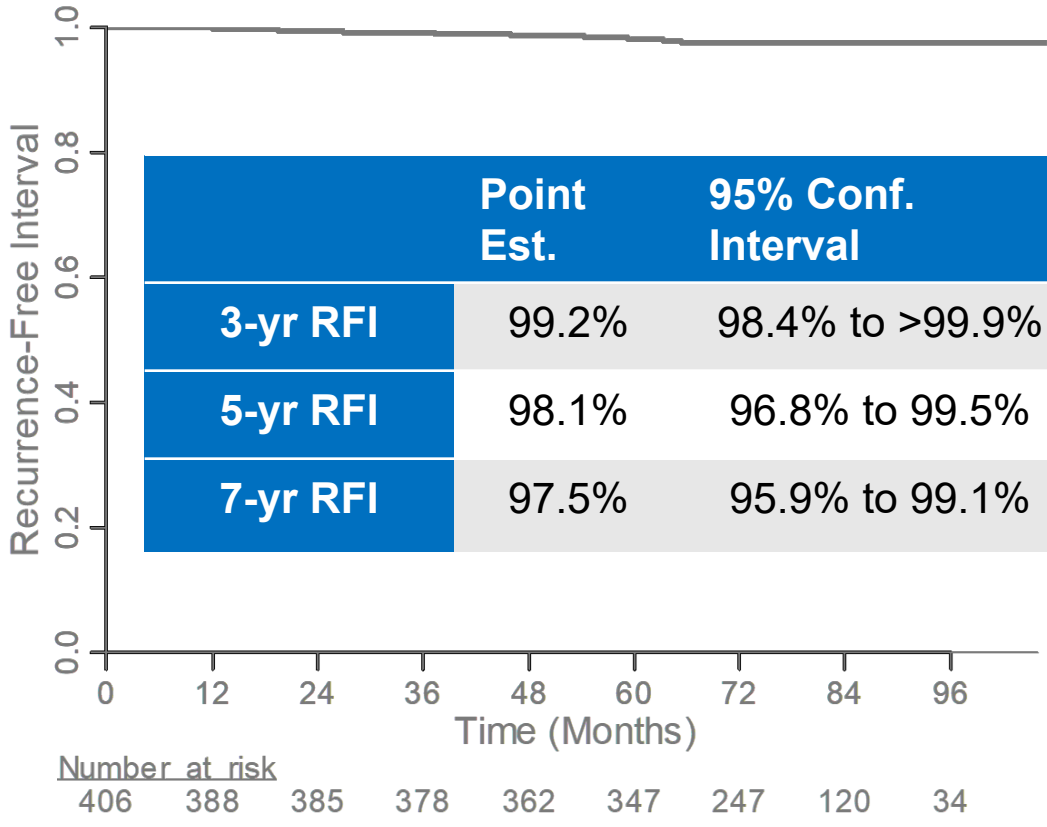
APT: OUTCOMES AT 7 YRS

DISEASE-FREE SURVIVAL



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

RECURRENCE FREE INTERVAL

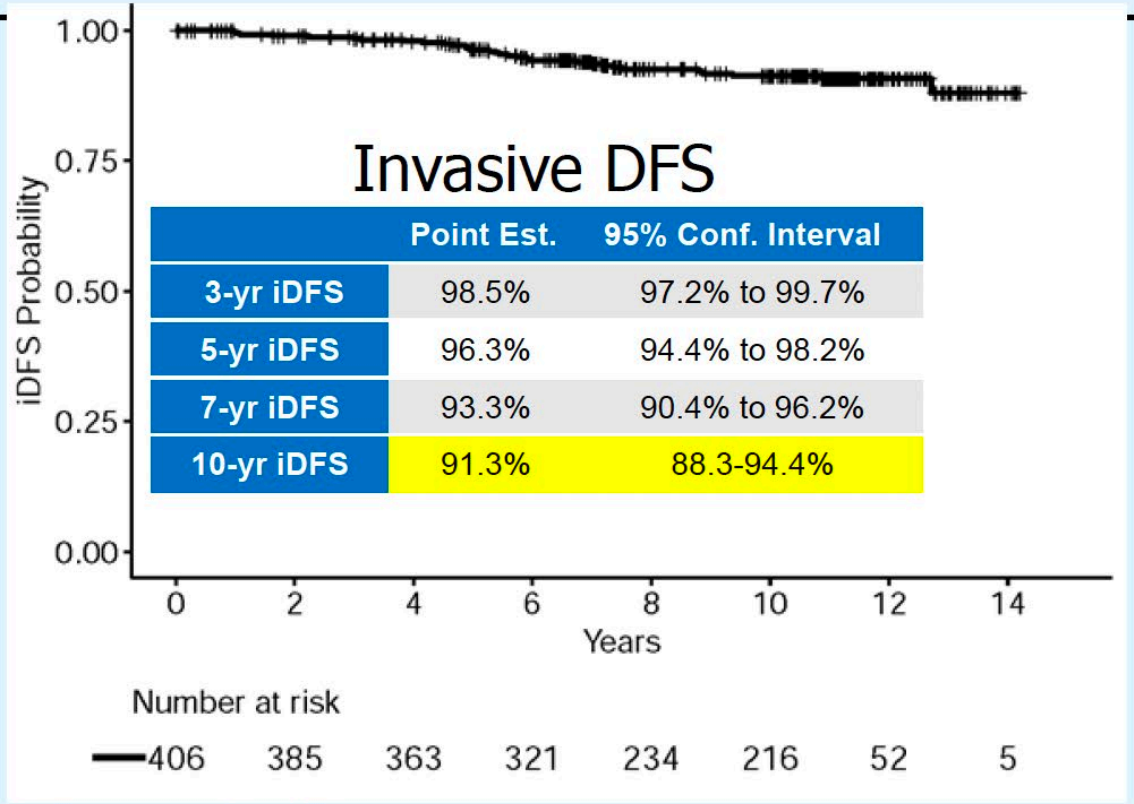


	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to >99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%

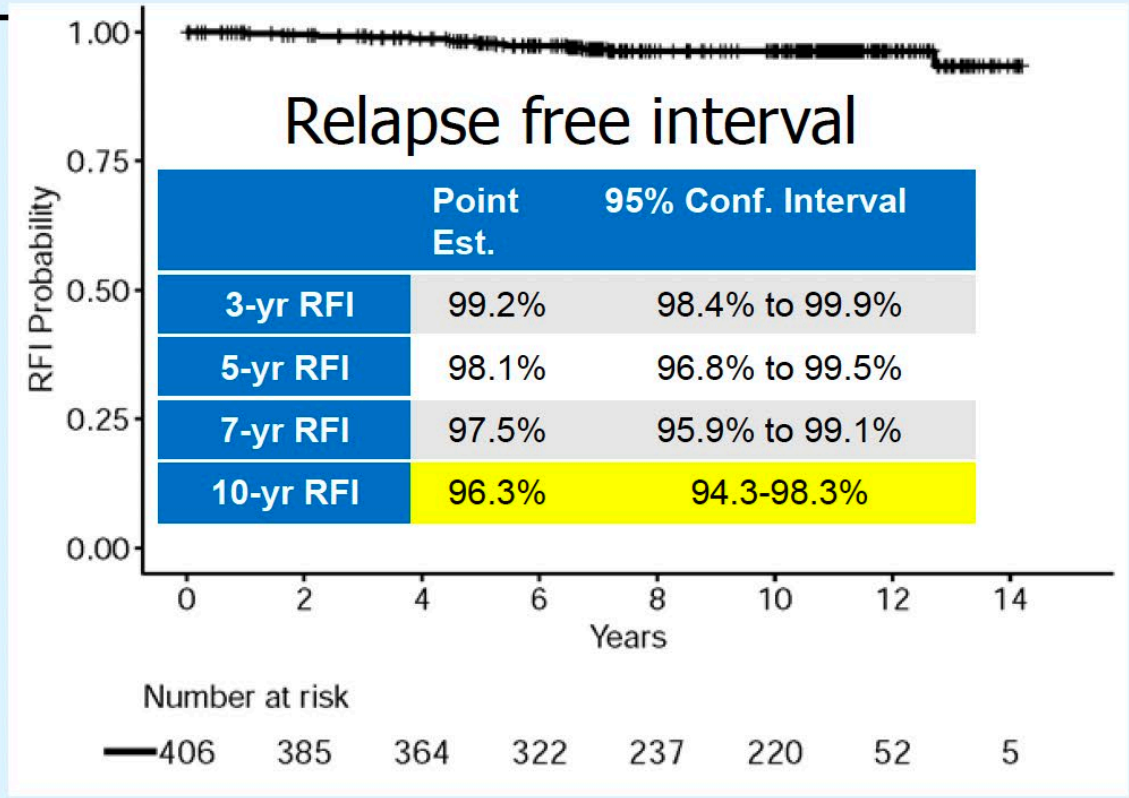
RFI Events=
- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**

Tolaney SM et al, NEJM 2015
Tolaney SM et al, JCO 2019

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**

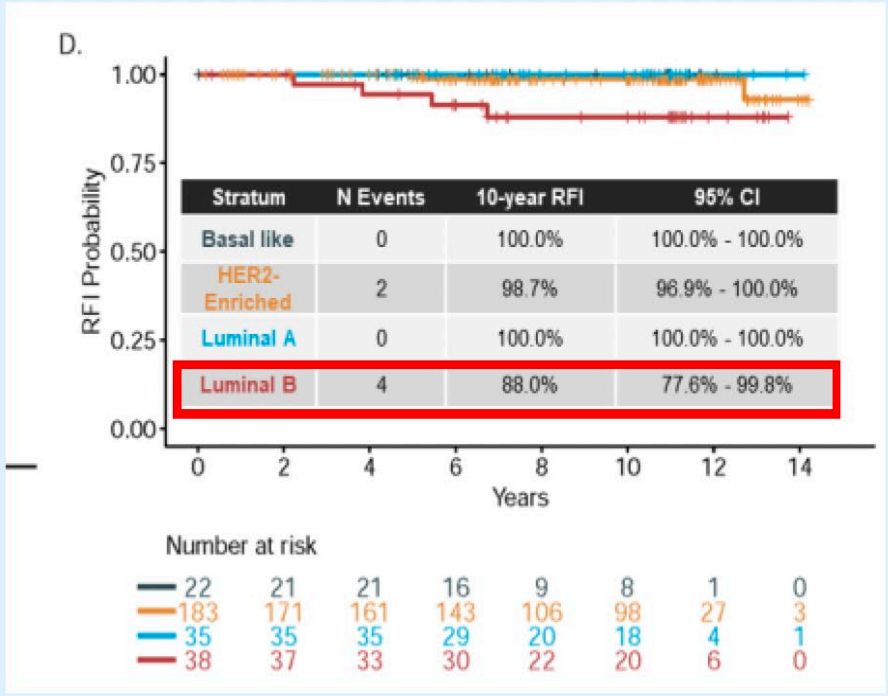
Ten-year OS for the ITT population: 94.3% (95% CI: 91.8% - 96.8%)

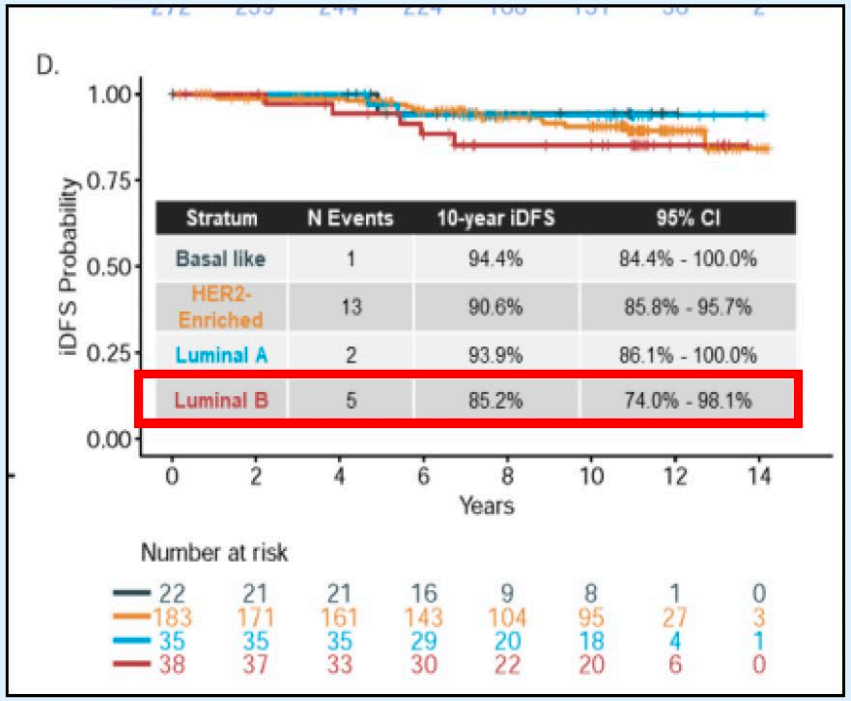
10-year BCSS was 98.8% (95% CI: 97.6% - 100.0%)

Tolaney SM, SABCS 202

Biomarker work from APT to help select patients for less therapy

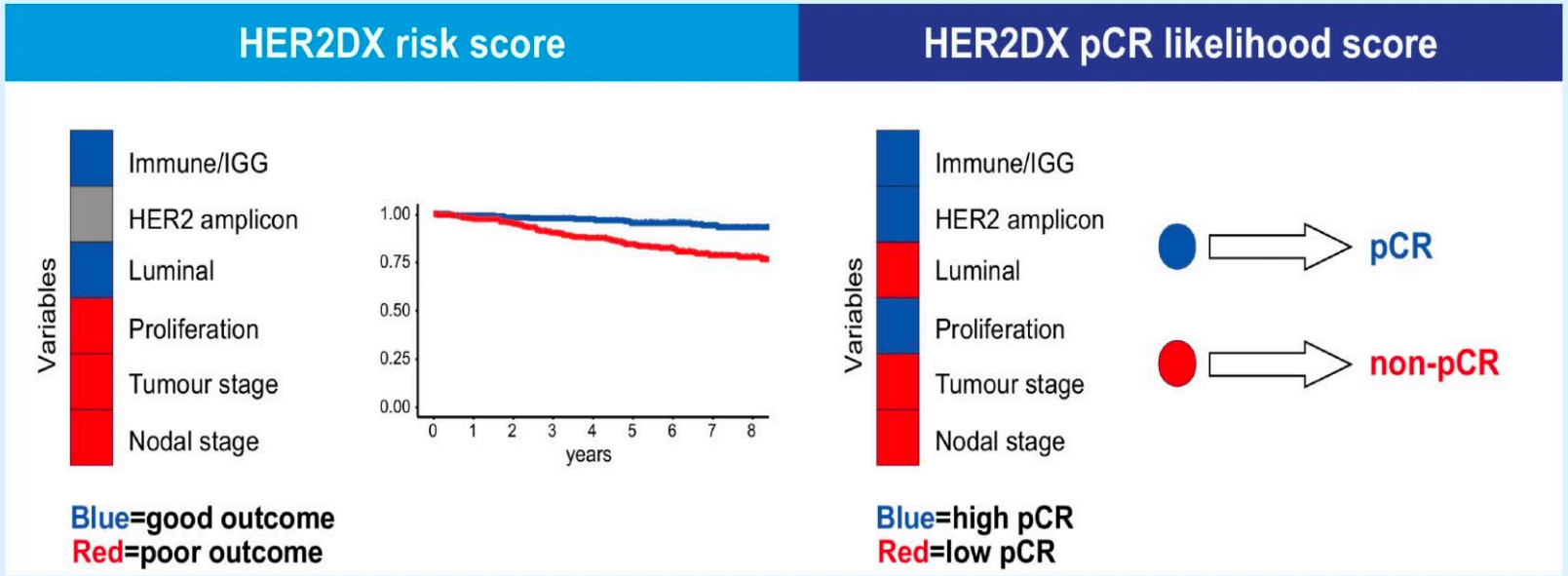
- **No difference in outcome based on hormone receptor status**
- RFI fairly similar comparing based on low, intermediate, and high levels of tumor infiltrating lymphocytes.
- Lower RFI and iDFS in those with luminal B compared to other PAM50 subtypes





Tolaney SM, SABCS 2022

HER2DX: Score to fine tune patient selection for less therapy?



- Single score that incorporates **clinical and genomic data** to help predict disease free survival outcome (risk score) and chance of pCR
- Integrates tumor size, nodal status, and 4 gene expression signatures relating to immune infiltration, proliferation, luminal differentiation and expression of HER2 amplicon.
  - Red: high score of that variable is associated with worse outcome; Blue: high score of that variable is associated with better outcome. Grey: no association with the clinical endpoint.

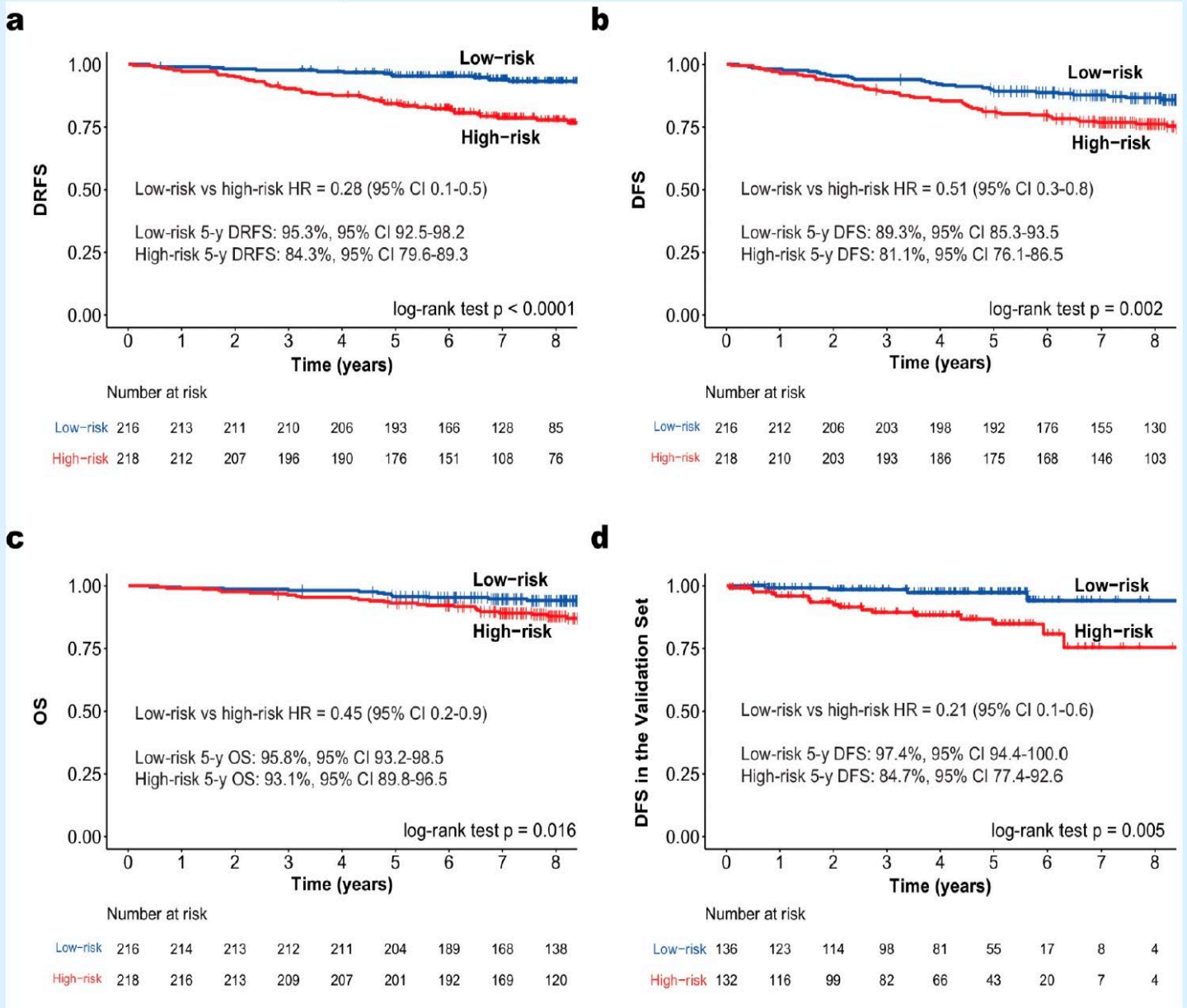
Prat eBioMedicine 2022;75

HER2DX: Score to fine tune patient selection for less therapy?

Risk score trained on 432 HER2+ tumors from Short-HER (a=DRFS, b=DFS, c=OS) and validated with 268 tumors from independent cohort (d)

Continuous HER2DX risk score significantly associated with DFS (p=0.002)

Prat eBioMedicine 2022;75

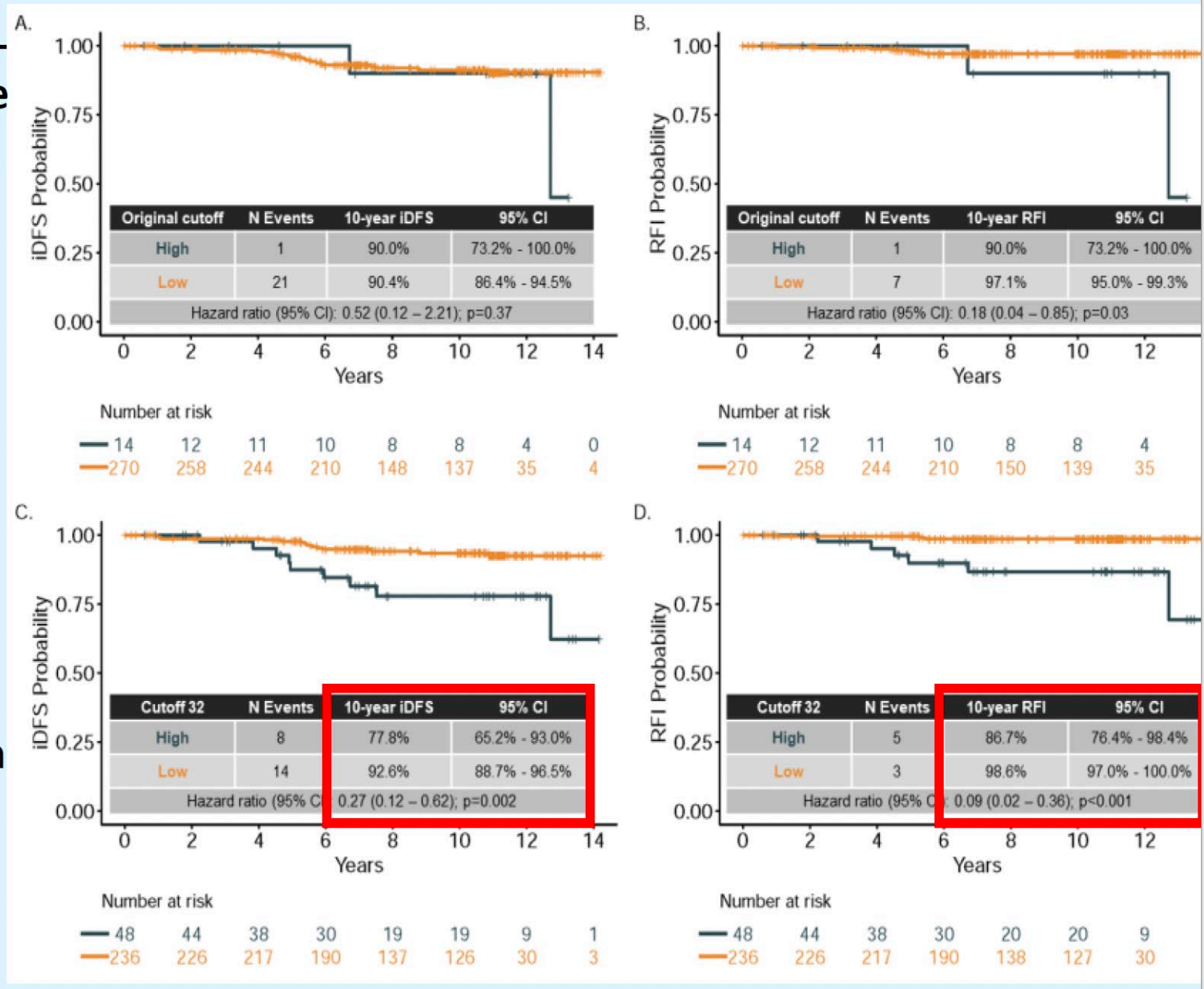


HER2DX RESULTS FROM APT STUDY

- **HER2DX risk-score as a continuous variable was significantly associated with iDFS** (HR per 10-units increment=1.24; 95%CI:1.01-1.54; p=0.04) **and RFI** (HR per 10-units increment=1.45; 95%CI:1.09-1.93; p=0.01).

- Using a HER2DX score cutoff of 50, 4.9% of patients in APT were HER2DX high-risk
  - Using this cutoff, HER2DX low risk disease had a significantly better RFI (Fig B) but not iDFS (Fig A)

- A **HER2DX score cutoff of 32** was optimal in distinguishing low vs high-risk disease for both iDFS (Fig C) and RFI (Fig D)



Tolaney SM, SABCS 2022

International guidelines recommend the APT treatment regimen in patients with small, node-negative tumors

St. Gallen Expert Consensus

Adjuvant therapy: HER2-targeted therapy[1]

Paclitaxel and trastuzumab is an effective regimen for **stage I** breast cancers with low rates of recurrence

NCCN Breast Cancer Guidelines

Systemic adjuvant treatment[2]

Adjuvant chemotherapy with weekly paclitaxel and trastuzumab[3] can be considered for **stage I** HER2-positive cancers, particularly if the primary cancer is ER-negative

Primary Breast Cancer Clinical Practice Guidelines

Adjuvant systemic treatment[4]

Luminal B HER2-positive tumours are treated with chemotherapy, endocrine therapy and trastuzumab [I, A].* No randomised data exist to support omission of chemotherapy in this group. However, in **small, node-negative tumours**, the combination of single-agent paclitaxel and trastuzumab provides excellent results

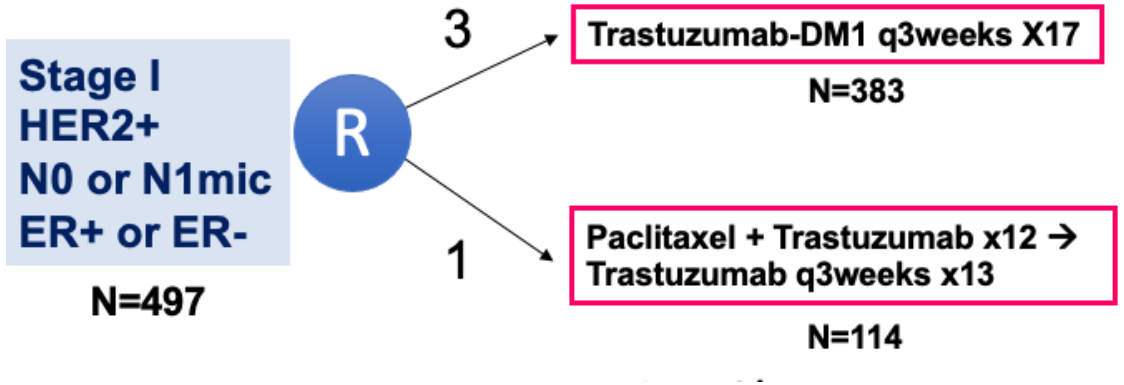
* Level of evidence **I:** Evidence from at least one large, randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity;
Grade of recommendation **A:** strong evidence for efficacy with a substantial clinical benefit, strongly recommended.
ER, oestrogen receptor.

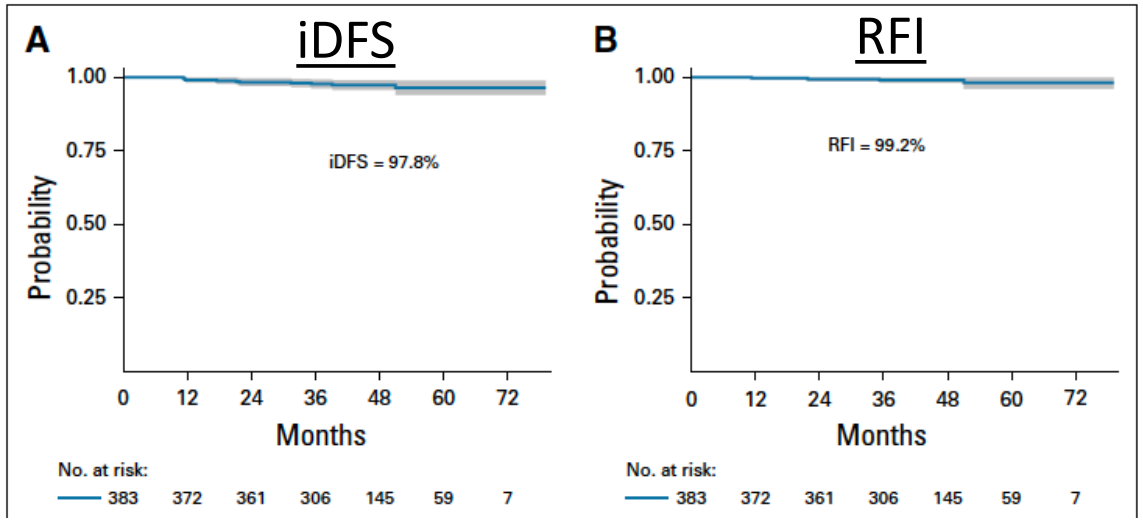
1. Curigliano G, *et al. Ann Oncol* 2017; **28**:1700–1712; 2. NCCN Breast Cancer Guidelines. Version 3, 2017;
3. Tolaney SM, *et al. N Engl J Med* 2015; **372**:134–141; 4. Senkus E, *et al. Ann Oncol* 2015; **26(Suppl. 5)**:v8–30.

APT: Implications

- **Paclitaxel and trastuzumab (TH) can be considered a reasonable and appealing approach for the majority of patients with stage I HER2+ breast cancer**
  - **Not all patients require adjuvant trastuzumab-based chemotherapy (particularly T1aN0)**
  - **Standard regimens from the pivotal trials can be considered for patients with particularly high risk features**

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





Co-Primary Endpoints:
- 3-year DFS in T-DM1 arm
- Compare clinically relevant toxicities between the 2 arms

Patient characteristic	ATEMPT
T ≤ 1 cm	43% (11% T1a)
HR+	75%
N1mic	NR

- 3yr IDFS similar in both groups (97.8% T-DM1)
- Toxicity profiles of both regimens similar:
  - Identical rates of clinically relevant toxicities (46%)
  - TH: More neuropathy and alopecia
  - T-DM1: Higher discontinuation rate with T-DM1 >50% of discontinuations occurred after 6 months; >50% not protocol-mandated

Tolaney SM et al, JCO, 2021
Ruddy KJ et al, BCRT, 2021

ATEMPT 5-year outcomes

	T-DM1 (N=383)
3-year iDFS	97.8% 10 events
5-year iDFS	97.0% 11 events[1,2]
5-year RFI	98.3% 6 events
5-year OS	97.8% 3 events
5-year BCSS	99.4%

1. 11 iDFS events: 3 distant recurrences, 3 non-related deaths, 3 contralateral HER2- breast cancers, 2 ipsilateral recurrences (1 HER2+)

2. 5-year iDFS similar for HR negative/positive and for tumors <1 cm or ≥ 1 cm

Tarantino P, SABCS 2022

ATEMPT & APT 5-year outcomes

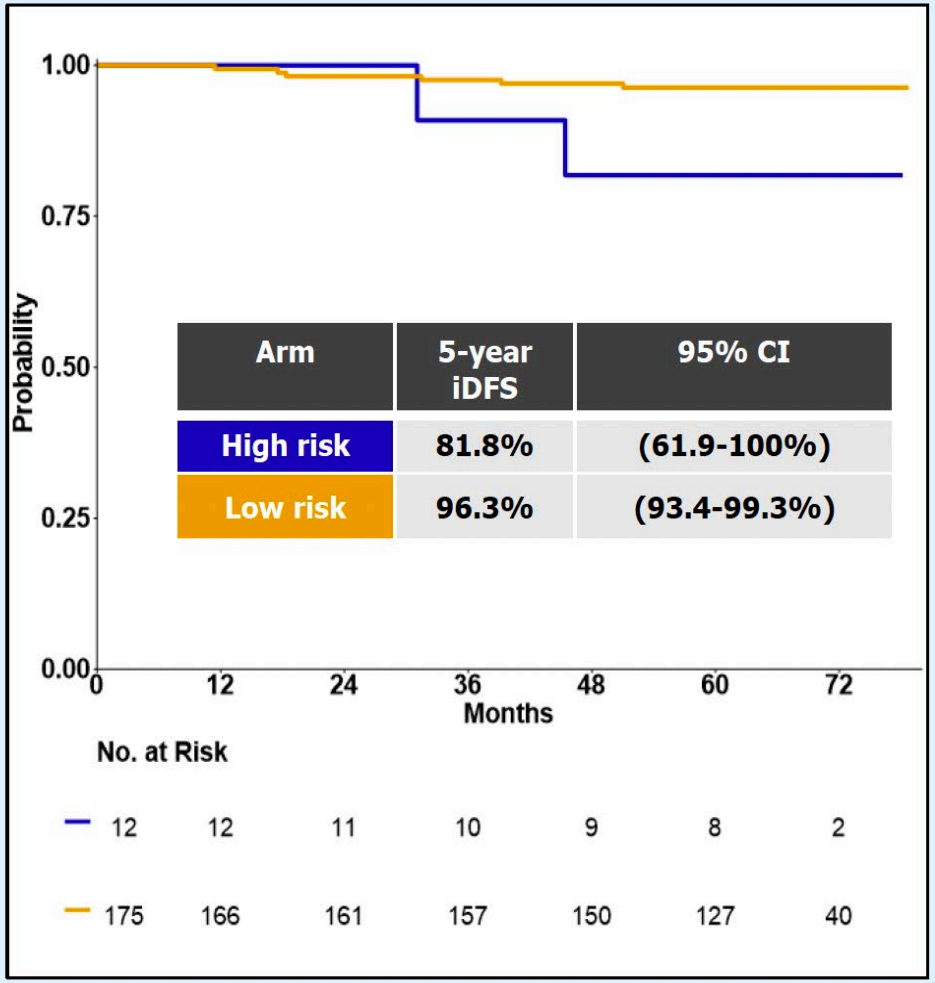
	T-DM1 (N=383)	TH (ATEMPT) (N=114)	TH (APT) (N=406)
3-year iDFS	97.8% 10 events	93.4% 8 events	98.5%
5-year iDFS	97.0% 11 events*	91.1% 9 events	96.3%
5-year RFI	98.3% 6 events	93.2% 7 events	98.1% 7 events
5-year OS	97.8% 3 events	97.9%	98.7% 5 events
5-year BCSS	99.4%	Not reported	99.7% 1 event

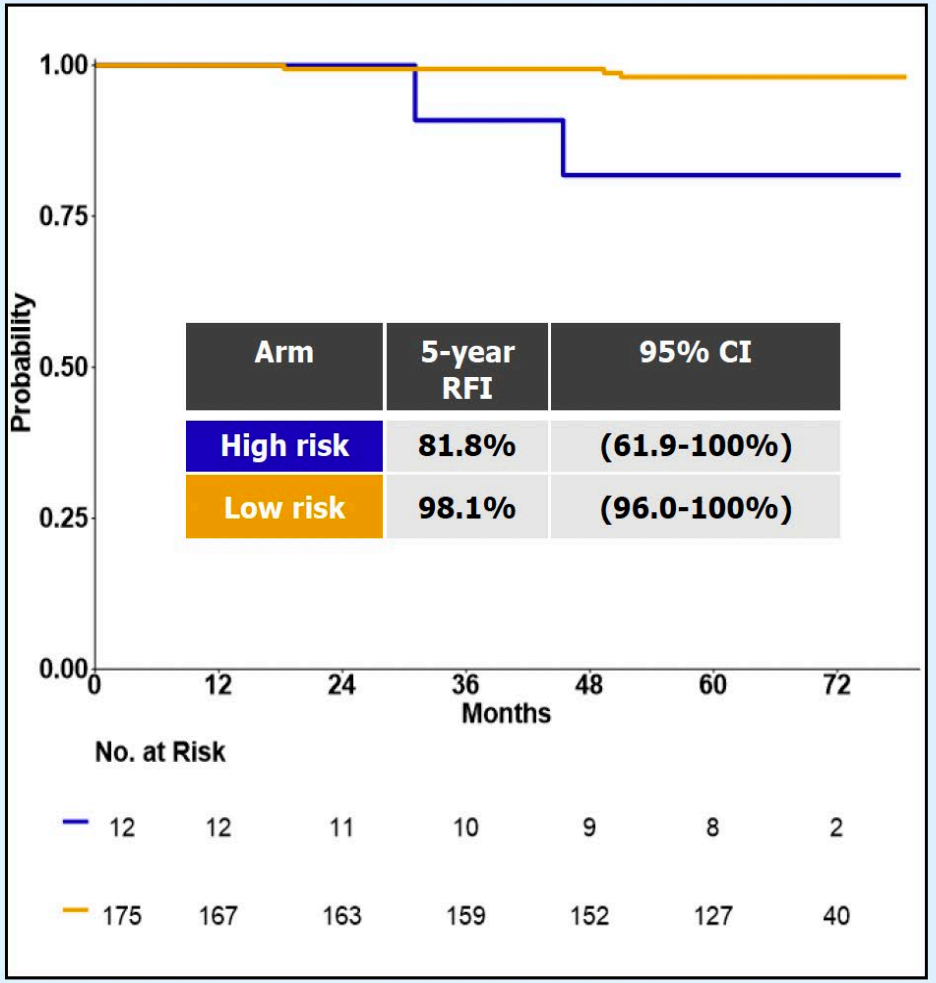
Tarantino P, SABCS 2022; Tolaney S J Clin Oncol 2019;37.

ATEMPT: HER2DX Analysis

In total, 187 patients enrolled in the trial had successful HER2DX testing (147 receiving T-DM1, 40 receiving TH).

Using a cutoff of 50, HER2DX low-risk patients had significantly higher 5-year RFI (98.1% vs 81.8%, HR 0.10 [0.02-0.57], p=0.01) **and numerically higher 5-year iDFS** (96.3% vs 81.8%, HR 0.20 [0.04-0.98], p=0.05) than those at high risk.

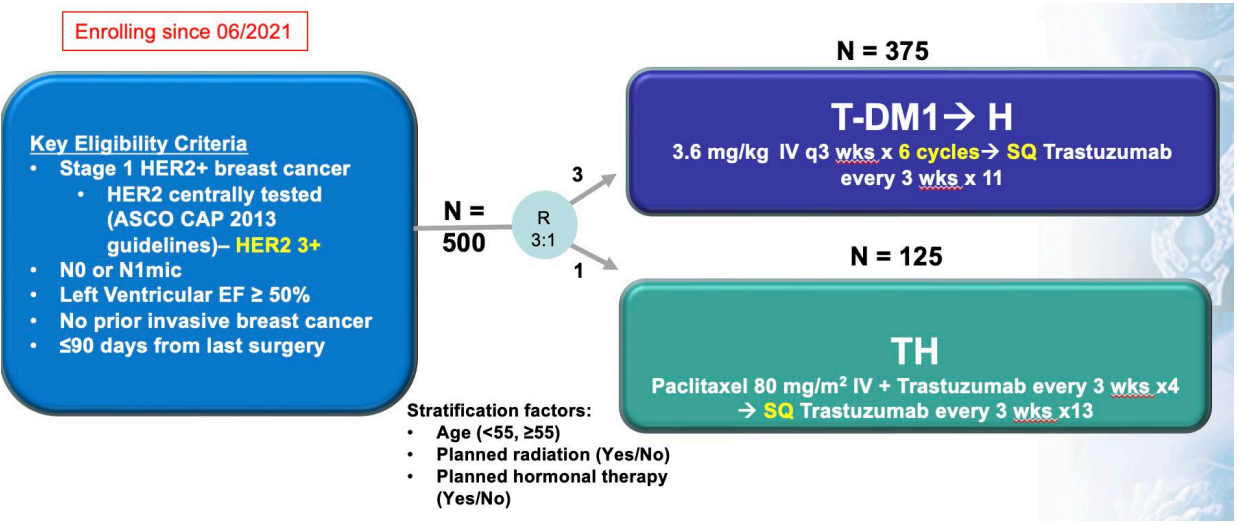




Tarantino P, SABCS 2022

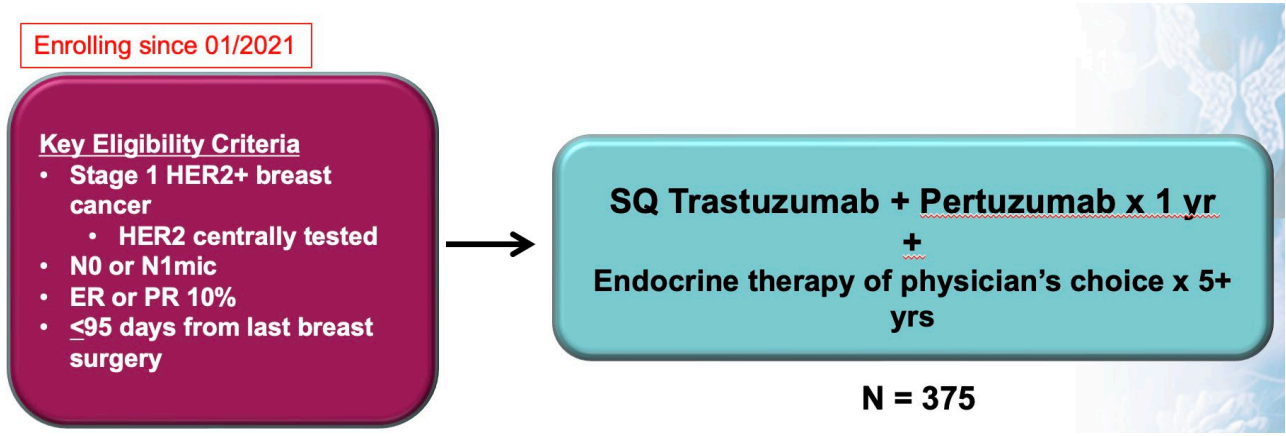
Ongoing de-escalation trials for stage I HER2+ breast cancer

ATEMPT 2.0



- Evaluating efficacy of six cycles of T-DM1 followed by trastuzumab vs. TH

ADEPT



- Evaluating efficacy of SQ HP + ET x 5 yrs

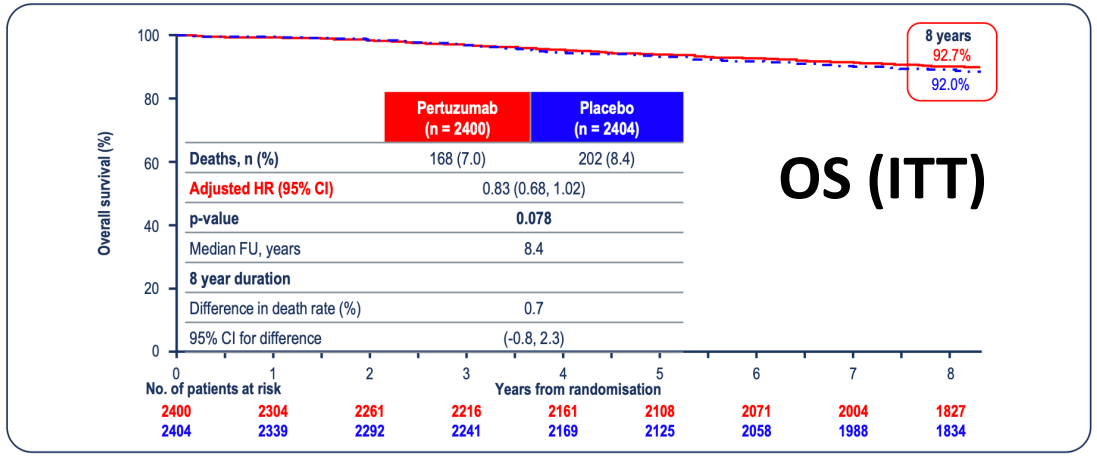
APHINITY: 3rd interim OS analysis (median f/u 8.4 years)

Trial design:

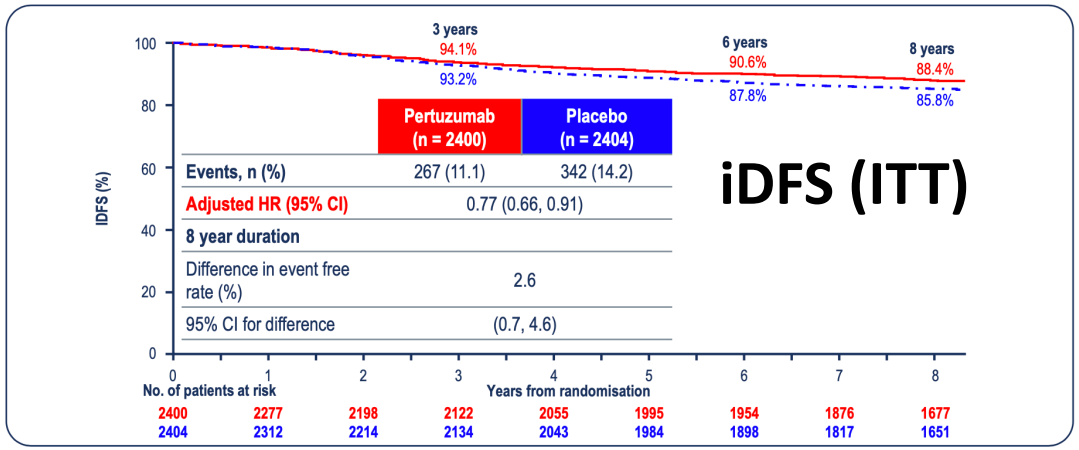
- Randomly assigned pts with high risk node neg or node pos HER2+ BC to receive adjuvant chemo + trastuzumab with pertuzumab vs. placebo

Results:

- Excellent survival at 8 yr median f/u for both groups
- No survival benefit with long f/u, many rescue options
- iDFS benefit seen only in **node+** disease



Node + 91.1% vs 89.2% (+1.9%)
Node – 95.5% vs 96.4% (-0.9%)

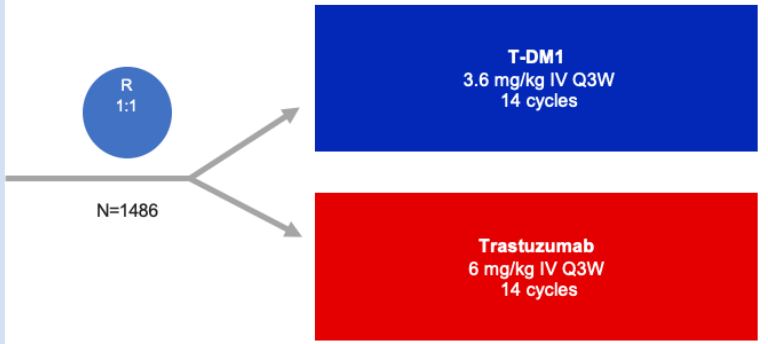


Node +: 86.1% vs 81.2% (+4.9%), HR 0.72 (0.6, 0.87)
Node -: 92.3% vs 93.3% (-1%)

Loibl S et al, ESMO virtual plenary, July 2022

KATHERINE: Escalating therapy if residual disease post NACT

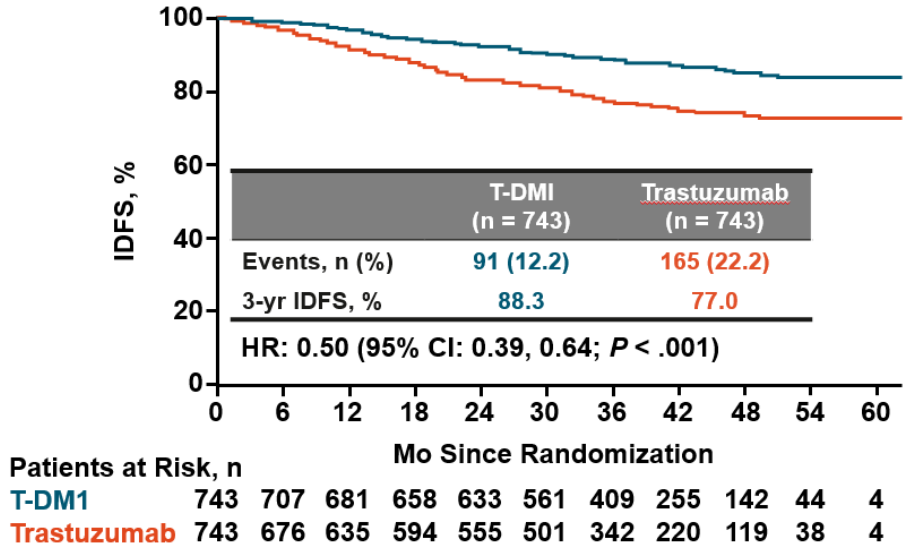
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



Radiation and endocrine therapy per protocol and local guidelines

~72% HR+
18% prior P
75% prior AC
22% ypT1a,b,mic N0

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done



Results:

- 3yr IDFS 88.3% vs. 77.0%
- Distant mets: 10.5% vs 15.9%
- Benefit seen in all subgroups

von Minckwitz et al. N Engl J Med. 2019

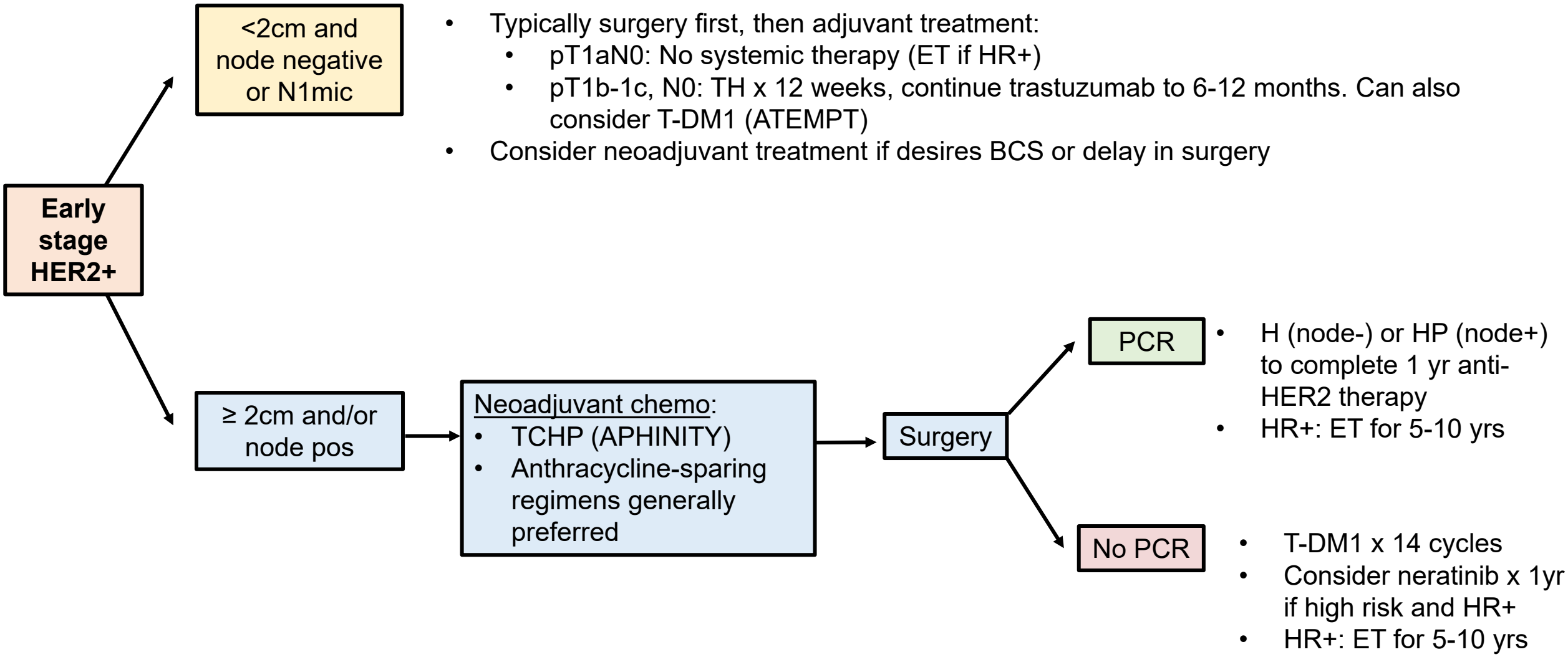
Ongoing trials of interest for patients with residual disease after NACT

- **CompassHER2-RD trial**
  - T-DM1 + tucatinib vs. T-DM1 x 14 cycles
  - If HR+ must be node+

- **DESTINY Breast05**
  - Inoperable at presentation OR ypN1-3 at surgery
  - Trastuzumab deruxtecan vs. T-DM1 x 14 cycles

- **ASTEFANIA**
  - T-DM1+ atezolizumab vs. T-DM1 x 14 cycles
  - Stratify by PDL-1 status, centrally confirmed
  - Impassion050 – adding atezolizumab to neoadjuvant chemo/HP **did not** improve pCR rates *Huober J et al. J Clin Oncol epub June 28,2022*

Roadmap: Early stage HER2+ breast cancer



Huppert 2022