HER2-Positive Breast Cancer Updates

Bora Lim, MD
Associate Professor
Director, Translational Research for Morgan Welch IBC Program
Chief, Section of Translational Research
Breast Medical Oncology

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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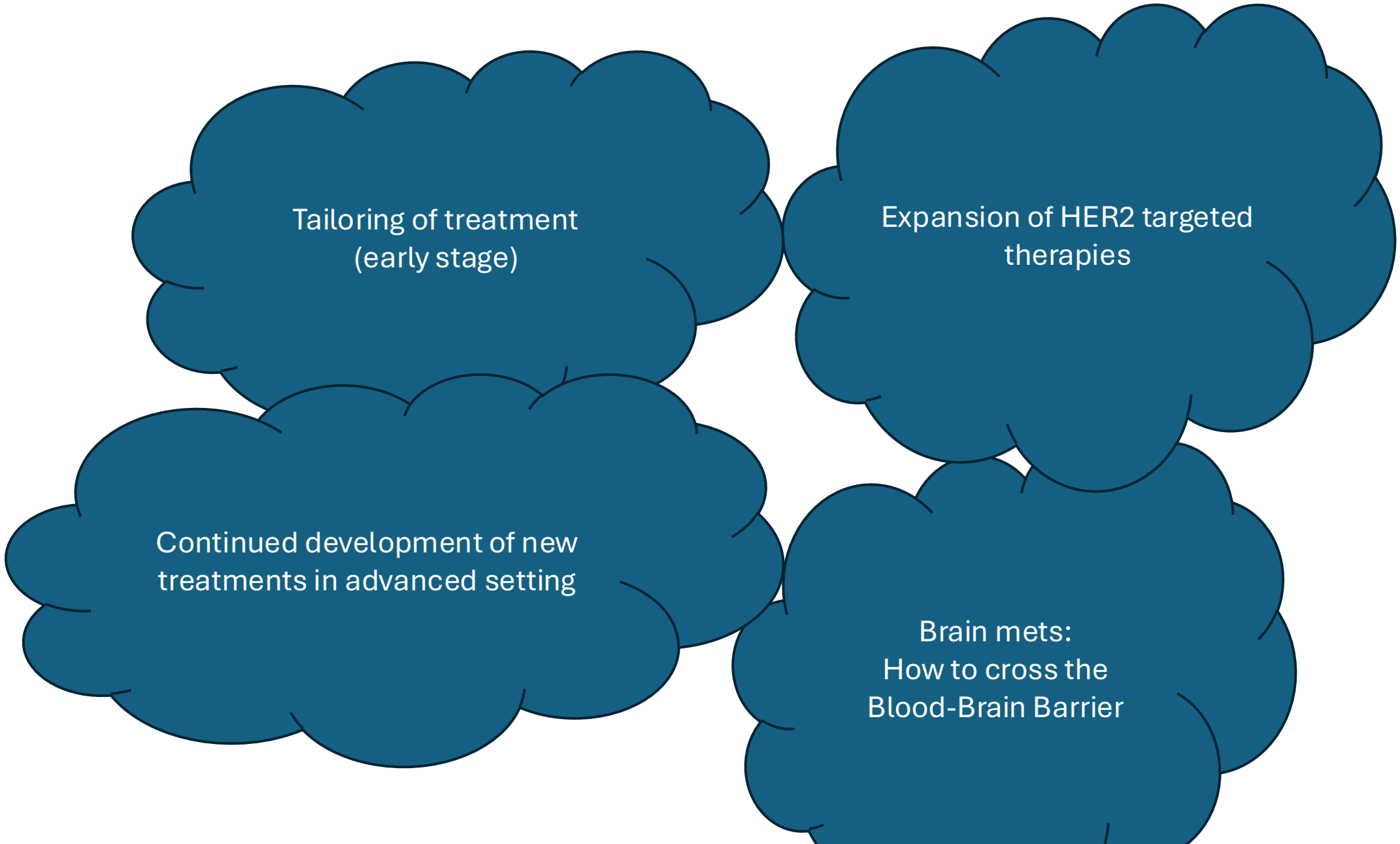
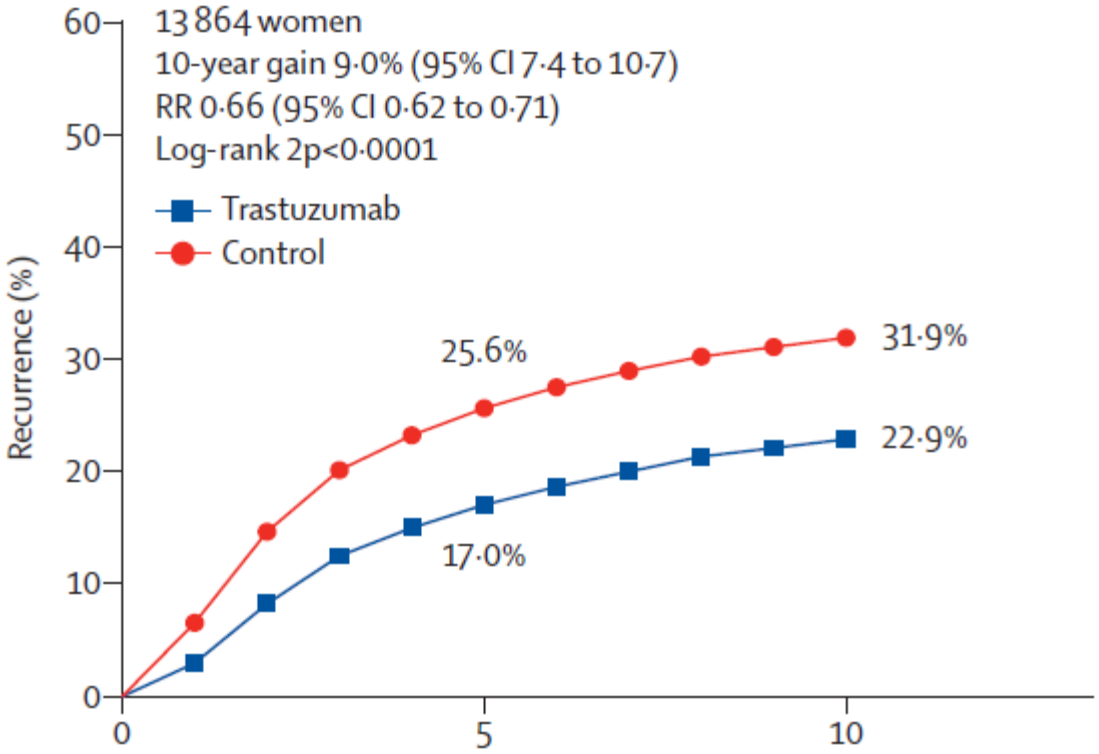
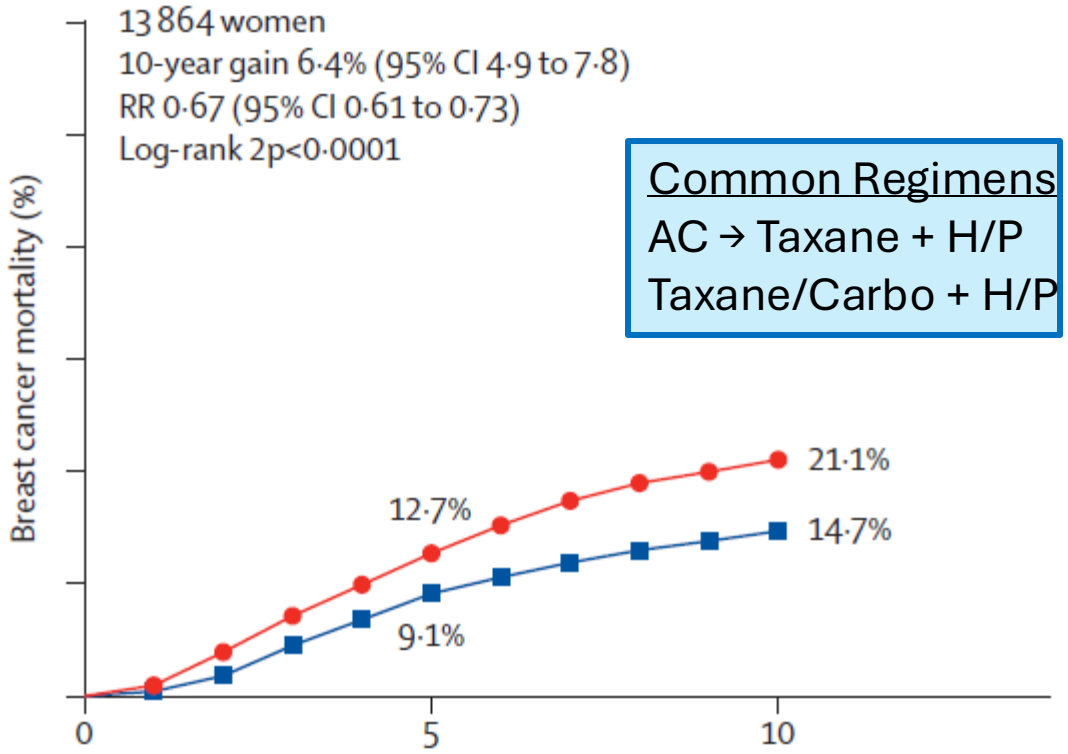

Tailoring of treatment
(early stage)
Expansion of HER2 targeted
therapies
Continued development of new
treatments in advanced setting
Brain mets:
How to cross the
Blood-Brain Barrier

Adjuvant Trastuzumab Benefit: Oxford Overview Analysis



Recurrence rates per year (% [events/woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Trastuzumab	4·10 (1469/35 853)	1·53 (422/27 648)	0·95 (75/7858)
Control	6·24 (1385/22 180)	1·87 (291/15 601)	1·12 (43/3835)
Rate ratio (95% CI)	0·62 (0·58–0·66)	0·83 (0·72–0·95)	0·91 (0·63–1·31)
from (O–E)/V	−284·0/591·3	−29·6/154·9	−2·5/25·3



Common Regimens
AC → Taxane + H/P
Taxane/Carbo + H/P

Death rates per year (%; 95% CI) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
	1·99 (1·85–2·13)	1·38 (1·25–1·51)	0·75 (0·57–0·93)
	2·73 (2·53–2·94)	2·18 (1·97–2·40)	1·15 (0·83–1·46)
	0·70 (0·63–0·76)	0·63 (0·56–0·70)	0·64 (0·47–0·88)
	−113·6/312·9	−84·2/179·8	−10·9/24·6

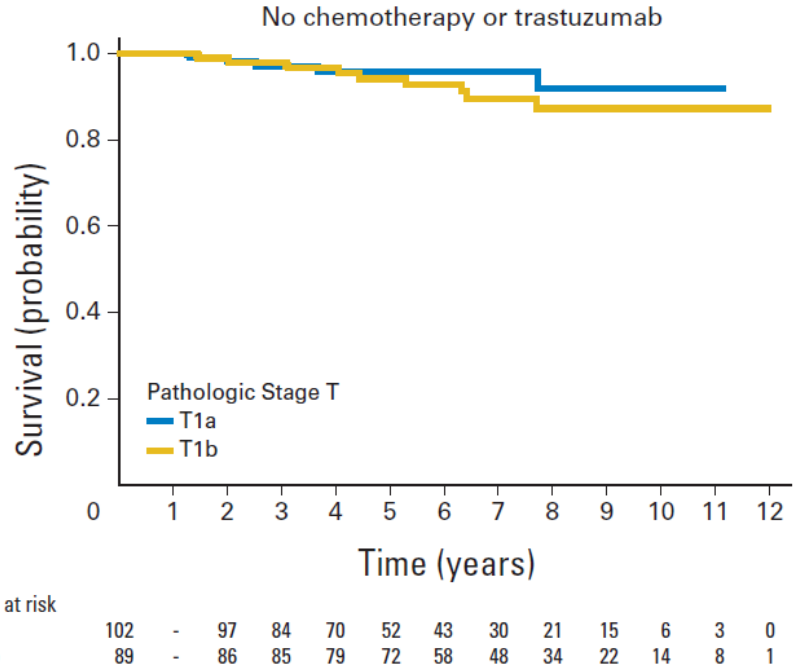
Early Breast Cancer Trialists' Collaborative group (EBCTCG) Lancet Oncol 2021

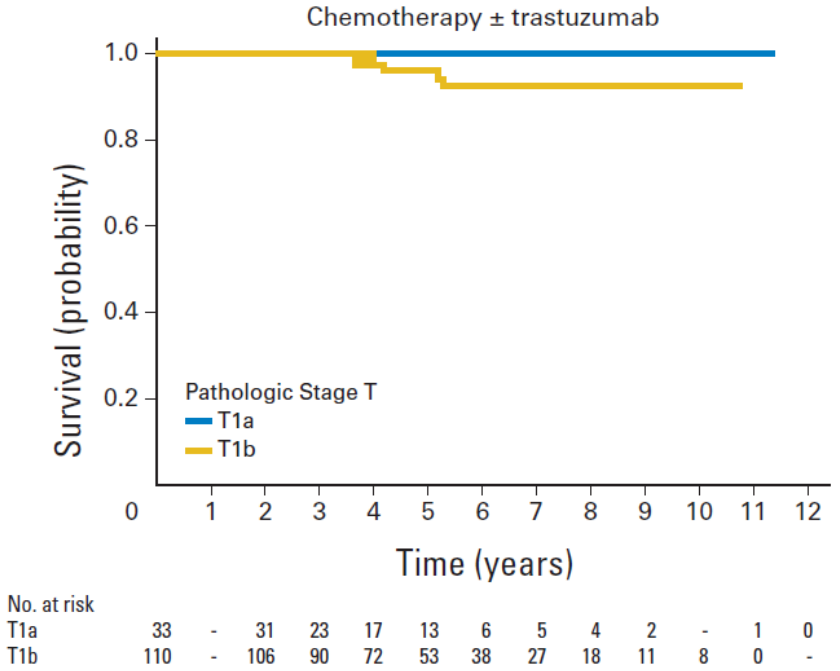
Low-Risk HER2+ Breast Cancer Outcomes Data from NCCN

The Dilemma of Studying Treatment Impact of Low-Risk Breast Cancer

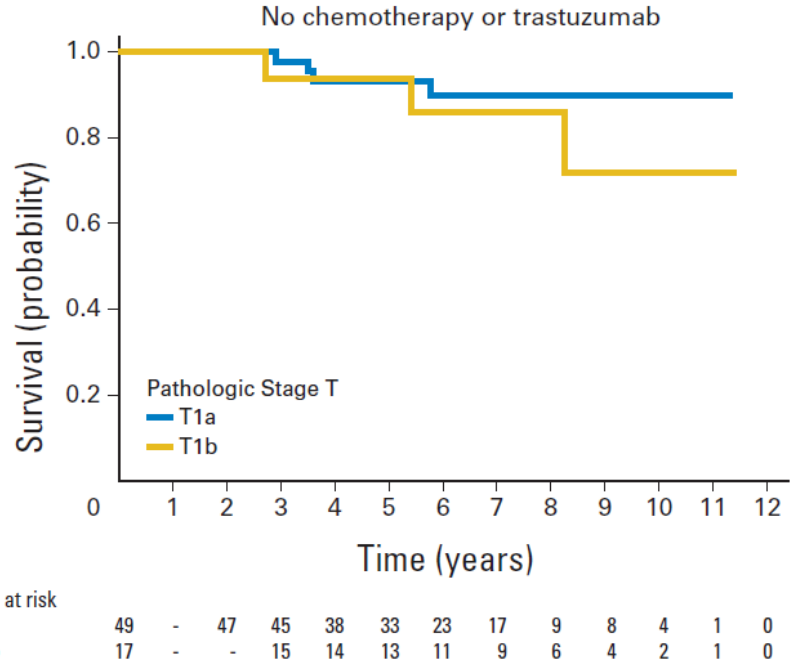
Retrospective Data Allows For Modeling of Single-Arm Studies

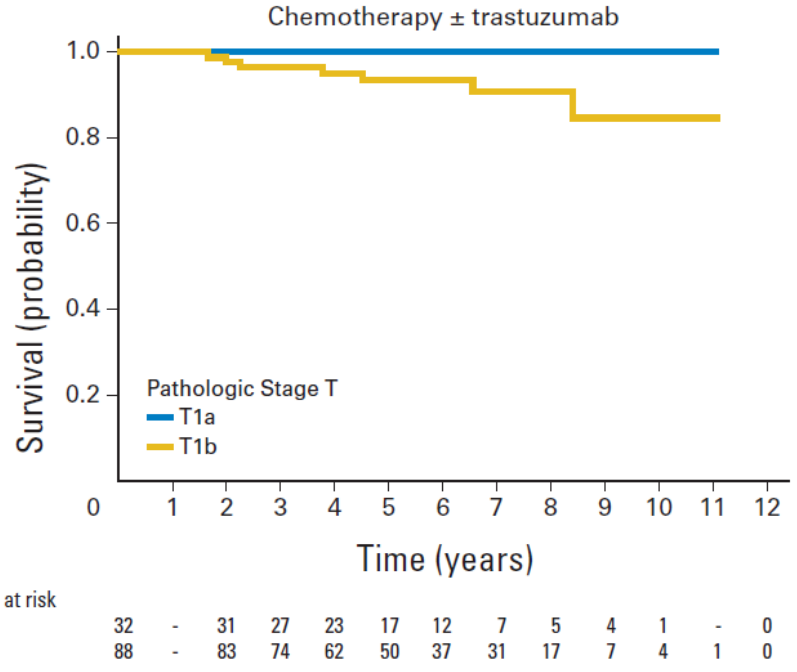
HER+ HR+





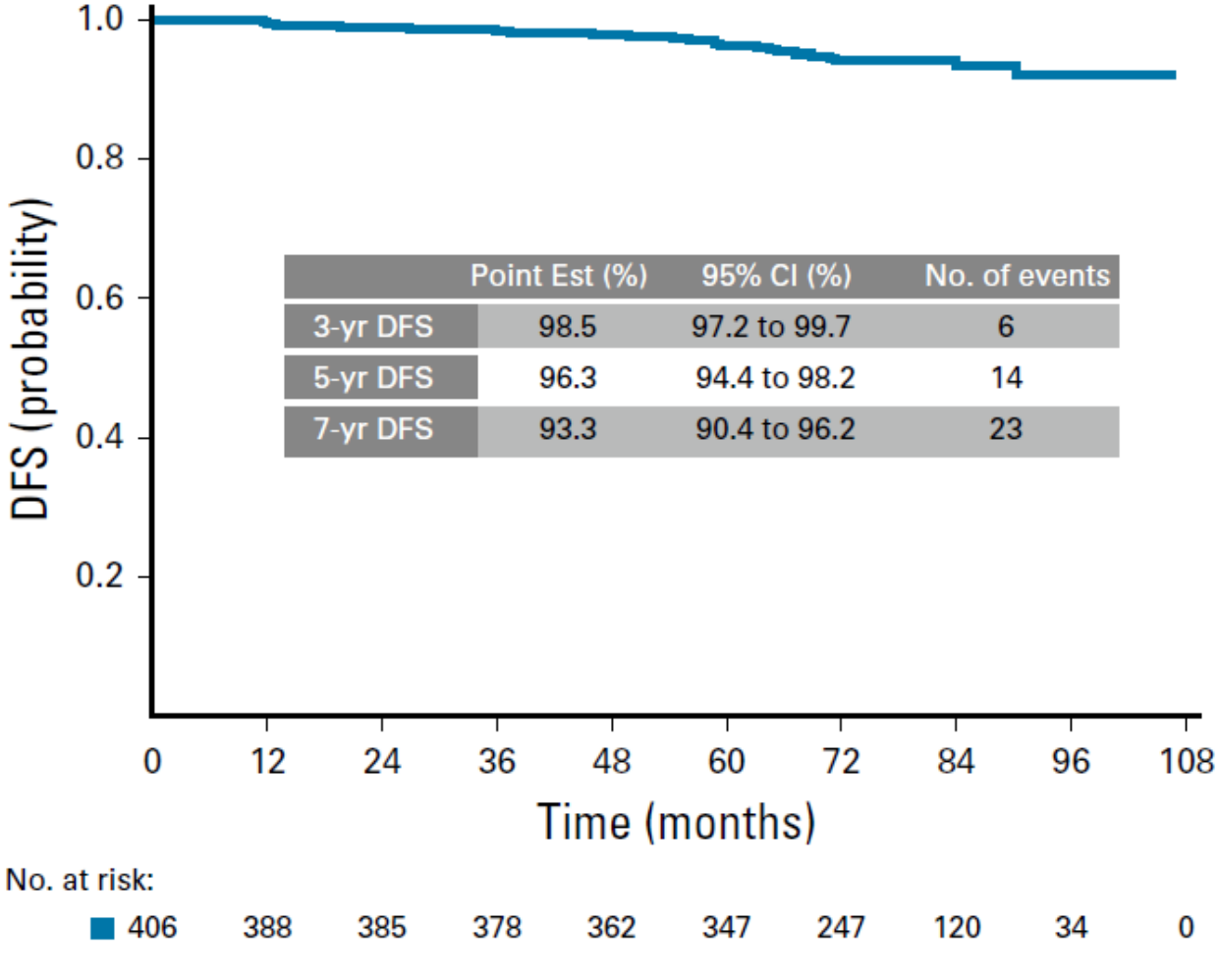
HER+ HR-



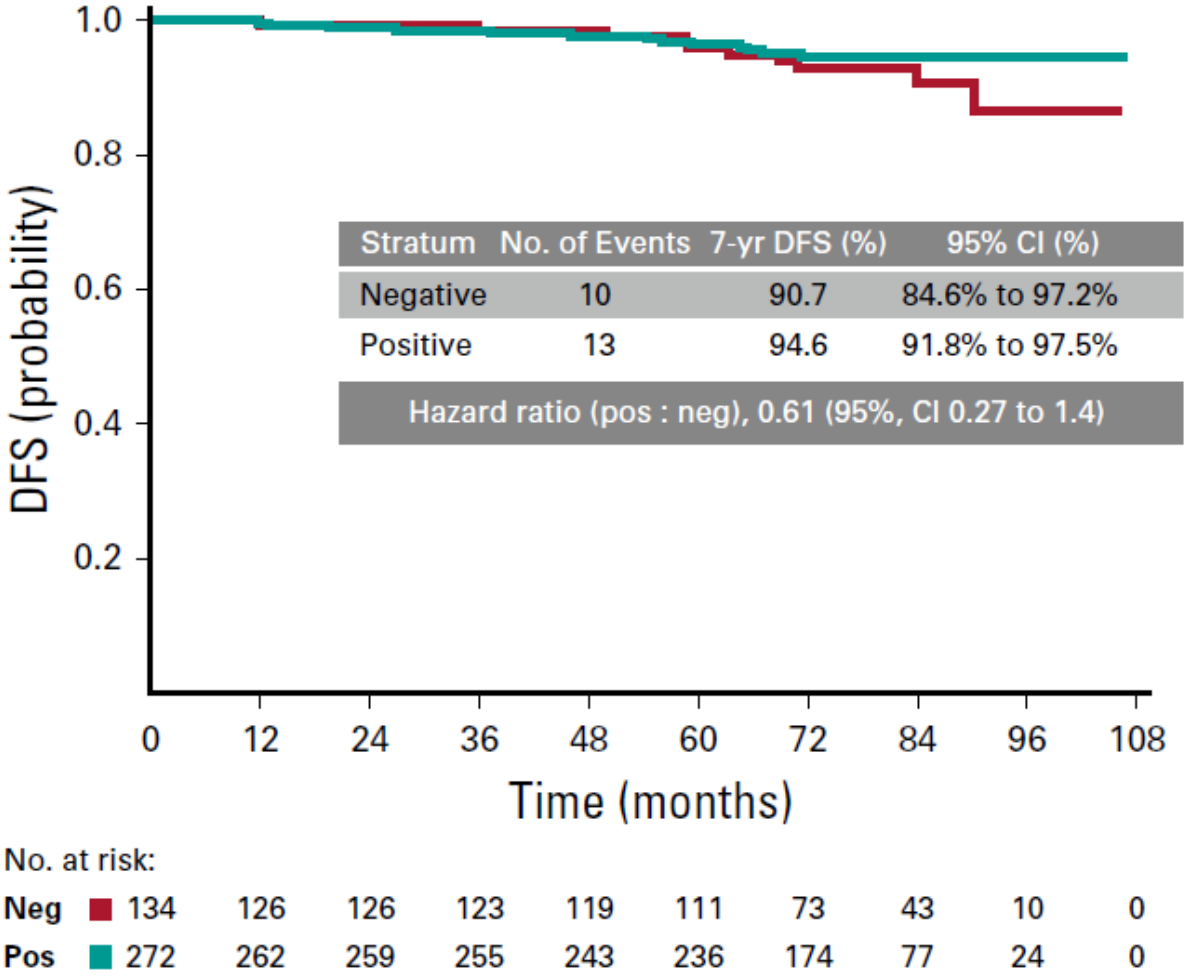


Vaz-Luis I et al. J Clin Oncol 2014

APT Trial for 1-3 cm/Node-Negative HER2+ Breast Cancer
Single-Arm Trial: Weekly Paclitaxel x 12 + Trastuzumab x 1 Year Total



	Point Est (%)	95% CI (%)	No. of events
3-yr DFS	98.5	97.2 to 99.7	6
5-yr DFS	96.3	94.4 to 98.2	14
7-yr DFS	93.3	90.4 to 96.2	23



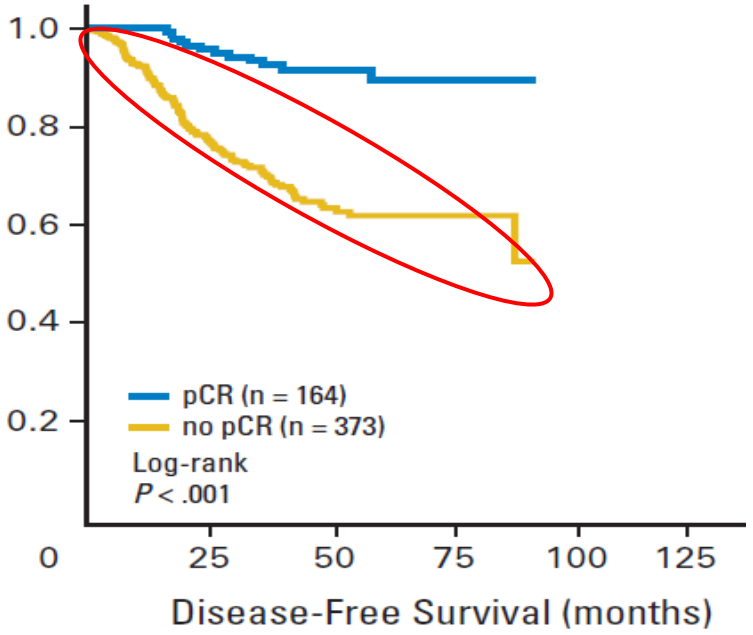
Stratum	No. of Events	7-yr DFS (%)	95% CI (%)
Negative	10	90.7	84.6% to 97.2%
Positive	13	94.6	91.8% to 97.5%

Hazard ratio (pos : neg), 0.61 (95%, CI 0.27 to 1.4)

Tolaney S et al. New Eng J Med 2015; Tolaney S et al. J Clin Oncol

Pathological Response to Neoadjuvant Therapy
Rationale of down-tailoring

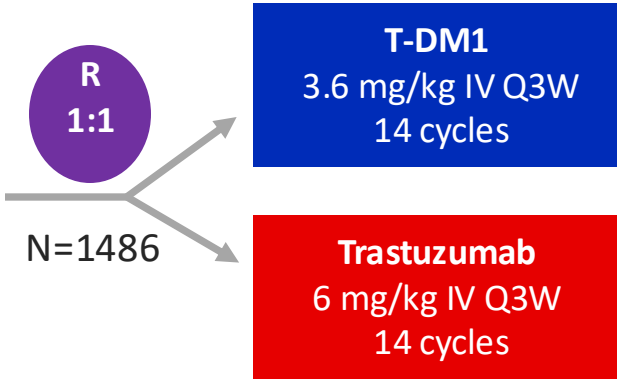
Outcomes after HER2-Directed Neoadjuvant Therapy

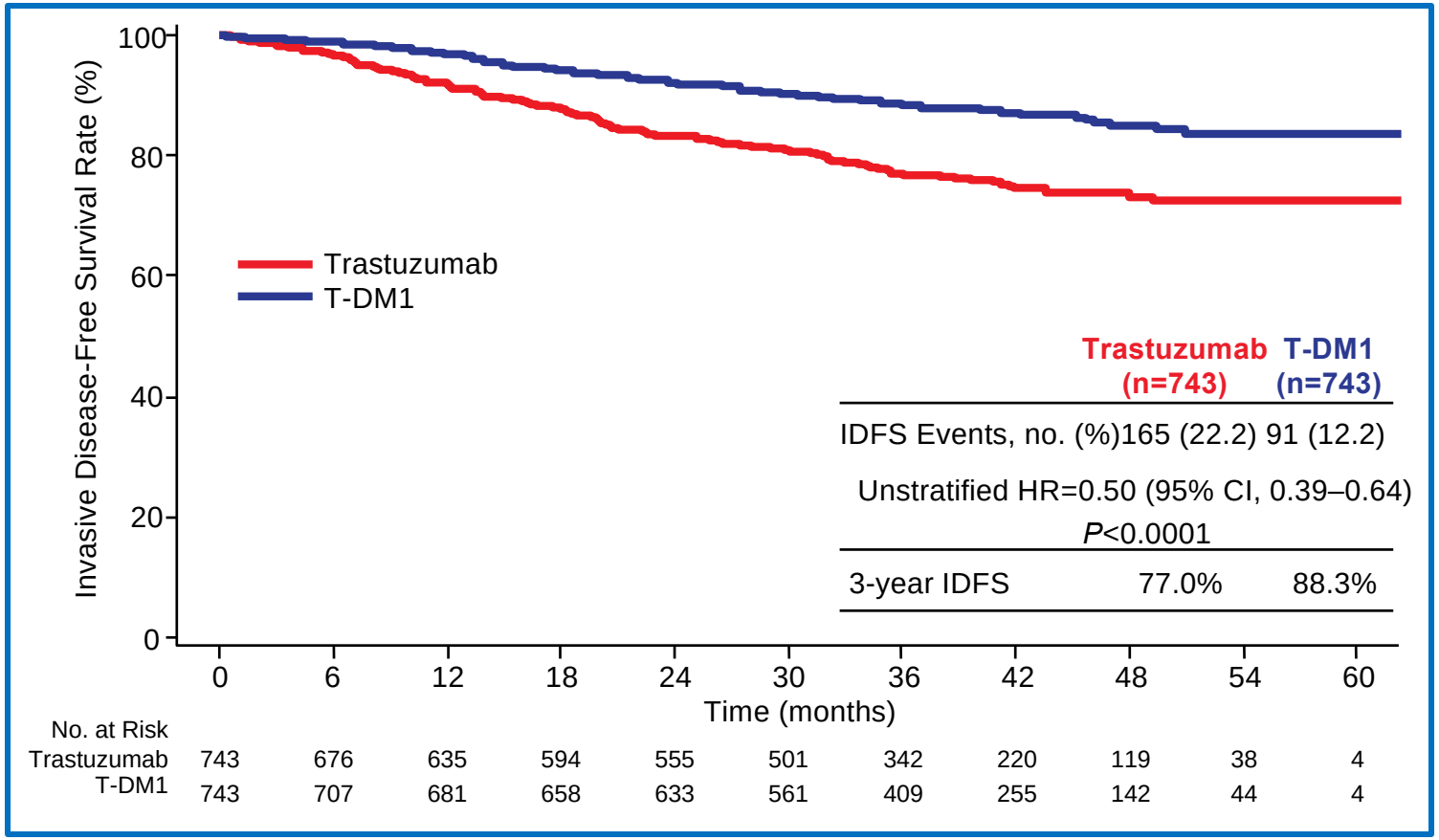


von Minckwitz G, et al. J Clin Oncol 2012

Led to pathological response-adapted trial
cT1c-4/N0-3 HER2+ (central review)
6+ cycles chemo,
9+ weeks trastuzumab

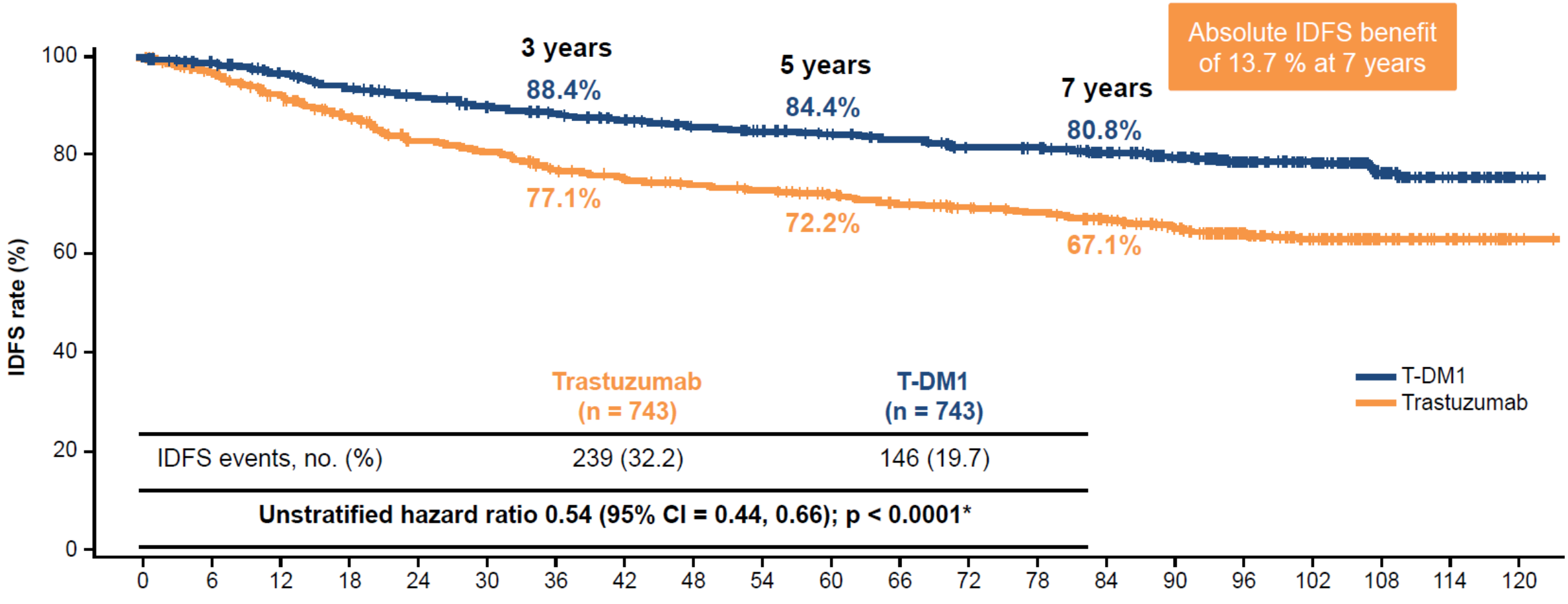
KATHERINE Trial





von Minckwitz G et al. NEJM 2018.

KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



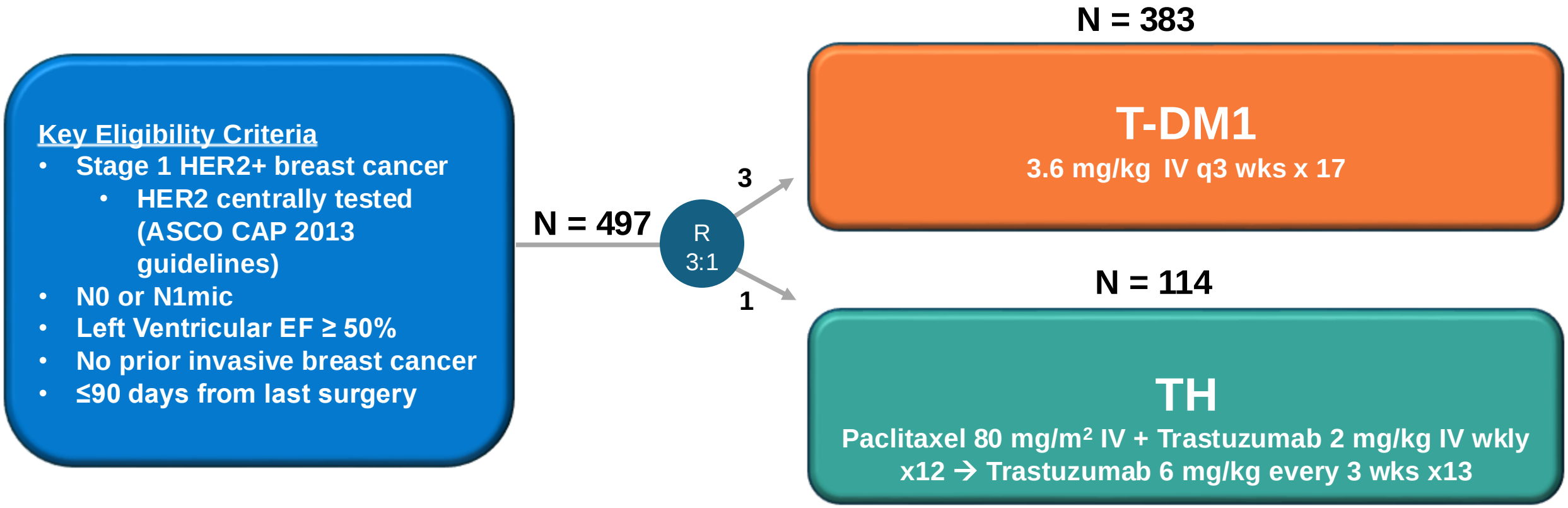
No. at risk																					
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Loibl S et al. SABCS 2023. Abstract GS03-12.

Study Design: ATEMPT Trial

Designed and Powered to Compare Toxicities and Estimate (Not Compare) Disease-Free Survival



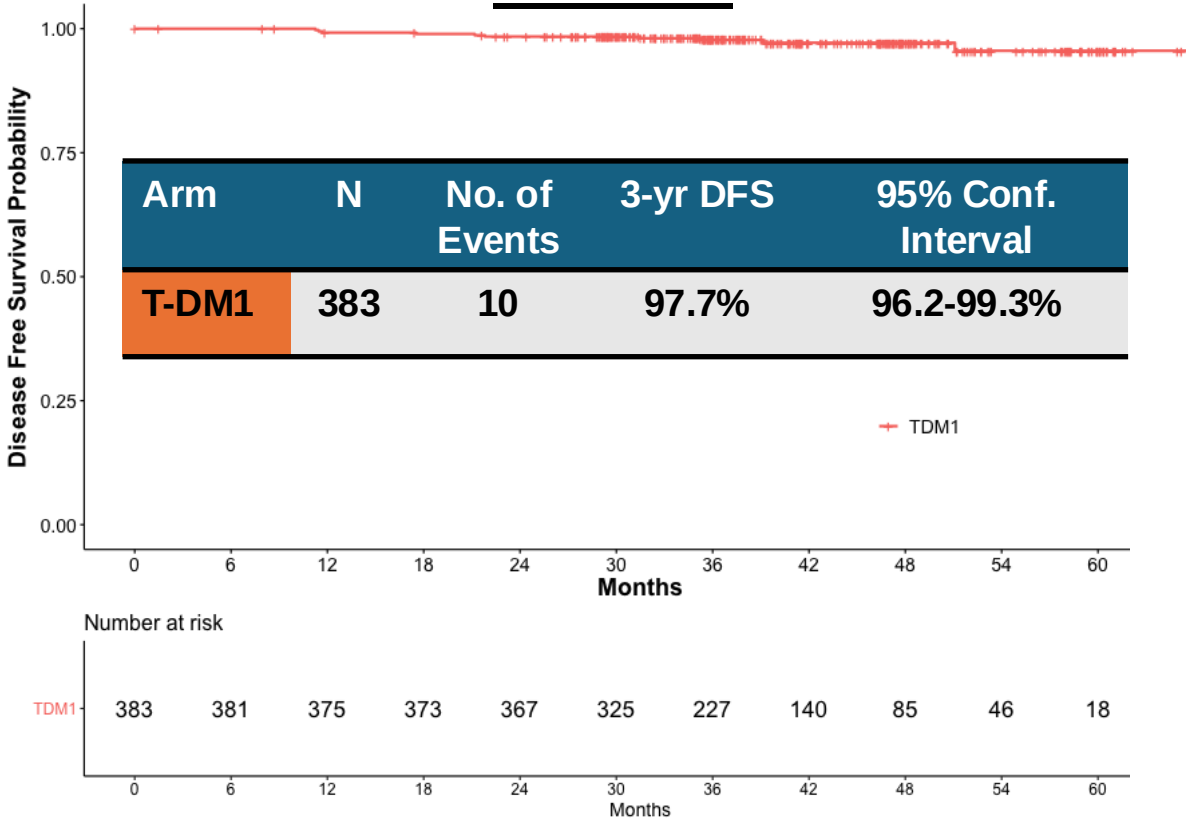
Stratification factors:
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

*Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

Tolaney S et al. SABCS 2019. Abstract GS1-05.

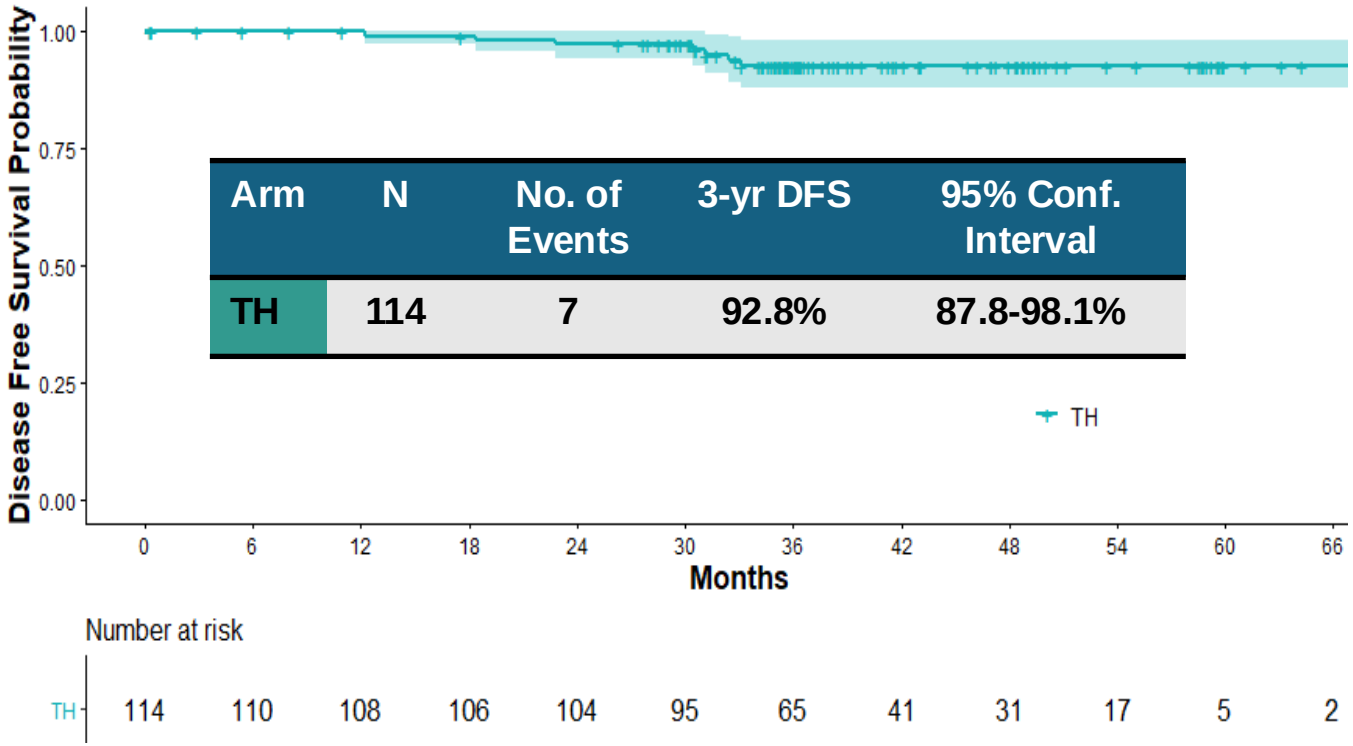
Disease-Free Survival: ATEMPT

T-DM1



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
T-DM1	383	10	97.7%	96.2-99.3%

TH

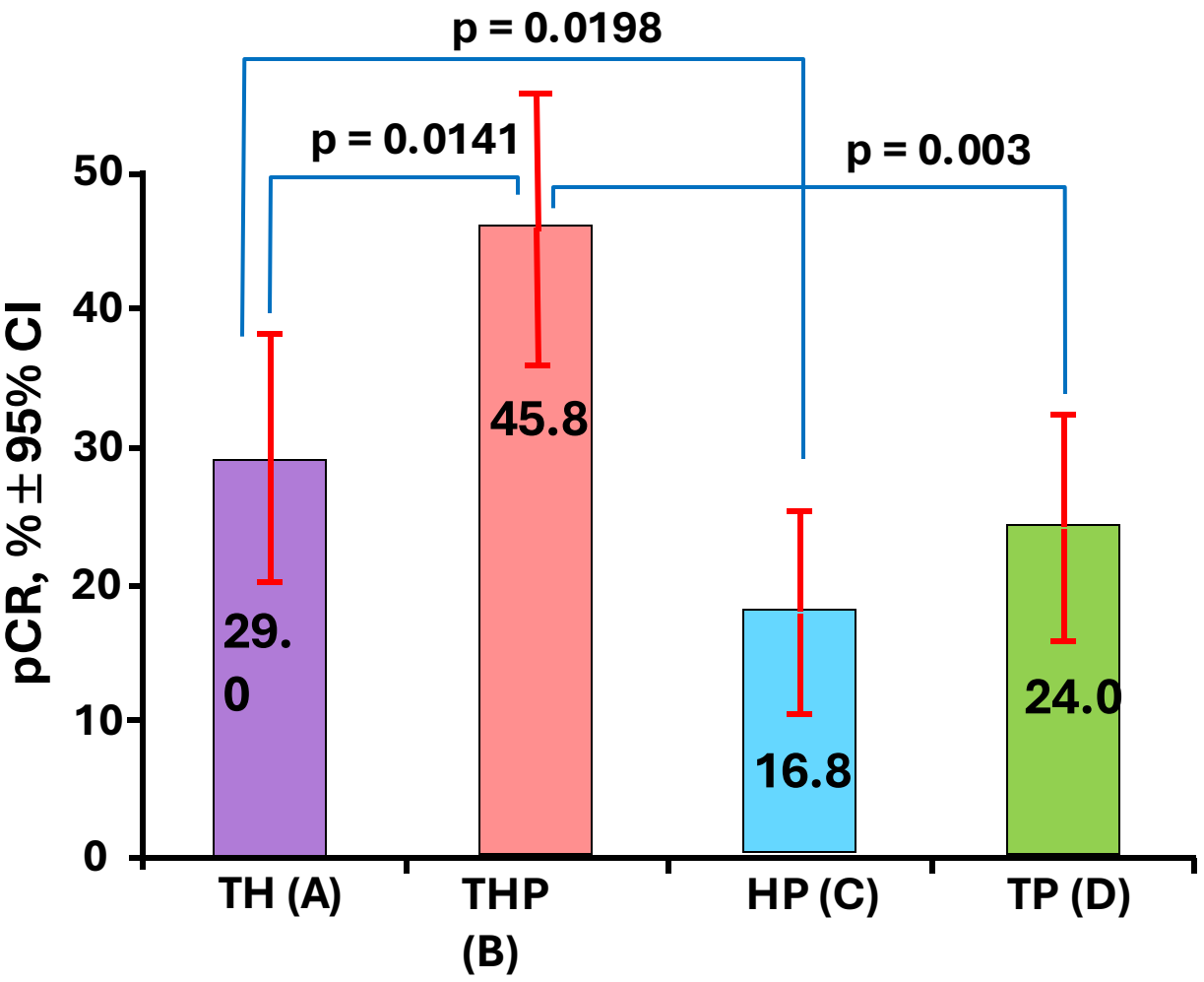


Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
TH	114	7	92.8%	87.8-98.1%

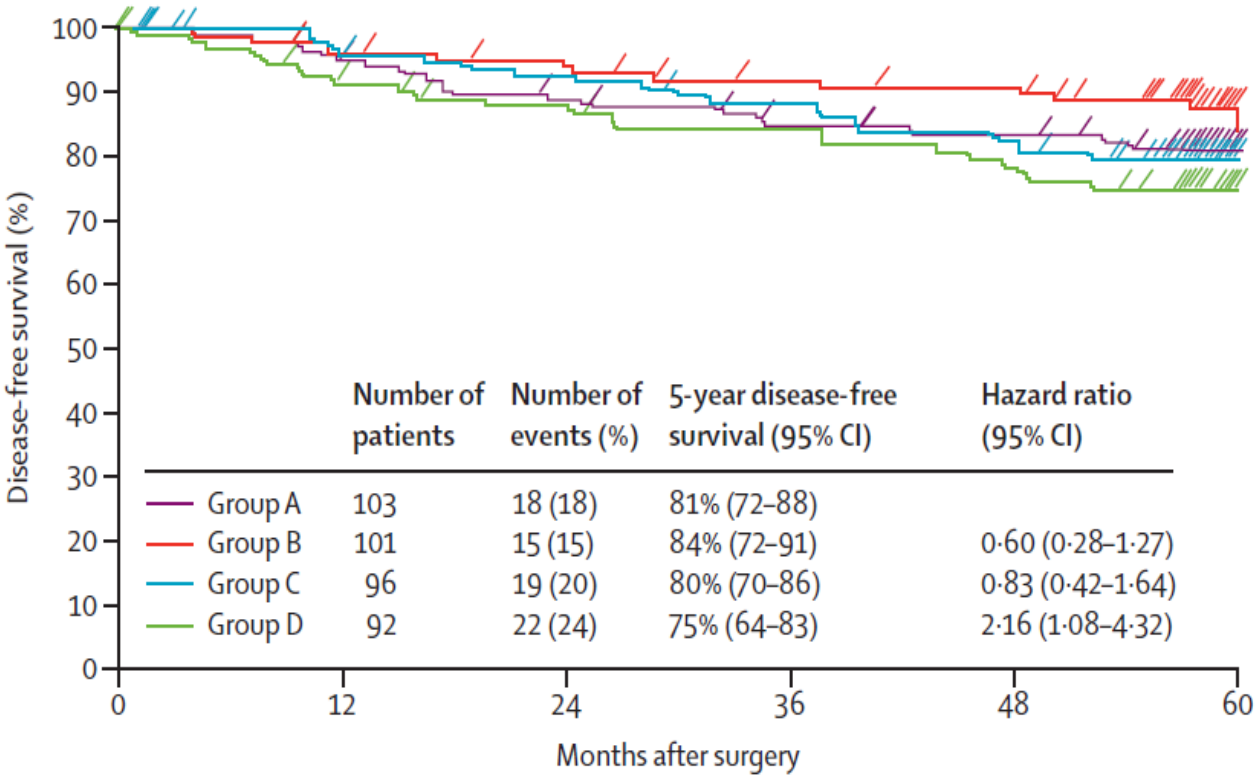
	Arm 1: T-DM1 (n = 383)	Arm 2: TH (n = 114)
Symptomatic Congestive Heart Failure	3 (0.8%)	1 (0.9%)
Asymptomatic declines in LVEF (≥15%)	5 (1.3%)	7 (6.1%)

Tolaney S et al. SABCS 2019. Abstract GS1-05.

NeoSphere Trial: Neoadjuvant Docetaxel, Pertuzumab and Trastuzumab pCR Rates in Different Combinations - ITT Population Summary



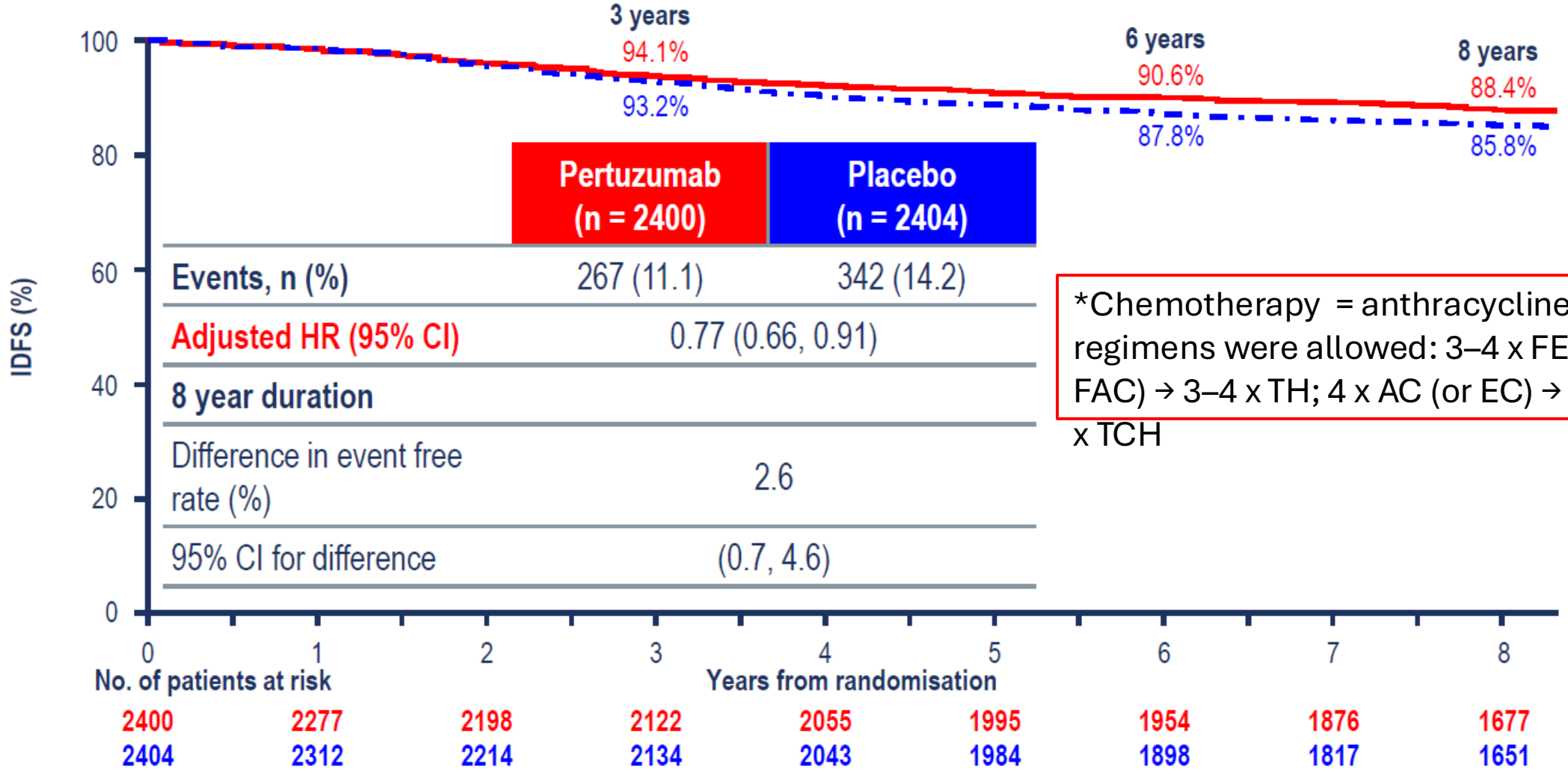
H, trastuzumab; P, pertuzumab; T, docetaxel



Led to accelerated FDA approval of docetaxel, trastuzumab and pertuzumab for stage II/III HER2+ breast cancer

Gianni L et al. Lancet Oncol 2012; Gianni L et al. Lancet Oncol 2016.

APHINITY Trial: Phase III Trial of Adjuvant Chemotherapy* with Trastuzumab +/- Pertuzumab x 1 Year (Concurrent and Maintenance) – 8.4 Year F/U



*Chemotherapy = anthracycline/(TCH) regimens were allowed: 3–4 x FEC (or FAC) → 3–4 x TH; 4 x AC (or EC) → 4 x TH; 6 x TCH

Loible, S et al. ESMO 7/14/2022 Plenary

Summary: Adaptive Therapy (Escalation and De-escalation) in HER2+ Early Stage Breast Cancer

Adjuvant (up front Surgery)

(best for cT1+/N1+)

Node Negative </= 2cm

Paclitaxel + Trastuzumab

Consider TCH or for larger node-negative

> 2cm or Node+

Chemotherapy + Trastuzumab + Pertuzumab

Neoadjuvant

(best for cT2+/N1+)

Chemotherapy + Trastuzumab + Pertuzumab

Surgery

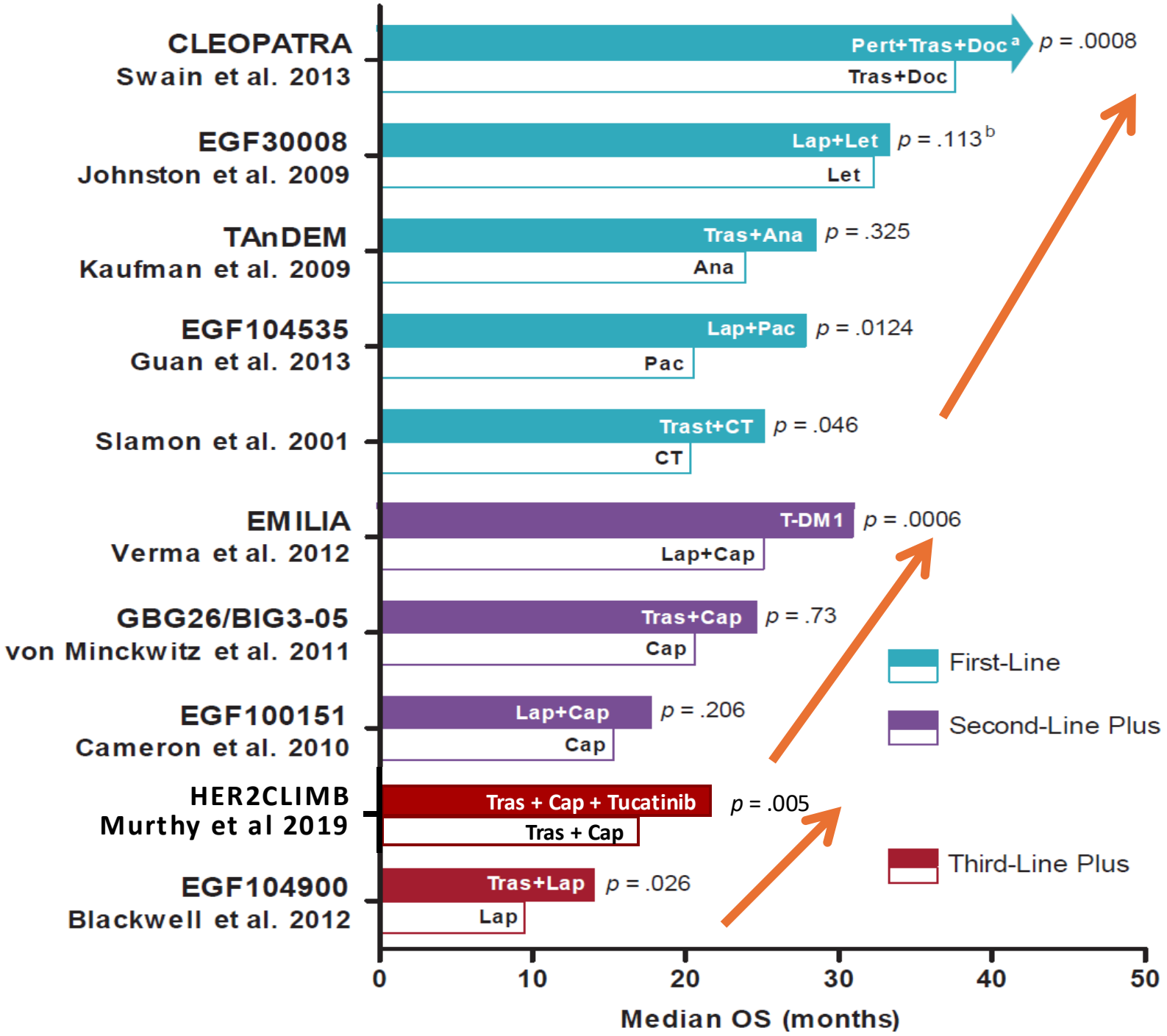
PCR

Trastuzumab +/- Pertuzumab
To complete 1 year
TP for bulkier disease at presentation

No PCR

TDM-1 every 3 weeks x 14

Neratinib for Higher Risk, HR+



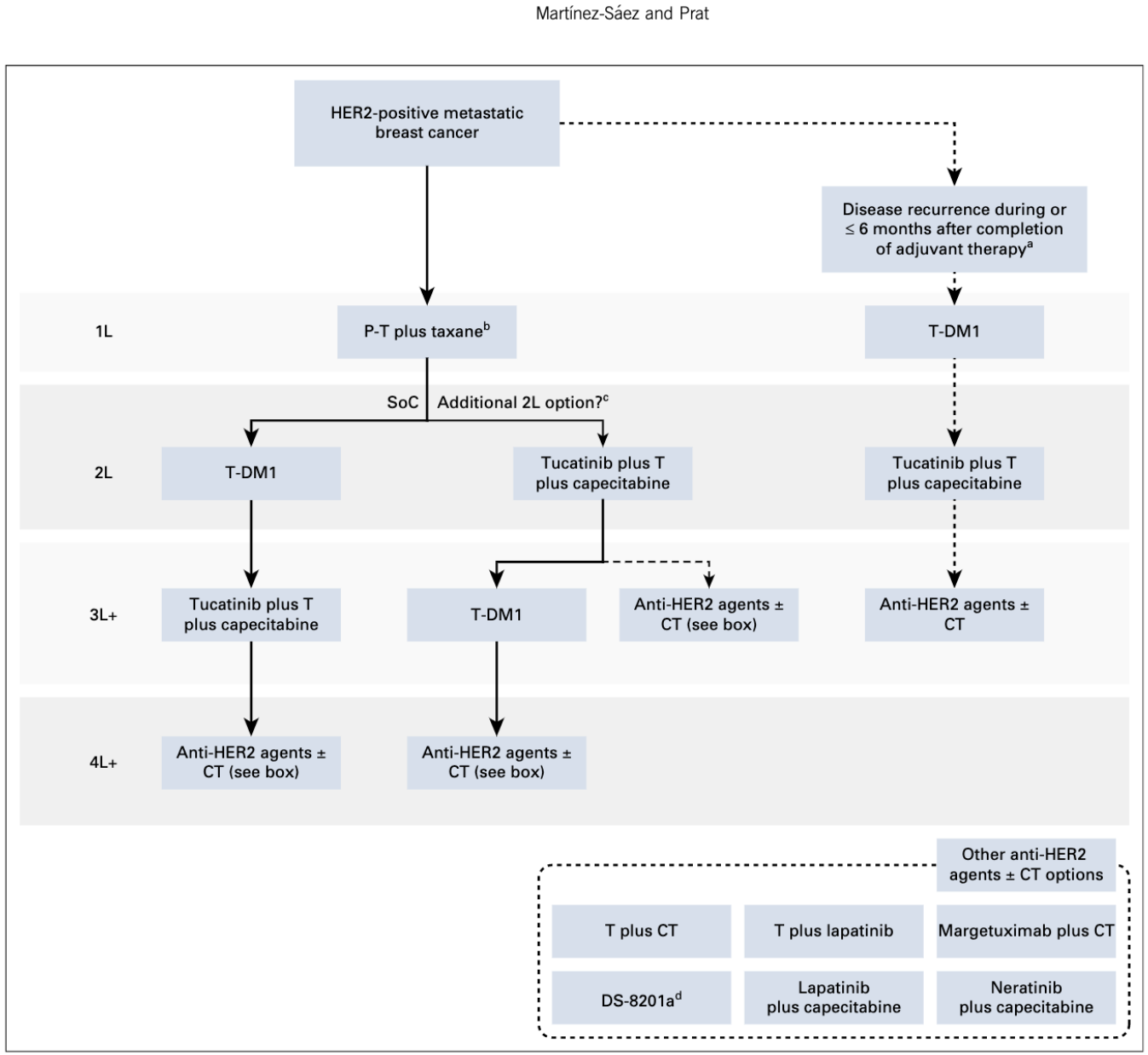
HER2+ Metastatic Breast Cancer:

Serial Improvements in Survival with Newer Agents and Combinations

BUT.... Rare "Cures"

Modified from:
Verma S, et al. Oncologist 2013

Current recommended mHER2 therapy – in 2022



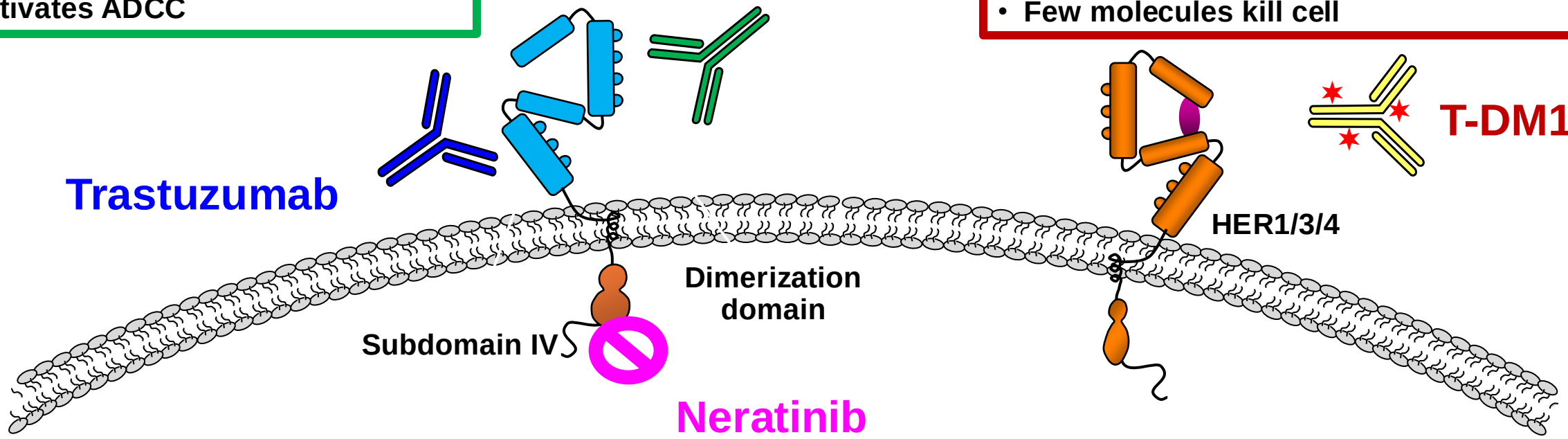
- But, also dependent on the changes in NAT and AT
- Novel combination with other ADC
- ADC/Ab + TKI still in question
- Combination with immunotherapy has not shown clear benefit

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

Trastuzumab, Pertuzumab, Neratinib and T-DM1: Complementary Mechanisms

Pertuzumab:
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

T-DM1:
- Immunoconjugate with emtansine
- Internalizes and dissociates
- Few molecules kill cell



Trastuzumab:
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Lapatinib, Neratinib:
- Inhibit intracellular kinase domain of HER2, HER1 (EGFR)

Landscape of HER2 Targeted Therapies and Emerging New Agents

Monoclonal Antibodies
- Trastuzumab
- Pertuzumab
- Margetuximab
- Patritumumab

Bispecific Antibodies
- Zanidatamab (ZW25)
- Zenocutuzumab (MCLA 128)
- GBR 1302 (HER2xCD3)

Immunological Combinations
- Checkpoint blockade
- TGF-β/PD-L1 bispecific peptide
- Anti-HER2/anti-CD3 bispecific Ab

Small Molecule Inhibitors
- Lapatinib
- Neratinib (for MBC)
- Tucatinib
- Pyrotinib
- Poziotinib
- Afatinib
- TAS-0728
- ZN-A-1041

Antibody-Drug Conjugate (ADCs)
- T-DM1
- Trastuzumab deruxtecan (DS 8201a)
- ARX788
- PF-06804103
- A166
- MEDI-4276

Other Receptor Pathway Mediators
- IGF-IR
- PI3K
- mTOR
- HSP90
- HDAC
- CDK 4/6
- PARP/DNA Repair

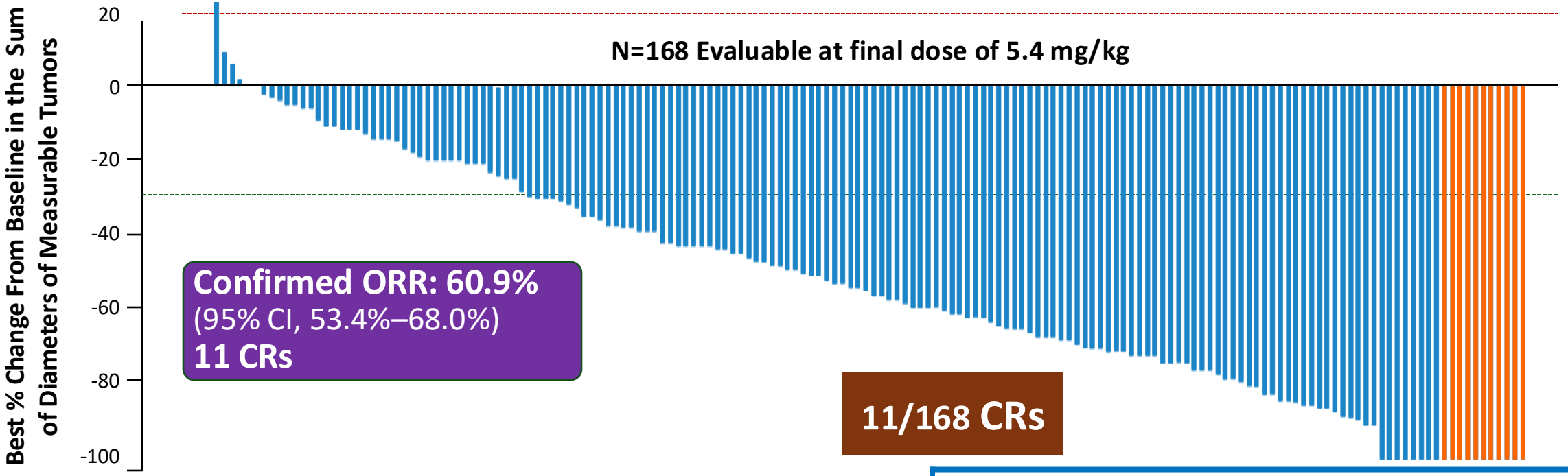
HER2-Targeted Combinations
- Immunoconjugates + TKIs

Approved

Approved since 2019

Investigational

DESTINY-Breast01 Trial: Phase 2 Study of Trastuzumab Deruxtecan (T-DXd)

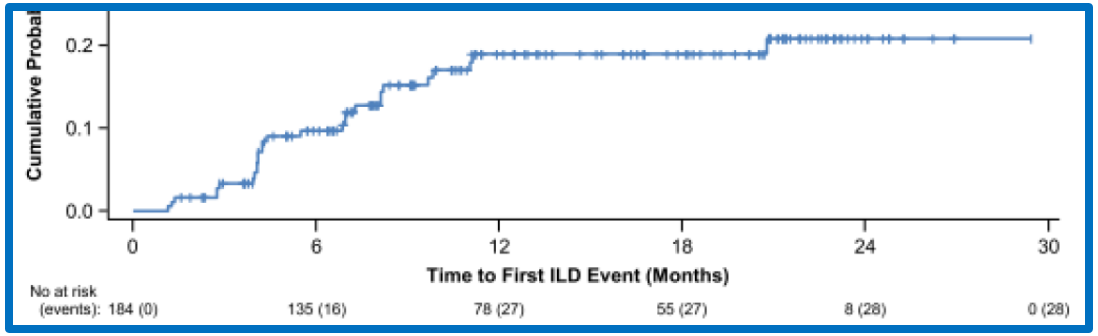


Median lines of therapy = 6 (range 2-17)	Patients, % T-DXd 5.4 mg/kg (N=184)
Trastuzumab	100
T-DM1	100
Pertuzumab	65.8
Other anti-HER2 therapies	54.3
Hormone therapy	48.9
Other systemic therapy	99.5

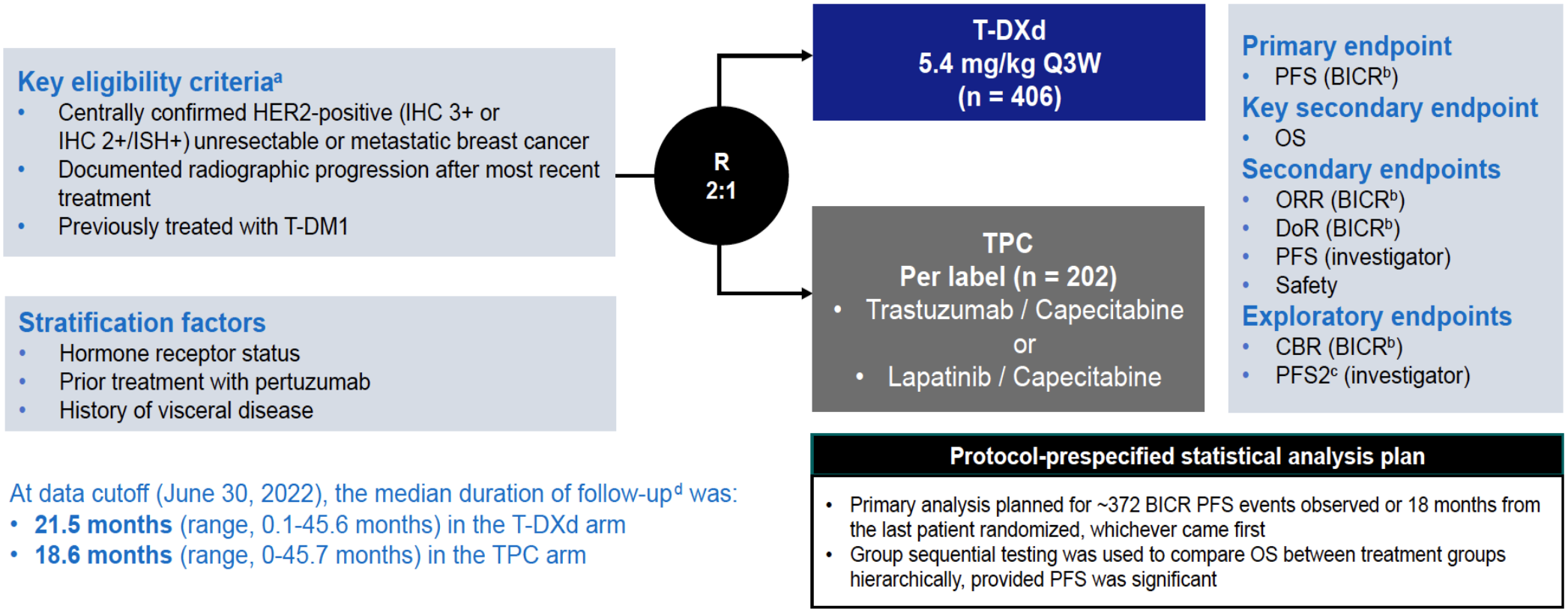
Modi S, et al NEJM 2019

Interstitial Pneumonitis at 5.4 mg/kg (N=184)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**



DESTINY-B02: Randomized, Phase 3, open label, multicenter study



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

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.

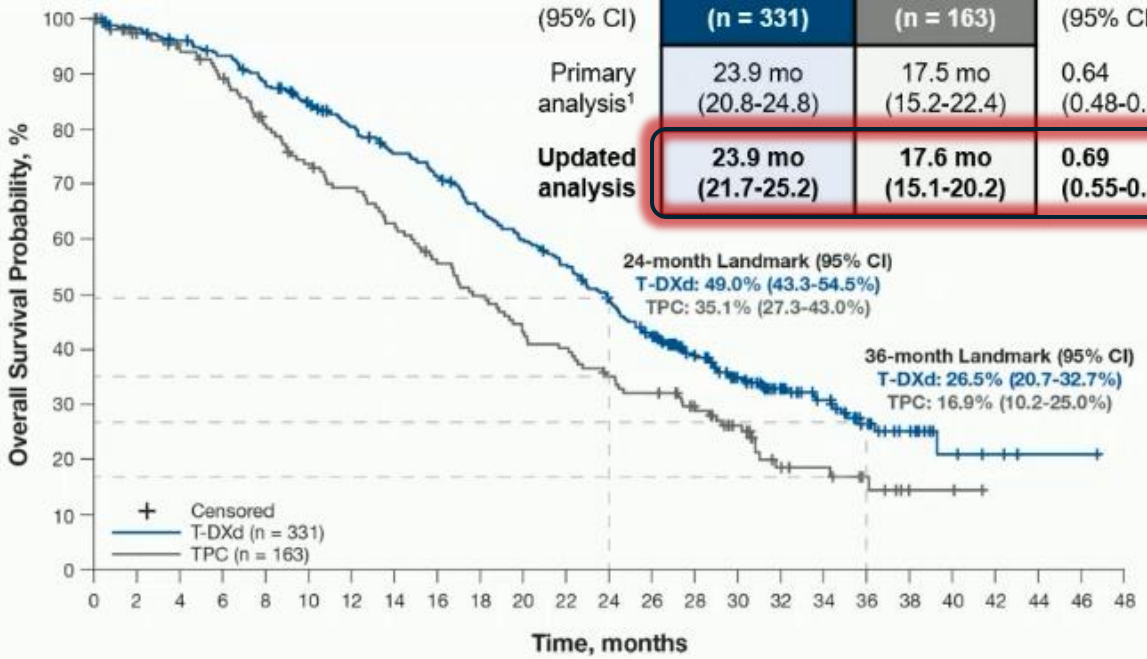
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization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

Krop I, et al SABCS 2022

Updated OS (median 32 months) by investigator

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



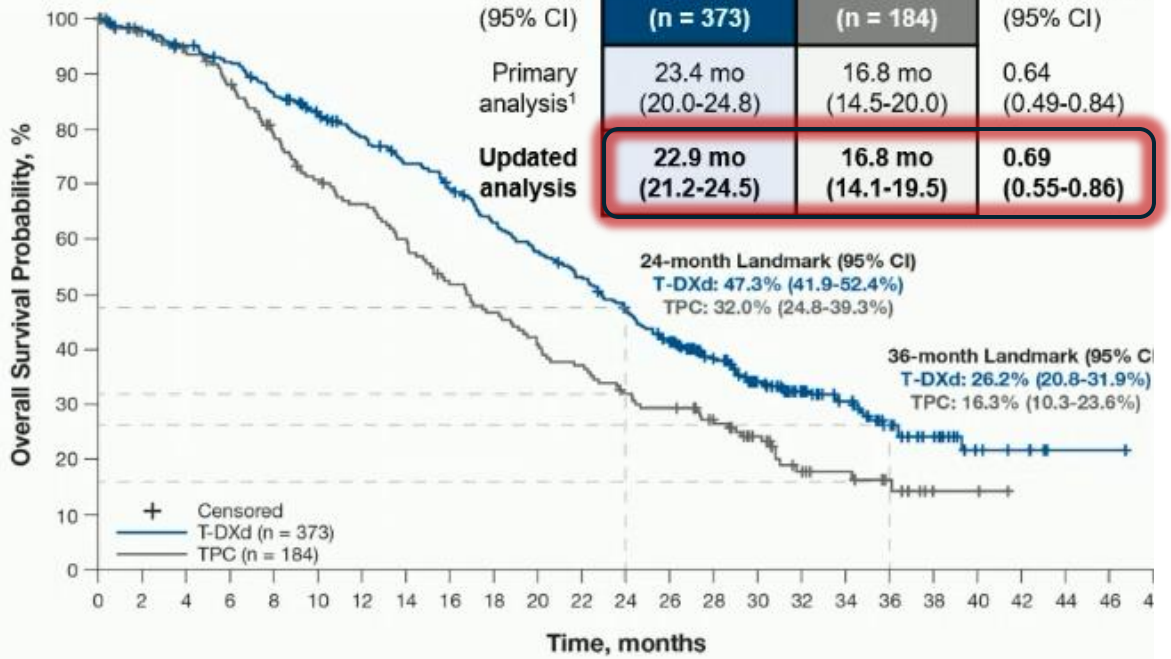
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 156 147 136 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 66 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 206 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 16 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

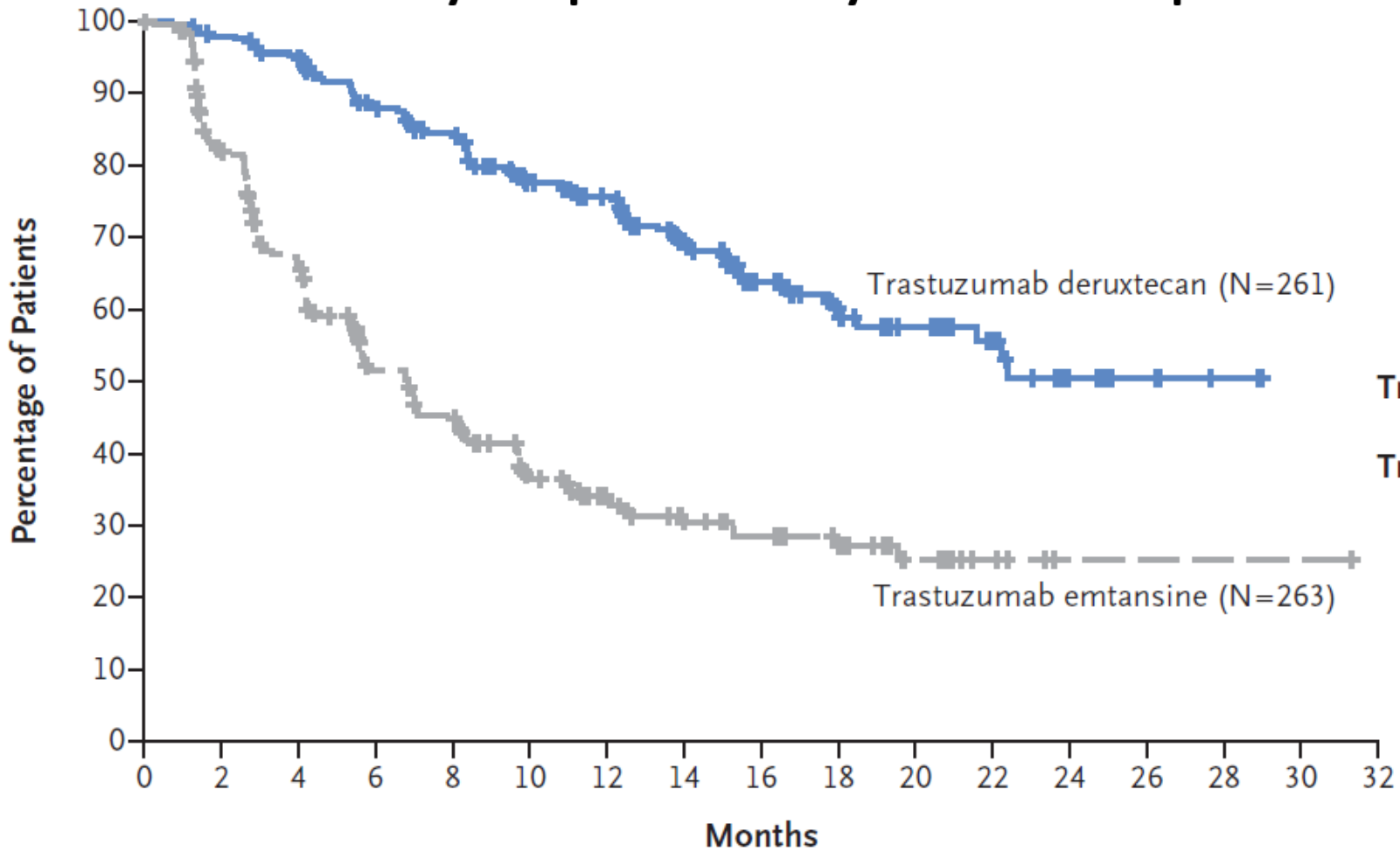
HR, hormone receptor; mo, month; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

Modi S, el at. ESMO 2023

Destiny-Breast03 Randomized trial T-DXd vs. T-DM1

Primary Endpoint: PFS by blinded independent central review



	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

No. at Risk

Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2	
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	1	0

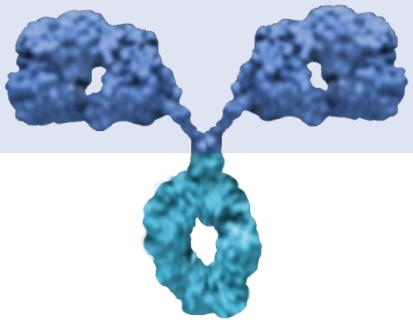
Cortés J, et al. NEJM 2022

Margetuximab: Fc engineering Alters Fc Receptor Affinities

Trastuzumab

Fab:

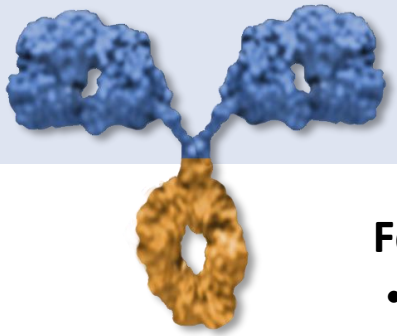
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



Fc:

- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab[1,2]



Fab:

- Same specificity and affinity
- Similarly disrupts signaling

Fc engineering:

- ↑ Affinity for activating Fcγ RIIIA (**CD16A**)
- ↓ Affinity for inhibitory Fcγ RIIB (**CD32B**)

SOPHIA Study Design[3]

HER2+ advanced breast cancer

- **≥2 prior anti-HER2 therapies, including 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)

→ ***1:1 Randomization (N=536)***

→ **Arm 1**
Margetuximab (15 mg/kg Q3W) + **chemotherapy** in 3-week cycles

→ **Arm 2**
Trastuzumab (8 mg/kg loading → 6 mg/kg Q3W) + **chemotherapy** in 3-week cycles

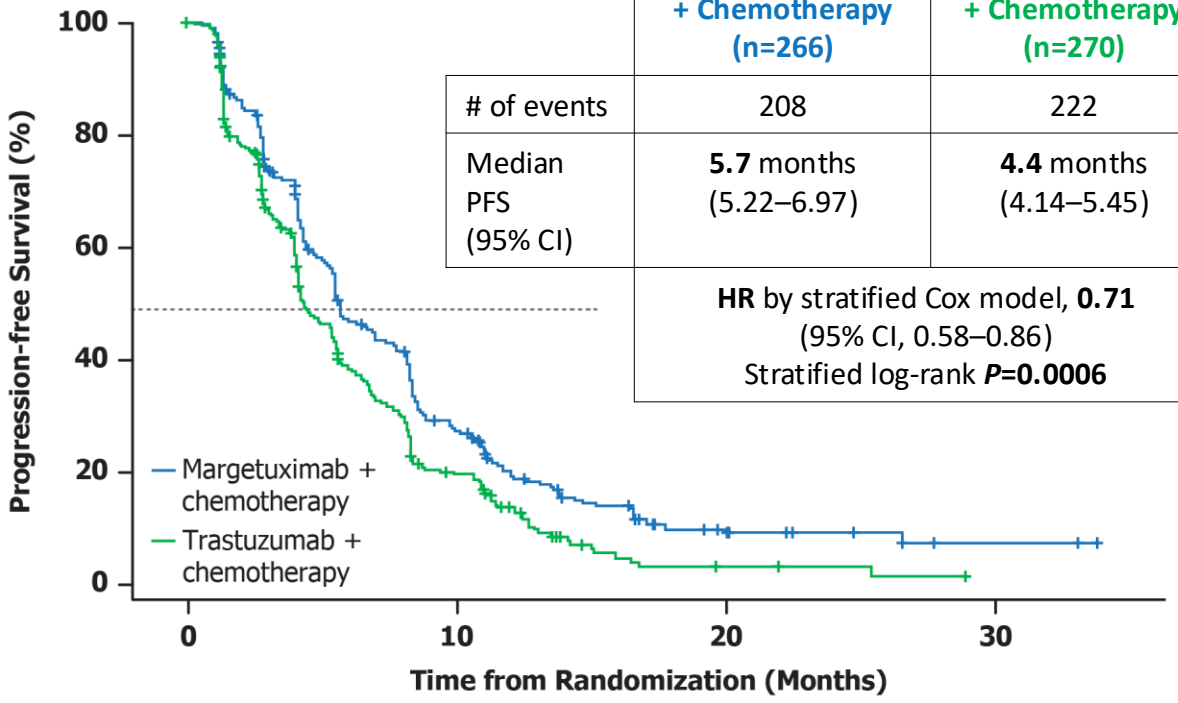
1. Nordstrom JL, et al. Breast Cancer Res 2011; 2. Stavenhagen JB, et al. Cancer Res 2007
3. Rugo, HR, et al. SABCS 2019

SOPHIA Trial - ITT Population: 2nd Interim OS Analyses[b] (n=536)

Investigator-Assessed PFS

29% Risk Reduction of Disease Progression

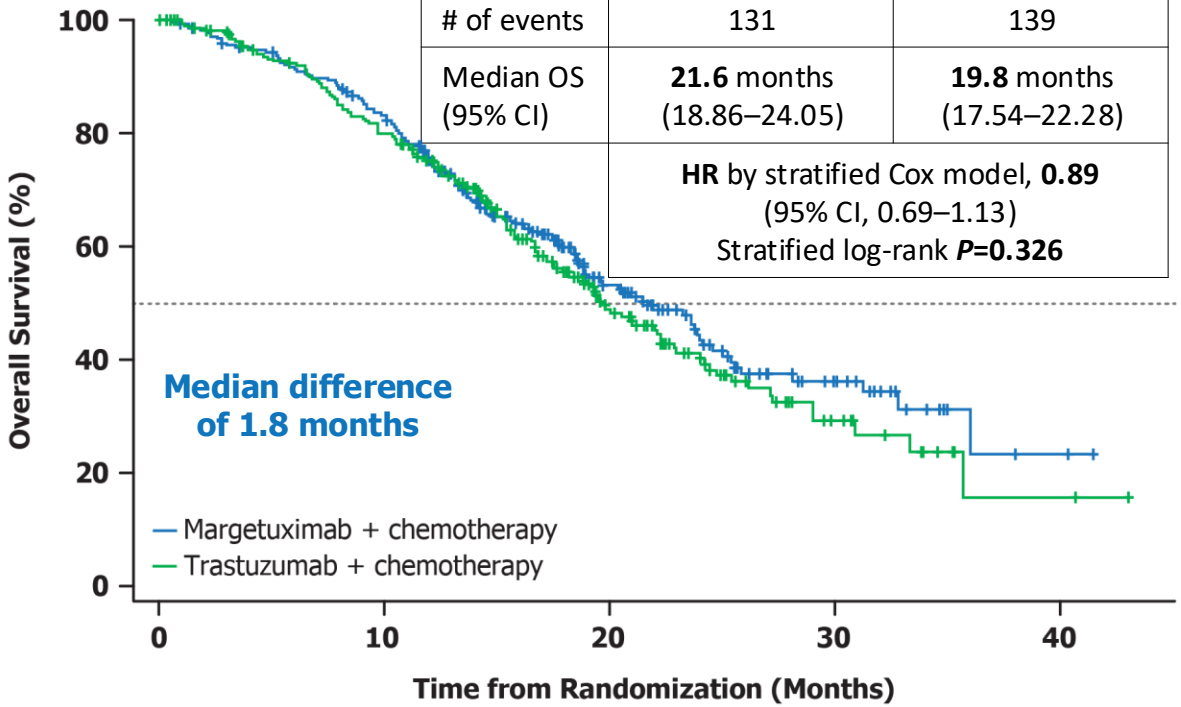
	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	208	222
Median PFS (95% CI)	**5.7** months (5.22–6.97)	**4.4** months (4.14–5.45)
	HR by stratified Cox model, **0.71** (95% CI, 0.58–0.86) Stratified log-rank ***P*=0.0006**	



Margetuximab	266	210	137	100	62	36	25	14	11	6	5	3	2	2	0
Trastuzumab	270	192	108	72	42	20	8	4	3	2	2	1	0		

OS Analysis

	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	131	139
Median OS (95% CI)	**21.6** months (18.86–24.05)	**19.8** months (17.54–22.28)
	HR by stratified Cox model, **0.89** (95% CI, 0.69–1.13) Stratified log-rank ***P*=0.326**	



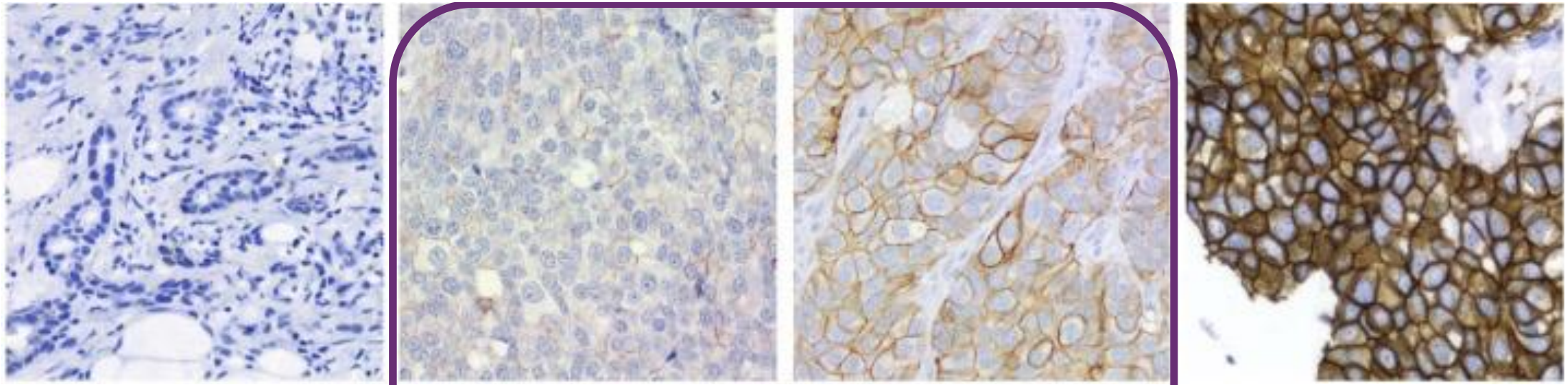
Margetuximab	266	259	249	239	230	214	188	159	131	107	80	64	47	35	31	22	14	9	3	2	2	0			
Trastuzumab	270	260	246	236	218	205	183	160	126	102	74	57	43	30	22	16	10	6	2	2	2	1	0		

Median follow-up: 15.6 months

[b]OS analysis performed as of September 10, 2019 data cutoff, after 270 (70%) of 385 events needed for final OS analysis had occurred

Rugo, HR, et al. JAMA Oncol 2021

Classification of HER2 in Breast Cancer



Adapted from: Marchiò. Semin Cancer Biol. 2021:72:123

Table 1. Baseline Demographics and Clinical Characteristics of 197 matched pairs

Primary HER2 Status	Total Population (n=197)	HER2-Low Patients (n=48)	HER2-0 Patients (n=37)	HER2-Positive Patients (n=112)
Age in Years at Time of Initial Metastatic Diagnosis, median (min, max)	49.5 (26.6, 76.3)	54.5 (27.2, 76.3)	52.9 (26.6, 70.6)	44.2 (27.2, 72.3)
<50, n (%)	102 (51.78)	14 (29.17)	16 (43.24)	72 (64.29)
Site involved at time of initial metastatic diagnosis				
Brain Only	57 (28.93)	12 (25.53)	7 (18.92)	38 (33.93)
Brain and Extracranial disease (Liver, lung, bone, other)	139 (70.56)	35 (74.47)	30 (81.08)	74 (66.07)
Time from Initial Metastatic Diagnosis to CNS Diagnosis in years, median (min, max)	0.24 (0.0, 13.1)	0.70 (0.0, 5.9)	0.08 (0.0, 6.9)	0.9(0.0, 13.1)
0-1 year	121 (61.42)	27 (56.25)	26 (70.27)	68 (60.71)
>1 year to 2 years	21 (10.66)	5 (10.42)	4 (10.81)	12 (10.71)
>2 years	55 (27.92)	16 (33.33)	7 (18.92)	32 (28.57)
Lines of metastatic treatment prior to CNS Resection, median (min, max)	1 (0, 15)	1 (0, 9)	0 (0, 6)	1 (0, 15)
Receipt of Systemic Treatment after CNS Resection, Y or N	147 (74.62)	36 (75.00)	28 (75.68)	83 (74.11)
Receipt of CNS radiation therapy, Y or N	165 (83.76)	42 (87.50)	29 (78.38)	94 (83.93)

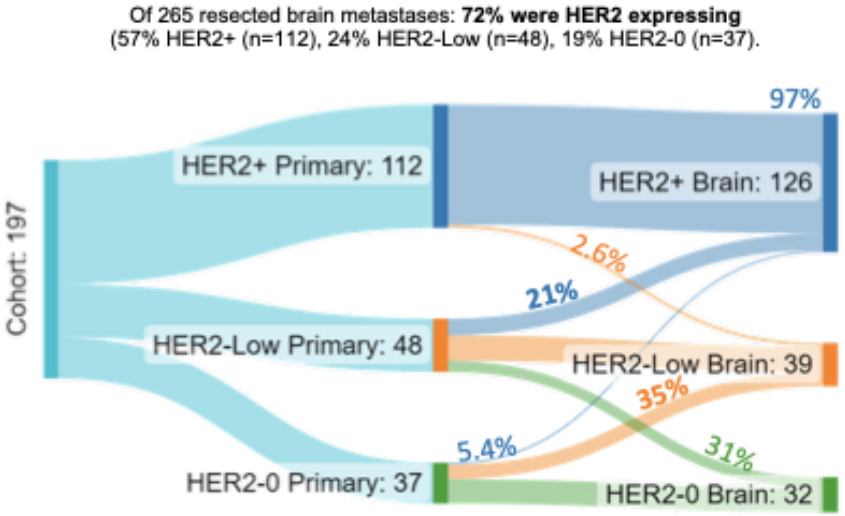
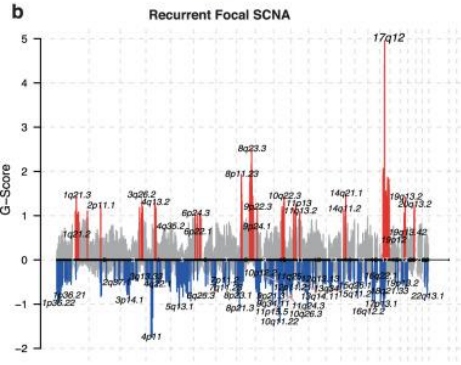


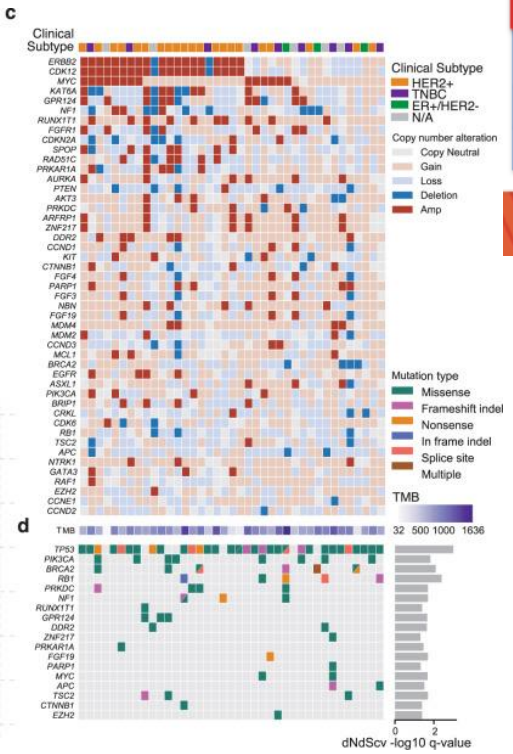
Fig. 2 Subtype Switching From Primary to Brain Metastases (N=197 pairs)

a

Significant (q-value < 0.25) GISTIC arm level alterations

	# Genes	Cohort	Type	Frequency	z-score	q-value
1q	1955	Shared	AMP	0.79	4.36	< 0.001
8p	580	Shared	DEL	0.865	4.44	< 0.001
8q	859	Shared	AMP	0.88	4.78	< 0.001
17p	683	Shared	DEL	0.825	4.01	< 0.001
17q	1592	Prim	DEL	0.7	3.32	< 0.001
5q	1427	Mets	DEL	0.76	2.59	< 0.10
19p	995	Mets	DEL	0.8	2.81	< 0.10
19q	1709	Mets	DEL	0.75	2.64	< 0.10
20p	355	Prim	AMP	0.66	2.66	< 0.10
4p	489	Prim	DEL	0.57	1.8	< 0.25
4q	1049	Prim	DEL	0.56	1.75	< 0.25
6p	1173	Prim	AMP	0.6	2.29	< 0.25
9q	1113	Mets	DEL	0.7	1.78	< 0.25
10q	1268	Mets	DEL	0.7	2.13	< 0.25
11q	1515	Prim	DEL	0.57	1.82	< 0.25
13q	654	Prim	DEL	0.58	2	< 0.25
18q	446	Mets	DEL	0.74	1.84	< 0.25
20q	753	Prim	AMP	0.6	2.03	< 0.25

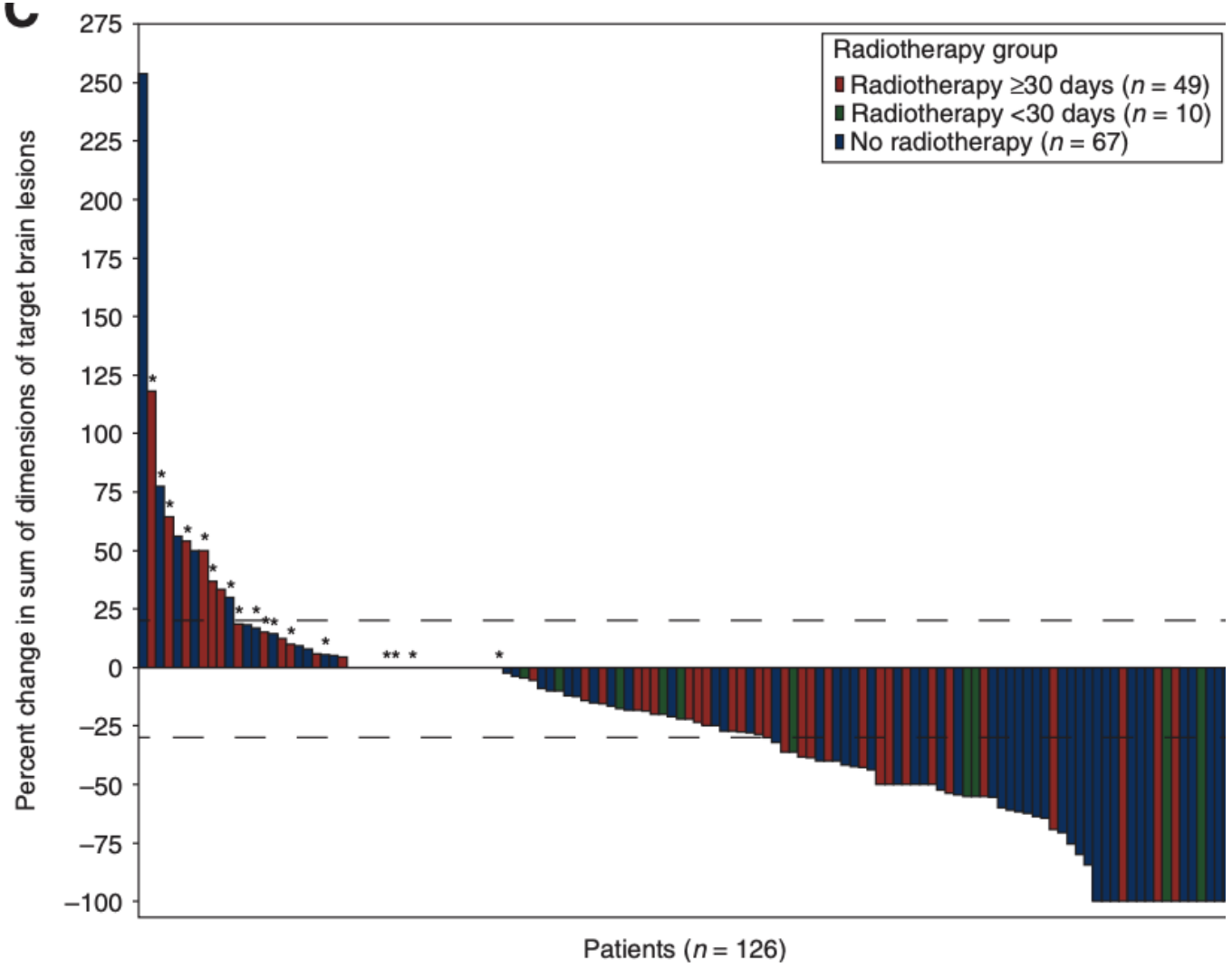




Nat Commun. 2022; 13: 514.
Cosgrove et al.

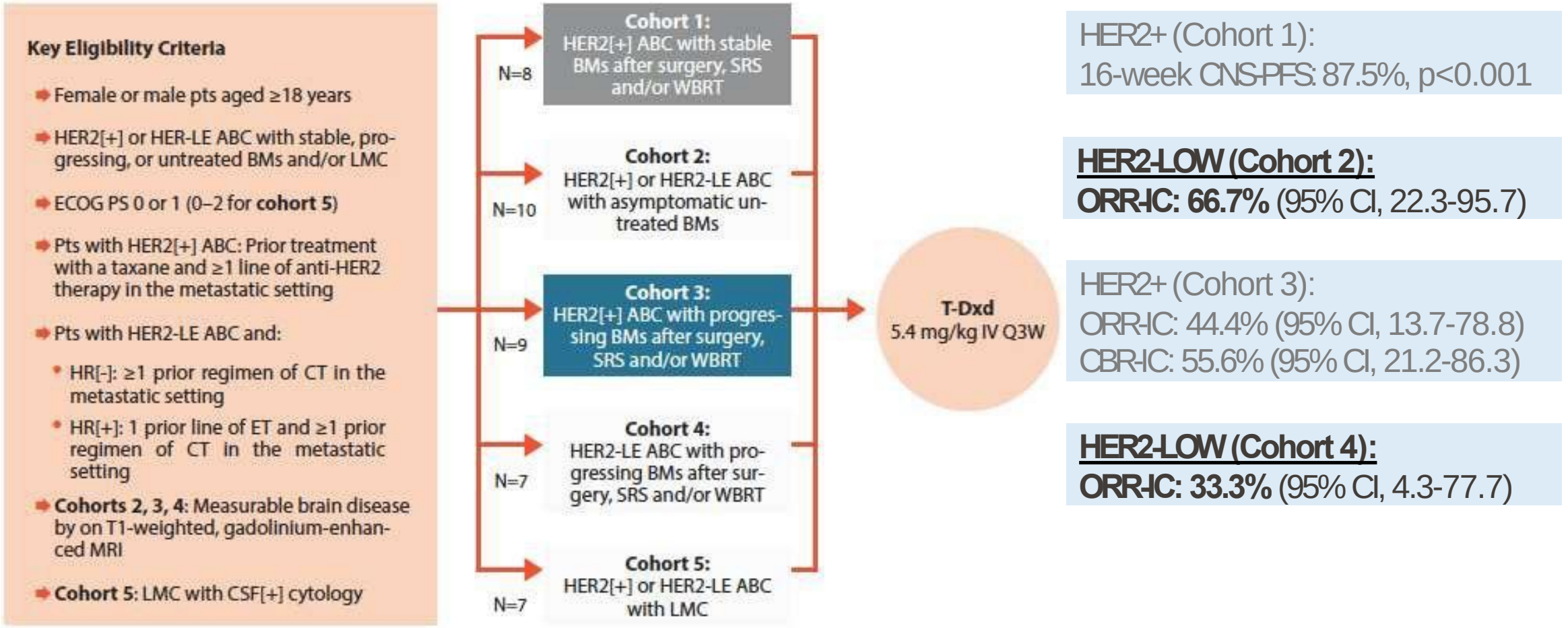
CNS mets and T-DxD (KAMILLA)

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



Montemurro F et al. Ann Onc 2020

DEBRAH (T-DxD in CNS met patients)



HER2+ (Cohort 1):
16-week CNS-PFS: 87.5%, p<0.001

HER2-LOW (Cohort 2):
ORR-IC: 66.7% (95% CI, 22.3-95.7)

HER2+ (Cohort 3):
ORR-IC: 44.4% (95% CI, 13.7-78.8)
CBR-IC: 55.6% (95% CI, 21.2-86.3)

HER2-LOW (Cohort 4):
ORR-IC: 33.3% (95% CI, 4.3-77.7)

Vaz Batista M et al. SABCS 2021, Abstract PD4-06; Pérez-García JM et al. SABCS 2022; Abstract PD7-02.

Advanced Stage/Metastatic HER2+ Breast Cancer

Note – tissue testing mandatory at initial recurrence and should be considered at progression if feasible

First Line
- **"De Novo"**
- **Recurrence after > 1 year from adjuvant trastuzumab (H, HP)**

Taxane + Trastuzumab + Pertuzumab (HP) x 4-8, then HP maintenance until progression with best endocrine therapy for ER/PR+

Should patients have brain MRI at diagnosis regardless of symptoms?

Second Line
- **<1 year from adjuvant HP/T-DM1**
- **Following (H/HP)**

Fam-trastuzumab deruxtecan

Second/Third Line

Tucatinib, trastuzumab, capecitabine - ?preferred for CNS disease

Fourth/Fifth Line

Margetuximab + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)

Fourth/Fifth Line

Neratinib + Capecitabine

Thank you!!