Advancement in HER2-Directed Therapy for Breast Cancer

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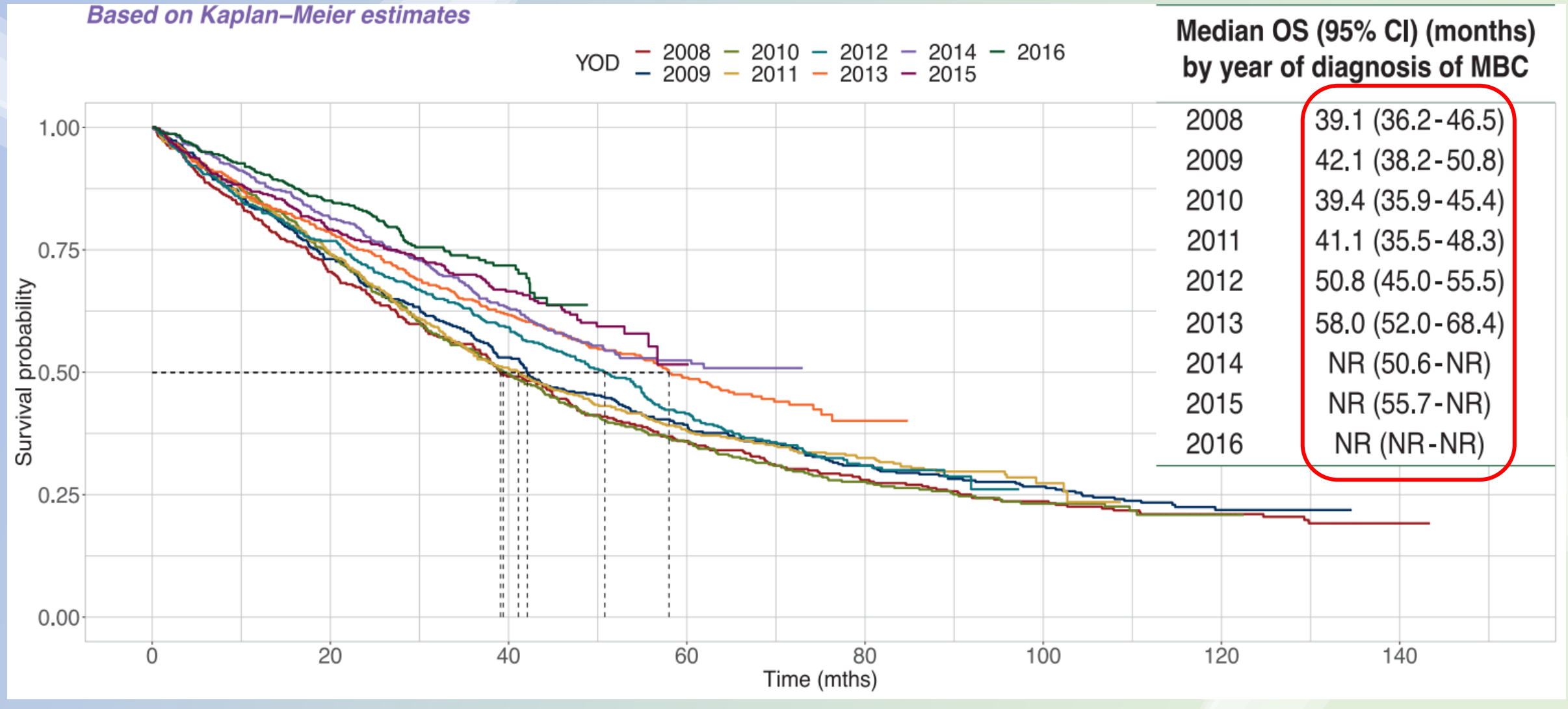
- HER2+ metastatic breast cancer (mBC)
- HER2 low mBC

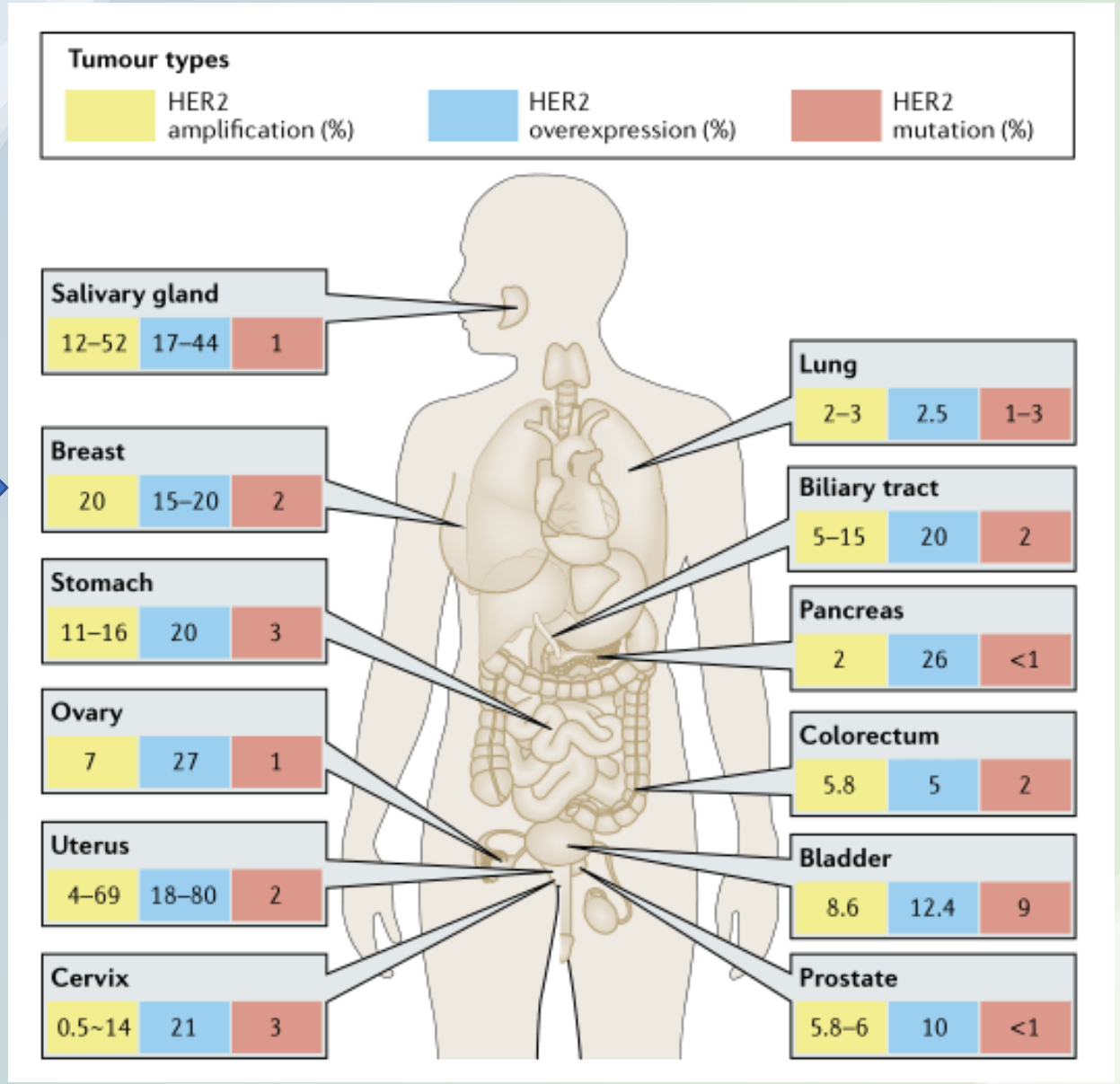
Overall Survival in HER2 + mBC by Year of Diagnosis



Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

Grinda T, et al. ESMO Open. 2021

HER2 abnormality



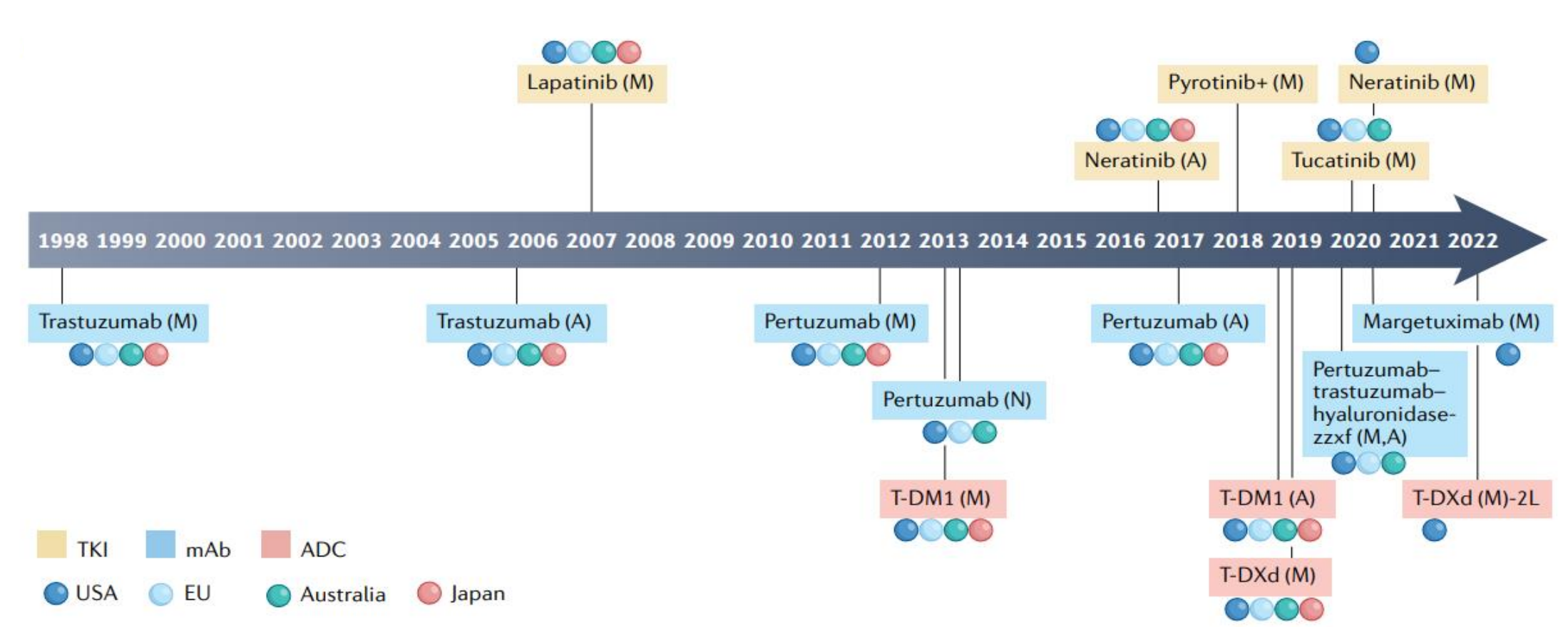
Do-Youn Oh & Yung-Jue Bang. Nature Review Clinical Oncol. 2019

Approval of HER2 targeted therapy

- **Monoclonal Antibody (mAb):** Trastuzumab, Pertuzumab, Margetuximab
- **Tyrosine Kinase Inhibitor (TKI):** Tucatinib, Lapatinib, Neratinib
- **Antibody Drug Conjugate (ADC):** T-DM1, T-Dxd

SM Swain, et al. Nature Review Drug Discovery. 2023

Approval of HER2 targeted therapy



A. Neoadjuvant/Adjuvant setting
M. Metastatic setting

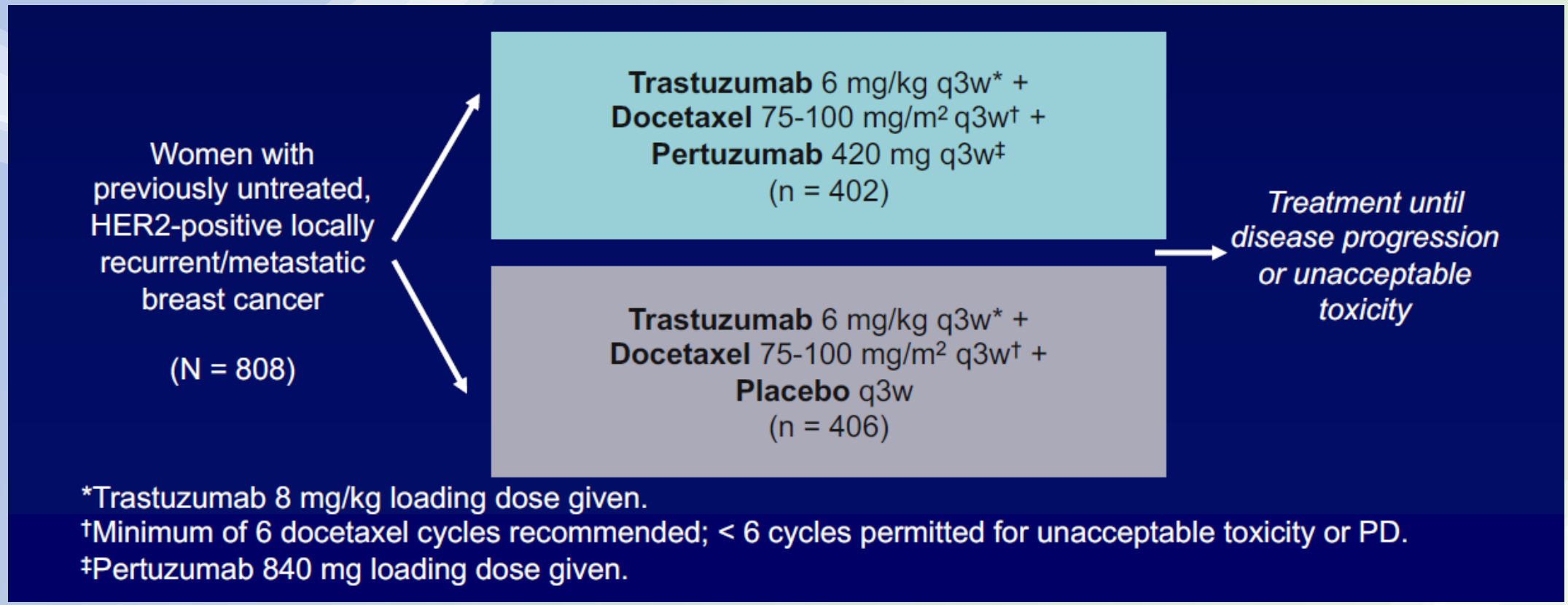
TKI: Tyrosine Kinase Inhibitor
mAb: Monoclonal Antibody
ADC: Antibody Drug Conjugate

SM Swain, et al. Nature Review Drug Discovery. 2023

1L Therapy *for HER2+ mBC*

- **Taxane+Trastuzumab+Pertuzumab (THP)** - CLEOPATRA
- **T-Dxd +/- Perutuzumab** - Destiny Breast -09

CLEOPATRA Study Design

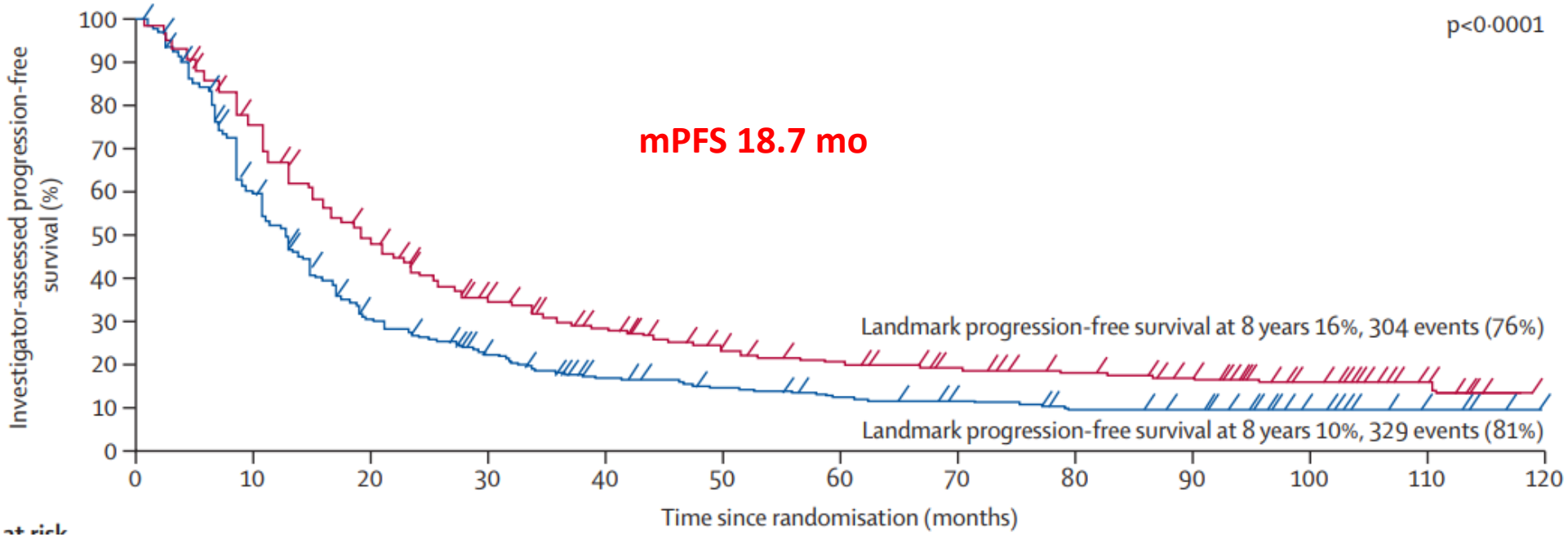


Primary endpoint: PFS
Secondary endpoint: OS, Safety

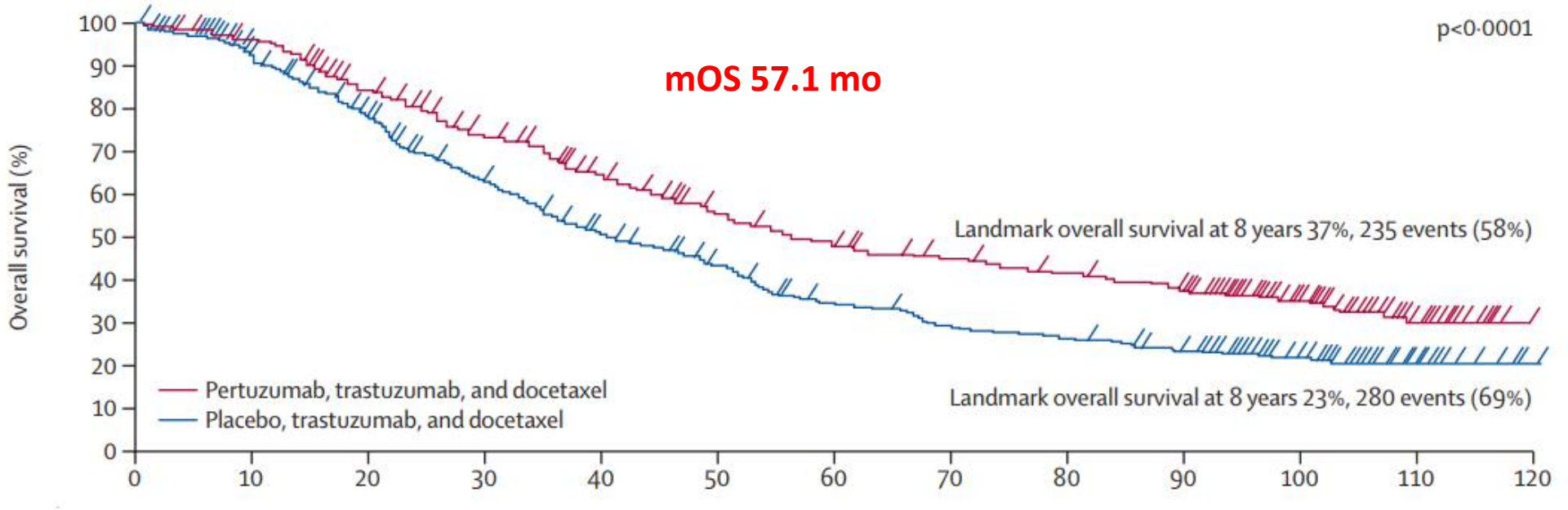
Baselga J, et al. SABCS 2011. Abstract S5-5

CLEOPATRA End-of-Study Results

Median follow up ~100 months



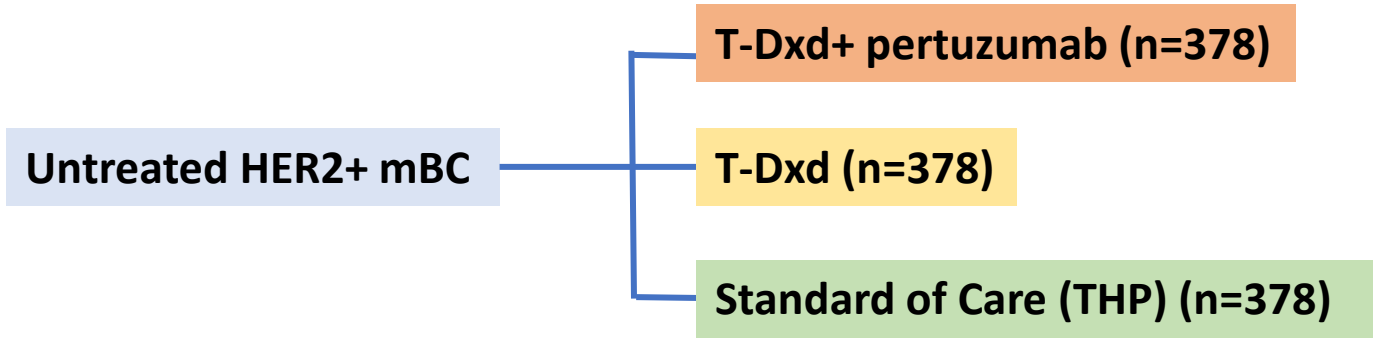
THP is the current standard 1L therapy for HER2+ mBC



SM Swain, et al. Lancet Oncol. 2020

Things might change… Destiny-Breast 09 Study

DB09- T-Dxd (Trastuzumab deuraxican**) with or without pertuzumab vs THP (**Taxane, trastuzumab and pertuzumab**) in HER2-positive, untreated mBC**



Primary Endpoint: PFS

2L Therapy *for HER2+ mBC*

- **TDM1 -** EMILIA
- **T-Dxd -** Destiny Breast -03
- **Tucatinib+Capcitabine+Tratuzuamb -** HER2CLIMB

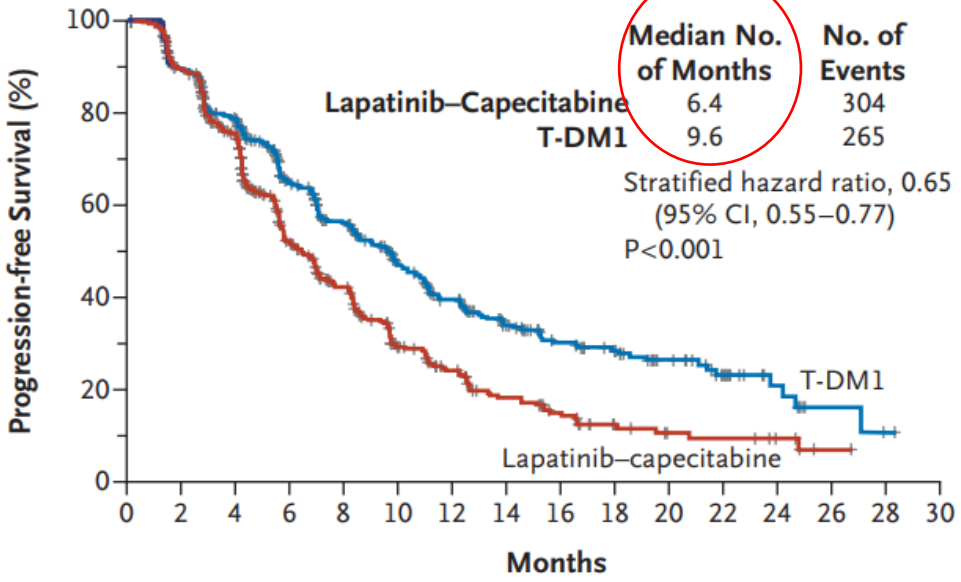
EMILIA Study

- HER2+ mBC
- Progressed on trastuzumab and taxane

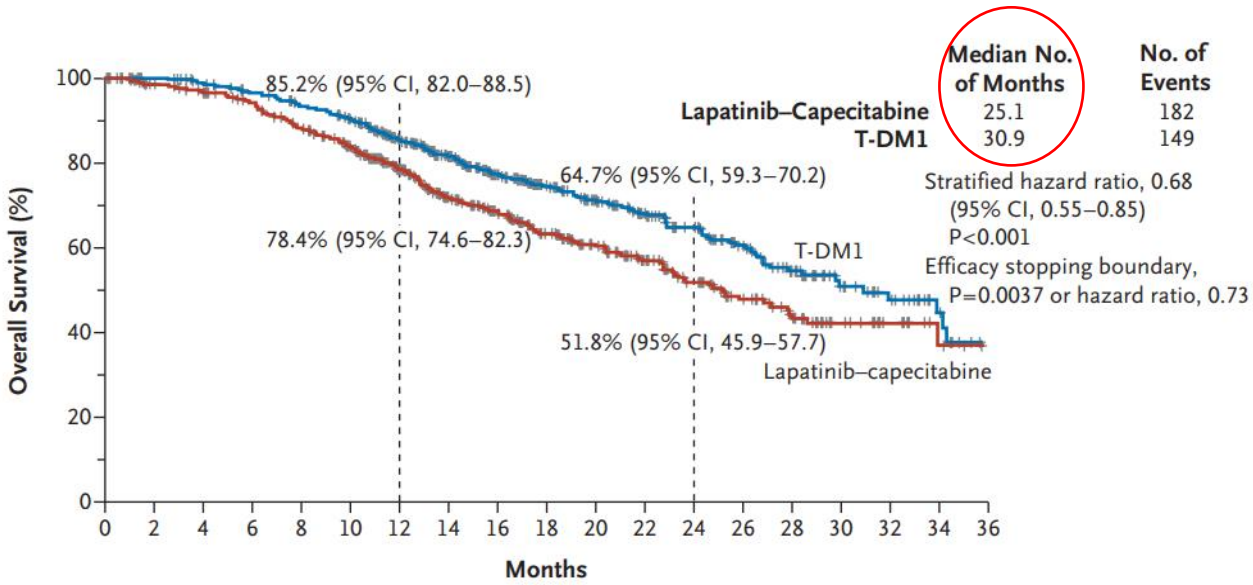
1:1

- T-DM1
- Lapatinib + Capecitabine

PFS



OS

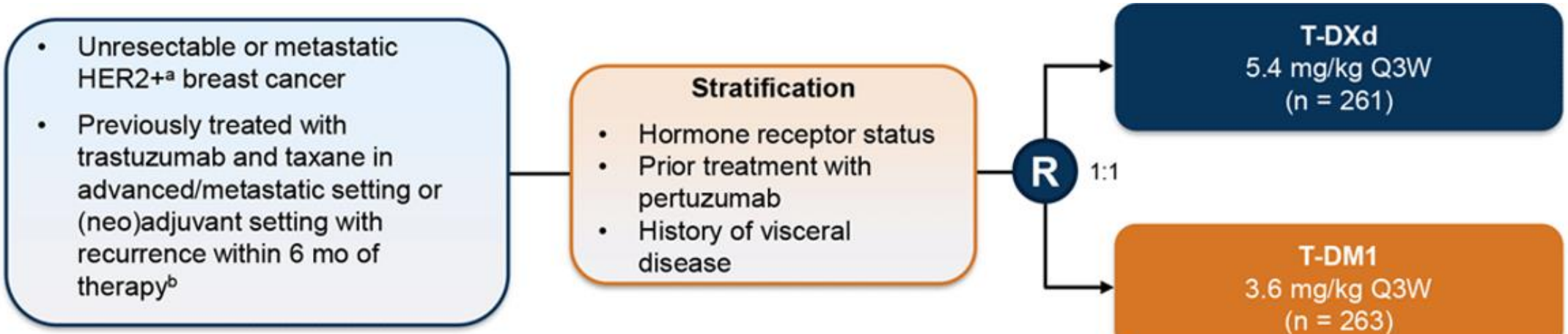


TDM1 became the standard 2L therapy for HER2+ mBC

Verma S, et al. NEJM. 2012

Things have changed…Destiny-Breast 03

Destiny-Breast 03 Study Design

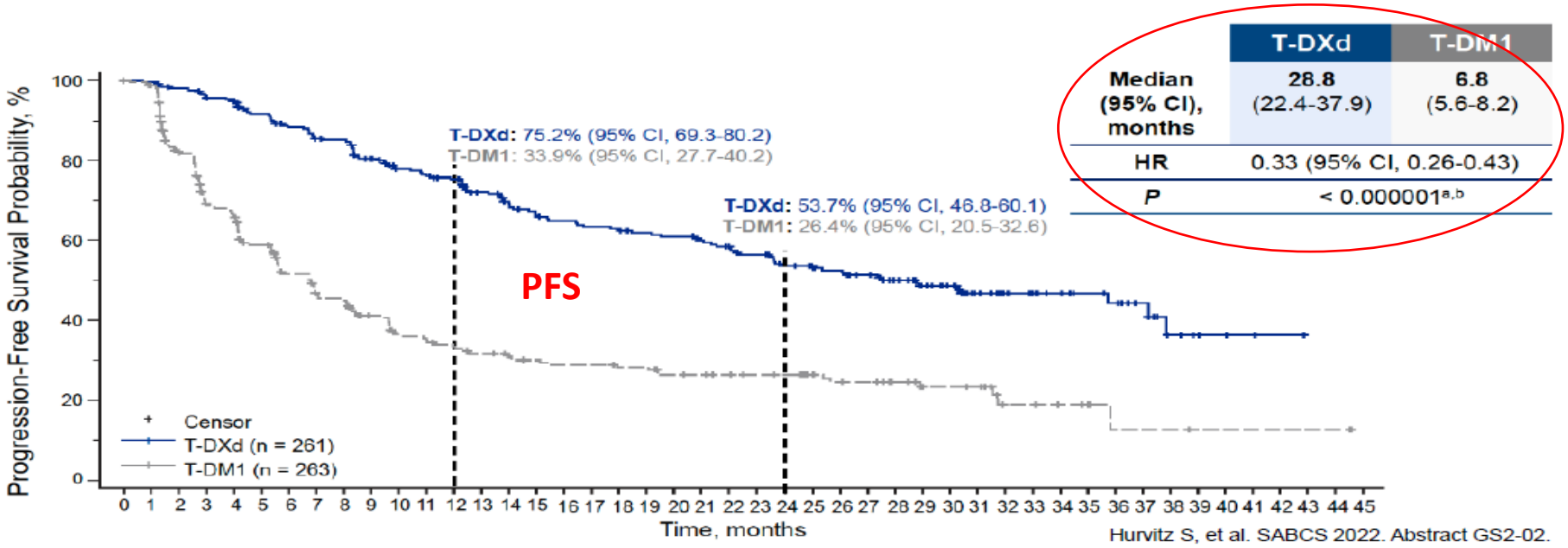


- **Primary endpoint:** PFS (BICR)
- **Key secondary endpoint:** OS[c]
- **Secondary endpoints:** ORR (BICR and investigator), DOR (BICR), and safety

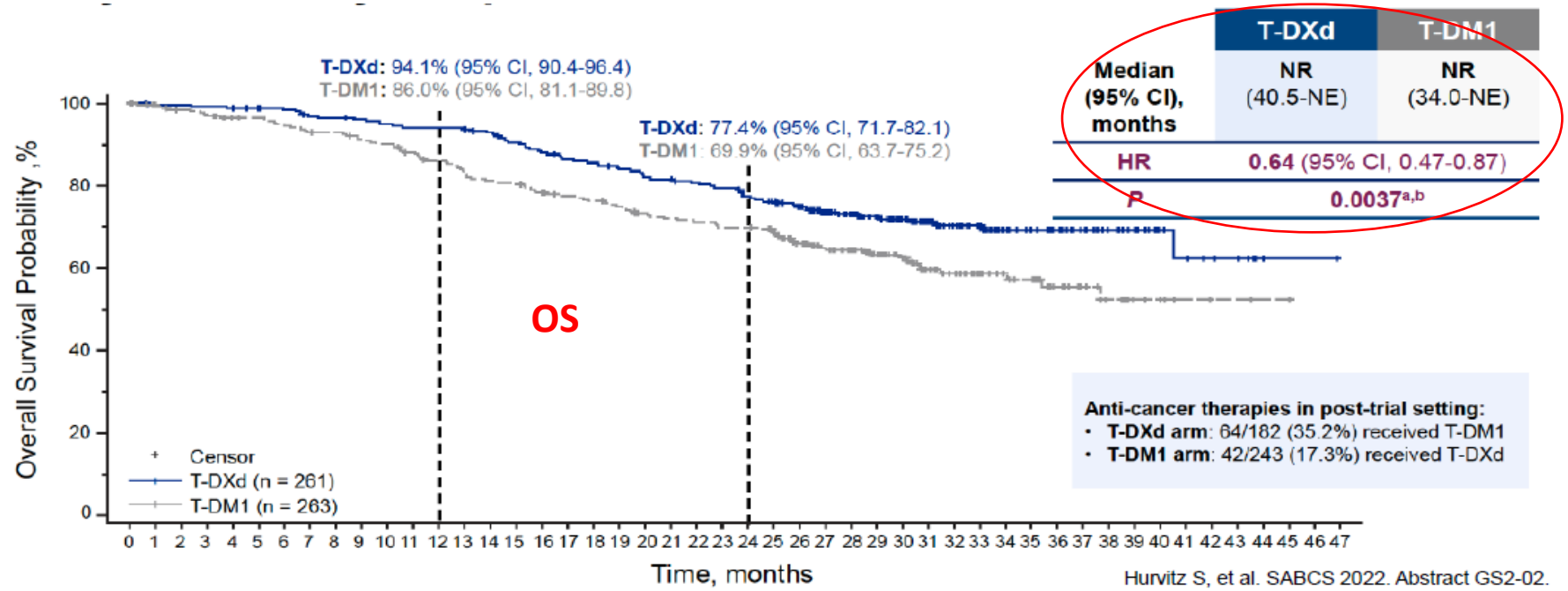
Cortes J et al. ESMO 2021. Abstract LBA1.

DB 03: PFS and OS

T-Dxd has replcaed TDM1 and become the standard 2L therapy for HER2+ mBC



Hurvitz S, et al. SABCS 2022. Abstract GS2-02.

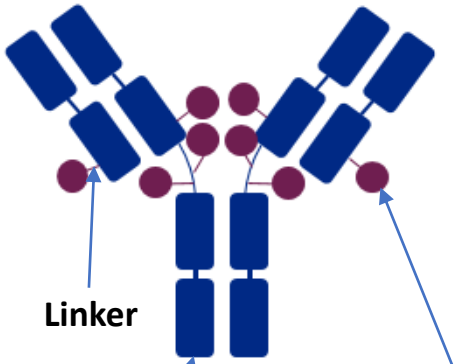


Hurvitz S, et al. SABCS 2022. Abstract GS2-02.

Hurvitz SA, et al. Lancet 2023

Characteristic Difference Between T-Dxd and T-DM1
Both are Antibody Drug Conjugate

Trastuzumab deruxtecan (T-DXd)



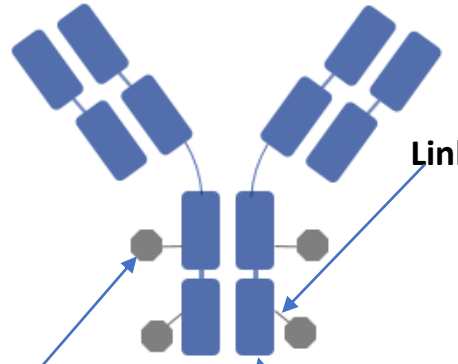
Linker

Payload(the drug): Topoisomerase I inhibitor

Anti-HER2 antibody

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

Trastuzumab emtansine (T-DM1)



Linker

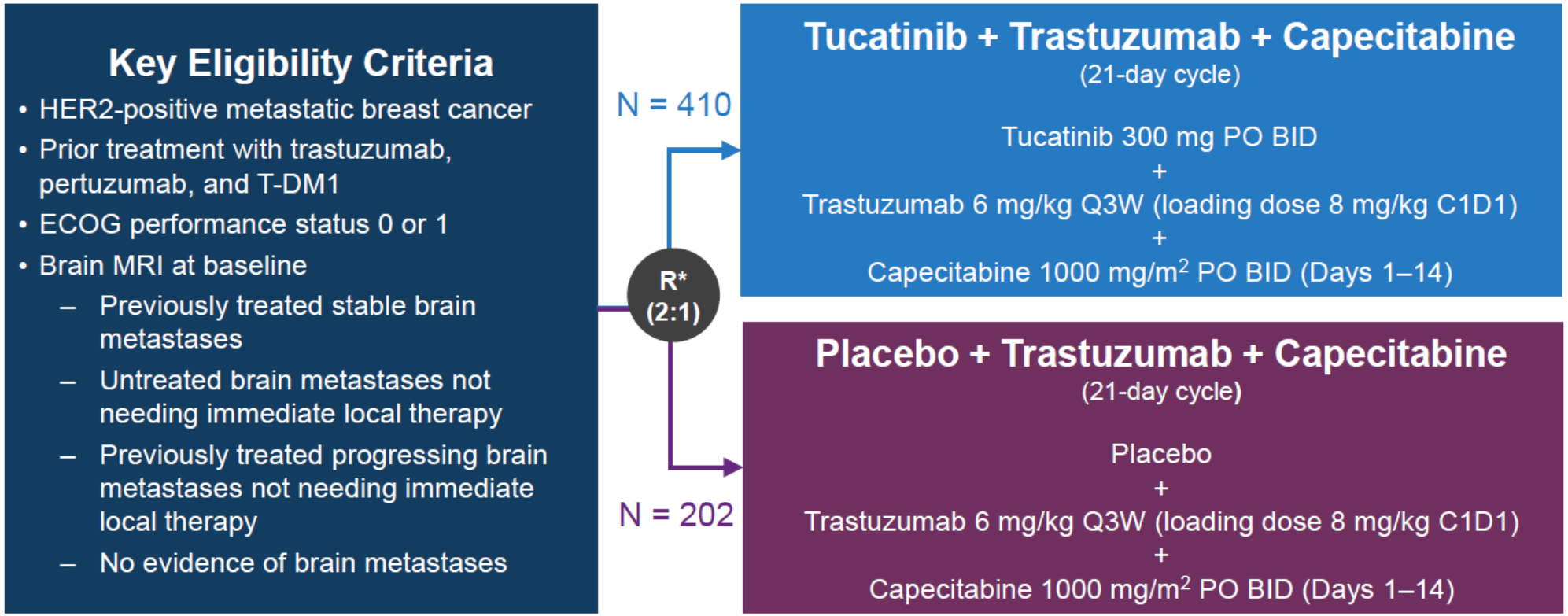
Payload(the drug): Anti-microtubule

Anti-HER2 antibody

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

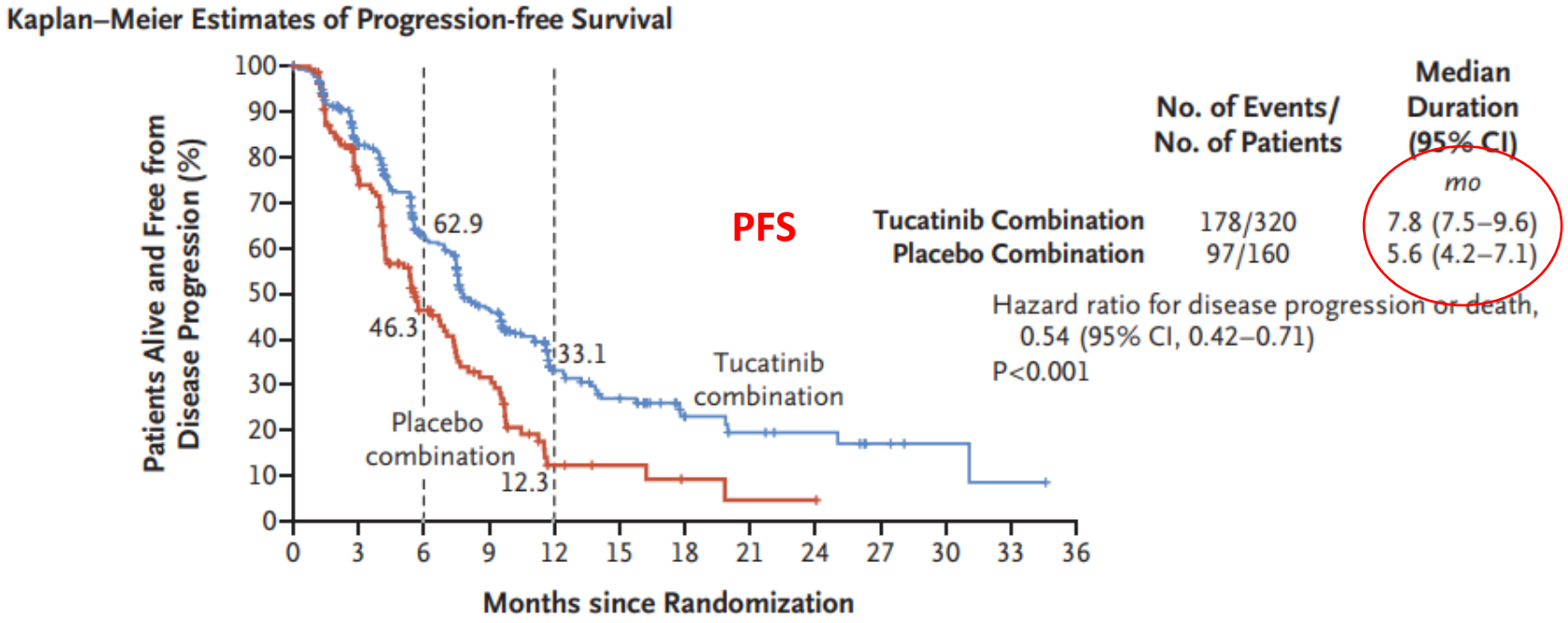
Other 2L therapy option – HER2CLIMB

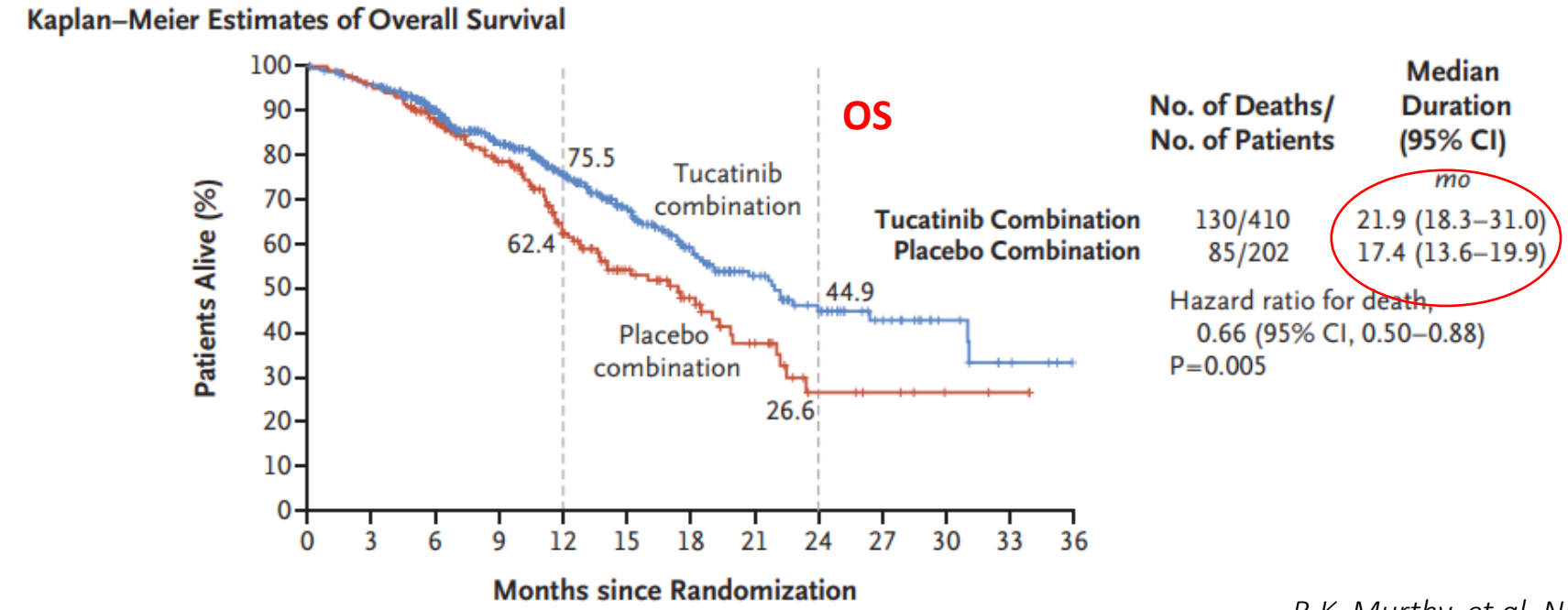
HER2CLIMB Study Design



HER2CLIMB: PFS and OS

2020, FDA approved this regimen for HER2+mBC after at least 1L of therapy



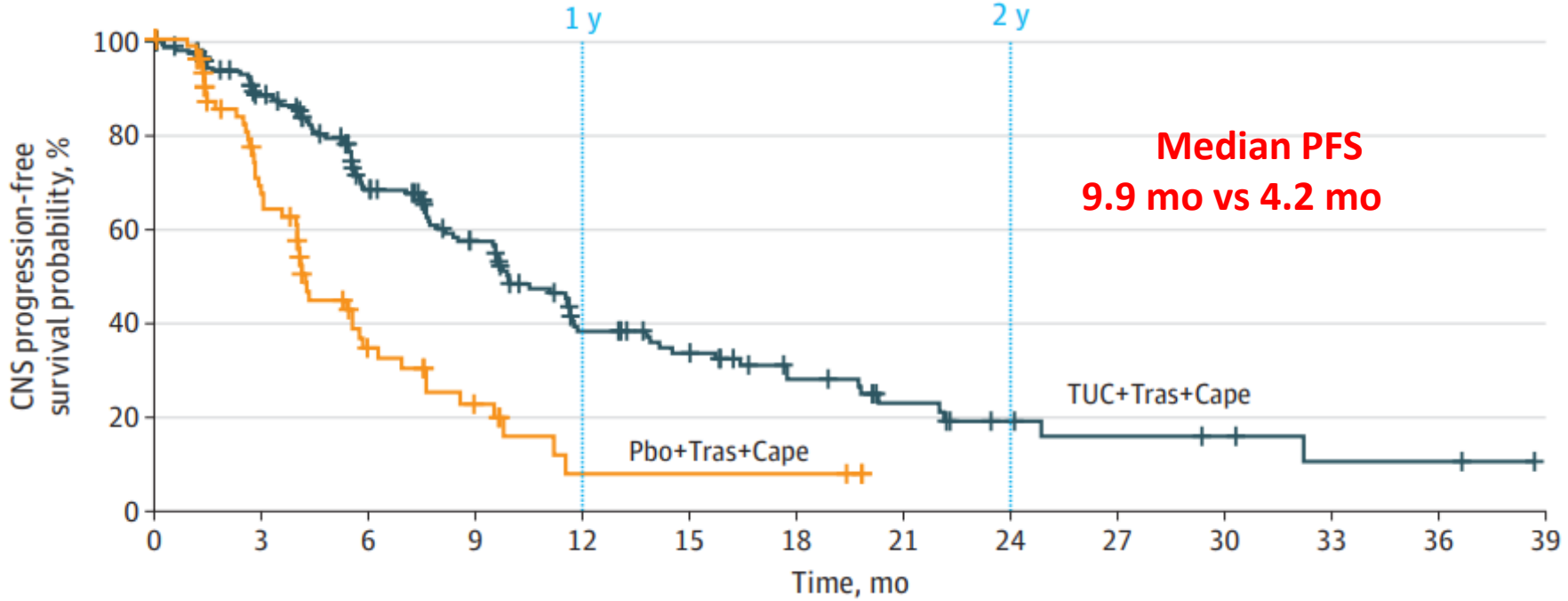


R.K. Murthy, et al. NEJM 2020

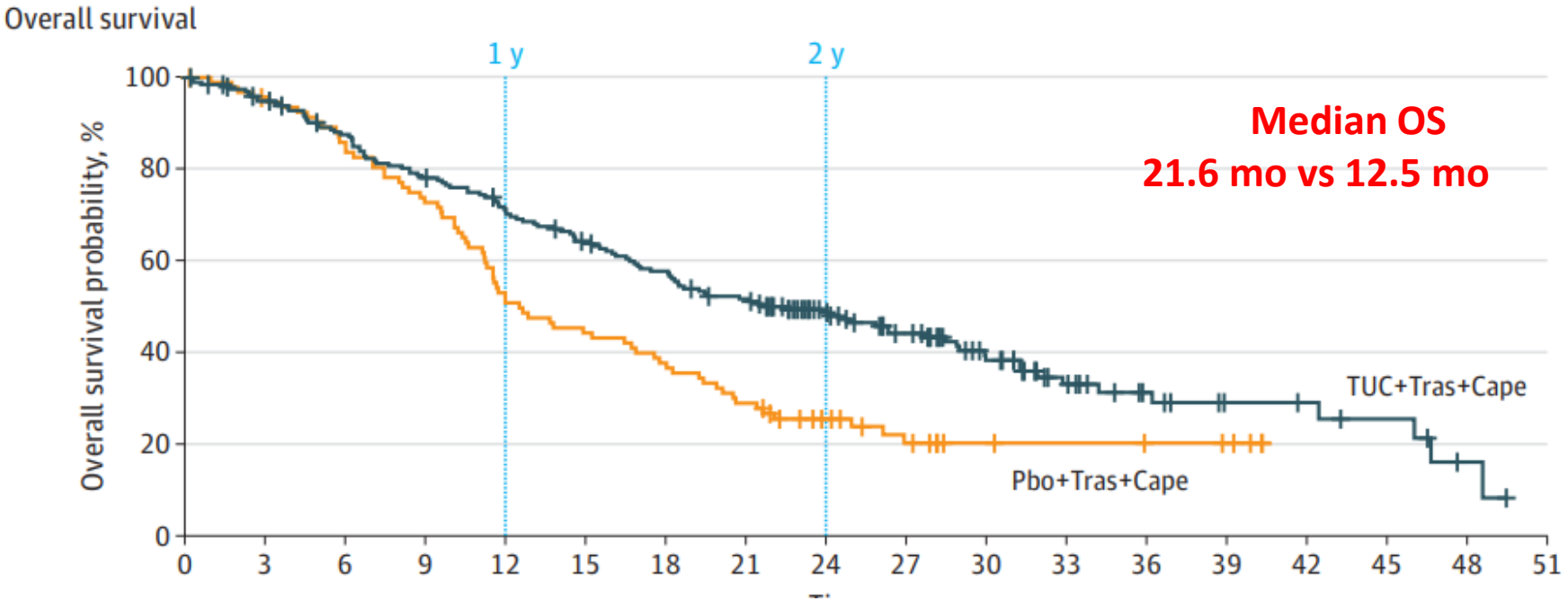
HER2CLIMB:

Patients with Brain Metastases

Tucatinib triplet is the Preferred regimen for patients with brain metastases



Median PFS
9.9 mo vs 4.2 mo



Median OS
21.6 mo vs 12.5 mo

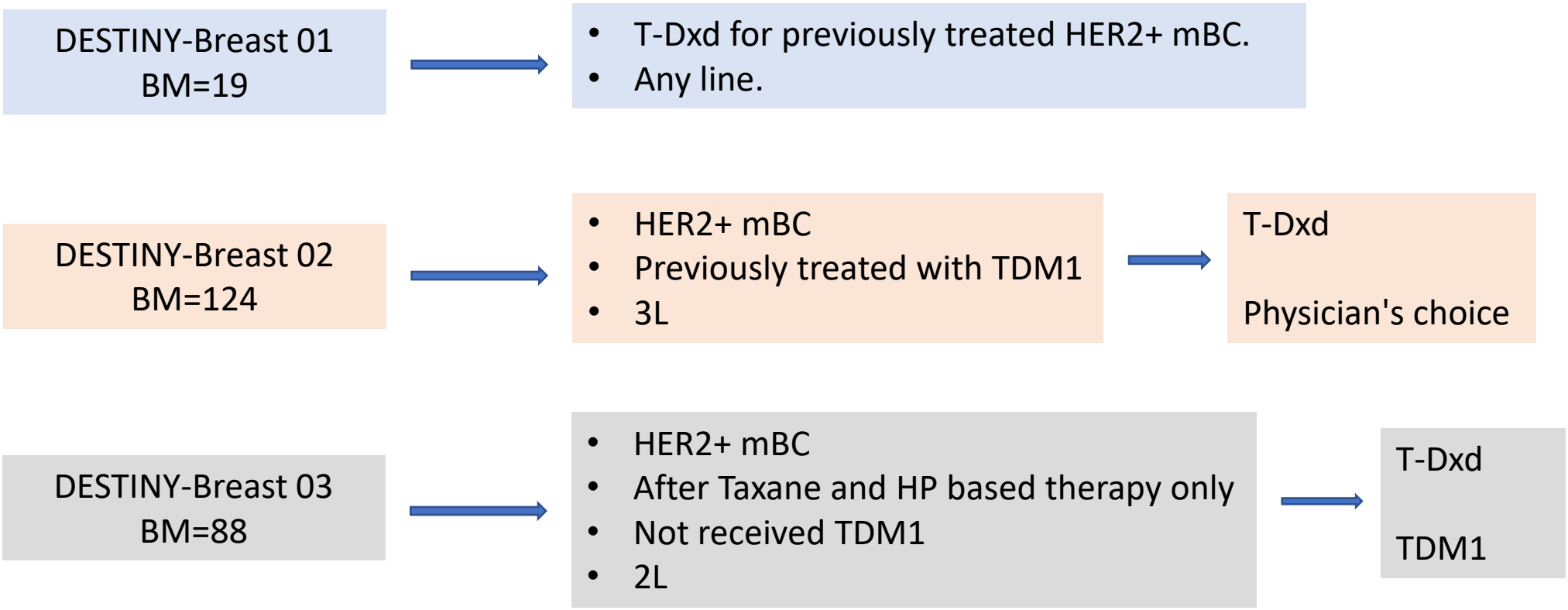
Nanci Lin, et al. JAMA Oncol. 2022

Second Line Therapy *for HER2+ mBC*

- **TDM1 ⟶ 4L**
- **T-Dxd 2L or 3L**
- **Tucatinib + Capecitabine + trastuzumab 2L or 3L**
  (Preferred for patients with brain met)

Preferred regimen for brain met may change…

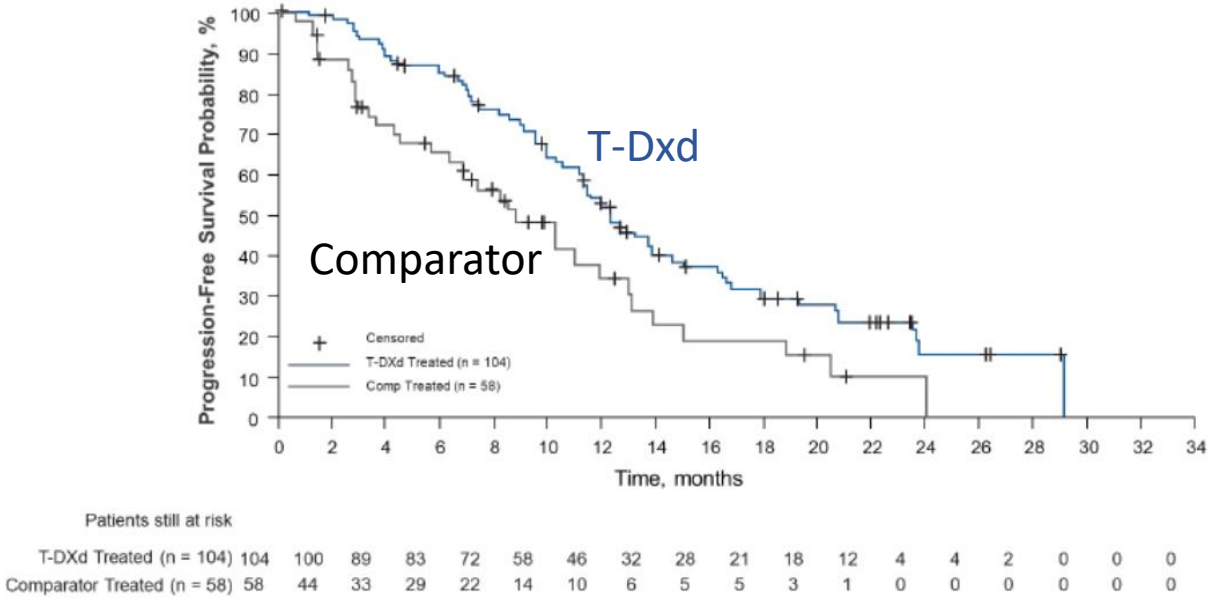
DESTINY-Breast 01, 02, and 03 Pooled analysis of T-dxd in HER2+ mBC with Brain Metastases (BM)



Hurvitz SA, et al. ESMO 2023. Abstract 3770

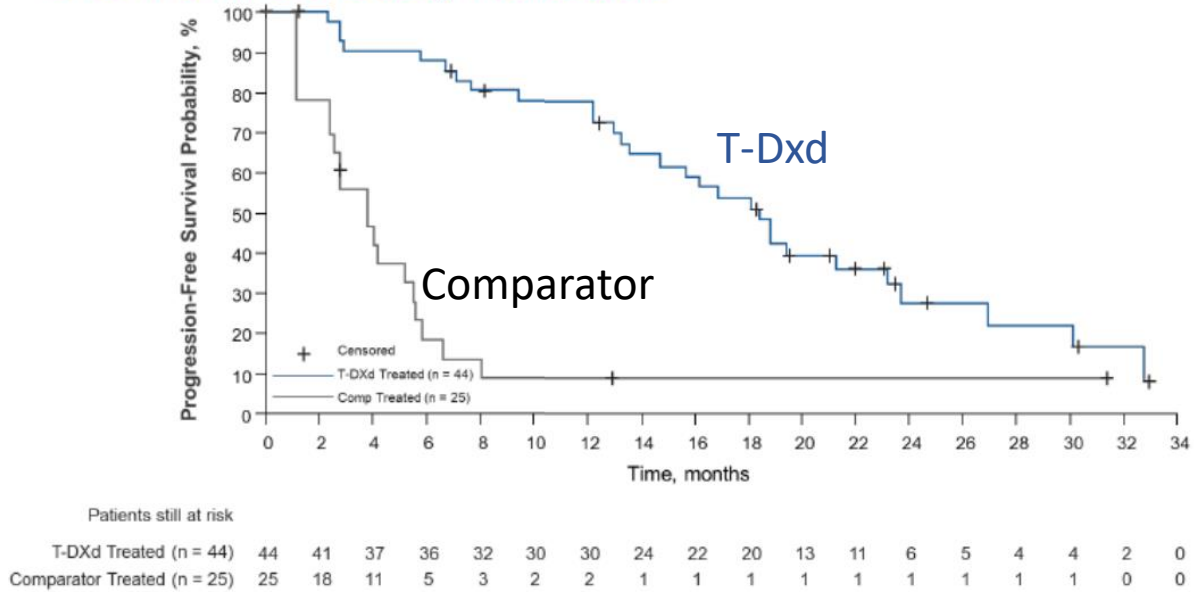
DESTINY-Breast 01, 02, and 03 Pooled analysis of T-dxd in HER2+ mBC with BM

CNS-PFS in Treated/Stable BMs



Treated/Stable BM	T-Dxd n=104	Comparator (n=58)
Median CNS-PFS, mo (95% CI)	12.3 (11.1-13.8)	8.7(6.3-11.8)
HR (95% CI)	**0.59 (0.39, 0.89)**	

CNS-PFS in Untreated/Active BMs



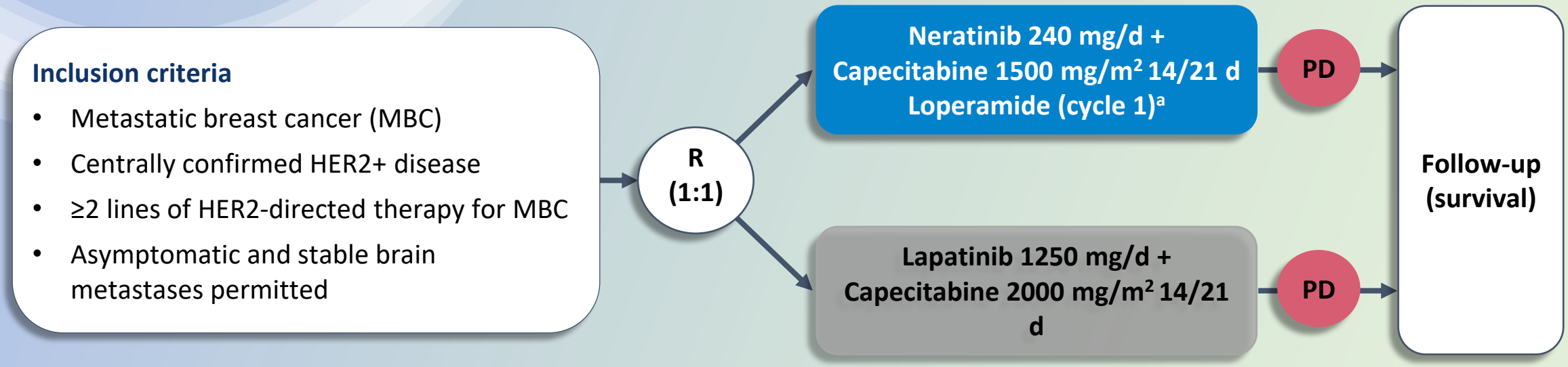
untreated/active BM	T-Dxd n=44	Comparator (n=25)
Median CNS-PFS, mo (95% CI)	18.5(13.6,23.3)	4.0(2.7, 5.7)
HR (95% CI)	**0.19 (0.11, 0.35)**	

Hurvitz SA, et al. ESMO 2023. Abstract 3770

4L therapy and Beyond *for HER2 + mBC*

- **Neratinib + Capecitabine** - NALA Study

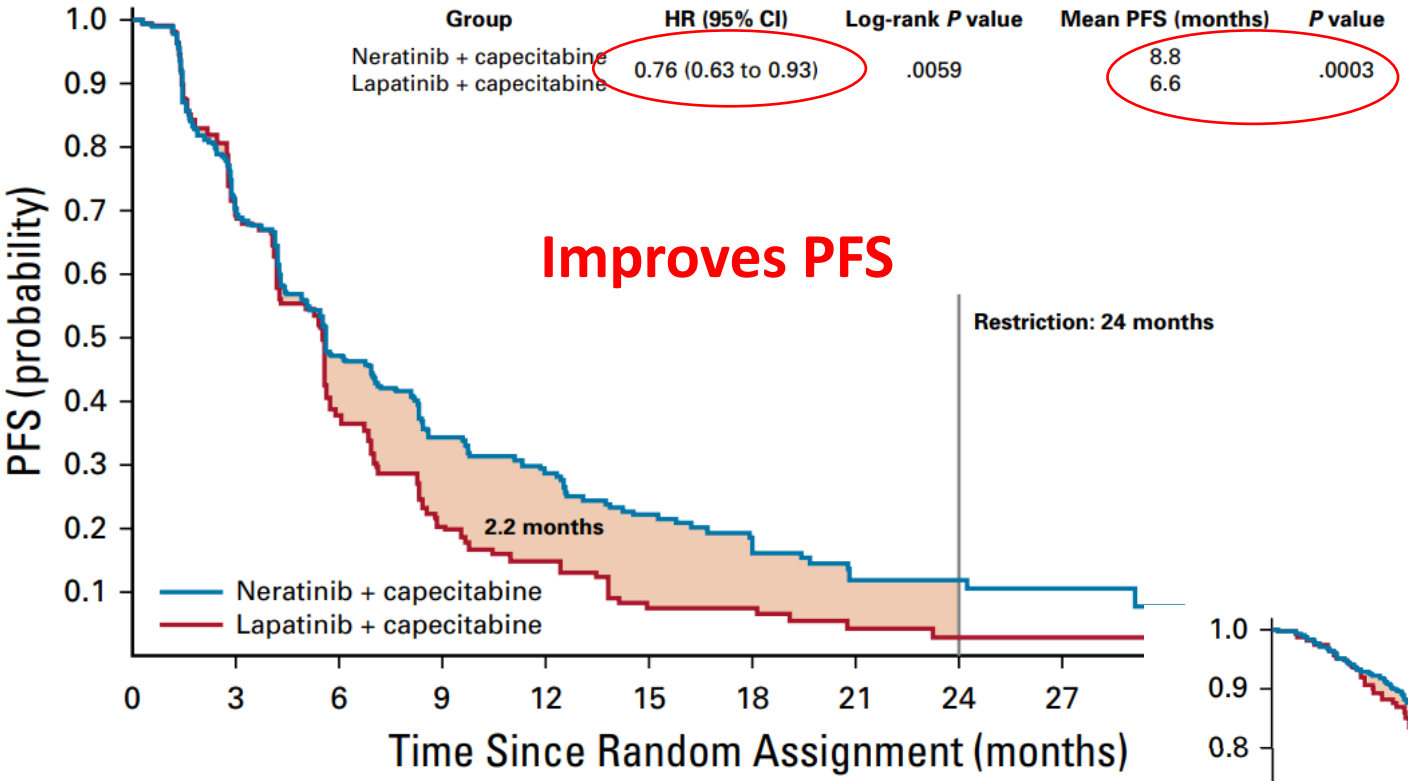
NALA Study Design

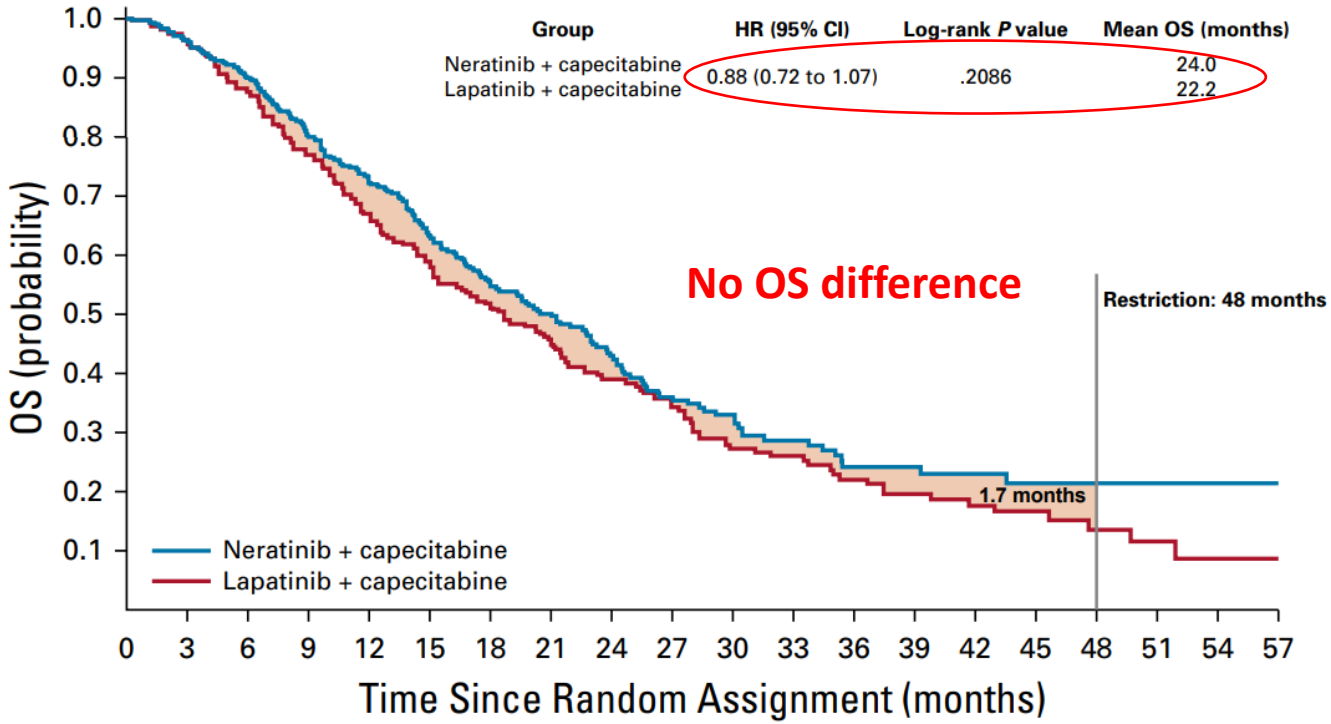


Endpoints

- Co-primary: PFS (centrally confirmed) and OS

Saura C et al. ASCO 2019; Abstract 1002.





C. Saura, et al. JCO. 2022

Evolution of PFS and OS of HER2+ mBC with different regimen

	mPFS	mOS
Taxan, Trastuzumab, Pertuzumab (1L)	18.7	57.1
T-Dxd (2L)	28.8	NR
Tucatinib, Capecitabine, Trastuzmab (2L, 3L)	7.8	21.9
T-DM1 (>3L)	9.6	30.9
Neratinib + Capecitabine (> 3L)	8.8	24

1. SM Swain, et al. Lancet Oncol. 2020
2. SA Hurvitz et al. Lancet 2023
3. R.K. Murthy et al. NEJM 2020
4. C. Saura, et al. JCO. 2022
5. Verma S, et al. NEJM. 2012

On Going Studies for HER2+ Breast Cancer

Table 1 | Select HER2-targeted antibody–drug conjugates in development

Drug name (company)	Linker type	Payload	Payload MOA	DAR	Clinical trial ID	Clinical trial data	Reference
Trastuzumab duocarmycin (Synthon/Byondis B.V.)	Cleavable	Duocarmycin (vc-seco-DUBA)	DNA alkylator	2.8	NCT04602117 (phase I), NCT03262935 (phase III)	Phase III trial SYD985 vs TPC: median PFS 7 vs 4.9 mo; HR 0.64, P=0.002	Saura Manich et al.[144]
Disitamab vedotin (RC48-ADC) (RemGen Co./Seagen)	Cleavable	MMAE	Microtubule inhibitor	4	NCT02881190 (phase I), NCT03500380 (phase II), NCT04400695 (phase III)	Phase I trial in HER2$^+$ cancers: ORR 15%; DCR 45%	Xu et al.[216]
A166 (Kluss Pharma/ Sichuan Kelun-Biotech Biopharmaceutical Co. Ltd)	Cleavable	Duo-5	Microtubule inhibitor	2.8	CTR20181301 NCT03602079 (phase I)	Phase I trial in advanced solid tumours: ORR 59-71% based on the dose, DCR ~85%	Hu et al.[217]
ALT-P7 (Alteogen, Inc.)	Cleavable	MMAE	Microtubule inhibitor	2	NCT03281824 (phase I)	Phase I trial in HER2$^+$ MBC: DCR 72%, CBR 32%	Park et al.[218]
ARX788 (Ambryx)	Non-cleavable	AS269- synthetic dolastatin	Microtubule inhibitor	2	CTR20171162 (phase I), NCT04829604 (phase II)	Phase I trials in HER2$^+$ MBC: ORR 66%; DCR 100%	Hurvitz et al.[219]
BB-1701 (Bliss Biopharmaceutical)	Cleavable	Eribulin	Microtubule inhibitor	4	NCT04257110 (phase I)	Not applicable	Not applicable
DB-1303 (Duality Bio, Inc.)	Cleavable	DXd derivative	Topoisomerase 1 inhibitor	8	NCT05150691 (phase I)	Not applicable	Not applicable
DX126-262 (Hangzhou DAC)	Unknown	Tubulysin	Microtubule inhibitor	NR	CTR20191224 (phase I)	Not applicable	Zhang et al.[220]
FS-1502/IKS014 (Shanghai Fosun Pharmaceutical Industrial Development Co, Ltd)	Unknown	MMAE	Microtubule inhibitor	NR	NCT03944499 (phase I)	Not applicable	Fasching[221]
Zanidatamab zovodotin (ZW49) (Zymeworks, Inc.)	Cleavable	Auristatin based	Microtubule inhibitor	2	NCT03821233 (phase I)	Phase I trial in advanced solid tumours. ORR 13%; DCR 50%; CBR 25%; MTD not reached	Jhaveri et al.[222]

- HER2+ metastatic breast cancer

- **HER2 low, ultra low, and zero breast cancer**
  - **Definition**
  - **Distribution**
  - **Why it matters**

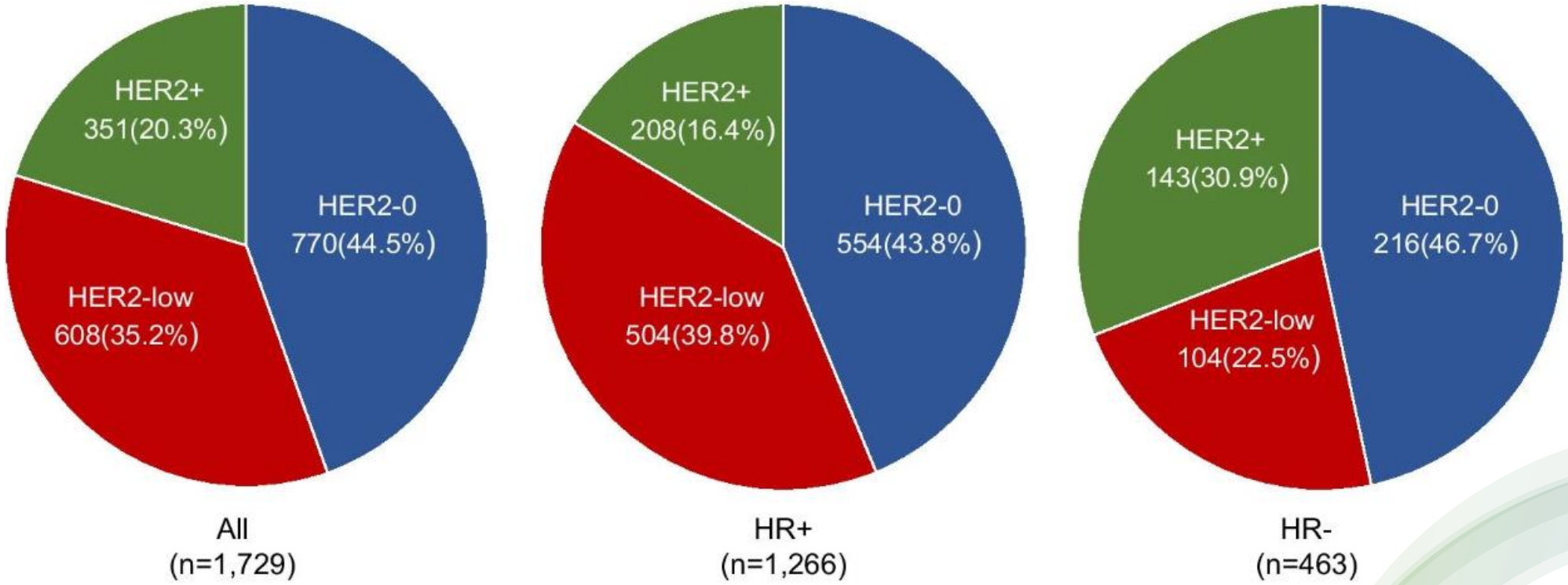
HER2 Low Definition

IHC score	HER2 FISH	HER2 status
0	N/A	Negative
1+	N/A	Negative
2+	Not Amplified	Negative
3+	N/A	Positive

HER2 Low

1. P Tarantino, et al. JCO. 2020

HER2 Low Breast Cancer Distribution



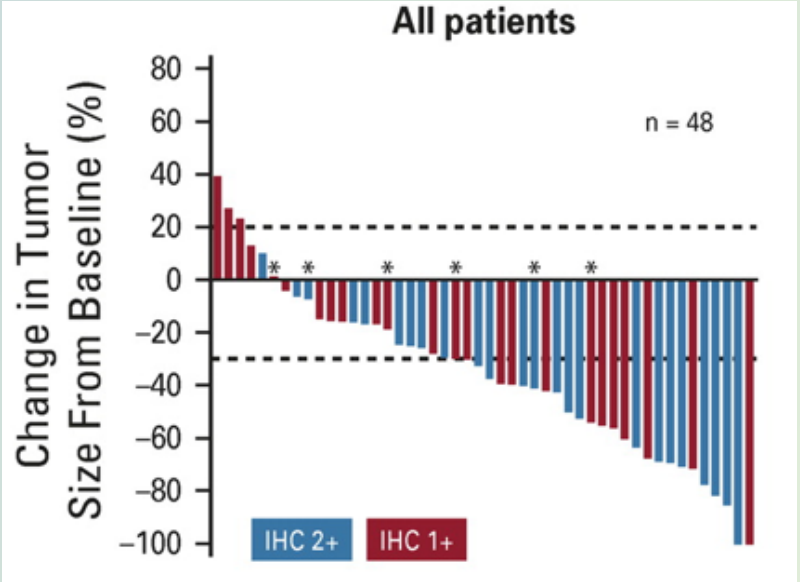
SP Gampenrieder, et al. Breast Cancer Reseach.2021

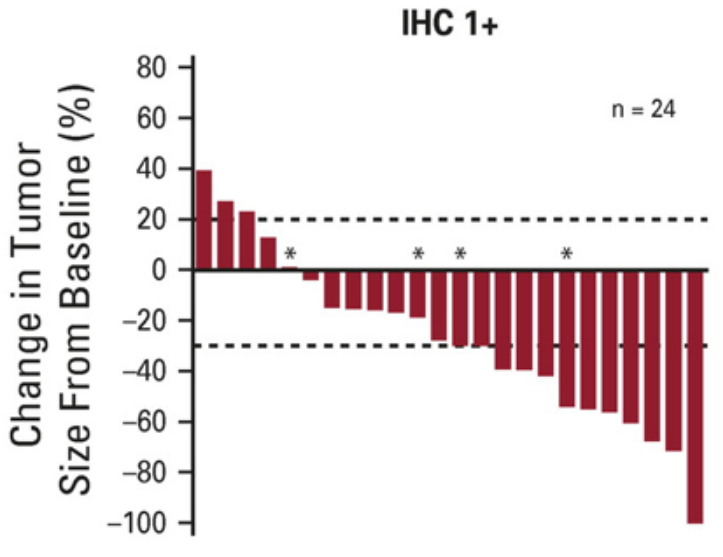
- HER2+ metastatic breast cancer

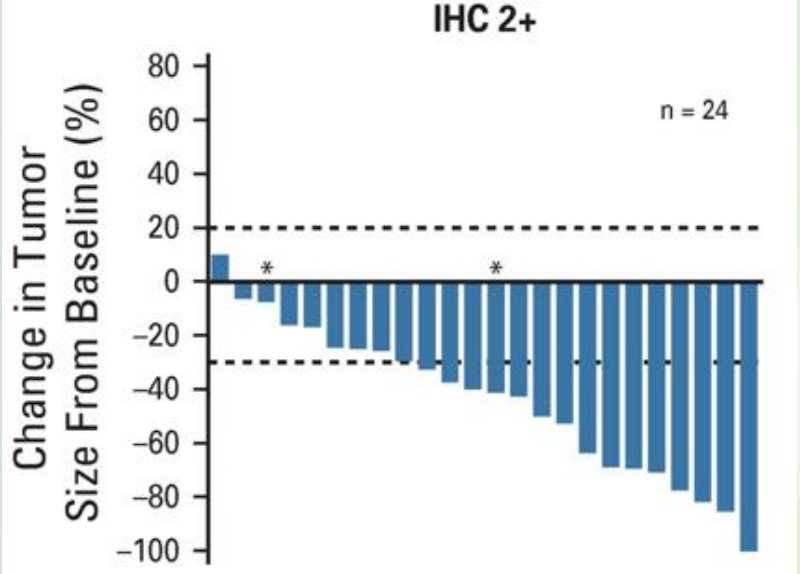
- **HER2 low, ultra low, and zero breast cancer**
  - Definition
  - Distribution
  - **Why HER2 low matters**

T-DXd in HER2-Low mBC

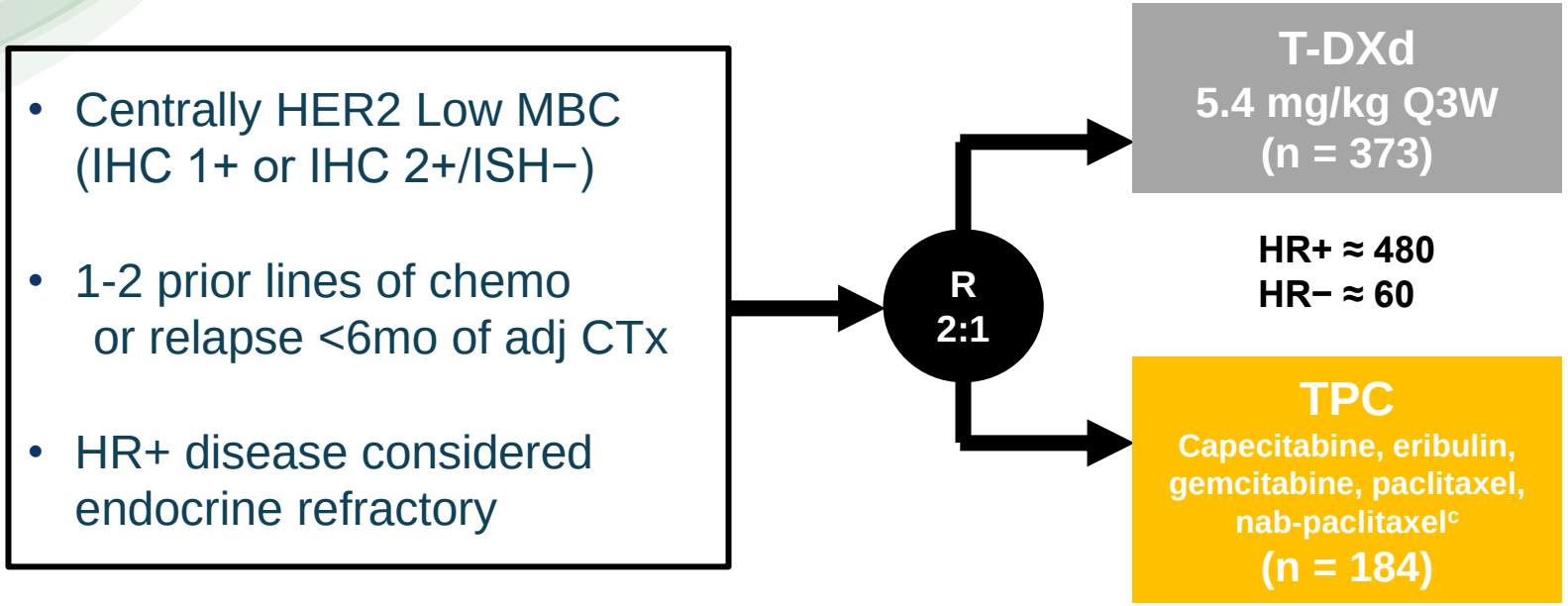
- HER2 Low mBC
- Median prior lines: 7.5
- ORR = 37%
- mDOR = 10.4 mo
- mPFS = 11 mo







DESTINY-Breast 04: Phase 3 Study of T-DXd for HER2-low mBC



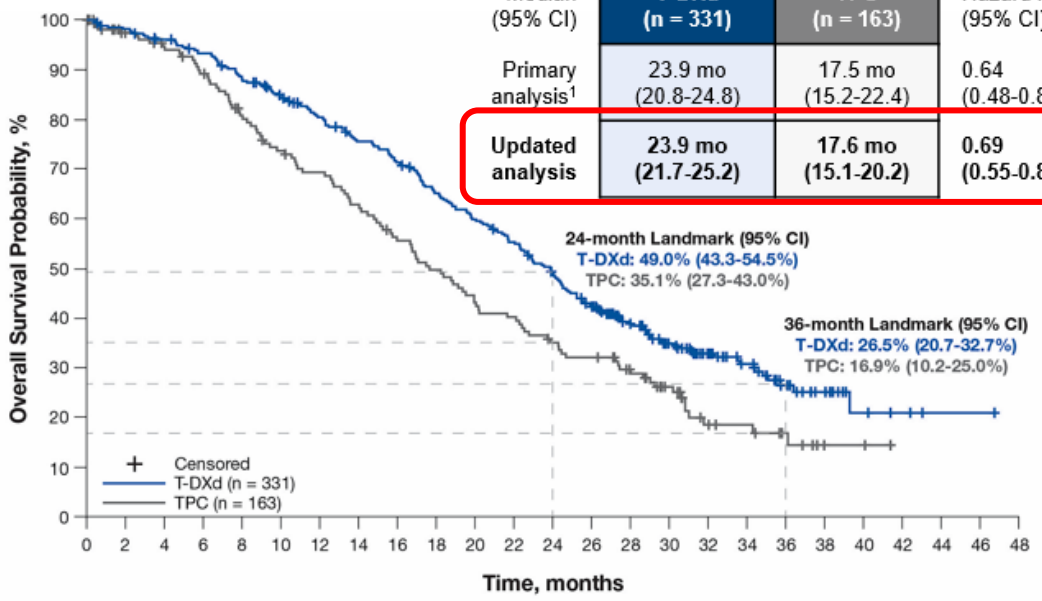
Primary endpoint: PFS

Modi S, et al. N Engl J Med. 2022 Jul 7;387(1):9-20.

DB-04: Overall Survival (med 32 mo f/u)

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)**



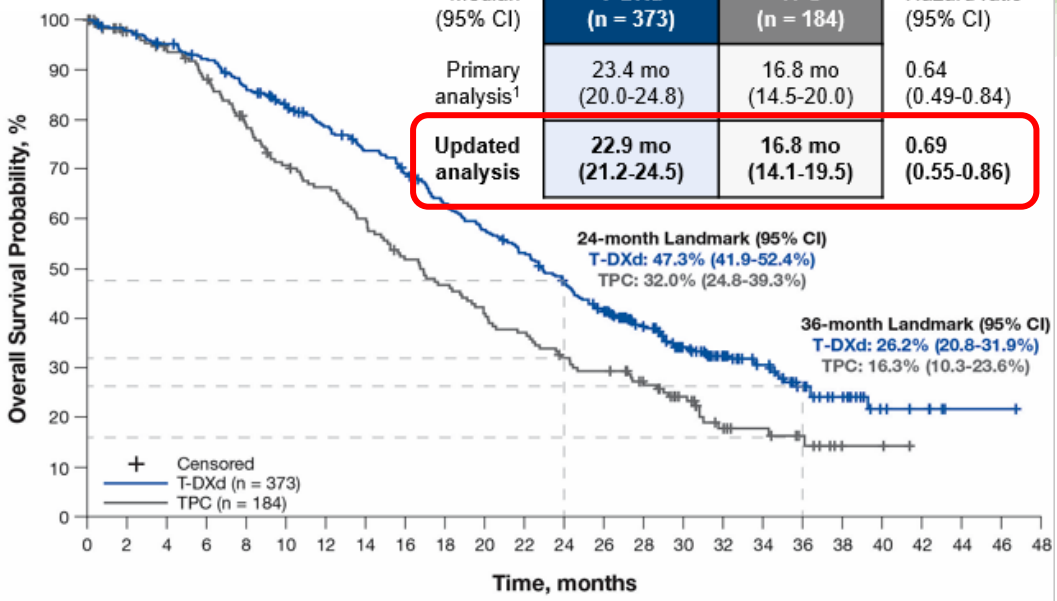
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 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 68 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) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

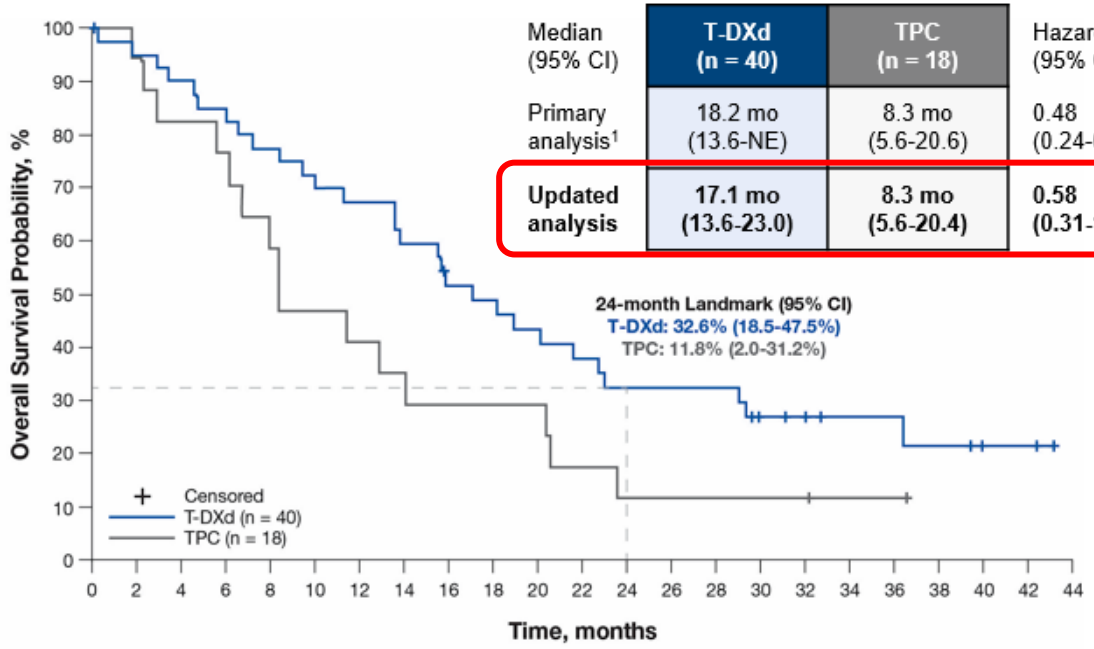
TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

Modi S et al. N Engl J Med. 2022

DB-04 : Efficacy in the HR− Cohort (med 32 mon f/u)

TNBC

Overall Survival

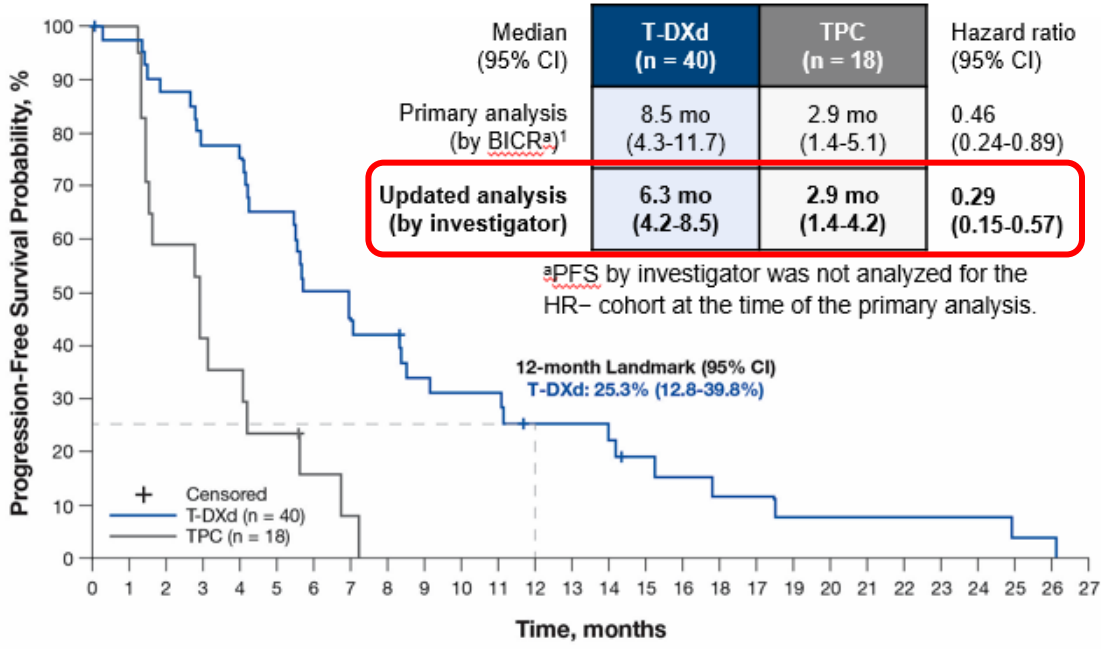


Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.

Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Modi S et al. N Engl J Med. 2022

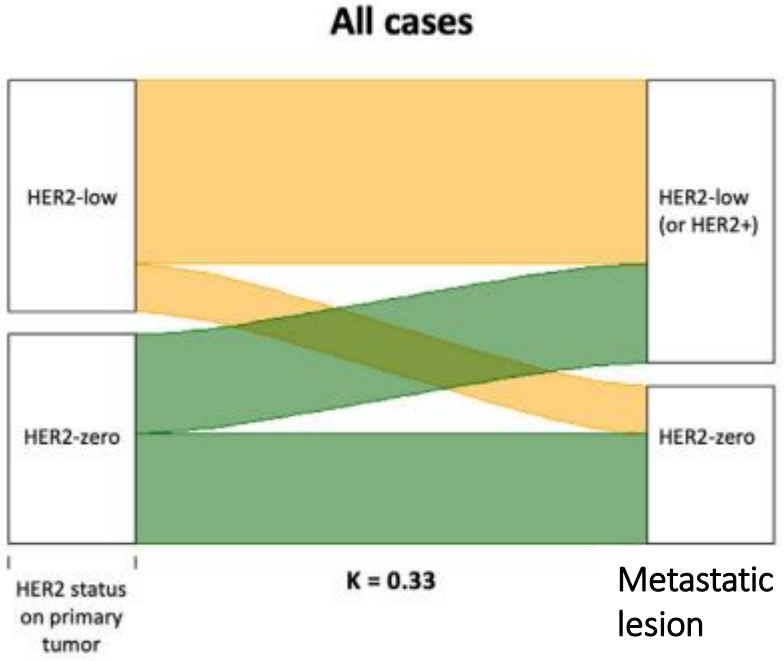
Challenges

1. **Low Concordance Among Pathologists Between HER2 IHC 0 and HER2 IHC 1+**

Among 18 experienced pathologists there was **only 26% concordance** between the diagnoses of HER2 IHC 0 and HER2 IHC 1+

- Digital Pathology?
- Quantitative Methods?
- RT-qPCR?

2. **HER2 Expression evolution**

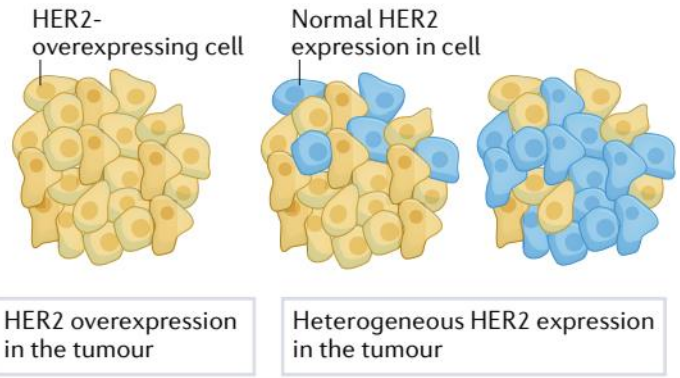


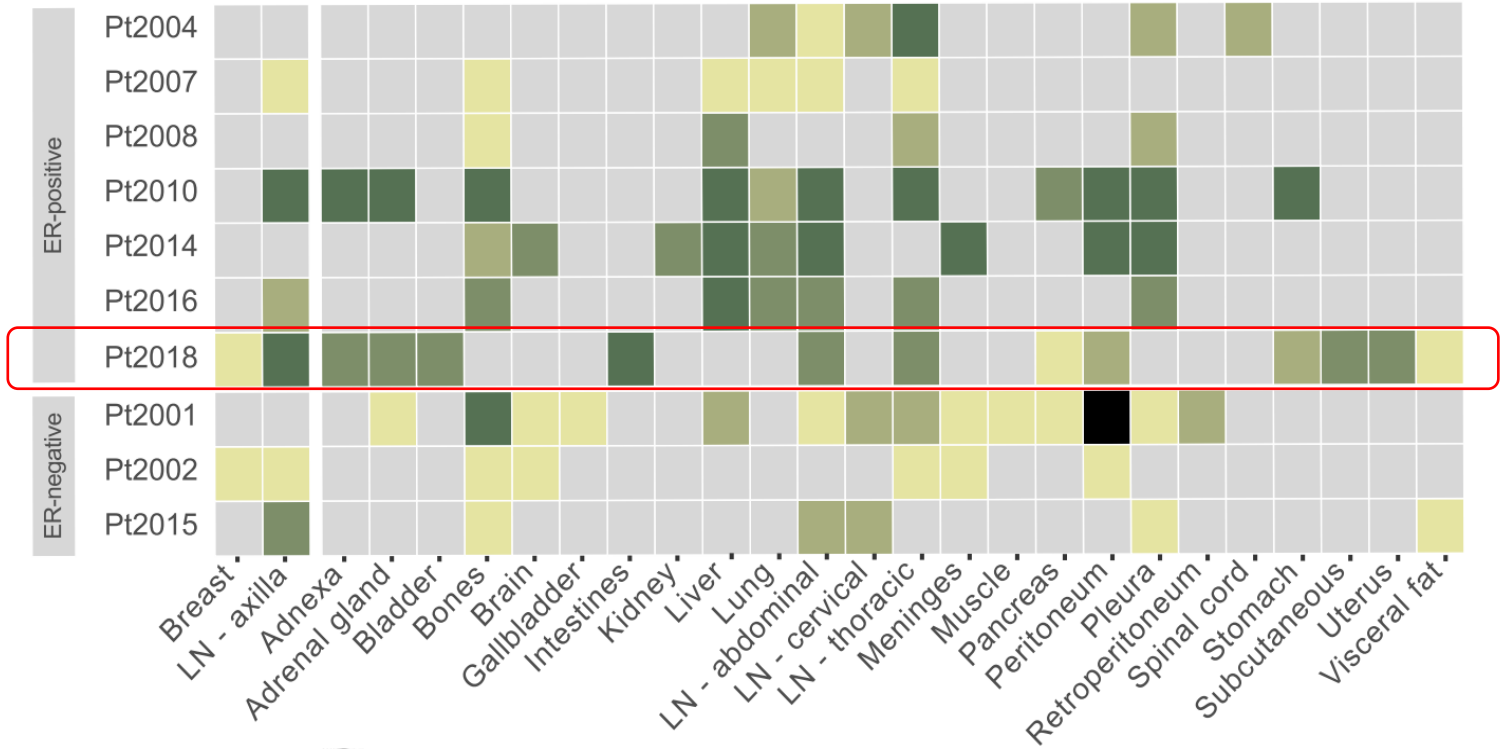
- Repeat biopsy?
- Liquid testing?

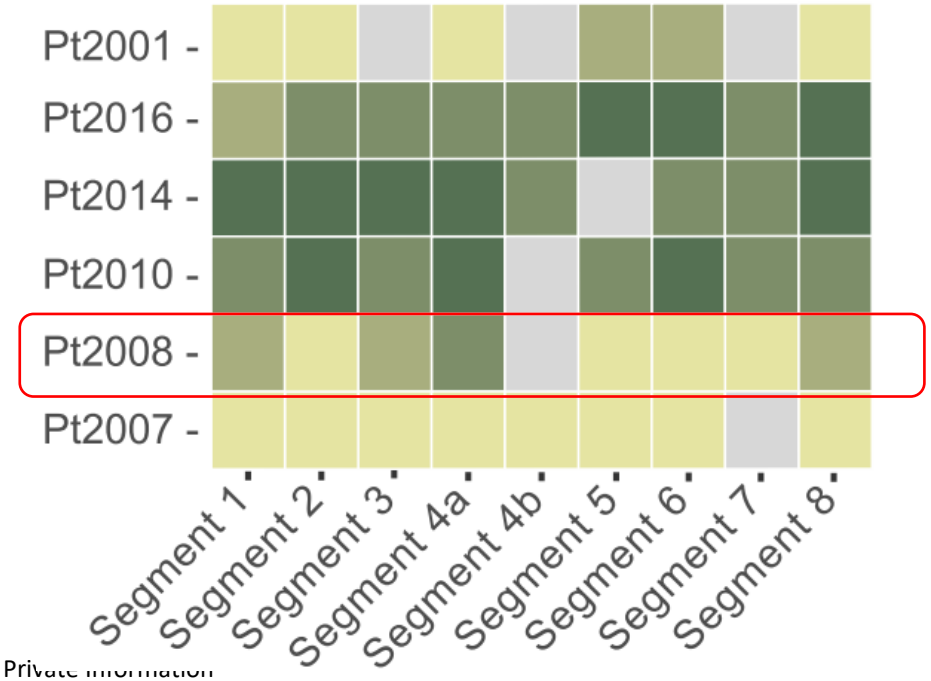
1. *Fernandez, et al. JAMA Oncol. 2022*
2. *P. Tarantino, et all. Euro J of Cancer. 2022*

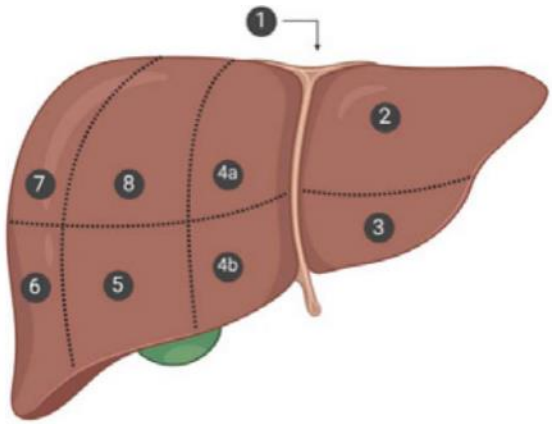
Challenges

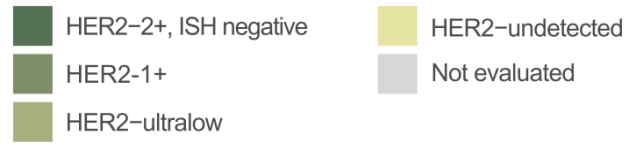
3. Tumor heterogeneity







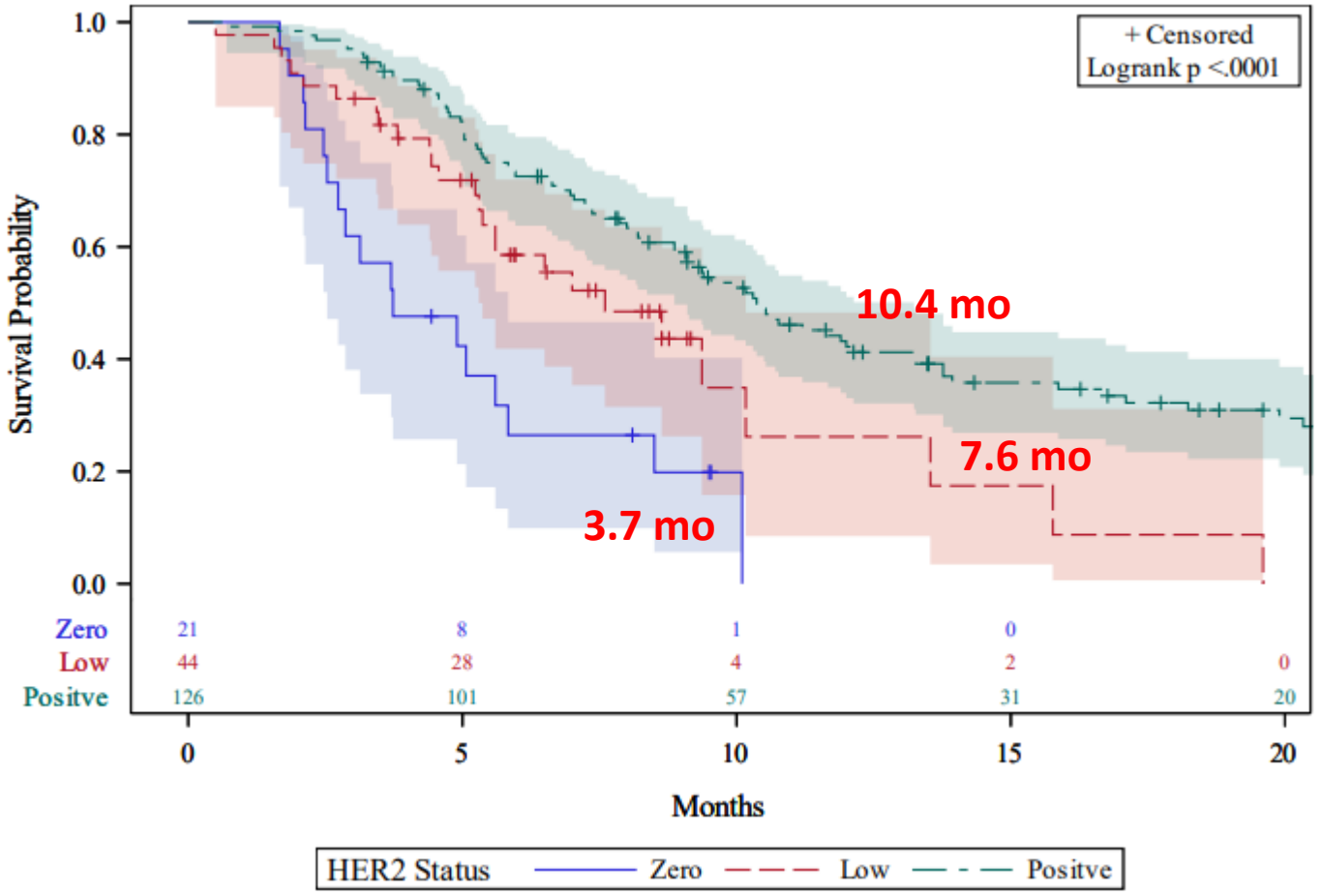




1. *Fernandez, et al. JAMA Oncol. 2022*
2. *Geukens E, et al. Euro J of Cancer, 2023*

RELIEVE- real world mBC response to T-Dxd by HER2 Expression

Time to Next Treatment (TTNT) by HER2 Expression

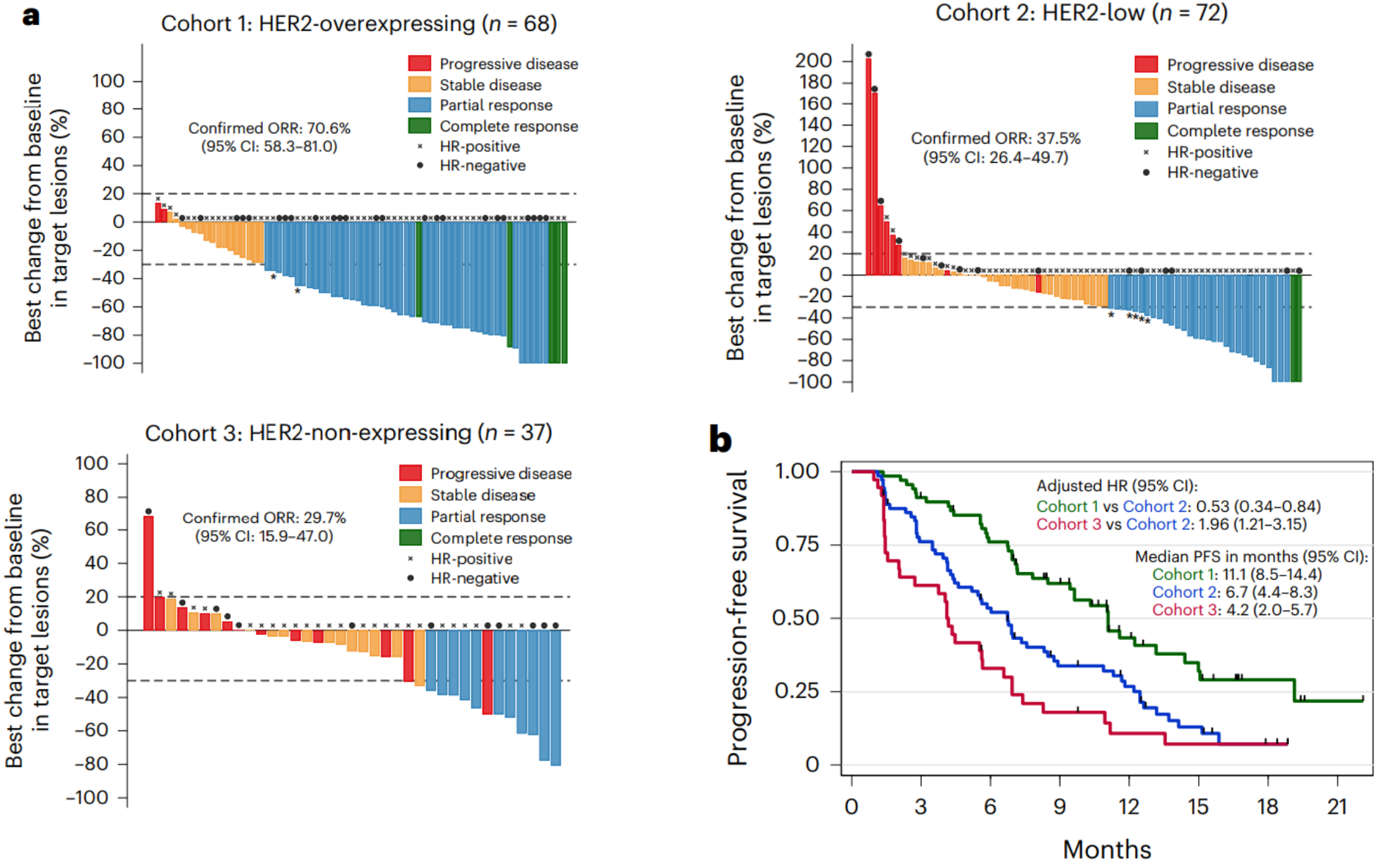


Change of HER2 Status	mTTNT	P value
HER2-Low -> HER2-0	3.0 mo	
HER2-0-> HER2- Low	5.6 mo	
Stable HER2 Low	9.4 mo	*P*=0.006

Lower HER2 expression, lower response to T-Dxd

Tarantino P, et al. SABCS. 2023

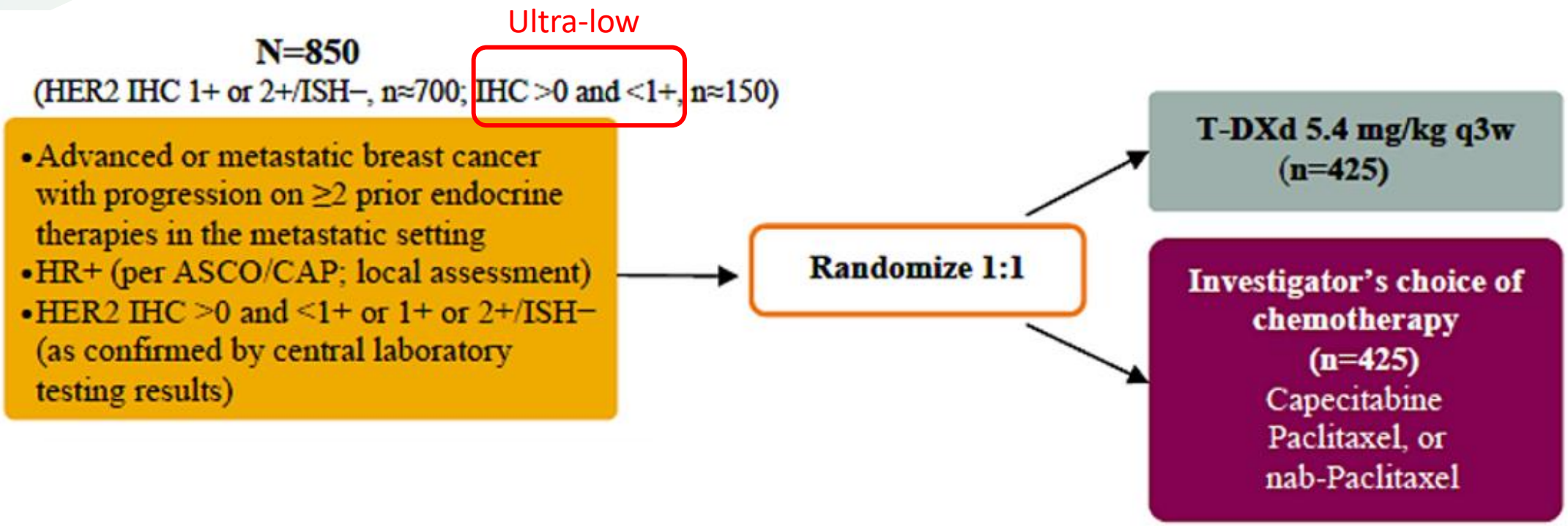
DAISY Study: T-Dxd in mBC with variable HER2 expression



- *Anti-tumor activity from T-dxd regardless HER2 expression*
- *ORR decreases as HER2 expression decreases*

Mosele F et al. Nature Medicine 2023

DESTINY-Breast 06:
T-DXd vs Investigator's choice for HER2 low and ultra-low BC



In Summary

- HER2+ mBC survival has improve significantly
- Many novel HER2 directed therapies are under investigation for HER2+ mBC
- HER2 low expression BC could still response to HER2 directed therapy
- More accurate HER2 testing methods is needed