EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

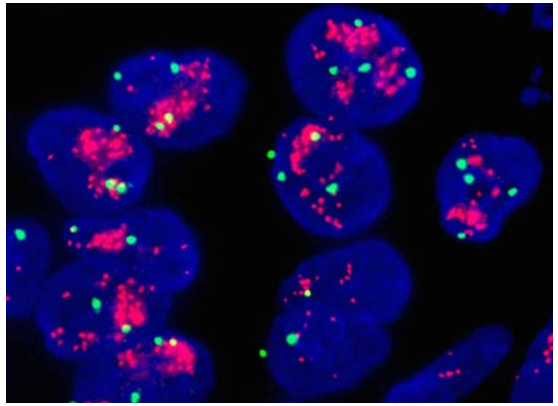
Updates in HER2+ Breast Cancer

Jane Lowe Meisel, MD
Associate Professor of Hematology and Medical Oncology
Associate Vice Chair of Faculty Development and Promotions
Winship Cancer Institute of Emory University

HER2+ Breast Cancer: A rapidly advancing field

- HER2 overexpression is present in 20% of breast cancers and predicts who will benefit from HER2-directed therapy
  - Trastuzumab was first approved for use in the US in 1998

- Recent developments:
  - Neoadjuvant therapy for locally advanced cancers has allowed for more personalized, risk-adapted adjuvant approaches
  - Pivotal trials have allowed de-escalation of therapies for the earliest-stage disease
  - Many more HER2-targeted agents to use in the early-stage and metastatic setting
  - Antibody-drug conjugates approved for use in metastatic HER2-low disease have changed how we think about HER2 status



HER2 FISH slide: positive for gene amplification

J Clin Oncol. 2018;36(20):2105. Epub 2018 May 30.

Early-Stage HER2+ Disease

High risk disease: neoadjuvant therapy

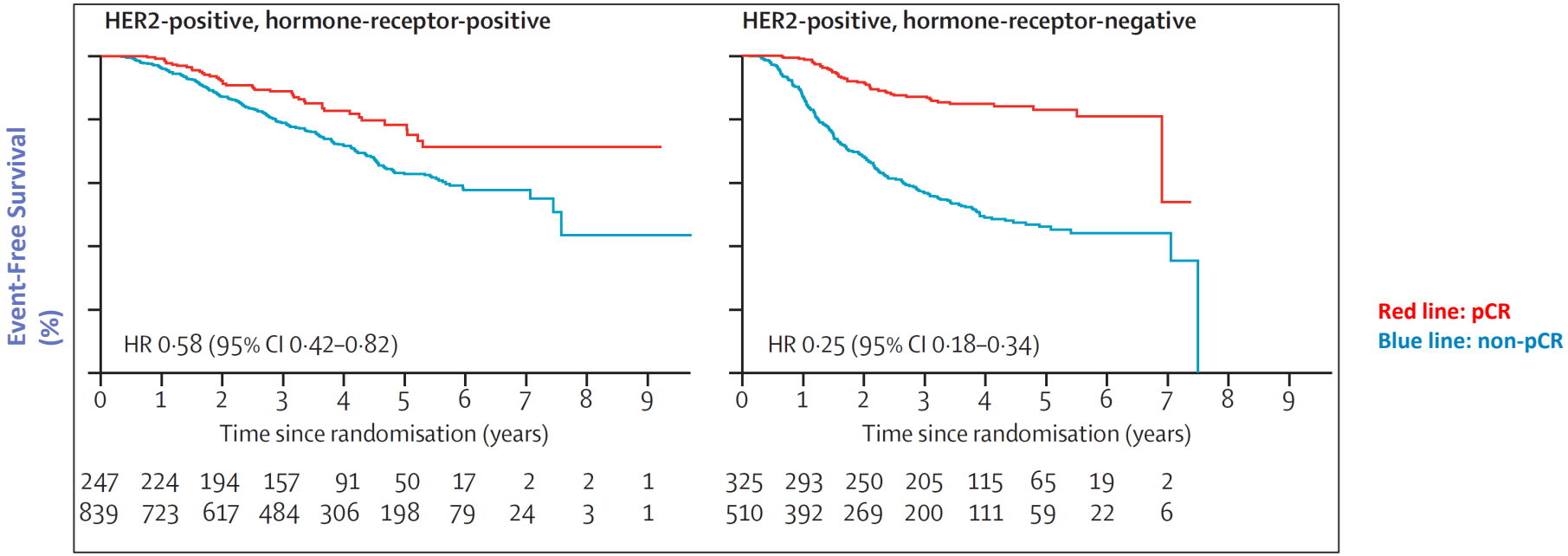
- NeoSphere and Tryphaena defined dual antibody therapy + chemotherapy as standard of care for patients with locally advanced HER2+ breast cancer

	Regimen	Duration	pCR	P value
NEOSPHERE (N=417)	TH		29%	
	TP	12 w	24%	
	THP		45.8%	0.0141
	HP		16.8%	
TRYPHAENA (N=225)	FECHP → THP		61.6%	
	FEC → THP	24 w	57.3%	
	TCbHP		66.2%	

- In US: AC x 4→ THP x 4, or TCHP x 6
  - TRAIN-2 showed high rates of pathologic complete response (pCR) with or without anthracyclines

The meaning of pCR

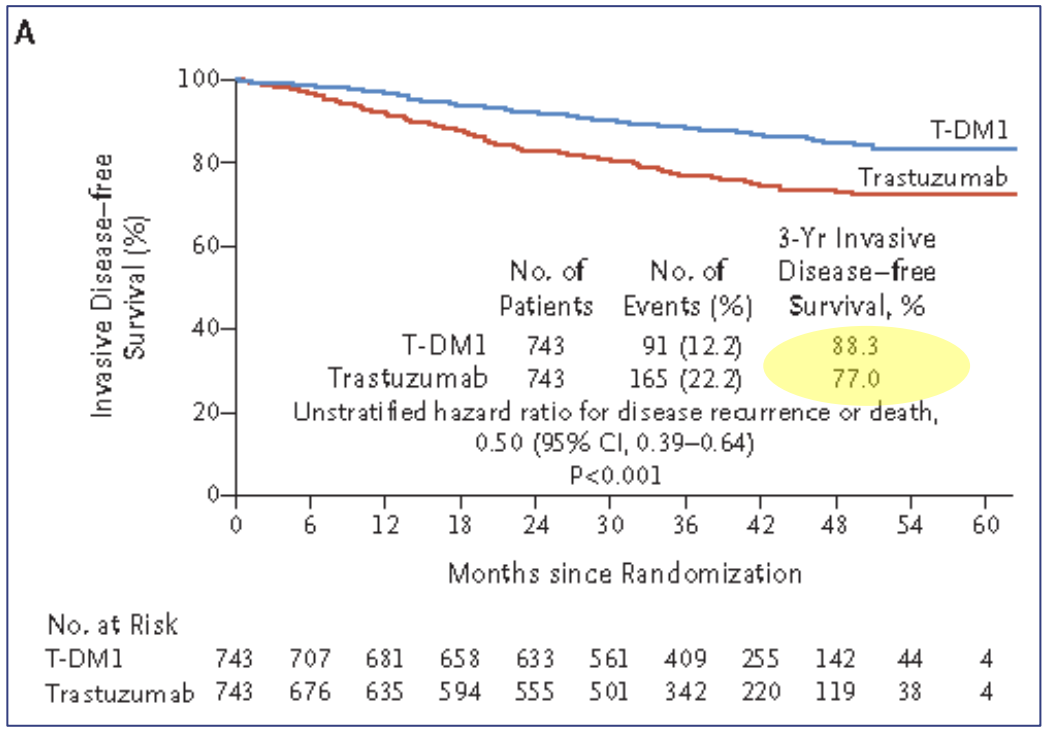
- Getting to pCR with NACT is predictive of outcome, particularly for HER2+ HR- patients

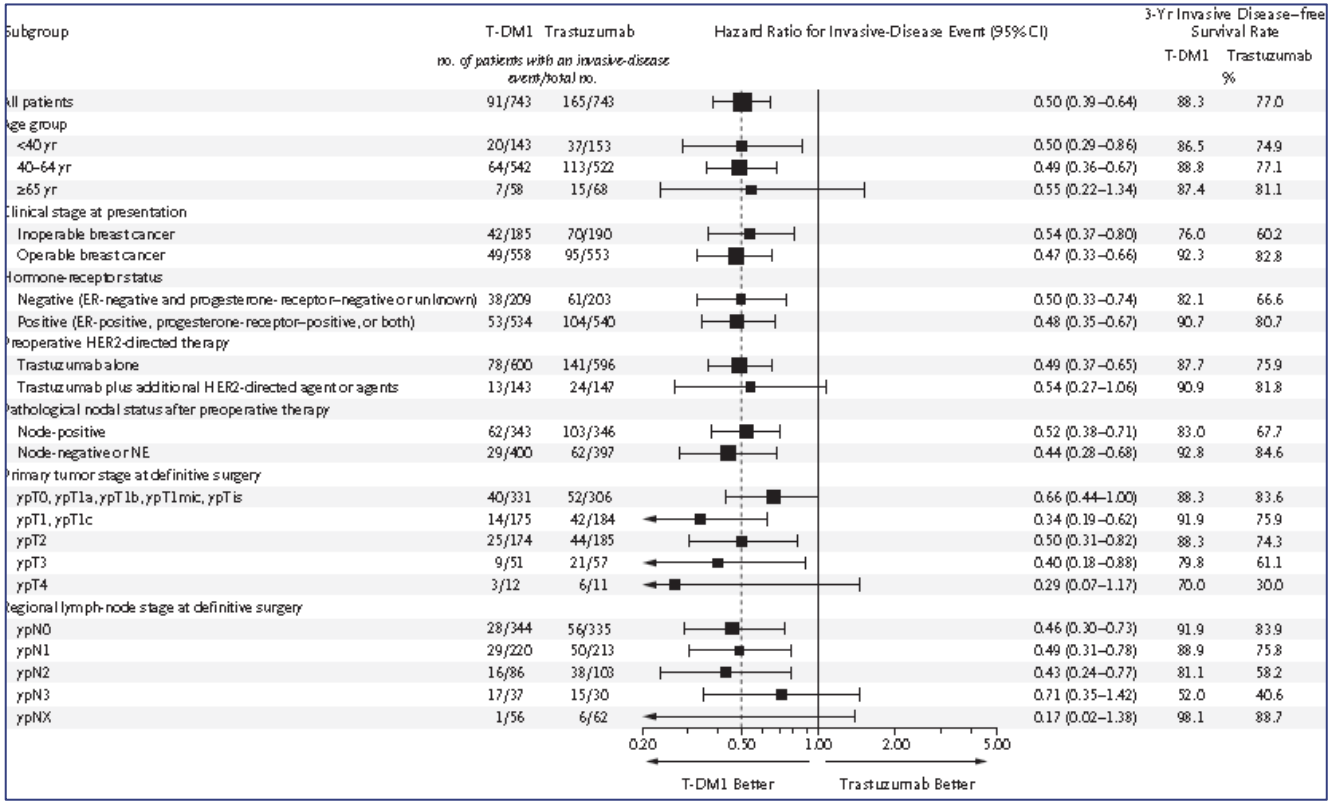


- What are the best ways to escalate therapy in patients with non-pCR?
- If patients get to pCR quickly, can we reduce the amount of NACT they receive?

Lancet 2014 Jul 12;384(9938):164-72.

KATHERINE: Adjuvant trastuzumab vs T-DM1 in the setting of residual disease

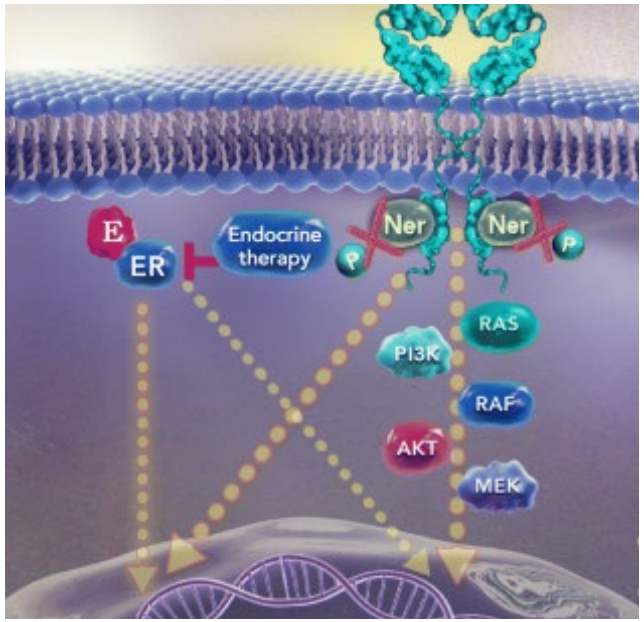




N Engl J Med. 2019;380(7):617.

ExteNET: extended adjuvant neratinib

- This trial evaluated 1y adjuvant oral neratinib after completion of adjuvant therapy (+/- endocrine therapy)
  - At five years, there was a 2.5% improvement in IDFS for neratinib vs placebo in ITT; 4.4% for HR+ and 0.1% for HR-
  - Crosstalk between ER and HER2 was felt to potentially play a role
- Given significant diarrhea with the drug, and treatment fatigue on the part of patients, additional analyses done to see which groups benefit the most
  - In HR+ patients who started therapy <1y from last trastuzumab, IDFS improved by 5.1% with neratinib
    - In patients in this category who had non-pCR to NACT, they achieved a 7.4% improvement in IDFS with neratinib



Martin et al. Lancet Oncol. 2017 Dec;18(12). Clin Breast Cancer. 2021;21:80. Clinical Drug Investigation 39, 221–229.

Future directions

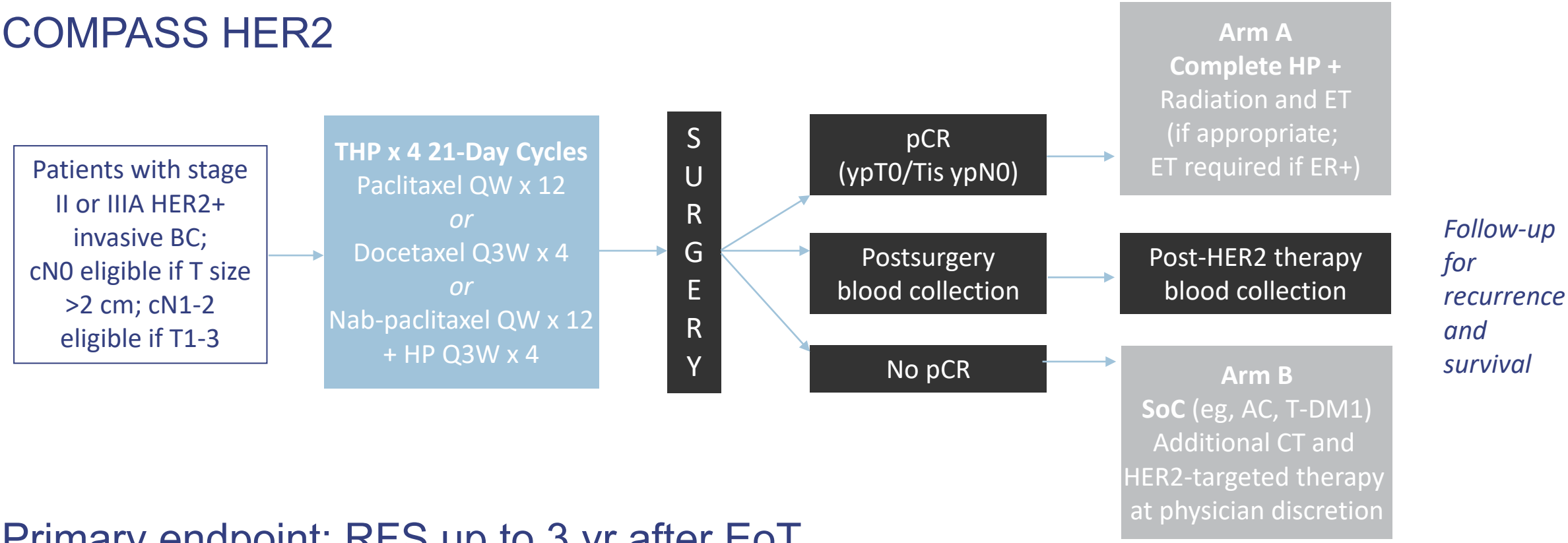
- DESTINY Breast 05: Trastuzumab deruxtecan (T-Dxd) vs trastuzumab emtansine (T-DM1) in high-risk HER2+ patients with residual invasive breast cancer after NACT (NCT04622319)

- COMPASS-HER2 RD: T-DM1 and tucatinib compared with T-DM1 alone in preventing relapses in patients with high-risk HER2+ breast cancer (NCT04457596)

- ***If still “more” becomes a new standard of care for these highest-risk patients, we have to continue to rededicate ourselves to optimizing side effect management and support of these patients

We can do more – but can we also safely do less?

- COMPASS HER2

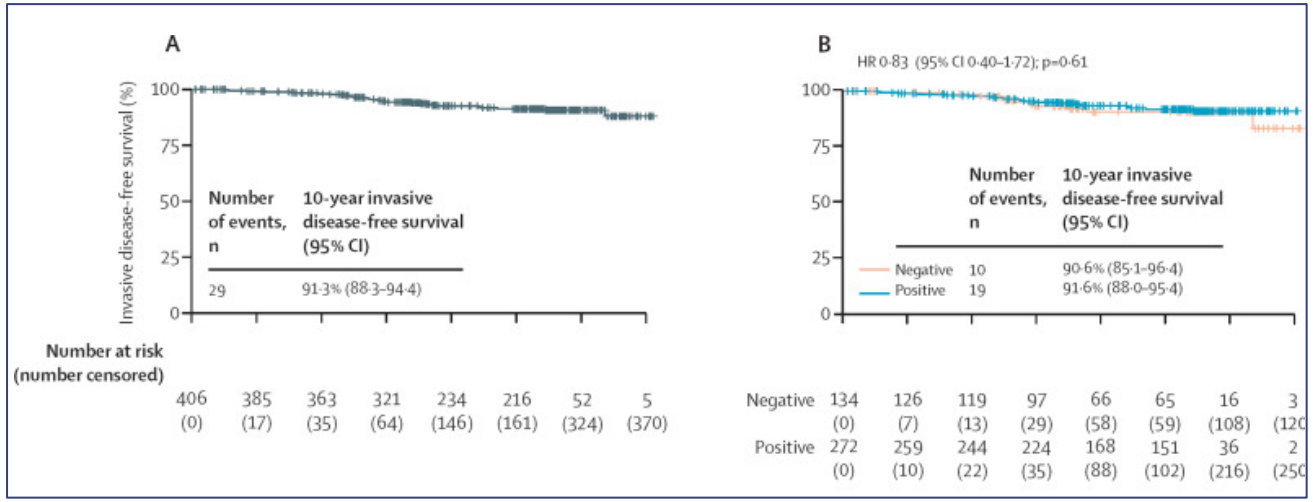


- Primary endpoint: RFS up to 3 yr after EoT
- Secondary endpoints: IDFS, DDFS, DRFS, RFI, OS, EFS, safety

Low-risk early stage disease

- The APT trial evaluated the safety and efficacy of 12 weeks of paclitaxel/trastuzumab (followed by 9 months of trastuzumab) in patients with ≤ 3cm node-negative HER2+ breast cancer

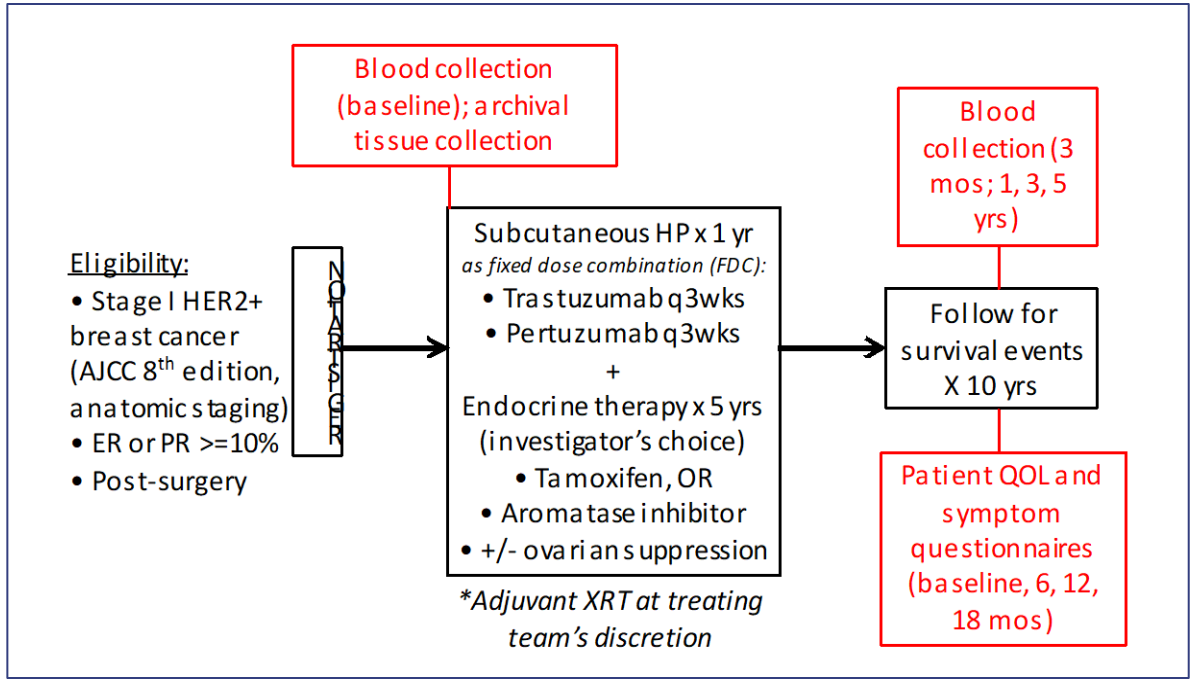
  - 3y IDFS: 98.7%
  - 7y IDFS: 93.3%
  - 10y IDFS: 91.3%



- This became a new standard of care

Future directions

- ADEPT: a chemo-free regimen for early stage HR+ HER2+ patients?



- Duration and mode of administration of anti-Her2 therapy:
  - Multiple trials have evaluated the possibility of shorter courses of trastuzumab for low-risk patients
  - Subcutaneous trastuzumab and trastuzumab/pertuzumab are now approved in addition to IV

Lancet Oncol. 2013;14(8):741. Ann Oncol. 2015; 26 (7): 1333. J Clin Oncol. 2018;36S: .

Advanced HER2+ Disease

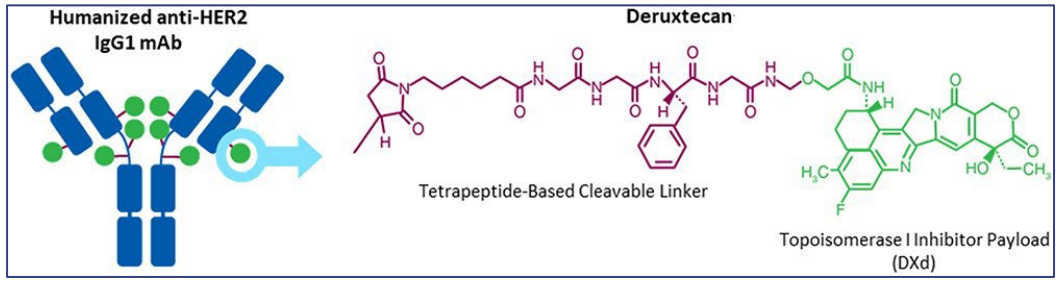
Standard of care: Early 2020

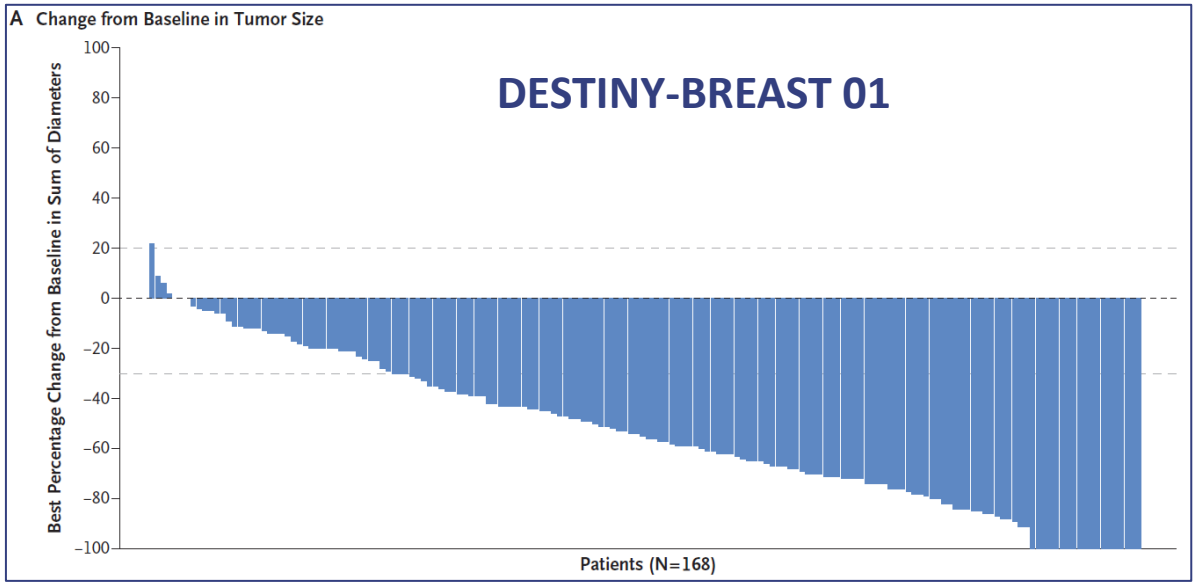
- First line:
  - Taxane + trastuzumab + pertuzumab
    (T/P=dual monoclonal antibody)
- Second line:
  - T-DM1
    (antibody-drug conjugate)
- Third line:
  - Capecitabine + lapatinib, capecitabine + trastuzumab, lapatinib + trastuzumab
    (L=TKI)
  - Trastuzumab + alternate chemotherapy

Since then: Extraordinary progress

Drug	Route	Mechanism of action	Partner drug	Special features
Trastuzumab deruxtecan	IV	Antibody drug conjugate targeting HER2	None	High membrane permeability and drug/antibody ratio
Tucatinib	PO	Reversible TKI targeting HER2	Capecitabine + trastuzumab	CNS penetration
Neratinib	PO	Irreversible TKI targeting HER1, HER2, HER4	Capecitabine	CNS penetration
Margetuximab	IV	Her2-directed antibody	Chemotherapy	Optimized Fc region to optimize antibody-dependent cellular toxicity

Trastuzumab deruxtecan (T-Dxd)





Unique features:

-High potency payload
-High drug to antibody ration (~8)
-Payload with short systemic half-life
-Tumor selective (cleavable linker)
-Membrane permeable payload

- Single-arm phase 2 study of T-Dxd for HER2+ MBC
- Median 6 prior lines of therapy; overall response rate 61%
- Median PFS 16.4 months

Chem Pharm Bull (Tokyo). 2019; 67 (3): 173-185. Clin Cancer Res 2016; 22 (20): 5097-5108. Pharmacol Ther. 2018; 181:126-142. Cancer Sci 2016; 107 (7): 1039-1046. Modi S et al N Eng J Med. 2020; 382 (7): 610-21.

DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd

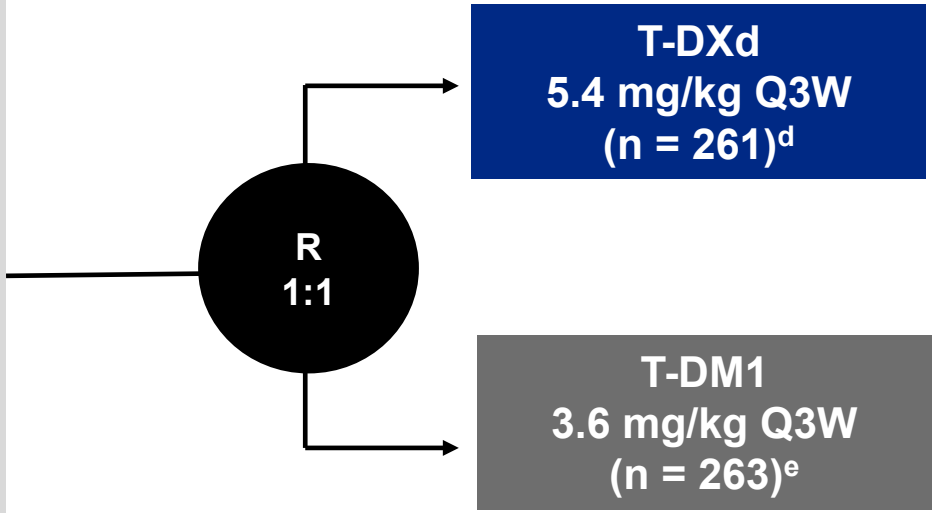
An open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer that has been previously treated with trastuzumab and a taxane[b]
- Could have clinically stable, treated brain metastases[c]
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment

Stratification factors

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



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

Secondary endpoints

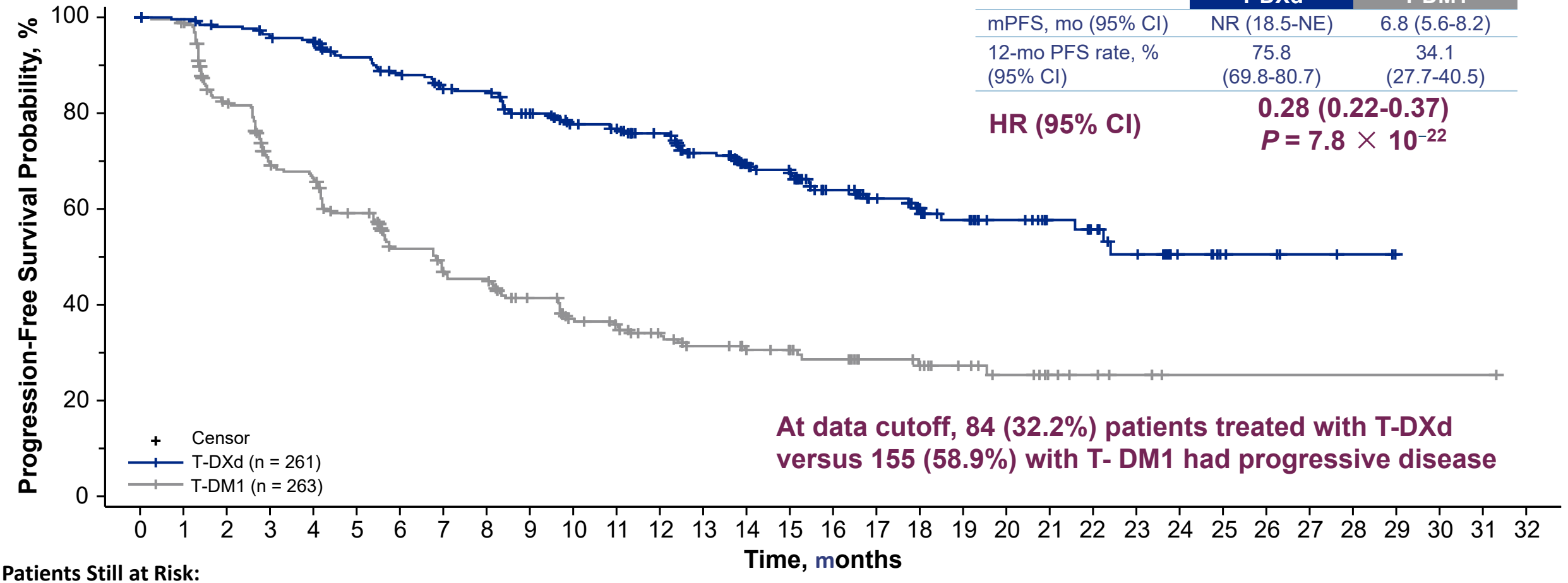
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

- At the time of data cutoff (May 21, 2021), 125 (48.6%) T-DXd patients and 214 (82.0%) T-DM1 patients had discontinued treatment
- Median follow up was 15.9 months
- BMs were measured at baseline by CT or MRI and lesions were monitored throughout the study

BICR, blinded independent central review; BM, brain metastasis; CT, computed tomography; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MRI, magnetic resonance imagining; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]Prior to protocol amendment, patients with stable, untreated BM were eligible. [d]4 patients were randomly assigned but not treated. [e]2patients were randomly assigned but not treated.

Primary Endpoint: PFS by BICR

	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	



At data cutoff, 84 (32.2%) patients treated with T-DXd versus 155 (58.9%) with T- DM1 had progressive disease

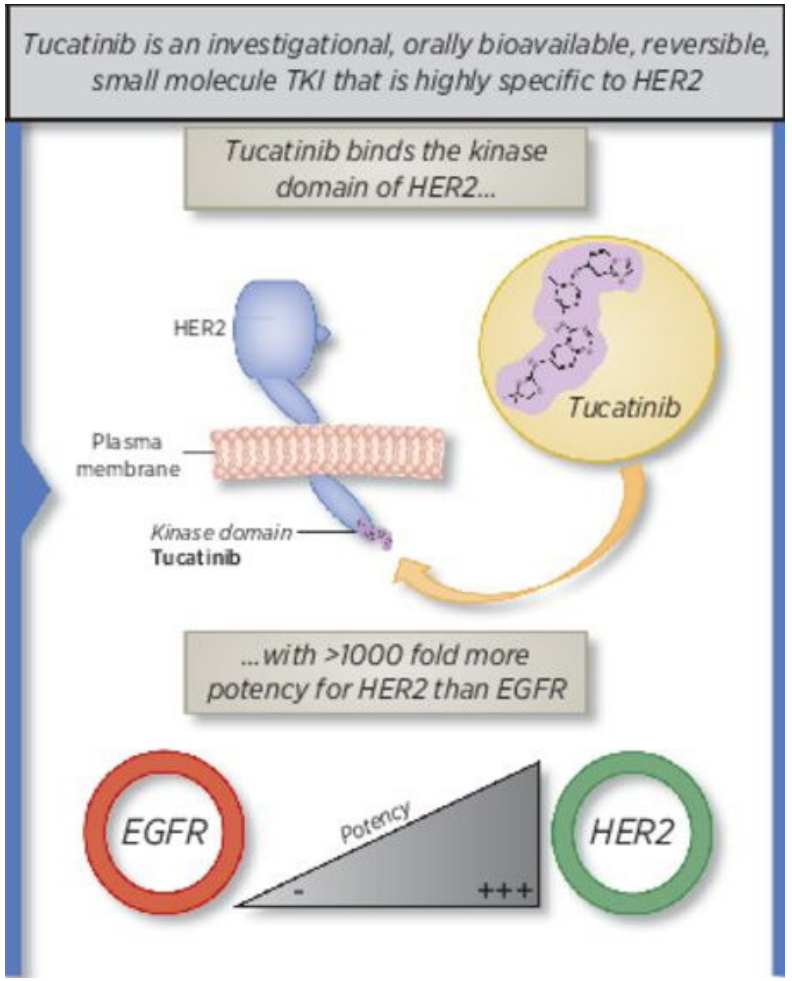
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0			
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and was 13.9 months (range, 11.8-15.1) for T-DM1.
Cortés et al. *Ann Oncol*. 2021; 32(suppl_5):S1283-S1346. 10.1016/annonc/annonc741

Tucatinib

- Orally bioavailable, highly potent TKI
- Highly selective for HER>EGFR
  - Because of this, fewer EGFR-related toxicities (diarrhea, rash)
  - More favorable side effect profile may lead to better compliance, fewer dose reductions, and longer duration of treatment
- Superior activity compared with other TKIs in preclinical models of brain metastases



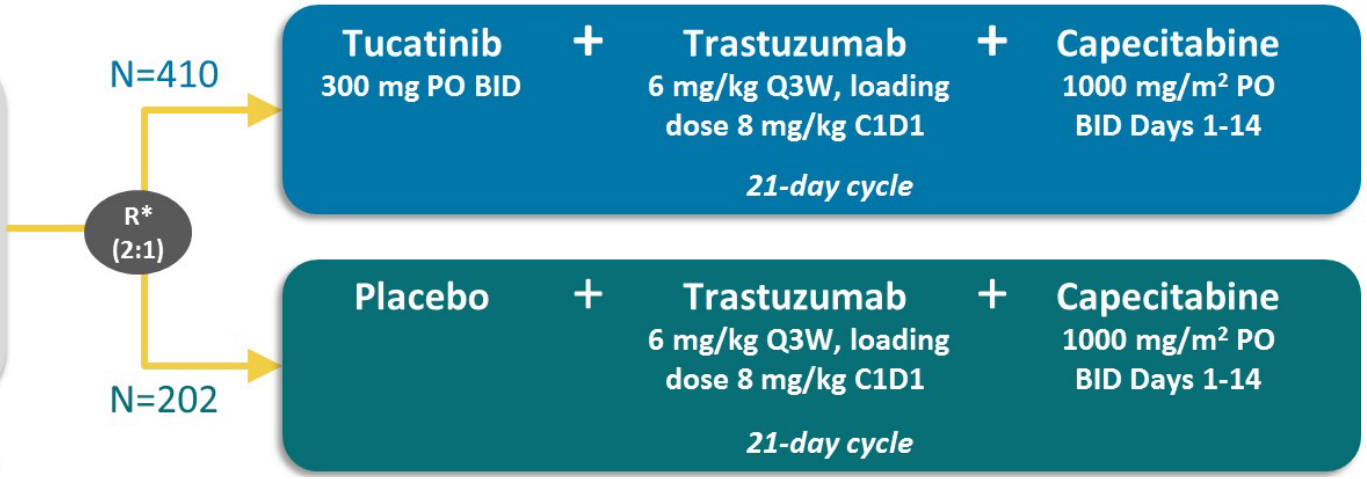
Dinkel V et al, AACR 2012, Abstract 852. Mol Cancer Ther. 2020; 19 (4): 976-987.

HER2CLIMB

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline

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

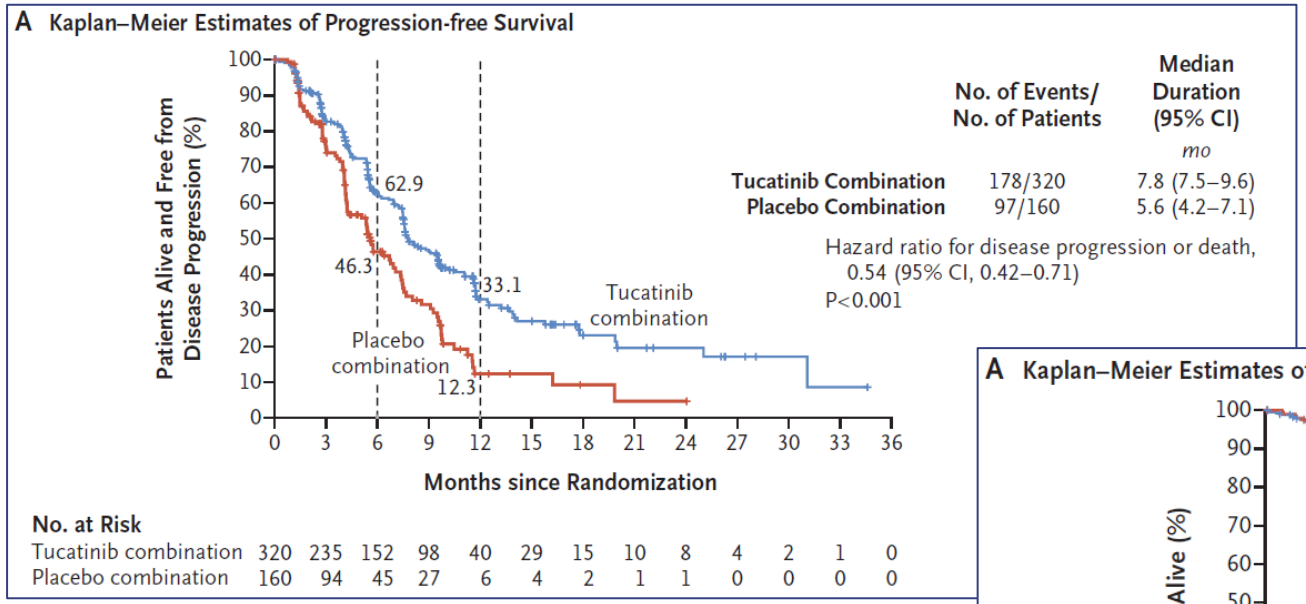


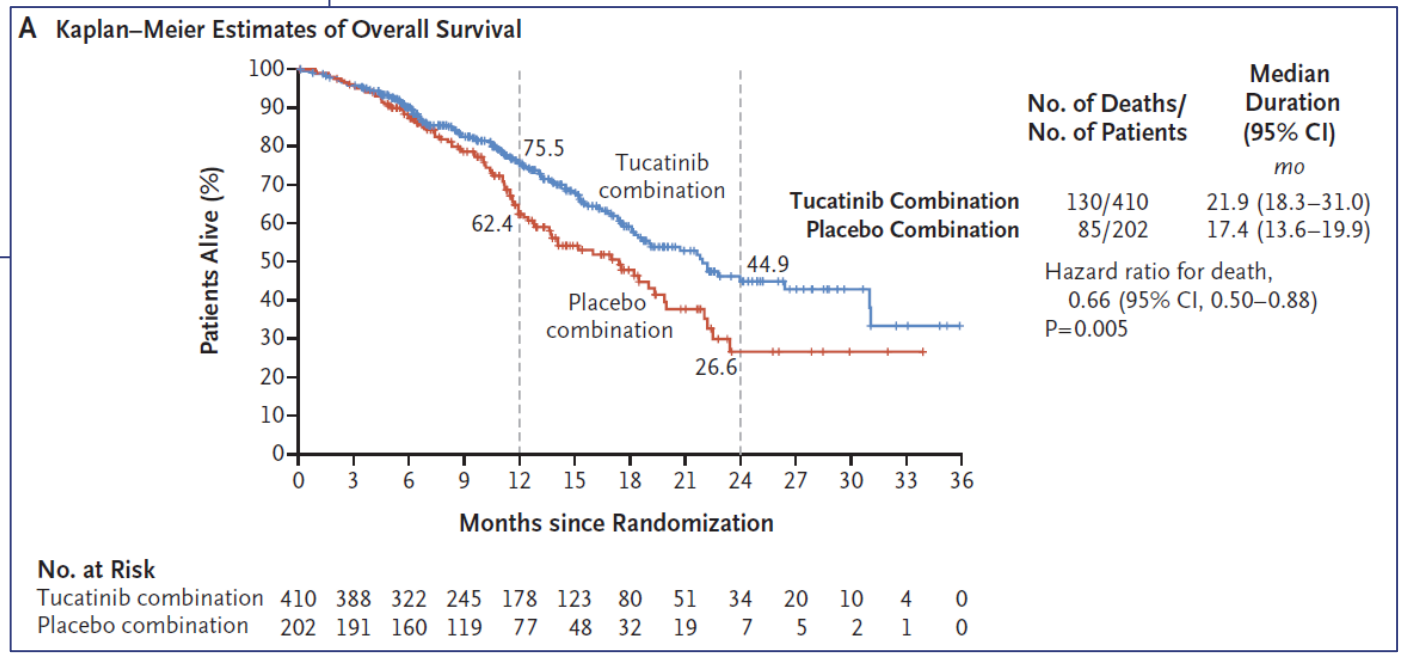
Brain Metastasis population included:

- Previously treated stable BM
- Untreated BM not needing immediate local therapy
- Previously treated progressing BM not needing immediate local therapy
- No evidence of BM

All Patients With BM, n	N = 291
Treated stable BM	**117**
Active BM	**174**
Treated progressing	108
Untreated	66

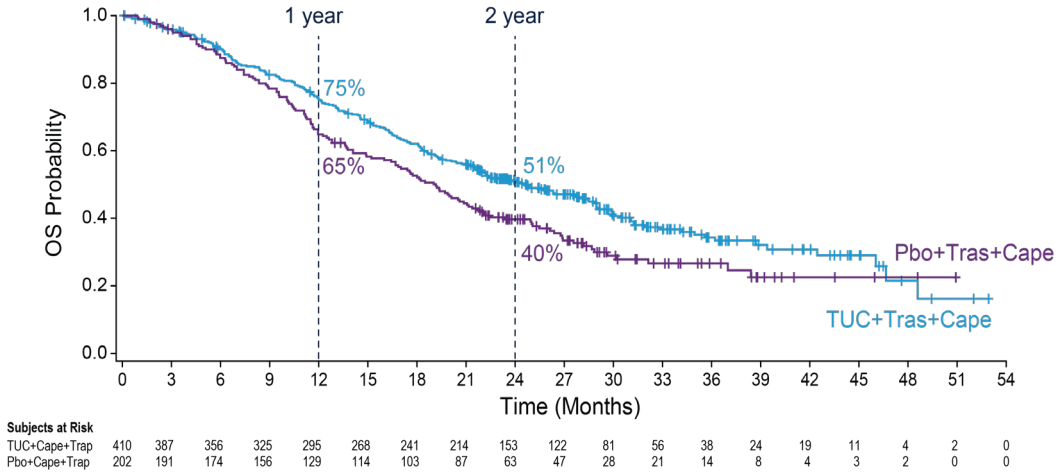
HER2CLIMB: Primary results



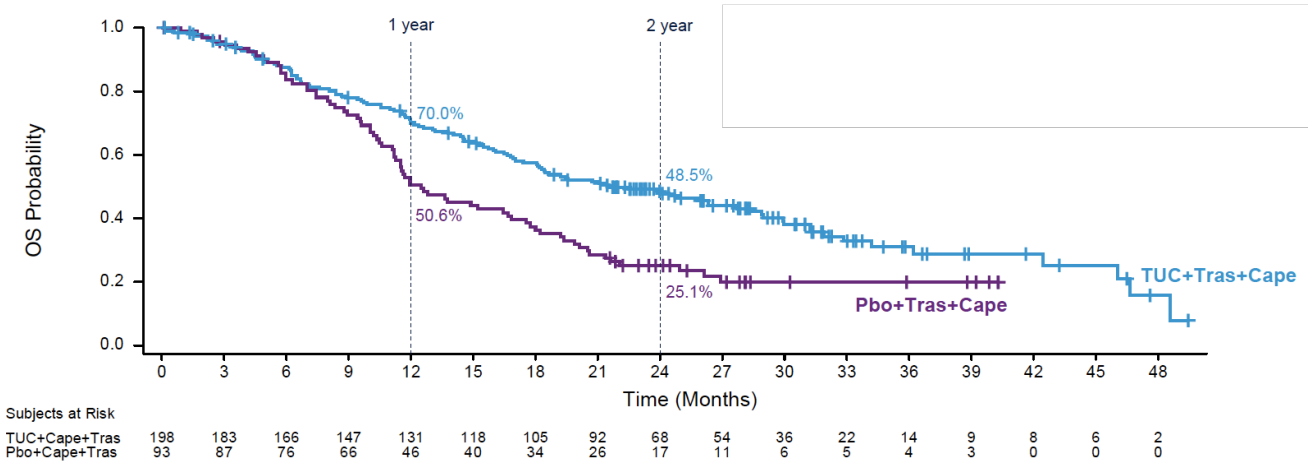


Murthy RK et al. *N Engl J Med.* 2020;382:597-609.

HER2CLIMB Updated Survival Analysis



OS for total population (n=612)



OS for all patients with brain mets (291)

	Events	HR (95% CI)	*P* Value	Median OS (95% CI)
TUC+Tras+Cape	233/410	0.73 (0.59, 0.90)	0.004	24.7 months (21.6, 28.9)
Pbo+Tras+Cape	137/202			19.2 months (16.4, 21.4)

	Events	HR (95% CI)	*P* value	Median OS (95% CI)
TUC+Tras+Cape	118/198	0.600 (0.444, 0.811)	0.00078	21.6 months (18.1, 28.5)
Pbo+Tras+Cape	71/93			12.5 months (11.2, 16.9)

Curigliano G et al. Presented at American Society of Clinical Oncology Annual Meeting. June 4-8, 2021; Abstract 1043.
Lin NU et al. Presented at the San Antonio Breast Cancer Symposium. December 7-10, 2021. Abstract PD4-04.

Tucatinib: future possibilities

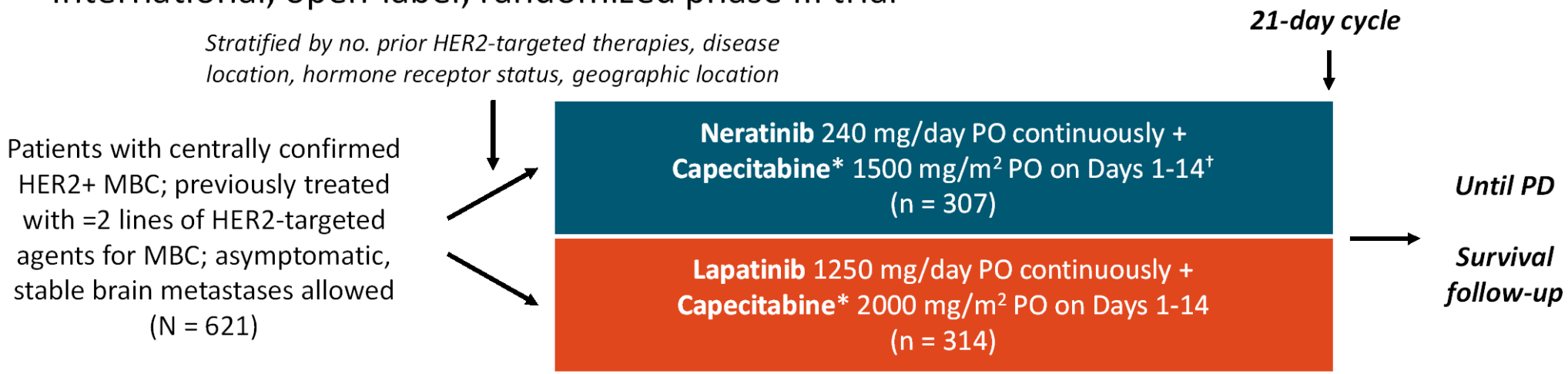
- Trials looking at tucatinib in other spaces:
  - T-DM1 + placebo or tucatinib (NCT03975647; actively recruiting)
  - Trastuzumab deruxtecan + placebo or tucatinib (NCT04539938, actively recruiting)
  - Trastuzumab/pertuzumab + tucatinib or placebo (NCT05132582; actively recruiting)
  - Tucatinib + palbociclib + letrozole (NCT03054363; fully enrolled)

OTHER PLANNED STUDIES

- Tucatinib + margetuximab + capecitabine
- Alpelisib + tucatinib in HER2+ PIK3CA mutant breast cancer

NALA: Neratinib/Cape vs Lapatinib/Cape in HER2+ MBC With =2 Prior Lines of HER2-Targeted Agents

- International, open-label, randomized phase III trial

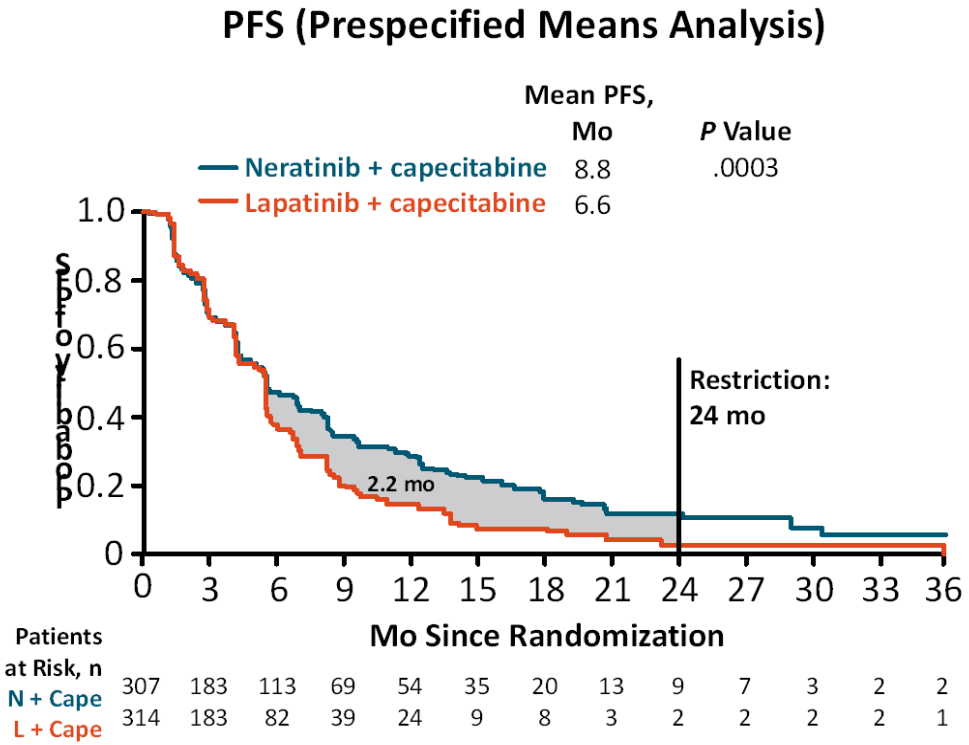


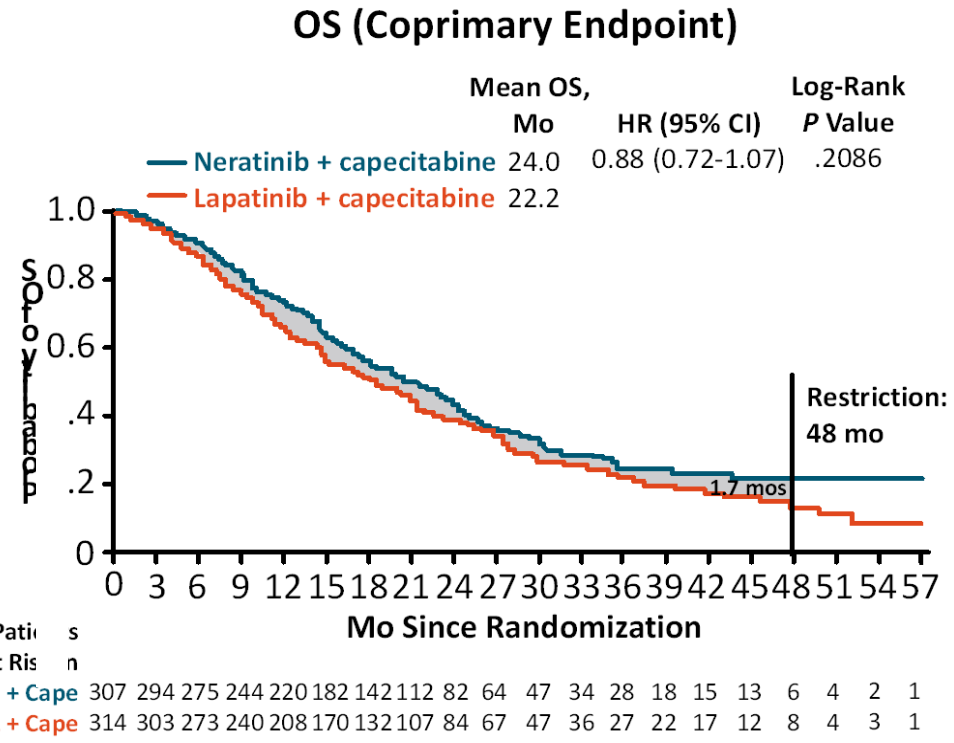
*BID in 2 evenly divided doses. †Loperamide administered at 4 mg with first neratinib dose followed by 2 mg Q4H for first 3 days, followed by 2 mg every 6-8 hr through end of cycle 1; as needed thereafter.

- Co-primary endpoints = OS, PFS (centrally confirmed)
- Secondary endpoints = locally determined PFS, ORR, CBR, safety, PROs, intervention for CNS mets

Saura. JCO. 2020; 38: 3138

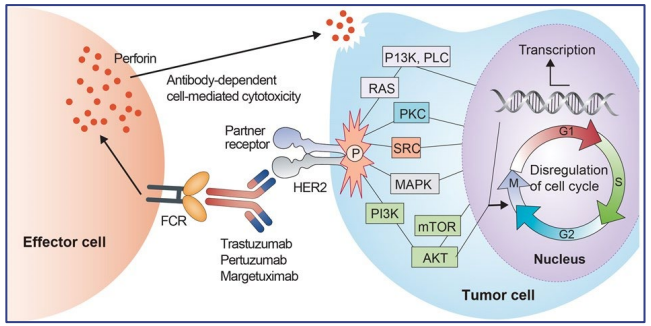
NALA results





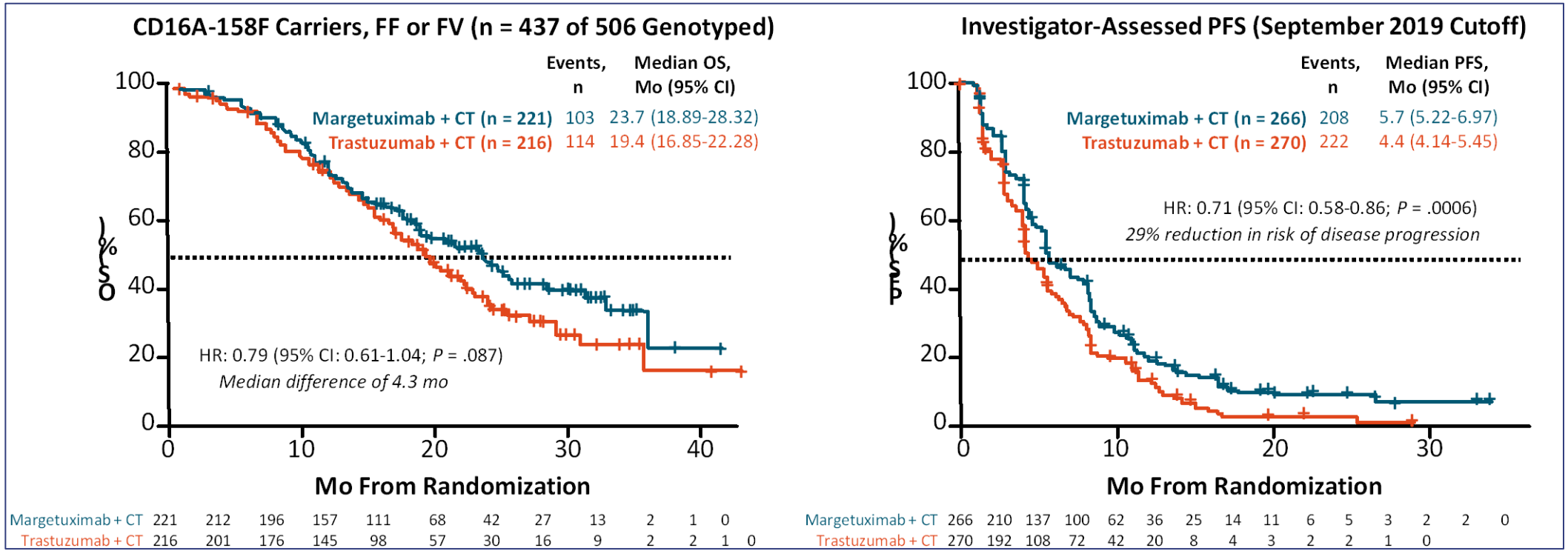
	Neratinib	Lapatinib
ORR	33%	27%
18-month PFS	16%	7%
Mean OS	24 mo	22 mo

Margetuximab



- Same specificity and affinity to HER2 as trastuzumab with similar ability to disrupt signaling
- However, due to increased affinity for Fc CD16A and decreased affinity for CD32B, it may enhance innate immunity and provide more potent ADCC stimulation

SOPHIA Trial

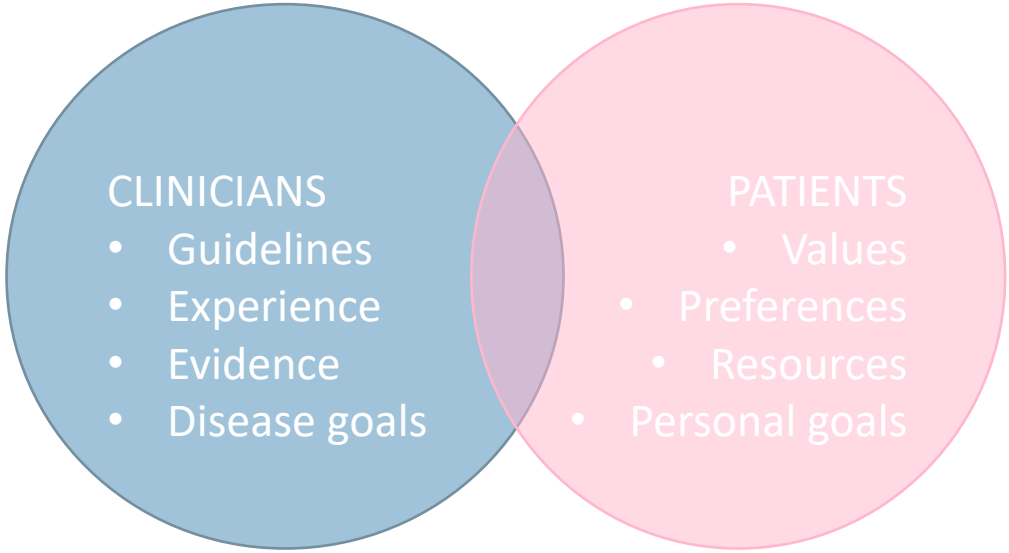


Picture courtesy of creativebiolabs.net. JAMA Oncol. 2021;7(4):573-584.

Standard of care: early 2023

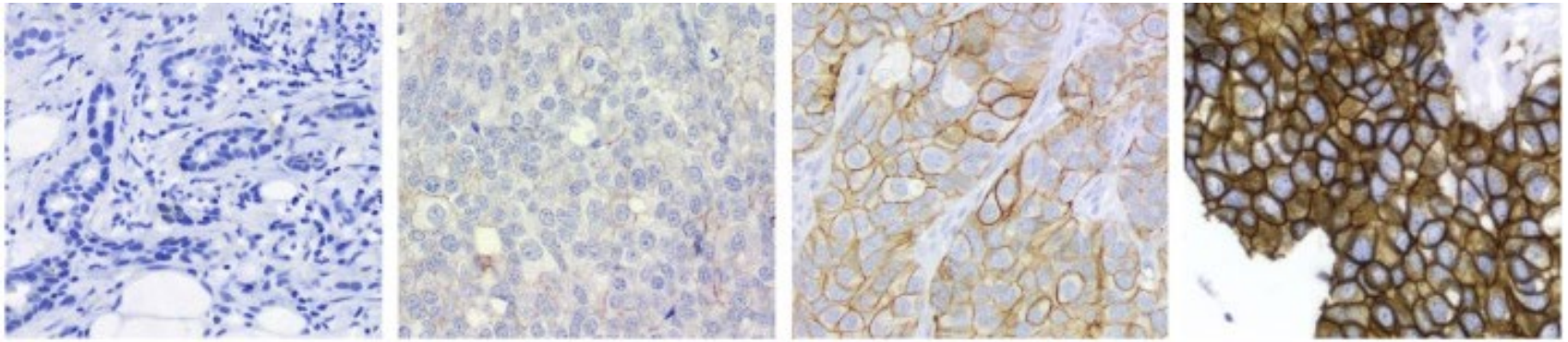
- First line
  - Taxane/trastuzumab/pertuzumab
- Second line
  - T-Dxd
- Third line
  - HER2-CLIMB regimen*
- Fourth line – multiple options
  - T-DM1
  - Neratinib/capecitabine
  - Margetuximab + chemo
  - Trastuzumab + chemo

- Because of so many different options with different side effects, shared decisionmaking and careful re-evaluation really becomes key



HER2-low advanced breast cancer

- Defined as cancer with HER2 IHC scores of 1+/2+ but ISH negative
  - Heterogeneous, lots of HR co-expression
- Until recently, HER2-low was treated as HER2 negative
- **DESTINY-Breast 04**: the first study to look at a medication specifically in a HER2-low population (trastuzumab deruxtecan)

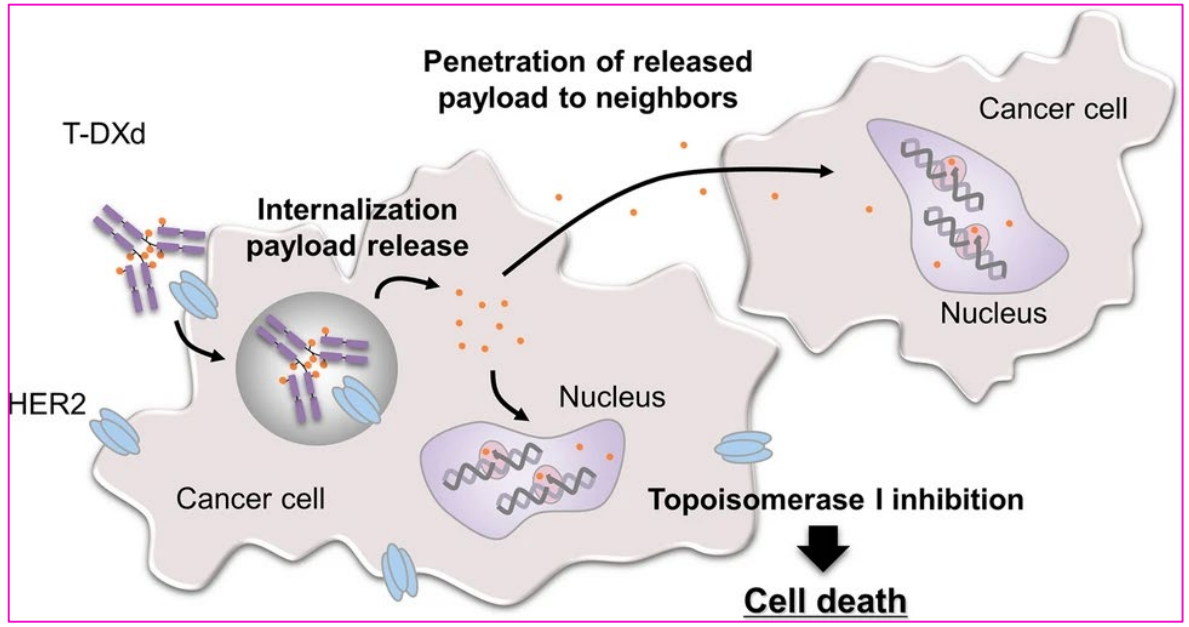


Seminars in Cancer Biology: 72 (2021), 123-135.

Rationale for use of T-Dxd for HER2-low mBC

- Drug biology:
  - Highly potent topoisomerase-1 inhibitor payload
  - 8:1 drug-antibody ratio
  - Bystander effect

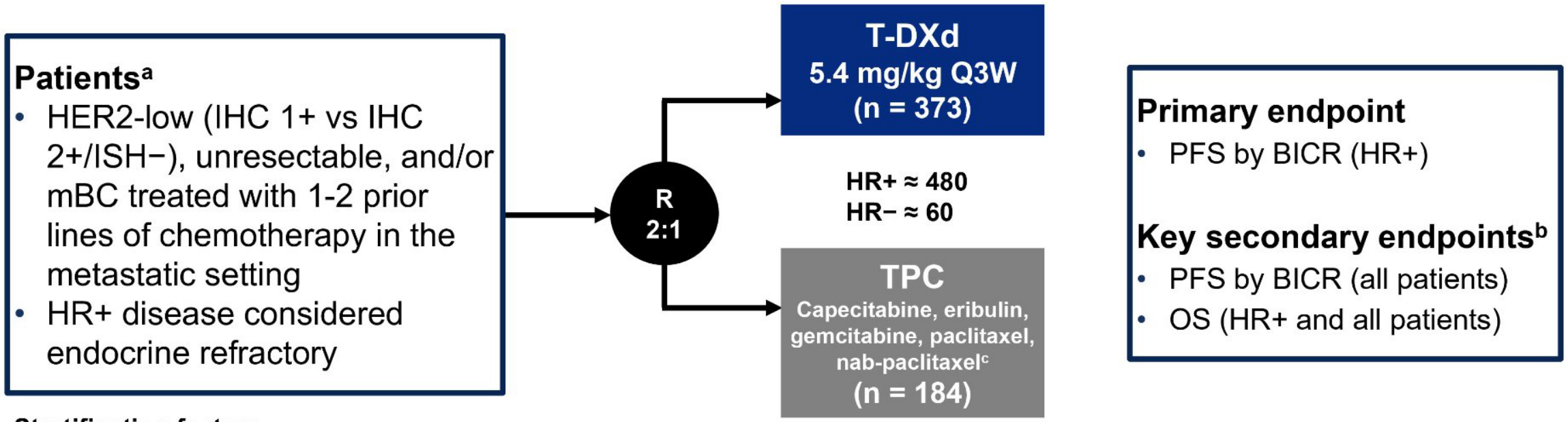
- Results from a phase 1b study reported efficacy in Her2-low MBC with a median PFS of 11.1 months and ORR 37%



J Clin Oncol 2020 Jun 10;38(17):1887-1896. Gastric Cancer 24 (2021): 780–789.

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−

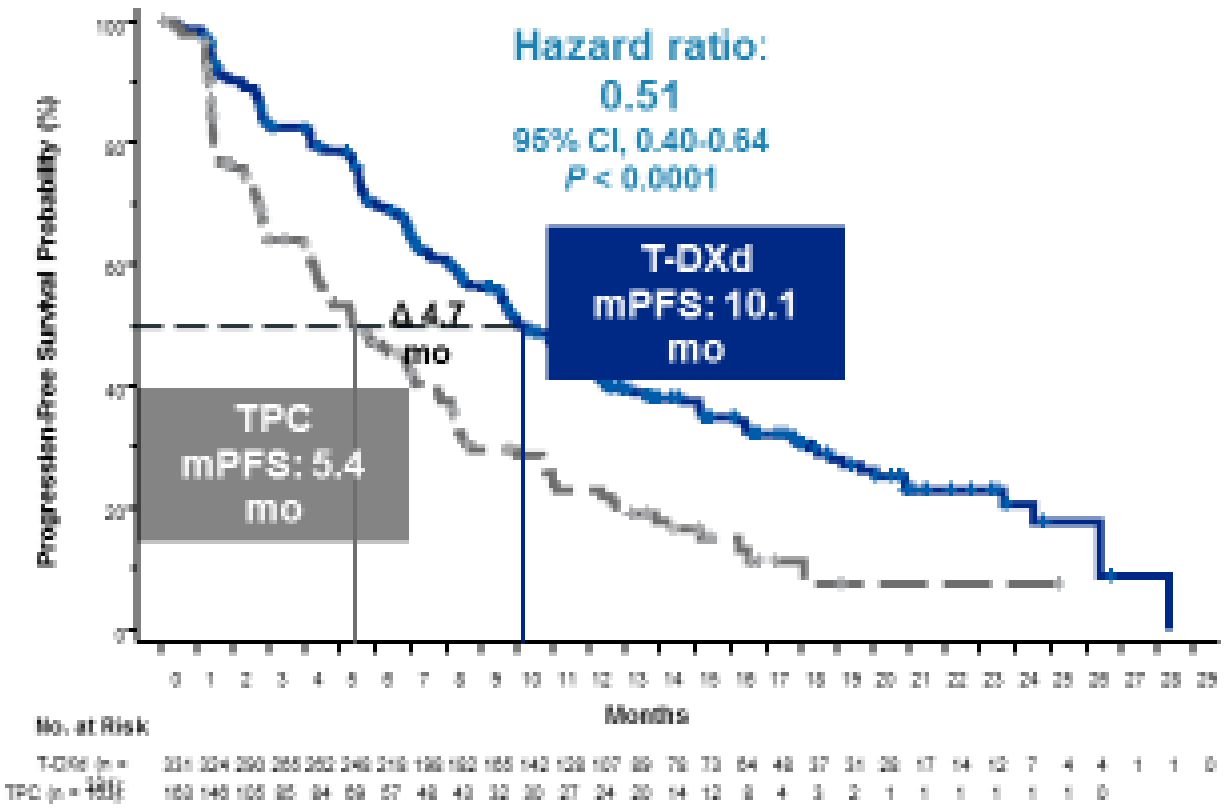
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; 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.

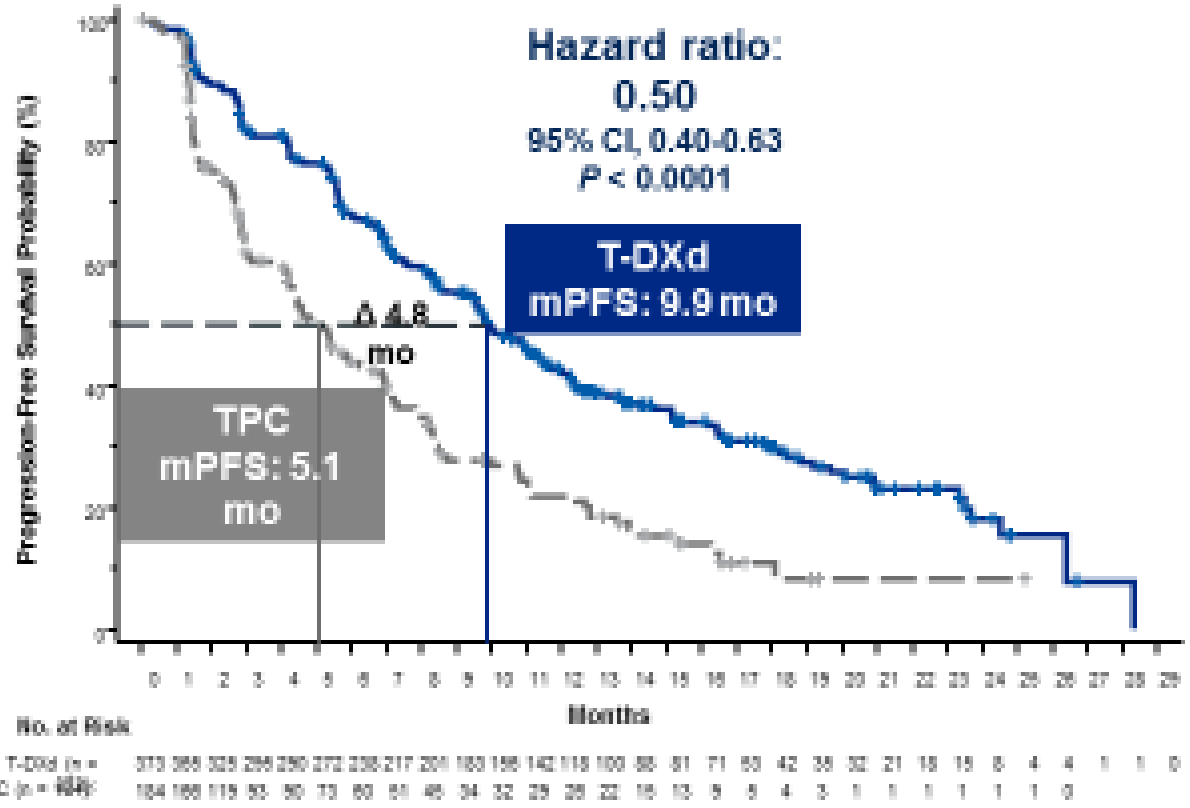

2022 ASCO
ANNUAL MEETING
ASCO Plenary Session
Sunday, June 5, 2022
ASCO
2022 ASCO
ANNUAL MEETING
ASCO Plenary Session
2022 ASCO
ANNUAL MEETING
ASCO Plenary Session
2022 ASCO
ANNUAL MEETING
ASCO Plenary Session
Sunday, June 5, 2022

PFS in HR+ and All Patients

Hormone receptor–positive



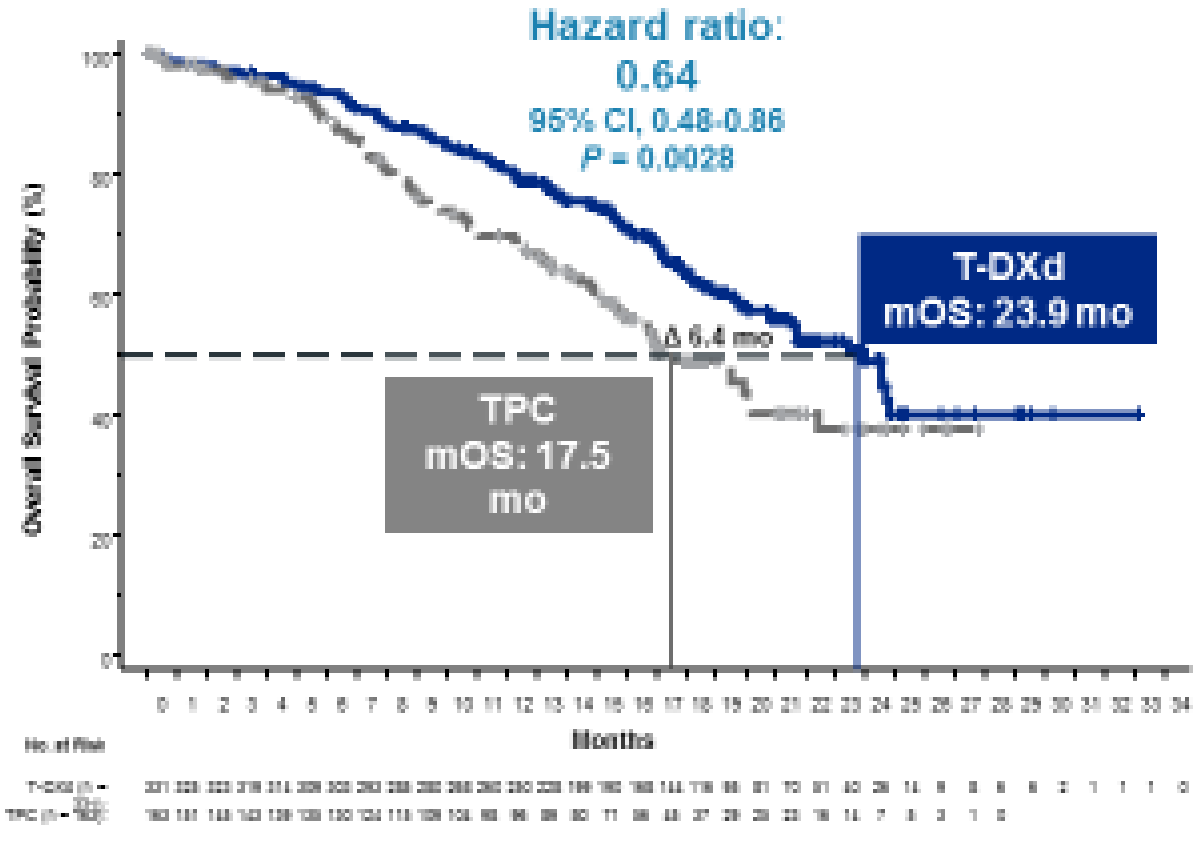
All patients



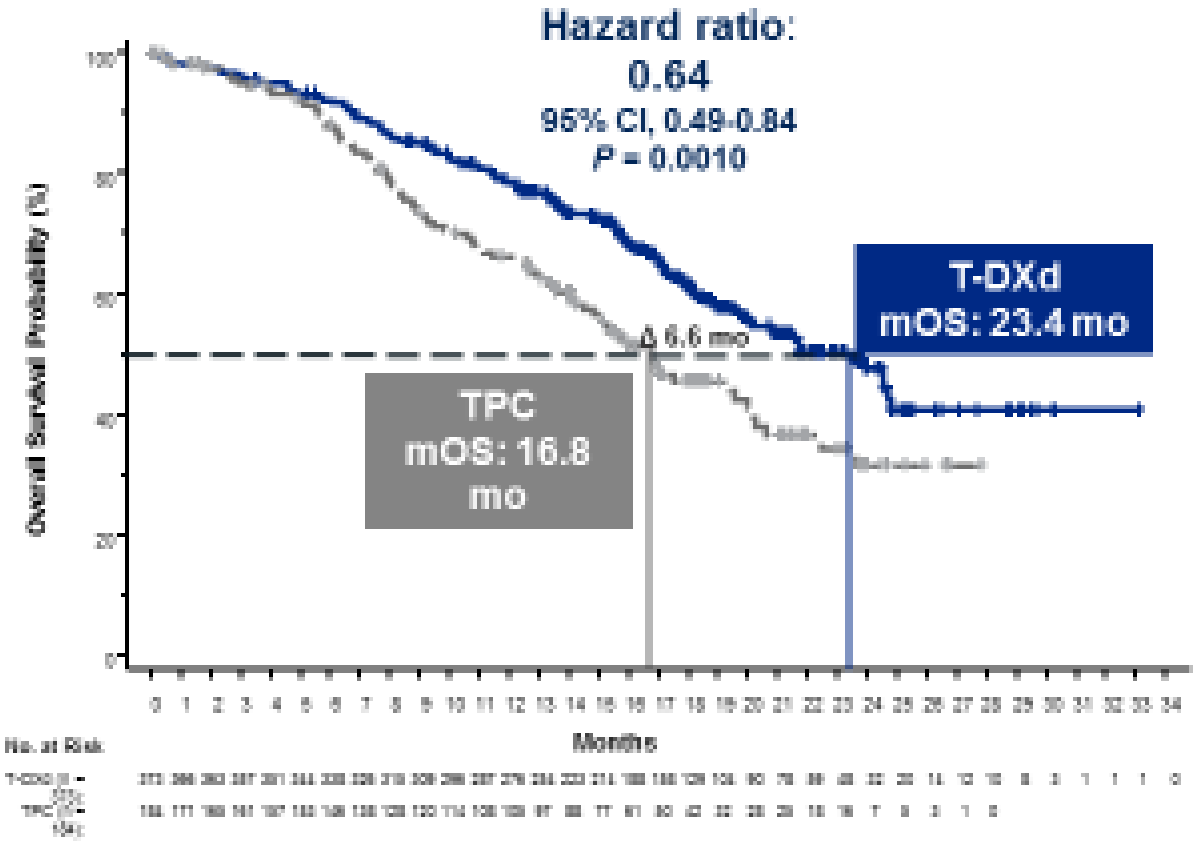
PFS by blinded independent central review.
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



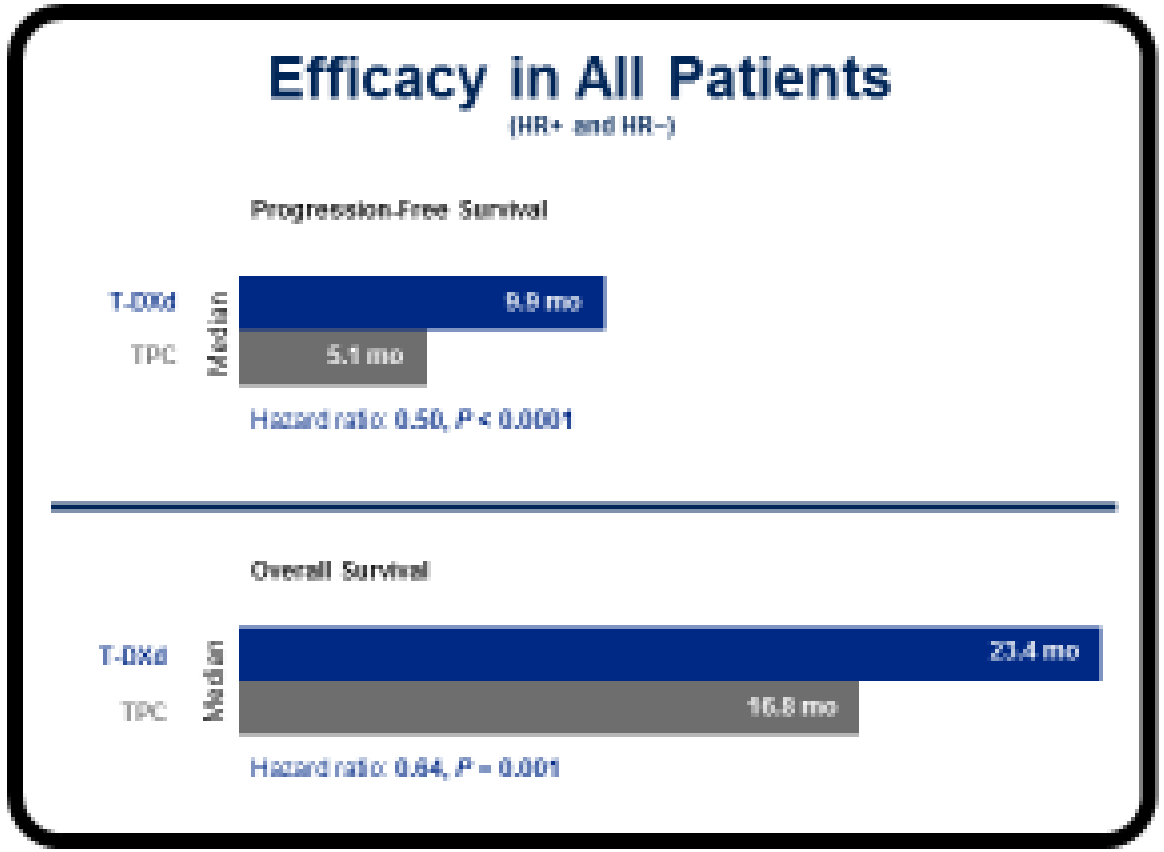
All patients



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

DESTINY-Breast04 establishes T-DXd as the new standard of care in HER2-low, HR+/HR− mBC

- T-DXd is the first HER2-targeted therapy to demonstrate unprecedented statistically significant and clinically meaningful improvement in PFS and OS versus TPC
- Similar magnitude of benefit across all subgroups, including HER2 IHC status and prior CDK4/6i use
- Safety is consistent with the known safety profile and showed an overall positive benefit-risk
- DESTINY-Breast04 establishes HER2-low (IHC 1+, IHC 2+/ISH−) mBC as a new targetable patient population, with T-DXd as a new standard of care



CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; HER2, human epidermal growth factorreceptor2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Conclusions

- The management of HER2+ breast cancer has improved by leaps and bounds over the past 3 years
- We have many new drugs in the metastatic setting; and the ability to personalize treatment much more upfront
- Given all the options available, shared decision making and optimization of side effects becomes even more important

Conclusions

- HER2-low disease is now a new entity, and we must look back at pathology reports for all of our patients with “HER2-negative” metastatic breast cancer to see if they fit this picture
- T-Dxd is a great option for HR+ HER2+ patients who have progressed beyond endocrine therapy and can be considered for HR- HER2+ patients as well
- We hope that additional ADCs and other drugs and drug combinations will be available for HER2-low disease in due time

Thank you!

2016

2018-2019

2022