Her2-positive breast cancer

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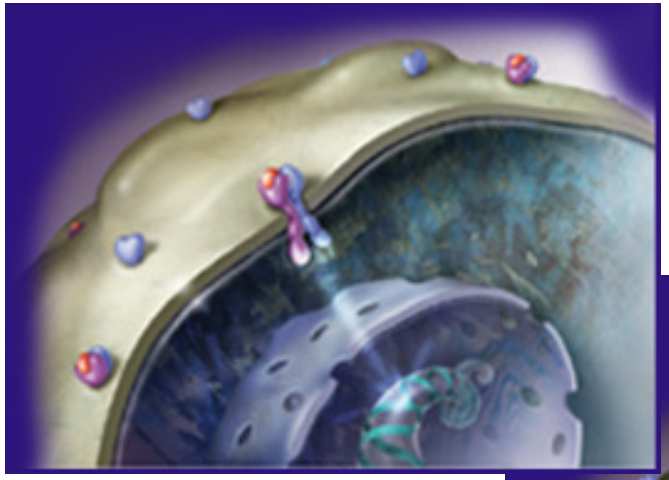
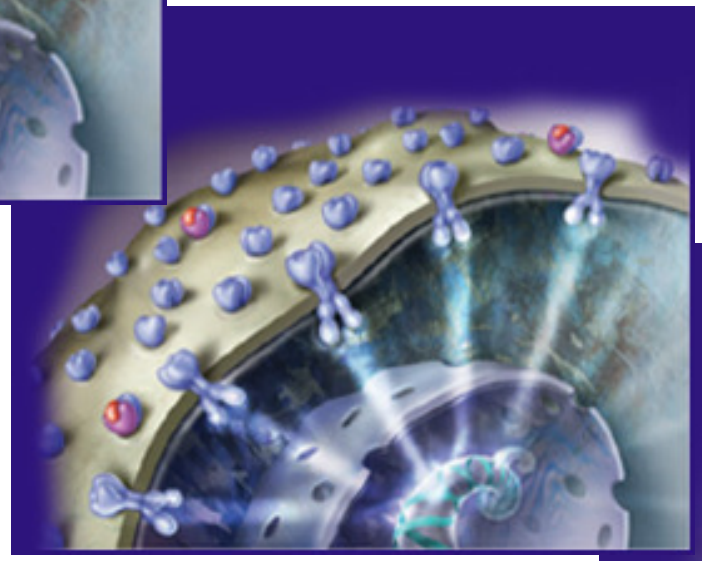
HER2 Signals Cells to Divide

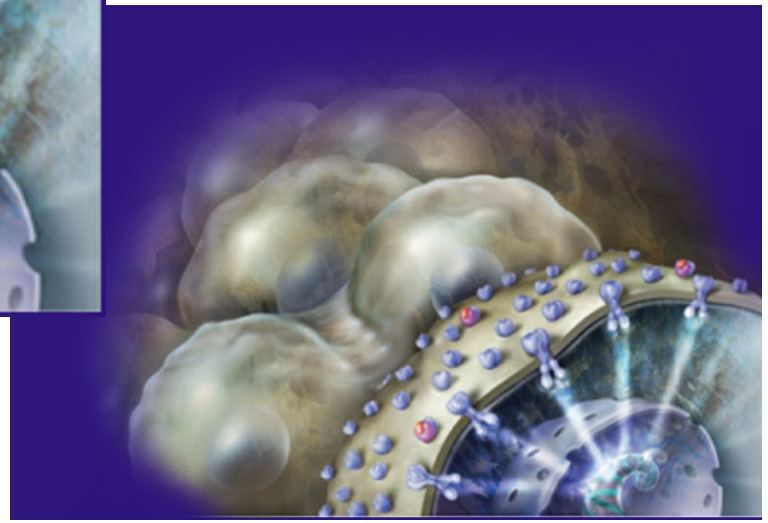


Normal

HER2 is overexpressed in ~20%-30% of breast cancers



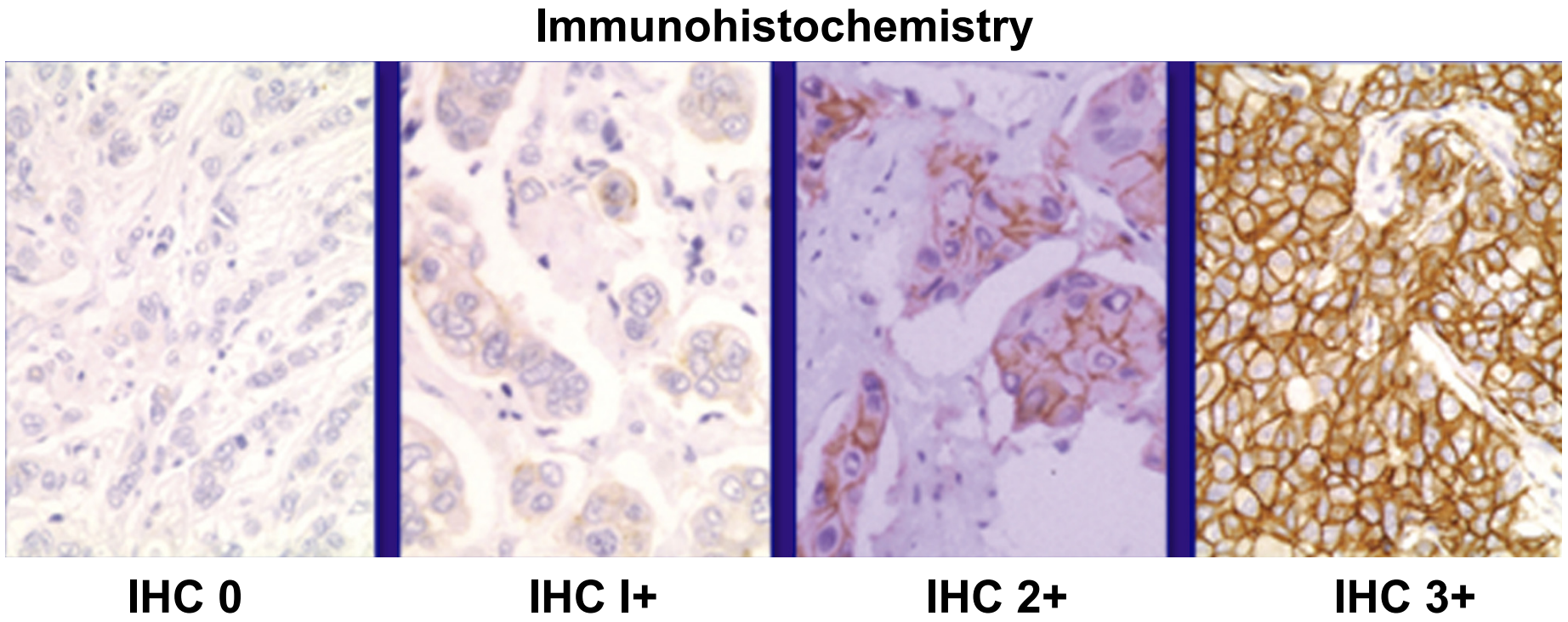
Overexpressed HER2



Excessive cellular division

Berger et al. *Cancer Res.* 1988;48:1238.
Roskoski. *Biochem Biophys Res Commun*. 2004;319:1.
Rowinsky. *Annu Rev Med*. 2004;55:433.
Slamon et al. *Science*. 1987;235:177.

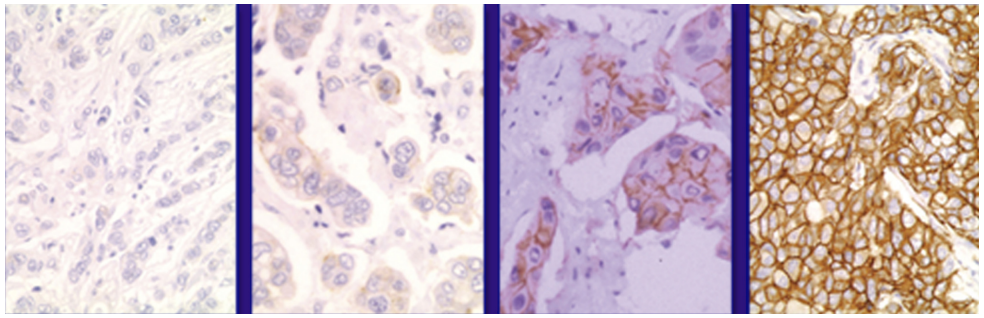
IHC Test Measures HER2 Protein Overexpression



- IHC is scored on a 0-3+ scale based on staining intensity and completeness of membrane staining

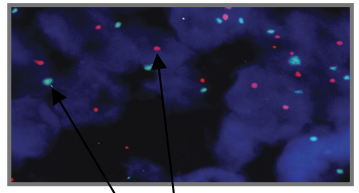
HercepTest® PI. 3rd ed.

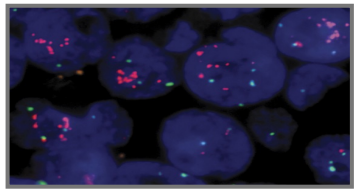
HER2 Protein Overexpression Clinical Discrimination



IHC 0 IHC I+ IHC 2+ IHC 3+

Her 2 negative

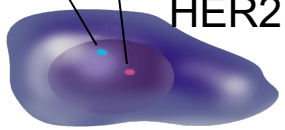


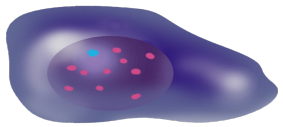


Her 2 Positive

Chromosome 17 centromere

HER2 gene



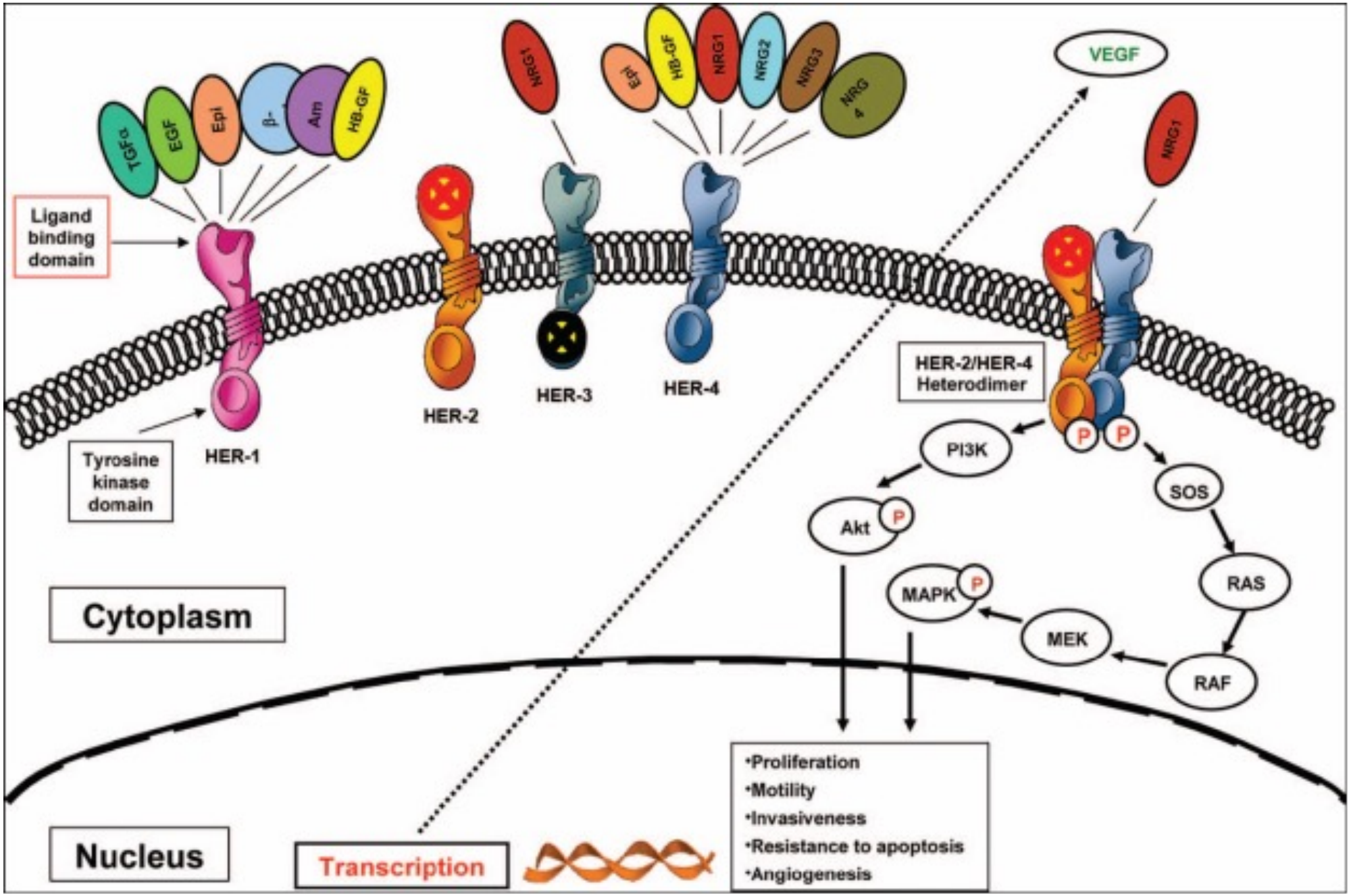


HER2-normal Ratio <2.0

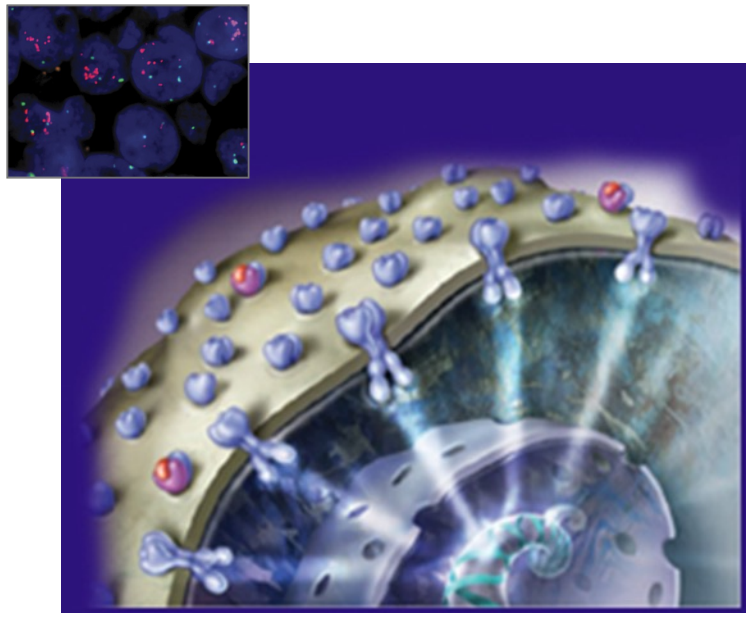
HER2-amplified Ratio ≥2.0

Treatment pathway follows the ER status

Treatment driven down the Her 2 pathway


TGFα
EGF
Epi
β-
Am
HB-GF
NRG1
Epi
HB-GF
NRG1
NRG2
NRG3
NRG 4
VEGF
NRG1
Ligand binding domain
HER-1
HER-2
HER-3
HER-4
HER-2/HER-4 Heterodimer
Tyrosine kinase domain
P
P
PI3K
SOS
Akt
P
RAS
MAPK
P
MEK
RAF
Cytoplasm
Nucleus
Transcription
•Proliferation
•Motility
•Invasiveness
•Resistance to apoptosis
•Angiogenesis

Today’s options in Her 2 Targeted Therapy

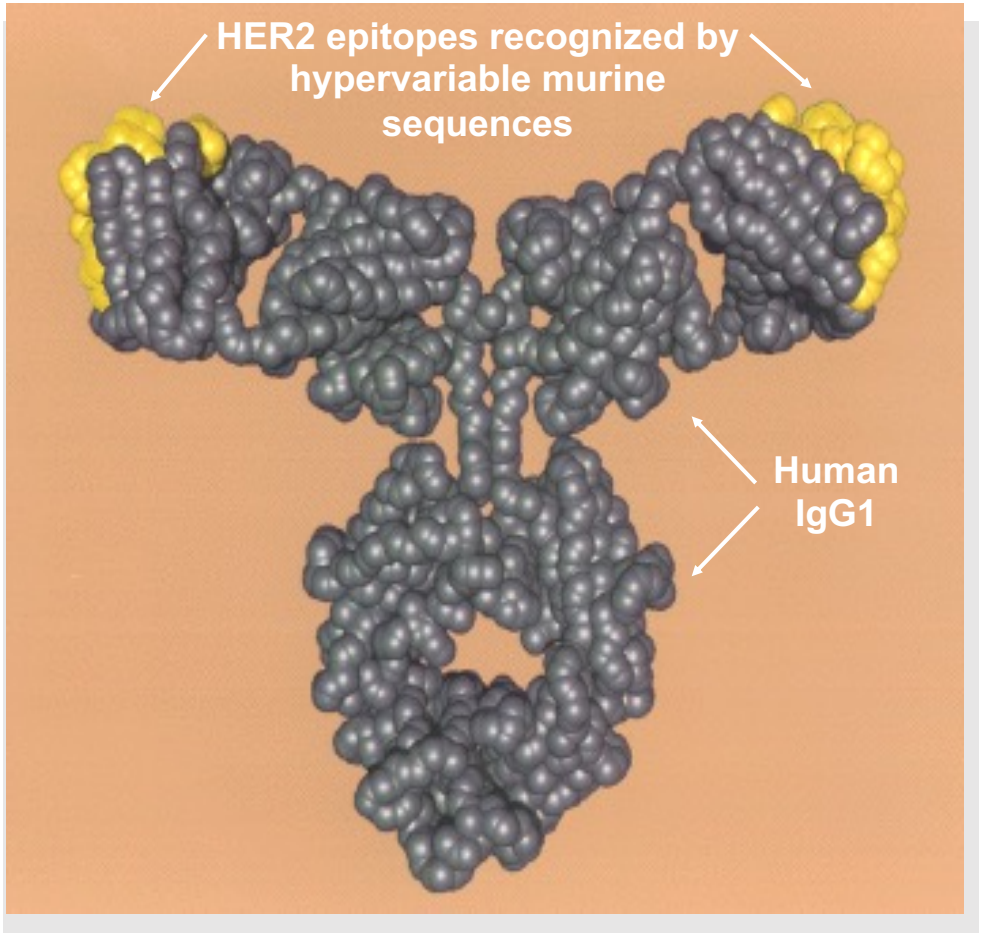


Overexpressed HER2

1998-2020

- trastuzumab
- pertuzumab
- ado-emtansine-trastuzumab [TDM-1]
- trastuzumab-deruxtecan [T-DXd]
- margetuximab
- lapatinib
- neratinib
- tucatinib

trastuzumab: Humanized Anti-HER2 MAb



- Targets HER2 protein
- Selectively binds with high affinity ($K_d \leq 0.5$ nM)
- 95% human, 5% murine

Key Data Sets in HER2-Positive Breast Cancer

- DESTINY-Breast03: Trastuzumab deruxtecan (T-DXd) vs T-DM1 in HER2-positive metastatic breast cancer (mBC)
- DESTINY-Breast01: Updated results of Phase II trial of T-DXd in HER2-positive mBC
- HER2CLIMB: Updated results with tucatinib/trastuzumab/capecitabine in HER2-positive mBC
- KATHERINE: Subgroup analysis of adjuvant T-DM1 vs trastuzumab in patients with residual disease
- ATEMPT: Adjuvant T-DM1 vs paclitaxel in Stage I HER2-positive BC
- ExteNET: Final OS analysis with neratinib in HER2-positive localized BC

Progress Has Been Made in HER2+ mBC, yet Unmet Need Persists

Standard of Care[a]

1L **Trastuzumab + pertuzumab + taxane, CLEOPATRA:** mPFS = 18.7 months[1]

- mBC 1L standard-of-care was established in the CLEOPATRA trial[1,2]

2L+ **T-DM1, EMILIA:** mPFS = 9.6 mo[3]

- EMILIA trial established T-DM1 as 2L+ standard-of-care
- In the changing treatment landscape, more recent clinical trials and real-world studies have demonstrated mPFS outcomes with T-DM1 in the range of 6-7 months[2,4-7]
  - mPFS for T-DM1 in the randomized KATE2 was 6.8 months (2020)[4]

3L+ **T-DXd DESTINY-Breast01:** mPFS = 19.4 months[8]

- T-DXd demonstrated robust activity in a 3L+ phase 2 single arm study, leading to regulatory approvals globally[2,8]

Given these data, T-DXd was evaluated in a head-to-head trial versus T-DM1 in previously treated HER2+ mBC

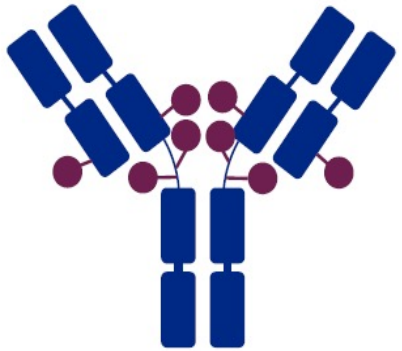
1L, first line; 2L, second line; 3L, third line; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]Not intended for cross-trial comparison.

1. Swain SM et al. *N Engl J Med*. 2015;372:724-34. 2. Pérez J et al. *Expert Opin Biol Ther*. 2021;21:811-24. 3. Verma S et al. *N Engl J Med*. 2012;367:1783-91. 4. Emens LA et al. *Lancet Oncol*. 2020;21:1283-95. 5. Daniels et al. *Breast*. 2021;58:106-12. 6. Lupichuk S et al. *Breast Cancer (Auckl)*. 2019;13:1178223419879429. 7. Vici P et al. *Oncotarget*. 2017;8:56921-56931. 8. Modi S et al. Presented at San Antonio Breast Cancer Symposium. 2020. Poster PD3-06.

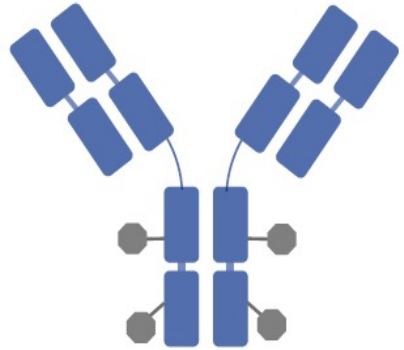
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



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

Trastuzumab emtansine (T-DM1)[5]



ADC, antibody-drug conjugate; MoA, mechanism of action.
[a]The clinical relevance of these features is under investigation.

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.

The NEW ENGLAND JOURNAL of MEDICINE

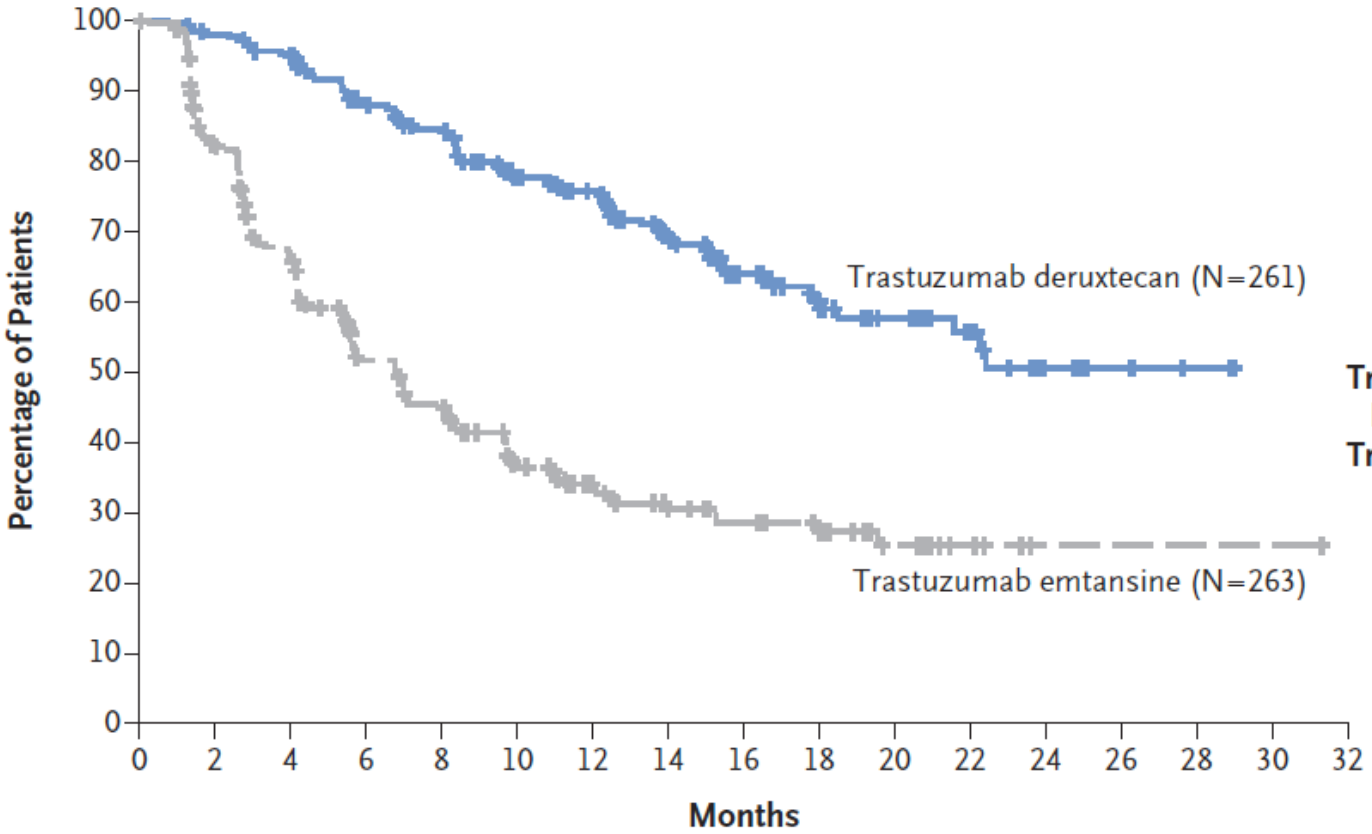
ORIGINAL ARTICLE

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

N Engl J Med 2022;386:1143-54.
DOI: 10.1056/NEJMoa2115022

DESTINY-Breast03: Progression Free Survival



	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)

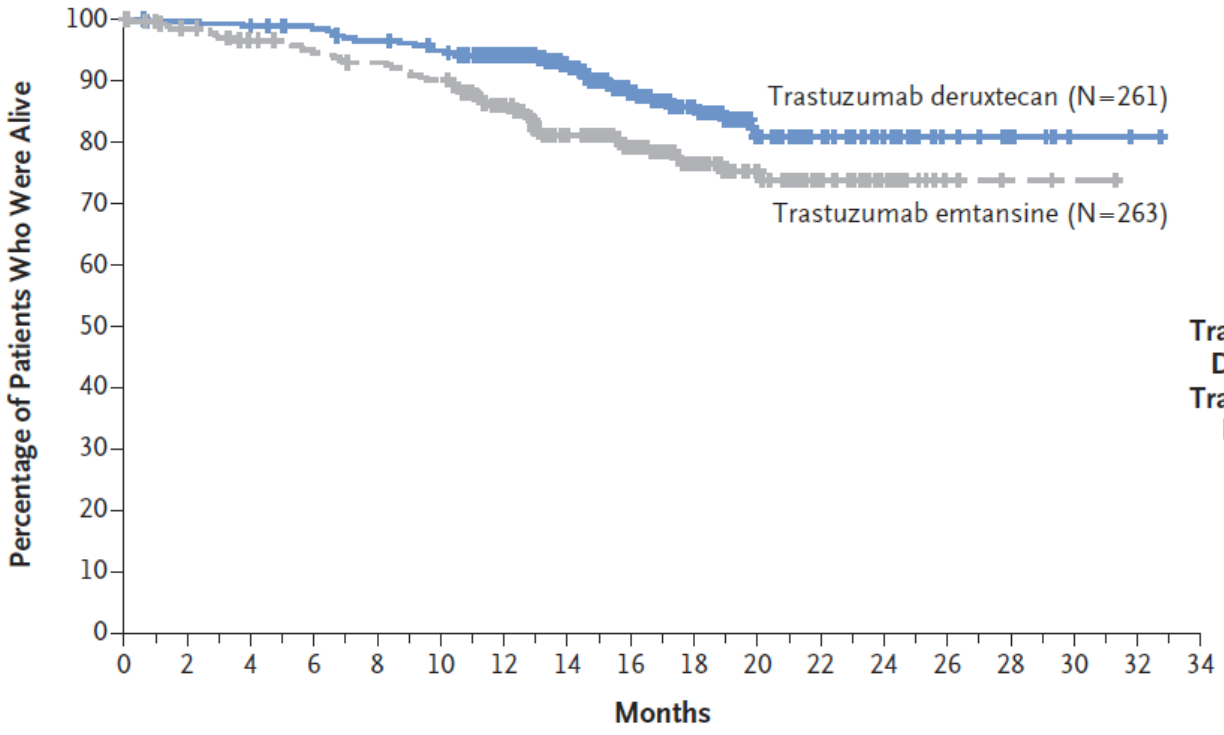
Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

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	0

NEJM 2022; 386:1143-54

DESTINY-Breast03: Overall Survival



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55
(95% CI, 0.36–0.86)
P=0.007

No. at Risk

Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

NEJM 2022; 386:1143-54

DESTINY-Breast03: Drug-Related Treatment-Emergent Adverse Events in ≥20% of Patients

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Cortés J et al. ESMO 2021;Abstract LBA1.

DESTINY-Breast03: Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

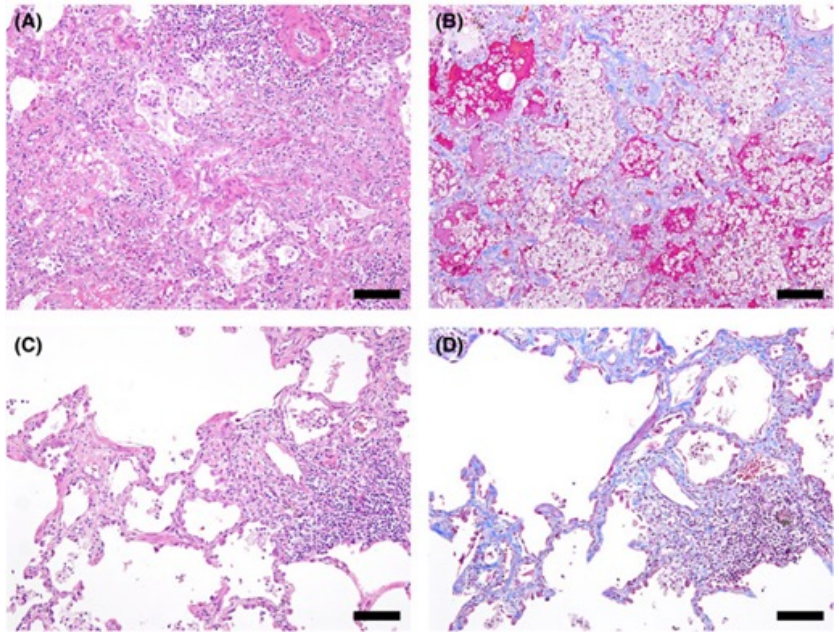
- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

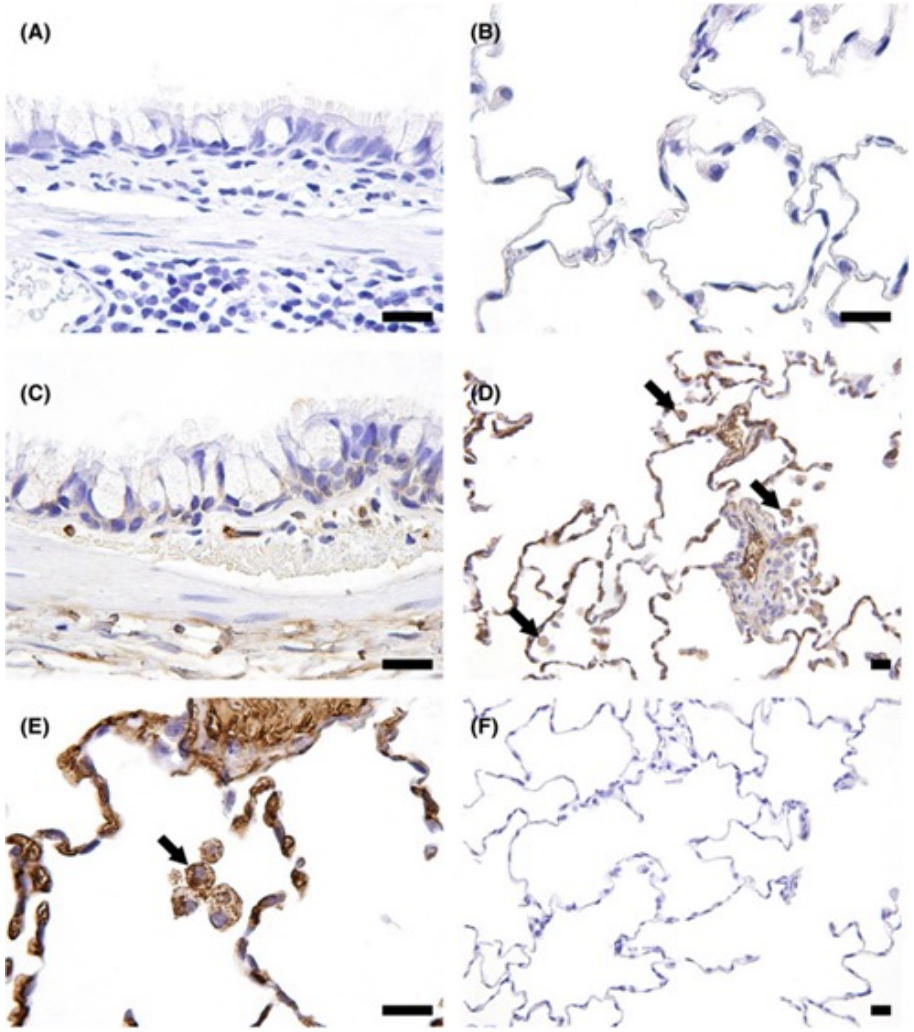
LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

Cortés J et al. ESMO 2021;Abstract LBA1, NEJM 2022; 386:1143-54

T-DXd induces dose dependent and dose-frequency dependent interstitial pneumonitis





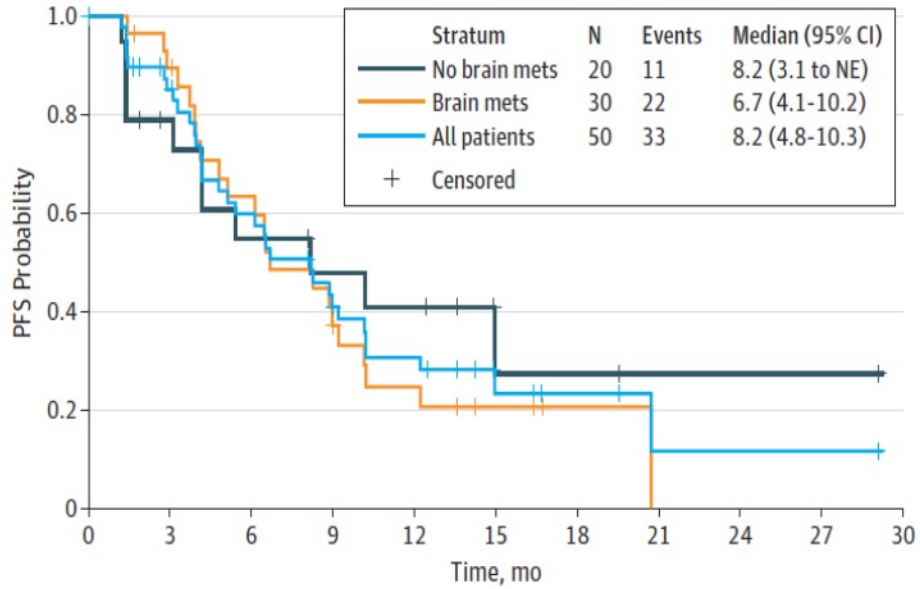
Kumagi, et al. *Cancer Sci.* 2020 doi: 10.1111/cas.14686

JAMA Oncology | Original Investigation

Tucatinib Combined With Ado-Trastuzumab Emtansine in Advanced *ERBB2/HER2*-Positive Metastatic Breast Cancer
A Phase 1b Clinical Trial

Virginia F. Borges, MD, MMSc; Cristiano Ferrario, MD; Nathalie Aucoin, MD; Carla Falkson, MD; Qamar Khan, MD; Ian Krop, MD, PhD; Stephen Welch, MD; Alison Conlin, MD; Jorge Chaves, MD; Philippe L. Bedard, MD; Marc Chamberlain, MD; Todd Gray, MD; Alex Vo, MD; Erika Hamilton, MD

Figure 2. Kaplan-Meier Plot of Progression-Free Survival (PFS) Among Patients Treated With the Maximum Tolerated Dosage of Tucatinib Combined With Ado-Trastuzumab Emtansine



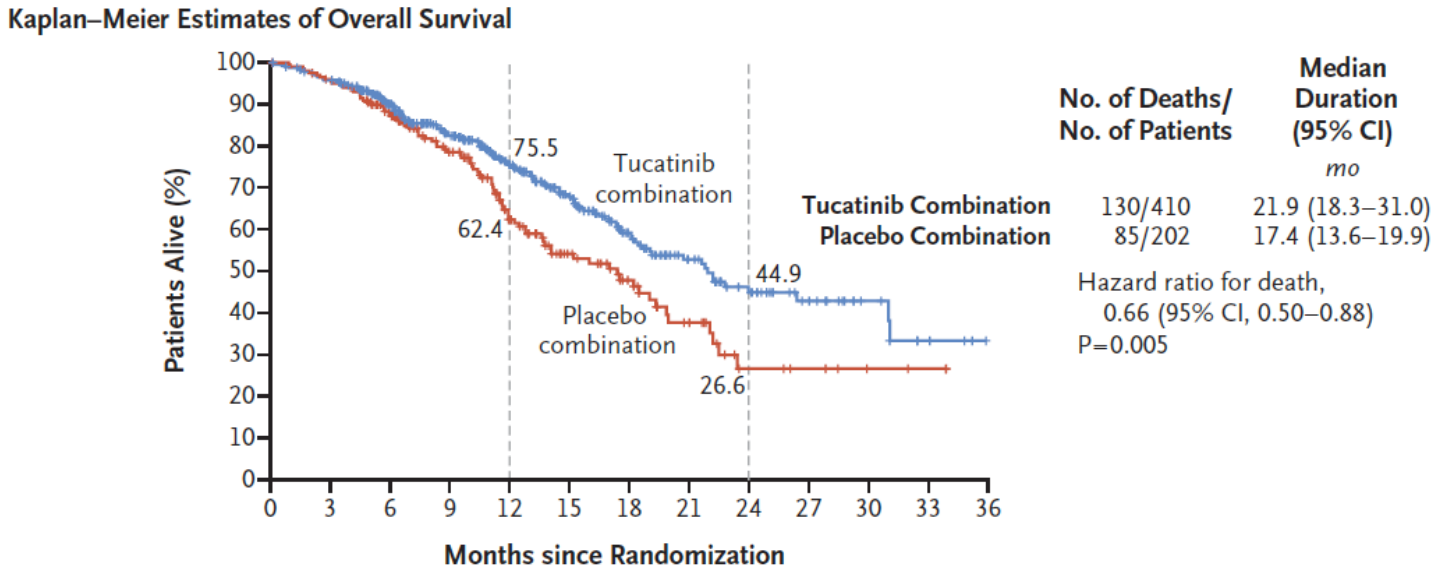
Findings In this phase 1b study of 57 patients with metastatic or unresectable locally advanced *ERBB2/HER2*-positive breast cancer treated previously with trastuzumab and a taxane, the maximum tolerated dosage of tucatinib combined with ado-trastuzumab emtansine was determined to be 300 mg administered orally twice daily; the objective response rate was 48%; and median progression-free survival was 8.2 months.

- **Adverse events**: nausea (72%), diarrhea (60%), fatigue (56%), epistaxis (44%), headache (44%), vomiting (42%), constipation (42%), decreased appetite (40%);

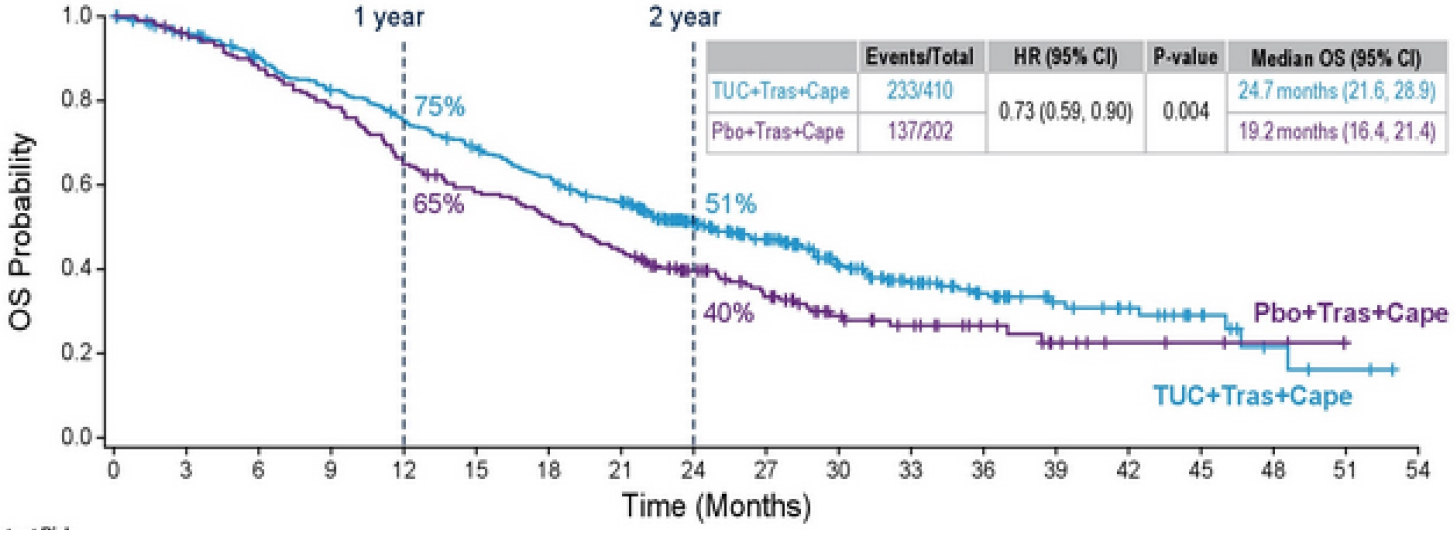
- Majority AEs grade 1 or 2.
- Tucatinib-related toxic reactions ≥ grade 3: thrombocytopenia (7 patients; 14%) and transaminitis (6 patients; 12%).

Acceptable safety profile and preliminary antitumor efficacy

HER2CLIMB: Overall Survival

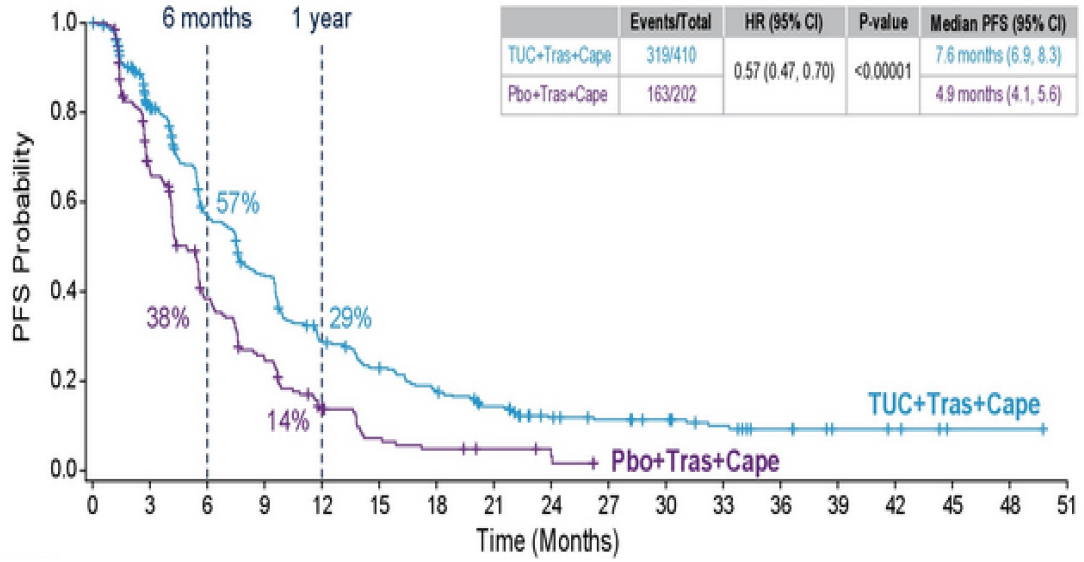


NEJM 2020;382:597-609



Curigliano G et al. ASCO 2021;Abstract 1043

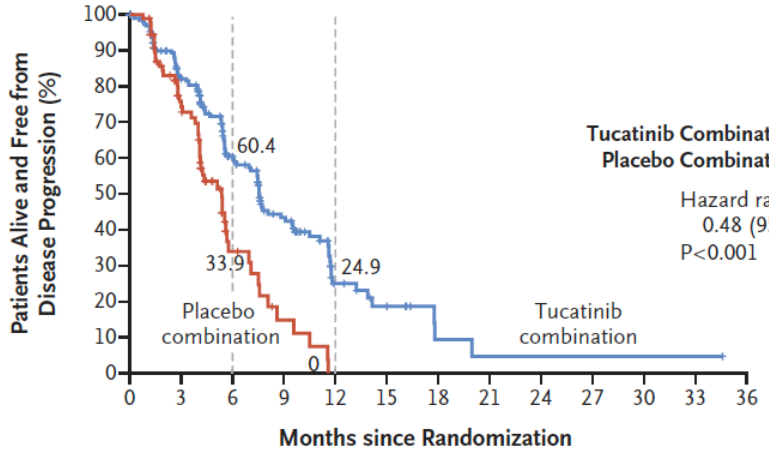
HER2CLIMB: Progression-Free Survival (PFS)



	Events/Total	HR (95% CI)	P-value	Median PFS (95% CI)
TUC+Tras+Cape	319/410	0.57 (0.47, 0.70)	<0.00001	7.6 months (6.9, 8.3)
Pbo+Tras+Cape	163/202			4.9 months (4.1, 5.6)

Curigliano G et al. ASCO 2021;Abstract 1043

Kaplan–Meier Estimates of Progression-free Survival among Patients with Brain Metastases



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	106/198	7.6 (6.2–9.5)
Placebo Combination	51/93	5.4 (4.1–5.7)

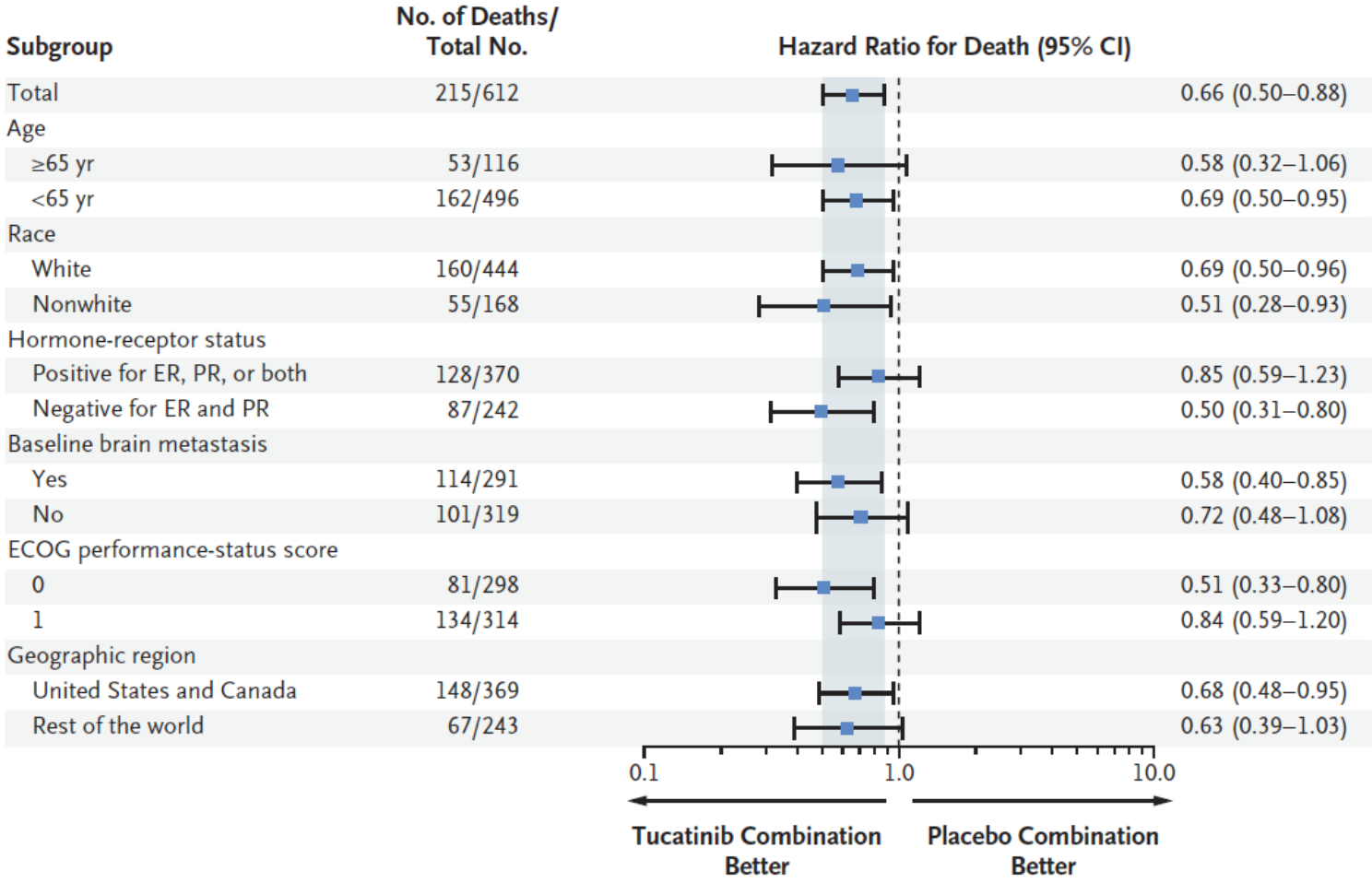
Hazard ratio for disease progression or death, 0.48 (95% CI, 0.34–0.69)
P<0.001

No. at Risk

Tucatinib combination	198	144	78	45	14	8	2	1	1	1	1	1	0
Placebo combination	93	49	12	4	0	0	0	0	0	0	0	0	0

NEJM 2020;382:597-609

HER2CLIMB: Subgroup analysis of overall survival



NEJM 2020;382:597-609

HER2CLIMB: Safety Outcomes

Select adverse events	Tucatinib (n = 404)		Placebo (n = 197)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	99.3%	55.2%	97.0%	48.7%
Diarrhea	80.9%	12.9%	53.3%	8.6%
PPE syndrome	63.4%	13.1%	52.8%	9.1%
Nausea	58.4%	3.7%	43.7%	3.0%
Fatigue	45.0%	4.7%	43.1%	4.1%
Vomiting	35.9%	3.0%	25.4%	3.6%
Stomatitis	25.5%	2.5%	14.2%	0.5%
Increased AST	21.3%	4.5%	11.2%	0.5%
Increased ALT	20.0%	5.4%	6.6%	0.5%

Murthy RK et al. SABCS 2019;Abstract GS1-01; Murthy RK et al. *N Engl J Med* 2020;382(7):597-609.

ARTICLE IN PRESS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Adjuvant T-DM1 versus trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analyses from KATHERINE

E. P. Mamounas[1,2*], M. Untch[3], M. S. Mano[4], C.-S. Huang[5], C. E. Geyer Jr[1,6], G. von Minckwitz[7], N. Wolmark[1,8], X. Pivot[9], S. Kuemmel[10,11], M. P. DiGiovanna[12], B. Kaufman[13], G. Kunz[7,14], A. K. Conlin[1,15], J. C. Alcedo[16], T. Kuehn[17], I. Wapnir[1,18], A. Fontana[19], J. Hackmann[7,20], J. Polikoff[1,21], M. Saghatchian[22], A. Brufsky[1,23], Y. Yang[24], M. Zimovjanova[25], T. Boulet[26], H. Liu[27], D. Tesarowski[28], L. H. Lam[28], C. Song[28], M. Smitt[28,29] & S. Loibl[7,30]

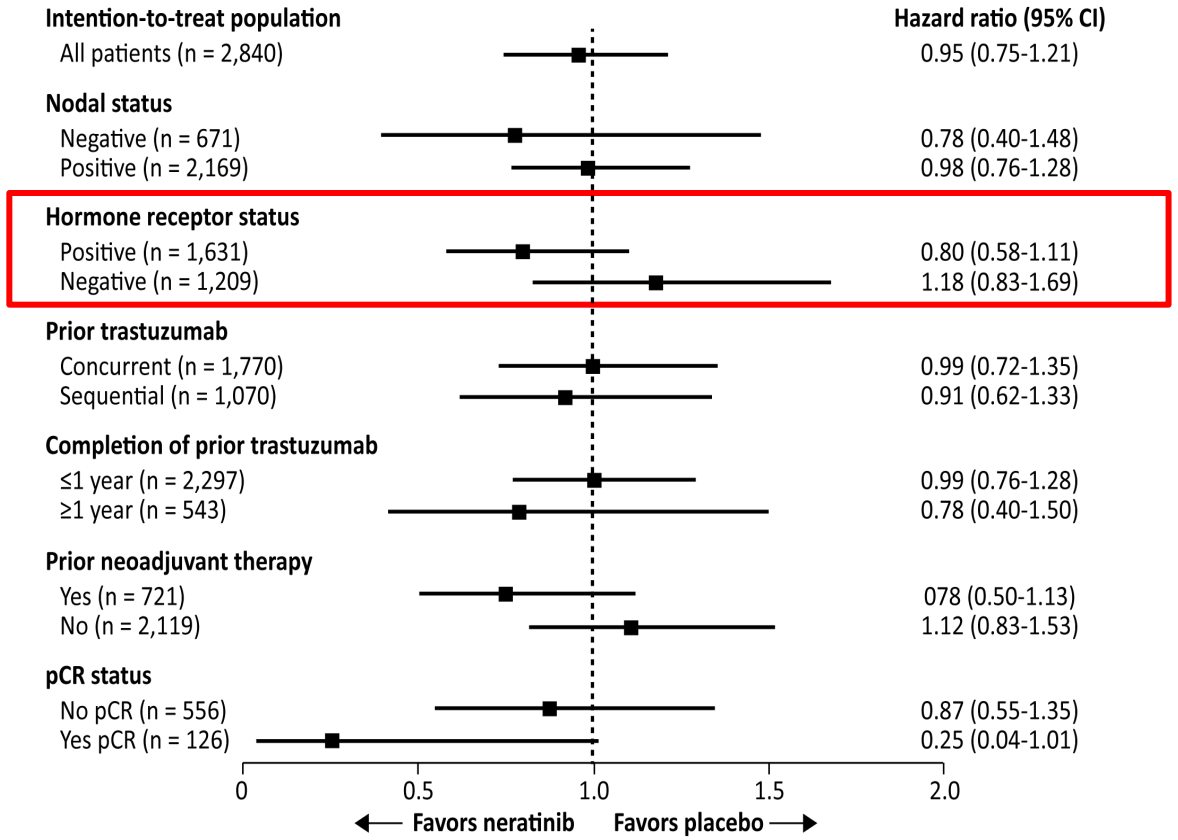
KATHERINE: Central Nervous System Recurrence Events

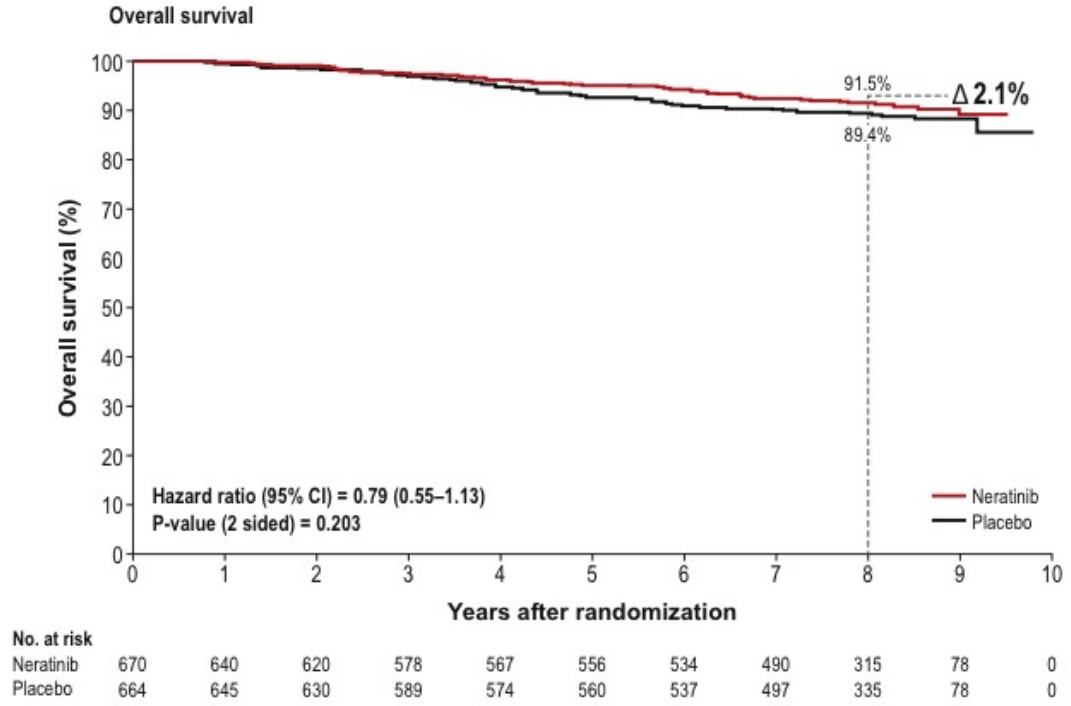
	T-DM1 (n = 743)	Trastuzumab (n = 743)
Patients with CNS recurrence	45 (6.1%)	40 (5.4%)
At first IDFS event[a]	44 (5.9%)	32 (4.3%)
After first IDFS event[b]	1 (0.1%)	8 (1.1%)
Patients with CNS as only event[c]	36 (4.8%)	21 (2.8%)
Median time to CNS recurrence	17.5 months	11.9 months

T-DM1 = trastuzumab emtansine; CNS = central nervous system; IDFS = invasive disease-free survival
CNS recurrence [a]within or [b]after 61 days of first IDFS event or at [c]any time

Mamounas EP et al. *Ann Oncol* 2021;32(8):1005-14.

ExteNET: Final Overall Survival Analysis





Holmes FA et al. SABCS 2020;Abstract PD3-03.

Chan A et al, Clinical Breast Cancer, Feb 2021

ExteNET: Cumulative Incidence of CNS Recurrences

Population or subgroup	Events, n		Cumulative incidence of CNS recurrences	
	Neratinib	Placebo	Neratinib	Placebo
Intention-to-treat population (n = 2,840)	16	23	1.3%	1.8%
HR-positive/≤1-year population (EU indication) (n = 1,334)	4	12	0.7%	2.1%
Prior neoadjuvant therapy (n = 1,334)				
No (n = 980)	3	6	0.7%	1.5%
Yes (n = 354)	1	6	0.7%	3.7%
pCR status (n = 354)				
No (n = 295)	1	5	0.8%	3.6%
Yes (n = 38)	0	1	0	5.0%

Holmes FA et al. SABCS 2020;Abstract PD3-03, update and further analysis Lin N et al, SABCS 2021, Abstract P2-13-05

The CompassHER2 Trials: COMprehensive use of Pathologic response ASSessment to optimize therapy in HER2-positive breast cancer

CompassHER2-pCR (preop and postop pCR)

Eligibility
HER2+ breast ca
Stage II/III3a
(T2-3, N0-2)
Newly diagnosed, no prior therapy

Registration

EA1181 preop
THP x 4 (12 weeks)

pac weekly or doc q3w (T)
PLUS
trastuzumab (H) &
pertuzumab (P) q3w

Research biopsy

Surgery

EA1181 if pCR (~40%)
Complete 1y of HP
with no further chemo

CompassHER2-RD (postop non-pCR)

A011801 if RD (~60%)

Group 1: COMPASS HER2 pCR participants -> AC, Carbo/HP x 4

Group 2: SOC chemo and HER2-directed therapy -> no further chemo

Eligibility
HER2+ RD
-Any ER-
-if ER+ must be N+
(~30% of A011801 patients expected to come from EA1181)
-T1-4 N0-3 disease at presentation

Registration

R
1:1

T-DM1/placebo x 14 cycles

T-DM1/tucatinib x 14 cycles

Primary Objective (clinical)

EA1181 3y RFS in patients with pCR (*3y RFS H_0=92%, H_1≥95%, 1p=0.025, n=1250*)

A011801 3y iDFS in patients with RD *(3y iDFS H_0=82%, H_1≥87%, HR=0.70, 2p=0.05, n=988)*

Thank you!