
بسم الله الرحمن الرحیم

20th Congress of Iranian Society of Medical Oncology & Hematology

بیستمین کنگره سراسری انجمن پزشکان انکولوژی و هماتولوژی ایران (سال ۱۴۰۰)

IRANIAN SOCIETY OF MEDICAL ONCOLOGY AND HEMATOLOGY
ISMOH

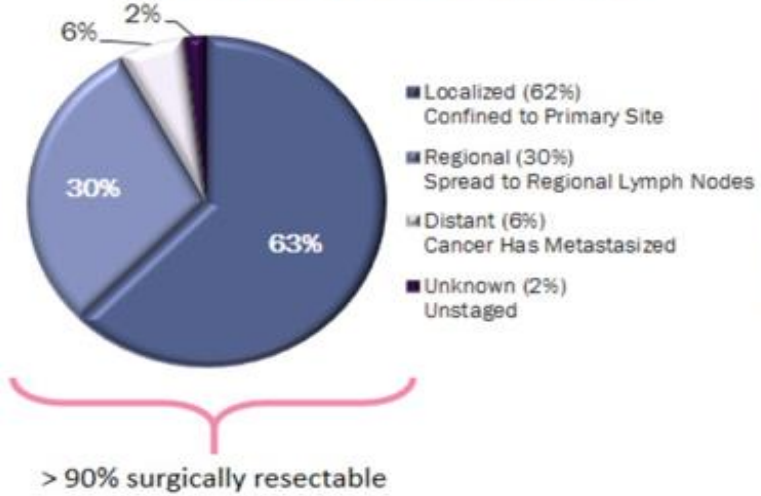
HER2+ MBC

S.H.Mirpour;MD
Medical Oncologist;GUMS;1400/10/17

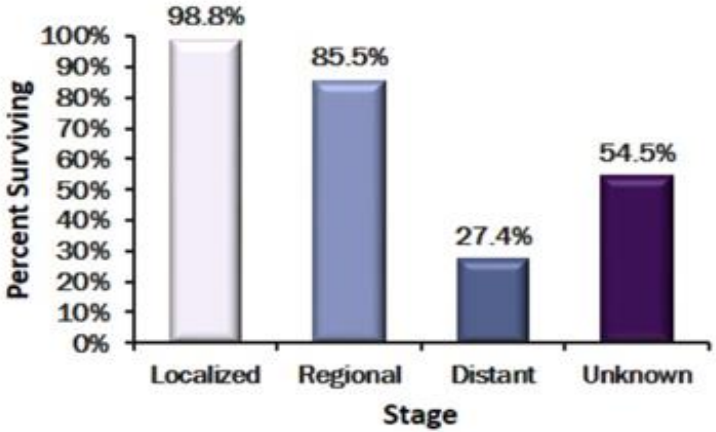
Breast Cancer

US Incidence and 5-Year Relative Survival (2010–2016)

Percent of Cases by Stage



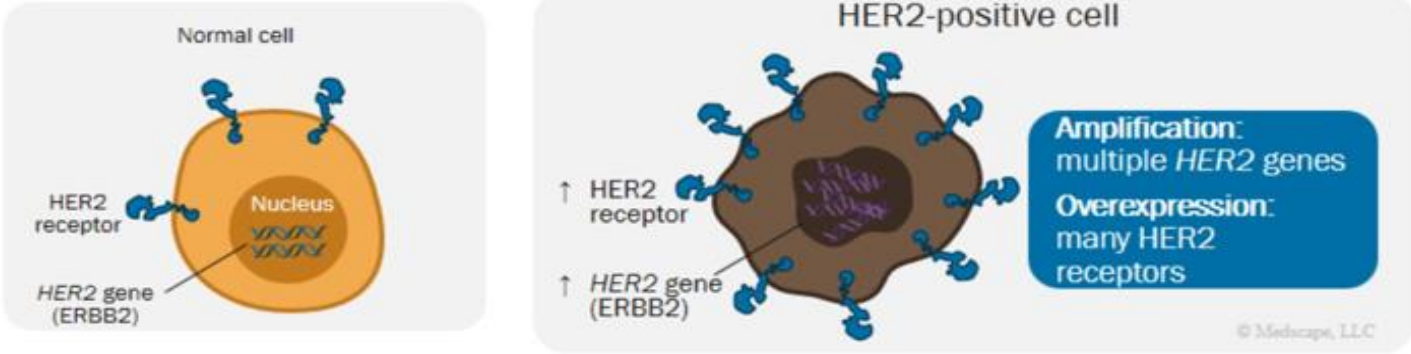
5-Year Relative Survival



Seer Cancer Stat Facts. 2020.

HER2-Positive Breast Cancer
Background

- Makes up ~20% of all BCs[a]
- Amplification of HER2 and overexpression of HER2 protein
  - Leads to expression of ≥ ~1.0 × 10^6 HER2 molecules/tumor cell surface[b]
  - Drives cancer: makes it more aggressive; resistant to conventional therapies
  - Led to development of HER2-directed therapies → significantly improved patient outcomes



a. Santa-Maria CA, et al. *Oncology (Williston Park)*. 2016;30:1-7; b. Phillips GDL, et al. *Cancer Res*. 2008;68:9280-9290; c. DeMichele A, et al. *JADPRO*. 2016;1-26.

ASCO/CAP Guidelines: Histopathologic Discordance and When To Order A New HER2 Test

Do not order a new HER2 Test if:

Initial result: HER2- Negative

and

Histologic grade 1 carcinoma of:

- Infiltrating ductal or lobular carcinoma, ER- and PgR-positive
- Tubular (at least 90% pure)
- Mucinous (at least 90% pure)
- Cribriform (at least 90% pure)
- Adenoid cystic carcinoma (90% pure) and often triple-negative

Order a new HER2 Test if:

Initial result: HER2- positive

and

Histologic grade 1 carcinoma of:

- Infiltrating ductal or lobular carcinoma, ER- and PgR-positive
- Tubular (at least 90% pure)
- Mucinous (at least 90% pure)
- Cribriform (at least 90% pure)
- Adenoid cystic carcinoma (90% pure) and often triple-negative

Order a new HER2 Test if:

Initial result: HER2- negative (core needle biopsy)

and

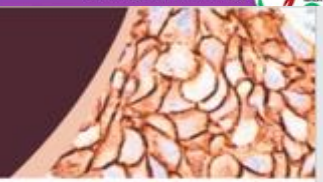
One of the following:

- Tumor is grade 3
- Amount of invasive tumor in the core biopsy is small
- Resection specimen contains high grade carcinoma morphologically distinct from that in core
- Questionable specimen handling of core biopsy or test is suspected to be negative on basis of testing error

Wolff. JCO. 2018;36:2105.

Slide credit: clinicaloptions.com

When to Test/Re-Test Breast Cancer for HER2



For EBC:

- In the initial biopsy (determines sequence and type of therapies)
- Repeat after neoadjuvant CT: may be repeated if negative initially

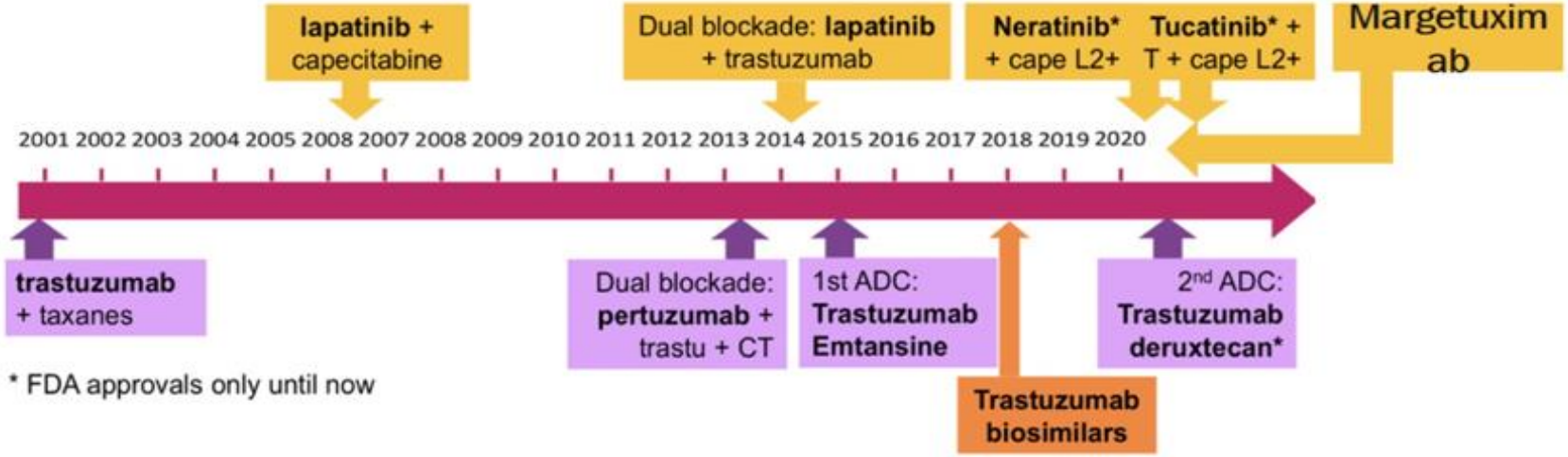
FOR ABC:

- Metastatic BC should be biopsied at least once (preferably at the diagnosis of metastasis) and biomarkers (ER and HER2) reassessed
- If discordance between primary and metastatic status, targeted therapy is recommended if the marker is positive in at least 1 of them

Cardoso F, et al. *Ann Oncol*. 2020. [Epub ahead of print]

HER-Positive MBC

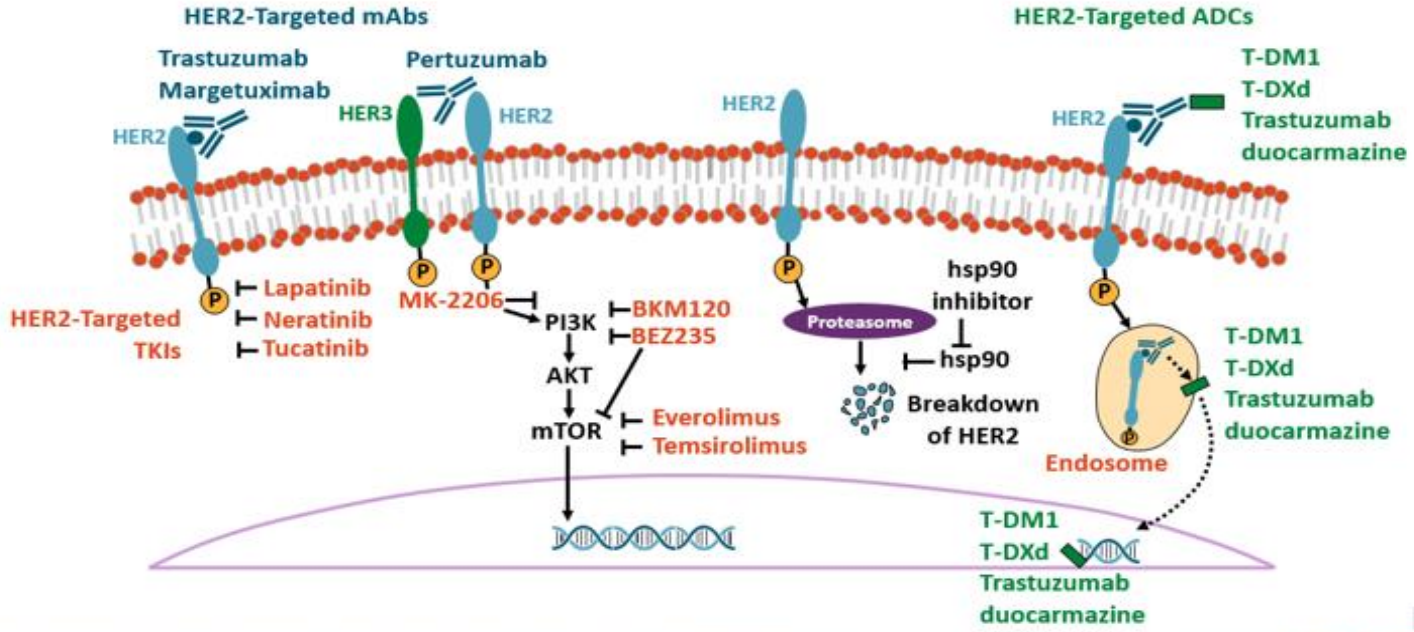
HER2+ MBC – Evolution of available treatments



* FDA approvals only until now

ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer,

Targeted Therapies for HER2+ Breast Cancer

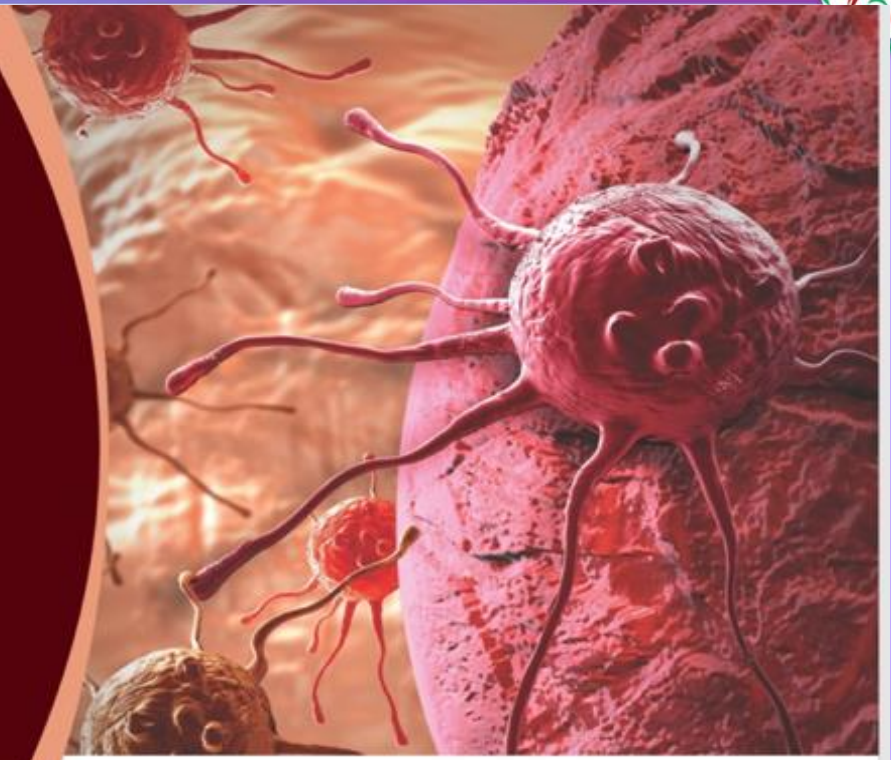


Gajria. Expert Rev Anticancer Ther. 2011;11:263. Pernas. Ther Adv Med Oncol. 2019:11:1758835919833519.

Slide credit: clinicaloptions.com

A Medscape LIVE! CONFERENCE

Selecting and Sequencing Treatment: Metastatic Treatments in Context

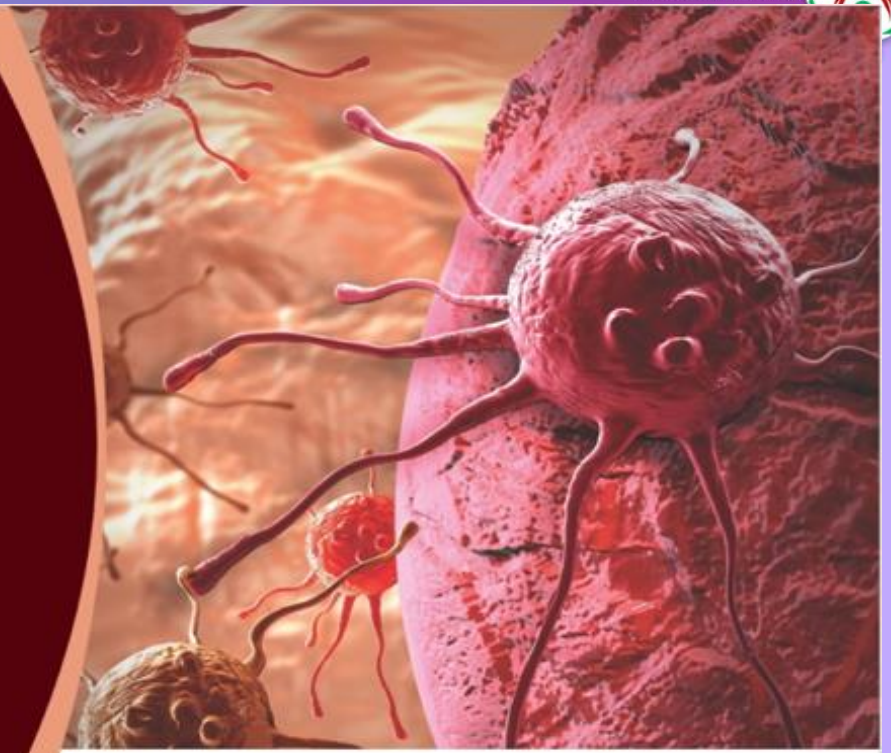


Shanu Modi, MD
Breast Medical Oncologist
Memorial Sloan Kettering Cancer Center
Associate Professor of Medicine
Weill Cornell Medical College
New York City, New York

Medscape Oncology

A Medscape LIVE! CONFERENCE

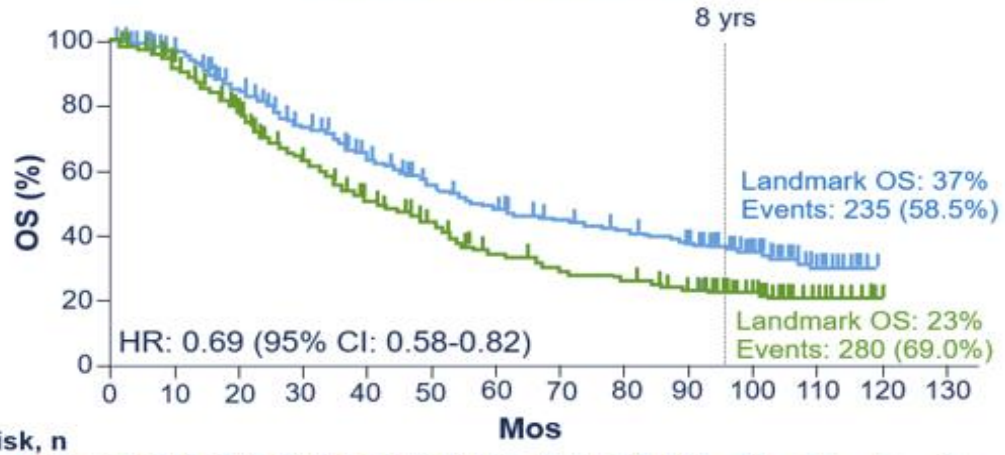
First-Line Setting



Medscape Oncology

CLEOPATRA: Standard First-line Treatment for HER2+ MBC With Docetaxel/Trastuzumab/Pertuzumab

End of Study OS in ITT Population*



Median OS, Mos	
THP	57.1
TH + Pbo	40.8

Patients at Risk, n

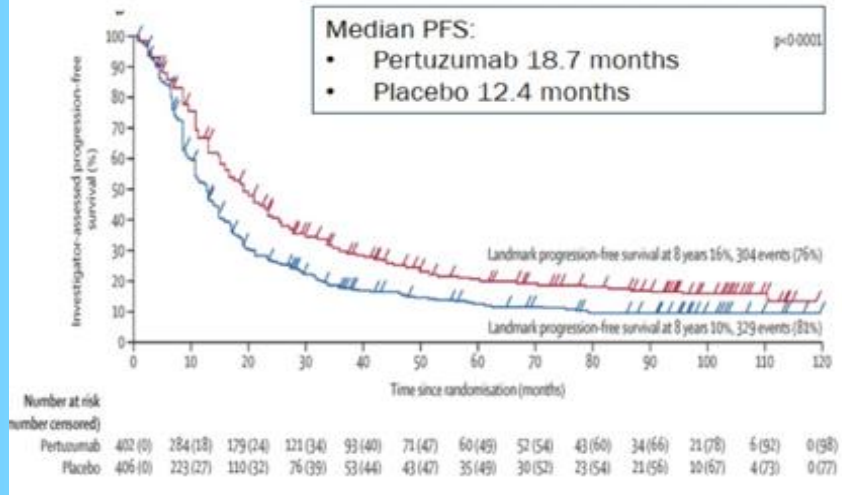
THP	402	371	318	269	228	188	165	150	137	120	71	20	0	0
TH + Pbo	406	350	289	230	181	149	115	96	88	75	44	11	1	0

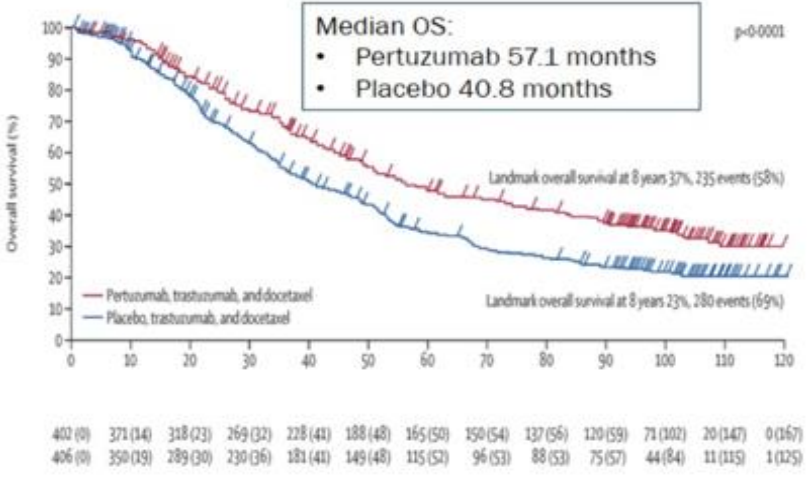
*Crossover patients were analyzed in the placebo arm.

H = trastuzumab; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival; P = pertuzumab; Pbo = placebo; T = docetaxel.
Swain. ASCO 2019. Abstr 1020.

CLEOPATRA End-of-Study Results

Adding Pertuzumab to Taxane+Trastuzumab Improves PFS and OS (Median Follow-Up ~100 months)





PFS, progression-free survival.
Swain S et al, Lancet Oncol 2020;21:519-530.

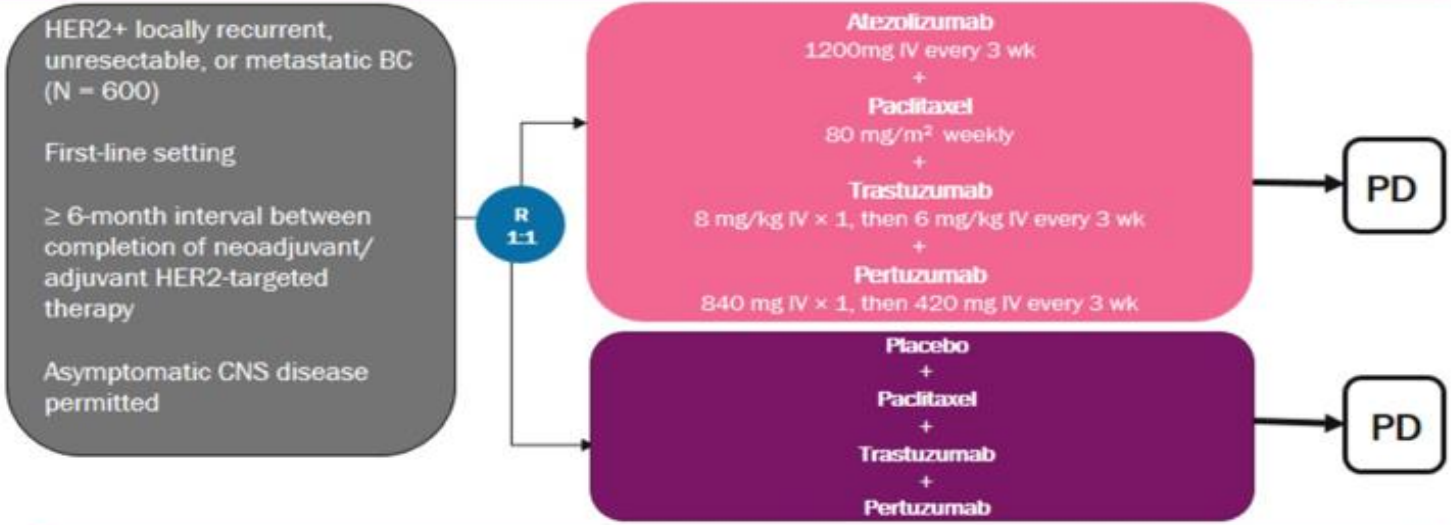
2021 Standard of Care

The Evolving Treatment Landscape for HER2-Positive BC

First-Line[a,b]
Trastuzumab + Pertuzumab + Taxane

Adapted from: a. NCCN® guidelines. Breast cancer. V1.2021; b. Cesca MG, et al. *Cancer Treat Rev*. 2020;88:102033.

NRG-BR004 Trial Design

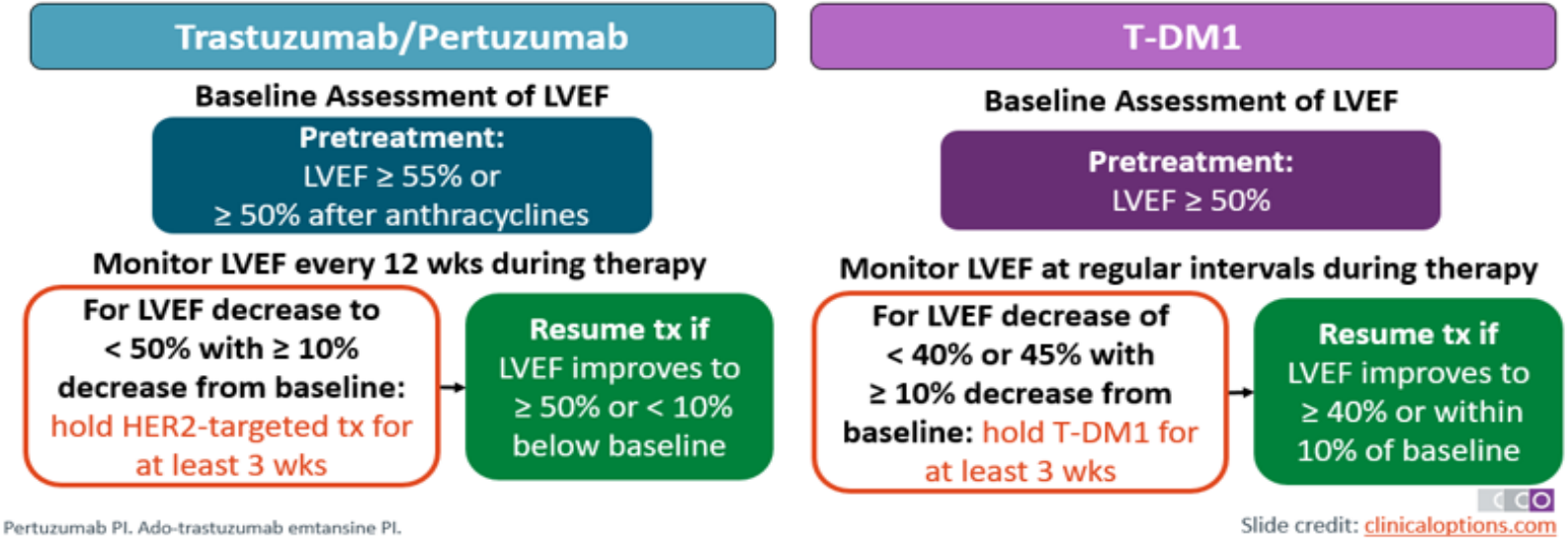


- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, duration of response, incidence of brain metastases, safety

ClinicalTrials.gov. NCT03199885.

Considerations for Cardiac Dysfunction During Adjuvant Trastuzumab/Pertuzumab or T-DM1

- Both HER2-targeted therapy and anthracyclines can result in decreased LVEF and CHF (subclinical or clinical cardiac failure)

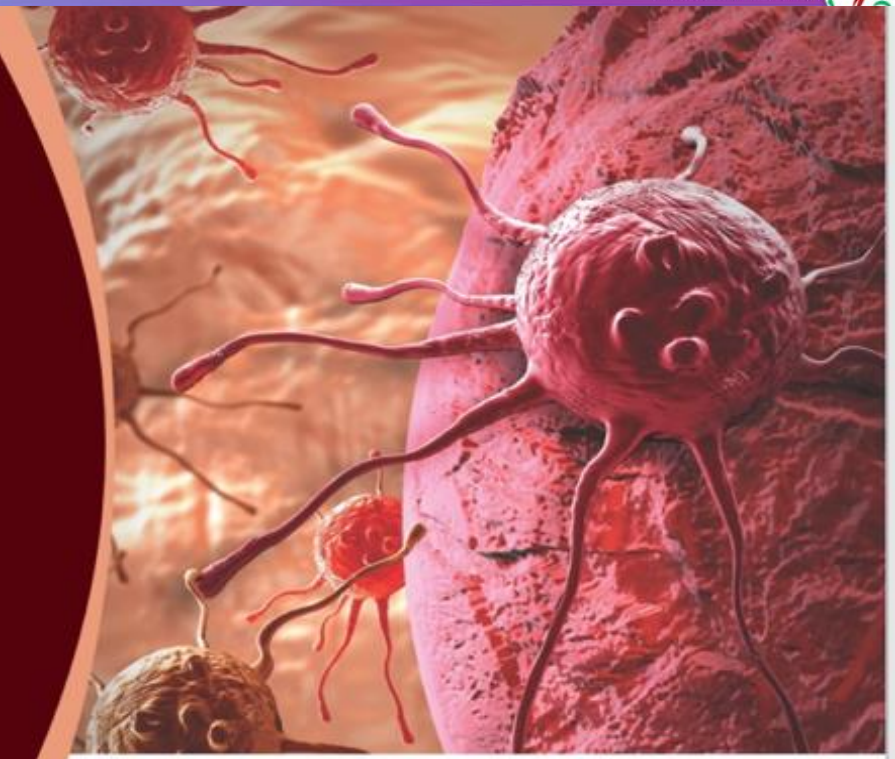


Pertuzumab PI. Ado-trastuzumab emtansine PI.

Slide credit: clinicaloptions.com

A Medscape LIVE! CONFERENCE

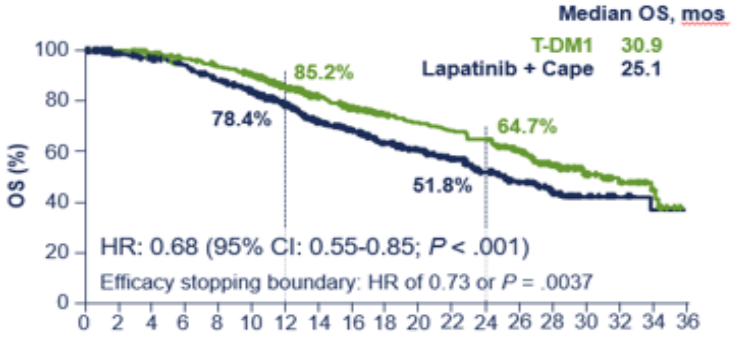
Second-Line Setting



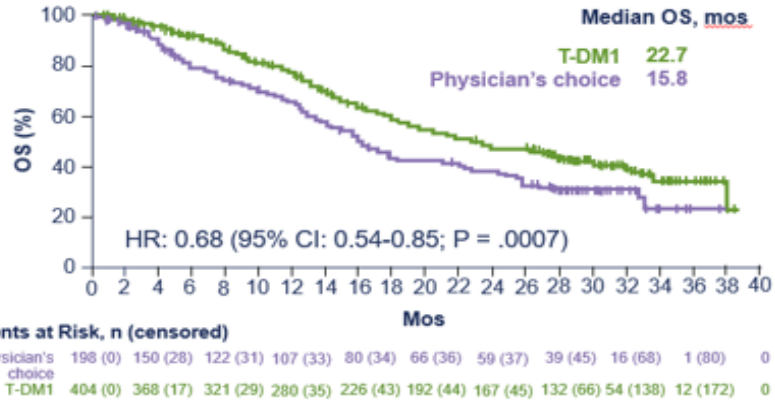
Medscape Oncology

EMILIA and TH3RESA: Standard Second-line Therapy for HER2+ MBC With T-DM1 After Progression on HER2-Targeted Agents

EMILIA[1]: Randomized phase III study of T-DM1 vs lapatinib + capecitabine for HER2+ MBC with progression on trastuzumab + taxane (N = 991)



TH3RESA[2]: Randomized phase III study of T-DM1 vs physician's choice for HER2+ MBC with progression on a taxane, lapatinib, and ≥2 HER2-targeted regimens including trastuzumab (N = 602)

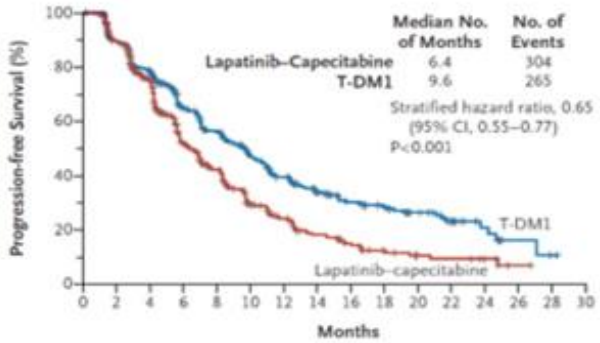


Cape = capecitabine; MBC = metastatic breast cancer; T-DM1 = trastuzumab emtansine.
1. Verma. NEJM. 2012;367:1783. 2. Krop. Lancet Oncol. 2017;18:743.

T-DM1: Survival Improvements

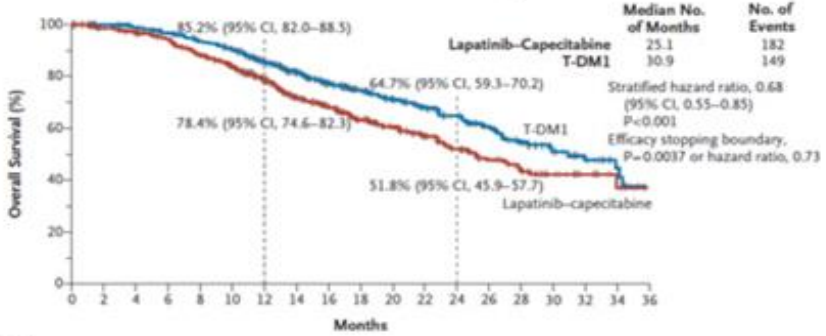
PLACE IN THERAPY: SECOND LINE AND BEYOND

3.2-mo PFS Improvement



No. at Risk															
Lapatinib–capecitabine	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

5.8-mo OS Improvement



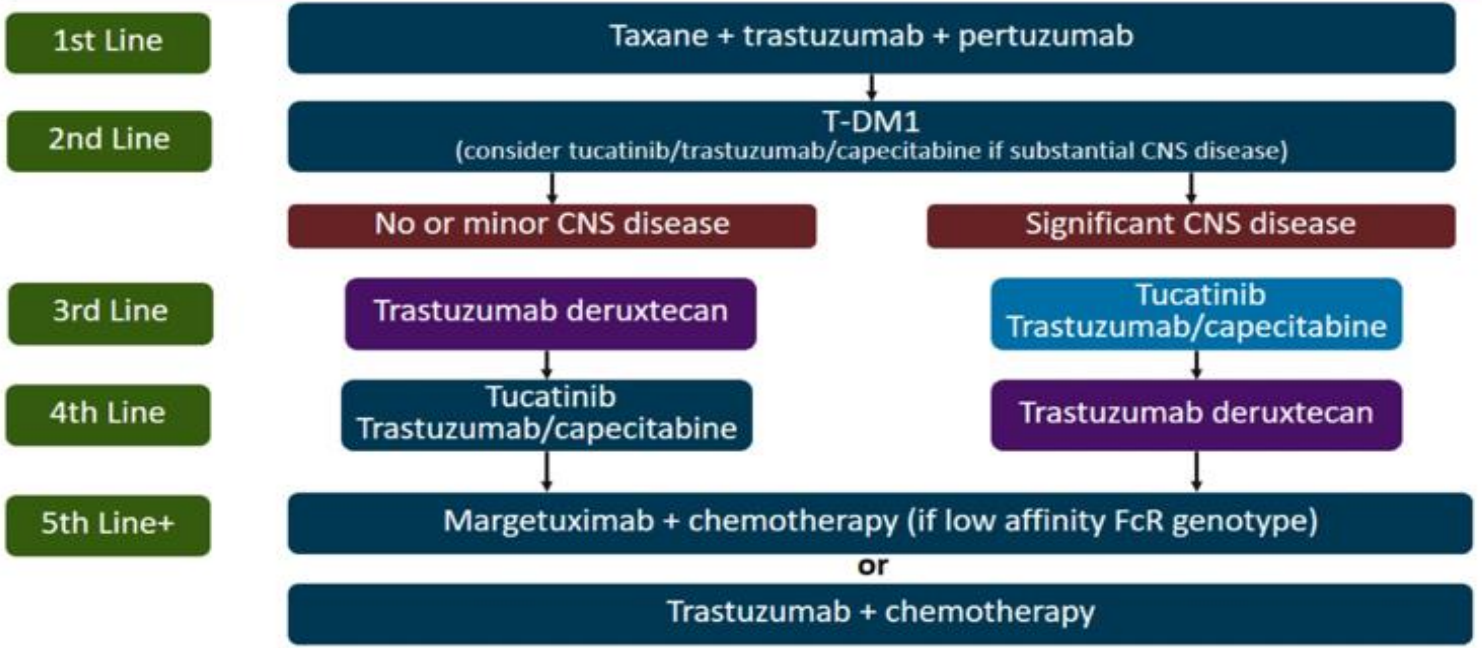
No. at Risk																			
Lapatinib–capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Common AEs with lapatinib: diarrhea and palmar-plantar erythrodysesthesia
Common AEs with T-DM1: thrombocytopenia

Verma S, et al. *N Engl J Med*. 2012;367:1783-1791.

Approach to Therapy for Metastatic HER2-Positive Disease

Move to Personalization

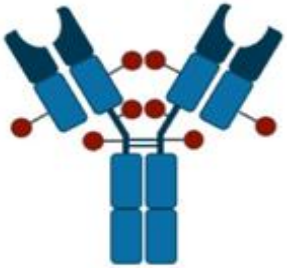


Trastuzumab Deruxtecan: A Novel HER2 ADC

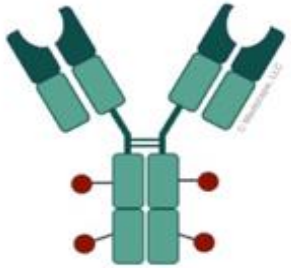
Characteristic Differences Between T-DXd and T-DM1

HER2-Targeting ADCs With similar mAb Backbone

T-DXd[a-d]*	ADC Attributes	T-DM1[c-e]
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



T-DXd[a]



T-DM1[e]

MOA, mechanism of action; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
*The clinical relevance of these features is under investigation.

a. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67:173-185; b. Ogitani Y et al. Clin Cancer Res. 2016;22:5097-5108; c. Trail PA, et al. Pharmacol Ther. 2018;181:126-142; d. Ogitani Y, et al. Cancer Sci. 2016;107:1039-1046; e. LoRusso PM, et al. Clin Cancer Res. 2011;17:6437-6447; Cortes J, et al. ESMO 2021. Abstract LBA16.

DESTINY- Breast01: CNS Subgroup Analysis of Trastuzumab Deruxtecan (T-Dxd)

Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: a subgroup analysis of the DESTINY-Breast01 trial

Guy Jerusalem,[1] Yeon Hee Park,[2] Toshinari Yamashita,[3] Sara A. Hurvitz,[4] Shanu Modi,[5] Fabrice Andre,[6] Ian E. Krop,[7] Xavier Gonzalez,[8] Peter S. Hall,[9] Benoit You,[10] Cristina Saura,[11] Sung-Bae Kim,[12] Cynthia R. Osborne,[13,14] Yasuaki Segara,[15] Eriko Tokunaga,[16] Yali Liu,[17] Jillian Cathcart,[17] Caleb Lee,[17] Christophe Perrin[18]

N = 24 of 168 enrolled patients; all received T-Dxd
~20% were CNS treatment-naïve.

Prior CNS treatment, %[b]

Radiotherapy only	54.2
Surgery only	4.2
Radiotherapy + surgery	20.8
None reported	20.8

Intent-to-treat analysis *	CNS subgroup (n=24)	All patients (N=184)
Confirmed ORR by ICR, n (%)	**14 (58.3)** (95% CI, 36.6-77.9)	**112 (60.9)** (95% CI, 53.4-68.0)
CR	1 (4.2)	11 (6.0)
PR	13 (54.2)	101 (54.9)
SD	8 (33.3)	67 (36.4)
PD	1 (4.2)	3 (1.6)
Not evaluable	1 (4.2)	2 (1.1)
Duration of response (CR or PR), median	16.9 months (95% CI, 5.7-16.9)	14.8 months (95% CI, 13.8-16.9)

*Of the 24 in the CNS subgroup, 17 had CNS lesions at baseline, of which n = 15 were evaluable of the 15, n = 13 had CNS radiation within 60 days of randomization.

PFS for CNS subgroup = 18.1 months vs 16.4 months for total cohort illustrating sustained response.

Jerusalem GH, et al. ASCO 2021. Poster 526

DESTINY-Breast03: Trastuzumab Deruxtecan vs Trastuzumab Emtansine in Previously Treated HER2+ Metastatic Breast Cancer

CCO Independent Conference Highlights*

of the *ESMO 2021 Conference,*
September 17-20, 2021, Virtual

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

Supported by educational grants from AstraZeneca; Daiichi Sankyo, Inc.; Exelixis, Inc.; and Ipsen Biopharmaceuticals, Inc.

CLINICAL CARE OPTIONS®
ONCOLOGY

DESTINY-Breast03: Study Design

- Randomized, multicenter, open-label phase III study

Stratification by HR status, prior treatment with pertuzumab, history of visceral disease

Patients with unresectable or metastatic HER2+ breast cancer previously treated with trastuzumab + taxane in advanced/metastatic setting (N = 524)

Trastuzumab Deruxtecan
5.4 mg/kg Q3W
(n = 261)

Trastuzumab Emtansine
3.6 mg/kg Q3W
(n = 263)

Median follow-up
T-DXd: 16.2 mo
T-DM1: 15.3 mo

- **Primary endpoint:** PFS by BICR
- **Secondary endpoints:** OS (key), ORR (BICR and investigator), DoR (BICR), PFS (investigator), safety
- Interim PFS analysis data cutoff: May 21, 2021
- IDMC recommendation to unblind study on July 30, 2021

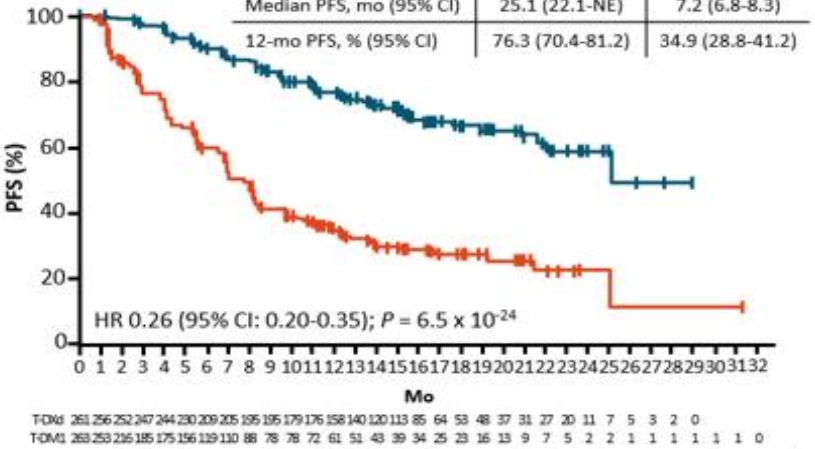
Cortes. ESMO 2021. Abstr LBA1.

Slide credit: clinicaloptions.com

DESTINY-Breast03: PFS by Investigator Assessment, OS (Secondary Endpoints)

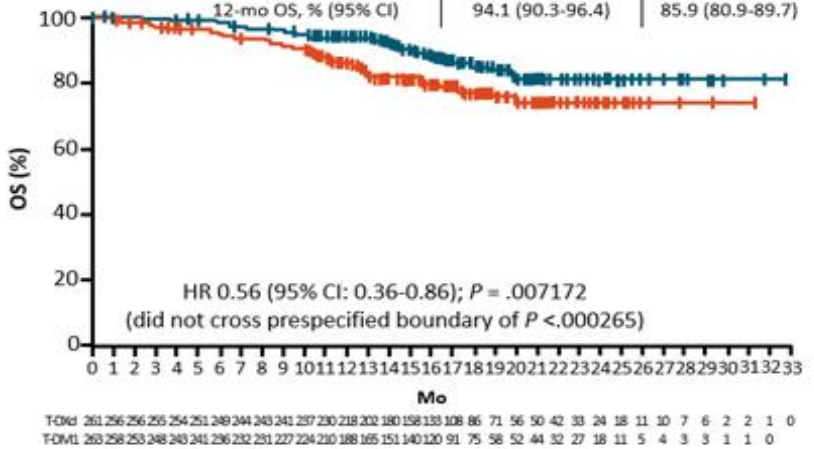
PFS by Investigator Assessment

	T-DXd (n = 261)	T-DM1 (n = 263)
Median PFS, mo (95% CI)	25.1 (22.1-NE)	7.2 (6.8-8.3)
12-mo PFS, % (95% CI)	76.3 (70.4-81.2)	34.9 (28.8-41.2)



OS (Early Data)

	T-DXd (n = 261)	T-DM1 (n = 263)
Median OS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS, % (95% CI)	94.1 (90.3-96.4)	85.9 (80.9-89.7)

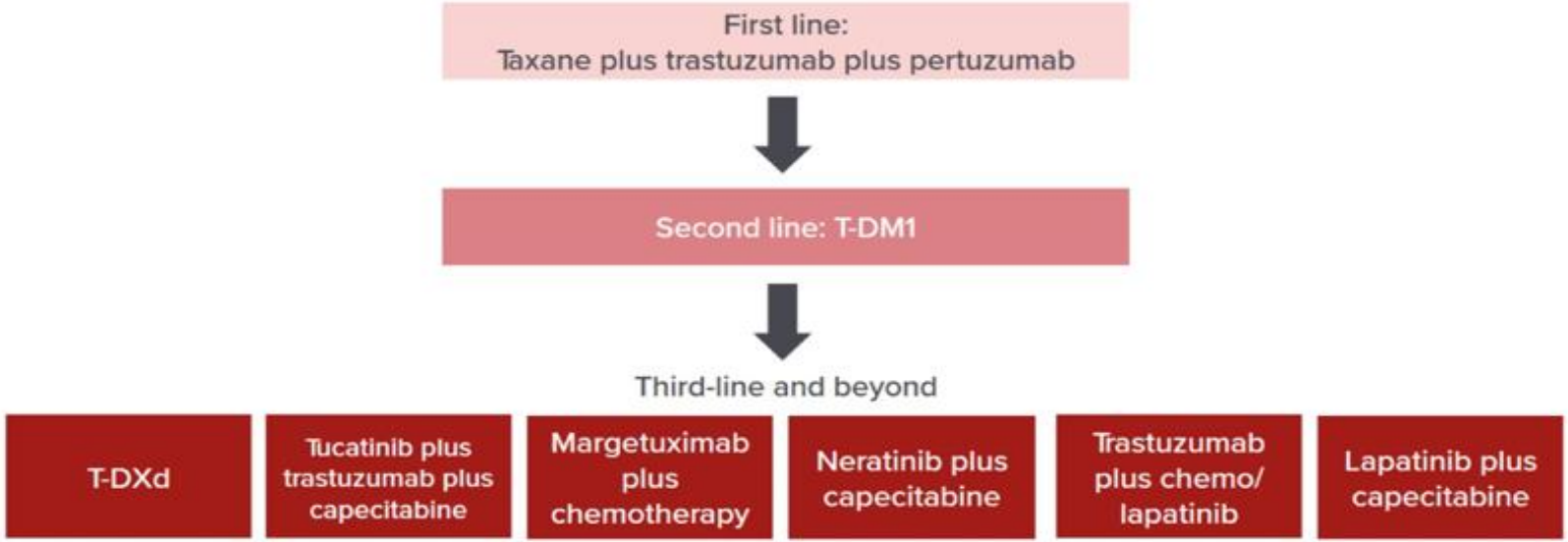


- PFS benefit with T-DXd consistent across key subgroups, including those defined by HR status, prior pertuzumab, visceral disease, brain metastases, and number of prior lines of therapy

Cortes. ESMO 2021. Abstr LBA1. Reproduced with permission.

Slide credit: clinicaloptions.com

What Is Next for HER2-Positive Breast Cancer?



Slide courtesy of Erika Hamilton, MD.

What Is Next for HER2-Positive Breast Cancer?

First line:
Taxane plus trastuzumab plus pertuzumab

↓

Second line: T-DM1

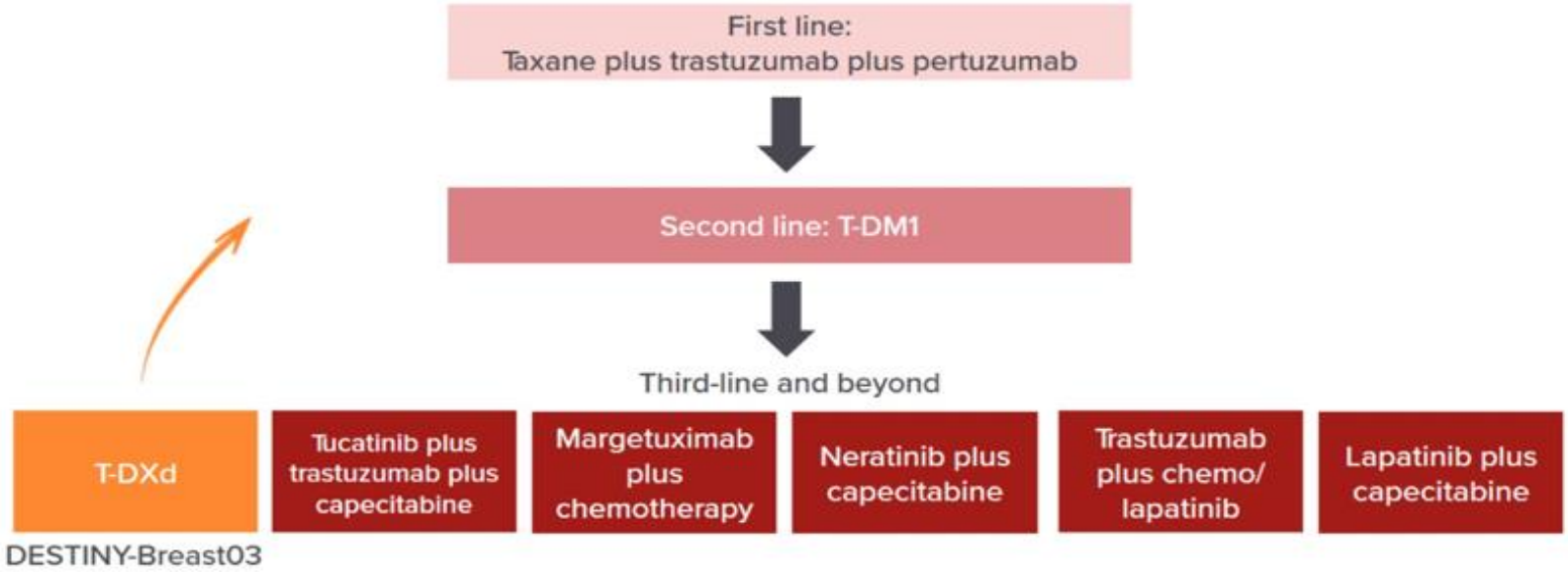
↓

Third-line and beyond

T-DXd	Tucatinib plus trastuzumab plus capecitabine	Margetuximab plus chemotherapy	Neratinib plus capecitabine	Trastuzumab plus chemo/ lapatinib	Lapatinib plus capecitabine
DESTINY-Breast03					

Slide courtesy of Erika Hamilton, MD.

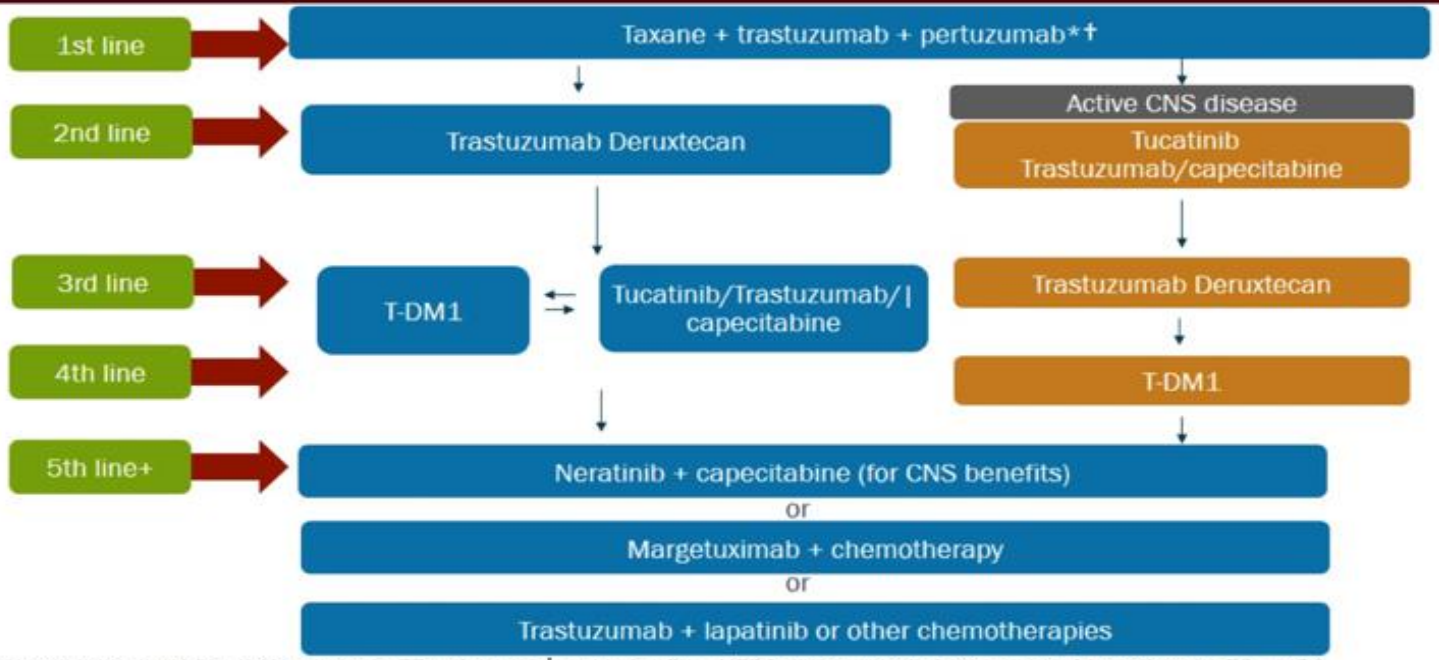
What Is Next for HER2-Positive Breast Cancer?



Slide courtesy of Erika Hamilton, MD.

2021 Approach to Therapy for Metastatic HER2+ BC

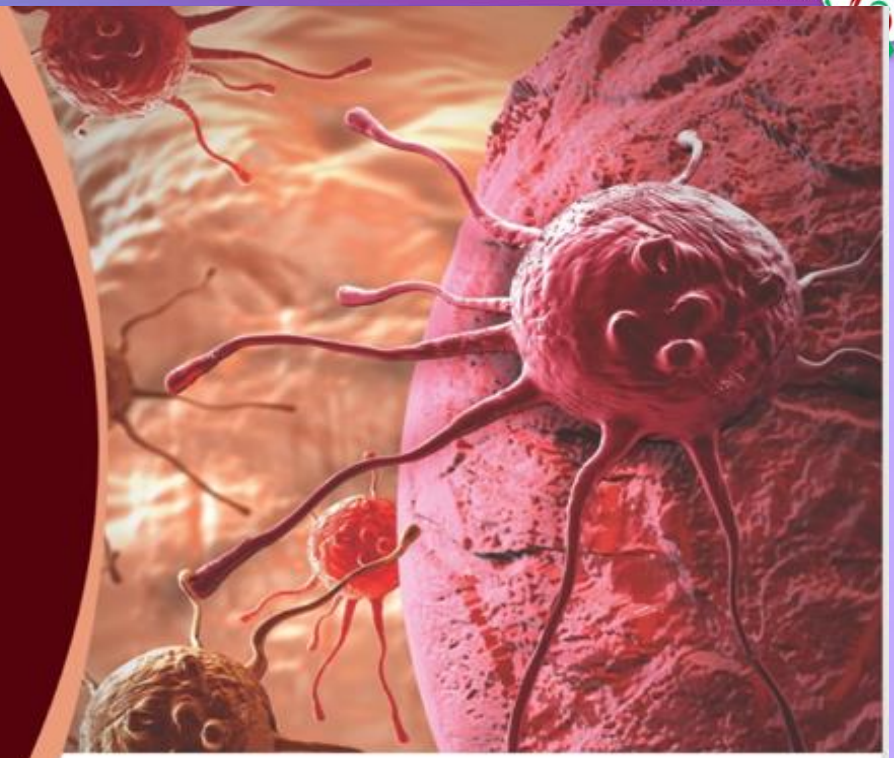
Current Approach for Metastatic HER2+ Breast Cancer



*AI+TP in select cases and for maintenance in ER+ disease; †endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC.

A Medscape LIVE! CONFERENCE

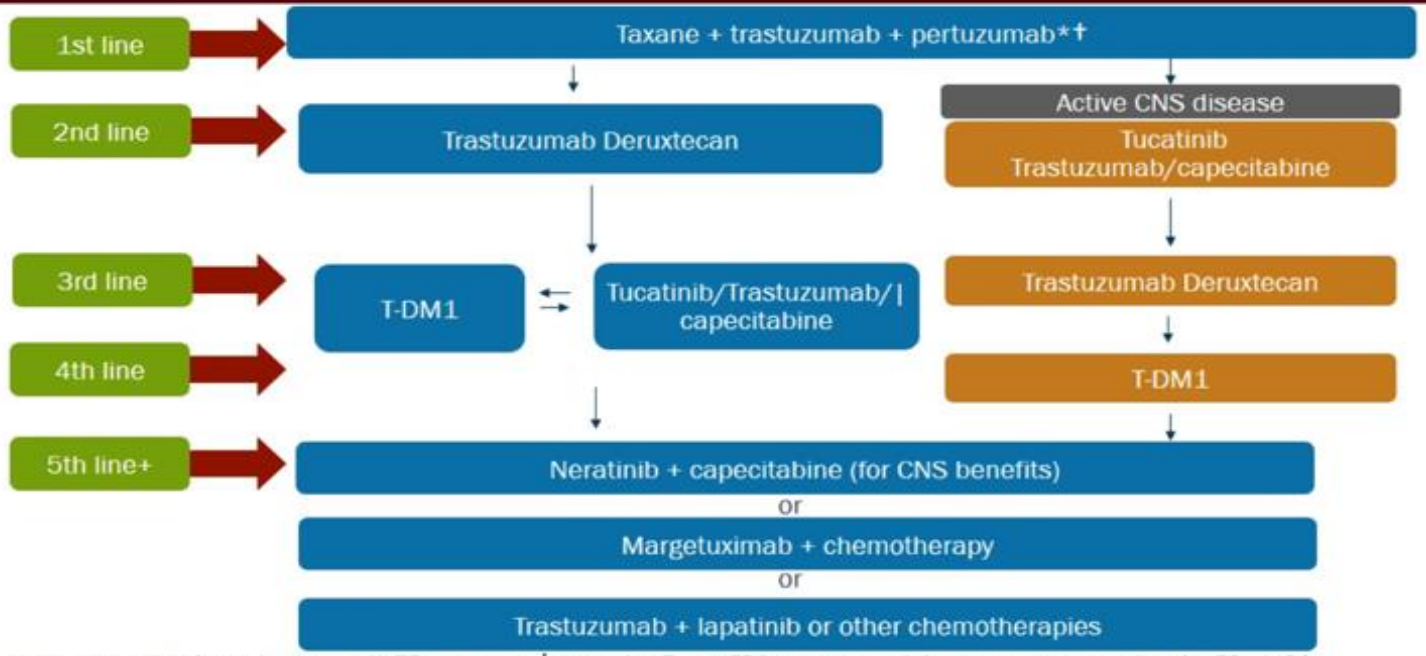
Third-Line Setting and Beyond...



Medscape Oncology

2021 Approach to Therapy for Metastatic HER2+ BC

Current Approach for Metastatic HER2+ Breast Cancer



*AI+TP in select cases and for maintenance in ER+ disease; †endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC.

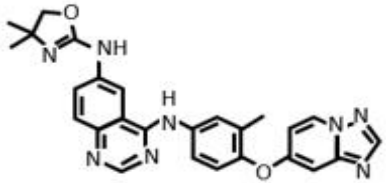
Characteristics of HER2 Kinase Inhibitors

TKI	Mechanism of Binding	Targets (IC_{50})				MTD
		HER1	HER2	HER4	Others	
Lapatinib	Reversible	++ 11nM	+++ 9 nM	+ 367 nM	ERK1, ERK2, AKT	1250/1500 mg
Neratinib	Irreversible	+ 92 nM	+ 59 nM	-	SRC, KDR	240 mg
Tucatinib	Reversible	- 10,000 nM	+++ 8 nM	-		600 mg
Pyrotinib	Irreversible	+++ 13 nM	+++ 38 nM	-		400 mg
Afatinib	Irreversible	++++ 0.5 nm	++ 14 nM	++++ 1 nM		40 mg

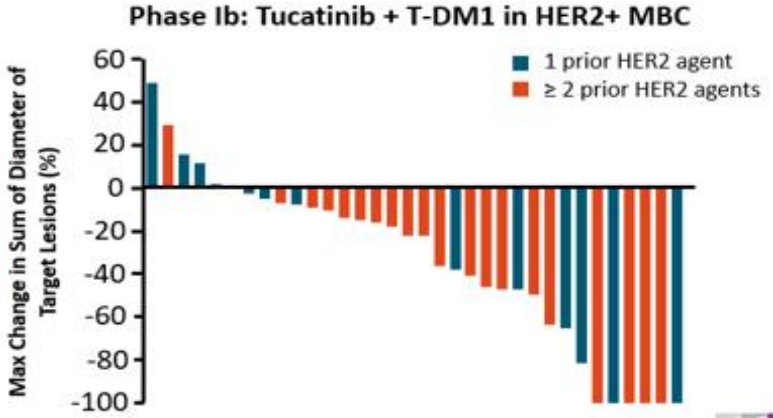
MTD, maximum tolerated dose; TKI, tyrosine kinase inhibitor
Le Du F, et al. J Cancer. 2021;154:175-189

Tucatinib: HER2-Selective TKI

- Less EGFR-associated toxicity than other HER2-targeted TKIs
- CNS penetration
- Well tolerated and active in combinations (eg, with T-DM1, capecitabine, or trastuzumab)



Agent	Cellular Selectivity, IC_{50} (nM)	
	HER2	EGFR
Tucatinib	8	4000
Neratinib	7	8
Lapatinib	49	31



Borges. ASCO 2016. Abstr 513. Borges. JAMA Oncol. 2018;4:1214.

Slide credit: clinicaloptions.com

HER2CLIMB: Phase II Study Design

- Randomized, double-blind, placebo-controlled, active comparator, global phase II trial
  - Data cutoff: February 8, 2021; median f/u: 29.6 mo

Stratified by brain mets (yes vs no), ECOG PS (0 vs 1), and region (US or Canada vs rest of world)

21-day cycles

Patients with HER2+ MBC; prior trastuzumab, pertuzumab, and T-DM1; ECOG PS 0/1; brain mets allowed* (N = 612)

2:1

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m² PO BID on Days 1-14
(n = 410)

Placebo PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m² PO BID on Days 1-14
(n = 202)

Crossover from placebo to tucatinib arm was allowed after the completion of the primary analysis

First crossover: February 2020

*All patients had baseline MRI. Included previously treated stable mets, untreated mets not needing immediate local therapy, and previously treated progressing mets not needing immediate local therapy.

- **Primary endpoint**: PFS (RECIST v 1.1 by BICR); **secondary endpoints:** OS, PFS in patients with brain mets, ORR, safety
- **Exploratory analysis reported here:** OS in patients with brain metastases; CNS-PFS, DOR-IC; ORR-IC (response after crossover not included in current analysis)

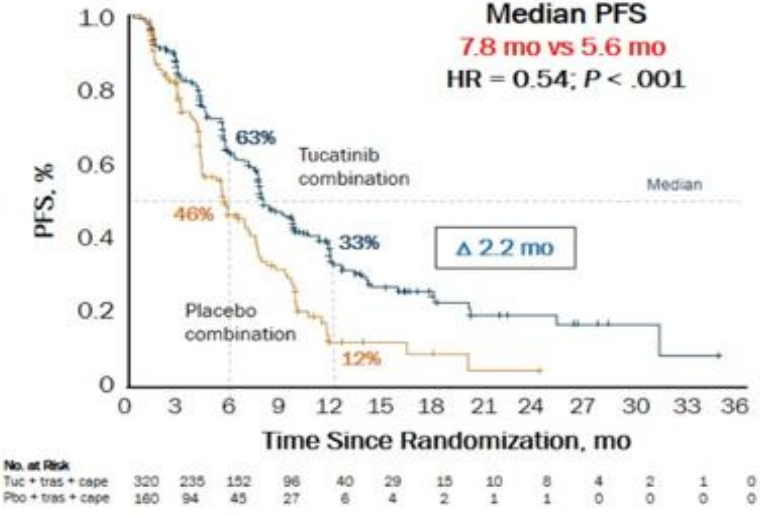
Murthy. NEJM. 2020;382:597-609. Lin. JCO. 2020;38:2610. Lin. ASCO 2020. Abstr 1005.
Curigliano. ASCO 2021. Abstr 1043. Lin. SABCS 2021. Abstr PD4.04

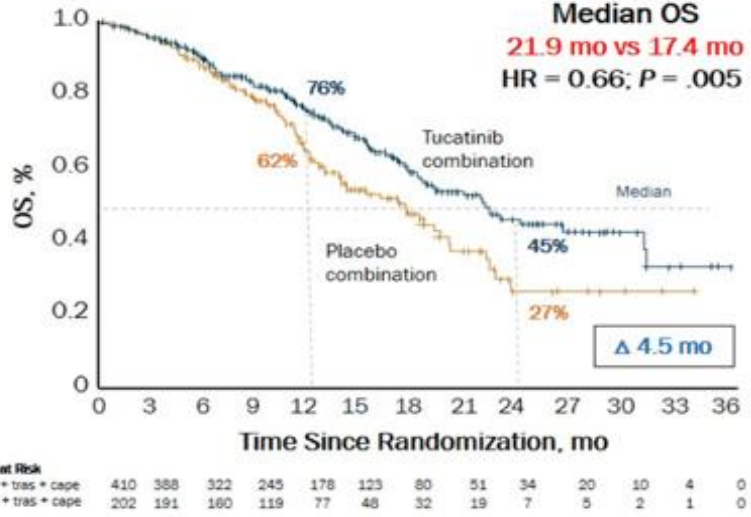
Slide credit: clinicaloptions.com

HER2CLIMB: Randomized Phase 2 Trial of Tucatinib

Median Duration of Follow-Up of 14 Months

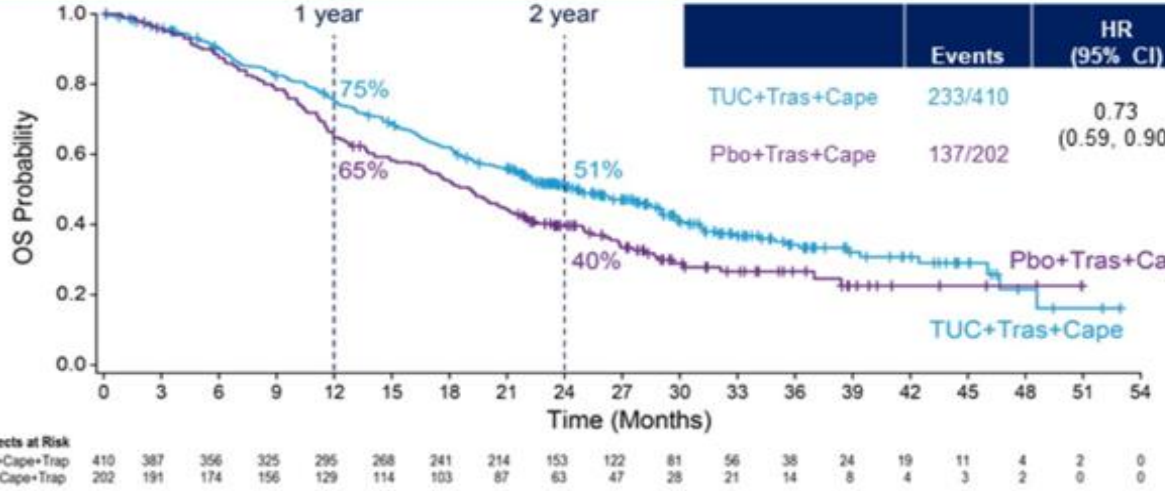
Tucatinib Improves PFS and OS





Murthy R, et al. N Engl J Med. 2020;382:597-609.

HER2CLIMB: Updated Overall Survival
Median Follow-Up 29.6 Months



	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)

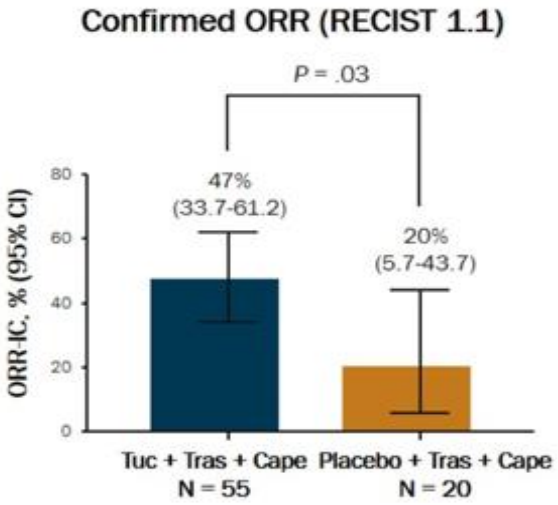
Δ 5.5 mo

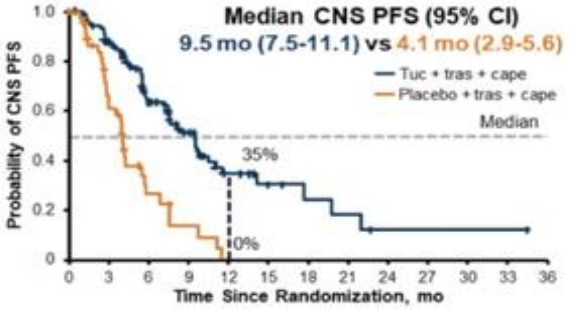
a Median overall study follow-up: 29.6 months

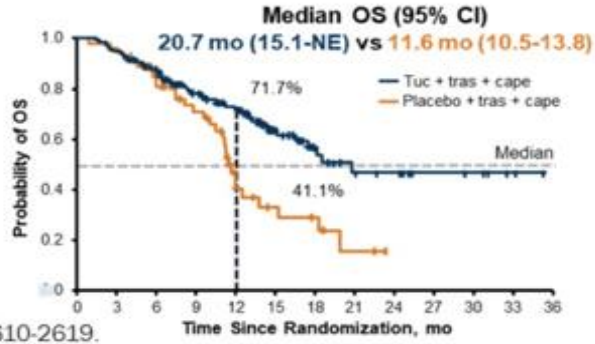
- OS benefit with tucatinib was maintained with longer follow-up with a 5.5 month improvement in median OS in the tucatinib arm vs placebo arm
- Sensitivity analyses accounting for cross-over showed consistent results with ITT analysis

ITT, intention-to treat.
Curigliano G, ASCO® 2021. Abstract 1043.

Tucatinib for Patients With Active Brain Metastases
Improves ORR, CNS PFS, and OS







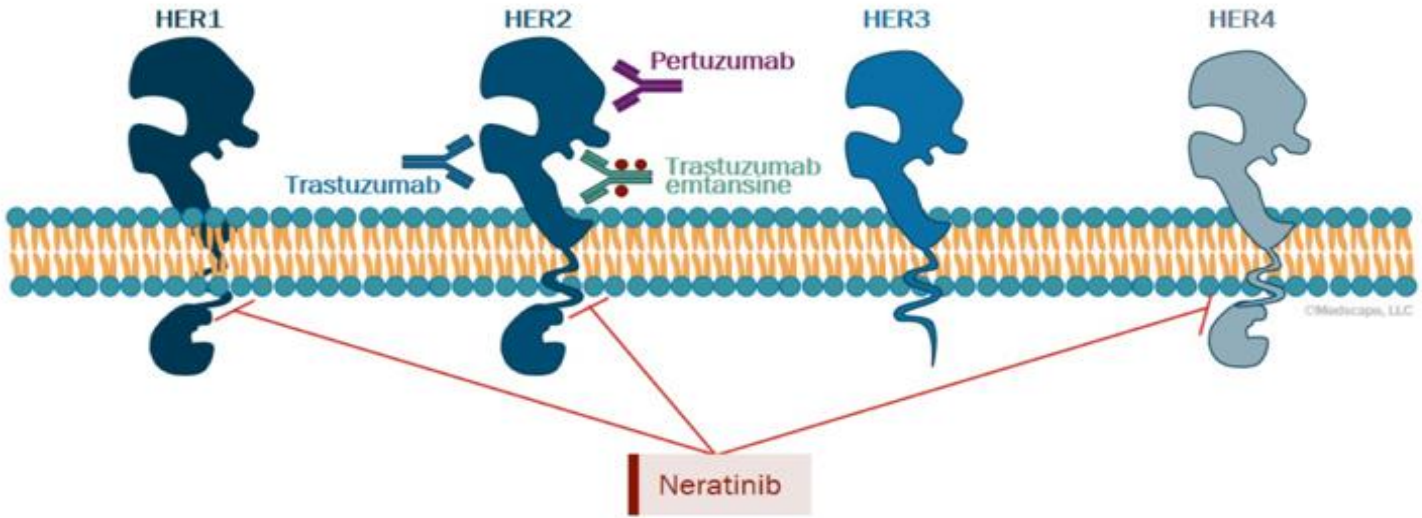
Murthy R et al. N Engl J Med. 2020;382:597-609; Lin NU et al. J Clin Oncol. 38;2020:2610-2619.

HER2CLIMB: Investigators' Conclusions

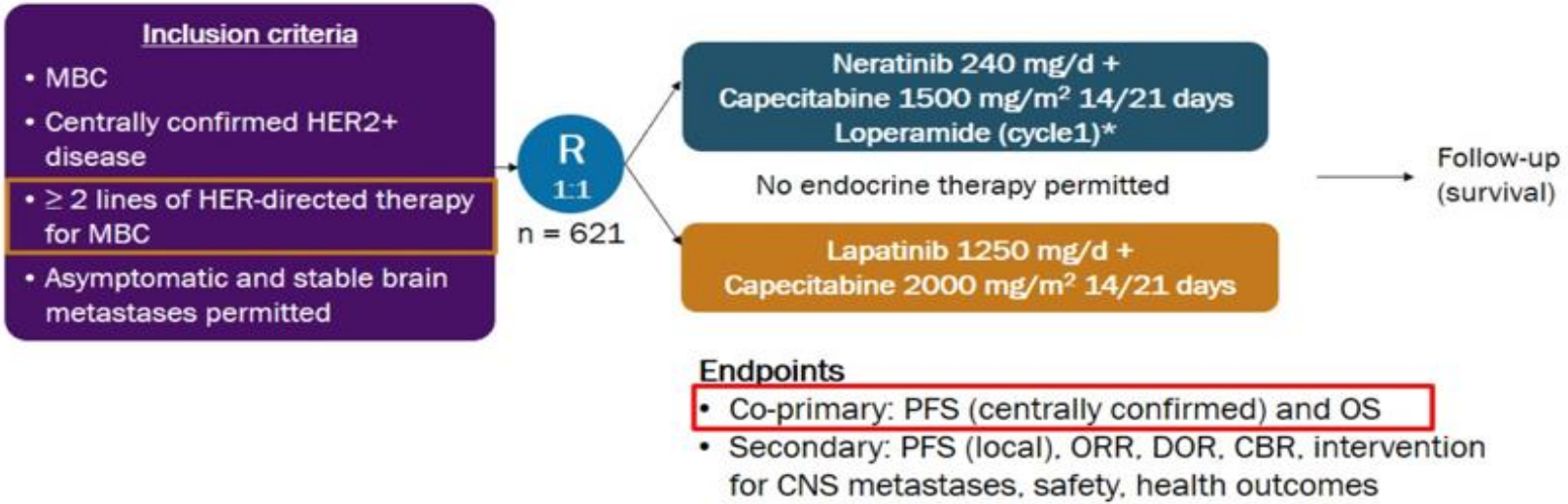
- At a total follow-up of 29.6 mo, the combination of tucatinib, trastuzumab, and capecitabine improved OS in patients with active or treated/stable brain metastases
  - 9.1-mo improvement in all patients with brain metastases
  - 9.6-mo improvement in patients with active brain metastases
  - 5.2-mo improvement in patients with treated/stable brain metastases
- In patients with active brain metastases and measurable intracranial lesions at baseline, DOR-IC was nearly 3-fold higher with tucatinib added to trastuzumab and capecitabine
- Tucatinib, trastuzumab, and capecitabine continued to confer a clinically meaningful CNS-PFS benefit corresponding to a delay in brain progression
- The combination of tucatinib, trastuzumab, and capecitabine is an active regimen for patients with HER2-positive MBC and active or stable brain metastases

Lin. SABCS 2021. Abstr PD4.04.

Neratinib
A Pan-HER Kinase Inhibitor



NALA
Phase 3 Trial of Neratinib for HER2+ MBC

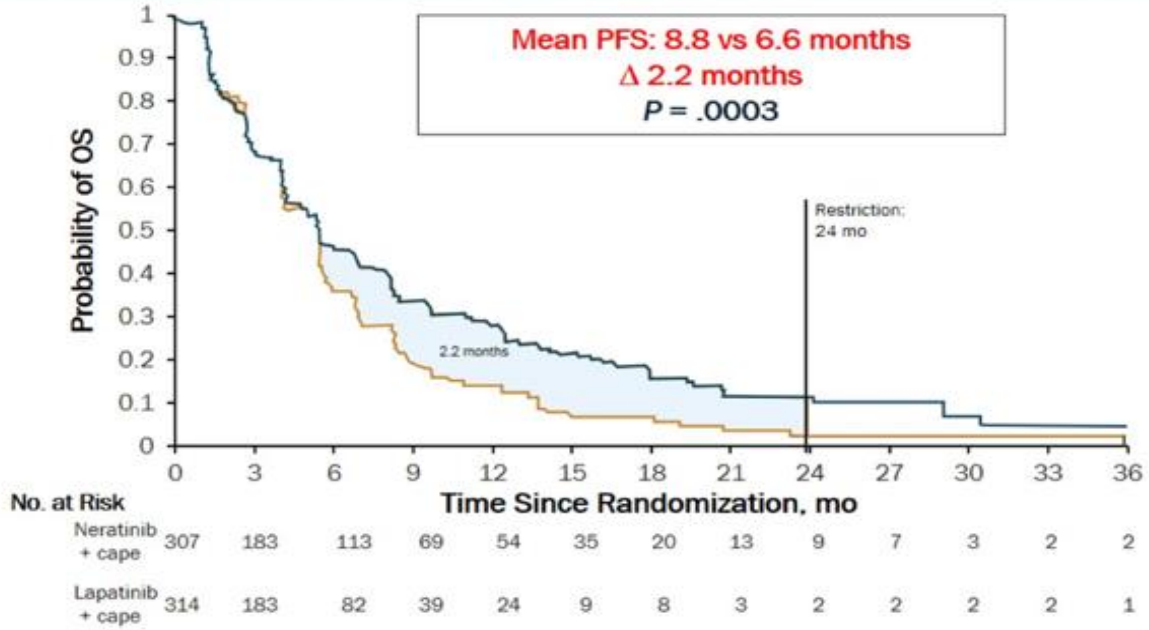


Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DOR, CBR, intervention for CNS metastases, safety, health outcomes

*Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 hours for the first 3 days, then loperamide 2 mg every 6-8 hours until end of cycle 1; thereafter as needed.
CBR, clinical benefit rate.
Saura C, et al. J Clin Oncol 2020;38:3138-3149.

NALA Trial: Centrally Confirmed Mean PFS
Primary Endpoint

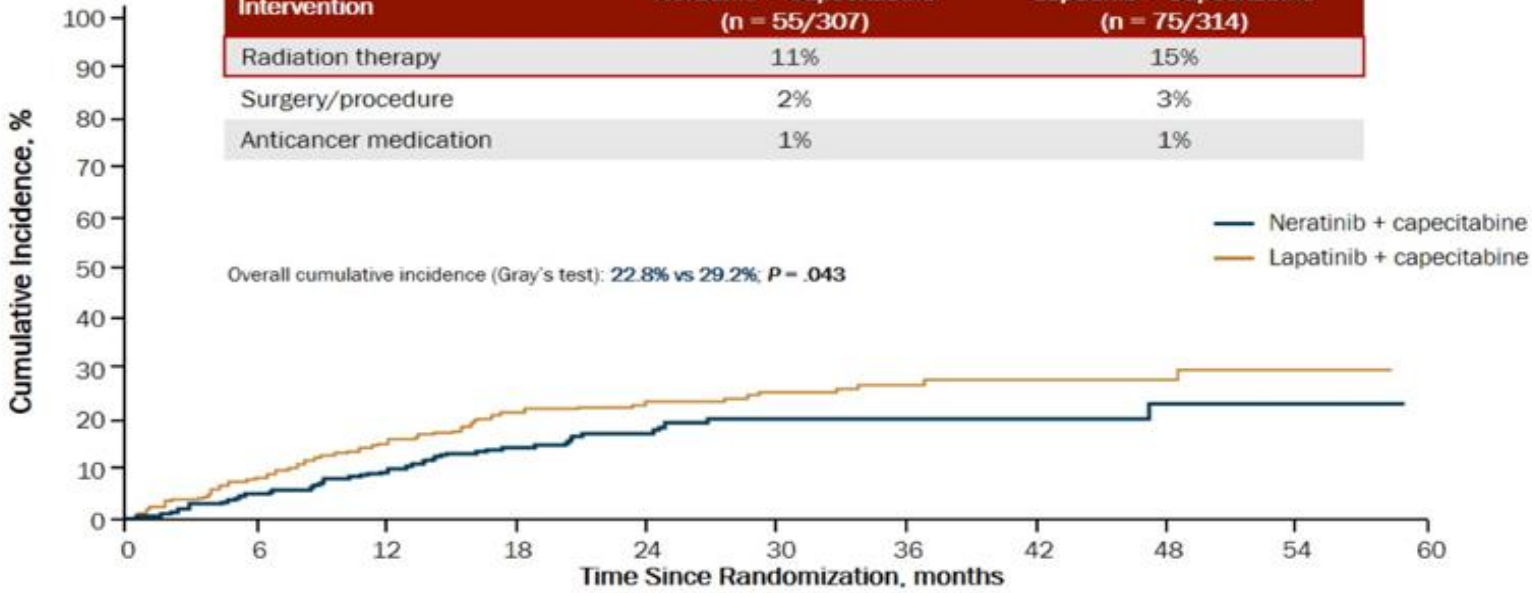


Saura C, et al. J Clin Oncol. 2020;38:3138-3149.

NALA Trial

*CNS Benefits in Favor of Neratinib**

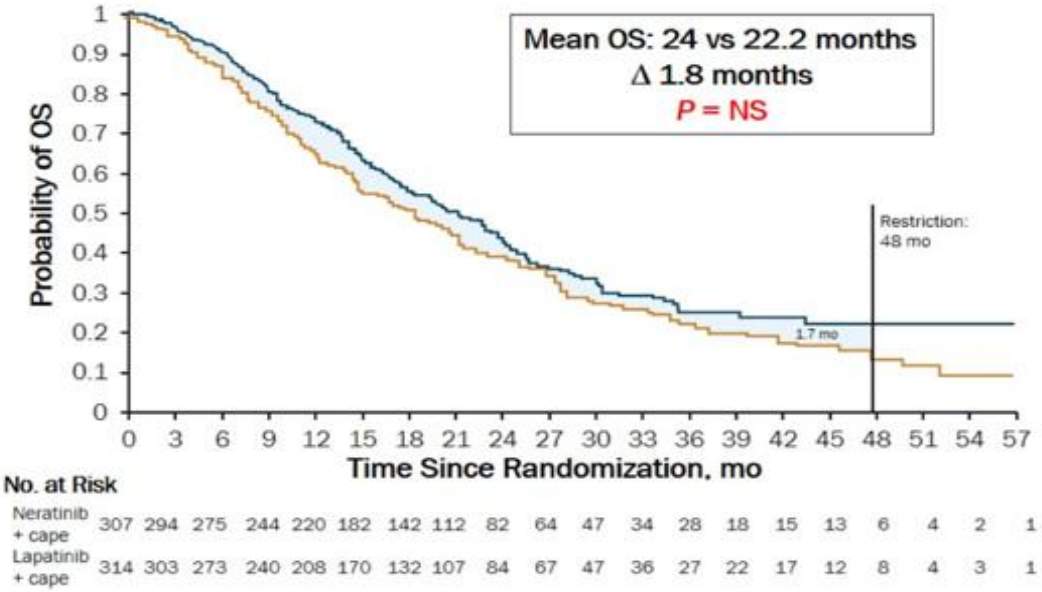
Intervention	Neratinib + Capecitabine (n = 55/307)	Lapatinib + Capecitabine (n = 75/314)
Radiation therapy	11%	15%
Surgery/procedure	2%	3%
Anticancer medication	1%	1%



*Cumulative incidence of intervention for symptomatic brain mets.

Saura C, et al. J Clin Oncol. 2020;38:3138-3149.

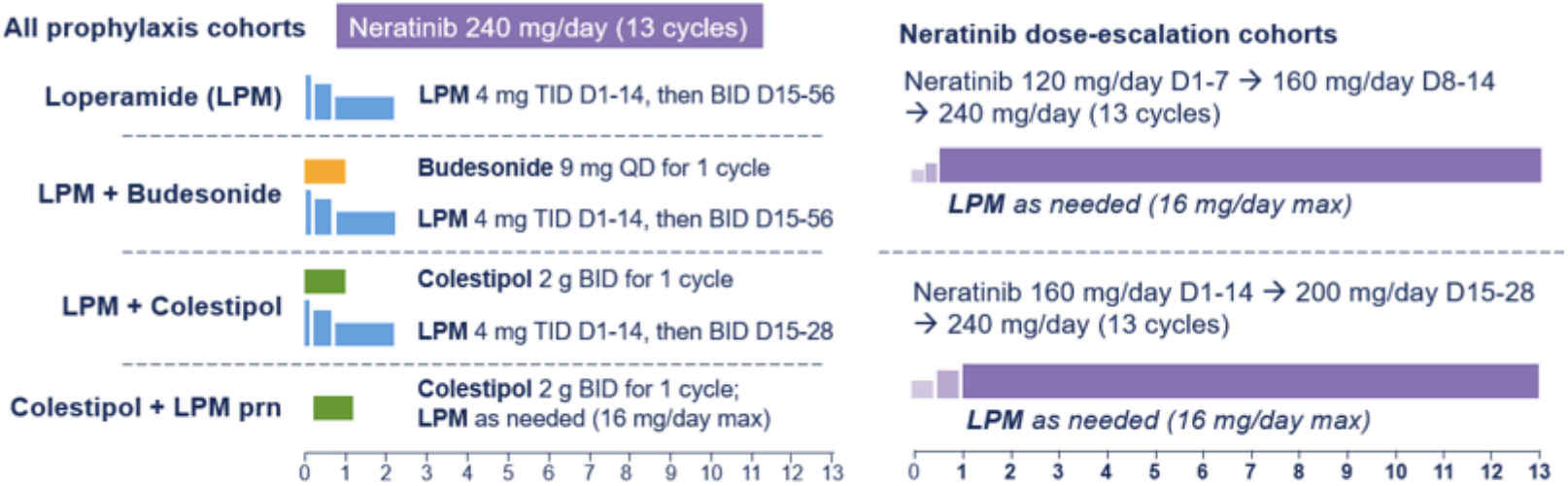
NALA Trial: No Difference in OS
Primary Endpoint



Saura C, et al. J Clin Oncol. 2020;38:3138-3149.

Phase II CONTROL Trial: Antidiarrheal Prophylaxis for Neratinib-Associated Diarrhea in Early HER2+ BC

- Open-label phase II trial enrolled adults with stage I-IIIC HER2+ BC who completed trastuzumab-based adjuvant therapy* within 1 yr or who d/c due to AE (N = 501)



*28-day cycles. Treatment-emergent diarrhea also managed with neratinib interruption/reduction, BSC. Data cutoff: August 26, 2019.;
*Includes trastuzumab, trastuzumab + pertuzumab, and T-DM1.
BC = breast cancer; AE = adverse event; d/c = discontinued; LPM = loperamide; tx = treatment.
Chan. SABCS 2019. Abstr P5-14-03. Chan. Lancet Oncol. 2016;17:367. Hurvitz. SABCS 2017. P3-14-01.

FDA Approval of Next-Generation HER2 TKIs for HER2-Positive MBC

- On February 25, 2020, the FDA approved neratinib in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive BC who have received ≥ 2 previous HER2-targeted regimens in the metastatic setting
  - Administration: 240 mg taken orally once daily with food on days 1-21 of a 21-day cycle in combination with capecitabine (750 mg/m^2 taken orally twice daily) on days 1-14 of a 21-day cycle until PD or unacceptable toxicity
    - Dose interruptions or modifications recommended on individual patient safety/tolerability
- On April 17, 2020, the FDA approved tucatinib in combination with trastuzumab/capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2+ BC, including patients with brain metastases, who have received ≥ 1 previous HER2-targeted regimens in the metastatic setting
  - Administration: 300 mg taken orally twice daily with or without food
    - Reduce dose to 200 mg orally twice daily for patients with severe hepatic impairment

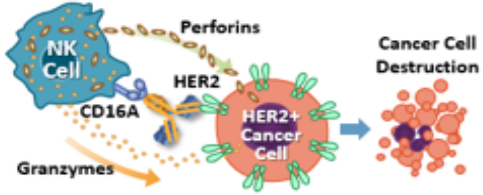
Neratinib PI. Tucatinib PI.

Slide credit: clinicaloptions.com

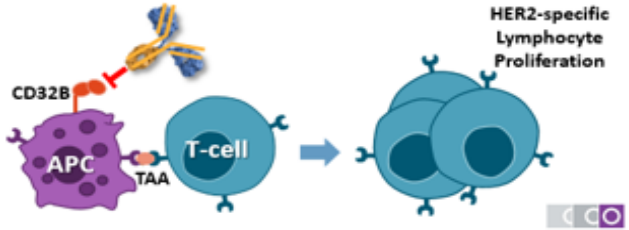
Margetuximab: Novel HER2-Targeted Monoclonal Antibody

- Margetuximab has the same specificity, affinity to HER2 as trastuzumab with similar ability to disrupt signaling
- However, via Fc engineering with intent to activate immune responses, margetuximab has altered Fc receptor affinity
  - Trastuzumab: WT IgG1 effector domains; binds and activates immune cells
  - Margetuximab: Increased affinity for activating Fcγ RIIIA (CD16A) and decreased affinity for inhibitory Fcγ RIIB (CD32B)

Increased CD16A Affinity:
Enhance Innate Immunity/More Potent ADCC Stimulation



Decreased CD32B Affinity:
Enhance Adaptive Immunity/Increase Immune Activation



Nordstrom. Breast Cancer Res. 2011;13:R123. Nordstrom. ASCO 2019. Abstr 1030.

Slide credit: clinicaloptions.com

SOPHIA: Margetuximab vs Trastuzumab in HER2+ Advanced Breast Cancer After ≥ 2 HER2 Therapies

- Randomized, open-label phase III trial (data cutoff: September 30, 2019)

Stratified by CT, no. of prior lines of tx (> 2 vs ≤ 2), no. of metastatic sites (> 2 vs ≤ 2)

Patients with HER2+ advanced BC with ≥ 2 previous anti-HER2 therapies, including pertuzumab; 1-3 prior lines of tx for metastatic disease; prior brain metastasis allowed if treated/stable
(N = 536)

→ **Margetuximab** 15 mg/kg Q3W + **CT*** in 3 wk cycles (n = 266)

→ **Trastuzumab** 8 mg/kg loading → 6 mg/kg Q3W + **CT*** in 3-wk cycles (n = 270)

*Investigators choice of CT: capecitabine, eribulin, gemcitabine, or vinorelbine.

- Sequential primary endpoint: PFS, OS
- Secondary endpoints: ORR by central blinded analysis, investigator-assessed PFS
- Tertiary and exploratory endpoints: investigator-assessed CBR, DoR, safety, and effect of CD16A, CD32A, and CD32B alleles on margetuximab efficacy

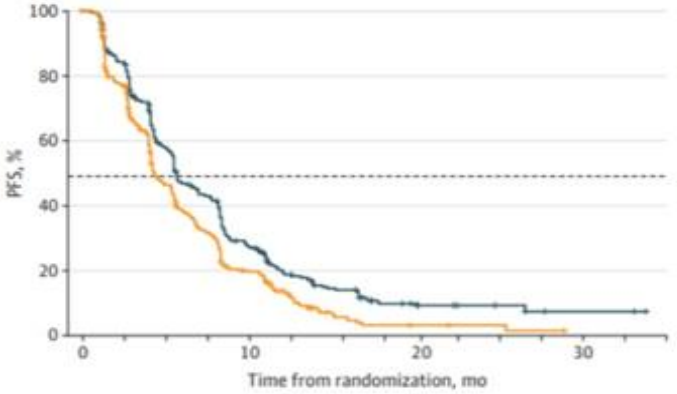
Rugo. SABCS 2019. Abstr GS1-02.

Slide credit: clinicaloptions.com

Phase 3 SOPHIA Trial: Primary PFS Endpoint

24% Risk Reduction in Disease Progression

C PFS by investigator, September 2019 cutoff



No. at risk

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		

	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	208	222
Median PFS (95% CI)	5.7 mo (5.22-6.97)	4.4 mo (4.14-5.45)
3-mo PFS rate	74% (68%-79%)	67% (61%-72%)
6-mo PFS rate	47% (41%-53%)	38% (32%-45%)
9-mo PFS rate	29% (24%-35%)	20% (16%-26%)

HR by stratified Cox model, 0.71 (95% CI, 0.58-0.86)
Stratified log-rank $P < .001$
29% Risk reduction of disease progression[b]

Rugo HS, et al. JAMA Oncol. 2021;7:573-584.

Planned Exploratory PFS and OS Analysis by FcγR Genotypes

PFS Analysis[a]

Margetuximab benefit appears to be increased in low-affinity CD16A-158F allele carriers

		Median PFS (95% CI), Months: Margetuximab + Chemotherapy	Median PFS (95% CI), Months: Trastuzumab + Chemotherapy	HR by Unstratified Cox Model	95% CI	Unstratified Log-Rank *P* Value
	All patients	5.8 (5.52–6.97)	4.9 (4.17–5.59)	0.78	(0.61–0.98)	0.044
Activating function	CD16A/F carrier (FV or FF), n=437	6.9 (5.55–8.15)	5.1 (4.14–5.59)	0.68	(0.52–0.90)	0.005
	CD16A/FF, n=192	8.2 (5.52–10.51)	5.6 (4.50–8.31)	0.69	(0.46–1.05)	0.080
	CD16A/FV, n=245	6.3 (5.52–7.23)	4.3 (4.01–5.59)	0.71	(0.50–1.01)	0.055
	CD16A/VV, n=69	4.8 (2.46–5.65)	5.6 (2.86–11.04)	1.78	(0.87–3.62)	0.110
	CD32A/RR, n=122	5.7 (4.80–10.55)	5.5 (2.76–8.21)	0.69	(0.42–1.17)	0.166
	CD32A/RH, n=247	6.9 (5.55–8.15)	5.6 (4.17–6.67)	0.74	(0.52–1.06)	0.101
	CD32A/HH, n=137	5.6 (3.29–8.28)	4.1 (2.79–5.59)	0.80	(0.49–1.30)	0.365
Inhibitory function	CD32B/I*, n=380	5.8 (5.59–7.66)	5.5 (4.17–5.65)	0.85	(0.64–1.13)	0.265
	CD32B/T†, n=117	6.0 (4.14–9.6)	5.5 (2.79–7.16)	0.63	(0.36–1.10)	0.098

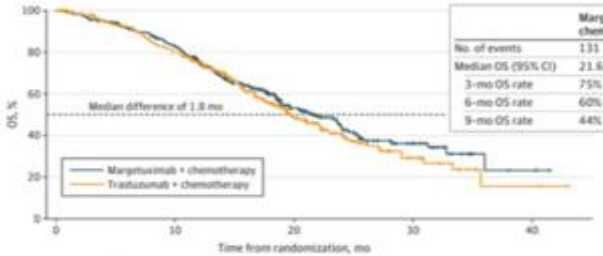
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0

Margetuximab Better | Trastuzumab Better

*Non-alpha allocating, exploratory analysis.

†CD32B/TT not included on forest plot because n=9 is too small (5 on margetuximab, 4 on trastuzumab) to make analysis meaningful.

OS in the ITT Population[b]



	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	131	139
Median OS (95% CI)	21.6 mo (18.86–24.05)	19.8 mo (17.54–22.28)
3-mo OS rate	75% (70%–80%)	75% (70%–80%)
6-mo OS rate	60% (53%–66%)	56% (49%–62%)
9-mo OS rate	44% (36%–51%)	40% (33%–48%)

HR by stratified Cox model, 0.89 (95% CI, 0.69–1.13)
Stratified log-rank *P* = .33
Median follow-up, 15.6 mo

a. Rugo HS, et al. ASCO® 2019. Abstract 1000. b. Rugo HS, et al. JAMA Oncol. 2021;7:573-584.

Phase III TULIP: [vic]-Trastuzumab Duocarmazine vs Physician's Choice Treatment in Previously Treated HER2+ Advanced Breast Cancer

CCO Independent Conference Highlights*

of the *ESMO 2021 Conference,*
September 17-20, 2021, Virtual

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

CLINICAL CARE OPTIONS®

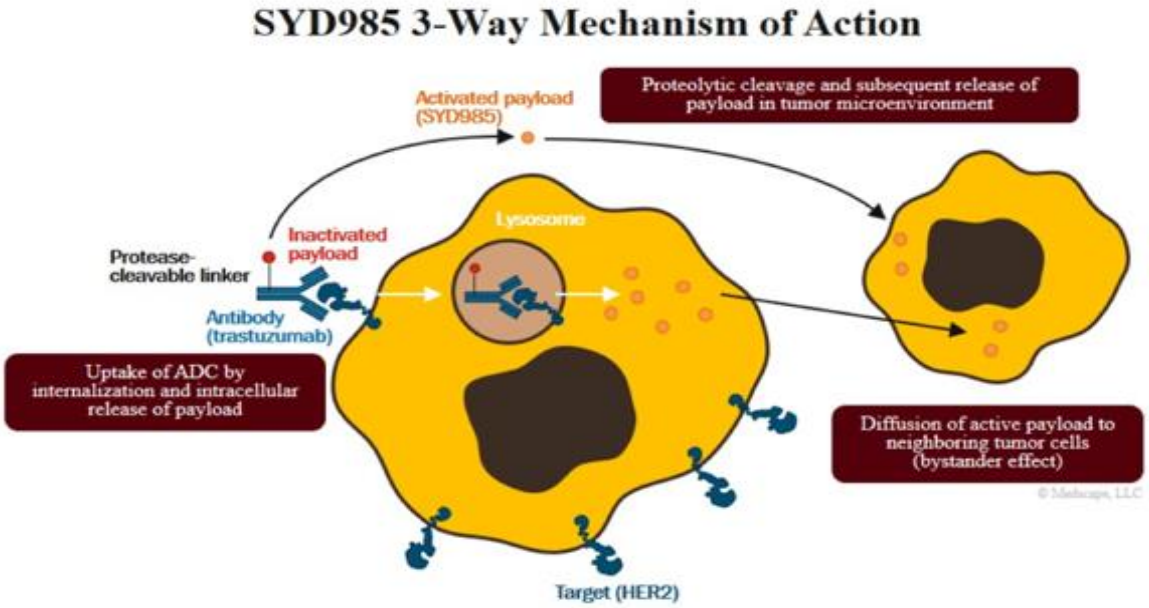
Provided by Clinical Care Options, LLC

Supported by educational grants from AstraZeneca, Daiichi Sankyo, Inc., Exelixis, Inc. and Ipsen Biopharmaceuticals, Inc.

CLINICAL CARE OPTIONS®
ONCOLOGY

SYD985: [vic-]Trastuzumab Duocarmazine

- HER2-targeting ADC based on trastuzumab
- Protease cleavable linker with a DNA alkylating toxin duocarmycin
- Toxin incorporated into the linker-drug as an inactive prodrug
- Proteolytic cleavage results in release of the active toxin



Saura C, et al. J Clin Oncol 2018;36(Suppl): Abstract 1014; Hofland P. ADC review. Accessed September 29, 2021. www.adcreview.com.

TULIP: Study Design

- Randomized, multicenter, open-label phase III study

Stratification by region (European Union + Singapore vs North America), prior therapies for MBC (1-2 vs >2), prior pertuzumab (Y/N)

Patients with locally advanced or metastatic HER2+ breast cancer with ≥2 prior therapies for metastatic disease or T-DM1 for metastatic disease; treated brain metastases allowed
(N = 437)

2:1

[vic]-Trastuzumab Duocarmazine 1.2 mg/kg IV Q3W
(n = 291)

Physician's Choice of CT*
(n = 146)

Until PD or unacceptable toxicity

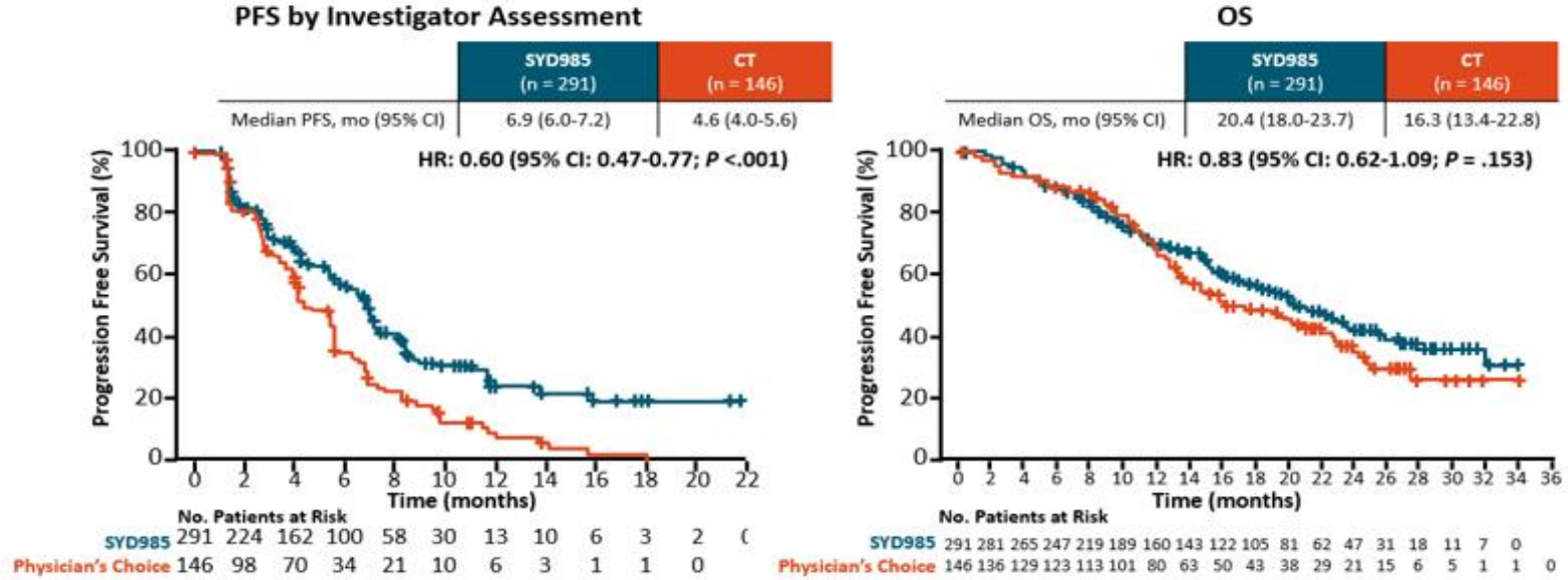
*Lapatinib + capecitabine, trastuzumab + capecitabine, trastuzumab + vinorelbine, or trastuzumab + eribulin.

- Primary endpoint: PFS by BICR
- Secondary endpoints: PFS (investigator), OS, ORR, HRQoL

Manich. ESMO 2021. Abstr LBA15. NCT03262935.

Slide credit: clinicaloptions.com

TULIP: PFS by Investigator Assessment, OS (Secondary Endpoints)



Manich. ESMO 2021. Abstr LBA15. Reproduced with permission.

Slide credit: clinicaloptions.com

TULIP: Conclusions

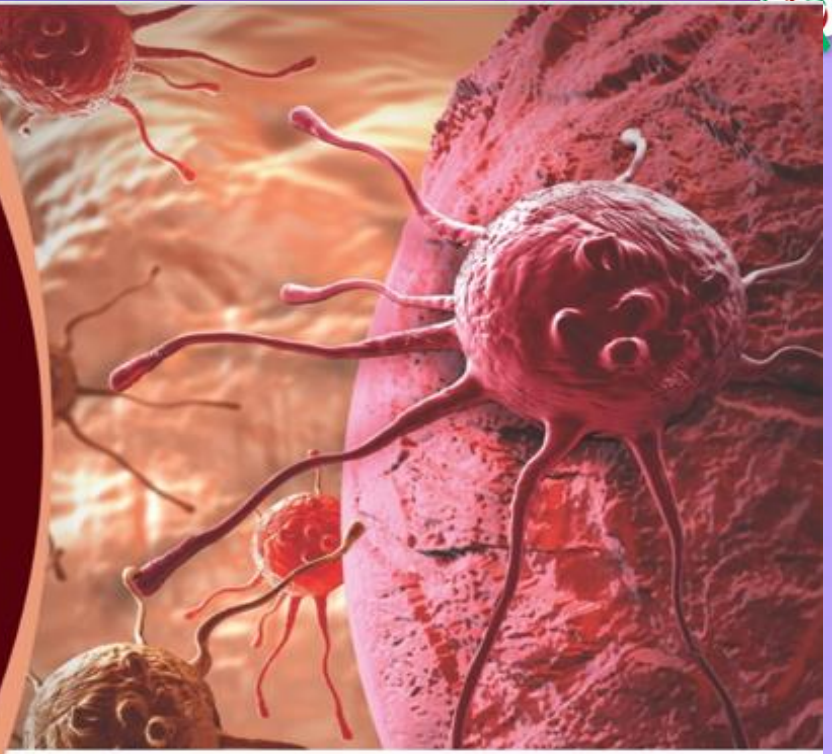
- In the phase III TULIP study, use of [vic]-trastuzumab duocarmazine significantly prolonged PFS (by central review) compared with physician's choice of chemotherapy in patients with previously treated HER2+ locally advanced or metastatic breast cancer
  - Median PFS: 7.0 vs 4.9 mo, respectively (HR: 0.64; *P* = .002)
- Eye toxicity was most common AE; mitigated with prophylactic eye drops, regular eye exams, treatment discontinuation or delay
- Investigators suggest [vic]-trastuzumab duocarmazine may be a new treatment option for patients with pretreated HER2+ locally advanced or metastatic breast cancer

Manich. ESMO 2021. Abstr LBA15.

Slide credit: clinicaloptions.com

A Medscape LIVE! CONFERENCE

Treatment Approaches for HER2-Positive Brain Metastases



Carey K. Anders, MD
Medical Director
Duke Cancer Center Brain Tumor Clinic
Duke Cancer Center Breast Clinic
Duke Health
Durham, North Carolina

HER2, human epidermal growth factor receptor 2.

Medscape Oncology

Breast Cancer Brain Metastases

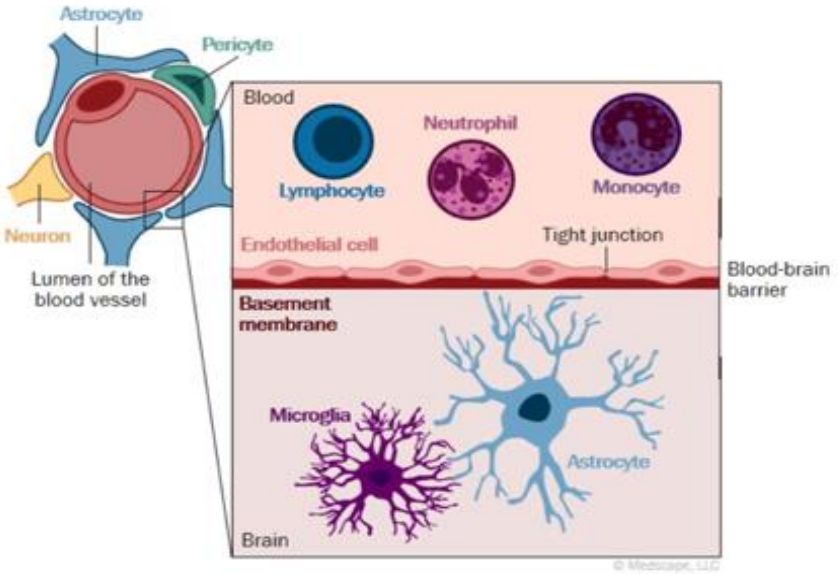
Increasingly common consequence of advanced breast cancer

- Incidence 30% HER2+,[a] 50% triple-negative advanced BC[b]

Blood brain barrier, efflux pumps in brain endothelium limit exposure to cytotoxics

Clinical trials frequently excluded patients with CNS disease

- Few trials specifically targeting patients with brain metastases



CNS, central nervous system.
a. Bendell JC, et al. Cancer. 2003; 97:2972-2977; b. Lin NU, et al. Cancer. 2008;113:2638-2645.

Current ASCO Guidelines for Managing HER2+ Brain Metastases

- Routine surveillance with imaging in the absence of symptoms is not recommended
- Low threshold for performing diagnostic brain MRI if any neurologic symptoms suggestive of BM
- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched
- For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, HER2-targeted therapy according to the algorithms for treatment of HER2+ MBC

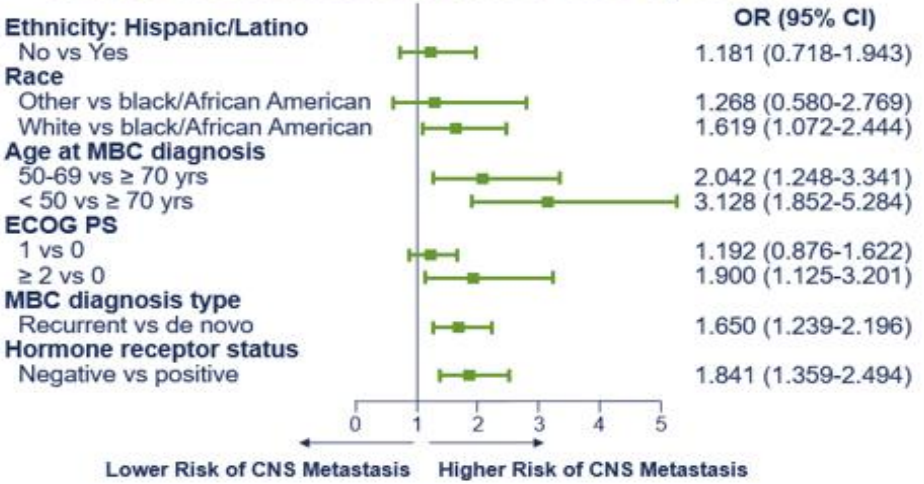
Ramakrishna. J Clin Oncol. 2018;36:2804.

Slide credit: clinicaloptions.com

In HER2+ MBC, CNS Disease Remains Incurable Despite Current Treatment Options

- ≥ 50% of patients with HER2+ MBC will develop brain metastases[1]
- Lapatinib + capecitabine approved in this setting but few patients respond
  - In a pooled analysis, CNS ORR was 21.4%, median PFS was 4.1 mos, median OS was 11.2 mos[1]
- Neratinib + capecitabine approved in this setting in Feb 2020
- Trastuzumab + capecitabine + tucatinib approved in this setting in April 2020
- T-DM1, trastuzumab, and pertuzumab do not penetrate the CNS under normal conditions

Risk of CNS Metastasis in HER2+ MBC by Subgroup[2]



CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; MBC = metastatic breast cancer; OR = odds ratio; PS = performance status; T-DM1 = trastuzumab emtansine.

1. Petrelli. Eur J Cancer. 2017;84:141. 2. Hurvitz. Clin Cancer Res. 2019;25:2433.

Initial Approach to Brain Metastases

- Biopsy if first/only site of recurrence
- Surgery to remove lesion causing increased intracranial pressure, solitary or few ipsilateral lesions
- Gross total resection
- Histology, IHC biomarkers, and molecular profiling
- Postoperative radiation to resection cavity
  - 50% recurrence rate in 1-2 yrs without RT

Slide credit: clinicaloptions.com

Therapeutic Approaches to BCBM in HER2-Positive Disease

Current Landscape of Systemic Options for HER2+ BCBM

Small Molecule TKI Combinations

- Lapatinib + capecitabine
- Neratinib + capecitabine
- Tucatinib + capecitabine + trastuzumab

ADCs

- T-DM1?
- Trastuzumab deruxtecan?

Slide credit: clinicaloptions.com

CEREBEL: CNS Metastasis at First Relapse in HER2+ MBC With Lapatinib/Cape vs Trastuzumab/Cape

- Randomized phase III study

21-day cycle

Stratified by prior trastuzumab, lines of prior tx for MBC (0 vs ≥ 1)

Patients with HER2+ MBC, any line of tx, including prior anthracyclines or taxanes; **no CNS metastasis** (N = 540)

→ **Lapatinib** 1250 mg/day + **Capecitabine** 2000 mg/m²/day on Days 1-14

→ **Trastuzumab*** 6 mg/kg Q3W + **Capecitabine** 2500 mg/m²/day on Days 1-14

*Loading dose of 8 mg/kg.

Endpoint	L + Cape (n = 251)	T + Cape (n = 250)	*P* Value
CNS as first site of progression, n (%)	8 (3)	12 (5)	.360
Incidence of CNS progression at any time, n (%)	17 (7)	15 (6)	.865
Median time to first CNS progression, mos (range)	5.7 (2-17)	4.4 (2-27)	NR
Median PFS, mos • Trastuzumab naive	6.6 6.3	8.1 10.9	.021 NR
Median OS, mos	22.7	27.3	.095
ORR, %	27	32	NR

- Primary endpoint: CNS as first site of relapse
- Secondary endpoints: PFS, OS
- Trial closed early for futility in lapatinib + capecitabine arm

Cape = capecitabine; CNS = central nervous system; L = lapatinib; MBC = metastatic breast cancer; NR = not reported; T = trastuzumab; tx = therapy.
Pivot. JCO. 2015;33:1564.

Neratinib in HER2+ MBC: Study Design

- Pooled analysis of 3 multicenter phase II or III trials

NALA
Metastatic HER2+ BC, ≥ 2 lines of HER2-directed therapy for metastatic disease, asymptomatic and stable brain metastases permitted
(N = 621)

→ **Neratinib** 240 mg/day + **Capecitabine** 1500 mg/m² 14/21 days* (n = 307)

→ **Lapatinib** 1250 mg/day + **Capecitabine** 2000 mg/m² 14/21 days (n = 314)

NEfERT-T
Metastatic HER2+ BC, previously untreated recurrent and/or metastatic disease, asymptomatic and stable brain metastases permitted
(N = 479)

→ **Neratinib** 240 mg/day + **Paclitaxel** 80 mg/m² 14/21 D1,8,15, Q28D (n = 242)

→ **Trastuzumab** 4 mg/kg then 2 mg/kg QW + **Paclitaxel** 80 mg/m² 14/21 D1,8,15, Q28D (n = 237)

TBCRC 022
Metastatic HER2+ BC and measurable, progressive CNS metastases
(N = 37)

→ **Neratinib** 240 mg/day + **Capecitabine** 1500 mg/m² 14/21 days* (n = 37)

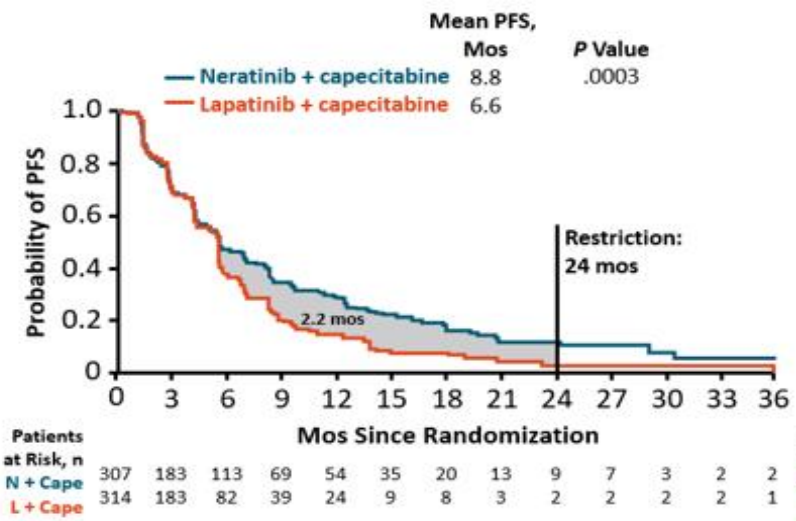
*Dosed with loperamide in cycle 1.

Awada. SABCS 2019. Abstr P2-20-01.

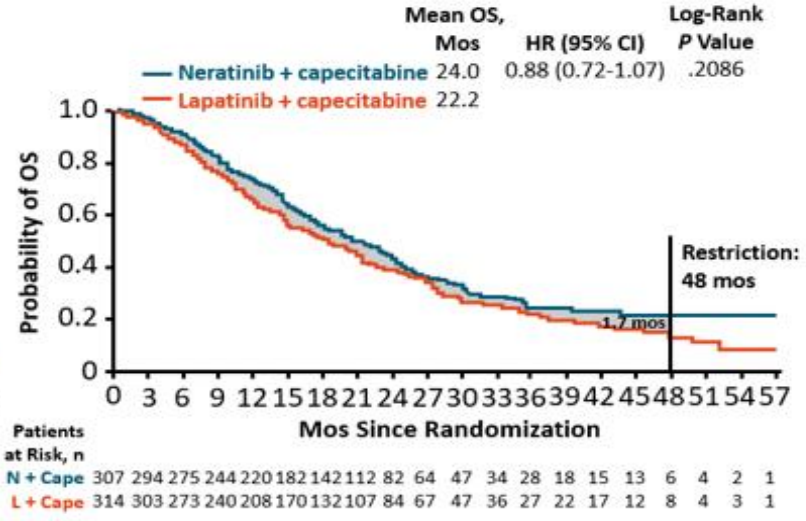
Slide credit: clinicaloptions.com

NALA: Survival

PFS (Prespecified Means Analysis)



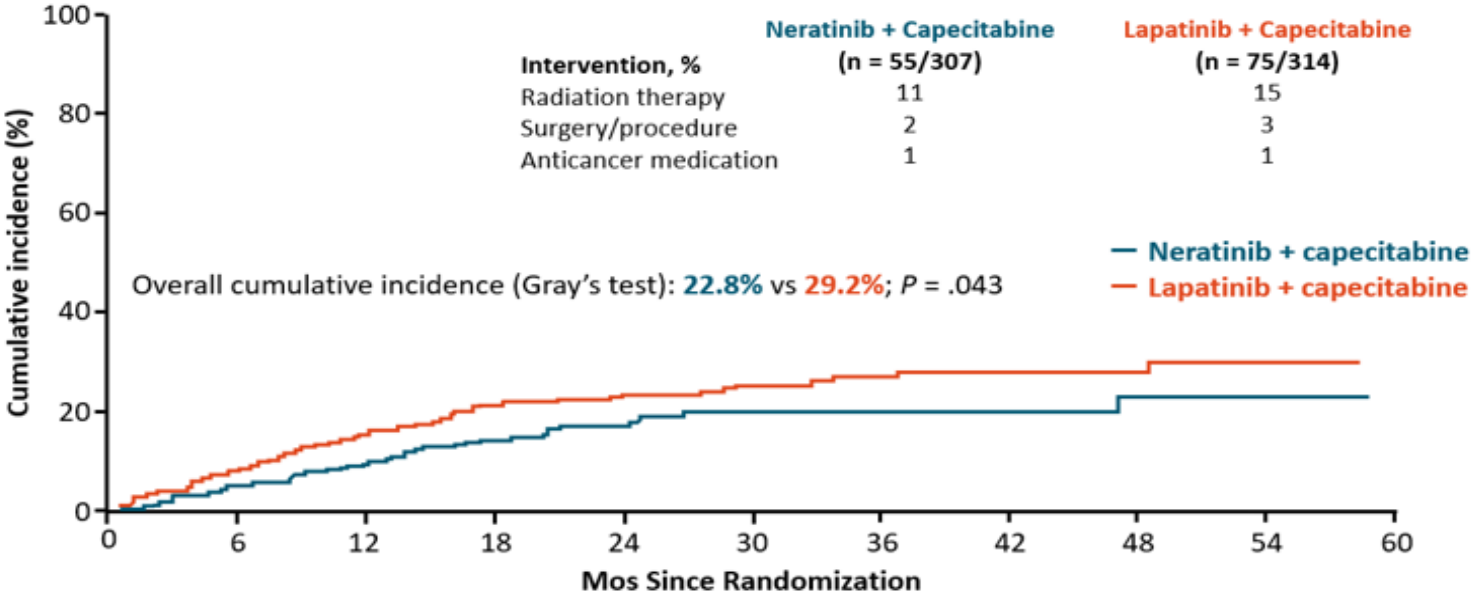
OS (Coprimary Endpoint)



Saura. J Clin Oncol. 2020;38:3138.

NALA: Time to Intervention for CNS Metastases

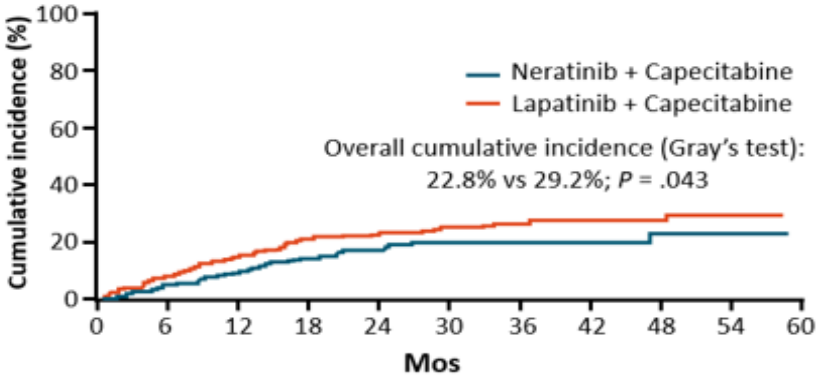
Intervention, %	Neratinib + Capecitabine (n = 55/307)	Lapatinib + Capecitabine (n = 75/314)
Radiation therapy	11	15
Surgery/procedure	2	3
Anticancer medication	1	1



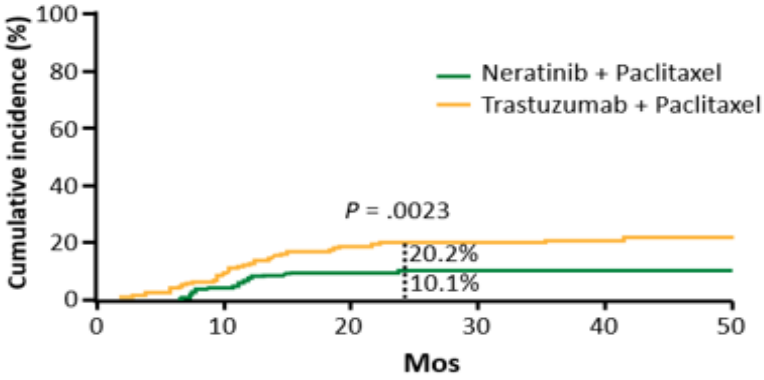
Saura. J Clin Oncol. 2020;38:3138.

Neratinib in HER2+ MBC: Cumulative Incidence of CNS Events

NALA: cumulative incidence of intervention for CNS metastases



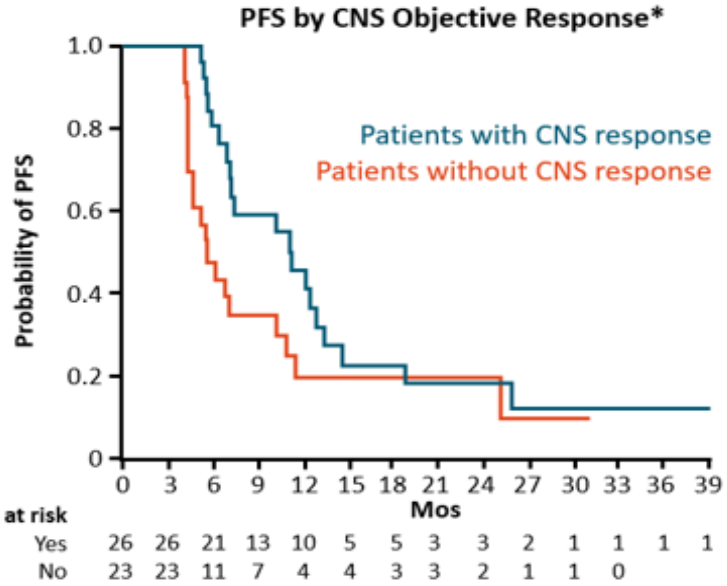
NEfERT-T: cumulative incidence of symptomatic or progressive CNS lesions



Awada. SABCS 2019. Abstr P2-20-01. Reproduced with permission.

Slide credit: clinicaloptions.com

Neratinib in HER2+ MBC: PFS by CNS Objective Response (Combined Trials)



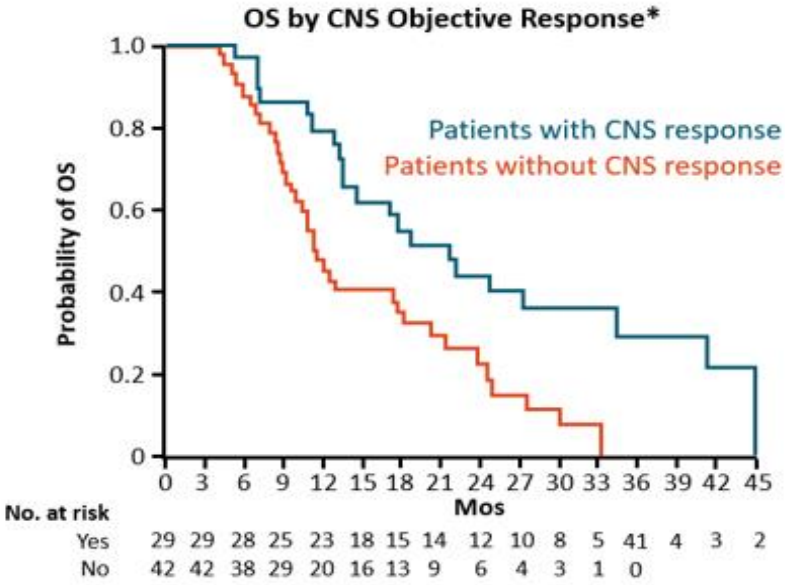
	Events, n (%)	Median PFS, Mos	HR (95% CI)	Log-Rank *P* Value
Patients with CNS response	20 (76.9)	11.3	0.58 (0.31-1.10)	.087
Patients without CNS response	19 (82.6)	5.6		

*PFS for CNS and systemic disease.

Awada. SABCS 2019. Abstr P2-20-01. Reproduced with permission.

Slide credit: clinicaloptions.com

Neratinib in HER2+ MBC: OS by CNS Objective Response (Combined Trials)



	Events, n (%)	Median OS, Mos	HR (95% CI)	Log-Rank *P* Value
Patients with CNS response	21 (72.4)	27.1	0.43 (0.24-0.76)	.003
Patients without CNS response	36 (85.7)	11.5		

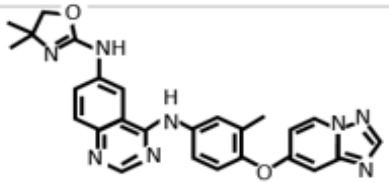
Awada. SABCS 2019. Abstr P2-20-01. Reproduced with permission.

Slide credit: clinicaloptions.com

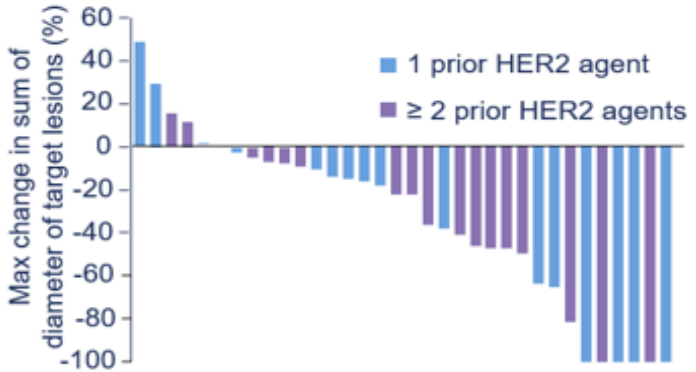
Tucatinib: HER2-Selective TKI

- Less EGFR-associated toxicity than other HER2-targeted TKIs
- CNS penetration
- Well tolerated and active in combinations (eg, with T-DM1, capecitabine, or trastuzumab)

Agent	Cellular Selectivity, IC_{50} (nM)	
	HER2	EGFR
Tucatinib	8	4000
Neratinib	7	8
Lapatinib	49	31

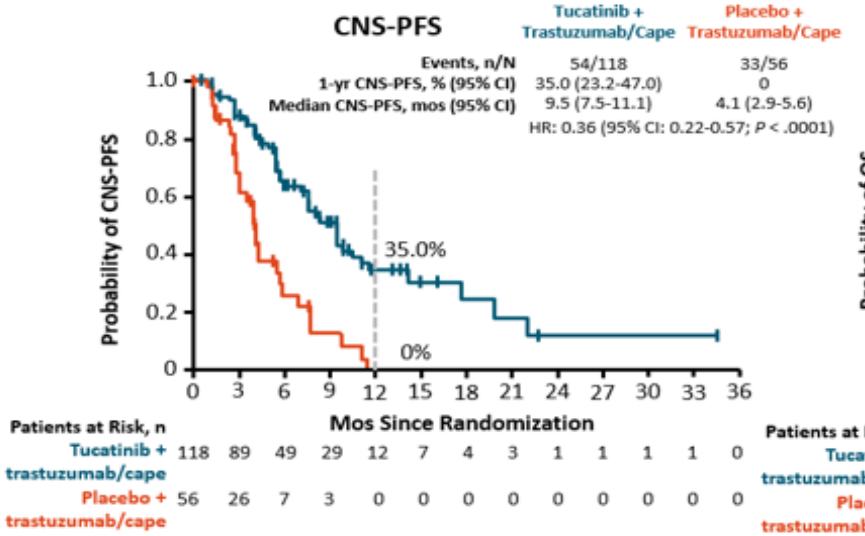


Phase Ib: Tucatinib + T-DM1 in HER2+ MBC
Overall Response in Patients with Measurable Disease

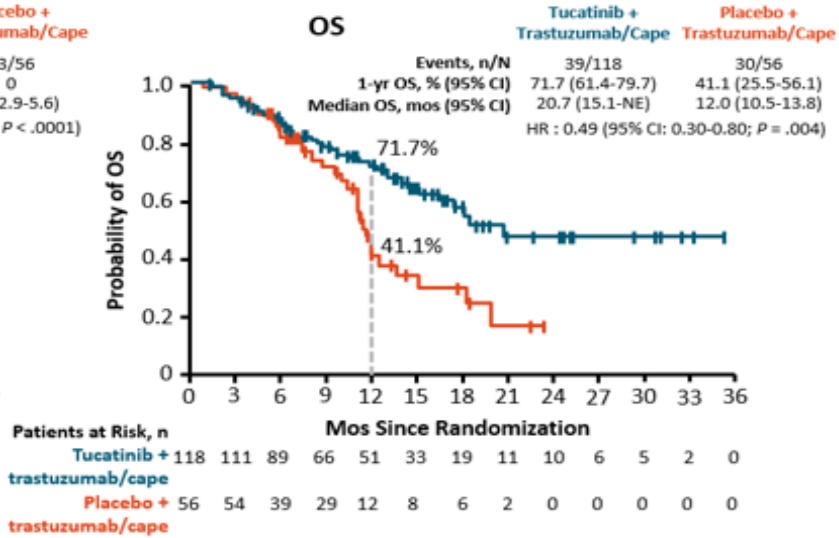


CNS = central nervous system; MBC = metastatic breast cancer; T-DM1 = trastuzumab emtansine; TKI = tyrosine kinase inhibitor.
Borges. ASCO 2016. Abstr 513. Borges. JAMA Oncol. 2018;4:1214-1220.

HER2CLIMB Intracranial Activity: CNS-PFS and OS in Patients With Active Brain Metastases



64% reduction in risk of CNS progression or death

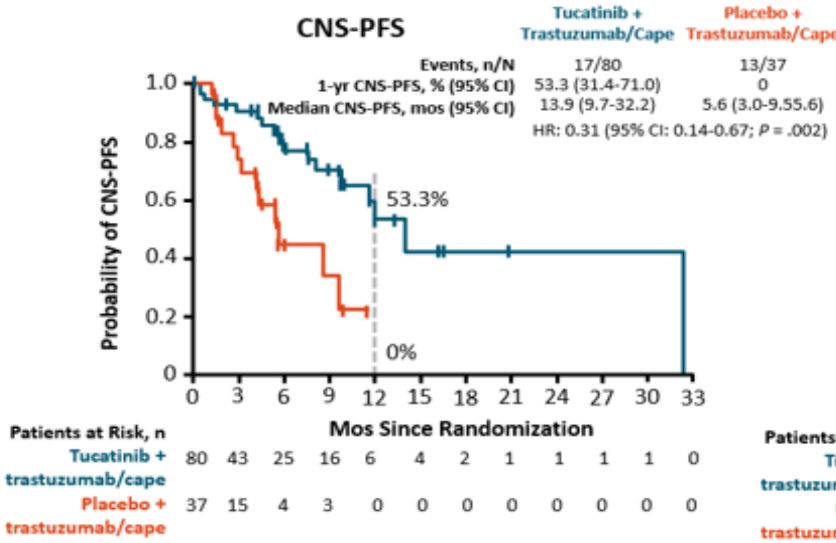


51% reduction in risk of death

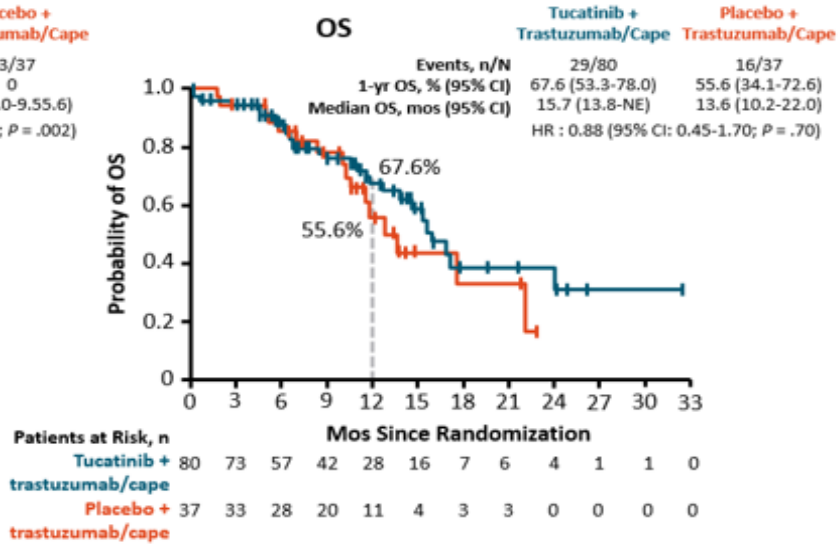
Lin. ASCO 2020. Abstr 1005. Lin. J Clin Oncol. 2020;38:2610.

Slide credit: clinicaloptions.com

HER2CLIMB Intracranial Activity: CNS-PFS and OS in Patients With Stable Brain Metastases



69% reduction in risk of CNS progression or death

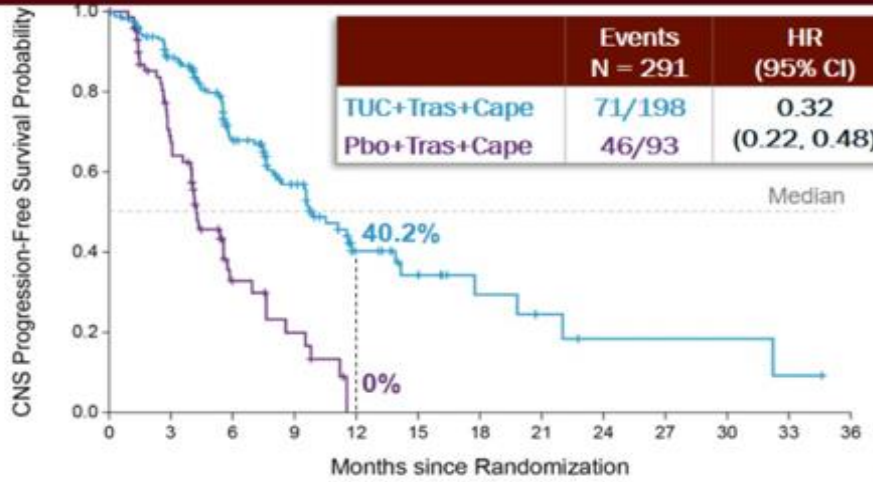


12% reduction in risk of death

Lin. ASCO 2020. Abstr 1005. Lin. J Clin Oncol. 2020;38:2610.

Slide credit: clinicaloptions.com

CNS-PFS Benefit in Patients With Brain Metastases



	Events N = 291	HR (95% CI)	*P* Value
TUC+Tras+Cape	71/198	0.32 (0.22, 0.48)	< .00001
Pbo+Tras+Cape	46/93		

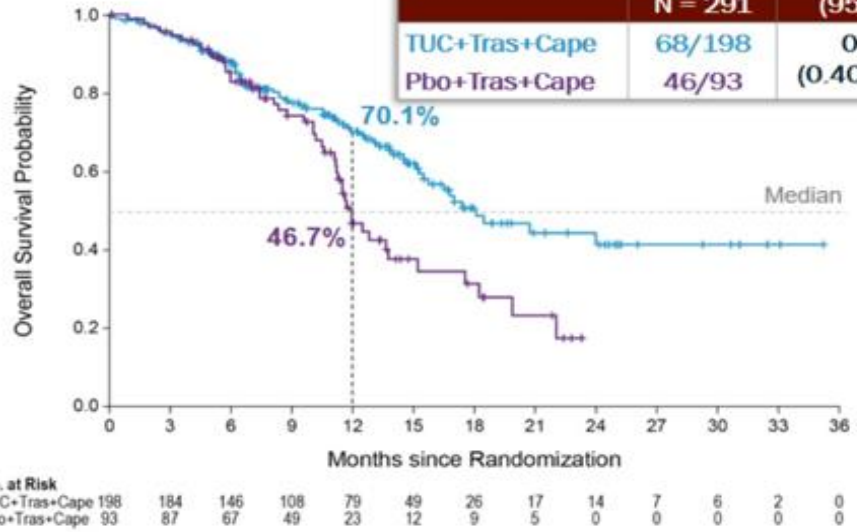
Risk of CNS progression or death was reduced by 68% in patients with brain metastases

One-year CNS-PFS (95% CI):	
TUC+Tras+Cape 40.2% (29.5, 50.6)	Pbo+Tras+Cape 0%
Median CNS-PFS (95% CI):	
9.9 months (8.0, 13.9)	4.2 months (3.6, 5.7)

Stable BrMets:	13.9 mos	5.6 mos
Active BrMets:	9.5 mos	4.1 mos

CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment.
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.
PFS, progression-free survival.
Lin N, et al. ASCO® 2020. Abstract 1005

OS Benefit in Patients With Brain Metastases



	Events N = 291	HR (95% CI)	*P* Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	.005
Pbo+Tras+Cape	46/93		

Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape 70.1% (62.1, 76.7)	Pbo+Tras+Cape 46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

Stable BrMets:	15.7 mos	13.6 mos
Active BrMets:	20.7 mos	11.6 mos

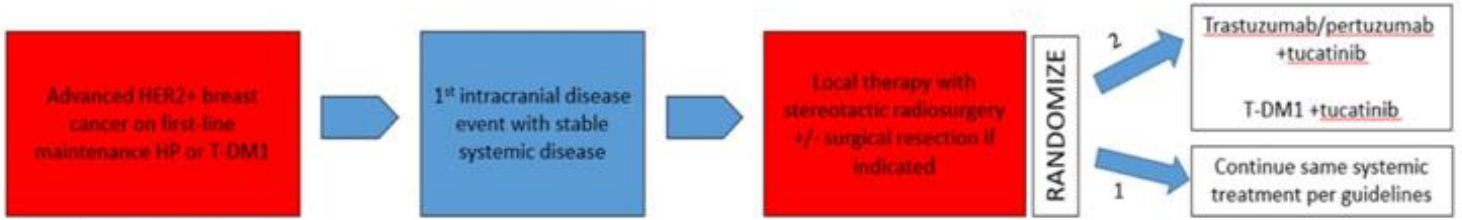
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

OS, overall survival.

Lin N, et al. ASCO® 2020. Abstract 1005

BRIDGET Study: Tucatinib as Secondary Prevention for HER2-Positive Breast Cancer Brain Metastases

Randomized phase 2, multicenter, clinical trial of tucatinib added to maintenance HP or T-DM1 in pts with CNS metastases as first site of progression in metastatic HER2+ advanced breast cancer with stable systemic disease



ER+/HER2+ disease allowed, endocrine therapy can continue

Stratify: HP or T-DM1 treatment, >/=2 brain metastases

PI: Dr Sarah Sammons (Duke Cancer Institute)
HCRN coordinating center
Anticipating opening Q4 2021

Primary objective: Intracranial PFS (RANO-BM)
Secondary objectives: PFS, OS, CBR, PROs, safety, time to next line therapy

CBR, clinical benefit rate; PRO, patient-reported outcome; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases..
Hamilton E, et al. Ann Oncol. 2021;32(suppl 2): Abstract 128TiP.

HER2-Positive Leptomeningeal Disease

TBCRC049: Tucatinib + Trastuzumab/Capecitabine in HER2+ MBC With Leptomeningeal Metastases

- Investigator-initiated, nonrandomized, open-label, phase II trial

Adults with HER2+ MBC with newly diagnosed, untreated leptomeningeal metastases, KPS >50 (N = 17)

→

36 months

Tucatinib 300 mg PO BID, Days 1- 21
Trastuzumab
6 mg/kg IV, every 21 days*
Capecitabine
1000 mg/mg2 PO BID, Days 1-14

*Loading dose of 8 mg/kg on cycle 1, Day 1, if maintenance was not given within the previous 30 days.

Assessments:
- Blood and CSF at BL and each cycle
- Neuroaxis MRI at screening and very 6 wk
- Neurologic exam/NANO scoring every cycle
- Extracranial CT/PET-CT every 4 wk
- Evaluation per RECIST at screening and every 4 wk
- QoL
- Symptom burden

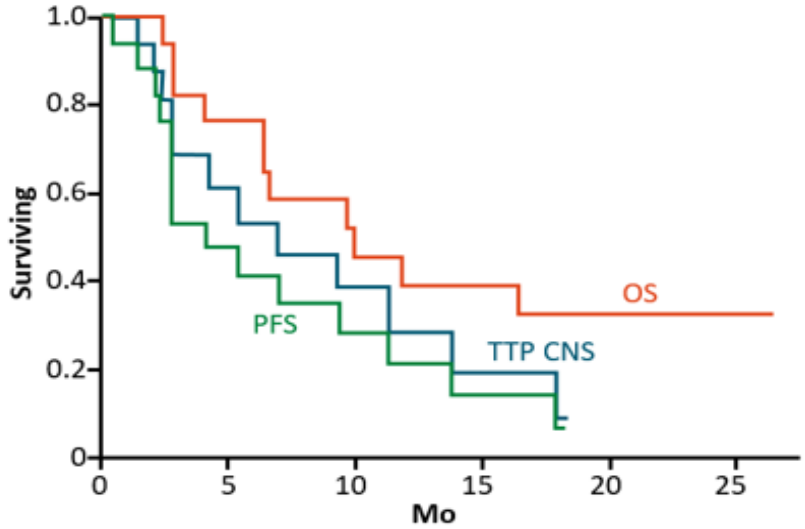
→ Continue until PD, AE, or other treatment per SoC

- Primary endpoint: OS
- Key secondary endpoints: PFS, CBR, OR in CNS and extra-CNS disease, safety
- Biospecimen analysis: PK and non-PK studies; semiquantitative cytology, protein, glucose from CSF
- Terminated early due to poor accrual post tucatinib FDA approval

Murthy. SABCS 2021. Abstr PD4.02. NCT03501979.

Slide credit: clinicaloptions.com

TBCRC049: Tucatinib + Trastuzumab/Capecitabine Survival and Disease Progression



Data cutoff: July 20, 2021

Survival and Disease Progression	
Patients alive at data cutoff, n/N (%)	6/17 (35)
Median follow-up, mo (range)	18 (9.0-26.7)
Median no. of treatment cycles, n (range)	5 (2-7)
Median time to CNS progression, mo (95% CI)	6.9 (2.3-13.8)
Median OS, mo (95% CI)	10 (4.1-NR)

Murthy. SABCS 2021. Abstr PD4.02. Reproduced with permission.

TBCRC049: Investigators' Conclusions

- Median OS was 10 mo with tucatinib + trastuzumab/capecitabine in patients with HER2-positive MBC and leptomeningeal metastases compared with 4-5 mo in historical controls, representing a clinically meaningful OS benefit[1-3]
- TBCR049 provides the first prospective evidence of clinical benefit for HER2-positive leptomeningeal disease
- Safety profile was consistent for previous studies with tucatinib in combination with trastuzumab and capecitabine[4,5]
- Tucatinib and its primary metabolite, ONT-9993, were detected in the plasma and CSF[6]
- Ongoing studies are needed to evaluate oral drugs that penetrate the CNS in this patient population

1. Murthy. SABCS 2021. Abstr PD4.02. 2. Morikawa. Clin Breast Cancer. 2017;17:23. 3. Carausu. ESMO Open. 2021;6:100150
4. Murthy. NEJM. 2020;382:597. 5. Murthy. Lancet Oncol. 2018;19:880. 6. Stringer-Reasor. ASCO 2021. Abstr 1044.

T-DM1 Activity in Breast Cancer With CNS Metastases

- Single case report, followed by:
  - 10-patient case series[1]
    - **ORR: 30%**
    - 3 PR, 2 SD > 6 mos
    - Median intracranial PFS: 5 mos
  - 39-patient case series[2]
    - **ORR: 44%**
    - 17/39 PR
    - Median PFS: 6.1 mos
  - 87-patient case series (response to T-DM1 in brain mets available for 53 patients)[3]
    - **ORR: 24.5%**
    - 2 CR, 11 PR
    - Median PFS: 7 mos

1. Bartsch. Clin Exp Metastasis. 2015;32:729. 2. Jacot. Breast Cancer Res Treat. 2016;157:307. 3. Fabi. Breast. 2018;41:137.

Slide credit: clinicaloptions.com

KAMILLA: Phase 3b Study of TDM1 in Patients With HER2+ Breast Cancer Brain Metastases

N = 398 (n = 126 with measureable) brain mets of 2002 enrolled; all received T-DM1.

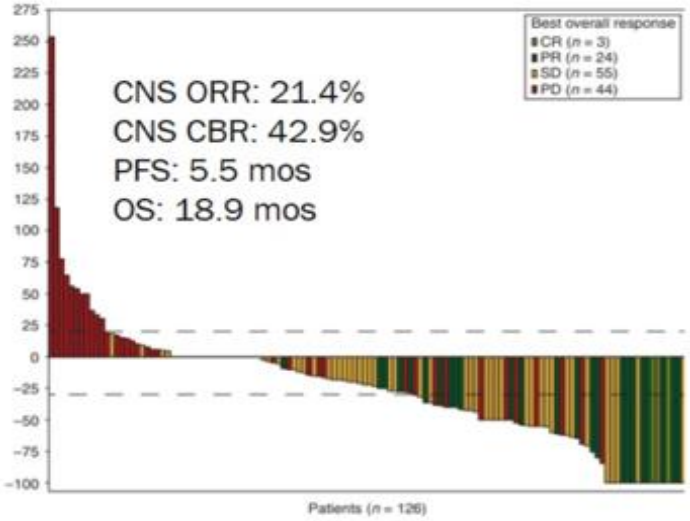


Table 1. Demographics and disease characteristics at baseline

	BM at baseline (*n* = 398)	No BM at baseline (*n* = 1604)
Prior lines of treatment of metastatic disease, *n* (%)		
None	9 (2.3)	18 (1.1)
1L	93 (23.4)	474 (29.6)
2L	91 (22.9)	355 (22.1)
3L	75 (18.8)	283 (17.6)
4L	49 (12.3)	152 (9.5)
≥5L	74 (18.6)	242 (15.1)
Prior brain radiotherapy (any setting), *n* (%)	226 (56.8)	NA[c]

Intracranial activity seen in heavily-pretreated patient Populatoin; combination strategies with T-DM1 + HER2 TKIs ongoing.

Montemurro F, et al. Ann Oncol; 2020;31:1350-1358.

DESTINY- Breast01: CNS Subgroup Analysis of Trastuzumab Deruxtecan (T-Dxd)

Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: a subgroup analysis of the DESTINY-Breast01 trial

Guy Jerusalem,[1] Yeon Hee Park,[2] Toshinari Yamashita,[3] Sara A. Hurvitz,[4] Shanu Modi,[5] Fabrice Andre,[6] Ian E. Krop,[7] Xavier Gonzalez,[8] Peter S. Hall,[9] Benoit You,[10] Cristina Saura,[11] Sung-Bae Kim,[12] Cynthia R. Osborne,[13,14] Yasuaki Sagara,[15] Eriko Tokunaga,[16] Yali Liu,[17] Jillian Cathcart,[17] Caleb Lee,[17] Christophe Perrin[18]

N = 24 of 168 enrolled patients; all received T-Dxd
~20% were CNS treatment-naïve.

Prior CNS treatment, %[b]

Radiotherapy only	54.2
Surgery only	4.2
Radiotherapy + surgery	20.8
None reported	20.8

Intent-to-treat analysis *	CNS subgroup (n=24)	All patients (N=184)
Confirmed ORR by ICR, n (%)	**14 (58.3)** (95% CI, 36.6-77.9)	**112 (60.9)** (95% CI, 53.4-68.0)
CR	1 (4.2)	11 (6.0)
PR	13 (54.2)	101 (54.9)
SD	8 (33.3)	67 (36.4)
PD	1 (4.2)	3 (1.6)
Not evaluable	1 (4.2)	2 (1.1)
Duration of response (CR or PR), median	16.9 months (95% CI, 5.7-16.9)	14.8 months (95% CI, 13.8-16.9)

*Of the 24 in the CNS subgroup, 17 had CNS lesions at baseline, of which n = 15 were evaluable of the 15, n = 13 had CNS radiation within 60 days of randomization.

PFS for CNS subgroup = 18.1 months vs 16.4 months for total cohort illustrating sustained response.

Jerusalem GH, et al. ASCO 2021. Poster 526

Newer Oral Pan-HER TKIs

PHENIX: Pyrotinib with Capecitabine in HER2+ MBC

- Capecitabine + pyrotinib or placebo; crossover on PD allowed
  - N=279; not all received trastuzumab for metastatic disease
- PFS improved with pyrotinib
  - 11.1 vs 4.1 months, HR 0.18 ($P < .001$)
- Improved ORR and CBR
- Primary toxicity
  - 31% ≥ grade 3 diarrhea, 98.4% all grade
  - Increased HFS, mucositis, count suppression

Phase II Trial: Poziotinib in Pretreated HER2+ MBC Patients

- 2 cohorts:
  - 24mg PO QD 14d on/7d off (n=30); 16mg PO QD x 21d (n=27)
  - 73% pts prior T, P, T-DM1
- Primary toxicity:
  - 30% ≥ grade 3 diarrhea, 85-90% all grade
  - 6% ≥ grade 3 mucositis, rash, mucosal inflammation, nausea

Efficacy Results (Evaluable Population)

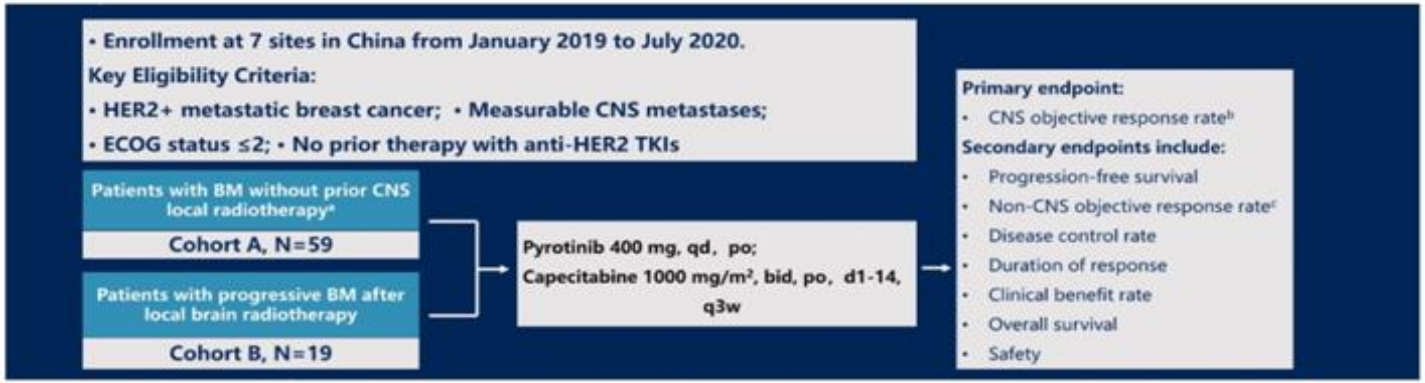
Efficacy outcome	Poziotinib 24 mg (N = 30)	Poziotinib 16 mg (N = 27)
ORR (CR+PR), % [95% CI]	23.3 [9.9, 42.3]	22.2 [8.6, 42.3]
PFS (mos), median (range)	3.0 (0.9, 10.8)	4.9 (0.1, 19.8)
DoR (mos), median (range)	5.6 (3.0, 9.6)	13.8 (4.4, 18.7)

Jiang. ASCO 2019. Abstr 1001. Brufsky. SABCS 2020. PD-1-07

Slide credit: clinicaloptions.com

PERMEATE Phase 2 Study: Pyrotinib and Capecitabine in HER2+ Breast Cancer Brain Metastases

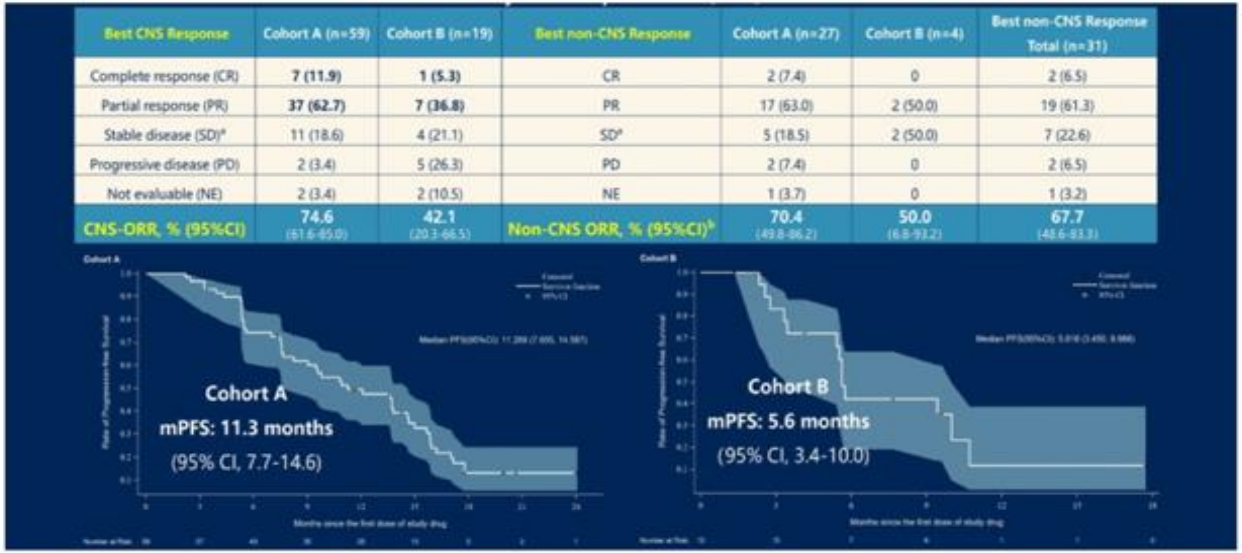
- More than 30% pts with HER2+ metastatic breast cancer will develop brain metastases
- Small-molecule TKIs have the potential to penetrate the blood brain barrier more effectively
- Previous phase 2 study have demonstrated the efficacy and safety of pyrotinib in combination with capecitabine in HER2+ metastatic breast cancer



Yan M, et al. ASCO® 2021. Abstract 1037..

PERMEATE Trial: ORR

Best CNS Response	Cohort A (n=59)	Cohort B (n=19)	Best non-CNS Response	Cohort A (n=27)	Cohort B (n=4)	Best non-CNS Response Total (n=31)
Complete response (CR)	7 (11.9)	1 (5.3)	CR	2 (7.4)	0	2 (6.5)
Partial response (PR)	37 (62.7)	7 (36.8)	PR	17 (63.0)	2 (50.0)	19 (61.3)
Stable disease (SD)[a]	11 (18.6)	4 (21.1)	SD[a]	5 (18.5)	2 (50.0)	7 (22.6)
Progressive disease (PD)	2 (3.4)	5 (26.3)	PD	2 (7.4)	0	2 (6.5)
Not evaluable (NE)	2 (3.4)	2 (10.5)	NE	1 (3.7)	0	1 (3.2)
CNS-ORR, % (95%CI)	74.6 (61.6-85.0)	42.1 (20.3-66.5)	Non-CNS ORR, % (95%CI)[b]	70.4 (49.8-86.2)	50.0 (6.8-93.2)	67.7 (48.6-83.3)



Cohort Characteristics:

Cohort A: no prior XRT
- -18% de novo
- -54% CNS only
- -35% first line

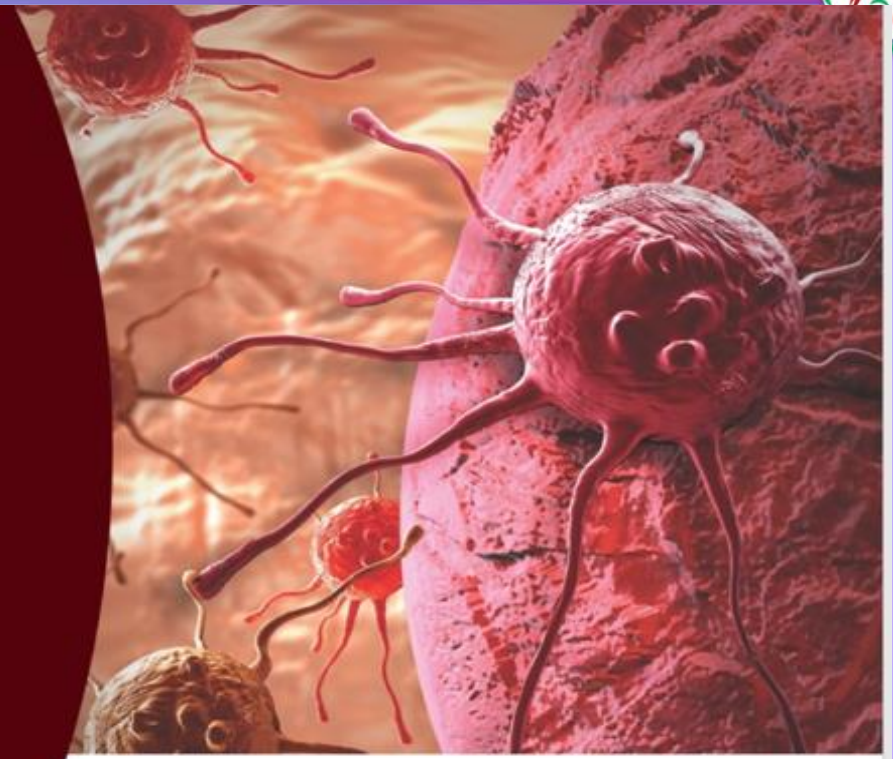
Cohort B: PD after XRT
- -15% de novo
- -79% CNS only
- -16% first line

CNS and non-CNS ORR Similar in both cohorts

XRT, radiotherapy.
Yan M, et al. ASCO® 2021. Abstract 1037..

A Medscape LIVE! CONFERENCE

Thank you for your attention.



Document (Times New Roman 24)

پایان