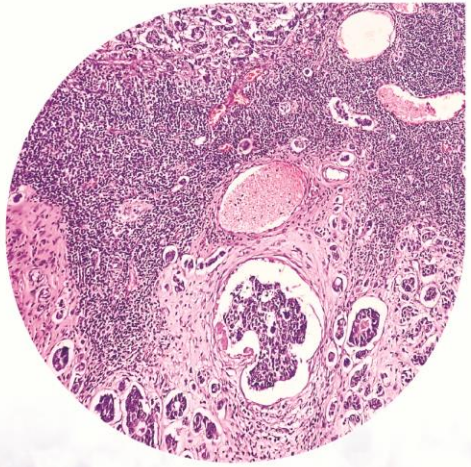
Global Breast Cancer Academy



Global Breast Cancer Academy Europe

14 November 2023

Sponsored by Seagen Inc.

APTITUDE HEALTH

Global Breast Cancer Academy

Welcome and meeting overview

Nadia Harbeck

APTITUDE HEALTH

Meet the Faculty

CHAIR

Nadia Harbeck, MD, PhD
Ludwig-Maximilian University of Munich,
Germany

FACULTY

Giuseppe Curigliano, MD, PhD
University of Milan, European Institute of Oncology,
Italy

Sara Tolaney, MD
Harvard Medical School,
Dana-Farber Cancer Institute,
Boston, MA, USA

Anna Berghoff, MD, PhD
Medical University of Vienna,
Austria

Virtual Plenary Sessions

Time (UTC +1)	Title	Speaker
16.30 – 16.40	Welcome and meeting overview; introduction to the voting system	Nadia Harbeck
Is Everything Well in the Evolving World of HER2+ mBC Treatment?		
16.40 – 17.00	Major advances in early lines of treatment	Nadia Harbeck
17.00 – 17.20	What are the treatment options after second line?	Giuseppe Curigliano
17.20 – 17.35	Overcoming resistance to HER2-directed therapies	Sara Tolaney
17.35 – 17.50	Modern treatment approaches for patients with brain metastases	Anna Berghoff
17.50 – 18.00	Break	
How Does HER2+ mBC Treatment Look Today and Tomorrow?		
18.00 – 18.30	Panel discussion on sequencing strategies: Use the best up front or keep it for later lines?	Nadia Harbeck and all faculty
18.30 – 18.50	The future of clinical studies: Lessons from real-world data and new entities; HER2-low BC	Giuseppe Curigliano
18.50 – 19.20	BC case-based panel discussion • Case 1 HER2+ mBC – what do we do after T-DXd? – Elie Rassy • Case 2 HER2+ mBC – what do we do with CNS progression? – Rodrigo Sánchez-Bayona • Discussion – panelists: all faculty	Nadia Harbeck and all faculty
19.20 – 19.30	Session close	Nadia Harbeck

Global Breast Cancer Academy

Introduction to the voting system

Nadia Harbeck

APTITUDE HEALTH

Question 1

Which languages do you speak? Select all that apply.

A. Arabic
B. English
C. French
D. German
E. Italian
F. Polish
G. Spanish
H. Other

Question 2

In the last 12 months, how many patients with HER2+ mBC have you treated?

A. ≤5
B. 6–15
C. 16–25
D. 26–35
E. ≥36

Question 3

Which of the following randomized clinical trials enrolled HER2+ mBC patients with active, untreated brain metastases? Select all that apply.

A. CLEOPATRA
B. DESTINY-Breast01
C. EMILIA
D. HER2CLIMB
E. MONALEESA-3
F. None of the above

Question 4

According to the current ESMO guidelines (v1.1 May 2023), which of the following treatment options are recommended in third line for HER2+ mBC patients with no, unknown, or stable brain metastases? Select all that apply.

A. Lapatinib plus capecitabine
B. Margetuximab plus chemotherapy
C. Neratinib plus capecitabine
D. Trastuzumab deruxtecan (T-DXd)
E. Trastuzumab emtansine (T-DM1)
F. Tucatinib plus capecitabine plus trastuzumab

Objectives

Understand major advances in early lines of treatment for HER2+ mBC

Learn about potential treatment options after second line treatment for HER2+ mBC

Understand changes in HER2 expression during treatment with HER2-targeted agents

Gain insights into the care of HER2+ mBC patients with CNS metastases

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Explore current and future sequencing strategies in HER2+ mBC

Objectives

- Understand major advances in early lines of treatment for HER2+ mBC
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- Understand changes in HER2 expression during treatment with HER2-targeted agents
- Gain insights into the care of HER2+ mBC patients with CNS metastases
- Engage in patient case-based panel discussions and comprehensively discuss available treatment options
- Explore current and future sequencing strategies in HER2+ mBC

Global Breast Cancer Academy

Major advances in early lines of treatment for HER2+ mBC

Nadia Harbeck

APTITUDE HEALTH

LMU KLINIKUM
Gemeinsam. Fürsorglich. Wegweisend.

Major advances in early lines of treatment

of HER2+ *metastatic* breast cancer

LMU Breast Center | 12/7/2023 | Nadia Harbeck, MD, PhD

Brustzentrum im Klinikum der Universität München

CCC MÜNCHEN COMPREHENSIVE CANCER CENTER LMU KLINIKUM

TUMORZENTRUM MÜNCHEN | TZM

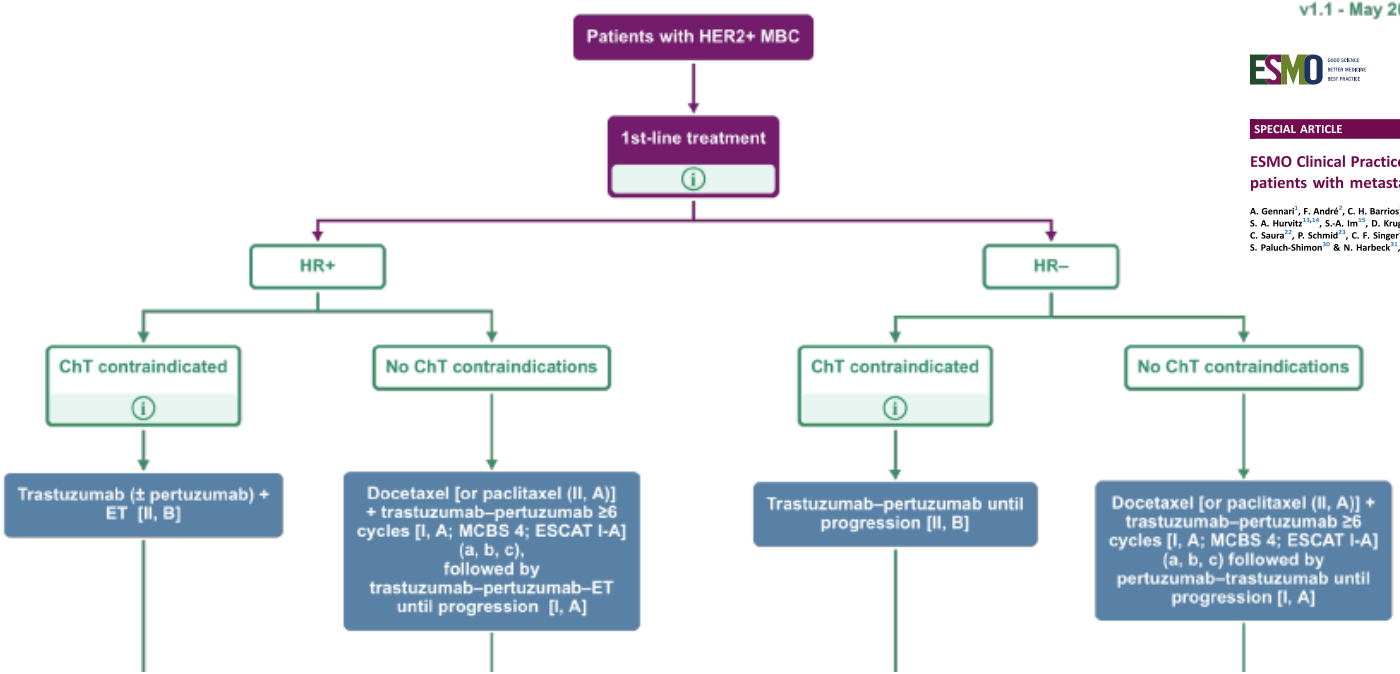
Disclosures

Potential conflicts of interest

- Honoraria for lectures and/or consulting: Amgen, AstraZeneca, Daiichi Sankyo, Gilead, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Sanofi, Seagen, Viatris, Zuellig Pharma
- Institution: Clinical phase II–IV trials
- Other: Co-director West German Study Group (WSG)

ESMO *metastatic* breast cancer guidelines

HER2+ first line



v1.1 - May 2023

ESMO

ANNALS OF ONCOLOGY

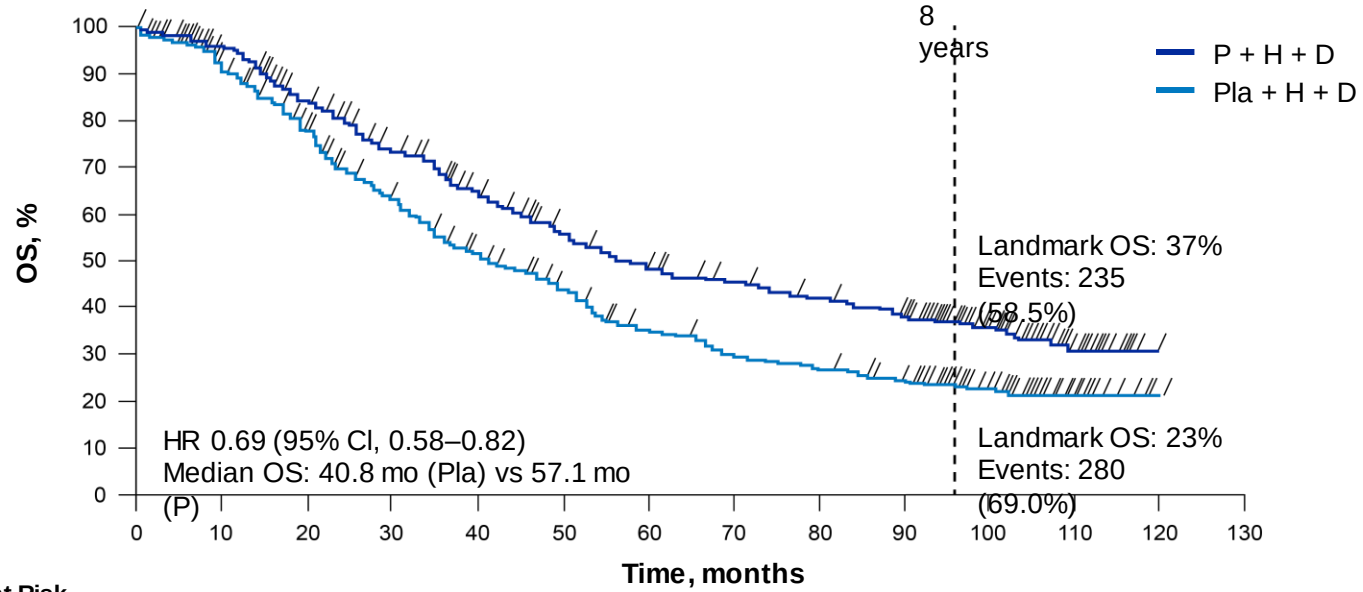
SPECIAL ARTICLE

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆

A. Gennari[1], F. André[2], C. H. Barrios[3], J. Cortés[4,5,6,7], E. de Azambuja[8], A. DeMichele[9], R. Dent[10], D. Fenlon[11], J. Gligorov[12], S. A. Hurvitz[13,14], S.-A. Im[15], D. Krug[16], W. G. Kunz[17], S. Loi[18], F. Penault-Llorca[19], J. Ricke[5,17], M. Robson[20], H. S. Rugo[21], C. Saura[22], P. Schmid[23], C. F. Singer[24], T. Spanic[25], S. M. Tolaney[26], N. C. Turner[27], G. Curigliano[28], S. Loibl[29], S. Paluch-Shimon[30] & N. Harbeck[31], on behalf of the ESMO Guidelines Committee*

Gennari A, et al. *Ann Oncol*. 2021;32:1475-1492; esmo.org.

CLEOPATRA:
End-of-study OS in the ITT population*



No. at Risk

P + H + D	40	37	31	26	22	18	16	15	13	12	71	20	0	0
Pla + H + D	2	1	8	9	8	8	5	0	7	0	44	11	1	0
	40	35	28	23	18	14	11	96	88	75				
	6	0	9	0	1	9	5							

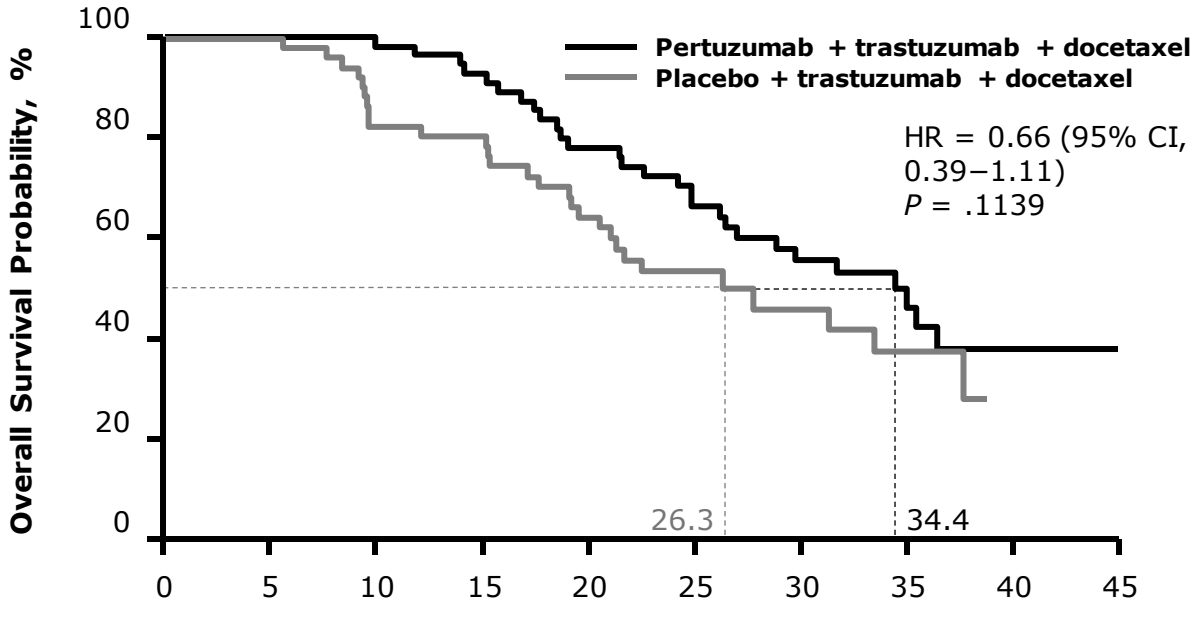
*Crossover patients were analyzed in the Pla arm. OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan-Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs. Subgroup analyses are unstratified.

D, docetaxel; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; P, pertuzumab; Pla, placebo.

Swain SM, et al. ASCO 2019. Abstract 1020.

CLEOPATRA:

Overall survival in patients with CNS metastases as first site of progression



n at risk										
Placebo arm	51	51	42	40	30	16	11	7	0	0
Pertuzumab arm	55	55	54	50	42	33	24	12	8	1

Swain SM, et al. *Ann Oncol*. 2014;25: 1116-1121.

Metastatic HER2+, HR+ breast cancer

PERUSE: Type of taxane

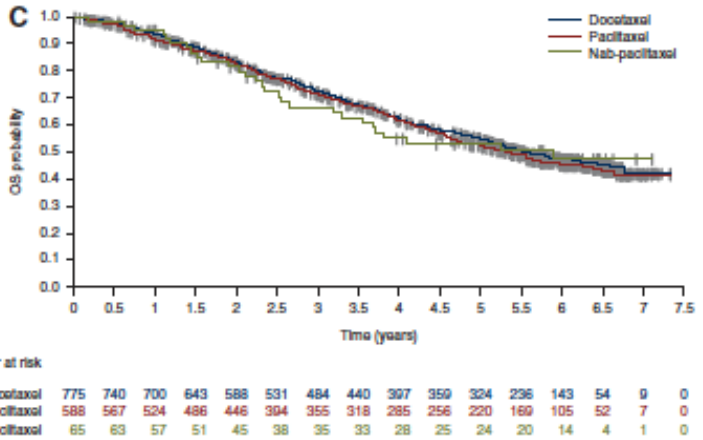
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

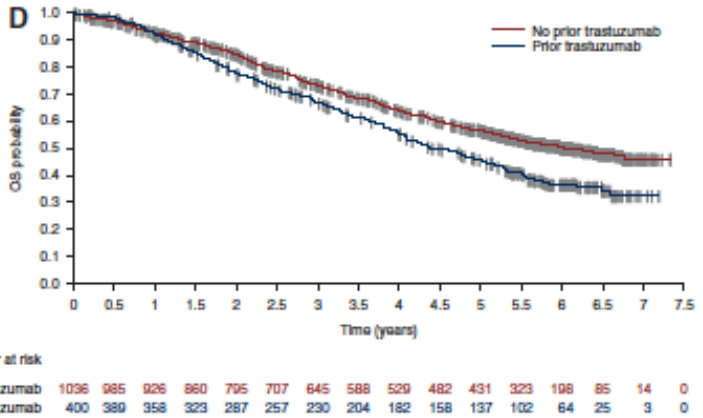
ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication

D. Miles[1*], E. Ciruelos[2,3], A. Schneeweiss[4], F. Puglisi[5,6], T. Peretz-Yablonski[7], M. Campone[8], I. Bondarenko[9], Z. Nowecki[10], H. Errihani[11], S. Paluch-Shimon[12†], A. Wardley[13,14‡], J.-L. Merot[15], P. Trask[16], Y. du Toit[17¶], C. Pena-Murillo[17], V. Revelant[18], D. Klingbiel[19] & T. Bachelot[20], on behalf of the PERUSE investigators[‡]

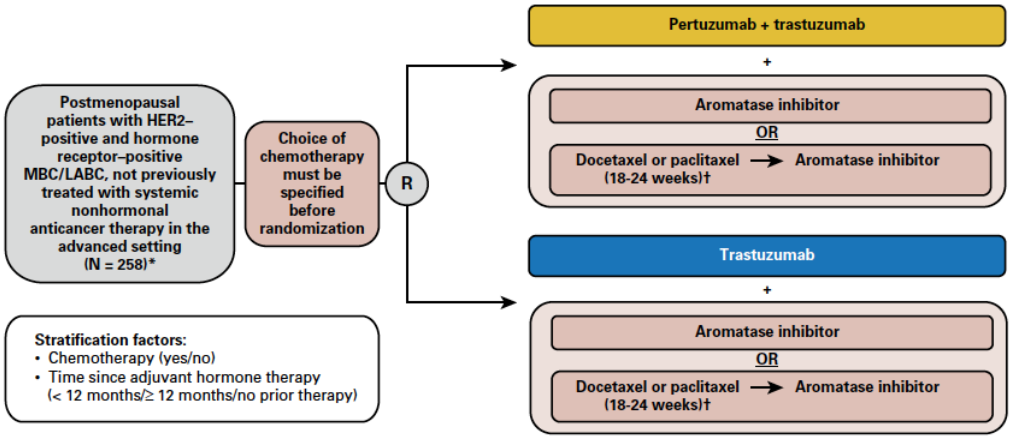




Miles D, et al. *Ann Oncol*. 2021;32:1245-1255.

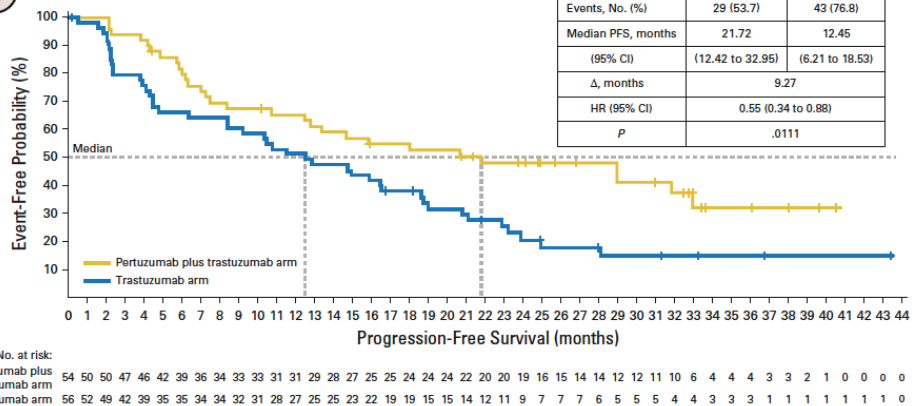
Metastatic HER2+, HR+ breast cancer

PERTAIN: Endocrine therapy plus dual blockade



No induction CT

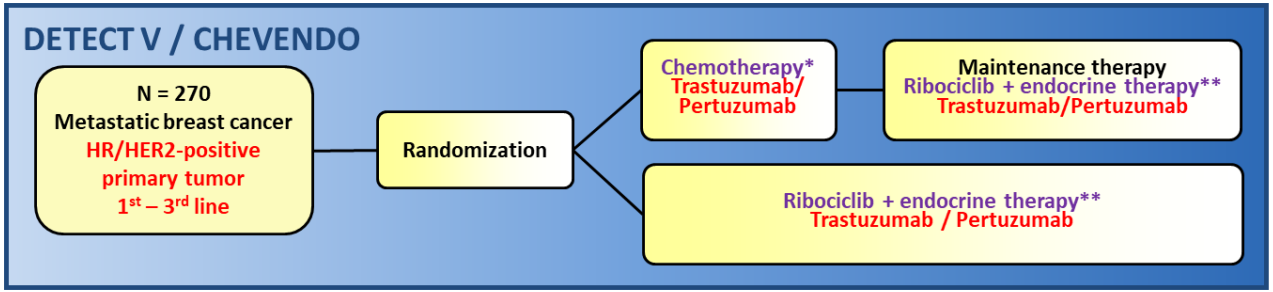
	Pertuzumab Plus Trastuzumab Arm (n = 54)	Trastuzumab Arm (n = 56)
Events, No. (%)	29 (53.7)	43 (76.8)
Median PFS, months	21.72	12.45
(95% CI)	(12.42 to 32.95)	(6.21 to 18.53)
Δ, months	9.27	
HR (95% CI)	0.55 (0.34 to 0.88)	
P	.0111	



Rimawi M, et al. *J Clin Oncol*. 2018;36:2826-2835.

Metastatic HER2+, HR+ breast cancer

DETECT V



* Capecitabine, Docetaxel, Paclitaxel, Vinorelbine, Eribulin, nab-Paclitaxel

** Fulvestrant, Exemestane, Letrozole, Anastrozole, GnRH-analogue

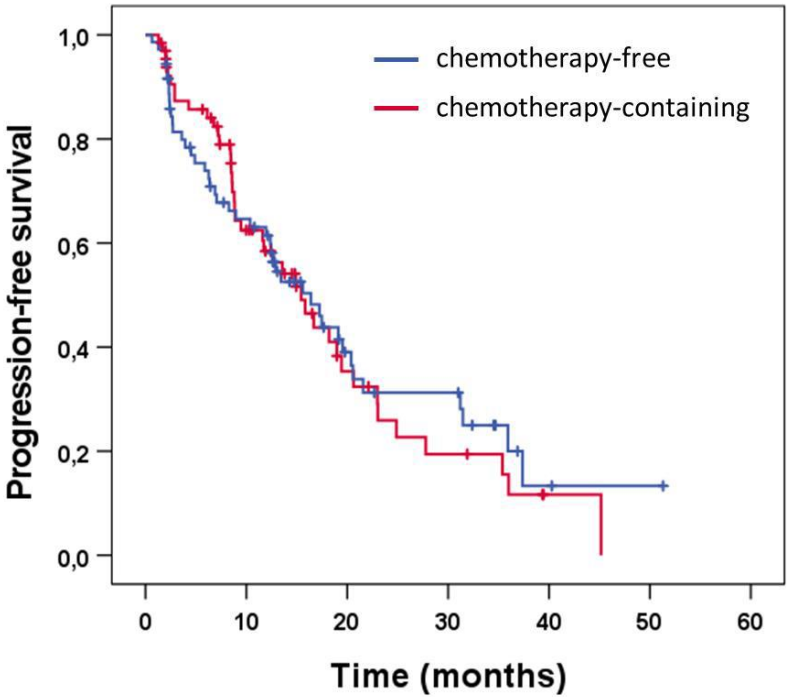
The results reported here are based on 162 patients for whom end of study was documented at the time of data cut off for this interim analysis (80 and 82 patients in the chemotherapy-free and chemotherapy-containing arm, respectively). The analyzed cohort comprised 121 patients randomized before and 41 patients randomized after the addition of the CDK 4/6 inhibitor ribociclib; 122 patients were in the 1st line setting.

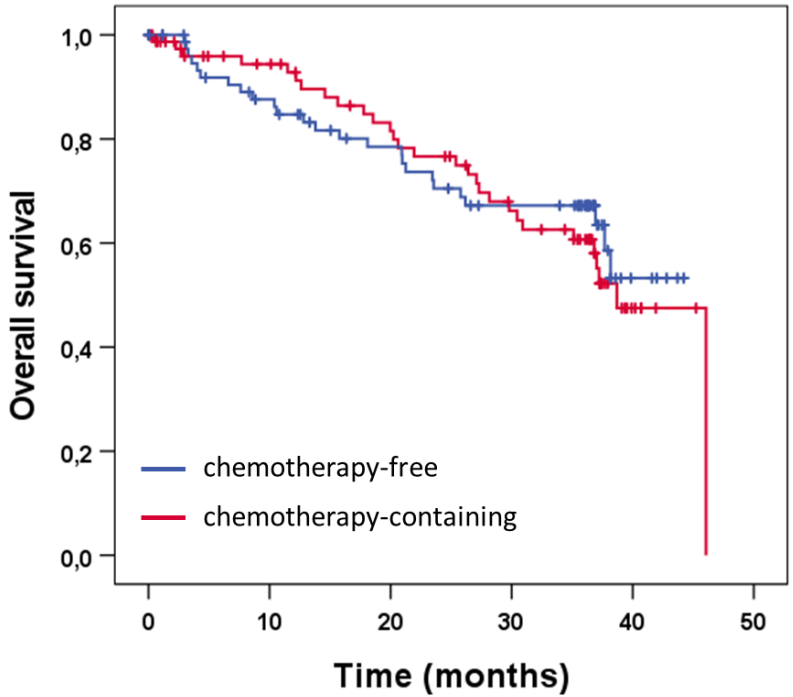
Chemotherapies administered together with dual HER2-targeted treatment were mainly capecitabine (34%), vinorelbine (26%), docetaxel (16%), and paclitaxel (17%). Endocrine combination partners in the chemotherapy-free arm were mainly letrozole (48%), fulvestrant (21%), and exemestane (13%).

Janni W, et al. SABCS 2022. Abstract PD18-07.

Metastatic HER2+, HR+ breast cancer

DETECT V

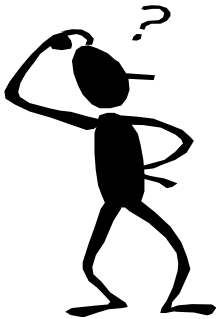




Janni W, et al. SABCS 2022. Abstract PD18-07.

Metastatic HER2+ breast cancer
Current standards

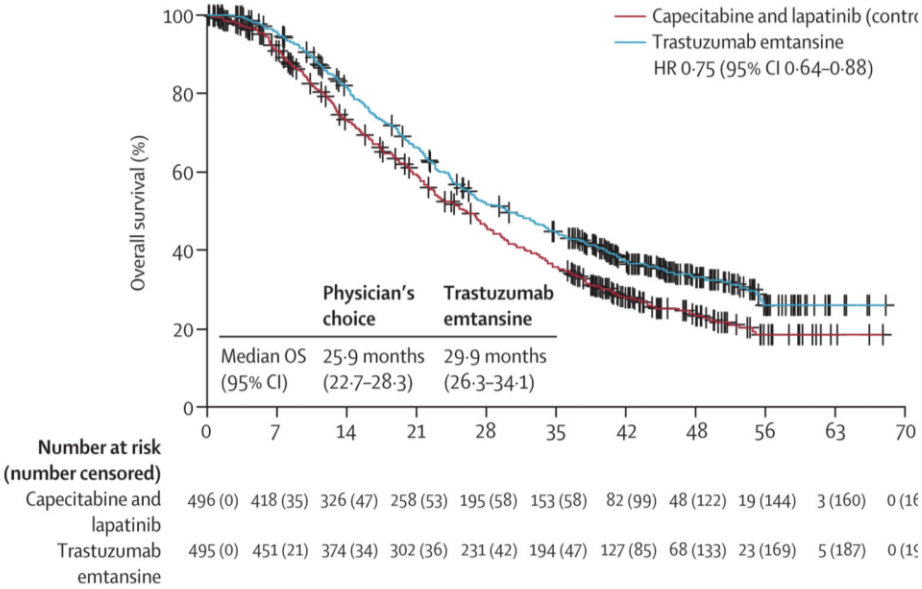
- Development of the current second-line therapy standard



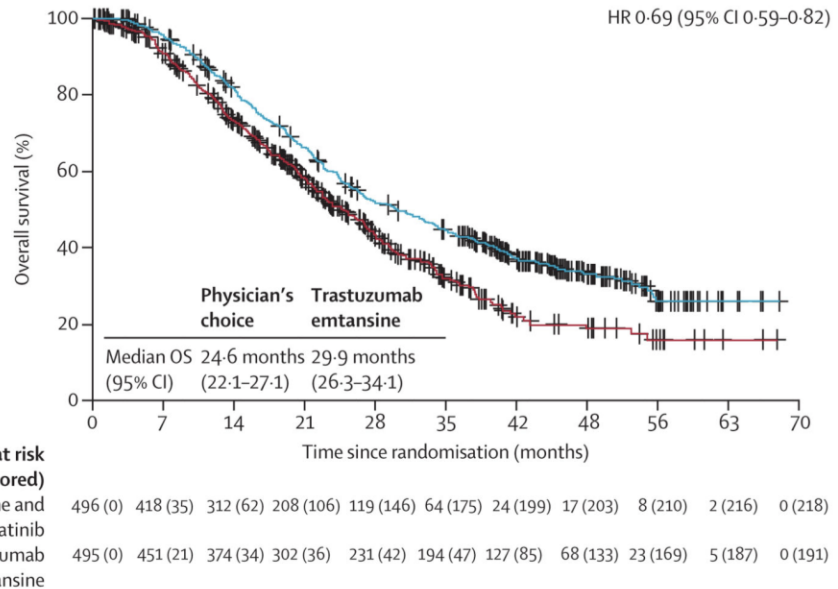
Metastatic HER2+ breast cancer

EMILIA: T-DM1 in second line – OS

ITT



Censored after crossover

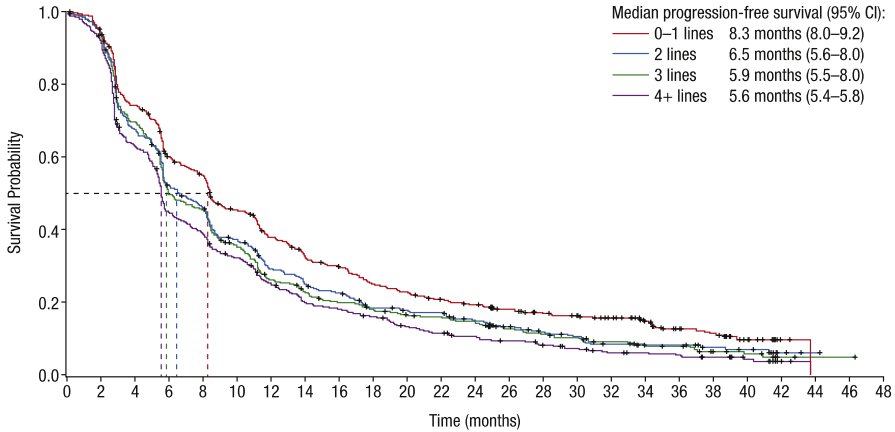


Diéras V, et al. *Lancet Oncol.* 2017;18:732-742.

Metastatic HER2+ breast cancer

T-DM1 efficacy according to line of therapy (KAMILLA)

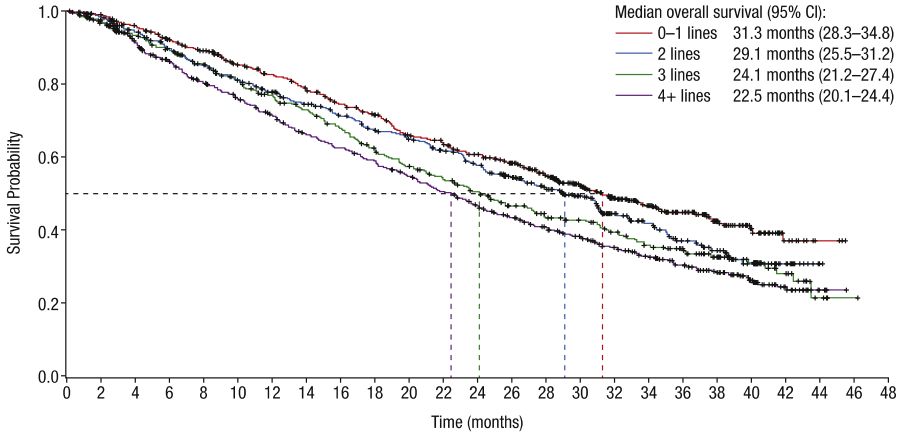
PFS



Number at risk:

0–1 lines	594	549	434	345	311	253	209	174	160	134	122	109	100	88	77	69	62	46	29	26	12	2	0	0	0
2 lines	446	407	287	219	192	153	118	101	91	71	65	64	52	42	35	31	22	17	17	12	10	3	1	0	0
3 lines	358	326	244	174	158	120	89	75	65	57	51	48	44	34	30	27	22	18	17	10	8	2	1	1	0
4+ lines	517	472	320	226	197	160	122	97	88	77	62	53	46	40	33	28	21	19	17	13	8	2	0	0	0

OS



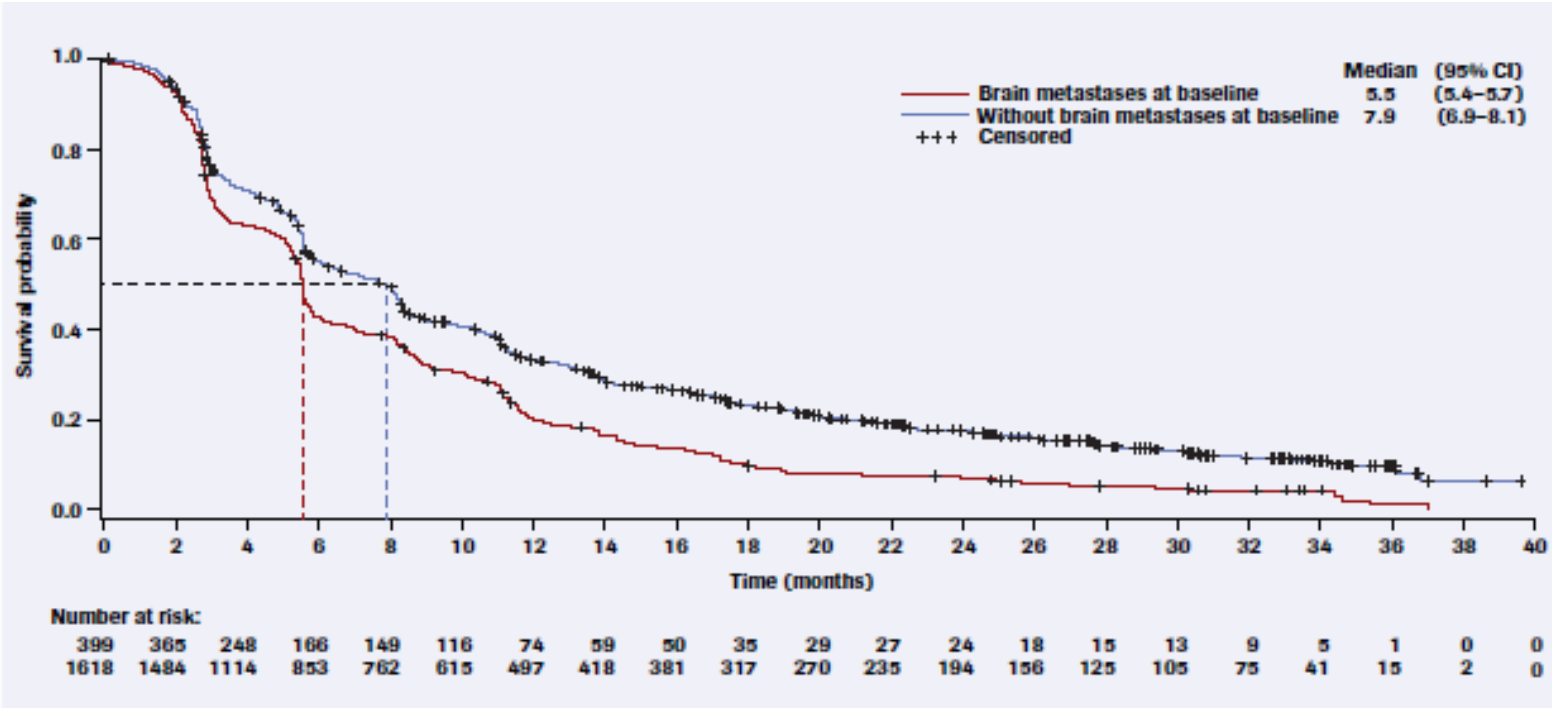
Number at risk:

0–1 lines	594	583	557	552	500	463	441	415	388	366	334	318	293	266	231	192	160	135	100	68	40	14	3	0	0
2 lines	446	435	397	371	347	326	304	284	265	247	236	218	200	179	152	126	92	75	58	45	27	15	1	0	0
3 lines	358	342	317	297	281	260	241	227	209	188	173	158	144	125	110	103	91	77	66	48	34	17	4	1	0
4+ lines	517	497	451	413	380	356	330	301	285	268	246	226	204	183	165	144	123	107	89	70	47	26	4	0	0

Montemurro F, et al. *Eur J Cancer*. 2019;109:92-102.

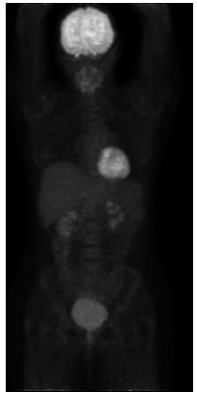
Metastatic HER2+ breast cancer

T-DM1 efficacy in patients with brain mets (KAMILLA)

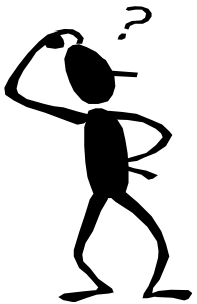


Montemurro F, et al. SABCS 2016. Abstract P1-12-10.

Breast cancer
Patient case



- ED 2012 Breast cancer right side, 35 years
  - cT2 (32 mm) cN1 cM1 (liver), premenopausal
  - HR+ (ER 90%, PR–) HER2 3+
- Begin with paclitaxel weekly + trastuzumab (pertuzumab not yet approved)
- PET-CT @3 months: PR liver mets w/o metabolism: GnRH + TAM, trastuzumab
- After 10 months: Surgery primary tumor (patient request); BCS (R1)
- After 11 months: SSM (implant): ypT3 (>5 cm), locoregional progression (LN)

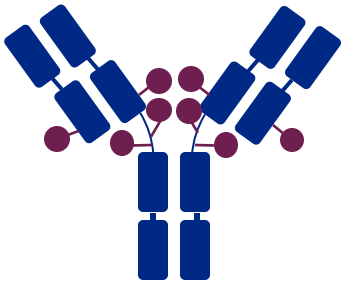


- **Multidisciplinary tumor board (MTB)**
  - Inclusion into KAMILLA trial (T-DM1 safety trial)
  - cCR for >10 years on T-DM1 monotherapy
  - Aug 2023: switch to trastuzumab maintanance

Fictional patient case; for didactic purposes only.

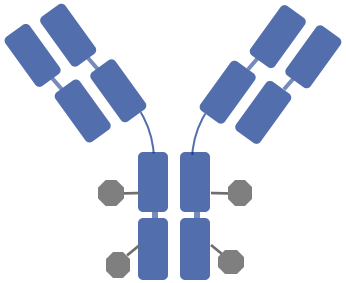
ADC characteristic differences between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



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

Trastuzumab emtansine (T-DM1)[5]

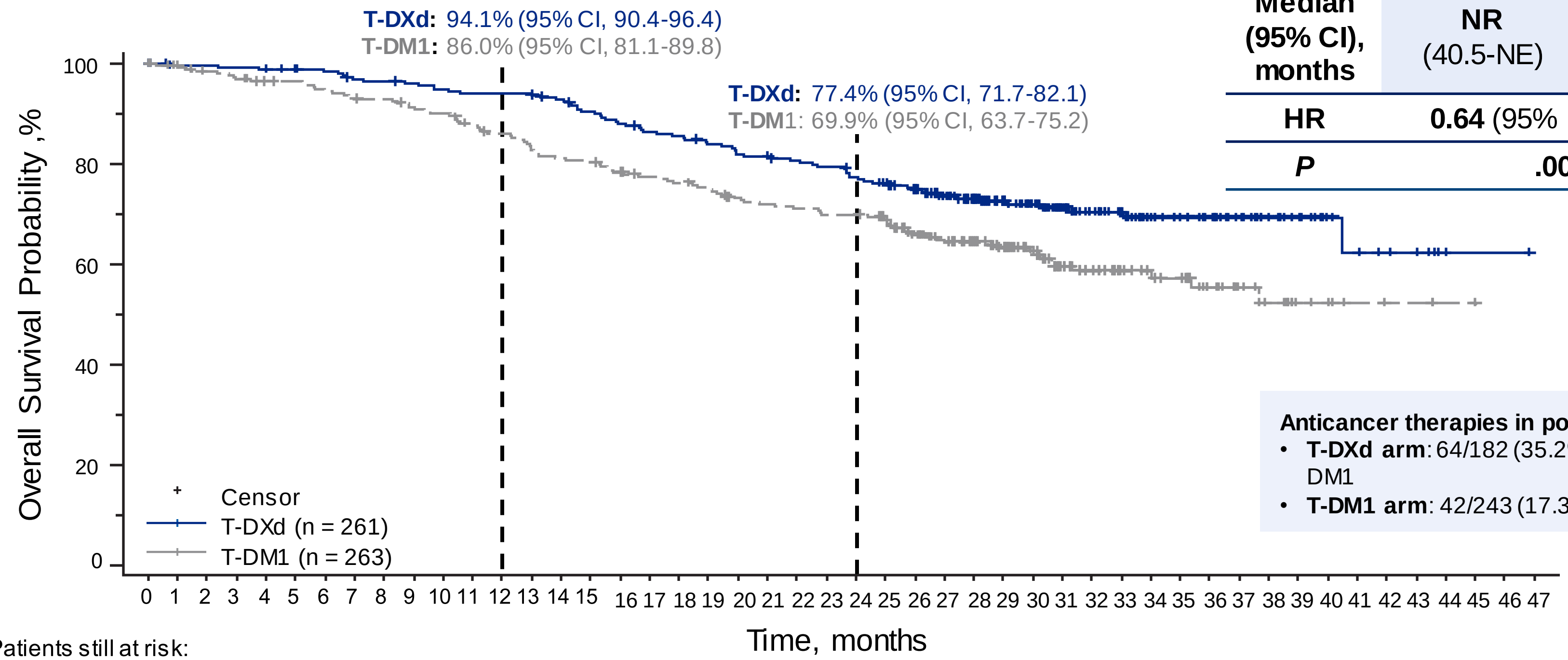


ADC, antibody-drug conjugate; MOA, mechanism of action.
[a]The clinical relevance of these features is under investigation.,

1. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-185; 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-5108; 3. Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142; 4. Ogitani Y, et al. *Cancer Sci.* 2016;107:1039-1046; 5. LoRusso PM, et al. *Clin Cancer Res.* 2011;17:6437-6447.

Key secondary endpoint: Overall survival

	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**.0037**[a,b]	



Anticancer therapies in posttrial setting

- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Patients still at risk:

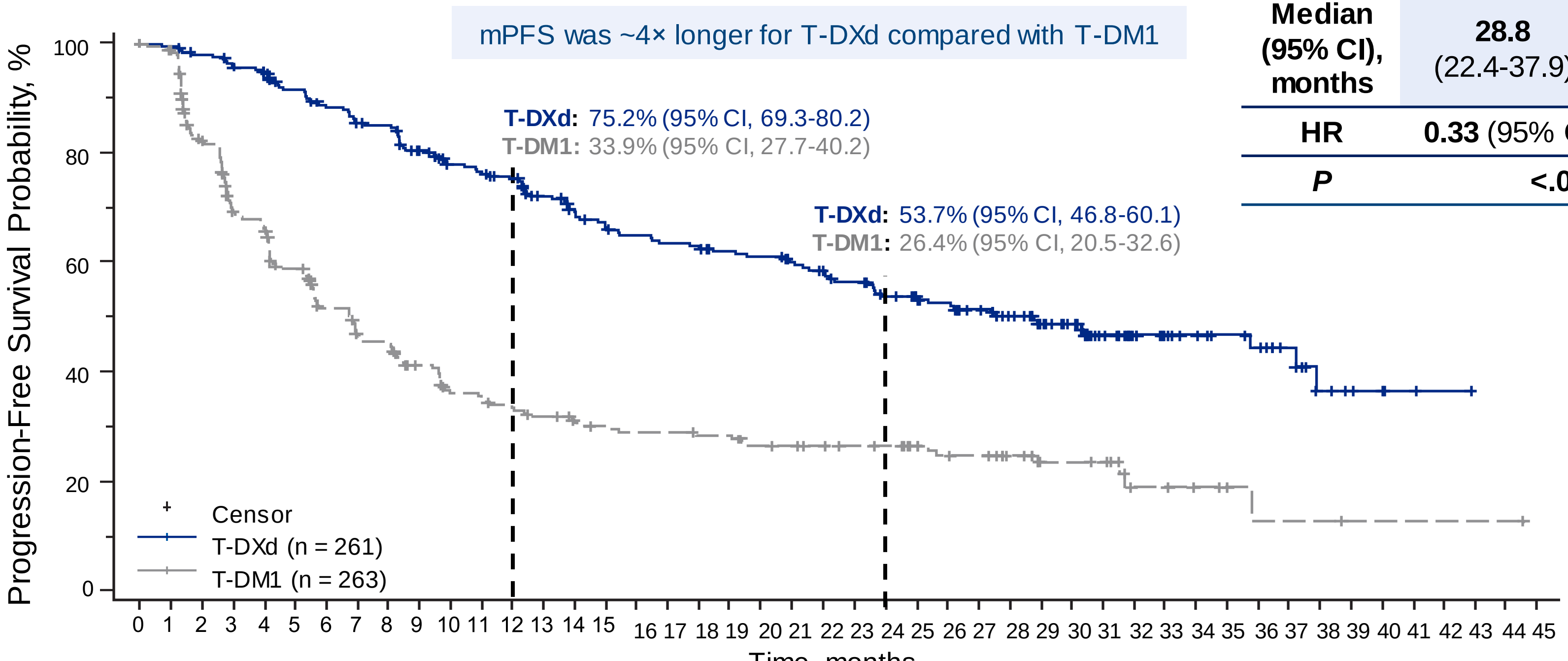
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164

	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
T-DXd	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = .013) and was statistically significant. [b]Two-sided from stratified log-rank test.

Updated primary endpoint: PFS by BICR

	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	**0.33** (95% CI, 0.26-0.43)	
P	**<.000001**[a,b]	

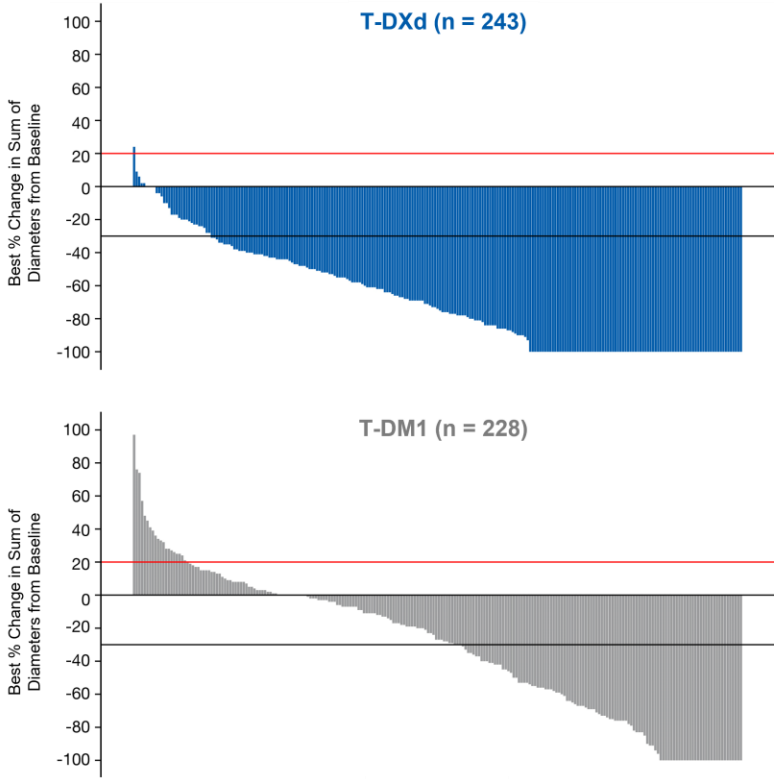


Patients still at Risk:

T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

Confirmed ORR and other efficacy endpoints



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	<.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	<.0001	
mDOR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

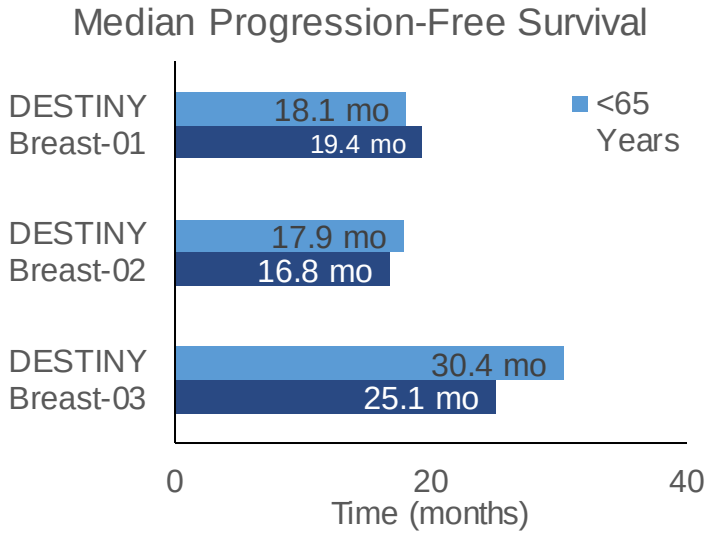
BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDOR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Red line at 20% indicates progressive disease; black line at −30% indicates partial response.
[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

PFS2 and post-study anticancer treatment

	T-DXd n = 261	T-DM1 n = 263
Median PFS2 by investigator,[a] mo (95% CI)	40.5 (40.5-NE)	25.7 (18.5-34.0)
	HR, 0.47 (95% CI, 0.35-0.62)	
Patients who discontinued treatment, n (%)	182 (70.8)	243 (93.1)
Any post-study anticancer treatment,[b] n (%)	130 (71.4)	191 (78.6)
Trastuzumab	43 (23.6)	90 (37.0)
T-DXd	**3 (1.6)**	**42 (17.3)**
T-DM1	**64 (35.2)**	**24 (9.9)**
Pertuzumab	15 (8.2)	28 (11.5)
Taxane	13 (7.1)	32 (13.2)
Taxane and trastuzumab	7 (3.8)	28 (11.5)
Other anti-HER2[c]	39 (21.4)	88 (36.2)
Anti-HER2 TKI	38 (20.9)	87 (35.8)
Other anti-HER2 antibody or ADC	1 (0.5)	4 (1.6)
Hormone therapy	25 (13.7)	30 (12.3)
Other systemic therapy	75 (41.2)	147 (60.5)

ADC, antibody-drug conjugate; HR, hazard ratio; PFS2, progression-free survival on the next line of therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.
[a]From the time of randomization to second progression. [b]Patients may have received more than 1 type of post-study anticancer treatment. Denominator is the number of patients who discontinued study treatment. [c]Includes anti-HER2 TKI and other anti-HER2 antibody or ADC.

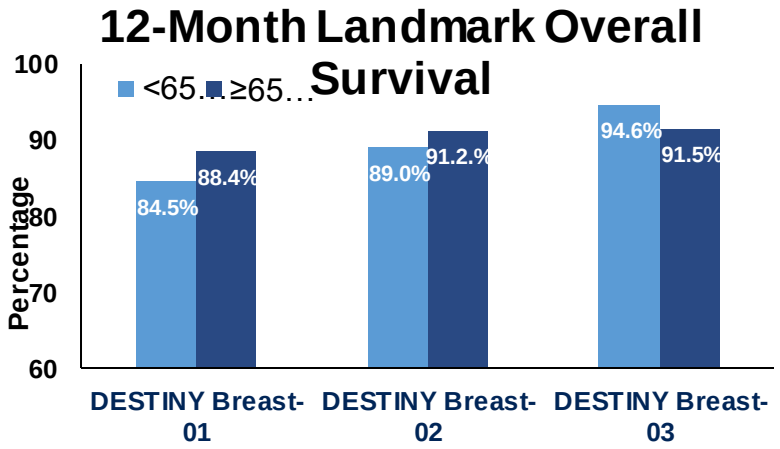
Descriptive efficacy according to age for T-DXd[a]



- Efficacy in patients aged <65 and ≥65 years treated with T-DXd was generally similar; however, no formal comparison was made

Median Overall Survival

	DESTINY-Breast01		DESTINY-Breast02		DESTINY-Breast03	
	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
mOS, months (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)



[a]Efficacy data were not pooled due to bias induced by the heterogeneity of the study population. Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022. mOS, median overall survival; NE, not estimable; NR, not reached; T-DXd, trastuzumab deruxtecan.

Overall safety summary

Type of Adverse Event, n (%)	T-DXd n = 257	T-DM1 n = 261
Any-grade TEAE	256 (99.6)	249 (95.4)
Drug related	252 (98.1)	228 (87.4)
Grade ≥3 TEAEs	145 (56.4)	135 (51.7)
Drug related	121 (47.1)	110 (42.1)
Serious TEAEs	65 (25.3)	58 (22.2)
Drug related	33 (12.8)	20 (7.7)
TEAEs associated with drug discontinuation	55 (21.4)	24 (9.2)
Drug related	51 (19.8)	17 (6.5)
TEAEs associated with dose reduction	66 (25.7)	38 (14.6)
Drug related	65 (25.3)	38 (14.6)
TEAEs associated with drug interruption	136 (52.9)	76 (29.1)
Drug related	108 (42.0)	45 (17.2)
TEAEs associated with an outcome of death	6 (2.3)	6 (2.3)
Drug related	0	0

- Median treatment duration
  - **T-DXd:** 18.2 mo (range, 0.7-44.0)
  - **T-DM1:** 6.9 mo (range, 0.7-39.3)
- Rates of grade ≥3 TEAEs were similar between the T-DXd (56.4%) and T-DM1 (51.7%) treatment arms
- The most common drug-related TEAEs associated with discontinuation were
  - **T-DXd:** pneumonitis (5.8%), ILD (5.1%), and pneumonia (1.9%)
  - **T-DM1:** platelet count decreased (1.5%), pneumonitis (1.1%), and thrombocytopenia (1.1%)

Relationship to study drug was determined by the treating investigator.
ILD, interstitial lung disease; mo, month; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

Most common TEAEs 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				
Anemia	95 (37.0)	24 (9.3)	51 (19.5)	17 (6.5)
Platelet count decreased	64 (24.9)	20 (7.8)	114 (43.7)	52 (19.9)
White blood cell count decreased	60 (23.3)	16 (6.2)	16 (6.1)	2 (0.8)
Gastrointestinal disorders				
Nausea	198 (77.0)	18 (7.0)	79 (30.3)	1 (0.4)
Vomiting	133 (51.8)	4 (1.6)	28 (10.7)	2 (0.8)
Constipation	96 (37.4)	0	51 (19.5)	0
Diarrhea	83 (32.3)	3 (1.2)	21 (8.0)	2 (0.8)
General disorders				
Fatigue	79 (30.7)	15 (5.8)	53 (20.3)	2 (0.8)
Headache	61 (23.7)	1 (0.4)	40 (15.3)	0
Investigations				
Neutrophil count decreased	79 (30.7)	41 (16.0)	30 (11.5)	8 (3.1)
Aspartate aminotransferase increased	72 (28.0)	2 (0.8)	108 (41.4)	14 (5.4)
Alanine aminotransferase increased	59 (23.0)	4 (1.6)	83 (31.8)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	78 (30.4)	4 (1.6)	46 (17.6)	1 (0.4)
Weight decreased	58 (22.6)	6 (2.3)	23 (8.8)	2 (0.8)
Skin and subcutaneous tissue disorders				
Alopecia	102 (39.7)	1 (0.4)[a]	9 (3.4)	0

Adverse events were managed according to the protocol. [a]Cases of alopecia reported during the study were graded on the basis of the clinical judgment of the investigator. One case of alopecia was categorized as grade 3 by the investigator despite grade 3 alopecia not being recognized by the NCI Common Terminology Criteria. The event outcome was reported as recovered by the investigator.
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

Adjudicated drug-related interstitial lung disease/pneumonitis

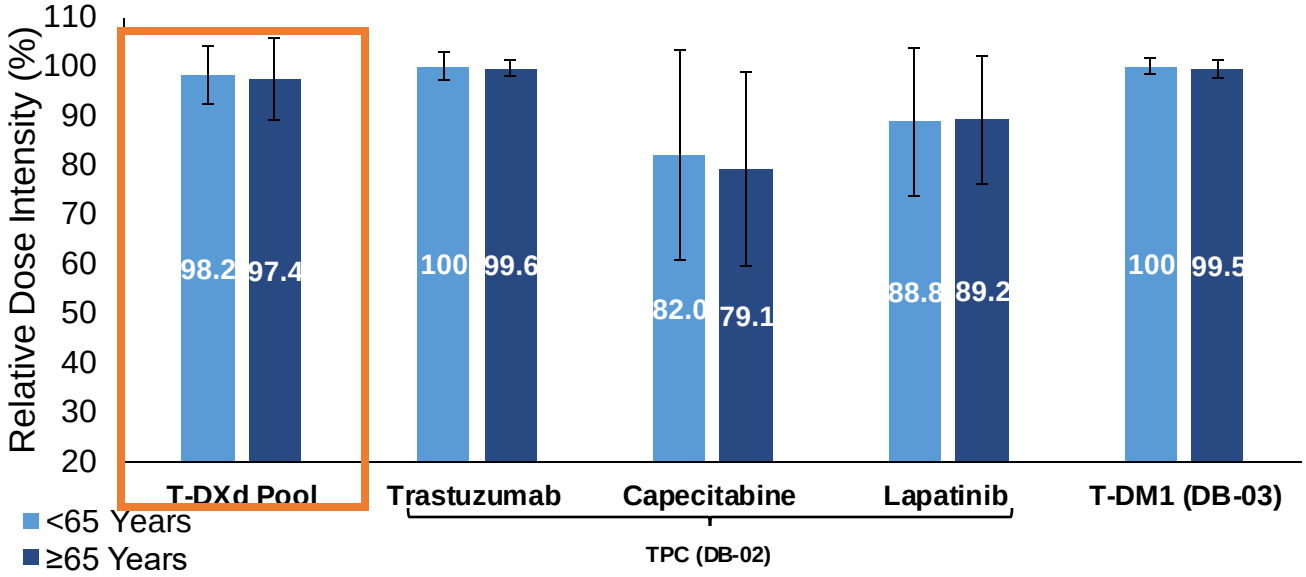
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- **Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]**
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were four additional grade 1, eight additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Modi S, et al. *N Engl J Med.* 2020;382:610-621; 2. Powell CA, et al. *ESMO Open.* 2022;7:100554; 3. Cortes J, et al. *N Engl J Med.* 2022;386:1143-1154.

Relative dose intensity



- Relative dose intensity was similar between <65 and ≥65 age groups, regardless of treatment received

[a]Relative dose intensity (%) = (dose intensity/planned dose intensity) × 100.
DB, DESTINY-Breast; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Most common grade ≥3 drug-related TEAEs in ≥5% of patients

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Grade ≥3[a] drug-related TEAEs, n (%)	**291 (43.6)**	**96 (54.2)**	**13 (39.4)**	**48 (30.6)**	**12 (31.6)**	**5 (62.5)**	**82 (40.2)**	**28 (49.1)**	**3 (37.5)**
Neutropenia[b]	117 (17.5)	41 (23.2)	4 (12.1)	5 (3.2)	1 (2.6)	1 (12.5)	6 (2.9)	3 (5.3)	0
Fatigue[c]	52 (7.8)	20 (11.3)	5 (15.2)	1 (0.6)	1 (2.6)	1 (12.5)	2 (1.0)	0	0
Nausea	43 (6.4)	15 (8.5)	4 (12.1)	3 (1.9)	0	0	0	1 (1.8)	0
Anemia[d]	42 (6.3)	20 (11.3)	3 (9.1)	1 (0.6)	0	0	6 (2.9)	6 (10.5)	1 (12.5)
Leukopenia[e]	42 (6.3)	15 (8.5)	2 (6.1)	0	0	0	3 (1.5)	0	0
Lymphopenia[f]	28 (4.2)	11 (6.2)	1 (3.0)	2 (1.3)	0	0	2 (1.0)	1 (1.8)	0
Thrombocytopenia[g]	28 (4.2)	9 (5.1)	0	2 (1.3)	0	0	47 (23.0)	19 (33.3)	2 (25.0)
Transaminases increased[h]	18 (2.7)	1 (0.6)	0	1 (0.6)	1 (2.6)	0	16 (7.8)	4 (7.0)	0
Diarrhea	9 (1.3)	4 (2.3)	0	10 (6.4)	2 (5.3)	1 (12.5)	2 (1.0)	0	0

- Patients ≥65 years of age experienced more grade ≥3 TEAEs across all trials

[a]Grade ≥3 drug-related TEAEs present in ≥5% of patients, sorted in descending order of frequency in the T-DXd pooled arm for the <65 years age group. Grade ≥3 drug-related TEAEs calculated in all patients in the analysis set. [b]Neutropenia includes the preferred terms neutrophil count decreased and neutropenia. [c]Fatigue includes the preferred terms fatigue, asthenia, malaise, and lethargy. [d]Anemia includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [e]Leukopenia includes the preferred terms white blood cell count decrease and leukopenia. [f]Lymphopenia includes the preferred terms lymphocyte count decreased and lymphopenia. [g]Thrombocytopenia includes the preferred terms platelet count decreased and thrombocytopenia. [h]Transaminases increased includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased.
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event; TPC, treatment of physician's choice.

PRESENTED BY: Ian Krop, MD, PhD

Adjudicated drug-related ILD/pneumonitis[a]

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Any grade, n (%)	**79 (11.8)**	**31 (17.5)**	**5 (15.2)**	**0**	**1 (2.6)**	**0**	**6 (2.9)**	**2 (3.5)**	**1 (12.5)**
1	21 (3.1)	7 (4.0)	0	0	0	0	3 (1.5)	1 (1.8)	0
2	48 (7.2)	20 (11.3)	5 (15.2)	0	0	0	2 (1.0)	1 (1.8)	1 (12.5)
3	4 (0.6)	3 (1.7)	0	0	1 (2.6)	0	1 (0.5)	0	0
4	0	0	0	0	0	0	0	0	0
5	6 (0.9)	1 (0.6)	0	0	0	0	0	0	0

- Rates of adjudicated ILD/pneumonitis were generally higher in patients ≥65 years of age across all trials compared with patients <65 years of age
- Most drug-related ILD/pneumonitis cases were of low grade

[a]No ILD/pneumonitis cases were pending adjudication at the respective data cutoff dates (DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022).
ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

ESMO *metastatic* breast cancer guidelines

HER2+ second line

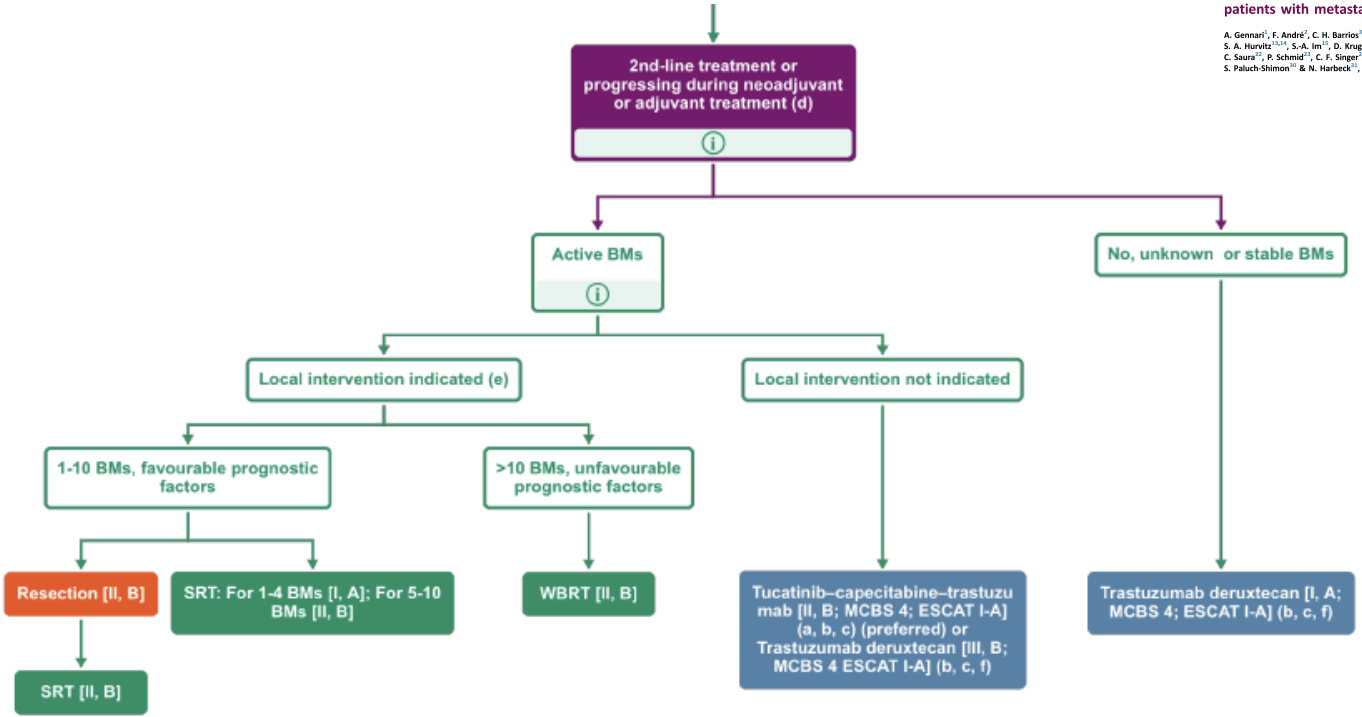
ESMO

ANNALS OF ONCOLOGY

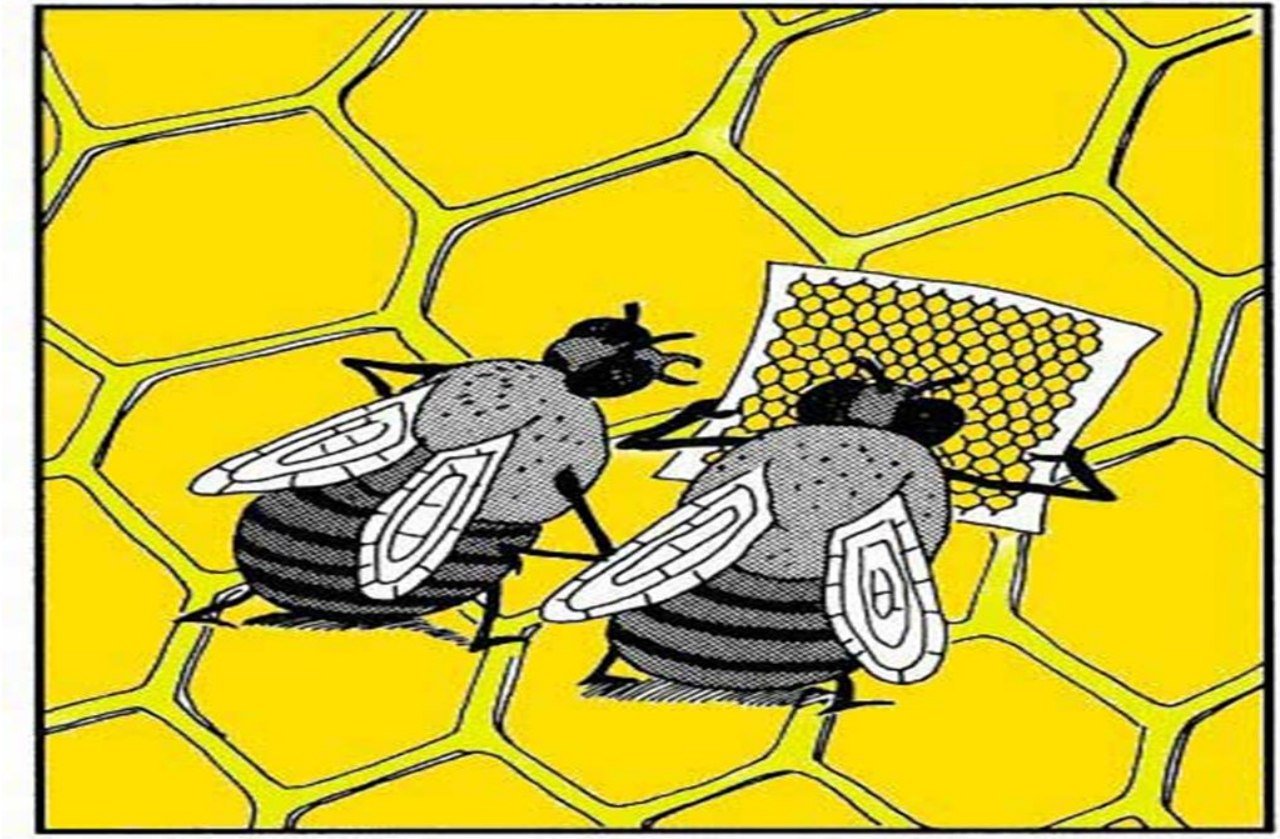
SPECIAL ARTICLE

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆

A. Gennari[1], F. André[2], C. H. Barrios[3], J. Cortés[4,5,6,7], E. de Azambuja[8], A. DeMichele[9], R. Dent[10], D. Fenlon[11], J. Gligorov[12], S. A. Hurvitz[13,14], S.-A. Im[15], D. Krug[16], W. G. Kunz[17], S. Loi[18], F. Penault-Llorca[19], J. Ricke[5,17], M. Robson[20], H. S. Rugo[21], C. Saura[22], P. Schmid[23], C. F. Singer[24], T. Spanic[25], S. M. Tolaney[26], N. C. Turner[27], G. Curigliano[28], S. Loibl[29], S. Paluch-Shimon[30] & N. Harbeck[31], on behalf of the ESMO Guidelines Committee*



Gennari A, et al. *Ann Oncol*. 2021;32:1475-1492; esmo.org.


So, Where are we exactly?

HER2+ metastatic breast cancer
First- and second-line standards

LMU KLINIKUM

- **First line:** CLEOPATRA regimen (taxane plus trastuzumab plus pertuzumab)
  - For HER2+, HR+: endocrine backbone feasible – phase III evidence lacking
- **Second line:** DESTINY-Breast 03 demonstrated better PFS and OS for trastuzumab deruxtecan (T-DXd) vs T-DM1
  - Safety of T-DXd comparable with that of chemotherapy
  - ILD (grade 5 toxicities) requires proactive patient education and treatment
  - Current clinical trials aim to establish T-DXd in earlier disease settings
- If limited access to T-DXd: EMILIA established T-DM1 in second line on the basis of PFS and OS advantage vs Cap-Lap; T-DM1 well tolerated, CNS efficacy in small cohorts
- Final treatment concept in HER2+ MBC depends on patient characteristics (comorbidities), prior treatments, drug availability and access, reimbursement, and patient preferences

ESMO *metastatic* breast cancer guidelines

HER2+ third line and beyond

ESMO

ANNALS OF ONCOLOGY

SPECIAL ARTICLE

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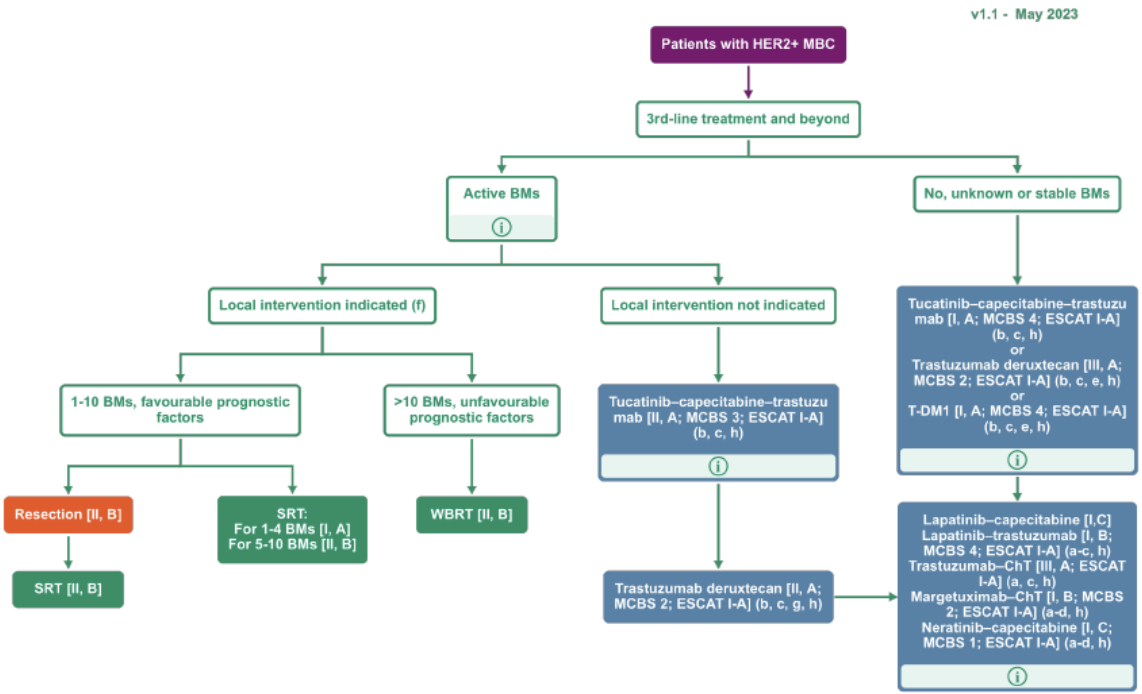
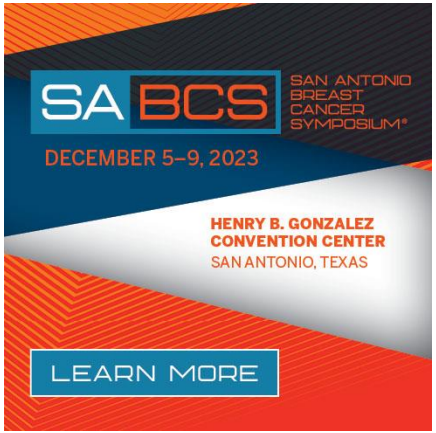


Gennari A, et al. *Ann Oncol*. 2021;32:1475-1492; esmo.org.

Where can we find further new data and information . . .

. . . in breast cancer?

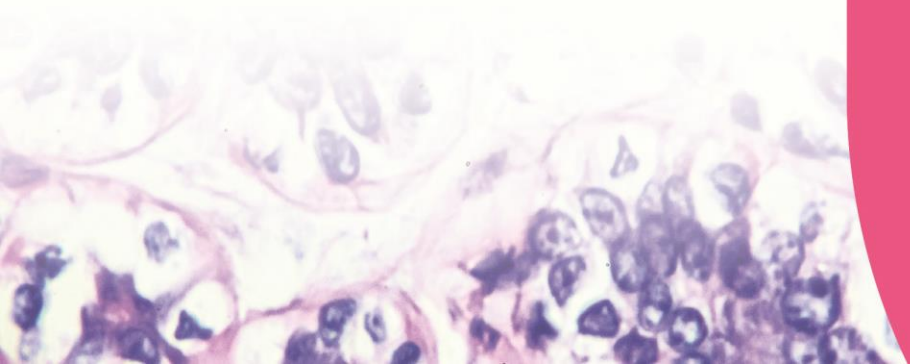


SINGAPORE 2023 ESMO ASIA

SINGAPORE
1-3 DECEMBER 2023

Global Breast Cancer Academy

Q&A



APTITUDE HEALTH

Objectives

Understand major advances in early lines of treatment for HER2+ mBC

Learn about potential treatment options after second line treatment for HER2+ mBC

Understand changes in HER2 expression during treatment with HER2-targeted agents

Gain insights into the care of HER2+ mBC patients with CNS metastases

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Explore current and future sequencing strategies in HER2+ mBC

Global Breast Cancer Academy

What are the treatment options after second line?

Giuseppe Curigliano

APTITUDE HEALTH

What are the treatment options after early lines?

Giuseppe Curigliano, MD, PhD
University of Milano and Istituto Europeo di Oncologia
Milano, Italia

UNIVERSITÀ DEGLI STUDI
DI MILANO

IEO
Istituto Europeo
di Oncologia

Disclosures

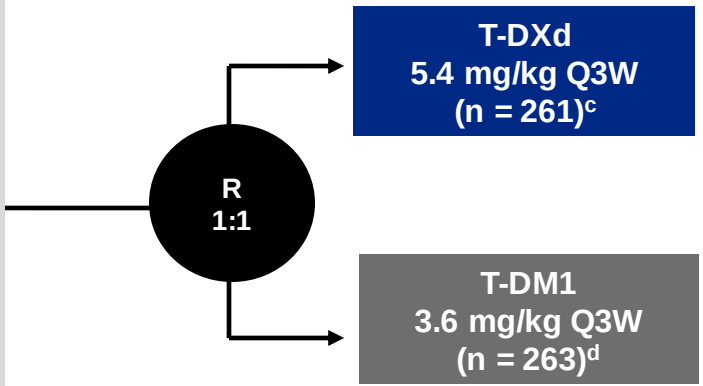
- Board member: Ellipses
- Consultant: Lilly, Novartis, Seattle Genetics, Roche-Genentech
- Research grants to my institute: MSD, AstraZeneca
- Speakers' bureau: Pfizer, Lilly, Novartis, Roche-Genentech, Samsung, Celltrion
- Stock ownership: None

DESTINY-Breast03: First randomized phase III 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
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment
  - Prior to protocol amendment, patients with stable, untreated BM were eligible

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



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

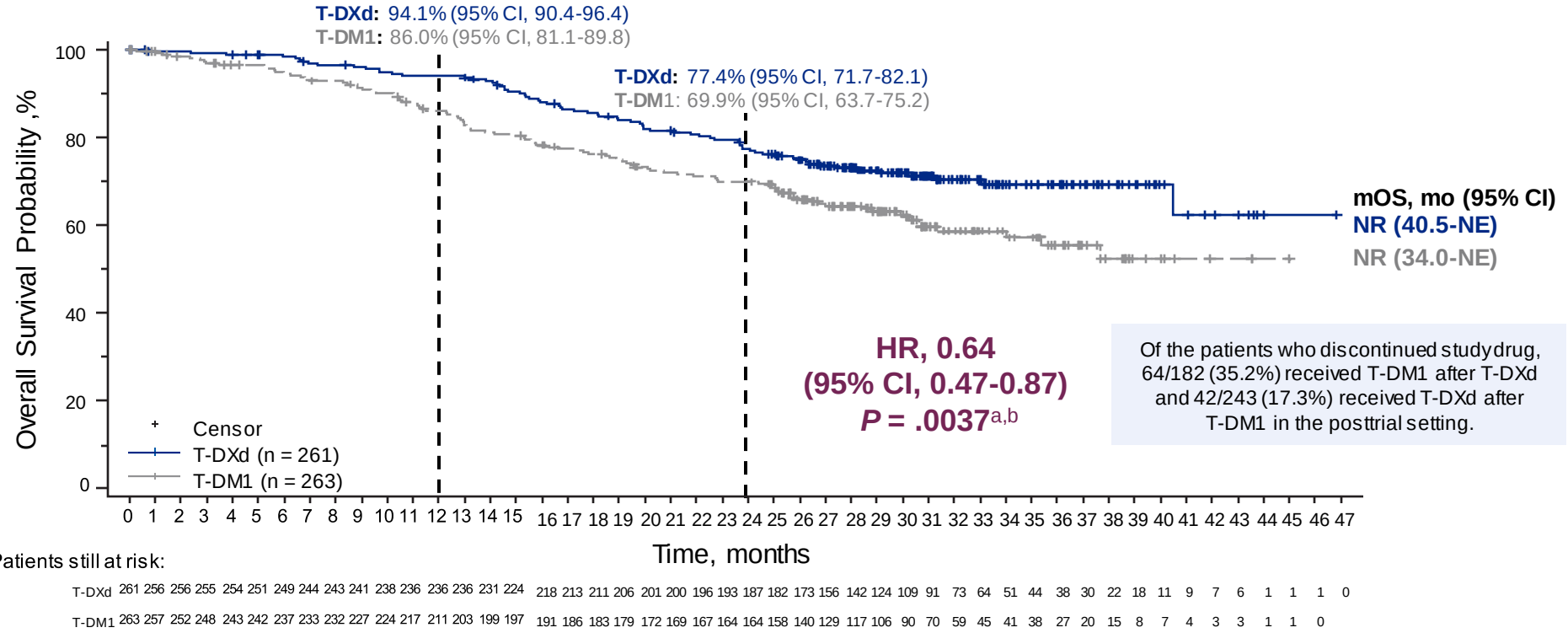
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

- Median follow-up was 15.9 months
- 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
- 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 imaging; 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.

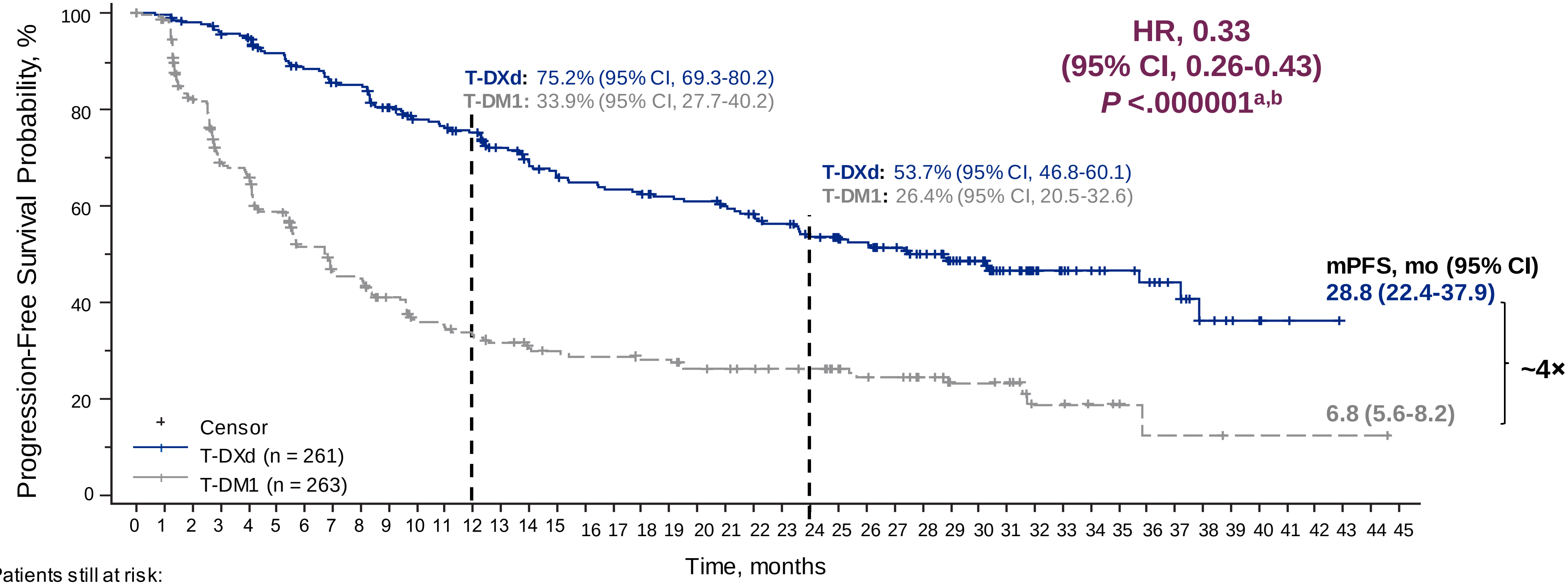
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]Four patients were randomly assigned but not treated. [d]Two patients were randomly assigned but not treated.

Key secondary endpoint: Overall survival



HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = .013) and was statistically significant. [b]Two-sided.

Updated primary endpoint: PFS by BICR



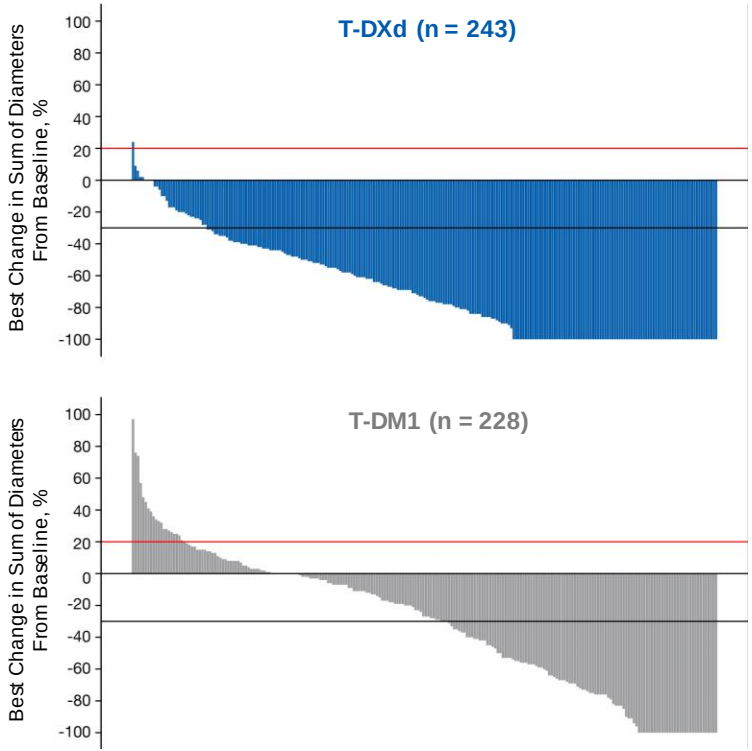
Patients still at risk:

T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]Two-sided. [b]Nominal *P* value.

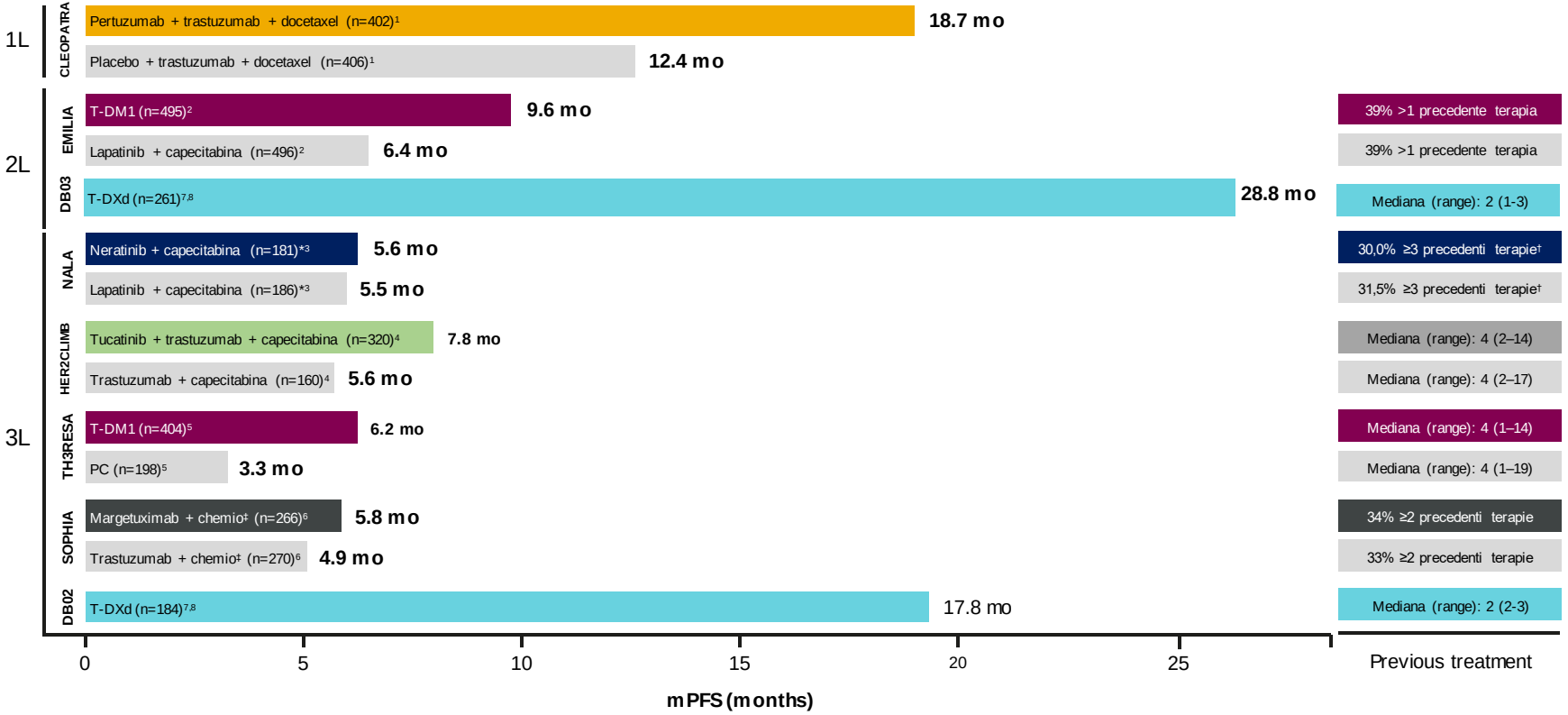
Confirmed ORR and other efficacy endpoints



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	<.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	<.0001	
mDOR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDOR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease;
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Red line at 20% indicates progressive disease; black line at −30% indicates partial response.
[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

HER2+ mBC: Unprecedented data



*Dati solo per pazienti con stato HR+; mPFS per ITT 5,6 mesi per neratinib + capecitabina (n=307) e 5,5 mesi per lapatinib + capecitabina (n=314).
†Regimi mirati anti-HER2; le terapie non anti-HER2 sono state escluse da questa percentuale.
‡A scelta dell'investigatore: capecitabina, eribulina, gemcitabina o vinorelbina.

Swain SM, et al. ASCO 2019. Abstract 1020; Diéras V, et al. *Lancet Oncol*. 2017;18:732-742; Saura C, et al. *J Clin Oncol*. 2020;38:3138-3149; Murthy RK, et al. *N Engl J Med*. 2020;382:597-609; Krop IE, et al. *Lancet Oncol*. 2014;15:689-699; Rugo HS, et al. ASCO 2019. Abstract 1000; Saura C, et al. ESMO 2021. Abstract 279P; Hurvitz SA, et al. *Lancet*. 2023;401:105-117.

Treatment algorithm: BEFORE and AFTER Destiny Breast-03

	ChT* + trastuzumab + pertuzumab	I line	CLEOPATRA
	T-DM1	II line	DB-03, HER2CLIMB
Tucatinib + trastuzumab + capecitabine**	Trastuzumab deruxtecan	III line	DB-01, HER2CLIMB

The good news: an expanding arsenal of available regimens

HER2+ advanced breast cancer
Beyond second-line treatment

Preferred options

- Trastuzumab deruxtecan
- Tucatinib + trastuzumab + capecitabine

The bad news: lack of data after progression to T-DXd

*ET instead of ChT for selected patients. **Preferred for patients with active brain metastases.

T-DM1

Target Antigen: HER2 (trastuzumab vehicle)

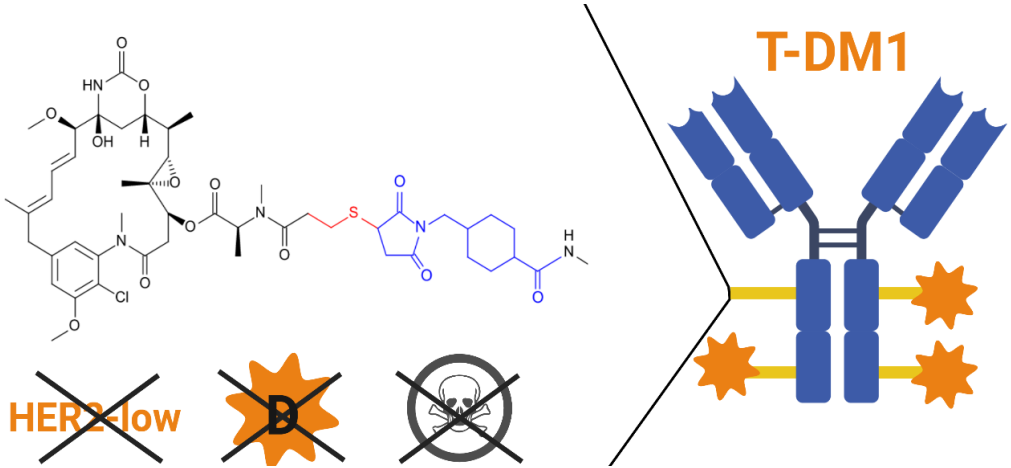
mAb isotype: IgG1

Linker type: non-cleavable

Payload (class): DM1 (Maytansinoid)

Payload action: Microtubule inhibitor

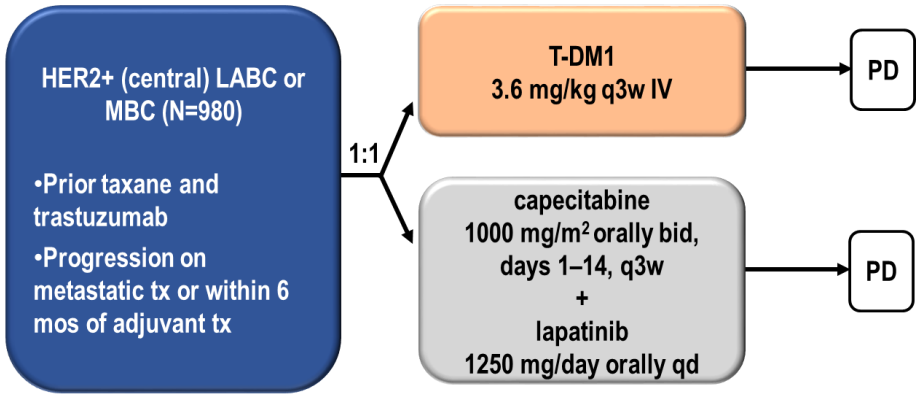
DAR: 3.5 (mean)



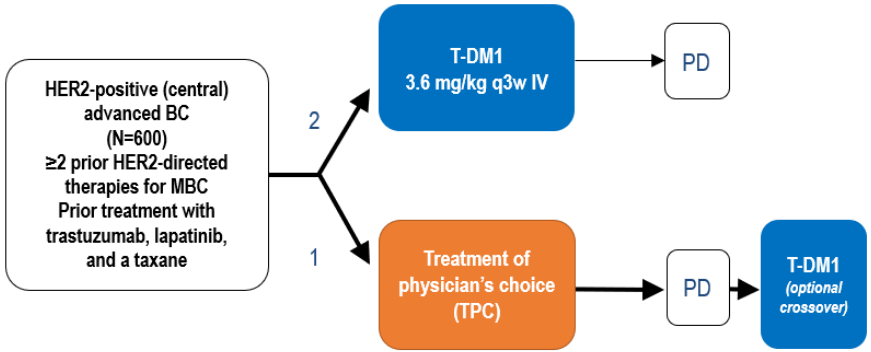
Legend: HER2-low = Targets HER2-low tumors; D = Diffusible cytotoxic moiety; = Bystander killing effect

Corti C, et al. *Cancers*. 2021;13:2898.

EMILIA: T-DM1 vs lapatinib + capecitabine

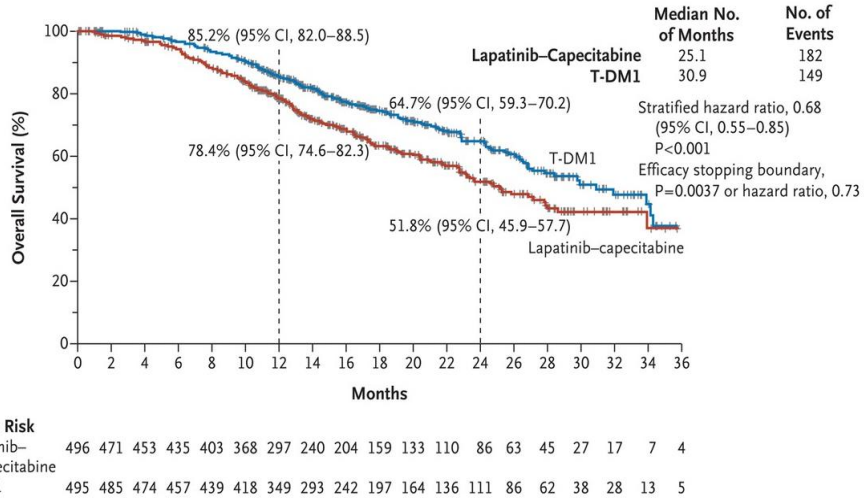


TH3RESA: T-DM1 vs clinician's choice



Verma S, et al. *N Engl J Med*. 2012;367:1783-1791; Krop IE, et al. *Lancet Oncol*. 2017;18:743-754.

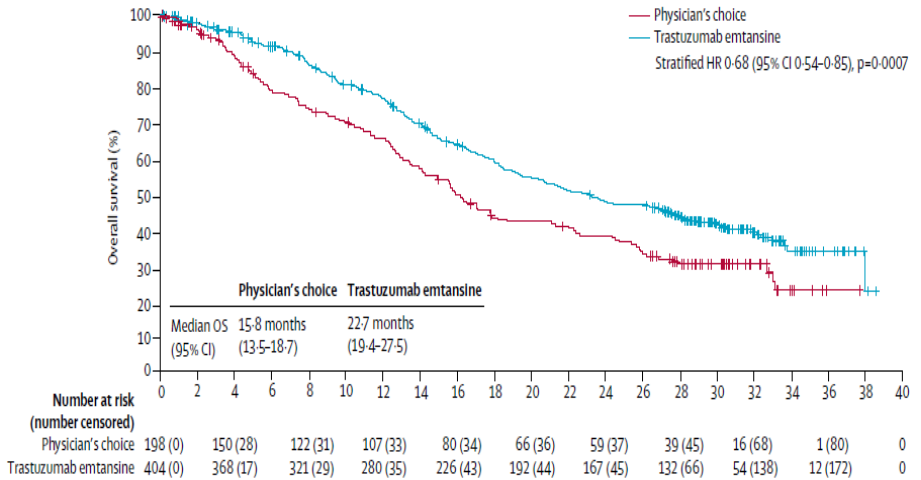
EMILIA: T-DM1 vs lapatinib + capecitabine



Better PFS vs lapatinib plus capecitabine (median, 10 vs 6 months; HR 0.65, 95% CI 0.55-0.77)

Better OS (median, 31 vs 25 months; HR 0.68, 95% CI 0.55-0.85), maintained with longer follow-up (>40 months; crossover allowed)

TH3RESA: T-DM1 vs clinician's choice



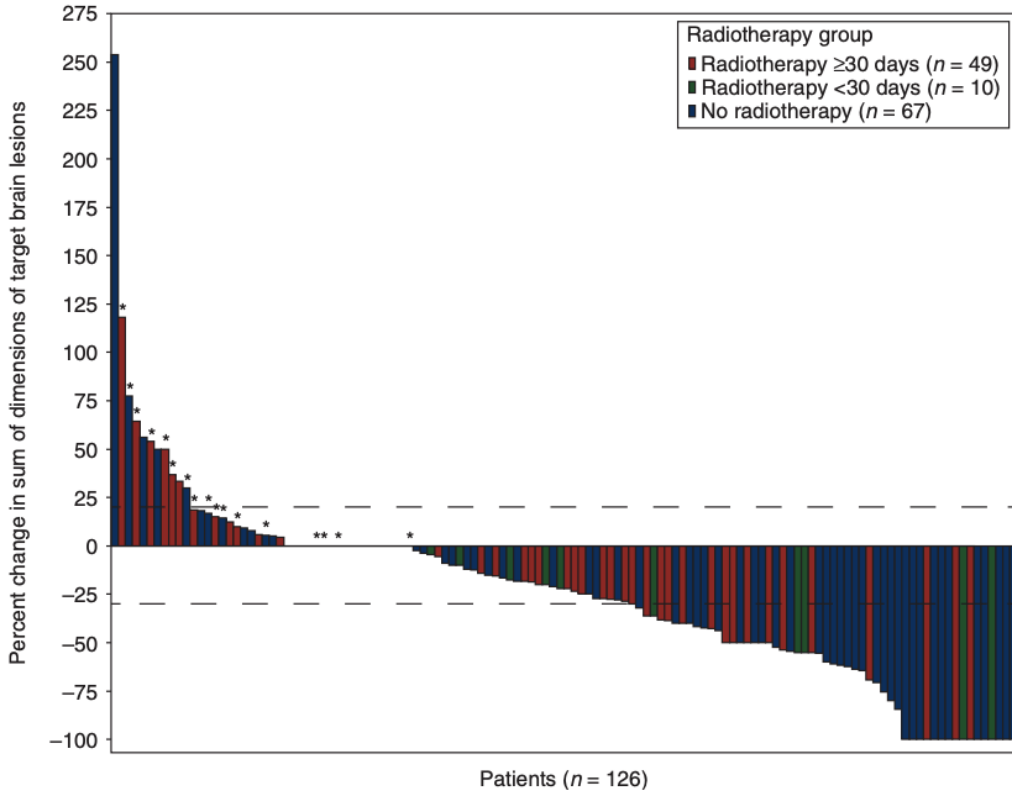
Better PFS (median, 6.2 vs 3.3 months; HR 0.53, 95% CI 0.42-0.66)

Better OS (median, 22.7 vs 15.8 months; HR 0.68, 95% CI 0.54-0.85)

Verma S, et al. *N Engl J Med*. 2012;367:1783-1791; Krop IE, et al. *Lancet Oncol*. 2017;18:743-754.

Intracranial activity of T-DM1

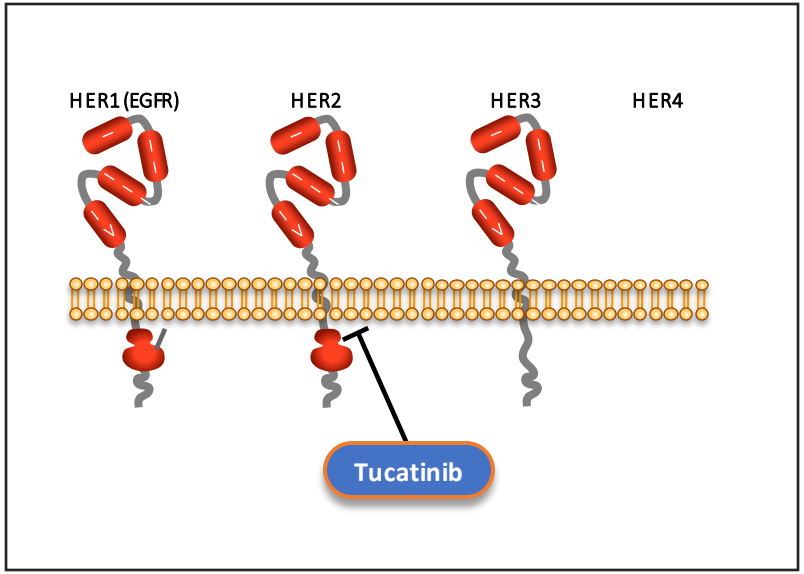
Among 126 patients with measurable brain mets in the KAMILLA trial, ORR was 21%, with a median PFS of 5.5 months and a median OS of 18.9 months



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

Tucatinib

Highly HER2-selective tyrosine kinase inhibitor, with minimal inhibition of EGFR that allows to reduce EGFR-related toxicities compared with other HER2 TKIs



HER2CLIMB: Tucatinib

- Patients with LA or metastatic HER2-positive MBC
- Central *HER2* testing
- Prior treatment with taxane, trastuzumab, pertuzumab, and T-DM1 in any setting
- No prior treatment with neratinib, afatinib, or any experimental EGFR/HER2 TKI
- No prior lapatinib in previous 12 months
- No prior capecitabine for MBC
- Patients with untreated or progressive brain metastases eligible

(N = 480)

R
2:1

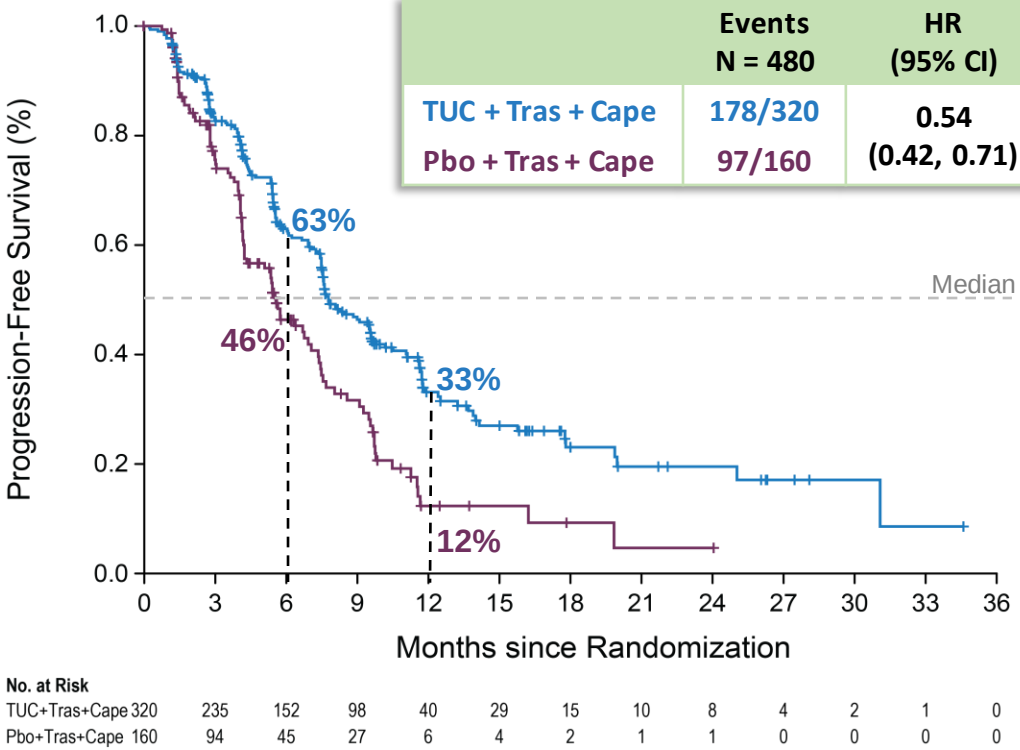
Tucatinib + capecitabine + trastuzumab
(n = 320)

Placebo + capecitabine + trastuzumab
(n = 160)

Treat until PD, unacceptable toxicity

ClinicalTrials.gov. NCT02614794.

Progression-free survival in the primary-endpoint population



	Events N = 480	HR (95% CI)	*P* Value
TUC + Tras + Cape	178/320	0.54 (0.42, 0.71)	<.00001
Pbo + Tras + Cape	97/160		

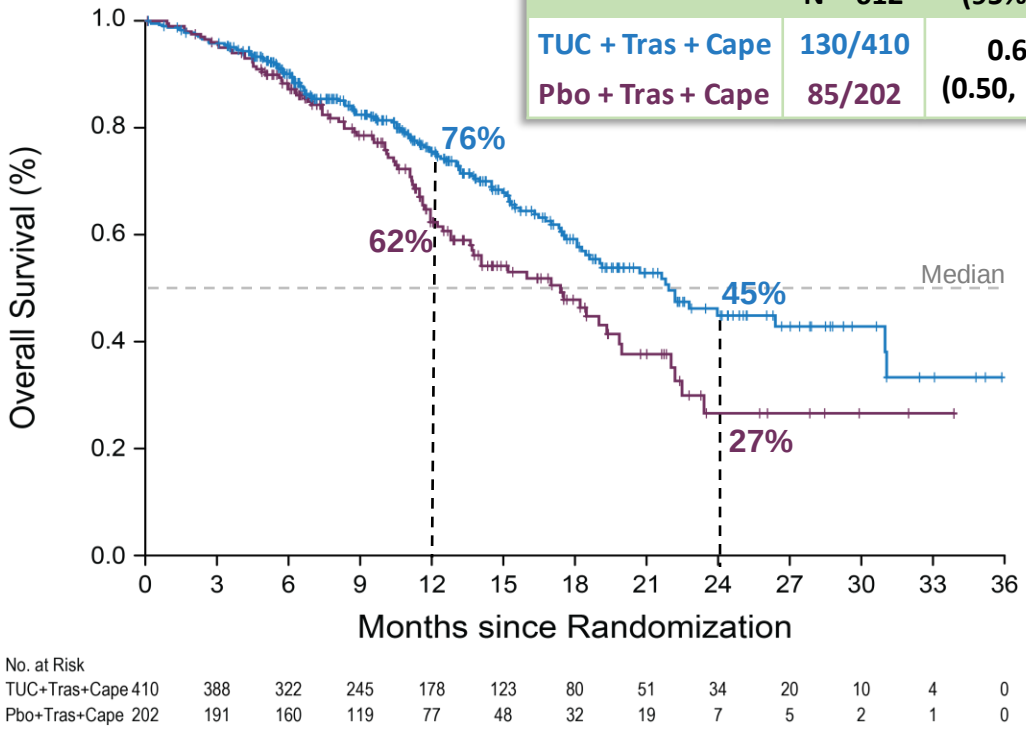
Risk of progression or death was reduced by 46% in the primary-endpoint population

One-year PFS (95% CI):	
TUC + Tras + Cape	Pbo + Tras + Cape
33% (27, 40)	12% (6, 21)
Median PFS (95% CI):	
7.8 months (7.5, 9.6)	5.6 months (4.2, 7.1)

Prespecified efficacy boundary for PFS: *P* = .05
Data cutoff: Sep 4, 2019

Overall survival in the total study population

	Events N = 612	HR (95% CI)	*P* Value
TUC + Tras + Cape	130/410	0.66 (0.50, 0.88)	.00480
Pbo + Tras + Cape	85/202		

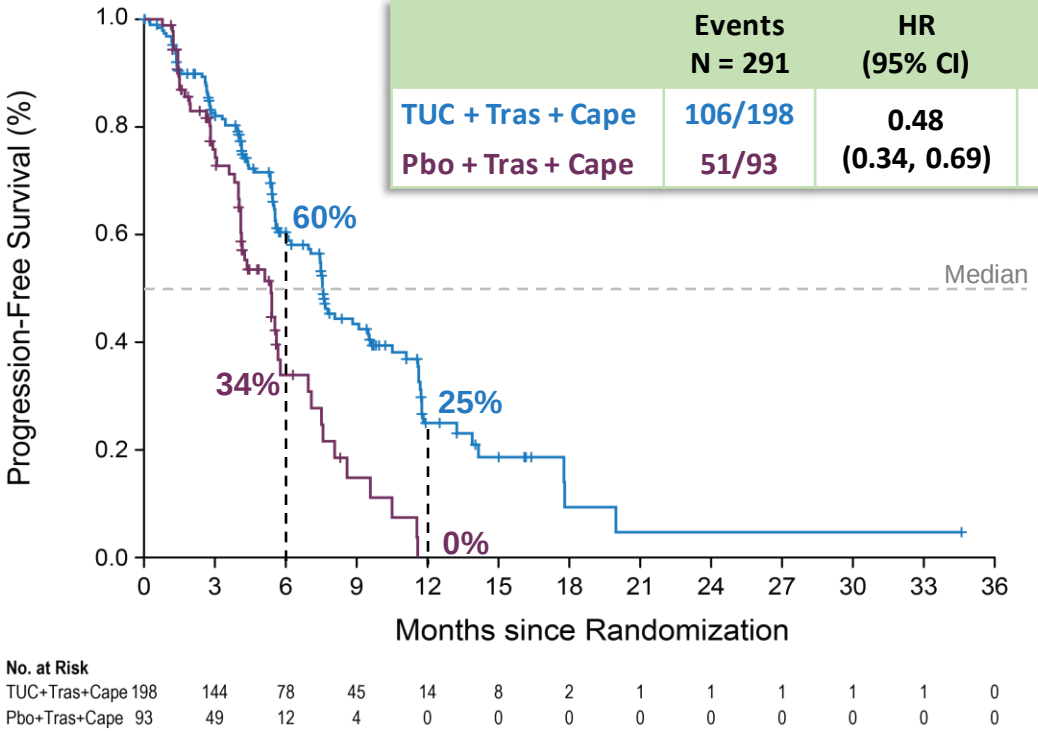


Risk of death was reduced by 34% in the total population

Two-year OS (95% CI):	
TUC + Tras + Cape	Pbo + Tras + Cape
45% (37, 53)	27% (16, 39)
Median OS (95% CI):	
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

Prespecified efficacy boundary for OS (*P* = .0074) was met at the first interim analysis.
Data cutoff: Sep 4, 2019

Progression-free survival for patients with brain metastases



	Events N = 291	HR (95% CI)	*P* Value
TUC + Tras + Cape	106/198	0.48 (0.34, 0.69)	<.00001
Pbo + Tras + Cape	51/93		

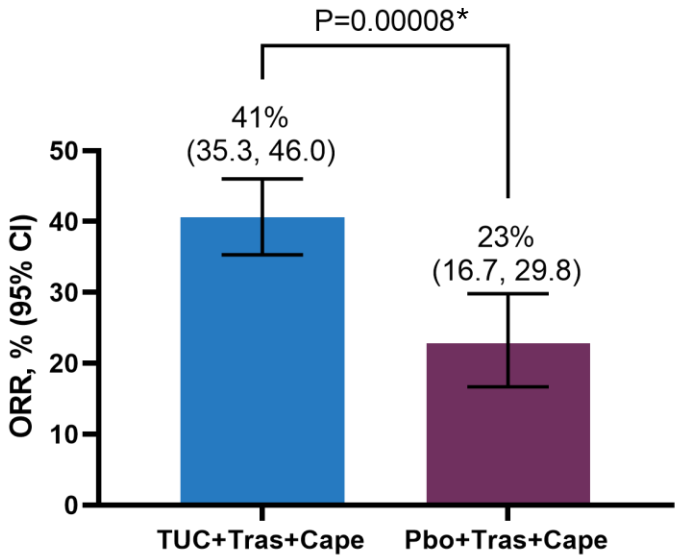
Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

One-year PFS (95% CI):	
TUC + Tras + Cape	Pbo + Tras + Cape
25% (17, 34)	0%
Median PFS (95% CI):	
7.6 months (6.2, 9.5)	5.4 months (4.1, 5.7)

Prespecified efficacy boundary for $PFS_{BrainMets}$ (P = .0080) was met at the first interim analysis.
Data cutoff: Sep 4, 2019

Confirmed objective response rate in the total study population

Confirmed Objective Response Rate (RECIST 1.1, BICR)



*Stratified Cochran-Mantel-Haenszel *P* value for ORR.

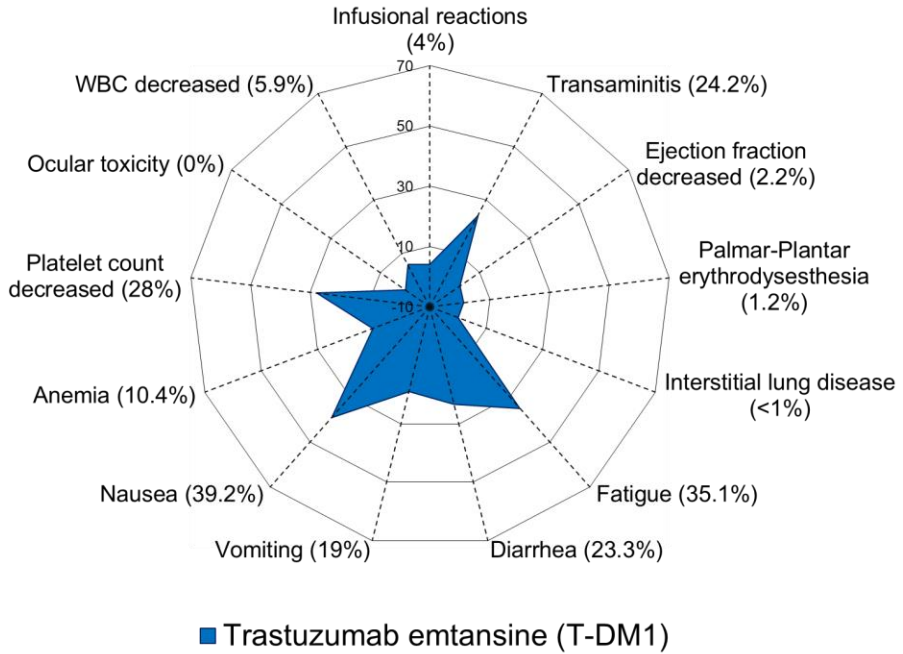
Response, n (%)	Patients With Measurable Disease N = 511 TUC + Tras + Cape n = 340	Pbo + Tras + Cape n = 171
Best overall response[a]		
Complete response (CR)	3 (1)	2 (1)
Partial response (PR)	135 (40)	37 (22)
Stable disease (SD)	155 (46)	100 (59)
Progressive disease (PD)	27 (8)	24 (14)
Not evaluable	0	1 (1)
Not available[b]	20 (6)	7 (4)
Time to response (months), median (min, max)	1.4 (1.1, 9.7)	1.4 (1.2, 15.7)
Clinical benefit rate (CR + PR + SD >6 months)	60%	38%

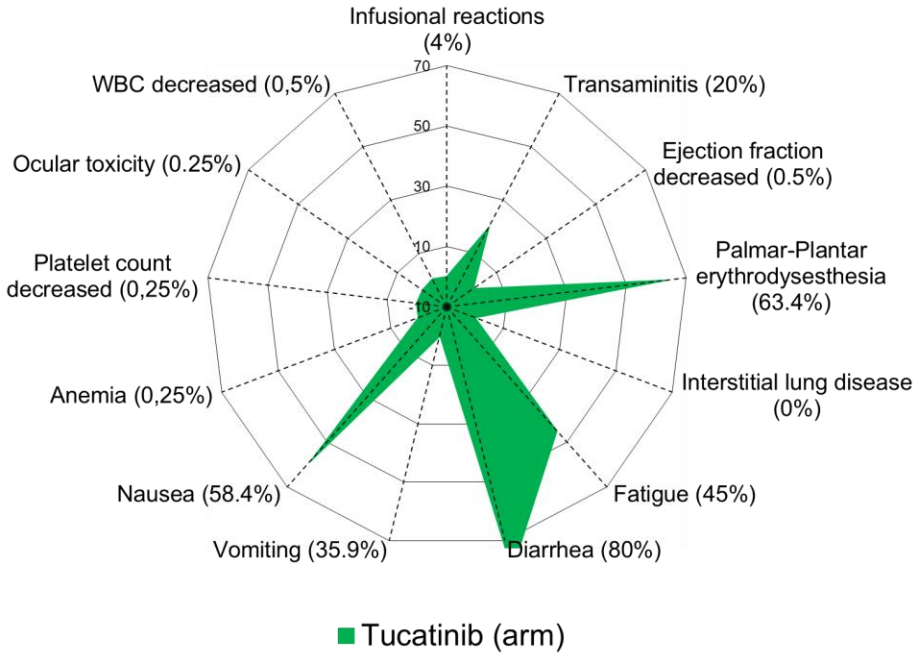
[a]Confirmed best overall response assessed per RECIST 1.1.
[b]Patients with no postbaseline response assessments.

	T-DM1	Tucatinib
Sequence	No efficacy data after T-DXd	No efficacy data after T-DXd
Brain metastases	Mainly pretreated/stable brain mets. **Retrospective evidence/subgroup analyses**[1-4] Moderate intracranial activity	198 (48%) patients with CNS disease **Active brain mets included in HER2CLIMB**[5]. **100% pts pretreated with T-DM1**[5] **High intracranial activity**
Activity after dual blockade	**Few solid data** on the use of **T-DM1 after dual blockade** (*clinical gap*)[6-12]	100% pts pretreated with trastuzumab and pertuzumab[5]

1. Krop IE, et al. *Ann Oncol*. 2015;26:113119; 2. Bartsch R, et al. *Clin Exp Metastasis*. 2015;32:729-737; 3. Montemurro F, et al. *Ann Oncol*. 2020;31:1350-1358; 4. Jacot W, et al. *Breast Cancer Res Treat*. 2016;157:307-318; 5. Murthy RK, et al. *N Engl J Med*. 2020;382:597-609; 6. Dzimitrowicz H, et al. *J Clin Oncol*. 2016;34:3511-3517; 7. Vici P, et al. *Oncotarget*. 2017;8:56921-56931; 8. Fabi A, et al. *Future Oncol*. 2017;13:2791-2797; 9. Noda-Narita S, et al. *Breast Cancer*. 2019;26:492-498; 10. Tiwari S, et al. *Cancer Res*. 2018;78(4 suppl):P5-21-5-26; 11. Conte B, et al. *Clin Breast Cancer*. 2020;20:E181–E187; 12. Urruticoechea A, et al. *J Clin Oncol*. 2017;35(suppl): abstract 1023.

T-DM1 and tucatinib-based triplet: Toxicity profiles





Note: Patients treated with T-DM1 in the EMILIA trial experienced an overall higher rate of bleeding compared with those treated with capecitabine plus lapatinib (30% vs 16%, respectively), though the rate of serious bleeding events was low in both arms (1.4% vs 0.8%)

Verma S, et al. *N Engl J Med*. 2012;367:1783-1791; Murthy RK, et al. *N Engl J Med*. 2020;382:597-609.

Analysis plan

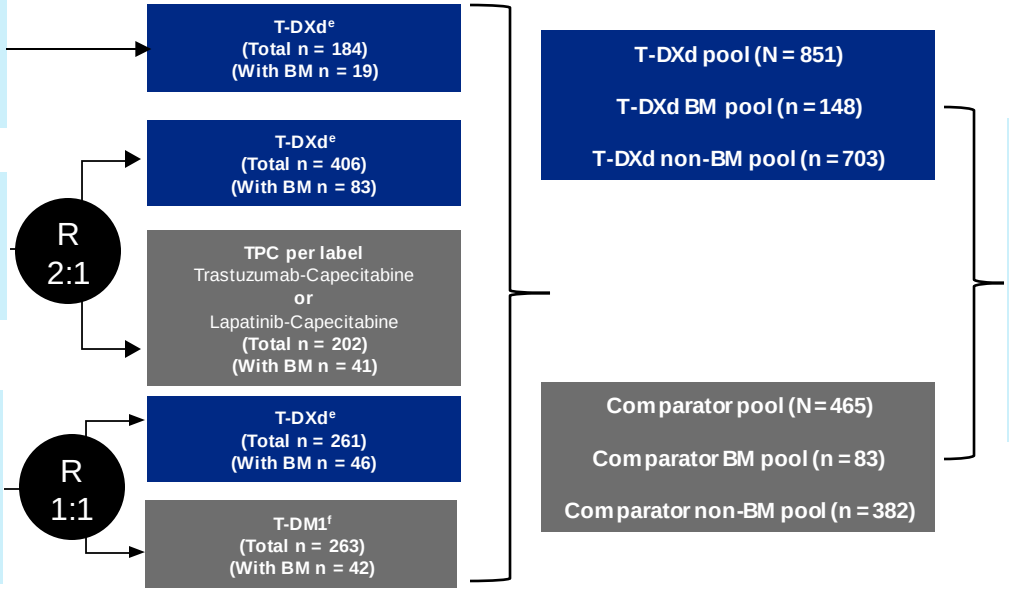
Inclusion Criteria

DESTINY-Breast01[1]	DESTINY-Breast02 and DESTINY-Breast03[2-4]
• Patients with asymptomatic, previously locally treated, and stable BMs	• Initially, **patients with previously untreated and asymptomatic BM were eligible** • After protocol amendments, only patients with treated, asymptomatic BMs were allowed

DESTINY-Breast01 (N = 253)[a,b]
- Phase II study
- Patients previously treated with T-DM1
- Patients with asymptomatic and previously locally treated BM eligible
- Prior BM therapy within 60 days prohibited

DESTINY-Breast02 (N = 608)[a,c]
- Phase III study
- Patients previously treated with T-DM1
- Patients with asymptomatic and previously treated/untreated BM eligible
- Prior BM therapy within 14 days of randomization prohibited

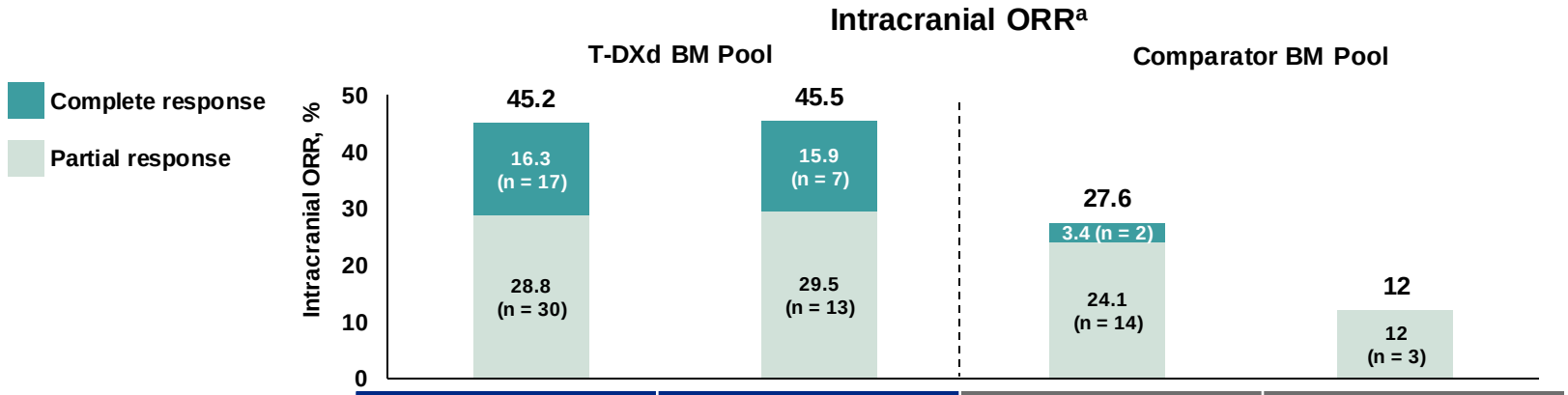
DESTINY-Breast03 (N = 524)[a,d]
- Phase III study
- Patients previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy
- Patients with asymptomatic and previously treated/untreated BM eligible
- Prior BM therapy within 14 days of randomization prohibited



Endpoints
- IC-ORR (CR + PR in brain) per BICR per RECIST v1.1
- IC-DOR per BICR
- CNS-PFS per BICR
- Safety and tolerability

The BM and non-BM pools were determined by BICR at baseline among all patients on the basis of mandatory brain CT/MRI screening

Exploratory best IC response, ORR, and DOR per BICR



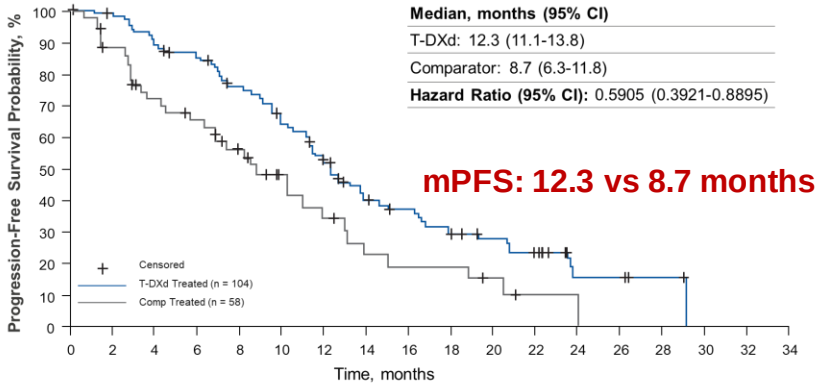
	Treated/Stable BMs (n = 104)	Untreated/Active BMs (n = 44)	Treated/Stable BMs (n = 58)	Untreated/Active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/Missing	6 (5.8)	8 (18.2)	7 (12.1)	2 (8.0)
IC-DOR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	NA[b]

- **T-DXd consistently demonstrated superior rates of IC responses over comparator in patients with treated/stable and untreated/active BMs**
- **A trend in prolonged median IC-DOR was most pronounced in the untreated/active BMs subgroup**

BM, brain metastasis; BICR, blinded independent central review; DOR, duration of response; IC, intracranial; NA, not available; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.
This table considers both target and non-target lesions at baseline. Lesions in previously irradiated areas were not considered measurable target lesions unless there was demonstrated progression in the lesion.
[a]IC-ORR was assessed per RESIST v1.1. [b]IC-DOR NA due to small number of responders (n <10).

Exploratory CNS PFS per BICR

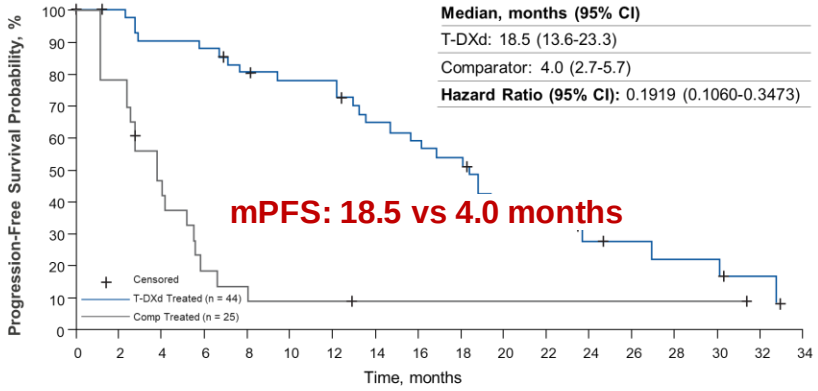
Treated/Stable BMs



Patients still at risk

T-DXd Treated (n = 104)	104	100	89	83	72	58	46	32	28	21	18	12	4	4	2	0	0	0
Comparator Treated (n = 58)	58	44	33	29	22	14	10	6	5	5	3	1	0	0	0	0	0	0

Untreated/Active BMs



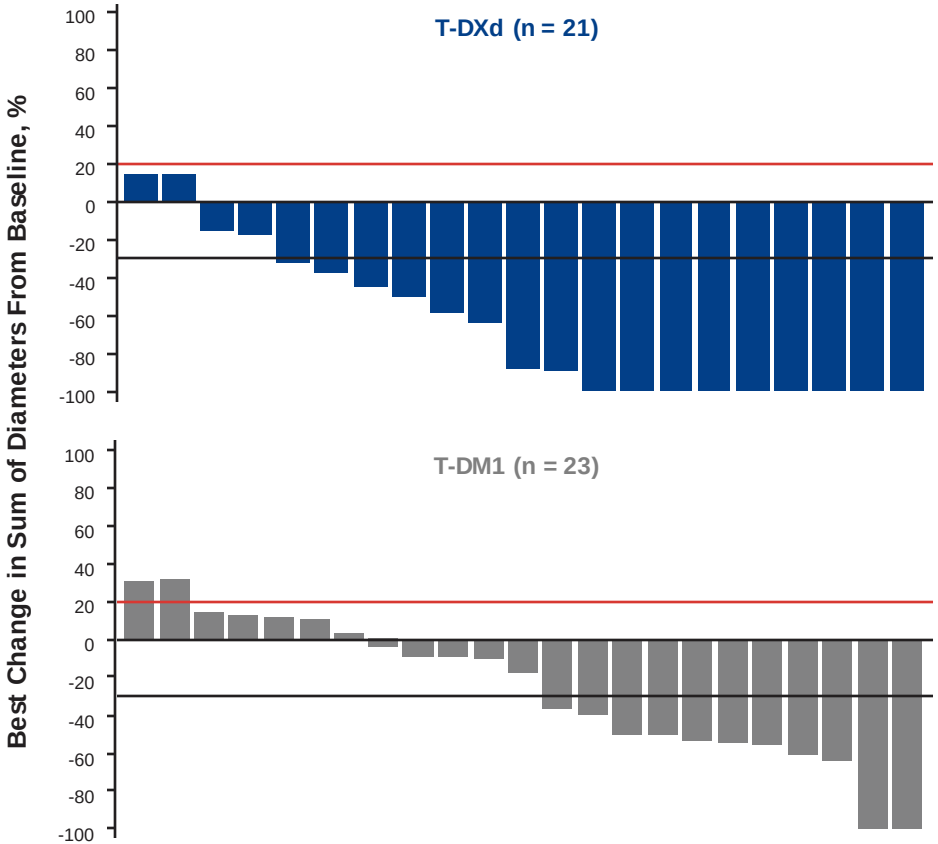
Patients still at risk

T-DXd Treated (n = 44)	44	41	37	36	32	30	30	24	22	20	13	11	6	5	4	4	2	0
Comparator Treated (n = 25)	25	18	11	5	3	2	2	1	1	1	1	1	1	1	1	1	0	0

Numerically longer median CNS PFS was observed in patients with treated/stable and active BMs randomized to T-DXd vs comparator

BICR, blinded independent central review; BM, brain metastasis; CNS, central-nervous system; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
CNS-PFS was defined by BICR as only radiological progression.

Intracranial response per BICR using RECIST 1.1



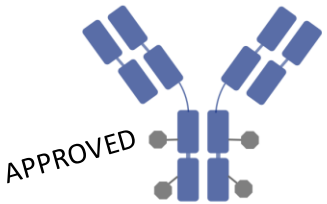
	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of patients in the full analysis set with brain metastases tumor assessment

Hurvitz SM, et al. SABCS 2021. Abstract GS2-02.

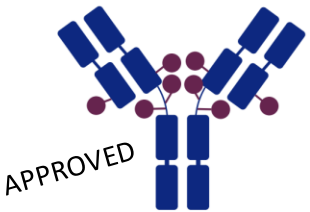
Other anti-HER2 ADCs in HER2+ mBC

Trastuzumab emtansine (T-DM1)[5]



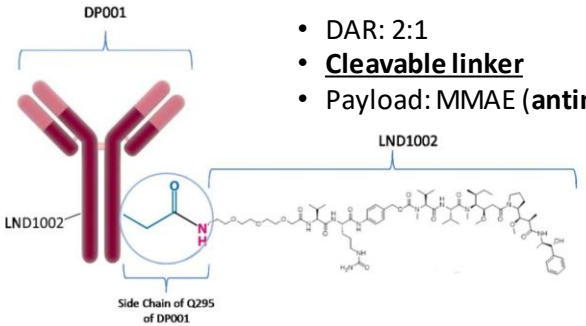
- DAR: 3.5:1
- Non-cleavable linker
- Payload: emtansine (**antimicrotubule**)

Trastuzumab deruxtecan (T-DXd)[1]



- DAR: 8:1
- Cleavable linker
- Payload: deruxtecan (**anti-TOPO1**)

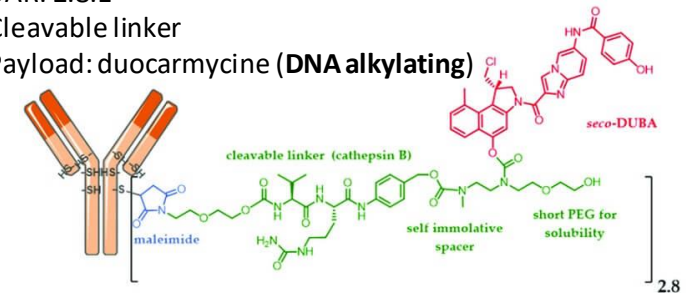
DP303c



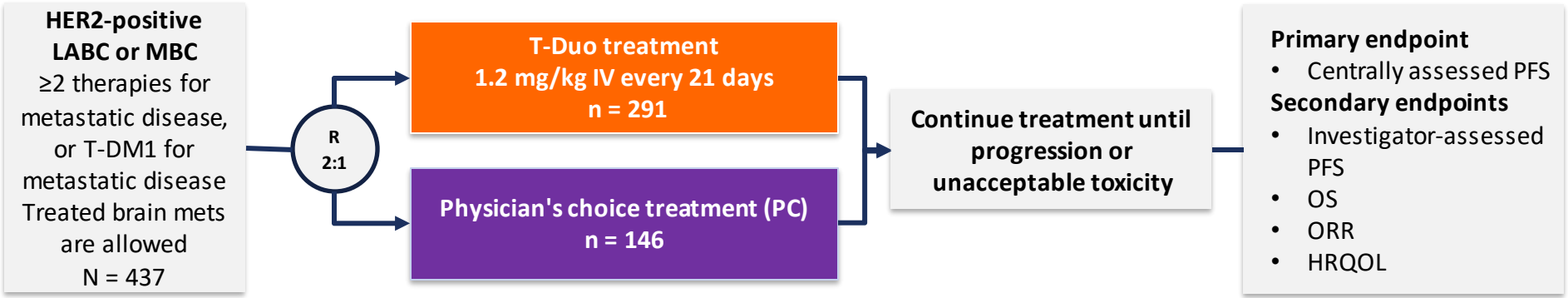
- DAR: 2:1
- **Cleavable linker**
- Payload: MMAE (**antimicrotubule**)

Trastuzumab duocarmazine

- DAR: 2.8:1
- Cleavable linker
- Payload: duocarmycine (**DNA alkylating**)



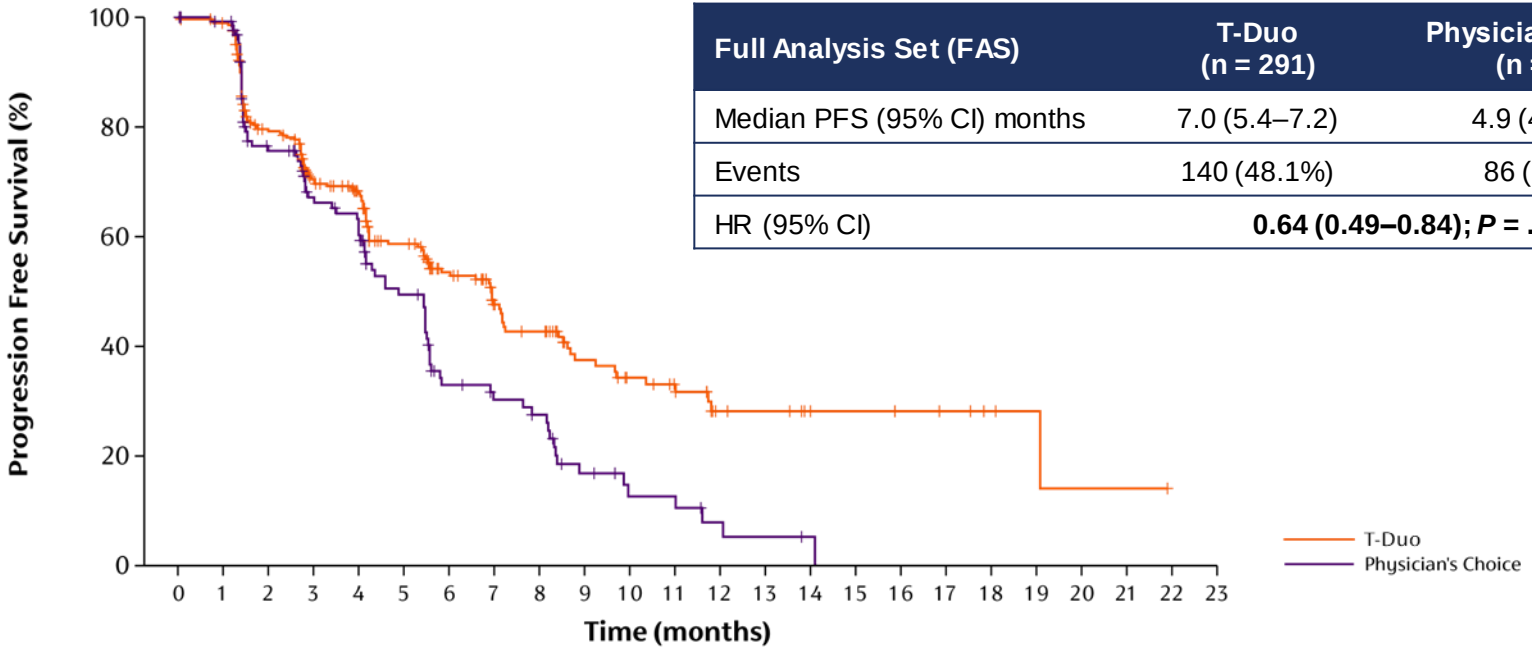
TULIP: Phase III trial design



Stratification, Treatment, Participating Countries

- **Stratification factors**
  - Region (EU + Singapore vs North America)
  - Number of prior treatment lines for LMBC/MBC (1-2 vs >2)
  - Prior treatment with pertuzumab (yes vs no)
- **Physician's choice**
  - **Lapatinib + Capecitabine**
  - **Trastuzumab + Capecitabine**
  - **Trastuzumab + Vinorelbine**
  - **Trastuzumab + Eribulin**
- **NCT03262935**
- **83 sites**
  - USA, Canada, Belgium, Denmark, France, Italy, Netherlands, Spain, Sweden, UK, Singapore

TULIP: Centrally reviewed PFS – primary endpoint



Full Analysis Set (FAS)	T-Duo (n = 291)	Physician's Choice (n = 146)
Median PFS (95% CI) months	7.0 (5.4–7.2)	4.9 (4.0–5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	**0.64 (0.49–0.84); *P* = .002**	

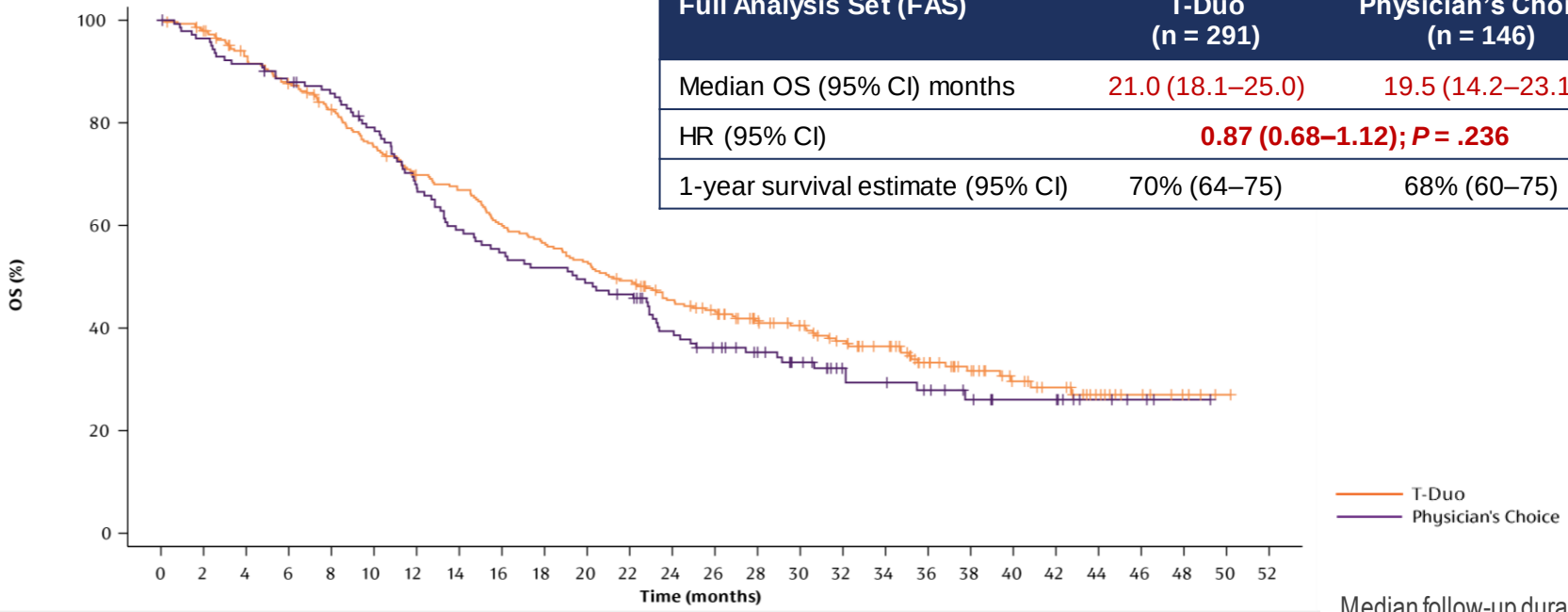
No. Patients at Risk																						
T-Duo	291	278	208	167	150	109	83	59	51	35	28	24	13	12	9	8	6	5	3	2	1	1	0
Physician's Choice	146	125	86	69	64	44	26	22	19	10	6	6	3	2	1	0							

Saura C, et al. ESMO 2021. Abstract 279P.

Median follow-up duration at data cutoff 6.8/7.8 months for T-Duo and physician's choice groups

TULIP: Overall survival

Full Analysis Set (FAS)	T-Duo (n = 291)	Physician's Choice (n = 146)
Median OS (95% CI) months	21.0 (18.1–25.0)	19.5 (14.2–23.1)
HR (95% CI)	**0.87 (0.68–1.12); *P* = .236**	
1-year survival estimate (95% CI)	70% (64–75)	68% (60–75)



No. Patients at Risk

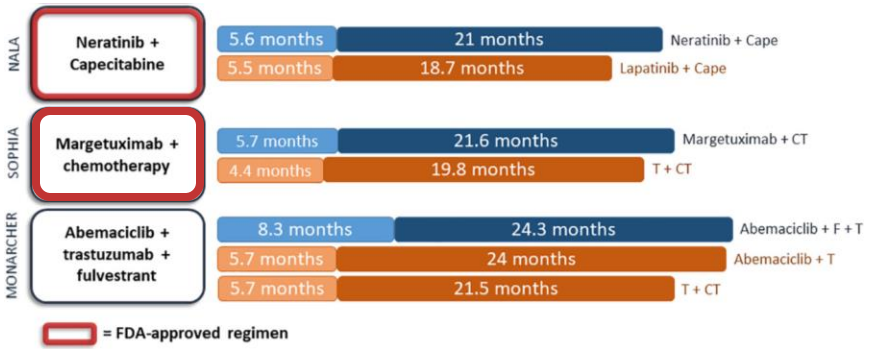
T-Duo	291	281	261	245	228	207	190	182	164	154	144	133	118	108	93	83	72	63	47	38	27	22	13	8	4	1	0
Physician's Choice	146	136	129	122	117	107	92	80	74	70	66	62	49	43	38	31	23	21	18	14	10	10	5	3	1	0	

Median follow-up duration at data cutoff 35.6/32.0 months for T-Duo and physician's choice groups

Giuseppe Curigliano, MD, PhD

Later-line options: An expanding arsenal

Setting	Regimen	Category of Evidence
First line[i]	Pertuzumab + trastuzumab + docetaxel[k]	1
	Pertuzumab + trastuzumab + paclitaxel[k]	2A
Second line[j]	Fam-trastuzumab deruxtecan-nxki[j,l,m]	1
	Ado-trastuzumab emtansine (T-DM1)[j]	2A
Third line and beyond	Tucatinib + trastuzumab + capecitabine[k,n]	1
	Trastuzumab + docetaxel or vinorelbine[k,o]	2A
	Trastuzumab + paclitaxel ± carboplatin[k,o]	2A
	Capecitabine + trastuzumab or lapatinib[k,o]	2A
	Trastuzumab + lapatinib[k,o] (without cytotoxic therapy)	2A
	Trastuzumab + other agents[k,o,p,q]	2A
	Neratinib + capecitabine[o]	2A
	Margetuximab-cmkb + chemotherapy[o] (capecitabine, eribulin, gemcitabine, or vinorelbine)	2A

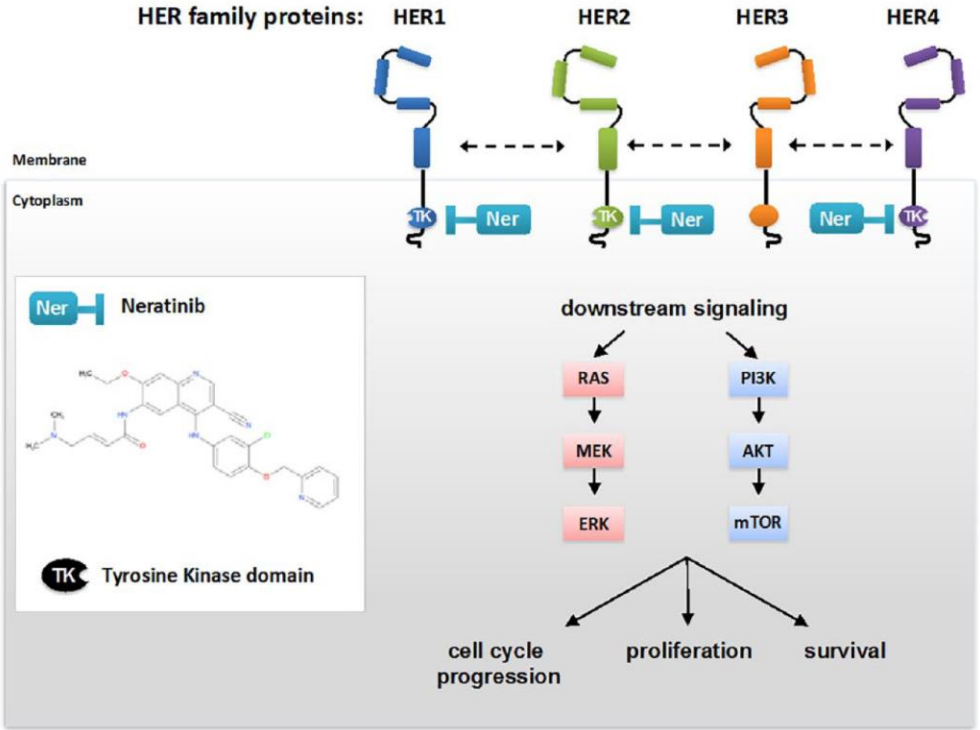


Optimal sequence is not known!

Consider comorbidities, treatment-related toxicity, prior treatments, patient preferences

Adapted from Tarantino P, et al. *Biochim Biophys Acta Rev Cancer.* 2021;1875:188487; National Comprehensive Cancer Network. NCCN Breast Cancer Guidelines.

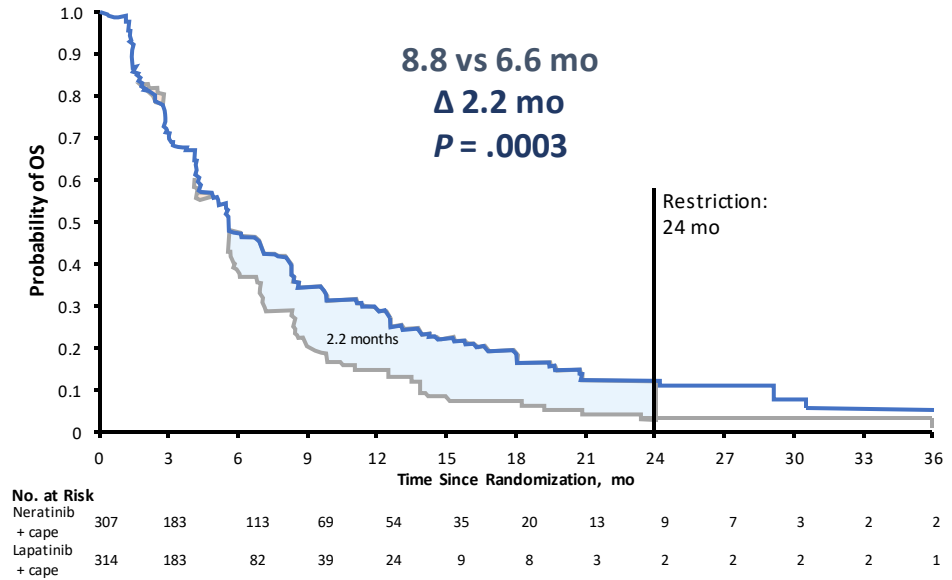
Neratinib: A pan-HER kinase inhibitor



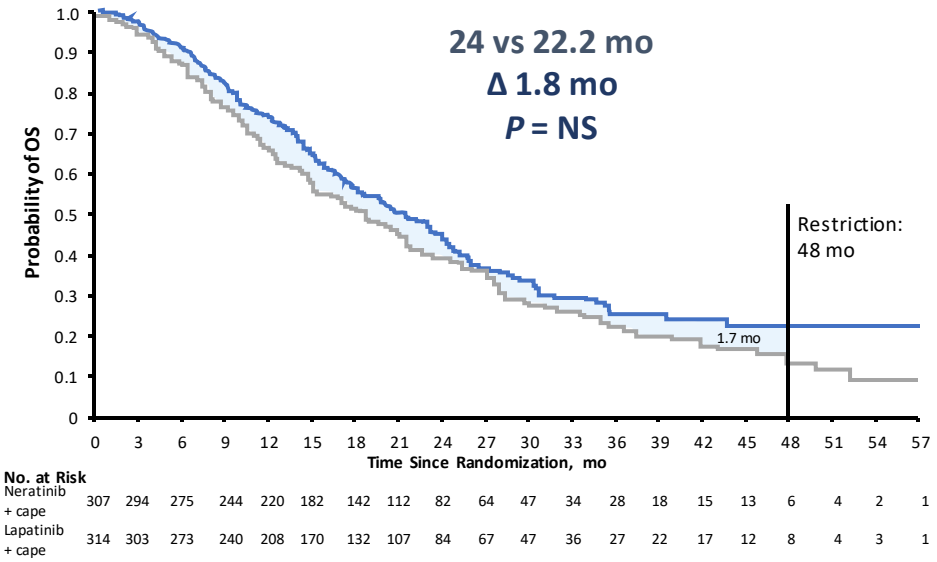
Paranjpe R, et al. *Ann Pharm.* 2019;53:612-620.

NALA trial: Neratinib (vs lapatinib) + capecitabine

Centrally Confirmed PFS



Overall Survival



- 1-yr PFS: **29%** vs 15%
- ORR: **33%** vs 27% (*P* = .1201)

Approved by the FDA in February 2020 for patients with HER2+ MBC who have received ≥2 prior HER2-directed regimens

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

NALA trial: Treatment-emergent adverse events (TEAEs)

Safety Outcome	Neratinib + Capecitabine (n = 303)		Lapatinib + Capecitabine (n = 311)	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Any TEAE	100	61	99	60
Diarrhea	83	24	66	13
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2

Treatment discontinuations due to TEAE: N+C = 10.9% vs. L+ C = 14.5%

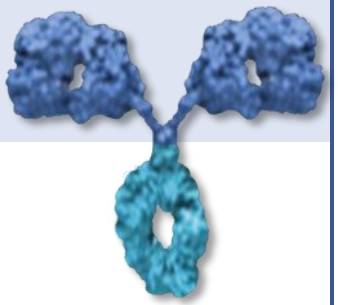
Saura C, et al. *J Clin Oncol*. 2020;38:3138-3149.

Margetuximab

Trastuzumab

Fab

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



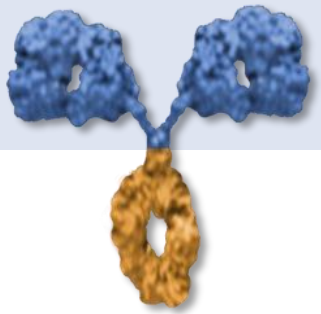
Fc

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

Margetuximab[1,2]

Fab

- Same specificity and affinity
- Similarly disrupts signaling



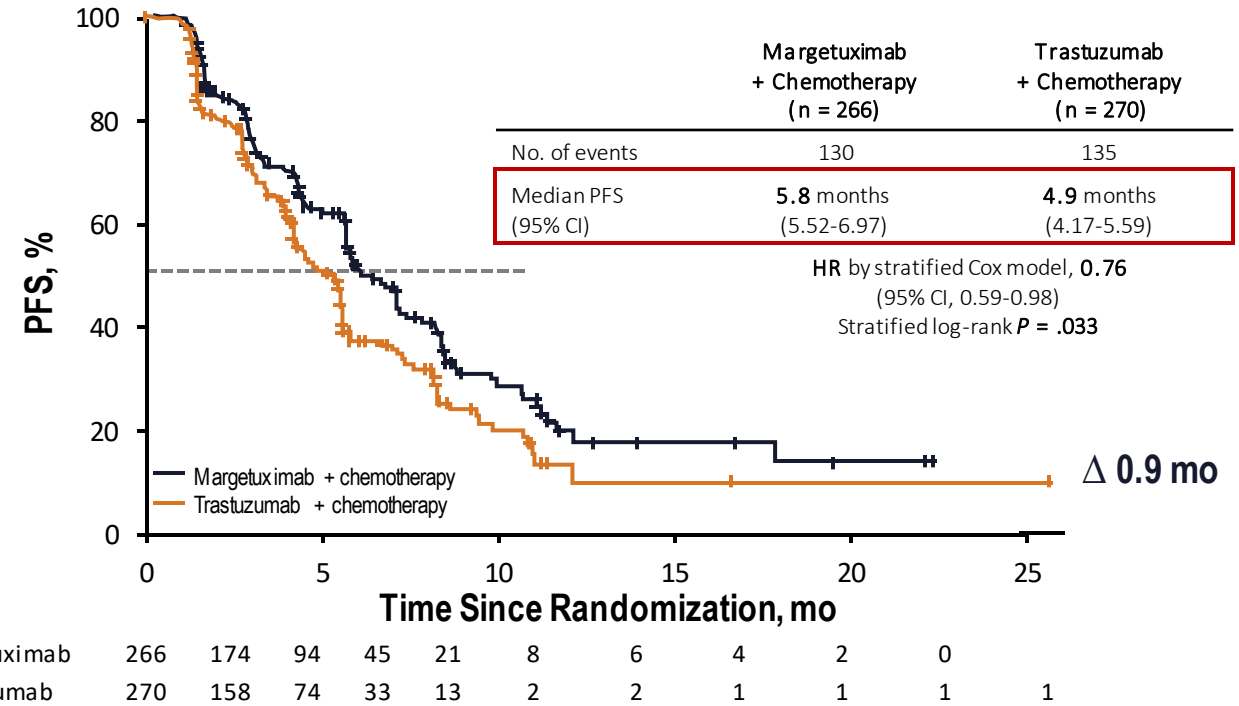
Fc engineering:

- ⬆ Affinity for activating Fcγ RIIIA (**CD16A**)
- ⬇ Affinity for inhibitory Fcγ RIIB (**CD32B**)

Nordstrom JL, et al. *Breast Cancer Res*. 2011;13:R123; Stavenhagen JB, et al. *Cancer Res*. 2007;67:8882-8890.

SOPHIA trial: Margetuximab (vs trastuzumab) + chemotherapy

24% Risk Reduction of Disease Progression



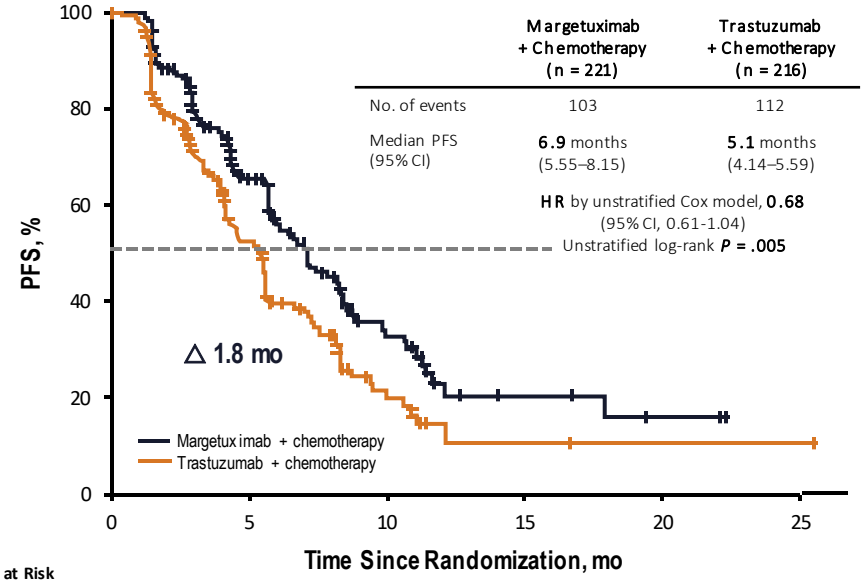
Approved by the FDA in December 2020 for patients with HER2+ MBC who have received ≥2 prior HER2-directed regimens

Rugo H, et al. SABCS 2019. Abstract GS1-02.

SOPHIA trial: Exploratory analysis by genotype

CD16A FF or FV, n = 437 of 506 Genotyped (86%)

PFS

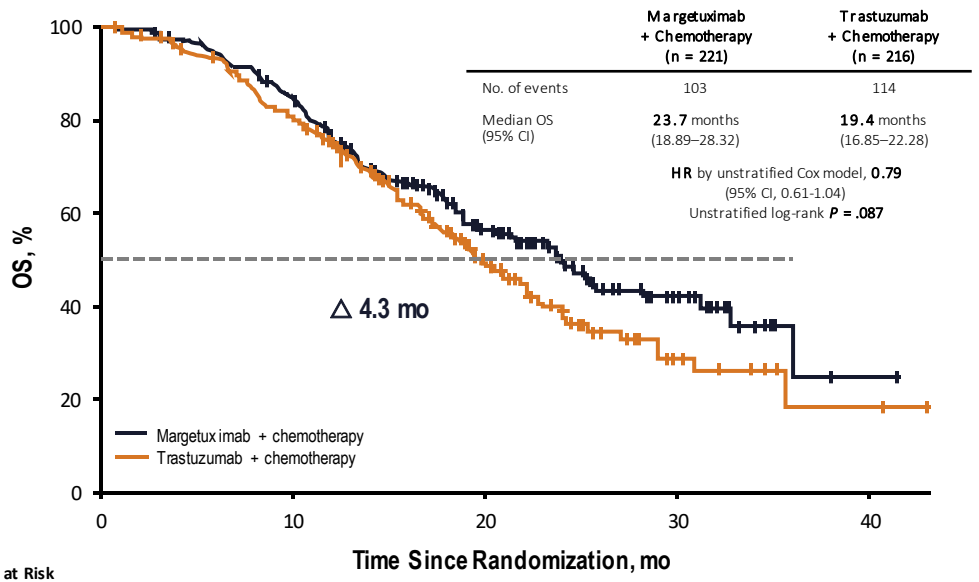


	Margetuximab + Chemotherapy (n = 221)	Trastuzumab + Chemotherapy (n = 216)
No. of events	103	112
Median PFS (95% CI)	**6.9** months (5.55–8.15)	**5.1** months (4.14–5.59)

HR by unstratified Cox model, **0.68** (95% CI, 0.61-1.04)
Unstratified log-rank ***P*** **= .005**

No. at Risk											
Margetuximab	221	157	84	42	21	8	6	4	2	0	
Trastuzumab	216	129	62	30	11	2	2	1	1	1	1

OS



	Margetuximab + Chemotherapy (n = 221)	Trastuzumab + Chemotherapy (n = 216)
No. of events	103	114
Median OS (95% CI)	**23.7** months (18.89–28.32)	**19.4** months (16.85–22.28)

HR by unstratified Cox model, **0.79** (95% CI, 0.61-1.04)
Unstratified log-rank ***P*** **= .087**

No. at Risk																						
Margetuximab	221	219	212	204	196	181	157	135	111	91	68	55	42	31	27	19	13	8	2	1	1	0
Trastuzumab	216	210	201	192	176	165	145	123	98	81	57	43	30	21	16	11	9	6	2	2	2	1	0

1. Rugo HS, et al. ASCO 2019. Abstract 1000; 2. Rugo HS, et al. SABCS 2019. Abstract GS1-02.

Trastuzumab + chemotherapy

Later lines: multiple available options of trastuzumab + chemotherapy (platinum salts, vinorelbine, gemcitabine, liposomal anthracyclines, more) or endocrine treatment + chemotherapy

In modern era, all achieve 15-30% ORR and 4-6 months of median PFS

Two main rules:

MAINTAIN HER2 BLOCKADE IN LATER LINES

CONSIDER ENROLLMENT IN CLINICAL TRIALS

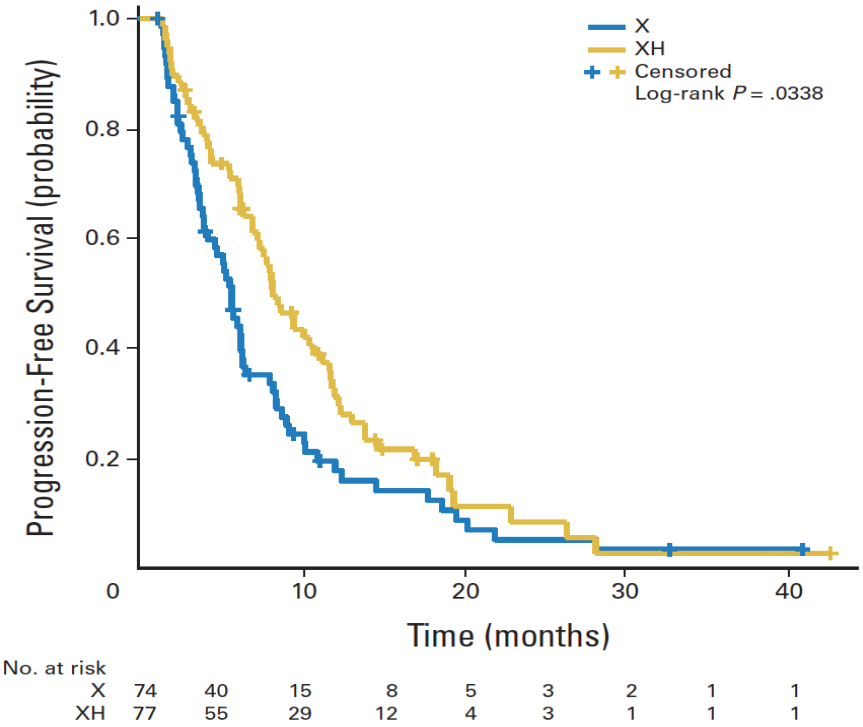
Maintain HER2 blockade in later lines

Maintaining HER2 blockade improves outcomes in patients progressing to prior trastuzumab-containing treatments

Capecitabine + trastuzumab vs capecitabine

- PFS 8.2 months vs 5.2 months (*P* = .03)
- ORR 48% vs 27% (*P* = .01)

Patients not pretreated with pertuzumab, ADCs, or TKIs

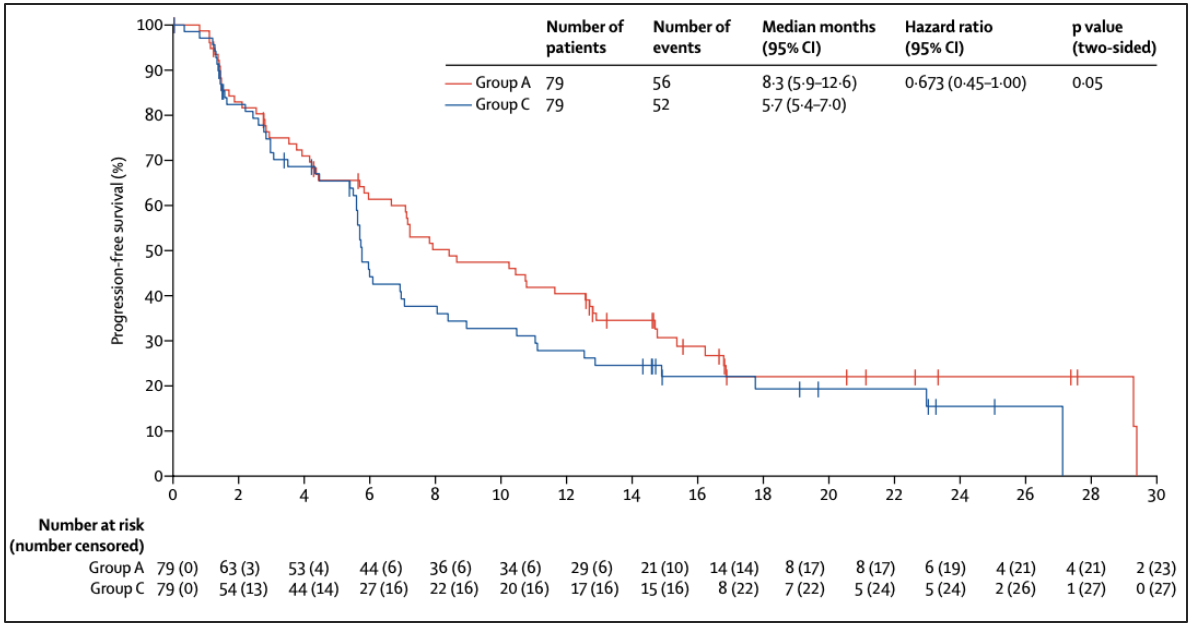


von Minckwitz G, et al. *J Clin Oncol*. 2009;27:1999-2006; Waddell T, et al. *Br J Cancer*. 2011;104:1675-1679; Petrelli F, et al. *Clin Breast Cancer*. 2013;13:81-87.

monarcHER: Abemaciclib + trastuzumab + fulvestrant

About 50% of HER2+ MBC coexpress HR (triple positive). Could CDK4/6 inhibition improve outcomes after progression to several lines of treatment?

In a randomized phase II trial (n = 237), abemaciclib + trastuzumab + fulvestrant outperformed chemo + trastuzumab in patients with triple-positive MBC (mPFS 8.3 vs 5.7 months)



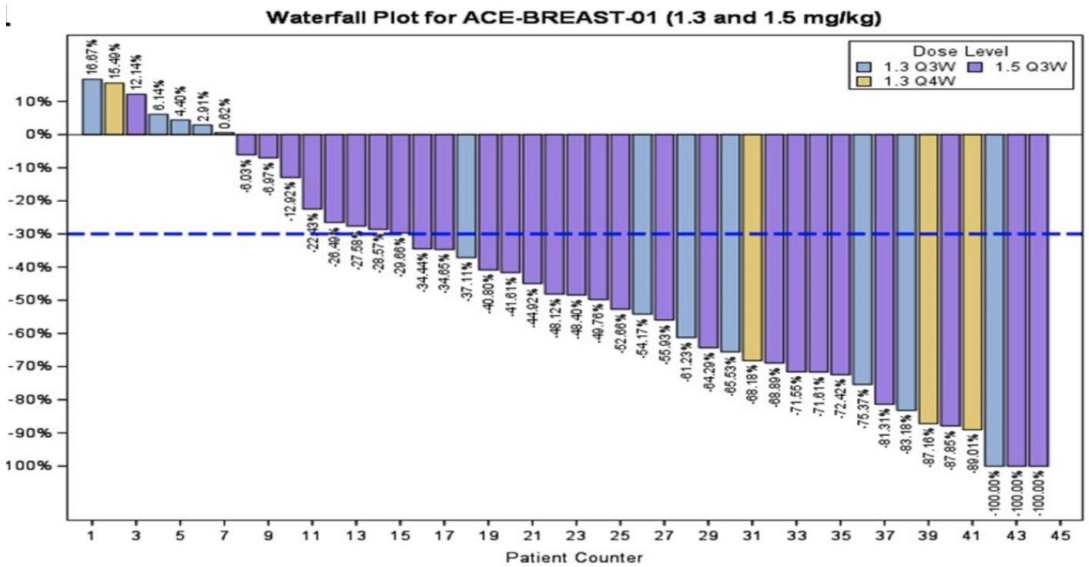
Tolaney SM, et al. *Lancet Oncol*. 2020;21:763-775.

ARX788

Novel anti-HER2 ADC, consisting of trastuzumab site-specifically conjugated to the tubulin inhibitor AS269

Phase I trial: ORR 50-66% among 108 heavily pretreated patients with HER2+ MBC

Main TRAEs: ocular AEs, interstitial lung disease (34%), transaminitis



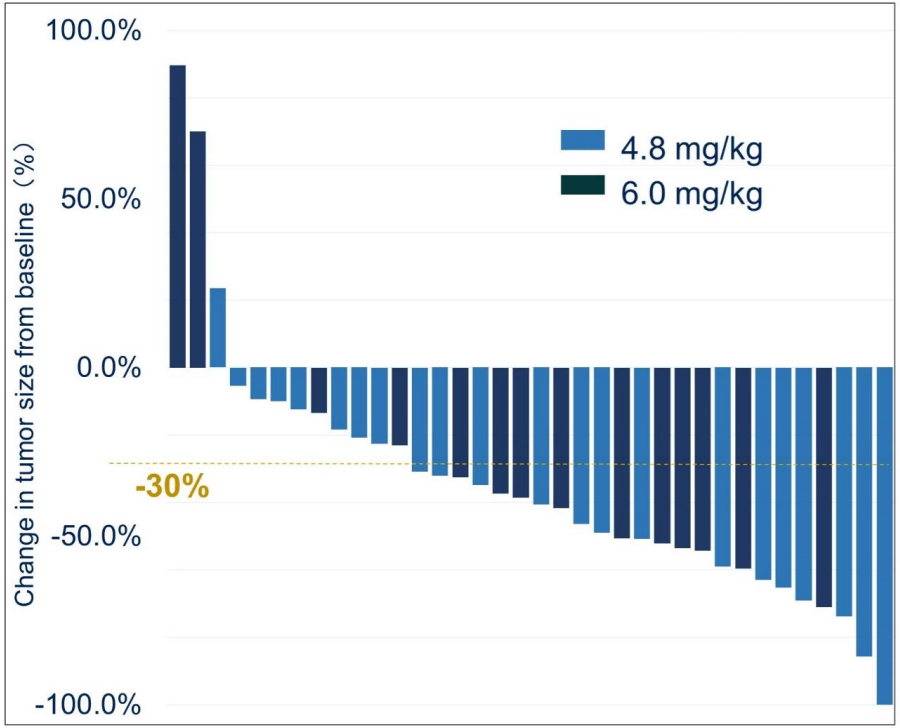
Hurvitz SA, et al. ASCO 2021. Abstract 1038.

A166

Novel anti-HER2 ADC, consisting of trastuzumab site-specifically conjugated to the antimicrotubule agent Duo-5

Phase I trial: ORR 60-70% among 36 heavily pretreated patients with HER2+ MBC

Main TRAEs: ocular AEs, peripheral neuropathy, electrolyte imbalances



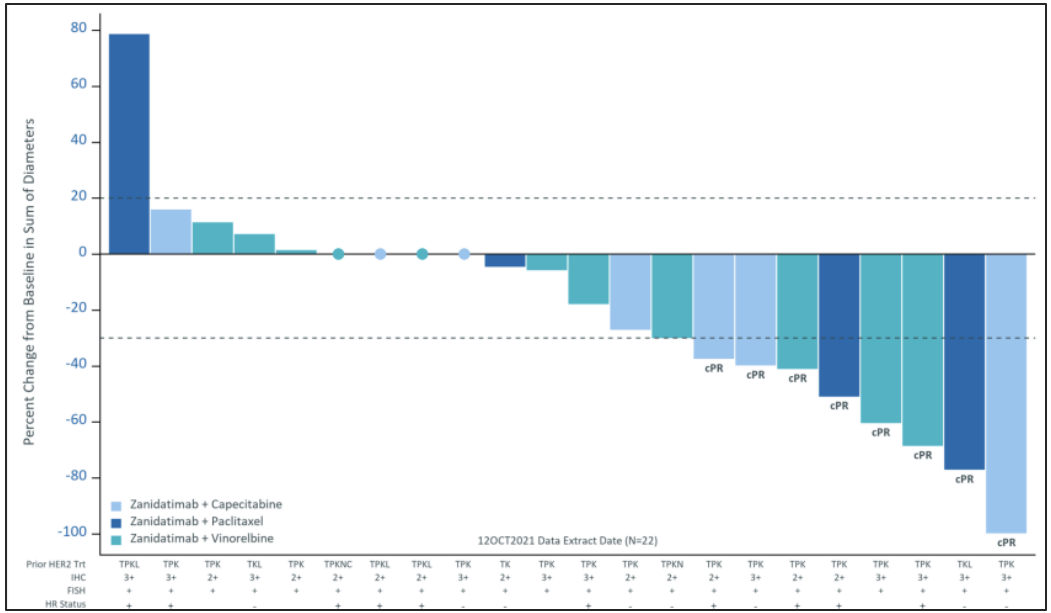
Hu X, et al. ASCO 2021. Abstract 1037.

Zanidatamab (ZW25) + chemotherapy

HER2-targeted bispecific antibody targeting both trastuzumab- and pertuzumab-binding domains

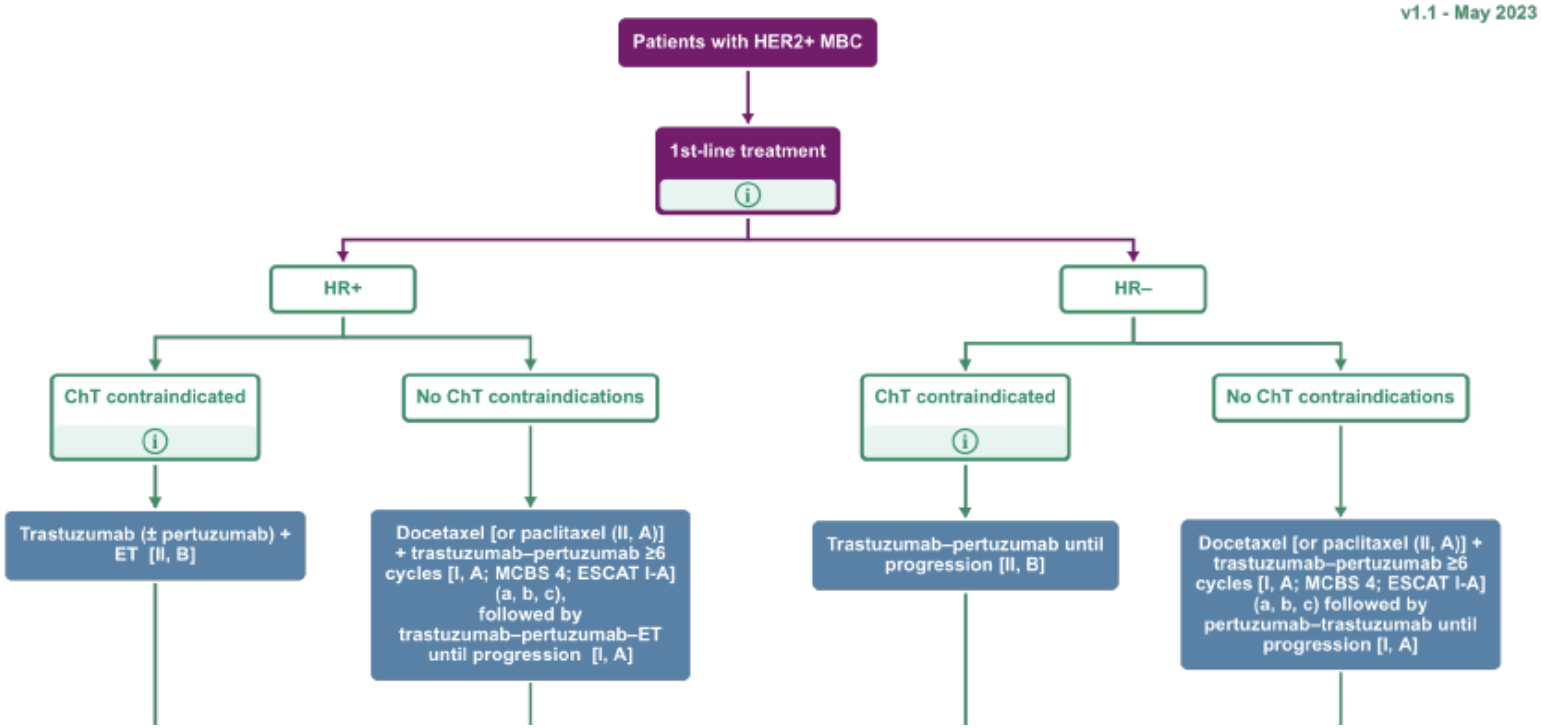
Phase I trial: ORR 36% and median PFS 7.3 months among 24 pretreated patients with HER2+ MBC

Main TRAEs: diarrhea, infusion-related reactions

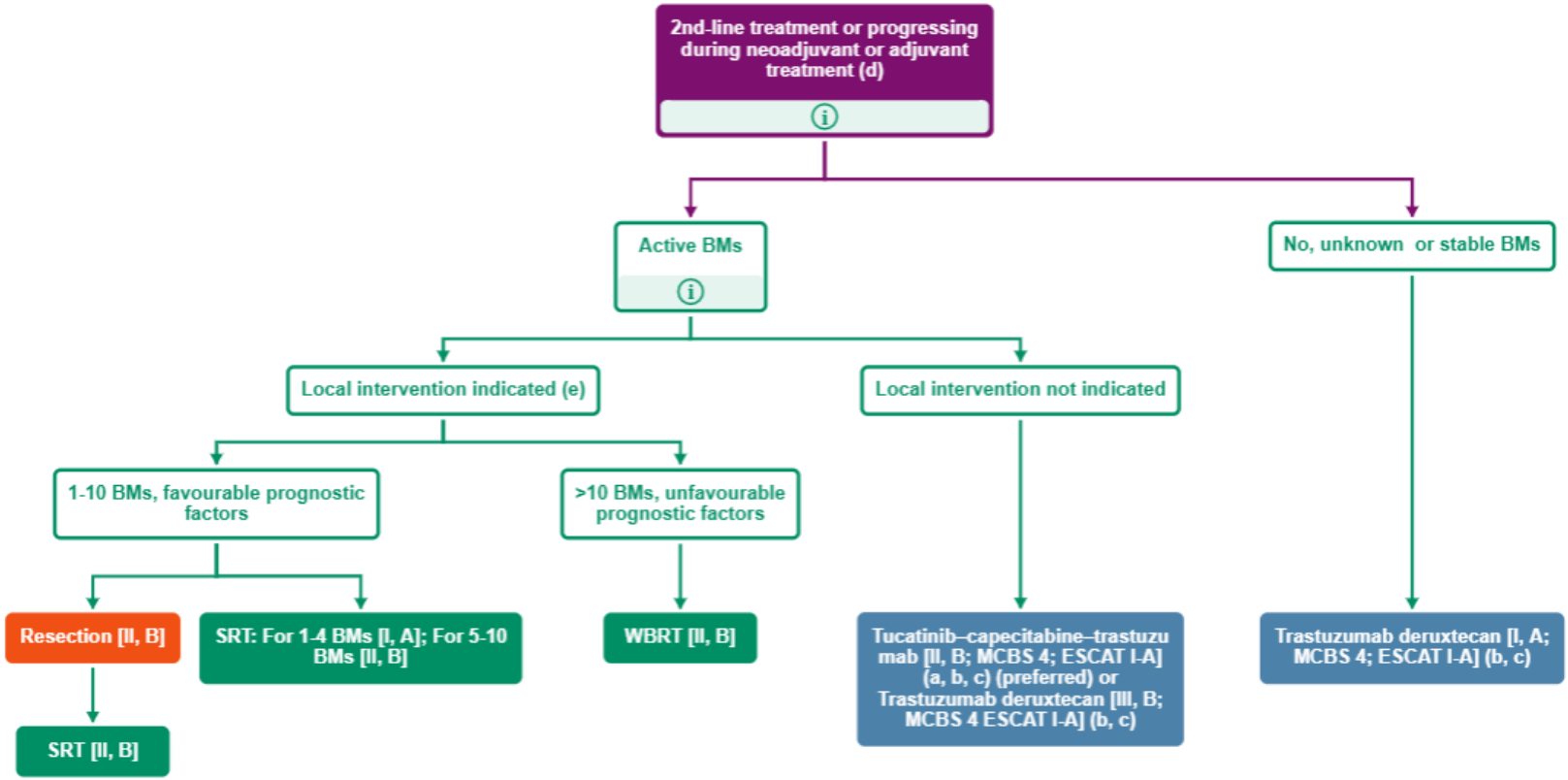


Hurvitz SA, et al. SABCS 2021. Abstract 182.

ESMO Living Guidelines V1.1 2023

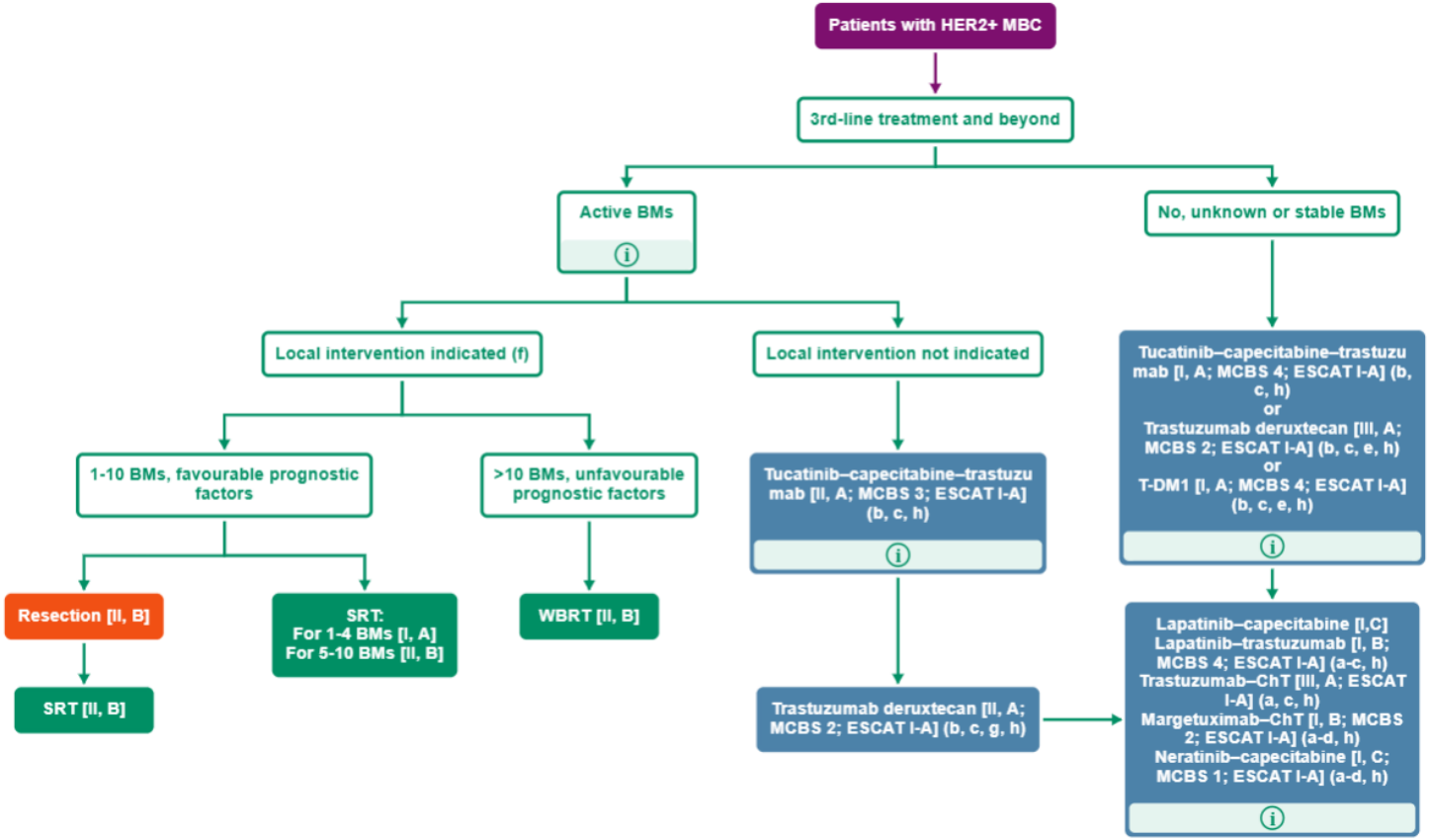


ESMO Living Guidelines V1.1 2023



ESMO Living Guidelines V1.1 2023

New Slide



Conclusions

A rapidly enlarging arsenal of anti-HER2 agents is available for the second-line-and-beyond treatment of HER2+ MBC. However, we have no efficacy data after progression to T-DXd

The currently preferred third-line options are **T-DM1** or the **tucatinib triplet**, with the choice depending on patient- and disease-related factors

Neratinib (+ cape), margetuximab (+ chemo), or multiple combinations of trastuzumab and chemotherapy are further FDA-approved options for later lines of treatment

Despite no data in the modern era, it is reasonable to keep HER2 blockade across all lines of treatment

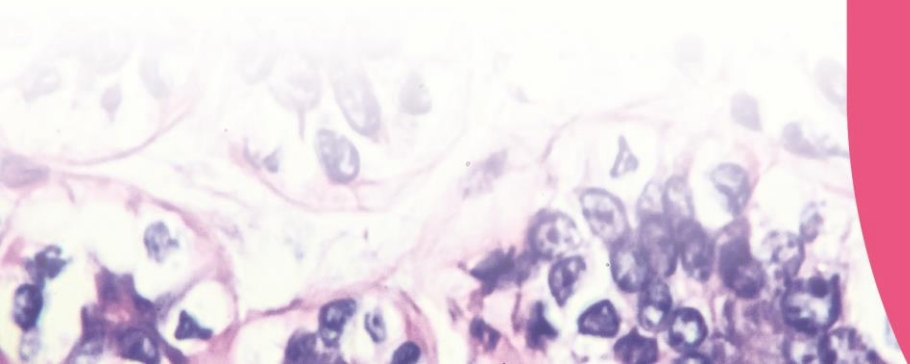
Multiple highly active agents in early- and late-phase testing. Always consider enrollment in clinical trials!

Thank you to my team!

giuseppe.curigliano@ieo.it

Global Breast Cancer Academy

Q&A



APTITUDE HEALTH

Objectives

Understand major advances in early lines of treatment for HER2+ mBC

Learn about potential treatment options after second line treatment for HER2+ mBC

Understand changes in HER2 expression during treatment with HER2-targeted agents

Gain insights into the care of HER2+ mBC patients with CNS metastases

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Explore current and future sequencing strategies in HER2+ mBC

Global Breast Cancer Academy

Overcoming resistance to HER2-directed therapies

Sara Tolaney

APTITUDE HEALTH

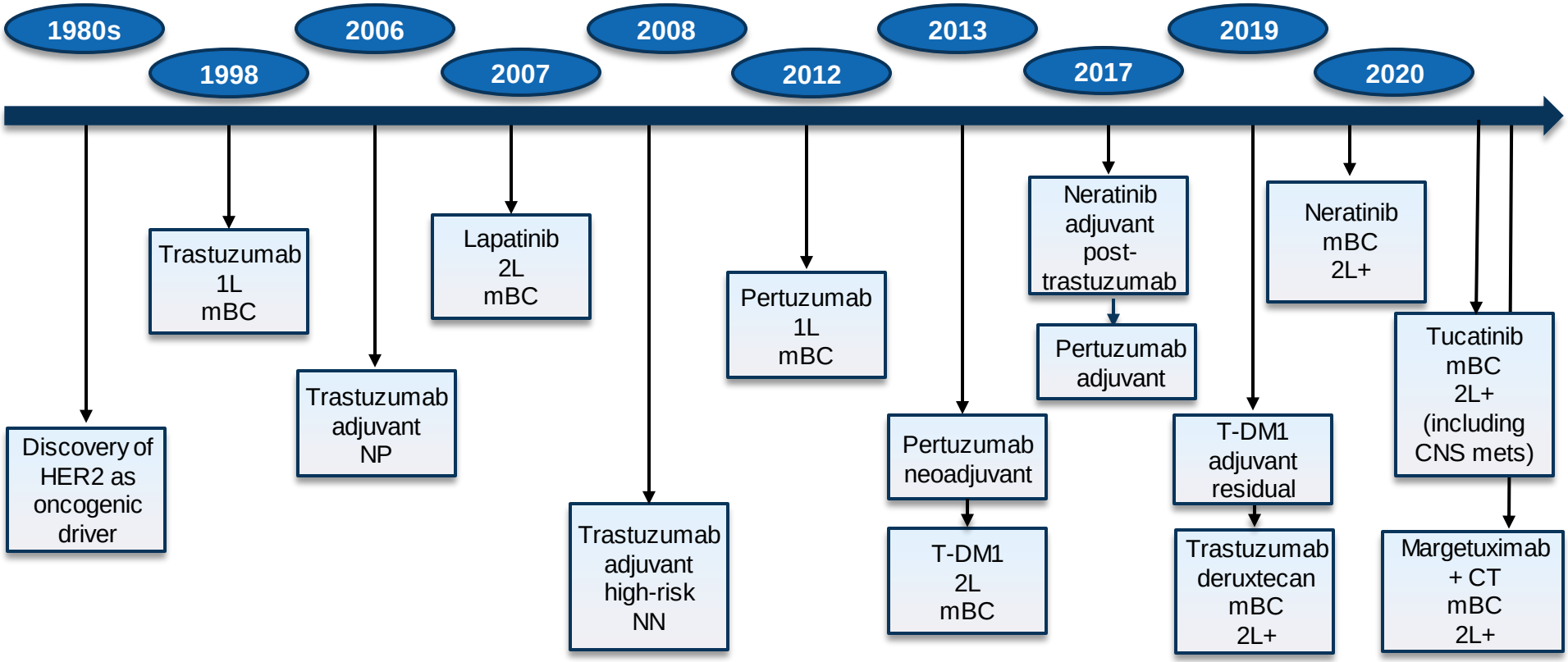
Overcoming Resistance to HER2-Directed Therapies

Sara M. Tolaney, MD, MPH

HARVARD MEDICAL SCHOOL

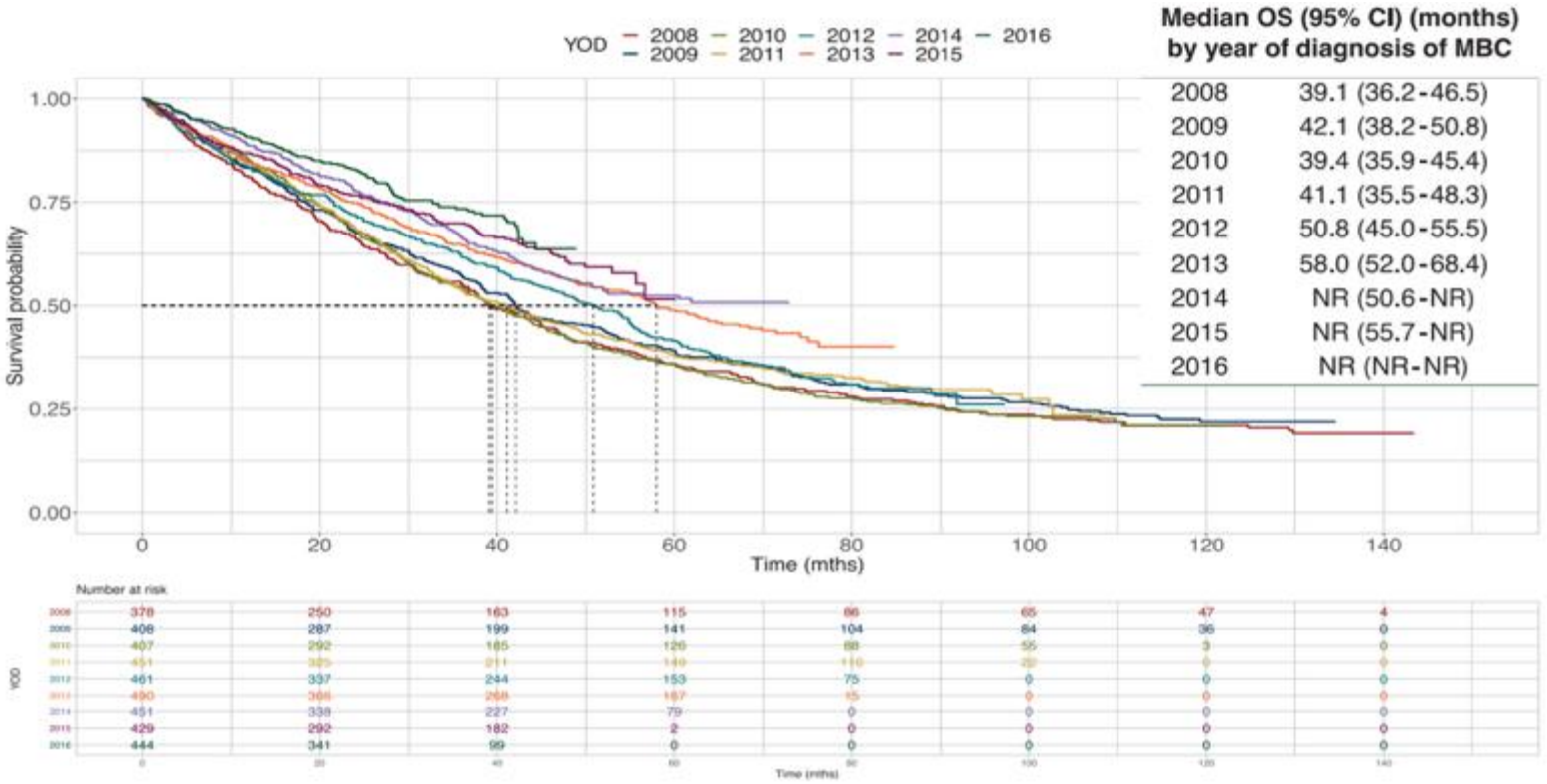
Dana-Farber Cancer Institute

HER2-Targeted Therapies: Timeline of Approvals



Overall Survival in HER2+ mBC by Year of Diagnosis

ESME-MBC Registry

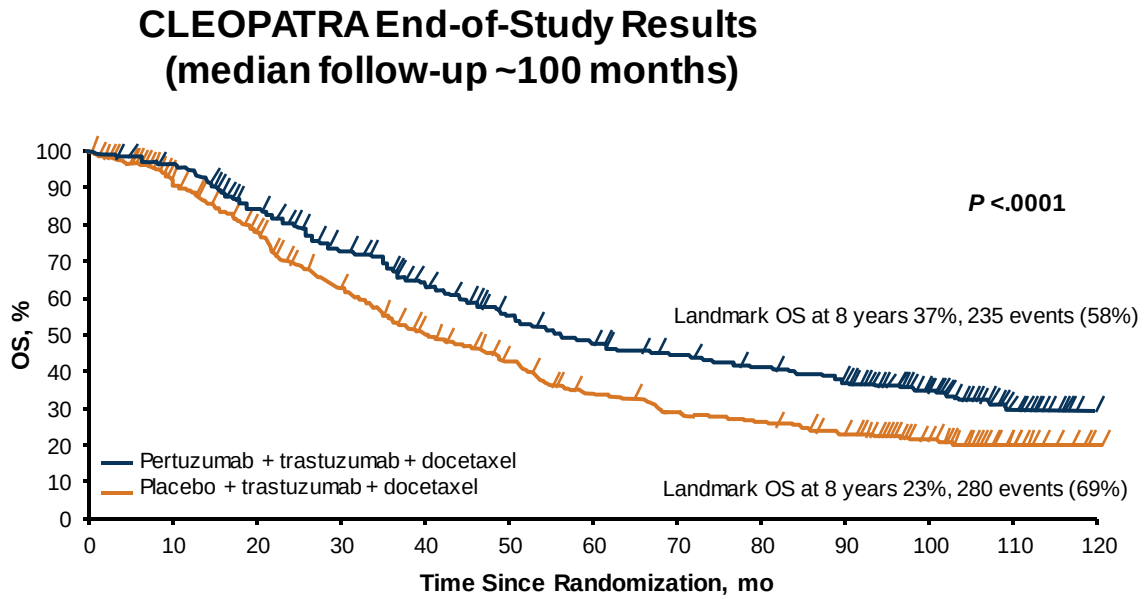


Median OS (95% CI) (months) by year of diagnosis of MBC

2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

Grinda T, et al. *ESMO Open*. 2021;6:100114.

Overall Survival in Patients With Advanced *HER2*+ mBC



Median OS
with TP-based initial therapy:
57.1 months

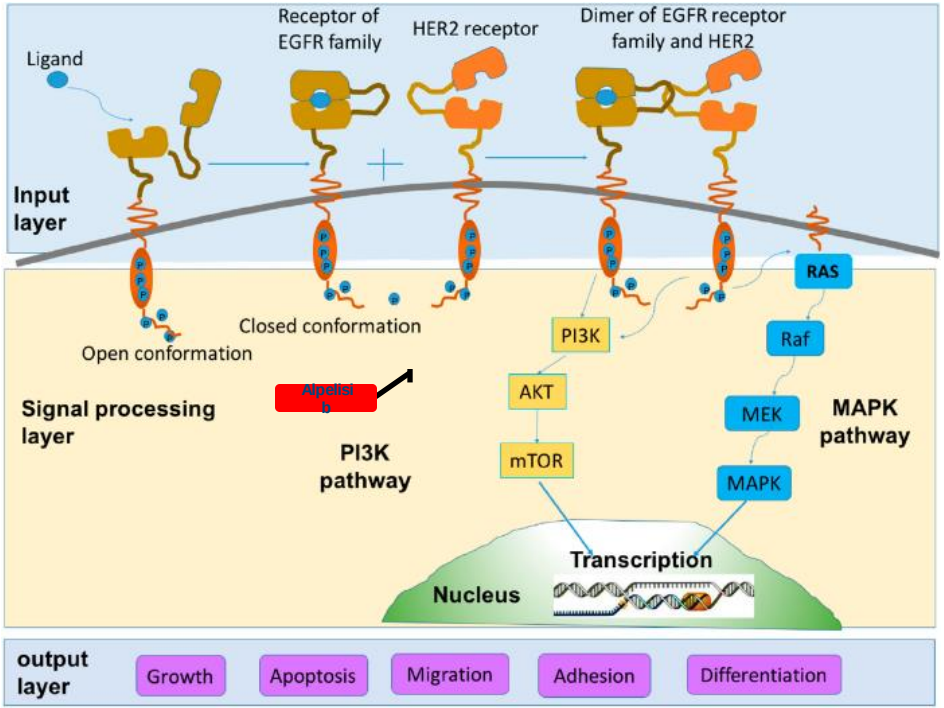
No. at Risk (number censored)

Pertuzumab	402 (0)	371 (14)	318 (23)	269 (32)	228 (41)	188 (48)	165 (50)	150 (54)	137 (56)	120 (59)	71 (102)	20 (147)	0 (167)
Placebo	406 (0)	350 (19)	289 (30)	230 (36)	181 (41)	149 (48)	115 (52)	96 (53)	88 (53)	75 (57)	44 (84)	11 (115)	1 (125)

Swain SM, et al. *Lancet Oncol*. 2020;21:519-530.

PI3K in HER2+ Breast Cancer

- HER2 promotes the proliferation, survival, and invasiveness of cancer cells via PI3K and MAPK signaling pathways[1-3]
- *PIK3CA* alterations occur in up to 40% of HER2+ breast cancers[4,5]
  - PI3K pathway activation, which frequently results from *PIK3CA* gain-of-function mutations, is associated with poorer response and resistance to trastuzumab[6-10]

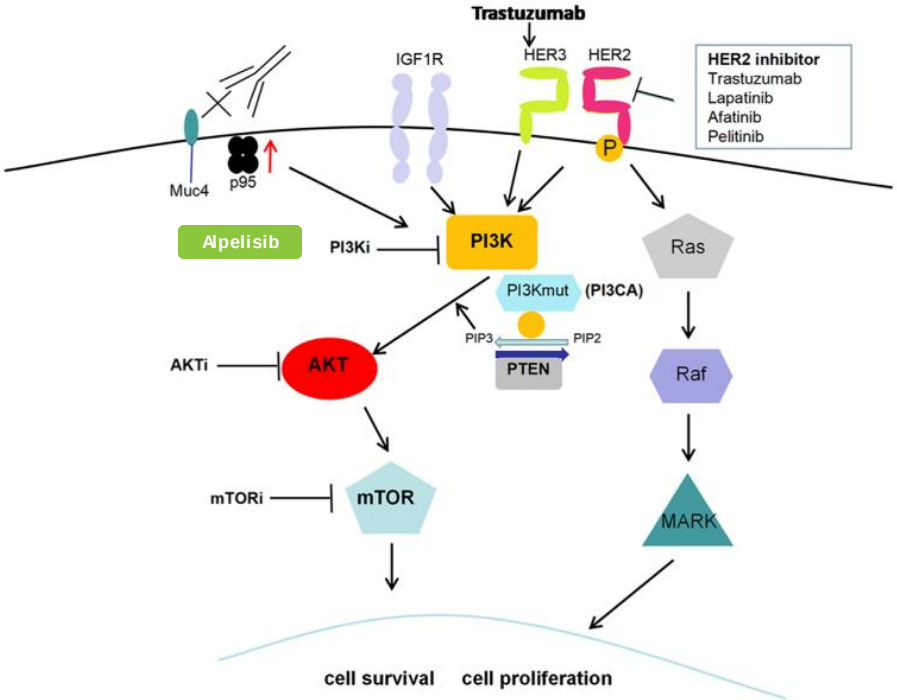


Reprinted from Lv Q, et al. *Int J Mol Sci*. 2016;17(12):2095. https://creativecommons.org/licenses/by/4.0/[11]

1. Luque-Cabal M, et al. *Clin Med Insights Oncol*. 2016;10(suppl 1):21-30; 2. Wang J, Xu B. *Signal Transduction and Targeted Therapy*. 2019;4:34; 3. Turke AB, et al. *Cancer Res*. 2012;72(13):3228-3237; 4. Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70; 5. Razavi P, et al. *Cancer Cell*. 2018;34(3):427-438.e6; 6. Berns K, et al. *Cancer Cell*. 2007;12:395-402; 7. Kataoka Y, et al. *Ann Oncol*. 2010;21(2):255-262; 8. O'Brien N, et al. *Clin Cancer Res*. 2014;20(13):3507-3520; 9. Esteva F, et al. *Am J Pathol*. 2010;177(4):1647-1656; 10. Razis E, et al. *Breast Cancer Res Treat*. 2011;128(2):447-456; 11. Lv Q, et al. *Int J Mol Sci*. 2016;17(12):2095.

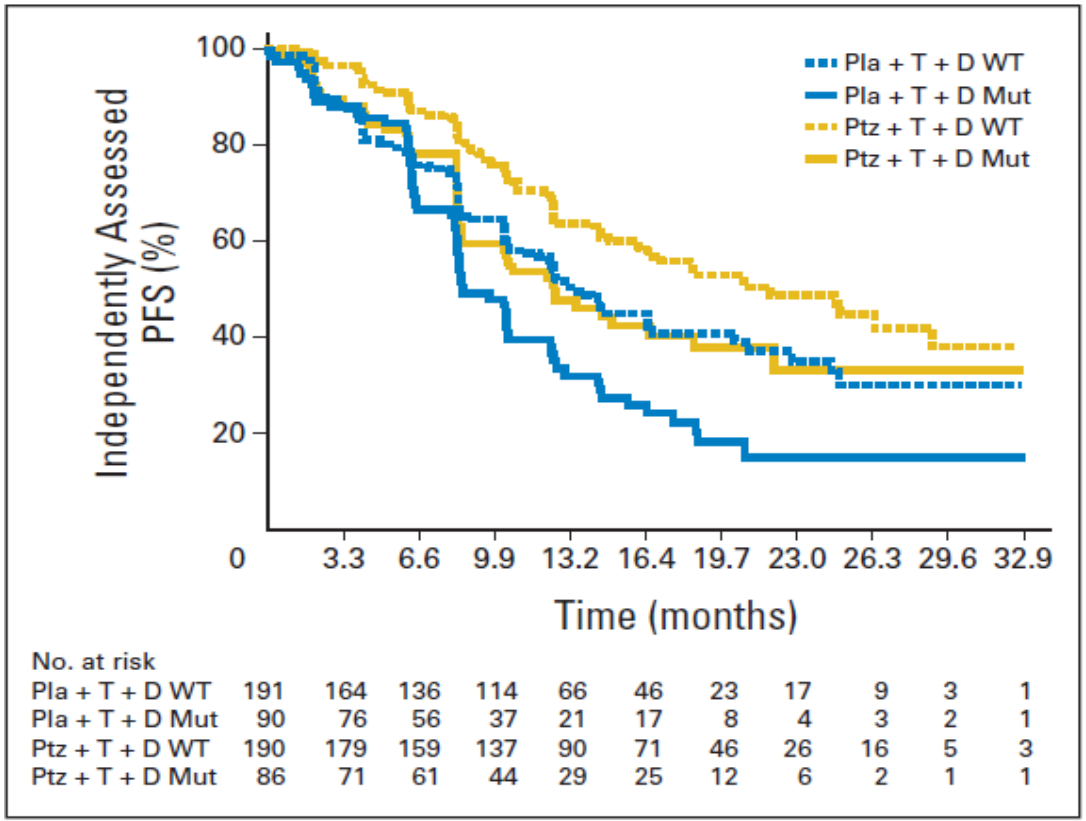
Resistance in HER2+ Disease Due to PI3K Activation

- Abnormal activation of the PI3K/AKT/mTOR pathway is associated with resistance to anti-HER2 therapy
  - *PIK3CA* mutations promote anti-HER2 therapy resistance through p110α activation
  - Treatment with trastuzumab increases HER3 expression, which subsequently leads to resistance to anti-HER2 therapy via PI3K/AKT pathway activation



ABC, advanced breast cancer; AKT(i), protein kinase B (inhibitor); HER2, human epidermal growth factor receptor 2; mTOR, mechanistic target of rapamycin; PI3K(i), phosphoinositide 3-kinase (inhibitor).

Outcomes in CLEOPATRA by *PI3K*m Status



Docetaxel 75-100 mg Q3W.

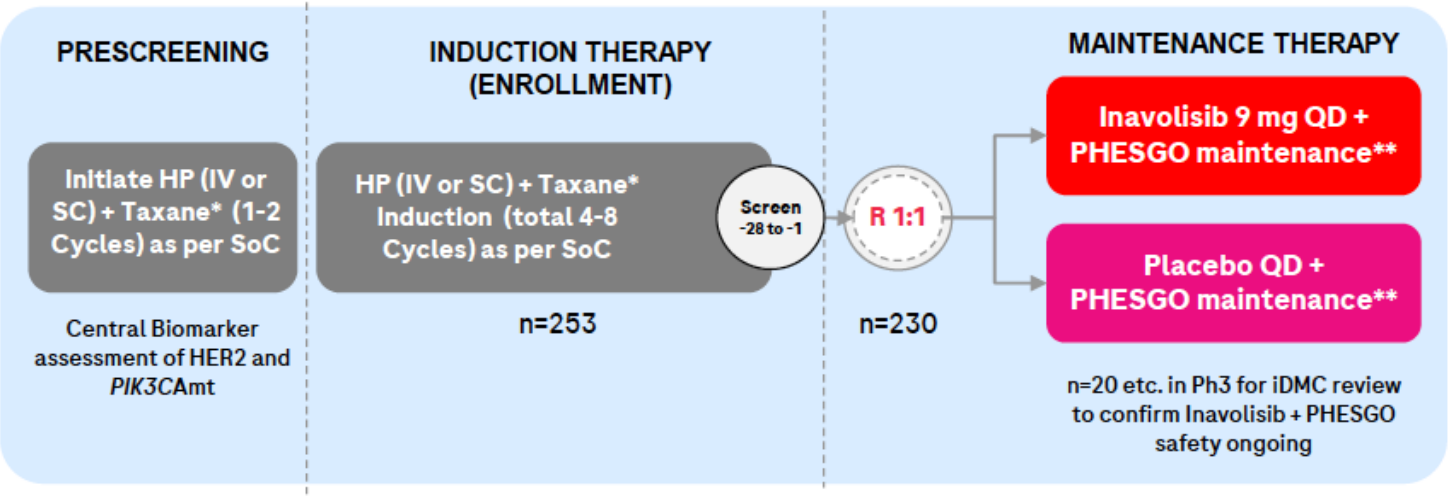
1. Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119; 2. Baselga J, et al. *J Clin Oncol.* 2014;32(33):3753-3761.

INAVO122 (WO44263):
Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of inavolisib + Phesgo vs. placebo + Phesgo after induction therapy in patients with *PIK3CA*-mutated HER2-positive locally advanced or mBC

Roche

Inclusion criteria
- HER2+ by tissue (central)
- *PIK3CA*mut by tissue (central)
- Dx of metastatic disease >6 months from completion of prior neo/adjuvant therapy
- Treated with T-DXd who discontinued after 4-8 cycles due to reasons different than disease progression

Stratification factors
- Response to induction (CR/PR vs. SD)
- HR+ vs HR-
- De novo vs. relapsed disease



*Docetaxel, paclitaxel or nab-paclitaxel upon investigators choice as per SoC
**Concomitant ET after chemo induction allowed for HR+ pts upon investigator choice as per SoC (Tamoxifen, aromatase inhibitors or fulvestrant) ± OFS [ovarian function suppression]

Primary Endpoint: PFS per investigator

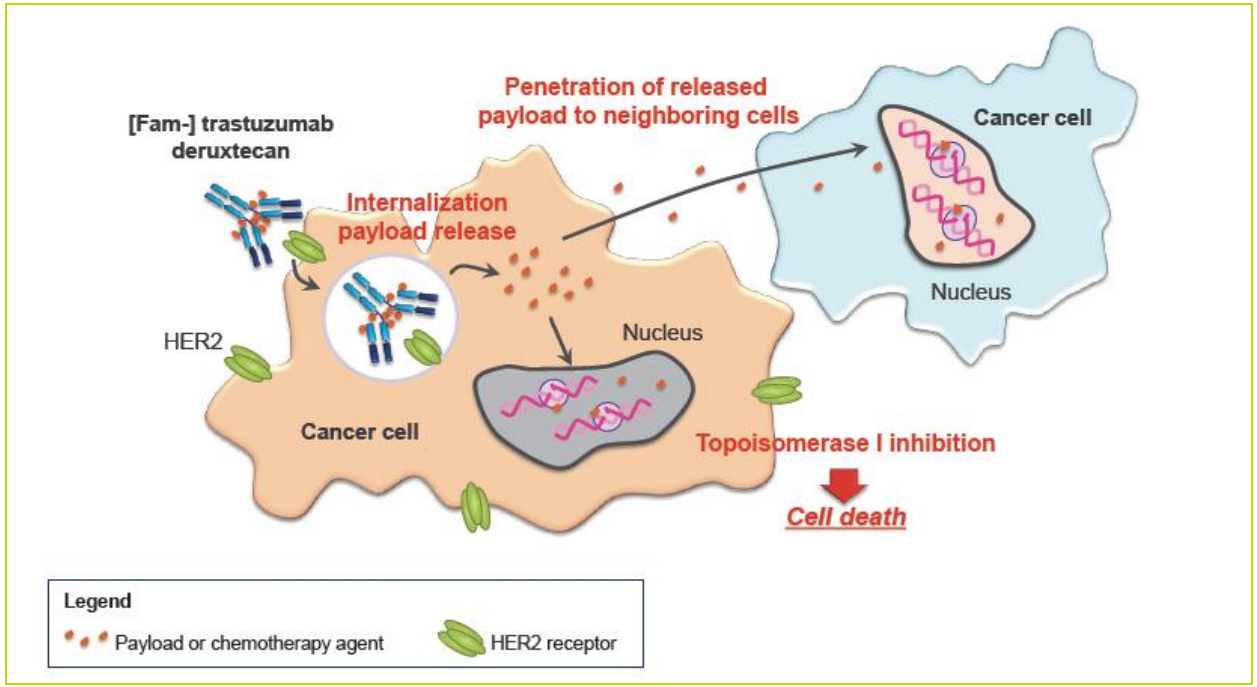
Key secondary Endpoint: OS

Secondary Endpoints:
- ORR, DOR, CBR, PFS2, safety, PK, PROs

Exploratory Endpoints:
- Changes in disease/ treatment-related symptoms, WPAI scores, EQ-5D-5L questionnaire, PRO-CTCAE, FACT-G
- Biomarkers associated with response to study treatment

HR+ BC INAVOLISIB

T-DXd Can Overcome HER2 Heterogeneity via Bystander Effect



ADCC, antibody-dependent cellular cytotoxicity; HER2, human epidermal growth factor receptor 2; Topo-1, topoisomerase 1.

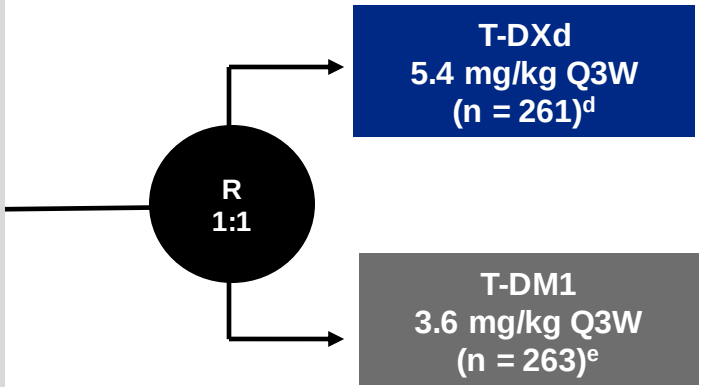
1. Ogitani Y, et al. *Cancer Sci*. 2016;107:1039-1046; 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097-5108.

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

An open-label, multicenter study (NCT03529110)

Patients (N = 524)
- Unresectable or metastatic HER2+[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

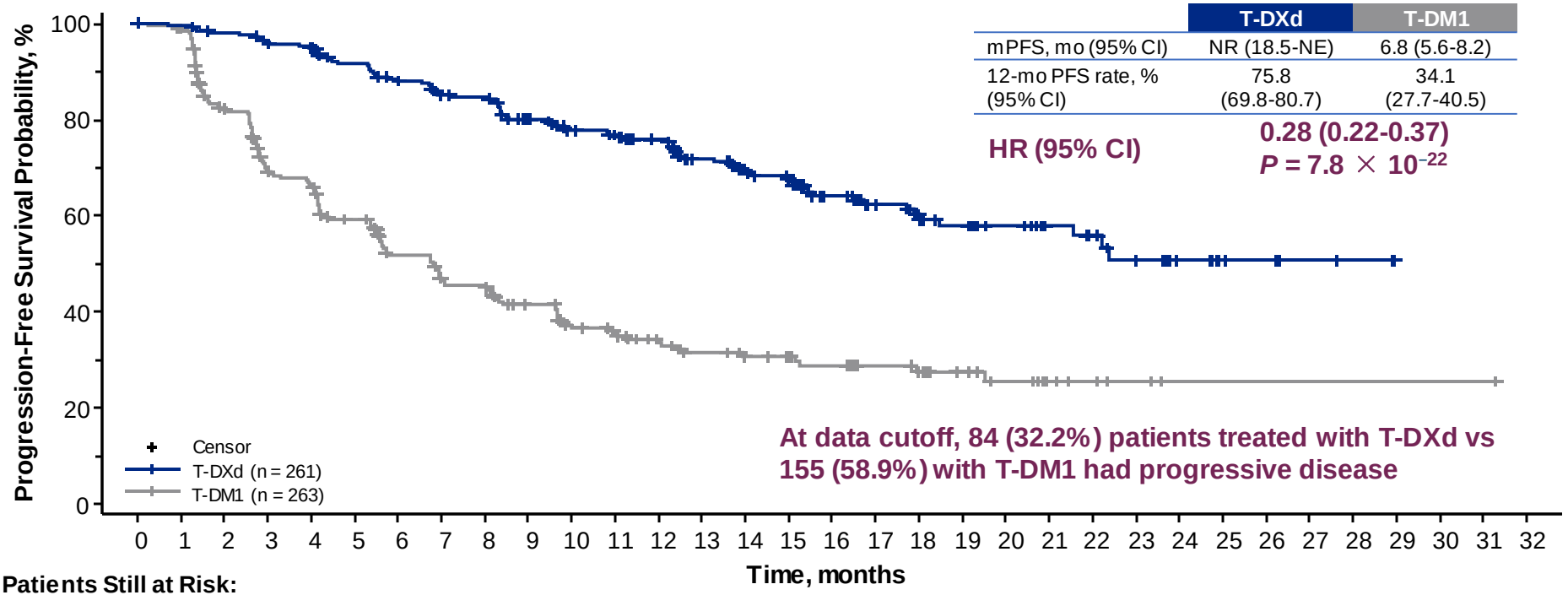
- At the time of data cutoff (May 21, 2021), 125 (48.6%) T-DXd patients and 214 (82.0%) T-DM1 patients had discontinued treatment
- Median follow-up was 15.9 months
- BMs were measured at baseline by CT or MRI and lesions were monitored throughout the study

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]Four patients were randomly assigned but not treated. [e]Two patients were randomly assigned but not treated.

Cortés J, et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03: 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 vs 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

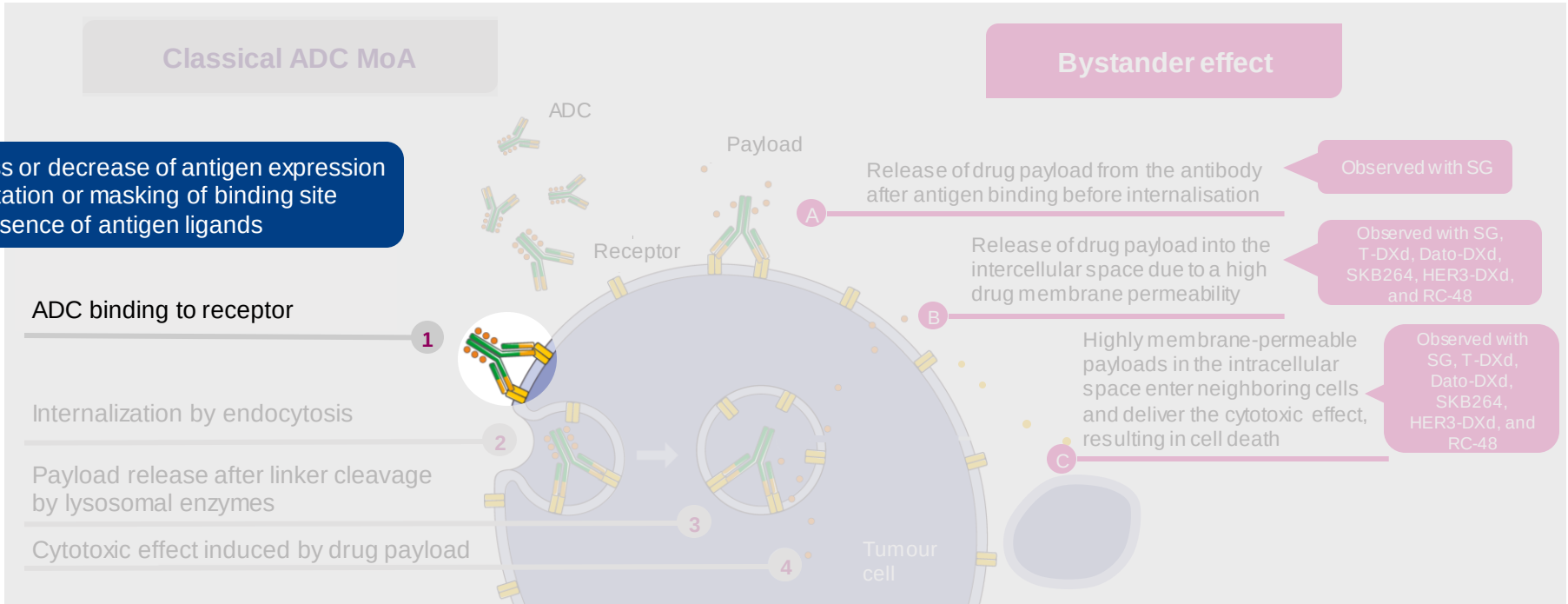
BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

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

The Complexity of ADCs Provides Many Opportunities for Resistance to Emerge: Antigen Expression[1,2]

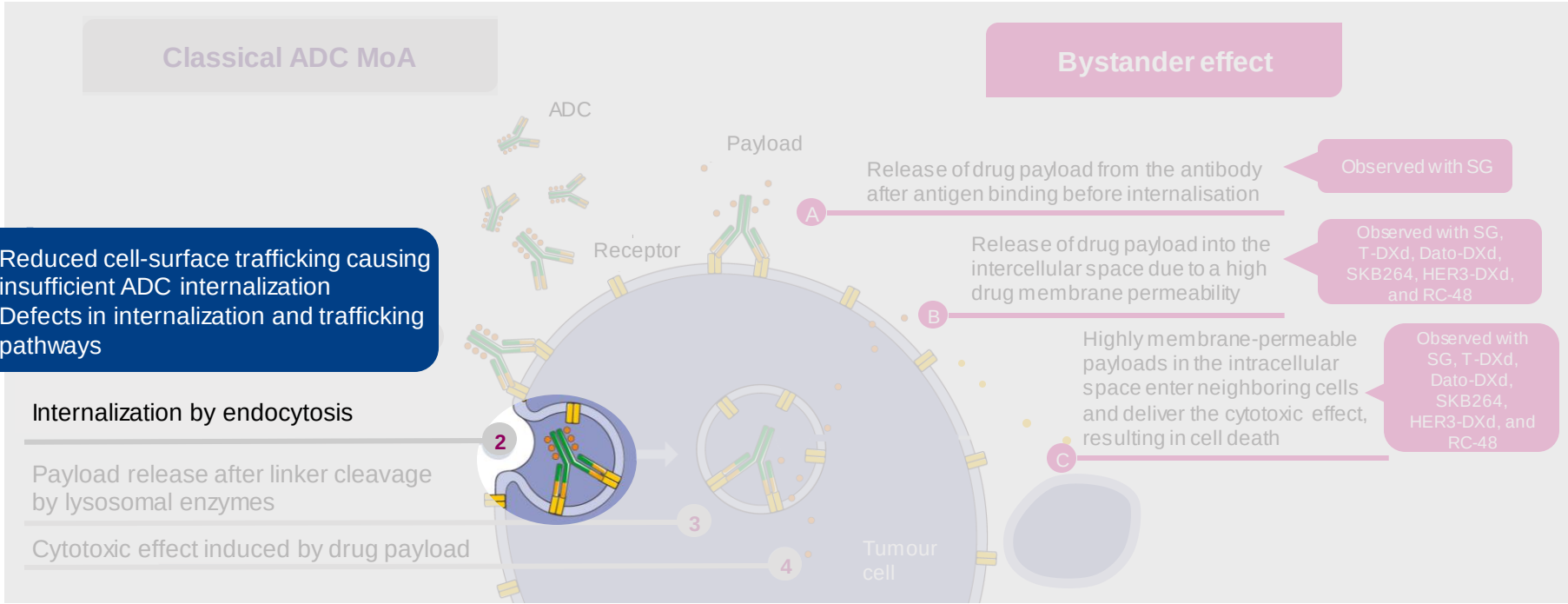
- Loss or decrease of antigen expression
- Mutation or masking of binding site
- Presence of antigen ligands



ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; HER3, human epidermal growth factor 3; MoA, mechanism of action; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.

1. Hunter FW, et al. *Br J Cancer.* 2020;122:603-612; 2. Rinnerthaler G, et al. *Int J Mol Sci.* 2019;20:1115.

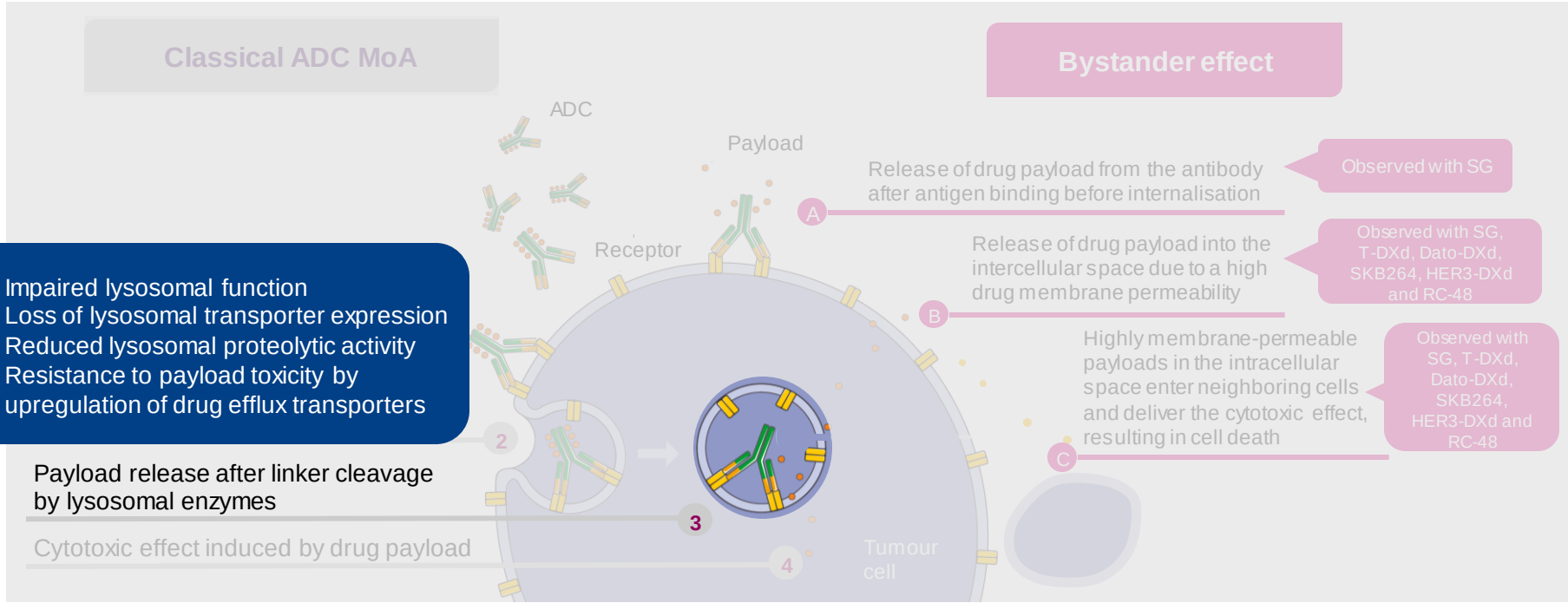
The Complexity of ADCs Provides Many Opportunities for Resistance to Emerge: Internalization and Linker Cleavage[1,2]



ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; HER3, human epidermal growth factor 3; MoA, mechanism of action; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.

1. Hunter FW, et al. *Br J Cancer.* 2020;122:603-612; 2. Rinnerthaler G, et al. *Int J Mol Sci.* 2019;20:1115.

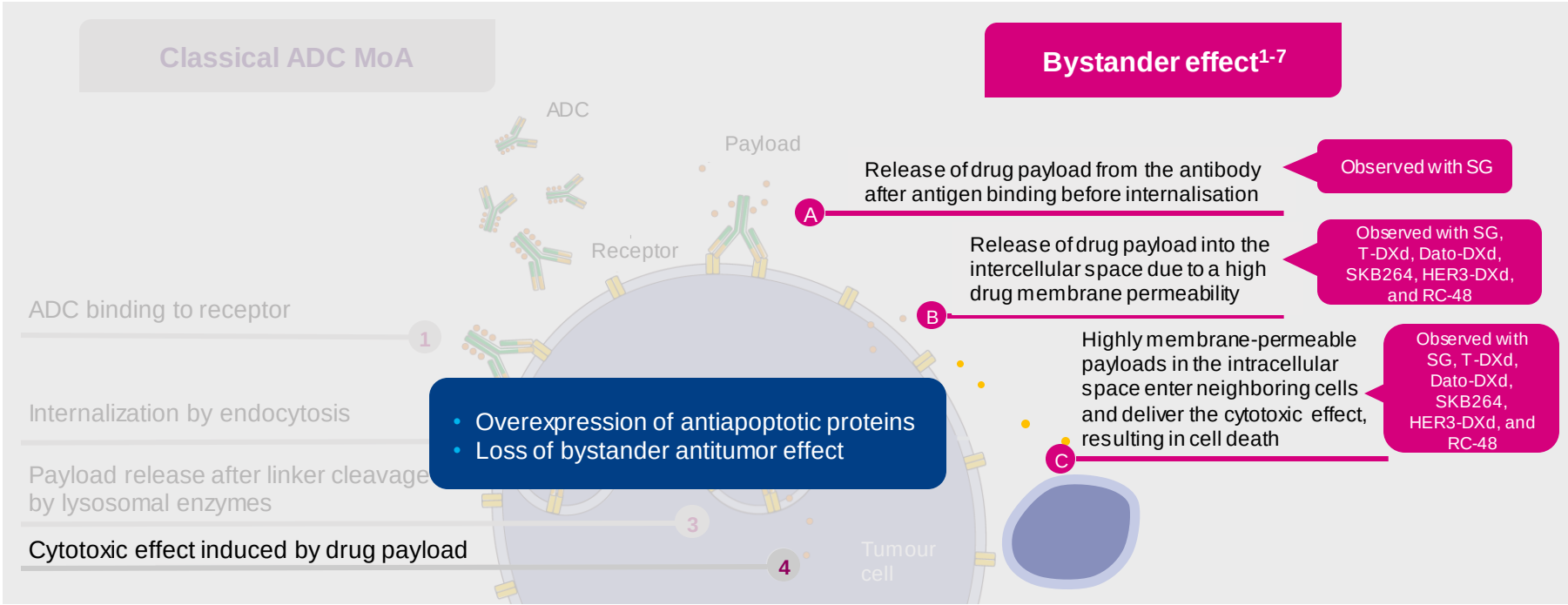
The Complexity of ADCs Provides Many Opportunities for Resistance to Emerge: ADC Processing[1,2]



ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; HER3, human epidermal growth factor 3; MoA, mechanism of action; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.

1. Hunter FW, et al. *Br J Cancer.* 2020;122:603-612; 2. Rinnerthaler G, et al. *Int J Mol Sci.* 2019;20:1115.

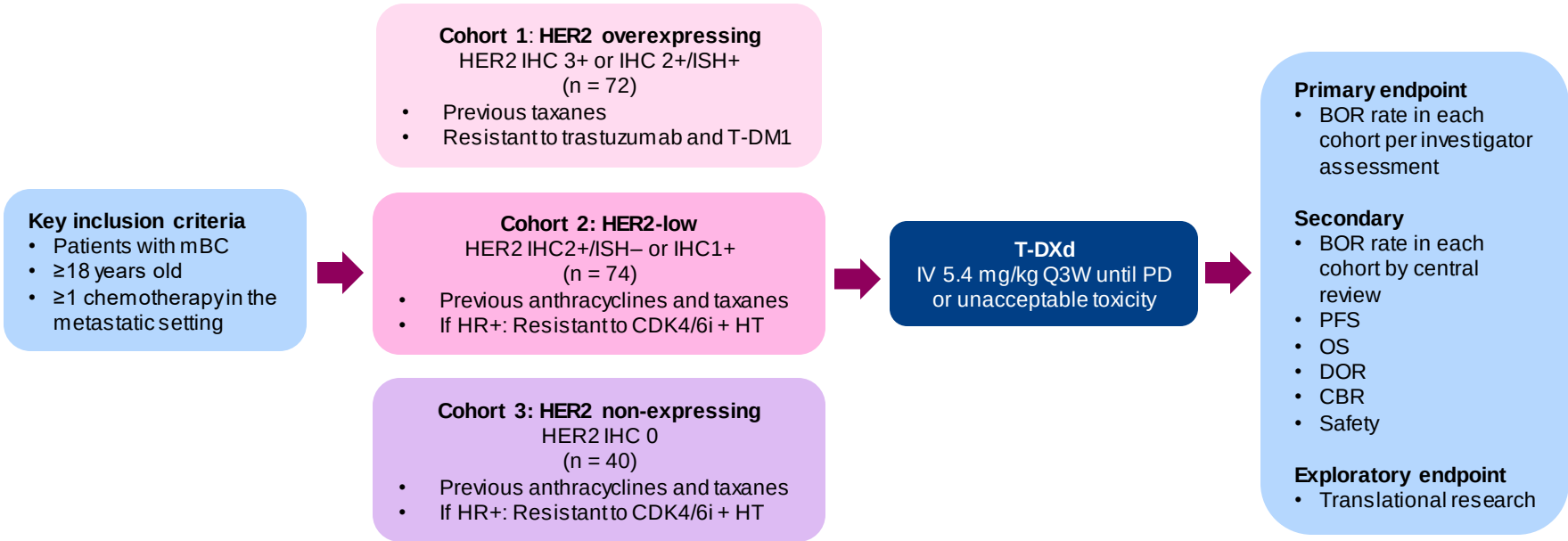
The Complexity of ADCs Provides Many Opportunities for Resistance to Emerge: Payload Release[1,2]



ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; HER3, human epidermal growth factor 3; MoA, mechanism of action; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.
Please see slide notes for references.

The Phase II DAISY Trial Investigated Response and Resistance to T-DXd by HER2 Expression in mBC[1,2]

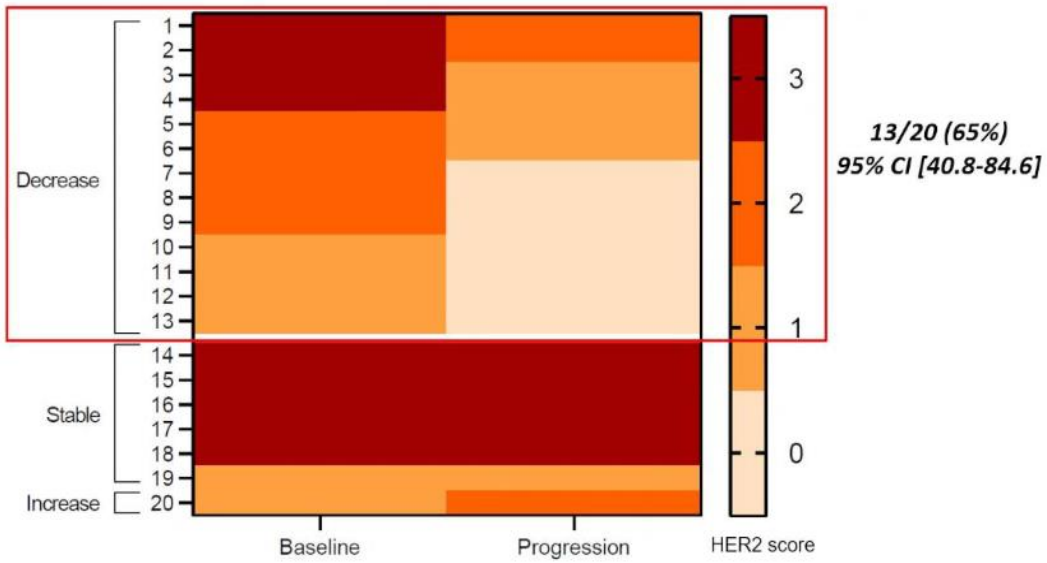
DAISY study design (NCT04132960)



BOR, best objective response; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HT, hormone therapy; IHC, immunohistochemistry; ISH, *in situ* hybridization; IV, intravenous; mBC, metastatic breast cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. National Institute of Health (NIH). NCT04132960. Available at: https://clinicaltrials.gov/ct2/show/NCT04132960. Accessed October 2023; 2. Mosele F, et al. ESMO 2022. Abstract LBA1.

Exploratory Endpoint: In DAISY, 65% (13/20) of Patients Presented a Decrease of HER2 Expression at Progression



25 FFPE samples at baseline and progression

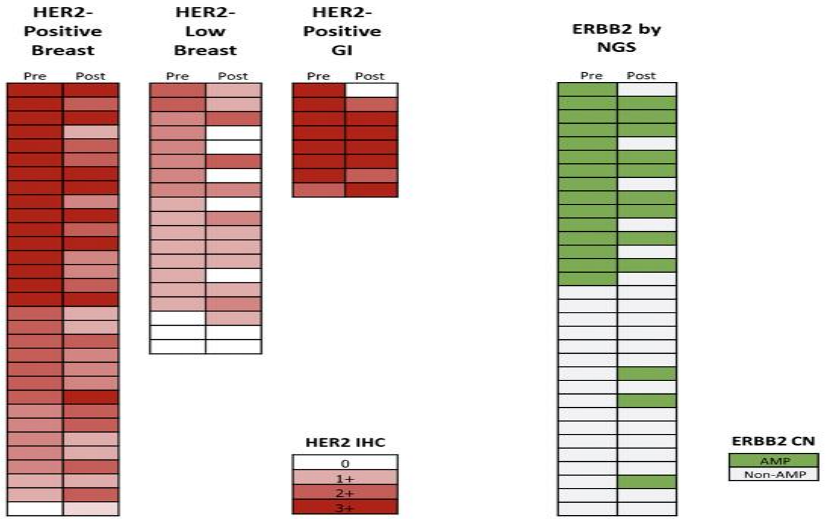
- 9 HER2 IHC 3+ or IHC 2+/ISH+
- 11 HER2 IHC 2+/ISH– or IHC 1+
- 5 IHC 0

HER2 status by standard IHC

Five patients HER2 IHC 0: 4 stable and 1 to IHC.
FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
Mosele F, et al. ESMO 2022. Abstract LBA1.

HER2 Target Expression post-TDXd Exposure

- Clinically reported HER2 IHC on pre- and post- Tx biopsies
- Pts received at least 2 cycles of T-DXd
- IHC via Ventana Assay
- MSK-IMPACT NGS on paired pre-and post-tx samples when available

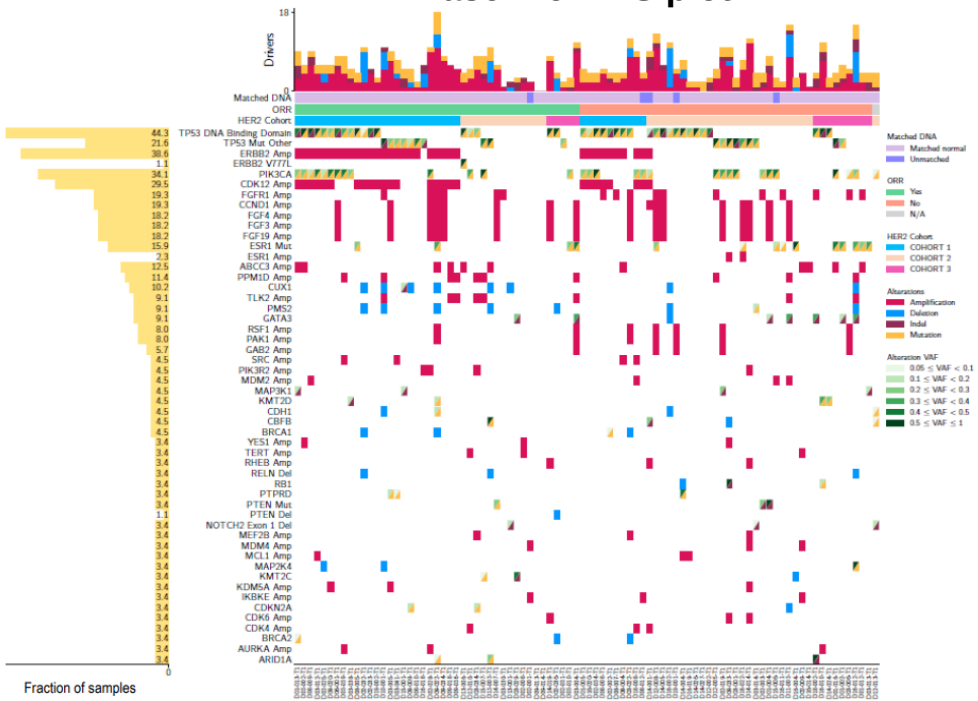


Tumor Type	N	Median Time on Tx (Wks)	Median HER2 IHC Post-Tx	IHC 0 Post-Tx N (%)
HER2-Positive Breast	32	30	2+ (1-3)	0 (0)
Her2-Low Breast	19	21	1+ (0-2)	7 (36)
Gastroesophageal	7	12	3+ (0-3)	1 (14.2)
Colorectal	4	9	2+ (2-3)	0 (0)
Total	62	23.5	2+ (0-3)	8 (12.9)

Drago J et al, *ASCO* 2023.

Exploratory Endpoint: WES Revealed No Recurrent Driver Alterations Associated With Resistance

Baseline WES plot



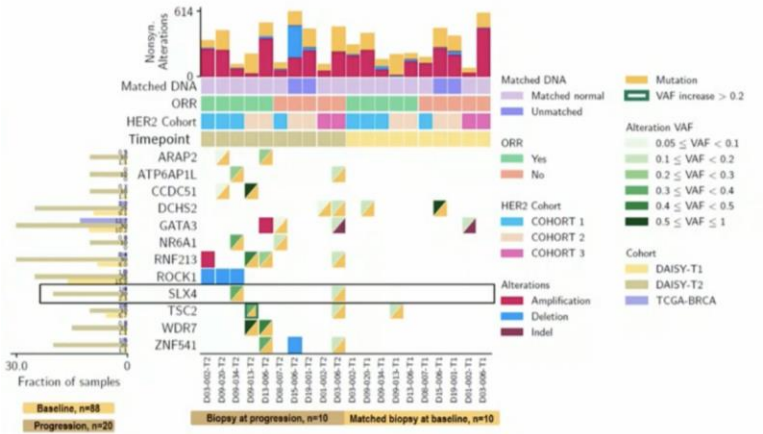
4/5 patients with *ERBB2* hemizygous deletion showed no response to T-DXd[a], indicating *ERBB2* hemizygous deletions may be associated with T-DXd up-front resistance

[a]Of the 4 patients, 2 patients had HER2-low and 2 patients HER2-null expression.
HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan; WES, whole exome sequencing.
Mosele MF, et al. ESMO 2022. Abstract LBA72.

Exploratory Endpoint: *SLX4* Mutations Could Induce DXd Resistance; However, Further Research Is Required to Confirm This Finding

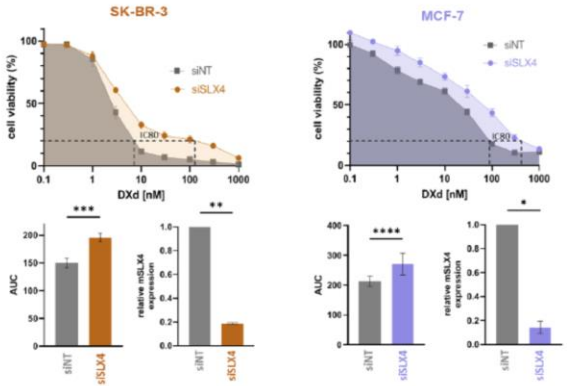
20% (4/20) of patients had *SLX4* mutations at progression

20 tumor biopsies at progression with 10 baseline matched samples



- The *SLX4* gene encodes for a DNA repair protein that regulates endonuclease
- *SLX4's* role in camptothecin resistance is unclear
- 2 of the mutations were acquired (ie, not detectable in baseline samples)
- Matched baseline biopsies were not available for the remaining 2 patients

SK-BR3 and MCF-7 BC cell lines treated with DXd for 5 days



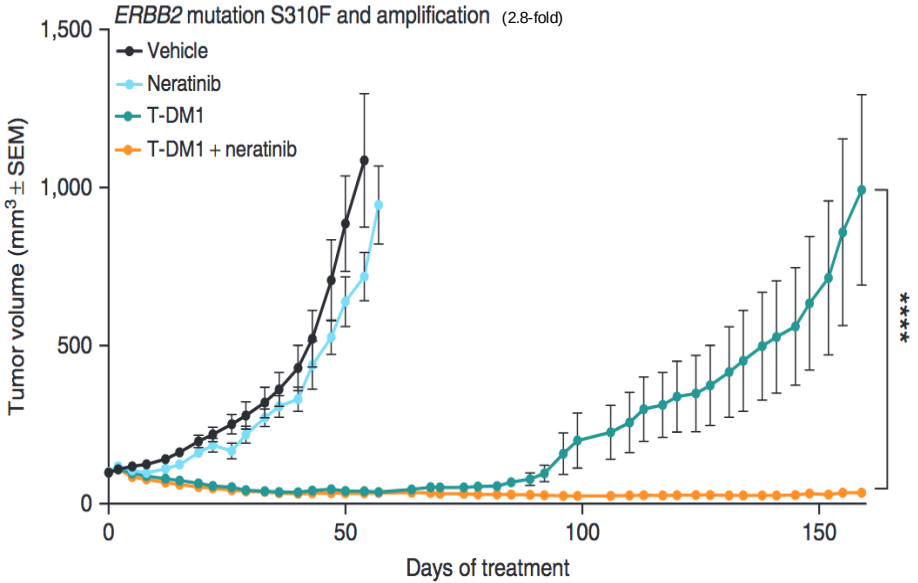
	SK-BR-3	MCF-7
$IC80_{siNT}$	8.18nM	95.10nM
$IC80_{siSLX4}$	167.27nM	502.40nM

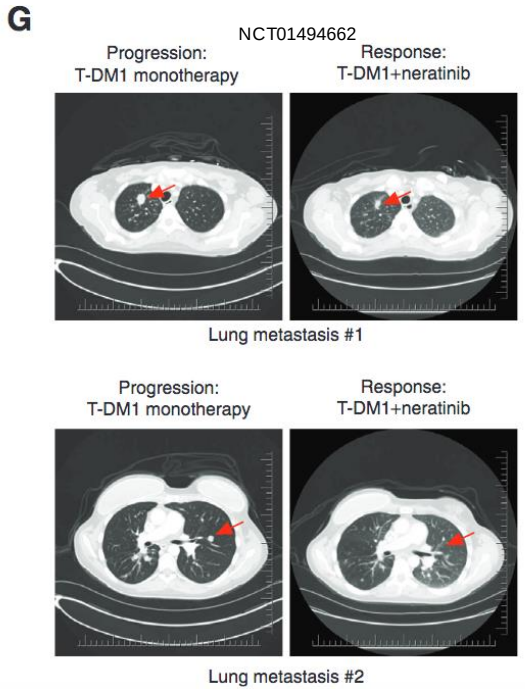
- *SLX4*-depleted SK-BR3 and MCF-7 BC cell lines required a higher quantity of DXd for cell death
- *SLX4* mutations could mediate DXd resistance

BC, breast cancer; *BRCA*, breast cancer gene; DXd, deruxtecan; HER2, human epidermal growth factor receptor 2; ORR, objective response rate.

Mosele MF, et al. ESMO 2022. Abstract LBA72.

Drug combinations:
Increasing ADC Activity with Irreversible TKIs





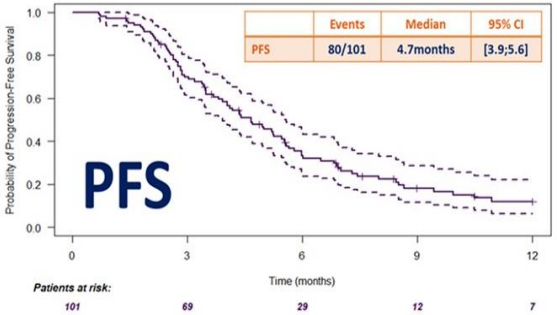
Li, Michelini, Misale et al., Cancer Discov, 2020

Efficacy for Tucatinib/Cape/Trastuzumab after T-DXd in HER2+ MBC

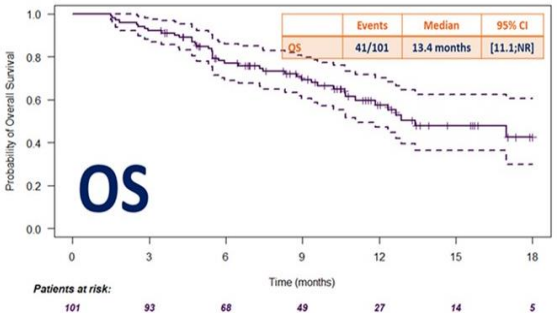
French Retrospective Study

Characteristics, n (%)		n=101
Female		101 (100%)
Age (years), median (range)		56 (30-84)
Age	<65 years	79 (78.2%)
	≥65 years	22 (21.8%)
Stage IV at initial diagnosis		34 (34.3%)
Hormone receptor status	ER and/or PR-positive	72 (71.3%)
	ER and PR-negative	29 (28.7%)
Prior lines of therapy, median (range)	Overall	5 (2-16)
	Metastatic setting	4 (2-15)
Previous therapies	Trastuzumab	100 (99.0%)
	Pertuzumab	82 (81.2%)
	T-DM1	94 (93.1%)
	Lapatinib	33 (32.7%)
	T-DXd	101 (100.0%)
	Median duration of T-DXd (months)	8.9 (1.4-31.4)
Brain metastases		39 (38.6%)
TTC immediately after T-DXd		86 (85.1%)
Reason for T-DXd discontinuation	Progression	82 (81.1%)
	Toxicity	18 (17.8%)
	Unknown	1 (1.1%)

Median Follow-up: 11.6 months [10.5-13.4]



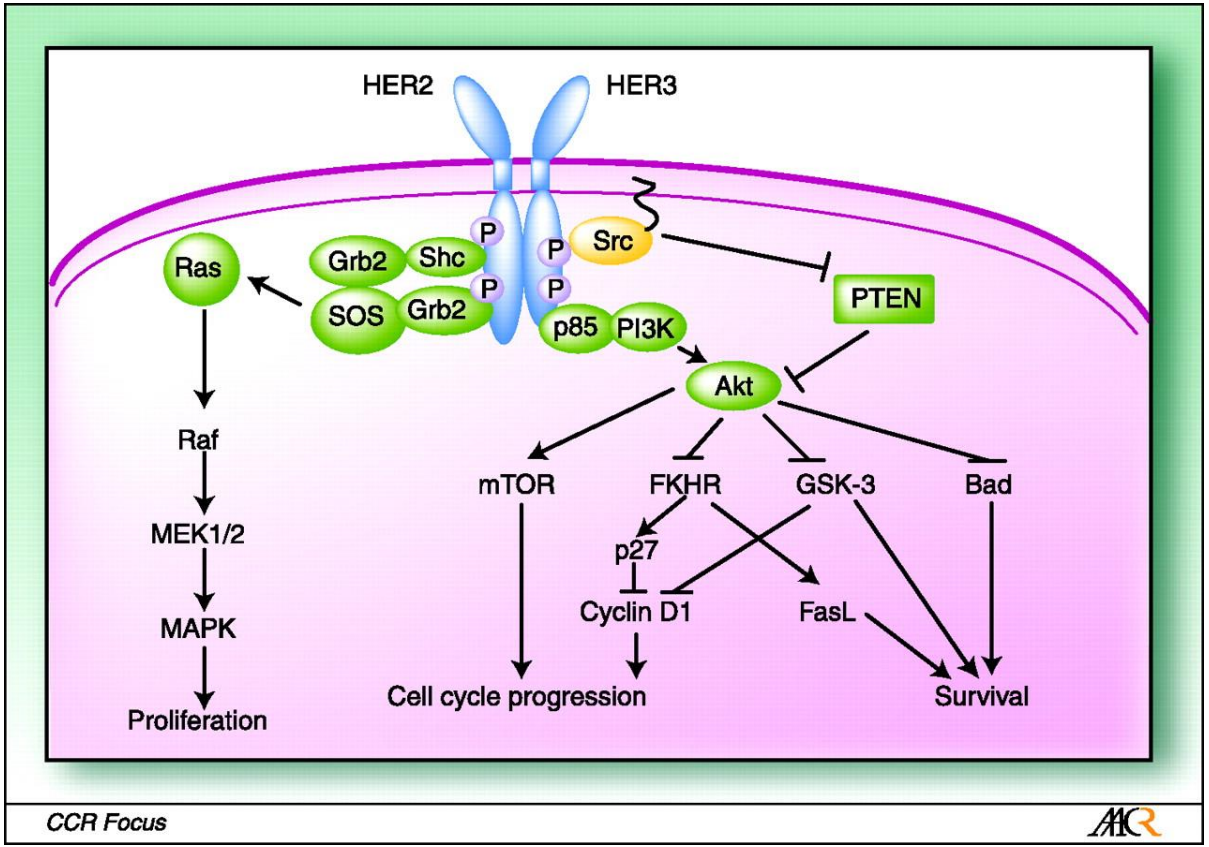
Estimated PFS at 6 months (95% CI)
33.1% [24.8;44.3]
Estimated PFS at 12 months (95% CI)
11.9% [6.4;22.1]



Estimated OS at 6 months (95% CI)
77.0% [69.0;86.0]
Estimated OS at 12 months (95% CI)
57.5% [47.2;66.1]

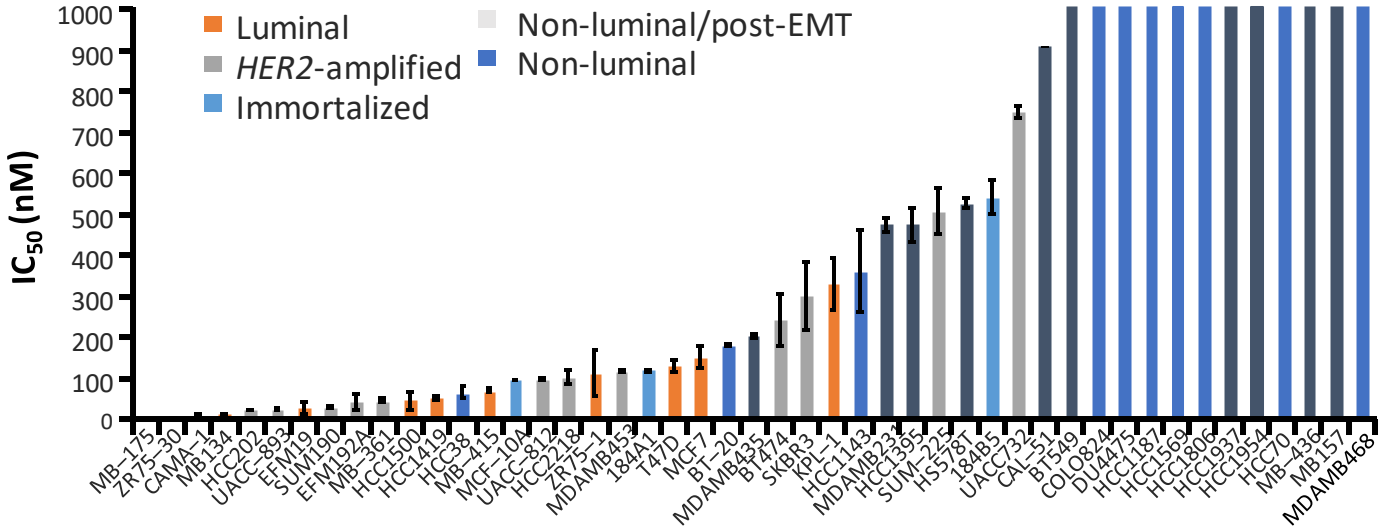
Frenel J et al, ASCO 2023

Cyclin D1 Lies Downstream of HER2



Lin NU, Winer EP. *Clin Cancer Res*. 2007;13:1648-1655.

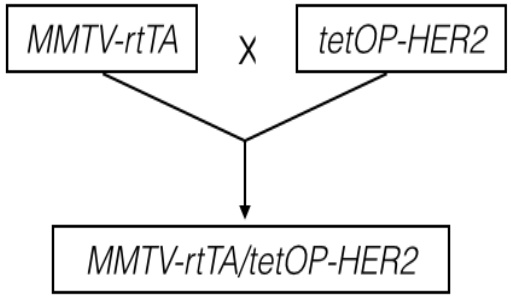
CDK4/6 Inhibitors Preferentially Inhibit Proliferation of Luminal ER+ and HER2+ Human Breast Cancer Cell Lines In Vitro

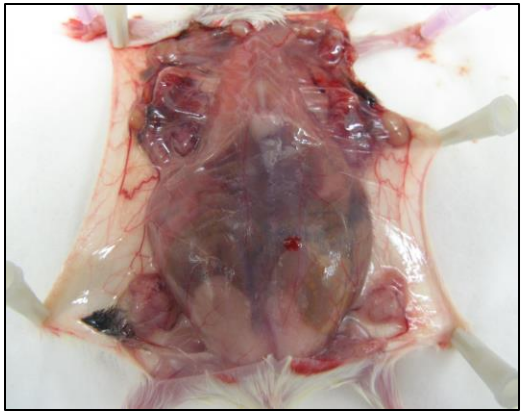


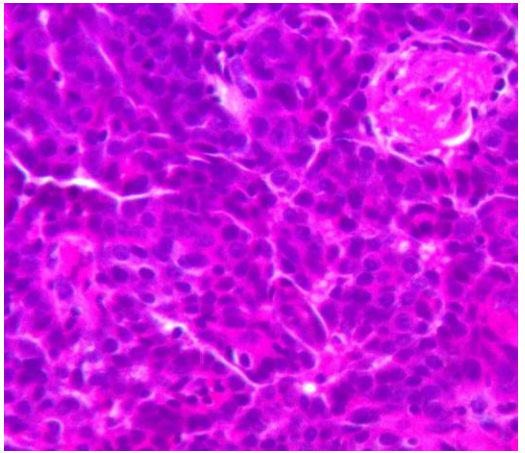
Luminal ER+ and *HER2*-amplified breast cancer cell lines are most sensitive to CDK4/6 inhibition of proliferation

Finn RS, et al. *Breast Cancer Res*. 2009;11:R77.

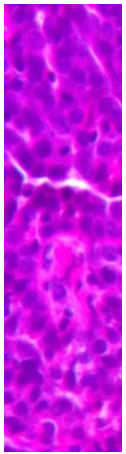
A Mouse Model of HER2-Driven Breast Cancer

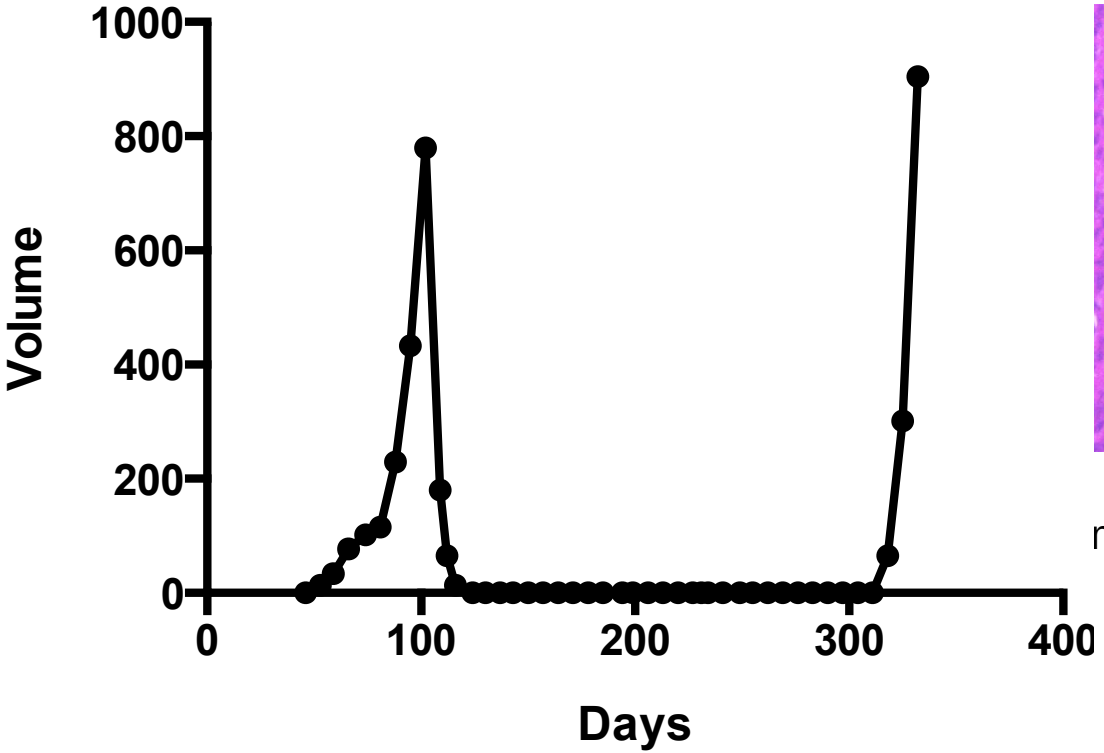


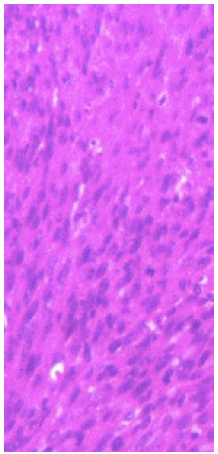




Modeling Disease Recurrence in HER2-Driven Breast Cancer





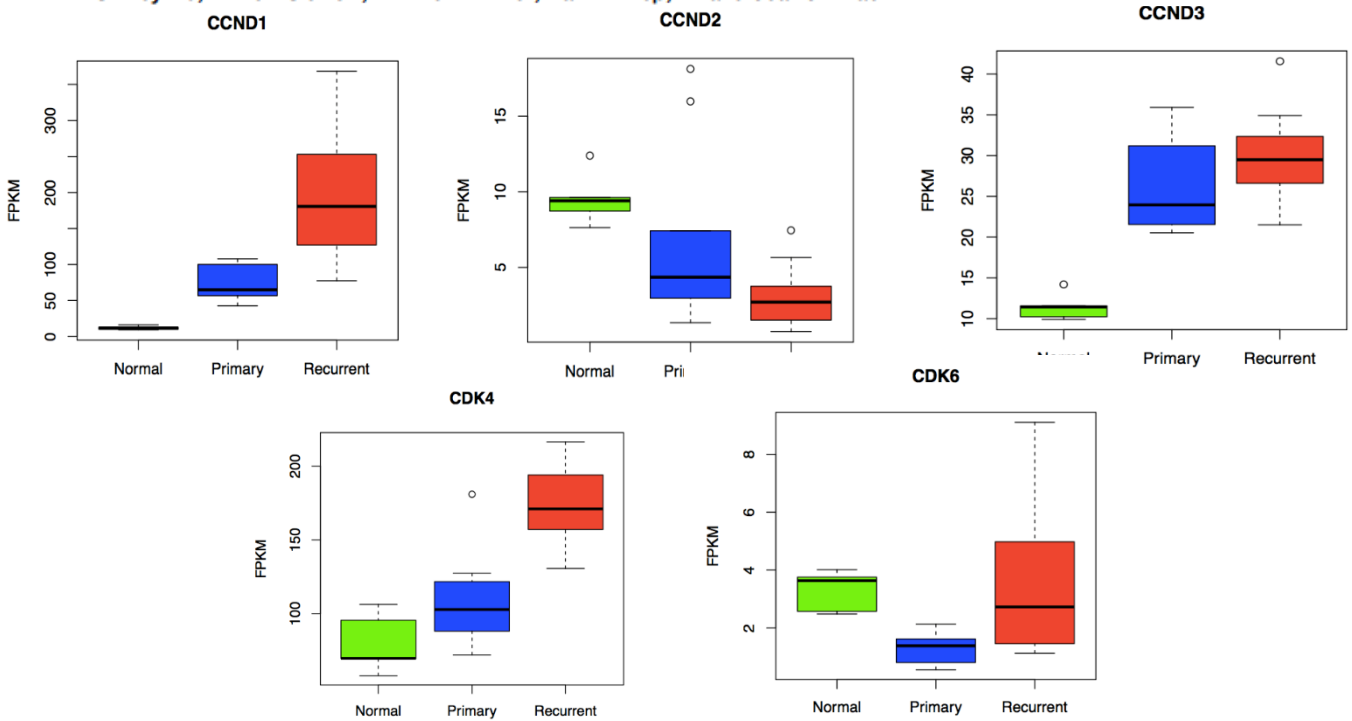


mor (6–9 months)

Cancer Cell
Article

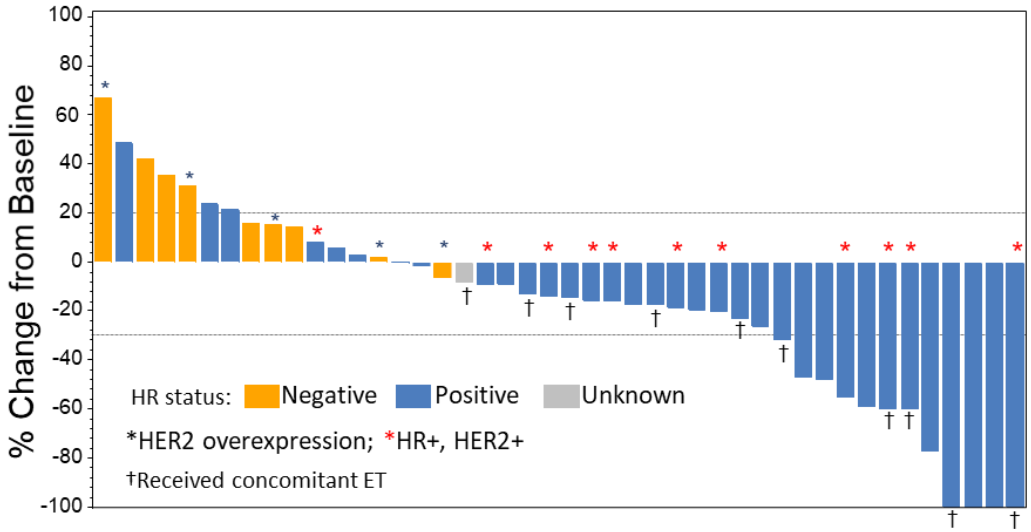
Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors

Shom Goel,[1,*] Qi Wang,[2,16] April C. Watt,[2] Sara M. Tolaney,[1] Deborah A. Dillon,[3] Wei Li,[4,5] Susanne Ramm,[6,7] Adam C. Palmer,[6,8,9] Haluk Yuzugullu,[2] Vinay Varadan,[10] David Tuck,[11,17] Lyndsay N. Harris,[12] Kwok-Kin Wong,[1] X. Shirley Liu,[4,5] Piotr Sicinski,[2,13] Eric P. Winer,[1] Ian E. Krop,[1,18] and Jean J. Zhao[2,14,15,18,*]



Clinical Data: Abemaciclib in HR+, HER2+ Metastatic Breast Cancer

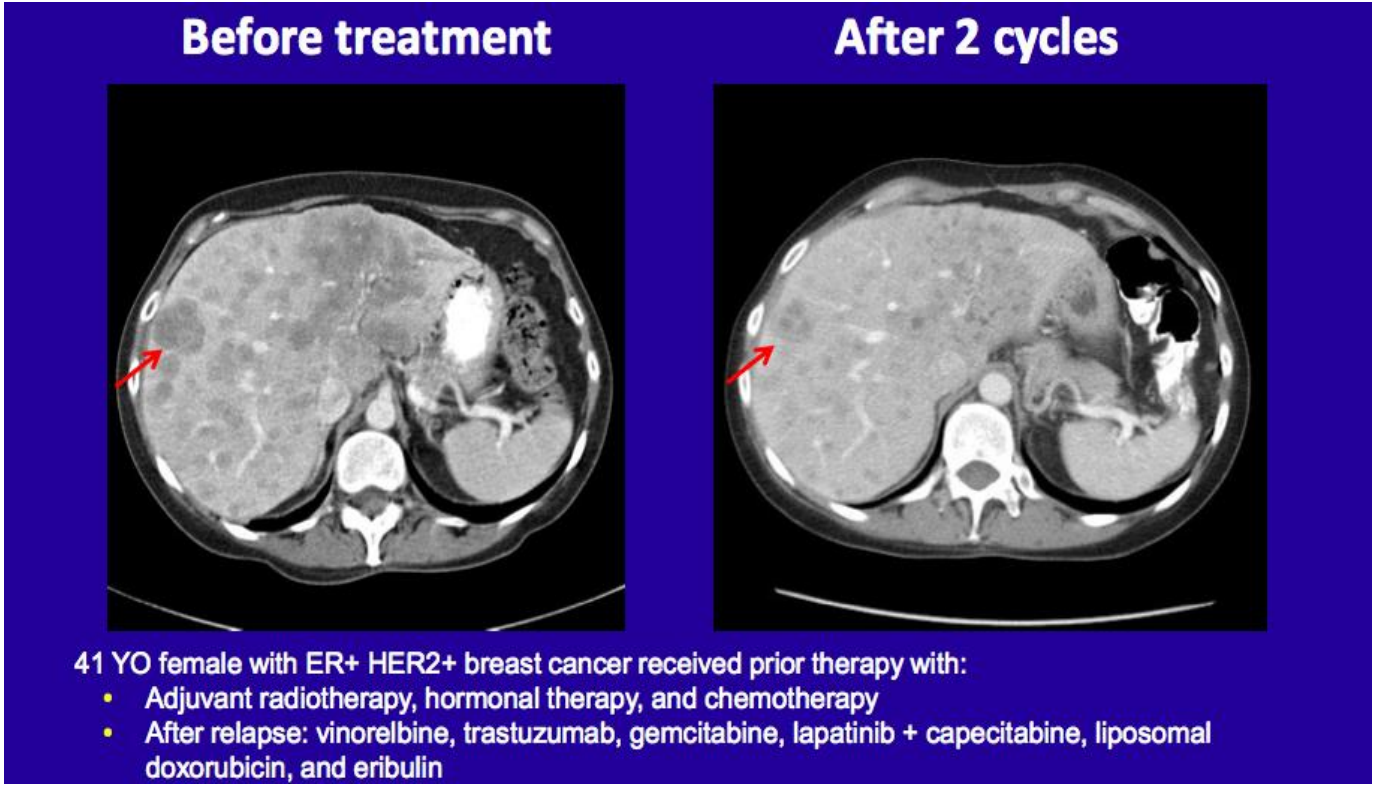
- Abemaciclib has demonstrated antitumor activity in HR+, HER2+ metastatic breast cancer
  - In study JPBA, an ORR of 36% was observed in a subset of 11 patients with HR+, HER2+ mBC. Three of the 4 responders were receiving concomitant endocrine therapy



ORR: 36% HR+, HER2+

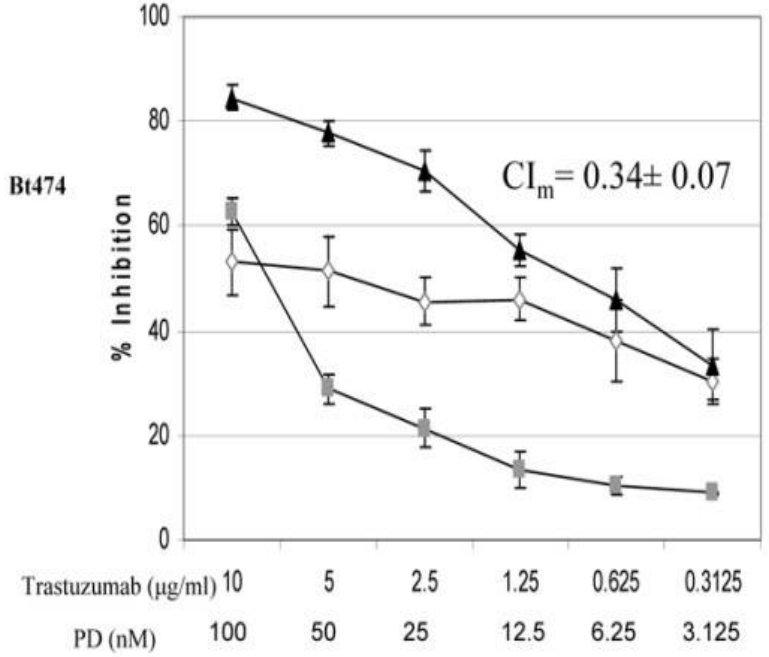
Tolaney SM, et al. SABCS 2014. Abstract 763.

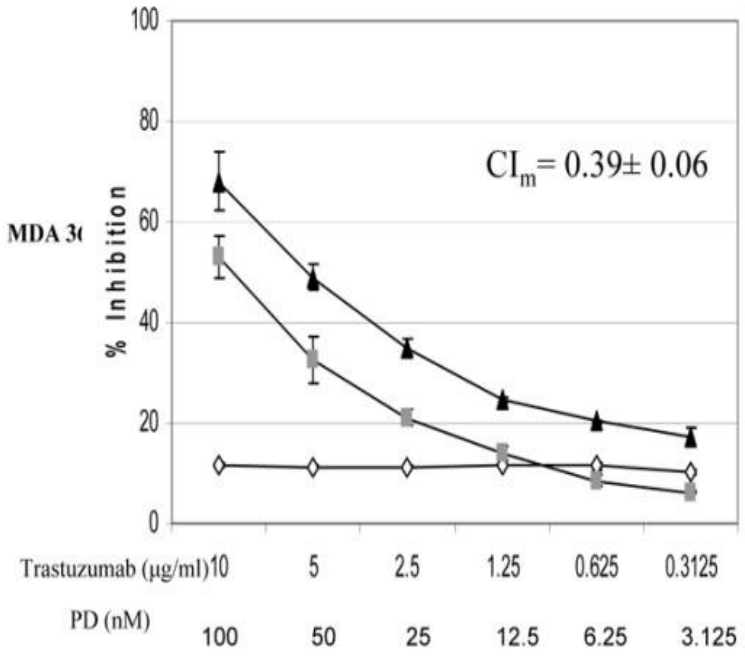
Abemaciclib in ER+, HER2+ Disease



Tolaney SM, et al. SABCS 2014. Abstract 763.

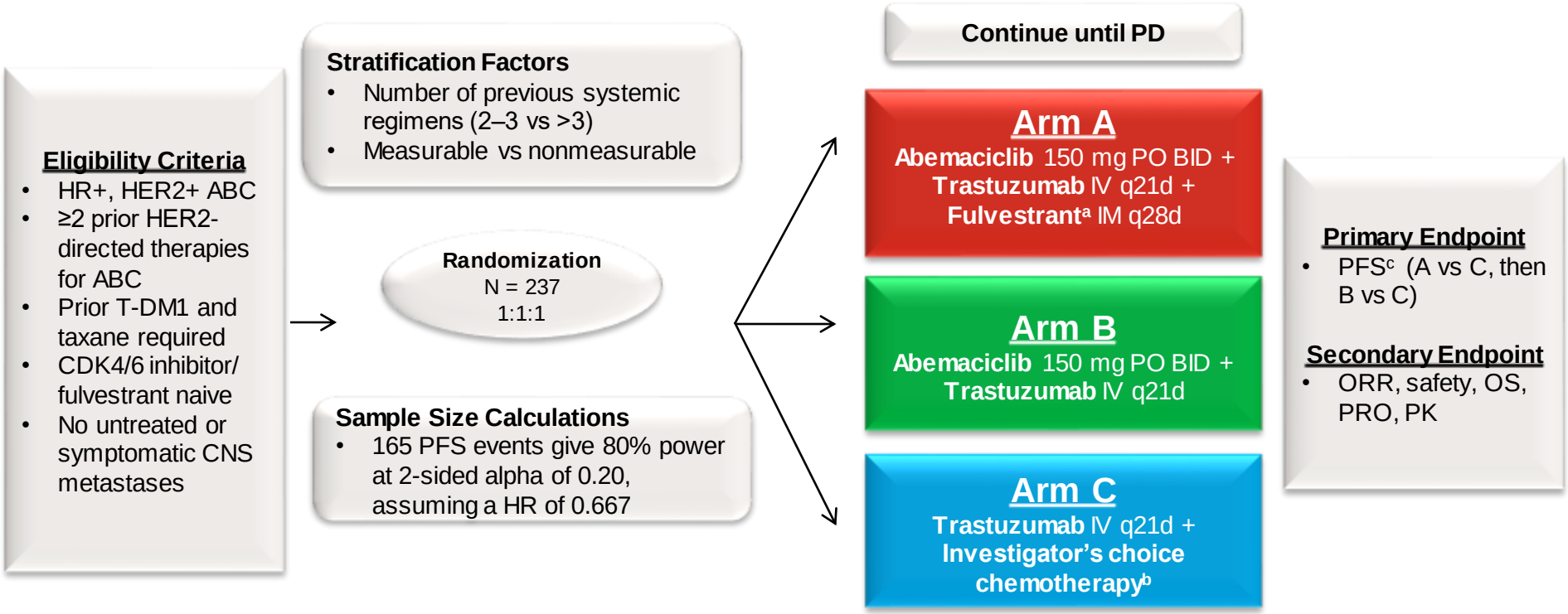
Activity of Combined Trastuzumab-CDK4/6 Inhibition in HER2+ Cells





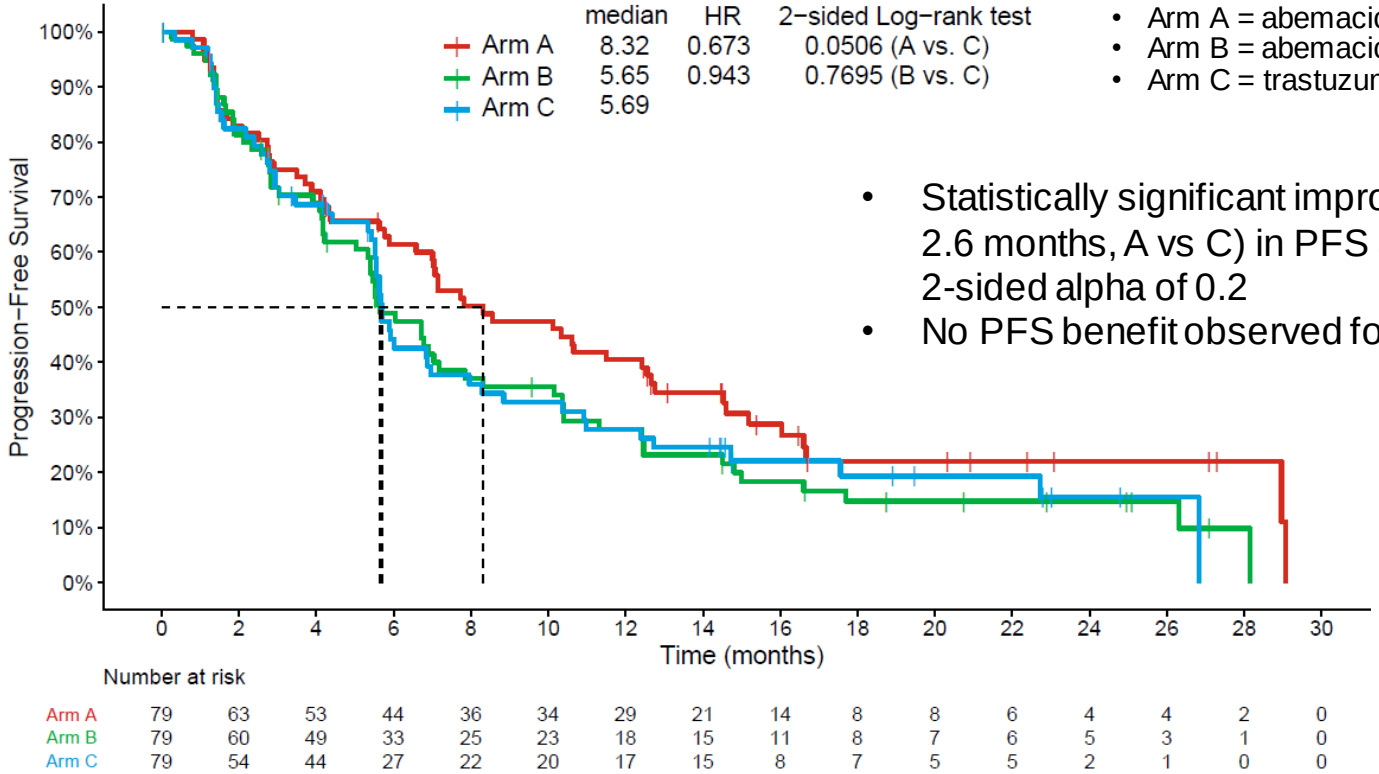
Finn RS, et al. *Breast Cancer Res*. 2009;11:R77.

monarcHER STUDY DESIGN



ABC, advanced breast cancer; BID, twice daily; HR+, hormone receptor-positive; HER2(+), human epidermal growth factor receptor-2 (positive); ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; q21d, every 21 days; PRO, patient-reported outcomes.
[a]Dosing per fulvestrant label. [b]Standard-of-care single-agent chemotherapy should include approved drug in breast cancer. [c]Investigator assessed.
Tolaney SM, et al. ESMO 2019. Abstract 1470; Tolaney SM, et al. *Lancet Oncol.* 2020;21:763-775.

Primary Endpoint: PFS

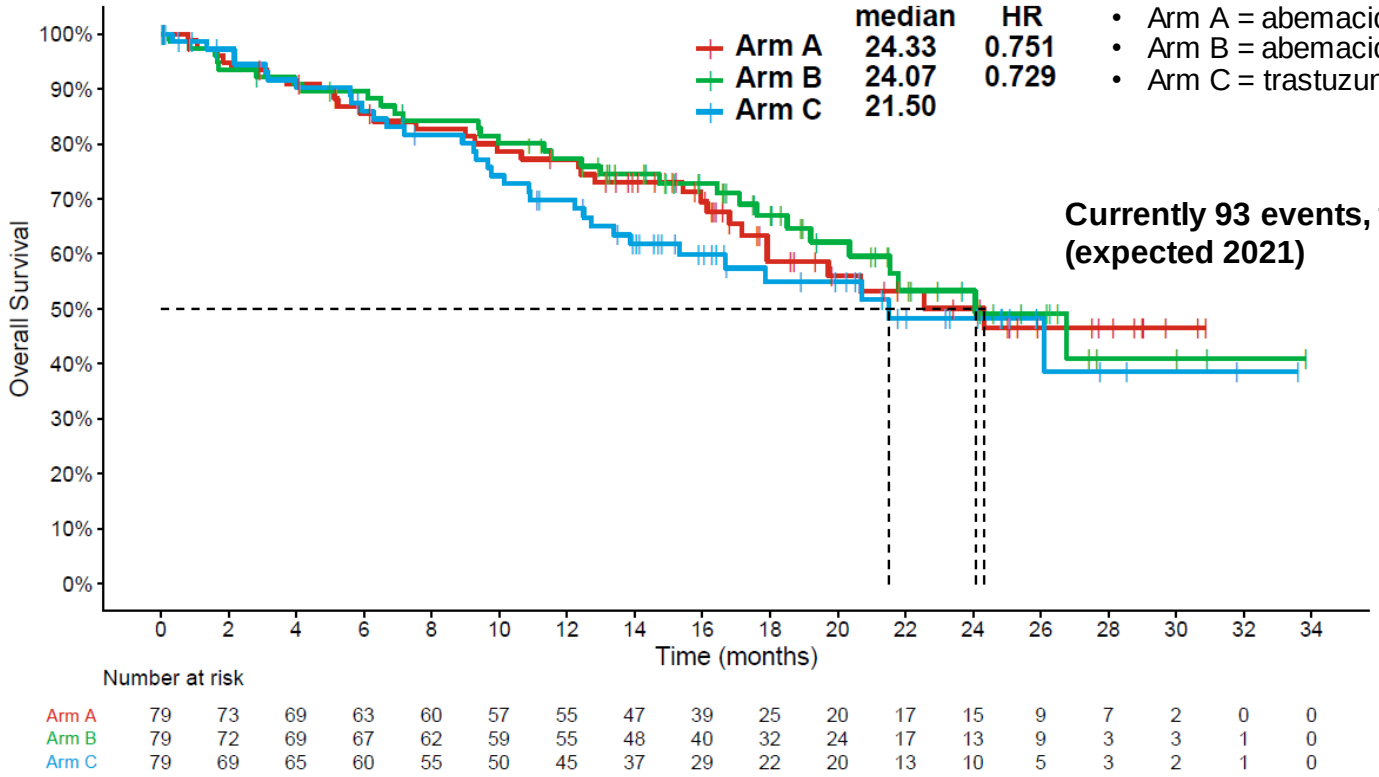


- Arm A = abemaciclib + trastuzumab + fulvestrant
- Arm B = abemaciclib + trastuzumab
- Arm C = trastuzumab + chemotherapy

- Statistically significant improvement (Δ = 2.6 months, A vs C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs C

Tolaney SM, et al. ESMO 2019. Abstract 1470; Tolaney SM, et al. *Lancet Oncol*. 2020;21:763-775.

Overall Survival: EXPLORATORY Analysis*



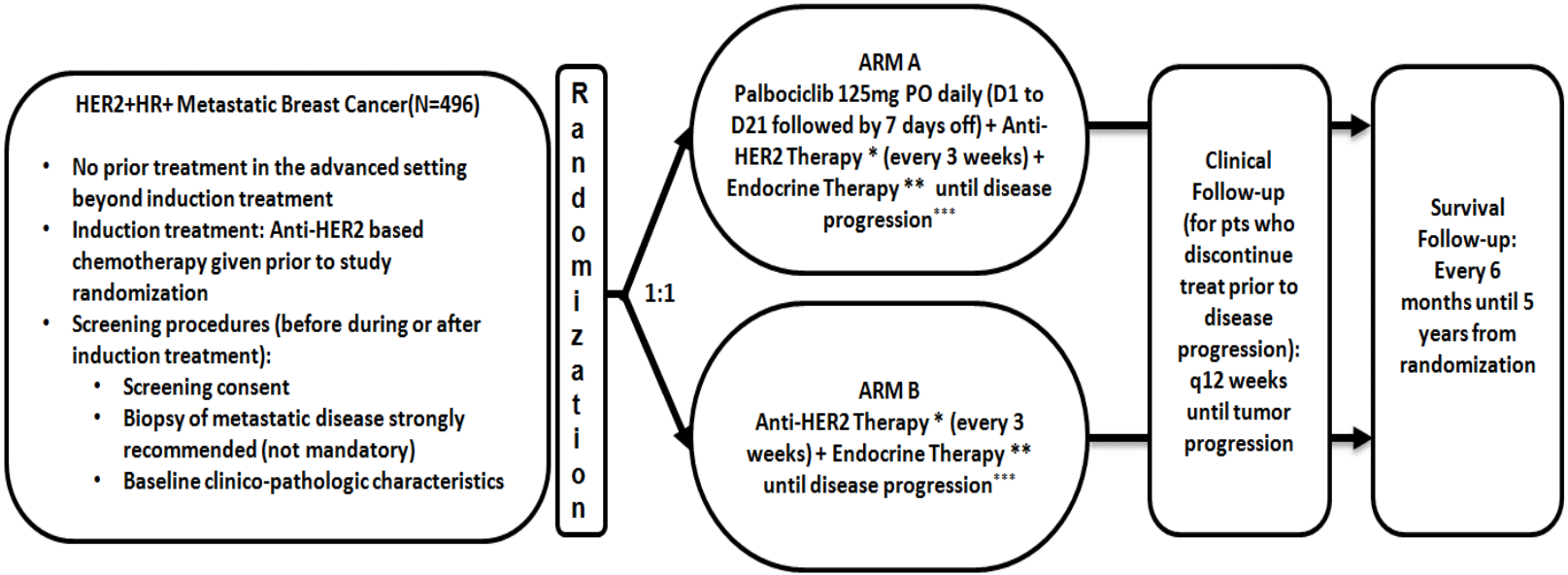
- Arm A = abemaciclib + trastuzumab + fulvestrant
- Arm B = abemaciclib + trastuzumab
- Arm C = trastuzumab + chemotherapy

Currently 93 events, final at 158 (expected 2021)

***Prespecified criteria for formal testing not met.**

Tolaney SM, et al. ESMO 2019. Abstract 1470; Tolaney SM, et al. *Lancet Oncol*. 2020;21:763-775.

AFT-38: PATINA Trial



Goal: To demonstrate that the addition of palbociclib to the first-line treatment of HER2+, HR+ invasive breast cancer improves outcomes for patients diagnosed with metastatic disease

N = 496

PI: Metzger
NCT02947685

Summary

- HER2-directed therapies have revolutionized outcomes; however, resistance still develops
- *PI3K* mutations are seen in 30–40% of HER2+ disease, and can lead to resistance to HER2-directed therapy
  - Studies combining PI3Ki with dual HER2-directed therapy are ongoing
- Multiple mechanisms of resistance to ADCs are possible, and more work is needed to better understand the key drivers of resistance and how to best overcome them
- Cyclin D1 amplification is a mechanism of resistance to HER2-directed therapy that may be overcome with CDK4/6 inhibition

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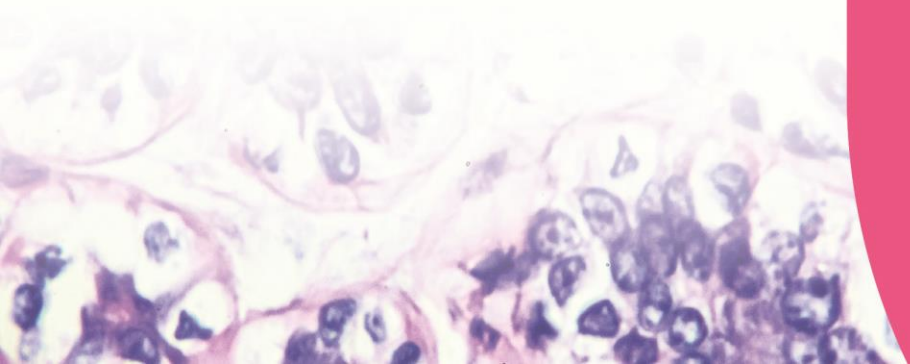
Q&A



APTITUDE HEALTH

Objectives

Understand major advances in early lines of treatment for HER2+ mBC

Learn about potential treatment options after second line treatment for HER2+ mBC

Understand changes in HER2 expression during treatment with HER2-targeted agents

Gain insights into the care of HER2+ mBC patients with CNS metastases

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Explore current and future sequencing strategies in HER2+ mBC

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Modern treatment approaches for HER2+ mBC patients with brain metastases

Anna Berghoff

APTITUDE HEALTH

Question 1

How long is the median survival of patients with good performance score, limited number of BM, young age, and HER2+ breast cancer BM?

A. 7 months

B. 12 months

C. 18 months

D. 24 months

Question 2

Which of the following systemic therapies have proven activity in asymptomatic HER2+ BC BM patients?

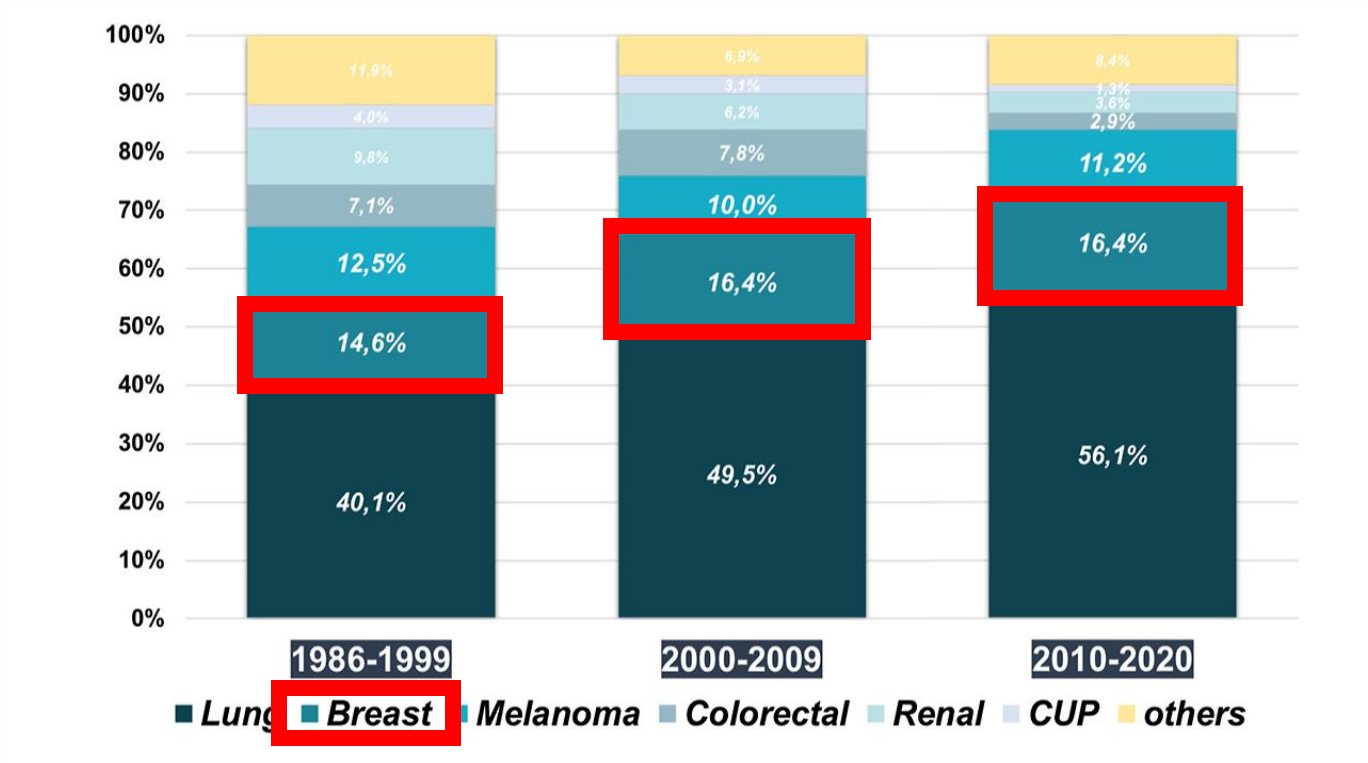
A. T-DXd

B. Tucatinib + trastuzumab + capecitabine

C. Lapatinib + capecitabine

D. All of the above

Incidence of BM in Breast Cancer



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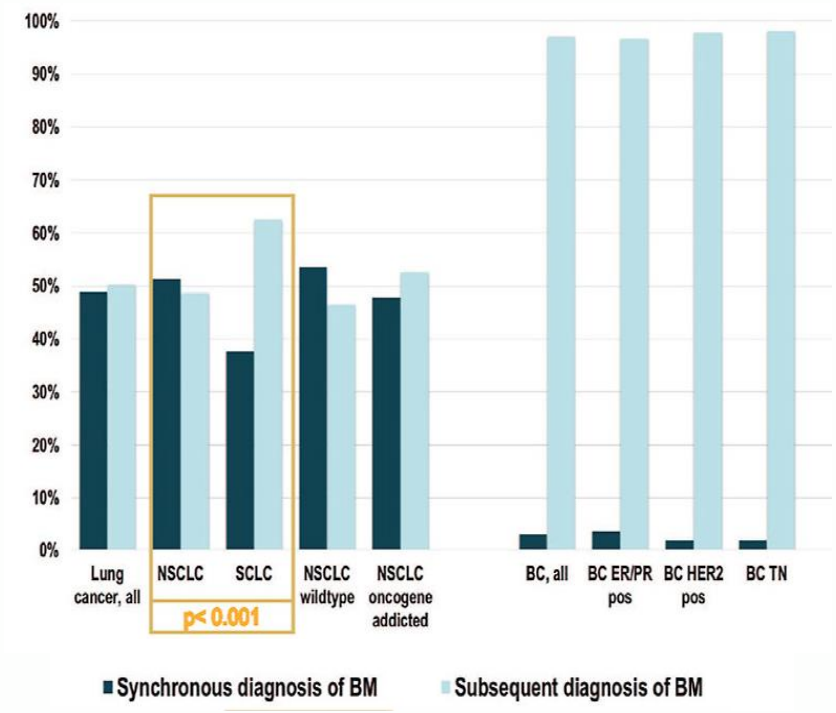
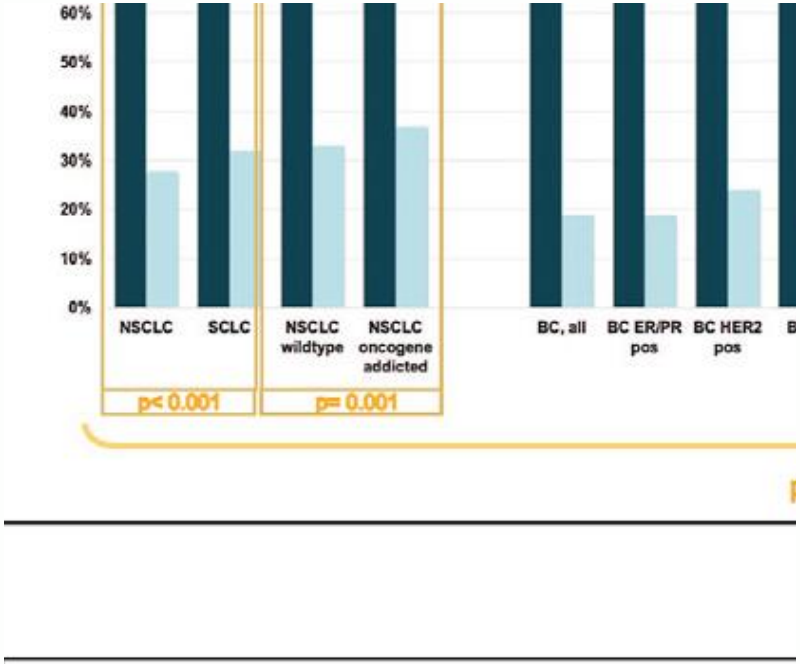
Steindl A, et al. *Eur J Cancer.* 2022;162:170-181.

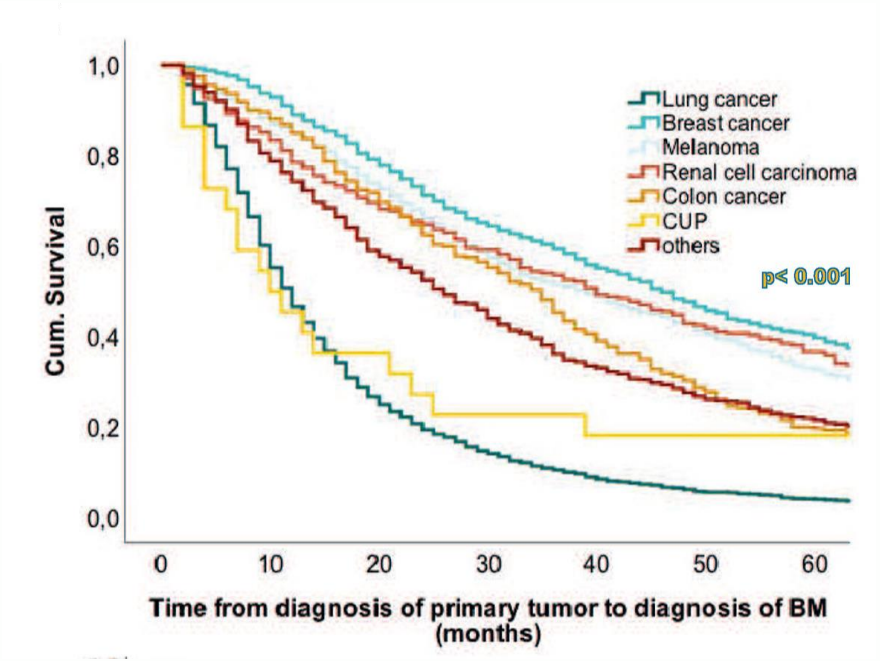
Timing of BM in HER2+ BC

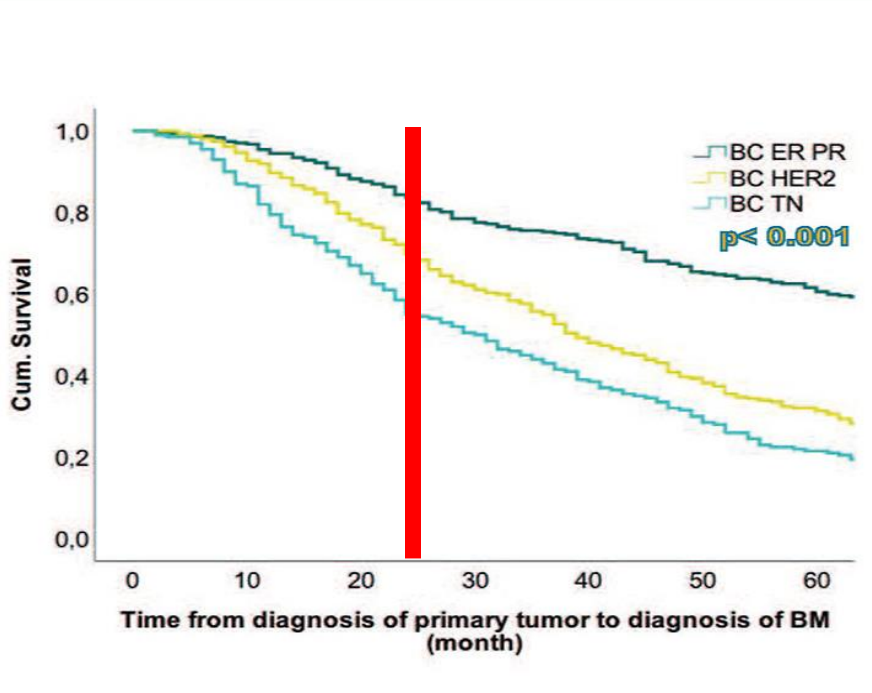




Steindl A, et al. *Eur J Cancer.* 2022;162:170-181.

Favorable Survival Prognosis of BM in HER2+ BC → Prevention of Toxicity





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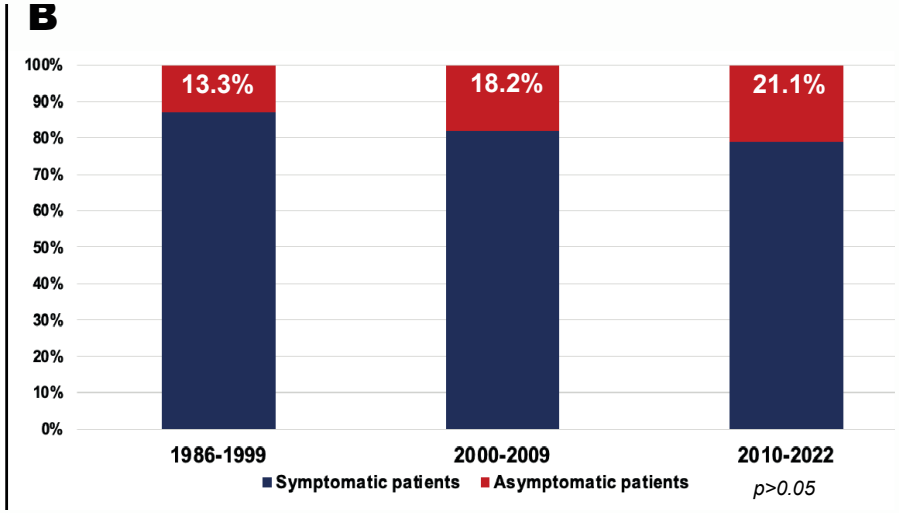
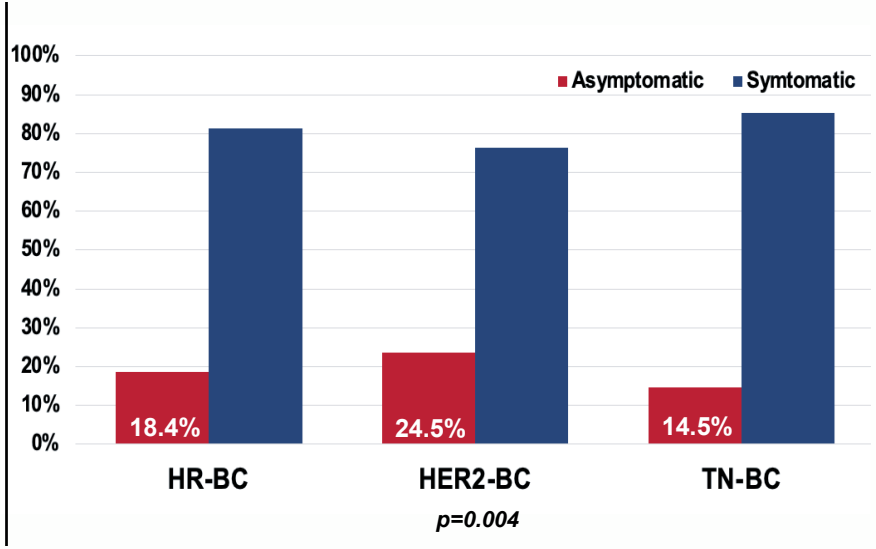
Steindl A, et al. *Eur J Cancer.* 2022;162:170-181.

Factors Impacting Treatment: Symptoms





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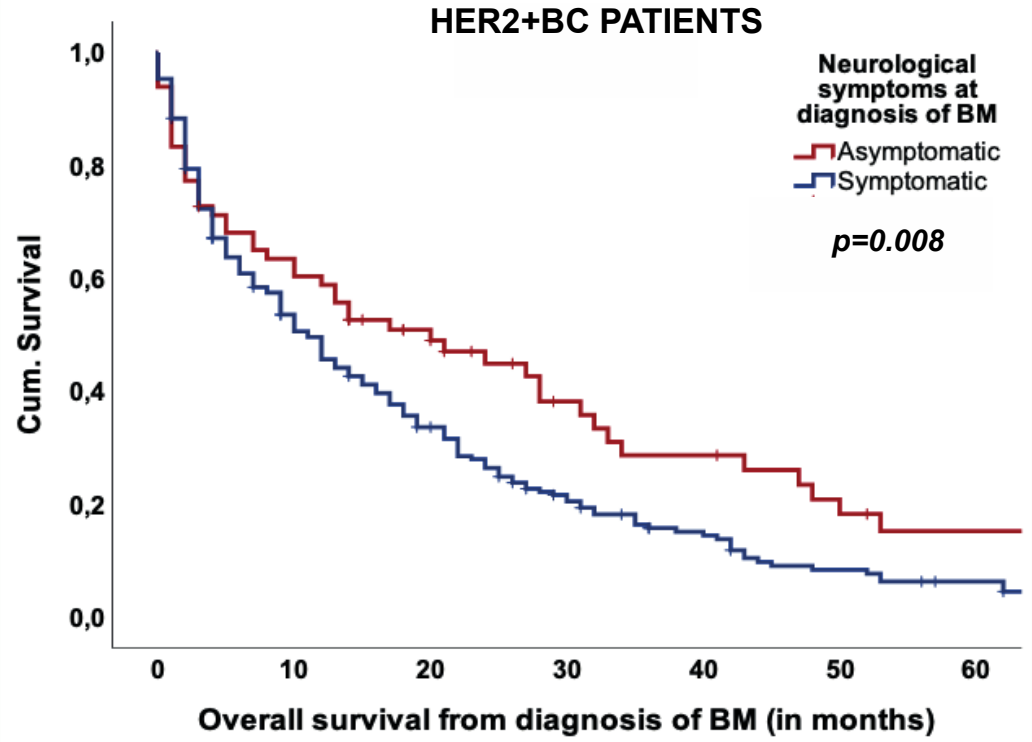
Steindl A, . . . Berghoff AS. Submitted.

Survival Prognosis Associated With Symptomatic Burden



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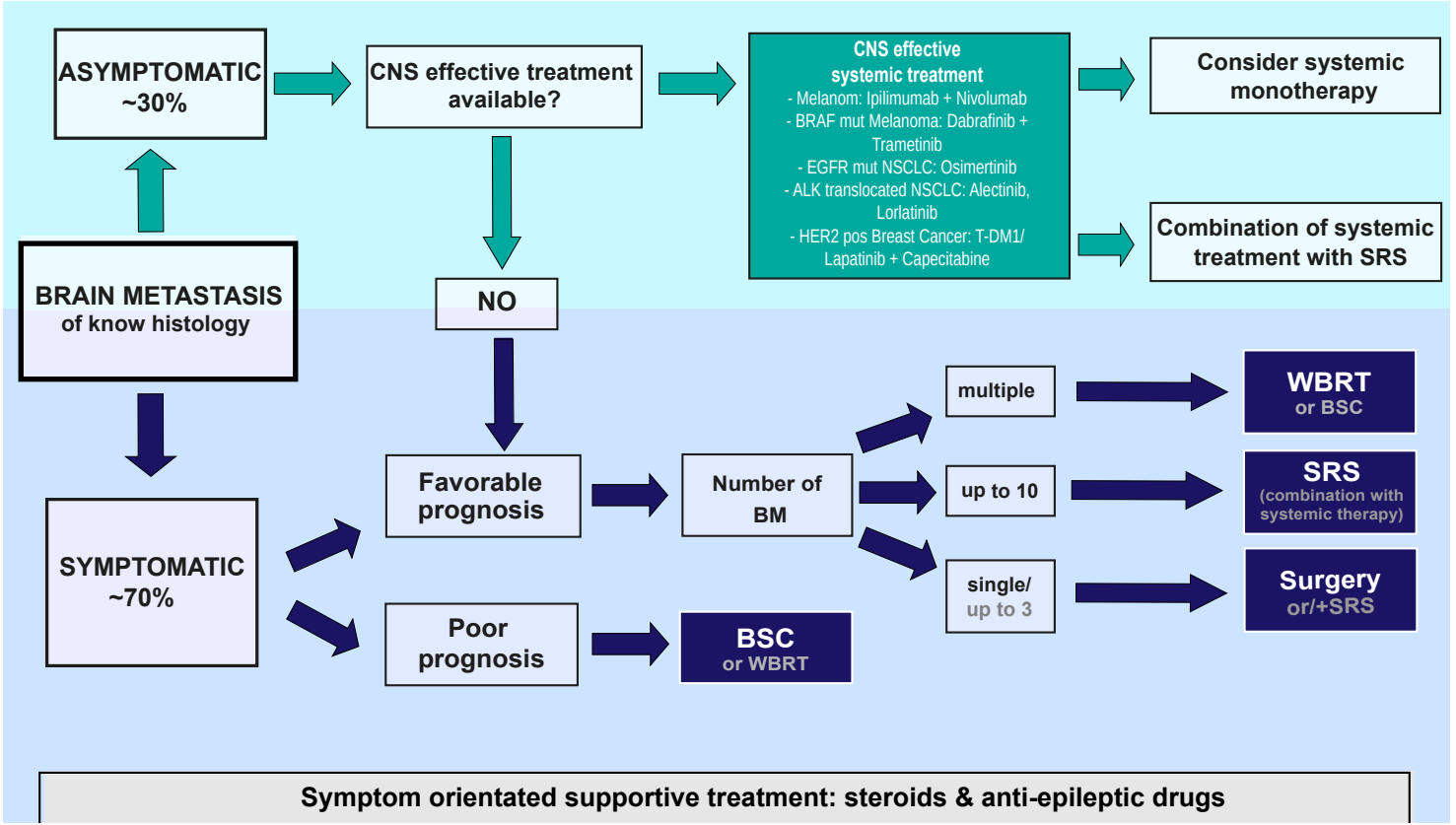
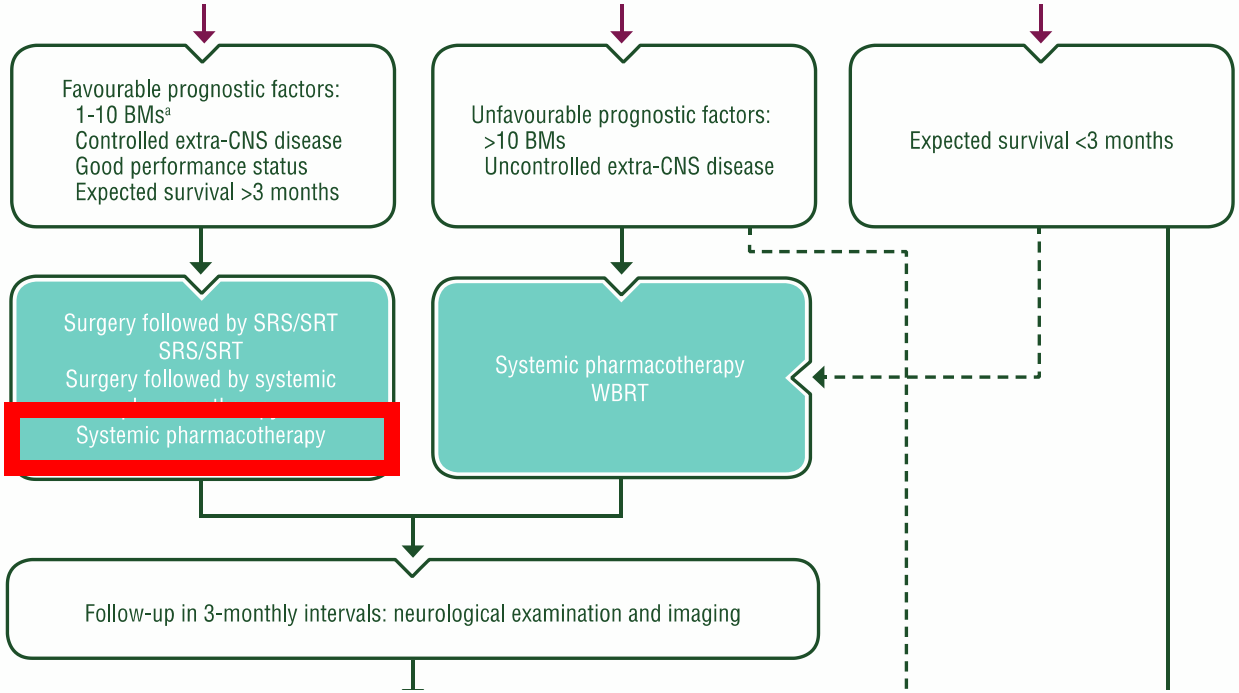
Steindl A, . . . Berghoff AS. In review.

Treatment Strategies in Brain Metastases



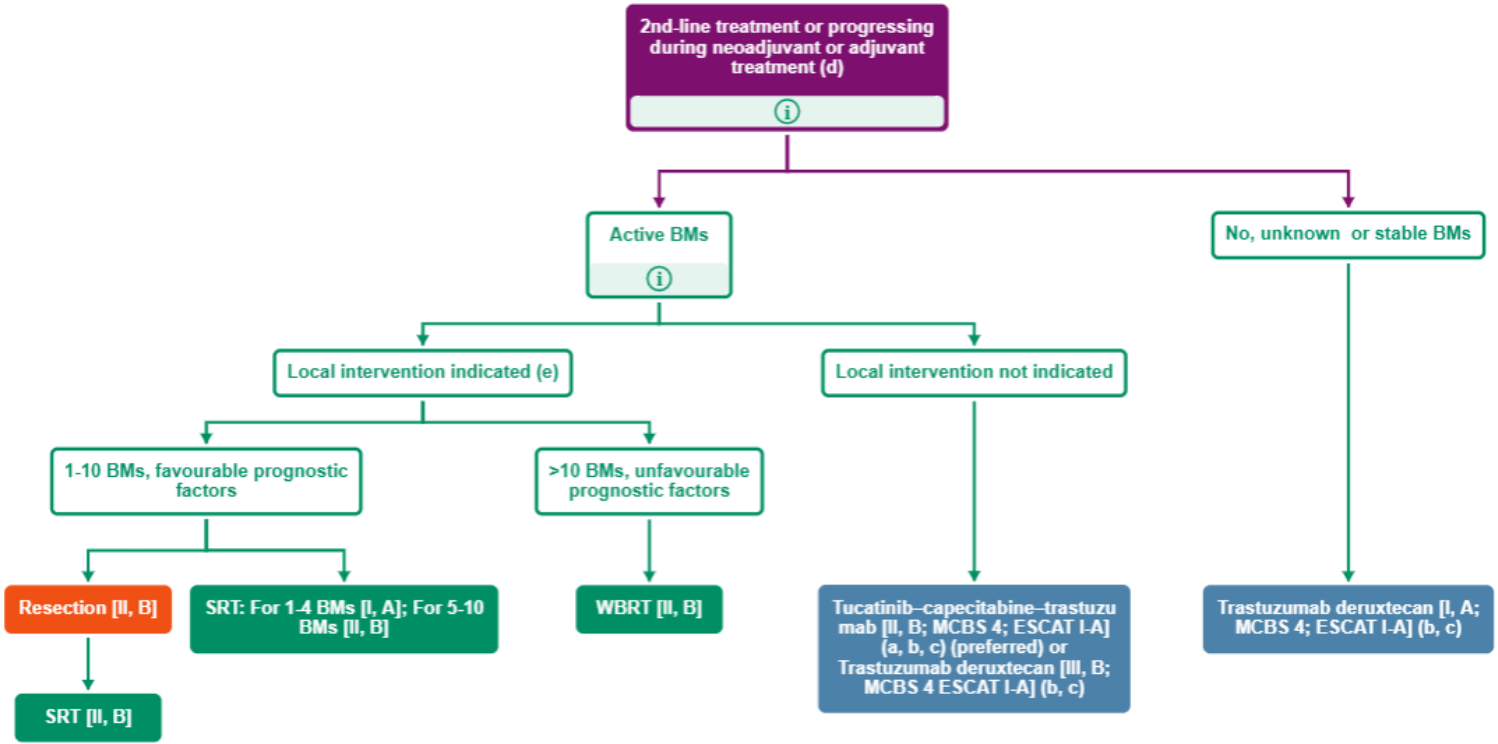
Steindl A, Berghoff AS. *Expert Rev Anticancer Ther*. 2020;21(3):325-339.

EANO-ESMO Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-Up of Patients With Brain Metastasis From Solid Tumors



Le Rhun E, et al. *Ann Oncol.* 2021;32(11):1332-1347.

ESMO Clinical Practice Guideline



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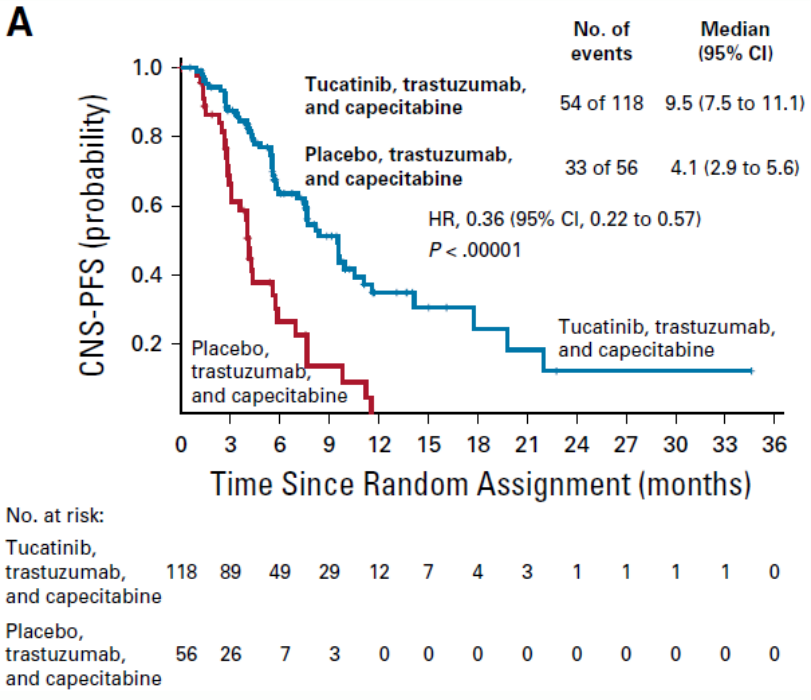
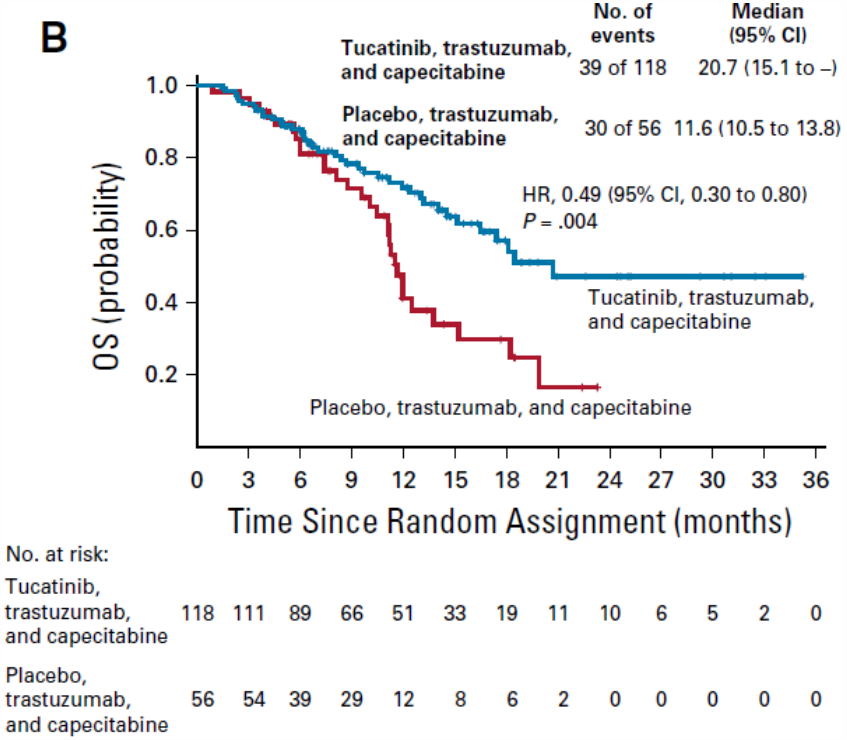
Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495; ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023.

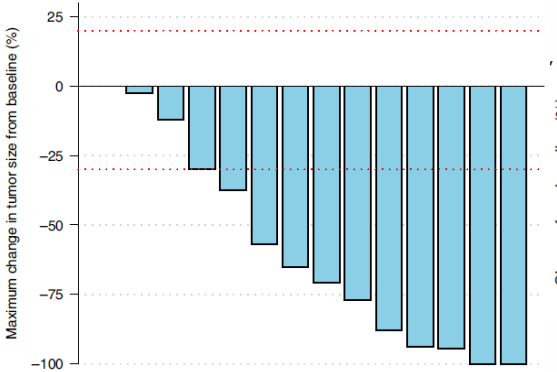
HER2CLIMB: Tucatinib + Trastuzumab + Capecitabine

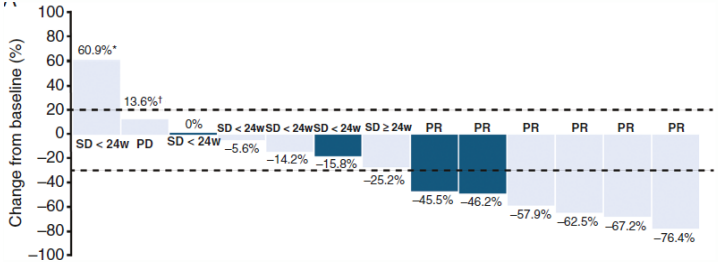


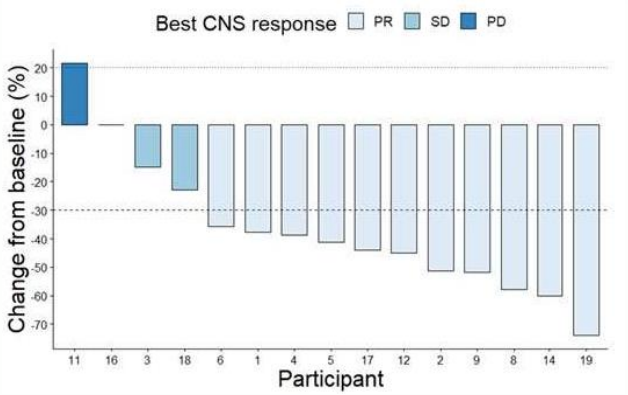


Lin NU, et al. *J Clin Oncol.* 2020;38(23):2610-2619.

ADCs Are Effective in BM: T-DXd







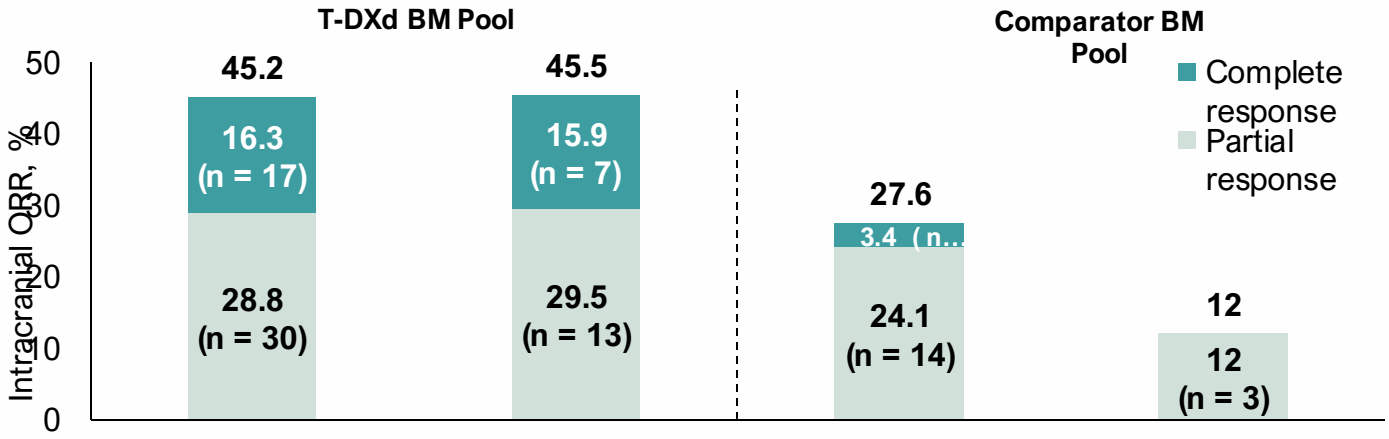
TUXEDO-1[1]
RR 73.3%

DEBBRAH[2]
RR 46.2%

DFCI/Duke/MDACC Series[3,4]
RR 73%

1. Bartsch R, et al. *Nat Med.* 2022;28(9):1840-1847; 2. Pérez-García JM, et al. *Neuro Oncol.* 2023;25(1):157-166;
3. Kabraji S, et al. SABCS 2021. Abstract PD4-05; 4. Kabraji S, et al. *Clin Cancer Res* 2023;29(1):174-182.

T-DXd Is Effective in BM: Combined DESTINY-Breast01/02/03



	Treated/Stable BMs (n = 104)	Untreated/Active BMs (n = 44)	Treated/Stable BMs (n = 58)	Untreated/Active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/missing	6 (5.8)	8 (18.2)	7 (12.1)	2 (8.0)
IC-DOR, median, months (95% CI)	12.3 (9.1–17.9)	17.5 (13.6–31.6)	11.0 (5.6–16.0)	NA

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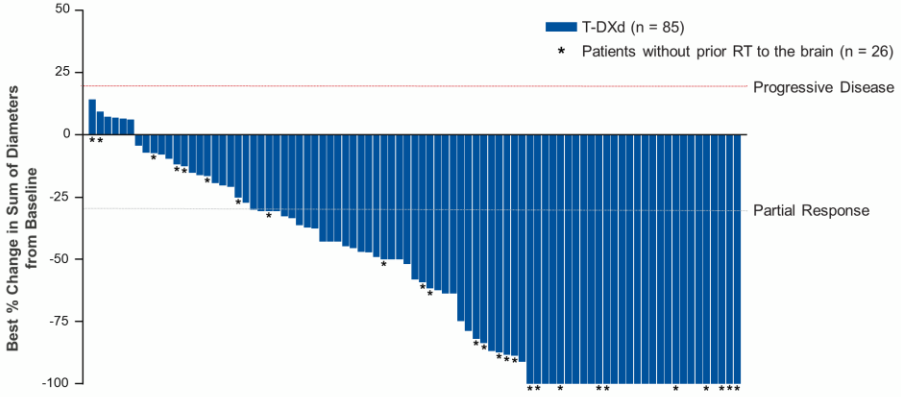
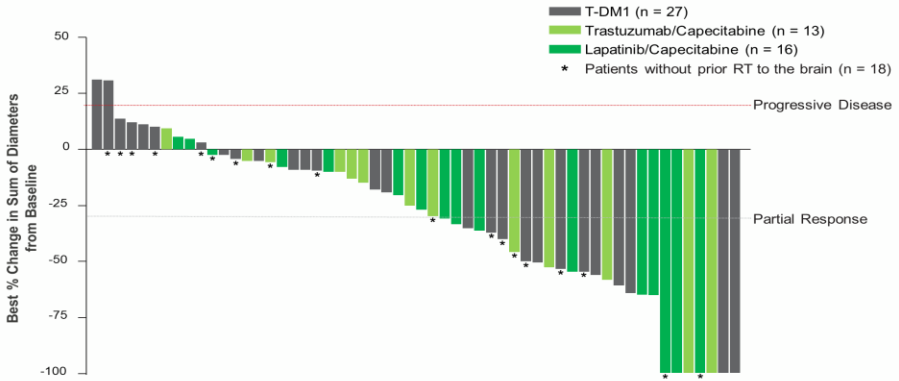
Hurvitz SA, et al. ESMO 2023. Abstract 3770.

T-DXd: Combined DESTINY-Breast01/02/03





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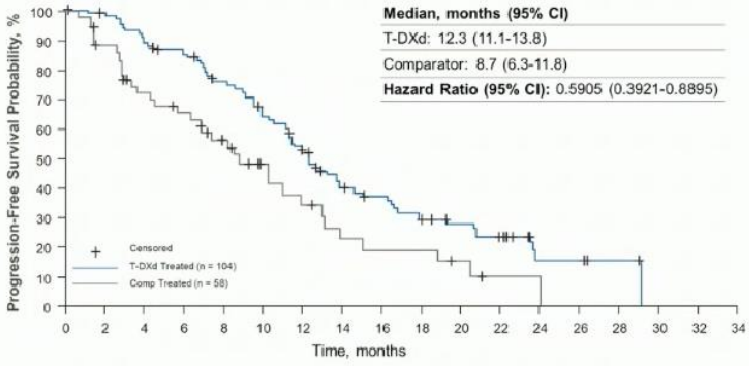
Hurvitz SA, et al. ESMO 2023. Abstract 3770.

T-DXd: Combined DESTINY-Breast01/02/03

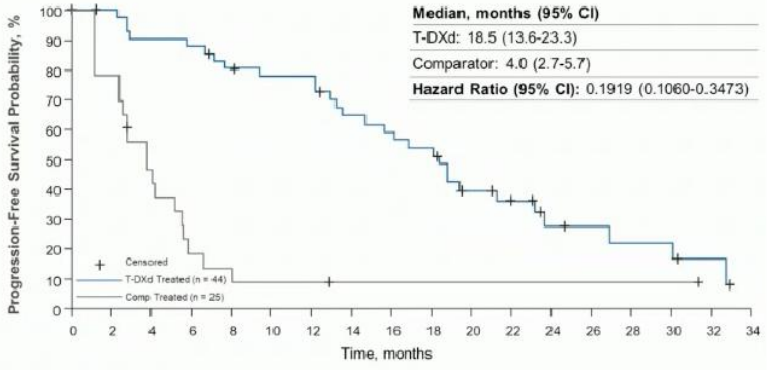
Treated/Stable BMs



Patients still at risk

T-DXd Treated (n = 104)	104	100	89	83	72	58	46	32	28	21	18	12	4	4	2	0	0	0
Comparator Treated (n = 58)	58	44	33	29	22	14	10	6	5	5	3	1	0	0	0	0	0	0

Untreated/Active BMs

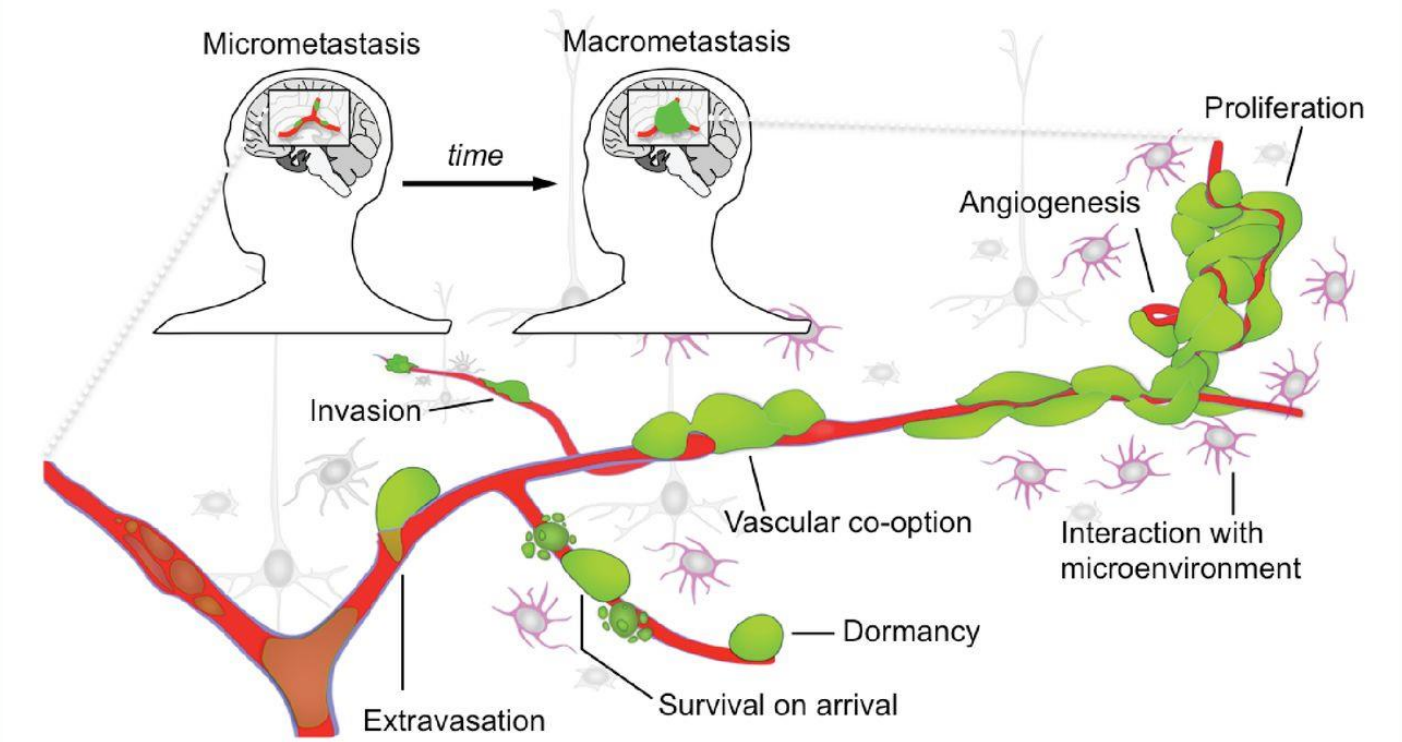


Patients still at risk

T-DXd Treated (n = 44)	44	41	37	36	32	30	30	24	22	20	13	11	6	5	4	4	2	0
Comparator Treated (n = 25)	25	18	11	5	3	2	2	1	1	1	1	1	1	1	1	1	0	0

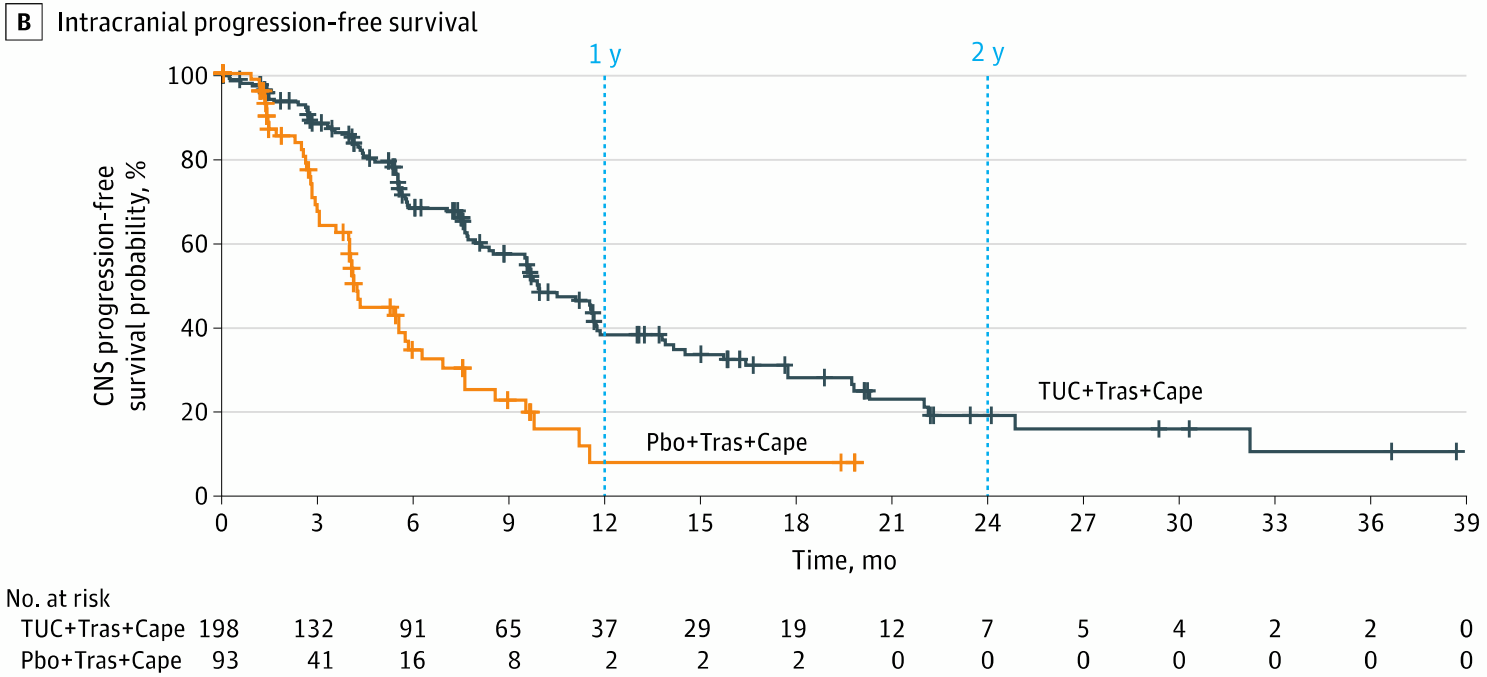
Hurvitz SA, et al. ESMO 2023. Abstract 3770.

Prevention: The Better Idea?



Preusser M, et al. *ESMO Open.* 2018;3:e000262.

BM Prevention in HER2+ BC: HER2CLIMB



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Lin NU, et al. *JAMA Oncol.* 2023;9(2):197-205.

Summary: Modern Treatment of HER2+ BC BM

- Treatment sequences for BM treatment
  - Adaptation of prognostic assessment?
  - Systemic treatment particular in asymptomatic patients
    - HER2CLIMB
    - ADC
  - Combination of local and systemic treatment

- BM prevention
  - Secondary endpoint?

Thank you for your attention!

Anna.Berghoff@meduniwien.ac.at

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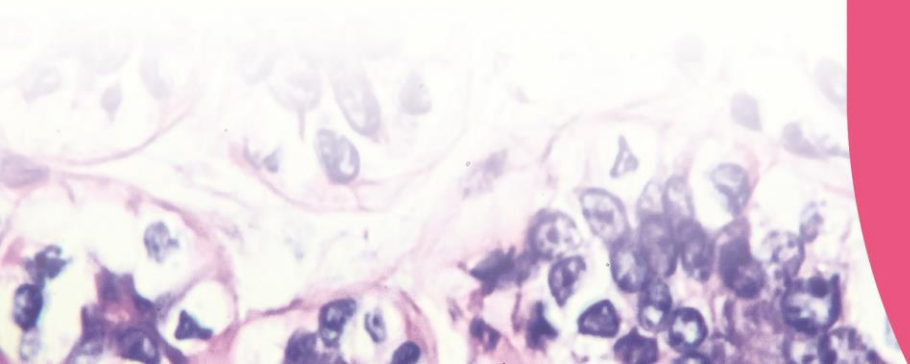
Q&A



APTITUDE HEALTH

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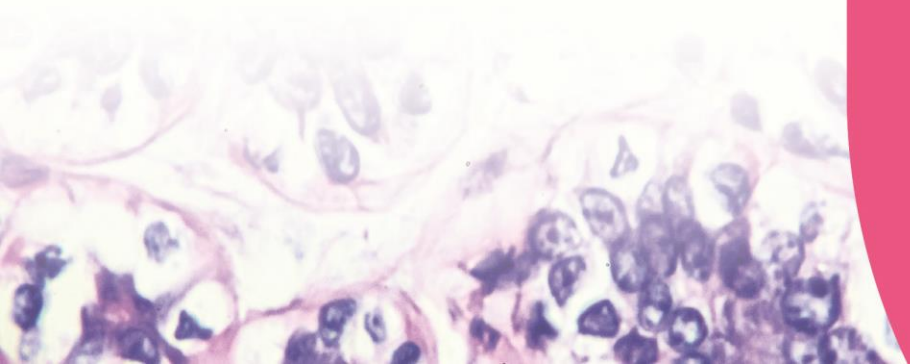
Break



APTITUDE HEALTH

Objectives

Understand major advances in early lines of treatment for HER2+ mBC

Learn about potential treatment options after second line treatment for HER2+ mBC

Understand changes in HER2 expression during treatment with HER2-targeted agents

Gain insights into the care of HER2+ mBC patients with CNS metastases

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Explore current and future sequencing strategies in HER2+ mBC

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Panel discussion on sequencing strategies: Use the best up front or keep it for later lines?

Nadia Harbeck and all faculty

APTITUDE HEALTH

Interactive Discussion

1. What is the optimal sequencing strategy of HER2-targeted agents in HER2+ mBC?
2. What drives the sequencing decisions?

We encourage our audience to ask questions using the Q&A box

Objectives

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Global Breast Cancer Academy

The evolution of clinical studies: Lessons from real-world data and new entities; HER2-low BC

Giuseppe Curigliano

APTITUDE HEALTH

The future of clinical studies: Lessons from real-world data and new entities; HER2-low BC

Giuseppe Curigliano, MD, PhD
University of Milano and Istituto Europeo di Oncologia
Milano, Italia

UNIVERSITÀ DEGLI STUDI
DI MILANO

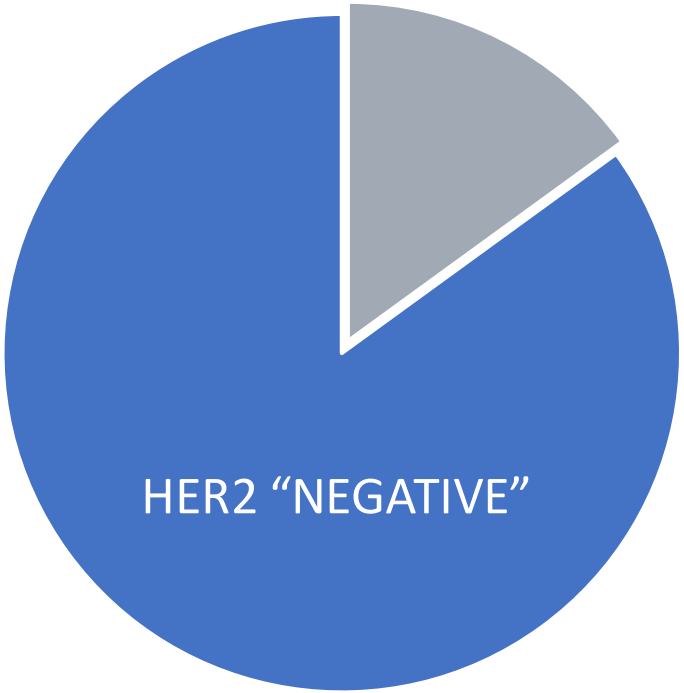
IEO
Istituto Europeo
di Oncologia

Disclosures

- Board member: Ellipses
- Consultant: Lilly, Novartis, Seattle Genetics, Roche-Genentech
- Research grants to my institute: MSD, AstraZeneca
- Speakers' bureau: Pfizer, Lilly, Novartis, Roche-Genentech, Samsung, Celltrion
- Stock ownership: None

New HER2-low segment

The “traditional” HER2 pie chart

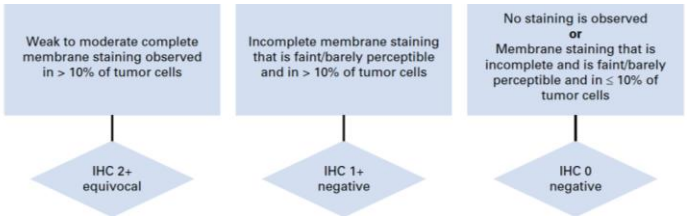


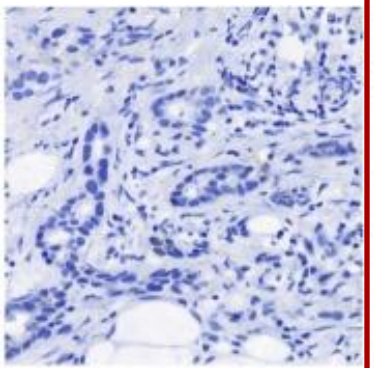
Conversely, those patients lacking *ERBB2* amplification are collectively defined **HER2 negative**

ERBB2, Erb-B2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
Adapted from Wolff A, et al. *J Clin Oncol.* 2018;36:2105-2122.

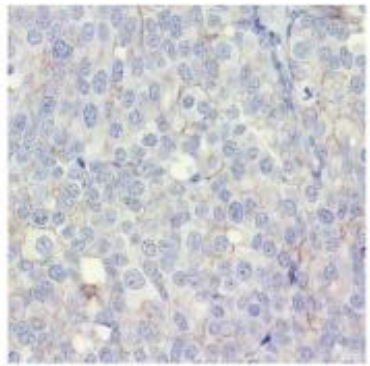
HER2 “negative”

10,000–1,000,000
HER2 receptors per cell

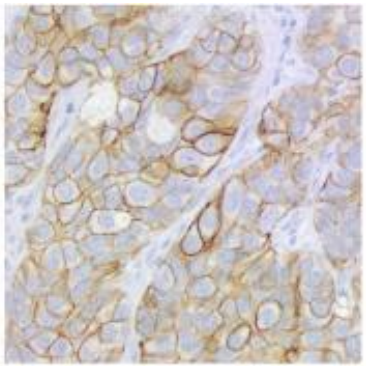




HER2
SCORE 0



HER2
SCORE 1+



HER2
SCORE 2+ / ISH-

No approved anti-HER2 treatment

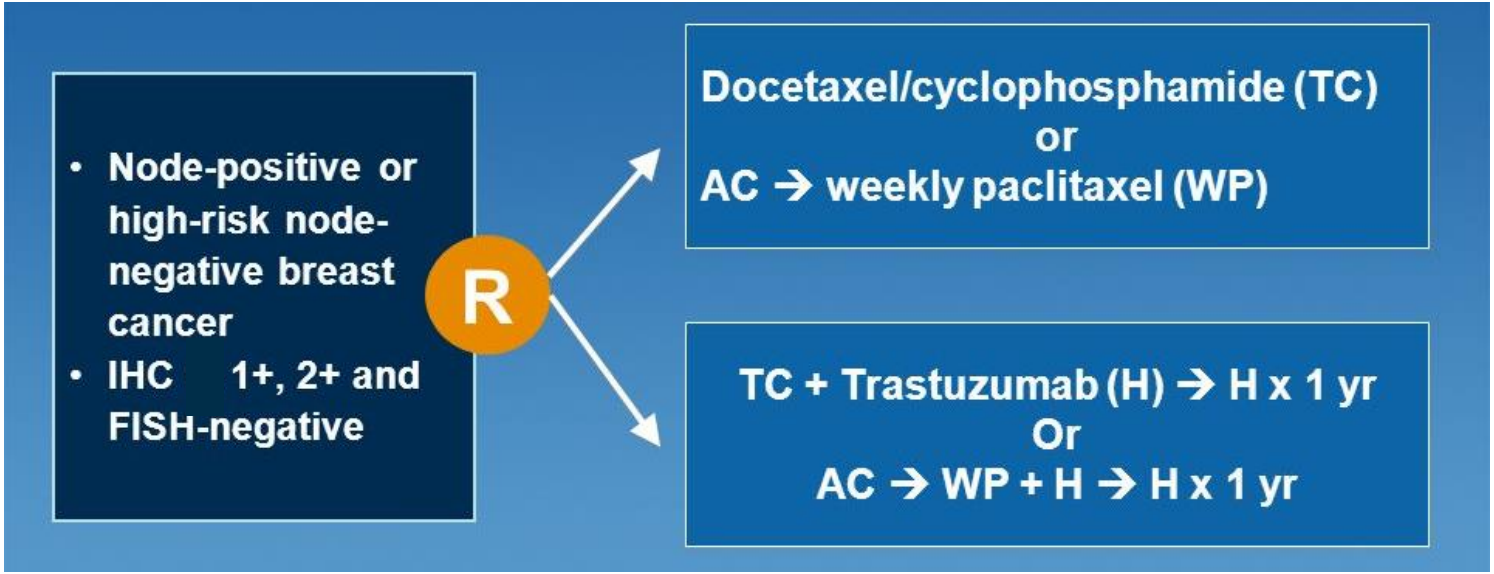
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Could they benefit from HER2 blockade?

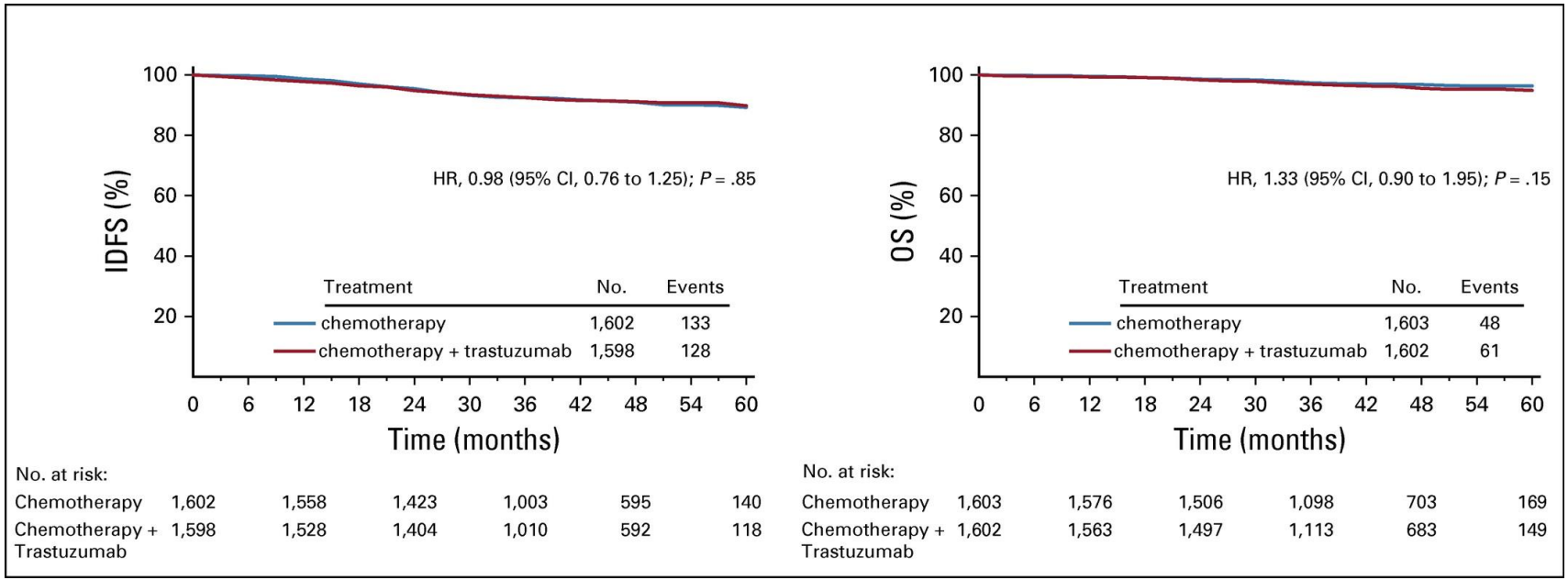
Adapted from Marchiò C, et al. *Semin Cancer Biol*. 2021;72:123-135.

NSABP B-47

A phase III trial was conducted to understand whether adjuvant trastuzumab is beneficial for HER2-low patients



NSABP B-47



NO BENEFIT of adjuvant trastuzumab for HER2-low patients

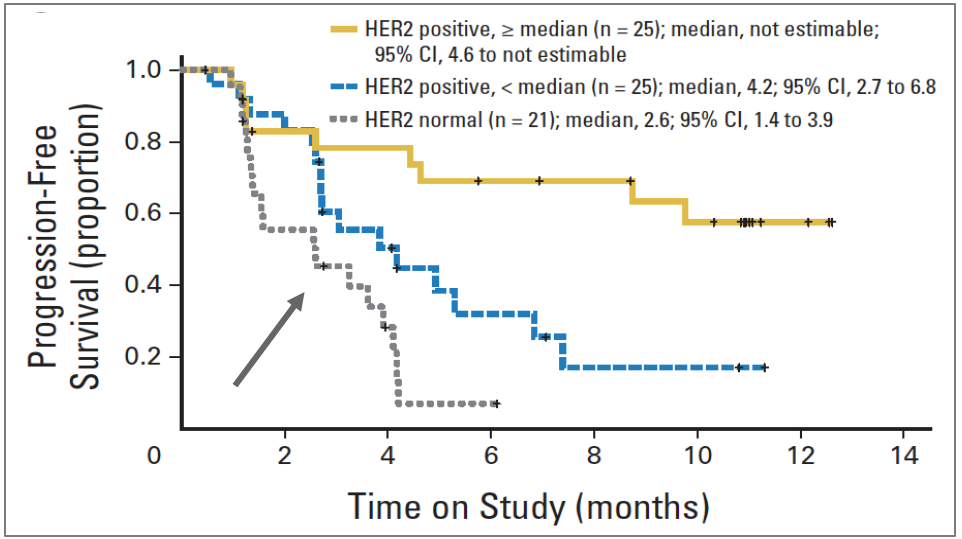
Adapted from Fehrenbacher L, et al. *J Clin Oncol.* 2020;38:444-453.

T-DM1 for HER2-low BC

Retrospective evaluation of T-DM1 in 21 cases of HER2-nonamplified MBC

Only 1 response (ORR 4.8%) and mPFS 2.6 months

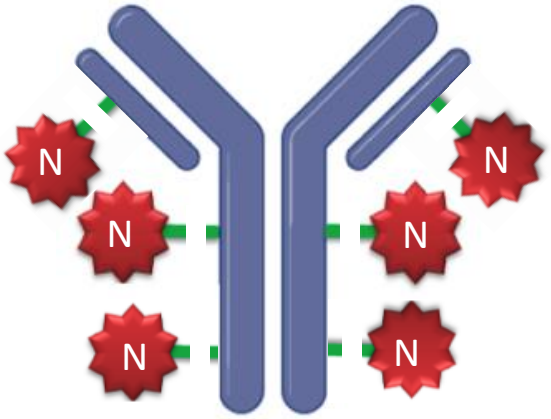
LITTLE ACTIVITY OF T-DM1 IN HER2-NEGATIVE mBC



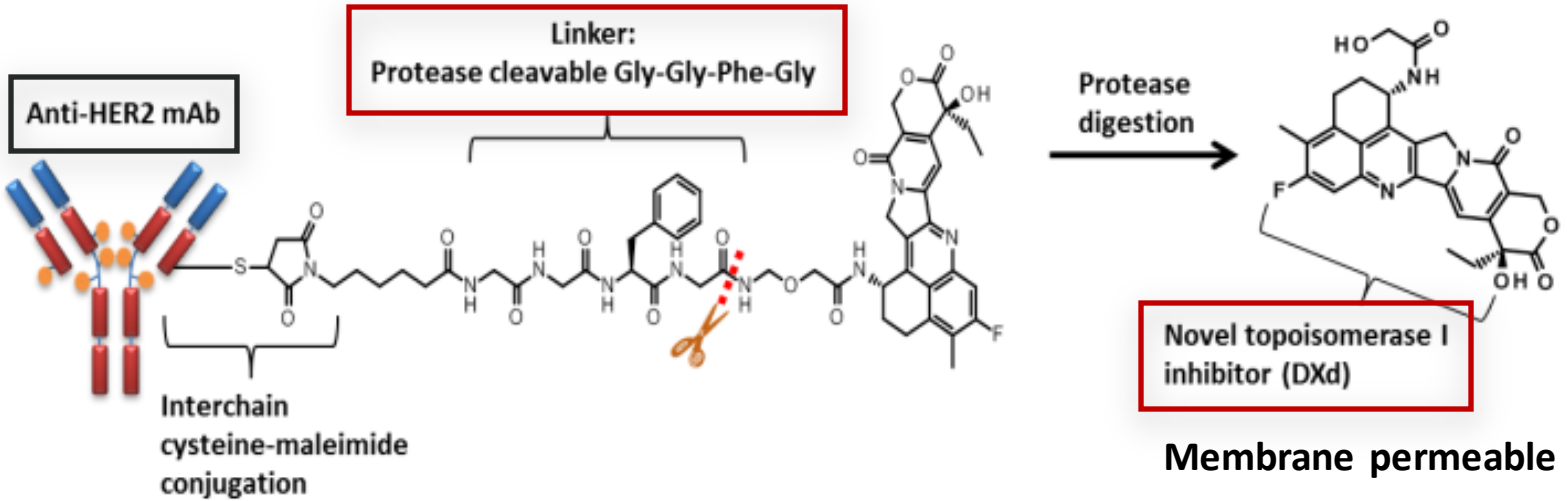
Adapted from Burris HA, et al. *J Clin Oncol.* 2011;29:398-405.

Novel conjugates for HER2-low BC

- Higher DAR
- Cleavable linker
- Novel payloads



Novel conjugates for HER2-low BC

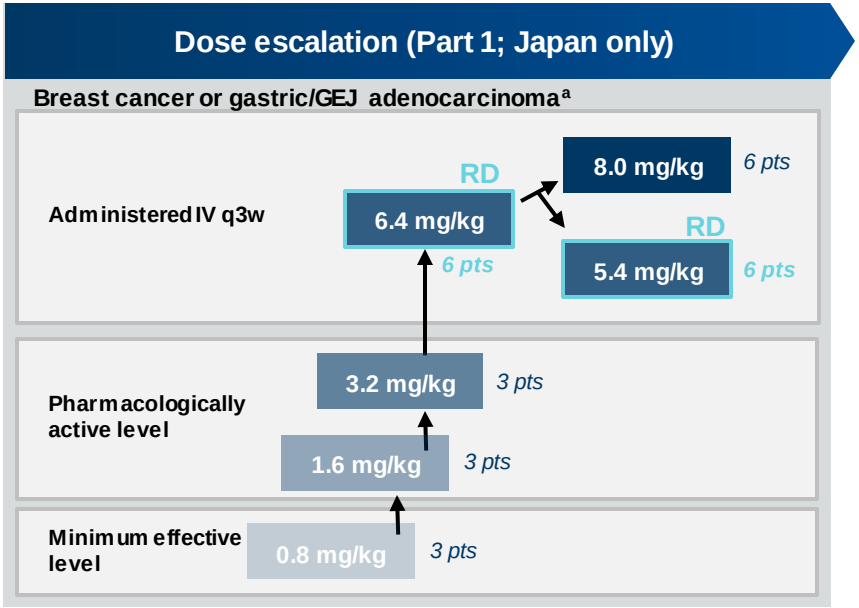


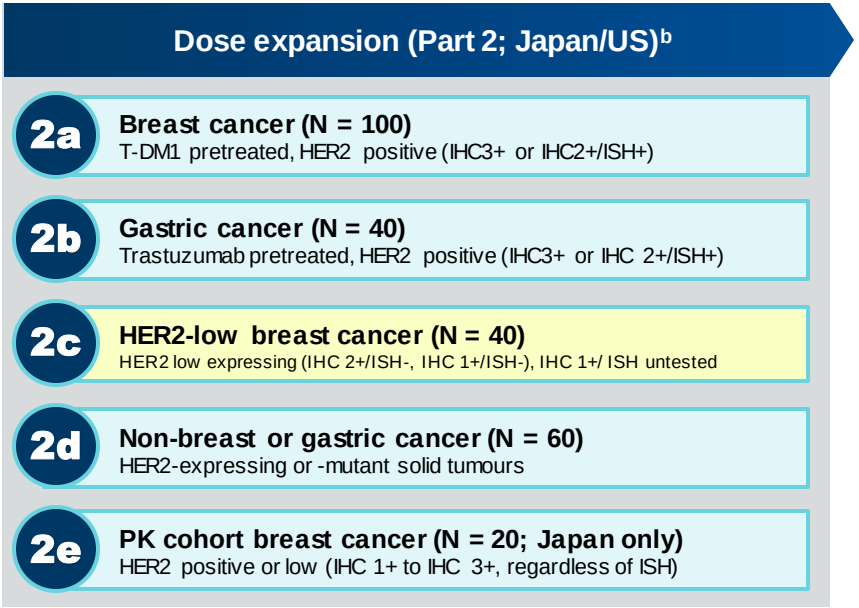
Membrane permeable

Highly potent

DAR: 8

Novel conjugates for HER2-low BC





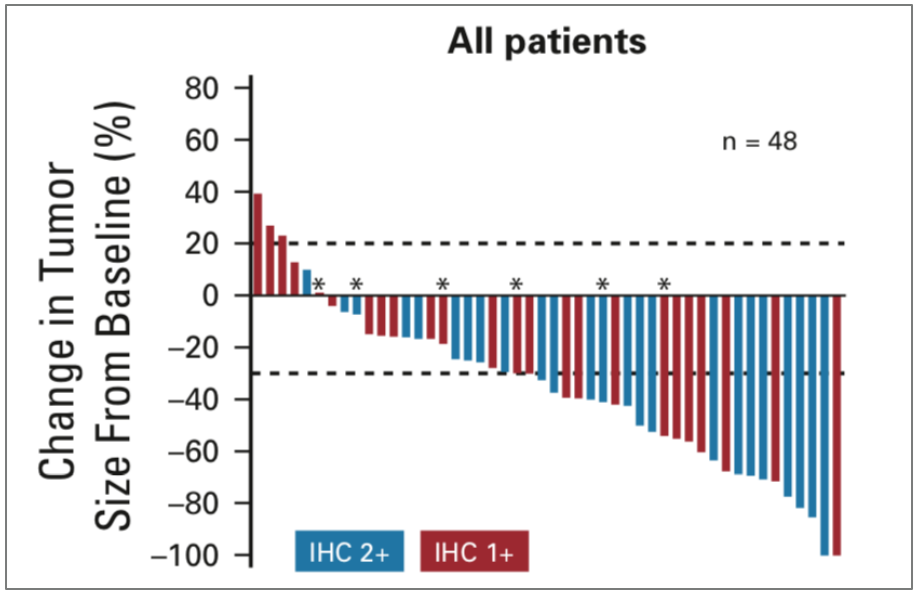
Doi T, et al. *Lancet Oncol* 2017;18:1512-1522; Iwata H, et al. ASCO 2018. Abstract 2501; Modi S, et al. *J Clin Oncol*. 2020;38:1887-1896.

Novel conjugates for HER2-low BC

First presented at ASCO 2018: results from a phase Ib study of **HER2 ADC (T-DXd)** suggested activity in HER2-low BC.

Among 54 highly pretreated (median 7.5) mBC patients with **HER2 IHC 1+ or 2+/FISH–**

- ORR 37%, with activity both in IHC 1+ and 2+
- mPFS 11 months

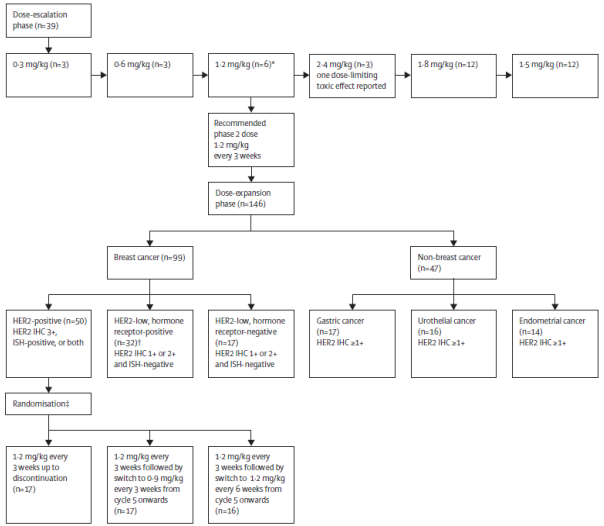


Modi S, et al. *J Clin Oncol*. 2020;38:1887-1896.

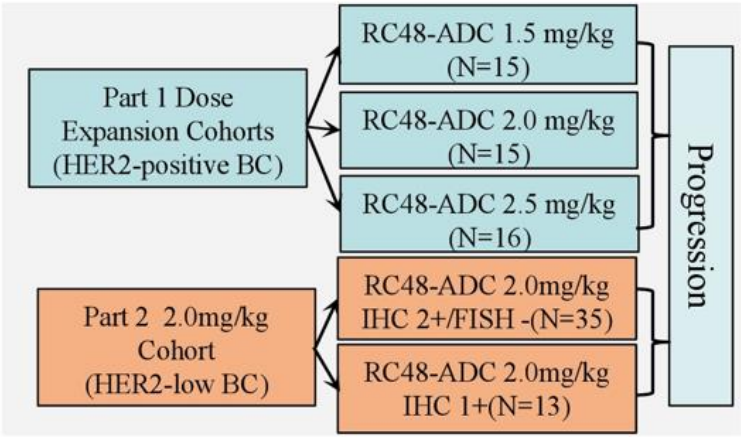
Novel conjugates for HER2-low BC

Two additional ADCs have shown activity in HER2-low (1+ or 2+/FISH–) mBC

Trastuzumab Duocarmazine (SYD985)



Disitamab Vedotin (RC48-ADC)

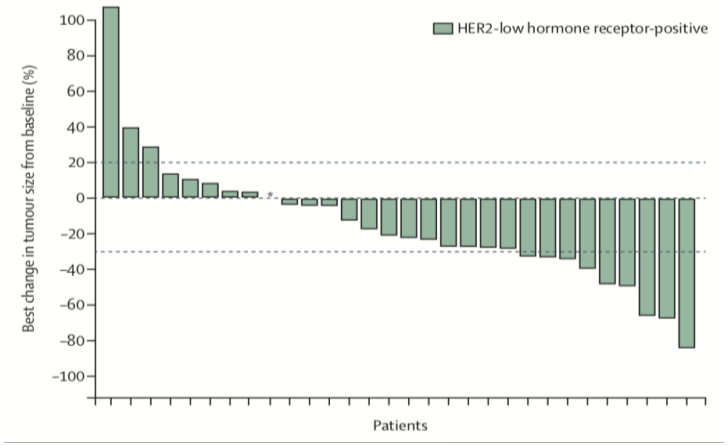


Banerji U, et al. *Lancet Oncol.* 2019;20:1124-1135; Wang J, et al. ASCO 2021.

Novel conjugates for HER2-low BC

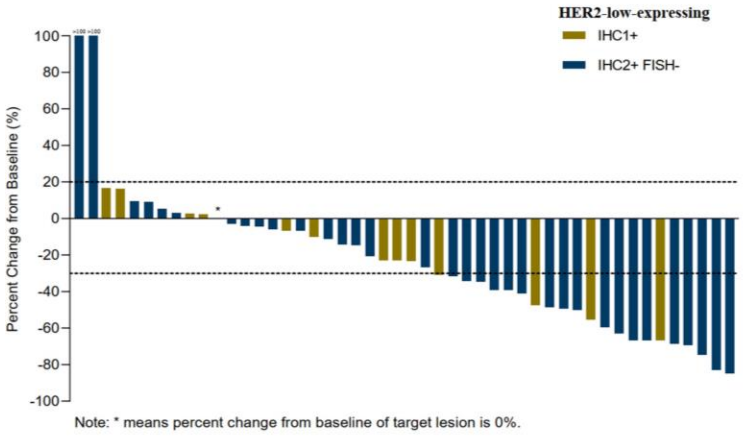
Two additional ADCs have shown activity in HER2-low (1+ or 2+/FISH–) mBC

Trastuzumab Duocarmazine (SYD985)[1]



49 HER2-low mBC patients: ORR 32%, mPFS 4 mo

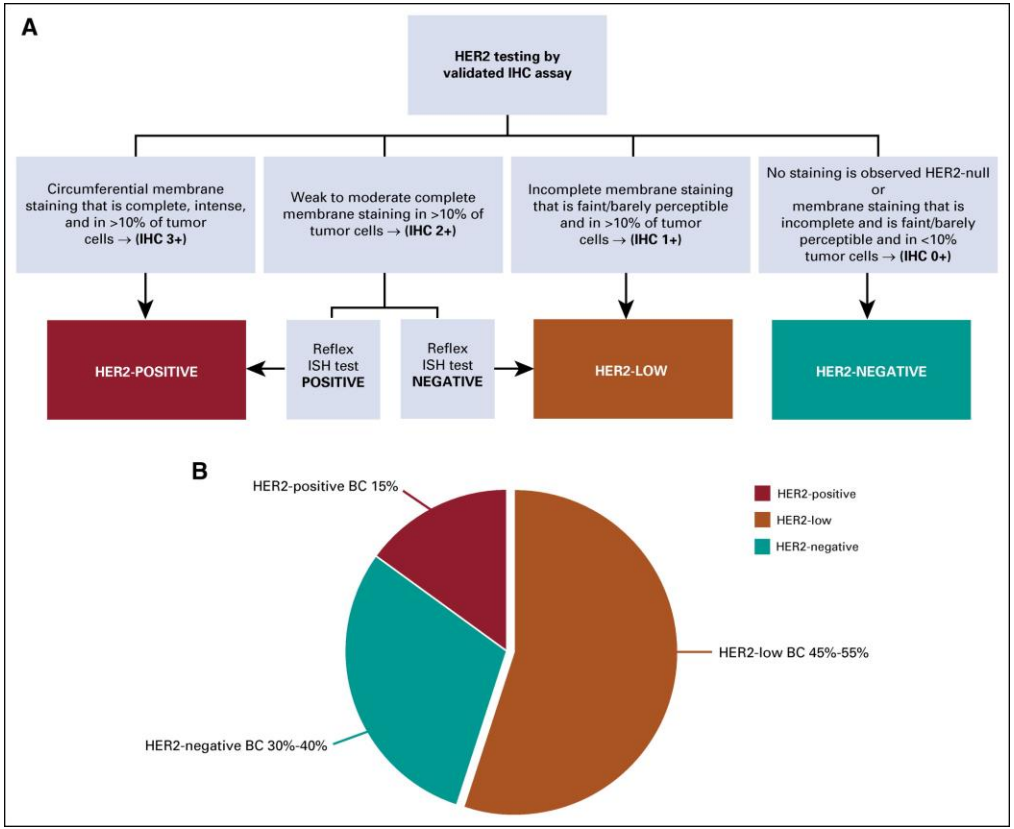
Disitamab Vedotin (RC48-ADC)[2]



48 HER2-low mBC patients: ORR 40%, mPFS 5.7 mo

Banerji U, et al. *Lancet Oncol.* 2019;20:1124-1135; Wang J, et al. ASCO 2021.

2020: Proposal of a new pie chart for HER2



Tarantino P, et al. *J Clin Oncol.* 2020;38:1951-1962.

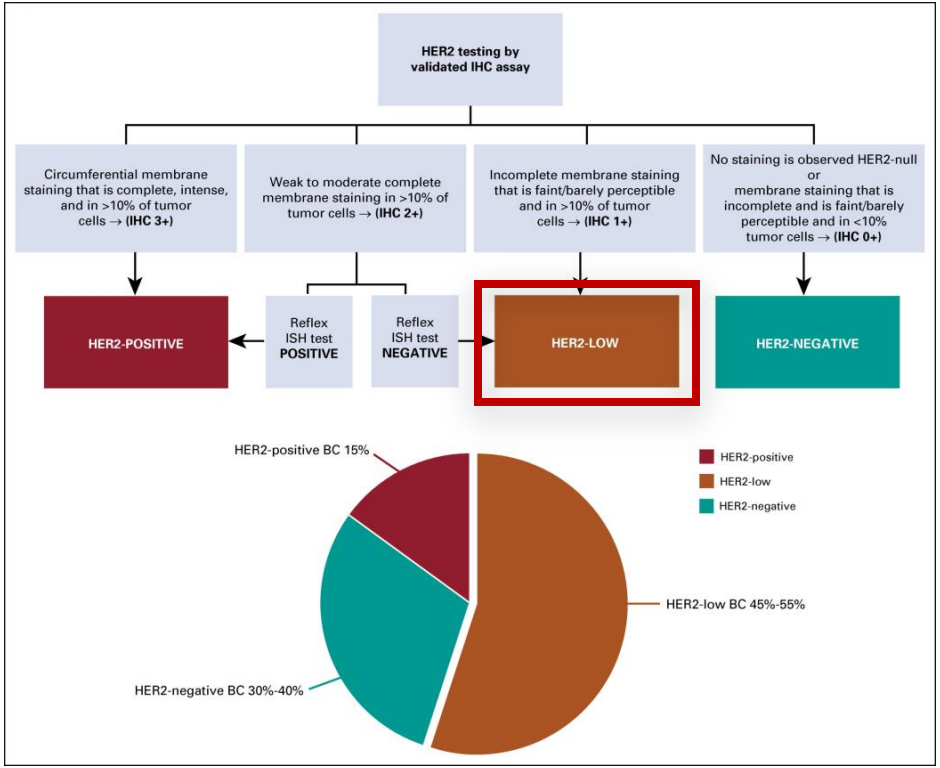
2020: Proposal of a new pie chart for HER2

About 50% of breast cancers are HER2 low, according to the current definition

Hormone receptors expressed?

YES → **HR+ HER2 LOW** *(~60% of HR+ tumors)*

NO → **TNBC HER2 low** *(~40% of TNBCs)*



Tarantino P, et al. *J Clin Oncol.* 2020;38:1951-1962.

DESTINY-Breast04 study design:

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]
- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, *nab*-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]
- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDKi, cyclin-dependent kinase 4/6 inhibitors; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

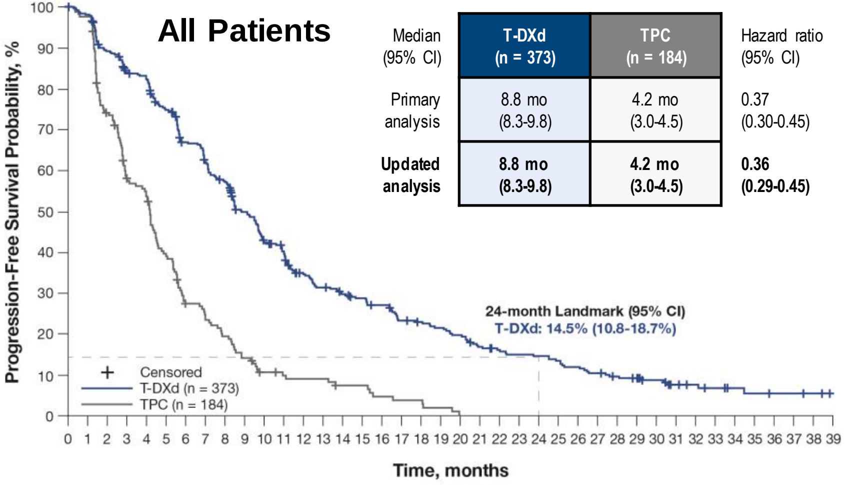
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only [IUO] assay system, at the time of study. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

1. Modi S, et al. *N Engl J Med*. 2022;387:9-20; 2. Harbeck N, et al. SABCS 2022. Poster P1-11-0; 3. Prat A, et al. SABCS 2022. Poster HER2-18.

Progression-free survival

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



Patients still at risk:

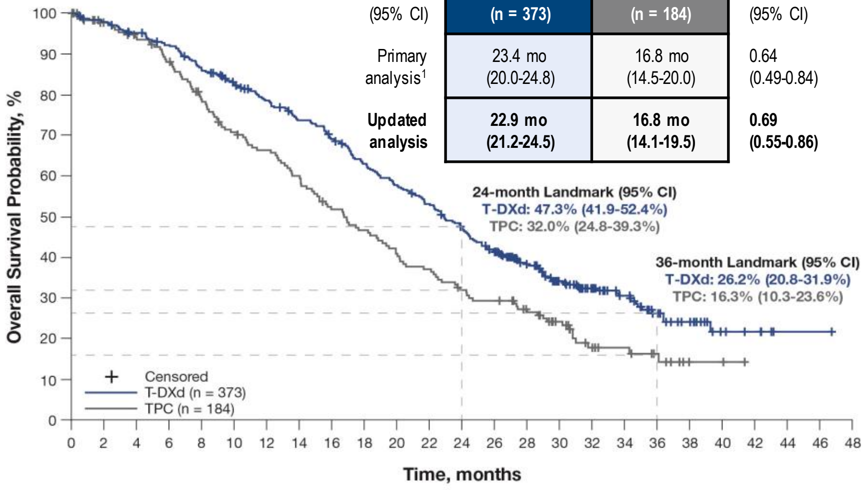
T-DXd (n = 373) 373 364 327 304 297 267 234 216 198 166 140 130 107 97 90 85 79 67 64 60 55 46 42 39 38 35 31 27 23 21 16 11 9 7 5 4 3 3 2 0

TPC (n = 184) 184 163 121 92 85 61 41 35 29 21 14 12 11 11 8 8 5 4 4 2 0

Overall survival

All Patients

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



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

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

Results from the 32-month median follow-up for DESTINY-Breast04 confirm the sustained clinically meaningful improvement for T-DXd vs TPC previously demonstrated in HER2-low (IHC 1+, IHC 2+/ISH−) mBC, regardless of HR status

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

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

Giuseppe Curigliano, MD, PhD

Overall safety summary

- Exposure-adjusted incidence rates for any-grade TEAEs were 1.2 and 2.6 per patient-year for the T-DXd and TPC arms, respectively
  - This supports that **longer T-DXd exposure does not increase toxicity**
- Overall, the safety profile is consistent with results from the primary analysis (data cutoff, January 11, 2022)
  - **Rates of ILD/pneumonitis remained unchanged with longer follow-up**, and rates of left ventricular dysfunction were consistent with previously observed rates

n (%)	Safety analysis set[a] T-DXd (n = 371)	TPC (n = 172)
TEAEs	369 (99.5)	169 (98.3)
Grade ≥3	202 (54.4)	116 (67.4)
Serious TEAEs	108 (29.1)	44 (25.6)
TEAEs associated with dose discontinuation	62 (16.7)	14 (8.1)
TEAEs associated with dose interruptions	155 (41.8)	73 (42.4)
TEAEs associated with dose reductions	89 (24.0)	65 (37.8)
TEAEs associated with deaths	15 (4.0)	5 (2.9)
Total on-treatment deaths[b]	14 (3.8)	8 (4.7)

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]On-treatment death is defined as death that occurred any time from date of first dose through 47 days after the last dose of the study treatment.
Modi S, et al. *N Engl J Med*. 2022;387:9-20.

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  - **Rates of ILD/pneumonitis remained unchanged with longer follow-up**, and rates of left ventricular dysfunction were consistent with previously observed rates

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	**24 (6.5)**	**4 (1.1)[a]**	0	**4 (1.1)[a]**	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0

n (%)	Safety analysis set[a] T-DXd (n = 371)	TPC (n = 172)
TEAEs	369 (99.5)	169 (98.3)
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Modi S, et al. *N Engl J Med*. 2022;387:9-20.

PFS2[a] and post-study anticancer therapies[b]

	HR+ Cohort		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median PFS2 by investigator, mo (95% CI)	15.5 (13.8-17.2)	10.5 (8.3-11.4)	15.4 (13.6-16.5)	9.7 (8.3-10.8)
Hazard ratio (95% CI)	0.51 (0.40-0.64)		0.51 (0.41-0.64)	
Post-study anticancer therapies				
Systemic treatment, n (%)	247 (74.6)	126 (77.3)	282 (75.6)	144 (78.3)
Targeted therapy[c]	119 (36.0)	70 (42.9)	134 (35.9)	75 (40.8)
CDK4/6 inhibitors	47 (14.2)	27 (16.6)	48 (12.9)	27 (14.7)
ADC	**16 (4.8)**	**15 (9.2)**	**18 (4.8)**	**15 (8.2)**
T-DXd	2 (0.6)	4 (2.5)	2 (0.5)	4 (2.2)
Sacituzumab govitecan	9 (2.7)	5 (3.1)	11 (2.9)	5 (2.7)
Endocrine therapy	102 (30.8)	56 (34.4)	103 (27.6)	57 (31.0)
Chemotherapy	222 (67.1)	109 (66.9)	257 (68.9)	126 (68.5)
Radiation, n (%)	32 (9.7)	25 (15.3)	37 (9.9)	29 (15.8)
Surgery, n (%)	3 (0.9)	1 (0.6)	5 (1.3)	1 (0.5)

ADC, antibody-drug conjugate; CDK, cyclin-dependent kinase; HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Defined as the time from date of randomization to the first documented progression per investigator assessment on next-line of systemic therapy or death due to any cause, whichever occurs first.
[b]Participants may have been treated with more than 1 type of post-study anticancer therapy. [c]Class includes CDK4/6 inhibitor, immunotherapy, antibody-drug conjugates, or no subclass specified.

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Surgery, n (%)			5 (1.3)	1 (0.5)

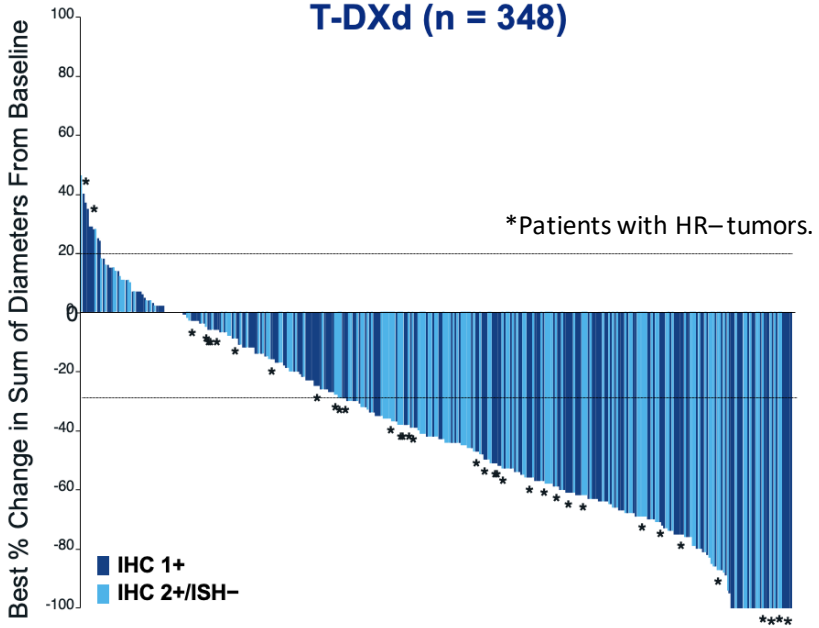
ADC sequence

How many had discontinued for ILD/toxicity?

ADC, antibody-drug conjugate; CDK, cyclin-dependent kinase; HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Defined as the time from date of randomization to the first documented progression per investigator assessment on next-line of systemic therapy or death due to any cause, whichever occurs first.
[b]Participants may have been treated with more than 1 type of post-study anticancer therapy. [c]Class includes CDK4/6 inhibitor, immunotherapy, antibody-drug conjugates, or no subclass specified.

Activity in IHC 1+ vs 2+/ISH–

Similar activity in terms of response rate and duration of PFS was observed in patients with IHC 1+ and 2+/ISH– disease

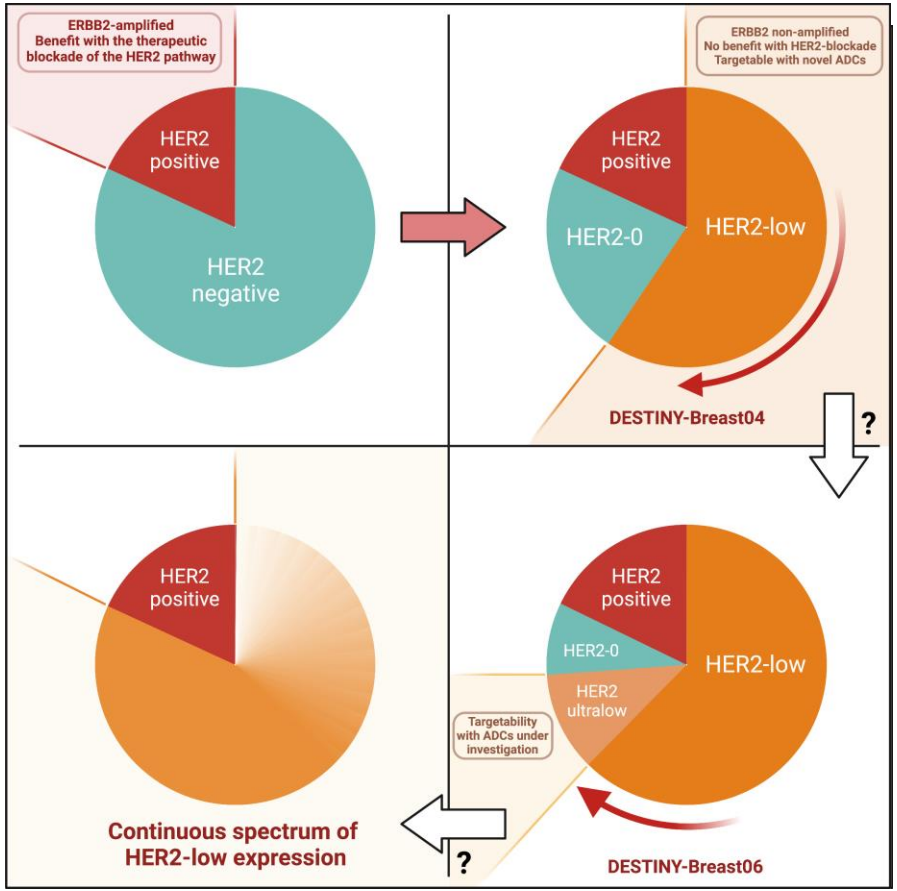


Subgroup Analysis: PFS in HR+

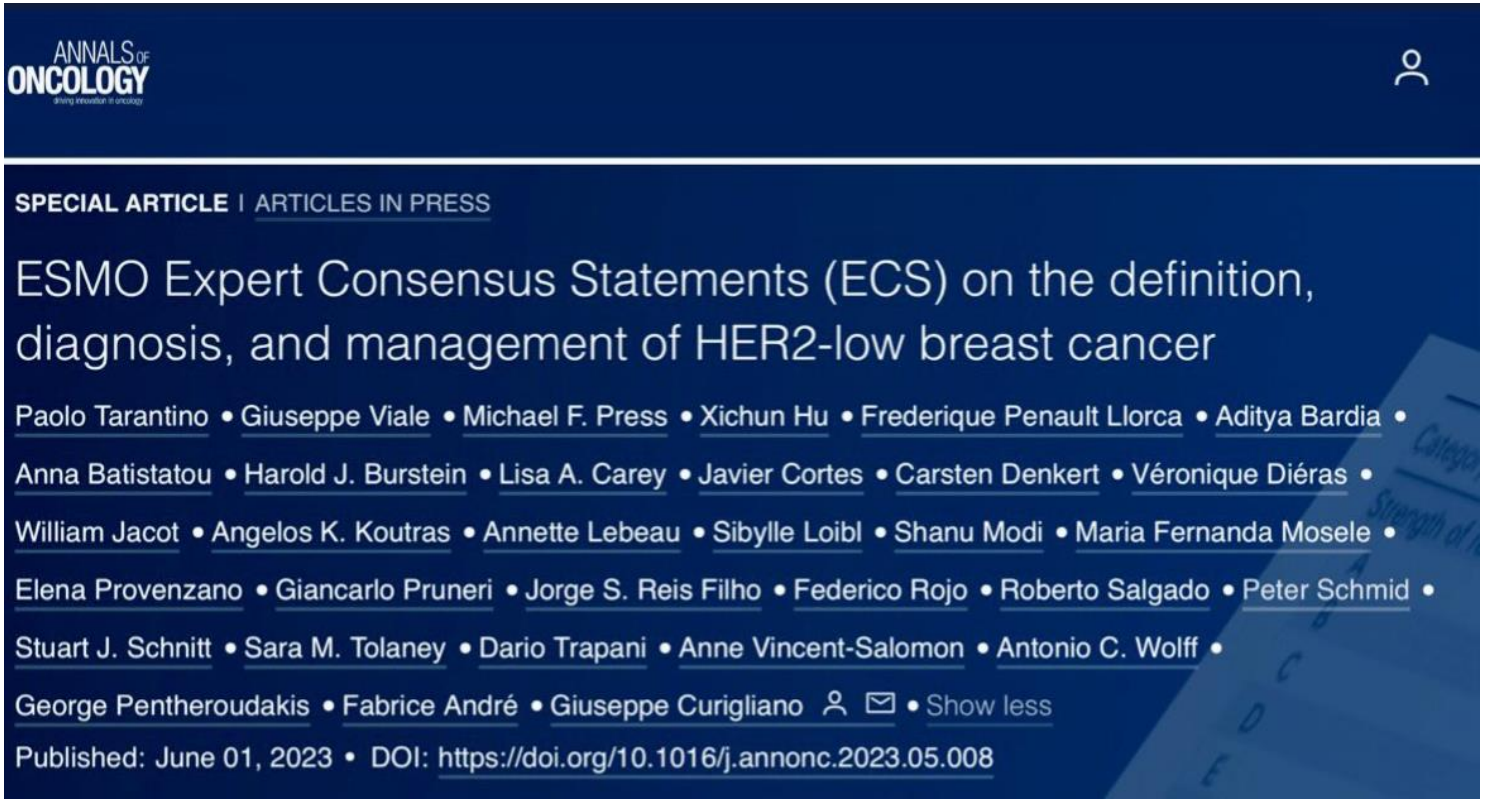
	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH–	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)

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

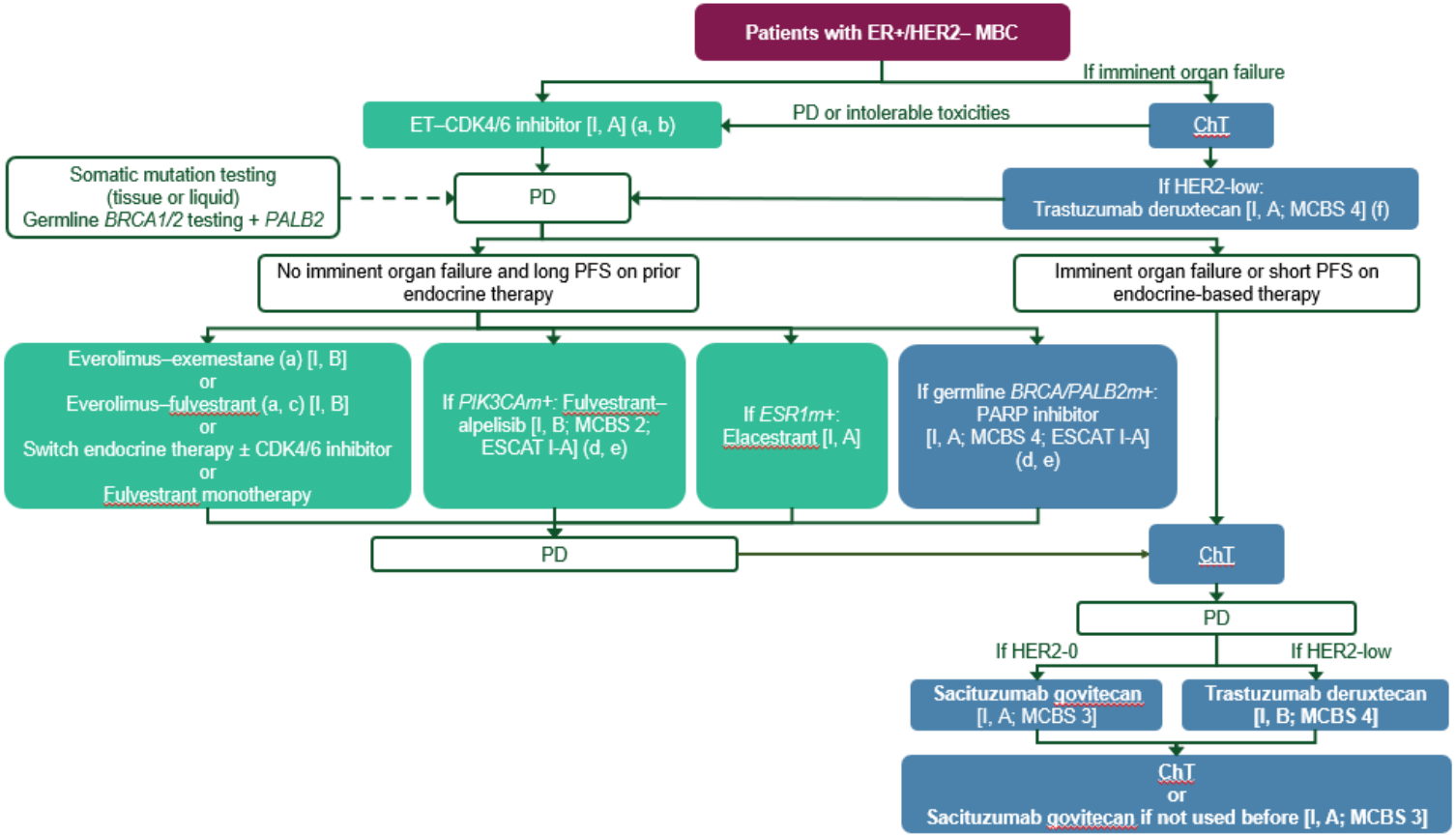
The future pie chart of HER2-low breast cancer



ESMO statements in HER2-low



ESMO Living Guidelines May 2023



ESMO Living Guidelines. May 2023.

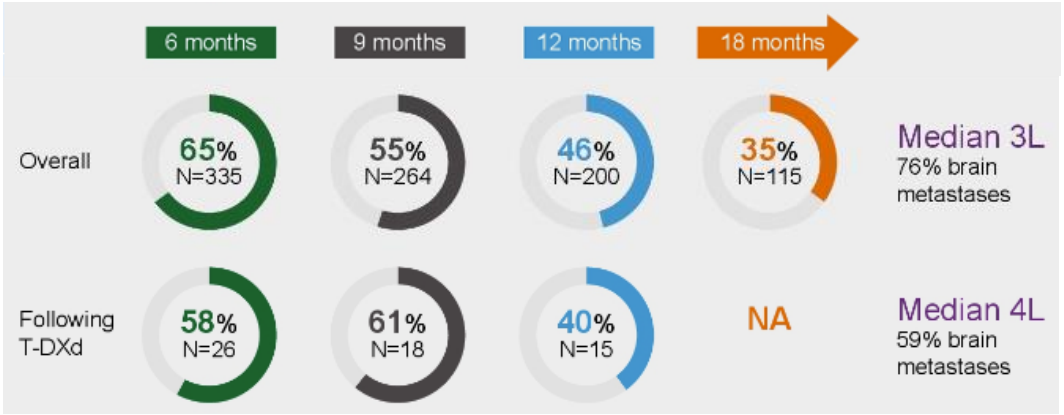
Real-world patient characteristics and treatment patterns associated with tucatinib therapy in patients with HER2+ metastatic breast cancer

Carey Anders,[1] Edward Neuberger,[2] Naomi RM Schwartz,[2] Karen Bartley,[2] Ling-I Hsu,[2] Gabriel Wong,[2] Matthew T Blahna,[2] Brian T Pittner,[2] Shu Wang,[3] Jane Meisel[4]

[1]Duke Cancer Institute, Durham, NC, USA; [2]Seagen Inc, Bothell, WA, USA; [3]Genesis Research, Hoboken, NJ, USA; [4]Winship Cancer Institute, Atlanta, GA, USA

Komodo Health Sentinel analysis: N = 528; prior lines 2L (1-3)

- Time to discontinuation 8.5 mo
- Time to next treatment 10.7 mo

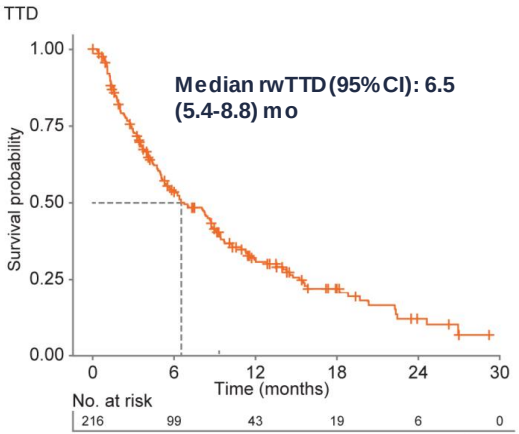


Anders CK, et al. ASCO 2023. Abstract 1051.

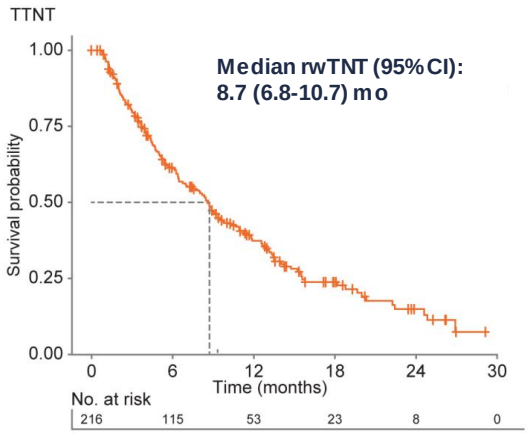
Real-world patient characteristics, treatment patterns, and clinical outcomes associated with tucatinib therapy in HER2+ mBC

Flatiron Database Overall Analysis N = 216; Prior Lines 2L (1-3)

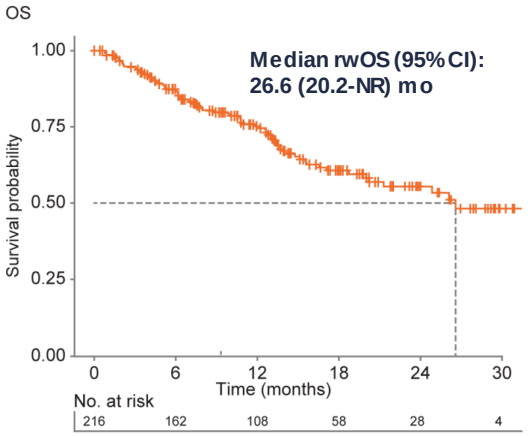
Time to discontinuation
6.5 mo



Time to next treatment
Median **8.7 mo**



Overall survival
Median **26.6 mo**



Tucatinib Immediately After T-DXd (n = 35): Prior Lines 3L (1-10)

Time to discontinuation
6.4 mo

Time to next treatment
Median **8.1 mo**

Overall survival
Median **13.9 mo**

reTTNT, real-world time to next treatment; rwOS, real-world overall survival; rwTTD, real-world time to treatment discontinuation.
Kaufman PA, et al. *Front Oncol*. 2023;13:1264861.

unicancer
Abstract #1014
ASCO meeting 2023
Poster Discussion Session - Breast Cancer—Metastatic 4th of June 2023

Efficacy of Tucatinib+Trastuzumab+Capecitabine (TTC) after Trastuzumab-deruxtecan (T-DXd) exposure in Her2-positive metastatic breast cancer. A French multicentre retrospective study.

Jean-Sebastien Frenel1, Jean Zeghondy2, Catherine Guerin1, Audrey Mailliez3, Elsa Volant1, Francois Poumeaud4, Anne Patsouris1, Monica Arnedos5, Caroline Bailleux6, Julie Cabal7, Loick Galland8, Alexandre De nonneville9, Severine Guiu Lahaye10, Florence Dalenc11, Barbara Pistilli2, Thomas Bachelot12, Pierre Martin13, Francois Bocquet1, Louis Larrouquere12, Delphine Loirat13

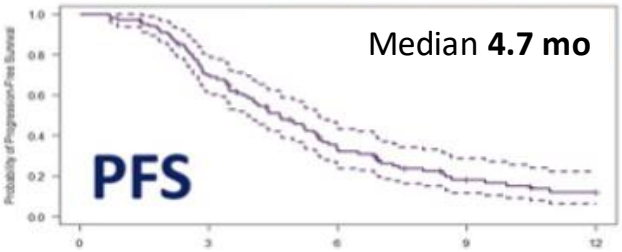
1Institut de Cancerologie de l'Ouest, Saint-Herblain, France; 2Gustave Roussy Cancer Center, Villejuif, France; 3Oscar Lambret Comprehensive Cancer Center, Lille, France; 4Oncopôle, Toulouse, France; 5Institut Bergonie, Bordeaux, France; 6Centre Antoine Lacassagne, Nice, France; 7Centre Eugene Marquis, Rennes, France; 8Centre Georges Francois Leclerc, Dijon, France; 9Institut Paoli Calmette, Marseille, France; 10Montpellier Cancer Institute, Montpellier, France; 11Claudius Régaud Institute Oncopôle, Toulouse, France; 12Medical Oncology, Centre Léon Bérard, Lyon, France; Institut Curie, Paris, France.

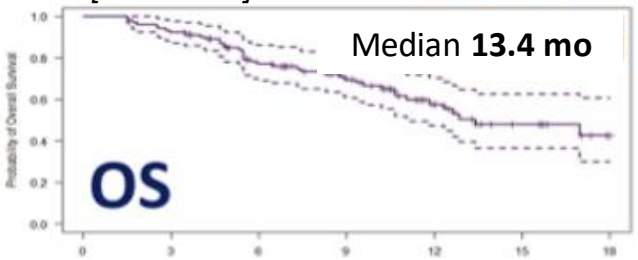
Institut de Cancérologie de l'Ouest
UCBG unicancer

UniCancer Analysis N = 101: Prior Lines 4L (2-15)

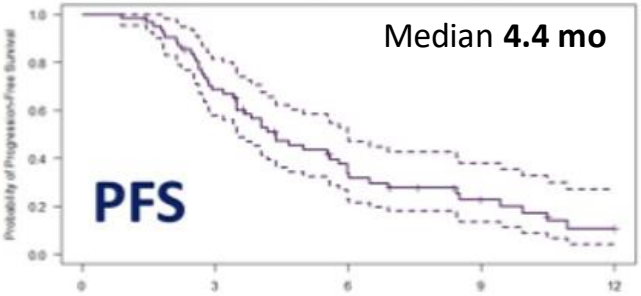
Overall Population (n = 101)

Median follow-up: 11 months [10.5-13.4]

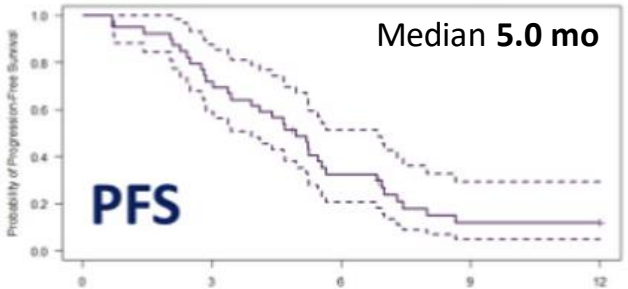




Patients without BM (n = 62)



Patients with BM (n = 39)



*Lapatinib/neratinib.

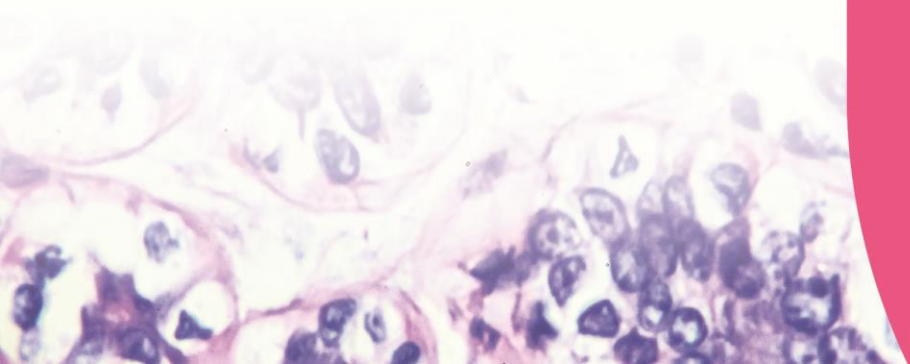
Frenel JS, et al. ASCO 2023. Abstract 1014.

Thank You

Giuseppe Curigliano, MD, PhD
giuseppe.curigliano@ieo.it

Global Breast Cancer Academy

Q&A



APTITUDE HEALTH

Objectives

Understand major advances in early lines of treatment for HER2+ mBC

Learn about potential treatment options after second line treatment for HER2+ mBC

Understand changes in HER2 expression during treatment with HER2-targeted agents

Gain insights into the care of HER2+ mBC patients with CNS metastases

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Explore current and future sequencing strategies in HER2+ mBC

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BC case-based panel discussion

Case 1: Elie El-Rassy

Case 2: Rodrigo Sánchez-Bayona

Moderator: Nadia Harbeck

APTITUDE HEALTH

Global Breast Cancer Academy

Case 1: HER2+ mBC – what do we do after T-DXd?

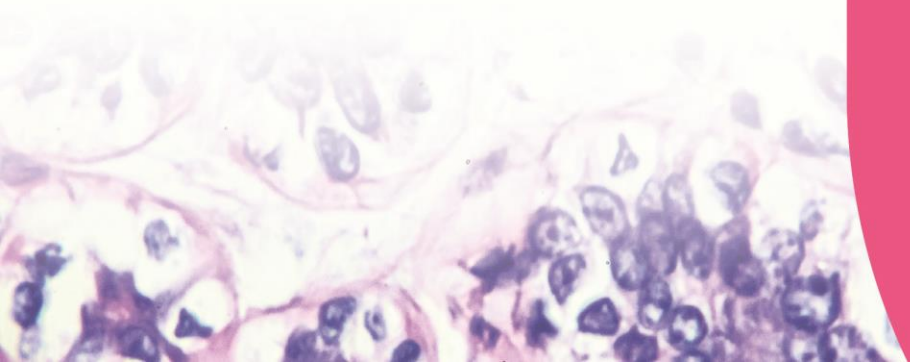
Elie Rassy MD MSc MPH

Department of Medical Oncology, Gustave Roussy

Oncostat U1018 INSERM, University Paris-Saclay

Department of Biostatistics & Epidemiology, Gustave Roussy, University Paris-Saclay

Villejuif, France



APTITUDE HEALTH

Declaration of interests

- Research support (institutional): Gilead
- Honoraria: Eli Lilly, Seagen
- Travel, accommodations, expenses: Pfizer, Roche, Mundipharma, Eli Lilly, Gilead
- Speakers Bureau: None

Case presentation

- Mrs AF
- 65 y/o
- Living in France
- Personal medical h/o
  - Hypertension; Rx ACEi
- Family medical h/o
  - Mother BC at 72 y/o

October 2016

- Right breast lump of 6 cm
- Workup: cT3N2M0
  - Invasive ductal carcinoma
  - ER 90%, PR 10%
  - HER2 score 1+
  - Grade III
  - Ki67 60%
- Neoadjuvant chemotherapy: EC 100 × 4 followed by P weekly × 4
- Surgery: mastectomy + LND pT1c(m)N1 → RCB III
- Radiotherapy: chest wall + LN (w/o axilla) 50 Gy/25 fractions
- Endocrine therapy: letrozole 2.5 mg/d
- Regular F/U: satisfying adherence to surveillance and ET
- 2017: sigmoid diverticulitis treated with antibiotics
  - Endoscopy: normal

Metastatic setting

- **September 2021**: multiple lung and bone metastases
  - Pathology: ductular invasive carcinoma, ER 100%, PR 2%, HER2 score 2+, FISH amplified
  - Molecular profiling
    - *PIK3CA* H1047R (0.97%)
    - *RB1* F473fs*5 (0.91%)
    - *TP53* R273L (11.9%), R273C (0.33%), splice site 97-4_131del39 (0.63%)
    - TMB: 5
    - Status MSS: MSS

- **First-line treatment** (PFS 15 mo)
  - CLEOPATRA regimen + letrozole maintenance
- **Second-line treatment**
  - Trastuzumab deruxtecan 5.4 mg/kg q3 weeks
  - At 3 months: CR
- **At 5 months**
  - Bowel perforation by peritoneal carcinomatosis
  - Urgent colostomy complicated by AKI and rhabdomyolysis

Question 1

***2021
70 y/o h/o diverticulitis 2017, colostomy
MBC HR+ HER2 amplified
1L: CLEOPATRA, maintenance ET
2L: DB-03

> T-DXd was withheld for 2 months
  - **PS 3**
  - Patient **dependent** on a **wheelchair** for **fatigue**
  - Persistent **diarrhea** after the **colostomy**

How would you treat the patient at this point?

- Supportive care, given the performance status and comorbidities
- Tucatinib + capecitabine + trastuzumab
- Letrozole + trastuzumab
- Chemotherapy + trastuzumab

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h/o: history; HR: hormone receptor; PS: performance status; y/o: years old.

Case continuation

***2021
70 y/o h/o diverticulitis 2017, colostomy
MBC HR+ HER2 amplified
1L: CLEOPATRA, maintenance ET
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- T-DXd was withheld for 2 months
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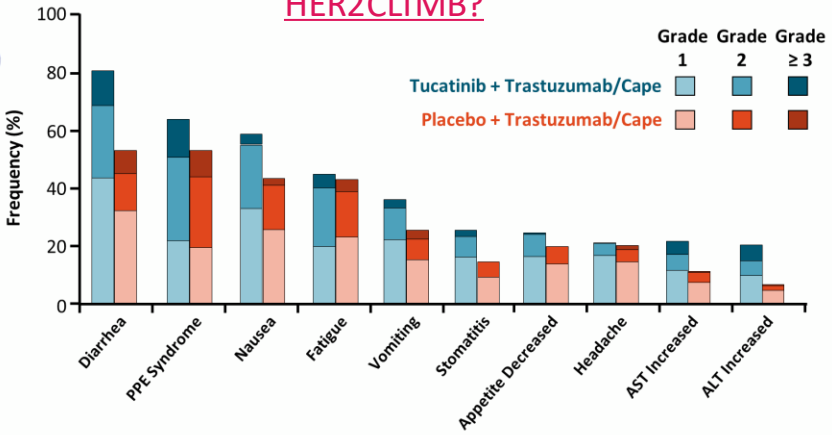
  - Persistent **diarrhea** after the **colostomy**

HER2CLIMB?



How would you treat the patient at this point?

- Supportive care, given the performance status and comorbidities
- Tucatinib + capecitabine + trastuzumab
- Letrozole + trastuzumab
- Chemotherapy + trastuzumab

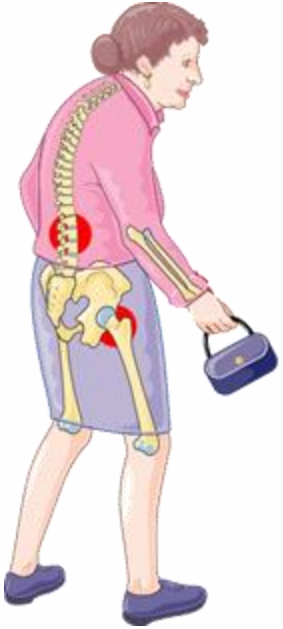
Diarrhea is the most common AE in both arms

- All grade: 81% w/tucatinib vs 53%; grade ≥3: 13% w/tucatinib vs 9%

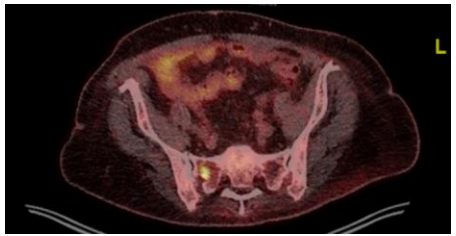
h/o: history; HR: hormone receptor; PS: performance status; y/o: years old.

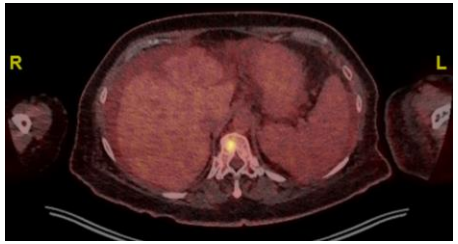
Question 2

***2021
70 y/o h/o diverticulitis 2017, colostomy 2022
MBC HR+ HER2 amplified
1L: CLEOPATRA, maintenance ET
2L: DB-03



- **Third line**: metronomic cyclophosphamide + trastuzumab s/c
  - At 3 months: CR, diarrhea resolved, and PS improved: PS 3 → PS 1
  - At 6 months → PD: bone, lymph nodes



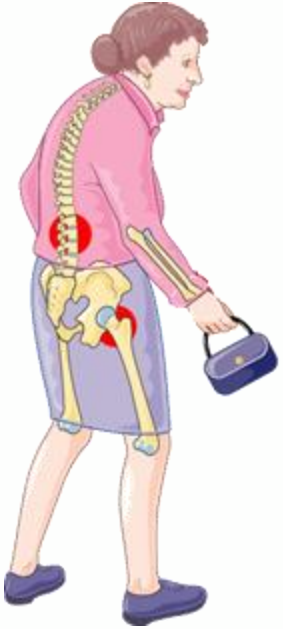


How would you treat the patient at this point?

- Supportive care, given her performance status and comorbidities
- Tucatinib + capecitabine + trastuzumab
- Letrozole + trastuzumab
- Chemotherapy + trastuzumab

Case continuation

***2021
70 y/o h/o diverticulitis 2017, colostomy 2022
MBC HR+ HER2 amplified
1L: CLEOPATRA, maintenance ET
2L: DB-03



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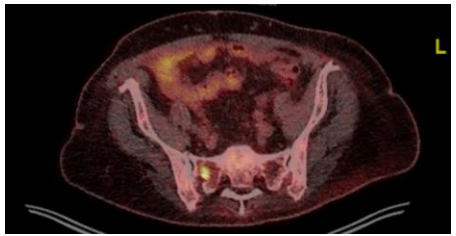
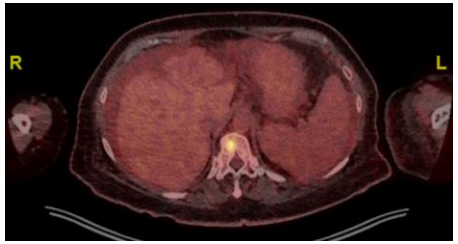




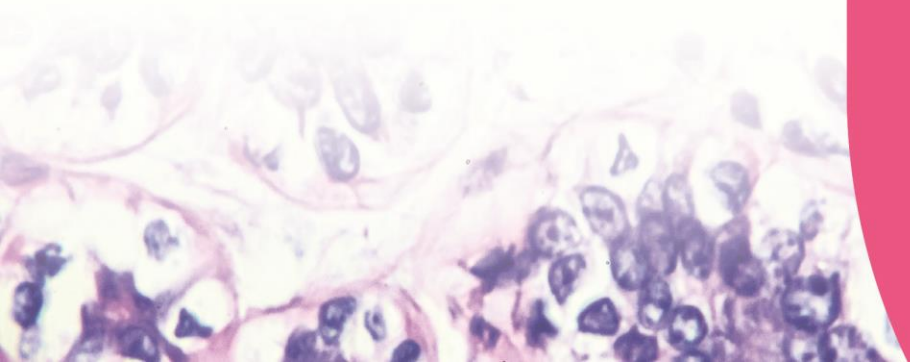
- **Fourth line**: Tucatinib + capecitabine + trastuzumab
  - At 3 weeks: patients is doing well, PS 1
  - Grade 1 diarrhea
  - Next PET scan in 2 months

Thank you for your attention

Global Breast Cancer Academy

Case 2: HER2+ mBC – what do we do with CNS progression?

Rodrigo Sánchez-Bayona, MD, PhD
Breast Cancer Unit – Oncology Department
Hospital Universitario 12 de Octubre, Madrid, Spain
ESMO Young Oncologists Committee Member



APTITUDE HEALTH

Patient Presentation

- 50-year-old woman, premenopausal. No relevant comorbidities
- Family history: father had prostate cancer at age 67

- **July 2022:** self-palpation of nodule in the left breast, no other symptoms
- Mammogram + breast US: spiculated nodule 30 × 25 mm in upper left quadrant of left breast (BI-RADS 4), 2 adenopathies in ipsilateral axilla
- Core needle biopsy: invasive ductal carcinoma, grade 2, ER 90%, PR 20%, HER2+ (HercepTest 3+), Ki-67: 60%
- Fine needle aspiration from axillary adenopathy: infiltration by carcinoma

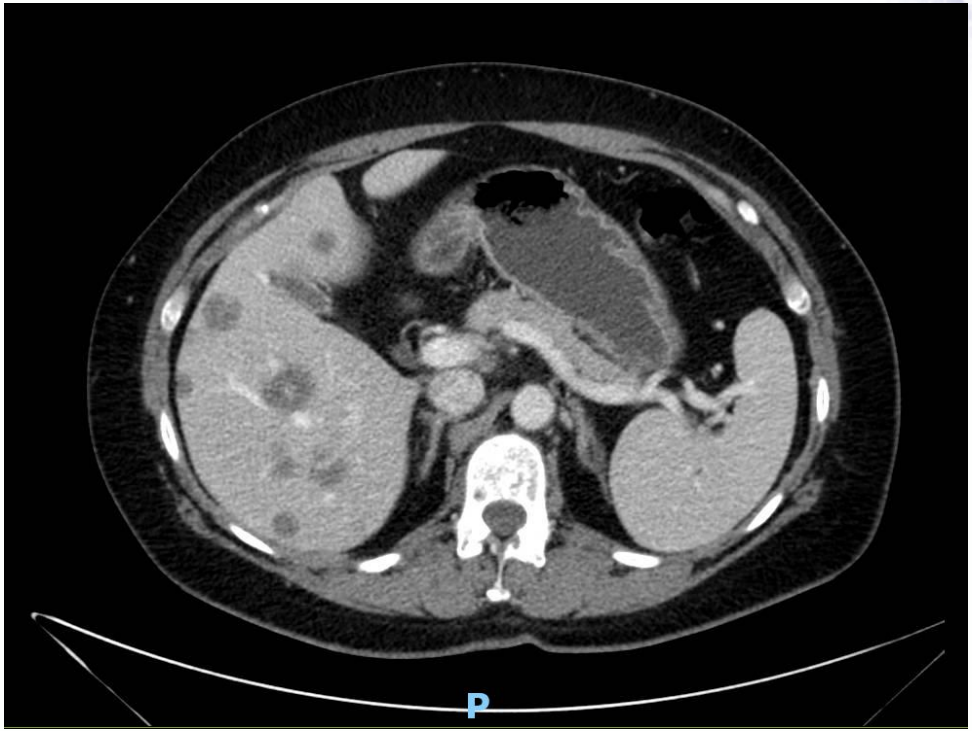
CT Scan

- Nodular lesion in the left breast, left axillary adenopathies, multiple liver lesions compatible with metastases

50-year-old, premenopausal woman

De novo stage IV HR+, HER2+ breast cancer

- Echocardiogram **July 2022**: LVEF 55%



First-Line Treatment

- Weekly paclitaxel + trastuzumab + pertuzumab
- Initiated in **August 2022**

- Echocardiogram **October 2022:** LVEF 38% (mildly symptomatic)

Question 1

What do we do now? How would you treat this patient?

A. Continue treatment, as the patient is mildly symptomatic
B. Continue treatment with the addition of a beta blocker
C. Pause treatment and monitor symptoms
D. Stop treatment and consult with cardiologist

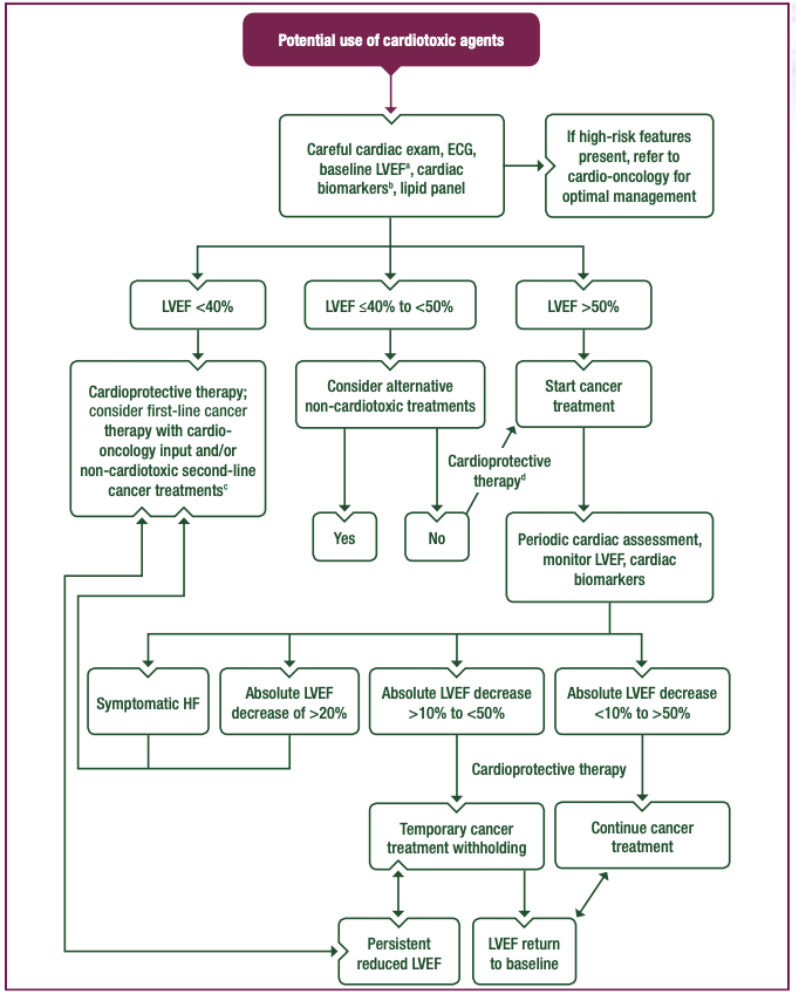
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations

G. Curigliano[1,2†], D. Lenihan[3†], M. Fradley[4], S. Ganatra[5], A. Barac[6], A. Blaes[7], J. Herrmann[8], C. Porter[9], A. R. Lyon[10], P. Lancellotti[11], A. Patel[12], J. DeCara[13], J. Mitchell[14], E. Harrison[15], J. Moslehi[16], R. Witteles[17], M. G. Calabro[18], R. Orecchia[1], E. de Azambuja[19], J. L. Zamorano[20], R. Krone[21], Z. Iakobishvili[22], J. Carver[23], S. Armenian[24], B. Ky[25], D. Cardinale[26], C. M. Cipolla[27], S. Dent[28] & K. Jordan[29], on behalf of the ESMO Guidelines Committee*



First-Line Treatment

- Weekly paclitaxel + trastuzumab + pertuzumab
- Initiated in **August 2022**

- Echocardiogram **October 2022:** LVEF 38% (mildly symptomatic)
- STOP anti-HER2 therapy, continue with paclitaxel
- Cardiology consultation: angiotensin-converting enzyme inhibitor (enalapril)

First-Line Treatment

- Weekly paclitaxel + trastuzumab + pertuzumab
- Initiated in **August 2022**

- Echocardiogram **October 2022:** LVEF 38% (mildly symptomatic)
- STOP anti-HER2 therapy, continue with paclitaxel
- Cardiology consultation: angiotensin-converting enzyme inhibitor (enalapril)

- Echocardiogram **November 2022:** LVEF 30%
- Cardiology: enalapril + beta blocker (bisoprolol)

First-Line Treatment

- Weekly paclitaxel + trastuzumab + pertuzumab
- Initiated in **August 2022**

- Echocardiogram **October 2022:** LVEF 38% (mildly symptomatic)
- STOP anti-HER2 therapy, continue with paclitaxel
- Cardiology consultation: angiotensin-converting enzyme inhibitor (enalapril)

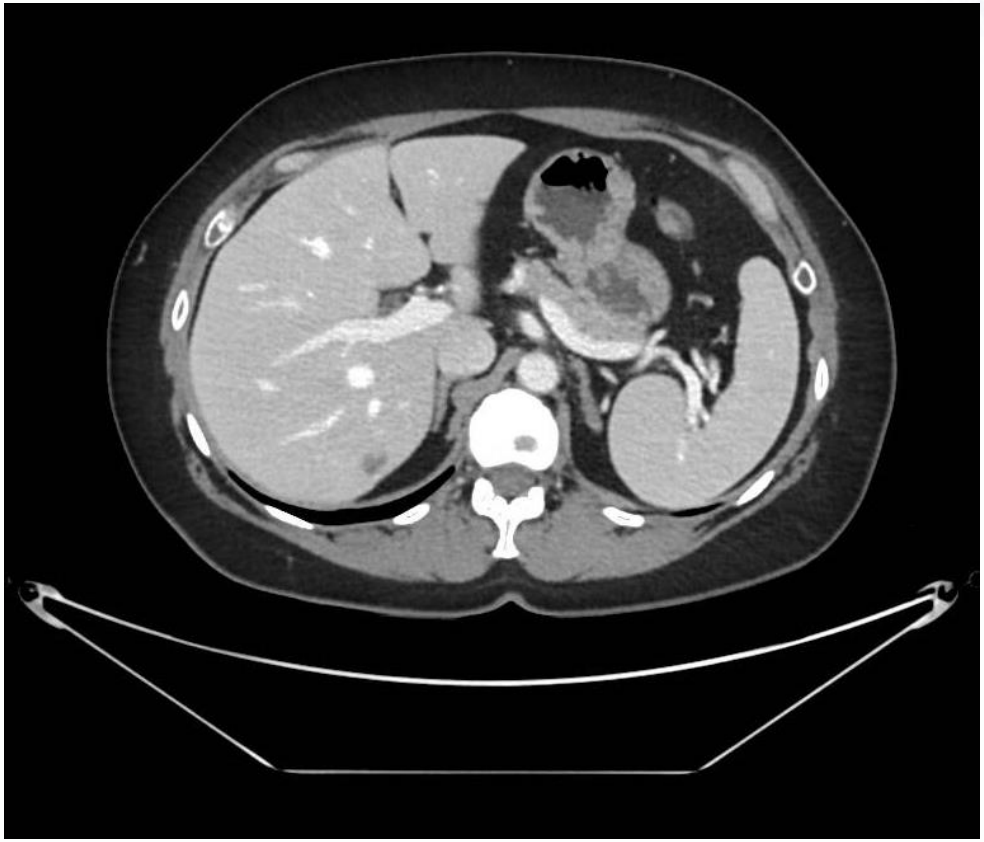
- Echocardiogram **November 2022:** LVEF 30%
- Cardiology: enalapril + beta blocker (bisoprolol)

- Echocardiogram **January 2023:** LVEF 55%
- Resume trastuzumab monotherapy + letrozole (bilateral adnexectomy in September 2022)

Maintenance Therapy

- Trastuzumab as maintenance treatment with complete locoregional response and major partial response in the liver

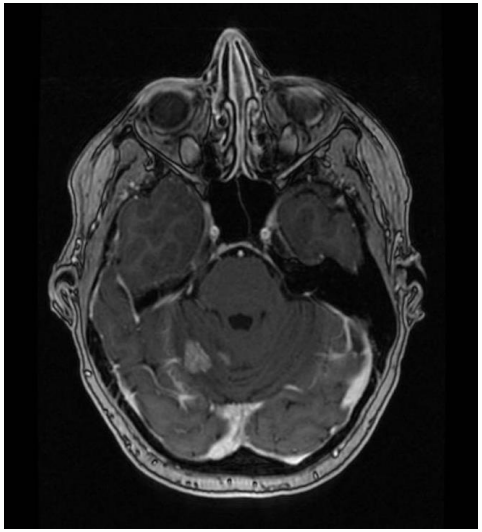
- Subsequent echocardiogram monitoring: LVEF 45%–50%, asymptomatic

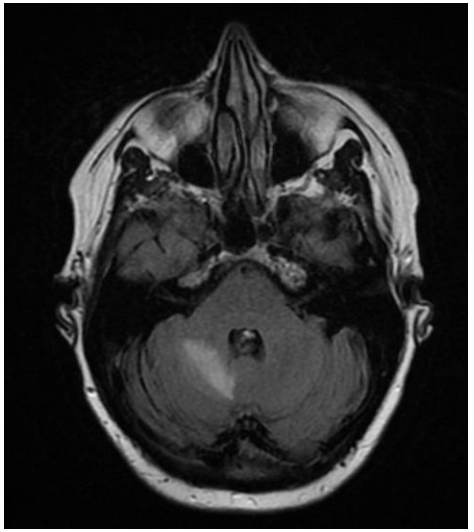


Disease Progression

- **August 2023:** Headache and dizziness

- Brain MRI
  - 2 nodular uptake foci are detected, infratentorial, with surrounding vasogenic edema compatible with metastatic involvement. They are found in close relationship with the tentorium, on the upper margin of the hemisphere right cerebellum
  - First focus measures 1.3 × 1 × 1 cm. The second focus measures 0.8 × 0.3 cm and is located immediately medial





Question 2

What would be our next step? How would you treat this patient?

A. Consult with radiation oncologist

B. Consult with neurosurgeon

C. Change systemic treatment without local intervention

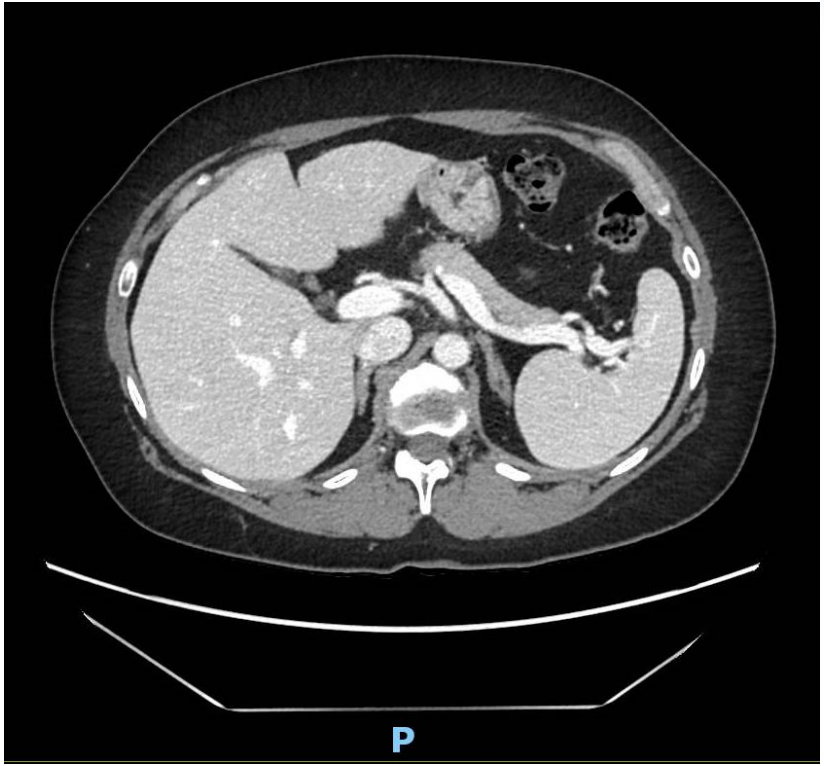
Case continuation

- Dexamethasone (good clinical response)

- Radiation oncology assessment
  - Radiosurgery, total dose of 35 Gy in 7 fractions of 5 Gy daily (5 sessions/week) on PTV of the lesions

Case continuation

- Dexamethasone (good clinical response)
- Radiation oncology assessment
  - Radiosurgery, total dose of 35 Gy in 7 fractions of 5 Gy daily (5 sessions/week) on PTV of the lesions
- Medical oncology assessment
  - 51-year-old woman
  - Stage IV de novo HR+, HER2+ breast cancer
  - CNS progression in the first 12 months since the initiation of first-line taxane + trastuzumab ± pertuzumab (discontinued due to significant LVEF decrease)

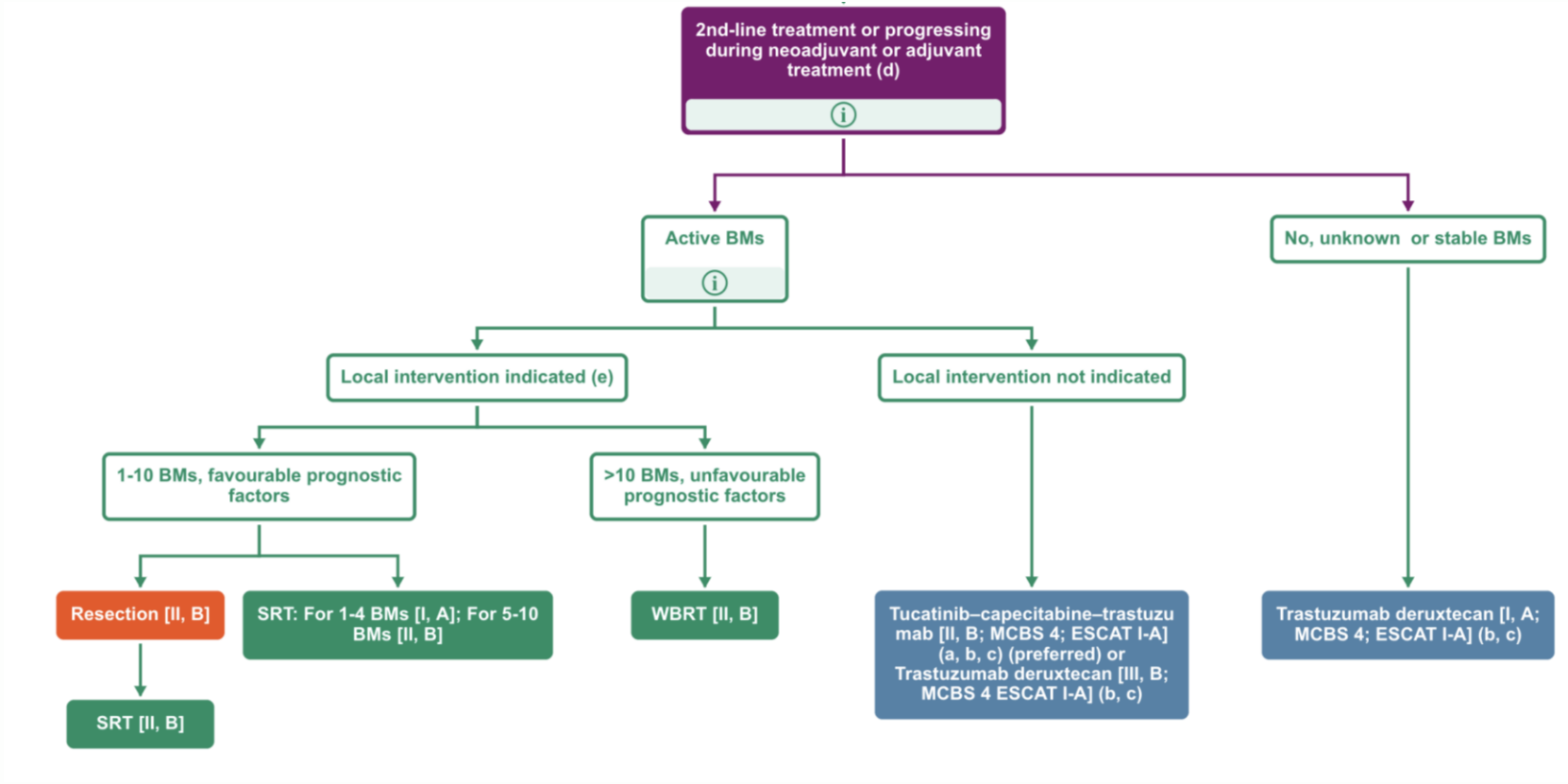


Question 3

What would be your choice for systemic treatment?

A. Resume to pertuzumab and continue trastuzumab
B. Switch to T-DXd
C. Switch to tucatinib combination

ESMO Metastatic Breast Cancer Living Guideline



ESMO Metastatic Breast Cancer Living Guideline: HER2-positive Breast Cancer. Version 1.1 – May 2023. https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/her2-positive-breast-cancer/her2-positive-breast-cancer/first-and-second-lines. Accessed Nov 9, 2023.

Second-Line Therapy

- Isolated CNS disease progression
- Extracranial: no evidence of disease
- Echocardiogram **August 2023**: LVEF 52%

- In **September 2023,** she initiates **tucatinib 300 mg/12hr + capecitabine 1500 mg/12 hr + trastuzumab 600 mg SC**
- Cardiology consultation: close monitoring with echocardiogram every 6–8 weeks
- Last visit (November 6)

- Adequate tolerance to treatment, no significant adverse events
- Echocardiogram **October 2023:** LVEF 51%

Global Breast Cancer Academy

ARS questions

Nadia Harbeck

APTITUDE HEALTH

Question 3 [REPEATED]

Which of the following randomized clinical trials enrolled HER2+ mBC patients with active, untreated brain metastases? Select all that apply.

A. CLEOPATRA
B. DESTINY-Breast01
C. EMILIA
D. HER2CLIMB
E. MONALEESA-3
F. None of the above

Question 4 [REPEATED]

According to the current ESMO guidelines (v1.1 May 2023), which of the following treatment options are recommended in third line for HER2+ mBC patients with no, unknown, or stable brain metastases? Select all that apply.

A. Lapatinib plus capecitabine
B. Margetuximab plus chemotherapy
C. Neratinib plus capecitabine
D. Trastuzumab deruxtecan (T-DXd)
E. Trastuzumab emtansine (T-DM1)
F. Tucatinib plus capecitabine plus trastuzumab

Global Breast Cancer Academy

Session close

Nadia Harbeck

APTITUDE HEALTH

Thank you!

- Thank you to our sponsor, expert presenters, and to you for your participation
- Please complete the **evaluation** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the website within a few weeks
- If you have a question for any of our experts that was not answered today, you can submit it through the GBCA website in our Ask the Experts section

THANK YOU!