Treatment approach to metastatic and HER2 over-expression breast cancer

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Outline

Milestone of targeting HER2 in MBC

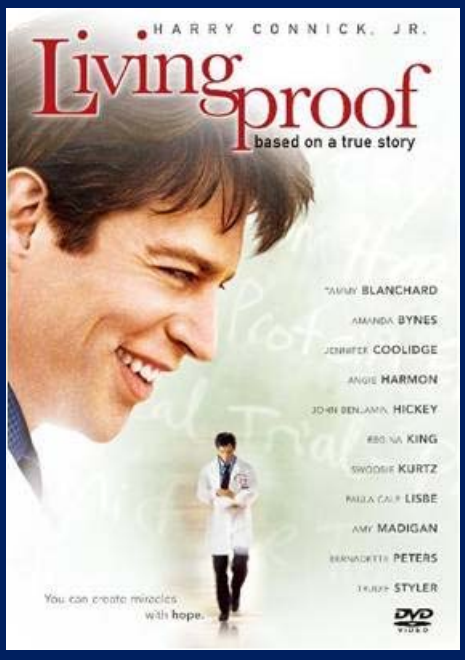
Recent advance in HER2 treatment

Milestone of HER2-targeting agent in MBC

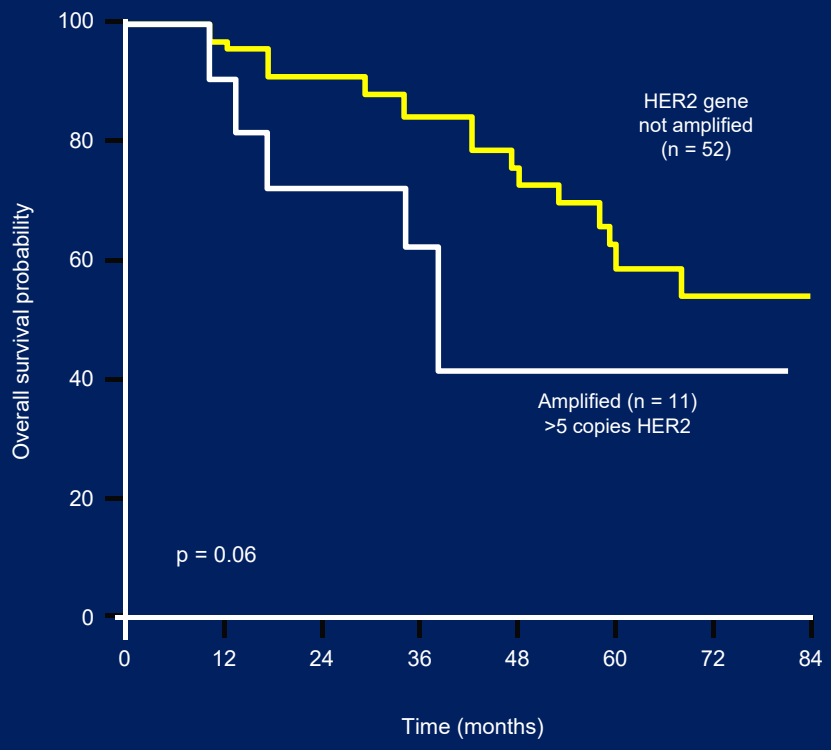
Discovery HER2 as a oncogene in BC

Pioneer of HER2 targeting journey

Dr. Dennis Slamon

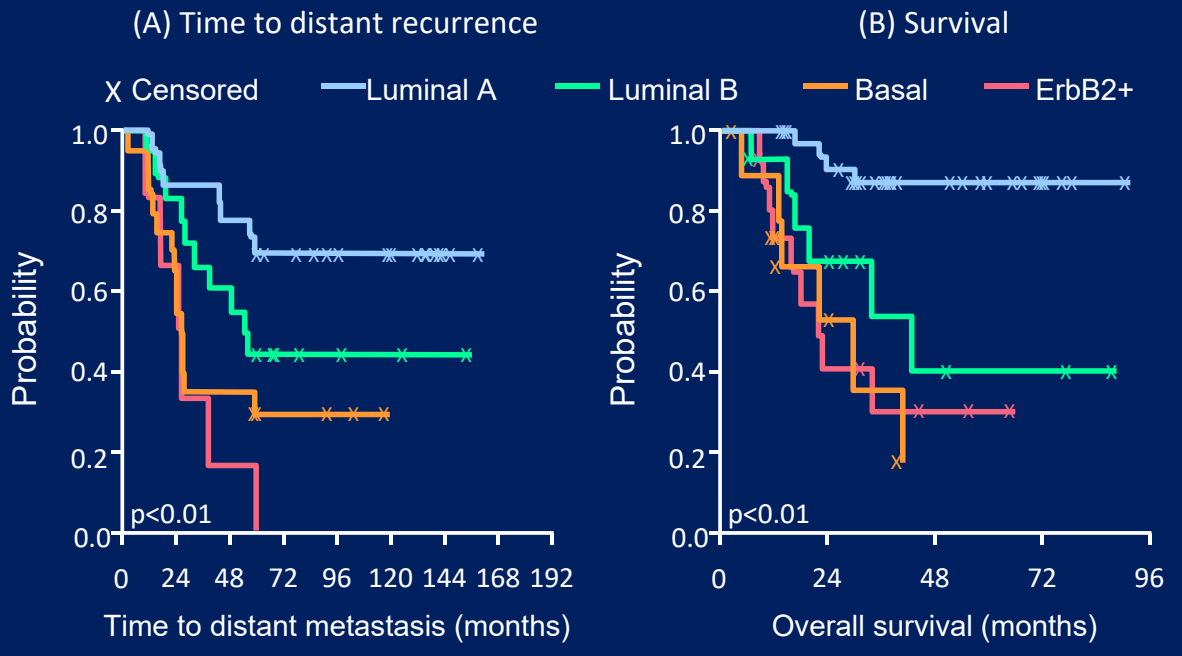


HER2 positive represent negative prognostic factor…



Slamon et al. 1987 Science

Recurrence of HER2-positive cancers: Time to recurrence and survival by tumor type



Sorlie et al. Proc Natl Acad Sci USA 2003;100:8418–8423

HER2 and breast cancer

HER2 is a negative prognostic factor in BC [1–3]

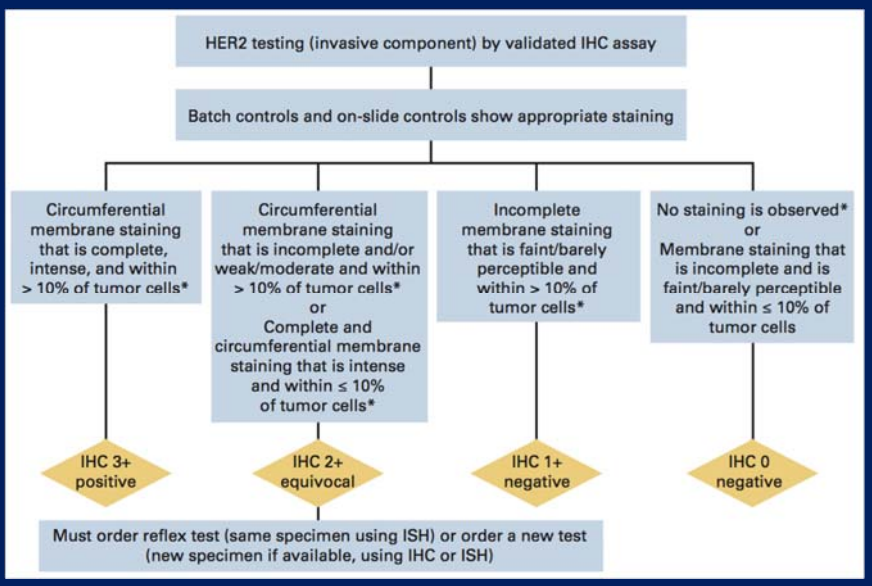
HER2 positivity correlates with aggressive breast cancer tumour behaviour [4]

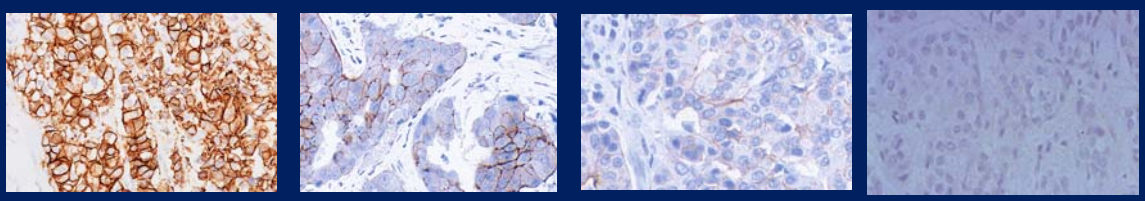
— Short disease-free interval
— Large tumour size
— High nuclear grade
— Positive nodal status

HER2 overexpression/*HER2* amplification occurs in around:
20–30% of BC tumors [1,2,5,6]

1. Seshadri et al. J Clin Oncol 1993;11:1936–1942
2. Slamon et al. Science 1987;235:177–182
3. Andrulis et al. J Clin Oncol 1998;16:1340–1349
4. Ross et al. Oncologist 2003;8:307–325
5. Paik et al. J Natl Cancer Inst 2000;92:1991–1998
6. Owens et al. Clin Breast Cancer 2004;5:63–69

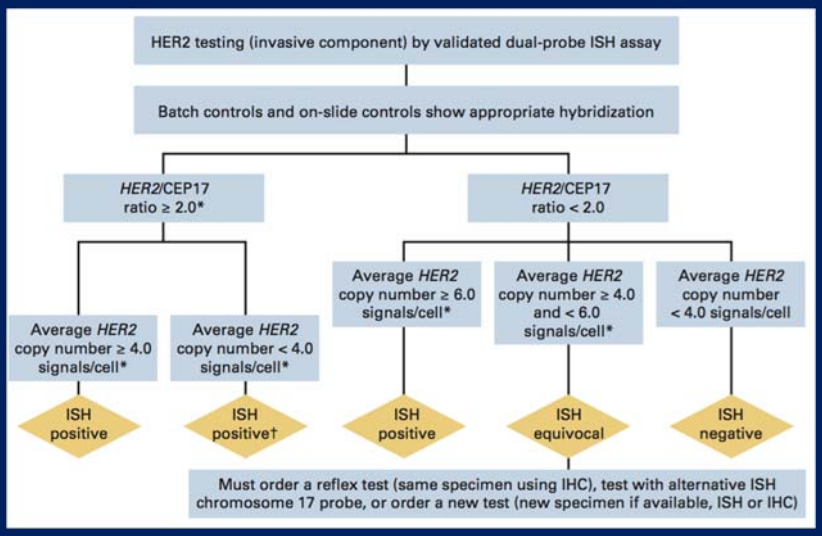
IHC scoring: semiquantitative interpretation of HER2 expression

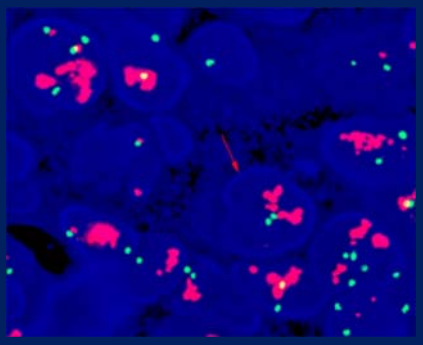




J Clin Oncol. 2013;31:3997-4013

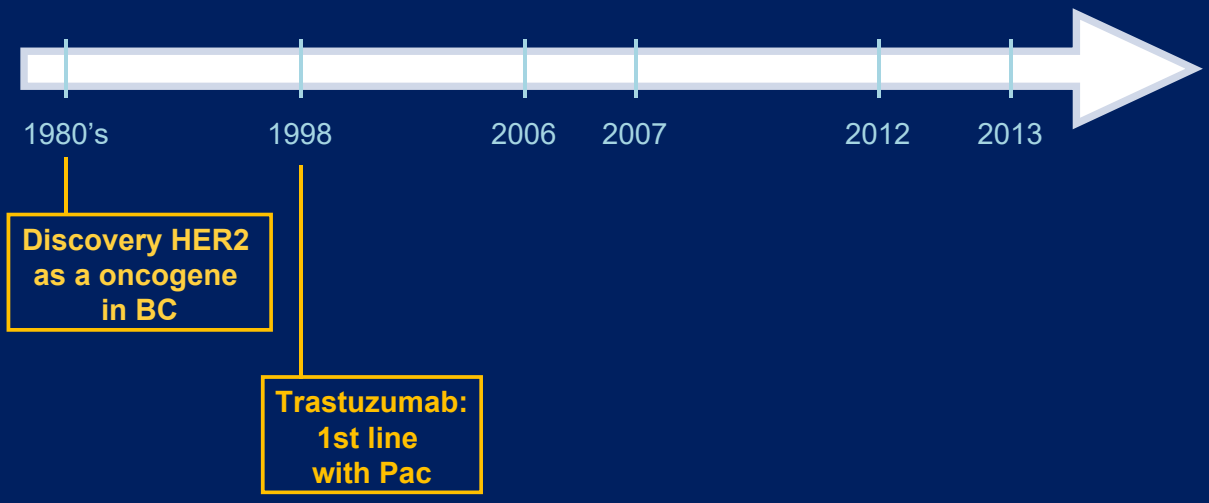
HER2 gene amplification detected by fluorescent in situ hybridization (FISH)



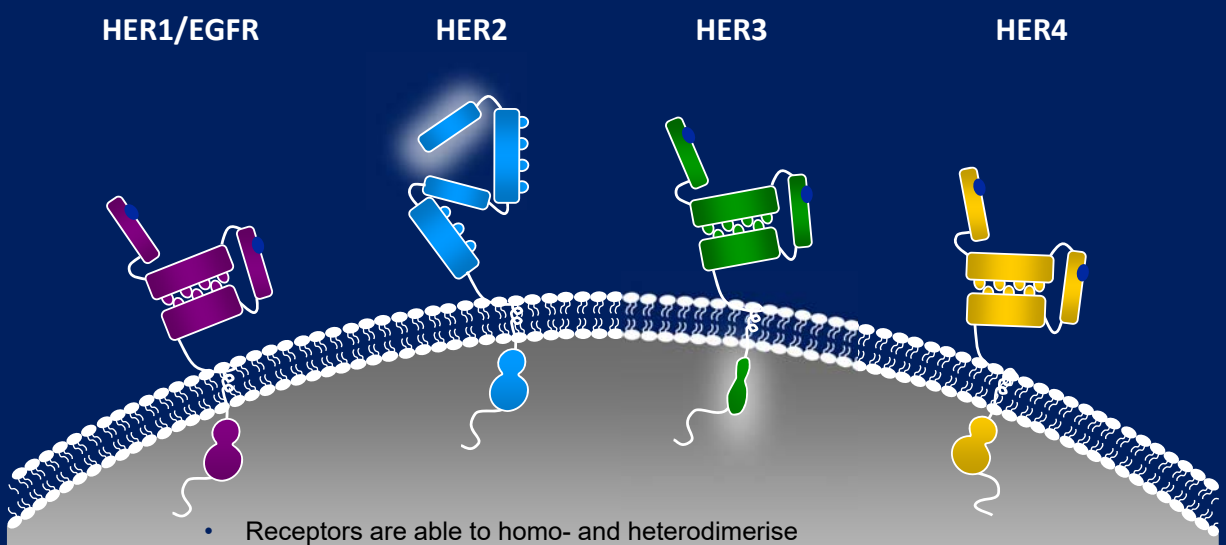


J Clin Oncol. 2013;31:3997-4013

Milestone of HER2-targeting agent in MBC



Four receptors in the HER family

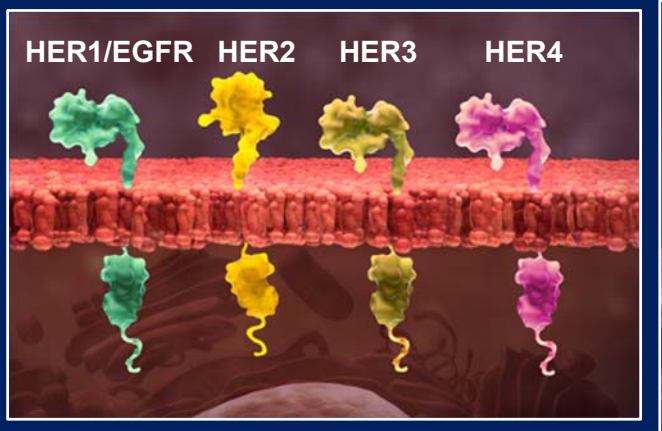


- Receptors are able to homo- and heterodimerise
- HER2 does not appear to have a direct ligand and HER3 lacks kinase activity
- However, HER2 and HER3 are highly complementary to each other

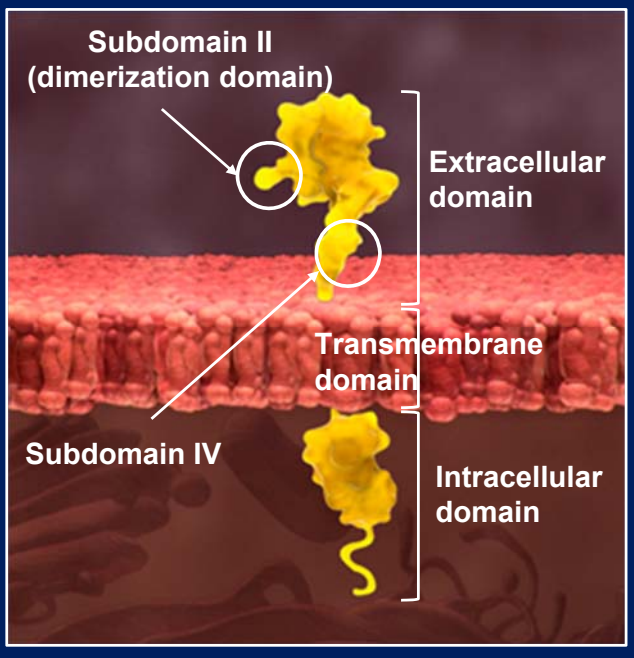
EGFR, epidermal growth factor receptor

Yarden & Sliwkowski. Nat Rev Mol Cell Biol 2001;2:127–137

Four receptors in the HER family

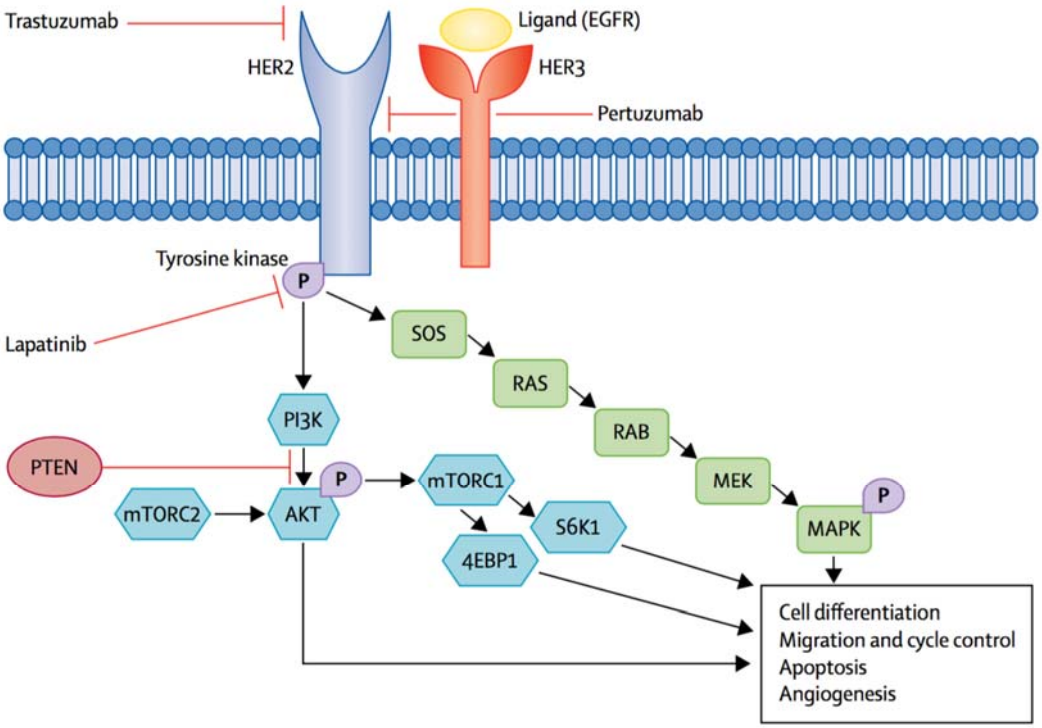


Receptors are able to homo- and heterodimerise



Franklin *et al. Cancer Cell* 2004; 5: 317–328; Yarden et al. *Nat Rev Mol Cell Biol* 2001; 2:127–137

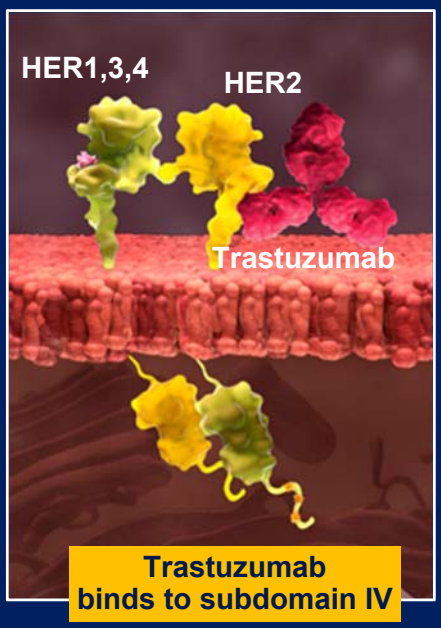
HER2 Signaling Pathway



Lancet 2017;389:2415–29

The First Saviour: Trastuzumab, an anti-HER2 antibody with three distinct mechanisms of action

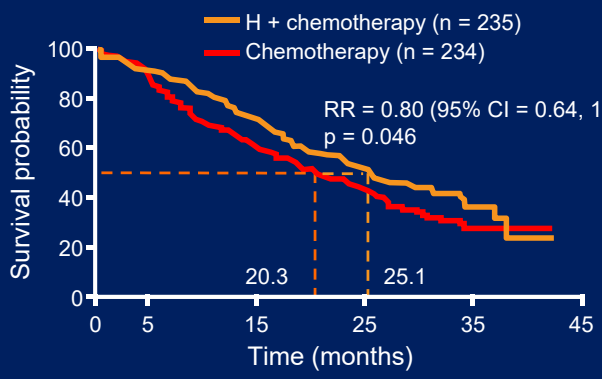
- **Inhibition of HER2-mediated intracellular signalling[1–5]**
- **Block of HER2 cleavage and shedding of the extracellular domain[1,10,11]**
- **Activation of antibody-dependent cellular cytotoxicity (ADCC)[6–9]**



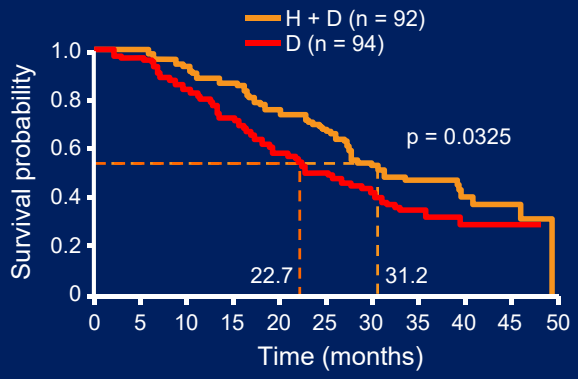
1. Nahta et al. Cancer Lett 2006; 232:123-138; 2. Fry. Breast Cancer Res 2001; 3:304-312; 3. Gershtein et al. Clin Chim Acta 1999; 287::59-67; 4. Yakes et al. Cancer Res 2002; 62:4132-4141; 5. Longva et al. Int J Cancer 2005; 116:359-367; 6. Nahta et al. Breast Cancer Res 2006; 8:215; 7. Clynes et al. Nat Med 2000; 6:443-446; 8. Gennari et al. Clin Cancer Res 2004; 10:5650-5655; 9. Arnould et al. Br J Cancer 2006; 94:259-267; 10. Molina et al. Cancer Res 2001; 61:4744-4749; 11. Loibl et al. ASCO 2011. Abstract 530.

Trastuzumab plus Taxane improved MBC survival

H0648g[1]

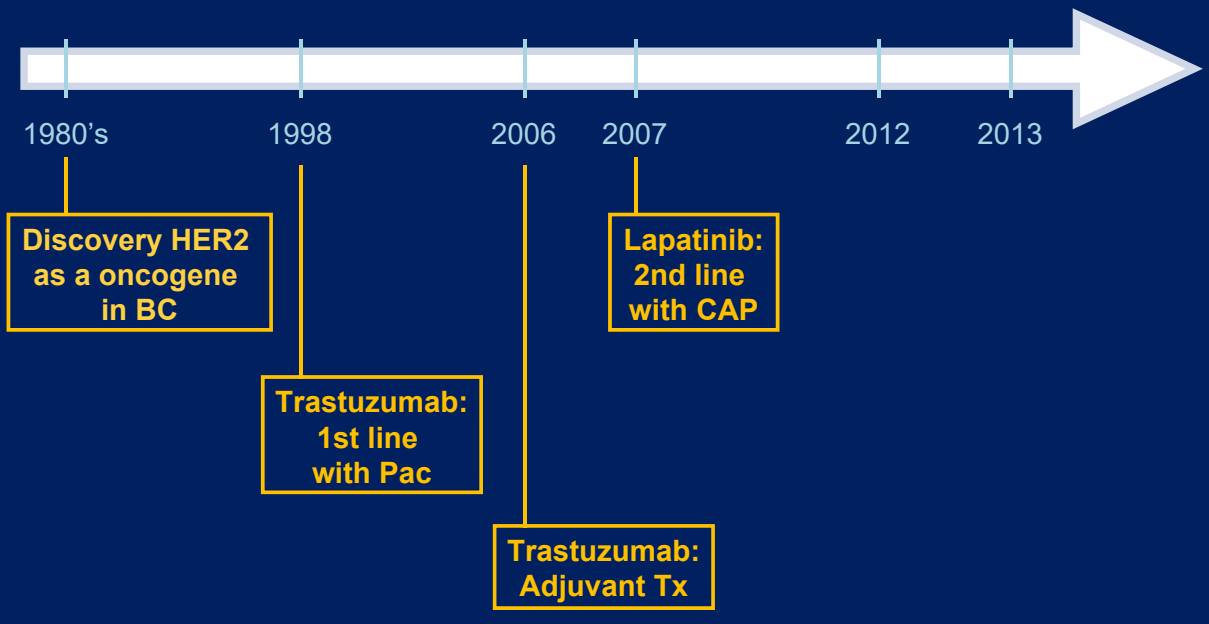


M77001[2]



Study	Median Survival, Mos: Chemotherapy Alone	Median Survival, Mos: Chemotherapy + Trastuzumab	HR (95% CI)	*P* Value
Paclitaxel (Slamon)[1]	20.3	25.1	0.80 (0.64-1.00)	0.046
Docetaxel (Marty)[2]	22.7	31.2	Not reported	.0325

Milestone of HER2-targeting agent in MBC



Trastuzumab Beyond Progression in Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: A German Breast Group 26/Breast International Group 03-05 Study

HER-2–positive,
locally advanced or mBC,
within prior trastuzumab <6 wks
open label,
phase III,
1:1 randomization

→ Capecitabine 2,500 mg/m² on days 1~14
(1,250 mg/m² semi- daily)
plus trastuzumab 6 mg/kg infusion every 3 weeks
(n=78)

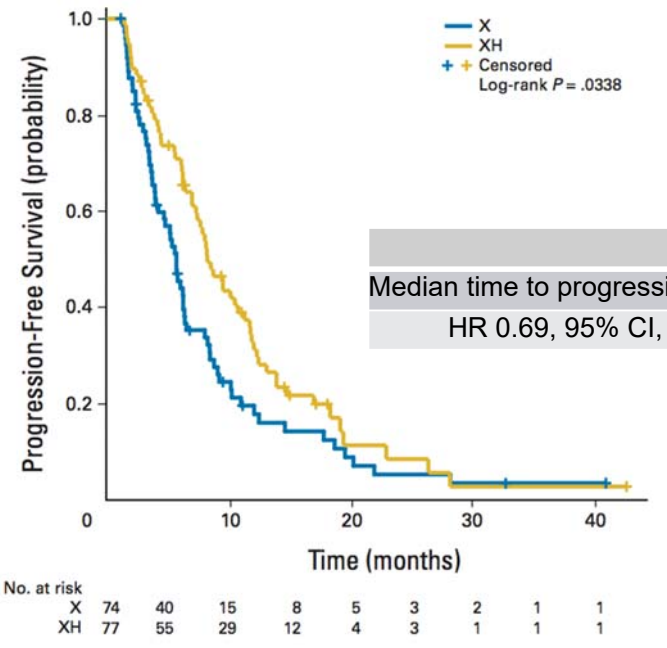
→ Capecitabine 2,500 mg/m² on days 1~14
(1,250 mg/m² semi- daily)
(n=78)

duration of previous trastuzumab Tx >12 wks

- Primary endpoint: time to progression
- Secondary endpoints: RR, OS, duration of response , safety

J Clin Oncol. 2009;27:1999-2006

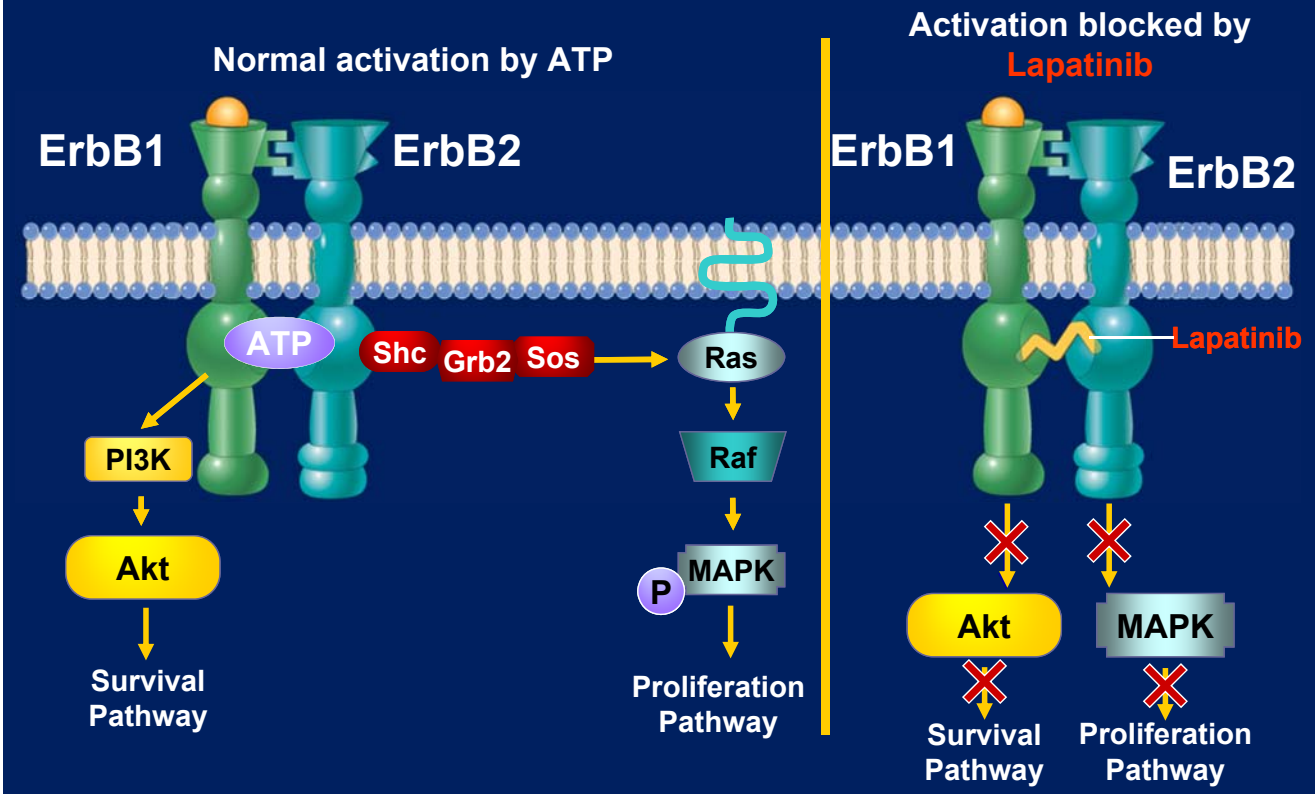
GBG26/BIG03-05 Trastuzumab beyond progression:progression-free survival



	X+H	X
Median time to progression	8.2	5.6
HR 0.69, 95% CI, 0.48~0.97; *P* =.0338		

J Clin Oncol. 2009;27:1999-2006

Lapatinib mechanism of action



Xia W, et al. Oncogene 2002;21:6255-63; Rusnak DW, et al. Mol Cancer Ther 2001;1:85-94.

EGF100151: Lapatinib + Capecitabine in Advanced HER2-positive Breast Cancer

Refractory, HER2+ LA or MBC previously treated with anthracycline, taxane, and trastuzumab
(N = 528 planned*)

→ Lapatinib 1250 mg daily + Capecitabine 2000 mg/m^2 daily for Days 1-14, 3-week cycles (n=198)

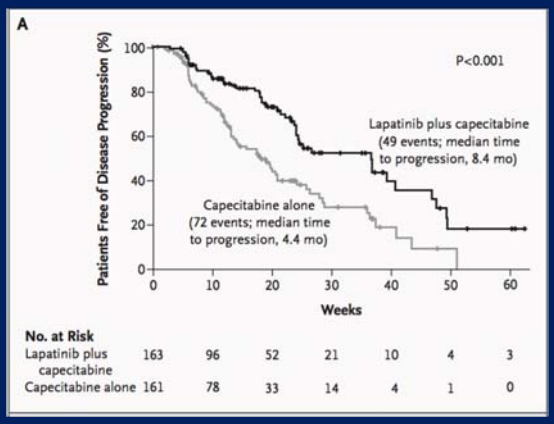
→ Capecitabine 2500 mg/m^2 daily for Days 1-14, 3-week cycles (n=201)

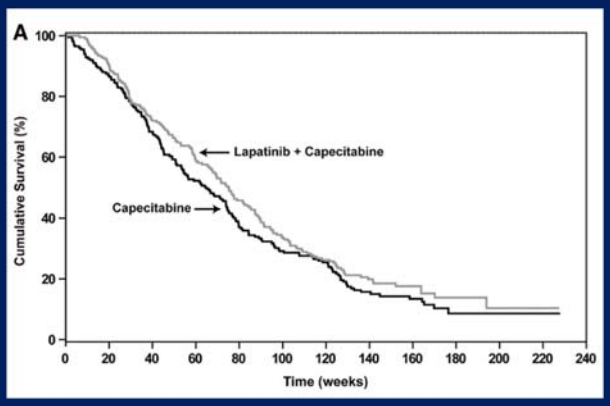
- Primary endpoint: time to progression
- Secondary endpoints: PRS, RR, OS, safety

J Clin Oncol. 2009;27:1999-2006

EGF100151: Lapatinib plus capecitabine after trastuzumab progression

No difference in overall survival





	X+L	X
Median time to progression (mo)	8.4	4.4
HR 0.49, 95% CI, 0.34~0.71; *P* <.0001		

	X+L	X
Median overall survival (wks)	75.0	64.7
HR 0.87, 95% CI, 0.70~1.08; *P* =.206		

Geyer, et al. N Engl J Med 2006;355:2733-43
Cameron D et al. Oncologist. 2010;15(9):924-34

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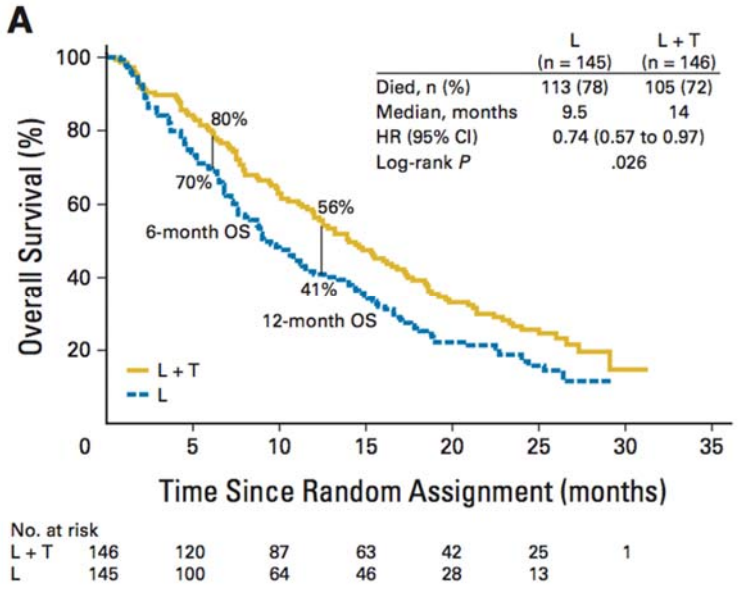
Lapatinib plus trastuzumab in HER2+ MBC after progression on trastuzumab: overall survival improved

phase III EGF104900 Study (n=291)



Blackwell KL, et al. J Clin Oncol. 2012;30:2585-92

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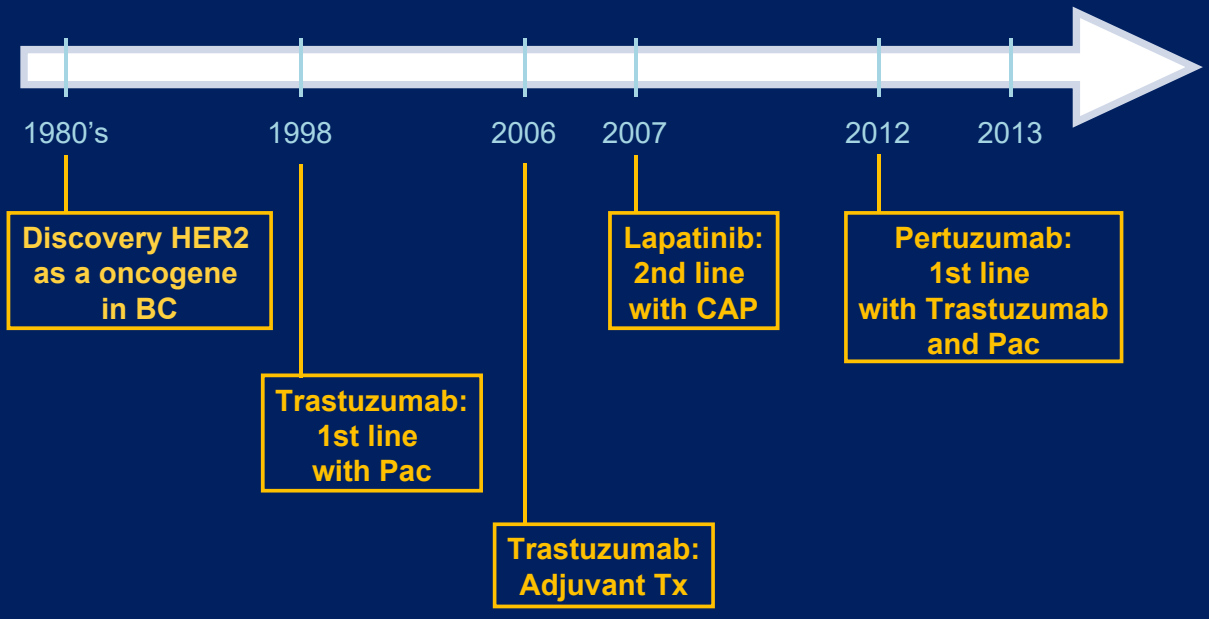
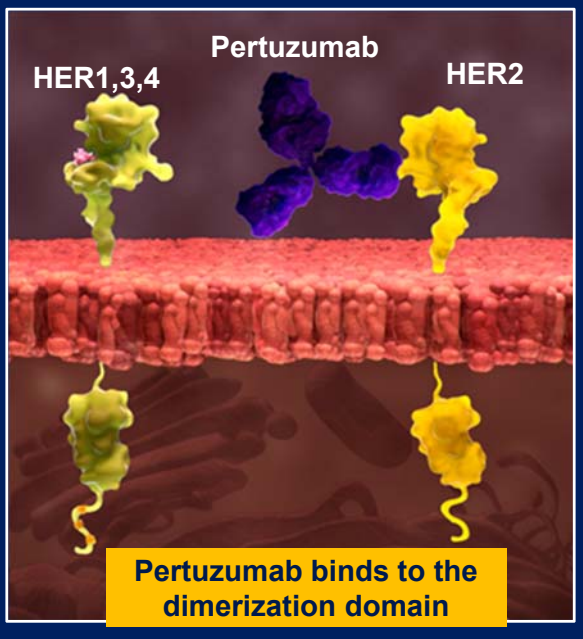
Milestone of HER2-targeting agent in MBC



Pertuzumab: first in a new class of HER2 dimerization inhibitors

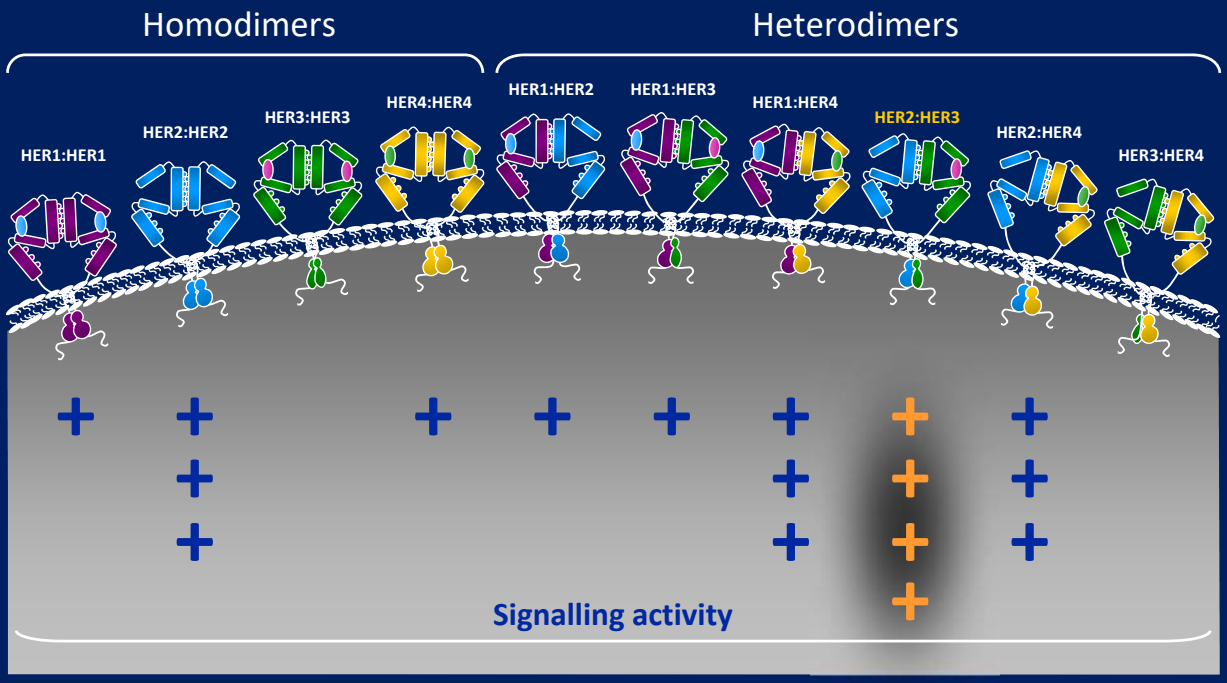
Key HER signalling pathways that mediate cancer cell proliferation and survival are inhibited by pertuzumab blockade of HER2 dimerisation[1–6]

In addition, pertuzumab has the potential to activate antibody-dependent cellular cytotoxicity[7]



1. Agus et al. Cancer Cell 2002; 2:127–137; 2. Hughes et al. Mol Cancer Ther 2009; 8:1885–1892; 3. Herbst et al. Clinical Cancer Res 2007; 13:6175–6181; 4. Baselga. Cancer Cell 2002; 2:93–95; 5. Citri et al. Exp Cell Res 2003; 284:54–65; 6. Franklin et al. Cancer Cell 2004; 5:317–328; 7. Scheuer et al. Cancer Res 2009; 69:9330–9336.

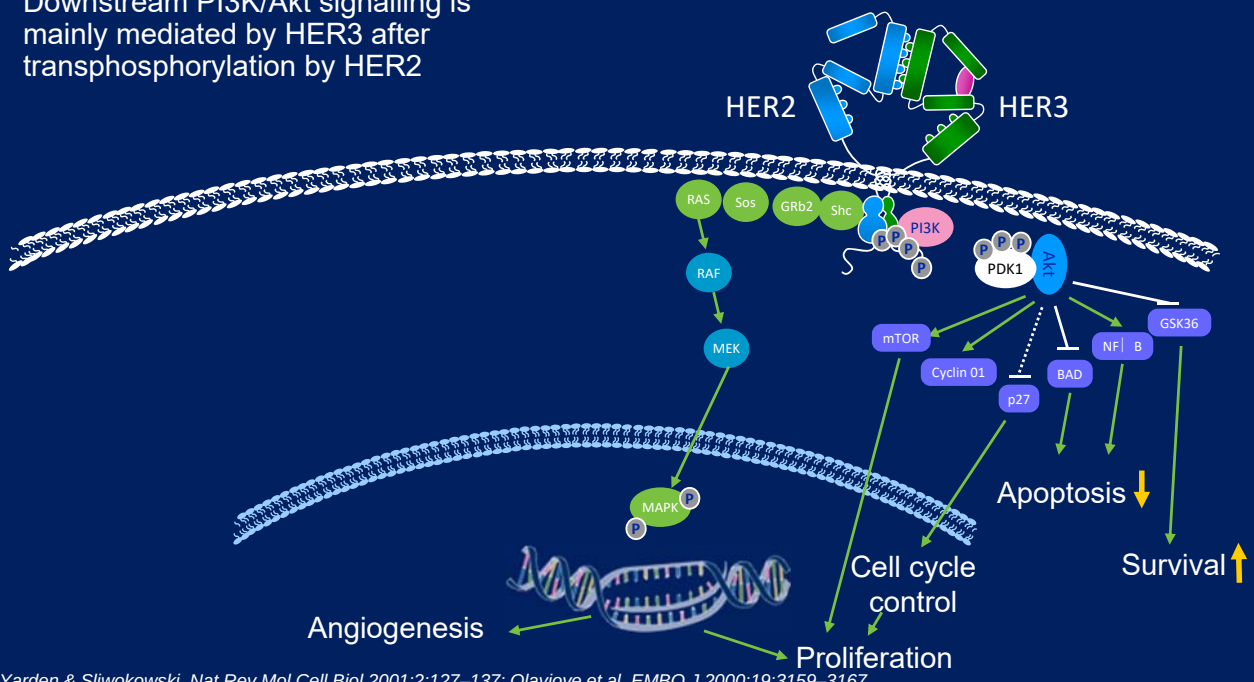
HER2:HER3 dimers initiate the strongest mitogenic signaling



Tzahar et al. Mol Cell Biol 1996;16:5276–5287; Citri et al. Exp Cell Res 2003;284:54–65; Huang et al. Cancer Res 2010;70:1204–1214

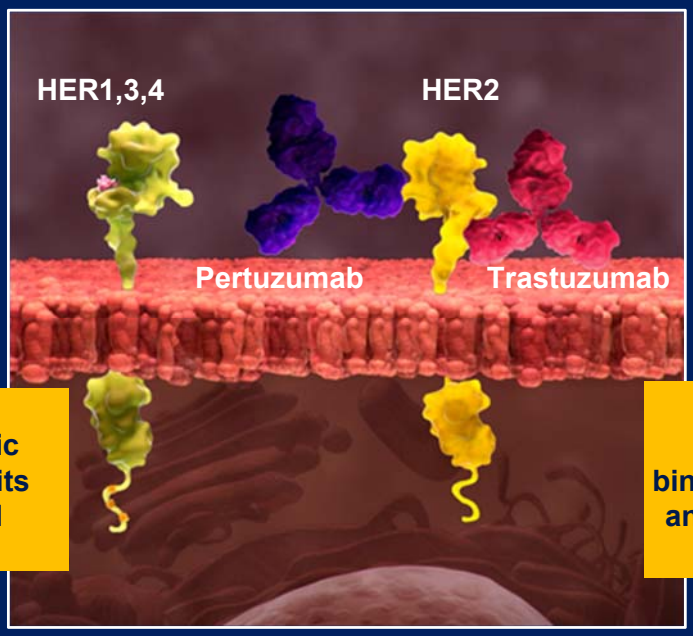
HER2:HER3 dimerization initiates multiple signalling pathways, including increased tumor cell proliferation

Downstream PI3K/Akt signalling is mainly mediated by HER3 after transphosphorylation by HER2



Yarden & Sliwokowski. Nat Rev Mol Cell Biol 2001;2:127–137; Olayioye et al. EMBO J 2000;19:3159–3167
Kim et al. J Biol Chem 1994;269:24747–24755; Soltoff et al. Mol Cell Biol 1994;14:3550–3558
Baselga & Swain. Nat Rev Cancer 2009;9:463–475; Rowinsky. Ann Rev Med 2004;55:433–457

HER2 dual blockade: Trastuzumab and pertuzumab bind to different HER2 domains, with complementary mechanisms of action



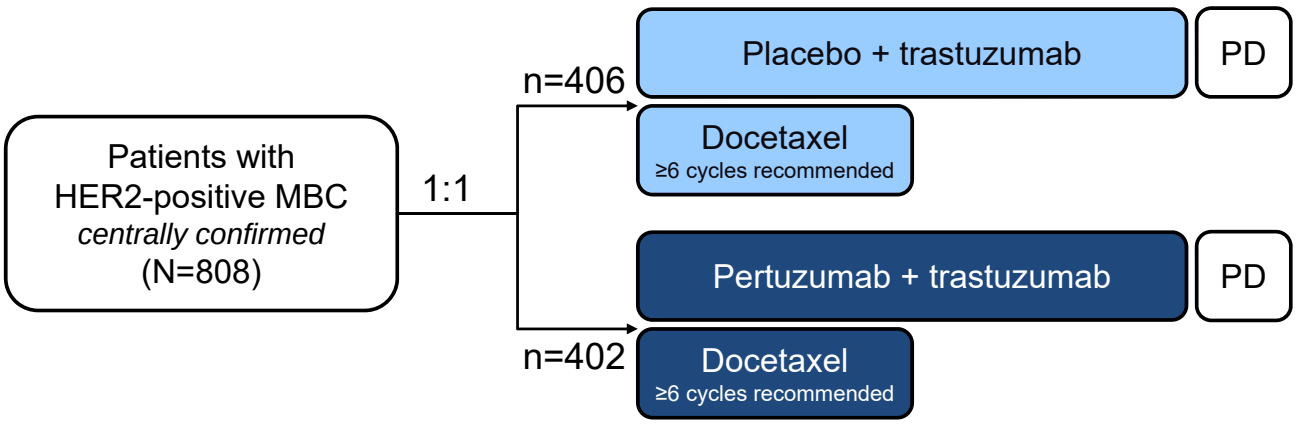
Pertuzumab binds to a specific domain and inhibits ligand-activated dimerization[2]

Trastuzumab binds to subdomain IV and activates ADCC[1]

The pertuzumab-trastuzumab regimen offers a more comprehensive HER2 blockade[3]

1. Cho et al. Nature 2003; 421:756–760; 2. Franklin. et al. Cancer Cell 2004; 5:317–328; 3. Baselga et al. Clin Breast Cancer 2010; 10:489-491.

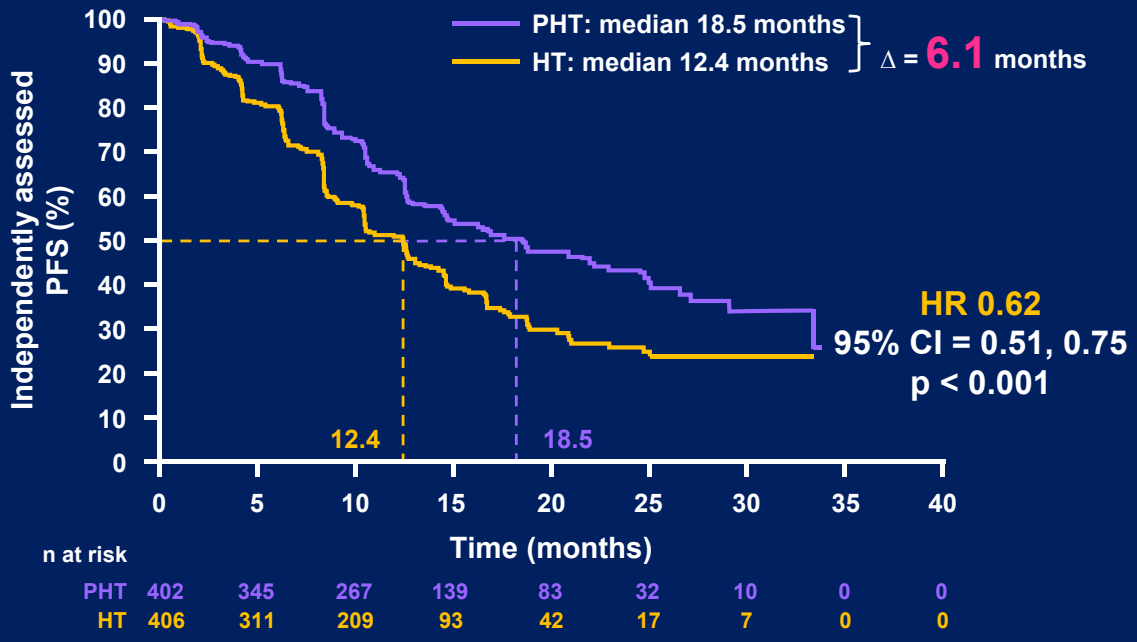
CLEOPATRA study design



- **Stratification factors:** geographic region, prior treatment status (neo/adjuvant chemotherapy received or not)
- **Primary endpoints:** Independently assessed PFS
- **Key secondary endpoints:** Overall survival, PFS by investigator assessment, safety

Baselga et al. N Engl J Med. 2012;366:109-19

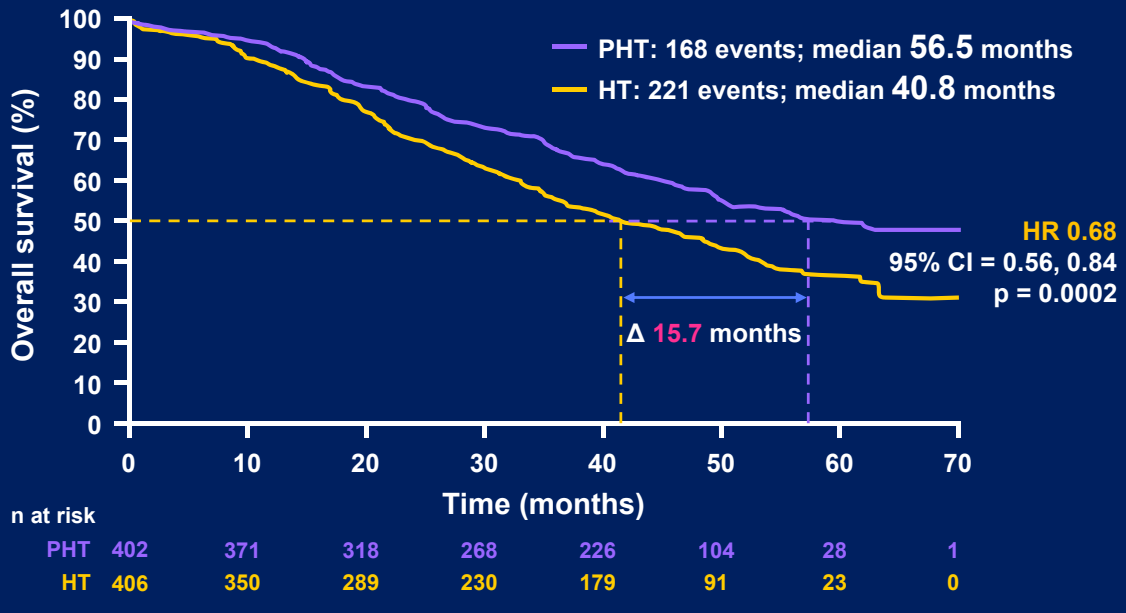
CLEOPATRA primary endpoint: Independently assessed PFS



Baselga et al. N Engl J Med. 2012;366:109-19

CLEOPATRA: final overall survival analysis

Median follow-up 50 months



Swain et al. N Engl J Med. 2015;372:724-34

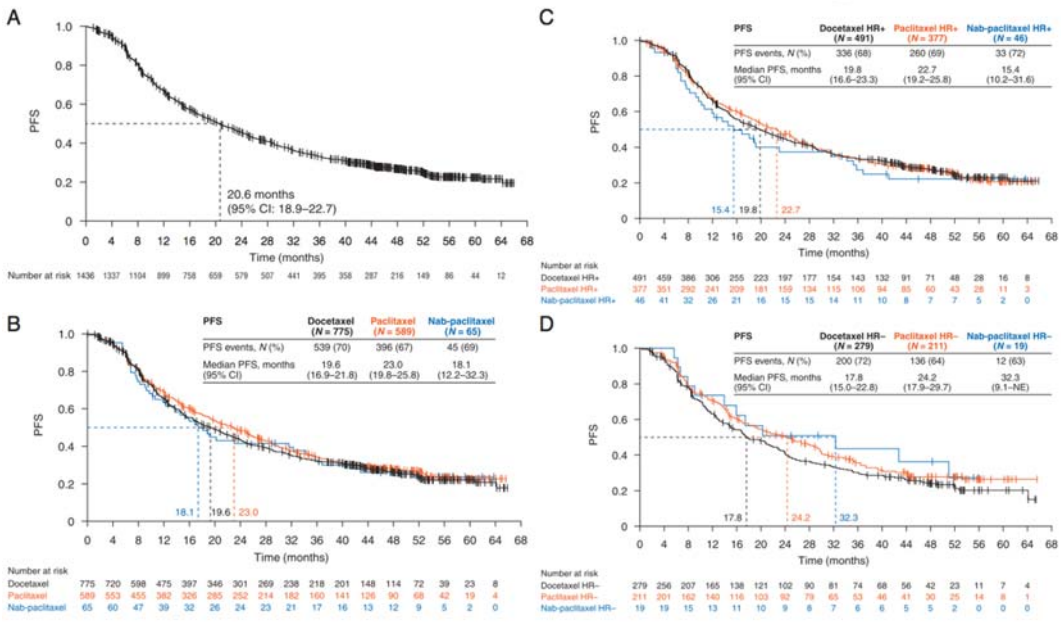
Adverse events (all grades) with ≥25% incidence or ≥5% difference between arms

n (%)	Placebo + trastuzumab + docetaxel[SEP](n=396)	Pertuzumab + trastuzumab + docetaxel[SEP](n=408)
Diarrhea	191 (48.2)	278 (68.1)
Alopecia	240 (60.6)	248 (60.8)
Neutropenia	197 (49.7)	216 (52.9)
Nausea	168 (42.4)	179 (43.9)
Fatigue	148 (37.4)	155 (38.0)
Rash	95 (24.0)	149 (36.5)
Decreased appetite	105 (26.5)	121 (29.7)
Mucosal inflammation	79 (19.9)	112 (27.5)
Asthenia	121 (30.6)	110 (27.0)
Vomiting	97 (24.5)	104 (25.5)
Peripheral edema	122 (30.8)	101 (24.8)
Pruritus	40 (10.1)	68 (16.7)
Constipation	101 (25.5)	63 (15.4)
Febrile neutropenia	30 (7.6)	56 (13.7)
Dry skin	23 (5.8)	44 (10.8)

Baselga et al. N Engl J Med. 2012;366:109-19

PERUSE: first-line pertuzumab combined with trastuzumab and taxane for HER2-positive MBC

Paclitaxel a valid alternative taxane backbone to docetaxel, offering similar PFS and ORR with a predictable safety profile



Ann Oncol. 2019;30:766-773

PHEREXA study: A phase III Study of Trastuzumab (H) + Capecitabine (X) ± Pertuzumab (P) after One Line of H-Based Therapy in the HER2-Positive MBC

- HER2-positive MBC (centrally confirmed)
- Prior taxane and H
- Progression during or after H-based therapy for MBC

N = 452

1

Arm A:
H (8 mg/kg→6 mg/kg) + X (1,250 mg/m²)
n = 224

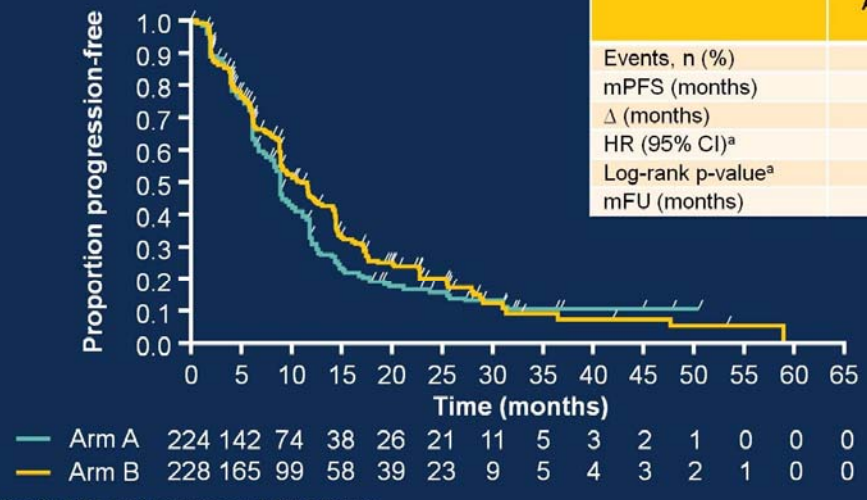
1

Arm B:
H (8 mg/kg→6 mg/kg) + X (1,000 mg/m²)
+ P (840 mg→420 mg)
n = 228

First pt included: Jan 30, 2010
Last pt included: Aug 12, 2013
Clinical cut-off: May 29, 2015

Presented By Ander Urruticoechea at 2016 ASCO Annual Meeting

Primary endpoint: PFS by independent review in ITT population

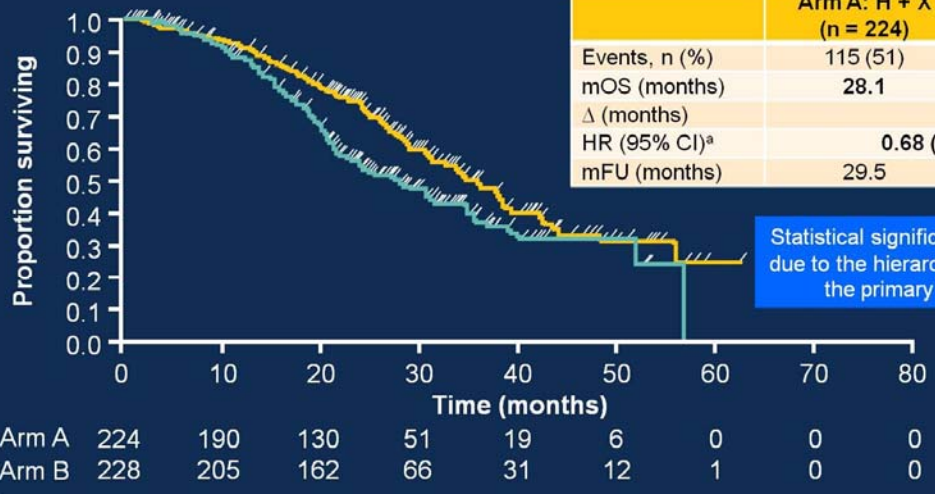


	Arm A: H + X (n = 224)	Arm B: H + X + P (n = 228)
Events, n (%)	158 (71)	168 (74)
mPFS (months)	**9.0**	**11.1**
Δ (months)	**2.1**	
HR (95% CI)[a]	**0.82 (0.65–1.02)**	
Log-rank p-value[a]	0.07	
mFU (months)	28.6	25.3

[a] Stratified. CI, confidence interval; FU, follow-up.

Presented By Ander Urruticoechea at 2016 ASCO Annual Meeting

Secondary endpoint: OS in ITT population



	Arm A: H + X (n = 224)	Arm B: H + X + P (n = 228)
Events, n (%)	115 (51)	98 (43)
mOS (months)	**28.1**	**36.1**
Δ (months)	**8.0**	
HR (95% CI)[a]	**0.68 (0.51–0.90)**	
mFU (months)	29.5	29.3

Statistical significance cannot be claimed due to the hierarchical testing of OS after the primary IRF PFS endpoint

[a] Stratified.

PRESENTED AT: ASCO ANNUAL MEETING '16

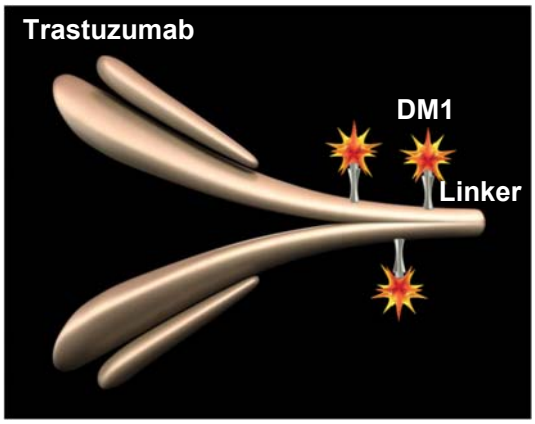
Presented by Ander Urruticoechea

Presented By Ander Urruticoechea at 2016 ASCO Annual Meeting

Milestone of HER2-targeting agent in MBC

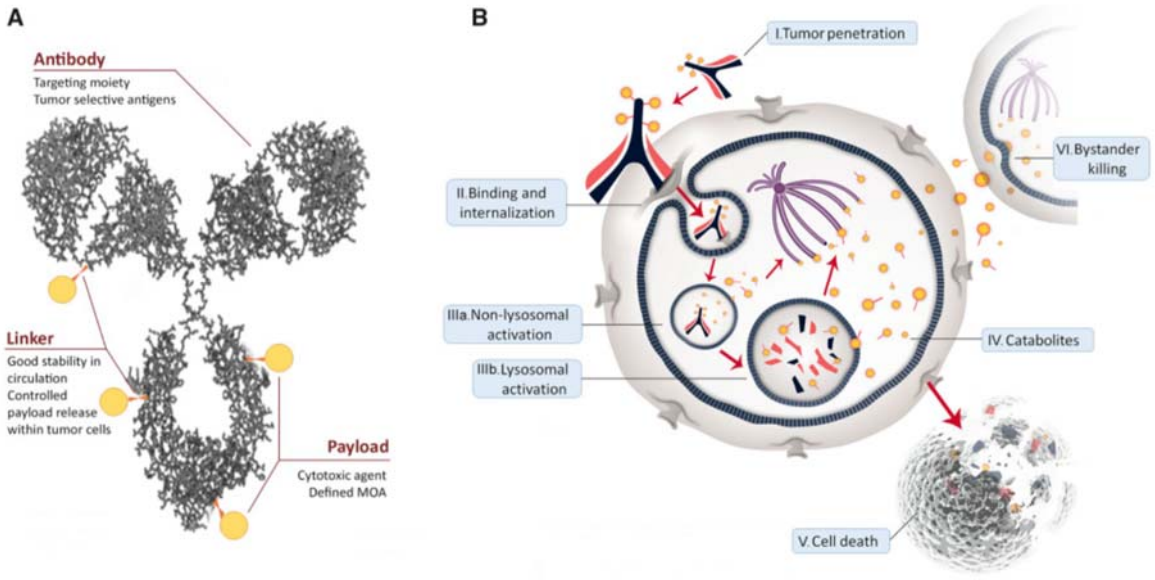
- **1980's**: Discovery HER2 as a oncogene in BC
- **1998**: Trastuzumab: 1st line with Pac
- **2006**: Trastuzumab: Adjuvant Tx
- **2007**: Lapatinib: 2nd line with CAP
- **2012**: Pertuzumab: 1st line with Trastuzumab and Pac
- **2013**: T-DM1: 2nd line Tx

Trastuzumab Emtansine (T-DM1)



- Novel antibody drug-conjugate.
- Trastuzuman linked to DM1, a microtubule inhibitor up to 400-fold more potent than paclitaxel.
- Average of 3.5 DM1 per antibody.
- T-DM1 binds o HER2 wit affinity similar to trastuzumab.

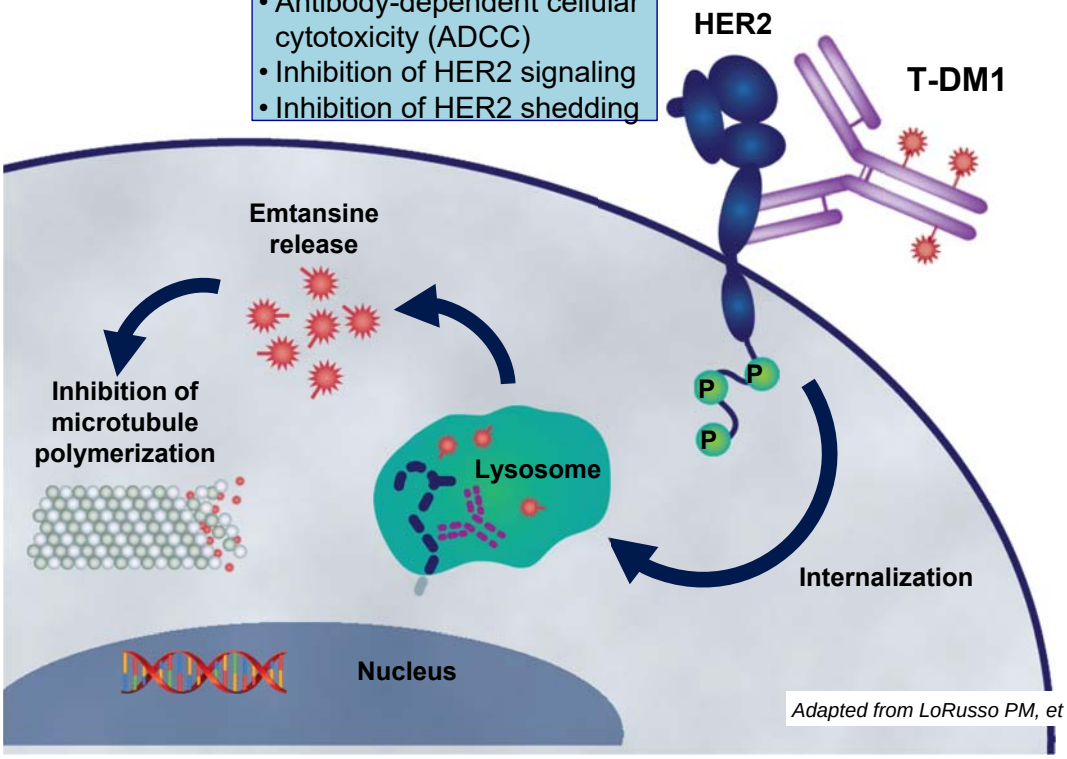
Antibody-drug conjugates (ADCs) structure and mechanism of action



2019 J Natl Cancer Inst.

Trastuzumab Emtansine (T-DM1): mechanism of action

Trastuzumab-specific MOA
- Antibody-dependent cellular cytotoxicity (ADCC)
- Inhibition of HER2 signaling
- Inhibition of HER2 shedding



Adapted from LoRusso PM, et al. Clin Cancer Res 2011.

EMILIA Study Design

HER2-positive LABC or MBC (N=980)

- Prior taxane and trastuzumab
- Progression on metastatic treatment or within 6 months of adjuvant treatment

1:1

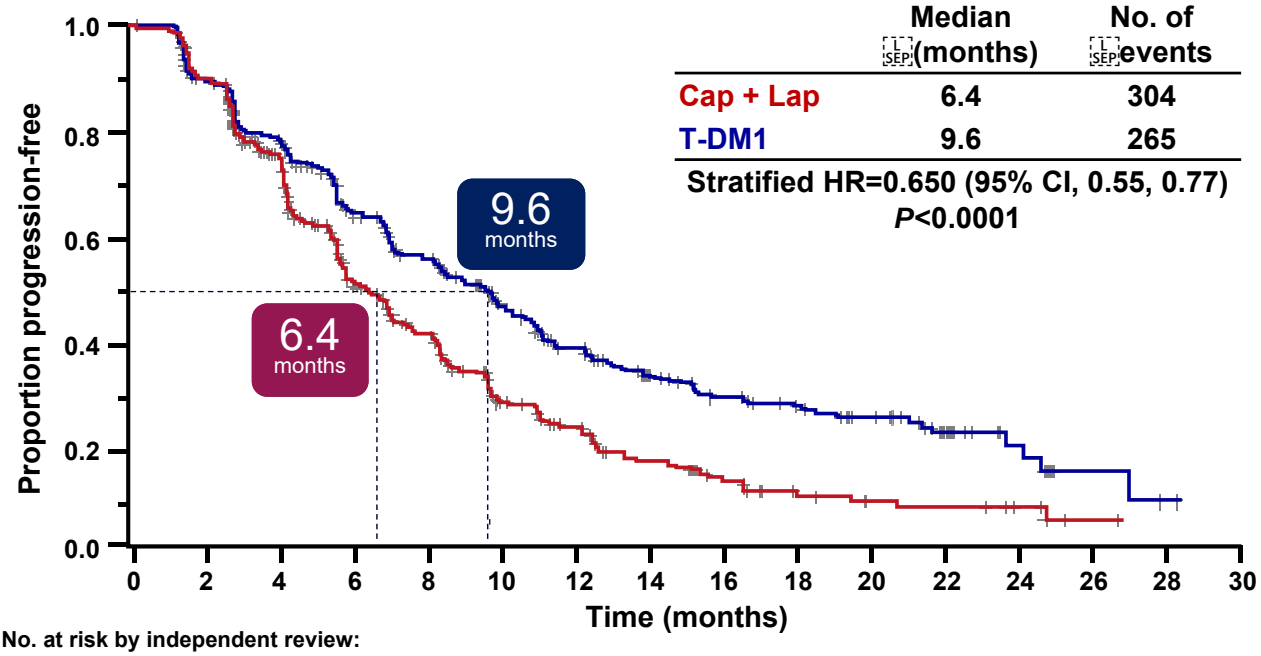
T-DM1
3.6mg/kg q3w IV
→ PD

Capecitabine
1000 mg/m² PO bid, days 1–14, q3w
+
Lapatinib
1250 mg/day PO qd
→ PD

- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary endpoints:** PFS by independent review, OS, and safety
- **Key secondary endpoints:** PFS by investigator, ORR, DOR

S. Verma et al. N Engl J Med 2012;367:1783-91

EMILIA: PFS by Independent Review



	Median (months)	No. of events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)
P<0.0001

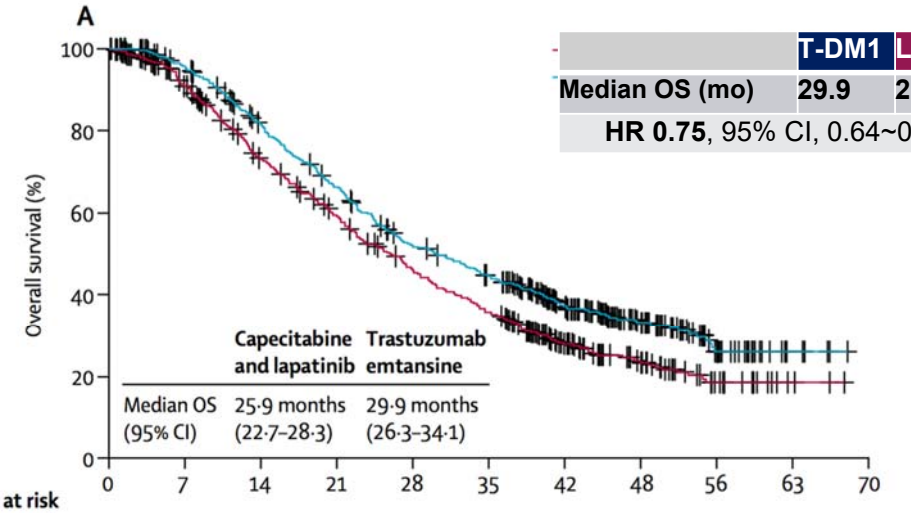
No. at risk by independent review:

Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

S. Verma et al. N Engl J Med 2012;367:1783-91

Overall survival of ITT population

Median follow-up 41·9 (control) and 47·8 months (T-DM1) group



	T-DM1	L+X
Median OS (mo)	29.9	25.9
HR 0.75, 95% CI, 0.64~0.88		

Number at risk (number censored)

Capecitabine and lapatinib	496 (0)	418 (35)	326 (47)	258 (53)	195 (58)	153 (58)	82 (99)	48 (122)	19 (144)	3 (160)	0 (163)
Trastuzumab emtansine	495 (0)	451 (21)	374 (34)	302 (36)	231 (42)	194 (47)	127 (85)	68 (133)	23 (169)	5 (187)	0 (191)

Lancet Oncol. 2017;18:732-742

Adverse Events

Grade ≥3 AEs With Incidence ≥2%

	Cap + Lap (n=488)		T-DM1 (n=490)	
Adverse Event	**All Grades, %**	**Grade ≥3, %**	**All Grades, %**	**Grade ≥3, %**
Diarrhea	79.7	**20.7**	23.3	1.6
Hand-foot syndrome	58.0	**16.4**	1.2	0.0
Vomiting	29.3	**4.5**	19.0	0.8
Neutropenia	8.6	**4.3**	5.9	2.0
Hypokalemia	8.6	**4.1**	8.6	2.2
Fatigue	27.9	**3.5**	35.1	2.4
Nausea	44.7	**2.5**	39.2	0.8
Mucosal inflammation	19.1	**2.3**	6.7	0.2
Thrombocytopenia	2.5	0.2	28.0	**12.9**
Increased AST	9.4	0.8	22.4	**4.3**
Increased ALT	8.8	1.4	16.9	**2.9**
Anemia	8.0	1.6	10.4	**2.7**

S. Verma et al. N Engl J Med 2012;367:1783-91

T-DM1 is NOT associated with typical chemotherapy toxicity

- **No alopecia**
- **Significant nausea, diarrhea, fatigue, neutropenia, neuropathy are rare (<3% patients)**
- **Cardiac toxicity rare (<2%)**

S. Verma et al. N Engl J Med 2012;367:1783-91

MARIANNE study Design

- HER2-positive (central) LABC[a] or MBC
- No prior chemotherapy for LABC/MBC
- >6 months from prior neo-/adjuvant vinca alkaloid or taxane chemotherapy

N = 1095

Trastuzumab + docetaxel (n=365)
(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m^2 q3w) **OR**
Trastuzumab + paclitaxel
(4 mg/kg LD then 2 mg/kg + 80 mg/m^2 qw)

T-DM1 + placebo[b] (n=367)
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

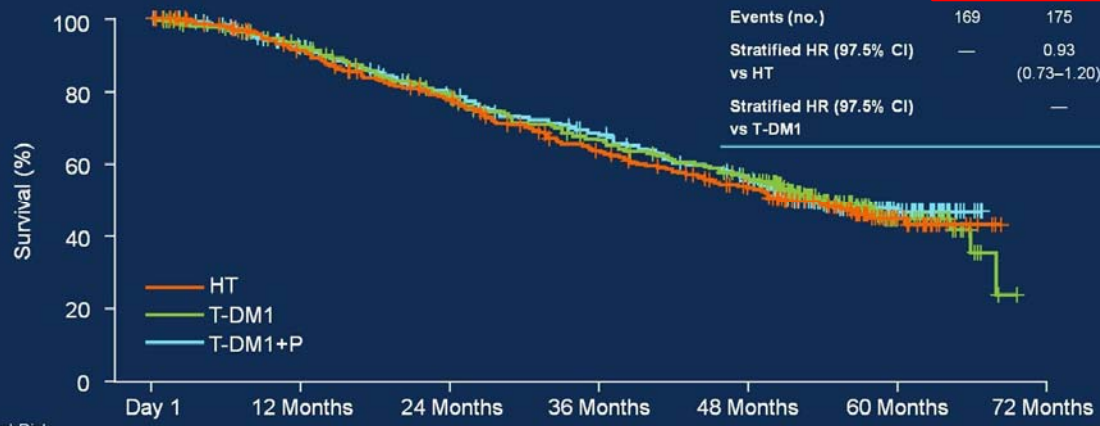
T-DM1 + pertuzumab (n=363)
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

- Stratification factors: World region, Prior neo-/adjuvant therapy (if Yes: prior trastuzumab/lapatinib), Visceral disease
- Primary end point: PFS by independent review facility (IRF), non-inferiority and superiority assessed
- Key secondary end points: OS, PFS by investigator, ORR, Safety, Patient-reported outcomes

Edith Perez et al. at 2017 ASCO Annual Meeting

MARIANNE: final analysis of overall survival

	HT n=365	T-DM1 n=367	T-DM1+P n=363
Median OS (mo.)	50.9	53.7	51.8
Events (no.)	169	175	168
Stratified HR (97.5% CI) vs HT	—	0.93 (0.73–1.20)	0.86 (0.67–1.11)
Stratified HR (97.5% CI) vs T-DM1		—	1.00 (0.78–1.28)



No. at Risk

	Day 1	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
HT	365	303	251	197	155	28	
T-DM1	367	322	264	216	176	37	
T-DM1+P	363	309	257	217	172	41	

Edith Perez et al. at 2017 ASCO Annual Meeting

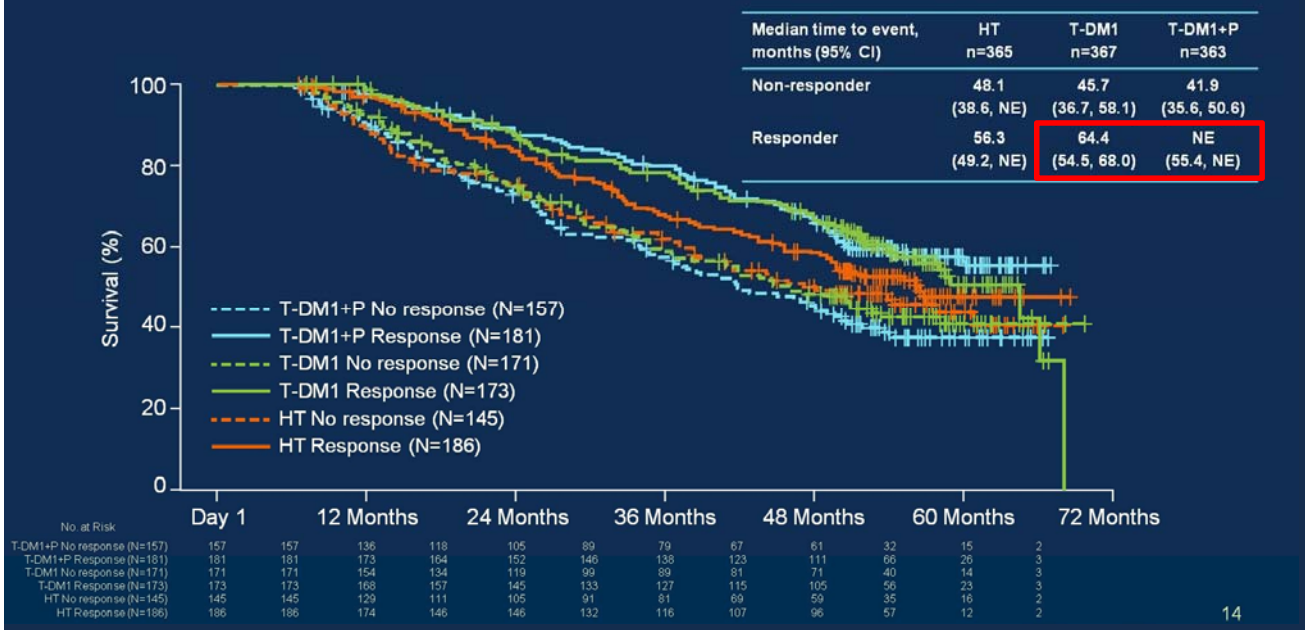
MARIANNE: landmark analysis of overall survival

At primary PFS analysis[1]	HT (n=365)	T-DM1 (n=367)	T-DM1+P (n=363)
ORR, %	67.9	59.7	64.2
Median DOR, months	12.5	20.7	21.2

- Does this longer DOR in T-DM1 patients translate into OS?
- An exploratory post-hoc Landmark analysis was conducted
  - Landmark time was 6.5 months from randomization (~ 3 tumor assessments)
    - At 6.5 months, less than 10% of patients had died or dropped out (HT 9%; T-DM1 6%; T-DM1 + P 7%) while most of the responses had already been observed (HT 95%; T-DM1 96%; T-DM1 + P 94%)

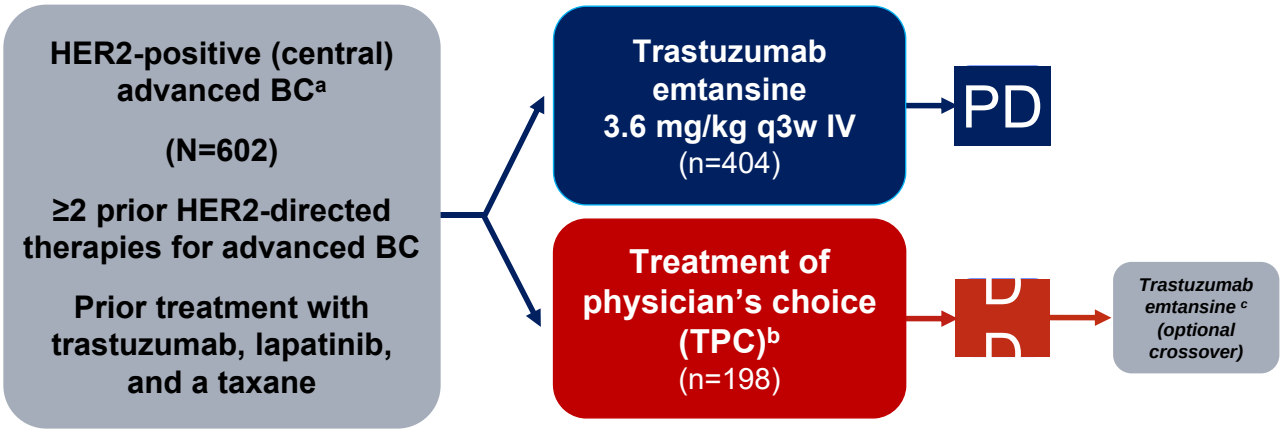
Edith Perez et al. at 2017 ASCO Annual Meeting

MARIANNE: landmark analysis of overall survival



Edith Perez et al. at 2017 ASCO Annual Meeting

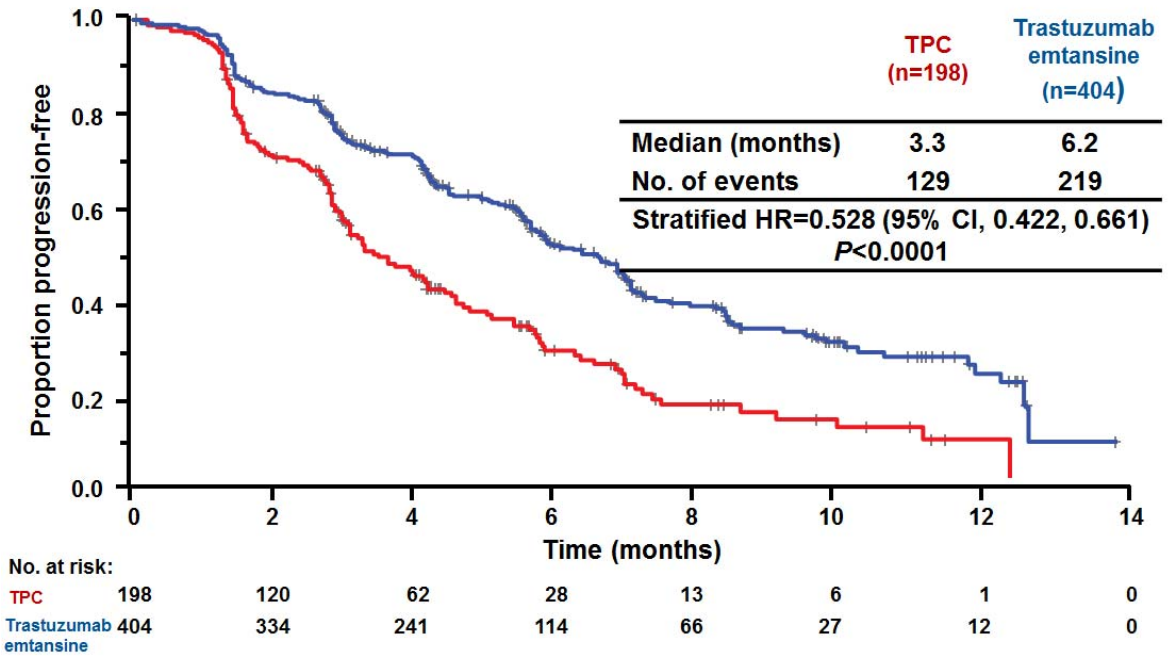
TH3RESA



- **Stratification factors: World region, number of prior regimens for advanced BC,[d] presence of visceral disease**
- **Co-primary endpoints: PFS by investigator and OS**
- **Key secondary endpoints: ORR by investigator and safety**

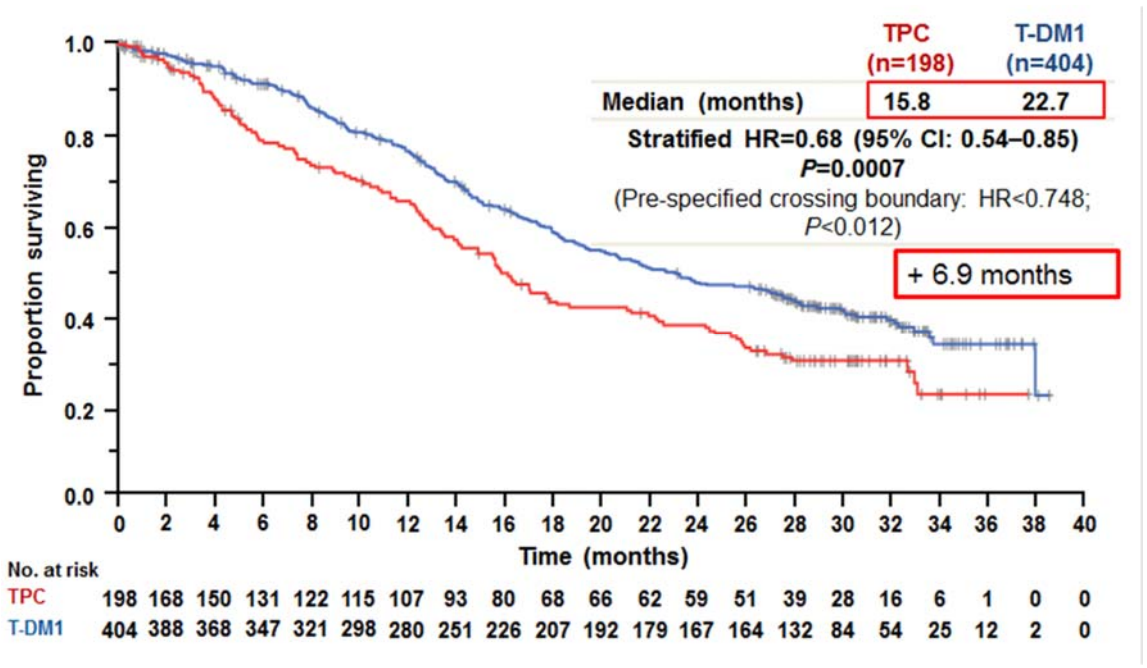
I.Krop et al. Lancet Oncol. 2017;18:732-742

TH3RESA: progression free survival



I.Krop et al. Lancet Oncol. 2017;18:732-742

TH3RESA: overall survival



I.Krop et al. Lancet Oncol. 2017;18:732-742

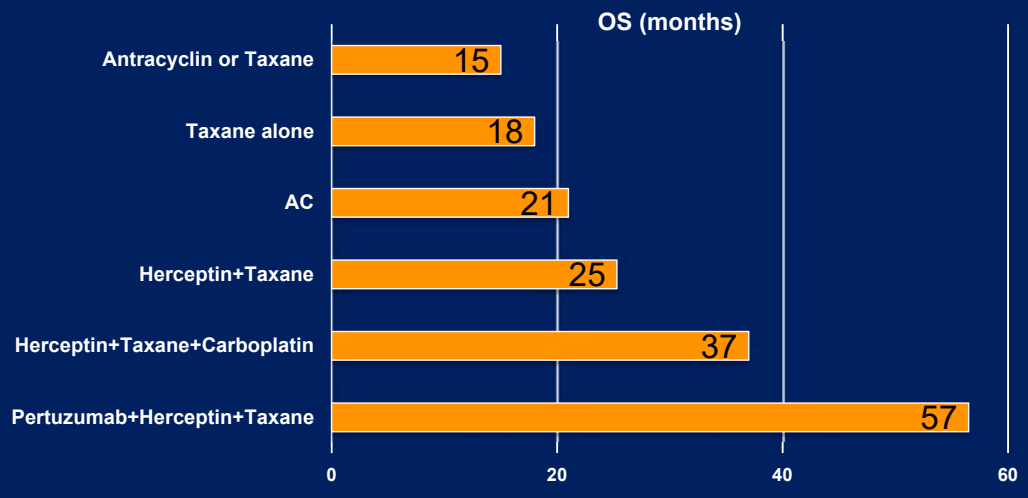
Pivotal study result of T-DM1

Trial	MARIANNE	EMILIA	TH3RESA
Setting	1st line	2nd line	3rd line
Study arm	T-DM1 T-DM1+P H+Taxane	T-DM1 Lap+CAP	T-DM1 TPC
Overall response rate	59.7% 64.2% 67.9%	**43.6%** 30.8%	**31.3%** 8.6%
Progression-free survival	**14.1M** 15.2M 13.7M	**9.6M*** 6.4M (HR 0.65)	**6.2M*** 3.3M (HR 0.52)
Overall survival	**53.7M** 41.8M 50.9M	**29.9M*** 25.9M (HR 0.69)	**22.7M*** 15.8M (HR 0.68)

Results of key trials determining clinical practice in advanced/metastatic HER2+ disease

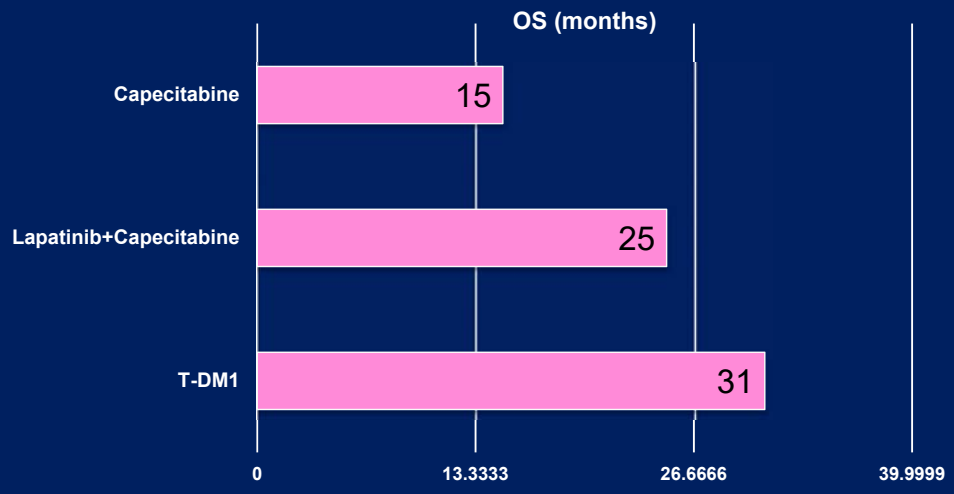
Trial	n	Line of treatment	Treatment arms	PFS	OS
CLEOPATRA	808	1st line; TFI > 12 months	PTH vs TH[1SEP]	18.7 m vs 12.4m **(HR 0.62)** (0.51–0.75)	56.5m vs 40.8 m **(HR 0.68)** (0.56–0.84)
EMILIA	991	2nd line	T-DM1 vs Cap + Lap	9.6m vs 6.4m **(HR 0.65)** (0.55–0.77)	29.9 m vs. 25.9 m **(HR 0.75)** (0.64–0.88)
TH3RESA	602	≥2nd line (after progression on taxane, trastuzumab and lapatinib)	T-DM1 vs physician's choice	6.2 M vs 3.3m **(HR 0.53)** (0.42–0.66)	22.7m vs.15.8 m **(HR 0.68)** (0.54–0.85)
EGF100151	399	≥2nd line (after progression on trastuzumab, taxane and anthracycline)	Cap+ Lap vs Cap	8.2m vs.4.4m **(HR 0.49)** (0.34–0.71)	74wk vs. 64.7wk (HR 0.87) (0.70-1.07)
EGF104900	296	≥2nd line (after progression on trastuzumab)	T+ Lap+ vs. Lap	11 wks vs. 8 wks **(HR 0.73)** (0.57–0.93)	14 vs. 10 months (HR 0.75) (0.53–1.07)

Recent survival improvements in 1L HER2+ MBC



1. Chan S, et al. J Clin Oncol 1999; 17:2341–2354
2. Slamon DJ, et al. N Engl J Med 2001; 344:783–792
3. Marty M, et al. J Clin Oncol 2005; 23:4265–4274
4. Swain S, et al. N Engl J Med 2015; 372:724–734
5. Valero V, et al. J Clin Oncol 2011; 29:149–156.

Recent survival improvements in 2L HER2+ MBC



1. Cameron D, et al. Breast Cancer Res Treat 2008; 112:533–543
2. Verma S, et al. N Engl J Med 2012: 367:1783–1791
3. Erratum, N Engl J Med 2013; 368:2442

Real World Data on OS in MBC

	Year of Diagnosis					
OS (m)	2008	2009	2010	2011	2012	2013
HR+ HER2- (N=9.908)	43.7 (40.2-46.6)	42.0 (38.9-44.6)	40.9 (38.0-43.4)	42.0 (39.2-45.0)	44.5 (41.8-47.3)	40.3 (37.8-ND)
HER2+ (N=2.861)	38.6 (33.6-44.6)	42.3 (38.3-50.8)	40.1 (35.2-45.6)	42.3 (36.5-49.8)	51.1 (46.5-ND)	Not Reached
HR- HER2- (N=2.317)	15.1 (12.7-16.4)	15.1 (13.0-17.4)	14.7 (13.2-17.0)	14.0 (11.4-15.9)	13.9 (11.4-15.9)	14.1 (12.5-15.5)

Carlos Barrios at 2019 ASCO Annual Meeting

Outline

Milestone of targeting HER2 in MBC

Recent advance in HER2 treatment

Anti-HER2 directed TKI in Development

Agent	Target	Reported results of efficacy in HER2-positive advanced disease	CNS ORR (monotherapy)	CNS ORR in combination with capecitabine	Phase of development
Neratinib[60,61]	Irreversible pan-HER	**Single-agent** ORR 56% (phase II)	8%	49% (phase II)	US FDA approved only in the adjuvant setting III (metastatic) NALA-NCT01808573
Tucatinib [62–64]	Selectively inhibits HER2 relative to EGFR	**In combination with capecitabine and trastuzumab:** ORR 61% PFS of 7.8m **In combination with T-DM1:** ORR 48% PFS 8.2 m (phase Ib)	5–9% (+trastuzumab)	42% (+trastuzumab)	II HER2CLIMB-NCT02614794
Pyrotinib[65]	Irreversible pan-HER	**Single-agent** ORR 50%, CBR 61%, PFS 35.4 w (phase I) **In combination with capecitabine** ORR 78.5% PFS 18 m (phase II)	NA	NA	III NCT003080805
Poziotinib[66]	Irreversible pan-HER	**Single-agent** DCR 75% PFS 4 m (phase II)	NA	NA	II

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Pernas S, Tolaney SM. Ther Adv Med Oncol 2019, Vol. 11: 1–16
DOI: 10.1177/1758835919833519

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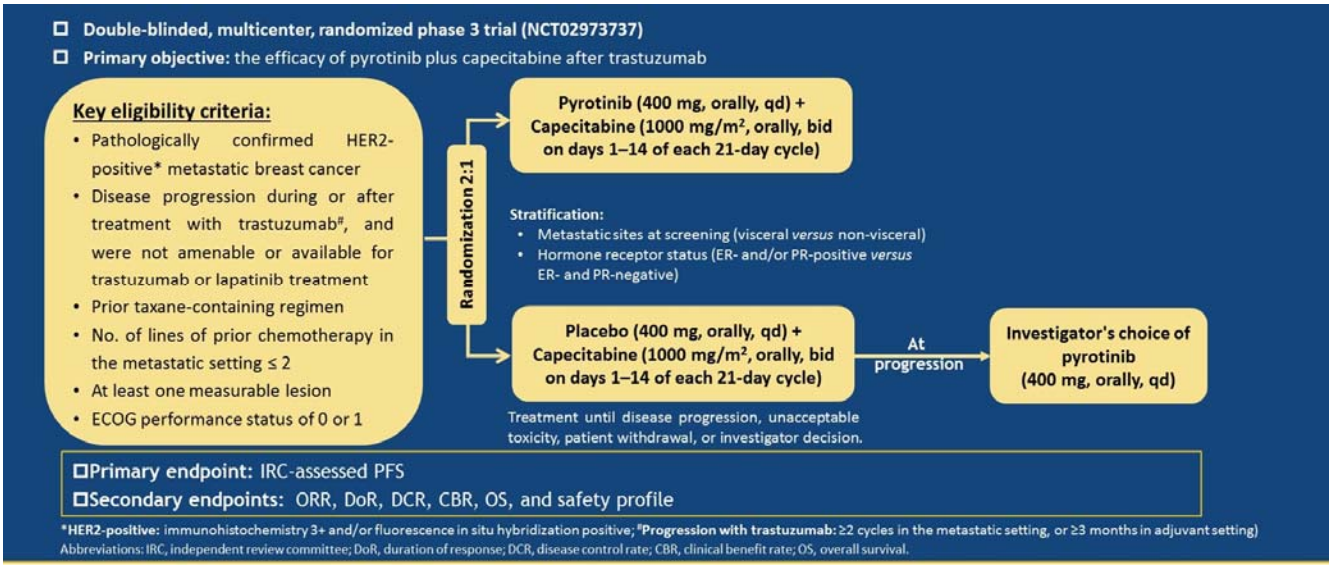
PHENIX Study Design: Pyrotinib combined with capecitabine in HER2+ MBC previously treated with trastuzumab and taxanes



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PHENIX study: baseline characteristics and previous treatment

	Pyrotinib plus capecitabine (n=185)	Placebo plus capecitabine (n=94)
Age, median (range), years	50 (24–70)	50 (20–71)
ECOG performance status, n (%)		
0	80 (43.2)	30 (31.9)
1	105 (56.8)	64 (68.1)
Hormone receptor status, n (%)		
ER- and/or PR-positive	100 (54.1)	51 (54.3)
ER- and PR-negative	85 (45.9)	43 (45.7)
Metastatic sites at screening, n (%)		
Visceral	147 (79.5)	72 (76.6)
Non-visceral	38 (20.5)	22 (23.4)
Brain metastases		
Present at screening, n	21	10
Received local therapy, n (%)	6 (28.6)	2 (20.0)
Did not receive local therapy, n (%)	15 (71.4)	8 (80.0)

	Pyrotinib plus capecitabine (n=185)	Placebo plus capecitabine (n=94)
Previous trastuzumab therapy, n (%)	185 (100)	94 (100)
For advanced disease	114 (61.6)	63 (67.0)
As neo/adjuvant therapy	85 (45.9)	40 (42.6)
Both	14 (7.6)	9 (9.6)
Duration of trastuzumab therapy		
n	98	57
Median (range), days	170 (2–2154)	144 (1–701)
<6 weeks, n (%)	13 (13.3)	10 (17.5)
6-12 weeks, n (%)	13 (13.3)	11 (19.3)
>12 weeks, n (%)	72 (73.5)	36 (63.2)
Previous therapy in the metastatic setting		
n	125	72
1 line, n (%)	70 (56.0)	47 (65.3)
2 lines, n (%)	44 (35.2)	18 (25.0)
3 or 4 lines, n (%)	3 (2.4)	2 (2.8)
Other, n (%)	8 (6.4)	5 (6.9)

Abbreviation: ER, estrogen receptor; PR: progesterone receptor.

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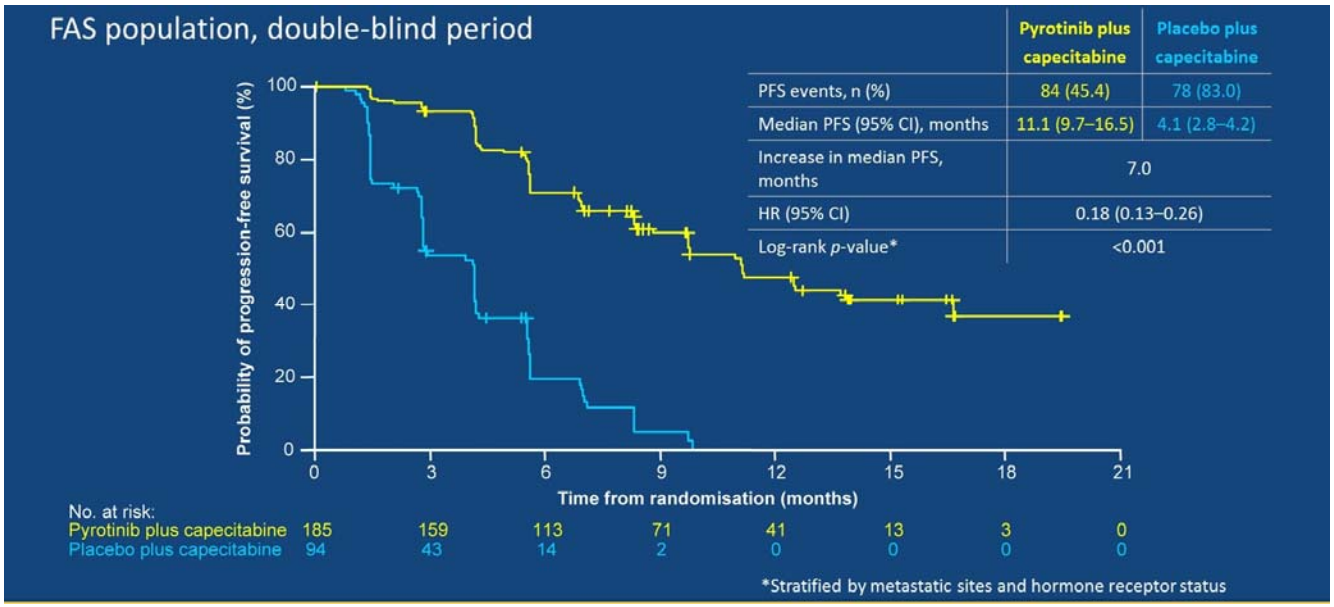
PHENIX primary endpoint: IRC-assessed PFS



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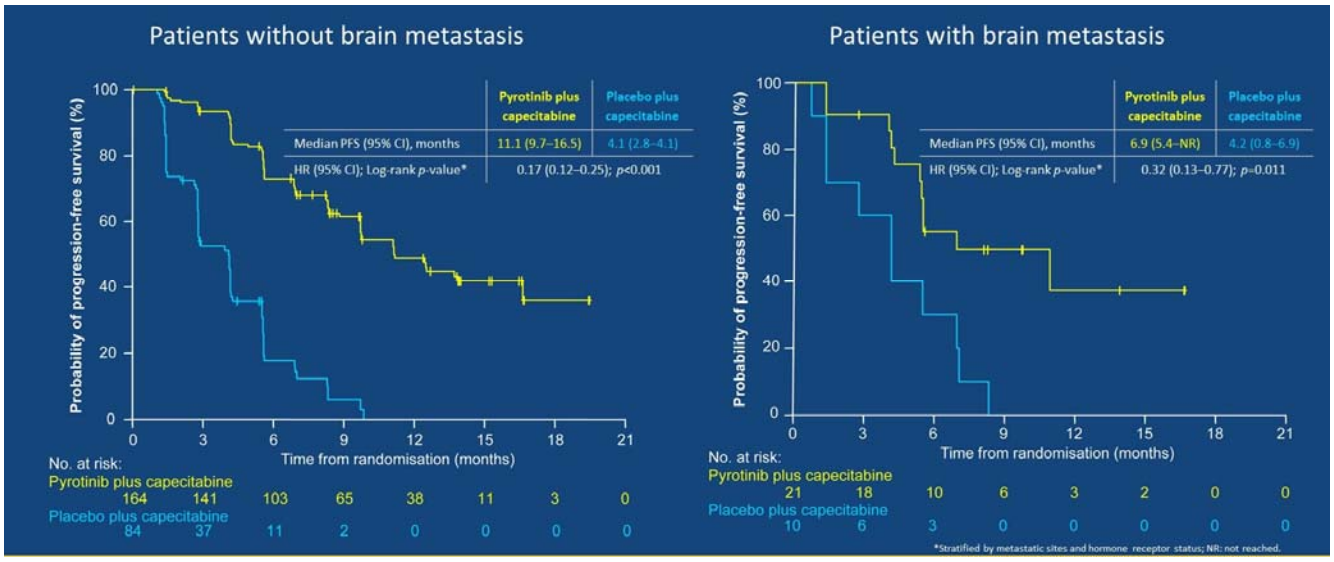
PHENIX: brain metastasis



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Margtuximab: Fc-engineered to Activate Immune responses

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 FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

Margetuximab Binding to FcγR Variants:

Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4x ↓

1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

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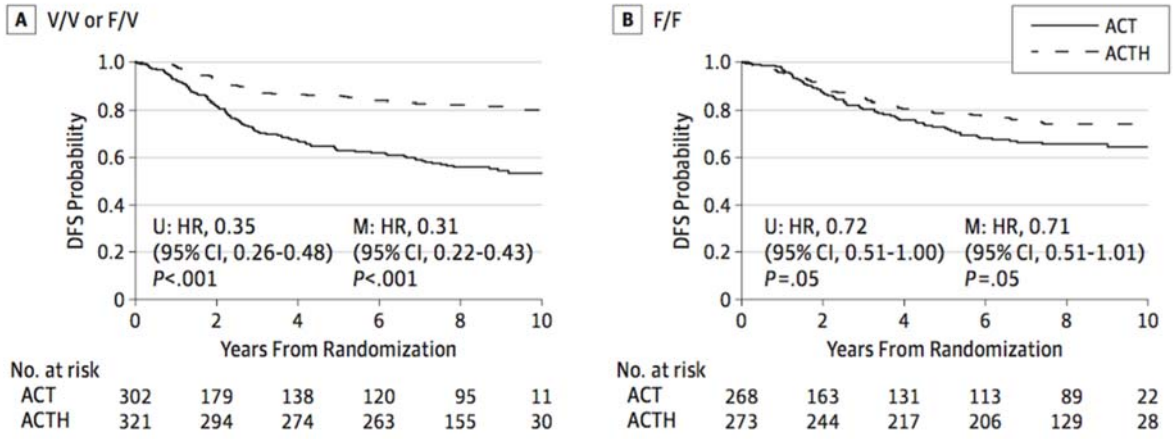
Association of polymorphism in FCGR3A with degree of Trastuzumab benefit: analysis of adjuvant NSABP B-31 trial



Patients with genotypes FCB3A-158V/V or FCB3A-158V/F had greater benefit from trastuzumab (HR, 0.31; 95% CI, 0.22-0.43; P < .001) than homozygous for the low-affinity allele (HR, 0.71; 95% CI, 0.51-1.01; P = .05)

JAMA Oncol. 2017;3:335-341

CD16A genotype may predicts anti-HER2 antibody benefit

- Two retrospective studies of HER2+ MBC[1] and early breast cancer[2] suggest patients with lower affinity CD16A-158F allele have lower PFS and ORR with trastuzumab than those homozygous for higher affinity CD16A-158VV
  - Two other retrospective studies showed no association between FcγR genotypes and outcome with adjuvant trastuzumab in early breast cancer[3,4]
- **Hypothesis**: Greater margetuximab benefit in lower binding CD16A-158F carriers
  - Increased affinity of margetuximab for CD16A-158F over trastuzumab (wild-type IgG1)
- **SOPHIA is first prospective* analysis of FcγR genotype impact on anti-HER2 antibody efficacy**

*Non-alpha allocating, exploratory analysis.
ORR=objective response rate; PFS=progression-free survival.

1. Musolino A, et al. *J Clin Oncol.* 2008;26(11):1789-1796. 2. Gavin PG, et al. *JAMA Oncol.* 2017;3(3):335-341.
3. Hurvitz SA, et al. *Clin Cancer Res.* 2012;18(12):3478-3486. 4. Norton N, et al. *Cancer Immunol Res.* 2014;2(10):962-969.

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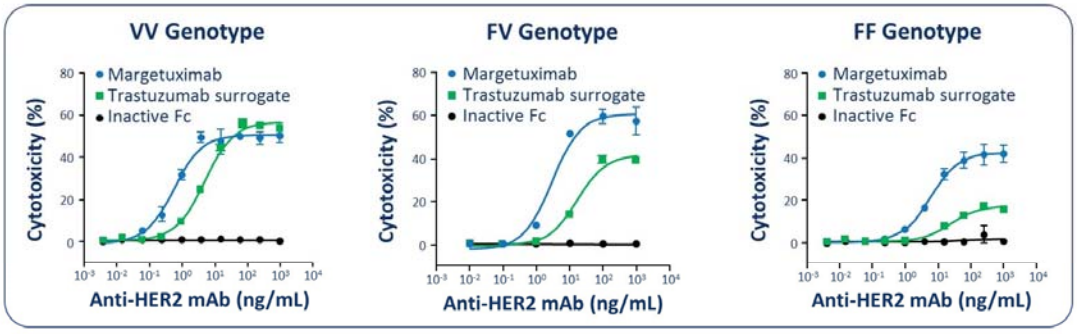
Margetuximab Enhances Innate Immunity *in Vitro*

Greater relative cytotoxicity of margetuximab with NK cells from CD16A-158F allele carriers



Preclinical Assay of Antibody-Dependent Cellular Cytotoxicity (ADCC)[1]

Effector Cells: Human NK cells from donors with CD16A genotypes 158VV, 158FV, and 158FF
Target Cells: JIMT-1 HER2+ breast cancer cell line resistant to trastuzumab antiproliferative activity
Cellular Assay: 3:1 Effector:Target ratio; 24-hour incubation time; endpoint: % lactate dehydrogenase release

mAb=monoclonal antibody; NK=natural killer.

Nordstrom JL, et al. *Breast Cancer Res.* 2011;13(6):R123.

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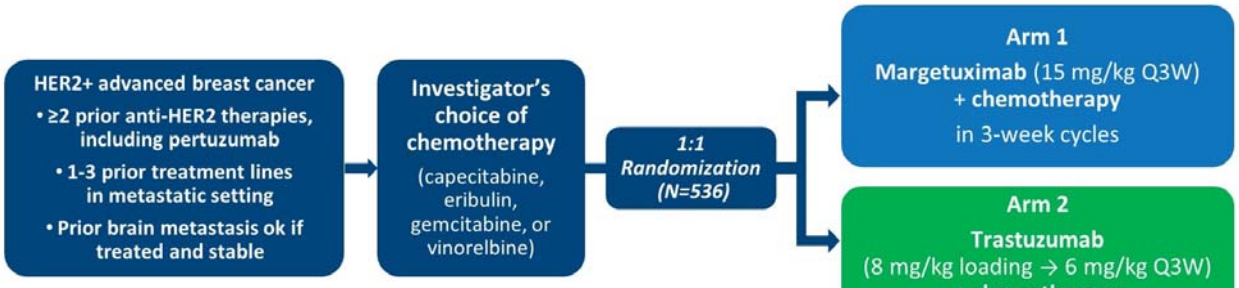
CP-MGAH22-04 (SOPHIA) Design



Sequential Primary Endpoints	• **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• PFS (Investigator assessed) • Objective response rate (by CBA)
Tertiary/Exploratory Endpoints	• Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

Stratification:
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

HR=hazard ratio; CBA=central blinded analysis.

1. Rugo HS, et al. *J Clin Oncol*. 2016;34(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. www.clinicaltrials.gov/ct2/show/NCT02492711. Accessed April 8, 2019.

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SOPHIA ITT population: Prior Cancer Therapy

	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
Settings of prior therapy		
Adjuvant and/or neoadjuvant	**158 (59%)**	**145 (54%)**
Metastatic only	108 (41%)	125 (46%)
Prior metastatic lines of therapy		
≤2	175 (66%)	180 (67%)
>2	91 (34%)	90 (33%)
Prior anti-HER2 therapy		
Trastuzumab	**266 (100%)**	**270 (100%)**
Pertuzumab	**266 (100%)**	**269 (100%)**
T-DM1	**242 (91%)**	**247 (92%)**
Lapatinib	41 (15%)	39 (14%)
Other HER2	6 (2%)	6 (2%)
Prior chemotherapy		
Taxane	252 (95%)	249 (92%)
Anthracycline	118 (44%)	110 (41%)
Platinum	34 (13%)	40 (15%)
Prior endocrine therapy	126 (47%)	133 (49%)

Treatment arms overall balanced

ITT population: N=536.

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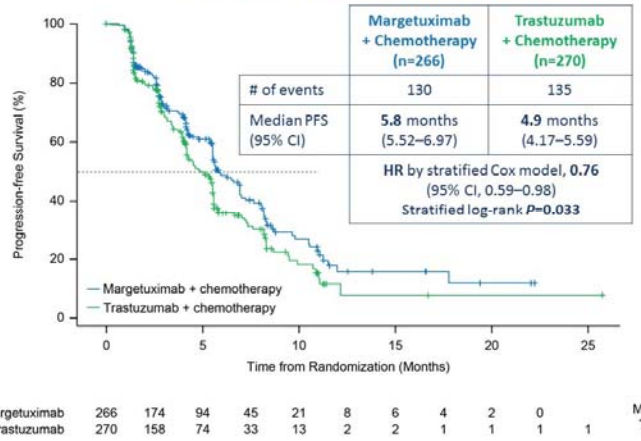
PFS Analysis in ITT Population

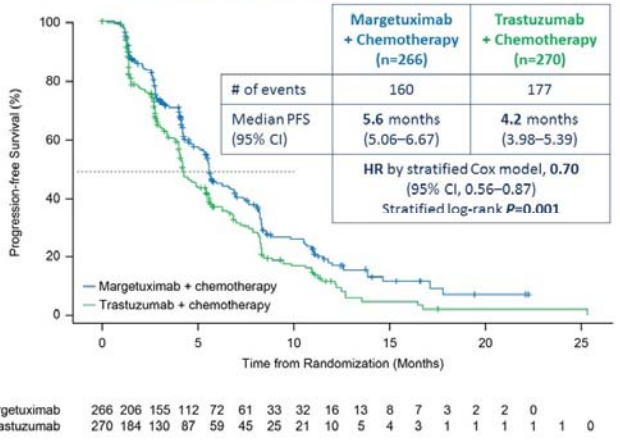
24% Risk Reduction of Disease Progression
Central Blinded Analysis (Primary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	130	135
Median PFS (95% CI)	**5.8** months (5.52–6.97)	**4.9** months (4.17–5.59)
HR by stratified Cox model, **0.76** (95% CI, 0.59–0.98) Stratified log-rank ***P*=0.033**		

Margetuximab	266	174	94	45	21	8	6	4	2	0	
Trastuzumab	270	158	74	33	13	2	2	1	1	1	1

30% Risk Reduction of Disease Progression
Investigator Assessed (Secondary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	160	177
Median PFS (95% CI)	**5.6** months (5.06–6.67)	**4.2** months (3.98–5.39)
HR by stratified Cox model, **0.70** (95% CI, 0.56–0.87) Stratified log-rank ***P*=0.001**		

Margetuximab	266	206	155	112	72	61	33	32	16	13	8	7	3	2	2	0
Trastuzumab	270	184	130	87	59	45	25	21	10	5	4	3	1	1	1	1	1	0

- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

ITT population: N=536. CI=confidence interval.

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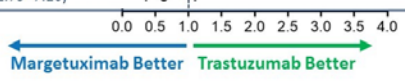
Planned* Exploratory PFS Analyses by FcγR Genotypes (CBA)

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

		Median PFS (95% CI), Months: Margetuximab + Chemotherapy	Median PFS (95% CI), Months: Trastuzumab + Chemotherapy	HR by Unstratified Cox Model	95% CI	Unstratified Log-Rank *P* Value
	All patients	5.8 (5.52–6.97)	4.9 (4.17–5.59)	0.78	(0.61–0.99)	0.044
Activating function	CD16A/F carrier (FV or FF), n=437	6.9 (5.55–8.15)	5.1 (4.14–5.59)	0.68	(0.52–0.90)	0.005
	CD16A/FF, n=192	8.2 (5.52–10.51)	5.6 (4.50–8.31)	0.69	(0.46–1.05)	0.080
	CD16A/FV, n=245	6.3 (5.52–7.23)	4.3 (4.01–5.59)	0.71	(0.50–1.01)	0.055
	CD16A/VV, n=69	4.8 (2.46–5.65)	5.6 (2.86–11.04)	1.78	(0.87–3.62)	0.110
	CD32A/RR, n=122	5.7 (4.80–10.55)	5.5 (2.76–8.21)	0.69	(0.41–1.17)	0.166
	CD32A/RH, n=247	6.9 (5.55–8.15)	5.6 (4.17–6.67)	0.74	(0.52–1.06)	0.102
	CD32A/HH, n=137	5.6 (3.29–8.28)	4.1 (2.79–5.59)	0.80	(0.49–1.30)	0.365
Inhibitory function	CD32B/II†, n=380	5.8 (5.55–7.66)	5.5 (4.17–5.65)	0.85	(0.64–1.13)	0.265
	CD32B/IT†, n=117	6.0 (4.14–NA)	5.5 (2.79–7.16)	0.63	(0.36–1.10)	0.098



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

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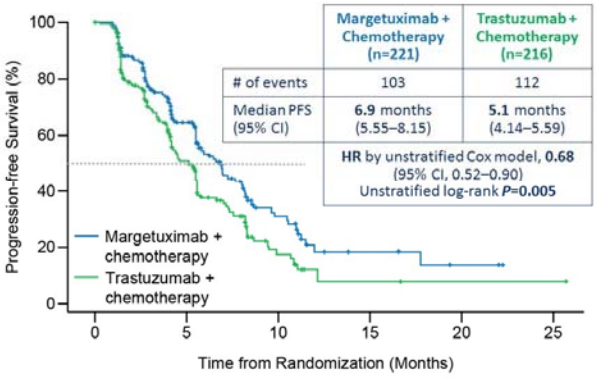
Planned Exploratory PFS Analysis by CD16A Genotype, by CBA

506 patients genotyped (94%)

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

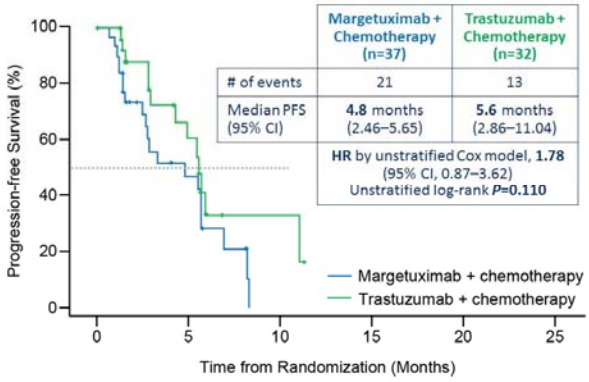


	Margetuximab + Chemotherapy (n=221)	Trastuzumab + Chemotherapy (n=216)
# of events	103	112
Median PFS (95% CI)	**6.9** months (5.55–8.15)	**5.1** months (4.14–5.59)

HR by unstratified Cox model, **0.68** (95% CI, 0.52–0.90)
Unstratified log-rank ***P*=0.005**

Margetuximab	221	157	84	42	21	8	6	4	2	0
Trastuzumab	216	129	62	30	11	2	2	1	1	1

VV, n=69 of 506 (14%)



	Margetuximab + Chemotherapy (n=37)	Trastuzumab + Chemotherapy (n=32)
# of events	21	13
Median PFS (95% CI)	**4.8** months (2.46–5.65)	**5.6** months (2.86–11.04)

HR by unstratified Cox model, **1.78** (95% CI, 0.87–3.62)
Unstratified log-rank ***P*=0.110**

Margetuximab	37	16	10	3	0	
Trastuzumab	32	18	10	2	2	0

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NALA study design

Inclusion criteria

- Metastatic breast cancer (MBC)
- Centrally confirmed HER2+ disease
- ≥2 lines of HER2-directed therapy for MBC
- Asymptomatic and stable brain metastases permitted

R (1:1)

n=621

Neratinib 240 mg/d + Capecitabine 1500 mg/m² 14/21 d Loperamide (cycle 1)[a] → PD

No endocrine therapy permitted

Lapatinib 1250 mg/d + Capecitabine 2000 mg/m² 14/21 d → PD

Follow-up (survival)

Stratification variables

- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

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

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

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NALA: baseline characteristics

	Neratinib + Capecitabine (n=307)	Lapatinib + Capecitabine (n=314)
Age <65 years, n (%)	244 (79)	248 (79)
Geographic region, n (%)		
Europe	121 (39)	123 (39)
North America	59 (19)	65 (21)
Rest of world	127 (41)	126 (40)
HR+ (ER+ and/or PR+), n (%)	181 (59)	186 (59)
Disease location at enrollment, n (%)		
Non-visceral only	60 (20)	61 (19)
Visceral	247 (80)	253 (81)
De novo metastatic disease, n (%)	139 (45)	136 (43)
No. of prior HER2 targeted therapies for MBC, n (%)		
2	215 (70)	215 (68)
≥3	92 (30)	99 (32)
Prior HER2 therapies for MBC, n (%)		
Trastuzumab only	124 (40)	113 (36)
Trastuzumab + pertuzumab	24 (8)	23 (7)
Trastuzumab + T-DM1	58 (19)	64 (20)
Trastuzumab + pertuzumab + T-DM1	101 (33)	114 (36)

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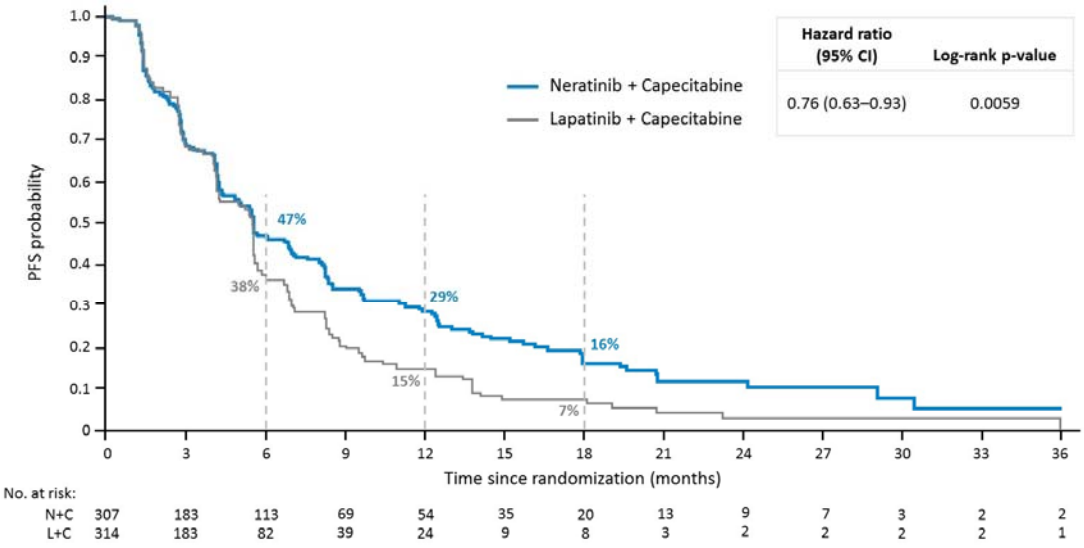
NALA: centrally confirmed PFS (co-primary endpoint)



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HER2 TKI summary

Drug	Lapatinib	Naratinib	Pyrotinib	Tucatinib
Reversibility	Reversible	Irreversible	Irreversible	Reversible
Target	HER1, 2	HER1, 2, 4	HER1, 2, 4	**HER2**
Route	Oral	Oral	Oral	Oral
Dosage	1250mg daily D1~D14 Q3W	240mg daily	400mg daily	300mg BID
AE	Diarrhea Skin rash	Diarrhea	Diarrhea HFR	Diarrhea Nausea Liver function

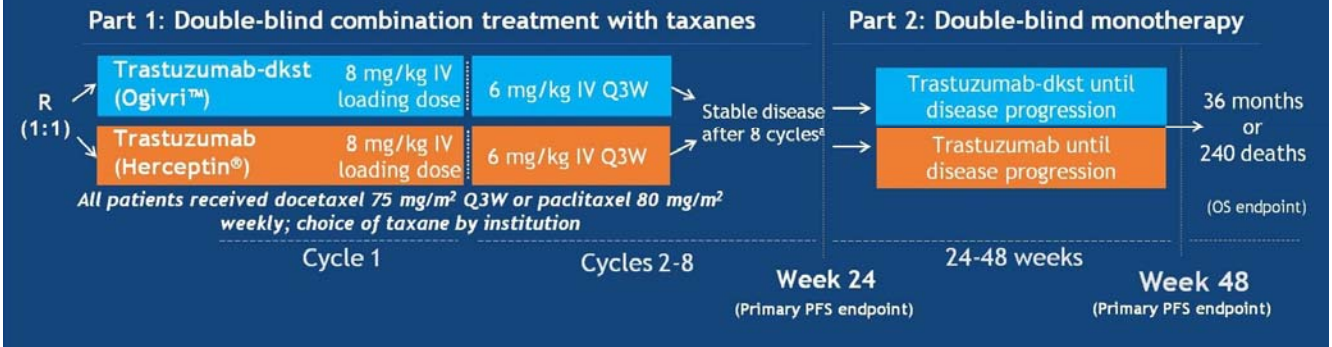
Summary of third line study

Study	Lapatinib* (n=324)	Naratinib (n=621)	Margetuximab (n=536)
Control group	CAP	L+CAP	H+C/T
HR+	153(47%)	181(59%)	334(62%)
Prior (neo)adjuvant Tx	16(5%)	0(0%)	303(57%)
No. of prior HER2 MBC Tx			
2	- -(- -)	215(70%)	355(66%)
≥3	- -(- -)	92(30%)	181(34%)
Prior HER2 Tx			
H only	100(100%)	124(40%)	0(0%)
P+H	0(0%)	24(8%)	47(9%)
T+T-DM1	0(0%)	58(19%)	0(0%)
H+P+T-DM1	0(0%)	101(33%)	489(91%)
PFS (months)	**8.4 vs 4.4**	**8.8 vs 6.6**	**5.8 vs 4.9**
HR (PFS)	**0.47 (0.32~0.68)**	**0.76 (0.63~0.93)**	**0.76 (0.59~0.98)**

**2nd line setting*

HERITAGE Study Design: Confirmatory Double-blind International Study

Designed per FDA and EMA guidelines to detect any potentially clinically meaningful differences between biosimilar and originator trastuzumab



EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization. [a]Continue 3-week cycles; if stable disease after 8 cycles, can continue combination treatment from part 1 at investigator's discretion.
Rugo et al. *JAMA*. 2017;317:37-47.

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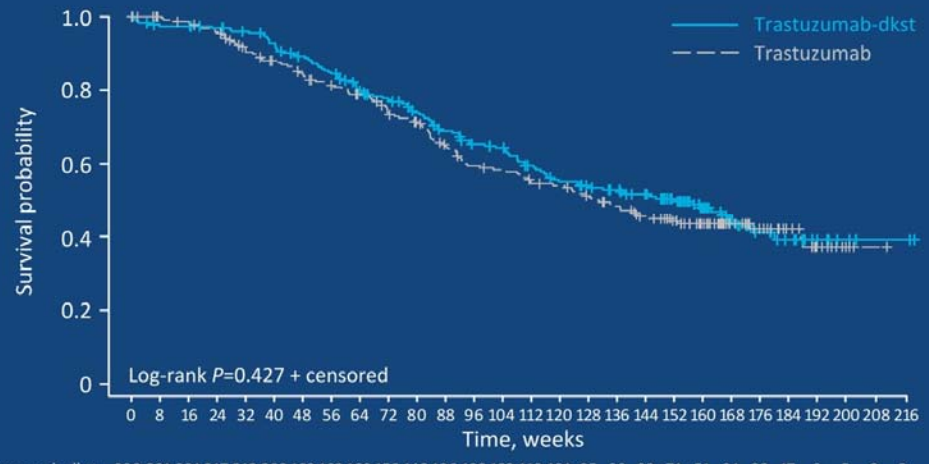
Overall Survival at 36 Months



Trastuzumab-dkst	230	221	221	217	212	203	192	182	168	159	148	136	126	122	110	101	95	90	83	71	51	31	22	17	9	5	2	2
Trastuzumab	228	221	217	210	195	185	177	168	160	148	139	124	112	109	101	99	91	84	75	65	52	36	27	19	11	5	1	0

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Landscape of Trastuzmab Biosimliars in US

				Availability
Mylan	Ogivri	Approved[7]	Agreement in place[20]	Not Launched
Pfizer	Trazimera	Approved[10]	Agreement in place[21]	Not Launched
Celltrion	Herzuma	Approved[8]	No agreement; litigation dismissed[19]	Not Launched
Samsung Bioepis	Ontruzant	Approved[9]	No agreement; ongoing litigatoin[18]	Not Launched
Amgen	ABP-980	Under Review after Resubmission[12]	No agreement; ongoing litigation[18]	Not Launched
Tanvex	TX-05	Phase 3 Clinical Trial ongoing[13]	No Agreement	Not Launched

Top to bottom: the order in which Herceptin biosimilar commercial launches are expected to

https://www.biosimilardevelopment.com

As of Apirl 2019:

- 4 Trastuzumab biosimliars approved by FDA
- 2 others with phase III studies
- Trastuzumab-dkst will commercially launch in mid 2019

Globally, there are 10 trastuzumab biosimiliars in different stages of development

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Anti-HER2 directed Antibody Conjugates in Development

Agent	Anti-HER2 MAb/payload (target)	Drug to antibody ratio	Linker drug	Phase of development	ORR in HER2-positive	ORR in HER2 low (IHC1+/2+/ISH-)
Trastuzumab-DM1 (T-DM1)[7]	Trastuzumab/ DM1 (anti-tubulin)	3.5	Noncleavable	US FDA Approved	43.6%	———
Trastuzumab duruxtecan (DS-8201a)[39]	Trastuzumab/ exatecan derivative (topoisomerase I inhibitor)	8	Cleavable	II/III NCT03248492 NCT03529110 NCT03523585	54.5%	50%
SYD985[40]	Duocarmycin derivative (alkylating agent)	2.8	Cleavable	III NCT03262935	33%	HR + 27% HR – 40%
XMT-1522[41]	XMT-1519/ monomethyl auristatin (anti-tubulin)	12	Cleavable	I NCT02952729	unknown	unknown
ARX788	Anti-HER2 MAb/ auristatin analog 269 (AS269) (anti-tubulin)	1.9	Non-cleavable	I NCT03255070	unknown	unknown
DHES0815A	Trastuzumab/ alkylator	2	Cleavable	I NCT03451162	unknown	unknown

Pernas S, Tolaney SM. Ther Adv Med Oncol 2019, Vol. 11: 1–16
DOI: 10.1177/1758835919833519

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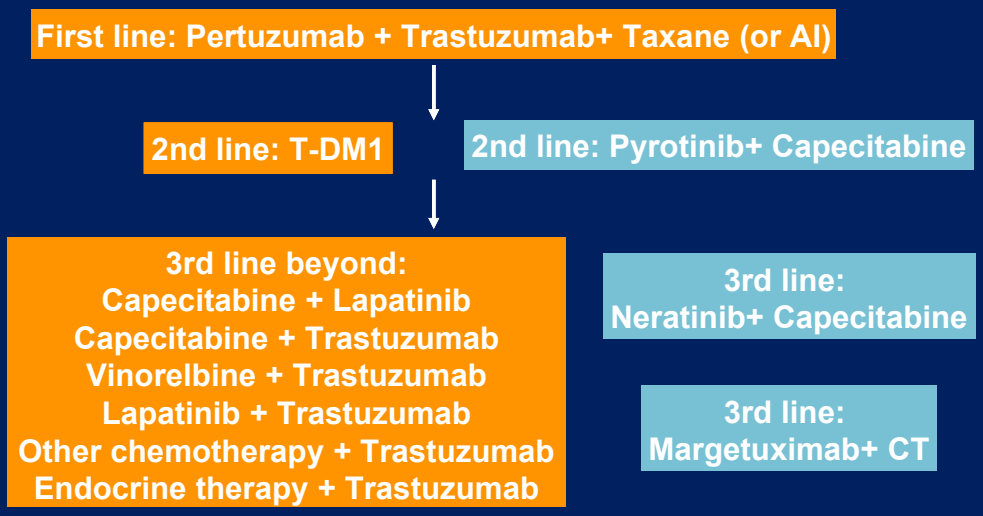
Treatment approach for HER2+ MBC



Sequence by patient's preference

Benefit of Pertuzumab in 2nd line use is less than 1st line
T-DM1 could be used in >2nd line setting

Adapted from Carlos Barrios at 2019 ASCO Annual Meeting

Take Home Message

Survival of HER2-positive MBC is improving.

Pertuzumab-based dual blockade treatment currently is the treatment choice in HER2-positive MBC.

T-DM1 remained 2nd line management in HER2-positive MBC, which is also effective in 3rd line.

More and more **HER2 TKI** shows clinical benefit in treatment in either 2nd line or beyond, which might have great impact in the future.

HER2 biosimilar is on the wave.

Thanks for your attention

questions and comments welcome