La biologia molecolare «driver» delle scelte terapeutiche: k mammario HER2+

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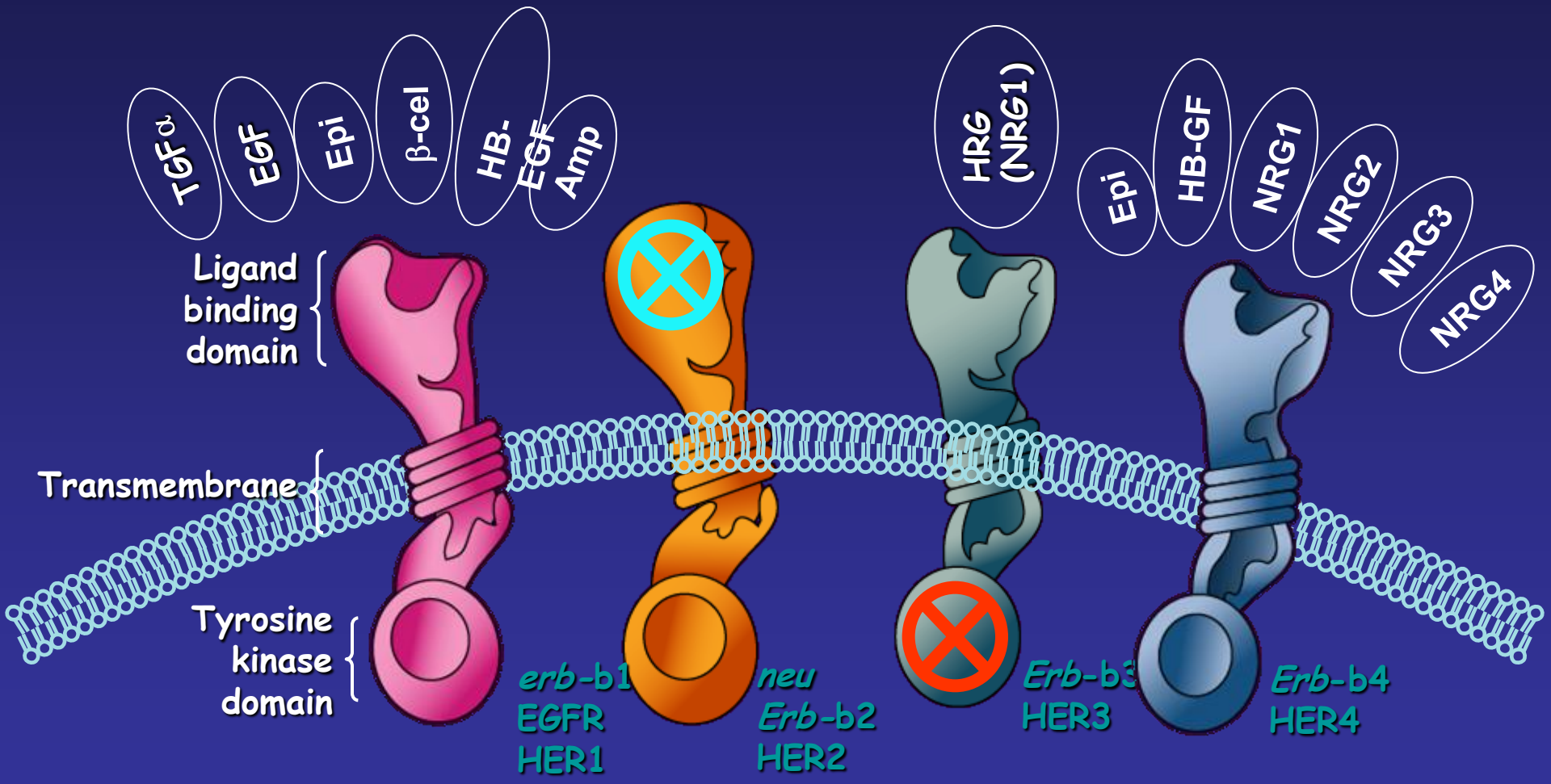
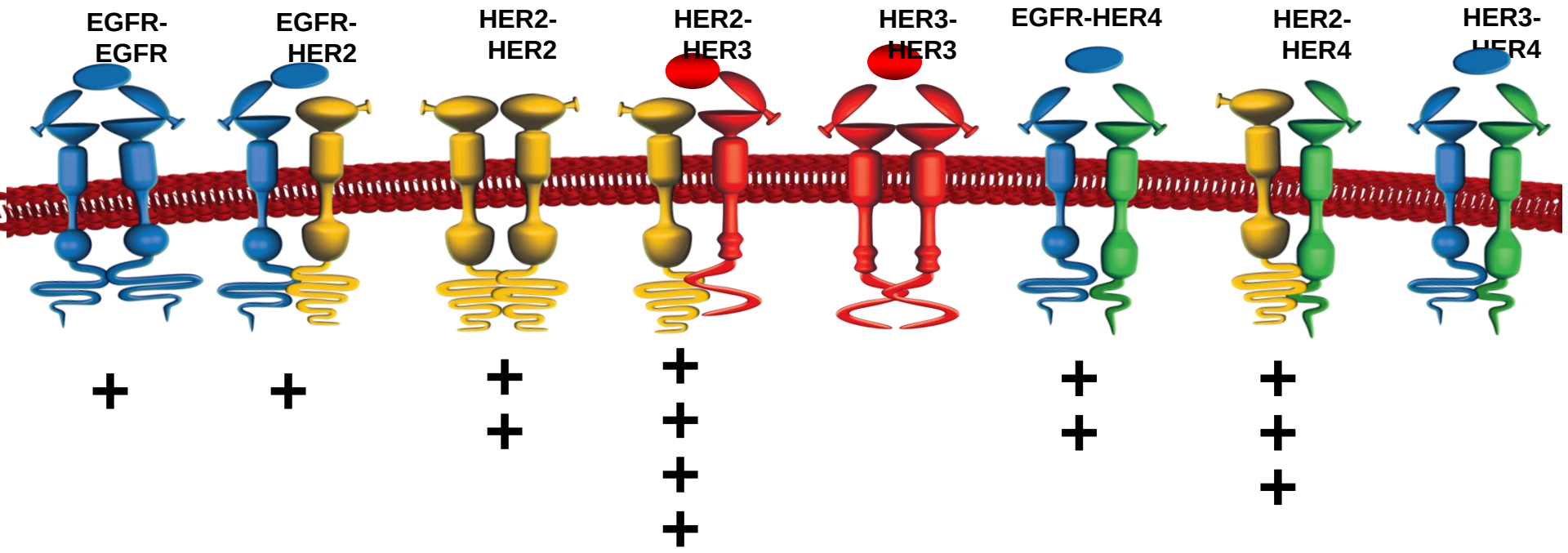
Verona, 18 settembre 2015

The HER Family

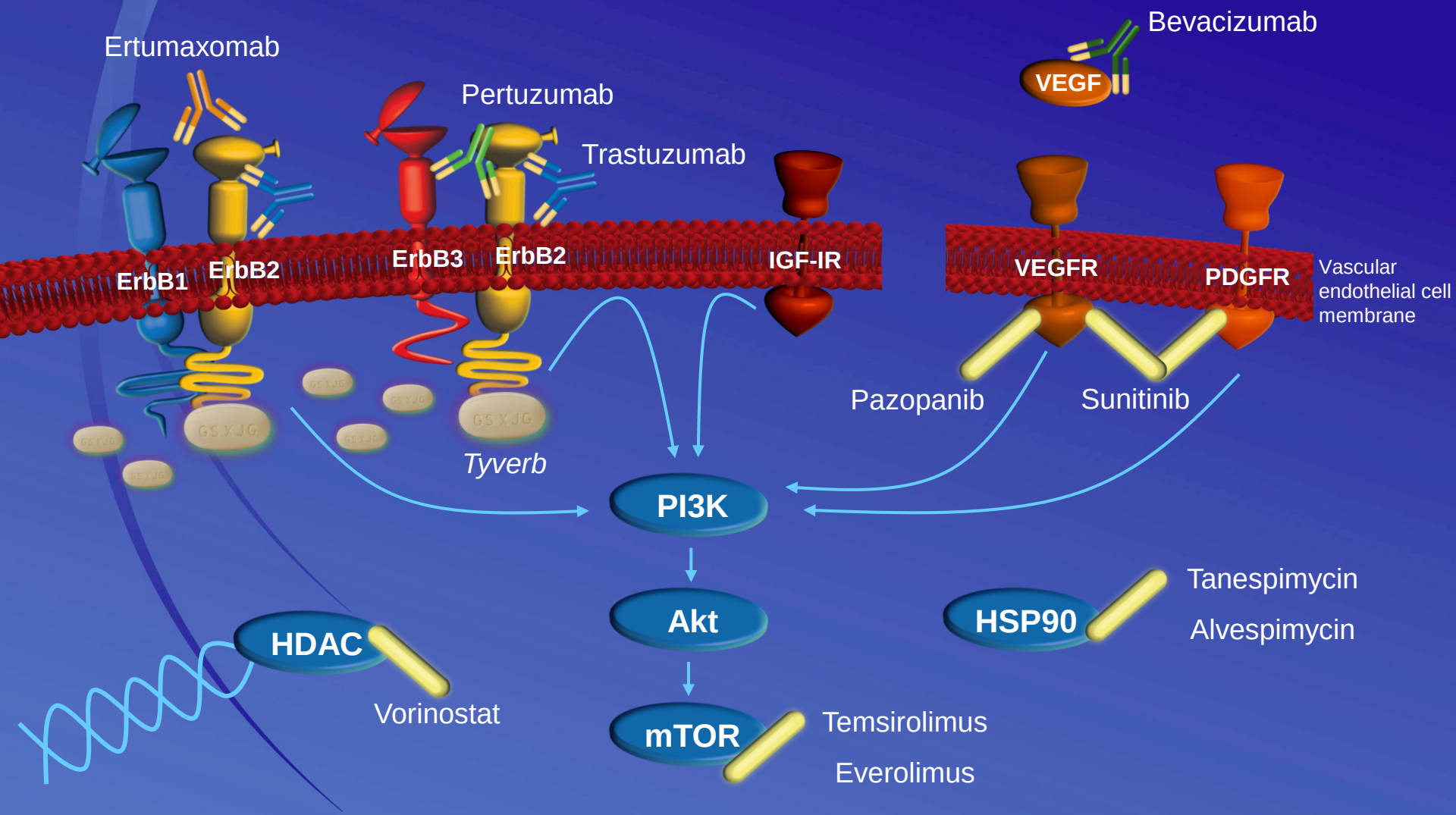


Potenza di segnale di diversi dimeri HER



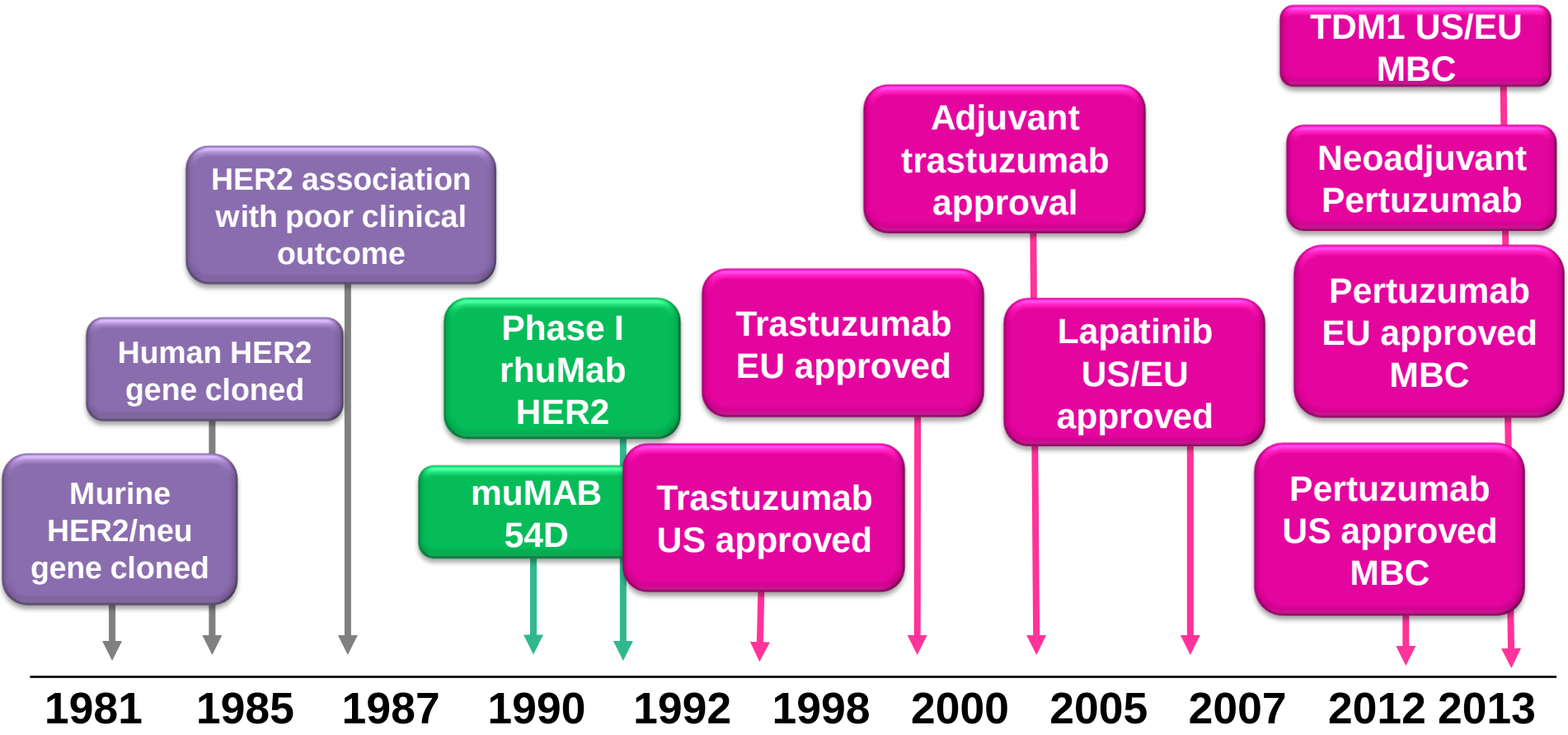
Modificata da Tortora 2009

Targets and bullets in breast cancer

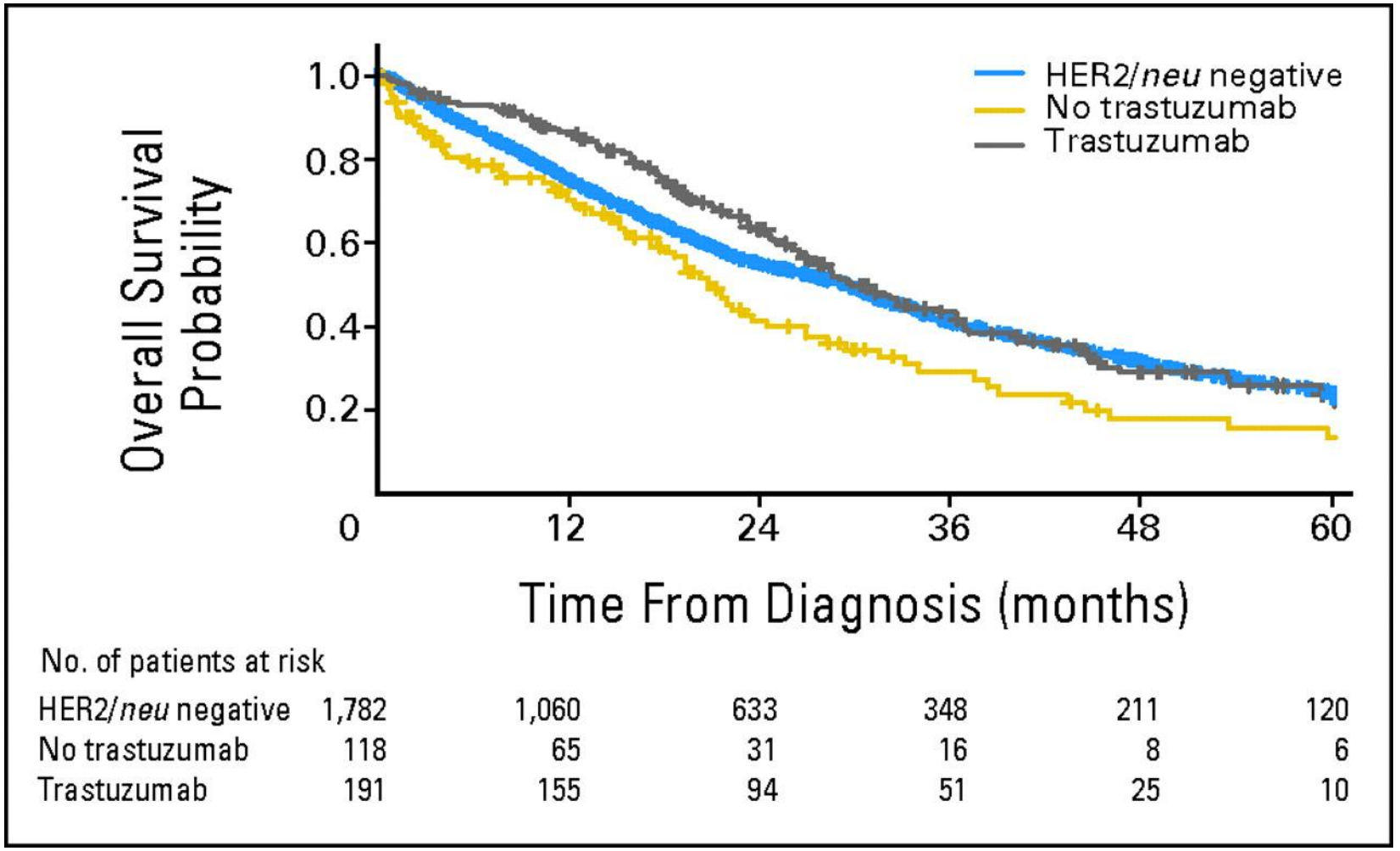


HDAC=histone deacetylase

Milestones in the treatment of HER2+ BC



Overall survival by trastuzumab treatment group.



No. of patients at risk

HER2/*neu* negative	1,782	1,060	633	348	211	120
No trastuzumab	118	65	31	16	8	6
Trastuzumab	191	155	94	51	25	10

Dawood S et al. JCO 2010;28:92-98

JOURNAL OF CLINICAL ONCOLOGY

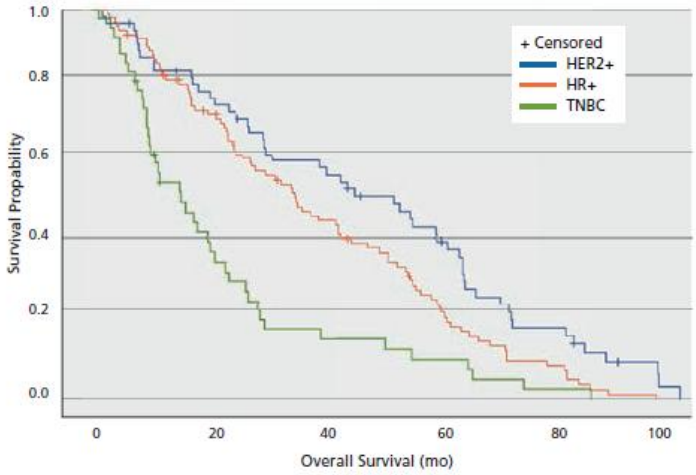
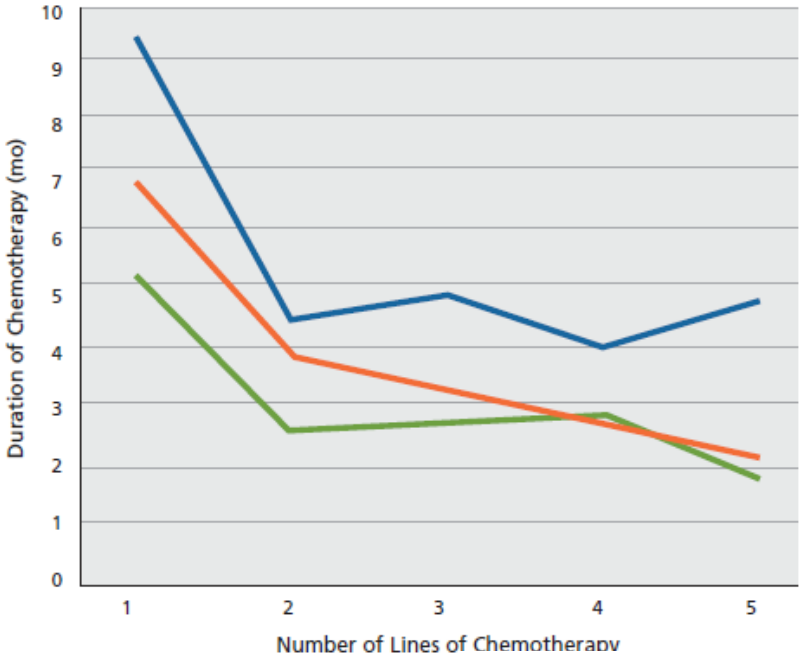


Figure 4 Kaplan-Meier curves for overall survival by subtype from the date of metastatic breast cancer diagnosis.
Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.



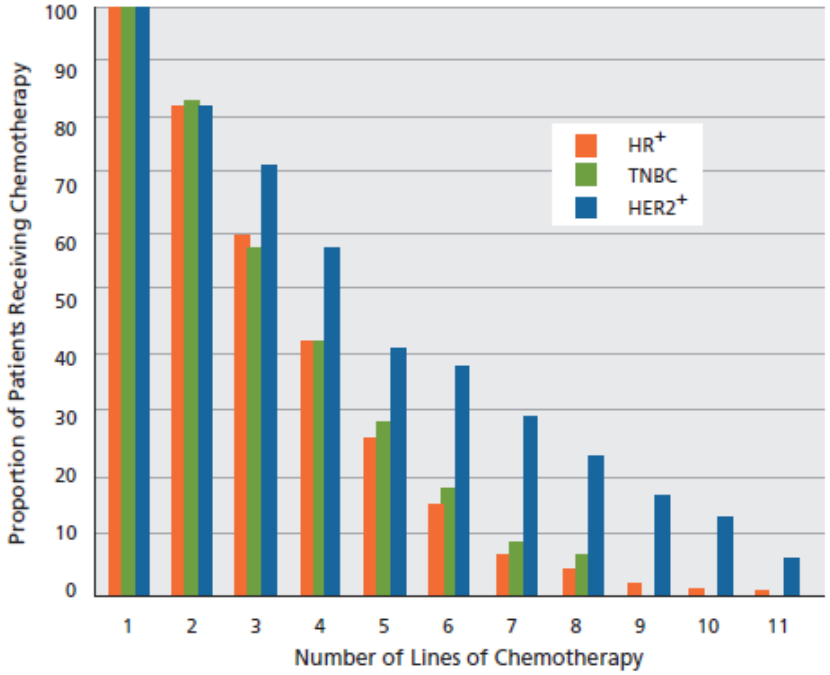
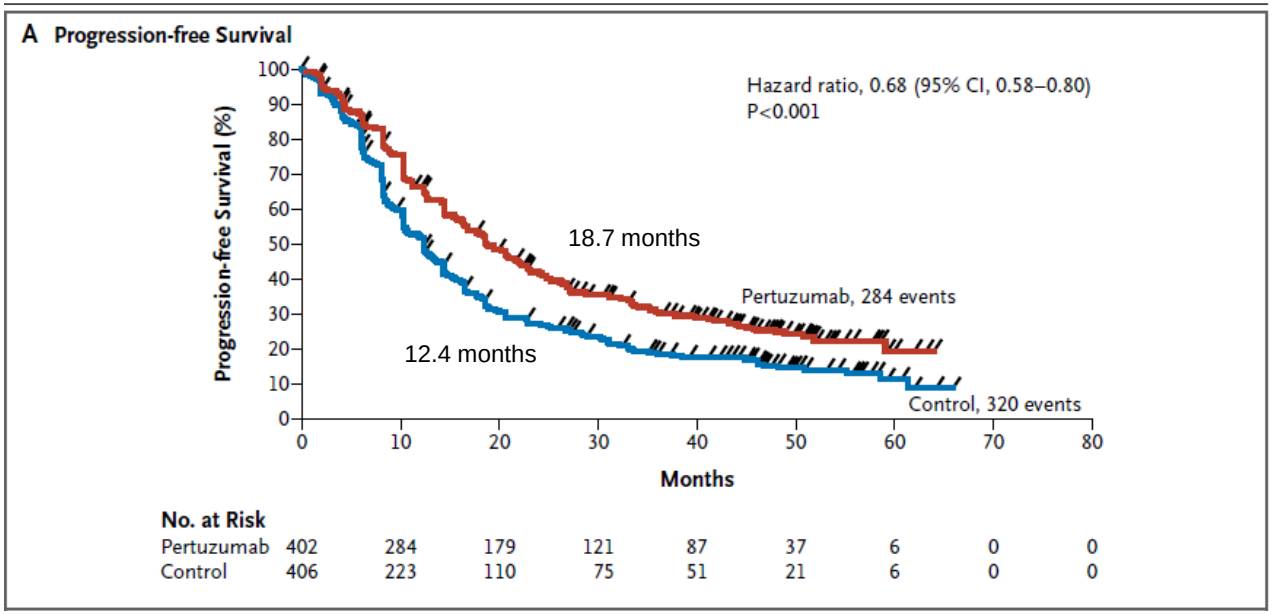


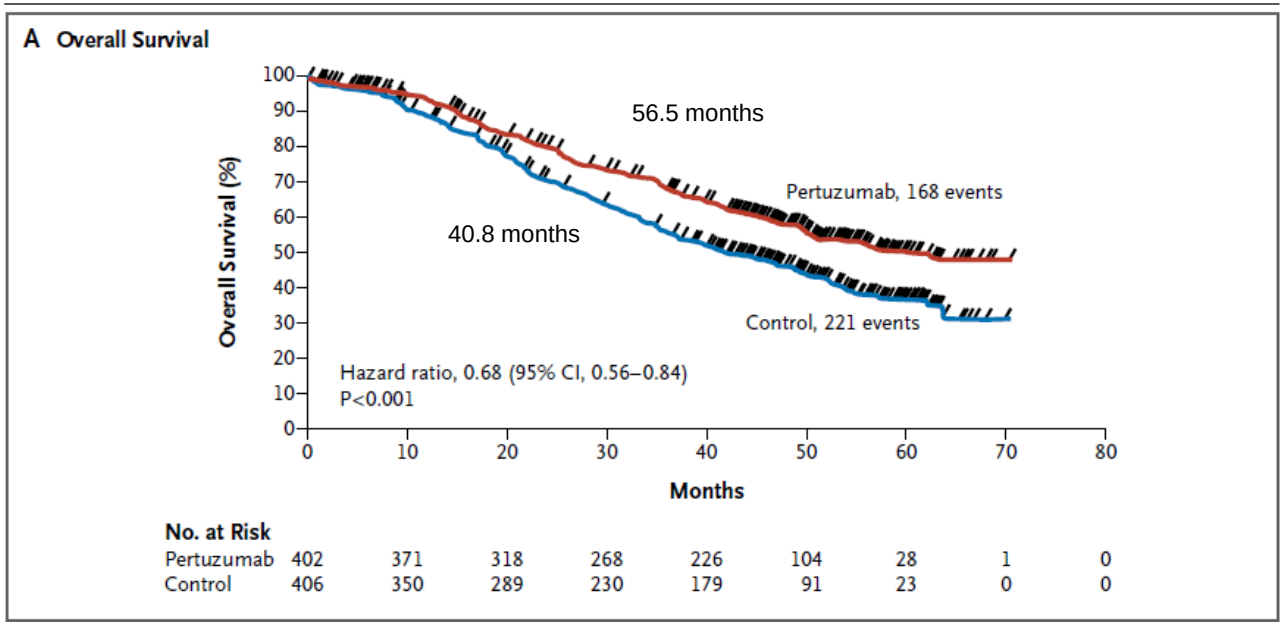
Figure 2 Number of lines of chemotherapy by line and subtype.
Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.

ORIGINAL ARTICLE

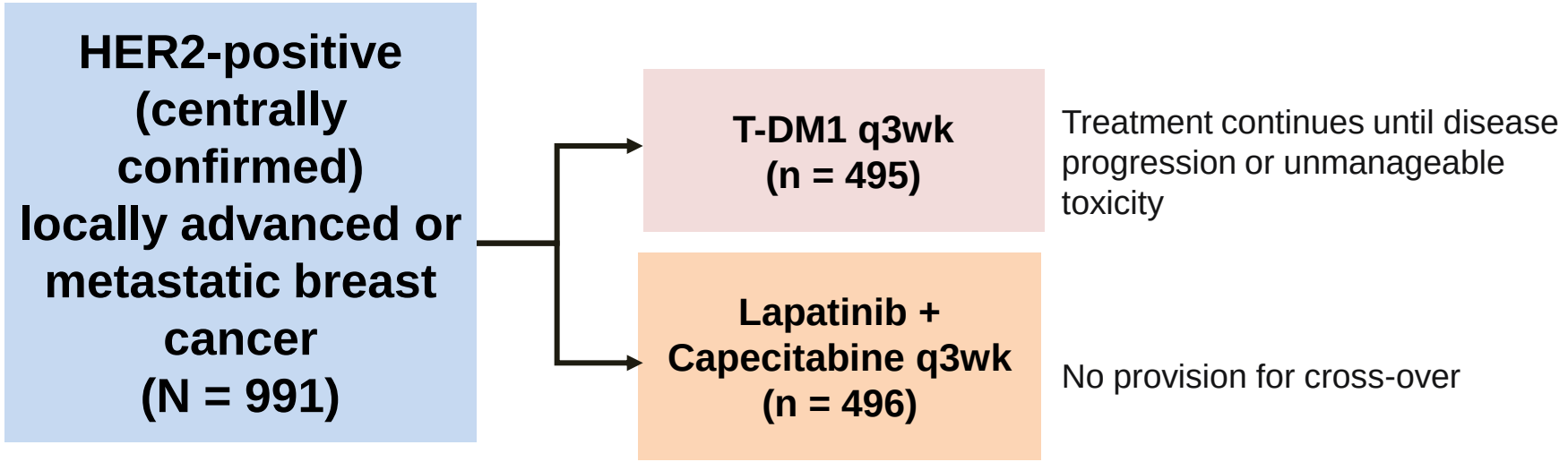
N Engl J Med 2015;372:724-34.

Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer





EMILIA Study Design



- Primary endpoints: PFS by IRF, OS, safety
- Secondary endpoints: OS, QOL: FACT-B

Key inclusion criteria

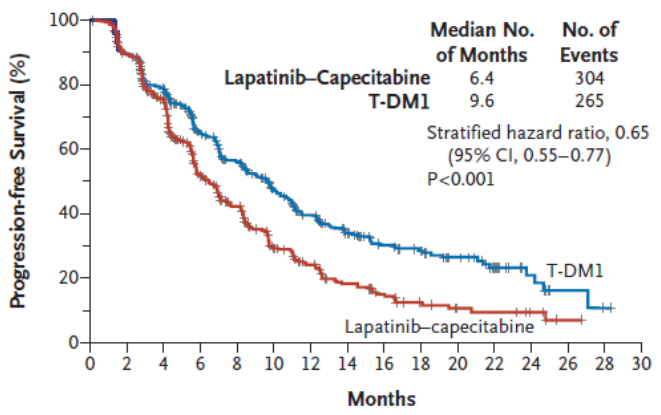
- Previous treatment to include a taxane and trastuzumab in adjuvant, locally advanced or metastatic setting
- Documented progression of disease during or after treatment for advanced/metastatic disease, or within 6 mos of completing adjuvant therapy

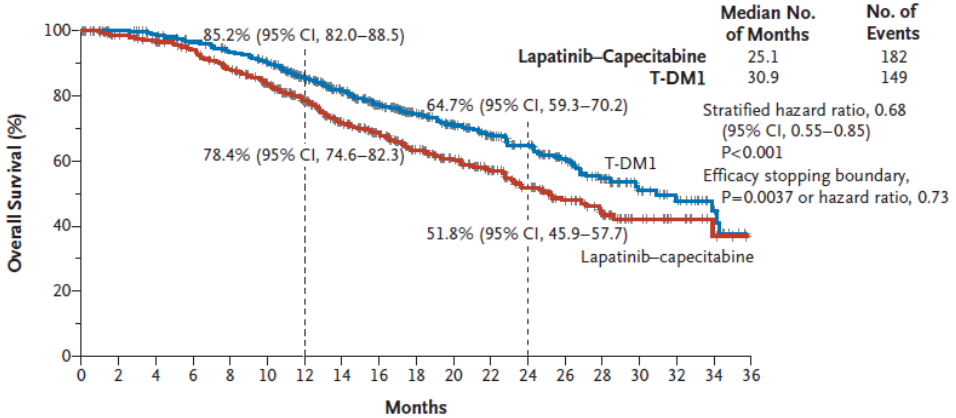
Verma S, et al. N Engl J Med. 2012;367:1783-1791.

The NEW ENGLAND JOURNAL of MEDICINE

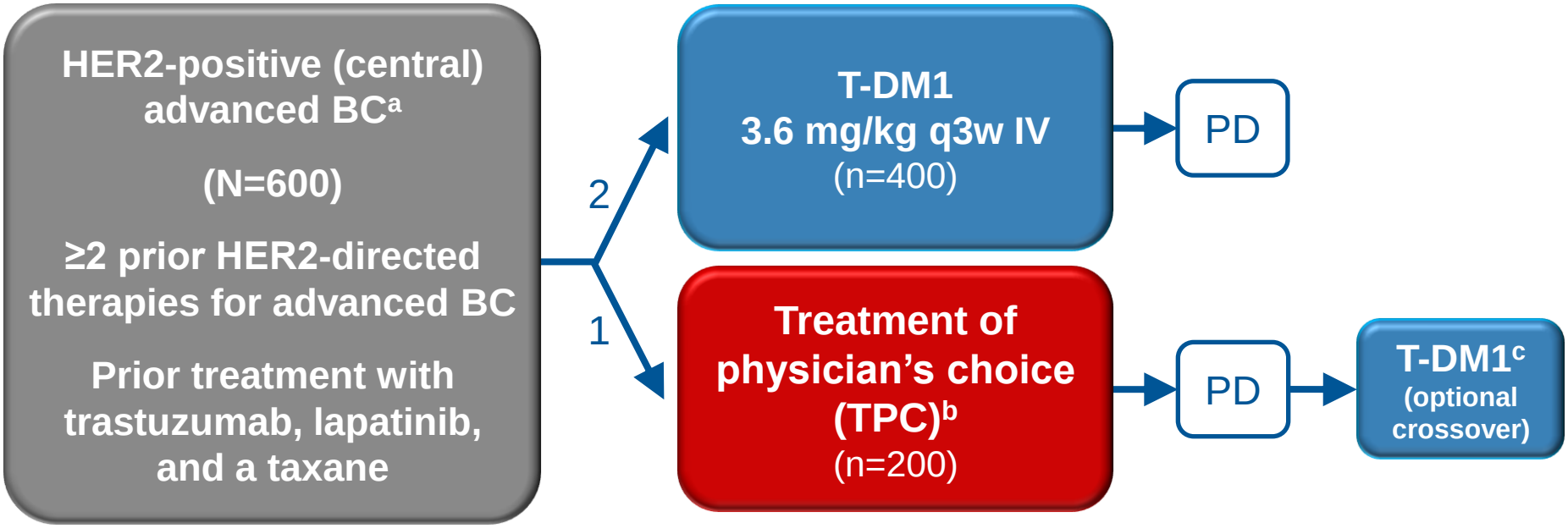
ESTABLISHED IN 1812 NOVEMBER 8, 2012 VOL. 367 NO. 19

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer





TH3RESA Study Schema



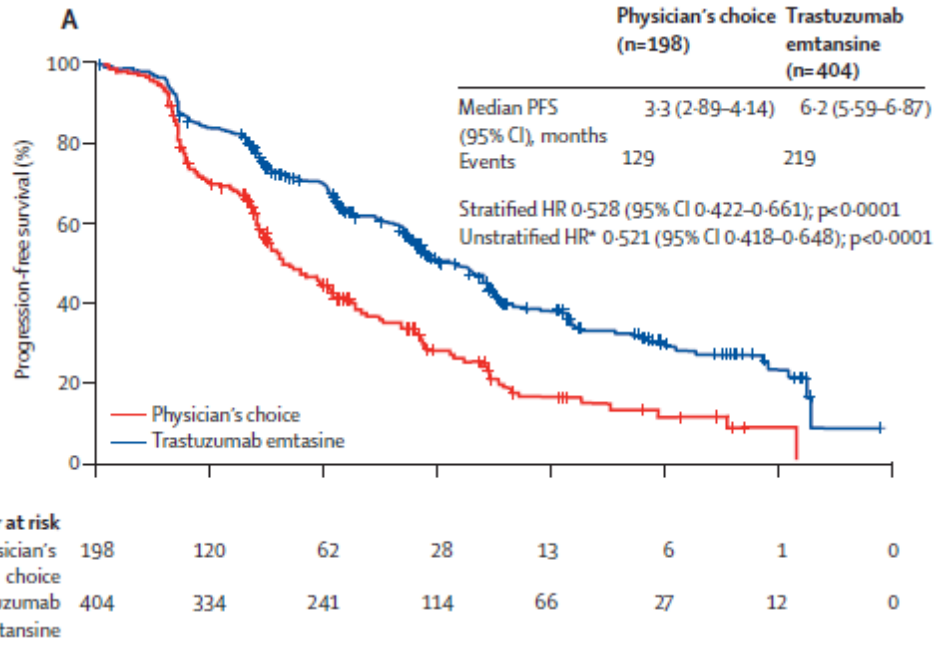
- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

[a] Advanced BC includes MBC and unresectable locally advanced/recurrent BC.
[b] TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
[c] First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.
[d] Excluding single-agent hormonal therapy.
BC, breast cancer; IV, intravenous; ORR, objective response rate; PD, progressive disease; q3w, every 3 weeks.

Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial

*Ian E Krop, Sung-Bae Kim, Antonio González-Martín, Patricia M LoRusso, Jean-Marc Ferrero, Melanie Smitt, Ron Yu, Abraham C F Leung, Hans Wildiers, on behalf of the TH3RESA study collaborators**

Lancet Oncol 2014



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
(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m² q3w) **OR**
Trastuzumab + paclitaxel
(4 mg/kg LD then 2 mg/kg + 80 mg/m² qw)

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

T-DM1 + pertuzumab
(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

LD, Loading dose. [a]Locally progressive or recurrent and not amenable to resection with curative intent; [b]Pertuzumab placebo.

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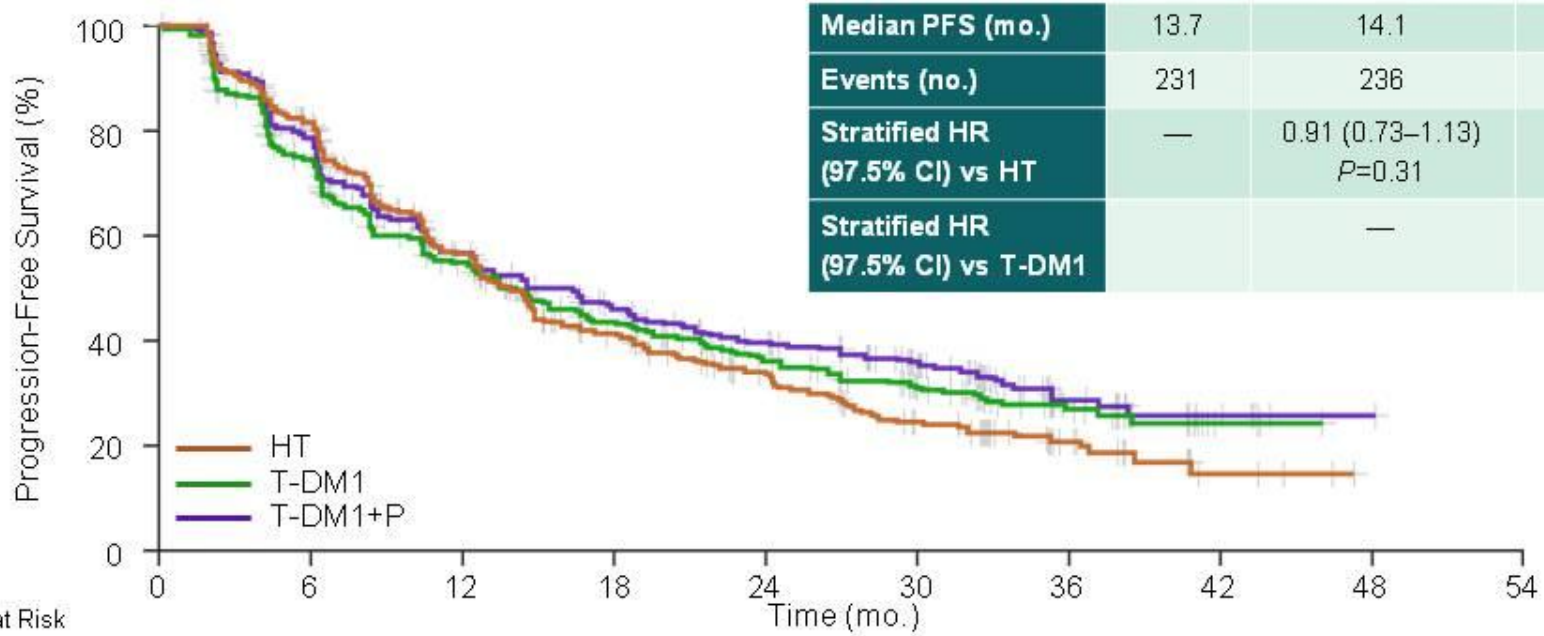
Progression-Free Survival by IRF

	HT	T-DM1	T-DM1+P
Median PFS (mo.)	13.7	14.1	15.2
Events (no.)	231	236	217
Stratified HR (97.5% CI) vs HT	—	0.91 (0.73–1.13) *P*=0.31	0.87 (0.69–1.08) *P*=0.14
Stratified HR (97.5% CI) vs T-DM1		—	0.91 (0.73–1.13)



No. at Risk

HT	365	265	163	107	75	50	21	5	
T-DM1	367	257	176	133	104	67	28	3	
T-DM1+P	363	261	177	135	109	75	25	5	1

Non-inferiority: Established if the upper limit of the 97.5% CI for the HR is below 1.1765 (non-inferiority margin).

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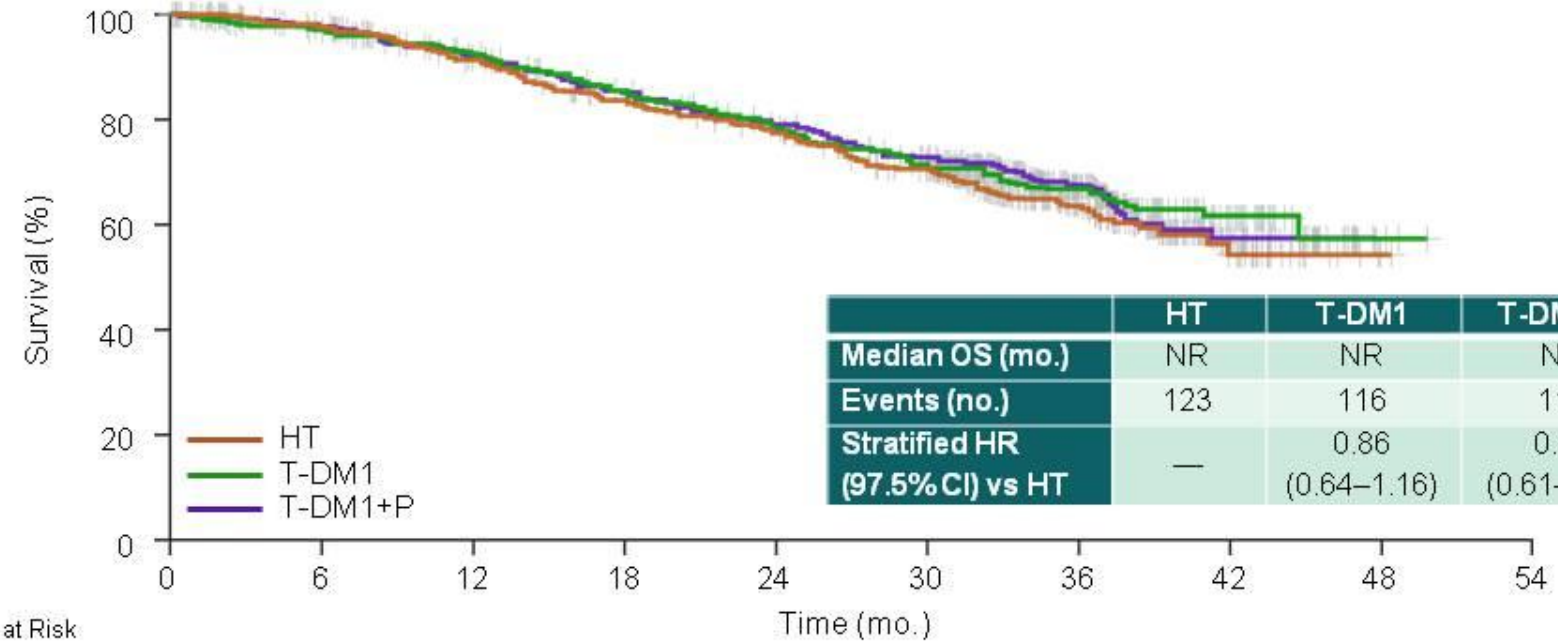
Overall Survival (First Interim Analysis)



	HT	T-DM1	T-DM1+P
Median OS (mo.)	NR	NR	NR
Events (no.)	123	116	115
Stratified HR (97.5% CI) vs HT	—	0.86 (0.64–1.16)	0.82 (0.61–1.11)

No. at Risk									
HT	365	335	303	273	250	218	98	25	1
T-DM1	367	345	321	291	263	224	104	37	3
T-DM1+P	363	341	309	282	257	231	106	28	1

NR, not reached.

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Conclusions

- T-DM1 and T-DM1+P demonstrated non-inferior PFS compared with HT, but were not superior to HT
- The addition of P to T-DM1 did not improve PFS
- T-DM1 was better tolerated than HT
  - Fewer grade ≥3 AEs and less treatment discontinuations due to AEs observed with T-DM1 vs HT
  - No febrile neutropenia; less neuropathy, diarrhoea and alopecia seen with T-DM1
  - More transaminase elevation and thrombocytopenia observed with T-DM1
- Health-related quality of life maintained for a longer duration with T-DM1
- T-DM1 is an alternative treatment option to HT in previously untreated HER2-positive MBC

Lessons from Neoadjuvant Trials -1

Chemotherapy	CT Regimen	CT duration	pCR ypT0/is ypN0	Ref
Anthra/Taxane; 24 weeks	EC → Docetaxel	24	44.6	Untch, Lancet Oncol 2012
	EC → Docetaxel	24	48.0	Alba, GEICAM
	FEC → wPaclitaxel	24	56.5*	Buzdar, Lancet Oncol 2013
	wPaclitaxel → FEC	24	54.2*	Buzdar, Lancet Oncol 2013
	FEC → w P	24	54.0	Holmes, BMC 2013
	AP → Paclitaxel → CMF	30	38.0	Gianni, Lancet 2010
	wP → FEC	24	25.0	Guarneri, JCO 2012
Taxane; 12 weeks	Docetaxel	12	21.5	Gianni, Lancet Oncol 2012
	w Paclitaxel	12	27.6	Baselga, Lancet 2012

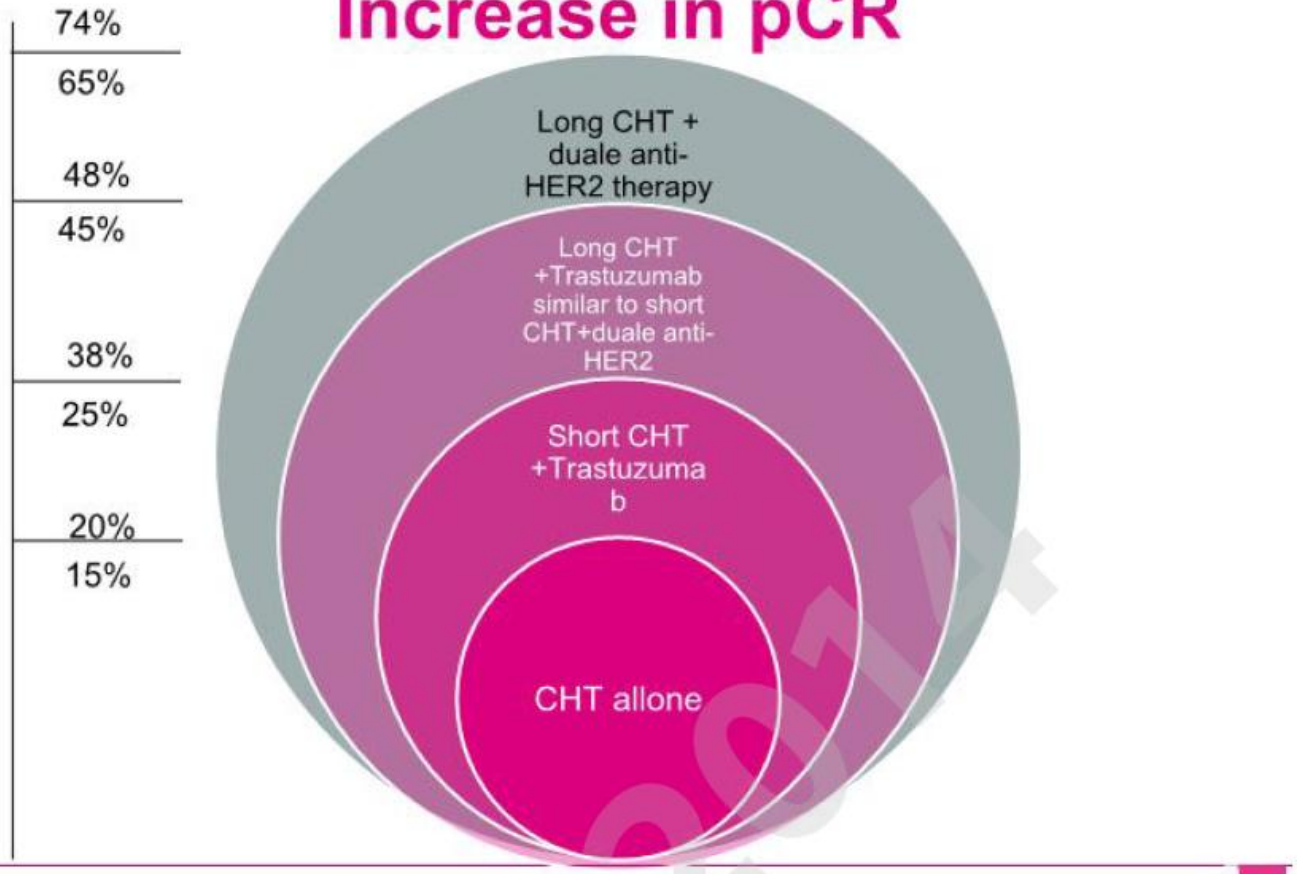
* ypT0 y pN0

Lessons From Neoadjuvant Trials -2

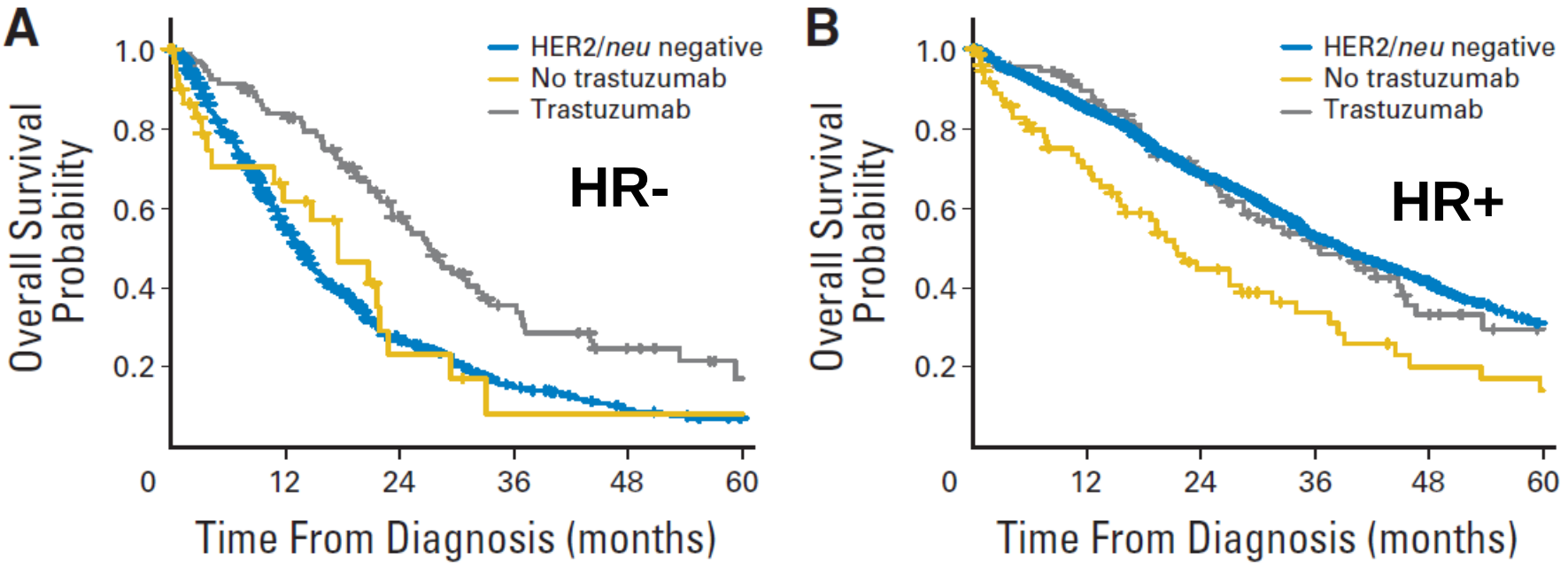
Trial	CT	weeks	Anti HER2	ypT0/is (%)	Ref
NEOSPHERE	Docetaxel	12	H	29.0	Gianni, Lancet Onc 2012
	Docetaxel	12	P	24.0	
	Docetaxel	12	HP	45.8	
	no	12	HP	16.8	
TRYPHAENA	FEC→ Doc	18	HP	61.6	Scheneeweiss, Ann Oncol 2013
	FEC→ Doc	18	HP*	57.3	
	Carbo-Doc	18	HP	66.2	

(*) HP started after FEC

Increase in pCR



Overall survival stratified by trastuzumab treatment group and according to HR status



Dawood S, et al. J Clin Oncol 2010;28:92-8.

Anti-HER2 Tx w/o chemoTx

TH (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)

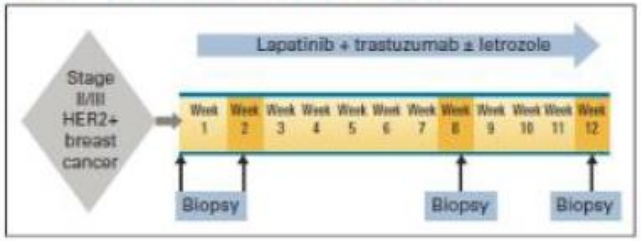
THP (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

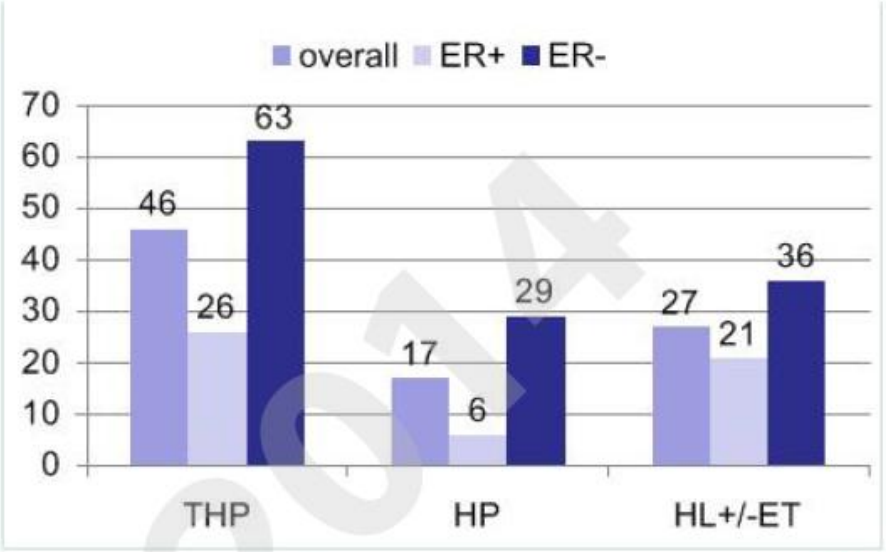
HP (n=107)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

TP (n=96)
docetaxel (75→100 mg/m²)
pertuzumab (840→420 mg)

SURGERY

Study dosing: q3w x 4





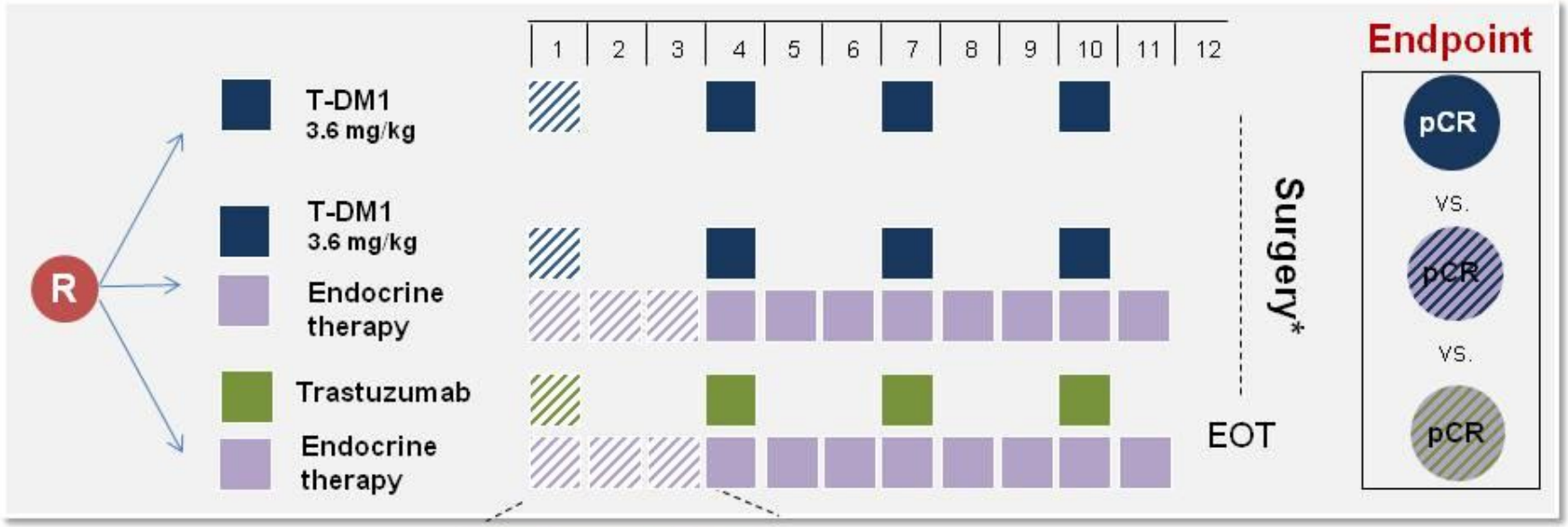
Gianni L, et al. Lancet Oncol 2012;
Rimawi M et al. J Clin Oncol 2013

ADAPT HER2+/HR+: Rationale

- In HER2+ early breast cancer, current standard (chemo- + anti-HER2 therapy) is independent of hormone receptor (HR) status
- HER2+/HR+ (*triple positive*) breast cancer is a distinct entity
- pCR after neoadjuvant chemo- + anti-HER2 therapy:
  - rates differ according to HR-status
  - impact on survival differs according to HR-status
- Combined targeted blockade (endocrine + anti-HER2 therapy) without systemic chemotherapy may be an effective neoadjuvant strategy

Cortazar et al, Lancet 2014; Rimawi et al, JCO 2013

ADAPT HER2+/HR+: Trial Design



*Standard chemotherapy recommended after surgery; trastuzumab to be completed, for total of one year.

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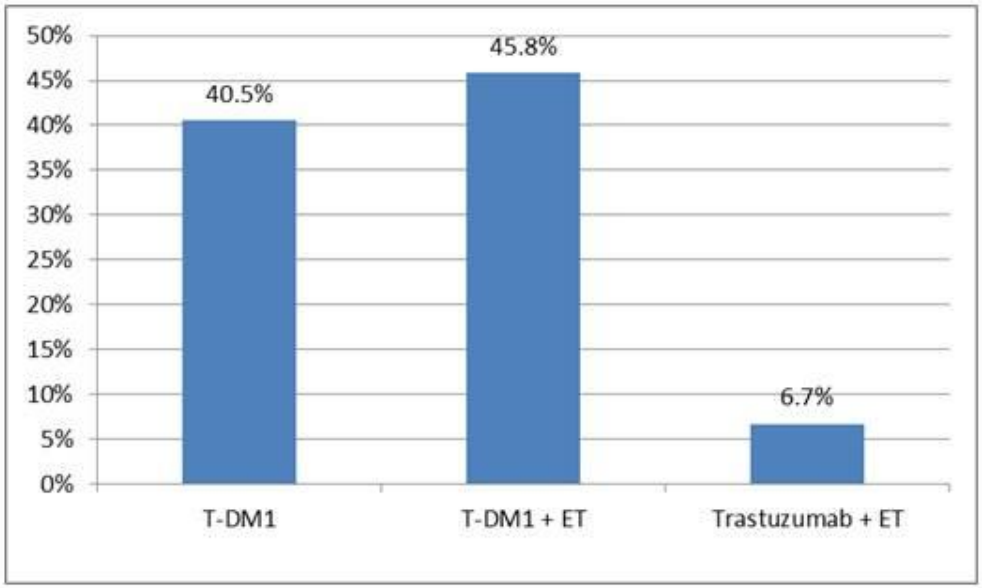
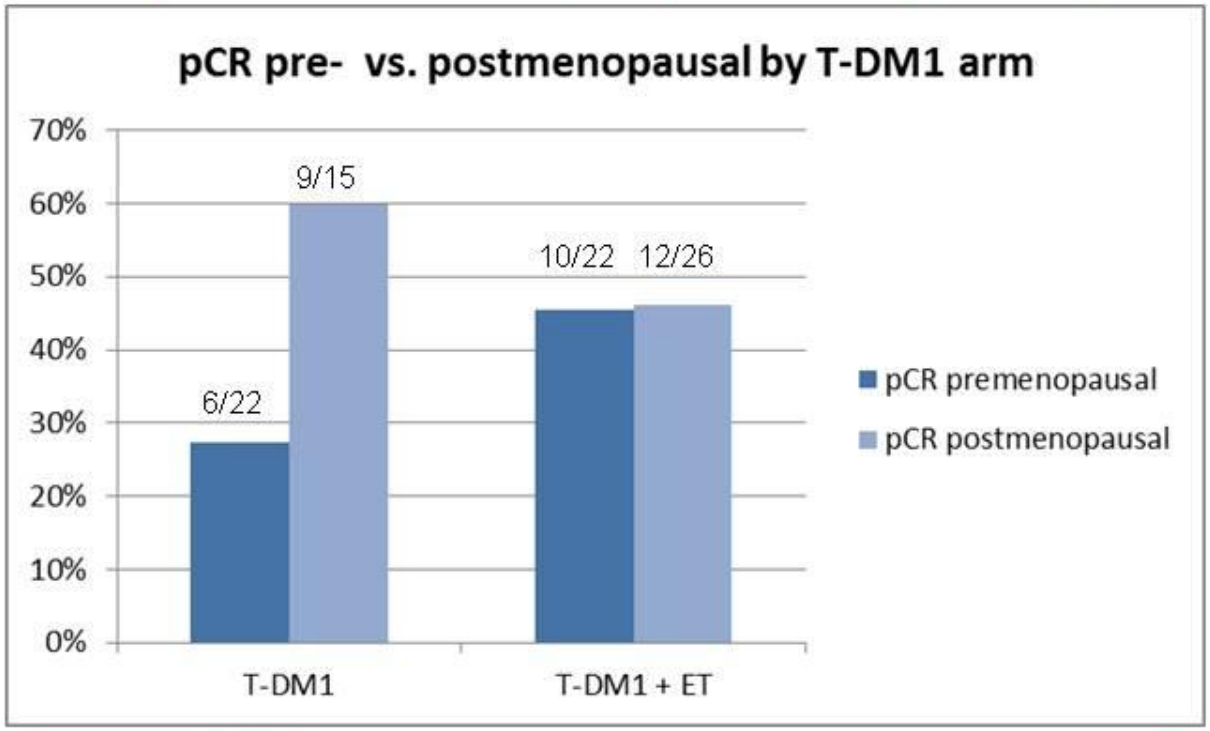
ADAPT HER2+/HR+: pCR
(no invasive tumor in breast and nodes)



- pCR rates substantially higher in T-DM1 containing arms (p<0.001 A or B vs. C)

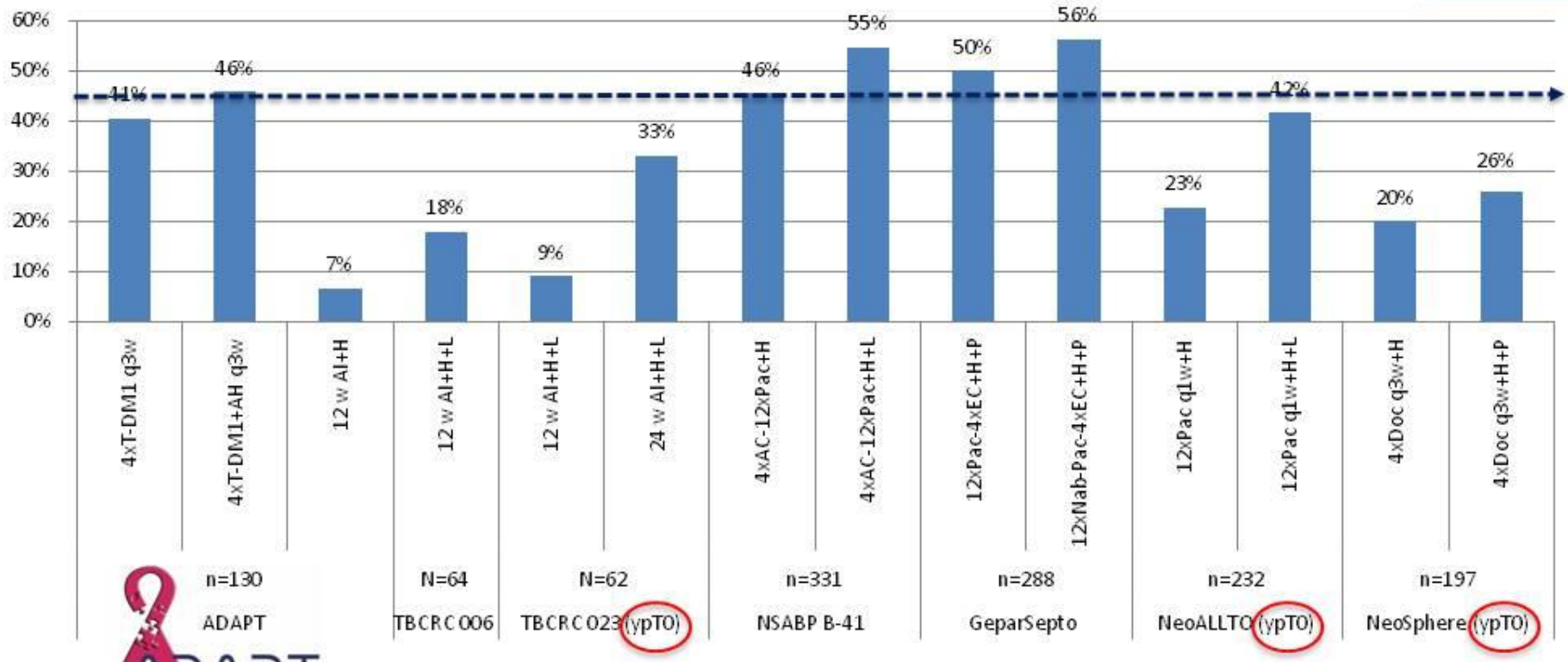
ADAPT HER2+/HR+: Efficacy of adding endocrine therapy to T-DM1 differs by menopausal status (exploratory analysis)



Presented By Nadia Harbeck at 2015 ASCO Annual Meeting

pCR rates in HER+/HR+ early breast cancer

WSG
WOMEN'S HEALTHCARE STUDY GROUP



ADAPT

Rimawi et al, 2013; Rimawi et al, 2014; Robidoux et al, 2013; Untch et al, 2014; Baselga et al, 2012; Gianni et al, 2012.

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ADAPT HER2+/HR+: Conclusions from pre-planned interim analysis

- **More than 40% pCR (breast and nodes) in T-DM1 treated patients** after 12 weeks without *systemic* chemotherapy:
  - 40.5% T-DM1; 45.8% T-DM1 + ET; 6.7% trastuzumab + ET
- **Very low overall toxicity**; no new safety signals detected
- Adding endocrine therapy to T-DM1 increases pCR in pre- but not in postmenopausal patients (exploratory analysis)
- Early response biomarkers:
  - No trend for Ki-67 (3-week vs. baseline) as predictor of pCR
  - Early therapy effect impacted Ki-67 quantification in 3-week biopsy (low cellularity in 43.1%) and was associated with pCR

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HER2+ HR+ early breast cancer: Future perspectives

- Therapy de-escalation is possible
- TDM-1 single agent warrants further evaluation
- Full data set needed to substantiate interim findings:
  - Confirm efficacy and impact of additional endocrine therapy
  - Assess early-response biomarkers, mutation analysis, and subtypes
- Comparison T-DM1 single agent vs. standard chemotherapy + dual blockade (trastuzumab + pertuzumab) needed

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Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review

Results: A total of 38 articles were included in the review. Hair loss consistently ranked amongst the most troublesome side effects, was described as distressing, and may affect the body image.

Psycho-Oncology **17**: 317–328 (2008)

Phase II Randomized Study of Trastuzumab Emtansine Versus Trastuzumab Plus Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer

Table 2. Adverse Events of Any Grade Occurring in ≥ 25% and/or Grade ≥ 3 Occurring in ≥ 5% of Patients in Either Treatment Group

	All Grade				Grade ≥ 3*			
	HT (n = 66)†		T-DM1 (n = 69)†‡		HT (n = 66)†		T-DM1 (n = 69)†‡	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Hematologic								
Neutropenia§	**43**	**65.2**	**11**	**15.9**	**41**	**62.1**	**4**	**5.8**
Thrombocytopenia§	**4**	**6.1**	**19**	**27.5**	2¶	3.0	5¶	7.2
Leukopenia§	17	25.8	7	10.1	**16**	**24.2**	**0**	
Febrile neutropenia	9	13.6	0		9	13.6	0	
Anemia	18	27.3	9	13.0	3	4.5	2	2.9
Nonhematologic								
Alopecia	**44**	**66.7**	**3**	**4.3**	—‖		—‖	
Fatigue	30	45.5	34	49.3	3	4.5	3	4.3
Nausea	29	43.9	34	49.3	0		2	2.9
Diarrhea	**30**	**45.5**	**11**	**15.9**	2	3.0	0	
Peripheral edema	**29**	**43.9**	**7**	**10.1**	4	6.1	0	
Increased AST	**4**	**6.1**	**30**	**43.5**	0		6	8.7
Pyrexia	15	22.7	28	40.6	1	1.5	0	
Headache	**12**	**18.2**	**28**	**40.6**	0		0	
Back pain	21	31.8	19	27.5	3	4.5	1	1.4
Epistaxis	6	9.1	19	27.5	0		0	
Dyspnea	18	27.3	10	14.5	2	3.0	0	
Arthralgia	20	30.3	16	23.2	1	1.5	0	
Cough	14	21.2	18	26.1	0		0	
Vomiting	17	25.8	17	24.6	0		2	2.9
Increased ALT	4	6.1	18	26.1	0		7	10.1
Pneumonia	1	1.5	6	8.7	0		4	5.8

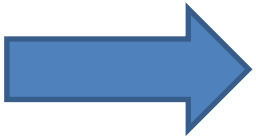
J Clin Oncol 31:1157-1163. © 2013

STUDIO NA-PHER2/FM-14-B01

«Trattamento **neoadiuvante** con l'inibitore CDK4,6 Palbociclib nel carcinoma mammario HER2-positivo e RE positivo: effetto su Ki67 e apoptosi prima, durante e dopo il trattamento»

- Carcinoma mammario operabile (>1.5 cm) o LABC
- Non metastatico
- Non pretrattato
- Unilaterale
- HER2 pos e ER pos

32 pz previste



HPPF

Trastuzumab (8/6 mg/kg q21 x 6 cicli)

Pertuzumab (840/420 mg q21 x 6 cicli)

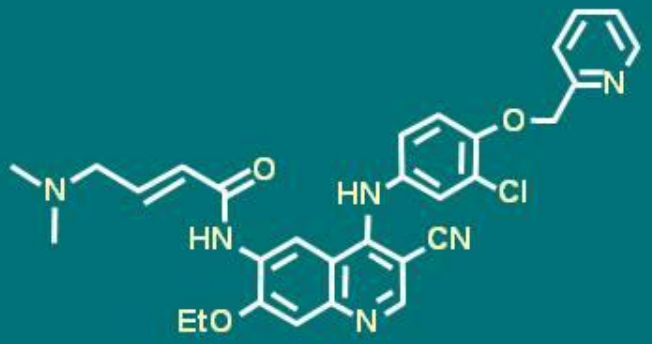
Palbociclib (125 mg os/die x 3/4 sett x 5 cicli)

Fulvestrant (500 mg i.m. 1,14→q 28 x 6 somm)

Obiettivi primari:

- caratterizzare i cambiamenti di Ki67 dal basale, a dopo 2 settimane e all'intervento chirurgico (22 sett dall'inizio di HPPF)
- caratterizzare i cambiamenti sui meccanismi di apoptosi dal basale, a dopo 2 settimane e all'intervento chirurgico (22 sett dall'inizio di HPPF)
- Profilo di tollerabilità

Neratinib



- Oral tyrosine kinase inhibitor of HER1, 2, 4
- In vivo data[1]:
  - ↓ HER2 receptor autophosphorylation
  - Inhibits cell proliferation & irreversible binding of cysteine residue in ATP-binding pocket
- BT474 cells: inhibition of MAPK, Akt phosphorylation, ↓ Cyclin D1, p27 induction
- Xenografts: rapid (<28 days) dose-dependent & sustained tumor growth regression
- Phase 2 trial[2] (n=136) trastuzumab-pretreated cohort (66) – naïve (70)
  - ORR: 24% & 56% respectively
  - 16-week PFS: 59% & 78% respectively

[1]Rabindran S et al Cancer Res 2004
[2]Burstein H et al J Clin Oncol 2010

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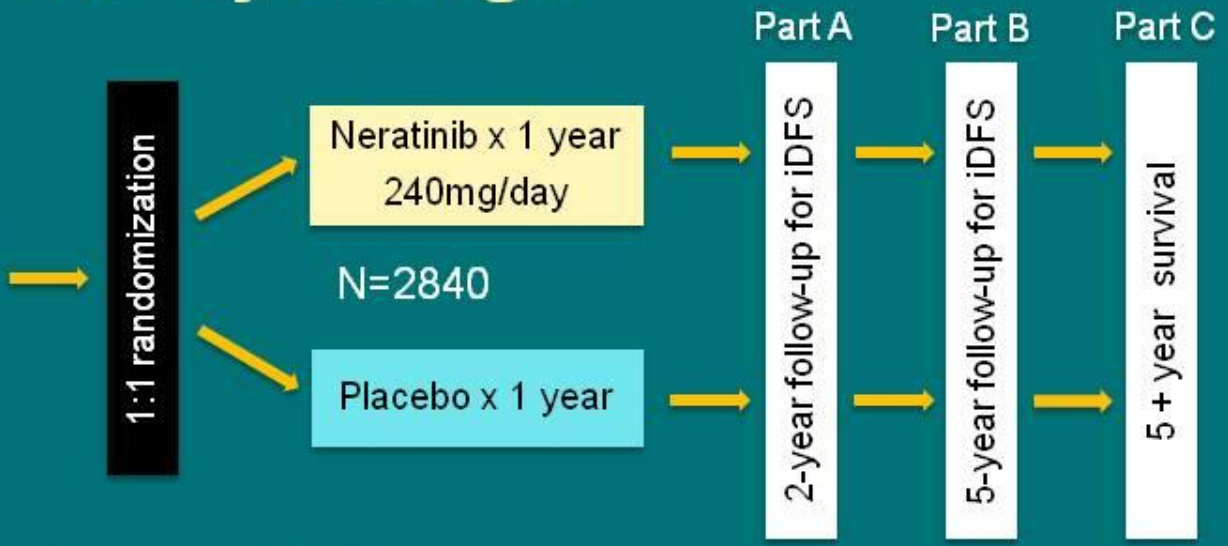
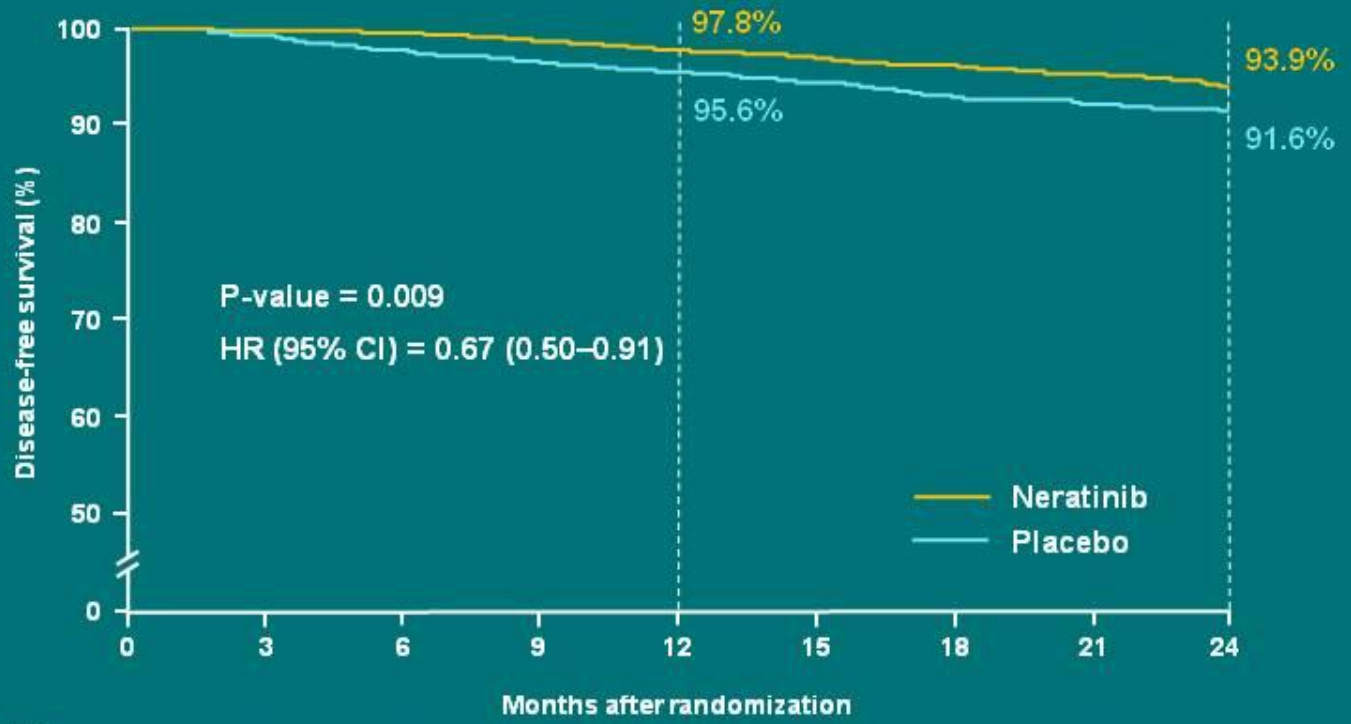
Study Design

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab & chemotherapy
- Lymph node –/+ or residual invasive disease after neoadjuvant therapy
- ER/PR + or –



- Primary endpoint: invasive disease-free survival (iDFS)
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- Other analyses: biomarkers, health outcome assessment (FACT-B, EQ-5d)
- Stratified by: nodes 0, 1–3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Primary Endpoint: Invasive DFS (ITT)



No. at risk									
Neratinib	1420	1291	1260	1229	1189	1150	1108	1033	662
Placebo	1420	1367	1324	1292	1243	1209	1163	1090	704

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Presented By Arlene Chan at 2015 ASCO Annual Meeting

Safety (Adverse Events ≥10%)

n (%)	Neratinib (n=1408)		Placebo (n=1408)	
	All grades	Grade 3–4	All grades	Grade 3–4
Diarrhea	1343 (95.4)	562 (39.9)	499 (35.4)	23 (1.6)
Nausea	605 (43.0)	26 (1.8)	303 (21.5)	2 (0.1)
Fatigue	382 (27.1)	23 (1.6)	283 (20.1)	6 (0.4)
Vomiting	369 (26.2)	47 (3.3)	113 (8.0)	5 (0.4)
Abdominal pain, general	340 (24.1)	24 (1.7)	144 (10.2)	3 (0.2)
Headache	278 (19.7)	8 (0.6)	275 (19.5)	6 (0.4)
Abdominal pain, upper	212 (15.1)	11 (0.8)	96 (6.8)	3 (0.2)
Rash	211 (15.0)	5 (0.4)	100 (7.1)	0
Decreased appetite	170 (12.1)	3 (0.2)	40 (2.8)	0
Muscle spasms	159 (11.3)	1 (0.1)	45 (3.2)	1 (0.1)
Dizziness	146 (10.4)	3 (0.2)	128 (9.1)	3 (0.2)
Arthralgia	86 (6.1)	2 (0.1)	162 (11.5)	4 (0.3)

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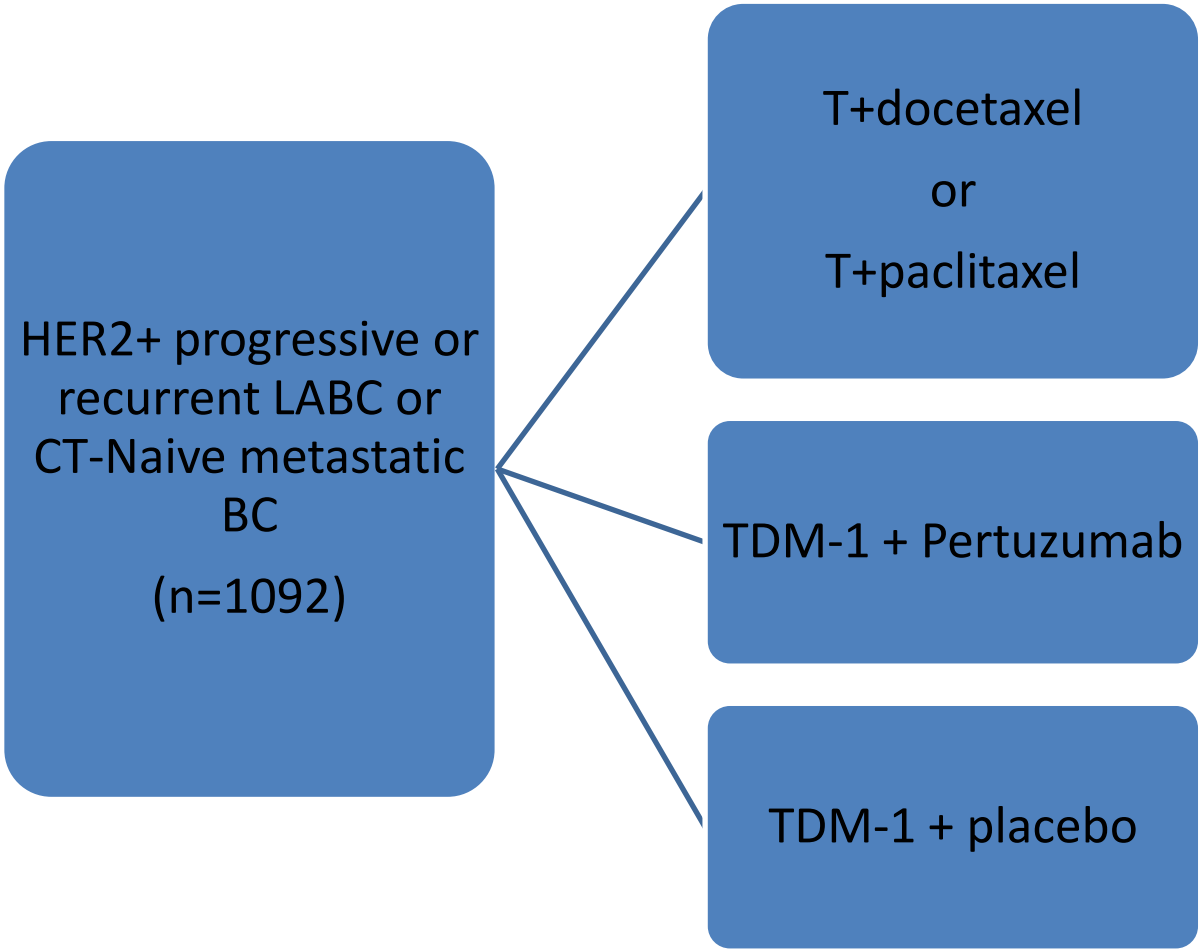
backup

Phase III Marianne study



- Study met non-inferiority endpoint, showing similar PFS among the three arms
- Study did not meet PFS superiority for TDM-1 containing regimens

Treatment Approach For Patient Presenting With HER2+ MBC in 2013

First Line: Taxane + Trastuzumab + Pertuzumab

Second Line: TDM-1

<u>Third, Fourth, Fifth, Sixth Line:</u>

Capecitabine + Lapatinib

Capecitabine + Trastuzumab

Vinorelbine + Trastuzumab

Lapatinib + Trastuzumab

Pertuzumab + Trastuzumab (?? if no prior Pertuzumab)

Other chemotherapy + Trastuzmab

Endocrine Therapy + Trastuzumab

Presented By Eric P. Winer, MD at 2013 Breast Cancer Symposium

Optimizing the use of new HER2 targeted agents in advanced disease:

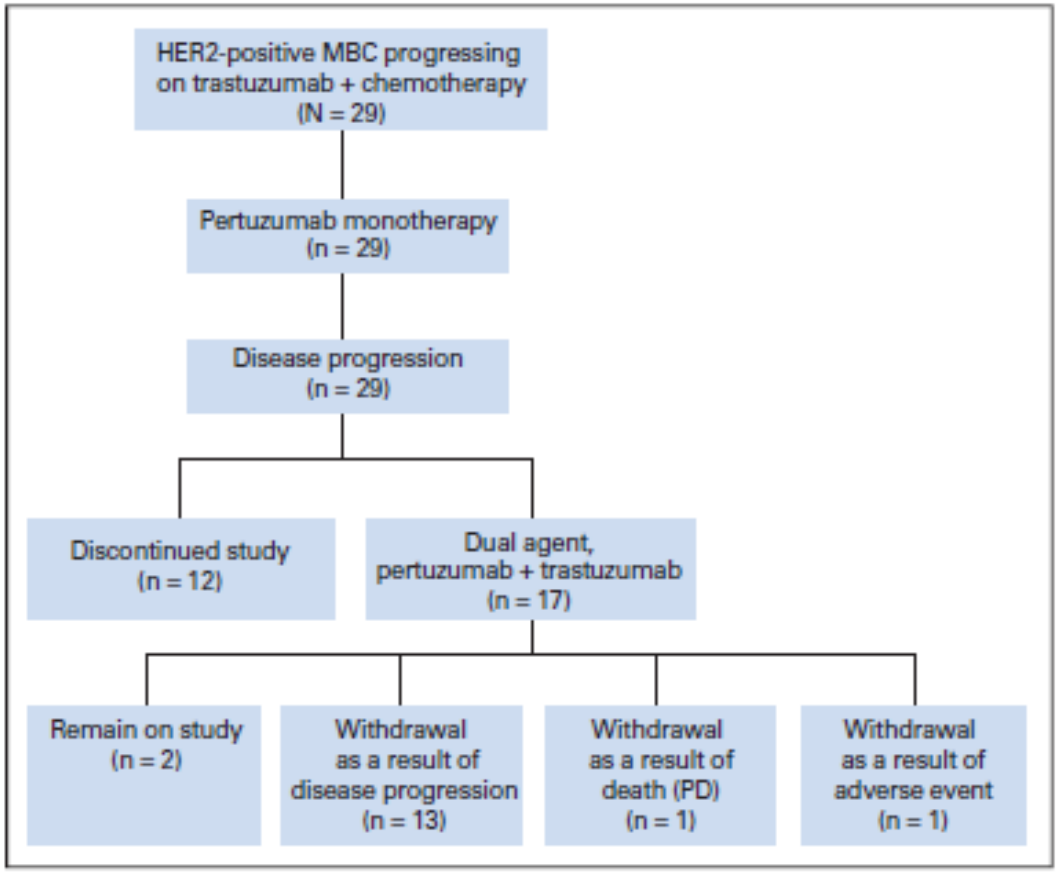
No known brain metastases

	Trastuzumab (T) naive or T- "sensitive" population (adj. T-free interval ≥ 1y)	**Trastuzumab (T) pretreated and doubt about T- "sensitivity" (adj. T-free interval < 1 y)**
1st line	Docetaxel + T+ Pertuzumab	T-DM1
2nd line	T-DM1	Lapatinib + Capecitabine
3rd line	Lapatinib + Capecitabine	Lapatinib + Trastuzumab
4th line	Lapatinib + Trastuzumab	Trastuzumab + Chemo

Pertuzumab Monotherapy After Trastuzumab-Based Treatment and Subsequent Reintroduction of Trastuzumab: Activity and Tolerability in Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

Javier Cortés, Pierre Fumoleau, Giulia Valeria Bianchi, Teresa M. Petrella, Karen Gelmon, Xavier Pivot, Shailendra Verma, Joan Albanell, Pierfranco Conte, Ana Lluch, Stefania Salvagni, Veronique Servent, Luca Gianni, Maurizio Scaltriti, Graham A. Ross, Joanna Dixon, Tania Szado, and José Baselga

J Clin Oncol 30:1594-1600. © 2012



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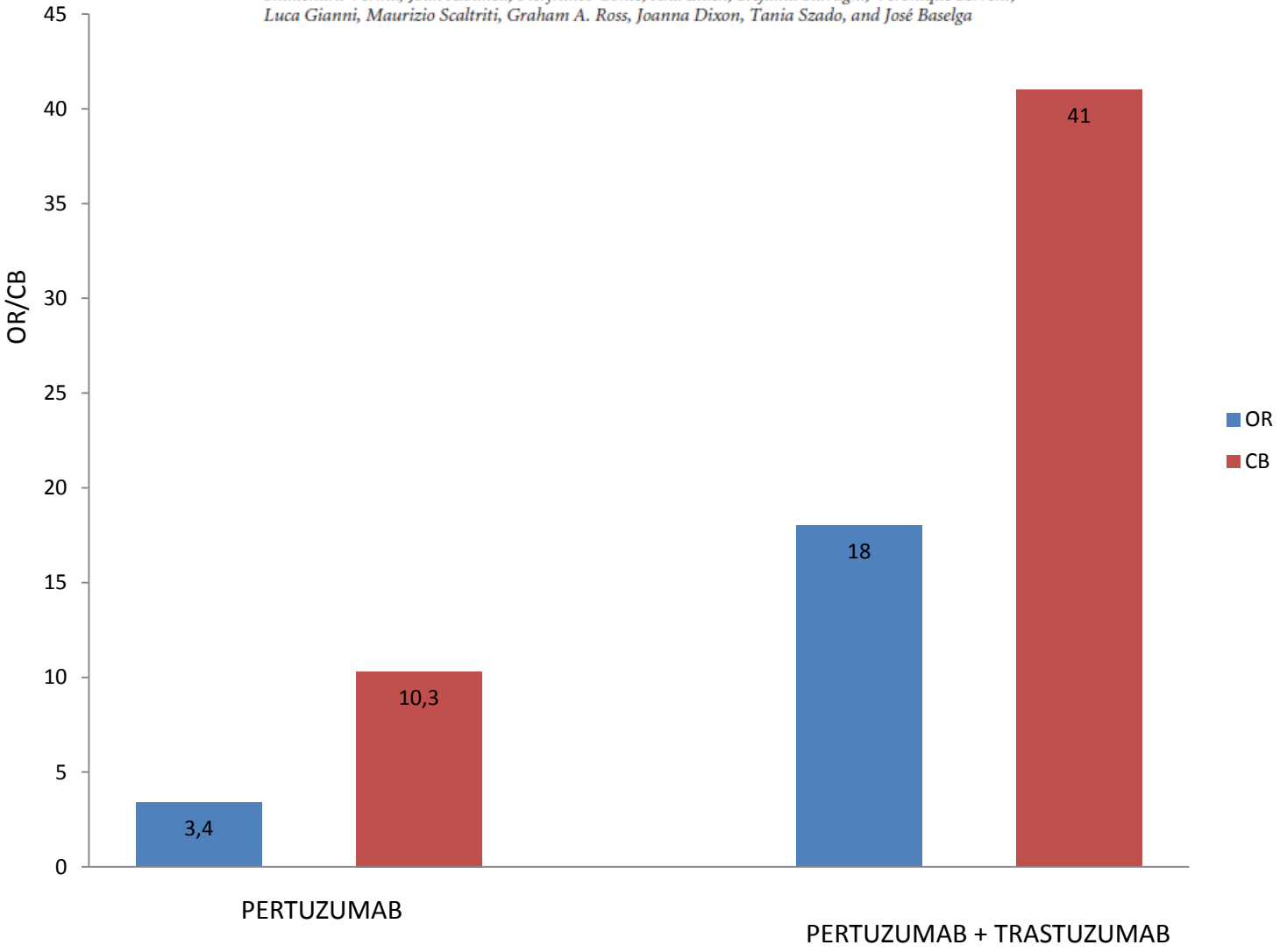

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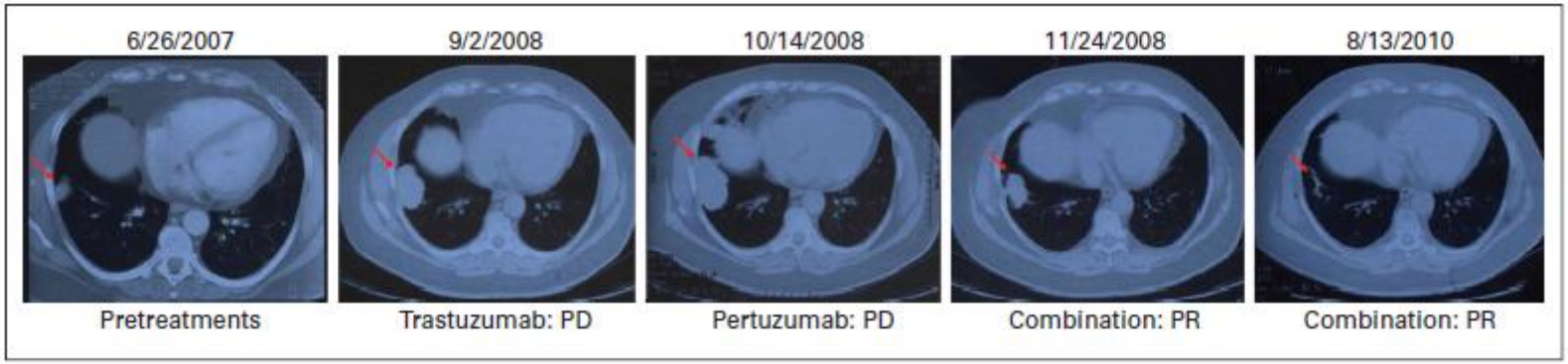

Fig 3. Series of computed tomography scans from one patient illustrating the response to the reintroduction of trastuzumab after pertuzumab monotherapy. PD, progressive disease; PR, partial response.

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Second Line: TDM-1

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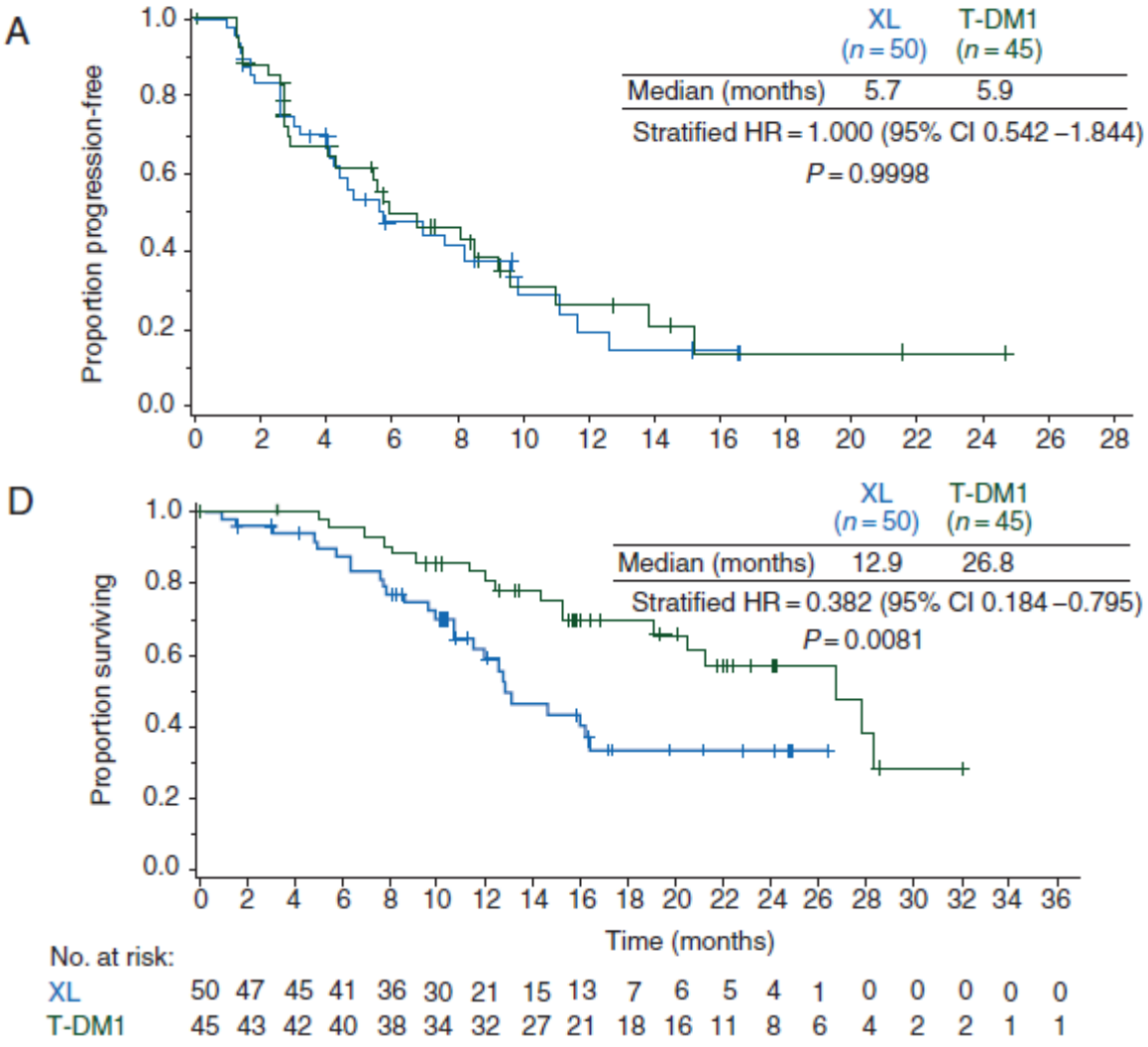
Other chemotherapy + Trastuzmab

Endocrine Therapy + Trastuzumab

Presented By Eric P. Winer, MD at 2013 Breast Cancer Symposium

Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA†

Annals of Oncology 26: 113–119, 2015



TPC Treatment Category

TPC treatment category	TPC (n=184[a])	
Combination with HER2-directed agent, %	**83.2**	
Chemotherapy[b] + trastuzumab	68.5	T-containing 80.4
Lapatinib + trastuzumab	10.3	
Hormonal therapy + trastuzumab	1.6	
Chemotherapy[b] + lapatinib	2.7	
Single-agent chemotherapy,[b] %	**16.8**	

[a] Includes patients who received study treatment.
[b] The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.