Enhancing Response in HER2-Positive Breast Cancer

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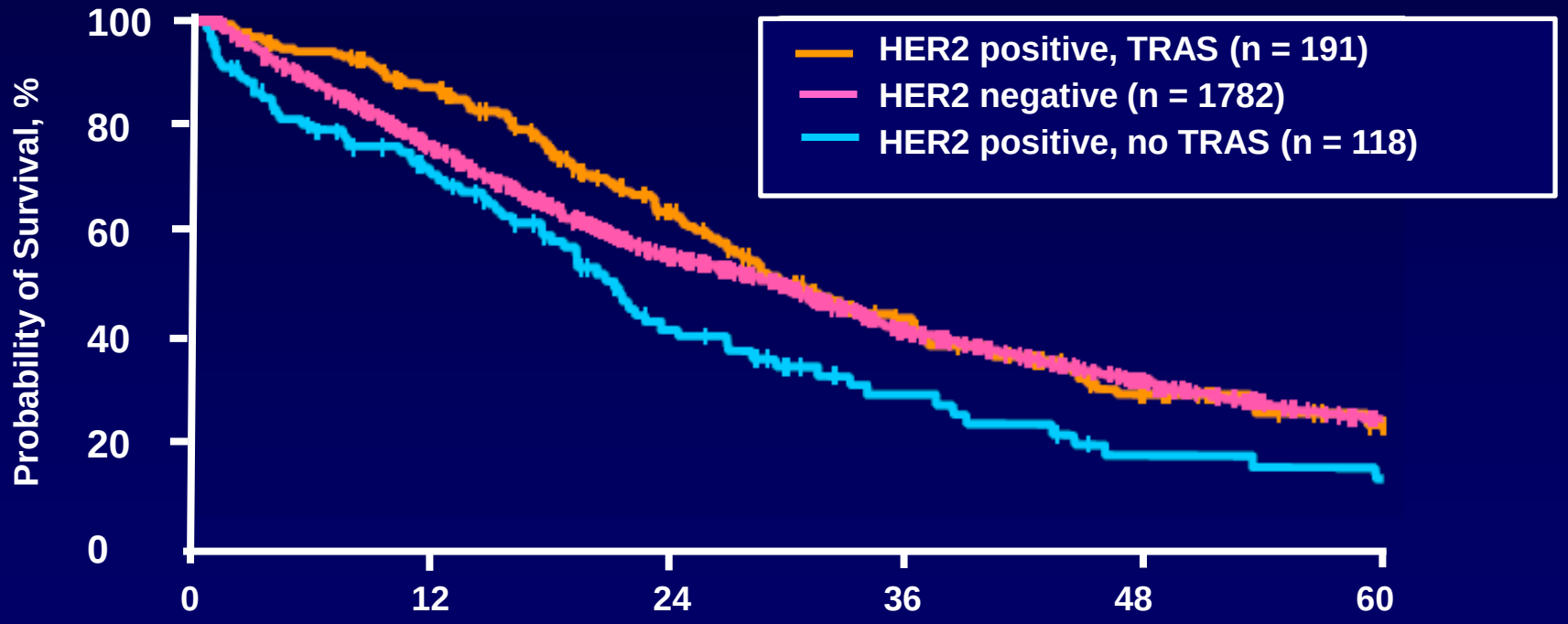
prIME oncology

Trastuzumab Has Changed the Natural History of HER2-Positive Breast Cancer

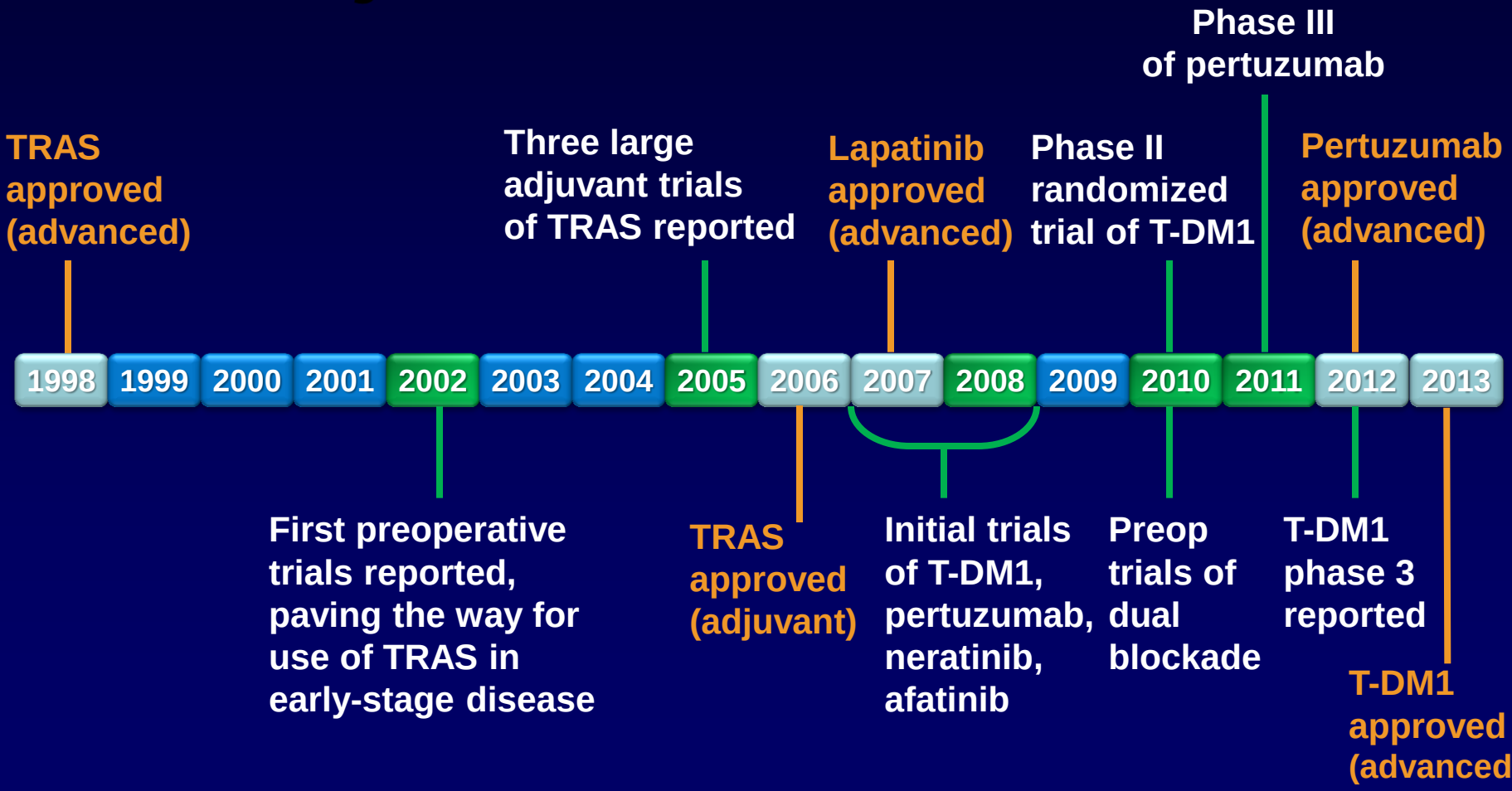
- **Patients with HER2-positive metastatic breast cancer (MBC) now have comparable outcomes with HER2-negative MBC**



TRAS, trastuzumab

Dawood S, et al. *J Clin Oncol.* 2010;28(1):92-98.

HER2-Positive Breast Cancer: Major Clinical Advances



BC, breast cancer; T-DM1, trastuzumab emtansine

Krop I, et al. *Cancer Res.* 2011;71(24): Abstract ES1-3.

Case Presentation

- **Linda is a 43-year-old woman who was referred for treatment of newly diagnosed breast cancer after presenting to her primary physician complaining of cough and dyspnea**

- **Imaging showed 4 cm mass in the right breast, right axillary/subpectoral/mediastinal lymphadenopathy, moderate right pleural effusion, pleural thickening on the right side, and multiple peri centimeter nodules in both lungs**

Case Presentation

- Biopsy of the breast revealed an invasive ductal carcinoma, high grade, estrogen receptor (ER) positive (50%, 2+) progesterone receptor (PR) negative, HER2 3-positive breast cancer
- Pleural fluid cytology: Positive for metastatic breast cancer
- What first line regimen would you offer this patient?

Review of First-Line Options

Chemotherapy Plus Trastuzumab in Metastatic Disease

	Slamon, et al n = 469			Marty, et al n = 186		
Treatment arms	**AC or PAC* vs AC or PAC →TRAS**			**DOC vs DOC →TRAS†**		
Time to disease progression (months)	4.6	7.4	*P* value <.001	6.1	11.7	*P* value .0001
Response rate	32%	50%	<.001	34%	61%	.0002
Median OS (months)	20	25	.046	23	31	.0325

AC, anthracycline, cyclophosphamide; PAC, paclitaxel; DOC, docetaxel; OS, overall survival

Hudis CA. *N Engl J Med.* 2007;357(1):39-51. Slamon DJ, et al. *N Engl J Med*. 2001;344:783-792. Marty M, et al. *J Clin Oncol.* 2005;23(19):4265-4274.

Hormonal Therapy in HER2-Positive Metastatic Breast Cancer

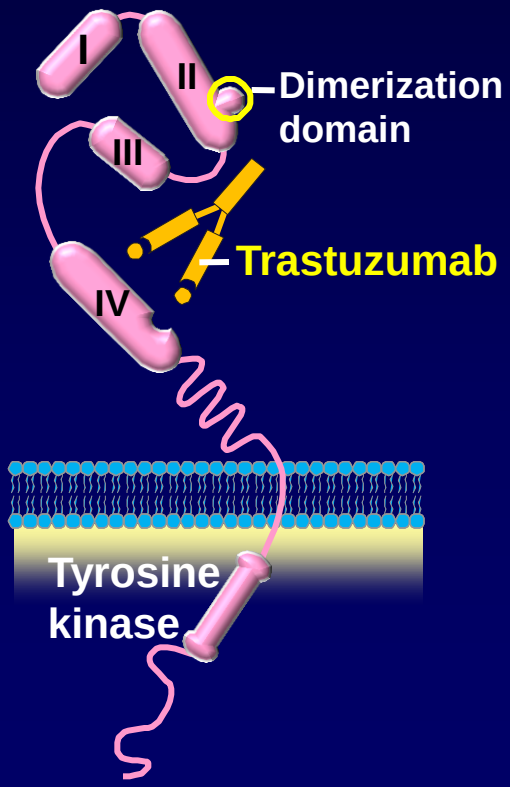
Regimen	ORR, %	Median PFS, months
Trastuzumab (N = 114; HER2 positive, n = 79)[1]	26	3.5-3.8
Anastrozole/trastuzumab (n = 103)[2]	20	4.8
Anastrozole (n = 104)[2]	7	2.4
Lapatinib/letrozole (n = 642)[3]	28	8.2
Letrozole (n = 644)[3]	15	3.0
Lapatinib (N = 138)[4]	24	NA

ORR, overall response rate; PFS, progression-free survival

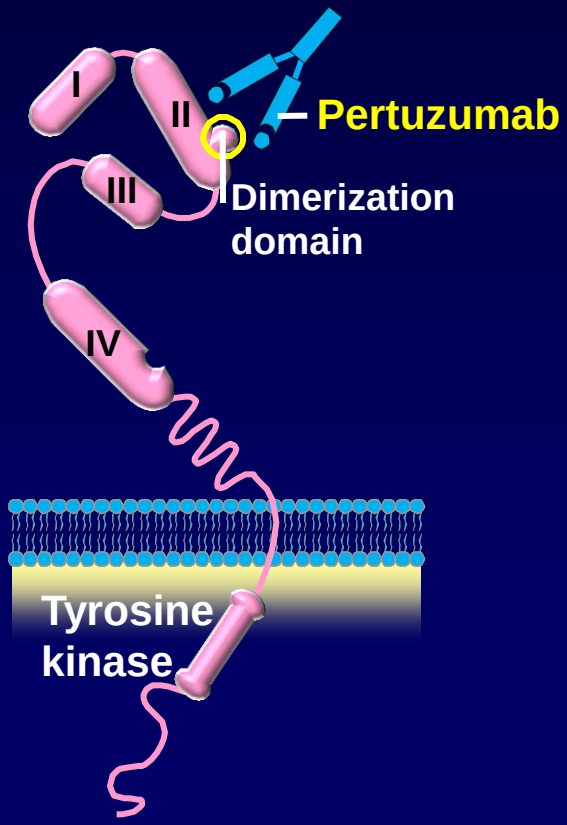
1. Vogel C, et al. *J Clin Oncol*. 2002;20(3):719-726. 2. Kaufman B, et al. *J Clin Oncol*. 2009;27(33):5529-5537.
3. Johnston S, et al. *J Clin Oncol*. 2009;27(33):5538-5546. 4. Gomez HL, et al. *J Clin Oncol*. 2008;26:2999-3005.

MOA of Trastuzumab vs Pertuzumab[1,2]

Inhibition through direct antibody binding



Inhibition through dimerization inhibition



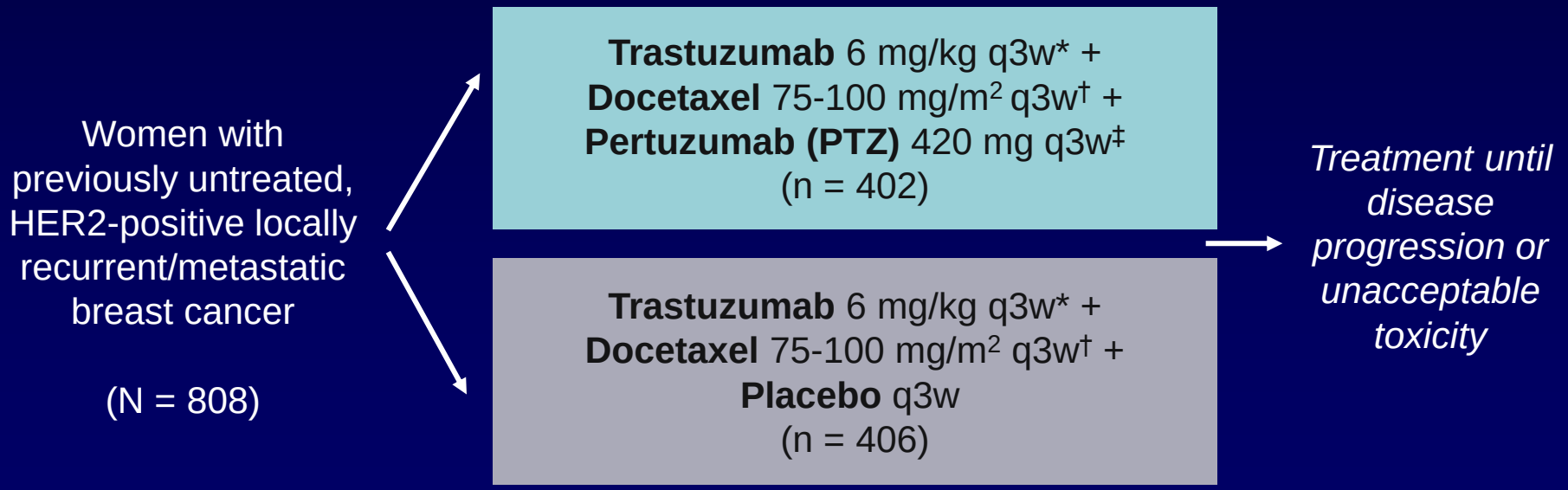
- TRAS does not bind or sterically hinder HER2 dimerization domain
- Pertuzumab blocks dimerization of HER2 with HER3
- Modeling studies suggest that the colocalization of both HER2 mABs triggers formation of additional contacts of TRAS with HER2 (but only in presence of pertuzumab)

MOA, mechanism of action; mABs, monoclonal antibodies

1. Reprinted from Baselga J, et al. *Nat Rev Cancer*. 2009;9:463-475. 2. Fuentes G, et al. *Breast Cancer Res*. 2011;13:R54.

CLEOPATRA: Study Design

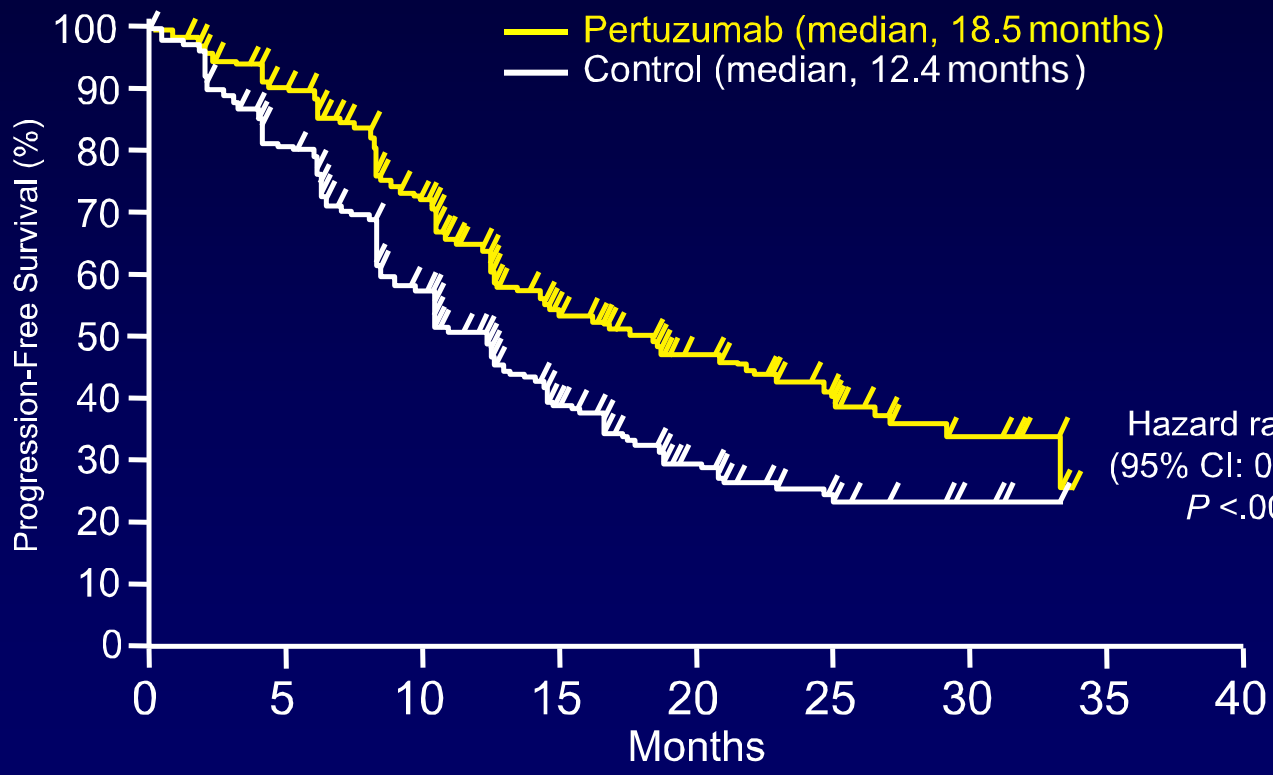
- **Primary endpoint: PFS (independently assessed)**
- **Secondary endpoints: PFS (investigator assessment), ORR, OS, Safety**



*Trastuzumab 8 mg/kg loading dose given
†Minimum of 6 docetaxel cycles recommended; <6 cycles permitted for unacceptable toxicity or progressive disease (PD)
‡Pertuzumab 840 mg loading dose given

Baselga J, et al. Presented at: 34th Annual San Antonio Breast Cancer Symposium; December 6-10, 2011; San Antonio, Texas. Abstract S5-5.

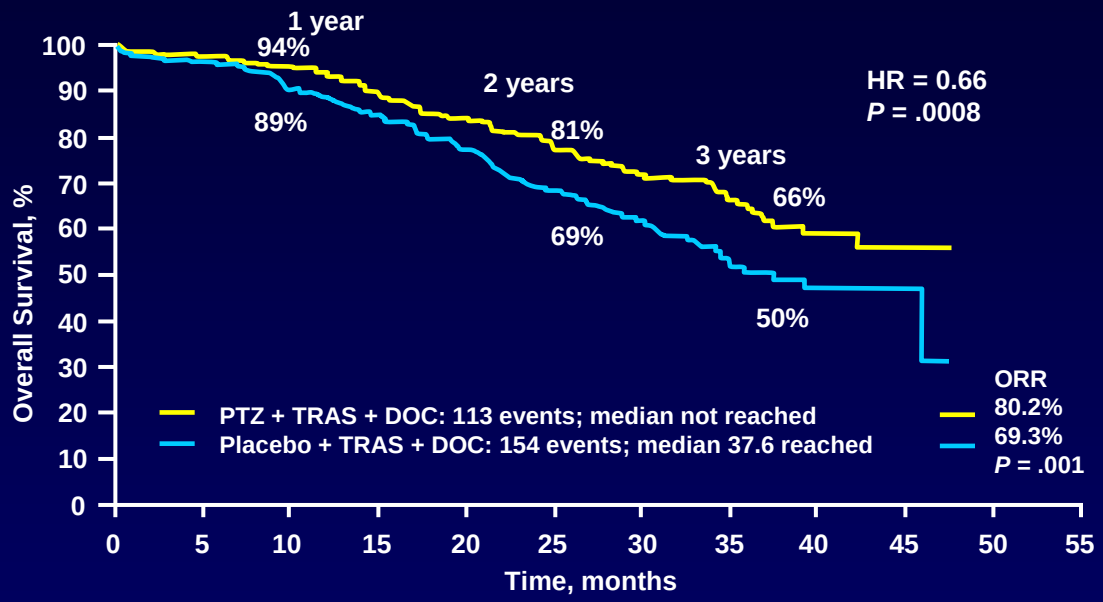
CLEOPATRA: PFS Independent Assessment



No. at risk									
Pertuzumab	402	345	267	139	83	32	10	0	0
Control	406	311	209	93	42	17	7	0	0

Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. Swain S, et al. *Lancet Oncol.* 2013;14(6):461-471.

CLEOPATRA Overall Survival



ESMO 2014 update on OS at 50 months median follow-up

PTZ + TRAS + DOC	Placebo + TRAS + DOC	
56.5 months	40.8 months	HR = 0.68, *P* = .0002

- **48 patients crossed over from placebo to PTZ arm after previous report of OS benefit**
- **Long-term cardiac safety profile maintained**

Swain S, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 3500PR.

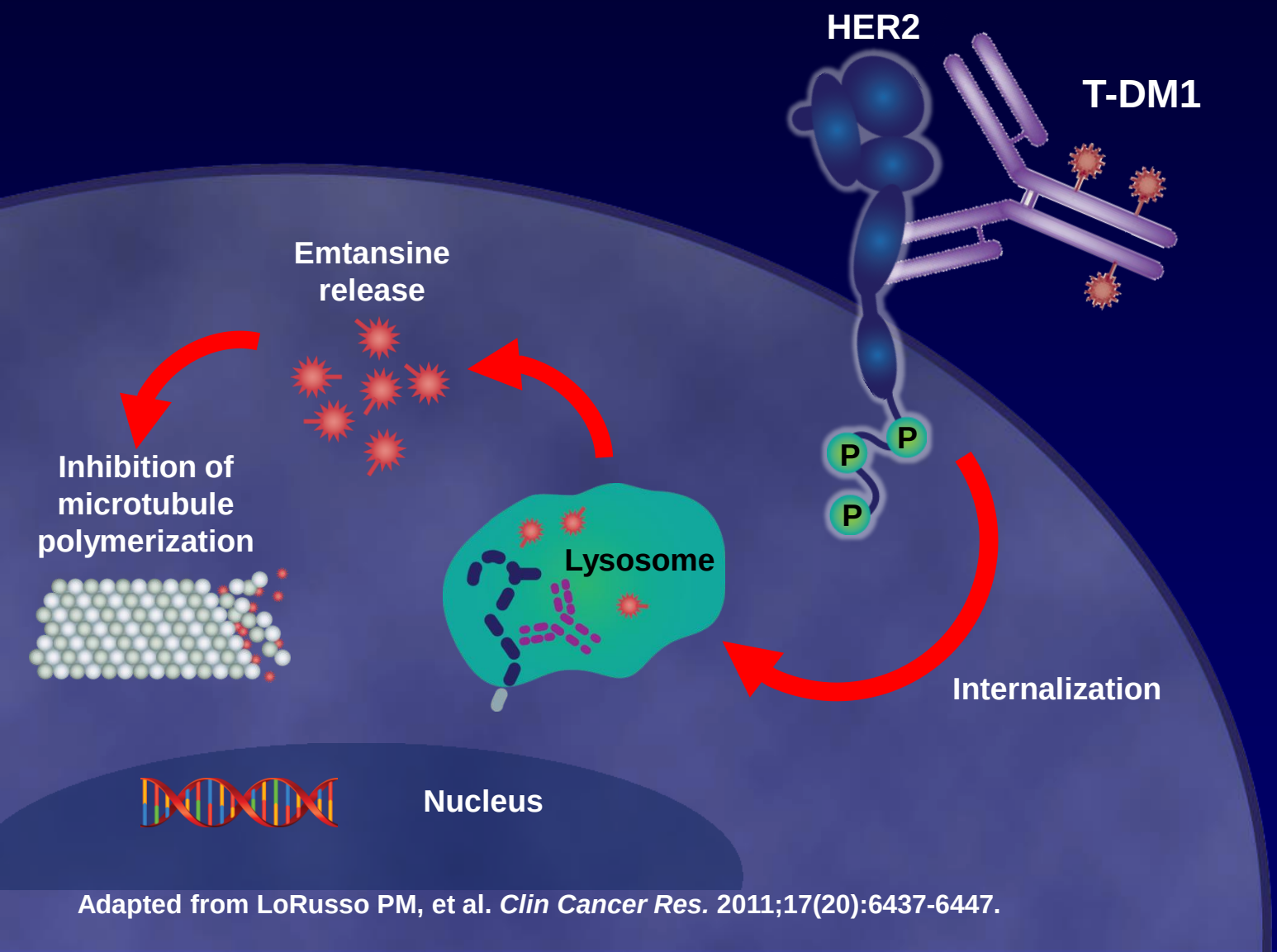
HR by ER/PR status

	No of patients	HR (95%)
OS		
All	808	0.66 (0.52-0.84)
ER/PR-positive	388	0.73 (0.50-1.06)
ER/PR-negative	408	0.57 (0.41-0.79)
PFS		
All	808	0.69 (0.58-0.81)
ER/PR-positive	388	0.76 (0.60-0.97)
ER/PR-negative	408	0.62 (0.49-0.78)

Swain S, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 3500PR.

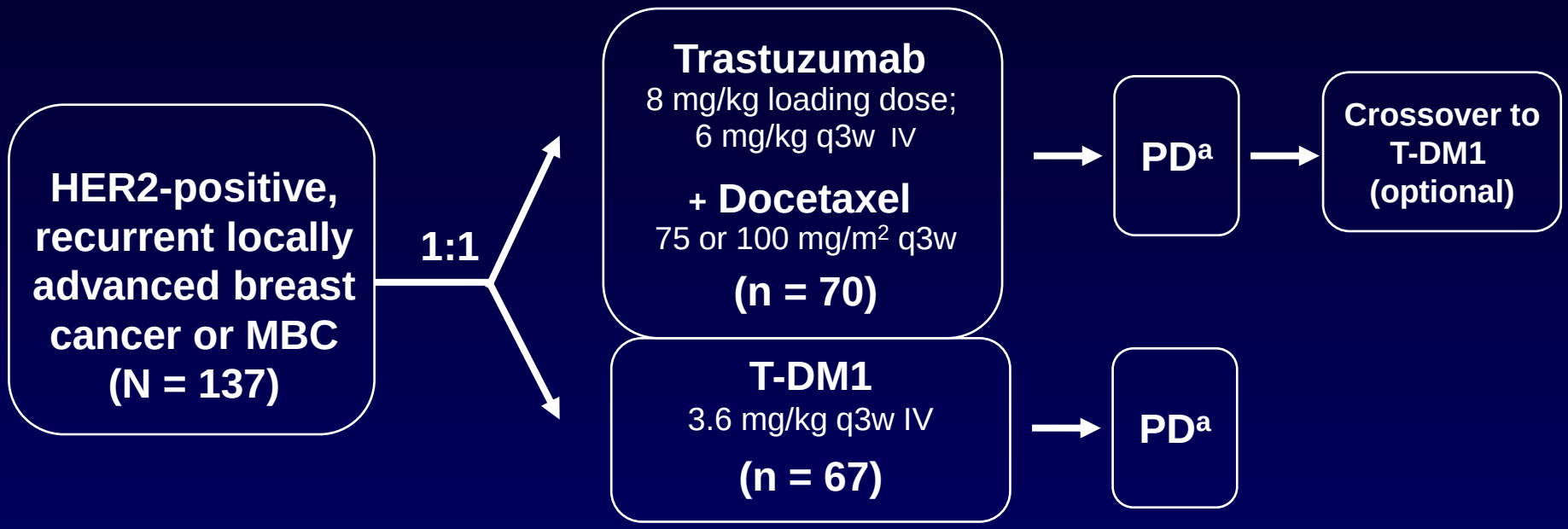
Other Options on the Forefront for First-Line?

T-DM1: Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res.* 2011;17(20):6437-6447.

TDM4450 Study Design



- **Randomized, phase II, international, open-label study[b]**
- **Stratification factors: World region, prior adjuvant trastuzumab therapy, disease-free interval**
- **Primary end points: PFS by investigator assessment, and safety**
- **Data analyses were based on clinical data cut of Nov 15, 2010 prior to T-DM1 crossover**
- **Key secondary end points: OS, ORR, DOR, CBR, and QOL**

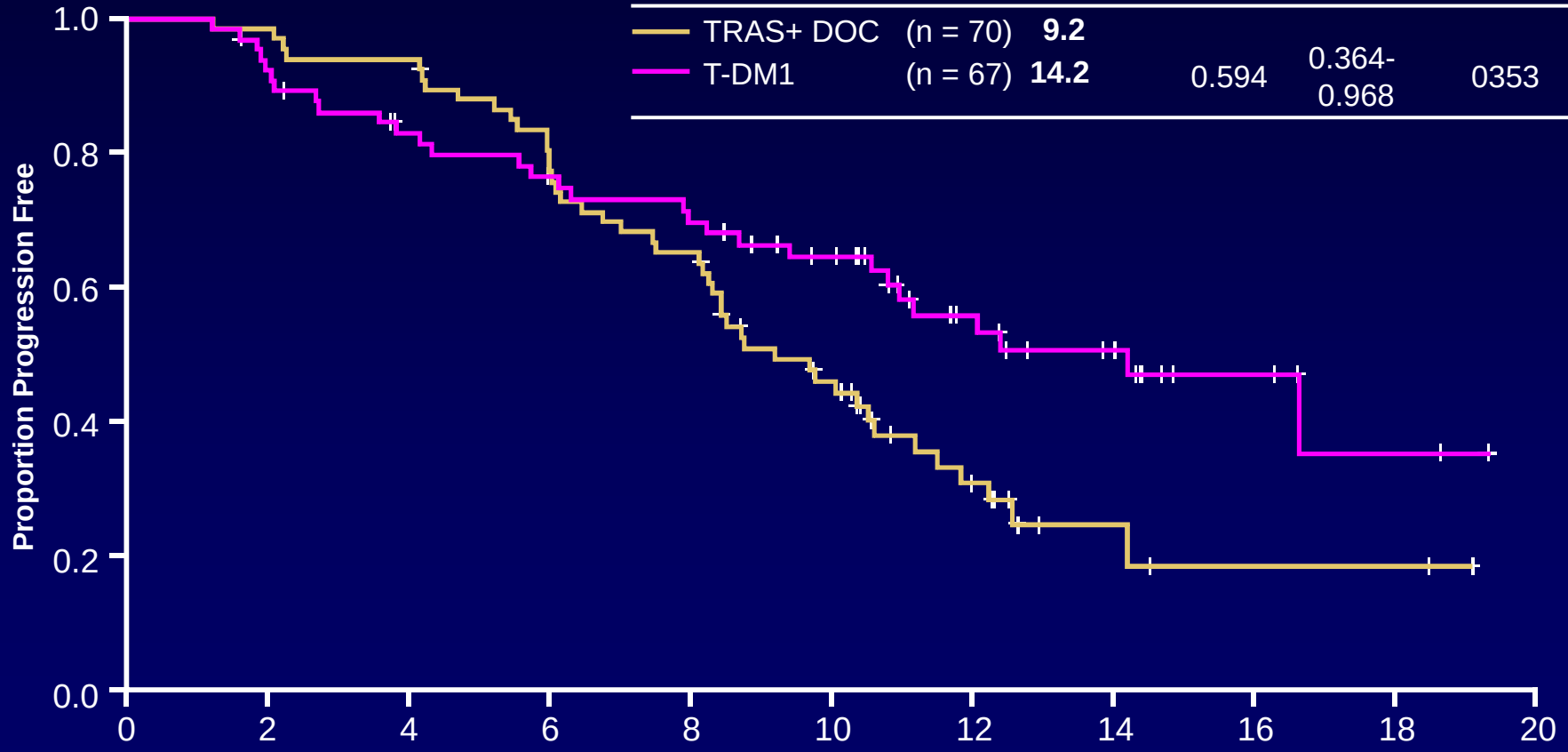
[a]Patients were treated until PD or unacceptable toxicity
[b]This was a hypothesis generating study; the final PFS analysis was to take place after 72 events had occurred

DOR, duration of response; CBR, clinical benefit rate; QoL, quality of life

Hurvitz SA, et al. *J Clin Oncol*. 2013;31(9):1157-1163.

TDM4450 PFS by Investigator: Randomized Patients

		Median PFS, months	Hazard ratio	95% CI	Log-rank *P* value
TRAS+ DOC	(n = 70)	**9.2**			
T-DM1	(n = 67)	**14.2**	0.594	0.364-0.968	0353



Number of patients at risk

TRAS + DOC	70	66	63	53	43	27	12	4	2	2	0
T-DM1	67	60	51	46	42	35	22	15	6	3	0

Hazard ratio and log-rank *P* value were from stratified analysis

Hurvitz SA, et al. *J Clin Oncol*. 2013;31(9):1157-1163.

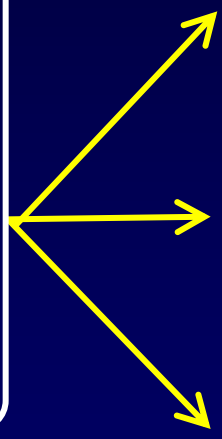
First-Line mBC Phase III MARIANNE Study: BO22589/TDM4788g

n = 1092

FPI July 6, 2010

Patients stratified by:

- World region
- Neo/Adjuvant therapy (Y/N)
  - Trastuzumab and/or lapatinib based therapy (Y/N)
- Visceral disease (Y/N)



Arm A
Trastuzumab + taxane (until PD)
N = 364

Arm B
T-DM1 + pertuzumab (until PD)
N = 364

Arm C
T-DM1 + pertuzumab placebo (until PD)
N = 364

Patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer

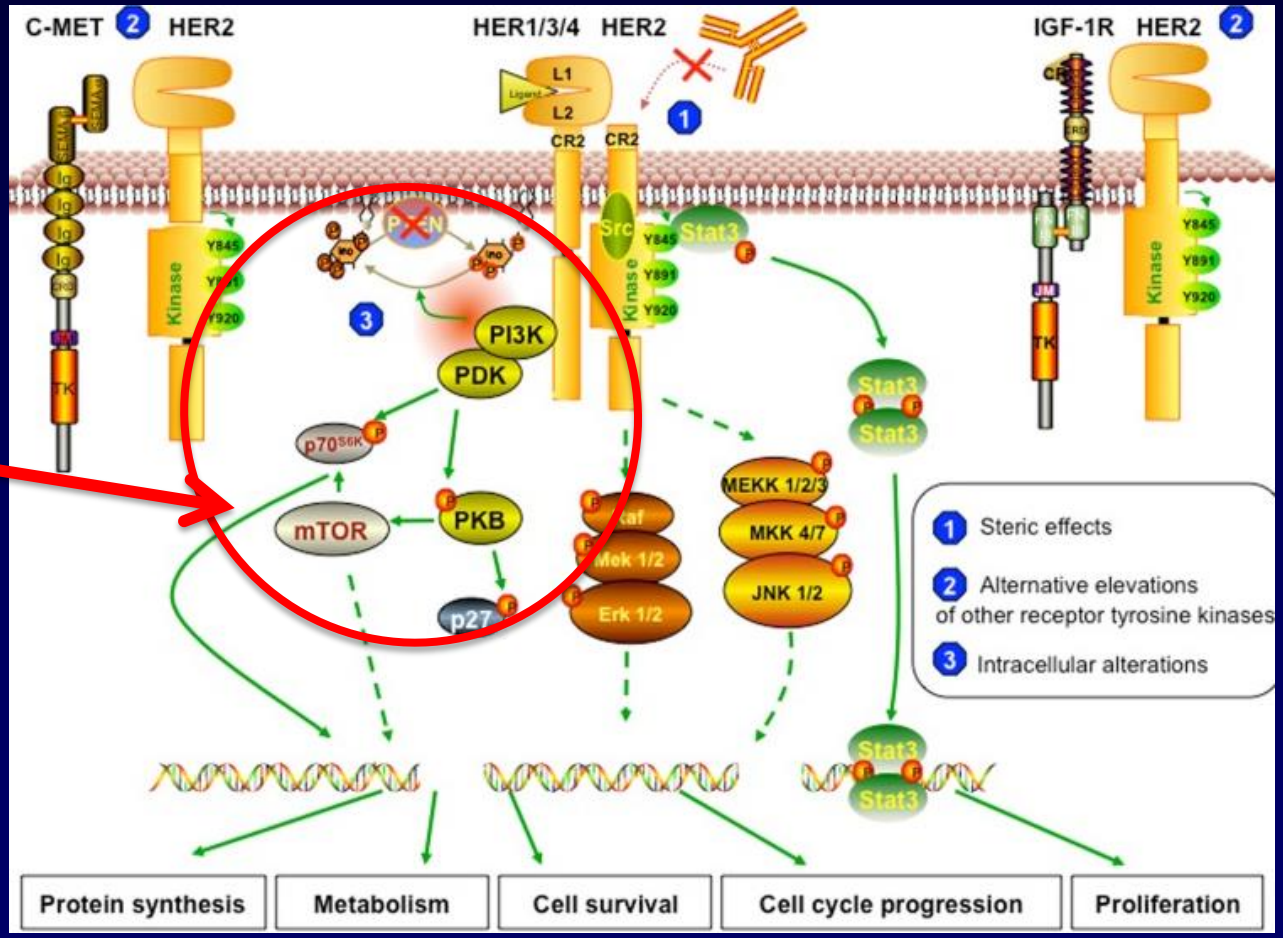
- Primary endpoints: PFS as assessed by IRF; Safety
- Secondary endpoints: OS; PFS by investigator; PRO analyses; Biomarkers
- Non-inferiority followed by Superiority analysis between each of the experimental arms and the control arm
- Interim futility analysis: Option to drop experimental arm

Ellis PA, et al. *J Clin Oncol.* 2011;29(15S): Abstract TPS102.

Mechanisms of Resistance

Activated PI3K-AKT-mTOR pathway

- **Loss PTEN**
- **Activating mutation PI3K**
- **Activation mutation AKT**



Vu T, et al. *Front Oncol*. 2012;2:62.

BOLERO-1/TRIO 019: Trial Design

N = 719

- Locally advanced or metastatic HER2+ breast cancer
- No prior therapy for advanced or metastatic disease (except endocrine therapy)
- Prior (neo)adjuvant TRAS and/or chemotherapy allowed[1]
- Measurable disease or presence of bone lesions (lytic or mixed)

Randomized 2:1

Everolimus (10 mg PO daily) + Paclitaxel[2] + Trastuzumab[3]

Placebo + Paclitaxel[2] + Trastuzumab[3]

Stratification factors:
- Prior neo/adjuvant TRAS
- Visceral metastases

Therapy until disease progression or intolerable toxicity[4]

Endpoints

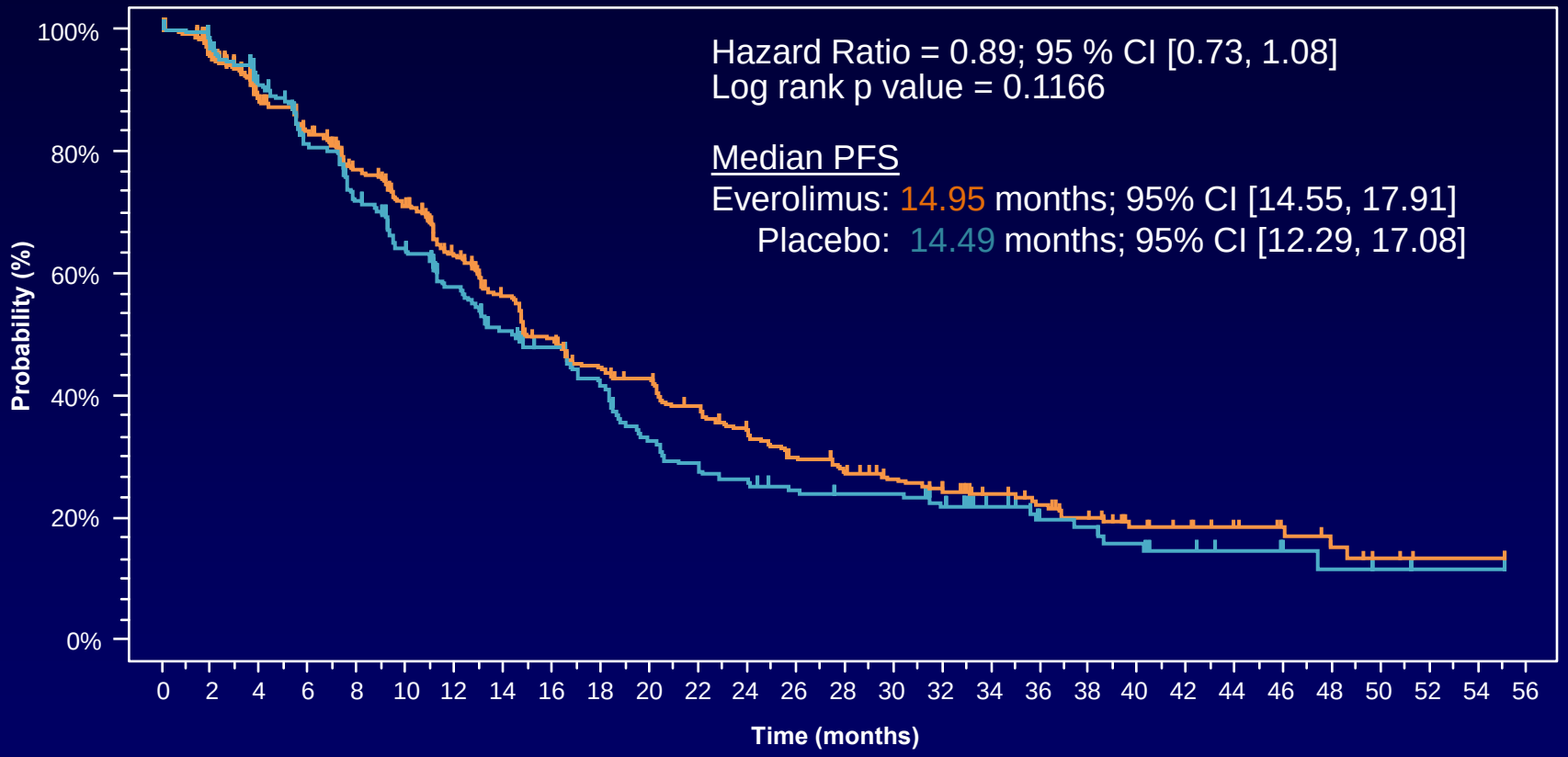
- **Primary: PFS (investigator-assessed)**
  - **Overall population and**
  - **HR$^-$ subpopulation**
- Secondary:
  - OS, ORR, CBR, Time to response, Safety, Duration of response

[1]Discontinued > 12 mo before randomization;
[2]Paclitaxel: 80 mg/m^2 weekly;
[3]Trastuzumab: 4 mg/kg loading dose on day 1 at cycle 1 followed by 2 mg/kg weekly doses
[4]Patients could discontinue any study treatment due to AEs; other study treatments continued until disease progression or intolerable toxicity

ABC, advanced breast cancer; CBR, clnical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

Hurvitz SA, et al. Presented at: 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract S6-01.

BOLERO-1/TRIO 019: PFS by Investigator Assessment (Full Study Population)



No. of patients still at risk

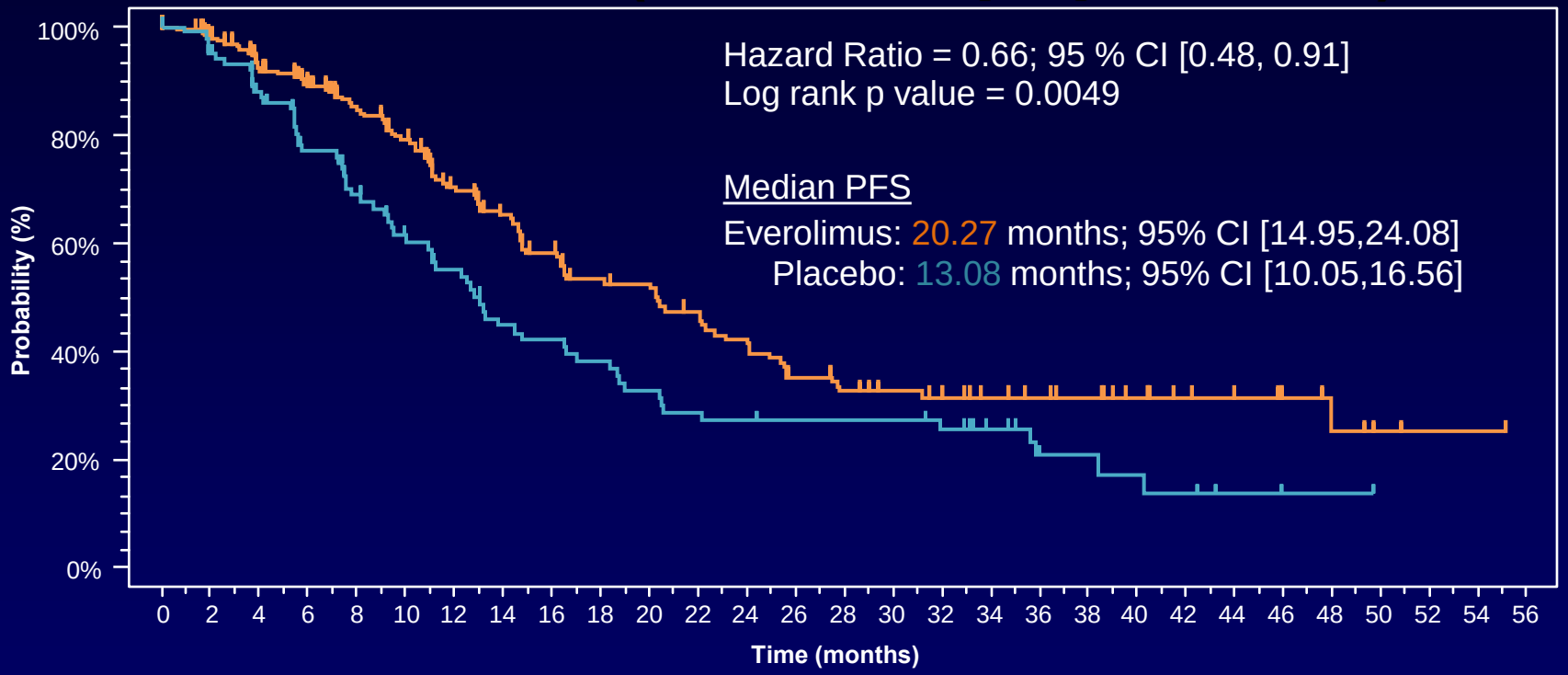
Everolimus	480	416	365	324	289	260	217	178	151	130	122	107	94	80	72	63	58	48	42	35	26	21	17	13	10	5	3	3	0
Placebo	239	221	199	166	144	123	106	91	80	69	53	47	43	38	36	36	31	24	17	15	12	9	7	6	4	3	1	1	0

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

- **Final PFS analysis was based on 425 PFS events observed in the full population**

Hurvitz SA, et al. Presented at: 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract S6-01.

BOLERO-1/TRIO 019: PFS by Investigator Assessment (HR– Subpopulation)



No. of patients still at risk

Everolimus	208	183	166	151	138	125	100	84	73	64	62	55	49	40	35	32	30	24	21	19	15	11	10	7	5	2	1	1	0
Placebo	103	96	83	68	58	49	43	34	32	28	24	21	20	19	19	19	17	13	7	6	5	4	2	1	1	0	0	0	0

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

- Sensitivity analysis without censoring patients at the start of new antineoplastic therapy:
  - Median PFS and 95% CIs
    - 20.27 mo (14.82, 24.08) for EVE [n = 102]
    - 12.88 mo (10.94, 16.56) for PBO [n = 68]
  - HR=0.66 [0.48, 0.9], p = 0.0043

Hurvitz SA, et al. Presented at: 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract S6-01.

BOLERO-1/TRIO 019: Most Frequent Adverse Events (Safety set) [> 25% in the EVE Arm]

AE/Grade, %	EVE + TRAS + PAC (N = 472)			PBO + TRAS + PAC (N = 238)		
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Non-hematologic						
Stomatitis	67	**13**	**0**	32	**1**	**0**
Diarrhea	57	**9**	**0**	47	**4**	**0**
Alopecia	47	**<1**	**0**	53	**0**	**0**
Rash	40	**1**	**0**	21	**<1**	**0**
Cough	40	**<1**	**0**	33	**1**	**0**
Pyrexia	39	**2**	**0**	27	**1**	**0**
Fatigue	35	**5**	**0**	36	**3**	**0**
Pneumonitis*	16	**4**	**1**	4	**<1**	**0**
Hematologic						
Neutropenia	38	**21**	**4**	25	**11**	**4**
Anemia	31	**9**	**1**	16	**3**	**0**

Deaths, %	Full Population		HR– subpopulation	
	EVE + TRAS + PAC (N = 472)	PBO + TRAS + PAC (N = 238)	EVE + TRAS + PAC (N = 206)	PBO + TRAS + PAC (N = 103)
On-treatment deaths	**4.7**	**0.8**	**3.4**	**1.9**
Due to disease progression	1.1	0.8	0.5	1.9
Due to AE	3.6	0	2.9	0

***AE of clinical importance**

EVE, Everolimus; HR, hormone receptor; PAC, Paclitaxel; PBO, Placebo; TRAS, Trastuzumab.

Hurvitz SA, et al. Presented at: 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract S6-01.

Summary: Optimal Choice First-Line Setting 2015

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Sharon H. Giordano, Sarah Temin, Jeffrey J. Kirshner, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Ana M. Gonzalez-Angulo, Ian Krop, Jennifer Levinson, Nancy U. Lin, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Naren Ramakrishna, and Eric P. Winer

- **Clinicians should recommend combination of trastuzumab, pertuzumab and a taxane for first-line treatment, unless contraindication to taxane use**
- **If ER+, can consider endocrine therapy + trastuzumab or lapatinib in selected cases**

Giordano SH, et al. *J Clin Oncol*. 2014;32(19):2078-2099.

Case Continued

- Linda receives first-line pertuzumab/ trastuzumab/docetaxel for 6 cycles
- She has a complete response
- She continues on pertuzumab/trastuzumab for 1 year when imaging reveals a new 2 cm lesion in the liver and several new subcentimeter nodules in the lungs
- What second-line therapy do you recommend?

Case Continued

What second-line therapy do you recommend?

A. **T-DM1**

B. **Resume docetaxel (or paclitaxel) and continue trastuzumab/pertuzumab**

C. **Continue trastuzumab/pertuzumab, add in tamoxifen**

D. **Vinorelbine, trastuzumab, everolimus**

E. **Lapatinib and capecitabine**

Treatment Beyond Progression

We Do Know: Continued HER2 Blockade After Progression on Trastuzumab Is Beneficial

Author	Agents	N	TTP	PFS	OS
Von Minckwitz, et al	Capecitabine + trastuzumab vs capecitabine	156	8.2 months vs 5.6 months, *P* = .03	NR	25.5 months vs 20.4 months *P* = .257
Geyer, et al	Capecitabine + lapatinib vs capecitabine	324	8.4 months vs 4.4 months, *P*<.001	8.4 months vs 4.1 months, *P*<.001	19 months vs 16 months *P* = .206
Blackwell, et al	Lapatinib + trastuzumab vs lapatinib	296	NR	12 weeks vs 8.1 weeks, *P* = .008	14 months vs 9.5 months, *P* = .026

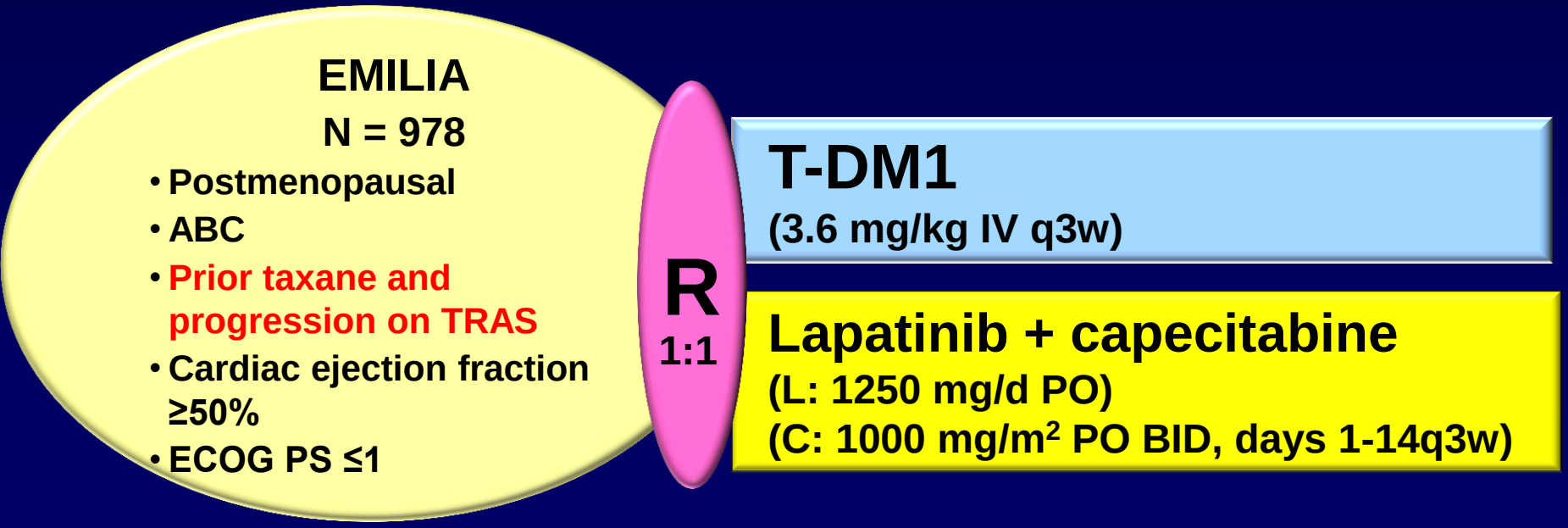
TTP, time to progression

Blackwell K, et al. *J Clin Oncol.* 2012:30(21):2585-2592. Cameron D, et al. *Oncologist.* 2010:15(9):924-934. Geyer CE, et al. *N Engl J Med*. 2006;355(26):2733-2743. Von Minckwitz G, et al. *J Clin Oncol*. 2009:27(12):1999-2006.

EMILIA: T-DM1 Phase III Trial Design

Key endpoints

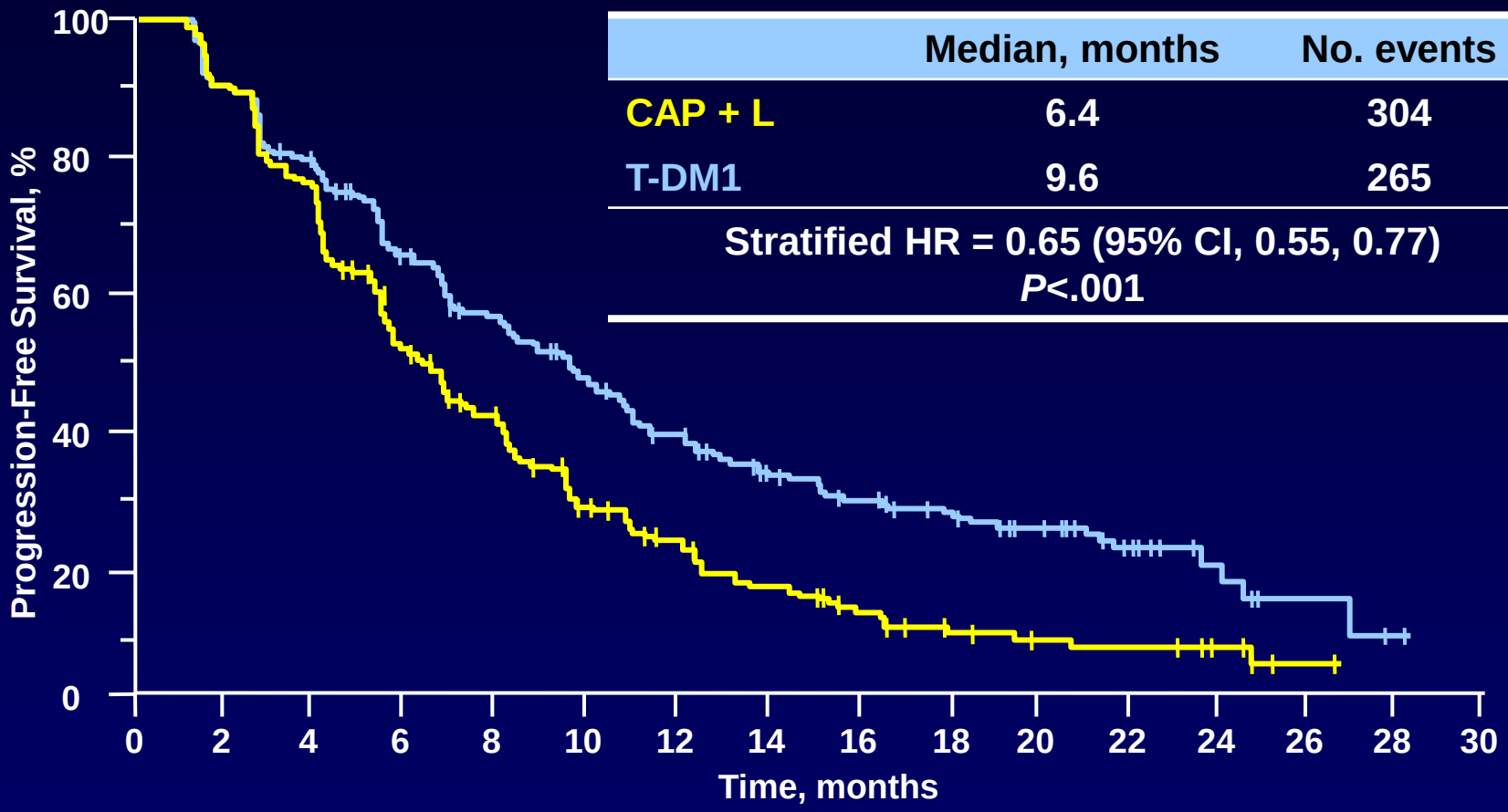
- **Primary:** Progression-free survival (PFS, central assessment), safety, OS
- **Secondary:** Objective response, duration of objective response, PFS (investigator review)
- **Stratification factors:** World region, number of prior chemo regimens for ABC or unresectable LABC, presence of visceral disease



Estimated Study Completion Date: April 2014

1. Blackwell KL, et al. *J Clin Oncol.* 2012;20(suppl): Abstract LBA1. 2. Verma S, et al. *N Engl J Med*. 2012;367(12):183-1791.

EMILIA: PFS by Independent Review



	Median, months	No. events
CAP + L	6.4	304
T-DM1	9.6	265

Stratified HR = 0.65 (95% CI, 0.55, 0.77)
P<.001

No. at risk by independent review:

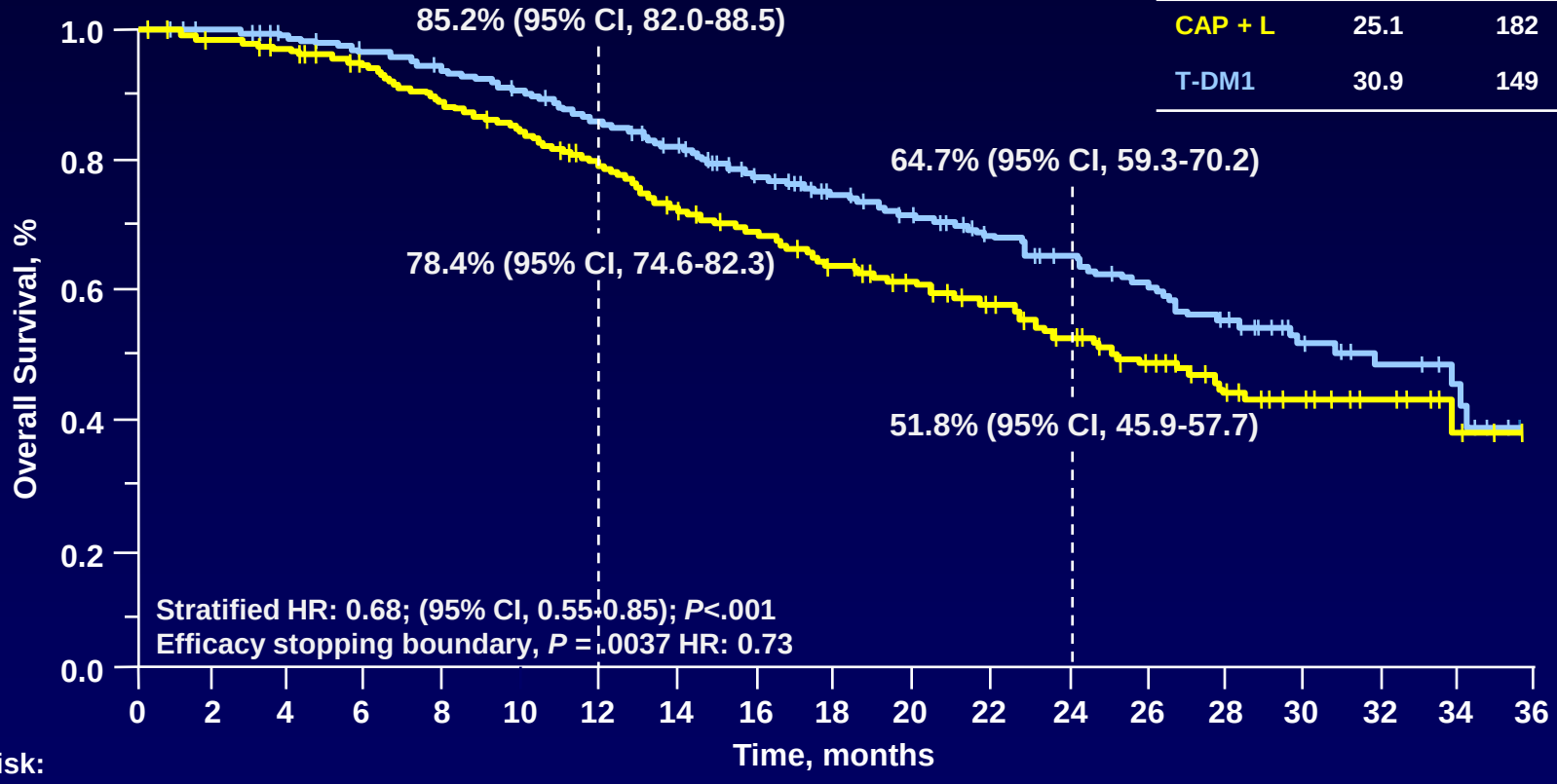
CAP + L	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

CAP, capecitabine; L, lapatinib

Verma S, et al. *N Engl J Med.* 2012;367(19):1783-1791.

EMILIA: OS

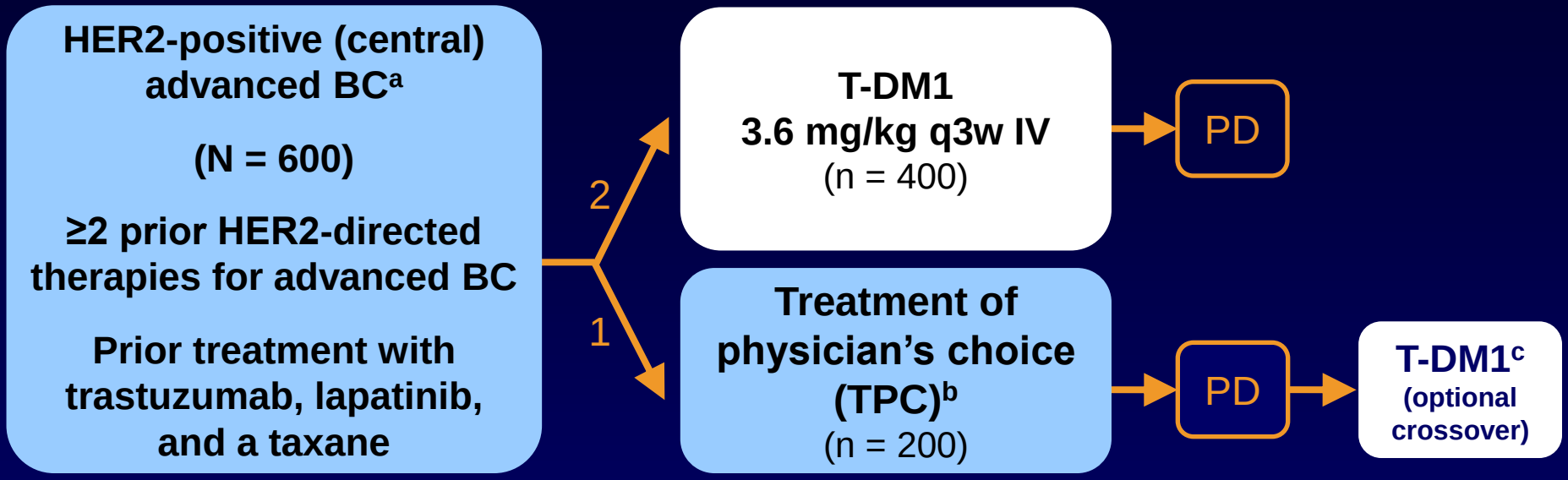
	Median, months	No. events
CAP + L	25.1	182
T-DM1	30.9	149



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

Verma S, et al. *N Engl J Med.* 2012;367(19):1783-1791.

TH3RESA Study Schema



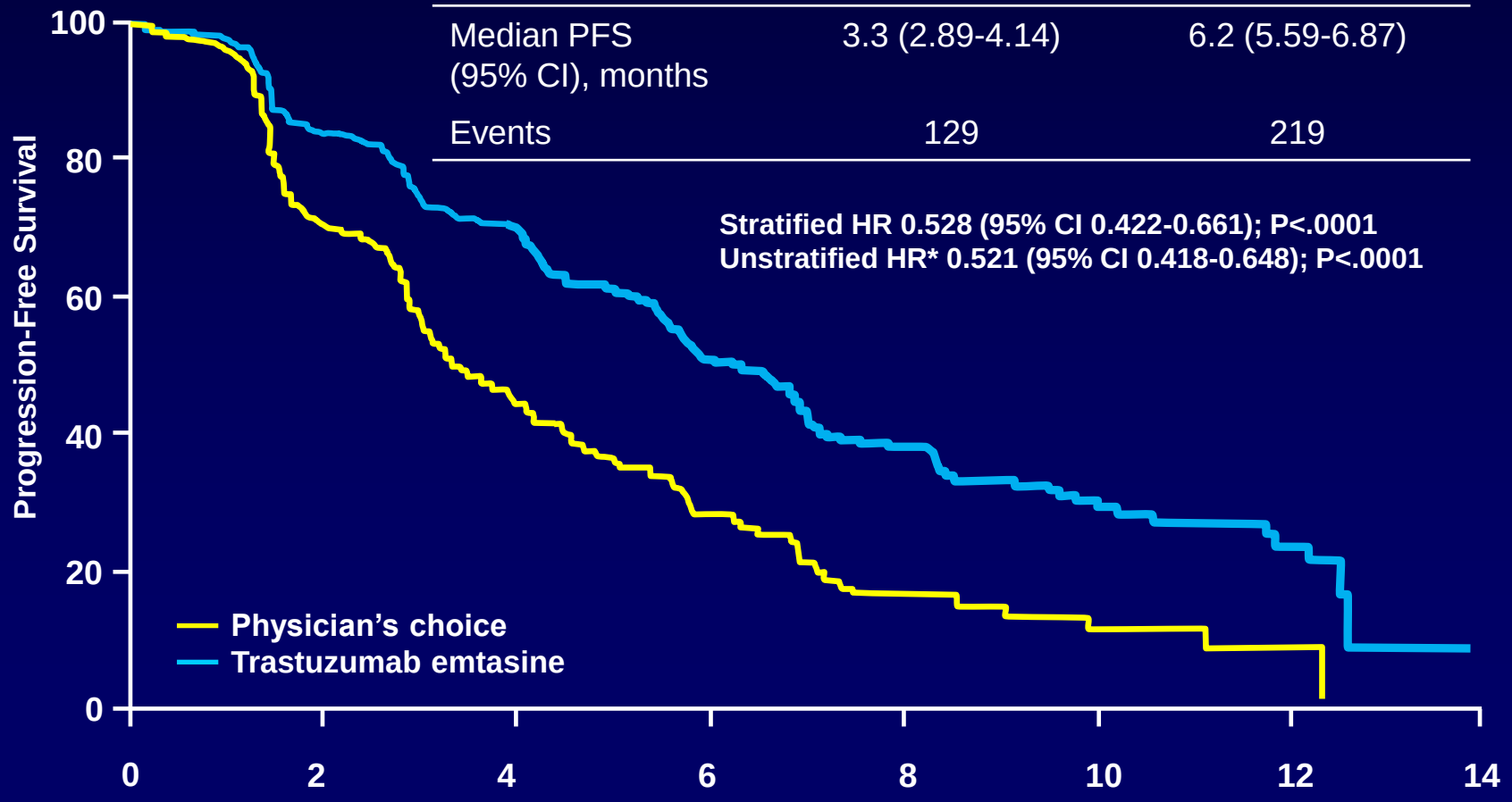
- **Stratification factors: World region, number of prior regimens for advanced BC,[d] presence of visceral disease**
- **Co-primary endpoints: PFS by investigator and OS**
- **Key secondary endpoints: ORR by investigator and safety**

[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

Krop IE, et al. *Lancet Oncol*. 2014;15(7):689-699.

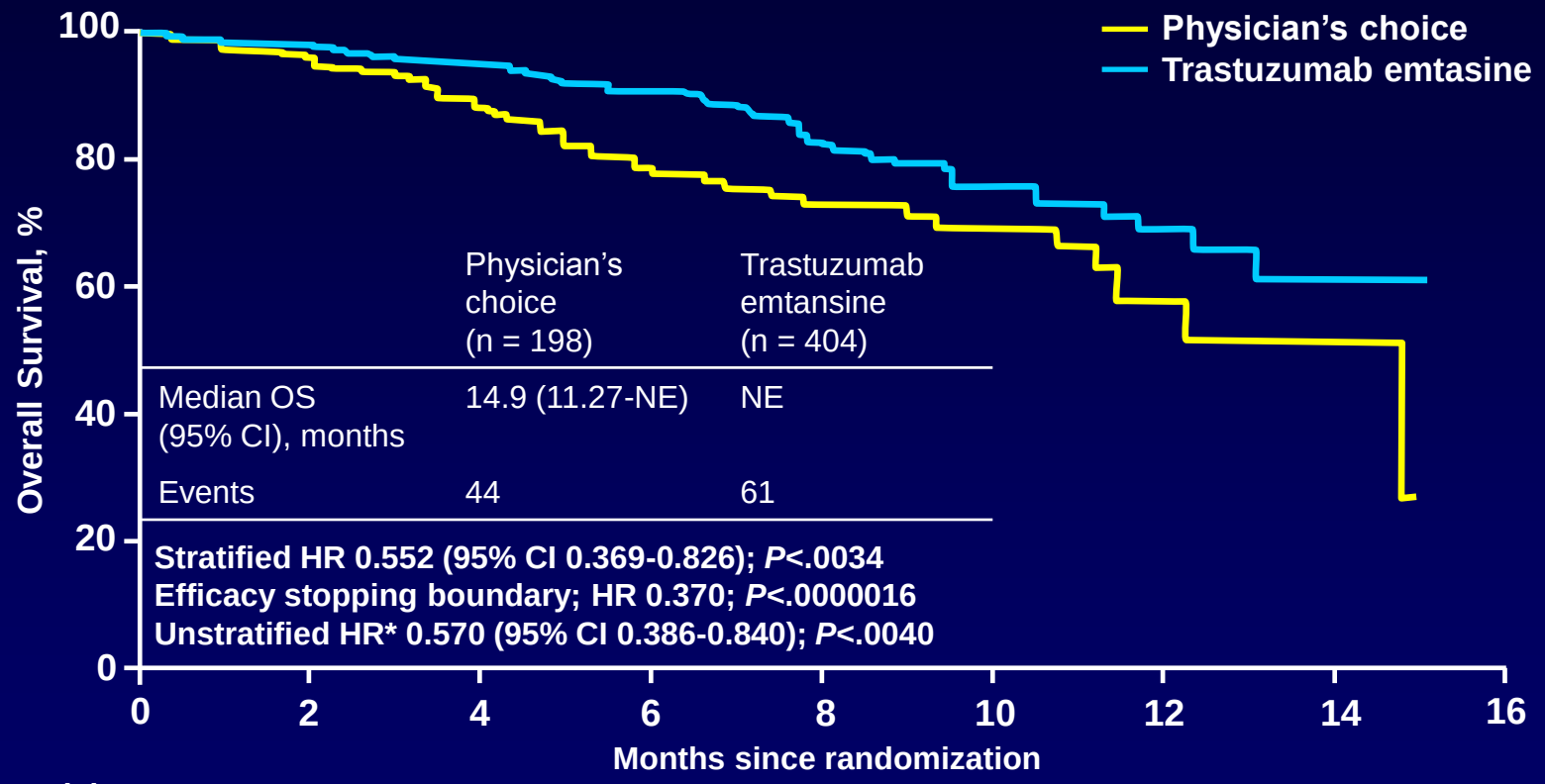
TH3RESA: PFS (Investigator Assessment)

	Physician's choice (n = 198)	Trastuzumab emtansine (n = 404)
Median PFS (95% CI), months	3.3 (2.89-4.14)	6.2 (5.59-6.87)
Events	129	219



Krop IE, et al. *Lancet Oncol*. 2014;15(7):689-699.

TH3RESA
Overall Survival



Number at risk									
Physician's choice	198	169	125	80	51	30	9	3	0
Trastuzumab emtansine	404	381	316	207	137	65	30	7	0

Krop IE, et al. *Lancet Oncol*. 2014;15(7):689-699.

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

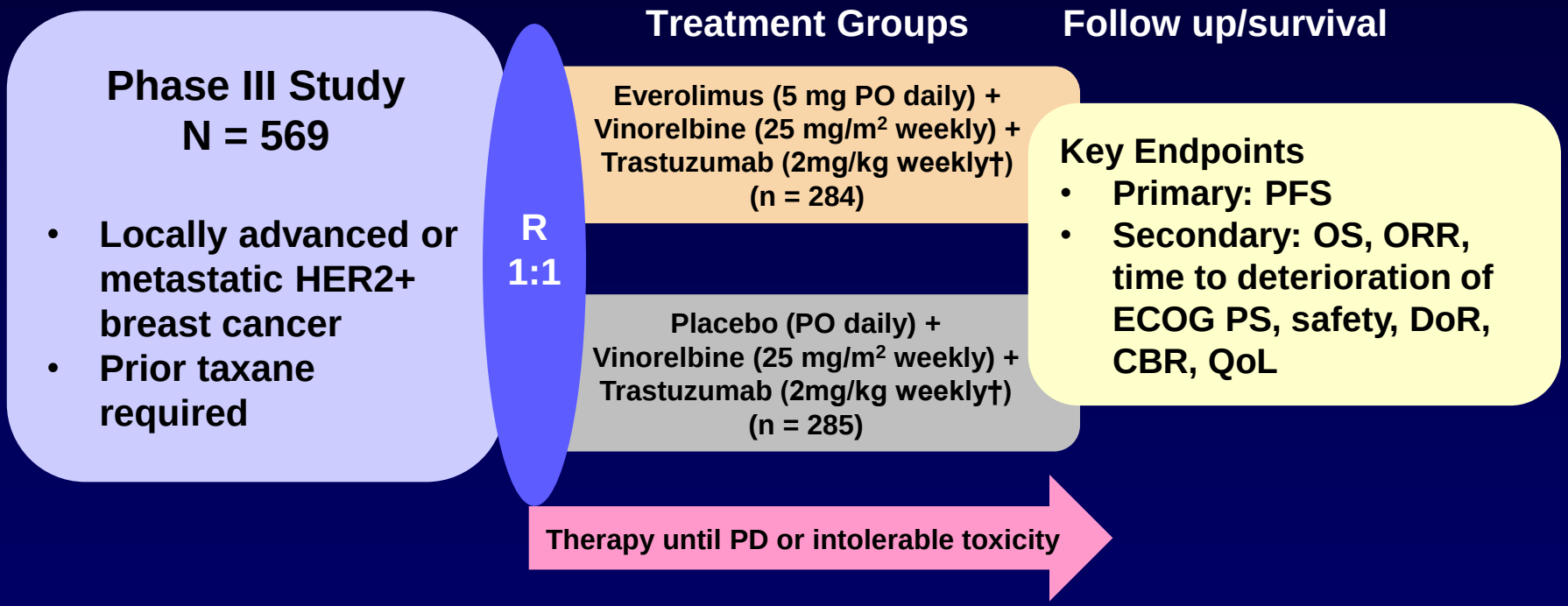
Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Sharon H. Giordano, Sarah Temin, Jeffrey J. Kirshner, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Ana M. Gonzalez-Angulo, Ian Krop, Jennifer Levinson, Nancy U. Lin, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Naren Ramakrishna, and Eric P. Winer

- **If a patient's HER2+ ABC has progressed during or after first-line HER2-targeted therapy, T-DM1 as second-line therapy should be recommended**
- **If a patient finished trastuzumab based adjuvant treatment in ≤12 months before recurrence, second-line HER2-targeted therapy should be recommended**

Giordano SH, et al. *J Clin Oncol*. 2014;32(19):2078-2099.

BOLERO-3 Study Design



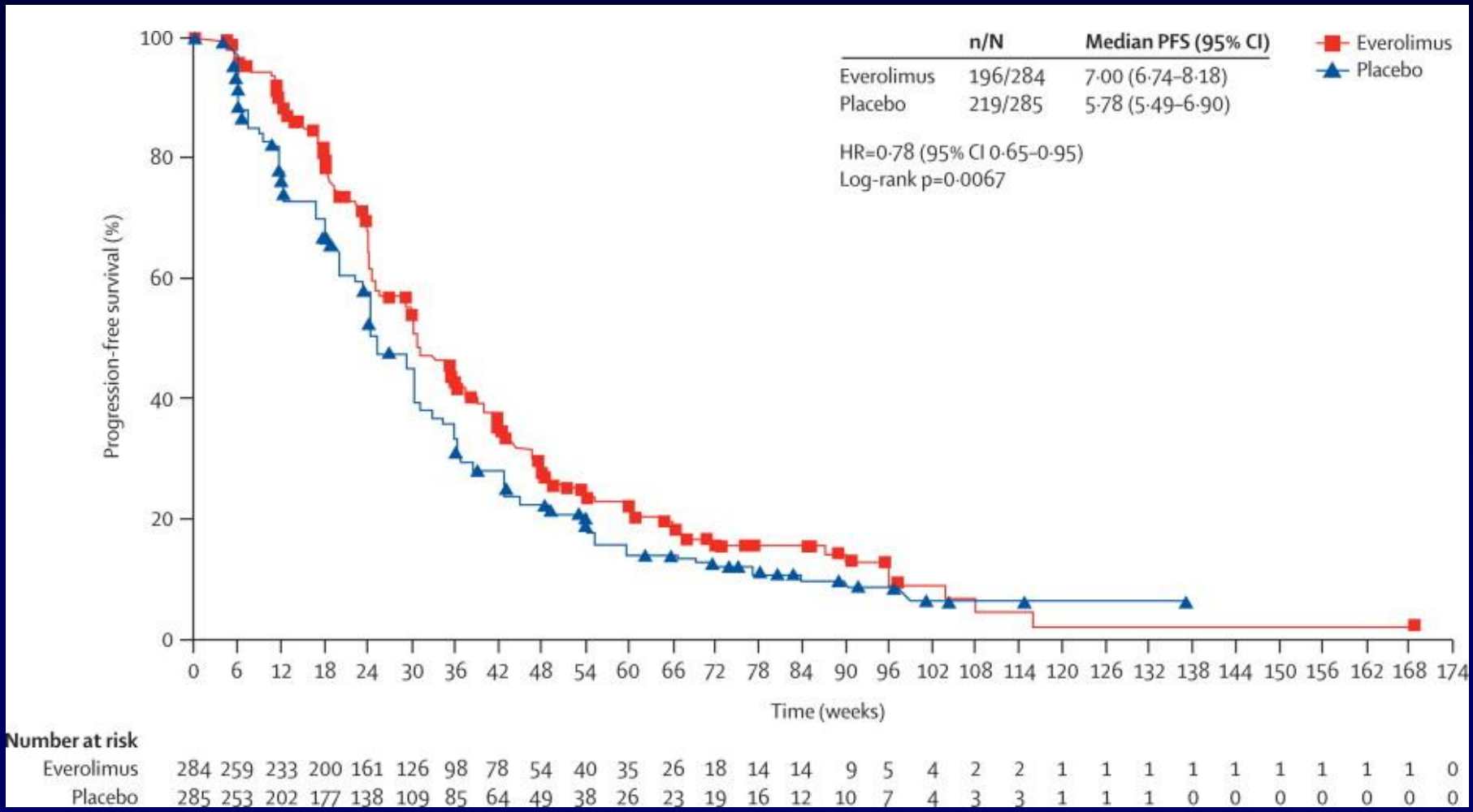
- Stratification by prior lapatinib use (yes/no)

*Resistance to prior trastuzumab required
†Following a 4-mg/kg loading dose on day 1, cycle 1
PO, oral

O'Regan R, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 505.

BOLERO-3

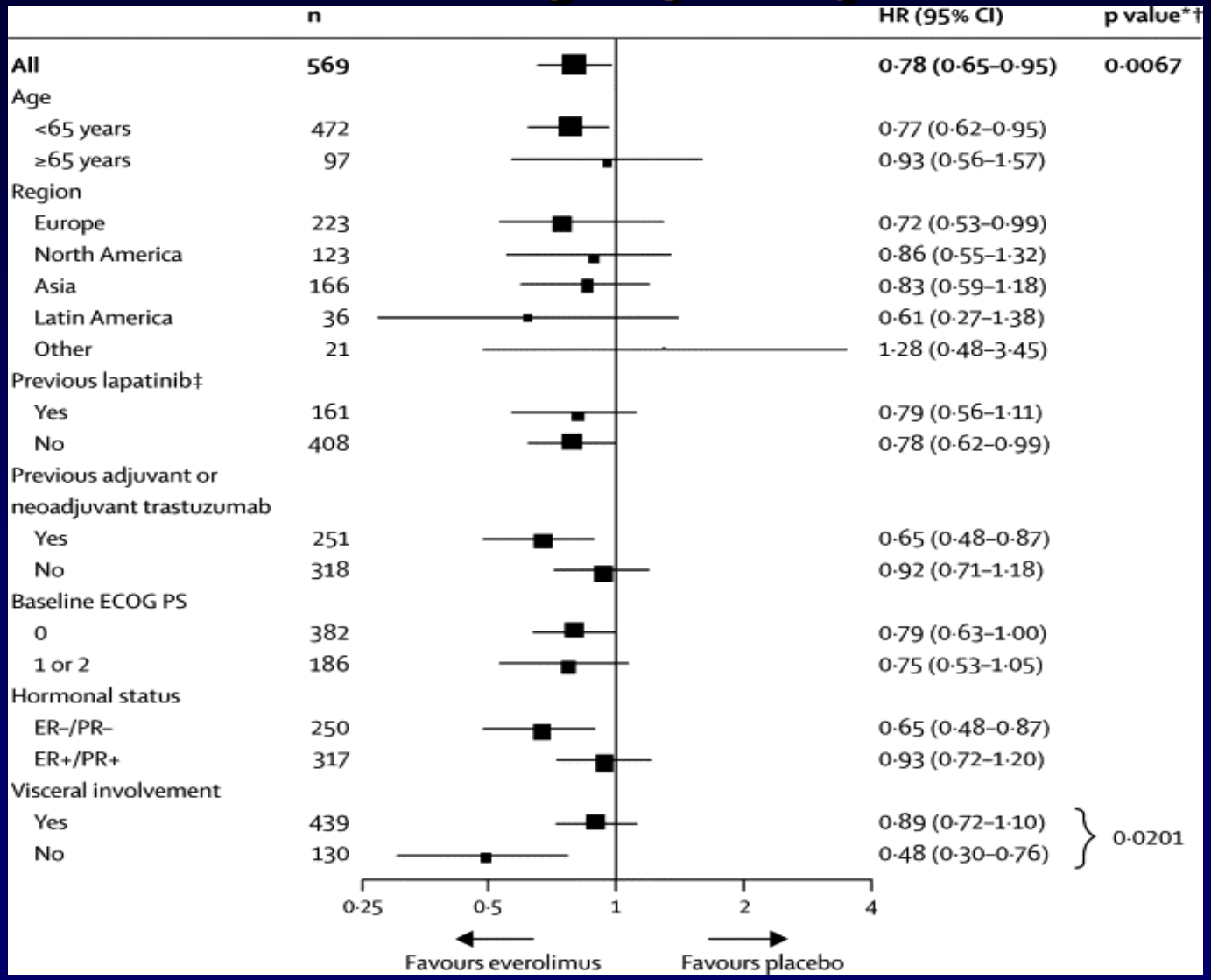
Improved locally assessed PFS with everolimus



Andre F, et al. *Lancet Oncol*. 2014:15(8):e304-e305.

BOLERO-3

PFS Subgroup Analysis



Andre F, et al. *Lancet Oncol*. 2014:15(8):e304-e305.

Current Approach to HER2+ MBC

- First line: Pertuzumab-Trastuzumab-Taxane
  - Future: T-DM1+pertuzumab?
- Second line: T-DM1
- Third line: Many options…optimal timing unknown
  - Lapatinib-trastuzumab
  - Lapatinib-capecitabine
  - Trastuzumab-other chemo

HER2-Targeted Therapies Under Evaluation

- MM-302 (HER2 targeted pegylated liposomal doxorubicin using anti-HER2 antibody)
- Neratinib (irreversible pan-HER inhibitor)
- CDK4/6 inhibitors
- PI3K pathway inhibition + HER2-blockade in HR-/HER2+?
- PI3K pathway inhibition + HER2-blockade + endocrine tx in HR+/HER2+?
- Vaccines

Striking Success:

The Emergence of New Targeted Treatment Strategies for Advanced Breast Cancer