Lo studio BOLERO-1

Quali potranno essere le future ricadute nella pratica clinica?

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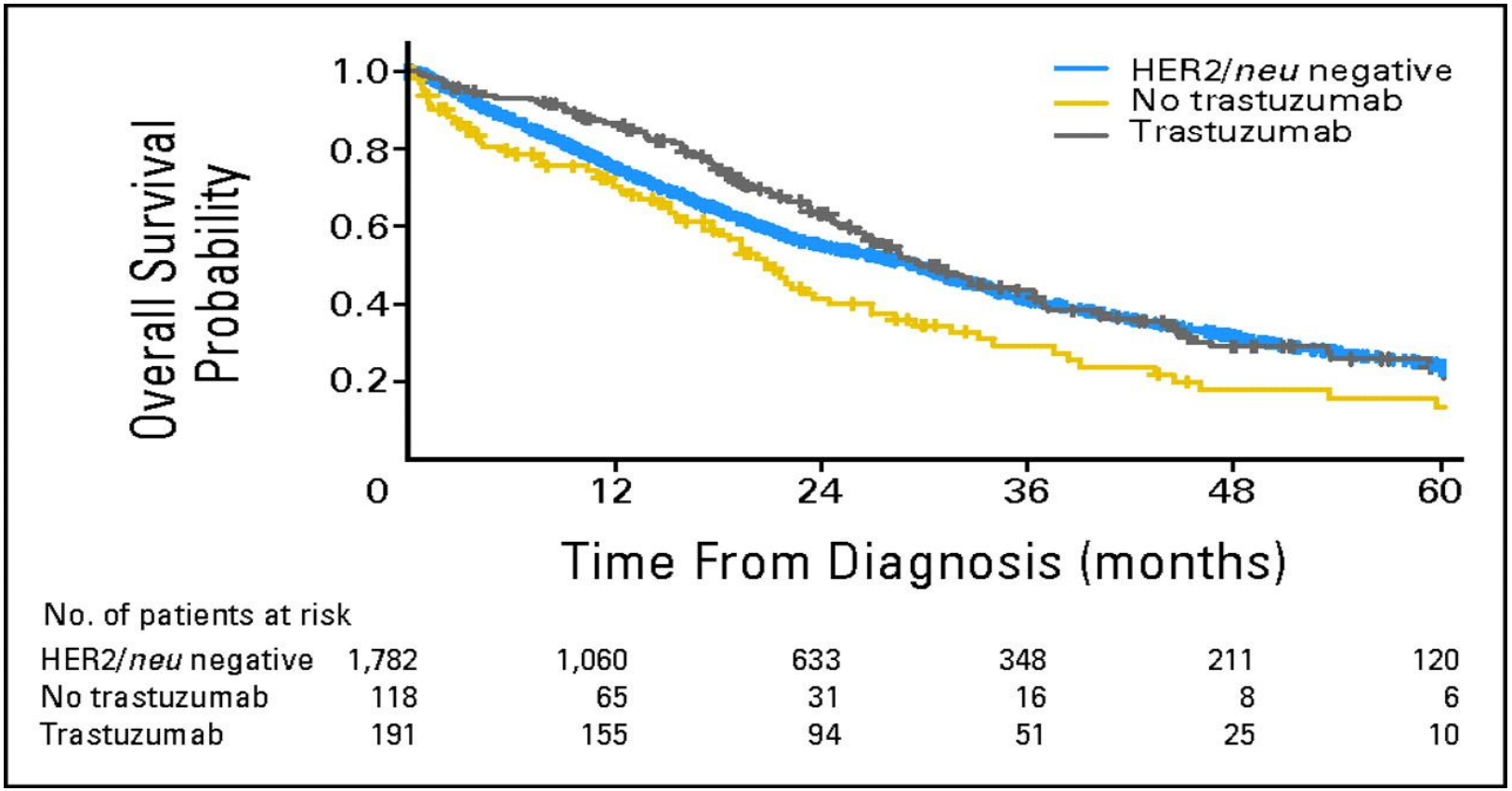
Trento

TRASTUZUMAB

most important breakthrough in the management of BC

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



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

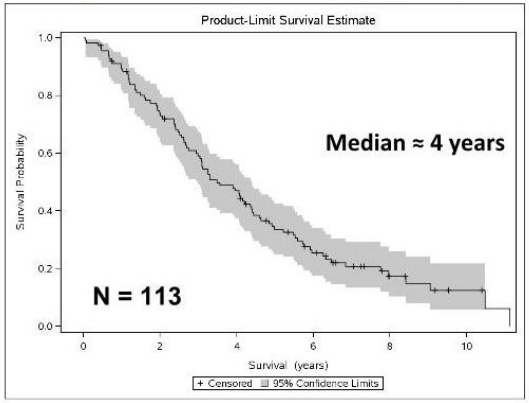
Dawood, S. et al. J Clin Oncol; 28:92-98 2010; Slamon DJ, et al. N Engl J Med. 2001;344:783-792. 2. Marty M, et al. J Clin Oncol. 2005;23:4265-4274.

Need for further optimisation of HER2 + BC treatment

- The natural history of HER2-positive MBC has evolved with trastuzumab-based therapy with median OS after diagnosis of metastases now exceeding 3 years

- The disease has been transformed from a rapidly lethal illness to one in which episodes of disease progression are punctuated by long periods of tumor control

Overall Survival in Patients With Systemic Relapses in Post-Trastuzumab Era



Olsen et al, The Breast 2012

- Despite initial response to anti-HER2 therapy, approximately 50% of patients with HER2-positive MBC experience disease progression within a year, requiring further intervention to prolong life

- Therefore, novel agents tor strategies hat can delay resistance are needed for patients with HER2^{+} advanced breast cancer

Since Then….

A Plethora of gods and demigods….

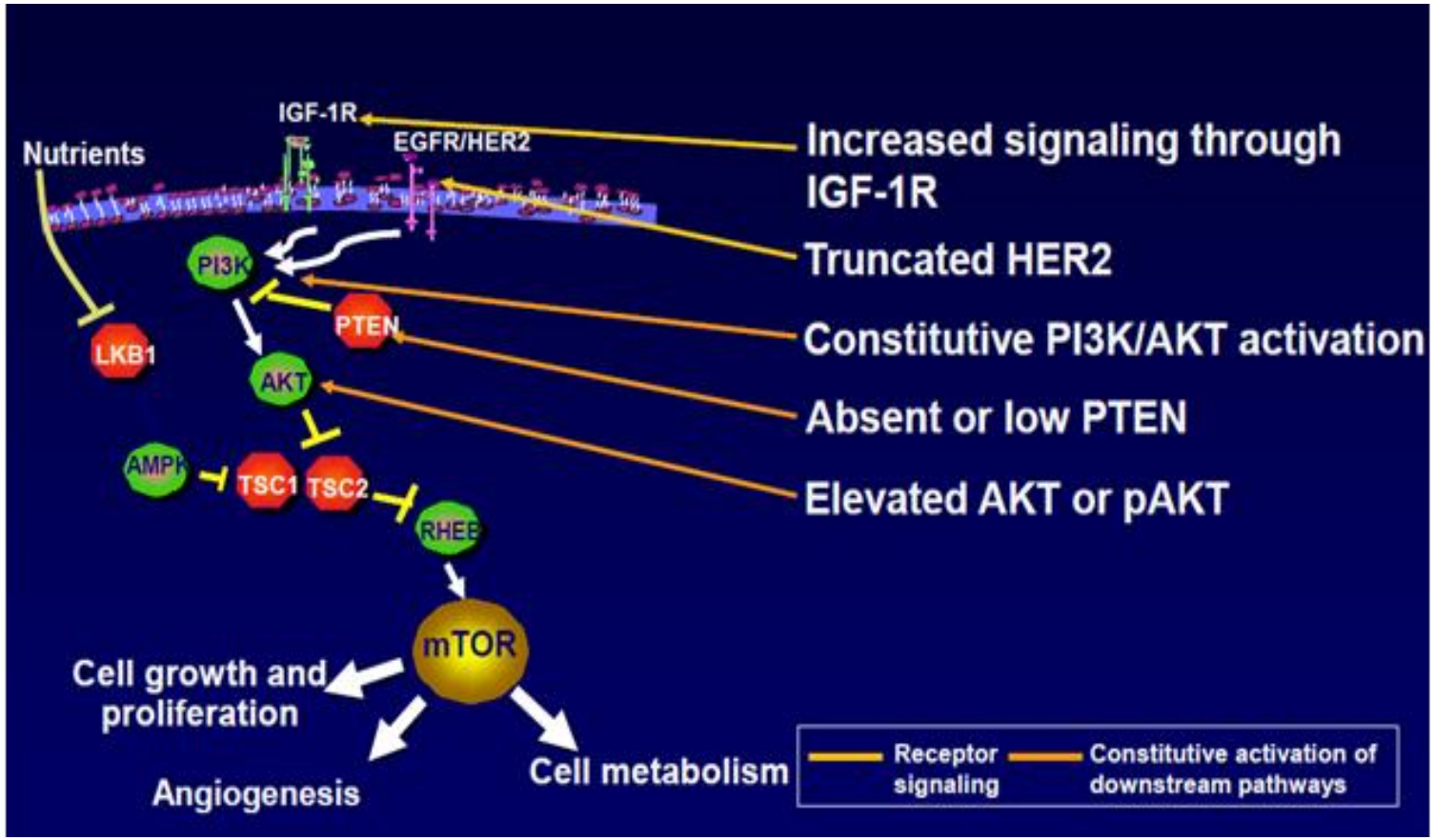
Trastuzumab = Zeus

Lapatininb, Pertuzumab, T-DM1…;

Who wins? Who marries whom? Who remains on the scene?

Who enters the scene first?

Trastuzumab Resistance Mechanisms



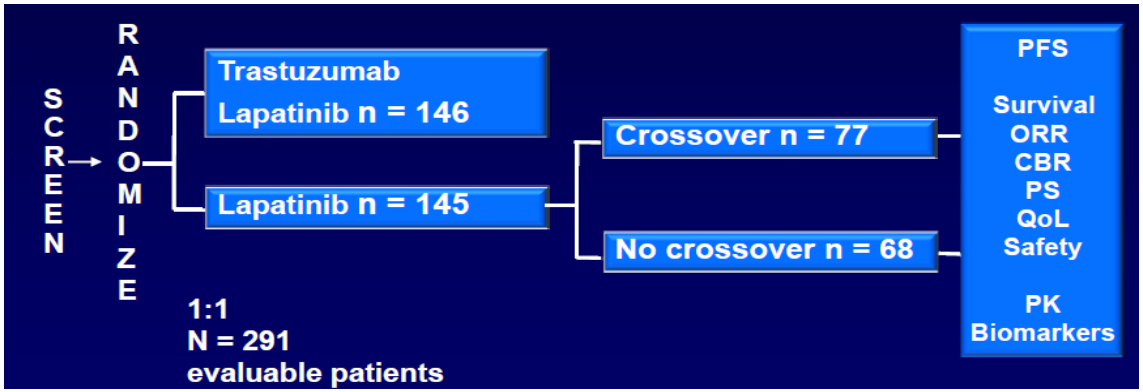
Widakowich C, et al. *Anticancer Agents Med Chem.* 2008,8(5):488-496
Johnston SR. *Clin Cancer Res.* 2005;11(2 suppl):889s-899s.

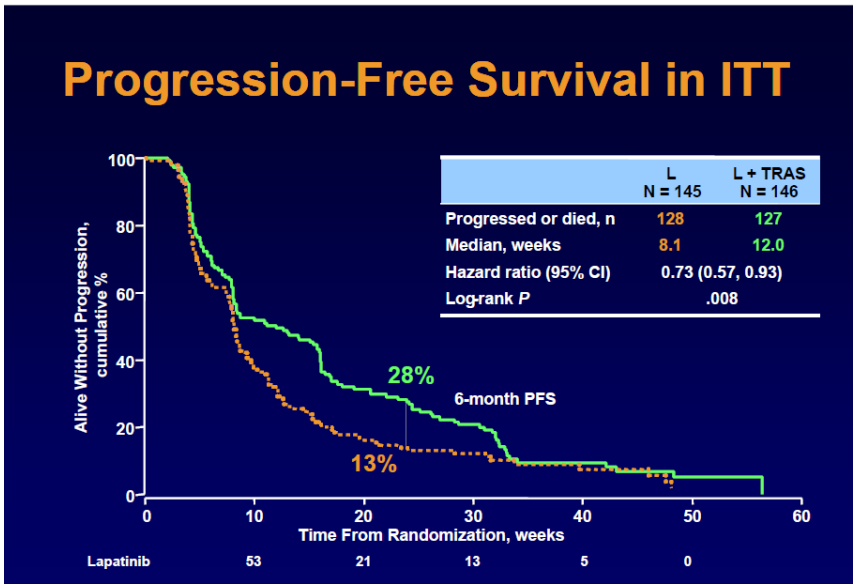
How to improve outcomes and delay/overcome anti-HER2 resistance?

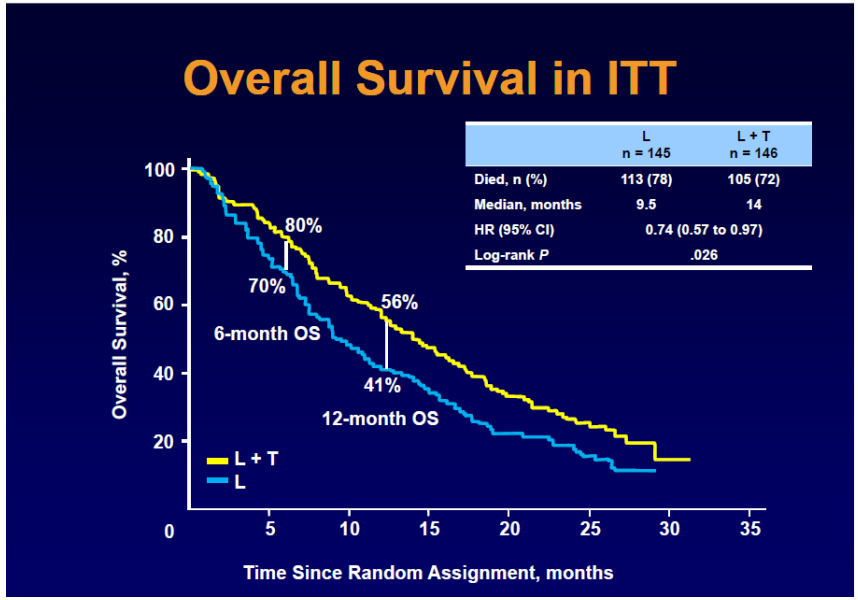
- Using other chemo-combinations (chemo doublet + H)
  - BCIRG 007 (TH vs TCH) ***Valero V et al J Clin Oncol 29:149-156. 2011***
  - Trastuzumab + Pac vs Trastuzumab + Pac + Myocet ***Baselga J et al; Ann Oncol 2014***
  - **NO**
- Using other newer anti-HER2 (lapatinib)
  - NCIC CTG MA.31 (Trastuzumab + Taxane vs Capecitabine + Taxane) **Gelmon** ***KA et al; J Clin Oncol. 2015 Mar 16. pii: JCO.2014.56.9590***
  - **NO**
- Combination with other target agents
  - Tandem (Anastrazole vs Anastrazole + Trastuzumab) ***kaufmann et al; JCO 2008***
  - Letrozole vs Letrozole + lapatinib) ***Johnston et al; JCO 2009***
  - Electra (Letrozole vs Letrozole + Trastuzumab) ***Houber J The Breast, 21 (1) , 27-33, 2012***
  - **Maybe**
- Combination with other antiHER2 (dual blockade)
  - **YES**

Phase III Trial of Lapatinib in Combination With Trastuzumab for Patients With HER2-Positive Trastuzumab-Resistant MBC

Pts with HER2+ MBC progressing on prior trastuzumab-based therapies

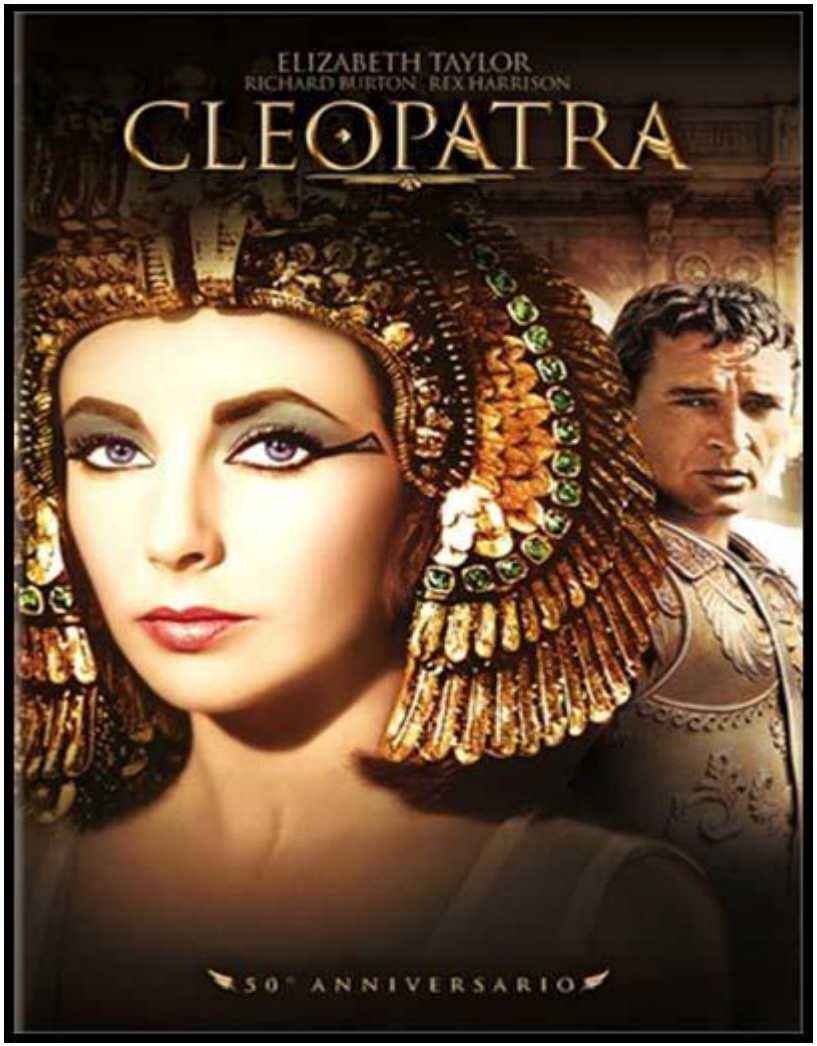






Blackwell K, et al. *J Clin Oncol.* 2010;28(7):1124-1130.

Pertuzumab and Trasuzumab, the best performance in first line….

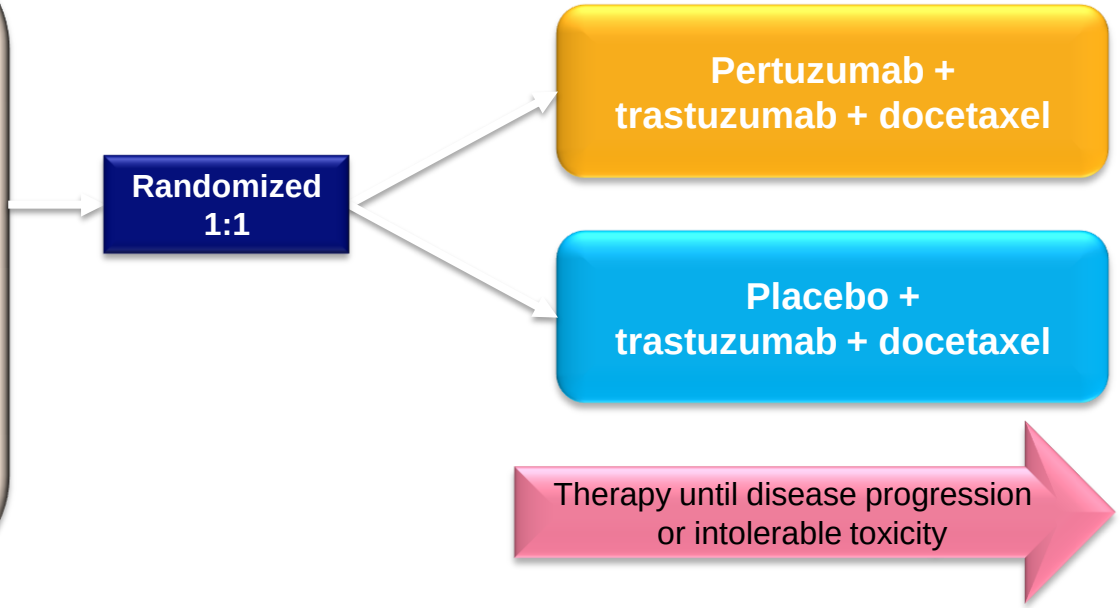


CLEOPATRA: Study Design

- Phase 3 trial in first-line HER2$^+$ advanced breast cancer

N = 808

- Locally recurrent, unresectable, or metastatic HER2$^+$ breast cancer
- Not previously treated for metastatic disease
- (Neo)adjuvant chemotherapy with or without TRAS permitted
- Disease-free ≥ 12 months since (neo)adjuvant treatment
- Measurable or nonmeasurable disease
- ECOG PS of 0 or 1



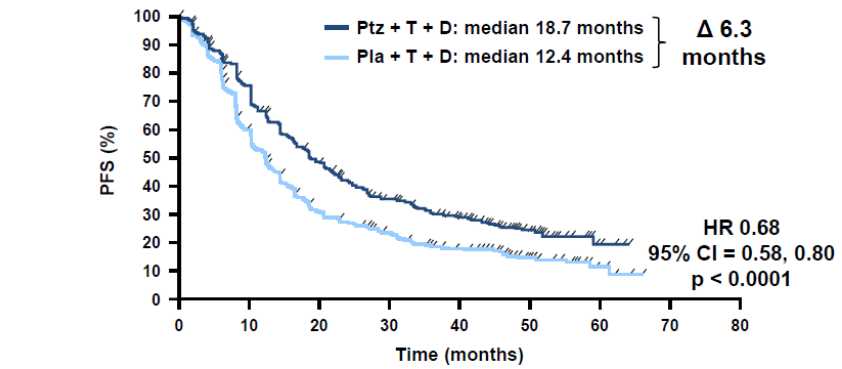
Key endpoints:
Primary: PFS (central)
Secondary: OS, PFS (investigator), ORR, safety

Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119.

CLEOPATRA: Results

Updated PFS

Investigator-Assessed

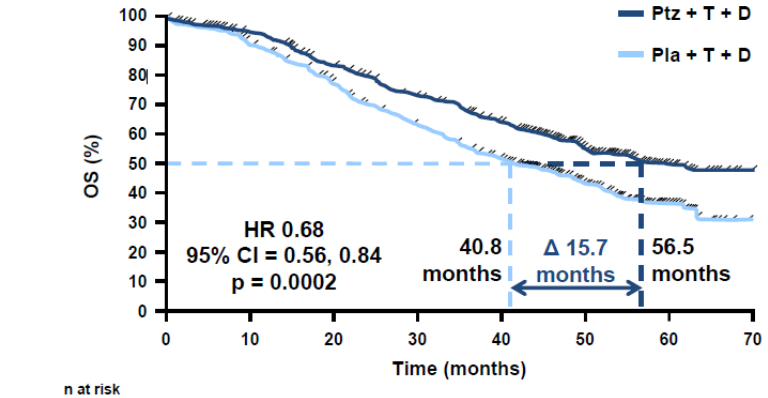


ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

16

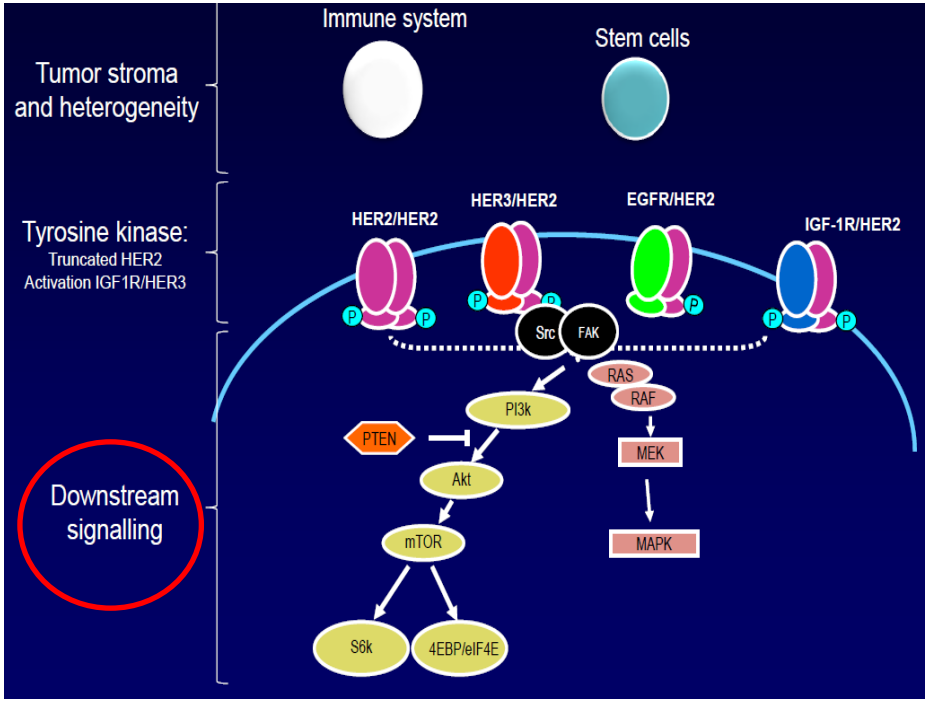
Final OS Analysis

Median follow-up 50 months (range 0–70 months)



ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Alternative target agents to overcome trastuzumab resistance in HER2+ disease

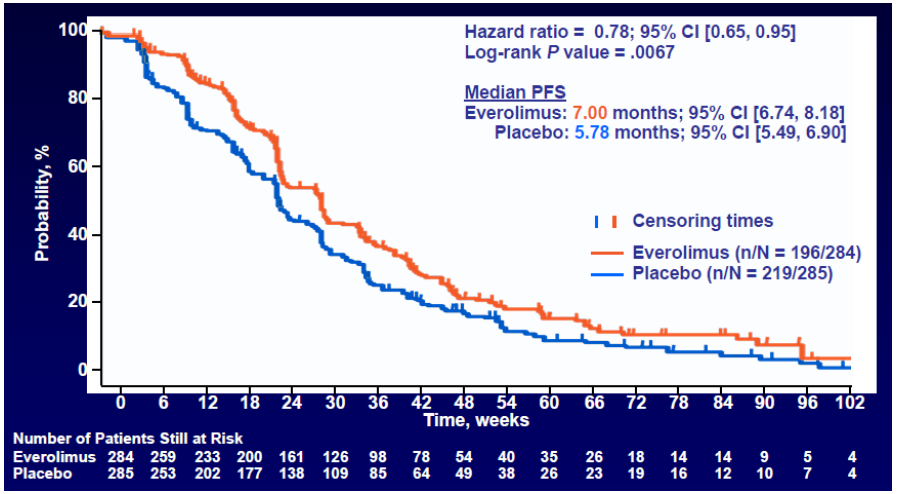


- Most other therapies studied in this setting have focused on continued HER2 inhibition.
- At least in part, resistance to trastuzumab is sustained by altered intracellular signalling
- Aberrant PI3K/AKT/mTOR Pathway Activation May Lead to HER2–Targeted Therapy Resistance
- mTOR is a key intracellular point of convergence for a number of cellular signaling pathways
- mTOR inhibition can sensitize HER2-overexpressing breast cancer to HER2-directed therapy
- To date, Everolimus is the first non-HER2-targeted therapy to address the underlying mechanism of trastuzumab resistance.

Activity of the mTOR Inhibitor Everolimus in HER2$^+$ Breast Cancer

- In preclinical models, mTOR inhibitors synergize with trastuzumab and have shown to cause complete regression of mouse HER2+ mammary tumours (Lu et al, 2007)
- EVE + TRAS and the chemotherapy PAC demonstrated promising activity in patients with HER2$^+$ advanced breast cancer who progressed during prior trastuzumab and taxane therapy (N = 55)
  - Overall response rate, 21.8%; clinical benefit rate, 36.4%
  - Median PFS, 5.5 months
  - Median OS, 18.1 months

- In BOLERO-3, the addition of EVE to TRAS + vinorelbine resulted in
  - Median PFS: 7 vs 5.78 months; *P* = .0067: a 22% reduction in the risk of progression
- Exploratory analysis of biomarkers in the BOLERO-3 trial suggests that the addition of everolimus may be most beneficial in patients with **low PTEN or high pS6 levels** (Jerusalem et al, 2013).



Zhu Y, et al. *Tumour Biol*. 2012;33(5):1349-1362. 2. Lu CH, et al. *Clin Cancer Res*. 2007;13(19):5883-5888. 3. Miller TW, et al. *Clin Cancer Res*. 2009;15(23):7266-7276. 4. Zhang X, et al. *Eur J Cancer*. 48(10):1581-1592. 5. Hurvitz SA, et al. *Breast Cancer Res Treat*. 2013;141(3):437-446. 6. Andre F, et al. *Lancet Oncol*. 2014;15(6):580-591.

Activity of the mTOR Inhibitor Everolimus in HER2^{+} Breast Cancer

- BOLERO-1 was based on the evaluating whether inhibiting mTOR early in metastatic disease will help delay the development of resistance to HER2-targeted therapy

Other divinities to marry to the gods
(Trastuzumab & Co)
of Olympus?

BOLERO-1/TRIO 019: Study 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.

Difficult to beat Cleopatra

Pertuzumab + Trastuzumab + docetaxel in first line

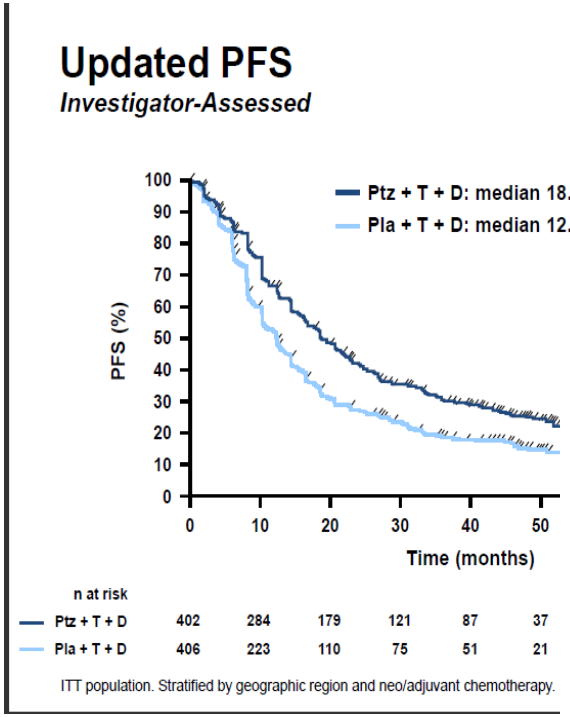
Everolimus + Trastuzumab + Paclitaxel in first line

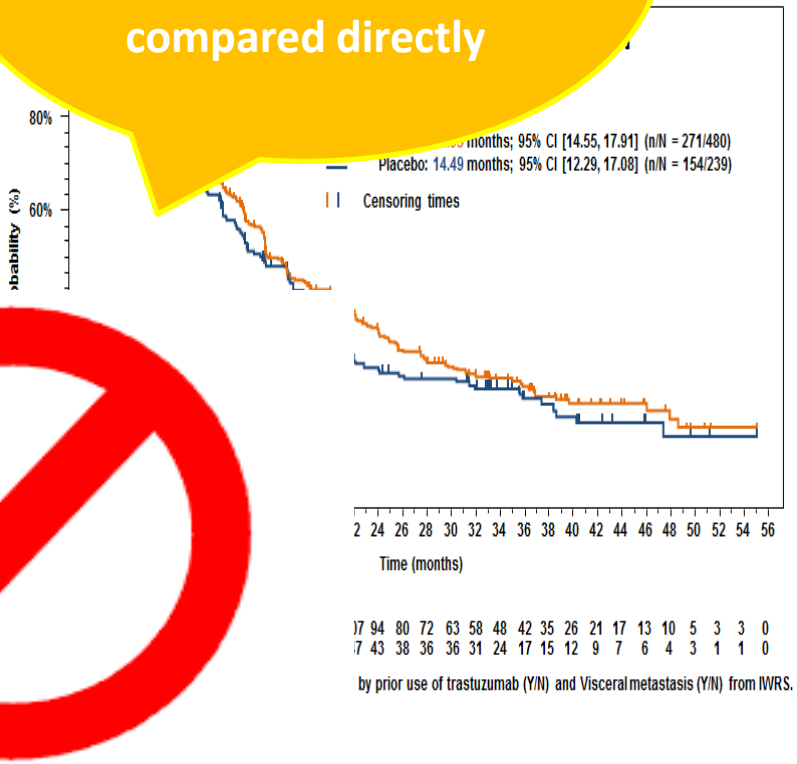
Difficult to beat Cleopatra

CLEOPATRA

Pertuzumab + Trastuzumab + docetaxel in first line

These data are from different trials and should not be compared directly





BOLERO-1 vs. CLEOPATRA: Baseline Characteristics

	BOLERO-1				CLEOPATRA[1]	
	Full Population		HR⁻ subpopulation		Overall population	
Characteristic, %	EVE + TRAS + PAC (N = 480)	PBO + TRAS + PAC (N = 239)	EVE + TRAS + PAC (N = 208)	PBO + TRAS + PAC (N = 103)	PTZ + TRAS + DOC (N = 402)	PBO + TRAS + DOC (N = 406)
Median age, years (range)	54 (23 - 86)	52 (19 - 82)	56 (29 - 85)	53 (24 - 82)	54 (46 - 60)	54 (46 - 61)
Race						
Caucasian	45	41	46	38	61	58
Asian	41	44	41	46	32	33
Other	14	15	13	17	7	9
ECOG performance status						
0	58	62	61	63	68	61
1	42	38	39	37	31	39
Extent of disease at study entry						
Locally advanced disease	7	7	8	8	22 non-visceral	22 non-visceral
Metastatic disease	93	93	92	92	78 visceral	78 visceral
Hormone receptor status						
HR+	57	57	0	0	47	49
HR–	43	43	100	100	53	48
Visceral involvement	70	71	65	70		
Lung	45	43	43	41	NA	NA
Liver	37	46	33	49		
Lung and liver	15	21	14	20		
Bone involvement	44	49	33	45	NA	NA

BOLERO-1 vs. CLEOPATRA: Safety profile (> 25% in either study)

AE/Grade, %	BOLERO-1 EVE + TRAS + PAC (N = 472)			CLEOPATRA[1] PTZ + TRAS + DOC (N = 408)	
	Any	Grade 3	Grade 4	Any	Grade 3/4
Non-hematologic					
Stomatitis	67	13	0	NA	NA
Diarrhea	57	9	0	68	9
Alopecia	47	<1	0	60	0
Rash	40	1	0	37	1
Cough	40	<1	0	NA	NA
Pyrexia	39	2	0	NA	NA
Fatigue	35	5	0	38	2
Epistaxis	33	0	0	NA	NA
Peripheral edema	33	1	0	24	<1
Nausea	33	1	0	44	1
Peripheral neuropathy	29	4	0	NA	NA
Headache	28	1	0	NA	NA
Vomiting	26	1	0	25	1
Decreased appetite	23	1	0	30	2
Mucosal inflammation	NA	NA	NA	27	1
Asthenia	20	2	0	27	2
Hematologic					
Anemia	31	9	1	NA	NA
Neutropenia	38	21	4	53	49

In today, tomorrow and…. day after tomorrow clinical practice

- Everolimus in HER2 + disease not ascended to Olympus….confined to Tarturus??

success with

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HER2-
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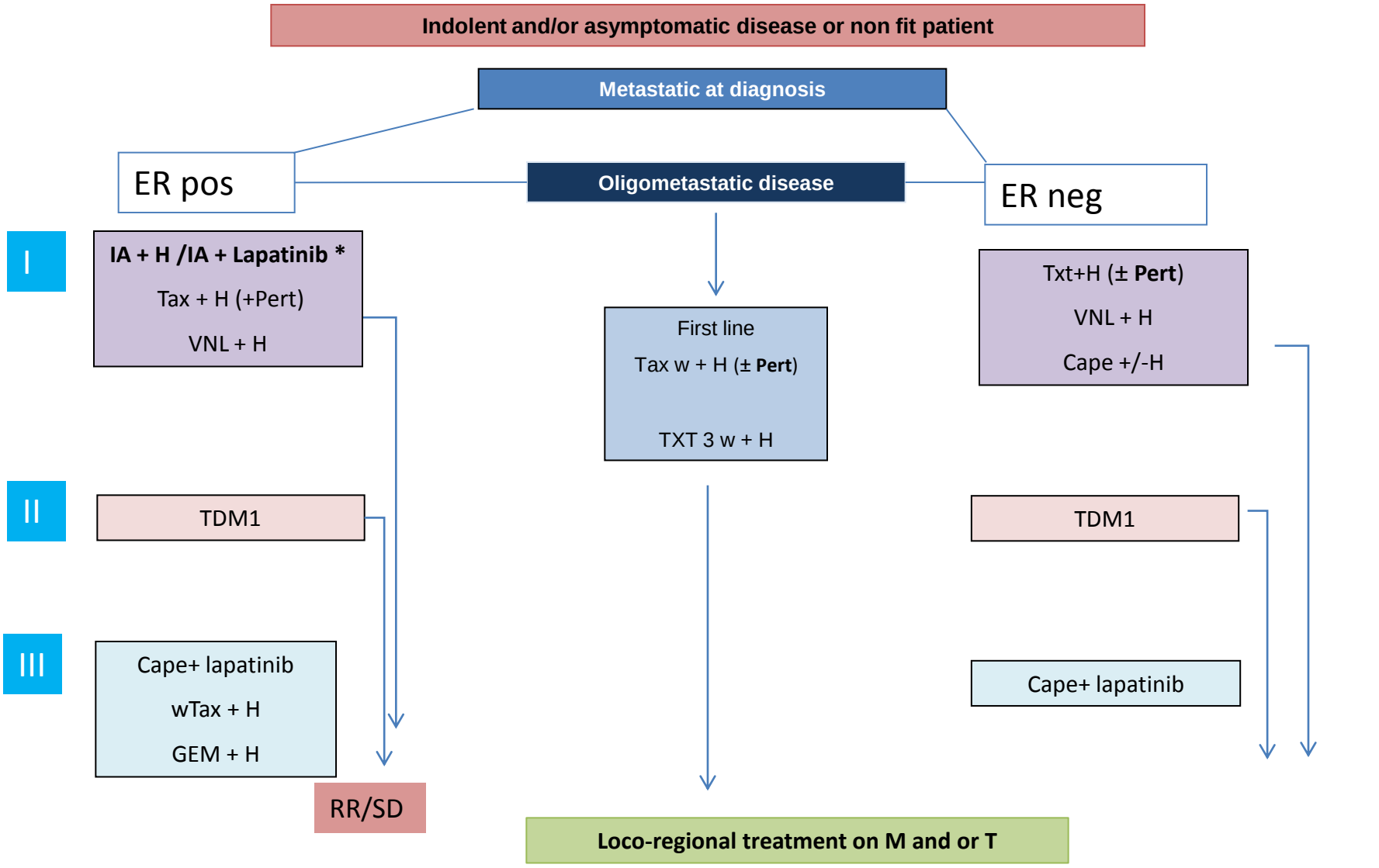
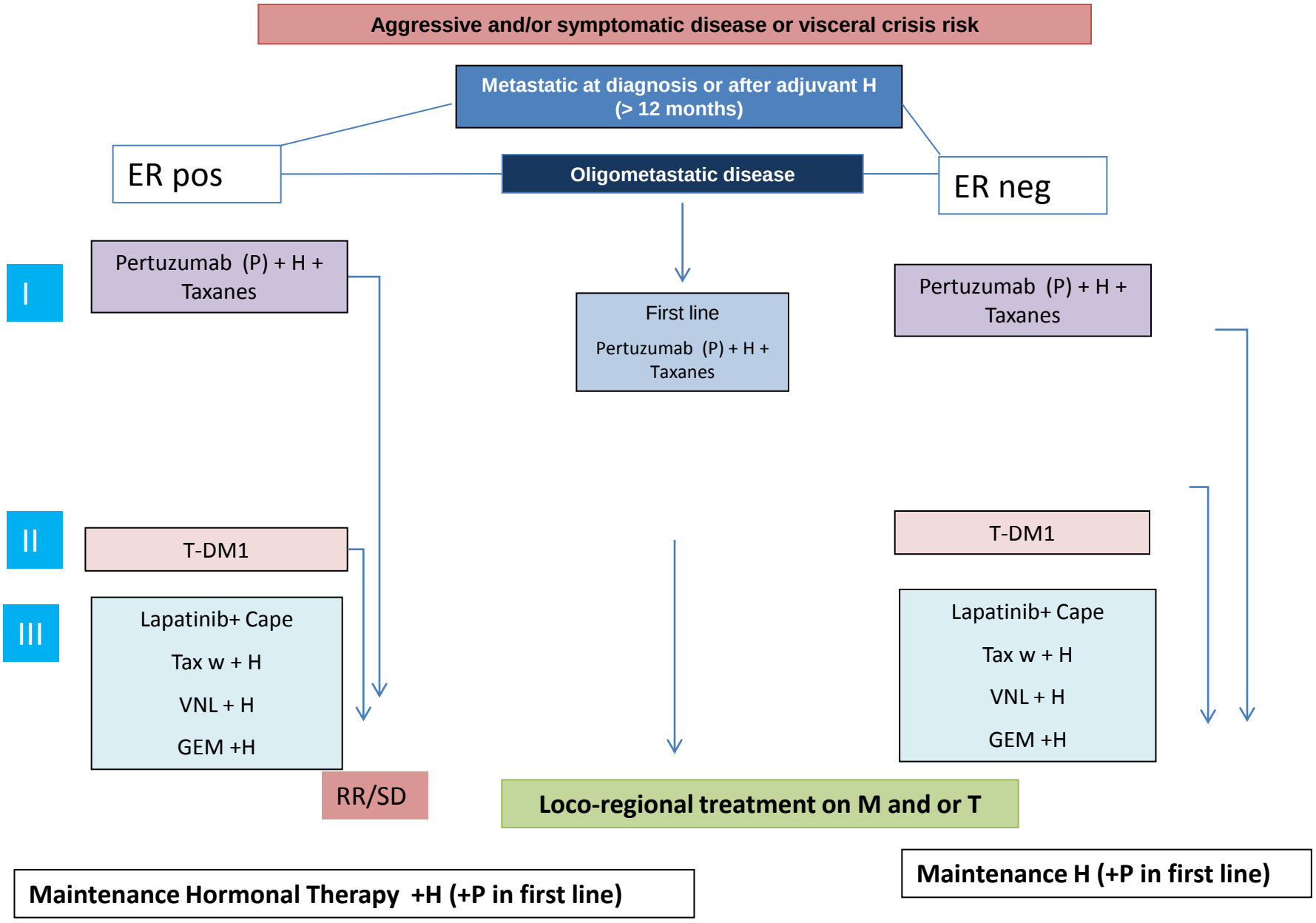
umors

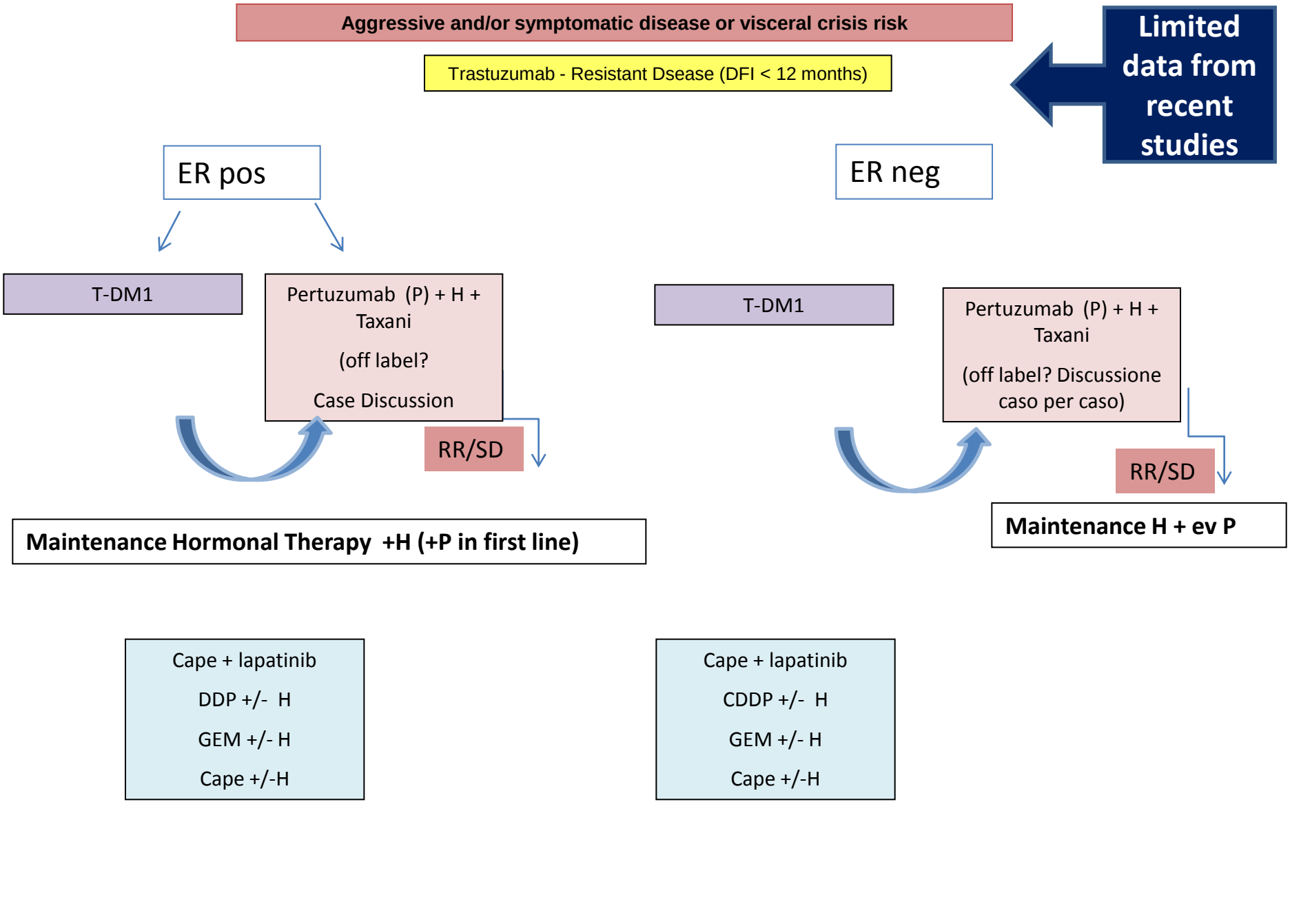
Gianni L; ESMO 2014

HER 2 +MBC



* In selected post-menopausal cases


Aggressive and/or symptomatic disease or visceral crisis risk
Metastatic at diagnosis or after adjuvant H (> 12 months)
ER pos
Oligometastatic disease
ER neg
I
Pertuzumab (P) + H + Taxanes
First line
Pertuzumab (P) + H + Taxanes
Pertuzumab (P) + H + Taxanes
II
T-DM1
T-DM1
III
Lapatinib+ Cape
Tax w + H
VNL + H
GEM +H
Lapatinib+ Cape
Tax w + H
VNL + H
GEM +H
RR/SD
Loco-regional treatment on M and or T
Maintenance Hormonal Therapy +H (+P in first line)
Maintenance H (+P in first line)


Aggressive and/or symptomatic disease or visceral crisis risk
Trastuzumab - Resistant Dsease (DFI < 12 months)
Limited data from recent studies
ER pos
ER neg
T-DM1
Pertuzumab (P) + H + Taxani
(off label?
Case Discussion
RR/SD
T-DM1
Pertuzumab (P) + H + Taxani
(off label? Discussione caso per caso)
RR/SD
Maintenance H + ev P
Maintenance Hormonal Therapy +H (+P in first line)
Cape + lapatinib
DDP +/- H
GEM +/- H
Cape +/-H
Cape + lapatinib
CDDP +/- H
GEM +/- H
Cape +/-H

BOLERO-1/TRIO 019

- The addition of everolimus to trastuzumab plus paclitaxel in the first-line MBC setting did not improve outcomes but did **provide a "signal"** in particular in the hormone receptor–negative subset.
- The data validate preliminary observations from other studies that the treatment effect of everolimus differs based on HR expression in patients with HER2-positive MBC in the absence of hormonal therapy
- In BOLERO-3 clinical benefit appeared more pronounced in the HR^- subpopulation

	PFS Hazard Ratio (95% CI)
HR^- subpopulation	0.65 (0.48-0.87)
HR^+ subpopulation	0.93 (0.72-1.20)

- Similar observations were described in recent phase 3 trials with other HER2-targeted agents, such as lapatinib, pertuzumab (CLEOPATRA), and T-DM1 (EMILIA), and in 7 trials in the neoadjuvant setting

Andre F, et al. *Lancet Oncol*. 2014;15(6):580-591.

A Different Treatment Effect in the HR⁻ Subpopulation

- In HER2⁺ breast cancer, patients with HR⁻ disease may derive greater PFS benefit from targeted therapies, since the absence of a functional hormone receptor may eliminate a potential escape mechanism for HER2-targeted therapies
- Substantial cross-talk exists between HER2 and ER pathways
- Inhibition of HER2 alone increases activation of ER transcription which may:
  - act as an escape mechanism from HER2-directed agents
  - provide alternative signals for the cells to survive
- The combination of everolimus and trastuzumab could be enhanced if the ER is inhibited concomitantly in HR+/HER2+ population

Blackwell KL, et al. *J Clin Oncol*. 2012;30(21):2585-2592.. Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791Nahta R, O'Regan RM. *Breast Cancer Res Treat* 2012; **135:** 39–48.

Considerations and future implications

- Ongoing studies are evaluating the benefits of adding PI3K/mTOR inhibitors to endocrine therapy and HER2-targeted therapy in HER2+, HR+ MBC:
  - **NCT02152943:** Everolimus, letrozole, and trastuzumab in patients with HER2+, ER+ ABC and other solid tumors
  - **NCT01791478**: BYL719 (α-specific PI3K inhibitor), letrozole, and trastuzumab in patients with HER2+, ER+ ABC
- Evaluation of the combination everolimus/trastuzumab/endocrine therapy in HR+/HER2+++ mBC as
  - maintenance strategy post-chemotherapy ?????
  - Concomitantly to chemotherapy????
- Data extrapolated from Tam + Chemo (20 ys old) studies : NOT give them at the same time as chemotherapy.
- Perhaps that is wrong: other endocrine therapies work by different mechanisms
  - Some trials are now looking at adding other endocrine therapies like an aromatase inhibitor with chemotherapy

Considerations and future implications

- The effect of everolimus might have been obscured by the use of paclitaxel, which inhibits tumors with PI3K alterations.
- To study trastuzumab plus everolimus without chemotherapy would be interesting for a better indication of reversing a component of HER2 therapy resistance

- Finally, pertuzumab and trastuzumab emtansine are being studied for adjuvant treatment of breast cancer and for first-line treatment of MBC
- How to use these agents after patients are exposed to pertuzumab/trastuzumab/lapatinib/TDM1 in the adjuvant setting is not known, but efficacy is likely to be lower than what has been reported to date????

Murthy RK et al. Cancer 2014

Future Directions: New Targeted Agents Being Investigated in Clinical Trials in HER-Positive Advanced Breast Cancer