Metastatic breast cancer: Optimal therapy for HER-2 positive disease

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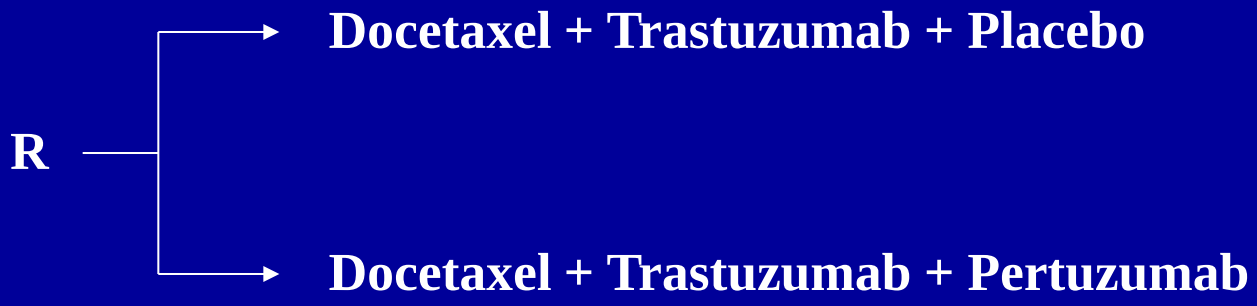
Topics

- First-line therapy
- Endocrine therapy + anti-HER-2 vs. Chemotherapy + anti-HER-2
- Second-line therapy
- Beyond the second line
- Treatment of HER-2 negative (primary) shifted to HER-2 positive (metastases)

Pertuzumab in the first-line treatment: The Cleopatra trial

No. = 808 HER-2+ pts. with advanced disease, no prior therapy for M+



- **no prior (neo) adjuvant therapy = 53.4%**
- **if prior (neo) adjuvant therapy: disease-free interval ≥ 1 yr.**
- **prior (neo) adjuvant trastuzumab = 10.8%**
- **non-visceral disease = 22%**

Baselga J et al, New Engl J Med 366: 109-19, 2012

Docetaxel administration in the Cleopatra trial

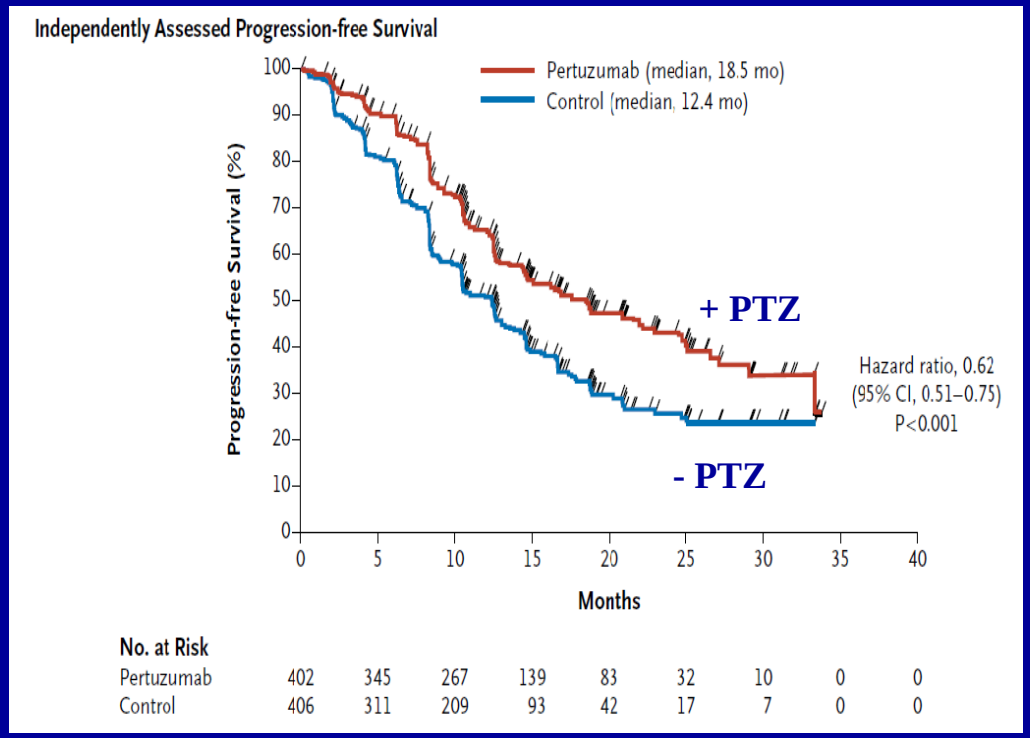
Starting dose = 75 mg/m^2 d1 q 3 wks

	Pertuzumab	Placebo
Escalation to 100 mg/m^2 (% pts)	12	15
Median no. of cycles	8 (6-10)	8 (6-10)
Reduction below 75 mg/m^2 (% pts)	25	23
Delays, discontinuations, reductions in infusion rates (% of cycles)	13	12

Swain SM et al, Lancet Oncol 14: 461-71, 2013

PFS and OS (2nd interim analysis) results in the Cleopatra trial

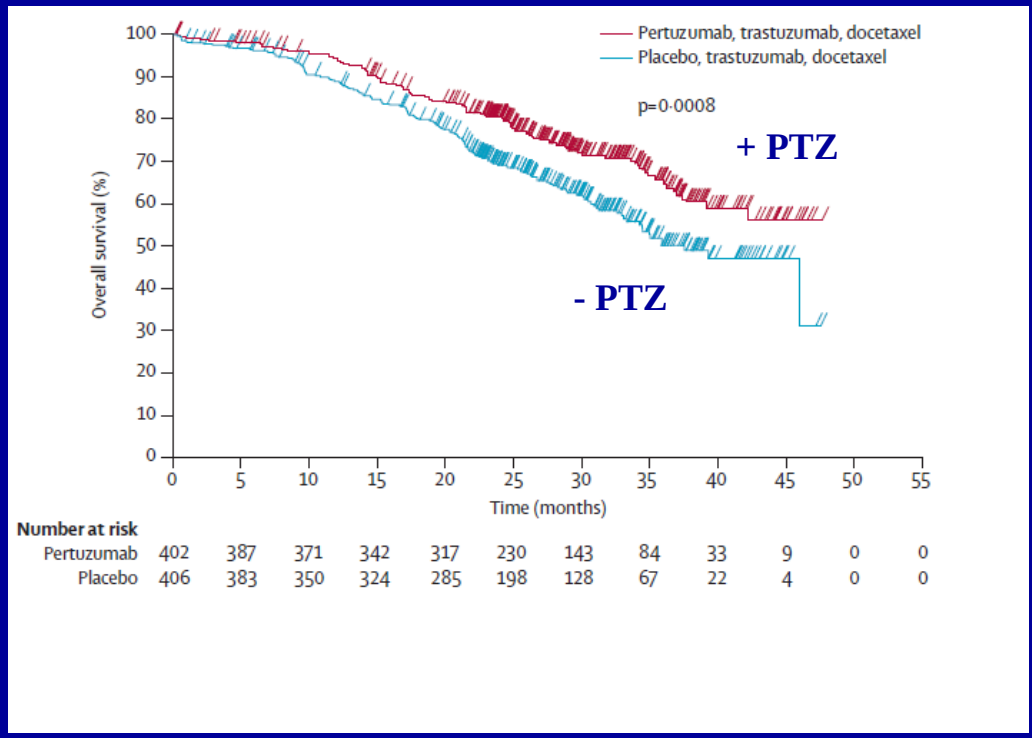
PFS*



HR = 0.62 (0.51 – 0.75)

p < 0.001

OS•



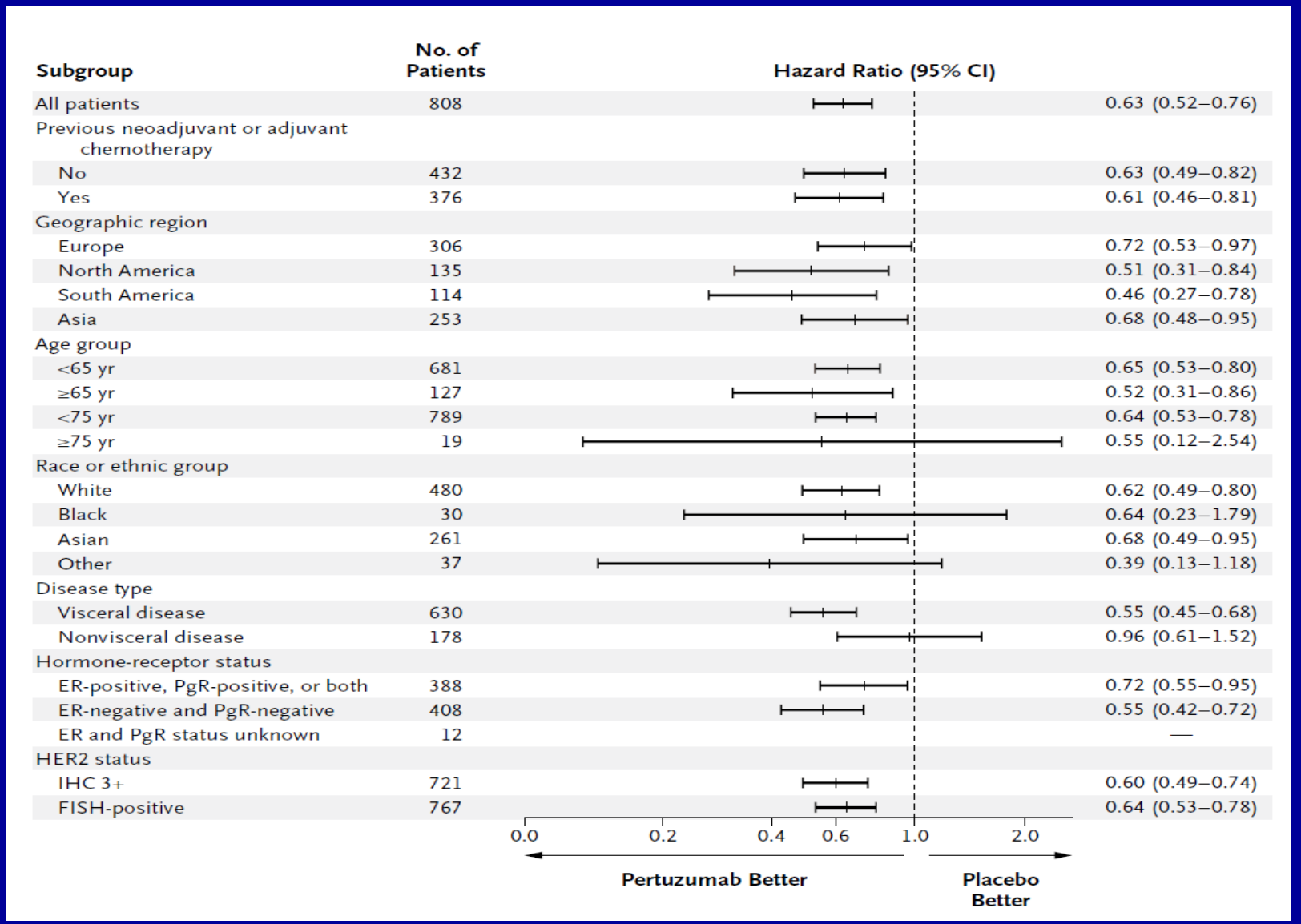
HR = 0.66 (0.52 – 0.84)

p = 0.0008

⚠ **No cross-over allowed**

*** Baselga J et al, New Engl J Med 2012; •Swain SM et al, Lancet Oncol 2013**

PFS results in pre-specified sub-groups



Baselga J et al, New Engl J Med 2012

PFS results by prior trastuzumab treatment

Prior (neo) adjuvant trastuzumab (N=88)	All pts (N = 808)
HR = 0.62 (0.35 – 1.07)	HR = 0.62 (0.51 – 0.75)
	p < 0.001

What's about patients relapsing within 1 year from the end of (neo) adjuvant trastuzumab?

No data available from this trial

Baselga J et al, New Engl J Med 2012

Side-effects in the Cleopatra trial

	Pertuzumab (N = 408)		Placebo (N = 396)	
	G1-G2 %	G3-G4 %	G1-G2 %	G3-G4 %
Diarrhea	59	9	43	5
Rash	36	1	23	1
Mucositis	26	1	19	1
Febrile neutropenia	-	13	-	7

No increase of cardiac dysfunction with Pertuzumab

Swain SM et al, Lancet Oncol 2013

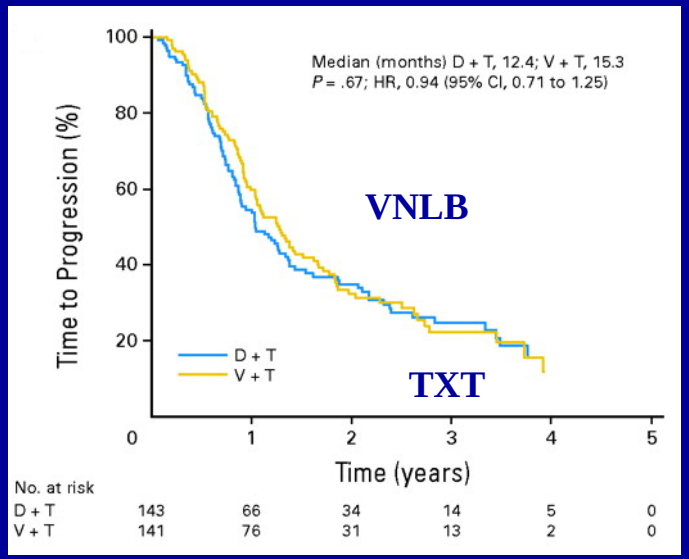
Pertuzumab in the first-line treatment
Conclusions

- **Robust evidence from a Phase III trial**
- **Evidence of activity in the pre-specified subgroups including the cohort pre-treated with (neo) adjuvant trastuzumab**
- **Lack of activity in the non-visceral mets. cohort (play of chance? No. = 178 pts.)**
- **Lack of data in pts. relapsing within 1 year from adjuvant trastuzumab. However, Phase II data support the combination of trastuzumab and pertuzumab in pts. progressing to trastuzumab (Baselga J et al, J Clin Oncol 2010)**
- **Is docetaxel the best partner? If Docetaxel, start at 75 mg/m^2 d1, q 3 wks**

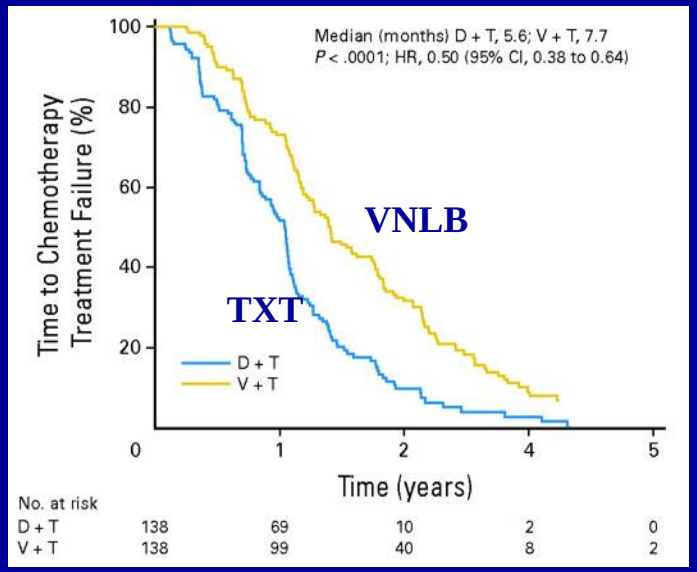
Docetaxel + Trastuzumab vs. Vinorelbine + Trastuzumab: The HERNATA Phase III trial

No. = 284 HER-2+ pts. with advanced disease, no prior chemo for M+

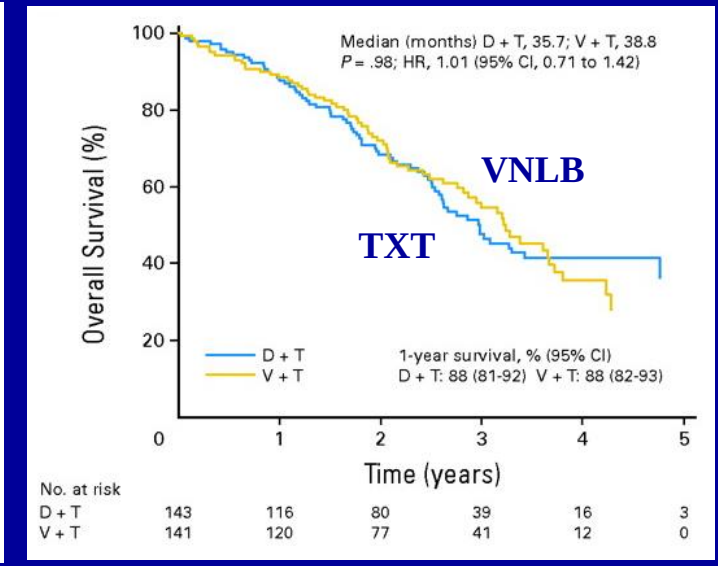
TTP



TTF



OS

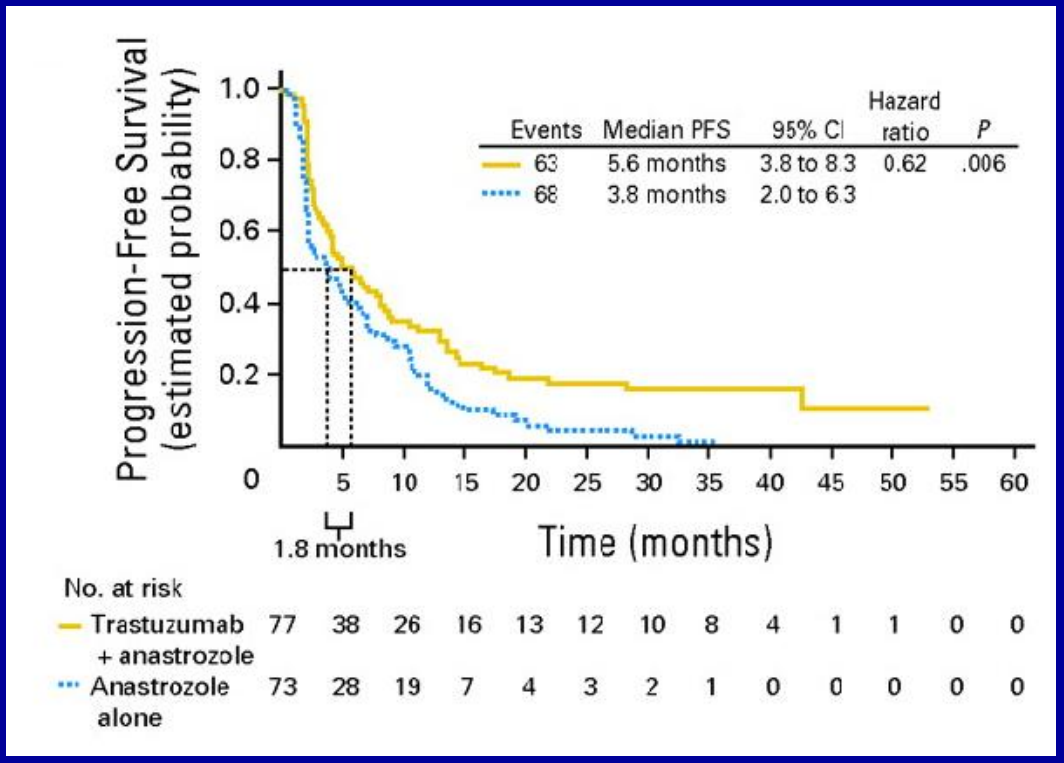


Andersson M et al, J Clin Oncol 29: 264-71, 2010

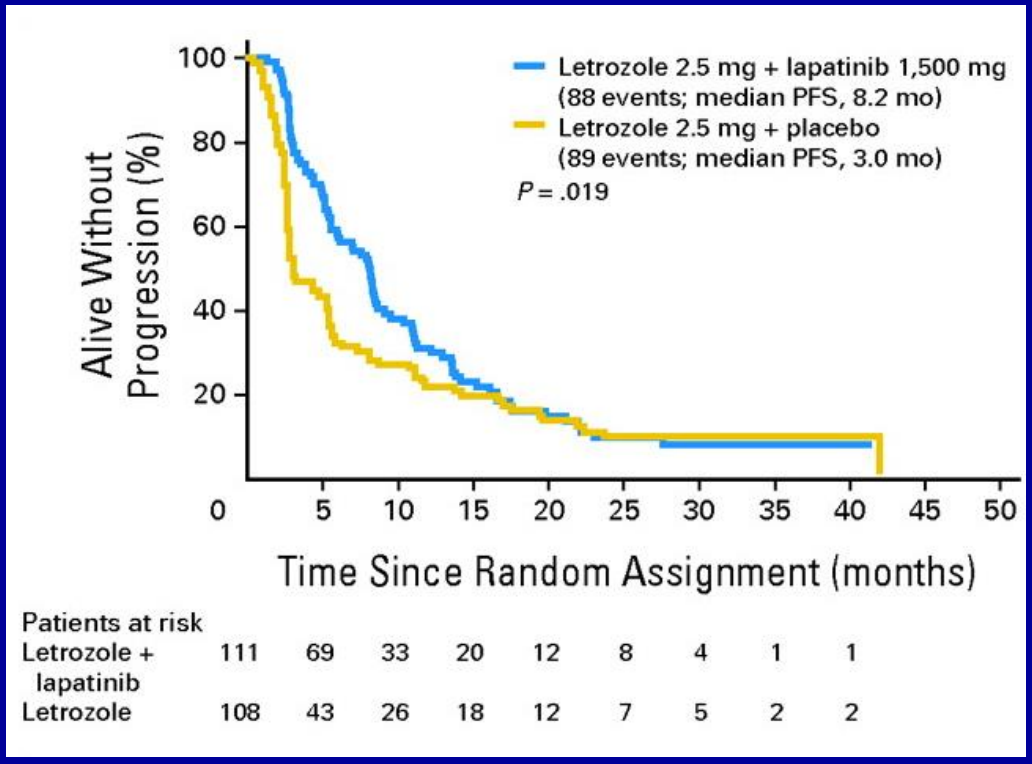
Endocrine therapy vs. the same + anti-HER-2 treatment: two Phase III trials (Progression-free survival results)

HR+/Her 2+ advanced breast cancer, first-line therapy, no prior trastuzumab

No. = 207* → anastrozole
No. = 207* → anastrozole + Trastuzumab



No. = 219** → letrozole + placebo
No. = 219** → letrozole + lapatinib



*Kaufman B et al, J Clin Oncol 27: 5529-37, 2009; **Johnston S et al, J Clin Oncol 27: 5538-46, 2009

Endocrine therapy + anti-HER-2 treatment as a first-line therapy: Conclusions

- Impression of less benefit than chemotherapy + anti-HER-2 (⚠ comparison between different trials)
- Better toxicity profile than chemotherapy + anti-HER-2 (particularly when endocrine therapy plus trastuzumab)
- Option to be considered for patients with clinically non-aggressive disease
- No reasons to hypothesize that different results could be observed if anti-HER-2 in combination with other endocrine therapies (AIs largely used in the adjuvant setting)

Second-line therapy: TDM-1 vs. Capecitabine-Lapatinib
The EMILIA Phase III trial

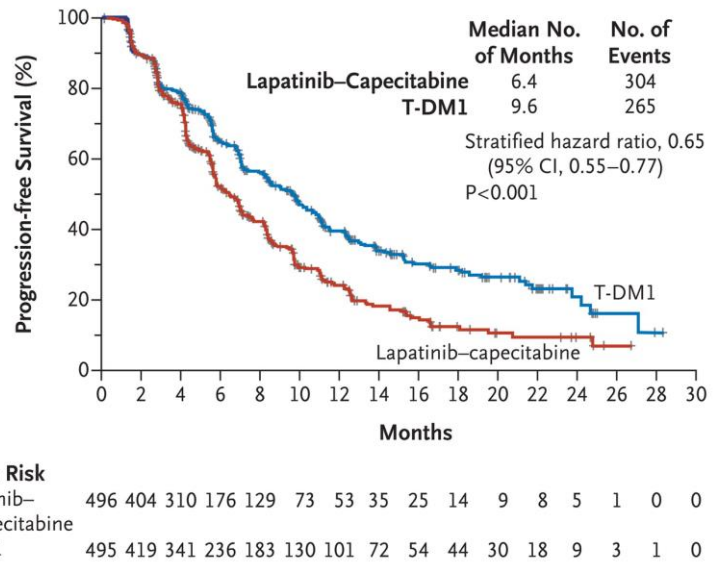
No. = 991 HER-2+ pts. with advanced disease, all pre-treated with taxanes and trastuzumab

- **16% of patients (No. = 155) received the study treatments as a 1° line therapy after a short interval (≤ 6 months) from the end of adjuvant trastuzumab**

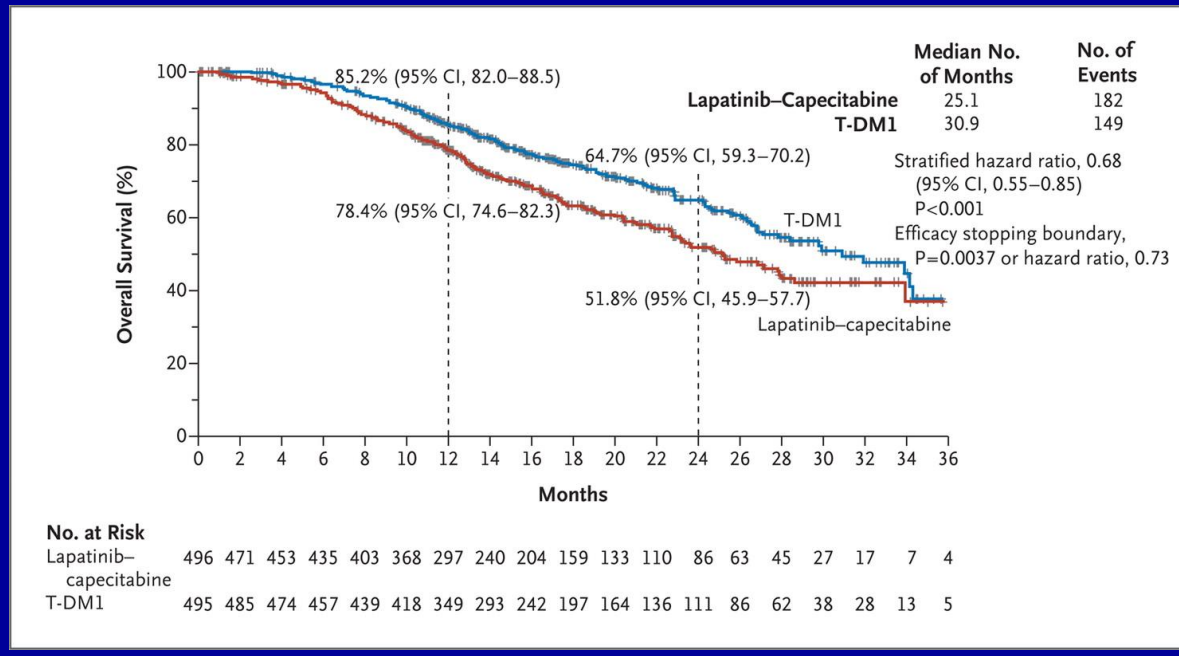
Verma S et al, New Engl J Med 367: 1783-91, 2012

PFS and OS (2nd interim analysis) results in the EMILIA trial

PFS



OS



- No clear interaction between sub-groups and treatment activity
- ⚠ No cross-over

Verma S et al, New Engl J Med 2012

Side-effects in the EMILIA trial

	TDM-1 (No. = 397)		Capecitabine-Lapatinib (No. = 389)	
	Any G %	G3-G4 %	Any G %	G3-G4 %
Diarrhea	23.3	1.6	79.7	20.7
HFS	1.2	-	58	16.4
Vomiting	19	0.8	29.3	4.5
Mucositis	6.7	0.2	19.1	2.3
Elevated ALT	16.9	2.9	8.8	1.4
Elevated AST	22.4	4.3	9.4	0.8
Thrombocytopenia	28	12.9	2.5	0.2

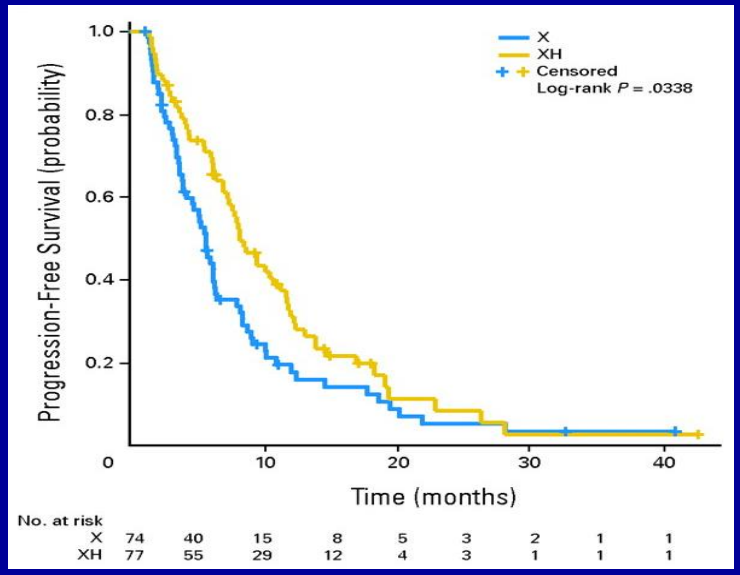
Verma S et al, New Engl J Med 2012

TDM-1 as second-line therapy: Conclusions

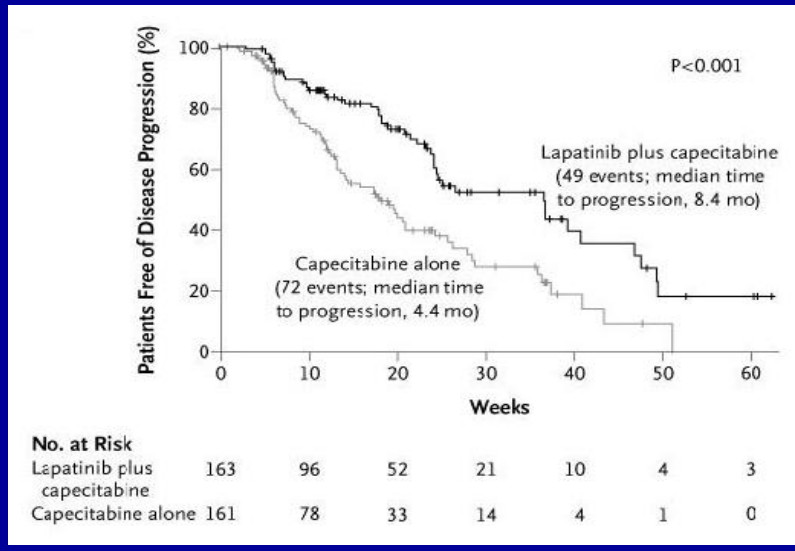
- **Robust evidence from a Phase III trial**
- **No clear interactions between subgroups and treatment activity**
- **As an alternative 1° line therapy option to taxane + trastuzumab + pertuzumab in patients relapsing within 1 year from the end of adjuvant trastuzumab**
- **Lack of data in patients progressig to trastuzumab + pertuzumab**

Beyond the second-line: PFS results from different trials

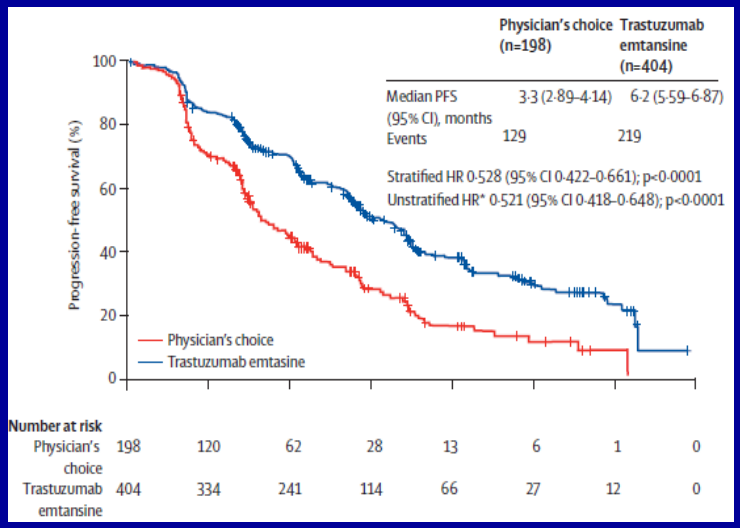
Cape vs. Cape + Trastuzumab*



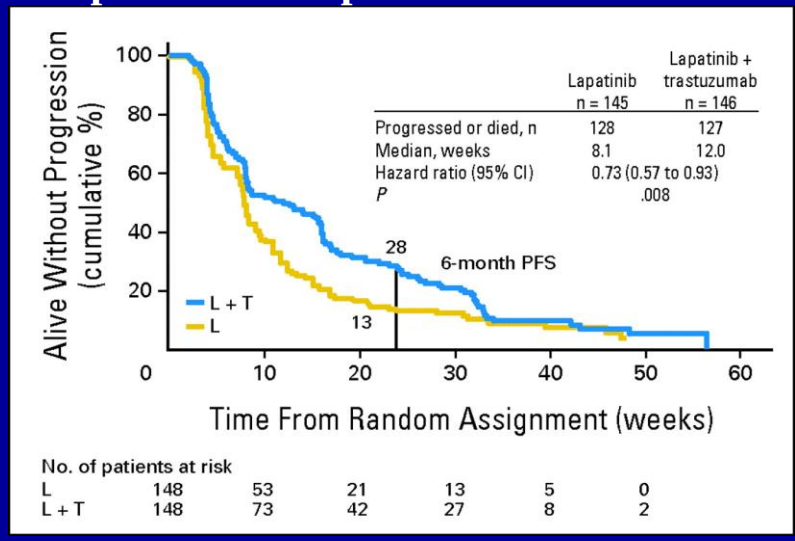
Cape vs. Cape + Lapatinib**



TDM-1 vs. other treatment•



Lapatinib vs. Lapatinib + Trastuzumab••



* von Minckwitz G et al, J Clin Oncol 2009; ** Geyer CE et al, New Engl J Med 2006; • Krop IE et al, Lancet Oncol 2014; •• Blackwell KL et al, J Clin Oncol 2010

Beyond the second-line: summary table of the different trials

Trial	Treatments	No. pts.	Prio anti-HER-2	PFS benefit	OS benefit	% cross-over
EGF**	Cape vs. Cape + L	324	Trast.	Yes	No	No
GBG*	Cape vs. Cape + Trast.	151	Trast.	Yes	No	± 50%
EGF•• 104900	L vs. L + Trast.	296	Trast.	Yes	Yes	52%
Theresa•	TDM-1 vs. other	602	Trast. and L	Yes	Trend	22%

* von Minckwitz G et al, J Clin Oncol 2009; ** Geyer CE et al, New Engl J Med 2006; • Krop IE et al, Lancet Oncol 2014; •• Blackwell KL et al, J Clin Oncol 2010

Beyond the second-line: Conclusions

- **No data for patients pre-treated with the sequence Taxane + Trastuzumab + Pertuzumab ⟶ TDM-1**

- **if prior treatment with the sequence Trastuzumab + Chemo ⟶ Lapatinib + Capecitabine: TDM-1 seems to be the best option**

- **if prior Trastuzumab + Chemo : 4 options**

  -TDM-1

  -Trastuzumab + Lapatinib

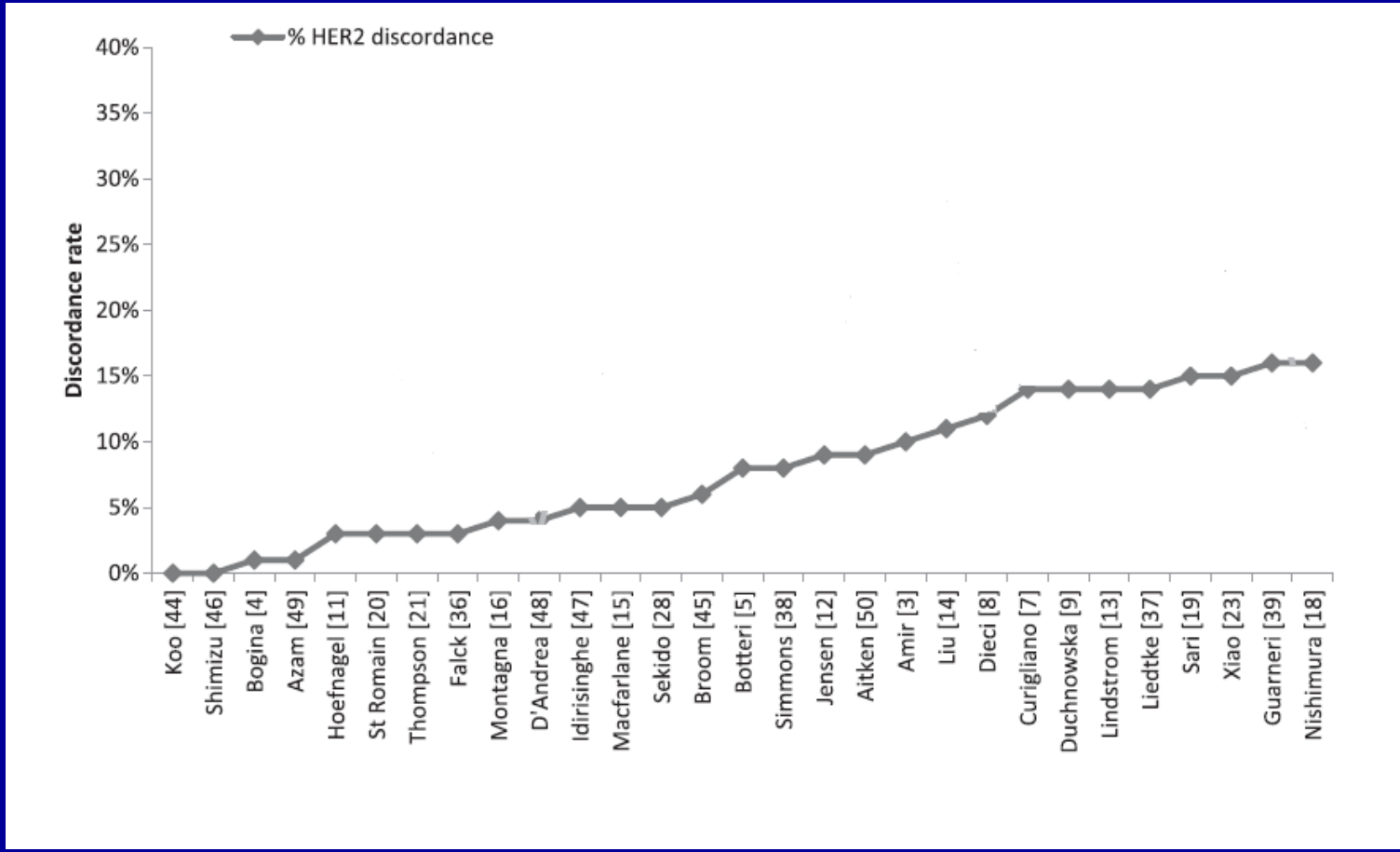
  -Trastuzumab + Capecitabine (or other chemo)

  -Lapatinib + Capecitabine

Treatment of HER-2 negative (primary) shifted to HER-2 positive (metastases)

Size of the problem

Analysis of 29 studies comparing HER-2 status between matched primary and metastatic tumor samples



Turner NH and Di Leo A, Cancer Treat Rev 39:947-57, 2013

Pitfalls for most of the reported studies

- **Most of the studies have a retrospective design and a limited sample size**
- **Importantly, in most of these studies HER-2 status from the primary and the metastatic sites has not been re-assessed at the same time using the same technical procedures**

Impact of a shift in HER-2 status on physician's treatment decisions (evaluable in 14 of the 29 studies)

- if HER-2 loss ⟶ stop anti-HER-2 in 41/69 cases (59%)
- if HER-2 gain ⟶ start anti-HER-2 in 61/80 cases (76%)

Turner NH and Di Leo A, Cancer Treat Rev 2013

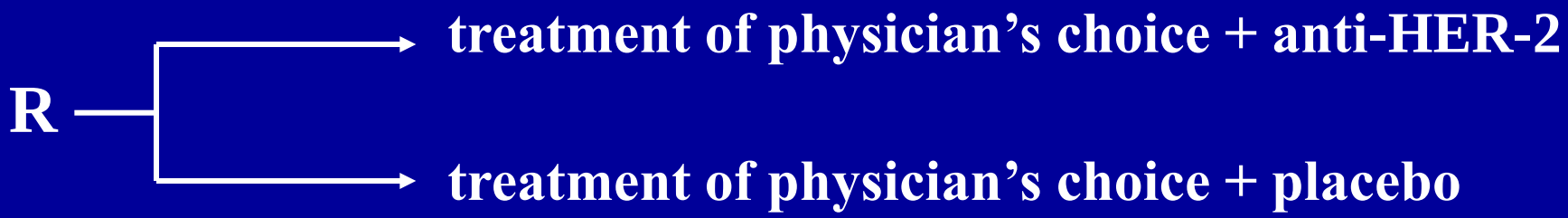
Is the rate of change in physician's treatment decisions the most clinically relevant parameter?

Probably not!

Impact of the selected treatment on clinical outcome is more relevant

The missing evidence….

A randomised trial for pts. with HER-2 negative primary tumor and HER-2 + advanced disease



How much is clinically relevant to biopsy the metastatic site(s)?

- Highly relevant if doubts about the presence of metastatic disease
- Highly relevant if HER-2 status on the primary can not be evaluated properly
- Less relevant to select a treatment in daily practice, particularly in the case active treatment options are available
- Important in the context of research projects

Acknowledgments

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