Systemic therapy for HER2+ Advanced Breast Cancer

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DISCLOSURES

Consultant/Ad Board:

Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Teva

MANAGEMENT OF HER-2 + MBC:

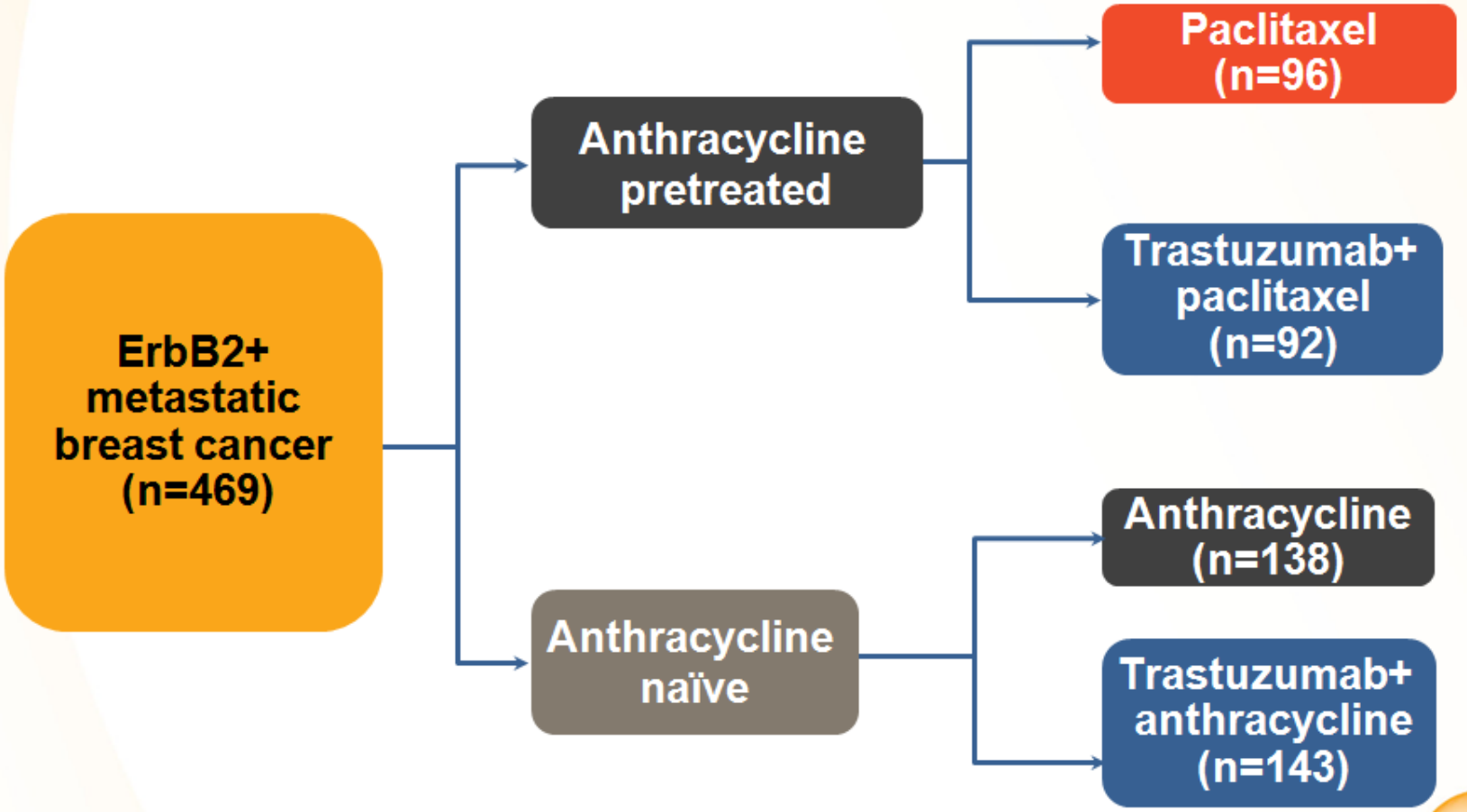
- **ABC: primary or metastatic HER-2 status?**
- **Pivotal trials**
- **Combinations with CT and ET: when & which agents?**
- **Continue HER-2 blockade beyond progression (change of paradigm)**
- **Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?**
- **Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed**
- **Important problem of brain metastases**

HER-2 POSITIVE MBC

Anti-HER-2 therapy should be offered early to all HER-2+ MetaBC patients, except in the presence of contra-indications for use of such therapy (LoE: 1 A). (91%)

Chemotherapy ± trastuzumab in the first-line treatment of ErbB2+ metastatic breast cancer

Study design: H0648g Phase III registration trial

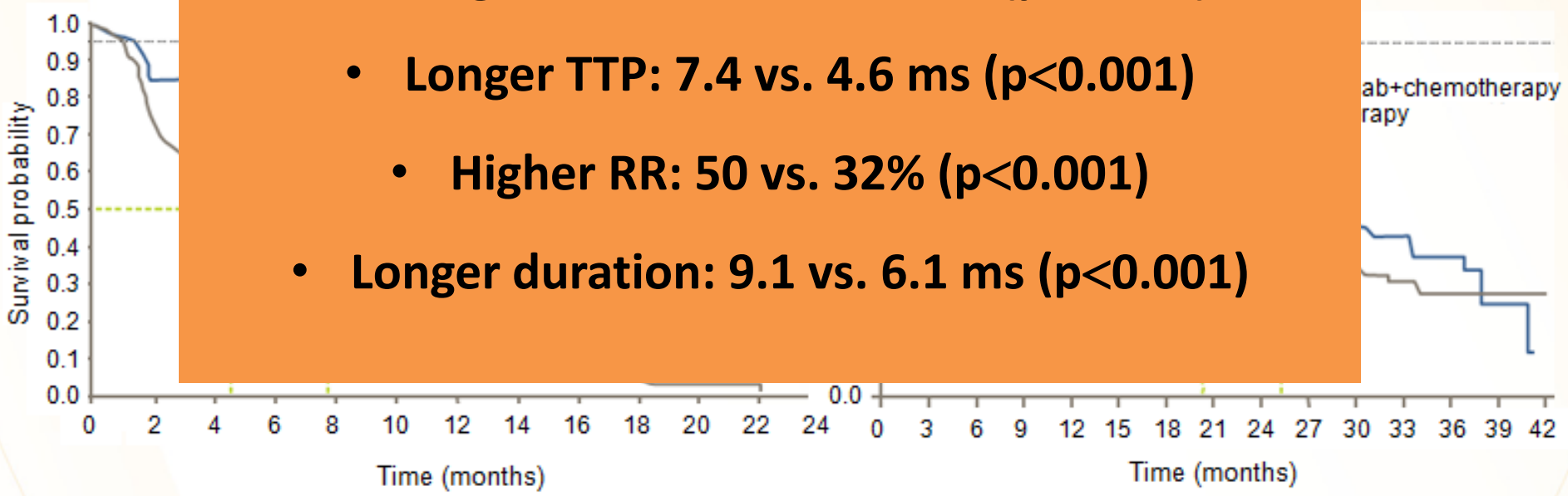


Slamon *et al. N Engl J Med* 2001;344:783–92

Chemotherapy±trastuzumab in the first-line treatment of ErbB2+ metastatic breast cancer

H0648g trial

- **Longer OS: 25.1 vs. 20.3 ms (p=0.046)**
- **Longer TTP: 7.4 vs. 4.6 ms (p<0.001)**
- **Higher RR: 50 vs. 32% (p<0.001)**
- **Longer duration: 9.1 vs. 6.1 ms (p<0.001)**



Slamon *et al. N Engl J Med* 2001;344:783–92

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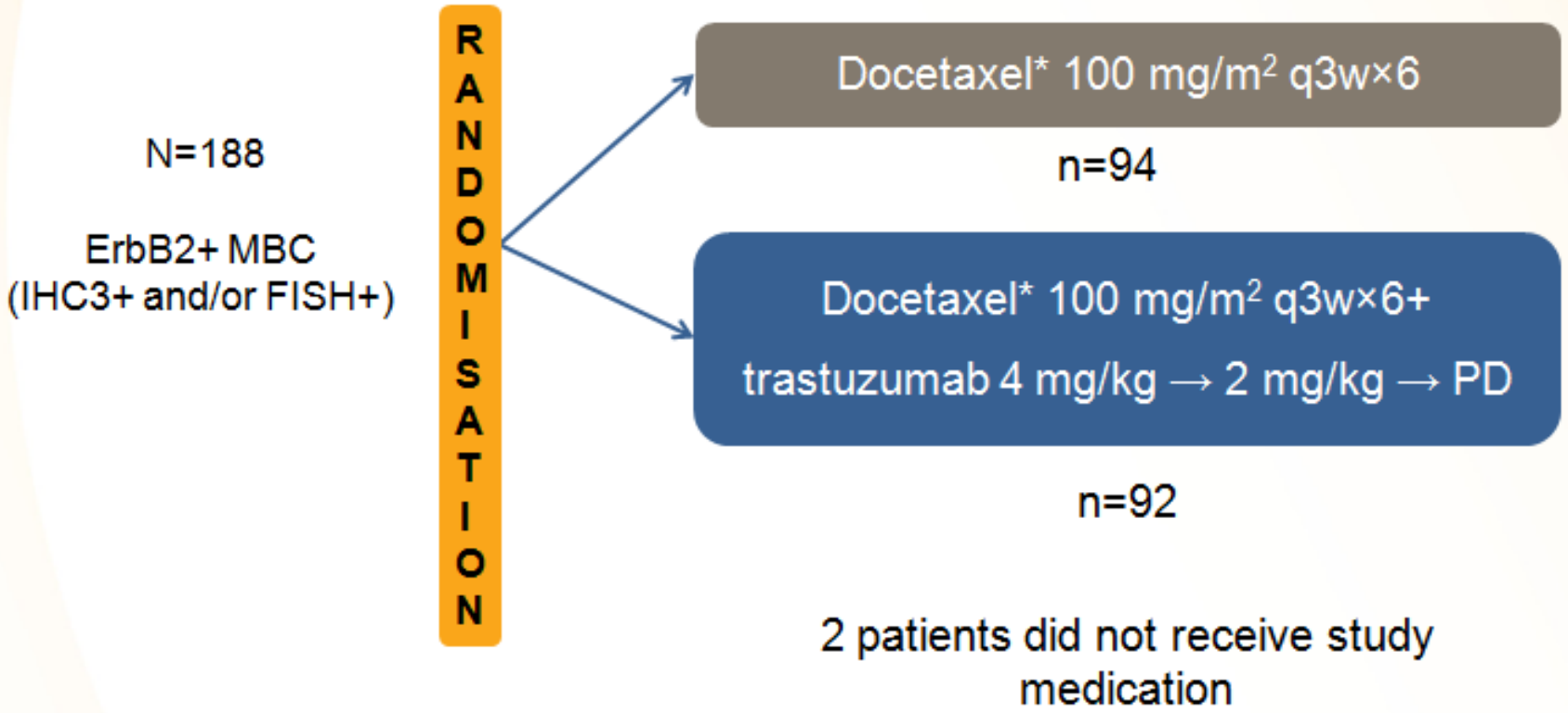
First-line treatment of ErbB2+ metastatic breast cancer with docetaxel±trastuzumab

Study design: M77001 trial (Phase II trial)



*Patients progressing on docetaxel alone could cross over to receive trastuzumab
IHC, immunohistochemistry; FISH, fluorescence *in-situ* hybridisation; MBC, metastatic breast cancer; PD, progressive disease; q, every

Marty *et al. J Clin Oncol* 2005;23:4265–74

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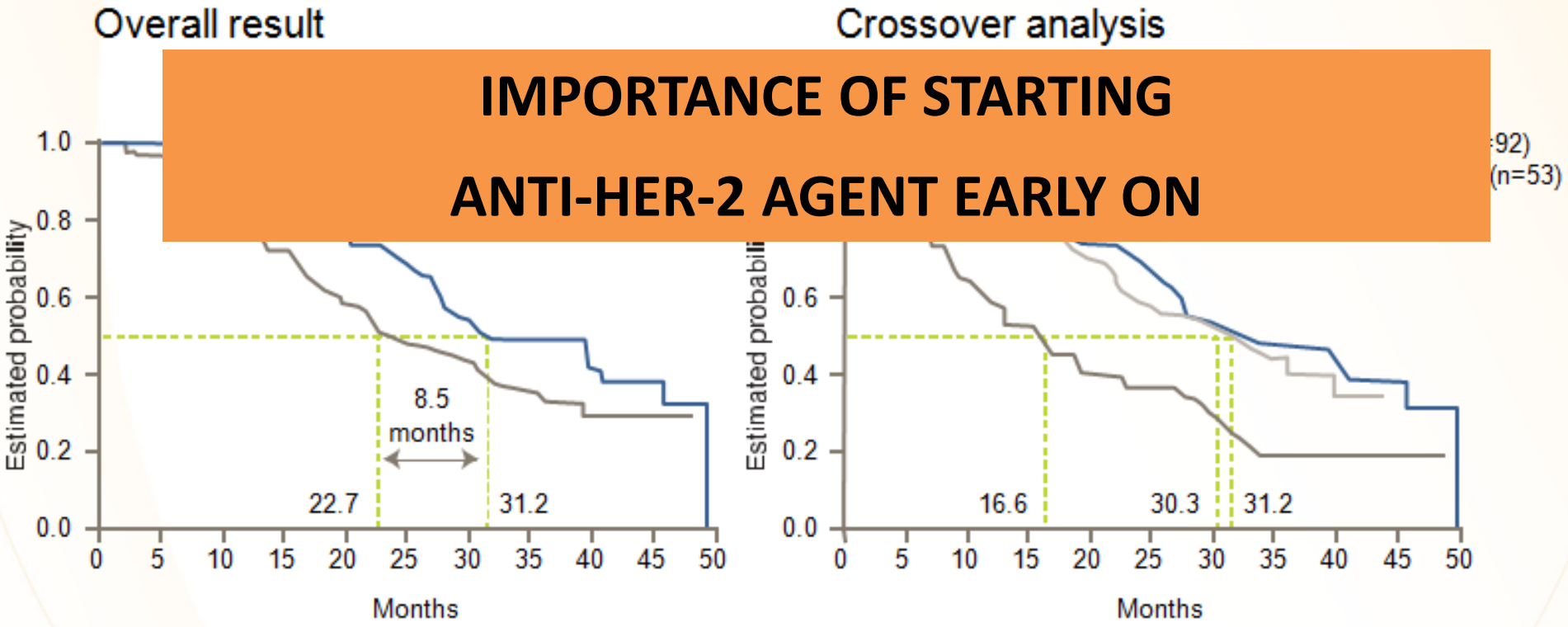
First-line treatment of ErbB2+ metastatic breast cancer with docetaxel±trastuzumab

Overall survival: M77001 trial

IMPORTANCE OF STARTING

ANTI-HER-2 AGENT EARLY ON



Median values are shown

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ER + / HER-2+ MBC

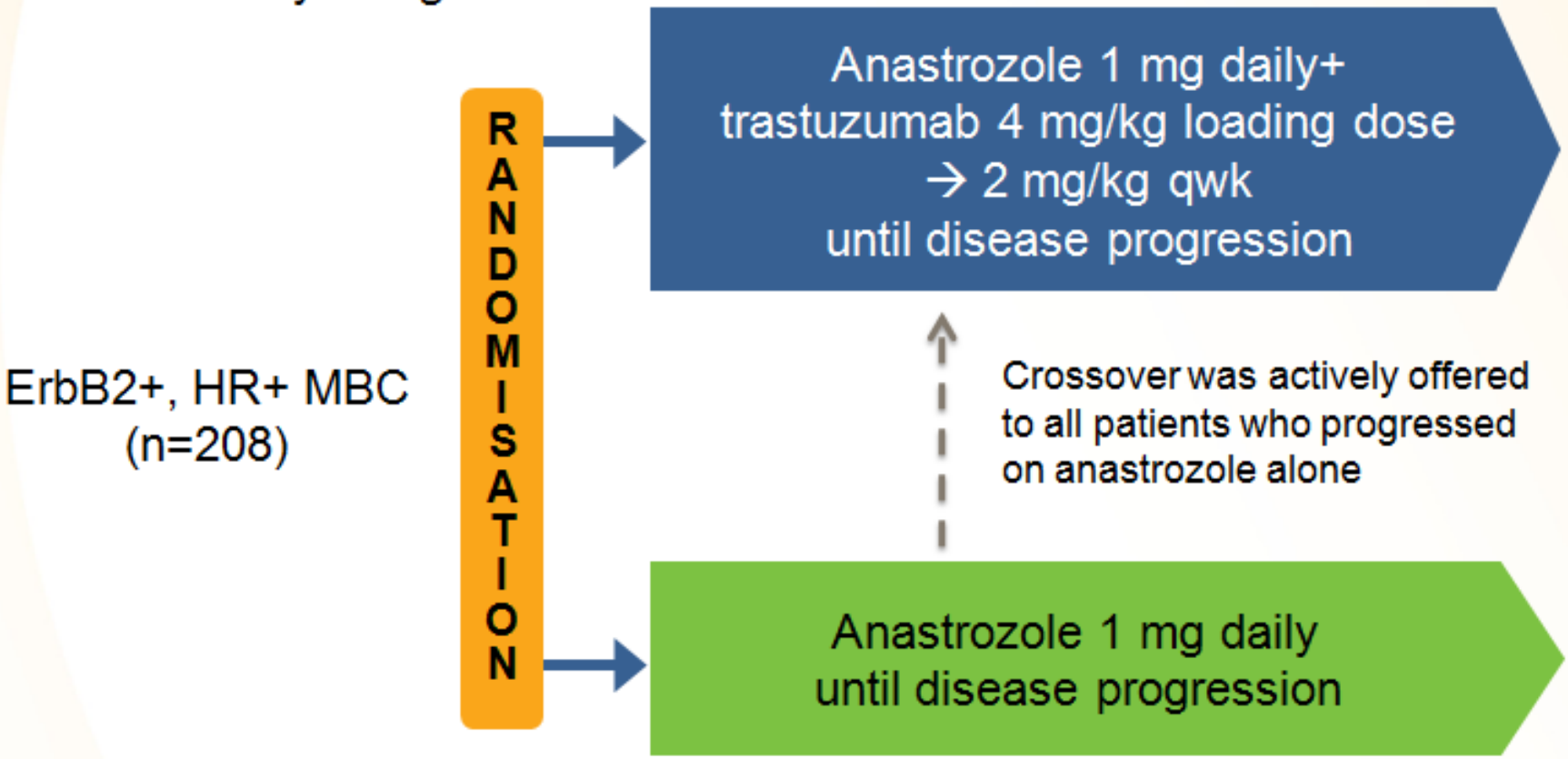
For highly selected patients* with ER+/HER-2+ MBC, for whom ET is chosen over CT, ET should be given in combination with anti-HER-2 therapy (either trastuzumab or lapatinib) since the combination provides PFS benefit (i.e. "time without CT") compared to ET alone. (LoE: 1 A) (72%)

The addition of anti-HER-2 therapy to ET in the 1st line setting has not led to a survival benefit but long-term follow was not collected in the available trials.
In addition, this strategy is currently being directly compared with CT + anti-HER2 therapy.

*** Will be defined in the manuscript**

First-line anastrozole ± trastuzumab in HR+ and ErbB2+ metastatic breast cancer

TAnDEM study design



HR, hormone receptor; MBC, metastatic breast cancer; q, every; TAnDEM, TrAstuzumab in Dual HER2 ER-Positive Metastatic breast cancer

Kaufman *et al. J Clin Oncol*. 2009;27:5529–37

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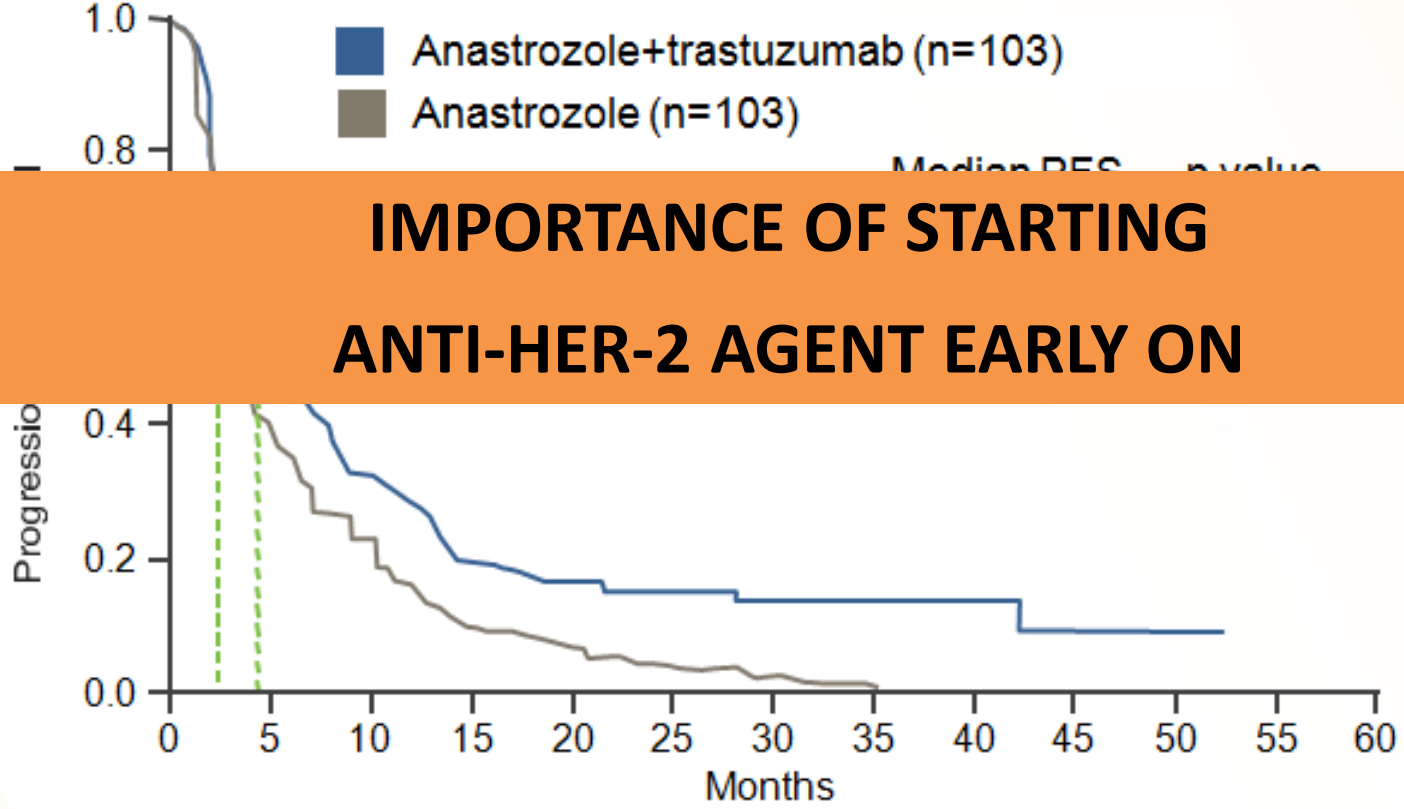
First-line anastrozole ± trastuzumab in HR+ and ErbB2+ metastatic breast cancer

TAnDEM trial: PFS



IMPORTANCE OF STARTING

ANTI-HER-2 AGENT EARLY ON

HR, hormone receptor; PFS, progression-free survival; TAnDEM, TrAstuzumab in Dual HER2 ER-Positive Metastatic breast cancer

Kaufman *et al*. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol* 27(33), 2009:5529–37. Reprinted with permission.

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ER + / HER-2+ MBC

For patients with ER+/HER-2+ MBC, for whom CT + anti-HER2 therapy was chosen as 1st line therapy and provided a benefit, it is reasonable to use ET + anti-HER2 therapy as maintenance therapy, after stopping CT, although this strategy has not been studied.

(LoE: 1 C) (80%)

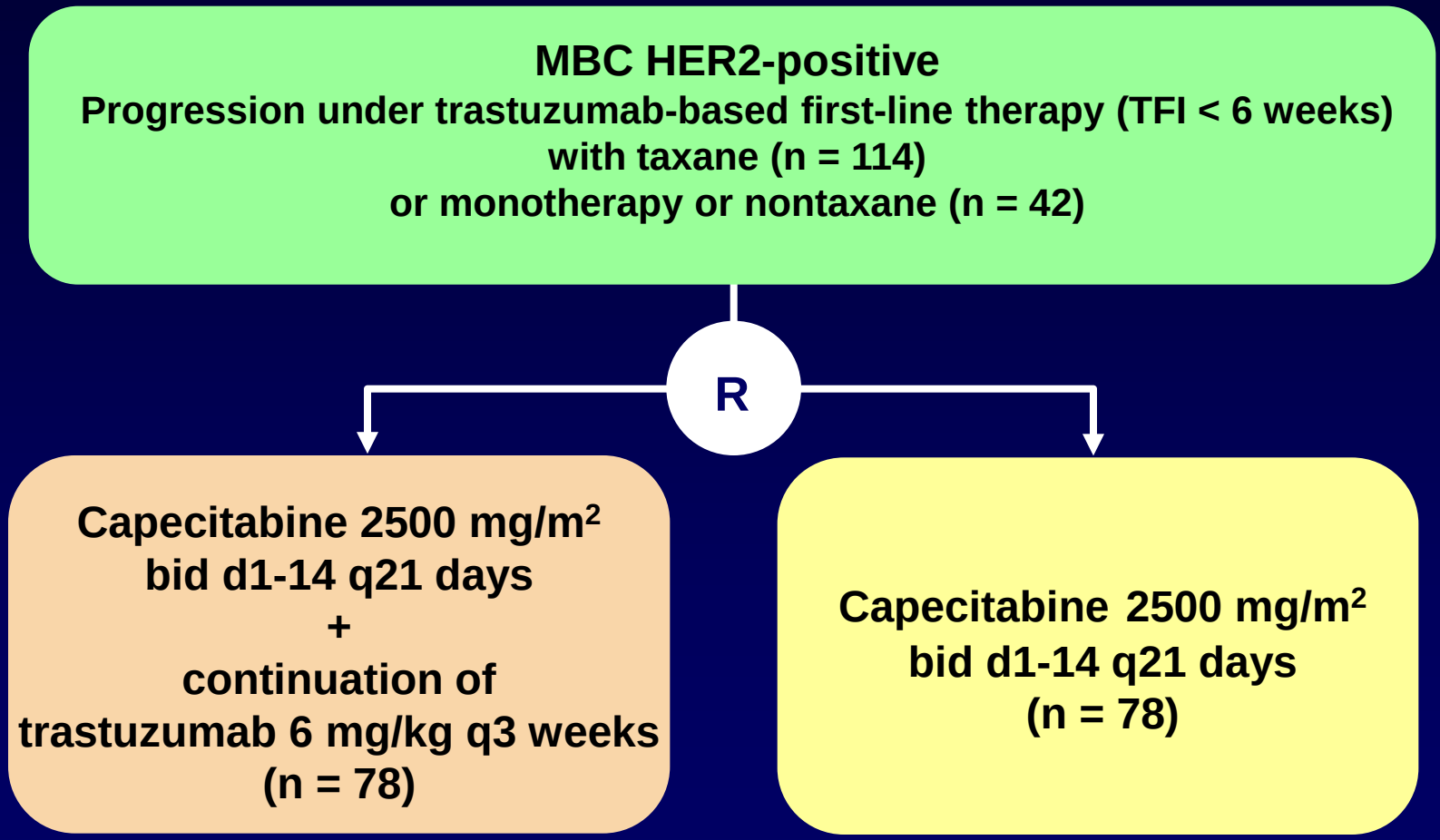
HER-2 POSITIVE MBC

MAIN MESSAGES:

All patients with HER-2+ MBC who relapse after adjuvant anti-HER-2 therapy should be considered for further anti-HER-2 therapy, except in the presence of contraindications (LoE: 1 B) (97%)

CHANGE IN PARADIGM IN ONCOLOGY!

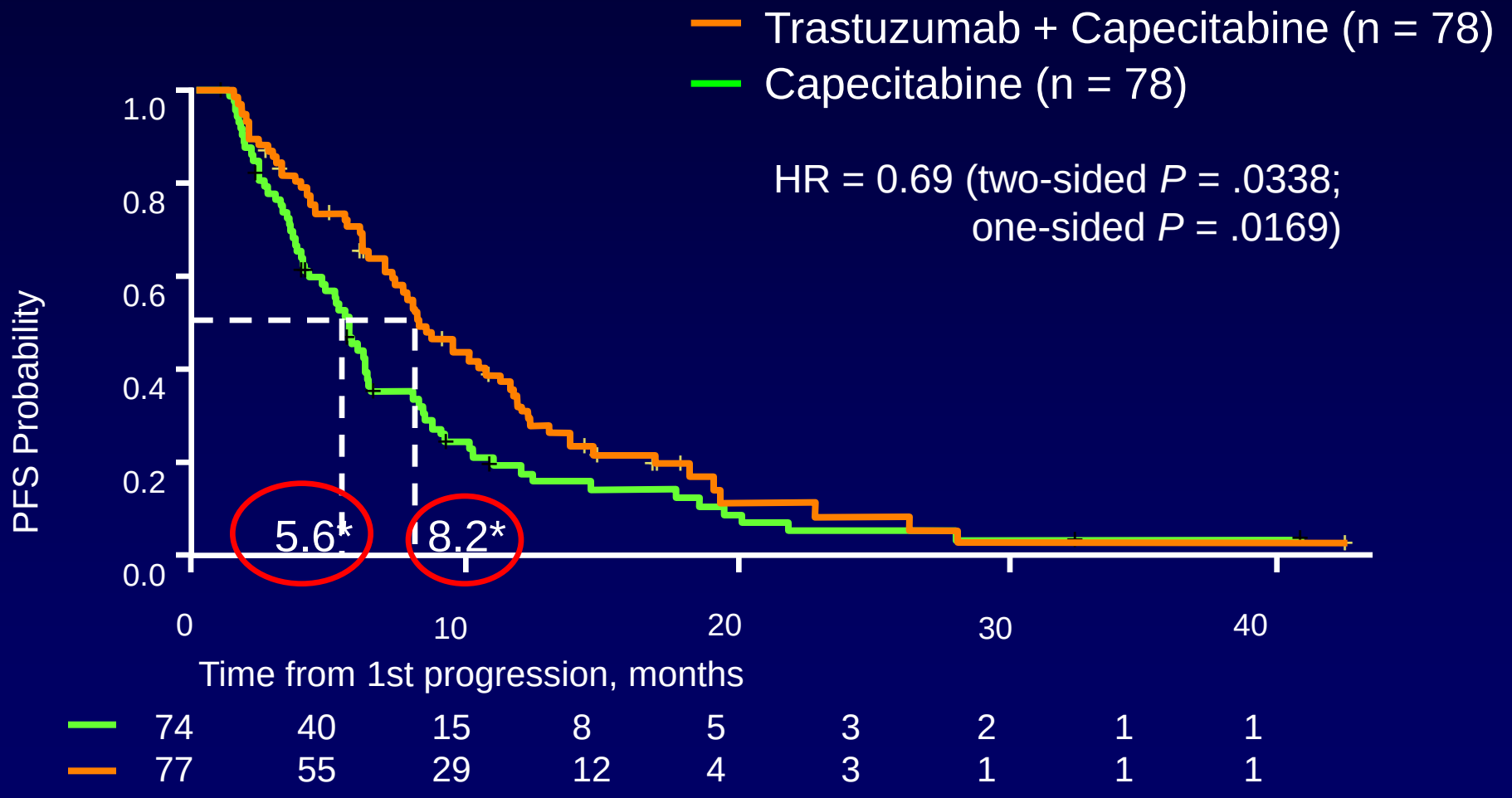
Trastuzumab Beyond Trastuzumab: GBG-26 Study



R, randomization;
TFI, treatment-free interval;
MBD, metastatic breast cancer

Von Minckwitz G, et al. *J Clin Oncol.* 2009;27(12):1999-2006.

Continuation of Trastuzumab Prolongs Time to Progression by Nearly 3 Months



Von Minckwitz G, et al. *J Clin Oncol.* 2009;27(12):1999-2006.

*Median TTP in months
TTP, time to progression; HR hazard ratio

HER-2 POSITIVE MBC

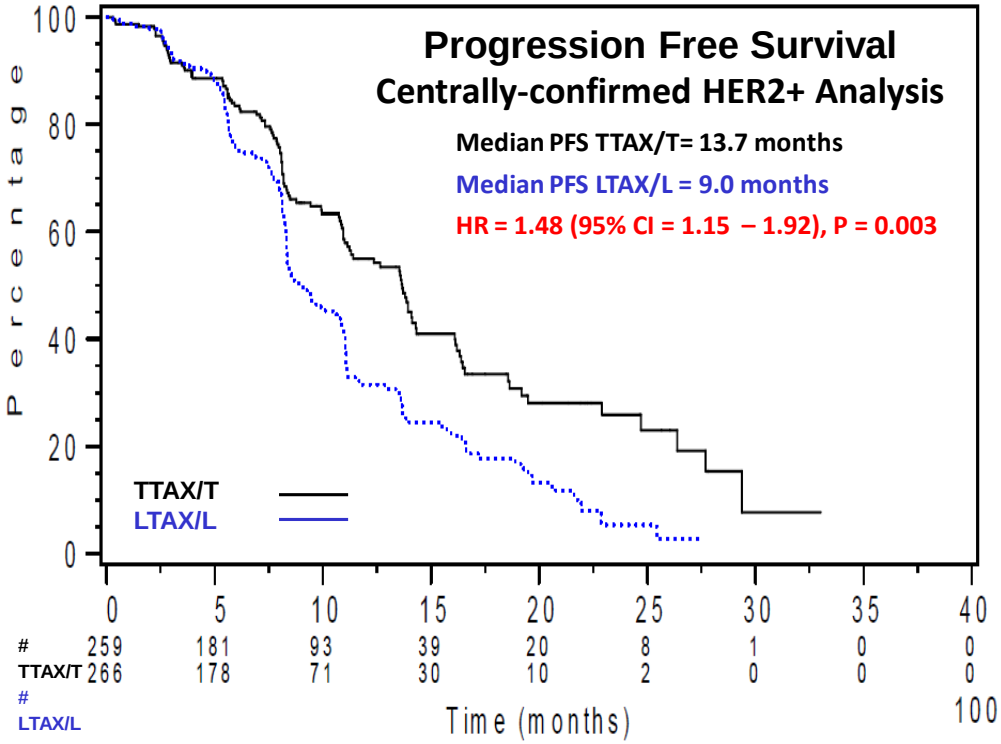
In patients achieving a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost.

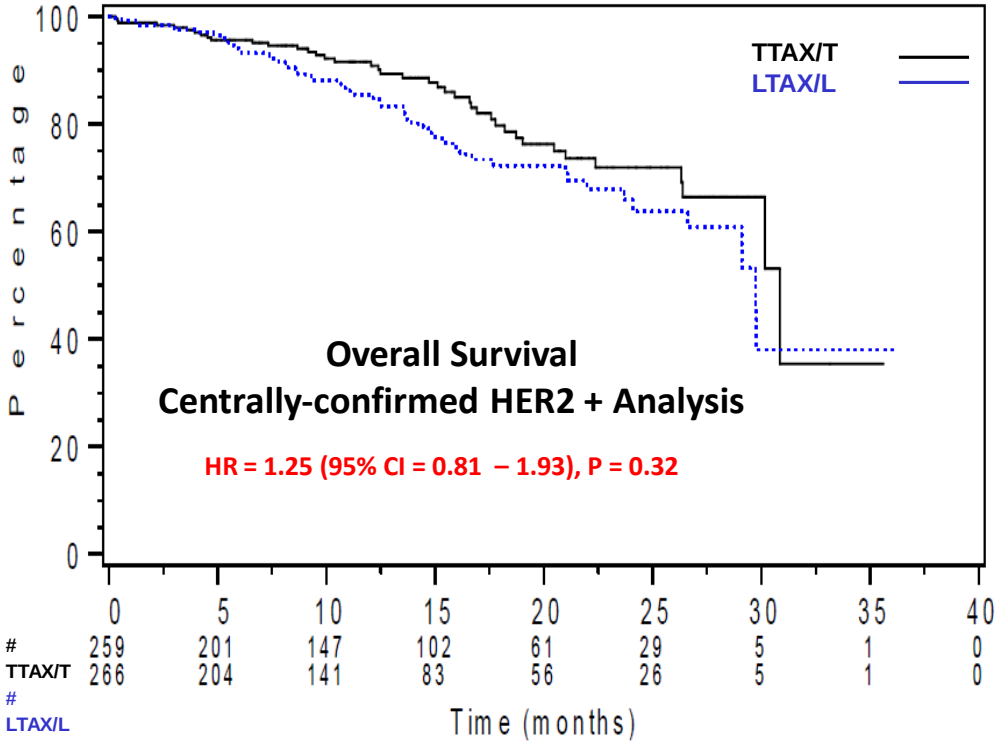
Stopping anti-HER2 therapy, after several years of sustained complete remission, may be considered in some patients, particularly if treatment re-challenge is available in case of progression.
(LoE: Expert Opinion) (93%)

HER-2 POSITIVE MBC

In the 1st line setting, for HER-2+ MBC previously treated (in the adjuvant setting) or untreated with trastuzumab, combinations of CT + trastuzumab are superior to combinations of CT + lapatinib in terms of PFS and OS. (LoE: 1 A) (85%)

MA.31/ EGF108919
COMPLETE TRIAL





Gelmon, K. ASCO 2012

MA.31/ EGF108919 COMPLETE TRIAL
Treatment Discontinuations

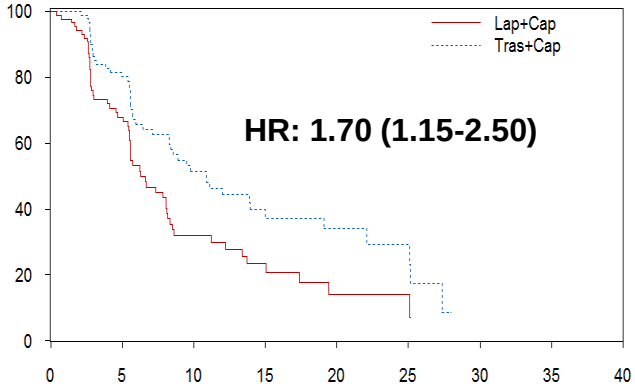
OFF PROTOCOL TREATMENT (n = 382)		
	LTAX/L=202	TTAX/T=180
Reason	Number (%)	Number (%)
Death	5 (2.5)	10 (5.6)
Intercurrent Illness	3 (1.5)	3 (1.7)
Progressive Disease	143 (70.8)	121 (67.2)
Toxicity	36 (17.8)	19 (10.6)
Refused Treatment	2 (1.0)	4 (2.2)
Symptomatic Progression	4 (2.0)	3 (1.7)
Other	9 (4.5)	20 (11.1)

Gelmon, K. ASCO 2012

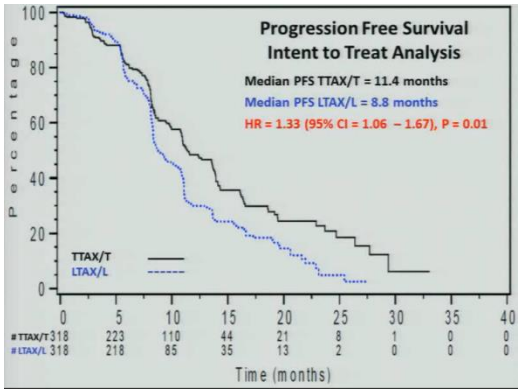
NEW QUESTION:

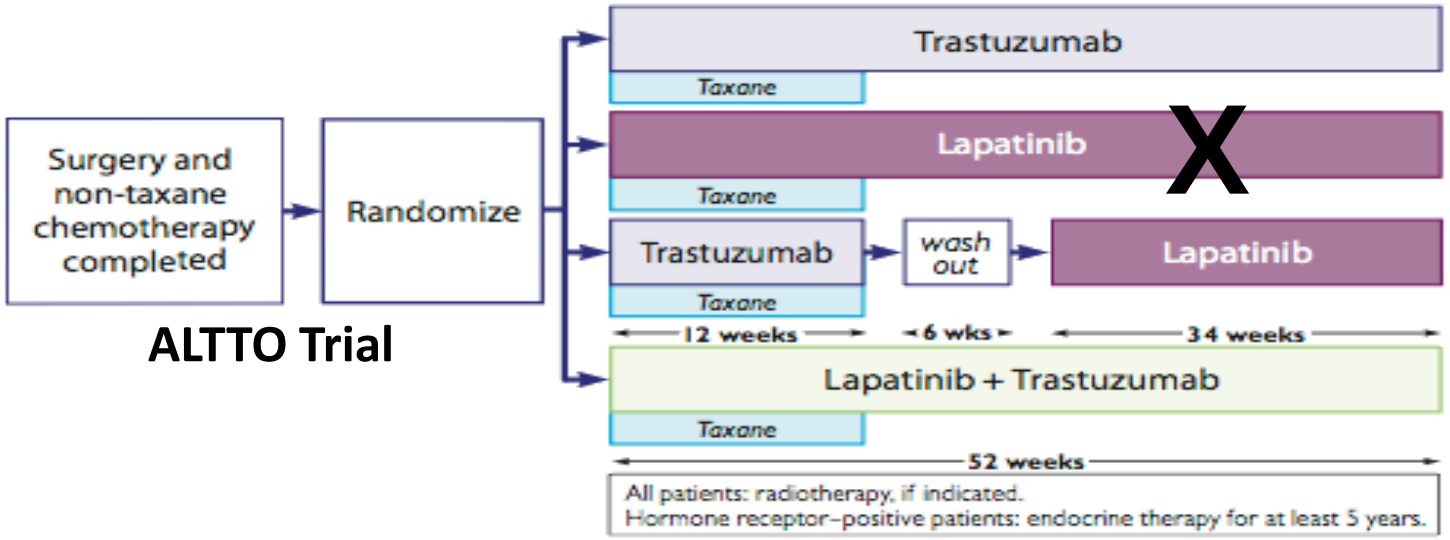
The optimal timing to use lapatinib?

CEREBEL trial



MA 31 Trial

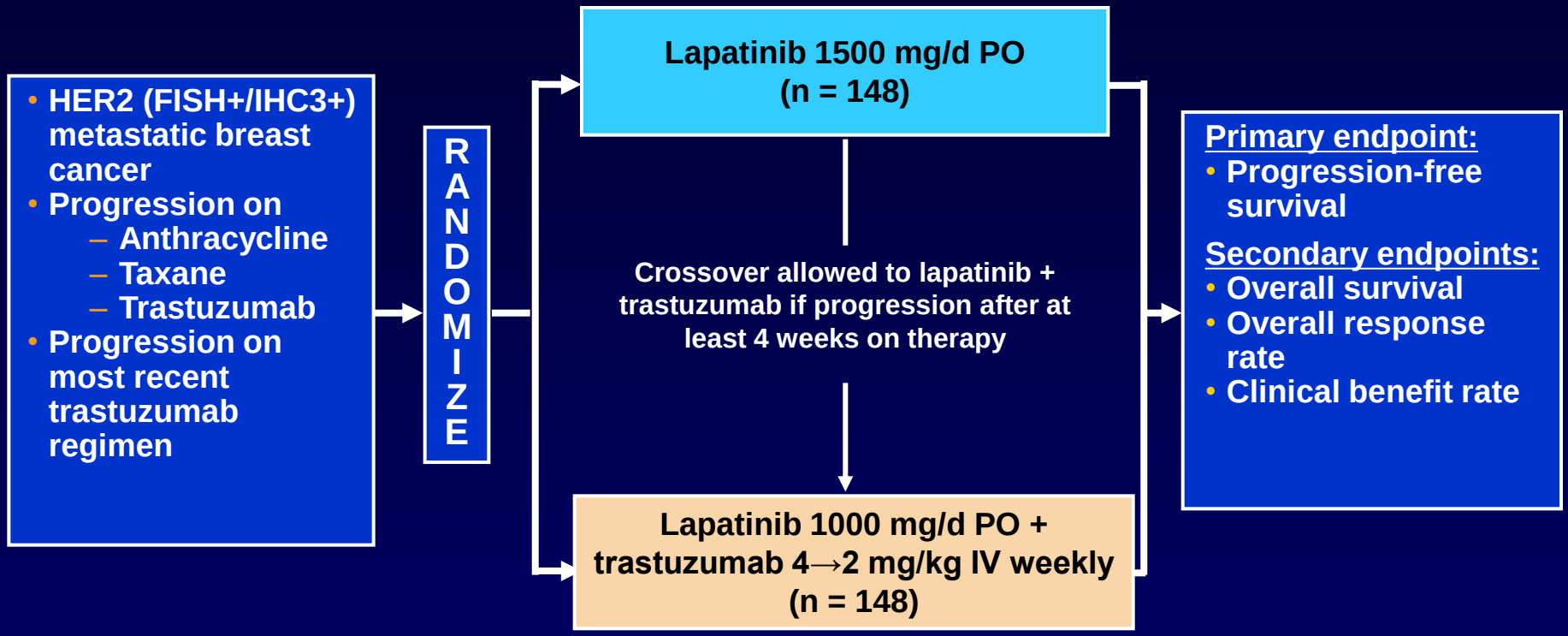




ALTTO Trial

ADAPTED FROM JAVIER CORTES

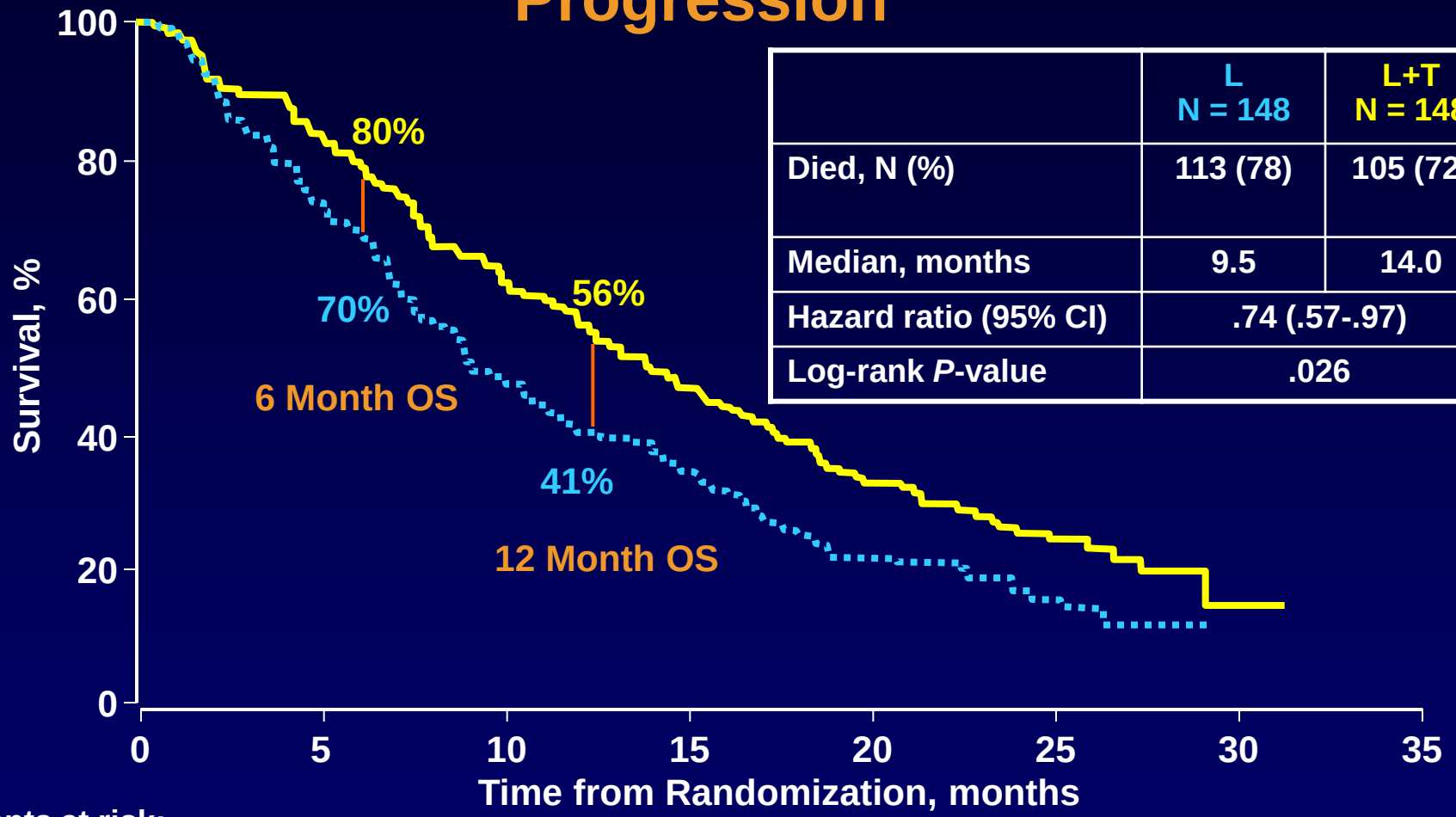
EGF104900: Phase III Study Evaluated Dual HER2 Blockade



- Staging occurred at 4, 8, 12, 16 weeks, and then every 8 weeks
- Steady state of single-agent lapatinib occurs at approximately 7 days

Blackwell KL, *J Clin Oncol* 2010;28(7):1124-1130.
Blackwell KL, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 61.

EGF104900: Significant Overall Survival (OS) Benefit With Trastuzumab + Lapatinib Following Disease Progression



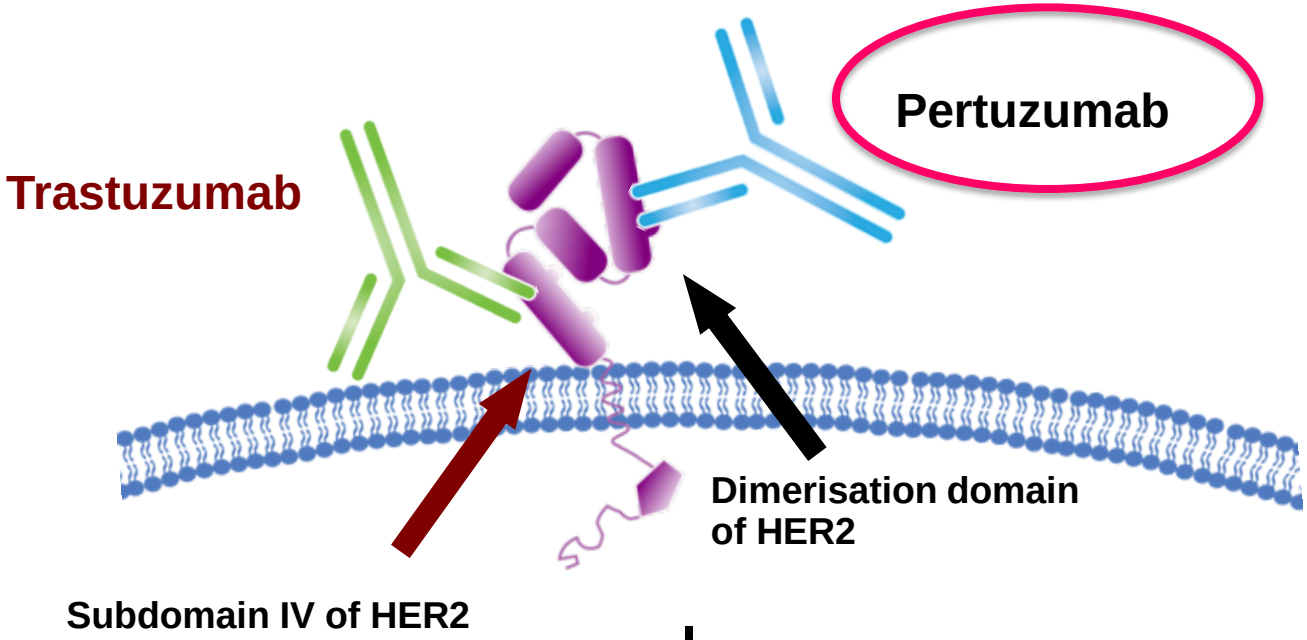
	L N = 148	L+T N = 148
Died, N (%)	113 (78)	105 (72)
Median, months	9.5	14.0
Hazard ratio (95% CI)	.74 (.57-.97)	
Log-rank *P*-value	.026	

Patients at risk:

L	148	121	88	64	43	25	1
L+T	148	102	65	47	28	13	

Blackwell KL, et al. *Cancer Res.* 2009;69(Suppl 2): Abstract 61.

Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity

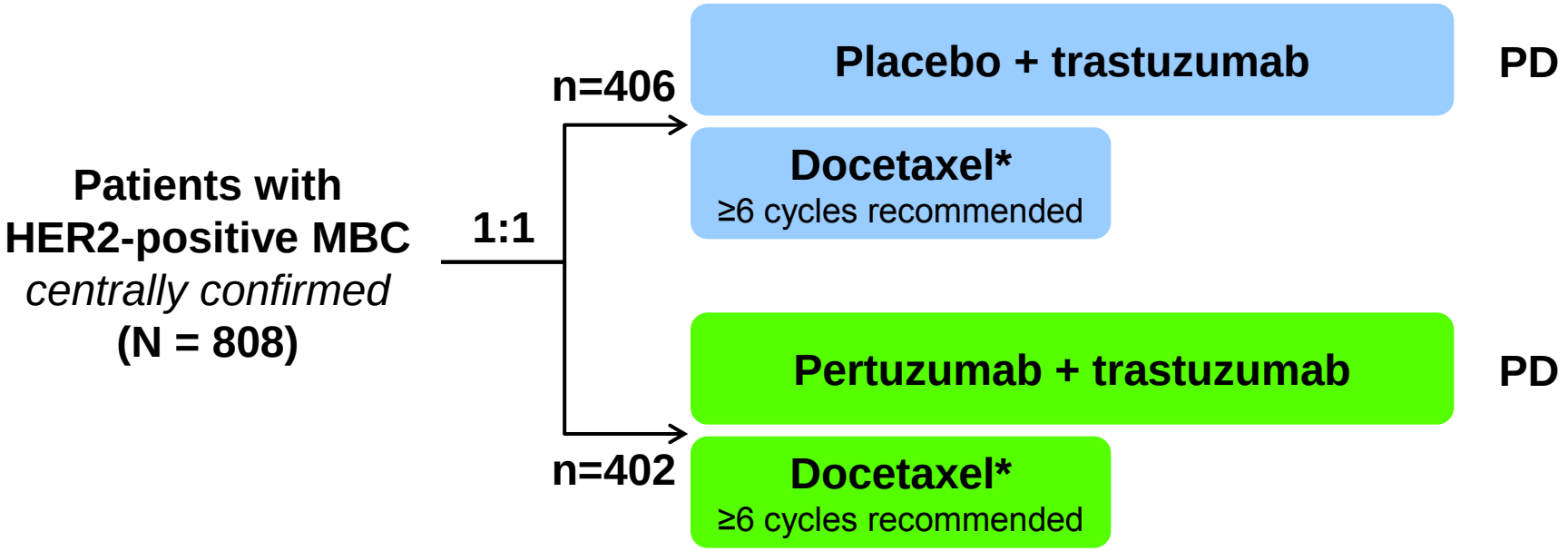


- Trastuzumab suppresses HER2 activity
- Flags [illegible] by the immune system

- Pertuzumab inhibits HER2 heterodimerization
- [illegible] signaling pathways
- Flags cells for destruction by the immune system

THE CONCEPT OF DUAL BLOCKADE

CLEOPATRA TRIAL: Phase III, Randomized, Double-Blind, Placebo-Controlled; Placebo + Trastuzumab + Docetaxel vs. Pertuzumab + Trastuzumab + Docetaxel in Patients with Previously Untreated HER-2+ MBC



- **PRIMARY ENDPOINT: PFS**
- **Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)**

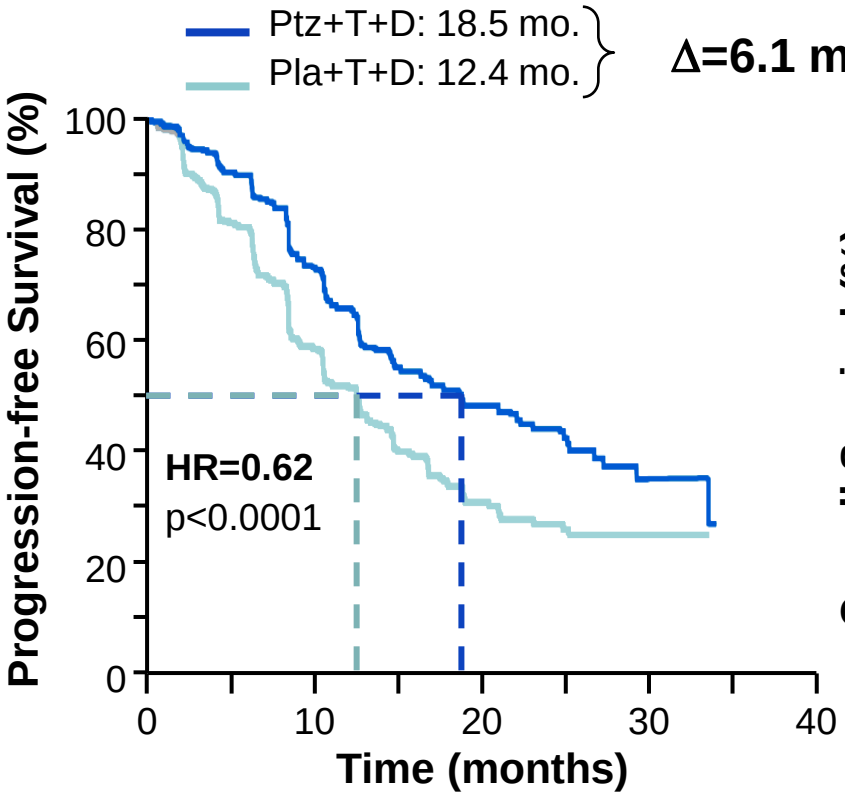
***<6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion**

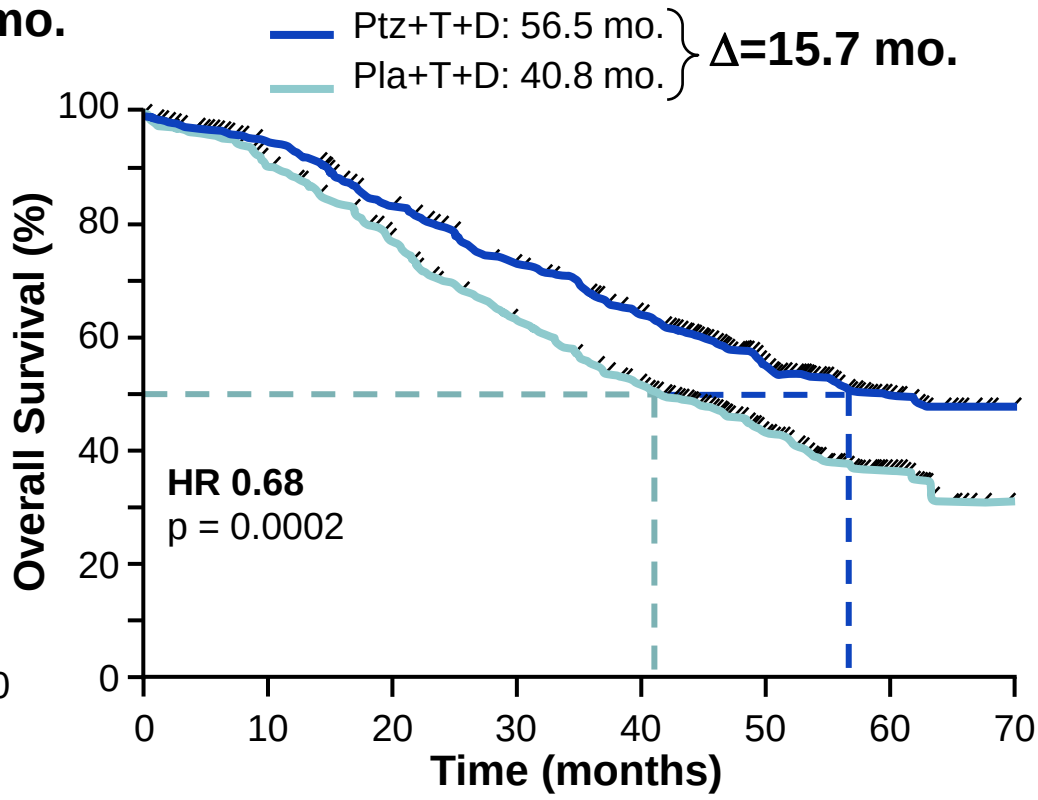
Baselga, J. SABCS 2011

CLEOPATRA TRIAL: *Median PFS and OS*

CAUTION!!!!

Only 21% -26% pts had previously received (neo)adjuvant trastuzumab





Baselga et al., NEJM 2012., Swain et al., NEJM, 2015.

Overall survival subgroup analyses

- An exploratory subgroup analysis was performed for patients who had **received prior neoadjuvant and/or adjuvant trastuzumab therapy** (**88 patients**). The observed hazard ratio of **0.68 (95% CI 0.30–1.55)** indicates overall survival benefit in the pertuzumab arm for this subpopulation.

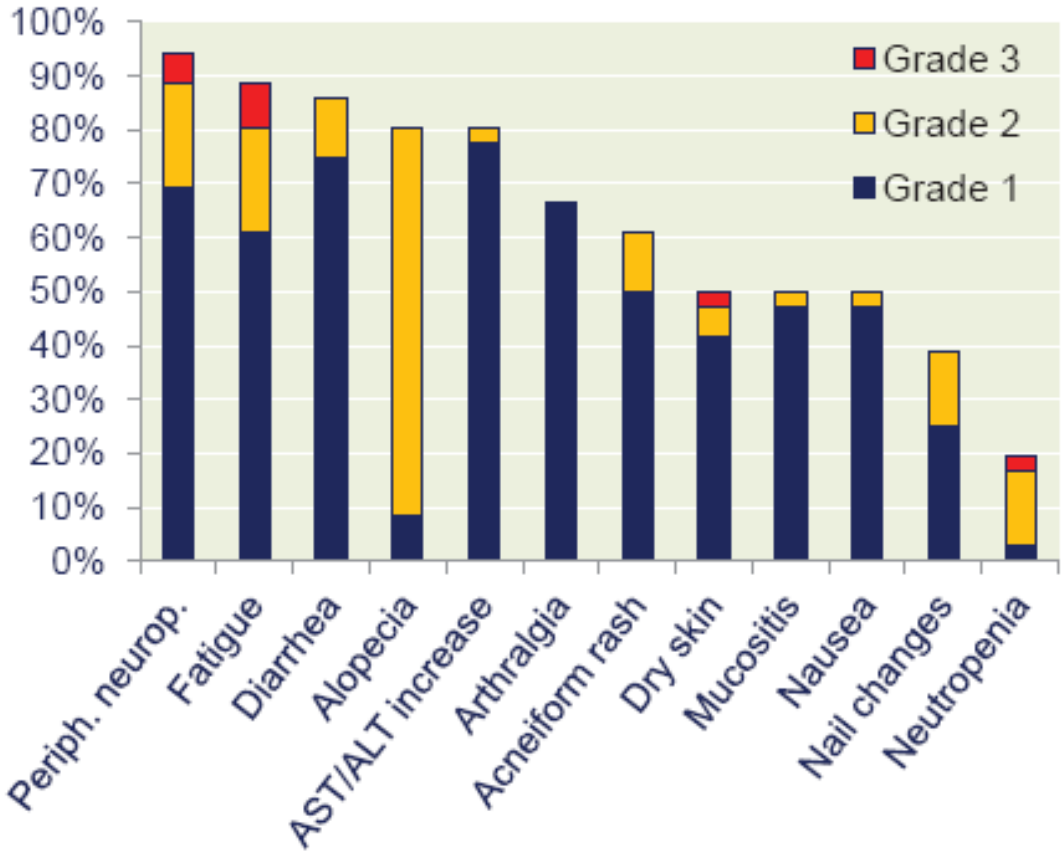
Adverse events (all grades) with ≥25% incidence or ≥5% difference between arms

n (%)	Placebo + trastuzumab + docetaxel (n=396)	Pertuzumab + trastuzumab + docetaxel (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)

Highlighted are adverse events with ≥5% higher incidence

No increase in cardiac toxicity!

Phase II Study of Pertuzumab, Trastuzumab, and Weekly Paclitaxel



- 36 evaluable pts with 1st or 2nd line HER2+ MBC
- ORR = 47%
- No cardiac events

Datko F et al, SABCS 2012. Abstract P5-18-20

Safety of pertuzumab plus trastuzumab plus vinorelbine for 1st line treatment of pts with HER2-+ LABC or MBC

Edith A. Perez, José Manuel López-Vega, Lucia Del Mastro, Thierry Petit, Claudio Zamagni, Ulrich Freudensprung, Lydie Bastière-Truchot, Ru Walker, Michael Andersson. SABCS 2013, Poster 2-16-10

Discussion

- A cross-study comparison of the incidence of selected AEs (Table 4) suggests that the safety profile of the combination of pertuzumab, trastuzumab, and vinorelbine observed to date in VELVET compares favorably with those seen previously in CLEOPATRA (pertuzumab, trastuzumab, and docetaxel) and HERNATA (trastuzumab and vinorelbine). However, it should be noted that it is difficult to compare results from different clinical trials.

Table 4. Cross-study comparison of the VELVET, CLEOPATRA, and HERNATA trials

	VELVET	CLEOPATRA[12*]	HERNATA[7,†]
Median (range) number of chemotherapy cycles	9 (0–21)	8 (1–35)	10.5 (2–42)
Median chemotherapy dose intensity, mg/m²/week	14.99[‡]	24.6	NR
Incidence of selected AEs, %			
Diarrhea	49.1	66.8	11.6[§]
Alopecia	23.6	60.9	NR
Grade ≥3 neutropenia	23.6[‖]	48.9	41.5
Febrile neutropenia	5.7	13.8	10.8
Grade ≥3 leukopenia	8.5[¶]	12.3	21

AE, adverse event; NR, not reported

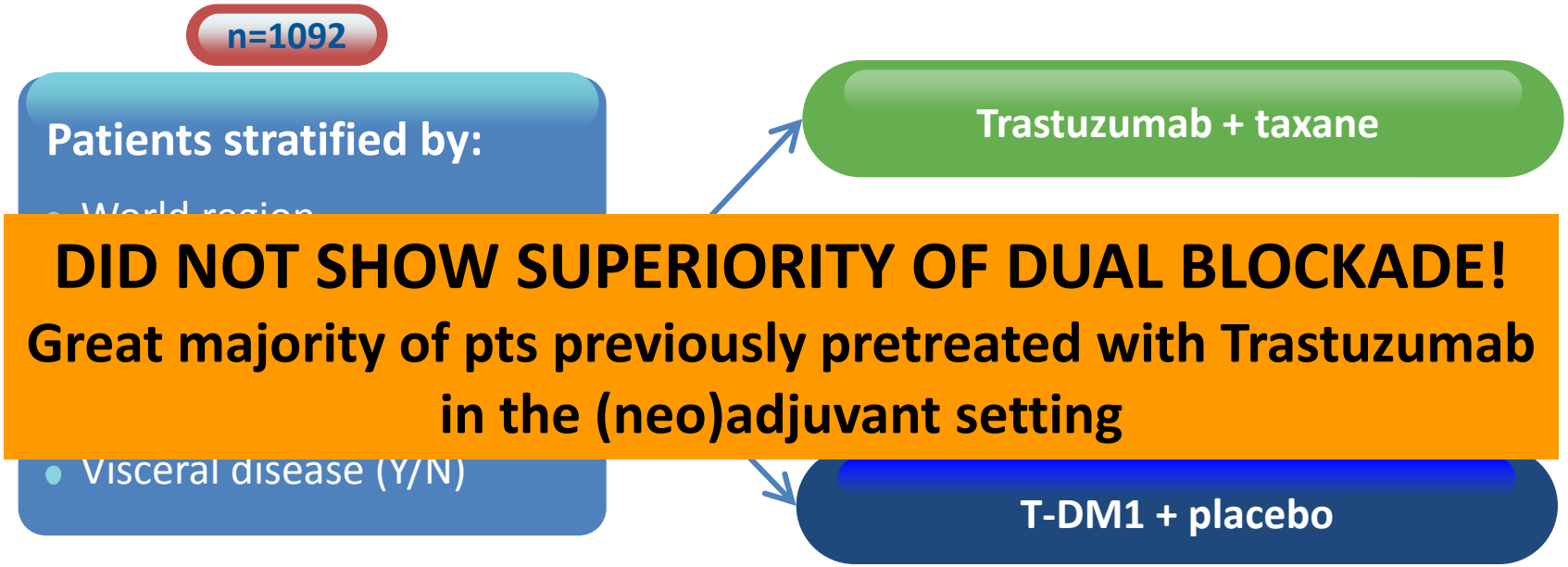
* Pertuzumab, trastuzumab, and docetaxel arm; † Trastuzumab and vinorelbine arm; ‡ First six cycles only; § Grade 2–4 only, grade 1 toxicities NR; ‖ Pooled 'neutropenia' and 'neutrophil count decreased' preferred terms; ¶ Pooled 'leukopenia' and 'white blood cell count decreased' preferred terms

Conclusions

- There was an acceptable safety profile with the combination of pertuzumab, trastuzumab, and vinorelbine, and no new safety signals were observed.
- The incidences of alopecia and of grade ≥3 hematologic AEs are currently lower than those observed previously with trastuzumab plus vinorelbine[7] or with pertuzumab plus trastuzumab plus docetaxel.[12]
- Based on encouraging interim safety data, enrollment into Cohort 2 began in April 2013 and completed in September 2013. Final efficacy data from both cohorts are expected in 2015.

1st Line Phase III MARIANNE Study

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



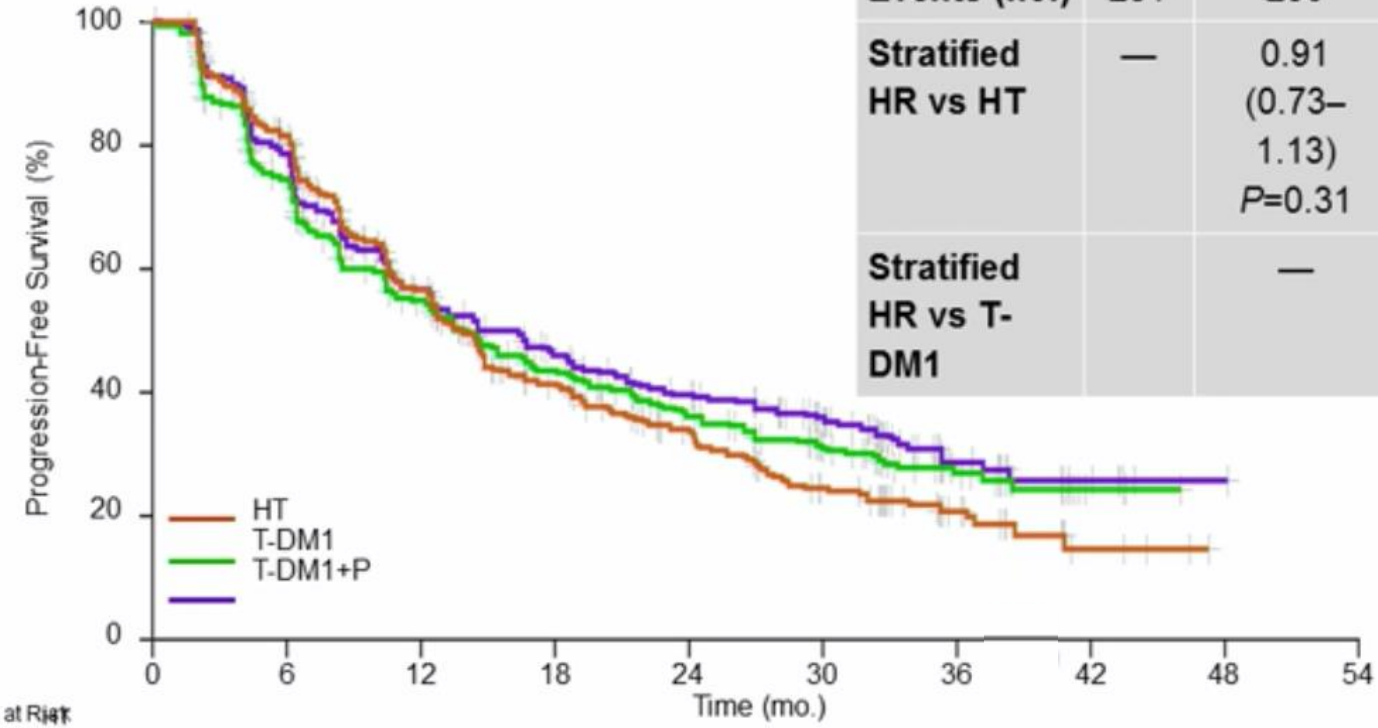
DID NOT SHOW SUPERIORITY OF DUAL BLOCKADE!

Great majority of pts previously pretreated with Trastuzumab in the (neo)adjuvant setting

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

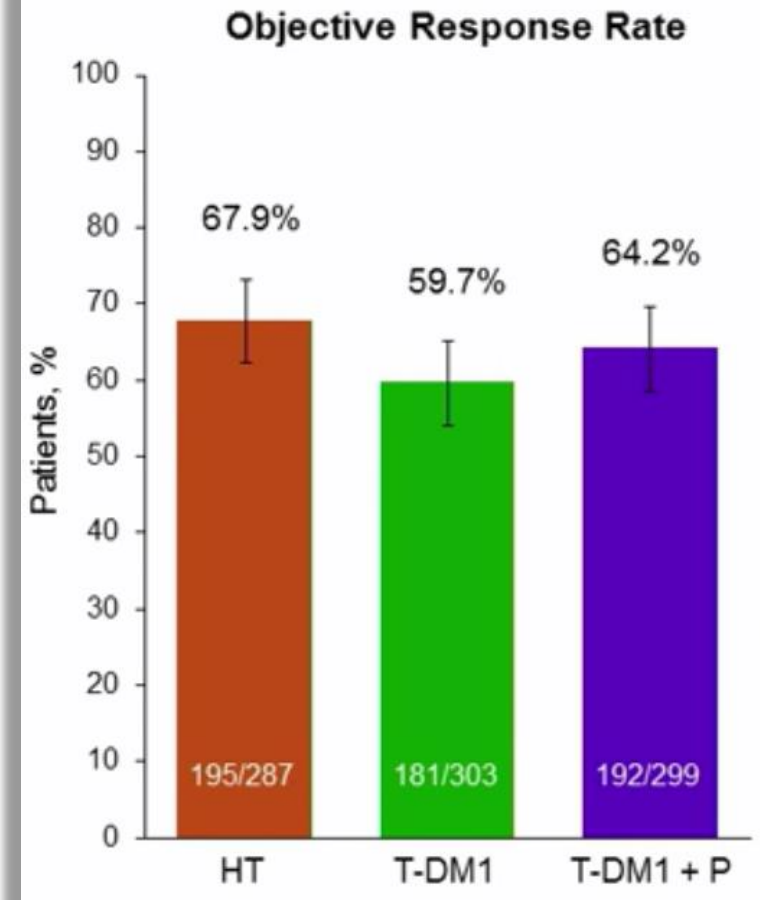
Progression-Free Survival by IRF

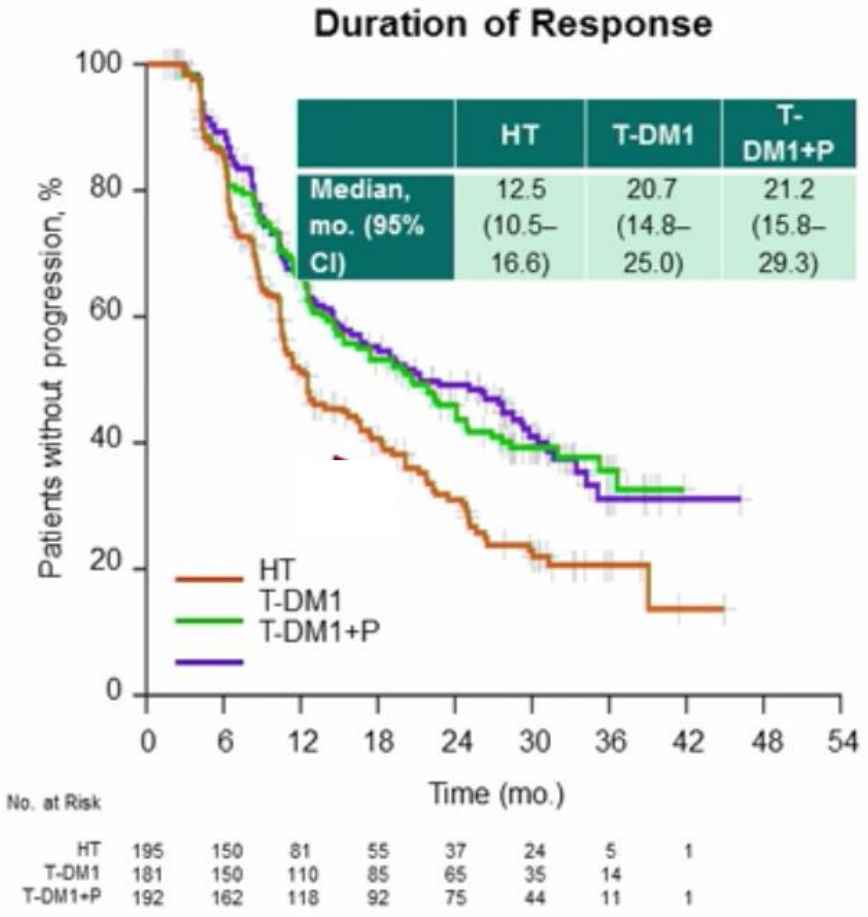
	HT	T-DM1	T-DM1+P
Median PFS (mo.)	13.7	14.1	15.2
Events (no.)	231	236	217
Stratified HR vs HT	—	0.91 (0.73–1.13) *P*=0.31	0.87 (0.69–1.08) *P*=0.14
Stratified HR vs T-DM1		—	0.91 (0.73–1.13)



No. at Risk								
T-DM1	365	265	163	107	75	50	21	5
T-DM1+P	367	257	176	133	104	67	28	3
	363	261	177	135	109	75	25	5	1

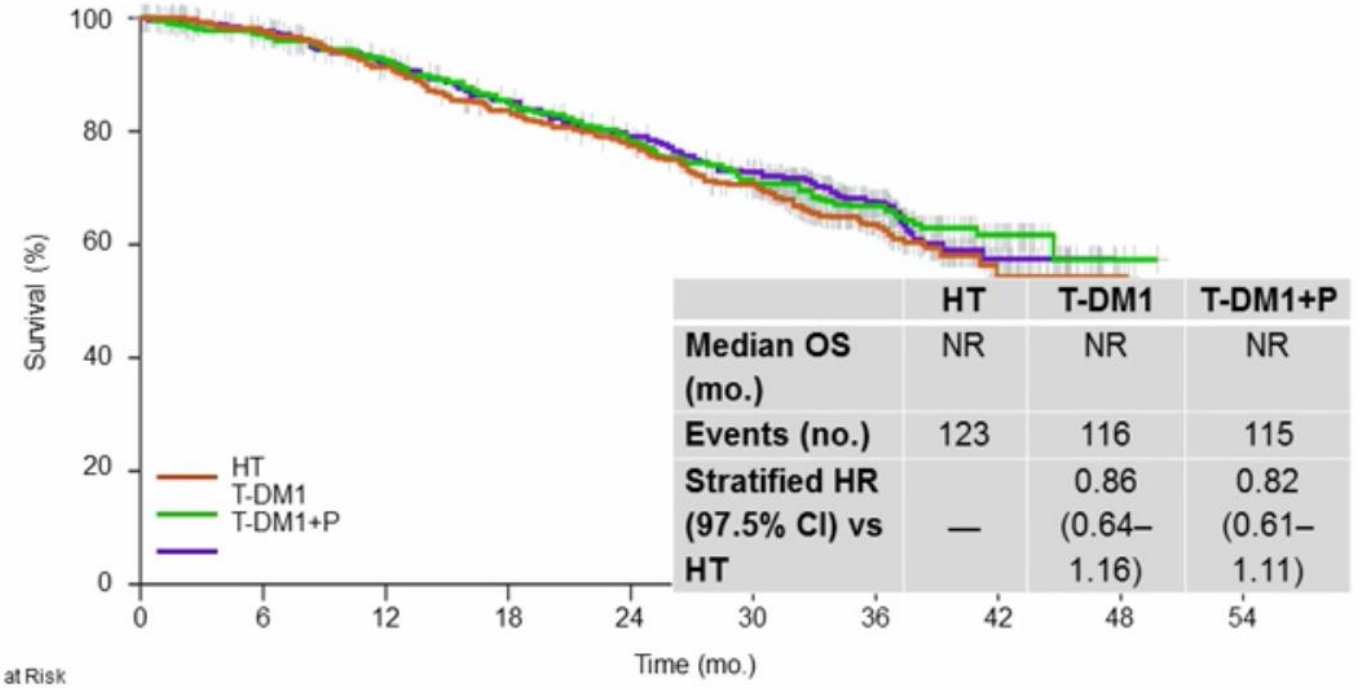
Objective Response and Duration of Response





	HT	T-DM1	T-DM1+P
Median, mo. (95% CI)	12.5 (10.5–16.6)	20.7 (14.8–25.0)	21.2 (15.8–29.3)

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)

- **T-DM1 treatment resulted in non-inferior but not superior PFS compared with trastuzumab plus a taxane in pts with locally advanced or metastatic HER2+ BC.**

- **The addition of pertuzumab to T-DM1 provided no efficacy benefit**

PHEREXA study design
NCT01026142

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

N = 452

1

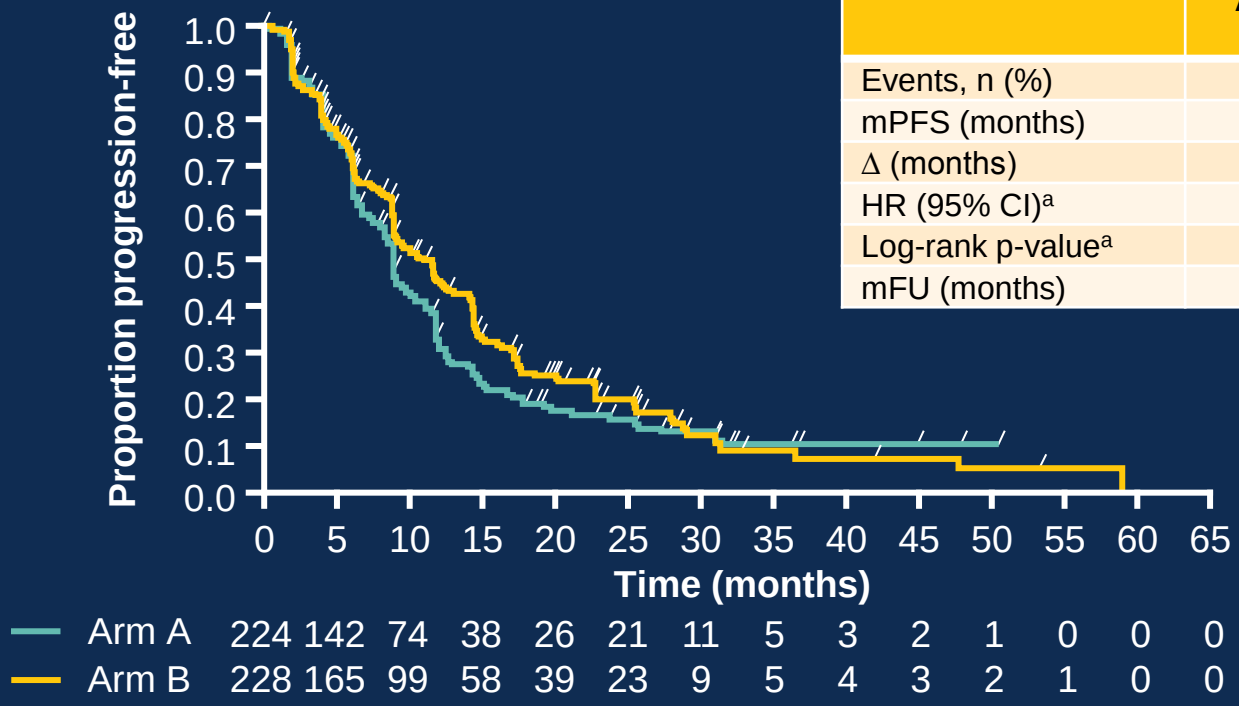
1

Arm A:
H (8 mg/kg→6 mg/kg) + X (1,250 mg/m^2)
n = 224

Arm B:
H (8 mg/kg→6 mg/kg) + X (1,000 mg/m^2)
+ 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

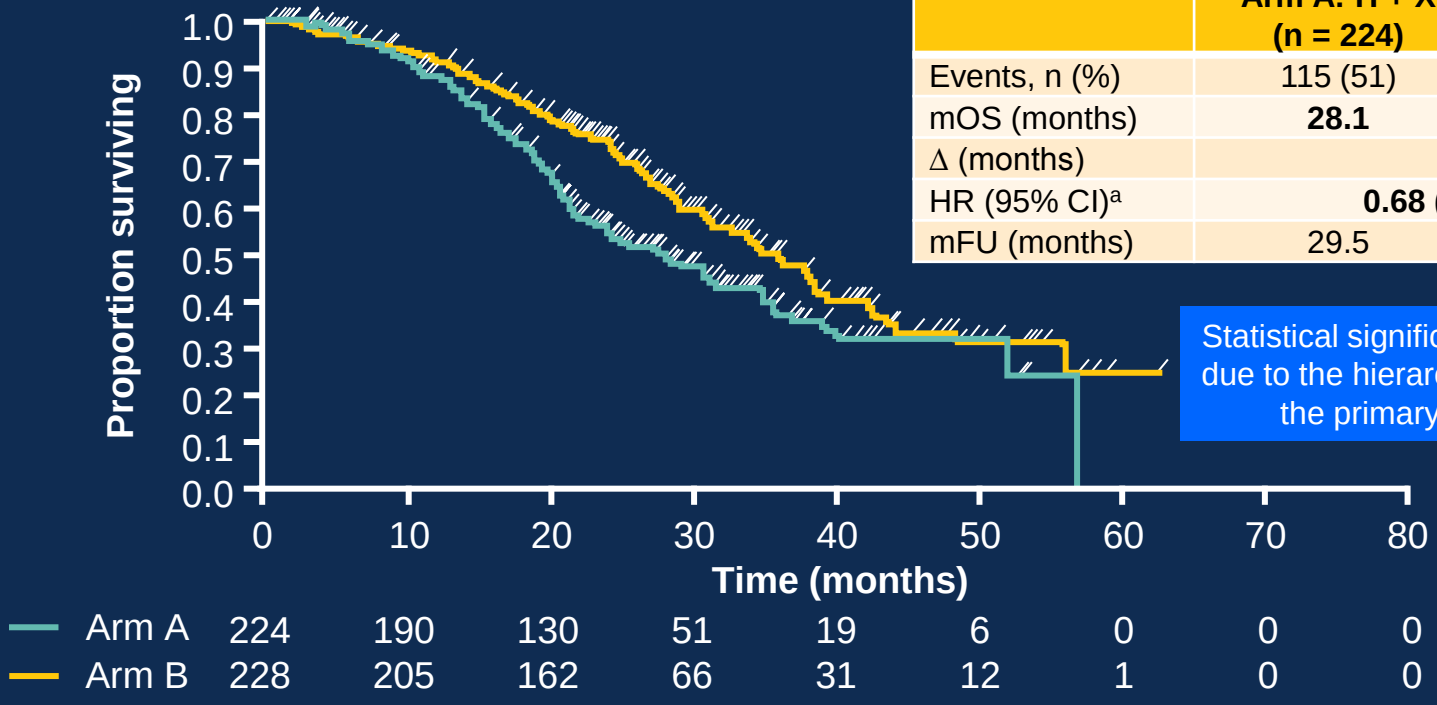
Primary analysis: PFS by independent review facility
ITT population



	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.

Secondary analysis: OS
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.

HER-2 POSITIVE MBC: 1st line

The standard 1st line therapy for patients previously untreated with anti-HER-2 therapy is the combination of CT + trastuzumab and pertuzumab, because it has proven to be superior to CT + trastuzumab in terms of OS in this population.
(LoE: 1 A) (86%)

For patients previously treated (in the (neo)adjuvant setting) with anti-HER-2 therapy, the combination of CT + trastuzumab and pertuzumab is an important option for 1st line therapy. (LoE: 1 A) (76%)

Few (88) of these pts were treated in the Cleopatra trial and all with trastuzumab-free interval > 12 months.

HER-2 POSITIVE MBC

There are currently no data supporting the use of dual blockade with trastuzumab + pertuzumab and CT beyond progression (i.e. continuing dual blockade beyond progression) and therefore this 3 drug regimen should not be given beyond progression outside clinical trials.

(86%)

There are no data on how to treat patients who have a relapse after receiving CT + trastuzumab + pertuzumab in the early setting.

HER-2 POSITIVE MBC

In a HER-2+ MBC patient, previously untreated with the combination of CT + trastuzumab + pertuzumab, it is acceptable to use this treatment after 1st line, although currently no data exists in this setting.

(LoE: Expert Opinion) (76%)

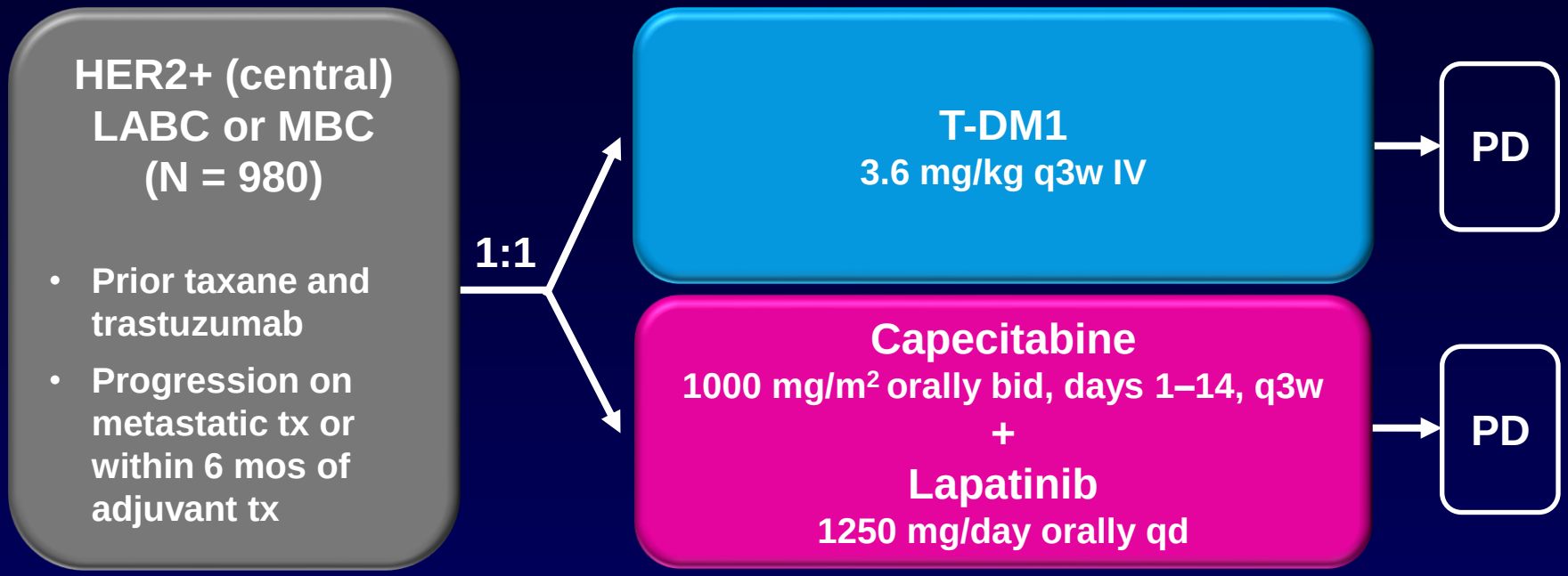
HER-2 POSITIVE MBC

After 1st line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2nd line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician's choice).

T-DM1 should be preferred in patients who have progressed through at least 1 line of trastuzumab-based therapy, because it provides an OS benefit.
(LoE: 1 A) (88%)

However, there are no data on the use of T-DM1 after dual blockade with trastuzumab + pertuzumab.

EMILIA Study Design



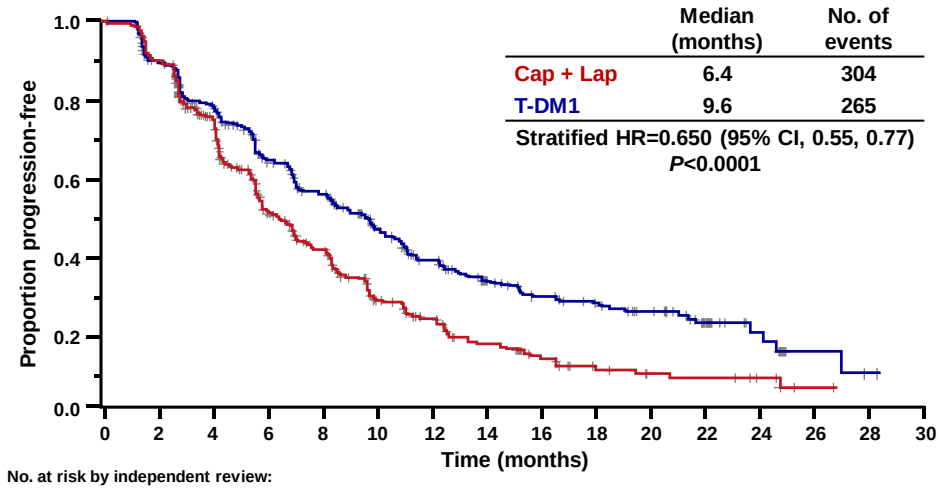
- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Blackwell K, et al. *J Clin Oncol.* 2012;30(15S): Abstract LBA1 & Vema S et al, ESMO 2012

EMILIA Study

T-DM1 vs Cap+Lap

Progression-Free Survival 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

Unstratified HR=0.66 (*P*<0.0001).

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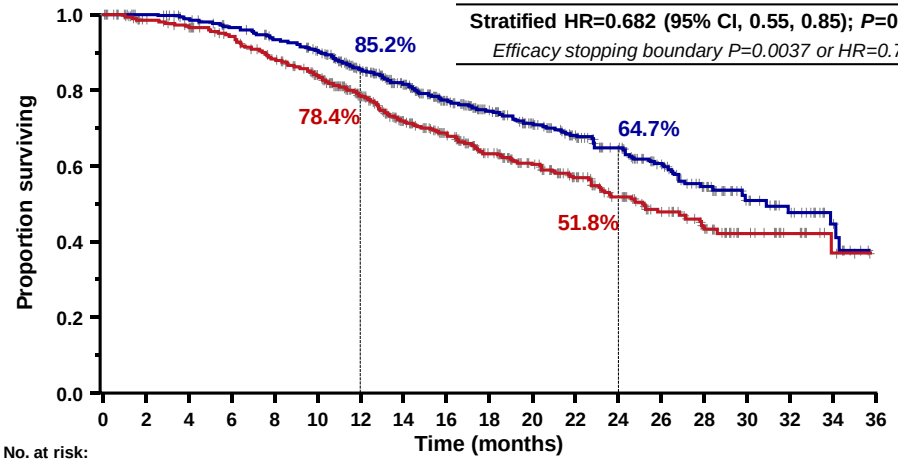
www.esmo2012.or

~5 MS BENEFIT IN OS

Probably a new standard of care!

Overall Survival: Confirmatory Analysis



	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006
Efficacy stopping boundary P=0.0037 or HR=0.727

No. at risk:

Cap + Lap	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

Data cut-off July 31, 2012; Unstratified HR=0.70 (*P*=0.0012).

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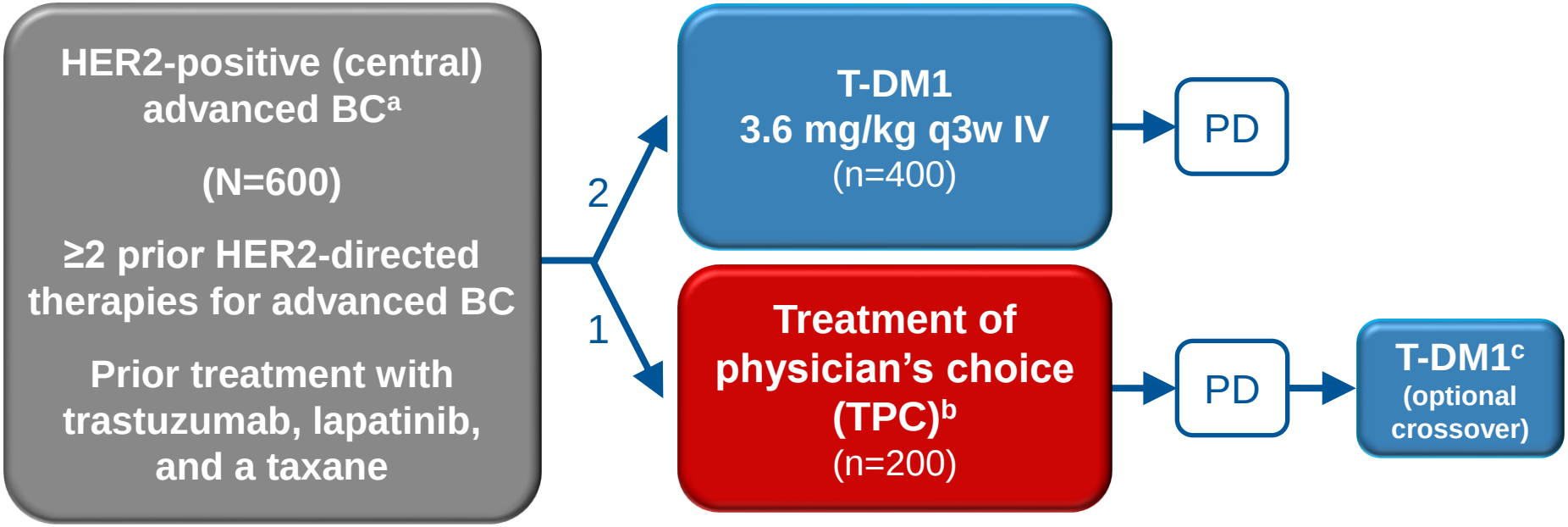
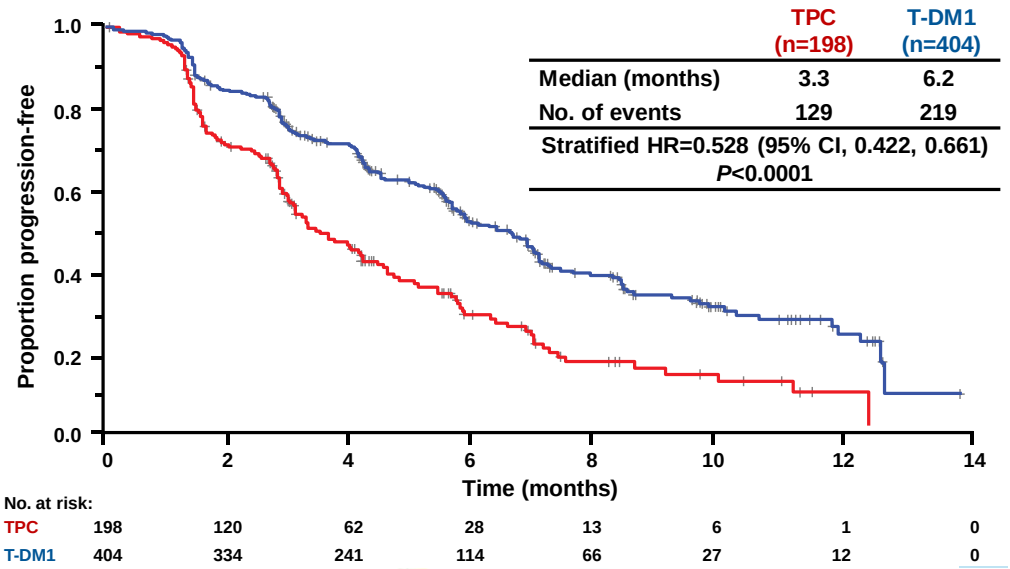
TH3RESA Study Schema



- **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.

PFS by Investigator Assessment



	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

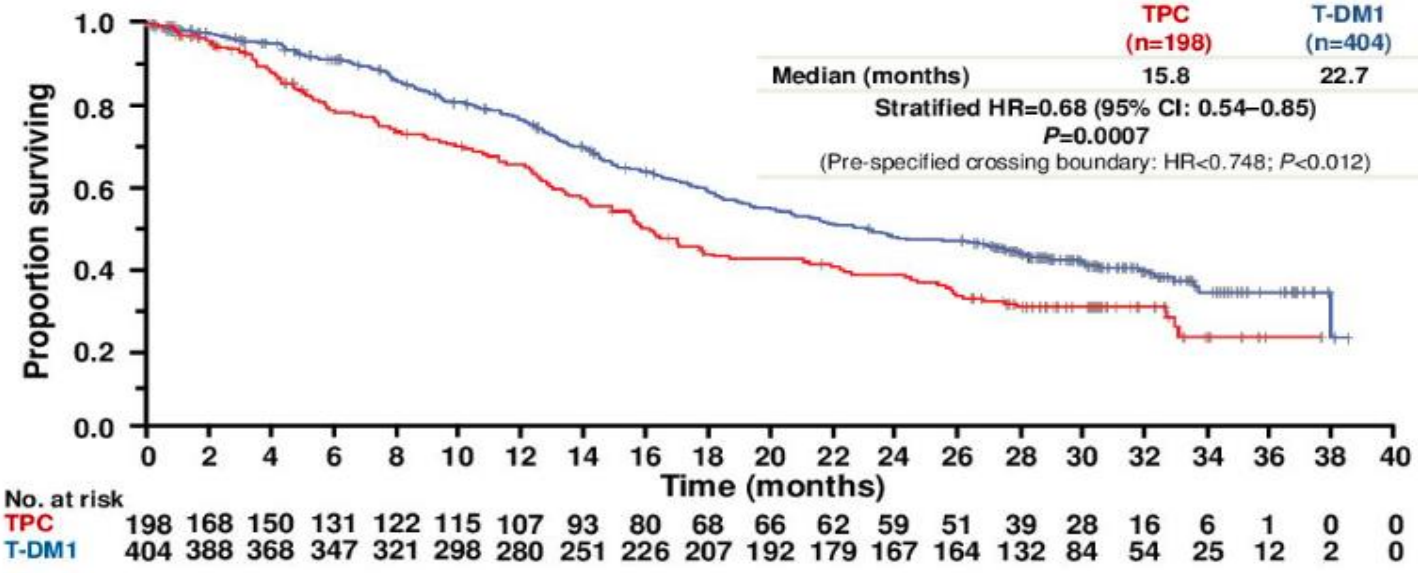
Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

SUPERIOR PFS

44.9% of TPC arm pts received T-DM1 crossover therapy

3 ms OS BENEFIT

Final OS Analysis



	TPC (n=198)	T-DM1 (n=404)
Median (months)	15.8	22.7

Stratified HR=0.68 (95% CI: 0.54–0.85)
P=0.0007
(Pre-specified crossing boundary: HR<0.748; *P*<0.012)

COMMON TOXICITIES OF T-DM1

- Thrombocytopenia
  - Grade ≥3 in approximately 10% of patients
  - Nadir on day 8; Nadir is typically lowest in cycle 1
  - Not typically cumulative
  - Usually manageable with dose reduction
  - Severe hemorrhage is rare, but small number of cases have been reported

- Transaminase elevation
  - Grade ≥3 in approximately 5% of patients
  - Not typically cumulative
  - Usually manageable with dose reduction
  - Severe hepatic dysfunction very rare

Diéras et al, SABCS 2012, Abstract P5-18-06

UNCOMMON TOXICITIES OF T-DM1

- Pneumonitis (≈1% of pts)
  - Typically grade 1/2
  - T-DM1 should be discontinued

- Nodular regenerative hyperplasia (<0.5%)
  - Can lead to noncirrhotic portal hypertension
  - Requires biopsy to diagnose
  - T-DM1 should be discontinued

Diéras et al, SABCS 2012, Abstract P5-18-06

HER-2 POSITIVE MBC

In patients achieving a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost.

Stopping anti-HER2 therapy, after several years of sustained complete remission, may be considered in some patients, particularly if treatment re-challenge is available in case of progression.
(LoE: Expert Opinion) (93%)

HER-2 POSITIVE MBC: CHEMOTHERAPY COMPONENT

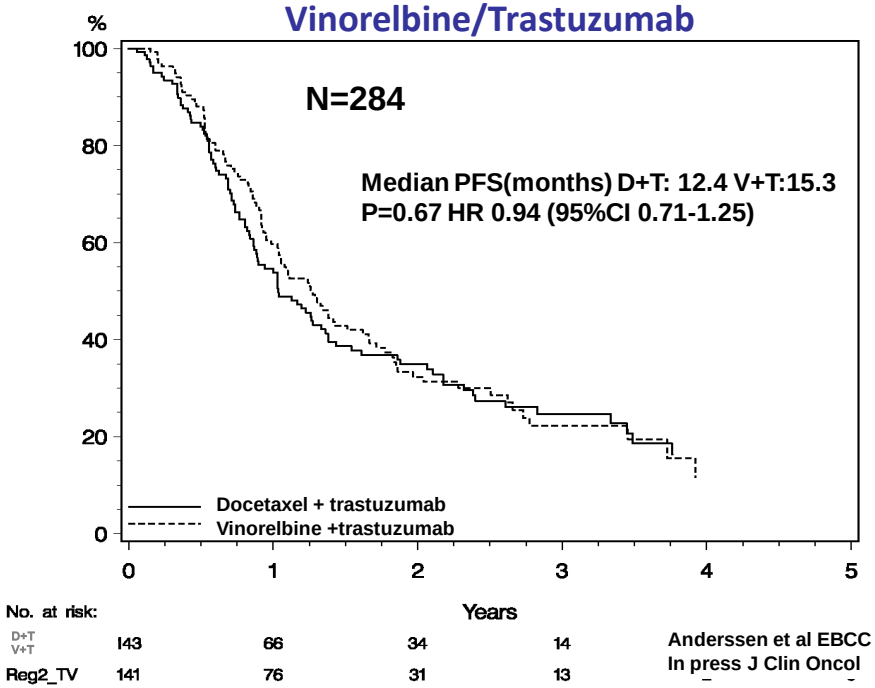
Regarding the CT component of HER-2 positive MBC treatment:

When pertuzumab is not given, 1st line regimens for HER-2 MBC can include trastuzumab combined with a vinorelbine or a taxane.
(LoE: 1 A) (88%)

Differences in toxicity between these regimens should be considered and discussed with the patient in making a final decision.
Other CT agents can be administered with trastuzumab but are not as well studied and are not preferred.

In manuscript: Single agent vinorelbine in association with anti-HER-2 therapy has shown superior or equal efficacy compared to taxanes and has a better tolerability.

HERNATA Trial of Docetaxel/Trastuzumab vs Vinorelbine/Trastuzumab



Anderssen et al EBCC 2010
In press J Clin Oncol

Extrapolating from HER-2+ disease:
Vinorelbine seems at least as good as taxane and significantly less toxic

Vinorelbine & Capecitabine: Consistent efficacy results & NO ALOPECIA

TRAVIOTA:
Taxane + Trastuzumab vs. Vinorelbine + Trastuzumab

First-line MBC
No prior trastuzumab
Measurable Disease
N=81

- Paclitaxel or Docetaxel + Trastuzumab
- Vinorelbine + Trastuzumab

	RR	TTP
Taxane Arm	58%	6.0 months
Vinorelbine Arm	66%	8.5 months

p=0.09

Burstein HJ, et al. *Cancer.* 2007;110:965-972.

HER-2 POSITIVE MBC: CHEMOTHERAPY COMPONENT

For later lines of therapy, trastuzumab can be administered with several CT agents, including but not limited to, vinorelbine (if not given in 1st line), taxanes (if not given in 1st line), capecitabine, eribulin, liposomal anthracyclines, platinum, gemcitabine, or metronomic CM.
(LoE: 2 A) 891%)

The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.

HER-2 POSITIVE MBC: CHEMOTHERAPY COMPONENT

CT agents to combine with a dual blockade of trastuzumab + pertuzumab are docetaxel (LoE: 1 A) or paclitaxel (LoE: 1 B).

Also possible are vinorelbine (LoE: 2 A) and nab-paclitaxel (LoE: 2 B).

(86% Consensus)

New anti-HER agents

Margetuximab-Fc-optimized anti-HER2 Monoclonal Ab

- Derived from 4D5, parent antibody of trastuzumab
  - Margetuximab and trastuzumab bind same epitope on HER2 with high affinity
- Fc domain modifications enhance NK cell and macrophage activation
  - Enhanced binding to low affinity variants of activating Fcγ receptor, CD16A
  - Diminished binding to inhibitory Fcγ receptor, CD32B
- Enhanced antibody dependent cell-mediated cytotoxicity *in vitro*
- Patients with high affinity Fc receptors had prolonged PFS with trastuzumab (*Musolino et al., J Clin Oncol 26: 1789-96 (2008))*
- SOPHIA will test if enhanced ADCC leads to superior outcomes in HER+ MBC

Nordstrom JL, et al. Breast Cancer Research 13:R123, 2011.

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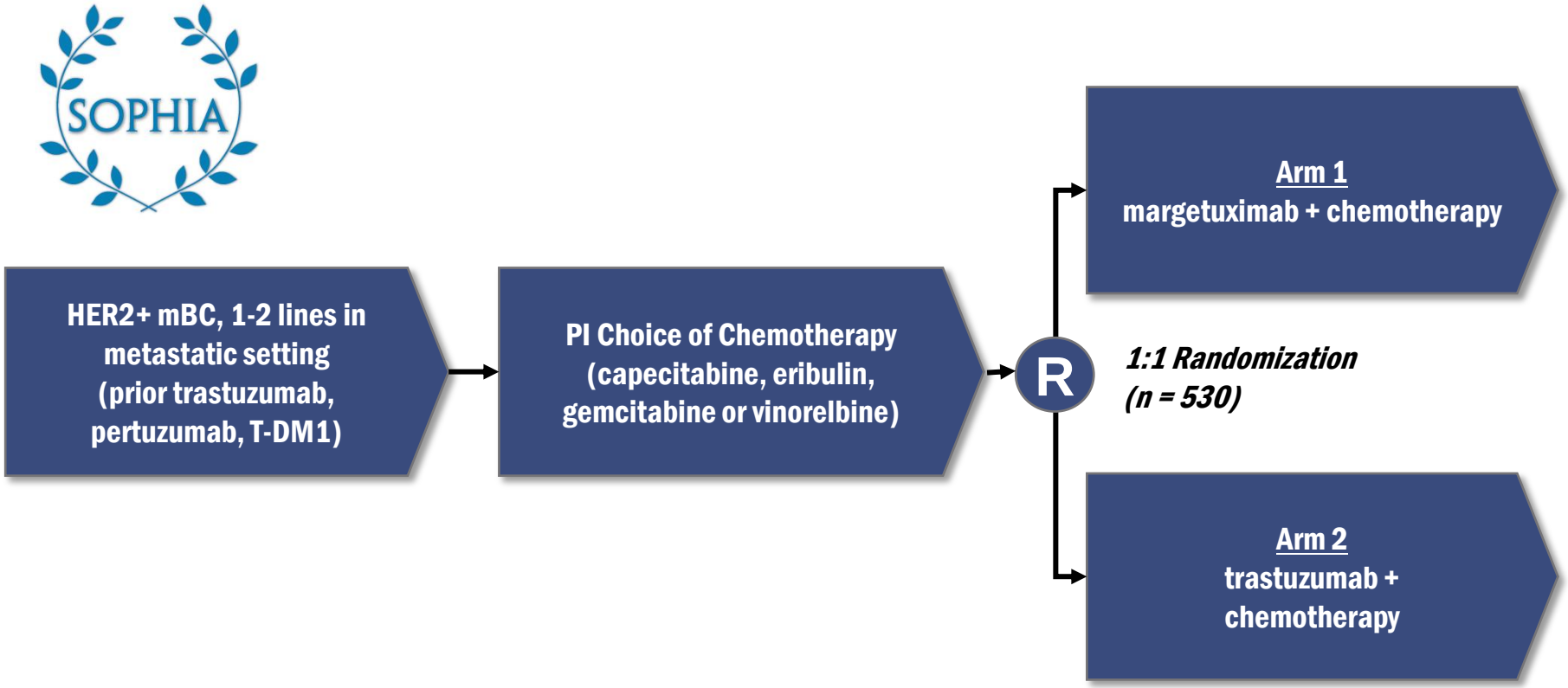
SOPHIA Study to Establish Superiority to Trastuzumab



Sequential Primary Endpoints: Progression-Free Survival & Overall Survival:

PFS (N=257, HR=0.67, α=0.05, power=90%)

OS (N=358, HR=0.75, α=0.05, power=80%)

Brain Metastases

Incidence of CNS Metastases in Trastuzumab-Treated Patients

Case Series	Patient Population	#	Overall	%
Bendell et al, 2003	Trastuzumab-treated	42	123	34
Clayton et al, 2004	Trastuzumab-treated	23	93	25
Lai et al, 2004	Trastuzumab-treated	38	79	48.1
Lower et al, 2003	Trastuzumab-treated	22	87	26
	Non-trastuzumab-treated	58	190	31
Pinder et al, 2007	Trastuzumab-treated first-line	95	231	41
	Non-trastuzumab-treated	12	61	20
Shmueli et al, 2004	Trastuzumab-treated	10	41	21
Stemmler et al, 2006	Trastuzumab-treated	42	136	30.9
Yardley et al, 2007	HER2-positive MBC	236	768	30.7
Yau et al, 2006	Trastuzumab-treated	23	87	26.4

BRAIN METASTASES

Patients with a single or a small number of potentially resectable brain metastasis should be treated with surgery or radiosurgery. Radiosurgery is also an option for some unresectable brain metastases.
(LoE: 1 B) (92%)

If surgery/radiosurgery is performed it may be followed by whole brain radiotherapy but this should be discussed in detail with the patient, balancing the longer duration of intracranial disease control and the risk of neurocognitive effects (LoE: 1 B) (72%)

✓ A multi-disciplinary discussion including neurosurgeons, radiation oncologists and medical oncologists is indispensable in determining the optimal treatment for each patient.
✓ The treatment plan can also be a combination of these three available therapeutic approaches

HER-2 POSITIVE MBC & BRAIN METASTASES

Because patients with HER2+ve MBC and brain metastases can live for several years, consideration of long term toxicity is important and less toxic local therapy options (e.g. stereotactic RT) should be preferred to whole brain RT, when available and appropriate (e.g. in the setting of a limited number of brain metastases).

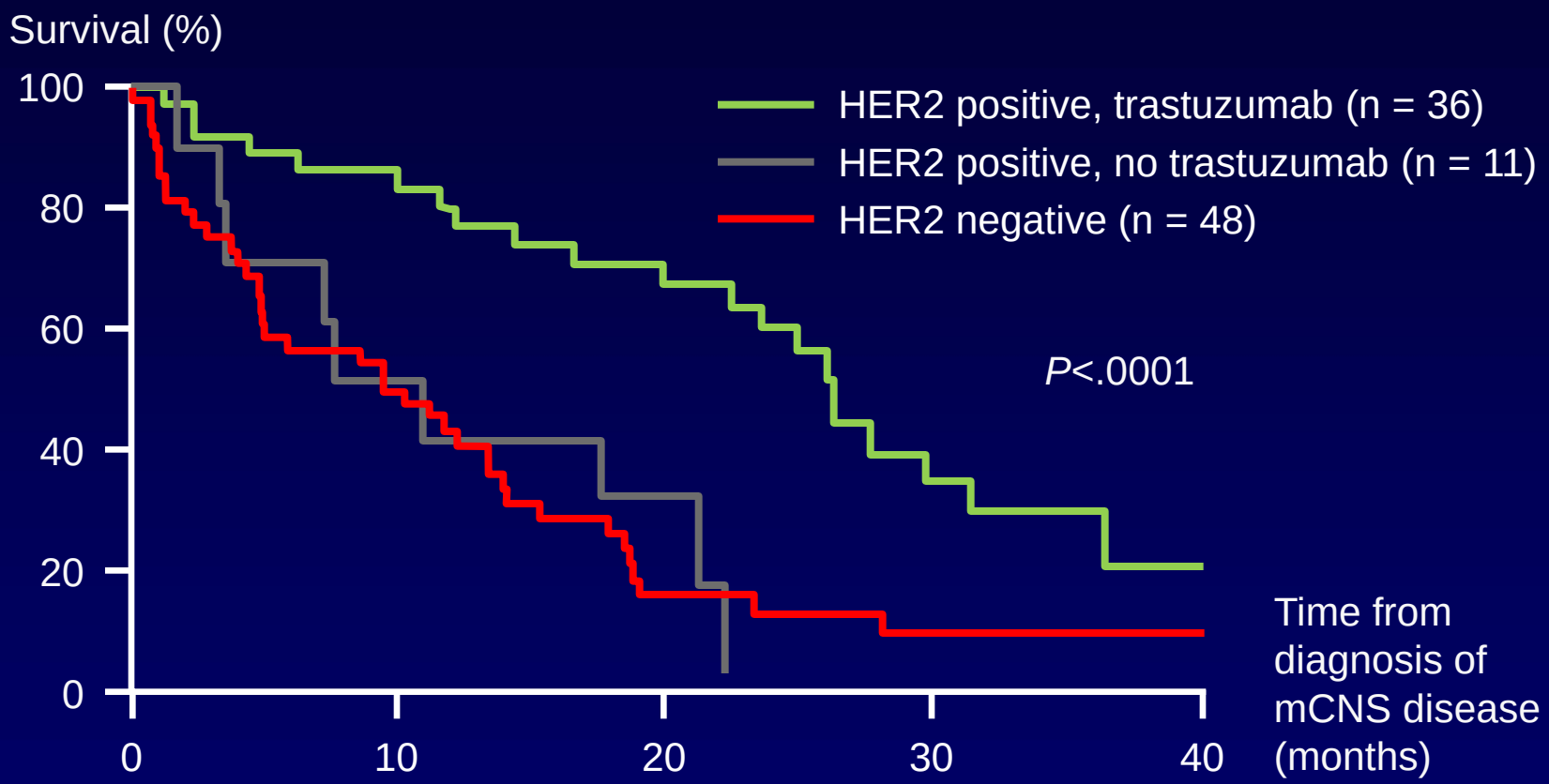
(LoE: 1C) (89%)

HER-2 POSITIVE MBC & BRAIN METASTASES

in patients with HER2 positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed.
(LoE: 1 C) (95%)

For patients with HER2 positive cancers where brain metastases are the only site of recurrence, the addition of CT to local therapy is not known to alter the course of the disease.
It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped.
(LoE: 1 C) (83%)

Trastuzumab Improves Survival in Patients With mCNS Disease: U S Retrospective Analysis



Kirsch DG, et al. *J Clin Oncol.* 2005;23(9):2114-2116.

LANDSCAPE STUDY: a FNCLCC phase II study with lapatinib and capecitabine in pts with brain metastases from HER-2+ MBC before whole brain RT

Primary endpoint: CNS volumetric response

45 pts

CNS-OR: 29/43 = 67.4% (95% CI: 52-81)

CNS volumetric change	N = 43 (%)	
≥ 80% reduction	9	(20.9)
50-<80% reduction	20	(46.5)
20- <50% reduction	6	(14)
> 0- <20% reduction	2	(4.7)
Progression*	6	(14)

* 2 patients had extra-CNS disease progression

NSS improvement: 14/24 = 58.3% (95% CI: 36.6-77.9)

IMP: pts previously untreated with WBRT; phase 2 study

Bachelot et al, ASCO 2011

CEREBEL Study: A Phase III Randomized Open-Label Study of Lapatinib plus Capecitabine vs Trastuzumab + Capecitabine in HER2-Positive Metastatic Breast Cancer

Inclusion Criteria:

- Stage IV HER2+ breast cancer
- Prior anthracycline and a taxane
- Pri… trast… pern…
- LVI… func…

Main Exclusion Criteria:

- History and/or current evidence of CNS metastases
- Prior therapy with lapatinib or ErbB2 inhibitor other than trastuzumab

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Capecitabine 2500 mg/m^2 bid d1-14 q21 days

…g/kg→

Lapatinib 1250 mg PO qd continuously

+

capecitabine 2000 mg/m^2/d
PO days 1-14 q3 weeks

EARLY CLOSURE!!

475 pts enrolled

40% completed 12 months, had PD or died

- **Primary endpoint: Incidence of CNS metastases at site of first relapse**
- **Secondary endpoints: Incidence of CNS progression at any time, time to first CNS progression, PFS, OS, ORR, CBR, duration of response, toxicity, pharmacogenetics, and biomarker analysis**

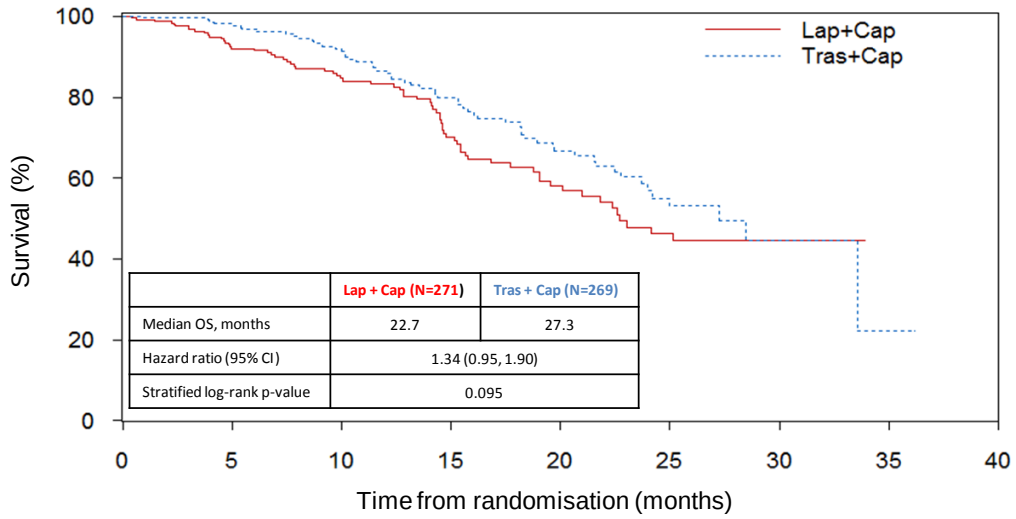
Primary endpoint: CNS endpoints (modified ITT)

	Lapatinib + capecitabine (N=251)	Trastuzumab + capecitabine (N=250)	OR (95% CI)	p-value
CNS as first site of relapse, n (%)	8 (3)	12 (5)	0.65 (0.26, 1.63)	0.360
Incidence of CNS progression at any time, n (%)	17 (7)	15 (6)	1.14 (0.52, 2.51)	0.8646
Time to first CNS progression, median (range)	5.7 (2–17)	4.4 (2–27)	-	-

LOW NUMBER OF BRAIN METS

TRASTUZUMAB + CAPECITABINE BETTER

OS (ITT population)



Subjects at risk

Lap + Cap	271	194	129	79	48	27	7
Tras + Cap	269	207	140	97	61	29	6	1

HER-2 POSITIVE MBC

All patients with HER-2+ MBC who relapse after adjuvant anti-HER-2 therapy should be considered for further anti-HER-2 therapy, except in the presence of contraindications (LoE: 1 B) (97%)

The choice of the anti-HER-2 agent will depend on country-specific availability, the specific anti-HER-2 therapy previously administered, and the relapse free interval. (88%)

The optimal sequence of all available anti-HER-2 therapies is currently unknown. (88%)

The optimal duration of anti-HER-2 therapy for MBC (i.e. when to stop these agents) is currently unknown. (97%)

MANAGEMENT OF HER-2 + MBC:

MANY QUESTIONS SILL UNANSWERED

- Optimal duration of anti-HER-2 therapy for ABC (indefinitely?)
- At progression should only the cytotoxic drug be changed of both the cytotoxic and the anti-HER-2 agent
- Is treatment beyond PD also true for other anti-HER-2 agents?
- Dual blockade for everyone or some?
- The role of the dual blockade without CT
- Triple blockade?
- Best sequence of anti-HER-2 therapies
- Mechanisms of resistance & ways to overcome it; Predictive markers (role of PI3K mutations,...)
- NEW ANTI-HER-2 AGENTS in development

Bridging the Gap

ABC4

European School of Oncology
learning to care

Advanced Breast Cancer

2-4 November 2017 • Lisbon, Portugal

Fourth International Consensus Conference

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