SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

ESMO Clinical Practice Guidelines Metastatic HER2 + Breast Cancer

Evidence to Support Clinical Case Presentation

Updated with data from San Antonio Breast Cancer Symposium, 2015

December 20th, 2015

Rebecca Dent, MD FRCP (Canada)

Senior Consultant, National Cancer Center Singapore

Associate Professor, Duke-NUS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

Disclosures

Consulting or advisory role: AstraZeneca, Celgene, Novartis, Pfizer, Roche

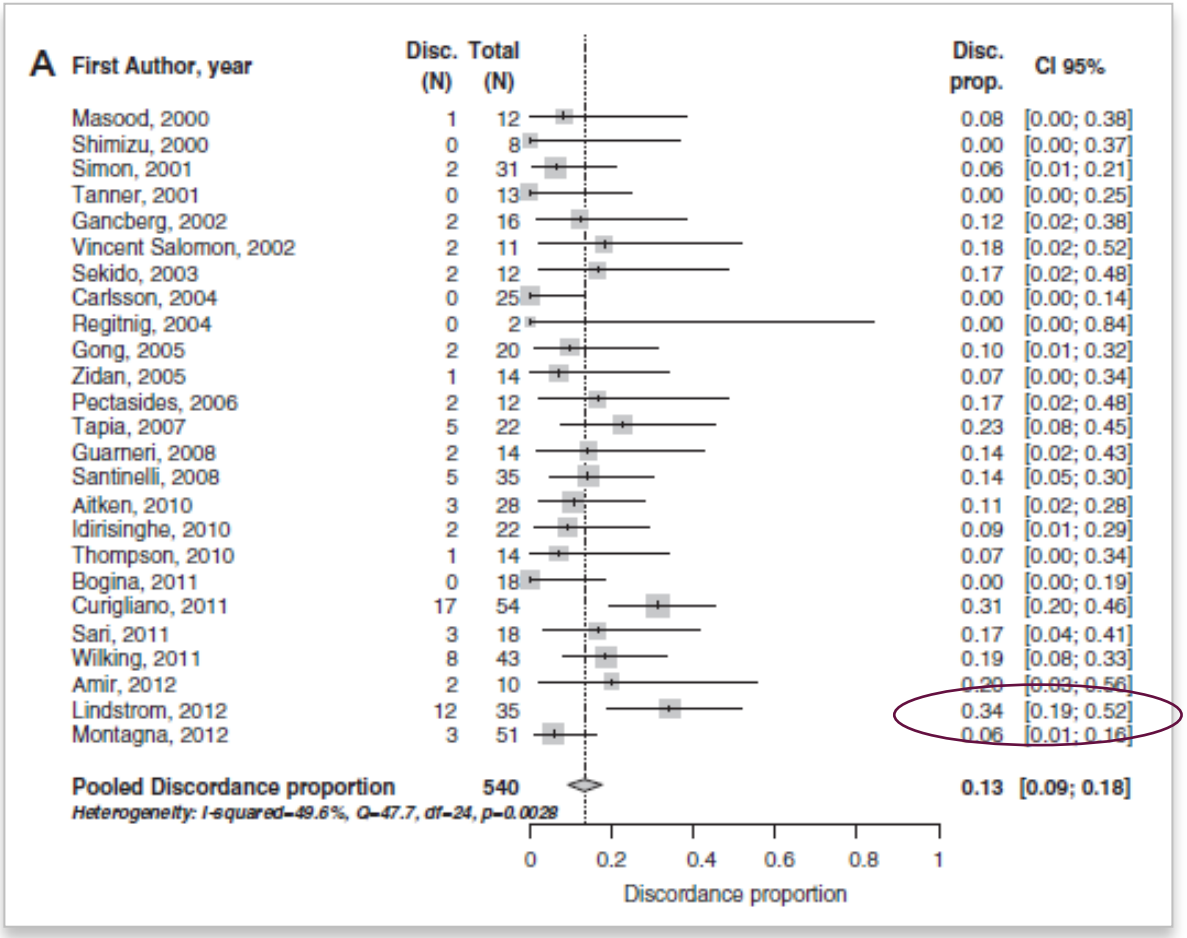
Travel grants: Eisai, Roche, Merck

Case Summary:

- T2N2 ER - PR -, HER2 + BC
  - Treated with Anthracycline/Taxane- Herceptin x 1 year
  - Adjuvant Radiation
- Current situation
  - 1 year after completing adjuvant Herceptin - Isolated Ipsilateral supraclavicular LN recurrence
- No major comorbidities and organ dysfunctions

Should we biopsy her left supraclavicular LN?

YES!



Proportion of negative conversion for HER2

Aurilio et al. EJC 2014; 50: 277– 289

…but would this alter our treatment choice?

Table 2 Change in management based on biopsy

Reference	Number of patients	Therapy changed (%)
Lindstrom *et al.* [7]	1,010	23 (HER2) 50 (ER)
Curigliano *et al.* [9]	255	12.1
Amir *et al.* [2]	289	14.2
Bogina *et al.* [11]	140	7.3
Amir *et al.* [4]	121	14
Simmons *et al.* [15]	40	20
Thompson *et al.* [5]	137	17.5

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

Criscitiello et al. BCR 2014; 16: 205

Repeat biopsy - ESMO CPG

A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time
(LoE: II C)

Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible (LoE: II C)

If the results of tumour biology in the metastatic lesion differ from the primary tumour, it is currently unknown which result should be used for treatment-decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of targeted therapy (ET and/or anti-HER-2 therapy) when receptors are positive in at least one biopsy, regardless of timing (LoE: Expert opinion)

Cardoso et al. Breast. 2012; 21: 242-52

In real practice…

- Threshold to biopsy should be lower when:
  - the radiological work-up has identified one single lesion,
  - when the patient has a history of more than one cancer,
  - when the suspicion of an alternative diagnosis is high
    - Clinical course is not in keeping with natural history of disease (ie ER + breast cancer with extensive visceral relapse within 6 months of adjuvant therapy)

Foukakis et al. Ann Oncol 2012; 23 (Suppl. 10): x349–x353

What is the optimal 1st line therapy HER2 directed therapy?

PFS, progression-free survival
OS, overall survival

Cardoso et al. Ann Oncol 2014; 25: 1871-88; Cardoso et al. Breast 2014; 23: 489-502; Gelmon et al. JCO 2015; 33:1574-83; Pivot et al. JCO 2015; 33:1564-73

Pivotal 1st line Phase 3 Trials Trastuzumab

Study	Median Survival, Mos		HR (95% CI)	P Value
	Chemotherapy Alone	Chemotherapy + Trastuzumab		
Paclitaxel (Slamon)[1]	20.3 →	25.1	0.80 (0.64-1.00)	.046
Docetaxel (Marty)[2]	22.7 →	31.2	Not reported	.0325

1. Slamon DJ, et al. N Engl J Med. 2001;344:783-792.
2. Marty M, et al. J Clin Oncol. 2005;23:4265-4274.

HERNATA: Trial Design

HER2-positive MBC/LABC
- **First line therapy**

1:1

N = 143 — **Q 3 w***
Docetaxel 100 mg/m² day 1 +
Trastuzumab (8) 6 mg/kg day 1

N = 141 — **Q 3 w***
Vinorelbine 30-35 mg/m² days 1+8**
Trastuzumab (8) 6 mg/kg day 1

A randomized, multicenter, phase III trial conducted at institutions in Denmark, Sweden, and Norway

Endpoints
- Primary: TTP
- Secondary: OS, 1-year survival rate of response, time to treatment failure (TTF), toxicity and tolerability

***Treatment duration to PD or unacceptable toxicity**
****vinorelbine dose per institutional preference**

LABC, locally advanced breast cancer; MBC, metastatic breast cancer; OS, overall survival; PD, progressive disease; TTF, time to failure; TTP, time to progression

Doce + Trastuzumab (D+T) vs Vino + Trastuzumab (V+T)

Outcome	D+T (n = 143)	V+T (n = 141)	*P* Value
Median TTP, months	12.4	15.3	.67
Median OS, months	35.7	38.8	.98
Median TTF, months	5.6	7.7	< .0001
Toxicity Grade 3/4	**D+T (n = 139)**	**V+T (n = 138)**	***P* Value**
Febrile neutropenia	37.4	10.8	< .001
Leukopenia	40.3	21.0	< .001
Infection	23.7	13.0	.006
Fever	4.3	0	.03
Neuropathy (sensory)	30.9	3.6	< .001
Edema	5.8	0	.003
Nail changes	7.9	0.7	.005

* Only statistically significant toxicity included in the table

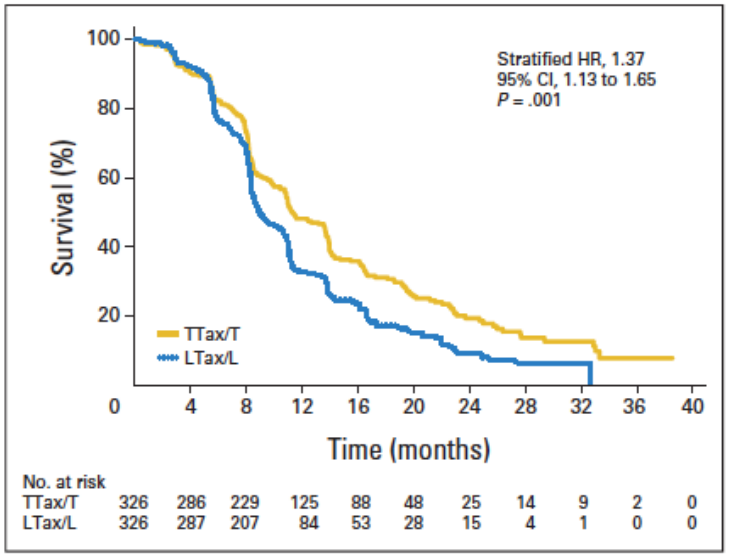
Andersson M, et al. *J Clin Oncol.* 2011;29(3):264-271.

1st line HER2 + Therapy - ESMO CPG

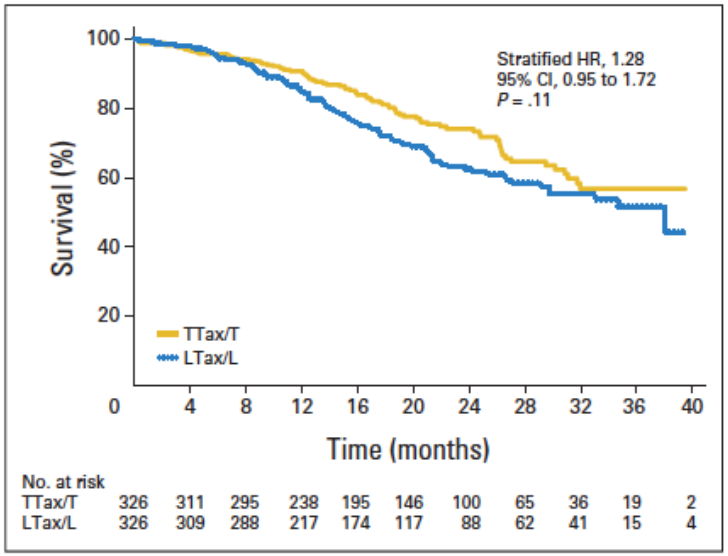
In the 1st line setting, for HER-2+ MBC previously treated (in the adjuvant setting) or untreated with trastuzumab, combinations of ChT + trastuzumab are superior to combinations of ChT + lapatinib in terms of PFS and OS (LoE: I A)

1st line Taxane + Lapatinib vs. Taxane + Trastuzumab (NCIC CTG MA.31)

Progression-free survival



Overall survival



	Lapatinib + Taxane	Trastuzumab + Taxane	Hazard ratio	P-value
ORR	54%	55%		
PFS	9.0 months	11.3 months	1.37	0.001
OS	NR	NR	1.28	0.11

At the interim analysis, Lapatinib arm had inferior PFS – NCIC DSMC recommended disclosure and notification of patients. Final analysis with 395 PFS events presented here

Gelmon et al. JCO 2015;1574-1583

1st line HER2 + Therapy - ESMO CPG

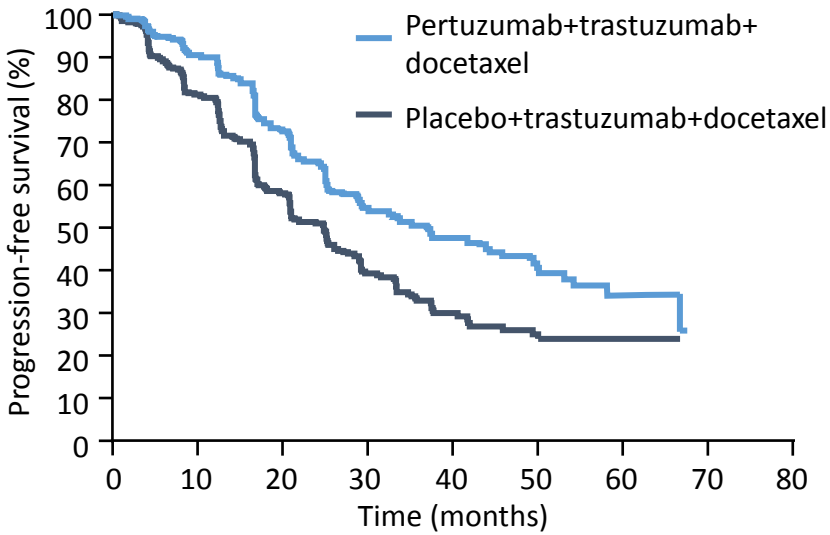
In 1st line therapy, the combination of CT + trastuzumab and pertuzumab is superior to CT + trastuzumab, primarily for previously untreated HER-2+ MBC, making it the preferred treatment option since it is associated with OS benefit. (LoE: 1 A) (90%)

It is currently unknown how this treatment compares to other anti-HER-2 options such as T-DM1 (Trastuzumab Emtansine).

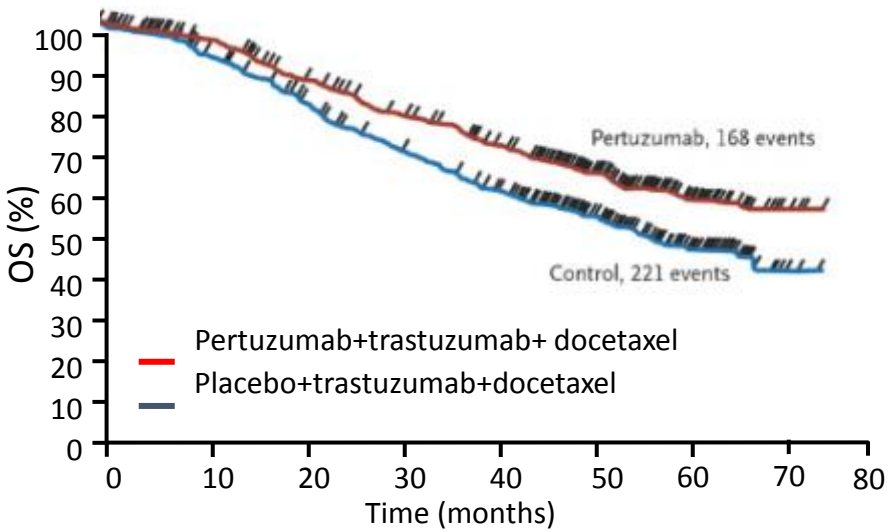
CLEOPATRA:

1st-line Pertuzumab + Trastuzumab

Progression-free survival[1]



Overall survival[2]



	Pertuzumab+ trastuzumab+docetaxel	Placebo+ trastuzumab+docetaxel	Hazard ratio	P-value
ORR[1]	80.2%	69.3%		**0.0001**
PFS[1]	18.7 months	12.4 months	**0.69**	**<0.0001**
OS[2]	56.5 months	40.8 months	**0.66**	**0.0001**

Most common adverse events ≥Grade 3 in the pertuzumab+trastuzumab+docetaxel group:[1]
Neutropenia (48.9%), febrile neutropenia (13.8%), leukopenia (12.3%) and diarrhoea (7.9%)

Median follow-up: 30 months. PFS, progression-free survival; OS, overall survival.

1. Baselga et al. N Engl J Med 2012;366:109; 2. Swain et al. NEJM 2015;724:734.

CLEOPATRA: Exposure to docetaxel in patients from Asia

Docetaxel dose reductions below 75 mg/m2 occurred in 47% of patients from Asia compared with13% of patients from other regions.

But did not adversely affect efficacy in patients from Asia, with PFS and overall survival being comparable with that of patients from other regions.

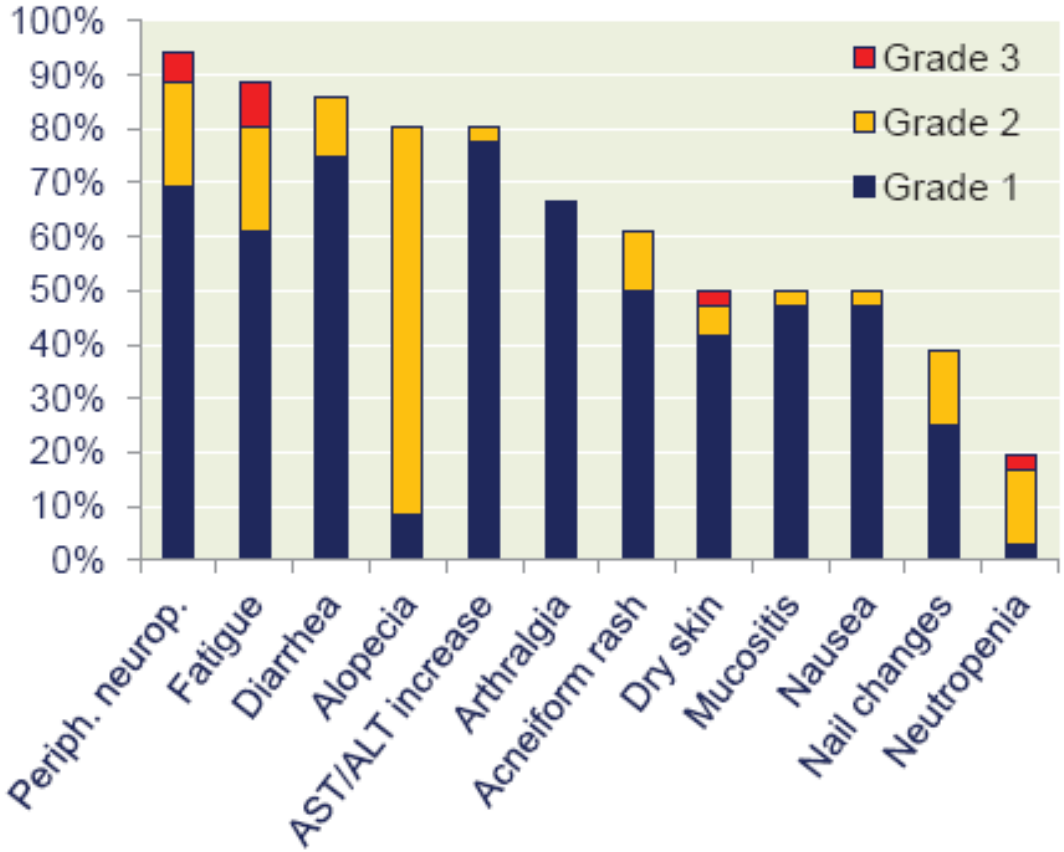
A reduction in the docetaxel starting dose should therefore be considered in patients from Asia…

				PHT n = 125
Median				20.0 (1–50)
Median				9.0 (1–30)
Median				23.9
Docetax				1 (0.8)
Docetaxel (%)				
One				62 (49.6)
Two				61 (48.8)
				1 (0.8)
Docetax				
No, n (%)	97 (36.1)	78 (27.7)	45 (35.2)	31 (24.8)
Yes, n (%)	172 (63.9)	204 (72.3)	83 (64.8)	94 (75.2)
	166/172 (96.5)	194/204 (95.1)	79/83 (95.2)	91/94 (96.8)

Data cut-off: May 2011
* Includes patients with initial dose escalation to 100 mg/m^2 followed by two subsequent dose reductions
H, trastuzumab; P, pertuzumab; T, docetaxel

Swain SM, *et al*. *The Oncologist* 2014; **19**:1–9

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

Edith A. Perez et al. 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

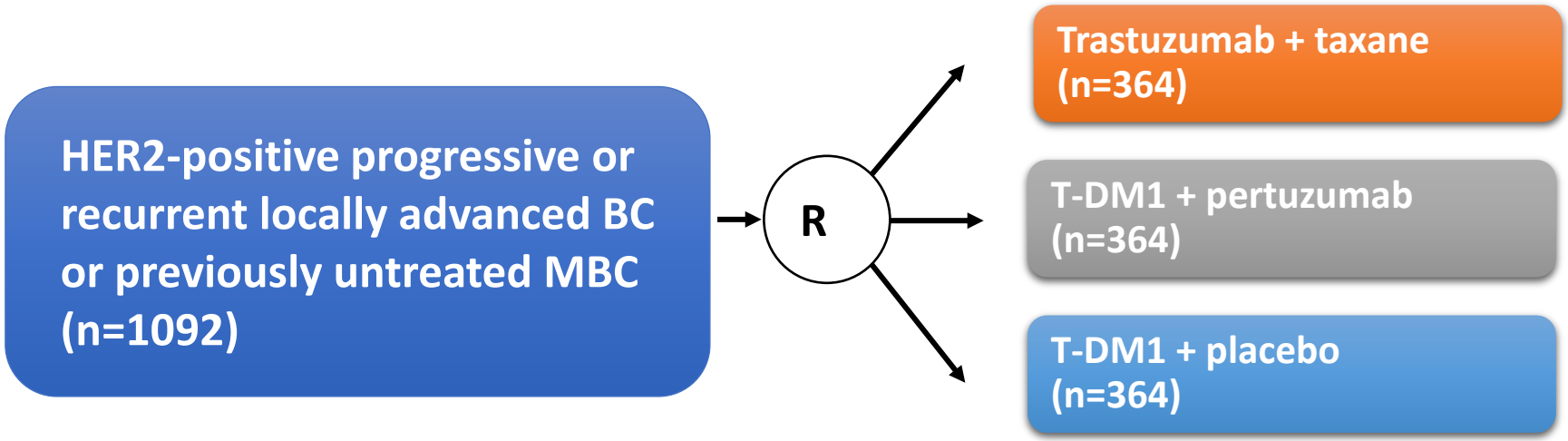
* Pertuzumab, trastuzumab, and docetaxel arm; † Trastuzumab and vinorelbine arm; ‡ First six cycles only; § Grade 2–4 only, grade 1 toxicities NR; ‖ Pooled 'neutropenia' and 'neutrophil count decreased' preferred terms; ¶ Pooled 'leukopenia' and 'white blood cell count decreased' preferred terms

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.

MARIANNE:

Phase III study of T-DM1 with or without Pertuzumab vs Taxane and Trastuzumab (no Pertuzumab)



	Trastuzumab + Taxane	T-DM1 + Placebo	T-DM1 + Pertuzumab	Hazard ratio	P-value
ORR	67.9%	59.7%	64.2%	NR	NR
PFS	13.7 m	14.1m	15.2m	HR 0.91 HR 0.87	p=0.31 p=0.14
OS	NR	NR	NR	HR 0.86	p NR p NR

Ellis et al

Comparison of patient populations Limited prior *Adjuvant Trastuzumab* Therapy

	MARIANNE (ASCO 2015)	CLEOPATRA (NEJM 2015)	BOLERO1 (SABCS 2014)	MA-31 (ASCO 2012)
Chemo	Docetaxel/Paclitaxel	Docetaxel	Paclitaxel	Taxane
Anti-HER2 regimens tested	T-DM1 or T-DM1 + Pertuzumab	Trastuzumab + Pertuzumab *(vs TRAS)*	Trastuzumab + Everolimus 10mg OD *(vs TRAS)*	Lapatinib *(vs TRAS)*
De novo metastatic	55%	53%	≈ 50%	43%
Prior adj. trast. (and interval >1y)	**31%**	**11%**	**10%**	**18%**

The results of most of these trials are relevant today only for de novo metastatic patients

Adapted from M. Piccart St. Gallen 2015 Presentation

Prior Trastuzumab Efficacy Data

Adjuvant Trastuzumab DFI > 1year

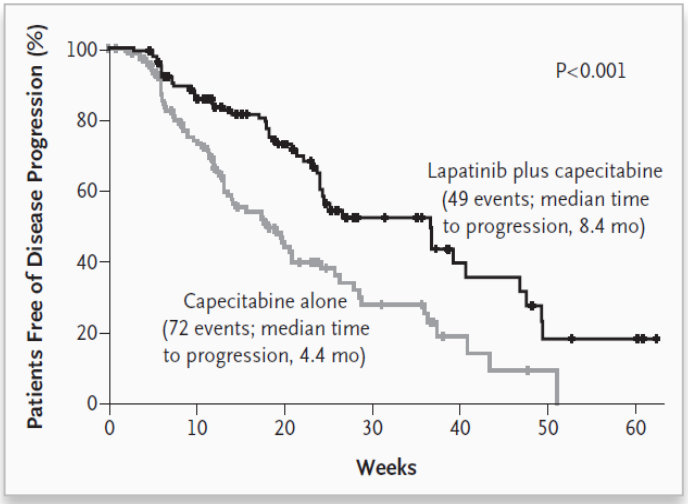
	MARIANNE (ASCO 2015)	CLEOPATRA (NEJM 2015)[1]	BOLERO1 (SABCS 2014)	MA-31 (ASCO 2012)
PFS	***10.3 months vs 15.2 months*** (T-DM1)	***10.4 months vs. 16.9 months*** *(p value not reported)*	*NR*	*NR*
OS	*NR*	***46.6 months vs 53. 8 months*** *(p value not reported)*	*NR*	*NR*

1 Swain et al NEJM Correspondence 2015

2nd line metastatic HER2+: ESMO CPG

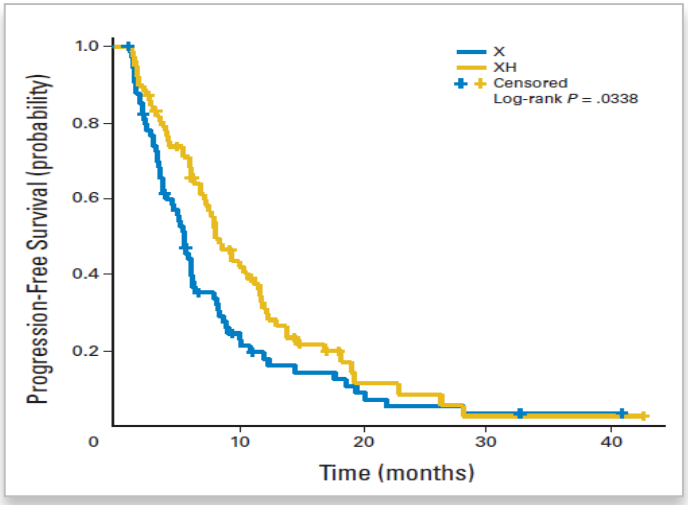
Patients whose tumours progress on an anti-HER-2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER-2 therapy with subsequent treatment since it is beneficial to continue suppression of the HER-2 pathway (LoE: I B)

EGF100151



PFS

GBG-26



PFS

Cardoso et al. Breast. 2012; 21: 242-52;
Geyer et al. NEJM 2006; 355: 2733-43; von Minckwitz et al. JCO 2009; 27: 1999-2006.

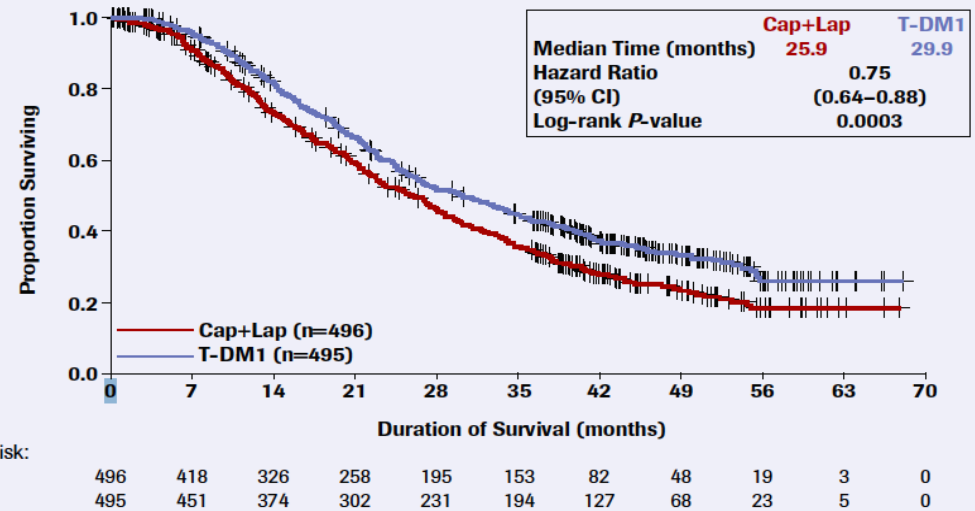
2nd line metastatic HER2+ cont…: ESMO CPG

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, since it provides an OS benefit (LoE: I A)

EMILIA
OS Update

SABCS 2015
V. Dieras

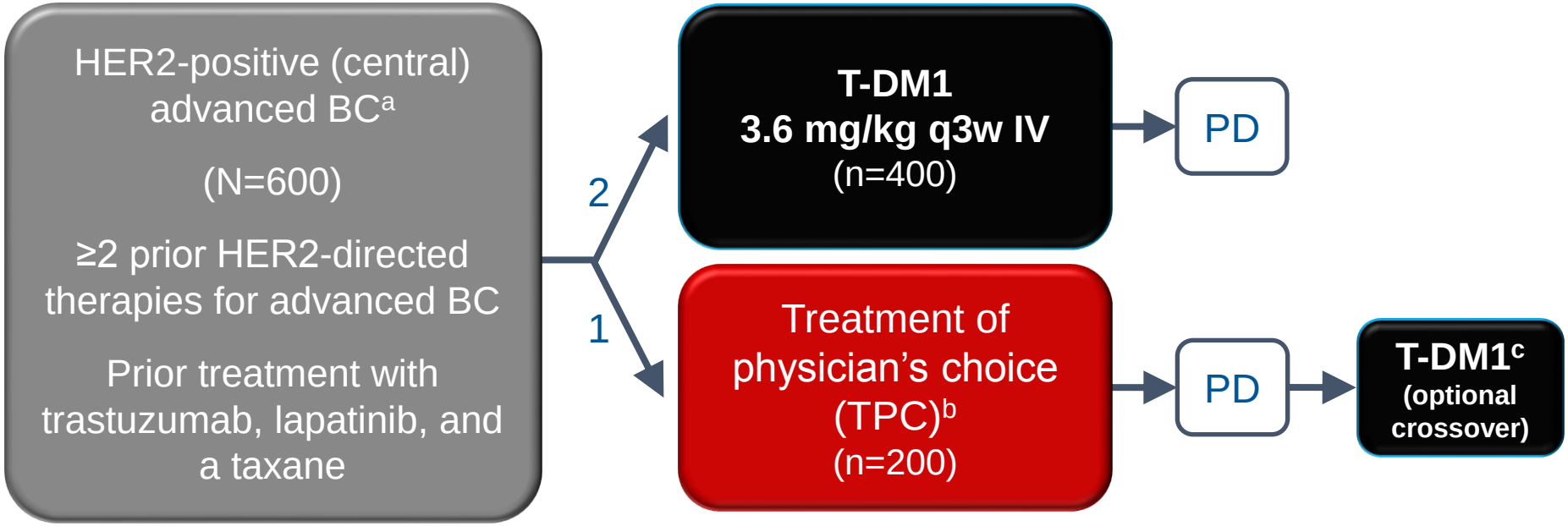
Figure 3. Final overall survival in the intent-to-treat population



Cap+Lap, capecitabine plus lapatinib; CI, confidence interval; T-DM1, trastuzumab emtansine.

Cardoso et al. Ann Oncol 2014; 25: 1871-88; Cardoso et al. Breast 2014; 23: 489-502; Verma et al. NEJM 2012; 367: 1783-91

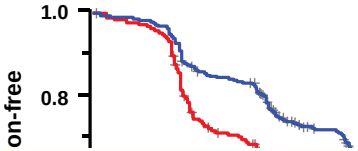
TH3RESA Study Schema – 3rd line or greater



- **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

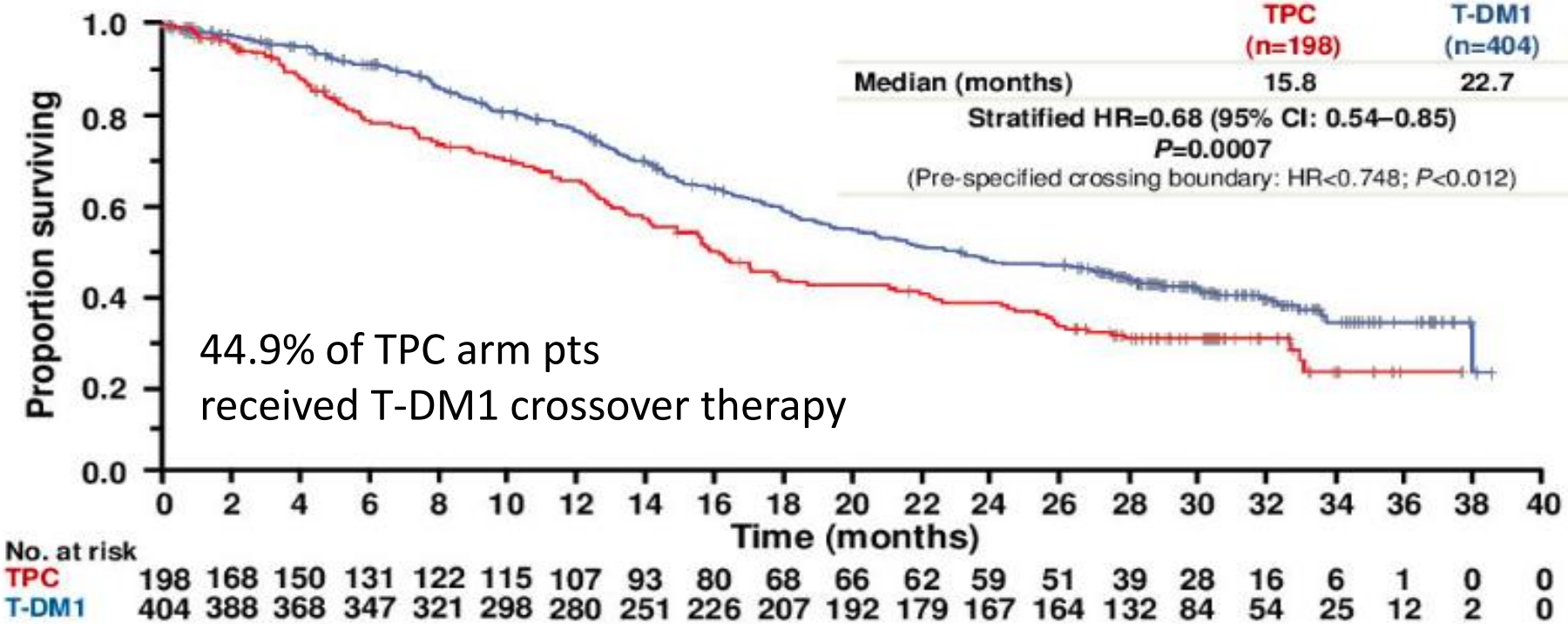


	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219
Stratified HR=0.528 (95% CI, 0.422, 0.661)		

SUPERIOR PFS

Final OS Analysis

SABCS 2015



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

	0	2	4	6	8	10	12	14	16
	Time (months)								
No. at risk:									
TPC	198	169	125	80	51	30	9	3	0
T-DM1	404	381	316	207	127	65	30	7	0

44 patients in the TPC arm received crossover T-DM1 treatment after documented progression.
Unstratified HR=0.57 (*P*=0.004).

TH3RESA: Treatment Choice in TPC Arm

- 80.4% of pts assigned to TPC arm received trastuzumab-containing combination regimen

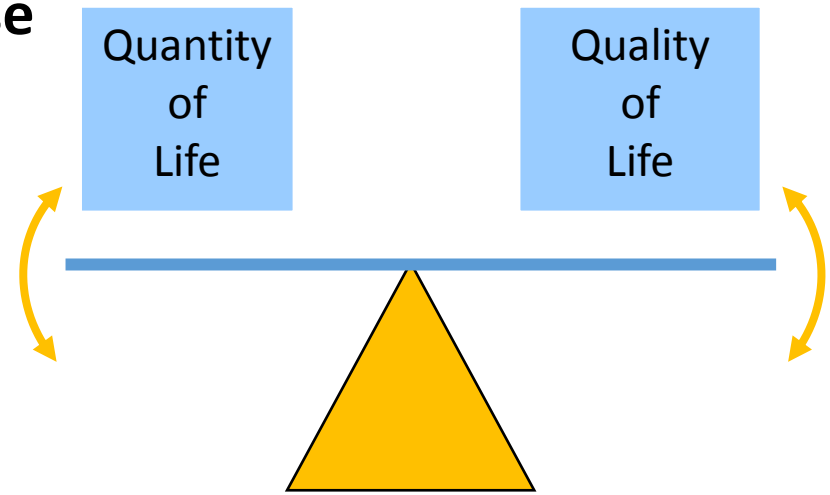
Treatment Regimen in TPC Arm, %	TPC (n = 184)
Combination regimen including anti-HER2 agent	83.2
▪ Chemotherapy* + trastuzumab	68.5
▪ Lapatinib + trastuzumab	10.3
▪ Hormonal therapy + trastuzumab	1.6
▪ Chemotherapy + lapatinib	2.7
Single-agent chemotherapy*	16.8

*Most commonly used chemotherapy agents: vinorelbine, gemcitabine, eribulin, paclitaxel, docetaxel.

Wildiers H, et al. SABCS 2015. Abstract S5-05.

Remember the Goals of Treatment!

- **Balancing treatment efficacy and toxicity is the main objective**
- **Goals of treatment:**
  - **Improve survival** *(very few agents achieve it!)*
  - **Delay disease progression**
  - **Prolong duration of response**
  - **Palliate symptoms**
  - **Improve or maintain quality of life**
  - **Transform into a chronic disease**



Courtesy Fatima Cardoso

HER2-targeted therapies are recommended across international treatment guidelines (ASCO, ESMO, NCCN, AGO)[1–4]*

First line

- Pertuzumab + trastuzumab + docetaxel[2–4]
- Pertuzumab + trastuzumab + paclitaxel[2,3#]
- Anti-HER2 therapy (trastuzumab or lapatinib) + chemotherapy[1–3]
- T-DM1 (relapse within 6 months after taxane and trastuzumab pre-treatment)[3]
- Trastuzumab monotherapy[1–3#]
- AI + trastuzumab or lapatinib (ER-positive BC)[1–3]

Second line

- T-DM1[2–4]
- Lapatinib + capecitabine[1–3]
- Trastuzumab + capecitabine[2#]
- Trastuzumab ± chemotherapy[1–3#]
- Trastuzumab + lapatinib[1–3#]
- Pertuzumab + trastuzumab plus either taxane or any other second-line chemotherapy[3#]
- AI + anti-HER2 therapy (ER-positive BC)[3]

Third line

- T-DM1[3,4]
- Lapatinib + capecitabine[1,3]
- Trastuzumab + lapatinib[1,3#]
- Trastuzumab + chemotherapy (treatment beyond progression)[1,3#]
- Trastuzumab + pertuzumab[3#]

AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; AI, aromatase inhibitor; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; TGA, Therapeutic Goods Administration.

* Please refer to product-specific labels in your country for indications approved in your market. International guidelines may not be in line with current national guidelines

# Denotes recommendations that are outside of the TGA-approved indication in Australia

1. Cardoso F, *et al. Ann Oncol* 2012; **23(Suppl 7)**:vii11–vii19; 2. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (v1_2014); 3. http://www.ago-online.de/en/guidelines-mamma/march-2014/; 4. Giordano SH, *et al. J Clin Oncol* 2014; **32**:2078–2099.

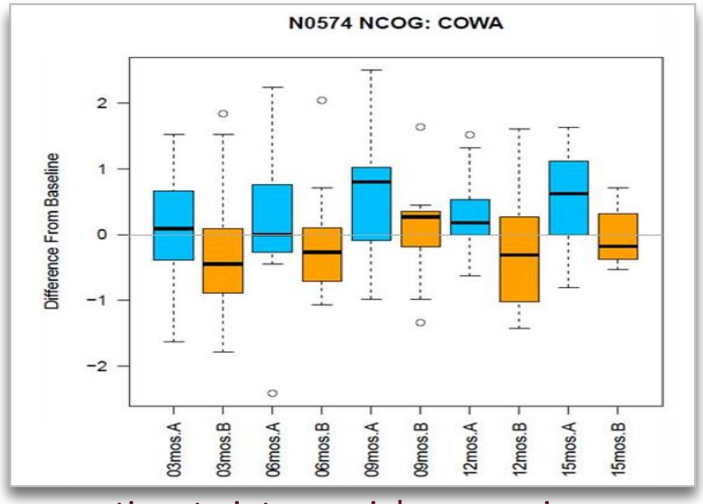
Acknowledgements

- Fatima Cardoso
- Elżbieta Senkus
- Sunil Verma
- ESMO

HER2+ brain metastases: ESMO CPG

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: IC)

NCCTG N0574



time to intracranial progression
cognitive function

RT, radiotherapy

Cardoso et al. Ann Oncol 2014; 25: 1871-88; Cardoso et al. Breast 2014; 23: 489-502; Brown et al. ASCO 2015; LBA4