

The logo features a white stopwatch icon with a large number '5' inside the circular dial. To the right of the stopwatch, the word 'Minute' is written in a large, bold, white sans-serif font, and 'Journal Club' is written below it in a smaller, white sans-serif font.

5 Minute Journal Club

POST-SABCS Issue 2, 2013

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CME Information

LEARNING OBJECTIVES

- Appraise recent clinical research findings from the second interim survival analysis of the CLEOPATRA study and the subset analysis of patients based on age, and apply this information to the treatment of patients with metastatic HER2-positive breast cancer.
- Recall the benefits and risks of combining HER2-targeted antibodies with chemotherapeutic agents for the treatment of HER2-positive advanced breast cancer.
- Understand the association between PI3 kinase mutational status and prognosis in patients with HER2-positive metastatic breast cancer.
- Evaluate the efficacy and safety of adding eribulin mesylate to trastuzumab for patients with HER2-positive advanced breast cancer.
- Compare the toxicity profile of T-DM1 across multiple studies in metastatic HER2-positive breast cancer, and consider this information in the selection of optimal HER2-targeted later-line therapy.

CME Information (Continued)

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FACULTY DISCLOSURES

The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Consulting Agreements: Genentech BioOncology, Novartis Pharmaceuticals Corporation.

CME Information (Continued)

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The new world of HER2-positive breast cancer

Last week I met with the new Physician-in-Chief at Memorial Sloan-Kettering Cancer Center, Dr José Baselga, and after talking a bit about his vision for the future of that preeminent institution we focused on a corner of oncology he has influenced mightily throughout his career, breast cancer research. Not surprisingly, we spent much of our time reviewing anti-HER2 treatment — which has witnessed the FDA approval of 2 new agents in the past 9 months.

Dr Baselga got things started by commenting on the Phase III trial he chaired, CLEOPATRA, which clearly demonstrated a substantial boost in efficacy when the HER2 dimerization inhibitor pertuzumab (P) was added to docetaxel and trastuzumab (T) as first-line therapy for metastatic HER2-positive disease. In the trial progression-free survival (PFS) increased from 12.4 to 18.5 months with a similar safety profile, and although the magnitude of this landmark finding surprised many observers, Dr Baselga stated that he fully expected the results based on the substantial antitumor activity seen when P was added to T in patients with disease progression on T in a prior Phase II trial.

We then chatted about the antibody-drug conjugate trastuzumab emtansine (T-DM1) and the EMILIA trial that exploded onto the scene during the ASCO 2012 plenary session, revealing T-DM1's clear-cut superiority in both efficacy

(PFS and overall survival) and tolerability over an established and frequently used regimen (capecitabine/lapatinib) among patients who had previously been treated with T + a taxane. As the agent was just approved 2 weeks before the interview, our conversation took on a different tone, as for the first time I was able to ask an investigator the practical (rather than hypothetical) question of current sequencing of therapy for metastatic HER2-positive disease. Dr Baselga, in commenting on this complex issue that has likely been discussed at every tumor board on the planet, slowly removed his eyeglasses, carefully put them on the desk, thought for a moment and then voiced his perspective, which is similar to those I have heard recently from Dr Eric Winer and others: "Some people are so excited about T-DM1 that they want to use it first line, but I think this is a time for intellectual calm. Right now, trastuzumab, pertuzumab and a taxane is our standard first-line treatment, with T-DM1 as second line."

For the record, he and his Memorial colleagues usually choose paclitaxel as a partner for T + P, partially based on the reassuring Phase II data the group reported at San Antonio with this regimen. As I have been known to do, I tried to push Dr Baselga a bit regarding his strong feeling not to use T-DM1 first line and asked him how he would approach an 85-year-old patient with ER-negative, HER2-positive metastatic breast cancer for whom traditional chemotherapy might be out of place. He, however, stuck to his guns, commenting that a short taxane course (with T + P) in many fit, older patients is a well-tolerated life investment that results in a median progression-free interval of 18 months.

Whatever the algorithm is for now, it may very well change in a year or so when the MARIANNE study reports. This crucial Phase III first-line trial compares T + a taxane to T-DM1 alone or with P. Dr Baselga very clearly stated his opposition to

the nonprotocol use of T-DM1 combined with P until more trial data become available, and other investigators, including Dr Winer, have done the same.

Of course, many other complex questions remain about the treatment of metastatic HER2-positive breast cancer, and below we review some of the more interesting efforts unveiled in San Antonio that attempt to provide needed answers:

1. More from the CLEOPATRA trial: Overall survival benefit; biomarker analysis; effects in older patients

With 154 deaths in the control group and 113 in the T + P + docetaxel arm, **the study** has now allowed crossover to P. In terms of biomarkers, according to Dr Baselga, who presented **these data** in San Antonio, perhaps the key factor moving forward will be the identification of PI3-kinase mutations in approximately 25% of HER2-positive tumors and the potential use of PI3-kinase alpha inhibitors, which are currently being evaluated. Finally, although only 126 patients in **CLEOPATRA** were older than age 65, the benefit they derived from treatment was similar to what was seen with younger patients.

2. Choice of chemotherapy to combine with T + P

Referred to earlier, a **San Antonio report** from Memorial demonstrated a 76% 6-month PFS rate in 33 evaluable patients receiving T + P + weekly paclitaxel. No unexpected toxicities were encountered, and this work provides additional strength to the conclusion everyone, including the NCCN, had already reached, namely that paclitaxel is a reasonable agent to combine with T and P. To obtain more real-world perspectives on this issue, an international single-arm study (**PERUSE**) is now evaluating T + P with 3 different taxanes (paclitaxel, *nab* paclitaxel and docetaxel).

3. Pooled safety analysis of single-agent T-DM1

These data from 882 patients on 6 clinical trials (including EMILIA) revealed few clinically apparent toxicities but did document transient laboratory abnormalities, such as thrombocytopenia and abnormal liver function tests, in a quarter or more of patients. Overall, treatment discontinuation due to toxicity was observed in only 55 patients (6.2%).

4. Eribulin combined with T

Indefinite anti-HER2 treatment is now a standard part of care for patients with HER2-positive metastatic disease, and as new chemotherapy agents are developed, studies are needed to document whether these are safe and efficacious partners for T. **This report** of 40 patients demonstrated what most observers expected — efficacy similar to other chemotherapy/T combinations (55% CR + PR) and acceptable tolerability comparable to what has been reported with eribulin alone.

For the next issue of this series we review the many San Antonio papers on genomic markers, including yet another analysis with the 21-gene recurrence score in tumor specimens from a prior randomized adjuvant trial, in this case NSABP-B-28, which evaluated the addition of paclitaxel to AC.

Neil Love, MD

Research To Practice

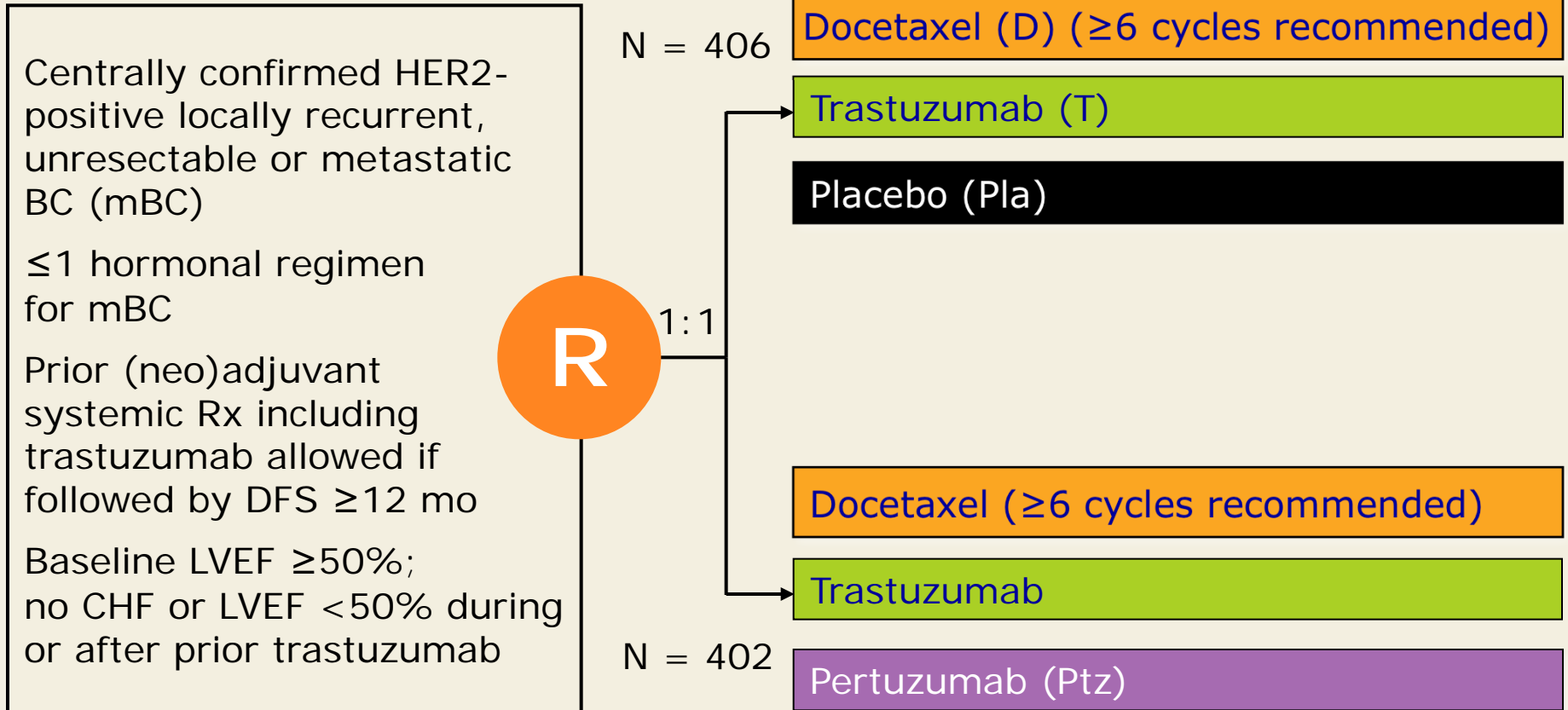
Miami, Florida

**Confirmatory Overall Survival (OS)
Analysis of CLEOPATRA: A
Randomized, Double-Blind,
Placebo-Controlled Phase III Study
with Pertuzumab, Trastuzumab, and
Docetaxel in Patients (pts) with
HER2-Positive First-Line (1L)
Metastatic Breast Cancer (MBC)**

Swain SM et al.

Proc SABCS 2012; Abstract P5-18-26.

CLEOPATRA Study Design



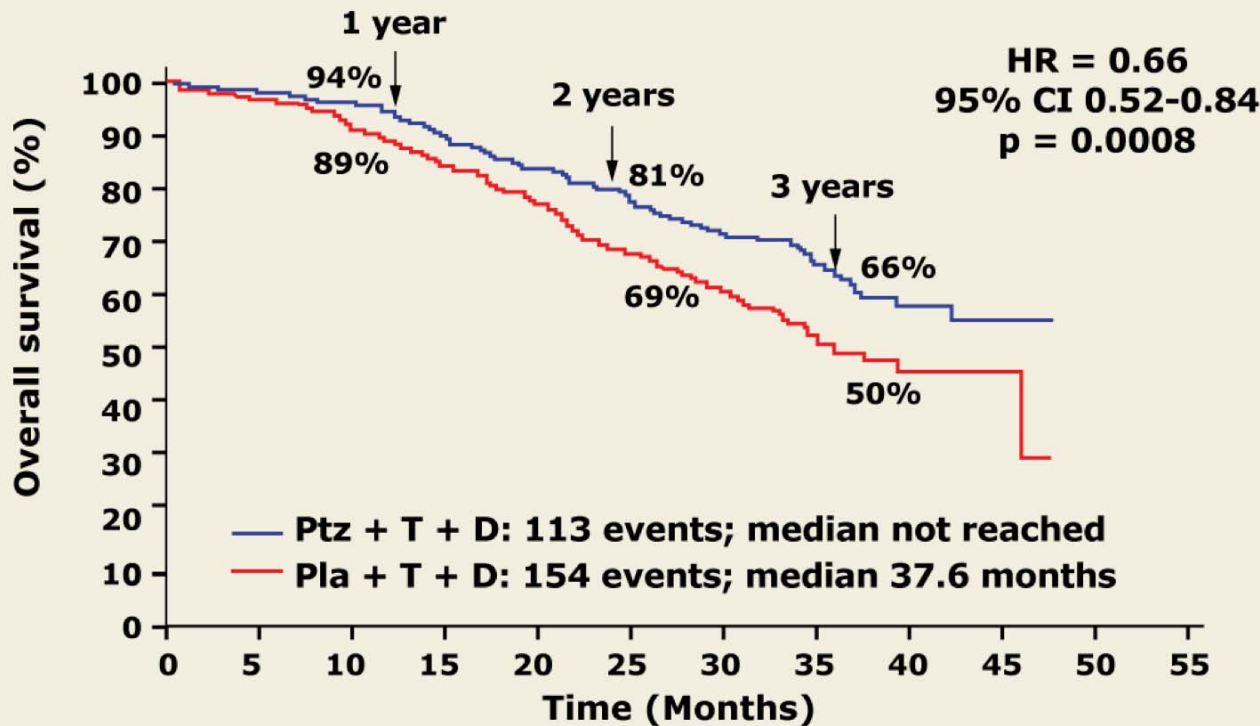
Primary endpoint: Independently assessed progression-free survival (PFS)

CLEOPATRA: Primary Efficacy Analysis

Independently assessed	Ptz + T + D (n = 402)	Pla + T + D (n = 406)	Hazard ratio	<i>p</i> -value
Median PFS	18.5 mo	12.4 mo	0.62	<0.001
Deaths in interim overall survival analysis, n (%) [*]	69 (17.2%)	96 (23.6%)	0.64	0.005

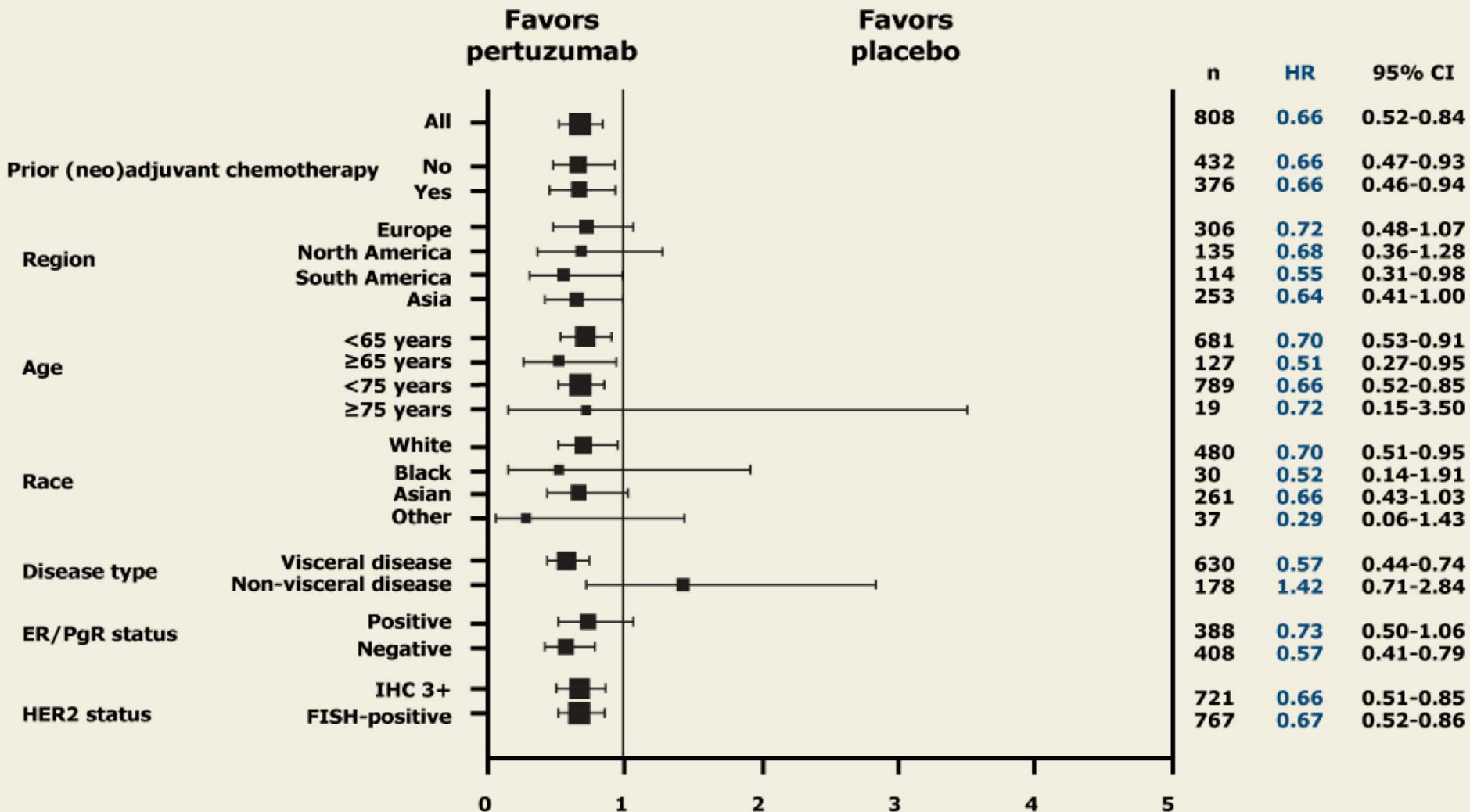
* Not significant because analysis did not meet O'Brien-Fleming stopping boundary; a strong trend was evident toward overall survival benefit with pertuzumab

CLEOPATRA: Overall Survival (Confirmatory Analysis)



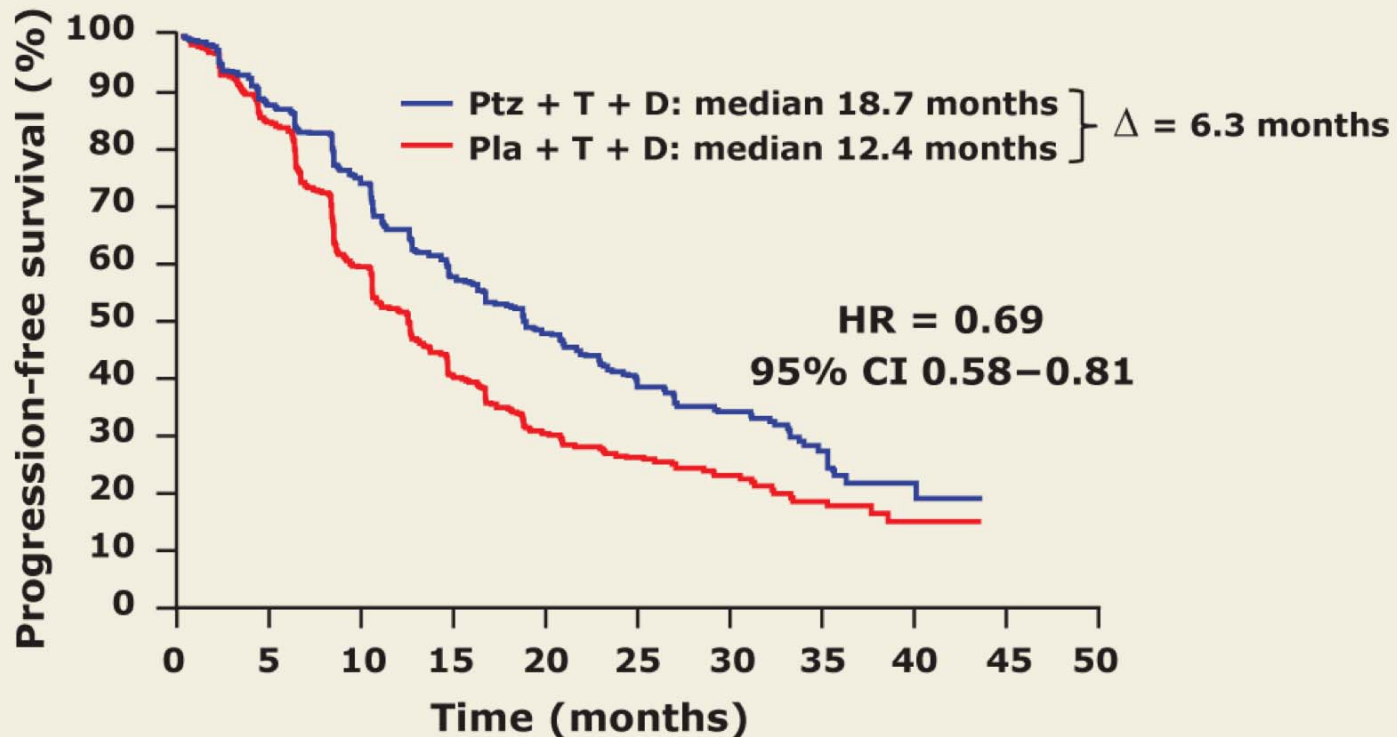
- Crossed O'Brien-Fleming stopping boundary and was therefore deemed statistically significant.
- Analysis was performed after 267 deaths and 69% of the prespecified total number of events for the final analysis had occurred.
- Median follow-up in both arms = 30 months

CLEOPATRA: Overall Survival in Predefined Subgroups



With permission from Swain SM et al. *Proc SABCS 2012*; Abstract P5-18-26.

CLEOPATRA: Follow-Up Analysis — Updated Investigator-Assessed PFS



- At the time of the data cutoff, 296 (72.9%) patients on the placebo arm and 257 (63.9%) on the pertuzumab arm had experienced a PFS event. These results were exploratory only.
- This updated analysis of investigator-assessed PFS was consistent with the results from the primary PFS analyses.

CLEOPATRA: Select All-Grade Adverse Events (AEs)

AEs with $\geq 25\%$ incidence or $\geq 5\%$ difference between arms	Ptz + T + D (n = 408)	Pla + T + D (n = 396)
Diarrhea	68.1%	48.2%
Rash	36.5%	24.0%
Mucosal inflammation	27.5%	19.9%
Peripheral edema	24.8%	30.8%
Pruritus	16.7%	10.1%
Constipation	15.4%	25.5%
Febrile neutropenia	13.7%	7.6%
Dry skin	10.8%	5.8%

Ptz + T + D did not increase the incidence of cardiac adverse events compared to Pla + T + D.

CLEOPATRA: Grade ≥ 3 Adverse Events

Grade ≥ 3 adverse events (incidence $\geq 5\%$)	Ptz + T + D (n = 408)	Pla + T + D (n = 396)
Neutropenia	49.0%	46.0%
Febrile neutropenia	13.7%	7.6%
Leukopenia	12.3%	14.9%
Diarrhea	9.1%	5.1%

Mucosal inflammation (Grade ≥ 3) was reported in 1% of patients in the placebo arm and 1.5% of patients in the pertuzumab arm.

Author Conclusions

- At the second interim analysis, CLEOPATRA demonstrated a statistically significant and clinically meaningful improvement in OS with the addition of pertuzumab to trastuzumab/docetaxel as first-line therapy for HER2-positive mBC.
 - As a consequence of the statistically significant survival benefit, patients who were still receiving study treatment on the placebo arm were offered crossover to the pertuzumab arm.
 - The final exploratory analysis of OS is event driven and will take place when 385 events have been reached.
- No new safety signals compared to the primary analysis were reported with 1 more year of follow-up.
- These results indicate that combined HER2 blockade and chemotherapy with pertuzumab/trastuzumab/docetaxel can be considered a standard first-line therapy for patients with HER2-positive mBC.

Investigator Commentary: Confirmatory OS Analysis of CLEOPATRA — Pertuzumab with Trastuzumab and Docetaxel as First-Line Therapy for HER2-Positive mBC

Changes in the first-line setting for patients with mBC have been coming along rapidly. The primary analysis of CLEOPATRA reported a significant improvement in PFS, and, as expected, this current analysis reported an improvement in OS. The authors confirmed little increase in toxicity compared to dual taxane/trastuzumab therapy. This report solidifies that the appropriate strategy is to administer a taxane in combination with trastuzumab and pertuzumab in the first-line setting.

Recent data have shown similar efficacy with docetaxel/trastuzumab and vinorelbine/trastuzumab but lower toxicity with the vinorelbine versus the docetaxel combination. The results of CLEOPATRA have given us impetus for an ongoing trial called VELVET that I have the honor of leading. This Phase II trial is for patients who are eligible to receive first-line therapy for HER2-positive mBC. In the first cohort, which we have already enrolled, patients will receive pertuzumab and trastuzumab sequentially. The second cohort will receive pertuzumab and trastuzumab together. Vinorelbine will be given to both cohorts.

Interview with Edith A Perez, MD, January 17, 2013

Biomarker Analyses in CLEOPATRA: A Phase III, Placebo-Controlled Study of Pertuzumab in HER2- Positive, First-Line Metastatic Breast Cancer (MBC)

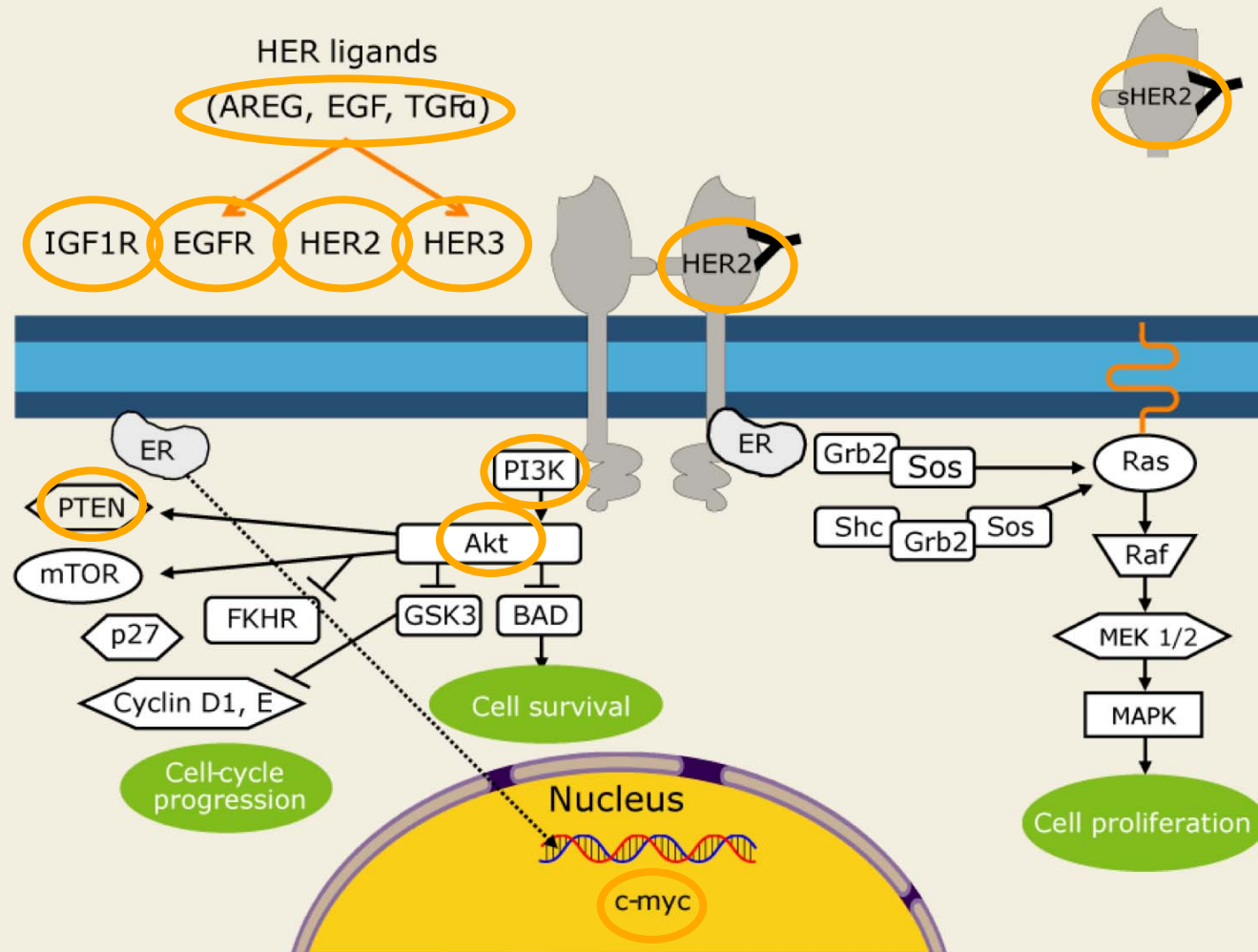
Baselga J et al.

Proc SABCS 2012; Abstract S5-1.

Background

- The Phase III CLEOPATRA study reported that pertuzumab (Ptz), trastuzumab (T) and docetaxel (D) prolonged progression-free survival (PFS) and overall survival (OS) in patients with untreated HER2-positive metastatic breast cancer compared to placebo (Pla), T and D.
 - PFS: 18.5 vs 12.4 months, HR 0.62, $p < 0.001$ (*NEJM* 2012;366:109)
 - OS: Median not yet reached vs 37.6 months, HR 0.66, $p = 0.0008$ (*Proc SABCS* 2012;Abstract P5-18-26)
- **Current analysis objective:** A panel of biomarkers was assessed in tumor tissue and in serum samples from patients on the CLEOPATRA trial to explore their potential predictive and/or prognostic value.

CLEOPATRA: Potential Biomarkers Along the HER2 Pathway Selected for Assessment



With permission from Baselga J et al. *Proc SABCS 2012*; Abstract S5-1.

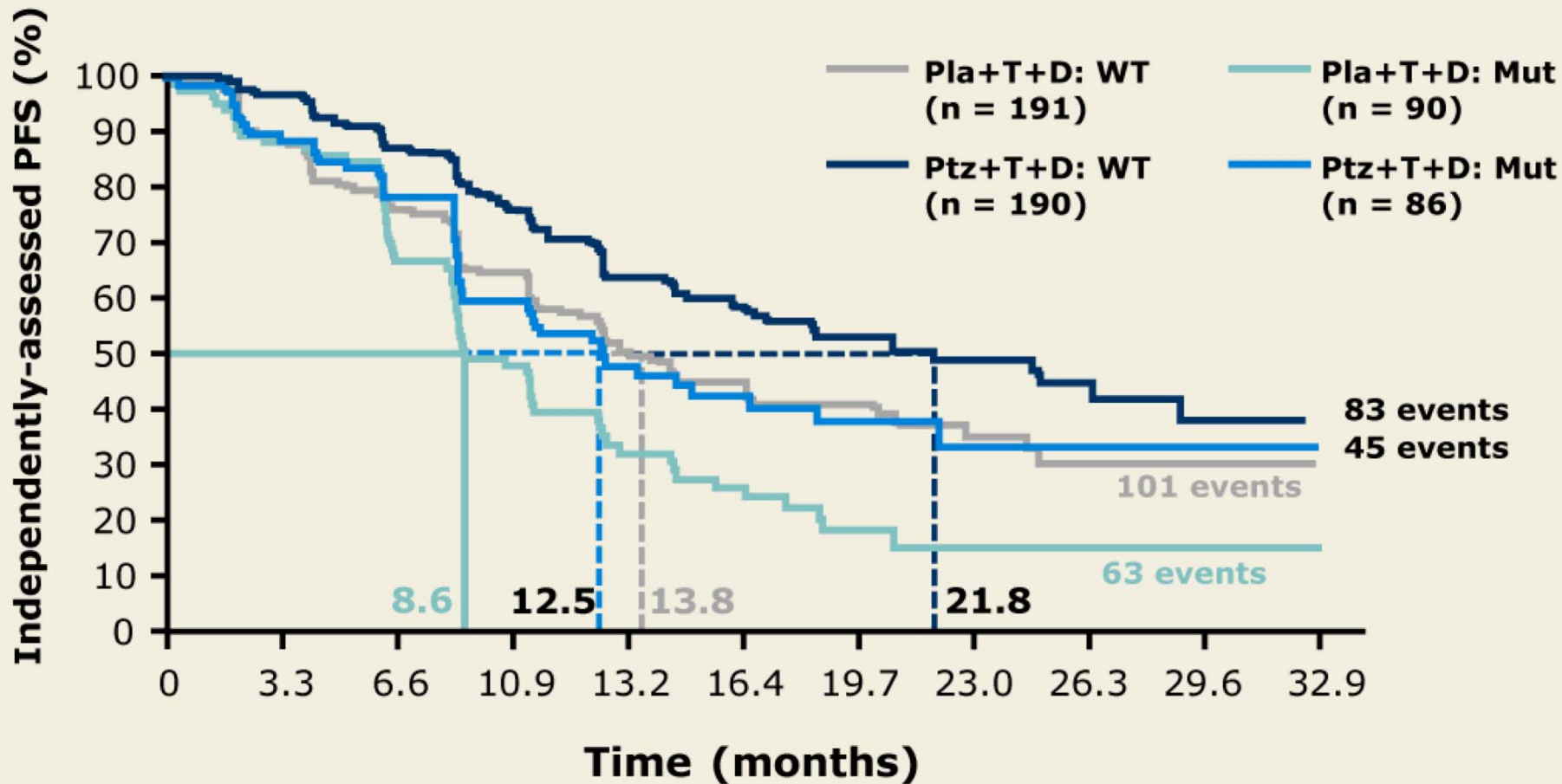
Statistical Methods

- Exploratory subgroup analyses of PFS by biomarker level
 - No adjustment for multiple testing was made
- Two types of correlations were investigated:
 - Predictive effects
 - Qualitative association of biomarkers with pertuzumab treatment benefit
 - Prognostic effects independent of treatment arm
 - Relationship of each biomarker to clinical outcome (both arms pooled)
- Median values were used as cutoffs for high/low biomarker levels, except for:
 - c-myc (target:centromere ratio ≥ 2)
 - PIK3CA (wild type [WT] versus mutant [MUT])
 - 8 mutations: 420R, 542K, 545K, 545A, 545G, 1047R, 1047L and 1047Y at 4 hotspots in exons 7, 9 and 20

Author Summary and Conclusions — Overall

- These analyses confirmed HER2 as the only marker for selecting patients for HER2-targeted therapy (data not shown).
 - This was despite comprehensive exploration of a broad panel of candidate biomarkers.
- Results were consistent with the TRYPHAENA (ESMO 2012; Abstract 202P) and NeoSphere (SABCS 2011; Abstract S5-1) studies.
- The lack of a HER2 treatment-naïve control arm in the CLEOPATRA trial may have resulted in the absence of a signal for other biomarkers.

CLEOPATRA: PIK3CA Mutation Is Associated with Poorer Prognosis *Both Arms*



CLEOPATRA: Shorter Median PFS Observed with Mutated PIK3CA While Treatment Effect is Maintained

<i>PIK3CA status</i>	Pla + T + D			Ptz + T + D			
	n	Events	Median (mo)	n	Events	Median (mo)	Hazard ratio
Mut	90	63	8.6	86	45	12.5	0.64
WT	191	101	13.8	190	83	21.8	0.67
Overall	406	242	12.4	402	191	18.5	0.62

- The prognostic impact of PIK3CA mutations cannot be attributed to a specific mutation, nor to mutation(s) in a specific exon, based on the available data set.
 - 182 mutations detected overall (32%)
 - Number of mutations in exon 7 = 12; exon 9 = 39; exon 20 = 131

Author Summary and Conclusions — PI3K

- Mutations in PIK3CA were not associated with resistance to pertuzumab, as patients derived similar additional benefit independent of PIK3CA mutational status.
- However, the PIK3CA mutational status may identify patients with poorer prognoses and particular unmet medical needs.
 - Previous studies have shown mutated PIK3CA to be associated with lapatinib resistance (*Cancer Res* 2008;68:9221) and poorer prognosis after trastuzumab therapy (*Cancer Cell* 2007;12:395).
 - Other studies have shown good prognoses with mutated PIK3CA, particularly in hormone receptor-positive tumors (*Breast Cancer Res* 2012;14:R28; *Proc Natl Acad Sci USA* 2010;107:10208).
- Clinical trials of HER2-targeted molecules in combination with PI3K pathway-targeted agents may therefore be justified based on the findings of this study.

Investigator Commentary: CLEOPATRA — Biomarker Analyses of a Phase III, Placebo-Controlled Study of Pertuzumab in HER2-Positive, First-Line Metastatic Breast Cancer

We are traveling in the direction of developing a type of tumor profile that would indicate which HER2-positive tumors will be exquisitely sensitive to targeted therapies and in which situations chemotherapy will not be needed. This is remarkable if we think back to 10 years ago when HER2-positive cancer was the most aggressive breast cancer tumor type we encountered. Now we are considering whether it could be treated without chemotherapy regimens in the neoadjuvant setting. Much change has occurred in the field.

I believe we will identify a patient population that does not need chemotherapy. We know from the NEOSPHERE data set, and most importantly from the CLEOPATRA data set, that tumors harboring PI3 kinase mutations respond less. PI3 kinase is downstream of HER2, and if the gene is mutant, tumors are probably less sensitive to inhibition of HER2 upstream. We also know from the CLEOPATRA biomarker study that higher levels of HER2 correlate with greater benefit. Lastly, we know that higher levels of HER3 correlate with better outcome. So I am optimistic and convinced that we will develop a signature for HER2 dependency.

Interview with José Baselga, MD, PhD, March 9, 2013

Pertuzumab in Combination with Trastuzumab and Docetaxel in Elderly Patients with HER2-Positive Metastatic Breast Cancer in the CLEOPATRA Study

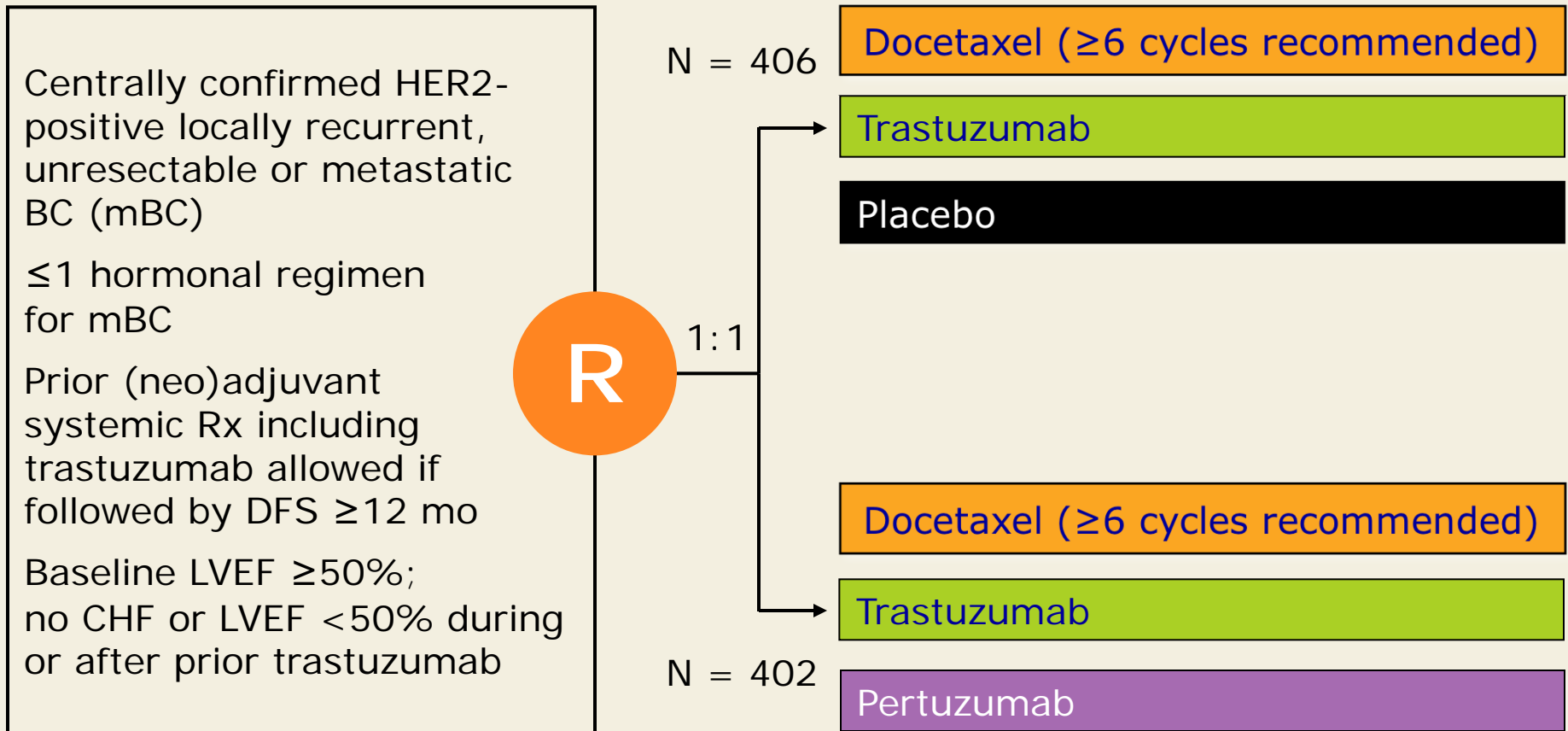
Miles D et al.

Proc SABCS 2012; Abstract P5-18-01.

Background

- Patients aged ≥ 65 years are underrepresented in trials of cancer treatments, thus limiting the availability of efficacy and safety data for new therapies in this population.
- The results from the Phase III CLEOPATRA trial evaluating the addition of pertuzumab versus placebo to trastuzumab/docetaxel for patients with HER2-positive metastatic breast cancer (mBC) (*NEJM* 2012; 366:109):
 - Demonstrated a significant improvement in PFS with pertuzumab by independent review.
 - Led to the FDA approval of pertuzumab/trastuzumab/docetaxel as first-line therapy for HER2-positive mBC.
- **Study objective:** To compare the efficacy and safety of pertuzumab/trastuzumab/docetaxel according to age group for patients in the CLEOPATRA trial (<65 versus ≥ 65 years).

CLEOPATRA Study Design



Primary endpoint: Independently assessed progression-free survival (PFS)

Independently Assessed PFS (ITT Population)

	<65 years		≥65 years	
	PL/T/D (n = 339)	Pert/T/D (n = 342)	PL/T/D (n = 67)	Pert/T/D (n = 60)
Median PFS	12.5 mo	17.2 mo	10.4 mo	21.6 mo
Hazard ratio	0.65		0.52	
95% CI	0.53-0.80		0.31-0.86	
<i>p</i> -value	<0.0001		0.0098	

PL = placebo; Pert = pertuzumab; T = trastuzumab; D = docetaxel

Exposure to Docetaxel Treatment

	<65 years		≥65 years	
	PL/T/D (n = 332)	Pert/T/D (n = 346)	PL/T/D (n = 65)	Pert/T/D (n = 61)
Median no. of cycles administered (range)	8.0 (1-41)	8.0 (1-35)	6.5 (1-26)	6.0 (1-16)
Median dose intensity, mg/m ² /week	24.8	24.5	24.8	24.8
Dose escalation, n (%) [*]	53 (16.0)	41 (11.8)	8 (12.3)	7 (11.5)
Dose reduction, n (%) [†]	72 (21.7)	85 (24.6)	17 (26.2)	19 (31.1)

* Dose escalation to 100 mg/m²; † Dose reduction to <75 mg/m²

Most Common Adverse Events: Overall (O) and After (A) Docetaxel Discontinuation

All grades (O/A, %)	<65 years		≥65 years	
	PL/T/D	Pert/T/D	PL/T/D	Pert/T/D
Diarrhea	44.9/8.4	66.2/16.5	53.8/12.5	70.5/32.7
Neutropenia	51.2/3.7	54.3/2.0	41.5/2.5	44.3/0
Fatigue	36.1/7.9	36.1/10.0	40.0/12.5	45.9/16.3
Rash	22.9/6.0	34.7/10.8	30.8/7.5	27.9/16.3
Asthenia	29.2/7.9	25.7/10.8	35.4/7.5	27.9/4.1
Dysgeusia	14.8/0.9	16.8/0.8	20.0/0	27.9/4.1
Febrile neutropenia	7.8/0	14.7/0	6.2/0	8.2/0

Overall, the proportion of patients ≥65 y receiving G-CSF was lower than that of patients <65 y.

Most Common Adverse Events (≥Grade 3)

	<65 years		≥65 years	
	PL/T/D (n = 332)	Pert/T/D (n = 346)	PL/T/D (n = 65)	Pert/T/D (n = 61)
Neutropenia	47.0%	50.3%	40.0%	41.0%
Leukopenia	15.4%	12.7%	10.8%	9.8%
Febrile neutropenia	7.8%	14.7%	6.2%	8.2%
Diarrhea	4.8%	6.6%	6.2%	14.8%
Fatigue	2.7%	2.0%	6.2%	3.3%
Peripheral neuropathy	1.8%	1.7%	1.5%	8.2%
LVSD	2.4%	1.2%	4.6%	1.6%
Asthenia	1.2%	2.9%	3.1%	0%

Author Conclusions

- Treatment with Pert/T/D demonstrated a superior PFS by independent review in patients aged <65 years and ≥65 years compared with PL/T/D.
- In patients aged ≥65 years versus <65 years:
 - There were more dose reductions of docetaxel.
 - There was a lower median number of docetaxel cycles, which likely explains the lower incidence of neutropenia and febrile neutropenia and the less frequent use of G-CSF.
- The safety and efficacy data reported in the CLEOPATRA trial suggest that in patients with good ECOG PS, the combined use of Pert/T/D should not be limited by patient age.
- The PERUSE study will investigate the tolerability and efficacy of first-line Pert/T with one of a choice of taxanes in patients with HER2-positive mBC (NCT01572038).

Investigator Commentary: Pertuzumab/Trastuzumab/Docetaxel for Elderly Patients with HER2-Positive mBC

The results of the subset analysis of the CLEOPATRA trial based on age demonstrated that patients benefit from combination therapy with pertuzumab, trastuzumab and docetaxel irrespective of age. These results are consistent with what was found with anti-HER2 therapy in the adjuvant setting. It is a reminder that breast cancer should be managed based on the biology of the disease and the patient's overall condition rather than age.

Interview with Edith A Perez, MD, January 17, 2013

Anytime I see a survival advantage in any population of patients facing incurable metastatic breast cancer, I feel as if we're making some progress in this area. To see the survival data from CLEOPATRA was exciting, and it was nice to see that the elderly population from CLEOPATRA not only derived a benefit but seemed to tolerate treatment well. No large outstanding safety signal was apparent. They required more dose reductions, but in general there were no more treatment-related deaths, and the responses appeared to be similar across the age groups.

Interview with Kimberly L Blackwell, MD, January 8, 2013

A Phase II Study of Pertuzumab, Trastuzumab, and Weekly Paclitaxel in Patients with HER2-Overexpressing Metastatic Breast Cancer

Datko F et al.

Proc SABCS 2012; Abstract P5-18-20.

Background

- The Phase III CLEOPATRA study reported that pertuzumab, trastuzumab and docetaxel prolonged progression-free survival (PFS) and overall survival (OS) in the first-line setting for patients with HER2-positive metastatic breast cancer (mBC) compared to placebo, trastuzumab and docetaxel.
 - PFS: 18.7 vs 12.4 months, HR 0.69
 - OS: Median not yet reached vs 37.6 months, HR 0.66, $p = 0.0008$ (*Proc SABCS 2012*; Abstract P5-18-26)
- There is evidence that weekly paclitaxel is superior to every 3-week paclitaxel and less toxic than docetaxel (*NEJM* 2008; 358(16):1663).
- **Study objective**: To evaluate the efficacy and safety of pertuzumab and trastuzumab with weekly paclitaxel for patients with HER2-positive mBC.

Phase II Study Design

HER2-positive mBC (IHC 3+ or FISH ≥ 2.0)

0-1 prior treatments in metastatic setting

Measurable or non-measurable disease

Ejection fraction $\geq 50\%$

No cardiac morbidities within 12 months

Target accrual n = 69



q week



q 3 weeks



q 3 weeks



q 4 cycles



ECHO



Paclitaxel 80 mg/m² q week



Pertuzumab 840 mg load \rightarrow 420 mg q 3 weeks



Trastuzumab 8 mg/kg load \rightarrow 6 mg/kg q 3 weeks

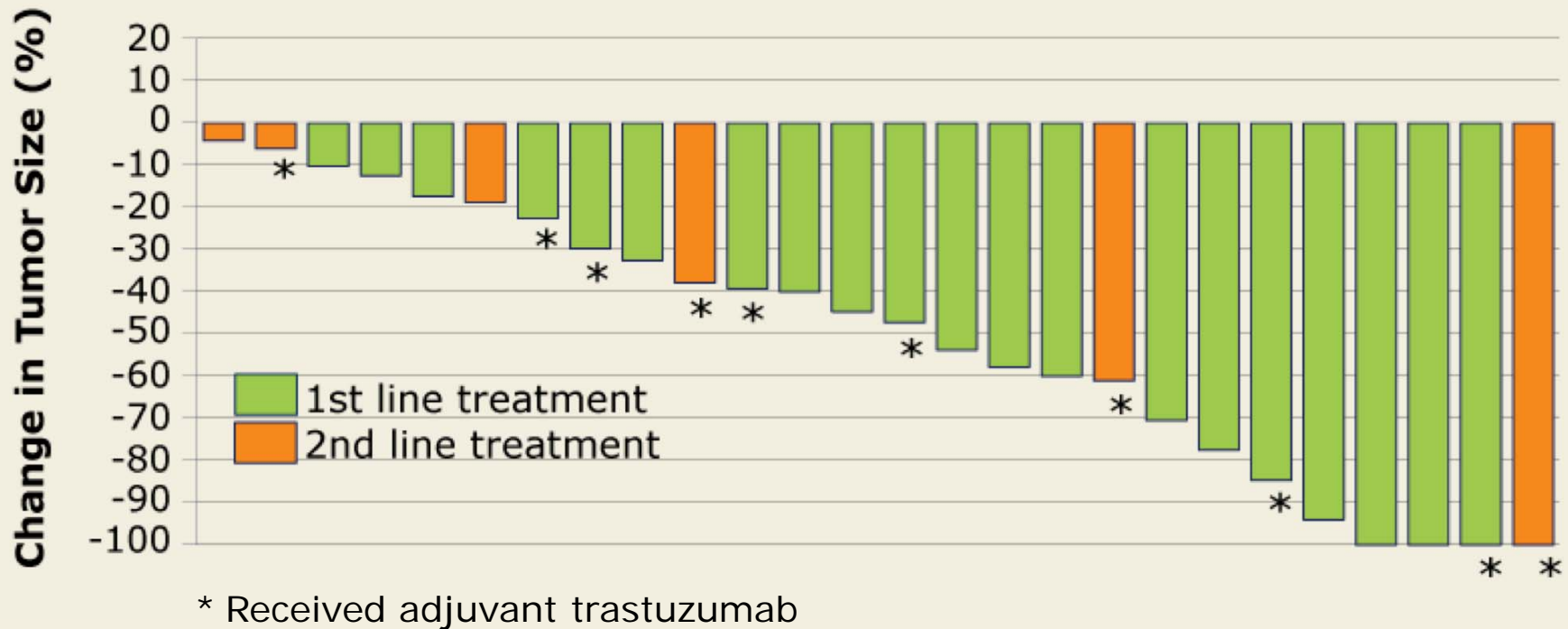
1 cycle = 3 weeks

Primary objective: Proportion of patients progression free at 6 months

Efficacy Results

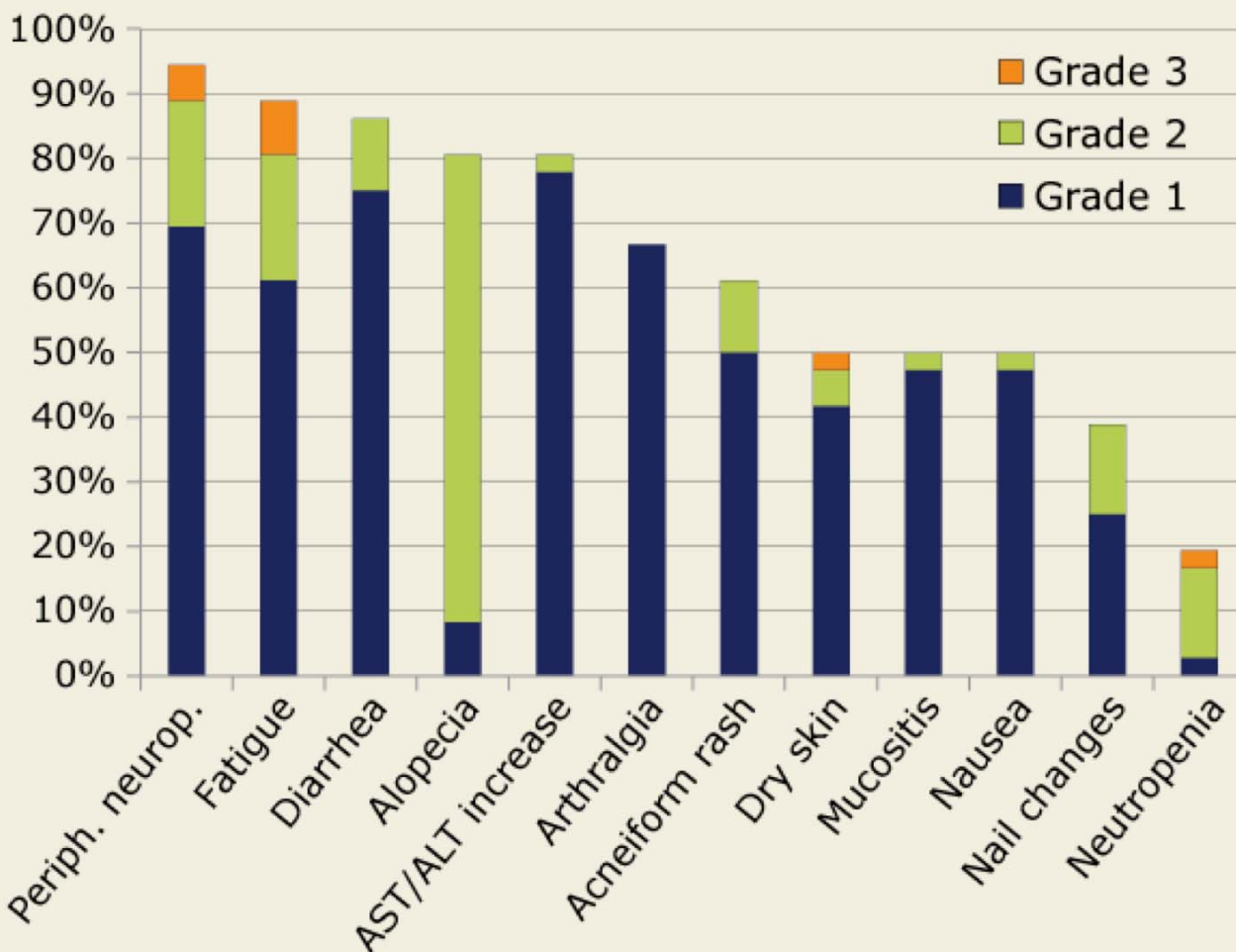
	Evaluatable patients (n = 33)	Intent-to-treat population (n = 36)
6-month PFS	25 (76%)	25 (69%)
Complete response	3 (9%)	3 (8%)
Partial response	14 (42%)	14 (39%)
Stable disease	8 (24%)	8 (22%)
Progressive disease	8 (24%)	8 (22%)
Not evaluable for per-protocol efficacy	3 (8%)	

Best Response in Evaluatable Patients with Measurable Disease (n = 26)



With permission from Datko F et al. *Proc SABCS 2012*; Abstract P5-18-20.

Select All-Grade Adverse Events (n = 36)



With permission from Datko F et al. *Proc SABCS 2012*; Abstract P5-18-20.

Cardiac Safety

- No cardiac events have yet to be reported on this Phase II trial (data cutoff, 11/12/12).
- One patient experienced an asymptomatic LVEF decline (Grade 2).
 - EF declined from 57% to 47% at 9 months in a 61-year-old woman with history of cardiomyopathy controlled with cardiac medications.
 - She was taken off study.
 - No additional intervention was required.
 - On a 3-month follow-up echocardiogram, her EF was 44%.

Author Conclusions

- Preliminary results of this single-center Phase II study of patients with HER2-positive mBC treated with pertuzumab, trastuzumab and weekly paclitaxel in the first- or second-line setting indicate that 76% of evaluable patients are progression free at 6 months.
- Accrual is ongoing, with no unexpected toxicities or cardiac events to date.
- Pertuzumab was recently FDA approved in combination with trastuzumab and docetaxel as first-line therapy for HER2-positive mBC.
- If the estimate of safety and activity is similar to results with docetaxel in the Phase III CLEOPATRA trial, this Phase II study will provide support for weekly paclitaxel as an alternative option in combination with trastuzumab and pertuzumab in this setting.

Investigator Commentary: A Phase II Study of Pertuzumab, Trastuzumab and Weekly Paclitaxel in Patients with HER2-Overexpressing Metastatic Breast Cancer

In view of the significant improvement in progression-free survival demonstrated in the initial report on the CLEOPATRA study — which evaluated the addition of pertuzumab to trastuzumab/docetaxel as first-line therapy for HER2-positive mBC — and the significant improvement in overall survival now also reported in the confirmatory analysis, I believe it makes a lot of sense for continued research to be performed evaluating other agents in combination with pertuzumab and trastuzumab.

This Phase II study evaluating the addition of paclitaxel to trastuzumab/pertuzumab indicates that this combination is also feasible. As expected, trastuzumab is an interesting agent among all of the anti-HER2 drugs in that it is easily combined with multiple chemotherapy regimens. I'm happy that we have the data evaluating the trastuzumab/pertuzumab antibody combination with docetaxel and that we now have preliminary data on this combination with paclitaxel. We will also soon have data from my Phase II VELVET trial, which is evaluating this dual antibody combination with vinorelbine.

Interview with Edith A Perez, MD, January 17, 2013

A Single-Arm Phase IIIb Study of Pertuzumab and Trastuzumab with a Taxane as First-Line Therapy for Patients with HER2-Positive Advanced Breast Cancer (PERUSE)

Bachelot T et al.

Proc SABCS 2012; Abstract OT1-1-02.
(Ongoing Trials Session)

Background

- Pertuzumab (P) is a HER2 heterodimerization inhibitor that recognizes an epitope on HER2 distinct from that bound by trastuzumab (H); hence their complementary mechanisms of action result in a more comprehensive HER2 blockade.
- The Phase III CLEOPATRA trial reported significantly improved PFS in patients (pts) receiving P + H + docetaxel versus H + docetaxel as first-line treatment for HER2-positive metastatic breast cancer (BC) (*NEJM* 2012; 366:109).
- **Study objective:** This ongoing trial will evaluate the safety and efficacy of P + H with one of a choice of taxanes as first-line therapy for patients with HER2-positive advanced BC.

PERUSE Key Eligibility Criteria

Eligibility (N = 1,500*)

Women/men with HER2+ advanced BC (metastatic or locally recurrent)
No prior systemic antihormonal therapy in the metastatic setting
Prior (neo)adjuvant H and/or lapatinib allowed if no disease progression during treatment
Disease-free interval ≥ 6 mo
ECOG PS 0-2
LVEF $\geq 50\%$
No clinical or radiographic evidence of CNS metastases or clinically significant cardiovascular disease
No other malignancy in the past 5 y except carcinoma in situ of the cervix or basal cell carcinoma

* To be enrolled over 18 mo; first patient enrolled on May 31, 2012

PERUSE Phase IIIb Study Design

- Global, open-label, single-arm, Phase IIIb study (NCT01572038)
- Therapy: P + H + taxane (docetaxel or paclitaxel or *nab* paclitaxel, by choice of investigator)
 - P: 840 mg initial dose, 420 mg maintenance, IV, q3wk
 - H: 8 mg/kg initial dose, 6 mg/kg maintenance, IV, q3wk
 - Taxane: According to local guidelines
 - Cycle 1: P d1, H d2; other cycles: P, H, taxane, in any order
- Patients with hormone receptor-positive disease can receive endocrine therapy with P + H after completion of taxane therapy.
- P will be provided to pts still receiving the investigational agent at study end who are eligible to enter an extension study to collect safety data and prespecified efficacy measures.

Study Endpoints

Primary endpoint:

- Safety and tolerability

Secondary endpoints:

- Progression-free survival
- Overall survival
- Overall response rate
- Clinical benefit rate
- Duration of response
- Time to response
- Health-related quality of life

Planned Analyses

- Primary analysis will be of Grade ≥ 3 adverse events (AEs) related to pertuzumab.
- Further analysis of safety endpoints will include incidence and severity of all AEs and serious AEs, cause of death, premature discontinuation from study, incidence of congestive heart failure, LVEF over the course of the study and laboratory test abnormalities.
- The incidence of select safety variables will be analyzed overall and by subgroups (country, age, ECOG performance status and type of taxane).
- Best overall response will be assessed by number and proportion of responders and nonresponders, together with 2-sided 95% confidence intervals.

Planned Analyses (Continued)

- Incidence of baseline covariates on overall response rate will be analyzed in an exploratory manner.
- All pts will be followed until final analysis, to be done 45 mo after the last pt has been enrolled or all pts in the study have withdrawn consent or died or if the study is prematurely terminated, whichever occurs first.
- In addition to the final analysis, 5 interim analyses for safety and efficacy are planned after enrollment of 100, 350, 700, 1,100 and 1,500 pts. Results will be reviewed by an Independent Data Monitoring Committee.

Investigator Commentary: Ongoing Phase IIIb PERUSE Study of Pertuzumab and Trastuzumab with a Taxane as First-Line Therapy for Patients with HER2-Positive Advanced Breast Cancer

The CLEOPATRA study demonstrated a significant improvement in progression-free survival and an overall survival benefit when patients with HER2-positive metastatic breast cancer received pertuzumab and trastuzumab in combination with docetaxel. Based on these results, it is logical for continued research investigating anti-HER2 antibodies in combination with other taxanes and nontaxane agents to maintain efficacy while minimizing toxicity for patients. Several Phase II trials are evaluating combinations of new agents with pertuzumab and trastuzumab. This is good science to follow, and I would enroll patients on this ongoing trial.

Interview with Edith A Perez, MD, January 17, 2013

Trastuzumab Emtansine in HER2-Positive Metastatic Breast Cancer: Pooled Safety Analysis from Seven Studies

Diéras V et al.

Proc SABCS 2012; Abstract P5-18-06.

Background

- Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) that inhibits HER2 signaling and induces antibody-dependent cellular cytotoxicity.
- In a Phase III study, T-DM1 improved overall survival (OS) and progression-free survival (PFS) compared to lapatinib/capecitabine in previously treated HER2-positive locally advanced or metastatic breast cancer (BC) (*NEJM* 2012;367:1783):
 - OS: 30.9 mo vs 25.1 mo (HR = 0.68; $p < 0.001$)
 - PFS: 9.6 mo vs 6.4 mo (HR = 0.65; $p < 0.001$)
 - Incidence of Grade ≥ 3 adverse events (AEs) was lower with T-DM1
- **Study objective:** To perform an integrated safety analysis of single-agent T-DM1 based on data from patients with unresectable locally advanced or metastatic BC.

Study Methods

- Analysis of safety data from patients (n = 882) with locally advanced or metastatic BC from 7 Phase I to III clinical studies of T-DM1 at 3.6 mg/kg (q3wk):
 - Study A: Phase III TDM4370g/BO21977 (EMILIA)
 - Study B: Phase II TDM4450g/BO21976
 - Study C: Phase II TDM4374g
 - Study D: Phase II TDM4258g
 - Study E: Phase II TDM4688g
 - Study F: Phase I TDM3569g
 - Study G: Phase II TDM4529g/BO25430 (open-label extension of TDM3569g, TDM4258g, TDM4374g, TDM4688g and TDM4450g)

Study Methods (Continued): Characteristics of Pooled Studies

- All studies assessed AEs, basic laboratory data, vital signs, physical examination findings and left ventricular ejection fraction (LVEF) per schedules.
- Laboratory assessments typically occurred weekly during the first several treatment cycles.
- AEs were graded according to the NCI-CTCAE v3.0 criteria.
- AEs were reported up to 30 days after the last dose of study medication, until early termination visit or at the initiation of another anticancer therapy, whichever occurred first.
- Afterward, investigators reported only deaths from any cause and serious AEs (SAEs) that were considered to be related to prior study treatment.
- All baseline characteristics excluding prior therapies were similar across studies.

Select AEs in Patients Who Received T-DM1 (Incidence $\geq 20\%$)

n = 882	Any grade	Grade 3	Grade 4
Fatigue	45.4%	3.1%	0.1%
Nausea	42.3%	1.0%	0%
Headache	28.7%	0.6%	0%
Thrombocytopenia	28.7%	8.3%	1.9%
Constipation	25.5%	0.6%	0%
Increased AST	23.0%	4.0%	0.1%
Diarrhea	20.3%	0.9%	0%
Hypokalemia*	14.4%	2.9%	0%
Increased ALT*	15.2%	2.8%	0%
Anemia*	13.7%	2.5%	0%

* AEs with Grade 3 or 4 incidence $\geq 2\%$.

Overview of AEs

- The most commonly reported AEs (any grade) were fatigue, nausea, headache, thrombocytopenia and constipation.
- With the exception of fatigue, the most commonly reported Grade ≥ 3 AEs were related to laboratory test abnormalities.
- A total of 55 patients (6.2%) discontinued T-DM1 due to AEs.
 - Most common AEs also responsible for dose reductions included mainly thrombocytopenia (1.4%) and increased AST/ALT (0.8%/0.5%).
- SAEs were reported in 18.6% of patients.
- During treatment or within 30 days of last T-DM1 dose, 9 patients experienced AEs leading to death.
 - Of these, 4 were deemed by the investigator to be T-DM1 related (hepatic failure, hepatic function abnormality, bacterial sepsis and metabolic encephalopathy).

Hepatotoxicity

- The incidence of increased transaminases was similar across studies but slightly higher in Study B.
- Increases in mean AST and ALT were generally transient:
 - Proportion of patients with Grade ≥ 3 increased AST/ALT did not increase over time.
 - Most patients continued T-DM1 therapy after appropriate dose modifications.
- All-grade increases in serum bilirubin occurred in 24 patients. These were of Grade 3 in 3 patients, with no grade 4 events.
- Out of 882 patients, 3 cases of biopsy-confirmed nodular regenerative hyperplasia (NRH) were recorded; these patients had clinical or radiographic signs of portal hypertension.

Thrombocytopenia

- This was the primary dose-limiting toxicity associated with T-DM1.
- Grade 3 or 4 thrombocytopenia generally occurred within cycles 1 and 2.
- Thrombocytopenia was not fully reversible in all patients, but with the appropriate dose modifications, platelet counts recovered sufficiently to allow treatment continuation.
- Of 122 patients with Grade 3 or 4 thrombocytopenia:
 - Grade 1 bleeding: 51 (41.8%)
 - Grade 2 bleeding: 4 (3.3%)
 - Grade 3 or 4 bleeding: 6 (4.9%)
- Grade 3 or 4 bleeding events and Grade 3 or 4 thrombocytopenia did not occur concurrently in any of the patients.

Incidence of Thrombocytopenia and Hemorrhage (HMG) with T-DM1 by Grade (G)

HMG	Thrombocytopenia (n)						
	G0	G1	G2	G3	G4	G5	Total
G0	125	280	115	54	7	0	581
G1	19	108	69	42	9	0	247
G2	2	17	16	4	0	0	39
G3	2	1	5	5	1	0	14
G4	0	1*	0	0	0	0	1*
G5	0	0	0	0	0	0	0
Total	148	407	205	105	17	0	882

* Patient had Grade 4 GI hemorrhage on study day 797 after the most recent T-DM1 dose, but the event resolved in a day and was considered to be unrelated to T-DM1.

Cardiac Safety

- Cardiac dysfunction (SMQ-narrow; “cardiac failure”) was infrequent: 1.5%
 - Majority of patients experienced Grade 1 or 2 events (11/13).
 - Two of 13 patients experienced Grade 3 decreased ejection fraction.
- Patients with a postbaseline LVEF <40%: 4 (0.5%)
- Patients with LVEF decline from baseline ($\geq 15\%$ to <50%): 16 (1.8%)
- Patients who discontinued T-DM1 due to cardiac disorders: 3 (0.3%):
 - Atrial fibrillation (n = 1)
 - Left ventricular dysfunction (n = 1)
 - Decreased ejection fraction (n = 1)

Author Conclusions

- The safety profile was consistent across studies, and the most commonly reported Grade ≥ 3 AEs were thrombocytopenia (10.2%) and increased AST (4.1%).
- The majority of thrombocytopenia AEs were of Grade 1 or 2.
 - Six patients experienced Grade 3 or 4 thrombocytopenia and hemorrhage, but these AEs were not temporally related.
 - Whereas most Grade ≥ 3 thrombocytopenia did not fully recover to baseline, platelet counts recovered in nearly all patients, allowing treatment continuation.

Author Conclusions (Continued)

- Increases in serum transaminases were generally transient, allowing patients to continue treatment at the same/reduced dose.
 - Three cases of NRH were reported among the 882 patients exposed to single-agent T-DM1; NRH should be considered if noncirrhotic portal hypertension occurs.
- The safety profile of T-DM1 is consistent with the theoretical concept underlying the design of ADCs — that targeting delivery of chemotherapy to tumors and restricting chemotherapy release to intracellular compartments reduces systemic toxicity.

Investigator Commentary: A Pooled Safety Analysis of T-DM1 in HER2-Positive Metastatic Breast Cancer

From our experiences with the EMILIA trial, T-DM1 is an easy drug to administer to patients. In this trial, the dose intensity for T-DM1 was 100%, so we are able to get this drug into patients well. The Grade 3 and 4 toxicities associated with the agent were mainly laboratory abnormalities such as elevations in AST and ALT liver enzymes. An unusual phenomenon described in other studies of T-DM1 is transient thrombocytopenia that usually occurs between days 8 and 10 of the treatment cycle. If you do not look for it between the 21-day treatment cycles, you might miss it. The cause of this transient thrombocytopenia is under investigation, but it is hypothesized that the agent must have some binding affinity to platelets.

As a practicing clinician, what is meaningful about the toxicities associated with T-DM1 that we observed on the EMILIA trial is that they did not affect the patient's quality of life. I believe T-DM1 is an active agent that appears to be superior to lapatinib and capecitabine in terms of survival. It may be what we have been searching for — a cancer treatment without the side effects of chemotherapy.

Interview with Kimberly L Blackwell, MD, June 26, 2012

Eribulin Mesylate + Trastuzumab as First-Line Therapy for Locally Recurrent or Metastatic HER2- Positive Breast Cancer: Results from a Phase 2, Multicenter, Single-Arm Study

Vahdat L et al.

Proc SABCS 2012; Abstract P5-20-04.

Background

- Eribulin mesylate is a nontaxane inhibitor of microtubule dynamics of the halichondrin class of antineoplastic drugs.
- The Phase III EMBRACE study demonstrated a survival benefit with eribulin relative to commonly used agents for patients with locally recurrent or metastatic breast cancer (mBC) who previously received at least 2 chemotherapeutic regimens for advanced disease (*Lancet* 2011; 377(9769):914).
 - Median overall survival was significantly improved in women who received eribulin versus treatment of physician's choice.
 - 13.1 mo vs 10.6 mo: HR 0.81, $p = 0.041$
- **Study objective**: To evaluate the antitumor activity and safety of eribulin mesylate in combination with trastuzumab as first-line therapy for patients with locally recurrent or metastatic HER2-positive breast cancer.

Baseline Characteristics

Parameter	Eribulin/trastuzumab (n = 40)
Mean age, y	58.1
Metastatic sites (%)	
Liver	52.5
Lung	42.5
Bone	35.0
ER+ disease (%)	67.5
Mean time from original diagnosis, y	2.4
Prior trastuzumab* (%)	40.0
Prior taxane or anthracycline (%)	50.0

* The majority of these patients received trastuzumab in the (neo)adjuvant setting, and 1 patient received it in the metastatic setting.

Phase II Study Design

As of October 26, 2012, 40 of the 52 planned patients had received at least 1 dose of eribulin (enrollment closed).

Eligibility

- Locally recurrent BC or HER2+ mBC
- No prior chemotherapy treatment for locally recurrent or metastatic HER2+ breast cancer
- One prior HR/endocrine treatment and 1 prior HER2+ treatment allowed



Eribulin mesylate
1.4 mg/m² IV
days 1, 8 q21 days
+
trastuzumab
Initial dose: 8 mg/kg IV
Subsequent doses:
6 mg/kg IV day 1, q21 days

Primary objective: Objective response rate (ORR)

- Data have not fully matured. Preliminary results are presented.

Best Tumor Responses

	Eribulin/ trastuzumab (n = 40)
Objective response rate	55.0%
Complete response (CR)	5.0%
Partial response (PR)	50.0%
Stable disease (SD)	37.5%
Progressive disease (PD)	2.5%
Not evaluable/unknown	5.0%
Clinical benefit rate (CR/PR/SD)*	62.5%
Disease control rate (CR/PR/SD)	92.5%

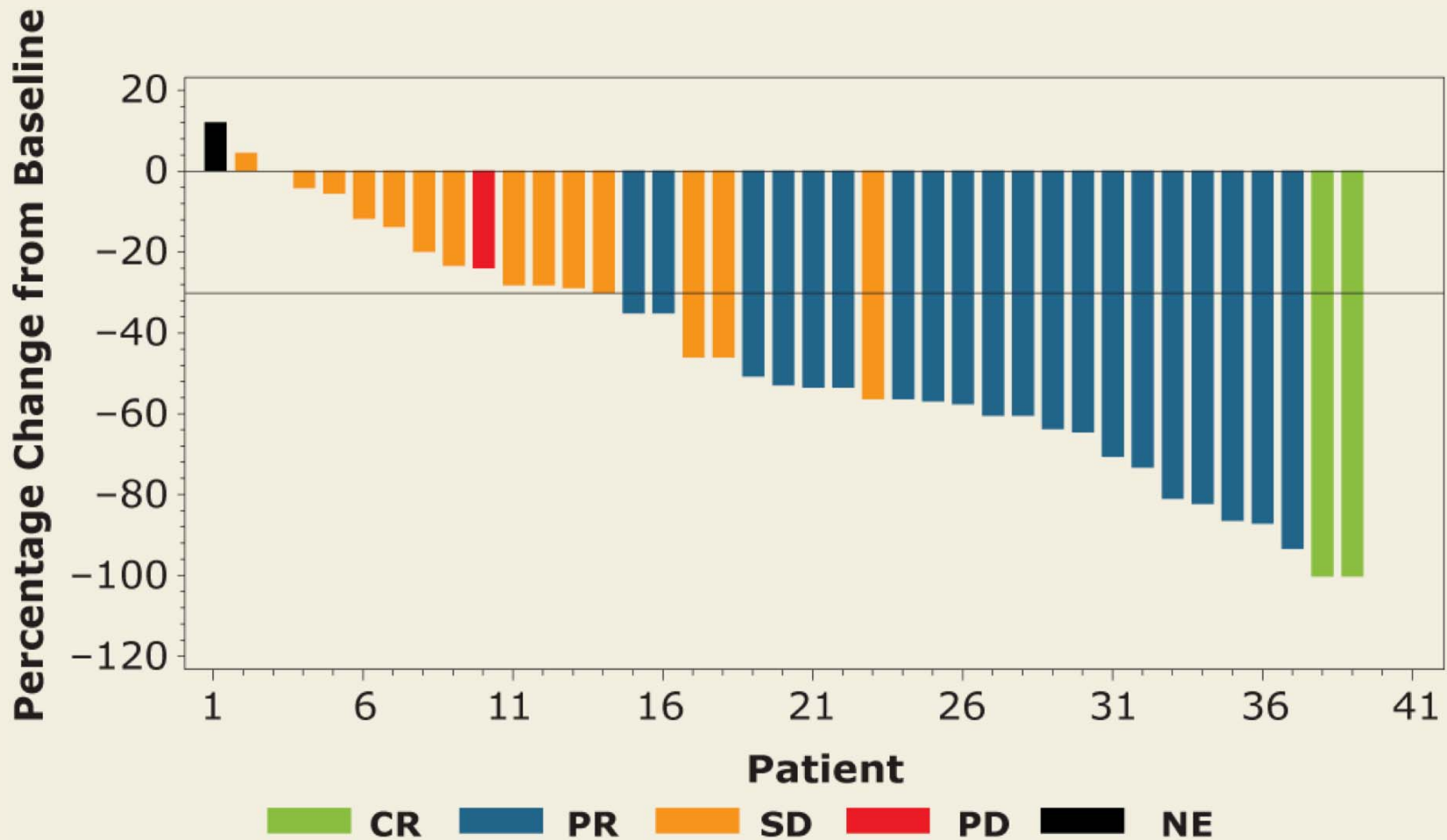
* Of at least 180 days in duration

Secondary Efficacy Outcomes

	All patients	ER+ patients	ER- patients
Median PFS (n = 40, 27, 11)	9.2 mo	7.1 mo	13.9 mo
Median TTR (n = 22, 14, 6)	1.3 mo	1.3 mo	1.3 mo
Median DOR (n = 22, 14, 6)	6.7 mo	6.5 mo	6.7 mo

PFS = progression-free survival; TTR = time to response;
DOR = duration of response

Maximum Percent Change of Tumor Summed Diameters from Baseline for Evaluable Patients (n = 40)



With permission from Vahdat L et al. *Proc SABCS 2012*; Abstract P5-20-04.

Select Adverse Events (n = 40)

Adverse event (AE)	All grades	Grade 3/4
Alopecia	82.5%	—
Neutropenia	60.0%	35.0%
Fatigue	57.5%	2.5%
Peripheral neuropathy	47.5%	12.5%
Anemia	22.5%	2.5%
Dysgeusia	25.0%	0%
AE leading to eribulin discontinuation	12.5%	
AE leading to eribulin dose reduction	20.0%	

Author Conclusions

- These preliminary results suggest that the combination of eribulin and trastuzumab appears to have considerable activity with an acceptable toxicity profile as first-line therapy for HER2-positive locally advanced or metastatic breast cancer.
- Most commonly observed treatment-related AEs included:
 - Alopecia, fatigue, neutropenia, peripheral neuropathy and nausea
- Most common Grade 3/4 AE was neutropenia.
- This study has completed enrollment, and final results are expected by December 2013.

Investigator Commentary: A Phase II Study of Eribulin Mesylate and Trastuzumab as First-Line Therapy for Locally Recurrent or Metastatic HER2-Positive Breast Cancer

People have been eagerly awaiting these data for some time. Eribulin has single-agent activity in the setting of advanced breast cancer, so I'm not surprised that these investigators demonstrated a high response rate when eribulin was administered in combination with trastuzumab for patients with locally recurrent or metastatic HER2-positive disease.

Interview with Edith A Perez, MD, January 17, 2013

This interim analysis of a Phase II study reported a response rate of more than 50% and a clinical benefit rate of more than 60% with eribulin/trastuzumab. Progression-free survival was also reasonable. A number of dose reductions and delays and a fair amount of discontinuation were reported. Dose reduction or delay was necessary for approximately 1 in 5 patients, but those adjustments appeared to be related to eribulin-based toxicities such as asthenia, peripheral neuropathy and neutropenia. We don't know whether it's possible that trastuzumab was "turning up the volume" on those side effects because there was no eribulin-alone arm. It wouldn't surprise me because with some of the biologic agents an augmentation of what you traditionally consider to be the cytotoxic side effects is apparent.

Interview with Lisa A Carey, MD, January 17, 2013