

A SPECIAL MEETING REVIEW EDITION

**Highlights in the Management of Breast Cancer From the
2012 San Antonio Breast Cancer Symposium (SABCS)**

A Review of Selected Presentations From the 2012 CTSC-AACR
San Antonio Breast Cancer Symposium (SABCS)
December 4–8, 2012 • San Antonio, Texas

Special Reporting on:

- Biomarker Analyses in CLEOPATRA: A Phase III, Placebo-Controlled Study of Pertuzumab in HER2-Positive, First-Line Metastatic Breast Cancer
- HERA TRIAL: 2 Years Versus 1 Year of Trastuzumab After Adjuvant Chemotherapy in Women With HER2-Positive Early Breast Cancer at 8 Years of Median Follow-Up
- Relative Effectiveness of Letrozole Compared to Tamoxifen for Patients With Lobular Carcinoma in the BIG 1-98 Trial
- Trastuzumab Plus Adjuvant Chemotherapy for HER2-Positive Breast Cancer: Final Planned Joint Analysis of Overall Survival (OS) From NSABP B-31 and NCCTG N9831
- Confirmatory Overall Survival Analysis of CLEOPATRA: A Randomized, Double-Blind, Placebo-Controlled Phase III Study With Pertuzumab, Trastuzumab, and Docetaxel in Patients With HER2-Positive First-Line Metastatic Breast Cancer
- Final Analysis of Overall Survival for the Phase III CONFIRM Trial: Fulvestrant 500 mg Versus 250 mg

PLUS Meeting Abstract Summaries

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Important Safety Information

Boxed WARNING: Embryo-Fetal Toxicity

- **Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception**

- Verify pregnancy status prior to the initiation of PERJETA. Advise patients of the risks of embryo-fetal death and birth defects and the need for contraception during and after treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant
- Encourage women who may be exposed to PERJETA during pregnancy to enroll in the MoTHER Pregnancy Registry by contacting 1-800-690-6720
- Monitor patients who become pregnant during PERJETA therapy for oligohydramnios

Additional Important Safety Information

Left Ventricular Dysfunction

- Left ventricular dysfunction, which includes symptomatic left ventricular systolic dysfunction (LVSD) (congestive heart failure) and decreases in left ventricular ejection fraction (LVEF), occurred in 4.4% of patients in the PERJETA-treated group and 8.3% of patients in the placebo-treated group
- Assess LVEF prior to initiation of PERJETA and at regular intervals (eg, every 3 months) during treatment to ensure that LVEF is within your institution's normal limits
- Withhold PERJETA and Herceptin and repeat LVEF assessment within 3 weeks in patients with significant decrease in LVEF. Discontinue PERJETA and Herceptin if the LVEF has not improved or has declined further

Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis

- PERJETA has been associated with infusion and hypersensitivity reactions
- When all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group ($\geq 1.0\%$) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting

FOR THE FIRST-LINE TREATMENT OF HER2+* METASTATIC BREAST CANCER

STRENGTHEN HER DEFENSE

Indication: PERJETA™ (pertuzumab) is a HER2/neu receptor antagonist indicated in combination with Herceptin® (trastuzumab) and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

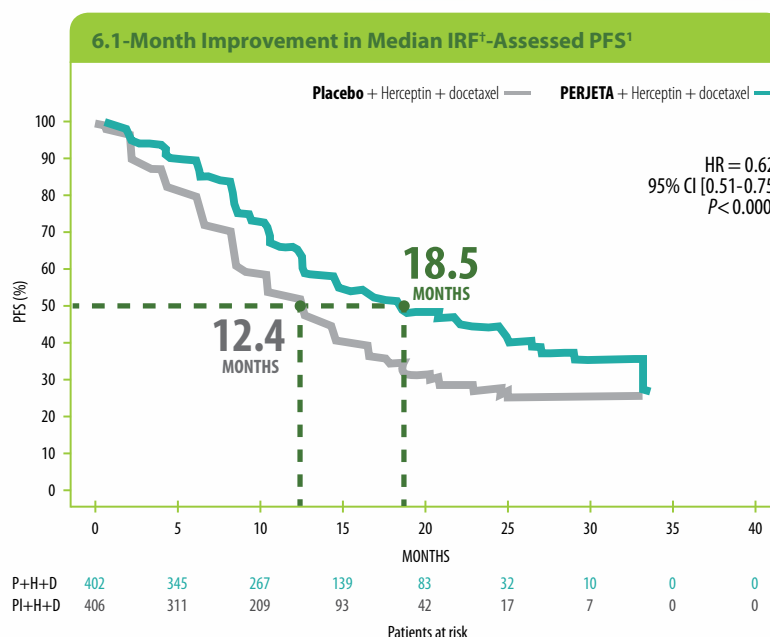
Extend progression-free survival (PFS) with an FDA-approved HER2 dimerization inhibitor^{1,2}

- Consistent PFS results were observed across a broad range of patient subgroups¹
- At the time of analysis, there were 191 (47.5%) and 242 (59.6%) patients with a PFS event in the PERJETA + Herceptin + docetaxel and placebo + Herceptin + docetaxel arms, respectively¹
- The most common adverse reactions (ARs) (>30%) seen with the PERJETA-based regimen were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy¹

*HER2+ = human epidermal growth factor receptor 2 positive.

¹IRF = independent review facility.

²Stratified by prior treatment status and geographic region.



- In the randomized trial, the overall frequency of hypersensitivity reactions/anaphylaxis was 10.8% in the PERJETA-treated group and 9.1% in the placebo-treated group
- If a significant infusion reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions

HER2 Testing

- Detection of HER2 protein overexpression is necessary for selection of patients appropriate for PERJETA therapy because these are the only patients studied and for whom benefit has been shown

Most Common Adverse Reactions

- The most common adverse reactions (>30%) seen with PERJETA in combination with Herceptin and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy

Please see brief summary of PERJETA full Prescribing Information including Boxed WARNING for additional Important Safety Information on the following pages.



For more information, scan the QR code or visit www.PERJETA.com.

PERJETA™
pertuzumab

STRENGTHEN HER2 SUPPRESSION

References: 1. PERJETA Prescribing Information. Genentech, Inc. June 2012. 2. Baselga J, Cortés J, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-119.

**PERJETA™ (pertuzumab)
INJECTION, FOR INTRAVENOUS USE
INITIAL U.S. APPROVAL: 2012**

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception. (5.1, 8.1, 8.6)

1 INDICATIONS AND USAGE

PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

PERJETA can cause fetal harm when administered to a pregnant woman. Treatment of pregnant cynomolgus monkeys with pertuzumab resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death. If PERJETA is administered during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

Verify pregnancy status prior to the initiation of PERJETA. Advise patients of the risks of embryo-fetal death and birth defects and the need for contraception during and after treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MoTHER Pregnancy Registry by contacting 1-800-690-6720 [see Patient Counseling Information (17)].

Monitor patients who become pregnant during PERJETA therapy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of intravenous hydration in the management of oligohydramnios due to PERJETA exposure is not known.

5.2 Left Ventricular Dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. In the randomized trial, PERJETA in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel [see Clinical Studies (14.1)]. Left ventricular dysfunction occurred in 4.4% of patients in the PERJETA-treated group and 8.3% of patients in the placebo-treated group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in 1.0% of patients in the PERJETA-treated group and 1.8% of patients in the placebo-treated group [see Adverse Reactions (6.1)]. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

PERJETA has not been studied in patients with a pretreatment LVEF value of $\leq 50\%$, a prior history of CHF, decreases in LVEF to $< 50\%$ during prior trastuzumab therapy, or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to $> 360 \text{ mg/m}^2$ of doxorubicin or its equivalent.

Assess LVEF prior to initiation of PERJETA and at regular intervals (e.g., every three months) during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is $< 40\%$, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold PERJETA and trastuzumab and repeat LVEF assessment within approximately 3 weeks. Discontinue PERJETA and trastuzumab if the LVEF has not improved or has declined further, unless the benefits for the individual patient outweigh the risks [see Dosage and Administration (2.2)].

5.3 Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis

PERJETA has been associated with infusion and hypersensitivity reactions [see Adverse Reactions (6.1)]. An infusion reaction was defined in the randomized trial as any event described as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. The initial dose of PERJETA was given the day before trastuzumab and docetaxel to allow for the examination of

PERJETA-associated reactions. On the first day, when only PERJETA was administered, the overall frequency of infusion reactions was 13.0% in the PERJETA-treated group and 9.8% in the placebo-treated group. Less than 1% were grade 3 or 4. The most common infusion reactions ($\geq 1.0\%$) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group ($\geq 1.0\%$) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting.

In the randomized trial, the overall frequency of hypersensitivity/anaphylaxis reactions was 10.8% in the PERJETA-treated group and 9.1% in the placebo-treated group. The incidence of Grade 3 – 4 hypersensitivity/anaphylaxis reactions was 2% in the PERJETA-treated group and 2.5% in the placebo-treated group according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI - CTCAE) (version 3). Overall, 4 patients in PERJETA-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions [see Dosage and Administration (2.2)].

5.4 HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for PERJETA therapy because these are the only patients studied and for whom benefit has been shown [see Indications and Usage (1) and Clinical Studies (14)]. In the randomized trial, patients with breast cancer were required to have evidence of HER2 overexpression defined as $3+$ IHC by Dako Herceptest™ or FISH amplification ratio ≥ 2.0 by Dako HER2 FISH PharmDx™ test kit. Only limited data were available for patients whose breast cancer was positive by FISH but did not demonstrate protein overexpression by IHC.

Assessment of HER2 status should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
- Left Ventricular Dysfunction [see Warnings and Precautions (5.2)]
- Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical trials, PERJETA has been evaluated in more than 1400 patients with various malignancies and treatment with PERJETA was predominantly in combination with other anti-neoplastic agents.

The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive metastatic breast cancer treated in the randomized trial. Patients were randomized to receive either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated group. No dose adjustment was permitted for PERJETA or trastuzumab. The rates of adverse events resulting in permanent discontinuation of all study therapy were 6.1% for patients in the PERJETA-treated group and 5.3% for patients in the placebo-treated group. Adverse events led to discontinuation of docetaxel alone in 23.6% of patients in the PERJETA-treated group and 23.2% of patients in the placebo-treated group. Table 1 reports the adverse reactions that occurred in at least 10% of patients on the PERJETA-treated group.

The most common adverse reactions ($> 30\%$) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common NCI - CTCAE (version 3) Grade 3 – 4 adverse reactions ($> 2\%$) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment arms compared with patients

of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%).

Table 1 Summary of Adverse Reactions Occurring in $\geq 10\%$ of Patients on the PERJETA Treatment Arm in the Randomized Trial

Body System/ Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407		Placebo + trastuzumab + docetaxel n=397	
	Frequency rate % All Grades %	Frequency rate % Grades 3-4 %	Frequency rate % All Grades %	Frequency rate % Grades 3-4 %
General disorders and administration site conditions				
Fatigue	37.6	2.2	36.8	3.3
Asthenia	26.0	2.5	30.2	1.5
Edema peripheral	23.1	0.5	30.0	0.8
Mucosal inflammation	27.8	1.5	19.9	1.0
Pyrexia	18.7	1.2	17.9	0.5
Skin and subcutaneous tissue disorders				
Alopecia	60.9	0.0	60.5	0.3
Rash	33.7	0.7	24.2	0.8
Nail disorder	22.9	1.2	22.9	0.3
Pruritus	14.0	0.0	10.1	0.0
Dry skin	10.6	0.0	4.3	0.0
Gastrointestinal disorders				
Diarrhea	66.8	7.9	46.3	5.0
Nausea	42.3	1.2	41.6	0.5
Vomiting	24.1	1.5	23.9	1.5
Constipation	15.0	0.0	24.9	1.0
Stomatitis	18.9	0.5	15.4	0.3
Blood and lymphatic system disorders				
Neutropenia	52.8	48.9	49.6	45.8
Anemia	23.1	2.5	18.9	3.5
Leukopenia	18.2	12.3	20.4	14.6
Febrile neutropenia*	13.8	13.0	7.6	7.3
Nervous system disorders				
Neuropathy peripheral	32.4	3.2	33.8	2.0
Headache	20.9	1.2	16.9	0.5
Dysgeusia	18.4	0.0	15.6	0.0
Dizziness	12.5	0.5	12.1	0.0
Musculoskeletal and connective tissue disorders				
Myalgia	22.9	1.0	23.9	0.8
Arthralgia	15.5	0.2	16.1	0.8
Infections and infestations				
Upper respiratory tract infection	16.7	0.7	13.4	0.0
Nasopharyngitis	11.8	0.0	12.8	0.3
Respiratory, thoracic and mediastinal disorders				
Dyspnea	14.0	1.0	15.6	2.0
Metabolism and nutrition disorders				
Decreased appetite	29.2	1.7	26.4	1.5
Eye disorders				
Lacrimation increased	14.0	0.0	13.9	0.0
Psychiatric disorders				
Insomnia	13.3	0.0	13.4	0.0

*In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

The following clinically relevant adverse reactions were reported in $< 10\%$ of patients in the PERJETA-treated group:

Skin and subcutaneous tissue disorders: Paronychia (7.1% in the PERJETA-treated group vs. 3.5% in the placebo-treated group)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (5.2% in the PERJETA-treated group vs. 5.8% in the placebo-treated group)

Cardiac disorders: Left ventricular dysfunction (4.4% in the PERJETA-treated group vs. 8.3% in the placebo-treated group) including symptomatic left ventricular systolic dysfunction (CHF) (1.0% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

Immune system disorders: Hypersensitivity (10.1% in the PERJETA-treated group vs. 8.6% in placebo-treated group)

Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab after Discontinuation of Docetaxel

In the randomized trial, adverse reactions were reported less frequently after discontinuation of docetaxel treatment. All adverse reactions in the PERJETA and trastuzumab treatment group occurred in $< 10\%$ of patients with the exception of diarrhea (19.1%), upper respiratory tract infection (12.8%), rash (11.7%), headache (11.4%), and fatigue (11.1%).

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to PERJETA.

Patients in the randomized trial were tested at multiple time-points for antibodies to PERJETA. Approximately 2.8% (11/386)

of patients in the PERJETA-treated group and 6.2% (23/372) of patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies to PERJETA with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

There are no adequate and well-controlled studies of PERJETA in pregnant women. Based on findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. The effects of PERJETA are likely to be present during all trimesters of pregnancy. Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on C_{max} . If PERJETA is administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA, the patient should be apprised of the potential hazard to the fetus. If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MoTHER Pregnancy Registry

by contacting 1-800-690-6720 [see *Patient Counseling Information* (17)].

Animal Data

Reproductive toxicology studies have been conducted in cynomolgus monkeys. Pregnant monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on C_{max} . Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on C_{max}). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

8.3 Nursing Mothers

It is not known whether PERJETA is excreted in human milk, but human IgG is excreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from PERJETA, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of PERJETA and the importance of the drug to the mother [See *Warnings and Precautions* (5.1), *Clinical Pharmacology* (12.3)].

8.4 Pediatric Use

The safety and effectiveness of PERJETA have not been established in pediatric patients.

8.5 Geriatric Use

Of 402 patients who received PERJETA in the randomized trial, 60 patients (15%) were ≥ 65 years of age and 5 patients (1%) were ≥ 75 years of age. No overall differences in efficacy and safety of PERJETA were observed between these patients and younger patients.

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics

of pertuzumab between patients < 65 years ($n=306$) and patients ≥ 65 years ($n=175$).

8.6 Females of Reproductive Potential

PERJETA can cause embryo-fetal harm when administered during pregnancy. Counsel patients regarding pregnancy prevention and planning. Advise females of reproductive potential to use effective contraception while receiving PERJETA and for 6 months following the last dose of PERJETA.

If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MoTHER Pregnancy Registry by contacting 1-800-690-6720 [see *Patient Counseling Information* (17)].

8.7 Renal Impairment

Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited pharmacokinetic data available [see *Clinical Pharmacology* (12.3)].

8.8 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab.

10 OVERDOSAGE

No drug overdoses have been reported with PERJETA to date.

Genentech

A Member of the Roche Group

PERJETA™ (pertuzumab)

Manufactured by:

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A Member of the Roche Group

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

Pertuzumab is an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody that prevents HER2 receptor heterodimerization, which has complementary mechanisms of action with trastuzumab. CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) is a pivotal international, randomized, double-blind, placebo-controlled, phase III trial.^{1,2} A total of 808 patients with centrally-confirmed HER2-positive breast cancer were randomized to receive docetaxel plus placebo and trastuzumab or docetaxel plus pertuzumab and trastuzumab. The primary endpoint was progression-free survival (PFS). In addition, and pertinent to this presentation of the data, collection of tumor tissue and serum samples was mandatory. Tumor tissue from archival samples represented over 90% of the collections in this study.

CLEOPATRA was presented at the 2011 San Antonio Breast Cancer Symposium (SABCS),¹ and the study results were published.² The primary endpoint was met, with an improvement of PFS from 12.4 months to 18.5 months. Importantly, a statistically significant improvement occurred in overall survival (OS).

The objective of the current analysis was to explore whether, within the HER2-positive patient population, further subgroups based on biomarker

profiles could be identified that derived differential benefit from HER2-targeted therapies.³ Therefore, a panel of biomarkers that was predefined by the protocol was assessed in tumor tissue and serum samples to explore their potential predictive and overall prognostic value. Analyzing the samples required a significant effort with the collection of many samples.

A number of markers were analyzed by several methods. Immunohistochemistry and a modified H-score

assessed HER2, HER3, insulin-like growth factor (IGF)-1R, PTEN, and pAKT. Quantitative reverse transcriptase polymerase chain reaction (PCR) by concentration ratio assessed *HER1*, *HER2*, *HER3*, *AREG*, and betacellulin tumor mRNA levels. Fluorescence in situ hybridization (FISH) analyzed *c-Myc*. Mutational analyses through PCR-based methods examined 8 hotspots within *PIK3CA* on tumor DNA and *FcyR* polymorphisms in DNA extracted from whole blood.

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)

This single-arm phase IIIb trial will combine pertuzumab and trastuzumab plus a taxane (docetaxel, paclitaxel, or nab-paclitaxel) in patients with HER2-positive advanced breast cancer in the first-line treatment setting (Abstract OT1-1-02). The study plans to enroll 1,500 patients over 18 months, with a patient population that is reasonably representative of patients who present to oncology centers. The trial will obtain data on patient subgroups of special interest, including elderly patients, visceral versus non-visceral disease, performance status, type of taxane, and prior exposure to trastuzumab in the neoadjuvant setting. Patients will receive pertuzumab and trastuzumab every 3 weeks, and a taxane according to local guidelines. The antibodies and chemotherapy will be administered until disease progression, unacceptable toxicity, or the predefined study end. After the taxane course is completed, patients with hormone receptor-positive disease will have the option to receive endocrine therapy in conjunction with the antibodies. The primary endpoint of the trial is safety and tolerability. The secondary endpoints are PFS, OS, overall response rate, clinical benefit rate, duration of response, time to response, and health-related quality of life. The primary analysis will be of AEs that are grade 3 or above and related to pertuzumab.

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Enzyme-linked immunosorbent assay analyzed serum levels of the HER2 extracellular domain, *AREG*, epidermal growth factor, and transforming growth factor- α . The different assays had different sample sizes because of both the performance of the assays as well as a predefined priority ranking.

An exploratory subgroup analysis of PFS by biomarker level was conducted, with no adjustments made for multiple testing. Two types of correlations were investigated. One was predictive effects, which looked at qualitative associations of biomarkers with pertuzumab treatment benefit. The second was prognostic effects independent of the treatment arm, which looked for relationships of each biomarker to clinical outcome, with both arms pooled. Median values were used as cut-offs for high and low levels of biomarkers, except for *c-Myc*, where the target was a centromere ratio of 2 or greater, and for *PIK3CA*, where wild-type was compared with mutant and where 8 mutations at 4 hotspots in exons 7, 9, and 20 were examined.

The first part of the study explored potential predictive biomarkers. A consistent effect favoring pertuzumab was observed in the group of serum markers, independent of any biomarkers in the group. The same applies for HER ligands and for receptor tyrosine kinases in tumor tissues, where a consistent treatment effect was observed in all biomarkers. Even in the cases of low versus high HER2 protein or of low versus high IGF-1R, the observed differences were well within the boundaries of variation. Finally, the same consistent effects for predictive biomarkers were observed for intracellular pathway markers, where pertuzumab was favored.

Biomarkers were also analyzed independent of the treatment arms to explore their prognostic effects. Among the serum markers pooled from both arms, low levels of soluble HER2 were a marker of better prognosis (hazard ratio [HR], 1.23; $P=.0433$; Figure 1). When HER ligands and receptor

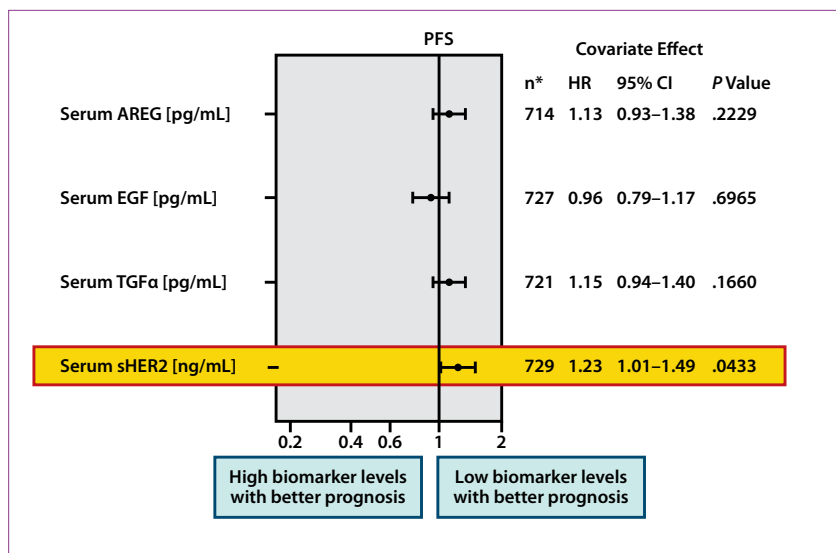


Figure 1. In a biomarker subgroup analysis of the CLEOPATRA trial, low levels of soluble HER2 were a marker of better prognosis. *HR, <1.00 in all cases; $P<.0001$). AREG=amphiregulin; CI=confidence interval; CLEOPATRA=Clinical Evaluation of Pertuzumab and Trastuzumab; EGF=epidermal growth factor; sHER2=soluble human epidermal growth factor receptor 2; HR=hazard ratio; PFS=progression-free survival; TGF α =transforming growth factor-alpha. Adapted from Baselga J et al. Paper presented at: CTRC-AACR San Antonio Breast Cancer Symposium; December 5-8, 2012; San Antonio, TX. Abstract S5-1.

tyrosine kinases were examined in both arms, high HER2 mRNA (HR, 0.77; $P=.0080$) or protein (HR, 0.83; $P=.0502$) and high HER3 mRNA (HR, 0.81; $P=.0348$) were markers of better prognosis, although the effect was of borderline significance in this exploratory analysis.

Among the intracellular pathway markers, tumors with wild-type *PIK3CA* had a better prognosis, while those harboring mutations to *PIK3CA* had a worse outcome (HR, 0.63; 95% confidence interval [CI], 0.49–0.80; $P=.0001$). By far, this was the strongest prognostic marker. Among patients treated in the trastuzumab plus placebo arm, those with tumors harboring *PIK3CA* mutations had a worse prognosis, with a median PFS of 8.6 months versus 13.8 months in the wild-type arm. Among patients treated in the pertuzumab plus trastuzumab arm, the prognosis was again worse in the subset with a *PIK3CA* mutation (PFS of 12.5 months) than in the subset with wild-type *PIK3CA* (PFS of 21.8 months). Notably, the

treatment benefit with pertuzumab was conserved with both the wild-type and mutant *PIK3CA* tumors.

To summarize the findings on *PIK3CA* kinase biomarkers, those patients who harbor *PIK3CA* mutations clearly have a worse prognosis. However, the treatment benefit is maintained. Patients with a mutation in *PIK3CA* have a median PFS of 8.6 months in the trastuzumab-alone arm and 12.5 months in the pertuzumab arm. The available data set does not allow the prognostic impact of *PIK3CA* mutations to be attributed to a specific mutation or to mutations in a specific exon.

The patients with wild-type *PIK3CA* had a median PFS of 13.8 months in the trastuzumab-alone arm and 21.8 months in the pertuzumab arm. The risk was similar for patients with the *PIK3CA* mutation (HR, 0.64; 95% CI, 0.43–0.93), for those with wild-type *PIK3CA* (HR, 0.67; 95% CI, 0.50–0.89), and for the entire study population (HR, 0.62; 95% CI, 0.51–0.75).

A longitudinal study of serum markers explored whether serum mark-

A Phase III, Open-Label, Randomized, Multicenter Study of Eribulin Mesylate Versus Capecitabine in Patients With Locally Advanced or Metastatic Breast Cancer Previously Treated With Anthracyclines and Taxanes

No statistically significant superiority of eribulin mesylate versus capecitabine regarding OS or PFS was demonstrated by this phase III trial in patients with locally advanced or metastatic breast cancer who had previously been treated with anthracyclines and taxanes (Abstract S6-6). The median OS was 15.9 months with eribulin and 14.5 months with capecitabine (HR, 0.879; 95% CI, 0.770–1.003; $P=.056$). Independent review found a median PFS of 4.1 months with eribulin ($n=554$) and 4.2 months with capecitabine ($n=548$; HR, 1.079; 95% CI, 0.932–1.250; $P=.305$). Prespecified subgroup analysis found that particular patient subgroups may achieve greater therapeutic benefit from eribulin, including patients whose breast cancer is triple-negative (HR, 0.702), estrogen-receptor-negative (HR, 0.779), and HER2-negative (HR, 0.838). Both eribulin and capecitabine had AE profiles consistent with their previously known side effects. Notable hematologic AEs included neutropenia (54% of patients in the eribulin arm vs 16% in the capecitabine arm) and febrile neutropenia (2% vs <1%). Nonhematologic AEs of note included hand-foot syndrome (<1% in the eribulin arm vs 45% in the capecitabine arm), alopecia (35% vs 4%), diarrhea (14% vs 29%), vomiting (12% vs 17%), and peripheral sensory neuropathy (13% vs <1%).

ers could be early detectors of disease progression. Samples were collected at multiple time points, including baseline, week 9, and then at the time of disease progression. No correlation was observed between serum marker levels and disease progression, and no difference was observed between the treatment arms.

In summary, this analysis confirms that HER2 is the only marker for selecting patients for HER2-targeted therapy, despite a comprehensive exploration of a broad panel of candidate biomarkers. This finding is consistent with the TRYPHAENA (Trastuzumab Plus Pertuzumab in Neoadjuvant HER2-Positive Breast Cancer)⁴ and NeoSphere (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation)⁵ studies that were presented at previous SABCs meetings.

The lack of a HER2-treatment-naïve control arm may have resulted in the absence of a signal for other biomarkers in CLEOPATRA. 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 prognosis and particular unmet medical needs. Prior studies have shown that mutant *PIK3CA* is associated with lapatinib resistance⁶ and with poorer prognosis after trastuzumab therapy.⁷ Other studies have shown good prognosis with mutant *PIK3CA*, particularly in hormone receptor-positive tumors.⁸⁻¹⁰ Based on the data presented, these findings may justify clinical trials of HER2-targeted mol-

ecules in combination with *PIK3CA*-pathway-targeted agents.

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HERA TRIAL: 2 Years Versus 1 Year of Trastuzumab After Adjuvant Chemotherapy in Women With HER2-Positive Early Breast Cancer at 8 Years of Median Follow-Up

In 2005, the results of large randomized trials, including HERA (Herceptin Adjuvant), demonstrated statistically significant disease-free survival (DFS) benefit for 1 year of trastuzumab compared with no trastuzumab for patients with HER2-positive early breast cancer.^{1,2} A secondary objective of HERA was to assess whether trastuzumab given for 2 years was superior to treatment for 1 year.³ The protocol was revised to focus on this comparison after 2005. HERA is the only trial testing trastuzumab duration longer than 1 year.

The HERA trial was a large international trial that involved all regions of the world except the United States. It was conducted as a partnership between the Breast International Group (BIG) and Russia, and it recruited 5,102 women in a little over 3 years. The HERA design was pragmatic, as it allowed oncologists around the world to select their preferred neoadjuvant or adjuvant chemotherapy regimen. After completion of surgery, chemotherapy, and radiation, the patients were randomized into observation, 1 year of trastuzumab, or 2 years of trastuzumab. The HER2 status had to be centrally confirmed prior to randomization, and the patients had to have very good heart function, with a left ventricular ejection fraction (LVEF) of 55% or greater.

Of note, after the release of the strikingly positive results of HERA and 2 other US adjuvant trastuzumab trials at the 2005 American Society of Clinical Oncology (ASCO) meeting,^{1,2} 52% of the 1,698 women in the observation arm selectively crossed over to receive trastuzumab. This may be the highest crossover rate observed in all the adjuvant trastuzumab trials.

The comparison of 2 years versus 1 year of trastuzumab was based on a

12-month landmark analysis following randomization into 1 of 2 trastuzumab duration arms. The trial planned for 2 interim analyses and 1 final analysis, with the final analysis being planned for 725 DFS events to obtain 80% power to detect a true HR of 0.08. The current analysis was reported with 734 DFS events at a median of 8 years follow-up.

The patient characteristics in the 1-year and 2-year trastuzumab cohorts were well-balanced with respect to demographics and baseline disease characteristics. About half of the patients had hormone receptor-positive tumors. A total of 52% of the patients were younger than 50 years. About one-third of the patients had node-negative disease. A total of 94% of the patients were exposed to an

anthracycline and 25% to a taxane. Importantly, trastuzumab compliance in both duration arms was good. In the trastuzumab 1-year arm, 9.5% of the patients discontinued treatment prior to completion of 1 year for reasons other than a DFS event. In the 2-year arm, 17.8% interrupted treatment prematurely, with 10.5% discontinuing before the end of the first year and 7.3% before the end of the second year.

The Kaplan-Meier DFS survival curves for the 2-year and 1-year trastuzumab arms showed no difference (HR, 0.99; $P=.86$; Figure 2). When a predefined exploratory analysis based on locally determined hormone receptor status was performed, 2-year trastuzumab was not found to improve DFS in either subgroup.

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

Analysis of the CLEOPATRA trial showed that patients younger than 65 years and those ages 65 years and older had superior PFS by independent review from treatment with pertuzumab plus trastuzumab plus docetaxel as compared with placebo plus trastuzumab plus docetaxel (Abstract P5-18-01). Among patients younger than 65 years, the independently assessed median PFS in the ITT population was 12.5 months in the placebo arm and 17.2 months in the pertuzumab arm (HR, 0.65; 95% CI, 0.53–0.80; $P<.0001$). Among patients ages 65 and older, the independently assessed median PFS in the ITT population was 10.4 months in the placebo arm and 21.6 months in the pertuzumab arm (HR, 0.52; 95% CI, 0.31–0.86; $P=.0098$). Both age groups had higher incidences of diarrhea, neutropenia, dysgeusia, and febrile neutropenia in the pertuzumab arm than in the placebo arm. Among patients ages 65 and older, diarrhea, fatigue, asthenia, decreased appetite, vomiting, and dysgeusia were more frequent than in the younger age group, whereas neutropenia and febrile neutropenia were less frequent. The older subgroup had more docetaxel dose reductions and a lower median number of docetaxel cycles. These reductions, along with less frequent use of granulocyte colony-stimulating factors, likely explain the lower incidence of neutropenia and febrile neutropenia in patients ages 65 and older compared with those younger than 65.

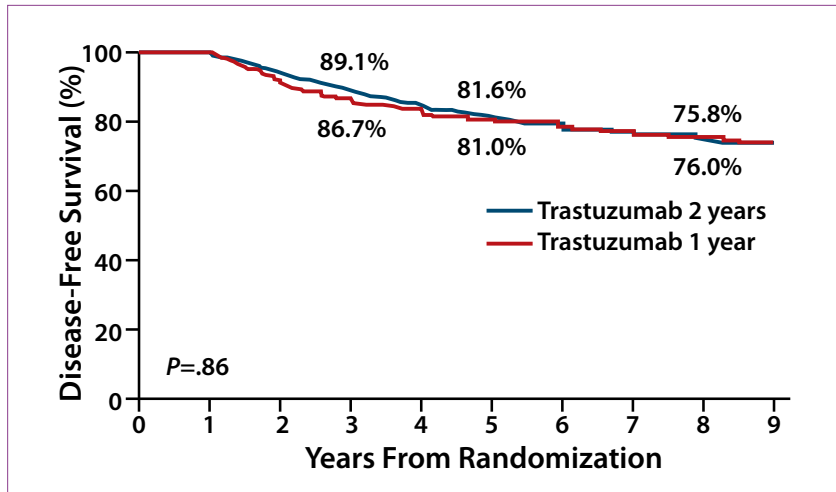


Figure 2. In the HERA trial, there was no significant difference in disease-free survival between 1 year of trastuzumab and 2 years of trastuzumab according to Kaplan-Meier analysis. CI=confidence interval; HERA=Herceptin Adjuvant; HR=hazard ratio. Adapted from Goldhirsch A et al. Paper presented at: CTCR-AACR San Antonio Breast Cancer Symposium; December 5-8, 2012; San Antonio, TX. Abstract S5-2.

The 1-year and 2-year trastuzumab curves for OS are superimposable at 8 years of median follow-up (HR, 1.05; $P=.63$). At a much shorter follow-up of 4 years, the 1-year and 2-year trastuzumab arms also had similar DFS (HR, 0.89; $P=.20$). At 4 years of follow-up, a statistically insignificant separation of the curves for the 1-year and 2-year trastuzumab arms occurred in the hormone receptor–negative cohort (HR, 0.82; 95% CI, 0.64–1.04; $P=.10$). This trend points to the need for long follow-up in these adjuvant trials, even in an aggressive disease like HER2-positive breast cancer.

Regarding safety, more patients in the 2-year trastuzumab arm experienced at least 1, and up to 3 or 4, adverse events (AEs). The patients in the 2-year trastuzumab arm had a 20.4% rate of grade 3 or 4 AEs, which was statistically significant. The 2-year trastuzumab arm also had more frequent asymptomatic or mild cardiac endpoints, which were known as secondary cardiac endpoints (7.2% vs 4.1% in the 1-year trastuzumab arm). In contrast, primary cardiac endpoints, which are severely symptomatic cardiac endpoints that involved New York Heart Association Class 3 or 4

confirmed by a cardiologist, an LVEF below 50% with a drop of at least 10% below baseline, or cardiac death, were rare. No difference in primary cardiac endpoints occurred between the 1-year and 2-year trastuzumab arms. Fatal AEs occurred in approximately 1% of the patients.

When the cumulative incidence of cardiac endpoints over 9 years from randomization was examined, the primary cardiac endpoints were found to be rare with no difference between the 2 arms. When both primary and secondary cardiac endpoints were examined, the constant event rate seen in the 2 arms during the first year of exposure was continued for a second year in the 2-year trastuzumab arm. However, the curves became horizontal, indicating that cardiac events were extremely rare after completion of trastuzumab.

In summary, this analysis of 2-year versus 1-year trastuzumab found no evidence of long-term benefit from 2 years compared with 1 year when trastuzumab was given sequentially after chemotherapy. Secondary cardiac endpoints and other AEs increased in the 2-year trastuzumab arm. The majority of cardiac endpoints occurred during trastuzumab administration.

An upcoming research publication will show that the majority of the cardiac endpoints are reversible. The transient DFS advantage for the 2-year arm in the hormone receptor–negative cohort highlighted the need for long-term follow-up in trials investigating different durations of adjuvant trastuzumab.

An updated analysis of 1-year trastuzumab versus observation at a median follow-up of 8 years was complicated by 2 important points. Of the 1,698 patients in the observation arm, 885 crossed over to receive trastuzumab after 2005. Previous intent-to-treat (ITT) results published at a median follow-up of 4 years suggested a decrease in the effects of trastuzumab.⁴ A progressively smaller apparent DFS benefit of 1 year of trastuzumab in the ITT population occurred through 2008 (HR, 0.54 at 1 year median follow-up, 0.64 at 2 years median follow-up, 0.76 at 4 years median follow-up, and 0.76 at 8 years median follow-up). Although this finding generated some concern in 2008, the good news in 2012 was that no further attenuation of benefit occurred with a median follow-up of 8 years. Instead, a very robust reduction in the risk of DFS events occurred for patients receiving 1 year of trastuzumab. The hormone receptor–positive and hormone receptor–negative cohorts have the same pattern for DFS analysis.

Analysis of OS of the ITT population for 1-year trastuzumab versus observation found, at 4 years median follow-up in 2008, that the OS benefit was 0.85, which was lower than that at 1-year median follow-up (HR, 0.76) and at 2 years median follow-up (HR, 0.66).⁴ However, analysis of OS in the ITT population at 8 years of median follow-up in 2012 found no further attenuation of benefit (HR, 0.76). Instead, a very robust decrease in the risk of death (24%) occurred. This was also seen consistently in the 2 cohorts of hormone receptor–positive and hormone receptor–negative patients.

In conclusion, when 1-year trastuzumab versus observation were

compared, the results at 8 years of median follow-up showed a sustained and statistically significant DFS and OS benefit for 1-year trastuzumab versus observation in the ITT analysis, despite selective crossover. Thus, 1 year of trastuzumab remains the standard of care as part of an adjuvant treatment for patients with HER2-positive early breast cancer. The benefit for 1-year

trastuzumab compared with observation was shown across hormone receptor-positive and hormone receptor-negative cohorts.

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Relative Effectiveness of Letrozole Compared to Tamoxifen for Patients With Lobular Carcinoma in the BIG 1-98 Trial

The BIG 1-98 trial compared the relative effectiveness of letrozole with tamoxifen for patients with lobular carcinoma.¹ This international phase III trial was coordinated by the International Breast Cancer Study Group with BIG.

Lobular carcinoma is the second most-common breast cancer histologic subtype after ductal carcinoma, and it represents 10% of the global breast cancer population. Classical lobular is the most common variant of lobular carcinoma and is mostly represented by hormone receptor-positive and HER2-negative breast cancer. The important role of letrozole in the adjuvant treatment of postmenopausal women who have hormone receptor-positive breast cancer is well-known, although data describing its effectiveness are limited, particularly for patients who are diagnosed with classical lobular carcinoma.

At the 2011 SABCS, the genomic analysis of 183 lobular tumors showed that lobular carcinoma is mostly represented by luminal A, or low-proliferative tumors, followed by luminal B, or high-proliferative tumors.² Additionally, a previous analysis of the BIG 1-98 data showed that the magnitude of benefit of letrozole versus tamoxifen is greater among patients with high-proliferative tumors.³

The overall aim of this study was to evaluate the effectiveness of adjuvant letrozole compared with tamoxifen for patients with lobular carcinoma, while taking into consideration the distribution of luminal A and luminal B subtypes. In the BIG 1-98 international phase III trial, postmenopausal women with hormone receptor-positive breast cancer were randomized to receive 5 years of adjuvant tamoxifen or letrozole, or their sequences. This

present analysis focused on monitoring the arms of this study, which has a median follow-up of 8.4 years.

The study population was restricted to patients whose pathology data were centrally reviewed regarding histologic subtypes, hormone receptors, HER2, and KI-67. The analytic board included 2,599 ductal cancers and 324 classical lobular cancers that were classified as hormone receptor-positive and HER2-negative by central

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

This single-center, phase II study of patients with HER2-positive metastatic breast cancer who were treated with pertuzumab, trastuzumab, and weekly paclitaxel in the first- or second-line setting found that 25 (76%) evaluable patients were progression-free at 6 months (Abstract P5-18-20). Among the evaluable patients, 3 (9%) had a complete response at 6 months, 14 (42%) had a partial response, and 8 (24%) had stable disease, whereas 8 (24%) had disease progression. Patients enrolled in the study must have HER2-positive metastatic breast cancer with 0 or 1 prior treatments in the metastatic setting, an ejection fraction of 50% or greater, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function. Accrual is ongoing. The most common AEs of all grades were peripheral neuropathy, fatigue, diarrhea, alopecia, and an increase in aminotransferase/alanine aminotransferase. Grade 3 events experienced by patients on the trial included peripheral neuropathy, fatigue, dry skin, and neutropenia. One incident of grade 4 sepsis and 1 of grade 4 hypersensitivity occurred. No cardiac events had occurred as of November 12, 2012. One patient experienced grade 2 asymptomatic LVEF decline, as her ejection fraction decreased from 57% to 47%. She was taken off the study and required no further intervention.

Results of a Randomized Phase II Study of PD 0332991, a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination With Letrozole Versus Letrozole Alone for First-Line Treatment of ER+, HER2- Advanced Breast Cancer (TRIO-18)

Median PFS improved to 26.1 months with the combination of PD 0332991 and letrozole versus 7.5 months with letrozole alone (HR, 0.37; $P < .001$) in patients with ER-positive and HER2-negative breast cancer (Abstract S1-6). These phase II results confirm the preclinical observations of PD 0332991 in breast cancer models. The combination of PD 0332991 and letrozole was generally well-tolerated. The most frequent AE was uncomplicated neutropenia, which occurred in 70 patients in the PD 0332991 and letrozole arm, including 5 cases of grade 4 neutropenia. Among the patients enrolled in the letrozole-only arm, 4 cases of neutropenia occurred, with none of grade 4. The median duration of treatment was 8.9 months in the PD 0332991 and letrozole arm and 5.1 months in the letrozole-only arm. Currently, treatment is still ongoing for 47 patients (56%) in the PD 0332991 and letrozole arm and 31 patients (38%) in the letrozole-only arm. Reasons for study discontinuation included progressive disease (26% in the PD 0332991 arm vs 51% in the letrozole-only arm), AEs (10% vs 1%, respectively), death (1% vs 0%, respectively), consent withdrawn (6% vs 4%, respectively), other (1% in the letrozole-only arm), and not treated (1% vs 5%, respectively). A randomized phase III study is planned to start in 2013.

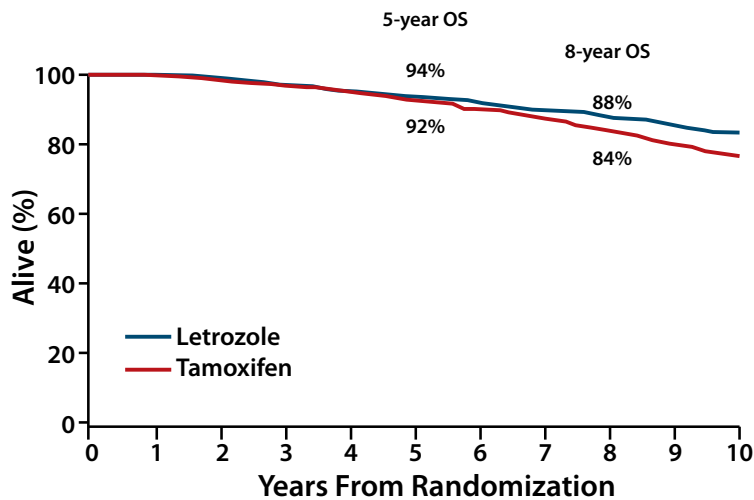


Figure 3. In the BIG 1-98 trial, patients with ductal carcinoma had a statistically significant benefit from letrozole as compared with tamoxifen. BIG=Breast International Group; OS=overall survival. Adapted from Metzger O et al. Paper presented at: CTRC-AACR San Antonio Breast Cancer Symposium; December 5-8, 2012; San Antonio, TX. Abstract S1-1.

pathology review. The study population of lobular and ductal tumors was further classified into luminal A and luminal B subtypes, with a KI-67 cutoff of 14%. Importantly, note that definition is based on an immunohistochemistry surrogate and does not equate to

a genomic classifier. The luminal A and luminal B subsets were different in the lobular and ductal populations, and a greater proportion of the luminal A subset was in the lobular subset.

DFS and OS were estimated using the inverse probability of censor-

ing weighted analysis.⁴ This method provides a better estimate of treatment benefit among patients who fit the analysis in the BIG 1-98 trial due to the high selective crossover rates (25%) from tamoxifen to letrozole after the initial study results were presented in 2005. This analysis weighed the follow-up for the women who stayed on tamoxifen so that they accounted for both themselves and also for the censored follow-up of matched patients who crossed over. Multivariate Cox variation models of DFS and OS evaluated the correlation of clinical pathologic characteristics to outcome.

The DFS curves of the ductal populations treated with letrozole or with tamoxifen were separated by an HR of 0.8, which was statistically significant (95% CI, 0.68–0.94). Among patients with lobular carcinoma, those treated with letrozole had a statistically significant greater DFS than those treated with tamoxifen (HR, 0.48; 95% CI, 0.31–0.74). Patients with ductal carcinoma experienced a 20% reduction in the hazard of DFS events, whereas patients with lobular carcinoma experienced a 52% reduction. The difference was significantly related to histology ($P = .03$).

When the treatment groups were considered based on luminal A and luminal B subsets, the lobular patients in the luminal A subset who were treated with tamoxifen had worse DFS outcomes, while lobular patients treated with letrozole had outcomes that were comparable to patients treated with either letrozole or tamoxifen. Among the patients in the luminal B subset, patients treated with tamoxifen had worse DFS outcomes for both lobular and ductal cancers. Regarding OS results, patients with ductal carcinoma had a statistically significant benefit from letrozole over tamoxifen (HR, 0.73; 95% CI, 0.60–0.89; Figure 3). Patients with lobular carcinoma who were treated with tamoxifen had worse OS outcomes, whereas those treated with letrozole had OS outcomes that were similar to those with

ductal carcinoma who were treated with letrozole. Letrozole was associated with a greater magnitude of benefit in the lobular subset (HR, 0.4) compared with the ductal subset (HR, 0.73). This difference was again related to histology (interaction $P=.045$).

The multivariate analysis for DFS found interactions between treatment and histology ($P=.006$) and between treatment and subtype ($P=.01$). When corrected for classic clinical pathologic variables, lobular patients classified as luminal B derived a greater magnitude of benefit in favor of letrozole (HR, 0.33), followed by lobular patients classified as luminal A (HR, 0.49) and ductal patients classified as luminal B (HR, 0.64). The relative effect of letrozole versus tamoxifen was not significant with the present model for ductal patients classified as luminal A (HR, 0.95).

The multivariate analysis for OS found an interaction for treatment and histology ($P=.035$). When corrected for classic clinical pathologic variables, such as tumor size, nodal status, and

histologic grades, a greater magnitude of benefit favored letrozole in the lobular subset (HR, 0.39) compared with the ductal subset (HR, 0.69).

In conclusion, letrozole was associated with statistically significant reductions in DFS and OS events for both lobular and ductal carcinoma. The magnitude of benefit of adjuvant letrozole was higher among patients with luminal B tumors for both histologic subtypes (classical lobular and ductal carcinoma). The magnitude of benefit of adjuvant letrozole was higher for patients diagnosed with lobular carcinoma compared with ductal carcinoma.

These results were based on an unplanned analysis, and further validation of these results is needed. The biologic underpinnings explaining the differential effect of letrozole compared with tamoxifen in the subset of lobular cancers should be investigated. Since letrozole is an approved regimen for postmenopausal women with hormone receptor–positive breast cancer, clinicians might consider letrozole

over tamoxifen for the upfront treatment of patients diagnosed with lobular carcinoma, regardless of proliferation status. The relative effectiveness of letrozole compared with tamoxifen is being investigated in the sequential arms of the BIG 1-98 trial.

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Trastuzumab Plus Adjuvant Chemotherapy for HER2-Positive Breast Cancer: Final Planned Joint Analysis of Overall Survival (OS) From NSABP B-31 and NCCTG N9831

The combined 10-year survival results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials were analyzed for efficacy.¹ These 2 parallel clinical trials investigated the use of paclitaxel and trastuzumab following anthracycline chemotherapy for adjuvant treatment of high-risk HER2-positive breast cancer.

The NSABP B-31 trial opened to accrual in February of 2000. Patients were randomized to receive 4 cycles of

standard doxorubicin cyclophosphamide chemotherapy every 3 weeks followed by 4 cycles of paclitaxel at 175 mg/m² every 3 weeks or the same chemotherapy with trastuzumab added weekly for 52 weeks starting with the first paclitaxel dose.

The NCCTG N9831 trial opened to accrual in the intergroup between May and July of 2000, and its design was parallel to NSABP B-31, except N9831 has 3 arms. The control arm and arm C were the same as in B-31, except that paclitaxel was given weekly

at 80 mg/m² for 12 weeks. As in B-31, trastuzumab was given weekly for 52 weeks. In both trials, patients with hormone receptor–positive tumors received hormone therapy after completing chemotherapy. Arm B of N9831 also gave trastuzumab, but the trastuzumab started after completion of all chemotherapy, with the goal of assessing the risk-benefit of starting trastuzumab sequentially versus concurrently with paclitaxel. Patients in Arm B of N9831 were not included in this combined data set analysis.

PHARE Trial Results of Subset Analysis Comparing 6 to 12 Months of Trastuzumab in Adjuvant Early Breast Cancer

PHARE (Protocol of Herceptin as Adjuvant Therapy With Reduced Exposure) failed to show that 6 months of trastuzumab is noninferior to 12 months (Abstract S5-3), as DFS results favored 12 months over 6 months of trastuzumab (HR, 1.28; 95% CI, 1.05–1.56; $P=.29$). The PHARE trial randomized 3,382 patients with HER2-positive early breast cancer who had received at least 4 cycles of neoadjuvant chemotherapy on a 1:1 basis to treatment with either 6 or 12 months of trastuzumab. Patients were stratified based on whether the trastuzumab was administered concomitantly or sequentially with chemotherapy and on their estrogen receptor status. The 2 arms of the trial were well matched in disease and treatment characteristics. Treatment with 12 months of trastuzumab was favored over 6 months for all subgroups analyzed, which included estrogen receptor–negative (HR, 1.34), estrogen receptor–positive (HR, 1.23), sequential chemotherapy (HR, 1.41), concomitant chemotherapy (HR, 1.15), age younger than 50 years (HR, 1.38), age 50 years or older (HR, 1.22), negative nodal status (HR, 1.33), positive nodal status (HR, 1.25), tumor less than 2 cm (HR, 1.02), and tumor 2 cm or larger (HR, 1.28). Notably, estrogen receptor status and sequential or concomitant chemotherapy affected outcomes of treatment lengths. For patients with estrogen-negative tumors, 12 months of trastuzumab was favored over 6 months for both sequential (HR, 1.57) and concomitant (HR, 1.10) chemotherapy. For patients with estrogen-positive tumors, 12 months of trastuzumab was again favored over 6 months for both sequential (HR, 1.25) and concomitant (HR, 1.23) chemotherapy.

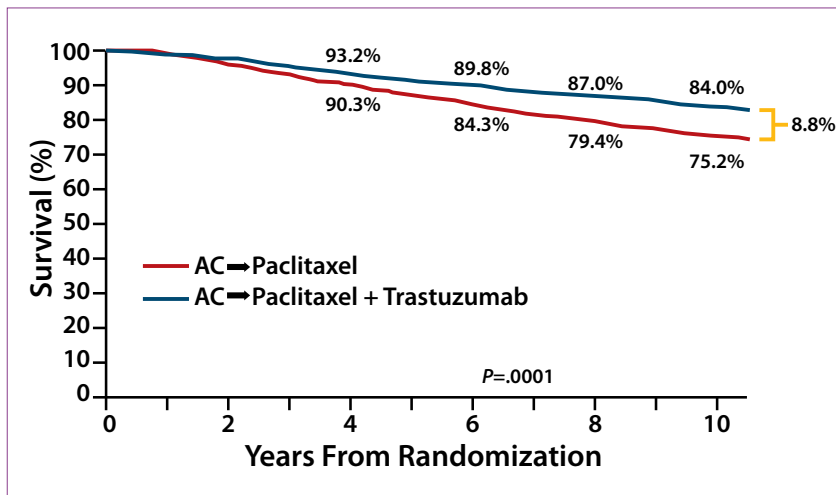


Figure 4. The combined 10-year survival results from the NSABP B-31 and NCCTG N9831 trials showed that the addition of trastuzumab to paclitaxel following adjuvant chemotherapy with doxorubicin plus cyclophosphamide (AC) was associated with significant and substantial improvement in overall survival, with a relative risk reduction of 37%. NCCTG=North Central Cancer Treatment Group; NSABP=National Surgical Adjuvant Breast and Bowel Project. Adapted from Romond E et al. Paper presented at: CTRC-AACR San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Abstract S5-5.

Because of the marked similarity of the control arms and the similarity of the B-31 trastuzumab arm with arm C of N9831, the leadership of the 2 trials submitted a proposal to

the National Cancer Institute's Cancer Therapy Evaluation Program and subsequently to the US Food and Drug Administration to perform a combined efficacy and data analysis. The proposal

was approved in January 2005 prior to analysis of the data.

At the ASCO meeting in May of 2005, the first interim analysis was presented.^{2,3} A median follow-up of just 2 years showed a 52% reduction in DFS events and a 33% reduction in mortality with the addition of trastuzumab to standard chemotherapy.

Eligibility for each protocol required documented informed consent. The patients had to have invasive HER2-positive breast cancer resected by lumpectomy or mastectomy, plus axillary dissection with pathologically clear margins and initially pathologically involved axillary nodes. In May 2003, N9831 was amended to allow randomization of patients with high-risk, node-negative disease. Patients were excluded if they had significant past or active cardiac disease, and a baseline LVEF measurement was required to be at or above the local institution's lower limit of normal.

The studies enrolled 4,046 patients, including 2,102 on B-31 and 1,944 on arms A and C of N9831. The patient and tumor characteristics were balanced across the arms of each protocol and were similar across the protocols. Half of the patients in all arms were under age 50. Approximately 93% of the patients in the joint analysis had node-positive disease, while 45% had tumors that did not express either estrogen or progesterone receptors. Approximately 40% of the tumors were T1 cancers and 9% were T3 cancers.

The median follow-up was 8.4 years as of September 2012. The primary efficacy endpoint was DFS, and it included all randomized patients according to ITT. The secondary endpoint was OS, which was also analyzed by ITT. According to the predefined statistical plan for the combined data analysis, the first interim analysis was to occur after 355 DFS events had occurred, which was reported in 2005.³ The definitive OS analysis was to occur when 710 patients had died from any cause.

In asymptomatic patients, LVEF was monitored at regular intervals. Patients who were randomized to trastuzumab but had an ejection fraction below the lower limit of normal after adjuvant doxorubicin plus cyclophosphamide (AC) or who had a drop in ejection of more than 15% from baseline after receiving AC were not permitted to take trastuzumab. This led to 102 women, approximately 5% of those assigned to the trastuzumab arm, not receiving trastuzumab because of cardiac symptoms during AC or a post-AC decrease in LVEF that precluded initiation of the antibody. These patients are included in the ITT analysis. Similarly, 413 women, who represented about 20% of the control arm, received trastuzumab after the first interim analysis reported positive results in 2005. These patients are also included in the ITT analysis.

The DFS results were updated based on 1,153 events: 680 events in the AC followed by paclitaxel arms, and 473 events in the AC followed by paclitaxel plus trastuzumab arms (HR, 0.60; $P < .0001$). This represents an overall relative risk reduction at 10 years of 40% for a DFS event. The absolute improvement in the Kaplan-Meier estimate of DFS was 11.5% at 10 years.

When focusing on the cumulative incidence of DFS events as a first event, distant recurrences occurred in 19.4% of the control group versus 11.2% of the trastuzumab group. Local and regional recurrences occurred in approximately 6% of the group that did not receive trastuzumab and in approximately 4% of the group that received trastuzumab, which was a reduction of one-third. The 2 arms were comparable in their rates of contralateral breast cancers, other secondary primary cancers, and death without recurrence.

When focusing specifically on distant recurrence as a first event, the hormone receptor-positive cohort experienced recurrences in both arms, but the Kaplan-Meier curves continued to separate over the 10-year time period to a difference of 9.6% at 10 years. For patients with hormone receptor-negative tumors, the separation of the curves stopped after about 7 years, but so did the recurrences in both arms. The recurrence rates for those with hormone receptor-negative tumors plateaued at 21.5% and 11.9%, which was a difference of 9.6%.

The definitive OS results are based on 704 patients who have died so far: 418 in the AC followed by paclitaxel arm, and 286 in the arms with trastuzumab (HR, 0.63; 95% CI, 0.54–0.73; $P < .0001$; Figure 4). The reduction in mortality was 37%. The absolute difference in the Kaplan-Meier estimate of survival was 2.9% at 4 years, 5.5% at 6 years, 7.6% at 8 years, and 8.8% at 10 years ($P < .0001$ for all). The Kaplan-Meier estimate was that 84% of the patients who received trastuzumab in combination with this chemotherapy regimen, most of whom had node-positive disease, are alive 10 years after their diagnosis of breast cancer.

When the causes of death in each arm were examined, a little more than three-quarters of the deaths were due to breast cancer. Approximately 80 patients in each arm have died from a second primary cancer, other causes, or undetermined reasons.

The survival benefit from trastuzumab was present and substantial for all subsets of patients, regardless of age, hormone receptor status, tumor size, or number of positive nodes. Although the CIs within these subgroups all overlap, when the OS was analyzed by regimen, even older patients gained significant absolute

survival benefit. Also, patients with the highest number of involved axillary nodes and those with large tumors gained significant absolute survival benefit. When OS was examined by hormone receptor status, the survival benefit was seen for both hormone receptor-positive and hormone receptor-negative subsets (HR, 0.61 and 0.64, respectively).

In summary, at a median survival of 8.4 years, the addition of trastuzumab to paclitaxel following AC chemotherapy was associated with significant and substantial improvement in OS, with a relative risk reduction of 37%. For patients with high-risk, HER2-positive breast cancer, treatment with this regimen reduces the risk of a DFS event at 10 years by 40%. The relative risk reduction benefit for both DFS and OS was present and of similar magnitude in virtually all subsets of patients analyzed. For patients with hormone receptor-positive disease, the absolute reduction and the rate of distant recurrence as a first event continued to improve over time with trastuzumab, reaching 9.6% at 10 years. For patients with hormone receptor-negative disease, the absolute risk of distant recurrence as a first event was reduced by 9.6% at 7 years, and after that, distant recurrence from breast cancer was unlikely.

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Confirmatory Overall Survival Analysis of CLEOPATRA: A Randomized, Double-Blind, Placebo-Controlled Phase III Study With Pertuzumab, Trastuzumab, and Docetaxel in Patients With HER2-Positive First-Line Metastatic Breast Cancer

When the primary analysis of independently-assessed PFS in the CLEOPATRA trial was conducted, a significant improvement occurred with pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel.¹ The median PFS was prolonged by 6.1 months—from 12.4 months in the placebo arm to 18.5 months in the pertuzumab arm (HR, 0.62; 95% CI, 0.51–0.75; $P < .0001$). The pertuzumab arm had slightly higher incidences of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. An interim analysis of OS, which was conducted at the same time as the preliminary analysis of PFS, showed a strong trend favoring pertuzumab plus trastuzumab plus docetaxel (HR, 0.64; 95% CI, 0.46–0.88), although the results were immature.

This second interim analysis of survival, which represents the confirmatory and definitive OS results from CLEOPATRA, was performed with 1 additional year of follow-up.² The patients received pertuzumab or placebo and trastuzumab until disease progression or unacceptable toxicity. Patients were recommended to receive at least 6 cycles of docetaxel, with fewer cycles allowed for disease progression or unacceptable toxicity and more cycles allowed at the discretion of the investigator. The study drugs were administered on a 3-week schedule.

To be eligible for the study, the patients had to have centrally confirmed, HER2-positive, locally recurrent, unresectable, or metastatic breast cancer. The primary endpoint was independently assessed PFS, and secondary endpoints

included OS, PFS by investigator assessment, and safety. Survival was followed every 18 weeks until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor.

The final OS analysis was planned for 385 deaths, to provide 80% power to detect a 33% improvement in OS in the pertuzumab arm (HR, 0.75). The data cut-off for the second interim analysis occurred in May 2012, which was 1 year after the cut-off for the primary analysis. The study protocol and statistical analysis plan were amended to specify that the Lan-DeMets α -spending function with the O'Brien-Fleming stopping boundary would be applied. This was done to allow formal statistical interpretation of the second interim OS analysis without inflating the type I error.

The second interim OS analysis was performed after 267 deaths and 69% of the prespecified total number of events for the final analysis had occurred, which was after a median follow-up of 30 months in both arms. The pertuzumab arm had a consistent survival benefit (HR, 0.66; 95% CI, 0.52–0.84; $P = .0008$; Figure 5). This benefit was consistent for all subgroups analyzed, except for nonvisceral disease. An exploratory subgroup analysis of the 88 patients who had received prior neoadjuvant and/or adjuvant trastuzumab showed an OS benefit in the pertuzumab arm for this subpopulation (HR, 0.68; 95% CI, 0.30–1.55).

The investigator-assessed PFS was updated, with a PFS event experienced by 296 (72.9%) patients in

Primary Results of BEATRICE, a Randomized Phase III Trial Evaluating Adjuvant Bevacizumab-Containing Therapy in Triple-Negative Breast Cancer

BEATRICE (Bevacizumab Adjuvant Therapy in Triple-Negative Breast Cancer) found no statistically significant improvement in invasive DFS with the addition of 1 year of bevacizumab to adjuvant chemotherapy for triple-negative breast cancer versus adjuvant chemotherapy alone (HR, 0.87; 95% CI, 0.72–1.07; $P = .1810$; Abstract S6-5). This study was the first randomized phase III trial specifically in early triple-negative breast cancer. Bevacizumab was discontinued in 234 (18%) patients due to AEs. During the chemotherapy phase, grade 3 or higher AEs were experienced by 679 (53%) of the patients treated with chemotherapy alone and 816 (63%) of the patients treated with chemotherapy and bevacizumab. During the observation or single-agent bevacizumab phase, grade 3 or higher AEs were experienced by 88 (7%) patients in the chemotherapy-only arm and by 263 (20%) patients in the bevacizumab arm. Of particular interest, patients receiving bevacizumab had more congestive heart failure/left ventricular dysfunction, hypertension, and proteinuria. This interim OS analysis occurred after 59% of required events (stratified HR, 0.84; 95% CI, .64 to 1.12; log-rank $P = .2318$). To assess any potential impact of bevacizumab on OS, the prespecified OS analysis will be performed after 340 deaths or a median follow-up of 5 years, whichever is earlier. These results are expected in late 2013.

the placebo arm at a median of 18.7 months and 257 (63.9%) patients in the pertuzumab arm at a median of 12.4 months (HR, 0.96; 95% CI, 0.58–0.81). Subgroup analysis of investigator-assessed PFS found that all subgroups maintained the benefit associated with pertuzumab treatment.

More patients in the placebo arm than in the pertuzumab arm received subsequent therapy for breast cancer following discontinuation of the study treatment. Among the patients who received subsequent breast cancer therapy, the treatments were generally balanced between the 2 arms. Patients could not be treated with pertuzumab as subsequent therapy before the study was unblinded. The patients in the pertuzumab arm had a longer median time on study treatment (17.4 months) than those in the placebo arm (11.4 months). Both arms had a similar exposure to docetaxel.

The AEs reported at this second interim OS analysis were similar to those reported at the primary analysis. No new safety concerns were reported after this additional year of follow-up. The patients in the pertuzumab arm had higher incidences of at least 5% of diarrhea, rash, mucosal inflammation, pruritus, febrile neutropenia, and dry skin (all grades). The AEs of 26.4% of patients in the placebo arm and 28.1% in the pertuzumab arm were treated with granulocyte colony-stimulating factors.

Patients in the pertuzumab arm had higher incidences of grade 3 or higher neutropenia, febrile neutropenia, and diarrhea by at least 2% compared with the placebo arm. As the cycle number increased, the number of patients experiencing febrile neutropenia and diarrhea was considerably reduced. Notably, a median of 8 cycles of docetaxel was administered in both arms, and no further episodes of febrile neutropenia were reported following discontinuation of docetaxel. Patients in the pertuzumab arm did not have an increased incidence of cardiac AEs compared with those in the placebo arm.

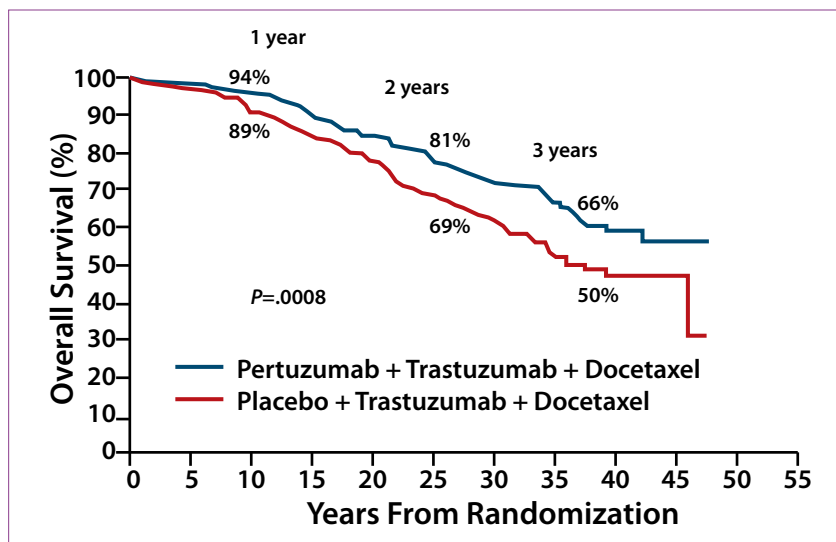


Figure 5. A second interim overall survival analysis of the CLEOPATRA trial showed a consistent survival benefit with the addition of pertuzumab to trastuzumab plus docetaxel. CLEOPATRA=Clinical Evaluation of Pertuzumab and Trastuzumab. Adapted from Swain S et al. Paper presented at: CTRC-AACR San Antonio Breast Cancer Symposium; December 11-15, 2012; San Antonio, TX. Abstract P5-18-26.

The pertuzumab arm had more all-grade AEs than the placebo arm (10,475 vs 8,927). When the number of AEs was adjusted for the length of time on study treatment, the rate of AEs per patient-year of treatment was slightly lower in the pertuzumab arm (16.9% vs 18.7%). Most deaths in the safety population were attributed to disease progression. Both study arms had a similar number of deaths due to AEs, with febrile neutropenia or infections being the most common causes of death due to an AE.

In conclusion, a statistically significant and clinically meaningful improvement in OS with pertuzumab was demonstrated by CLEOPATRA at the second interim analysis. Therefore, this analysis was the confirmatory OS analysis, and it was consistent with both the first interim OS analysis and the primary analysis of independently assessed PFS.¹ Pertuzumab showed a durable treatment effect in combination with trastuzumab and docetaxel. At the time of data cut-off, 68 patients in the placebo arm and 104 in the pertuzumab arm were still alive and on study treatment. Due to the statistically

significant survival benefit, the patients who were still receiving study treatment in the placebo arm were offered cross-over to the pertuzumab arm. The final OS analysis is event-driven, will occur when 385 events have been reached, and will be exploratory only.

With 1 more year of follow-up, no new safety signals were reported compared with the primary analysis. No evidence indicates cumulative or late toxicity associated with pertuzumab at this point. Based on these results, the combination of HER2 blockage and chemotherapy with pertuzumab plus trastuzumab plus docetaxel can be considered standard of care for patients with HER2-positive metastatic breast cancer in the first-line setting.

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Final Analysis of Overall Survival for the Phase III CONFIRM Trial: Fulvestrant 500 mg Versus 250 mg

CONFIRM (Comparison of Faslodex in Recurrent or Metastatic Breast Cancer) was a phase III trial that compared 2 different doses of fulvestrant in menopausal patients with advanced breast cancer.¹ The main eligibility criteria were for patients to be postmenopausal, have advanced disease, and be estrogen-receptor (ER)-positive. This phase III trial was double-blind and placebo-controlled. Accordingly, patients from the control arm received fulvestrant at 250 mg as well as an injection of placebo on days 0, 14, and 28, and then every 28 days. Patients from the experimental arm received 2 injections of fulvestrant at 250 mg according to the same schedule as the control arm.

Regarding prior endocrine hormone therapy, the patients eligible for CONFIRM were relapsing while on adjuvant endocrine therapy or within 1 year of the end of adjuvant endocrine therapy. For patients who had progressed after more than 1 year after the end of their adjuvant endocrine therapy, or for those with de novo advanced breast cancer, first-line endocrine therapy was mandatory for inclusion in the CONFIRM trial.

The patient characteristics were well balanced between the 2 study arms. All patients had locally defined ER-positive tumors. Approximately two-thirds of the patients had progesterone receptor-positive tumors. More than half of the patients had visceral involvement. Notably, approximately one-third of the patients did not receive adjuvant endocrine therapy despite ER-positive tumors, because these patients had de novo advanced disease. Fulvestrant was the first-line therapy for approximately half of the patients in this trial, and it was a second-line therapy for advanced disease for the remaining half.

The primary endpoint of this trial was PFS, and these results were first presented at the SABCS 3 years ago and fully reported in the *Journal of Clinical Oncology*.² Fulvestrant 500 mg is superior to 250 mg (HR, 0.80; $P=.006$). The secondary endpoint was OS, which was reported when 50% of the events had occurred. This was at the same time as the analysis of PFS, and was also reported 3 years ago. A numerical increase in survival occurred for patients receiving fulvestrant 500 mg over 250 mg (HR, 0.84; $P=.091$).

These survival data led to the decision to amend the statistical analysis plan and to perform a second survival analysis. The second survival analysis had to be reported when 75% of events had occurred. This was an exploratory survival analysis. No alpha was retained for this analysis because the 5% had been used for the first OS analysis. Accordingly, no adjustment for multiplicity was feasible in the context of this second survival analysis.

The methodology involved monitoring the patients every 3 months to check their survival status. Serious AEs were recorded for all patients who were still on treatment, and information was collected on the first subsequent therapy given after progression on fulvestrant.

At the time of data cut-off for the 75% survival analysis, a minority of patients (approximately 3%) were still receiving treatment. Approximately 10% of the study population was still alive but not on treatment. As planned, overall, more than 75% of the study population had died at the time of data cut-off.

At 75% data maturity, the OS curves showed a numerical increase in survival for patients receiving fulvestrant 500 mg (HR, 0.81; $P=.016$) (Figure 6). Notably, this is a nominal P value and cannot be claimed as statistically significant because this study was designed as an exploratory analysis. The entire alpha was spent for the first survival analysis, and no adjustment

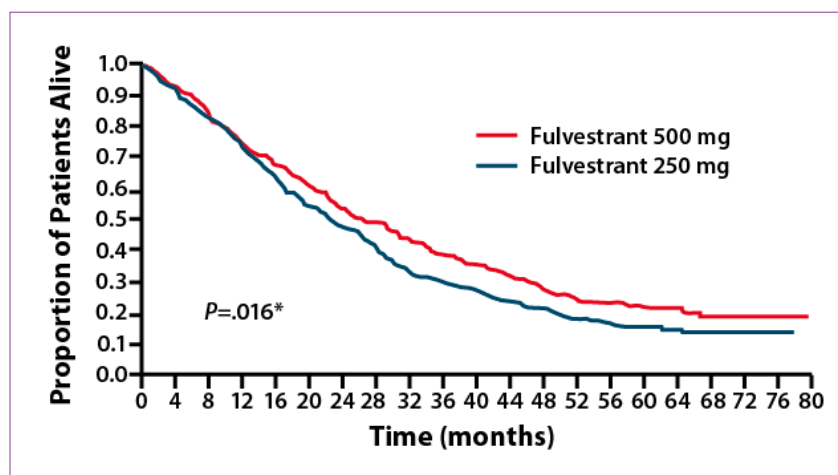


Figure 6. Overall survival in the phase III CONFIRM trial, which compared fulvestrant at 500 mg and 250 mg. *The P value of .016 is nominal and is not considered statistically significant. CONFIRM=Comparison of Faslodex In Recurrent or Metastatic Breast Cancer. Adapted from Di Leo A et al. Final analysis of overall survival for the phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg. Paper presented at the 2012 San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. Abstract S1-4.

Overall Survival Results of a Multicenter Randomized Phase II Study in Locally Advanced Breast Cancer Patients Treated With or Without Neoadjuvant Trastuzumab for HER2 Positive Tumor (REMAGUS 02 Trial)

Among patients with stage II–III breast cancer, those with HER2-positive breast cancer who received trastuzumab had a significantly higher OS than patients with HER2-negative tumors at 5 years (Abstract P1-14-03). In patients with HER2-positive tumors, pCR was not a surrogate of survival, although a trend existed toward better DFS in HER2-positive patients who achieved a pCR ($P=.081$). The rate of pCR did not significantly influence DFS ($P=.22$) or OS ($P=.56$). This study enrolled 340 patients with stage II–III breast cancer, including 120 patients with HER2-positive tumors. The patients were randomized to receive neoadjuvant chemotherapy with or without trastuzumab. Patients with hormone-receptor-positive tumors received adjuvant hormone therapy. The patients with HER2-positive tumors received trastuzumab in the neoadjuvant ($n=54$) or adjuvant ($n=52$) setting. After a median follow-up of 51.6 months, the median DFS was statistically superior for the HER2-positive patients who were treated with chemotherapy plus neoadjuvant trastuzumab compared with the other groups ($P=.018$). Patients who received neoadjuvant or adjuvant trastuzumab did not differ in their OS and DFS rates. However, OS was influenced by tumor size ($P=.03$) and estrogen receptor expression ($P=.06$), whereas DFS was influenced by clinical lymph node status ($P=.049$) and progesterone receptor expression ($P=.046$).

for multiplicity was possible. However, these data highlight the consistency between the 2 different survival analyses, since the 50% events analysis had an HR of 0.84 and the 75% events analysis had an HR of 0.81.

The next step was to rule out the hypothesis that the suggested benefit in survival was mainly the consequence of an imbalance in the first subsequent therapy that was given after progression to fulvestrant. Information on first subsequent therapy was collected for approximately two-thirds of the patients who took part in the clinical trial. These analyses found that more than 90% of the patients participating in the study received their first subsequent therapy after progression on fulvestrant.

Another conclusion from these analyses is that, when the antitumor activity of the first subsequent therapy was defined as objective response or clinical benefit rate, this activity seems to be comparable between the 2 study arms.

The investigators also considered the crossover rate for patients initially treated with fulvestrant 250 mg. The crossover rate of 2.1% out of 374 patients was quite low because crossover was not initially planned for in the context of this clinical trial. When the results of the PFS analysis were available, the protocol was amended to offer crossover to patients who were initially on fulvestrant 250 mg. However, at that time, most of the patients had progressed on fulves-

trant 250 mg and were being treated with other systematic therapies.

No clinically relevant differences occurred in the number of serious AEs or in the number of causally related serious AEs. The fulvestrant 500 mg treatment group had 5 serious AEs with the outcome of death, while the 250 mg treatment group had 7. Again, clinically relevant differences were not found between the 2 treatment groups.

In conclusion, this exploratory OS analysis at 75% maturity suggests that fulvestrant 500 mg improves OS over fulvestrant 250 mg, with a 4-month increase in median OS and a 19% reduction in the relative risk of death. These results are consistent with the previously reported PFS and OS data.² Analysis of first subsequent therapies did not support an imbalance between the 2 study arms. Only 2% of the patients crossed over from fulvestrant 250 mg to 500 mg. However, the activity for fulvestrant 500 mg after pretreatment with 250 mg is unknown. Accordingly, the low crossover rate cannot be the main reason explaining the observed survival difference. The safety results did not support any clinically relevant difference between fulvestrant 250 mg and 500 mg, and they are consistent with the previously reported safety profile of fulvestrant 500 mg.

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Commentary

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Presentations at the 2012 San Antonio Breast Cancer Symposium (SABCS) included data from many clinical trials that have the potential to impact clinical care. Study agents included letrozole, tamoxifen, fulvestrant, pertuzumab, trastuzumab, bevacizumab, and eribulin mesylate.

Data from several different analyses of existing studies were presented regarding the use of hormone therapy for breast cancer. The Breast International Group (BIG) 1-98 trial compared letrozole and tamoxifen in patients with lobular carcinoma.¹ It showed that patients with highly proliferative tumors have a greater benefit from letrozole than tamoxifen. An interesting analysis of this study was presented at the 2012 SABCS.² It focused on distribution of luminal A and luminal B subtypes and found relatively similar results to the parent study: letrozole had somewhat more activity than tamoxifen in this very hormone-sensitive disease, which is not particularly surprising.

Dr. Angelo Di Leo presented updated results of the CONFIRM (Comparison of Faslodex in Recurrent or Metastatic Breast Cancer) trial, which compared 2 doses of fulvestrant: 250 mg with a loading dose versus 500 mg.³ The CONFIRM trial was developed in response to several findings. The original dose approved by the US Food and Drug Administration (FDA) was 250 mg. In clinical practice, fulvestrant was less effective than expected based on its mechanism

of action and previously reported data supporting the use of other hormone therapies in hormone-responsive advanced breast cancer. Fulvestrant takes 3 months to reach steady state and thus mandates a loading dose, which was not how the drug was initially approved. In addition, the steady state level was not as high as initially modeled in preclinical studies. Lastly, increasing the dose does not increase toxicity, suggesting that the previously approved dose of 250 mg was not the maximum tolerated dose. Initial data from CONFIRM showed that doubling the dose improved response and progression-free survival (PFS) in patients with metastatic hormone-receptor-positive breast cancer, and these results led to the approval of the higher dose many years after the initial approval of fulvestrant.⁴ The final analysis showed improved overall survival with the double dose.³ Although improved overall survival had been shown in the earlier results of CONFIRM, it was more clearly significant in this analysis. The new analysis further solidified the importance of using the FDA-approved dose of fulvestrant. It also has implications regarding drug development in general. Sometimes a drug may lack benefit or contribute toxicity due to the dose or schedule, which can result in negative studies.

Dr. Sandra Swain presented a second interim analysis of the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial, which showed a consistent survival benefit for pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer.⁵ The initial data from the CLEOPATRA trial showed that survival was improved with the addition of pertuzumab to trastuzumab and docetaxel, but the survival advantage did not meet the prespecified O'Brien-Fleming stopping boundary⁶; in other words, the difference was statistically significant in terms

of the *P* value, but it did not meet the study's criteria for significance (the prediction, beyond a shadow of a doubt, that the estimate of survival will be accurate). The final survival analysis of CLEOPATRA showed a highly statistically significant difference in survival, favoring the addition of pertuzumab to chemotherapy and trastuzumab.⁵

Dr. José Baselga presented a biomarker analysis of the CLEOPATRA trial.⁷ There are biomarkers that help define prognosis in patients with HER2-positive disease, but we are still anxiously searching for biomarkers that predict which patients will benefit from one therapy versus another in terms of factors such as safety and cost effectiveness. It is critical to understand which tumors require the addition of new agents. For example, in the early-stage setting, some patients' tumors will respond well to trastuzumab and chemotherapy and will therefore derive relatively less benefit from the addition of pertuzumab, and it is likely that some tumors, despite expression of HER2, are low risk and could possibly do well either without systemic treatment, or with antibody therapy alone. We do not currently know how to identify these patients and their tumors before treatment. In fact, although it is generally believed that the tumor is the primary determinant for whether additional therapy is needed, the host may also play a role in ways that are not well understood. This issue is less of a problem with antibody therapy, such as was used in CLEOPATRA, but it is certainly possible. The biomarker analysis of CLEOPATRA echoed the findings of countless other biomarker studies. It confirmed that HER2 is the only marker for selecting patients for HER2-targeted therapy,^{8,9} despite a comprehensive exploration of a broad panel of candidate biomarkers.⁷ The CLEOPATRA analysis did not, however, identify a biomarker to predict which patients benefit from the addition of a novel therapeutic agent, such as pertuzumab. More research is needed; adjuvant trials will be critical, as will the utilization of additional panels

of markers that might ultimately lead to a larger analysis using a supercomputer-type system that might be able to select a panel of genes to predict those tumors that are unlikely to do well without the addition of a new drug. Currently, it appears that patients with an overall better prognosis benefit more from the addition of new drugs than do patients with a poor prognosis. It is not yet possible to identify a group of patients who will have unique benefit from the addition of pertuzumab.

Another analysis from the CLEOPATRA trial examined whether pertuzumab in combination with trastuzumab and docetaxel was superior to standard docetaxel and trastuzumab in elderly patients.¹⁰ Indeed, the benefits appeared to be relatively similar in the older population as compared to the population as a whole. The older population did not appear to experience additional toxicity, confirming results of previous studies in HER2-positive disease that focused on the additive benefit of HER2-targeted therapies.¹¹

Much has been learned about the duration of trastuzumab. The use of 1 year of trastuzumab as adjuvant therapy was not based on a strong scientific rationale. In estrogen receptor (ER)-negative, HER2-positive breast cancer, the highest risk of recurrence is in the first 3–5 years; most patients recur within 3 years.¹² One year of trastuzumab seemed feasible, safe, and financially accessible, so it was used in adjuvant trials. Once those trials showed dramatic early improvement in outcome,¹³ there was interest in whether a very short course of exposure could result in similar outcome. A shorter course would be easier for the patient to tolerate and much more cost effective, which is particularly important in countries where trastuzumab has not been widely applied due to cost. Another question about adjuvant therapy was whether 2 years of trastuzumab would be better than 1 year, a question evaluated by the HERA (Herceptin Adjuvant) trial.¹⁴ We have been

waiting for these data for a long time, and such a long wait often suggests that any difference is narrow or nonexistent. Indeed, that was the case in the HERA trial. Two years of trastuzumab showed no difference compared to 1 year of trastuzumab, solidifying 1 year as the maximum-needed duration for patients with early-stage breast cancer.

The PHARE (Protocol of Herceptin as Adjuvant Therapy With Reduced Exposure) trial evaluated 6 months of trastuzumab versus 12 months, and it showed that 12 months seemed to be somewhat superior to the shorter duration.¹⁵ Results from this study have been presented twice, once at the European Society for Medical Oncology 2012 Congress¹⁶ and now at the SABCS.¹⁵ Both analyses showed that 12 months is superior to 6 months and should continue to be the standard duration of trastuzumab for HER2-positive breast cancer. Interestingly, there was no important difference in toxicity between the 2 durations. There are several additional studies looking at shorter durations of trastuzumab, which will be reported in the next few years. Based on what we

have seen so far, it is unlikely that this conclusion will change.

Updated data were presented from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials combined analysis.¹⁷ The longer follow-up of patients with HER2-positive breast cancer who were randomized to receive standard anthracycline-based and taxane-based chemotherapy with or without trastuzumab again showed a significant improvement in overall survival, if anything increasing over time, with the addition of trastuzumab. This finding is impressive, particularly given the fact that a substantial number of patients crossed over to receive trastuzumab after the initial data were released and the studies were closed to accrual. Similar to the trials in the metastatic setting, this study suggested that the earlier trastuzumab is used in patients with HER2-positive breast cancer, the better off patients are. Trastuzumab added to this type of chemotherapy in the adjuvant setting not only improved disease-free survival but continued to improve overall survival,

Final Progression-Free Survival Analysis of BOLERO-2: A Phase III Trial of Everolimus for Postmenopausal Women With Advanced Breast Cancer

This 18-month analysis of the BOLERO-2 (Breast Cancer Trials of Oral Everolimus) trial confirmed that everolimus 25 mg daily plus everolimus 10 mg daily produced significant, durable PFS benefits in patients with hormone-receptor-positive, HER2-negative breast cancer that progressed after initial nonsteroidal aromatase inhibitor treatment compared with placebo plus everolimus 10 mg daily (Abstract P6-04-02). Local assessment found a median PFS of 7.8 months with additional everolimus versus 3.2 months with placebo plus everolimus (HR, 0.45; $P < .0001$), while central assessment found a median PFS of 11.0 months versus 4.1 months (HR, 0.38; $P < .0001$). The effect of treatment with everolimus plus everolimus was consistent among all the prospectively defined subgroups. The everolimus plus everolimus regimen reduced risk for PFS events by 61% in patients who progressed after adjuvant therapy. Regardless of the presence of visceral or bone metastases, everolimus plus everolimus improved PFS by more than 4 months. Among patients with visceral metastases, everolimus plus everolimus reduced the risk of PFS by 53% (HR, 0.47; 95% CI, 0.37–0.60), while it reduced PFS risk by 59% (HR, 0.41; 95% CI, 0.31–0.55) for patients without visceral metastases. The everolimus plus everolimus arm had fewer OS events (25.4%) than the placebo plus everolimus arm (32.2%). The everolimus plus everolimus arm had AEs consistent with the safety profile of everolimus.

if anything even more so now in this updated analysis. Studies are evaluating the addition of novel therapeutics, such as lapatinib and pertuzumab, to adjuvant trastuzumab, and data should be available in the next few years. Data from the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial) study examining lapatinib in sequence with trastuzumab may be reported as early as next year.¹⁸

Bevacizumab continues to have difficulty in the field of breast cancer. Dr. David Cameron presented the first results of the BEATRICE (Bevacizumab Adjuvant Therapy in Triple-Negative Breast Cancer) trial, which examined the addition of bevacizumab to standard chemotherapy in patients with so-called triple-negative breast cancer.¹⁹ Since this trial was developed, there has been an appreciation of the enormous heterogeneity in triple-negative breast cancer. The initial suggestion that bevacizumab might be uniquely effective in triple-negative disease came from a second-line study, the RIBBON-2 (A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy for Second-Line Treatment of HER2-Negative Metastatic Breast Cancer) trial, as well as a meta-analysis of the first-line trials.²⁰ One might look at the BEATRICE trial now and appreciate that it was a very high-risk trial from the start. It is now known that some patients with triple-negative breast cancer have tumors that are very sensitive to chemotherapy. BEATRICE was trying to identify an additive benefit of bevacizumab in patients whose tumors showed upfront resistance to the standard approach, although it is not clear that this population is the most likely one to benefit from the addition of antiangiogenic therapy. Indeed, BEATRICE showed no additional benefit in disease-free or overall survival when bevacizumab was added to standard chemotherapy in patients with early-stage triple-negative breast cancer.

When stratified by different subsets, there was still no difference in outcome with the addition of bevacizumab.

There was an important in-depth biomarker analysis from the BEATRICE study that may help to identify biomarkers that could predict benefit from bevacizumab.²¹ Because the BEATRICE trial showed no benefit to the study agent, it was hard to focus on a subset that did benefit and that could allow for identification of a biomarker. It might be that a combined analysis of the correlative science data from the BEATRICE trial with forthcoming data from the Eastern Cooperative Oncology Group (ECOG) 5103 trial,²² the adjuvant cooperative group trial in the United States, will help to identify potential predictive markers. There were some encouraging data in BEATRICE, potentially associating levels of the vascular endothelial growth factor (VEGF) 2 receptor with outcome. However, previous studies had looked at plasma VEGF-A levels, which did not show any correlation with trial endpoints in BEATRICE. Finding a biomarker or biomarkers that predict response to antiangiogenic therapy remains an elusive goal that will hopefully be clarified at least to some degree by ongoing trials.

The EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) trial led to the approval of eribulin mesylate in the treatment of patients with heavily pretreated metastatic breast cancer.²³ Dr. Peter Kaufman presented results from a follow-on study to the EMBRACE trial.²⁴ This open-label, randomized phase III trial compared eribulin to capecitabine in patients with metastatic breast cancer who had been treated with anthracyclines and taxanes. The different administration schedules of eribulin (1.4 mg/m² on days 1 and 8 of a 3-week schedule) and capecitabine (1,250 mg/m² twice daily on days 1–14 of a 3-week schedule) complicate the analysis. The dose of capecitabine could be adjusted as needed, but the administration of eribulin could lead to toxicity the weeks

following administration. As eribulin has been used more widely, there has been a better understanding that the primary toxicity from this agent is bone marrow suppression; when this toxicity is countered by dose modification and/or the use of growth factors, patients often do very well and are able to tolerate the drug for long durations. In this trial, the toxicity profiles of capecitabine and eribulin were quite different, as expected. The trial had initially hypothesized that eribulin would be superior to capecitabine, but both agents were effective, and there was no difference in outcome in patients treated with either eribulin or capecitabine. This trial solidifies the usefulness of both eribulin and capecitabine as treatments for advanced breast cancer, and it also confirms prior studies suggesting that order of administration of standard chemotherapy agents does not affect survival. In contrast, the order of therapy in the HER2-positive population does appear to be important, as benefits have been seen when HER2-targeted therapy is administered earlier in the course of disease.

A small phase II trial examined the toxicity of weekly paclitaxel used in combination with pertuzumab and trastuzumab.²⁵ The regimen was very safe, and the National Comprehensive Cancer Network guidelines list pertuzumab and trastuzumab in combination with a taxane as a standard of care, suggesting that weekly paclitaxel could be substituted for every-3-week docetaxel at 75 mg/m² with impunity. The potential benefit of adding pertuzumab would not be changed by partnering with a different taxane.

Dr. Martine Piccart presented a final PFS analysis of the BOLERO-2 (Breast Cancer Trials of Oral Everolimus) trial.²⁶ BOLERO-2 is a phase III trial that compared exemestane plus placebo to exemestane and the mammalian target of rapamycin inhibitor everolimus in postmenopausal patients with hormone-receptor-positive metastatic breast cancer that had progressed on a nonsteroidal aromatase inhibitor.

The initial analysis of this trial led to the approval of everolimus in this setting due to a dramatic improvement in PFS. The final PFS analysis at 18 months continued to show an improvement in PFS with the addition of everolimus and confirmed that the magnitude of benefit was not due to early analysis; in other words, the magnitude of benefit did not decrease over time. We also saw that the absolute difference in survival continues to increase over time favoring the everolimus arm, although the final survival analysis requires a much larger number of events than are currently available and is expected sometime later next year. It is encouraging that the number of events is still low; it shows that patients are living longer than was initially expected. Toxicity was similar to that found in the initial analysis. Mucositis seemed to be the primary adverse event; it led to a modest number of treatment reductions and, more rarely, to discontinuation. As everolimus has been used more commonly in the population of patients treated in the clinic, we have better learned how to manage toxicity with strategies such as reducing the dose and educating our patients about the risks of mucositis. Many clinicians are using preventive approaches. At my institution, we have been using a steroid-containing mouthwash prophylactically and have been very pleased with the results. Another strategy is to put the pill in a marshmallow or another food substance so that it will not come into contact with the oral mucosa. The ability to reduce the mucositis associated with everolimus will improve this agent's ability to be used and thereby increase the benefit it can offer to patients.

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