

A SPECIAL MEETING REVIEW EDITION

**Highlights in Metastatic Breast Cancer From the 2012
American Society of Clinical Oncology Annual Meeting**

June 1–5, 2012 • Chicago, Illinois

Special Reporting on:

- Primary Results From EMILIA, a Phase III Study of Trastuzumab Emtansine (T-DM1) Versus Capecitabine (X) and Lapatinib (L) in HER2-Positive Locally Advanced or Metastatic Breast Cancer (MBC) Previously Treated With Trastuzumab (T) and a Taxane
- Quality of Life Assessment in CLEOPATRA, a Phase III Study of Trastuzumab Plus Docetaxel With or Without Pertuzumab in Metastatic Breast Cancer
- NSABP B-38: Definitive Analysis of a Randomized Adjuvant Trial Comparing Dose-Dense (DD) AC→Paclitaxel (P) Plus Gemcitabine (G) With DD AC→P and With Docetaxel, Doxorubicin, and Cyclophosphamide (TAC) in Women With Operable, Node-Positive Breast Cancer
- BOLERO-1: A Randomized, Phase III, Double-Blind, Placebo-Controlled Multicenter Trial of Everolimus in Combination With Trastuzumab and Paclitaxel as First-Line Therapy in Women With HER2-Positive (HER2+), Locally Advanced or Metastatic Breast Cancer (BC)
- CALGB 40502/NCCTG N063H: Randomized Phase III Trial of Weekly Paclitaxel (P) Compared to Weekly Nanoparticle Albumin Bound Nab-Paclitaxel (NP) or Ixabepilone (Ix) With or Without Bevacizumab (B) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer (MBC)
- Adverse Events With Pertuzumab and Trastuzumab: Evolution During Treatment With and Without Docetaxel in CLEOPATRA

PLUS Meeting Abstract Summaries

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PERJETATM pertuzumab

PERJETA: for the first-line treatment of HER2+* metastatic breast cancer

Indication

PERJETATM (pertuzumab) is a HER2/neu receptor antagonist indicated 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.

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

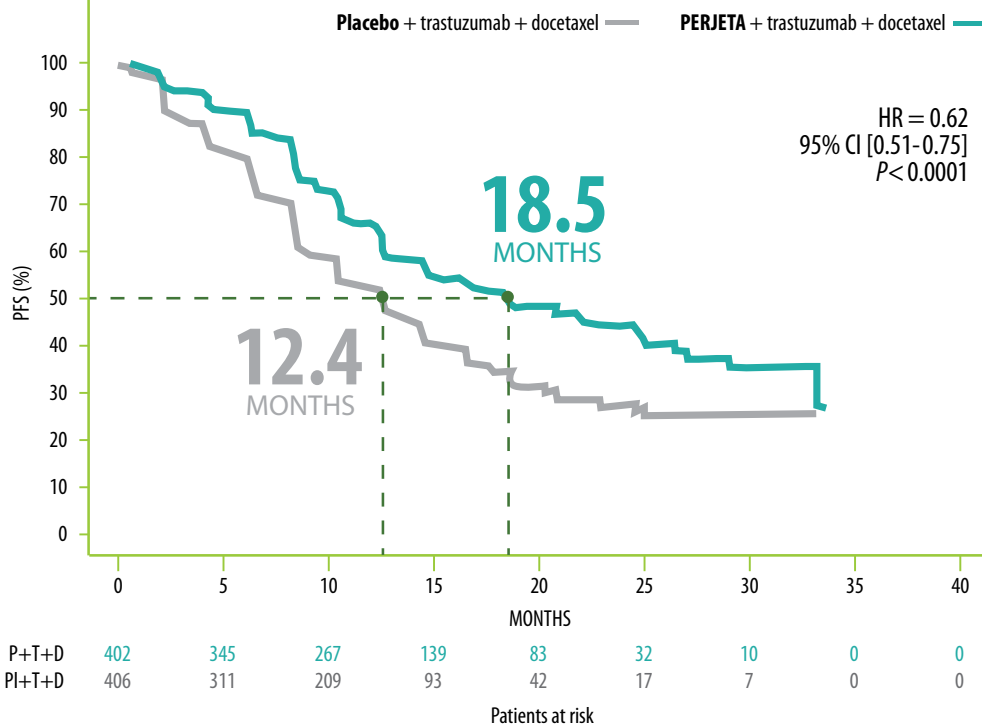
Left Ventricular Dysfunction

- 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 trastuzumab and repeat LVEF assessment within 3 weeks in patients with significant decrease in LVEF. Discontinue PERJETA and trastuzumab 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

6.1-Month Improvement in Median IRF[†]-Assessed PFS[‡]¹



[†]IRF = independent review facility.
[‡]PFS = progression-free survival.

Select Important Safety Information: Most Common Adverse Reactions

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.¹

- 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 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 trastuzumab 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.

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

Reference: 1. PERJETA Prescribing Information. Genentech, Inc. June 2012.

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

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PERJETA[™]
pertuzumab

**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 HER2FISH 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 % All Grades %	
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 \geq 65 years of age and 5 patients (1%) were \geq 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 \geq 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:

Genentech, Inc.

A Member of the Roche Group

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PERJETA is a trademark

of Genentech, Inc.

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Primary Results From EMILIA, a Phase III Study of Trastuzumab Emtansine (T-DM1) Versus Capecitabine (X) and Lapatinib (L) in HER2-Positive Locally Advanced or Metastatic Breast Cancer (MBC) Previously Treated With Trastuzumab (T) and a Taxane

Trastuzumab emtansine (T-DM1) is an antibody drug conjugate comprising trastuzumab and emtansine that includes the DM1 toxin and a stable linker. After extracellular binding to human epidermal growth factor receptor 2 (HER2), T-DM1 is internalized into the lysosome, where the linker is cleaved, releasing emtansine. Emtansine disrupts microtubule assembly; it binds to the same site on tubulin as vinca alkaloids such as vinorelbine but with 20-fold greater affinity. In vitro assays demonstrated a 25–500-fold greater potency of emtansine over paclitaxel.¹

In 2 single-arm clinical studies, T-DM1 yielded objective response rates (ORRs) of 25.9% and 34% in metastatic breast cancer patients who had received prior trastuzumab.^{2,3} In a randomized phase II study of 137 metastatic breast cancer patients, first-line T-DM1 significantly improved progression-free survival (PFS) over trastuzumab plus docetaxel (14.2 months vs 9.2 months; hazard ratio [HR], 0.59; $P=.035$).⁴ In a randomized phase III trial of patients previously treated with trastuzumab, lapatinib plus capecitabine improved PFS over capecitabine alone (8.4 months vs 4.4 months; HR, 0.48; $P<.001$).⁵

Kimberly L. Blackwell, MD, presented results from the prospective randomized phase III EMILIA (An Open-Label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine Plus Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer) trial, which enrolled first-, second-, and third-line metastatic breast cancer patients previously treated

with a taxane.⁶ The control arm of EMILIA was based on a phase III study in which combined capecitabine plus lapatinib significantly prolonged time to progression relative to capecitabine alone in patients with HER2-positive breast cancer who had received prior anthracycline, taxane, and trastuzumab therapy (8.4 months vs 4.4 months; HR, 0.49; $P<.001$). No prior treatment

ABSTRACT SUMMARY Cardiac Tolerability of Pertuzumab Plus Trastuzumab Plus Docetaxel in Patients With HER2-Positive Metastatic Breast Cancer in the CLEOPATRA Study

A new study analyzed cardiac safety data from the CLEOPATRA trial (Abstract 533). In the trial, LVEF was assessed by echocardiogram or multigated acquisition scan at baseline, every 9 weeks during treatment, at treatment discontinuation, and up to 3 years thereafter. In the safety population of 804 patients, the incidence of any cardiac disorder of any grade was similar with or without pertuzumab (14.5% vs 16.4%, respectively). The most frequent cardiac adverse event was left ventricular systolic dysfunction (LVSD) of grade 1 or greater and was more common in the placebo arm (8.3% vs 4.4%). At the time of data cutoff, 8 of 11 (72.7%) symptomatic LVSD events had resolved, and none were fatal. All patients who developed symptomatic LVSD had 1 or more potential cardiac risk factors, such as prior anthracycline or trastuzumab, radiation, or smoking. Univariate Cox regression analysis showed that development of LVSD was associated with prior anthracycline therapy and prior radiation therapy. Cardiac adverse events in this trial were largely reversible, not progressive, and clinically manageable. The incidence of cardiac adverse events or LVSD was not greater for patients receiving the dual antibody combination plus docetaxel compared with trastuzumab plus docetaxel.

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with capecitabine and lapatinib was allowed. The trial randomized patients to receive either T-DM1 monotherapy (3.6 mg/kg) every 3 weeks (n=495) or capecitabine (1,000 mg/m²) twice daily for 14 days plus daily lapatinib (1,250 mg) during a 3-week cycle (n=496).

Patients were stratified based on world region, number of prior chemotherapeutic regimens for metastatic breast cancer or unresectable, locally-advanced breast cancer, and presence of visceral disease. The primary endpoints were PFS by independent review, overall survival (OS), and safety. Secondary endpoints were PFS by investigator review, ORR, and patient-reported outcomes. The final OS analysis is anticipated to occur in early 2014.

Patient enrollment occurred from February 2009 through October 2011. Data cutoff for the current analysis was January 14, 2012. Patient characteristics, including disease characteristics, were well balanced between the 2 arms. Median duration of follow-up was 12.4 months in the capecitabine plus lapatinib arm and 12.9 months in the T-DM1 arm. Prior treatments included trastuzumab (100%) taxanes (100%), anthracyclines (61%), and endocrine therapy (41%). Sixteen percent of patients had received trastuzumab in the adjuvant setting, and over half of the patients had received more than 1 year of trastuzumab. Median time between prior trastuzumab dose and trial initiation was 1.5 months in each arm. In both arms, 12% of patients had not received any prior therapy for their metastatic disease. Median planned dose intensities were 77% for capecitabine, 93% for lapatinib, and 99.9% for T-DM1. In the control arm, dose reductions were required for capecitabine in 53% of patients and for lapatinib in 27% of patients. Dose reductions were required in 16% of patients in the T-DM1 arm.

PFS was 9.6 months with T-DM1 treatment compared to 6.4 months with capecitabine and lapatinib (HR, 0.650; 95% confidence interval [CI], 0.55–0.77; $P < .0001$) (Figure 1). Thus,

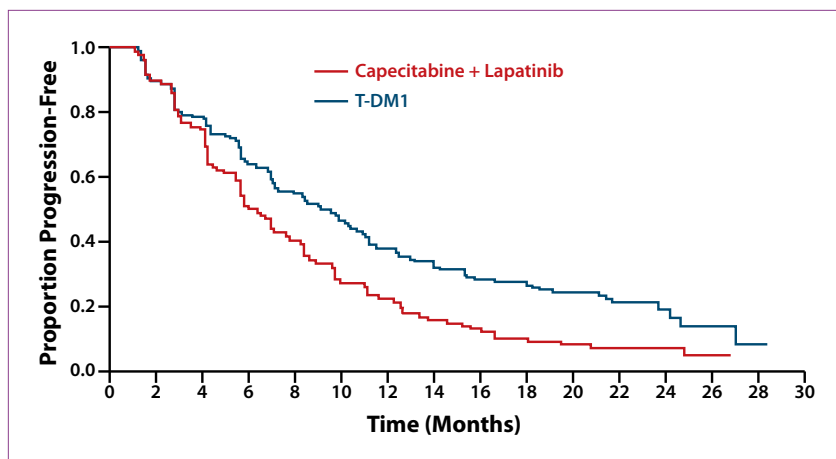


Figure 1. Progression-free survival in the EMILIA trial. CI=confidence interval; EMILIA=An Open-Label Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine Plus Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer. T-DMI= trastuzumab emtansine. Data from Blackwell KL et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract LBA1.

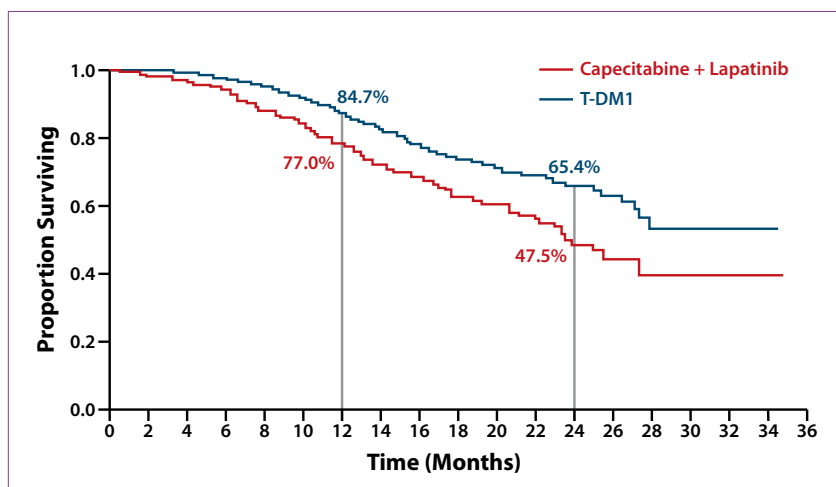


Figure 2. Overall survival in the EMILIA trial. CI=confidence interval; EMILIA=An Open-Label Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine Plus Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer. T-DMI= trastuzumab emtansine. Data from Blackwell KL et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract LBA1.

EMILIA met its primary endpoint of PFS. Investigator-assessed PFS results were consistent with the independent review. Prespecified analyses showed a benefit for most subgroups examined, including world region, treatment line for metastatic disease, and the presence or absence of visceral disease. Most clinically relevant subgroups favored T-DM1, including age, estrogen receptor status, and exact line of metastatic therapy. No benefit was discerned for

the small subgroup of patients at least 65 years of age, and no subgroup analysis favored the control arm.

The trial also showed a favorable outcome for OS among patients in the T-DM1 arm (not yet reached vs 23.3 months in the capecitabine/lapatinib arm; HR, 0.621; 95% CI, 0.48–0.81; $P = .0005$) (Figure 2). However, the interim stopping boundary based on the number of death events had not yet been reached. Preplanned analysis

ABSTRACT SUMMARY A Phase III, Multicenter, Randomized Trial of Maintenance Versus Observation After Achieving Clinical Response in Patients With Metastatic Breast Cancer Who Received Six Cycles of Gemcitabine Plus Paclitaxel as First-Line Chemotherapy (KCSG-BR 0702, NCT00561119)

In a prospective, randomized, multicenter phase III study, 324 patients with metastatic breast cancer received 6 cycles of first-line paclitaxel (75 mg/m² intravenously) on day 1 plus gemcitabine (1,250 mg/m² orally) on days 1 and 8 of each 3-week cycle (Abstract 1003). Patients with a response to the initial treatment were randomized to either maintenance paclitaxel and gemcitabine or observation. The primary endpoint was PFS. Secondary endpoints included OS, toxicity, quality of life, and response duration. The response rate to initial treatment was 50%, and the disease control rate was 78.6%. The patients who responded to initial paclitaxel and gemcitabine treatment were randomized to either paclitaxel and gemcitabine (n=116) or observation (n=115). After a median follow-up of 33 months, median PFS was significantly increased in the maintenance chemotherapy arm (12.0 months vs 8.3 months; $P=.030$). The adjusted HR for the PFS benefit with maintenance paclitaxel and gemcitabine was 0.73. The PFS benefit from maintenance chemotherapy was greater in patients with hormone receptor-positive disease (HR, 0.52; $P=.019$). Median OS was also superior for the maintenance paclitaxel and gemcitabine arm (36.8 months vs 28.0 months; $P=.048$). Neurotoxicity was elevated in the maintenance paclitaxel and gemcitabine arm but was not significant (HR, 0.65; $P=.210$). Quality of life appeared similar for both groups.

showed an absolute difference in OS of 7.7% at 1 year and 17.9% at 2 years in favor of T-DM1. The ORR was 43.6% for T-DM1 versus 30.8% for the capecitabine/lapatinib arm ($P=.0002$). A 6.1-month absolute improvement in median duration of response was observed for T-DM1 in patients with an objective response (12.6 months vs 6.5 months).

The trial collected patient-reported outcomes and precise adverse events from all patients. Symptom progression was evaluated using the subset of the Functional Assessment of Cancer Therapy (FACT) Breast Trial Outcome index that examines physical and functional well-being as well as symptoms specific to breast cancer. Time to symptom progression was extended with T-DM1

(7.1 months vs 4.6 months; HR, 0.80; 95% CI, 0.67–0.95; $P=.0121$).

Adverse events of any grade occurred with similar frequency in both arms. However, a greater number of adverse events of grade 3 or higher were reported for patients treated with capecitabine and lapatinib (57% vs 40.8%). Moreover, a higher percentage of patients in the control arm required treatment discontinuation due to an adverse event (10.7% vs 5.9%). Five deaths occurred in the capecitabine plus lapatinib arm, and 1 death occurred in the T-DM1 treatment arm. Decreases in left ventricular ejection fraction (LVEF) were infrequent in both arms.

Grade 3/4 non-hematologic adverse events of 2% or greater that occurred at a higher rate in the capecitabine plus lapa-

tinib arm included diarrhea (20.7% vs 1.6%), hand-foot syndrome (16.4% vs 0.0%), vomiting (4.5% vs 0.8%), hypokalemia (4.1% vs 2.2%), fatigue (3.5% vs 2.4%), nausea (2.5% vs 0.8%), and mucosal inflammation (2.3% vs 0.2%). The T-DM1 arm showed a higher incidence of grade 3/4 increased aspartate aminotransferase (4.3% vs 0.8%) and increased alanine aminotransferase (2.9% vs 1.4%). Grade 3/4 hematologic adverse events with greater frequency in the capecitabine plus lapatinib arm included neutropenia (4.3% vs 2.0%) and febrile neutropenia (1.0% vs 0.0%). The T-DM1 arm had higher rates of grade 3/4 anemia (2.7% vs 1.6%) and thrombocytopenia (12.6%).

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Quality of Life Assessment in CLEOPATRA, a Phase III Study of Trastuzumab Plus Docetaxel With or Without Pertuzumab in Metastatic Breast Cancer

Studies in HER2-positive breast cancer have shown that combining 2 anti-HER2 agents, such as trastuzumab plus pertuzumab¹⁻³ or trastuzumab plus lapatinib,^{4,5} improves efficacy compared with monotherapy. The combination of trastuzumab plus pertuzumab without chemotherapy showed a particularly good safety profile.¹⁻³ Because treatment for metastatic breast cancer is not curative, new therapy must provide clinical benefit while maintaining a high degree of patients' health-related quality of life (HRQoL).

Cancer patients are concerned by HRQoL factors such as pain, fear of recurrence, and fatigue. The Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire presents questions related to physical, social/family, emotional, and functional well-being. Additional concerns pertaining specifically to patients with breast cancer include their sense of attractiveness and femininity. The breast cancer subscale was therefore added to measure symptoms and issues relevant in breast cancer (FACT-B).

Javier Cortés, MD, and colleagues presented HRQoL data from the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial,⁶ which randomized patients to trastuzumab plus docetaxel with or without pertuzumab and included HRQoL as a secondary endpoint.⁷ Time to symptom progression was assessed using the FACT-B questionnaire with the combined score of physical well-being plus functional well-being plus the Breast Cancer Subscale from the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB). Female patients completed questionnaires within 3 days prior to each tumor assessment until independently determined disease progression. Questionnaires were translated into local lan-

guages and validated. To measure clinically significant and meaningful changes in HRQoL outcomes, a minimally important difference in an HRQoL metric has been defined as the smallest difference in the domain score of interest that patients perceive as important in terms of benefit or harm and that would lead clinicians to consider a change in management. The minimally important difference is 7–8 points for the FACT-B total score, 5–6 points for the TOI-PFB score, and 2–3 points for the Breast Cancer Subscale Domain Score. Therefore, symptom progression was defined as a decrease from baseline of at least 5 points in the TOI-PFB score.

A median 8 cycles of docetaxel were administered in each treatment arm. Adverse events reported more frequently in the pertuzumab arm compared with the placebo arm included

diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. The events occurred primarily during the period of coadministration of docetaxel with the 2 antibodies. Median PFS was 18.5 months in the pertuzumab-containing arm compared with 12.4 months in the placebo control arm (HR, 0.62; 95% CI, 0.51–0.75; $P < .0001$).

From the total randomized population of 808 patients, 806 were female and completed the FACT-B questionnaire, including 402 patients in the pertuzumab arm and 404 patients in the placebo arm. At least 75% of patients in both arms completed the FACT-B questionnaire beyond the first year. The FACT-B questionnaire was completed every 9 weeks; the percentage of patients completing the questionnaire at each interval was consistent with the percentage of patients undergoing

ABSTRACT SUMMARY LUX-Breast 1: Randomized, Phase III Trial of Afatinib and Vinorelbine Versus Trastuzumab and Vinorelbine in Patients With HER2-Overexpressing Metastatic Breast Cancer (MBC) Failing One Prior Trastuzumab Treatment

Afatinib is a tyrosine kinase inhibitor that irreversibly blocks signaling from all ErbB family dimers. In a phase II trial of patients with HER2-positive metastatic breast cancer who had progressed on trastuzumab, afatinib monotherapy demonstrated clinical activity, with PFS of 15.1 weeks and ORR of 10% (Lin NU et al. *Breast Cancer Res Treat*. 2012;133:1057-1065). LUX-Breast 1 is an open-label, multicenter, randomized, phase III trial comparing the efficacy and safety of afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-positive metastatic breast cancer who progressed on 1 prior trastuzumab treatment (Abstract TPS649). The ongoing trial, which began enrollment in June 2010, is randomizing 780 patients 2:1 to receive vinorelbine (25 mg/m²) weekly plus either afatinib (40 mg) orally daily or trastuzumab (2 mg/kg loading dose followed by 4 mg/kg weekly). Treatment continues in the absence of disease progression or unacceptable toxicity. The primary endpoint is PFS. Secondary endpoints include OR, OS, and safety. Biomarker analyses will include central laboratory testing of archival tumor tissue for HER2, hormone receptors, and EGFR. Exploratory analyses of HER receptor and HER ligand reprogramming, putative resistance markers, and EGFR response signature will be conducted on fresh tissue biopsies.

ABSTRACT SUMMARY Impact of Adjuvant Trastuzumab on Outcomes of HER2-Positive Breast Cancer Patients Treated With HER2-Targeted Therapy in the Metastatic Setting

Many women with HER2-positive breast cancer have received trastuzumab as adjuvant treatment. This study examined whether previous trastuzumab therapy influences the effects of subsequent treatment for metastatic disease (Abstract 527). The authors examined outcome among women with HER2-positive disease who received trastuzumab or lapatinib in the first-line setting. Among the 523 patients in the analysis, 76 had received trastuzumab in the adjuvant setting and 447 had not. A complete or partial response was achieved by 48% of patients who had not received adjuvant trastuzumab and 13% of patients who had received it ($P<.0001$). The odds ratio was 0.27 (CI, 0.13–0.56; $P=.0004$) after the authors adjusted for age, disease-free interval, postmenopausal status, stage at presentation, ER/PR status, and nuclear grade. Overall survival from first evidence of metastasis was significantly longer in the patients who had not received adjuvant trastuzumab (39 months vs 24 months; HR, 1.8, 95% CI, 1.3–2.4).

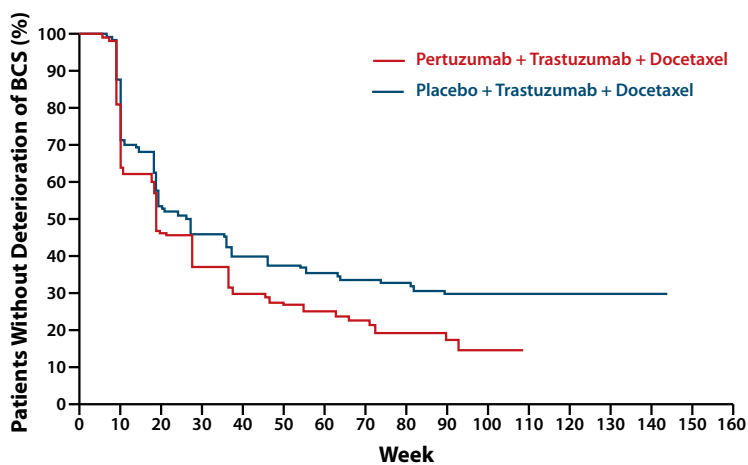


Figure 3. Kaplan-Meier curve from a health-related quality of life analysis from the CLEOPATRA trial indicating that the deterioration of the breast cancer subscale (BCS) was similar for patients receiving a pertuzumab-containing regimen and a placebo control until approximately 20–30 weeks. CLEOPATRA=Clinical Evaluation of Pertuzumab and Trastuzumab. Data from Cortés J et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 598.

tumor assessments on schedule. Based on the TOI-PFB composite score of FACT-B, 59.5% of patients in the pertuzumab arm and 56.7% of patients in the placebo arm experienced symptom progression during the study.

Median time to event was 18.4 weeks in the pertuzumab arm versus 18.3 weeks in the placebo arm, consistent with approximately 6 treatment cycles

($P=.7161$). Sensitivity analysis replacing missing data with the worst score showed a median time to event of 18.1 weeks for each arm ($P=.9366$). Kaplan-Meier analysis of patients without symptom progression yielded curves that largely overlapped for the 2 treatment arms.

Mean baseline TOI-PFB scores were 63.7 in the pertuzumab arm and 62.2 in the control arm out of a maxi-

mum possible score of 96, with higher scores representing greater HRQoL. At cycle 6, the pertuzumab arm and the placebo arm showed mean changes from baseline in the TOI-PFB score of -3.0 and -3.5, respectively. The mean reductions were smaller with subsequent cycles. The 2 treatment arms showed similar changes from baseline through approximately cycle 21, after which the mean TOI-PFB score increased for patients receiving pertuzumab and decreased for patients receiving placebo. Of note, the number of patients completing the questionnaire, and hence the sample size, decreased over time.

The Kaplan-Meier estimate for experiencing a PFS event after 1 year of study treatment was 35% for the pertuzumab-containing regimen and 49% for placebo control. An exploratory analysis was undertaken to investigate the time to deterioration in breast cancer symptoms and functions. A reduction of at least 2 points from baseline breast cancer subscale was considered the minimum clinically important reduction. Kaplan-Meier analysis indicated that the deterioration of the breast cancer subscale was similar for the 2 treatment arms until approximately 20–30 weeks, at which point the curve representing the placebo arm shows an increased rate of breast cancer subscale deterioration relative to the pertuzumab arm (Figure 3). The analysis also yielded a median time to deterioration in the breast cancer subscale domain score of 26.7 weeks in the pertuzumab arm and 18.3 weeks in the placebo arm (HR, 0.77; 95% CI, 0.64–0.93; $P=.0061$). Sensitivity analysis for time to deterioration in the breast cancer subscale domain score of at least 2 points was conducted by replacing missing data with the worst score and yielded an HR of 0.80 (95% CI, 0.66–0.96; $P=.0156$).

As with the change in TOI-PFB score over time, the mean changes in the breast cancer subscale domain scores from baseline for both arms were similar until approximately cycle 21, after which the scores generally improved for the pertuzumab arm and worsened in the

placebo arm, consistent with a delay in the time to onset of specific breast cancer symptoms. The authors concluded that adverse events associated with the pertuzumab-containing regimen did not result in deterioration of HRQoL and that the addition of pertuzumab to trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer offers both a clinical and HRQoL benefit.

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NSABP B-38: Definitive Analysis of a Randomized Adjuvant Trial Comparing Dose-Dense (DD) AC→Paclitaxel (P) Plus Gemcitabine (G) With DD AC→P and With Docetaxel, Doxorubicin, and Cyclophosphamide (TAC) in Women With Operable, Node-Positive Breast Cancer

Sandra M. Swain, MD, presented the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-38 trial, a randomized phase III study that compared 3 treatment regimens in women with operable, node-positive breast cancer.¹ Doxorubicin plus cyclophosphamide (AC) followed by dose-dense paclitaxel has been considered a standard adjuvant regimen based on the CALGB-9741 findings.² Because the addition of gemcitabine to paclitaxel improved the outcome in patients with metastatic breast cancer, this combination was chosen for evaluation in the adjuvant setting. Docetaxel plus AC (TAC), an optimal docetaxel-containing regimen, was also the treatment in one of the investigational arms of the NSABP B-30 trial³ and therefore was included in the current study. The study allowed for the first direct comparison of the

ABSTRACT SUMMARY A Phase III Clinical Trial to Compare Trastuzumab (T) Given Concurrently With Radiation Therapy (RT) to RT Alone for Women With HER2+ DCIS Resected by Lumpectomy (Lx): NSABP B-43

The rationale for using trastuzumab in ductal carcinoma in situ (DCIS) is based partly on the ability of anti-HER2 agents to enhance radiation sensitivity. The ongoing NSABP B-43 trial is designed to examine the efficacy of trastuzumab given during whole breast irradiation (WBI) (Abstract TPS657). After lumpectomy for pure DCIS, each patient's lesion will be tested for HER2 status via central IHC analysis. Lesions with a score of HER2 2+ undergo FISH analysis. Patients with HER2 3+ or FISH+ tumors are randomly assigned to WBI alone or to WBI plus 2 doses of trastuzumab (8 mg/kg followed by 6 mg/kg) 3 weeks apart. The primary endpoints are to determine whether trastuzumab decreases ipsilateral breast cancer recurrence, ipsilateral skin cancer recurrence, or ipsilateral DCIS. Secondary endpoints include invasive or DCIS disease-free survival; invasive or DCIS recurrence-free interval; invasive, regional, or distant recurrence; contralateral invasive or DCIS breast cancer; OS; and post-treatment amenorrhea. The trial will accrue 2,000 patients throughout 7.9 years. Definitive analysis of primary endpoints will be performed at 163 ipsilateral breast cancer events. As of March 31, 2012, the trial had randomized 878 patients and collected 1,217 (33%) eligible specimens out of 3,647 specimens centrally tested, a rate lower than expected. No trastuzumab safety signals were observed.

ABSTRACT SUMMARY A Combination of Pertuzumab, Trastuzumab, and Vinorelbine for First-Line Treatment of Patients With HER2-Positive Metastatic Breast Cancer: An Open-Label, Two-Cohort, Phase II Study (VELVET)

The combination of trastuzumab plus vinorelbine has shown comparable efficacy to trastuzumab plus docetaxel with an improved safety profile in HER2-positive metastatic breast cancer. The ongoing VELVET trial is a multicenter, open-label, 2-cohort, phase II trial that will examine dual HER2 blockade by trastuzumab and pertuzumab in combination with vinorelbine (Abstract TPS653). Eligible patients have HER2-positive, locally advanced breast cancer or metastatic breast cancer not previously treated in the metastatic setting. The trial will enroll patients into 2 cohorts of 105 patients each. The treatment cycle is 3 weeks. All patients will receive vinorelbine (25 mg/m² on days 1 and 8 of cycle 1, followed by 30–35 mg/m² on days 1 and 8 of each subsequent cycle). Patients in cohort 1 will receive sequential trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) and pertuzumab (840 mg loading dose followed by 420 mg) on day 1 of each cycle. Patients in cohort 2 will receive the same treatment for cycle 1; if treatment is well tolerated, trastuzumab and pertuzumab will be delivered in the same infusion bag for cycles 2 and greater. The trial's primary endpoint is overall response rate as assessed by independent review committee. Secondary endpoints include overall response rate as assessed by the investigator, PFS, TTP, OS, safety and tolerability, and quality of life.

received pegfilgrastim or filgrastim, and erythropoietin was recommended for patients with hemoglobin of less than 11 g/dL.

The study had 2 primary endpoints. One was to determine whether the addition of gemcitabine to AC plus paclitaxel could improve disease-free survival (DFS) relative to either of the other 2 treatment regimens. The other primary endpoint was to compare DFS from TAC versus AC plus paclitaxel. Secondary aims included OS and toxicity profiles among the 3 treatment arms.

The trial, which opened on October 1, 2004 and closed on May 3, 2007, accrued 4,894 patients. Eligibility criteria included node status of pN1, pN2a, pN3a, or pN3b according to the American Joint Committee on Cancer.⁴ Hormone receptor status had to be determined locally, and no prior breast cancer treatment was allowed. An amendment in August 2005 excluded patients with HER2-positive disease after 1,105 patients had been randomized.

Patient characteristics were well balanced among the 3 arms. Approximately half of the patients were postmenopausal, and 80% of tumors were hormone receptor-positive. Therapy was completed in 91% of patients in the TAC arm and in 88% of patients in each of the dose-dense arms. Median follow-up was 5.3 years.

Kaplan-Meier analysis showed no difference in DFS for the gemcitabine-containing arm compared to either of the control arms. Five-year DFS was 80.6% in the AC plus paclitaxel and gemcitabine arm versus 82.2% (HR, 1.07; *P*=.41) in the AC plus paclitaxel arm and 80.1% (HR, 0.93; *P*=.39) in the TAC arm (Figure 4). There was also no significant difference in DFS between the TAC and standard dose-dense AC plus paclitaxel regimens (HR, 0.87; *P*=.074). Comparison of subgroups from the gemcitabine-containing regimen versus either TAC or dose-dense AC plus paclitaxel alone showed no significant differences based on estrogen receptor status, number of positive nodes, type of surgery, or extent of radiation.

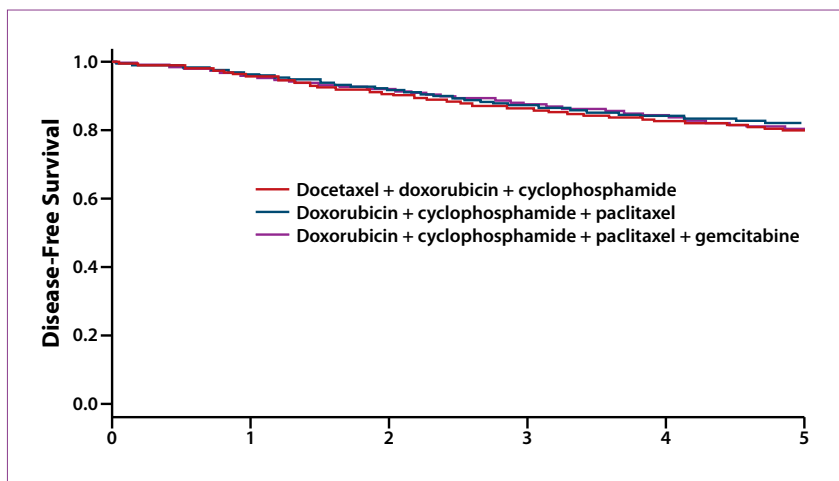


Figure 4. Disease-free survival in the NSABP B-38 trial. NSABP=National Surgical Adjuvant Breast and Bowel Project. Data from Swain SM et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract LBA 1000.

safety and efficacy of these 3 regimens in a single prospective trial.

Patients were stratified by number of positive nodes, hormone receptor status, and type of surgery with extent of planned radiation therapy. Patients in the TAC arm received docetaxel (75 mg/m²), doxorubicin (50 mg/

m²), and cyclophosphamide (500 mg/m²) every 3 weeks for 6 cycles. For the dose-dense arms, patients received doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²), with paclitaxel (175 mg/m²) alone or with gemcitabine (2,000 mg/m²) every 2 weeks for 4 cycles. All patients

No differences in OS were observed among the 3 treatment arms. Five-year OS was 90.8% in the AC plus paclitaxel and gemcitabine arm versus 89.1% (HR=0.85; $P=.13$) in the AC-P group and 89.6% (HR=0.86; $P=.17$) in TAC group. DFS between the 2 control arms was also similar (HR, 1.01; $P=.96$). The dose-dense regimens showed numerically increased rates of grade 3 toxicities (TAC, 36%; AC plus paclitaxel, 41%; AC plus paclitaxel plus gemcitabine, 42%). Rates of grade 4 or 5 toxicities were similar among all 3 treatment arms. As expected, rates of specific grade 3/4 toxicities varied among the treatment regimens. Febrile neutropenia was highest in the TAC arm at 9% versus 3% in each of the other arms ($P<.001$). Diarrhea was also more frequent in the TAC arm at 7% versus 2% in the other 2 arms ($P<.001$). LVEF systolic dysfunction occurred with less than 1% frequency in the TAC arm and was not observed in the other 2 arms ($P=.039$).

Grade 3/4 sensory neuropathy, allergic reaction, increased ALT, and rash occurred at less than 1% frequency in the TAC arm. These events were significantly more frequent with the other regimens. In the AC plus paclitaxel arm and the AC plus paclitaxel and gemcitabine arm, grade 3/4 sensory neuropathy was 7% and 6%, respectively ($P<.001$); allergic reaction was 2% and 1%, respectively ($P=.028$); increased ALT was 1% and 2%, respectively ($P=.003$); and rash was 1% and 2%, respectively ($P=.004$).

Grade 2 anemia increased significantly in the dose-dense arms (24% for AC plus paclitaxel alone, 31% for patients receiving gemcitabine, and 12% for TAC; $P<.001$). Two grade 5 thrombosis or embolism events occurred in the TAC arm versus none in the other 2 arms ($P=.23$). One of these events was associated with sepsis, and neither patient received erythropoietin. In the dose-dense arms, approximately 50% of patients received erythropoietin versus 35% of

patients in the TAC arm. Exploratory analyses based on erythropoietin use showed no significant difference in DFS ($P=.953$) or OS ($P=.825$).

Transfusions were given to 6% of patients who received AC plus paclitaxel, 9% of patients who received the same treatment plus gemcitabine, and 4% of patients who received TAC ($P<.001$). The number of deaths on treatment was higher in the TAC arm, but the difference was not significant ($P=.2$). The number of cases of acute myeloid leukemia/myelodysplastic syndrome was higher in the dose-dense arms but was also not significant ($P=.46$).

In summary, comparison of the 3 treatments showed no differences in efficacy. However, toxicity profiles differed, with more neuropathy, erythropoietin use, and anemia in

the dose-dense arms versus more febrile neutropenia and diarrhea in the TAC arm.

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ABSTRACT SUMMARY Pertuzumab in Combination With Trastuzumab Plus an Aromatase Inhibitor in Patients With Hormone Receptor–Positive, HER2-Positive Metastatic Breast Cancer: A Randomized Phase II Study (PERTAIN)

The PERTAIN (A Randomised, Two-Arm, Open-Label, Multicentre Phase II Trial Assessing the Efficacy and Safety of Pertuzumab Given in Combination With Trastuzumab Plus an Aromatase Inhibitor in First Line Patients With HER2-Positive and Hormone-Receptor Positive Advanced [Metastatic or Locally Advanced] Breast Cancer) trial is investigating the efficacy of trastuzumab plus pertuzumab combined with an aromatase inhibitor (AI) as first-line therapy for metastatic breast cancer (Abstract TPS654). The trial is the first to examine whether blocking HER2 activity through the combination of trastuzumab plus pertuzumab, in combination with endocrine therapy, can restore or enhance endocrine sensitivity in patients with hormone receptor–positive breast cancer that is also HER2-positive. The patient population in this international, multicenter, open-label, phase II trial includes postmenopausal women with HER2-positive and hormone receptor–positive breast cancer. The study protocol randomizes patients 1:1 to receive trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks) plus an aromatase inhibitor (anastrozole 1 mg or letrozole 2.5 orally daily), with or without pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks). Patients in either arm may also receive induction docetaxel or paclitaxel for up to 18 weeks at the investigator's discretion. Patients must not have received prior treatment with anti-HER2 agents except trastuzumab and/or lapatinib in the neoadjuvant or adjuvant setting. The primary endpoint is PFS, with secondary endpoints of OS, ORR, clinical benefit rate, and other endpoints to determine safety, efficacy, and quality of life. The expected enrollment is 250 patients.

BOLERO-1: A Randomized, Phase III, Double-Blind, Placebo-Controlled Multicenter Trial of Everolimus in Combination With Trastuzumab and Paclitaxel as First-Line Therapy in Women With HER2-Positive (HER2+), Locally Advanced or Metastatic Breast Cancer (BC)

The use of trastuzumab has greatly improved the prognosis of patients with HER2-positive breast cancer, yet the majority of patients develop resistance to the antibody, with subsequent disease progression within 1 year.^{1,2} Multiple mechanisms can contribute to trastuzumab resistance, including aberrant activation of the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway.^{3,4} In vitro studies suggest that inhibition of the PI3K/AKT/mTOR pathway may restore sensitivity to trastuzumab^{5,6} and that the combination of mTOR inhibitors plus trastuzumab can synergistically inhibit breast cancer cell growth.⁷ In mice with PTEN-

deficient xenografts that overexpressed HER2, mTOR inhibition sensitized the response to trastuzumab.⁸

Everolimus is an orally bioavailable sirolimus derivative and inhibitor of mTOR that has yielded promising results in regimens for advanced and metastatic breast cancer. Phase I or Ib studies of everolimus and trastuzumab plus either paclitaxel or vinorelbine have yielded ORRs of 15–44% and median PFS rates of 4–8 months with acceptable safety in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab.^{9–11} In a phase II trial of women with trastuzumab-resistant, HER2-positive metastatic breast cancer, most patients experienced a benefit from

treatment with everolimus plus weekly trastuzumab and paclitaxel,¹² suggesting that everolimus can reverse resistance to trastuzumab in this setting. Median PFS was approximately 26 weeks, and treatment was well tolerated. Maintenance therapy consisting of everolimus plus trastuzumab prolonged PFS to a median 41 weeks with adequate safety in heavily pretreated patients with HER2-positive metastatic breast cancer after discontinuation of chemotherapy.¹³

The multicenter, international, double-blind, randomized, placebo-controlled, phase III BOLERO-I (Breast Cancer Trials of Oral Everolimus) study, presented by Sara M. Hurvitz, MD, is being conducted to determine the effectiveness of adding everolimus to trastuzumab plus paclitaxel in HER2-positive, locally advanced or metastatic breast cancer.¹⁴ Patients are randomized 2:1 to receive either everolimus (10 mg daily) or placebo, respectively, plus paclitaxel (80 mg/m²) on days 1, 8, and 15 and trastuzumab (2 mg/kg loading dose on day 1 followed by 2 mg/kg on days 1, 8, 15, and 22) of each 28-day cycle.

The BOLERO-I trial will include women with histologically or cytologically confirmed invasive breast cancer with local recurrence that is not amenable to curative surgical treatment or radiologic evidence of metastatic disease; measurable disease or bone lesions, including lytic or mixed, in the absence of measurable disease; Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate organ and hematologic functions.

ABSTRACT SUMMARY Phase II Neoadjuvant Trial With Carboplatin and Eribulin Mesylate in Patients With Triple-Negative Breast Cancer

Eribulin mesylate is a non-taxane inhibitor of microtubule elongation that has shown single-agent clinical activity in breast cancer and other solid tumors. This open-label, multicenter, phase II clinical trial of 30 patients with stage I–III, histologically confirmed, triple-negative breast cancer is investigating eribulin plus carboplatin in the neoadjuvant setting (Abstract TPS1134). The primary endpoint of the trial is to determine the partial complete response in the enrolled patient population. Secondary endpoints include determination of the clinical response rate, toxicity, and measurement of TLE3 as a biomarker of response to eribulin treatment. Patients will receive a total of 4 cycles of treatment administered every 3 weeks. The first 10 patients will receive eribulin (1.4 mg/m² administered over 2–5 minutes) on days 1 and 8 followed by carboplatin (area under the curve of 6 administered over 30 minutes) on day 1. After enrollment of the first 10 patients, the study will be suspended temporarily for data analysis. If the safety evaluation shows more than 60% grade 3 or 4 neutropenia or more than 15% grade 3 or 4 peripheral neuropathy, then the dose of eribulin will be reduced to 1.1 mg/m². Definitive surgery will be performed 3–8 weeks after the end of treatment.

The patients will be HER2-positive by local laboratory testing. They are trastuzumab-naïve or received prior trastuzumab and/or chemotherapy, including taxanes, in the neoadjuvant or adjuvant setting at least 12 months prior to randomization. Prior endocrine therapy for metastatic breast cancer must be discontinued due to disease progression prior to randomization. Patients will be excluded if they were previously treated with an mTOR inhibitor, received treatment other than hormonal therapy for locally advanced or metastatic disease, had 25% or more of their bone marrow treated with radiotherapy within 4 weeks prior to randomization, or have a history of brain metastases.

Patients were gathered from 176 study centers in 27 countries. Planned accrual includes 478 patients in the everolimus arm and 239 patients in the control arm, with patient stratification based on presence of visceral metastases and prior neoadjuvant or adjuvant treatment with trastuzumab. The primary endpoint is PFS. Secondary endpoints include OS, ORR (including complete or partial response), safety, clinical benefit rate, time to response, duration of response, and pharmacokinetics.

PFS distribution will be estimated using the Kaplan-Meier method. HRs and 95% CIs will be estimated using a stratified Cox regression model. Between-group comparison of PFS will be determined using a stratified log-rank test at 1-sided 2.5% significance level. One interim analysis is planned after 309 PFS events, and 1 final PFS analysis is planned after 514 PFS events (anticipated in late 2013). Final OS analysis will be performed after 434 deaths.

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ABSTRACT SUMMARY Phase III Open-Label, Randomized, Multi-center Study of NKTR-102 Versus Treatment of Physician's Choice (TPC) in Patients (pts) With Locally Recurrent or Metastatic Breast Cancer (MBC) Previously Treated With an Anthracycline, a Taxane, and Capecitabine (ATC)

NKTR-102 (etirinotecan pegol) consists of a topoisomerase I inhibitor, irinotecan, conjugated to polyethylene glycol. Conjugation to a macromolecule decreases the peak concentration and provides a more continuous drug concentration profile. This ongoing open-label, randomized, multicenter, phase III trial is investigating single-agent NKTR-102 versus treatment of physician's choice (Abstract TPS1140). Female patients who received prior therapy with an anthracycline, a taxane, and capecitabine (ATC), or prior TC if anthracycline treatment was contraindicated, will be randomized 1:1 to receive either NKTR-102 (145 mg/m² over 90 minutes) every 21 days without premedication, or treatment of physician's choice. The latter will include 1 of the following: eribulin mesylate, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. The primary efficacy endpoint is OS. Secondary endpoints include ORR by Response Evaluation Criteria In Solid Tumors v1.1, clinical benefit rate (defined as ORR plus SD >6 months), PFS, and quality of life. Pharmacokinetic sampling will be performed in a subset of patients, and circulating tumor cells will be serially assessed for potential predictive markers of toxicity and response. Enrollment of approximately 840 patients is planned through late 2013.

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CALGB 40502/NCCTG N063H: Randomized Phase III Trial of Weekly Paclitaxel (P) Compared to Weekly Nanoparticle Albumin Bound Nab-Paclitaxel (NP) or Ixabepilone (Ix) With or Without Bevacizumab (B) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer (MBC)

Hope S. Rugo, MD, presented results from the Cancer and Leukemia Group B (CALGB) and the North Central Cancer Treatment Group (NCCTG). The goal of the CALGB 40502/NCCTG N063H randomized phase III trial was to explore the potential for superior efficacy and reduced toxicity from either nab-paclitaxel or ixabepilone compared to the control arm of weekly paclitaxel.¹ The control arm of weekly paclitaxel (90 mg/m²) was chosen to mirror the experimental arm of ECOG 2100, in which patients received weekly paclitaxel combined with bevacizumab.^{2,3} The dose of weekly nab-paclitaxel (150 mg/m²) was based on a random-

ized, phase II trial in which this agent improved PFS.⁴ The chosen dose of ixabepilone (15 mg/m²) reflects the relative intolerance to higher dosages in phase II trials.^{5,6} Bevacizumab (10 mg/m² every 2 weeks) added to paclitaxel was shown to prolong PFS relative to paclitaxel monotherapy.²

The primary objectives of the trial were to compare PFS with nab-paclitaxel versus paclitaxel, and with ixabepilone versus paclitaxel, both in the setting of bevacizumab. Secondary objectives presented at the meeting included time to treatment failure (TTF), OS, and toxicity, including grade 3 peripheral neuropathy. Secondary objectives to be presented at a later date include overall response

duration, 12-month PFS, and multiple correlative endpoints.

The trial was designed with a 90% power to detect an HR for PFS of 0.73, based on enrollment of 900 patients. The design assumed a median PFS of 11 months for the control arm, based on the results from ECOG 2100, and was powered to detect a 4-month increase in PFS. A planned interim analysis allowed for stopping for either superiority or futility of each experimental arm relative to the control arm. After 165 events, the first interim analysis conducted for PFS and ixabepilone compared to paclitaxel crossed the futility boundary for superiority; therefore, the ixabepilone arm was closed to accrual on July 8, 2011.

Enrollment of 900 patients was planned, with patients equally randomized to each of the 3 arms. Patients were stratified based on adjuvant taxane use and hormone receptor status. Patients with stable disease or better could discontinue chemotherapy and continue on bevacizumab monotherapy after 6 cycles of treatment. Eligible patients had measurable disease, had not received prior chemotherapy for their advanced disease, and were at least 12 months past receipt of adjuvant taxanes.

By March 2011, 669 patients had already been enrolled, and the trial protocol was amended to allow optional use of bevacizumab. In total, the trial enrolled 799 patients, 99% of whom were female, from November 2008 through November 2011, including 283 to the paclitaxel arm, 271 to the nab-paclitaxel arm, and 245 to the ixabepilone arm. Despite the protocol

ABSTRACT SUMMARY A Phase II, Single-Arm, Feasibility Study of Dose-Dense Doxorubicin and Cyclophosphamide (AC) Followed by Eribulin Mesylate for the Adjuvant Treatment of Early-Stage Breast Cancer (EBC)

Based on the antitumor activity of eribulin mesylate as a late-line treatment for metastatic breast cancer, investigation of its activity in early stage breast cancer is warranted. This ongoing single-arm, single-center, phase II study will aim to determine the feasibility of eribulin as adjuvant therapy following dose-dense doxorubicin and cyclophosphamide (AC) for patients with HER2-normal, early-stage breast cancer (Abstract TPS1145). Eighty patients with histologically confirmed, HER2-normal, stage I-III invasive breast cancer will receive 4 cycles of dose-dense AC consisting of doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²) on day 1 every 14 days, followed by eribulin (1.4 mg/m² over 2-5 minutes) on days 1 and 8 every 21 days. Growth factors are provided on day 2 of AC cycles. During eribulin treatment, patients receive growth factors only for neutropenia. Feasibility is determined by the ability of patients to complete the eribulin treatment without any dose delay or reduction and will be calculated with or without consideration of the successful use of growth factor as a dose delay. A treatment completion rate of 80% will be used as the target for feasibility.

amendment, 98% of patients received bevacizumab. Median follow-up for all surviving patients as of the data cutoff date of April 26, 2012 was 12 months. Patient characteristics and disease characteristics were well balanced among the 3 arms. Forty-four percent of patients were previously exposed to adjuvant taxanes. Approximately 70% of patients had hormone receptor-positive disease; the majority of patients had visceral metastases and a disease-free interval greater than 1 year.

PFS analysis failed to demonstrate superiority of either experimental arm compared to paclitaxel, and weekly ixabepilone appeared to be significantly inferior to weekly paclitaxel. Median PFS was 10.6 months for paclitaxel, 7.6 months for ixabepilone ($P<.001$), and 9.2 months for nab-paclitaxel ($P=.12$). Even after adjusting for the effects of clinical variables, multivariate Cox proportional hazard results for PFS showed that ixabepilone was significantly worse than paclitaxel and nab-paclitaxel was not better. Consistent with data from other trials, prior exposure to taxanes correlated with reduced PFS ($P=.002$), and the presence of hormone receptor-positive disease correlated with improved PFS ($P=.04$).

Unplanned subset analyses of PFS in patients with estrogen receptor-positive disease (Figure 5) or triple-negative disease (Figure 6) revealed no significant differences relative to the total study population. Exploratory analysis of dose reductions occurring prior to the start of cycle 3 showed that 45% of patients receiving nab-paclitaxel and 15% of patients in each of the other 2 arms received at least 1 dose reduction. Consistent with these findings, more patients discontinued ixabepilone or nab-paclitaxel compared to paclitaxel.

TTF was significantly shorter in the 2 experimental arms compared to the control arm (paclitaxel, 7.1 months; nab-paclitaxel, 5.4 months [$P=.0005$]; ixabepilone, 5.1 months [$P=.0014$]). OS was similar for each

ABSTRACT SUMMARY Results From a Phase Ib Study of Trastuzumab Emtrastine (T-DM1), Paclitaxel (T), and Pertuzumab (P) in Patients With HER2-Positive Metastatic Breast Cancer (MBC) Previously Treated With Trastuzumab

The combination of T-DM1 weekly or every 3 weeks plus weekly paclitaxel (80 mg/m²), with or without pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks), was evaluated in a multi-institutional, open-label, dose-escalation, phase Ib trial with a 3+3 design (Abstract 528). Patients with HER2-positive, locally advanced or metastatic breast cancer who had received prior HER2-directed therapy were enrolled. The primary objectives were to characterize the safety and tolerability of the regimens, and to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of T-DM1 with these regimens. The study established the MTD of T-DM1 (3.6 mg/kg) every 3 weeks plus weekly paclitaxel either in the absence of pertuzumab or with the addition of pertuzumab. An MTD of T-DM1 (2.4 mg/kg) weekly plus weekly paclitaxel was obtained in the absence of pertuzumab, and the MTD did not change with the addition of pertuzumab. The MTD of T-DM1 in the combined treatment was the same as that of single-agent T-DM1 every week or every 3 weeks, and the combinations showed a manageable safety profile. No DLTs were observed in the cohorts, and no unexpected safety signals arose for any of the drugs. The ORR was 39.7%, including 1 confirmed CR and 22 confirmed PRs, among 58 evaluable patients in the entire study.

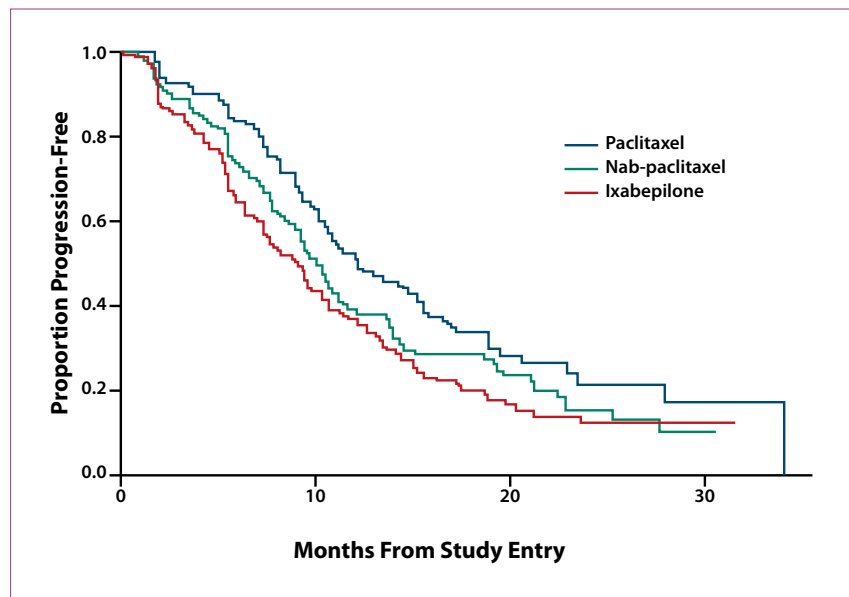


Figure 5. Unplanned subset analyses of progression-free survival in patients with estrogen receptor-positive disease in the CALGB 40502/NCCTG N063H trial. CALGB=Cancer and Leukemia Group B; NCCTG=North Central Cancer Treatment Group. Data from Ruqo HS et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract CRA1002.

treatment arm (paclitaxel, 26 months; nab-paclitaxel, 27 months [$P=.92$]; ixabepilone, 21 months [$P=.10$]).

Hematologic and non-hematologic grade 3 or higher adverse events were more frequent in patients receiving

nab-paclitaxel compared to those receiving paclitaxel ($P<.0001$ and $P=.0002$, respectively). Fewer hematologic, but more non-hematologic, adverse events occurred with ixabepilone compared to paclitaxel ($P=.004$ and $P=.005$, respectively).

The rate of grade 2 sensory neuropathy was similar among the 3 treatment arms; however, the rate of grade 3 peripheral neuropathy was 25% in both the nab-paclitaxel arm ($P=.012$) and the ixabepilone arm ($P=.022$) compared to 16% in the control arm. In general, chemotherapy toxicities were more frequent in the experimental arms compared to the control arm, and the incidence of motor neuropathy was significantly higher in patients treated with nab-paclitaxel (10%; $P=.0003$) or ixabepilone (6%; $P=.021$) compared to paclitaxel (2%).

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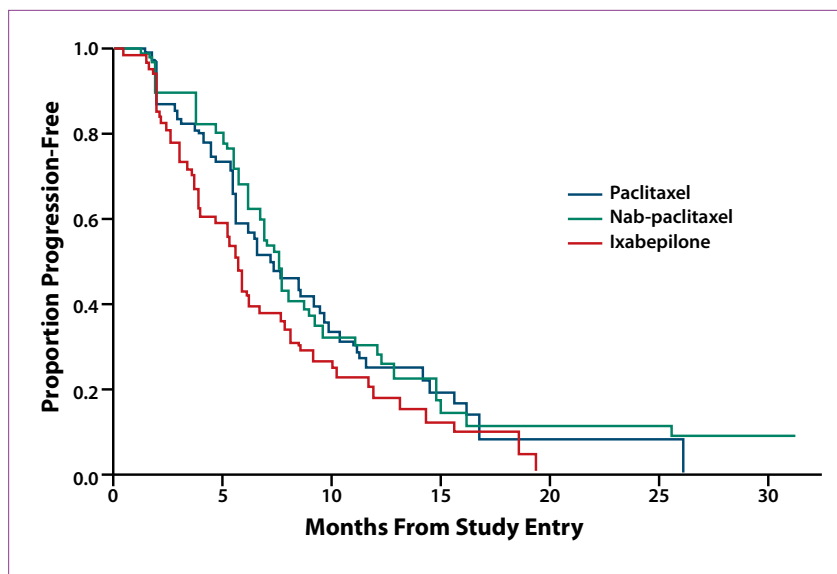


Figure 6. Unplanned subset analyses of progression-free survival in patients with triple-negative disease in the CALGB 40502/NCCTG N063H trial. CALGB=Cancer and Leukemia Group B; NCCTG=North Central Cancer Treatment Group. Data from Rugo HS et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract CRA1002.

ABSTRACT SUMMARY Cardiac Safety in a Phase II Study of Trastuzumab Emtansine (T-DM1) Following Anthracycline-Based Chemotherapy as Adjuvant or Neoadjuvant Therapy for Early-Stage HER2-Positive Breast Cancer

The clinical safety and feasibility of T-DM1 following adjuvant or neoadjuvant, anthracycline-based treatment were examined in a single-arm, open-label, phase II study of patients with early-stage, HER2-positive breast cancer (Abstract 532). After completing 4 cycles of AC every 2 or 3 weeks, or 3–4 cycles of 5-fluorouracil, epirubicin, and cyclophosphamide every 3 weeks, patients received up to 17 cycles of T-DM1 (3.6 mg/kg every 3 weeks). The study's 2 primary endpoints were safety and the rate of prespecified cardiac events after 12 weeks of T-DM1 treatment. Although no patients discontinued T-DM1 due to cardiac events and no prespecified cardiac adverse events were reported, 5 of 143 cardiac-evaluable patients had non-prespecified cardiac adverse events suspected by the investigator to be caused by T-DM1, including 1 grade 4 atrial fibrillation. Based on data from 148 patients who had received at least 1 T-DM1 treatment, the most common T-DM1-related adverse events of any grade with at least 15% frequency were nausea (27.0%), headache (20.9%), epistaxis (16.9%), asthenia (15.5%), and epistaxis (15.5%). T-DM1-related serious adverse events were reported in 5 patients. Adverse events caused T-DM1 discontinuation in 6 patients. Preliminary data from 49 patients show a pathologic complete response rate of 54.0% (95% CI, 39.3–67.3%).

Adverse Events With Pertuzumab and Trastuzumab: Evolution During Treatment With and Without Docetaxel in CLEOPATRA

Trastuzumab and pertuzumab both bind to HER2 but with distinct binding sites and complementary mechanisms of action. Hence, combining these 2 monoclonal antibodies could induce a more comprehensive blockade of HER2 signaling. The antibody combination has shown greater efficacy relative to trastuzumab alone, both in the HER2-positive neoadjuvant setting and in metastatic breast cancer, and is well tolerated in the absence of chemotherapy.¹⁻³

José Baselga, MD, PhD, presented safety data comprising non-cardiac adverse events during and after treatment with docetaxel from the randomized, placebo-controlled, phase III CLEOPATRA trial.⁴ The trial randomized 406 patients to receive trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) plus docetaxel (75 mg/m², escalating to 100 mg/m² if tolerated) and 402 patients to receive the same treatment plus pertuzumab (840 mg loading dose followed by 420 mg) administered intravenously every 3 weeks.⁵ At least 6 cycles of docetaxel were recommended.

The primary endpoint was independently assessed PFS. Secondary endpoints included OS, investigator-assessed PFS, ORR, and safety. The data cutoff for the primary analysis was May 2011. Treatment with the 2 anti-HER2 antibodies plus docetaxel significantly improved median PFS compared with the control arm (18.5 months vs 12.4 months; HR, 0.62; 95% CI, 0.51–0.74; *P*<.0001).

Two patients in each arm did not receive any treatment. In the placebo arm, 8 patients received at least 1 dose of pertuzumab; in the pertuzumab arm, 1 patient received placebo only. Thus, the safety populations were

Table 1. Adverse Events in the CLEOPATRA Trial

	Placebo + Trastuzumab + Docetaxel		Pertuzumab + Trastuzumab + Docetaxel	
	Overall (%)	Postdocetaxel (%)	Overall (%)	Postdocetaxel (%)
Diarrhea	46.3	9.0	66.8	19.1
Alopecia	60.5	1.6	60.9	0.7
Neutropenia	49.6	3.5	52.8	1.7
Nausea	41.6	9.8	42.3	7.4
Fatigue	36.8	8.6	37.6	11.1
Rash	24.2	6.3	33.7	11.7
Decreased appetite	26.4	2.7	29.2	6.4
Mucosal inflammation	19.9	1.6	27.8	3.0
Asthenia	30.2	7.8	26.0	9.7
Peripheral edema	30.0	10.2	23.11	7.4
Constipation	24.9	5.9	15.1	3.7
Febrile neutropenia	7.6	0.0	13.8	0.0
Dry skin	4.3	0.8	10.6	2.3

CLEOPATRA=Clinical Evaluation of Pertuzumab and Trastuzumab.

Data from Baselga J et al. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2012;30(18 suppl): Abstract 597.

397 patients in the placebo arm and 407 patients in the pertuzumab arm. Patients received a median 8 cycles of docetaxel in both treatment arms, with a median dose intensity of 24.8 mg/m² per week versus 24.6 mg/m² per week. Patients in the placebo arm received a median of 15 cycles (range, 1–50) of treatment compared to a median of 18 cycles (range, 1–56) in the pertuzumab-containing arm.

Patients were allowed to discontinue all study treatment, docetaxel only, or antibody treatment following previous discontinuation of docetaxel. Adverse events led to discontinuation of study treatment in the placebo arm versus the pertuzumab-containing

arm, respectively, as follows: discontinuation of all study treatment (5.3% vs 6.1%), discontinuation of docetaxel only (23.2% vs 23.8%), and discontinuation of placebo plus trastuzumab or pertuzumab plus trastuzumab (1.3% vs 2.0%).

Although the study protocol recommended that patients receive at least 6 cycles of docetaxel, patients were allowed to discontinue the taxane therapy if they received the maximum benefit from it. Prior to cycle 6, 2.5% of patients in the placebo arm and 3.2% in the pertuzumab arm discontinued docetaxel due to an adverse event. After discontinuation of docetaxel, the most frequent

ABSTRACT SUMMARY Adjuvant Zoledronic Acid (ZOL) in Postmenopausal Women With Breast Cancer and Those Rendered Postmenopausal: Results of a Meta-Analysis

In the AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) trial (*N Engl J Med*. 2011;365:1396-1405), women with early stage breast cancer appeared to benefit from zoledronic acid. A meta-analysis was undertaken to determine whether this benefit would be maintained among postmenopausal women with early stage breast cancer (Abstract 513). Data were gathered from the following clinical trials: AZURE, ABCSG-12 (Austrian Breast and Colorectal Cancer Study Group; SABCS 2011, Abstract S1-2), ZO-FAST (Zometa-Femara Adjuvant Synergy Trial [European]; SABCS 2009, Abstract 4082), Z-FAST (Zometa-Femara Adjuvant Synergy Trial [North American]; SABCS 2009, Abstract 4082), EZO-FAST (Zometa-Femara Adjuvant Synergy Trial [worldwide]; SABCS 2009, Abstract 4082), NSABP-B34 (National Surgical Adjuvant Breast and Bowel Project B34; SABCS 2011, Abstract S-3), and GAIN (German Adjuvant Intergroup Node Positive; SABCS 2011, Abstract S2-4). (Although the ABCSG-12 study included only premenopausal women, all were treated with goserelin, which effectively rendered them postmenopausal.) In these studies, a total of 8,735 postmenopausal women had been randomized to zoledronic acid versus a control or clodronate/ibandronate versus a control. In the 5 studies of zoledronic acid, this treatment was associated with a significant benefit in disease-free survival (hazard ratio, 0.76; $P=.006$). In the studies of clodronate and ibandronate, this regimen was associated with a risk reduction of 18% ($P=.00075$). The authors concluded that the use of zoledronic acid as an adjuvant treatment for postmenopausal women with early stage breast cancer has substantial benefits.

adverse events of any grade decreased markedly (Table 1). However, the frequency of diarrhea remained elevated in the pertuzumab arm, with a rate of 66.8% before versus 19.1% after docetaxel discontinuation. Other adverse events, which continued at a frequency above 10% after docetaxel discontinuation, included peripheral edema (10.2%) in the control arm, and rash (11.7%) and fatigue (11.1%) in the pertuzumab arm.

Also after discontinuation of docetaxel, adverse events of at least grade 3 occurring at a rate of 1% or more in the placebo arm versus the pertuzumab arm, respectively, included hypertension (1.2% vs 1.7%), diarrhea (0.0% vs 1.0%), left ventricular systolic dysfunction (2.0% vs 0.7%), fatigue (1.2% vs 0.7%), and neutropenia (1.6% vs 0.0%).

During study treatment, 7 patients died before and 2 patients died after discontinuation of docetaxel in the placebo arm. In the pertuzumab arm, 7 patients died before and 1 patient died after cessation of docetaxel treatment. The numbers exclude deaths related to disease progression and those that occurred during survival follow-up. The number of patients experiencing febrile neutropenia, diarrhea, or rash decreased with increasing cycle number. In the pertuzumab arm, 3 patients discontinued docetaxel only and 2 patients discontinued all study treatment due to rash.

In the placebo arm, febrile neutropenia occurred at a rate of 11.7% in patients from Asia compared with 5.6% of patients enrolled from the rest of the world. In the pertuzumab arm, 25.6% of patients from Asia and 8.5%

of patients from the rest of the world experienced febrile neutropenia. In the placebo arm, no patients discontinued treatment due to febrile neutropenia whereas in the pertuzumab arm, 4 patients discontinued docetaxel only and 1 patient discontinued all study treatment due to febrile neutropenia. The median duration of all episodes of diarrhea was 29.5 days in the pertuzumab arm compared with 12.0 days in the control arm. Six patients in the pertuzumab arm and 2 patients in the control arm discontinued either all study treatment or docetaxel only.

The authors concluded that the combination of pertuzumab, trastuzumab, and docetaxel did not limit the dose of docetaxel that could be delivered and that the combination of pertuzumab and trastuzumab, plus either concurrent or sequential chemotherapy, may also be well tolerated in patients with HER2-positive, early breast cancer.

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Commentary

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Several presentations at the 2012 Annual Meeting of the American Society of Clinical Oncology (ASCO) offered important insights into the management of patients with metastatic breast cancer. Some relevant biomarker studies provided data in the adjuvant setting. New clinical trial data and analysis were presented regarding trastuzumab emtansine (T-DM1), nab-paclitaxel, gemcitabine, and other therapies.

Clinical Trial Data

The phase III EMILIA (An Open-Label Study of Trastuzumab-MCC-DM1 [T-DM1] vs Capecitabine+Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer) trial compared the combination of capecitabine and lapatinib versus single-agent T-DM1 in patients with metastatic breast cancer who have previously been treated with trastuzumab and a taxane.¹ Capecitabine plus lapatinib is the only regimen approved by the US Food and Drug Administration (FDA) for patients with refractory human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The EMILIA trial demonstrated significant improvement in progression-free survival in patients who received T-DM1 compared to those who received capecitabine and lapatinib. The improvement in progression-free survival was accompanied by a lower toxicity profile. It is likely that data from the EMILIA trial will promptly lead to FDA approval of T-DM1 in the refractory HER2-positive setting.

The cardiac safety of T-DM1 has been established in previous trials, such as TDM4450G.^{2,3} Chau T. Dang, MD, presented cardiac safety results from a pilot phase II study of T-DM1 following anthracycline-based chemotherapy as adjuvant or neoadjuvant therapy in early-stage HER2-positive breast cancer.⁴ No patients discontinued T-DM1 due to cardiac events, and no prespecified cardiac adverse events were reported. Among 143 cardiac-evaluable patients, 5 had non-prespecified cardiac adverse events, including 1 grade 4 atrial fibrillation, which were suspected by the investigators to be caused by T-DM1.

The FinHER (Finland Herceptin) trial was a correlative analysis of outcome to determine whether phosphoinositide 3-kinase mutations

correlate to outcome in HER2-positive patients receiving chemotherapy with or without trastuzumab.⁵ The investigators found that PI3 kinase mutations did not have any impact on benefit (or lack of benefit) to trastuzumab. This is important information that can be added to the report presented by Perez and colleagues at the 2011 ASCO meeting demonstrating a lack of correlation of tumor PTEN expression on response to adjuvant trastuzumab.⁶

Hope S. Rugo, MD, presented data from a study by the Cancer and Leukemia Group B (CALGB) and the North Central Cancer Treatment Group (NCCTG) examining the use of weekly paclitaxel compared to weekly nab-paclitaxel or ixabepilone with bevacizumab as first-line

ABSTRACT SUMMARY A Phase Ib Dose-Escalation Study of Eribulin Mesylate in Combination With Capecitabine in Patients With Advanced/Metastatic Cancer

This open-label, dose-escalation, phase Ib study was designed to determine the maximum tolerated dose (MTD) of eribulin mesylate and capecitabine, 2 drugs with non-overlapping key toxicities (Abstract 2552). Enrolled patients had advanced solid malignancies refractory to standard therapies. Patients received eribulin mesylate intravenously by schedule 1 (1.2, 1.6, or 2.0 mg/m² on day 1; n=19) or schedule 2 (0.7, 1.1, or 1.4 mg/m² on days 1 and 8; n=15), in combination with oral capecitabine 1,000 mg/m² twice daily on days 1–14 of the 21-day cycle. The drug combination yielded no unexpected toxicities. The MTD for eribulin combined with capecitabine was 1.6 mg/m² for schedule 1 and 1.4 mg/m² for schedule 2, and the MTD of schedule 2 appeared to provide superior drug exposure to eribulin. Patients on schedule 2 completed a greater number of treatment cycles than those on schedule 1. Eribulin pharmacokinetics were dose-proportional and were schedule- and capecitabine-independent. Stable disease was the best overall tumor response in 36.8% of patients on schedule 1 and 80.0% of patients on schedule 2.

therapy for locally recurrent or metastatic breast cancer (a very small number of patients did not receive bevacizumab).⁷ This study demonstrated that neither ixabepilone nor nab-paclitaxel was superior to weekly paclitaxel in combination with bevacizumab. Ixabepilone appeared to be inferior. Based on these data, it appears that weekly paclitaxel is the appropriate antitubulin to use in combination with bevacizumab. It should be noted, however, that this trial used a weekly dose of nab-paclitaxel that is higher than that typically used in this setting. Further analysis of the trial data that considers the potential impact of the higher dose of nab-paclitaxel used, particularly in regard to tolerability, may alter the study's interpretation.

Sandra Swain, MD, presented results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-38 trial.⁸ The goal of this study was to determine whether adding a second chemotherapy drug to a regimen of neoadjuvant doxorubicin plus cyclophosphamide following paclitaxel would improve pathologic complete response and disease-free survival. The addition of gemcitabine did not improve efficacy at a follow-up of more than 5 years.

Ongoing Trials

There are several ongoing trials of great interest. BOLERO-1 (Breast Cancer Trials of Oral Everolimus) is examining everolimus in combination with trastuzumab and paclitaxel in the first-line setting of patients with HER2-positive metastatic breast cancer.⁹ The BOLERO-2 trial demonstrated that everolimus added to the benefit of exemestane in the refractory estrogen receptor-positive setting.¹⁰ The results of BOLERO-1 are eagerly awaited.

Pertuzumab was recently approved by the FDA for use in combination with trastuzumab and a taxane based on results from the

ABSTRACT SUMMARY Tumor PIK3CA Mutations, Lymphocyte Infiltration, and Recurrence-Free Survival (RFS) in Early Breast Cancer (BC): Results From the FinHER Trial

Analysis of the FinHER (Finland Herceptin) trial aimed to determine whether *PIK3CA* mutations and lymphocyte infiltration are prognostic in patients with early breast cancer treated with adjuvant trastuzumab (Abstract 507). Patients (N=1,010) were randomized to receive 3 cycles of docetaxel or vinorelbine, followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide. Patients with HER2-positive breast cancer were further randomized to receive or not receive 9 weeks of trastuzumab. In a prior analysis, increased benefits were seen in patients receiving docetaxel or trastuzumab (*J Clin Oncol*. 2009;27:5685-5692). Neither *PIK3CA* nor *ERBB2* mutations were associated with relapse-free survival. In patients with HER2-positive breast cancer, no interaction was found between the benefit seen with trastuzumab and the presence of the *PIK3CA* mutation. Increasing lymphocyte infiltration was associated with increased relapse-free survival in patients with ER-negative/HER2-negative breast cancer. In HER2-positive breast cancer, the benefit of trastuzumab increased with the amount of lymphocyte infiltration. At 3 years, relapse-free survival was 96% for extensive lymphocyte infiltration versus 78% for nonextensive lymphocyte infiltration among patients treated with trastuzumab. The authors concluded that *PIK3CA* mutations were not prognostic; lymphocyte infiltration was a strong prognostic factor in patients with ER-negative, HER-negative breast cancer; and extensive lymphocyte infiltration predicts benefit from adjuvant trastuzumab.

CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial, in which this regimen improved progression-free survival and overall survival compared to a taxane and trastuzumab.¹¹ Taxanes, however, are associated with alopecia. In addition, use of pertuzumab, trastuzumab, and a taxane together requires the patient to be in the treatment room for several hours. The idea behind the VELVET (A Study of Pertuzumab in Combination With Herceptin [Trastuzumab] and Vinorelbine in First Line in Patients With Metastatic or Locally Advanced HER2-Positive Breast Cancer study) trial is to use vinorelbine, instead of a taxane, as the backbone chemotherapy.¹² Vinorelbine is a chemotherapy agent that appears to be as efficacious as a taxane in combination with trastuzumab. An important advantage to vinorelbine is that it does not lead to alopecia. In the VELVET trial, the first cohort of patients will

receive the 3 drugs sequentially. The second cohort will receive pertuzumab and trastuzumab at the same time. The goal is to identify a regimen with lower toxicity and a shorter duration of administration.

Another relevant large, randomized global trial (BEACON [Breast Cancer Outcomes With NKTR-102]) compares the pegylated form of irinotecan versus physician standard of care in the refractory HER2-normal breast cancer setting.¹³ The goal of this 840-patient study is to evaluate whether the pegylated form of irinotecan can improve overall survival. Although the use of overall survival as the primary endpoint is very rigorous, it is the correct approach to conducting trials of novel agents in the refractory breast cancer setting.

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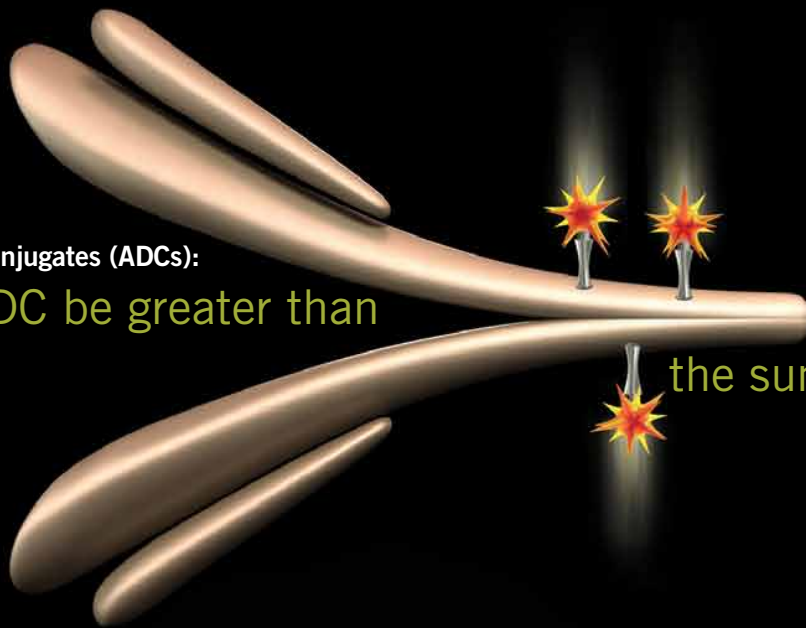
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