5 Minute Journal Club

Key SABCS Presentations

Issue 7, 2011

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Research To Practice®

CME Information

LEARNING OBJECTIVES

- Apply the results of new research to your recommended total duration of adjuvant chemotherapy for patients with early breast cancer and zero to three positive axillary nodes.
- Identify the incremental efficacy and toxicity associated with the addition of capecitabine to the adjuvant management of high-risk early breast cancer.
- Recognize the rationale for employing a more intensive capecitabine-containing adjuvant regimen for patients with early TNBC.
- Compare and contrast the rate of pathologic complete response among patients with and without TNBC treated with neoadjuvant capecitabine, epirubicin and docetaxel.
- Appraise the interim safety data for capecitabine maintenance therapy after standard adjuvant chemotherapy for triple-negative early breast cancer.
- Recall the early safety findings with adjuvant docetaxel, cyclophosphamide and bevacizumab in the management of HER2-normal early-stage breast cancer.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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FACULTY DISCLOSURES

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

William J Gradishar, MD
Director, Breast Medical Oncology
Professor of Medicine
Robert H Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Advisory Committee: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc, EMD Serono Inc, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi-Aventis.

Four vs 6 Cycles of Doxorubicin and Cyclophosphamide (AC) or Paclitaxel (T) as Adjuvant Therapy for Breast Cancer in Women with 0-3 Positive Axillary Nodes: CALGB 40101 — A 2 x 2 Factorial Phase III Trial: First Results Comparing 4 vs 6 Cycles of Therapy

Shulman LN et al.

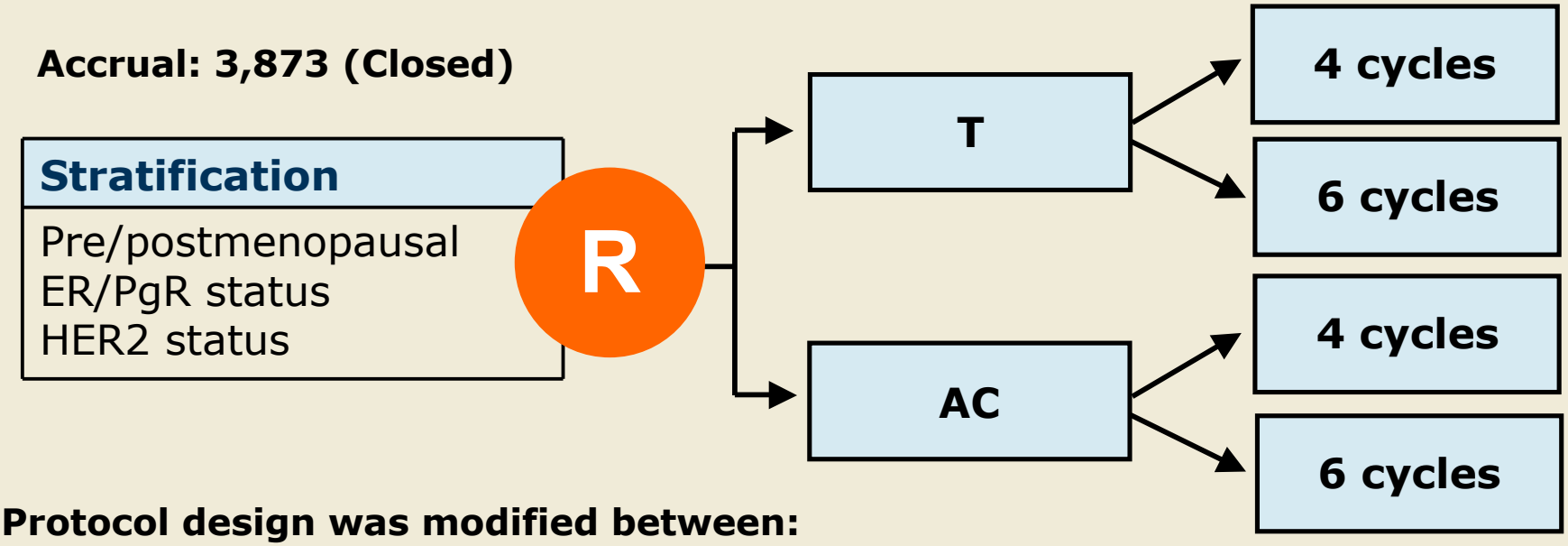
Proc SABCS 2010;Abstract S6-3.

Study Objectives

- **Primary Objectives**
  - Determine the equivalence of T with AC for relapse-free survival (RFS)
  - Determine if longer therapy (6 cycles) is superior to shorter therapy (4 cycles), regardless of agent, regarding RFS
- **Secondary Objectives**
  - Overall survival (OS)
  - Toxicities
  - Impact of 6 cycles versus 4 cycles in regard to induction of menopause in premenopausal women
  - Quality of life

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

CALGB-40101: Study Design



Protocol design was modified between:

- 2002-2003: AC q 3 wks x 4 or 6, T q wk x 12 or 18
- 2003-2008: AC q 2 wks x 4 or 6, T q 2 wks x 4 or 6
- 2008-2010: AC q 2 wks x 4, T q 2 wks x 4

Current analysis:

- 4 versus 6 cycles of therapy
- Data on AC versus T not yet released by Data and Safety Monitoring Board

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

Efficacy Data and Select Grade 3 and 4 Adverse Events

Median follow-up: 4.6 years

Number of Cycles	4-Year RFS	Hazard Ratio	*p*-value
4 cycles 6 cycles	91.8% 91.6%	1.10	0.420
Number of Cycles	**4-Year OS**	**Hazard Ratio**	***p*-value**
4 cycles 6 cycles	96.4% 95.3%	1.31	0.097

Toxicity	AC x 4 (n = 796)	AC x 6 (n = 790)	T x 4 (n = 798)	T x 6 (n = 789)
Neutropenia	26%	34%	3%	3%
Neuropathy	0%	0%	6%	13%
Anemia	2%	6%	0%	1%

There were 10 patients with Grades 3 to 5 cardiac events, but the percent is <1%

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

AML/MDS

- A total of 6 patients developed AML or MDS that was diagnosed 11-27 months after AC therapy:
  - AML: 5 patients
  - MDS: 1 patient
- Five patients developed AML/MDS in the AC x 6 study arm.
- One patient developed AML/MDS in the AC x 4 study arm.
- Five patients have died (including the one patient with MDS).
- No cases of AML/MDS were observed among the patients who received paclitaxel.

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

Author Conclusions

- Six cycles of AC or T for patients with primary breast cancer and 0 to 3 positive axillary nodes is not superior to 4 cycles of therapy.
- Although there are only 288 RFS events to this point, based on the present data, the Bayesian predictive probability of concluding superiority of 6 cycles (a primary goal of the study) with 567 RFS events is only 0.001.
- No interaction was evident between these findings and ER or HER2 status or whether the patient received AC or T (data not shown).

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

Investigator Commentary: Number of Cycles of Chemotherapy for Early Breast Cancer

CALGB-40101 was modified many times since it was opened in 2002, but in essence the study demonstrated that more cycles of adjuvant chemotherapy — whether it's six cycles of AC or paclitaxel — is not better than four cycles of the same chemotherapy. This was true for patients with ER-positive and ER-negative breast cancer. The statisticians are confident that this result will not change with more follow-up and a greater number of events. In short, more cycles of adjuvant chemotherapy does not make a difference in patient outcomes.

Interview with William J Gradishar, MD, January 4, 2011

First Efficacy Results of a Randomized, Open-Label, Phase III Study of Adjuvant Doxorubicin Plus Cyclophosphamide, Followed by Docetaxel with or without Capecitabine, in High-Risk Early Breast Cancer

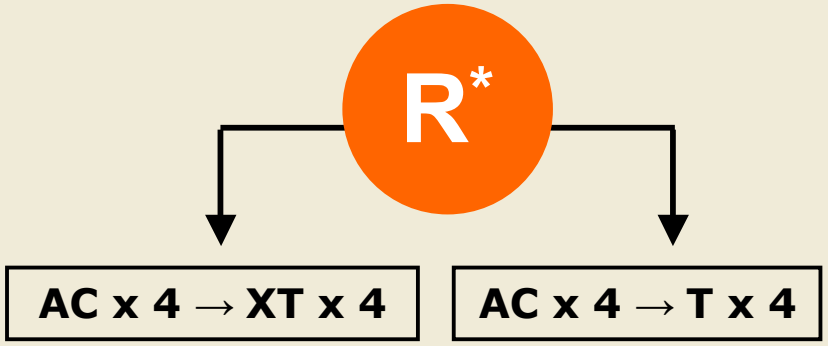
O'Shaughnessy J et al.

Proc SABCS 2010;Abstract S4-2.

US Oncology 01-062 Study Design

Accrual: 2,611 (Closed)

Eligibility
Aged 18 to 70 years
High-risk, histologically confirmed breast cancer
Node-positive or if node-negative: tumor >2 cm or >1 cm and ER/PR-negative
Surgically resectable disease
No evidence of metastasis



AC = doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, d1, q3wk

XT = capecitabine 825 mg/m^2 bid, d1-14; docetaxel 75 mg/m^2, d1, q3wk

T = docetaxel 100 mg/m^2, d1, q3wk

Primary endpoint: Disease-free survival

Secondary endpoints: Overall survival and safety

*Patients with HER2-positive disease could receive trastuzumab after ASCO 2005

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract S4-2.

Survival and Safety

	AC → XT	AC → T	HR (95% CI); *p*-value
5-year disease-free survival (DFS)	89%	88%	0.84 (0.67-1.05); *p* = 0.125
5-year overall survival (OS)	94%	92%	0.68 (0.51-0.92); *p* = 0.011
Adverse events	99.8%	100%	NR
Serious adverse events	20.2%	15.6%	NR

NR, not reported

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract S4-2.

Author Conclusions

- There was no improvement in DFS with AC → XT versus AC → T (89% vs 88%; $p = 0.125$).
- Patients treated with AC → XT had a significantly greater OS (94%) compared to those treated with AC → T (92%) ($p = 0.011$).
  - These results must be interpreted with caution due to the lower than expected event rate at 5 years.
- Exploratory Ki-67 analysis suggested benefit of capecitabine in patients with more highly proliferative cancers (data not shown).
- The incidence of adverse events including serious adverse events was similar between the groups.
- In the AC → XT group, there were higher rates of Grade 3 hand-foot syndrome (18.1% vs 3.8%) and Grade 3 or 4 stomatitis (9.1% vs 4.5%) and diarrhea (5.1% vs 2.9%).
- Grade 3 or 4 febrile neutropenia was higher in the AC → T group (13.1%) vs the AC → XT group (9.4%).

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract S4-2.

FinXX Final 5-Year Analysis: Results of the Randomised, Open-Label, Phase III Trial in Medium-to-High Risk Early Breast Cancer

Joensuu H et al.

Proc SABCS 2010;Abstract S4-1.

FinXX Phase III Study Design

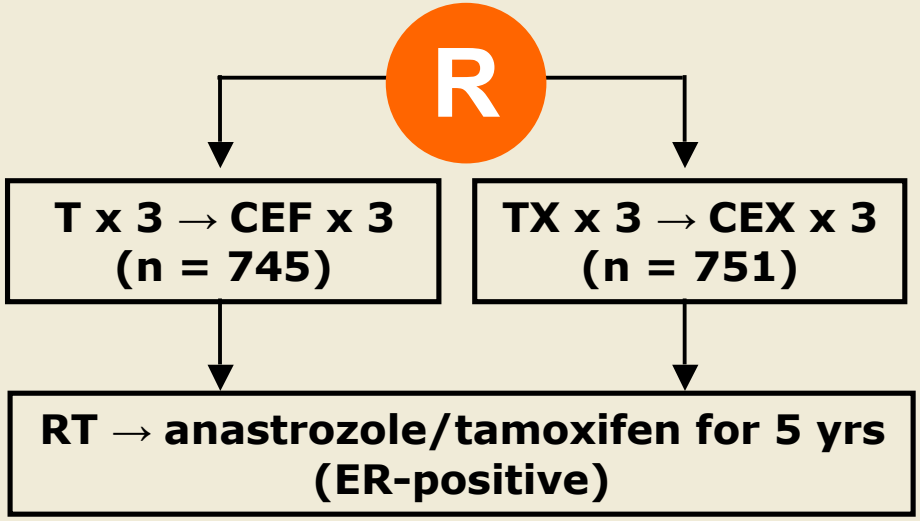
Eligibility (N = 1,500)

Histologically confirmed invasive node-positive breast cancer or node-negative if tumor > 20 mm and PR-negative

<65 years old

Primary objective:

Recurrence-free survival (RFS) at 5 years



T = docetaxel

CEF = cyclophosphamide, epirubicin, 5-FU

TX = capecitabine, docetaxel

CEX = cyclophosphamide, epirubicin, capecitabine

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

Survival Outcomes (Median Follow-Up 5 Years)

	T/CEF (n = 745)	TX/CEX (n = 751)	HR (95% CI)	*p*-value
Recurrence-free survival				
3-year rate	88.9%	92.4%	0.66 (0.47-0.94)	0.02
5-year rate	84.1%	86.6%	0.79 (0.60-1.04)	0.087
Overall survival				
3-year rate	95.3%	96.1%	—	—
5-year rate	89.7%	92.6%	0.73 (0.52-1.04)	0.080

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

RFS by Biologic Subtype (Exploratory Analysis)

Biologic Subtype	HR	*p*-value
ER+ and/or PR+, HER2- (n = 1,009)	0.91	0.591
ER+ and/or PR+, HER2+ (n = 163)	1.11	0.845
ER- and PR-, HER2- (n = 202)	**0.48**	**0.0177**
ER- and PR-, HER2+ (n = 122)	0.91	0.786

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

Grade 3/4 Adverse Events

Adverse Event	T/CEF (n = 743)	TX/CEX (n = 751)	*p*-value
Neutropenia	98.1%	86.0%	<0.0001
Hand-foot syndrome	0.3%	11.2%	<0.0001
Infection with neutropenia	12.4%	5.8%	<0.0001
Nail effects	0.5%	4.9%	<0.0001
Febrile neutropenia	8.8%	4.4%	0.0008
Stomatitis	1.6%	4.2%	0.0048
Myalgia	7.8%	1.9%	<0.0001

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

Author Conclusions

- TX/CEX did not improve RFS or OS significantly compared to T/CEF.
- Exploratory subgroup analyses suggest:
  - TX/CEX is more effective than T/CEF in patients with triple-negative breast cancer.
  - TX/CEX is more effective than T/CEF in patients with >3 axillary metastases (data not shown).
  - TX/CEX improves breast cancer-specific survival (data not shown).

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

Investigator Commentary: Incorporation of Capecitabine into Adjuvant Therapy for Medium- to High-Risk Early BC

The large US Oncology trial evaluated adjuvant AC followed by docetaxel (T) with or without capecitabine (X). If I "cut to the chase," the disease-free and overall survival curves for the two arms appeared superimposable, although there was a suggestion of a survival benefit with AC followed by XT. Additionally, they suggested that patients with a high Ki-67 derived the greatest benefit from the addition of capecitabine, but I'm not confident that this offers an advantage compared to AC → T.

Interview with William J Gradishar, MD, January 4, 2011

Integration of Capecitabine into Anthracycline- and Taxane-Based Adjuvant Therapy for Triple Negative Early Breast Cancer: Final Subgroup Analysis of the FinXX Study

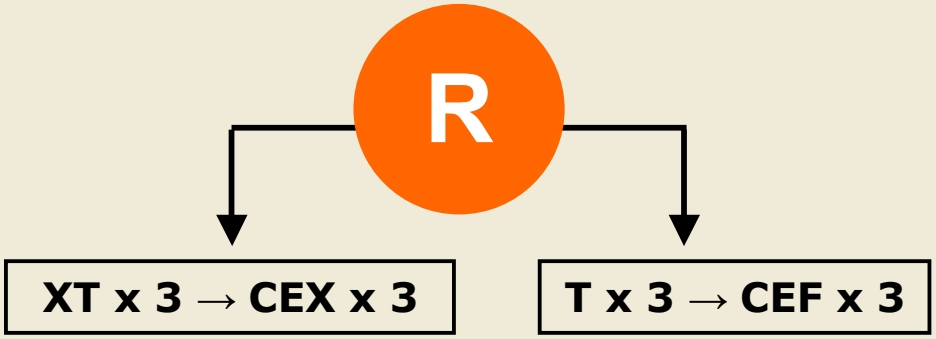
Lindman H et al.

Proc SABCS 2010;Abstract PD01-02.

FinXX Study Design

Accrual: 1,500 (Closed)

Eligibility
Age 18 to 65 years
Histologically confirmed invasive, node-positive breast cancer or node-negative if tumor >20 mm and PR-negative
WHO PS 0-1
No previous neoadjuvant chemotherapy



XT = capecitabine 900 mg/m^2 bid, d1-15; docetaxel 60 mg/m^2, d1

T = docetaxel 80 mg/m^2, d1

CEX = cyclophosphamide 600 mg/m^2, d1; epirubicin 75 mg/m^2, d1; capecitabine 900 mg/m^2 bid, d1-15, q3wk

CEF = cyclophosphamide 600 mg/m^2, d1; epirubicin 75 mg/m^2, d1; 5-fluorouracil 600 mg/m^2, d1, q3w

Primary objective: To perform a 5-year exploratory analysis of a subgroup of patients from the FinXX study with triple-negative early breast cancer (TNBC)

Lindman H et al. *Proc SABCS* 2010;Abstract PD01-02.

5-Year Survival in TNBC (n = 202)

	XT → CEX (n = 93)	T → CEF (n = 109)	HR (95% CI); *p*-value
Relapse-free survival	84.5%	70.3%	0.48 (0.26-0.88); 0.018
Distant disease-free survival	84.5%	70.9%	0.51 (0.28-0.95); 0.035
Overall survival	89.1%	75.6%	0.42 (0.20-0.87); 0.019
Deaths	10.8%	23.9%	NR
Deaths due to breast cancer	7.5%	22.9%	NR

HR, hazard ratio

Lindman H et al. *Proc SABCS* 2010;Abstract PD01-02.

Author Conclusions

- The FinXX trial was the first to report the efficacy of capecitabine in combination with anthracycline/taxane-containing therapy in the adjuvant treatment of early breast cancer.[1]
- The final 5-year subgroup analyses of TNBC, a population with a high unmet need, reported significant benefits in all endpoints for patients receiving the capecitabine-containing regimen XT → CEX compared to the standard arm T → CEF.[2]
  - Relapse-free survival, 84.5% vs 70.3%
  - Distant disease-free survival, 84.5% vs 70.9%
  - Overall survival, 89.1% vs 75.6%
- The estimated risk reduction of relapse or death in patients with TNBC was around 50% in patients receiving XT → CEX.[2]
- The findings from this subgroup analysis are exploratory and must be confirmed in other studies.[2]

[1] Joensuu H et al. *Lancet Oncol* 2009;10:1145-51; [2] Lindman H et al. *Proc SABCS* 2010;Abstract PD01-02.

Review of Capecitabine for the Treatment of Triple-Negative Early Breast Cancer

Steger GG et al.

Proc SABCS 2010;Abstract PD01-03.

Methods

- **Objective:**
  - To assess the potential benefit of capecitabine in patients with triple-negative breast cancer (TNBC) treated on the ABCSG-24 and FinXX trials.
- **Patient eligibility:**
  - Neoadjuvant ABCSG-24: Operable breast cancer except T4d with or without nodal involvement (*Proc ECCO-ESMO* 2009;Abstract 4BA)
  - Adjuvant FinXX: Invasive breast cancer at medium to high risk of recurrence (*Lancet Oncol* 2009;10:1145)
- **Treatments:**
  - ABCSG-24: Neoadjuvant epirubicin (E) and docetaxel (T) with or without capecitabine (X)
  - FinXX: Adjuvant T → cyclophosphamide/epirubicin/5-fluorouracil (CEF) or XT → CEX

Steger GG et al. *Proc SABCS* 2010;Abstract PD01-03.

Primary Efficacy Analysis

Pathologic Complete Response (pCR) Rate			
ABCSG-24 study	**ET + X**	**ET**	***p*-value**
All patients (n = 255, 257)	24.3%	16.0%	0.02
Patients with TNBC (n = 29, 19)	47.5%	31.2%	NS
3-Year Relapse-Free Survival (RFS)			
FinXX study	**XT → CEX**	**T → CEF**	***p*-value**
All patients (n = 747, 753)	92.5%	88.9%	0.02

NS, not significant

Steger GG et al. *Proc SABCS* 2010;Abstract PD01-03.

TNBC Subgroup Analysis

ABCSG-24 study	TNBC (n = 122)	Non-TNBC (n = 348)	Odds ratio (95% CI)	*p*-value
pCR, all patients	39.3%	10.9%	5.29 (3.22-8.68)	<0.0001
pCR, ET + X group	47.5%	13.2%	5.95 (3.05 -11.59)	<0.0001
pCR, ET group	31.2%	8.6%	4.80 (2.25-10.23)	<0.0001
FinXX study	**TNBC**	**Non-TNBC**	**Hazard ratio (95% CI)**	***p*-value**
RFS, all patients	81.7%	92.2%	0.43 (0.29-0.63)	<0.001

- Within the TNBC subgroup of patients in the FinXX study, 3-year RFS was significantly longer in the capecitabine-containing arm (n = 93) than in the control arm (n = 109): 87.7% vs 76.6% (HR: 0.43, p = 0.024)

Steger GG et al. *Proc SABCS* 2010;Abstract PD01-03.

Author Conclusions

- Patients with TNBC have a high unmet therapeutic need with generally worse prognosis than patients with non-TNBC.
- Initial data with capecitabine in early breast cancer are promising, with the randomized Phase III ABCSG-24 and FinXX trials demonstrating significant improvements in pCR and RFS, respectively, with the addition of capecitabine to standard (neo)adjuvant regimens.
- Subgroup analyses from these studies report additional benefit of capecitabine therapy in patients with TNBC.
- An ongoing study (CIBOMA collaborative group Phase III trial) is evaluating capecitabine as maintenance therapy after adjuvant anthracycline/taxane for patients with TNBC.
  - First study utilizing capecitabine to specifically target patients with early TNBC
  - Interim safety data also presented at SABCS 2010 (Lluch A et al. *Proc SABCS* 2010;Abstract P5-10-15)

Steger GG et al. *Proc SABCS* 2010;Abstract PD01-03.

Investigator Commentary: Incorporation of Capecitabine into Adjuvant Therapy for High-Risk Early BC

In the subgroup analysis of FinXX, patients with triple-negative breast cancer (TNBC) who received adjuvant XT → CEX experienced an improvement in overall survival, distant disease-free survival and relapse-free survival compared to those who received T → CEF. Several studies have suggested that patients with TNBC may benefit from a more intense therapeutic approach.

In the review of capecitabine for the treatment of early breast cancer in ABCSG-24 and FinXX, they demonstrated, not surprisingly, that patients with TNBC experienced worse outcomes. They also suggested that the patients with TNBC who received capecitabine-containing regimens had better outcomes that were equivalent to patients with non-TNBC.

Interview with William J Gradishar, MD, January 4, 2011

First Safety Data from a Randomized Phase III (CIBOMA/2004-01/GEICAM 2003-11) Trial Assessing Adjuvant Capecitabine Maintenance Therapy After Standard Chemotherapy for Triple-Negative Early Breast Cancer

Lluch A et al.

Proc SABCS 2010;Abstract P5-10-15.

Study Design

Accrual: 816 (Open)

Eligibility

- **Operable node-positive (or node-negative with tumor diameter ≥1 cm)**
- **Centrally confirmed TNBC**
- **No evidence of metastatic disease**
- **6-8 cycles of prior anthracycline and/or taxane-based chemo or 4 cycles of doxorubicin/cyclophosphamide (for node-negative disease) in the (neo)adjuvant setting**

R

Safety data reported for first 400 patients (pts)

Capecitabine
1,000 mg/m^2 BID d1-14 q3wks x 8

Observation

Lluch A et al. *Proc SABCS* 2010;Abstract P5-10-15.

Treatment-Related Grade 3/4 Adverse Events*

Outcome	Capecitabine (n = 207)	Observation (n = 193)
Hand-foot syndrome†	17.4%	—
Diarrhea	2.9%	—
Fatigue	1.9%	—
Vomiting	1.0%	—
Nail changes	1.0%	—
Elevated bilirubin	1.0%	—
Irregular menses	0.5%	7.8%

* Grade 3/4 events occurring in ≥2 patients in either treatment arm;
† Grade 3 only

Lluch A et al. *Proc SABCS* 2010;Abstract P5-10-15.

Proportion of Cycles with Treatment Discontinuation Due to Toxicity

Cycles, %	N = 1,440
Toxicity	12.2%
Hand-foot syndrome	7.4%
Neutrophils/granulocytes	1.2%
Diarrhea	1.1%
Mucositis/stomatitis	0.5%
Leukocytes	0.4%
Fatigue	0.3%

Lluch A et al. *Proc SABCS* 2010;Abstract P5-10-15.

Selected Reasons for Discontinuation

Rationale, n (%)	Capecitabine (n = 207)	Observation (n = 193)
Withdrawal request by pt	16 (7.8%)	2 (1.0%)
Unacceptable toxicity	15 (7.2%)	1 (0.5%)
Disease relapse	5 (2.4%)	7 (3.7%)
Tx interuption >3 wks	4 (1.9%)	—
Death	3 (1.4%)	2 (1.0%)
Protocol deviation	2 (1.0%)	1 (0.5%)
Lost to follow-up	1 (0.5%)	1 (0.5%)

Lluch A et al. *Proc SABCS* 2010;Abstract P5-10-15.

Author Conclusions

- The safety profile of adjuvant capecitabine as maintenance therapy is consistent with its known toxicity profile.
- More than 75% of patients are able to complete their treatment as planned, with approximately 15% of patients discontinuing due to toxicity or patient withdrawal.
- Ongoing recruitment with an accrual of 876 patients is planned.

Lluch A et al. *Proc SABCS* 2010;Abstract P5-10-15.

Investigator Commentary: Maintenance Capecitabine After Adjuvant Chemotherapy for Triple-Negative Breast Cancer

The CIBOMA/GEICAM investigators demonstrated that administering maintenance capecitabine after standard adjuvant chemotherapy for patients with triple-negative early breast cancer was not associated with excessive capecitabine-associated side effects, and hand-foot syndrome and diarrhea were the most common adverse events. This was a preliminary report, and efficacy data are not yet available.

Interview with William J Gradishar, MD, January 4, 2011

The Swiss have been investigating metronomic cyclophosphamide and methotrexate as maintenance therapy in the adjuvant setting. We were interested in joining the Swiss study, but we were unhappy about approaching patients to undergo a year of maintenance therapy.

I have used capecitabine a lot as a single agent for metastatic disease, and it may not be a “slam dunk” to administer it as maintenance therapy, even though it’s orally administered. Patients must be carefully watched because they “soldier on” and do not always report symptoms. Using maintenance capecitabine will require careful management and watching the dose closely. However, if this approach turns out to be positive, then we will all be using maintenance therapy.

Interview with Kathleen I Pritchard, MD, December 30, 2010

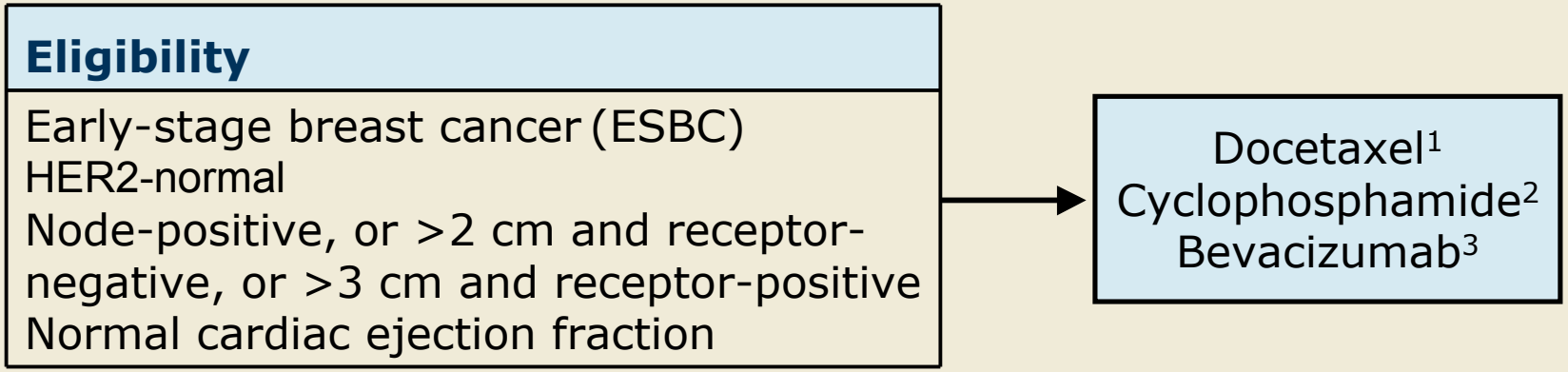
Bevacizumab (Bev) in Combination with Docetaxel (T) and Cyclophosphamide (C) as Adjuvant Treatment (AdjRx) for Patients (Pts) with Early Stage (ES) Breast Cancer (BrCa) and Normal HER-2 Status. A Pilot Evaluation

Crown J et al.

Proc SABCS 2010;Abstract P5-10-17.

Methods

Accrual = 106 (Closed)



Patients were monitored clinically, with blood pressure (BP) measurements before each bevacizumab infusion, regular echocardiograms and serial estimations of B-type natriuretic peptide (BNP) and troponin.

[1] 75 mg/m^2 day 1 q3wk x 4
[2] 600 mg/m^2 day 1 q3wk x 4
[3] 15 mg/kg day 1 q3wk x 18

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17;
ClinicalTrials.gov Identifier NCT00911716.

Patient Disposition

	TC + Bev (n = 106)
Therapy completion (all phases)	46 (43.4%)
Still on treatment	39 (36.8%)
Removal from study	21 (19.8%)
Hypertension	6 (5.66%)
Intestinal perforation	2 (1.89%)

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17.

Select Serious Adverse Events (SAEs)*

n (%)	TC + Bev
SAEs (all types, any grade)†	21 (19.8%)
Neutropenia	5 (4.7%)
Neutropenic sepsis	3 (2.8%)
Cellulitis	3 (2.8%)
Pyrexia	2 (1.9%)
GI perforation	2 (1.9%)

* Occurring in >1% of patients on study

† 34 SAEs (31 involved hospital admissions, 3 were serious for other reasons) occurred on study in these 21 patients

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17.

Hypertension and Cardiac Toxicity

Hypertension (HTN)	TC + Bev (n = 106)
HTN (while on study)	**41 (39.8%)**
HTN (requiring antihypertensives)	35 (85.4%)
Time to onset of hypertension (median)	154 days

Cardiac toxicity; median ejection fraction (EF) at baseline = 67%	
Drop in EF of 10-15% from baseline	22 (21.2%)
Drop in EF of 15-20% from baseline	6 (5.8%)
Drop in EF of >20% from baseline	2 (1.9%)
Drop in EF to <50%	8 (7.7%)

No cases of congestive heart failure observed. Serial estimations of BNP and troponin indicated no significant changes throughout the study treatment.

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17.

Author Conclusions

- The spectrum and frequency of bevacizumab toxicity in this study were similar to those reported for patients with metastatic breast cancer and other types of cancer.
- Hypertension was the principal cause of treatment discontinuation, but cardiac toxicity appeared to be limited.
- Intestinal perforation can also occur in patients with ESBC even without history of previous abdominal surgery or intestinal chronic diseases.
- These toxicities can occur in the post-chemotherapy phase of bevacizumab therapy.
- Patients enrolled on randomized trials of bevacizumab-containing adjuvant therapy require careful monitoring for toxicity.

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17.

Investigator Commentary: Safety of Bevacizumab in Combination with Docetaxel/Cyclophosphamide in the Adjuvant Setting

This pilot study by Crown and colleagues was a small, single-arm clinical trial with approximately 100 patients. They demonstrated that it was feasible to administer bevacizumab with adjuvant docetaxel and cyclophosphamide. No surprises were observed with respect to side effects.

Some hypertension occurred, which is predictable, but no significant cardiac signal was observed. Obviously, we cannot make any comments whatsoever about efficacy, so the key data will come from the large, ongoing trials evaluating bevacizumab in the adjuvant setting.

Interview with William J Gradishar, MD, January 4, 2011