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Key Findings in the Clinical Management of Invasive Breast Cancer: Highlights from the 32nd Annual San Antonio Breast Cancer Symposium

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Target Audience

The target audience for this program includes oncologists and other healthcare professionals involved in the treatment of breast cancer.

Learning Objectives

Upon completion of this educational activity, participants should be better able to:

- Incorporate clinical data describing new therapeutic agents or strategies into clinical practice to improve pathologic response rates in patients in the neoadjuvant therapy setting
- Discuss updated efficacy and toxicity data for adjuvant therapy options used in the early breast cancer setting
- Describe the strengths and weaknesses of significant clinical trials of agents designed to improve response and survival rates in the metastatic breast cancer setting
- Explain the implications of genetic analysis and biomarkers on treatment selection and response as they currently relate to patients with breast cancer

Statement of Need

In 2009, breast cancer remained the number one diagnosed cancer and second-leading cause of cancer-related deaths in US women. An estimated 192,310 new cases of invasive breast cancer will be diagnosed and 40,170 women will die from this disease. Following the two-decade rise that began in the 1980s, the incidence rate for breast cancer decreased by 3.5% a year from 2001-2004. It has been postulated that this may be related to the reduction in the use of hormone replacement therapy and the adoption of mammography screening. Fortunately, the death rate for women with breast cancer has also declined by about 20% from 1991 (32.69 deaths per 100,000) to 2003 (25.19 deaths per 100,000). It is estimated that 15% of the decline in breast cancer mortality was due to screening mammography and 19% was related to adjuvant treatments. Significant improvements have occurred in the management of women with breast cancer although many questions remain. As clinicians encounter these patients in practice and need to make informed decisions about controversial treatment topics, discussion and debate of these issues are necessary to improve the long-term outcomes of these patients. Continuing medical education programs are important vehicles to assist in the timely distribution and application of this key information in order to improve patient outcomes.

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Introduction

The 32nd Annual San Antonio Breast Cancer Symposium held December 9-13, 2009 provided a comprehensive review of the state of breast cancer research and treatment today and explored promising leads for future research and development. Highlights of newly reported data further disseminate scientific advancement, knowledge, and insight gained from this international scientific symposium.

Endocrine Therapy

Intergroup Exemestane Study

Aromatase inhibitors (AIs) are an accepted adjuvant treatment in postmenopausal women before or after surgery for estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive breast cancer. The Intergroup Exemestane Study (IES), first published in 2004, established exemestane, a steroidal AI, as an adjuvant endocrine therapy after 2-3 years of tamoxifen. Bliss et al reported on the long-term outcome of 4,724 postmenopausal women with ER-positive/unknown early breast cancer enrolled in IES.¹ The objective of this analysis was to evaluate breast cancer-free survival (BCFS), sites of distant recurrence, and incidence of non-breast secondary primary cancers, and to provide a sensitive estimate of the true impact of adjuvant intervention on breast cancer outcome.

Patients enrolled in IES received 2-3 years of tamoxifen and those who were disease free were subsequently randomized to receive 2-3 years of exemestane or an additional 2-3 years of tamoxifen. After 5 years of endocrine therapy, patients were monitored in post-treatment follow-up. This analysis represents a median of 91 months of follow-up since randomization with 91% of surviving patients receiving ≥ 6 years of follow-up and representing 32,296 women-years of follow-up.

The original cohort had a mean age of 64.2 years, with 44.2% of patients being node positive and 32.6% of patients having received adjuvant chemotherapy. A total of 2.6% of patients were later found to have ER-negative disease, leaving 4,599 patients for this analysis of ER-positive/unknown disease.

The overall survival (OS) significantly favored exemestane with an absolute difference of 1.4% at 5 years and 2.4% at 9 years ($P = 0.04$; HR = 0.86

[95% CI: 0.75-0.99]). Disease-free survival (DFS) also favored exemestane at 5 years (3.0%) and 8 years (4.4%) ($P = 0.0009$; HR 0.82 [95% CI: 0.73-0.92]). The annual DFS event rates remained constant at approximately 4% per year with a risk of local recurrence or second primary breast cancer of approximately 0.5% per year.

The BCFS rate was calculated as DFS omitting intercurrent deaths (defined as deaths of known cause prior to relapse). The investigators state this represents a sensitive estimate of true treatment effect on breast cancer outcome. Breast cancer-free survival events are presented in **Table 1**. Breast cancer-free survival significantly favored exemestane with an absolute difference of 2.8% at 5 years and 4.1% at 8 years ($P = 0.001$; HR = 0.81 [95% CI: 0.71-0.92]). When analyzed by on-treatment and post-treatment periods, BCFS favored exemestane in the on-treatment period (years 0-2.5; HR = 0.60) and this benefit was maintained in the post-treatment period (years 2.5-9; HR = 0.94). When stratified by prognostic subgroups, all subgroups favored treatment with exemestane, including node-negative and node-positive disease, with or without use of prior chemotherapy, ER-positive and ER-unknown status, duration of tamoxifen use prior to randomization, and age at randomization. The overall BCFS effect was associated with an HR of 0.79, ($P < 0.001$).

Table 1. Breast Cancer-Free Survival Events

	Exemestane n = 2294	Tamoxifen n = 2305	Total
Total BCFS – first events	425	508	933
· Distant recurrence including breast cancer deaths and unknown cause of death	311	360	671
· Local recurrence only	72	89	161
· Breast cancer second primary	42	59	101
Intercurrent deaths	105	114	219

A strong relationship between breast cancer mortality and time to distant recurrence was observed ($P = 0.01$; HR = 0.83 [95% CI: 0.72-0.96]), with events presented in **Table 2**.

Table 2. Relationship Between Distant Recurrence and Death

	Exemestane n = 2294	Tamoxifen n = 2305	Total
Distant recurrence known site*	303	346	649
Breast cancer death, no previous distant recurrence [†]	16	24	40
Death from unknown cause [‡]	26	37	63
Total	345	407	752

*Included patients where DFS was local recurrence or breast second primary and distant recurrence followed.

[†]Included all deaths following local recurrence and breast second primary.

[‡]Death from unknown cause conservatively treated as breast cancer death.

The most common site of first reported distant recurrence was visceral only (exemestane, n = 116; tamoxifen, n = 113), followed by bone only (exemestane, n = 75; tamoxifen, n = 109). The incidence of non-breast second cancers included 106 in the exemestane arm and 159 in the tamoxifen arm, demonstrating an unexpected lower number of non-breast secondary primary cancers with exemestane treatment. A patient's age at randomization was found to have no effect on risk of distant recurrence; however, second primary cancers were more frequent in patients aged ≥ 70 years ($P = 0.005$).

In summary, exemestane treatment after 2-3 years of tamoxifen demonstrated persistent improvement in breast cancer outcomes out to 9 years. The protective effect on relapse rate, achieved with the sequential tamoxifen to exemestane regimen, is maintained for at least 5 years post-treatment completion and is associated with a continued OS benefit.

Tamoxifen Exemestane Adjuvant Multicenter Trial

While IES established the role of exemestane after 2-3 years of tamoxifen (compared to 5 years tamoxifen), the phase III Tamoxifen Exemestane Adjuvant Multicenter (TEAM) trial prospectively compared 5 years of upfront exemestane with 2.5- 3 years of tamoxifen followed by exemestane as first-line adjuvant treatment in postmenopausal women with hormone-sensitive early breast cancer.

In 2001, the TEAM trial began enrollment to randomized women to receive open-label exemestane 25 mg/day or tamoxifen 20 mg/day. In 2004, the study protocol was modified such that patients originally randomized to tamoxifen would be switched to exemestane after 2.5-3 years. An additional 2,500 patients were recruited and randomized under the new study design. The revised study included 2 coprimary endpoints, DFS among patients receiving tamoxifen or exemestane at 2.75 years, and DFS among patients receiving exemestane or tamoxifen followed by exemestane at 5 years, the latter which was presented by Rea et al.²

A total of 9,779 patients were accrued from 9 countries. The 2 treatment arms were well balanced across patient characteristics, with 47% of patients in both arms being node positive and 100% of patients in both arms being ER- and/or PgR-positive.

At a median of 5.1 years, 60% of patients had completed 5 years of follow-up. The number of DFS events is presented in **Table 3**. There was no significant difference in 5-year DFS between sequential therapy (85.4%) and exemestane (85.7%) ($P = 0.604$; HR = 0.97 [95% CI: 0.88, 1.08]). Five-year OS was also similar between sequential therapy (90.6%) and exemestane (90.5%) ($P = 0.999$, HR = 1.0 [95% CI: 0.89, 1.14]). Time to recurrence (TTR) was also not significant at 5 years (10.9% vs 10.2%, $P = 0.293$; HR = 0.94 [95% CI: 0.83, 1.06]). When stratified by nodal status, there remained no significant difference in 5-year DFS.

Table 3. Disease-Free Survival Events (Intent-To-Treat)

Event	Tamoxifen → Exemestane (n = 4868)	Exemestane (n = 4898)	Total (n = 9766)
Total DFS events	714	712	1426
Local recurrence only*	68	59	127
New primary breast cancer	33	40	73
Distant metastasis	420	400	820
Intercurrent deaths	193	213	406

*Includes ipsilateral breast cancer.

Treatment-emergent gynecological, endocrine, and metabolic related adverse events are presented in **Table 4**. Sequential therapy was associated with significantly more endometrial cancer, endometrial abnormalities, vaginal discharge, vaginal bleeding, and other vulvovaginal disorders, hot flushes, venous thrombosis, and muscle cramps. Exemestane therapy was associated with significantly more vaginal dryness, hyperlipidemia, hypertension, fractures, osteoporosis, arthralgia, and carpal tunnel syndrome.

No difference in efficacy was demonstrated between the 2 treatment arms, including DFS, TTR, and OS. The safety profile was consistent with the known side effects associated with monotherapy with either exemestane or tamoxifen. Thus, TEAM indicated that for postmenopausal women with endocrine-sensitive breast cancer either 5 years of upfront exemestane or tamoxifen followed by exemestane may be appropriate treatment.

Table 4. Treatment-Emergent Adverse Events

	Tamoxifen → Exemestane		Exemestane		P value
	n	%	n	%	
Gynecological, Endocrine, Metabolic					
Endometrial cancer	17	0.4	7	0.1	0.040
Endometrial abnormalities	187	3.9	20	0.4	< 0.001
Vaginal discharge	402	8.4	123	2.5	< 0.001
Vaginal bleeding	243	5.0	114	2.3	< 0.001
Other vulvovaginal disorders	94	2.0	64	1.3	0.017
Vaginal dryness	264	5.5	321	6.6	0.022
Hot flushing/sweats	2127	44.2	1812	37.3	< 0.001
Hyperlipidemia	134	2.8	227	4.7	< 0.001
Cardiovascular					
Arrhythmia	133	2.8	170	3.5	0.042
Cardiac failure	36	0.7	55	1.1	0.063
Myocardial ischemia/infarction	60	1.2	77	1.6	0.183
Cerebrovascular ischemia	35	0.7	51	1.1	0.112
Other arterial thrombosis	14	0.3	12	0.2	0.680
Embolism	43	0.9	45	0.9	0.944
Venous thrombosis	97	2.0	45	0.9	< 0.001
Hypertension	215	4.5	293	6.0	0.001
Musculoskeletal					
Fractures	170	3.5	249	5.1	< 0.001
Osteoporosis	259	5.4	478	9.9	< 0.001
Arthralgia	961	20.0	1140	23.5	< 0.001
Carpal tunnel syndrome/other nerve compression disorders	126	2.6	166	3.4	0.024
Muscle cramps/disorders	302	6.3	188	3.9	< 0.001

Fulvestrant and Anastrozole in Combination Trial

While the AI anastrozole has established efficacy in the treatment of hormone-dependent postmenopausal breast cancer, many patients with advanced disease develop resistance. Fulvestrant is a selective estrogen receptor down-regulator (SERD) with a dose-response effect that down regulates ER receptors in human breast cancer. The Fulvestrant and Anastrozole in Combination Trial (FACT) evaluated the efficacy of fulvestrant administered as a loading dose regimen with anastrozole versus anastrozole alone in women with hormone receptor-positive breast cancer at first relapse. Bergh et al presented the first results from this worldwide study.³

The authors hypothesized that the combination of fulvestrant and anastrozole might counteract resistance by increasing ER blockade through different yet synergistic mechanisms of action. FACT enrolled both postmenopausal women with ER-positive and/or PgR-positive advanced breast cancer and premenopausal women on a luteinizing hormone-releasing hormone analogue (LHRHa) with ER-positive and/or PgR-positive advanced breast cancer. A total of 514 patients were randomized to receive combination therapy with fulvestrant (500 mg IM day 1 and 250 mg IM days 14 and 28, followed by 250 mg IM monthly) and anastrozole (1 mg PO) or monotherapy with anastrozole (1 mg PO). Patients were treated until disease progression. The primary endpoint was time to progression (TTP).

Eligible patients had histological or cytological confirmed disease with locally recurrent disease unsuitable for treatment of metastatic breast cancer (MBC). Patients had to be candidates for endocrine therapy as their first-line systemic treatment for recurrent disease. Patients who relapsed after or while on adjuvant endocrine therapy with tamoxifen or adjuvant AI therapy were eligible provide they had a 12-month recurrence-free interval.

The fulvestrant/anastrozole (F/A) arm included 258 patients with a median age of 65 years. The anastrozole alone (A) arm included 256 patients with a median age of 63 years. Patient characteristics were well balanced across treatment arms with 180 and 4 patients receiving prior endocrine therapy or AI therapy, respectively, in the F/A arm and 166 and 1 patients receiving prior endocrine therapy or AI therapy, respectively, in the A arm. The majority of patients in both arms were ER-positive and PgR-positive with no patients enrolled with ER-negative/PgR-negative disease.

The median TTP was 10.8 months in the F/A arm and 10.2 months in the A arm ($P = 0.91$; HR = 0.99), with 77.5% and 78.1% of patients progressing in each arm. Subgroup analysis did not identify any group that received significant TTP benefit from F/A. Response rates are summarized in **Table 5**. Overall survival was not significantly different between the 2 arms with a median OS of 37.8 months in the F/A arm and 38.2 months in the A arm ($P = 1.00$; HR = 1.00).

Table 5. Response Rates With Fulvestrant/Anastrozole and Anastrozole Alone

Best Objective Response	Fulvestrant/Anastrozole (n = 258) n (%)	Anastrozole (n = 256) n (%)
Complete response (CR)	4 (1.6)	4 (1.6)
Partial response (PR)	37 (14.3)	34 (13.3)
Stable disease (SD) (≥ 24 weeks)	101 (39.1)	103 (40.2)
Clinical benefit rate (CBR) (CR + PR + SD)	142 (55.0)	141 (55.1)
Progressive disease	68 (26.4)	83 (32.4)

Prespecified adverse events in the safety population were similar across both treatment arms with only hot flushes significantly more common in the F/A arm ($P < 0.01$). The most common adverse events were GI disturbances, joint disorders, hot flushes, and urinary tract infections. Eleven deaths occurred in the F/A arm and 5 deaths occurred in the A arm, although this was not a statistically significant difference. No deaths were believed to be due to drug-related adverse events.

This prospective, randomized study demonstrated no clinical advantage with the addition of fulvestrant to anastrozole and the authors conclude that this combination regimen cannot be recommended for use in this patient population.

VEGF-Inhibitor Incorporation into Chemotherapy Regimens

Metastatic Breast Cancer

Two studies presented explored the utility of bevacizumab-containing chemotherapy regimens in the treatment of locally recurrent or metastatic breast cancer. In the first, Miles et al presented the final results of the phase III AVADO (AVAstin plus DOcetaxel) trial, which compared bevacizumab + docetaxel with placebo + docetaxel for the first-line treatment of locally recurrent or MBC.⁴

Bevacizumab in combination with standard therapies has demonstrated significant efficacy with limited toxicity across multiple tumor types. Three phase III trials (E2100, AVADO, and RIBBON-1) have reported data that indicate the addition of bevacizumab to first-line chemotherapy significantly improves progression-free survival (PFS) and overall response rate (ORR). This analysis represents mature OS data at a median follow-up of 29 months.

AVADO randomized 736 patients from 26 countries to 3 treatment arms:

- Docetaxel 100 mg/m² + placebo q3weeks x 9 (n = 241)
- Docetaxel 100 mg/m² + bevacizumab 7.5 mg/kg q3weeks x 9 (n = 248)
- Docetaxel 100 mg/m² + bevacizumab 15 mg/kg q3weeks x 9 (n = 247)

Patients were treated until disease progression. After the primary analysis, patients receiving the placebo-containing regimen were eligible to receive open-label bevacizumab in addition to docetaxel until disease progression. After progression, all patients were offered bevacizumab with second-line anticancer therapy in a post-study treatment phase. Patient characteristics were well balanced across treatment arms, with a median age of 54 years (arm B) to 55 years (arms A and C). The majority of patients were ER-positive/PgR-positive.

The median PFS was 8.2 months (arm A), 9.0 months (arm B), and 10.1 months (arm C) ($P = 0.1163$, arm A vs arm B; $P = 0.0061$, arm A vs arm C). When censored for non-protocol treatment prior to progression, the median PFS was 8.1 months (arm A), 9.0 months (arm B), and 10.0 months (arm C) ($P = 0.0450$, arm A vs arm B; $P = 0.0002$, arm A vs arm C). The ORR was 46.4% (arm A), 55.2% (arm B), and 64.1% (arm C) ($P = 0.0739$, arm A vs arm B; $P = 0.0003$ arm A vs arm C). Survival outcomes are presented in **Table 6**. There was no statistical significance in median survival between the treatment arms.

Table 6. Survival Outcomes

	Placebo + Doc (Arm A) N = 241	Bev 7.5 + Doc (Arm B) N = 248	Bev 15 + Doc (Arm C) N = 247	P value* (Arm A vs Arm B)	P value* (Arm A vs Arm B)
1-year survival	76%	81%	84%	0.198	0.02
Median OS (median follow-up 25 months)	31.9 months	30.8 months	30.2 months	0.7198	0.8528

*P value of exploratory nature.

The addition of bevacizumab had limited impact on the safety profile of docetaxel. Serious adverse events were reported in 32.5% (arm A), 37.3% (arm B), and 42.9% (arm C) of patients. Increases in serious adverse events in arm C may have been due to a greater number of docetaxel cycles administered than in the placebo arm. Adverse events leading to death occurred in 2.6% (arm A), 1.6% (arm B), and 1.6% (arm C) of patients. Notable grade 3 adverse events are described in **Table 7**. There was no indication of an increase in gastrointestinal perforation, wound healing, or venous thrombotic events with the addition of bevacizumab.

Table 7. Common Grade 3 Adverse Events

	Arm A	Arm B	Arm C
Neutropenia	17.3%	19.8%	19.8%
Febrile neutropenia	11.7%	15.1%	16.6%
VTE	3.5%	1.6%	1.2%
Hypertension	1.3%	0.8%	4.5%

Despite the lack of a significant improvement in OS, data continue to be collected in an effort to better define median survival in this patient population. Updated PFS and ORR were consistent with earlier analyses and supported 15 mg/kg bevacizumab (arm C) as superior to placebo + docetaxel (arm A). The 7.5 mg/kg bevacizumab arm (arm B) also demonstrated a treatment benefit as compared to placebo + docetaxel (arm A), although the effect was less pronounced.

RIBBON-2, conducted by Brufsky et al, evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for the second-line treatment of HER2-negative MBC.⁵ A total of 684 patients were enrolled and were randomized in a 2:1 fashion to receive bevacizumab or placebo in combination with the investigator's choice of 1 of 4 chemotherapies. Chemotherapy options included a taxane (paclitaxel 90 mg/m²/week for 3 of the 4 weeks; paclitaxel 175 mg/m², nab-paclitaxel 260 mg/m², docetaxel 75-100 mg/m², all given q3wk), gemcitabine (1250 mg/m² on days 1 and 8 q3weeks), capecitabine (2000 mg/m² days 1-14 q3weeks), or vinorelbine (30 mg/m²/week). Bevacizumab or placebo was administered at 10 mg/kg q2weeks or 15 mg/kg q3weeks, depending on the chemotherapy regimen. Patients were treated until disease progression.

Eligible patients were 18 years of age with measurable or non-measurable HER2-negative MBC with 1 prior treatment, excluding the use of prior bevacizumab or another VEGF inhibitor. The primary endpoint was investigator-assessed PFS pooled across all of

the chemotherapy regimens. Secondary endpoints included OS, PFS by individual chemotherapy, and ORR. Patient distributions across treatment types are described in **Table 8**.

Table 8. Treatment Distribution

	Taxane	Gemcitabine	Capecitabine	Vinorelbine
Patients	304 (44.4%)	160 (23.4%)	144 (21.1%)	76 (11.1%)
Bevacizumab	201	108	97	53
Placebo	103	52	47	23

Patient characteristics were well balanced across treatment arms. The median age was 55 years in both the placebo arm and the bevacizumab arm. Of note, visceral disease was present in 70% of patients in the placebo arm and 74% of patients in the bevacizumab arm and triple-negative breast cancer (TNBC) was more frequent in the bevacizumab arm.

At a median follow-up of 15 months, the median PFS was 5.1 months in the placebo arm and 7.2 months in the bevacizumab arm ($P = 0.0072$; HR = 0.78). Progression-free survival was significantly improved for patients receiving bevacizumab for each of the chemotherapy types with the exception of vinorelbine. The bevacizumab + vinorelbine arm may not have reached statistical significance due to the small sample size ($n = 53$). The ORR was 29.6% in the placebo arm and 39.5% in the bevacizumab arm ($P = 0.0193$). Interim analysis of OS was 16.4 months and 18.0 months for the placebo arm and the bevacizumab arm, ($P = 0.3741$) although this represents just 57% of required events.

Across all chemotherapy cohorts, the incidence of bevacizumab-related adverse events was consistent with data from previous studies. Serious adverse events were reported in 17.6% of patients in the placebo arm and 24.5% of patients in the bevacizumab arm. Adverse events leading to discontinuation occurred in 7.2% and 13.3% of the placebo and bevacizumab arms, respectively. Neutropenia occurred more frequently in the bevacizumab arm (14.5% vs 17.7%) as did hypertension (0.5% vs 9.0%).

RIBBON-2 met its primary endpoint with significant improvement in PFS with the addition of bevacizumab to chemotherapies used for the second-line

treatment of metastatic breast cancer. Progression-free survival results were generally consistent across all chemotherapy subgroups (with the exception vinorelbine). The tolerability profile was consistent with previously reported trials.

Neoadjuvant Bevacizumab Use

Neoadjuvant bevacizumab is increasingly being used in conjunction with chemotherapy in the treatment of breast cancer. It is plausible that the use of an antiangiogenic such as bevacizumab may impact surgical outcomes. Golshan et al conducted 2 studies to evaluate the effect of neoadjuvant bevacizumab on surgical events.⁶

The first trial enrolled 28 patients with TNBC who received 4, 3-week cycles of cisplatin (75 mg/m² q3weeks x 12). Surgery was performed 4 weeks after the last chemotherapy treatment. The second trial enrolled 51 patients who received 4, 3-week cycles of cisplatin (75 mg/m² q3weeks x 12)/ bevacizumab (15 mg/kg q3weeks x 3). Surgery was allowed 6 weeks after the last dose of bevacizumab, with bevacizumab not given with the last cycle of neoadjuvant chemotherapy. Postoperatively, patients received doxorubicin and cyclophosphamide (AC) plus bevacizumab or AC/paclitaxel plus bevacizumab.

Patient characteristics between the 2 trials were well balanced with a median age of 50 years in both arms. All patients had an ECOG performance status of 0. In Trial 1, 14% of patients achieved a clinical complete response (cCR), 35% of patients achieved a clinical partial response (cPR), and 35% of patients achieved SD. In Trial 2, 27% of patients achieved a cCR, 53% of patients achieved a cPR, and 18% achieved SD. Breast conserving treatment was used in 46% of patients in Trial 1 and 57% of patients in Trial 2, with 54% and 43% of patients receiving a mastectomy, respectively.

There was no significant difference in the rate of surgical complications between Trial 1 (39%) and Trial 2 (43%) ($P = 0.82$) (**Table 9**). The frequency of toxicities was not significantly different between the 2 trials ($P = 0.81$). Of note, all 8 patients with wound breakdown on Trial 2 required surgical debridement and/or wound vac placement vs 0/2 patients with wound breakdown on Trial 1.

Table 9. Surgical Complications

	Trial 1 N = 28	Trial 2 N = 51	P value
All complications	39%	43%	0.82
Wound breakdown	7%	16%	NS
Hematoma requiring operative intervention	7%	10%	NS
Seroma requiring multiple aspirations	18%	10%	NS
Abscess	7%	0%	NS
Loss of reconstruction	0/5 (0%)	4/8 (50%)	0.10

Surgical complications were common in both preoperative platinum therapy trials in this data comparison, with and without bevacizumab. The data suggest that the use of expanders or implants may be problematic for patients treated with neoadjuvant bevacizumab as there was a trend toward more wound-related events in this group; however, results from randomized controlled studies (CALGB 40603/NSABP B-40) are needed to determine the optimal approach in this setting.

Multi-Kinase Inhibitor-Containing Regimens **Sorafenib**

The TIES (Trials to Investigate the Efficacy of Sorafenib in breast cancer) program comprises 4 phase IIb randomized, double-blind, placebo-controlled screening trials in HER2-negative breast cancer. Gradishar et al presented 1 of the TIES trials that evaluated the efficacy and safety of sorafenib in combination with paclitaxel as first-line therapy in patients with locally recurrent or MBC.⁷

A total of 237 patients with HER2-negative, locally recurrent or MBC were randomized to receive sorafenib (400 mg, orally, BID, continuously) or placebo in combination with paclitaxel (90 mg/m², IV, weekly, 3 weeks on/1 week off). Previous cytotoxic (non-metastatic), endocrine, or radiation therapy was allowed. The majority of patients were enrolled at centers in India, with the United States and Brazil also participating. The primary endpoint was PFS.

The treatment arms were well balanced for patient characteristics with a mean age of 50.6 years in the sorafenib arm and 53.1 years in the placebo arm, the

majority of patients having an ECOG performance status of 0 or 1 and visceral metastatic disease.

Study outcomes are described in **Table 10**. Overall survival data are still maturing.

Table 10. Efficacy Outcomes

	Sorafenib + Paclitaxel (n = 119)	Placebo + Paclitaxel (n = 118)	P value
Median PFS	6.9 months	5.6 months	0.0857
Median TTP	8.1 months	5.6 months	0.0171
Median duration of response	5.6 months	3.7 months	0.0079
ORR	67%	54%	0.0234
CR	8 (7%)	5 (4%)	-
PR	72 (61%)	59 (50%)	-
SD	16 (13%)	32 (27%)	-
Progressive disease	9 (8)	17 (14)	-

Adverse events were similar between the 2 treatment arms with the exception of hand/foot skin reaction (HFSR), which occurred in 55% of the patients in the sorafenib arm and 25% of patients in the placebo arm. Grade 3/4 toxicities (sorafenib arm vs placebo) included HFSR (30% vs 3%), asthenia (7% vs 3%), peripheral neuropathy (6% vs 7%), neutropenia (13% vs 7%), and anemia (11% vs 6%). There were 16 (14%) deaths in the sorafenib arm and 4 (3%) deaths in the placebo arm. In the sorafenib arm, 7 (6%) deaths were due to progressive disease, 2 (2%) deaths were due to adverse events related to treatment (malaria and liver dysfunction), and 7 (6%) deaths were due to adverse events unrelated to treatment. In the placebo arm, 2 (2%) deaths were due to progressive disease, no deaths were due to adverse events related to treatment, and 2 (2%) deaths were due to adverse events unrelated to treatment. The authors noted a number of deaths due to unusual causes such as meningitis, malaria, and pulmonary TB, which occurred in patients enrolled in India and these events may have skewed the PFS outcomes.

A second study (SOLTI-0701), by Baselga et al, evaluated the role of sorafenib + capecitabine in patients with locally advanced or metastatic breast cancer. SOLTI-0701, a multinational (Spain, France, Brazil), double-blind, randomized, placebo-controlled

phase IIb study, enrolled 220 patients with locally advanced or metastatic breast cancer.⁸ Patients had HER2-negative disease, no brain metastases, and fewer than 2 prior chemotherapy regimens. Patients were randomized to receive capecitabine (1000 mg/m², orally, BID, for 14 of every 21 days) + placebo or capecitabine + sorafenib (400 mg, orally, BID, continuously). The primary endpoint was PFS.

Patient characteristics were well balanced across treatment arms with a median age of 55.1 years in the sorafenib arm and 55.4 years in the placebo arm. The majority of patients had received prior chemotherapy for nonmetastatic disease with an anthracycline and approximately half had received chemotherapy for MBC.

The most common grade 3 adverse event was HFSR (**Table 11**). A total of 65% of patients in the sorafenib arm discontinued treatment and 79% of patients in the placebo arm discontinued treatment. Reasons for discontinuation included adverse events (15% vs 7%), progressive disease (45% vs 66%), and death (0% vs 1%) in the sorafenib and placebo arms, respectively. Eight patients in the sorafenib arm and 2 patients in the placebo arm discontinued due to HFSR.

The median PFS was 6.4 months in the sorafenib arm and 4.1 months in the placebo arm ($P = 0.0006$, HR = 0.576). In the sorafenib arm, 1.7% of patients achieved CR and 36.5% of patients achieved PR, for an ORR of 38.3%. In the placebo arm, 0.9% of patients

achieved CR and 29.8% of patients achieved PR, for an ORR of 30.7%. There was no statistical significance in ORR between the 2 treatment arms ($P = 0.1229$).

In both prespecified and exploratory subgroup analyses, combination treatment provided benefit across all categories, with no significant variation by age or hormone receptor status. When patients were analyzed by treatment status, median PFS for first-line patients was 7.6 months and 4.1 months with sorafenib and placebo, respectively ($P = 0.0022$; HR = 0.498). Median PFS for second-line patients was 5.2 months and 4.1 months for sorafenib and placebo, respectively ($P = 0.0339$; HR = 0.652).

The combination of sorafenib + capecitabine resulted in improved PFS in this patient population that was reasonably tolerable with the exception of the percentage of HFSR reported in the combination arm. As demonstrated by both Gradishar et al and Baselga et al, appropriate strategies to prevent or lessen HFSR need to be developed to avoid excessive toxicity. A phase III registration trial with sorafenib + capecitabine in breast cancer is planned.

Sunitinib

A trial by Barrios et al, evaluated the efficacy and safety of sunitinib, an oral, multi-targeted tyrosine kinase inhibitor in the treatment of breast cancer.⁹ Sunitinib has demonstrated single-agent activity in heavily pretreated patients. This phase III study randomized

Table 11. Common Adverse Events

	Sorafenib + Capecitabine All Grades	Sorafenib + Capecitabine Grade 3/4	Placebo + Capecitabine All Grades	Placebo + Capecitabine Grade 3/4
HFSR	89%	45%	63%	13%
Diarrhea	53%	5%	30%	5%
Mucosal inflammation	32%	1%	19%	4%
Asthenia	24%	0%	27%	2%
Rash	22%	3%	8%	0%
Hypertension	17%	1%	12%	2%
Fatigue	14%	2%	13%	1%
Musculoskeletal pain	12%	2%	6%	0%
Dyspnea	12%	5%	12%	4%
Neutropenia	11%	5%	4%	3%

patients with previously treated HER2-negative advanced breast cancer to receive sunitinib 37.5 mg continuous daily dose or capecitabine 1000-1250 mg/m² BID days 1-14 q3weeks. The primary endpoint was a 33% proportional increase in median PFS in the intent-to-treat (ITT) population. At the first planned interim analysis the independent monitoring committee recommended discontinuing enrollment due to the futility of reaching the primary analysis.

At the time of analysis, 482 patients from 119 centers worldwide were enrolled. The patient characteristics were well balanced across treatment arms, with a mean age of 53 years in the sunitinib arm and 52 years in the capecitabine arm. The majority of patients were hormone receptor-positive and approximately one-third of patients had TNBC.

The median PFS was 2.8 months and 4.2 months in the sunitinib and capecitabine arms, respectively ($P = 0.002$; HR = 1.47). The ORR also favored capecitabine at 11.3% vs 16.4% ($P = 0.11$), as did the CBR at 19.3% vs 27.0% ($P = 0.05$). The median duration of response and OS was 6.9 months and 15.3 months in the sunitinib arm and 9.3 months and 24.6 months in the capecitabine arm.

Serious adverse events were reported in 30% of patients receiving sunitinib and 17% of patients receiving capecitabine. Selected grade 3/4 adverse events are presented in **Table 12**. Dose reductions were required in 28% of patients in the sunitinib arm and 35% of patients in the capecitabine arm. Discontinuation due to adverse events occurred in 15% of patients in the sunitinib arm and 9% of patients in the capecitabine arm. Discontinuation due to an adverse event related to study drug occurred in 11% of patients receiving sunitinib and 5% of patients receiving capecitabine.

Table 12. Selected Grade 3/4 Adverse Events

	Sunitinib	Capecitabine
Diarrhea	6%	5%
Fatigue	7%	1%
HFSR	8%	16%
Hypertension	4%	0%
Neutropenia	11%	4%
Thrombocytopenia	8%	1%

The primary endpoint of PFS was not met in this study and there was no significant difference in OS. Although some patients did receive benefit from sunitinib, sunitinib was not found to be superior to capecitabine in this setting. The tolerability of each agent was similar to previously reported safety profiles. Phase III studies with sunitinib in combination with chemotherapy and other agents are ongoing in advanced breast cancer.

HER2 Targeted Regimens

Metastatic Breast Cancer

Both lapatinib and trastuzumab have demonstrated clinical benefit in the treatment of breast cancer. In addition, preclinical data indicate a synergistic effect between lapatinib and trastuzumab. Blackwell et al conducted a phase II study comparing lapatinib to lapatinib + trastuzumab in women with HER2-positive breast cancer that had progressed on previous anthracyclines, taxane, and trastuzumab therapy.¹⁰ These data represent an updated survival analysis.

This study enrolled 296 women who were randomized to lapatinib 1500 mg/day PO (n = 148) or lapatinib + trastuzumab 2 mg/kg IV weekly (n = 148). There was a planned crossover from the lapatinib arm to the lapatinib + trastuzumab combination arm. The majority of patients had an ECOG performance status of 0 or 1 and patients in both arms had received a median of 3 prior trastuzumab-containing regimens. A total of 77 (52%) patients crossed over from the lapatinib arm to the lapatinib + trastuzumab arm, including 20 at week 4, 20 at week 8, and 37 after week 8.

It was previously reported that the ORR was 6.9% and 10.3% for the lapatinib arm and lapatinib + trastuzumab arm, respectively ($P = 0.46$; HR = 1.5). Complete response + PR was achieved in 12.4% of patients in the lapatinib arm and 24.7% of patients in the lapatinib + trastuzumab arm ($P = 0.01$). Median PFS was also significant in favor of lapatinib + trastuzumab at 8.1 weeks and 12.0 weeks ($P = 0.008$; HR = 0.73). At the previous planned interim analysis, there was a 2.0-month improvement in median OS, which was not significant ($P = 0.106$; HR = 0.75). The updated OS data are presented in **Table 13**.

Table 13. Overall Survival (Intent-to-Treat)

	Lapatinib n = 145	Lapatinib + Trastuzumab n = 146	P value	HR
Median OS	9.5 months	14 months	0.026	0.74
6-month OS	70%	80%	-	-
12-month OS	41%	56%	-	-

The majority of adverse events were grade 1/2. The only grade 3/4 event that occurred in $\geq 5\%$ of patients was diarrhea, with 7% of patients in the lapatinib arm and 8% of patients in the lapatinib + trastuzumab arm affected. Cardiac adverse events are described in **Table 14**.

Table 14. Cardiac-Related Adverse Events

	Lapatinib	Lapatinib + Trastuzumab
Number of grade 3/4 events	1	3
Number of serious adverse events	3	10
Number of events related to drug	2	10
Number of fatal events	0	1 (PE)

These updated OS data indicate that there is a significant OS benefit with lapatinib + trastuzumab as compared to lapatinib alone. Overall, there was a 26% reduction in the risk of dying with the addition of trastuzumab. This survival benefit was observed despite 52% of patients crossing over from the lapatinib arm to the lapatinib + trastuzumab arm. The authors concluded that these data further strengthen the NCCN guidelines that include combination therapy with lapatinib + trastuzumab as a preferred regimen for trastuzumab-exposed breast cancer. An ongoing phase III study (ALTT0) is further characterizing the utility of lapatinib \pm trastuzumab for the treatment of breast cancer.

Adjuvant Therapy

BCIRG-006 also aimed to further characterize the role of trastuzumab with or without an anthracycline-based chemotherapy regimen, comparing 2 experimental arms, AC \rightarrow TH (doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab) and TCH (docetaxel, carboplatin, and trastuzumab) with 1 comparator arm, AC \rightarrow T (doxorubicin and

cyclophosphamide followed by docetaxel), in women with HER2-positive early breast cancer. Outcomes from BCIRG-006 have been previously been reported, with this update by Slamon et al representing the third planned efficacy analysis at a median follow-up of 65 months.¹¹ Crossover was allowed, with 23 patients (2.1%) randomized to AC \rightarrow T crossing over to receive trastuzumab, leaving approximately 98% of the control arm for this analysis.

Patients were well balanced across all 3 treatment arms. Of note, 29% of patients in each arm were node negative. The primary endpoint was DFS (**Table 15**).

Table 15. Survival Outcomes

	Arm A AC \rightarrow T	Arm B AC \rightarrow TH	Arm C TCH	P value (A vs B)	P value (A vs C)
DFS	75%	84%	81%	< 0.001	0.04
Number of DFS events	257	185	214	< 0.001	0.21
OS	87%	92%	91%	< 0.001	0.038
Number of deaths	141	94	113	< 0.001	0.038
DFS, node negative only	85%	93%	90%	0.003	0.057
OS, node negative only	93%	97%	96%	0.02	0.11
DFS, node positive	71%	80%	78%	0.0003	0.013
DFS, ≥ 4 positive nodes	61%	73%	72%	0.002	0.002

A total of 2,948 patients were available for topoisomerase IIa (TOP2A) amplification analysis. Disease-free survival among patients with no TOP2A coamplification was 70%, 83%, and 80% for arm A, arm B, and arm C, respectively. For patients with TOP2A coamplification, DFS was 83%, 85%, and 82% for arm A, arm B, and arm C, respectively. There were an additional 29 DFS events in the TCH arm. However, more grade 3/4 congestive heart failure (CHF) and more treatment-related leukemia was reported in the AC \rightarrow TH arm.

Adverse events that occurred significantly less often in the AC \rightarrow TH arm included anemia and thrombocytopenia. Adverse events that occurred significantly less often in the TCH arm included arthralgia, myalgia, stomatitis, vomiting, sensory neuropathy, motor neuropathy, nail changes,

neutropenia, and leukopenia. The treatment arms were well balanced for cardiac risk factors. No cardiac-related deaths occurred in the study, to date. Patients experiencing > 10% lost of LVEF included 11% in the AC→T arm, 19% in the AC→TH, and 9% in the TCH arm ($P < 0.001$, arm A vs arm B; $P = 0.19$, arm A vs arm C).

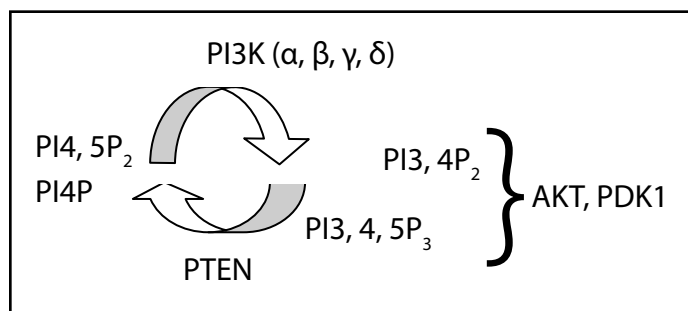
This third analysis of BCIRG-006 demonstrates that trastuzumab provides a similar and significant advantage for DFS and OS when used in conjunction with anthracyclines-based (AC→TH) and nonanthracycline-based (TCH) therapy. This advantage is seen in both high-risk and low-risk patients. The acute and chronic toxicity profile of TCH was better than AC→TH across almost all parameters measured.

Novel Agents

WR Sellers presented an overview of the science behind several new agents in clinical trials for the treatment of breast cancer.¹² The phosphoinositide-3 kinase pathway (PI3K) is a key oncogenic pathway in breast cancer where direct mutation of PIK3 α , loss-of-function of PTEN, and amplification of HER2 can all result in constitutive pathway activation. The PI3K pathway integrates extracellular growth factor signals with nutrient and other environmental conditions such as hypoxia to enact directed changes in cell proliferation, survival, and migration, in addition to the regulation of key metabolic pathways such as glucose homeostasis. Constitutive activation of the PI3K pathway can lead to unrestricted proliferation and cell survival.

One key step in the identification of potential targets and therapeutic agents that work within the PI3K pathway is the identification of the impact of specific PI3K alterations and mutations (**Figure 1**).

Figure 1.



Point mutations in PI3K can change PI3K from a regulatory enzyme to a constitutive enzyme. Research has demonstrated that, in cancer cell lines, PI3K α mutants do not invariably activate AKT, nor do they necessarily require AKT. Further investigation found that PIK3 mutants are driven by PIK3 mutations and require PI3K to continue growth, making PI3K a potential target for cancer treatment. PI3K knockout cells were created and transduced with activator TK. Transduction was not possible in HER2 cells, which required the presence of the α isoform of PI3k.

In PTEN null cells, PTEN suppression is removed and the downstream AKT and PDK are activated. Researchers hypothesized that identifying the specific isoform of PI3K required for AKT activity in the absence of PTEN would allow for the development of specific therapeutic agents. Colony formation assays demonstrated that while PI3K α is not required for AKT activity in PTEN null cells, the loss of PI3K β attenuated AKT, downstream signaling, and cell growth. However, Sellers cautioned that additional studies have indicated that the specific PI3K isoform required may differ by cell and tissue type. Additional studies demonstrated that both the loss of PTEN and constitutive activation of PI3K α could each induce resistance to trastuzumab. Studies are ongoing to elucidate why, if HER2 signaling depends on PI3K α , loss of PTEN can also create trastuzumab resistance.

Given that PIK3 α mutations confer dependence on PI3K α , PTEN loss of function confers dependence on PI3K β , and HER2 amplification confers dependence on PI3K α , Sellers et al examined over 1,000 cell lines to identify PI3K mutations that predict for sensitivity or insensitivity to PI3K α selective inhibitor compounds. BEZ235 was identified as an inhibitor of all isoforms of PI3K as well as mTOR. In breast cancer cell lines tested, those cells with HER2 amplification or PI3K α mutations were BEZ235-sensitive, undergoing apoptosis, while cells with PTEN mutations or deletions were BEZ235-resistant. A phase I trial with BEZ235 in breast and colon cancer is underway. A significant number of patients have achieved partial metabolic response by PET scan, including 1 patient who had received 13 prior treatments.

BKM120, a type I PI3K inhibitor is also in phase I clinical trials. Partial response and tumor shrinkage has been demonstrated, with consistent metabolic response at

higher doses. Additional work continues to identify specific PI3K pathway genetic alterations that elicit specific target dependencies.

Conclusion

There was a wealth of state-of-the-art information presented at the 32nd Annual San Antonio Breast Cancer Symposium for cancer researchers, clinicians, and patients to take back and incorporate into practice. The 33rd Annual San Antonio Breast Cancer Symposium will be held December 8-12, 2010. Additional information can be obtained at <http://www.sabcs.org>.

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