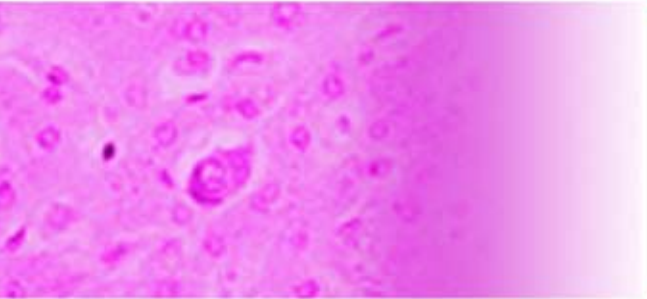


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New Frontiers in Biologic Therapy: ASCO Breast Cancer Therapy Update

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Table of Contents *(click the section you wish to view)*

Introduction 1

Advancements in Endocrine Responsive Disease 1

EGFR/HER Inhibition – New Approaches to a Proven Target..... 1

Small Molecules, Big Bang 2

Targeted Intracellular Drug Delivery With Trastuzumab..... 2

Anti-VEGF as First-Line Therapy in Advanced or Metastatic Breast Cancer..... 3

Further Evidence Supporting First-Line Bevacizumab + Chemotherapy for Metastatic Breast Cancer 3

Emerging Tyrosine Kinase Inhibitor Targets – Beyond EGFR Family 4

Dasatinib Demonstrates Single-Agent Activity in Patients With Advanced Breast Cancer..... 4

PARP Inhibitors – The Next Major Breakthrough for MBC? 5

BSI-201 Synergy With Conventional Chemotherapy 5

Olaparib Exhibits Dose-Dependent Tolerability and Effectiveness..... 6

Cytotoxic Chemotherapy – A Mainstay of Treatment 6

Molecular and Genetic Profiling – The Magic 8 Ball?..... 7

Prognosis and 10-Year Survival With 70-Gene Assay..... 7

References..... 8

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Target Audience

The target audience for the program includes medical, surgical, and radiation oncologists, as well as allied oncology healthcare professionals charged with the care of patients with breast cancer.

Learning Objectives

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

- Summarize the efficacy and safety results from key trials introducing use of novel agents and/or mechanisms
- Select appropriate chemotherapy/biologic combination regimens based on current understanding of clinical markers, efficacy, and safety profiles
- Describe advances in the development and integration of biologic therapies for the management of patients with breast cancer in novel disease settings and combinations
- Evaluate emerging new therapeutic options for treatment of breast cancer by reviewing ongoing and planned clinical trials

Statement of Need

Significant improvements have occurred in the management of women with breast cancer. As many of these advances are incorporated into the formulation of treatment guidelines, their dissemination to the medical oncology community is critical for their adaptation and potential to impact 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.

Media: Newsletter

Estimated time to complete activity: 1.5 hours

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Introduction

The 45th Annual Meeting of the American Society of Clinical Oncology (ASCO) was held in Orlando, Florida from May 29-June 2, 2009. The ultimate objective was to “focus on personalizing cancer care”. Experts from around the world met to announce and consider new experimental and clinical breast cancer data. This newsletter will highlight both adjuvant and metastatic disease information presented at the meeting, including significant findings in HER-2-based therapies, EGFR-based therapies, antiangiogenic-based therapies, and triple negative disease, as well as therapies under investigation.

Advancements in Endocrine Responsive Disease

Tumor genesis and progression in breast cancer is, in a majority of cases, influenced by estrogen receptor (ER) expression. Employing ER inhibition in ER positive breast cancer effectively increases cure rates in early breast cancer, improves patient outcome in advanced breast cancer, and prevents breast cancer in high-risk patients. Unfortunately, resistance to ER inhibition remains problematic, despite the introduction of additional anti-ER therapies, such as anastrozole and fulvestrant. However, emerging evidence illuminating ER biology and resistance pathways suggest molecular crosstalk between ER and other growth factor signaling pathways.¹ Therapies that disrupt crosstalk between ER and other growth factor pathways represent a promising approach to overcome resistance in breast cancer.

Epidermal growth factor receptor (EGFR, also known as HER) is a family of four receptor subtypes (EGFR-1/HER-1, EGFR-2/HER-2, EGFR-3/HER-3, EGFR-4/HER-4) that exist on the surface of cells and provide a binding site for ligands such as epidermal growth factor. Ligand attachment results in EGFR homodimerization or heterodimerization and tyrosine kinase signaling, triggering downstream activity that results in DNA synthesis and cellular proliferation. Mutations in HER also may result in continuous tyrosine kinase activation, thus predisposing cells to uncontrolled cell division. HER overexpression is a common finding in many tumor types, including breast cancer.

Small-molecule EGFR-1 tyrosine kinase inhibitors such as gefitinib may effectively inhibit EGFR-associated cellular proliferation in ER-positive breast cancer. Originally evaluated by Cristofanelli and colleagues, patients were randomized to receive anastrozole +/- gefitinib. Presented

during the American Society of Clinical Oncology annual meeting in 2008, the results showed that those who received the combination treatment had a longer median progression-free survival (PFS) versus those who received endocrine therapy alone (14.5 vs 8.2 months). Further examining the role of endocrine therapy +/- gefitinib, Carlson and collaborators presented a phase II study combining gefitinib with endocrine therapy in patients with metastatic estrogen receptor positive and/or progesterone receptor positive (ER+/PR+) breast cancer not previously treated with endocrine therapy.² Patients received 250 mg oral gefitinib once daily in combination with 1 mg oral anastrozole once daily (AG, n = 73) or gefitinib 250 mg with intramuscular fulvestrant once every 4 weeks (FG, n = 69). Clinical benefit was defined as complete response (CR) plus partial response (PR) plus stable disease (SD) for at least 6 months as described by Response Evaluation Criteria in Solid Tumors (RESIST). For the AG treatment arm, clinical benefit was observed in 42% of patients while 3% experienced CR, 21% PR, and 18% stable disease. Results from the FG arm for clinical benefit were 38% while 4% experienced CR, 17% PR, and 17% stable disease. Treatment termination for disease progression (74% versus 75%) and toxicity (7% and 10%) was similar for AG and FG, respectively. Grade 3-5 toxicities occurring in $\geq 5\%$ of patients were diarrhea (5% and 13%), SGOT elevation (7% and 8%), and infection without neutropenia (1% and 6%) for AG and FG, respectively. While demonstrating similar activity to FG, gefitinib plus anastrozole was less toxic and appears to be a better combination for phase III evaluation.

EGFR/HER Inhibition – New Approaches to a Proven Target

Therapies targeting HER-2 in breast cancer have benefited patients for years. Adjuvant trastuzumab has an extensive evidence base with more than 13,000 patients treated in 4 major trials.³ Over time, however, patients are relapsing despite adjuvant trastuzumab. To improve outcomes in HER-2 cancer, we must better understand the biology of the disease, develop new agents, and develop new combinations of agents.³

Studies describing combined inhibition of EGFR-1 and HER-2 with BIBW 2992 and combination therapy with neratinib plus trastuzumab were presented, as was a study utilizing trastuzumab as a transport molecule for the cytotoxin DM1.



Small Molecules, Big Bang

While the first small molecule tyrosine kinase inhibitors are active against a single receptor subtype, subsequent agents inhibit tyrosine kinase activity across multiple receptors. Lapatinib, the first of these multikinase inhibitors, exerts reversible inhibition of EGFR and HER2 kinases while BIBW-2992 and neratinib (described below) are irreversible inhibitors. While the clinical significance of this difference is not known, the new TKIs appear promising. It is postulated this irreversible inhibition of multiple EGFR subtypes will optimally inhibit tumor cell proliferation and survival and overcome resistance to first generation tyrosine kinase inhibitors. Preliminary results of an ongoing phase II study evaluating the efficacy of BIBW 2992 were reported by Hickish and colleagues.⁴

To date, 41 patients with advanced metastatic HER-2 positive disease who have failed trastuzumab therapy have received 50 mg oral BIBW 2992 once daily until disease progression. Thus far, of 34 patients evaluated for response, a partial response has been observed in 4 patients. Consistent with toxicities observed with other EGFR tyrosine kinase inhibitors, cutaneous adverse events and diarrhea were most common. While these events were noted as manageable, grade 3 cutaneous reactions and diarrhea occurred in 4 and 9 patients, respectively.

The second generation tyrosine kinase inhibitor neratinib (HKI-272), which also irreversibly inhibits EGFR-1 and HER-2 tyrosine kinase, was studied in combination with trastuzumab and results were reported by Swaby and collaborators.⁵

In part 1 of this 2-part phase II trial designed to assess 16-week PFS, patients received either 160 mg or 240 mg oral neratinib once daily plus trastuzumab 4 mg/kg intravenous loading then 2 mg/kg weekly; in part 2, patients received 240 mg oral neratinib once daily with 2 mg/kg intravenous trastuzumab weekly.

All patients had stage IIIB, IIIC, or IV breast cancer, were HER-2 positive, and had progressed following ≥ 1 trastuzumab-containing cytotoxic chemotherapy regimen. A total of 45 patients were enrolled in the study, and 33 were evaluable for efficacy. Of the patients with metastatic disease, 46% received 1 prior trastuzumab-based regimen while 51% received ≥ 2 prior regimens containing trastuzumab. Progression-free survival at 16 weeks was observed in 45% of patients, and the median PFS was 16 weeks. The overall response rate (ORR) was 29%.

No dose-limiting toxicities were reported; however, 2 patients reported adverse events leading to neratinib withdrawal (1 grade 2 diarrhea, 1 grade 3 angioedema). The most common adverse events included diarrhea (91%), nausea (51%), anorexia (40%), vomiting (38%), and asthenia (29%). Grade 3 and 4 adverse events were gastrointestinal in nature and most often were diarrhea (16%). The median onset of diarrhea was 2 days and symptoms responded to standard antidiarrheals.

The investigators concluded that the combination of neratinib with trastuzumab demonstrated antitumor activity without significant or unexpected toxicity in patients with advanced breast cancer with progression following trastuzumab therapy.

Despite the small size and preliminary nature of these 2 studies, the tolerability and effectiveness of second generation tyrosine kinase inhibitors in advanced breast cancer appears promising.

Targeted Intracellular Drug Delivery With Trastuzumab

Despite the positive impact trastuzumab therapy has made in the treatment of metastatic breast cancer, additional improvements are needed. A humanized monoclonal antibody directed against HER-2, trastuzumab, is an excellent candidate for targeted intracellular drug delivery when conjugated with cytotoxic agents, such as the anti-microtubule derivative DM1 (T-DM1). Preliminary results of 1 phase II study describing this “smart bomb” strategy were presented by Vogel and co-investigators.⁶ In this study, 112 patients with progressive HER-2 positive metastatic breast cancer despite receiving HER-2 targeted therapy were treated with 3.6 mg/kg intravenous T-DM1 every 3 weeks. Primary objectives for this trial were assessment of ORR and of safety and tolerability. All patients had previously received trastuzumab for an average of 18 months, and 60% of patients had previously received lapatinib, an orally active EGFR-1 and HER-2 tyrosine kinase inhibitor, for an average of 6 months. When confirmed by an independent review facility, an ORR (CR + PR per RECIST) was observed in 25% (0% and 25%, respectively) of patients. HER-2 status was strongly correlated with objective response (OR). In the 75 patients with HER-2 status confirmed by a central lab, 32% objectively responded, and 44% clinically benefited (CR + PR + SD ≥ 6 months) from the regimen. Of interest, there appeared to be no loss of activity in patients who received prior lapatinib therapy. This subpopulation experienced a 23.9% OR as assessed by the independent review facility.

While discussing this poster, Dr Mackey of Cross Cancer Institute pointed out that patients experienced no dose-limiting cardiotoxicity, transient thrombocytopenia, and that TDM-1 appears less toxic than taxane/trastuzumab combination therapy.⁷ The most common grade 3/4 toxicity was thrombocytopenia and occurred in 7.1% of patients.

Anti-VEGF as First-Line Therapy in Advanced or Metastatic Breast Cancer

Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), one of the most potent proteins supporting the formation of new capillaries surrounding the tumor. The combination of a VEGF inhibitor, such as bevacizumab, with cytotoxic chemotherapy represents an attractive therapeutic option that provides direct cytotoxicity with reduced tumor growth and metastasis via angiogenesis inhibition. Two large phase III trials previously demonstrated that bevacizumab combined with weekly paclitaxel or docetaxel as first-line therapy for metastatic breast cancer improved PFS compared with either taxane alone.^{8,9}

Dr Dickler of the Memorial Sloan-Kettering Cancer Center (Discussion at ASCO) stated that the ECOG 2100 trial comparing weekly paclitaxel to paclitaxel + bevacizumab as initial therapy for metastatic breast cancer set the standard for evaluating bevacizumab in this setting.^{8,10} Although the combination did not result in an increase in overall survival (OS), the significant improvement in PFS (11.8 months for combination versus 5.9 months for paclitaxel alone) propelled the combination regimen to first-line therapy for advanced breast cancer. Likewise, PFS data presented in the AVADO trial by Miles and collaborators in 2008 investigating docetaxel + bevacizumab as first-line therapy in patients with locally recurrent or metastatic breast cancer were significantly improved compared to docetaxel alone. Mature OS data from this study are widely anticipated.⁹

In the preclinical setting, ixabepilone, a microtubule stabilizing agent plus bevacizumab demonstrated greater activity than paclitaxel plus bevacizumab in human tumor models.¹¹ Ixabepilone, a first in class epothilone B analog, demonstrates reduced susceptibility to the activity of drug efflux pumps compared with taxanes. This attribute may explain the enhanced anti-angiogenesis and antitumor effect observed with ixabepilone in combination with anti-angiogenesis agents observed in tumor models. In addition, ixabepilone has demonstrated activity as a single agent in early and metastatic breast cancer and in combination with capecitabine for patients with metastatic breast cancer.¹²⁻¹⁹

Further Evidence Supporting First-Line Bevacizumab + Chemotherapy for Metastatic Breast Cancer


Results of a large phase III study by Robert and collaborators again show the addition of bevacizumab to standard first-line chemotherapy regimens used to treat metastatic breast cancer results in statistically significant improvement in PFS.²⁰

ECOG 2100 and the AVADO study demonstrated that bevacizumab in combination with first-line taxanes improved PFS; RIBBON-1 was designed to demonstrate the clinical benefit of combining bevacizumab with other chemotherapy used in metastatic breast cancer. Patients were randomized in 2:1 ratio to receive 15 mg/kg bevacizumab every 3 weeks (B) + chemotherapy or placebo (pl) + chemotherapy. Chemotherapy consisted of either 2000 mg/m² capecitabine (Cap) daily for 14 days, taxane (T) (260 mg/m² nab-paclitaxel or 75 or 100 mg/m² docetaxel) every 3 weeks, or anthracycline (Ant) based chemotherapy every 3 weeks. At progression, all patients were eligible for B with second-line chemotherapy. The patients receiving capecitabine with or without placebo were analyzed as a separate cohort from those receiving a taxane or anthracycline due to negative results with capecitabine + bevacizumab in a prior study involving a different population of heavily pretreated metastatic breast cancer patients.

RIBBON-1 enrolled 1,237 patients with locally recurrent, HER-2 negative breast cancer who had received no prior cytotoxic therapy for MBC (Cap, 615; T or Ant, 622). Outcome as assessed by an independent review committee found a statistically significant improvement in PFS and ORR when bevacizumab was added to chemotherapy (Table 1), but no difference in median or overall survival. These results were consistent regardless of the chemotherapy utilized.

Table 1

	Capecitabine		Taxane or Anthracycline	
	Placebo	Bevacizumab	Placebo	Bevacizumab
PFS (months)	6.2	9.8	8.3	10.7
	P = 0.0011; HR 0.68 (0.54-0.86)		P = 0.04; HR 0.77 (0.6-0.99)	
ORR (%)	23.6	35.4	37.9	51.3
	P = 0.0097		P = 0.0054	



In terms of safety, grade ≥ 3 proteinuria and hypertension, both known to be associated with bevacizumab, were increased in all bevacizumab groups and were not unexpected. Patients receiving a taxane had increased bleeding events, febrile neutropenia, and neutropenia. Importantly, there was no increase in treatment-related mortality in any group.

According to Dr Robert, RIBBON-1 provides a third randomized phase III trial demonstrating the efficacy and safety of combining bevacizumab with first-line chemotherapy, including non-taxane containing regimens.

Dr Miller followed Dr Robert with a discussion on the data.²¹ Bevacizumab, she said, is clearly an important component of initial chemotherapy for HER-2 negative breast cancer, increasing response rate and prolonging PFS. While she reminded that OS was not improved in any of the 3 trials, the studies were not powered to detect a difference in this endpoint, and suggested that a meta-analysis of these trials may help clarify.

Encouraging clinical activity and safety results with first-line combination ixabepilone + bevacizumab compared to paclitaxel + bevacizumab for metastatic breast cancer in 122 patients who had not received chemotherapy for locally advanced or metastatic breast cancer were reported by Rugo and co-investigators.²² Patients received 16 mg/m² intravenous ixabepilone on days 1, 8, and 15 every 28 days with 10 mg/kg bevacizumab intravenous every 2 weeks (Arm A, n = 45), 40 mg/m² intravenous ixabepilone every 3 weeks for 4 cycles then reduced to 32 mg/m² with 15 mg/kg intravenous bevacizumab every 3 weeks (Arm B, n = 45), or 90 mg/m² intravenous paclitaxel once weekly; 3 weeks on then 1 week off, with 10 mg/kg intravenous bevacizumab every 2 weeks (Arm C, n = 32). Treatment continued until disease progression or unacceptable toxicity occurred.

Overall response rates (CR + PR) were similar across all 3 arms, with 50% for Arm A (4% CR, 46% PR), 71% for Arm B (2% CR, 69% PR), and 56% for Arm C (9% CR, 47% PR). These rates compare favorably with the 49% historical response rate observed with paclitaxel + bevacizumab.⁸ Grade 3 or 4 neutropenia was most common in Arm B (55%) compared with Arms A (11%) and C (22%), although febrile neutropenia was low in all arms (2% Arm B, 0% arms A and C). Peripheral neuropathy rates were similar in Arms A, B, and C (18%, 22%, and 25%) and also compare favorably with the 25% peripheral response rate previously observed with paclitaxel + bevacizumab. Notably, the toxicity profiles of these 2 agents do not overlap, thus enhancing patient

tolerability. These preliminary efficacy results suggest that combination therapy with ixabepilone + bevacizumab may represent an attractive treatment option for patients in the future. Final PFS data are anticipated in 2010, and results of CALGB 40502, an ongoing phase III cooperative group trial comparing ixabepilone + bevacizumab with nab-paclitaxel + bevacizumab and paclitaxel + bevacizumab, are forthcoming.²³

Further insight into the role of bevacizumab in metastatic breast cancer therapy will be provided by the E1105 trial, randomizing patients with HER-2 positive breast cancer to trastuzumab, paclitaxel, and carboplatin, with or without bevacizumab.²⁴ Additionally, the CALGB 40503 study randomizing patients to endocrine therapy (letrozole or tamoxifen) with or without bevacizumab will help elucidate the role of this combination.²⁵ RIBBON-3, currently in concept only, is designed to determine the optimal duration of therapy.

Emerging Tyrosine Kinase Inhibitor Targets – Beyond EGFR Family

Src tyrosine kinase is a messenger in numerous intracellular pathways. It plays a key role in signaling from ER and HER-2 receptors, and pathways involved in osteoclast function in normal bone as well as bone metastases.²⁶ Elevated Src expression has been demonstrated in breast cancer, and therapeutic agents that target and interrupt Src signaling may disrupt tumor growth. Preclinical data suggest that dasatinib, an orally active dual inhibitor of BCR/ABL and Src tyrosine kinase, may effectively inhibit breast tumor growth, metastasis, and osteoclast activity.²⁷⁻²⁹

Dasatinib Demonstrates Single-Agent Activity in Patients With Advanced Breast Cancer

A phase II study evaluating dasatinib in patients with advanced ER+/PR+ breast cancer was presented by Mayer and colleagues.³⁰ Seventy patients with HER-2 amplified or ER+/PR+ advanced breast cancer with progression following chemotherapy with taxanes and/or anthracyclines were initially treated with 100 mg oral dasatinib twice daily on a continuous schedule. Due to poor tolerability as evidenced by fluid retention, fatigue, and GI toxicity in the first 23 patients enrolled, the protocol was amended to allow a starting dose of 70 mg twice daily. Of 69 response evaluable patients, there were 3 partial responders and 6 patients with stable disease lasting at least 16 weeks, for an overall disease control rate of 13% (9/69). Notably, all 9 controlled tumors were ER+/PR+ and 2 were also HER-2-amplified, thus translating to a 17% (9/54) disease control rate in patients with fully evaluable disease.

The most common drug-related adverse events in the 70 mg group included fatigue/asthenia (57%), diarrhea (47%), headache (34%), nausea (34%), abdominal pain (32%), pleural effusion (26%), rash (23%), and dyspnea (21%). The most frequent drug-related grade 3-4 adverse events in the 70 mg group included fatigue/asthenia (15%) and dyspnea (6%). Grade 3-4 laboratory abnormalities were limited to hypophosphatemia (100 mg bid = 9%, 70 mg bid = 2%), but were otherwise uncommon.

Twice-daily dasatinib monotherapy was active in this pretreated population with ER+/PR+ breast cancer. Ongoing studies combining better tolerated once-daily dasatinib with hormonal therapies will further clarify its therapeutic potential.

PARP Inhibitors – The Next Major Breakthrough for MBC?

The poly(ADP-ribose) polymerase (PARP) enzyme represents an important new research focus in metastatic breast cancer therapy. One of the myriad functions of PARP is to repair single-strand DNA breaks induced by DNA damaging agents such as chemotherapy or radiation. In healthy cells, BRCA1/BRCA2 and PARP work in unison to repair DNA damage. However, in tumor cells with mutated BRCA1/BRCA2, as found in about 5% of breast cancer cases in the United States, PARP is the primary means of DNA repair.^{31,32} Agents that inhibit PARP, therefore, should preferentially kill tumor cells deficient in BRCA1/BRCA2, while causing minimal damage to tissue³² with normal levels of these proteins. Furthermore, PARP inhibitors augment the cytotoxicity of DNA-damaging agents and radiation, making them an attractive addition to chemotherapy regimens.³³

Women with triple negative breast cancer (TNBC), whose tumors lack receptors for estrogen, progesterone, and HER-2, share clinical and pathologic features with BRCA1 related breast cancers.^{31,34} BRCA function may be lost in TNBC, and BRCA1 related cancers are triple negative in approximately 80% of cases.³¹ Gene expression studies show PARP-1 to be upregulated in triple negative tumors, suggesting that PARP may be a good target for these otherwise invisible tumors. Due to both the aggressive nature of TNBC and limited therapeutic options, 30% of patients with these tumors develop metastases. Once diagnosed with metastatic breast cancer, PFS is less than 4 months with chemotherapy and median OS is 13 months for patients with TNBC.³⁴

BSI-201 Synergy With Conventional Chemotherapy

O'Shaughnessy and colleagues reported improved OS and PFS for women with TNBC when the PARP inhibitor BSI-201 was given in combination with gemcitabine/carboplatin compared with chemotherapy alone.³⁴

The combination of gemcitabine and carboplatin was chosen, O'Shaughnessy explained, due to preclinical evidence suggesting synergy between the 2 agents resulting in double strand DNA breaks and intrastrand DNA cross links, repair of which relies in part on BRCA1/BRCA2. Additionally, the gemcitabine+carboplatin combination has demonstrated activity in metastatic breast cancer with response rates of 21-53%. Finally, BSI-201 was shown to potentiate the antitumor effects of both carboplatin and gemcitabine in TNBC cells.

A total of 123 patients in this randomized phase II study received 1000 mg/m² intravenous gemcitabine and intravenous carboplatin (AUC = 2) on days 1 and 8, with or without 5.6 mg/kg intravenous BSI-201 on days 1, 4, 8, and 11 every 21 days. More than 50% of patients had received prior adjuvant chemotherapy and approximately 40% received previous therapy for metastatic disease. The objectives of this study were to evaluate BSI-201 in combination with gemcitabine/carboplatin (G/C) in subjects with metastatic TNBC.

Gene expression studies, evaluated in 50 patients, verified that PARP-1 was upregulated in the majority of patients. The combination of BSI-201 with gemcitabine+carboplatin tripled both the ORR (48% versus 16%, $P = 0.002$) as well as the clinical benefit rate (62% versus 21%, $P = 0.0002$). Progression-free survival increased from 3.3 months to 6.9 months (HR = 0.342, $P < 0.0001$), and OS increased from 5.7 months to 9.2 months (HR = 0.348, $P = 0.0005$). The frequency and nature of hematologic and non-hematologic adverse events did not differ between arms, nor was there a difference in the need for dose reduction. While these findings are significant, a phase III study in this patient population planned to begin in summer 2009 will further elucidate the role of BSI-201.



Olaparib Exhibits Dose-Dependent Tolerability and Effectiveness

In a separate phase II trial, the PARP inhibitor olaparib demonstrated activity in patients confirmed as BRCA1/BRCA2 carriers with advanced refractory breast cancer.³²

In this study presented by Dr Tutt, olaparib was given orally on a continuous cycle to 2 sequential cohorts. The first cohort received olaparib at the previously determined maximum tolerated dose of 400 mg twice daily, while the second group received 100 mg twice daily.

A total of 27 patients exposed to a median of 3 prior lines of chemotherapy were enrolled in each dose cohort. The 400 mg dose was more effective than the 100 mg dose at improving PFS (5.7 months versus 3.8 months, respectively). Also, for patients in the 400 mg cohort, the ORR = 41%, CR = 4%, and PR = 37%, compared to 22%, 0%, and 22% for 100 mg, respectively.

Overall, olaparib was well tolerated. However, grade 3 fatigue, nausea, and vomiting were reported more often in the 400 mg group. No patients stopped therapy due to adverse events in the higher dose group, while 1 patient in the lower dose group who stopped therapy following a seizure was found to have brain metastases. A total of 8 patients required dose reduction.

According to Dr Tutt, this study with olaparib in BRCA-deficient breast cancer provides positive proof of concept for high activity and tolerability of a genetically defined targeted therapy in a group of heavily pre-treated patients with advanced breast cancer.

While early results with PARP inhibitors suggest these agents have significant clinical activity and are well tolerated, confirmatory trials to further define their role in TNBC and/or with chemotherapy are needed. Many questions regarding the pharmacokinetic and pharmacodynamic parameters of these agents have yet to be fully explored. What is the best dose and frequency? How should dosing be timed in relation to cytotoxic dosing? When is the best time to start a PARP inhibitor? What role will there be in the adjuvant setting, if any? Will there be a role for chronic use in patients with BRCA mutations?²³³ And importantly, what will be the mechanism of resistance?³¹

Cytotoxic Chemotherapy – A Mainstay of Treatment

Despite the advances made in metastatic breast cancer therapy with targeted therapies, cytotoxic chemotherapy remains a cornerstone of therapy for many patients. Both combination and single-agent chemotherapy have a role in the management of metastatic breast cancer, with combination therapy often preferable for patients requiring urgent reduction in their tumor burden.^{35,36} For patients with prior anthracycline exposure, the addition of capecitabine to docetaxel and gemcitabine to paclitaxel improves response rates, time to progression, and OS over either taxane alone when used as first-line metastatic breast cancer treatment.^{35,37,38} Two phase III studies evaluating the primary endpoint of time to progression and secondary endpoints of ORR and OS with gemcitabine combination therapy in patients with metastatic breast cancer were presented.

In the study conducted by Nielsen and co-investigators, 337 patients with HER-2 negative locally advanced or metastatic breast cancer were randomized to 1000 mg/m² gemcitabine (G) on day 1 and 8 plus 75 mg/m² docetaxel (T) on day 1 every 21 days (GT, n = 170) or 100 mg/m² docetaxel (T) on day 1 every 21 days (T, n = 167) as first- or second-line therapy for MBC.³⁹ Time to progression for both groups and OS rates were reported as similar for both groups, as were ORR (GT = 37% and T = 32%) and complete response rates (GT = 3%, T = 3%). Grade 3 and 4 hematologic toxicities were common, especially neutropenia (GT = 22%/52%; T = 15%/53%); thrombocytopenia was more common in GT (16%) compared to T (< 1%). The most commonly reported grade 3 and 4 non-hematologic toxicities of fatigue (GT = 9%; T = 11%) and stomatitis (5% each arm) were similar between the 2 groups, although neuropathy was more common in T (16%) than GT (6%). While gemcitabine plus docetaxel appears to improve time to progression and response rates similarly to docetaxel alone, the combination appears to result in greater risk of platelet toxicity.

A study described by Seidman and colleagues compared gemcitabine + docetaxel (GD) with capecitabine + docetaxel (CD) and included a predetermined alternate, single-agent crossover (GD to C or CD to G).³⁵ Patients were randomized to receive 1000 mg/m² gemcitabine (G) on day 1 and 8 plus 75 mg/m² docetaxel (D) on day 1 every 21 days (GD, n = 239), or 1000 mg/m² capecitabine (C) twice daily for days 1-14 plus 75 mg/m² docetaxel (D) on day 1 every 21 days (CD, n = 236). Upon disease progression, patients were given crossover C or G at doses and schedules identical to

induction. Of note, the CD arm employed a 20% lower dose of capecitabine than previously reported trials due to the high incidence of hand-foot syndrome in those trials.

All patients had locally advanced or metastatic disease and had received no more than 1 prior course of chemotherapy for metastatic breast cancer; patients with previous taxane exposure were excluded. Time to progression, OS, and ORR were comparable between the 2 combination regimens. However, exploratory analysis showed time to progression was longer for GD to C crossover monotherapy compared to CD to G by 5 months; this finding was not statistically significant. Regarding adverse effects, GD resulted in greater myelosuppression than CD, but similar rates of febrile neutropenia. Grade 3-4 gastrointestinal toxicities, mucositis, and hand-foot syndrome were greater with CD; fatigue and elevated liver function tests with GD. One quarter of patients receiving CD developed grade 3-4 hand foot syndrome. Toxicity related discontinuation rates were higher in the CD arm. Similarly efficacious to CD as demonstrated in this study, GD may represent a more favorable toxicity profile for select patients.

Molecular and Genetic Profiling – The Magic 8 Ball?

According to NCCN consensus guidelines, molecular profiling for breast cancer prognosis may be used in patients with ER-positive, HER-2 negative, and lymph node-negative disease. Current proposed NCCN clinical risk assessment suggests adjuvant treatment for the majority of patients with these prognostic indicators. The 70-gene profile MammaPrint™ assay is validated as an independent prognostic indicator for patients with lymph node-negative and positive disease. Specifically, prognostic prediction by MammaPrint™ may more accurately identify patients who are candidates for adjuvant chemotherapy plus endocrine therapy.

A persistent uncertainty exists in identifying patients with node-negative breast cancer requiring adjuvant chemotherapy, and those who may be spared this aggressive treatment. Commonly, patient age along with tumor grade, stage, and hormone receptor status are considered when making this determination. Recently, molecular profiling has also become a variable in the equation. When evaluating patients with primary tumors characterized as 0.6-1.0 cm with unfavorable features, or > 1 cm and node negative, hormone receptor positive, and HER-2 negative, NCCN consensus guidelines propose the 21-gene RT PCR assay (Oncotype DX™) for breast

cancer prognosis and to aid in estimating the likelihood of recurrence and benefit from chemotherapy. An alternate gene expression assay, MammaPrint™, analyzes a 70-gene expression profile from breast tumor tissue of patients with early-stage, node-negative breast cancer to assign clinical prognosis. Test results are used to predict distant metastasis-free survival (DMFS), and patients with a good prognosis at 10 years versus those with a high risk for recurrence.

Prognosis and 10-Year Survival With 70-Gene Assay

A meta-analysis presented by de Snoo and co-investigators evaluated tumor samples from 566 patients with ER positive, HER-2 negative, and lymph node negative breast cancer enrolled in 5 different studies.⁴⁰ The prognostic value of MammaPrint™ was compared with NCCN guidelines. Tumor samples were classified using MammaPrint™ as either “good” or “poor” prognosis; using NCCN guidelines, patients were divided into “low” or “high” risk groups. Ten-year breast cancer specific survival (BCSS) was analyzed according to both MammaPrint™ and NCCN guidelines. Over a median patient follow-up of 3.5 years, MammaPrint™ determined 67% and 33% of patients to have “good” and “poor” prognosis, respectively. Per NCCN guidelines, 7% and 93% were classified as “low” and “high” risk, respectively. During follow-up, 62% of patients received no adjuvant treatment, 17% received endocrine therapy only, 2% received chemotherapy only, and 20% of patients received endocrine therapy + chemotherapy. At 10 years, BCSS was 91% and 67% for the “good” prognosis group compared to the “poor” prognosis group (HR 4.0, $P < 0.001$) with MammaPrint™ risk assessment. Per NCCN guidelines, BCSS was 86% for the “low” risk group and 83% for the “high” risk group (HR 1.11, $P = 0.888$). The investigators conducted multivariate analysis, adjusting for known prognostic factors and adjuvant therapy and determined that only MammaPrint™ and histological grade were independent predictors for 10-year BCSS with hazard ratios of 2.8 ($P = 0.008$) and 1.9 ($P = 0.015$), respectively.

In this analysis, MammaPrint™ proved its utility as a strong independent prognostic indicator in patients with ER positive, HER-2 negative, lymph node negative breast cancer. MammaPrint™ reclassified approximately 66% of patients classified using NCCN guidelines as “high” risk patients as having an overall “good” prognosis, suggesting that integrating the 70-gene profile into clinical risk assessment and treatment selection algorithms may benefit patients with endocrine responsive early breast cancer. These results are retrospective, and should be interpreted with caution. Results from the ongoing prospective MINDACT (Microarray

In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy) study, designed to confirm that patients with a “low” risk molecular prognosis and “high” risk clinical prognosis can be safely spared chemotherapy without jeopardizing DMFS, are anticipated following successful completion of patient accrual.

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