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3 Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II trial

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TNBC is a subtype of breast cancer that shares similar features with breast cancer gene 1 (BRCA1)-related breast cancers and tends to display aggressive behavior. Poly (ADP-ribose) polymerase (PARP1), which is an enzyme of cell proliferation and DNA repair, inhibits BRCA-deficient cells. In this study, a potent PARP inhibitor (BSI-201) in combination with gemcitabine/carboplatin was analyzed in patients with TNBC. Patients eligible for study participation had measurable disease and 2 or less previous cytotoxic regimens for ER-, PR-, and HER2-negative metastatic breast cancer. Patients were randomized 1:1 to gemcitabine (1,000 mg/m²) and carboplatin (area under the concentration curve=2) or gemcitabine and carboplatin plus BSI-201 (5.6 mg/kg intravenous biweekly). Patients were given gemcitabine and carboplatin on days 1 and 8 and BSI-201 on days 1, 4, 8, and 11, every 21 days. Study endpoints included clinical benefit rate (CBR; complete response + partial response + stable disease ≥6 months), progression-free survival (PFS), and overall survival (OS). In an analysis of the first 86 patients (120 planned patients), it was found that patients receiving BSI-201 plus gemcitabine/carboplatin had improved CBR, median PFS, and median OS when compared with gemcitabine/carboplatin alone (Table 1). Adverse events were similar in both groups. The authors concluded that the preliminary analysis showed increased efficacy with BSI-201 plus gemcitabine/carboplatin versus gemcitabine/carboplatin alone. The combination was well tolerated with no significant toxicities reported when BSI-201 was added. Updated data for CBR, PFS, and OS for all 120 patients, along with correlative analyses of PARP expression will be presented later.

Table 1. Efficacy of BSI-201 with G/C in TNBC

	G/C (n=44)	G/C+BSI- 201 (n=42)	HR (95% CI)	P value
CBR (%)	12	52		.0012
Median PFS (days)	87	211	0.30 (0.15–0.59)	.0003
Median OS (days)	169	>254	0.24 (0.09–0.61)	.0012

CBR=Clinical benefit rate; G/C=gemcitabine/carboplatin;
HR=hazard ratio; OS=overall survival; PFS=progression-free survival;
TNBC=triple-negative breast cancer.

1004 Neratinib in combination with trastuzumab for the treatment of advanced breast cancer: A phase I/II study

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The safety and preliminary efficacy of neratinib, an orally administered irreversible pan-ErbB receptor tyrosine kinase inhibitor, combined with trastuzumab, was studied in this phase I/II trial. The study recruited patients with advanced ErbB2+ breast cancer that progressed after trastuzumab therapy. The primary endpoint was 16-week PFS rate. Forty-five patients with a mean age of 52 years were enrolled. The study comprised 2 parts, the first being dose escalation. In part 1, 8 patients received either a 160-mg or 240-mg daily dose of neratinib plus a 4 mg/kg intravenous loading dose of trastuzumab, followed by a weekly trastuzumab dose of 2 mg/kg. In part 2, 37 patients were given weekly trastuzumab plus neratinib 240 mg daily. Timed blood samples were collected for pharmacokinetic analysis, which is still ongoing. Cohorts 1 and 2 in part 1 (4 patients each) were fully enrolled. No dose limiting toxicities were observed. Safety analysis found that the most common adverse events of any grade were diarrhea (91%), nausea (51%), anorexia (40%), vomiting (38%),

and asthenia (27%); the main grade 3/4 adverse events included diarrhea (13%), nausea (4%), and vomiting (4%). Adverse events leading to withdrawal occurred in 2 patients receiving neratinib 240 mg. No congestive heart failure or significant drops of left ventricular ejection fraction were reported. Of all patients, 33 were evaluable for efficacy with an objective response rate of 27% (95% confidence interval [CI], 13–46%), median PFS of 19 weeks (95% CI, 15–32 weeks), and a 16-week PFS rate of 47% (95% CI, 29–63%). It was determined that the combination of neratinib and trastuzumab was clinically active and well tolerated with no significant or unforeseen toxicities.

1005 RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC).

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Previous phase III studies have confirmed improvement in PFS when bevacizumab, in combination with weekly paclitaxel or docetaxel, was given as first-line therapy for MBC compared to either agent alone. This study examined the addition of bevacizumab to standard first-line

chemotherapy regimens for MBC. Patients were randomized 2:1 to receive bevacizumab plus chemotherapy or placebo plus chemotherapy. The chemotherapy used was capecitabine- (2,000 mg/m² for 14 days), taxane- (either nab-paclitaxel 260 mg/m² or docetaxel 75 or 100 mg/m² every 3 weeks) or anthracycline-based (every 3 weeks). Bevacizumab or placebo was administered at 15 mg/kg every 3 weeks. Patients were enrolled in the study if they had MBC or locally recurrent disease, no prior cytotoxic treatment, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, HER2-negative disease, and no central nervous system metastases. The primary endpoint was investigator-assessed PFS, and secondary endpoints included OS, objective response rate, independent review of PFS, and safety. All patients were eligible for bevacizumab with second-line chemotherapy if progression occurred. The study enrolled 1,237 patients (capecitabine, 615; taxane, 307; anthracycline 315) from December 2005 until August 2007 in 22 countries. The median follow-up was 15.6 months in the capecitabine cohort and 19.2 months in the taxane plus anthracycline cohort. PFS and OS were improved in the taxane plus anthracycline cohort when compared to the capecitabine cohort. The median PFS in patients treated with a taxane plus anthracycline was 8.0 months versus 5.7 months in the capecitabine-treated patients. The median OS was 23.8 months and 21.2 months in the taxane plus anthracycline and capecitabine groups, respectively (Table 2). OS data are limited, and safety was in line

Table 2. RIBBON-1: Efficacy findings

	Capecitabine (n=615) Placebo (n=206)	Bevacizumab (n=409)	Taxane + Anthracycline (n=622) Placebo (n=207)	Bevacizumab (n=415)
Median PFS (months)	5.7	8.6	8.0	9.2
HR (95% CI)	0.688 (0.564–0.840)		.644 (0.522–0.795)	
Log-rank <i>P</i> value	.0002		<.0001	
ORR* (%)	38 (23.6)	115 (35.4)	67 (37.9)	177 (51.3)
<i>P</i> value	.0097		.0054	
Median OS (months)	21.2	29.0	23.8	25.2
HR (95% CI)	0.847 (0.631–1.138)		1.032 (0.774–1.376)	
Log-rank <i>P</i> value	.2706		.8298	

CI=confidence interval; HR=Hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

* Includes only patients with measurable disease at baseline

with the results of previous trials of bevacizumab. The investigators concluded that the addition of bevacizumab to first-line capecitabine-, taxane-, or anthracycline-based chemotherapy for MBC patients produced a statistically significant improvement in PFS.

1022 Pertuzumab monotherapy following trastuzumab-based treatment: Activity and tolerability in patients with advanced HER2-positive breast cancer.

J Cortes, J Baselga, T Petrella, K Gelmon, P Fumoleau, S Verma, X Pivot, G Ross, T Szado, L Gianni

To evaluate the activity of pertuzumab monotherapy in patients with HER2-positive MBC that had progressed on trastuzumab therapy after 3 or less lines of chemotherapy, a third cohort of patients was added to the 2 cohorts (n=66) that were previously evaluated by Gelmon and colleagues. This previous study, reported at last year's American Society of Clinical Oncology meeting, demonstrated that pertuzumab plus trastuzumab was active in this patient population. In the current study, patient selection remained the same, except for the requirement that at least 1 month pass between the last dose of trastuzumab and study start. The patients were given pertuzumab therapy, and if they failed to respond or responded and then experienced progression, trastuzumab was added. Twenty-nine patients were recruited and given standard 21-day schedules of the antibodies. The investigators observed good tolerability with mild diarrhea and rash (with no clinical cardiac event) as the main adverse events. To date, 2 responses have been observed and several patients have ongoing stable disease. Fourteen patients received trastuzumab and pertuzumab following inadequate response or response followed by relapse on pertuzumab monotherapy. Of the 14 patients, 2 who had progressed during trastuzumab therapy did not respond to pertuzumab monotherapy, but developed confirmed response when trastuzumab was added to pertuzumab. The investigators concluded that pertuzumab monotherapy is active against HER2-positive breast cancer that has progressed during trastuzumab-based therapy. The combination of the 2 agents seems to be more active than either agent alone,

especially in patients who have failed both antibodies administered separately. The use of this combination is therefore acceptable in clinical trials.

CRA501 Phase II trial of the oral PARP inhibitor olaparib in BRCA deficient advanced breast cancer

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Olaparib, a novel, orally active PARP inhibitor that causes synthetic lethality in homozygous BRCA-deficient cells, has been evaluated in a phase I trial, which identified 400 mg twice daily as the maximum tolerated dose and showed some efficacy in BRCA-deficient ovarian cancer. This international, multicenter, proof-of-concept, single arm, phase II study assessed the efficacy of olaparib in confirmed BRCA1/BRCA2 carriers with advanced refractory breast cancer. The study also evaluated safety and tolerability. It was composed of 2 patient cohorts who received continuous oral olaparib in 28-day cycles initially at 400 mg twice daily (n=27) followed by 100 mg twice daily (n=27). Patients were eligible for enrollment if they had confirmed BRCA1/BRCA2 mutation and recurrent measurable chemotherapy-refractory breast cancer. The primary efficacy endpoint was best objective response post baseline, and secondary endpoints included PFS and CBR. By November 2008, 54 patients who had received a median of 3 prior lines of chemotherapy were enrolled in the study. Of these patients, 27 received 400 mg twice daily (18 BRCA1 deficient, 9 BRCA2 deficient); 24 of 27 patients were evaluated in the efficacy analysis. The objective response rate was 38%. Treatment related toxicities were mostly mild in severity (grade 1/2), with fatigue (33%), nausea (26%), vomiting (15%), and anemia (4%) being reported. Treatment-related grade 3 or higher toxicities were observed in 5 patients: fatigue (n=3), nausea (n=2), and anemia (n=1). The subsequent 100 mg twice-daily cohort included 27 patients; no data are currently available for this cohort. This study suggests that 400 mg olaparib is well tolerated and highly active in advanced chemotherapy-refractory BRCA-deficient breast cancer. Toxicity in BRCA1/BRCA2 carriers was similar to that in noncarriers.