5 Minute Journal Club

Key SABCS Presentations

Issue 3, 2011

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CME Information

LEARNING OBJECTIVES

- Compare and contrast the efficacy and safety of bevacizumab-containing therapy by breast cancer subtype and patient age.
- Counsel patients with triple-negative breast cancer (TNBC) about the benefits and risks of first-line chemotherapy in combination with bevacizumab.
- Cite the rates of pathologic complete response and serious adverse events when bevacizumab is combined with neoadjuvant epirubicin and cyclophosphamide or doxorubicin for patients with untreated HER2-negative early breast cancer.
- Recall the synergistic antiproliferative and apoptotic effects of iniparib with gemcitabine and/or carboplatin in a triple-negative breast cancer cell line.
- Describe the early activity and safety of the combination of iniparib and irinotecan in the treatment of metastatic breast cancer (mBC).
- Recognize how BRCA1 promoter methylation and resultant BRCA1 deficiency found in sporadic triple-negative breast cancer may confer tumor sensitivity to PARP inhibition.
- Explain the results of a randomized Phase II trial evaluating the combination of cetuximab and cisplatin for patients with mTNBC.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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

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No real or apparent conflicts of interest to disclose.

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

Final Overall Survival Results, Including Analysis of Patients with Triple-Negative Disease and Aged ≥70 Years, from the Athena Study Evaluating First-Line Bevacizumab-Containing Therapy for Locally Recurrent (LR)/ Metastatic Breast Cancer (mBC)

Pritchard KI et al.

Proc SABCS 2010;Abstract P2-16-06.

Study Design

Accrual: 2,264 (Closed)

Eligibility
HER2-negative LR/mBC
No prior chemotherapy for LR/mBC; no concomitant endocrine therapy
No uncontrolled hypertension
No increased risk of hemorrhage
No surgery in previous 28 days

→ **Bevacizumab + chemotherapy*, until disease progression**

* Taxane-based or alternative, excluding anthracycline, if taxane is not considered standard of care

Primary objective: Assess safety of bevacizumab in combination with chemotherapy as first-line treatment for LR/mBC in routine oncology practice.
Secondary objectives: Time-to-progression (TTP) and overal survival (OS).

Pritchard KI et al. *Proc SABCS* 2010;Abstract P2-16-06.

Chemotherapy Combination Partners

Chemotherapy	Patients (%)
Paclitaxel monotherapy	34
Docetaxel monotherapy	33
Taxane combination	11
Capecitabine monotherapy	5
Vinorelbine monotherapy	3
Non-taxane combination	2
Other monotherapy	<1
Sequential chemotherapy*	12

*Switching chemotherapy regimen before disease progression while continuing bevacizumab.

Pritchard KI et al. *Proc SABCS* 2010;Abstract P2-16-06.

Subgroup Analyses of TTP and OS

Subgroup	# of pts	Median TTP (months)	Median OS (months)	1-year OS (%)
All	2264	9.7	25.2	72.7
TNBC	585	7.2	18.3	59.8
Non-TNBC	1616	10.6	27.3	77.3
Age $\geq$ 70	176	10.4	20.5	68.2
Age < 70	2088	9.6	25.5	73.0
Weekly paclitaxel monotherapy	325	10.6	24.5	71.7
3-weekly paclitaxel monotherapy	285	9.1	24.7	67.4
Docetaxel monotherapy	741	9.1	25.5	76.0

TNBC = triple-negative breast cancer

Pritchard KI et al. *Proc SABCS* 2010;Abstract P2-16-06.

Conclusions

- Mature results from the ATHENA study conducted with patients treated in routine oncology practice demonstrate median OS of 25.2 months.
  - Consistent with reported Phase III trials evaluating first-line chemotherapy plus bevaciuzmab (25.2 to 30.2 months)
- No new safety signals emerged with longer follow-up and 21% of patients remained on bevacizumab > 1yr (data not shown).
- Subgroup analyses suggest that bevacizumab-containing therapy is an effective treatment in important patient populations with limited available treatment options.
  - TNBC: median OS = 18.3 months
  - Aged $\geq$ 70: median OS = 20.5 months

Pritchard KI et al. *Proc SABCS* 2010;Abstract P2-16-06.

Meta-Analysis of Patients with Triple-Negative Disease from Three Randomized Trials of Bevacizumab and First-Line Chemotherapy as Treatment for Metastatic Breast Cancer

O'Shaughnessy J et al.

Proc SABCS 2010;Abstract P6-12-03.

Background

- Phase III trials have demonstrated improved progression-free survival (PFS) with the addition of bevacizumab (Bev) to first-line chemotherapy in a subset of patients with TNBC.
  - PFS RIBBON-1: 6.1 months (Bev + capecitabine arm)
  - PFS E2100: 10.6 months (Bev + weekly paclitaxel arm)
- A meta-analysis of individual patient data from the three randomized trials confirmed increased PFS but found no difference in OS (*J Clin Oncol* 2010;28:1005).
- **Current Study Goals:** Using individual patient data, assess the pooled efficacy and safety results for the subpopulation of patients with TNBC treated in three Phase III trials of first-line chemotherapy plus Bev.

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract P6-12-03.

Efficacy Summary (n = 621 Patients with TNBC)

Outcome	Bevacizumab + chemotherapy (n = 363)	Chemotherapy alone (n = 258)	Hazard ratio*	*p*-value
Objective response	42%	23%	—	<0.0001
Progression-free survival (PFS), events	71%	75%	0.649	<0.0001
Median PFS	8.1 months	5.4 months		
Overall survival (OS), events	68%	67%	0.959	0.6732
Median OS	18.9 months	17.5 months		
One-year OS rate	70.9%	64.8%	—	0.1140

* Unstratified analysis

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract P6-12-03.

Safety Summary (n = 615 Patients with TNBC)

Select Grade ≥3 Adverse Events	Bevacizumab + chemotherapy (n = 360)	Chemotherapy alone (n = 255)
Hypertension	7.5%	1.6%
Proteinuria	1.7%	0%
GI perforation	0.3%	0.4%
ATE, VTE	1.7%, 3.3%	0.4%, 4.3%
Bleeding	2.2%	0.4%
Sensory neuropathy	9.7%	9.4%
Febrile neutropenia	4.7%	2.7%
Neutropenia	8.1%	5.1%

ATE = arterial thromboemoblic event; VTE = venous thromboembolic event

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract P6-12-03.

Conclusions

- This meta-analysis of 621 patients with metastatic TNBC confirms the improvement in PFS previously reported in subgroup analyses from the three Phase III trials of first-line bevacizumab plus chemotherapy (RIBBON-1, E2100, AVADO).
  - Current median PFS of 8.1 months in TNBC is encouraging when compared to a typical range of 2 to 6 months with chemotherapy alone.
- No significant improvement in OS was observed.
- The safety profile of bevacizumab plus chemotherapy was consistent with previous reports.

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract P6-12-03.

Neoadjuvant Chemotherapy with or without Bevacizumab: Primary Efficacy Endpoint Analysis of the GEPARQUINTO Study (GBG 44)

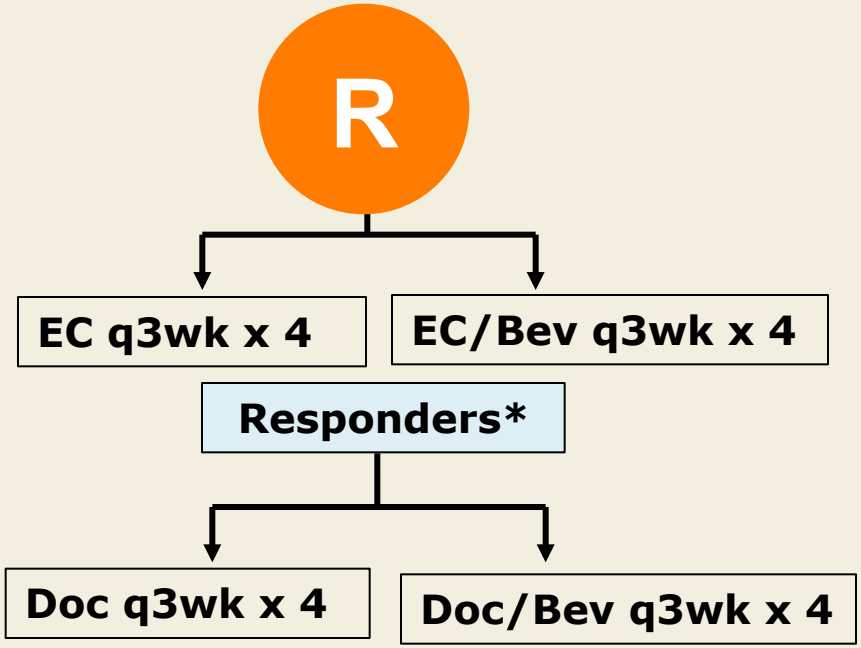
von Minckwitz G et al.

Proc SABCS 2010;Abstract S4-6.

Study Design

Accrual: 1,948 (Closed)

Eligibility
Untreated breast cancer
Breast lesion ≥2 cm (by palpation) or ≥1 cm (by ultrasound)
HER2-negative
Tumor stage **cT4 or cT3** **cT2 (if HR- or cN+)** **cT1 (if HR- or pNSLN+)**
Normal organ function



E = epirubicin 90 mg/m^2
C = cyclophosphamide 600 mg/m^2
Doc = docetaxel 100 mg/m^2
Bev = bevacizumab 15 mg/kg

Primary objective: pCR rate

*Nonresponders were randomized to other treatments

von Minckwitz G et al. *Proc SABCS* 2010;Abstract S4-6.

Results

Outcome	EC-Doc n = 968	EC-Doc+Bev n = 959	*p*-value
pCR[1]	15%	17.5%	NS
pCR (other definition)[2]	18.5%	20.3%	NS
pCR (other definition)[3]	21.3%	23.9%	NS
Breast conservation rate	66.6%	65.8%	NR

pCR definitions:
[1]Defined as no invasive/noninvasive residual in breast and nodes based on central pathology report review
[2]No invasive residual in breast and nodes
[3]No invasive residual in breast
NS, nonsignificant; NR, not reported

von Minckwitz G et al. *Proc SABCS* 2010;Abstract S4-6.

Multivariate Analysis of pCR According to Subtype*

Subtype	Odds Ratio[1]
Overall	1.21
ER/PgR-negative	1.42
ER/PgR-positive	1.05
T1-3 and N0-2	1.17
T4 or N3	1.70

* Predefined and stratified

[1] Odds ratio >1 favors more patients with pCR on the EC-Doc + Bev arm.

von Minckwitz G et al. *Proc SABCS* 2010;Abstract S4-6.

Conclusions

- The addition of bevacizumab to neoadjuvant therapy for patients with early HER2-negative breast cancer does not significantly increase pCR.
- Toxicity was increased by adding bevacizumab (data not shown)
  - Serious adverse events occurred in 11.8% of EC group, 15.7% of EC-Bev group, 12.9% of Doc group and 23.1% of Doc+Bev group.
  - Events with major increases due to bevacizumab included febrile neutropenia, nausea, mucositis, general condition and wound healing.
- Multivariate analysis by breast cancer subtype suggests the addition of bevacizumab in the triple-negative population may improve pCR rate.

von Minckwitz G et al. *Proc SABCS* 2010;Abstract S4-6.

Investigator Commentary: First-Line Bevacizumab-Containing Therapy in Triple-Negative Metastatic BC

The ATHENA trial was an effort to get a "real world" look at various chemotherapy agents with bevacizumab as first-line therapy in routine oncology clinical practices. In this update, the investigators focused on patients with advanced triple-negative breast cancer (TNBC) and demonstrated that these patients had a less favorable time to disease progression and overall survival than do other "flavors" of breast cancer, even when treated with bevacizumab. The randomized studies suggest that bevacizumab can improve time to disease progression in TNBC, but because the overall rate of growth in TNBC is quicker, the difference in time to progression gains is smaller despite the use of bevacizumab.

In the updated meta-analysis, O'Shaughnessy and colleagues focused on outcomes in advanced TNBC and showed that adding bevacizumab to chemotherapy modestly improves the response rate from approximately 23 to 42 percent, which translates into improvements in progression-free survival of about 2.5 months but no difference in overall survival. There are potential benefits of bevacizumab in the first-line setting, but the absolute gains are modest, in part because of the rapid trajectory of progression in TNBC.

Interview with Harold J Burstein, MD, PhD, December 22, 2010

Investigator Commentary: GEPARQUINTO (GBG 44): Neoadjuvant Chemotherapy/Bevacizumab in HER2-Negative BC

GEPARQUINTO was a large study with over 1,000 HER2-negative patients. It was a complicated trial in which patients received epirubicin/cyclophosphamide (EC) with or without bevacizumab followed by docetaxel with or without bevacizumab after four cycles for responding patients.

The pathologic complete response (pCR) rate — defined as no invasive disease or noninvasive disease in the breast or lymph nodes — was not significantly different between the EC/docetaxel and the EC/docetaxel with bevacizumab arms. Even when evaluating outcome by other definitions of pCR, no differences were observed. Additionally, no difference in the rate of breast conservation was achieved with the addition of bevacizumab.

The only subset for whom there was a suggestion of benefit from bevacizumab — and this has been seen in trials of bevacizumab in the metastatic setting — was the group of patients with triple-negative breast cancer. Of course, it's a subset analysis, so it is difficult to make any strong conclusions.

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

Phase 1b Study of Iniparib (BSI-201) Combined with Irinotecan for Treatment of Metastatic Breast Cancer[1]

Cell Cycle Effects of Iniparib plus Gemcitabine and Carboplatin in a Triple Negative Breast Cancer Cell Line[2]

Promoter CpG Methylation of BRCA1 Predicts Sensitivity to PARP Inhibitors in Breast Cancer[3]

[1]Moulder S et al.
Proc SABCS 2010;Abstract P6-15-01.

[2]Ossovskaya V et al.
Proc SABCS 2010;Abstract P5-06-09.

[3]Veeck J et al.
Proc SABCS 2010;Abstract S4-8.

A Phase 1b Study to Assess the Safety and Tolerability of Iniparib (BSI-201) in Combination with Irinotecan for the Treatment of Patients with Metastatic Breast Cancer (MBC)

Moulder S et al.

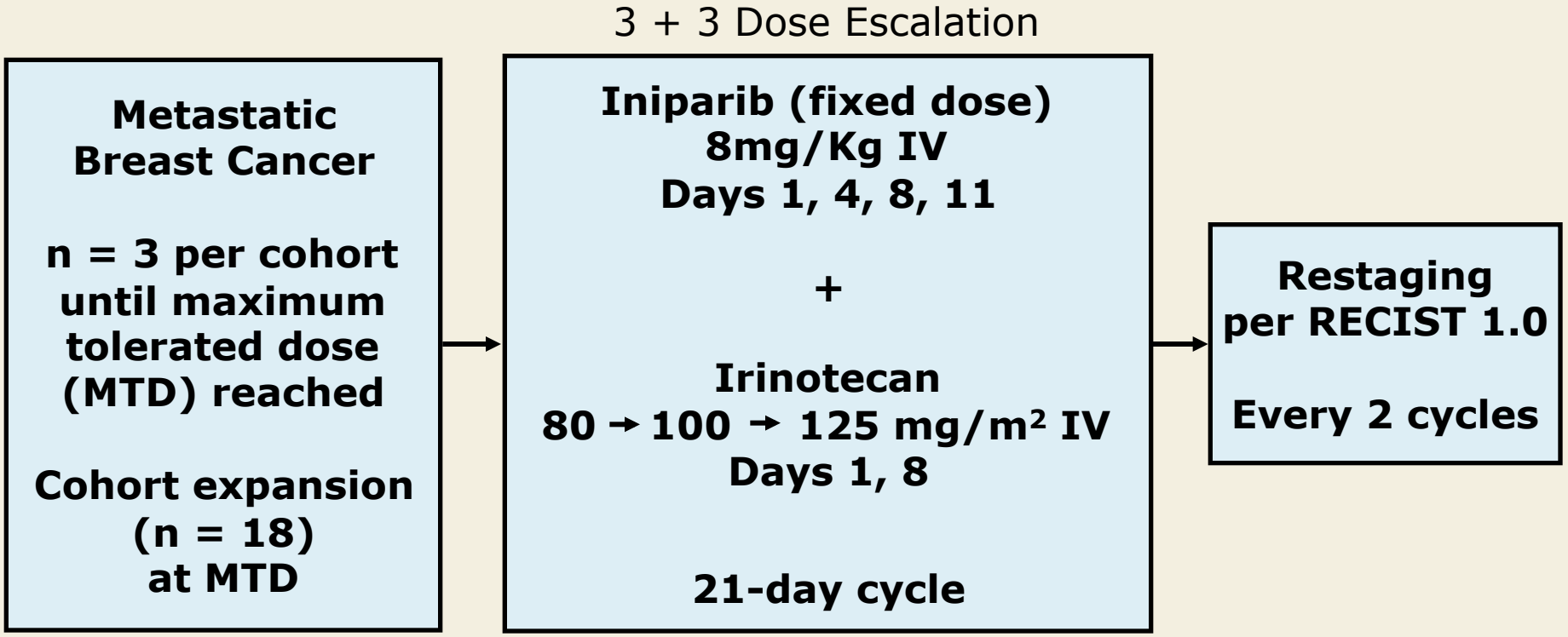
Proc SABCS 2010;Abstract P6-15-01.

Key Eligibility Criteria

- Adenocarcinoma of the breast.
- Progressive locoregional or metastatic disease.
- Bi-dimensionally measurable indicator lesion ≥ 2cm.
- Prior treatment with at least one regimen containing an anthracycline, an anthraquinone or a taxane.
- Maximum of one adjuvant regimen and two regimens for metastatic disease.

Moulder S et al. *Proc SABCS* 2010;Abstract P6-15-01.

Study Schema



Primary Endpoint: Safety and tolerability
Objective response rate

Secondary Endpoint: Clinical benefit rate (CBR) defined as OR + SD ≥ 6 cycles

Moulder S et al. *Proc SABCS* 2010;Abstract P6-15-01.

Safety Results

		Iniparib + Irinotecan 80mg/m² (n = 3)	Iniparib + Irinotecan 100mg/m² (n = 6)	Iniparib + Irinotecan 125mg/m² (n = 25)
Neutropenia	All Grades	33.3%	16.7%	44.0%
	Grade 3/4	0.0%	16.7%	32.0%
Anemia	All Grades	33.3%	50.0%	48.0%
	Grade 3/4	0.0%	0.0%	8.0%
Diarrhea	All Grades	33.3%	50.0%	68.0%
	Grade 3/4	0.0%	0.0%	12.0%
Fatigue	All Grades	66.7%	66.7%	56.0%
	Grade 3/4	0.0%	0.0%	12.0%

MTD not reached at the maximal dose combination allowed in the protocol

Moulder S et al. *Proc SABCS* 2010;Abstract P6-15-01.

Efficacy Results

	Iniparib + Irinotecan 80mg/m² (n = 3)	Iniparib + Irinotecan 100mg/m² (n = 6)	Iniparib + Irinotecan 125mg/m² (n = 25)
Overall Response Rate (ORR)	0%	16.7%	31.8%
Complete Response Rate (CR)	0%	0%	4.5%
Partial Response Rate (PR)	0%	16.7%	27.3%
Clinical Benefit Rate (ORR + SD > 6 cycles)	33.3%	16.7%	45.5%

Moulder S et al. *Proc SABCS* 2010;Abstract P6-15-01.

Conclusions

- Iniparib in combination with irinotecan was well tolerated and was associated with a manageable rate of Grade 3/4 adverse events.
- MTD was not reached with the combination of iniparib and irinotecan at the highest per-protocol dose combination.
- Dosing of 8 mg/kg iniparib in combination with 125 mg/m^2 irinotecan was active in MBC, demonstrating an ORR of 31.8% and CBR of 45.5%.
- This proof-of-concept Phase 1b study supports the promising safety and efficacy profile of iniparib in combination with DNA-damaging chemotherapy.

Moulder S et al. *Proc SABCS* 2010;Abstract P6-15-01.

Cell Cycle Effects of Iniparib, a PARP Inhibitor, in Combination with Gemcitabine and Carboplatin in the MDA-MB-468(-) Triple-Negative Breast Cancer (TNBC) Cell Line

Ossovskaya V et al.

Proc SABCS 2010;Abstract P5-06-09.

Methods

- Triple-negative MDA-MB-468 (-) cells were selected by fluorescence-activated cell sorting (FACS) of HER2-negative cells.
- Cells confirmed as triple negative were treated for 72 hours with iniparib (100 μM), gemcitabine (1 or 2 nM), and/or carboplatin (5 or 10 μM), with vehicle as a negative control.
- Cell proliferation was evaluated.
- Apoptotic cells were quantified.
- Cell cycle arrest and DNA damage were evaluated.

Ossovskaya V et al. *Proc SABCS* 2010;Abstract P5-06-09.

Results

	G, 1 nM + C, 5 μM (Low-Dose)	Iniparib Plus G + C (Low-Dose)	G, 2 nM + C, 10 μM (High-Dose)	Iniparib Plus G + C (High-Dose)
Cell Viability	55%	35%	40%	28%

	G, 1 nM	Iniparib Plus G, 1 nM	C, 5 μM	Iniparib Plus C, 5 μM	G, 1 nM + C, 5 μM	Iniparib Plus G, 1 nM + C, 5 μM
Apoptotic Cells*	3.2%	5.7%	2.3%	5.7%	4.7%	8.8%

* Apoptotic cells in vehicle-treated control = 1.3%
Addition of iniparib to C and G+C potentiated S-phase and G2/M cell cycle arrest at 72 hours after treatment compared to vehicle-treated control.

G = Gemcitabine, C = Carboplatin

Ossovskaya V et al. *Proc SABCS* 2010;Abstract P5-06-09.

Conclusions

- Iniparib potentiated the effects of gemcitabine and/or carboplatin in triple-negative MDA-MB-468 cells.
- Addition of iniparib to gemcitabine and/or carboplatin increased induction of apoptosis, S-phase and G2/M cell cycle arrest and DNA damage coinciding with mitotic arrest.
- These results support the clinical rationale of combining iniparib with gemcitabine + carboplatin in treatment of patients with triple-negative breast cancer.

Ossovskaya V et al. *Proc SABCS* 2010;Abstract P5-06-09.

Promoter CpG Methylation of BRCA1 Predicts Sensitivity to PARP Inhibitors in Breast Cancer

Veeck J et al.

Proc SABCS 2010;Abstract S4-8.

Introduction

- PARP inhibitors have been shown to selectively kill BRCA1/2 mutated cancer cells in vitro, which promoted the design of clinical trials to evaluate these agents in patients with BRCA1 germline mutated breast and ovarian cancers.
- However, inherited breast and ovarian cancers are rare.
- Aberrant BRCA1 promoter methylation is more common in sporadic breast cancer cases and contributes to the "BRCA phenotype" of these cancers.
- The sensitivity of cell lines harboring aberrant BRCA1 promoter methylation to PARP inhibitors is unknown.
- **Current study objective**:
  - To analyze whether BRCA1 promoter methylation mediates sensitivity to PARP inhibition in cancerous cells.

Veeck J et al. *Proc SABCS* 2010;Abstract S4-8.

Methods

- Breast cancer cell lines containing either wild-type ($BRCA^{+/-}$) or homozygous deletion of BRCA1 genes ($BRCA^{-/-}$) or BRCA1 promoter methylation ($BRCA1^{m}$) were used.
  - MDA-MB-231 BRCA1-proficient cell line: $BRCA^{+/-}$, $p53^{-}$
  - MDA-MB-436 BRCA1-deficient cell line: $BRCA^{-/-}$, $p53^{-}$
  - UACC3199 BRCA1-deficient cell line: $BRCA1^{m}$, $p53^{-}$
- The cell lines were screened for their sensitivity to the PARP inhibitors 3-ABA, DPQ and NU1025.
- Sensitivity to PARP inhibitors was assessed by:
  - Cell proliferation assays (XTT assay)
  - Extent of DNA damage induced by PARP inhibition (γ-H2AX assay)
  - Amount of persistent DNA damage after PARP inhibition (comet assay).
- Frequency of BRCA1 promoter methylation was also assessed in 68 cases of sporadic triple-negative breast cancers.

Veeck J et al. *Proc SABCS* 2010;Abstract S4-8.

Summary and Conclusions

- Proliferation of BRCA1-deficient cell lines (MDA-MB-436 and UACC3199) was sensitive to all three PARP inhibitors tested, whereas proliferation of the BRCA1-proficient cell line (MDA-MB-231) was more resistant to PARP inhibition.
- The extent of DNA damage conferred by PARP inhibition was similar in all three cell lines tested, indicating that DNA damage conferred by PARP inhibition is independent of BRCA1 status.
- The amount of persistent DNA damage after one week of PARP inhibition was greater in the BRCA1-deficient cell lines than in the BRCA1-proficient cell line where levels of persistent DNA damage were low.
- BRCA1 promoter methylation was detected in 37% (25/68) of sporadic triple-negative breast cancer samples analyzed.
- BRCA1 promoter methylation may be assessed as a biomarker of response in current and ongoing clinical trials of PARP inhibitors in breast and ovarian cancers.

Veeck J et al. *Proc SABCS* 2010;Abstract S4-8.

Investigator Commentary: Evaluation of the PARP Inhibitor Iniparib in Breast Cancer

The preclinical study by Ossovskaya and colleagues demonstrated that adding iniparib to carboplatin/gemcitabine in a triple-negative cancer cell line could potentiate several important cell cycle events, including apoptosis, S-phase and G2/M cell cycle arrest and DNA damage at the time of mitotic arrest. So these observations are preclinical correlates of that which will hopefully be validated in the clinic — namely, that iniparib can make chemotherapy more effective.

In a provocative randomized Phase II study, the addition of iniparib to carboplatin/gemcitabine in patients with triple-negative advanced breast cancer improved overall survival compared to chemotherapy alone. Based on the strength of that result, investigators are beginning to study iniparib in a variety of other contexts. Moulder and colleagues evaluated iniparib in combination with irinotecan, which is believed to target the DNA, in a Phase IB study of patients with metastatic breast cancer and demonstrated that 30 percent of the patients experienced a tumor response. Based on these results, the investigators are planning on conducting a Phase II study with this combination.

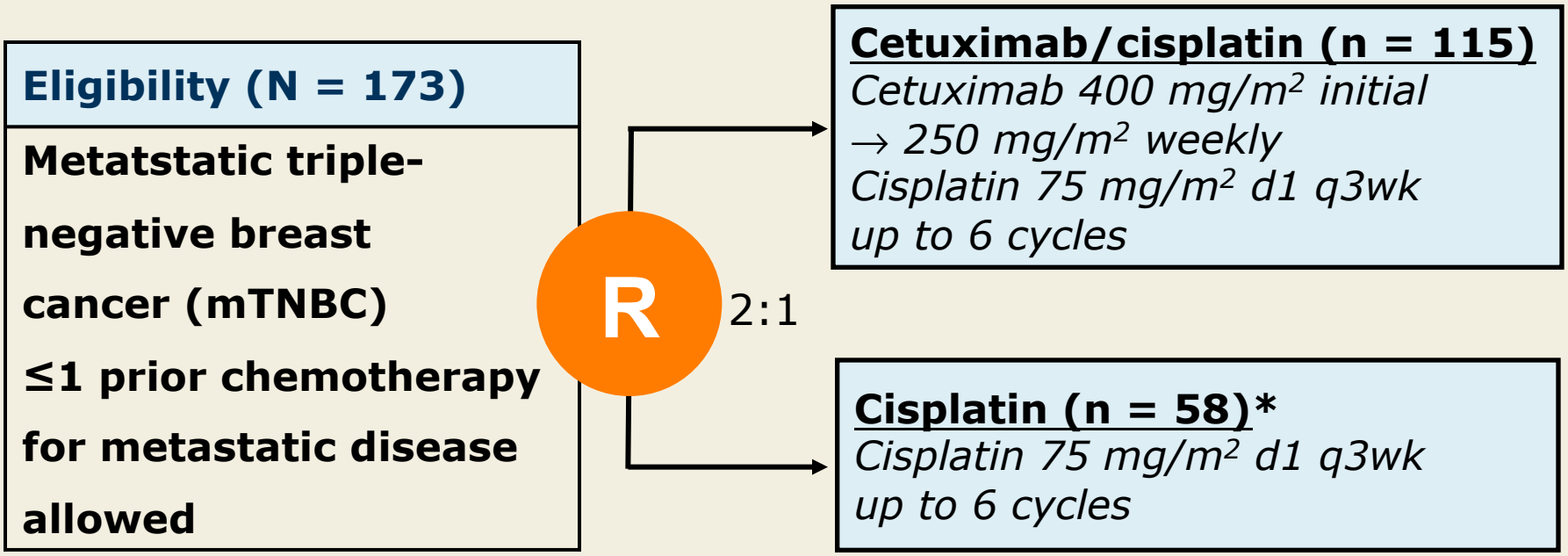
Interview with Harold J Burstein, MD, PhD, December 22, 2010

Cetuximab + Cisplatin in Estrogen Receptor-Negative, Progesterone Receptor-Negative, HER2-Negative (Triple-Negative) Metastatic Breast Cancer: Results of the Randomized Phase II BALI-1 Trial

Baselga J et al.

Proc SABCS 2010;Abstract PD01-01.

BALI-1 Trial Schema



** Crossover allowed: 31 patients receiving cisplatin alone switched to cetuximab/cisplatin after first disease progression.*

Baselga J et al. *Proc SABCS* 2010;Abstract PD01-01.

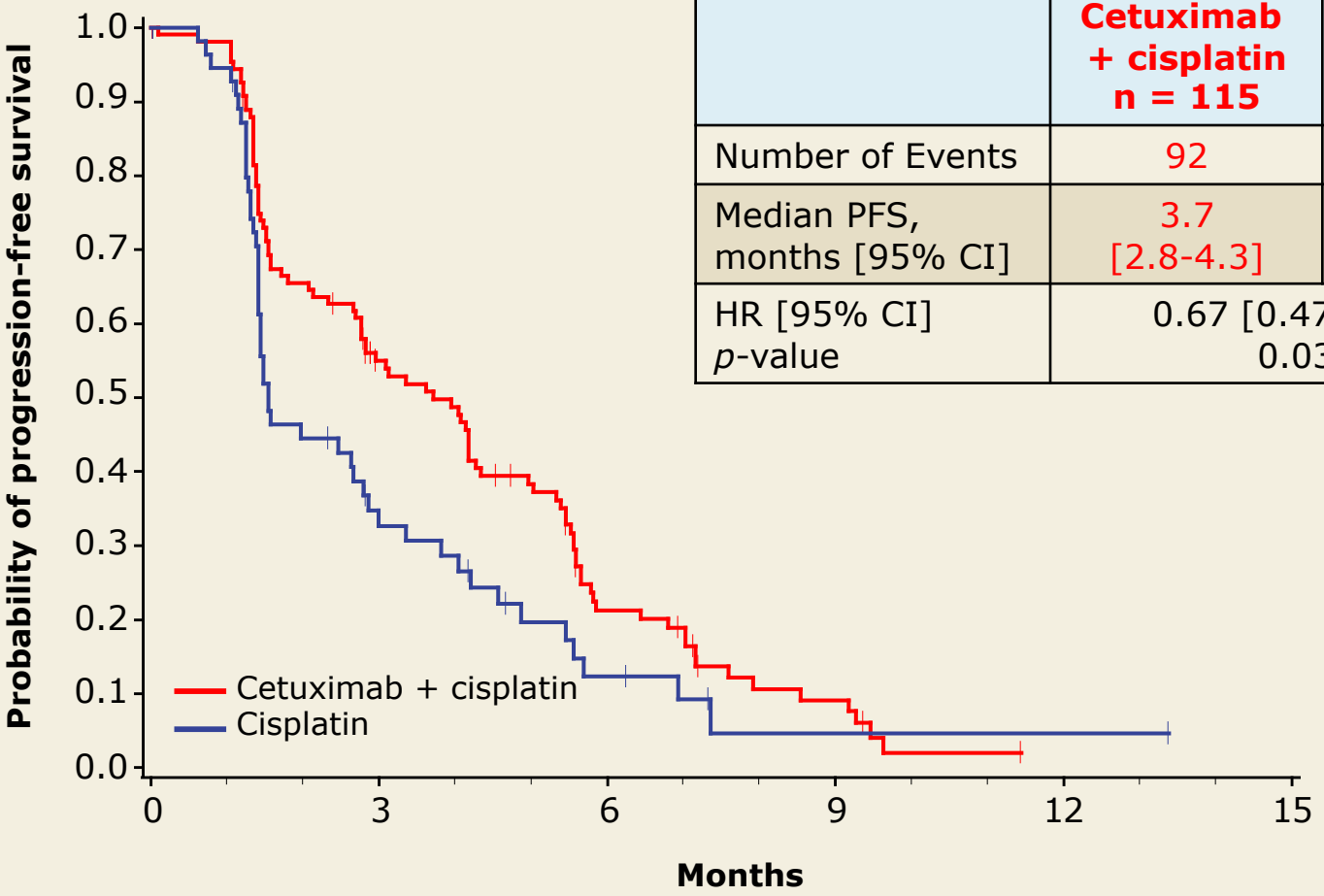
Response Rates

Best Response	Cetuximab + Cisplatin (n = 115)	Cisplatin Alone (n = 58)
Overall response (ORR)*	20.0%	10.3%
Complete response (CR)	1.7%	1.7%
Partial response (PR)	18.3%	8.6%
Stable disease	41.7%	31.0%
Progressive disease	29.6%	53.4%
Odds ratio (95% CI)	2.13 (0.81-5.59)	
p-value	0.11	

*ORR > 20% was a prespecified criterion to demonstrate superiority of cetuximab + cisplatin over cisplatin alone.

Baselga J et al. *Proc SABCS* 2010;Abstract PD01-01.

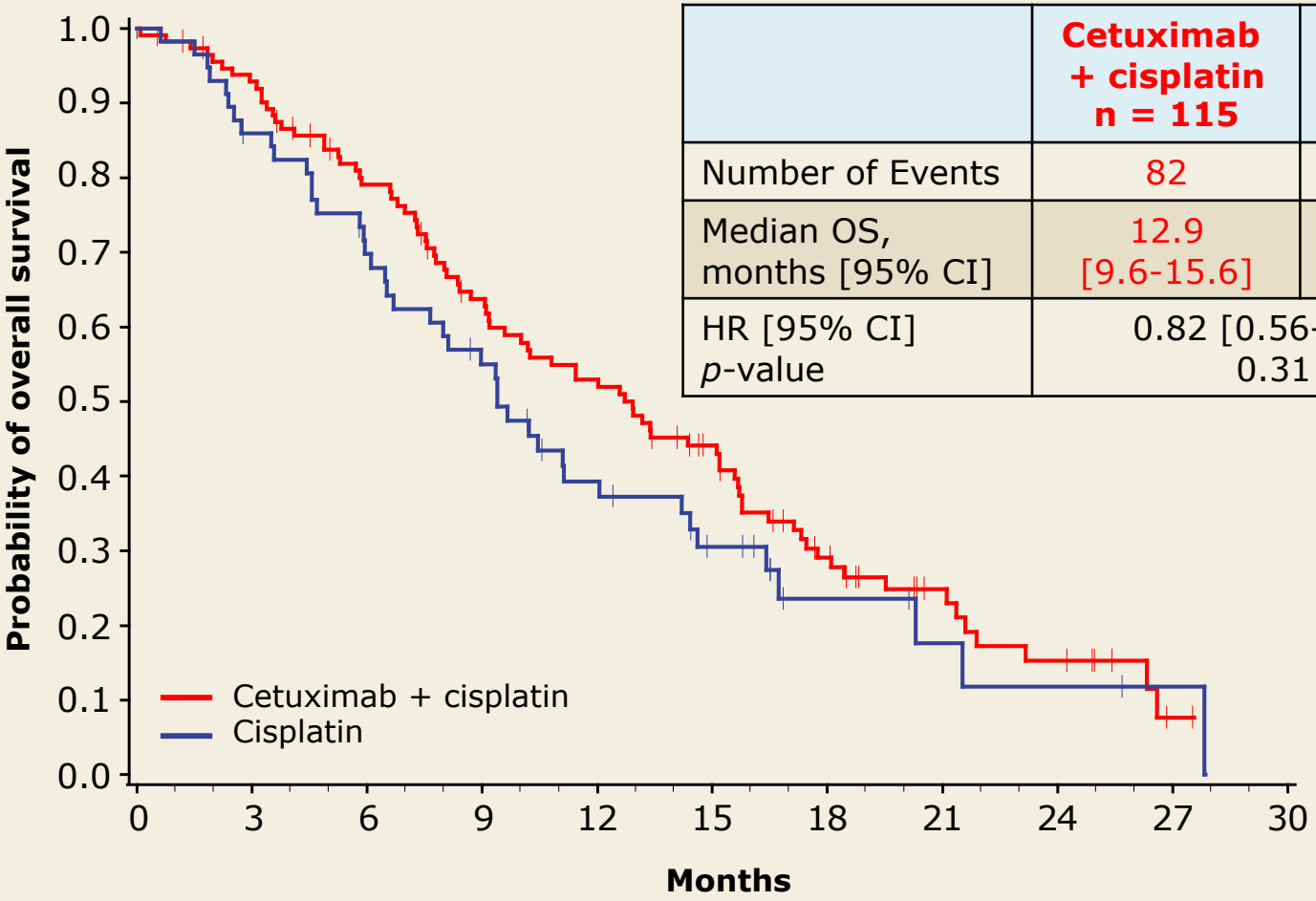
Progression-Free Survival (PFS)



	Cetuximab + cisplatin n = 115	Cisplatin n = 58
Number of Events	92	47
Median PFS, months [95% CI]	3.7 [2.8-4.3]	1.5 [1.4-2.8]
HR [95% CI] *p*-value	0.67 [0.47-0.97] 0.03	

With permission from Baselga J et al. *Proc SABCS* 2010;Abstract PD01-01.

Overall Survival (OS)



	Cetuximab + cisplatin n = 115	Cisplatin n = 58
Number of Events	82	42
Median OS, months [95% CI]	12.9 [9.6-15.6]	9.4 [6.7-14.2]
HR [95% CI] *p*-value	0.82 [0.56-1.20] 0.31	

With permission from Baselga J et al. *Proc SABCS* 2010;Abstract PD01-01.

Select Adverse Events (AEs)

Grade 3/4 (≥5% in either arm)	Cetuximab/Cisplatin (n = 114)	Cisplatin Alone (n = 57)
Neutropenia	9.6%	5.3%
Fatigue	8.8%	7.0%
Nausea/vomiting	8.8%	10.6%
General health deterioration	0%	5.3%
Grade 3/4 events in patients receiving cetuximab		
Acne-like rash*	14.0%	0%
Infusion-related reaction*	2.6%	0%
Hypomagnesemia	3.5%	1.8%

*Special AEs (composite categories): no Grade 4 events reported

Baselga J et al. *Proc SABCS* 2010;Abstract PD01-01.

Summary

- The addition of cetuximab to cisplatin doubled the ORR compared to cisplatin alone (20.0% vs 10.3%) in patients with metastatic TNBC.
- Since the ORR for the cetuximab and cisplatin arm did not exceed 20%, the superiority of this regimen over cisplatin alone was not confirmed.
- The addition of cetuximab to cisplatin significantly improved PFS compared to cisplatin alone (3.7 mos vs 1.5 mos, $p = 0.03$).
- A clinically meaningful but not statistically significant improvement in OS was shown with the addition of cetuximab to cisplatin.
- The toxicity profile of cetuximab/cisplatin was manageable.

Baselga J et al. *Proc SABCS* 2010;Abstract PD01-01.

Investigator Commentary: Randomized Phase II BALI-1 Study of Cisplatin ± Cetuximab in Metastatic TNBC

A lot of interest has arisen in trying to determine how active the platinum agents might be in triple-negative breast cancer because of the suggestion that platinum agents are DNA-damaging drugs and many triple-negative tumors have extensive chromosomal abnormalities.

In the Phase II BALI-1 study of patients with metastatic TNBC, the investigators demonstrated that the response rate with cisplatin alone was approximately 10 percent, which increased to 20 percent with the addition of the EGFR antibody cetuximab. The median time to disease progression was only 1.5 months with chemotherapy alone and about 3.5 months with chemotherapy and cetuximab. Unfortunately, this was a relatively modest and short time to progression. It will be interesting to see whether this is a sufficiently robust result that investigators will want to build on by studying other cisplatin or cetuximab combinations.

In previous work, investigators at North Carolina also demonstrated modest response rates from combining cetuximab with platinum chemotherapy, but to date that has not moved clinicians to use this in practice.

Interview with Harold J Burstein, MD, PhD, December 22, 2010