



Key SABCS Presentations
Issue 3, 2011

Preclinical and Clinical Proof-of-Concept Studies of PARP Inhibitors with or without DNA-Damaging Chemotherapeutic Agents for TNBC

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVES

- 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.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — 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:

Harold J Burstein, MD, PhD
Associate Professor of Medicine
Harvard Medical School
Breast Oncology Center
Dana-Farber Cancer Institute
Boston, Massachusetts

No real or apparent conflicts of interest to disclose.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Lilly USA LLC, Millennium Pharmaceuticals Inc, Myriad Genetics Inc, Novartis

Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

Last review date: January 2011

Expiration date: January 2012

Click here for papers on the modest benefit observed in patients with TNBC receiving chemotherapy and either [bevacizumab](#) or [cetuximab](#).

Click here for papers on a [Phase IB trial](#) combining the PARP inhibitor iniparib and irinotecan in metastatic breast cancer, a study on the [in vitro effects of iniparib](#) on a TNBC cell line and a [fascinating report](#) suggesting that epigenetic promoter methylation of BRCA genes may correlate with BRCAness and response to PARP inhibitors.

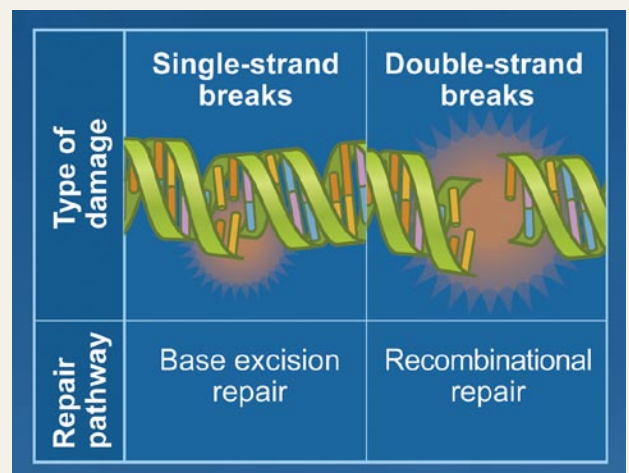
I love my job and feel profoundly privileged to have the opportunity to listen to the great minds in the field and was reminded of this during an annual December visit to the Lone Star State where, as usual, I never made it to the River Walk but sure heard a lot of interesting stuff. One of the highlights was my first ever interview with Alan Ashworth, director of the Breakthrough Breast Cancer Research Centre in London and one of the emerging research giants in the field. This conversation for our audio series was an amazing lesson in the biology and treatment implications of tumor DNA repair and occurred hours after he received a major award from the meeting and gave a brilliant and highly understandable lecture on this subject. This issue of our series profiles a number of San Antonio papers related to management of TNBC (see above links), but the biology and therapeutics discussed by Professor Ashworth seem a lot more encouraging for the future of this disease subset. Below find a few choice highlights of the interview.



Professor Alan Ashworth

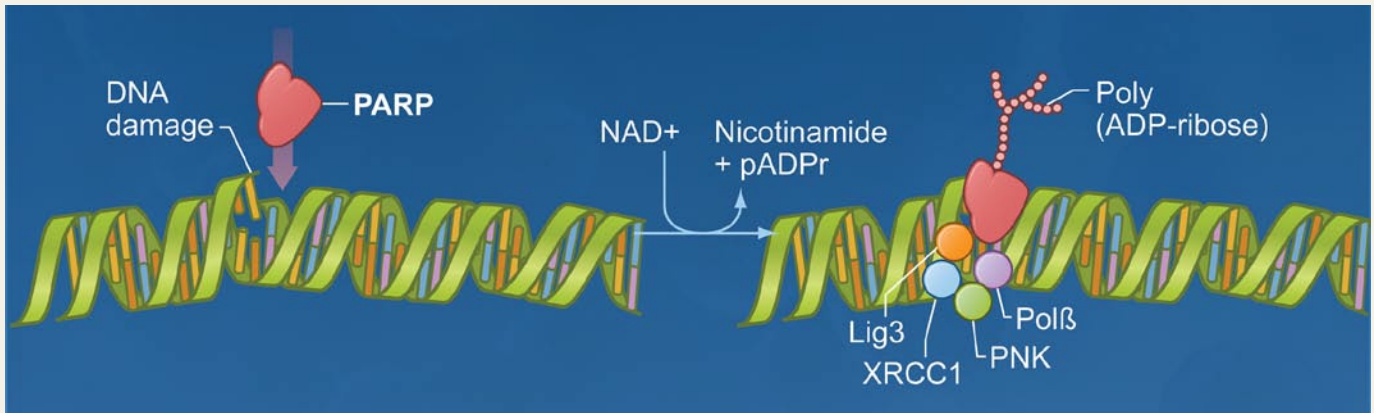
Dr Love: What do we know about BRCA mutations and DNA repair?

Prof Ashworth: The BRCA1 and BRCA2 genes are involved in a repair pathway for double-strand DNA breaks that occur very close to each other. An elaborate mechanism called homologous recombination fixes some of these double-strand breaks, and BRCA2 and BRCA1 are critical for homologous recombination.



Where does PARP fit in?

PARP is a very active enzyme involved in the repair of single-strand breaks in DNA or modified bases. It binds to DNA damage and adds multiple sugar molecules to the DNA that act as a beacon to recruit other components of DNA repair.

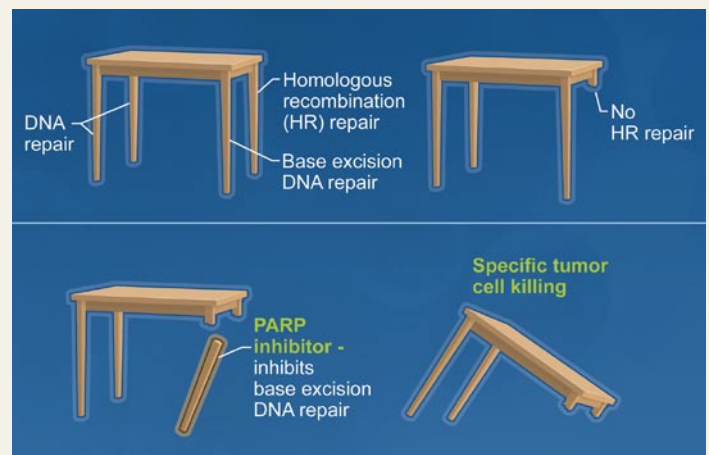


What about PARP inhibitors?

The PARP enzyme was discovered in the early 1960s, and PARP inhibitors have been around for 20-odd years. Most of the early ones were not very potent or specific. Recently a number of more specific and potent PARP inhibitors have been developed.

How does this tie in to synthetic lethality?

Synthetic lethality is about exploiting the genetic defects in tumors and involves an underlying linkage between two biochemical pathways in which a defect in one pathway (eg, homologous recombination) doesn't have any ostensible effects, and then a separate defect in another (eg, DNA base excision repair) has no ostensible effects but



when you put them together, you get a combination or synthesis of lethality.

What are your thoughts on the concept of BRCAness – particularly as it relates to triple-negative breast cancer?

BRCAness is when you have a defect in the pathway of homologous recombination not caused by mutations in BRCA1 or BRCA2. Triple-negative

tumors look like the tumors that arise in BRCA1 mutation carriers, and that's part of the reason we developed this concept. One can imagine assays for BRCAness that involve measuring DNA repair processes in tumors, and this could become the ultimate gold standard to determine whether a patient might respond to a PARP inhibitor.

It sounds like we aren't there yet.

We're close. The recently published work of Nick Turner in my lab focuses on RAD51, which switches on in response to DNA damage as a marker of homologous recombination. Patients with tumors that don't have RAD51 tend to resemble the phenotypes of BRCAness and look more like triple-negative cancers. So if we can prove this in a prospective trial, we believe it can be used in patient selection for PARP inhibitors.

What about emerging work on assays for PARP?

There is a school of thought that PARP levels might correlate with response to PARP inhibitors. It's kind of a traditional view of a target and drug that go together. I believe that's missing the point a bit in terms of what synthetic lethality is. All the data so far are either preliminary or unpublished, and we'd like to see proper studies to establish whether PARP levels are related to response to treatment.

Do you think that's what eventually will be demonstrated?

No, I don't think so. But that's my guess. I have no proof of that.

After listening intently to this master professor for more than 60 minutes, together we joined a stellar faculty at a symposium our CME group hosted that night on, what else, TNBC. During that meeting, Prof Ashworth further elaborated on these topics and we explored other molecular and clinical developments in this patient subset that is about as common as HER2-positive disease ([click here](#) to see the symposium slides). By the end my head was spinning but my spirits were lifted because although SABCS 2010

**Clinical and Translational Advances in
Management of TNBC**

December 10, 2010

Professor Alan Ashworth, FRS

Kimberly L Blackwell, MD

Lisa A Carey, MD

Edith A Perez, MD

Eric P Winer, MD

might not have altered very much in terms of practical management of TNBC, major and exciting changes seem to be just around the corner.

Next up on this San Antonio highlight series: Seven years after another memorable interview — when Soon Paik first told us about the NSABP data on Oncotype DX® — more data and the announcement of a new node-positive trial on the use of genomic assays in the selection of patients for adjuvant chemotherapy.

Neil Love, MD

Research To Practice

Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in each activity.

This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

This email was sent to you by Dr Neil Love and Research To Practice. To unsubscribe to future email requests and announcements, [click here](#). To unsubscribe from all email communications, including CME/CNE activities sent by Research To Practice, [click here](#). To update your information on our current distribution lists, [click here](#).

Preclinical and Clinical Proof-of-Concept Studies of PARP Inhibitors with or without DNA-Damaging Chemotherapeutic Agents for TNBC

Presentations discussed in this issue

Ossovskaya V et al. **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.** San Antonio Breast Cancer Symposium 2010; **Abstract P5-06-09**.

Moulder S et al. **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).** San Antonio Breast Cancer Symposium 2010; **Abstract P6-15-01**.

Veeck J et al. **Promoter CpG methylation of BRCA1 predicts sensitivity to PARP inhibitors in breast cancer.** San Antonio Breast Cancer Symposium 2010; **Abstract S4-8**.

Slides from presentations at SABCS 2010 and transcribed comments from a recent interview with Harold J Burstein, MD, PhD (12/22/10)

Phase 1b Study of Iniparib (BSI-201) Combined with Irinotecan for Treatment of Metastatic Breast Cancer¹

Cell Cycle Effects of Iniparib plus Gemcitabine and Carboplatin in a Triple Negative Breast Cancer Cell Line²

Promoter CpG Methylation of BRCA1 Predicts Sensitivity to PARP Inhibitors in Breast Cancer³

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

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

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

Research
To Practice®

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.

Research
To Practice®

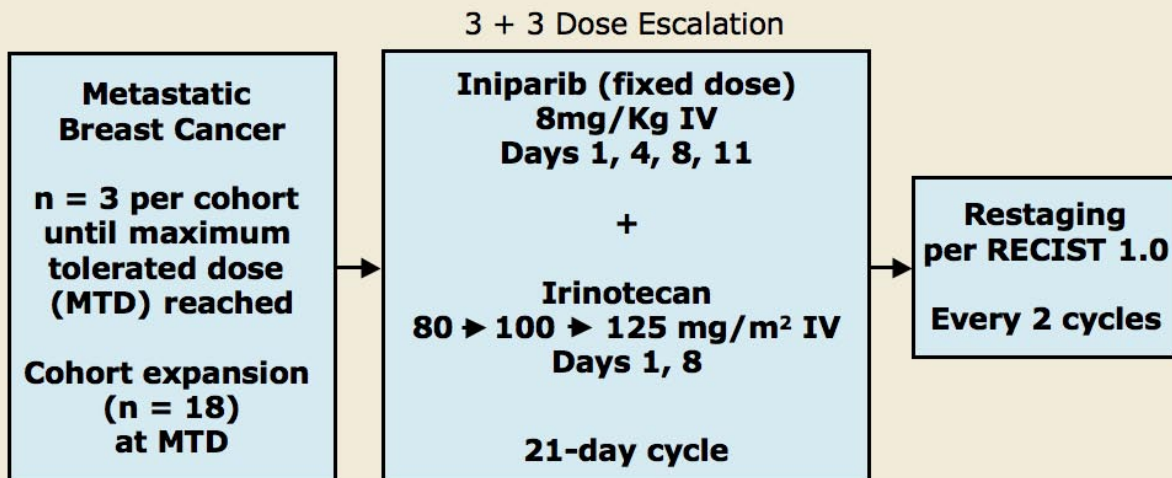
Key Eligibility Criteria

- Adenocarcinoma of the breast.
- Progressive locoregional or metastatic disease.
- Bi-dimensionally measurable indicator lesion \geq 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.*

Research
To Practice®

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.

Research
To Practice®

Safety Results

		Iniparib + Irinotecan 80mg/m ² (n = 3)	Iniparib + Irinotecan 100mg/m ² (n = 6)	Iniparib + Irinotecan 125mg/m ² (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.

Research
To Practice®

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.

Research
To Practice®

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/m² 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.

Research
To Practice®

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.

Research
To Practice®

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 μ M), gemcitabine (1 or 2 nM), and/or carboplatin (5 or 10 μ M), 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.*

Research
To Practice®

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.

Research
To Practice®

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.

Research
To Practice®

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

Veeck J et al.

Proc SABCS 2010;Abstract S4-8.

Research
To Practice®

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.*

Research
To Practice®

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.

Research
To Practice®

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.

Research
To Practice®

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

Research
To Practice®