5 Minute JournalClub

Key SABCS Presentations

Issue 3, 2011

EGFR Inhibition with Cetuximab in Patients with Metastatic Triple-Negative Breast Cancer (mTNBC)

For more visit ResearchToPractice.com/5MJCSABCS2011

Research To Practice®

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 OBJECTIVE

- Explain the results of a randomized Phase II trial evaluating the combination of cetuximab and cisplatin for patients with mTNBC.

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 presentation, 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

5 MinuteJournalClub

Key SABCS Presentations
Issue 3, 2011

Click here for papers on the modest benefit observed in patients with TNBC receiving chemotherapy and either **bevacizumab** or **cetuximab**.

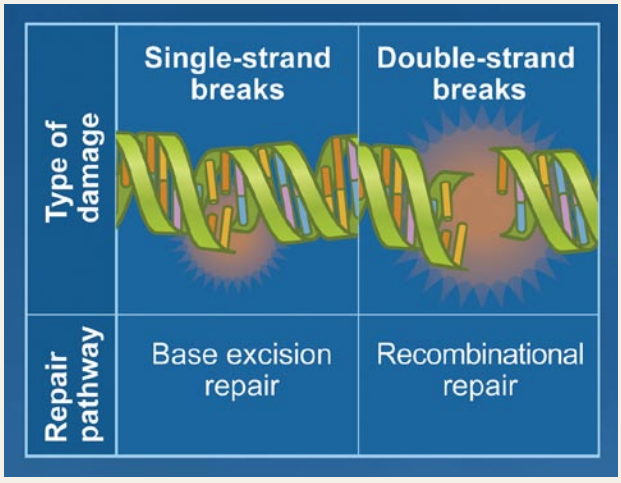
Click here for papers on a **Phase IB trial** combining the PARP inhibitor iniparib and irinotecan in metastatic breast cancer, a study on the **in vitro effects of iniparib** on a TNBC cell line and a **fascinating report** suggesting that epigenetic promoter methylation of BRCA genes may correlate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

Professor Alan Ashworth

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.

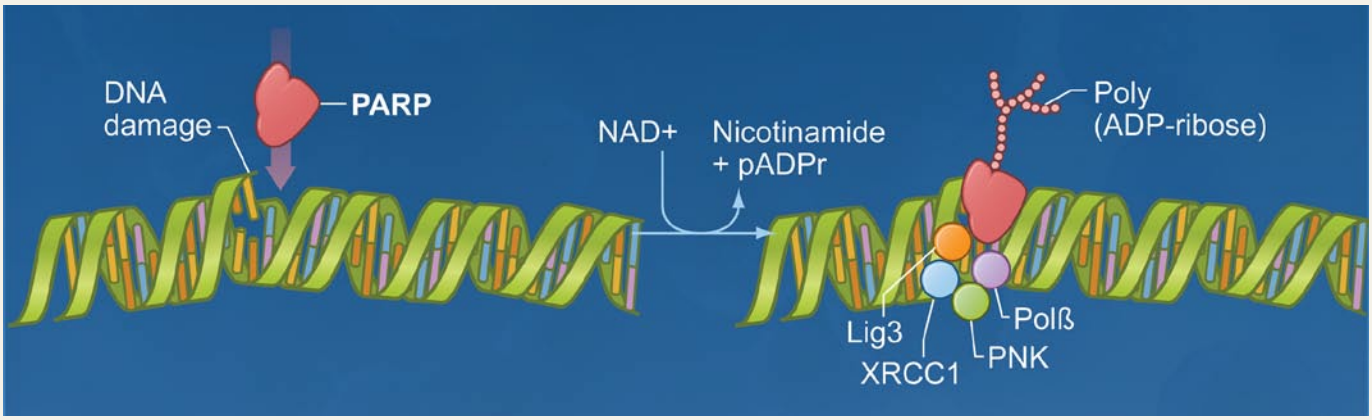
Dr Love: What do we know about BRCA mutations and DNA repair?

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?

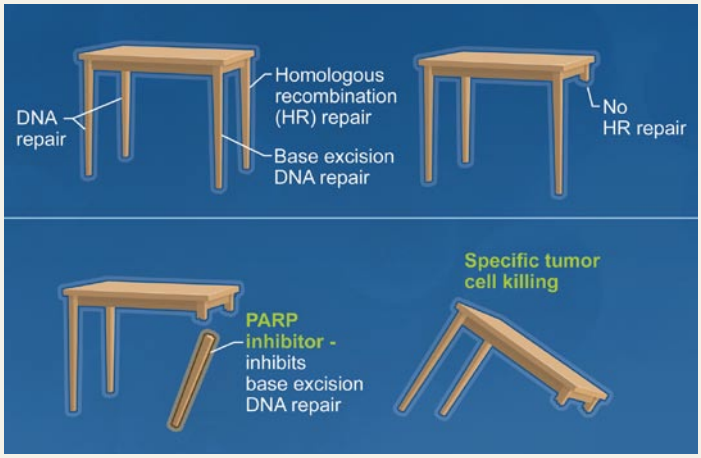
PARP is a very active enzyme involved in the repair of single-strand breaks in DNA or modified bases. It binds to DNA damage and adds multiple sugar molecules to the DNA that act as a beacon to recruit other components of DNA repair.



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 lethalities.

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 it 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

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 Onco*type* 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

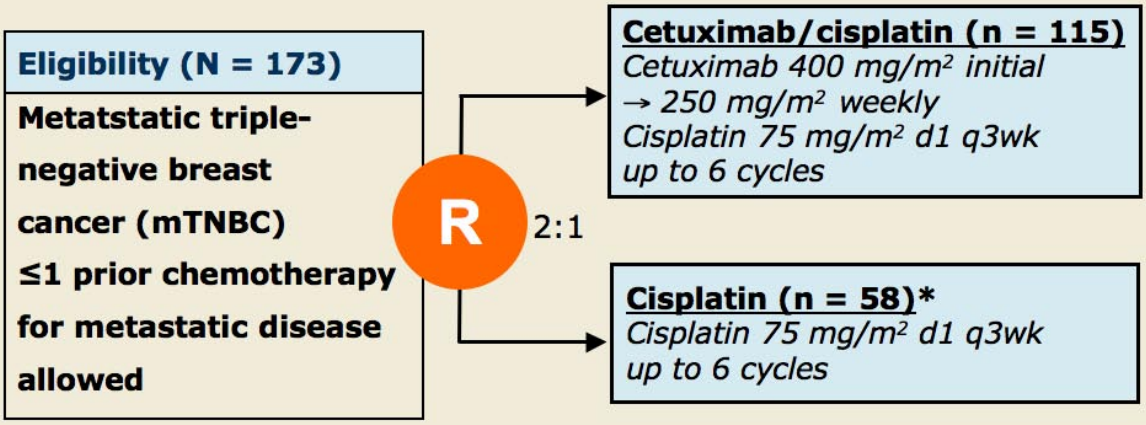
EGFR Inhibition with Cetuximab in Patients with Metastatic Triple-Negative Breast Cancer (mTNBC)

Presentation discussed in this issue

Baselga J et al. **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.** San Antonio Breast Cancer Symposium 2010;**Abstract PD01-01**.

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

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.

Research To Practice®

Response Rates

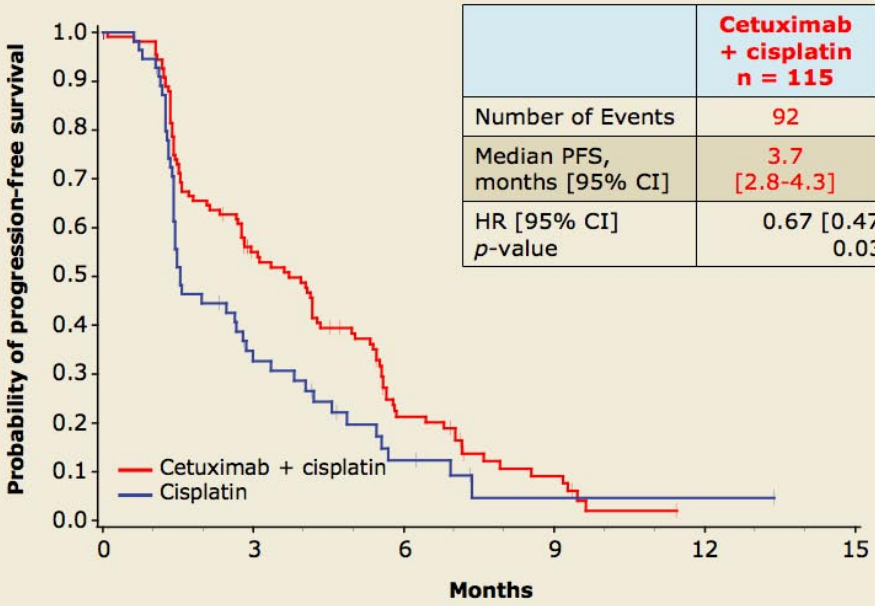
Best Response	Cetuximab + Cisplatin (n = 115)	Cisplatin Alone (n = 58)
Overall response (ORR)*	20.0%	10.3%
Complete response (CR)	1.7%	1.7%
Partial response (PR)	18.3%	8.6%
Stable disease	41.7%	31.0%
Progressive disease	29.6%	53.4%
Odds ratio (95% CI)	2.13 (0.81-5.59)	
p-value	0.11	

*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.

Research To Practice®

Progression-Free Survival (PFS)

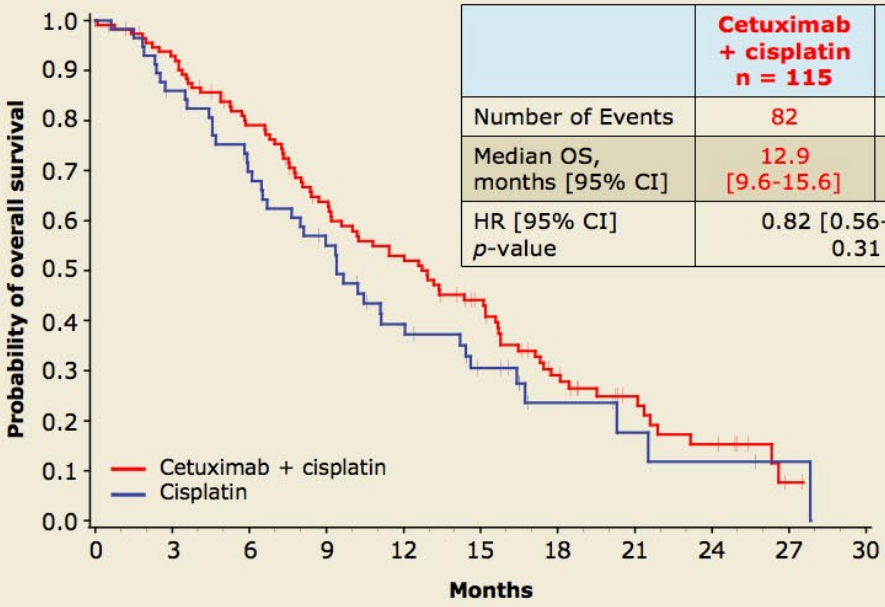


	Cetuximab + cisplatin n = 115	Cisplatin n = 58
Number of Events	92	47
Median PFS, months [95% CI]	3.7 [2.8-4.3]	1.5 [1.4-2.8]
HR [95% CI] *p*-value	0.67 [0.47-0.97] 0.03	

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

Research To Practice®

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.

Research To Practice®

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.

Research To Practice®

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.

Research To Practice®

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