5 Minute JournalClub

Key SABCS Presentations
Issue 3, 2011

Phase III Study and Meta-Analysis Results with Bevacizumab and First-Line Chemotherapy for Metastatic Breast Cancer (mBC)

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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

- 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.

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

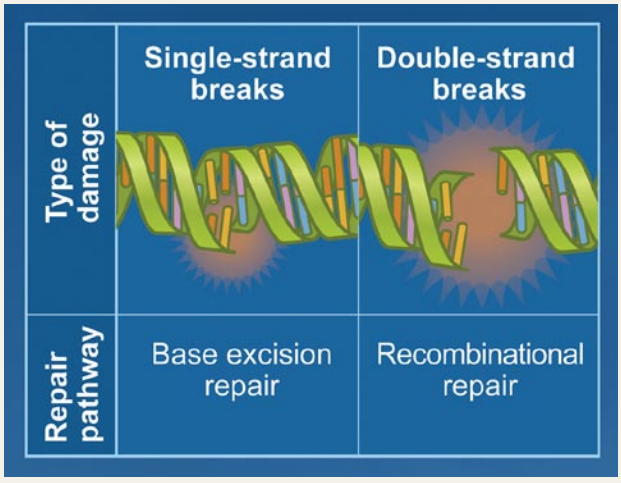
Click here for papers on a **Phase IB trial** combining the PARP inhibitor iniparib and irinotecan in metastatic breast cancer, a study on the **in vitro effects of iniparib** on a TNBC cell line and a **fascinating report** suggesting that epigenetic promoter methylation of BRCA genes may correlate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

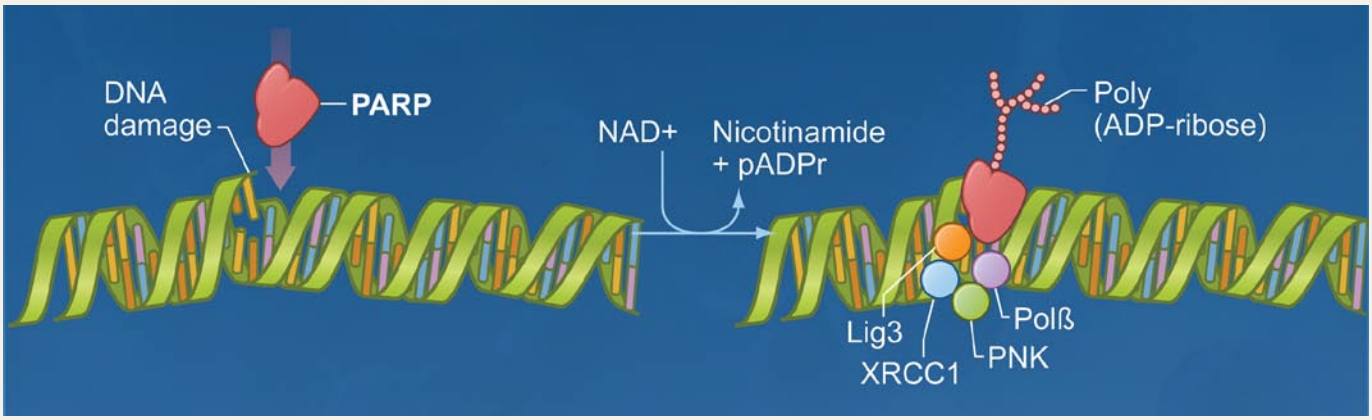
Dr Love: What do we know about BRCA mutations and DNA repair?

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?

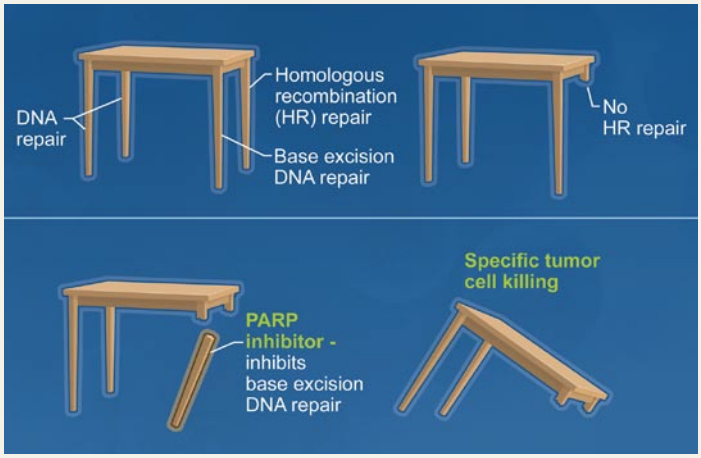
PARP is a very active enzyme involved in the repair of single-strand breaks in DNA or modified bases. It binds to DNA damage and adds multiple sugar molecules to the DNA that act as a beacon to recruit other components of DNA repair.



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
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Phase III Study and Meta-Analysis Results with Bevacizumab and First-Line Chemotherapy for Metastatic Breast Cancer (mBC)

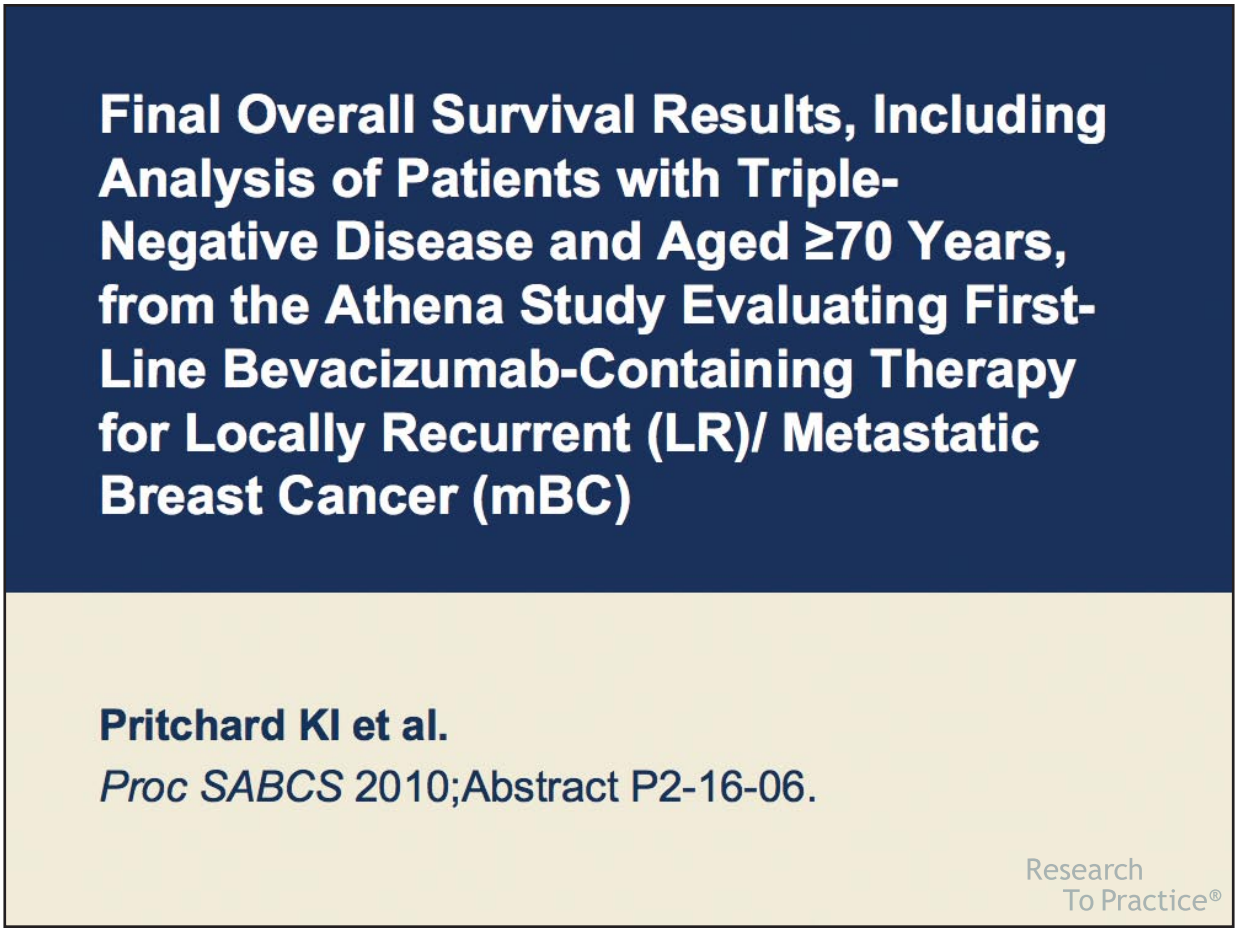
Presentations discussed in this issue

Pritchard KI et al. **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).** San Antonio Breast Cancer Symposium 2010;**Abstract P2-16-06**.

O'Shaughnessy J et al. **Meta-analysis of patients with triple-negative disease from three randomized trials of bevacizumab and first-line chemotherapy as treatment for metastatic breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract P6-12-03**.

Von Minckwitz G et al. **Neoadjuvant chemotherapy with or without bevacizumab: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44).** San Antonio Breast Cancer Symposium 2010;**Abstract S4-6**.

Slides from presentations at SABCS 2010 and transcribed comments from recent interviews with Harold J Burstein, MD, PhD (12/22/10) and William J Gradishar, MD (1/4/11)



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.

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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.

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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 ≥ 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 ≥ 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.

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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.

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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)

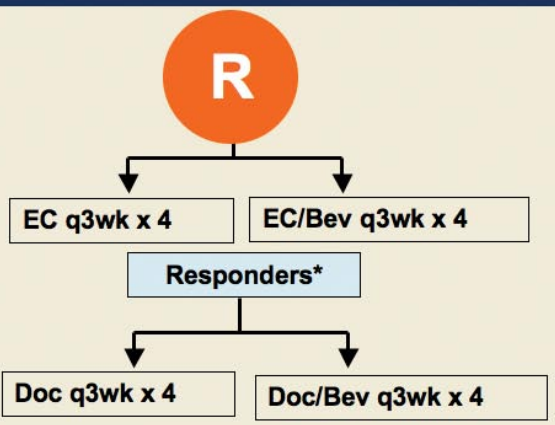
von Minckwitz G et al.

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.

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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.

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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.

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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.

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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

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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

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