5 Minute JournalClub

Double-Blind, Randomized Phase IIb Study of Paclitaxel with or without Sorafenib for Patients with HER2-Negative Advanced Breast Cancer

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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 where 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

- Review the potential benefit of combining sorafenib with paclitaxel as first-line therapy for HER2-negative advanced breast cancer.

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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:

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IN THIS ISSUE:

- Phase II: **Sorafenib shows trend to improved PFS with paclitaxel**
- Phase II: **Sorafenib improves PFS with capecitabine**
- Phase II: **Sunitinib has similar or inferior effect as capecitabine**
- Mechanism of action of TKIs: **Spectacular *NEJM* artwork** (best in the biz)

During a 2008 interview, I queried leukemia maven Dr Michael Keating about current clinical trials in CML. "Imatinib is the Big Dog, and while there are Phase III studies comparing it to second-generation TKIs, they're trying to prove that something's better than magic." Nine years after the FDA approval of what sure seems like magic, last month at ASH nilotinib actually was shown to be superior to imatinib when using state-of-the-art CML RT-PCR and FISH assay technology. The unexpected bottom line is, in a disease that's more than 90 percent "curable" with imatinib treatment, the rate of accelerated phase/blast transformation with nilotinib was 0.4 percent compared to 3.9 percent for imatinib. That, along with equal or better tolerability, might just be practice changing in the near future.

Meanwhile, investigators are desperately looking for TKIs in other cancers that come close to the Big Dog, and other than GIST, perhaps the greatest success has been in non-small cell lung cancer, in which first EGFR mutant tumors and now EML4-ALK fusion cancers seem to fit the oncogene addiction model and respond pretty well to TKIs.

On the angiogenic side of the equation, renal cell cancer seems to lead the way, with the VEGFR TKIs sunitinib and sorafenib benefiting many or most treated patients, although a long way from magic. In breast cancer, most of the encouraging TKI news has been with HER2-positive tumors, for which lapatinib has significant antitumor activity both with chemo and trastuzumab, and neratinib, another HER2 TKI, is demonstrating promising activity.

HER2-negative tumors are a different matter, and until San Antonio, it was difficult to get excited about what was seen. However, in back-to-back oral presentations, Bill Gradishar and then Jose Baselga reported two Phase II randomized trials demonstrating PFS advantages when sorafenib was added to paclitaxel in one study and capecitabine in another. Dermatologic toxicity was substantial, particularly when

sorafenib was combined with capecitabine, suggesting the need for dose/schedule adjustments in future trials.

At a breast cancer roundtable we hosted last week in our Miami studio with an impressive faculty of nine investigators, it was noted that sorafenib got its moniker partly in recognition of RAF inhibitory properties but that the agent is also known to inhibit PDGFR, along with what is thought to be its major effect on VEGF blockade. I shared with the group my recent surprise when another MD Anderson leukemia wizard, Dr Farhad Ravandi, told me that sorafenib is also being evaluated clinically as an FLT3 inhibitor in patients with AML.

The two Phase II sorafenib studies reported at San Antonio are part of an integrated set of four Phase II trials called the TIES program, and roundtable participant Cliff Hudis noted that Memorial and ACORN are participating in the effort by evaluating capecitabine or gemcitabine, with or without sorafenib. During the roundtable discussion Edith Perez stated she thought that this complex multitargeted TKI might end up having similar anti-angiogenic activity as bevacizumab but with the important option of oral administration, although the faculty was uncertain whether sorafenib will end up in daily breast cancer clinical practice.

As suggested by **our graphics slide set** on potential mechanisms of action of TKIs in cancer, there is an urgent need to dissect the specific pathways affected by the panoply of novel targeted agents like sorafenib. Only this will allow us to exchange our current organ-based cancer treatment strategy for a molecular one as we learn how to select the correct biologic agent for the appropriate patient.

Next up on 5-Minute Journal Club: More from San Antonio and a simultaneous *Lancet Oncology* publication on the SWOG node-positive Onco*type* DX® study: No surprises, and more evidence to take action.

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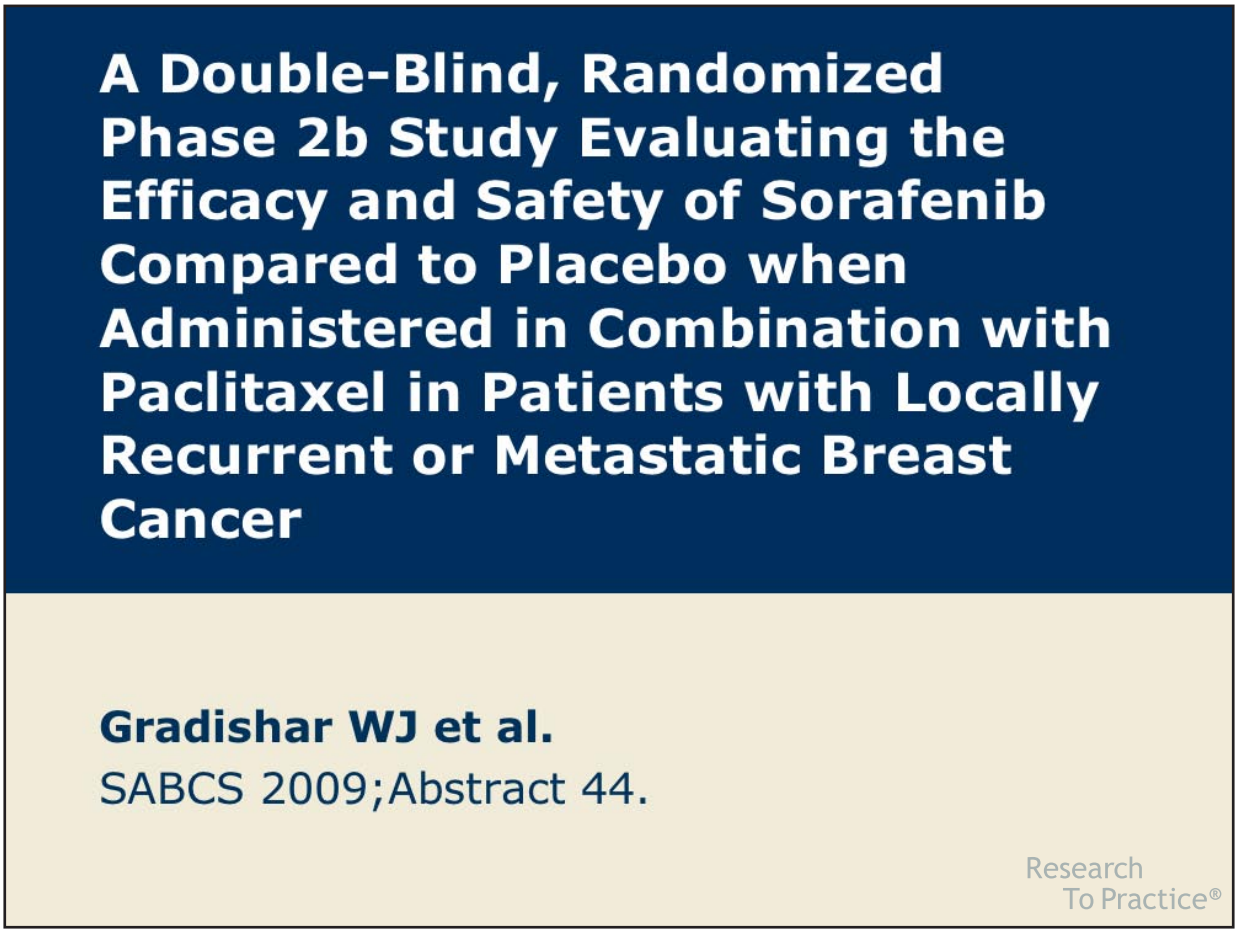
Double-Blind, Randomized Phase IIb Study of Paclitaxel with or without Sorafenib for Patients with HER2-Negative Advanced Breast Cancer

Presentation discussed in this issue

Gradishar WJ et al. **A double-blind, randomized Phase IIb study evaluating the efficacy and safety of sorafenib compared to placebo when administered in combination with paclitaxel in patients with locally recurrent or metastatic breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 44**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Adam M Brufsky, MD, PhD (12/23/09)



Introduction

- Phase III trial of first-line paclitaxel and bevacizumab (bev) in patients with metastatic breast cancer (mBC) has demonstrated improved efficacy when compared to paclitaxel alone (*NEJM* 2007;357:2666).
  - Median progression free survival (PFS) = 11.8 mos vs 5.9 mos
  - Objective response rate (ORR) = 36.9% vs 21.2%
- Phase II trials have demonstrated modest single-agent activity with sorafenib in patients with heavily pre-treated mBC (*JCO* 2009;27:11, *AntiCancer Drugs* 2009;20:616).
- Phase I trial of combined paclitaxel, carboplatin and sorafenib therapy has shown regimen to be well tolerated in patients with advanced solid tumors (*Clin Cancer Res* 2008;14:4836).
- **Current Study Objectives:**
  - Assess the safety and efficacy of paclitaxel combined with sorafenib compared to paclitaxel and placebo for locally recurrent or metastatic BC (mBC).

Gradishar W et al. SABCS 2009;Abstract 44.

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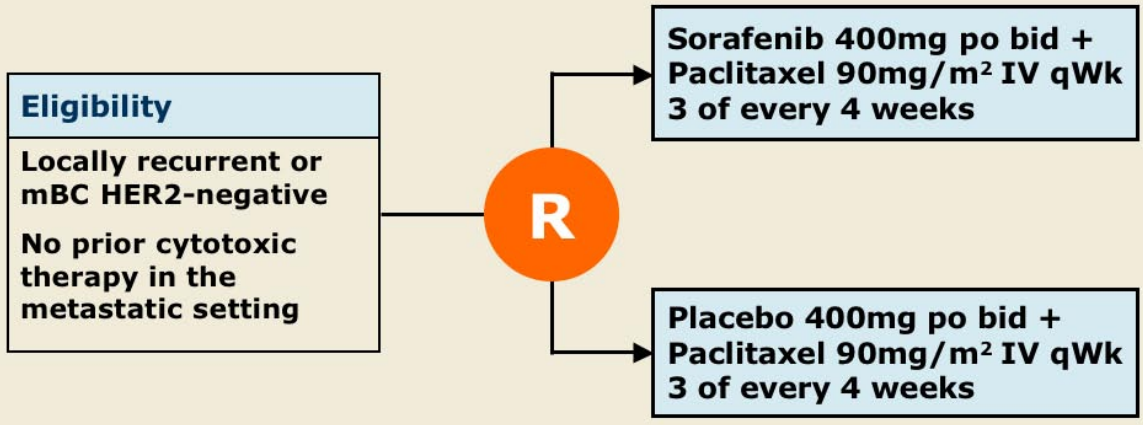
Phase IIb Double-Blind Study of Sorafenib Compared to Placebo When Combined with Paclitaxel



Gradishar W et al. SABCS 2009;Abstract 44.

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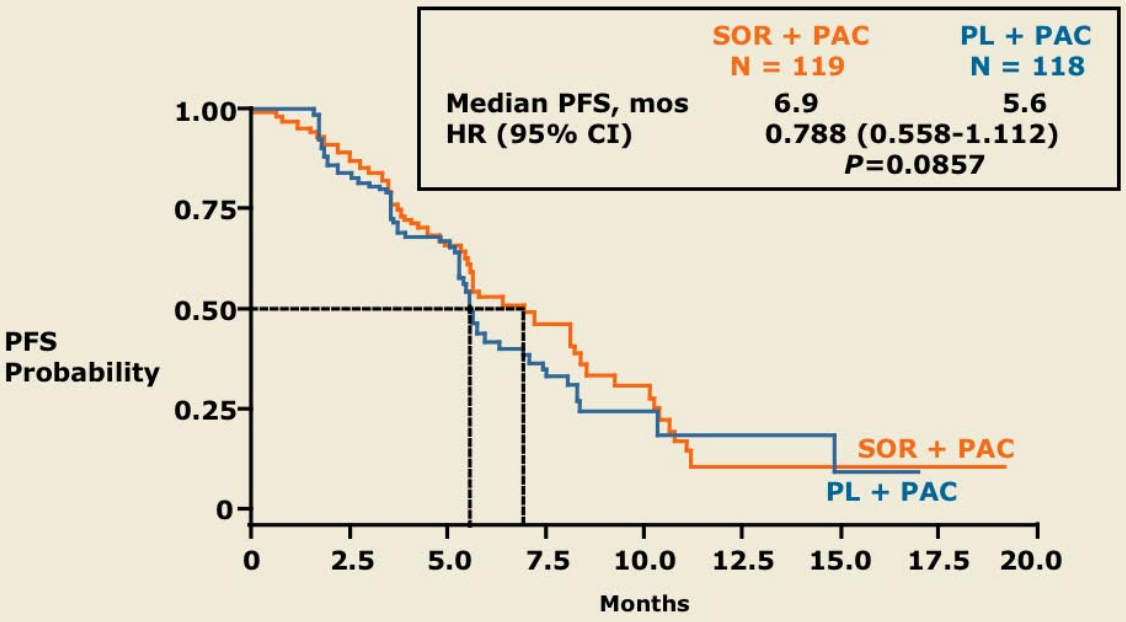
Primary Endpoint: PFS (Intent-to-Treat Population)



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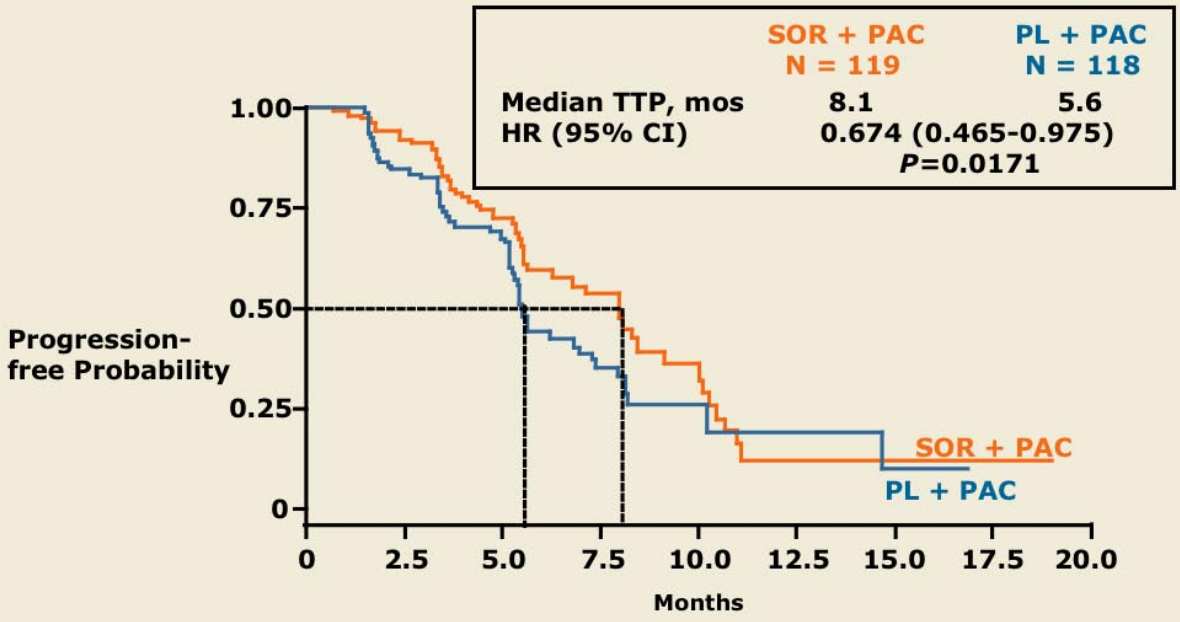
Secondary Endpoint: Time to Progression (Intent-to-Treat Population)



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Response Rate

Clinical Response, n (%)	Sorafenib + Paclitaxel (n=119)	Placebo + Paclitaxel (n=118)	*p*-value
Overall response rate Complete response Partial response	80 (67%) 8 (7%) 72 (61%)	64 (54%) 5 (4%) 59 (50%)	0.0234
Stable disease	16 (13%)	32 (27%)	—
Progressive disease	9 (8%)	17 (14%)	—
Median duration of response*	5.6 mos	3.7 mos	0.0079

**Calculated for responders only. Nonresponders were assigned a value of zero.*

Gradishar W et al. SABCS 2009;Abstract 44.

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Select Adverse Events - Grade 3/4 (Safety Population)

Adverse Events	Sorafenib + Placebo (n=115)	Placebo + Paclitaxel (n=118)
Hand-foot syndrome	**30%**	**3%**
Asthenia	7%	3%
Peripheral neuropathy	6%	7%
Neuropathy	5%	1%
Neutropenia	13%	7%
Anemia	10%	6%
Vomiting	3%	0%
Stomatitis	3%	0%

Gradishar W et al. SABCS 2009;Abstract 44.

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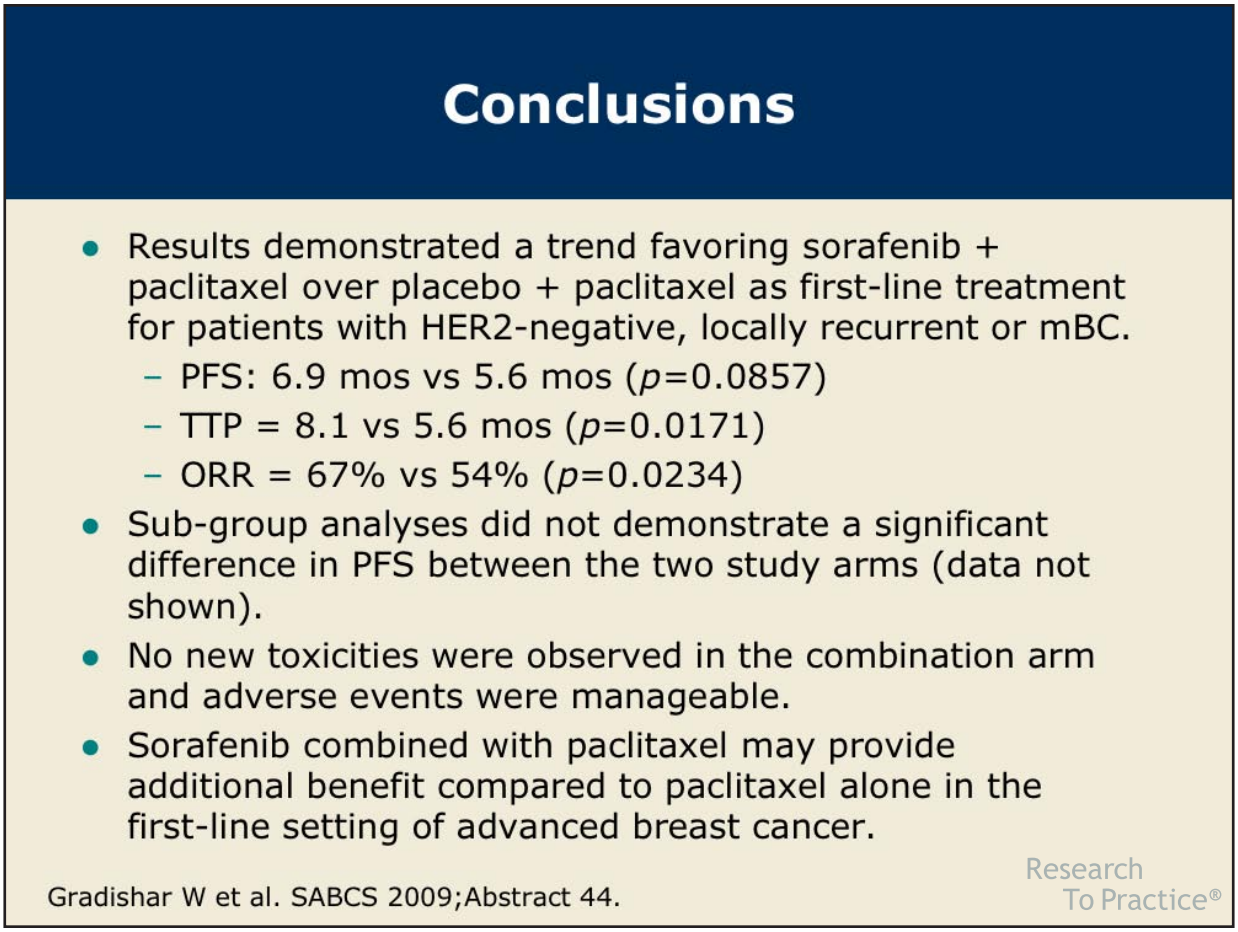

ADAM M BRUFSKY, MD, PhD: Gradishar and his colleagues examined the activity of sorafenib, a multitargeted tyrosine kinase inhibitor against VEGF, EGFR, VGFR1 and VGFR2, in advanced breast cancer. The idea behind this study is great, especially since we know that activity with sorafenib already exists in both renal cell and hepatocellular carcinoma. Therefore, it's possible that sorafenib is also active in breast cancer.

This trial is part of the TIES program, a program comprising different trials investigating the efficacy of sorafenib worldwide. In this particular study, eligible patients need to have locally recurrent or metastatic breast cancer that must be HER2/neu-negative. The study design is straightforward, with 220 patients randomly assigned to first-line therapy with weekly paclitaxel at the ECOG-E2100 dose of 90 mg/m^2 with or without sorafenib.

Interestingly, the difference in progression-free survival (PFS) between the two arms was not statistically significant. As a result, a subgroup analysis was performed to see if one group deviated wildly from the others, but none were identified. The secondary endpoint of time to disease progression seemed to illustrate more of a benefit with the combination arm: 8.1 months compared to 5.6 months. But one must be cautious when evaluating these trials in which the endpoint chosen to depict the data is a little outside of the primary endpoint. The response rate also seemed to be higher with

the sorafenib arm: 67 versus 54 percent. Regarding adverse events, the major issue observed was hand-foot syndrome, which is often seen in sorafenib trials.

Overall, this study indicates potential trends toward improvement in efficacy with the addition of sorafenib to paclitaxel. The only difference between this study and previous trials is that this is a large, randomized, Phase II experience. Appropriately, the investigators suggest that this could lead to a large Phase III study. But I don't believe there is a take-home message for the practicing oncologist quite yet. Personally, I would not use sorafenib with paclitaxel as first-line therapy just yet.

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