5 Minute JournalClub

SOLTI-0701 — A Double-Blind, Randomized Phase IIb Study of Capecitabine with or without Sorafenib in 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

- Evaluate the potential benefit of capecitabine and sorafenib as first- and second-line therapy for advanced breast cancer.

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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.

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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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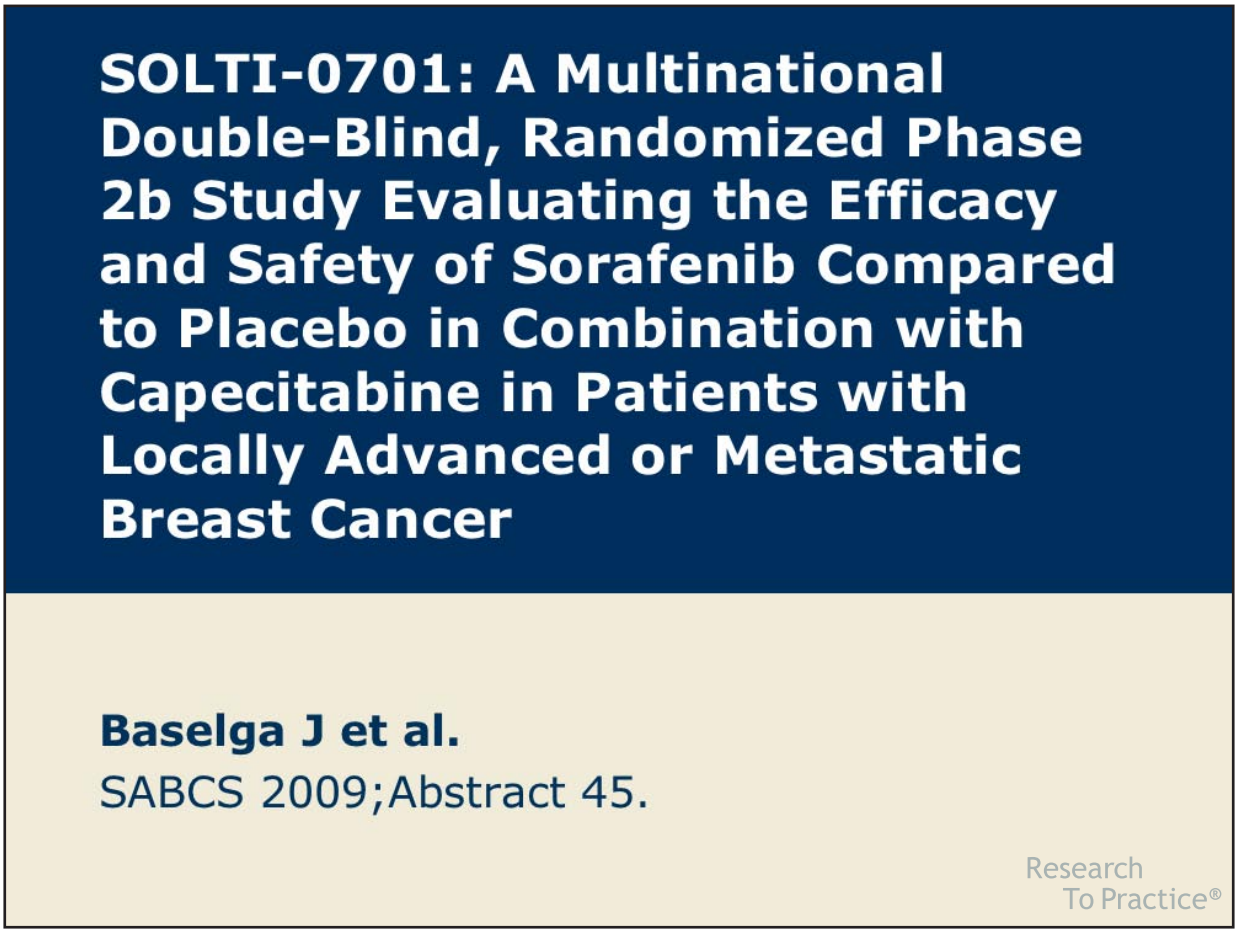
SOLTI-0701 — A Double-Blind, Randomized Phase IIb Study of Capecitabine with or without Sorafenib in Advanced Breast Cancer

Presentation discussed in this issue

Baselga J et al. **SOLTI-0701: A multinational double-blind, randomized Phase 2b study evaluating the efficacy and safety of sorafenib compared to placebo when administered in combination with capecitabine in patients with locally advanced or metastatic breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 45**.

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 capecitabine (CAP) combined with anti-VEGF agent bevacizumab demonstrated an improved objective response rate (ORR) in patients with metastatic breast cancer, though progression-free survival (PFS) was not prolonged (*JCO* 2005;23:792).
  - ORR: 19.8% (combination) vs 9.1% (CAP alone)
  - PFS: 4.86 mos vs 4.17 mos
- Sorafenib (SOR), a multi-targeted tyrosine kinase inhibitor (TKI), targets VEGF receptors VEGFR1 and VEGFR2.
- Phase I studies have found combination therapies containing SOR and CAP to be safe and feasible (*Ann Oncol* 2007;18:Abstract 402, *ASCO* 2008;Abstract 369).
- **Current Study Objectives:**
  - Assess the efficacy and safety of combination therapy with sorafenib and capecitabine in patients with advanced breast cancer.

Baselga J et al. SABCS 2009;Abstract 45.

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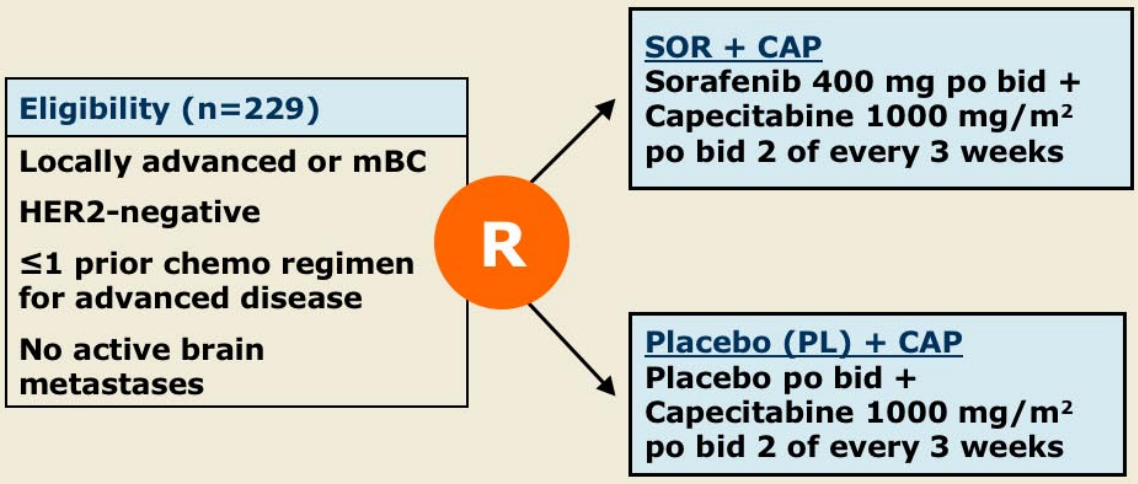
SOLTI-0701: Phase IIb, Double-blind, Placebo-Controlled Study of Sorafenib Combined with Capecitabine



Baselga J et al. SABCS 2009;Abstract 45.

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Efficacy Results

Efficacy Parameter	SOR + CAP	PL + CAP	Hazard Ratio	*p*-value
Progression-free survival (PFS)				
Intent-to-treat (n=115, 114)	6.4 mos	4.1 mos	0.576	0.0006
1st-line patients (n=50, 62)	7.6 mos	4.1 mos	0.498	0.0022
2nd-line patients (n=65, 51)	5.7 mos	4.1 mos	0.652	0.0339
ORR (n=115, 114)	38.3%	30.7%	—	0.1229
Complete response	1.7%	0.9%		
Partial response	36.5%	29.8%		
Stable disease	43.5%	37.7%		
Progressive disease	10.4%	23.7%		

Baselga J et al. SABCS 2009;Abstract 45.

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

Adverse Events	SOR + CAP (N=112)	PL + CAP (N=112)
Hand-foot syndrome	**45%**	**13%**
Diarrhea	5%	5%
Dyspnea	5%	4%
Neutropenia	5%	3%

Most common adverse events related to treatment discontinuation in sorafenib and placebo arms:

- **Hand-foot skin reaction: 8 vs 2 patients**
- **Diarrhea: 1 vs 3 patients**

Baselga J et al. SABCS 2009;Abstract 45.

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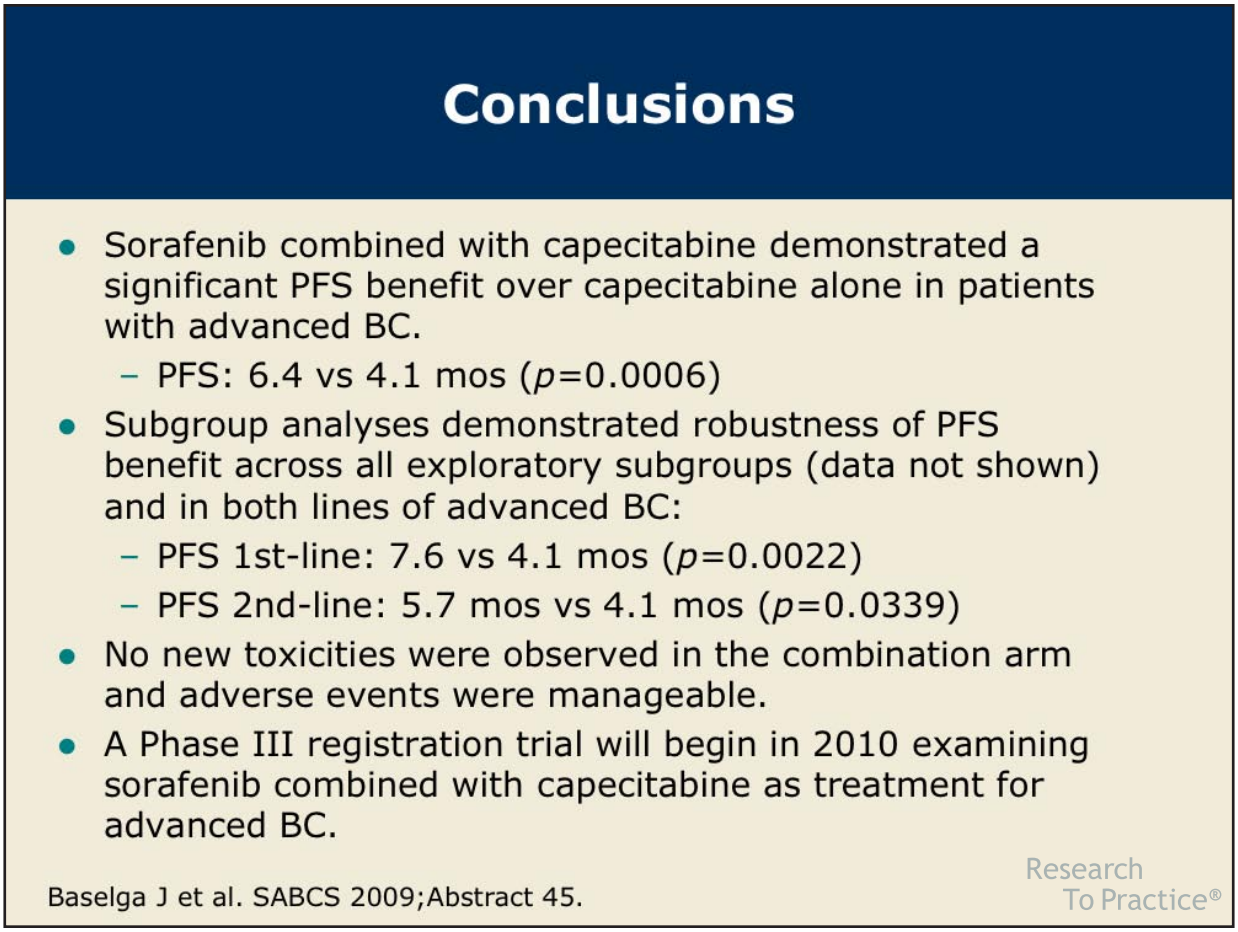

DR BRUFSKY: José Baselga and a group of European investigators presented the SOLTI-0701 trial analyzing first-line and second-line therapy. This trial was conducted in Spain, France and Brazil and comprised 220 patients with metastatic breast cancer. Patients were randomly assigned to receive capecitabine two weeks out of three, with or without sorafenib. The design of the trial is straightforward and similar to that of RIBBON 1 and RIBBON 2. Results were average, as expected. Fairly substantial hand-foot syndrome and moderate diarrhea occurred, and as a consequence some patients were forced to discontinue therapy. Interestingly, sorafenib and capecitabine demonstrated a reduction in the risk of disease progression of almost 40 to 50 percent, with a progression-free survival of 6.4 months versus 4.1 months with placebo and capecitabine.

Overall the data are promising with a benefit in PFS in the experimental arm. There was an even greater benefit for patients receiving sorafenib in the first-line setting compared to those receiving it in the second-line setting. Remarkably, both the first-line and the second-line placebo arms maintained a 4.1-month progression-free survival. Though this is not a crucial point, one would typically expect the progression-free survival in the placebo arm to be greater in the first line than in the second line, but this was not the case.

Again, there is some promising activity with sorafenib, which will serve as the basis for a Phase III registrational trial. I believe the take-home message from this and the Gradishar study (see presentation 1 of this 5MJC issue) is that sorafenib has potential but is not yet ready for prime time.

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