5 Minute JournalClub

Sunitinib versus Capecitabine 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

- Summarize the efficacy and safety of sunitinib relative to capecitabine as systemic treatment of taxane- and anthracycline-exposed 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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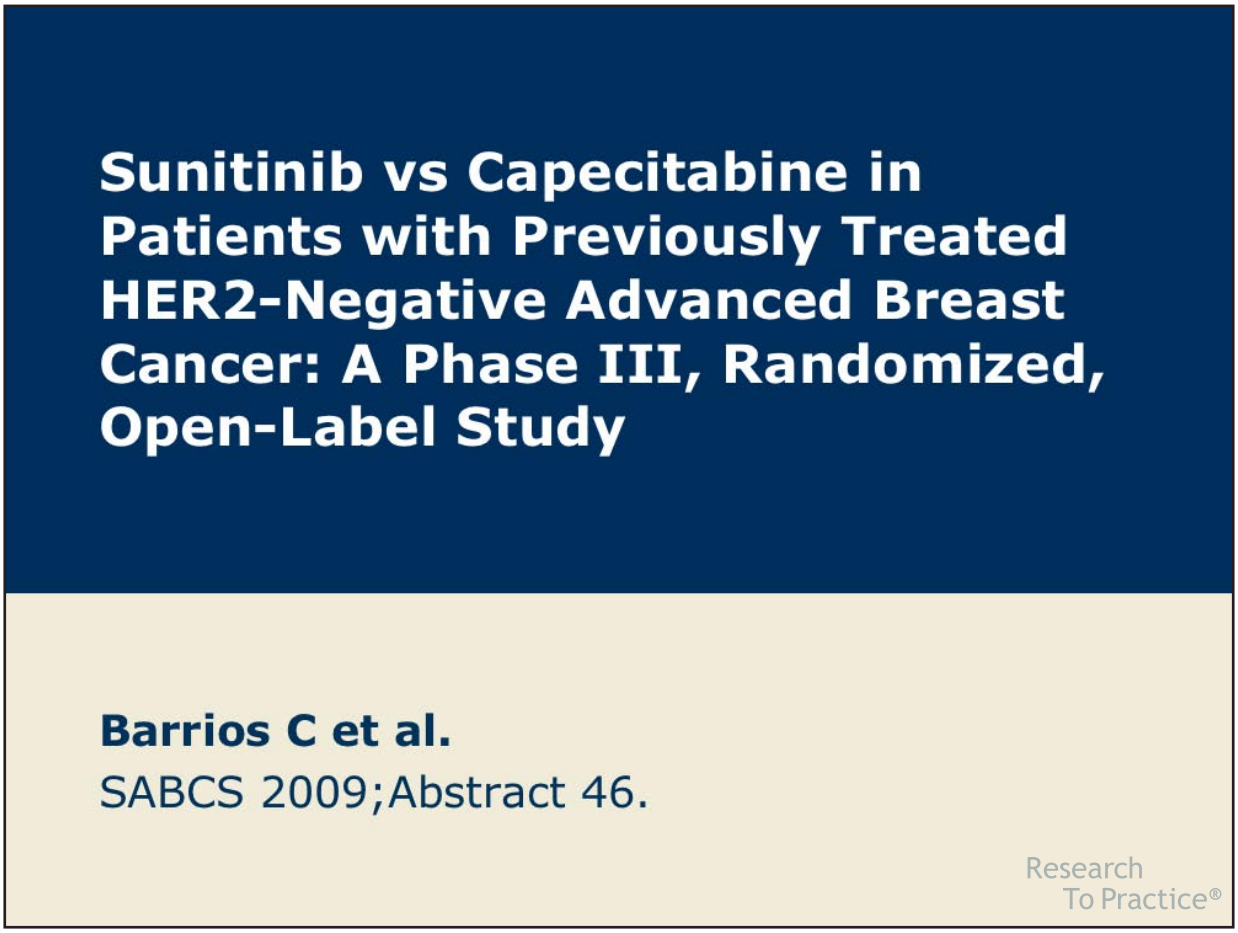
Sunitinib versus Capecitabine for Patients with HER2-Negative Advanced Breast Cancer

Presentation discussed in this issue

Barrios C et al. **Sunitinib vs capecitabine in patients with previously treated HER2-negative advanced breast cancer: A Phase III, randomized, open-label study.** San Antonio Breast Cancer Symposium 2009;**Abstract 46**.

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



Introduction

- Therapeutic inhibition of angiogenic signaling through the VEGFR/PDGFR pathways has previously been demonstrated to improve breast cancer (BC) outcome (*Nat Clin Pract Oncol* 2007;4:536).
- Single agent sunitinib, a multitargeted inhibitor of VEGFR/PDGFR, demonstrated activity in a Phase II trial with heavily pretreated patients with advanced BC (*JCO* 2008;26:1810).
  - Objective response rate (ORR): 11%
- Capecitabine is an approved standard of care for patients with advanced BC (ABC) and disease progression after anthracycline and taxane therapies.
- **Current study objectives:**
  - Compare the efficacy and safety of sunitinib versus capecitabine in patients with HER2-negative ABC whose disease has progressed after anthracycline and taxane therapies.

Barrios C et al. SABCS 2009;Abstract 46.

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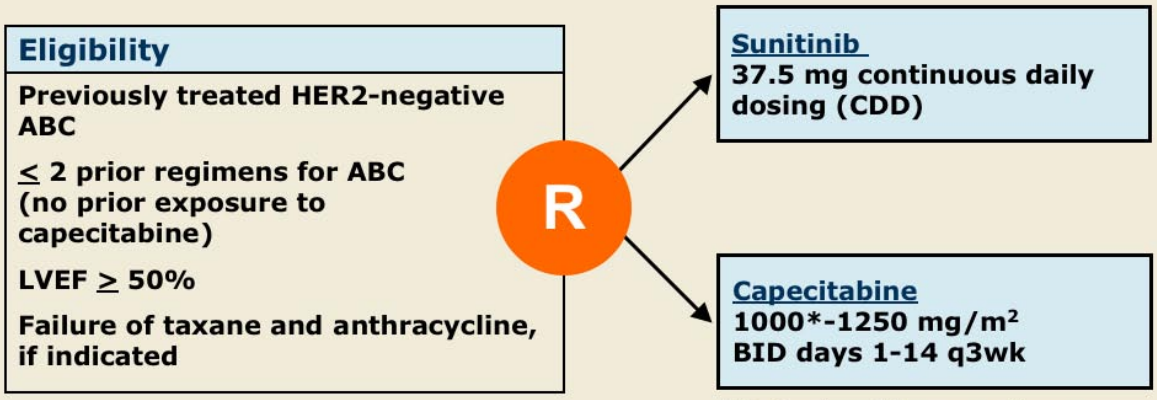
Study 1107: A Phase III, Multicenter, Open-Label Trial of Sunitinib vs Capecitabine in Advanced Breast Cancer

Accrual = 482/planned 700
(Trial closed by IDMC due to futility of reaching superior primary endpoint [progression free survival, PFS])



**Patients >65 years of age*

Barrios C et al. SABCS 2009;Abstract 46.

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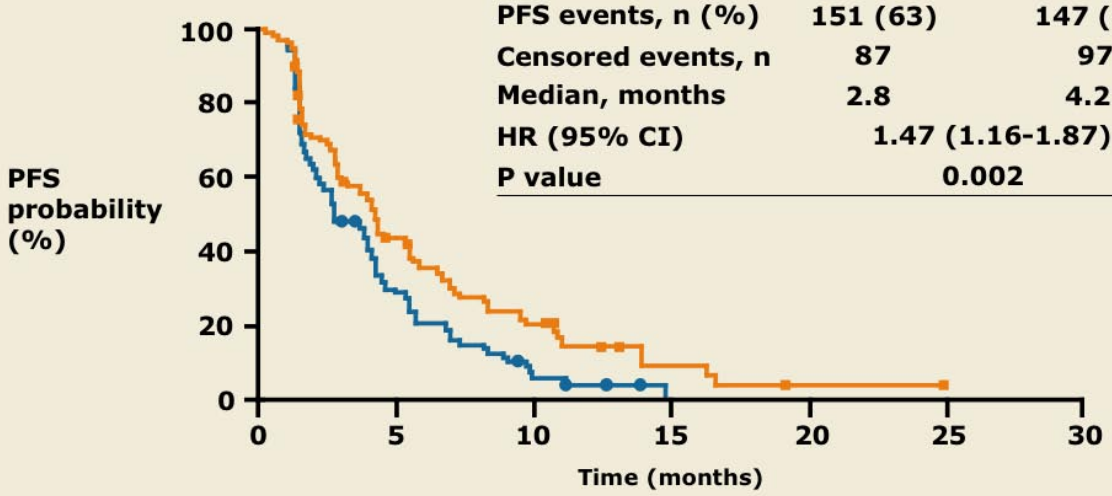
Progression-Free Survival*



	Sunitinib N = 238	Capecitabine N = 244
PFS events, n (%)	151 (63)	147 (60)
Censored events, n	87	97
Median, months	2.8	4.2
HR (95% CI)	1.47 (1.16-1.87)	
P value	0.002	

* Investigator assessment

With permission from Barrios C et al. SABCS 2009;Abstract 46.

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Overall Response*

Response Parameter	Sunitinib (n=238)	Capecitabine (n=244)	Odds Ratio	*p*-value
Objective response rate	11.3%	16.4%	0.65	0.11
Clinical benefit rate	19.3%	27.0%	0.65	0.05
Median duration of response	6.9 mo	9.3 mo	—	NA

* Investigator assessment

Barrios C et al. SABCS 2009;Abstract 46.

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Dose Reductions/Discontinuations and Serious Adverse Events (SAE)

Dose Parameter (%)	Sunitinib N=238	Capecitabine N=240
Median relative dose intensity	73	95
Dose reductions/interruptions	28/52	35/46
Discontinuations due to AEs Related to study drug	15 11	9 5
All-Causality SAEs (%)		
Patients with any SAE	30	17
Diarrhea	2	3
Dyspnea	2	2
Pleural effusion	2	3
Pneumonia	2	0
Thrombocytopenia	2	<1

Barrios C et al. SABCS 2009;Abstract 46.

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Conclusions

- The primary endpoint of improved PFS was not met in patients with ABC when sunitinib monotherapy was compared to capecitabine.
  - Median PFS: sunitinib 2.8 mo vs capecitabine 4.2 mo
- No statistically significant difference in overall survival (OS) was observed.
  - OS: sunitinib, 15.3 mo vs capecitabine, 24.6 mo (p = 0.35)
- No new safety-related events were identified
- The sunitinib relative dose intensity administered may have been inadequate.
  - Median dose intensity: sunitinib 73% vs capecitabine 95%
- Anti-angiogenic approach in BC may require a chemotherapy partner.

Barrios C et al. SABCS 2009;Abstract 46.

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DR BRUFSKY: This presentation demonstrates that all multitargeted tyrosine kinase inhibitors are not created equal. The trial was designed not as an equivalence trial, but as a superiority trial, which is a bit surprising for a single-agent biological being compared to chemotherapy. The trial was stopped because it was not possible for sunitinib to be superior to capecitabine for treatment of HER2-negative, advanced breast cancer. In fact, sunitinib had almost no benefit.

The progression-free survival in the capecitabine arm was 4.2 months and in the sunitinib arm it was 2.8 months, which is the time between two CT scans in measurable disease. The patients' disease progressed through their sunitinib treatment. This trial clearly demonstrates that there's no benefit to sunitinib in this setting and this is not a drug that I would use. These anti-angiogenic drugs need to be used with caution because their benefit is not clear in different settings.

There's one last sunitinib trial left, which is a comparison of sunitinib and capecitabine versus capecitabine alone. It is similar in design to the SOLTI trial, which evaluates the combination of sorafenib and capecitabine (see presentation 2 of this 5MJC issue). Those data will likely be presented at ASCO 2010. If that study is negative, I believe sunitinib is finished as a drug for metastatic breast cancer, unfortunately.

Dr Brufsky is Associate Professor of Medicine and Associate Division Chief of Hematology/Oncology at the University of Pittsburgh, Co-Director of the Comprehensive Breast Cancer Center and Associate Director for Clinical Investigation at the University of Pittsburgh Cancer Institute in Pittsburgh, Pennsylvania.