



*Key ASCO Presentations*  
Issue 5, 2010

**Clinical Trials Evaluating the Role  
of Sentinel Node Resection (SNR)  
in Early-Stage Breast Cancer**

## CME INFORMATION

### OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and 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 patients with diverse forms of cancer.

### LEARNING OBJECTIVES

- Compare and contrast morbidity and long-term outcomes with SNR versus ALND in patients with clinically and histologically node-negative early breast cancer.
- Apply the results of new research to the appropriate use of IHC testing for patients with negative sentinel nodes by H&E.
- Counsel patients with T1N0M0 breast cancer and H&E-detected sentinel node metastases about the benefits and risks of completion ALND.

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No real or apparent conflicts of interest to disclose.

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To go directly to the slides and commentary, [click here](#).

The oral sessions on breast cancer in Chicago this year reflected a huge volume of ongoing research, and as usual there were lots of important messages for oncologists in practice, including the following:

**1. Axillary node dissection is on the way out, while intraoperative breast irradiation may be on the way in**

[Several related trial reports](#) were the highlight of one major oral session. The NSABP confirmed what most have believed for years: There is no value in axillary dissection for a patient with a clinically negative axilla and a well-performed negative sentinel node biopsy. Two American College of Surgeons trials demonstrated no prognostic value in IHC staining of H&E-negative sentinel nodes and showed that axillary dissection may not be necessary in all patients with positive sentinel nodes. Finally, the legendary trial champion Mike Baum [proved that](#) 30 minutes of intraoperative radiation therapy with a \$300,000 device may yield comparable results to six weeks of conventional radiation therapy in patients after lumpectomy.

**2. Anti-HER2 therapy continues to gallop along**

[Kathy Miller's early data](#) evaluating the fascinating combination of the chemo/trastuzumab conjugate T-DM1 plus the novel anti-HER2 dimerization inhibitor pertuzumab demonstrated safety, and a related study revealed some possible tissue correlates with efficacy. It's challenging to think of a more creative systemic strategy presented at ASCO.

**3. More of the same and something new for advanced disease**

[Two presentations on bevacizumab/chemotherapy](#) reinforced much of what we already knew. The first, Joyce O'Shaughnessy's presentation of a mini-meta-analysis of first-line bev/chemo trials confirmed the benefit of this agent on progression-free but not overall survival. This seems to be an emerging theme in cancers with long natural histories, as first-line trials often fail to show a survival benefit, whereas studies with patients who have received multiple prior treatments may show a survival advantage, perhaps because of the complexities of post-first-line therapy, including the potential for crossover. Chris Twelves' ASCO data set

demonstrating a survival advantage with the [new antitubulin agent eribulin](#) is a clear example of this increasingly discussed phenomenon.

In a second presentation addressing anti-angiogenic therapy for advanced breast cancer, Adam Brufsky's reanalysis of the second-line RIBBON 2 trial demonstrated what most believed already: The impact of bev seems relatively independent of its chemo partner.

Next up on 5-Minute Journal Club: The once-mighty imatinib gets another shove out the door with new data on dasatinib, nilotinib and bosutinib in CML.

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# Clinical Trials Evaluating the Role of Sentinel Node Resection (SNR) in Early-Stage Breast Cancer

## Presentations discussed in this issue

Krag DN et al. **Primary outcome results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients.** *Proc ASCO 2010*; [Abstract LBA505](#).

Cote R et al. **ACOSOG Z0010: A multicenter prognostic study of sentinel node (SN) and bone marrow (BM) micrometastases in women with clinical T1/T2 N0 M0 breast cancer.** *Proc ASCO 2010*; [Abstract CRA504](#).

Giuliano AE et al. **ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node.** *Proc ASCO 2010*; [Abstract CRA506](#).

**Slides from presentations at ASCO 2010 and transcribed comments from recent interviews with Kathy D Miller, MD (6/11/10) and Eric P Winer, MD (7/6/10)**

## Clinical Trials Evaluating the Role of Sentinel Node Resection in Patients with Early-Stage Breast Cancer

**Krag DN et al.**  
*Proc ASCO 2010*; [Abstract LBA505](#).

**Cote R et al.**  
*Proc ASCO 2010*; [Abstract CRA504](#).

**Giuliano AE et al.**  
*Proc ASCO 2010*; [Abstract CRA506](#).

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## Overview

- Data from three clinical trials evaluating the role of sentinel node biopsy were presented at ASCO 2010.
  - NSABP-B-32: A Phase III trial comparing sentinel node (SN) resection to conventional axillary lymph node dissection (ALND) in clinically node-negative breast cancer.<sup>1</sup>
  - ACOSOG Z0010: A multicenter prognostic study of SN and bone marrow (BM) micrometastases in clinical T1-2 N0 M0 breast cancer.<sup>2</sup>
  - ACOSOG Z0011: A randomized trial of ALND in clinical T1-2 N0 M0 breast cancer with a positive sentinel node.<sup>3</sup>

<sup>1</sup> Krag DN et al. *Proc ASCO 2010*;Abstract LBA505; <sup>2</sup> Cote R et al. *Proc ASCO 2010*;Abstract CRA504; <sup>3</sup> Giuliano AE et al. *Proc ASCO 2010*;Abstract CRA506. Research To Practice®

## NSABP-B-32: Introduction

- Trial design: Patients were randomly assigned to SN resection plus ALND (Group 1) versus SN resection alone (Group 2) with ALND performed only if sentinel nodes were positive.
- Eligibility: Operable, clinically node negative, invasive breast cancer.
- Primary endpoints: Overall survival, disease-free survival and regional control.
- 5,611 patients enrolled, of which 3,989 (71.1%) were SN negative and followed for events.
  - Follow-up information is available for 99% of these patients (1,975 in Group 1 and 2,011 in Group 2).
- Median time on study was 95.3 months.

Krag DN et al. *Proc ASCO 2010*;Abstract LBA505.

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## NSABP-B-32: Efficacy Data

	Group 1	Group 2	Group 1 vs Group 2
5-year overall survival (OS) <sup>1</sup>	96.4%	95.0%	—
OS unadjusted HR	—	—	1.20 ( $p = 0.12$ )
OS adjusted HR <sup>2</sup>	—	—	1.19 ( $p = 0.13$ )
5-year disease-free survival (DFS) <sup>1</sup>	89.0%	88.6%	—
DFS unadjusted HR	—	—	1.05 ( $p = 0.54$ )
DFS adjusted HR <sup>2</sup>	—	—	1.07 ( $p = 0.57$ )
<b>Recurrences</b>	<b>Group 1</b>	<b>Group 2</b>	<b><i>p</i>-value</b>
Local recurrences	54	49	0.55
Regional node recurrences as first event	8	14	0.22

<sup>1</sup> Kaplan-Meier estimates, <sup>2</sup> HR adjusted for lumpectomy vs mastectomy, tumor size and patient age

Krag DN et al. *Proc ASCO 2010*;Abstract LBA505.

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## NSAPB-B-32: Conclusions

- No significant differences were observed in OS, DFS or regional control between the patients who underwent SN resection plus ALND (Group 1) versus those who underwent SN resection alone (Group 2).
- Morbidity was decreased in patients who underwent SN resection alone (data not shown).
- When the SN is negative, SN surgery alone with no further ALND is an appropriate, safe and effective therapy for patients with clinically node-negative breast cancer.

Krag DN et al. *Proc ASCO 2010*;Abstract LBA505.

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## **Investigator comment on the results of NSABP-B-32: Sentinel node resection versus axillary dissection in clinically node-negative breast cancer**

NSABP-B-32 didn't provide any surprises. Women who had negative sentinel node biopsies were randomly assigned to axillary node dissection or not. There were no differences in disease-free or overall survival between the groups, although those who underwent axillary lymph node dissection were more likely to experience complications. Essentially, this study indicates that in patients with a negative sentinel node biopsy there is absolutely no reason to consider further surgery.

*Interview with Eric P Winer, MD, July 6, 2010*

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## **ACOSOG Z0010: Introduction**

- Trial design: Patients underwent lumpectomy and SN biopsy with bilateral iliac crest bone marrow (BM) aspiration.
  - BM and histologically negative SN were centrally assessed by immunohistochemistry (IHC) for cytokeratin.
- Eligibility: Clinical T1/T2, N0, M0 breast cancer
- 5,210 patients were found to be eligible and evaluable.
  - Histologic SN metastases were found in 1,215 patients (24.0%).
  - IHC detected an additional 349 patients (10.0%) with SN metastases.
  - BM metastases were identified by IHC in 104 of 3,413 (3.0%) patients examined.

Cote R et al. *Proc ASCO* 2010;Abstract CRA504.

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## ACOSOG Z0010: Overall Survival (OS) Data

	H&E negative & IHC positive	H&E negative & IHC negative	H&E positive	
5-year OS by SN status	96%	96%	93%	
<b>OS Data for SN H&amp;E Negative Patients</b>				
	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
SN IHC negative SN IHC positive	1.00 (ref) 0.92 (0.63, 1.33)	0.65	1.00 (ref) 0.86 (0.44, 1.68)	0.66
BM IHC negative BM IHC positive	1.00 (ref) 1.90 (1.13, 3.20)	0.016	1.00 (ref) 1.82 (0.78, 4.23)	0.16

\*Adjusted for multiple other prognostic factors (eg, sentinel node IHC status, ER, age, tumor size, treatment effect, etc)

Cote R et al. *Proc ASCO* 2010;Abstract CRA504.

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## ACOSOG Z0010: Conclusions

- 5-year OS was 93% in patients with H&E-positive SNs.
- Detection of BM occult metastases by IHC identifies patients with clinical T1/2, N0, M0 at significantly increased risk for death; however, it is not an independent prognostic factor (HR = 1.90,  $p = 0.016$  on univariable analysis; HR = 1.82,  $p = 0.16$  on multivariable analysis adjusted for other important prognostic factors).
- IHC detected SN metastases do not appear to impact overall survival (HR = 1.92,  $p = 0.65$  on univariable analysis; HR = 0.86,  $p = 0.66$  on multivariable analysis).
- Routine examination of SN by IHC is not supported in this patient population by this study.

Cote R et al. *Proc ASCO* 2010;Abstract CRA504.

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## **Investigator comment on the results of ACOSOG Z0010: Prognostic significance of sentinel node and bone marrow micrometastases**

ACOSOG Z0010 provided practice-changing data. Despite the recommendations of ASCO and the College of American Pathologists, immunohistochemistry (IHC) is still being performed on H&E-negative sentinel nodes — it's routinely performed. We now have Phase III data that clearly indicate it is not important to perform IHC on sentinel nodes negative on H&E because it does not inform us about prognosis and it can lead us to harm patients, because it clearly influences treatment decisions in ways that we can now conclude are inappropriate.

*Interview with Kathy D Miller, MD, June 11, 2010*

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## **Investigator comment on the results of ACOSOG Z0010: Prognostic significance of sentinel node and bone marrow micrometastases**

ACOSOG Z0010 is an important trial that involved over 5,000 women and evaluated two separate issues. They investigated the prognostic implication of finding isolated tumor cells via IHC in a sentinel node and the implications of finding IHC-detected cells within the bone marrow.

They demonstrated that women who had micrometastatic involvement on H&E staining had a worse outcome than those who did not, but there was no prognostic implication associated with finding isolated tumor cells by IHC on a sentinel node biopsy. Importantly, the investigators in this trial were blinded to the results, so their treatments were not adjusted based on finding isolated tumor cells. The practice of performing IHC routinely on a sentinel node biopsy should go by the wayside as a result of this study. I believe there may be one exception, which is, if for whatever reason a pathologist believes he or she is seeing something that they want to define further or if a patient has invasive lobular cancer, in which it's often difficult with routine H&E to identify tumor cells, then the use of IHC may be worth considering. Otherwise, for the patient who has a negative sentinel node biopsy by H&E, there is no role at this time for further staining.

*Interview with Eric P Winer, MD, July 6, 2010*

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## ACOSOG Z0011: Introduction

- Trial design: Patients with clinically node-negative breast cancer who underwent SN biopsy and had 1 or 2 SN with H&E-detected metastases were randomly assigned to ALND or no further axillary specific treatment.
- Eligibility: Clinical T1-2, N0 breast cancer, H&E detected metastases in SN, lumpectomy with whole breast irradiation, and adjuvant systemic therapy by choice.
- Primary endpoints: OS, DFS and locoregional control.

Giuliano AE et al. *Proc ASCO* 2010;Abstract CRA506.

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## ACOSOG Z0011: Efficacy Data

	SN biopsy only (n = 436)	ALND (n = 420)	p-value
Locoregional recurrence <sup>1</sup>			0.11
Local (breast)	1.8%	3.6%	
Regional (axilla, supraclavicular)	0.9%	0.5%	
Total	2.8%	4.1%	
5-year OS <sup>2</sup>	92.5%	91.8%	0.25
5-year DFS <sup>2</sup>	83.9%	82.2%	0.14

<sup>1</sup> Median follow-up is 6.3 years

<sup>2</sup> Median follow-up is 6.2 years

*"It is highly improbable that the 0.9% or 2.8% locoregional recurrence with SN only would significantly impact survival."*

Giuliano AE et al. *Proc ASCO* 2010;Abstract CRA506.

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# ACOSOG Z0011: Conclusions

- No significant difference in DFS or OS between patients treated with SN biopsy alone or with SN biopsy followed by ALND.
- Only older age, estrogen receptor-negative status and lack of adjuvant systemic therapy were associated with worse OS by multivariable analysis (data not shown).
- This study does not support the routine use of ALND in limited nodal metastatic breast cancer. The role of this operation should be reconsidered.

Giuliano AE et al. *Proc ASCO* 2010;Abstract CRA506.

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## **Investigator comment on the results of ACOSOG Z0011: Axillary dissection in patients with a positive sentinel node**

ACOSOG Z0011 was a bold study, which unfortunately did not reach its accrual goal. An important eligibility criterion was that women had to undergo conservative surgery and radiation therapy, in which the lower portion of the axilla is included. As a result, we cannot necessarily apply these findings to women who have a mastectomy.

They found that women who had a sentinel node biopsy only had no higher rate of in-breast recurrence and no higher rate of axillary recurrence than women who had a full axillary lymph node dissection (ALND). It's worth pointing out that among the women who had the full ALND, 27 percent had additional positive lymph nodes found at the time of surgery. So, in general, these women were at relatively low risk of having additional axillary disease.

This study does not indicate that we should abandon ALND in all women who have a positive sentinel lymph node. If a woman has a positive sentinel node biopsy, is planning to have a lumpectomy and radiation therapy and is at relatively low risk of having additional disease in the axilla, then ALND may be safely omitted.

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**Interview with Eric P Winer, MD, July 6, 2010**



## Implications for Clinical Practice

- IHC of H&E-negative sentinel nodes is not useful clinically.
- Since only one in 33 bone marrow is IHC-positive and since it is not an independent prognostic factor, IHC of bone marrow provides no clinically important benefit in women with negative sentinel nodes.
- ALND does not add benefit to sentinel lymph node biopsy alone in patients with clinically node-negative disease
- ALND is of no clinical benefit in women with positive sentinel nodes, with the following caveats:
  - <3 positive nodes, nodes not matted, breast-conserving therapy with whole breast irradiation, adjuvant systemic therapy as needed.

Wood W. ASCO 2010;Discussant.

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