5 Minute JournalClub

Assessment of the Prognostic Role of HER2 Overexpression in Patients with Node-Negative, pT1a-b 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

- Consider the impact of HER2 overexpression on the clinical outcome of patients with node-negative breast cancer with small tumor size during decision-making on trastuzumab-based treatment.

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Advisory Committee: Abraxis BioScience, Bristol-Myers Squibb Company, Celgene Corporation, Eisai Inc, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, Sanofi-Aventis, Wyeth; Consulting Agreement: Millennium Pharmaceuticals Inc.

The following faculty reported no real or apparent conflicts of interest:

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IN THIS ISSUE:

Shortly before the recent Pro Bowl in Miami, our CME group hosted a marquee event of our own about ten minutes from the stadium as nine breast cancer "all stars" came together in our sound studio for a daylong think tank audio recording. It's not surprising that my mental highlight film from the meeting includes many innovative ideas and poignant comments by the soft-spoken and super-smart Harvard maven, Dr Paul Goss.

In a follow-up audio interview with Paul, he thoughtfully discussed several patients from his practice. The case that stood out for me was a 38-year-old woman who came for a second opinion after having received several different chemo/anti-HER2 regimens for metastatic disease. This patient's original primary tumor was ER-positive, HER2-positive, but on recurrence a vertebral biopsy revealed HER2-positive, ER-*negative disease*, and she had not received endocrine therapy since the disease recurred.

According to Paul, at this point the woman was sick and tired of being sick and tired of chemo, which in part prompted his highly interesting and somewhat unusual treatment recommendation of the combination of letrozole, trastuzumab and lapatinib, an innovative biologic triplet that makes a lot more sense since Kim Blackwell's stunning **San Antonio presentation** profiled in our slide set, which compared lapatinib to trastuzumab/lapatinib in patients with heavily pretreated metastatic disease. Her presentation was an update of the data that were just published in the *Journal of Clinical Oncology*.

Listening to Paul's case, I was particularly interested in his explanation for using endocrine therapy in spite of a recent ER-negative biopsy, which was based on his concern about the possibility of sampling error particularly because the tissue biopsied was bone, which he feels is ripe for inaccuracies. An equally important factor in his recommendation is the relative lack of toxicity with hormone therapy and the recent data supporting the addition of anti-HER2 therapy to up-front endocrine treatment of metastatic disease. Paul and others believe that anti-HER2 treatment may potentiate

endocrine therapy by a variety of mechanisms including interference with ligand-independent ER activation.

In terms of the HER2 part of this interesting triplet, Paul, like most San Antonio attendees, was very impressed with the trastuzumab/lapatinib data set — one of the very few recent trials to demonstrate a survival benefit in metastatic disease in spite of a built-in crossover design. Dr Goss believes part of the explanation for this finding is that these patients had received so many prior therapies that post-trial intervention had less impact. Another important principle borne out by this study is the potential benefit of continuing trastuzumab beyond disease progression, which was previously supported by the German trial of trastuzumab/capecitabine in patients with disease progression on trastuzumab with other chemo agents. During the think tank, the faculty commented on the sea change in approach to patients with metastatic HER2-positive disease that resulted from this study and the trastuzumab/lapatinib trial in which continuous anti-HER2 therapy has quickly become routine clinical practice.

Although many viewed the recent Pro Bowl as a sham in which the participants seemingly could have cared less about the outcome, I smile inwardly reflecting on a pretty amazing day with Paul and our other "All Pro" investigators. The intriguing clinical and laboratory science discussed that "Super" day suggests that the biology of this disease is finally coming together in a way that maybe will soon have a meaningful impact on patient care.

Next up on 5-Minute Journal Club: San Antonio excitement on bone-targeted therapy.

Neil Love, MD
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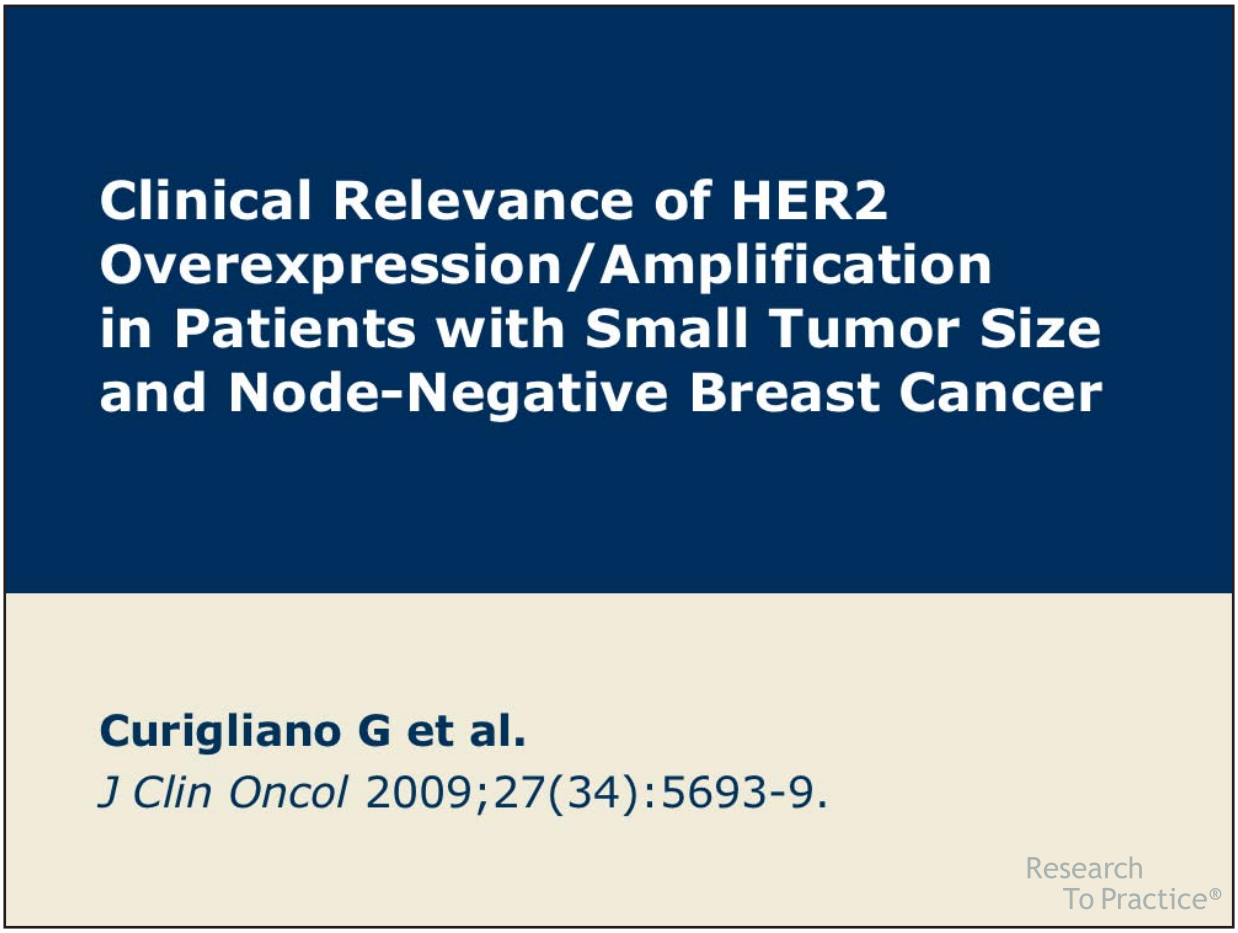
Assessment of the Prognostic Role of HER2 Overexpression in Patients with Node-Negative, pT1a-b Breast Cancer

Presentations discussed in this issue

Curigliano G et al. **Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer.** *J Clin Oncol* 2009;27(34):5693-9. **Abstract**

Gonzalez-Angulo AM et al. **High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller.** *J Clin Oncol* 2009;27(34):5700-6. **Abstract**

Slides from two journal articles and transcribed comments from Luca Gianni, MD and Eric P Winer, MD at a satellite symposium (12/12/09) and from a recent interview with Paul E Goss, MD, PhD (2/1/10)



Introduction

- Results of various randomized trials have led to the indication of adjuvant trastuzumab as a standard treatment option for patients with HER2-positive breast cancer (*NEJM* 2005;353:1659, *NEJM* 2005;353:1673; SABCS 2009;Abstract 62).
- Data regarding use of trastuzumab for patients with HER2+ tumors ≤ 1 cm is lacking.
- HER2 is an independent poor prognostic factor in patients with node-negative breast cancer (BC) (*JCO* 2008;26:5697).
- A better understanding of the prognostic impact of HER2 overamplification in pT1a-b, node-negative tumors may aid the clinician decision-making process with regard to use of adjuvant trastuzumab in this disease subset.
- **Current study objective**
  - Assess prognostic impact of HER2 amplification/overexpression in patients with node-negative pT1a-b breast cancer

Curigliano G et al. *J Clin Oncol* 2009;27(34):5693-9.

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Methods

- Identification of study group of patients who underwent surgery, from the European Institute of Oncology database (1999-2006):
  - Primary breast cancer: pN0; M0; ≤ 1 cm tumor size
  - HER2/neu protein overexpression or gene amplification
  - No preoperative chemotherapy or trastuzumab therapy
- A matched cohort to node-negative disease was selected based on:
  - Hormone receptor (ER/PgR) status, age (± 5 years), year of diagnosis (± 2 years)
- Statistical methods:
  - χ^2 test for differences between disease-free survival (DFS) in study and control groups by ER/PgR status
  - Cox proportional hazard ratios (HR) were stratified by matched set to compare patients with HER2-positive and HER2-negative disease.

Curigliano G et al. *J Clin Oncol* 2009;27(34):5693-9.

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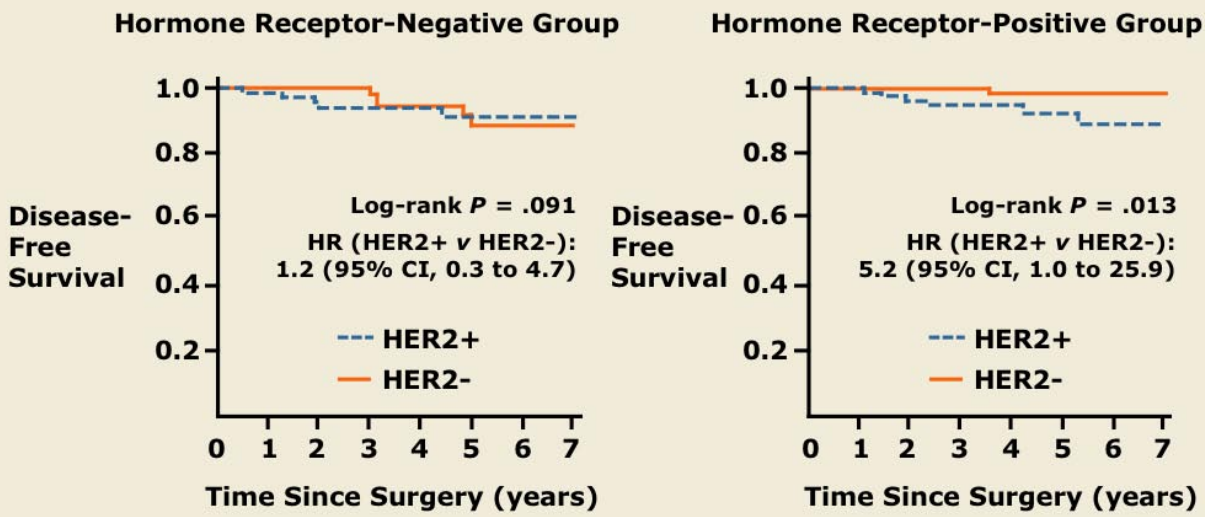
DFS in pT1a-b, pN0, M0 HER2-Positive and Matched HER2-Negative Comparison Groups



Curigliano G et al. *J Clin Oncol* 2009;27(34):5693-9.
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Results (median follow-up 4.6 years)

Survival	Hormone Receptor-Negative		Hormone Receptor-Positive	
	HER2-Positive (n=71)	HER2-Negative (n=71)	HER2-Positive (n=79)	HER2-Negative (n=158)
5-year DFS, (95% CI)	91% (84-99)	92% (84-100)	92% (86-99)	99% (96-100)
Overall survival	97%	100%	97%	99%
	p=0.93			

- **Overall HR (HER2-positive:HER2-negative) = 2.4, p=0.09**
- **In patients with hormone receptor-positive disease, HER2 positivity remained associated with a worse prognosis:**
  - **HR (multivariate analysis) = 5.1 (95% CI, 1.0-25.7)**

Curigliano G et al. *J Clin Oncol* 2009;27(34):5693-9.

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Conclusions

- Women with HER2-positive disease have an increased risk of recurrence, irrespective of hormone receptor status (HR= 2.4, p=0.09).
- HER2 overexpression is associated with an adverse prognosis in patients with ER/PgR-positive, pT1a-b, node-negative disease.
  - HR for DFS = 5.2 (95% CI, 1.0-25.9)
- The main limitations of the study are related to the retrospective analysis, the restricted follow-up, small sample size and the limited number of total events.
- In this series of patients, a 50% reduction in the risk of disease recurrence achieved by adjuvant trastuzumab would translate into a 4-5% absolute benefit that would justify its use.

Curigliano G et al. *J Clin Oncol* 2009;27(34):5693-9.

High Risk of Recurrence for Patients With Breast Cancer Who Have Human Epidermal Growth Factor Receptor 2–Positive, Node-Negative Tumors 1 cm or Smaller

Gonzalez-Angulo AM et al.

J Clin Oncol 2009;27(34):5700-6.

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Introduction

- Trastuzumab incorporated into various adjuvant chemotherapy regimens has demonstrated improvements in DFS and OS for patients with HER2+ BC (*NEJM* 2005;353:1659, *NEJM* 2005;353:1673; SABCS 2009;Abstract 62).
- In the setting of node-negative small tumors (≤1 cm), available data regarding HER2+ disease recurrence at 5 and 10 years is limited.
- National Comprehensive Cancer Network (NCCN) guidelines do not recommend systemic anti-HER2 therapy for tumors less than 1 cm due to a lack of supportive data.
- **Current study objectives:**
  - Evaluate the risk of recurrence in women diagnosed with T1a and T1b, node-negative, HER2–positive breast cancer (BC).

Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6.

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Methods

- Retrospective review performed of MD Anderson Cancer Center (MDACC) Breast Cancer Management System database.
  - 965 eligible patients with T1a-bN0M0 BC diagnosed between 1990 and 2002
  - Patients who received adjuvant chemotherapy or trastuzumab excluded
- Pathologist reviewed HER2 positivity was defined as IHC 3+ or ratio of 2.0 or greater by FISH.
  - Percent of patients with HER2-positive tumors = 10%

Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6.

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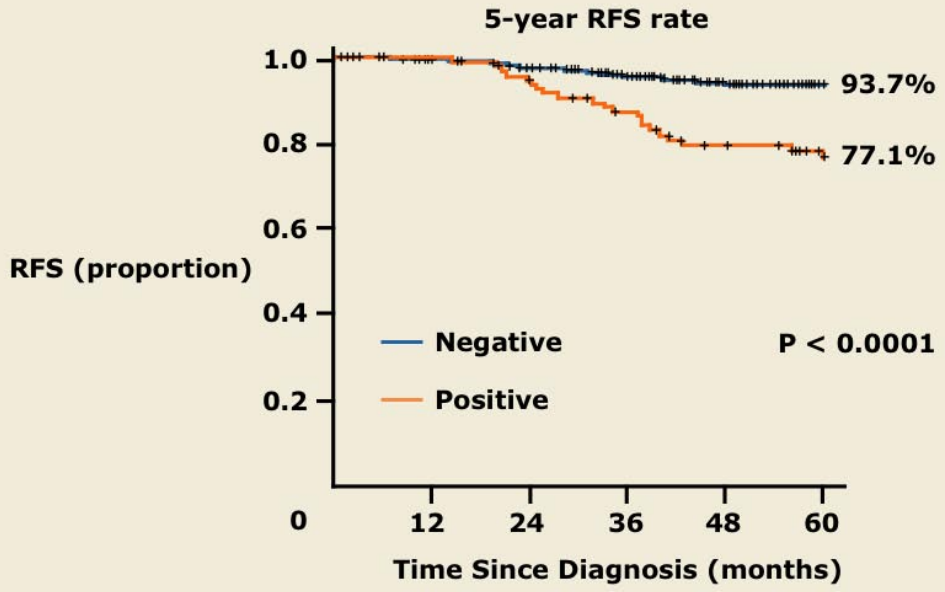
Recurrence-Free Survival (RFS) by HER2 Status



Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6.
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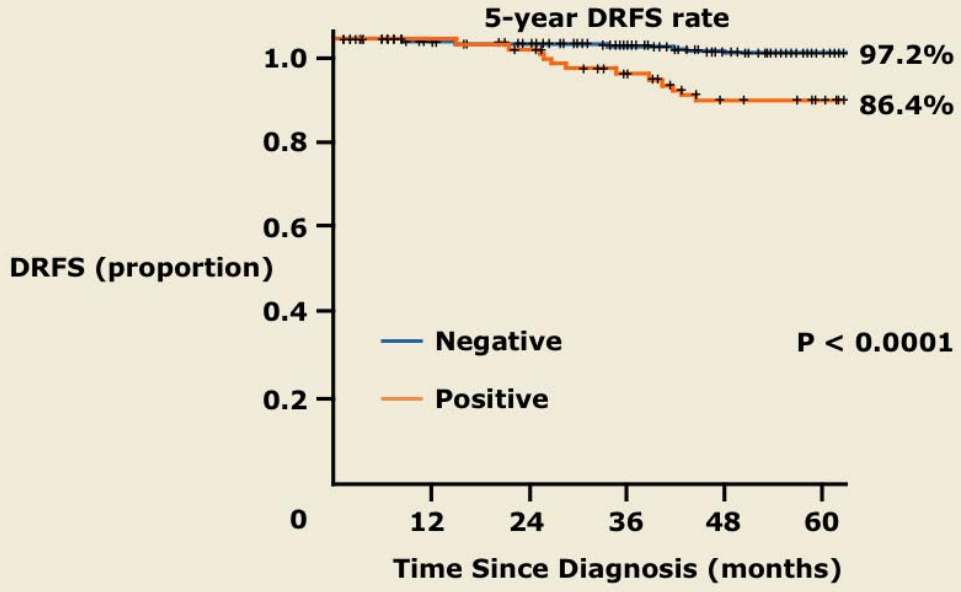
Distant Recurrence-Free Survival (DRFS) by HER2 Status



Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6.
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Multivariate Analyses by Survival Status

Comparative variable	RFS			DRFS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
HER2 status (+ vs -)	**2.68**	1.44-5.0	0.002	**5.30**	2.23-12.62	0.0002
Hormone receptor status (+ vs -)	0.41	0.23-0.72	0.002	0.59	0.25-1.37	0.219
Age at diagnosis, years*	0.96	0.94-0.98	0.001	0.73	0.32-1.7	0.467

** Continuous variable; HR=hazard ratio.*

Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6.

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Summary and Conclusions

- Patients with HER2+ BC had worse DRFS and RFS than patients with HER2-negative BC.
  - DRFS at 5 years: 86.4% vs 97.2%, $p < 0.0001$
  - RFS at 5 years: 77.1% vs 93.7%, $p < 0.0001$
- Patients with HER2+ tumors had increased risks of recurrence and distant recurrence than those with HER2-negative tumors.
  - RFS: Hazard Ratio = 2.68, $p = 0.002$
  - DRFS: Hazard Ratio = 5.30, $p = 0.0002$
- Patients with HER2-positive T1abN0M0 tumors have a significant risk of relapse and should be considered for systemic, anti-HER2 adjuvant therapy.

Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6.

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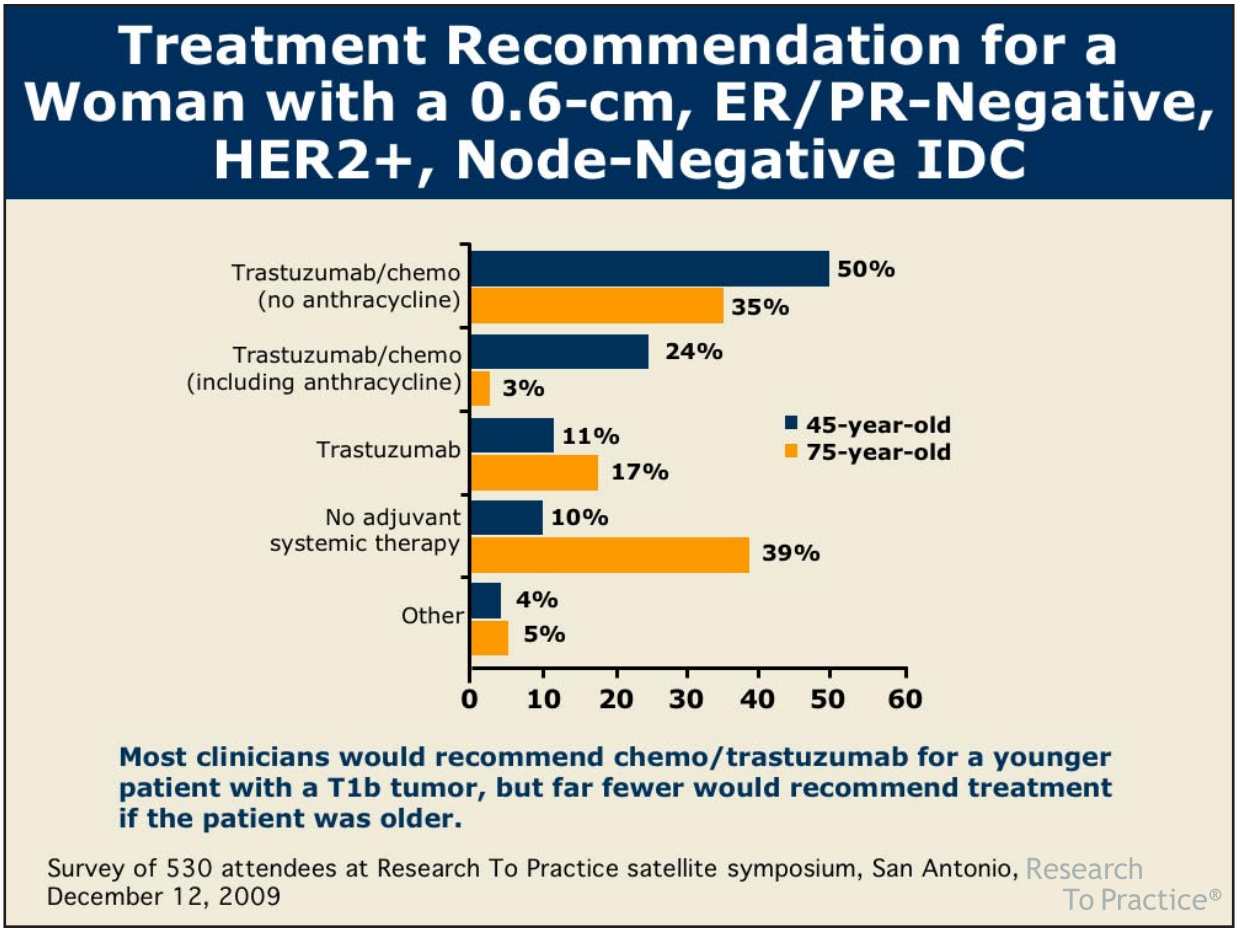

DR WINER: This is the vexing question that has plagued oncologists and patients to some extent more than any others since the adjuvant trastuzumab data were reported. Virtually no patients who had tumors smaller than one centimeter with negative lymph nodes were entered in the trials. In the CIRG trial, almost 30 percent of the patients had negative lymph nodes. HERA had close to 30 percent. In the NSABP trial there were no patients with negative lymph nodes, and the North Central/ Intergroup trial had fewer than 15 percent.

I don't believe that any of us question the potential benefit of trastuzumab in this setting — the benefit of trastuzumab has been consistent across all patient groups. Generally speaking, there is a reduction in the risk of recurrence in the range of 50 percent, maybe a little bit less than that as the studies mature. The big questions for these patients with small tumors are what is the event rate and how big a risk do they face?

This study, conducted by the European School of Oncology in Milan, was recently published in the *Journal of Clinical Oncology* in December of 2009. The event rate was in the range of eight to nine percent and was actually similar for patients whether they had ER-positive or ER-negative disease.

Although the event rate was low, it still is high enough that, at least for some patients and many medical oncologists, it would trigger a decision to consider

therapy, particularly a therapy that could reduce this risk by 50 percent — such as trastuzumab.

DR GOSS: The question exists as to how to manage clinically early-stage breast cancer that is HER2-positive with small primary tumors. We don't know the long-term natural history of HER2-positive breast cancer. We know that it's a marker of early recurrence and higher recurrence risk in both ER-positive and ER-negative breast cancer, but we don't know the annual hazard of recurrence or the cumulative risk recurrence rate.

The FDA approved trastuzumab initially for patients with node-positive, HER2-positive breast cancer, based on trial results in which the majority of patients had node-positive disease. After the results of the HERA trial the regulatory authorities expanded the indication worldwide to include patients with node-negative breast cancer with tumors larger than one centimeter.

However, many physicians and patients asked: If my tumor is smaller than one centimeter and HER2-positive, what is my risk, and does it merit aggressive therapy with either systemic chemotherapy or anti-HER2 therapy?

DR WINER: These data were presented at the 2008 San Antonio Breast Cancer Symposium and recently published in the *Journal of Clinical Oncology*. This was a retrospective analysis from MD Anderson on 965 total patients with T1a and b (ie, tumors one centimeter or smaller), node-negative, HER2-positive breast cancer. Roughly 10 percent of these patients had HER2-positive disease, so about 100 patients. The median follow-up was 74 months, and there were a total of 72 disease recurrences at five years.

The five-year disease-free survival was 77 percent for patients with HER2-positive disease and 94 percent for patients with HER2-negative disease.

DR GOSS: Dr Gonzalez-Angulo and colleagues from MD Anderson show that HER2-positive tumors smaller than or equal to one centimeter have a five-year risk of recurrence of up to 23 percent. Our group at Massachusetts General Hospital has published that there is a 10 percent rate of recurrence over five years, cumulatively, for HER2-positive tumors smaller than one centimeter in size. There's a spectrum in the rate of recurrence, but either way, these patients seem to have a higher risk of recurrence than non-HER2-matched controls, and it's worrisome.

DR WINER: Approximately 15 percent of the patients with HER2-positive disease had a distant recurrence through five years versus three percent for patients with HER2-negative disease.

DR GIANNI: We try to treat node-negative, HER2-positive, small tumors with trastuzumab to take advantage of the fact that in the HERA trial we had 30 percent of all patients with node-negative breast cancer and, overall, there was no difference in the effect of trastuzumab on disease-free survival for those patients than for

those with node-positive breast cancer. If the tumor is very small, I would offer the opportunity of a treatment containing trastuzumab in a young woman.

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Dr Goss is Professor of Medicine at Harvard Medical School, Director of Breast Cancer Research at MGH Cancer Center and Co-director of the Breast Cancer Disease Program, DF/HCC in Boston, Massachusetts.

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