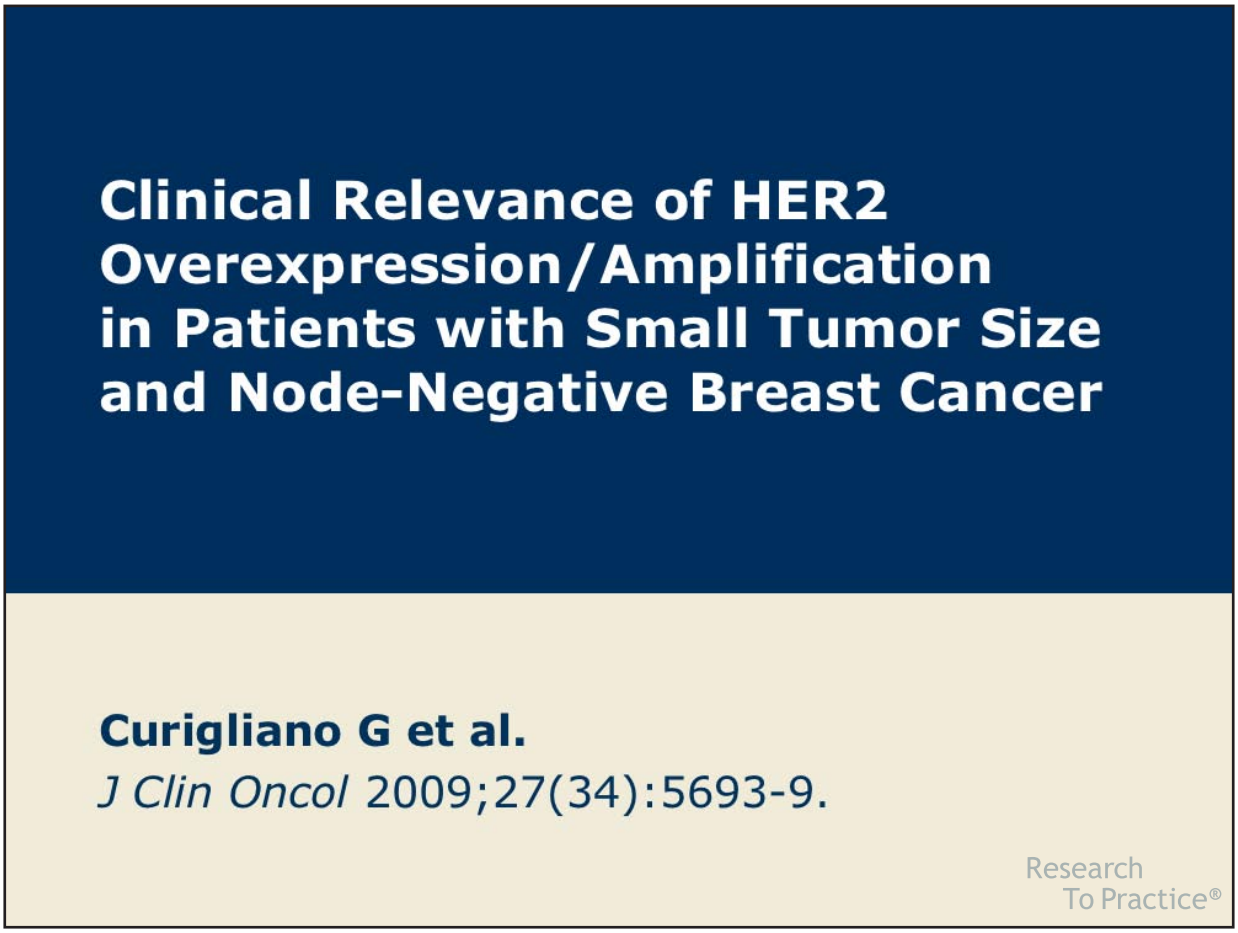
Assessment of the Prognostic Role of HER2 Overexpression in Patients with Node-Negative, pT1a-b Breast Cancer

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



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

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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.

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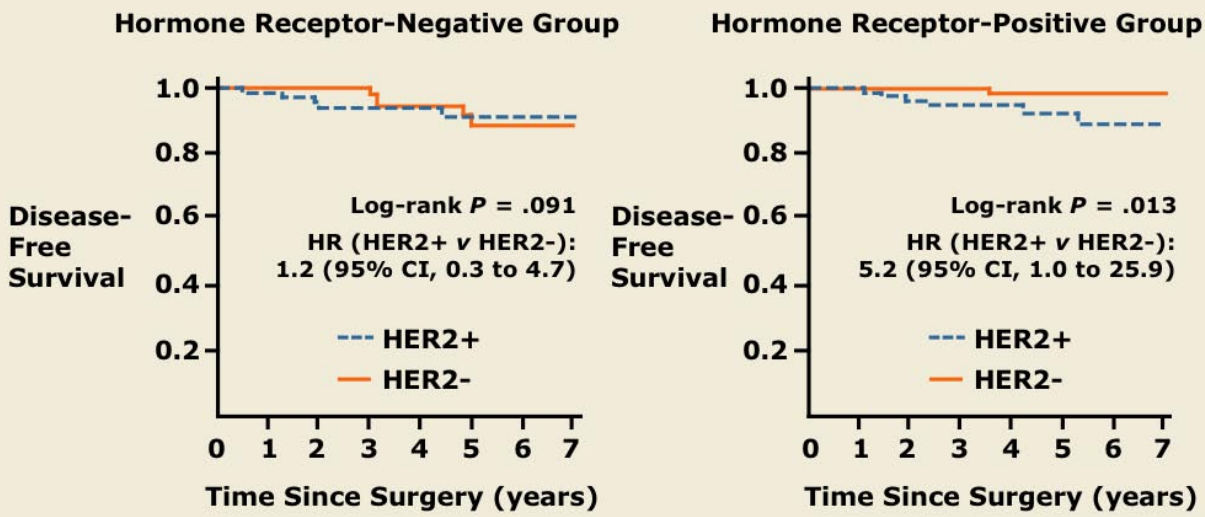
DFS in pT1a-b, pN0, M0 HER2-Positive and Matched HER2-Negative Comparison Groups



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)**

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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%

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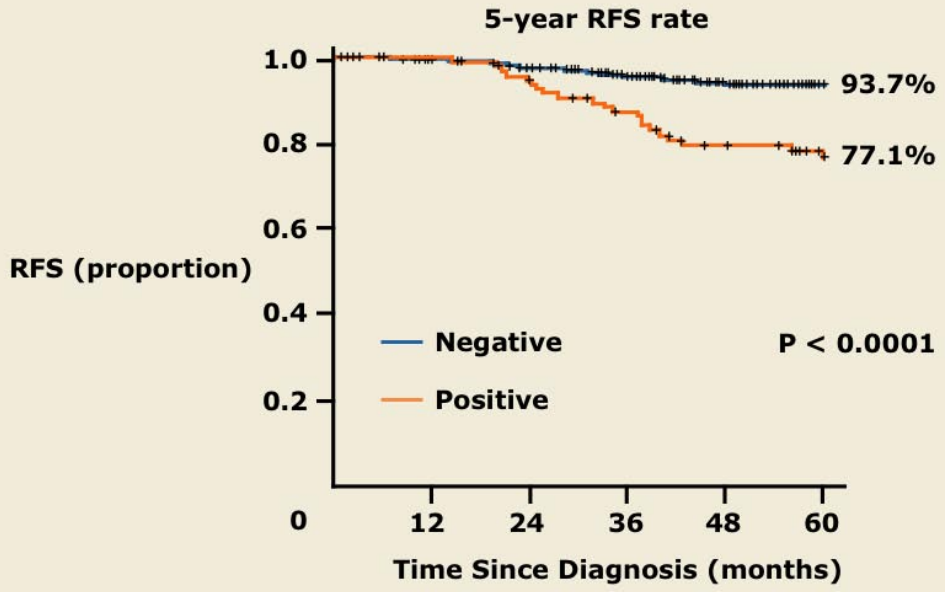
Recurrence-Free Survival (RFS) by HER2 Status



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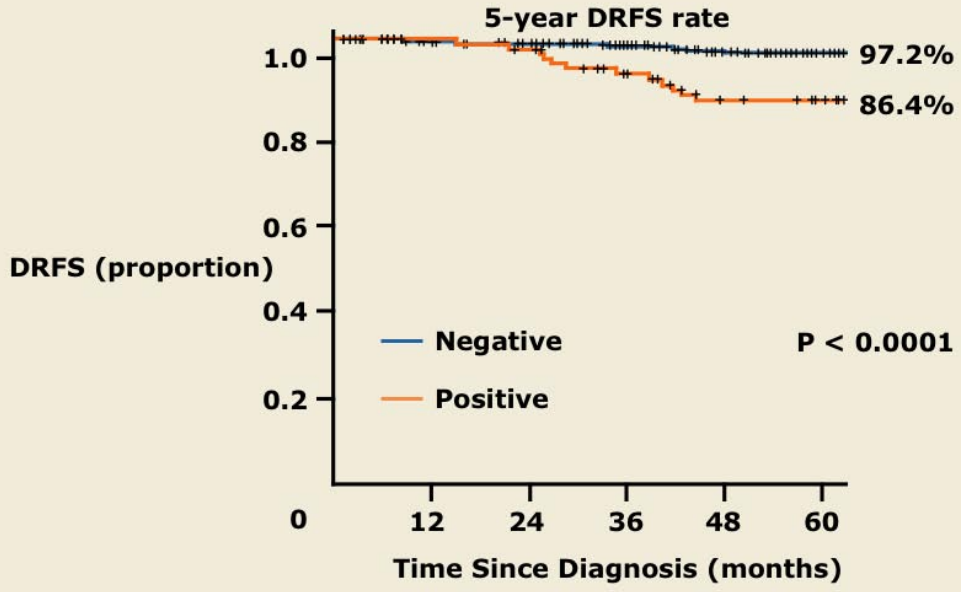
Distant Recurrence-Free Survival (DRFS) by HER2 Status



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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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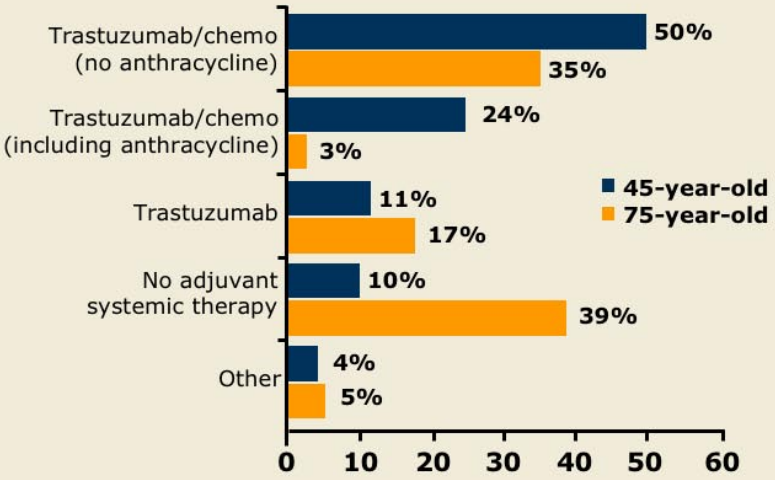
Treatment Recommendation for a Woman with a 0.6-cm, ER/PR-Negative, HER2+, Node-Negative IDC



Most clinicians would recommend chemo/trastuzumab for a younger patient with a T1b tumor, but far fewer would recommend treatment if the patient was older.

Survey of 530 attendees at Research To Practice satellite symposium, San Antonio, December 12, 2009

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