

# Trastuzumab-related cardiotoxicity: A population-based study in older patients with breast cancer.

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# Outline



- Background
- Specific Aims
- Methods/ Subject selection
- Preliminary results (Specific Aim 1)
- Questions for the group
- Limitations
- Discussion

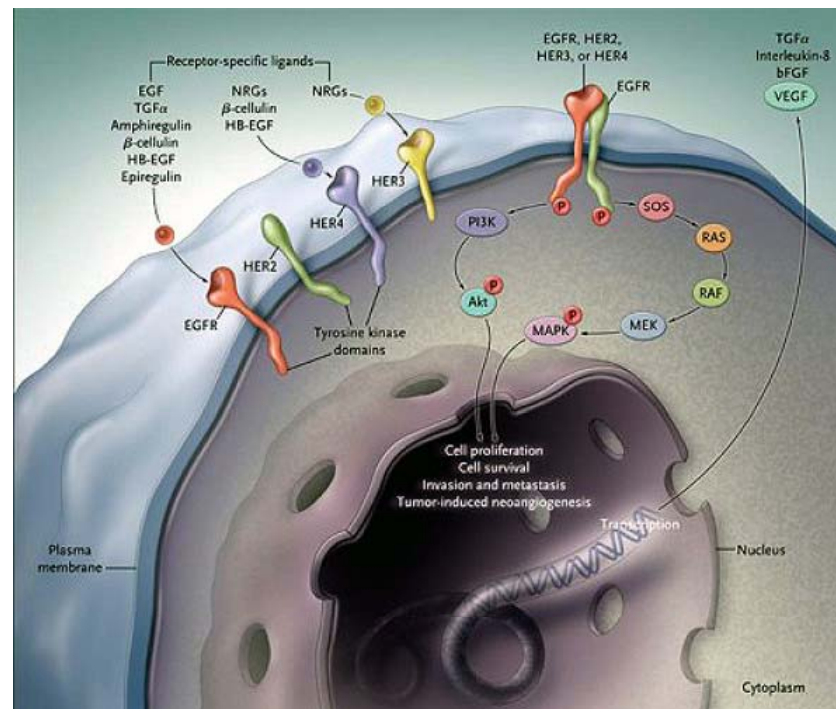
# Background



- Breast Cancer is the second most common cause of cancer death among women in the U.S.
  - In 2009 > 194,280 cases were diagnosed and 40,610 deaths occurred.
- Breast cancer is a heterogeneous disease.
  - Prognosis and treatment depend on tumor subtype.
  - Breast cancer subtypes:
    - ✦ Hormone Receptor Positive (ER+ and/or PR-; Her2-)
    - ✦ Her2-neu amplified
    - ✦ Triple negative (ER and PR and Her2 -)

# Her2-amplified breast cancer

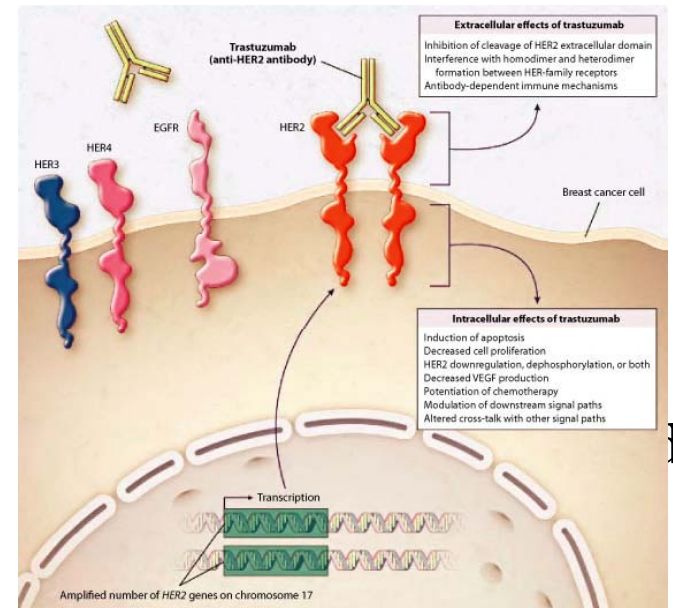
- 20-30% invasive breast cancers.
- Poor prognosis
- Tumors more likely to be high grade and to have nodal involvement.



# Trastuzumab



- Advances in systemic therapies have substantially improved survival and quality of life in breast cancer patients.
- Trastuzumab (Herceptin) is a humanized-monoclonal antibody targeted against Her2-neu.
- Trastuzumab has become a critical component in the management of Her2+ tumors.
- Improves outcomes in patients with metastatic disease and improves DFS OS when combined with chemo.
  - FDA approval: 1998 for MBC, 2006 adjuvant.



# Trastuzumab



- Trastuzumab is very well tolerated, is associated with minimal side effects.
- Associated with increased risk of cardiotoxicity – manifested as cardiac dysfunction and CHF
  - Attributed to Her2 signaling blockade in cardiac myocytes.
- The incidence of reported cardiotoxicity varies according to the definition used.
  - 2-7% monotherapy
  - 2-13% combination with non-anthracycline chemotherapy.
  - More than 15% when combined with anthracyclines.
- Combined analysis of NSABP-B31, N9831 demonstrated a rate of symptomatic CHF of 0.6% vs 2.9%.
  - Age was significantly associated with a higher risk of CHF
    - ✦ >50 yo HR 2.80 (95%CI 1.44-5.61)

# Relevance



- Reports suggest that Trastuzumab-related cardiotoxicity is higher outside clinical trials.
- Clinical trial participants tend to be younger and in better health (less comorbidities) than the general population.
- There is no-population based studies evaluating rates or risk factors associated with Trastuzumab-related cardiotoxicity.
- No data of cardiotoxicity in patients treated for long periods of time .
- No data on the adequacy of monitoring.

# Specific aims



- **Aim 1**
  - To identify the rate of trastuzumab-related cardiotoxicity in older breast cancer patients. We will estimate the rates of CHF diagnosis, hospital discharge with CHF diagnosis, and death from CHF in these patients.
- **Aim 2**
  - To identify the risk factors associated with trastuzumab-related cardiotoxicity in older breast cancer patients.
- **Aim 3**
  - To determine in our patient population whether cardiac monitoring before and during trastuzumab treatment had been consistent with current recommendations.



# Methods- Subject selection



- **SEER-Medicare database**
  - patients  $\geq$  66 years old
  - Diagnosis of breast cancer stage I-IV
  - Treated with chemotherapy at any point since the date of diagnosis.
  - Medicare part a and B and not be members of an HMO for one year prior to breast cancer diagnosis.
  - **EXCLUSION CRITERIA:**
    - ✦ Prior claim for CHF
    - ✦ Hx of prior malignancy
    - ✦ Unknown stage at diagnosis
    - ✦ Non-carcinoma histology

# Specific aim 1



- To identify the rate of trastuzumab-related cardiotoxicity in older breast cancer patients. We will estimate the rates of CHF diagnosis, hospital discharge with CHF diagnosis, and death from CHF in these patients.
  - CHF will be defined using ICD-9 codes (425, 428, 785.51) appearing at least twice and separated by 30 days.
  - Trastuzumab use will be identified using HCPCJ code J9355.
  - Analysis will be performed separately for CHF diagnosis, hospital admissions for CHF and death secondary to CHF.
  - Time dependent analysis for CHF among trastuzumab-treated patients

## Specific aim 2



- To identify the risk factors associated with trastuzumab-related cardiotoxicity in older breast cancer patients.
  - Covariates examined will include age, comorbidities, cardiac-specific comorbidities, duration of treatment, frequency of trastuzumab treatment, prior radiation therapy, breast cancer laterality and chemotherapeutic agent used in combination with trastuzumab.

# Specific aim 3



- To determine in our patient population whether cardiac monitoring before and during trastuzumab treatment had been consistent with current recommendations.
  - Estimate the proportion of Trastuzumab-treated patients who underwent adequate cardiac monitoring.
    - ✦ Adequate cardiac monitoring: Baseline evaluation and monitoring every 3 months during treatment and upon completion of treatment.
  - Evaluate most frequent method used and evaluate if there are geographical variations.
    - ✦ Consistency over time .

## Preliminary Results- Cohort

Breast cancer Diagnosis, histology confirmed,  $\geq 66$  yo, diagnosed 1998-2007

150,690

Medicare A&B coverage and no HMO 12 months before and after diagnosis

100,422

Chemotherapy treatment

21,049

Exclude prior CHF diagnosis (n=5,683), excluded stage 0 (572)

17,684

Final cohort 17,684 patients. Of them 2,037 (11.52%) received Trastuzumab treatment

# Patient characteristics

		All Patients (%) (N=17,684)	Trastuzumab Users (%) (N=2,037)	Other Chemo users (%) (N=15,647)	P-value
<b>Age</b>	66-70	7562(42.76)	40.6	43.04	<.0001
	71-75	5445(30.79)	28.72	31.06	
	76-80	3172(17.94)	18.8	17.82	
	>80	1505 (8.51)	11.88	8.07	
<b>Gender</b>	Female	17511(99.02)	99.46	98.96	0.0326
	Male	173(0.98)	0.54	1.04	
<b>Race</b>	White	14700(83.13)	82.38	83.22	0.1954
	Black	1374 (7.77)	7.46	7.81	
	Other	1610 (9.10)	10.16	8.97	
<b>Marital Status</b>	Married	8983(50.80)	48.99	51.03	0.2235
	Not married	8039(45.46)	47.13	45.24	
	Unknown	662(3.74)	3.88	3.73	
<b>Region</b>	California+Hawaii	5722(32.36)	33.48	32.21	<.0001
	Atlanta+Rural Georgia	726(4.11)	3.98	4.12	
	Connecticut	1263(7.14)	7.36	7.11	
	Detroit	1649(9.32)	6.68	9.67	
	Iowa	1288(7.28)	4.76	7.61	
	Kentucky	1203(6.80)	7.22	6.75	
	Louisiana	1177(6.66)	7.17	6.59	
	New Jersey	2537(14.35)	15.91	14.14	
	New Mexico	514(2.91)	3.98	2.77	
	Seattle	987(5.58)	5.55	5.59	
	Utah	618(3.49)	3.93	3.44	

# Patient characteristics

		All Patients (%) (N=17,684)	Trastuzumab Users (%) (N=2,037)	Other Chemo users (%) (N=15,647)	P-value
<b>Surgery</b>	BCS	7502(42.42)	35.69	43.3	<.0001
	Mastectomy	8731(49.37)	50.37	49.24	
	No Surgery	1362(7.7)	13.25	6.98	
	Unknown	89(0.5)	0.69	0.48	
<b>Charlson Comorbidity</b>	0	13729(77.64)	78.74	77.49	0.4194
	1	3108(17.58)	16.84	17.67	
	2+	847(4.79)	4.42	4.84	
<b>Radiation Therapy</b>	No	9013(50.97)	57	50.18	<.0001
	Yes	7985(45.15)	39.57	45.88	
	Unknown	686(3.88)	3.44	3.94	
<b>Education Level</b>	1st quartile	4394(24.85)	25.23	24.8	0.1397
	2nd quartile	4399(24.88)	25.43	24.8	
	3rd quartile	4428(25.04)	26.17	24.89	
	4th quartile	4463(25.24)	23.17	25.51	
<b>Poverty Level</b>	1st quartile	4400(24.88)	26.02	24.73	0.3949
	2nd quartile	4404(24.9)	25.53	24.82	
	3rd quartile	4408(24.93)	24.05	25.04	
<b>Estrogen Receptor</b>	Negative	4886(27.63)	44.48	25.44	<.0001
	Positive	10423(58.94)	44.87	60.77	
	Unknown	2375(13.43)	10.65	13.79	

		<b>All Patients (%) (N=17,684)</b>	<b>Trastuzumab Users (%) (N=2,037)</b>	<b>Other Chemo users (%) (N=15,647)</b>	<b>P-value</b>
<b>Year of Diagnosis</b>	1998	1012(5.72)	2.26	6.17	<.0001
	1999	1084(6.13)	3.39	6.49	
	2000	2162(12.23)	8.15	12.76	
	2001	2197(12.42)	6.73	13.17	
	2002	2077(11.75)	6.33	12.45	
	2003	1887(10.67)	8.2	10.99	
	2004	1981(11.20)	10.06	11.35	
	2005	1802(10.19)	16.94	9.31	
	2006	1733(9.8)	18.41	8.68	
	2007	1749(9.89)	19.54	8.63	
<b>Stage</b>	1	3996(22.6)	17.97	23.2	<.0001
	2	8621(48.75)	39.27	49.98	
	3	2854(16.14)	21.55	15.43	
	4	1481(8.37)	15.51	7.45	
	Unknown	732(4.14)	5.69	3.94	
<b>Lymph Nodes</b>	Negative	6459(36.52)	31.62	37.16	<.0001
	Positive	8867(50.14)	48.7	50.33	
	Unknown	2358(13.33)	19.69	12.51	
<b>Grade</b>	Grade 1	1888 (10.68)	3.34	11.63	<.0001
	Grade2	6259(35.39)	25.87	36.63	
	Grade 3	7785 (44.02)	61.02	41.81	
<b>Estrogen Receptor</b>	Negative	4886(27.63)	44.48	25.44	<.0001
	Positive	10423(58.94)	44.87	60.77	
	Unknown	2375(13.43)	10.65	13.79	
<b>Progesterone Receptor</b>	Negative	6869(38.84)	57.63	36.4	<.0001
	Positive	8240(46.6)	30.88	48.64	
	Unknown	2575(14.56)	11.49	14.96	



# CHF

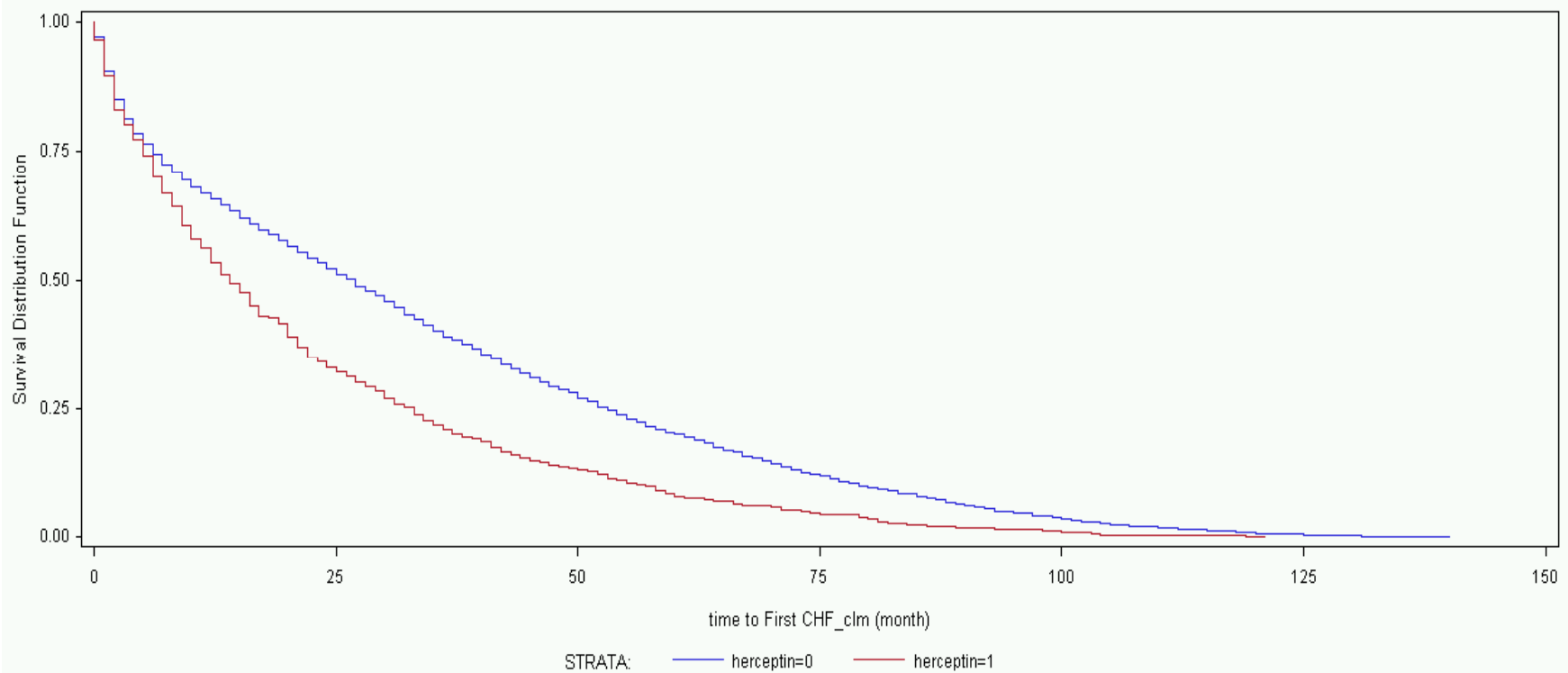


		All Patients (%) (N=17,684)	Trastuzumab Users (%) (N=2,037)	Other Chemo users (%) (N=15,647)	P-value
Pts with CHF	Yes	5,498(31.09%)	714(35.05)	4784(30.57)	<.0001
	No	12,186(68.91%)	1323(64.95)	10863(69.43)	

		All Patients (%) (N=17,684)	CHF Patients (%) (N=5,498)	non CHF Patients (%) (N=12,186)	P-value
Pts using Trastuzumab	Yes	2,037(11.52%)	714(12.99)	1323(10.86)	<.0001
	No	15,647(88.48%)	4784(87.01)	10863(89.14)	

HR= 1.504 (95%CI)

# Time to event (CHF) between Trastuzumab and not trastuzumab users



# Questions for the group



- Cohort
  - Include only SEER-Medicare
  - Add data from Texas Cancer Registry
    - Combined analysis? Vs Separate analysis?

Breast cancer Diagnosis, histology confirmed,  $\geq$  66 yo, diagnosed 1998-2007, Medicare A&B coverage and no HMO 12 months before and after diagnosis.

100,422

Excluded prior CHF, stage 0 and received Chemotherapy treatment

17,684

17.6%

Final cohort 17,684 patients. Of them 2,037 (11.52%) received Trastuzumab treatment. 5,498 (31.09%) of the total cohort developed CHF

Breast cancer Diagnosis, histology confirmed,  $\geq$  66 yo, diagnosed 1998-2007, Medicare A&B coverage and no HMO 12 months before and after diagnosis.

23,992

Excluded prior CHF, stage 0 and received Chemotherapy treatment

4078

17.6%

Cohort 4,078 patients.. IF 11.52% of them received Trastuzumab treatment (470)  
IF 31.09% of the cohort developed CHF, total number of events 1,268

## Comparison SEER-Medicare / CERCIT

		<b>CERCIT</b>	<b>SEER</b>
		<b>23,992(100)</b>	<b>100,422(100)</b>
Age	66-70	6895(28.74)	25705(25.6)
	71-75	6221(25.93)	25428(25.32)
	76-80	5239(21.84)	23138(23.04)
	>80	5637(23.5)	26151(26.04)
Gender	Female	23814(99.26)	99632(99.21)
	Male	178(0.74)	790(0.79)
Race	Unknown	23(0.1)	
	White	20980(87.45)	85266(84.91)
	Black	1969(8.21)	6951(6.92)
	Other	109(0.45)	830(0.83)
	Asian	111(0.46)	3506(3.49)
	Hispanic	771(3.21)	3869(3.85)
	N.Am Native	29(0.12)	
Poverty	1st quartile	5904(24.61)	25088(24.98)
	2nd quartile	5879(24.5)	25111(25.01)
	3rd quartile	5915(24.65)	25096(24.99)
	4th quartile	5890(24.55)	25127(25.02)
	Unknown	404(1.68)	
Education	1st quartile	5902(24.6)	25080(24.97)
	2nd quartile	5902(24.6)	25074(24.97)
	3rd quartile	5891(24.55)	25086(24.98)
	4th quartile	5893(24.56)	25182(25.08)
	Unknown	404(1.68)	

		<b>CERCIT</b>	<b>SEER</b>
		<b>23992(100)</b>	<b>100422(100)</b>
<b>Year at diagnosis</b>	1998	n/a	5829(5.8)
	1999	n/a	5995(5.97)
	2000	n/a	11193(11.15)
	2001	3442(14.35)	11621(11.57)
	2002	3644(15.19)	11357(11.31)
	2003	3646(15.2)	11280(11.23)
	2004	3432(14.3)	11181(11.13)
	2005	3367(14.03)	10923(10.88)
	2006	3282(13.68)	10494(10.45)
	2007	3179(13.25)	10549(10.5)
<b>Urban</b>	Big Metro	12226(50.96)	5659(56.36)
	Metro	6538(27.25)	28755(28.64)
	Urban	1533(6.39)	6092(6.07)
	Less Urban	3221(13.43)	7370(7.34)
	Rural	472(1.97)	1605(1.6)
<b>Tumor grade</b>	Grade 1	7019(29.26)	20141(20.06)
	Grade 2	4297(17.91)	38359(38.2)
	Grade 3	8714(36.32)	28227(28.11)
	Unknown	3962(16.51)	13695(13.64)
<b>Surgery</b>	Breast conserving	7748(45.83)	56279(56.04)
	Mastectomy	6713(39.71)	36692(36.54)
	No surgery	1721(10.18)	7016(6.99)
	Unknown	724(4.28)	435(0.43)
	Missing	7086	
<b>Radiation</b>	None	3973(63.59)	56503(56.27)
	Yes	1524(24.39)	41115(40.94)
	Unknown	751(12.02)	2804(2.79)
	Missing	17744	

## References

1. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-92, 2001
2. Vogel CL, Cobleigh MA, Tripathy D, et al: Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 20:719-26, 2002
3. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 353:1659-72, 2005
4. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 353:1673-84, 2005
5. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al: Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 354:809-20, 2006
6. Viani GA, Afonso SL, Stefano EJ, et al: Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. *BMC Cancer* 7:153, 2007
7. Yeh ET, Bickford CL: Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 53:2231-47, 2009
8. Ewer MS, O'Shaughnessy JA: Cardiac toxicity of trastuzumab-related regimens in HER2-overexpressing breast cancer. *Clin Breast Cancer* 7:600-7, 2007
9. Perez EA, Suman VJ, Davidson NE, et al: Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 26:1231-8, 2008
10. Seidman A, Hudis C, Pierri MK, et al: Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 20:1215-21, 2002
11. Suter TM, Procter M, van Veldhuisen DJ, et al: Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol* 25:3859-65, 2007
12. Tripathy D, Slamon DJ, Cobleigh M, et al: Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. *J Clin Oncol* 22:1063-70, 2004
13. Russell SD, Blackwell KL, Lawrence J, et al: Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. *J Clin Oncol* 28:3416-21
14. Guarneri V, Lenihan DJ, Valero V, et al: Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol* 24:4107-15, 2006
15. McArthur HL, Chia S: Cardiotoxicity of trastuzumab in clinical practice. *N Engl J Med* 357:94-5, 2007
16. Pinder MC, Duan Z, Goodwin JS, et al: Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 25:3808-15, 2007