Do we have to change our anti-cancer strategy in case of cardiac toxicity?

Point of view of the oncologist

Guy Jerusalem, MD, PhD

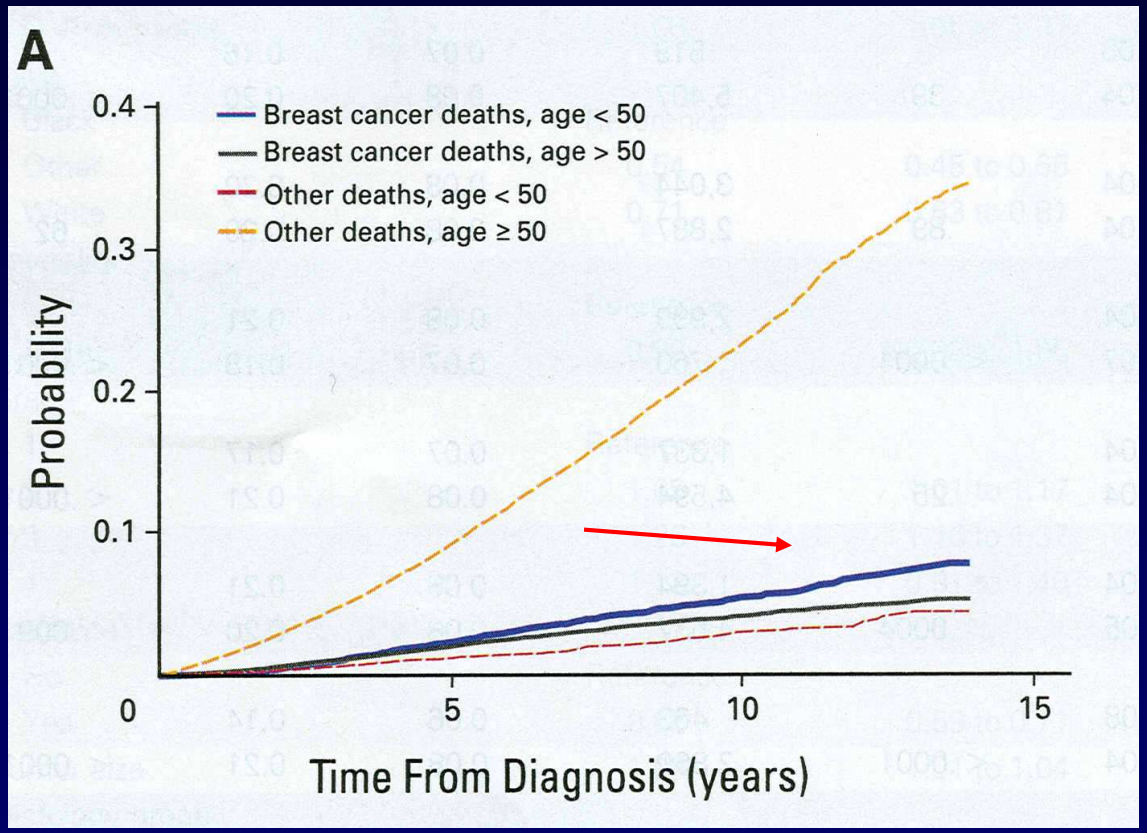
CHU Sart Tilman Liège

Anticancer therapy: cardiac toxicity

- New anticancer therapies have led to long life expectancy for many patients
- Treatment related co morbidities have become an issue for cancer survivors

- Cardiac toxicity vary from mild ECG changes to serious arrhythmias, myocarditis, pericarditis, MI & heart failure

Cardiac disease does matter in early stage breast cancer



Patients (age at least 50) with early stage breast cancer are 4x more likely to die of non-cancer conditions (up to 45 % are cardiac in nature)

Hanrahan, et al. JCO 25: 4952-4960, 2007

Anticancer therapy and cardiac toxicity: the drug

- Reversible (at least partially)? Monitoring
- Cumulative dose-dependent? Adapt regimen
- Major risk factors well known? Patient selection

Anticancer therapy and cardiotoxicity: specific oncological situations

- **Childhood tumors:**
  - **curative treatment, not adjuvant**
  - **low incidence**
  - **anthracyclines frequently used**
- **Very long life expectancy**
- **Risk factors? How to adapt treatment?**

Anticancer therapy and cardiotoxicity: specific oncological situations

Adjuvant treatment of common cancers, such as breast cancer

Avoid or reduce exposure to cardiotoxic drugs such as anthracyclines:

Anthracycline free adjuvant regimens or sequential therapy with taxanes, reducing cumulative toxicity

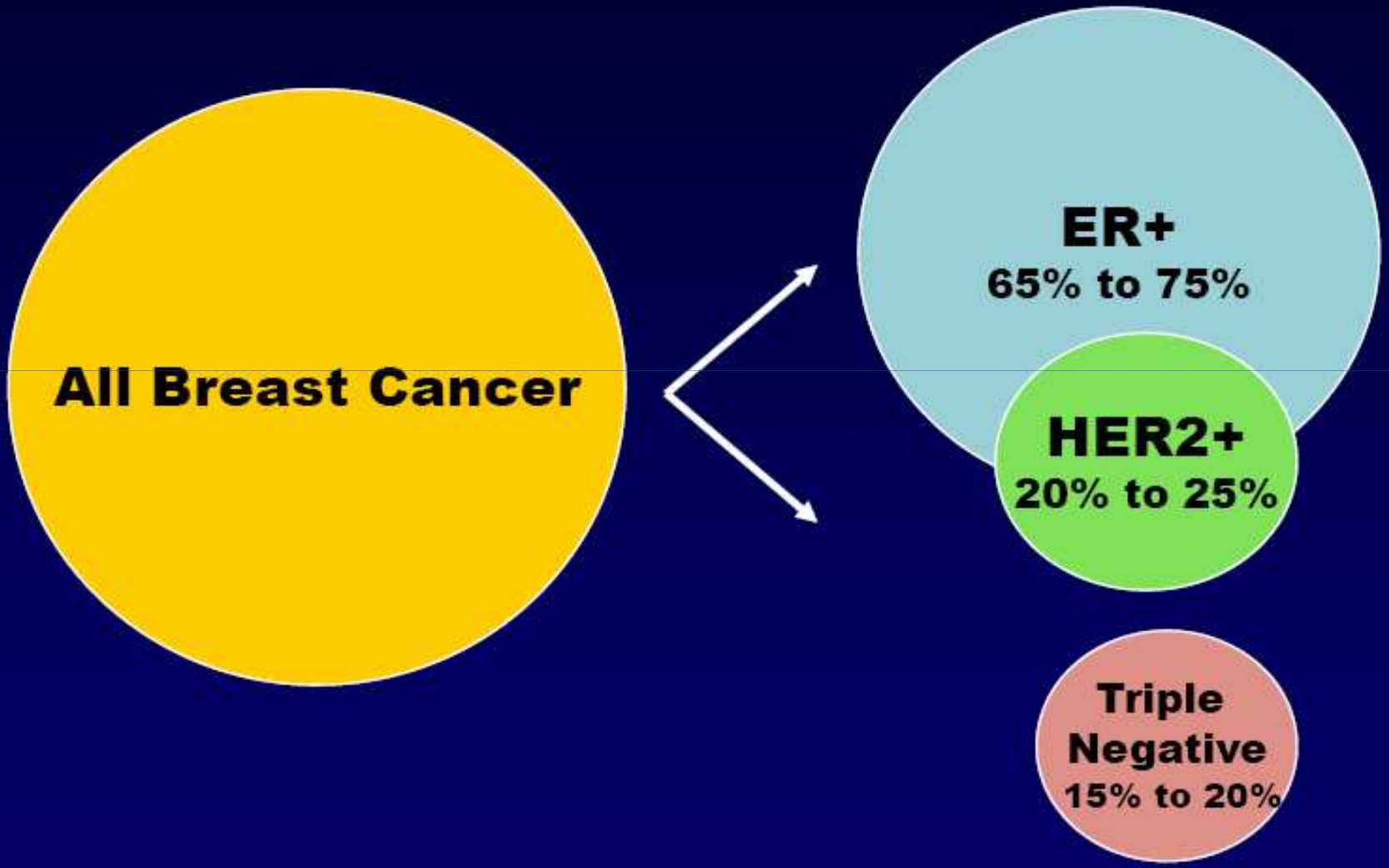
Anticancer therapy and cardiotoxicity: specific oncological situations

Challenges:

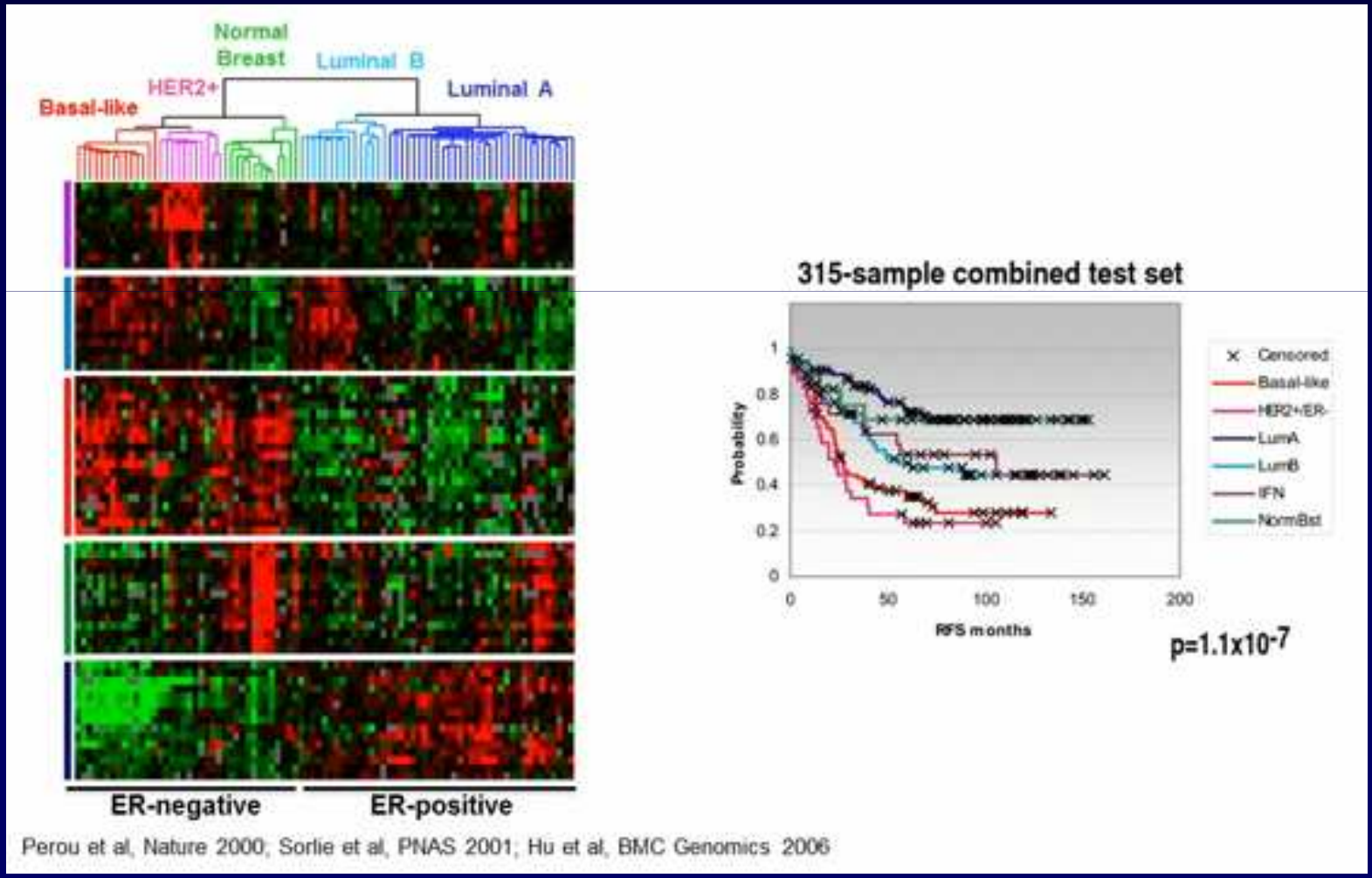
- **Long term follow-up if late occurrence of cardiotoxicity**
- **Outcome in the real world setting??? (highly selected, exclusion of patients with high risk of cardiotoxicity, younger patients in clinical trials)**

Patient selection is a key factor (oncological and cardiotoxicity risk?)

Breast Cancer Subsets

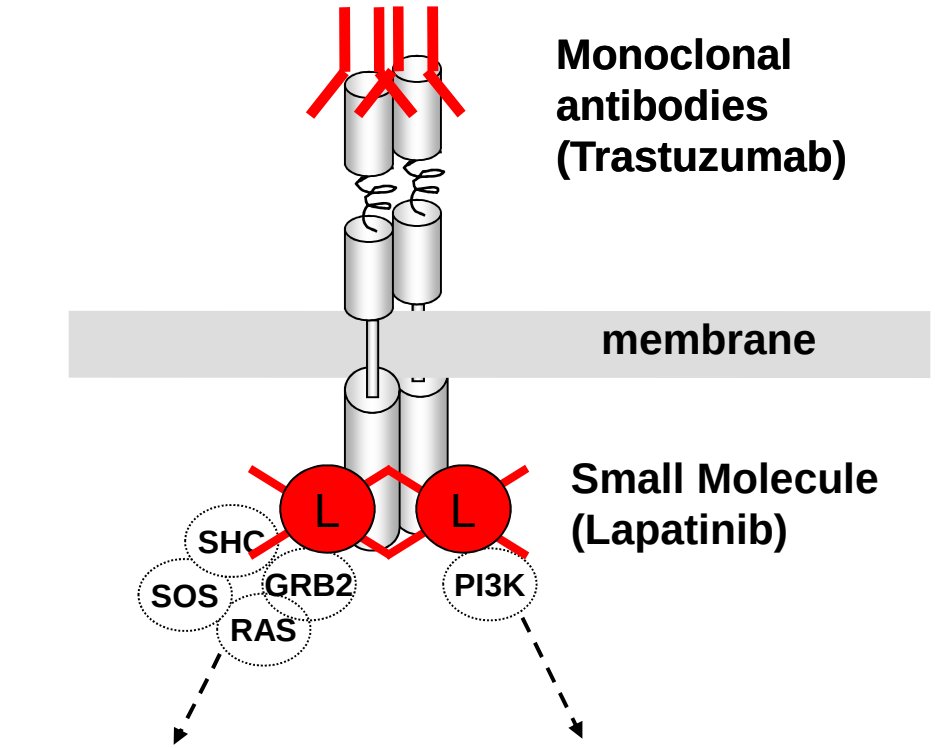


Intrinsic molecular subtypes of breast cancer



Perou et al, Nature 2000; Sorlie et al, PNAS 2001; Hu et al, BMC Genomics 2006

Therapeutic Strategies

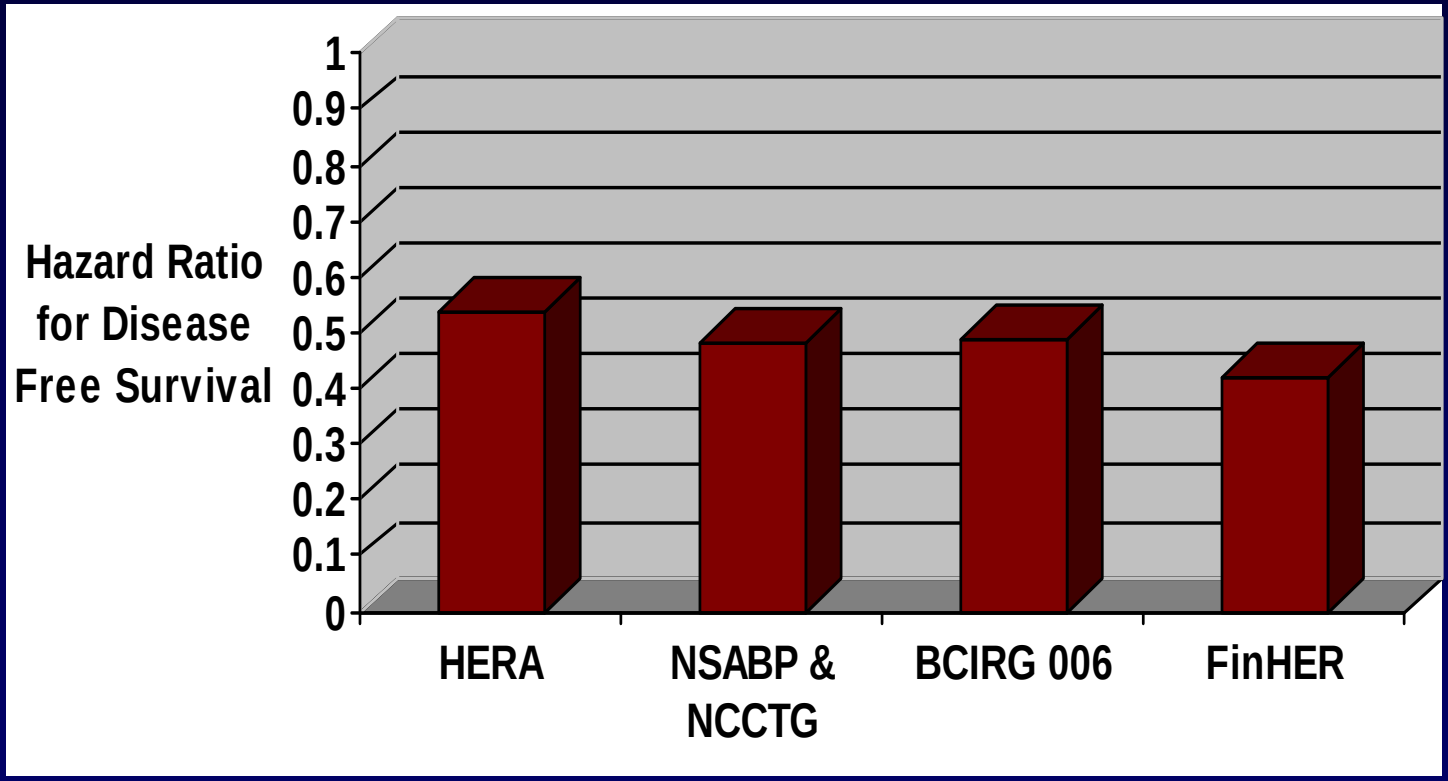


No Growth- No Proliferation – No Survival

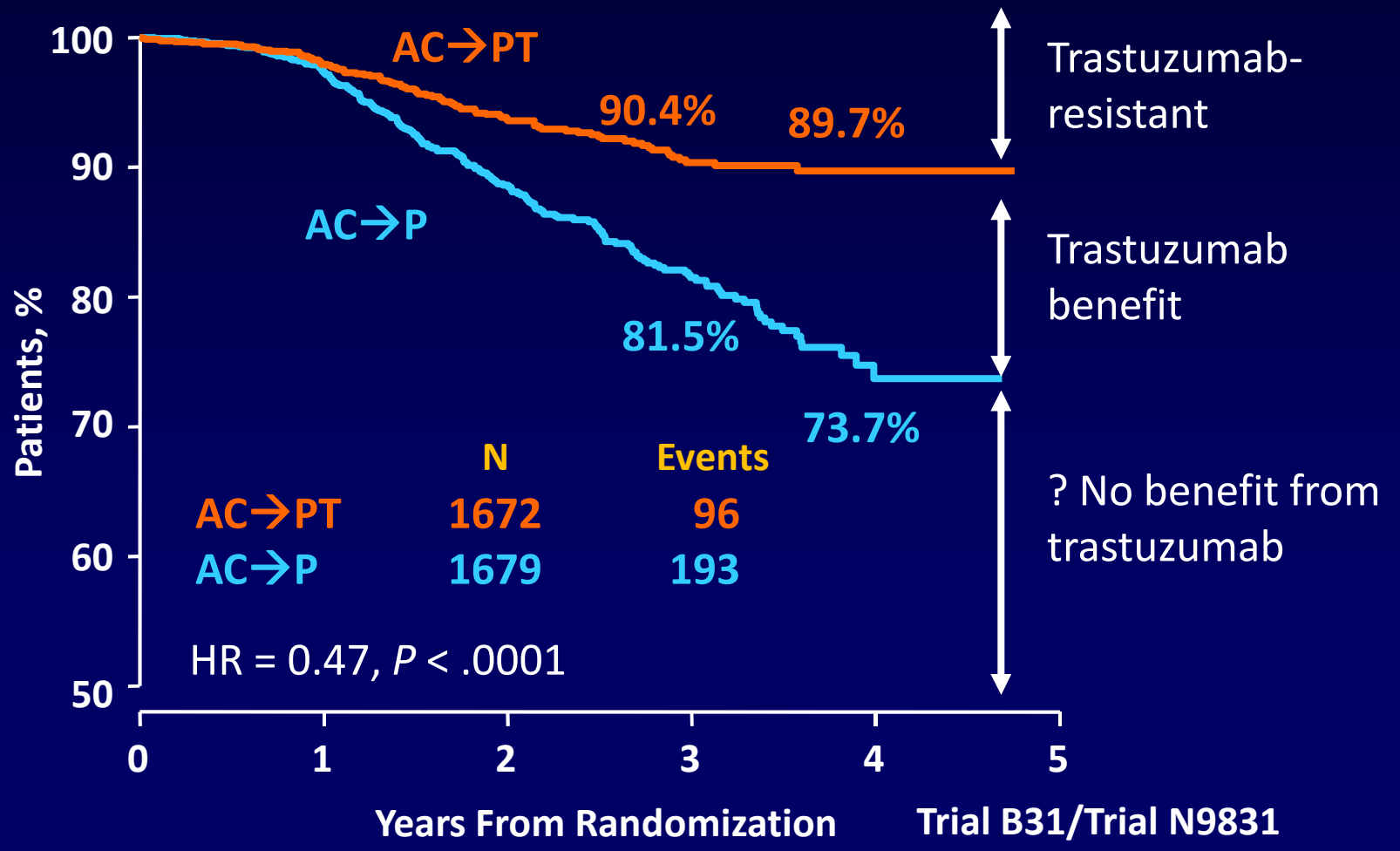
- Monoclonal antibodies can block the RTK signal from the outside
- Small molecules can block the RTK signal at the source

Adjuvant Trastuzumab Trials

MAJOR IMPROVEMENTS IN DFS

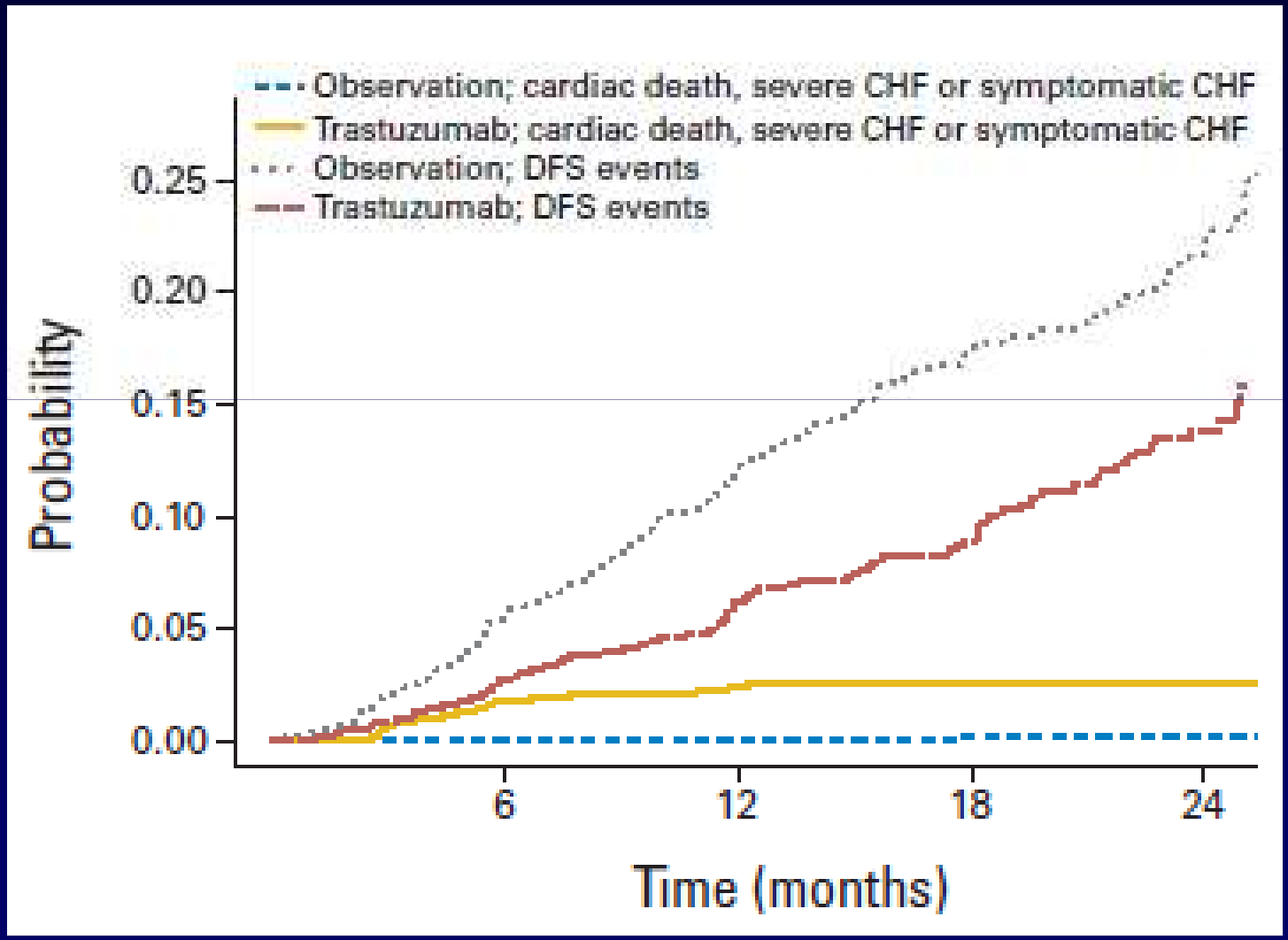


Adjuvant Trastuzumab: Time to First Distant Recurrence



AC, cyclophosphamide + doxorubicin; P, paclitaxel; T, trastuzumab.
Adapted from Romond EH, et al. *New Engl J Med.* 2005;353(16):1673-1684.

Cardiac toxicity: trastuzumab (HERA study)

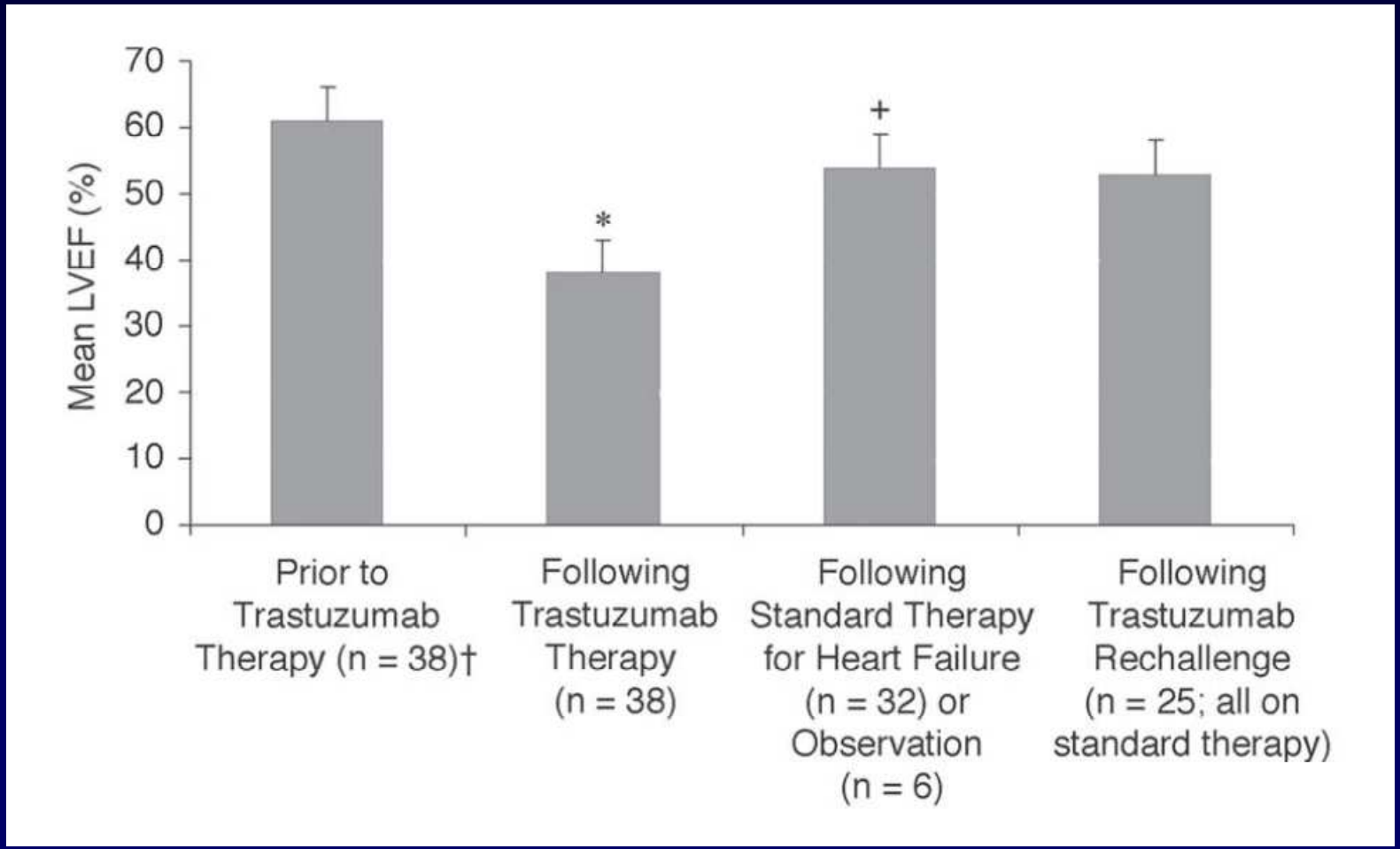


Suter et al. J Clin Oncol 25: 3859-65, 2007

Anticancer therapy: HER2 positive breast cancer

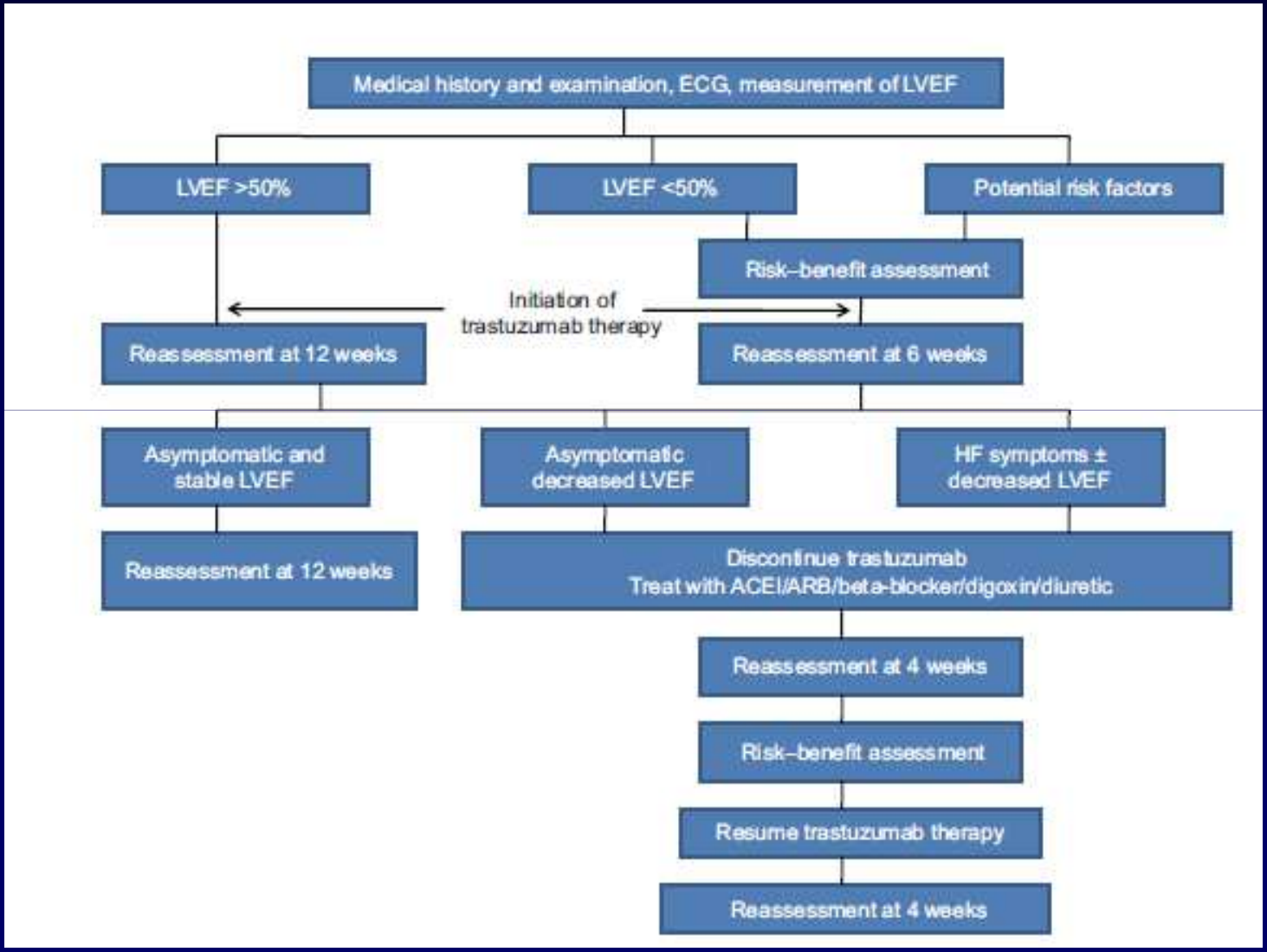
- Use of anthracyclines?
- Use of trastuzumab?
- Combined treatment or sequential treatment?

Trastuzumab: Changes in left ventricular ejection fraction



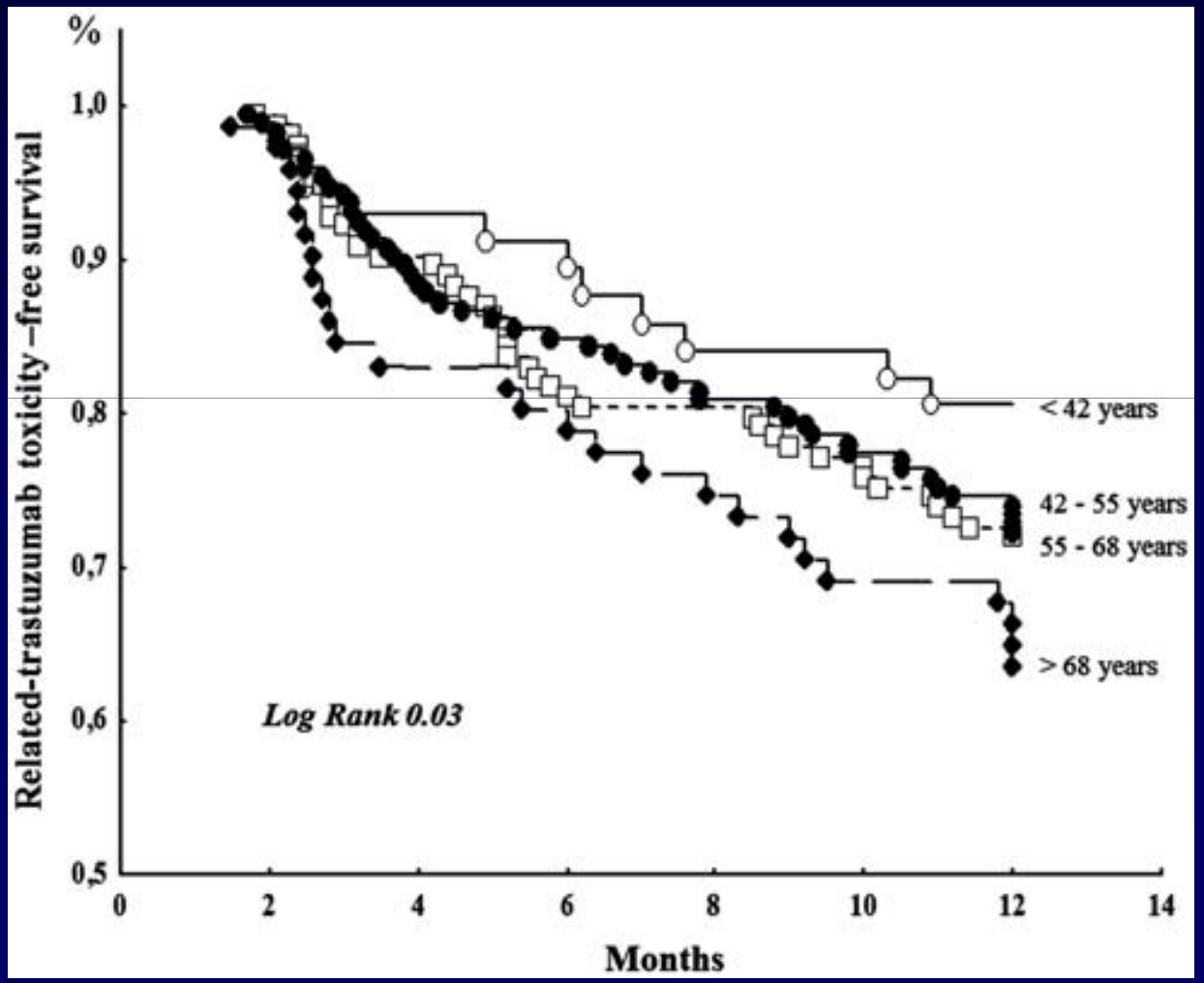
Ewer, et al. JCO 23: 7820-6, 2007

Trastuzumab: cardiac monitoring



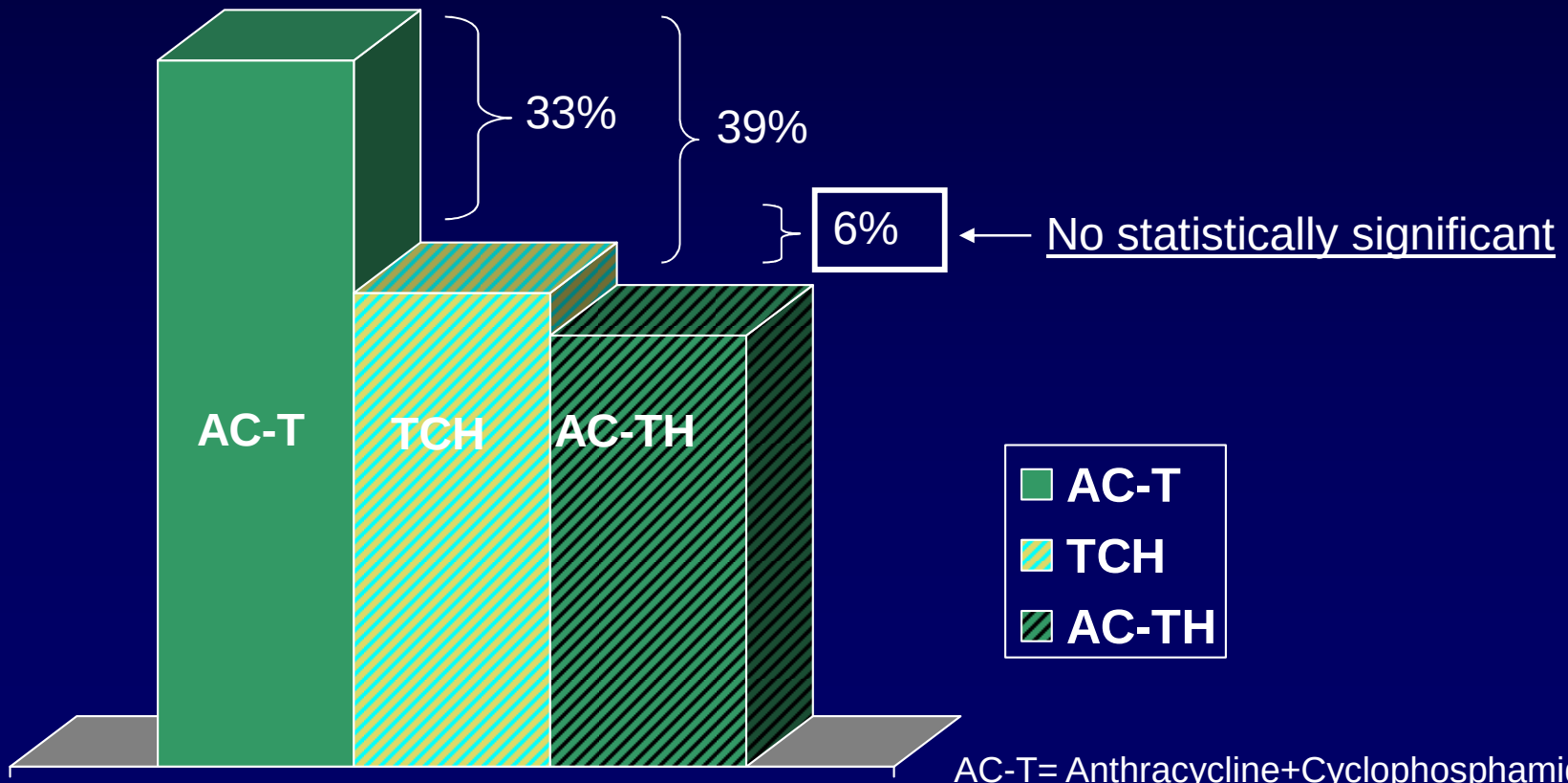
Martin M et al., The Oncologist 14: 1-11, 2009

Adjuvant trastuzumab cardiotoxicity



Tarantini et al. Ann Oncol 23: 3058-63, 2012

BCIRG 006: Risk of relapse



Risk of **relapse**

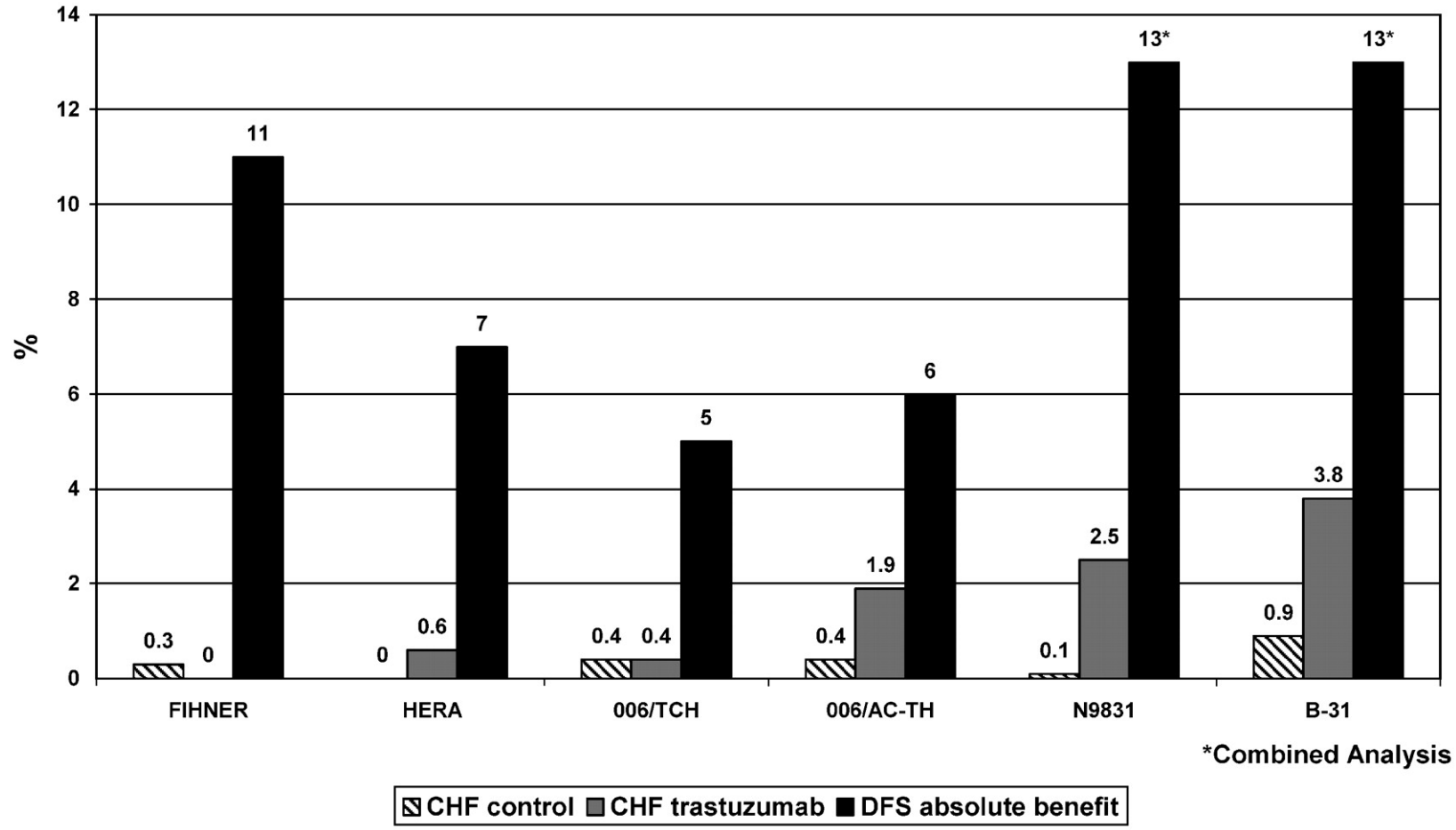
AC-T= Anthracycline+Cyclophosphamide +Taxotère®
TCH= Taxotère®+Carboplatine+Herceptin®
AC-TH= AC-T+Herceptin®

BCIRG 006 : cardiotoxicity

	AC-T N = 1050	AC-TH N = 1068	TCH N = 1056
Cardiac related death	0	0	0
CHF NYHA grade III IV	4	20	4

- Trastuzumab used without prior anthracycline is largely more safe
- Benefit : difference between AC-TH and TCH isn't statistically significant
- **Why not using Herceptin as first agent?**

Cardiac toxicity: trastuzumab



Bird B R H , and Swain S M Clin Cancer Res 2008;14:14-24

NSABP B-31
Cardiac Risk Score

Factors associated with risk of developing a cardiac event:

- **Use of hypertensive medications**
- **Age >49**
- **Baseline LVEF <54**

$$\text{Risk Score} = 100 \times \frac{7.4(0.03 \times \text{Age}) - (0.10 + \text{baseline LVEF}) + (0.68 \times C)}{4.82}$$

C = HTN medication status: none = 0; yes = 1

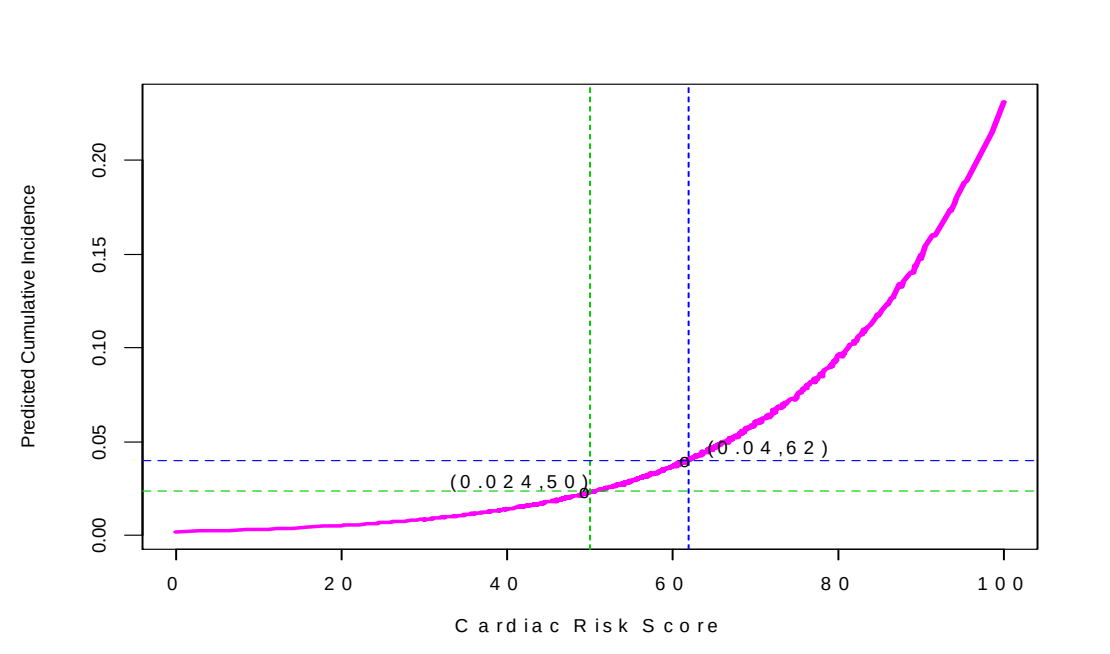
Rostagi P, Adjuvant Breast Oral Session, ASCO 2007

NSABP B-31
Cardiac Risk Score

Example:

62 yo woman on antihypertensive medication

Baseline LVEF = 60%



Cardiac Risk Score = **82**

3-year predicted incidence of symptomatic heart failure/cardiac death ≅ **10%**

Future Directions

PREVENTION ?

- Pre-emptive use of *ACE inhibitors* or *beta-blockers* in may prevent cardiotoxicity

EARLY DETECTION

- Cardiac biomarkers may help identify high risk patients

CLOSE COLLABORATION !!!