Cancer as a Precursor to Heart Failure

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Conflict of Interest Disclosures

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- **Consulting fees**: Pfizer, Alnylam, Eidos, Ionis/Akcea

Outline

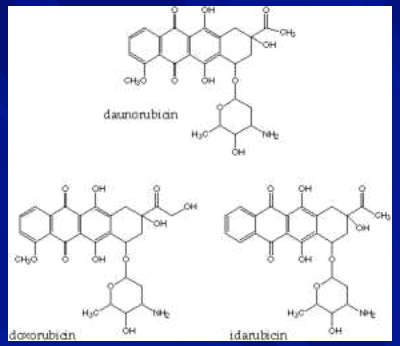
- Cancer-therapy-specific toxicities
  - Anthracyclines
  - Her2 inhibitors
  - Immune checkpoint inhibitors
- Focus on when (and when not!) to screen
- Not covered…
  - Anti-VEGF TKIs
  - 5-FU vasospasm
  - Proteasome inhibitor toxicity (e.g. carfilzomib)
  - BTK inhibitor toxicity (e.g. ibruitinib)
  - Many others!

Anthracyclines

Anthracyclines

- Potent anti-neoplastic agents for multiple tumors
  - Doxorubicin, daunorubicin, idarubicin, epirubicin,
  - Breast CA, lymphoma, leukemia, sarcoma

- Mechanism/toxicity:
  - Likely largely via effects on topoisomerase II
  - Ultimately → free radical formation → injury



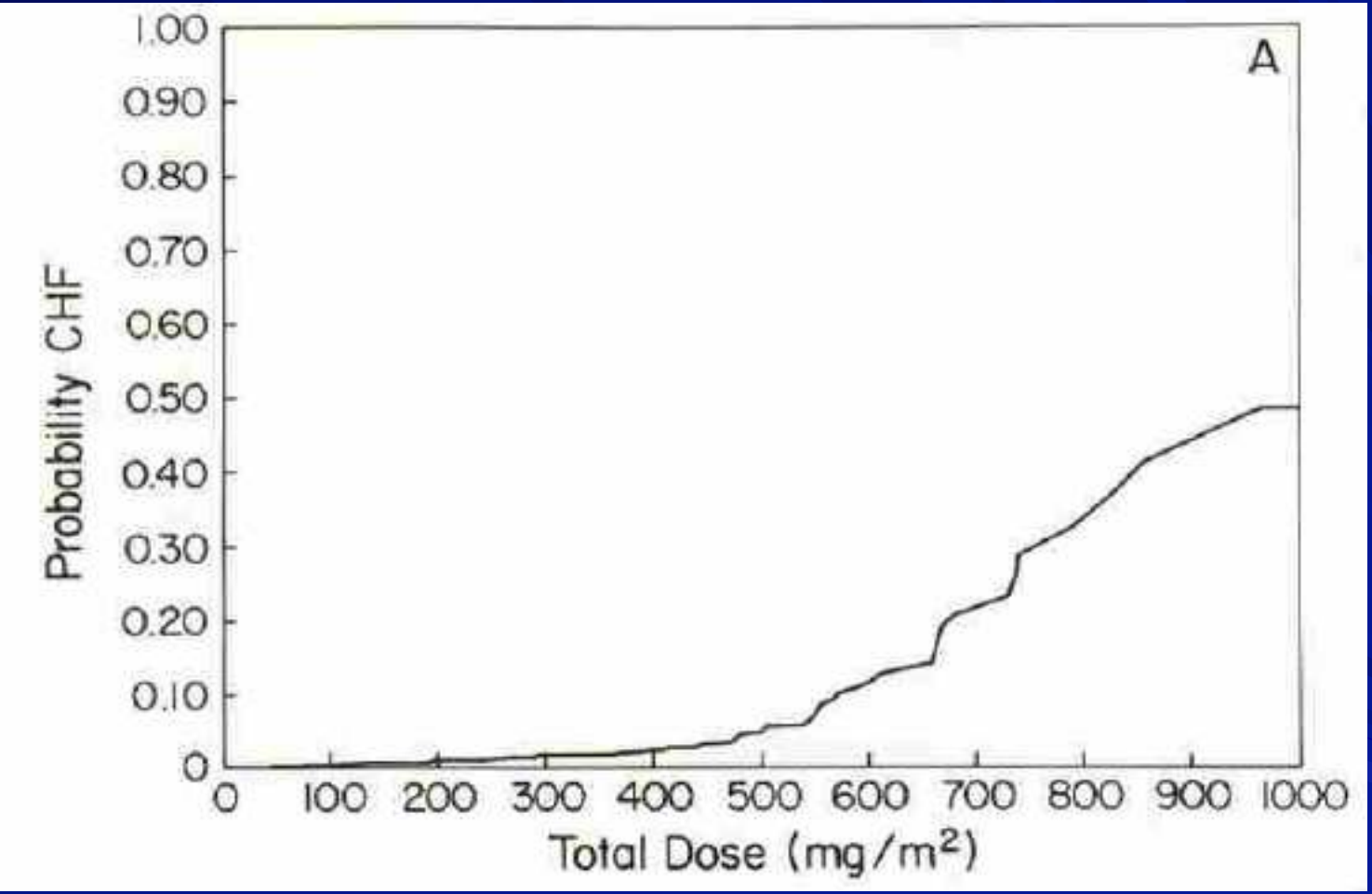
Should We Believe The Doxorubicin Label?

- "The probability of developing impaired myocardial function… is estimated to be 1-2% at a total cumulative dose of 300 mg/m2 of doxorubicin, 3-5% at a dose of 400 mg/m2, 5-8% at 450 mg/m2, and 6-20% at 500 mg/m2."

- "Treatment of doxorubicin-induced congestive heart failure includes the use of digitalis, diuretics, afterload reducers such as ACE-inhibitors, low salt diet, and ***bed rest***. Such interventions may relieve symptoms ***and improve the functional status*** of the patient."

Adapted from https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050467s070lbl.pdf

Primary Source of Those Numbers…



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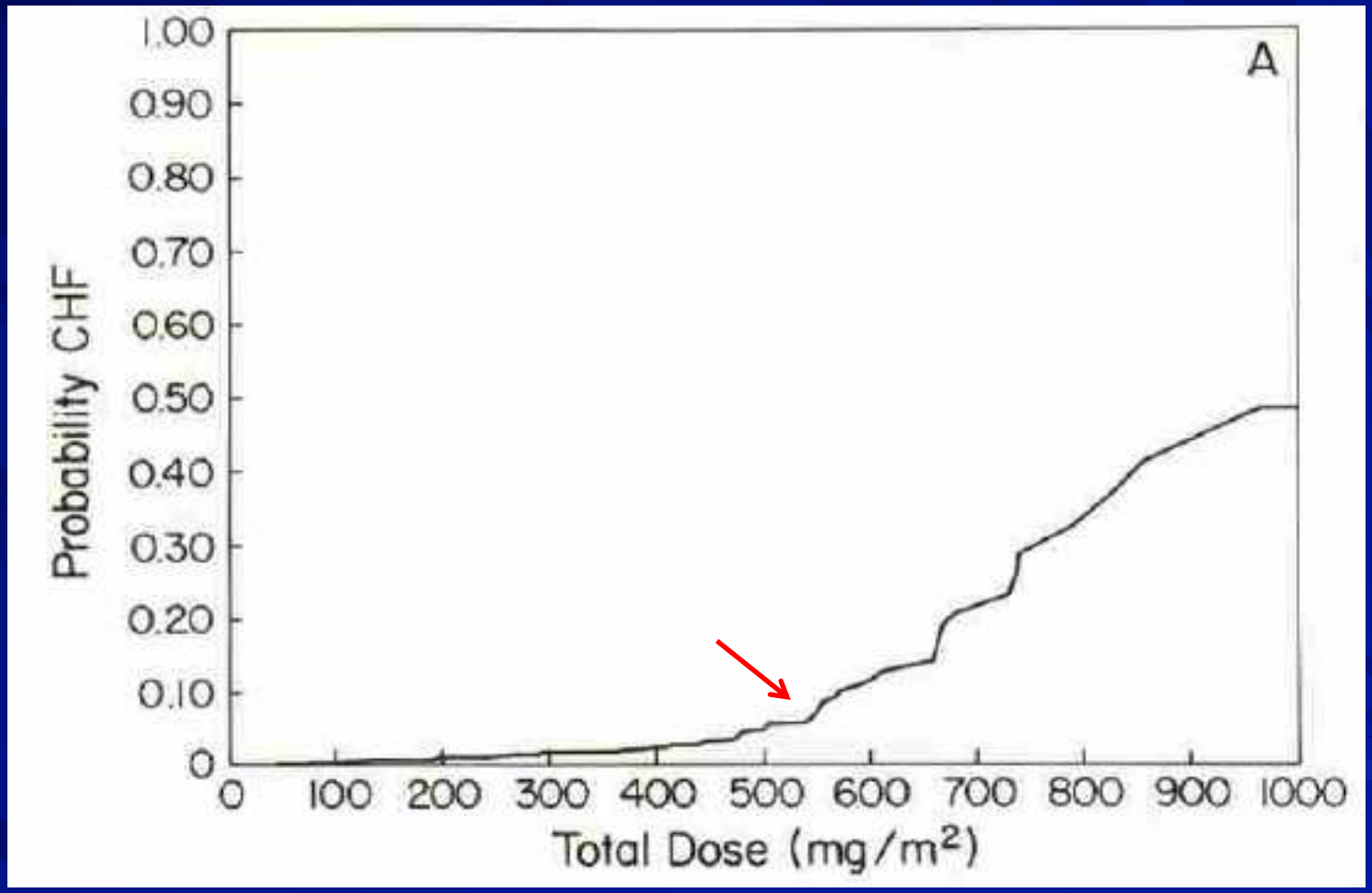

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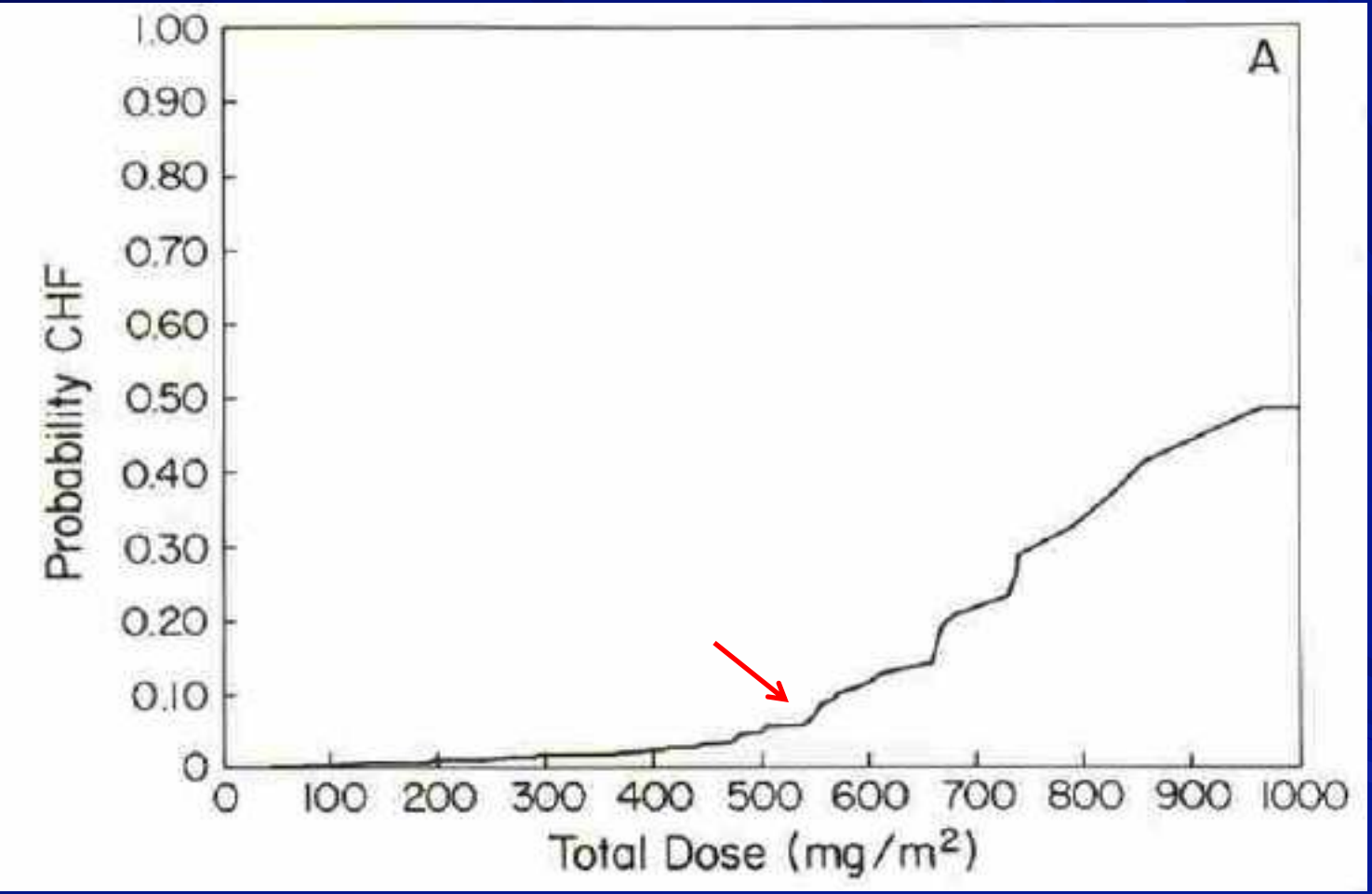

Adapted from Von Hoff et al. Ann Int Med. 1979;91:710-7.

A Subsequent Evaluation…

- Study of three anthracycline trials
  - Significant event:
    - Symptomatic CHF or
    - EF drop >20% or
    - **EF drop >10% from normal to below LLN**, or
    - EF drop >5% in patient already below LLN
  - So the data is not just off, but is off...
    - **By a full order of magnitude!!!**

	All studies (n = 630 patients, 149 events)	
Dose (mg/m^2)	%	SE
50	0.4	0.3
100	0.5	0.3
150	6.5	1.0
200	7.8	1.2
250	8.8	1.2
300	16.2	1.7
350	17.9	1.9
400	32.4	3.2
450	37.9	3.5
500	53.9	4.2
550	65.4	4.6
600	72.0	4.8
650	80.6	4.9
700	86.2	4.8
750	86.2	4.8
800	90.8	4.9
850	100.0	—

Adapted from Swain et al. Cancer. 2003;97:2869-79.

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Adapted from Swain et al. Cancer. 2003;97:2869-79.

How Often *Should* We Screen LVEF in Patients Who Receive Anthracyclines?

A) We shouldn't define a monitoring threshold.
B) At baseline, at the end of treatment, then q3 months for 12 months after completing treatment, and then annually thereafter.
C) After 200 mg/m2.
D) At 240 mg/m2 and every 50 mg/m2 thereafter.
E) At 360 mg/m2 and every 2 cycles thereafter.
F) At completion of therapy, and after every cycle above 240 mg/m2.
G) We should discourage screening unless symptoms or physical exam signs point to cardiac toxicity.

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G) We should discourage screening unless symptoms or physical exam signs point to cardiac toxicity.

Each of these Strategies are Endorsed By Major Groups/Societies – As of Today!!!

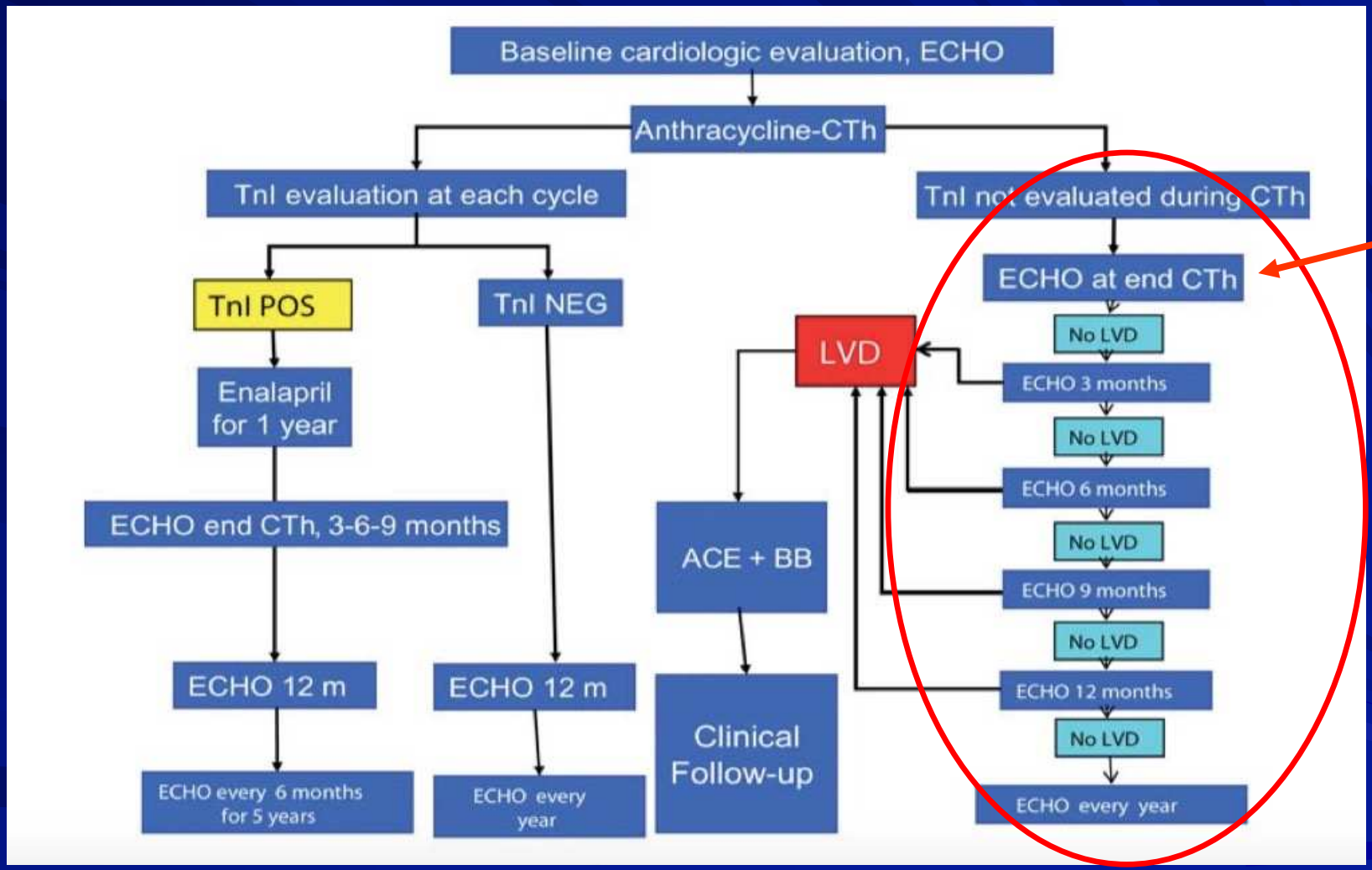
Society Recommendations: What is a Well-Meaning Clinician to Do?

- **"Routine screening or testing for cardiovascular disease in asymptomatic patients beyond careful history and physical examination are not warranted."**

  - American Cancer Society survivorship guideline, 2016

Adapted from Up-to-Date, Accessed Februrary 3, 2019, European Heart J 2016;37:2768-2801, J Am Soc Echo 2014;27:911-39, J Clin Onc 2016;34:611, J Clin Oncol 2017;35:893, Ann Oncol 2012;23 Suppl 7:vii155-66.

ESMO Guidelines: Anthracycline Monitoring (!)



Adapted from Ann Oncol 2012;23 Suppl 7:vii155-66.

Talk About Mixed Messages!

- Should we not screen at all? Should we screen 6 times in year 1 and then annually?

- My recommendations for LVEF screening with anthracyclines:
  - Baseline
  - At 300 mg/m2 and every 50 mg/m2 thereafter
  - At end-of therapy (regardless of total dose)

- High-risk cases (e.g. borderline LVEF):
  - Consider anthracycline-free regimen if appropriate
  - GDMT if already LV dysfunction
  - Closer monitoring
  - Other options…

Prolonged Infusion Protocols

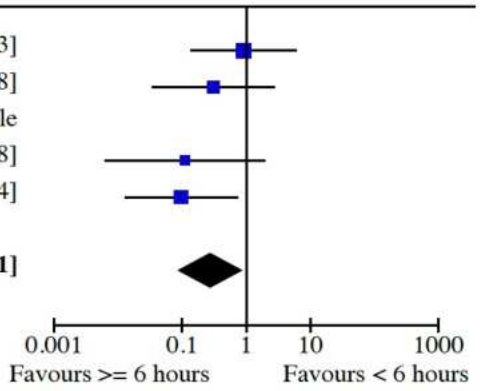
Analysis 1.1. Comparison 1: Infusion duration less than 6 hours versus infusion duration 6 hours or more, Outcome 1: Clinical heart failure

Study or Subgroup	>= 6 hours Events	Total	< 6 hours Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Casper 1991	2	43	2	39	32.4%	0.91 [0.13 , 6.13]
Hortobagyi 1989	1	27	3	25	24.7%	0.31 [0.03 , 2.78]
Lipshultz 2002	0	57	0	64		Not estimable
Shapira 1990	0	31	4	31	14.4%	0.11 [0.01 , 1.98]
Zalupski 1991	1	122	10	118	28.5%	0.10 [0.01 , 0.74]
Total (95% CI)		**280**		**277**	**100.0%**	**0.27 [0.09 , 0.81]**
Total events:	4		19			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.05$, df = 3 (P = 0.38); $I^2 = 2\%$

Test for overall effect: Z = 2.33 (P = 0.02)

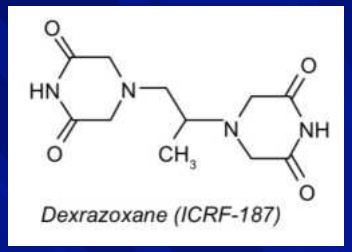
Test for subgroup differences: Not applicable



Adapted from van Dalen et al. Cochrane Database Syst Rev. 2016;3(3):CD005008.

Dexrazoxane

- Developed in 1950s by Eastman Kodak Company & Ciba Geigy Corporation as jet fuel additive & for textile manufacturing



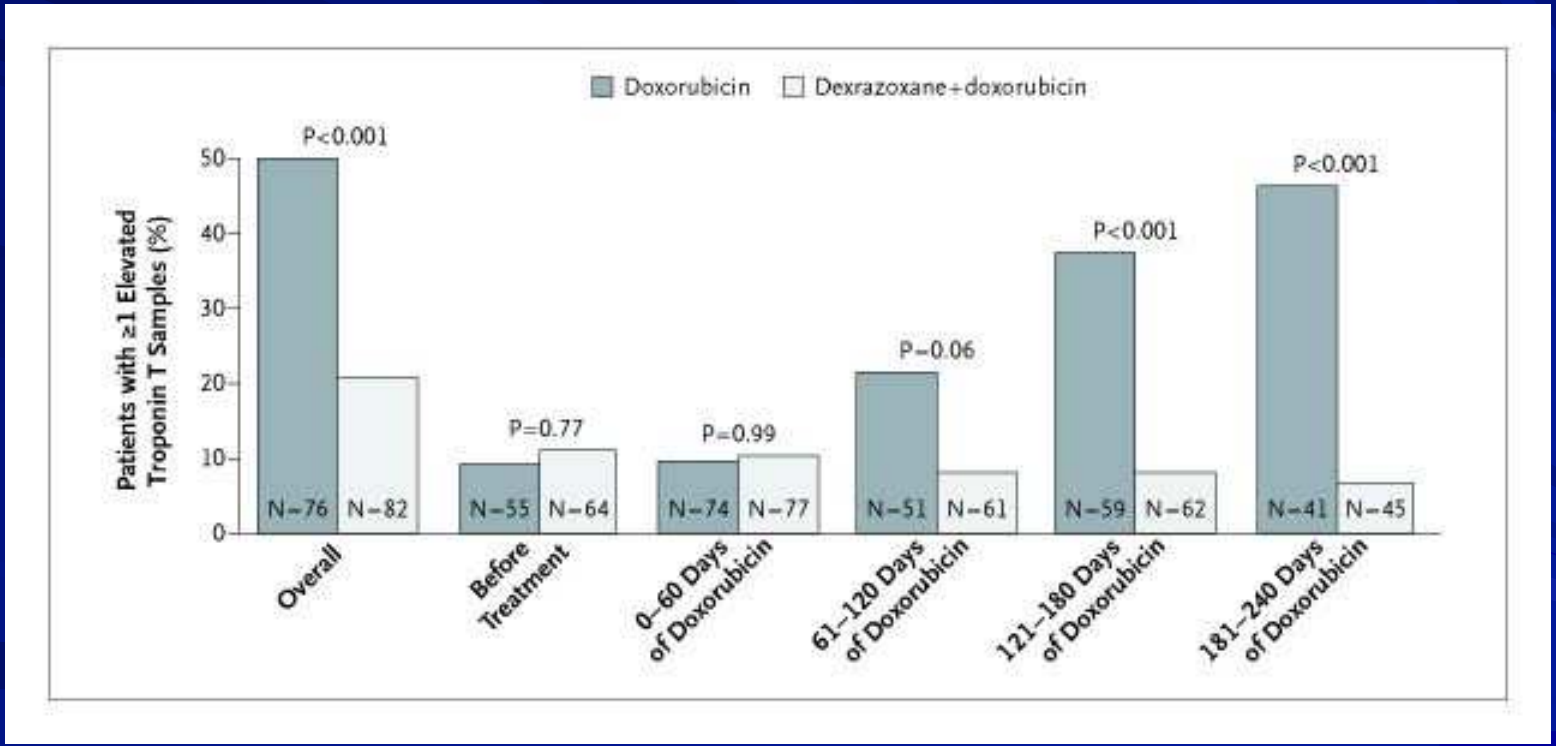
Dexrazoxane (ICRF-187)

- Then developed therapeutically as antineoplastic agent!
  - Toxicity too high → abandoned
- Subsequently discovered to ameliorate anthracycline cardiotoxicity (as well as anthracycline extravasation injuries)

Adapted from Langer. Cancer Manag Res. 2014;6:357-363.

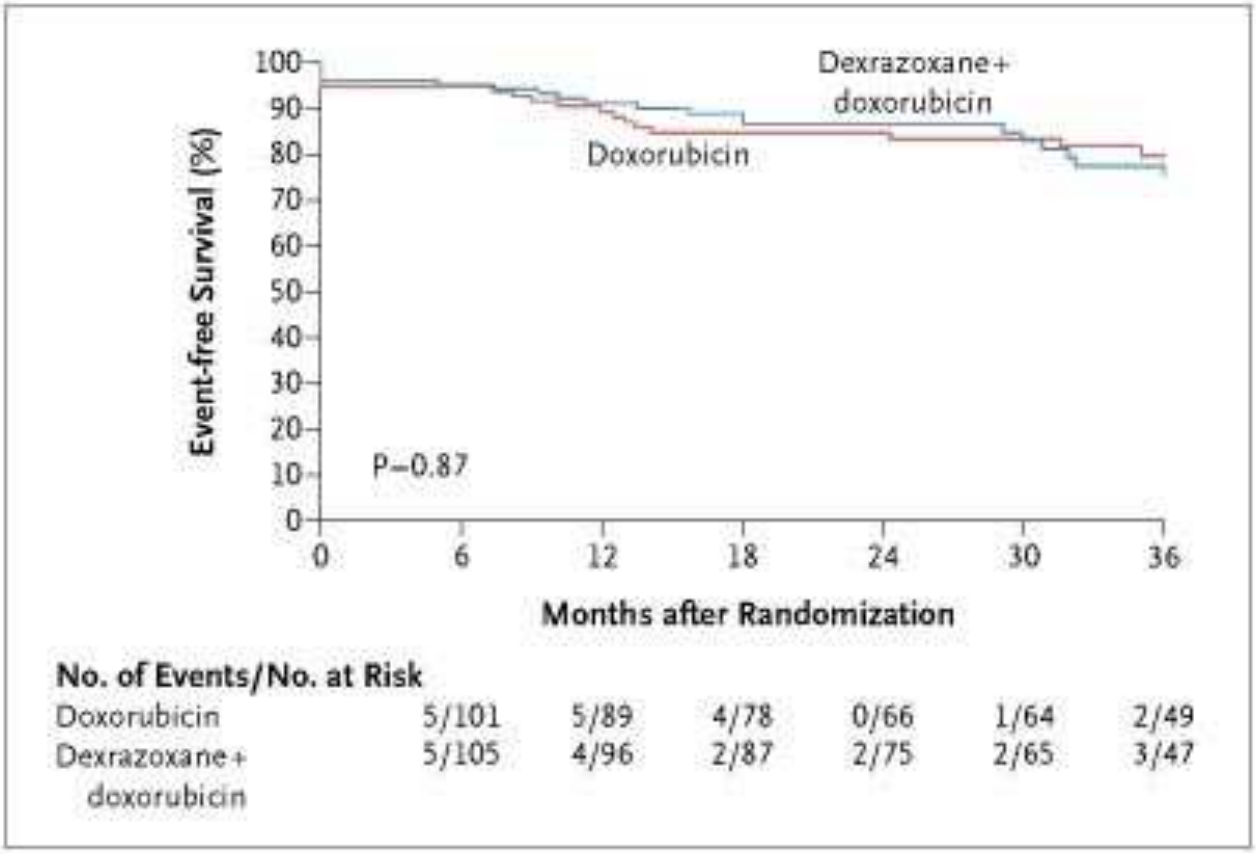
Dexrazoxane: Evidence for Myocardial Protection

- Study published in NEJM (2004)
- Evaluated troponin T in children receiving doxorubicin +/- dexrazoxane for high-risk ALL



Adapted from Lipshultz et al. NEJM. 2004;351:145-53.

Disease-Free Survival Unchanged



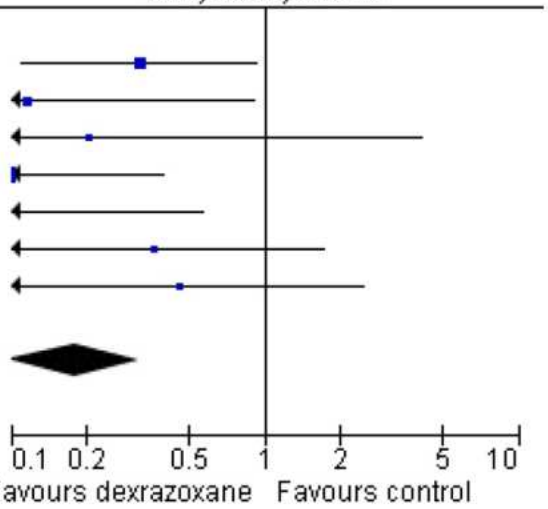
Adapted from Lipshultz et al. NEJM. 2004;351:145-53.

Cochrane Review of Dexrazoxane: Clinical Heart Failure

Study or Subgroup	Dexrazoxane Events	Dexrazoxane Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lipshultz 2004	0	105	0	101		Not estimable
Lopez 1998	4	63	13	66	18.4%	0.32 [0.11, 0.94]
Marty 2006	1	85	8	79	12.0%	0.12 [0.01, 0.91]
Schwartz 2009	0	107	2	109	3.6%	0.20 [0.01, 4.19]
Speyer 1992	2	76	20	74	29.4%	0.10 [0.02, 0.40]
Swain 1997a(088001)	0	168	15	181	21.7%	0.03 [0.00, 0.58]
Swain 1997a(088006)	2	81	7	104	8.9%	0.37 [0.08, 1.72]
Venturini 1996	2	84	4	78	6.0%	0.46 [0.09, 2.46]
Total (95% CI)		**769**		**792**	**100.0%**	**0.18 [0.10, 0.32]**
Total events	11		69			

Heterogeneity: $Chi^2 = 5.49$, $df = 6$ ($P = 0.48$); $I^2 = 0\%$

Test for overall effect: $Z = 5.67$ ($P < 0.00001$)



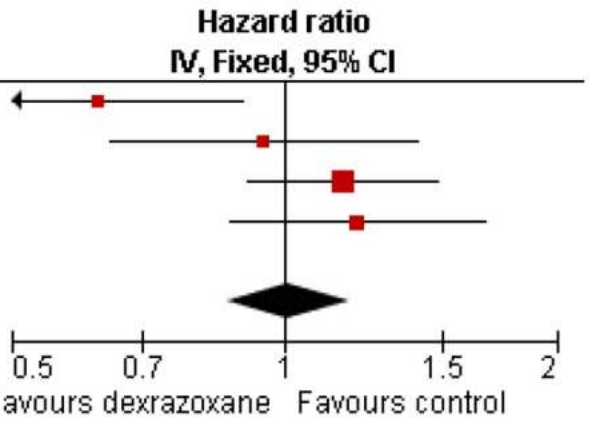
Adapted from van Dalen et al. Cochrane Database Syst Rev. 2011;6:CD003917.

Dexrazoxane: Progression-Free Survival

Study or Subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, Fixed, 95% CI
Marty 2006	-0.4708	0.1852	18.5%	0.62 [0.43, 0.90]
Speyer 1992	-0.0508	0.1981	16.2%	0.95 [0.64, 1.40]
Swain 1997a(088001)	0.1508	0.1227	42.2%	1.16 [0.91, 1.48]
Swain 1997a(088006)	0.1863	0.166	23.1%	1.20 [0.87, 1.67]
Total (95% CI)			**100.0%**	**1.01 [0.86, 1.18]**

Heterogeneity: $Chi^2 = 9.28$, $df = 3$ ($P = 0.03$); $I^2 = 68\%$

Test for overall effect: $Z = 0.14$ ($P = 0.89$)

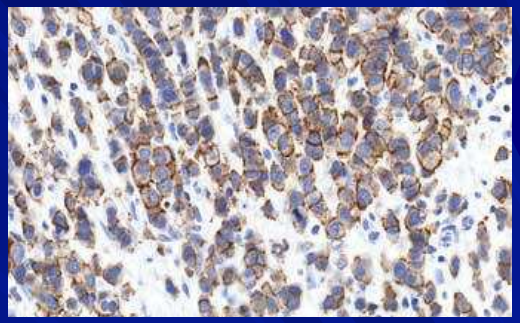


Adapted from van Dalen et al. Cochrane Database Syst Rev. 2011;6:CD003917.

Her-2 Inhibitors

Trastuzumab

- Human epidermal growth factor receptor-2 (Her2)
  - Gene discovered/cloned 1983
  - Amplified and/or overexpressed in 25-30% breast CA
  - Denotes more aggressive tumor/shorter survival



- Trastuzumab
  - Murine monoclonal Ab against extracellular domain of Her2 protein

Original Trastuzumab Pivotal Trial

- Patients:
  - Women with metastatic breast CA with HER2 overexpression/no prior Rx for the metastatic disease.
- Intervention:
  - Chemotherapy + trastuzumab (H) or chemotherapy alone

The New England Journal of Medicine

VOLUME 344 MARCH 15, 2001 NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

ABSTRACT

Background The *HER2* gene, which encodes the growth factor receptor HER2, is amplified and HER2 is overexpressed in 25 to 30 percent of breast cancers, increasing the aggressiveness of the tumor.

Methods We evaluated the efficacy and safety of trastuzumab, a recombinant monoclonal antibody against HER2, in women with metastatic breast cancer that overexpressed HER2. We randomly assigned 234 patients to receive standard chemotherapy alone and 235 patients to receive standard chemotherapy plus trastuzumab. Patients who had not previously received adjuvant (postoperative) therapy with an anthracycline were treated with doxorubicin (or epirubicin in the case of 36 women) and cyclophosphamide with (143 women) or without trastuzumab (138 women). Patients who had previously received adjuvant anthracycline were treated with paclitaxel alone (96 women) or paclitaxel with trastuzumab (92 women).

Results The addition of trastuzumab to chemotherapy was associated with a longer time to disease progression (median, 7.4 vs. 4.6 months; P<0.001), a higher rate of objective response (50 percent vs. 32 percent, P<0.001), a longer duration of response (median, 9.1 vs. 6.1 months; P<0.001), a lower rate of death at 1 year (22 percent vs. 33 percent, P=0.008), longer survival (median survival, 25.1 vs. 20.3 months; P=0.046), and a 20 percent reduction in the risk of death. The most important adverse event was cardiac dysfunction, which occurred in 27 percent of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8 percent of the group given an anthracycline and cyclophosphamide alone; 13 percent of the group given paclitaxel and trastuzumab; and 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was potentially severe and, in some cases, life-threatening, the symptoms generally improved with standard medical management.

Conclusions Trastuzumab increases the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2. (N Engl J Med 2001; 344:783-92.)

DESPITE advances in the diagnosis and treatment of breast cancer, more than 44,000 women in the United States will die this year of metastatic disease.[1,2] Although objective responses to some chemotherapy regimens are common, few patients with metastatic disease are cured,[3,4] and treatments frequently cause substantial adverse effects.

A growth factor receptor gene,[5,7] human epidermal growth factor receptor (*HER2*), is amplified in 25 to 30 percent of breast cancers and in these cases the encoded protein is present in abnormally high levels in the malignant cells.[8,9] Women with breast cancers that overexpress HER2 have an aggressive form of the disease with significantly shortened disease-free survival and overall survival.[8-12] Laboratory studies indicate that amplification of *HER2* has a direct role in the pathogenesis of these cancers,[13-17] thereby providing investigators with an opportunity to target a therapeutic agent directly against the alteration.

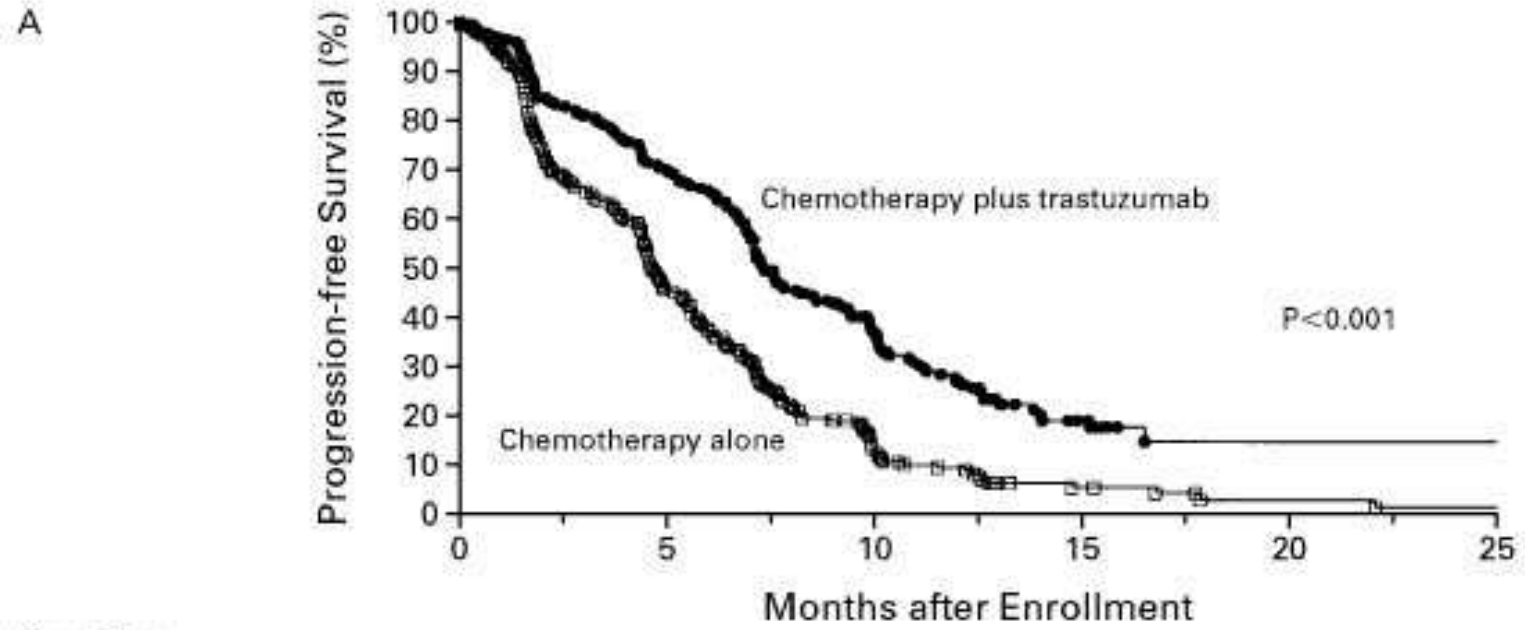
Several murine monoclonal antibodies against the extracellular domain of the HER2 protein were found to inhibit the proliferation of human cancer cells that overexpressed HER2, both in vitro and in vivo.[18-20] To minimize immunogenicity, the antigen-binding region of one of the more effective antibodies was

From the Division of Hematology and Oncology, UCLA School of Medicine, Los Angeles (D.J.S., B.L.-J.); the Departments of Oncology, McGill University, Montreal (B.L.-J.); Medical Affairs, Genentech, South San Francisco, Calif. (S.S., V.P., A.B.); IntraBiotics, Mountain View, Calif. (H.F.); the Department of Biomatrics, University of Washington, Seattle (T.F.); the Department of Obstetrics and Gynecology, Frauenklinik von Rosen Kreuz, Munich, Germany (W.E.); the Departments of Oncology, Rush–Presbyterian–St. Luke's Medical Center, Chicago (J.W.); the Department of Oncology, Hospital General Universitari Vall d'Hebron, Barcelona, Spain (J.B.); and the Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York (L.N.). Address reprint requests to Dr. Slamon at UCLA School of Medicine, Division of Hematology/Oncology, 11-244 Factor Bldg., 10833 Le Conte, Los Angeles, CA 90095-1678, or at dslamon@mednet.ucla.edu.

*Additional study investigators are listed in the Appendix.

Adapted from Slamon et al. NEJM. 2001;344:783-92.

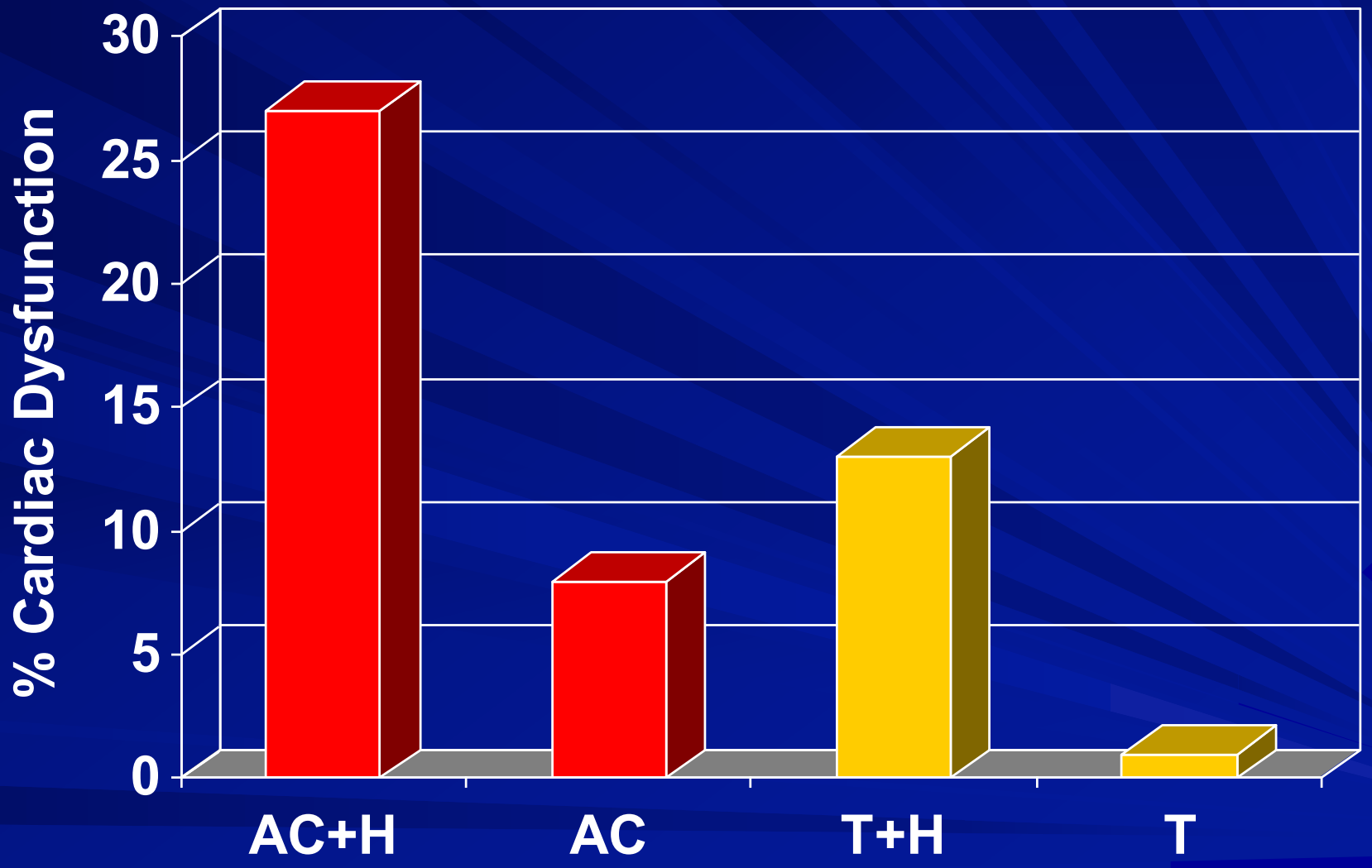
Progression-Free Survival



No. at Risk				
Chemotherapy plus trastuzumab	235	152	63	15
Chemotherapy alone	234	103	25	6

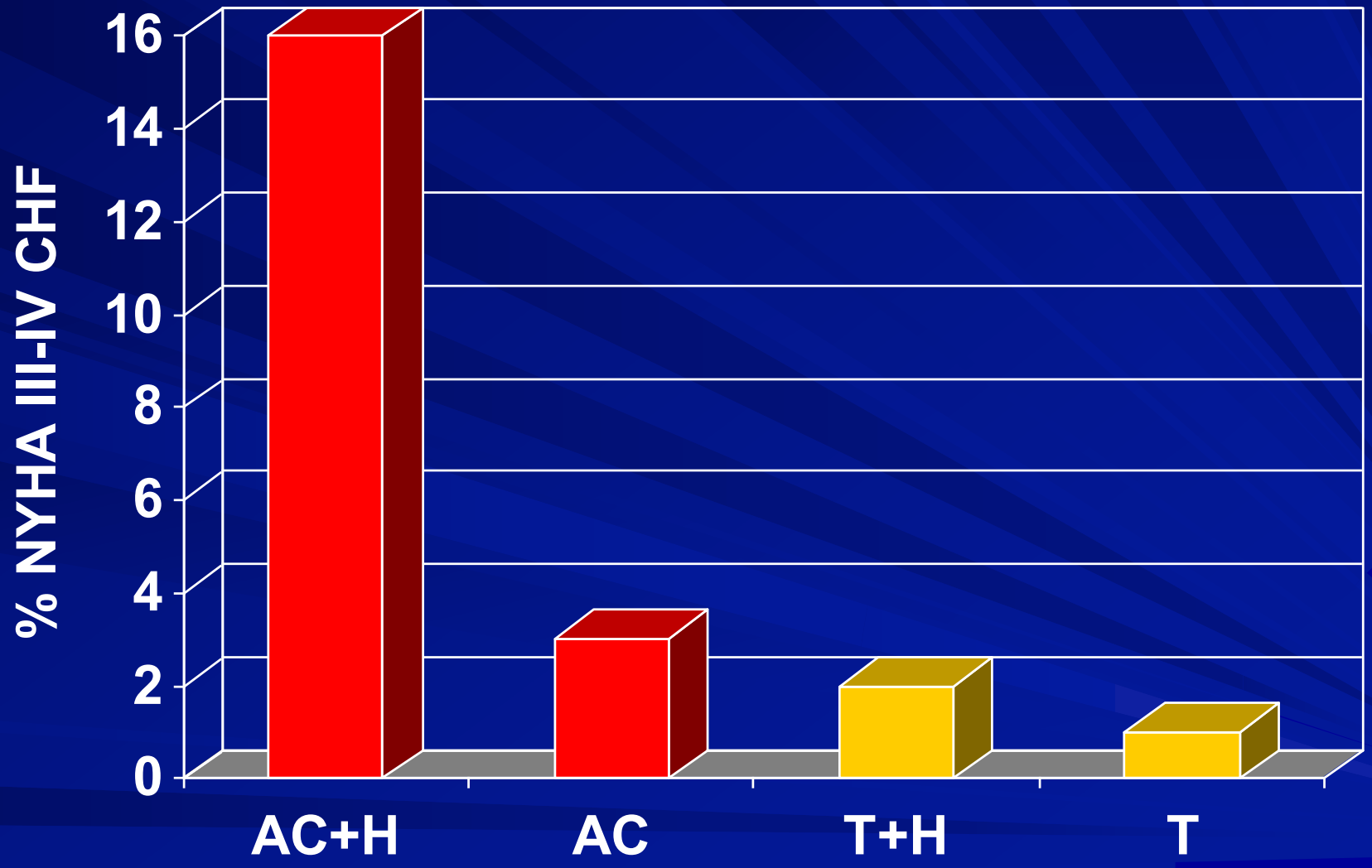
Adapted from Slamon et al. NEJM. 2001;344:783-92.

The Bad News (Independent Review)



Adapted from Slamon et al. NEJM. 2001;344:783-92.

The Worse News: NYHA Class III-IV



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HERA Trial

- 3386 patients randomized to
  - Trastuzumab x 1 year
  - Observation
- 94% had received anthracycline-based therapy prior to randomization
- LVEF assessment at times:
  - 0, 3, 6, 12, 18, 24, 30, 36, and 60 months
- The data for 1693 randomized to trastuzumab…


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Trastuzumab-Associated Cardiac Adverse Effects in the Herceptin Adjuvant Trial

Data adapted from Suter et al. J Clin Oncol. 2007;25:3859-65.

HERA Trial: Low CV Event Rates!

- NYHA Class III/IV HF: 0.6% (!)
- LVEF drop ≥10% to EF <50%: 3.0%
- And that's despite doing 9 EF assessments by protocol over 5 years of follow-up (!)

Data adapted from Suter et al. J Clin Oncol. 2007;25:3859-65.

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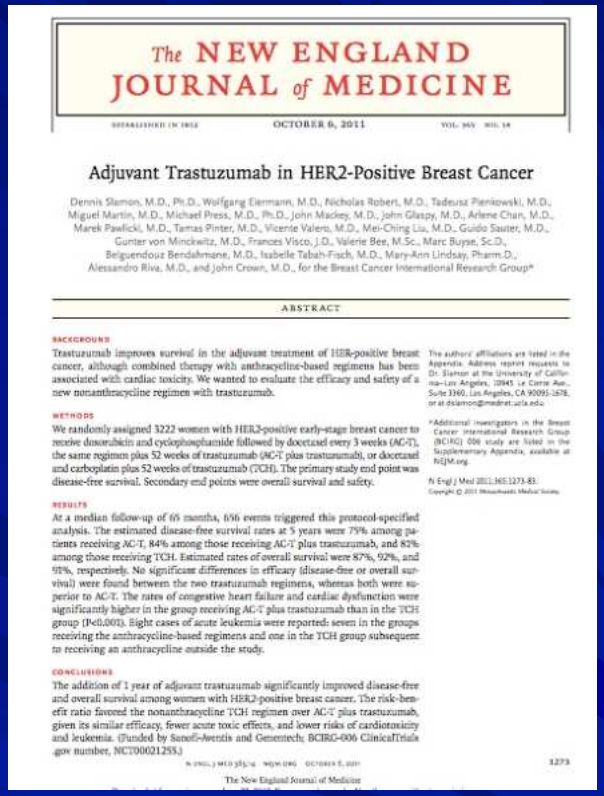
Is this higher than what would be expected in the general population?

Data adapted from Suter et al. J Clin Oncol. 2007;25:3859-65.

Comparing All 3 Strategies

- 3222 patients with HER2+ operable breast CA randomized to:
  - ACT: Adriamycin-Cytoxan (AC) + docetaxel (T)
  - ACTH: ACT + trastuzumab (H)
  - TCH: T + carboplatin + H
  - Median f/u: 65 months (!)



The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 6, 2011

Adjuvant Trastuzumab in HER2-Positive Breast Cancer

Dennis Slamon, M.D., Ph.D., Wolfgang Eiermann, M.D., Nicholas Robert, M.D., Tadeusz Pienkowski, M.D., Miguel Martin, M.D., Michael Press, M.D., Ph.D., John Mackey, M.D., John Glaspy, M.D., Arlene Chan, M.D., Marek Pawlicki, M.D., Tamas Pinter, M.D., Vicente Valero, M.D., Mei-Ching Liu, M.D., Guido Sauter, M.D., Gunter von Minckwitz, M.D., Frances Visco, J.D., Valerie Bee, M.Sc., Marc Buyse, Sc.D., Belguendouz Bendahmane, M.D., Isabelle Tabah-Fisch, M.D., Mary-Ann Lindsay, Pharm.D., Alessandro Riva, M.D., and John Crown, M.D., for the Breast Cancer International Research Group*

ABSTRACT

BACKGROUND

Trastuzumab improves survival in the adjuvant treatment of HER-positive breast cancer, although combined therapy with anthracycline-based regimens has been associated with cardiac toxicity. We wanted to evaluate the efficacy and safety of a new nonanthracycline regimen with trastuzumab.

METHODS

We randomly assigned 3222 women with HER2-positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). The primary study end point was disease-free survival. Secondary end points were overall survival and safety.

RESULTS

At a median follow-up of 65 months, 656 events triggered this protocol-specified analysis. The estimated disease-free survival rates at 5 years were 75% among patients receiving AC-T, 84% among those receiving AC-T plus trastuzumab, and 81% among those receiving TCH. Estimated rates of overall survival were 87%, 92%, and 91%, respectively. No significant differences in efficacy (disease-free or overall survival) were found between the two trastuzumab regimens, whereas both were superior to AC-T. The rates of congestive heart failure and cardiac dysfunction were significantly higher in the group receiving AC-T plus trastuzumab than in the TCH group ($P<0.001$). Eight cases of acute leukemia were reported: seven in the groups receiving the anthracycline-based regimens and one in the TCH group subsequent to receiving an anthracycline outside the study.

CONCLUSIONS

The addition of 1 year of adjuvant trastuzumab significantly improved disease-free and overall survival among women with HER2-positive breast cancer. The risk–benefit ratio favored the nonanthracycline TCH regimen over AC-T plus trastuzumab, given its similar efficacy, fewer acute toxic effects, and lower risks of cardiotoxicity and leukemia. (Funded by Sanofi-Aventis and Genentech; BCIRG-006 ClinicalTrials.gov number, NCT00021255.)

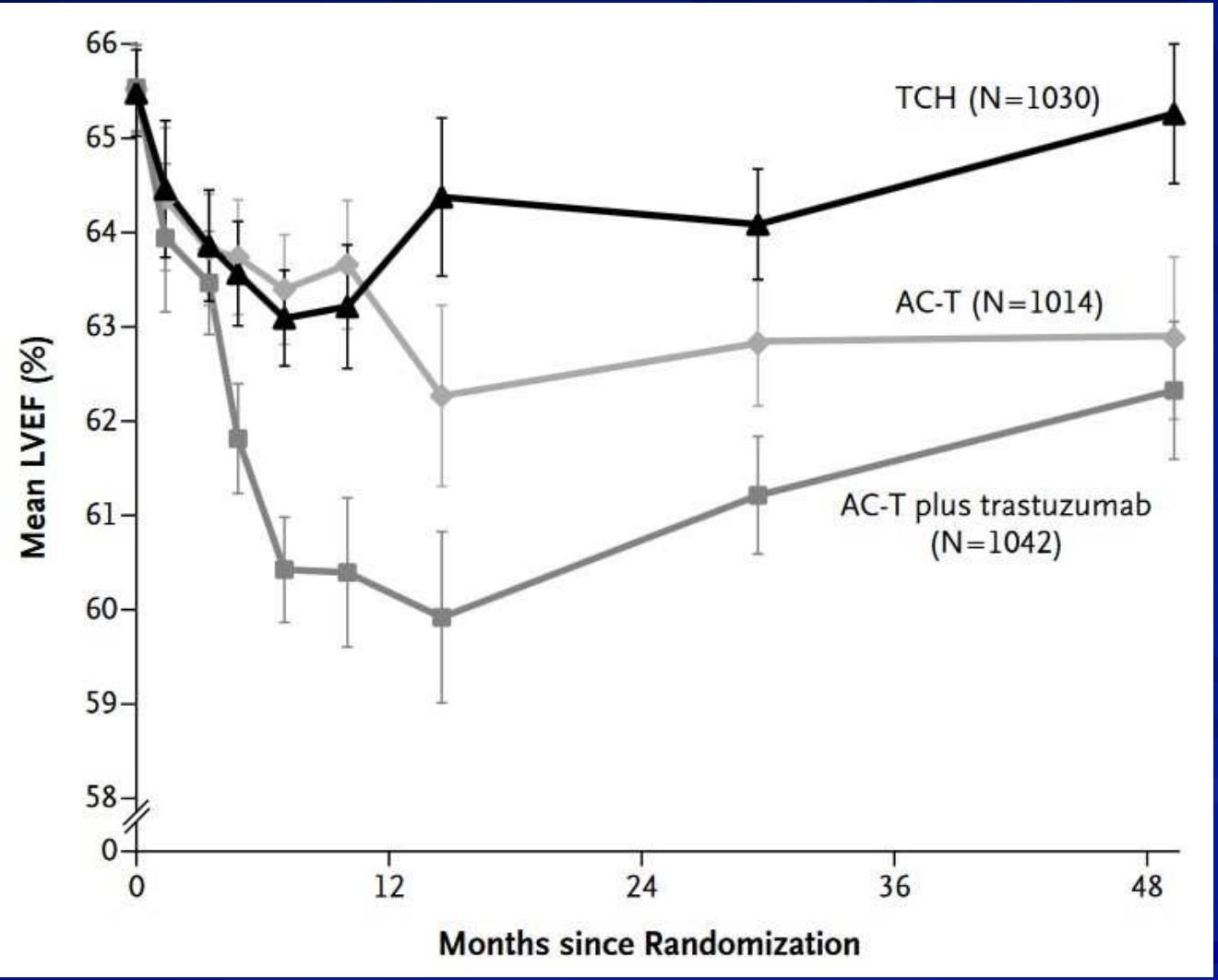
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Slamon at the University of California–Los Angeles, 10945 Le Conte Ave., Suite 3360, Los Angeles, CA 90095-1678, or at dslamon@mednet.ucla.edu.

*Additional investigators in the Breast Cancer International Research Group (BCIRG) 006 study are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2011;365:1273-83.

Data adapted from Slamon et al. N Engl J Med. 2011;365:1273-1283.

LVEF in Each Arm



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Outcomes

Table 2. Therapeutic Index for Critical Clinical Events.*

Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
		number of events	
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1†

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That's Incredibly Important Data!

- So over a >5 year period…
- Grade 3/4 CHF – TCH (trastuzumab without anthracycline):
  - 4/1030 = 0.4%!
  - That's less than 1 in 1000 people per year!
  - Is this higher than we would have seen with placebo?

Trastuzumab Label

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [*see Boxed Warning: Cardiomyopathy*]. Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- Baseline LVEF measurement immediately prior to initiation of Herceptin
- LVEF measurements every 3 months during and upon completion of Herceptin
- Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction [*see Dosage and Administration (2.2)*]
- LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.

Adapted from https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5256lbl.pdf, accessed Sep. 2, 2018.

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So How Many Echos is That?

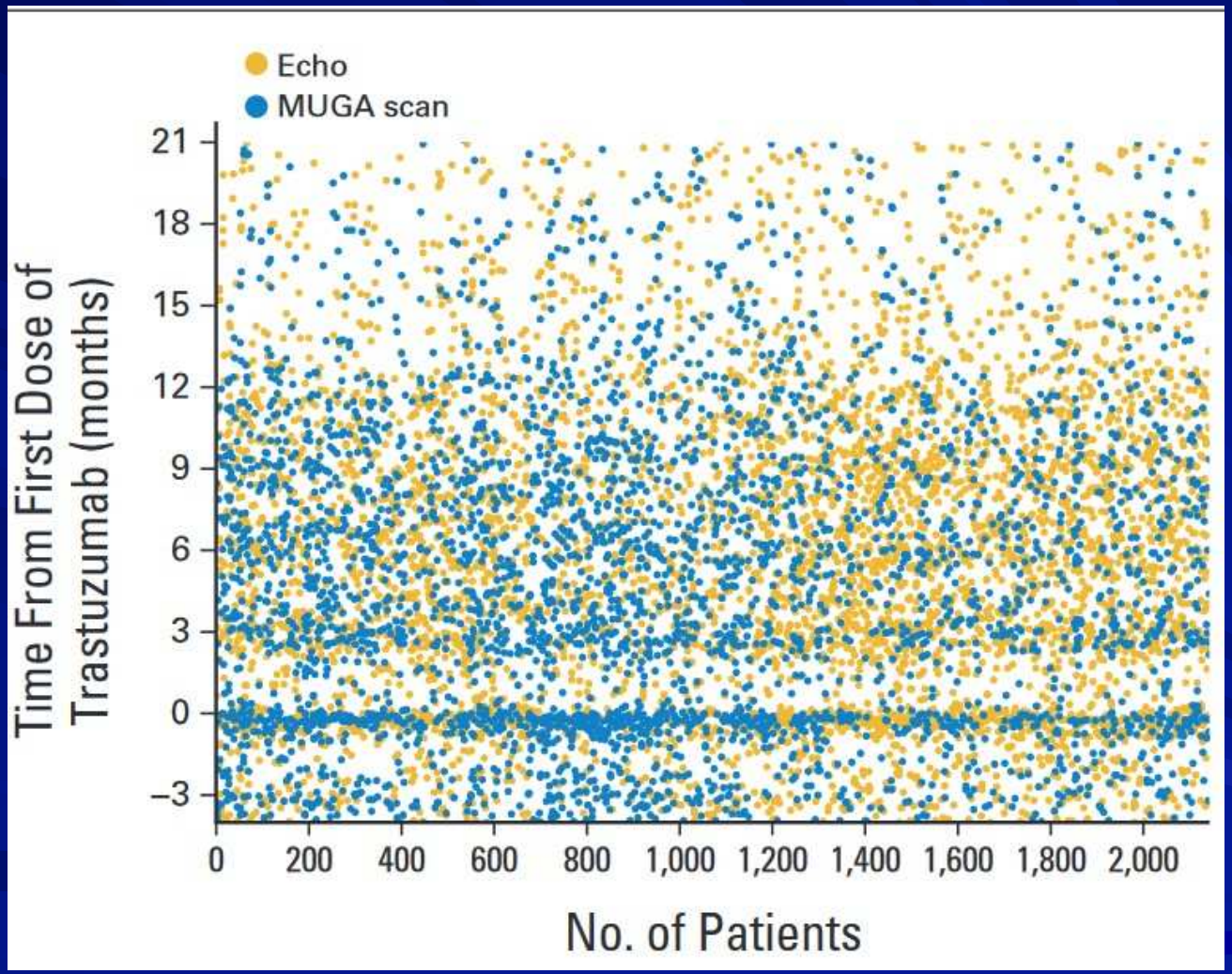
- Let's consider a typical adjuvant trastuzumab dosing schedule, and assume there is never any LVEF drop requiring more frequent echos…
  - Baseline: 1 echo
  - During therapy: 4 echos
  - After therapy: 4 echos
  - **Total: 9 echos!**

- Why the seeming overkill?

What does this lead to?

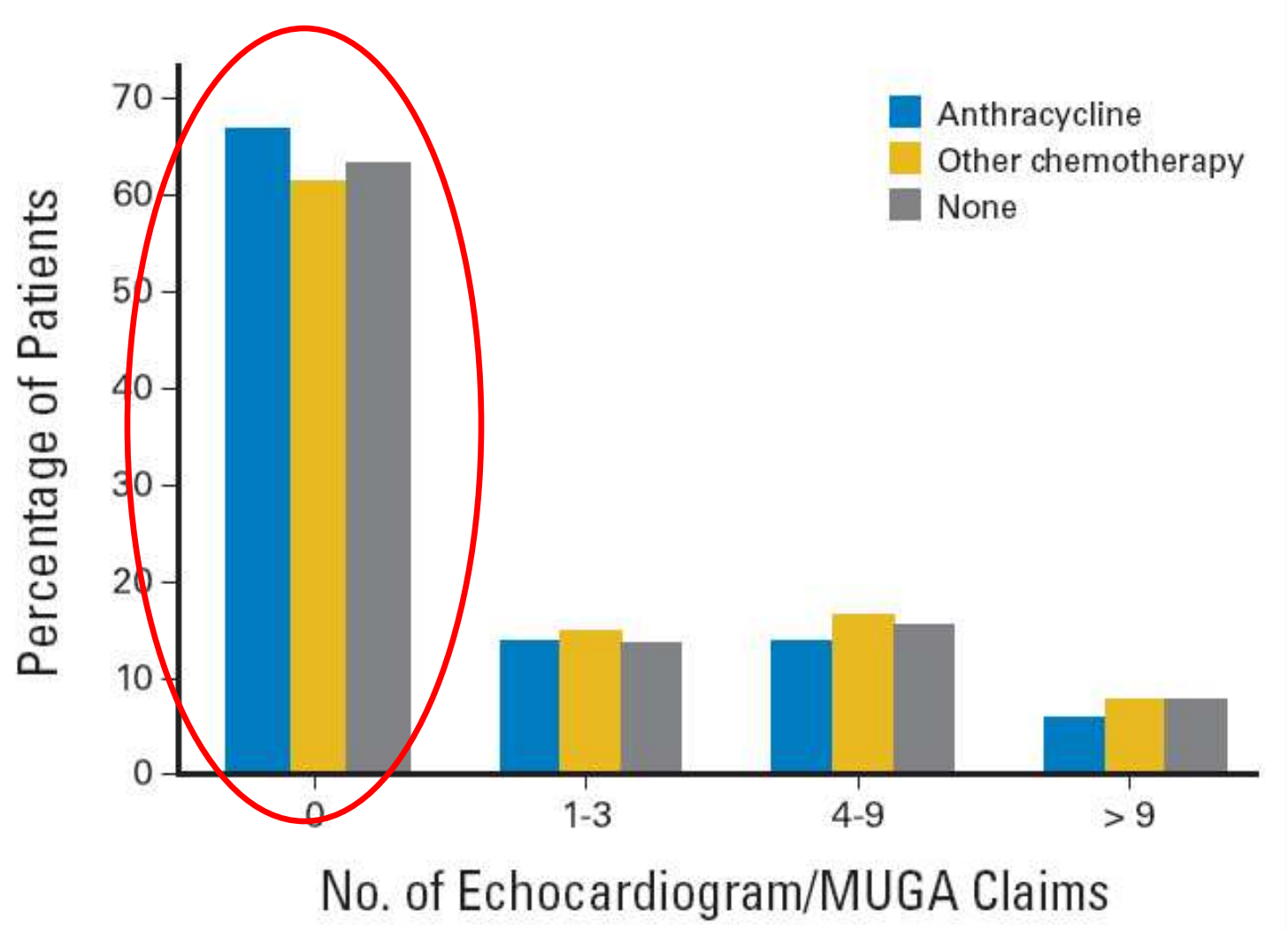
Oncologists are voting with their feet.

That Clears it Up!



Adapted from Chaves-MacGregor et al. J Clin Onc. 2015;33:2176-83.

Most Oncologists Don't Screen at All



Adapted from Pinder et al. J Clin Onc. 2007;25:3808-15.

So What Have We Learned?

- Anthracycline + concomitant trastuzumab
  - Unacceptably high cardiotoxicity
- Anthracycline + sequential trastuzumab
  - Significant cardiotoxicity, routine monitoring appropriate
- Trastuzumab w/o anthracycline
  - Very little cardiotoxicity, routine monitoring not appropriate
- But… Screening recommendations don't reflect this knowledge!

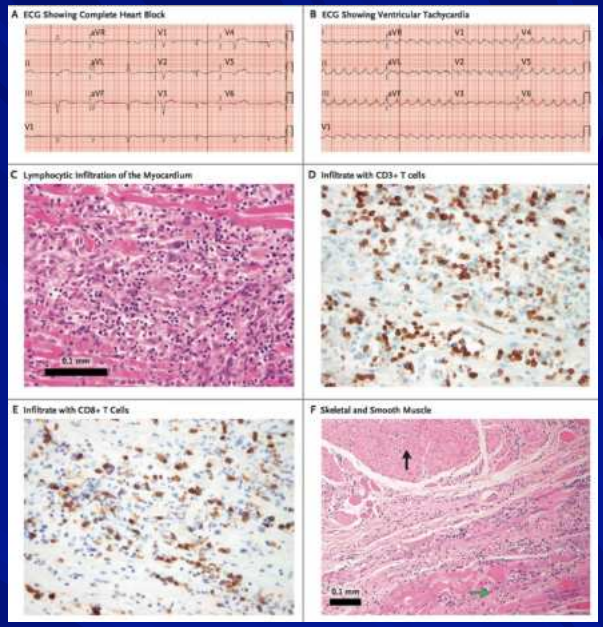
Immune Checkpoint Inhibitors

Checkpoint Inhibitors

- Major recent advance in cancer therapies
- Basic mechanism: Unleash 'checkpoints' on the immune system → attack tumors
  - Prototypes:
    - Anti-CTLA-4 antibody (e.g.ipilimumab),
    - Anti-programmed death-1 (PD-1) antibody (e.g. nivolumab, pembrolizumab) or PD-L1 antibody (e.g. atezolizumab)
  - Problem: Toxicity from unleashed immune action on normal tissues → GI, skin, endocrine, hepatic, pulmonary toxicity
- Obvious next question...
  - Could they cause myocarditis?
- Answer:
  - Yes, and it can be very bad/fatal
  - Fortunately, seems fairly uncommon…
- *In clinical trials, no routine testing for myocarditis by biochemical analysis or cardiac imaging...*

NEJM Report

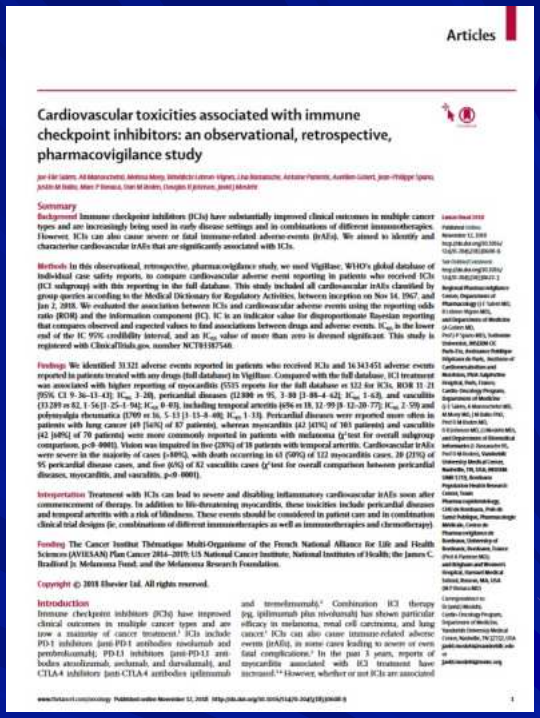
- Reported on 2 fatal cases of patients treated with nivolumab/ipilimumab who developed fulminant myocarditis clinical picture
- Postmortem autopsies
- Findings:
  - Both with T-cell & macrophage infiltrates
  - Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors
  - PDL-1 highly expressed on myocardial tissue
- Interrogated Bristol-Meyers Squibb corporate safety databases
  - 18/20594 patients (0.09%) with drug-related SAEs of myocarditis were reported
  - More common with ipi/nivo combination Rx than with nivolumab alone (0.27% vs. 0.06%)



Adapted from Johnson et al. New Engl J Med. 2016;375:1749-1755.

Follow-Up Checkpoint Inhibitor Study

- Analyzed VigiBase – WHO's global database of case safety reports
  - Compared ICI vs. non-ICI therapy
- Myocarditis reporting odds ratio: 11.21 (!)
  - OR 4.3 for combination therapy vs. monotherapy



Articles

Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study

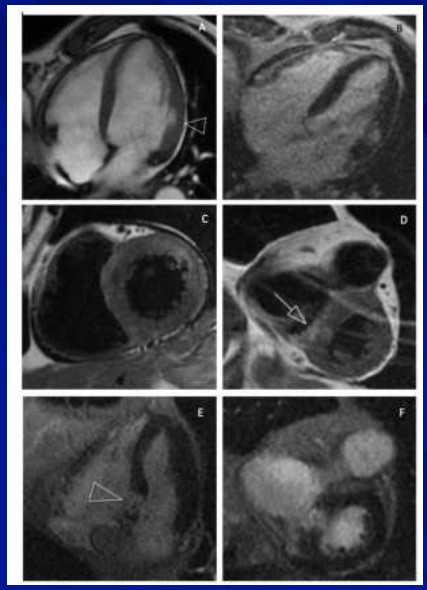
Summary

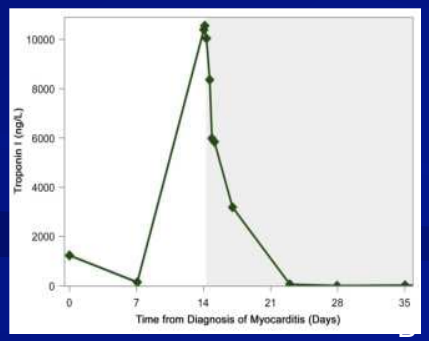
Introduction

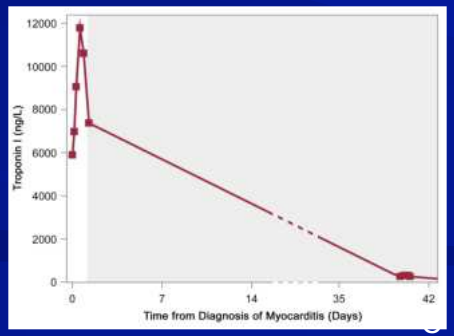
Adapted from Salem et al. Lancet Oncol. 2018.

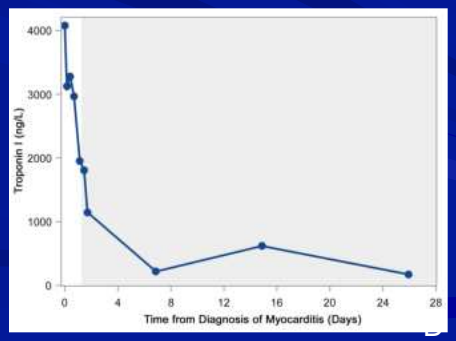
Stanford ICI Troponin Screening

- Began a regular troponin screening protocol of ICI-treated patients at Stanford in September, 2019
- Between 9/19 - 6/20, screened 214 patients
  - Troponin I tested at baseline & every 2-4 weeks after each dose of ICI up to the 10th dose
- 3 found to have ICI myocarditis
  - Peak troponin 4080-11780 ng/L (!)
  - Unlikely any of them would have been otherwise detected









Adapted from Waliany et al. JACC: CardioOncology. 2021;3:137-139.

Summary

Dizzying Array of Toxicities – Need for Cardio-Oncology Specialists!

Table 1. Incidence of Cardiotoxicity in Selected Chemotherapeutic Agents[2,4,5,9,11,13–31]

Class/Drug	Selected Indication	HF	Hypertension	Myocardial Ischemia	Thromboembolism
Anthracyclines					
Doxorubicin	Breast, lymphoma	Very common	…	…	…
Daunorubicin	Leukemia	Very common	…	…	…
Epirubicin	Breast, gastric	Very common	…	…	…
Idarubicin	Leukemia	Very common	…	…	…
Mitoxantrone	Leukemia	Common	Rare	Rare	…
Alkylating agents					
Cyclophosphamide	Hematologic	…	…	…	Very rare
Cisplatin	Bladder, lung, ovarian	…	…	…	Common
Ifosfamide	Cervical, sarcoma	Very common	…	…	Very rare
Antimicrotubule agents					
Paclitaxel	Breast, lung	Very rare	…	Rare	…
Docetaxel	Breast, lung	Rare	Rare	Rare	…
Antimetabolites					
5-Fluorouracil	Gastrointestinal	Very rare	…	Very common	…
Capecitabine	Colorectal, breast	…	…	Common	Rare
Hormone therapies					
Tamoxifen	Breast	…	Very common	Very rare	Rare
Anastrozole	Breast	…	Very common	Rare	Rare
Monoclonal antibody–based targeted therapies					
Trastuzumab	Breast, gastric	Very common	Rare	…	Very rare
Bevacizumab	Colorectal	Common	Very common	Rare	Very common
Small molecule–targeted therapies					
Imatinib	Leukemia, GIST	Rare	…	Rare	Very rare
Dasatinib	Leukemia, GIST	Rare	Rare	Rare	Rare
Sorafenib	RCC, HCC	Common	Very common	Rare	Rare
Sunitinib	GIST, RCC	Very common	Very common	Rare	Very common
Lapatinib	Breast	Rare	…	…	…
Nilotinib	Leukemia	Rare	Rare	Very common	Very common
Ponatinib	Leukemia	Rare	Rare	Very common	Very common
Bortezomib	Multiple myeloma	Rare	Very rare	Very rare	Very rare
Other					
Everolimus	RCC	Common	Very common	…	Very rare
Temsirolimus	RCC	Common	Very common	very common	Rare
Thalidomide	Multiple myeloma	Rare	Rare	Common	Very common
Lenalidomide	Multiple myeloma	Rare	Rare	Common	Very common

GIST indicates gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HF, heart failure; RCC, renal cell carcinoma; …, not well-established complication or unknown; very rare, <1%; rare, 1% to 5%; common, 6% to 10%; and very common, >10%.

Adapted from Witteles et al. Circulation. 2015;132:1835-1845.

Conclusions – My Takes

- Anthracyclines:
  - ‘Classic’ cardiotoxicity – still a major problem!
  - Generally underscreening occurs
- Trastuzumab:
  - Cardiotoxicity very dependent on +/- anthracyline exposure
  - A mix of underscreening/overscreening occurs
- ICI cardiotoxicity
  - Fairly uncommon – but can be deadly
  - Role for prospective screening?
- The field is complex – need for CardioOncology specialists!

Thank you!

@Ron_Witteles