FDA Perspective: How Does Cardiotoxicity Impact Drug Approval?

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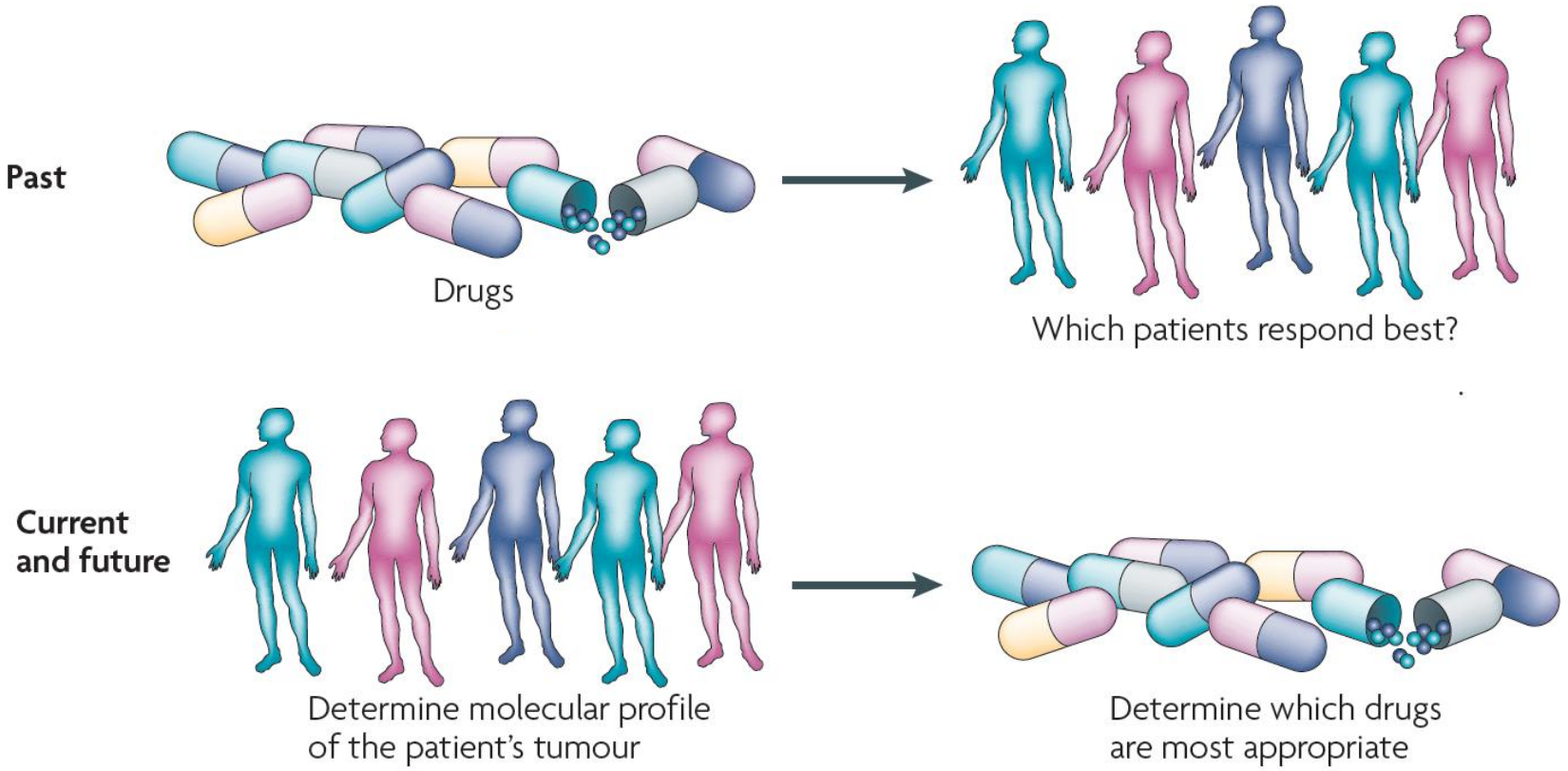
Outline

- Background: Cancer Therapy Evolution
- Cardiovascular Adverse Events
- Benefit:Risk Considerations
- What do we do today
- What is missing or needs improvement

Cancer Therapy Evolution



Yap, Nat Rev Cancer, 2010

Cardiovascular Adverse Effects

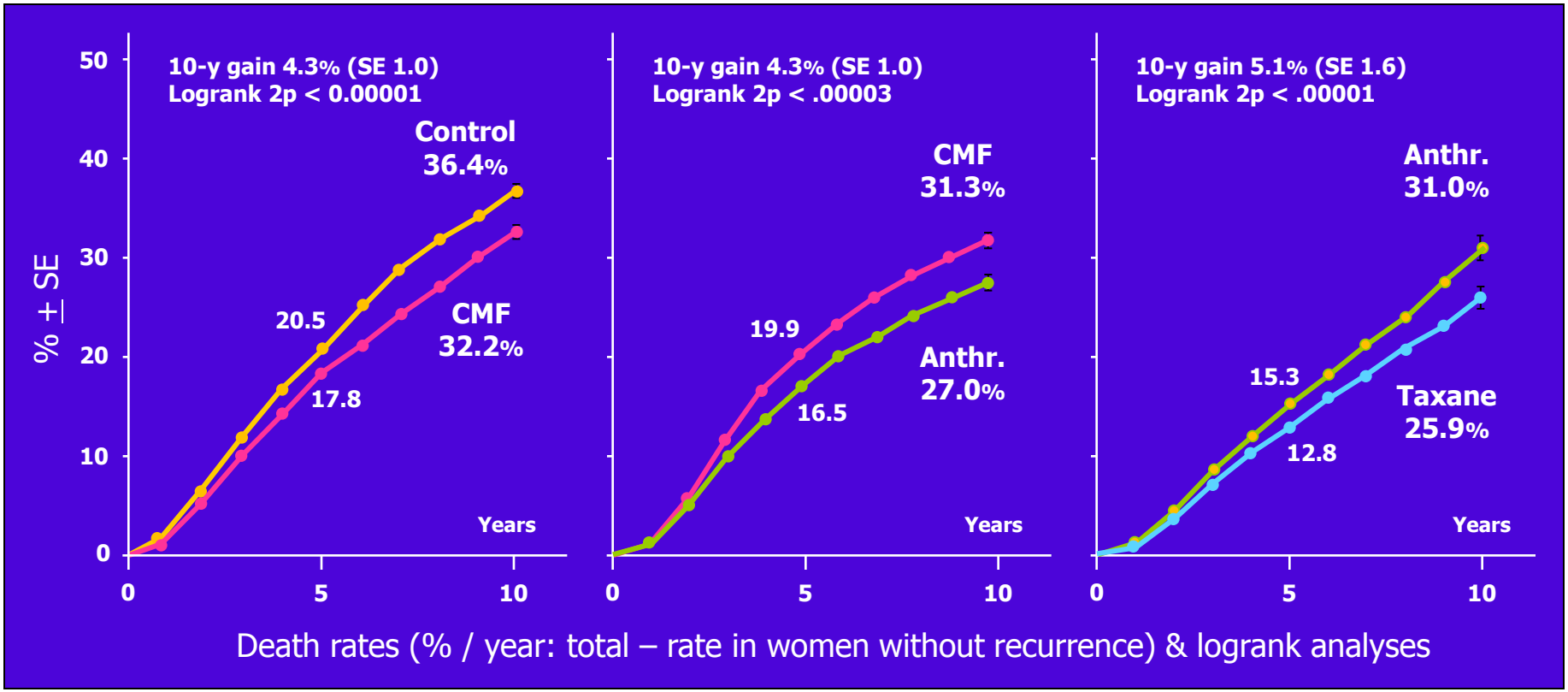
	Cardio-myopathy	Ischemia	↑ Arrhythmias QT prolongation	↑ BP	Pericardial Disease	PE DVT ATE
Anthracyclines	X					
Anti HER 2	X					
TKIs	X	X	X	X		
VEGF Inhibitors		X	X	X		
Radiotherapy					X	
Tamoxifen						X

Consider Benefit of Cancer Treatment and Risk of Cardiotoxicity

- During drug development
- When evaluating the drug for regulatory approval
- When the clinician considers treating the patient

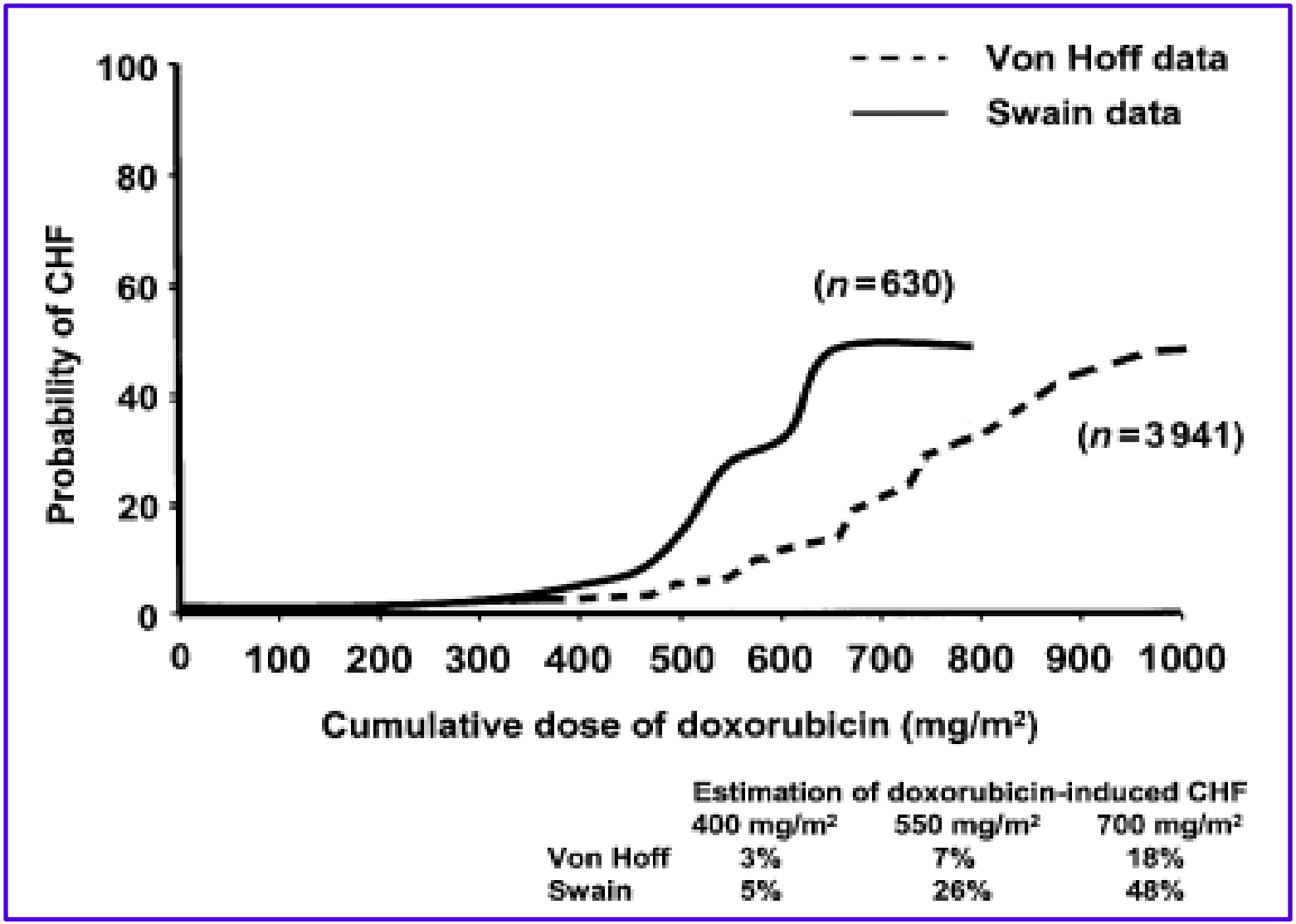
Early Breast Cancer Trialists' Collaborative Group (EBCTCG) updated (2005-6) meta-analyses

Breast Cancer Mortality



Peto et al, SABCS 2007

Anthracycline Cumulative Dose and CHF Risk



Estimation of doxorubicin-induced CHF			
	400 mg/m²	550 mg/m²	700 mg/m²
Von Hoff	3%	7%	18%
Swain	5%	26%	48%

Wouters et al, 2005.

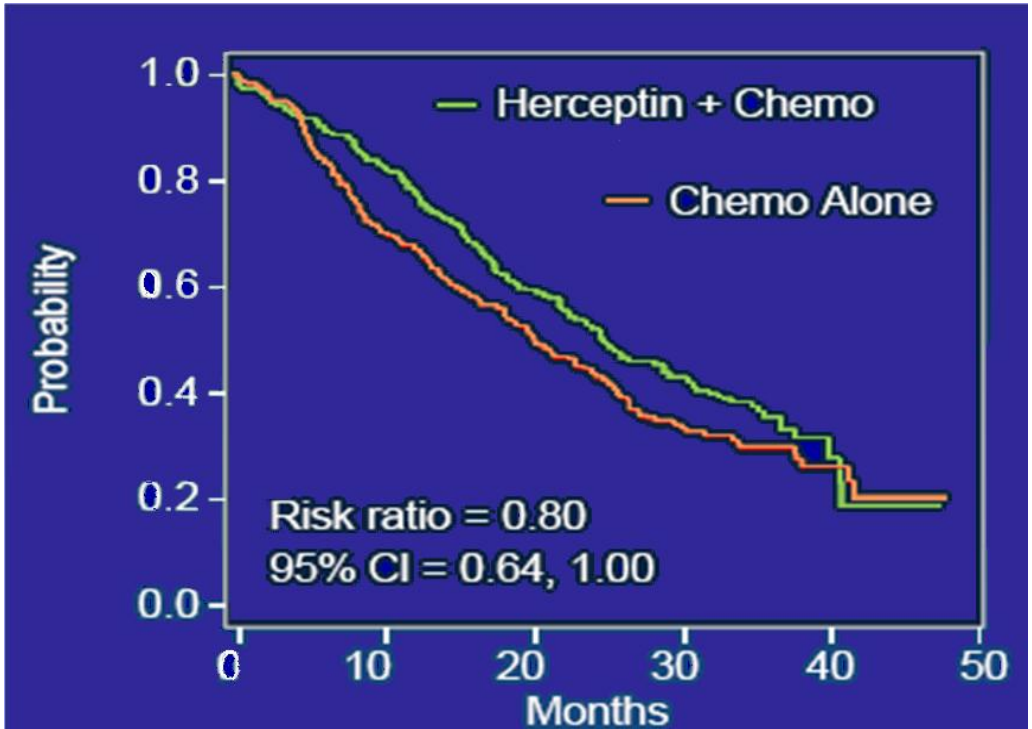
Trastuzumab Survival: Metastatic Breast Cancer

469

Chemotherapy (AC or Paclitaxel)

Herceptin

Chemotherapy Alone



Incidence of Cardiac Dysfunction in Trastuzumab MBC studies

Arm	NYHA I-IV		NYHA III-IV	
	Trastuzumab	Control	Trastuzumab	Control
AC	28%	7%	19%	3%
Paclitaxel	11%	1%	4%	1%
Mono therapy	7%	N/A	5%	N/A

Trastuzumab Adjuvant Trials

Studies	DFS		CHF Incidence
	HR	*p* Value	
NSABP B31/NCCTG 9831 AC → TH vs AC → T	0.48	< 0.0001	2%
HERA Chemo → H vs obs	0.54	< 0.0001	2%
BCIRG 006 TCH vs AC → T AC → TH vs AC → T	0.67 0.60	< 0.0006 < 0.0001	0.4% 2%

Where are we now?

- Breast cancer mortality is decreasing
- Therapy based on molecular subtypes
- Identifying patients who don't need anthracyclines
- Combination therapies increase risk of cardiotoxicity
- Need to decrease cardiotoxicity

When to do Cardiovascular Monitoring During Drug Development

1. Drug Class
   - If drugs with similar targets have known cardiovascular toxicity
   - If there is tissue cross-reactivity (biologics)
   - If MOA/pathway/knockouts suggest cardiovascular toxicity
2. Pre-Clinical Studies
   - ECG changes in non-rodents
   - Histopathology (myocardial necrosis, significant inflammation)
3. Clinical
   - Cardiotoxicity in another clinical study
   - Combination therapy with overlapping cardiotoxicity
   - Patient population at increased risk e.g. prior anthracycline therapy, prior chest radiotherapy, ischemia

Recommendations for Phase 1 and 2 Studies

- Specific eligibility criteria: exclude patients at risk
- Conservative dose-escalations due to cardiac concerns
- Baseline and follow-up monitoring including ECG, LVEF (Echo or MUGA), frequent BP and QTc assessments
- Criteria for dose modifications, delays and drug discontinuations
- Criteria for rechallenge
- QT prolongation studies

Recommendations for Phase 3 Studies

- Definition of cardiac events
- Stopping rules for excess cardiac toxicity
- Use same cardiac imaging modality throughout the study
- Central reading recommended to avoid reader variability
- Endpoints: cardiac safety may be needed as a co- primary endpoint
- Long term follow-up

What is Missing or Does Not Work Well Today

- Better understanding of cardiotoxicity and repair at clinical and molecular level
- Identify patients at risk of cardiotoxicity
- Decrease cardiotoxicity risk:
  - early serum cardiac biomarkers
  - chemoprotection
- Early detection of cardiotoxicity
- Need good evidence addressing optimal monitoring intervals