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Redefining Cardiac Eligibility Thresholds in Oncology Trials. Role of Cardiovascular Core Labs

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Cardiac Safety Research Consortium Think Tank, Oct 2017

Disclosures

- No financial disclosures
- Cardiology PI for SAFE-HEaRt, investigator-initiated study funded by Genentech, Inc.

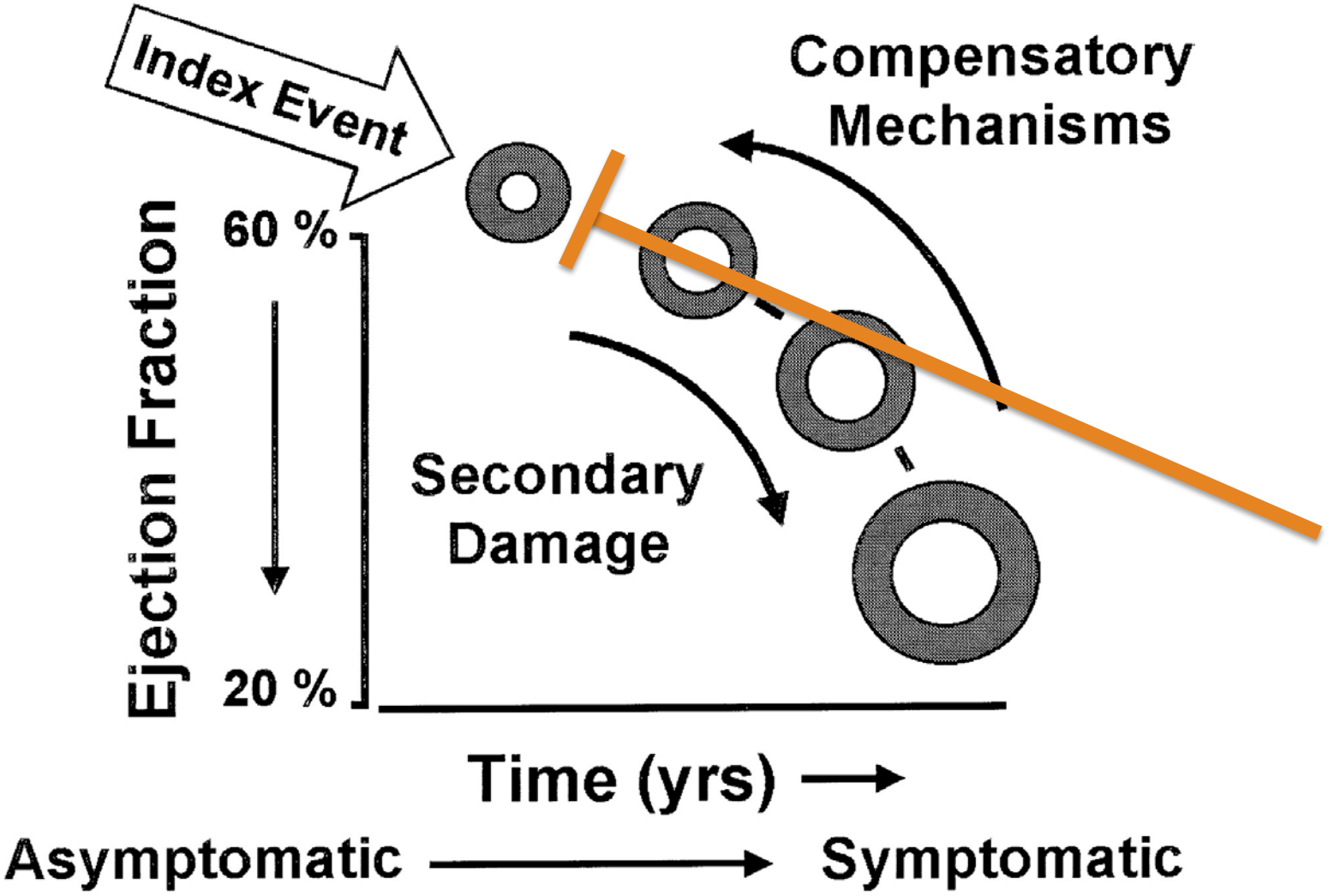
Objectives

- **Definition of CV Endpoints**
  - CV Safety Signal - CV Outcome
- **Eligibility and Stopping Thresholds**
  - "Direct" (Clinically meaningful) vs Surrogate Endpoints
- **Cardiovascular Core Lab Role**
- **Putting it All Together: Pragmatic CV safety trial**

Definition of CV Endpoints

- **CV Safety Signal ~ CV Outcome of Interest**
  - **Cardiomyopathy/Heart failure**
  - Heterogeneous (ischemic, non-ischemic)
- **CV Endpoints**
  - **Direct:** CV Death and Heart Failure Hospitalization
  - **Surrogate – Validated Surrogate Endpoints**
    - **LVEF/RVEF**, LVEDV, LVESV, RVEDV, RVESV, LV mass
    - **GLS**, diastolic function, aorto-ventricular coupling
    - **Serum Biomarkers**

Pathophysiology Model



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Eligibility and Stopping Thresholds

- **Eligibility**
  - No clinical heart failure, no existing cardiomyopathy
- **Cancer Therapeutic Stopping Thresholds**
  - **Clinical HF**
  - **Symptomatic arrhythmia/ischemia**
  - Adjudication critical!
  - **NO Stopping for changes in routine surrogate markers***: LVEF, LVEDVI, GLS, serum biomarkers

Role of the CV Imaging Core Lab

- **Protocol development**
- **Definition of CV Imaging Endpoints**
  - Choice of technique (Echo, cardiac MR)
- **Standardized acquisition**
  - Protocol-based site instruction and training
- **Independent, centralized and standardized analysis**
  - Quality Control
- **Data review and interpretation**

A pilot study evaluating the cardiac SAFEty of HER2 targeted therapy in patients with HER2 positive breast cancer and reduced left ventricular function

- Investigator-initiated, supported by Genentech, Inc.
- Chair (PI): Sandra Swain
- Cardiology Co-Chair: Ana Barac
- MGUH/LCCC PI: Filipa Lynce
- MSKCCC PI: Chau Dang (Cardiology: Anthony Yu)
- IND for trastuzumab, pertuzumab and TDM-1

ClinicalTrials.gov Identifier: NCT01904903

Rationale

- Trastuzumab improves survival in early and metastatic breast cancer, limited by cardiac dysfunction
  - 19% NYHA III/IV HF in metastatic BC trial
- **0-4% symptomatic HF and cardiac death** in the adjuvant trastuzumab trials; **14-18% temporarily discontinued** trastuzumab due to asymptomatic decline in LVEF
- FDA label
- **Hypothesis:** Trastuzumab may be safe in patients with reduced LVEF if on optimized cardiac therapy

ClinicalTrials.gov Identifier: NCT01904903

Eligibility criteria

- HER2+ breast cancer stage I-IV
- LVEF $\geq 40\%$ and $< 50\%$
- Treatment with trastuzumab, trastuzumab + pertuzumab or T-DM1
- No HF in last 12 months nor current HF
- No concomitant use of anthracyclines in the last 50 days

ClinicalTrials.gov Identifier: NCT01904903

Study phases

Informed consent

Study enrollment

- **Research echo**
- **Tn-I, pregnancy**
- **EKG**
- **stress test**

- **6 min walk**
- **hsTnT, NT-proBNP, research bloodwork**

Patient meets eligibility criteria

Screening/ preenrollment procedures

Treatment phase

Screen failures

- **BB (carvedilol)**
- **ACEi/ARB titrated to max tolerated dose**
- **Start HER2 therapy**

10 days

maximum 12 months

ClinicalTrials.gov Identifier: NCT01904903

Cardiac monitoring

LVEF* (**Core lab read**) q6 weeks x 3 evaluations and then q3 months

Asymptomatic

LVEF ≤35% or drop ≥10% of baseline

No

Continue HER2 therapy

Yes

Repeat echo. If confirmed, off study

Symptoms suggestive of HF

Cardiology evaluation. If confirmed HF (CRP), off study

Secondary endpoints:

- **Δ GLS, LVEDVI, LVESVI**
- **Δ Serum biomarkers**
- **Delays in treatment**

Core lab reporting

Appendix I. : Core Lab Case Report Form

Safe Heart

Echo Core Lab Case Report Form

Patient ID _____ Interval: _____

Procedure Date: _ _ _____ If Other _____

dd-mmm-yyyy

Baseline EF ___ %

2D LV and LA Measurements

- ☐ NE LVIDd ___ cm
- ☐ NE LVIDs ___ cm
- ☐ NE IVSd ___ cm
- ☐ NE LVPWd ___ cm
- ☐ NE LA Volume ___ ml

LV Ejection Fraction

2D Measurements

- ☐ NE LVEDV ___ ml
- ☐ NE LVESV ___ ml
- ☐ NE LVEF ___ %

3D Measurements

- ☐ NE LVEDV 3D ___ ml
- ☐ NE LVESV 3D ___ ml
- ☐ NE LVEF 3D ___ %

☐ NE Visual EF ___ %

Diastolic Function Assessment

- ☐ NE MV E Wave ___ cm/sec
- ☐ NE MV A Wave ___ cm/sec
- ☐ NE MV E/A ___
- ☐ NE Septal E' ___ cm/sec
- ☐ NE Septal E/E' ___
- ☐ NE Diastolic Function _____

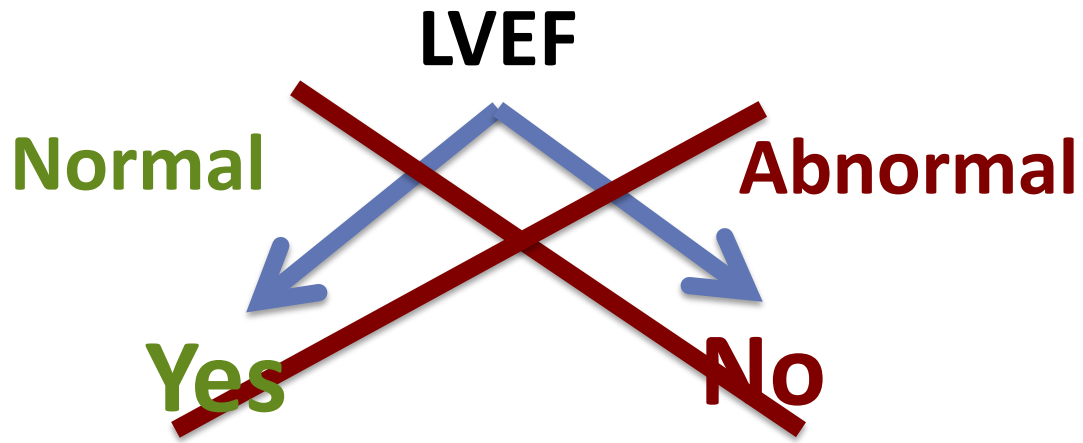
Longitudinal Strain (Q Lab)

- ☐ NE AP4 ___ %
- ☐ NE AP2 ___ %
- ☐ NE AP3 ___ %
- ☐ NE Global ___ %

Clinical decision making

1. **LVEF 3D**
2. **LVEF 2D**
3. **LVEF visual estimate**

Redefining Cardiac Eligibility ~~Thresholds~~



Cancer Treatment Therapeutic

Clinical Trial CV Endpoints

- Clinical
- Comprehensive and validated surrogate outcomes
- Standardized collection and analysis

Improved CV Safety and Overall Outcomes

Thank you

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