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

Ana Barac, MD, PhD, FACC
Associate Professor of Medicine, Georgetown University
MedStar Heart and Vascular Institute, Washington DC
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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
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 ≥ 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
Patient meets eligibility criteria

Informed consent

Screening/ preenrollment procedures

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

Screen failures

Study enrollment

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

Treatment phase

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

10 days

maximum 12 months

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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

## Clinical decision making

1. LVEF 3D
2. LVEF 2D
3. LVEF visual estimate
Redefining Cardiac Eligibility Thresholds

LVEF

Normal

Abnormal

Yes

No

Clinical Trial CV Endpoints

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

Improved CV Safety and Overall Outcomes

Cancer Treatment Therapeutic
Thank you

Ana.Barac@medstar.net