Designing and Implementing Cardio-oncology Safety Registries

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Director, Clinical Research
I will not discuss off label use or investigational use in my presentation.

I have financial relationships to disclose:

- Research support from: Acorda, Inc; Takeda, Inc.
- Consultant (modest): Roche, Amgen, Prothena, BMS
Important research questions

- Identify the clinical factors related to recovery of ventricular function
- Understand the impact on cancer outcomes of discontinuation of chemotherapy resulting from cardiotoxicity.
- Clarify the cardiac risk factors and cancer related characteristics that accompany cardiac dysfunction in patients receiving cancer therapy.
PREDICT Study Overview:
A multicenter study in patients undergoing anthracycline-based chemotherapy to assess the effectiveness of using biomarkers to detect and identify cardiotoxicity and describe treatment.

The Predict Study Team
(Lenihan, Ky, Warneke, Lagrone, Feng, Fisch)
PREDICT Study flow diagram

597 Enrolled

- Excluded after enrollment (n = 10)
  - Followed 0 to 0.46 mos.
    - 4 Ineligible
    - 4 Withdrew consent
    - 2 Insurance reasons

- No completion visit (n = 76)
  - Event (n = 9)
    - Followed 0.82 – 8.57 mos.
      - 5 Death
      - 3 Withdrew consent
      - 1 Lost to follow-up
  - No Event (n = 67)
    - Followed 0.10 to ≥ 13 mos.
      - 30 Death
      - 23 Withdrew consent
      - 8 Lost to follow-up
      - 6 Relocation

- Completion visit (n = 511)
  - Event (n = 48)
    - Followed 0.0 – 12.91 mos.
      - 24 followed < 11 mos.
  - No Event (n = 463)
    - Followed 9.86 to ≥13 mos.
## PREDICT: Clinical Predictors of Cardiotoxicity

<table>
<thead>
<tr>
<th>Label</th>
<th>Value</th>
<th>Event</th>
<th>Total</th>
<th>Cases</th>
<th>Odds ratio</th>
<th>ChiSq</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>(%)</td>
<td>OR 95% CL</td>
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<td>BNP at start of anthracyline (per unit increase)</td>
<td>(10.95)</td>
<td>1.011</td>
<td>1.003</td>
<td>1.018</td>
<td>8.1869</td>
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<td>Baseline BNP</td>
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<td>64</td>
<td>77</td>
<td>(16.88)</td>
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<td>BNP &lt; 50</td>
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<td>367</td>
<td>407</td>
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<td>20</td>
<td>(35.00)</td>
<td>4.893</td>
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<td>BNP &lt; 100</td>
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<td>418</td>
<td>464</td>
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<td>Age at registration (years) (per unit increase)</td>
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<td>1.048</td>
<td>1.023</td>
<td>1.074</td>
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<td>116</td>
<td>(17.24)</td>
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<td>Breast</td>
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<td>325</td>
<td>354</td>
<td>(8.19)</td>
<td>1.000</td>
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<td>No</td>
<td>46</td>
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### Univariate predictors of cardiotoxicity

- BMI > 30
- Current or former smoker
- Hypertension
- Family history of heart disease
- Elevated blood pressure
- Age > 65 years
- Diabetes
- BNP at start of anthracyline (per unit increase)
- Baseline BNP
  - BNP 50 or more
  - BNP < 50
- Baseline BNP
  - BNP 100 or more
  - BNP < 100
- Age at registration (years) (per unit increase)
- Sex
  - Male
  - Female
- Race /ethnicity 2 category
  - NonWhite or Hispanic
  - White, nonHispanic
- Smoking status
  - Current smoker
  - Previous smoker
  - Nonsmoker
- Cancer diagnosis
  - Lymphoma
  - Other
  - Breast
- Number of cardiac risk factors (of 17, including age) (per unit increase)
- Chemotherapy prior to baseline
  - Yes
  - No
Are there things on the cancer therapy horizon that could be concerning for heart failure or serious cardiac events?
Cardiovascular SAEs in RCTs
Phase 3 Carfilzomib Trials

• ASPIRE Trial

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<tr>
<th>Event</th>
<th>Carfilzomib Group (N=392)</th>
<th>Control Group (N=389)</th>
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<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
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<tr>
<td>Dyspnea</td>
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<td>11 (2.8)</td>
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<td>Hypertension</td>
<td>56 (14.3)</td>
<td>17 (4.3)</td>
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<tr>
<td>Acute renal failure†</td>
<td>33 (8.4)</td>
<td>13 (3.3)</td>
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<tr>
<td>Cardiac failure‡</td>
<td>25 (6.4)</td>
<td>15 (3.8)</td>
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<tr>
<td>Ischemic heart disease§</td>
<td>23 (5.9)</td>
<td>13 (3.3)</td>
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</table>

Total Cardiac AEs 26.6% 11.4% 15.6% 5.7%
Total Cardiac AEs + Dyspnoea 46% 14.2% 30.5% 7.5%
DVT/PE 10.2% 6.2%
Understanding Cardiac Issues in Multiple Myeloma patients: An ongoing Prospective Observation of Cardiac Safety with Proteasome Inhibition (PROTECT) study

- This is a prospective, non-randomized, non-interventional, multi-institutional study.
- 130 patients will be enrolled, who will be initiated with either (1) Bortezomib-based (BOR) or (2) Carfilzomib-based (CAR) therapy based on hematologist’s decision.

Sites:
- Vanderbilt University Medical Center
- University of Pennsylvania
- *Dana Farber at Harvard
- *University of Alabama
- *pending

Patient with relapsed or refractory multiple myeloma screened for eligibility

Enrolled and initially treated with Bortezomib-based chemotherapy (N=65)
- 6 cycles of chemotherapy
- Ongoing monitoring for outcomes

Enrolled and initially treated with Carfilzomib-based chemotherapy (N=65)
- 6 cycles of chemotherapy
- Ongoing monitoring for outcomes
## Schedule of Cardiac Safety Monitoring

<table>
<thead>
<tr>
<th>Study Visits / Procedures</th>
<th>Baseline Assessments</th>
<th>Cycle 1 Visit‡</th>
<th>Cycle 2 Visit‡</th>
<th>Cycle 3 Visit‡</th>
<th>Cycle 4 Visit‡</th>
<th>Cycle 5 Visit‡</th>
<th>Cycle 6 Visit‡</th>
<th>6Mo./12 Mo./EOSj</th>
<th>18 Mo./Phone F/U</th>
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<td>Physical Exam and Vitals</td>
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<td>6 Minute Hall Walk</td>
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<td>Xf</td>
<td>Xc</td>
<td>X</td>
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<td>X</td>
<td>Oc</td>
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<td>Xh</td>
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<td>Xc</td>
<td>X</td>
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<td>X</td>
<td>Oc</td>
<td>X</td>
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<td>Xh</td>
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<td>Xc</td>
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<td>X</td>
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<td>X</td>
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<td>Overall Survival Status</td>
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<td>X</td>
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</tbody>
</table>

X required testing; O optional testing; ‡Denotes chemotherapy cycle;
### Suspected Cardiac Events (VUMC only)

<table>
<thead>
<tr>
<th>Suspected Cardiac Event</th>
<th># of events</th>
<th># of individuals</th>
<th>BOR-treated patients</th>
<th>CAR-treated patients</th>
<th>CTCAE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome (ACS) which includes MI</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>grade 2 (n=3) grade 3 (n=3)</td>
</tr>
<tr>
<td>Arterial and/or venous thromboembolism</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>grade 1 (n=1) grade 2 (n=1)</td>
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<tr>
<td>Dyspnea</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>grade 1 (n=1) grade 2 (n=1)</td>
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<tr>
<td>Hypertension</td>
<td>11</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>grade 3 (n=9) grade 4 (n=2)</td>
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<td>Symptomatic arrhythmia requiring treatment</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>grade 5 (n=1) grade (n=)</td>
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<td>Symptomatic heart failure</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>grade 2 (n=1) grade 3 (n=6)</td>
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<td>Other (syncope)</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>grade 2 (n=0) grade 3 (n=1)</td>
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<td><strong>Total # of suspected cardiac events</strong></td>
<td>30</td>
<td>23</td>
<td>2</td>
<td>21</td>
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</table>

9 patients on the study were lost to follow up as a result of:
- Chose to be treated locally (n=3)
- Deceased due to disease progression (n=5)
- Stopped chemotherapy due to a Cardiac Event (n=1, CAR)
Time to Event from initiation of PI therapy

- ACS
- Hypertension
- Heart failure
- AVT
- Dyspnea
- Other

Time to event in days

- Arrhythmia
Cardiotoxicity: Recovery Registry (CTR)

The purpose of the Cardiotoxicity: Recovery Registry is to clarify the mechanisms of cardiovascular toxicity, recognize the typical presentation and discern the best methods for clinical detection, describe optimal therapeutic options as well as identify potential strategies for prevention of cardiac dysfunction.

The specific aims of the cardiac safety registry are:

- Identify the cancer therapeutics and the cancer conditions in which cardiac dysfunction, potentially as a result of cancer therapy, can recover back to pre-chemotherapy levels or improve substantially with effective cardiac treatment

- Describe the clinical tools that are most useful and cost effective at enhancing recovery of cardiac dysfunction

- Detail the therapeutic strategies that are most useful and cost effective at promoting recovery of cardiac dysfunction
Cardiotoxicity: Recovery Registry (CTR)
Candidate patients to enroll

- All patients treated for cancer who have **cardiac dysfunction** during or after cancer therapy
- **Cardiac dysfunction**: Any evidence of heart failure (defined by symptoms, physical exam abnormalities, LVEF/imaging changes and/or cardiac biomarker evidence)
<table>
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<th>Baseline visit</th>
<th>6 month visit</th>
<th>1 year follow up</th>
<th>2 year follow up</th>
<th>3 year follow up</th>
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**CTCAE Version 4.0**

**Suspected Cardiac Event**

- Symptomatic heart failure
- Acute coronary syndrome (ACS) which includes MI
- Sudden cardiac death
- Symptomatic arrhythmia requiring treatment
- Arterial and/or venous thromboembolism
- Dyspnea
- Hypertension
- Pulmonary Hypertension
- Other

**Date of Cardiac Event**

- [ ] Must provide value

**Date of Cardiac Event Resolution**

- [ ] Must provide value

**CTCAE name for Event**

- [ ] Must provide value

**CTCAE Grading**

- [ ] Must provide value

**Cardiac Event Confirmed By**

- Echocardiogram
- MUGA Scan
- ECG
- Cardiac Catheterization
- Physical Exam
- Cardiac Enzymes
- High Cholesterol
- Hypertension
- Heart Attack
- Angina
- Arrhythmia
- Heart Failure
- Coronary Disease
- Heart Angioplasty/Stents
- Heart Surgery
- Leaky Heart Valve
- Stenotic Heart Valve
- Syncope/Loss of Consciousness

**New or Worsening Diagnoses**

- [ ] Must provide value
Infrastructure for multicenter trials already established at VUMC

- Principal Investigator/Faculty Oversight
- REDCAP web-based relational database already created and utilized
- Multiple clinical research coordinators
  - Consents
  - Data and blood collection
  - Follow-up
  - Research Project Tracking
- Core Lab for Translational and Clinical Research
  - Biospecimen processing, storage, release, and testing
- Regulatory and Compliance
  - IRB approval/Budgets and Contracts
- Scientific Review Committee
  - Faculty, Staff, Researchers
- Steering Committee
  - Administrative Oversight/Quarterly Online Meeting/Stats
- Synthetic Derivative/Biovie
  - EMR de-identified database of Clinical/DNA
Ongoing or Completed Cardio-Oncology Multicenter Research Projects

• PREDICT (anthracycline therapy)
• PROTECT (proteasome inhibitor therapy)
• CREST (anti-VEGF based therapy)
• VITAL Amyloidosis (NEOD001-anti AL amyloid ab)
• PACE (Breast Cancer observation of cardiac outcomes)
• Biomarker Pilot (cardiac biomarker feasibility)
• HGF levels (novel biomarkers) in Cardiac Amyloidosis
Cardiotoxicity: Recovery Registry (CTR)
Initial Cardio-Oncology Centers

- Vanderbilt University Medical Center
- University of Pennsylvania
- Ottawa Hospital Cancer Center, Ottawa, CA
- University of British Columbia, Vancouver, CA
- Brigham and Women’s/Dana Farber
- University Health Network, Toronto, CA