Designing and Implementing Cardio-oncology Safety Registries

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Presenter Disclosure Information

FDA CV toxicity in Oncology Workshop 9.22.16

- 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

NCI Community Oncology Cardiotoxicity Task Force 2013
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

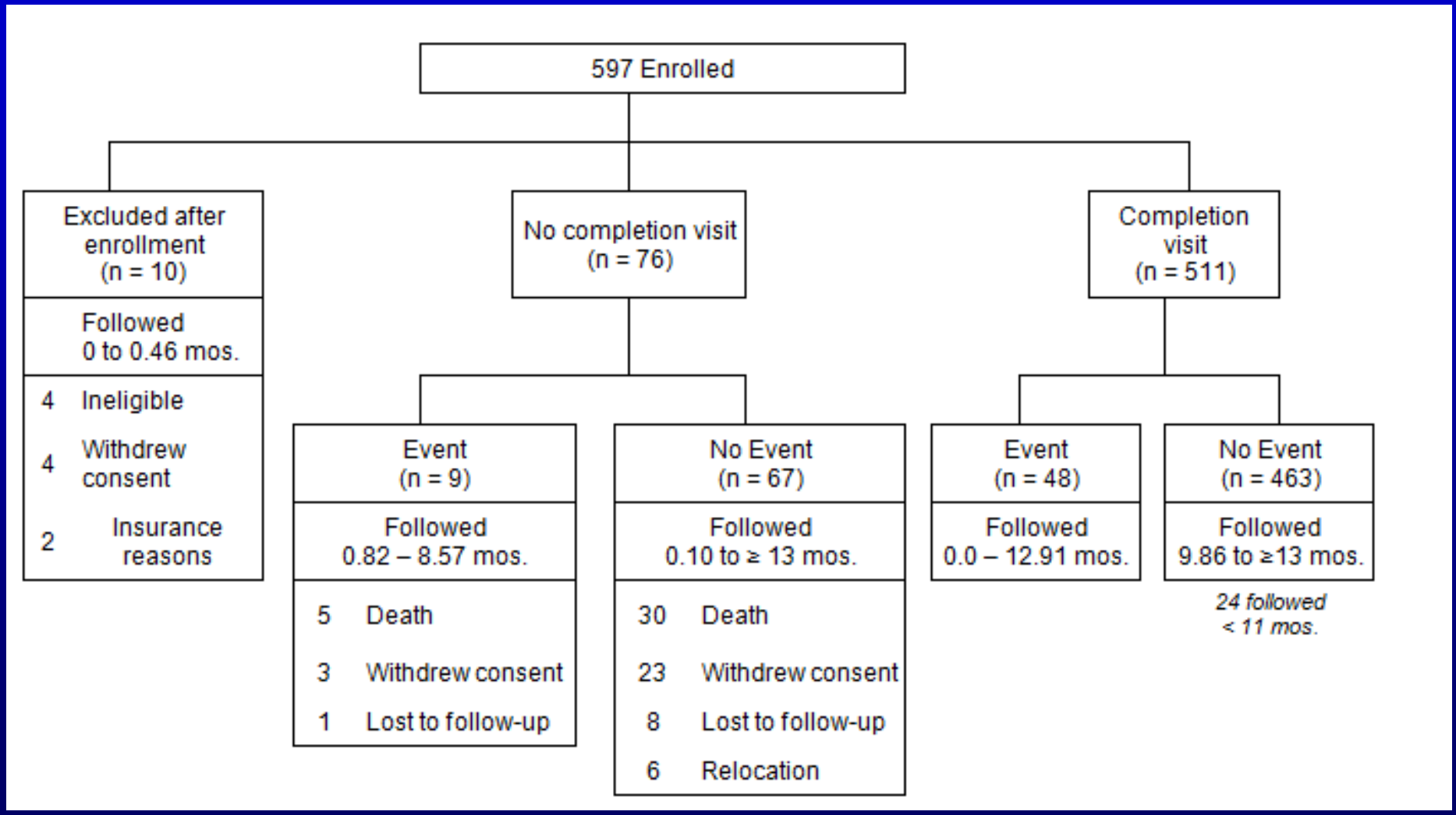
PREDICT Study Overview:

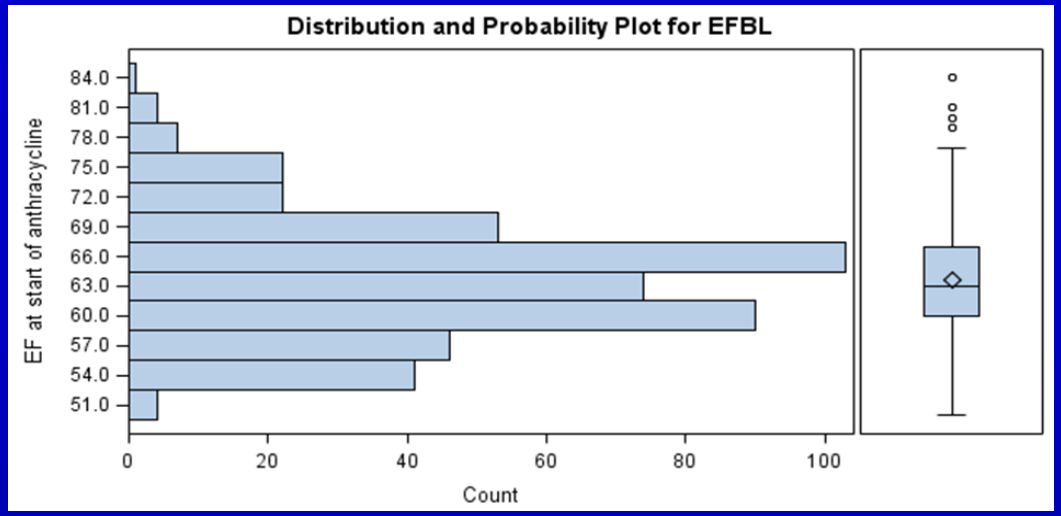
A multicenter study in **P**atients undergoing anth**R**acycline-based chemotherapy to assess the **E**ffectiveness of using biomarkers to **D**etect and **I**dentify **C**ardiotoxicity and describe **T**reatment

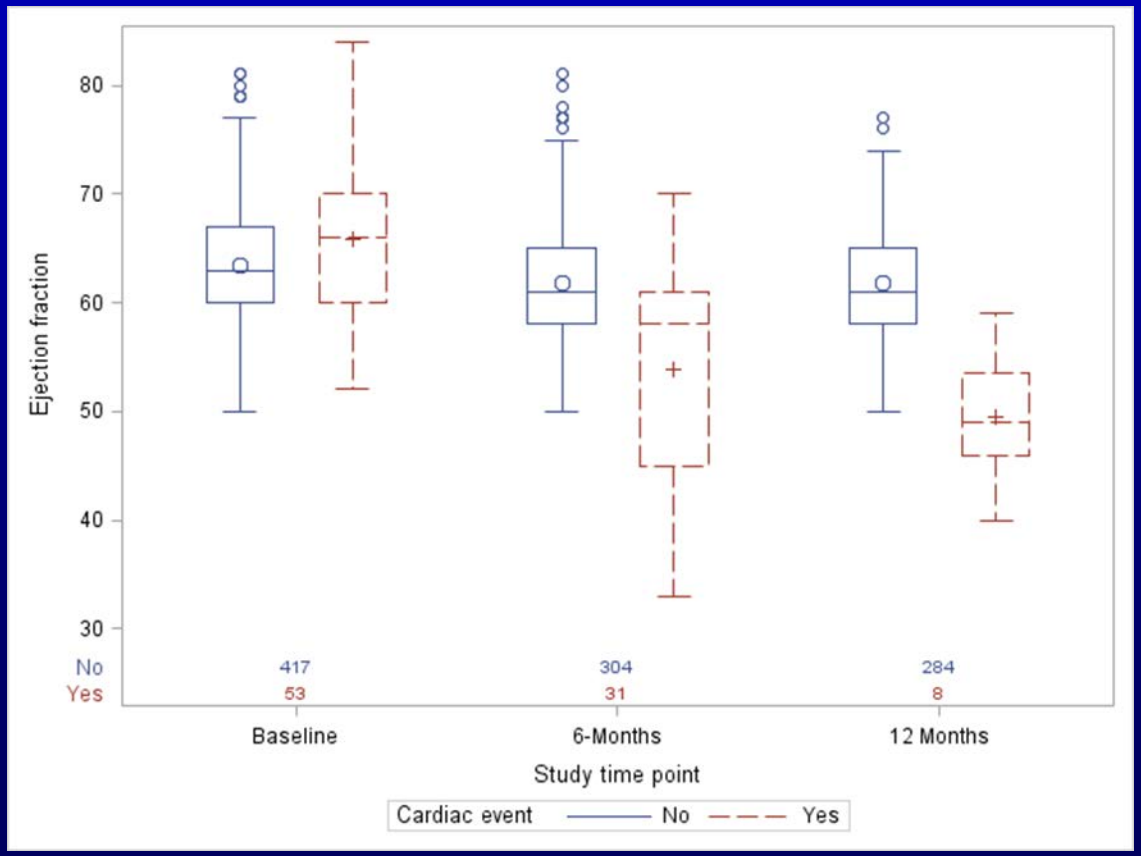
The Predict Study Team

(Lenihan, Ky, Warneke, Lagrone, Feng, Fisch)

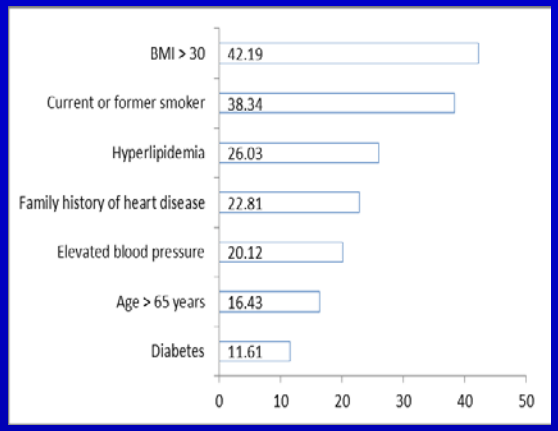
PREDICT Study flow diagram




Distribution and Probability Plot for EFBL
EF at start of anthracycline
84.0
81.0
78.0
75.0
72.0
69.0
66.0
63.0
60.0
57.0
54.0
51.0
0
20
40
60
80
100
Count


Ejection fraction
80
70
60
50
40
30
No
Yes
417
53
304
31
284
8
Baseline
6-Months
12 Months
Study time point
Cardiac event
No
Yes

PREDICT: Clinical Predictors of Cardiotoxicity



Univariate predictors of cardiotoxicity

Label	Value	Event		Total	Cases	Odds ratio			ChiSq	P
						OR	95% CL			
		Yes	No		(%)		Lower	Upper		
BNP at start of anthracycline	(per unit increase)	53	431	484	(10.95)	1.011	1.003	1.018	8.1869	0.0042
Baseline BNP	BNP 50 or more	13	64	77	(16.88)	1.864	0.944	3.678	3.2224	0.0726
	BNP < 50	40	367	407	(9.83)	1.000	.	.	.	.
Baseline BNP	BNP 100 or more	7	13	20	(35.00)	4.893	1.859	12.881	10.3364	0.0013
	BNP < 100	46	418	464	(9.91)	1.000	.	.	.	.
Age at registration (years)	(per unit increase)	55	438	493	(11.16)	1.048	1.023	1.074	14.8385	0.0001
Sex	Male	19	61	80	(23.75)	3.262	1.758	6.053	14.0601	0.0002
	Female	36	377	413	(8.72)	1.000	.	.	.	.
Race /ethnicity 2 category	NonWhite or Hispanic	19	124	143	(13.29)	1.298	0.717	2.351	0.7425	0.3889
	White, nonHispanic	36	305	341	(10.56)	1.000	.	.	.	.
Smoking status	Current smoker	11	59	70	(15.71)	1.642	0.781	3.452	1.7100	0.1910
	Previous smoker	13	106	119	(10.92)	1.080	0.544	2.143	0.0485	0.8257
	Nonsmoker	31	273	304	(10.20)	1.000	.	.	.	.
Cancer diagnosis	Lymphoma	20	96	116	(17.24)	2.335	1.264	4.312	7.3382	0.0068
	Other	6	17	23	(26.09)	3.957	1.448	10.811	7.1923	0.0073
	Breast	29	325	354	(8.19)	1.000	.	.	.	.
Cancer diagnosis	Other	26	113	139	(18.71)	2.579	1.457	4.564	10.5725	0.0011
	Breast	29	325	354	(8.19)	1.000	.	.	.	.
Number of cardiac risk factors (of 17, including age)	(per unit increase)	55	438	493	(11.16)	1.285	1.076	1.536	7.6404	0.0057
Chemotherapy prior to baseline	Yes	9	30	39	(23.08)	2.661	1.190	5.951	5.6816	0.0171
	No	46	408	454	(10.13)	1.000	.	.	.	.

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

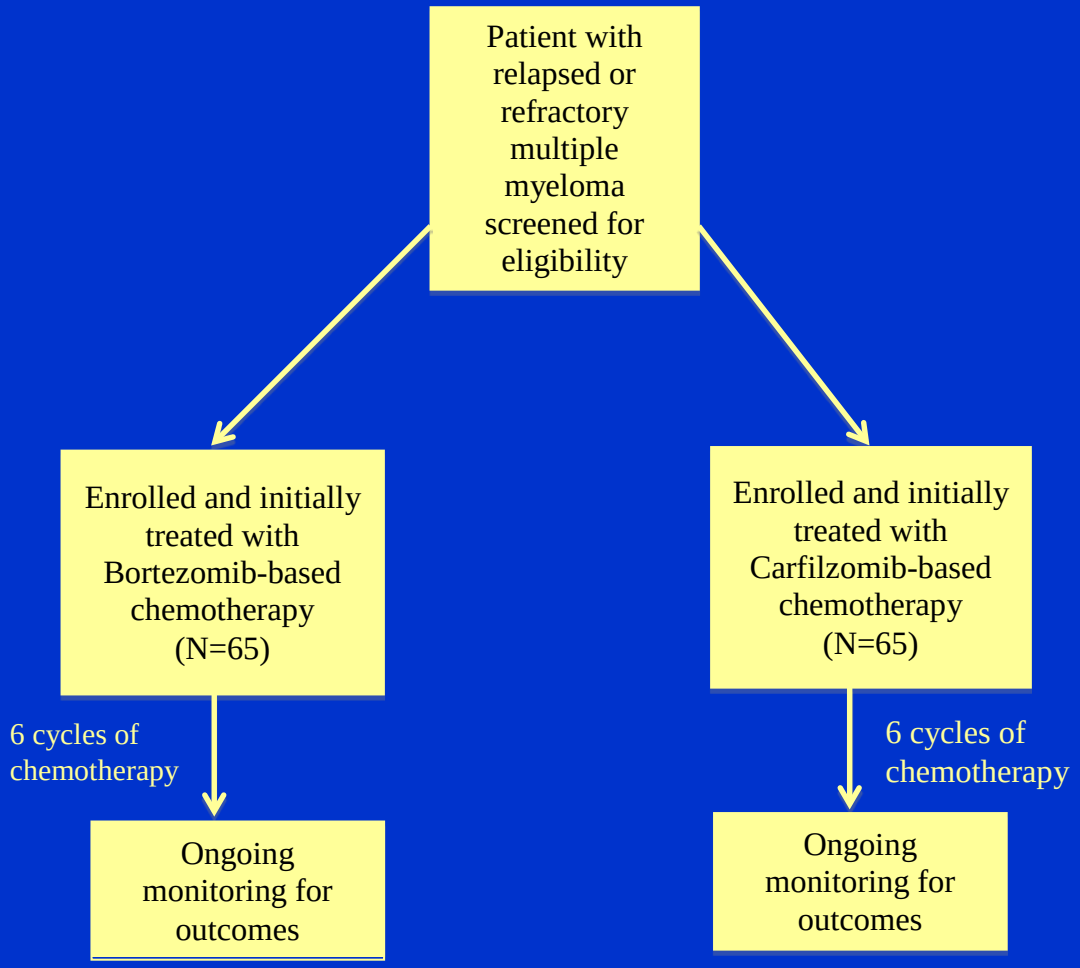
Table 3. Adverse Events in the Safety Population.*

Event	Carfilzomib Group (N=392)		Control Group (N=389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	number of patients (percent)			
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure†	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure‡	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease§	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

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

Schedule of Cardiac Safety Monitoring

Study Visits / Procedures	Baseline Assessments	Cycle 1 Visit‡		Cycle 2 Visit‡		Cycle 3 Visit‡		Cycle 4 Visit‡		Cycle 5 Visit‡		Cycle 6 Visit[i‡]		6Mo./ 12 Mo./ EOS[j]	18 Mo./ Phone F/U	Any Cardiac Event[d]
Informed Consent	X															
Medical History and prior treatments	X															
Physical Exam and Vitals	X	X		X		X		X		X		X		X		X
6 Minute Hall Walk	X											X		X		
ECG	X			X				X				X				
BNP or NT-proBNP(local)	X	X[f]	X[c]	X	X[c]	X	X[c]	X	O[c]	X	O[c]	X	O[c,]	X[h]		X[h]
Troponin I or T (local)	X	X[f]	X[c]	X	X[c]	X	X[c]	X	O[c]	X	O[c]	X	O[c,]	X[h]		X[h]
Correlative samples	X	X[f]	X[c]	X	X[c]	X	X[c]	X	O[c]	X	O[c]	X	O[c,]	X[h]		X[h]
cMRI[b]	O							O								
TTE[e]	X			X				X				X		X[g]		X[g]
MDASI-HF	X	X[f]		X		X		X		X		X		X		X
Cardiac CTCAE assessment (v. 4)	X	X[f]		X		X		X		X		X		X		X
Overall Survival Status														X	X	X

X required testing; O optional testing; ‡Denotes chemotherapy cycle;

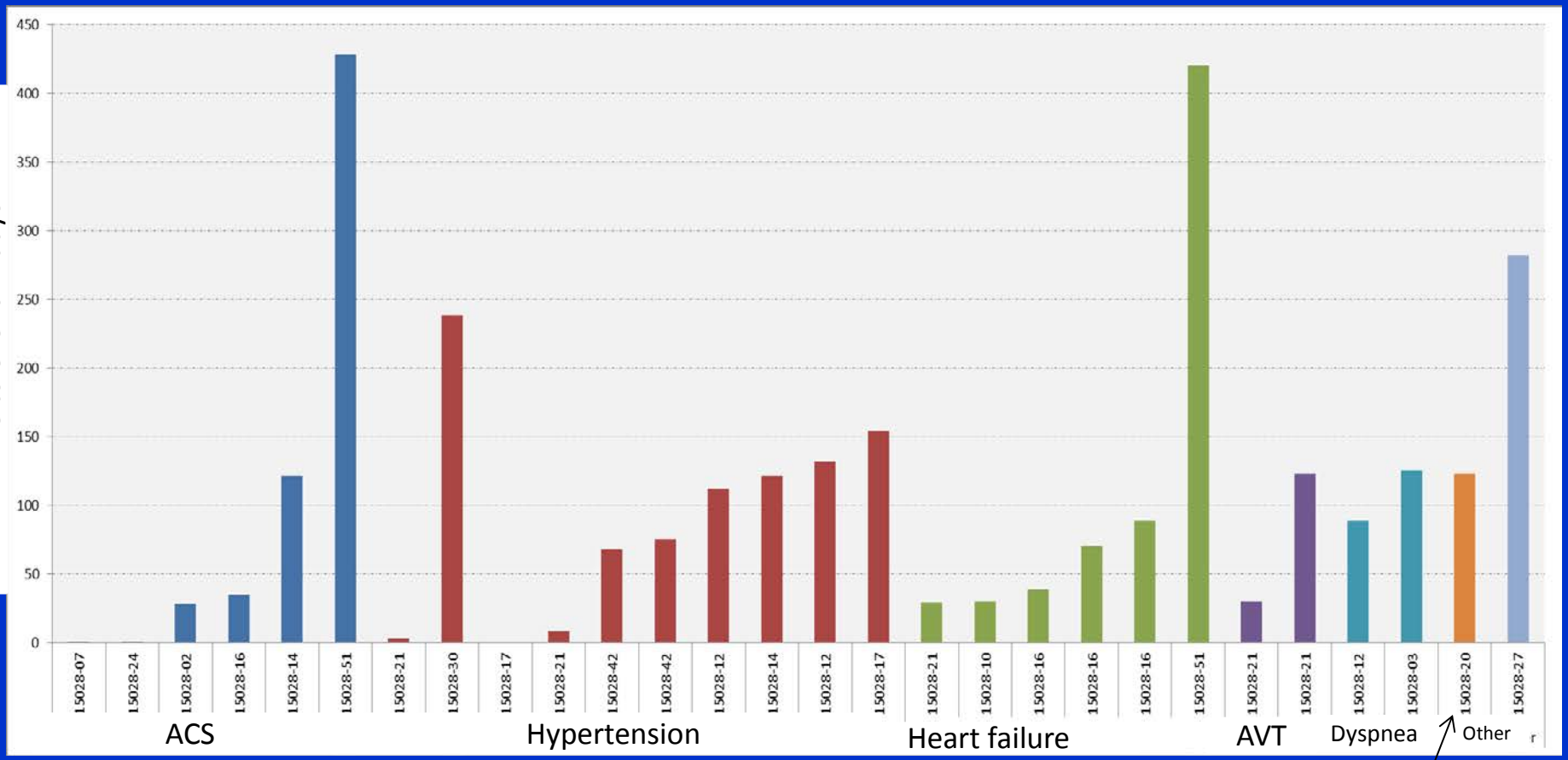
Suspected Cardiac Events (VUMC only)

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

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



Cardiotoxicity: Recovery Registry (CTR)

The purpose of the **Cardiotoxicity: Recovery Registry** is 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*

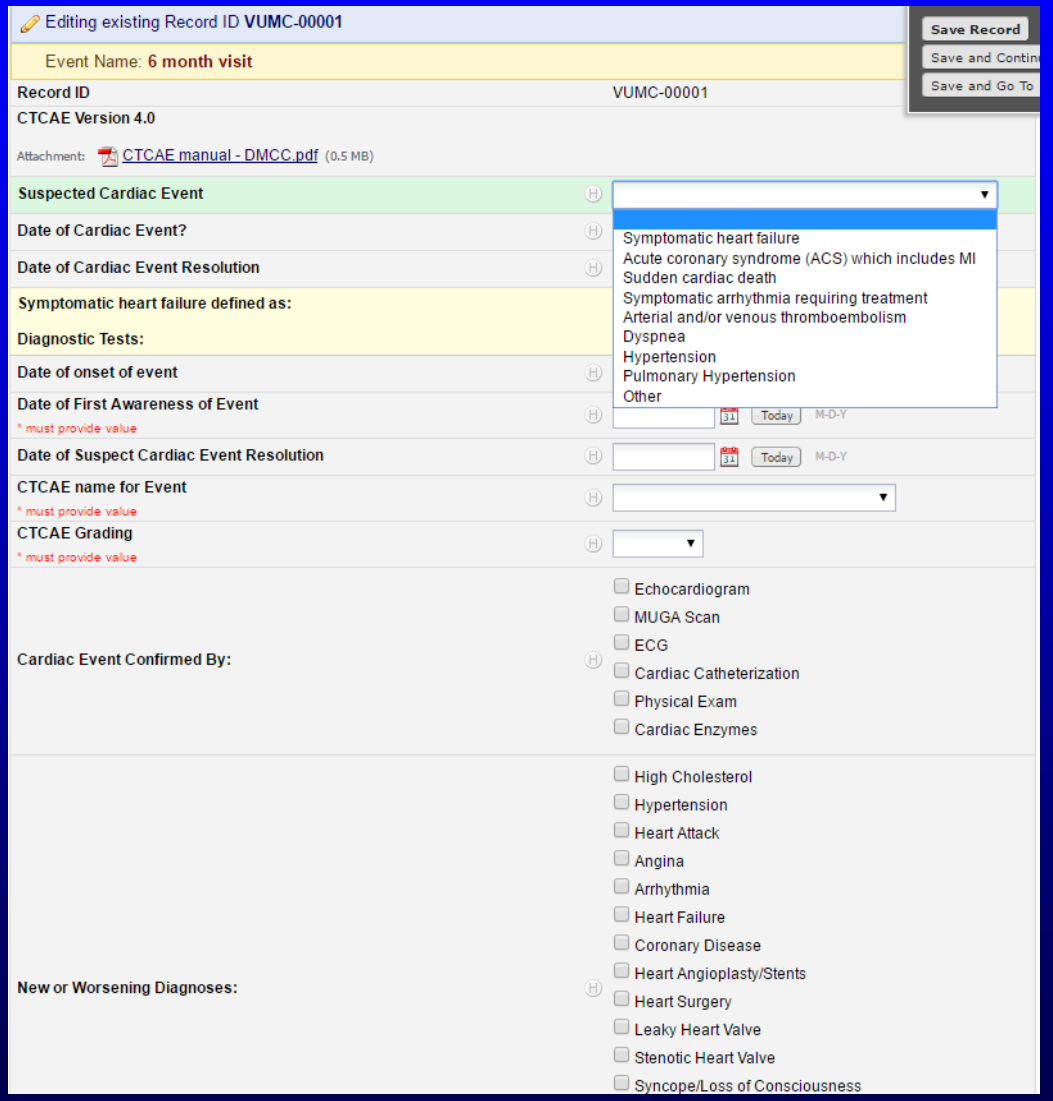
- *Describe the clinical tools that are most useful and cost effective at enhancing recovery of cardiac dysfunction*

- *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)

Data Collection Instrument	Baseline visit	6 month visit	1 year follow up	2 year follow up	3 year follow up	Phone followup
Inclusion/exclusion Checklist	●					
Enrollment Form Basic Info	○					
Physical Exam and Vitals	○	○	○	○	○	
Medical History	○	○	○	○	○	
Cardiac And Other Related Medications	○	○	○	○	○	○
Baseline Labs	○		○	○	○	
ECHO data	○		○	○	○	
ECG	○		○	○	○	
MRI	○		○	○	○	
6 Minute Walk Test	○	○	○	○	○	
Sensitive Information Questionnaire	○					
Health Status Questionnaires	○		○	○	○	
Cardiovascular risk factors	○	○	○	○	○	
Past And Present Cancer History	○		○	○	○	
Chemotherapy Treatment 1	○	○	○	○	○	
Chemotherapy Treatment 2	○	○	○	○	○	
Chemotherapy Treatment 3	○	○	○	○	○	
Chemotherapy Treatment 4	○	○	○	○	○	
Chemotherapy Treatment 5	○	○	○	○	○	
Suspected Cardiac Event	○	○	○	○	○	○
Phone interview questionaire						○
Outcomes			○	○	○	
Follow Up Survival Status			○	○	○	
Notes To File	○	○	○	○	○	○
Study Exit Form	○	○	○	○	○	○



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/Bioview
  - 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