VANDERBILT UNIVERSITY
MEDICAL CENTER

CV Endpoint Adjudication:

What Makes a Case Non-Assessable?

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Is Heart Failure Present?

Case 1:

- 64 y/o F treated with an experimental drug in a patient with a pulmonary disease
- Cardiac safety determined by periodic LVEF and clinical exam
- Routine data collection is completely recorded in the CRFs

Table 2. Definition: Cardiac Dysfunction SEVERITY GRADE					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50-40%; 10-19% drop from baseline	Resting ejection fraction (EF) 39-20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-type Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences, urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or the ability to do so only at an elevation in the filling pressure.					

Case 1: Data

- Is heart failure present?
- Is there any toxicity from the drug? (ie, is it treatment related?)

	visit 1	2	3	4
LVEF	68*	54	51	55
HR	96	56	56	80
SBP	166	110	110	140
Dyspnea grade	1	2	2	2

* LVEF done by MUGA

☐ **Symptomatic Heart Failure: (Demonstrated by at least one item in two of the three following categories)**

Physical Findings:

☐ Yes	☐ No	JVD				
☐ Yes	☐ No	Crackles				
☐ Yes	☐ No	Edema				
☐ Yes	☐ No	S3				

Diagnostic Tests:

☐ Yes	☐ No	Pulmonary Edema on CXR				
☐ Yes	☐ No	BNP>200pg/ml *if Yes:* BNP:				

Symptoms of HF:

☐ Yes	☐ No	PND	☐ Yes	☐ No	Orthopnea	
☐ Yes	☐ No	SOB	☐ Yes	☐ No	Weight Gain	
☐ Yes	☐ No	Swelling	☐ Yes	☐ No	Other:_____	
☐ Yes	☐ No	Fatigue				

☐ **Asymptomatic LV Dysfunction (LVEF reduction of 10% to <50% or a decrease of >15% from baseline)**

Is there a arterial vascular event?

Case 2

- 55 y/o M who has DM is being treated with an experimental agent for cancer
- Cardiovascular event safety determined by CTCv4 criteria
- No specific data testing as part of the protocol for vascular safety
- Routine data is in CRF

Arterial vascular event?

- Pt has no documented CV disease at baseline
- Systolic BP: 182 at baseline, 176 at 3 mo, 162 at 6 mo
- TIA occurred at 3 months
- Peripheral ischemia noted at 6 months
- So: is this a treatment emergent event?
- Is this caused by the study drug?

Possible arterial vascular events

- Acute coronary syndrome
- TIA/CVA
- Peripheral vascular ischemia
- Intestinal ischemia
- Vasculitis
- Raynaud’s
- Troponinitis
- Others……

The Boston Globe

Ariad cancels trial of leukemia drug

By Robert Weisman | GLOBE STAFF OCTOBER 19, 2013

Cambridge biotech Ariad Pharmaceuticals Inc. abruptly terminated a pivotal clinical trial of its leukemia drug Friday, a move that raised new safety questions and sent the company's shares plunging more than 40 percent.

By ending the late-stage trial of Iclusig, Ariadessentially abandoned a plan that had been considered key to its future: turning the pill — already on sale in the United States and Europe for use by patients whose cancers resist other treatments — into a "first-line" medicine for those newly diagnosed with chronic myeloid leukemia.

Ariad executives said they decided, in concert with the Food and Drug Administration, to discontinue their so-called Epic clinical study after early data from 150 sites in 20 countries showed patients taking Iclusig in the study experienced problems such as blood clots leading to heart attacks, strokes, and blocked arteries. The company didn't immediately disclose how many patients suffered those side effects or whether any died.

The official announcements regarding adverse events lack detail on the nature of the vascular events associated with ponatinib. Are the events due to rapidly progressive atherosclerosis, arterial thrombosis, arterial embolism, or some other vascular process, such as vasospasm? Defining the exact nature of adverse events is critical for developing strategies that might reduce the risk of cardiovascular toxic effects or even prevent their occurrence altogether so that the anticancer efficacy of ponatinib can be maximally exploited.

From: Groarke J, et al NEJM Nov 6 2013

Challenges with adjudication

- Adequate clinical data is needed to determine a diagnosis, especially for Heart Failure (symptoms, labs, vitals)
- For vascular events, must have:
  - Careful risk factors/Phys. Exam at baseline
  - Coexistent meds
  - Difficulty for ascertaining the relationship to the study medication