New Therapies: What are the Cardiovascular Concerns?

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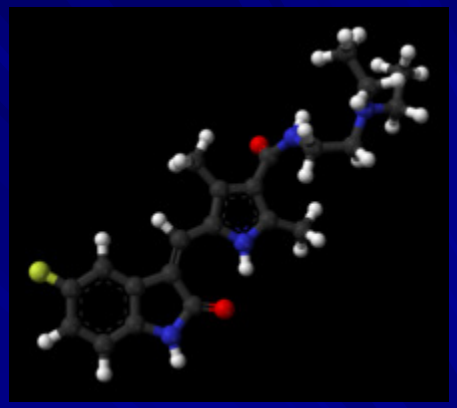
Outline

- How do we assess toxicity?
  - Real-world example
  - How does this get us into trouble?
- Specific “New agents”
  - VEGF inhibitors
  - Nilotinib/Ponatinib
  - Proteasome inhibitors
  - BTK inhibitors
  - Checkpoint inhibitors
- Final thoughts

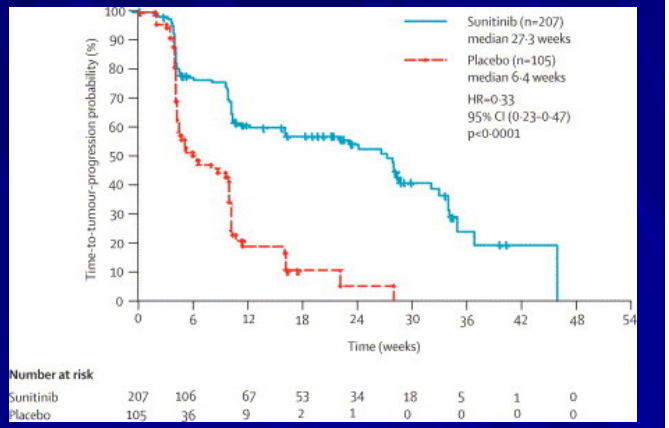
Tyrosine Kinase Inhibitors

- Tyrosine kinases: Critically involved in many cellular functions
- Inhibition can have profound effects on tumor growth/survival
  - Examples: Imatinib, sunitinib, sorafenib
- Broader inhibition → broader anti-neoplastic activity
  - Also potential for more off-target side-effects
- Sunitinib
  - Broadly active tyrosine kinase inhibitor – notably inhibits VEGF
  - FDA approved for 3 different tumors
- We can learn a lot from this story…

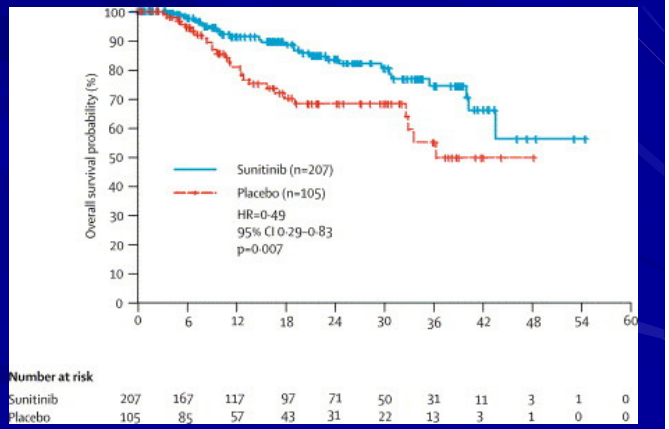


Sunitinib – First Phase III Trial

- Phase III study for GI stromal tumors (GIST), Lancet 2006
- 312 patients given sunitinib or placebo
- Cardiac monitoring: MUGA at screening, end of each cycle, and treatment end
  - MUGA data not provided in article



Time to Tumor Progression



Overall Survival

Adapted from Demetri et al. Lancet. 2006;368:1329-38.

Table of Adverse Events

	Sunitinib (n=202)			Placebo (n=102)		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Non-haematological*						
Fatigue	58 (29%)	10 (5%)	0 (0%)	20 (20%)	2 (2%)	0 (0%)
Diarrhoea	52 (26%)	7 (3%)	0 (0%)	8 (8%)	0 (0%)	0 (0%)
Skin discolouration	50 (25%)	0 (0%)	0 (0%)	6 (6%)	0 (0%)	0 (0%)
Nausea	47 (23%)	1 (1%)	0 (0%)	10 (10%)	1 (1%)	0 (0%)
Anorexia	38 (19%)	0 (0%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Dysgeusia	36 (18%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Stomatitis	30 (15%)	1 (1%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Vomiting	30 (15%)	1 (1%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Hand-foot syndrome	19 (9%)	9 (4%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Rash	24 (12%)	2 (1%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Asthenia	18 (9%)	6 (3%)	0 (0%)	2 (2%)	2 (2%)	0 (0%)
Mucosal inflammation	24 (12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dyspepsia	22 (11%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Hypertension	15 (8%)	6 (3%)	0 (0%)	4 (4%)	0 (0%)	0 (0%)
Epistaxis	14 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hair-colour changes	14 (7%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Dry mouth	13 (6%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Glossodynia	11 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Haematological						
Anaemia†	117 (58%)	7 (4%)	0 (0%)	59 (58%)	2 (2%)	0 (0%)
Leucopenia	104 (52%)	7 (4%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Neutropenia	86 (43%)	17 (8%)	3 (2%)	4 (4%)	0 (0%)	0 (0%)
Lymphopenia	80 (40%)	18 (9%)	1 (1%)	31 (30%)	2 (2%)	1 (1%)
Thrombocytopenia	72 (36%)	8 (4%)	1 (1%)	4 (4%)	0 (0%)	0 (0%)

Data are number (%). *Treatment-related. †Anaemia was included in the table, despite a difference of less than 5% between the treatment groups, because of its frequency and clinical relevance in GIST.

Table 2: **Adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in per-protocol population**

Adapted from Demetri et al. Lancet. 2006;368:1329-38.

Sunitinib (Sutent): Data vs. Label

We noted no evidence of a systematic mean decrease in left ventricular ejection fraction in either treatment group, and no patients were reported to have had clinical evidence of congestive heart failure

Lancet GIST Study A, October 2006

Sutent Prescribing Information. http://www.pfizer.com/files/products/uspi_sutent.pdf & Demetri et al. Lancet. 2006;1329-38.

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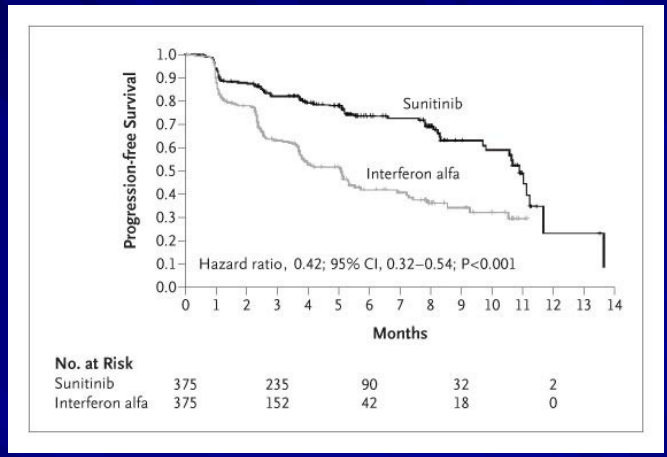
Sunitinib – Second Phase III Study

- 750 patients with untreated metastatic renal-cell CA randomized to receive:
  - Sunitinib
  - Interferon alfa
- Normal LVEF at baseline & cardiac monitoring performed



Data adapted from Motzer et al. NEJM. 2007;356:115-24.

Heart Failure: Phase III Study

Variable	Sunitinib (N=375)			Interferon Alfa (N=360)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	percent					
Adverse event						
Diarrhea†	53	5	0	12	0	0
Fatigue†	51	7	0	51	11	1
Nausea	44	3	0	33	1	0
Stomatitis	25	1	0	2	1	0
Vomiting†	24	4	0	10	1	0
Hypertension†	24	8	0	1	1	0
Hand–foot syndrome†	20	5	0	1	0	0
Mucosal inflammation	20	2	0	1	1	0
Rash	19	1	1	6	1	0
Asthenia	17	4	0	20	4	0
Dry skin	16	1	0	5	0	0
Skin discoloration	16	0	0	0	0	0
Changes in hair color	14	0	0	1	0	0
Epistaxis	12	1	0	1	0	0
Pain in a limb	11	1	0	3	0	0
Headache	11	1	0	14	0	0
Dry mouth	11	0	0	6	1	0
Decline in ejection fraction	10	2	0	3	1	0
Pyrexia	7	1	0	34	0	0
Chills	6	1	0	29	0	0
Myalgia	5	1	0	16	1	0
Influenza-like illness	1	0	0	7	1	0

Data adapted from Motzer et al. NEJM. 2007;356:115-24.

Study 2: More Confusion

Variable	Sunitinib (N=375)			Interferon Alfa (N=360)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
			percent			
Decline in ejection fraction	10	2	0	3	1	0

NEJM metastatic renal cell CA (MRCC) Study, January, 2007

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Which of *These* is Accurate?

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NEJM Treatment-Naïve MRCC Study, January 11, 2007

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Sutent Prescribing Information (Pfizer), February 2007

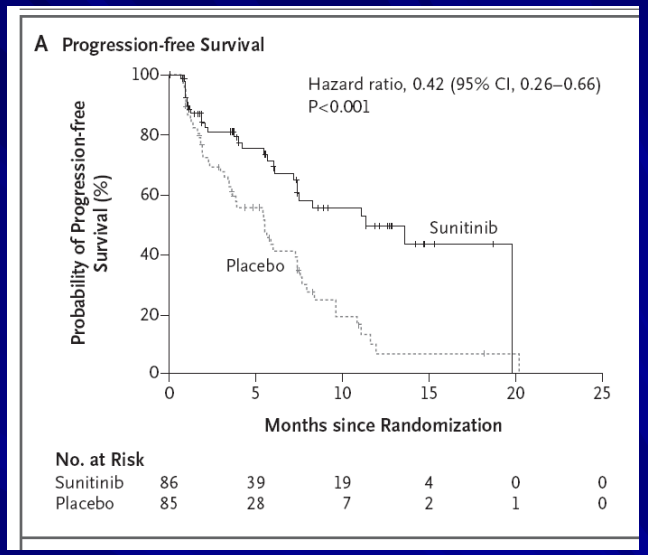
In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.

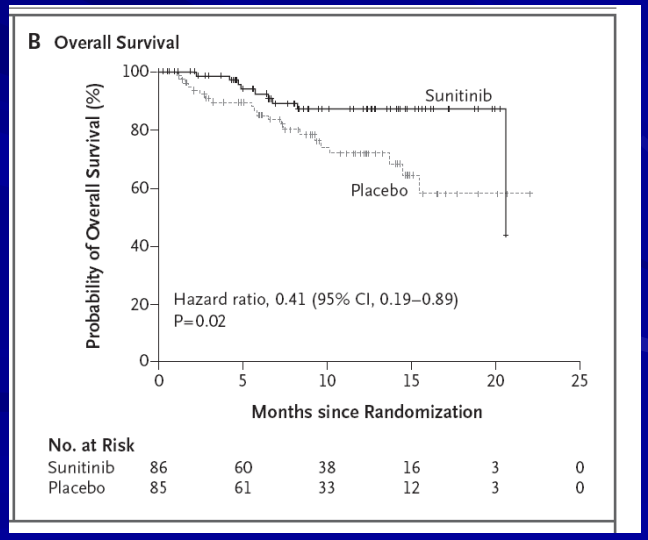
Sutent Prescribing Information (Pfizer), May 2011

Sutent Prescribing Information. http://www.pfizer.com/files/products/uspi_sutent.pdf *& Motzer et al. NEJM. 2007;356:115-24.*

2011: Another Trial, Still Confusion

- 171 patients with pancreatic neuroendocrine tumors (PNET) randomized to receive:
  - Sunitinib
  - Placebo
- No cardiac imaging built in!
  - Note: First patient randomized in *June 2007*
  - Highlights how this has been thought to be a non-issue or trivial issue based on original Phase III studies
  - Treatment-related heart failure deaths – 2 out of 83 patients!





Adapted from Raymond et al, NEJM. 2011;364:501-13.

Continued Inconsistencies: 2011

Five patients who received sunitinib and nine patients who received placebo died during the trial period (from the first study-drug dose until 28 days after the last dose). The deaths were attributed to the disease under study, with the exception of grade 5 cardiac failure (in one patient who received sunitinib) and grade 5 dehydration (in one patient who received placebo), which were both considered to be related to the study drug.

NEJM Phase III PNET Trial, Published February 10, 2011

In the Phase 3 pNET study, cardiac failure leading to death was reported in 2/83 (2%) patients on SUTENT and no patients on placebo.

Sutent Prescribing Information (Pfizer), May 2011

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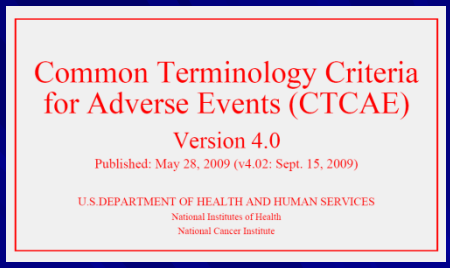
How Can This Happen?

Three Culprit Reasons

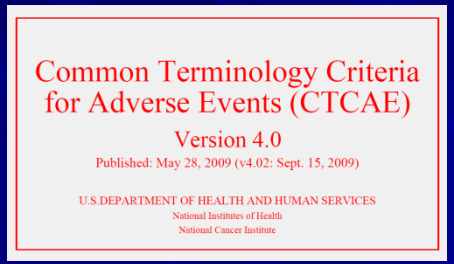
Issue 1: CTCAE

- Oncology trial mechanism for grading adverse events
- Far ahead of other fields
- Goal: Have standard definitions for adverse events
- Essentially 100% use/acceptance across Oncology clinical trials



Why the Problems?

- Semantics, semantics, semantics
- Clinical scenario:
  - 50 y.o. man with renal cell CA
  - Enrolls in clinical trial of promising new therapy
  - Pre-treatment LVEF: 60%
  - Post-treatment LVEF: 35%
  - Patient is ‘asymptomatic’ from cardiac standpoint
- How should the Oncologist grade this according to CTCAE?



Turns to CTCAE Table of Contents…

CONTENTS

Found it! It's Grade 0

Cardiac disorders					
	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 mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					

Oops – Is it Grade 1?

Cardiac disorders					
	Grade				
Adverse Event	1	2	3	4	5
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-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.					

Grade 2 Events
(By Way of Comparison…)

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					

But Wait…

CONTENTS

Maybe It's Grade 3?

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
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.					

Make a Little More Sense Now?

In the treatment-naïve MRCC study, 78/375 (21%) and 44/360 (12%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Thirteen patients on SUTENT (4%) and four on IFN-α (1%) experienced declines in LVEF of >20% from baseline and to below 50%. Left ventricular dysfunction was reported in three patients (1%) and CHF in one patient (<1%) who received SUTENT.

Sutent Prescribing Information (Pfizer), February 2007

Sutent Prescribing Information. http://www.pfizer.com/files/products/uspi_sutent.pdf.

Issue 2: When is an Adverse Event an Adverse Event?

- Answer: When it is reported by the local site investigator
- When might that make sense?
  - Symptom or exam finding in which the subtlety of being the physician taking the history or performing the exam matters
- When might that not make sense?
  - Objective laboratory or imaging finding
  - Examples: Neutropenia, drop in ejection fraction

Issue 3: Even if an Adverse Event is Reported it May Not Count

- Why? It may not be labeled as a "treatment-related" adverse event (TRAE)
- Idea: Prevent 'bad luck' from affecting trial results
  - Example: Car accident
- Why can this be a problem?
  - How do you ever pick up a signal for a previously unknown side-effect?
  - Unexpected side-effects will almost always get missed

TRAEs

Data are number (%). *Treatment-related. †Anaemia was included in the table, despite a difference of less than 5% between the treatment groups, because of its frequency and clinical relevance in GIST.

Table 2: **Adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in per-protocol population**

Lancet GIST study, October, 2007

* Listed are all treatment-related adverse events of interest and those occurring in at least 10% of patients in the sunitinib group. All severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

NEJM Renal Cell CA study, January, 2007

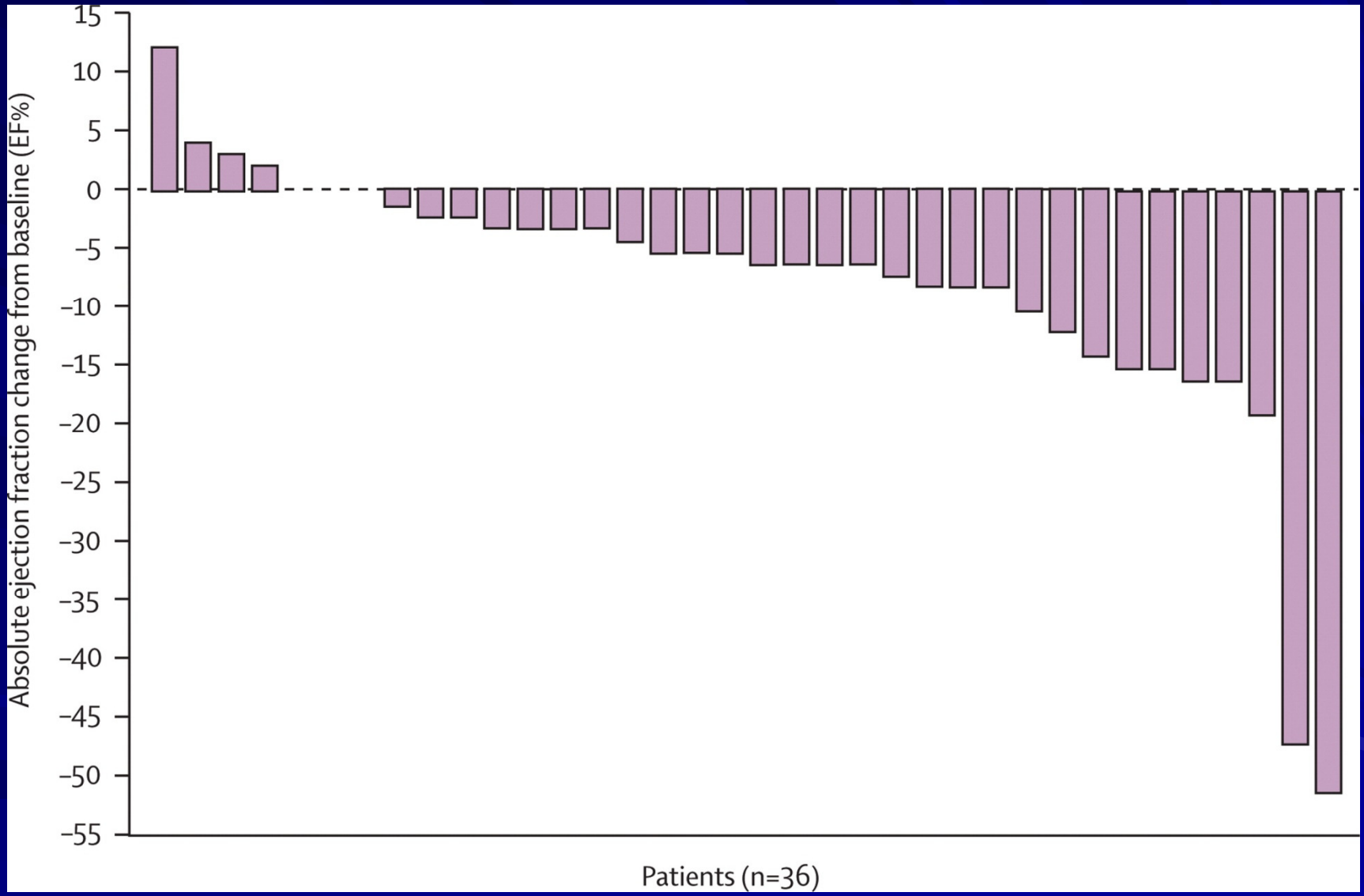
Adapted from Motzer et al. NEJM. 2007;356:115-24 and Demetri et al. Lancet. 2006;1329-38

How Big of a Problem is This?

- Probably bigger than any of us think…
- While the problems with CTCAE are unique to cardiac monitoring in cancer trials, the other issues can apply to most clinical trial adverse event monitoring
- Note: These studies appeared in NEJM (x2) and Lancet

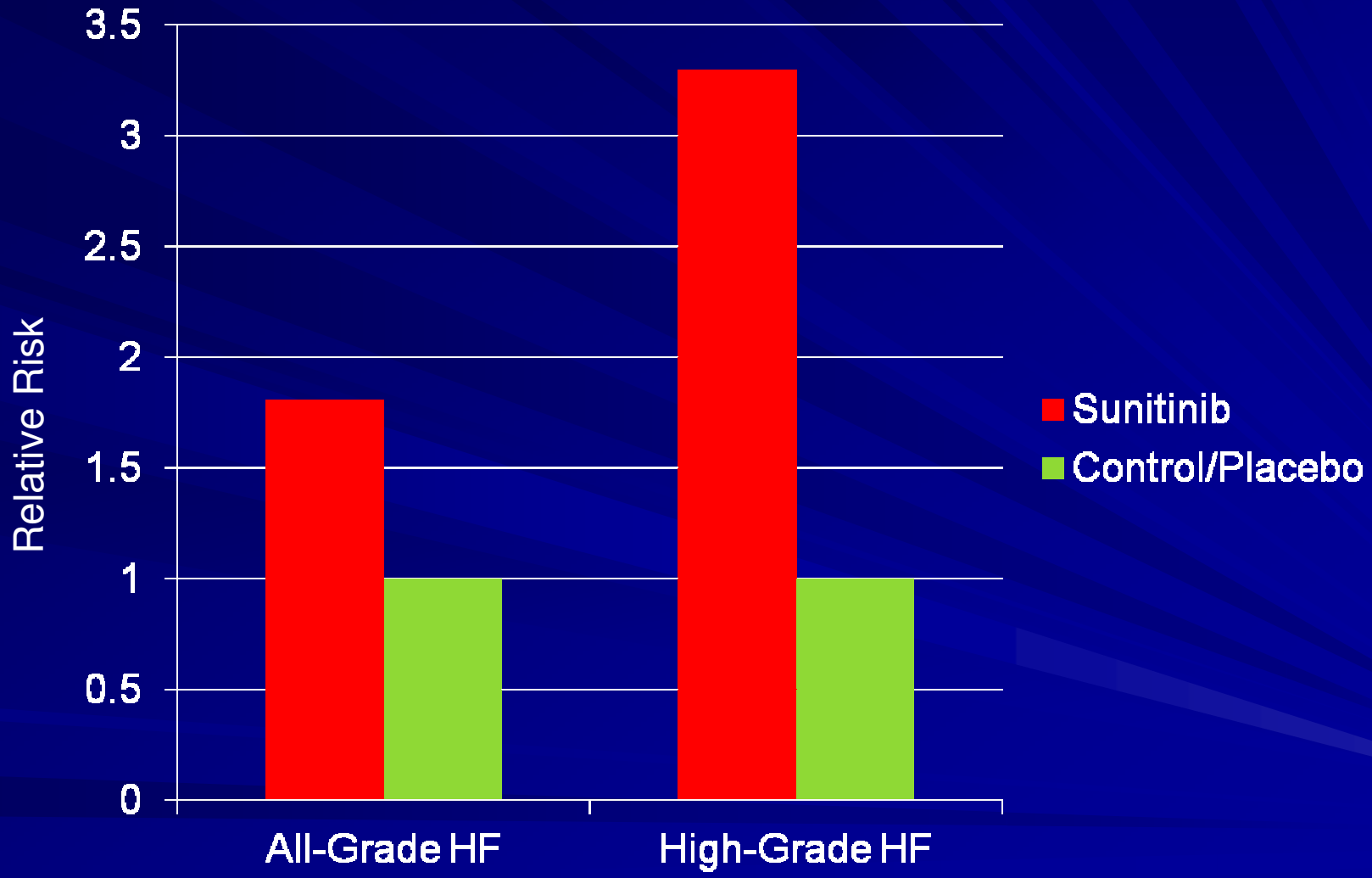
Does This Matter?

It Matters: Subsequent Sunitinib Data



Adapted from Chu et al. Lancet. 2007;370:2011-3.

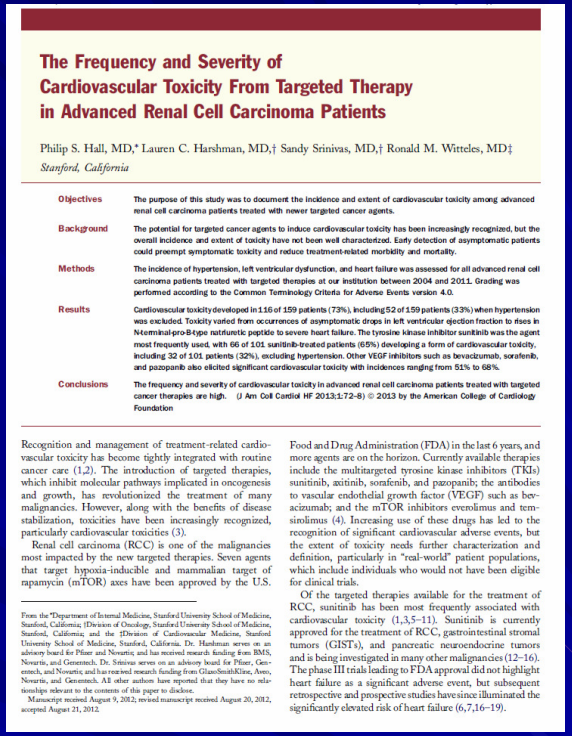
It Matters: Meta-Analysis of Sunitinib: Relative Risk of HF (P<0.001)



Adapted from Richards et al. J Clin Oncol. 2011;29:3450-6.

Stanford Study

- Initiated in late 2007 in Stanford GU Oncology clinics for all patients receiving targeted therapy:
  - VEGF TKIs (Sunitinib, sorafenib, pazopanib, bevacizumab)
  - mTOR inhibitors: Everolimus, temsirolimus
- Included:
  - EKG (baseline)
  - TTE (baseline & q 3 months)
  - NT-BNP & troponin I (baseline & q3 months)
  - BP assessment (monthly)
  - Note: Extra TTE/biomarker assessment at 1 month when logistically possible



The Frequency and Severity of Cardiovascular Toxicity From Targeted Therapy in Advanced Renal Cell Carcinoma Patients

Philip S. Hall, MD,* Lauren C. Harshman, MD,† Sandy Srinivas, MD,† Ronald M. Witteles, MD‡
Stanford, California

Objectives The purpose of this study was to document the incidence and extent of cardiovascular toxicity among advanced renal cell carcinoma patients treated with newer targeted cancer agents.

Background The potential for targeted cancer agents to induce cardiovascular toxicity has been increasingly recognized, but the overall incidence and extent of toxicity have not been well characterized. Early detection of asymptomatic patients could preempt symptomatic toxicity and reduce treatment-related morbidity and mortality.

Methods The incidence of hypertension, left ventricular dysfunction, and heart failure was assessed for all advanced renal cell carcinoma patients treated with targeted therapies at our institution between 2004 and 2011. Grading was performed according to the Common Terminology Criteria for Adverse Events version 4.0.

Results Cardiovascular toxicity developed in 116 of 159 patients (73%), including 52 of 159 patients (33%) when hypertension was excluded. Toxicity varied from occurrences of asymptomatic drops in left ventricular ejection fraction to rises in N-terminal-pro-B-type natriuretic peptide to severe heart failure. The tyrosine kinase inhibitor sunitinib was the agent most frequently used, with 66 of 101 sunitinib-treated patients (65%) developing a form of cardiovascular toxicity, including 32 of 101 patients (32%), excluding hypertension. Other VEGF inhibitors such as bevacizumab, sorafenib, and pazopanib also elicited significant cardiovascular toxicity with incidences ranging from 51% to 68%.

Conclusions The frequency and severity of cardiovascular toxicity in advanced renal cell carcinoma patients treated with targeted cancer therapies are high. (J Am Coll Cardiol HF 2013;1:72–8) © 2013 by the American College of Cardiology Foundation

Recognition and management of treatment-related cardiovascular toxicity has become tightly integrated with routine cancer care (1,2). The introduction of targeted therapies, which inhibit molecular pathways implicated in oncogenesis and growth, has revolutionized the treatment of many malignancies. However, along with the benefits of disease stabilization, toxicities have been increasingly recognized, particularly cardiovascular toxicities (3).

Renal cell carcinoma (RCC) is one of the malignancies most impacted by the new targeted therapies. Seven agents that target hypoxia-inducible and mammalian target of rapamycin (mTOR) axes have been approved by the U.S. Food and Drug Administration (FDA) in the last 6 years, and more agents are on the horizon. Currently available therapies include the multitargeted tyrosine kinase inhibitors (TKIs) sunitinib, axitinib, sorafenib, and pazopanib; the antibodies to vascular endothelial growth factor (VEGF) such as bevacizumab; and the mTOR inhibitors everolimus and temsirolimus (4). Increasing use of these drugs has led to the recognition of significant cardiovascular adverse events, but the extent of toxicity needs further characterization and definition, particularly in "real-world" patient populations, which include individuals who would not have been eligible for clinical trials.

Of the targeted therapies available for the treatment of RCC, sunitinib has been most frequently associated with cardiovascular toxicity (1,3,5–11). Sunitinib is currently approved for the treatment of RCC, gastrointestinal stromal tumors (GISTs), and pancreatic neuroendocrine tumors and is being investigated in many other malignancies (12–16). The phase III trials leading to FDA approval did not highlight heart failure as a significant adverse event, but subsequent retrospective and prospective studies have since illuminated the significantly elevated risk of heart failure (6,7,16–19).

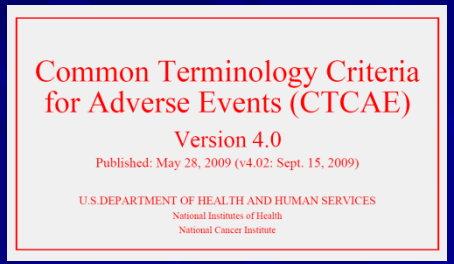
From the *Department of Internal Medicine, Stanford University School of Medicine, Stanford, California; †Division of Oncology, Stanford University School of Medicine, Stanford, California; and the ‡Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California. Dr. Harshman serves on an advisory board for Pfizer and Novartis; and has received research funding from BMS, Novartis, and Genentech. Dr. Srinivas serves on an advisory board for Pfizer, Genentech, and Novartis; and has received research funding from GlaxoSmithKline, Aveo, Novartis, and Genentech. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 9, 2012; revised manuscript received August 20, 2012, accepted August 21, 2012.

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Assessment of Toxicity

- Performed using CTCAE v4.0
  - Problems with CTCAE? Yes, but…
  - Universal system for grading toxicities
- Toxicities assessed:
  - Heart failure
  - Ejection fraction decreased
  - Cardiac troponin I increased
  - Hypertension



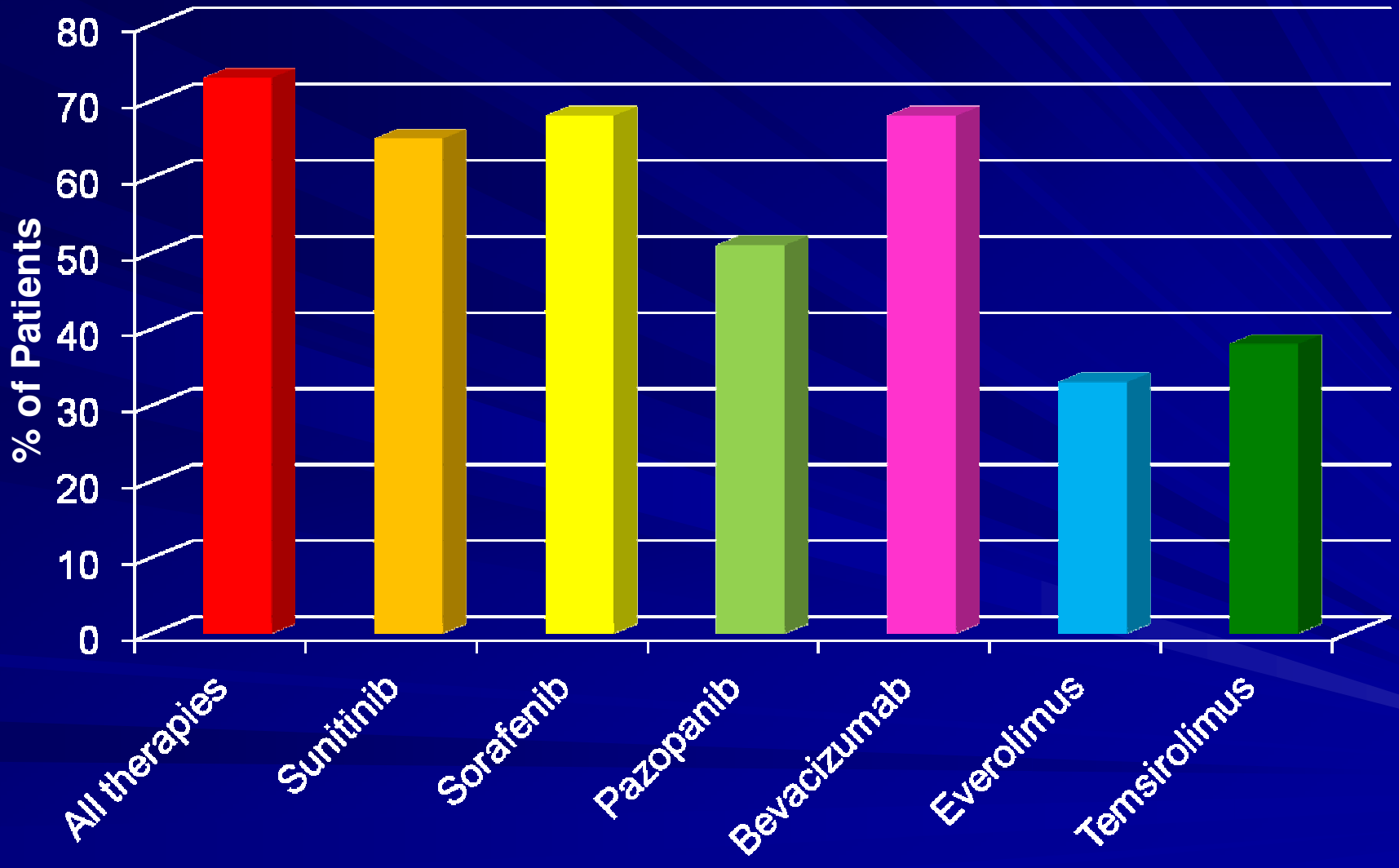
“Hypertension”

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Pediatric: Same as adult	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death

“Hypertension”

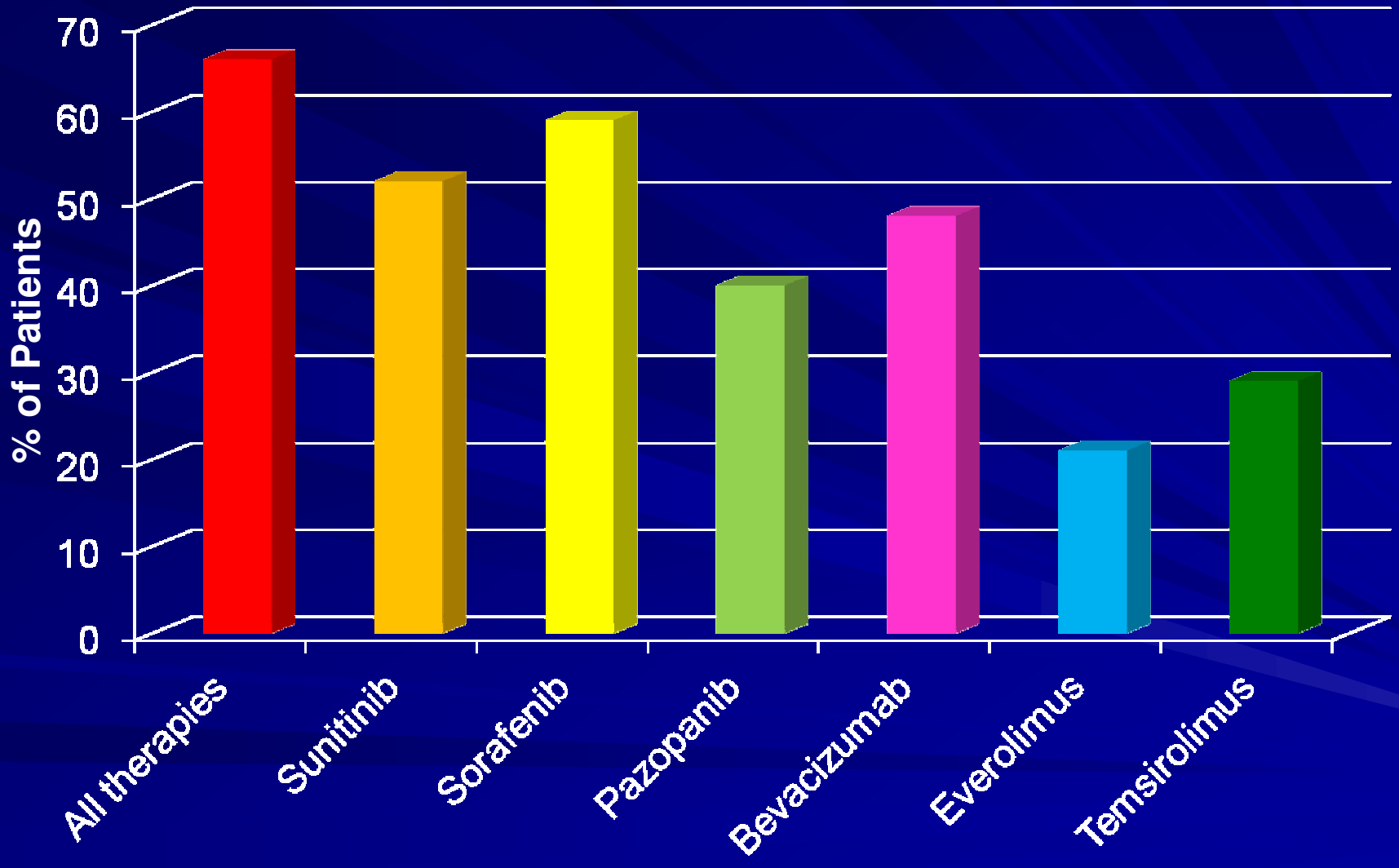
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Pediatric: Same as adult	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death

Any Cardiovascular Toxicity



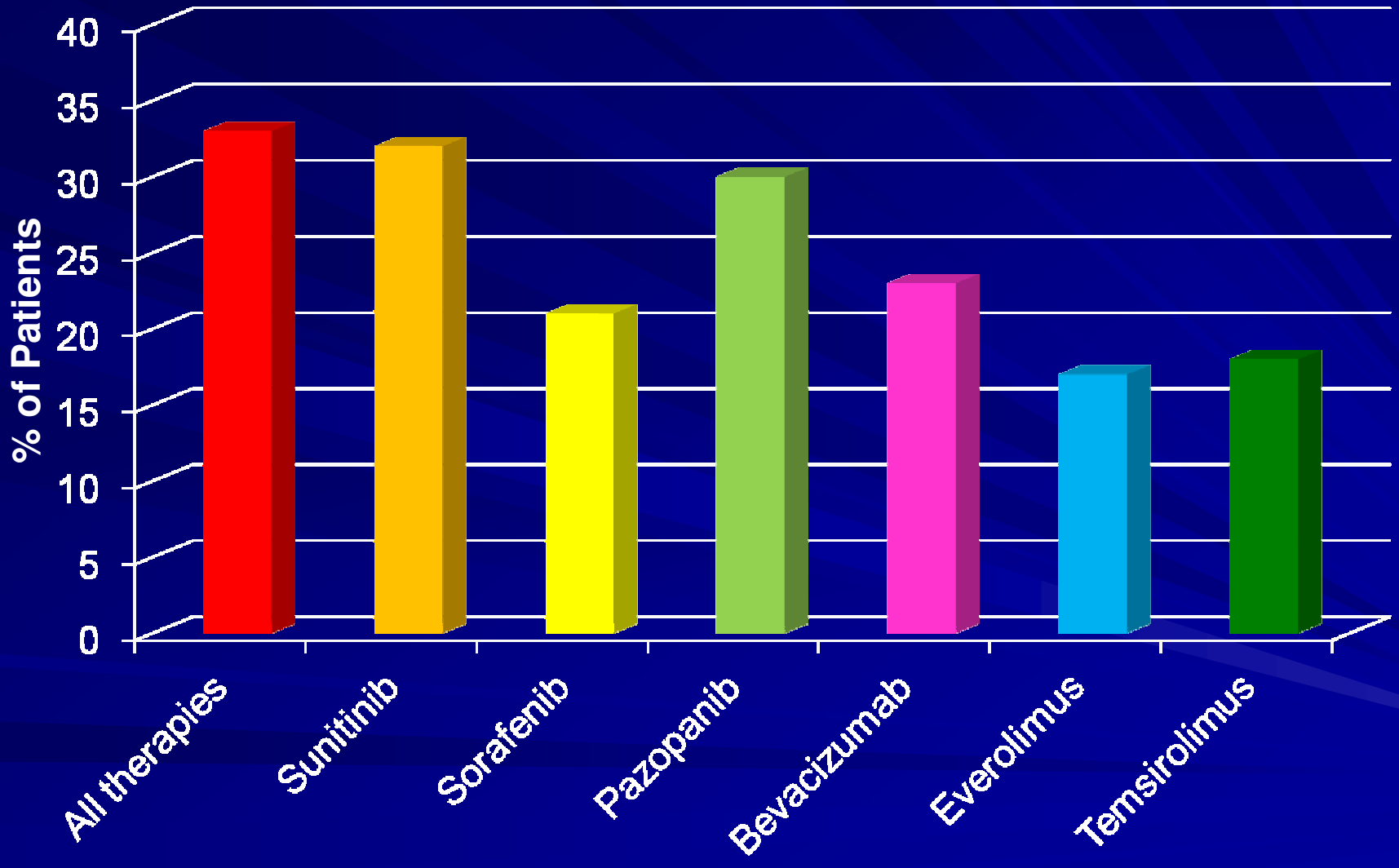
Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Hypertension (Grade 2+)



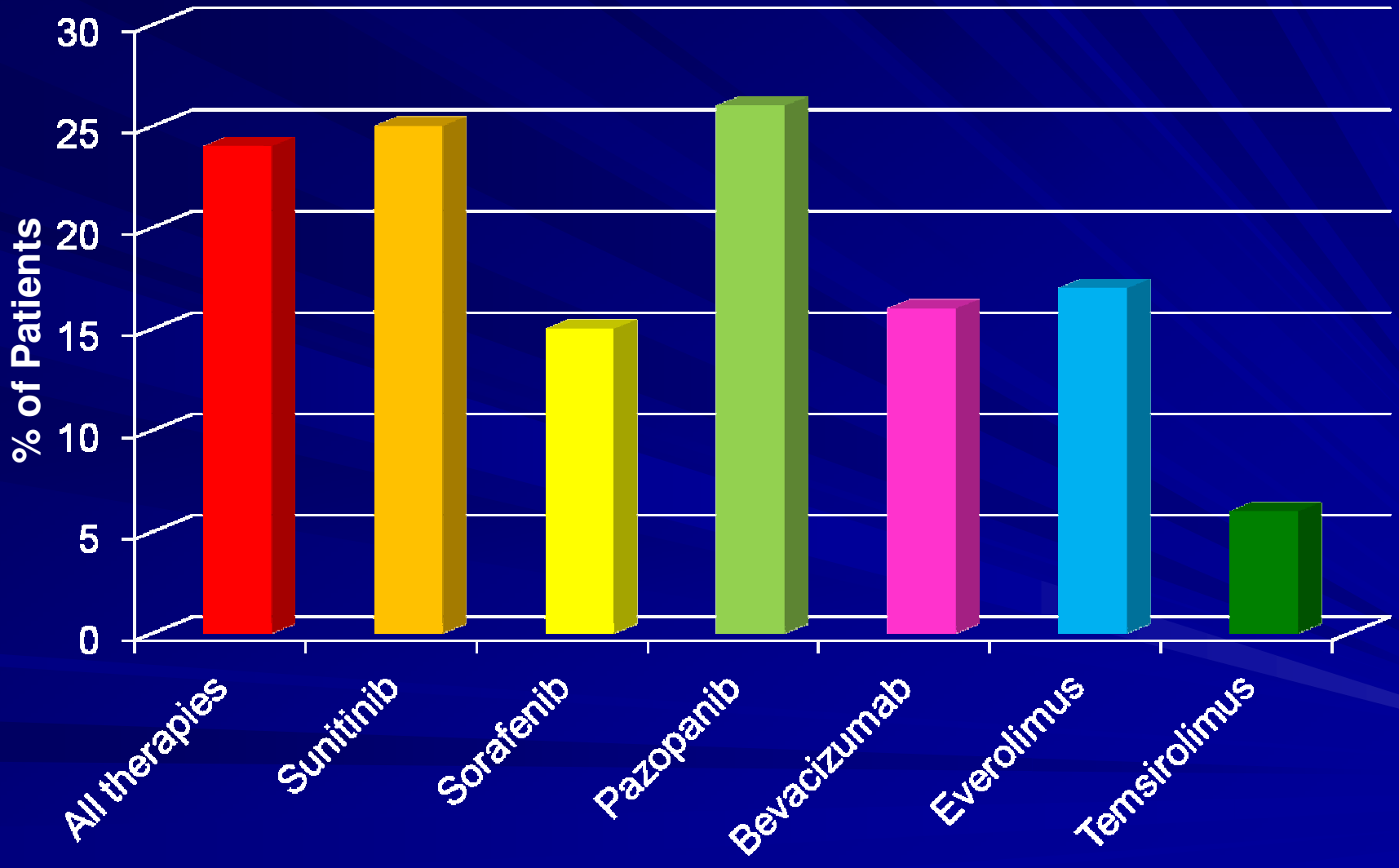
Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Non-Hypertension Toxicity



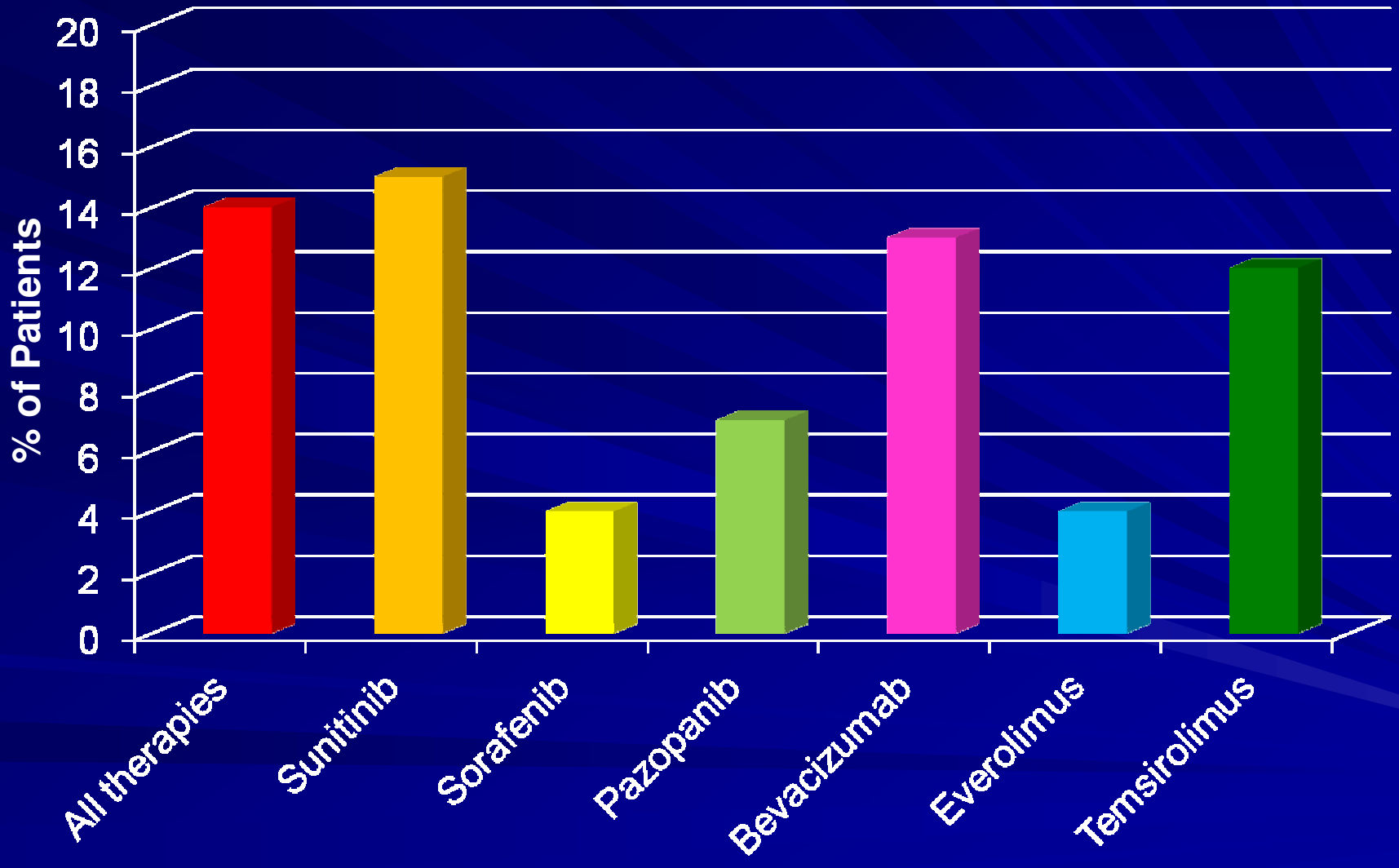
Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Elevated NT-pro-BNP



Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Decreased LVEF (Grade 2-4)



Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Hypertension

- Preexisting HTN: 47%
- Treatment with anti-hypertensive agents during therapy:
  - At least 1 agent: 85% of patients
  - At least 2 agents: 52% of patients

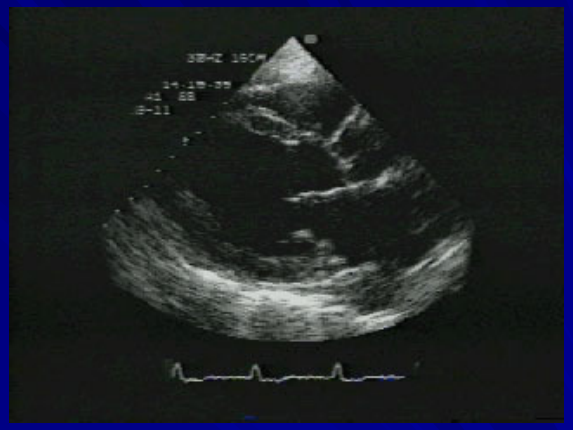
Table 4 Cardiac Medications Before/During Cancer Therapy

	Beta-blockers	ACEI/ARB	CCB	Diuretics
Pre-treatment	22%	26%	14%	19%
Initiation or dose increase with treatment	24%	25%	47%	14%

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Outcomes of Those with LVEF Drops

- 23 patients with LVEF drops
  - 19 received standard HF therapy with BB & ACE-I or ARB
    - Improved LVEF: 9 patients
    - No change in LVEF: 6 patients
    - No further LVEF assessments: 4 patients
  - 4 did not receive standard HF therapy
    - 2 improved LVEF with cessation of cancer therapy alone
    - 2 had no further LVEF assessments due to entering hospice for end-stage malignancy



Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Proposed Screening Algorithm

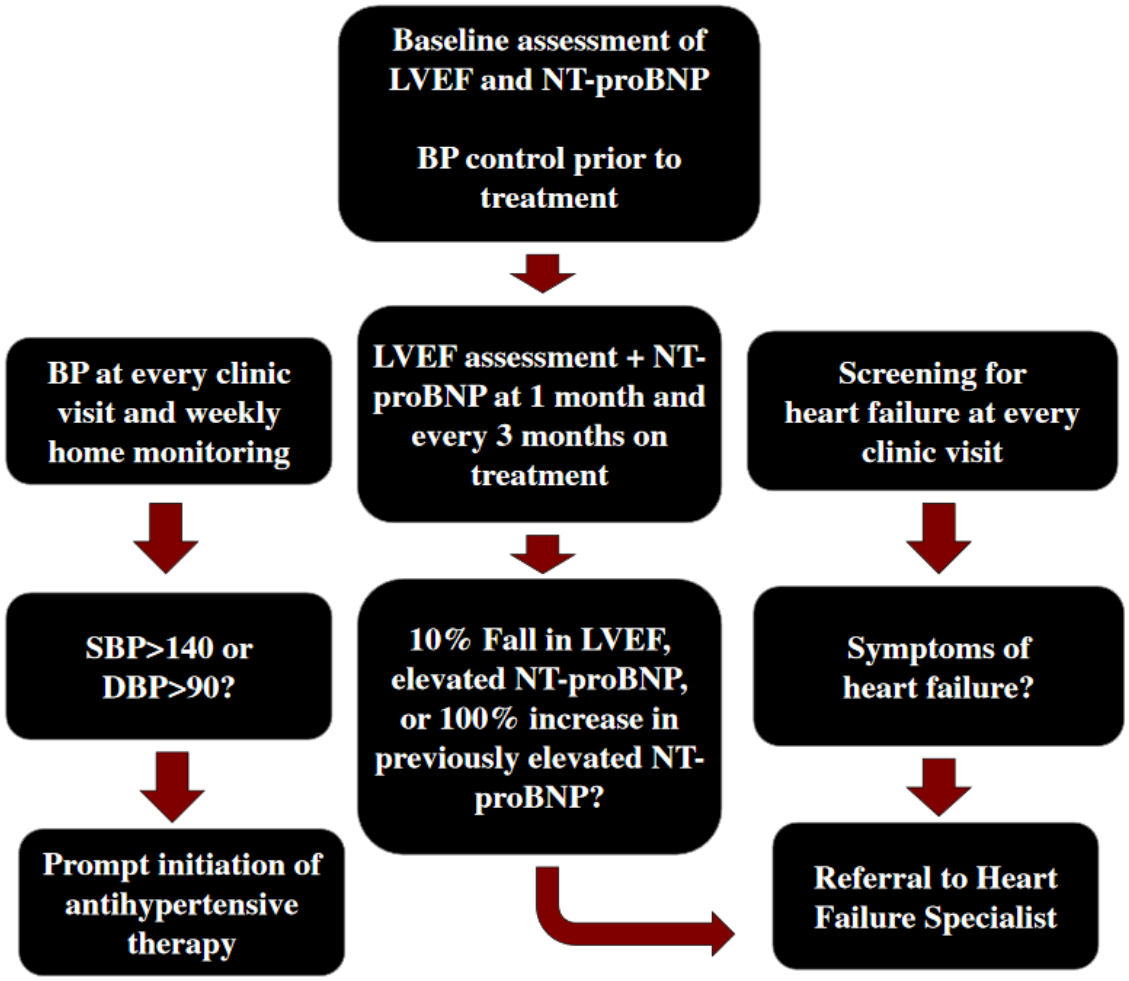


Figure 2 The Stanford Monitoring Algorithm for Targeted Therapies

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.

Pazopanib vs. Sunitinib

- Trial of 1110 patients published in NEJM 2013
- Front-line therapy for RCC
- TTE or MUGA obtained every 3 cycles
  - "Cardiac dysfunction" = 13% Pazopanib, 11% Sunitinib

Supplementary Table S7. Summary of Patients With On-Therapy Left Ventricular Ejection Fraction Dysfunction Symptoms of Cardiac Dysfunction (Safety Population)

		Patients, n (%)	
		Pazopanib N = 554	Sunitinib N = 548
Patients meeting one or more cardiac dysfunction criteria		47 (13)	42 (11)
Criterion 1.	Symptoms of cardiac dysfunction[a]	4 (1)	4 (1)
Criterion 2	≥15% absolute decline in LVEF compared to baseline[a]	32 (9)	34 (9)
Criterion 3	≥10% absolute decline in LVEF compared to baseline and below LLN[a]	24 (7)	20 (5)

Abbreviations: LLN, lower limit of normal range; LVEF, left ventricular ejection fraction.

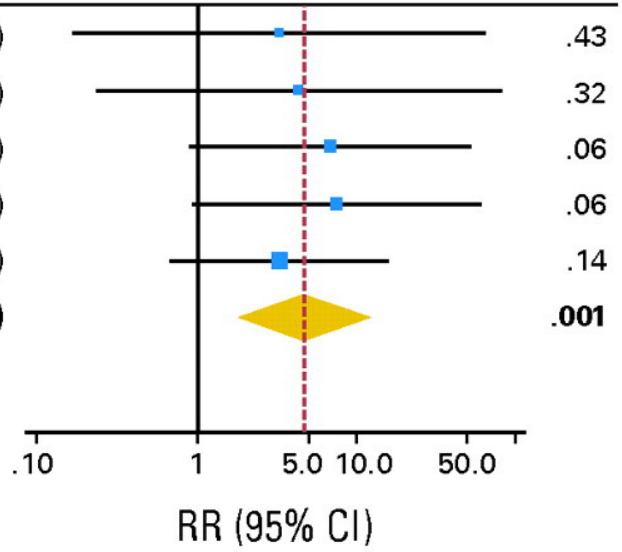
[a] Percentages are based on 362 pazopanib patients and 369 sunitinib patients with post-baseline LVEF assessment or symptoms of cardiac dysfunction.

Adapted from Motzer et al. N Engl J Med. 2013;369:722-731.

Bevacizumab: Relative Risk for Grade 3+ 'CHF' –

	No. of events/Total no. Bevacizumab	Control	RR (95% CI)	*P*
Miles et al, 2010	3/497	0/233	3.29 (0.17 to 63.42)	.43
Brufsky et al, 2009	4/458	0/221	4.35 (0.24 to 80.50)	.32
Robert et al, 2009	14/817	1/403	6.91 (0.91 to 52.33)	.06
Miller et al, 2007	8/365	1/346	7.58 (0.95 to 60.32)	.06
Miller et al, 2005	7/229	2/215	3.29 (0.69 to 15.64)	.14
Overall	**36/2,366**	**4/1,418**	**4.74 (1.84 to 12.19)**	**.001**

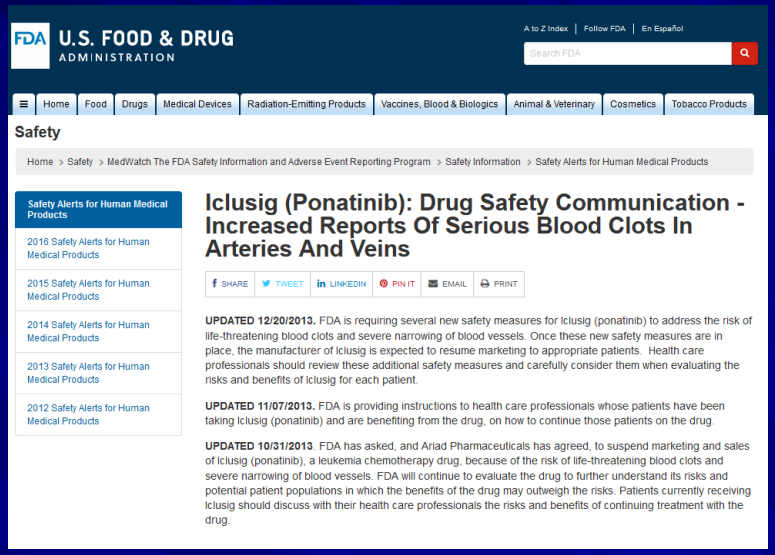
Test for heterogeneity: $Q = 0.60$; $P = .963$; $I^2 = 0\%$

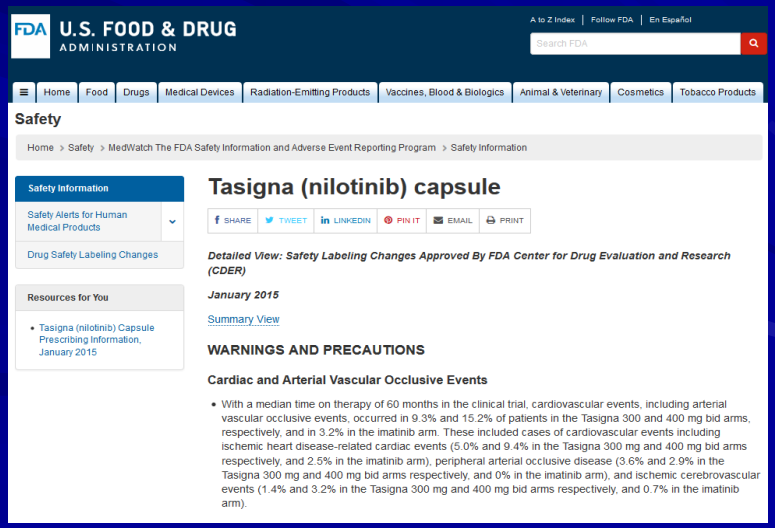


Adapted from Choueiri et al. J Clin Onc. 2011;29:632-8.

Other TKIs – More Trouble…

- Trastuzumab (its own talk…)
- 'Multitargeted' TKIs
  - Imatinib (largely case-report level)
  - Dasatinib: Pulmonary hypertension, pleural effusions
  - Nilotinib/ponatinib: Vascular thrombosis (High rates!)

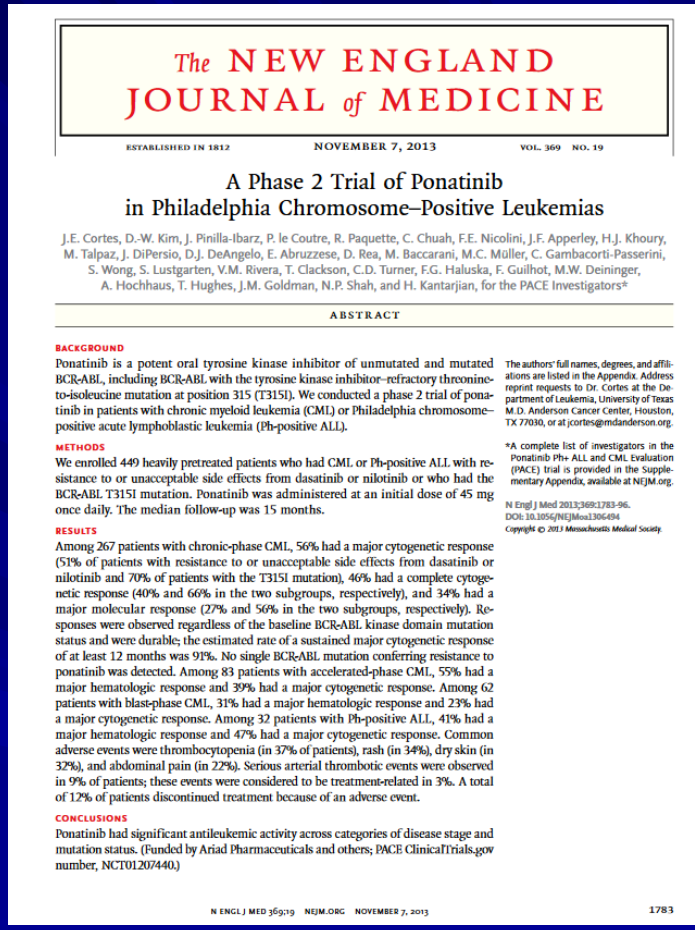




Adapted from http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm370971.htm and http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm218929.htm, Accessed January 3, 2017.

The Ponatinib Story…

- Ponatinib: Potent oral TKI
  - Active against BCR-ABL mutation including form resistant to other TKIs
- Phase 2 open-label trial of 449 CML/ALL patients x 15 months who had failed dasatinib/nilotinib
- Manuscript doesn't report specific cardiac monitoring other than usual CTCAE
- Per manuscript…
  - Cites arterial thrombotic events "possibly" treatment related = 4.5%
  - If ignore treatment relation → 15.6% (!)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 7, 2013 VOL. 369 NO. 19

A Phase 2 Trial of Ponatinib in Philadelphia Chromosome–Positive Leukemias

J.E. Cortes, D.-W. Kim, J. Pinilla-Ibarz, P. le Coutre, R. Paquette, C. Chuah, F.E. Nicolini, J.F. Apperley, H.J. Khoury, M. Talpaz, J. DiPersio, D.J. DeAngelo, E. Abruzzese, D. Rea, M. Baccarani, M.C. Müller, C. Gambacorti-Passerini, S. Wong, S. Lustgarten, V.M. Rivera, T. Clackson, C.D. Turner, F.G. Haluska, F. Guilhot, M.W. Deininger, A. Hochhaus, T. Hughes, J.M. Goldman, N.P. Shah, and H. Kantarjian, for the PACE Investigators*

ABSTRACT

BACKGROUND

Ponatinib is a potent oral tyrosine kinase inhibitor of unmutated and mutated BCR-ABL, including BCR-ABL with the tyrosine kinase inhibitor–refractory threonine-to-isoleucine mutation at position 315 (T315I). We conducted a phase 2 trial of ponatinib in patients with chronic myeloid leukemia (CML) or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph-positive ALL).

METHODS

We enrolled 449 heavily pretreated patients who had CML or Ph-positive ALL with resistance to or unacceptable side effects from dasatinib or nilotinib or who had the BCR-ABL T315I mutation. Ponatinib was administered at an initial dose of 45 mg once daily. The median follow-up was 15 months.

RESULTS

Among 267 patients with chronic-phase CML, 56% had a major cytogenetic response (51% of patients with resistance to or unacceptable side effects from dasatinib or nilotinib and 70% of patients with the T315I mutation), 46% had a complete cytogenetic response (40% and 66% in the two subgroups, respectively), and 34% had a major molecular response (27% and 56% in the two subgroups, respectively). Responses were observed regardless of the baseline BCR-ABL kinase domain mutation status and were durable; the estimated rate of a sustained major cytogenetic response of at least 12 months was 91%. No single BCR-ABL mutation conferring resistance to ponatinib was detected. Among 83 patients with accelerated-phase CML, 55% had a major hematologic response and 39% had a major cytogenetic response. Among 62 patients with blast-phase CML, 31% had a major hematologic response and 23% had a major cytogenetic response. Among 32 patients with Ph-positive ALL, 41% had a major hematologic response and 47% had a major cytogenetic response. Common adverse events were thrombocytopenia (in 37% of patients), rash (in 34%), dry skin (in 32%), and abdominal pain (in 22%). Serious arterial thrombotic events were observed in 9% of patients; these events were considered to be treatment-related in 3%. A total of 12% of patients discontinued treatment because of an adverse event.

CONCLUSIONS

Ponatinib had significant antileukemic activity across categories of disease stage and mutation status. (Funded by Ariad Pharmaceuticals and others; PACE ClinicalTrials.gov number, NCT01207440.)

The authors' full names, degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Cortes at the Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, or at jcortes@mdanderson.org.

*A complete list of investigators in the Ponatinib Ph+ ALL and CML Evaluation (PACE) trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2013;369:1783-96.
DOI: 10.1056/NEJMoa1306494

Adapted from Cortes et al, New Engl J Med. 2013; 369:1783-1796

Later Analysis… Uh-Oh

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ICLUSIG safely and effectively. See full prescribing information for ICLUSIG.

ICLUSIG® (ponatinib) tablets for oral use
Initial U.S. Approval: 2012

WARNING: ARTERIAL THROMBOSIS and HEPATOTOXICITY

See full prescribing information for complete boxed warning

Arterial Thrombosis:

- **Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke have occurred in Iclusig-treated patients. In clinical trials, serious arterial thrombosis occurred in 8% of Iclusig-treated patients. Interrupt and consider discontinuation of Iclusig in patients who develop arterial thrombotic events *(2.3) (5.1)*.**

2012 – FDA Approval

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ICLUSIG safely and effectively. See full prescribing information for ICLUSIG.

ICLUSIG® (ponatinib) tablets for oral use
Initial U.S. Approval: 2012

WARNING: ARTERIAL OCCLUSION, VENOUS THROMBOEMBOLISM, HEART FAILURE, and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

- **Arterial occlusion has occurred in at least 35% of Iclusig-treated patients including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Interrupt or stop Iclusig immediately for arterial occlusion. A benefit-risk consideration should guide a decision to restart Iclusig (5.1).**
- **Venous thromboembolism has occurred in 6% of Iclusig-treated patients. Monitor for evidence of thromboembolism. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism (5.2).**
- **Heart failure, including fatalities, occurred in 9% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure (5.3).**
- **Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected (2.3, 5.4).**

After Subsequent Analysis…

Adapted from http://www.iclusig.com/PI and http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203469lbl.pdf. Accessed January 3, 2017.

Proteasome Inhibitors – Another Case Example

The Carfilzomib Story – Instructive

- Proteasome inhibitors: Disrupts ubiquitin-proteasome pathway → cellular apoptosis
- Ubiquitin-proteasome system: Involved in normal cardiomyocyte function → theoretical risk for cardiotoxicity from proteasome inhibition
- Bortezomib/Carfilzomib: Proteasome inhibitors, approved for treatment of myleoma
  - Carfilzomib: Irreversibly binds to proteasome → sustained effect
- Cardiac events in this population: Causality can be difficult to determine (particularly if no control!)
  - Symptoms/events can be due to:
    - Treatment toxicity
    - Non-cardiac symptoms (e.g. fatigue/dyspnea)
    - Bone-marrow shunting/high-output heart failure
    - Fluid-retention due to IVF and/or steroids
    - Amyloidosis (often unrecognized)

Bortezomib Data

- Original trial in NEJM (2005)
  - Bortezomib vs. High-dose dexamethasone
  - No prospective cardiac monitoring reported
- Out of 663 patients randomized/received drug…
  - Cardiac deaths possibly related to study drug:
    - Bortezomb: 3
    - Dexamethasone: 1 (sudden death)
  - "The incidence of cardiac disorders during treatment with bortezomib and dexamethasone was 15% and 13%, respectively… 7 patients receiving bortezomib (2%) and 8 receiving dexamethasone (2%) had CHF during the study."
- Adverse event table only lists adverse events reported by ≥ 15% (!) of patients

Table 3. Adverse Events during Treatment Reported by 15 Percent or More of Patients Receiving Bortezomib or Dexamethasone, Including Grade 3 and Grade 4 Events.

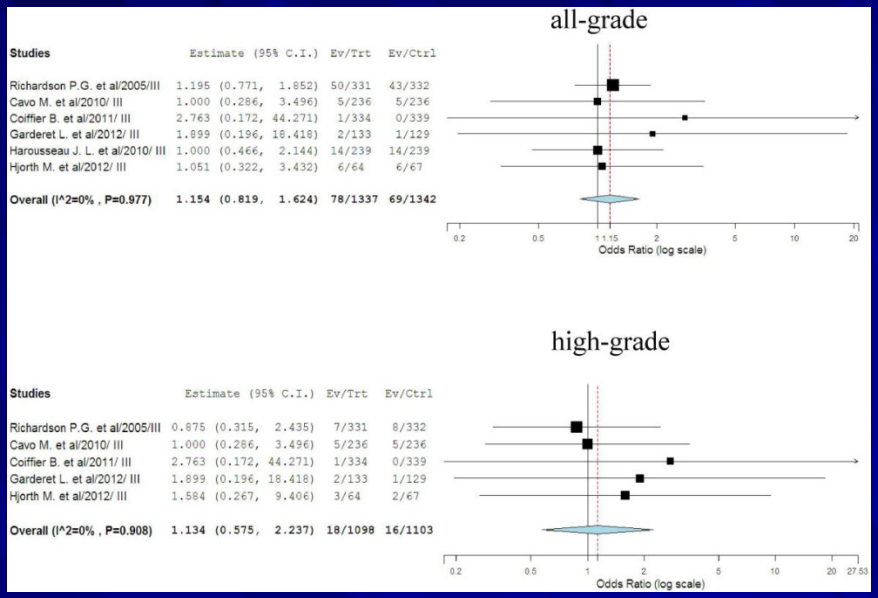
Event	Bortezomib (N=331)			Dexamethasone (N=332)		
	All Adverse Events	Grade 3 Events	Grade 4 Events*	All Adverse Events	Grade 3 Events	Grade 4 Events†
	number (percent)					
≥1 Event	331 (100)	203 (61)	45 (14)	327 (98)‡	146 (44)‡	52 (16)
Diarrhea	190 (57)	24 (7)	0	69 (21)‡	6 (2)‡	0
Nausea	190 (57)	8 (2)	0	46 (14)‡	0‡	0
Fatigue	140 (42)	17 (5)	1 (<1)	106 (32)‡	12 (4)	0
Constipation	140 (42)	7 (2)	0	49 (15)‡	4 (1)	0
Peripheral neuropathy	120 (36)	24 (7)	2 (1)	29 (9)‡	1 (<1)‡	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)‡	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)‡	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)‡	18 (5)‡	4 (1)§
Anemia	87 (26)	31 (9)	2 (1)	74 (22)	32 (10)	3 (1)
Headache	85 (26)	3 (1)	0	43 (13)‡	2 (1)	0
Anorexia	75 (23)	9 (3)	0	14 (4)‡	1 (<1)§	0
Cough	70 (21)	2 (1)	0	35 (11)‡	1 (<1)	0
Paresthesia	68 (21)	5 (2)	0	27 (8)‡	0§	0
Dyspnea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)‡	4 (1)‡	0‡
Rash	61 (18)	4 (1)	0	20 (6)‡	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)‡	5 (2)	0
Abdominal pain	53 (16)	6 (2)	0	12 (4)‡	1 (<1)	0
Bone pain	52 (16)	12 (4)	0	50 (15)	9 (3)	0
Pain in limb	50 (15)	5 (2)	0	24 (7)‡	2 (1)	0
Muscle cramps	41 (12)	0	0	50 (15)	3 (1)	0

Adapted from Richardson et al. New Engl J Med. 2005;352:2487-2498.

Bortezomib Meta-Analysis

- 2014 Meta-Analysis of 25 clinical trials with 5718 patients
- Included prospective Phase 2/3 trials which reported incidence of cardiotoxicity
  - Included LVEF decline, “CHF”, cardiomyopathy, cardiac arrest, and cardiac arrhythmia
- Overall incidence: 3.8%
  - High-grade toxicity: 2.3%
- Not significantly increased vs. control groups

- My (admittedly anecdotal) take: Bortezomib cardiotoxicity is not a significant clinical problem



Adapted from Xiao et al. PLoS One. 2014;9:e87671.

2012: Carfilzomib Signals?

- June 2012: FDA publishes briefing document for Oncologic Drugs Advisory Committee (ODAC)
- Points out there were 9 deaths due to cardiac issues during Phase 2 trials involving 526 myeloma patients
  - 23% experienced cardiac side-effects of any degree of severity, including CHF, cardiac arrest, or arrhythmia
  - Onyx pharmaceuticals only cited 4 deaths; FDA identified 5 more
- Notes it is “very concerned” about “severe toxicities, including deaths” observed w/carfilzomib use
- July 20, 2012: Carfilzomib approved
  - Original approval based on 266 patient Phase-2 study of patients who had relapsed myeloma after receiving bortezomib-based & thalidomide-based regimens

Wording on FDA Label

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia

Death due to cardiac arrest has occurred within a day of KYPROLIS administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of KYPROLIS. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Withhold KYPROLIS for Grade 3 or 4 cardiac events until recovery and consider whether to restart KYPROLIS based on a benefit/risk assessment [see *Dosage and Administration (2.4)*]. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.

Adapted from http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf, accessed December 30, 2016.

Analysis of 526 Patients in Phase 2 Carfilzomib Studies

- Dose-reduction due to cardiac AE: 6 patients (1.1%)
- Treatment discontinuation due to cardiac AE: 23 patients (4.4%)
  - CHF (1.5%)
  - Cardiac arrest (1.0%)
  - Myocardial ischemia (0.6%)
- AE occurring within 1 day of dosing: 62 patients (11.8%)
- No control arms so unclear causality vs. disease itself
- Notes that per sponsor, 5 cardiac AE deaths, 3 patients died from disease progression but with associated cardiac component – all felt "possibly related to carfilzomib"

Grouped adverse event, n, (%)	Any AE	≥Grade3	SAE
Any cardiac	116 (22.1)	50 (9.5)	41 (7.8)
Cardiac arrhythmia	70 (13.3)	12 (2.3)	11(2.1)
Cardiac failure	38 (7.2)	30 (5.7)	26 (4.9)
Ischemic heart disease	18 (3.4)	7 (1.3)	5 (1.0)
Cardiomyopathy	9 (1.7)	3 (0.6)	2 (0.4)

Adapted from Siegel et al. Haematologica. 2013;98:1753-1761.

ASPIRE Study

- Carfilzomib/lenalidomide/dexamethasone vs. lenalidomide/dexamethasone for relapsed myeloma
  - 792 patients, randomly assigned
  - 24-month survival: 73.3 vs. 65.0% (favoring carfilzomib)
- Adverse events (all grades/grade 3 or higher):
  - Dyspnea: 19.4%/2.8% vs. 14.9%/1.8%
  - Cardiac failure: 6.4%/3.8% vs. 4.1%/1.8%
- "Cardiac failure" included (in decreasing order of frequency): Cardiac failure, congestive cardiac failure, pulmonary edema, hepatic congestion, cardiopulmonary failure, acute pulmonary edema, acute cardiac failure, and right ventricular failure.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

A. Keith Stewart, M.B., Ch.B., S. Vincent Rajkumar, M.D., Meletios A. Dimopoulos, M.D., Tamás Masszi, M.D., Ph.D., Ivan Špička, M.D., Ph.D., Albert Oriol, M.D., Roman Hájek, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., David S. Siegel, M.D., Ph.D., Georgi G. Mihaylov, M.D., Ph.D., Vesselina Goranova-Marinova, M.D., Ph.D., Péter Rajnics, M.D., Ph.D., Aleksandr Suvorov, M.D., Ruben Niesvizky, M.D., Andrzej J. Jakubowiak, M.D., Ph.D., Jesus F. San-Miguel, M.D., Ph.D., Heinz Ludwig, M.D., Michael Wang, M.D., Vladimír Maisnar, M.D., Ph.D., Jiri Minarik, M.D., Ph.D., William I. Bensinger, M.D., Maria-Victoria Mateos, M.D., Ph.D., Dina Ben-Yehuda, M.D., Vishal Kukreti, M.D., Naseem Zojwalla, M.D., Margaret E. Tonda, Pharm.D., Xinqun Yang, Ph.D., Biao Xing, Ph.D., Philippe Moreau, M.D., and Antonio Palumbo, M.D., for the ASPIRE Investigators*

ABSTRACT

BACKGROUND

Lenalidomide plus dexamethasone is a reference treatment for relapsed multiple myeloma. The combination of the proteasome inhibitor carfilzomib with lenalidomide and dexamethasone has shown efficacy in a phase 1 and 2 study in relapsed multiple myeloma.

METHODS

We randomly assigned 792 patients with relapsed multiple myeloma to carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group). The primary end point was progression-free survival.

RESULTS

Progression-free survival was significantly improved with carfilzomib (median, 26.3 months, vs. 17.6 months in the control group; hazard ratio for progression or death, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P=0.0001). The median overall survival was not reached in either group at the interim analysis. The Kaplan–Meier 24-month overall survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively (hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; P=0.04). The rates of overall response (partial response or better) were 87.1% and 66.7% in the carfilzomib and control groups, respectively (P<0.001; 31.8% and 9.3% of patients in the respective groups had a complete response or better; 14.1% and 4.3% had a stringent complete response). Adverse events of grade 3 or higher were reported in 83.7% and 80.7% of patients in the carfilzomib and control groups, respectively; 15.3% and 17.7% of patients discontinued treatment owing to adverse events. Patients in the carfilzomib group reported superior health-related quality of life.

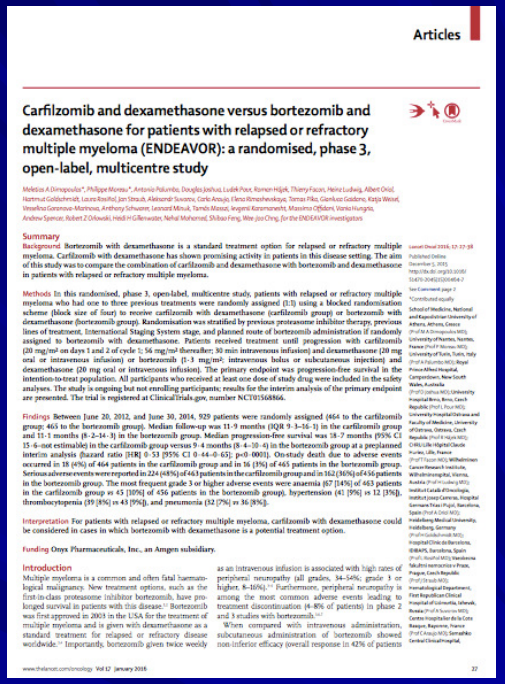
CONCLUSIONS

In patients with relapsed multiple myeloma, the addition of carfilzomib to lenalidomide and dexamethasone resulted in significantly improved progression-free survival at the interim analysis and had a favorable risk–benefit profile. (Funded by Onyx Pharmaceuticals; ClinicalTrials.gov number, NCT01080391.)

Adapted from Stewart et al. New Engl J Med. 2015;372:142-152.

ENDEAVOR Study

- ENDEAVOR Study:
  - Carfilzomib/dex vs. bortezomib/dex
  - 929 patients randomized, median f/u 12 months
  - Median progression-free survival: 18.7 months vs. 9.4 months (favoring carfilzomib)
  - SAE: 48% in carfilzomib group, 36% bortezomib
    - HTN: 9% vs. 3%
- Deaths:
  - Carfilzomib: 22 (5%) – 5 due to cardiac events
  - Bortezomib: 21 (5%) – 6 due to cardiac events
- Stopped due to dyspnea: 1 patient (carfilzomib), 5 patients (bortezomib)



Articles

Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study

Meletios A Dimopoulos*, Philippe Moreau*, Antonio Palumbo, Douglas Joshua, Ludek Pour, Ramon Hájek, Thierry Facon, Heinz Ludwig, Albert Oriol, Hartmut Goldschmidt, Laura Rosiñol, Jan Straub, Aleksandr Suvorov, Carla Araujo, Elena Rimashevskaya, Tomas Pika, Gianluca Gaidano, Katja Weisel, Vimalina Goranova-Marinova, Anthony Schwarer, Leonard Minuk, Tamás Masszi, Ievgenii Karamanenk, Massimo Offidani, Vania Hungria, Andrew Spencer, Robert Z Orlowski, Heidi H Gillenwater, Nehal Mohamed, Shibao Feng, Wee Joo Chng, for the ENDEAVOR investigators

Summary

Background Bortezomib with dexamethasone is a standard treatment option for relapsed or refractory multiple myeloma. Carfilzomib with dexamethasone has shown promising activity in patients in this disease setting. The aim of this study was to compare the combination of carfilzomib and dexamethasone with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma.

Methods In this randomised, phase 3, open-label, multicentre study, patients with relapsed or refractory multiple myeloma who had one to three previous treatments were randomly assigned (1:1) using a blocked randomisation scheme (block size of four) to receive carfilzomib with dexamethasone (carfilzomib group) or bortezomib with dexamethasone (bortezomib group). Randomisation was stratified by previous proteasome inhibitor therapy, previous lines of treatment, International Staging System stage, and planned route of bortezomib administration if randomly assigned to bortezomib with dexamethasone. Patients received treatment until progression with carfilzomib [20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² thereafter; 30 min intravenous infusion] and dexamethasone [20 mg oral or intravenous infusion) or bortezomib [1·3 mg/m²; intravenous bolus or subcutaneous injection] and dexamethasone [20 mg oral or intravenous infusion]. The primary endpoint was progression-free survival in the intention-to-treat population. All participants who received at least one dose of study drug were included in the safety analyses. The study is ongoing but not enrolling participants; results for the interim analysis of the primary endpoint are presented. The trial is registered at ClinicalTrials.gov, number NCT01568866.

Findings Between June 20, 2012, and June 30, 2014, 929 patients were randomly assigned (464 to the carfilzomib group; 465 to the bortezomib group). Median follow-up was 11·9 months (IQR 9·3–16·1) in the carfilzomib group and 11·1 months (8·2–14·3) in the bortezomib group. Median progression-free survival was 18·7 months (95% CI 15·6–not estimable) in the carfilzomib group versus 9·4 months (8·4–10·4) in the bortezomib group at a preplanned interim analysis (hazard ratio [HR] 0·53 [95% CI 0·44–0·65]; p<0·0001). Onstudy death due to adverse events occurred in 18 (4%) of 464 patients in the carfilzomib group and in 16 (3%) of 465 patients in the bortezomib group. Serious adverse events were reported in 224 (48%) of 463 patients in the carfilzomib group and in 162 (36%) of 456 patients in the bortezomib group. The most frequent grade 3 or higher adverse events were anaemia (67 [14%] of 463 patients in the carfilzomib group vs 45 [10%] of 456 patients in the bortezomib group), hypertension (41 [9%] vs 12 [3%]), thrombocytopenia (39 [8%] vs 43 [9%]), and pneumonia (32 [7%] vs 36 [8%]).

Interpretation For patients with relapsed or refractory multiple myeloma, carfilzomib with dexamethasone could be considered in cases in which bortezomib with dexamethasone is a potential treatment option.

Funding Onyx Pharmaceuticals, Inc., an Amgen subsidiary.

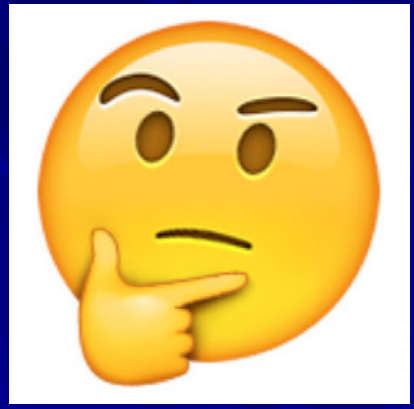
Introduction

Multiple myeloma is a common and often fatal haematological malignancy. New treatment options, such as the first-in-class proteasome inhibitor bortezomib, have prolonged survival in patients with this disease.[1] Bortezomib was first approved in 2003 in the USA for the treatment of multiple myeloma and is given with dexamethasone as a standard treatment for relapsed or refractory disease worldwide.[2] Importantly, bortezomib given twice weekly as an intravenous infusion is associated with high rates of peripheral neuropathy (all grades, 34–54%; grade 3 or higher, 8–16%).[3,4] Furthermore, peripheral neuropathy is among the most common adverse events leading to treatment discontinuation (4–8% of patients) in phase 2 and 3 studies with bortezomib.[3,4,5] When compared with intravenous administration, subcutaneous administration of bortezomib showed non-inferior efficacy (overall response in 42% of patients

Adapted from Dimopoulos et al. Lancet Oncol. 2016;17:28-38.

ENDEAVOR Study

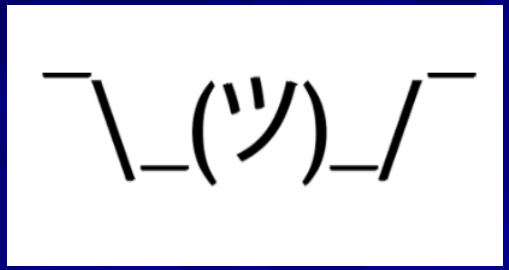
- Cardiac failure SAE ≥ Grade 3:
  - Carfilzomib: 8 subjects (1.7%)
  - Bortezomib: 3 subjects (0.7%)
- Atrial fibrillation SAE ≥ Grade 3:
  - Carfilzomib: 5 subjects (1.1%)
  - Bortezomib: 4 subjects (0.9%)
- Dyspnea SAE ≥ Grade 3:
  - Carfilzomib: 8 subjects (1.7%)
  - Bortezomib: 0 subjects (0%)
- Cardiac failure AE (any grade, not necessarily SAE):
  - Included in decreasing order of frequency, “cardiac failure, EF decreased, pulmonary edema, acute cardiac failure, congestive cardiac failure, acute pulmonary edema, RV failure, acute LV failure, chronic cardiac failure, cardiopulmonary failure, hepatogular reflex (!!!), and LV failure”
  - Carfilzomib: 38 subjects (8.2%)
  - Bortezomib: 13 subjects (2.9%)



Adapted from Dimopoulos et al. Lancet Oncol. 2016;17:28-38.

ENDEAVOR Echo Substudy

- Preplanned substudy of 151 patients:
  - TTE at baseline, every 3 months, and end of treatment, analyzed centrally
  - Endpoint: Significant LVEF reduction (≥10% reduction if started with LVEF≤55% or to <45% if started >55%) at 24 weeks from baseline
- Only one patient with LVEF reduction during 24 weeks (in bortezomib arm)
- Three more patients had LVEF reduction at any time during the study (2 carfilzomib, 1 bortezomib)



Adapted from Dimopoulos et al. Lancet Oncol. 2016;17:28-38.

Ibrutinib – Atrial Fibrillation

- Bruton tyrosine kinase (BTK) inhibitor in the B-cell receptor signaling pathway
- Effective in CLL, SLL, mantle cell lymphoma, Waldenstrom's macroglobulinemia
- Randomized trials → apparent increase in risk of atrial fibrillation
  - Possible mechanism: BTK-related kinases present in human heart, interact with PI3K-Akt pathway → important in stress response
  - Mice with less PI3K-Akt activity → much more AF
- 2016: Meta-analysis published of 20 manuscripts, including 4 randomized trials
- Relative risk in full meta-analysis (20 studies): 3.5
- Randomized trials → most important data, as those without control arm raise question of new diagnoses because of increased surveillance

Letters to *Blood* — blood

To the editor:

The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis

Darryl P. Leong,[1,2,*] François Caron,[1,*] Christopher Hillis,[3] Annie Duan,[1] Jeff S. Healey,[1,2] Graeme Fraser,[3] and Deborah Siegal[2]

[1]The Population Health Research Institute, [2]Department of Medicine, and [3]Department of Oncology, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase in the B-cell receptor signaling pathway. In randomized trials, ibrutinib is effective as first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) (compared with chlorambucil),[1] for relapsed/refractory CLL/SLL (compared with ofatumumab or combined with bendamustine/rituximab),[2,3] or for relapsed/refractory mantle cell lymphoma (compared with temsirolimus),[4] with promising results in the treatment of Waldenström macroglobulinemia.[5] It is anticipated that ibrutinib will become an important part of the therapeutic armamentarium for these conditions. Randomized trials suggest that ibrutinib may increase the risk of atrial fibrillation (AF) as compared with chlorambucil[1] or ofatumumab.[2] In the general population, AF is strongly associated with heart failure and arterial thromboembolism, which result in substantial morbidity and mortality. There is uncertainty over the magnitude of the increase in AF risk attributable to ibrutinib because the absolute numbers of incident AF cases are small in individual studies.

We undertook a systematic review and meta-analysis to (1) estimate the magnitude of the increase in AF risk among ibrutinib recipients, as compared with alternative therapies and (2) quantify the frequency of AF reported among ibrutinib recipients. We searched MEDLINE and EMBASE, and proceedings from the American Society of Hematology, the European Haematology Association, and the American Society of Clinical Oncology for articles describing AF rates in recipients of ibrutinib. The following search terms were used: ibrutinib; imbruvica; or PCI-32765. Animal studies, case reports, case series (ie, that reported on consecutive AF cases), cross-sectional studies, editorials, phase I/dose-finding studies, and conference abstracts more than 12 months old were excluded.

Two independent reviewers screened the articles' titles and abstracts for eligibility. Cases of disagreement were resolved by a third reviewer. Papers identified after title and abstract screening were obtained in full. When data from the same cohort of participants were presented in different papers, only the manuscript with the larger sample size was included in the meta-analysis. The following data were extracted from eligible full text manuscripts: design, disease, sample size, treatments, participant age and sex, follow-up duration, AF rates, and where reported, AF ascertainment strategies, past history of cardiovascular disease, AF, or hypertension.

Statistical analysis was performed using STATA 14 (StataCorp, College Station, TX). To evaluate the increase in the risk of incident AF, the primary meta-analytic approach was a fixed effects model using the Mantel-Haenszel method. A sensitivity analysis was performed using a DerSimonian and Laird random effects model. Heterogeneity of studies was evaluated by Cochran's Q and the I^2 statistic. Pooled AF rates were estimated as follows: we multiplied the median follow-up duration by the sample size. Crude study-specific AF rates were then calculated by dividing the number of incident AF cases by the total number of person-months follow-up. AF rates were then pooled using the "metaprop" command in STATA, which computes the pooled estimates after the Freeman-Tukey double arcsine transformation to stabilize the variances.

The search strategy yielded 1871 unique abstracts. Thirty-nine full text manuscripts and 44 conference abstracts were reviewed. Of these 83 papers, 63 were excluded because they lacked data on the occurrence of AF (n = 45), did not study ibrutinib (n = 2), were dose-finding studies (n = 1) or case series (n = 1), or included data that were presented in another included manuscript (n = 14). Thus, 20 manuscripts, reporting on the occurrence of AF in individuals treated with ibrutinib, contributed to the meta-analysis (Table 1).[6-25] Four of these studies were randomized controlled trials, 10 phase II studies, one prospective cohort study, and 5 retrospective cohort studies. In total, 14 studies included CLL/SLL patients; 5 studies included mantle cell lymphoma patients; 2 studies included Waldenström macroglobulinemia patients, and one study included follicular lymphoma patients.

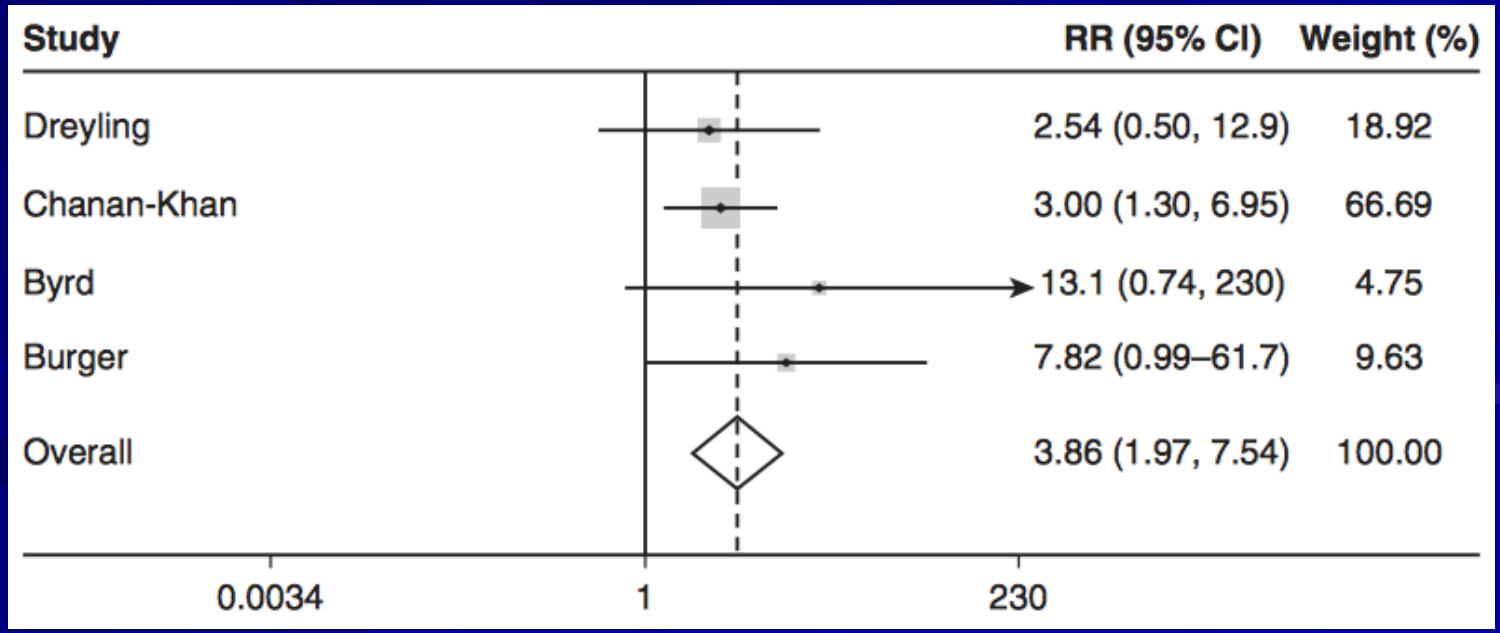
Among the 4 randomized trials of ibrutinib, the pooled relative risk (95% confidence interval, CI) of AF associated with ibrutinib as compared with the comparator was 3.9 (2.0-7.5, $P < .0001$) according to the fixed effects model (Figure 1). By the random effects model, the pooled relative risk (95% CI) of AF in ibrutinib recipients was 3.5 (1.8-6.9, $P < .0001$). The I^2 statistic for heterogeneity was 0%, and the heterogeneity χ^2 was 1.74 ($P = .6$), suggesting homogeneity of results among the randomized trials. Over median follow-ups of up to 26 months, the pooled rate (95% CI) of AF among ibrutinib recipients among all 20 studies cited was 3.3 (2.5-4.1) per 100 person-years. The pooled rate (95% CI) of AF among participants receiving the nonibrutinib therapy in the 4 randomized trials included was 0.84 (0.32-1.6) per 100 person-years.

This analysis suggests that ibrutinib consistently increases the risk of incident AF compared with alternative therapies. The incidence rates of AF observed in the general adult population have been previously described. Among 7983 community-dwelling adults aged 60-64 years screened by electrocardiogram twice during a mean 6.9 years, the incidence (95% CI) of AF was 0.55 (0.42-0.71) per 100 person-years.[26] In the Framingham study, AF incidence was measured by annual questionnaires, by annual electrocardiograms, and from hospital records. The incidence of AF among men aged 65-74 years was 1.8 per 100 person-years, and among women aged 65-74 years was 1.0 per 100 person-years.[27] Thus the rate of AF among ibrutinib recipients is substantially higher than the incidence rate observed among the general population. The mechanism(s) by which ibrutinib may promote AF are unknown. Although Bruton tyrosine kinase and tec protein kinases, which are inhibited by ibrutinib, are expressed in cardiac tissue,[24,25] further research is needed to elucidate specific molecular pathways.

Adapted from Leong et al. Blood. 2016;128:138-140.

Ibrutinib – Atrial Fibrillation

- Total AF among 759 ibrutinib patients & 759 control (placebo or other chemotherapy) patients:
  - Ibrutinib: 40 patients (5.3%)
  - Control: 10 patients (1.3%)
- Note: Real rates likely higher because:
  - Regular rhythm monitoring ***not*** built into trials
  - Highest risk patients may have been excluded



Adapted from Leong et al. Blood. 2016;128:138-140.

Checkpoint Inhibitors

- Major recent advance in cancer therapies → enormous development
- Basic mechanism: Unleash 'checkpoints' on the immune system → attack tumors
  - Prototypes:
    - Anti-CTLA-4 antibody (e.g.ipilimumab),
    - Anti-programmed death-1 (PD-1) antibody (e.g. nivolumab, pembrolizumab)
  - Problem: Toxicity from unleashed immune action on normal tissues → GI, skin, endocrine, hepatic, pulmonary toxicity
- Obvious next question...
  - Could they cause myocarditis?
- Answer:
  - Yes, and it can be very bad/fatal
  - Fortunately, seems fairly uncommon…
- In clinical trials, no routine testing for myocarditis by biochemical analysis or cardiac imaging...

NEJM Report

- Reported on 2 fatal cases of patients treated with nivolumab/ipilimumab who developed fulminant myocarditis clinical picture
  - Both with severe electrical instability
- Postmortem autopsies & sequencing of cell types in myocardial infiltrates
- Findings:
  - Both with T-cell & macrophage infiltrates
  - Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors & skeletal muscles
  - PDL-1 highly expressed on myocardial tissue
- Interrogated Bristol-Meyers Squibb corporate safety databases
  - 18/20594 patients (0.09%) with drug-related SAEs of myocarditis were reported
  - More common with combination Rx than with nivolumab alone (0.27% vs. 0.06%)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Douglas B. Johnson, M.D., Justin M. Balko, Pharm.D., Ph.D., Margaret L. Compton, M.D., Spyridon Chalkias, M.D., Joshua Gorham, B.A., Yaomin Xu, Ph.D., Mellissa Hicks, Ph.D., Igor Puzanov, M.D., Matthew R. Alexander, M.D., Ph.D., Tyler L. Bloomer, M.D., Jason R. Becker, M.D., David A. Slosky, M.D., Elizabeth J. Phillips, M.D., Mark A. Pilkinton, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D., Gregory Plautz, M.D., Daniel S. Reshef, M.D., M.P.H., Ph.D., Jonathan S. Deutsch, M.D., Raquel P. Deering, Ph.D., Benjamin A. Olenchock, M.D., Ph.D., Andrew H. Lichtman, M.D., Dan M. Roden, M.D., Christine E. Seidman, M.D., Igor J. Koralnik, M.D., Jonathan G. Seidman, Ph.D., Robert D. Hoffman, M.D., Ph.D., Janis M. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D., Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.

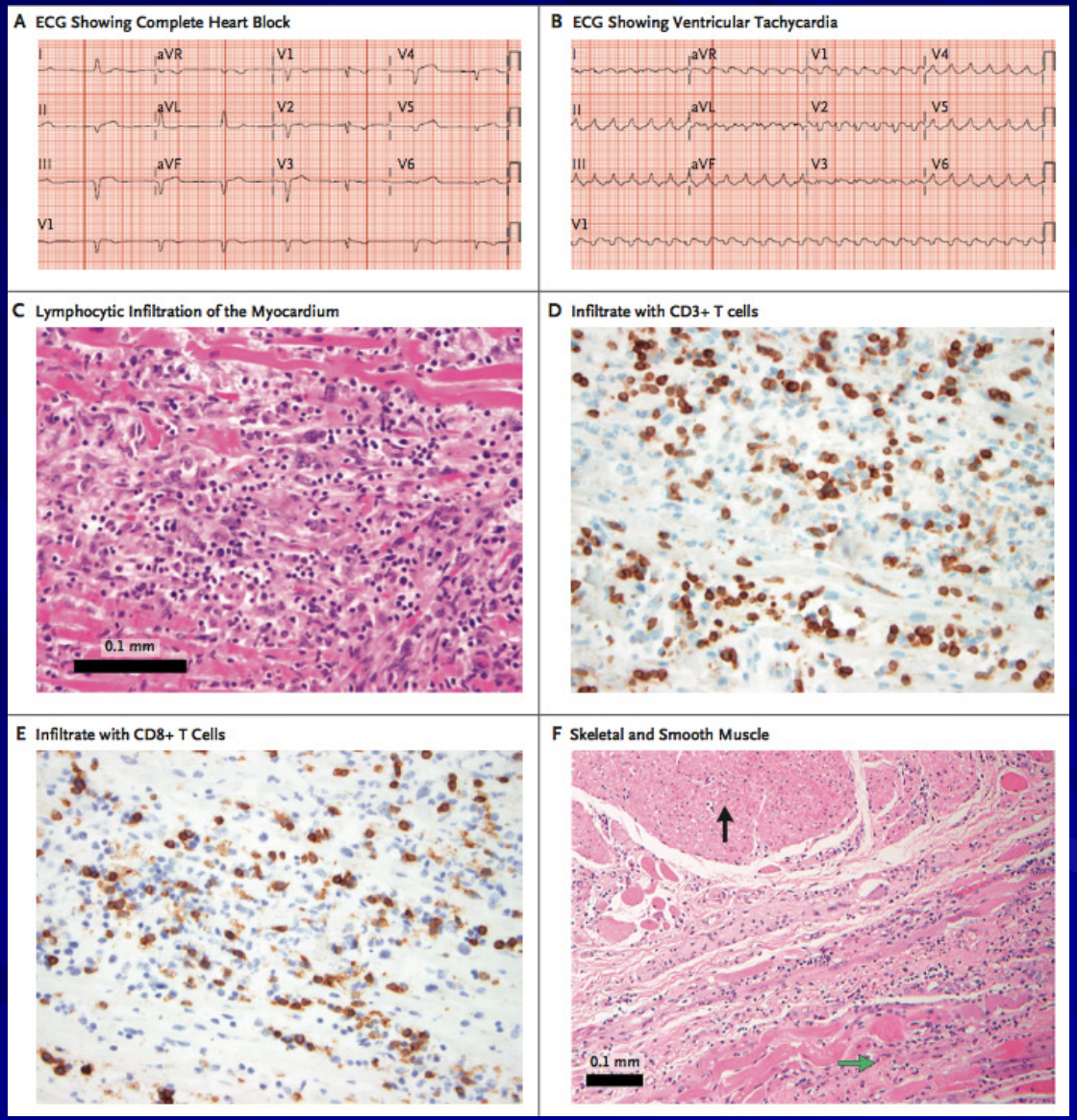
SUMMARY

Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high-grade, immune-related adverse events can occur, particularly with combination immunotherapy. We report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T-cell and macrophage infiltrates. Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T-cell–driven drug reaction. (Funded by Vanderbilt–Ingram Cancer Center Ambassadors and others.)

IMMUNE CHECKPOINT INHIBITORS HAVE TRANSFORMED THE TREATMENT of several cancers by releasing restrained antitumor immune responses.[1] Ipilimumab, an anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) antibody, and nivolumab, an anti–programmed death-1 (PD-1) antibody, have individually improved survival in patients with melanoma, and early results suggest that their combination further enhances antitumor activity and survival.[2-5] Other adverse events associated with these agents include dermatitis, endocrinopathies, colitis, hepatitis, and pneumonitis, which are all thought to arise from aberrant activation of autoreactive T cells.[6,7] These toxic effects are more frequent and severe when ipilimumab and nivolumab are used in combination.[4] Here, we report two cases of lethal myocarditis accompanied by myositis in patients treated with a combination of nivolumab and ipilimumab.

Adapted from Johnson et al. New Engl J Med. 2016;375:1749-1755.

NEJM Report



Adapted from Johnson et al. New Engl J Med. 2016;375:1749-1755.

Dizzying Array of Toxicities – Need for Cardio-Oncology Specialists!

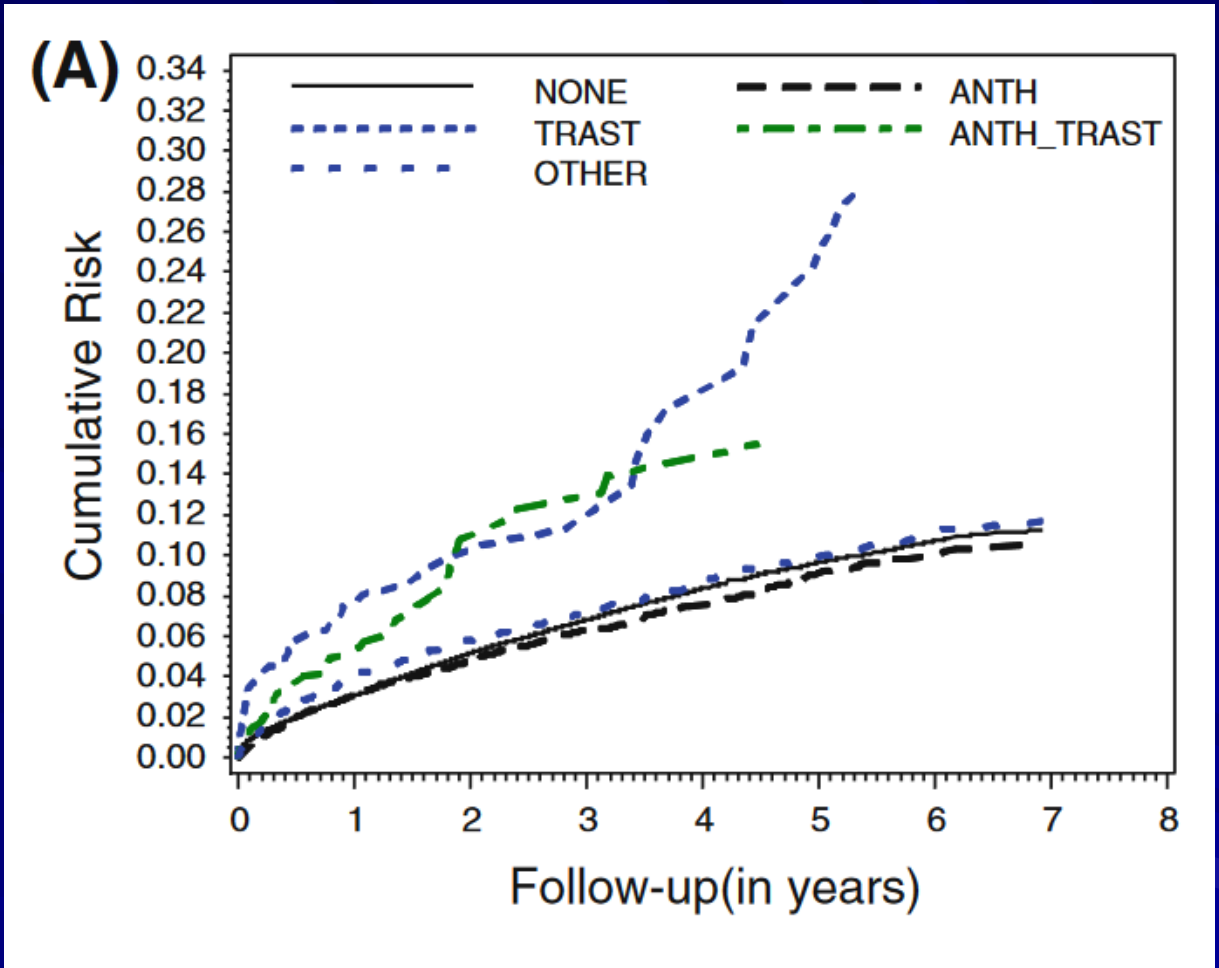
Table 1. Incidence of Cardiotoxicity in Selected Chemotherapeutic Agents[2,4,5,9,11,13–31]

Class/Drug	Selected Indication	HF	Hypertension	Myocardial Ischemia	Thromboembolism
Anthracyclines					
Doxorubicin	Breast, lymphoma	Very common	…	…	…
Daunorubicin	Leukemia	Very common	…	…	…
Epirubicin	Breast, gastric	Very common	…	…	…
Idarubicin	Leukemia	Very common	…	…	…
Mitoxantrone	Leukemia	Common	Rare	Rare	…
Alkylating agents					
Cyclophosphamide	Hematologic	…	…	…	Very rare
Cisplatin	Bladder, lung, ovarian	…	…	…	Common
Ifosfamide	Cervical, sarcoma	Very common	…	…	Very rare
Antimicrotubule agents					
Paclitaxel	Breast, lung	Very rare	…	Rare	…
Docetaxel	Breast, lung	Rare	Rare	Rare	…
Antimetabolites					
5-Fluorouracil	Gastrointestinal	Very rare	…	Very common	…
Capecitabine	Colorectal, breast	…	…	Common	Rare
Hormone therapies					
Tamoxifen	Breast	…	Very common	Very rare	Rare
Anastrozole	Breast	…	Very common	Rare	Rare
Monoclonal antibody–based targeted therapies					
Trastuzumab	Breast, gastric	Very common	Rare	…	Very rare
Bevacizumab	Colorectal	Common	Very common	Rare	Very common
Small molecule–targeted therapies					
Imatinib	Leukemia, GIST	Rare	…	Rare	Very rare
Dasatinib	Leukemia, GIST	Rare	Rare	Rare	Rare
Sorafenib	RCC, HCC	Common	Very common	Rare	Rare
Sunitinib	GIST, RCC	Very common	Very common	Rare	Very common
Lapatinib	Breast	Rare	…	…	…
Nilotinib	Leukemia	Rare	Rare	Very common	Very common
Ponatinib	Leukemia	Rare	Rare	Very common	Very common
Bortezomib	Multiple myeloma	Rare	Very rare	Very rare	Very rare
Other					
Everolimus	RCC	Common	Very common	…	Very rare
Temsirolimus	RCC	Common	Very common	very common	Rare
Thalidomide	Multiple myeloma	Rare	Rare	Common	Very common
Lenalidomide	Multiple myeloma	Rare	Rare	Common	Very common

GIST indicates gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HF, heart failure; RCC, renal cell carcinoma; …, not well-established complication or unknown; very rare, <1%; rare, 1% to 5%; common, 6% to 10%; and very common, >10%.

Adapted from Witteles et al. Circulation. 2015;132:1835-1845.

Remember: Real World ≠ Clinical Trials



Incidence of CHF in 47,806 real-world breast cancer patients from SEER database

Adapted from Du et al. Med Oncol. 2011;28:S80-S90.

Conclusions: My Take on the 'New Agents'

- For most new therapies, true risk of cardiac toxicity is hard to know
  - Lack of routine monitoring
  - Confusing/misleading adverse event reporting
  - Lack of data transparency
- Risks of overstating & understating event rates
- My best assessment as of now:
  - TKIs (Sunitinib, Sorafenib, etc.):
    - Hypertension risk = Certain/common
    - Cardiomyopathy risk = Present/less common – likely varies based on breadth of "kinome" inhibition
  - Ponatinib/Nilotinib – Thrombosis!
  - Proteasome inhibitors (Bortezomib, Carfilzomib)
    - Bortezomib toxicity: Not clear it even exists
    - Carfilzomib toxicity: Probably exists, ? Risk overestimated
  - BTK inhibitors (Ibrutinib)
    - Atrial fibrillation risk: Very real, fairly common
  - Checkpoint inhibitors
    - Clearly exists, but not common
    - When it occurs – at least without prospective screening – it appears to be often severe/life-threatening

Final Thoughts: Be Careful!

"Data is like garbage. You better know what you are going to do with it before you collect it."

-Mark Twain