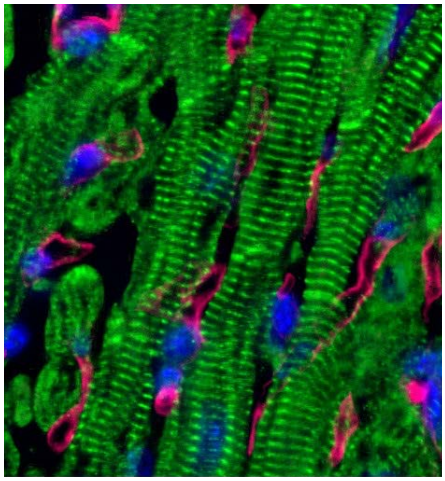
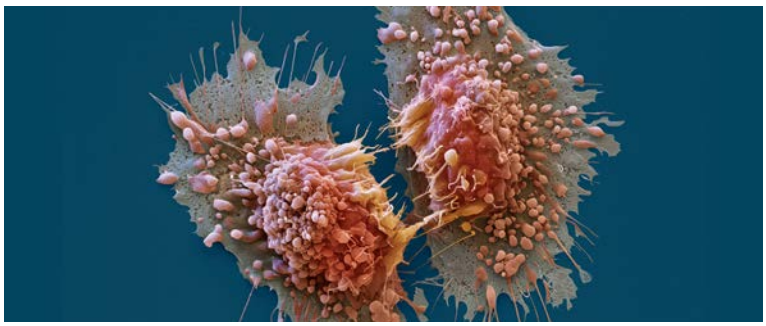




Cardiovascular toxicity of targeted cancer therapies: Clinical considerations and potential mechanism

Brian Jensen MD
Associate Professor of Medicine and Pharmacology
UNC School of Medicine

Fundamental question at hand:

Why are some targeted cancer therapies associated with cardiotoxicity ?

Examples to consider:

1. Trastuzumab/HER2 antagonists
2. Kinase inhibitors
3. Immune checkpoint inhibitors

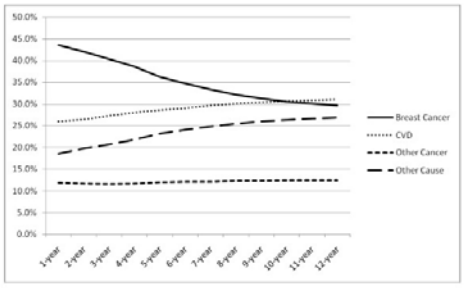
What is cardio-oncology?

What: A growing multidisciplinary field concerned with understanding and managing heart disease in patients who have been or soon will be treated for cancer.

Who: Cardiologists, medical oncology providers, surgical oncology providers, radiation oncology providers…

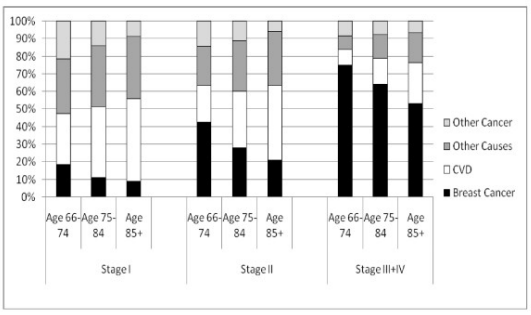
Why cardio-oncology?

Cancer patients die from cardiovascular disease



Cause of death
CV disease 15.9%
Breast cancer 15.1%

Higher stage at diagnosis increased likelihood of death from breast cancer

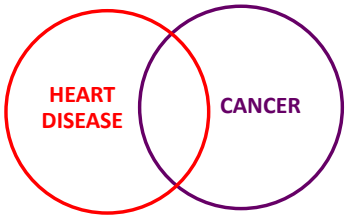


63,566 women with breast cancer from the SEER-Medicare database
Median follow-up 9 years
Of those women who died of CV disease, only 25% carried a CV diagnosis at enrollment

Patnaik JL Breast Cancer Res. 2011 (13):3

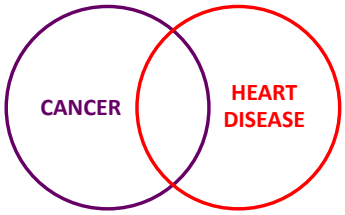
Who are Cardio-oncology patients?

"Comorbid"



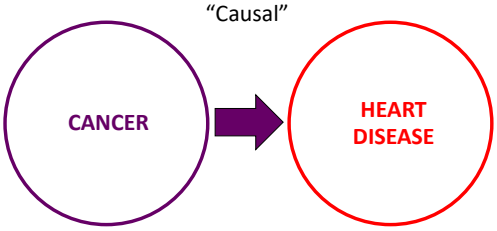
64 year-old smoker with a history of CAD s/p PCI is diagnosed with NSCLCA

"Survivorship"



74 year-old woman with a distant history of breast cancer presents with atrial fibrillation

"Causal"

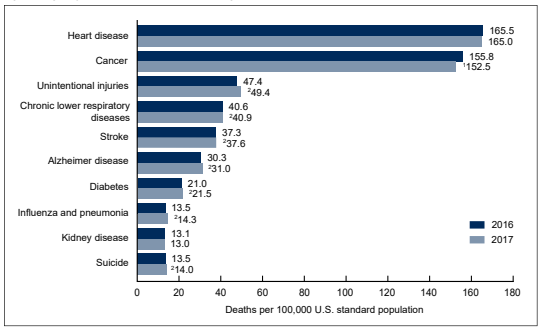


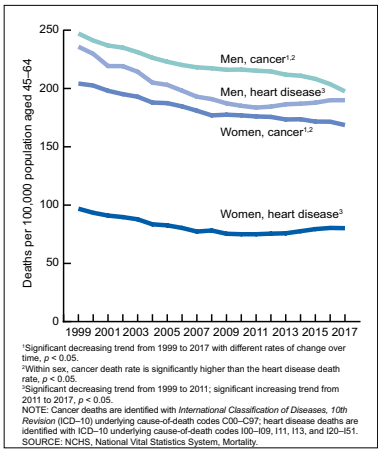
48 year-old woman with a history of Non-Hodgkin lymphoma s/p CHOP presents with heart failure and an EF of 20%

63 year-old woman with ovarian CA on active treatment with Avastin presents with a BP of 174/98 mmHg.

Heart disease and cancer remain leading causes of death in the U.S.

Figure 4. Age-adjusted death rates for the 10 leading causes of death: United States, 2016 and 2017



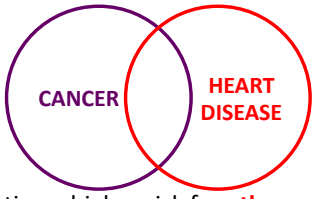


1Significant decreasing trend from 1999 to 2017 with different rates of change over time, $p < 0.05$.
2Within sex, cancer death rate is significantly higher than the heart disease death rate, $p < 0.05$.
3Significant decreasing trend from 1999 to 2011; significant increasing trend from 2011 to 2017, $p < 0.05$.
NOTE: Cancer deaths are identified with *International Classification of Diseases, 10th Revision* (ICD–10) underlying cause-of-death codes C00–C97; heart disease deaths are identified with ICD–10 underlying cause-of-death codes I00–I09, I11, I13, and I20–I51.
SOURCE: NCHS, National Vital Statistics System, Mortality.

Figure 2. Death rates for cancer and heart disease among adults aged 45–64, by sex: United States, 1999–2017

CDC/NVSS May 22 2019

Cancer is associated with increased risk of subsequent CV disease

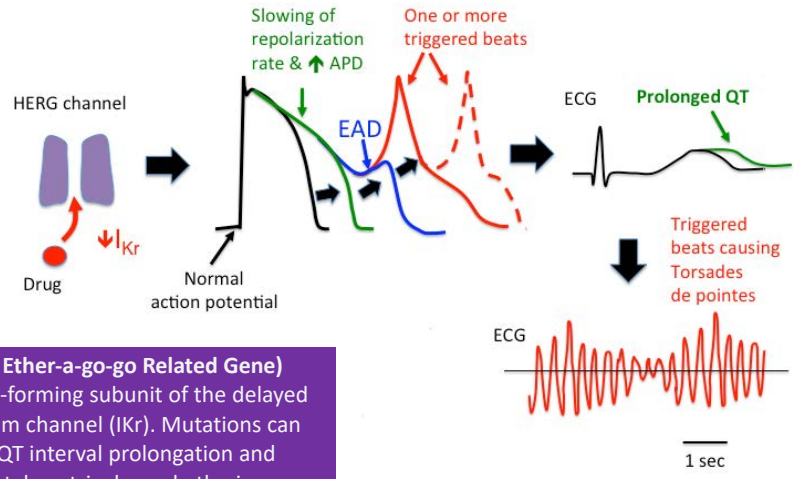


- Survivors have a 10 times higher risk for **atherosclerosis**
- Survivors have a 5.9 times higher risk of **heart failure**
- Survivors have a 6.3 times the risk for **pericardial disease**
- Survivors have a 4.8-fold greater risk for **valvular heart disease**
- Risks are particularly high among survivors who had received **anthracycline drugs**, such as doxorubicin, or **high-dose radiation** therapy to the chest as part of their cancer treatment

Oeffinger et al, NEJM, 2006
Childrens Cancer Research Fund

hERG channel testing predicts QT prolongation

…but not cardiomyocyte injury or heart failure

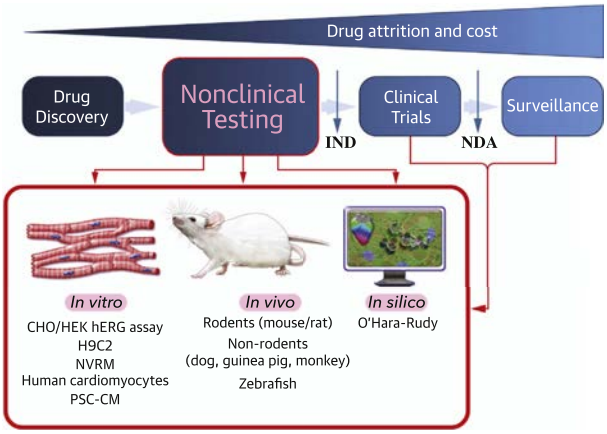


hERG (human Ether-a-go-go Related Gene)
Encodes the pore-forming subunit of the delayed rectifier potassium channel (IKr). Mutations can contribute to QT interval prolongation and potentially fatal ventricular arrhythmias

www.novreslab.com

Preclinical testing for potential cardiotoxicity

Should it be expanded? If so…how?

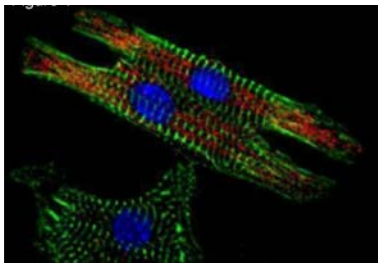


International Council for Harmonization: ICH S7A focuses primarily on potential for inducing ventricular arrhythmias but also suggests measurement of blood pressure, heart rate and ECGs if potential for cardiotoxicity is considered high.

JACC: Basic Transl Sci. 2016. (1) 5: 386-98

Contrasting cardiomyocytes and cancer

Cardiomyocytes

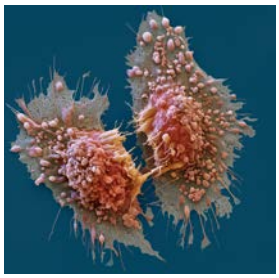


Terminally differentiated

Very limited regeneration

Energy derived from fatty acids

Cancer cells



Undifferentiated

Nearly limitless replication

Energy derived from glucose and glutamine

The differences between cardiomyocytes and cancer cells suggest the possibility that we could develop truly targeted and “cardiosafe” cancer drugs.

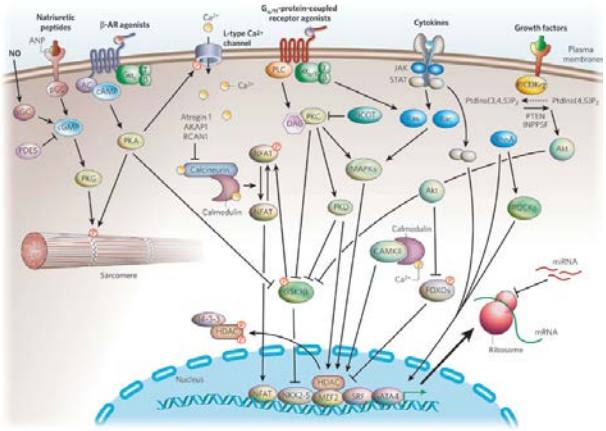
Heart failure vs. cancer…

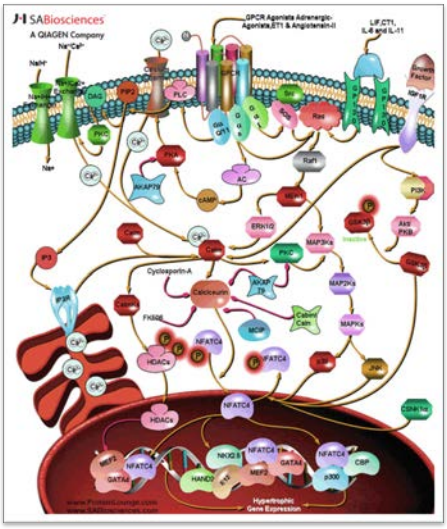
Compare and contrast

Heart failure		Cancer
Cellular hypertrophy	✗	Cellular hyperplasia
Vascular rarefaction	✗	Angiogenesis
Enhanced glucose metabolism Impaired oxidative phosphorylation	✓	Enhanced glucose metabolism Impaired oxidative phosphorylation Warburg effect: aerobic glycolysis
Inflammation	✓	Inflammation
Oxidative stress	✓	Oxidative stress

Signaling in the failing heart

Complex…like cancer





Some oncogenic pathways are also cardioprotective

Can we predict cardiotoxicity of targeted therapy?

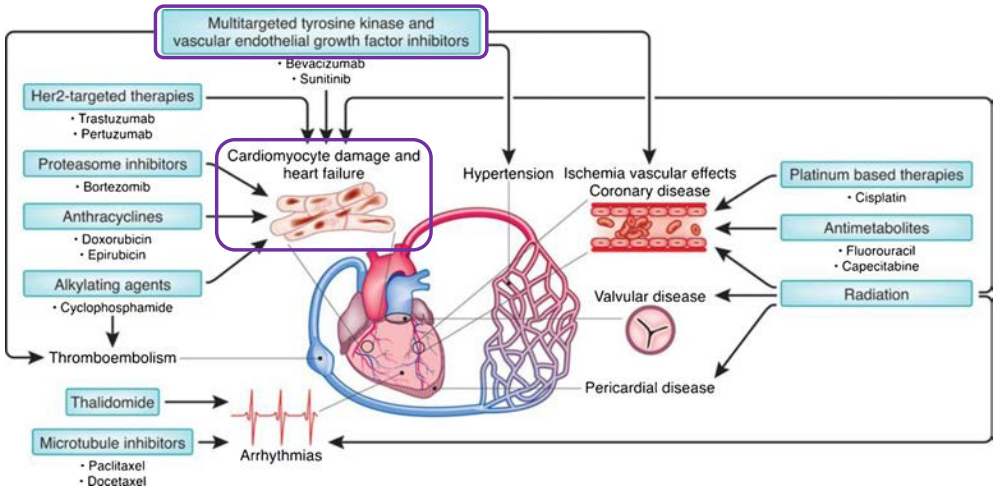
…not very well

Target	Cardioprotective?	Drug example	Heart failure?
HER2 (ErbB2)	Yes	Herceptin	Yes
MEK-ERK	Yes	Trametinib	Yes
PDGFR	Yes	Sunitinib	Yes
EGFR	Yes	Erlotinib	No
PI3 Kinase/Akt	Yes	Idelalisib	No
VEGFR	No	Bevacizumab	Yes
CDK4/6	No	Palbociclib	No *
BTK	No	Ibrutinib	No**
ALK	?	Crizotinib	No***

* Ribociclib causes QT prolongation
** Ibrutinib causes arrhythmias
*** Crizotinib causes bradycardia

Cardiotoxicity of kinase inhibitors

…the most common class of novel targeted cancer therapies

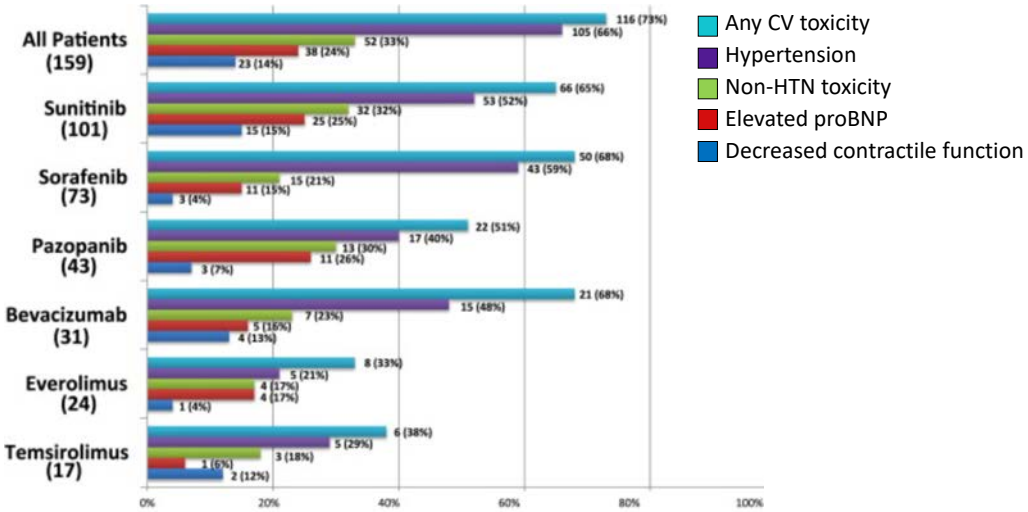


Kinase inhibitors generally do not kill cardiomyocytes, so how do they lead to heart failure?

Babiker HM. Critical Reviews in Oncology / Hematology 126 (2018) 186–200

Toxicity from targeted therapies: scope of the problem

Kinase Inhibitors in the treatment of Renal Cell CA (and others)

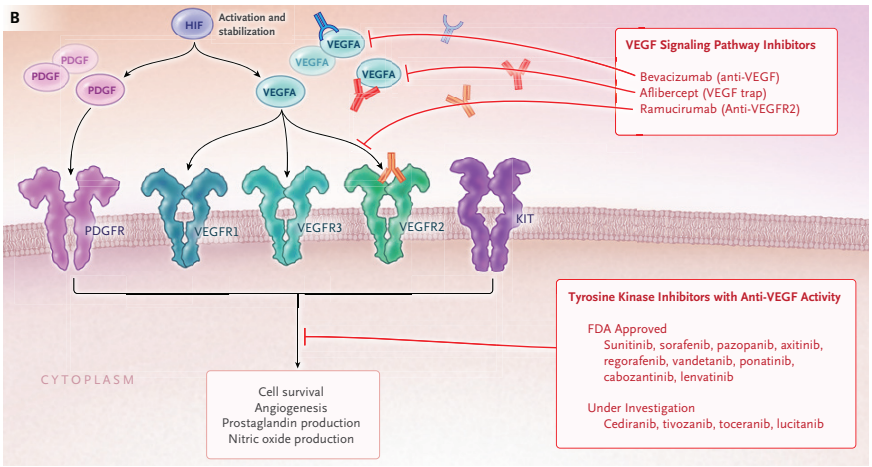


Hypertension is most common, but cardiomyopathy/heart failure occurs in 4-15%

JCHF. 2013;1(1):72-78

Targeted cancer therapies

VEGF signaling pathway: on-target CV toxicity (?)

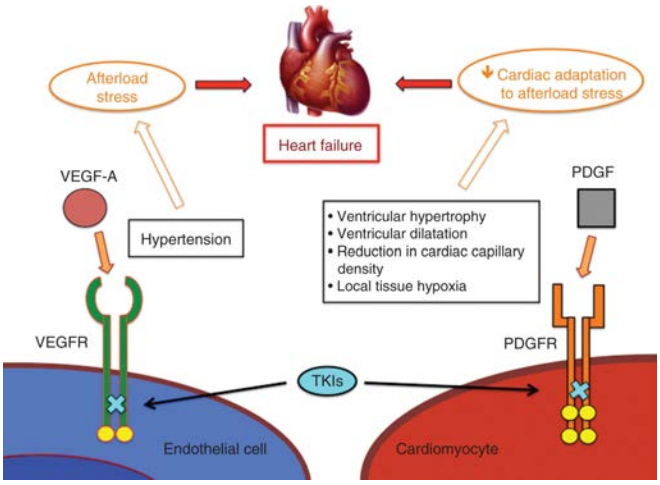


Tumors require angiogenesis to proliferate. Targeted therapies block angiogenesis by blocking the effects of VEGF, which decreases NO bioavailability. Hypertension is a frequent response, due to the importance of NO to endothelial function.

Moslehi JJ N Engl J Med 2016;375:1457-67

Multiple mechanisms of KI cardiotoxicity

Direct myocardial effects and indirect effects from vasculature (?)



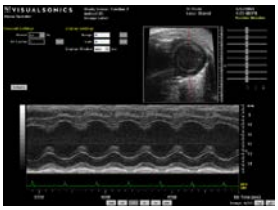
Multitargeted kinase inhibitors (e.g. sunitinib and sorafenib) target both PDGFR and VEGFR
PDGFRs and VEGFRs both are protective in cardiomyocytes

Expert Opinion on Drug Safety **2015,** 14, 253-267

Do mice accurately model human KI cardiotoxicity?

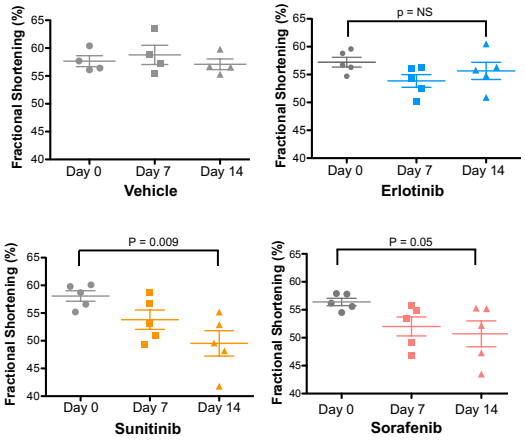
Echocardiography measures cardiac contractile function

Conscious transthoracic echocardiography



Calculating fractional shortening

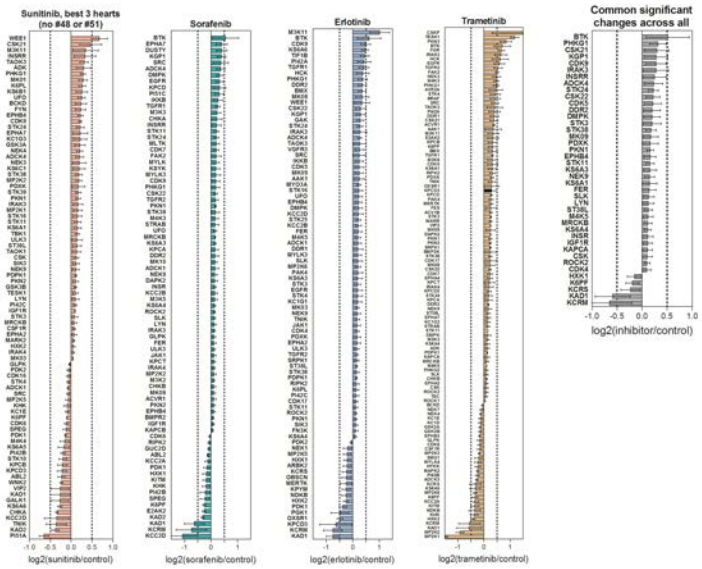
Once daily oral gavage with kinase inhibitors or vehicle
Echocardiogram at Day 7 and 14
Sacrifice at Day 14



Fractional shortening is an index of contractile function

Can we identify the molecular basis of KI cardiotoxicity?

Kinome profiling (MIB/MS)



Dynamic Reprogramming of the Kinome in Response to Targeted MEK Inhibition in Triple-Negative Breast Cancer

Cell

James S. Duncan,[1,8] Martin C. Whittle,[1,8] Kazuhiro Nakamura,[1] Amy N. Abell,[1] Alicia A. Midland,[2] Jon S. Zawistowski,[1] Nancy L. Johnson,[1] Deborah A. Granger,[1] Nicole Vincent Jordan,[1] David B. Darr,[2] Jerry Usary,[3] Pei-Fen Kuan,[4] David M. Smalley,[5] Ben Major,[3] Xiaping He,[3] Katherine A. Hoadley,[3] Bing Zhou,[3,6] Norman E. Sharpless,[3,6] Charles M. Perou,[3] William Y. Kim,[2,8] Shawn M. Gomez,[2] Xin Chen,[7] Jian Jin,[7] Stephen V. Frye,[7] H. Shelton Earp,[1,8] Lee M. Graves,[1] and Gary L. Johnson[1,*]

Multiplexed inhibitor beads (MIBs) bind activated kinases from hearts of mice treated by KIs

↓

Mass spectrometry quantitates the bound kinases

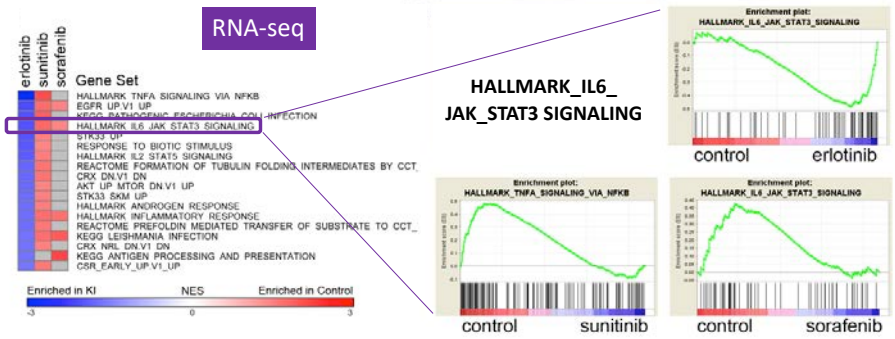
↓

Treatment	Kinases assayed	Upregulated	Downregulated
Erlotinib	200	70	18
Sunitinib	214	54	30
Sorafenib	215	62	18

Why isn't erlotinib cardiotoxic?

Its target, EGFR, is cardioprotective…

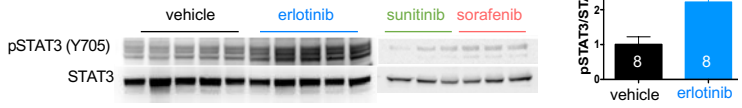
RNA-seq



HALLMARK_IL6_ JAK_STAT3 SIGNALING

RNA-seq suggested that the JAK-STAT pathway was upregulated by erlotinib, but downregulated by sunitinib and sorafenib.

Western blot



Immunoblotting confirmed activation of STAT3 by erlotinib

Stuhlmiller et al. J Am Heart Assoc. 2017 Oct 19

STAT3 upregulation facilitates tumor "escape" from EGFR inhibition

Similarities between heart and tumor?

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 16

Overcoming resistance of targeted EGFR monotherapy by inhibition of STAT3 escape pathway in soft tissue sarcoma

Xiaochun Wang[1,3], David Goldstein[2], Philip J. Crowe[1,3], Mark Yang[3], Kerryn Garrett[4,5], Nikolajs Zeps[4,5] and Jia-Lin Yang[1,3]

INTERNATIONAL JOURNAL OF ONCOLOGY 46: 2083-2095, 2015

Continuous exposure of non-small cell lung cancer cells with wild-type EGFR to an inhibitor of EGFR tyrosine kinase induces chemoresistance by activating STAT3

JIE TANG[1], FUCHUN GUO[2], YANG DU[1], XIAOLING LIU[2], QING QIN[2], XIAOKE LIU[2], TAO YIN[3], LI JIANG[1] and YONGSHENG WANG[2]

SCIENTIFIC REPORTS

OPEN

Development of Erasin: a chromone-based STAT3 inhibitor which induces apoptosis in Erlotinib-resistant lung cancer cells

Received: 7 July 2017
Accepted: 28 November 2017
Published online: 12 December 2017

Christian Lis[1], Stefan Rubner[1], Martin Roatsch[1], Angela Bergi[1], Tyler Gilcrest[1], Darwin Fu[1], Elizabeth Nguyen[1], Anne-Marie Schmidt[1], Harald Krautscheid[1], Jens Meiler[2] & Thorsten Berg[1]

Oncolmmunology 2:12, e27091; December 2013; © 2013 Landes Bioscience

EGFR-mediated tumor immunoescape

The imbalance between phosphorylated STAT1 and phosphorylated STAT3

Fernando Concha-Benavente[1], Raghvendra M Srivastava[2], Soldano Ferrone[3], and Robert L Ferris[1,2,4,*]

RESEARCH ARTICLE

CANCER www.SCIENCESIGNALING.org 29 March 2016 Vol 9 Issue 421 ra33

JAK2 inhibition sensitizes resistant EGFR-mutant lung adenocarcinoma to tyrosine kinase inhibitors

Sizhi P. Gao,[1] Qing Chang,[1] Ninghui Mao,[1] Laura A. Daly,[1] Robert Vogel,[2] Tyler Chan,[1] Shu Hui Liu,[1] Eirini Bournazou,[1] Erez Schori,[1] Haiying Zhang,[3] Monica Red Brewer,[4,5] William Pao,[4,5] Luc Morris,[6] Marc Ladanyi,[7,8] Maria Arcila,[7] Katia Manova-Todorova,[9] Elisa de Stanchina,[10] Larry Norton,[1,11] Ross L. Levine,[1,8,11] Gregoire Altan-Bonnet,[2] David Solit,[1,8,11,12] Michael Zinda,[13] Dennis Huszar,[13]* David Lyden,[3,14,15]† Jacqueline F. Bromberg[1,11]†

STAT3 activation is cardioprotective

Potentially mitigating effects of EGFR inhibition (?)

frontiers in Cardiovascular Medicine

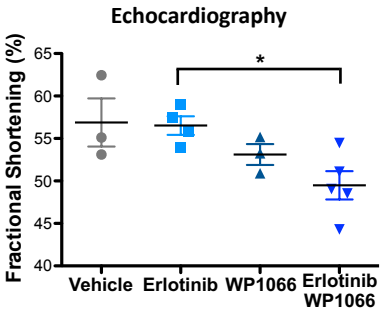
REVIEW
published: 30 November 2015
doi: 10.3389/fcvm.2015.00036

Pivotal Importance of STAT3 in Protecting the Heart from Acute and Chronic Stress: New Advancement and Unresolved Issues

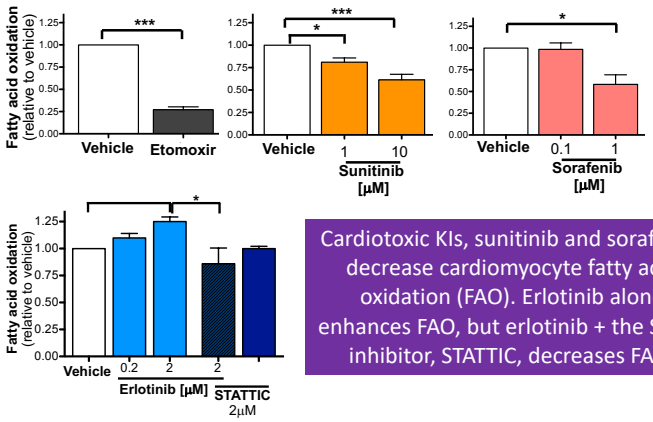
*Fouad A. Zouein[1], Raffaele Altara[2], Qun Chen[3], Edward J. Lesnefsky[3,4,5], Mazen Kurdi[2,6] and George W. Booz[2]**

Combined EGFR and STAT3 inhibition is cardiotoxic

Caution for combination targeted therapy?



Neither erlotinib (EGFR inhibitor) nor WP1066 (STAT3 inhibitor) affects cardiac contractile function independently. In combination they cause cardiomyopathy.

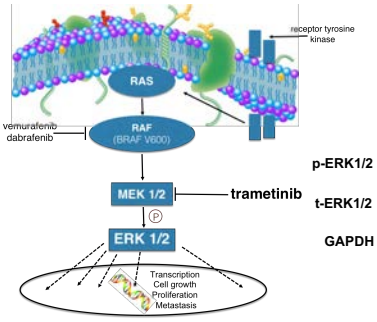


Cardiotoxic KIs, sunitinib and sorafenib, decrease cardiomyocyte fatty acid oxidation (FAO). Erlotinib alone enhances FAO, but erlotinib + the STAT3 inhibitor, STATTIC, decreases FAO.

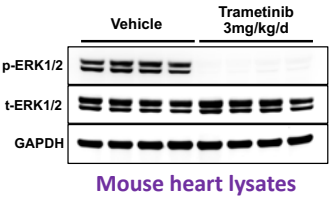
Stuhlmiller et al. J Am Heart Assoc. 2017 Oct 19

Trametinib causes reversible cardiomyopathy and heart failure

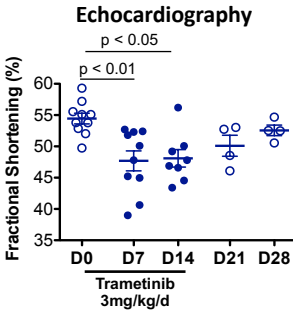
…in mice like in (some) humans



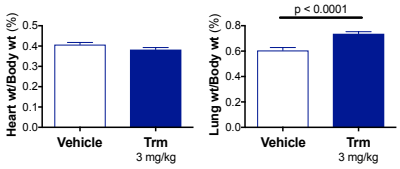
Ras-Raf-MEK-ERK oncogenic signaling pathway



Mouse heart lysates

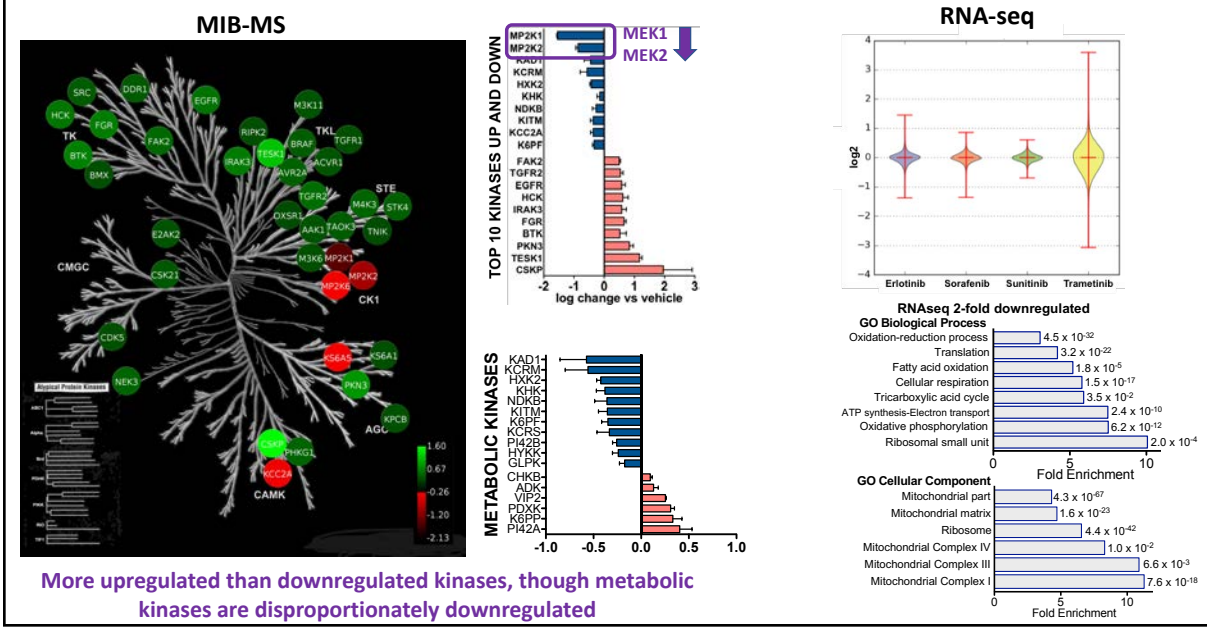


Reversible decrease in contractile function



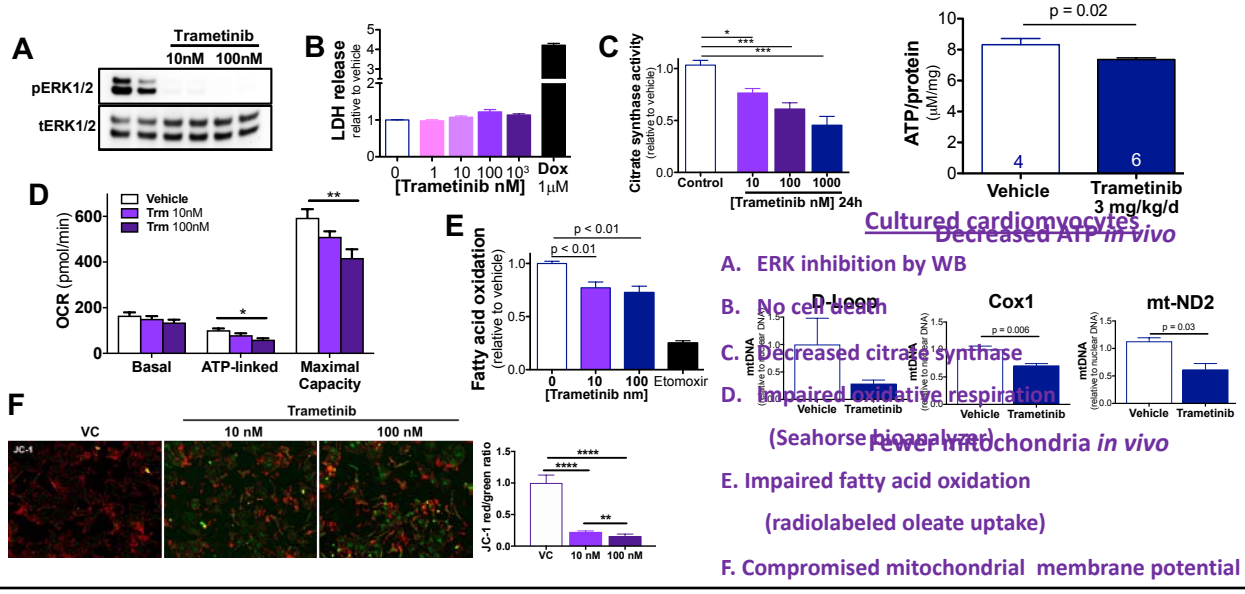
Increased lung weight consistent with pulmonary edema (heart failure)

MIB-MS and RNA-seq suggest metabolic injury



More upregulated than downregulated kinases, though metabolic kinases are disproportionately downregulated

Trametinib impairs mitochondrial number and function *in vivo* and *in vitro*



Cultured cardiomyocytes

Decreased ATP *in vivo*

A. ERK inhibition by WB

B. No cell death

C. Decreased citrate synthase

D. Impaired oxidative respiration

(Seahorse bioanalyzer)

Fewer mitochondria *in vivo*

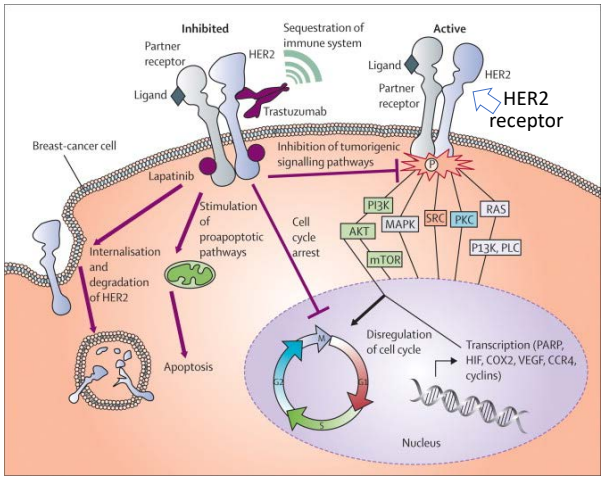
E. Impaired fatty acid oxidation

(radiolabeled oleate uptake)

F. Compromised mitochondrial membrane potential

The unexpected cardiotoxicity of trastuzumab

An early model of toxicity from "targeted therapies"



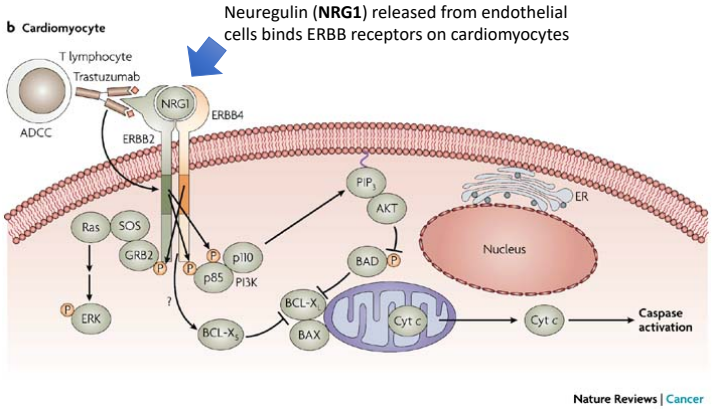
HER2 (erbB2) oncogene overexpression promotes tumor cell proliferation in 15-20% of breast cancers

Trastuzumab (Herceptin) is a humanized monoclonal antibody against HER2

Trastuzumab revolutionized breast cancer treatment. In early RCTs, HER2+ patients had a 30-40% reduction in mortality with trastuzumab.

Lancet Oncology 2009:; 10(12) 1179-87

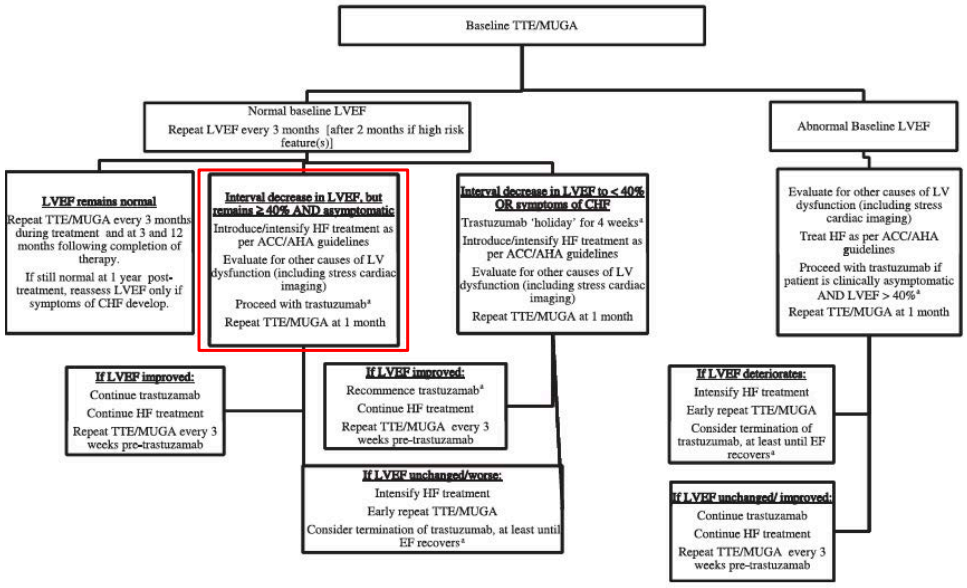
The unexpected cardiotoxicity of trastuzumab



The mechanism of toxicity is not entirely known, but likely involves disabling of beneficial cross-talk between endothelial cells and myocytes via neuregulin (NRG).

Cardiotoxicity occurs in 3-27% of patients treated with trastuzumab
- ✧ Not dose-dependent
- ✧ Usually reversible and asymptomatic decline in EF
- ✧ Risk factors: age, comorbidities, concomitant anthracycline use

Force et al. Nat Rev Cancer 2007. 7: 332-344



Conclusion: Monitor every 3 months. Continue trastuzumab and start ACEi or beta-blocker if EF declines (but remains > 40% and patient is asymptomatic)

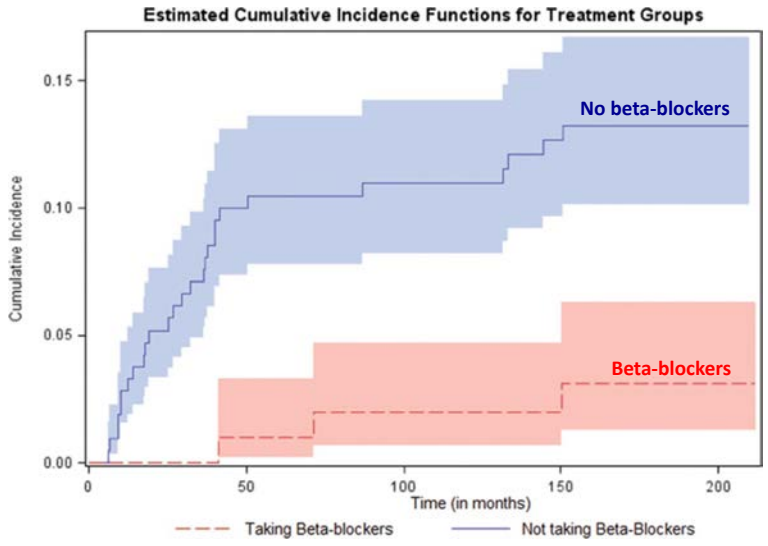
Groarke…Cheng, Moslehi. *Medical Clinics of North America*, 2012.

Issues with Monitoring

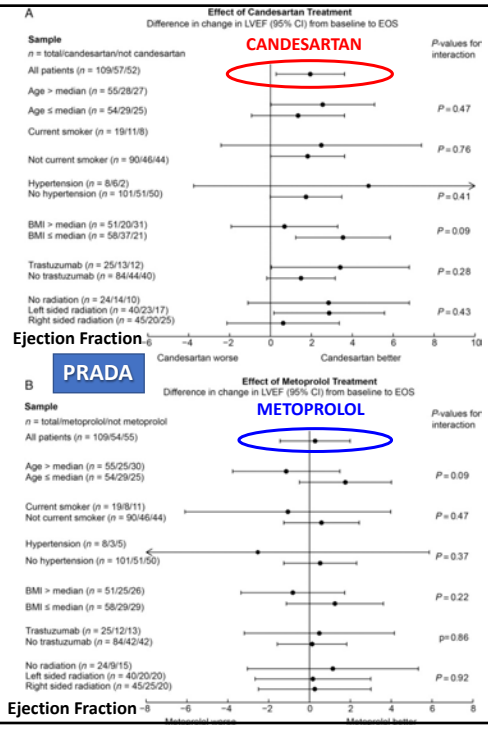
More testing ≠ Better care

- Trastuzumab
  - Toxicity can occur quickly
  - Monitoring results in delays or discontinuation, which decreases efficacy
  - May be hard to convince patient to restart
- Anthracyclines
  - Can occur very late – years after Rx
  - Cannot tell if the DCM is drug related
  - Unclear interval for screening echo (5 years?)

Beta-blockers attenuate risk of heart failure in HER2+ breast cancer patients (observational)



Sinziana Seicean et al. Circ Heart Fail. 2013;6:420-426



MANTICORE

Patients: 99 patients with normal EF taking trastuzumab.

Design: Randomized 1:1:1 to bisoprolol, perindopril, or placebo during trastuzumab-based chemotherapy for 24 months. Cardiac magnetic resonance imaging parameters were assessed at baseline, at 3 months, at 12 months, and at 24 months

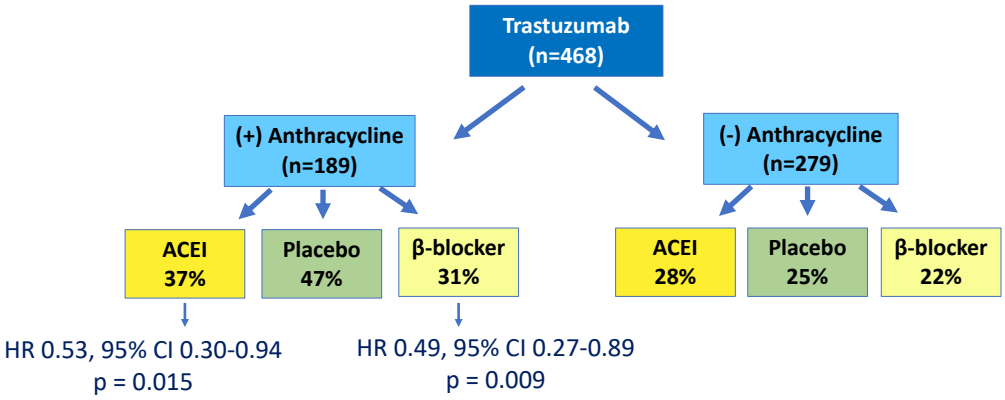
Outcomes: Bisoprolol significantly prevented reduction in left-ventricular ejection fraction from baseline vs placebo (*P* = .001) and also prevented trastuzumab interruptions due to drop in left-ventricular ejection fraction (*P* = .002). Post-treatment left-ventricular ejection fraction declined from 61% to 56% for placebo, from 62% to 59% for perindopril, and from 62% to 61% for bisoprolol.

2015 San Antonio Breast Cancer Symposium. Abstract S1-05.
Eur Heart J. 2016 Jun 1; 37(21): 1671–1680.

ACE Inhibitor or β-Blocker with Trastuzumab

Primary outcome (decrease in LVEF >10%):

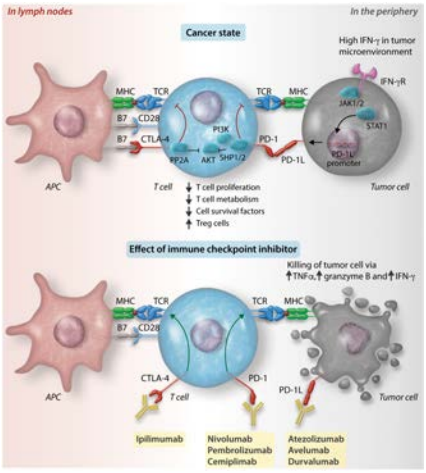
Lisinopril 30% vs carvedilol 29% vs placebo 32% (p > NS)

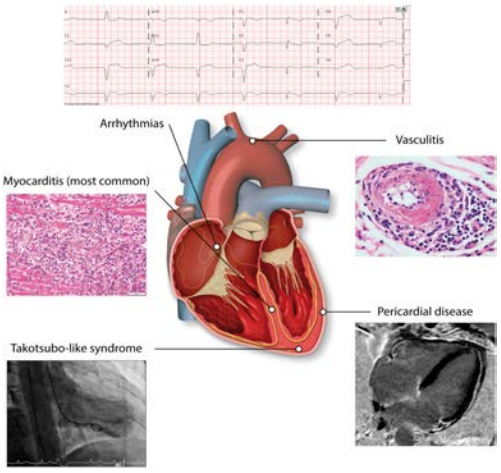


J Am Coll Cardiol 2019; 73:2859-2868

CV toxicities of checkpoint inhibitors

Relatively rare but potentially fatal





Cardiovascular Research, Volume 115, Issue 5, 15 April 2019, Pages 854–868

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

N ENGL J MED 375;18 NEJM.ORG NOVEMBER 3, 2016

HPI: 65 year-old woman with metastatic melanoma presents with atypical chest pain, dyspnea, and fatigue 12 days after receiving first dose of the monoclonal anti-PD1 antibody, nivolumab (1mg/kg), and ipilimumab (3mg/kg), a monoclonal anti-CTLA-4 antibody.

Past Medical History: Melanoma, Hypertension. No other cardiac risk factors

Initial laboratory evaluation:

CK 17,720 unit/L
CK-MB > 600 ng/mL
cTnI initial 4.7 ng/mL
subsequent 51.3 ng/mL

ECG: non-specific interventricular conduction delay (not present on prior ECGs)

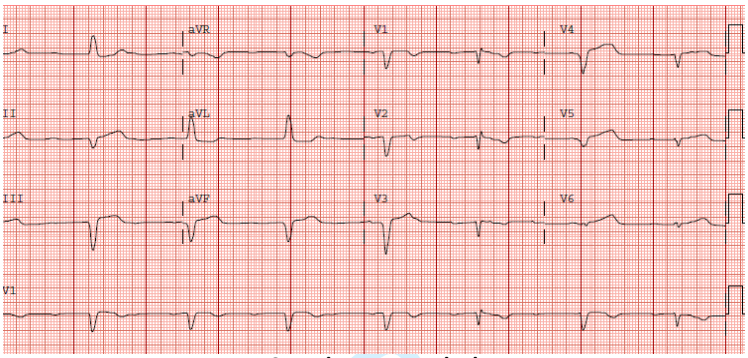
Echocardiogram: Preserved LV ejection fraction (EF 73%)

Hospital Course

Diagnosis: Myocarditis and myositis

Treatment: Methylprednisolone 2mg/kg/day

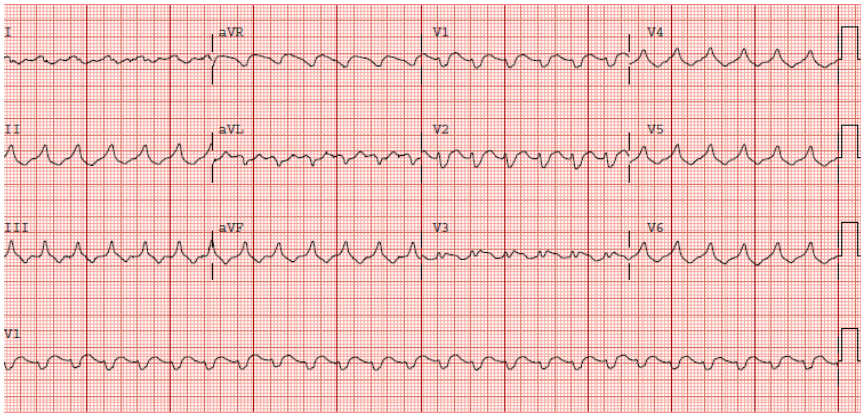
Clinical course…



Complete Heart Block

N ENGL J MED 375;18 NEJM.ORG NOVEMBER 3, 2016

Hospital Course



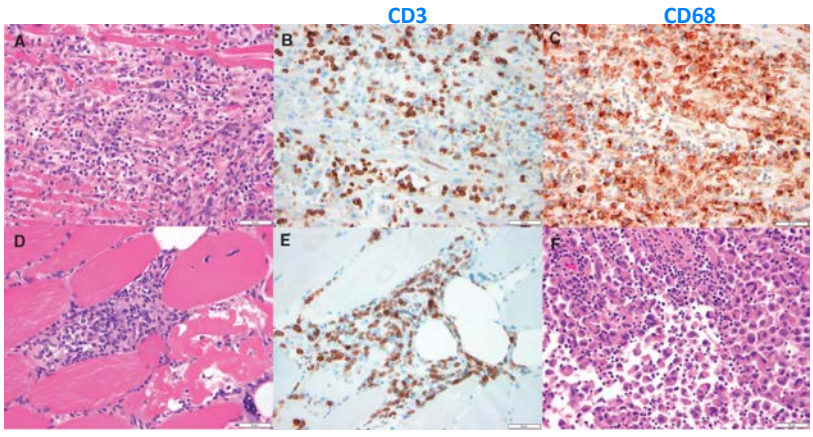
Ventricular arrhythmias

Clinical course: Despite treatment, her course was characterized by multisystem organ failure and refractory ventricular arrhythmias, leading to death.

N ENGL J MED 375;18 NEJM.ORG NOVEMBER 3, 2016

CV toxicities of checkpoint inhibitors

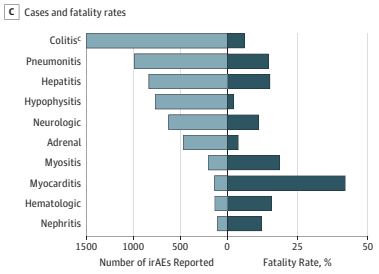
Myocarditis: clonal expansion of lymphocytes



Cardiovascular Research, Volume 115, Issue 5, 15 April 2019, Pages 854–868

ICI Myocarditis: Rare but potentially fatal

Higher risk in (older) women?



JAMA Oncol. 2018;4(12):1721-1728

Incidence likely < 1%
Case fatality approaches 40%

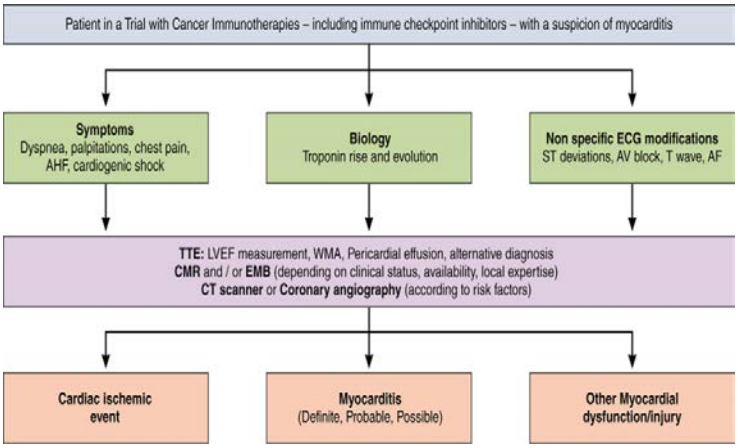
JAMA Oncol. Published online August 22, 2019

Table 2. Multivariate Logistic Analysis of Patients With Myocarditis[a]

Characteristic	Total Cases, No.	Cases of Myocarditis	Proportion of Myocarditis (95% CI)	Odds Ratio (95% CI) Crude	Odds Ratio (95% CI) Adjusted	*P* Value[b]
Sex						
Male	748 314	533	0.071 (0.065-0.078)	1 [Reference]	1 [Reference]	
Female	1 199 488	370	0.031 (0.028-0.034)	0.43 (0.38-0.49)	0.44 (0.38-0.51)	<.001
Not reported	31 355	11	0.035 (0.018-0.063)	0.49 (0.27-0.89)	0.42 (0.21-0.84)	.01
Age, y						
<75	1 652 576	857	0.052 (0.048-0.055)	1 [Reference]	1 [Reference]	
≥75	326 581	57	0.017 (0.013-0.023)	0.34 (0.26-0.44)	0.19 (0.14-0.28)	<.001
ICIs						
Nonuser	1 966 061	809	0.041 (0.038-0.044)	1 [Reference]	1 [Reference]	
User	13 096	105	0.802 (0.656-0.970)	19.63 (16.01-24.08)	9.66 (7.16-13.05)	<.001
ICIs[c,d]						
Female sex	4798	34	0.709 (0.491-0.989)	NA	1.92 (1.24-2.97)	.004
Age ≥75 years	2442	26	1.065 (0.697-1.556)	NA	7.61 (4.29-13.50)	<.001
Concomitant use of other ICIs	1557	21	1.349 (0.837-2.054)	NA	1.93 (1.19-3.12)	.008

ICI myocarditis: diagnosis

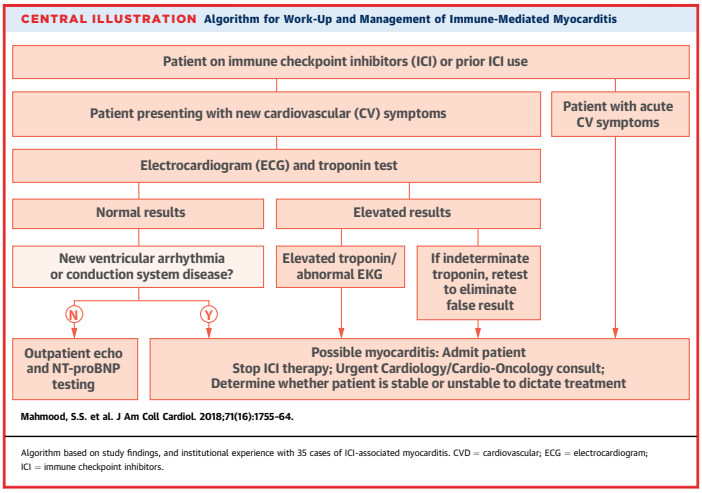
Maintain a high index of suspicion despite low frequency



Circulation 2019. Volume: 140. Issue: 1. Pages: 80-91

ICI myocarditis: treatment

Warning: evidence-free zone



Treatment: 1. High dose solumedrol
2. Hemodynamic support as needed
3. Stop the ICI

Thank You

Questions?
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Epic InBasket
Pager: 919-216-1804