# Cardiovascular Toxicities Associated with Checkpoint Inhibitors


Javid J. Moslehi, M.D.
Director, Cardio-Oncology Program
Assistant Professor of Medicine
Vanderbilt School of Medicine
Nashville, TN
www.cardioonc.org

# Disclosures

- Consultation (Paid)
  - Novartis, Pfizer, Bristol-Myers Squibb, Takeda/Millennium, Ariad, Acceleron, Vertex, Incyte, Rgenix, Verastem, Pharmacyclics, StemCentRx, Heat Biologics, Daiichi Sankyo, Regeneron

- Consultation (Not Paid)
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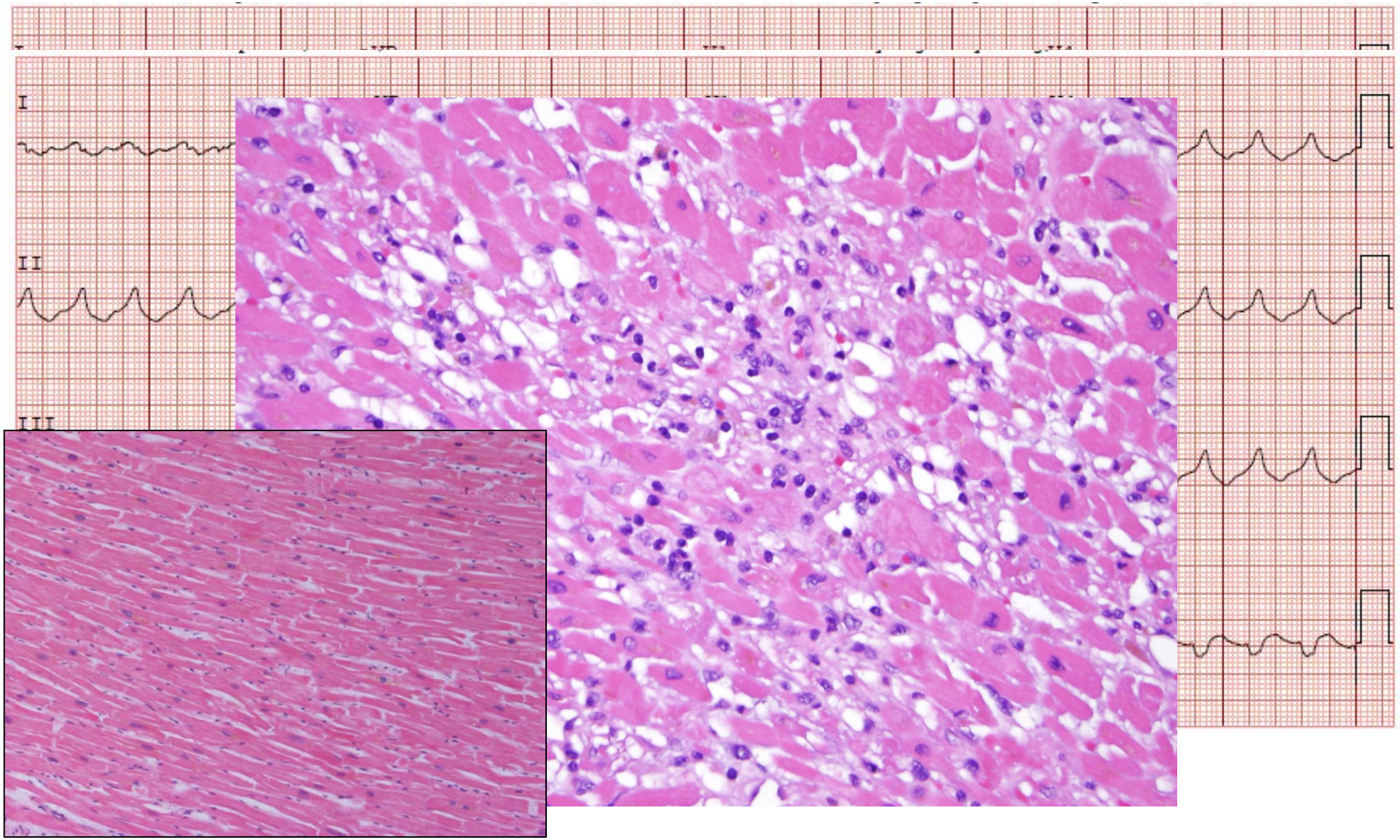
  - U.S. Federal and Drug Administration (FDA)

- Research Grants:
  - Pfizer, Bristol-Myers Squibb

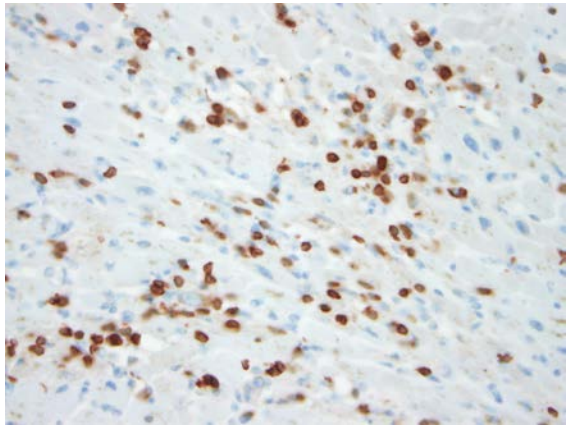
# Immune Checkpoint-Inhibitor Associated Myocarditis




Johnson…Sosman, Moslehi. *NEJM*. 2016. 375(18):1749-1755.

# T Cell Infiltrates in the Heart

CD3



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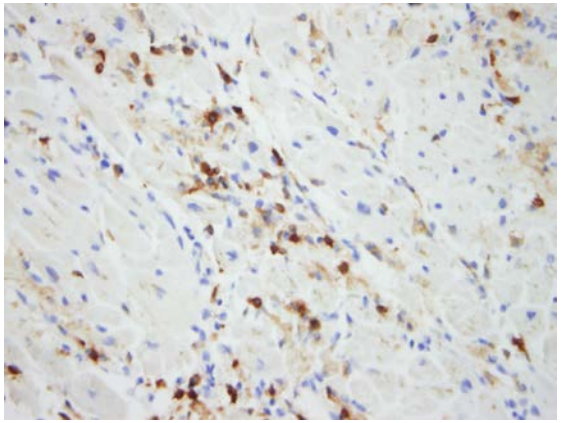

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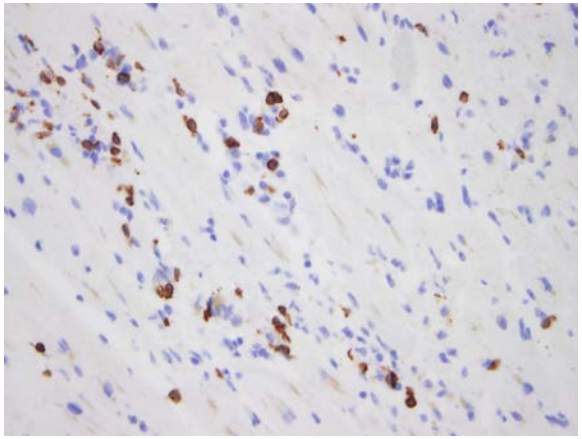

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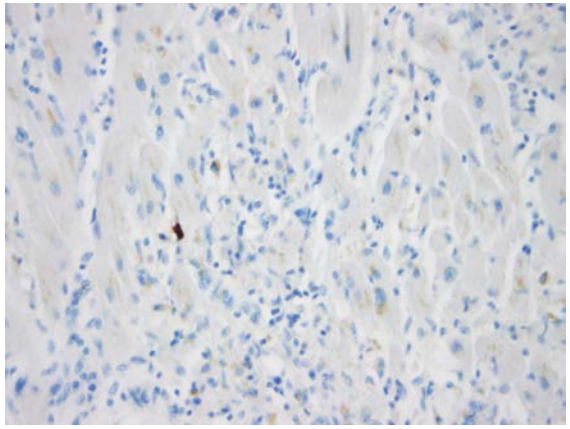

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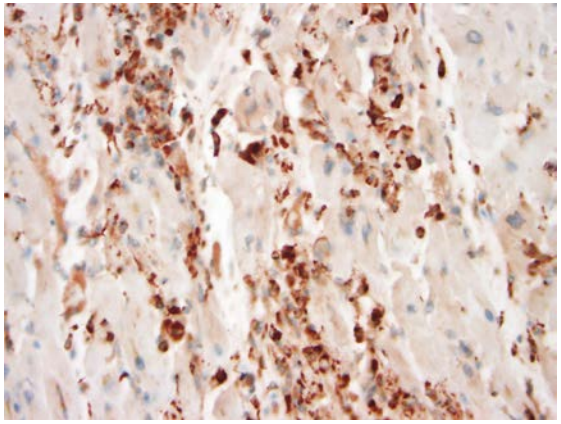

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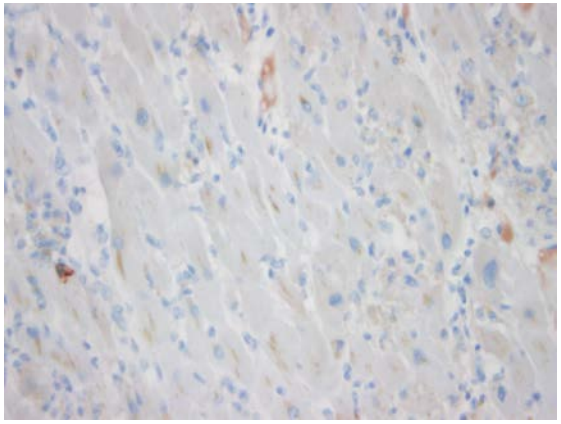
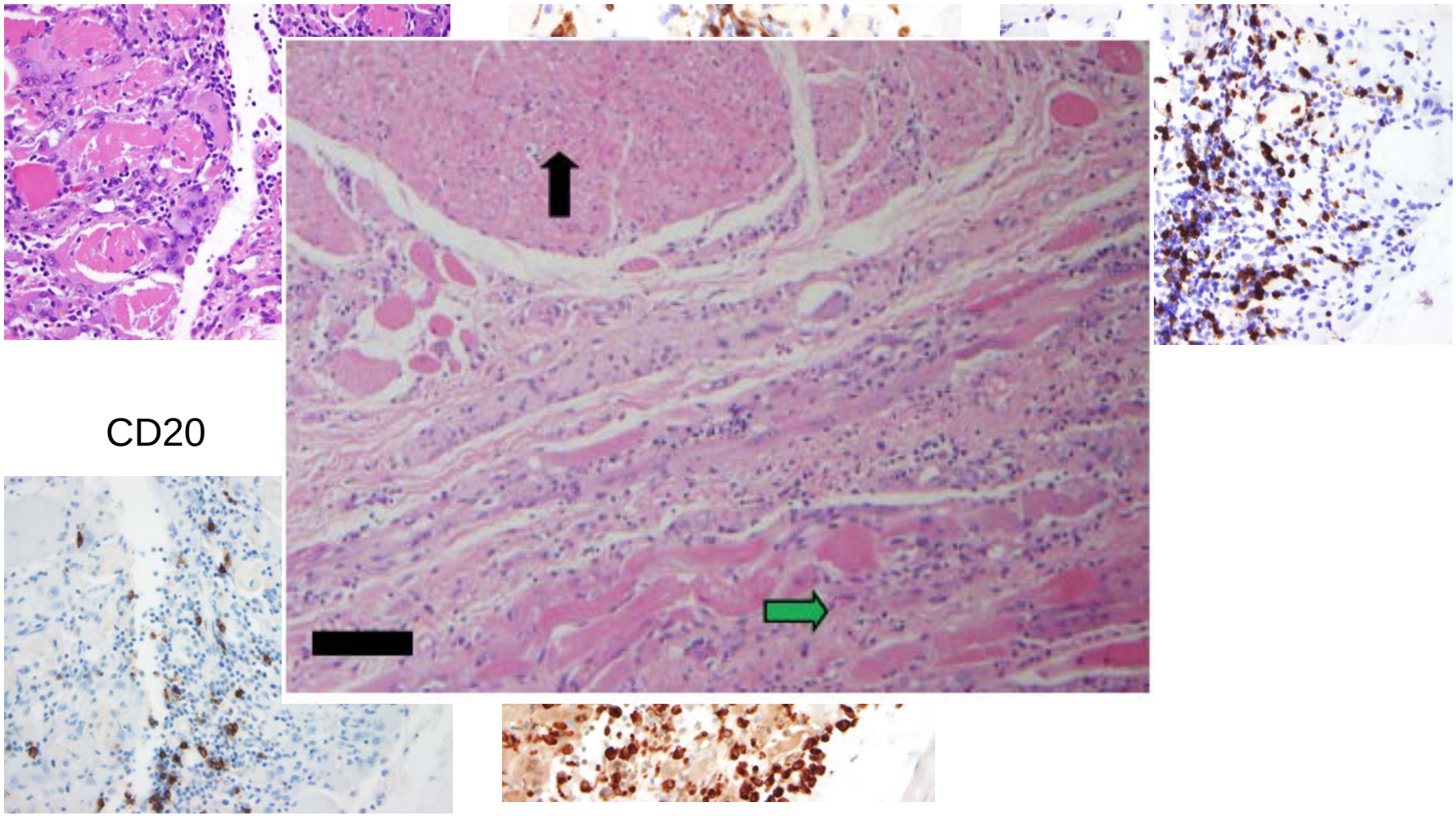


Johnson, Balko….Sosman, Moslehi *NEJM*. 2016.

# T Cell Infiltrates in the Skeletal Muscle




Johnson, Balko….Sosman, Moslehi *NEJM*. 2016.

# Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome

Clinical Questions

Incidence?

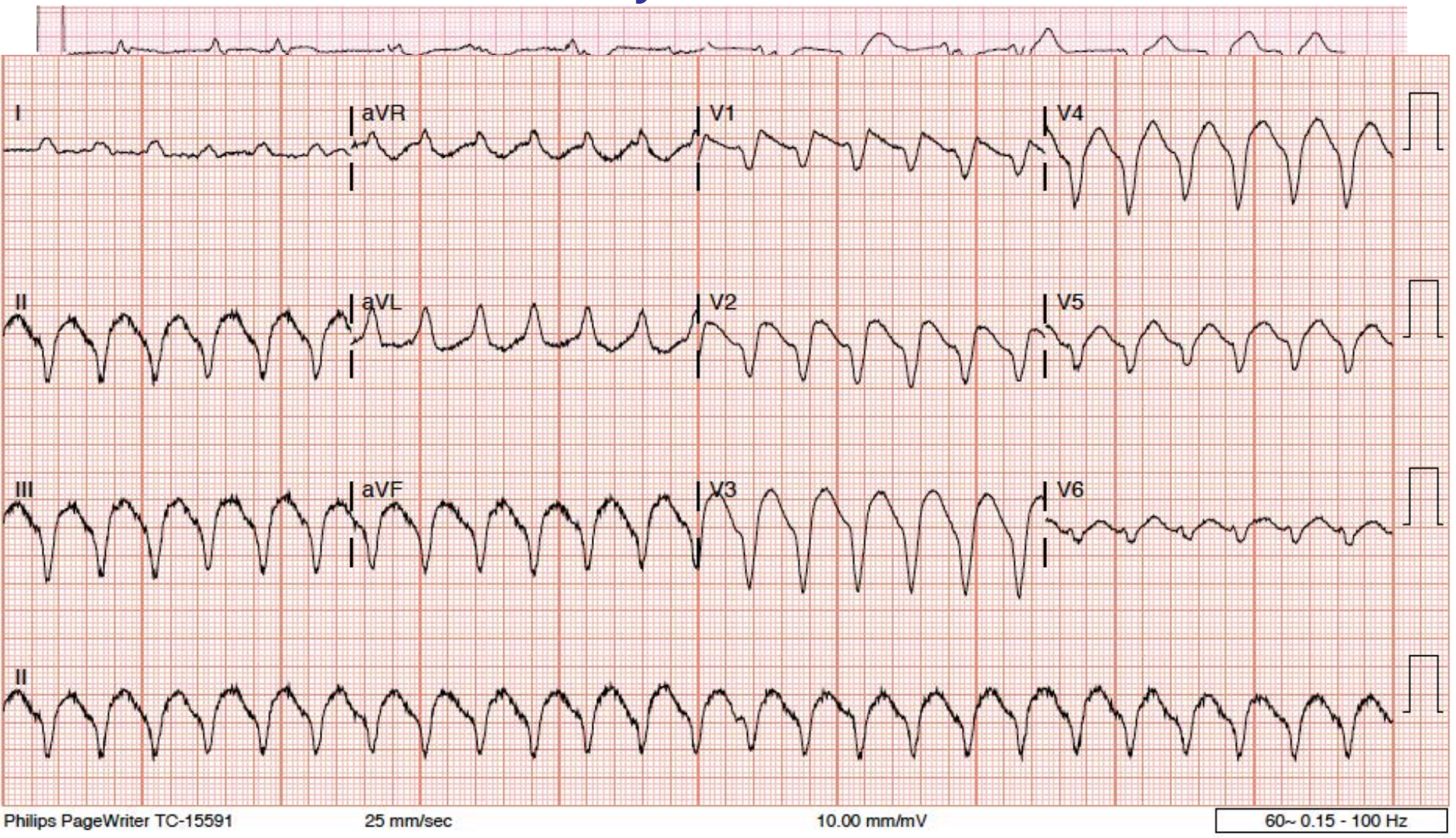
Clinical presentation?

Treatment?

↑

Immune Checkpoint Inhibitor-Associated Myocarditis

# Electrocardiographic (EKG) Disturbances with Immune-Checkpoint Inhibitor Associated Myocarditis




Courtesy of Olenchock, BWH. Ahmad, Yale

# Incidence of myocarditis and myositis with ipilimumab and nivolumab treatment

**Table 1. Incidence of Myocarditis and Myositis in Patients Receiving Nivolumab or Ipilimumab plus Nivolumab.**

| Characteristic | Nivolumab (N=17,620) | Nivolumab plus Ipilimumab (N=2974) |
|---|---|---|
| | *no. (%)* | |
| Myocarditis | | |
| Any* | 10 (0.06) | 8 (0.27) |
| Fatal events | 1 (<0.01) | 5 (0.17) |
| Myositis | | |
| Any | 27 (0.15) | 7 (0.24) |
| Fatal events | 2 (0.01) | 1 (0.03) |

Johnson, Balko….Sosman, Moslehi *NEJM*. 2016.
Nina Kola, Gregory Plautz, Dan Reshef,
Jonathan Deutch. Bristol-Myers Squibb.

# Common Terminology Criteria for Adverse Events (CTCAE)

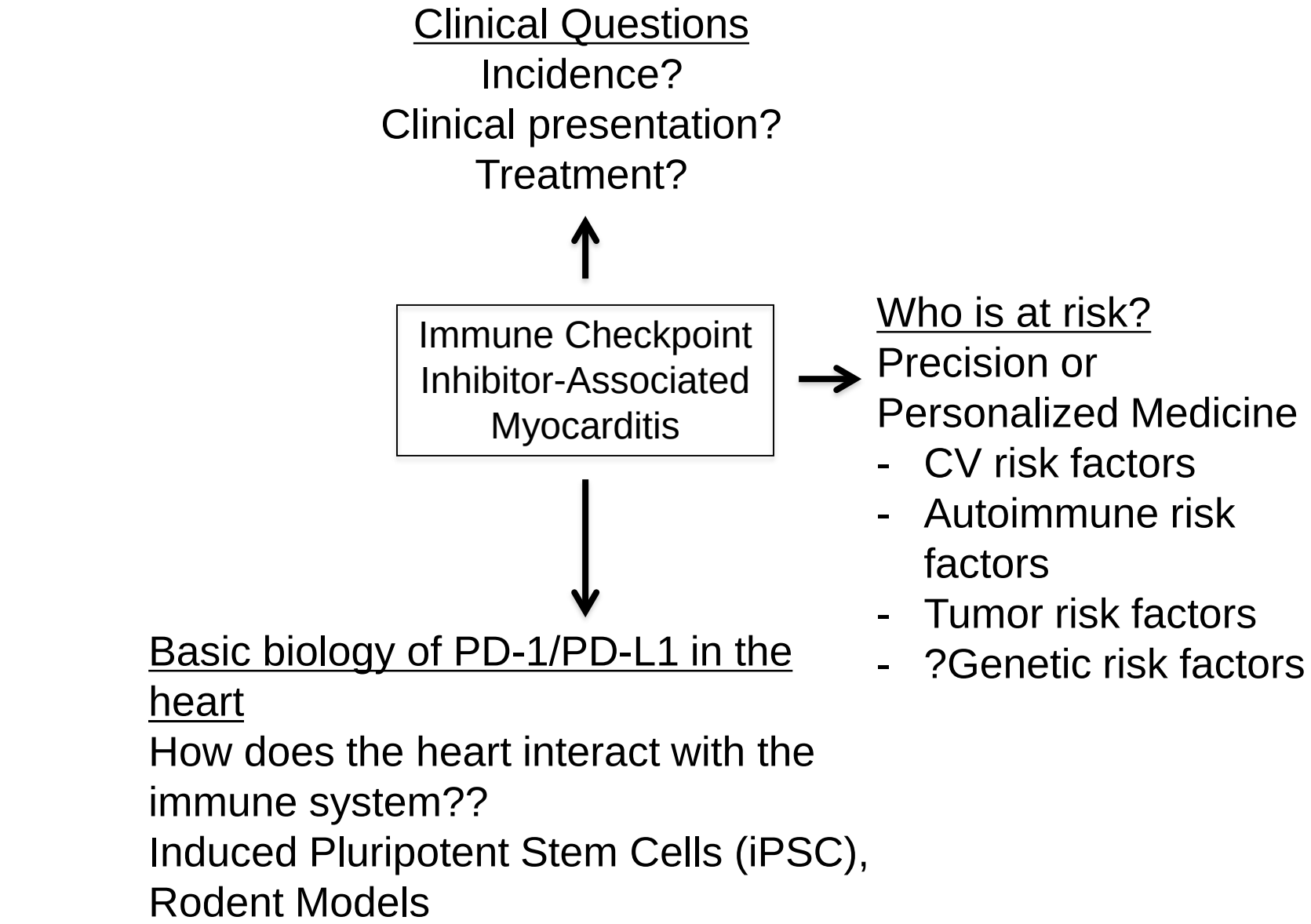
## Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

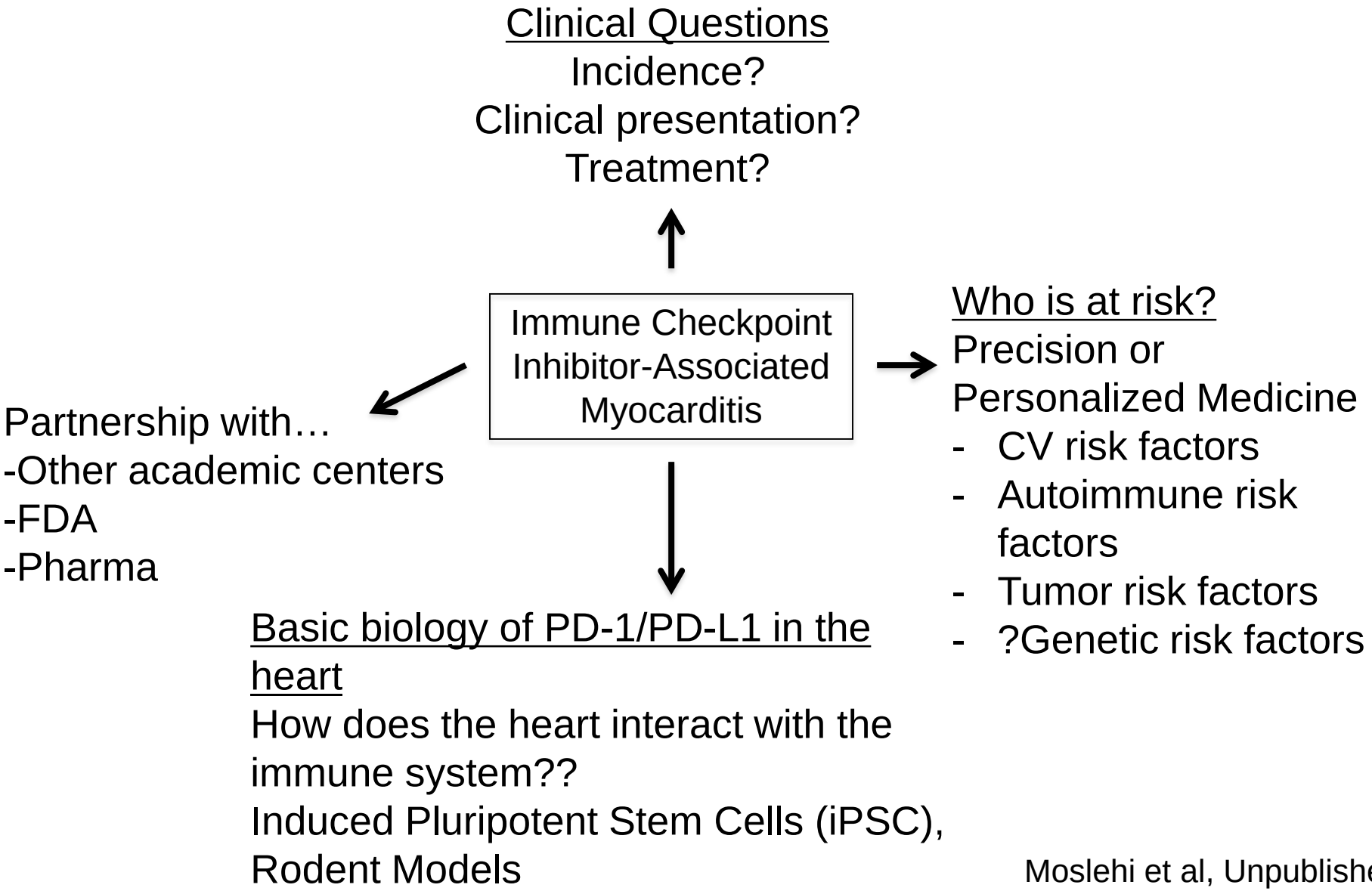
U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

| Cardiac disorders | | | | | |
|---|---|---|---|---|---|
| | Grade | | | | |
| **Adverse Event** | **1** | **2** | **3** | **4** | **5** |
| Myocarditis | 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 inflammation of the muscle tissue of the heart. | | | | | |
| Atrioventricular block complete | - | Non-urgent intervention indicated | Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker) | Life-threatening consequences; urgent intervention indicated | Death |
| Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles. | | | | | |
| Atrioventricular block first degree | Asymptomatic, intervention not indicated | Non-urgent intervention indicated | - | - | - |
| Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds. | | | | | |
| Chest pain - cardiac | Mild pain | Moderate pain; limiting instrumental ADL | Pain at rest; limiting self care ADL | - | - |
| Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation. | | | | | |
| Conduction disorder | Mild symptoms; intervention not indicated | Moderate symptoms | Severe symptoms; intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |
| Definition: A disorder characterized by pathological irregularities in the cardiac conduction system. | | | | | |

# Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome



# Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome




Moslehi et al, Unpublished.

# Other cases of Immune checkpoint-inhibitor associated myocarditis?

**From:** EDERHY Stéphane <stephane.ederhy@aphp.fr>
**Date:** Monday, February 20, 2017 at 5:12 AM
**To:** Javid Moslehi <javid.moslehi@vanderbilt.edu>
**Subject:** Cardiotoxicity and Immune checkpoints inhibitors

Dear Pr Moslehi

As you know we read with great interest your recent manuscript in the New England Journal of Medicine describing two cases of cardiotoxicity due to immune check point inhibitors. I would like to have your expert opinion on a clinical case. One of my colleagues had received yesterday a 35 years old patient treated with a combination of immune checkpoints inhibitors for melanoma. She developed dyspnea, heart failure then cardiogenic shock despite prednisolone. This morning a Left ventricular assist device was implanted due to refractory cardiogenic shock. Cardiac magnetic resonance performed at admission was in favor of myocarditis (left and right ventricle).LVEF measured with echo found an LVEF of 20 %. The ECG found an Right bundle brunch block. Troponin was 200 ng/ml. Due to the severity of this clinical scenario, we would like to try to propose to this patient plasma exchange. Have you ever tried such management in this particular context, do you think this proposition is of interest ?
Best regards
Stephane Ederhy

Stephane EDERHY, Praticien Hospitalier, Service de cardiologie – Pr Cohen

Hôpitaux Universitaires Est Parisien, Hopital Saint Antoine, 184 Rue du Faubourg Saint-Antoine, 75 571 Paris cedex 12

Ligne directe : 01 49 28 25 03, Secrétariat : 01 49 28 28 75, Fax : 01 49 28 24 35


720 Rutland Avenue
Ross building, #1049
Baltimore, MD 21205 USA
Phone (410) 614-3085
Fax (410) 367-2149
Appointments: (443) 997-0270
djudge@jhmi.edu

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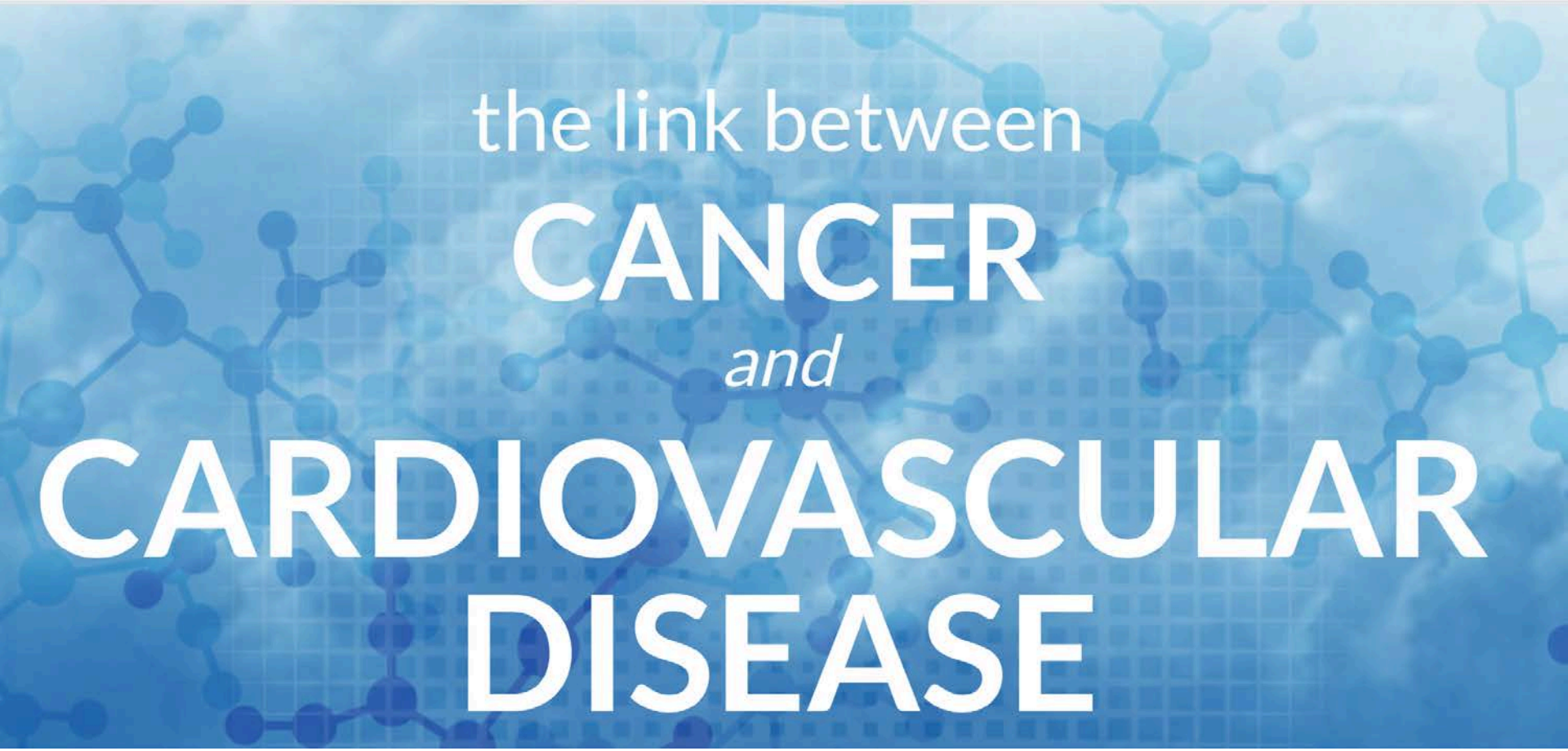
the link between
CANCER
and
CARDIOVASCULAR
DISEASE

# Step 1- Initial Information (contact form)

**Please complete the survey below.**

Thank you!

## Requesting Physician Information

1) **First Name:**

2) **Last Name:**

3) **Email Address:**

4) **Phone Number:**
* must provide value

**Requested time for call-back (please offer 5, 30-minute time periods.)**

5) **Time 1:**

6) **Time 2:**

# Increasing Complexity of Use of Immunotherapies in Oncology

**Table 3. Selected Ongoing Phase 3 Trials of Combination Therapy with Immune Checkpoint Blockers and Vaccines as First-Line Treatment for Advanced Renal-Cell Carcinoma.**

| Treatment | Primary End Point | Estimated No. of Patients Enrolled | Trial | ClinicalTrials.gov No. |
|---|---|---|---|---|
| Pembrolizumab–lenvatinib vs. everolimus–lenvatinib vs. sunitinib | Progression-free survival | 735 | CLEAR | NCT02811861 |
| Nivolumab–ipilimumab vs. sunitinib | Progression-free survival and overall survival | 1070 | CheckMate 214 | NCT02231749 |
| Atezolizumab–bevacizumab vs. sunitinib | Progression-free survival and overall survival in PD-L1–detectable tumors | 900 | IMmotion151 | NCT02420821 |
| Avelumab–axitinib vs. sunitinib | Progression-free survival | 583 | JAVELIN Renal 101 | NCT02684006 |
| Pembrolizumab–axitinib vs. sunitinib | Progression-free survival and overall survival | 840 | KEYNOTE-426 | NCT02853331 |
| Autologous dendritic-cell immunotherapy–sunitinib vs. sunitinib | Overall survival | 450 | ADAPT | NCT01582672 |

Choueiri, Motzer. *New England Journal of Medicine*, 2017. 376(4):354-366.

# Conclusions

- Myocarditis is a new clinical phenomenon that ia a rare (but clinically significant) complication of cancer immunotherapy
  - myositis with rhabdomyolysis
  - early progressive and refractory cardiac electrical instability
- Initial mechanistic studies show that robust T cell and macrophage infiltrates
- Need for multi-institutional efforts to understand the pathophysiology of myocarditis and multi-pronged approach to understand who is at risk of developing myocarditis

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Kris Swiger (Fellow)

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Andrew Lichtman
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Janis Taube

**Yale**

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Tariq Ahmed

**Bristol-Myers Squibb**

Nina Kola
Gregory Plautz
Dan Reshef
Jonathan Deutch

# Vanderbilt Cardio-Oncology Program

**Clinical Program**

**Heart Failure**
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Lynne Stevenson

**Genetics**
Quinn Wells
Dan Roden

**Arrhythmia/EP**
Bill Stevenson
Greg Michaud
Roy John

**Cardiac Surgery**
Ash Shah

**Vascular Medicine**
Josh Beckman
Esther Kim
Jon Brown

**Translational Core Lab**
Yan-Ru Su

Javid Moslehi
David Slosky
Allen Naftilan
Hank Jennings

Oncology

**Education**
Vanderbilt Cardio-Oncology
Fellowship
Joe-Elie Salem
Kris Swiger
Wendy Bottinor
Javid.moslehi@vanderbilt.edu

**Basic Research Program**

**Moslehi Laboratory**
Donald Okoye
Calvin Sheng
Mary Barber

Translational Research
Thomas Wang
Quinn Wells
Dan Roden

Vascular Biology
Jon Brown
Hind Lal
David Harrison
Richard Gumina

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