CME OUTFITTERS

Immune Checkpoint Inhibitor Cardiotoxicity: Contributing Factors, Appropriate Treatments, and Retreatment Options

Supported by an educational grant from
Bristol Myers Squibb

CME OUTFITTERS

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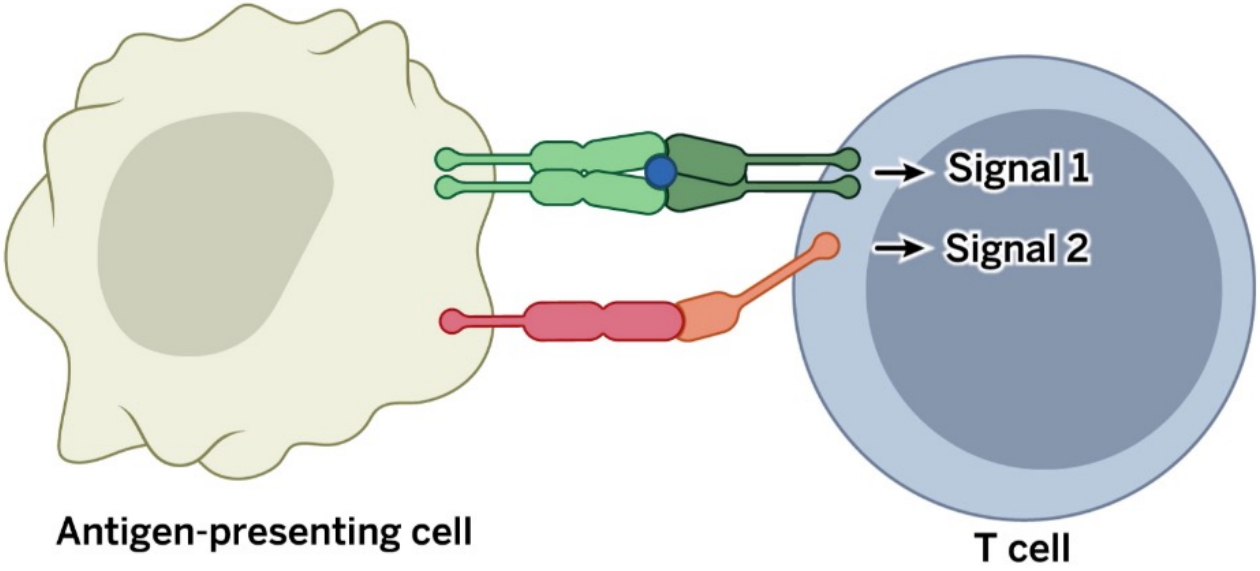
Learnings Objectives

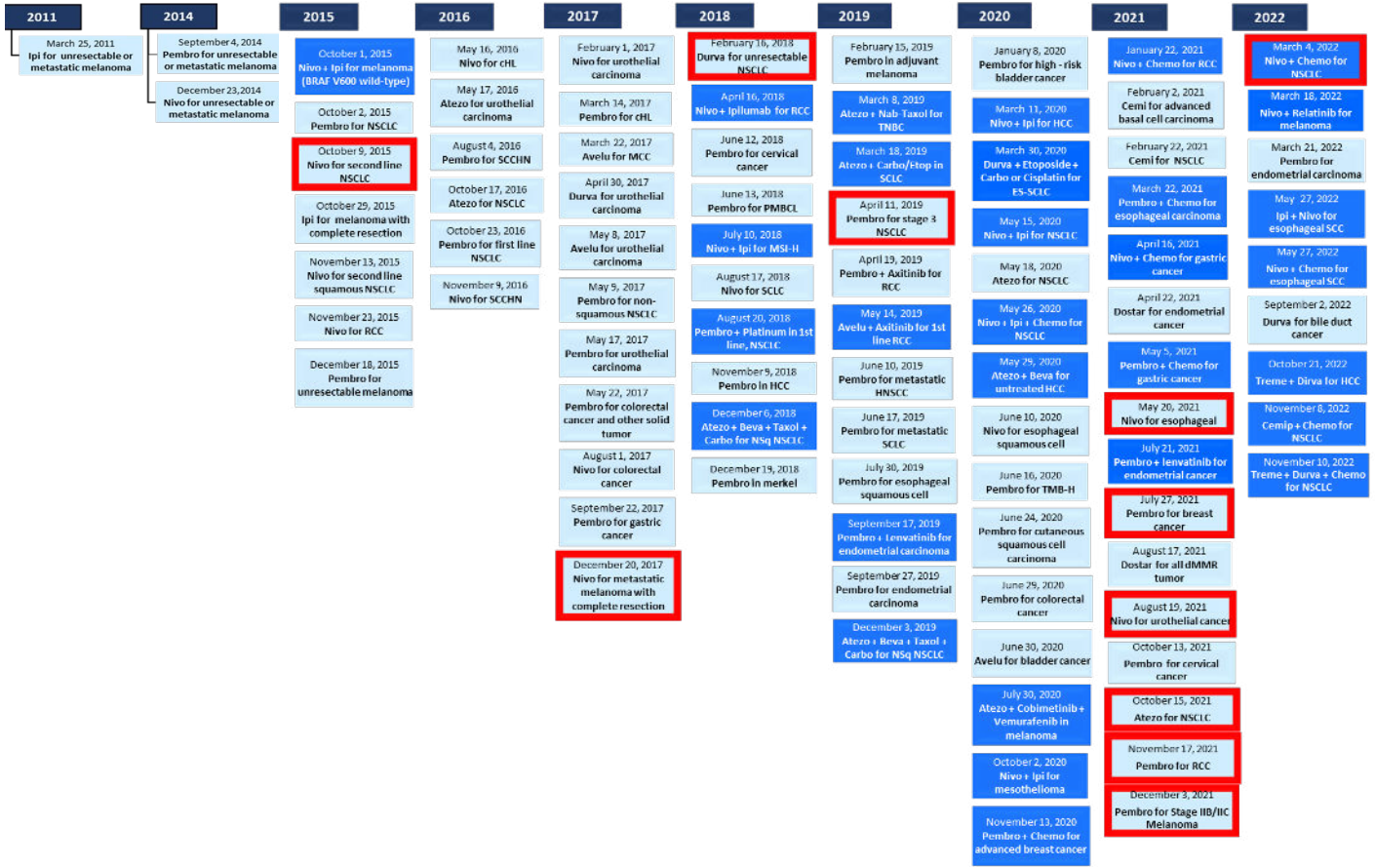
1. Summarize factors contributing to cardiotoxicity associated with ICI use.
2. Differentiate risk of outcome severity in patients after experiencing ICI-related cardiotoxicity.
3. Select appropriate treatment approaches for ICI-related cardiotoxicity.
4. Appraise current clinical evidence for and against ICI rechallenge in patients experiencing CV AEs after ICI therapy.

Mechanism of Action of Immune Checkpoint Inhibitors

Immunology 101



FDA Approval History of ICI Therapies

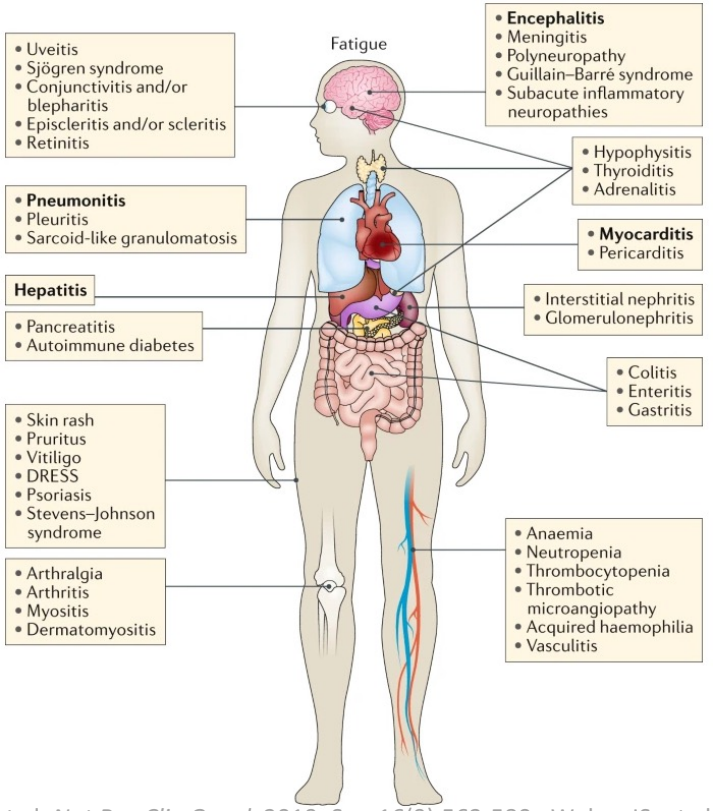


CME OUTFITTERS

irAE Management Guidelines

Thompson, J et al. NCCN Website. 2022. https://www.nccn.org/professionals/physician_gls/pdf/ immunotherapy.pdf. Accessed November 15, 2022.; Haanen J, et al. *Ann Oncol*. 2022 Oct 18. [Epub ahead of print].; Brahmer JR, et al. *J Immunother Cancer*. 2021;9(6):e002435.; Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073-4126. Epub 2021 Nov 1. Erratum in: *J Clin Oncol*. 2022;40(3):315.

Overview of irAEs



- Disruption of the homeostatic mechanisms induces a unique spectrum of side effects called irAEs
- irAEs reported in 74-90% and ≥3 grade in 14-55% of patients
- Most common irAEs: dermatitis, enterocolitis, transaminitis, and endocrinopathies
- Most fatal irAEs: myocarditis, neurotoxicity
- If untreated, they can rapidly progress to life-threatening conditions and may also be fatal
- Very little evidence base for treatment
  - Temporary or permanent ICI discontinuation
  - Corticosteroids
  - 2nd line immunosuppression

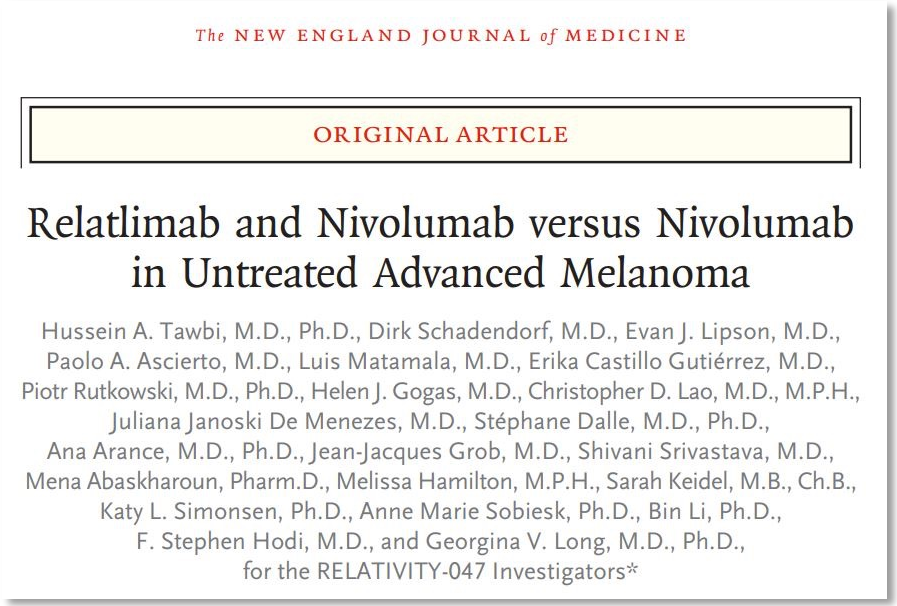
Martins F, et al. *Nat Rev Clin Oncol*. 2019; Sep;16(9):563-580; Weber JS, et al. *J Clin Oncol* 2012; Jul 20;30(21):2691-7. Arnaud-Coffin P, et al. Int J Cancer. 2019;145(3):639-648. Duan J, et al. JAMA Oncol. 2020;6(3):375-384.

Incidence of ICI-related Myocarditis

- Johnson, et al. (2016): Single agent, 0.06%, dual agents, 0.27%
- Hu, et al. (2017): Cumulative rate of significant cardiac events, 5.2%
- Mahmood, et al. (2018): 1.14%
- Oren, et al. (2020): 0.36%
- Waliany, et al. (2021): 1.4%

Johnson DB, et al. *NEJM*. 2016 Nov 3;375(18):1749-1755; Hu YB, et al; AME Academic Lung Cancer Cooperation Group. *Transl Lung Cancer Res*. 2017 Dec;6(Suppl 1):S8-S20; Mahmood SS, et al. *J Am Coll Cardiol*. 2018 Apr 24;71(16):1755-1764; Oren O, et al. *Am J Cardiol*. 2020 Jun 15;125(12):1920-1926; Waliany S, et al. *JACC CardioOncol*. 2021;3(1):137-139.

Incidence of ICI-related Myocarditis



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma

Hussein A. Tawbi, M.D., Ph.D., Dirk Schadendorf, M.D., Evan J. Lipson, M.D., Paolo A. Ascierto, M.D., Luis Matamala, M.D., Erika Castillo Gutiérrez, M.D., Piotr Rutkowski, M.D., Ph.D., Helen J. Gogas, M.D., Christopher D. Lao, M.D., M.P.H., Juliana Janoski De Menezes, M.D., Stéphane Dalle, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean-Jacques Grob, M.D., Shivani Srivastava, M.D., Mena Abaskharoun, Pharm.D., Melissa Hamilton, M.P.H., Sarah Keidel, M.B., Ch.B., Katy L. Simonsen, Ph.D., Anne Marie Sobiesk, Ph.D., Bin Li, Ph.D., F. Stephen Hodi, M.D., and Georgina V. Long, M.D., Ph.D., for the RELATIVITY-047 Investigators*

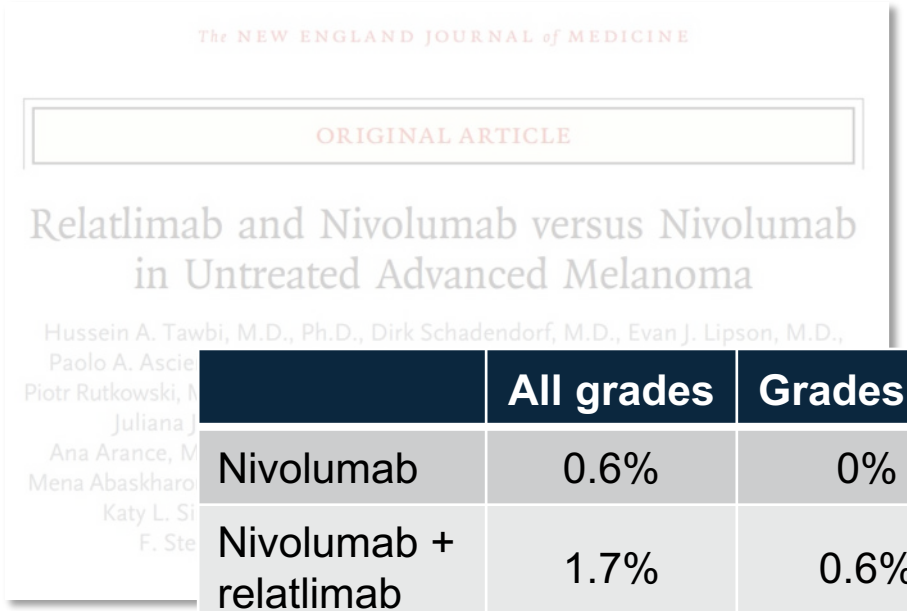
Myocarditis (all grades)

0.6% Nivolumab

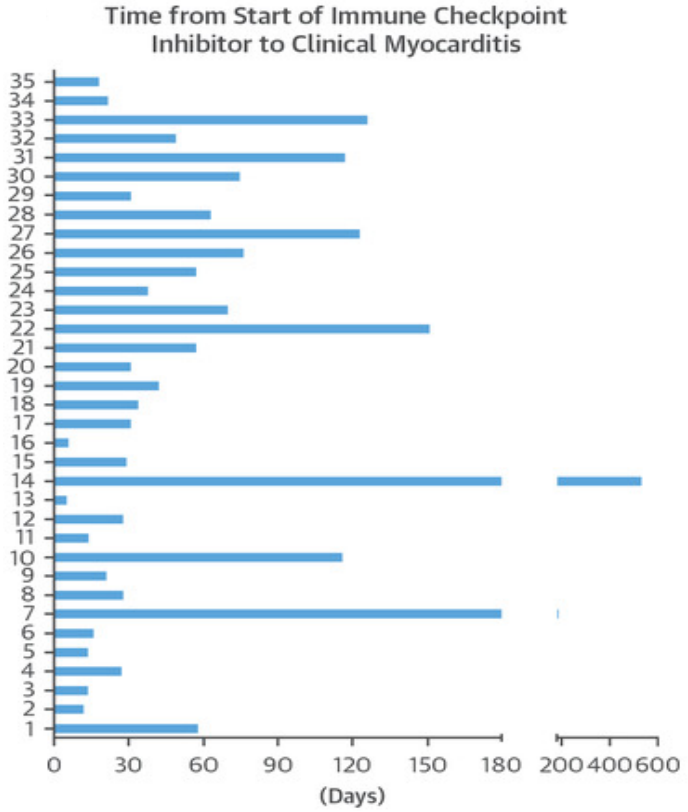
1.7% Nivolumab + relatlimab

Tawbi HA, Schadendorf D, Lipson EJ, et al. *New England Journal of Medicine*. 2022;386(1):24-34.

Incidence of ICI-related Myocarditis



	All grades	Grades 3/4
Nivolumab	0.6%	0%
Nivolumab + relatlimab	1.7%	0.6%



Tawbi HA, Schadendorf D, Lipson EJ, et al. New England Journal of Medicine. 2022;386(1):24-34. Mahmood SS, et al. *J Am Coll Cardiol*. 2018;71(16):1755-1764.

Consult #1

70-year-old male

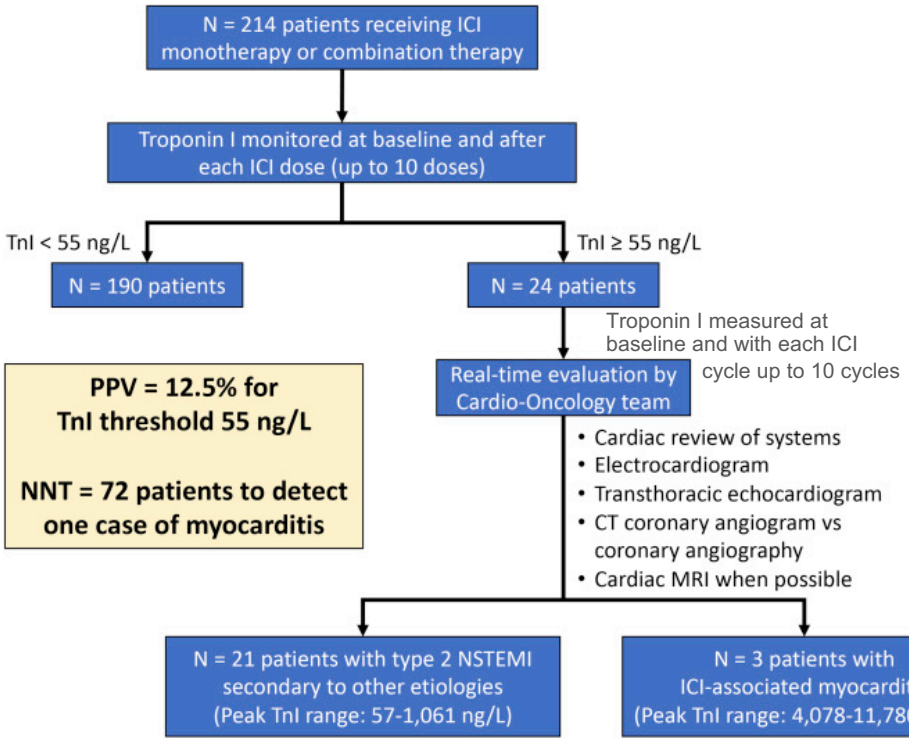
- Diabetes (Type II), Hypertension
- Dx: Metastatic NSCLC
- Treatment: PD-1 + platinum doublet chemotherapy
- Cycle 1, 10/1/2022
- Cycle 2, 10/22/2022
- Now presenting to clinic with significant fatigue

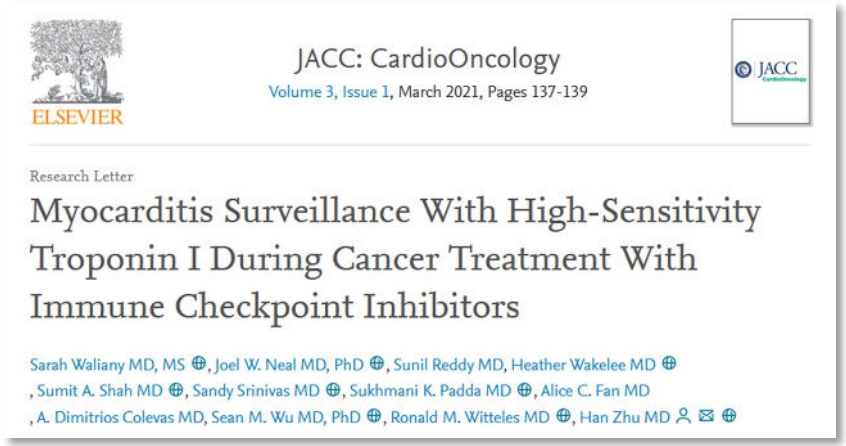
Surveillance for ICI-associated Myocarditis

Should a Cardio-Oncology assessment be recommended for all patients prior to immunotherapy treatment?

Every patient should have a baseline EKG and troponin testing prior to starting ICI therapy

Surveillance for ICI-associated Myocarditis



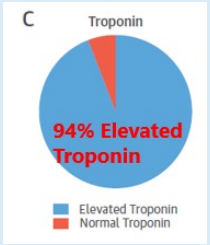


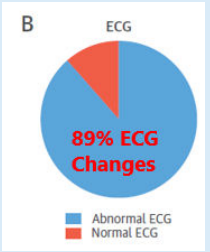
- Myocarditis: 1.4%
  - 11.2% troponin positive rate
  - Of 21 patients with positive hsTnI not attributed to myocarditis, 14.3% had a subsequent ICI delay due to abnormal hsTnI

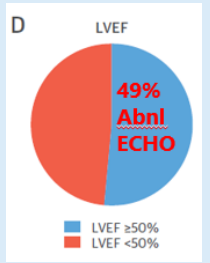
Waliany S, et al. *JACC CardioOncol*. 2021;3(1):137-139.

Detection Methods/Risk Stratification

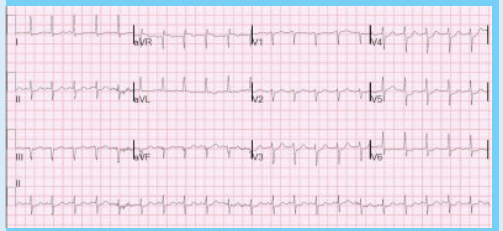
Mahmood 2018





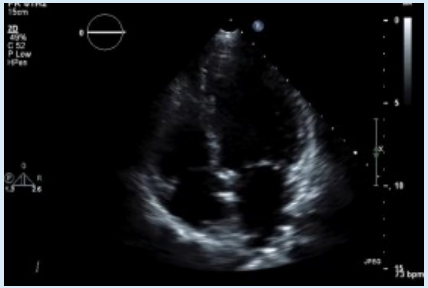


Zlotoff 2021



- 140 Myocarditis vs 179 controls
- Both QRS duration and QTc interval were similar at baseline
- QRS duration prolonged with myocarditis (110 + 22 ms, p<.001)
- Prolonged QRS increased risk of MACE (HR 3.28, p<.001)
- Each 10 msec prolongation = 1.3-fold increase in MACE

Awadalla 2020



- 101 Myocarditis vs 92 control
- GLS was similar at baseline
- 60% Myocarditis had norm. EF
- GLS decreased 14.1 (± 2.8%)
- 51% myocarditis cases experienced MACE, risk of MACE higher with lower GLS (regardless of EF)
- Each % of GLS reduction = 1.5-fold increase in MACE

Zhang 2020

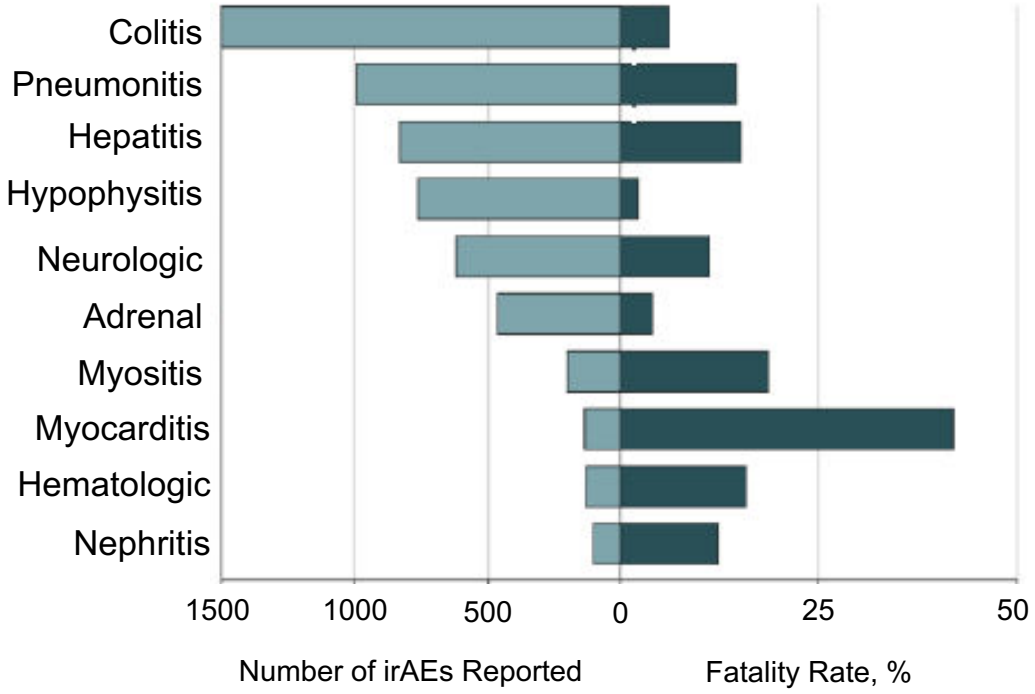
- Cardiac MRI is gold standard test for dx myocarditis. 103 pts (with myocarditis) had cardiac MRI.
- 61% had normal EF ≥ 50%
- Late gadolinium enhancement (LGE) was + in 48% (55% low EF group, 43% nl EF group)
- 40% had MACE, LGE had no prognostic significance

Mahmood SS, et al. *J Am Coll Cardiol*. 2018;71(16):1755-1764; Zlotoff DA, et al. *J Immunother Cancer*. 2021;9(3):e002007; Awadalla M, et al. *J Am Coll Cardiol*. 2020;75(5):467-478; Thavendiranathan P, et al. *J Am Coll Cardiol*. 2021;77(12):1503-1516.

Myocarditis

- Fatality rate of 20%-30%
- Significant Medical Complications
  - Complete Heart Block
  - Ventricular tachycardia
  - Shock
  - Cardiac arrest

Cases and fatality rates (Wang, et al., 2018)



Mahmood SS, et al. *J Am Coll Cardiol*. 2018;71(16):1755-1764; Wang DY, et al. *JAMA Oncol*. 2018;4(12):1721-1728. Erratum in: *JAMA Oncol*. 2018;4(12):1792.

Myocarditis Definition in Literature

Circulation

Definite Myocarditis
Pathology *or*
Diagnostic CMR + syndrome + biomarker or ECG *or*
ECHO WMA + syndrome + biomarker or ECG + negative angiography

Probable Myocarditis
Diagnostic CMR (no syndrome, biomarker or ECG) *or*
Suggestive CMR with either syndrome, ECG or biomarker *or*
ECHO WMA + syndrome (with either biomarker or ECG) *or*
Syndrome with PET scan evidence and no alt diagnosis

Possible Myocarditis
Suggestive CMR with no syndrome, ECG or biomarker *or*
ECHO WMA + syndrome or ECG only *or*
Elevated biomarker with syndrome or ECG and no alt diagnosis

European Heart Journal

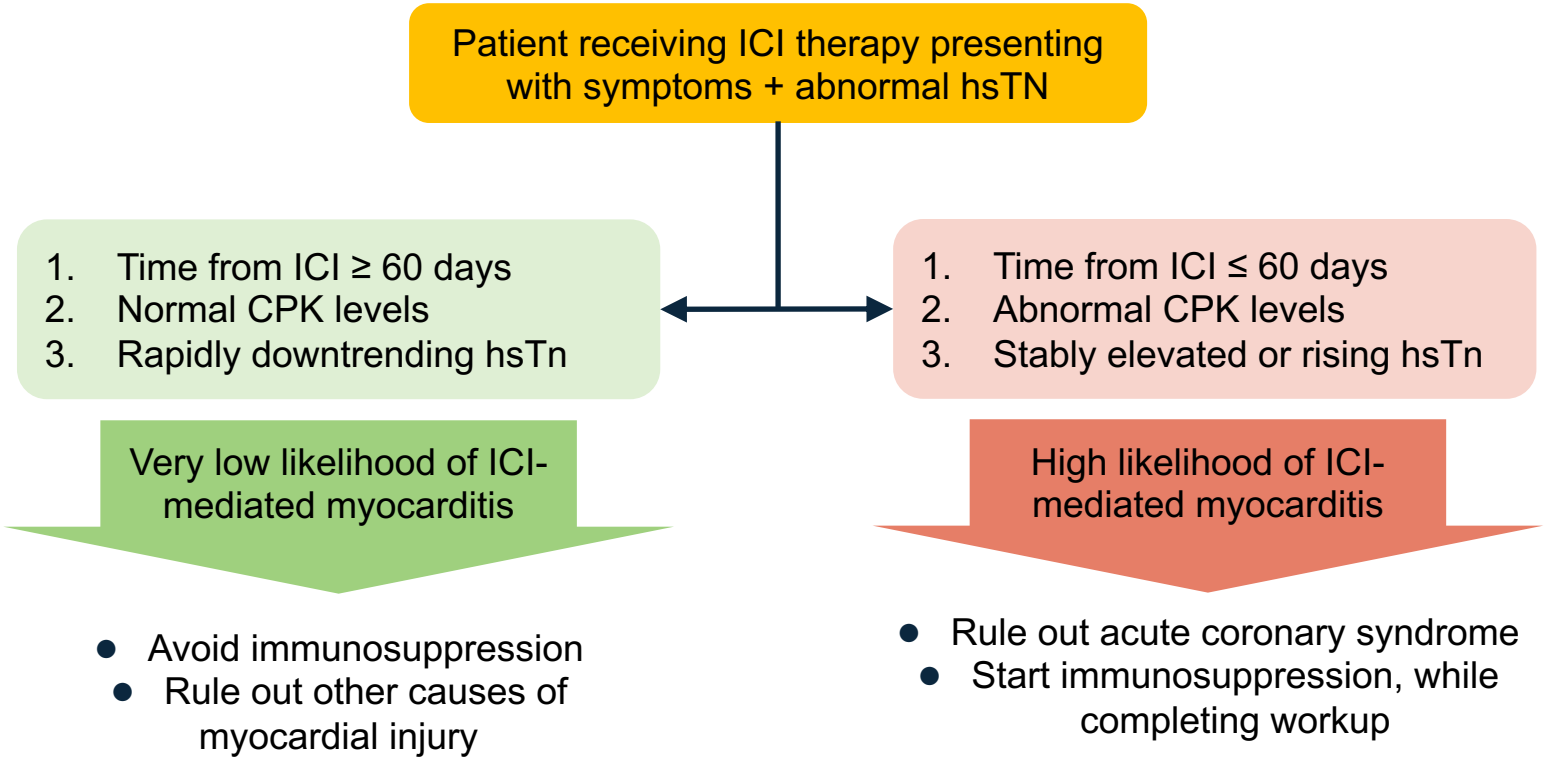
Definite Myocarditis
Pathological diagnosis *or*
Troponin Elevation with 1 **Major Criteria** *or*
Troponin Elevation with 2 **Minor Criteria**

Major Criteria
Cardiac MRI Diagnostic for Acute Myocarditis by Lake Louise Criteria

Minor Criteria
Clinical syndrome (fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, SOB, orthopnea, LE edema, palpitations, dizzy, syncope, shock)
Ventricular arrythmia, new conduction sys dx
Decline in EF, w/ or w/o WMA
Other irAE (esp myositis/MG)
Suggestive MRI (some but not all criteria)

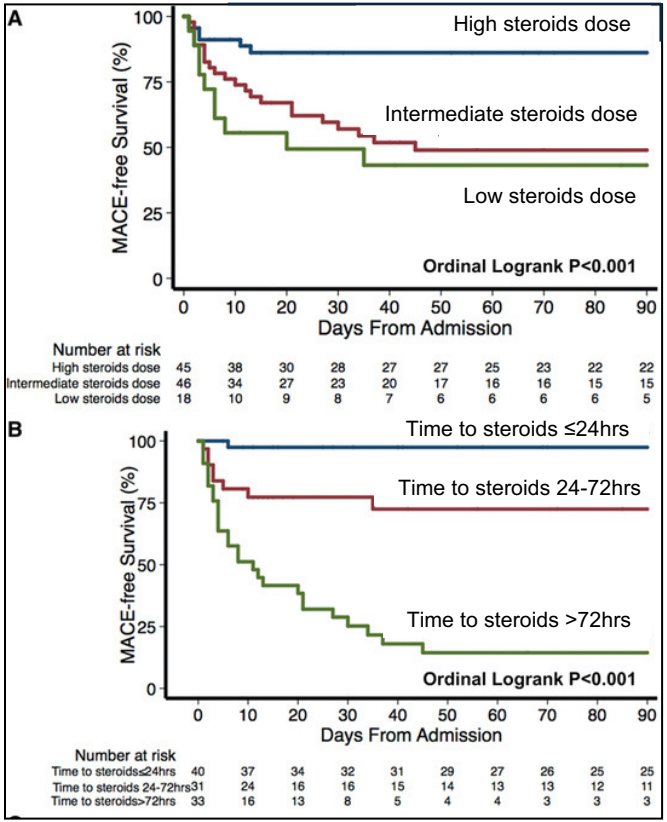
Bonaca MP, et al. *Circulation*. 2019 Jul 2;140(2):80-91; Herrmann J, et al. *Eur Heart J*. 2022;43(4):280-299. Thuny F, et al. *Eur Heart J*. 2022;43(42):4458-4468.

Simplified Myocarditis Definition



Vasbinder A, et al. JACC: *CardioOncology*. in press.

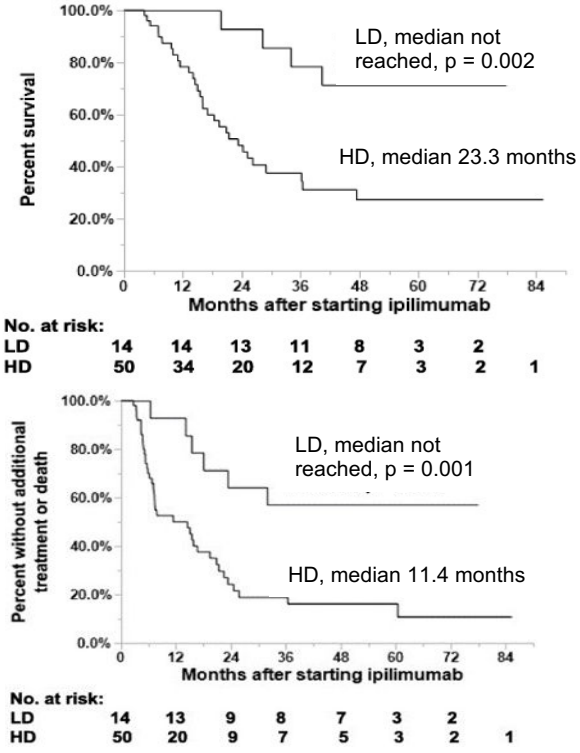
Informing Treatment Guidelines

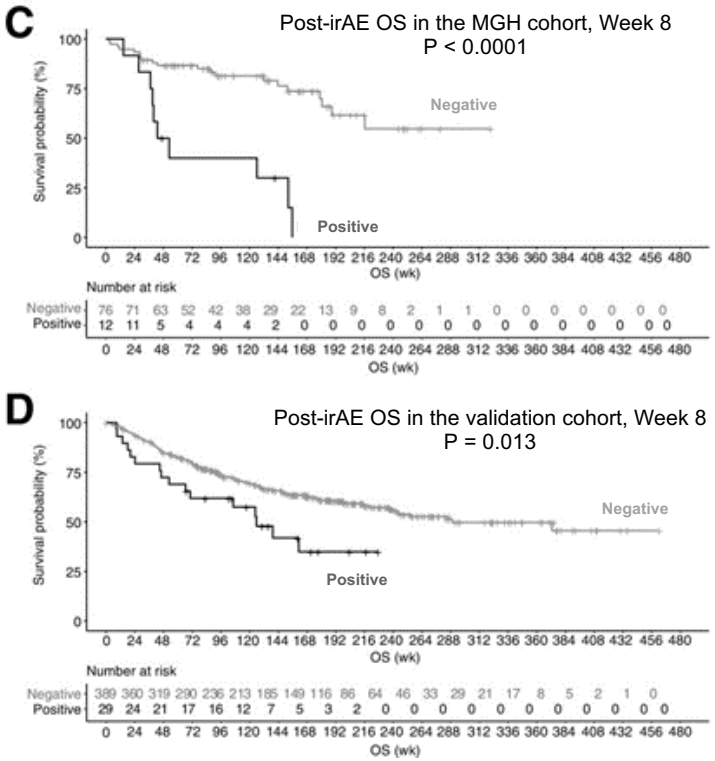


- Clearly an inverse relationship between initial dose of corticosteroids and MACE
  - High dose was associated with a 73% lower risk of MACE (HR 0.27)
- Earlier the better!
  - HR (<24 hr) = 0.03
  - HR (24-72 hr) = 0.3

Zhang L, et al. *Circulation*. 2020;141(24):2031-2034.

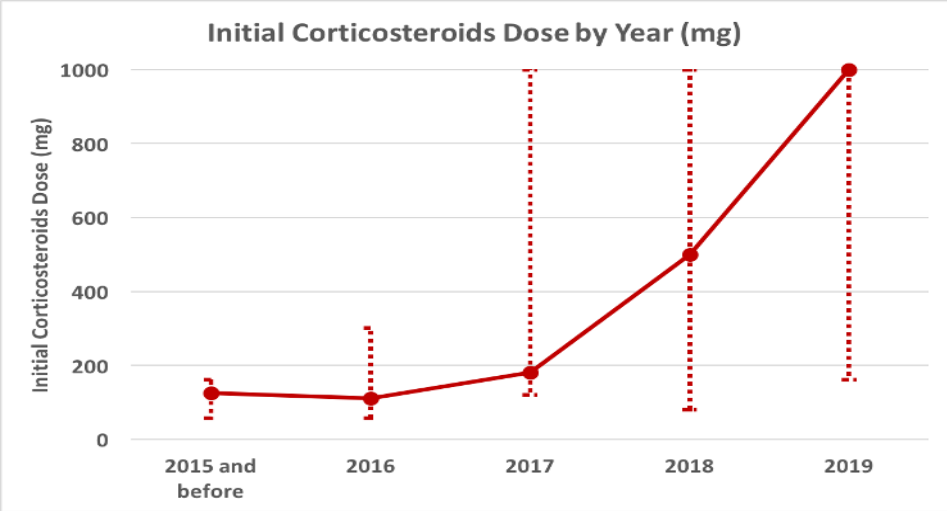
High MACE Rates, Despite Corticosteroids

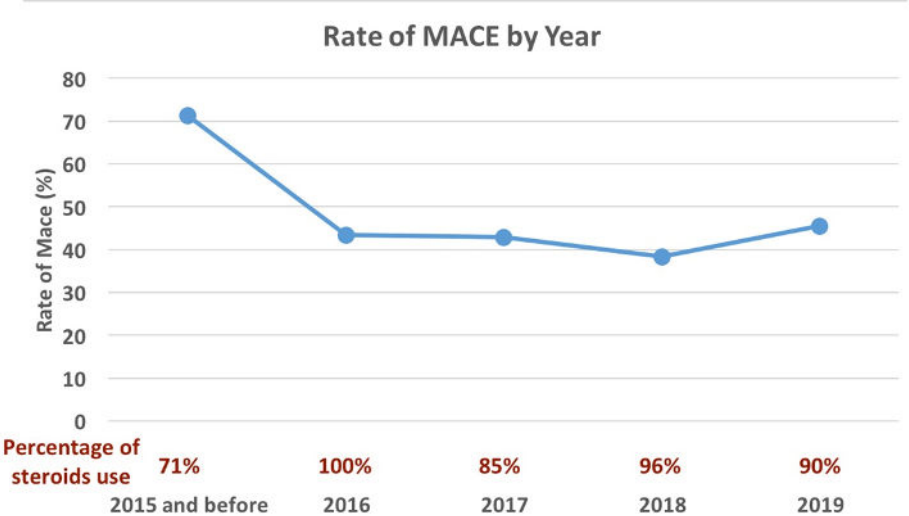




Faje AT, et al. *Cancer*. 2018;124(18):3706-3714; Bai X, et al. *Clin Cancer Res*. 2021;27(21):5993-6000.

High MACE Rates, Despite Corticosteroids

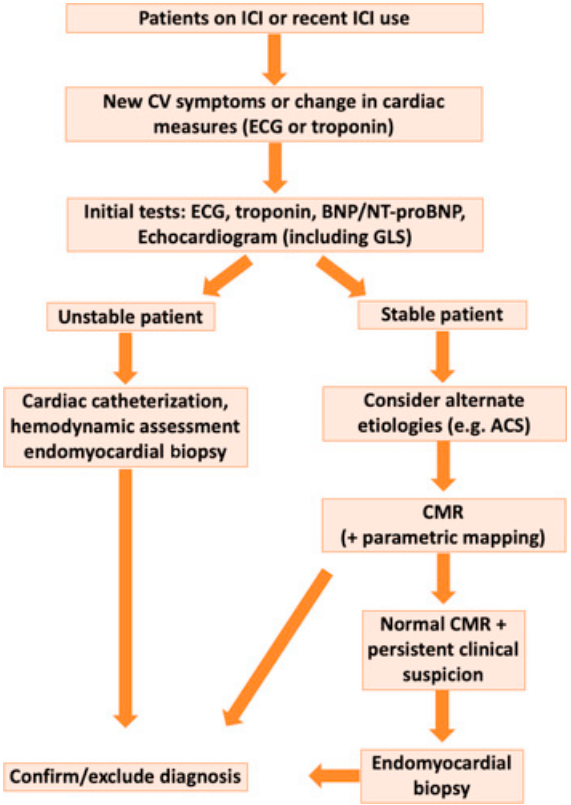




C. Lee, unpublished data.

Managing Refractory Cases

Zhang 2021



Frayberg 2021

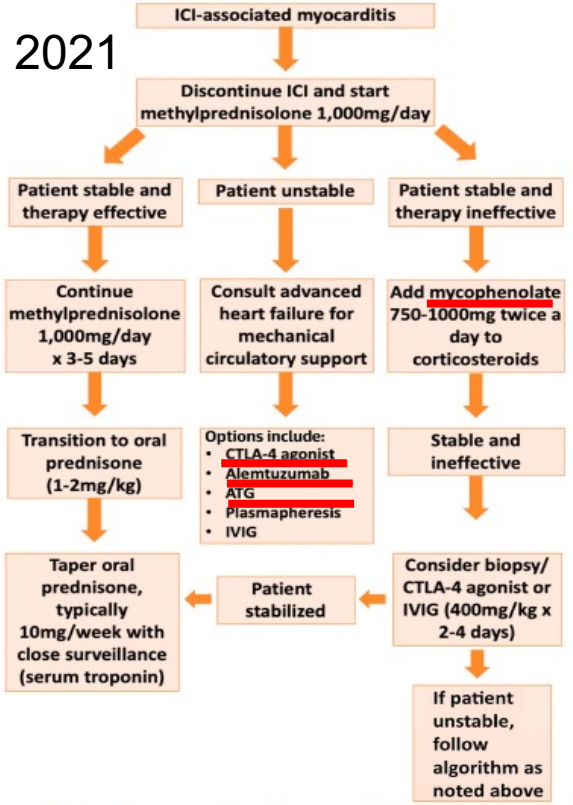
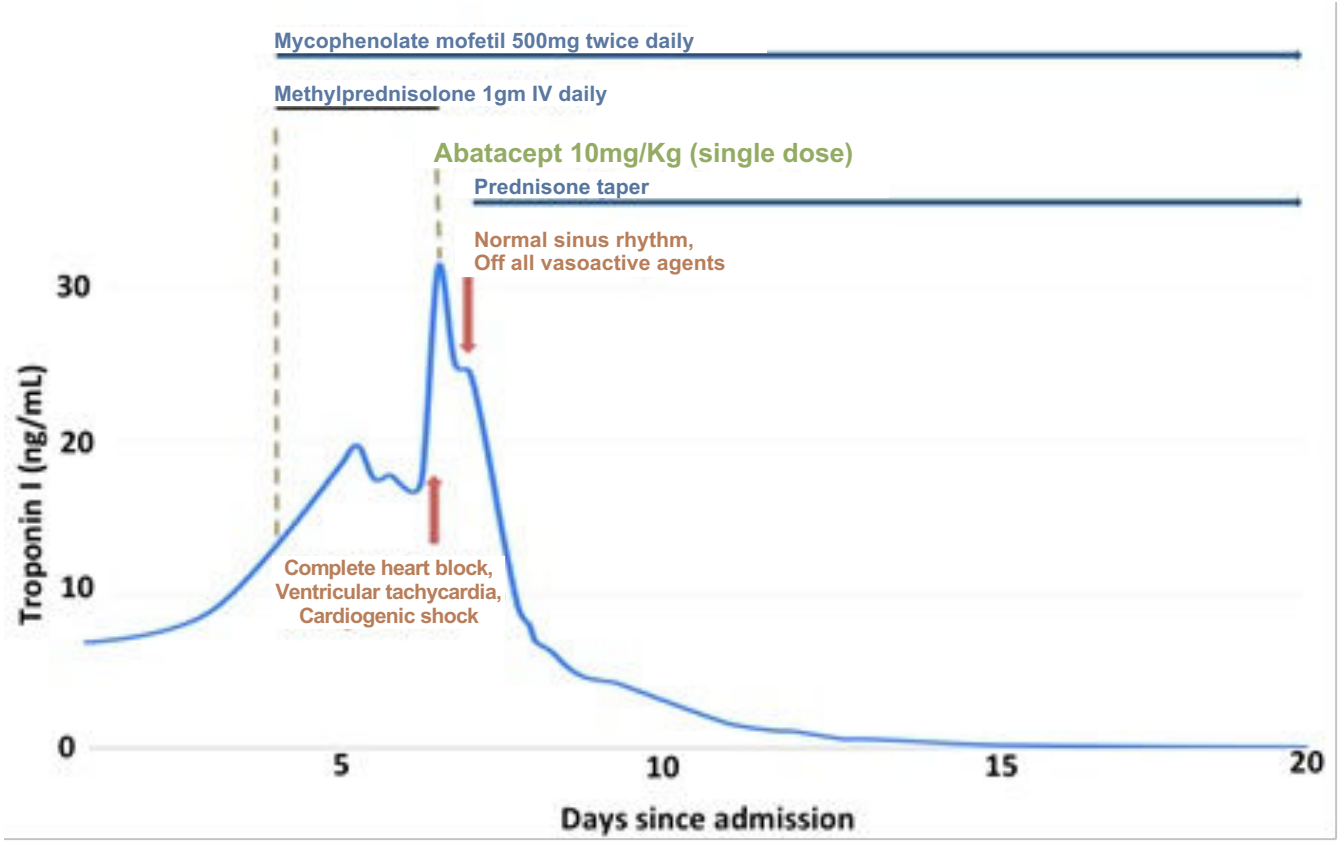


Fig. 2. Therapeutic approach to ICI myocarditis at Massachusetts General Hospital. (Source: *JACC: CardioOncology*

Zhang L, et al. *JACC: CardioOncology*. 2021;3(1):35-47; Frayberg M, et al. *Curr Treat Options Oncol*. 2021;22.

Managing Refractory Cases



S. Mahmood, unpublished data.

ATRIUM Study: Abatacept for ICI-induced Myocarditis

AbatacepT foR ImmUne checkpoint inhibitor associated Myocarditis

- A Phase 3, Investigator-Initiated, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Abatacept Compared to Placebo in Hospitalized Participants with Immune Checkpoint Inhibitor Associated Myocarditis

ATRIUM
Abatacept for Immune Checkpoint Inhibitor Associated Myocarditis

Abatacept in Immune Checkpoint Inhibitor Myocarditis (ATRIUM). https://clinicaltrials.gov/ct2/show/NCT05335928. Accessed November 20, 2022

Consult #2

- 55-year-old male
- No past medical history
- Dx: Metastatic Melanoma (BRAF wildtype) with brain metastasis
- Treatment: Combination IPI-NIVO x 2 cycles (responding!)
- Developed myocarditis-myositis
- Treated with steroids and tapered off < 8 weeks
- Now presenting six months later with progressive melanoma

ICI Rechallenge After irAE

- Vigibase – WHO – Self-report/incomplete information. 452 cases with ICI rechallenge.[1]
  - 28.8% recurred with initial irAE
  - Colitis/hepatitis/pneumonitis – higher rate of recurrence, adrenal events – lower risk
- 40 patients rechallenged - 43% recurrent irAE, 13% new irAE[2]
- 38 patients (lung cancer only) - 26% recurrence irAE, 28% new irAE[3]
- 80 patients (renal cell only) cohort – 45% rechallenged, 50% had subsequent irAE, 19% grade 3[4]
- 180 patients (melanoma only) cohort – 38.9% experienced at least one grade < 2 irAE[5]
- Specific toxicity:[6]
  - Colitis – up to 1/3 cases recurred (more severe = more likely to recur)
  - Pneumonitis – roughly 50% recurred, more with early onset irAE (2 deaths)

Roughly 30-50% recur with irAE, higher with early onset irAE, higher with more severe initial grade irAE

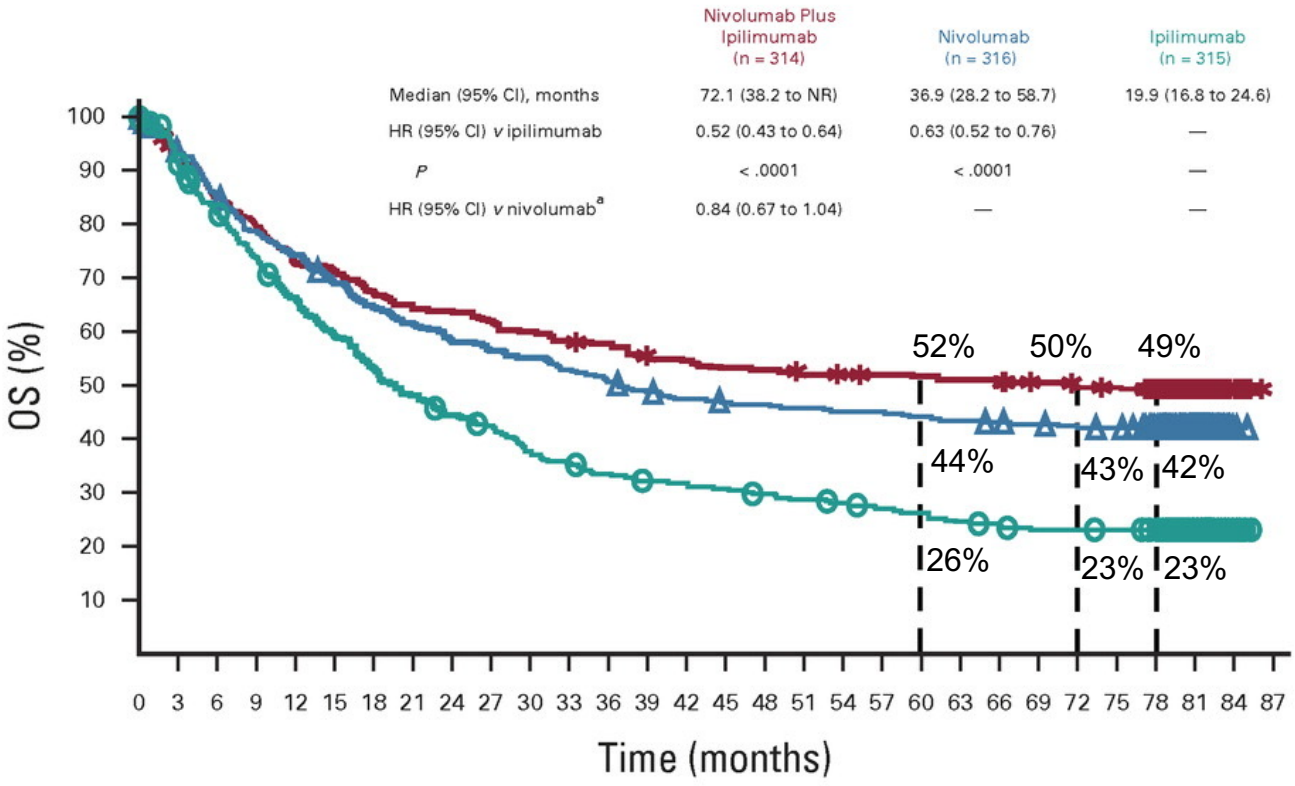
1. Dolladille C, et al. *JAMA Oncol*. 2020;6(6):865-871. 2. Simonaggio A, et al. *JAMA Oncol*. 2019;5(9):1310-1317. 3. Santini FC, et al. *Cancer Immunol Res*. 2018;6(9):1093-1099. 4. Abou Alaiwi S, et al. *J Immunother Cancer*. 2020;8(1). 5. Allouchery M, et al. *J Immunother Cancer*. 2020;8(2). 6. Abu-Sbeih H, et al. *J Clin Oncol*. 2019;37(30):2738-2745

Consult #3

- 72-year-old female
- Hypertension, hyperlipidemia, diabetes (type II)
- Dx: Metastatic Melanoma
- Treatment: PD-1 monotherapy
- irAEs: Hypothyroidism
- Response: Complete response
- Considering stopping ICI therapy

CheckMate-067: 6.5-year Follow Up

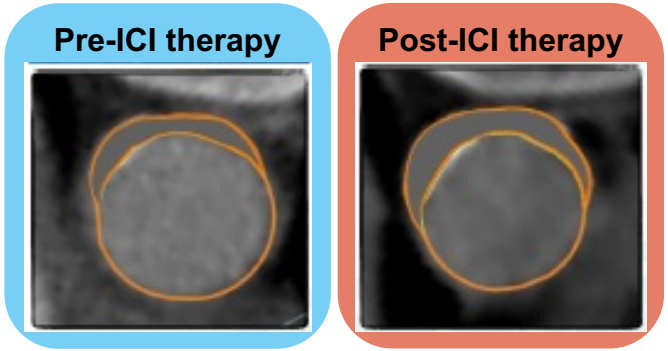
- Durable, improved clinical outcomes with nivolumab plus ipilimumab in patients with melanoma



Wolchok JD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. Journal of Clinical Oncology. 2021;40(2):127-137.

ICI Therapy-associated Atherosclerosis

- Immune checkpoints are critical negative regulators of atherosclerosis
- ICI use increased annual total plaque progression
  - 2.1% pre-ICI to 6.7% post-ICI (3-fold)

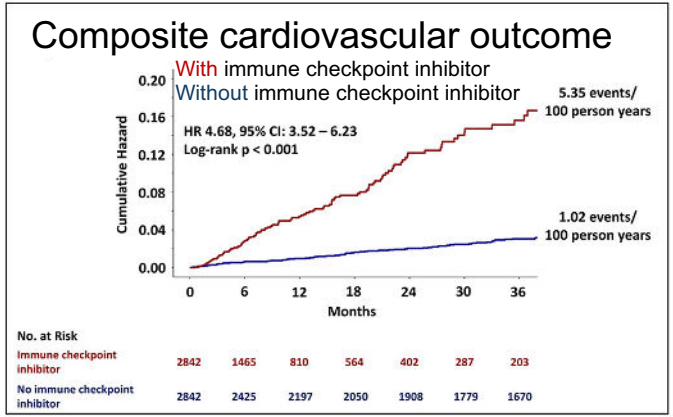


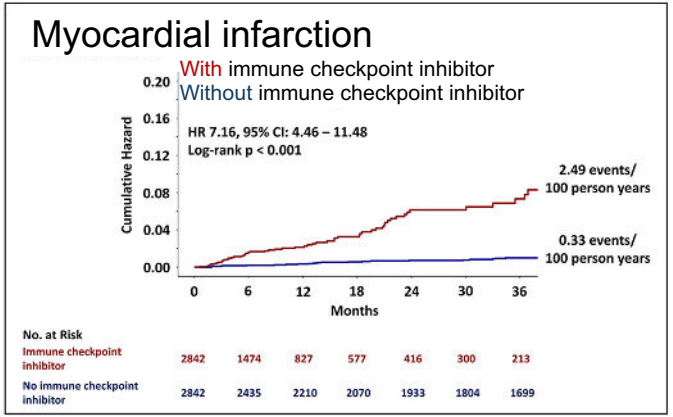
Absolute change		Prior scan → Baseline	Baseline → Post scan	P Value
Indexed change per year, mm^3/year	Total plaque volume	13.8 (−240, 122)	103 (0, 511)	0.02
	Non-calcified plaque volume	−18.2 (−274, 57)	53 (0, 382)	0.02

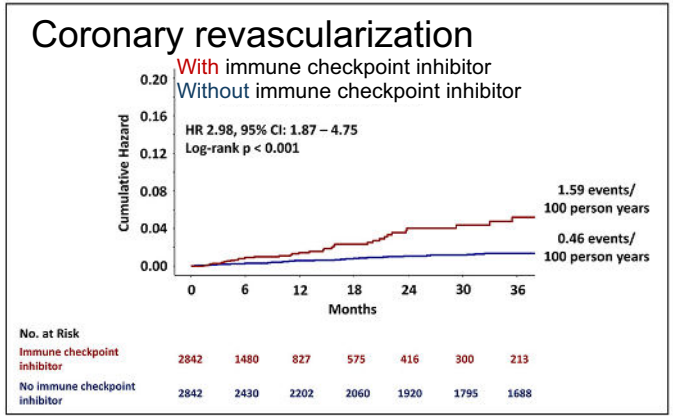
Patients treated with an ICI are at a higher risk for atherosclerotic cardiovascular events, and this risk is potentially modifiable

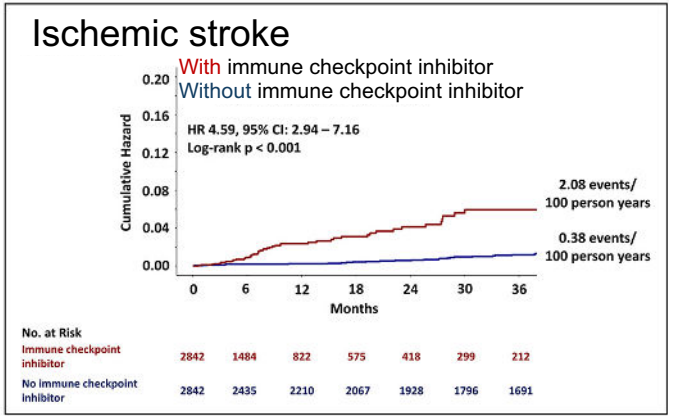
Drobni ZD, et al. *Circulation*. 2020;142(24):2299-2311.

Kaplan Meier Curves of Cumulative Hazards









Drobni ZD, et al. *Circulation*. 2020;142(24):2299-2311.

Summary

- Dual ICI therapy appears to be associated with greater risk of ICI-mediated cardiotoxicity
- Troponin levels, ECG changes, echocardiogram, and cardiac MRI may be useful in identifying myocarditis, but have limitations
- For patients experiencing myocarditis, discontinue ICI and begin steroid; additional immunosuppression may be necessary for patients refractory or unresponsive to steroids
- No clear guidance for possible rechallenge after ICI-mediated myocarditis; a third to half of patients will recur with an irAE after rechallenge

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Be vigilant for signs of cardiotoxicity; encourage pre-therapy cardiac evaluation (troponin levels, ECG)
- Employ early and high-dose immunosuppression for patients with ICI-mediated cardiotoxicity
- If rechallenging patients with ICI therapy after irAE consider treatment response, level of immunosuppression, and severity of irAE (cardiac/neurological irAEs are most fatal)

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