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Severe Immunotherapy Complications (SIC) Service: A Model Integrating Clinical Care and Clinical-Translational Research

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Financial Disclosures

In relation to this presentation, I declare that there are no conflicts of interest.

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Estimated # of Patients, > 270,000+

	Stage III % of Total Incidenc	Max Eligible w/o Recur.
NSCLC Stage III (post-chemoRT)	20%	19,435
	Stage III % of Total Incidenc	**Max Eligible w/o Recur.**
Melanoma Stage III (post-surgery)	7%	6,172
	Stage IV % of Total Incidenc	**Max Eligible w/o Recur.**
NSCLC Stage IV	51%	98,057
SCLC Extensive (Stage IV)	51%	14,656
Female Breast Stage IV	6%	15,906
Melanoma Stage IV	4%	4,036
RCC Stage IV	15%	11,180
Bladder Stage IV*	16%	12,785
Colon Stage IV	23%	23,130
Rectal Stage IV	19%	8,226
Hodgkin Lymphoma Stage IV	21%	1,716
Head & Neck squamous cell carcinoma St	50%	23,935
Merkel Cell carcinoma Stage IV	7%	112
Hepatocellular carcinoma Stage IV	26%	10,891
Microsatellite instability-high colorectal	NA	7,500
Microsatellite instability-high noncolorectal	NA	0
Gastric Stage IV	39%	10,665
Primary mediastinal large B-cell lymphoma	50%	890
Cervical Stage IV	17%	2,199
Citation: SEER 18, National Cancer Data Base (NCDB)		**271,492**

SEER, NCDB

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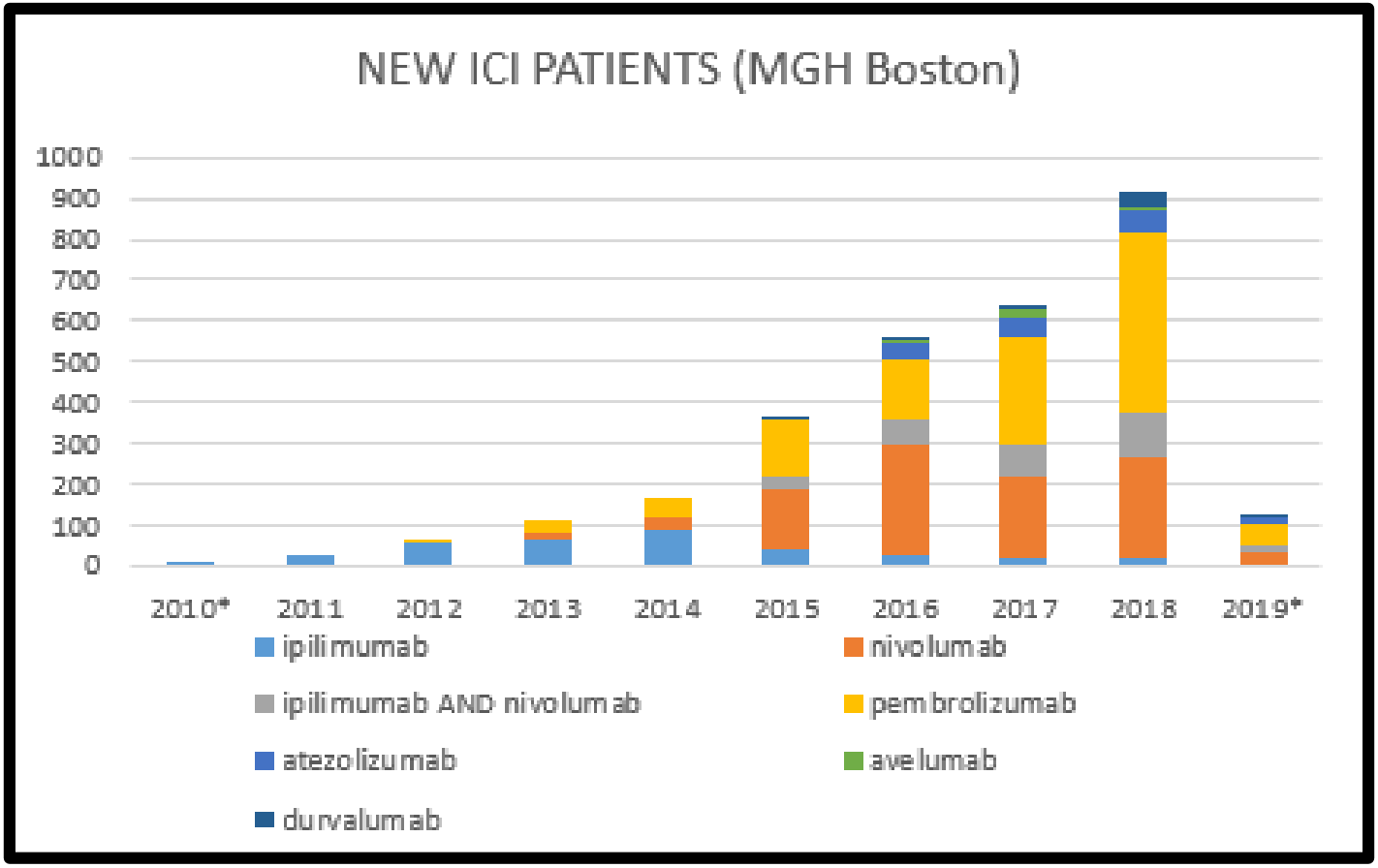
Immune Checkpoint Inhibitor (ICI) at MGH



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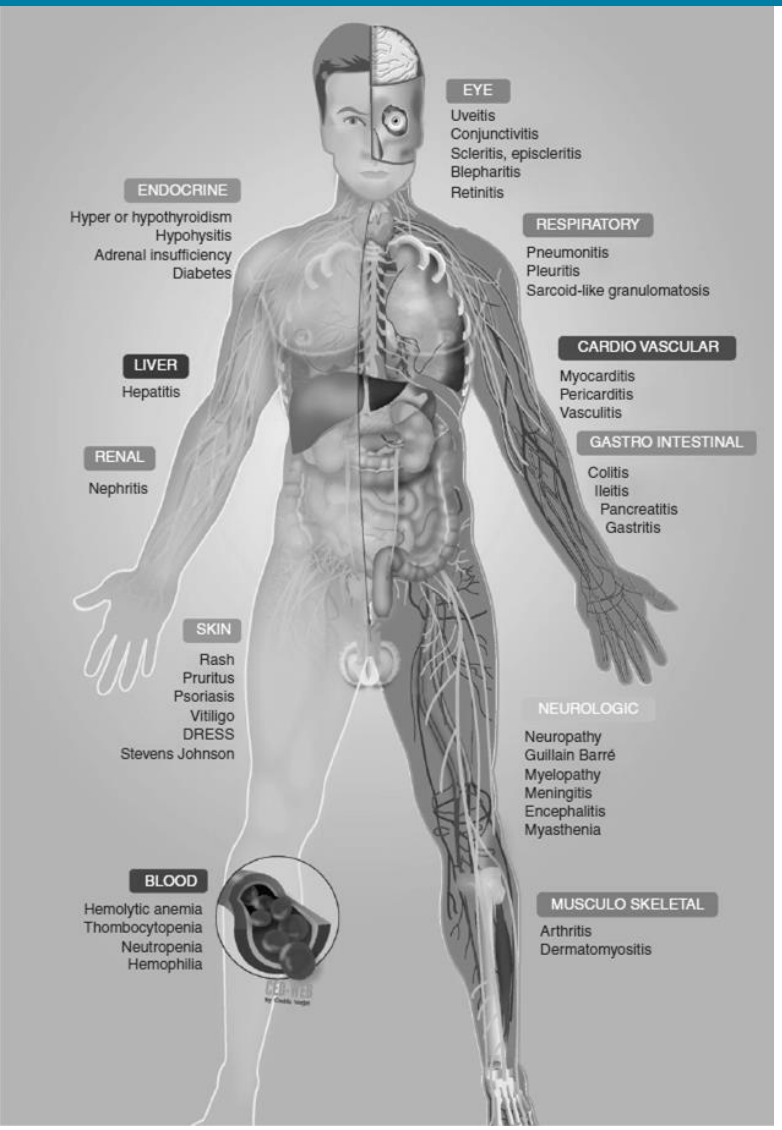
Immune-Related AEs (irAEs)



- Colitis
- Hepatitis
- Pneumonitis
- Endocrinopathies
- Myocarditis
- Nephritis
- Anemia/Neutropenia/Thrombocytopenias
- Arthritis
- Dermatitis
- Neuro Involvement
- Uveitis

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Champiat, Ann of Onc, 2016

Patient: DM

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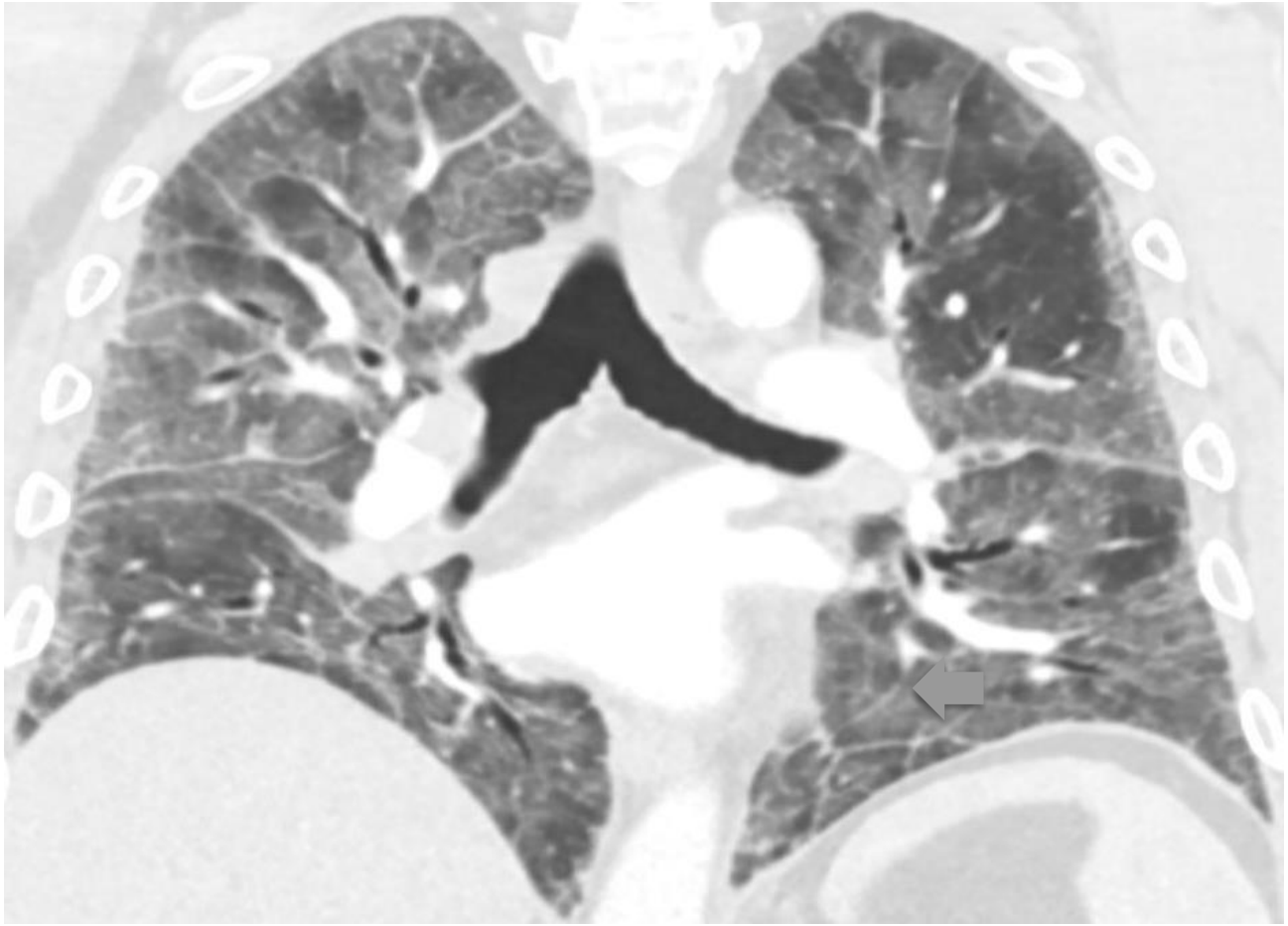
Chest CT 4/4/16 @6PM



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Many Questions, Few Answers

- *What is the best way to **prepare** physicians and teams for the wave of these case presentations? How do we assemble experts?*
- *Can we **define** these events and create a framework for the development of best practices to manage them?*
- *Can we develop **diagnostics** that help us detect immune related adverse events early, and with accuracy?*
- *Are there **biomarkers** to indicate if you are going to have an uncomplicated course or one like David's?*
- *What is the **underlying pathophysiology** of the clinical presentations? How can this lead to evidence-based treatments for toxicity?*
- *Can we uncover **predictors** for the development of severe toxicity? How can we develop a clinical prediction model to inform patients and providers?*

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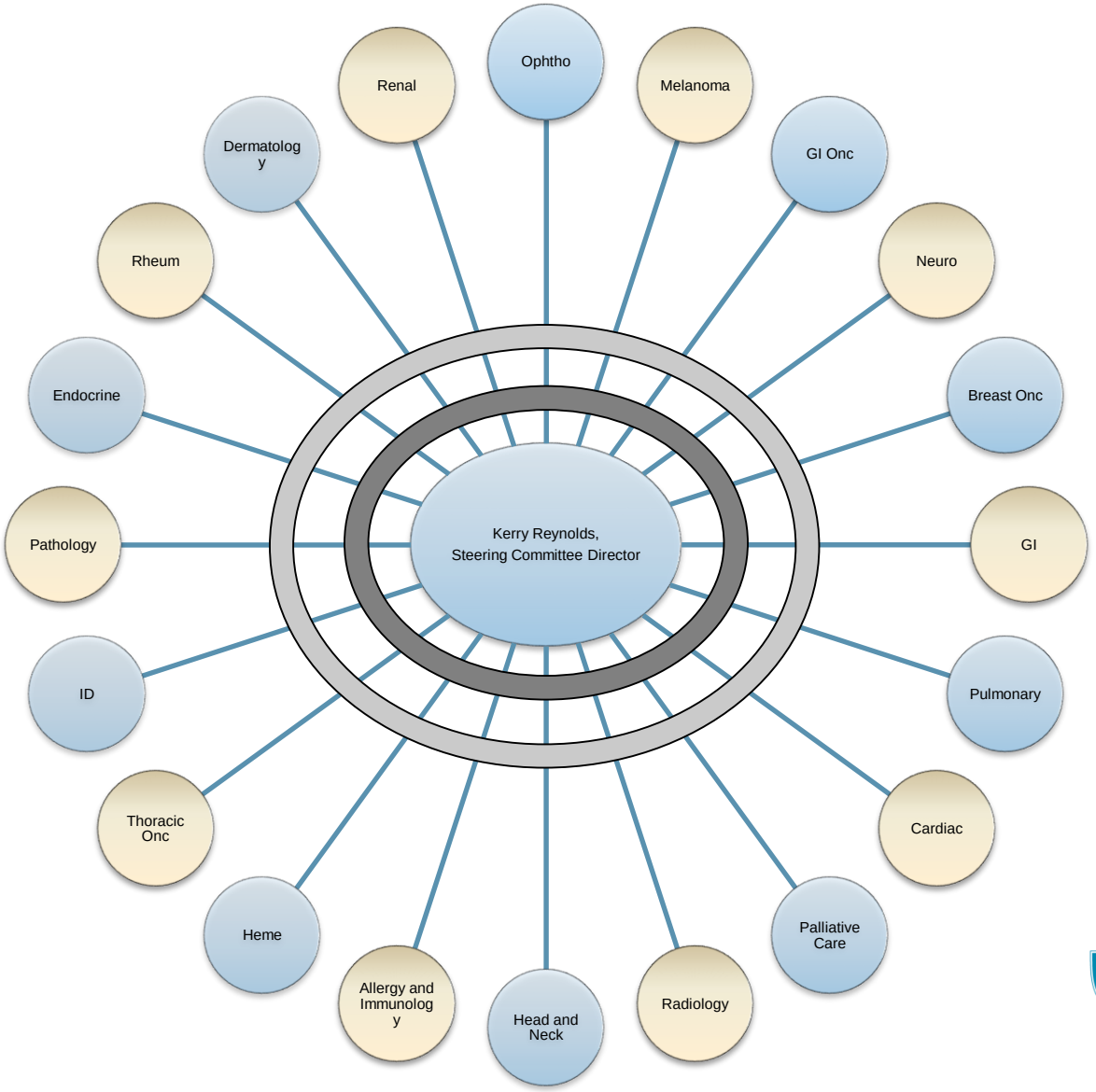
Immunotherapy Toxicity Service



Represents Clinical Research

Represents Translational Research

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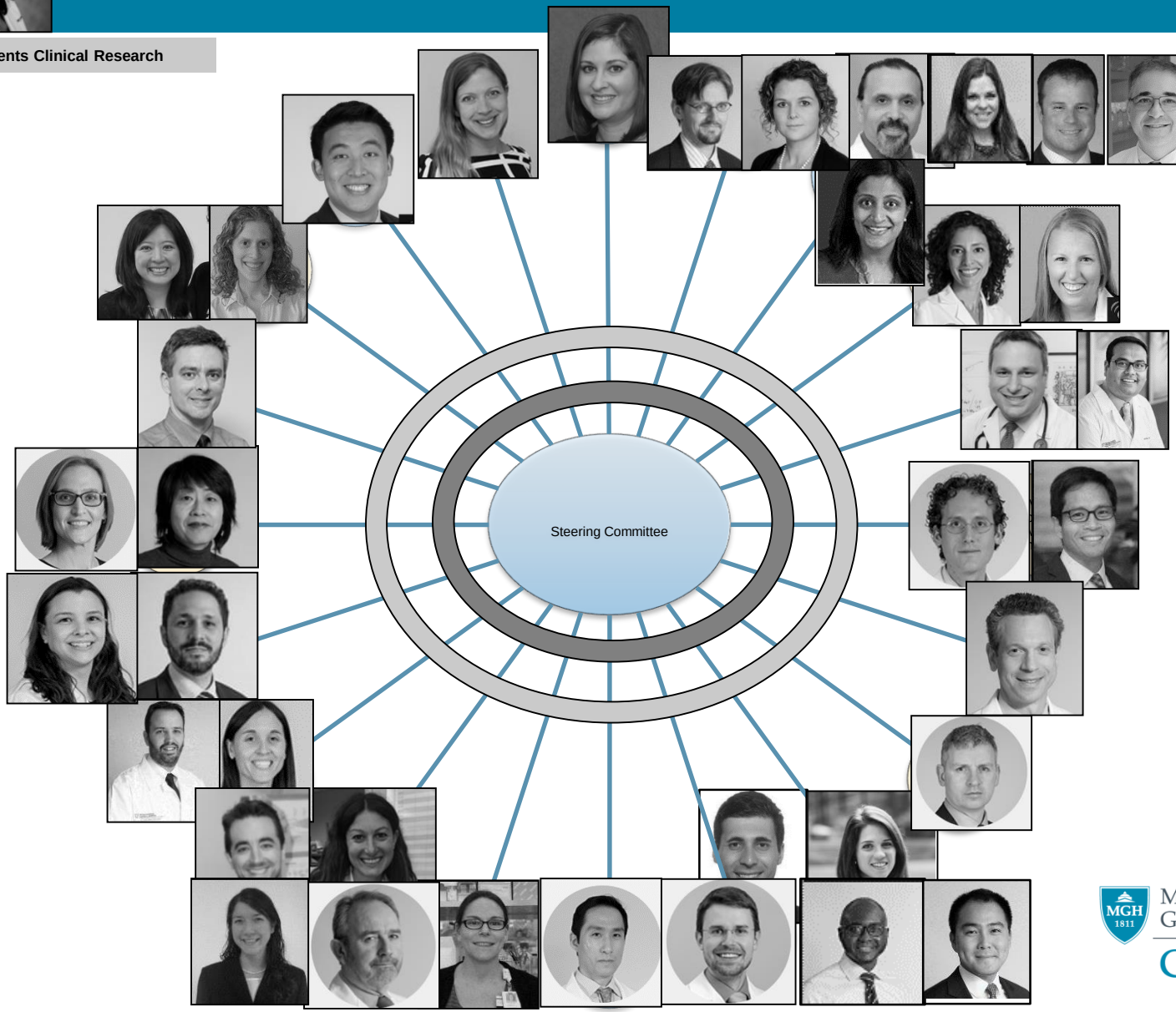
Immunotherapy Toxicity Service

Represents Clinical Research

Translational Research



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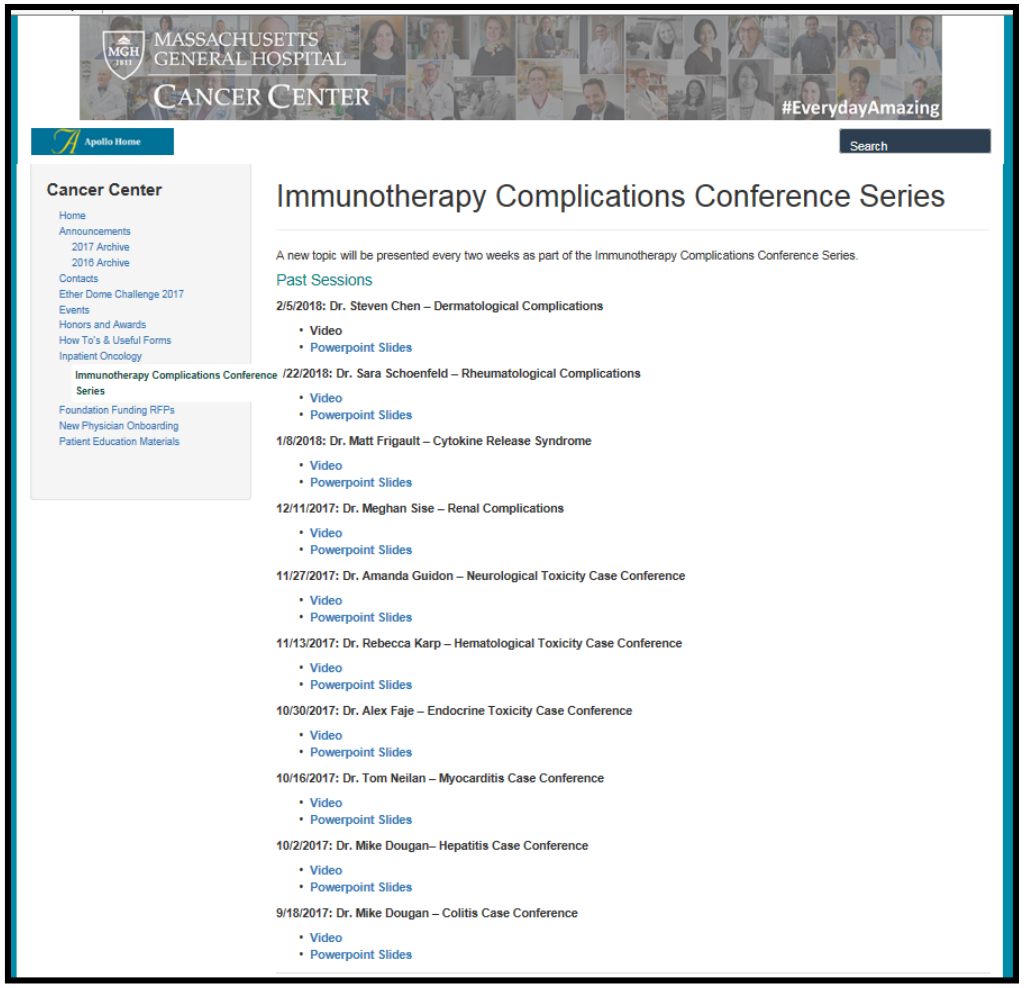
Vision – Educate Across Hospital/Community

Immunotherapy Toxicity Clinical Conference, YAWKEY 4-820, Monday 7 AM

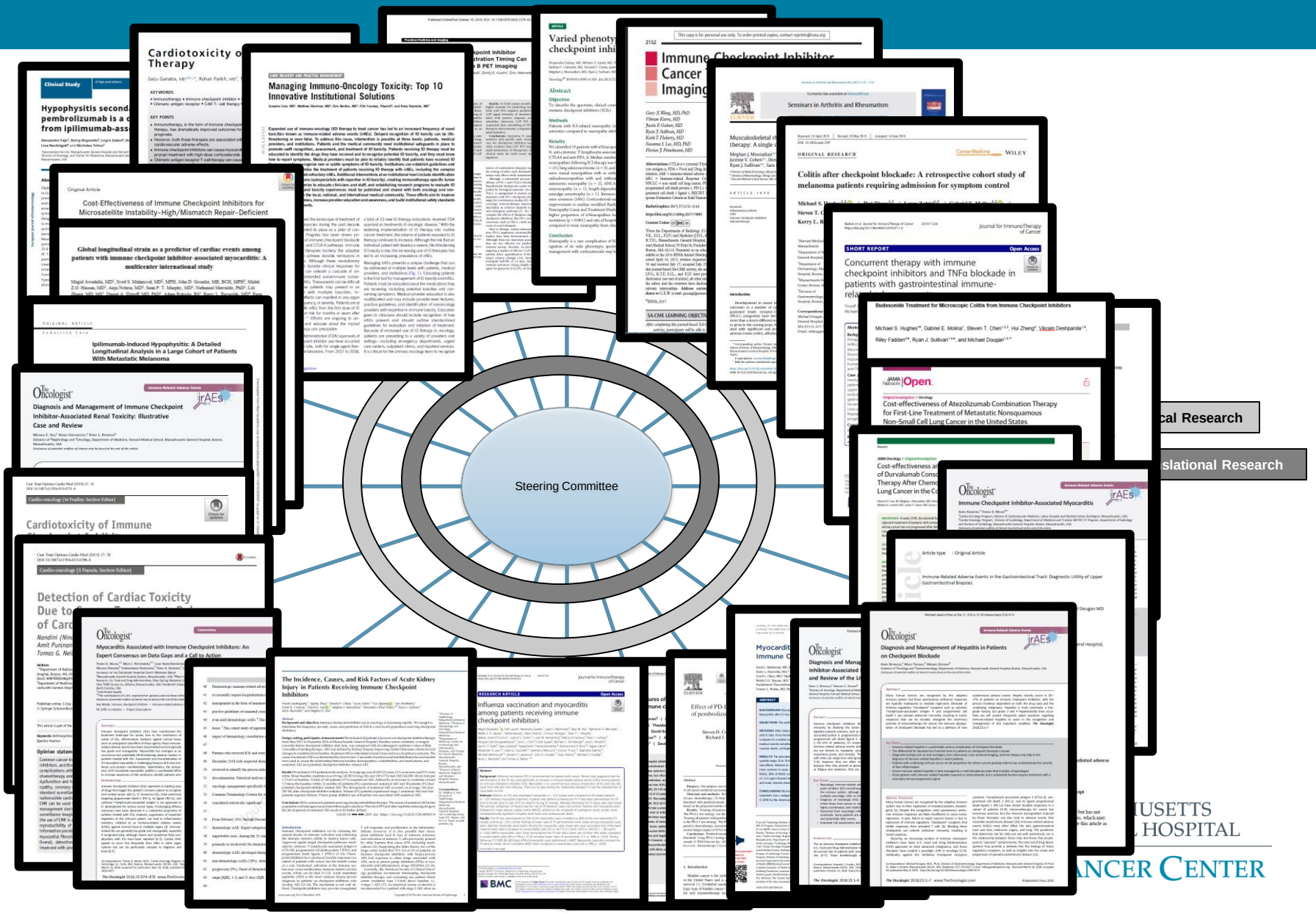








Immunotherapy Toxicity Service



Nephrology

The Incidence, Causes, and Risk Factors of Acute Kidney Injury in Patients Receiving Immune Checkpoint Inhibitors

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Correspondence: Dr. Meghan E. Sise, Division of Nephrology, Department of Internal Medicine, Massachusetts General Hospital, 165 Cambridge Street, Suite 302, Boston, MA 02114. Email: msise@partners.org

Abstract

Background and objectives Immune checkpoint inhibitor use in oncology is increasing rapidly. We sought to determine the frequency, severity, cause, and predictors of AKI in a real-world population receiving checkpoint inhibitors.

Design, setting, participants, & measurements We included all patients who received checkpoint inhibitor therapy from May 2011 to December 2016 at Massachusetts General Hospital. Baseline serum creatinine, averaged 6 months before checkpoint inhibitor start date, was compared with all subsequent creatinine values within 12 months of starting therapy. AKI was defined by Kidney Disease: Improving Global Outcomes criteria for fold changes in creatinine from baseline. Sustained AKI events lasted at least 3 days and was our primary outcome. The cause of sustained AKI was determined by chart review. Cumulative incidence and subdistribution hazard models were used to assess the relationship between baseline demographics, comorbidities, and medications, and sustained AKI and potential checkpoint inhibitor–related AKI.

Results We included 1016 patients in the analysis. Average age was 63 (SD 13) years, 61% were men, and 91% were white. Mean baseline creatinine was 0.9 mg/dl (SD 0.4 mg/dl), and 169 (17%) had CKD (eGFR<60 ml/min per 1.73 m²) at baseline. A total of 169 patients (17%) experienced AKI, defined by an increase in creatinine at least 1.5 times the baseline within 12 months; 82 patients (8%) experienced sustained AKI and 30 patients (3%) had potential checkpoint inhibitor–related AKI. The first episode of sustained AKI occurred, on average, 106 days (SD 85) after checkpoint inhibitor initiation. Sixteen (2%) patients experienced stage 3 sustained AKI and four patients required dialysis. Proton pump inhibitor use at baseline was associated with sustained AKI.

Conclusions AKI is common in patients receiving checkpoint inhibitor therapy. The causes of sustained AKI in this population are heterogenous and merit thorough evaluation. The role of PPI and other nephritis-inducing drugs in the development of sustained AKI needs to be better defined.

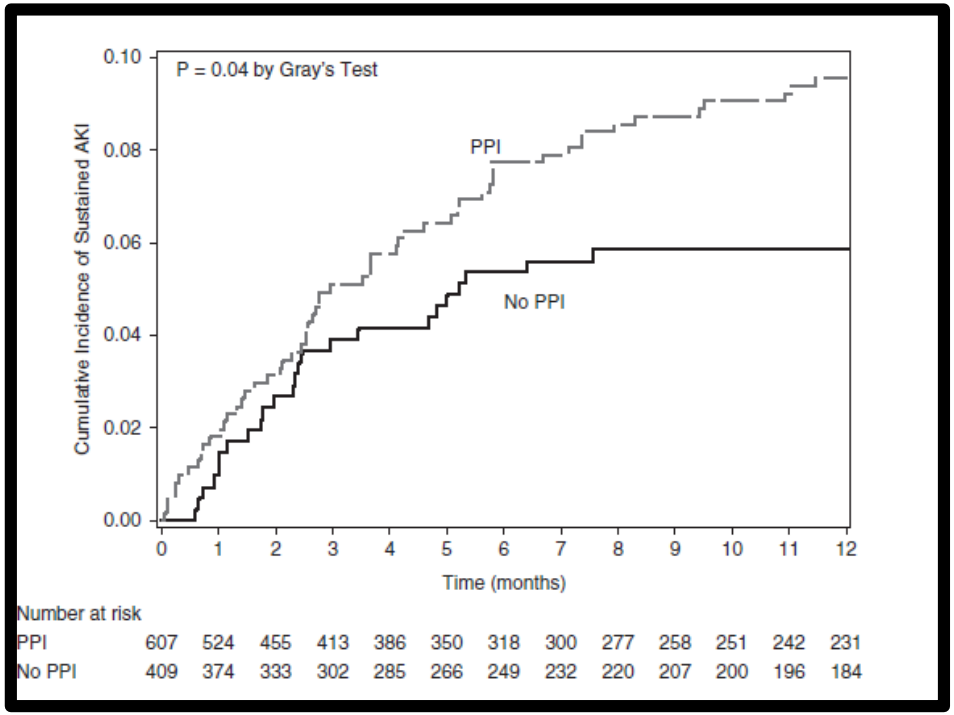
CJASN 14: ●●●–●●●, 2019. doi: https://doi.org/10.2215/CJN.00990119

Introduction

Immune checkpoint inhibitors act by releasing the natural breaks on immune activation and enhancing the immune system's ability to destroy tumor cells. Approved agents target checkpoint pathways mediated by cytotoxic T lymphocyte–associated antigen 4 (CTLA4), programmed cell death protein 1 (PD1), and programmed death ligand 1 (PDL1) (1–10). Checkpoint inhibitors have produced durable responses in a subset of patients with cancer, but the benefit comes at a cost. Unchecked activation of the immune system may cause multisystem, immune-related adverse events, which can be fatal (11,12). Acute interstitial nephritis (AIN) is the most common biopsy-proven diagnosis in patients on checkpoint inhibitors who develop AKI (13–16). The mechanism is not well defined. Checkpoint inhibitors may provoke unregulated T cell responses and proliferation in the tubulointerstitium; however, it is also possible that checkpoint inhibitors lead to loss of immune tolerance and activation of memory T cells previously primed by other haptens that cause AIN, including medications (12). Supporting the latter theory, two of the larger series found that 73% (14 of 19) of patients on immune checkpoint inhibitors with biopsy-proven AIN had exposure to other drugs associated with AIN, such as proton pump inhibitors (PPIs) or nonsteroidal anti-inflammatory drugs (NSAIDs) (13,14).

Currently, the American Society of Clinical Oncology guidelines recommend interrupting checkpoint inhibitor therapy and evaluating any patient whose serum creatinine rises 1.5-fold above baseline *i.e.*, ≥stage 1 AKI (17). An empirical course of steroids is recommended for a patient with stage 2 AKI when an

Seethapathy et al, CJASN, 2019



Proton Pump Inhibitor Associated with AKI

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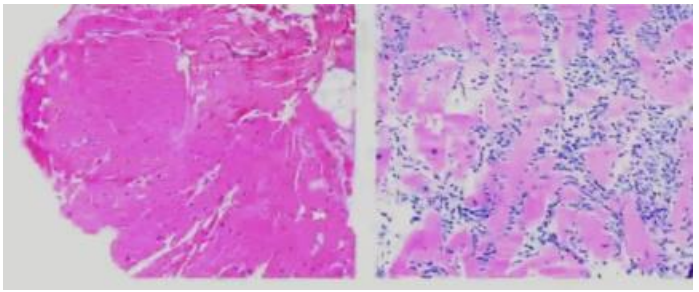
Example of SIC Service in Action

73 YOM w/ renal cell carcinoma (s/p nephrectomy), CKD (Cr 1.64), HTN that is 6 weeks out from first anti-PD-1 (with axitinib) for metastatic renal cell carcinoma.

Cycle 2 began the start of what he reports is “flu-like” symptoms – fatigue, dry cough, SOB, chest “constriction”, better when he sits up. He came to clinic for his 3rd dose found to be in aflutter/fib with HR in 150s. His troponin was 117. Stable hemodynamics. Looks well.

Cardiac RF: impressive calcifications on his chest CT, CKD, HTN

ECHO normal



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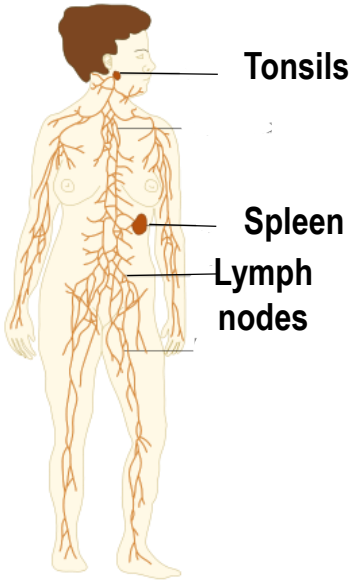
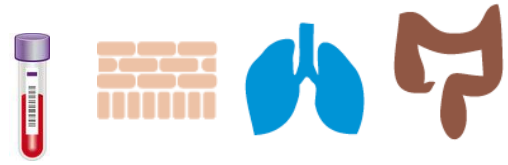
Next-Generation Microscope: Single Cell Genomics Strategies

Tissues to be profiled

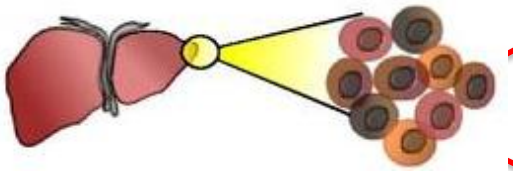
Lymphoid Organs



Non-Lymphoid "Barrier" Organs



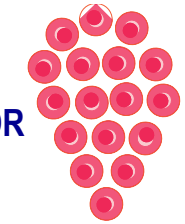
Sample dissociation,



Solid Tissue

Dissociated Tissue

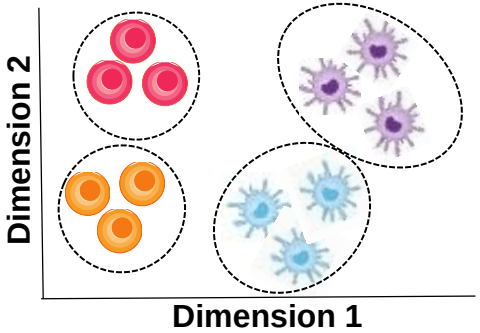
OR



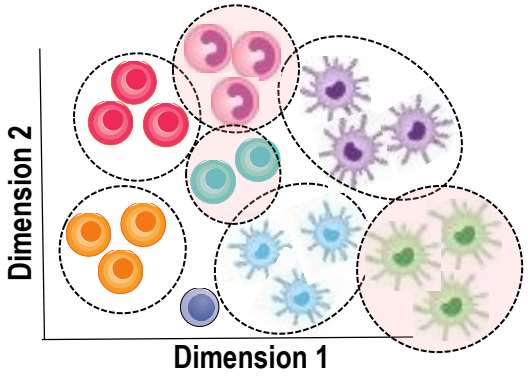
Single cell isolation

Single cell
RNA-Sequencing & analysis

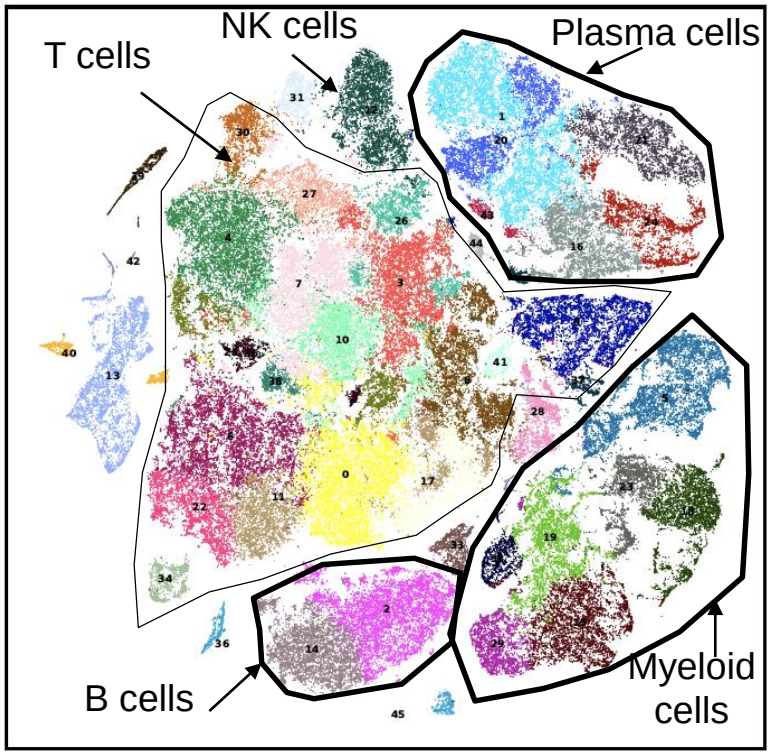
"Healthy" State



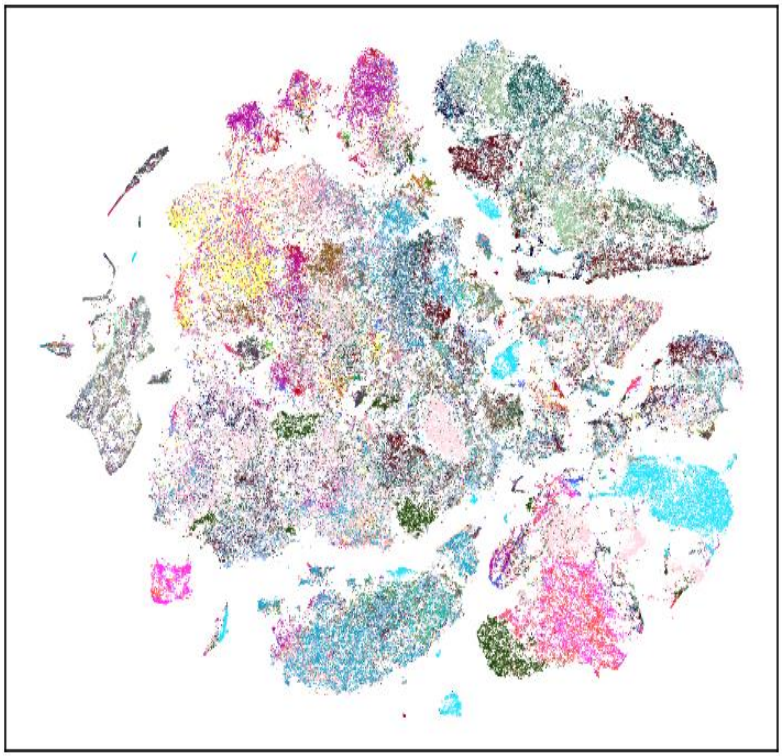
Disease State



Cellular Ecosystem Appears Shared Across Patients



Cells colored by patients (n=37)



Patient IDs:

AIH_1	SIC_40	SIC_89
SIC_1	SIC_42	SIC_94
SIC_2	SIC_43	SIC_97
SIC_5	SIC_53	SIC_100
SIC_8	SIC_55	SIC_105
SIC_13	SIC_57	SIC_109
SIC_19	SIC_58	SIC_121
SIC_25	SIC_60	SIC_126
SIC_31	SIC_68	SIC_132
SIC_32	SIC_69	SIC_134
SIC_33	SIC_71	SIC_139
SIC_35	SIC_82	SIC_141
SIC_36		

→There are shared biological programs driving irAEs (not patient specific)

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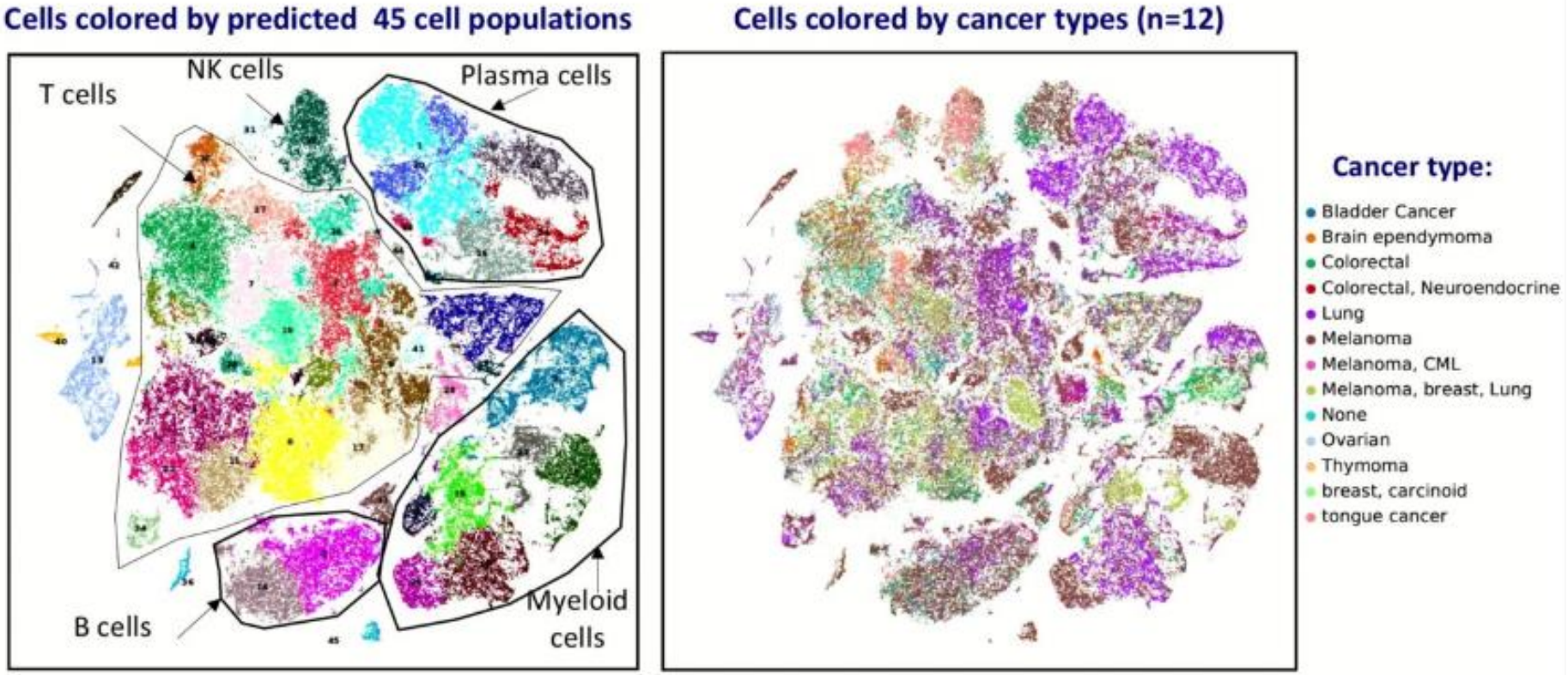
C Villani Lab 2019

Cellular Ecosystem Appears Shared Cancer Types



→ irAEs are more closely related to the immune system than to the tumor

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Outcomes of SIC Program

- Identify a set of biomarkers to be implemented in clinic
- Development of better therapeutic strategies to treat autoimmune-toxicities while maintaining anti-tumor immunity → inform next-generation mechanism-based clinical trial
- Further our understanding of early mechanisms leading to autoimmune diseases
- Identifying novel druggable targets with immunosuppressive potential
- **Train the next-generation** of physicians and scientists to embrace precision medicine
- Deliver world-class care and **help patients and their families** through the immunotherapy journey

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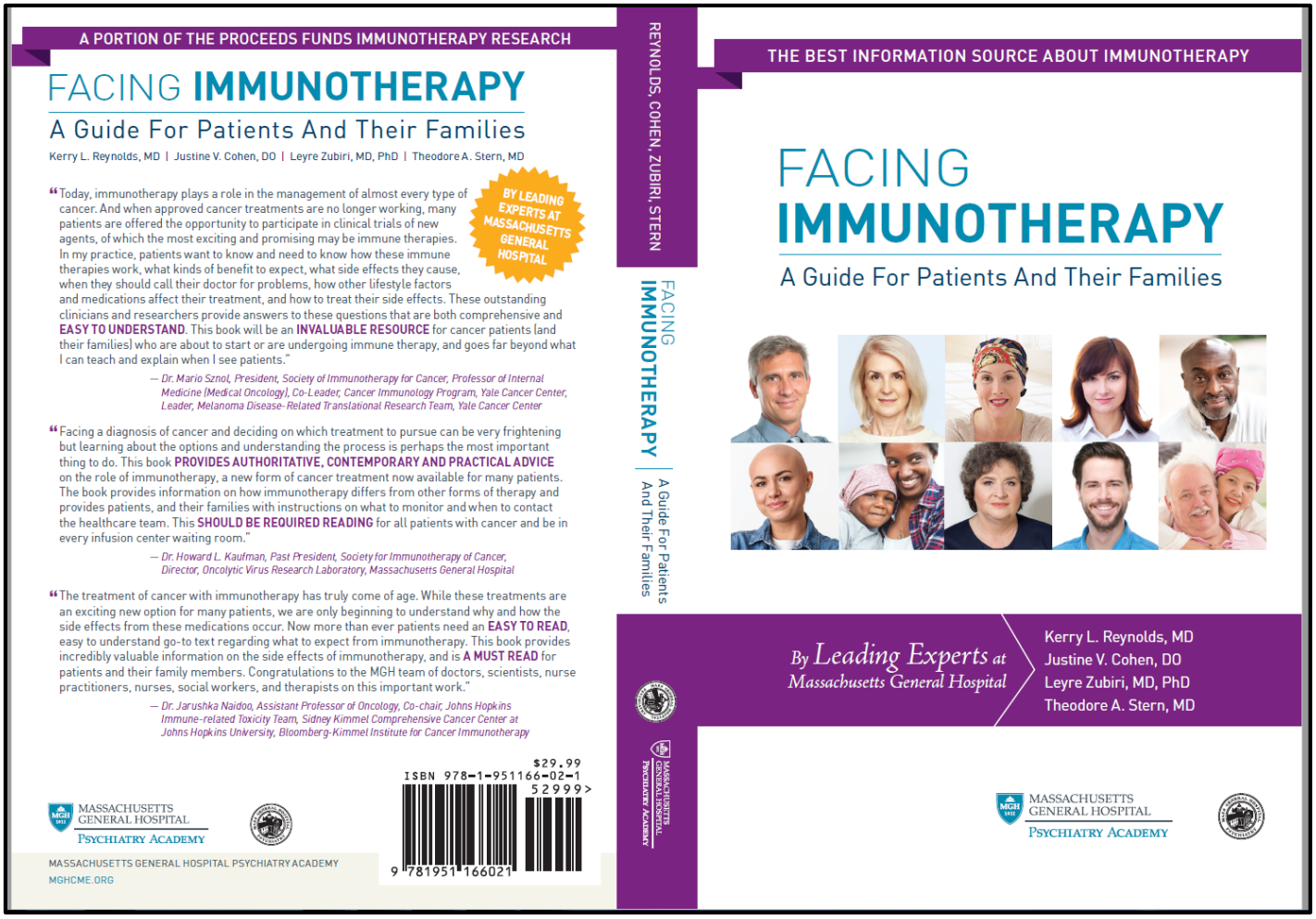
Facing Immunotherapy



Coming to Amazon.com Soon

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Thank You

Patients and Families
Dr. Daniel Haber, Cancer Center Director
Dr. Dave Ryan, Chief of Hem Onc, MGH
Dr. Keith Flaherty, Cancer Center
Dr. Chloe Villani, CIID, Cancer Center, MGH
Dr. Steven Blum, MD
Dr. Amanda Guidon, Neurology, MGH
Dr. LeeAnn Burton, Neurology, MGH
Dr. Michael Dougan, GI, MGH
Dr. Andy Chan, GI, MGH
Dr. Tom Neilan, Cardiology, MGH
Dr. Dan Zlotoff, Cardiology, MGH
Dr. Rebecca Karp, Hematology, MGH
Dr. Michael Mansour, Infectious Disease, MGH
Dr. Alyssa Letourneau, Infectious Disease, MGH
Dr. Alex Faje, Neuroendocrine, MGH
Dr. Michelle Rengarajan, Endocrine, MGH
Dr. Minna Kohler, Rheumatology, MGH
Dr. Sara Schoenfeld, Rheumatology, MGH
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Gabe Molina, Dermatology, MGH
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Dr. Xin Gao, GU, MGH
Dr. Mary Aronow, MEEI/ Ophthalmology
Dr. Meghan Sise, Renal, MGH
Dr. Harish Seethapathy, Renal, MGH
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Dr. Justine Cohen, Melanoma, U Penn
Dr. Don Lawrence, Melanoma, MGH Cancer Center
Dr. Russ Jenkins, Melanoma, MGH Cancer Center
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Dr. Aditya Bardia, Breast, MGH Cancer Center
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Dr. Florian Fintelmann, Radiology, MGH
Dr. Jong Park, Head and Neck, MGH
Dr. Aiden Long, Allergy and Immunology, MGH
Dr. Jocelyn Farmer, Allergy and Immunology, MGH
Dr. Sara Barmettler, Allergy and Immunology, MGH
Dr. Meghan Mooradian, Thoracic Oncology, MGH
Dr. Justin Gainor, Thoracic Oncology, MGH
Dr. Mari Mino-Knudson, Pathology, MGH
Dr. Ruth Foreman, Dermatopathology, MGH
Dr. Matthew Frigault, Heme Malignancies, MGH
Dr. Leyre Zubiri, Immunotherapy Toxicity Fellow
Mike Podolfi, Informatics, Partners ECare
Dr. Magid Adawallah, Fellow, Cardiology
Dr. Genevieve Boland, Surgical Oncology, MGH
Hellen Giang, Clinical Research, MGH
Elaina Phan, Clinical Research, MGH
Tariq Daouda, Villani Lab
Neal Smith, Villani Lab
Elizabeth Hockfield Byrne, Villani Lab

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QUESTIONS

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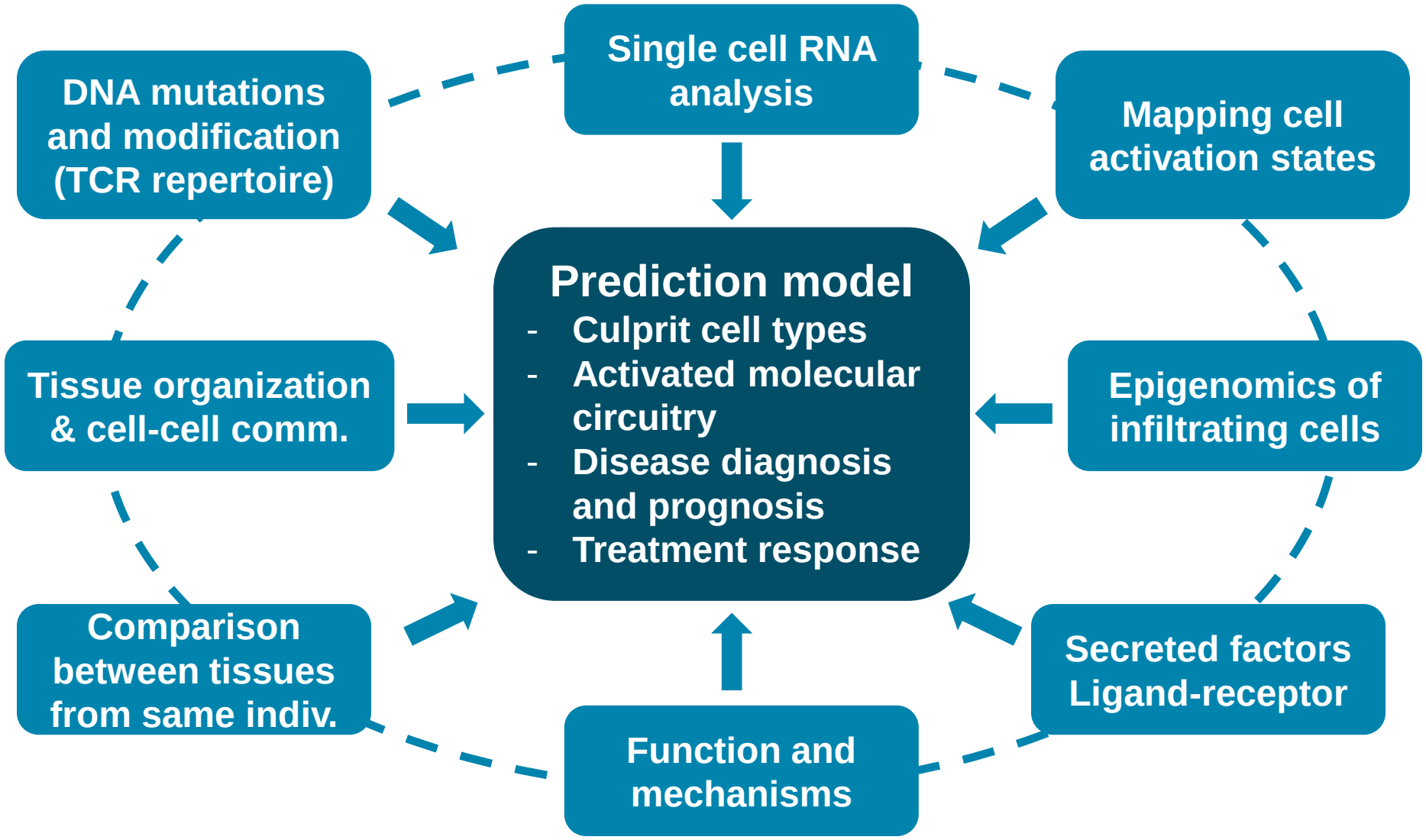
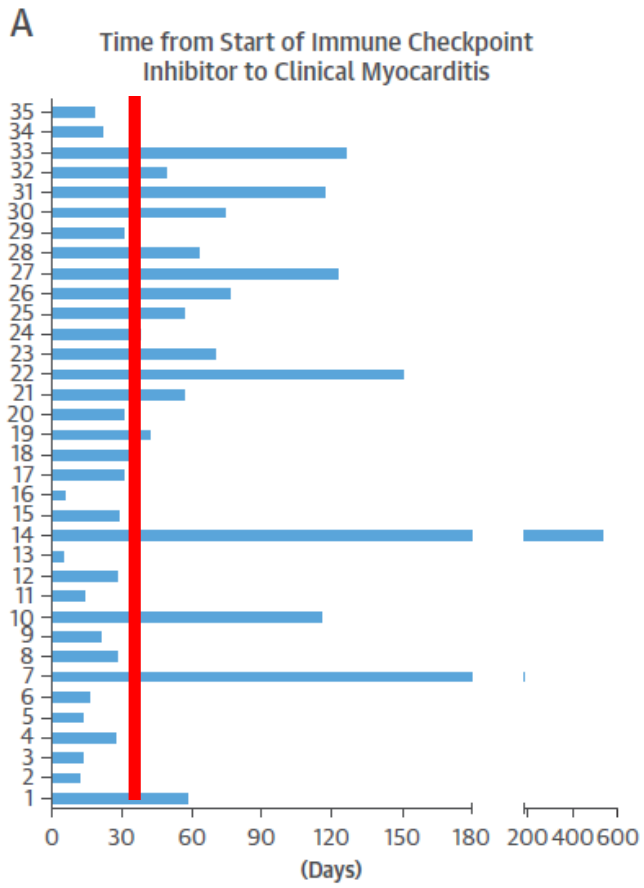
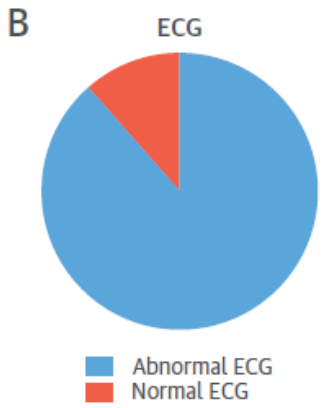
Developing irAEs Prediction Models

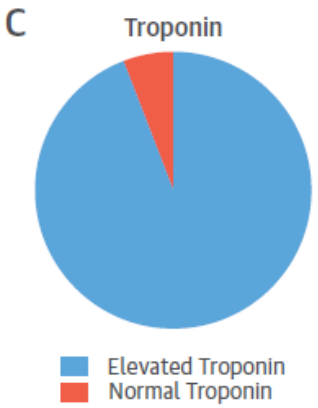


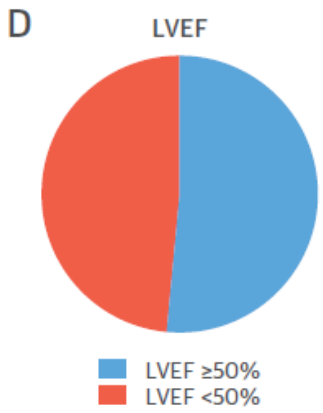
Cardiac Toxicity

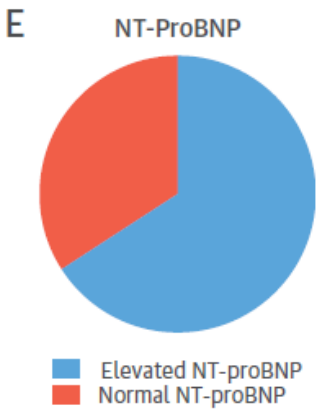
FIGURE 1 Clinical Presentation of Patients With ICI-Associated Myocarditis











S Mahmood, T Neilan, JACC, 2018

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Cardiology

Global longitudinal strain as a predictor of cardiac events among patients with immune checkpoint inhibitor-associated myocarditis: A multicenter international study

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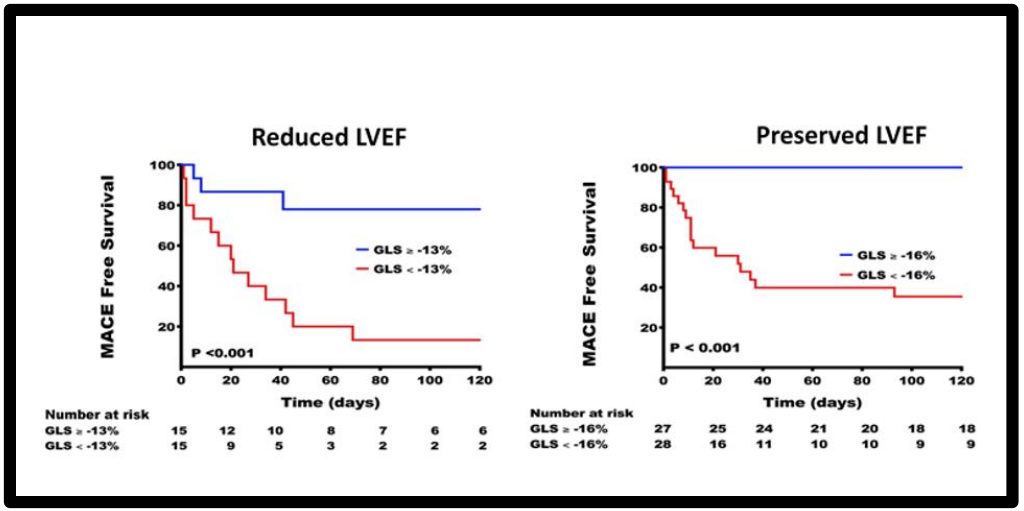

Adawalla et al, 2019, In Press JACC

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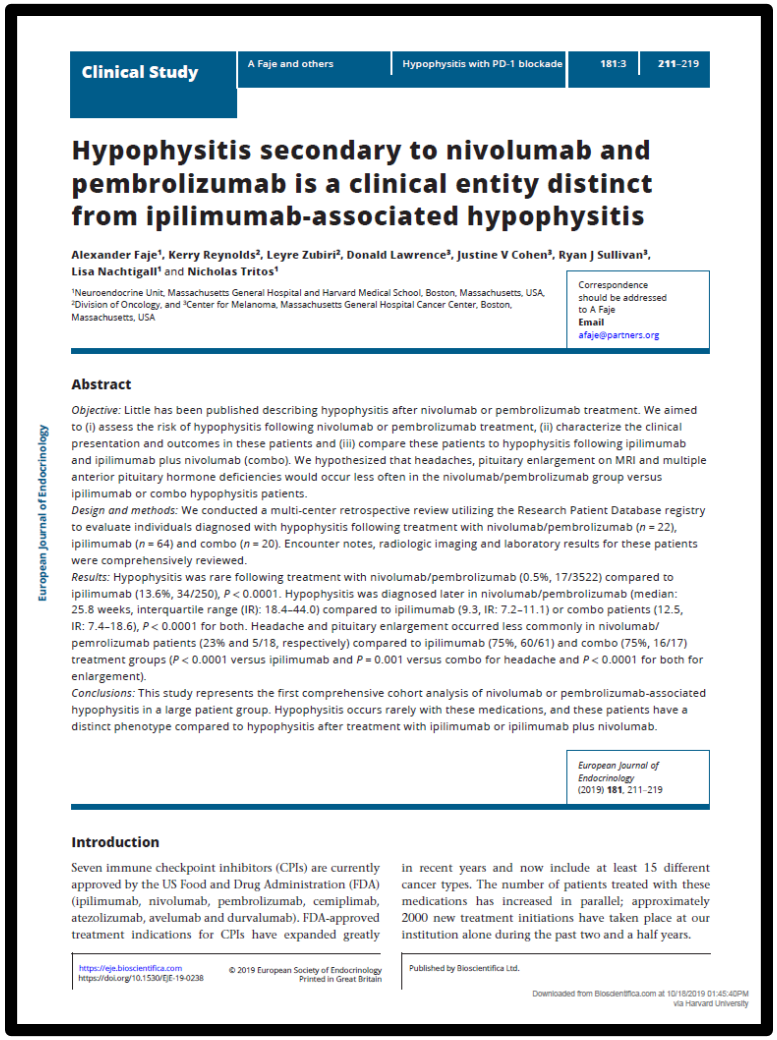

Clinical Study | A Faje and others | Hypophysitis with PD-1 blockade | 181:3 | 211–219

Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis

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Abstract

Objective: Little has been published describing hypophysitis after nivolumab or pembrolizumab treatment. We aimed to (i) assess the risk of hypophysitis following nivolumab or pembrolizumab treatment, (ii) characterize the clinical presentation and outcomes in these patients and (iii) compare these patients to hypophysitis following ipilimumab and ipilimumab plus nivolumab (combo). We hypothesized that headaches, pituitary enlargement on MRI and multiple anterior pituitary hormone deficiencies would occur less often in the nivolumab/pembrolizumab group versus ipilimumab or combo hypophysitis patients.

Design and methods: We conducted a multi-center retrospective review utilizing the Research Patient Database registry to evaluate individuals diagnosed with hypophysitis following treatment with nivolumab/pembrolizumab ($n = 22$), ipilimumab ($n = 64$) and combo ($n = 20$). Encounter notes, radiologic imaging and laboratory results for these patients were comprehensively reviewed.

Results: Hypophysitis was rare following treatment with nivolumab/pembrolizumab (0.5%, 17/3522) compared to ipilimumab (13.6%, 34/250), $P < 0.0001$. Hypophysitis was diagnosed later in nivolumab/pembrolizumab (median: 25.8 weeks, interquartile range (IR): 18.4–44.0) compared to ipilimumab (9.3, IR: 7.2–11.1) or combo patients (12.5, IR: 7.4–18.6), $P < 0.0001$ for both. Headache and pituitary enlargement occurred less commonly in nivolumab/pemrolizumab patients (23% and 5/18, respectively) compared to ipilimumab (75%, 60/61) and combo (75%, 16/17) treatment groups ($P < 0.0001$ versus ipilimumab and $P = 0.001$ versus combo for headache and $P < 0.0001$ for both for enlargement).

Conclusions: This study represents the first comprehensive cohort analysis of nivolumab or pembrolizumab-associated hypophysitis in a large patient group. Hypophysitis occurs rarely with these medications, and these patients have a distinct phenotype compared to hypophysitis after treatment with ipilimumab or ipilimumab plus nivolumab.

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Introduction

Seven immune checkpoint inhibitors (CPIs) are currently approved by the US Food and Drug Administration (FDA) (ipilimumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab and durvalumab). FDA-approved treatment indications for CPIs have expanded greatly in recent years and now include at least 15 different cancer types. The number of patients treated with these medications has increased in parallel; approximately 2000 new treatment initiations have taken place at our institution alone during the past two and a half years.

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Important Clinical Findings for PD1 Hypophysitis

- 0/50 had diabetes insipidus
- 48/49 had hypoadrenalism
- 3/42 had hypothyroidism
- 1/23 had hypogonadism

Fage et al, European Journal of Endocrinology, 2019

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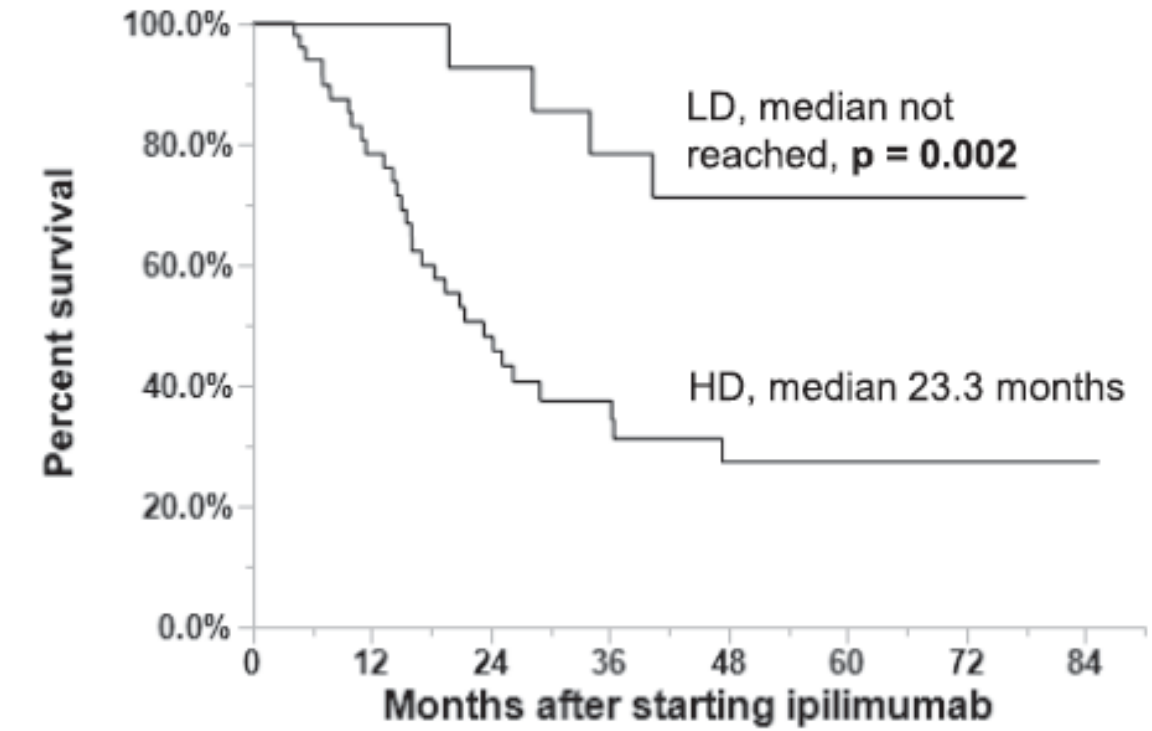
Outcomes in Patients on Steroids



Faje, Cancer, 2018

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Outcomes in Patients with Toxicity

Disease	Drug	Outcome	Study
Melanoma (N = 298)	Ipilimumab (CTLA4)	No difference in OS or TTF for irAEs or systemic steroids to treat irAE	Horvat, 2015
Mixed (N= 83)	Pembrolizumab (PD1)	Cutaneous AEs associated with improved PFS	Sanlorenz, 2015
Melanoma (N = 67)	Pembrolizumab (PD1)	Vitiligo = Higher RR	Hua, 2016
Melanoma (N = 576)	Nivolumab (PD1)	> 3 irAEs = Higher RR	Weber, 2017
Lung Cancer (N = 38)	Nivolumab (PD1)	Patients with irAEs = Higher RR and longer PFS	Sato, 2018
Lung Cancer (N = 134)	Nivolumab (PD1)	Patients with irAEs = Longer PFS and OS	Haratani, 2018
Melanoma (N = 98)	Ipiliumab (CTLA4)	Patients with hypophysitis = Improved OS	Faje, 2018