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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.

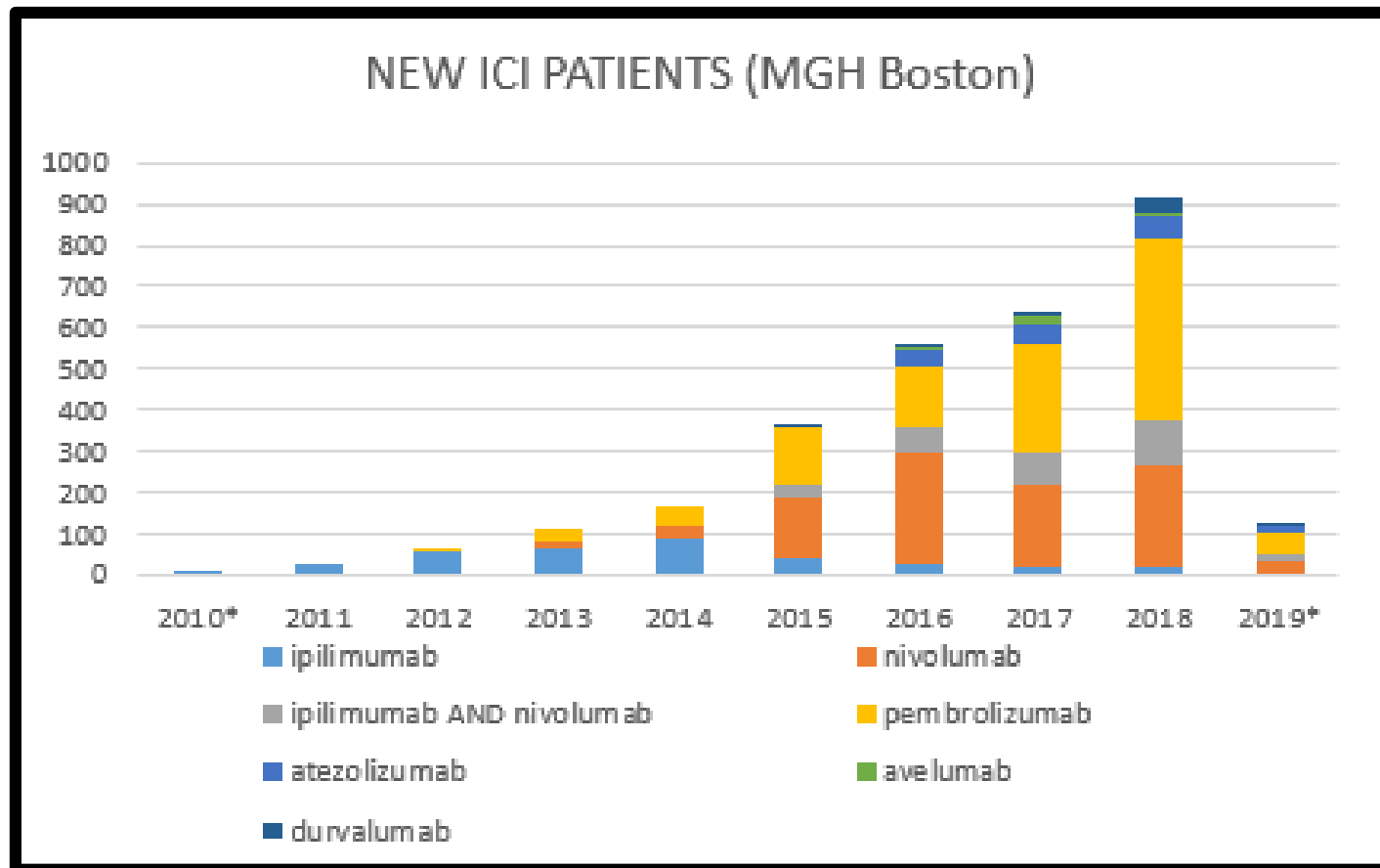
Estimated # of Patients, > 270,000+

	Stage III % of Total Incidence	Max Eligible w/o Recur.
NSCLC Stage III (post-chemoRT)	20%	19,435
	Stage III % of Total Incidence	Max Eligible w/o Recur.
Melanoma Stage III (post-surgery)	7%	6,172
	Stage IV % of Total Incidence	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 Stage IV	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

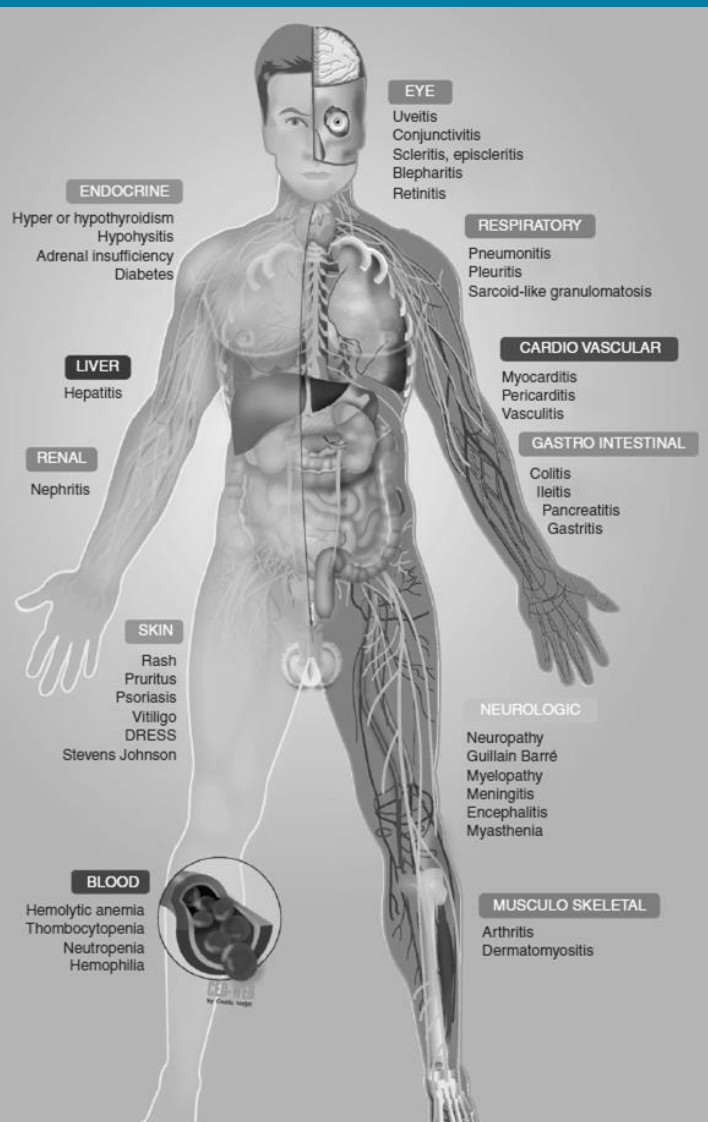
Citation: SEER 18, National Cancer Data Base (NCDB)

271,492

Immune Checkpoint Inhibitor (ICI) at MGH



Immune-Related AEs (irAEs)



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



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Patient: DM



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Chest CT 4/4/16 @6PM



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Many Questions, Few Answers

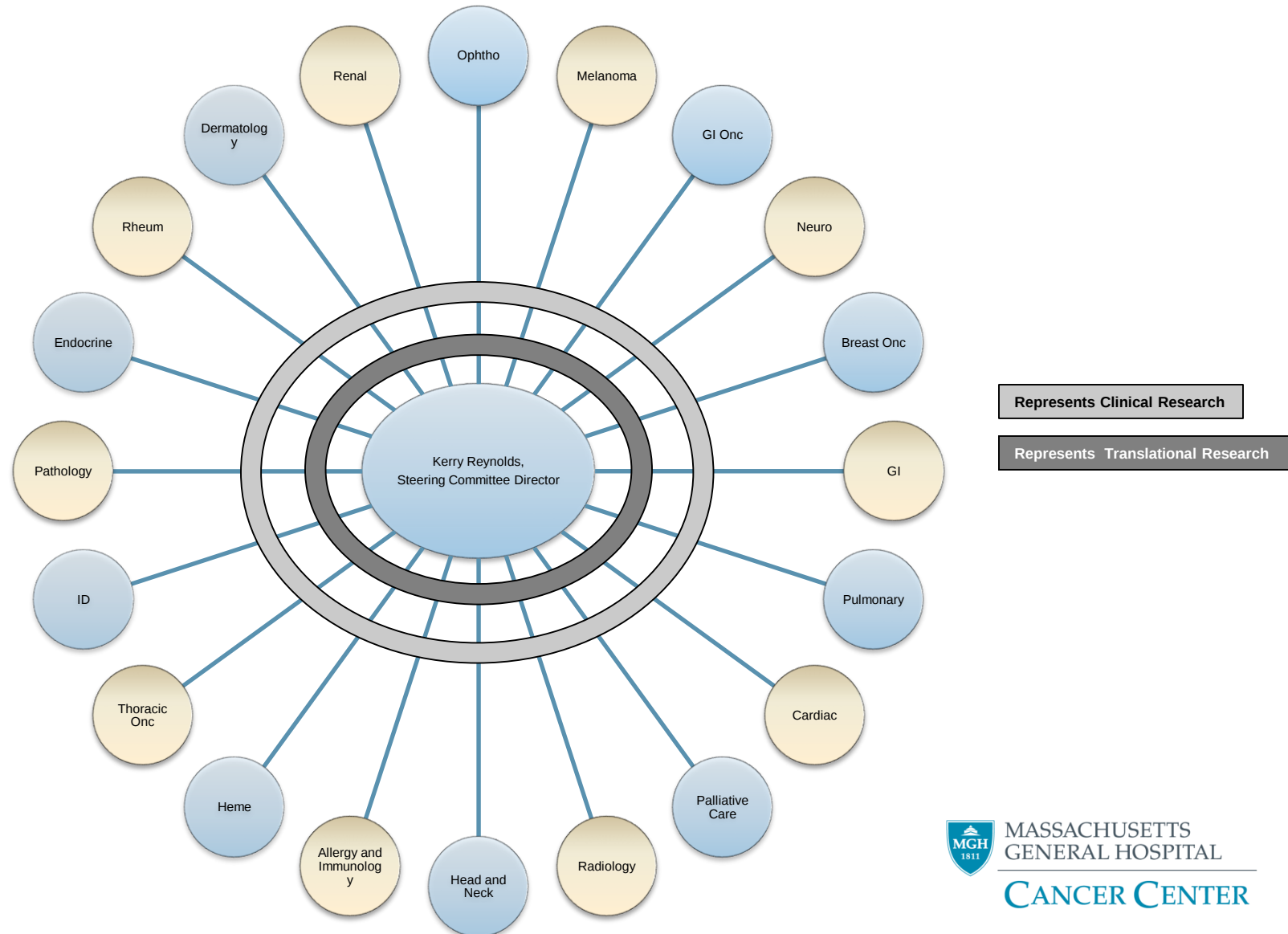
- *What is the best way to **prepare** physicians and teams for the wave of these case presentations? How do we assemble experts?*
- *Can we **define** these events and create a framework for the development of best practices to manage them?*
- *Can we develop **diagnostics** that help us detect immune 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



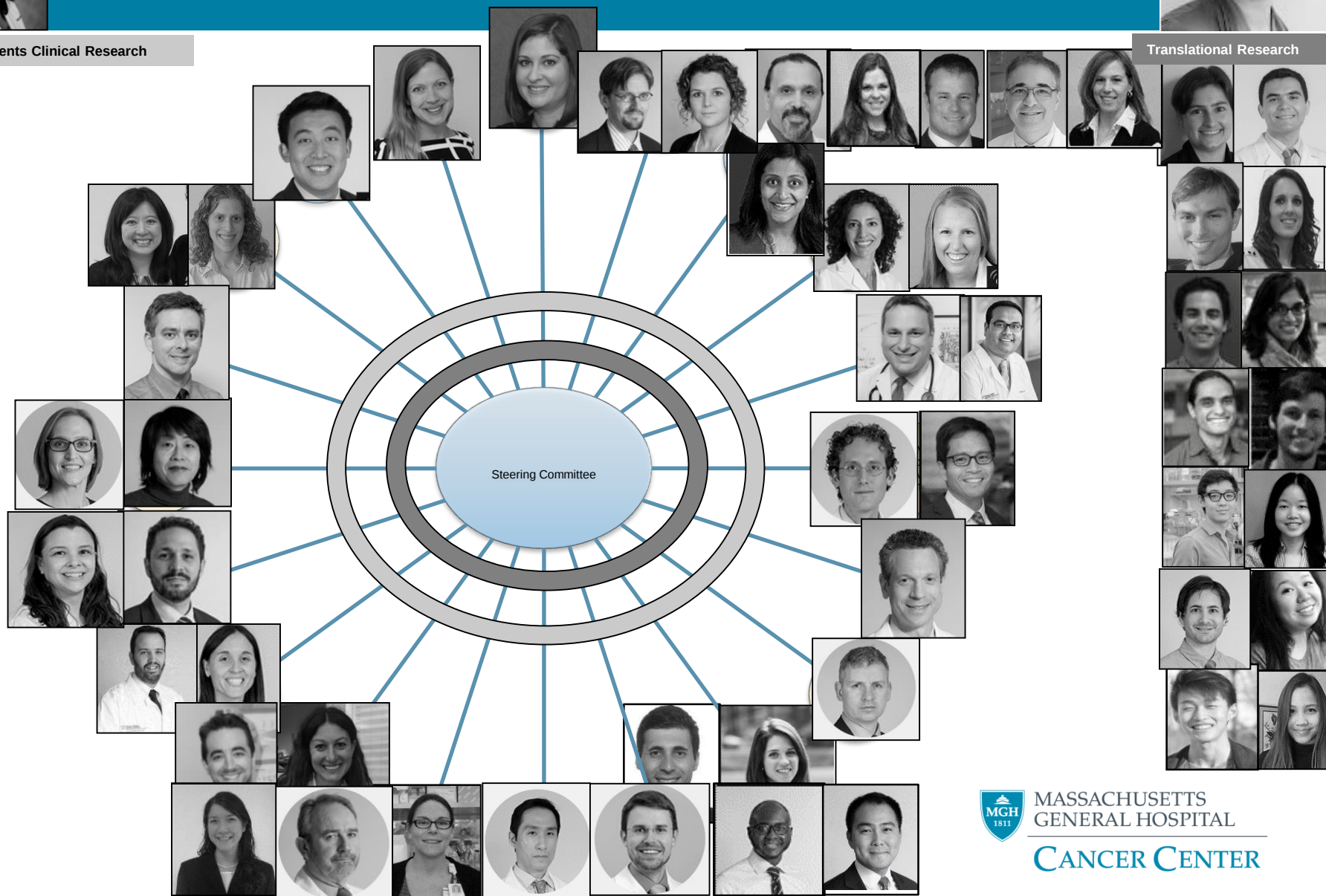


Immunotherapy Toxicity Service



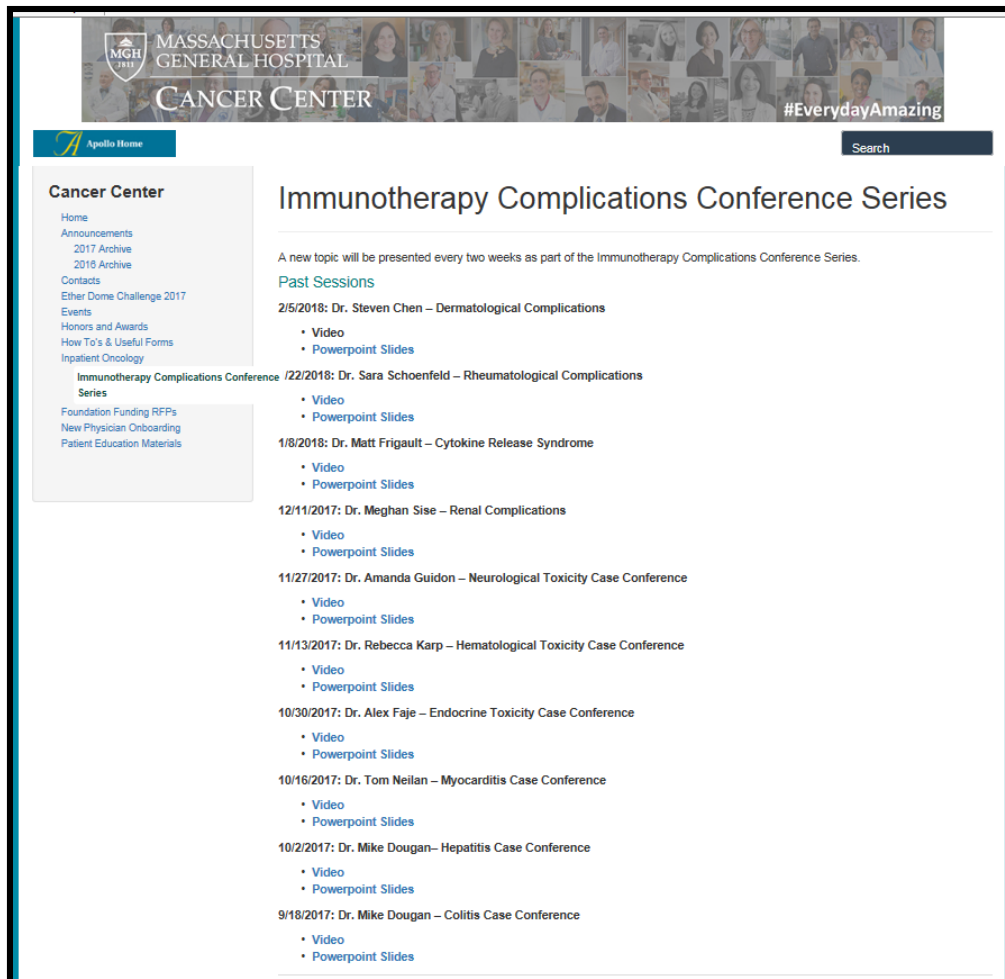
Represents Clinical Research

Translational Research



Vision – Educate Across Hospital/Community

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



The screenshot displays the website for the Massachusetts General Hospital Cancer Center. At the top, there is a banner with the MGH logo, the text "MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER", and a collage of people with the hashtag "#EverydayAmazing". Below the banner is a navigation bar with "Apollo Home" and a "Search" button. The main content area is titled "Immunotherapy Complications Conference Series". It includes a sidebar on the left with links for "Home", "Announcements", "2017 Archive", "2016 Archive", "Contacts", "Ether Dome Challenge 2017", "Events", "Honors and Awards", "How To's & Useful Forms", and "Inpatient Oncology". The main text area states: "A new topic will be presented every two weeks as part of the Immunotherapy Complications Conference Series." It lists "Past Sessions" with dates and topics, each with links for "Video" and "Powerpoint Slides".

Immunotherapy Complications Conference Series

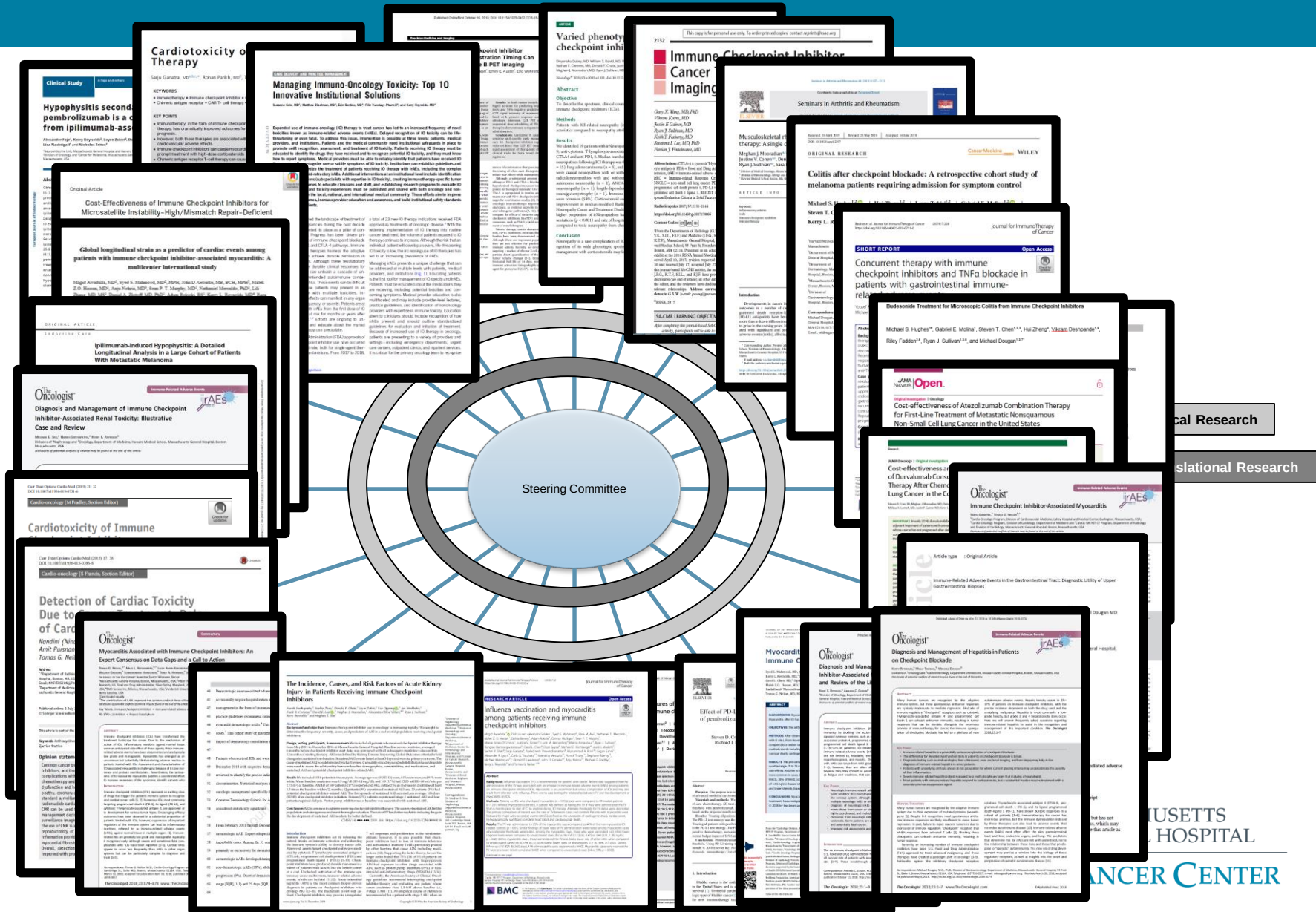
A new topic will be presented every two weeks as part of the Immunotherapy Complications Conference Series.

Past Sessions

- 2/5/2018: Dr. Steven Chen – Dermatological Complications
 - [Video](#)
 - [Powerpoint Slides](#)
- 2/22/2018: Dr. Sara Schoenfeld – Rheumatological Complications
 - [Video](#)
 - [Powerpoint Slides](#)
- 1/8/2018: Dr. Matt Frigault – Cytokine Release Syndrome
 - [Video](#)
 - [Powerpoint Slides](#)
- 12/11/2017: Dr. Meghan Sise – Renal Complications
 - [Video](#)
 - [Powerpoint Slides](#)
- 11/27/2017: Dr. Amanda Guidon – Neurological Toxicity Case Conference
 - [Video](#)
 - [Powerpoint Slides](#)
- 11/13/2017: Dr. Rebecca Karp – Hematological Toxicity Case Conference
 - [Video](#)
 - [Powerpoint Slides](#)
- 10/30/2017: Dr. Alex Faje – Endocrine Toxicity Case Conference
 - [Video](#)
 - [Powerpoint Slides](#)
- 10/16/2017: Dr. Tom Neilan – Myocarditis Case Conference
 - [Video](#)
 - [Powerpoint Slides](#)
- 10/2/2017: Dr. Mike Dougan – Hepatitis Case Conference
 - [Video](#)
 - [Powerpoint Slides](#)
- 9/18/2017: Dr. Mike Dougan – Colitis Case Conference
 - [Video](#)
 - [Powerpoint Slides](#)



Immunotherapy Toxicity Service





Nephrology

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

Harish Seethapathy,¹ Sophia Zhao,¹ Donald F. Chute,¹ Leyre Zubiri,² Yaa Oppong,¹ Ian Strohbehn,¹ Frank B. Cortazar,¹ David E. Leaf,³ Meghan J. Mooradian,² Alexandra-Chloe Villani,^{4,5} Ryan J. Sullivan,² Kerry Reynolds,² and Meghan E. Sise¹

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 heterogeneous 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

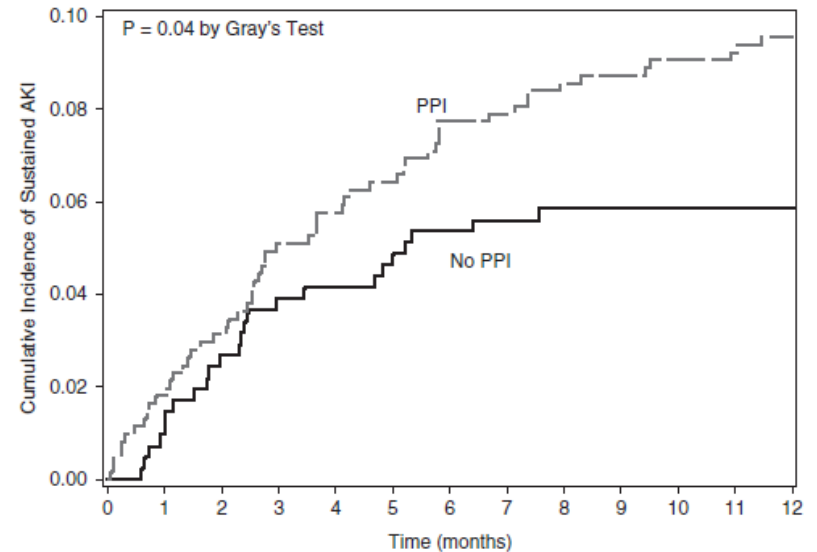
Immune checkpoint inhibitors act by releasing the natural breaks on immune activation and enhancing the immune system's ability to destroy tumor cells. Approved agents target checkpoint pathways mediated by cytotoxic T lymphocyte-associated antigen 4 (CTLA4), programmed cell death protein 1 (PD1), and 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 non-steroidal 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

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Number at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
PPI	607	524	455	413	386	350	318	300	277	258	251	242	231
No PPI	409	374	333	302	285	266	249	232	220	207	200	196	184

Proton Pump Inhibitor Associated with AKI



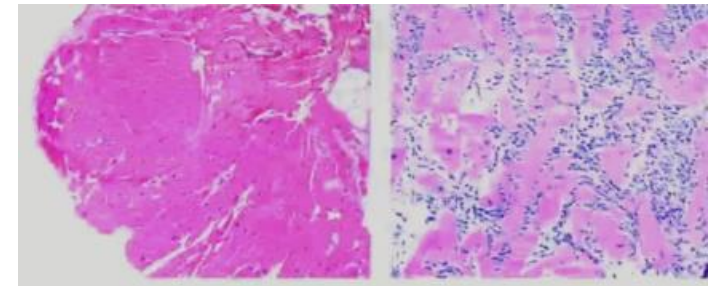
Example of SIC Service in Action

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



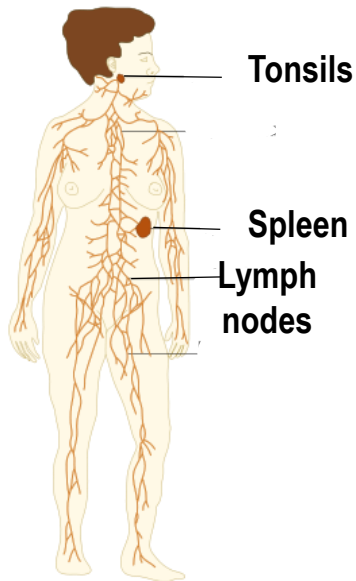
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Next-Generation Microscope: Single Cell Genomics Strategies

Tissues to be profiled

Lymphoid Organs



Non-Lymphoid "Barrier" Organs



Blood



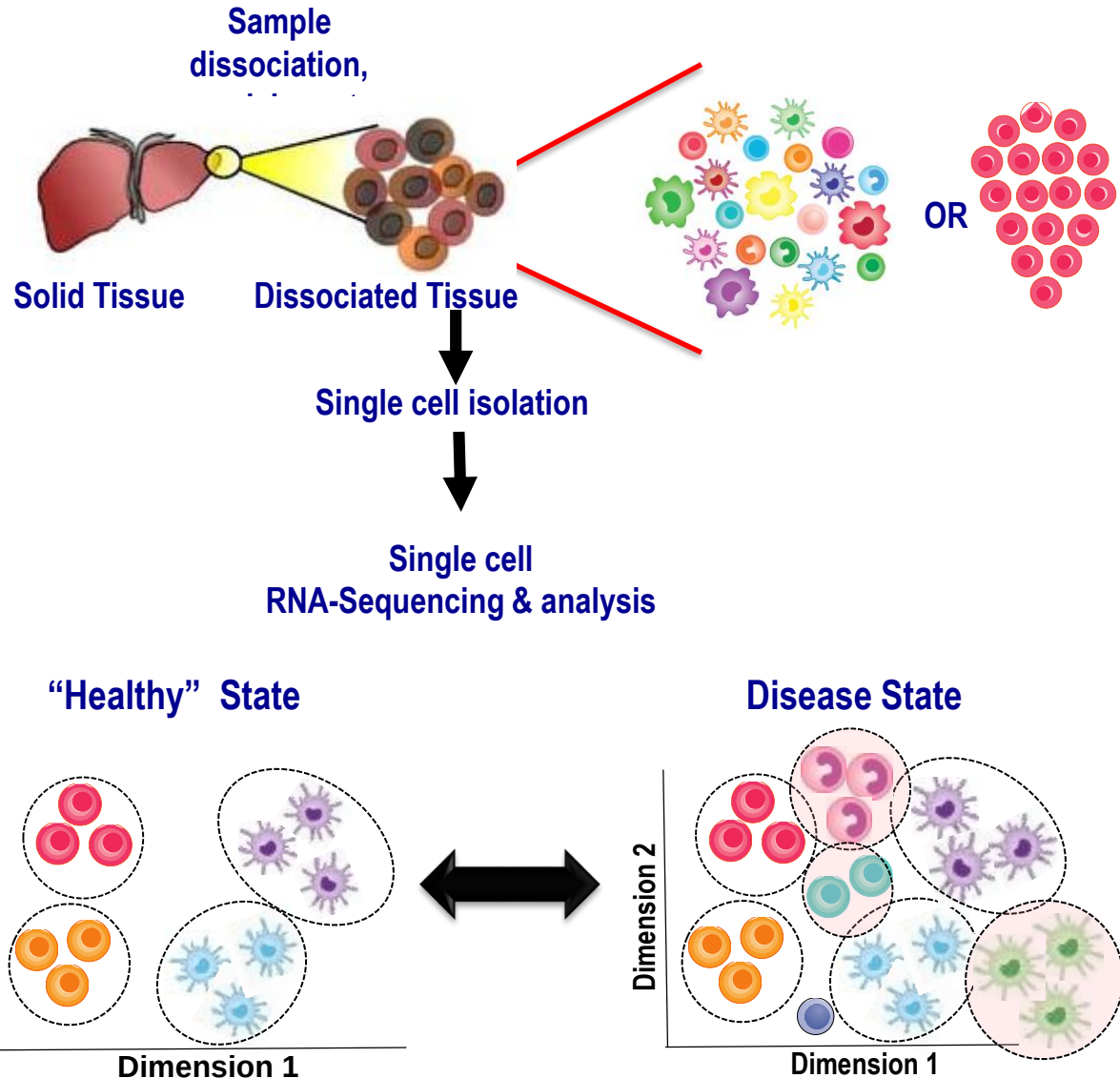
Skin



Lung

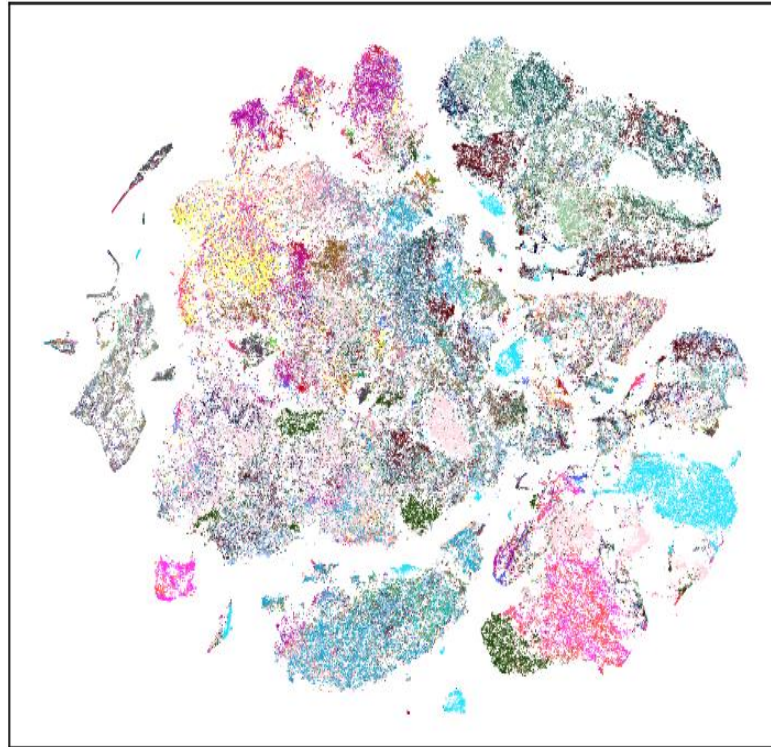
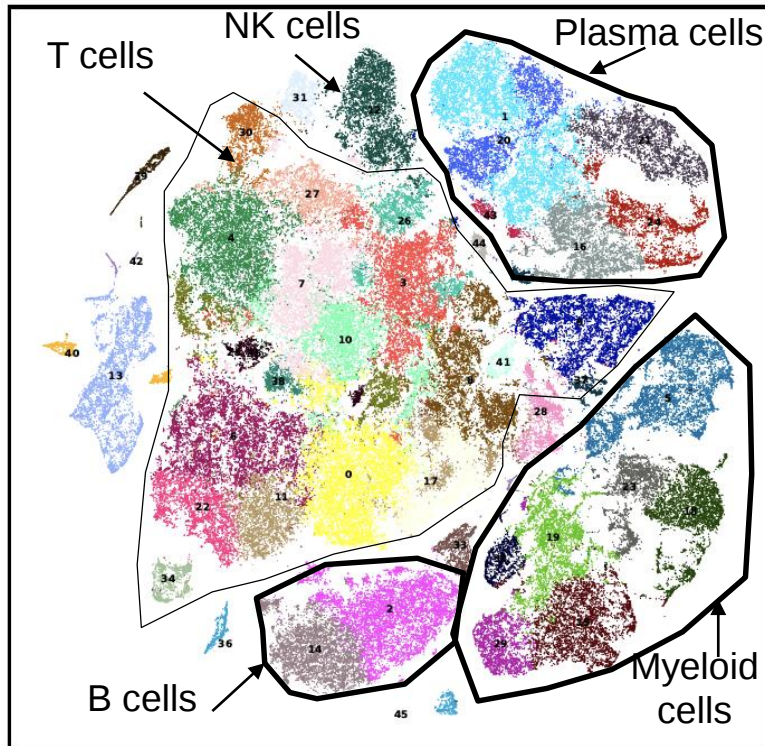


Gut



Cellular Ecosystem Appears Shared Across Patients

Cells colored by patients (n=37)



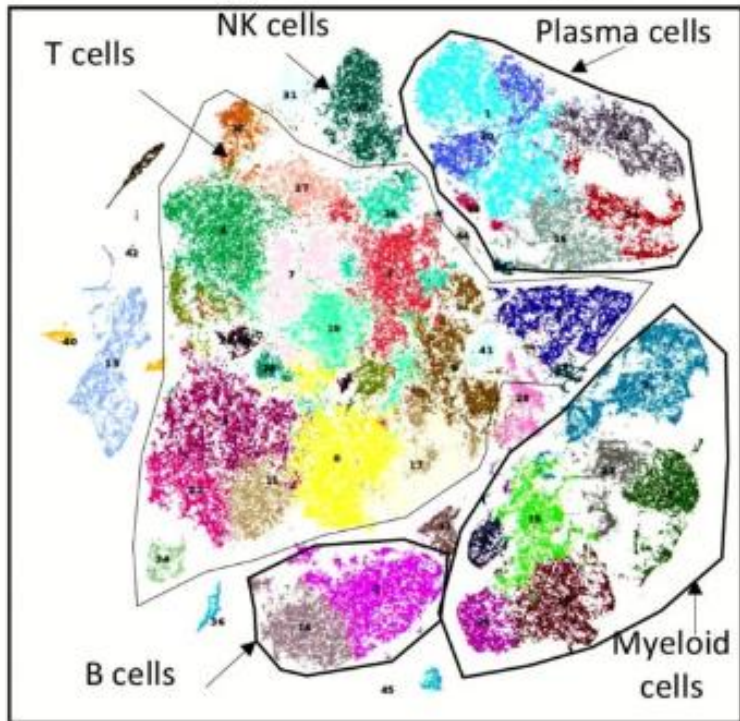
Patient IDs:

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		

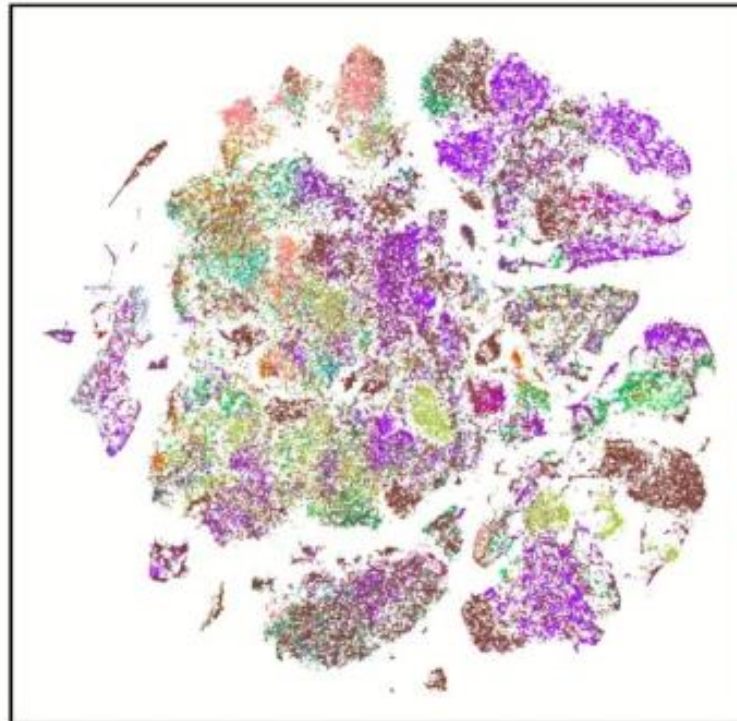
→ There are shared biological programs driving irAEs (not patient specific)

Cellular Ecosystem Appears Shared Cancer Types

Cells colored by predicted 45 cell populations



Cells colored by cancer types (n=12)



Cancer type:

- Bladder Cancer
- Brain ependymoma
- Colorectal
- Colorectal, Neuroendocrine
- Lung
- Melanoma
- Melanoma, CML
- Melanoma, breast, Lung
- None
- Ovarian
- Thymoma
- breast, carcinoid
- tongue cancer

→ 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

A PORTION OF THE PROCEEDS FUNDS IMMUNOTHERAPY RESEARCH

FACING IMMUNOTHERAPY

A Guide For Patients And Their Families

Kerry L. Reynolds, MD | Justine V. Cohen, DO | Leyre Zubiri, MD, PhD | Theodore A. Stern, MD

"Today, immunotherapy plays a role in the management of almost every type of cancer. And when approved cancer treatments are no longer working, many patients are offered the opportunity to participate in clinical trials of new agents, of which the most exciting and promising may be immune therapies. In my practice, patients want to know and need to know how these immune therapies work, what kinds of benefit to expect, what side effects they cause, when they should call their doctor for problems, how other lifestyle factors and medications affect their treatment, and how to treat their side effects. These outstanding clinicians and researchers provide answers to these questions that are both comprehensive and **EASY TO UNDERSTAND**. This book will be an **INVALUABLE RESOURCE** for cancer patients (and their families) who are about to start or are undergoing immune therapy, and goes far beyond what I can teach and explain when I see patients."

— Dr. Mario Sznol, President, Society of Immunotherapy for Cancer, Professor of Internal Medicine (Medical Oncology), Co-Leader, Cancer Immunology Program, Yale Cancer Center, Leader, Melanoma Disease-Related Translational Research Team, Yale Cancer Center

"Facing a diagnosis of cancer and deciding on which treatment to pursue can be very frightening but learning about the options and understanding the process is perhaps the most important thing to do. This book **PROVIDES AUTHORITATIVE, CONTEMPORARY AND PRACTICAL ADVICE** on the role of immunotherapy, a new form of cancer treatment now available for many patients. The book provides information on how immunotherapy differs from other forms of therapy and provides patients, and their families with instructions on what to monitor and when to contact the healthcare team. This **SHOULD BE REQUIRED READING** for all patients with cancer and be in every infusion center waiting room."

— Dr. Howard L. Kaufman, Past President, Society for Immunotherapy of Cancer, Director, Oncolytic Virus Research Laboratory, Massachusetts General Hospital

"The treatment of cancer with immunotherapy has truly come of age. While these treatments are an exciting new option for many patients, we are only beginning to understand why and how the side effects from these medications occur. Now more than ever patients need an **EASY TO READ**, easy to understand go-to text regarding what to expect from immunotherapy. This book provides incredibly valuable information on the side effects of immunotherapy, and is a **MUST READ** for patients and their family members. Congratulations to the MGH team of doctors, scientists, nurse practitioners, nurses, social workers, and therapists on this important work."

— Dr. Jarushka Naidoo, Assistant Professor of Oncology, Co-chair, Johns Hopkins Immune-related Toxicity Team, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Bloomberg-Kimmel Institute for Cancer Immunotherapy

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A Guide For Patients
And Their Families

THE BEST INFORMATION SOURCE ABOUT IMMUNOTHERAPY

FACING IMMUNOTHERAPY

A Guide For Patients And Their Families



By Leading Experts at
Massachusetts General Hospital

Kerry L. Reynolds, MD
Justine V. Cohen, DO
Leyre Zubiri, MD, PhD
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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
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Dr. Michael Mansour, Infectious Disease, MGH
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QUESTIONS



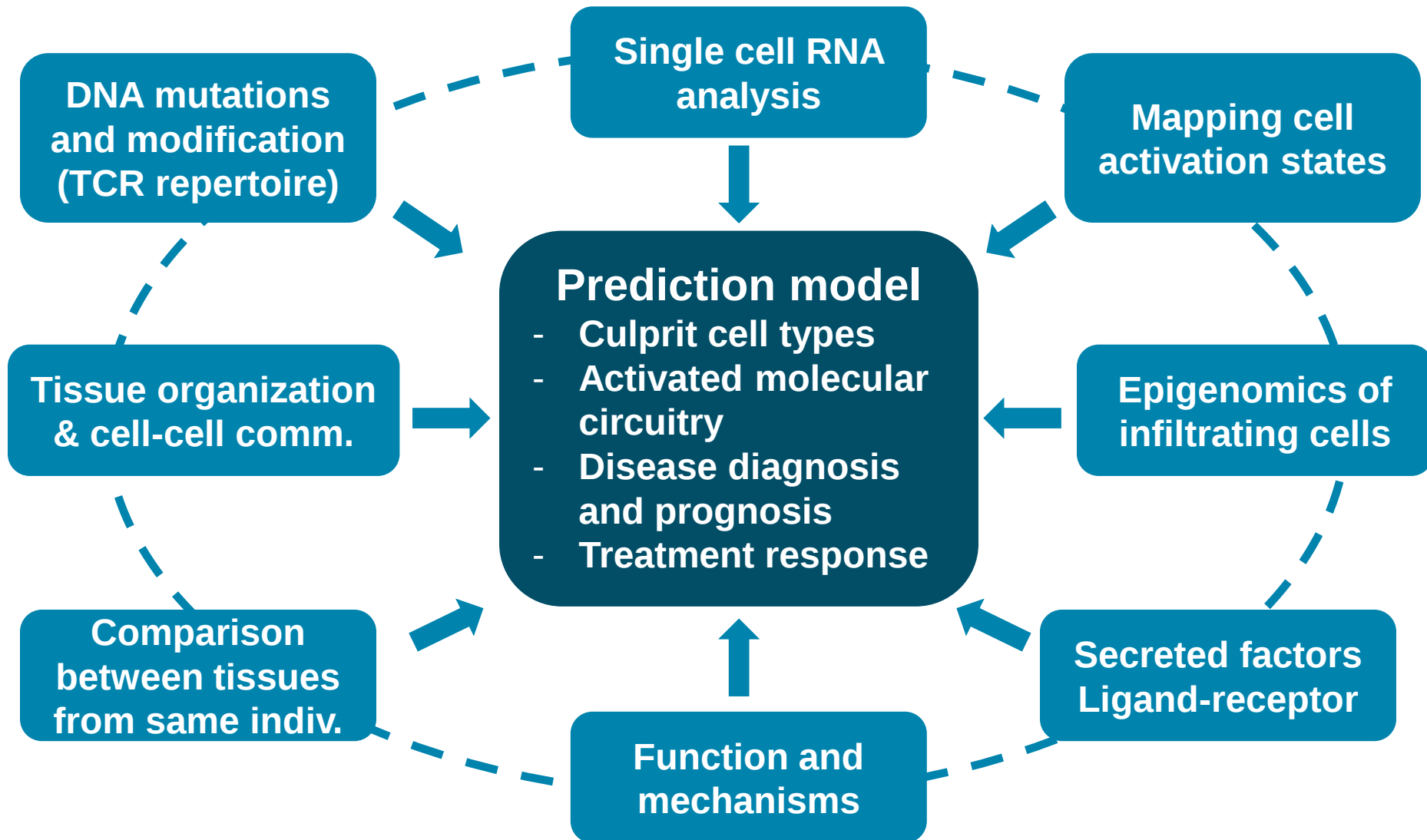
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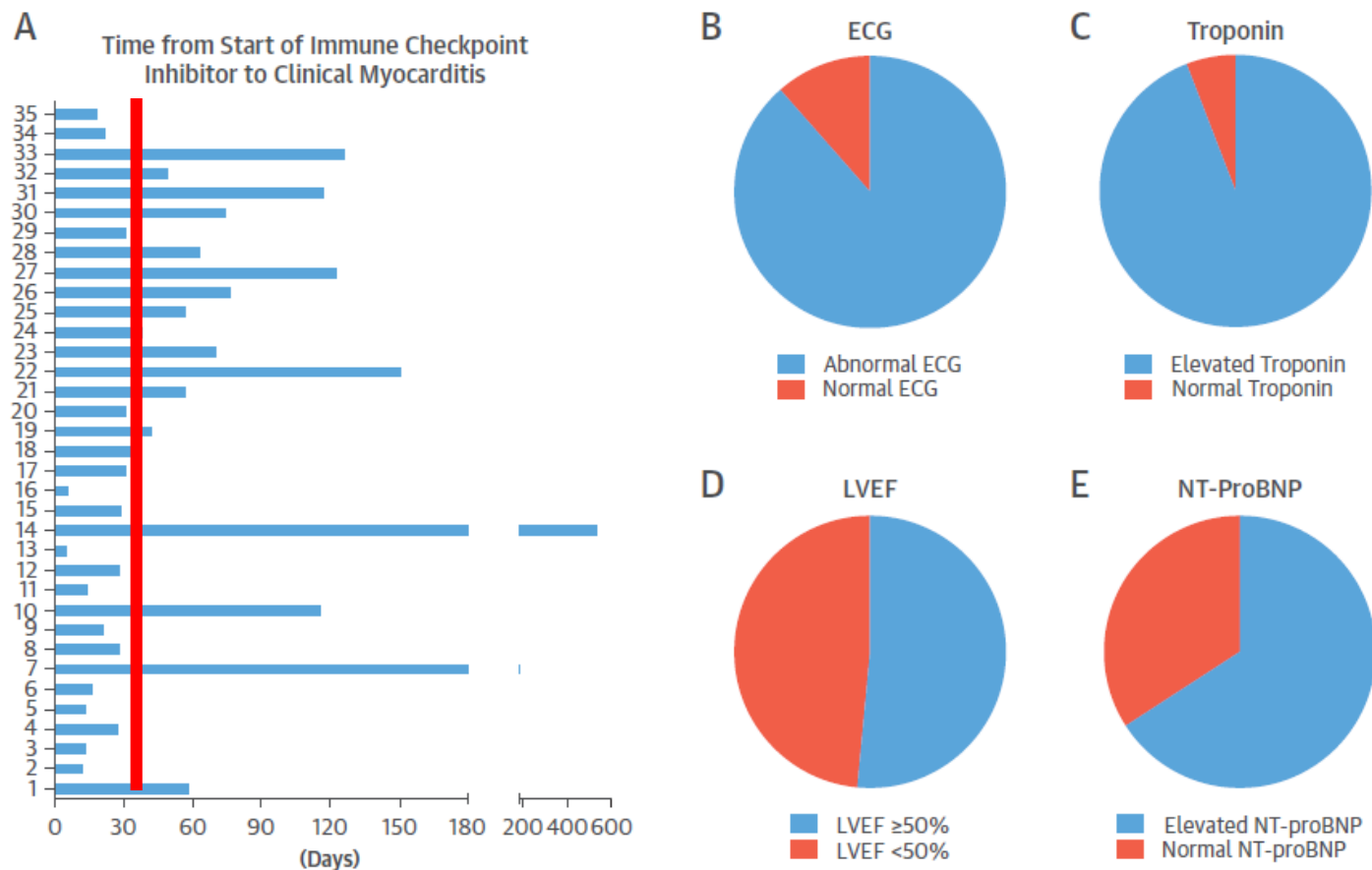
Developing irAEs Prediction Models





Cardiac Toxicity

FIGURE 1 Clinical Presentation of Patients With ICI-Associated Myocarditis



S Mahmood, T Neilan, JACC, 2018



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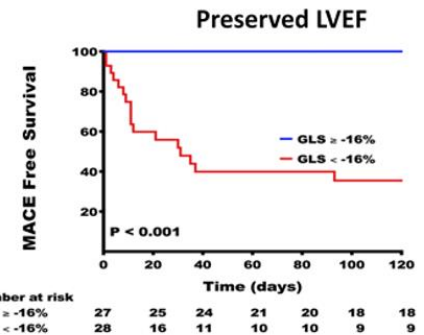
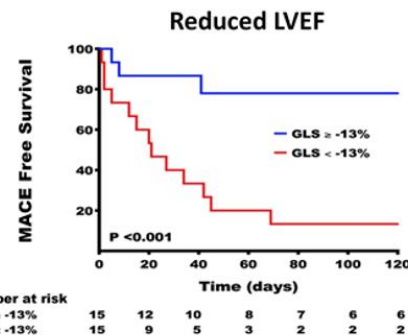
Cardiology

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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Endocrine

Clinical Study

A Faje and others

Hypophysitis with PD-1 blockade

1813

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/pembrolizumab 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

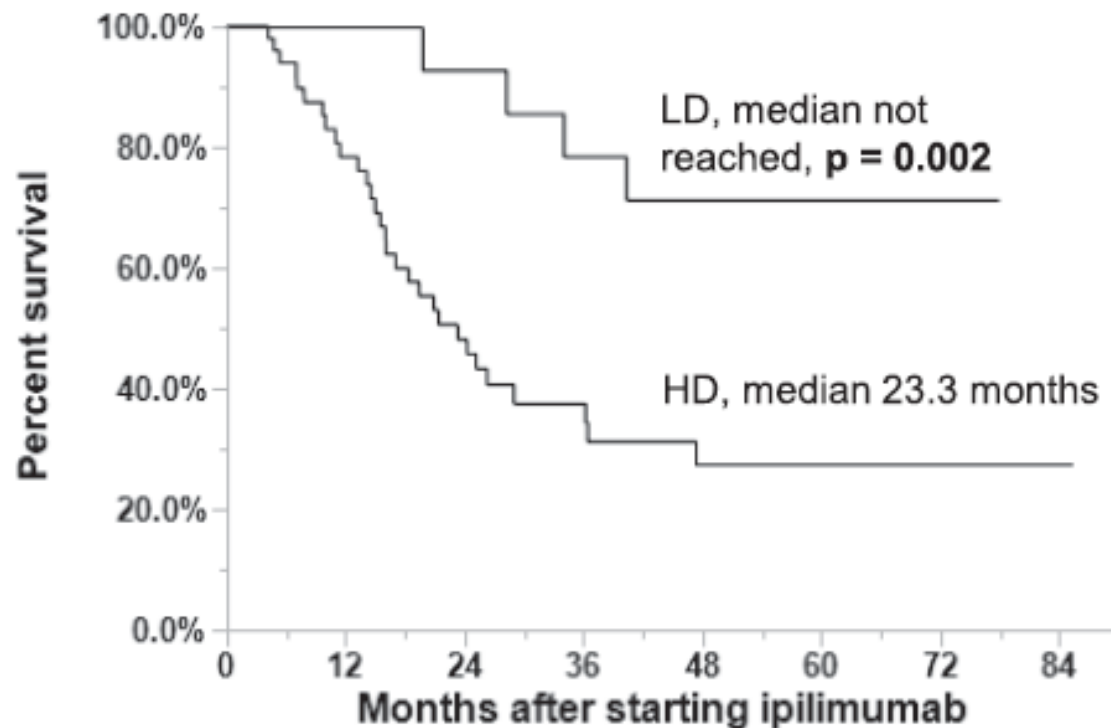
- 0/50 had diabetes insipidus
- 48/49 had hypoadrenalism
- 3/42 had hypothyroidism
- 1/23 had hypogonadism



MASSACHUSETTS
GENERAL HOSPITAL

CANCER CENTER

Outcomes in Patients on Steroids



No. at risk:

LD	14	14	13	11	8	3	2	
HD	50	34	20	12	7	3	2	1

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