NIH-AACR Cancer, Autoimmunity, and Immunology Conference

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Keynote Address
Arlene H. Sharpe, MD, PhD, FAACR
T cell costimulation in autoimmune diseases and cancer

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Department of Immunology
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Disclosure Information

NIH-AACR Cancer, Autoimmunity, and Immunology Conference
Arlene H. Sharpe

I have the following financial relationships to disclose:

Consultant for: Novartis AG, SU2C

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Employee of: Harvard Medical School

I will not discuss off label use and/or investigational use in my presentation.
Tumors evolve to evade immune attack

Tumor immunity is limited by physiologic regulatory mechanisms.
Two Signal Model and T Cell Activation
Manipulation of Costimulatory Pathways is of Therapeutic Interest

- **Tolerance Induction**
  - Transplantation
  - Autoimmunity

- **Immunostimulation**
  - Vaccines for Infectious Diseases
  - Tumor Immunity
• Positive and negative second signals
• Many negative second signals promote Tolerance
• Regulates naïve, effector, memory & regulatory T cells
• Many T cell Costimulatory Pathways
CTLA-4
The beginning of checkpoint blockade
**CTLA-4 was the first coinhibitory receptor discovered and translated to therapy**

- Fatal inflammatory phenotype of CTLA-4 ko mice convinced the field of the critical inhibitory function of CTLA-4
  - Death by 3-4 weeks of age
  - Massive splenomegaly and lymphadenopathy
  - Spontaneous T cell activation
  - Multiorgan lymphocytic infiltrates and tissue destruction

**Critical role for CTLA-4 in downregulating T cell activation**
CTLA-4 was the first coinhibitory receptor discovered and translated to therapy

• Fatal inflammatory phenotype of CTLA-4 ko mice convinced the field of the critical inhibitory function of CTLA-4

• CTLA-4 is key mediator of T cell tolerance
  - CTLA-4 controls regulatory T cells and self reactive effector cells
  - CTLA-4 polymorphisms associated with human autoimmune diseases
CHAI and LATAIE disease phenotype and mechanism.
CHAI: CTLA-4 haploinsufficiency with autoimmune infiltration
LATAIE: LRBA deficiency with autoantibodies, Treg defects, autoimmune infiltration. enteropathy

CTLA-4 was the first coinhibitory receptor discovered and translated to therapy

- Fatal inflammatory phenotype of CTLA-4 ko mice revealed critical inhibitory function of CTLA-4
- CTLA-4 is key mediator of T cell tolerance
  - Controls regulatory T cells and self reactive effector cells
  - CTLA-4 polymorphisms associated with human autoimmune diseases
- Blockade of CTLA-4 promotes anti-tumor immunity
- FDA approval for melanoma in 2011
Blockade of CTLA-4 as a strategy for tumor immunotherapy

Baumeister, Freeman, Dranoff, Sharpe Ann Rev Imm 2016
PD-1
Broadening the benefit of checkpoint blockade
The PD-1 Pathway Inhibits T Cell Responses

- Reduced TCR/CD28 Signaling
- Reduced Cytokine Production
- Reduced Target Cell Lysis
## Comparison of PD-L1 and PD-L2 Expression

<table>
<thead>
<tr>
<th></th>
<th>PD-L1 (B7-H1)</th>
<th>PD-L2 (B7-DC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematopoietic Cells</strong></td>
<td>DC, macrophages</td>
<td>DC, macrophages</td>
</tr>
<tr>
<td></td>
<td>B cells, T cells</td>
<td>B cells, Th2 cells</td>
</tr>
<tr>
<td><strong>Non-hematopoietic Cells</strong></td>
<td>Vascular Endothelium</td>
<td>few,</td>
</tr>
<tr>
<td></td>
<td>Epithelia, Liver</td>
<td>airway</td>
</tr>
<tr>
<td></td>
<td>Pancreatic islets,</td>
<td>epithelia</td>
</tr>
<tr>
<td></td>
<td>Placenta, Eye</td>
<td></td>
</tr>
<tr>
<td><strong>Stimuli</strong></td>
<td>Interferons ($\alpha, \beta, \gamma$)</td>
<td>IL-4+GM-CSF</td>
</tr>
<tr>
<td></td>
<td>potent inducers</td>
<td>$&gt; IFN-\gamma$</td>
</tr>
<tr>
<td><strong>Binding Partner(s)</strong></td>
<td>PD-1, B7-1</td>
<td>PD-1, RGMb</td>
</tr>
</tbody>
</table>
PD-1 inhibitory signals have multiple regulatory functions

- Counter-balance positive signals through TCR and costimulatory receptors
- Maintain immune tolerance
- Protect tissues from damage by immune responses
  - PD-L1 on non-hematopoietic cells can control resolution of inflammation and shield target organs from autoimmune attack
- Immune Homeostasis
PD-1:PD-L pathway Regulates Tolerance at Multiple Checkpoints

- Activation of self-reactive T cell by APC
- Function of self-reactive effector T cell
  - PD-L1 on BM vs. non BM cell
PD-1 pathway is a mediator of T cell exhaustion

• PD-1 pathway has been exploited by tumors and microbes to evade immune eradication

• PD-1/PD-L Pathway contributes to T cell dysfunction during chronic infection and cancer
Tumor-Infiltrating T cells (TIL) behave like exhausted T cells
PD-L1 in Cancer

- Expressed on cell surface of ~ 30% of solid tumors and selected hematologic malignancies
- Inhibits anti-tumor immune responses

Brown = PD-L1

Kidney tumor

Non-small cell lung cancer

Freeman, Rodig, Signoretti, McDermott; BWH & DFCI
PD-1 or PD-L1 Blockade unleashes anti-tumor T cell response

- PD-1 is highly expressed on T cells in tumors (TIL) and these are dysfunctional
- PD-L1 on tumor cells, hematopoietic & non hematopoietic cells
- PD-1 or PD-L1 Blockade can increase T cell function in tumors
Clinical translation:
FDA approved PD-1 & PD-L1 drugs

• Anti-PD-1
  – Nivolumab (Opdivo, BMS)
  – Pembrolizumab (Keytruda, Merck)
  – Cemiplimab (Libtayo, Sanofi/Regeneron)

• Anti-PD-L1
  – Atezolimumab (Tecentriq, Roche)
  – Durvalumab (Imfinzi, AstraZeneca)
  – Avelumab (Bavencio, EMD Serono/Pfizer)
Broad anti-tumor efficacy of anti-PD-1/PD-L1 inhibitors: Overall Response Rates (ORR)
There are more cancer immunotherapy targets than PD-1
T cells in Tumors Express Multiple Immunoinhibitory Receptors

These regulate the balance between T cell activation and tolerance and are druggable targets for tumor immunotherapy.
Do *Pdcd1* and *Lag3* contribute to disease severity in *Pdcd1*−/− mice?

**Heat Pancreas**

<table>
<thead>
<tr>
<th>Group</th>
<th>Moribund (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag3−/-Pdcd1−/- (n=100)</td>
<td>0</td>
</tr>
<tr>
<td>Lag3+/+Pdcd1+/+ (n=15)</td>
<td>1</td>
</tr>
<tr>
<td>Lag3−/-Pdcd1+/+ (n=15)</td>
<td>2</td>
</tr>
<tr>
<td>Lag3+/+Pdcd1−/- (n=15)</td>
<td>3</td>
</tr>
</tbody>
</table>

**Pancreas**

T cells can coexpress multiple inhibitory receptors

Blackburn et al., 2009 Nature Immunology 10: 29-37.

Co-blockade of PD-1 and another inhibitory receptor enables better rescue of dysfunctional T cells than blockade of a single inhibitory pathway, but ONLY PD-1 blockade alone has substantial effects.
The Future is Combination Therapy

- **PD-1 blockade + other immunoinhibitor blockade:**
  - *CTLA-4, LAG3, TIGIT, TIM-3, VISTA, CD47*

- **PD-1 blockade + immunostimulators:**
  - *anti-OX40, anti-CD137, ICOS, IL-2, TLR ligands, STING*

- **PD-1 blockade + kinase inhibitors, some chemotherapies:**
  - *Braf inhibitor, MEK inhibitor, cisplatin, CDK4/6, PARPi*

- **PD-1 blockade + others:**
  - *Angiogenesis blockade, radiation, HDAC inhibitors*

- **PD-1 blockade + cancer vaccine, oncolytic virus, CAR-T**
Immune-Mediated Adverse Events

Immune Homeostasis

Central tolerance
Peripheral tolerance

Natural breakdown of tolerance

What can we learn about normal immune homeostasis from autoimmunity and irAEs?

Therapy-induced loss of tolerance

Exacerbating preclinical autoimmunity
Inducing de novo autoimmunity
Direct toxicity of inhibitor
Bystander inflammation/ CRS
GI disruption

Can known risk factors for autoimmunity also predict risk of irAEs?

Genetics
Chance
Environment

Autoimmunity
Immune related adverse events
Critical Questions

- How do we identify who will respond?
- What are mechanisms of failure to respond?
- What are mechanisms of resistance?
- How do we identify who is at risk for adverse event?
- What are mechanisms of adverse events?
- How develop combination therapies?
  - Increase benefit with long duration and best safety?
Summary

• Success of Checkpoint blockade has led to a paradigm shift in cancer therapy

• Appreciation that tumor immunity is limited by physiologic immunoregulatory mechanisms

• Future is in Combination therapies
  - Extend benefit of immunotherapy

• Need better understanding of mechanisms that control anti-tumor immunity
  - Role of tumor microenvironment; host factors (age, gender, obesity, microbiome)
  - Integration of basic biology into next gen therapies and detailed evaluation of patients is essential to understand mechanisms of response, resistance, adverse events
  - Increase benefit and mitigate risks
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Rafi Ahmed, Emory University
Vijay Kuchroo, BWH
Dario Vignali, U Pitt
Gastrointestinal Toxicities

Speakers
Michael Dougan, MD, PhD
Erez Baruch, MD
Robert S. Bresalier, MD
Clinical Significance of Immunotherapy Induced Pancreatic Atrophy and Exocrine Pancreatic Insufficiency

Erez N. Baruch, MD
The Ella Lemelbaum Institute for Immuno-Oncology, Sheba Medical Center
Department of Clinical Microbiology and Immunology, Tel Aviv University
Israel
Disclosure

• Nothing to disclose

• I will be not talking about non-FDA approved indications
## Immunotherapy-induced diarrhea

- **Common Terminology Criteria for Adverse Events (CTCAE) v 5.0, 2017:**

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL</td>
<td>Increase of &gt;=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by an increase in frequency and/or loose or watery bowel movements.

| **Colitis** | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Abdominal pain; mucus or blood in stool | Severe abdominal pain; peritoneal signs | Life-threatening consequences; urgent intervention indicated | Death |

**Definition:** A disorder characterized by inflammation of the colon.
Immunotherapy-induced diarrhea

- **UpToDate 2018:**

  - **DIARRHEA/COLITIS** — Diarrhea is a common clinical attention to the diagnosis and treatment of the earliest toxicity.

  - **Manifestations** — Diarrhea/collitis most commonly pre

- **ESMO guidelines 2017:**

  - Gastrointestinal toxicity of anti-PD-1 antibodies

    Very few data are available about GI irAEs associated with anti-PD-1 MoAbs. Diarrhoea and colitis are more frequent with anti-CTLA4

- **After ruling out infection** – **diarrhea and colitis are considered as a single clinical entity**
Among immunotherapy patients – is all diarrhea colitis?

<table>
<thead>
<tr>
<th>Colitis Incidence</th>
<th>Anti-PD-1</th>
<th>Anti-CTLA-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>~20%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>1-2%</td>
<td>10%</td>
</tr>
</tbody>
</table>

• Diagnosis is mainly based on clinician discretion

• Tests – CBC, electrolytes, CRP, stool culture + PCR, endoscopy

• Management – Loperamide, PO corticosteroids, IV corticosteroids, anti-TNFα

• **Are there additional differential diagnoses?**
Diarrhea that doesn’t add up – the H.M. experience

- H.M., 37 y.o. M, Stage III Melanoma, adjuvant Pembrolizumab
- Cycle 13 (9 months): Multiple (~10) diarrheas per day
- Clinically diagnosed as colitis, corticosteroids resistant. Anti-PD-1 was stopped
- Weight loss, significant quality of life impairment
- Work-up continued for a year, included:
  - Colonoscopy x3
  - CT Enterography
  - Gut video capsule
  - Proctorectography
  - Repeated colon and ileum biopsies
  - Anal sphincter NC and EMG
H.M. - Review of History, lab tests and imaging

• Family physician review:
  • Diarrhea oriented history – foul-smelling, large amount stools, mainly after fatty meals
  • Blood lipase – 6 (7-60), amylase 43 (20-90)

• Radiologist review:

Baseline – 8 months since anti-PD-1 initiation, 1 month prior to symptoms

11 months since first symptoms, nearly 2 years since treatment initiation
Study aims

• Patient H.M.:
  • Fecal analysis – elastase 22 (normal >200), fats 31 (normal limit 6)
  • *Complete resolutions with pancreatic enzyme supplements*

• Raised several questions:
  • Was this an incidental finding or a non-reported toxicity?
  • Only in melanoma? Only anti-PD-1 related?
  • What is the incidence? Does each pancreatic atrophy lead to steatorrhea?
  • *Difference clinical characteristics in comparison to colitis?*
Study design

• A single center, retrospective case-control study

A search for immunotherapy (IO) patients with available consecutive abdominal CT scans

Identify patients with radiological evidence of Pancreatic Atrophy (PA)

**Is this really a toxicity?**
Compared to other IO patients matched by cancer type, age, gender, previous lines of treatment

**Double control**

**Is it clinically different than colitis?**
Compared to patients with IO-induced colitis
Pancreatic Atrophy (PA) patients:

- Were selected based on a qualitative assessment of an expert radiologist
- Defined as a decrement in pancreatic width on axial sections between pre-treatment and last follow-up scans
- Aim – will reflect “real-life” screening

Each study patient (PA + controls):

- Quantitative assessment of pancreatic volume (Intellispace Philipps Portal)
- Measurements of two expert radiologists (blinded to each other) were compared
Atrophy rate – a quantitative PA parameter

• Aims:
  • Enable comparison between patients with different pre-treatment pancreatic volume
  • Overcome potential radiological follow-up bias

\[
Atrophy\ rate = \frac{\Delta Pancreatic\ Volume}{\text{Baselines Pancreatic Volume}} / \Delta Months
\]
Results - patient population

Original study population (n=617):
- Anti-PD-1: 292 melanoma, 199 NSCLC, 2 HNSCC
- Anti-CTLA-4: 124 melanoma

Patients with consecutive abdominal CT scans available for review (n=403):
- Anti-PD-1: 195 melanoma, 159 NSCLC, 2 HNSCC
- Anti-CTLA-4: 47 melanoma

Patients with evidence for Pancreatic Atrophy (PA, n=31):
- Anti-PD-1: 15 melanoma, 8 NSCLC, 2 HNSCC
  - Anti-PD-1 anti-CTLA-4: 2 melanoma
  - Anti-CTLA-4: 4 melanoma

Case-control group:
25 PA cases vs. 41 IO controls

IO-Colitis group:
22 IO-induced colitis patients

Compared to
Results – radiological features of atrophy

• 31 patients had PA on qualitative CT assessment

• Volume decrement – median 43%, IQR 27-65%

• Radiological follow-up time – median 14.5 months, IQR 6.5-20

• PA was irreversible

• Atrophy rate was higher among anti-CTLA-4 mono or in combination with anti-PD-1 (n=6) in comparison to anti-PD-1 mono (n=25), p=0.003

• No data regarding blood amylase and lipase levels
Cases (PA patients) were matched to controls by age, gender, previous treatment lines.

25 cases were matched to 41 controls.

Similar pre-treatment median pancreatic volume – 69.5mL for cases, 75.7 controls, p=0.23.

Post-treatment – higher atrophy rate among PA patients (p=0.006).

PA is not related to disease, age or previous treatment lines - it is a new toxicity.
Pancreatic atrophy – clinical features

• No DM type 1. One patient had worsening of DM type 2

• 3 patients presented with radiological signs of pancreatitis, one with clinical pancreatitis, prior to PA development

• 4 patients (1% of entire cohort, 13% of PA cohort) developed Exocrine Pancreatic Insufficiency (EPI) with steatorrhea:
  • Diagnosis confirmed by fecal elastase-1 test (gold standard)
  • Normal serum amylase levels, two patients had post-PA low serum lipase levels
  • Atrophy rate among EPI patients and non-EPI PA patients was similar (p=0.87)
Exocrine pancreatic insufficiency versus colitis

• 4 EPI patients compared to 22 non-PA patients with IO-induced colitis

• IO-induced colitis was diagnosed based on clinical features, exclusion of an infectious disease, elevated CRP, response to corticosteroids.

• Colonoscopy was not a requirement for the diagnosis

• Both EPI and colitis group had similar radiological follow-up time – median 17.8 months for EPI versus 21.2 months for colitis, p=0.62
Exocrine pancreatic insufficiency versus colitis

- EPI symptoms were food-related, with classic description of steatorrhea.
- EPI had no severe abdominal pain, although one patient had clinical pancreatitis prior to EPI presentation.
- EPI symptoms manifested at a median of 9 months since initiation of ICI, while colitis at median of 2 months, $p=0.029$.

- **EPI symptoms completely resolved using oral pancreatic enzymes supplements**
Pancreatic atrophy was associated with lower survival

- Within the PA group – higher atrophy rates were associated with lower survival rate ($p<0.001$)
- PA patients had lower overall survival than their matched controls ($p=0.056$)
- Consistence with a report on tyrosine kinase inhibitors induced PA (Shinagare AB et al., Radiology 2016)
- Mechanism for this association is unknown
Discussion

• IO-induced PA and EPI was recently described in an Australian case-report (Long GV et al, Annals of Oncology 2017)

• Radiological evidence for PA reported in tyrosine kinase inhibitors – no data regarding EPI

• Mechanism - Currently unknown
  
  • Chronic indolent pancreatitis?

  • Anti-endothelial T-Cells response leading to vascular damage, resulting in atrophy?
Limitations

• PA was defined as qualitative, not quantitative parameter:
  • Quantitative volume measurements are time-consuming
  • Cannot be routinely performed in clinic

• Blood amylase and lipase levels were unavailable for the entire PA cohort:
  • Not routinely measured
  • All EPI patients had normal amylase, two had normal lipase
  • Australian EPI patient had normal lipase and amylase
  • Blood pancreatic enzyme levels seems to be non-contributing to diagnosis
Summary

- Pancreatic atrophy is a new toxicity of immune checkpoint inhibitors, developing in about 8% of patients regardless of their cancer type.
- Like other toxicities, a higher incidence is seen among anti-CTLA-4 or combination therapy.
- PA may result in exocrine pancreatic insufficiency (EPI) and steatorrhea; however, there is no correlation between radiological atrophy severity and the clinical outcome.
- EPI is an infrequent toxicity (1% of patients) which is:
  - Presented late into treatment (9 months)
  - Easily diagnosed using fecal elastase-1 test
  - Symptoms completely resolve using supplementary oral pancreatic enzymes, although the atrophy is irreversible.
Take home messages

- Colitis is by far the most common cause for diarrhea in patients undergoing treatment with immune checkpoint inhibitor (after exclusion of infectious disease)
- However, these drugs may also induce diarrhea which is not due to inflammation of the colon
- Suspect non-colitis diarrhea when:
  - Symptoms develop after many months of therapy
  - Medical history is not “colitis classic” – related to food, steatorrhea features, non-severe abdominal pain
  - Lab – normal CRP
  - Think wide – Pancreas, adrenal – review imaging, specific lab tests
- A non-colitis workup can save invasive endoscopies and treatment with corticosteroids
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• Gal Markel

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Gastrointestinal and Hepatic Complications of Immune Checkpoint Inhibitors

Robert S. Bresalier  M.D.

Professor of Medicine and Distinguished Professor in Gastrointestinal Oncology
University of Texas MD Anderson Cancer Center
Disclosures

- No Disclosure
- I will be not talking about non-FDA approved indications
Why Immunotherapy?

• **Cancer:**
  
  Myriad gene mutations  
  High genome instability  
  Many different diseases each with distinct genetic alterations  
  Targeting single mutations with targeted inhibitors almost always leads to disease relapse

• **Immunotherapy**
  
  Specificity  
  Memory  
  Adaptability
Immune Checkpoint Inhibitors

• Immune checkpoint inhibitors do not target the tumor cell, but target molecules involved in regulation of T cells (the “soldiers” of the immune system)

• The goal of therapy is not to activate the immune system to attack particular targets on tumor cells, but rather to remove inhibitory pathways that block effective antitumor T cell responses

• The immune response is dynamic and changes rapidly
# Immune Checkpoint Inhibitors and FDA Approvals

<table>
<thead>
<tr>
<th>Agents</th>
<th>Indication</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Unresectable or metastatic melanoma, melanoma (adjuvant), pediatric melanoma</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>Metastatic melanoma, Mesothelioma</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Metastatic melanoma, Metastatic non-small cell lung cancer, Hodgkin’s lymphoma, head/neck squamous CA, urothelial CA, gastric CA and gastroesophageal CA, solid tumors with high MSI or MRD</td>
<td>PD-1</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Metastatic melanoma, Metastatic non-small cell lung cancer, Advanced renal cell carcinoma, HCC, Hodgkin’s lymphoma, head/neck squamous cell CA, urothelial CA, Colorectal CA with high MSI or MRD</td>
<td>PD-1</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Merkel Cancer, urothelial cancer</td>
<td>PD-1</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Lung and urothelial cancer</td>
<td>PD-L1</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Urothelial cancer</td>
<td>PD-L1</td>
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</tbody>
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T-cell: Cytotoxic T lymphocyte antigen 4, programmed death-1  
Cancer cell: programmed death ligand-L1
<table>
<thead>
<tr>
<th></th>
<th><strong>Anti-CTL-4</strong></th>
<th><strong>Anti-PD-1</strong></th>
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<tbody>
<tr>
<td>Hard wired</td>
<td>Induced resistance</td>
<td></td>
</tr>
<tr>
<td>Targets CD28 pathway</td>
<td>Targets TCR pathway</td>
<td></td>
</tr>
<tr>
<td>Works during priming</td>
<td>Works on exhausted T cells</td>
<td></td>
</tr>
<tr>
<td>Expands clonal diversity</td>
<td>Does not expand clonal diversity</td>
<td></td>
</tr>
<tr>
<td>Primarily effects CD4 T cells</td>
<td>Primarily effects CD8 T cells</td>
<td></td>
</tr>
<tr>
<td>Can move T cells into “cold” tumors</td>
<td>Does not move T cells into tumors</td>
<td></td>
</tr>
<tr>
<td>Responses often slow</td>
<td>Responses usually rapid</td>
<td></td>
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<tr>
<td>Adverse events relatively frequent (up to 75%)</td>
<td>Adverse events less frequent (up to 30%)</td>
<td></td>
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<tr>
<td>Disease recurrence after response rare</td>
<td>Disease recurrence after response significant</td>
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</table>
Distribution of Immune-Related Adverse Events (irAEs)


European Journal of Cancer 54 (2016) 139-148
Time Trends of Spontaneous Reports to FDA Collected for Immune Checkpoint Inhibitors

Ipilimumab (Mar 2011)
- Mar 2011: Late Stage Melanoma

Pembrolizumab (Sept 2014)
- Jun 2018: Primary Mediastinal Large B-Cell Lymphoma
- Jun 2018: Recurrent/Metastatic Cervical Cancer PD-L1+
- Sep 2017: Advanced/Metastatic Gastric or Gastroesophageal PD-L1+
- May 2017: Solid Tumor with Specific Genetic Feature
- May 2017: Locally Advanced/Metastatic Urothelial Carcinoma
- May 2017: Metastatic Nonsquamous NSCLC Irrespective of PD-L1
- Mar 2017: Classical Hodgkin Lymphoma CHL
- Oct 2016: Metastatic NSCLC
- Aug 2016: Recurrent/Metastatic Head/Neck Squamous Cell Carcinoma
- Dec 2015: Patients with Advanced Melanoma
- Oct 2015: NSCLC
- Sep 2014: Advanced Melanoma

Nivolumab (Dec 2014)
- Aug 2017: Metastatic Colorectal Cancer
- Feb 2017: Urothelial Carcinoma
- Nov 2016: Head Neck Cancer
- May 2016: Hodgkin Lymphoma
- Nov 2015: Renal Cell Carcinoma
- Oct 2015: Advanced Lung Cancer
- Mar 2015: Lung Cancer
- Dec 2014: Advanced Melanoma

Ipilimumab + Nivolumab (Oct 2015)
- Oct 2015: BRAF V600 Wt Melanoma
- Jan 2016: Unresectable Melanoma
- Apr 2018: Advanced Renal Cell Carcinoma
- Jun 2018: Metastatic Colorectal Cancer

Atezolizumab (May 2016)
- Apr 2017: Advanced Bladder Cancer
- Oct 2016: Specific Type of Metastatic Lung Cancer
- May 2016: Urothelial Carcinoma

Avelumab (Mar 2017)
- May 2017: Urothelial Carcinoma
- Mar 2017: Metastatic Merkel Cell Carcinoma

Durvalumab (May 2017)
- Feb 2018: Unresectable Stage III NSCLC
- May 2017: Advanced Bladder Cancer
Immune-Related Adverse Events Resulting from Immunotherapy May Have a Delayed Onset and Prolonged Duration

Pharmacokinetic/Pharmacodynamic Differences Between Chemotherapy and Immunotherapy

J for Immunotherapy of Cancer 2017;5:95
Possible Mechanisms Underlying Immune-Related Adverse Events

Are these really the same as “autoimmune” diseases (eg “autoimmune hepatitis”)?

Maybe (we treat these as if they were)—but there are differences and there is much to learn regarding mechanisms.

Combination therapies (ICI’s or other agents) may convert immunologically “cold” tumors to those responsive to treatment with immune checkpoint inhibitors, but with increased toxicity.
FLYING BY THE SEAT OF YOUR PANTS
Meaning: “To proceed or work by feel or instinct without formal guidelines or experience”
Managing toxicaies associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group


Management of Immuno-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline


NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

Version 1.2018 — February 14, 2018
NCCN.org
Management of Immunotherapy-Related Toxicities, Version 1.2019

John A. Thompson, MD¹,†; Bryan J. Schneider, MD²,†; Julie Brahmer, MD, MSc³,†; Stephanie Andrews, MS, RN, ANP-BC⁴; Philippe Armand, MD, PhD⁵; Shailender Bhatia, MD¹; Lihua E. Budde, MD, PhD⁶; Luciano Costa, MD, PhD⁷; Marianne Davies, MSN, DNP⁸; David Dunnington, MA⁹; Marc S. Ernstoff, MD¹⁰,†; Matthew Frigault, MD¹¹; Brianna Hoffner, MSN¹²; Christopher J. Holmes, MD¹³; Mario Lacouture, MD¹⁴; Frederick Locke, MD⁴; Matthew Lunning, DO¹⁵; Nisha A. Mohindra, MD¹⁶; Jarushka Naidoo, MD³; Anthony J. Olszanski, MD, RPh¹⁷; Olalekan Oluwole, MD¹⁸; Sandip P. Patel, MD¹⁹; Sunil Reddy, MD²⁰; Mabel Ryder, MD²¹; Bianca Santomasso, MD, PhD¹⁴; Scott Shofer, MD, PhD²²; Jeffrey A. Sosman, MD²³; Momen Wahidi, MD²²; Yinhong Wang, MD, PhD²³,†; Alyse Johnson-Chilla, MS²⁴; and Jillian L. Scavone, PhD²⁴
NCCN/ASCO Guidelines on Management of Immunotherapy-Related Toxicities

Systematic review of 204 publications (38 systematic reviews and 166 primary studies)

“Much of the evidence consisted of observational data, consensus guidelines, case series and case reports. Due to the paucity of high-quality evidence on management of immune-related adverse events, recommendations are based on expert consensus”

J Clin Oncol 2018

NCCN Version 1.2018, February 14, 2018
Recommendations from the Society for Immunotherapy of Cancer Toxicity Management Working Group

The results represent consensus thinking by a multidisciplinary group of experts in the field but should not replace good clinical judgement or personalized drug management.

It is important to acknowledge that evidence gaps are considerable, consensus was not reached on all issues, and many questions remain unanswered.

J for Immunotherapy of Cancer 2017;5:95
Pre-treatment Evaluation (Baseline)

- History
  - Detailed questioning for autoimmune, infectious disease, endocrine and organ-specific disease history
  - History of base line bowel habit (frequency of bowel movements, usual stool consistency)
- Physical examination
- Blood tests
  - CBC, CMP, TSH, HbA1C, Free T4, Total CK, liver function tests (not specifically mentioned in NCCN guidelines)
  - Infectious disease screen: HBsAg, HBsAb, HBcAb, hCAb, CMV antibody, T-spot test, HIV antibody, HIV antigen
- Fasting lipid profile
- Dermatologic examination
  - Full skin and mucosal exam, taking note of the extent and type of lesions present
- Pulmonary tests
  - Baseline oxygen saturation on room air and during ambulation
- Cardiac tests
  - ECG
  - Troponin I or T: baseline and weekly for 6 weeks
Diarrhea and Colitis (Reviewed by Dr. Dougan)

![Graph showing incidence of irAEs (irritative adverse events) in various studies.](image)

- **irAEs**
  - Gastrointestinal (all grades)
  - Diarrhoea (all grades)
  - Colitis (all grades)
  - Gastrointestinal (grade 3 or 4)
  - Diarrhoea (grade 3 or 4)
  - Colitis (grade 3 or 4)

Selected studies:
- Hodi et al. 2010: ipilimumab 3mg/kg monotherapy (n=131)
- Hodi et al. 2010: ipilimumab 3mg/kg plus GP 100 (n=380)
- Robert et al. 2011: ipilimumab 10mg/kg plus dacarbazine (n=247)
- Garon et al. 2015: all pembrolizumab arms (n=495)
- Robert et al. 2015: nivolumab 3mg/kg (n=206)
- Weber et al. 2015: nivolumab 3mg/kg (n=286)
- Rizvi et al. 2015: nivolumab 3mg/kg (n=117)
Severe inflammation with large deep ulcerated mucosa

Moderate to severe inflammation with diffuse/patchy erythema, superficial ulcers, exudate, LOV

Mild inflammation with mild patchy erythema, aphtha, edema or normal mucosa

Wang Y et al. Inflamm Bowel Dis 2018
Acute diffuse inflammation (cryptitis, crypt abscess, superficial erosion, epithelial apoptosis)

Chronic inflammation (crypt architectural distortion, basal lymphoplasmocytosis)

LC (Increase in the intraepithelial lymphocytes);
CC (thickened sub-epithelial collagen band)

Wang Y et al. Inflamm Bowel Dis 2018
Does Acute Inflammation Lead to Chronic Inflammation?

Acute inflammation: Early effective treatment to prevent progression to chronic inflammation

Chronic inflammation: Anticipate long duration of immunosuppressive treatment
<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Increase of &lt; 4 stool per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4-6 stool per day over baseline; moderate increase in ostomy output compared to baseline; limited instrument ADL</td>
<td>Increase of &gt;/= 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Colitis</td>
<td>Asymptomatic; clinical or diagnostic observation only; intervention not indicated.</td>
<td>Abdominal pain; mucus or blood in stool</td>
<td>Severe abdominal pain; peritoneal signs</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>
Common Toxicity Elements for ICI Colitis Do Not Include Endoscopic or Histologic Findings. Need for Other Scoring Systems?

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s</th>
<th>ICPI colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoring system</td>
<td>Mayo Clinic UC score</td>
<td>CDAI</td>
<td>CTCAE v6.0</td>
</tr>
<tr>
<td>Endoscopic score</td>
<td>Mayo Clinic endoscopic score</td>
<td>SES-CD</td>
<td>??</td>
</tr>
<tr>
<td>Severity measurement</td>
<td>Clinical/endoscopy</td>
<td>Clinical/endoscopy</td>
<td>Clinical only</td>
</tr>
</tbody>
</table>
## Association of Colitis Grade with Endoscopic and Histologic Findings

<table>
<thead>
<tr>
<th></th>
<th>Colitis Grade 1 No. = 21</th>
<th>Colitis Grade 2–3 No. = 32</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endoscopic findings, no. (%)</strong></td>
<td></td>
<td></td>
<td>0.039</td>
</tr>
<tr>
<td>Inflammation</td>
<td>14 (67)</td>
<td>29 (91)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7 (33)</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Histology features, no. (%)</strong></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Inflammation</td>
<td>19 (90)</td>
<td>29 (91)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2 (10)</td>
<td>3 (9)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical remission ≠ Cure

?Value of repeat endoscopy

Pre-treatment

Post treatments
High dose steroid
2 doses of infliximab
3 doses of vedolizumab
## Significance of ulcers on endoscopy

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Ulcers N= 21</th>
<th>Group 2 No ulcers N= 32</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis treatment n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>8 (38.1)</td>
<td>23 (71.9)</td>
<td>0.023</td>
</tr>
<tr>
<td>Infliximab + steroids</td>
<td>13 (61.9)</td>
<td>9 (28.1)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea grade n (%) Grade 2-4</td>
<td>21 (100)</td>
<td>25 (78.1)</td>
<td>0.034</td>
</tr>
<tr>
<td>Colitis grade n (%) Grade 2-3</td>
<td>15 (71.4)</td>
<td>17 (53.1)</td>
<td>0.253</td>
</tr>
<tr>
<td>Repeat endoscopic findings n (%)</td>
<td></td>
<td></td>
<td>0.024</td>
</tr>
<tr>
<td>Ulcer</td>
<td>3/5 (60)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Non-ulcer inflammation</td>
<td>0 (0)</td>
<td>5/7 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2/5 (40)</td>
<td>2/7 (28.6)</td>
<td></td>
</tr>
</tbody>
</table>

Wang Y et al. Inflamm Bowel Dis 2018
Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients


Science
Volume 359(6371):97-103
January 5, 2018
Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis

Dubin et al Nature Communications 7:10391 February 2016
Composition of the intestinal microbiome between colitis-free and patients with inflammatory complications
Fecal Microbiota Transplant for Checkpoint Blockade-Mediated Colitis

1. Original colonoscopy at the diagnosis
2. After steroid+2 doses infliximab+1 dose of vedolizumab
3. 4 weeks after the FMT treatment

Wang unpublished data
Hepatotoxicity of immune checkpoint inhibitors: An evolving picture of risk associated with a vital class of immunotherapy agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Checkpoint target</th>
<th>Initial US approval (monotherapy)</th>
<th>Tumor types</th>
<th>Incidence of hepatotoxicity</th>
<th>Median time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (Yervoy)</td>
<td>CTLA-4</td>
<td>2011</td>
<td>Melanoma</td>
<td>4-11% (fatal in approximately 0.2%)</td>
<td>1.4 to 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>PD-1</td>
<td>2014</td>
<td>Melanoma Non-small cell lung cancer Head &amp; neck squamous cell cancer Classical Hodgkin lymphoma Urothelial carcinoma Microsatellite instability-high/mismatch repair deficient cancers Gastric cancer</td>
<td>0.7%</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>PD-1</td>
<td>2014</td>
<td>Melanoma Non-small cell lung cancer Renal cell carcinoma Classical Hodgkin lymphoma Head &amp; neck squamous cell cancer Urothelial carcinoma Microsatellite instability-high/mismatch repair deficient colorectal cancer Hepatocellular carcinoma</td>
<td>1.8% (13% in combination with ipilimumab)</td>
<td>3.3 (2.1 in combination with ipilimumab)</td>
</tr>
</tbody>
</table>

Based on data in the United States Prescribing Information (USPI)
Hepatotoxicity Associated with FDA-Approved Immune Checkpoint Inhibitors
(continued)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Checkpoint target</th>
<th>Initial US approval (monotherapy)</th>
<th>Tumor types</th>
<th>Incidence of hepatotoxicity</th>
<th>Median time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>PD-L1</td>
<td>2016</td>
<td>Urothelial carcinoma</td>
<td>0.9-1.3% (fatal in &lt;0.1%)</td>
<td>0.9-1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-small cell lung cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avelumab (Bavencio)</td>
<td>PD-L1</td>
<td>2017</td>
<td>Merkel cell carcinoma</td>
<td>0.9% (fatal in approximately 0.1%)</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urothelial carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durvalumab (Imfinzi)</td>
<td>PD-L1</td>
<td>2017</td>
<td>Urothelial carcinoma</td>
<td>1.1% (fatal in &lt;0.1%)</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-small lung cell cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on data in the United States Prescribing Information (USPI)
## Hepatotoxic Events Associated with Immune Checkpoint Inhibitors: Management Guidelines

<table>
<thead>
<tr>
<th>Hepatotoxicity CTCAE grade of severity</th>
<th>General recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥2 (AST and/or ALT &gt;3-5 times upper limit of normal (ULN) or total bilirubin &gt;1.5-3 times ULN)</td>
<td>1. Institute corticosteroids (Minimum 0.5-1.0 mg/d prednisone equivalent) AND 2. Withhold ICI (Do not restart until return to Grade 1 or baseline) AND 3. Monitor for changes in liver function (General principals include: a. Recheck LTs/INR/albumin every 3 d b. Review all potential hepatotoxic medications c. Rule out alternative viral or autoimmune etiologies)</td>
</tr>
<tr>
<td>Grade ≥3 (AST and/or ALT &gt;5 times ULN or total bilirubin &gt;3 times ULN)</td>
<td>1. Institute corticosteroids (1-2 mg/kg/d prednisone equivalent) AND 2. Permanent discontinuation</td>
</tr>
</tbody>
</table>

Based on data in the United States Prescribing Information (USPI)

Mycophenolate has been used in some clinical trials to treat patients with persistent severe hepatitis despite high-dose steroids
Comprehensive Meta-Analysis of Key Immune-Related Adverse Events from CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients

Table 2. Incidence of all-grade and high-grade of immune-related toxicities of novel ICIs in cancer patients

<table>
<thead>
<tr>
<th>Immune-related toxicities</th>
<th>No. trials</th>
<th>No. events</th>
<th>Incidence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>16</td>
<td>206/5,442</td>
<td>2.3 (1.3-3.9)</td>
</tr>
<tr>
<td>AST</td>
<td>14</td>
<td>330/3,855</td>
<td>6.5 (3.3-12.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>19</td>
<td>952/5,777</td>
<td>13.9 (10.6-18.0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15</td>
<td>244/4,622</td>
<td>5.1 (3.8-6.8)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>15</td>
<td>119/4,599</td>
<td>2.6 (2.0-3.7)</td>
</tr>
<tr>
<td>High grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>16</td>
<td>119/5,442</td>
<td>1.5 (0.9-2.5)</td>
</tr>
<tr>
<td>AST</td>
<td>14</td>
<td>94/3,855</td>
<td>1.5 (0.7-3.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>50/5,299</td>
<td>1.1 (0.7-1.7)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>5/4,144</td>
<td>0.3 (0.2-0.5)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>15</td>
<td>42/4,599</td>
<td>1.1 (0.7-1.7)</td>
</tr>
</tbody>
</table>

Table 4. Comparison between PD-1/PD-L1 and CTLA-4 inhibitors

<table>
<thead>
<tr>
<th>Immune-related toxicities</th>
<th>PD-1/PD-L1 inhibitors RR (95% CI)</th>
<th>CTLA-4 inhibitors RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>3.36 (1.36-8.33)</td>
<td>11.3 (6.05-21.1)</td>
<td>0.054</td>
</tr>
<tr>
<td>AST</td>
<td>1.71 (1.01-2.89)</td>
<td>1.92 (0.94-3.93)</td>
<td>0.745</td>
</tr>
<tr>
<td>Rash</td>
<td>1.59 (0.90-2.82)</td>
<td>3.94 (3.02-5.14)</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.05 (4.26-15.2)</td>
<td>4.64 (1.42-15.2)</td>
<td>0.352</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3.85 (1.23-12.1)</td>
<td>11.1 (0.62-199.8)</td>
<td>0.562</td>
</tr>
<tr>
<td>High grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>2.47 (0.90-6.72)</td>
<td>22.5 (6.37-79.4)</td>
<td><strong>0.021</strong></td>
</tr>
<tr>
<td>AST</td>
<td>1.26 (0.38-4.16)</td>
<td>5.05 (1.26-20.3)</td>
<td>0.168</td>
</tr>
<tr>
<td>Rash</td>
<td>0.91 (0.40-2.10)</td>
<td>3.55 (1.37-9.19)</td>
<td>0.052</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.85 (0.25-2.84)</td>
<td>2.02 (0.39-10.5)</td>
<td>0.421</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.49 (0.80-2.79)</td>
<td>3.02 (0.12-74.0)</td>
<td>0.798</td>
</tr>
</tbody>
</table>

De Velasco et al Cancer Immunology Research 2017
### Table 2. Incidence and Types of Immune Checkpoint Inhibitor-Related Fatalities
From Systematic Review and Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths, No. (%)</strong></td>
<td>58 (1.08)</td>
<td>33 (0.36)</td>
<td>12 (0.38)</td>
<td>19 (1.23)</td>
</tr>
<tr>
<td><strong>Type of fatal toxic effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>23 (40)</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (5)</td>
<td>14 (42)</td>
<td>5 (42)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>5 (9)</td>
<td>0</td>
<td>1 (8)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>9 (16)</td>
<td>4 (12)</td>
<td>3 (25)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>2 (4)</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Infectious</td>
<td>8 (14)</td>
<td>5 (15)</td>
<td>2 (18)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Hemorrhagic/thrombotic</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>1 (2)</td>
<td>2 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>3 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>2 (6)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Abbreviations:** CTLA-4, cytotoxic T lymphocyte antigen-4; PD-L1, programmed death ligand-1; PD-1, programmed death-1.
| Variable | No. (%) | | | | |
|---|---|---|---|---|
| | Ipilimumab (n = 193) | Anti-PD-1/PD-L1 (n = 333) | Combination (n = 87) | P Value |
| Types of cancer* | | | | <.001 |
| Melanoma | 136 (96) | 50 (18) | 49 (66) | | |
| Lung cancer | 0 | 152 (54) | 17 (23) | | |
| Other | 5 (4) | 78 (28) | 8 (11) | | |
| Type of fatal irAE | | | | | |
| Colitis | 135 (70) | 58 (17) | 32 (37) | <.001 |
| Pneumonitis | 15 (8) | 115 (35) | 12 (14) | <.001 |
| Hepatitis | 31 (16) | 74 (22) | 19 (22) | .23 |
| Hypophysitis | 10 (5) | 3 (1) | 2 (2) | .01 |
| Cardiac | 3 (2) | 27 (8) | 22 (25) | <.001 |
| Myositis | 1 (0.5) | 22 (7) | 11 (13) | <.001 |
| Nephritis | 1 (0.5) | 7 (2) | 3 (4) | .19 |
| Adrenal | 8 (4) | 6 (2) | 3 (4) | .26 |
| Neurologic | 11 (6) | 50 (15) | 7 (8) | .003 |
| Hematologic | 3 (2) | 14 (4) | 2 (2) | .22 |
| Other (skin, thyroid, diabetes, other gastrointestinal) | 13 (7) | 24 (8) | 7 (8) | .93 |
| Other clinical features | | | | | |
| Median time to irAE, days | 40 | 40 | 14 | .01 |
| >1 concurrent irAE, % | 27 (14) | 51 (15) | 24 (28) | .01 |
| Reporting year | | | | | |
| 2014 or before | 98 (51) | 3 (1) | 2 (2) | <.001 |
| 2015 | 45 (23) | 20 (6) | 9 (10) | <.001 |
| 2016 | 21 (11) | 88 (28) | 17 (20) | .001 |
| 2017 | 26 (13) | 192 (58) | 44 (51) | <.001 |
| 2018 (up to January 15) | 3 (2) | 30 (9) | 15 (17) | <.001 |

Abbreviations: irAE, immune-related adverse event; PD-L1, programmed death ligand-1; PD-1, programmed death-1.
* Percent of known (52 patients treated with ipilimumab; 53 with anti-PD-1/PD-L1, and 13 with combination did not list cancer types).
Time to Symptom Onset of Fatal Toxic Effects by ICI Regimen

<table>
<thead>
<tr>
<th></th>
<th>Median time to onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>40 days</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>40 days</td>
</tr>
<tr>
<td>Combination</td>
<td>14.5 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>15</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>34</td>
</tr>
<tr>
<td>Combination</td>
<td>6</td>
</tr>
</tbody>
</table>
Disproportionality analysis is a validated concept in pharmacovigilance that compares the proportion of selected AEs reported for a single drug or drug class (e.g., ICIs) with the proportion of the same AEs for a control group of drugs (e.g., other anticancer agents). The denominator in these analyses is the total number of reports of AEs for each group of drugs.

“…immune checkpoint inhibitors are associated with large post-marketing reports of diverse immune-related adverse events occurring in virtually any organ or tissue. This analysis…identified endocrine, hepatic and respiratory toxicities as emerging safety priorities."
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>ICI vs other ant-cancer agents</th>
<th>Anti-CTLA4 vs other anti-cancer agents including anti-PD1/PDL1</th>
<th>Anti-PD1/PDL1 vs other anti-cancer drugs including anti-CTLA4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>3.12 (2.81-3.47)</td>
<td>4.75 (4.09-5.52)</td>
<td>3.05 (2.72-3.42)</td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>1.55 (1.39-1.72)</td>
<td>1.02 (0.81-1.28)</td>
<td>1.80 (1.62-2.01)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>14.23 (11.90-17.00)</td>
<td>20.85 (17.34-25.07)</td>
<td>14.24 (12.04-16.84)</td>
</tr>
<tr>
<td>Liver disorder</td>
<td>1.18 (1.04-1.35)</td>
<td>1.70 (1.39-2.07)</td>
<td>1.80 (1.62-2.01)</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>0.91 (0.78—1.05)</td>
<td>1.14 (0.91-1.45)</td>
<td>0.87 (0.74-1.03)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1.04 (0.88-1.22)</td>
<td>1.59 (1.26-2.02)</td>
<td>0.96 (0.80-1.16)</td>
</tr>
<tr>
<td>Drug-induced liver injury</td>
<td>2.37 (1.96-2.86)</td>
<td>3.06 (2.28-4.10)</td>
<td>2.42 (1.97-2.96)</td>
</tr>
<tr>
<td>Hepatocellular liver injury</td>
<td>1.45 (1.20-1.75)</td>
<td>1.76 (1.30-2.40)</td>
<td>1.48 (1.21-1.82)</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>1.41 (1,17-1.70)</td>
<td>1.48 (1.06-2.06)</td>
<td>1.51 (1.24-1.85)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>2.11 (1.73-2.57)</td>
<td>0.71 (0.39-1.29)</td>
<td>2.51 (2.05-3.07)</td>
</tr>
<tr>
<td>CTCAE Term</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hepatobilary Disorders-Other</td>
<td>Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate ADL</td>
<td>Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL</td>
</tr>
<tr>
<td>CTCAE Term</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>&gt; 3 X ULN</td>
<td>&gt; 3-5 X ULN</td>
<td>&gt; 5-20 X ULN</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>&gt; 3 X ULN</td>
<td>&gt; 3-5 X ULN</td>
<td>&gt; 5-20 X ULN</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>&gt; 1.5 X ULN</td>
<td>&gt; 1.5-3 X ULN</td>
<td>&gt; 3-10 X ULN</td>
</tr>
</tbody>
</table>
Histologic Patterns in the Liver Patients Treated with Immune Checkpoint Inhibitors

- **Anti-CTLA-4**
  - Centrilobular necrosis, sinusoidal inflammatory infiltrates and fibrin ring granulomas

- **Anti-CTLA-4**
  - Endotheliitis
  - CD8+ cytotoxic T lymphocytes

- **Anti-PD1**
  - Active hepatitis with mild periportal and moderate lobular activity

De Martin et al J Hepatol 2018
### HEPATIC ADVERSE EVENT(S)

- Transaminitis without elevated bilirubin

### ASSESSMENT/GRADING

- Rule out viral etiology, disease-related hepatic dysfunction, other drug-induced transaminases elevations
- Consider GI evaluation
- Ultrasound
  - Consider magnetic resonance cholangiopancreatography (MRCP) if normal ultrasound
- Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)

### MANAGEMENT

- Continue immunotherapy, consider holding immunotherapy for concerning lab value trend
- Assess transaminases and bilirubin with increased frequency
- Hold immunotherapy
- Monitor liver function tests (LFTs) every 3-5 days
- Consider prednisone 0.5-1 mg/kg/day
- Permanently discontinue immunotherapy
- Initiate prednisone 1-2 mg/kg/day
- Consider inpatient care
- Monitor liver enzymes every 1-2 days
- Hepatology consultation
- If steroid refractory or no improvement after 3 days, consider adding mycophenolate
- Infliximab should not be used for hepatitis
- Permanently discontinue therapy; hospitalization; monitor liver enzymes daily; liver biopsy if no contraindication. Initiate prednisone/methylprednisolone 2 mg/kg/day. If steroid-refractory or no improvement after 3 days consider adding mycophenolate. Infliximab should not be used for hepatitis.

---

<table>
<thead>
<tr>
<th>HEPATIC ADVERSE EVENT(S)</th>
<th>ASSESSMENT/GRADING</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transaminitis without elevated bilirubin</td>
<td>• Rule out viral etiology, disease-related hepatic dysfunction, other drug-induced transaminases elevations</td>
<td>• Continue immunotherapy, consider holding immunotherapy for concerning lab value trend</td>
</tr>
<tr>
<td></td>
<td>• Consider GI evaluation</td>
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</tr>
<tr>
<td></td>
<td>• Ultrasound</td>
<td>• Hold immunotherapy</td>
</tr>
<tr>
<td></td>
<td>• Consider magnetic resonance cholangiopancreatography (MRCP) if normal ultrasound</td>
<td>• Monitor liver function tests (LFTs) every 3-5 days</td>
</tr>
<tr>
<td></td>
<td>• Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)</td>
<td>• Consider prednisone 0.5-1 mg/kg/day</td>
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<tr>
<td></td>
<td></td>
<td>• Permanently discontinue immunotherapy</td>
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</tbody>
</table>
NCCN 2019 Management of Immunotherapy-Related Hepatotoxicity

**HEPATIC ADVERSE EVENT(S)**
Grade >1 transaminitis with bilirubin >1.5x ULN (unless Gilbert’s syndrome)

**ASSESSMENT/GRADING**
- Rule out viral etiology, disease-related hepatic dysfunction, other drug-induced transaminase elevations
- Consider GI evaluation
- Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplements, and alcohol use)

**MANAGEMENT**
- Permanently discontinue immunotherapy
- Initiate methylprednisolone/prednisone 2 mg/kg/day
- Inpatient care
- Monitor liver enzymes daily
- Hepatology consultation
- If steroid refractory or no improvement after 3 days, consider mycophenolate
- Infliximab should not be used for hepatitis
MD Anderson Experience

- 5,762 Patients received immune checkpoint inhibitors for a variety of indications between 1/2010 and 3/2018
- Moderate hepatotoxicity (ALT 5-20 x ULN) 1.5%
- Severe hepatotoxicity (ALT > 20 X ULN) 0.26%
- Median number of ICE infusions before evident hepatotoxicity 3
- Mean interval from initiation of ICI to evident hepatotoxicity 57 days for anti-CTLA-4, 85 days for anti-PD-1/PDL-1, 56 days for combination therapy (NS)
- Recurrent ALT elevation in those who re-started ICI ani-CTLA-4 16%, anti-PD-1/PDL-1 15%, combination 28% (NS)

Abu-Sbeih et al 2018 (abstract)
What Is DILIN?

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has established the Drug-Induced Liver Injury Network (DILIN) to collect and analyze cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and alternative medicines, such as herbal products and supplements. Currently, DILIN is conducting 2 registry studies:

- **Retrospective Study.** To establish a nationwide registry of people who have experienced liver injury within the past 10 years after using drugs or Herbal and Dietary Supplements known as HDS.
- **Prospective Study,** to establish a nationwide registry of people who have experienced liver injury within the past 6 months after using certain drugs or alternative products.

**Causality Process and Web Application.** The diagnosis of drug-induced liver injury relies on evidence linking the injury to a specific drug or agent. DILIN uses "expert opinion" to determine the degree of association between the implicated medication(s) and the liver injury. This process is identified as DILIN Causality Case Adjudication which is the DILIN project primary Endpoint. The DILIN Causality Web Application is a system specifically developed for this purpose. This is a secure system which was developed by the DCRI IT group for the DILIN network based on an open source platform. The Causality Web Application's mission is to streamline the previous process which will include more efficient case management and seamless system integration to existing DILIN databases. The DILIN Causality Web Application is also providing greater consistency within the processes by applying business rules to user's input.

Interested in participating in this study? [Contact Us]

The DILIN Network Members at the Steering Committee Meeting on May 31, 2018

[Map of DILIN Network Members]
Drug-Induced Liver Injury Network

...there is a great need to develop an improved means of detecting, defining, and studying DILI in the United States. The DILIN Prospective Study is a multi-center study designed to gather clinical information and biological specimens on cases of suspected liver injury due to drugs and CAM. The goals of this study include the earlier recognition of DILI, especially due to newer drugs, development of standardized instruments and terminology to help identify cases of DILI, investigating clinical and genetic risk factors that predict DILI, and performing a careful longitudinal follow-up of DILI subjects. The biological samples collected will be used in future studies of the mechanisms and genetics of DILI.

**Prospective Study Inclusion**: evidence of liver injury that is known or suspected to be related to consumption of a drug or CAM product in the 6-month period prior to enrollment; and have documented clinically important DILI defined in terms of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (Alk Phos). Subjects will be excluded if there is acetaminophen hepatotoxicity, a competing cause of acute liver injury, or liver transplant prior to the development of drug- or CAM-induced liver injury.
Conclusions

• There is a paucity of high-quality prospectively collected evidence on management of immune-related adverse events and guideline recommendations are based on expert consensus. Therefore evidence gaps are considerable.

• Diarrhea and colitis are common side effects of immune checkpoint blockade (anti-CTL4 > anti-PD-1) and may occur at any time following initiation of treatment (and recur after cessation of treatment).

• Current grading systems and treatment guidelines for diarrhea and colitis are based on symptom-based Common Terminology Criteria for Adverse Events (CTCAE), and do not yet fully incorporate endoscopic, radiographic and histologic findings.

• The Gastroenterologist should be involved in a team approach for patients with grade 2 or higher symptoms
Conclusions (continued)

- Colonoscopy (with biopsy) is recommended for cases of grade 2 or higher diarrhea/colitis since evidence suggests that the presence of ulceration in the colon predicts a steroid-refractory course which may require early initiation of alternate therapy (infliximab, vedolizumab). Role of repeat colonoscopy?

- Currently IV steroids remain first line treatment for grade 2 or higher symptoms

- Case series suggest benefit of infliximab and vedolizumab for steroid refractory disease (how long do you wait?). Early infliximab for ulcerative disease?

- Liver toxicity is an emerging safety priority as the use of immune checkpoint inhibitors increases, and appears to be more common than with other chemotherapeutic agents

- The pattern of liver toxicity may differ between classes of iCIs, including histology. How this translates into treatment algorithms remains to be determined
Conclusions (continued)

- Current grading systems and treatment guidelines for liver toxicity are based on symptom-based Common Terminology Criteria for Adverse Events (CTCAE), and do not yet fully the full spectrum of liver function tests or histologic findings.

- While corticosteroids remain first line treatment for grade 2 or higher (based on elevated transaminases) or elevated transaminases + elevated bilirubin, who actually requires corticosteroid (or other) treatment is yet to be determined.

- The role of routine liver biopsies (outside of the research setting) for moderate to severe grades of toxicity remains to be determined.

- There is a great need to develop improved means of detecting, defining, and studying iCPI-related liver (and other) toxicity which incorporate objective criteria and prospective study designs.
Cytokines, Autoimmunity, and Immune-Related Adverse Events Refractory to Initial Therapy

Speakers
Jaruska Naidoo, MBBCh
Kelly Walkovich, MD
David Klatzmann, MD, PhD
Steroid-Refractory Pneumonitis and Prospective Studies for irAEs

Jarushka Naidoo, MB BCH
Assistant Professor of Oncology
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
Baltimore, MD
Disclosures

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AstraZeneca/MedImmune

Consulting:
Bristol Myers-Squibb
AstraZeneca/MedImmune
Roche/Genentech

Honoraria:
Bristol Myers-Squibb
AstraZeneca/MedImmune
Outline

• PD-1/PD-L1 Pneumonitis

• Steroid-refractory Pneumonitis Trial

• Prospective Studies for irAEs

• Other Clinical Research in irAE management
Pneumonitis with Anti-PD-1/PD-L1 Therapy

Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy


Naidoo et al, J Clin Oncol 2016
Pneumonitis with Anti-PD-1/PD-L1 Therapy
Risk Factors: JHH

Overall Incidence
39/205 cases: 19%

Cumulative Incidence

CIP Incidence Rates

<table>
<thead>
<tr>
<th>Stage</th>
<th>Events</th>
<th>Person-years</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II</td>
<td>5</td>
<td>32.9</td>
<td>0.77 (0.23, 2.14)</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
<td>46.7</td>
<td>1.42 (0.64, 3.02)</td>
</tr>
<tr>
<td>IV</td>
<td>19</td>
<td>96.7</td>
<td>REF</td>
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</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Events</th>
<th>Person-years</th>
<th>IRR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Adeno</td>
<td>17</td>
<td>119.7</td>
<td>REF</td>
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<tr>
<td>Squamous</td>
<td>16</td>
<td>49.1</td>
<td>2.29 (1.08, 4.83)</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>8.16</td>
<td>4.32 (1.24, 12.19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemo</th>
<th>Events</th>
<th>Person-years</th>
<th>IRR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td>26</td>
<td>138.4</td>
<td>REF</td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>40.1</td>
<td>1.46 (0.65, 3.06)</td>
</tr>
</tbody>
</table>

Risk factors for CIP at 1 year

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.42</td>
<td>(0.19, 0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.86</td>
<td>(0.38, 2.0)</td>
<td>0.72</td>
</tr>
<tr>
<td>Combination ICI</td>
<td>1.72</td>
<td>(0.80, 3.67)</td>
<td>0.16</td>
</tr>
<tr>
<td>Multivariate a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.38</td>
<td>(0.17, 0.82)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* a adjusted for prior chemotherapy and combination ICI
ICI: Immune Checkpoint Inhibitor
Pneumonitis with Anti-PD-1/PD-L1 Therapy
Survival: JHH

State 1: No CIP
State 2: CIP
State 3: Death

Graph: Fitted survival probability over time (days)
Anti-PD-1/PD-L1 Pneumonitis Challenges

• No current standard immunosuppressive therapy for patients who develop steroid-refractory PD-1/PD-L1 pneumonitis

• Patients who received TNF-inhibition after corticosteroids for grade 2+ pneumonitis had poor outcomes (death or infection, 2% patients)

• Bronchoscopy is not routinely done in patients with grade 2+ pneumonitis - Leads to diagnostic challenges (infection vs. progression vs. pneumonitis) - Mechanisms of pneumonitis are unknown

• Incidence of pneumonitis: 5% anti-PD-1/PD-L1, 10% with PD-1/CTLA-4.
### Anti-PD-1/PD-L1 Pneumonitis

**Immunosuppressive Alternatives**

<table>
<thead>
<tr>
<th><strong>Infliximab</strong></th>
<th><strong>IVIG</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Currently recommended immunosuppressive therapy based on early clinical trial experience&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• Benefit in paraneoplastic immune conditions&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>• TNF inhibition improves outcomes for patients with steroid-refractory colitis&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• Improved vital capacity, DLCO and walking distance on 6-minute walk-test in steroid-unresponsive IPF&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Selected case reports indicating benefit with infliximab for pneumonitis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>• Selected case reports indicating benefit with infliximab for pneumonitis&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

4. Rosenfeld et al, *Curr Treat Options Oncol* 2013
Anti-PD-1/PD-L1 Pneumonitis
Hypotheses and Aims

**Hypotheses:**

Steroid-refractory pneumonitis may be effectively treated with either infliximab or IVIG

Immunologic features of pneumonitis in lung biospecimens may correlate with severity of pneumonitis/response to treatment

Paired genomic and immunologic assays may identify pneumonitis biomarkers

**Aims:**

1. Assess whether Infliximab or IVIG results in clinical improvement in steroid-refractory pneumonitis

2. Evaluate the immunologic features of pneumonitis in lung tissue/BAL to identify prognostic features

3. Examine serial blood sample and baseline tumor tissue in enrolled patients and separate controls, to identify pneumonitis biomarkers
• PD-1/PD-L1 Pneumonitis

• Steroid-refractory Pneumonitis Trial

• Prospective Studies for irAEs

• Other Clinical Research in irAE management
ECOG-ACRIN Trial
Optimizing Immunosuppression for Steroid-Refractory PD-1/PD-L1 Pneumonitis

Patient with
Grade 2+
PD-1/PD-L1
Pneumonitis

Any solid/hematologic malignancy

Any PD-1/PD-L1 agent

Pneumonitis that has not improved to CTCAE grade 1 or less, after 2-10 days prednisone 1-2mg/kg/equivalent

No active infection

No radiologic evidence progressive cancer in lung

Pathogen-negative bronchoscopy

Pneumonitis Assessment
Day 1 Steroid-Refractory

1. Hb saturation (PaO2/FiO2 on ABG)
2. PFTs
3. High Res CT chest
4. Blood (correlatives)
5. Bronchoscopy +BAL (+/- biopsy)
6. Patient Reported Outcomes

Infliximab then Prednisone Taper 4-6 weeks

Pneumonitis Assessment
Day 14 Steroid-Refractory

1. Hb saturation (PaO2/FiO2 on ABG)
2. PFTs
3. High Res CT chest
4. Blood (correlatives)
5. Bronchoscopy +BAL (+/- biopsy)
6. Patient Reported Outcomes

IVIG x 5 days then Prednisone Taper 4-6 weeks

*Primary Endpoint:
• Improvement in PAO2/FiO2 on ABG from day 1, at 28-days

ECOG-ACRIN PI: Naidoo, Pulmonary PI: Rivera
# Anti-PD-1/PD-L1 Pneumonitis Correlative Analyses

## Circulating Biomarkers (whole blood/serum/PBMC)

- Multiparameter cytokine panel (mesoscale pre/post steroids/immunosuppression: IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-17, IL-23, TNF-α.)

- Autoantibody panel

- TCR sequencing/DNA and RNA analyses

## Tissue-based Biomarkers (BAL, Lung Tissue)

- **BAL:**
  - Flow cytometry for immune cell populations/cytokines
  - TCR sequencing

- **Lung tissue:**
  - Pathologic assessment
  - Immune cell subsets by IHC,
  - Immunofluorescence
BALF from PD-1/PD-L1 pneumonitis patients

Cell count, diff
Centrifugation

BALF supernatant aliquots

TCR Sequencing (Pardoll Lab)

BALF T Cell aliquots

T cell phenotype and activation
Treg profile
Macrophage activation

BAL Th response
Treg profile
Macrophage activation

BAL cytokine analysis

Mouse model of PD-1 pneumonitis

BALF: Bronchoalveolar lavage fluid

Human specimen receiving / processing

Translational studies

Complimentary Pre-clinical mouse model studies
Anti-PD-1/PD-L1 Pneumonitis

Lessons

• **Study Feasibility**
  - Incidence of pneumonitis 5-10%, steroid-refractory 2%
  - How many centers are needed to accrue?
  - Definitions for steroid-refractory and steroid-dependent
  - Power calculations based on limited historic data

• **Practical considerations**
  - Obtaining biospecimens: Is bronchoscopy pre-immunosuppression feasible at your institution?
  - How interpretable are mechanistic insights from specimens, post-steroids
  - Medical oncology and organ-specialist co-PIs
  - Need for integrated medicine and oncology clinical research staff
PD-1/PD-L1 Pneumonitis

Steroid-refractory Pneumonitis Trial

Prospective Studies for irAEs

Other Clinical Research in irAE management
Rituximab and Tocilizumab for Selected Steroid-dependent irAEs

Primary Endpoint:
Changes in T-cell and B-cell subsets by flow cytometry

Roche/Genentech imCORE
coPIs: Naidoo, Rizvi, Lacouture
Rituximab and Tocilizumab for irAs
Lessons

• **Study Design**
  - Definitions for steroid-refractory and steroid-dependent
  - Interpretation of correlative endpoints with a heterogeneous study population
  - Inclusion of all tumor types
  - Inclusion of patients on other studies
  - Selecting irAEs of interest, when mechanisms are largely unknown

• **Practical considerations**
  - Identifying a range of organ-specialist co-PIs with experience in irAEs
  - Need for integrated medicine and oncology clinical research staff
  - Coordinating both inpatient and outpatient treatments
  - Defining improvement in an irAE across organs
Outline

- PD-1/PD-L1 Pneumonitis
- Steroid-refractory Pneumonitis Trial
- Prospective Studies for irAEs
- Other Clinical Research in irAE management
Multidisciplinary Team for Managing irAEs

8 oncologists
4 oncology nurse specialists

20 medicine subspecialists

Allied specialists from pathology, pharmacy, radiology, and patient advocacy

In-person or electronic message referrals

Monthly interdisciplinary tumor-board style meeting
Clinical Goals
• Centralize discussion of complex irAE cases
• Identify new irAEs

Translational Goals
• Propose prospective irAE studies

Director:
Oncology: Naidoo

Hypotheses:

a) A multidisciplinary toxicity team will assist in the diagnosis and management of patients with irAEs at Johns Hopkins

b) Specific patient and treatment features may associate with the development of certain irAEs or irAE severity (grade)
Immune-Related Toxicity Team
Pilot Project: Operations

- Central group of 13 members
  - 2 co-chairs:
  - Naidoo (Oncology)
  - Cappelli (Rheumatology)
  - 8 Oncologists, 4 Oncology RNs
- Contactable by electronic referral 24-hours a day/7-days a week
- CC relevant medicine provider if relevant/requested
- Summary recommendations sent within 24-hours by IR Tox Team co-chairs
- Follow-up and case presentations at monthly tumor-board style meetings

**Referral to IR-Tox Team**

- Patient Initials: MRN:
- Referring Provider: Primary Provider:
- Name of Immunotherapy Agent(s):
- Duration of Immunotherapy:
- Tumor Type:
- Diagnostic Evaluation ordered/completed:
- Brief Summary:
- Specific Question:
- Request for medicine referral:

**24-Hour IR Tox Team Summary**

- Patient Initials: MRN:
- Replying Provider:
- Recommendations:
- Disclaimer: The decision of whether to implement these recommendations is at the discretion of the referring provider. For emergent cases patients should go to their nearest ER.
## Results: IR-Toxicity Team Referrals
### Patient Demographics and Oncologic History

| Patient Characteristics                      | (n=102, 100%) | | Patient Characteristics                      | (n=102, 100%) | |
|---------------------------------------------|---------------|-------------------------------------------------|
| **Age, median (IQR)**                       | 64 years (57,74) | **Treatment Setting**                            |               |
| **Gender**                                  |               | **Inpatient**                                    | 37 (36.3)     |
| Male                                        | 55 (53.9)     | **Outpatient**                                   | 65 (63.7)     |
| Female                                      | 47 (46.1)     | **Immune Checkpoint Inhibitor Therapy**          | 55 (53.9)     |
| **Smoking Status**                          |               | **Monotherapy**                                  |               |
| Former/Current                              | 39 (38.6)     | **Combination therapy**                          |               |
| Never                                       | 63 (61.8)     | **2-agents**                                     | 40 (39.2)     |
| **Race**                                    |               | **3-agents**                                     | 7 (6.9)       |
| Caucasian                                   | 83 (81.4)     | **Number of doses at referral, median (IQR)**   | 3 (2, 8)      |
| Black/African-American                      | 11 (10.8)     | **Receipt of Therapy**                           |               |
| Asian                                       | 7 (6.9)       | **Standard-of-Care**                             | 50 (49.0)     |
| Other                                       | 1 (1.0)       | **Clinical Trial**                               | 52 (51.0)     |
| **Active or Prior Autoimmune Disease**      |               | **Receipt of Therapy**                           |               |
| Yes                                         | 13 (12.7)     | **Standard-of-Care**                             |               |
| No                                          | 89 (87.3)     | **Clinical Trial**                               |               |
| **Tumor Type**                              |               |                                                 |               |
| Thoracic/Head and Neck                      | 40 (39.2)     |                                                 |               |
| Melanoma/Skin                               | 17 (16.7)     |                                                 |               |
| Gastrointestinal                            | 18 (17.6)     |                                                 |               |
| Genitourinary                               | 7 (6.9)       |                                                 |               |
| Gynecologic                                 | 8 (7.8)       |                                                 |               |
| Breast                                      | 4 (3.9)       |                                                 |               |
| Hematologic                                 | 7 (6.9)       |                                                 |               |
| Sarcoma                                     | 1 (1.0)       |                                                 |               |

*There were no missing data or outliers in this dataset.

Naidoo et al, JNCCN 2019 In Press
Most referrals were outpatients, those with lung cancer, and for suspected pulmonary toxicity.

A potential new irAE of bony inflammation was identified.

These data also identify the toxicities that have the greatest diagnostic dilemma: pneumonitis and neurologic irAEs.

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Study Results

Spectrum of suspected irAEs: Individual referrals

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Naidoo et al, JNCCN 2019 In Press
Study Results
Spectrum of confirmed irAEs: Treatment, grade, organ system

- Patients who received combination CPIs and those with a history of autoimmune disease were significantly more likely to develop a ≥ grade 3 toxicity by multivariate analysis.

Naidoo et al, JNCCN 2019 In Press
97% of respondents (58/60) found the IR-Tox Team helpful
- MD= 35, NP/PA=7, RN=15, Other=4

Naidoo et al, JNCCN 2019 In Press
Study Results
Toxicity team survey (cont.)

- 73% of respondents (58/60) thought a monthly tumor-board style meeting to support electronic referral was helpful
- <20% of respondents felt an irAE clinic would be of benefit

Naidoo et al, JNCCN 2019 In Press
Discussion

• The IR-Tox team was a well utilized new resource at JHH over a pilot period.
• Most referrals were received from outpatients, those with lung cancer, and for suspected pulmonary toxicity.
• Combination ICIs, pts with a history of autoimmune disease, were more likely to develop grade 3+ toxicity.
• Differences in diagnostic and management recommendations by the IR-tox team in those with low vs high grade irAEs

Conclusions

• The IR Tox Team is a new multidisciplinary paradigm applicable to selected patients with irAEs and related issues.
• These data highlight a new area of clinical need to integrate oncology and medicine specialists.
• This is of particular relevance in patients with multiple irAEs or those with prior autoimmune conditions.
• This group can be leveraged for both clinical and research initiatives
Colleagues and Collaborators

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Leveraging a Multi-Disciplinary Care Model for Primary Immunodeficiency Disorders to Understand Immune-Related Adverse Events

Kelly Walkovich, MD
Associate Professor, Pediatric Hematology/Oncology
University of Michigan, C.S. Mott Children’s Hospital
15 April 2019
Disclosures

• I have no relevant financial relationships to disclose.
• I will not discuss off-label and/or investigational therapy.
Primary Immunodeficiency Disorders (PIDD)

Collection of more than 354 unique genetically and mechanistically defined disorders encompassing:

- Elevated susceptibility to infection
- Increased risk of malignancy
- Heightened tendency for autoimmune disorders due to immune dysregulation

THE TEAM, THE TEAM, THE TEAM.

BO SCHEMBECHLER
Immune Checkpoint Inhibition

anti-CTLA-4
ipilimumab
tremilimumab

anti-PD-L1
durvalumab
atezolizumab
avelumab

anti-PD-1
nivolumab
pembrolizumab

Pharmacologic vs. Genetic Inhibition

Phenotypic Overlap

Cytotoxic T-Lymphocyte-Associated Protein 4 Haploinsufficiency-Associated Inflammation Can Occur Independently of T-Cell Hyperproliferation

Carole Le Coz¹, Brian E. Nolan², Melissa Saquib A. Lakhani⁴, Antonio Novelli⁶, Silvana Briuglia⁹, Tricia R. Bhatti⁸,¹⁰ and

Acquired Lipodystrophy Associated with Nivolumab in a Patient with Advanced Renal Cell Carcinoma


The Journal of Clinical Endocrinology & Metabolism
Endocrine Society
Potential Mechanisms

Immune checkpoint inhibition alters lipid metabolism in T-cells

- Altered fatty acid metabolism has previously been shown to be a driver of dysregulated immunity in other conditions (e.g. GVHD, SLE)

Altered T-cells may induce a pro-apoptotic effect on the adipocytes or have increased utilization of lipid material (thereby explaining the loss of subcutaneous fat)

Lipid metabolism may alter epigenetic mechanisms through acetyl co-A and histone acetylation that promote the clinical phenotype in susceptible individual

Mission: To provide a collaborative *multidisciplinary* environment to advance the education, clinical care, and research involving pediatric and adult patients with immuno-hematologic disorders.

Aims:

1. Enhance clinical communication between sub-specialties.
2. Provide immuno-hematology education opportunities.
3. Establish a platform for cooperative research studies.
Immune Related Adverse Events

With the introduction of immunotherapy to treat cancer, many patients are being cured of their malignancy but with an undefined long-term “cost” to their immune system.

- Will CAR-T cell patients treated for B-cell acute leukemia mirror XLA patients?
- Can supportive care recommendations for PIDD translate to immunotherapy patients for safer care?

Additionally, direct immunotherapy with immune checkpoint inhibitors are resulting in a multitude of immune-mediated complications.

- Mechanism of the autoimmunity mimicking PIDD?
- Targeted treatment options to mitigate the irAE?
Enhancing Multidisciplinary Communication

Topic Specific Listservs
• Cytopenias
• Malignancy in PIDD
• Immune-Related Adverse Events

• To join:
  email tomsmith@med.umich.edu
  or visit nicerconsortium.org
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Speakers
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Neurotoxicity associated with immune checkpoint inhibitor treatment

NIH-AACR Cancer, Autoimmunity, and Immunology Conference
April 15, 2019

Bianca D. Santomasso MD, PhD
Assistant Attending, Department of Neurology
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Disclosure Information

NIH-AACR Cancer, Autoimmunity, and Immunology April 15-16, 2019
Bianca D. Santomasso MD, PhD

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- and -

I will discuss the following off label use and/or investigational use in my presentation:
IVIG, Rituximab, Cyclophosphamide
Neurologic irAE first recognized as case reports:

Published in final edited form as:

Peripheral Neuropathy Associated with Ipilimumab: A Report of Two Cases

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Abstract

Ipilimumab, a monoclonal antibody targeting human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), was approved by the FDA and European Medicines Agency (EMA) for the treatment of metastatic melanoma. Immune related adverse effects can occur with the use of this agent, but peripheral nervous system problems are rare. We report two cases of ipilimumab-induced polyneuropathy.
Neurotoxicity from immune-checkpoint inhibition in the treatment of melanoma: a single centre experience and review of the literature


Results: In total, 413 immunotherapy treatment episodes in 352 patients were included, with median follow-up of 26.7 months. Ten cases of neurotoxicity were recorded, affecting 2.8% of patients overall, ranging from grade 1 to 4, affecting both central and peripheral nervous systems. A rate of 14% was noted with ipi + nivo. Three of five patients commenced on corticosteroids responded to these. Six patients had made a full recovery at the time of reporting. A favorable radiological response was found in 7 of the 10 cases. Unusual presentations are described in detail.
Neurologic Immune Related Adverse Events (irAE) are Diverse

Central Nervous System: brain, spinal cord
- Encephalitis
- Aseptic Meningitis
- PRES (posterior reversible encephalopathy syndrome)
- Transverse Myelitis
- Paraneoplastic Neurologic Syndromes

Peripheral Nervous System: peripheral nerves, neuromuscular junction, muscle
- Sensory neuropathy (painful or parasthesias)
- Motor and sensory neuropathy or Guillain Barre syndrome (GBS)
- Plexitis
- Myasthenia Gravis
- Myositis
Previous Experience with Neurologic irAE

- In a pooled analysis of 1500 patients with melanoma treated with anti-CTLA4, the rate of neurologic irAEs was 0.1%
  - Lack of recognition or underreporting
- Checkmate 067: Overall survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma did not report neurologic toxicity Larkin J et al. NEJM. 2015; 373

  - 2.8% overall; 14% with combination CTLA4/PD1 inhibition
  - 3.8% with CTLA4 inhibition; 6.1% with PD1 inhibition; 12% with combination CTLA4/PD1 inhibition; severe grade 3 to 4 events <1%
Retrospective Review of Neurologic irAE at MSKCC

- Identified all adult patients at MSKCC treated with CTLA-4, PD-1, or PD-L1 blocking antibodies alone or in combination(s) with other agents.
- Jan 1, 2010—Aug 31, 2017
- Spectrum of tumor types
- Demographics, time to onset, response to treatment

1. 5143 patients identified who received treatment with checkpoint blockade
2. 4850 patients evaluable after exclusion criteria
3. 81 patients with neurologic toxicities

Santomasso B, Malani R et al. ASCO Annual Meeting 2018
Timing of other irAE

Events involved the peripheral and central nervous system

- Sensory neuropathy: 15%
- Aseptic meningitis: 14%
- Encephalitis: 14%
- Myositis/myopathy: 14%
- Sensorimotor neuropathy: 17%
- AIDP-like: 5%
- Mononeuritis: 4%
- Paraneoplastic syndrome: 5%
- Myasthenia gravis: 5%
- Retinopathy: 3%
- Autonomic neuropathy: 2%
- PRES: 2%
- Vasculitis: 2%
- Brachial plexitis: 1%
- Myasthenia gravis: 5%
- Paraneoplastic syndrome: 5%
- Retinopathy: 3%
- Autonomic neuropathy: 2%
- PRES: 2%
- Vasculitis: 2%
- Brachial plexitis: 1%

Santomasso B, Malani R et al. ASCO Annual Meeting 2018
Case 1

- A 54 year old woman undergoing combination CTLA-4/PD1 inhibition for melanoma.
- She developed fever to 38.3 at home diffuse severe headache and neck stiffness. 3 episodes of vomiting and photophobia/phonophobia.
- Exam: She is able to provide a clear and detailed history. No focal findings.

Differential diagnosis
- CNS infection (bacterial>viral)
- Immune-mediated hypophysitis (headache)
- Aseptic meningitis

- MRI brain normal including pituitary normal
- CBC and comprehensive metabolic panel normal
- Hormone panel normal
- Lumbar puncture: 38 WBC with lymphocytic predominance, normal protein
  Starts empiric antibiotics while waiting for culture.
- Cytology and cultures negative
- Dexamethasone 4 mg BID \(\rightarrow\) symptoms recurred when tapered dose \(\rightarrow\) restarted with one month taper and resolved.
Aseptic Meningitis

Characterized by headache, neck stiffness, photophobia, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal!

- MRI of the brain with and without contrast + pituitary protocol
- AM cortisol, ACTH to rule out adrenal insufficiency
- Consider lumbar puncture: opening pressure, cell count, protein, glucose, cultures, PCR for HSV and other viruses depending on suspicion, cytology
- May see elevated WBC count with normal glucose, normal culture and gram stain; typically see elevated WBC count and reactive lymphocytes on cytology

### Management

| Gr1: not concerning to patient | Hold ICPI and discuss resumption only after taking into account the risks and benefits |
| Gr2: moderate, some interference with ADL | Empiric antiviral (IV acyclovir) and antibiotics until CSF results |
| Gr3: severe, limiting self care | Once bacterial and viral infection are negative, may closely monitor off corticosteroids or start oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg |

Need to rule out hypophysitis. CSF helpful! All cases very steroid responsive

Case 2

- A 67 year old man is being treated with single agent anti-PD1 inhibitor for metastatic bladder cancer
- After 4 doses at 2 week intervals, the patient is brought to the hospital for a week of confusion, short-term memory loss, decreased PO intake and generalized weakness at home. He may have had a mild fever at home.

- Exam: Fluent speech, 0/3 recall, inattentive. Doesn’t remember name of hospital or his cancer diagnosis. No focal CN or motor findings.

**Differential Diagnosis:**
- Infection (CNS or systemic)
- Metabolic derangement
- Stroke/seizure (if aphasia)
- New leptomeningeal disease or CNS metastatic disease

**Workup:**
- CBC, electrolytes, hormone panel
- Infectious workup with blood and urine cultures
- MRI of the brain
- Lumbar puncture
Case 2

- Labs including ACTH, cortisol, TSH, electrolytes, and CBC normal
- MRI brain: No metastasis, T2/FLAIR involving the mesial temporal lobes and insula
- Started on empiric coverage for viral encephalitis
- Lumbar puncture showed normal opening pressure, elevated WBC count 10 lymphocyte predominant, and normal protein
- Viral PCRs including HSV, cultures, and cytology were negative
- EEG: intermittent focal sharp waves left temporal.
- Started on 1 mg/kg/day methylprednisolone
- **Exam worsening**

- Started pulse steroids methylprednisolone 1 G daily plus IVIG for 5 days
- Improvement to baseline clinically
Encephalitis

Characterized by confusion, altered behavior, seizures, short-term memory loss, depressed level of consciousness, personality change, speech abnormality

• Neurologic consultation (any grade 2 or above)
• MRI of the brain may reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or may be normal
• Lumbar puncture: check cell count, protein, glucose, culture, PCR for HSV and other
• Viral PCRs depending on suspicion, cytology, oligoclonal bands, encephalitis panel
• EEG to evaluate for subclinical seizures
• Blood: CBC, ESR, CRP, ANCA, TPO and thyroglobulin Abs, paraneoplastic panel

Management

| All-grade encephalopathy (no grade 1) | Hold ICPi and discuss resumption only after taking into account the risks and benefits
| | Empiric antiviral (IV acyclovir) and antibiotics until CSF results
| | Trial of methylprednisolone 1-2 mg/kg
| | If no improvement in 24 hours, consider pulse methylprednisolone 1 G IV daily for 3-5 days plus IVIG 2G/kg over 5 days or PLEX
| | If no improvement, consider escalation to rituximab

Re-evaluate patient frequently. Escalation to pulse steroid dosing plus additional therapy often necessary.

Case 3

• A 68 year old man is being treated for MSI-high colorectal cancer with anti-PDL1
• After 6 doses, he develops unsteady gait and feeling of “shakiness” when walking. He notices he can’t feel his feet well and they are painful. No weakness.
• On exam: Diminished sensation. Romberg positive. Sensory ataxic gait.

Differential Diagnosis:
New leptomeningeal disease

MRI spine: Diffuse enhancement along the surface of the spinal cord

• LP CSF: 63W (89% lymphocytes, 5% variable lymphocytes), elevated protein, cytology negative for malignant cells; lymphocytes present
• Starts dexamethasone 8 mg BID
• Symptoms and imaging resolve. Steroid tapered over a month.
Case 4

- A 74 year old man undergoing combination CTLA-4/PDL1 inhibition for metastatic melanoma to lymph nodes.
- 3 days after 4th infusion he developed bilateral numbness in his feet which ascended to his waist. Worsening over days. Also leg weakness especially in the feet. Lower back pain, midline, non-radiating.
- He has fallen multiple times in the past 3 days and has bruising on legs
- Recently developed elevated LFTs and hypothyroidism.

- Exam: Bilateral foot drop. Absent movement of feet, decreased sensation up to anterior thigh, impaired proprioception to ankle, mild proximal leg and arm weakness. Symmetric. Absent DTRs throughout

  Differential diagnosis
  - leptomeningeal disease (but timing too fast)
  - spinal cord compression
Case 4

- Admitted to ICU
- NIF/VC OK
- MRI spine: no lesion
- Lumbar puncture was performed and showed 54 WBC with 98% lymphocytes, protein 62. Cytology negative.
- EMG/NCS showed moderately severe polyneuropathy with demyelinating features.

- Started on 2 mg/kg methylprednisolone and IVIG. Methylprednisolone increased to pulse dosing 1 G daily × 5 days, followed by steroid taper
- Gabapentin started for neuropathic pain and uptitrated.

- 2 months later walking with a cane, residual mild foot drop left foot.
Guillain-Barré (GBS, AIDP)

Progressive, most often symmetrical muscle weakness with reduced or absent DTRs. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. Typically ascending weakness (but not always). May involve diaphragm, facial weakness, bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.

- Neurologic consultation (any grade 2 or above)
- MRI of the spine (r/o compression and evaluate nerve root thickening)
- Lumbar puncture
- Electrodiagnostic tests

Management

<table>
<thead>
<tr>
<th>All-grade encephalopathy (no grade 1)</th>
<th>• Discontinue ICPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Admission to inpatient unit with capability of transfer to ICU-level of care</td>
</tr>
<tr>
<td></td>
<td>• Start IVIG or PLEX along with corticosteroids either methylpred 2-4 mg/kg (G2) or 1G daily x 5 days (G3-4)</td>
</tr>
<tr>
<td></td>
<td>• Pulmonary function monitoring</td>
</tr>
<tr>
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<td>• Monitor for concurrent autonomic neuropathy</td>
</tr>
</tbody>
</table>

Difficulty walking suggests muscle or nerve problem. Unlike classic GBS, there may be elevated WBC in CSF. Cytology should be sent.

Case 5

- A 74 year old man with metastatic melanoma is being treated with anti-CTLA4/PD1 indicates difficulty walking long distances
- One week later he notes difficulty getting out of bed in the morning.

- Exam: Noted to have lower extremity and neck weakness. The patient seems out of breath. 90% on room air. Facial weakness and right lid droop.

Differential Diagnosis:
  Stroke
  Metastasis
  Weakness with difficulty breathing and diurnal variation suggest MG

Workup:
  Hospital admit
  Neurology consult—they elicit history of swallowing difficulty
  Labs, cultures
  MRI brain and spine imaging
  LP
  Pyridostigmine challenge test is positive, as is EMG/NCS
Case 5

- Admitted to step-down for neurochecks and respiratory monitoring
- Started on pyridostigmine and 2mg/kg methylprednisolone.
- Plasmapheresis starts the next day
- Pulmonary function stable
- Improvement in exam over the next 3 days
- Steroids tapered over 2.5 months
Myasthenia Gravis (MG)

Fatigable and fluctuating weakness, more generally proximal than distal. Frequently has Occular and/or bulbar involvement. Neck weakness. May have respiratory weakness. May occur with myositis and/or myocarditis.

- Neurologic consultation (any grade 2 or above)
- AChR, antistroiated muscle abs in blood. Consider MuSK and LR4 if negative
- Consider MRI of brain or spine depending on symptoms
- Electrodiagnostic tests, rep stim
- Check CPK (myositis)
- If elevated CPK or any respiratory symptoms, perform cardiac workup (for myocarditis)

### Management

<table>
<thead>
<tr>
<th>Grade 3/4</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any weakness beyond ocular or very mild</td>
<td>• Discontinue ICPi&lt;br&gt;• Admit patient, may need ICU monitoring&lt;br&gt;• Consult neurology&lt;br&gt;• Start corticosteroids and initiate IVIG or plasmapheresis&lt;br&gt;• Pyridostigmine may be continued and increased as tolerated under guidance of neurology&lt;br&gt;• Pulmonary function monitoring</td>
</tr>
</tbody>
</table>

Difficulty walking suggests muscle or nerve problem. MG frequently occurs along with myositis and myocarditis

Mechanism of Neurologic irAEs?

- Histologic analysis shows inflammation with lymphocytic infiltrates supporting immune-mediated disease.

- Enhancement of antibody-mediated disease
  - In myasthenic syndromes cases, the presence of serum anti-ACh receptor antibodies is consistently found. *Suzuki et al. Neurology* 2017
  - One case of encephalitis was reported with anti-NMDA antibodies. Notably, this case improved only after IVIG and Rituximab. *Williams et al. JAMA Neurol.* 2016
  - Early B cell changes predict autoimmunity following combination ICB *Das et al. JCI* 2018
Paraneoplastic Neurologic Syndromes: Naturally occurring tumor immunity and autoimmunity

Figure 3. Spontaneous Regression of lung cancer in an Hu PND patient.

Darnell & DeAngelis, Lancet, 1993
Darnell et al, Cancer Research, 2000
Darnell & Posner NEJM, 2003
Case 7 Paraneoplastic Neurologic Syndrome

73 year old woman with metastatic Merkel Cell Carcinoma treated with anti-PDL1

Anti-PD-L1
4/15, 4/28, 5/13

4/28: Physical exam: axillary mass gone

Serum and CSF paraneoplastic panel positive for Anti-CRMP5 IgG
1: 15,340 serum and 1:1240 CSF
5 CSF specific oligoclonal bands

7 days post dose 3
develops rapidly progressive ataxia and dysmetria, vision problems, and cognitive changes with profound short term memory loss.

Starts immunomodulation with steroids, IVIG, cyclophosphamide, rituximab

ongoing CR
Paraneoplastic anti-CRMP5 Ab present at low titer in plasma before symptoms started

Immunoblot:

CRMP-5
General Principles of Neuro irAE management

- Neurology consult
  - if functional status is impaired by symptoms (Grade 2 or higher)
  - If persistent or worsening symptoms
  - If you are unsure
- Hospitalize if patient has moderate to severe symptoms or if rapidly progressing

Diagnostic Workup

- Complete blood count and metabolic panels
- Hormone levels if an endocrinopathy is suspected
- MRI brain and/or spine with and without contrast
- Antibody panels (paraneoplastic, myasthenia gravis)
- Lumbar puncture for signs of infection and to rule out leptomeningeal metastasis
- CSF findings of elevated cell count and/or elevated protein or oligoclonal bands can help support diagnosis of nIRAE
- EEG for altered mental status to look for subclinical seizures
- EMG and nerve conduction studies to evaluate nerve and muscle

Management

- Hold ICPi
- Steroids
- Neurology consult
- Consider IVIG or PLEX plus steroids for grade 3-4
- Consider pulse steroids for cases that are not improving and especially encephalitis and GBS (along with IVIG or PLEX)
- Consider Rituximab in refractory cases
Conclusions

• Neurologic irAE are diverse, affecting both the central and peripheral nervous system

• Optimal management not defined but may fall outside of routine practices for managing more common irAE (i.e. pulse dose steroids, IVIG, plasmapheresis, Rituximab)

• Presentations of classic neurologic conditions such as MG and GBS may be atypical: MG/myocarditis/myositis overlap; cells in CSF in GBS-like

• Some neuro irAEs, such as aseptic meningitis may respond more easily to treatment whereas others such as encephalitis, GBS, and myasthenia gravis may require a higher dose of steroids and additional immunosuppression

• Biomarkers are needed to predict patients at risk and identify patients for early intervention
Acknowledgements

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Jerome Posner
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Melanoma Research Alliance

The Society of MSK

PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

Memorial Sloan Kettering Cancer Center
IMMUNE CHECKPOINT INHIBITORS AND UVEITIS

H. Nida Sen, MD, MHS
Investigator, Lasker Scholar
Head, Clinical and Translational Immunology Unit
Director, Uveitis Clinic and Fellowship Program
NEI, NIH
Clinical Professor of Ophthalmology, GWU
I have no financial relationships to disclose.

- and -

I will discuss the following off label use and/or investigational use in my presentation:

Local and systemic corticosteroids for ocular inflammation

Immune checkpoint inhibitor use for non-FDA approved indications
IMMUNE CHECKPOINT INHIBITORS (ICI)

- Emerging therapeutic approach for metastatic or recurrent cancer with promising clinical efficacy

- Programmed cell death protein 1 (PD-1) inhibitors:
  - nivolumab and pembrolizumab
  - melanoma of the skin, non-small cell lung cancer, renal cell carcinoma, bladder cancer, squamous cell carcinoma of head and neck, and Hodgkin’s lymphoma

- Programmed cell death ligand 1 (PD-L1) inhibitors:
  - atezolizumab, avelumab, and durvalumab
    - urothelial carcinoma (UC), NSCLC, TNBC, SCLC
    - UC, Metastatic Merkel cell carcinoma (MCC)
    - NSCLC

- Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor:
  - Ipilimumab
    - melanoma, renal cell carcinoma and colorectal cancer

THE EXPANDING SCOPE OF CANCER IMMUNOTHERAPEUTICS

Adapted from the American Association for Cancer Research (AACR) Cancer Progress Report 2016
**Immune Checkpoint Inhibitors: PD-1/PDL-1, CTLA4**

- Blockade of these receptors upregulates the immune system against these malignant processes—removes the “brakes” on immune system.
- However, these checkpoint inhibitors are associated with a unique set of side effects through unbridled inflammation termed immune-related adverse events (irAEs).
HOW COMMON ARE irAES

• 80-90% of patients on CTLA-4 inhibitor (ipilimumab) experience irAEs
  • gastrointestinal (39.7%), endocrinopathies (33.7%), dermatologic (25.6%), ophthalmologic (10.3%)*, neurologic (9.8%), hematologic (3.8%), genitourinary (3.8%), respiratory (2.5%), musculoskeletal (1.7%), and cardiac (0.9%) autoimmune complications
    • *4.3% classified as uveitis

• 70% of patients on PD-1 or PD-L1 therapy experience irAEs
  • typically are less severe and slightly less common
    • 1% - 1.5% rate of uveitis

• up to 96% with combination therapy (Nivolumab and Ipilimumab)
  • 59% consisting of grade 3 or 4 inflammation
  • higher uveitis toxicity (6%) than either agent alone

• 70% of patients on PD-1 or PD-L1 therapy experience irAEs
  • typically are less severe and slightly less common
    • 1% - 1.5% rate of uveitis

• up to 96% with combination therapy (Nivolumab and Ipilimumab)
  • 59% consisting of grade 3 or 4 inflammation
  • higher uveitis toxicity (6%) than either agent alone
OCULAR SIDE EFFECTS

- Most common ocular SEs:
  Keratoconjunctivitis sicca (DES=1.2-24.2%) and uveitis (0.3%-6%)
  - Others: MG, inflammatory orbitopathy, keratitis, cranial nerve palsy, optic neuropathy, serous retinal detachment, extraocular muscle myopathy (n = 1), neuroretinitis (n = 1)
- Most managed with topical or periocular steroid injections

Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. CHECKPOINT INHIBITOR IMMUNE THERAPY: Systemic Indications and Ophthalmic Side Effects. Retina. 2018
WHY DOES IT MATTER?

• The recognition and understanding of immune related adverse events (irAEs) and their management is critical, as the development of immune related toxicity often limits the use of these otherwise effective cancer therapeutics.

• These AEs will only increase in a rapidly evolving era of cancer immunotherapy.
WHAT IS UVEITIS

• Inflammation of the uveal tissue
• Relatively rare (52/100K person yrs) but 15% blindness
Poliopsis
Vitiligo
Tinnitus
Meningismus
pleocytosis CSF
NEI EXPERIENCE

Cases were identified by retrospective chart review at three tertiary ophthalmology clinics in the US (National Eye Institute, The Washington D.C. Veterans Hospital, and Massachusetts Eye and Ear Institute).

- Retrospective EMR search
- Patients receiving ICIs and referred to ophthalmology for visual or ocular symptoms
11 patients were identified with ocular irAEs while being treated with a checkpoint inhibitor:

- 9 had uveitis:
  - 4 Anterior Uveitis
  - 1 Intermediate uveitis
  - 4 posterior or panuveitis
- 1 new onset KCS
- 1 Optic neuritis
UVEITIS

4 Anterior Uveitis:
- Average 18.8 weeks after the initiation of ICI
- Most common ICI was nivolumab, metastatic renal cell CA
- All responded to topical CS

1 Intermediate uveitis
- Occurred 24 weeks after ICI initiation (pembrolizumab) for metastatic cancer
- Mild with no CME
- Responded to topical CS (Durezol)

1 Panuveitis
- 20 weeks after initiation of ICI
- Nivolumab+ipilimumab for metastatic melanoma
- Responded well to X2 periocular CS injections

3 Posterior uveitis: VKH-like
- Average 10 weeks after ICI initiation (for treatment of malignant melanoma)
- Resolved with local or systemic CS

- All grade 2 or 3 (4 grade 2, 5 grade 3)
- No Grade 4 (severe)

Noble C, .. Apolo A, Lee JM, . Sen HN. Ocular Imm Inflam (in press)
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Reason for Treatment</th>
<th>Checkpoint Inhibitor</th>
<th>Timing Weeks</th>
<th>Initial Presentation</th>
<th>Eye Involvement</th>
<th>Ocular Treatment</th>
<th>ICI held/terminated/reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>F</td>
<td>Caucasian</td>
<td>Metastatic Colon Cancer</td>
<td>Pembrolizumab</td>
<td>9</td>
<td>Redness, small amount of discharge OU</td>
<td>Dry Eyes and Blepharitis</td>
<td>Artificial tears</td>
<td>Continued</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>African American</td>
<td>Metastatic Prostate Cancer</td>
<td>Durvalumab</td>
<td>1</td>
<td>Redness, sensitivity to light, tearing, eye redness and mucus discharge OU</td>
<td>NGAU: 1+ cell, 0 flare OU</td>
<td>Topical corticosteroids</td>
<td>Continued</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>Caucasian</td>
<td>Metastatic Renal Cell Carcinoma</td>
<td>Nivolumab</td>
<td>52</td>
<td>Floaters and blurry vision OS</td>
<td>NGAU OS: 0.5+ cell/2+flare, CME OS with recurrent CME 2 years after discontinuation of ICI</td>
<td>Topical corticosteroids</td>
<td>Yes - ocular toxicity</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>F</td>
<td>African American</td>
<td>Metastatic Renal Cell Carcinoma</td>
<td>Ipilimumab and Nivolumab</td>
<td>1</td>
<td>Difficulty reading</td>
<td>NGAU OU: 1+cell/1+flare. CN VI palsy</td>
<td>Topical and IV corticosteroid bolus</td>
<td>Yes - ocular toxicity</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>African American</td>
<td>Metastatic Renal Cell Carcinoma</td>
<td>Nivolumab</td>
<td>20</td>
<td>Significantly reduced vision, eye pain, headache, back pain and light sensitivity for 1 day</td>
<td>NGAU OU: 3+cell/2+flare, 360 iridolenticular synchia</td>
<td>Topical corticosteroids</td>
<td>Yes - progression of metastases</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>M</td>
<td>Asian</td>
<td>Metastatic Melanoma</td>
<td>Pembrolizumab</td>
<td>24</td>
<td>Floaters and irritation OD</td>
<td>Intermediate Uveitis: Trace vitreous cell with no evidence of vasculitis or CME</td>
<td>Topical corticosteroids</td>
<td>Yes - progression of metastases</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>M</td>
<td>Caucasian</td>
<td>Metastatic Melanoma</td>
<td>Ipilimumab and Nivolumab</td>
<td>20</td>
<td>Pain and blurry vision OD, blurry vision OS</td>
<td>Panuveitis OD: CME OD. NGAU OS. Recurrence 18 months after termination of ICI</td>
<td>Topical and local corticosteroids</td>
<td>Yes - ocular toxicity</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>F</td>
<td>Caucasian</td>
<td>Metastatic Melanoma</td>
<td>Ipilimumab and Nivolumab</td>
<td>4</td>
<td>Central scotoma OS with poliosis and vitiligo</td>
<td>VKH like reaction</td>
<td>Oral corticosteroids</td>
<td>Continued</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>M</td>
<td>Caucasian</td>
<td>Metastatic Melanoma</td>
<td>Pembrolizumab</td>
<td>8</td>
<td>Decrease vision, light sensitivity, redness OS&gt;OD</td>
<td>VKH like reaction</td>
<td>Topical corticosteroids</td>
<td>Continued</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>F</td>
<td>Caucasian</td>
<td>Metastatic Melanoma</td>
<td>Ipilimumab</td>
<td>18</td>
<td>Blurry vision and injection OU</td>
<td>VKH-like reaction OU</td>
<td>Topical and oral corticosteroids</td>
<td>Yes - severe systemic toxicity</td>
</tr>
<tr>
<td>11</td>
<td>68</td>
<td>M</td>
<td>Caucasian</td>
<td>Metastatic Prostate Cancer</td>
<td>Durvalumab</td>
<td>unknown</td>
<td>Left inferior scotoma with mild discomfort with extraocular movements</td>
<td>Optic neuropathy OS: 4+ disc edema OS. HVF 30-2: near complete central sparing inferior defect OS</td>
<td>IV corticosteroid bolus</td>
<td>Continued</td>
</tr>
</tbody>
</table>
WF with metastatic melanoma who presented with poliosis and vitiligo complaining of scotoma (central visual field defect).

Periocular CS injection, immunotherapy held

Immunotherapy restarted
CASE 1

- 50 year old CF with several days to weeks of blurry vision, both eyes

<table>
<thead>
<tr>
<th></th>
<th>Right Eye</th>
<th>Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual Acuity</strong></td>
<td>20/40 phni</td>
<td>20/40 ph 20/25</td>
</tr>
<tr>
<td><strong>IOP</strong></td>
<td>10</td>
<td>08</td>
</tr>
<tr>
<td><strong>Anterior Chamber</strong></td>
<td><strong>Tr cell/flare</strong></td>
<td><strong>Tr cell/flare</strong></td>
</tr>
<tr>
<td><strong>Iris</strong></td>
<td>+synechiae</td>
<td>+synechiae</td>
</tr>
<tr>
<td><strong>Lens</strong></td>
<td>Pigment on ant lens capsule</td>
<td>Pigment on ant lens capsule</td>
</tr>
<tr>
<td><strong>Anterior Vitreous</strong></td>
<td><strong>2+ cell</strong></td>
<td>1-2+ cell</td>
</tr>
</tbody>
</table>
H & P

• PMHx:
  • Metastatic melanoma (stage IIIB, progressed to IV): on systemic immunotherapy
    • Recent colitis s/p prednisone

• Meds:
  • Ipilimumab (Yervoy) + Nivolumab (Opdivo)
  • Yervoy d/c’ed after she developed colitis, on Opdivo maintenance currently
WORK-UP

- ROS: tinnitus, neck pain
- Labs: ACE, quantiferon gold, syphilis IgG checked – negative
ASSESSMENT

Diagnosis: Checkpoint inhibitor-associated uveitis

- Plan:
  - Given posterior leakage, switched to durezol QID
Prednisolone QID

s/p Durezol QID with taper

Vision improved to 20/25 OU
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Gender</th>
<th>Race/Ethnicity</th>
<th>Checkpoint Inhibitor Regimen</th>
<th>Cancer Diagnosis</th>
<th>Type of Uveitis</th>
<th>Unilateral vs Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>Female</td>
<td>White</td>
<td>Ipilimumab &lt;sup&gt;a&lt;/sup&gt;</td>
<td>Malignant melanoma</td>
<td>Anterior uveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>Female</td>
<td>White</td>
<td>Ipilimumab &lt;sup&gt;b&lt;/sup&gt;</td>
<td>Malignant melanoma</td>
<td>Posterior uveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>Female</td>
<td>N/A</td>
<td>Ipilimumab</td>
<td>Malignant melanoma</td>
<td>Panuveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>Male</td>
<td>White</td>
<td>Ipilimumab &lt;sup&gt;b&lt;/sup&gt;</td>
<td>Malignant melanoma</td>
<td>Panuveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>Male</td>
<td>White</td>
<td>Ipi-Nivo</td>
<td>Malignant melanoma</td>
<td>Anterior uveitis</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>Male</td>
<td>White</td>
<td>Ipi-Nivo &lt;sup&gt;c&lt;/sup&gt;</td>
<td>Malignant melanoma</td>
<td>Anterior uveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>Female</td>
<td>White</td>
<td>Ipi-Nivo &lt;sup&gt;d&lt;/sup&gt;</td>
<td>Malignant melanoma</td>
<td>Anterior uveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>Male</td>
<td>White</td>
<td>Ipi-Nivo</td>
<td>Malignant melanoma</td>
<td>Panuveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>Male</td>
<td>White</td>
<td>Ipi-Nivo &lt;sup&gt;d&lt;/sup&gt;</td>
<td>Malignant melanoma</td>
<td>Anterior uveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>Female</td>
<td>AA</td>
<td>Ipi-Nivo &lt;sup&gt;e&lt;/sup&gt;</td>
<td>Endometrial cancer</td>
<td>Anterior &amp; Intermediate uveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>Male</td>
<td>White</td>
<td>Nivolumab</td>
<td>Malignant melanoma</td>
<td>Panuveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>Female</td>
<td>White</td>
<td>Nivolumab</td>
<td>Hodgkin's lymphoma</td>
<td>Anterior uveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>13</td>
<td>45</td>
<td>Male</td>
<td>White</td>
<td>Pembrolizumab</td>
<td>Malignant melanoma</td>
<td>Panuveitis</td>
<td>N/A</td>
</tr>
<tr>
<td>14</td>
<td>68</td>
<td>Female</td>
<td>White</td>
<td>Pembrolizumab</td>
<td>Malignant melanoma</td>
<td>Panuveitis</td>
<td>Bilateral</td>
</tr>
<tr>
<td>15</td>
<td>43</td>
<td>Male</td>
<td>White</td>
<td>Pembrolizumab</td>
<td>Malignant melanoma</td>
<td>Optic Neuritis</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Indicates that while VKH like reaction may be restricted to patients treated for MM not all MM patients treated with ICI develop VKH-like uveitis

Sun M,… Sen HN, Gordon L. Ocular Imm Inflam (in press)
OCULAR SIDE EFFECTS

• Large prospective cohort of ICI treated patients study and national registry from Europe:
  • There was no systematic ophthalmologic examination
  • Prospective cohort and the declarative registry (ocular/visual complaints)
    • Prospective cohort: Of a total of 745 patients 3 developed moderate to severe ocular irAEs, providing a prevalence of 0.4% and an incidence of 0.7 per 1000 patient-months of treatment.
    • A declarative pharmacovigilance registry: Identified another 5 cases (2014-2018)

• DES and uveitis most common

• 50% grade 2, 50% grade 3 (CTCAE)
• 50% developed symptoms after their 2nd cycle

• Local and/or systemic corticosteroids in 7/8 patients

• 65% experienced additional (extraocular) irAEs (orbital myositis/myocarditis**)

• All were considered partial or complete responders to ICI

• Are irAEs associated with better antitumor efficacy?


From: Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non–Small-Cell Lung Cancer

**CONCLUSION**

<table>
<thead>
<tr>
<th><strong>Most ocular irAEs occur in the first 6 months – spectrum ranges from mild anterior uveitis to severe posterior uveitis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Majority respond well to topical/local corticosteroid (favorable)</strong></td>
</tr>
<tr>
<td><strong>VKH-like reaction is almost always associated with immunotherapy for metastatic melanoma</strong></td>
</tr>
<tr>
<td><strong>Important to investigate concurrent systemic irAEs</strong></td>
</tr>
<tr>
<td><strong>It is critical not to confuse metastatic disease or infection with an inflammatory side effect of immunotherapy</strong></td>
</tr>
</tbody>
</table>
THANK YOU

- Arthi Venkat, CCF
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- Robert Swan, M.D.
- Lynn K. Gordon, M.D., Ph.D.

- Carl Noble
- Ian A. Thompson MD
- Amy Yuan MD
- Andrea B. Apolo, MD
- Jung-Min Lee, MD
- George Papalioudis MD
- Shilpa Kodati
- Rachel Bishop MD
- M Teresa Magone MD
- Lucia Sobrin MD
INFECTIOUS UVEITIS

Toxoplasma

CMV retinitis
Combination Therapies

Speakers
Jonathan D. Schoenfeld, MD, MPH
Nicole Drezner, MD
Toxicities of Radiation-Immunotherapy Combinations

Jonathan Schoenfeld MD MPH
Melanoma Radiation Oncology Director and Center for Head and Neck Oncology
Director of Clinical Trial Development, Department of Radiation Oncology
Associate Professor of Radiation Oncology, Harvard Medical School
I have the following financial relationships to disclose:
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  Grant/Research support from: Merck, BMS
  Employee of: Brigham and Women’s Physician’s Organization

I will not discuss off label use and/or investigational use in my presentation.
Radiation/Immunotherapy Combinations Are Of Interest

Immune stimulating effects of local radiotherapy
Ngwa, Irabor, Schoenfeld et al. Nature Reviews Cancer 2018

Benefit of Durvalumab following chemoRT in Stage III NSCLC (PACIFIC Trial). Antonia, Villegas, Daniel et al. NEJM 2018
Evaluating Combined Radiation/Immunotherapy Toxicity is an Important Question

Numbers of PD-1/PD-L1 combination trials as of Sept 2017
Tang, Shalabi, Hubbard-Lucey Ann Oncol. 2018
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Numbers of PD-1/PD-L1 combination trials as of Sept 2017
Tang, Shalabi, Hubbard-Lucey Ann Oncol. 2018
Evaluating Combined Radiation/Immunotherapy Toxicity is an Important Question

- Irrespective of clinical trials, more than half of all oncology patients receive radiation at some point during their care
  - Key component of organ preservation therapy or adjuvant therapy in localized or locoregionally advanced disease
  - Palliative treatment of bone/brain/lung metastases

Numbers of PD-1/PD-L1 combination trials as of Sept 2017
Tang, Shalabi, Hubbard-Lucey Ann Oncol. 2018
Specific Concerns with Radiation Therapy

• Potential enhancement of autoimmune risks
• Impacts on more common and severe overlapping toxicities
  • Dermatitis
  • Pneumonitis
  • Colitis / Hepatitis
• Note: Important impact of dose, fractionation, field location/size, treatment technique, and concurrent therapy.
Potential for Enhancement of Local Radiation Effects with Immunotherapy

Clinical reports of local toxicity following radiation and interferon treatment

- Hazard et al. IJROBP 2002: neuropathy, radiation necrosis
- Nguyen et al. Melanoma Res 2003: grade 3-4 mucositis, dermatitis
- Perera et al. IJROBP 1997: neuropathy, stricture

Wildtype B16 melanoma model more sensitive to RT (20-25 Gy) compared to nude immunodeficient mice, and this effect is CD8+ T-cell dependent. Lee et al. Blood 2009
Outline

• Existing and emerging clinical data

• Path forward, challenges
Outline

• Existing and emerging clinical data

• Path forward, challenges
Tolerability of Radiation / Immune Checkpoint Blockade, Bang et al. IJROBP 2017

- Retrospective analysis of 133 consecutive patients with metastatic melanoma, renal cell cancer, and lung cancer treated at 5 affiliated centers
- Patients received standard of care palliative radiation and CTLA-4 and/or PD-1 blockade
Tolerability of Radiation / Immune Checkpoint Blockade, Bang et al. IJROBP 2017

- Overall rates of ir-AEs similar to patients historically treated with immune checkpoint blockade alone
- Few severe (grade 3 or higher) irAE; no associations between these and site, dose or timing of radiation
PD-L1 Inhibition Following Chemoradiation in Stage III NSCLC (PACIFIC), Antonia et al. NEJM 2017
PD-L1 Inhibition Following Chemoradiation in Stage III NSCLC (PACIFIC), Antonia et al. NEJM 2017

Table 3. Adverse Events of Any Cause.

<table>
<thead>
<tr>
<th>Event</th>
<th>Durvalumab (N = 475)</th>
<th>Placebo (N = 234)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade*</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td></td>
<td>number of patients</td>
<td>number (%)</td>
</tr>
<tr>
<td>Any event</td>
<td>460 (96.8)</td>
<td>142 (29.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>168 (35.4)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Pneumonitis or radiation pneumonitis†</td>
<td>161 (35.9)</td>
<td>16 (3.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>113 (23.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>106 (22.3)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>87 (18.3)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>70 (14.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>68 (14.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>66 (13.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62 (13.1)</td>
<td>21 (4.4)</td>
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<td>Arthralgia</td>
<td>59 (12.4)</td>
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</tr>
<tr>
<td>Pruritus</td>
<td>58 (12.2)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>58 (12.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>58 (12.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>56 (11.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>55 (11.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>52 (10.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>51 (10.7)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>50 (10.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>39 (8.5)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>36 (7.6)</td>
<td>14 (2.9)</td>
</tr>
</tbody>
</table>
PD-L1 Inhibition Following Chemoradiation in Stage III NSCLC (PACIFIC), Antonia et al. NEJM 2017

Grade 3-4 pneumonitis 2.6% with placebo and 3.4% with durvalumab
Limited Rates of Toxicities Generally Observed in Radiation Immunotherapy Studies

- **Retrospective:**
  - Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
  - Ahmed et al. Annals Onc 2015 (anti-PD-1)
  - Anderson et al. JITC 2018 (anti-PD-1)
  - Bang et al. IJROBP 2017 (anti-CTLA-4 and/or PD-1)
  - Barker et al. CIR 2013 (anti-CTLA-4)
  - Colaco et al. J Neurosurg 2016 (anti-CTLA-4 or PD-1)
  - Diao et al. J Neurosurg 2018 (anti-CTLA-4)
  - Fang et al. J. Neuroonc 2017 (anti-PD-1)
  - Hubbeling et al. J. Thoracic Oncol. 2018 (anti-PD-1)
  - Hwang et al. JAMA Onc 2017 (anti-PD-1)
  - Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
  - Kiess et al. IJROBP 2015 (anti-CTLA-4)
  - Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  - Patel et al. Am J Clin Oncol 2015 (anti-CTLA-4)
  - Qin et al. IJROBP 2016 (anti-CTLA-4)
  - Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

- **Prospective:**
  - Antonia et al. NEJM 2018 (PACIFIC study, anti-PD-L1 following conventional chemoRT)
  - Hiniker et al. IJROBP 2016 (anti-CTLA-4 with palliative RT)
  - Formenti et al. Nature Medicine 2018 (anti-CTLA-4 with hypofractionated RT)
  - Maity et al. Br J Cancer 2018 (anti-PD-1 with hypofractioned RT)
  - Luke et al. JCO 2018 (anti-PD-1 with SBRT)
  - Tang et al. CCR 2016 (anti-CTLA-4 with SBRT)
  - Tree et al. IJROBP 2018 (anti-PD-1 with hypofractionated RT)
  - Tywan St. Victor et al. Nature 2015 (anti-CTLA-4 with hypofractionated RT)
  - Sundahl et al. IJROBP 2018 (anti-CTLA-4 with hypofractionated RT)
  - Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)
Limited Rates of Toxicities Generally Observed in Radiation Immunotherapy Studies

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  – Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
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  – Qin et al. IJROBP 2016 (anti-CTLA-4)
  – Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

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  – Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

Hypofractionated radiation

Bang and Schoenfeld Ann Pall Med 2018
Limited Rates of Toxicities Generally Observed in Radiation Immunotherapy Studies

- Retrospective:
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  - Ahmed et al. Annals Onc 2015 (anti-PD-1)
  - Anderson et al. JITC 2018 (anti-PD-1)
  - Bang et al. IJROBP 2017 (anti CTLA-4 and/or PD-1)
  - Barker et al. CIR 2013 (anti-CTLA-4)
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  - Qin et al. IJROBP 2016 (anti-CTLA-4)
  - Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

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  - Luke et al. JCO 2018 (anti-PD-1 with SBRT)
  - Tang et al. CCR 2016 (anti-CTLA-4 with SBRT)
  - Tree et al. IJROBP 2018 (anti-PD-1 with hypofractionated RT)

Higher dose stereotactic body radiotherapy (SBRT) treatment

Bang and Schoenfeld Ann Pall Med 2018
Limited Rates of Toxicities Generally Observed in Radiation Immunotherapy Studies

• Retrospective:
  – Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
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  – Tree et al. IJROBP 2018 (anti-PD-1 with hypofractionated RT)
  – Sundahl et al. IJROBP 2018 (anti-CTLA-4 with hypofractionated RT)
  – Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

Fractionated chemoradiation (common treatment for locally advanced cancers)

Bang and Schoenfeld Ann Pall Med 2018
Many ongoing studies combining fractionated radiation and immune checkpoint blockade in localized/locoregionally advanced disease

Leeman and Schoenfeld, in press.
Many ongoing studies combining fractionated radiation and immune checkpoint blockade in localized/locoregionally advanced disease.

Leeman and Schoenfeld, in press.
Attention is Needed in Future Studies and With Longer Follow up: SRS and Immune Therapy

- Analysis of 480 patients treated with stereotactic radiosurgery (SRS) to the brain, 115 of whom were also treated with immune checkpoint blockade (ICB)

- Receipt of ICB was associated with symptomatic radiation necrosis after adjusting for tumor histology (HR 2.6, 95% CI 1.4-4.9), particularly in melanoma patients who received ipilimumab (HR 4.7, 95% CI 1.4-16.2)

Figure. Kaplan-Meier Curves Displaying Freedom From Symptomatic Necrosis as Stratified by Receipt of Immunotherapy vs No Receipt of Immunotherapy

Dr. Ayal Aizer

Martin et al. JAMA Oncology 2018
Attention is Needed in Future Studies and With Longer Follow up

- Nivolumab induced radiation recall pneumonitis
Attention is Needed in Future Studies: Radiation Induced Lymphopenia

Dr. Luke Pike

Pike et al. IJROBP 2018
Outline

• Existing and emerging clinical data

• Path forward, challenges
Concerns regarding theoretical and observed toxicities must be balanced by known clinical benefit

- For example, improved outcomes have been observed with immune checkpoint blockade and brain directed radiation
- No evidence to support arbitrary time cutoffs between therapies

Current Clinical Practice: No Evidence to Withhold/Delay Standard of Care Treatments

Outstanding Questions

- Who are the patients at risk for combined toxicities?
  - Impact of type of immune therapy
  - Impact of radiation parameters

- Are there relevant risks with novel immunotherapies?
  - e.g. new immune checkpoint inhibitors and combinations, intratumoral immune therapies, CAR-T cells, etc.
Challenges

• Time course of side effects can be delayed (both with immunotherapy and radiation)
  – Importance of multidisciplinary and extended follow-up after initiating combined therapy to identify longer term effects

• Attribution of side effects can be difficult (e.g. pneumonitis)
Attributing Lung Toxicity


Attribution can be Challenging

Right axillary radiotherapy for melanoma

Symptomatic pneumonitis 5 months following RT and 1.5 months following nivolumab therapy

Schoenfeld et al JITC 2019, in press.
Evolving Change Demonstrates Consolidation and GGO Outside of the Radiation Treatment Field Confined to the Ipsilateral Lung

Schoenfeld et al. JITC 2019, in press.
Updated PACIFIC Data:
Antonia et al. NEJM 2018

<table>
<thead>
<tr>
<th>Event</th>
<th>Durvalumab (N=475)</th>
<th>Placebo (N=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade*</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any event</td>
<td>460 (96.8)</td>
<td>145 (30.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>167 (35.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>114 (24.0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>106 (22.3)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Radiation pneumonitis*</td>
<td>96 (20.2)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>88 (18.5)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>72 (15.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>68 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>68 (14.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>63 (13.3)</td>
<td>21 (4.4)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>60 (12.6)</td>
<td>9 (1.9)</td>
</tr>
</tbody>
</table>

*Pneumonitis and radiation pneumonitis were assessed by investigators, with subsequent review and adjudication by the study sponsor.
Summary

• Immunotherapy toxicities overlap with potential radiation effects

• Initial data suggests standard of care and experimental approaches that combine radiation and immune checkpoint blockade are generally safe but more data are needed with longer follow up

• Challenges moving forward toxicity attribution, the variability and time course with which side effects develop, development of new drugs/therapies

• Value for education of the multidisciplinary team as more patients receive immunotherapy and radiation in the definitive setting
Regulatory perspectives on combination immuno-oncology trials and approvals

NIH-AACR Cancer, Autoimmunity, and Immunology Conference
April 15, 2019

Nicole Drezner, MD
Medical Officer, DOP2
U.S. Food and Drug Administration
Disclosure Information

I have no financial relationships to disclose

I will not discuss off label use and/or investigational use in my presentation
Outline

• FDA approvals in combination immuno-oncology
• Efficacy of combination therapies
  – Contribution of components
  – ADA
• Safety of combination therapies
• Biomarkers in immuno-oncology
Co-development of two or more drugs

• Co-development provides less information about the clinical safety and effectiveness than if the individual drugs are developed alone.
  – Combination is intended to treat a serious disease or condition
  – Strong biologic rationale for use of the combination
  – Non-clinical or clinical evidence suggesting the combination may provide an advantage over available therapy and is superior to the individual agents
  – Compelling reason why the drugs cannot be developed independently

• Appropriate study design:
  – AB vs. SOC/placebo
  – AB vs. A vs. B
  – AB vs. A

FDA Guidance for Industry, 2013
Combination therapies in immuno-oncology

• Two immuno-oncology agents
  – Immune checkpoint blockade removes inhibitory signals of T-cell activation
  – Addresses issue of compensatory upregulation of additional immune checkpoint molecules
  – Increased toxicity compared to single agent therapy
  – Combination anti-PD-1 and anti-CTLA4 agents approved; many studies ongoing using anti-Tim-3 and anti-LAG-3 combinations
  – Single agent and combinations approved for broad range of tumor types

• Immuno-oncology agent(s) in combination with chemotherapy
  – Addition of chemotherapy to immune checkpoint inhibitor therapy may enhance cytotoxic T-cell activity
  – Issues with sequence and scheduling
  – Multiple approvals in lung cancer

• Immuno-oncology agent(s) in combination with radiation therapy (*discussed in previous talk*)
## IO combination approvals: nivolumab + ipilimumab

<table>
<thead>
<tr>
<th>Approval date &amp; study title</th>
<th>Indication</th>
<th>Treatment arms</th>
<th>N</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/30/2015¹ CHECKMATE-069</td>
<td>Patients with BRAF V600-wt unresectable or metastatic melanoma</td>
<td>N+I vs. I+placebo</td>
<td>Total: 95/47</td>
<td>ORR (N+I vs. I in BRAF wt): 60% (48, 71) vs. 11% (3, 25) p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRAF wt: 72/37</td>
<td></td>
</tr>
<tr>
<td>1/23/2016 CHECKMATE-067</td>
<td>Patients with +BRAF V600-wt and V600 mutation-positive unresectable or metastatic melanoma</td>
<td>N+I vs. N vs. I</td>
<td>314/316/315</td>
<td>PFS (N+I vs. I) HR 0.42 (0.34, 0.51), p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS (N+I vs. I) HR 0.55 (0.44, 0.69), p&lt;0.0001</td>
</tr>
<tr>
<td>4/16/2018 CHECKMATE-214</td>
<td>Intermediate or poor risk previously untreated advanced RCC</td>
<td>N+I vs. sunitinib</td>
<td>425/422</td>
<td>OS HR 0.63 (0.44, 0.89) p&lt;0.0001</td>
</tr>
<tr>
<td>7/10/2018¹ CHECKMATE-142</td>
<td>MSI-H or dMMR mCRC that has progressed following tx with a fluoropyrimidine, oxaliplatin, and irinotecan</td>
<td>Multi-cohort N+I &amp; N</td>
<td>Total: 119/74</td>
<td>ORR 46% (35, 58) vs. 28% (17, 42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>W/prior tx: 82/53</td>
<td></td>
</tr>
</tbody>
</table>

¹: Accelerated approval

https://www.accessdata.fda.gov/scripts/cder/daf/
Efficacy issues

• Patient sample size (CHECKMATE-069)
• Contribution of components (CHECKMATE-069, CHECKMATE-214, CHECKMATE-142)
  – Use of nivolumab monotherapy vs. combination cohorts from other trials to isolate the effect of the nivolumab and ipilimumab components of the combined therapy
## IO and chemotherapy combination approvals

<table>
<thead>
<tr>
<th>IO Combination, study title, &amp; approval date</th>
<th>Indication</th>
<th>Treatment arms</th>
<th>N</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab with carboplatin and etoposide IMpower133 3/18/2019</td>
<td>1L ES-SCLC</td>
<td>Atezo, carbo, etoposide / placebo, carbo, etoposide</td>
<td>201/202</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.70 (0.54, 0.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.0069</td>
</tr>
<tr>
<td>Atezolizumab with bevacizumab, paclitaxel, and carboplatin IMpower150 12/6/2018</td>
<td>1L NSQ-mNSCLC</td>
<td>Atezo, paclitaxel, carbo / atezo, bev, paclitaxel, carbo / bev, paclitaxel, carbo</td>
<td>349/359/337</td>
<td>PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.71 (0.59, 0.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.0002</td>
</tr>
<tr>
<td>Pembrolizumab with carboplatin and paclitaxel/nab-paclitaxel KEYNOTE-407 10/30/2018</td>
<td>1L SQ-mNSCLC</td>
<td>Pembro, carboplatin, (nab)-paclitaxel / placebo, carboplatin, (nab)-paclitaxel</td>
<td>278/281</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.64 (0.49, 0.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.0017</td>
</tr>
<tr>
<td>Pembrolizumab with pemetrexed and platinum KEYNOTE-189 8/20/2018</td>
<td>1L NSQ-mNSCLC</td>
<td>Pembro, pemetrexed, IC platinum / placebo, pemetrexed, IC platinum</td>
<td>410/206</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.49 (0.38, 0.64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

https://www.accessdata.fda.gov/scripts/cder/daf/
Efficacy issues: ADA

- Development of anti-drug antibodies (ADA) against atezolizumab
  - Among 565 patients with NSCLC in OAK (monotherapy), 30% tested positive for ADA (median time to onset: 3 weeks)
  - Results in reduced systemic exposure to atezolizumab
  - Exploratory analyses: subset of patients who were ADA positive by week 4 (21%) appeared to have less efficacy (effect on OS) as compared to patients who tested negative for treatment emergent ADA by week 4

- In IMpower150, 36% of ADA-evaluable patients tested positive for ADA (83% prior to second dose). Ability of these binding ADA to neutralize atezolizumab is unknown.
  - Exploratory analyses: subset of ADA positive patients by week 4 (30%) appeared to have similar efficacy as compared to ADA negative patients

Source: TECENTRIQ USPI
Safety in immuno-oncology trials

• Unique group of immune-related adverse effects
  – Skin manifestations, colitis, hepatitis, pneumonitis, nephritis
  – More recently myocarditis, encephalitis described
• Incidence of any grade imAEs in single agent trials reported between 15-90%
• Rate of severe imAEs requiring immunosuppression and drug withdrawal reported between 0.5-13%
• Anti-CTLA-4 toxicities are dose dependent
### Safety results, nivo-ipi combination studies

<table>
<thead>
<tr>
<th>Immune-mediated AEs, %</th>
<th>CHECKMATE-142 + CHECKMATE-214 N-3 + I-1, n=666</th>
<th>CHECKMATE-067 + CHECKMATE-069 N-1 + I-3, n=407</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All gr</td>
<td>Led to d/c</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>21</td>
<td>NR</td>
</tr>
<tr>
<td>Dermatitis/rash</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>7</td>
<td>3.6</td>
</tr>
<tr>
<td>Colitis/diarrhea</td>
<td>9</td>
<td>3.2</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>7.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Hypophysitis/hypopituitarism</td>
<td>4.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Hypersensitivity/IRR</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>AKI/nephritis</td>
<td>4.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.7(^2)</td>
<td>0.5(^2)</td>
</tr>
</tbody>
</table>

1: Includes 3 fatal cases; 2: Includes data from RCC study only (n=547)
NR: Not reported

Source: OPDIVO USPI
### Safety results, nivo-chemo combination studies

<table>
<thead>
<tr>
<th>Immune-mediated AEs, %</th>
<th>KEYNOTE-189 Pembro+PC, n=405</th>
<th>KEYNOTE-407 Pembro+CP/nabP, n=278</th>
<th>Atezo+chemo, pooled¹ n=2421</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All gr</td>
<td>Gr 3-4</td>
<td>All gr</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7</td>
<td>0.5</td>
<td>8</td>
</tr>
<tr>
<td>Severe skin/cutaneous reaction/rash</td>
<td>2.0</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>4.0</td>
<td>0</td>
<td>7.2</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1.2</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Colitis/diarrhea</td>
<td>2.2</td>
<td>0.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>0.2</td>
<td>0.2</td>
<td>NR</td>
</tr>
<tr>
<td>Hypophysitis/hypopituitarism</td>
<td>0.7</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Hypersensitivity/IRR</td>
<td>2.5</td>
<td>0.2</td>
<td>2.9</td>
</tr>
<tr>
<td>AKI/nephritis</td>
<td>1.7</td>
<td>1.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4.4</td>
<td>1.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.2</td>
<td>0.2</td>
<td>NR</td>
</tr>
</tbody>
</table>

¹: Includes safety data from a pooled population of patients treated with atezolizumab and platinum-based chemotherapy across 5 clinical trials (IMpower133, IMpower130, IMpower131, IMpower132, and IMpower150)

Source: Gandhi et al 2018, Paz-Ares et al 2018, TECENTRIQ USPI, KEYTRUDA USPI
Assessment of imAEs in clinical trials

• Well-established management guidelines
• Clinical trial design requires standardized definitions of imAEs / AESIs across studies
  – AESIs are generally characterized as events that are a direct result of activation of the immune system
  – imAEs defined as any AESI that requires consideration of systemic intervention with steroids or endocrine therapy
  – Need for clear definition of preferred terms that comprise a given imAE
  – Described in clinical trials in terms of NCI CTCAE grading system – designed for use with cytotoxic drugs
• Standardized labeling, especially Warnings & Precautions
Biomarkers in IO studies: PD-L1

• Important role in inhibition of T cell-mediated immune response
• Expressed on the surface of tumor cells in various malignancies
• Correlation with prognosis is unclear
  – Different cut-offs for positivity
  – Different areas of measurement (tumor cells vs. tumor infiltrating lymphocytes)
  – Different assays
• Duration of treatment

Wang 2016, Udall 2018, Blumenthal 2017
PD-L1 tumor proportion score ≥ 50%


VS.

PD-L1 tumor expression ≥ 5%

Carbone et al 2017
Biomarkers in IO studies: TMB

• Measurement of mutations carried by tumor cells
• May predict outcomes with immunotherapy; being evaluated in multiple combination therapy approaches
• Typically measured through whole exome sequencing; many precision oncology platforms use next-generation sequencing of targeted gene panels

Alexandrov 2013
TMB as predictive biomarker?

• Current data mainly derived from retrospective analyses
• Each tumor mutation is considered equal
• Different platforms for assessment of TMB
• No clear cutoff across studies and disease type
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