Get Your CE IN THE MIDDAY
A Midday Symposium and Live Webinar conducted at the 2018 Midyear Clinical Meeting and Exhibition

Evolving Role of Immunotherapy in Cancer Treatment

Tuesday, December 4, 2018
11:30 a.m. – 1:00 p.m.
Anaheim, California

Agenda

11:30 a.m. – 11:35 a.m.
Welcome and Introductions
Christine Walko, Pharm.D., Activity Chair

11:35 a.m. – 11:50 a.m.
Current Immune Checkpoint Inhibitors and Mechanism of Action in Cancer Therapy
Christine Walko, Pharm.D.

11:50 a.m. – 12:10 p.m.
Evolving Biomarkers and Companion Diagnostic Testing
Christine Walko, Pharm.D.

12:10 p.m. – 12:55 p.m.
Patient Case-Initiating and Monitoring Immune Checkpoint Inhibitors
Ragini Kudchadkar, M.D.

12:55 p.m. – 1:00 p.m.
Immuno-oncology Toxicity Recognition and Management
Ragini Kudchadkar, M.D.

12:50 p.m. – 1:00 p.m.
Faculty Discussion and Audience Questions
Evolving Role of Immunotherapy in Cancer Treatment

CE IN THE MIDDAY
Evolving Role of Immunotherapy in Cancer Treatment

Christine M. Walko, Pharm.D., BCOP, FCCP, Activity Chair
Personalized Medicine Specialist, H. Lee Moffitt Cancer Center
Associate Professor, University of South Florida Morsani College of Medicine
Tampa, Florida

Ragini R. Kudchadkar, M.D.
Associate Professor of Hematology and Medical Oncology
Winship Cancer Institute, Emory University
Atlanta, Georgia

Provided by ASHP
Supported by an educational grant from Merck

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Christine M. Walko, Pharm.D., BCOP, FCCP
• Bristol-Myers Squibb and Merck: Honoraria received for participation in the Institute for Clinical Immuno-Oncology’s Melanoma Board

Ragini R. Kudchadkar, M.D
• Array, Immunocore, Bristol-Myers Squibb: Advisory Board member
• Merck: Research funding received

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Evolving Role of Immunotherapy in Cancer Treatment

Learning Objectives

- Identify the components of the human immune system and explain the mechanisms of action for using immune checkpoint inhibitors in cancer treatment.

- Examine the role of different companion diagnostic tests and interpret PD-L1 test results as they relate to selection of immune checkpoint inhibitor therapy.

- Analyze appropriate guidelines to guide management of common and less common immune related adverse effects from immune checkpoint inhibitors use.

- Formulate appropriate monitoring and management strategies for patients receiving immune checkpoint inhibitors.

On average how many cancer patients being treated with immunotherapies do you provide care to each month?

a. None-I am not directly involved in patient care
b. 1-10 patients/month
c. 11-30 patients/month
d. 31-50 patients/month
e. More than 50 patients/month
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Current Immune Checkpoint Inhibitors and Mechanism of Action in Cancer Therapy

Christine M. Walko, Pharm.D., BCOP, FCCP

Progression of Immunotherapy

- 1976: Spontaneous regressions in melanoma believed to be secondary to immune component
- 1986: Interferon-α approved for cancer immunotherapy
- 1991: MAGE-1: First tumor associated antigen cloned
- 2010: Sipuleucel-T is first autologous cellular immunotherapy approved for cancer (Prostate)
- 2014: Pembrolizumab and nivolumab both approved for advanced melanoma
- 2011: Ipilimumab approved for advanced melanoma
- 2017: Axicabtagene ciloleucel approved for DLBCL
- 2015: Nivolumab approved for advanced squamous NSCLC

Non-small cell lung cancer (NSCLC)
Diffuse large B-cell lymphoma (DLBCL)
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High dose (HD) IL-2 Therapy: Durable Responses

- HD IL-2 produces durable responses in 6% to 10% of patients with advanced melanoma or renal cell carcinoma (RCC)
- Few relapses in patients responding for over 2.5 years (therefore, can be considered cured)
- FDA approval in 1992 (RCC) and 1997 (melanoma)

Metastatic Melanoma (N = 270)

- CR (n = 17)
- PR (n = 26)
- CR + PR (n = 43)

Metastatic RCC (N = 255)

- CR
- PR
- All

CR=complete response; PR=partial response

History of Immunotherapy

<table>
<thead>
<tr>
<th>Interleukin-2</th>
<th>Ipilimumab</th>
<th>Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, Avelumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune target</td>
<td>Nonspecific T-cell growth factor</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>Approximate number of patients with ≥ grade 3 toxicities</td>
<td>85%</td>
<td>26%</td>
</tr>
<tr>
<td>Classic toxicities</td>
<td>Capillary leak syndrome with hypotension, fever, headache, myalgias, diarrhea, liver toxicity</td>
<td>Rash, diarrhea/colitis, liver toxicity, endocrine toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash diarrhea, liver toxicity, endocrine toxicity</td>
</tr>
</tbody>
</table>

CTLA-4: Cytotoxic T-lymphocyte-associated antigen-4
PD-1: Programmed Cell Death Protein-1

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CTLA-4 and PD-1 Pathways

- Ipilimumab: inhibits CTLA-4 on T-cells
- Pembrolizumab and nivolumab: inhibit PD-1 on T-cells, preventing binding to PD-L1 on tumor cells
- Atezolizumab, durvalumab, avelumab: inhibits PD-L1 on the tumor cell
- Ultimately, prevents immune system downregulation


Nivolumab Phase I Trial Design

N=296 patients
- Melanoma (n = 104)
- Non-small cell lung cancer (NSCLC) (n = 122)
- Renal cell carcinoma (n = 34)
- Prostate cancer (n = 17)
- Colorectal cancer (n = 19)

All patients had an ECOG performance status of ≤2 and measurable disease

Phase 1 dose escalation of anti-PD-1 inhibitor
- 0.1 to 10 mg/kg IV every 2 weeks for up to 12 cycles or until disease progression or complete response where therapy could continue
- Tumor samples analyzed for PD-L1 expression using immunohistochemistry (IHC)

Cohorts of 3-6 patients enrolled in each cohort
- 0.1, 0.3, 1.0, 3.0, and 10 mg/kg

Expansion groups enrolled after no maximum tolerated dose was found

ECOG=Eastern Cooperative Oncology Group
Summary of Results

- Antitumor activity was seen at all dose levels
- Objective response rate (complete or partial)
  - 28% in melanoma
  - 27% in renal cell carcinoma
  - 18% in NSCLC
- 65% of the responses were durable for 1 year or more in patients with >1 year follow up
- IHC staining for PD-1L predicted response rate
  - 0 of 17 responses in PD-1L negative tumors
  - 9 of 25 responses in PD-1L positive tumors

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FDA-Approved PD-L1 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Durvalumab</th>
<th>Avelumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merkel cell carcinoma</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Slide updated as of 10/10/2018

Continued Progression of Immunotherapy:

- **Adjuvant therapy approvals:**
  - *Ipilimumab* and *nivolumab* approved for adjuvant therapy of cutaneous melanoma following complete resection
  - *Durvalumab* approved for unresectable stage III NSCLC
- **Novel agents:**
  - *Talimogene laherparepvec* (“T-VEC”) approved for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
  - Chimeric antigen receptor T cell therapy *(CAR-T)*
- **Pembrolizumab** in combination with pemetrexed and carboplatin for first-line treatment of non-squamous NSCLC
- Approvals for novel indications and rare malignancies

Case Presentation 1: LR

- LR is a 64-year-old female who began experiencing a persistent cough with intermittent hemoptysis
  - Chest CT showed a right upper lobe (RUL) lung lesion and masses involving the liver and right adrenal gland indicative of stage IV disease
- Biopsy of the liver lesion shows adenocarcinoma consistent with primary lung malignancy
  - No targetable mutations are identified on next generation sequencing
  - PD-L1 tumor proportion score = 60%
- Creatinine clearance is 40 mL/min (moderate impairment)
- Treatment plan is for nivolumab. How should it be dosed?

Approved Adult Dosing Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>IV Dose</th>
<th>Infusion Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab*</td>
<td>240 mg every 2 weeks or 480 mg every 4 weeks</td>
<td>30 for both</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>200 mg every 3 weeks</td>
<td>30</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>1200 mg every 3 weeks</td>
<td>60 for first infusion then 30 subsequently</td>
</tr>
<tr>
<td>Avelumab</td>
<td>10 mg/kg every 2 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>10 mg/kg every 2 weeks</td>
<td>60</td>
</tr>
</tbody>
</table>

* FDA-approved dosing for single agent treatment only.

FDA-approved prescribing information for each agent
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Renal and Hepatic Dosing
Generally determined based on population PK studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Dosing Pharmacokinetic (PK) impact &lt;20-30%</th>
<th>Hepatic Dosing Proteolytic degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>No change for mild, moderate or severe impairment</td>
<td>No change for mild impairment</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>No change for mild, moderate or severe impairment</td>
<td>No change for mild impairment</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>No change for mild or moderate impairment</td>
<td>No change for mild impairment</td>
</tr>
<tr>
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<td>No change for mild or moderate impairment</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>No change for mild or moderate impairment</td>
<td>No change for mild impairment</td>
</tr>
</tbody>
</table>

FDA-approved prescribing information for each agent

Nivolumab Dose Approval

3 mg/kg over 60 min every 2 weeks
240 mg flat dose over 60 min every 2 weeks
480 mg flat dose over 30 min every 4 weeks

Dose exposure PK and safety studies

3/6/2018: supplemental Biologics License Application (sBLA) approved by FDA for flat dose over 30 minutes every 4 weeks based on analysis using model-based exposure-response

PK: pharmacokinetics

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**Pembrolizumab Flat Dosing**

- Pembrolizumab was dosed at 0.005 to 10 mg/kg in clinical trials with no MTD determined
  - 2 mg/kg every 3 weeks chosen for KEYNOTE-001 registration trial
  - Similar exposure was seen for this dose and 200 mg flat dosing every 3 weeks
- Budget impact analysis (first-line setting total annual cost in U.S. dollars based on Medicare average sales price):
  - Fixed dose: $3.4 billion
  - Weight-based dose: $2.6 billion

MTD=maximum tolerated dose


**Combination Dosing for Melanoma Checkmate 511**

*High-Dose vs Low-Dose Ipilimumab*

<table>
<thead>
<tr>
<th></th>
<th>G3/4 AE %</th>
<th>% CR</th>
<th>% PR</th>
<th>% SD</th>
<th>% PD</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO 3mg/kg + IPI 1 mg/kg</td>
<td>33.3</td>
<td>15</td>
<td>30.6</td>
<td>11.7</td>
<td>34.4</td>
<td>45.6</td>
</tr>
<tr>
<td>NIVO 1mg/kg + IPI 3 mg/kg</td>
<td>48.3</td>
<td>13.5</td>
<td>37.1</td>
<td>11.8</td>
<td>26.4</td>
<td>50.6</td>
</tr>
</tbody>
</table>

Lebbe C et al. ESMO 2018. Abstract LBA47.
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Case Presentation 1: LR

- LR is a 64-year-old female who began experiencing a persistent cough with intermittent hemoptysis
  - Chest CT showed a right upper lobe (RUL) lung lesion and masses involving the liver and right adrenal gland indicative of stage IV disease
- Biopsy of the liver lesion shows adenocarcinoma consistent with primary lung malignancy
  - No targetable mutations are identified on next generation sequencing
  - PD-L1 tumor proportion score = 60%
- Creatinine clearance is 40 mL/min (moderate impairment)
- Treatment plan is for nivolumab. How should it be dosed?

Should the nivolumab dosage be reduced in patients with moderate renal dysfunction?

a. Yes, by 25%
b. Yes, by 50%
c. No, dose reduction is not required
d. Nivolumab should not be given to patients with moderate renal dysfunction
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Which of the following is the best dosing regimen for nivolumab in this patient at this time?

a. 3 mg/kg IV over 60 min every 2 weeks
b. 200 mg IV over 30 min every 3 weeks
c. 240 mg IV over 30 min every 2 weeks
d. 480 mg IV over 30 min every 4 weeks

Combination Ipilimumab and Nivolumab Dosing

- FDA approved combination dosing for metastatic melanoma:
  - Nivolumab 1 mg/kg followed by ipilimumab 3 mg/kg on the same day, every 3 weeks x 4 doses
  - Nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 3 weeks

- NCT 02714218 enrolling to assess different doses:
  - Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg
  - Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg
  - Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg
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Evolving Biomarkers and Companion Diagnostic Testing
Christine M. Walko, Pharm.D., BCOP, FCCP

Biomarkers for Response to Immune Checkpoint Inhibitors

- Microsatellite instability
- Tumor mutation burden
- PD-L1 status
- Investigational
  - Tumor infiltrating lymphocytes (TIL)
  - DNA repair deficiency and ARID1A mutations
  - HLA class 1 genotype


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Microsatellite Instability (MSI)

- DNA mismatch repair (MMR) enzymes correct errors that occur during normal DNA replication
- Inactivation of these MMR enzymes results in more errors and the development of microsatellite fragments
  - Inactivation of MLH1, MSH2, MSH6, and/or PMS2
  - Can be germline or somatic (just occurring in the tumor)
- Frequency in solid tumors:
  - Colorectal cancer: 15%
  - Endometrial cancer: 22-33%
  - Other tumors: 5% or less
- Correlated with increased number of mutations


Current MSI-High Approvals

**Pembrolizumab**

- Treatment of adult and pediatric patients with unresectable or metastatic MSI-high or MMR deficient:
  - Solid tumors following prior therapy with no satisfactory alternatives
  - Colorectal cancer following prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan
  - Not yet established for pediatric patients with MSI-high central nervous system (CNS) tumors
- Data from 5 trials (n=149)
  - Objective response rate 39.6%
  - 11 complete responses
  - 48 partial responses

**Nivolumab**

- Treatment of adult and pediatric patients with unresectable or metastatic MSI-high or MMR deficient:
  - Colorectal cancer following prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan
- CheckMate 142 study (n=74)
  - Objective response 31.1%
  - Disease control for ≥ 12 weeks: 69%

Keytruda (pembrolizumab) prescribing information, 2018 Oct. Opdivo (nivolumab) prescribing information, 2018 Aug.


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Mutation Load and Immunotherapy

- Mutation burden indicates the number of non-synonymous mutations reported per megabase (Mb)
  - Cancers secondary to environmental exposures (UV light, cigarette smoking) or certain DNA damage deficiencies have higher mutation burdens
  - Correlation with neoantigens: novel antigens that can be recognized as non-self and enhance T-cell activation
- Improved median progression free survival (mPFS) in lung cancer patients with high mutation burden, irrespective of PD-L1 status


Case Presentation 2: LC

- LC is a 78-year-old female former light smoker who began experiencing persistent cough and intermittent abdominal pain
- Chest CT showed a right upper lobe (RUL) lung lesion and masses involving the liver and right adrenal gland
- Biopsy of the RUL lesion showed adenocarcinoma consistent with primary lung malignancy
  - EGFR, ALK, ROS1, BRAF, MET, and RET all negative

CT=computerized tomography
EGFR, ALK, ROS1, BRAF, MET, and RET refer to specific gene rearrangements that have been linked to lung cancer.
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PD-L1 Biomarker Diagnostic Tests

**Companion Diagnostic**
- In vitro diagnostic device that provides information **essential** for the safe and effective use of the associated drug
- PD-L1 IHC 22C3 pharmDx in NSCLC patients receiving pembrolizumab
  - Determines a Tumor Proportion Score (TPS)
  - $>50\%$ for first-line metastatic treatment
  - $>1\%$ for treatment following progression on platinum-based therapy

**Complementary Diagnostic**
- Improves the risk/benefit ratio of a specific drug but does not restrict access to the drug based on presence of the biomarker
- PD-L1 IHC 28-8 test for nivolumab in patients with melanoma and NSCLC
- VENTANA PD-L1 (SP142) Assay for atezolizumab in patients with NSCLC
  - PD-L1 membrane staining of any intensity in $>50\%$ of tumor cells or tumor infiltrating immune cells covering $>10\%$ in the NSCLC was associated with improved overall survival


Response and PD-L1 Expression: Non-Small Cell Lung Cancer (NSCLC)

- KEYNOTE-001 trial subset: NSCLC
  - 495 patients with advanced NSCLC treated with one of 3 different regimens of pembrolizumab
  - PD-L1 expression assessed in tumor samples by immunohistochemistry (IHC) and reported as a tumor proportion score (TPS)

ORR=objective response rate


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PD-L1 Expression

**Benefits**
- Immunohistochemical (IHC) testing is available and has correlated with response to PD-1 inhibitors in a variety of tumor types.
- Response rate across tumor types:
  - PD-L1 positive tumors: 48%
  - PD-L1 negative tumors: 15%
  - Correlation with progression free and overall survival is still being assessed.
- PD-L1 can be used to prioritize treatment options.

**Challenges**
- PD-L1 expression can vary over time and between tumor sites.
- PD-L1 can be located on the cell membrane (clinically relevant) or cytoplasm.
- Different tests may produce different results because antibodies have different affinities and specificities.
- Different specimen handling techniques may decrease sensitivity.
- Unclear threshold values across tests, malignancies, and PD-1 inhibitors.


Does LC qualify for first-line pembrolizumab based on her PD-L1 TPS of 70%?

a. Yes, first-line pembrolizumab is indicated
b. No, first-line pembrolizumab is not indicated
c. Pembrolizumab is not approved for first-line therapy for NSCLC
d. Pembrolizumab is not approved for any line of therapy for NSCLC
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Biomarker Future Directions

• Given the high cost and toxicity of immunotherapy agents, robust biomarkers will be helpful for optimizing therapy selection and sequencing

• Several trials have shown an association between number of somatic mutations in a tumor and response to immunotherapy
  – Ongoing trials are needed to determine threshold values
  – Differences between tumor types?

• PD-L1 expression has correlated with outcomes but responses are still seen in PD-L1 negative patients
  – Standardized assays with consistent threshold values
  – Consideration of differences between cancer types and PD-1 vs. PD-L1 inhibitors

Patient Cases and Initiating and Monitoring Immune Checkpoint Inhibitors

Ragini R. Kudchadkar, M.D.
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Metastatic Melanoma First Line Options:
How should a clinician decide between combination immuno-oncology vs. single agent immuno-oncology vs BRAF/MEK inhibitors?

- BRAF wild type
- BRAF mutated

Symptomatology
ECOG PS
Brain Metastases
Patient Preference

Case Presentation 3 - SS

54-year-old Caucasian male with no other past medical history presents with newly diagnosed Stage IV melanoma with metastases to the liver, lung, and brain
He elects to proceed with ipilimumab 3 mg/kg + nivolumab 1 mg/kg

Which of the following is appropriate in pre-treatment counseling?

- Rates of autoimmune toxicity are higher than with single agent PD1 treatment
- Patients may experience more than one autoimmune toxicity
- 20% of patients are hospitalized due to side effects
- Must complete all four doses to get benefit

Pre- and On-treatment Requirements

- Labs
  - How often?
  - Which labs are required?
  - Which labs are helpful?
- Diagnostic Studies
  - Staging imaging
  - Echo?
Case Presentation 4 - RW

67-year-old female with history of Rheumatoid Arthritis on Prednisone 10 mg orally daily has and newly diagnosed Stage IV BRAF WT melanoma with metastasis to the lungs.

Case Discussion 4 - RW

• How do you counsel patients with autoimmune disease starting immuno-oncology therapy?
• Can you treat patients on chronic immunosuppression?
• What are the benefits of immuno-oncology therapy in this population?
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Autoimmune Disorders Background

- There are more than 80 distinct autoimmune disorders:
  - 3-8% of the U.S. population estimated to have an autoimmune disorder
- Lifetime risk of inflammatory autoimmune disease is estimated to be 1:12 for women and 1:20 for men in the year before a cancer diagnosis
- Immunotherapy clinical trials did not include these patients


Ipilimumab in Autoimmune Disease

- Retrospective review of 30 patients (advanced melanoma and preexisting autoimmune disorders) treated with ipilimumab
  - Rheumatoid arthritis (n=6)
  - Psoriasis (n=5)
  - Inflammatory bowel disease, lupus, multiple sclerosis, or thyroiditis (n=2 for each) and other (n=7)
- 43% were receiving autoimmune therapy concurrently
- 27% had autoimmune exacerbations necessitating steroid therapy
- 50% had no autoimmune flare or immune-related adverse events
- Overall response = 20% (1 patient with durable CR)

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PD-1 Inhibitors in Autoimmune Disease

- Retrospective trial of 52 melanoma patients with preexisting autoimmune disorders treated with PD-1 inhibitors
  - Response rate = 33%
  - Flare requiring immunosuppression = 38%
    - Rheumatoid arthritis, polymyalgia rheumatica, Sjogren’s syndrome, psoriasis, and immune thrombocytopenic purpura
  - No flare was seen in patients with gastrointestinal (n=6) or neurological (n=5) disorders
  - Discontinuation due to flare = 2 patients


REISAMIC Registry Trial

- Registry of grade ≥ 2 immune-related adverse effects (irAE) in patients treated with anti-PD-1 antibodies
- 45 patients with a total of 53 preexisting autoimmune or inflammatory diseases were identified in the registry
  - Vitiligo (n = 17)
  - Psoriasis (n = 12)
  - Thyroiditis (n = 7)

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REISAMIC Registry Trial Results

- Most patients had melanoma (n = 36) or NSCLC (n = 6)
- At least one irAE was seen in 44.4% (n = 20) of patients
  - 11 were associated with a preexisting autoimmune disease flare
  - 15 of the 20 patients were able to continue treatment with the anti-PD-1 antibody
  - No difference in objective response or overall survival was seen


Immuno-oncology in patients with preexisting autoimmune disease

- Risk vs benefit ratio: Yes in metastatic, probably no in adjuvant
- Single agent appears “relatively” safe
- Minimal data with combination therapy (CTLA4/PD1 inhibitor) – likely higher risk of flare

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Immuno-oncology Toxicity Recognition and Management

Ragini R. Kudchadkar, M.D.

Immune-Related Adverse Events (irAEs)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Clinical Effects</th>
<th>All grades (grade 3/4)</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Rash, vitiligo, pruritus</td>
<td>47-68% (0-4%)</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>Diarrhea, colitis</td>
<td>31-46% (8-23%)</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Liver</td>
<td>Elevated enzymes, bilirubin, hepatitis</td>
<td>3-9% (3-7%)</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypophysitis, hypothyroidism</td>
<td>4-6% (1-5%)</td>
<td>After 9 weeks</td>
</tr>
</tbody>
</table>

Overall Grade 3/4:
- Ipilimumab 3 mg/kg 20-30%
- Ipilimumab 10 mg/kg 50%
- Nivolumab or pembrolizumab 10-15%
- Ipilimumab 3 mg/kg + nivolumab 1 mg/kg 50%

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**ASCO Guidelines: Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors**

- **Purpose:** To increase awareness, outline strategies and offer guidance on the recommended management of immune-related adverse effects (irAEs) in patient treated with immune checkpoint inhibitors (ICPi)
- Interprofessional panel across medical specialties
- Systematic review of 204 publications from 2000 to 2017

ASCO=American Society of Clinical Oncology


**Events in Patients Treated with Immune Checkpoint Inhibitors**

- **Skin toxicities**
  - Rash
  - Bullous dermatoses
  - Severe cutaneous adverse reactions
- **Gastrointestinal toxicities**
  - Colitis
  - Hepatitis
- **Lung toxicities**
  - Pneumonitis
- **Endocrine toxicities**
  - Primary hypothyroidism
  - Hyperthyroidism
  - Primary adrenal insufficiency
  - Hypophysitis
  - Diabetes mellitus

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Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

- Musculoskeletal toxicities
- Renal toxicities
- Nervous system toxicities
- Hematologic toxicities
- Cardiovascular toxicities
  - Myocarditis, arrhythmias, heart failure, vasculitis
  - Venous thromboembolism
- Ocular toxicities


Endocrine irAEs Overview

37 year-old Caucasian female with Stage IIIC resected melanoma s/p 3 doses of adjuvant ipilimumab 10 mg/kg presents with severe headaches

65 year-old Caucasian male with Stage IV melanoma s/p 2 doses of ipilimumab 3 mg/kg + nivolumab 1 mg/kg presents with severe fatigue, polyuria/polydipsia

61 year-old Caucasian male with Stage IV melanoma s/p 3 doses of ipilimumab 3 mg/kg + nivolumab 1 mg/kg presents with SOB and palpitations

30 year-old Caucasian female with Stage IV melanoma s/p 4 doses of pembrolizumab presents with low TSH, high T4 on routine labs

50 year-old Caucasian male with Stage IIIC resected melanoma on adjuvant trial of ipilimumab vs. nivolumab presents with fatigue

s/p=status post, SOB=shortness of breath
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Case Presentation 5: CM
(Endocrine Toxicity Management)

• CM is a 52-year-old male with PMH of type 2 diabetes mellitus.
• He is found to have a palpable axillary mass and ultimately diagnosed with stage IIIB melanoma and is started on nivolumab 3 mg/kg.
  – Week 2 of therapy he reports 1 week of low grade fever (100 °F) and body aches.
  – The heart monitor on his watch has shown his resting heart rate to be 80-90’s when it’s usually in the 60’s
  – He also has been experiencing fatigue (but still going to work) as well as queasiness but eating okay
  – Current temp is 36.8 °C, BP 113/72 mmHg, HR 99 BPM, and RR 18
  – Exam shows tachycardia but otherwise unremarkable

Case Presentation 5: CM
(Endocrine Toxicity Management)

• Lab work
  – Na 138 mmol/L, K 4.7 mmol/L, CO₂ 23, Glucose 270 mg/dL, Scr 0.86 mg/dL,
  – Total bilirubin 1.1 mg/dL, AST 153 U/L, ALT 96 U/L, LDH 210 U/L
  – Cortisol 4.9 mcg/dL, ACTH less than 5 pg/mL(1300 draw)
  – TSH 0.03 mIU/L, Free T4 greater than 5.5 ng/dL, T3 670 ng/dL

• Diagnosis?
  – Thyrotoxicosis
  – Grade 1 hepatitis
  – Type 1 Diabetes mellitus

TSH=thyroid stimulating hormone, T4=thyroxine, T3=triiodothyronine, ACTH=adrenocorticotropic hormone, Scr = serum creatinine
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Endocrine irAEs Overview

• Hyperthyroidism, hypothyroidism, hypopituitarism, type 1 diabetes mellitus
• Measure TSH, free T4, ACTH, cortisol
• FSH, LH, and testosterone
• Consider ACTH stimulation studies
• Can you give immunotherapy when endocrinopathies develop?

TSH=thyroid stimulating hormone, T4=thyroxine, ACTH=adrenocorticotropic hormone, FSH=follicle stimulating hormone, LH=luteinizing hormone

Hypothyroidism (Highlights)

<table>
<thead>
<tr>
<th>Grading (CTCAE)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1: TSH &lt; 10 mIU/L and asymptomatic</td>
<td>• Continue ICPI with monitoring of TSH and free T4</td>
</tr>
<tr>
<td>G2: Moderate symptoms, TSH persistently &gt; 10 mIU/L</td>
<td>• May withhold ICPI until symptoms resolve to baseline</td>
</tr>
<tr>
<td></td>
<td>• Consider endocrine consult</td>
</tr>
<tr>
<td></td>
<td>• Thyroid supplementation in symptomatic patients with TSH levels &gt; 10 mIU/L, monitor every 6-8 weeks while titrating</td>
</tr>
<tr>
<td>G3-4: Severe symptoms, life threatening consequences</td>
<td>• Withhold ICPI until symptoms resolve to baseline with appropriate thyroid supplementation</td>
</tr>
<tr>
<td></td>
<td>• Endocrine consultation</td>
</tr>
<tr>
<td></td>
<td>• May admit for IV therapy if bradycardia and/or hyperthermia</td>
</tr>
<tr>
<td></td>
<td>• All of the above from G2</td>
</tr>
</tbody>
</table>

CTCAE=Common Terminology Criteria for Adverse Events

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Case Presentation 5: CM
(Endocrine Toxicity Management)

• Labs take a few hours – Do you treat while waiting?
• Management of Endocrinopathies
  – Remember endocrinopathies are permanent
  – Beta Blockade
  – Consider Methimazole
  – Endocrinologists are my new best friend! 😊
    • Complete pituitary panel – AM ACTH, Cortisol, LH, FSH, Prolactin, Testosterone (wnl)
    • TSH Receptor Ab – less than 0.90 IU/mL (wnl)
    • Thyroid Stimulating Immunoglobulin 97% (wnl)
    • Glutamic Acid Decarboxylase Antibody 5.9 nmol/L (high)
    • Islet Cell Antibody IgG wnl
    • Started on Insulin
    • Long term, will develop hypothyroidism and require long-term thyroid hormone replacement

Comparison of Endocrine irAEs

• Meta-analysis of 38 randomized clinical trials with a total of 7551 patients
  – PD-1 inhibitor monotherapy
  – PD-L1 inhibitor monotherapy
  – CTLA-4 inhibitor monotherapy (ipilimumab)
  – Combination PD-1 and CTLA-4 inhibitors

• Results
  – Combination therapy had the highest rate of hypothyroidism (OR 3.81, p<0.001) and hyperthyroidism (OR 4.27, p=0.001) compared with ipilimumab alone
  – PD-1 inhibitor-treated patients had a higher risk of developing hypothyroidism (OR 1.89, p<0.03) compared with ipilimumab
  – Risk of hyperthyroidism (not hypothyroidism) was higher with PD-1 inhibitors compared with PD-L1 inhibitors (OR 5.36, p=0.002)
  – Hypophysitis was more common with ipilimumab than PD-1 inhibitors

OR= Odds ratio

Gastrointestinal irAEs Overview

- Although colitis is mostly discussed, can occur anywhere in GI tract (mucositis, enteritis)
- With single-agent immunotherapy, most commonly seen about 6-8 weeks after start of treatment
- Can be seen after any dose of immunotherapy
- Case reports of colitis after being off immunotherapy for 3-6 months
- Timing altered by combination CTLA-4 and PD-1 blockade
- Rarely seen in patient on maintenance immunotherapy (after more than 6 doses)


Case Presentation 6: RR

37-year-old Caucasian male with Stage IV melanoma from unknown primary source to the brain and lungs.
7/2017 Dose 1 Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg
8/2017 Presents for dose 2 c/o
- One week ago had one day of 6 loose stools, took loperamide and experienced improvement
- Now having 3 loose stools daily, mostly after meals, using loperamide prn
- Patient appears well – vital signs stable, lab work wnl
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Case Discussion 6: RR

What do you do next?

a. Proceed with dose 2, no new interventions
b. Delay dose 2
c. Start steroids for colitis
d. Give dose of infliximab
e. Consider use of budesonide
f. Any or all of above?

Case Discussion 6: RR- What did I do?

- Withheld dose, reevaluated after one week
- Started budesonide
- Note differences between extended-release budesonide tablets (Uceris®) and enteric-coated budesonide capsules (Entocort capsules®) in absorption – better colonic absorption with extended-release budesonide tablets (Uceris®)
- Reevaluation in one week:
  - Unable to obtain extended-release budesonide tablets (Uceris®) due to insurance
  - 8-10 loose stools per day
  - Labs, vital signs stable
Case Presentation 6: RR (continued)
(Gastrointestinal Toxicity Management)

- RR does well and after 1 week of oral prednisone 80 mg/day is now having formed stools and 2-3 bowel movements per day.

- How should the prednisone be tapered?

Case Presentation 6: RR (continued)
(Gastrointestinal Toxicity Management)

- RR does well until decreasing to prednisone 40mg per day.
  - He calls the clinic with increasing diarrhea at 6-8 loose stools per day

What do you do next?

- a. Increase prednisone to 1mg/kg/day (80mg/day), resume taper when stools are formed.
- b. Continue 40 mg/day of prednisone and bring him in for infliximab 5mg/kg IV.
- c. Increase prednisone to 60 mg/day (the lowest dosage recently associated with formed stools).
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Case Presentation 6: RR (continued)
(Gastrointestinal Toxicity Management)

- RR is increased to prednisone 60mg per day and given 1 dose of infliximab with full resolution of symptoms.
  - Tapered off corticosteroids over 1 month
  - Scans show a partial response

How do you proceed with future treatment?

a. Complete the rest of induction therapy with ipilimumab and nivolumab?
b. Discontinue nivolumab and ipilimumab?
c. Start maintenance nivolumab at 3mg/kg?

Colitis (highlights)

<table>
<thead>
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<tbody>
<tr>
<td>G1: Increase of &lt; 4 stools/day or mild increase in ostomy output</td>
<td>• May continue ICPi or withhold until &lt; G1&lt;br&gt;• Monitor dehydration</td>
</tr>
<tr>
<td>G2: Increase of 4-6 stools/day, moderate increase in ostomy output</td>
<td>• Withhold ICPi until ≤ G1 (may permanently d/c CLTA-4 inhibitors)&lt;br&gt;• Consult with Gastroenterology, consider EGD/colonoscopy to stratify for infliximab&lt;br&gt;• Initiate prednisone 1 mg/kg/day PO, taper over 4-6 weeks when ≤ G1</td>
</tr>
<tr>
<td>G3: Increase of ≥ 7 stools/day, incontinence, severe ostomy output, hospitalization needed</td>
<td>• As above for G3, with hospitalization for electrolyte replacement&lt;br&gt;• If symptoms ≥ 3-5 days or recur after improvement, consider IV methylprednisolone or infliximab</td>
</tr>
<tr>
<td>G4: Life threatening consequences</td>
<td>• Permanently discontinue ICPi&lt;br&gt;• Methylprednisolone 1-2 mg/kg/day IV&lt;br&gt;• Infliximab 5-10 mg/kg IV if refractory after 2-3 days</td>
</tr>
</tbody>
</table>

EGD=esophagogastroduodenoscopy

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Case Presentation 7: MR

- 33-year-old female is on adjuvant nivolumab for resected Stage III melanoma
- At her 1-month visit, reports pruritus. Exam is normal without rash
  - Do you continue with next cycle of treatment?
  - Recommendations?
    - Antihistamines, moisturizers, avoid hot showers
- Returns after cycle 2
  - Now what? Retreat?
    - Topical prescription steroids
    - Usually can continue immunotherapy tx

Dermatologic Side Effects

- Most common adverse event
  - Mostly low grade
  - Rash, pruritus, and vitiligo
  - Most resolve with symptomatic therapy: moisturizers, diphenhydramine, hydroxyzine
  - Topical prescription steroids okay
  - Oral corticosteroids for more severe cases (can try short course, but flare possible)
  - Case reports of Mu-Opioid Receptor Antagonist (naloxone)
  - T-cell infiltrate seen on biopsy specimens of the skin

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Rash/Inflammatory Dermatitis

<table>
<thead>
<tr>
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</table>
| G1: No affects on QOL or controlled with topical or oral antipruritic | • Topical emollients and/or mild/moderate potency topical corticosteroids  
• Avoid irritants and sun exposure |
| G2: Effects QOL and requires intervention | • Consider withholding ICPi  
• Consider prednisone (or equivalent) 1 mg/kg orally tapering over at least 4 weeks  
• Topical emollients and/or moderate/high topical corticosteroids |
| G3: G2 but failure to respond to G2 interventions | • Withhold ICPi and consult dermatology  
• Methylprednisolone 1-2 mg/kg IV, taper over > 4 weeks  
• Topical emollients and high topical corticosteroids |
| G4: All severe rashes not manageable with prior interventions and intolerable | • Withhold ICPi, consult dermatology, admit patient  
• Methylprednisolone 1-2 mg/kg IV, slow taper when toxicity resolves  
• Consider permanent discontinuation if other options |


Does occurrence of adverse effects correlate with treatment outcomes?

• Retrospective trial of 298 patients with metastatic melanoma treated with ipilimumab 3 mg/kg at Memorial Sloan Kettering Cancer Center
  
• Immune-related adverse events  
  – 19% discontinued treatment (most common: diarrhea)  
  – 35% of patients required corticosteroids  
  – 10% of patients required infliximab

• Overall survival and time to treatment failure were not associated with immune-related adverse events or treatment with corticosteroids

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Immunotherapy irAE Summary

- Importance of patient education
- Clinicians should maintain high index of suspicion for immunotherapy as cause of new side effects
- Dose adjustments are not recommended after restarting therapy following toxicity

<table>
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<tr>
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</table>
| Grade 1         | • Continue ICPI therapy with close monitoring  
• Exceptions: neurologic, hematologic and cardiac toxicities |
| Grade 2         | • Withhold ICPI for most toxicities, resume when resolved to ≤ G1  
• Prednisone 0.5-1 mg/kg/day orally or equivalent may be administered |
| Grade 3         | • Withhold ICPI for G3 toxicities  
• Start prednisone 1-2 mg/kg/day orally or methylprednisolone IV 1-2 mg/kg/day with taper over ≥ 4-6 weeks  
• If no improvement after 48-72 hours, then consider infliximab |
| Grade 4         | • Generally warrant permanent ICPI discontinuation (except for endocrine therapy controlled by hormonal replacement) |


Pearls in Managing irAEs

- Patient education is needed for early recognition of irAEs
- Nonspecific complaints might reflect endocrine (pituitary) toxicity
- Corticosteroids are effective – do not taper too quickly
- Consider infliximab or mycophenolate mofetil (MMF) in refractory cases
- Combination immunotherapies are associated with higher toxicity rates than single agent immunotherapy, but similar types of toxicities are seen
- Watch out for multiple irAEs in one patient, especially on combination (CTLA-4/PD-1 inhibitor) therapy
- Onset of irAEs in combination immunotherapy may be earlier than typically seen with single agent immunotherapy
- Consider prophylaxis if prolonged corticosteroids are required

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Which of these practice changes will you consider making?

• Describe the components of the normal human immune system and explain the mechanisms of action behind immune checkpoint inhibitors in cancer.
• Review the role of different companion diagnostic tests and interpret PD-L1 test results as they relate to selection of immune checkpoint inhibitor therapy
• Read the current protocols for the use of immunotherapy at my institution.
• Review current immunotherapy approvals and their place in therapy.
• Recognize the adverse effects associated with immunotherapy.
• Discuss with colleagues potential strategies for managing the adverse effects associated with immunotherapy (toxicity management).

Key Takeaways

• Key Takeaway #1
  – The role of immunotherapy in both solid tumors and hematologic malignancies continues to evolve rapidly

• Key Takeaway #2
  – Continued research into predictive biomarkers, such as PD-L1 expression, MSI status and mutation burden, is needed to balance clinical benefit and toxicity from immunotherapy

• Key Takeaway #3
  – Immune-related toxicities are unique to these agents and require rapid recognition and treatment commonly involving corticosteroids
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Questions? Contact EducServ@ashp.org!
Ragini R. Kudchadkar, M.D.
Associate Professor
Winship Cancer Institute of Emory University
Associate Director Hematology Oncology Fellowship Program
Atlanta, Georgia

Dr. Kudchadkar completed her Bachelor of Science degree in Neuroscience and Behavioral Biology and her Doctor of Medicine degree from Emory University. After completing her Internal Medicine residency at Emory University she completed her Hematology and Medical Oncology fellowship at the University of Colorado Health Sciences Center in Denver, Colorado.

Dr. Kudchadkar is a cutaneous oncologist specializing in drug development and clinical trials primarily for melanoma. Her other interests include how current melanoma therapies affect the natural immune function both in T-cells and B-cells. She is also interested in exploring new treatments for rare cutaneous disease such as advanced basal cell carcinoma, merkel cell carcinoma, and squamous cell carcinoma.

Dr. Kudchadkar is a member of the American Society of Clinical Oncology, the Society for Melanoma Research, and the American Association for Cancer Research. She has served on the National Comprehensive Cancer Network Melanoma guidelines committee. She has authored numerous book chapters, review articles, and peer-reviewed papers as well as presented nationally in melanoma and immunotherapy.

Christine M. Walko, Pharm.D., BCOP, FCCP, is a Personalized Medicine Specialist at the DeBartolo Family Personalized Medicine Institute at the H. Lee Moffitt Cancer Center and is also Associate Professor at the University of South Florida Morsani College of Medicine in Tampa, Florida. She is also the Chair of the Clinical Genomics Action Committee (CGAC) and attending on the Personalized Medicine Clinical Service at H. Lee Moffitt Cancer Center. Dr. Walko received her Doctor of Pharmacy from Duquesne University in Pittsburgh. She completed a pharmacy practice residency at Virginia Commonwealth University Health System/Medical College of Virginia Hospitals in Richmond, Virginia. She also completed a Hematology/Oncology specialty residency at the University of North Carolina (UNC) Hospitals and Clinics and a Hematology/Oncology fellowship at the University of North Carolina School of Pharmacy in Chapel Hill, North Carolina. She is a board certified oncology pharmacist.

She has researched and published extensively in oncology therapy and has presented nationally and internationally on oncology and pharmacogenomics and other topics related to treating patients with cancer.