Cancer Therapy Induced Autoimmune Diseases: Recognizing and Managing the Adverse Effects of Immune Checkpoint Inhibitors

6th Biennial Atlantic Canada Thoracic Oncology Conference
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Division of Medical Oncology
Dalhousie University
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Breakthrough of the Year: Science 2013

Cancer Immunotherapy

“This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumours are paying off – even if the future remains a question mark”
Learning Objectives

- Brief Review Mode of Action and Indications for Checkpoint Inhibitors In Lung Cancer
- Discuss How a Patient Should be Educated and Assessed Before Starting a Checkpoint Inhibitor
- Develop an System for How to Screen Patients for Adverse Effects After Therapy has Started
- Understand a General Approach for How Checkpoint Inhibitor Adverse Effects are Managed
Mode of Action of Checkpoint Inhibitors
Need a New Approach in Advanced Cancer to Attain Long-term Survival Benefit

- Surgical resection
- Radiation therapy
- Chemotherapy and targeted therapies

Host Immune system

Activated T cell

Immune-based therapies

Tumour Cell

Target
Role of the Immune System in Cancer

**Elimination**
Cancer immunosurveillance

Innate and adaptive immune cells recognize transformed cells and eliminate them

**Equilibrium**
Cancer dormancy

Adaptive immune cells prevent tumor outgrowth

**Escape**
Cancer progression

Tumors cells suppress, disrupt, or “escape” the immune system

- CD8\(^+\) T cell
- CD4\(^+\) T cell
- NK cell
- Tumor cells
- Normal cells
- Treg
T-cell Checkpoint Regulation

- T-cell responses are regulated through a complex balance of inhibitory (“checkpoint”) and activating signals.
- Tumours can dysregulate these pathways and consequently, the immune response.
- Targeting these pathways is an evolving approach to cancer therapy.

### Activating receptors
- CD28
- OX40
- CD137

### Inhibitory receptors
- CTLA-4
- PD-1
- TIM-3
- LAG-3

### Agonistic antibodies
- CD28
- OX40

### Antagonistic (blocking) antibodies

Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies

**Primming Phase Periphery**

CTLA-4 pathway blockade

- Dendritic cell
  - B7
  - CD28
  - MHC
  - Anti-CTLA-4

- T cell
  - + + +
  - TCR

**T-cell activation**

(cytokines, lysis, proliferation, migration to tumour)

**Effector Phase**

PD-1 pathway blockade

- T cell
  - + + +
  - MHC
  - TCR

- Tumour cell
  - + + +
  - MHC
  - TCR

- PD-1
  - PD-L1
  - PD-L2
  - Anti-PD-1/PD-L1
  - Anti-PD-1

CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.

Classes of Checkpoint Inhibitors

- Anti CTLA-4
- Anti PD-L1
- Anti PD-1
Review Current and Future Clinical Utility of Checkpoint Inhibitors in NSCLC
Overall Survival Pembrolizumab vs Platinum Based Chemotherapy in 1° line in Advanced NSCLC

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>NR</td>
<td>0.60 (0.41-0.89)</td>
</tr>
<tr>
<td>Chemo</td>
<td>64</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab
Overall Survival with Pembrolizumab vs. Docetaxel for PD-L1-Positive NSCLC Patients: Phase II/III, Randomized Study

PD-L1 TPS ≥50%

PD-L1 TPS ≥1%

<table>
<thead>
<tr>
<th></th>
<th>Pembrol. 2 mg/kg</th>
<th>Pembrol. 10 mg/kg</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, (95% CI)</td>
<td>14.9 (10.4-NR)</td>
<td>17.3 (11.8-NR)</td>
<td>8.2 (6.4-10.7)</td>
</tr>
</tbody>
</table>

HR = 0.54 for 2 mg/kg dose; \( P = 0.0002 \)
HR = 0.50 for 10 mg/kg dose; \( P < 0.0001 \)

<table>
<thead>
<tr>
<th></th>
<th>Pembrol. 2 mg/kg</th>
<th>Pembrol. 10 mg/kg</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, (95% CI)</td>
<td>10.4 (9.4-11.9)</td>
<td>12.7 (10.0-17.3)</td>
<td>8.5 (7.5-9.8)</td>
</tr>
</tbody>
</table>

HR = 0.71 for 2 mg/kg dose; \( P = 0.0008 \)
HR = 0.61 for 10 mg/kg dose; \( P < 0.0001 \)

Overall Survival with Nivolumab vs. Docetaxel for Pretreated Squamous NSCLC Patients: Phase III, Randomized Study

### CheckMate 017 (SQ NSCLC)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 135)</th>
<th>Docetaxel (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>110 (81)</td>
<td>128 (93)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>9.2 (7.3, 12.6)</td>
<td>6.0 (5.1, 7.3)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.62 (0.47, 0.80)</td>
<td></td>
</tr>
</tbody>
</table>

- 1-y OS rate = 42%
- 2-y OS rate = 23%
- 1-y OS rate = 24%
- 2-y OS rate = 8%

No. of patients at risk:
- Nivolumab: 135, 113, 86, 69, 57, 51, 38, 34, 29, 19, 14, 7, 1, 0
- Docetaxel: 137, 104, 69, 46, 33, 22, 17, 14, 11, 9, 6, 4, 1, 0

Barlesi et al, Poster ESMO 2016
Overall Survival with Nivolumab vs. Docetaxel for Pretreated Non-squamous NSCLC Patients: Phase III Randomized Study

CheckMate 057 (non-SQ NSCLC)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>228 (78)</td>
<td>247 (85)</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>12.2 (9.7, 15.1)</td>
<td>9.5 (8.1, 10.7)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.75 (0.63, 0.91)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nivolumab 292</td>
</tr>
<tr>
<td>2</td>
<td>Nivolumab 233</td>
</tr>
<tr>
<td>3</td>
<td>Nivolumab 194</td>
</tr>
<tr>
<td>4</td>
<td>Nivolumab 171</td>
</tr>
<tr>
<td>5</td>
<td>Nivolumab 148</td>
</tr>
<tr>
<td>6</td>
<td>Nivolumab 128</td>
</tr>
<tr>
<td>7</td>
<td>Nivolumab 112</td>
</tr>
<tr>
<td>8</td>
<td>Nivolumab 97</td>
</tr>
<tr>
<td>9</td>
<td>Nivolumab 81</td>
</tr>
<tr>
<td>10</td>
<td>Nivolumab 46</td>
</tr>
<tr>
<td>11</td>
<td>Nivolumab 18</td>
</tr>
<tr>
<td>12</td>
<td>Nivolumab 6</td>
</tr>
<tr>
<td>13</td>
<td>Nivolumab 0</td>
</tr>
<tr>
<td>14</td>
<td>Nivolumab 0</td>
</tr>
</tbody>
</table>

Barlesi et al, Poster ESMO 2016

\(^a\)Data on file
OVERALL SURVIVAL WITH 2ND LINE ATEZOLIZUMAB IN NSCLC

Overall Survival (%)

No. at Risk

Atezolizumab 425 407 382 363 342 326 305 279 260 248 234 223 218 205 198 188 175 163 157 141 116 74 54 41 28 15 4 1
Docetaxel 425 390 365 336 311 286 263 236 219 195 179 168 151 140 132 123 116 104 98 90 70 51 37 28 16 6 3

12-mo OS 55%
18-mo OS 40%
27%

Stratified HR.

Barlesi et al, Atezolizumab Phase III OAK Study.
I-O agents have a unique MoA, offering the opportunity for combination with other agents.
Combination Therapies: A Promising Strategy

Hypothetical slide illustrating a scientific concept that is beyond data available so far. These charts are not intended to predict what may actually be observed in clinical studies.

Overall survival results in treatment naïve, BRAF WT advanced melanoma patients after 2 years of follow up

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 72)</th>
<th>IPI (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR</td>
<td>24.8 (10.3–NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.58 (0.31–1.08)*</td>
<td></td>
</tr>
</tbody>
</table>

*Exploratory endpoint
NR = not reached

- 22/37 (60%) of patients randomized to IPI crossed over to receive any systemic therapy at progression

Subsequent therapies: Nivo + Ipi: 33%; Ipi: 33%

Possible Adverse Effects
Systemic Oncology Therapies

**CHEMOTHERAPY**
*Target*: rapidly dividing tumour and normal cells
*Adverse events*: diverse due to non-specific nature of therapy

**TARGETED THERAPIES**
*Target*: specific molecules involved in tumour growth and progression
*Adverse events*: reflect targeted nature

**I-O THERAPIES**
*Target*: immune system
*Adverse events*: unique events can occur as a result of immune-system activity

Different spectrum of adverse events with each type of therapy

Although adverse events may have different etiologies, some adverse events with I-O may present like those with other therapies

Require different management strategies

Anything in the body that can theoretically get inflamed, may be a side effect of checkpoint inhibitor therapy.
Key Considerations on Management of Immune-related Events

- Result from enhanced or excessive immune activity
- Early diagnosis and appropriate management is essential
- Health Care team and Patient education for early recognition
- Multidisciplinary Team approach is required for optimal management
- Systemic high-dose corticosteroids* may be required for severe events
- Can be severe or life-threatening, may involve various organs
- Delayed irAE may occur
- Unless an alternate etiology has been identified, consider all symptoms and signs as potential irAE

*with or without additional immunosuppressive therapy
Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and online Tool at https://www.yervoy.co.uk/
Classes of Checkpoint Inhibitors – Phase III

Anti CTLA-4
- Ipilimumab
- Tremelimumab

Anti PD-1
- Nivolumab
- Pembrolizumab

Anti PD-L1
- Durvalumab
- Atezolizumab
- Avelumab
Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies

CTLA-4 pathway blockade

CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed cell death 1; PD-L1/2 = PD ligand 1/2; TCR = T cell receptor.

# Immune Related Adverse Events with Checkpoint Inhibition

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Phase of study</th>
<th>Most frequent toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 4</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>I, II, III</td>
<td>Gastrointestinal: 15.3-35.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dermatologic: 43.5%</td>
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<td></td>
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<td></td>
<td>Endocrine: 3.9-7.6%</td>
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<td></td>
<td></td>
<td></td>
<td>Hepatic: 2.1-3.8%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1 or PD-L1</td>
<td>I, II, III</td>
<td>Rash: 9-26%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
<td></td>
<td>Pruritus: 8-24%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td></td>
<td></td>
<td>Diarrhea: 8-19%</td>
</tr>
<tr>
<td>Durvalumab</td>
<td></td>
<td></td>
<td>Fatigue: 16-36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumonitis: 1-5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Headache: 7-8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asthenia: 5-10%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dyspnea: 4-7%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Anemia: 2-4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Endocrine: 1.7-8%</td>
</tr>
<tr>
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</tbody>
</table>

# Nivolumab plus ipilimumab in chemotherapy-naïve patients: treatment-related AEs (based on grade 3–4 AEs in ≥3% of patients)

<table>
<thead>
<tr>
<th>Treatment related AE, n (%)</th>
<th>All grades</th>
<th>Grade 3–4</th>
<th>All grades</th>
<th>Grade 3–4</th>
<th>All grades</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with any treatment-related AE</td>
<td>22 (92)</td>
<td>14 (58)</td>
<td>21 (84)</td>
<td>11 (44)</td>
<td>43 (88)</td>
<td>25 (51)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (46)</td>
<td>3 (13)</td>
<td>6 (24)</td>
<td>2 (8)</td>
<td>17 (35)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td>5 (10)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>4 (17)</td>
<td>2 (8)</td>
<td>4 (16)</td>
<td>2 (8)</td>
<td>8 (16)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>AST increased</td>
<td>4 (17)</td>
<td>3 (13)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>5 (10)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>4 (17)</td>
<td>3 (13)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>5 (10)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4 (17)</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>6 (12)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (54)</td>
<td>2 (8)</td>
<td>11 (44)</td>
<td>1 (4)</td>
<td>24 (49)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (21)</td>
<td>1 (4)</td>
<td>7 (28)</td>
<td>1 (4)</td>
<td>12 (25)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>3 (13)</td>
<td>1 (4)</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>6 (12)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>4 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

| Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 25) | | | | | | |
| Total (N = 49) | | | | | | |
| Pts with any treatment-related AE | 21 (84) | 11 (44) | 43 (88) | 25 (51) |
| Diarrhea | 6 (24) | 2 (8) | 17 (35) | 5 (10) |
| Colitis | 4 (16) | 3 (12) | 5 (10) | 4 (8) |
| Lipase increased | 4 (16) | 2 (8) | 8 (16) | 4 (8) |
| AST increased | 1 (4) | 1 (4) | 5 (10) | 4 (8) |
| ALT increased | 1 (4) | 1 (4) | 5 (10) | 4 (8) |
| Pneumonitis | 2 (8) | 1 (4) | 6 (12) | 3 (6) |
| Fatigue | 11 (44) | 1 (4) | 24 (49) | 3 (6) |
| Rash | 7 (28) | 1 (4) | 12 (25) | 2 (4) |
| Amylase increased | 3 (12) | 1 (4) | 6 (12) | 2 (4) |
| Adrenal insufficiency | 2 (8) | 1 (4) | 4 (8) | 2 (4) |
| Lymphopenia | 1 (4) | 1 (4) | 2 (4) | 2 (4) |

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Kinetics of irAEs: Example for Ipilimumab

Kinetics of irAEs: Example for Nivolumab

Time to onset of select treatment-related AEs (any grade; n = 474)

- Skin (n = 155; 33%) 5.0 (0.1–57.0)
- Gastrointestinal (n = 66; 14%) 7.3 (0.1–37.6)
- Hepatic (n = 19; 4%) 7.7 (2.0–38.9)
- Pulmonary (n = 9; 2%) 8.9 (3.6–22.1)
- Endocrine (n = 36; 8%) 10.4 (3.6–46.9)
- Renal (n = 8; 2%) 15.1 (3.9–26.4)

Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs.

Circles represent median; bars signify ranges. The kinetics of AEs presented on the slide are for melanoma but may not reflect the kinetics of AEs in other tumor types.
Educating, Assessing and Caring for Patients Receiving Checkpoint Inhibitors
Stepwise Approach to Using IO Agents in Clinic

• **Medical History**
  • Specific questions on organ function which may be affected by immune related adverse reactions, for example:
    • Shortness of breath on exertion?
    • Rash?
    • Bowel function?
    • Previous history of autoimmune disease?

• **Physical examination**
  • Vital signs (with oximetry when clinically indicated), physical exam, weight, other significant findings

• **Laboratory investigations**
  • CBC, biochemistry, renal function, LFT, TSH, other endocrine function evaluation when appropriate
Stepwise Approach to Using IO Agents in Clinic

1. Patient education*
2. Multidisciplinary team (nurse, pharmacist, emergency, etc)
3. Involve Specialists
   - Gastroenterologist
   - Endocrinologist
   - Dermatologist
   - Pulmonologist
   - Ophthalmologist
   - Etc.

*Patient tools are available
Stepwise Approach to Using IO Agents in Clinic

- Initiate treatment according to prescribing Product Monograph
- Careful ongoing clinical assessment is necessary for early identification of irAEs
- irAEs can be severe or life-threatening if not identified early
- irAEs can occur any time
- Keep in mind that toxicity does not equal response
- Early recognition is key
- Consider all symptoms and signs as potential irAE
- Refer to organ-specific algorithms for the management of irAEs
Stepwise Approach to Using IO Agents in Clinic

If not vigilant, may result in more serious immune-related adverse events

- **Endocrine**
  - Hypothyroidism
  - Hyperthyroidism
  - Adrenal insufficiency
  - Hypophysitis

- **Pulmonary**
  - Pneumonitis
  - Interstitial lung disease
  - Acute interstitial pneumonitis

- **Neurologic**
  - Autoimmune neuropathy
  - Demyelinating Polyneuropathy
  - Guillain-Barre
  - Myasthenia Gravis like syndrome

- **Skin**
  - Dermatitis exfoliative
  - Erythema multiforme
  - Stevens Johnson Syndrome
  - Toxic Epidermal Necrolysis
  - Vitiligo
  - Alopecia

- **Eye**
  - Uveitis
  - Iritis

- **Hepatic**
  - Hepatic, autoimmune

- **Gastointestinal (GI)**
  - Colitis
  - Enterocolitis
  - Necrotizing colitis
  - GI perforation

- **Renal**
  - Nephritis, autoimmune
  - Renal failure
# Stepwise Approach to Using I-O Agents in Clinic

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th>Gastrointestinal</th>
<th>Endocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>New or worsening</td>
<td>Changes in normal bowel habits</td>
<td>Headache</td>
</tr>
<tr>
<td>• Shortness of breath</td>
<td>• Diarrhea</td>
<td>• Fatigue/weakness</td>
</tr>
<tr>
<td>• Dyspnea on exertion</td>
<td>• Blood or mucus in stool</td>
<td>• Severe dehydration</td>
</tr>
<tr>
<td>• Decrease in pulse oximetry</td>
<td>• Constipation</td>
<td>• Behavioural changes</td>
</tr>
<tr>
<td>• Cough</td>
<td>• Stomach pain/cramps</td>
<td>• Electrolyte disturbances</td>
</tr>
<tr>
<td>• Wheezing</td>
<td>• Nausea</td>
<td>• Hypotension</td>
</tr>
<tr>
<td></td>
<td>• Vomiting</td>
<td>• Heart rate and rhythm</td>
</tr>
<tr>
<td></td>
<td>• Weight loss</td>
<td>abnormalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic</th>
<th>Eyes</th>
<th>Constitutional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Liver function test (LFT)</td>
<td>• Inflammation of the tissues of the eye (conjunctivitis, uveitis, iritis, episcleritis)</td>
<td>• Fever</td>
</tr>
<tr>
<td>abnormalities, including</td>
<td>• Visual field defects</td>
<td>• Fatigue</td>
</tr>
<tr>
<td>elevations in AST, ALT, T.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bili</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Jaundice</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin</th>
<th>Neurological</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pruritus</td>
<td>• Sensory neuropathy</td>
<td>• Creatinine abnormalities</td>
</tr>
<tr>
<td>• Rash, peeling</td>
<td>• Motor neuropathy</td>
<td></td>
</tr>
<tr>
<td>• Skin excoriations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stepwise Approach to Using I-O Agents in Clinic

The majority of immune-related AEs are manageable and reversible with drug interruption ± corticosteroid. Steroid taper is generally required over at least one month.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Continue the drug?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (gr 1)</td>
<td>Monitor closely</td>
<td>Continue (except for pneumonitis consider delay)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Symptomatic management, Monitor closely, Oral corticosteroids if persistent toxicity</td>
<td>Delay the dose, Resume IO drug when AEs resolve to grade ≤ 1 or baseline</td>
</tr>
<tr>
<td>High (gr 3-4)</td>
<td>Administer high dose IV Corticosteroids, Symptomatic management, Monitor closely, Involve specialist consultant*</td>
<td>Discontinue I-O Drug permanently (Delay in some situations)</td>
</tr>
</tbody>
</table>

*In the event of grade 3 or 4 toxicity for practitioners in non-tertiary centres, consult with an oncologist or consider transfer to a tertiary centre.
Stepwise Approach to Using I-O Agents in Clinic

Re-challenging with Immune Checkpoint Inhibitors after irAEs:

- irAEs can be re-challenged with immune checkpoint inhibitors once ≤ grade 1
- irAEs should NOT be re-challenged in grade 3-4 with the exception of some situations (e.g., skin, perhaps diarrhea)
General Management Guidelines for irAEs

**Signs and Symptoms Present**

- **Rule out alternative etiologies**

  - **No**
  - **Yes**

**Determine severity using NCI CTCAE grading scale**

- **Grade 1**
  - Manage with symptomatic therapy

- **Any grade 2 or grade 3 skin toxicities**
  - Administer oral steroid therapy* Consider consulting organ-specific consultant

- **Grade 3 non-skin toxicity or any grade 4 toxicity**
  - Treat with high-dose steroid therapy* Consult organ-specific consultant

**Adverse Event Management**

- **ContINUE**
  - If no improvement to ≤ grade 1 after 1 week, manage as high-grade event

- **SUSPEND**
  - If no improvement

- **DISCONTINUE**

**I-O Therapy**

- Improve to ≤ grade 1

---

* e.g. prednisone 1 mg/kg daily, methylprednisolone 2 mg/kg IV or equivalent. Depending on the dose and length of time, if symptoms improve, gradually taper over a minimum of 4 weeks.
Role of the Pharmacist in AE Management

Pharmacists, as members of the interdisciplinary team, can:

• Counsel patients on AE management and provide education on early recognition and reporting of AEs

• Pharmacists can start a call back program to call patients at a scheduled time after treatment to go over education topics previously discussed to reinforce education

• Pharmacists can work with physicians on drug information questions regarding treatment options for AE management

• Pharmacists can counsel on corticosteroid side effects management and how to take corticosteroids properly

• Pharmacists can provide information on steroid tapers, conversions and drug information on immunosuppressants such as infliximab, mycophenolate mofetil
Role of the Nurse in AE Management

• Baseline assessment of symptoms

• Patient teaching about side effects:
  – Review of key side effects (Patient Brochure)
  – Importance of early recognition and reporting of side effects. Ensure patient has contact numbers to report side effects (Wallet Card)

• Ongoing assessment while on treatment (acute side effects) and post-treatment (possible late side effects)

• Provide support when experiencing side effects
  – Ways to minimize or manage symptoms
Organ Specific Immune-related Adverse Events
Organ Specific Immune-related Adverse Events

**Incidence**
- All grades: 10-25%
- Grades 3-4: 1-5%

**Symptoms**
- Diarrhea
- Stomach pain
- Nausea/vomiting/pain
- Blood in stool
- Constipation
- Abdominal cramping

**Assessment**
- Number of BM/day – at baseline and change during follow-up
- Presence of watery diarrhea
- Blood or mucus in stool

**Management**
- Most cases respond to symptomatic treatment (e.g., loperamide, hydration) or high-dose steroids with a long taper (over a month)
- Infliximab 5 mg/kg IV is used in steroid-refractory cases
- Consider GI consultation in patients with moderate to severe symptoms
- In patients symptomatic for enterocolitis, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms
- Prophylactic antibiotic for opportunistic infections

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events
## Organ Specific Immune-related Adverse Events

**Incidence***

- All grades: 7-25%
- Grades 3-4: 1<1%

Most cases are grade 1-2

**Symptoms / Assessment**

- Itchiness
- Redness
- Presence of rash or pruritus
- Peeling
- Skin excoriations

**Management**

Most cases are grade 1/2 and treatable with:

- Symptomatic therapy (e.g., antihistamines), and
- Topical therapy (e.g., moisturizing creams and topical steroids)
- Generally reversible
- Important to evaluate and identify alternative etiologies not attributable to I-O therapy (e.g., viral/bacterial infection)
- Do not administer I-O therapy if moderate-to-severe rash is present
- Prophylactic antibiotic for opportunistic infections
- Dermatologic consultation
- A good history should be taken to rule out other causes of skin issues and treat according to the toxicity grade

*I-O monotherapy (nembrilizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events
## Organ Specific Immune-related Adverse Events

### Incidence*
- All grades: 6.4-7.1%
- Grades 3-4: 1.6-2.6%

### Symptoms
- Jaundice
- Tiredness
- Nausea, vomiting
- Abdominal pain

### Assessment
- Liver function tests before each dose of I-O agents

### Management
- Delay I-O therapy if grade 2, discontinue if grade 3-4
- Increase frequency of monitoring
- Consider IV steroids if grade 3-4
- Add prophylactic antibiotics for opportunistic infections
- Consult gastroenterologist

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)*

If not vigilant, may result in more serious immune-related adverse events
# Organ Specific Immune-related Adverse Events

| Incidence* | • All grades: 10.9-14.4%  
|            | • Grades 3-4: 0.6-2.3% |
| Symptoms   | • Headaches  
|            | • Visual changes  
|            | • Fever  
|            | • Fatigue/weakness  
|            | • Mental status changes, confusion  
|            | • Hypotension  
|            | • Abdominal pain and/or unusual bowel habits |
| Assessment | • Monitor patients for signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism |
| Management | • Delay I-O therapy if grade 2, discontinue if grade 3-4**  
|            | • Consider IV steroids if grade 3-4  
|            | • Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms.  
|            | • Prophylactic antibiotic for opportunistic infections  
|            | • Consider endocrinologist consultation. Management using pharmaceutical thyroid products may be required. |

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

**Grade 3 neuroendocrine toxicity may not be reason to discontinue immunotherapy (if easily controlled by replacement steroids, a long course of replacement steroids will likely be needed (maybe permanent), but taper to maintenance levels and retreatment might be possible.

If not vigilant, may result in more serious immune-related adverse events.
## Organ Specific Immune-related Adverse Events

| Incidence* | • All grades: 2%  
  • Grades 3-4: <1% |
|---|---|
| Risk factors | • No underlying factor identified to date  
  • No apparent relationship to tumor type |
| Symptoms | • Cough, SOB/Dyspnea (rest or exertion), fever  
  • Asymptomatic radiographic changes |
| Assessment | • Pulse oximetry (rest and exertion)  
  • CXR and/or CT |
| Management | • Delay I-O therapy dosing  
  • Corticosteroids (IV or oral equivalent)  
  • → if not improving in 48 hrs or worsening, add immunosuppressants (e.g., infliximab, cyclophosphamide, IVIG, mycophenolate mofetil)  
  • Consider bronchoscopy, lung biopsy  
  • Prophylactic antibiotic for opportunistic infections  
  • Consider pulmonary and infectious disease consults |

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events.
Organ Specific Immune-related Adverse Events

**Incidence**
- < 1% of subjects treated with nivolumab or pembrolizumab monotherapy have experienced a related SAE of acute renal failure
- Case reports of renal dysfunction associated with ipilimumab have also been reported

**Onset**
- Most commonly present with elevations in serum creatinine

**Management**
- Steroids generally lead to clinical improvement/resolution
- Prophylactic antibiotic for opportunistic infections
- Consider nephrologist consultation

**Renal biopsy**
- May help distinguish inflammatory versus non-inflammatory etiologies

*1-O monotherapy (pembrolizumab, ipilimumab, nivolumab)
SAE= serious adverse event

If not vigilant, may result in more serious immune-related adverse events
irAE Summary

• Most of the immune-associated AEs are manageable with early recognition and treatment
  – Sometimes can be serious and potentially fatal
• Clinicians may not be accustomed to some of these AEs
  – Consider involving multidisciplinary teams for difficult cases
• Remain vigilant throughout and after treatment
  – Educate and encourage patients to monitor for and report symptoms of immune-associated AEs
• Some patients may have to discontinue treatment; follow management guidelines for immune-associated AEs to give patients the best chance of therapeutic success
Take Home Messages

- Checkpoint Inhibitors can result in autoimmune related adverse effects manifesting in ANY system
- Timing of onset may be delayed, including weeks-months AFTER drug has been discontinued
- Patient education is critical to ensure they inform the oncology team AND can advocate for themselves in non-oncology health care settings
Questions???