Consequences of immune activation: Management of common immune-related adverse events in Check Point Inhibition

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Objectives

- Case
- Define Immune related Adverse Event
- Incidence of IrAEs in CTLA-4 and PD-1 blockade
- Management of common IrAEs
- Clinical outcomes associated with immunosuppression
- Clinical outcomes associated with IRAEs
Case

50 yo F PMH thyroidectomy, metastatic clear cell RCC with bulky retroperitoneal and lung involvement

Oncologic History:

• Cytoreductive nephrectomy
• 4 cycles concurrent ipilimumab 1mg/kg and nivolumab 3mg/kg
• 1 cycle nivolumab 3mg/kg
Case

**HPI:**
Presented to ER with 6 days of generalized weakness, dysarthria, dizziness, confusion, isolated cranial nerve 7 palsy. PCP had prescribed steroids and acyclovir for Bells palsy one week ago which she never took.

**Vital Signs/Physical Exam:**

BP 89/69 mmHg | Pulse 95 | Temp(Src) 36.5 °C (Oral) | Resp 20 | SpO2 98% |

**GEN:** Alert, cooperative, lying in bed, conversant, NAD

**EYES:** Pupils equal and reactive. No scleral icterus.

**THROAT:** Oral cavity and pharynx normal, dry MM

**NECK:** Neck supple

**CHEST:** Normal effort. Clear to auscultation, without rales, rhonchi, wheezing or diminished breath sounds.

**CARDIAC:** Rhythm is regular. Normal S1 and S2. No gallop or murmurs.

**ABDOMEN:** Positive bowel sounds. No rebound tenderness, no guarding.

**EXTREMITIES:** Warm and well perfused. No peripheral edema.

**NEUROLOGICAL:** weakness to jaw clench on r>l; CNVII weakness to cheek puff (air leaks) r>l; CN 2-6, 8-12 intact, Motor: 4/5 b/l elbow extension, 4/5 b/l hip flexion, 5/5 knee extension b/l, 5/5 plantar/dorsiflexion b/l; Sensation: intact. Reflexes: 2+ throughout BUE, symmetric. Areflexic in BLE. Toes down-going bilaterally.
Case

CHEMISTRY/ HEMATOLOGY

Na 126, K 4.1, CO2 25, BUN 14, Cr 1.4, Glucose 96
Calcium 10.9, Mg 1.6
WBC 4.4, Hgb 12.2, HCT 0.37, PLT 380
ALT 76, AST 85, Aphos 271, Tbili 0.6, Alb 3.9
Cortisol 0.5
Cosyntropin stim: 0.5→0.4→0.4
ACTH 1.0
FT4 1.4
TSH 0.31

LUMBAR PUNCTURE

Nucleated WBCs 159
Lymphocytes 73
Protein 206
Glucose 73
Gram stain: no organisms, no WBC
HSV, VZV, EBV negative
Cytology negative
CSF flow cytometry: limited analysis, predominately T cells, no monoclonal B cell population
Clinical Development of CTLA-4 Blockade in Solid Tumors

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Molecule</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Fully human IgG1</td>
<td>Approved: advanced melanoma Phase III (melanoma, NSCLC, SCLC, CRPC, GBM, RCC)</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>Fully human IgG2</td>
<td>Phase III (HNSCC, NSCLC)</td>
</tr>
</tbody>
</table>
Clinical Development of Anti-PD-1 Inhibitors

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Molecule</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Fully human IgG4 PD-1</td>
<td>Approved (US): advanced melanoma, NSCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III (NSCLC, melanoma, RCC, HNSCC, GBM, gastric, bladder, MSI colorectal)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Fully human IgG4 PD-1</td>
<td>Approved (US): advanced melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III(HNSCC, NSCLC, melanoma, bladder, gastric/GE)</td>
</tr>
</tbody>
</table>
Immune related Adverse Events (IrAE)

- Adverse events (AEs) arising from immunologic enhancement
- Inflammatory in nature
- T-cell-mediated to self antigens
Immune-related Adverse Events
IrAEs CTLA-4 > PD-1 blockade

<table>
<thead>
<tr>
<th>CTLA-4</th>
<th>PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Negative regulator of T cell activation, serves a “physiologic break”</td>
<td>I. PD-1/PD-L1 interaction directly inhibits apoptosis tumor cell, promotes T effector cell exhaustion</td>
</tr>
<tr>
<td>II. Present on cell surface of CD4+ and CD8+ T lymphocytes</td>
<td>II. PD1 dampens the immune response of activated T cells during long-term antigen exposure</td>
</tr>
<tr>
<td>III. Inhibition <strong>activates</strong> and <strong>proliferates</strong> CD4+ and CD8+ T cells</td>
<td>III. Inhibition <strong>restores an antitumor immune response</strong> and produces tumor responses</td>
</tr>
</tbody>
</table>
Immune related Adverse Events

Preclinical Models:

CTLA-4 -/- mice → hyperproliferation of lymphocytes → diffuse lymphadenopathy → death 3-4 weeks of age due to severe myocarditis and pancreatitis (Tivol)

PD-1 -/- mice showed increased cellularity of both lymphoid and myeloid cells → moderate splenomegaly → normal and healthy life spans (Nishimura)


## CTLA-4 Blockade IrAEs

### Common (> 20%)
- Rash, pruritis
- Diarrhea/colicis

### Occasional (3-20%)
- Hepatitis/ liver enzyme abnormalities
- Endocrinopathies: hypophysitis, hypothyroidism, hyperthyroidism

### Rare (< 2%)
- Episcleritis/ uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barre, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia
- Toxic epidermal necrolysis, SJS
- Pneumonitis

Meta-analysis IrAEs in Ipilimumab- Bertrand 2015

Kinetics of IrAEs – CTLA-4 blockade

Skin 2-3 w  
GI/Hepatic 6-7 w  
Endocrine 9 w

# PD-1/PD-L1 Blockade IrAEs

<table>
<thead>
<tr>
<th>Occasional (5-20%)</th>
<th>Rare (&lt; 5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, pruritis, vitiligo</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Diarrhea/ colitis</td>
<td>Anemia</td>
</tr>
<tr>
<td>Hepatitis, liver/pancreatic enzyme abnormalities</td>
<td></td>
</tr>
<tr>
<td>Endocrinopathies: thyroid, adrenal, hypophysitis</td>
<td></td>
</tr>
</tbody>
</table>
Nivolumab IrAE Phase III Melanoma

Diarrhea 8-22% (1%)
Rash 4-26 (0%)
Pruritis 18%
Pneumonitis 1-5%
Hypothyroidism 4%
Transaminitis 4%

Combined CTLA-4 and PD-1 Blockade Toxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N = 313)</th>
<th>Nivolumab plus ipilimumab (N = 131)</th>
<th>Ipilimumab (N = 311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>311 (99.4)</td>
<td>316 (95.5)</td>
<td>312 (99.7)</td>
</tr>
<tr>
<td>Treatment-related adverse event</td>
<td>257 (82.1)</td>
<td>33 (16.3)</td>
<td>209 (66.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (19.2)</td>
<td>7 (2.2)</td>
<td>138 (44.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>107 (34.7)</td>
<td>4 (1.3)</td>
<td>110 (35.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>59 (18.8)</td>
<td>0</td>
<td>104 (33.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>81 (25.9)</td>
<td>2 (0.6)</td>
<td>126 (40.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (13.1)</td>
<td>0</td>
<td>81 (25.9)</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>18 (5.8)</td>
<td>0</td>
<td>58 (18.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34 (10.9)</td>
<td>0</td>
<td>56 (17.9)</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase level</td>
<td>12 (3.8)</td>
<td>4 (1.3)</td>
<td>55 (17.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (6.4)</td>
<td>1 (0.3)</td>
<td>48 (15.3)</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase level</td>
<td>12 (3.8)</td>
<td>3 (1.0)</td>
<td>48 (15.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>27 (8.6)</td>
<td>0</td>
<td>47 (15.0)</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (1.3)</td>
<td>2 (0.6)</td>
<td>37 (11.8)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>24 (7.7)</td>
<td>0</td>
<td>33 (10.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (7.3)</td>
<td>0</td>
<td>32 (10.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (4.5)</td>
<td>1 (0.3)</td>
<td>32 (10.2)</td>
</tr>
<tr>
<td>Treatment-related adverse event</td>
<td>24 (7.7)</td>
<td>16 (5.1)</td>
<td>114 (36.4)</td>
</tr>
</tbody>
</table>

* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

# Grading IrAE

## Common Terminology Criteria for Adverse Events v4.0

### Table 2

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Alternate Description*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild (apply event-specific NCI CTCAE grading criteria)</td>
<td>Transient or mild discomfort (&lt; 48 hours); no interference with the subject’s daily activities; no medical intervention/therapy required</td>
</tr>
<tr>
<td>2</td>
<td>Moderate (apply event-specific NCI CTCAE grading criteria)</td>
<td>Mild to moderate interference with the subject’s daily activities; no or minimal medical intervention/therapy required</td>
</tr>
<tr>
<td>3</td>
<td>Severe (apply event-specific NCI CTCAE grading criteria)</td>
<td>Considerable interference with the subject’s daily activities; medical intervention/therapy required; hospitalization possible</td>
</tr>
<tr>
<td>4</td>
<td>Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)</td>
<td>Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable</td>
</tr>
<tr>
<td>5</td>
<td>Death related to AE</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE.

* Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.
Rash/ pruritis

- Rash and pruritus
- Discrete, erythematous, minimally scaly, pruritic papules that can coalesce into thin plaques, most often involving the trunk and extremities
- Face and head, palms and soles usually spared

Vitiligo

- Incidence 3-4%
- Improved PFS (p< .005), OS (P< .003)

Algorithm for skin irAE management

**irAE skin management algorithm**

**Baseline:** consider prophylactic initiation of emollients or moisturizers

**Signs/symptoms:**
- Erythematous and/or maculopapular rash (10-30% BSA)
- Dry skin
- Pruritus, localized or diffuse intermittent
- Vitiligo (no intervention indicated)

**Mild (grade 1):**
- Moisturizers
- Topical interventions
- Monitor
- Continue ipilimumab

**Moderate (grade 2):**
- Topical steroids
- Antihistamines or other antipruritic agents
- Persistent symptoms after 1-2 weeks, consider course of oral steroids
- Consider dermatology consult if persists
- Continue ipilimumab (if improved/resolved)

**Severe (grade 3 or 4):**
- Systemic steroids, intravenous or oral
- Taper over ≥4 weeks once symptoms controlled
- Consider hospital admission
- Dermatology consult +/- biopsy
- Discontinue ipilimumab*

*If grade 3 rash improves to grade 1 or less, may consider resuming ipilimumab.

Leslie A. Facher et al. The Oncologist 2013;18:733-743
# Diarrhea/Colitis

**IPILIMUMAB**

- **37% diarrhea any grade, 11% grade 3-4**
- **8.0% colitis any grade, 4.9% grade 3-4**

**NIVOLUMAB**

- **10-21% diarrhea any grade, 1% grade 3-4**
- **2.2% colitis any grade, 1.8 % grade 3-4**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis</td>
<td>Asymptomatic, clinical or diagnostic observations only; no intervention</td>
<td>Abdominal pain; mucus or blood in stool</td>
<td>Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt; 4 stools a day over baseline</td>
<td>Increase 4-6 stools a day over baseline</td>
<td>Increase &gt; 7 stools a day over baseline, incontinence, hospitalization</td>
</tr>
</tbody>
</table>

Life threatening consequences, urgent intervention
Diarrhea/ Colitis

Endoscopic and histologic findings:
Beck and colleagues observed 3 different histologic subtypes:

I. Neutrophilic infiltrate (46%)
II. Lymphocytic infiltrate (15%)
III. Mixed neutrophilic/lymphocytic infiltrate (39%)

Descending colon most commonly involved

Kimberly E. Beck et al. JCO 2006;24:2283-2289
Diarrhea/ Colitis

Kimberly E. Beck et al. JCO 2006;24:2283-2289
Diarrhea/ Colitis

Mild: loperamide, fluids management, consider other etiologies, increase frequency of monitoring, continue treatment

Moderate: supportive care as above → symptoms > 5 days → corticosteroids (prednisone 0.5-1.0 mg/kg daily followed by taper)

Severe (grade 3): supportive care, administer systemic corticosteroids (prednisone 1-2 mg/kg followed by a taper)

Severe (grade 4): hospitalize, systemic steroids 2mg/kg prednisone daily. Taper over 3-6 weeks. Discontinue drug permanently

Treatment withheld for grade 2 and 3 toxicity until grade 0 or 1 achieved
Diarrhea/ Colitis

Consideration of alternative immunosuppressive therapy

1. Persistence of Grade 2 or higher diarrhea after 7 days of steroids
2. Symptoms severe and patient appears clinically ill

Infliximab 5mg/kg every 2 weeks
Endocrine IrAEs

**Hypophysitis:** secondary adrenal insufficiency (low cortisol, low ACTH), secondary hypothyroidism (low T4, low or normal TSH), MRI findings c/w pituitary inflammation

Primary adrenal insufficiency: rare. (low cortisol, high ACTH)

**Primary hypothyroidism:** THS > 10 with or without low FT4, or T3 levels

**Immune-related thyroiditis:** presence of suppressed TSH level with elevated FT4 and or T3 level
Grading of Endocrine events

**Adrenal insufficiency**

- **Grade 1**
  - Asymptomatic; clinical or diagnostic observations only; intervention not indicated

- **Grade 2**
  - Moderate symptoms; medical intervention indicated

- **Grade 3**
  - Severe symptoms; hospitalization indicated

- **Grade 4**
  - Life-threatening consequences; urgent intervention indicated

- **Grade 5**
  - Death

**Hypothyroidism**

- **Grade 1**
  - Asymptomatic; clinical or diagnostic observations only; intervention not indicated

- **Grade 2**
  - Symptomatic; thyroid replacement indicated; limiting instrumental ADL

- **Grade 3**
  - Severe symptoms; limiting self care ADL; hospitalization indicated

- **Grade 4**
  - Life-threatening consequences; urgent intervention indicated

- **Grade 5**
  - Death

**Hyperthyroidism**

- **Grade 1**
  - Asymptomatic; clinical or diagnostic observations only; intervention not indicated

- **Grade 2**
  - Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL

- **Grade 3**
  - Severe symptoms; limiting self care ADL; hospitalization indicated

- **Grade 4**
  - Life-threatening consequences; urgent intervention indicated

- **Grade 5**
  - Death
## CheckMate067 Endocrine Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab 3mg/kg Alone (N=313)</th>
<th>Nivolumab 1mg/kg plus Ipilimumab 3mg/kg (N=313)</th>
<th>Ipilimumab 3mg/kg alone (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Grade 3 or 4</td>
<td>Total Grade 3 or 4</td>
<td>Total Grade 3 or 4</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 (14.4) 2(0.6)</td>
<td>94 (30.0) 15 (4.8)</td>
<td>34 (10.9) 7 (2.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td><strong>27 (8.6)</strong> 0</td>
<td><strong>47 (15.0)</strong> 1 (0.3)</td>
<td>13 (4.2) 0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td><strong>13 (4.2)</strong> 0</td>
<td><strong>31 (9.9)</strong> 3 (1.0)</td>
<td>3 (1.0) 0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>2 (0.6) 1(0.3)</td>
<td><strong>24 (7.7)</strong> 5 (1.6)</td>
<td><strong>12 (3.9)</strong> 6 (1.9)</td>
</tr>
</tbody>
</table>
Hypophysitis

- Inflammation anterior pituitary gland
- Headaches, nausea, vomiting, fatigue, diarrhea, arthralgias, and/or mental status changes
- MRI: enlargement pituitary gland
- Central hypothyroidism, central adrenal insufficiency, hypogonadotrophic hypogonadism
- Growth Hormone, prolactin generally spared
Hypophysitis- management

- Measure TSH, FT4, cortisol, ACTH levels, testosterone, FSH, LH, IGF-1
- Initiate thyroid hormone replacement early
- For symptomatic adrenal crisis methylprednisolone 1-2 mg/kg IV initially followed by prednisone 1-2 mg/kg daily with taper
- Asymptomatic prednisone 1 mg/kg daily
- Consult endocrinology

# Hypothyroidism

<table>
<thead>
<tr>
<th>Primary hypothyroidism</th>
<th>Secondary hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Destructive thyroiditis</td>
<td>Hypophysitis related</td>
</tr>
<tr>
<td>High THS</td>
<td>Low TSH</td>
</tr>
<tr>
<td>Low free T4</td>
<td>Low free T4</td>
</tr>
<tr>
<td></td>
<td>Measure other pituitary hormones</td>
</tr>
</tbody>
</table>
Hyperthyroidism

- Subacute thyroiditis: triphasic clinical course
- Hyperthyroidism \( \rightarrow \) hypothyroidism \( \rightarrow \) normal thyroid function
- Initially TSH low, FT4 high
- + Anti-thyroglobulin antibodies, + anti- TPO antibodies
Hepatitis

- Occurs in 2-9% of cases with ipilimumab, 2-4% PD-1 inhibitors
- Monitor hepatotoxic medications
- Limit alcohol intake
- Screen hepatitis serologies
Hepatitis

Leslie A. Fecher et al. The Oncologist 2013;18:733-743
IrAEs- Honorable mention

- Episcleritis/ uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barre, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia, anemia
- Pneumonitis
- Myocarditis, pericarditis, vasculitis
Grade III/IV IrAEs and Clinical Response

IrAE, Need for Systemic Immunosuppression, and Effects of Survival and Time to Treatment Failure

- Retrospective, metastatic melanoma
- Ipilimumab 3 mg/kg
- 1,133 total doses ipilimumab
IrAE, Need for Systemic Immunosuppression, and Effects of Survival and Time to Treatment Failure

- IrAEs graded retrospectively by a single provider
- CTCAE Version 4.0
- Primary objective: Determine incidence of IrAEs associated with ipilimumab, incidence of systemic immunosuppression to treat IrAEs, association of these factors with OS, TTF

Troy Z. Horvat et al. JCO doi:10.1200/JCO.2015.60.8448
Effects IrAEs and Corticosteroid on OS

254 (85%) any grade
91 (31%) grade 3
20 (7%) grade 4
1 death
Treatment IrAEs

- 103 patients received systemic steroids (35%)
- 78 (grade 3 IrAE), 25 (grade 1/2)
- Diarrhea (50), hepatitis (22), dermatitis (21), endocrinopathies (14), uveitis (1), pneumonitis (1), seizure (1), arthritis (1)
- 31/103 treated with additional immunosuppression
  - 2 received mycophenylate for grade 3/4 hepatotoxicity
  - 29 received infliximab 5 mg/kg for diarrhea
The estimated median OS was 16.5 months (95% CI, 12.6 to 21.1) with an estimated 2-year survival rate of 39% (95% CI, 33% to 46%) (Fig 2A). The estimated median TTF was 5.7 months (95% CI, 5.1 to 6.4) for all patients (Fig 2B).

Troy Z. Horvat et al. JCO doi:10.1200/JCO.2015.60.8448
Landmark of correlates of overall survival (OS) and time to treatment failure (TTF) in patients treated with ipilimumab

Troy Z. Horvat et al. JCO doi:10.1200/JCO.2015.60.8448
Case

Admitted to 9300

Started on Dexamethasone 4 mg q 6 hours

Due to LP results one dose of IVIG was given for concern for GBS

She markedly improved after 24 hours of steroids, transitioned to prednisone 1mg/kg. Discharged with oncology and endocrine follow-up

She is doing well and scans show interval decrease in RP lesions and stable lung lesions

Final diagnosis Grade 3 Hypophysitis and Grade 3 Neurotoxicity
Conclusions

- Immune related adverse events are T-cell mediated inflammatory events
- Early initiation of immunosuppression reverses most IrAEs
- CTLA4 inhibition is more potent than PD1 inhibition
- Combined CTLA4/PD1 inhibition yields greatest toxicity
- Use of glucocorticoids does not affect outcomes
- Grade 3-4 IrAEs may be positive prognostic indicator
Thank You

Fab Five
Dr. DeCastro
Dr. Riedel
Sarah Overaker
Dr. Salama
Dr. Harrison
Dr. Ready
My man friend Luke and my dog