Management of Immune Checkpoint Inhibitor Related Toxicities

A Webinar for
HealthTrust Members
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- The presenter has no financial relationships with any commercial interests pertinent to this presentation.
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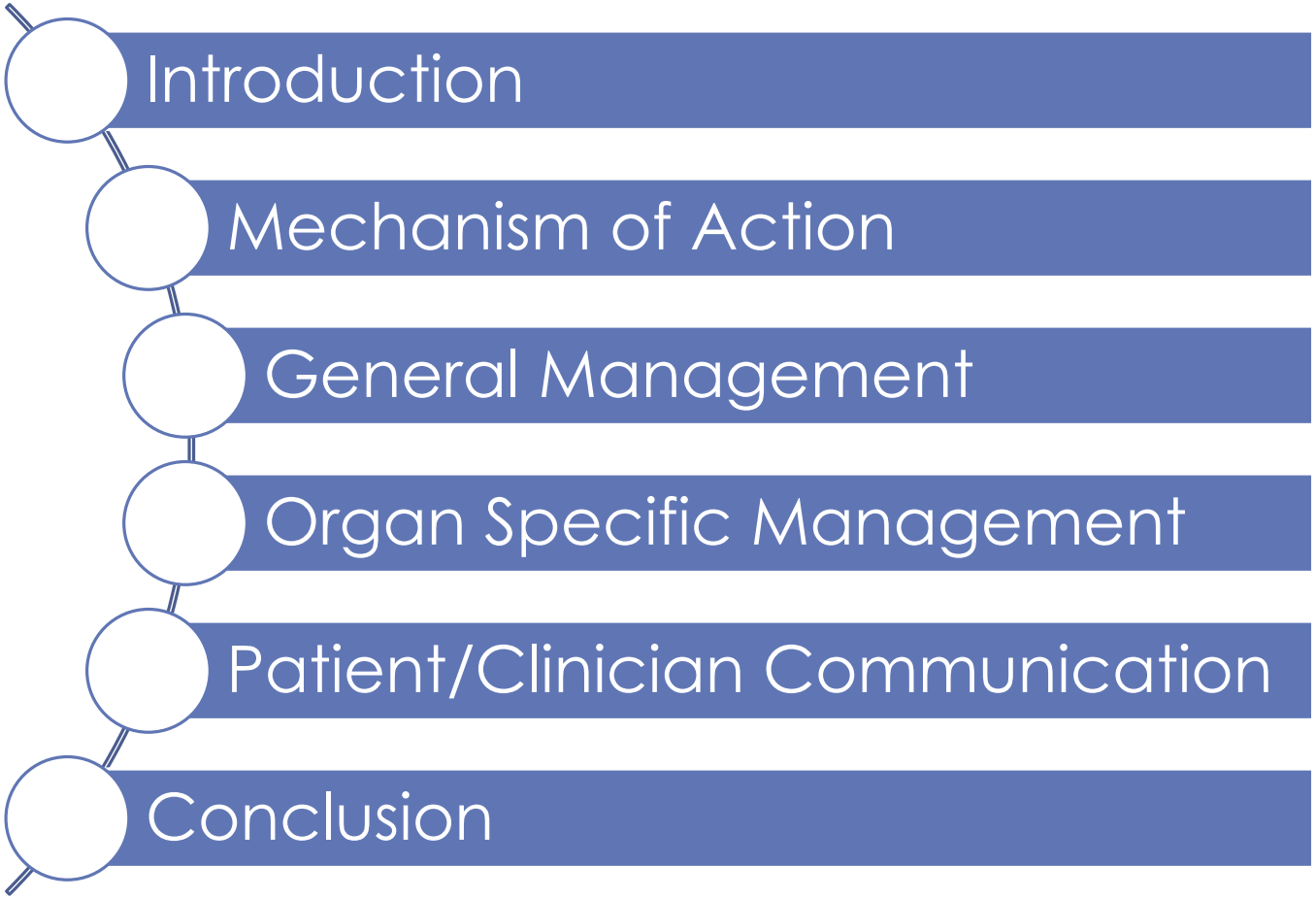
Learning Objectives

- Identify the mechanism of action of immune checkpoint inhibitors (ICPis)
- Discuss the management of the most common ICPi-related toxicities
- Demonstrate the importance of patient and clinical communication prior to and during treatment with ICPis

Overview


Introduction
Mechanism of Action
General Management
Organ Specific Management
Patient/Clinician Communication
Conclusion

Introduction

- Indications for use are expanding rapidly
- Adverse events can affect many different body systems at varying times during treatment
- Patient and clinician education are essential for the safe use of this class of medications

Mechanism of Action

- Checkpoint pathways: part of human immune system that control the immune response
- Can be manipulated to help cancer cells evade cytotoxic T-cell mediated death
  - Turn "off" immune system response to cancer cells
- ICPis prevent receptors and ligands from binding, thereby disrupting signaling
  - Turn "on" immune system response to cancer cells

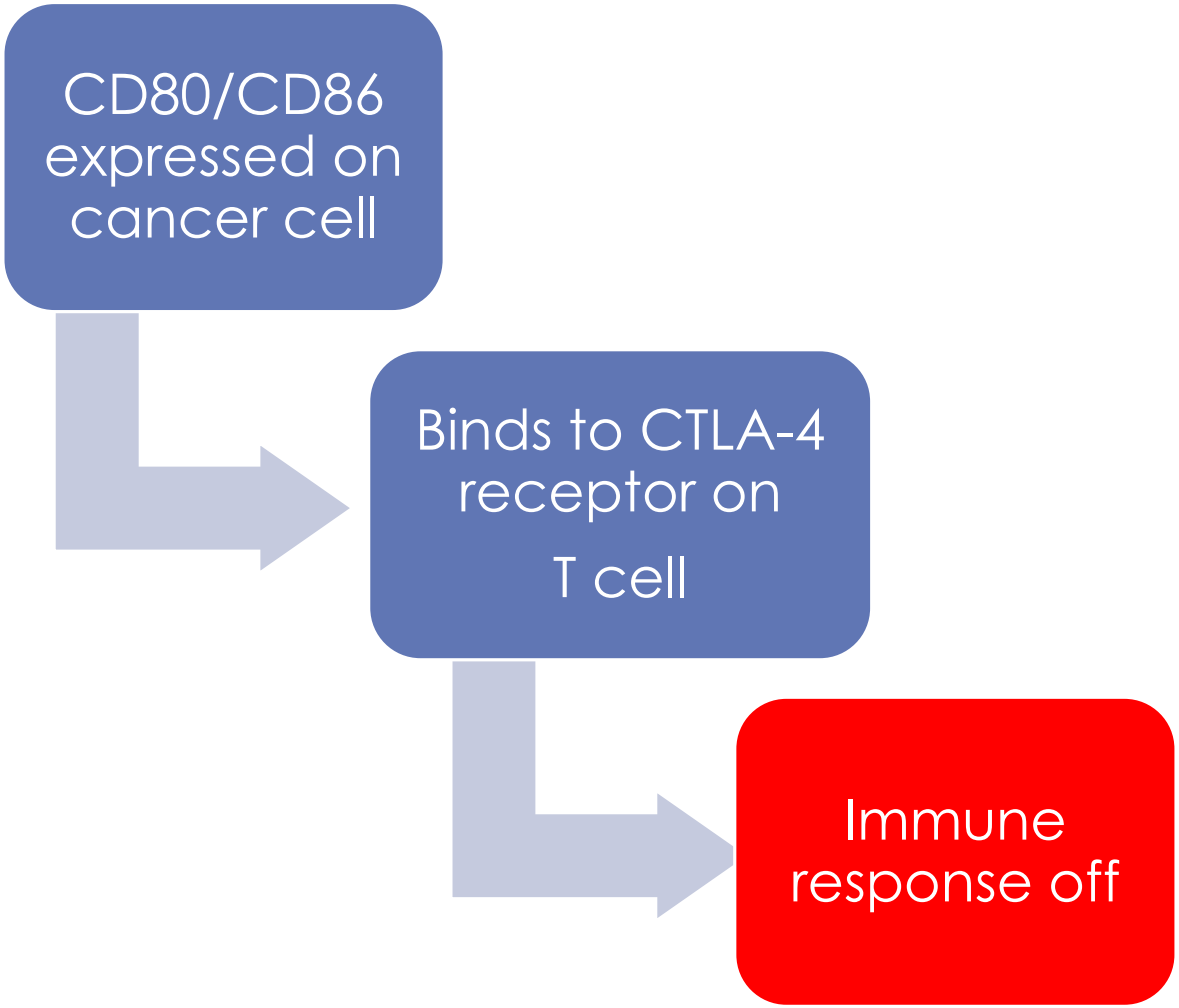
ICPi Targets

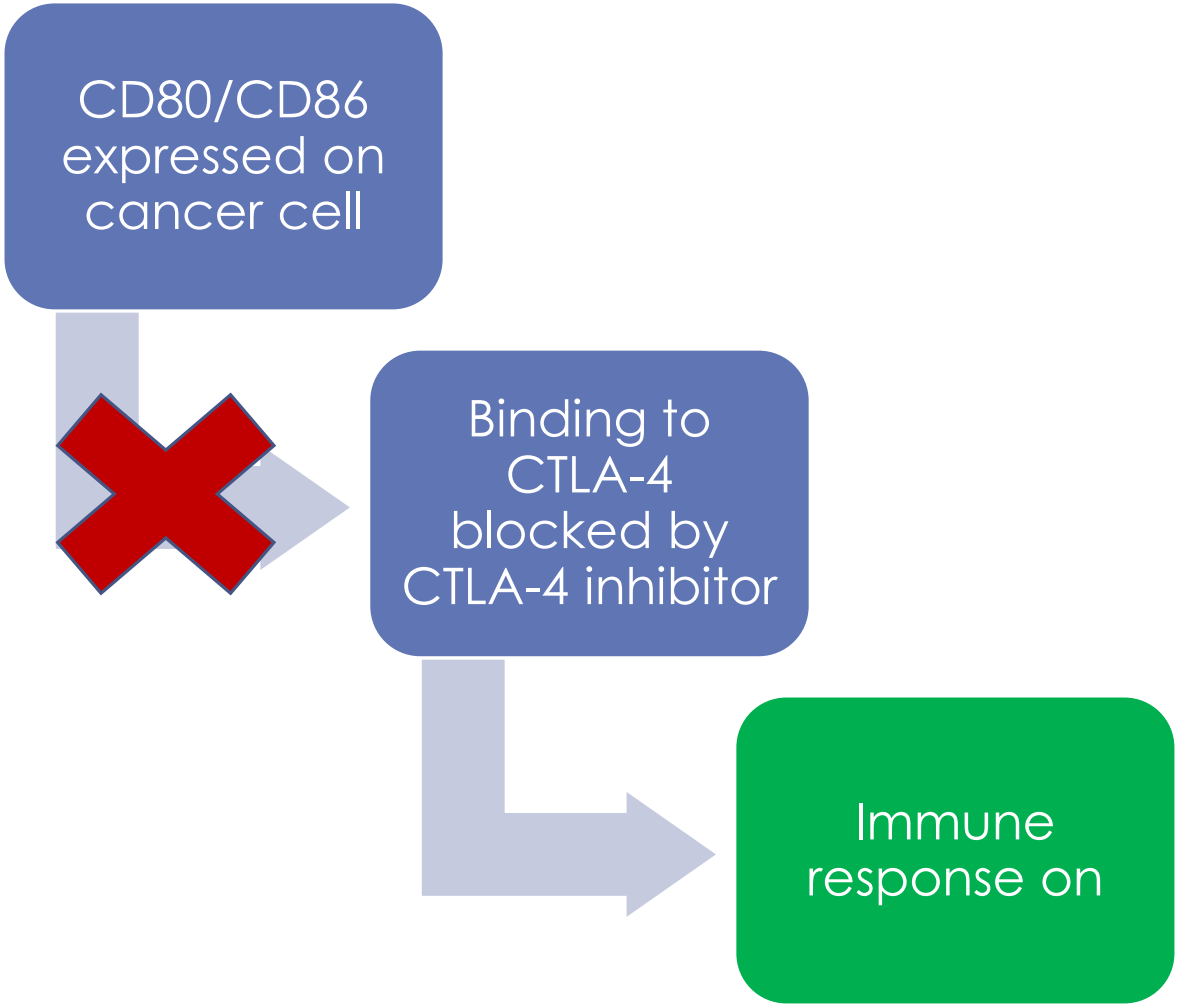
CTLA-4 Pathway

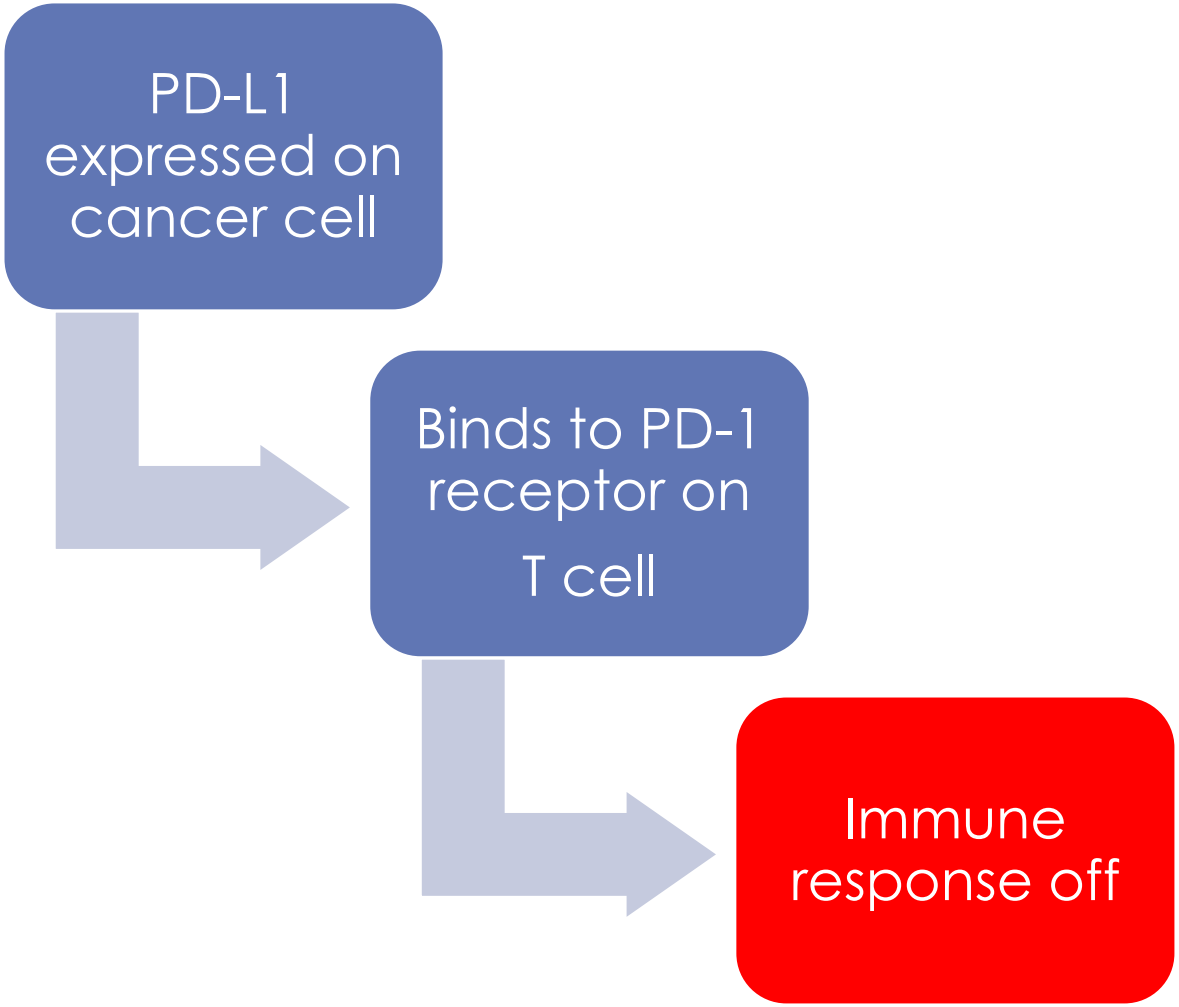
- Cytotoxic T-lymphocyte associated-4 (CTLA-4) receptor on cytotoxic T cells
- Binds to CD80/CD86 ligands on cells

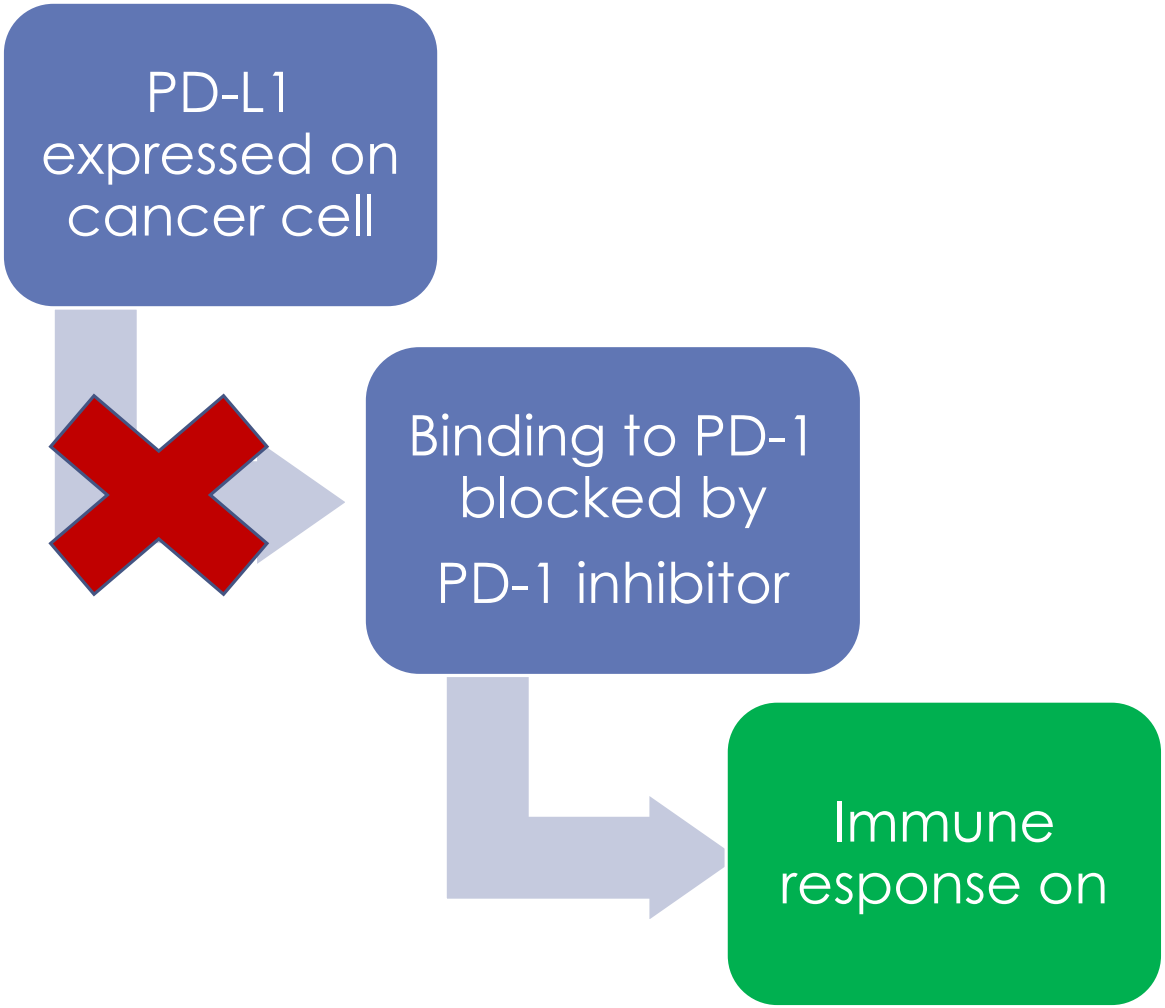
PD-1 Pathway

- Programmed cell death protein 1 (PD-1) receptor on cytotoxic T cells
- Binds to programmed death-ligand 1 (PD-L1) on cells


CD80/CD86 expressed on cancer cell
Binds to CTLA-4 receptor on T cell
Immune response off


CD80/CD86 expressed on cancer cell
Binding to CTLA-4 blocked by CTLA-4 inhibitor
Immune response on


PD-L1 expressed on cancer cell
Binds to PD-1 receptor on T cell
Immune response off


PD-L1 expressed on cancer cell
Binding to PD-1 blocked by
PD-1 inhibitor
Immune response on

Question 1

Which of the following is expressed on T cells and is a target of immune checkpoint inhibitors?

A. CD80
B. CD86
C. PD-1 receptor
D. PDL-1

Question 1- Answer

Which of the following is expressed on T cells and is a target of immune checkpoint inhibitors?

A. CD80
B. CD86
C. **PD-1 receptor**
D. PDL-1

Current FDA-Approved Medications

Generic Name	Brand Name	Target	Indication (s)*
Ipilimumab	Yervoy	CTLA-4	Colorectal, melanoma, renal cell carcinoma
Pembrolizumab	Keytruda	PD-1 receptor	Many
Nivolumab	Opdivo	PD-1 receptor	Many
Atezolizumab	Tecentriq	PD-L1 (ligand)	NSCLC Urothelial carcinoma
Durvalumab	Imfinzi	PD-L1 (ligand)	NSCLC Urothelial carcinoma
Avelumab	Bavencio	PD-L1 (ligand)	Merkel cell carcinoma Urothelial carcinoma
Cemiplimab-rwlc	Libtayo	PD-1 receptor	Cutaneous squamous cell carcinoma

*not an all inclusive list

General Management

- Patient and family caregivers should receive timely and up-to-date education
  - Medication
  - Mechanism of action
  - Possible immune-related adverse events (irAEs)
- Prior to initiating therapy and continuous throughout treatment and beyond
- New symptom onset – suspect the immunotherapy

Immune-related Adverse Events - Onset

Organ	Onset
Skin	Variable
Diarrhea/Colitis	5-10 weeks
Lung	2-24 months (median: 3 months)
Endocrine	Variable, typically ~1-5 months
Hepatic	5-12 weeks

****Estimations only – can occur at any point during and after treatment with an immune checkpoint inhibitor****

General Management

- Immune-related adverse events
  - Graded according to the CTCAE
    - Common Terminology Criteria for Adverse Events (version 5.0)
    - Different criteria for each organ

General Management

Grade 1
- Continue ICPi with close monitoring
- Exceptions: cardiac, hematologic, neurologic

Grade 2
- Consider holding ICPis and resume when toxicity improves to Grade 1 or better

Grade 3
- Hold ICPis and initiate high-dose corticosteroids

Grade 4
- Permanent discontinuation of ICPIs
- Exception: endocrinopathies

General Management

- Key goal: early intervention with corticosteroids
- Close consultation with disease-specific subspecialties encouraged
- Use of corticosteroids to treat irAEs has NOT been shown to reduce anti-tumor activity
- Avoid premedication with corticosteroids when possible
  - Potential mitigation of immunotherapeutic effectiveness in prophylactic setting

Monitoring Parameters

Laboratory Test	Frequency during immunotherapy treatment
CBC with differential	Every 2–3 weeks
Comprehensive metabolic panel	Every 2–3 weeks
TSH and free T4	Every 4–6 weeks
Morning ACTH and cortisol	Every 2–3 weeks

Special Populations

- Autoimmune conditions
- Solid organ transplant
- Prior stem cell transplant

Immune-related Adverse Events

- Skin
- Gastrointestinal
- Lung
- Endocrine

Skin Toxicities

- Many different etiologies
  - Maculopapular rash
  - Pruritis
  - Bullous dermatitis
  - Stevens Johnson Syndrome (SJS)
  - Toxic epidermal necrolysis (TEN)

Skin Toxicities - Rash

Grade 1

- Continue ICPi
- Treat symptomatically
  - Oral antihistamine
  - Topic emollients
  - Moderate potency topical steroids
  - Avoid skin irritants and sun exposure

Skin Toxicities - Rash

Grade 2

- Consider holding ICPi with weekly monitoring
- If not resolved, interrupt treatment until improved to Grade 1
- Treatment
  - Topical emollients, oral antihistamines
- Medium to high potency topical steroids
- Consider adding oral corticosteroid
  - Prednisone (or equivalent)0.5–1mg/kg daily until improved to Grade 1, then taper over at least 4 weeks

Skin Toxicities - Rash

Grade 3

- Hold ICPi
  - Consult dermatology to determine appropriateness of resuming ICPi
- Treatment
  - High potency topical steroids AND
  - Oral corticosteroid
    - Prednisone (or equivalent)0.5–1mg/kg until improved to Grade 1, then taper over at least 4 weeks

Skin Toxicities - Rash

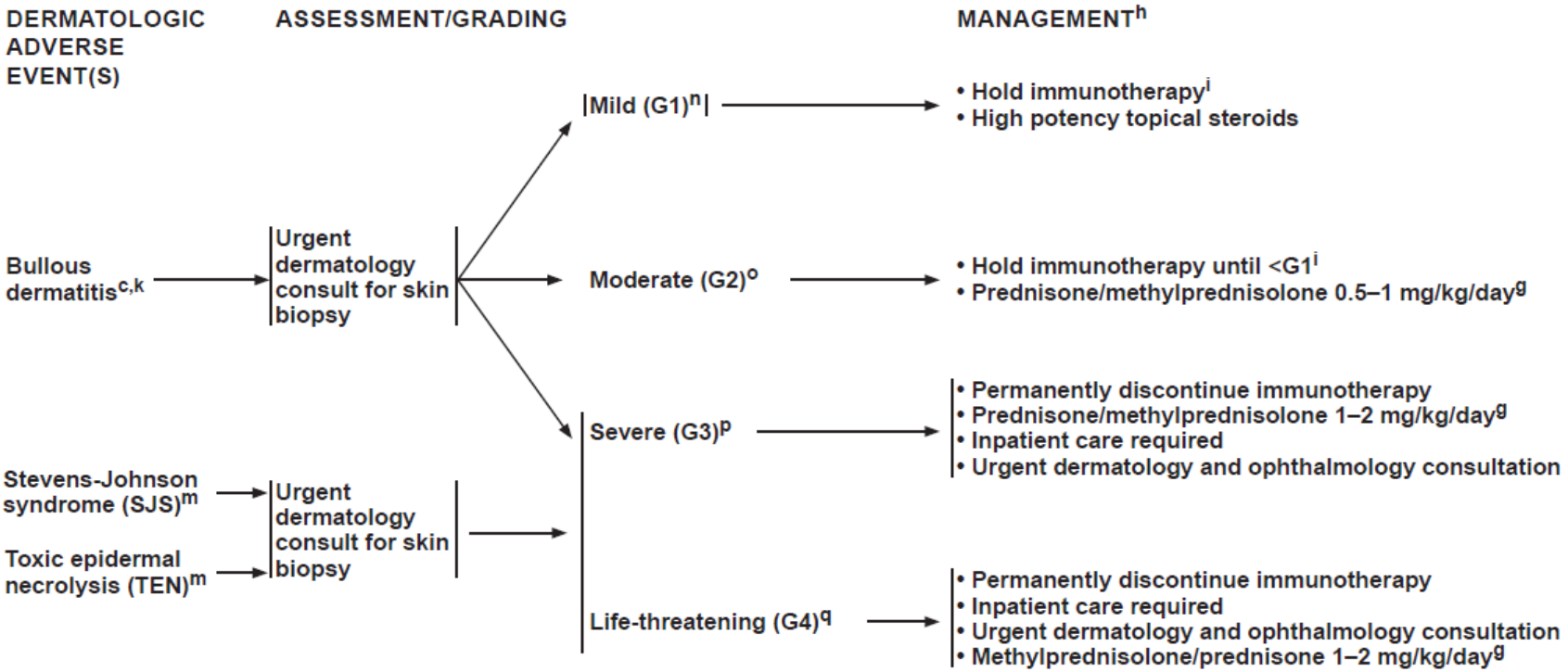
Grade 4

- Hold ICPi
  - Consult dermatology to determine appropriateness of resuming ICPi upon resolution of skin toxicity and steroids reduced to prednisone <10mg
- Admit with direct oncology and dermatology involvement
- Treatment
  - Systemic corticosteroid
    - Methylprednisolone (or equivalent)1–2 mg/kg with slow tapering when toxicity resolves
- Consider alternative neoplastic therapy

Skin Toxicities - Pruritis

Grade 1	Grade 2	Grade 3/4
• Continue ICPi • High potency topical steroids	• Consider holding ICPi until Grade 1 • Oral antihistamines • Dermatology consult	• Hold immunotherapy • Prednisone 0.5–1 mg/kg/day • GABA agonists • Consider aprepitant • Consider omalizumab • Urgent dermatology consult

Skin Toxicities – Blistering Disorders



Diarrhea/Colitis

Diarrhea Grade				
1	2	3	4	5
Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL;	Increase of ≥7 stools per day over baseline; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL;	Life – threatening consequences (eg hemodynamic collapse)	Death

Colitis Grade				
1	2	3	4	5
Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus, peritoneal signs	Life – threatening consequences (eg perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death

GI Toxicities – Diarrhea/Colitis

Grade 1

- Fewer than 4 bowel movements above baseline per day and no colitis symptoms
- Consider holding ICPi
- Treatment
  - Loperamide
  - Hydration
  - Close monitoring

GI Toxicities – Diarrhea/Colitis

- Necessary tests for patients presenting with Grade 2–4
  - Stool evaluation to rule out infectious etiology
    - Culture
    - C. Difficile
    - Ova and parasites
  - Abdominal/pelvic CT with contrast
  - GI consultation

GI Toxicities – Diarrhea/Colitis

Grade 2

- Hold immunotherapy
- Consult gastroenterology
- Systemic corticosteroids: methylprednisolone 1 mg/kg/day with slow taper over 4-6 weeks when toxicity resolves
- No response in 2–3 days
  - Increase to 2mg/kg/day
  - Consider infliximab
  - If infliximab refractory, consider vedolizumab

GI Toxicities – Diarrhea/Colitis

Grade 3

- Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity
- Consider inpatient care
- Systemic corticosteroids: methylprednisolone 1 mg/kg/day with slow taper over 4–6 weeks when toxicity resolves
- No response in 2–3 days
  - Consider infliximab
  - If infliximab refractory, consider vedolizumab

GI Toxicities – Diarrhea/Colitis

Grade 4

- Permanently discontinue immunotherapy
- Consider inpatient care
- Systemic corticosteroids: methylprednisolone 1 mg/kg/day with slow taper over 4–6 weeks when toxicity resolves
- No response in 2–3 days
  - Consider infliximab
  - If infliximab refractory, consider vedolizumab

Question 2

A 65-year old female presents for her next dose of nivolumab (Opdivo). She reports a two-day history of 10 stools per day (usually ~1 BM per day). Which medication should be initiated for the management of diarrhea?

A. Loperamide

B. Methylprednisolone

C. Infliximab

D. Vedolizumab

Question 2 - Answer

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A. Loperamide

B. **Methylprednisolone**

C. Infliximab

D. Vedolizumab

Lung Toxicities – Pneumonitis

Grade 1

- Hold immunotherapy
- Monitor patients weekly with history and physical, with or without a chest xray
- May resume ICPi with radiographic evidence of improvement or resolution
- If no improvement, treat as Grade 2

Lung Toxicities – Pneumonitis

Grade 2

- Hold immunotherapy until resolution to Grade 1 or less
- Consider empiric antibiotics, bronchoscopy with BAL
- Prednisone 1–2 mg/kg/day; slow taper by 5-10mg/week over 4-6 weeks when toxicity resolves
- Monitor every 3–7 days
- If no improvement after 48–72 hours of steroids, treat as Grade 3

Lung Toxicities – Pneumonitis

Grade 3/4

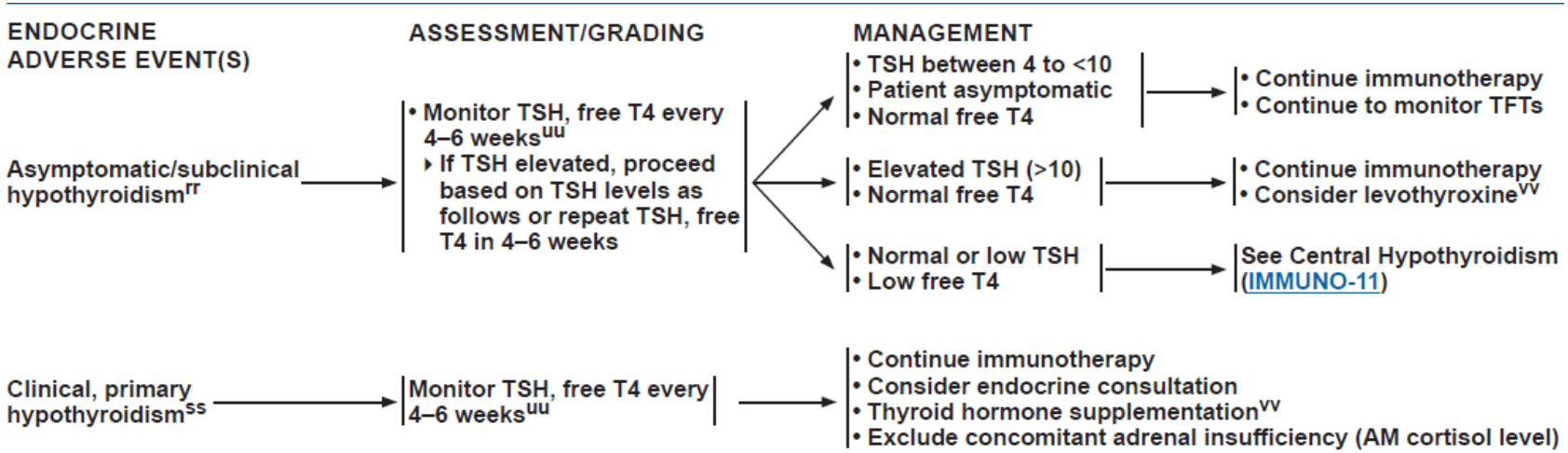
- Permanently discontinue immunotherapy
- Inpatient care
- Consider pulmonary and infectious disease consults
- Bronchoscopy with BAL to rule out infection and malignant lung infiltration
- Consider empiric antibiotics
- Methylprednisolone IV 1–2 mg/kg/day until symptoms improve to Grade 1 or less, then taper over ≥6 weeks
- If no improvement after 48 hours, consider:
  - Infliximab
  - Mycophenolate mofetil
  - Intravenous immunoglobulin

Endocrine Toxicities

Educate patients to inform health care provider immediately if they experience any of the following:

- Headaches that will not go away
- Unusual headache patterns
- Vision changes
- Rapid heartbeat
- Increased sweating
- Extreme tiredness or weakness
- Muscle aches
- Weight gain or weight loss
- Dizziness or fainting
- Feeling more hungry or thirsty than usual
- Hair loss
- Changes in mood or behavior
- Feeling cold
- Constipation
- Voice gets deeper
- Urinating more often than usual
- Nausea or vomiting
- Abdominal pain

Endocrine Toxicities - Hypothyroidism



Thyroid Hormone Supplementation

- Patients without risk factors: full replacement estimated with ideal body weight-based dose = **1.6 mcg/kg/day**
- Elderly, frail, or multiple comorbidities: consider titrating up from low dose, starting at **25–50 mcg/day**

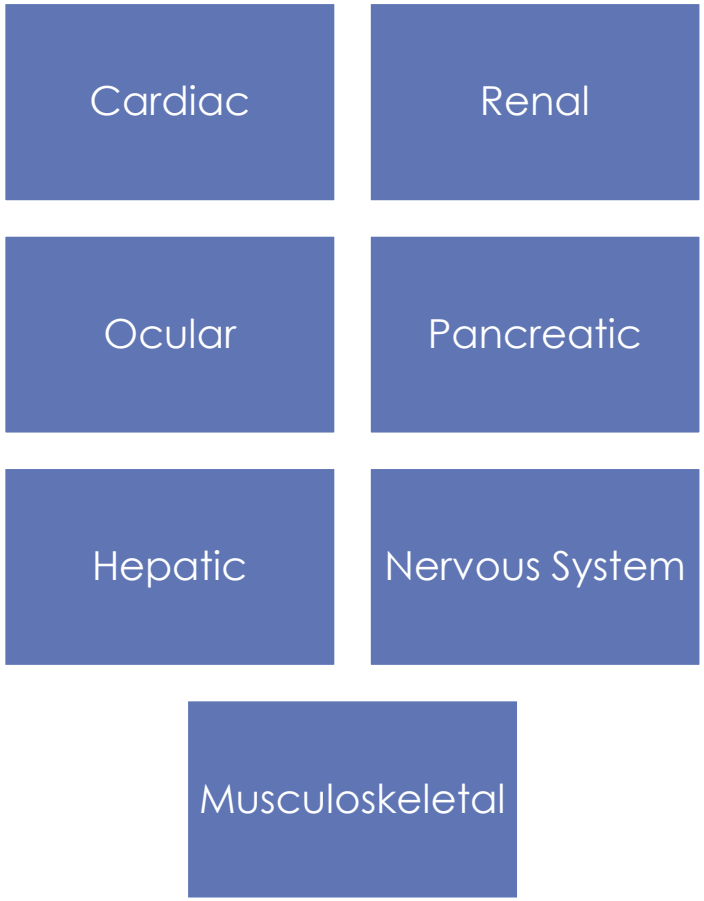
Other Endocrine Toxicities

- Hypophysitis
- Primary Adrenal Insufficiency
- Diabetes
- Hyperthyroidism

Refer to NCCN/ASCO guidelines for management recommendations

Immune-related Adverse Events

- Can occur in many other organs/body systems
- Refer to NCCN/ASCO guidelines for management recommendations



Immunotherapy Rechallenge

- Depending on severity of adverse event and organ system involved
- Use caution when considering restarting immunotherapy after significant iRAE
  - Close follow-up to monitor for recurrent symptoms

Immunotherapy Rechallenge

- In general, resumption of immunotherapy following grade 2 iRAEs can be considered upon resolution to ≤ Grade 1
- See NCCN guidelines for organ-specific considerations

Patient Education Concepts

Immunotherapy Background

- Immune system helps distinguish healthy cells from abnormal cells
- Tumor cells can block the ability of the immune cell to recognize them as foreign
- Immune checkpoint inhibitors prevent tumors from evading the body's natural immune system

Side effects

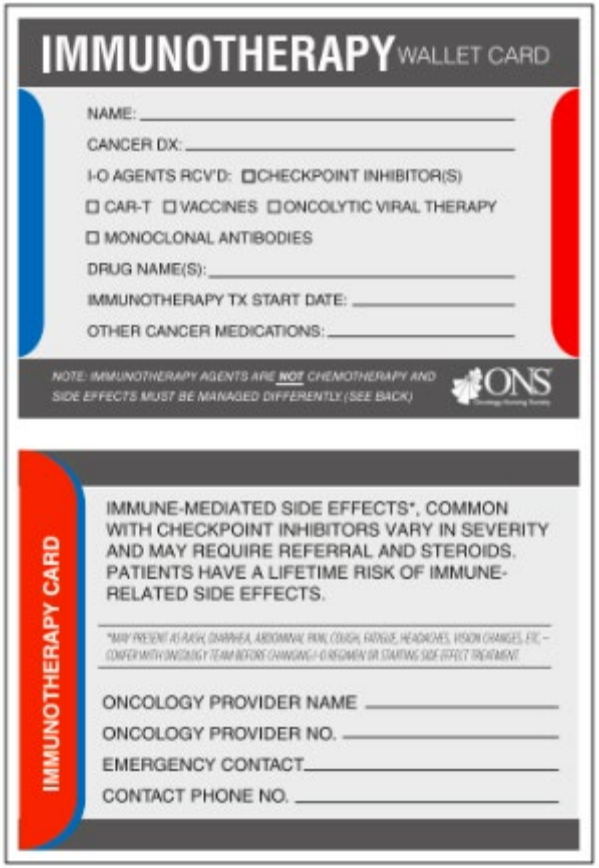
- Immunotherapy side effects differ from other types of cancer treatment
- Can affect one or several different organ systems
- Can occur at any time during or after treatment is completed
- Combination therapy may increase severity of adverse events
- Alert other health care providers about receiving immunotherapy

Monitoring & Treatment Response

- **Managing side effects early** can help with treating them effectively
  - Communication between patient/family and treatment center is essential
- Symptoms that may be considered unrelated (diarrhea) are often signs of immune checkpoint inhibitor side effects
- Regular monitoring will be done to assess treatment response
- May take longer to see a response

Patient Education Tools

- Every visit: ask about new symptoms or changes in health
- Questionnaires or standardized assessments
- Wallet cards with symptoms to watch for and how to reach health care provider



Question 3

A patient is planning to start pembrolizumab and will be educated on this medication prior to initiation. Which of the following are important counseling points for a patient beginning treatment with immunotherapy?

A. Adverse effects can occur in many organs and at any time during treatment
B. Immune checkpoint inhibitors are tolerated better than standard chemotherapy
C. Be sure to inform your oncology care team of new symptoms or changes to your health
D. All of the above
E. A and C

Question 3 - Answer

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C. Be sure to inform your oncology care team of new symptoms or changes to your health
D. All of the above
E. **A and C**

Conclusion

- Immune checkpoint inhibitor use is growing, with more medications and indications being studied
- Patients should be monitored closely for adverse events and treated according to published guidelines
- Patient and clinician education are essential for the safe use of this class of medications

References

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Q&A

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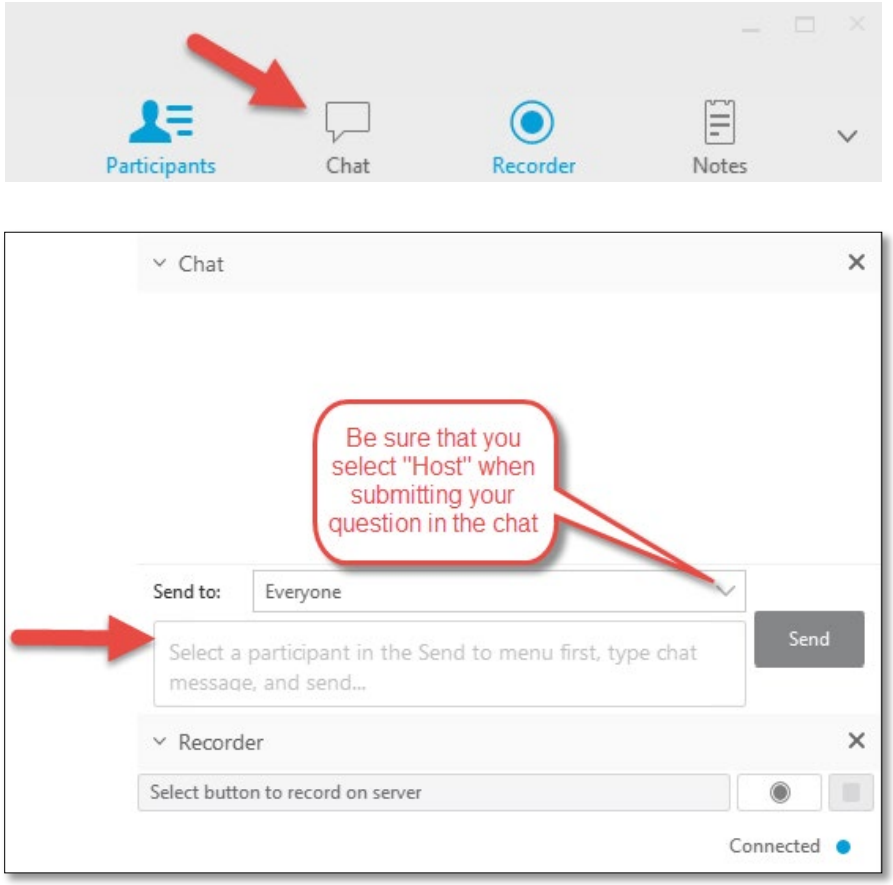

Thank you!

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