Immunotherapy Related Adverse Reactions

Helen Shih, NP, MPH
Thoracic Oncology
UCSF Helen Diller
Comprehensive Cancer Center

Disclosures

- Takeda- Speaker’s Bureau
- Merck- Speaker’s Bureau
- Astra Zeneca- Speaker’s Bureau

Immune-Related Adverse Events with PD-1/PD-L1 Therapy

Selected Adverse Events

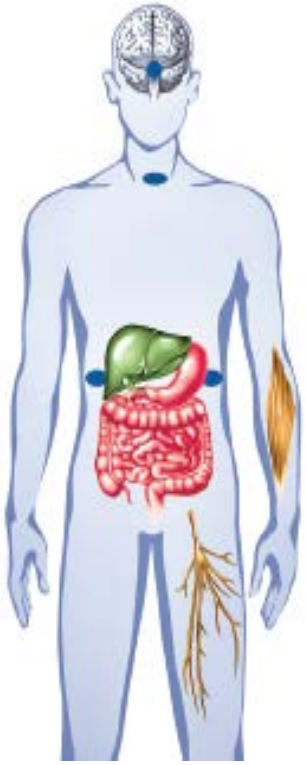
Hypophysitis

Thyroiditis

Adrenal Insufficiency

Enterocolitis

Dermatitis



Pneumonitis

Hepatitis

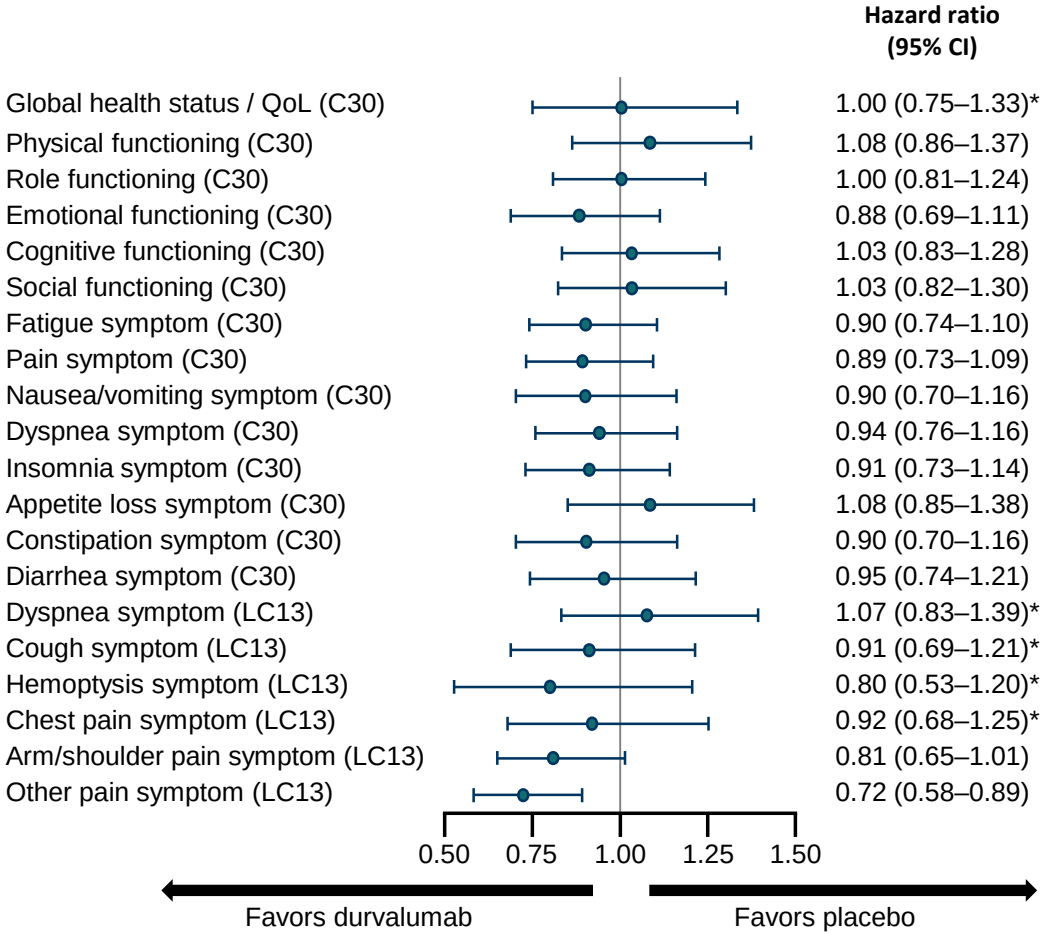
Pancreatitis

Neuropathy

Arthritis

- Inflammatory processes affecting any organ system
- Distinct mechanism of action from traditional chemotherapy-related side effects
- Evaluation and management are unique to this class of drugs
- May be exacerbated by underlying autoimmune conditions/presence of autoantibodies

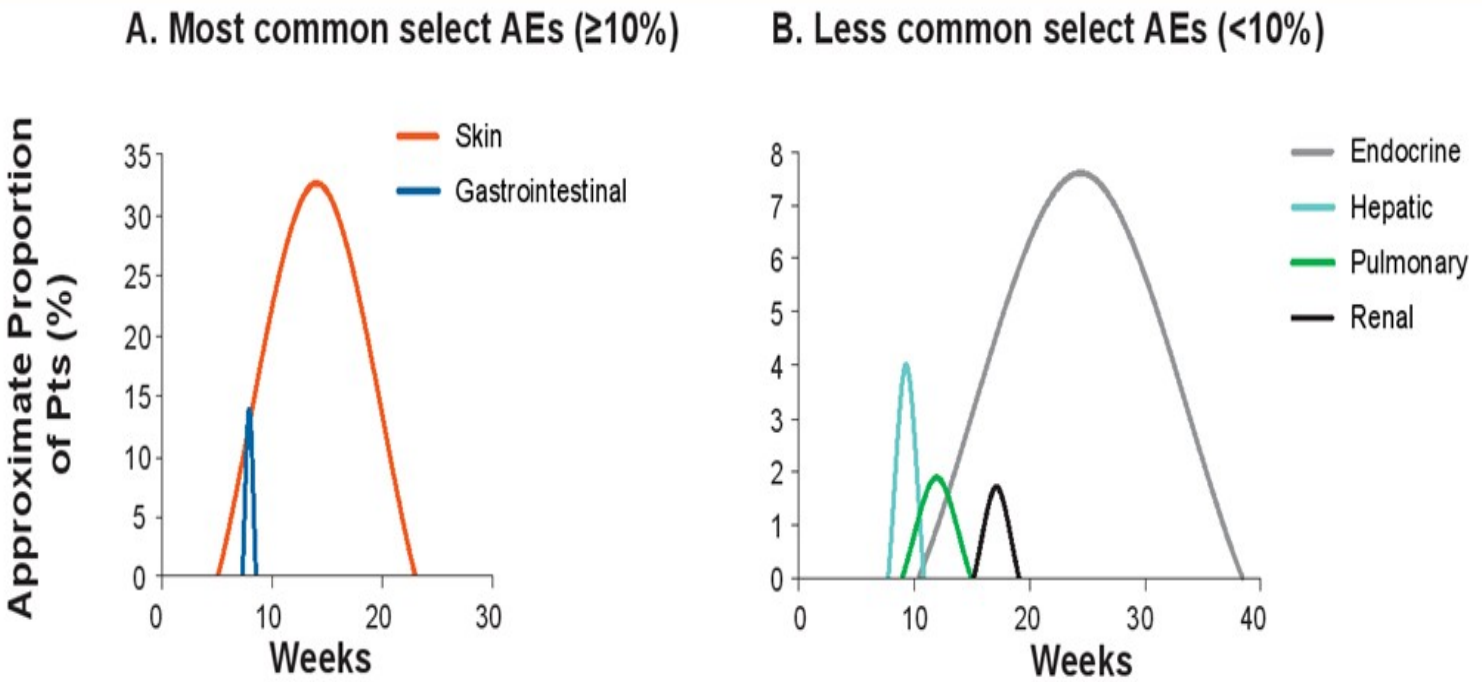
PACIFIC: Chemo-RT +/- Durvalumab
Time to Deterioration in Function and Symptoms



- No differences between Durvalumab and placebo in time to deterioration for functioning or most symptoms

*Figures in brackets denote 99% CI. 'Other pain' refers to anything other than chest pain and arm/shoulder pain
CI, confidence interval; QoL, quality of life; TTD, time to deterioration

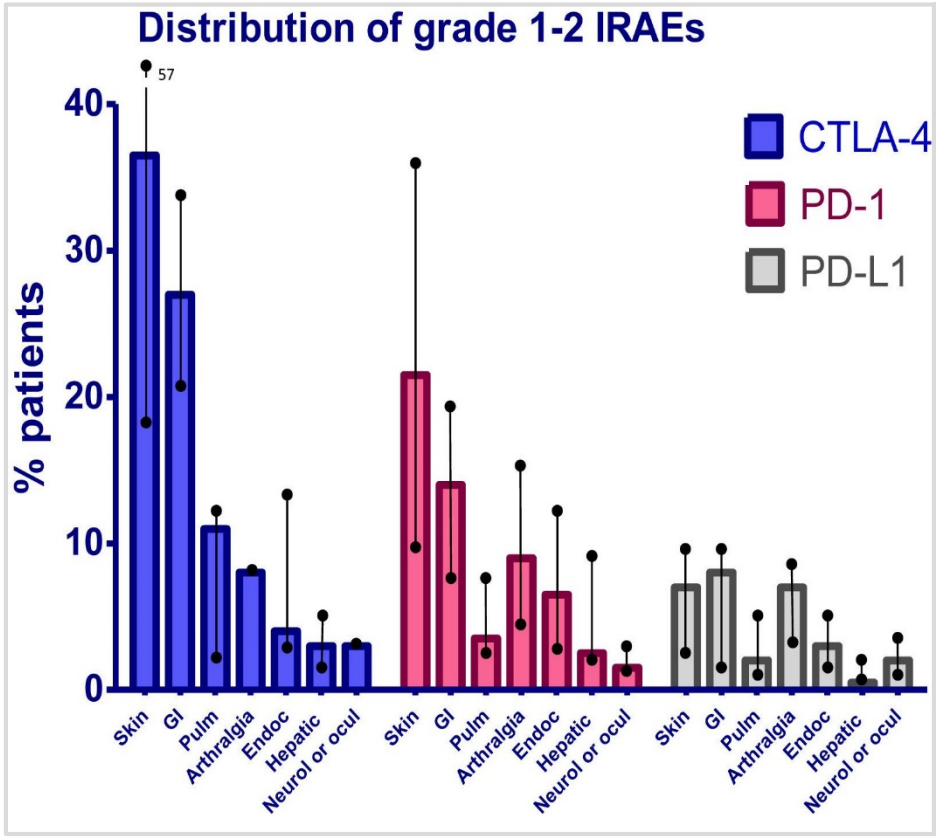
Time to onset of Immune-related AEs from PD-1/PD-L1 Agents

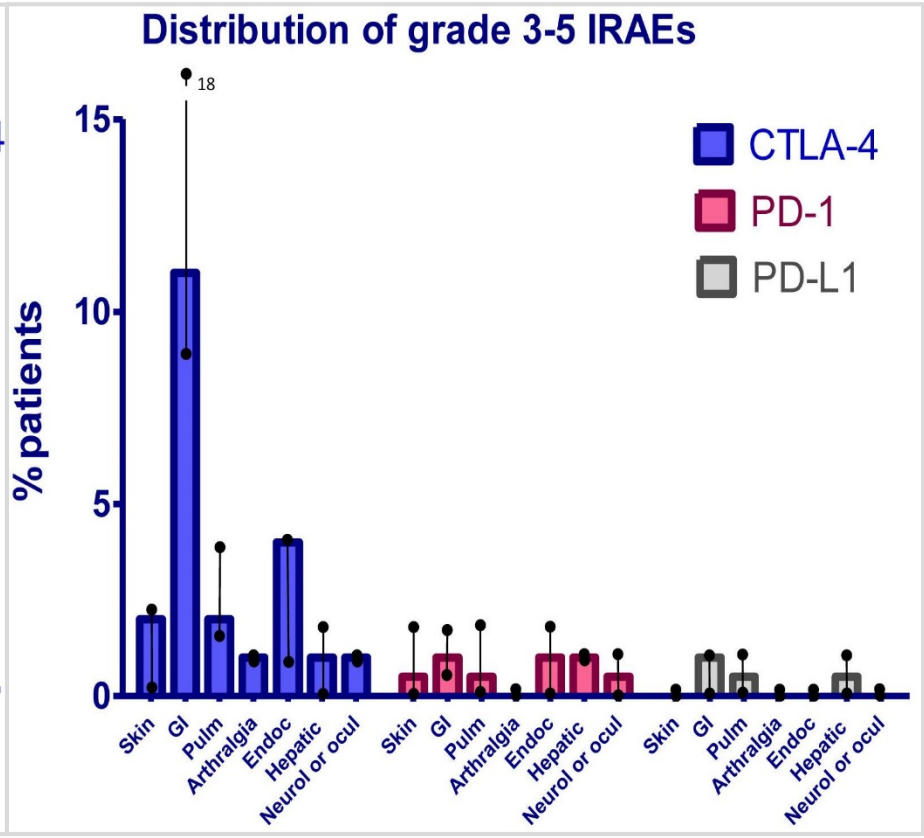


The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.

J Clin Oncol 33, 2015 (suppl; abstr 9018)

Incidence of Immune-Related AEs





Nivolumab Adverse Events (Non-Small Cell Lung Cancer)

Phase I dose-escalation cohort expansion trial for Patients with advanced Non Small Cell Lung Cancer (NSCLC) (squamous and non-squamous) heavily pretreated to receive nivolumab once every 2 weeks in 8-week cycles for up to 96 weeks

Toxicities do not appear dose-related

% Any Adverse Events* (Grade 3-4) by Dose

1 mg/kg (N=33)	3 mg/kg ** (n=37)	10mg/kg (n=59)
15.2%	13.5%	13.6%

- Patients were counted only once for "any adverse event"; data for only those events that were reported in at least 3% of the treated population was presented
- **nivolumab's indicated dose for NSCLC is 3 mg/kg

Most common Grade 3-4 adverse events (n=129):

Fatigue	3.1%
Decreased CD4 Lymphocytes	2.3%
Pneumonitis	2.3%

For those patients experiencing treatment-related adverse events of any grade, the most common were fatigue (24%), decreased appetite (12%), and diarrhea (10%)

3 treatment-related deaths were associated with pneumonitis; authors did not observe a relationship between the occurrence of pneumonitis and dose level or treatment duration. Higher grade select adverse events with immune etiologies were manageable in most cases through drug discontinuation, immune suppressive agents, and/or hormone replacement.

(source: Gettinger et al., 2015)

General Algorithm for irAE Management

Moderate irAEs

↓

Interrupt until grade 1

Glucocorticoids if persists >1 wk

Grade 3-4 irAEs

↓

High-dose glucocorticoids if persists >1 wk

Taper glucocorticoids when symptoms reach grade 1

Other immunosuppression if symptoms persist >3 d on IV glucocorticoids

Discontinue permanently for grade 4, unless controlled endocrinopathy

Reasons to Stop Therapy

↓

Grade 2 lasting > 6 wk, unless controlled endocrinopathy

Glucocorticoid cannot be reduced to 7.5 mg prednisone/d with ipilimumab or 10 mg/d within 12 wk with anti-PD-1

Grade 2-4 ocular irAEs not improving to grade 1 within 2 wk topical immunosuppression or requiring systemic treatment

Kumar V et al. *Front Pharmacol*. 20178:1-14.

Most irAEs occur within the first 3 months of treatment with an immunotherapy; some occur after the final dose of therapy

- Toxicities may be dose-dependent depending upon the immunotherapy (e.g. ipilumumab)
- irAEs can differ depending upon tumor types
- The severity of the toxicity (Grade 1 – 4) dictates how to manage the irAE
- In general, treatment is either withheld or discontinued in patients experiencing moderate or severe irAEs (Grade 2-4)
- Thyroid function, blood counts, liver function, and metabolic panels are tested/taken during treatment of checkpoint inhibitors
- The following slides will focus on the presentation and management of irAEs as they apply to ipilimumab, nivolumab, and pembrolizumab

CTCAE Guidelines

NCI-CTCAE Guidelines for Grading Select Adverse Reactions[1]

- The table lists NCI-CTCAE guidelines for grading the severity of select adverse reactions that may be associated with (pembrolizumab)[a]

	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	Asymptomatic: clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)
Colitis		Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated
Hypothyroidism		Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization Indicated	Life-threatening consequences; urgent intervention indicated
Hyperthyroidism		Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Endocrine disorders – other	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs.
[a]Grade 5 means death.

1. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) v4.0.* Bethesda, MD: National Cancer Institute 2009. NIH Publication 09-7473. Updated version CTCAE v4.03, June 14, 2010.

54

Presentation and Management of Dermatologic irAEs

- Dermatologic irAEs are the most frequently reported Adverse Events; they are typically mild to moderate in severity. (< 3% are grade 3 or higher); types of irAEs include:
  - Maculopapular rash and pruritis
  - Vitiligo, alopecia

Management:
Grade 1 – 2 : symptomatic therapy such as moisturizers, ointments, lowdose topical corticosteroids, antihistamines

Grade 3 – 4 : evaluate by a dermatologist, administration of systemic corticosteroids (prednisone or equivalent) and drug interruption

(sources: Tarhini, 2013; Kumar et al. 2017; IASLC, 2017)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash/Pruritis/ Dermatitis Vitiligo/ Lichenoid Implants	▪ Macules/papules covering <10% BSA with or without symptoms ▪ Mild localized pruritis	▪ Macules/papules covering 10-30% BSA with or without symptoms ▪ Intense or widespread, Intermittent skin changes; with scratching	▪ Macules/pustules covering >30% BSA with or without symptoms ▪ Intense or widespread, constant pruritis; limiting self-care	▪ N/A	▪ N/A
Work Up	▪ Rule out cellulitis, contact dermatitis, other drug reactions, sun exposure, radiation recall	▪ Rule out cellulitis, contact dermatitis, other drug reactions, sun exposure, radiation recall	▪ Rule out cellulitis, contact dermatitis, other drug reactions, sun exposure, radiation recall		
Treatment	▪ Topical steroids ▪ Anti-itch creams ▪ >1 week moderate potency steroid cream (Triamcinolone 0.1%)	▪ Consider holding treatment ▪ Topical steroids ▪ Anti-itch creams ▪ >1 week moderate potency steroid cream (Triamcinolone 0.1%) ▪ Antihistamines ▪ If no improvement, refer to dermatology	▪ Hold treatment ▪ Methylprednisolone 0.5-1 mg/day IV ▪ Antihistamines ▪ Refer to dermatologist		

Presentation and Management of Enterocolitis / Gastrointestinal irAEs

- Disregulation of GI mucosal immunity can result in diarrhea, colitis, abdominal pain, or blood/mucus in the stool without fever
- Diarrhea is a more common complaint with use of a CTLA-4 inhibitor vs. an anti-PD1

Management:
Grade 1: treat symptomatically
Grade 2: Oral steroids + PPI, consider prophylactic antibiotic
Grade 3 – 4 : discontinue treatment; rule out bowel perforation – if present do not administer corticosteroid; treat patient with high-dose intravenous methylprednisolone; other steroids can be used such as dexamethasone; with no improvement, consider single-dose infliximab, cyclosphosphamide, mycophenalate mofetil

(IASLC 2017 and Kumar et al. 2017)

Case Study

- A patient has been on Nivolumab for greater than 18 months with still stable disease and excellent performance status.
- He now calls in and states that he has > 7 bowel movements a day above baseline, and that all BM’s are loose. Denies blood or mucus in the stool.
- What tests would you perform?

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Colitis	▪ Asymptomatic ▪ Clinical or diagnostic observations only ▪ Intervention not indicated	▪ Abdominal pain ▪ Mucus or blood in stool	▪ Severe abdominal pain ▪ Change in bowel habits ▪ Medical intervention indicated ▪ Peritoneal signs	▪ Life-threatening consequences ▪ Urgent intervention indicated	▪ Death
Diarrhea	▪ 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 ▪ Moderate increase in ostomy output compared to baseline	▪ Increase of >7 stools per day over baseline ▪ Incontinence ▪ Hospitalization indicated ▪ Severe increase in ostomy output compared to baseline ▪ Limiting self-care ADLs	▪ Life-threatening consequences ▪ Urgent intervention indicated	▪ Death
Work Up	▪ Baseline blood work ▪ Stool for microscopy and cultures ▪ Viral PCR ▪ C. difficile toxin and cryptosporidium test	▪ Grade 1 recs ▪ Daily follow up ▪ Repeat labs every 3-5 days ▪ AXR (KUB)	▪ Grade 1 recs ▪ Daily blood tests ▪ CT abdomen/pelvis ▪ Repeat AXR (KUB)	▪ Grade 1 recs ▪ Daily blood tests ▪ CT abdomen/pelvis ▪ Repeat AXR (KUB)	

Case Study

- Baseline blood work
- Stool for microscopy and cultures
- Viral PCR
- C. Diff toxin and cryptosporidium test.

Case Study

• He is started on Prednisone 1 mg/kg day, but after 2 days, still has diarrhea after 2 days of steroids and bowel rest. What options would you consider next?

a) Increase steroids to 2 mg/kg

b) Hydrocortisone 200 mg + PPI

c) Cyclophosphamide

d) Mycophenolate mofetil.

• Same patient does well on oral steroids, but begins to have recurrent diarrhea when steroids are tapered. What dosing would you restart on?

Case Study

- We can discontinue Nivolumab and then continue retreating if the patient does begin to progress.
- If this same patient had only been on Nivo for 3 weeks, our goal is to keep the patient on treatment for as long as possible to determine if the treatment is working
- Referral to GI for biopsy once patient is stabilized to confirm that the diarrhea/colitis is truly an IRAE.

Treatment				
	▪ **Continue immunotherapy** ▪ Loperamide ▪ Oral fluid rehydration ▪ Avoid high fiber and lactose diet	▪ **Omit/defer next dose immunotherapy** ▪ Inform treating oncologist ▪ Consider gastroenterologist consult ▪ Oral loperamide ▪ Oral fluid rehydration ▪ Oral prednisolone 0.5-1 mg/kg/day max 80mg/day + PPI ▪ Consider budesonide 9 mg OD if no bloody diarrhea ▪ Consider prophylactic antibiotic ▪ Taper steroids over >2 months	▪ **Permanently discontinue immunotherapy** ▪ Hospital admission ▪ Inform oncologist ▪ Consult gastroenterologist ▪ Consult dietitian ▪ Consider early surgical consult if bleeding, pain, or distention ▪ IV hydration ▪ High dose IV corticoste- roids (Methylpredniso- lone 2 mg/kg/day or hydrocortisone 200 mg three times a day + PPI	▪ **Permanently discontinue immunotherapy** ▪ Hospital admission ▪ Inform oncologist ▪ Consult gastroenterologist ▪ Consult dietitian ▪ Consider early surgical consult if bleeding, pain, or distention ▪ IV hydration ▪ High dose IV corti- costeroids (Methylpredniso- lone 2 mg/kg/day or Hydrocortisone 200 mg three times a day + PPI	

Presentation and Management of Endocrinopathies

- Endocrinopathy irAEs include inflammation of the pituitary, thyroid, or adrenal glands and occurs in <5% of patients, with < 3% being Grade 3 or higher; endocrinopathies can present with non-specific symptoms including:

  - Headache and fatigue (most common)
  - Visual field defects
  - Decreased libido
  - Hypotension
  - Mental status change
  - Abdominal pain
  - Unusual bowel habits
  - Abnormal thyroid tests

Management:
Grade 1 – 2 : (excluding adrenalitis and hypophysitis) may resolve spontaneously; monitor closely with potential endocrinological consultation; short-term, high dose corticosteroids if needed with relevant hormone replacement
Hypophysitis: Grade 1 Hormone levels, Grade 2 oral prednisone Grade 3 or 4, permanently discontinue, oral prednisone.
Adrenal insufficiency: Grade 1-2 Hormone levels, Grade 3-4 Oral steroids. (If adrenal crisis, stabilize patient, r/o sepsis).

(sources: Tarhini, 2013; Kumar et al. 2017)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adrenal Insufficiency	▪ Asymptomatic ▪ Clinical or diagnostic observations only ▪ Intervention not indicated	▪ Moderate symptoms ▪ Medical intervention indicated	▪ Severe symptoms ▪ Hospitalization indicated	▪ Life-threatening consequences ▪ Urgent intervention indicated	▪ Death
Work Up	▪ Baseline 9 am cortisol level/cortisol challenge/stim test	▪ 9 am cortisol level/ cortisol challenge/ stim test ▪ Assess for fatigue, loss of energy, loss of appetite, nausea, vomiting, diarrhea, abdominal pain, weight loss, muscle weakness, orthostasis, anxiety, depression	▪ 9 am Cortisol level/ cortisol challenge/ stim test ▪ Assess for fatigue, loss of energy, loss of appetite, nausea, vomiting, diarrhea, abdominal pain, weight loss, muscle weakness, orthostasis, anxiety, depression	▪ 9 am cortisol level/ cortisol challenge/ stim test ▪ Assess for fatigue, loss of energy, loss of appetite, nausea, vomiting, diarrhea, abdominal pain, weight loss, muscle weakness, orthostasis, anxiety, depression	
Treatment	▪ **Continue immunotherapy**	▪ **Omit or defer immunotherapy** ▪ MRI brain	▪ **Withhold next cycle of immunotherapy** ▪ MRI brain ▪ Refer to endocrinology	▪ **Withhold next cycle of immunotherapy** ▪ MRI brain ▪ Refer to endocrinology	

Presentation and Management of Hepatotoxicities

- Inflammatory hepatitis has been reported in patients taking CTLA-4 inhibitors or PD-1 inhibitors. In patients taking ipilimumab, < 2% present with hepatotoxicity, ~1% are Grade 3-4. In Pembrolizumab < 1% display autoimmune hepatitis of any grade.

  - Liver tests should be performed to determine AST (aspartate animotransferase) or ALT (alanine aminotransferase) levels, most episodes are asymptomatic.

Management:

Monitor transaminases and bilirubin prior to each dose to exclude other causes of hepatitis. Grade 2 : AST or ALT levels >2.5 times but <= 5 times the upper limit of normal (ULN); total bilirubin > 1.5 times but < or = 3 times the ULN; treatment should be withheld.

Grade 3 or greater : AST or ALT > 5 times the ULN, bilirubin > 3 times the ULN; permanently discontinue treatment. Provide high-dose IV corticosteroid therapy; if refractory to corticosteroid, add tacrolimus. Consider cyclophosphamide or mycophenolate mofetil if no response despite therapeutic levels.

(sources: Tarhini, Kumar et al. 2017)

Presentation and Management of Pneumonitis

- Pneumonitis can present as cough, chest pain and shortness of breath; imaging should be considered; occurs with both CTLA-4 inhibitor and PD-1 use; higher rate of occurrence with anti-PD-1s (~3%)
  - Check O2 at rest and with activity.
  - CT of the Chest to rule out pulmonary embolism, pneumonia or disease progression.

Management:
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Grade 1: May present without symptoms, no intervention needed.
Grade 2: Withhold therapy. Prednisone 1-2 mg/kg. Taper slowly over 1 month.
Grade 3-4: Permanently discontinue therapy. Prednisone 1-2 mg/kg or IV methylprednisolone 2-4 mg/kg/day. Taper slowly over 1 month.

For moderate to severe symptoms or radiographic findings: Administer Pulmonary consultation is suggested as well as a bronchoscopy to evaluate for infectious etiology.

(IASLC 2017; Kumar et al. 2017)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis	▪ Asymptomatic ▪ Clinical or diagnostic observations only ▪ Intervention not indicated	▪ Symptomatic ▪ Medical intervention indicated ▪ Limiting instrumental ADL	▪ Severe symptoms ▪ Limiting self-care ADL ▪ Oxygen indicated	▪ Life-threatening respiratory compromise ▪ Urgent intervention indicated (e.g., tracheotomy or intubation)	▪ Death
Work Up	▪ Check pulse oximetry at rest and with activity	▪ Check pulse oximetry at rest and with activity ▪ 2 view CXR	▪ Check pulse oximetry at rest and with activity ▪ 2 view CXR ▪ CT of chest	▪ Check pulse oximetry at rest ▪ Arterial blood gas ▪ CT of chest	
Treatment	▪ Continue therapy	▪ Withhold therapy ▪ Administer steroids at a dose of 1-2 mg/kg/day prednisone equivalent ▪ Slow taper ▪ Resume therapy once Grade 0-1	▪ Permanently discontinue therapy ▪ Administer steroids at a dose of 1-2 mg/ kg/day prednisone equivalent ▪ Slow taper	▪ Administer steroids at a dose of 1-2 mg/kg/day prednisone equivalent ▪ Slow taper ▪ Initiate emergency medical treatment	

Other irAEs

Ocular irAEs:

- Eye inflammation from episcleritis, conjunctivitis, uveitis, ophthalmopathy associated with Graves disease
- Symptoms: photophobia, pain, dryness, blurred vision
- Recommended to consult with an ophthalmologist if experiencing visual disturbances

Neurologic irAEs:

- Guillain-Barre Syndrome, inflammatory myopathy, posterior reversible encephalopathy syndrome, aceptic meningitis, enteric neuropathy, transverse myelitis are a few neurologic irAEs associated with checkpoint inhibitors

➢ Symptoms: muscle weakness, sensory neuropathies, or motor neuropathies confirmed by examination

➢ Serious events are treated with corticosteroids; consultation with a neurologist recommended

(sources: Postow M., Callahan, M., and Wolchok, J., 2015)

About this Resource Guide

This guide is designed to help health care professionals address immunotherapy adverse events. This guide will assist in the grading, diagnostic work up, and management of the adverse events related to immunotherapy. This guide is divided into sections based on the organ system. A list of abbreviations can be found on the inside of the back cover for reference.

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Adverse Event Treatment

Resource Guide

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Abbreviations

ACTH	Adrenocorticotropic
Hormone ADH	Anti Diuretic Hormone
ADL	Activities of Daily Living
AXR	Abdominal X-Ray
CXR	Chest Radiography
FSH	Follicle-Stimulating Hormone
INR	International Ratio
LFT	Liver Function Test
LH	Luteinizing Hormone
KUB	Abdominal X-ray
N/A	Not Applicable
OD	Once Daily
PPI	Proton Pump Inhibitor
ULN	Upper Limits of Normal