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Autoimmunity and Immune Related Adverse Events

Michael Morse, MD

References/Guidelines

Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95
DOI 10.1186/s40425-017-0300-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[1†], A. Diab[2†], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[12†], M. S. Ernstoff[1*†] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

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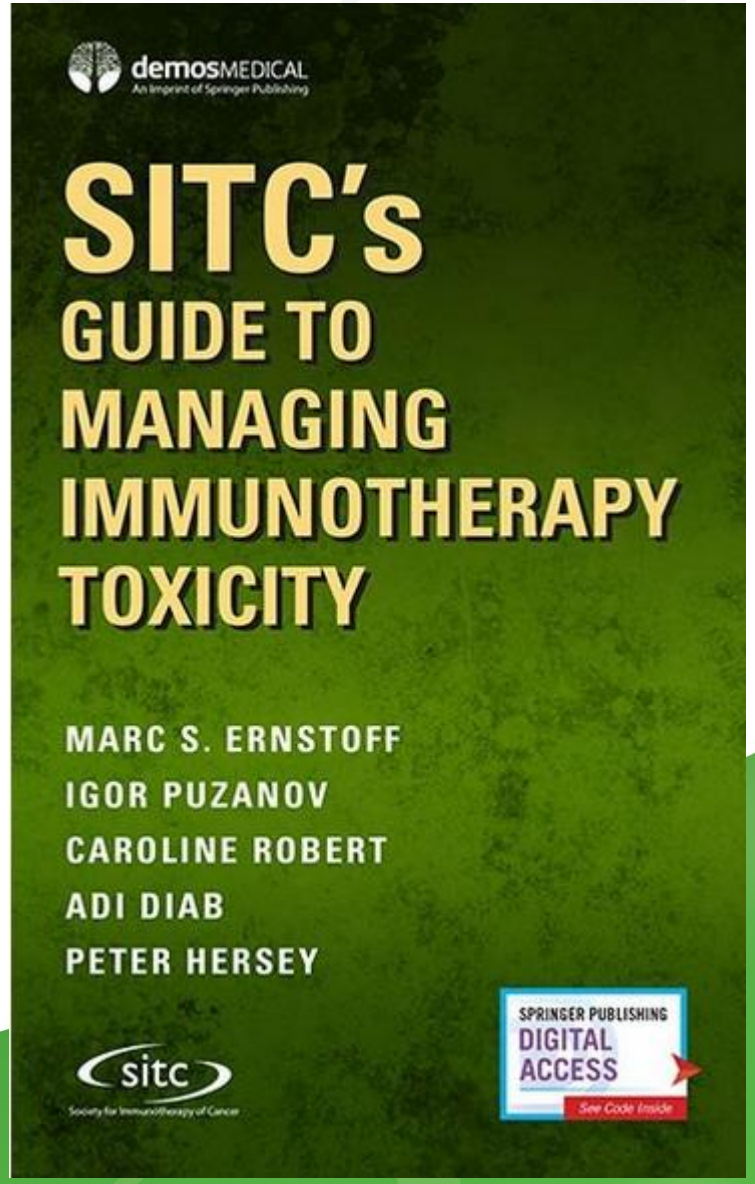

Publication Date: March 28, 2019

References/Guidelines

VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

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References/Guidelines

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 1.2020 — December 16, 2019

NCCN.org

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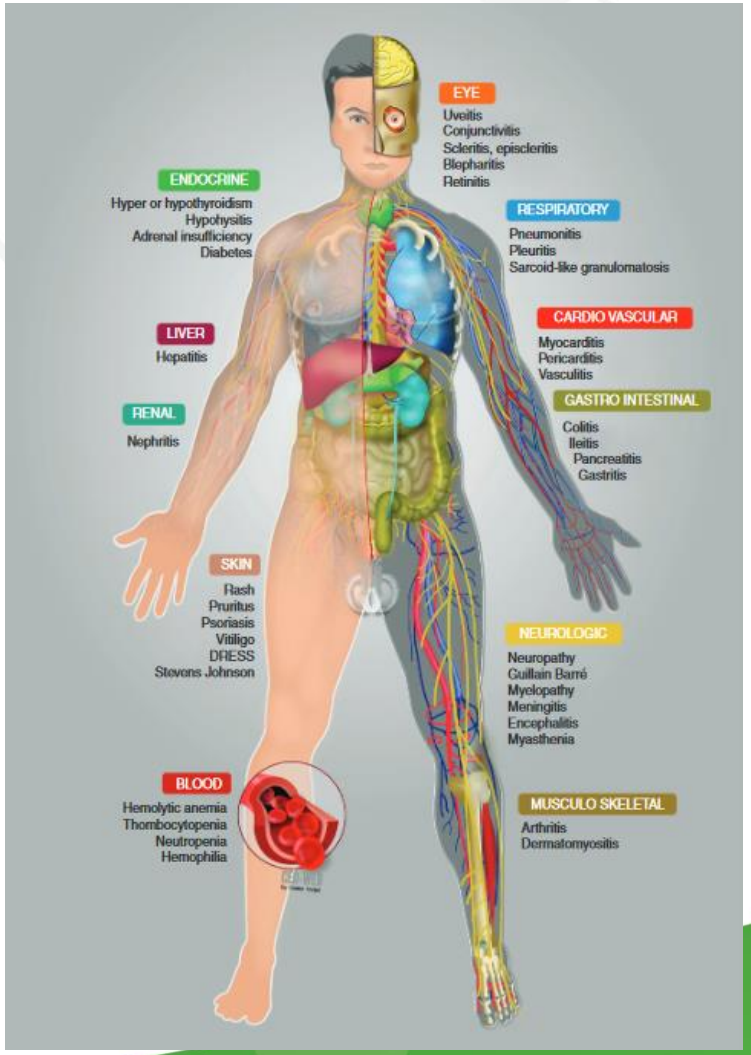
Spectrum of toxicity of immune checkpoint blockade



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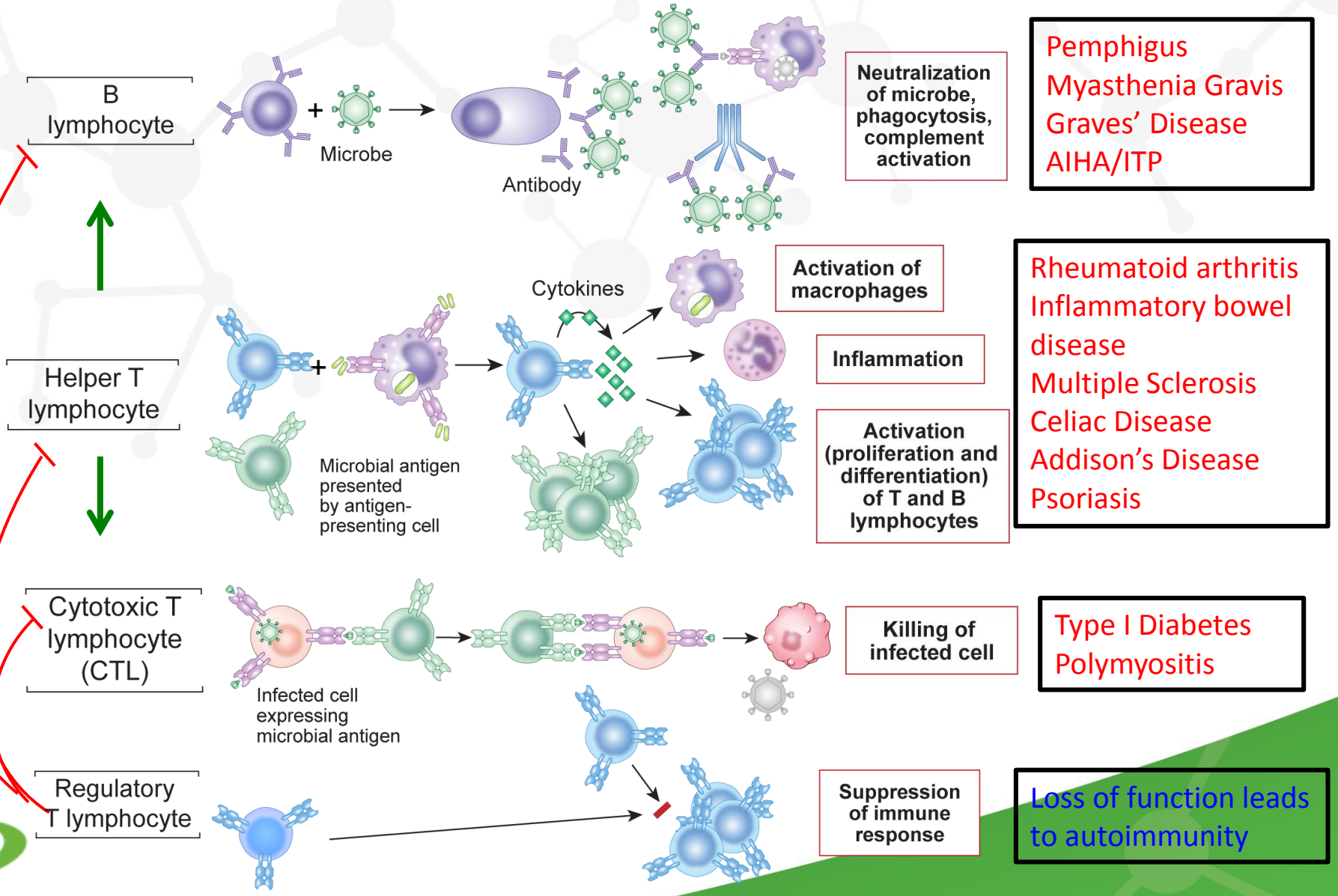
Champlat, Ann Oncol (2016) 27 (4): 559-574

Most Autoimmune Diseases are due to Failure of T cell Tolerance (even in those diseases that are antibody-mediated)

Immunologic Tolerance:
unresponsiveness of immune system to self antigens

Etiologies of autoimmune diseases



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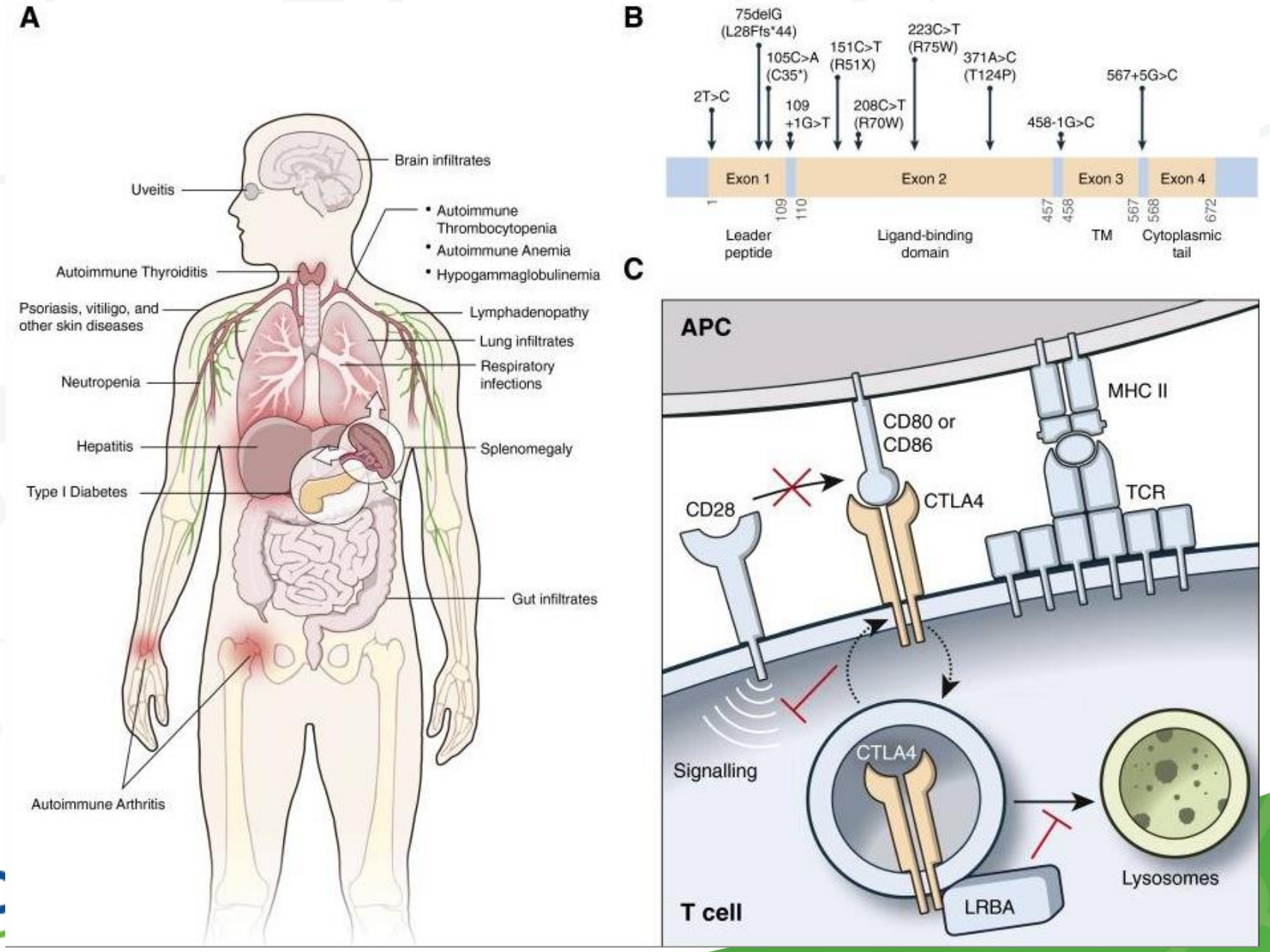
Role of CTLA4 and PD-L1 in autoimmune disease

- KO mice lacking CTLA-4 (Waterhouse, Science 1995;270:9858; Klocke, PNAS 2016;113:E238392)
  - Extensive infiltration of activated lymphocytes in lymph nodes, spleen and thymus, heart, lung, liver and pancreas (but not in the kidney)
  - Antibody levels strikingly elevated

- PD-1 deficient models
  - Depending on the strain, develop a lupus-like disease marked by glomerulonephritis and renal deposition of IgG3 and C3.
  - Majority of PD-1-deficient mice also developed inflammatory arthritis



CTLA-4 haplo-insufficiency with autoimmune infiltration" (CHAI)

LRBA deficiency with autoantibodies, Treg defects, autoimmune infiltration, and enteropathy" (LATAIE)

Blood 2016; 128:1037-1042

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Overview of possible mechanisms of irAE

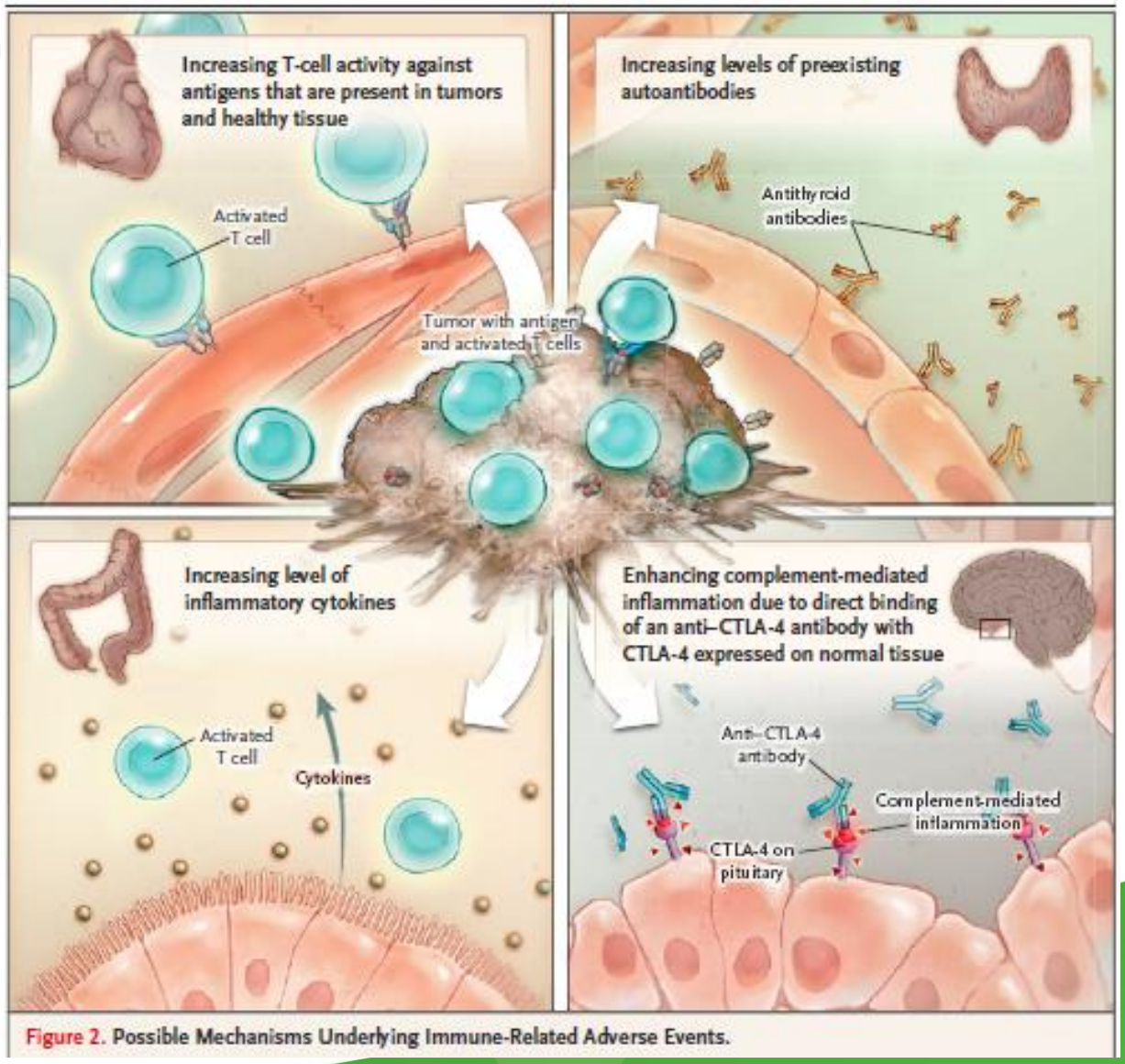

Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

N Engl J Med. 2018;378(2):158-168.

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Early and late irAEs may occur by distinct mechanisms

Early and common

Mucosal
Colitis
Rash
Pneumonitis

Global Regulatory T cell dysfunction

↓

Activation of Effector T cells (Th_{17})

↓

Recruitment of inflammatory cells (neutrophils)

Late and rare

Specific organ
Hypophysitis
(other endocrine)
Myocarditis; Neurologic
Arthritis; Vitiligo

Breakdown of organ specific tolerance

↓

Activation of tumor specific T cells that recognize antigen shared between tumor and healthy tissue: vitiligo, myocarditis

Activation of tissue specific anergic T cells that recognize antigen distinct from the tumor

T cell or antibody mediated tissue destruction

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TABLE 3 Potential influences on irAE development

Malignancy-related factors	Underlying host factors
Cancer type ICI treatment Molecular target[a] Monotherapy CCB Sequence of therapy[b] Possible Influences Duration of therapy Prior chemotherapy	Age Genetic predisposition to auto-immunity Pre-existing autoimmune dis-ease Microbiome

Weinmann, Rheumatology 2019;58:vii59vii67

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Toxicities vary by drug regimen

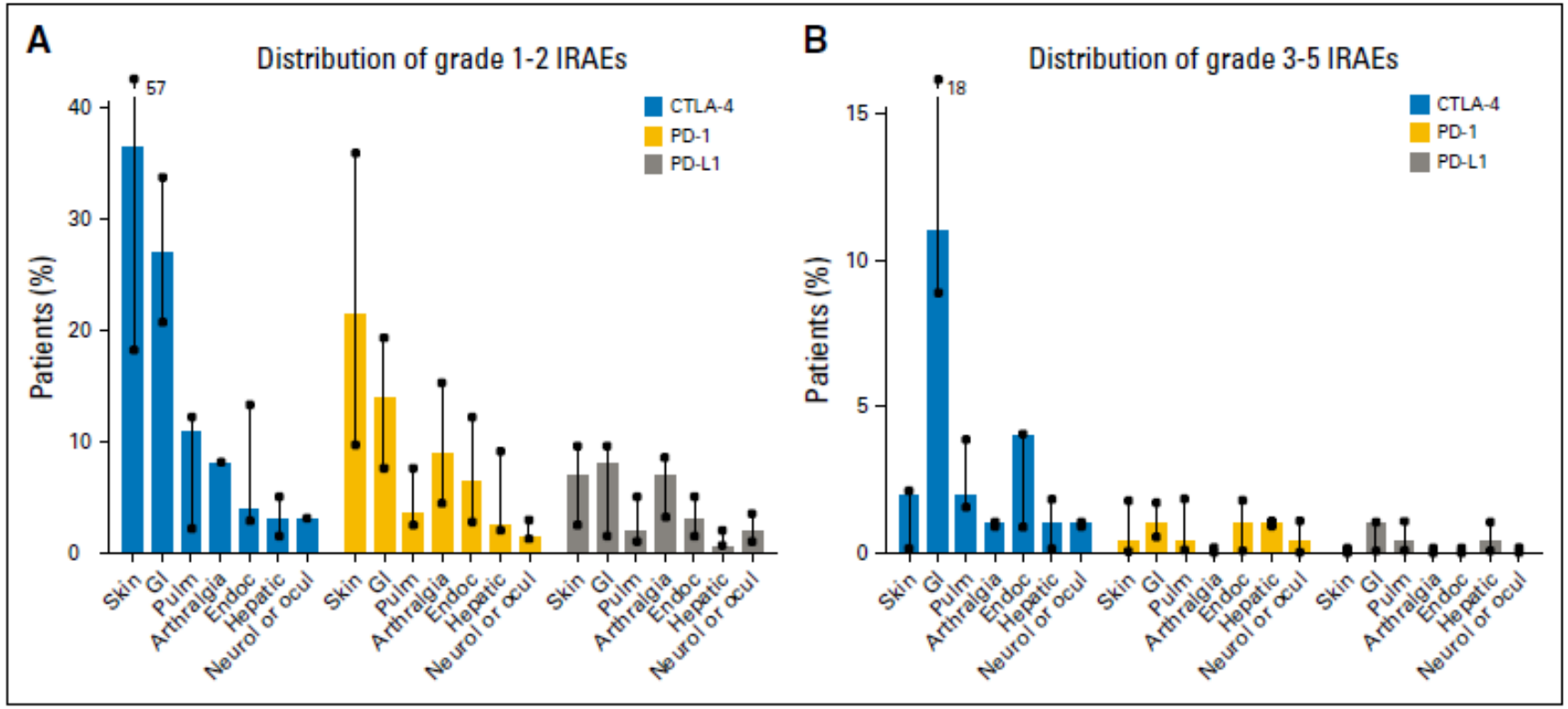

Fig A1. Distribution of (A) grade 1 to 2 and (B) grade 3 to 5 immune-related adverse events (irAEs) for all tumor types in the main clinical trials with anti–cytotoxic T-cell lymphocyte-4 (anti–CTLA-4), anti–programmed death 1 (PD-1), or anti–PD ligand 1 (PD-L1) antibodies as single therapies. The values quoted are the median (range) irAE rates for the set of clinical trials as a whole. Adapted from European Journal of Cancer, Vol 54, J.M. Michot et al, Immune-Related Adverse Events With Immune Checkpoint Blockade: A Comprehensive Review, 139-149, Copyright 2016, with permission from Elsevier. Endoc, endocrinology; Neurol, neurology; ocul, ocular; Pulm, pulmonary.

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Journal of Clinical Oncology 36, no. 17 (June 10 2018) 1714-1768.

TABLE 2 | Biomarkers for irAEs.

Biomarkers	Cancer type	Patient number	Treatment	Key data and clinical significance
Body composition parameters	Melanoma	84	Ipilimumab	Both sarcopenia and low MA were independent factors associated with high-grade irAEs.
Sex	Melanoma	140	Ipilimumab	Females were associated with higher rates of irAEs.
IL-6				IL-6 at baseline was negatively associated with irAE.
	Melanoma	26	Ipilimumab	Lower circulating IL-6 was significantly correlated with higher incidences of colitis-related irAEs.
	Melanoma	15	Nivolumab	Increases in circulating IL-6 after treatment were significantly associated with development of irAEs.
IL-17	Melanoma	35	Ipilimumab	Circulating IL-17 levels at baseline correlated with the incidence of grade 3 irAEs of diarrhea/colitis, indicating that increased levels of circulating IL-17 may be reflective of patients with subclinical colitis.
Soluble CD163, CXCL5	Melanoma	46	Nivolumab	The absolute change rate of soluble CD163 and CXCL5 after initial treatment was increased in patients with irAEs compared to those without irAEs.
Blood cell counts	Melanoma, RCC, urothelial carcinom	167	Anti-PD-1 antibodies	Absolute lymphocyte and eosinophil numbers at baseline and 1 month after initial treatment were independent factors associated with a higher incidence of irAEs of grade ≥2.
	Melanoma	44	Anti-PD-1 antibodies	Both baseline absolute eosinophil count and relative eosinophil count at 1 month significantly correlate with the occurrence of endocrine irAEs.
	Melanoma	101	Nivolumab	An increase in total WBC count and a decrease in relative lymphocyte count plus increase in relative neutrophil count on the same day of, or just prior to irAE occurrence were associated with development of lung or gastrointestinal irAEs.
autoantibodies	Melanoma, NSCLC	168	Nivolumab	TSH and TPOAb were associated with higher incidence of thyroid irAEs.
	Solid cancer including melanoma, NSCLC, RCC	27	Anti-PD-1 antibodies, atezolizumab	Patients positive for type 1 diabetes antibodies at the time of presentation developed diabetes-related irAEs after fewer cycles than those without autoantibodies.
T cell repertoire	Prostate cancer	42	Ipilimumab plus granulocyte-monocyte colony-stimulating	An early increase in diversity and the generation of new T- cell clones correlated with the development of irAEs.

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Nakamura Y *Front. Med.* 2019; *6:119.*

General principals of immunotherapy toxicity management

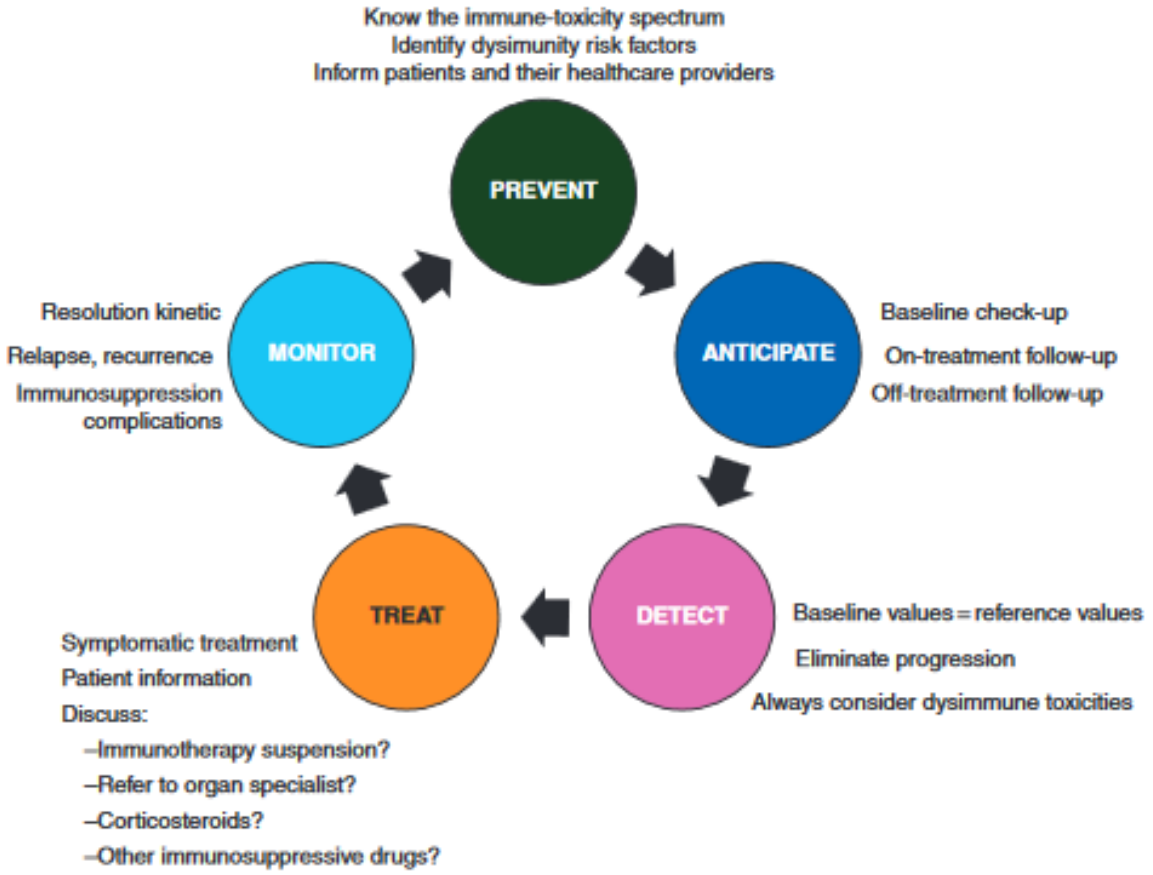

Figure 1. The five pillars of immunotherapy toxicity management.

Champlat, Ann Oncol (2016) 27 (4): 559-574

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Prevention ?

- Assess for personal and family history of autoimmune diseases.
  - digestive (Crohn's disease, ulcerative colitis, celiac disease),
  - skin (psoriasis)
  - Rheumatic (spondyloarthritis, rheumatoid arthritis, lupus)
  - endocrine (diabetes, thyroiditis)
  - respiratory (interstitial pneumonitis, sarcoidosis),
  - pancreatic (pancreatitis)
  - kidney (nephritis)
  - Hematological (hemolytic anemia, immunologic thrombocytopenic purpura),
  - neurological (myasthenia, multiple sclerosis)
  - eye (uveitis, scleritis,retinitis)
  - cardiovascular (heart failure, left ventricular systolic dysfunction, myocarditis, vasculitis)
- Chronic infections (Hepatitis B?)
- Chronic medications/exposures associated with autoimmune diseases
- Sites of disease where immune response may increase symptoms (lymphangitic spread)

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Anticipate

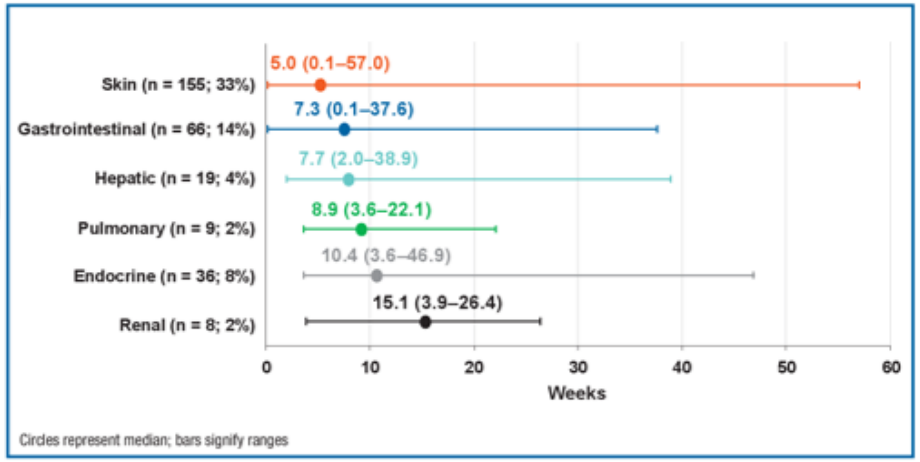
Table A2. Commonly Conducted Testing at Baseline Prior to ICPi Therapy*

Testing
Clinical
Physical examination, including physical stature, weight, body mass index, heart rate, and blood pressure
Comprehensive history, including autoimmune, organ-specific disease, endocrinopathy, neuropathy, and infectious disease
Questioning of general health, including appetite, bowel habits, and asthenia. Preexisting symptoms involving bowel movements, dyspnea, cough, rash, headaches, and arthralgia should be noted.
Laboratory
CBC + differential test
Complete metabolic panel that may include serum electrolytes (Na, K, Ca, CO_2), liver function (AST, ALT, alkaline phosphatase, γ-glutamyl transferase), creatinine, creatine kinase, total bilirubin
Glucose
Lactate dehydrogenase and aldolase
Thyroid-stimulating hormone, free thyroxine
Luteinizing hormone, follicle-stimulating hormone, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes
Urinalysis
Surveillance for latent tuberculosis
Virology including HIV, hepatitis C virus and hepatitis B virus, Epstein-Barr virus, cytomegalovirus
Troponin
Spirometry/diffusing capacity of lung for carbon monoxide
Imaging
Chest x-ray
Computed tomography
ECG

*Other testing may also be necessary based on patient's history and preexisting comorbidities and/or risk factors. *Journal of Clinical Oncology* 2018 361714-1768.

Time to onset and resolution of AEs with PD-1

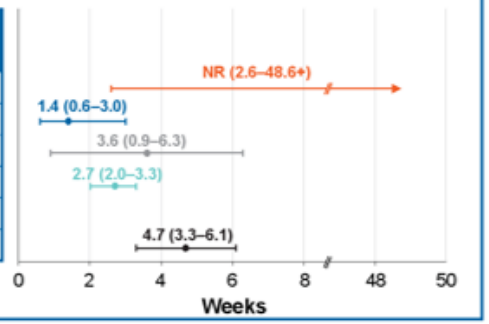
Figure 1. Time to onset of select treatment-related AEs (any grade; N = 474)



Some thyroid function may be restored over time
Dysfunction of the corticosteroid and gonadal axes is likely permanent

Figure 4. Time to resolution of select treatment-related AEs with IMs (grade 3–4)

	Grade 3–4, n	Cases resolved, n (%)
Skin	2	1 (50%)
Gastrointestinal	5	5 (100%)
Endocrine	2	2 (100%)
Hepatic	2	2 (100%)
Pulmonary	0	0
Renal	2	2 (100%)



Circles represent median; bars signify ranges
NR = not reached

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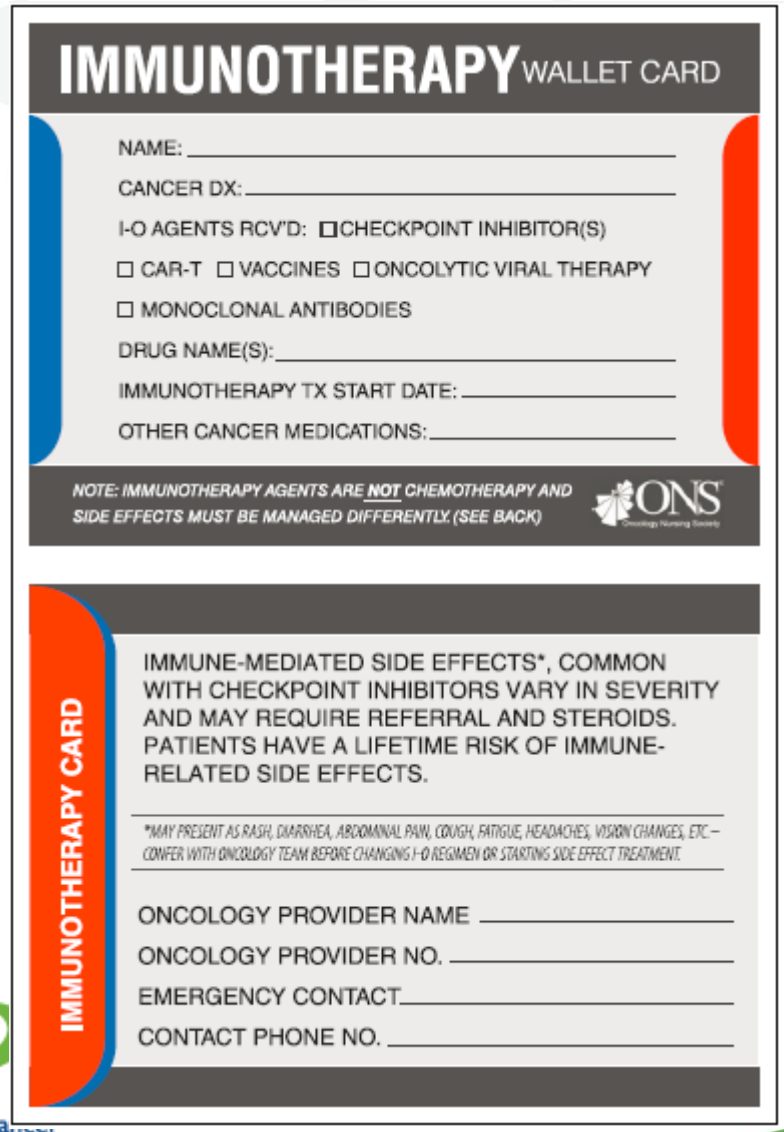
Informing others: Patient card



IMMUNOTHERAPY WALLET CARD

NAME: _____

CANCER DX: _____

I-O AGENTS RCV'D: ☐ CHECKPOINT INHIBITOR(S)

☐ CAR-T ☐ VACCINES ☐ ONCOLYTIC VIRAL THERAPY

☐ MONOCLONAL ANTIBODIES

DRUG NAME(S): _____

IMMUNOTHERAPY TX START DATE: _____

OTHER CANCER MEDICATIONS: _____

*NOTE: IMMUNOTHERAPY AGENTS ARE **NOT** CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY. (SEE BACK)*

ONS

IMMUNOTHERAPY CARD

IMMUNE-MEDIATED SIDE EFFECTS*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

**MAY PRESENT AS RASH, DIARRHEA, ABDOMINAL PAIN, COUGH, FATIGUE, HEADACHES, VISION CHANGES, ETC.—CONFER WITH ONCOLOGY TEAM BEFORE CHANGING I-O REGIMEN OR STARTING SIDE EFFECT TREATMENT.*

ONCOLOGY PROVIDER NAME _____

ONCOLOGY PROVIDER NO. _____

EMERGENCY CONTACT _____

CONTACT PHONE NO. _____

Name, Family name:
Immunotherapy drug(s):
I am currently receiving an immunotherapy which may increase the risk of occurrence of autoimmune diseases and in particular:

- pneumonitis (inflammation of the lungs)
- colitis (inflammation of the gut)
- hepatitis (inflammation of the liver)
- nephritis (inflammation of the kidneys)
- endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency (inflammation of the hormone producing organs)
- cutaneous rash (inflammation of the skin)

as well as other immune-related adverse events: neurological, hematological, ophthalmological,... **The management of these dysimmune adverse events is specific and sometimes urgent. It absolutely requires coordination with the health care team which has prescribed the treatment:**
Prescriber ID and contact information (reported at the back of this card)

Champlat, Ann Oncol (2016) 27 (4): 559-574

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Journal of Clinical Oncology 2018 361714-1768.

PRINCIPLES OF ROUTINE MONITORING

Baseline Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency)	Clinical exam at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • CT imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork • CBC with differential • Comprehensive metabolic panel • Infectious disease screening as indicated	Repeat every 2–3 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required.	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal imaging for suspected pancreatitis.
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (T4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 if abnormal thyroid function suspected. TPO antibodies if TSH is high, TRAbs if TSH is low.
Adrenal/Pituitary (ICI_ENDO-3) • Adrenal: Serum cortisol • Pituitary: TSH, free T4	Every 2–3 weeks during immunotherapy, then follow-up every 6–12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, adrenocorticotropic hormone (ACTH)
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Pulmonary function tests (PFTs) for high-risk patients	Repeat oxygen saturation tests based on symptoms	Chest CT to evaluate for pneumonitis, biopsy if needed to exclude other causes.
Cardiovascular (ICI_CARDIO-1) • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre–existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral.

General management of checkpoint blockade toxicity

Table 4. Typical management of irAEs

Severity—CTCAE grade	Ambulatory versus inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily[a]
3	Hospitalization	Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider intensive care unit	Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised	Discontinue permanently

Some dysimmune toxicities may follow a specific management: this has to be discussed with the organ specialist.

[a]Outside skin or endocrine disorders where immunotherapy can be maintained.

Observe

Early steroids

Aggressive steroids

Get really aggressive

Manage immuno-suppressive tox

Diarrhea/enterocolitis

Table 2. Common terminology criteria for adverse events (12)

Grade	Diarrhea	Colitis
1	Increase of <4 stools/d over baseline	Asymptomatic
2	Increase of >4–6 stools/d	Abdominal pain, mucous, and blood in the stools
3	Increase of ≥7 stools/d, incontinence, and limiting self-care activity of daily living	Severe pain, fever, peritoneal signs, and ileus
4	Life-threatening consequences (hemodynamic collapse)	Life-threatening consequences (perforation, ischemia, necrosis, bleeding, and toxic megacolon)
5	Death	Death

National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). Accessed on December 8, 2019.

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Diarrhea and colitis for different drug classes

	Diarrhea : Gr 3,4 %	Colitis: all (Gr 3,4) %
Anti-PD-1	1.3	1.4 (0.9)
Anti-PD-L1	0.3	1.0 (0.6)
Anti-CTLA4	7.9	9.1 (6.8)
Combination	9.2	13. (9.4)

Incidence of all-grade and grade 3–4 colitis more frequent in melanoma compared with both NSCLC and RCC treated with PD-1/PD-L1 inhibitor

Wang, ONCOIMMUNOLOGY 2017;6(10): e1344805

Higher rates of severe colitis and diarrhea with ipilimumab in the **adjuvant** setting

Higher Ipi dose: More diarrhea; colitis

	Diarrhea %	Colitis %
Ipi 3mg/kg	5	2
Ipi 10mg/kg	10	6

No dose dependence for anti-PD-1

Am J Gastroenterol 2019;00:1–9.

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Risks/Associations

- Role of microbiome
  - 50% of patients with diarrhea have pANCA Ab and anti-outer membrane protein C against enteric flora
  - Immune mediated colitis associated with decreased diversity of gut microbiome
- Elevated baseline IL-17 levels associated with increased colitis
- High peripheral eosinophil counts during Ipilimumab treatment associated with greater risk of GIirAEs
- Baseline fecal calprotectin not predictive of GI irAEs
- Pre-existing IBD
- Higher ipilimumab doses

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Bellaguarda, Am J Gastroenterology2019

Natural history

- Anti-CTLA4-induced colitis can present after 1-10 doses;
  - median onset: 4 weeks but has been reported up to 2 months after last dose
- Anti-PD-1 colitis can occur as early as 2-4 months into therapy, but can occur up to 2 years after starting therapy
- Symptoms: diarrhea, abdominal pain, hematochezia, fever, vomiting
- Colonic perforation in 1-2.2%
- Median time to resolution for grade 2-4 diarrhea is 3.4 weeks; for colitis 2 weeks
- Clinical symptoms do not always correlate with evidence of mucosal inflammation

Bellaguarda, Am J Gastroenterology2019

Lab findings

- CBC, CMP,
- CRP,
- total immunoglobulin A,
- tissue transglutaminase immunoglobulin A,
- thyroid-stimulating hormone
- Stool pathogens (*Clostridium difficile,* stool culture, ova and parasites, and viral pathogens)
- Pancreatic elastase to evaluate for exocrine pancreatic insufficiency.

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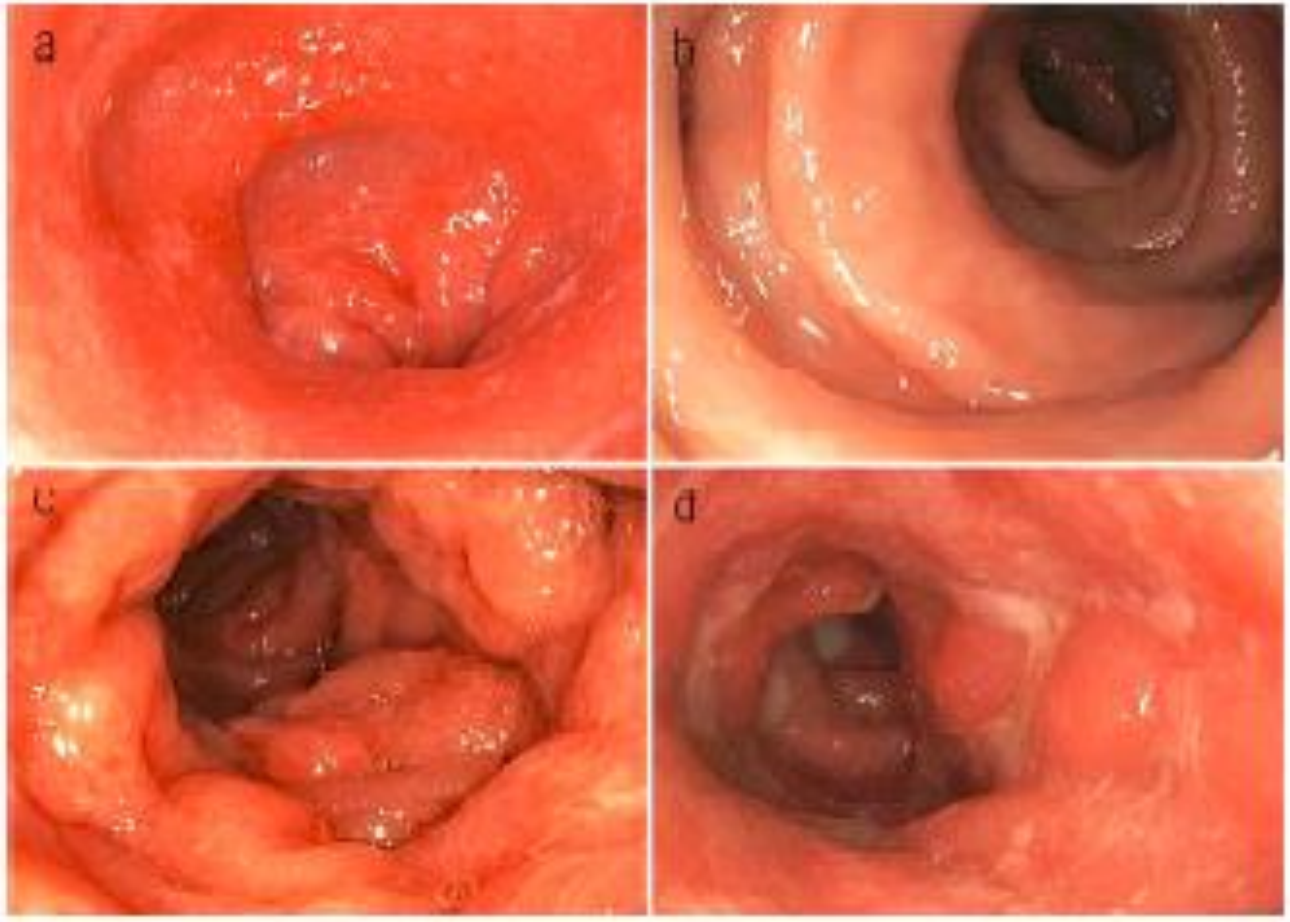
Colonoscopic/sigmoidoscopic findings



NOTE: 37% have normal colonoscopy

Bellaguarda, Am J Gastroenterology2019

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Colonoscopyfindings of IMC. Erythema, erosions (a); loss of vascular pattern (b); significant mucosal edema, erythema (c); ulcerations (dl.IMC = immune-mediated colitis

Enterocolitis: Pathologic findings

Histological findings	Immunological findings and platform used
Combined findings: Inflammatory infiltrate in the lamina propria composed of lymphocytes, neutrophils, eosinophils and plasma cells; neutrophilic crypt abscess formation; increased apoptotic activity within the crypt epithelium; crypt epithelial atrophy and crypt dropout. Chronic inflammatory changes including crypt distortion, basal plasmacytosis and paneth cell metaplasia. Granulomas (but uncommon). Lymphocytic colitis and collagenous colitis also described.	Immunohistochemistry and flow cytometry
Anti-PD-1: Features of acute colitis; chronic colitis (basal lymphoplasmacytosis and crypt architectural irregularity, paneth cell metaplasia); crypt abscesses; apoptosis; inflammatory infiltrate in the lamina propria composed of lymphocytes, neutrophils, eosinophils and plasma cells. Lymphocytic colitis and collagenous colitis.	Predominance of $CD8^+$ cells
Anti-CTLA-4: Features of acute colitis; chronic colitis (basal lymphoplasmacytosis and crypt architectural irregularity, paneth cell metaplasia); neutrophilic inflammation only; lymphocytic inflammation only; combined neutrophilic and lymphocytic infiltration; intra-epithelial neutrophilic lymphocytes; cryptitis; crypt abscesses; apoptosis; inflammatory infiltrate in the lamina propria composed of lymphocytes, neutrophils, eosinophils and plasma cells; granulomas. Lymphocytic colitis.	Predominance of $CD4^+$ cells with high TNFα expression. Significantly increased expression of the major Th-1 and Th-17 pro-inflammatory cytokines IFN-γ and IL-17A. No decrease in $FoxP3^+$ T regulatory cells.

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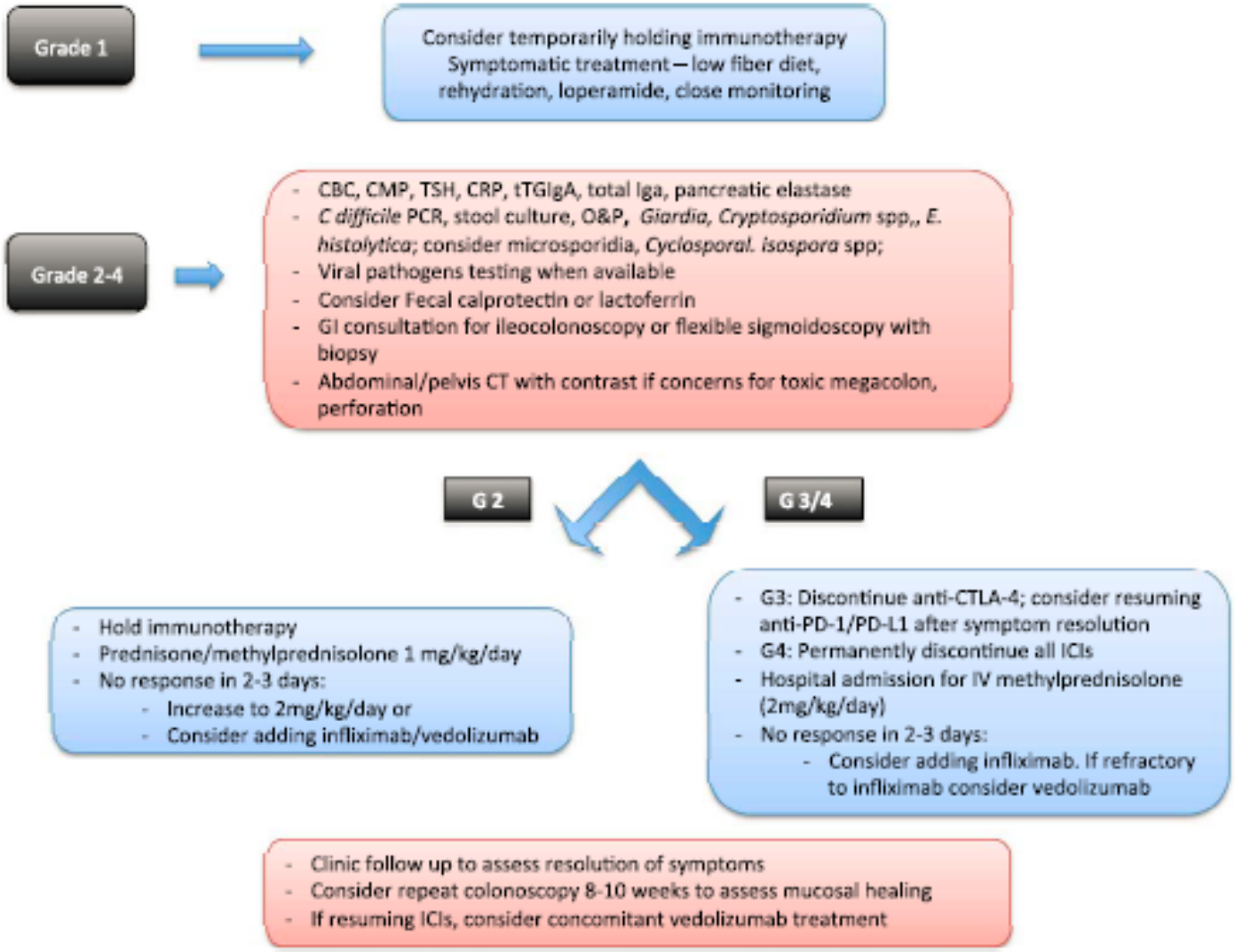
Ibraheim, Rheumatology 2019;58:vii17vii28

Colitis Management Points



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ICI-Pneumonitis

- Most common fatal irAE (accounts for 35% anti–PD-[L]1–related deaths)

Incidence:

- Clinical trials: 2.5–5% (monotherapy), 7–10% (combination ICI)
- Real world: 7–19%

Onset: mean 2.8 mo (9 d to 24 mo)

ICI-pneumonitis is likely increased in:

- NSCLC compared with melanoma (4.1% vs. 2.7%)
- Combination ICI inhibitors (especially PD-[L]1 and CTLA-4) (rate with anti-CTLA4 alone is very low)
- Radiation to the chest
- ICI-pneumonitis is possibly increased by:
    - Interstitial lung disease
    - Preexisting obstructive lung diseases (asthma and COPD) (25)
    - Certain histologies (adenocarcinoma compared to other NSCLC histologic subtypes) (36)
    - Treatment in combination with EGFR-TKIs (41–43)

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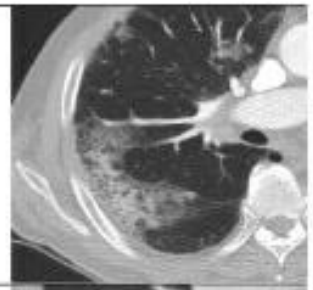
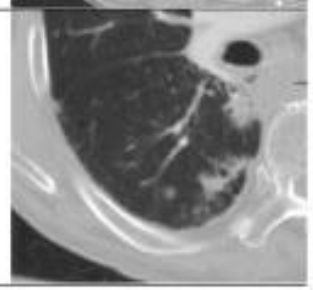
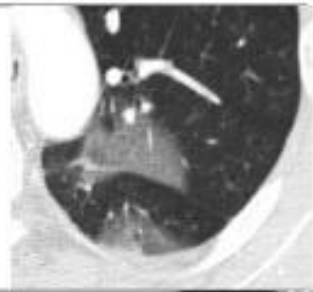
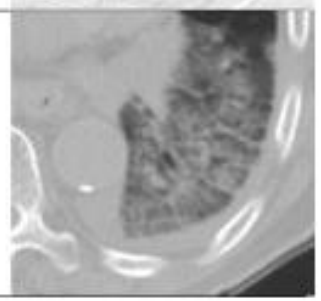
Sears, Am J Respir Crit Care Med Vol 200, Iss 6, pp e31–e43, Sep 15, 2019

Organizing pneumonia pattern	
a. Pure organizing pneumonia (n=11, 50.0%)	
b. Organizing pneumonia with bronchiolitis (n=5, 22.7%)	
Ground glass opacity pattern	
c. Pure ground glass opacity (n=3, 13.6%)	
d. Ground glass opacity with interlobular septal thickening (n=3, 13.6%)	

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Cho JY, Lung Cancer. 2018 Nov;125:150-156.

Pulmonary Toxicity Key Points

Grade 3-4 toxicities:

- Should permanently discontinue ICPi.
- Should prescribe empirical antibiotics and administer (methyl)prednisolone IV 1 to 2 mg/kg/d. No improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide. Taper corticosteroids over 4 to 6 weeks.
- Should consult pulmonary and infectious disease if necessary.
- Should offer bronchoscopy with bronchoalveolar lavage with or without transbronchial biopsy.
- Patients should be hospitalized for further management.

Skin Toxicity Key Points

Grade 1 toxicities:

- Should continue to offer ICPi.
- Should treat skin with topical emollients (if predominately dry skin is observed) and/or mild to moderate potency (hydrocortisone 2.5% or equivalent to triamcinolone 0.1% or equivalent) topical corticosteroids (signs of inflammation/redness with or without itching).
- Should counsel patients to avoid skin irritants and sun exposure.

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Skin Toxicity Key Points

Grade 2 toxicities

- May hold ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 or less and consider dermatology referral.
- Should treat skin with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids.
- Consider initiating prednisone (or equivalent) at dosing 1 mg/kg tapering over at least 4 weeks, depending on primary skin lesions observed on examination.

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Skin Toxicity Key Points

Grade 3 toxicities

- Should hold ICPi therapy and consult with dermatology
- Should treat skin with topical emollients, oral antihistamines, and high-potency topical corticosteroids.
- Initiate intravenously (IV) (methyl)prednisolone (or equivalent) dosed at 1 to 2 mg/kg and taper over at least 4 weeks.
- If not resolved, refer to dermatology.

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Skin Toxicity Key Points

Grade 4 toxicities

- Should immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) 10 mg or less.
- Should administer IV (methyl)prednisolone (or equivalent) dosed at 1 to 2 mg/kg, with slow tapering when the toxicity resolves.
- Should monitor closely for progression to severe cutaneous adverse reaction (SCAR).
- Should admit patient immediately /urgent consult by dermatology.
- Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to grade 1 or less.
- If ICPis are the patient's only option, consider restarting once these adverse effects have resolved to a grade 1 level.

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Skin Toxicity Key Points

Severe cutaneous adverse reactions, or SCARs, include, but are not limited to, SJS/TEN and DRESS (also called DIHS).

- Should permanently discontinue ICPi.
- Should admit patient immediately with consideration to a burn unit or ICU in the case of SJS/TEN and consult dermatology.
- Administer IV (methyl)prednisolone or equivalent 1 to 2 mg/kg with tapering when the toxicity resolves to normal.
- May consider IV immunoglobulin (IVIG) or cyclosporine as an alternative or in corticosteroid-refractory cases.
- Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.

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Immune-mediated Hepatitis Key Points

Grade 4 toxicities:

- Should permanently discontinue treatment with ICPi.
- Should administer 2 mg/kg/d methylprednisolone equivalents.
- If corticosteroid refractory or no improvement after 3 days, may offer mycophenolate mofetil.
- Should monitor laboratories daily; inpatient monitoring may be offered.
- Should not offer infliximab in the situation of immune-mediated hepatitis.
- Should refer to hepatology if no improvement is achieved with corticosteroid.
- Corticosteroid taper should be attempted over a period of 4-6 wks when symptoms improve to ≤ grade 1, reescalate if needed, optimal duration unclear.
- Consider transfer to tertiary care facility if necessary.

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Endocrine Toxicity Key Points

In most cases can continue ICB

Hormone replacement per endocrinology

- In some cases: May administer initial pulse dose therapy with prednisone 1 to 2 mg/kg oral daily (or equivalent) tapered over at least 1 to 2 weeks.

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Managing complications of immunosuppression

- Corticosteroid termination should follow a gradual decrease of doses over a period of at least 1 month.
- Consider antibiotic prophylaxis with trimethoprim/sulfamethoxazole (400 mg po qd) if corticosteroids ≥1 mg/kg are used.
  - Prophylaxis continued until steroid dose is below 10 mg per day.
- Consider testing patients for tuberculosis (quantiferon or TST) in case of severe toxicity requiring additional immunosuppressive drugs and introduce anti-tuberculosis prophylaxis if positive.
- Antifungal prophylaxis for > 12 weeks immunosuppression (?)

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Are toxicities associated with outcome ?

Ipilimumab: YES

Table 5. Relationship between IRAEs and response

	All	NR	PR + CR	*P*	Duration of response (mo), median (range)
IRAE					
None	53	52	1 (2%)	0.0004	18+
Only grade 1/2	36	28	8 (22%)		11 (4-30+)
Grade 3/4	50	36	14 (28%)		35 (7-53+)

Downey, Clin Cancer Res 2007;13:6681

Nivolumab: ?

	Nivo overall	Any Grade irAE	GR 3-4 irAE
ORR	31%	48.6%	27.8%

Weber J, ASCO 2015; Abstr 9018

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Is clinical benefit affected by steroids/immune modulators ?

Ipilimumab: No

Table 6. Duration of response in patients requiring steroid administration

	No. patients	Duration of response	Median (mo)	*P*
All responders	23		30.6	
Requiring steroids	12	6, 7, 9, 10, 11, 19, 28+, 29+, 31+, 43, 47+, 52+	19.3	0.23*
Not requiring steroids	11	4, 5, 6, 10, 17+, 17+, 18+, 22+, 30+, 50+, 53+	Not reached	

*By time-varying covariate analysis.

Downey, Clin Cancer Res 2007;13:6681

Nivolumab: No

Table 4. Response in pts who received or did not receive a systemic IM

	NIVO monotherapy with IM N = 139	NIVO monotherapy without IM N = 437
ORR, n (%), [95% CI]	40 (28.8) [21.4–37.1]	141 (32.3) [27.9–36.9]
BOR, n (%)		
CR	7 (5.0)	22 (5.0)
PR	33 (23.7)	119 (27.2)
SD	31 (22.3)	102 (23.3)
PD	63 (45.3)	173 (39.6)
Not evaluable	5 (3.6)	21 (4.8)
Median duration of response, mo (95% CI)	NR (9.3–NR)	22.0 (22.0–NR)
Median time to response, mo (range)	2.1 (1.2–8.8)	2.1 (1.4–9.2)

Pts evaluable for response had a baseline tumor assessment and a confirmatory scan at least 4 weeks after the first documented response
BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease

Weber J, ASCO 2015; Abstr 9018

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Reporting of toxicity

TABLE 2. Reporting of Clinical Consequences of Toxicity

	Patients Who Experience Toxicity								
Adverse Event	Dose Delay (No. and proportion of patients)	Dose Discontinuation* (No. and proportion of patients)	Timing of Toxicity Onset (median and range)†	Use of High-Dose‡ Steroids (No. and proportion of patients)	Duration of High-Dose Steroid Use (median and range)	Duration of Dose Tapering§ (median and range)	Additional Immune-Suppressing Agents (No. and proportion of patients who required escalation beyond steroids; specify drugs)	Time to Resolution of Toxicity‖ (median and range, percent of patients with unresolved toxicity)	Emergency Center Visit/ Hospitalization (No. and proportion of patients)
Adverse event 1 (e.g., colitis)									
Adverse event 2									
Adverse event 3									
Adverse event 4									

*Defined as the inability to continue on the protocol; may include irreversible toxicity and toxicity resulting in ineligibility for subsequent treatment.
†Days from cycle 1, day 1 to time of onset (include cycle, day and period from initiation of treatment).
‡Defined as at least 40 mg prednisone equivalents per day.
§If the protocol required collecting this information.
‖Define specifically if "resolution" refers to return to grade 1 or 0 (indicate whether this includes patients who are on steroids to manage adverse events).

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DOI: 10.1200/JCO.18.00145

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Summary

- Have a high level of suspicion for autoimmune mediated events
  - Very unusual events can occur
  - But include other etiologies in the differential
- Patient education
- Steroids
- Referral to other consultants
- Specialized immunosuppression by site of autoimmunity
- Clinical benefit possible even with steroids
- Re-”challenge” possible

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