



# 2018

28-30 JUNE  
VIENNA, AUSTRIA

SUPPORTIVE CARE  
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#MASCC18



# UPDATE ON RECOMMENDATIONS AND GUIDELINES

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June 28, 2018





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## **DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY**

Jennifer N. Choi, MD

### **DISCLOSURES**

Biotest AG: Consultant – Honoraria

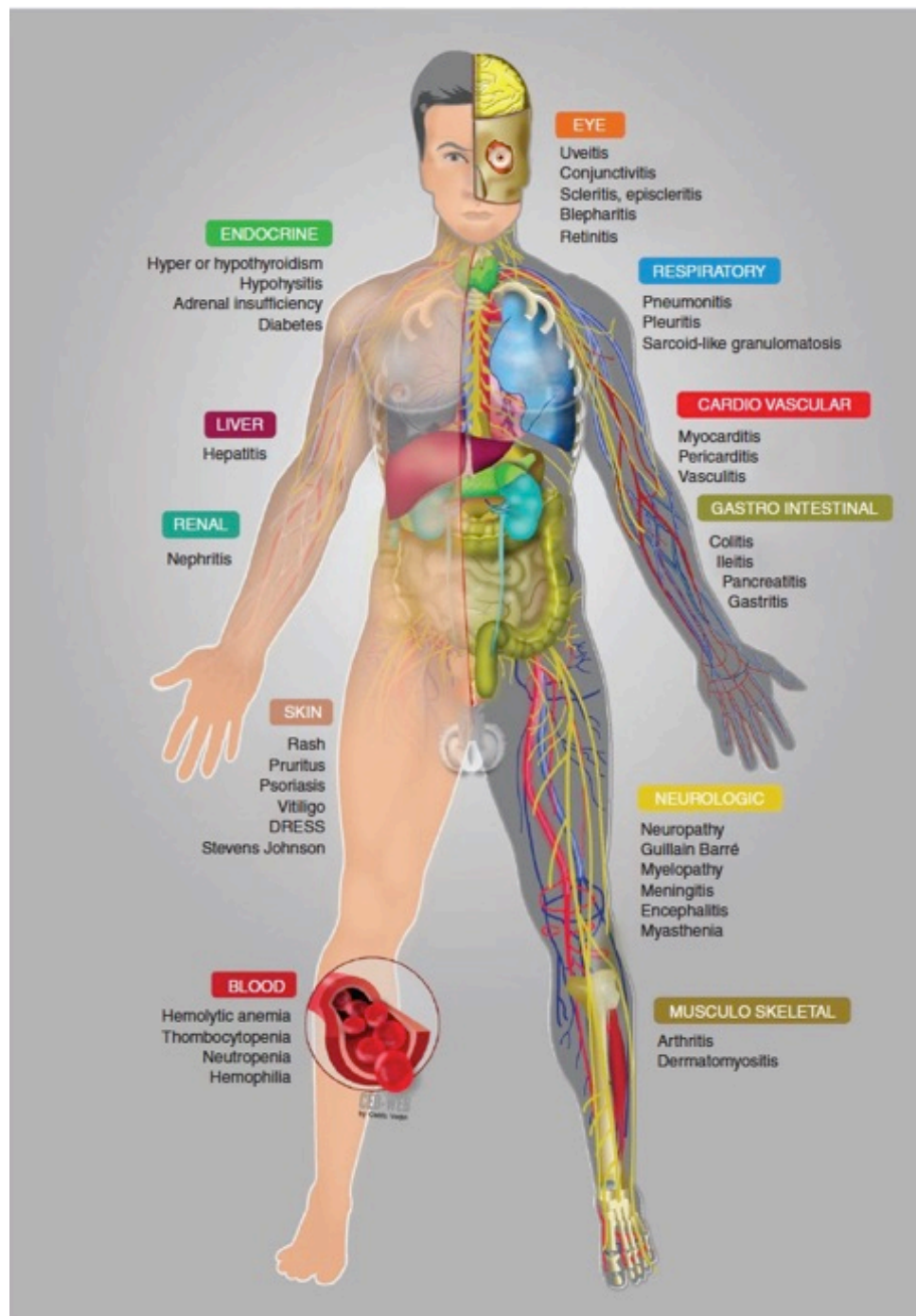
Bayer: Speaker – Honoraria

Incyte: Principal Investigator – Research

Veloce Pharmaceuticals: Principal Investigator –  
Research





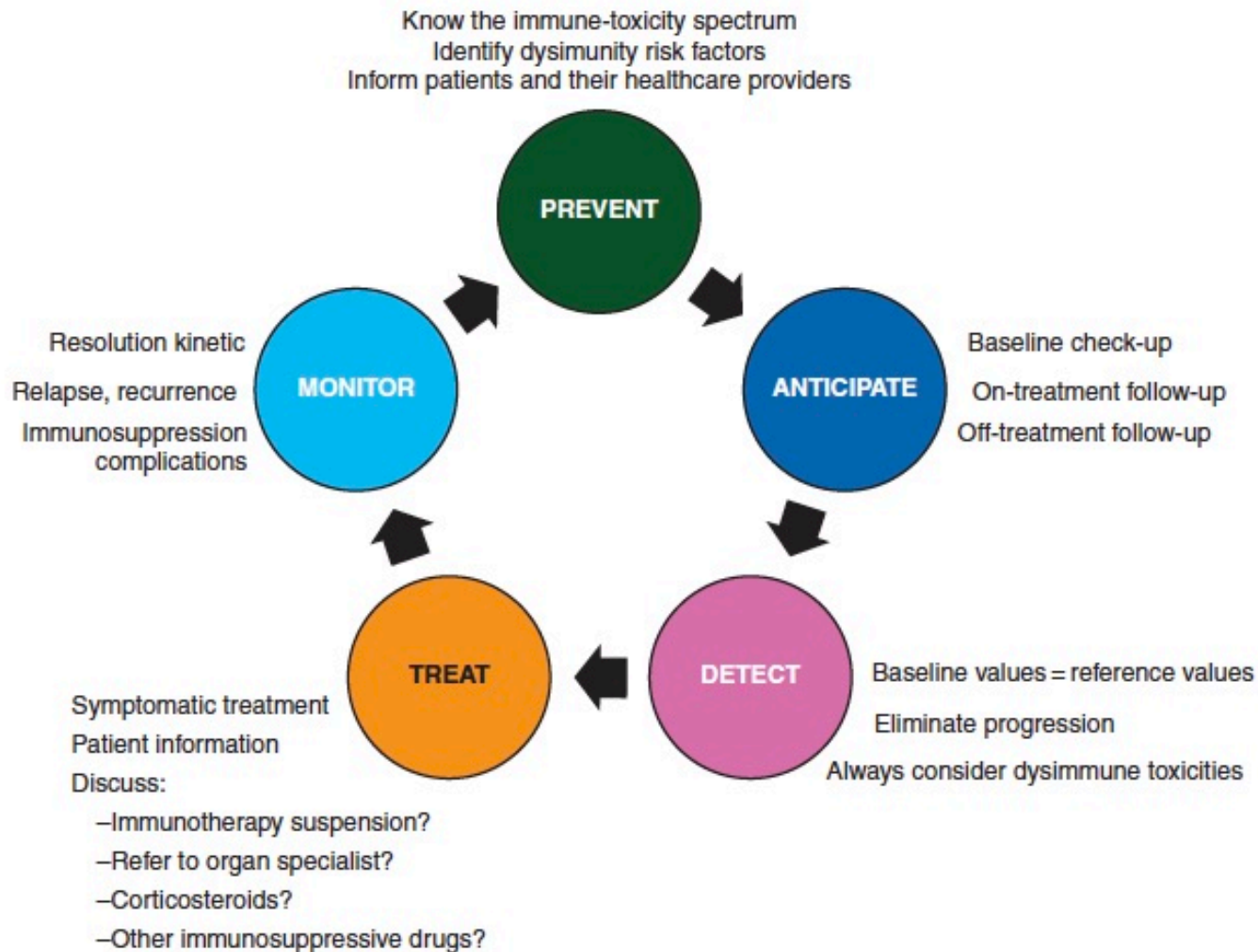


## Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper

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# 5 Pillars of Immunotherapy Toxicity Management





**Table 1.** Immune checkpoint blockade (ICB) toxicities

Frequent (>10%) ICB toxicities

Ipilimumab (anti-CTLA4): diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain

Nivolumab (anti-PD1): fatigue, rash, pruritus, diarrhea and nausea

Pembrolizumab (anti-PD1): diarrhea, nausea, pruritus, rash, arthralgia and fatigue

Rare (<10%) life-threatening ICB toxicities

Colitis and risk of gastrointestinal perforation

Pneumonitis including acute interstitial pneumonia/acute respiratory distress syndrome

Infusion reaction and anaphylactic shock

Type 1 diabetes and risk of diabetic ketoacidosis

Severe skin reactions, DRESS, Stevens Johnson syndrome

Hemolytic anemia or immune thrombocytopenia and hemorrhagic risk

Neutropenia and sepsis risk

Encephalopathy and neurological sequelae

Guillain-Barré syndrome and respiratory risk

Myelitis and motor sequelae

Myocarditis and cardiac insufficiency

Acute adrenal insufficiency and hypovolemic shock

Pleural and pericardial effusion

Nephritis

**Table 2.** Immunotherapy baseline checklist**Physical examination**

Performance status

Weight, size, body mass index

Heart rate and blood pressure

General symptoms such as asthenia or appetite should be evaluated as they are frequently affected

Particularly pay attention to pre-existing symptoms regarding: intestinal transit, dyspnea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia

History of fever or recent infection must be checked and investigated appropriately

Baseline electrocardiogram

Ongoing treatment

**Laboratory test**

Complete CBC

Serum electrolytes: Na, K, alkaline reserve, calcium, phosphorus, uric acid, urea, creatinine with estimated GFR (MDRD or CKD EPI)

Glycemia

Total bilirubin, AST, ALT, GGT, PAL

Albuminemia, CRP

TSH, T4

Cortisol and ACTH at 8 am

LH FSH estradiol testosterone

Proteinuria: morning sample, fasting if possible (g/l with concomitant dosing creatinine in mmol/l)—better than an urine dipstick to detect low levels of proteinuria and tubular proteinuria

Urinary sediment

Quantiferon tuberculosis or TST in case of anterior exposure

Virology: HIV, HCV and HBV serology

Antibody: ANA, TPO Ab, Tg Ab

If doable, we recommend a plasma/serum biobanking before the beginning of immunotherapy to retrospectively titrate at baseline any other factor of interest in case of development of toxicity with biological marker.

**Imaging**

X-ray chest imaging reference is recommended at baseline

The conventional pretherapeutic thoracic CT scan should be performed with thin sections with and without injection to have a baseline reference in case a pulmonary toxicity occurs.

Any other evaluation may also be necessary before starting immunotherapy depending on patient's history, symptoms or diseases detected at baseline.



**Table 2.** Immunotherapy baseline checklist

Physical examination

Performance status

Weight, size, body mass index

Heart rate and blood pressure

General symptoms such as asthenia or appetite should be evaluated as they are frequently affected

Particularly pay attention to pre-existing symptoms regarding: intestinal transit, dyspnea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia

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If adverse event, consider 3 potential etiologies:

1. disease progression
2. fortuitous event
3. treatment-related dysimmune toxicity

Digestive	Abdominal pain	<p>Tumor compression of the biliary tract, urinary tract, pancreatic ducts</p> <p>Peritoneal tumor invasion</p> <p>Tumor or iatrogenic bowel obstruction</p> <p>Intra-abdominal infection (cholecystitis ...)</p> <p>Hypercalcemia</p> <p>Pancreatitis (lithiasis, alcohol ...)</p> <p>Thrombosis</p>	<p>Dysimmune enterocolitis</p> <p>Dysimmune pancreatitis</p> <p>Dysimmune gastritis</p> <p>Dysimmune pericarditis</p> <p>Dysimmune myocarditis</p> <p>Dysimmune pleurisy</p> <p>Occlusive syndrome of enteric neuropathy</p> <p>Occlusive syndrome in dysimmune hypothyroidism</p> <p>Acute adrenal insufficiency</p> <p>Ketoacidosis due to dysimmune diabetes</p>
	Diarrhea	<p>Secondary to antibiotic use</p> <p>Enteropathy due to cancer</p> <p>Clostridium difficile</p> <p>Exocrine pancreatic insufficiency on tumor compression</p>	<p>Dysimmune enterocolitis</p> <p>Celiac disease</p> <p>Dysimmune hyperthyroidism</p>
	Nausea vomiting	<p>Bowel obstruction by the tumor</p> <p>Carcinomatous peritonitis</p> <p>Carcinomatous meningitis</p> <p>Intracranial hypertension</p> <p>Hypercalcemia</p> <p>Hyponatremia</p>	<p>Dysimmune meningitis</p> <p>Dysimmune enterocolitis</p> <p>Ketoacidosis due to dysimmune diabetes</p> <p>Dysimmune adrenal insufficiency</p> <p>Dysimmune nephropathy</p> <p>Dysimmune pancreatitis</p> <p>Dysimmune hepatitis</p>



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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)  
in partnership with the American Society of Clinical Oncology (ASCO)**

# **Management of Immunotherapy-Related Toxicities**

**(Immune Checkpoint Inhibitor-Related Toxicities)**

Version 1.2018 — February 14, 2018

**NCCN.org**

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# NCCN Guidelines Version 1.2018

## Management of Immunotherapy-Related Toxicities

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NCCN wishes to acknowledge the contributions of ASCO in supporting  
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[NCCN Guidelines Panel Disclosures](#)

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### NCCN Management of Immunotherapy-Related Toxicities Panel Members

#### Dermatologic Toxicity

- [Maculopapular Rash \(IMMUNO-1\)](#)
- [Pruritis \(IMMUNO-2\)](#)
- [Blistering Disorder \(IMMUNO-3\)](#)

#### [Gastrointestinal Toxicity \(IMMUNO-4\)](#)

#### [Hepatic Toxicity \(IMMUNO-5\)](#)

#### Pancreatic Toxicity

- [Elevation in Amylase/Lipase \(IMMUNO-7\)](#)
- [Acute Pancreatitis \(IMMUNO-8\)](#)

#### Endocrine Toxicity

- [Hyperglycemia/Diabetes Mellitus \(IMMUNO-9\)](#)
- [Thyroid \(IMMUNO-10\)](#)
- [Adrenal, Pituitary \(IMMUNO-11\)](#)
- [Hypophysitis \(IMMUNO-12\)](#)

#### [Pulmonary Toxicity \(IMMUNO-13\)](#)

#### [Renal Toxicity \(IMMUNO-15\)](#)

#### [Ocular Toxicity \(IMMUNO-16\)](#)

#### Nervous System Toxicity

- [Myasthenia Gravis \(IMMUNO-17\)](#)
- [Guillain-Barré Syndrome \(IMMUNO-18\)](#)
- [Peripheral Neuropathy \(IMMUNO-19\)](#)
- [Aseptic Meningitis \(IMMUNO-20\)](#)
- [Encephalitis \(IMMUNO-20\)](#)
- [Transverse Myelitis \(IMMUNO-21\)](#)

#### [Cardiovascular Toxicity \(IMMUNO-22\)](#)

#### Musculoskeletal Toxicity

- [Inflammatory Arthritis \(IMMUNO-23\)](#)
- [Myalgias/Myositis \(IMMUNO-24\)](#)

#### [Infusion/Related Reactions \(IMMUNO-25\)](#)

#### [Principles of Immunosuppression \(IMMUNO-A\)](#)

#### [Principles for Patient Education \(IMMUNO-B\)](#)

#### [Principles of Immunotherapy Rechallenge \(IMMUNO-C\)](#)

#### [Principles of Routine Monitoring \(IMMUNO-D\)](#)

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[nccn.org/clinical\\_trials/clinicians.aspx](http://nccn.org/clinical_trials/clinicians.aspx).

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

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DERMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT <sup>h</sup>
Maculopapular rash <sup>a</sup>	<ul style="list-style-type: none"> <li>• Total body skin exam, including mucosa</li> <li>• Assess for history of prior inflammatory dermatologic diseases</li> <li>• Consider biopsy if unusual features</li> </ul>	<p>Mild (G1)<sup>d</sup> →</p> <ul style="list-style-type: none"> <li>• Continue immunotherapy</li> <li>• Treatment with moderate potency topical steroids</li> <li>• Oral antihistamine</li> <li>• Topical emollient</li> </ul> <p>Moderate (G2)<sup>e</sup> →</p> <ul style="list-style-type: none"> <li>• Consider holding immunotherapy<sup>i</sup></li> <li>• Treatment with high potency topical steroids AND/OR</li> <li>• Prednisone 0.5–1 mg/kg/day<sup>g</sup></li> <li>• Oral antihistamine</li> <li>• Topical emollient</li> </ul> <p>Severe (G3–4)<sup>f</sup> →</p> <ul style="list-style-type: none"> <li>• Hold immunotherapy<sup>i</sup></li> <li>• Treatment with high potency topical steroids</li> <li>• Prednisone 0.5–1 mg/kg/day<sup>g</sup> (increase dose if no improvement)</li> <li>• Urgent dermatology consultation</li> </ul>
Pruritus <sup>b</sup>	→ <a href="#">IMMUNO-2</a>	
Blistering disorder <sup>c</sup>	→ <a href="#">IMMUNO-3</a>	

<sup>a</sup>Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and may be associated with pruritus.

<sup>b</sup>Characterized by an intense itching sensation.

<sup>c</sup>Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid.

<sup>d</sup>Macules/papules covering <10% body surface area (BSA) with or without symptoms (eg, pruritus, burning, tightness).

<sup>e</sup>Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living (ADLs).

<sup>f</sup>Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADLs.

<sup>g</sup>Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

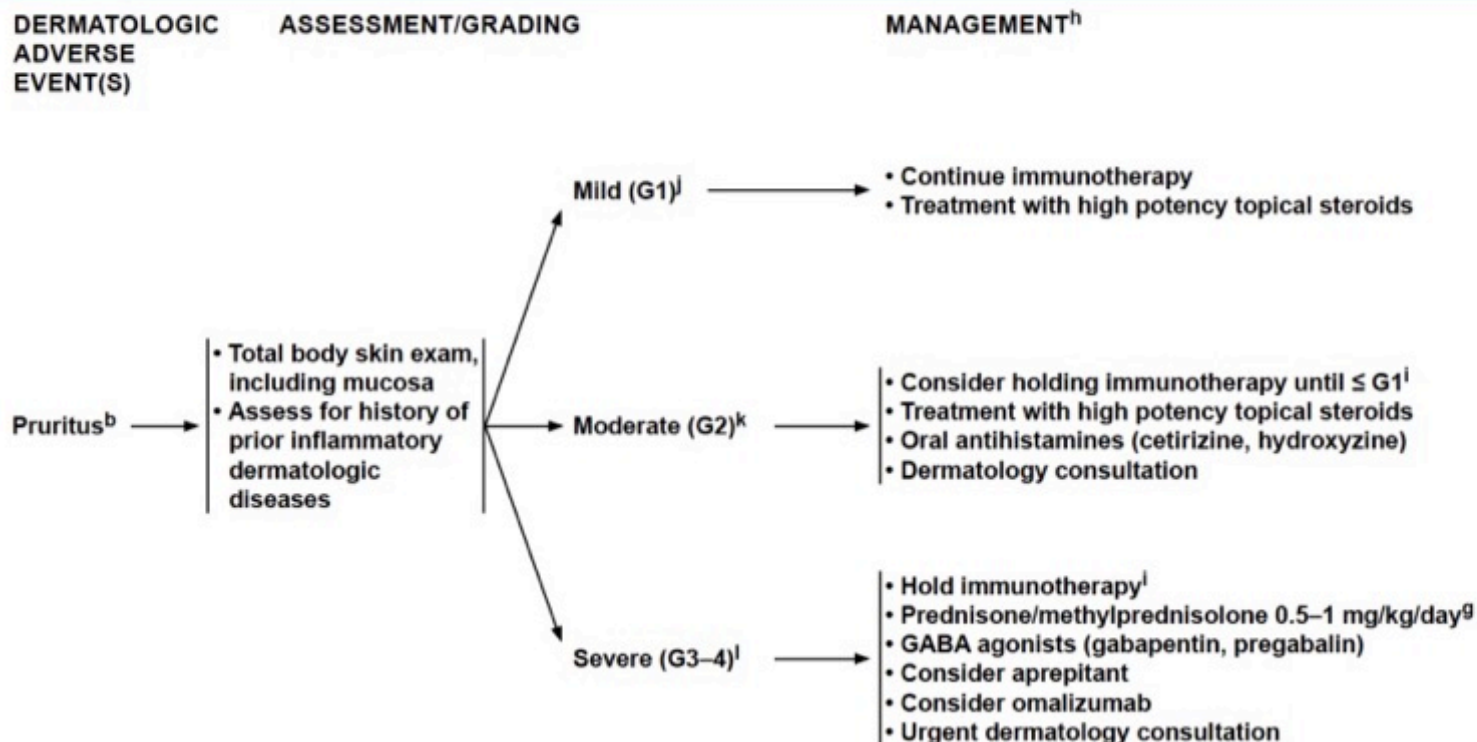
<sup>h</sup>See [Principles of Immunosuppression \(IMMUNO-A\)](#).

<sup>i</sup>See [Principles of Immunotherapy Rechallenge \(IMMUNO-C\)](#).

**Note:** All recommendations are category 2A unless otherwise indicated.

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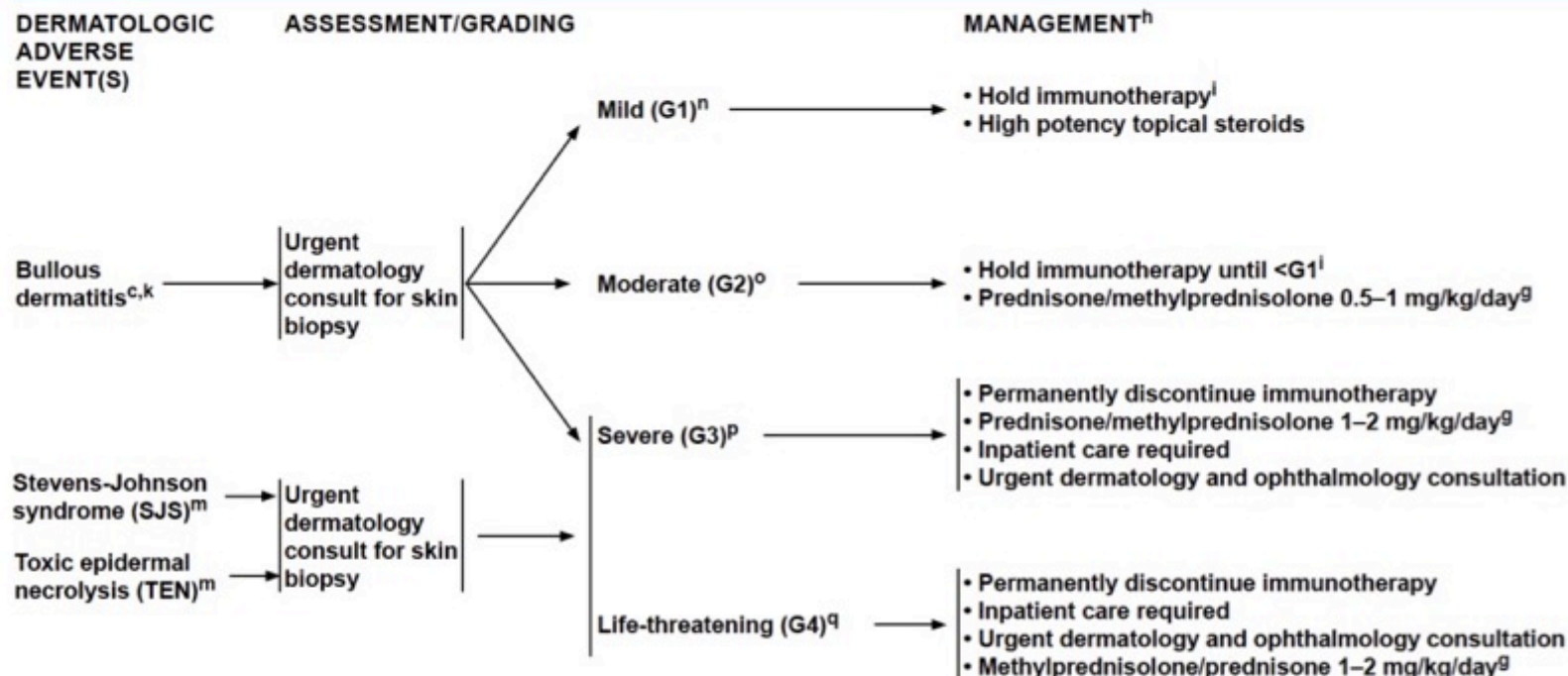
<sup>l</sup>Mild or localized.

<sup>k</sup>Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADLs.

<sup>l</sup>Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.

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<sup>c</sup>Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid.

<sup>g</sup>Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

<sup>h</sup>See [Principles of Immunosuppression \(IMMUNO-A\)](#).

<sup>i</sup>See [Principles of Immunotherapy Rechallenge \(IMMUNO-C\)](#).

<sup>k</sup>Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADLs.

<sup>m</sup>Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) should be treated as grade 3–4 bullous dermatitis. SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.

<sup>n</sup>Asymptomatic; blisters covering <10% BSA.

<sup>o</sup>Blisters covering 10%–30% BSA; painful blisters; limiting instrumental ADLs.

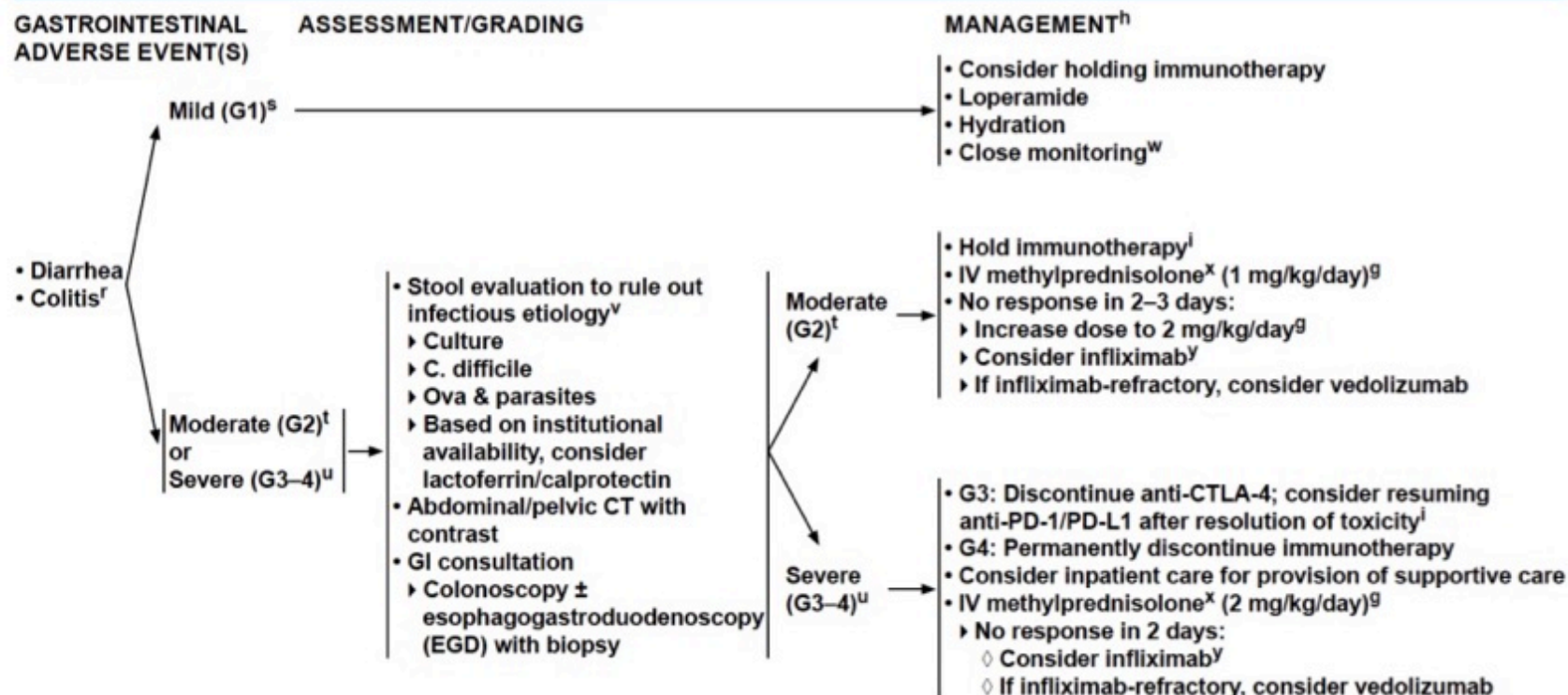
<sup>p</sup>Blisters covering >30% BSA; limiting self-care ADLs.

<sup>q</sup>Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated.

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<sup>g</sup>Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

<sup>h</sup>See [Principles of Immunosuppression \(IMMUNO-A\)](#).

<sup>i</sup>See [Principles of Immunotherapy Rechallenge \(IMMUNO-C\)](#).

<sup>r</sup>Symptoms include: abdominal pain, blood and mucus in the stool, fever.

<sup>s</sup>Fewer than 4 bowel movements above baseline per day and no colitis symptoms.

<sup>t</sup>4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.

<sup>u</sup>More than 6 bowel movements above baseline per day, colitis symptoms,

interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).

<sup>v</sup>It is not necessary to wait for test results before providing therapy to manage irAE.

<sup>w</sup>If progressive, consider stool evaluation to rule out infectious etiology.

<sup>x</sup>Convert to prednisone when appropriate.

<sup>y</sup>Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment.

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## 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. Brissil, 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. Santomaso, 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*

**Table 1.** Management of Skin irAEs in Patients Treated With ICPIs

## 1.0 Skin Toxicities

**1.1 Rash/inflammatory dermatitis**

Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [eg. Sweet syndrome], and others)

**Diagnostic work-up**

Pertinent history and physical examination

Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder

If needed, a biologic checkup, including a blood cell count and liver and kidney tests

Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms

Skin biopsy

Consider clinical monitoring with use of serial clinical photography

Review full list of patient medications to rule out other drug-induced cause for photosensitivity

Grading	Management
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPI Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPI and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPI therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	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) $\leq 10$ mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPIs if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level



### 1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS

Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug

#### Diagnostic work-up

Total body skin examination with attention to examining all mucous membranes as well as complete review of systems

Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease

A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well

Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pustulosis

Consider following patients closely using serial clinical photography

If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management

Primer on monitoring for complicated cutaneous adverse drug reactions:

Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements

Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN

#### All grades

In cases of suspected SJS or any mucous membrane involvement, discontinue ICPI treatment and monitor closely for improvement, regardless of grade

#### G1: NA

For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4

#### G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling

Hold ICPI and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement  
Consider following patients closely using serial photography  
Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids  
Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks

#### G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment)

Hold ICPI therapy and consult with dermatology  
Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum  
Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks  
Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection  
Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered  
For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)

#### G4: Skin erythema and blistering/sloughing covering $\geq$ 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting of DRESS/DIHS)

Permanently discontinue ICPI  
Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services  
Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc)  
Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal  
IVIg or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases  
Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations

Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity.

Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS

All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate



# General Principles of Management

- **Organ specialist or internal referral** needed for 2 reasons:
  - 1. Oncologists to learn proper management of specific immune-related adverse events
  - 2. Organ specialists to increase their knowledge about these drug-mediated toxicities
- Oncologists should define their **local organ specialist team** based on their interest and expertise on the topic, as well as availability and responsiveness to solicitation.
- **Organ specialist support should be sought as soon as the diagnosis and treatment of irAEs become difficult (i.e. > grade 1).** Specialist expertise is often needed for proper monitoring over time.

# General Principles of Management

- Guidelines are based on expert opinion.
  - No prospective trials yet on treatment of immunotherapy-related AEs.
  - Grades 3-5 irAEs occur with **greater frequency with CTLA-4 inhibitors** than with PD-1 or PD-L1 inhibitors.
  - Toxicity **more severe with combinations** of CTLA-4 and PD-1/PD-L1 inhibitors than with either class alone.
- 
- If a serious toxicity occurs, the checkpoint inhibitor **should be stopped** until the toxicity resolves or improves.
  - Studies of outcomes in patients who discontinue therapy due to AEs show **no statistically significant difference** in progression-free and overall survival.

# Principles of Immunosuppression

- **Corticosteroids** are mainstay of treatment of most irAEs.
- **Early intervention** with corticosteroids is key goal of management
- Use of corticosteroids to treat irAEs has **not** been shown to reduce anti-tumor efficacy.
  - BUT routine premedication with corticosteroids for nausea and infusion reactions is not recommended unless indicated
- **Longer steroid tapers** (>4 weeks, sometimes 6-8 weeks or longer) to prevent recurrent irAEs

- Prophylaxis:
  - **Pneumocystis jiroveci pneumonia (PJP)** if prednisone  $\geq 20$  mg QD x 4 or more weeks
  - **Fungal infections** (e.g. fluconazole) if prednisone  $\geq 20$  mg QD x 6-8 or more weeks
  - **PPI or H2 blockers** if higher risk of gastritis (e.g. NSAID use, anticoagulation) for duration of steroid therapy
  - If long term steroid use, give **vitamin D + calcium supplementation** to prevent osteoporosis.



# Principles of Immunosuppression

- **Anti-TNF $\alpha$  agents** (e.g. infliximab) are effective in management of some irAEs, especially colitis and inflammatory arthritis.
    - Test for **viral hepatitis B and C** prior
    - Monitor carriers carefully
    - Test for latent/active **TB**
  - If severe irAEs not responsive to steroids within 48-72 hours, **early (72 hrs) initiation of anti-TNF $\alpha$  therapy** may be warranted.
  - TNF $\alpha$  agents should be avoided in patients with immune-related hepatitis
    - Can consider **vedolizumab** (alpha-4 beta-7 integrin inhibitor) if both hepatitis and colitis
- 
- Patients with **pre-existing autoimmune conditions or organ transplant recipients** may be candidates for immune checkpoint blockade.
    - **Higher risk** of exacerbating baseline autoimmune conditions with **anti-CTLA-4**
    - Optimize immunosuppression for pre-existing autoimmune conditions (goal for **prednisone <10 mg QD** prior to initiating immunotherapy)
    - **Graft failure** has been reported

# Principles of Immunosuppression

- Patients with **prior allogeneic stem cell transplant** may be candidates for immunotherapy.
  - **Increased risk of transplant-related complications**, including GVHD (can be fatal).
- Patients with **history of HIV or viral hepatitis** may be candidates.
- Vaccines that are **inactivated or killed** are permissible.
  - Less clarity regarding live vaccine use

# Immunotherapy Patient Education

- Document **any underlying medical condition**, including autoimmune diseases
- **Record all medications**, including over-the-counter and herbal supplements
- Patients must use **effective birth control** during and for at least 5 months after final dose of immunotherapy
- **Breastfeeding is contraindicated** during and for at least 5 months after final dose of immunotherapy
- **Supportive care:**
  - Monitor blood glucose levels
  - PPI or H2 blockers
  - Antimicrobial and antifungal prophylaxis
  - Vitamin D + calcium supplementation



# Patient Education To Monitor and Be Prepared

- Importance for patients to self-monitor symptoms:

- Severe fatigue
- Headache
- Rash
- Cough
- Shortness of breath
- Chest pain
- Abdominal bloating
- Change in bowel pattern
- Weight loss
- Vision changes or eye pain
- Severe muscle weakness
- Severe muscle or joint pains
- Mood changes

- Symptoms can occur early, late, or after discontinuation of immunotherapy.
- Patients should monitor symptoms for at least 1 year following conclusion of immunotherapy.

# Patient Education

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The image shows two cards from the ONS (Oncology Nursing Society) Immunotherapy Patient Education kit. The top card is the 'IMMUNOTHERAPY WALLET CARD' with a blue and red border. It contains fields for patient information: NAME, CANCER DX, I-O AGENTS RCV'D (with checkboxes for CHECKPOINT INHIBITOR(S), CAR-T, VACCINES, ONCOLYTIC VIRAL THERAPY, and MONOCLONAL ANTIBODIES), DRUG NAME(S), IMMUNOTHERAPY TX START DATE, and OTHER CANCER MEDICATIONS. A note at the bottom states: 'NOTE: IMMUNOTHERAPY AGENTS ARE **NOT** CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY (SEE BACK)'. The ONS logo is in the bottom right corner. The bottom card is the 'IMMUNOTHERAPY CARD' with an orange and blue border. It features the text: '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.' Below this is a footnote: '\*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.' The card also has fields for ONCOLOGY PROVIDER NAME, ONCOLOGY PROVIDER NO., EMERGENCY CONTACT, and CONTACT PHONE NO.

**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**  
Oncology Nursing Society

**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.

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ONCOLOGY PROVIDER NAME \_\_\_\_\_

ONCOLOGY PROVIDER NO. \_\_\_\_\_

EMERGENCY CONTACT \_\_\_\_\_

CONTACT PHONE NO. \_\_\_\_\_

# Principles of Immunotherapy Rechallenge

- **Caution** when resuming immunotherapy -> very careful monitoring
- Resumption of immunotherapy following grade 2 irAEs can be considered **upon resolution to  $\leq$  grade 1**.
- If re-challenged and toxicity returns, permanently **discontinue** class of immunotherapy.
- Can **consider switching to other class** of immunotherapy
  - E.g. if patient experiences grade 3 or 4 toxicity from ipilimumab-containing regimen, can consider later therapy with a PD-1 or PD-L1 monotherapy after resolution of earlier toxicity.



**PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE**

**Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold**

<b>Skin</b>	<ul style="list-style-type: none"> <li>• Maculopapular rash and/or pruritus: consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).</li> <li>• Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN.</li> </ul>
<b>GI</b>	<ul style="list-style-type: none"> <li>• PD-1/PD-L1 agents: After grade 2–3 colitis, consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. In rare circumstances in which the patient cannot completely taper off steroids, immunotherapy may be resumed while patient is still on ≤10 mg steroid daily.</li> <li>• CTLA-4 agents: permanently discontinue if irAE is grade 2 or above.</li> </ul>
<b>Liver</b>	<ul style="list-style-type: none"> <li>• Transaminitis without elevated bilirubin: following a grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg daily.</li> <li>• Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 3–4) hepatitis.</li> </ul>
<b>Pancreas</b>	<ul style="list-style-type: none"> <li>• Grade 2 pancreatitis: consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase. Consider consultation with relevant pancreas specialist regarding resumption.</li> <li>• Permanent discontinuation is warranted for severe (grade 3–4) pancreatitis.</li> </ul>

**Note:** All recommendations are category 2A unless otherwise indicated.  
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[Continued](#)

**IMMUNO-C**  
**1 OF 2**

**PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE**

**Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold**

<b>Endocrine</b>	<ul style="list-style-type: none"> <li>• <b>Thyroid:</b> no discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs.</li> <li>• <b>Primary adrenal insufficiency:</b> after appropriate replacement endocrine therapy is instituted, immunotherapy may continue.</li> <li>• <b>Hypophysitis manifested by deficiency of TSH/ACTH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling:</b> immunotherapy may continue while replacement endocrine therapy is regulated.</li> <li>• <b>Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction):</b> hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms are controlled on &lt;10-mg daily steroid dose.</li> <li>• <b>T1DM with DKA:</b> consider resuming once DKA has been corrected and glucose level has stabilized.</li> </ul>
<b>Lung</b>	<ul style="list-style-type: none"> <li>• <b>Progressive grade 1 pneumonitis requiring a hold:</b> consider resuming upon radiographic evidence of improvement.</li> <li>• <b>Grade 2:</b> resume once pneumonitis has resolved to ≤ grade 1.</li> <li>• <b>Permanent discontinuation is warranted in the setting of severe (grade 3–4) pneumonitis.</b></li> </ul>
<b>Kidney</b>	<ul style="list-style-type: none"> <li>• <b>Grade 1–2 renal irAE:</b> hold immunotherapy per guidelines; upon resolution to ≤ grade 1, consider resuming concomitant with steroid if creatinine is stable.</li> <li>• <b>Permanent discontinuation is warranted in the setting of severe (grade 3–4) proteinuria.</b></li> </ul>
<b>Eye</b>	<ul style="list-style-type: none"> <li>• <b>Grade 2 irAE:</b> hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology upon resolution to ≤ grade 1.</li> <li>• <b>Permanent discontinuation of immunotherapy is warranted in the setting of severe (grade 3–4) uveitis or episcleritis.</b></li> </ul>
<b>Nervous System</b>	<ul style="list-style-type: none"> <li>• <b>Myasthenia gravis:</b> consider resuming immunotherapy after moderate (grade 2) AE based on steroid responsiveness. Permanently discontinue immunotherapy after grade 3–4 AE.</li> <li>• <b>GBS:</b> permanently discontinue immunotherapy for any grade GBS.</li> <li>• <b>Peripheral neuropathy:</b> following hold for grade 1–2 AE, consider resuming if symptoms resolve to ≤ grade 1 or if patient has well-controlled isolated painful sensory neuropathy.</li> <li>• <b>Aseptic meningitis:</b> consider resuming following mild to moderate AE if symptoms resolve to grade 0.</li> <li>• <b>Encephalitis:</b> permanent discontinuation is warranted in the setting of moderate to severe encephalitis (grade 2–4).</li> <li>• <b>Transverse myelitis:</b> discontinuation of immunotherapy following any-grade transverse myelitis.</li> </ul>
<b>Cardiovascular</b>	<ul style="list-style-type: none"> <li>• <b>Grade 1 myocarditis:</b> consider resuming upon resolution of symptoms.</li> <li>• <b>Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.</b></li> </ul>
<b>Musculoskeletal</b>	<ul style="list-style-type: none"> <li>• <b>Inflammatory arthritis (moderate to severe irAE requiring hold):</b> resume upon stabilization or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis that significantly impairs ADLs and quality of life.</li> </ul>

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PRINCIPLES OF ROUTINE MONITORING

Baseline Assessment <sup>a</sup>	Monitoring Frequency <sup>b</sup>	Evaluation for Abnormal Findings/ Symptoms
<b>Clinical:</b> <ul style="list-style-type: none"> <li>Physical examination</li> <li>Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease</li> <li>Neurologic examination</li> <li>Bowel habits (typical frequency/consistency)</li> </ul>	Clinical exam at each visit with AE symptom assessment	Follow-up testing based on findings, symptoms
<b>Imaging:</b> <ul style="list-style-type: none"> <li>CT imaging</li> <li>Brain MRI if indicated</li> </ul>	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
<b>General bloodwork:</b> <ul style="list-style-type: none"> <li>CBC with differential</li> <li>Comprehensive metabolic panel</li> <li>Infectious disease screening as indicated</li> </ul>	Repeat every 2–3 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
<b>Dermatologic</b> <ul style="list-style-type: none"> <li>Examination of skin and mucosa if history of immune-related skin disorder</li> </ul>	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated.
<b>Thyroid</b> <ul style="list-style-type: none"> <li>Thyroid-stimulating hormone (TSH), free thyroxine (T4)</li> </ul>	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.
<b>Adrenal/Pituitary</b> <ul style="list-style-type: none"> <li>Adrenal: Morning adrenocorticotropic hormone (ACTH) and cortisol</li> <li>Pituitary: TSH, free T4, and total T3</li> </ul>	Every 2–3 weeks during immunotherapy, then follow-up every 6–12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone
<b>Pulmonary</b> <ul style="list-style-type: none"> <li>Oxygen saturation (resting and with ambulation)</li> <li>Pulmonary function tests (PFTs)</li> </ul>	Repeat oxygen saturation tests based on symptoms	Chest CT to evaluate for pneumonitis, biopsy if needed to exclude other causes
<b>Cardiovascular</b> <ul style="list-style-type: none"> <li>ECG and total CK</li> <li>Cardiac biomarkers (ie, troponin I or T) if risk factors present</li> </ul>	Consider periodic testing for those with abnormal baseline or symptoms	Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)
<b>Pancreatic</b> <ul style="list-style-type: none"> <li>Baseline amylase/lipase</li> </ul>	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal imaging for suspected pancreatitis
<b>Musculoskeletal</b> <ul style="list-style-type: none"> <li>Joint examination/functional assessment as needed for patients with pre-existing disease</li> </ul>	No routine monitoring needed if asymptomatic	N/A

<sup>a</sup>Prior to initiating treatment, counsel patients on the warning signs and symptoms of immune-related adverse events.

<sup>b</sup>Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

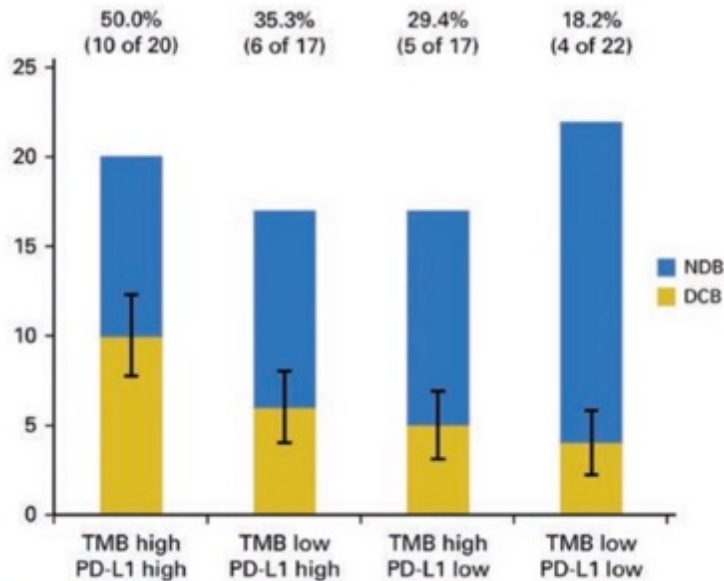
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# General Principle Updates

- Now available are **multidisciplinary guidelines of management** of irAEs based on expert opinion.
  - ASCO
  - NCCN
- As # of patients treated go from **hundreds to thousands**, more irAEs will be found and reported, and incidence rates may change.
- **Importance of:**
  - Careful monitoring; consider all differential diagnoses
  - Early intervention
  - Do not hesitate to use corticosteroids when indicated
  - Use prophylaxis
  - Follow guidelines for management and rechallenge
  - Utilize organ specialists/disease-specific specialties

# Research on Biomarkers for Response



**Figure 1.** Molecular determinants of response to PD-1 and PD-L1 blockade in patients with non-small cell lung cancer. A total of 240 patients were treated with anti-PD-1 or PD-L1, and had TMB profiled by targeted next-generation sequencing, of which 84 had PD-L1 immunohistochemistry performed.

Abbreviations: DCB, durable clinical benefit; NDB, no durable benefit; TMB, tumor mutational burden.

From Rizvi H, Sanchez-Vega F, La K, et al. Molecular determinants of response to anti-programmed cell death (PD)-1 and anti-programmed cell death-ligand 1 (PD-L1) blockade in patients with non-small-cell lung cancer profiled with targeted next-generation sequencing. Reprinted with permission. © 2018 All rights reserved. Rizvi H, et al: J Clin Oncol 2018;36:633–641.

- So far, results have been limited.
- High tumor mutational burden plus PD-L1 expression -> durable clinical benefit more likely

Thank You

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