oncology

CANCER IMMUNOTHERAPY

Pocket Guide

Unique Clinical Features

Tumor Response Kinetics

- Response patterns associated with immune checkpoint blockade may differ from those associated with conventional therapies, which has prompted the development of immune-related response criteria (irRC)[a]

Immune-Related Adverse Events (irAEs)

- By enhancing immune system function, immune checkpoint blockade can lead to autoinflammatory side effects called irAEs[b]

a. Wolchok JD, et al. *Clin Cancer Res.* 2009;15(23):7412-7420.
b. Weber JS, et al. *J Clin Oncol.* 2015;33(18):2092-2099.

Response Kinetics

RECIST vs irRC

Factor	RECIST	irRC
Measurement of tumor burden	• Unidimensional	• Bidimensional
CR	• Disappearance of all target and non-target lesions • Lymph nodes must regress to <10mm short axis • No new lesions • Requires confirmation	• Same as RECIST
PR	• ≥30% decrease in tumor burden compared to baseline • Requires confirmation	• ≥50% decrease in tumor burden compared to baseline • Requires confirmation
PD	• ≥20% plus 5mm absolute increase in tumor burden compared with nadir • Progression of non-target lesions and/or appearance of new lesions (at any single time point)	• ≥25% increase in tumor burden compared to most recent prior evaluation • New lesions added to tumor burden • Requires confirmation
SD	• Any response pattern that does not meet criteria for CR, PR, or PD	• Same as RECIST

RECIST = response evaluation criteria in solid tumors; CR = complete response; PR = partial response; PD = progressive disease; SD = stable disease

Agarwala SS. *Semin Oncol.* 2015;42Suppl 3:S20-S27.

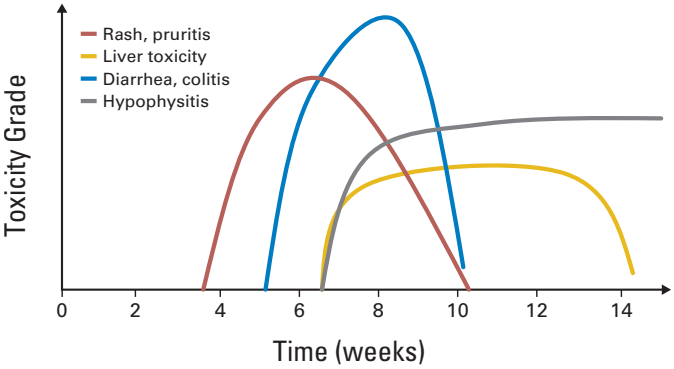
Key Points About Evaluating Activity

- Antitumor activity may appear delayed compared with cytotoxic therapies
- Patients may experience response after apparent progressive disease
- Development of new small lesions in the presence of other shrinking lesions may be clinically insignificant
- Durable stable disease may indicate response
- Development of progressive disease should be confirmed before discontinuing therapy

Agarwala SS. *Semin Oncol.* 2015;42 Suppl 3:S20-S27.

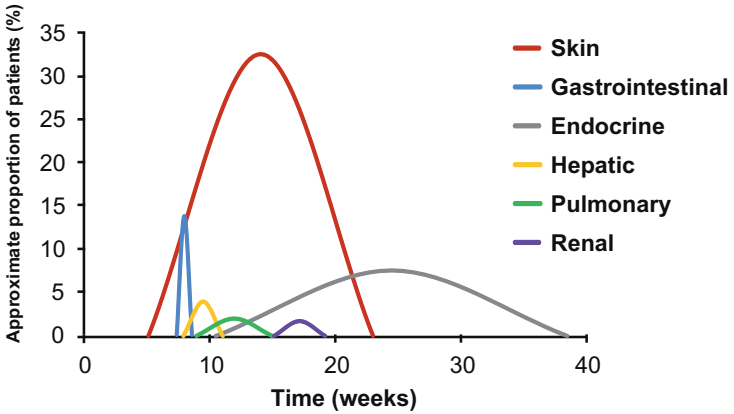
irAEs Kinetics

Ipilimumab in Melanoma



Weber JS, et al. *J Clin Oncol.* 2012;30(21):2691-2697.

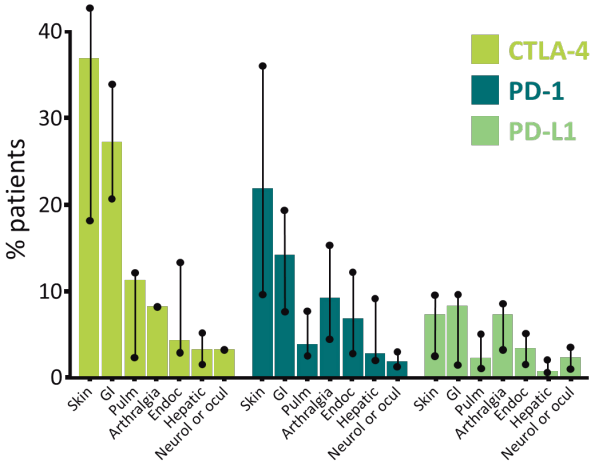
Nivolumab in Melanoma



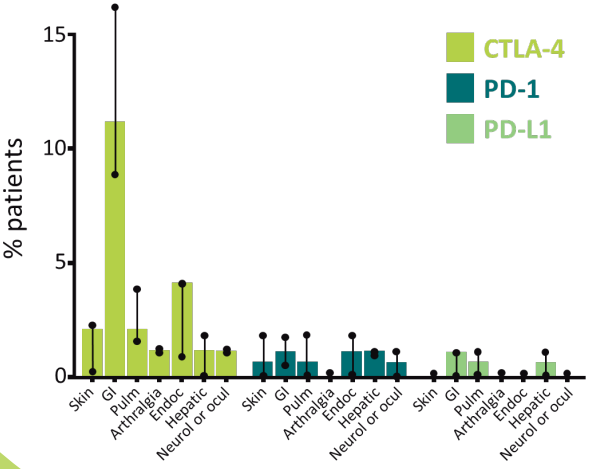
Weber JS, et al. Safety Profile of Nivolumab (NIVO) in Patients (pts) With Advanced Melanoma (MEL): A Pooled Analysis. Presented at the American Society of Clinical Oncology 2015 Annual Meeting; May 29-June 2, 2015; Chicago, IL.

irAEs Distribution

Grade 1-2 irAEs



Grade 3-5 irAEs



Michot JM, et al. *Eur J Cancer*. 2016;54:139-148. Reprinted with permission.

Ipilimumab vs Nivolumab vs Combo irAEs Reported in ≥10% of Patients

Patients Reporting Event %	NIVO + IPI (n=313)		NIVO (n=313)		IPI (n=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin	59.1	5.8	41.9	1.6	54.0	2.9
Pruritus	33.2	1.9	18.8	0	35.4	0.3
Rash	28.4	2.9	21.7	0.3	20.9	1.6
Rash maculo-papular	11.8	1.9	4.2	0.3	11.9	0.3
Gastrointestinal	46.3	14.7	19.5	2.2	36.7	11.6
Diarrhea	44.1	9.3	19.2	2.2	33.1	6.1
Colitis	11.8	7.7	1.3	0.6	11.6	8.7
Hepatic	30.0	18.8	6.4	2.6	7.1	1.6
Increase in alanine amino-transferase	17.6	8.3	3.8	1.3	3.9	1.6
Increase in aspartate amino-transferase	15.3	6.1	3.8	1.0	3.5	0.6
Endocrine	30.0	4.8	14.4	0.6	10.9	2.3
Hypothyroidism	15.0	0.3	8.6	0	4.2	0

Wolchok J, et al. Efficacy and safety results from a phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment-naive patients (pts) with advanced melanoma (MEL) (CheckMate 067). Presented at American Society of Clinical Oncology 2015 Annual Meeting; May 29-June 2, 2015; Chicago, IL.

Management of Selected irAEs

General Principles

- Responsibility of all health care providers
- *Early reporting by patients with close monitoring, and early intervention by health care providers*
- Provide thorough and continuous patient education about the signs and symptoms of irAEs
- Assess for signs and symptoms of irAEs before each cycle of immunotherapy
- Know management algorithm specific to each irAE
  - Safety profiles of immunosuppressants
- Monitor and manage toxicities of immunosuppressants
  - Hyperglycemia and diabetes
  - Opportunistic infection

CTCAE Severity Grade

Severity CTCAE Grade	Type of Patient Care	Steroids	Other immuno-suppressive drugs	Immuno-therapy and subsequent approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or oral systemic steroids 0.5-1 mg/kg/d	Not recommended	Suspend** temporarily
3	Hospitalization	Systemic steroids (oral or IV) 1-2 mg/kg/d for 3 d then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3-5 days of steroid course. Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization; consider the intensive care unit	Systemic steroids IV methylpred-nisolone 1-2 mg/kg/d for 3 d and then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3-5 days of steroid course. Organ specialist advised	Discontinue permanently

**Outside skin or endocrine disorders, where immunotherapy can be maintained.

CTCAE = common terminology criteria for adverse events

Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

Diarrhea and Colitis

Grade 1 (mild)	*<4 bowel actions per day over baseline:* supportive measures such as increasing oral fluid and anti-motility agents such as loperamide
Grade 2 (moderate)	*4–6 bowel actions per day over baseline:* withhold immune checkpoint inhibitor. As per Grade 1 if patient is well. If no improvement in 5 days, or if worsening of symptoms, commence steroids at a dose of 0.5–1 mg/kg per day of prednisolone (or IV equivalent) and continue until symptoms improve to Grade 1. If no improvement occurs, manage as per Grade 3. Steroids can be tapered over 2–4 weeks. Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the macroscopic and microscopic inflammation evident
Grade 3 (severe)	*>7 bowel actions per day over baseline:* admit patient to hospital for intravenous hydration and clinical observation as appropriate. Commence steroids at 1–2 mg/kg prednisolone or IV equivalent. If no improvement in 2–3 days, commence infliximab 5 mg/kg and continue steroids. Infliximab is contraindicated in patients with sepsis or a perforation. Sigmoidoscopy and biopsy recommended to exclude other causes. Once symptoms resolve to Grade 1, taper steroids over a minimum of 1 month (up to 3 months for severe cases). Infliximab may be re-administered at 2 and 6 weeks if symptoms persist or recur. Dietitian input recommended
Grade 4 (life threatening)	Urgent intervention indicated: management as per Grade 3. Involve gastroenterologist and surgeon in management. Permanently discontinue immune checkpoint inhibitor

Spain L, et al. *Cancer Treat Rev.* 2016;44:51-60. Reprinted with permission.

Hepatitis

Grade 1 (mild)	*ALT/AST up to 3 times ULN:* continue immune checkpoint inhibitor. Send viral serology looking for hepatitis A, B, C, and CMV and iron studies to look for underlying haemochromatosis. Advise against excessive alcohol intake
Grade 2 (moderate)	*3 to 5 times ULN:* withhold immune checkpoint inhibitor. Product information (Ipi, Nivo, Pembro) recommends initiation of steroids with prednisolone 1–2 mg/kg/day or IV equivalent. If patient is well, it is reasonable to re-check liver function every 2 days and initiate steroids if no improvement or worsening. Taper steroids over 4 weeks once liver function is at Grade 1 or at baseline
Grade 3 (severe)	*5 to 20 times ULN:* as per Grade 2 except that steroids should be initiated immediately. Ipilimumab should be permanently discontinued. Consider permanent discontinuation of anti-PD-1 drugs
Grade 4 (life threatening)	*>20 times ULN:* as per Grade 3. Permanently discontinue immune checkpoint inhibitor

Spain L, et al. *Cancer Treat Rev.* 2016;44:51-60.

Rash

Grade 1 (mild)	*<10% BSA:* symptomatic management with antihistamines for pruritus and topical steroid cream for localized pruritus and rash; continue immune checkpoint inhibitor if responding or stable
Grade 2 (moderate)	*0–30% BSA:* if tolerable, as per Grade 1; if intolerable, initiate systemic steroids (eg, oral prednisolone 0.5–1 mg/kg daily with a 1–2 week wean) and delay treatment until Grade 1 and steroids <10 mg. If symptoms persist or recur, consider skin biopsy and withholding drug
Grade 3 (severe)	*>30% BSA:* obtain a skin biopsy and dermatology consult. Initiate systemic steroids with 1 mg/kg of prednisolone or IV equivalent, with a 4 week taper. Withhold treatment until Grade 1
Grade 4 (life threatening)	*No formal definition.* Management as per Grade 3. Permanently discontinue immune checkpoint inhibitor

Spain L, et al. *Cancer Treat Rev.* 2016;44:51-60.

Pneumonitis

Grade 1 (mild)	*Asymptomatic; clinical or diagnostic observations; no intervention needed:* delay drug administration. Consider steroids (eg, prednisone 1 mg/kg/day PO or methylprednisolone 1 mg/kg/day IV). Follow-up: reassess management after 3 weeks. If completely resolved or non-drug related, continue treatment. If worsens, treat as Grade 2 or 3/4
Grade 2 (moderate)	*Symptomatic; medical intervention indicated; limits instrumental activities of daily living (ADLs):* delay drug administration. Consider hospitalization and daily monitoring of symptoms. Steroids recommended (eg, prednisone 1–2 mg/kg/day PO or methylprednisolone 1–2 mg/kg/day IV). Consider empiric antibiotics (if suspicious for concurrent infection). Follow-up: reassess management every 1–3 days. If improving, taper steroids and continue treatment if symptoms resolve completely. If worsens, treat as Grade 3/4
Grade 3 (severe)	*Limits self-care ADLs; oxygen indicated:* discontinue drug administration. Hospitalization. High dose steroids with methylprednisolone (eg, 1 g/day IV). Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy with biopsy. Reassess management daily. If not improving after 48 h or worsening, administer additional immunosuppressive therapy (eg, infliximab, mycophenolate, immunoglobulins). If improving, taper steroids. Discontinue treatment permanently
Grade 4 (life threatening)	*Urgent intervention indicated (eg, intubation):* as per Grade 3. Intensive care support required

Spain L, et al. *Cancer Treat Rev.* 2016;44:51-60.

Thyroid Dysfunction

Grade 1 (mild)	*Asymptomatic, no intervention needed:* monitor only
Grade 2 (moderate)	*Symptomatic or intervention indicated:* for hypothyroidism, commence levothyroxine. For hyperthyroidism, seek endocrinology input and start propranolol or atenolol for symptoms; steroids or carbimazole may be indicated pending underlying mechanism
Grade 3 (severe)	*As per Grade 2:* Hospitalization and specialist input are recommended. Initiate prednisolone 1–2 mg/kg or IV equivalent
Grade 4 (life threatening)	*As per Grade 3*

Spain L, et al. *Cancer Treat Rev.* 2016;44:51-60.

Nephritis

Grade 1 (mild)	*Creatinine >1–1.5 x baseline; proteinuria 1+, <1.0g/24 h:* monitor renal function, promote hydration and cessation of nephrotoxic drugs
Grade 2 (moderate)	*Creatinine >1.5–3.0 x baseline; proteinuria 2+, 1.0–3.4 g/24 h:* exclude non-immune causes, commence prednisolone 0.5–1 mg/kg. If worsens, manage as per Grade 3 and discontinue immune checkpoint inhibitor
Grade 3 (severe)	*Creatinine >3.0 x baseline; ≥3.5 g/24 h:* initiate prednisolone 1–2 mg/kg or IV equivalent. Consider renal biopsy. Discontinue immune checkpoint inhibitor
Grade 4 (life threatening)	*Creatinine >6.0 x ULN:* as per Grade 3

Spain L, et al. *Cancer Treat Rev.* 2016;44:51-60.

Hypophysitis

- Discontinue immune checkpoint inhibitor
- High-dose corticosteroid administration with a taper over 4 weeks
- Obtain endocrine consult
- Replace deficient hormones
- Symptoms will resolve with treatment
- Slow return of some endocrine function
- Most patients require life-long hydrocortisone supplement
- Use stress dose hydrocortisone in perioperative period and critical illness

Postow M. *ASCO Educational Book*. 2015:76-83; Fecher LA, et al. *Oncologist*. 2013;18:733-743.

Neurological Toxicities

- Relatively infrequent (<1% all grades) with IPI or PD-1
- Symptoms:
  - Numbness, tingling, foot drop and localized muscle weakness, or generalized ascending motor and diaphragmatic weakness
- Observed so far:
  - Myasthenia gravis (MG)-like syndrome
  - Peripheral neuropathy
- Management: get a neurology consult!
  - For Grade 2 or more, discontinue antibodies, work-up including labs and brain MRI, high dose corticosteroid administration with a prolonged taper, neurology consultation, and EMG, if appropriate
  - Hospitalize if MG-like syndrome
  - Consider rapidly moving to IVIG and infliximab if Grades 3-4 and without resolution of symptoms within 24-48 hours

Postow M. *ASCO Educational Book.* 2015:76-83; Fecher LA, et al. *Oncologist.* 2013;18:733-743.

Patient and Caregiver Education

Evaluate Education Needs

- Assess both patient and caregiver
  - Knowledge of therapy and the disease process
  - Educational level and preferred learning methods
- Develop a plan
- Implement teaching, using a variety of materials and methods
- Evaluate patient and caregiver for continued educational needs related to the therapy and disease process

Educate

- Describe signs and symptoms, including complications if not treated promptly
- Emphasize early recognition and prompt reporting of worsening condition
- Discuss preventative measures, if applicable
- Instruct patient to present agent-specific wallet card to all healthcare providers
- Stress compliance with corticosteroid therapy
- Provide supportive care instructions
- Explain that benefits of therapy outweigh potential risks, particularly when irAEs are recognized early and treated quickly

Provide Contact Information

- Whom to call
- Why to call
- When to call
- Where to call (MUST HAVE 24/7 clinician availability)

When to Call the Sub-Specialist

Skin	
Grades 1-2	No, manage the symptoms
Grades 3-4	Yes, consider a biopsy
GI	
Grades 1-2	Only if scoping changes the management
Grades 3-4	Only if therapy-refractory, or Grade 4
Hepatic	
Grades 1-2	No
Grades 3-4	Only if therapy-refractory, or Grade 4
Endocrine	
Grades 1-2	Yes, if symptomatic
Grades 3-4	Yes, always

Pancreatic	
Grades 1-2	No
Grades 3-4	Only if Grade 4 or symptomatic
Pulmonary	
Grades 1-2	Generally no, but consider
Grades 3-4	Almost always
Neurologic	
Grades 1-2	Generally yes, if Grade 2
Grades 3-4	Almost always
Renal	
Grades 1-2	No
Grades 3-4	Only if therapy-refractory

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