Side Effect: Immunotherapy

Recognition and Management of Immunotherapy Related Toxicities

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DISCLOSURES

Advisory role:

- Genentech, Merck, Pfizer, GSK, BMS, Pierre-Fabre, Sanofi Aventis, Astellas, OncoGenex, Janssen, BioClin

Speaker role:

- Pfizer, Merck, GSK, Novartis, Pierre-Fabre, Astellas, BioClin

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Summary of CTLA-4 Blockade Immune-Mediated Toxicities

- Toxicity related to ipilimumab appears to be dose related
- Toxicity-related death occurred in < 1% of cases

Common (> 20%)

- Rash, pruritus
- Fevers, chills, lethargy
- **Diarrhea/colitis**

Occasional (3% to 20%)

- Hepatitis/liver enzyme abnormalities
- Endocrinopathies: hypophysitis, thyroiditis, adrenal insufficiency

Rare (< 2%)

- Episcleritis/uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barré, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia
- Toxic epidermal necrolysis, Stevens-Johnson syndrome

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.
Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

- Toxicity less common than with anti-CTLA-4 but can be fatal

Occasional (5% to 20%)

- Fatigue, headache, arthralgia, fevers, chills, lethargy
- Rash: maculopapular, pruritus, vitiligo
  - Topical treatments
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis, liver/pancreatic enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

Rare (< 5%)

- **Pneumonitis**
  - Grade 3/4 toxicities uncommon
  - Low grade reversible with steroids and discontinuation
- Anemia

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697. Weber JS, et al. J Clin Oncol. 2015. [Epub ahead of print].

Most Common Treatment-Related Select Aes IPI/NIVO

Patients Reporting, % (Select AEs/Organ Category)	NIVO + IPI (N = 94)[a]		IPI (N =46)[a]	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Gastrointestinal select AEs	**51**	**21**	**37**	**11**
Diarrhea	45	11	37	11
Colitis	23	17	13	7
Hepatic select AEs	**28**	**15**	**4**	**0**
ALT increased	22	11	4	0
AST increased	21	7	4	0
Pulmonary select AEs	**12**	**2**	**4**	**2**
Pneumonitis	11	2	4	2
Renal select AEs	**3**	**1**	**2**	**0**
Creatine increased	2	1	0	0
Endocrine select AEs	**34**	**5**	**17**	**4**
Thyroid disorder	23	1	15	0
Hypothyroidism	16	0	15	0
Hypophysitis	12	2	7	4
Skin select AEs	**71**	**10**	**59**	**0**
Rash	42	5	26	0
Pruritus	35	1	28	0
Rash maculo-popular	16	3	17	0

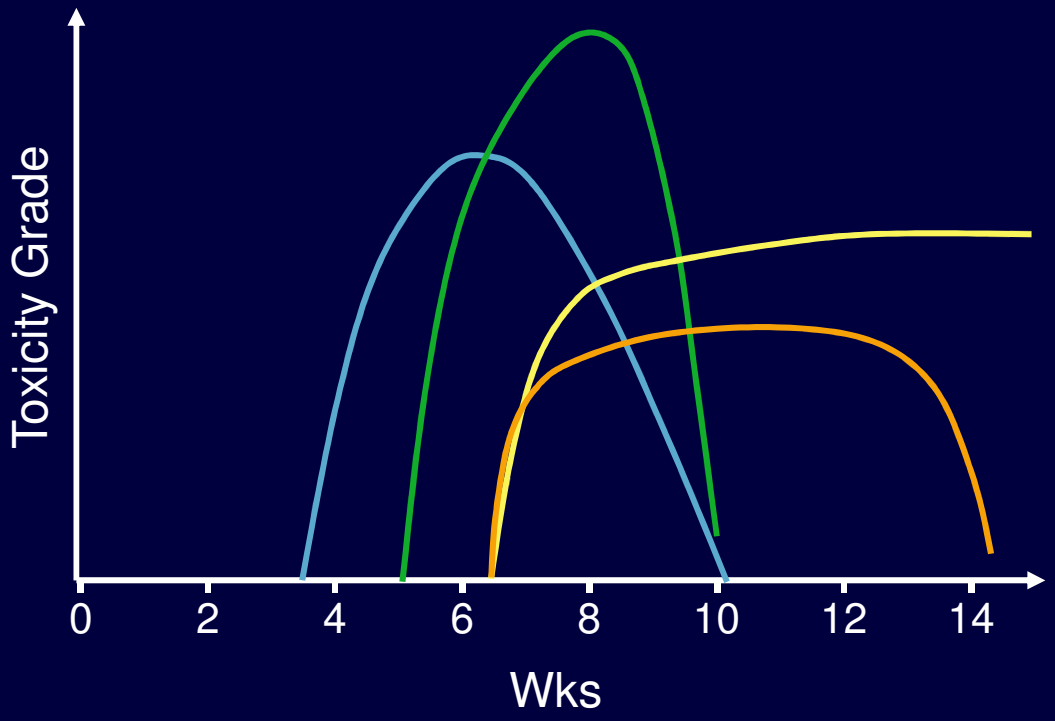
[a]Safety was evaluated in all patients who received at least one dose of study treatment

Database lock: January 30, 2015

Safety –Summary ipi /nivo

- The safety profile of ipilimumab and nivolumab is characterized by immune related adverse events
- There is the potential for increased frequency of drug related adverse events with nivolumab combined with ipilimumab over either agent as monotherapy, in particular for Lipase / Amylase, AST / ALT
- Skin toxicity, Uveitis, Neurological, Renal
- No new toxicities have been identified with the combination treatment
- Toxicities with the combination have been manageable and reversible following intervention with systemic steroids in alignment with established AE management algorithms

Kinetics of Appearance of irAEs with Checkpoint Blockade



- Rash, pruritus
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

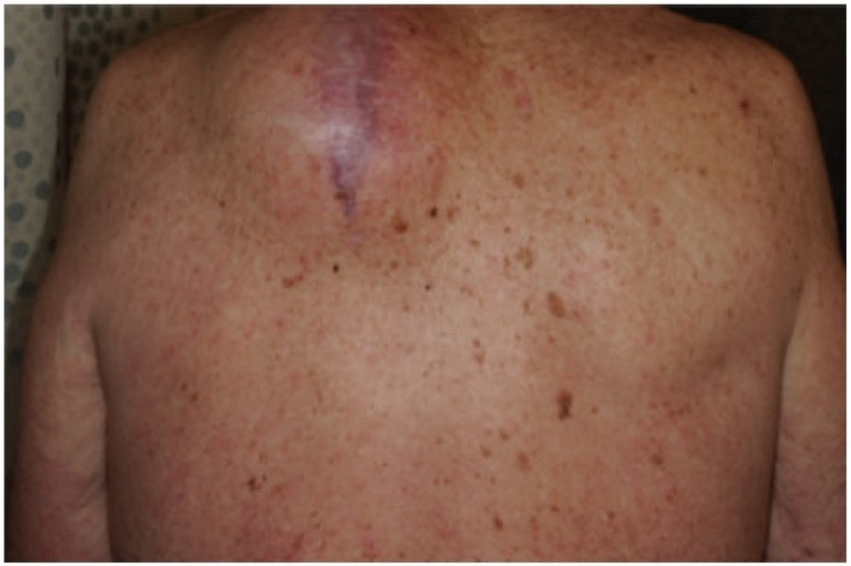
Average is 6-12 wks after initiation of therapy
Can occur within days of the first dose, after several mos of treatment, and after discontinuation of therapy
Rule out infections, metabolic causes, tumor effects, etc
Early recognition, evaluation, and treatment are critical

- Data from patients receiving anti-PD-1 antibodies Q2W for ≥ 3 yrs shows most irAEs occur by Week 24 (6 months)
- Toxicities with PD-1/PD-L1 agents may be slower to resolve than with ipilimumab, so long-term surveillance is advised.

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

Immunotherapy-Related Dermatitis

- Ipilimumab: skin toxicity most common irAE
  - Rare severe rashes require hospitalization
  - Sweet syndrome rarely described
- PD-1 inhibitors: oral mucositis and dry mouth more frequent
  - Oral corticosteroid rinses and topical lidocaine can be beneficial



- Nivolumab: rash (36%) and pruritus (28%) most common skin toxicities; grade 3/4 rare
  - Typically maculopapular and managed as outlined for ipilimumab

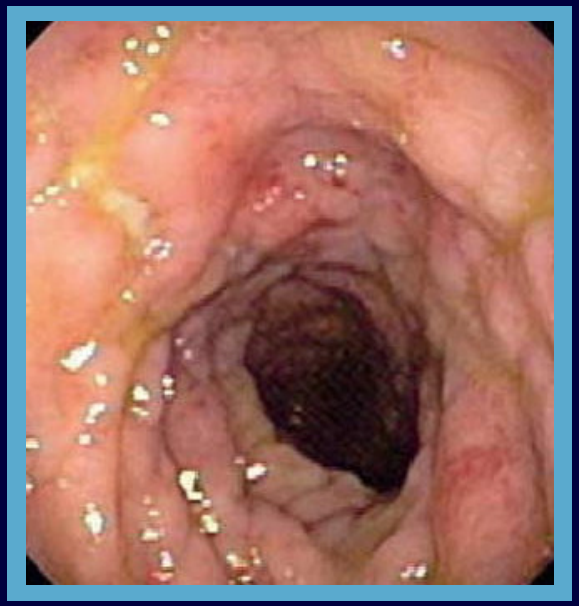
Howell M, et al. Lung Cancer. 2015;88:117-123.

Skin Toxicity: Learnings!!!

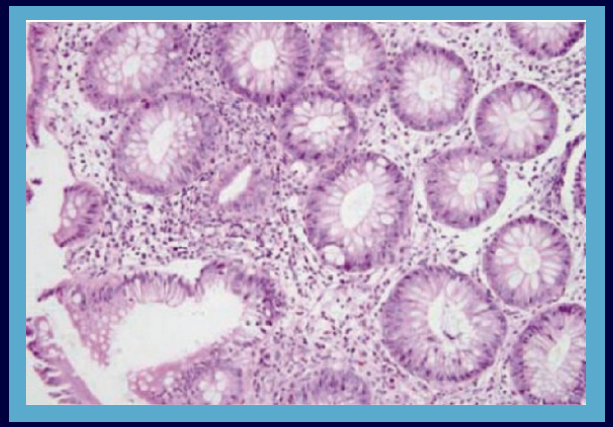
- If patient reports rash → visual exam!
- High-dose IV steroids for grade 3/4 rash
- Long taper upon improvement
- Severe reactions are rarely seen. Recently, a case of toxic epidermal necrolysis (TENS) occurred in a nivolumab/ ipilimumab combination study
- Educate pts regarding importance of immuno-suppression
- Compliance with oral steroids!

Colitis: Immune Checkpoint Inhibitor Toxicity

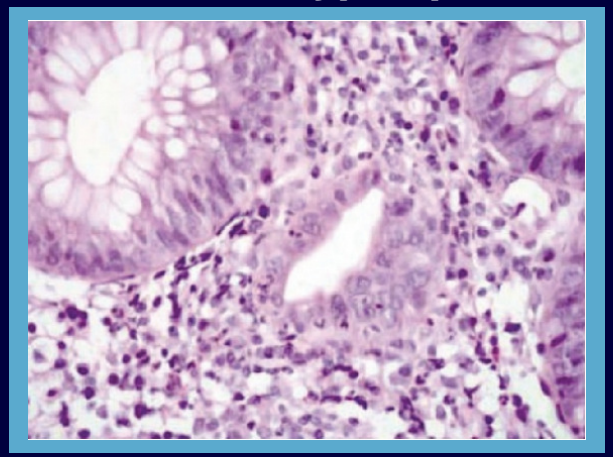
Ulceration in Descending Colon



Focal Active Colitis



Alterations in Crypt Epithelium



Maker AV, et al. Ann Surg Oncol. 2005;12:1005-1016.

Prompt Treatment of Colitis

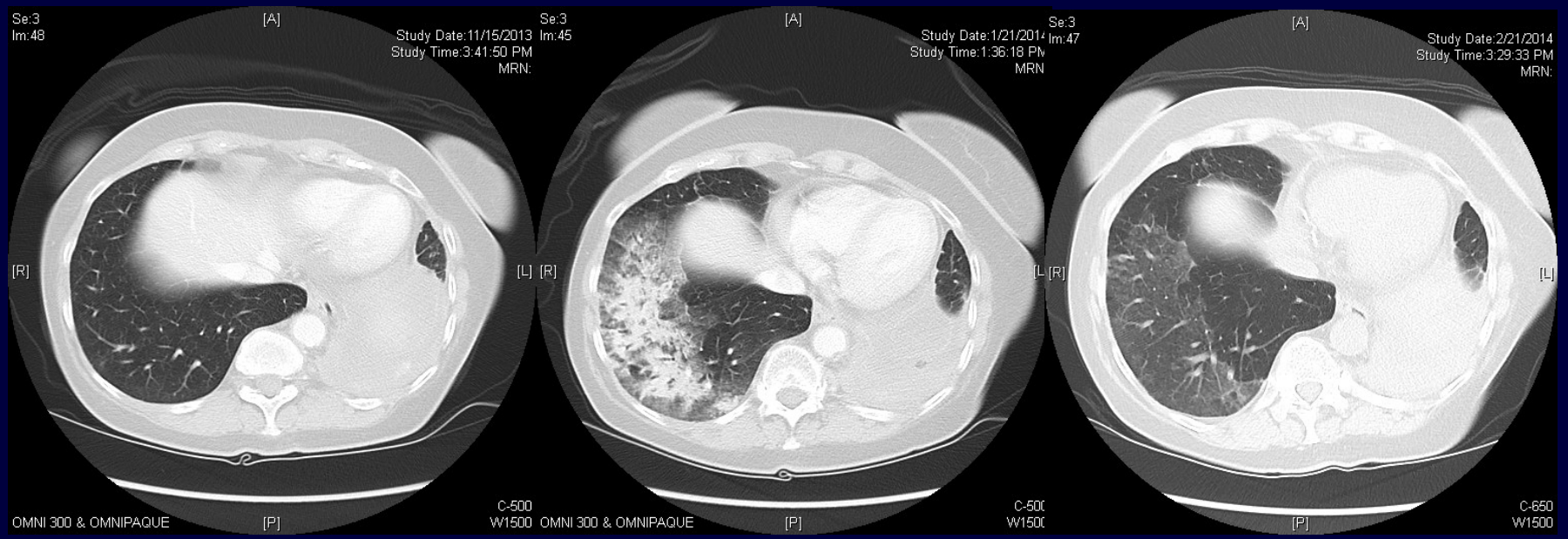
- A retrospective analysis of 836 trial patients showed that early initiation of steroid treatment for colitis led to faster resolution of symptoms than delayed steroid treatment[1]
- Several case studies support use of infliximab to further blunt immune response in steroid-refractory colitis[2,3]
- Bloody diarrhea uncommon, but may indicate more severe colitis[4]
- At colonoscopy, colitis typically affects the distal colon with sparing of rectum[4]

1. O' Day S, et al. ASCO 2011. Abstract 8554. 2. Pagès C, et al. Melanoma Res 2013; 23:227-230. 3. Merrill SP, et al. Ann Pharmacother 2014; 48:806–810. 4. Howell M, et al. Lung Cancer. 2015;88:117-123.

Pulmonary Toxicities related to Immunotherapy

- Several pulmonary inflammatory complications reported with ipilimumab. (sarcoidosis and organizing inflammatory pneumonia)
- Pneumonitis rarely in patients treated with PD-1 blocking agents, but with occasional fatal consequence in early trials. (< 3%)
- Symptoms of an upper respiratory infection, new cough, or SOB, pneumonitis should be considered and imaging is warranted
- In moderate to severe symptoms and/or radiographic findings, bronchoscopy should be considered to exclude infectious processes prior to starting immunosuppression.
- In severe cases, treatment with 2 mg/kg of intravenous methylprednisone and consideration of additional immunosuppression including infliximab, mycophenolate mofetil, cyclophosphamide if necessary

Immune-Related Pneumonitis



11/15/2013:
Pre-pneumonitis

1/21/14:
Pneumonitis

2/21/14:
Improved with steroids;
taper completed 3/7/14

Symptom Management: Neurologic

- Peripheral neuropathy (sensory and motor) has been reported in < 1% of pts treated with ipilimumab and even less frequently with anti–PD-1 therapy
  - May resolve spontaneously
- Encourage patient to report muscle weakness or sensory alterations
- Patient may present with muscle weakness or sensory neuropathies lasting > 5 days or motor neuropathies confirmed by physical exam
- *Rule out noninflammatory causes*: disease progression, infections (eg, Lyme disease), metabolic syndromes, and medications (eg, taxanes or platinum salts)
- Serious neurologic irAEs should be treated with corticosteroids
  - Consultation with neurology to consider additional treatment (eg, plasmapheresis, intravenous immunoglobulin) in some cases should also be considered

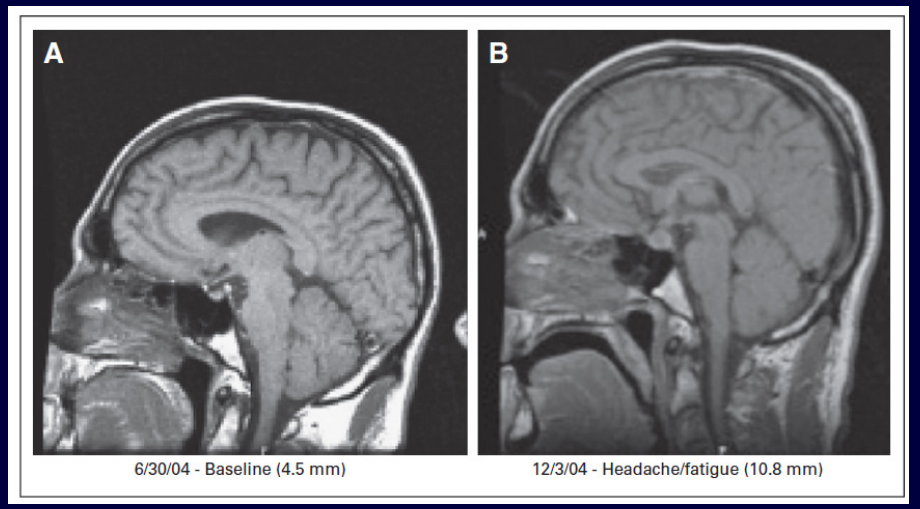
Endocrine Toxicities

- Following ipilimumab therapy, incidence of hypophysitis 8% and hypothyroidism/thyroiditis 6%; primary adrenal dysfunction rare
- Combination of ipilimumab and nivolumab associated with 22% incidence of thyroiditis or hypothyroidism and 9% incidence of hypophysitis
- Symptomatic relief for hypophysitis achieved with hormone replacement, although endogenous hormone secretion rarely recovered
  - Symptoms can include: Headache, fatigue, weakness, memory loss, impotence, personality changes, and visual-field impairment
  - Events can occur within weeks of beginning treatment but also have been noted to occur many months (while still on treatment)

Ryder M, et al. Endocr Relat Cancer. 2014;21:371-381.

Symptom Management: Hypophysitis

- Prompt therapy ameliorates symptoms and permits continued therapy
- 25% of pts with hypophysitis have normal pituitary MRI
- Monitor ACTH and cortisol levels in pts receiving checkpoint inhibitors
- Physiologic steroid replacement may be sufficient
  - Higher-dose in symptomatic pts (headaches and vision changes)



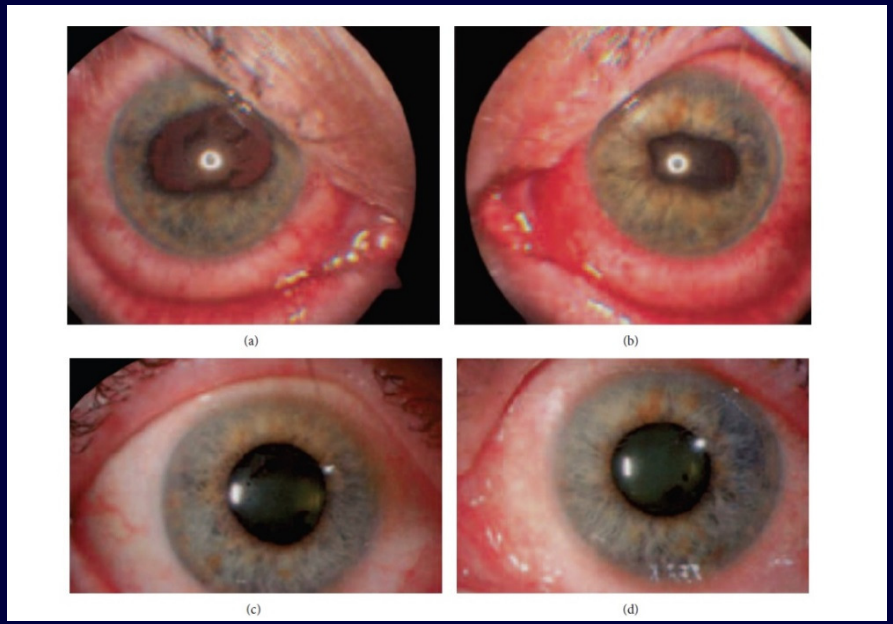
Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

Less Common Immune-Related Adverse Events

- Hematologic (hemolytic anemia, thrombocytopenia)
- Cardiovascular (myocarditis, pericarditis, vasculitis)
- Ocular (blepharitis, conjunctivitis, iritis, scleritis, uveitis)
- Renal (nephritis)
- Several case reports of rare autoimmune-based toxicities in pts treated with ipilimumab
  - Lupus nephritis
  - Inflammatory enteric neuropathy
  - Tolsosa-Hunt syndrome
  - Myocardial fibrosis
  - Acquired hemophilia A
  - Autoimmune polymyositis

Ipilimumab adverse reaction management guide.

Ipilimumab-Associated Uveitis



- Uveitis and episcleritis have been reported in < 1% of pts treated with ipilimumab or anti–PD-1 antibodies
- Symptoms typically occur ~ 2 mos following treatment: photophobia, pain, dryness of the eyes, blurred vision
- Treatment: topical steroids for grade 1/2 toxicity
- For grade ≥ 3 toxicity systemic corticosteroids and discontinuation of immunotherapy is required

Attia P, et al. J Clin Oncol. 2005;23:6043-6053. Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

Combinations of Checkpoint Blockade With Other Therapies: Toxicities TBD

- Targeted therapies
- Vaccines
- Metabolites
- Radiation Chemotherapy

Combinations

- Ipilimumab with dacarbazine resulted in frequent hepatotoxicity
- Dermatologic AEs common when carboplatin and paclitaxel were added
- Ipilimumab with vemurafenib also produced severe liver and kidney toxicities that limited development of this combination

Combinations

- Nivolumab + ipilimumab: Grade 3 to 4 toxicities 62%, although response rates 43% to 53% with long duration
  - Asymptomatic liver and pancreatic function abnormalities commonly observed.
  - PD-1 blockade could safely continue after resolution of grade 3 amylase and lipase elevations induced by combination therapy
- Delayed second irAEs also reported
  - Abnormal liver function tests observed weeks after colitis
  - Pneumonitis seen after pancreatic function elevation

Special Situations

- Patients with prior autoimmune diseases or a history of viral hepatitis have been excluded from receiving ipilimumab on trials, but recent data suggest that the drug can be given safely to those patients.

- Nonetheless, extreme caution should be taken in treating patients with recent or ongoing autoimmune conditions, particularly any type of inflammatory bowel disease.

- The key to successful management of checkpoint protein antibody toxicities is early diagnosis, high suspicion, excellent patient-provider communication, and rapid and aggressive use of corticosteroids and other immune suppressants for irAEs

Global Management of irAEs

- Effective management of severe irAEs based on
  - Early recognition: assess patients for signs/symptoms of enterocolitis, dermatitis, neuropathy, endocrinopathy, or hepatotoxicity at baseline and before each dose
  - Frequent monitoring
  - Use of corticosteroids (and/or other immunosuppressive therapies) combined with either delaying or discontinuing ipilimumab
- Experience from sites utilizing the following recommendations suggest that it minimizes morbidity and hospitalizations
- Screen patients for adverse events: Weekly call to pts for first 16 weeks
  - Review checklist to assess key symptoms
  - Reinforce importance of reporting any new or worsening symptom
- Monitor outpatients with ongoing AEs: minimum biweekly call
- For patients admitted to an outside hospital for AEs
  - Frequent contact with admitting physician and subspecialist
  - Provide guidance on detection and management of irAEs

Conclusions

- Toxicity is mostly low grade and can be treated with supportive treatment.
- A concerted effort to educate the whole multidisciplinary team needs to take place and development of accessible algorithms to ensure minimized risk with toxicity
- The key to successful management of checkpoint antibody toxicities is early diagnosis, high suspicion, excellent patient-provider communication, and rapid and aggressive use of corticosteroids and other immune suppressants for irAEs
- The majority of both nivolumab and ipilimumab related AEs to date have been reversible and manageable by delaying study drug ± administration of corticosteroids; other immunosuppressants may also be needed
- The following categories of AEs, requiring greater vigilance and early intervention: pulmonary, hepatic, renal, GI, endocrine, neurological, skin