IMMUNE-RELATED ADVERSE EVENTS:
A NEW CLINICAL LEARNING CURVE

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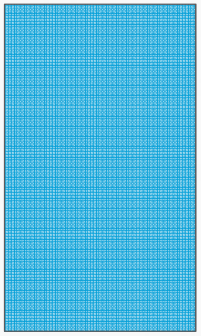


DISCLOSURES

- Scientific Consultant: Incyte, Inc.

TOXICITY

CONSIDERING THE *STATUS QUO* IN MEDICAL ONCOLOGY

STANDARDS OF CARE:
HEAD AND NECK CANCER

PULA HNSCC: CRT

Gr 3-5 Toxicity	RT alone N=98	CRT N=95
Mucositis	32 (33%)	43 (48%)
Leukopenia	1 (1%)	40 (42%)
Renal	1 (1%)	8 (8%)
Skin	13 (13%)	7 (7%)
All Grade 3-5	51 (52%)	85 (89%)
Toxic Death	2 (2%)	4 (4%)

"Toxicity was greater when chemotherapy was added to radiation….however, quite manageable, especially for a cooperative group setting."

Adelstein DJ et al. J Clin Oncol 2003;21:92-8.

R/M HNSCC: EXTREME

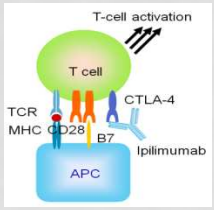
Gr 3-5 Toxicity	PF N=219	PF + Cetux N=215
Cardiac Events	16 (7%)	9 (4%)
Febrile Neutropenia	10 (5%)	10 (5%)
Sepsis	1 (<1%)	9 (4%)
Skin	1 (<1%)	20 (9%)
All Grade 3-5	164 (76%)	179 (82%)
Toxic Death	7 (3.3 %)	3 (1.4%)

"The AE profile in the chemotherapy-alone group was typical...and was not affected by the addition of cetuximab, except…sepsis… skin reactions."

Vermorken J et al. NEJM 2008;359:1116-27.

IMMUNE-RELATED ADVERSE EVENTS:
IPILIMUMAB AND A NEW KIND OF TOXICITY

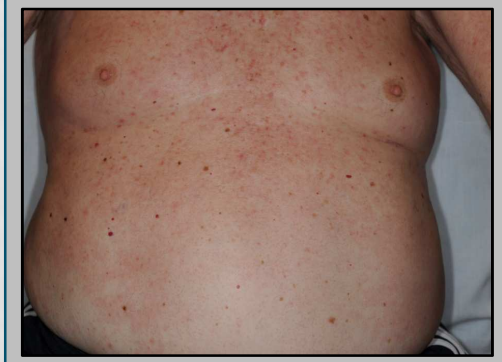
Immune-related AE (irAE)	Ipilimumab Alone (N=131)		Ipilimumab + gp100 (N=380)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any irAE	80 (61%)	19 (14.5%)	221 (58%)	39 (10%)
Dermatologic	57 (43.5%)	2 (1.5%)	152 (40%)	9 (2%)
Gastrointestinal	38 (29%)	10 (8%)	122 (32%)	22 (6%)
Endocrine	10 (8%)	5 (4%)	15 (4%)	4 (1%)
Hepatic	5 (4%)	0 (0%)	8 (2%)	4 (1%)
Other	6 (5%)	3 (2%)	12 (3%)	5 (1%)
Treatment-related deaths	15 (2.1%) across the study; 7(1%) were immune-related			

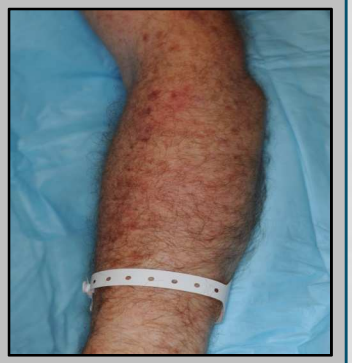


Hodi FS et al. NEJM 2010; 363(8):711-23.

DERMATOLOGIC irAEs:
MACULOPAPULAR RASH

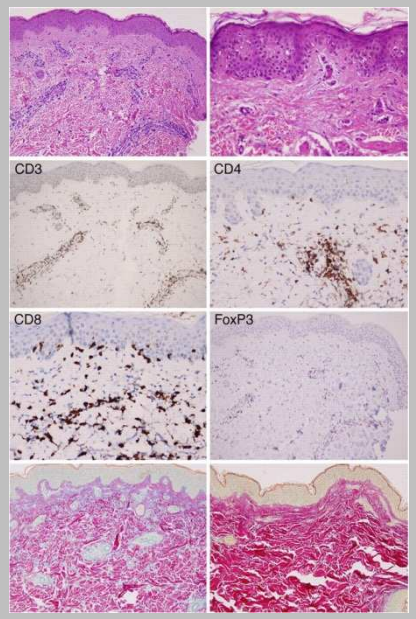
- **Clinical Presentation**
  - Pruritis
  - Rash





Courtesy of Ahmad Tarhini, MD, PhD

Physical Examination



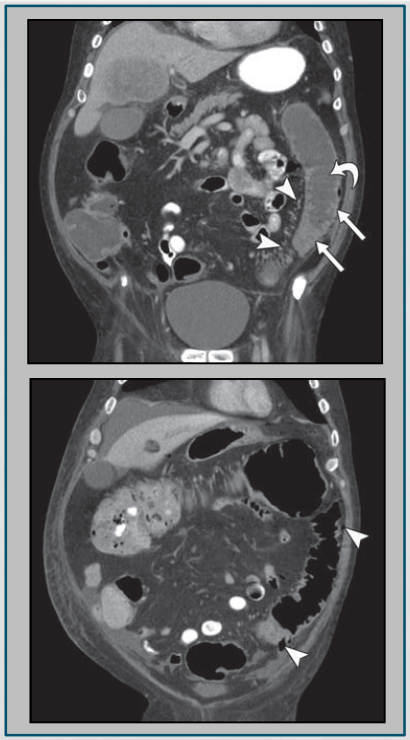
Hodi FS et al. PNAS 2008.

Histology

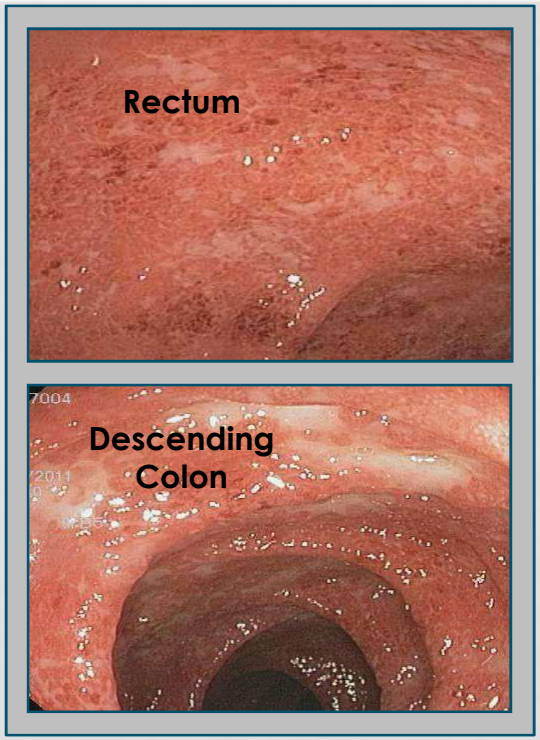
GASTROINTESTINAL irAES:
DIARRHEA/COLITIS

- **Clinical Presentation**
  - Diarrhea
  - Abdominal Pain
  - Distention
  - Peritonitis

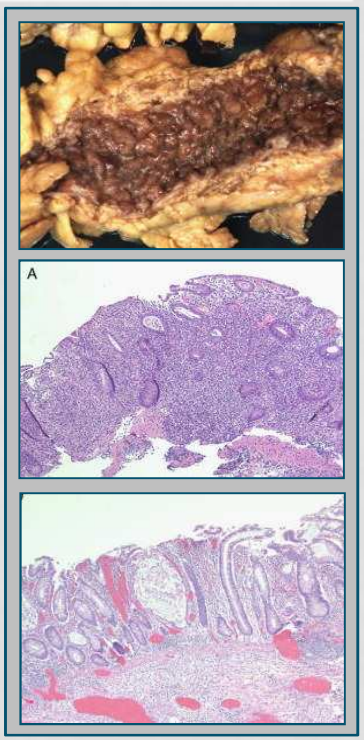
1. Won Kim K et al. AJR 2013.
2. Mitchell KA et al. J Clin Gastroenterol 2013.



Imaging



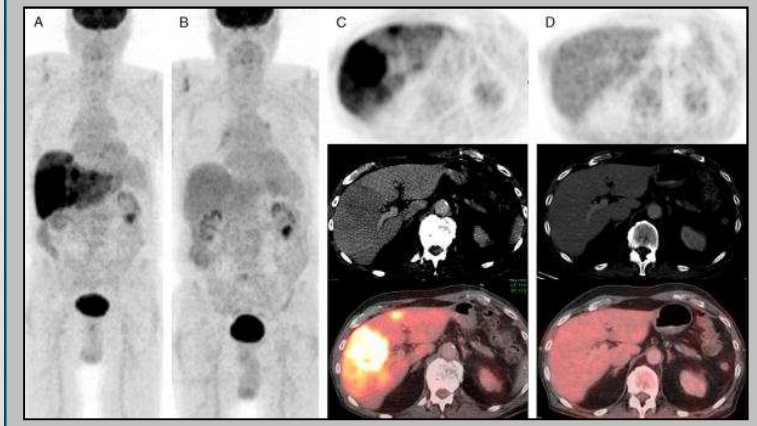
Endoscopy

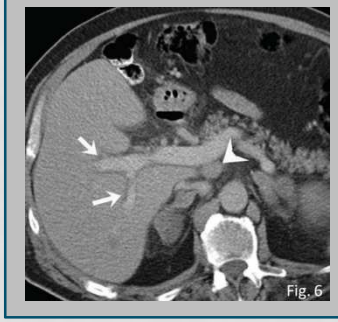


Histology

GASTROINTESTINAL irAES:
HEPATITIS

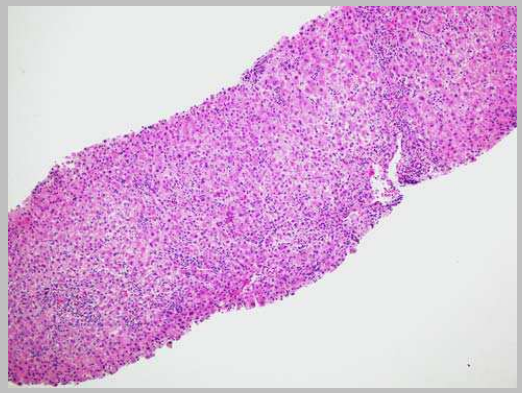
- **Clinical Presentation**
  - Elevated LFTs: AST, ALT, TBili
  - RUQ Pain
  - Jaundice





Imaging

1. Raad RA et al. Clin Nucl Med 2015.
2. Tirumani SH et al. Cancer Immunol Res 2015.



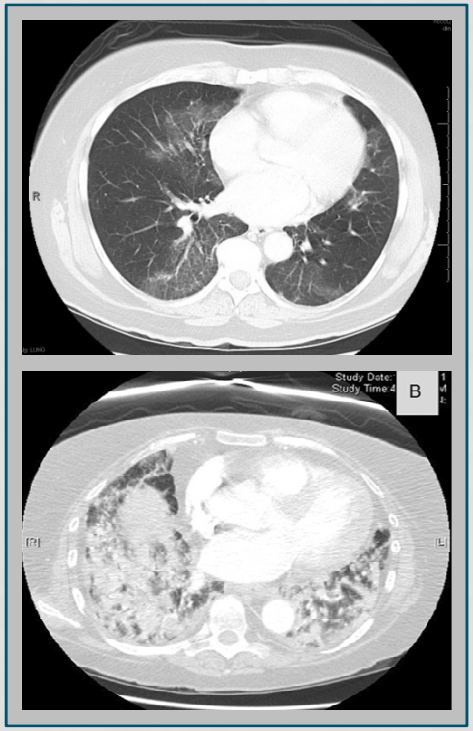
Johncilla M. Am J Surg Pathol 2015.

Histology:
Panlobar hepatitis

PULMONARY irAEs:
PNEUMONITIS

- **Clinical Presentation**
  - Dyspnea
  - Cough
  - Hypoxia
  - Incidental finding on restaging CT

1. Barjaktarevic IZ et al. Chest 2013.
2. Berthod G. et al. J Clin Oncol 2012.



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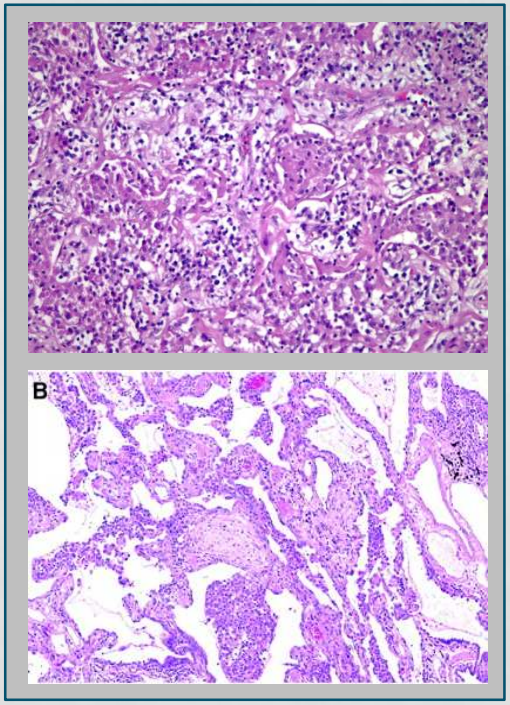
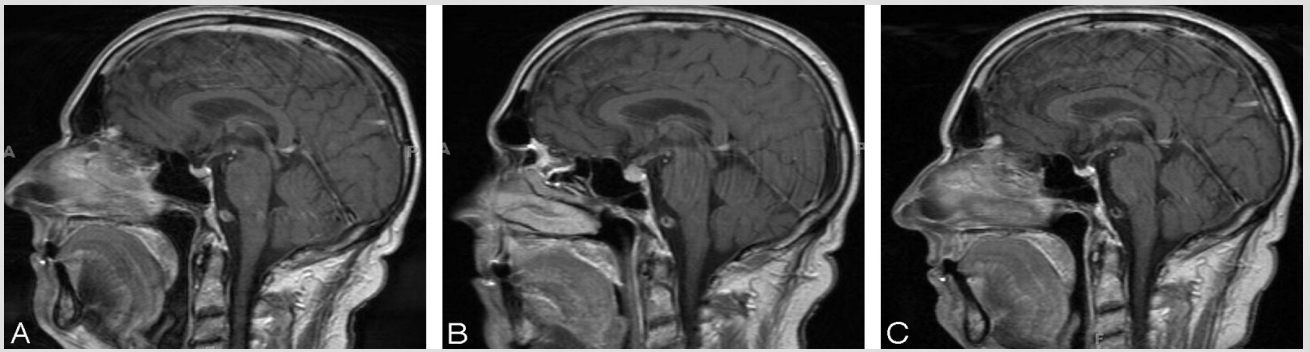


Histology

ENDOCRINE irAEs:
HYPOPHYSITIS

- **Clinical Presentation**
  - Headache
  - Visual disturbance
  - Incidental lab findings: low TSH, low cortisol, hyperkalemia, hyponatremia



MRI

Carpenter KJ et al. AJNR 2009; 30:1751-3.

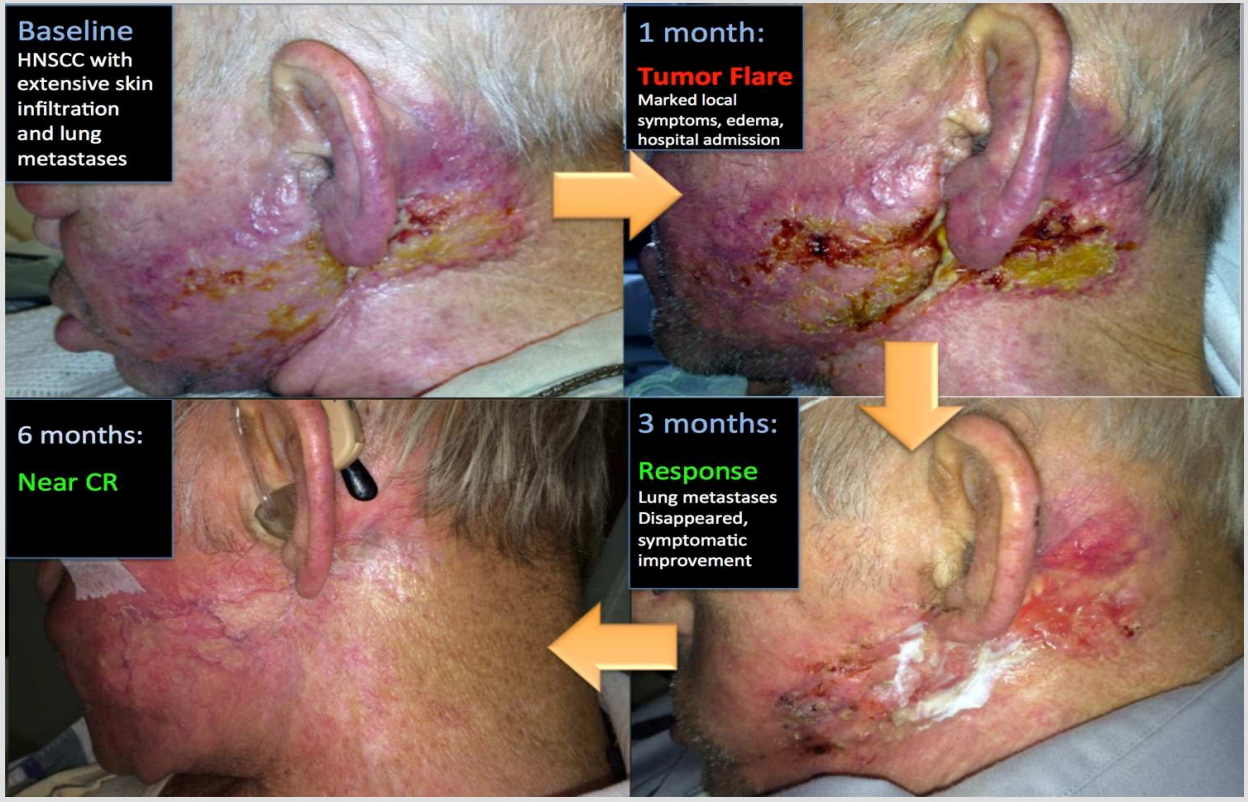
IrTOXICITY: FIRST-LINE TREATMENT

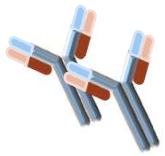
Corticosteroids

- Prednisone 0.5 – 2 mg/kg/day
- Slow taper

IMMUNE-RELATED PATTERN OF RESPONSE:
TUMOR FLARE OR PSEUDOPROGRESSION

Courtesy of T Seiwert, MD





PEMBROLIZUMAB (PD-1 mAB) IN R/M HNSCCC:

PRELIMINARY RESULTS FROM THE KEYNOTE-012 EXPANSION COHORT

T. SEIWERT et al, ASCO 2015

AE in ≥5 % of Patients	N = 132* N (%)
Any	79 (59.8)
Fatigue	20 (15.2)
Hypothyroidism	12 (9.1)
Decreased appetite	10 (7.6)
Rash	10 (7.6)
Dry skin	9 (6.8)
Pyrexia	9 (6.8)
Arthralgia	7 (5.3)
Nausea	7 (5.3)
Weight decreased	7 (5.3)

Grades 3-5 (≥2 patients)	N = 132* N (%)
Any	13 (9.8)
Swelling face	2 (1.5)
Pneumonitis	2 (1.5)

No treatment-related deaths

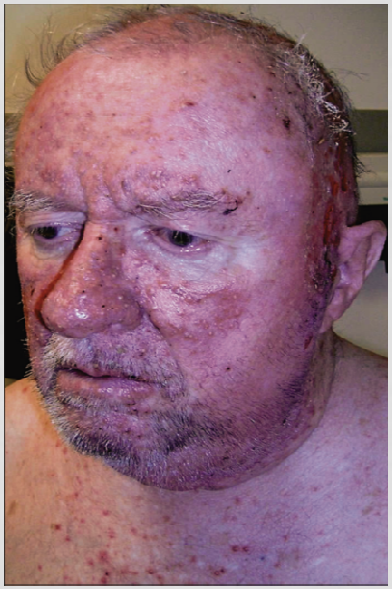
*Includes patients who received ≥1 dose of pembrolizumab
Data cut off date: March 23, 2015.

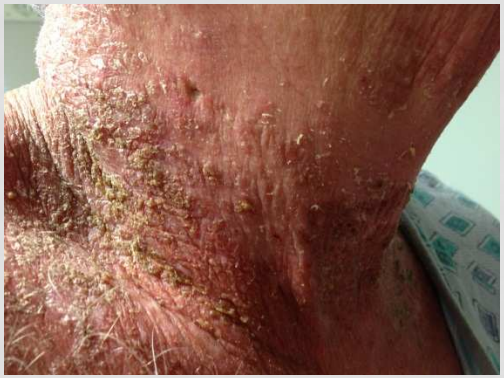
UNIQUE CONSIDERATIONS FOR MULTIMODALITY TRIALS

Toxicities from SOC

- Radiation
  - Mucositis, Dermatitis
  - Subacute thyroiditis, late hypothyroidism
  - Lymphopenia
- Chemotherapy
  - Cisplatin
    - Cytopenias
    - Renal toxicity
    - Neuropathy
  - 5-FU
    - Cytopenias
    - Diarrhea
    - Mucositis
- Cetuximab
  - Acneiform rash
  - Electrolyte wasting

Grade 3 Cetuximab Skin Toxicity





Bauman JE et al. Arch Dermatol 2007;143(7):889-892.

A PHASE IB STUDY OF CETUXIMAB, IPILIMUMAB & IMRT IN HIGH OR INTERMEDIATE RISK PULA HNSCC

UPCI 12-084; NCT01935921

	Week of Treatment									
	1	2	3	4	5	6	7	8	11	14
IMRT (70 Gy standard fx)		X	X	X	X	X	X	X		
Cetuximab (400/250 mg/m^2)	X	X	X	X	X	X	X	X		
Ipilimumab					X			X	X	X
Cohort -1: 1 mg/kg Cohort 1 **(start)**: 3 mg/kg Cohort 2 (de-escalation only): 6 mg/kg Cohort 3: 10 mg/kg										
Immune Biomarkers	X				X			X	X	X

Principal Investigator: Ferris
Med Onc Co-Chair: Bauman
CTEP-sponsored

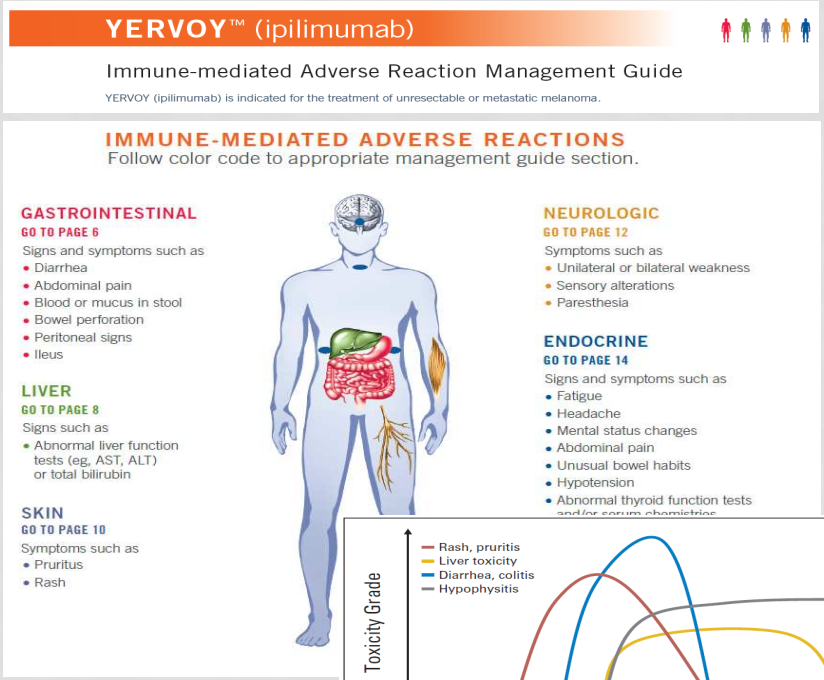
PRELIMINARY TOXICITY DATA

N=6; IPILIMUMAB 3 mg/kg

Immune-Related	Grade 1-2	Grade 3-4
Skin Rash	4/6 (67%)	2/6 (17%)†
Diarrhea/Colitis	0/6 (0%)	0/6 (0%)
Transaminitis	0/6 (0%)	0/6 (0%)
Regimen-related	**Grade 1-2**	**Grade 3-4**
Acute Thyroiditis	1/6 (20%)	0/6 (0%)
Late Hypothyroidism	1/6 (33%)	0/6 (0%)
Acute Radiation Dermatitis	0/6 (0%)	6/6 (100%)

† Dose-Limiting Toxicity: Grade 3 rash

THE NEW COMFORT ZONE



Weber JS et al. JCO 2012;30:2691-2697.

CONCLUSIONS

- Toxicity to immunotherapy occurs in unique but clinically recognizable patterns
  - Symptoms and signs
  - Kinetics
- Toxicities are responsive to immunosuppression
  - Corticosteroids in first line
- Tools are available to educate clinical investigators
- Combination trials must anticipate new and/or overlapping toxicities with conventional therapies

QUESTION 1

- True or False:
  - In recurrent or metastatic solid tumors, ipilimumab and other checkpoint inhibitors cause more treatment-related deaths than chemotherapy

QUESTION 1

- True or False:
  - In recurrent or metastatic solid tumors, ipilimumab and other checkpoint inhibitors cause more treatment-related deaths than chemotherapy

➢ **False**

QUESTION 2

- You are evaluating a 52 year old WM with metastatic melanoma, who initiated treatment with ipilimumab 3 mg/kg 3 weeks ago and presents for consideration of dose 2. His past medical history is significant for HTN and diverticulosis. He reports constipation of 3 days duration, left lower quadrant pain (LLQ), and a fever of 99°F. On examination, he is nontoxic with a temperature of 99.4°F. He has moderate tenderness to palpation in the LLQ. No rash or jaundice. You hold ipilimumab and take which of the following clinical steps?

  - Initiate prednisone at 0.5 mg/kg/day
  - Refer for colonoscopy
  - Perform contrasted CT of the abdomen/pelvis
  - Recommend stool softeners and senna

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  - ➢ **Perform contrasted CT of the abdomen/pelvis**
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QUESTION 3

- You are evaluated a 65 year old AAF with Stage IV adenocarcinoma of the lung, with metastatic disease to the liver, adrenal gland and bone. No history of CNS metastases. She initiated nivolumab 4 months ago, with initial stable disease, and now presents for restaging. Her past medical history is significant for 45 pack-years, HTN, and diverticulosis. She reports a new headache and visual hallucinations. You hold nivolumab and take which of the following clinical steps?

  - Initiate corticosteroids and follow up in one week.
  - Obtain serum TSH and cortisol. Initiate corticosteroids and admit the patient for urgent brain MRI.
  - Refer for EEG and start levetiracetam (Keppra).
  - Increase her fentanyl patch and breakthrough oxycodone, and follow up in one week.

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