JADPRO CE Regional Lectures

Clinical Advances and Case Studies in Immune Checkpoint Inhibitors in Oncology

Melanoma

Program Chairs

Brianna Hoffner
MSN, ANP-BC, AOCNP®
University of Colorado
Cancer Center

Laura J. Zitella
MS, RN, ACNP-BC, AOCN®
Stanford Health Care

Faculty

Whitney Lewis
PharmD, BCOP
The University of Texas MD
Anderson Cancer Center

Faculty Financial Disclosures

- Ms. Hoffner has received consulting fees/honoraria from Abbott, Array BioPharma, and Merck.
- Ms. Zitella has served on the advisory board for Array Biopharma and has equity interests/stock options in Kite Pharma.
- Dr. Lewis has nothing to disclose.

Planning Committee Financial Disclosures

- Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has served as a consultant for Pfizer and Eisai.
- Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has nothing to disclose.
- Annenberg Center for Health Sciences at Eisenhower
  - John Bayliss, VP, Business Development, spouse is an employee of Amgen, Inc.; Charles Willis, Director, Continuing Education, consults for Pfizer Inc.; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.
- Alana Brody, Lynn Rubin, and Patti McLafferty (Harborside Medical Education) have nothing to disclose.
- Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose.
- Claudine Kiffer and Annie Yueh (Harborside) have nothing to disclose.

This activity is supported by educational grants provided by AstraZeneca and Bristol-Myers Squibb.

Learning Objectives

- Differentiate between early and late adverse effects associated with immunotherapeutic agents.
- Recognize the differences between immunotherapeutic agents and chemotherapeutic agents: mechanisms of action, adverse effects, and toxicity management.
- Summarize data on currently available immunotherapeutic agents as they relate to durable treatment responses.
- Explain the utility of biomarker testing in selecting patients for immunotherapy and in predicting clinical outcomes.

Goal

- Demonstrate an understanding of the management of immunotherapy-based adverse events in patients with melanoma.

Melanoma

- 5.2% of all new cancer cases
  - Fifth most common cancer
- 1.6% of all cancer deaths
- 87,110 estimated new cases in 2017
  - Increasing at 1.4% each year over the past 10 years
- More common in men than women
  - Individuals with fair complexion at higher risk

Audience Response Question

Ipilimumab plus nivolumab in the treatment of melanoma:

A. Is FDA approved only for *BRAF*-negative mutations in the adjuvant and metastatic setting
B. Is FDA approved in the adjuvant setting for patients at high risk of disease recurrence following complete surgical resection
C. Is associated with an increased incidence of grade 3 or 4 treatment-related adverse events, but also increased overall survival as compared to single-agent therapy
D. Is associated with an increased incidence of grade 3 or 4 treatment-related adverse events and does not increase overall survival as compared to single-agent therapy
E. Increases median survival but not overall survival as compared to single-agent therapy.
F. Unsure

Approved Immunotherapies

- **High-dose IL-2:** FDA approved 1992
- **Ipilimumab**
  - 3/2011 FDA approved for unresectable or metastatic melanoma
  - 10/2015 FDA approved in the adjuvant setting for stage III melanoma
- **Pembrolizumab:** 9/2014 FDA approved for unresectable or metastatic melanoma
- **Nivolumab**
  - 12/2014 FDA approved for unresectable or metastatic melanoma
  - 12/20/2017 FDA approved for adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
  - 3/6/2018 FDA approved for Q4 week dosing

FDA = US Food and Drug Administration.

Approved Immunotherapies (cont.)

- **Ipilimumab + nivolumab**
  - 9/2015 FDA approved for unresectable or metastatic melanoma BRAF–
  - 1/23/16 FDA approved for unresectable or metastatic melanoma, any BRAF status
- **T-VEC (talimogene laherparepvec):**10/2015 FDA approved for unresectable melanoma

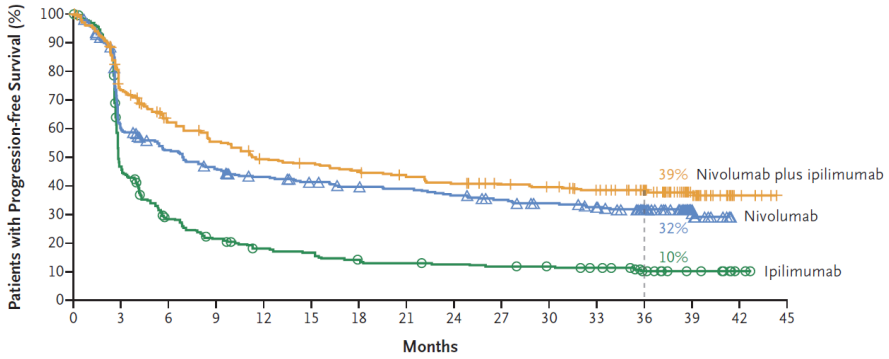
CheckMate 067

- Phase III trial of previously untreated advanced melanoma patients, randomized 1:1:1 to receive nivolumab + ipilimumab vs. nivolumab vs. ipilimumab
- 3-year overall survival outcomes
  - Median survival
    - Not yet reached in nivolumab + ipilimumab
    - 37.6 months nivolumab
    - 19.9 months ipilimumab
  - Overall survival
    - 58% nivolumab + ipilimumab
    - 52% nivolumab
    - 34% ipilimumab
- Treatment-related adverse events of grade 3 or 4
  - 59% ipilimumab + nivolumab
  - 21% nivolumab
  - 28% ipilimumab

Wolchok, J.D. (2017). Overall survival with combined nivolumab and ipilimumab in advanced melanoma. NEJM, 377(14).

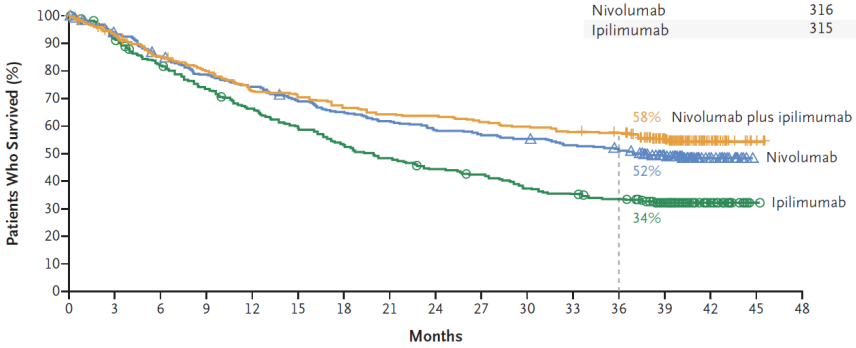
CheckMate 067 (cont.)

A Progression-free Survival



No. at Risk																
Nivolumab plus ipilimumab	314	218	175	155	136	131	124	117	110	104	100	92	75	29	5	0
Nivolumab	316	177	151	131	119	111	105	102	96	87	81	75	61	24	0	0
Ipilimumab	315	136	78	58	46	42	34	32	30	28	26	23	15	8	2	0

B Overall Survival



No. at Risk																
Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

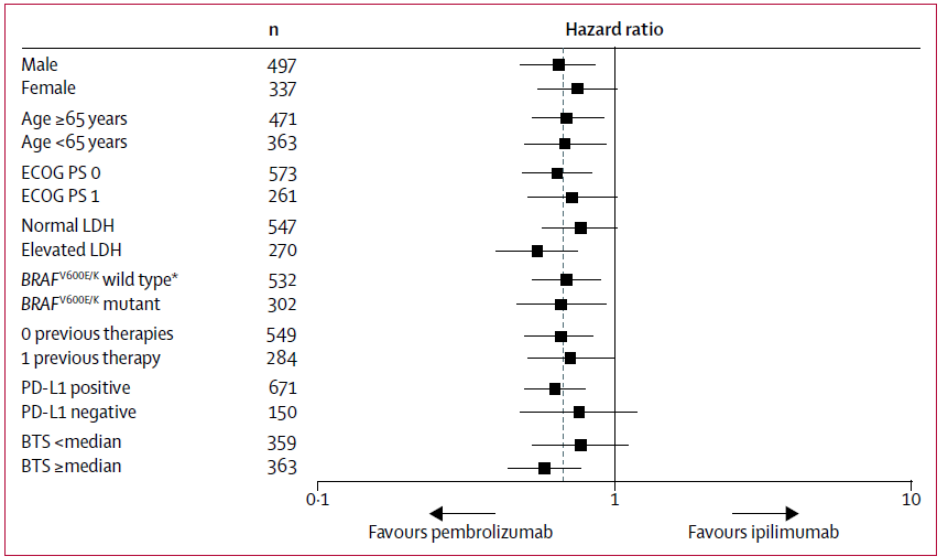
Wolchok, J.D. (2017). Overall survival with combined nivolumab and ipilimumab in advanced melanoma. NEJM, 377(14).

KEYNOTE-006

- Phase III of unresectable stage III or IV melanoma patients who had received up to one previous systemic therapy, randomized to receive one of two dose regimens of pembrolizumab (Q2 or Q3wk) or ipilimumab
- Median overall survival
  - Not reached in either pembrolizumab group
  - 16 months with ipilimumab
- 24-month overall survival
  - 55% pembrolizumab Q2 and Q3 week groups
  - 43% ipilimumab
- Pembrolizumab provides favorable benefit-risk profile in comparison with ipilimumab

Schachter, J. (2017). Pemrbolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicenter, randomized, open-label phase 3 study (KEYNOTE 006). Lancet, 390, 1853-62.

KEYNOTE-006 (cont.)



Overall survival in key subgroups

	Pembrolizumab every 2 weeks n=278		Pembrolizumab every 3 weeks n=277		Ipilimumab n=256	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any	229 (82%)	47 (17%)	213 (77%)	46 (17%)	190 (74%)	50 (20%)
Serious	34 (12%)	0	32 (12%)	0	44 (17%)	0
Led to discontinuation	19 (7%)	0	30 (11%)	0	23 (9%)	0
Led to death	1 (<1%)*	0	0	0	0	0
Observed in ≥10% of patients in any treatment group						
Fatigue	79 (28%)	1 (<1%)	64 (23%)	3 (1%)	43 (17%)	3 (1%)
Pruritus	56 (20%)	0	55 (20%)	0	67 (26%)	0
Diarrhoea	54 (19%)	7 (3%)	46 (17%)	3 (1%)	59 (23%)	7 (3%)
Rash	44 (16%)	0	48 (17%)	0	40 (16%)	0
Arthralgia	35 (13%)	0	38 (14%)	0	13 (5%)	0
Nausea	36 (13%)	0	37 (13%)	0	24 (9%)	0
Hypothyroidism	30 (11%)	0	23 (8%)	0	2 (1%)	0

Data are n (%). *Sepsis.

Table 3: Treatment-related adverse events

Schachter, J. (2017). Pemrbolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicenter, randomized, open-label phase 3 study (KEYNOTE 006). Lancet, 390, 1853-62.

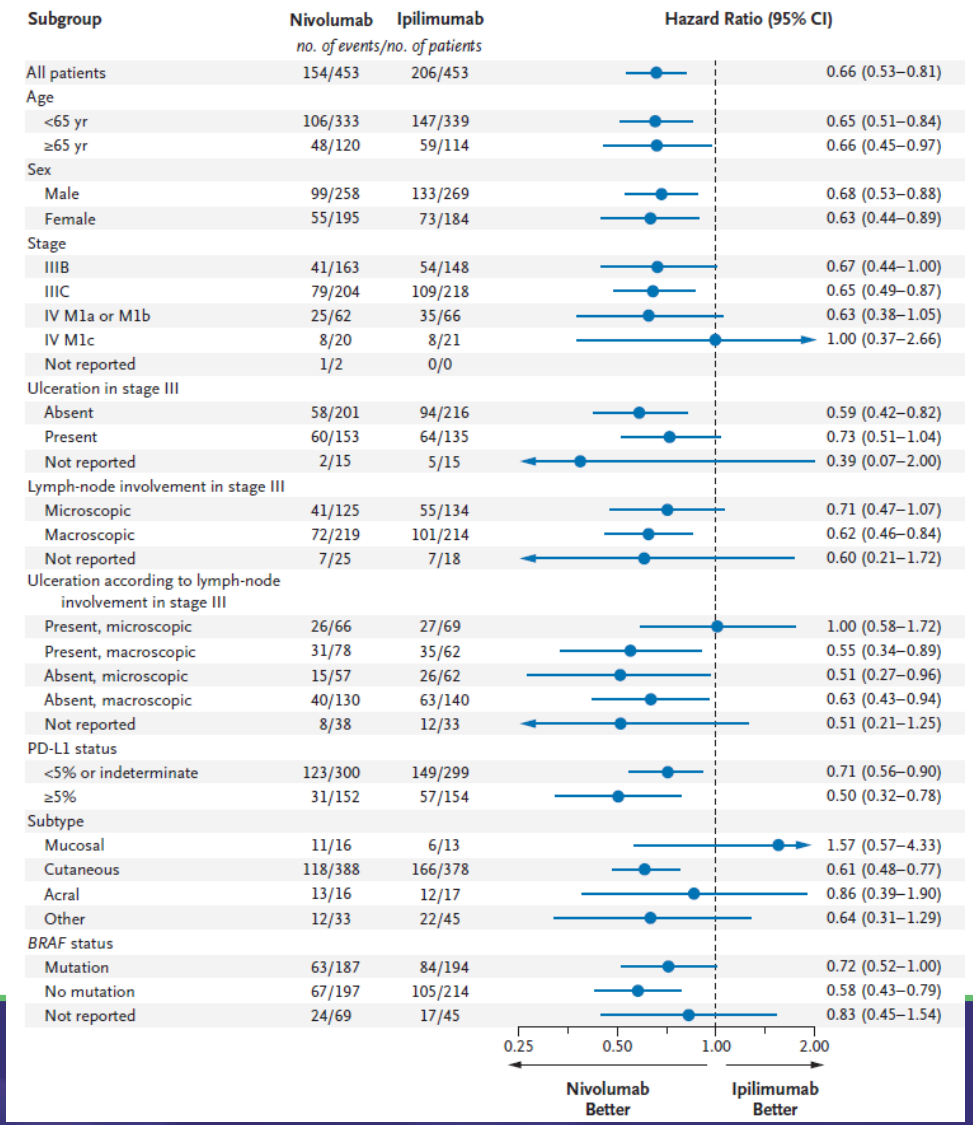
CheckMate 238

- Phase III study of patients who were undergoing complete resection of stage IIIB, IIIC, or IV melanoma to receive nivolumab or ipilimumab
  - Patients were treated up for a period of up to 1 year or until disease recurrence, unacceptable toxicity or withdrawal of consent
- A minimum follow up of 18 months, 12-month rate of recurrence-free survival
  - 70.5% nivolumab
  - 60.8% ipilimumab
- Treatment-related grade 3 or 4 adverse events
  - 14.4% nivolumab
  - 45.9% ipilimumab

Weber, J. et al. (2017). Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. NEJM, 377(19).

CheckMate 238 (cont.)

Subgroup analysis of disease recurrence or death

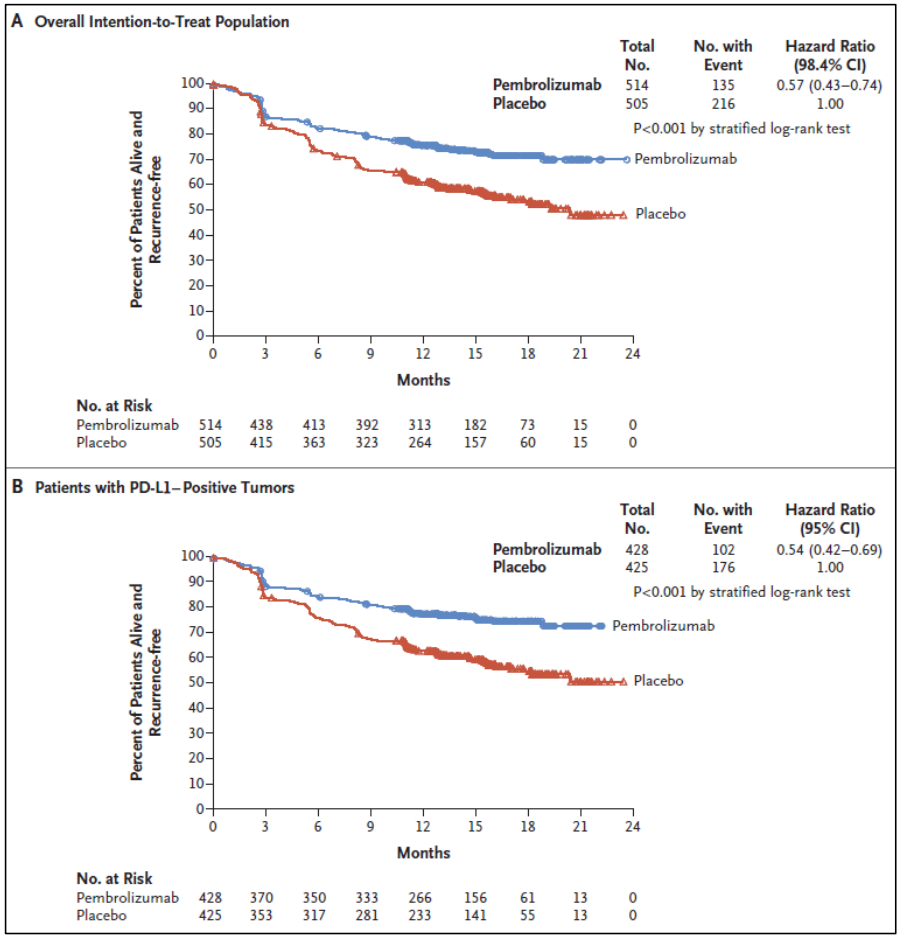


Subgroup	Nivolumab	Ipilimumab	Hazard Ratio (95% CI)
	no. of events/no. of patients		
All patients	154/453	206/453	0.66 (0.53–0.81)
Age			
<65 yr	106/333	147/339	0.65 (0.51–0.84)
≥65 yr	48/120	59/114	0.66 (0.45–0.97)
Sex			
Male	99/258	133/269	0.68 (0.53–0.88)
Female	55/195	73/184	0.63 (0.44–0.89)
Stage			
IIIB	41/163	54/148	0.67 (0.44–1.00)
IIIC	79/204	109/218	0.65 (0.49–0.87)
IV M1a or M1b	25/62	35/66	0.63 (0.38–1.05)
IV M1c	8/20	8/21	1.00 (0.37–2.66)
Not reported	1/2	0/0	
Ulceration in stage III			
Absent	58/201	94/216	0.59 (0.42–0.82)
Present	60/153	64/135	0.73 (0.51–1.04)
Not reported	2/15	5/15	0.39 (0.07–2.00)
Lymph-node involvement in stage III			
Microscopic	41/125	55/134	0.71 (0.47–1.07)
Macroscopic	72/219	101/214	0.62 (0.46–0.84)
Not reported	7/25	7/18	0.60 (0.21–1.72)
Ulceration according to lymph-node involvement in stage III			
Present, microscopic	26/66	27/69	1.00 (0.58–1.72)
Present, macroscopic	31/78	35/62	0.55 (0.34–0.89)
Absent, microscopic	15/57	26/62	0.51 (0.27–0.96)
Absent, macroscopic	40/130	63/140	0.63 (0.43–0.94)
Not reported	8/38	12/33	0.51 (0.21–1.25)
PD-L1 status			
<5% or indeterminate	123/300	149/299	0.71 (0.56–0.90)
≥5%	31/152	57/154	0.50 (0.32–0.78)
Subtype			
Mucosal	11/16	6/13	1.57 (0.57–4.33)
Cutaneous	118/388	166/378	0.61 (0.48–0.77)
Acral	13/16	12/17	0.86 (0.39–1.90)
Other	12/33	22/45	0.64 (0.31–1.29)
BRAF status			
Mutation	63/187	84/194	0.72 (0.52–1.00)
No mutation	67/197	105/214	0.58 (0.43–0.79)
Not reported	24/69	17/45	0.83 (0.45–1.54)

Weber, J. et al. (2017). Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. NEJM, 377(19).

KEYNOTE-054

- Phase III double-blind study evaluating pembrolizumab as adjuvant therapy in patients with resected, high-risk stage III melanoma.
  - 18 doses or until disease recurrence or unacceptable toxicity
- At median follow up of 15 months, recurrence-free survival 75.4% in pembrolizumab arm vs. 61% in placebo arm
  - 77.1% vs. 62.6% when selected for PD-L1+ tumors
- Adverse events grades 3–5 related to study reported in 14.7% of pembrolizumab patients and 3.4% of placebo patients



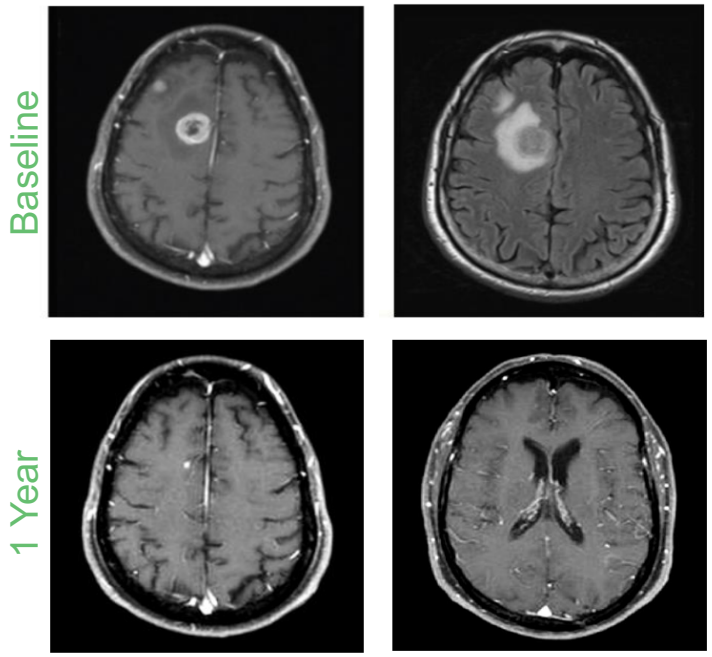
Eggermont, A.M., et al. (2018). Adjuvant pembrolizumab versus placebo in resected stage III melanoma. NEJM, doi: 10.1056/NEJMoa1802357

CheckMate 204

- Phase II study of nivolumab + ipilimumab in patients with untreated melanoma brain metastases
- 9 month follow-up presented at ASCO 2017
  - Intracranial ORR of 55%
  - 21% of patients with complete response
  - Median PFS not reached, 6-month PFS > 60%

ORR = overall response rate; PFS = progression-free survival; SRT = stereotactic radiotherapy.

Patient Case

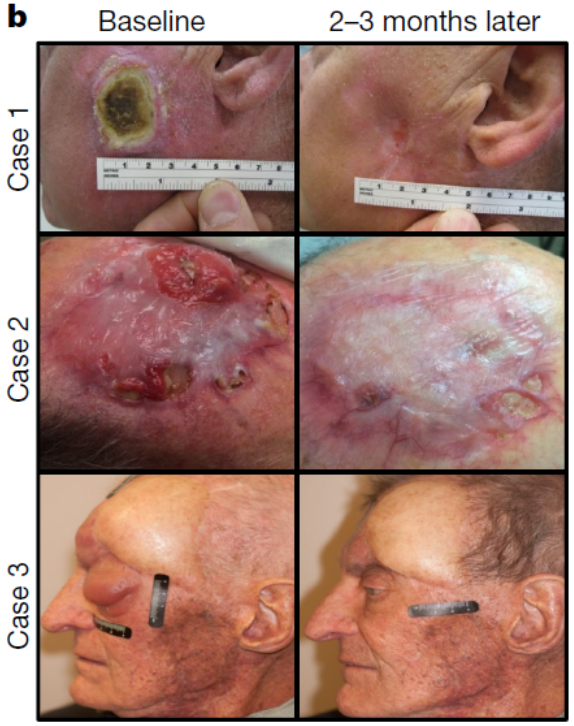


71 yo male with *BRAF* V600E-mutated melanoma, ~7 brain mets, no steroids or SRT

Tawbi, H. et al. (2017). Efficacy and safety of nivolumab plus ipilimumab in patients with melanoma metastatic to the brain: Results of the phase II study CheckMate 204. Abstract Number 9507, presented at ASCO 2017

PD-1 Blockade in Desmoplastic MEL

- Analysis of sixty patients with advanced desmoplastic melanoma (DM) treated with anti–PD-1 or PD-L1
  - Objective tumor responses in 70%
  - Complete response in 32%
- Whole-exome sequencing revealed high mutational load and frequent NF1 mutations

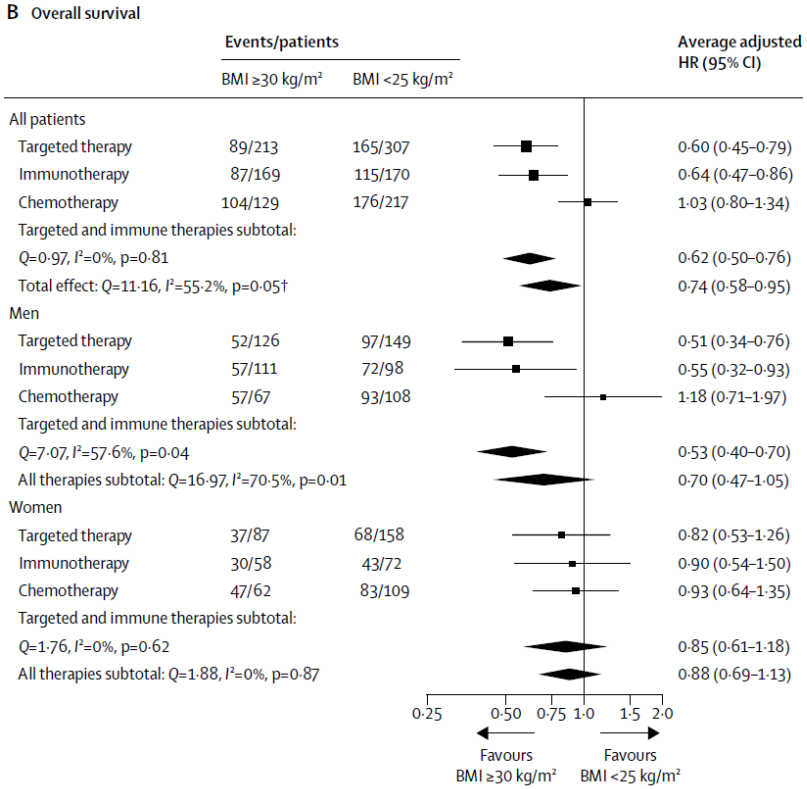


Images of three cases of DM that responded to PD-1 blockade

Eroglu, Z. et al. (2018). High response rate to PD-1 blockade in desmoplastic melanomas. Nature, 553.

Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis

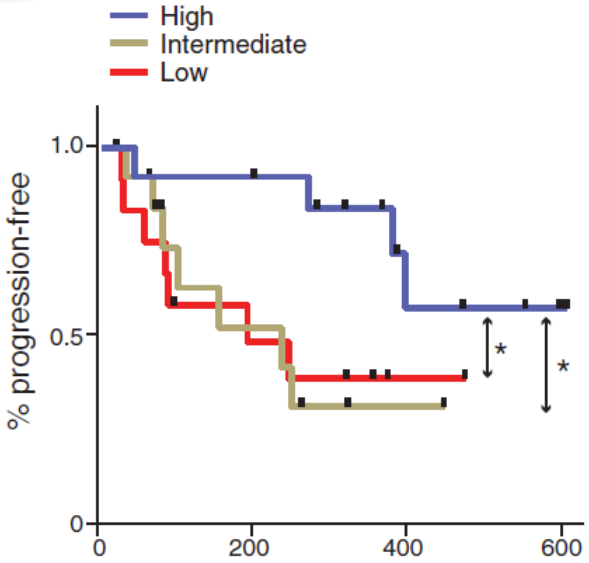
- Retrospective analysis of 2,046 patients with metastatic melanoma treated with targeted therapy, immunotherapy or chemotherapy
- Obesity, compared with normal BMI, associated with improved survival in patients with metastatic melanoma
  - Association mainly seen in male patients treated with targeted or immune therapy



McQuade, JL et al. (2018). Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective multicohort analysis. Lancet Oncology, 19.

Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients

- Study examined oral and gut microbiome of melanoma patients undergoing anti–PD-1 immunotherapy.
  - Significant differences noted in the diversity and composition of the patient gut microbiome of responders vs. nonresponders
  - Fecal microbiome samples showed higher alpha diversity and relative abundance of bacteria of the Ruminococcaceae family in responding patients



Kaplan-Meier plot of PFS by fecal diversity

Gopalakrishnan, V. et al. (2018). Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science, 359.

Audience Response Question

Ipilimumab plus nivolumab in the treatment of melanoma:

A. Is FDA approved only for *BRAF*-negative mutations in the adjuvant and metastatic setting
B. Is FDA approved in the adjuvant setting for patients at high risk of disease recurrence following complete surgical resection
C. Is associated with an increased incidence of grade 3 or 4 treatment-related adverse events, but also increased overall survival as compared to single-agent therapy
D. Is associated with an increased incidence of grade 3 or 4 treatment-related adverse events and does not increase overall survival as compared to single-agent therapy
E. Increases median survival but not overall survival as compared to single-agent therapy.
F. Unsure

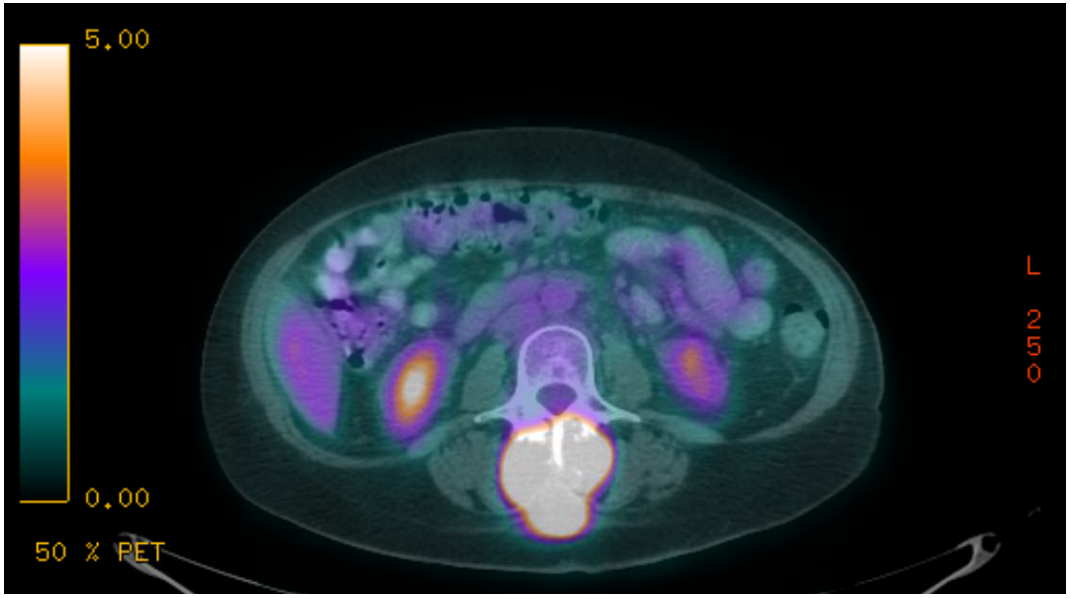
Case Study: MM

- MM is a 71-year-old female with stage IV melanoma diagnosed 6/2016
- PMH: Hypertension, hypercholesterolemia, asthma, vitiligo
- PSH: Hernia repair, back surgery
- Medications: Lisinopril, lorazepam, simvastatin, oxycodone

PMH = past medical history; PSH = past surgical history.

Case Study: MM (cont.)

- Baseline PET scan showing widely metabolic disease
  - Large lesion at L2



PET = positron emission tomography.

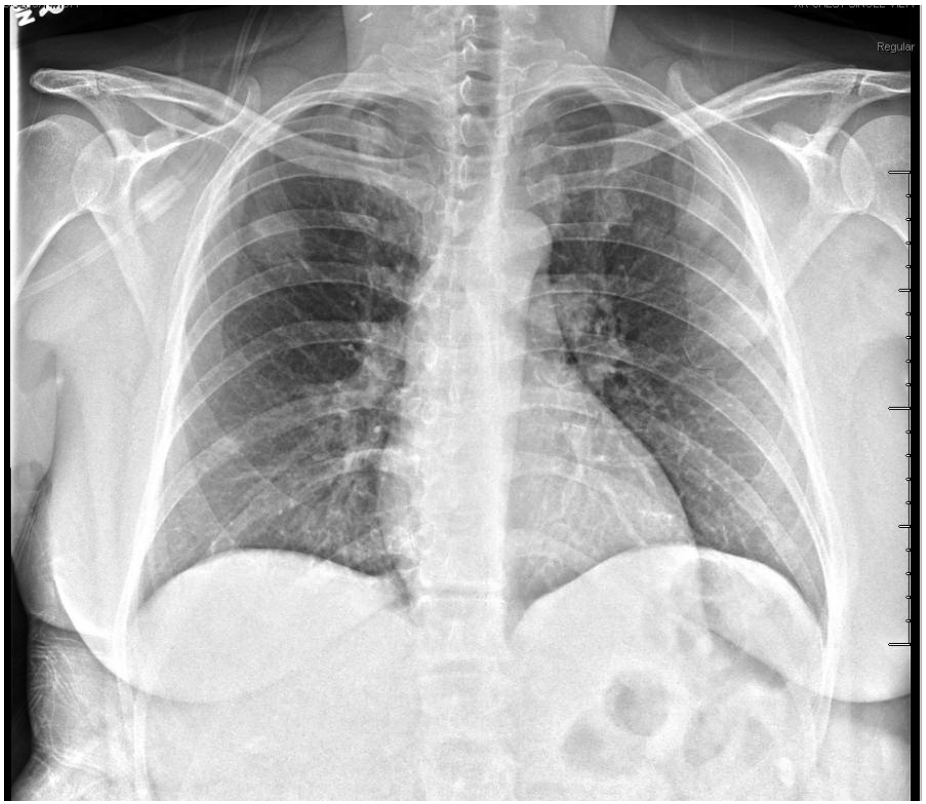
Image courtesy Matthew Burke, Smilow Cancer Hospital.

Case Study: MM (cont.)

- Initiated on ipilimumab (3 mg/kg) + nivolumab (1 mg/kg)
  - C1D1: 7/1/17
  - C2D1: 7/22/17
  - C3D1: 8/19/17
- On 8/27/17, MM presents to outside hospital complaining of fever, cough, and shortness of breath
  - Vitals: BP 125/86, HR 90, RR 22, O_2 90%, temp 100.1
  - Chest x-ray: read as pneumonia
  - Patient initiated on amoxicillin/clavulanate potassium 875 mg/125 mg q12h

BP = blood pressure; HR = heart rate; RR = respiratory rate; O2 = oxygen; temp = temperature; RML = right middle lobe.

Case Study: MM (cont.)



8/27/16

Images courtesy Matthew Burke, Smilow Cancer Hospital.

Case Study: MM (cont.)

- On 8/30/17, MM presents to clinic with continued low-grade fever, cough, and diarrhea (since 8/29/17)
- Denies sick contacts, dietary changes
- Approximately 8 loose bowel movements per day (baseline 1 bowel movement daily)
- No relief with loperamide
- Cough making it difficult to sleep at night

Grading Adverse Events

Grading toxicity:

Pneumonitis

Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)	Grade 5: Death
Asymptomatic, clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care; oxygen indicated	Life threatening respiratory compromise; urgent intervention indicated (tracheostomy, intubation)	

Hypoxia

Definition: A disorder characterized by decrease in the level of oxygen to the body.

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)	Grade 5: Death
	Decreased oxygen saturation with exercise (e.g., pulse ox < 88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse ox < 88%)	Life threatening airway compromise; urgent intervention indicated (tracheostomy, intubation)	

Grading Adverse Events (cont.)

Grading toxicity:

Diarrhea (increased frequency, loose, large volume, or liquidy stools)

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)	Grade 5: Death
- Increase of <4 stools/day over baseline - Mild increase in ostomy output compared to baseline	- Increase of 4-6 stools over baseline per day - Moderate increase of output in ostomy compared to baseline	- Increase of ≥7 stools over baseline per day; incontinence - Hospitalization indicated - Severe increase in ostomy output compared to baseline - Limiting self-care activities of daily living	- Life-threatening (e.g., perforation, bleeding, ischemic necrosis, toxic megacolon) - Urgent intervention required	

Colitis (inflammation of the intestinal lining)

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)	Grade 5: Death
Asymptomatic; clinical or diagnostic observation only; intervention not indicated	Abdominal pain, blood or mucus in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening (e.g., hemodynamic collapse); urgent intervention indicated	

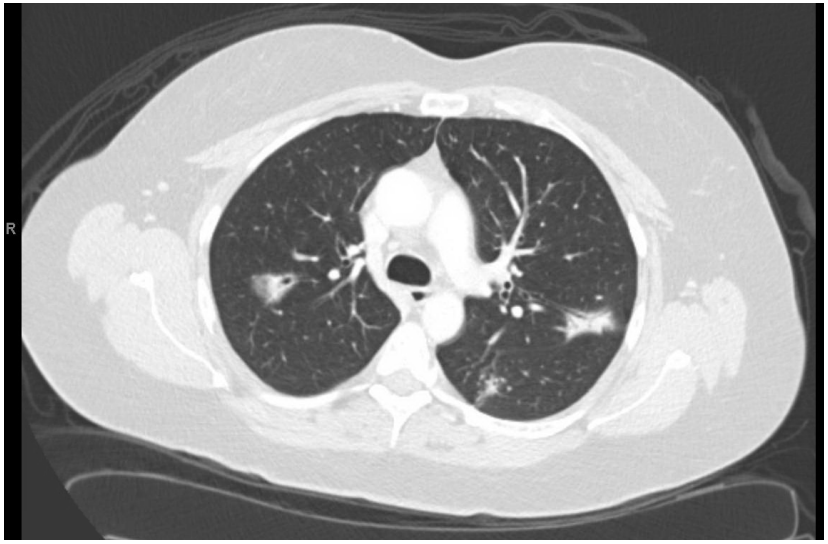
Case Study MM: Differential Diagnoses

- Grade 3 diarrhea differential diagnoses
  - Infectious diarrhea (including *C. diff*)
  - Antibiotic-associated diarrhea
  - Colitis secondary to immunotherapy
- Grade 2 cough vs. pneumonitis differential diagnoses
  - Infectious
  - Inflammatory
  - Irritation

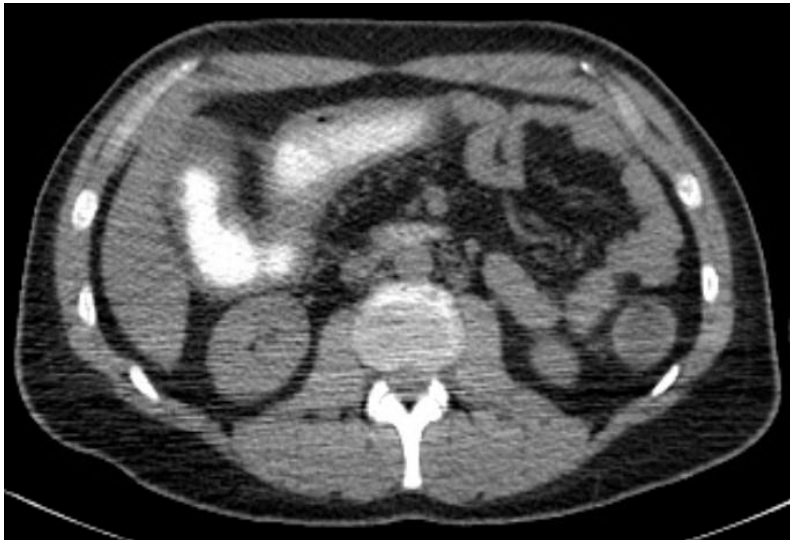
C. diff = *Clostridium difficile*.

Case Study MM: Imaging

Chest CT scan



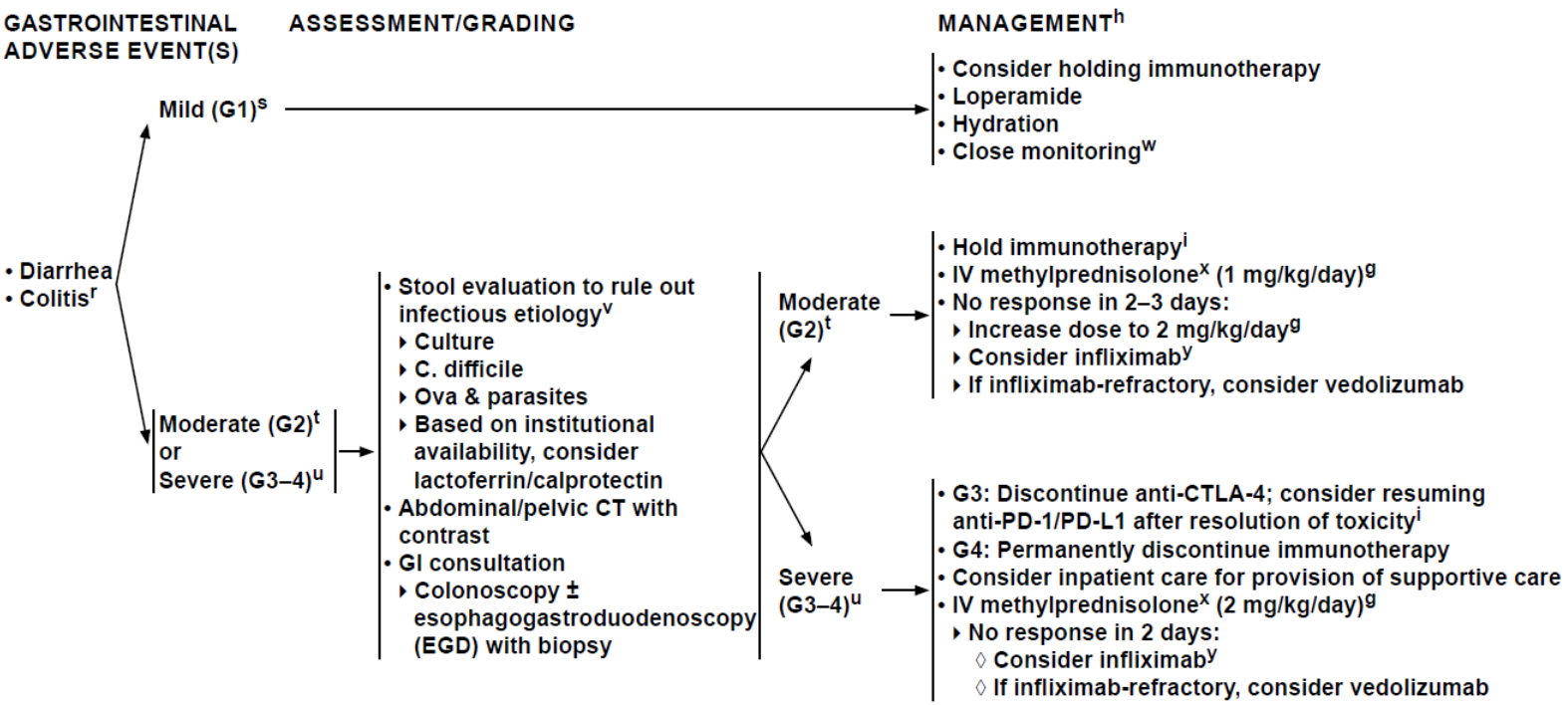
Abdominal CT scan



CT = computed tomography.

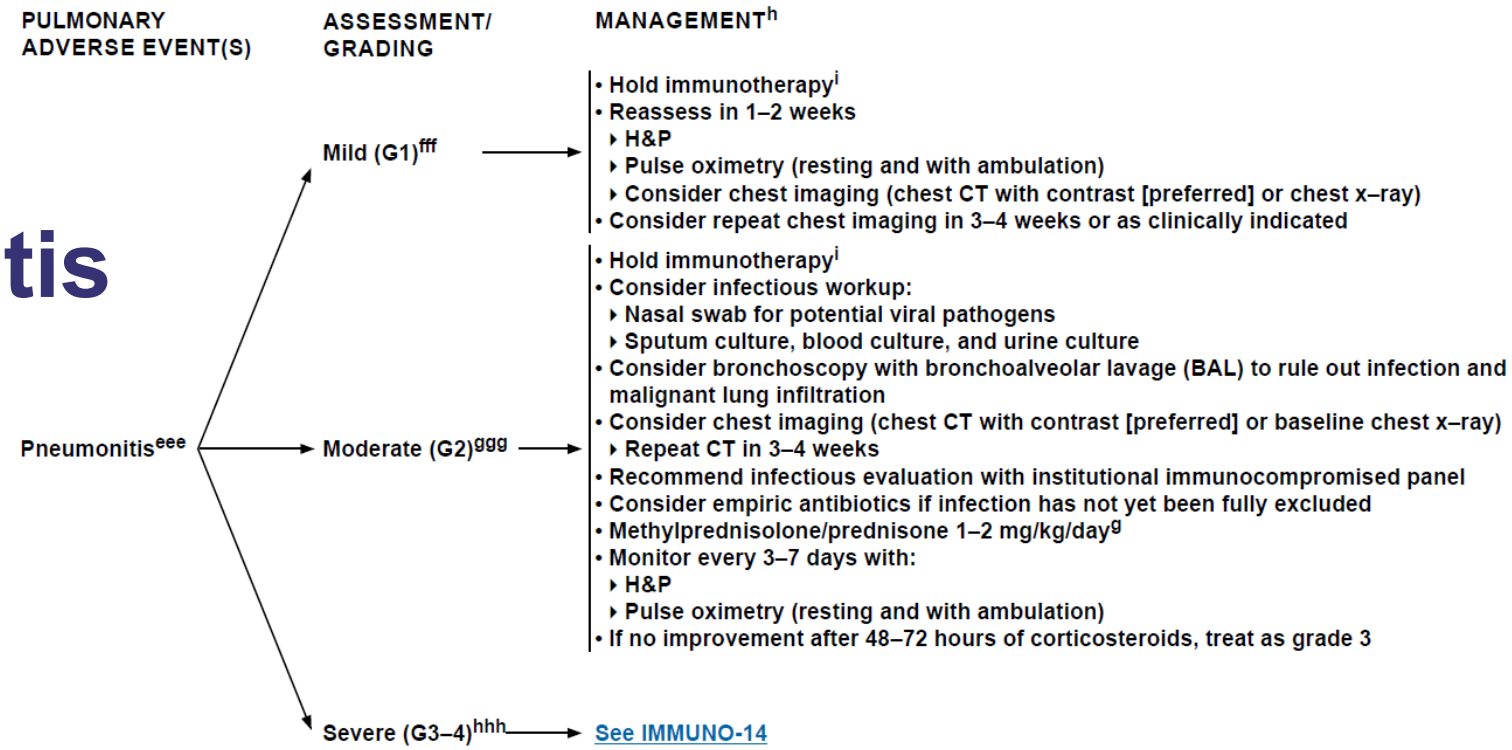
Images courtesy Brianna Hoffner, University of Colorado.

Grade 3 Colitis



[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[r]Symptoms include: abdominal pain, blood and mucus in the stool, fever.
[s]Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
[t]4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[u]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).
[v]It is not necessary to wait for test results before providing therapy to manage irAE.
[w]If progressive, consider stool evaluation to rule out infectious etiology.
[x]Convert to prednisone when appropriate.
[y]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.

Grade 2 Pneumonitis



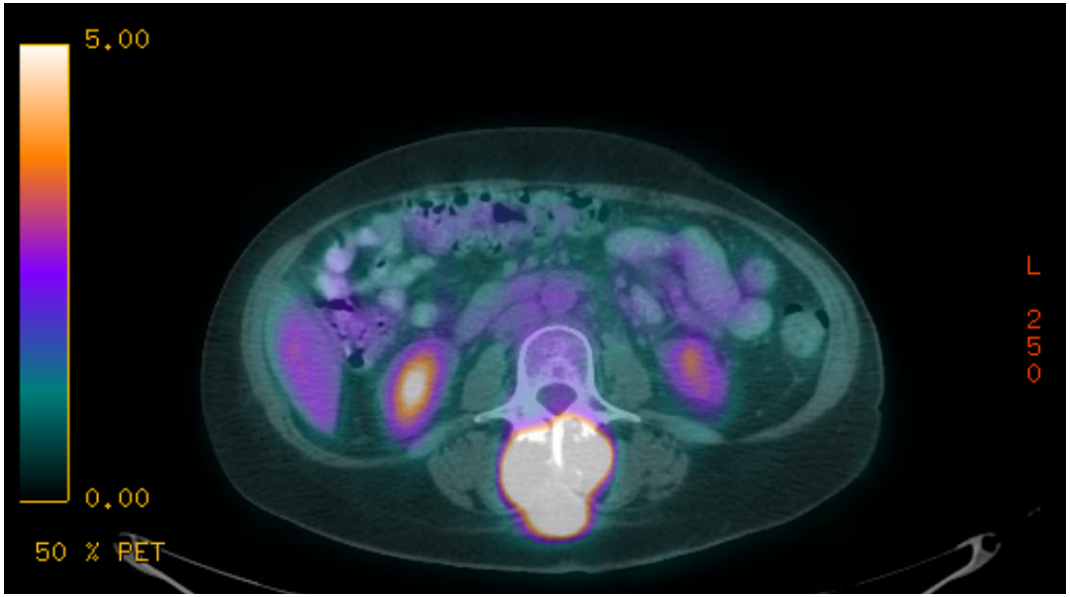
[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[eee]Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[fff]Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.
[ggg]Presence of new/worsening symptoms including: shortness of breath, cough, chest pain, fever, and increased oxygen requirement
[hhh]G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs; G4–life-threatening respiratory compromise.

Case Study MM: irAE Diagnoses

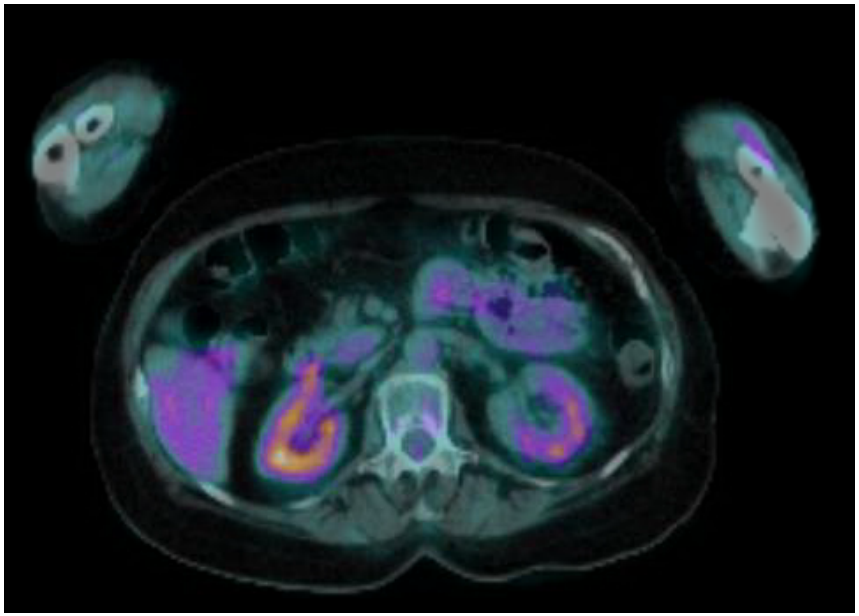
- Grade 3 colitis and grade 2 pneumonitis
  - Initiate steroid at 2 mg/kg of methylprednisone or equivalent
  - Recommend IV steroid initially with colitis symptoms due to gut absorption issues
  - Taper slowly (1 month)
  - Consider antibiotic prophylaxis during high-dose steroid
  - Discontinue immunotherapy

irAE = immune-related adverse event.

Case Study (cont.)



Baseline



After Three Doses