Immuno-oncology Toxicity management

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Conflicts of interest

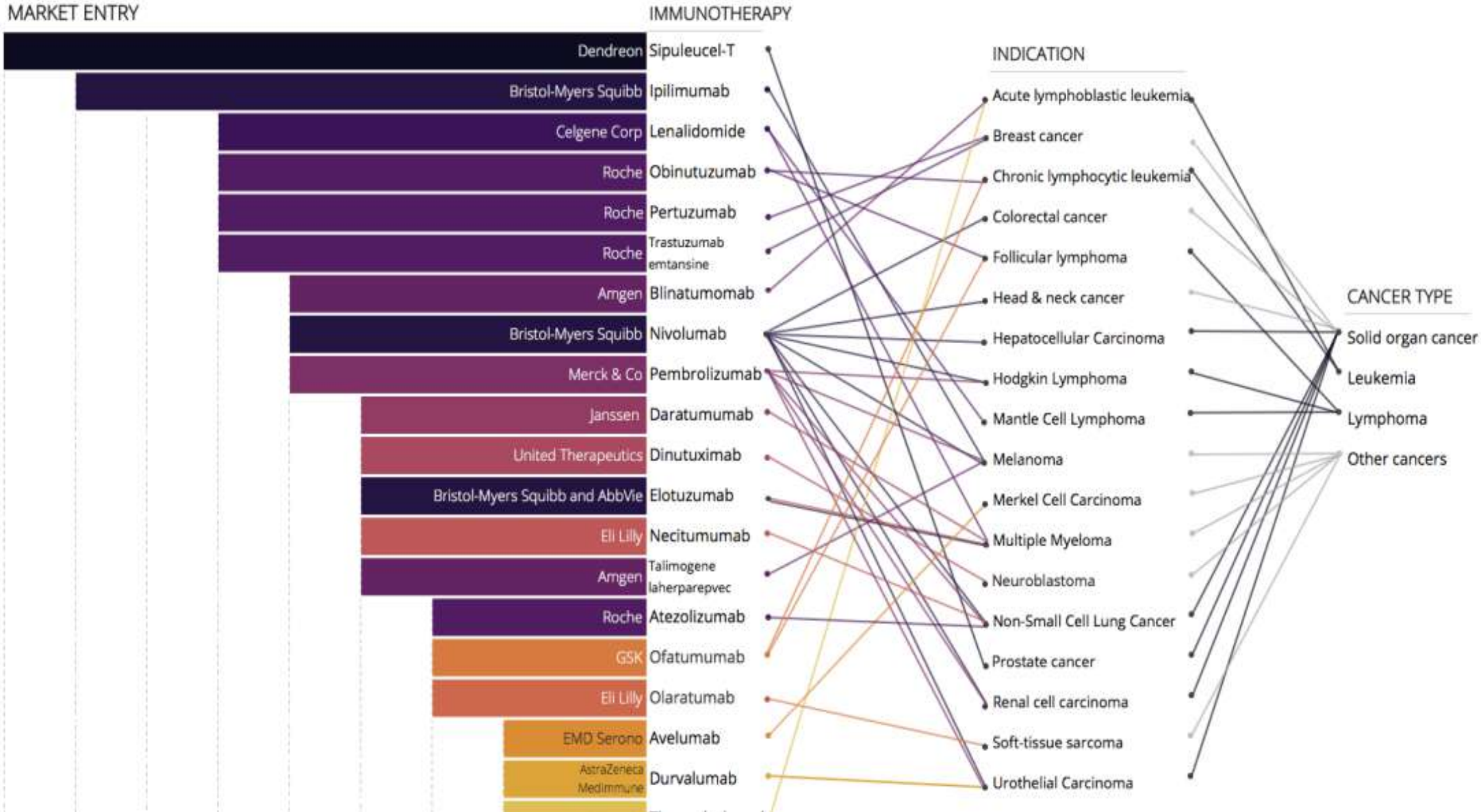
Advisory/Consulting Roles: BMS, Astra-Zeneca, Pfizer, Eli-Lilly, Novartis, Merck

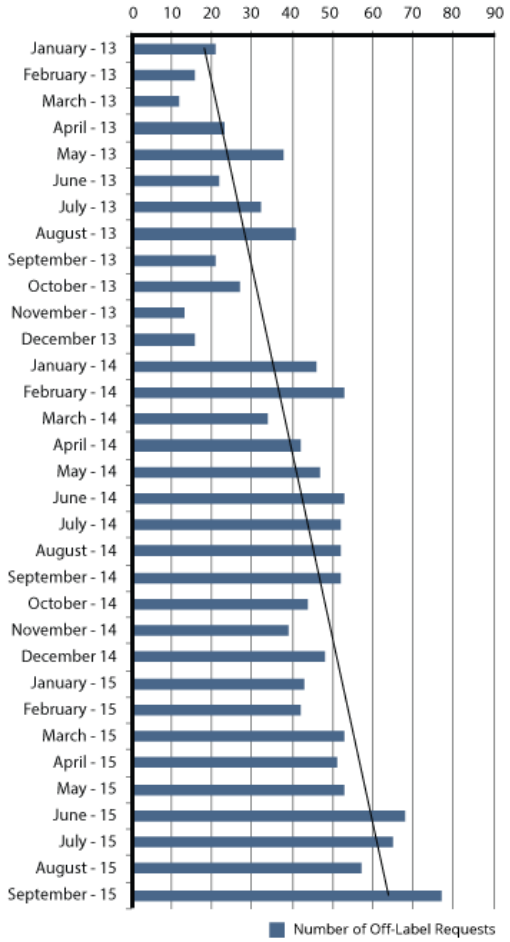
DMC Board Member: BMS

Trial Steering Committees: CCTG HN.9

Learning Objectives

- Discuss the toxicities of I-O treatment
- Discuss the management of I-O toxicities using a case-based approach
- Discuss when treatment must be discontinued and when a dose reduction is appropriate
- Discuss patient selection for I-O drugs


MARKET ENTRY
IMMUNOTHERAPY
INDICATION
CANCER TYPE
Dendreon
Sipuleucel-T
Bristol-Myers Squibb
Ipilimumab
Celgene Corp
Lenalidomide
Roche
Obinutuzumab
Roche
Pertuzumab
Roche
Trastuzumab emtansine
Amgen
Blinatumomab
Bristol-Myers Squibb
Nivolumab
Merck & Co
Pembrolizumab
Janssen
Daratumumab
United Therapeutics
Dinutuximab
Bristol-Myers Squibb and AbbVie
Elotuzumab
Eli Lilly
Necitumumab
Amgen
Talimogene laherparepvec
Roche
Atezolizumab
GSK
Ofatumumab
Eli Lilly
Olaratumab
EMD Serono
Avelumab
AstraZeneca Medimmune
Durvalumab
Acute lymphoblastic leukemia
Breast cancer
Chronic lymphocytic leukemia
Colorectal cancer
Follicular lymphoma
Head & neck cancer
Hepatocellular Carcinoma
Hodgkin Lymphoma
Mantle Cell Lymphoma
Melanoma
Merkel Cell Carcinoma
Multiple Myeloma
Neuroblastoma
Non-Small Cell Lung Cancer
Prostate cancer
Renal cell carcinoma
Soft-tissue sarcoma
Urothelial Carcinoma
Solid organ cancer
Leukemia
Lymphoma
Other cancers



Off-label I/O requests at the James Cancer Centre, OSU 2013-2015

I/O therapy is becoming more complex with doublet and triplet therapies entering clinical investigation

What does this mean for toxicity?

BIG IDEA

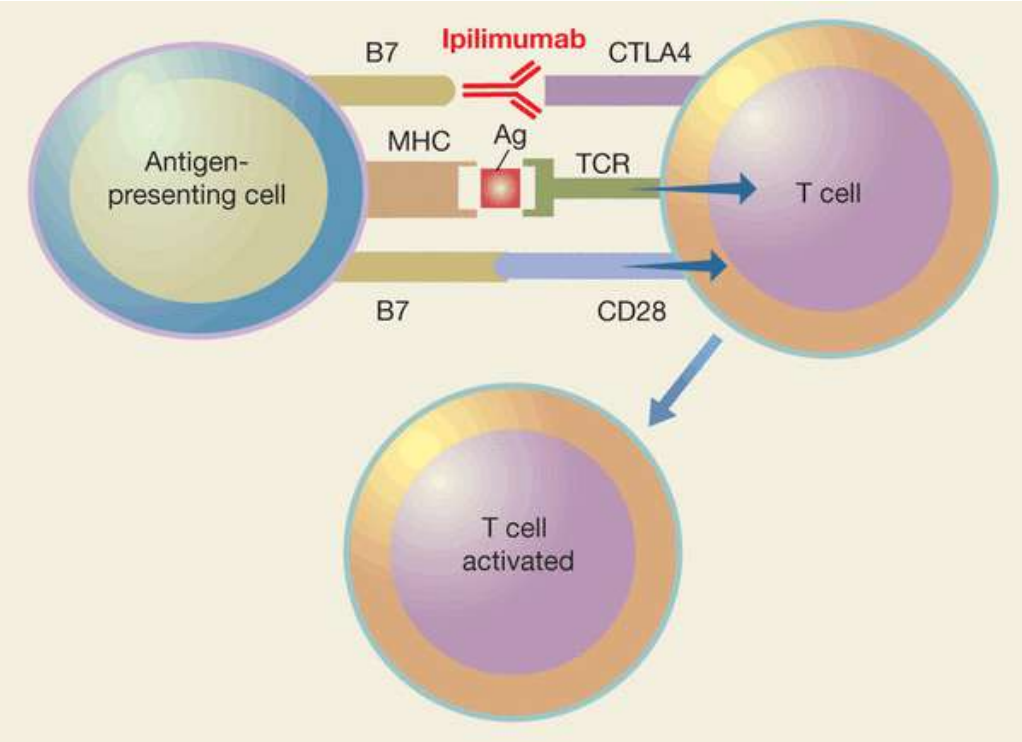
RISK FOR TOXICITY DEPENDS ON THE MECHANISM OF ACTION OF THE COMBINATION

Mechanism #1

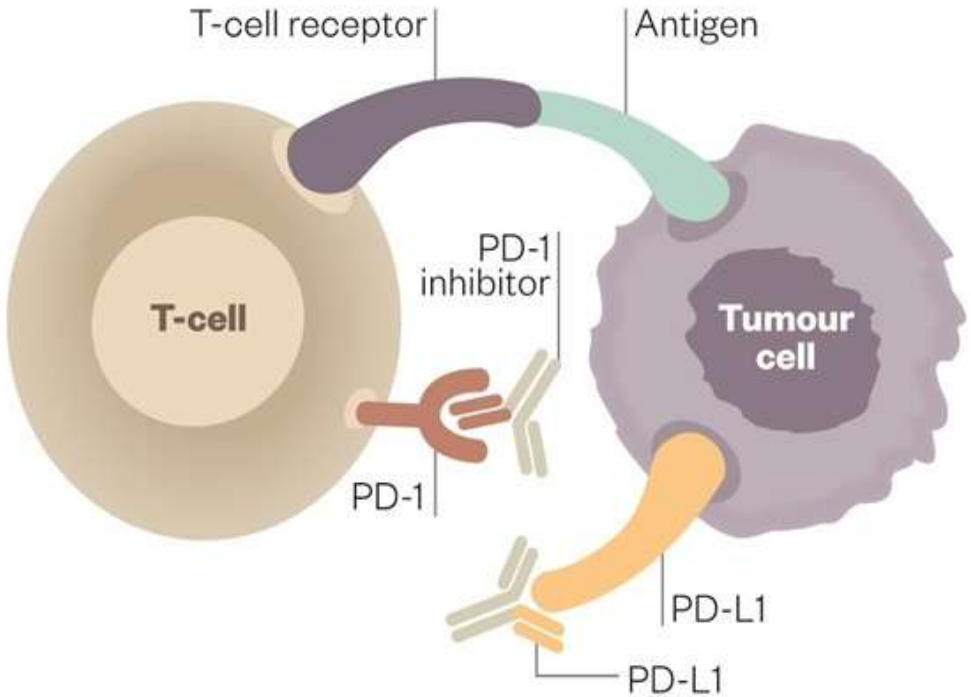
Each I/O agent in a combination activates an “independent” pro-inflammatory pathway

i.e.: ipilimumab/nivolumab, tremelimumab/durvalumab

CTLA4 Mechanism of Action



PD1/PDL1 Mechanism of Action



Each pathway has an “independent” way of causing toxicity
Rates of toxicity tend to be higher in these situations

CHECKMATE-067 Study

Ipilimumab/nivolumab vs. nivolumab vs. ipilimumab

Much higher toxicity rates for combination therapy over single agent therapy

59% vs. 21% vs. 28% grade 3 or high toxicity respectively

Table 2. Treatment-Related Adverse Events.*

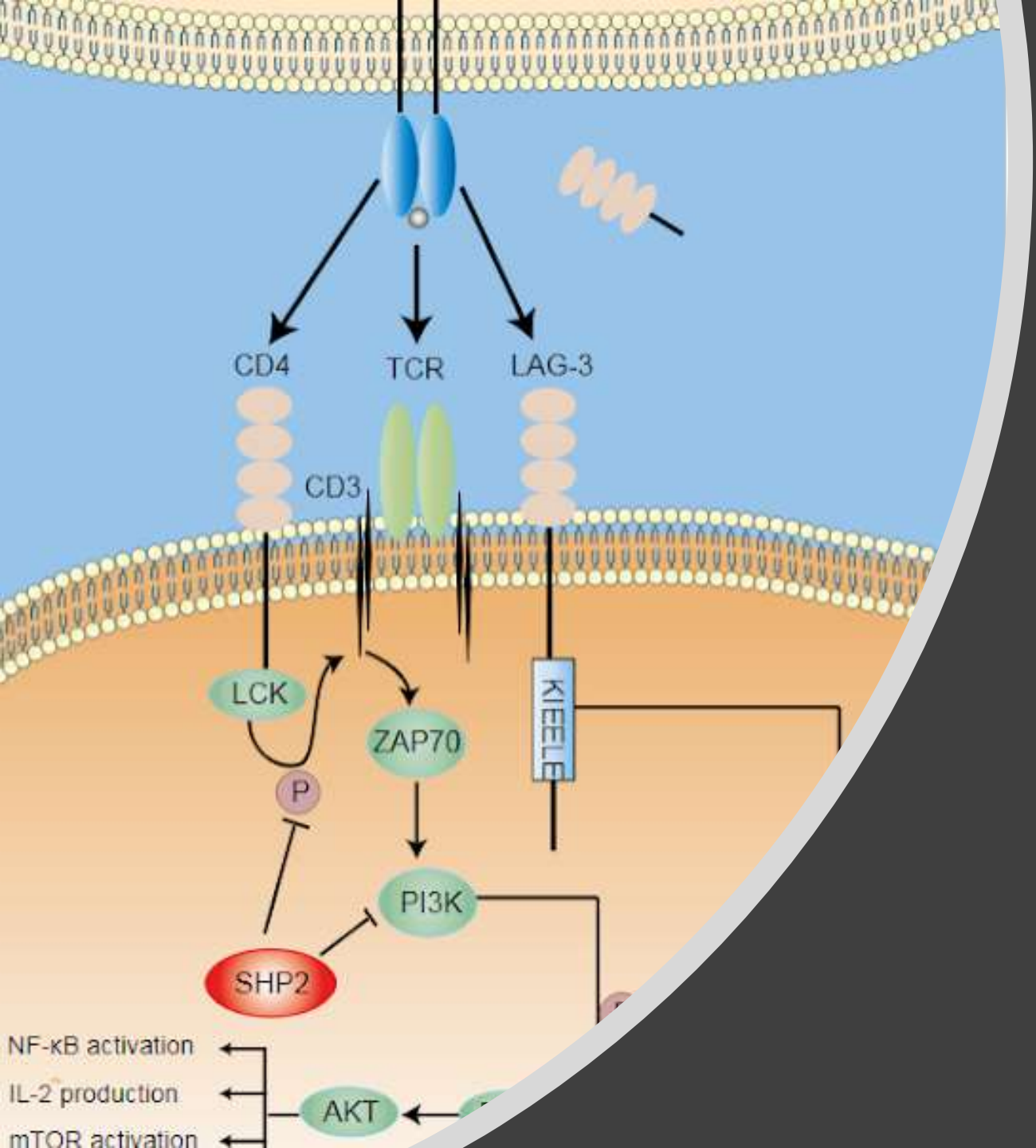
Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	25 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

* Shown are treatment-related adverse events of any grade that occurred in more than 5% of the patients in any treatment group who had one or more treatment-related adverse events of grade 3 or 4. The relatedness of the adverse event to treatment was determined by the investigators. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Two deaths that were considered by the investigators to be related to a study drug occurred in the nivolumab group (neutropenia) and in the ipilimumab group (colonic perforation) within 100 days after the last dose of study drug; two additional deaths in the nivolumab plus ipilimumab group (one due to cardiac insufficiency and autoimmune myocarditis, and one due to liver necrosis) that

Mechanism #2

Each I/O agent in a combination “synergistically” works in the same pathway

i.e.: nivolumab/relatlimab (anti-lag3), nivolumab/BMS-986179 (CD-73)



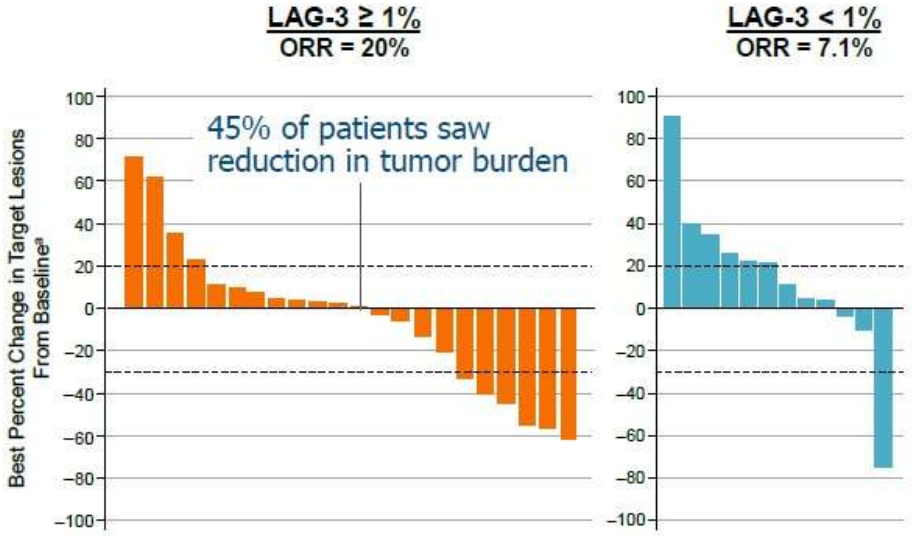
LAG3 is anti-inflammatory which can become hyperactivated when PD1/PDL1 inhibitors are used

Possible mechanism of resistance to PD1/PDL1 inhibitors

Ascierto et al., ESMO, 2017

Block Tumor Inhibition/Checkpoints: Anti-LAG3 May Overcome Anti-PD1 Resistance

Best Change From Baseline in Target Lesion Tumor Burden



- 8/48 patients analyzed had unknown LAG-3 status – data not shown

- Efficacy of anti-LAG3+Opdivo in heavily pretreated Melanoma patients who failed prior anti-PD1 therapy
- 76% of patients had 2 more prior systemic therapies including PD1+/-CTLA4
- LAG3+ appears to be a useful biomarker to enrich for potential benefit
- Safety profile similar to Opdivo monotherapy: 45% of patients experienced AEs (9% Gr3/4)

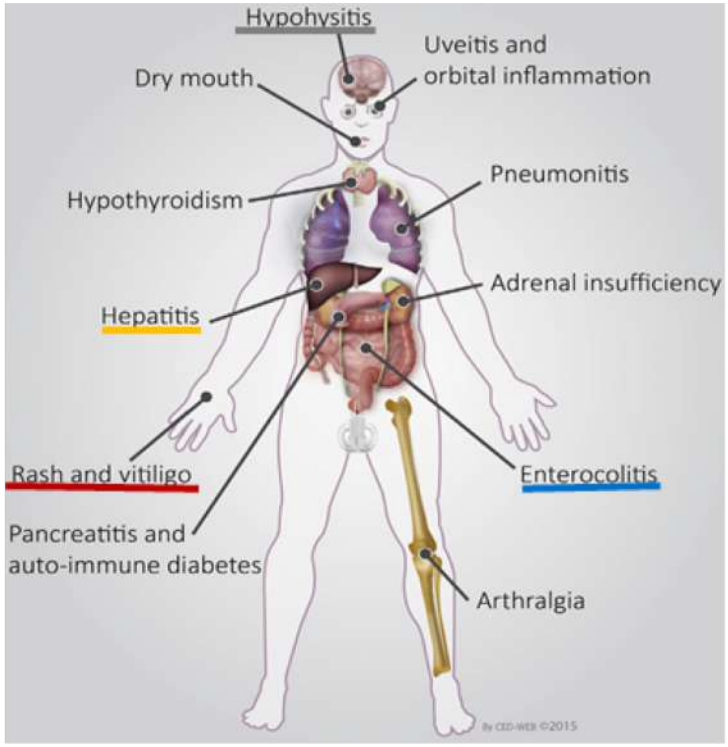
Ascierto et al., ESMO, 2017

No real significant change in toxicity for the combination vs. single agent nivolumab

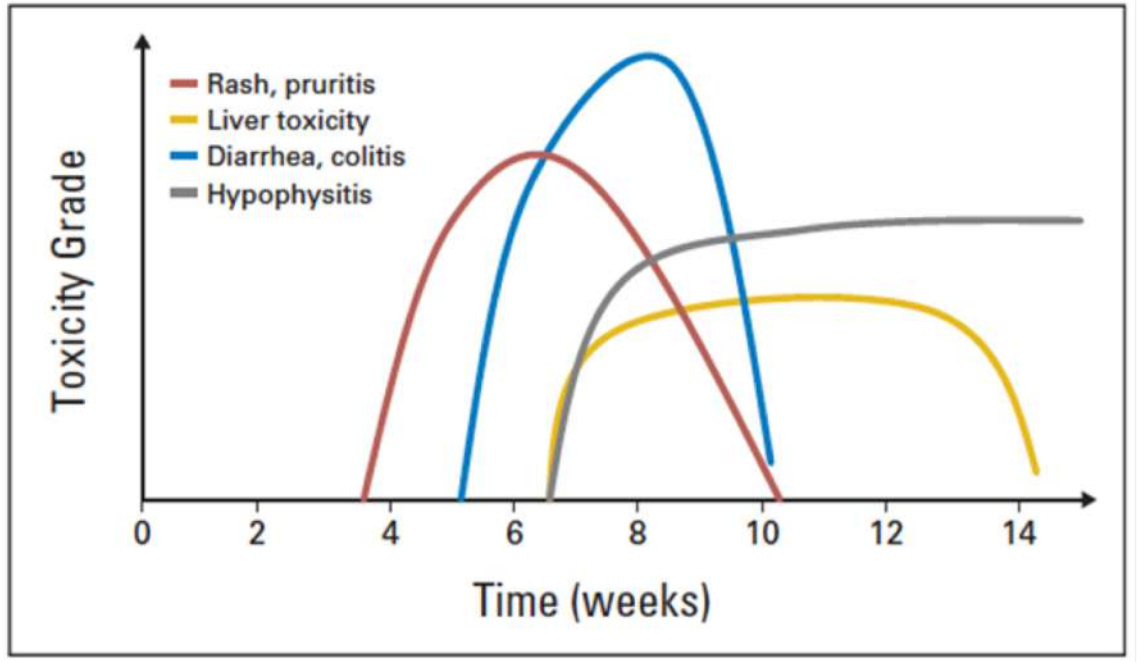
	All Patients[a] N = 270	
	Any Grade n (%)	Grade 3–4 n (%)
Any TRAE[b]	137 (51)	27 (10)
TRAEs in ≥ 5% of patients		
Fatigue	30 (11)	0
Pruritus	19 (7.0)	0
Diarrhea	18 (6.7)	3 (1.1)
Arthralgia	17 (6.3)	0
Infusion-related reaction	15 (5.6)	0
Any serious TRAE[b]	18 (6.7)	12 (4.4)
Serious TRAEs in > 1 patient		
Colitis	4 (1.5)	3 (1.1)
Pneumonitis	2 (0.7)	2 (0.7)
Myocarditis[c]	2 (0.7)	0
Pyrexia	2 (0.7)	0
Any TRAE leading to discontinuation[b]	11 (4.1)	8 (3.0)

Basic Principles of I/O Toxicity Management

Immune checkpoint inhibitors have unique side effect profiles

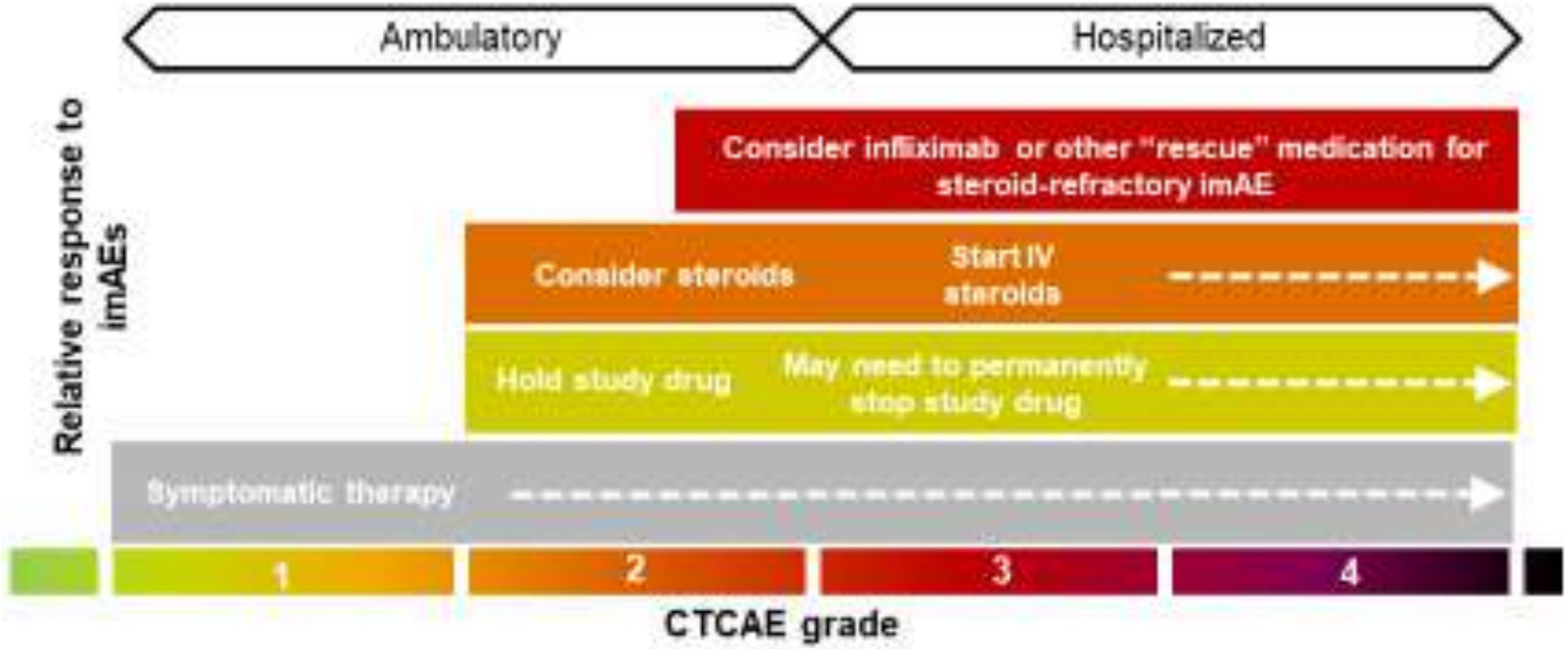


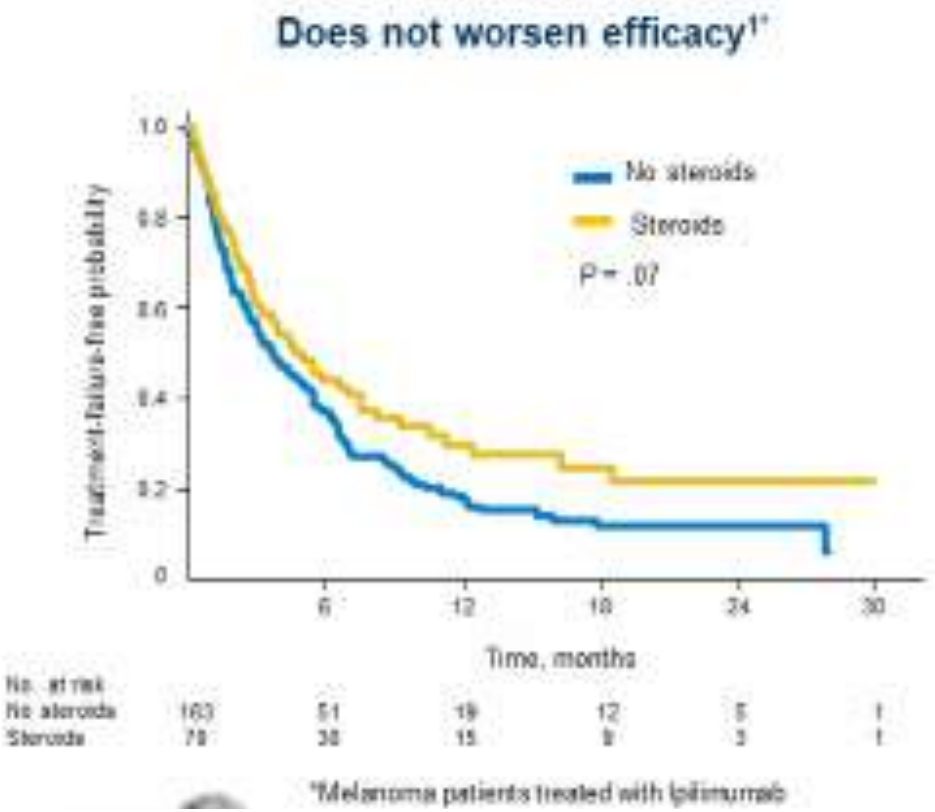
Michot et al, Eur J of Cancer (2016)

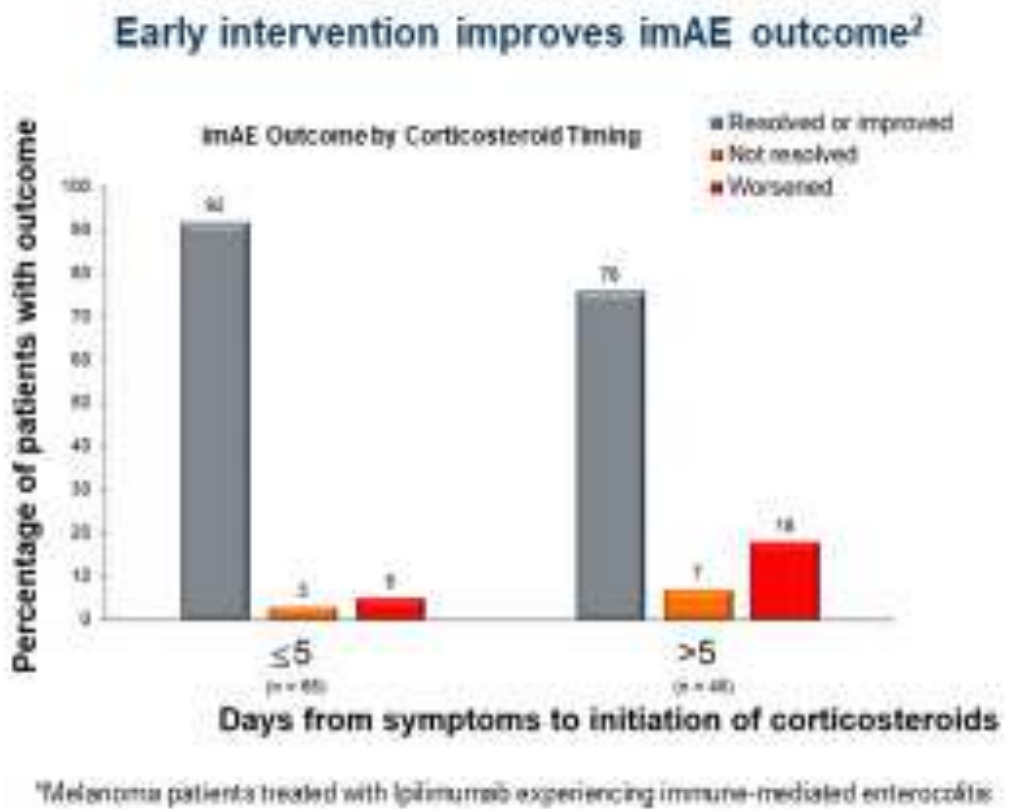


Weber et al, *JCO (2012)*

General Management Strategies For Immunotherapy Toxicity







Early Toxicity Intervention Improves Patient Outcome

Rescue Medication
Use of Drugs for Corticosteroid-Refractory imAEs

	Mycophenolate Mofetil (Cellcept ®)	Infliximab
Drug Information	• IMPDH inhibitor • Approved in combination with ciclosporin (cyclosporine) and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants	• Anti-TNFα chimeric human-murine mAb • Approved for patients with autoimmune disease (e.g. RA, Crohn's disease, psoriatic arthritis, etc.) and ulcerative colitis • **Should NOT be used for management of immune-related hepatitis**
Dosage form	• Available as 250 mg capsules, 500 mg film-coated tablets, powder for oral suspension, solution for infusion	• Available as 100 mg powder for concentrate for solution for infusion

Use of rescue medication depends on extent of toxicity – please always refer to Dosing Modification and Toxicity Management Guidelines November 1, 2017 Version before use

Labeling Information	• Dosing and administration of mycophenolate should always follow the recommended product label. CellCept Product Monograph	• Dosage and administration of infliximab should always follow the recommended product label : Remicade Product Monograph

Refer to the Product Monograph for complete information on drug administration, warnings and precautions for use

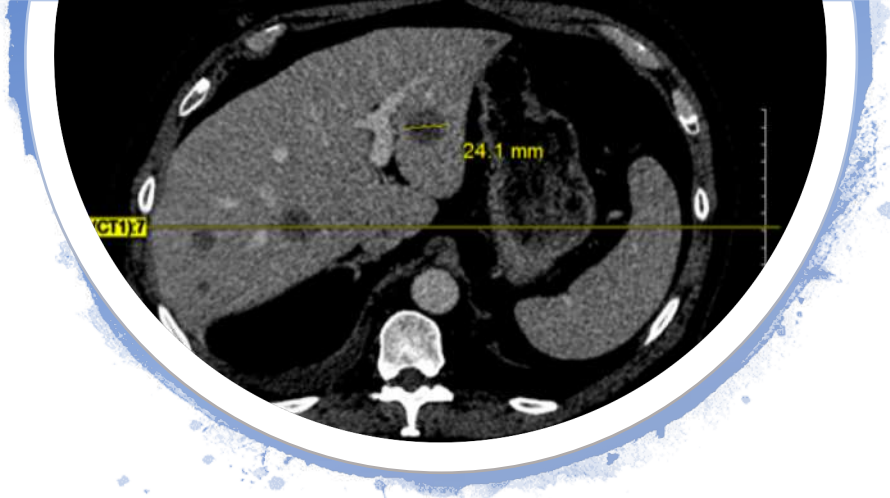
imAE = immune-mediated adverse event; IMPDH = inosine monophosphate dehydrogenase; mAb = monoclonal antibody; RA = rheumatoid arthritis; TNFα = tumour necrosis factor-α

The relevant CSP should always be consulted for specific study-related information

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.
2. European Medicines Compendium Summaries of Product Characteristics. https://www.medicines.org.uk/emc/. Accessed December 1, 2016.

Toxicity Case #1

Our 1st Case

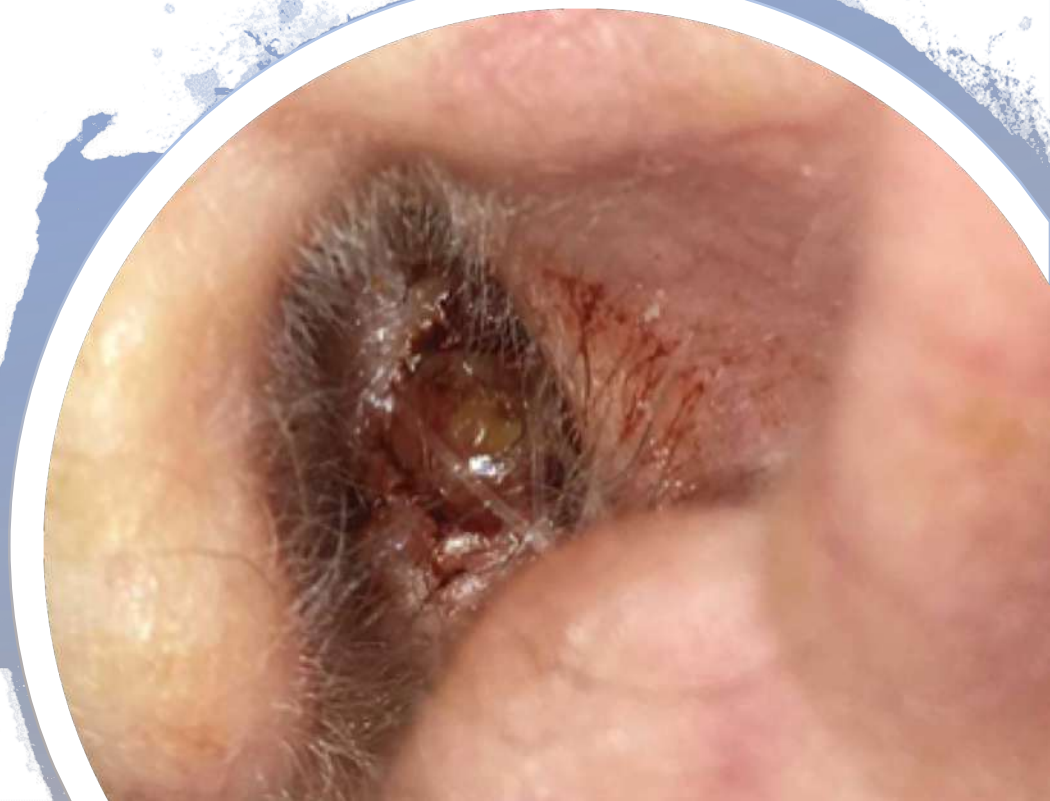


Stage IV melanoma, wedge resection of solitary lung metastasis Feb 2018

Calls with sudden appearance of

- multiple scalp metastases
- external auditory canal metastasis

Restaging scans reveal new multiple liver metastases and brain metastasis (asymptomatic)



Treatment Course

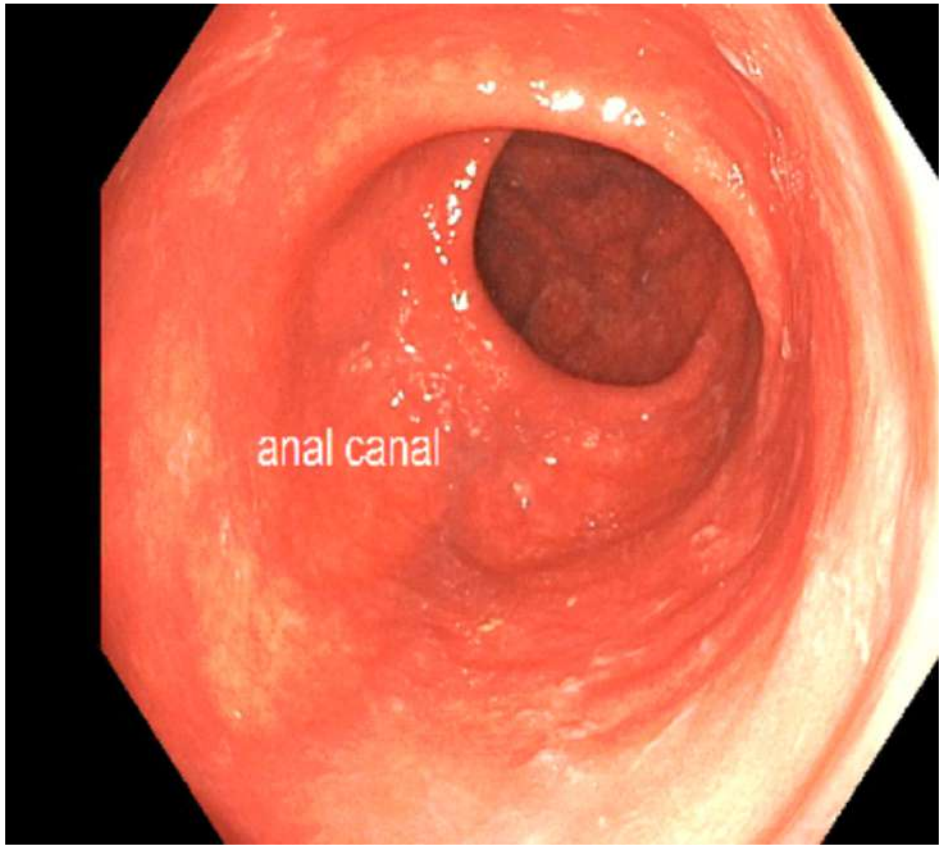
- Treated with anti-PD1 and anti-CTLA4 combo; March 2018.
- Cycle 1: grade 1 dry cough, SOB, diarrhea, headache, fever, rash; TSH low, fT4 high, started on beta blocker
- Cycle 2 at end of cycle, fever 39 deg, very loose stool, 8X per day, non-bloody, no melena, dehydrated on exam
- Response is observed on examination and imaging
- Grade 3 diarrhea
- Admitted to hospital (SAE)
  - C. difficile + cultures sent (neg)
  - Vancomycin + Ceftriaxone and Flagyl also started, suspected diverticulitis
  - Steroids IV given solumedrol 1 mg per kg; immodium tid.
  - Improvement in hospital (4-days) then discharged on oral steroids taper

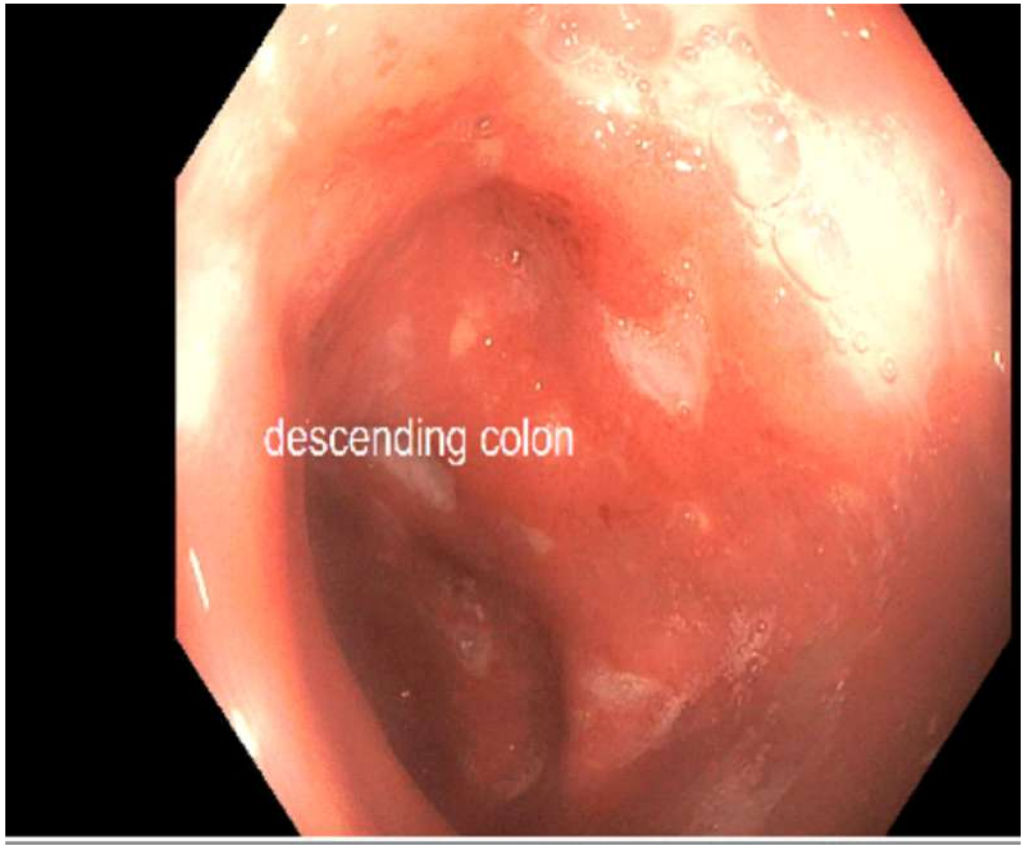
Mr. Case 1

- 11 days later, back in ER
- Prednisone (on taper) down to 45mg PO od
- 3 day history of nausea, vomiting, diarrhea
- Tender abdomen, temp 39.3
- CT abdomen: diffuse colonic mucosal hyperemia and mild adjacent colonic fatty stranding

Colonoscopy to terminal ileum revealing:

- 1. Erythema from anal verge through to cecum. Inflammation was predominant from the sigmoid colon through to the distal descending colon. There was significant superficial ulceration and friability. Multiple biopsies were taken.

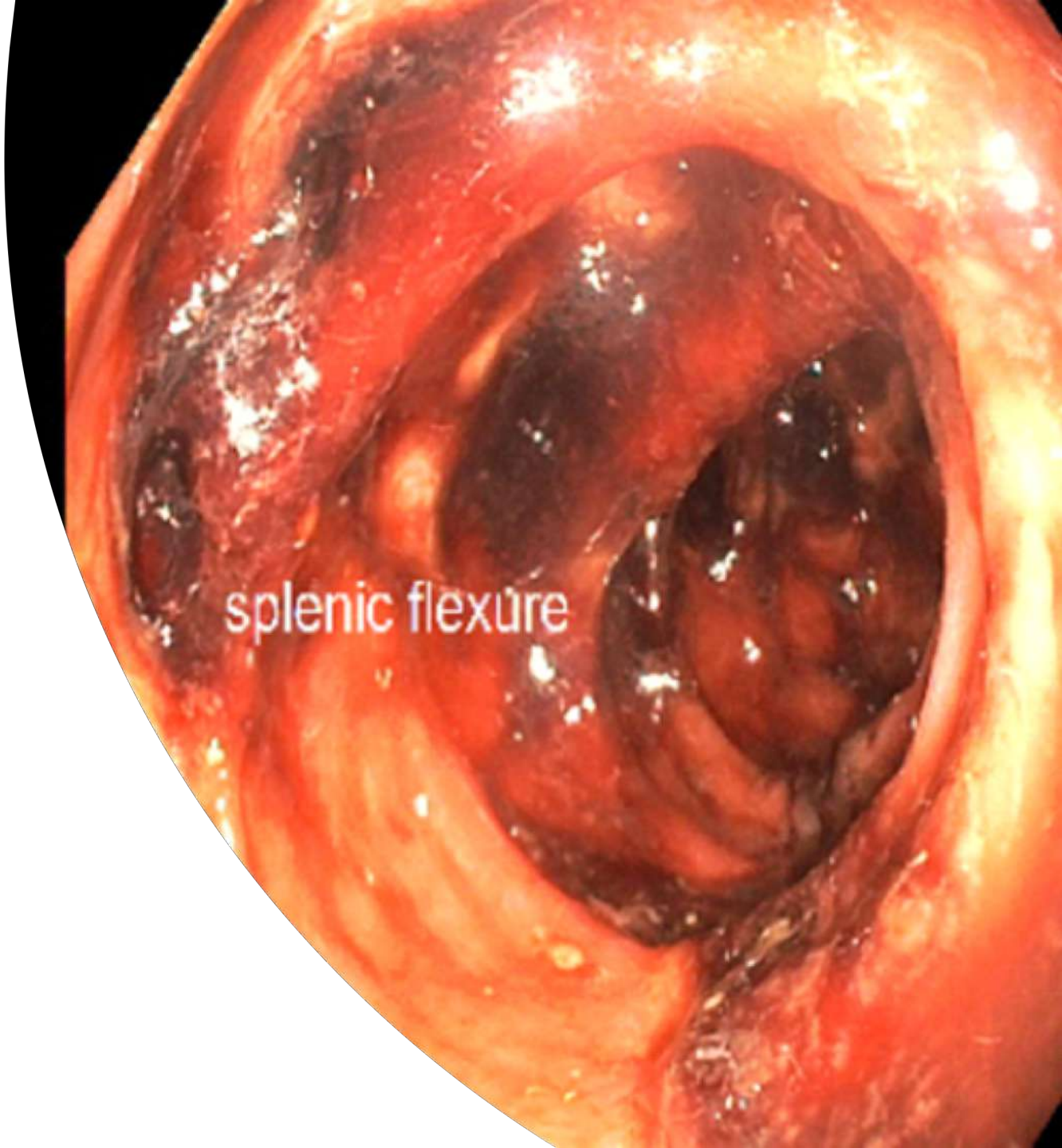




Colonoscopy Results

Things Start To Go Sour…

- IV Solumedrol 100mg bid
- Clinically stable, but in-hospital sudden onset of bright-red blood per rectum, clots
- Hemoglobin 114 --> 99
- Urgent Flexible Sigmoidoscopy: Ischemic colitis were identified near the splenic flexure. The colonic mucosa otherwise had mild inflammation.
- Urgent OR is required to address critical problem



Key Tests to Confirm the Diagnosis
Gastrointestinal Disorders

CT scan[1,2]	▪ Diffuse colitis ▪ Segmental colitis associated with diverticulosis
Histology[3-6]	▪ Inflammatory infiltrates ▪ Crypt microabscesses ▪ Architectural distortion ▪ May include evidence of CMV reactivation
Recto-Sigmoidoscopy or Colonoscopy[7,8] *As indicated*	▪ Ulceration ▪ Mucosal erythema ▪ Abnormal vascular patterns ▪ Friable mucosa ▪ Erosions ▪ Skip lesions and spontaneous bleeding (rare)

CMV = cytomegalovirus; CT = computed tomography; IHC = immunohistochemistry.

- **The relevant clinical study protocol should always be consulted for specific study-related information.**

Abdel-Rahman O, et al. *Immunotherapy* 2015;7(11):1213-1227; Kim KW, et al. *AJR Am J Roentgenol.* 2013;200(5):W468-W474; Verschuren EC, et al. *Clin Gastroenterol Hepatol.* 2016;14(6):836-842; Lord JD, et al. *Dig Dis Sci.* 2010;55(5):1396-1405; Coburn LA, et al. *PLoS One.* 2013;8(12):e82300; Ranjan P, et al. *J Dig Endosc.* 2015;6:133-138; Michot JM, et al. *Eur J Cancer.* 2016;54:139-148; Verschuren EC, et al. *Clin Gastroenterol Hepatol.* 2016;14(6):836-842.

CTCAE v4.03 Overview
Gastrointestinal Disorders

- Grade refers to the severity of the AE
- The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
• Mild **or** • Asymptomatic or mild symptoms **or** • Clinical or diagnostic observations only **or** • Intervention not indicated	• Moderate **or** • Minimal, local or non-invasive intervention indicated **or** • Limiting age-appropriate instrumental ADL[a]	• Severe or medically significant but not immediately life-threatening **or** • Hospitalization or prolongation of hospitalization indicated **or** • Disabling **or** • Limiting self care ADL[b]	• Life-threatening consequences **or** • Urgent intervention indicated	• Death related to AE

[a]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.; [b]Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events version 4.03.

1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

Toxicity Management
Gastrointestinal Disorders

Any Grade

- Monitor for symptoms that may be related to:
  - Diarrhea/enterocolitis, such as abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool
  - Bowel perforation, such as sepsis, peritoneal signs, and ileus
- Patients should be thoroughly evaluated to rule out any alternative etiology.
  - Disease progression, other medications, or infections (including clostridium difficile toxin)
- Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event.
- Use analgesics carefully since they can mask symptoms of perforation and peritonitis.

- **The relevant clinical study protocol should always be consulted for specific study-related information.**
- 1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 .

Toxicity Management
Gastrointestinal Disorders

Grade 1

- Monitor closely for worsening symptoms.
- Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g. American Dietetic Association colitis diet), loperamide, use of probiotics as per treating physician's clinical judgement.

Grade 2

- Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g. American Dietetic Association colitis diet), loperamide and/or budesonide.
- Promptly start prednisone 1–2 mg/kg/day or IV equivalent.
- If event does not respond within 3–5 days or worsens despite prednisone at 1–2 mg/kg/day or IV equivalent, obtain GI consult for consideration of further work-up (e.g. imaging and/or colonoscopy) to confirm colitis and rule out perforation and promptly start treatment with IV methylprednisolone 2–4 mg/kg/day.
- If no improvement within 3–5 days despite 2–4 mg/kg IV methylprednisolone, promptly start immunosuppressive (such as infliximab 5 mg/kg once every 2 weeks).
  Caution: Rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.
- Consult study physician if no resolution to Grade ≤1 in 3–4 days.
- Once improving, gradually taper corticosteroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment.[a]

Grade 3 or 4

- Promptly initiate IV methylprednisolone 2–4 mg/kg/day or equivalent.
- Monitor stool frequency and volume, maintain hydration.
- Urgent GI consult and imaging and/or colonoscopy, as appropriate.
- If no improvement within 3–5 days of IV methylprednisolone 2–4 mg/kg/day or equivalent, promptly start further immunosuppressive (e.g. infliximab 5 mg/kg once every 2 weeks).
- **Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.**
- Once improving, gradually taper corticosteroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment.[a]

[a]Refer to current National Comprehensive Cancer Network guidelines for treatment of cancer-related infections (category 2B recommendation).
IV = intravenous; GI = gastrointestinal; PJP = pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia).

•The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Dose Modifications
Gastrointestinal Disorders

Grade 1	Grade 2	Grade 3	Grade 4

• No dose modification.	• Hold study drug/study regimen dose until resolution to Grade ≤1.
	  • If toxicity worsens, treat as Grade 3 or Grade 4.
	  • If toxicity improves to Grade ≤1, then study drug/regimen can be resumed after completion of steroid taper (see Toxicity Management).
		• Permanently discontinue study drug/study regimen if toxicity does not improve to Grade ≤1 within 14 days.
		• Study drug/study regimen can be resumed after completion of steroid taper.
			• Permanently discontinue study drug/study regimen

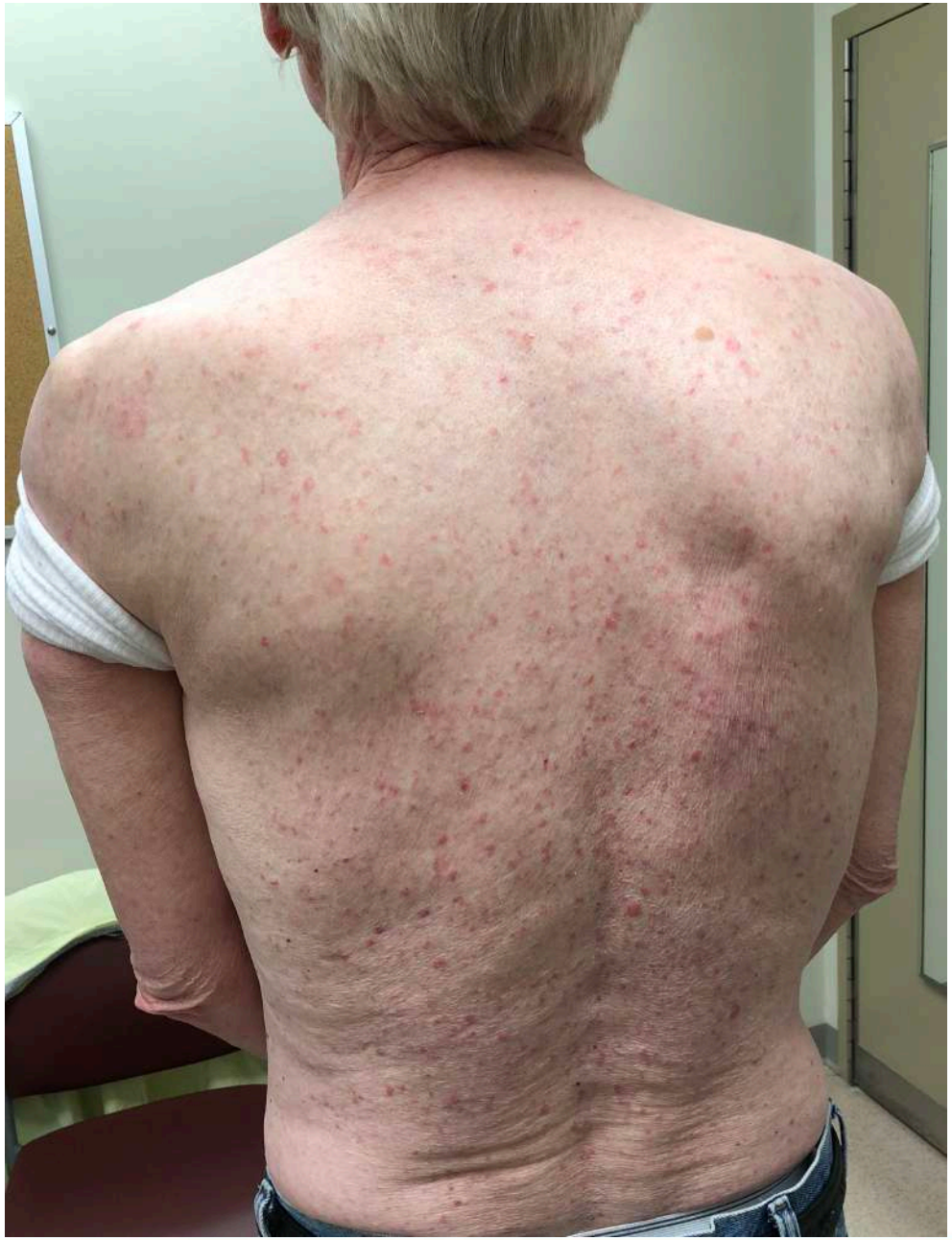
The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Case #2

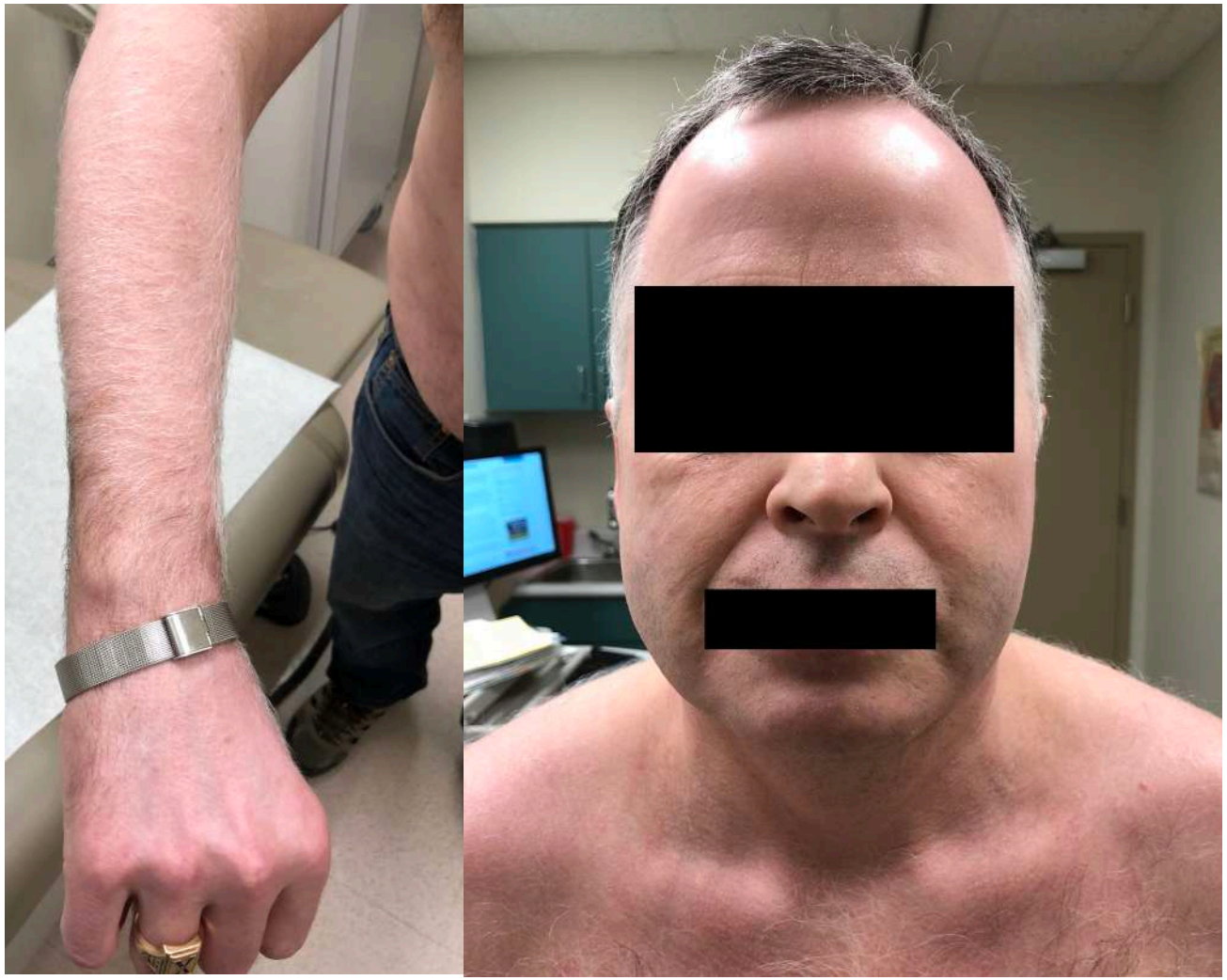
Mr. Brash

- Stage III melanoma
- Receiving anti-PD1 + anti-CTLA4
- After 4 weeks on treatment, develops maculopapular eruption on torso (grade 1-2), no pruritis, along with dry skin (grade 1)
- Rx betaderm 0.05% bid



Mr. White

- Stage III melanoma
- Asymptomatically detected on restaging scans to have brain metastases + pelvic nodal metastases
- Treated by anti-PD1 and anti-CTLA4 treatment
- Pneumonitis, fever, dehydration
- Treated by steroids --> taper off
- Complete response of melanoma



Development of Vitiligo, Poliosis

Signs and Symptoms
Skin Disorders

Signs and Symptoms[1-4]

- Asymptomatic rash
- Rash accompanied by pruritus
- Pruritus
- Erythema
- Vitiligo

Immune-mediated skin reactions[1,2]

- **Typically short onset time** after starting immune checkpoint inhibitors

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Spain L, et al. *Cancer Treat Rev*. 2016;44:51-60.
2. Lacouture ME, et al. *J Am Acad Dermatol*. 2014;71(1):161-169.
3. Naidoo J, et al. *Ann Oncol*. 2015;26(12):2375-2391.
4. Minkis K, et al. *J Am Acad Dermatol*. 2013;69(3):e121-e128.

CTCAE v4.03 Definitions
Skin Disorders (1 of 4)

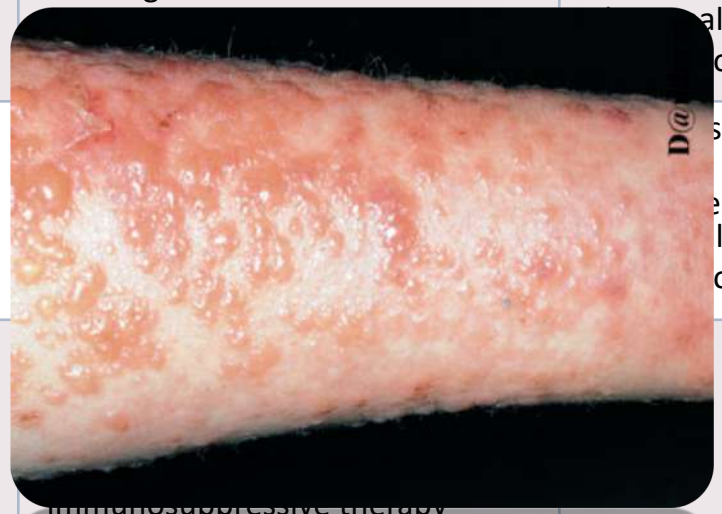
AE[a]	Grade 1	Grade 2	Grade 3	Grade 4
Bullous dermatitis	• Asymptomatic **or** • Blisters covering <10% BSA	• Blisters covering 10–30% BSA **or** • Painful blisters **or** • Limiting instrumental ADL[b]	• Blisters covering >30% BSA **or** • Limiting self care ADL[c]	• Blisters covering >30% BSA **or** • Associated with fluid or electrolyte abnormalities **or** • ICU care or burn unit indicated
Erythema multiforme	• Target lesions covering <10% BSA and not associated with skin tenderness	• Target lesions covering 10–30% BSA and associated with skin tenderness	• Target lesions covering >30% BSA and associated with oral or genital erosions	• Target lesions covering >30% BSA **or** • Associated with fluid or electrolyte abnormalities **or** • ICU care or burn unit indicated
Pruritus	• Mild or localised **or** • Topical intervention indicated	• Intense or widespread **or** • Intermittent **or** • Skin changes from scratching (e.g. edema, papulation, excoriations, lichenification, oozing/crusts) **or** • Oral intervention indicated **or** • Limiting instrumental ADL[b]	• Intense or widespread **or** • Constant **or** • Limiting self care ADL[c] or sleep **or** • Oral corticosteroid or immunosuppressive therapy indicated	• N/A

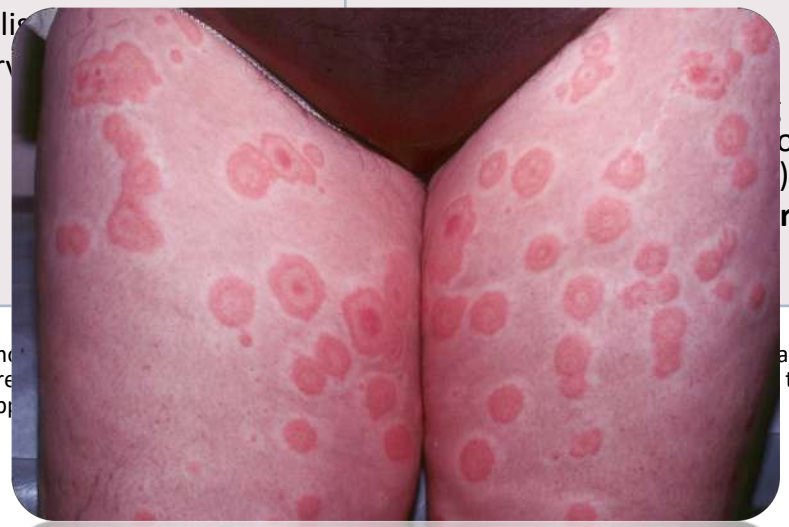
[a]AEs have been selected based on those most commonly observed with durvalumab and tremelimumab monotherapy and combination regimens; [b]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.; [c]Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
*Grade 5 definition: death. Grade 5 not applicable for pruritus.

1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

CTCAE v4.03 Definitions
Skin Disorders (1 of 4)

AE[a]	Grade 1	Grade 2	Grade 3	Grade 4
Bullous dermatitis	• Asymptomatic **or** • Blisters covering <10% BSA	• Blisters covering 10–30% BSA **or** • Painful blisters **or** • Limiting instrumental ADL[b]	• Blisters covering >30% BSA **or** • Limiting self care ADL[c]	• Blisters covering >30% BSA **or** • Associated with fluid or electrolyte alities **or** or burn unit indicated
Erythema multiforme	• Target lesions covering <10% BSA and not associated with skin tenderness	• Target lesions covering 10–30% BSA and associated with skin tenderness		sions covering >30% BSA ed with fluid or electrolyte lities **or** or burn unit indicated
Pruritus	• Mild or locali • Topical inter	(e.g. ons,) **or** r	indicated	





[a]AEs have been selected based on those m and combination regimens; [b]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.; [c]Self care taking medications and not bedridden.
*Grade 5 definition: death. Grade 5 not ap

1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

CTCAE v4.03 Definitions
Skin Disorders (2 of 4)

AE[a]	Grade 1	Grade 2	Grade 3	Grade 4
Purpura	• Combined area of lesions covering <10% BSA	• Combined area of lesions covering 10–30% BSA **or** • Bleeding with trauma	• Combined area of lesions covering >30% BSA **or** • Spontaneous bleeding	• N/A
Rash acneiform	• Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	• Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness **or** • Associated with psychosocial impact **or** • Limiting instrumental ADL[b]	• Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness **or** • Limiting self care ADL[c] **or** • Associated with local superinfection with oral antibiotics indicated	• Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated **or** • Life-threatening consequences
Rash maculo-papular	• Macules/papules covering <10% BSA with or without symptoms (e.g. pruritus, burning, tightness)	• Macules/papules covering 10–30% BSA with or without symptoms (e.g. pruritus, burning, tightness) **or** • Limiting instrumental ADL[b]	• Macules/papules covering >30% BSA with or without associated symptoms **or** • Limiting self care ADL[c]	• N/A

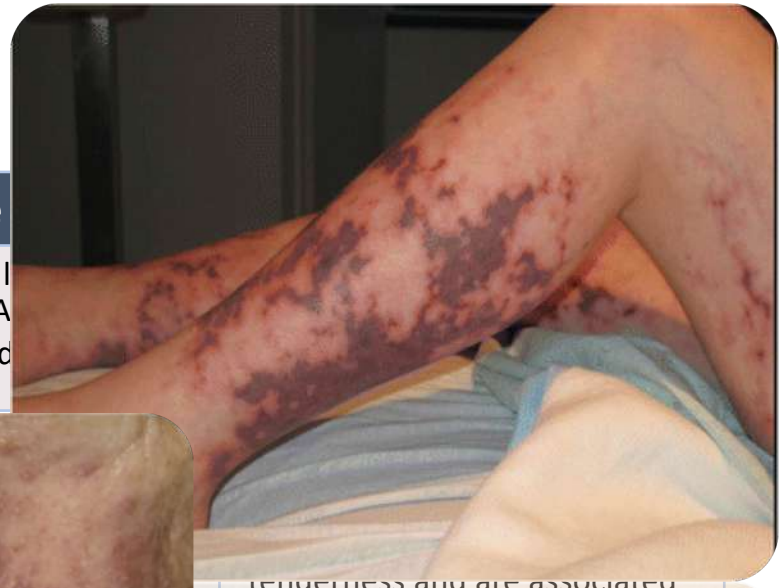
[a]AEs have been selected based on those most commonly observed with durvalumab and tremelimumab monotherapy and combination regimens; [b]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.; [c]Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
*Grade 5 definition: death. Grade 5 not applicable for purpura and rash maculopapular.

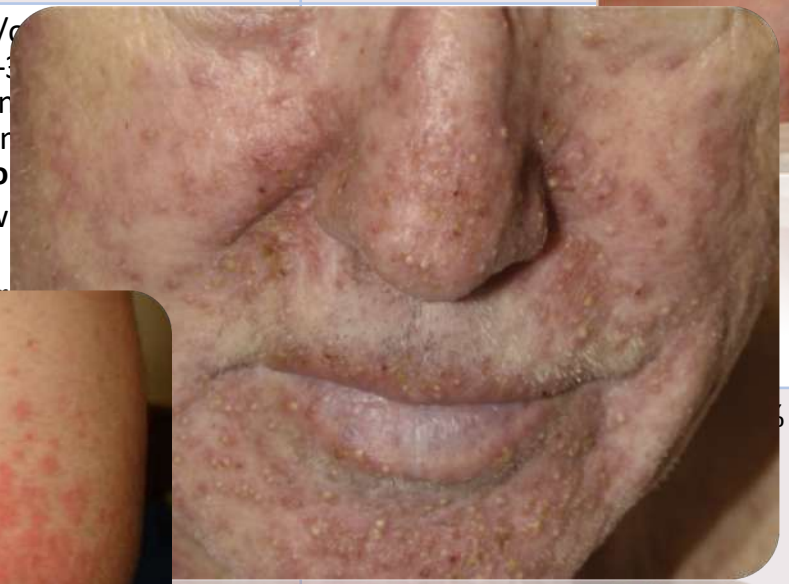
ADL = activities of daily living; AE = adverse event; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events version 4.03; IV = intravenous; N/A = not applicable.

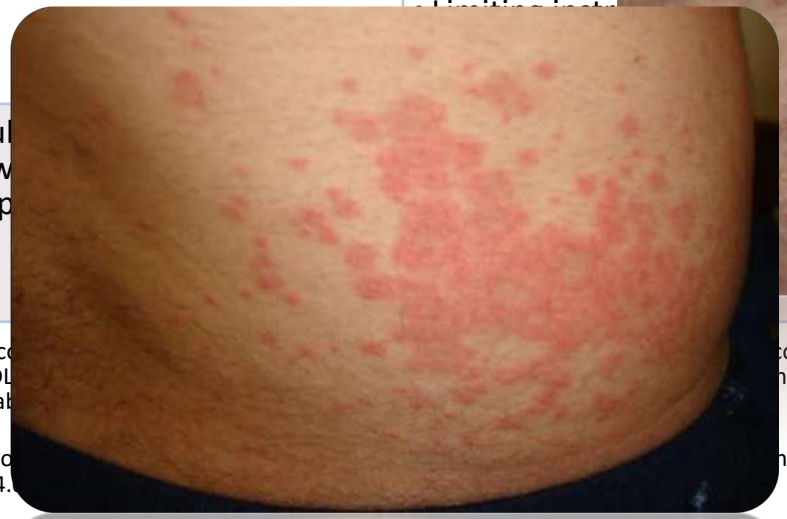
1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

CTCAE v4.03 Definitions
Skin Disorders (2 of 4)

AE[a]	Grade 1	Grade 2	Grade
Purpura	• Combined area of lesions covering <10% BSA	• Combined area of lesions covering 10–30% BSA **or** • Bleeding with trauma	• Combined area of l covering >30% BSA • Spontaneous bleed
Rash acneiform	• Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	• Papules and/c covering 10–3 may or may n with symptor tenderness **o** • Associated w impact **or**	with extensive superinfection with IV antibiotics indicated **or** • Life-threatening consequences
Rash maculo-papular	• Macul BSA w (e.g. p		• N/A







[a]AEs have been selected based on those most c combination regimens; [b]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.; [c]Self care ADL g medications and not bedridden.
*Grade 5 definition: death. Grade 5 not applicab

ADL = activities o n Terminology Criteria for Adverse Events version 4.

1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

CTCAE v4.03 Definitions
Skin Disorders (3 of 4)

AE[a]	Grade 1	Grade 2	Grade 3	Grade 4
Skin hypopigmentation	• Hypopigmentation or depigmentation covering <10% BSA **or** • No psychosocial impact	• Hypopigmentation or depigmentation covering >10% BSA **or** • Associated psychosocial impact	• N/A	• N/A
Skin ulceration	• Combined area of ulcers <1 cm **or** • Non-blanchable erythema of intact skin with associated warmth or edema	• Combined area of ulcers 1–2 cm **or** • Partial thickness skin loss involving skin or subcutaneous fat	• Combined area of ulcers >2 cm **or** • Full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	• Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss
Stevens-Johnson syndrome	• N/A	• N/A	• Skin sloughing covering <10% BSA with associated signs (e.g. erythema, purpura, epidermal detachment and mucous membrane detachment)	• Skin sloughing covering 10–30% BSA with associated signs (e.g. erythema, purpura, epidermal detachment and mucous membrane detachment)

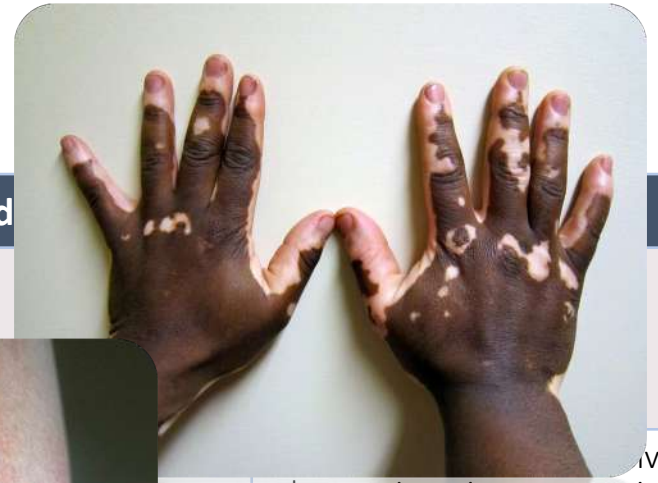
[a]AEs have been selected based on those most commonly observed with durvalumab and tremelimumab monotherapy and combination regimens.
*Grade 5 definition: death. Grade 5 not applicable for skin hypopigmentation.

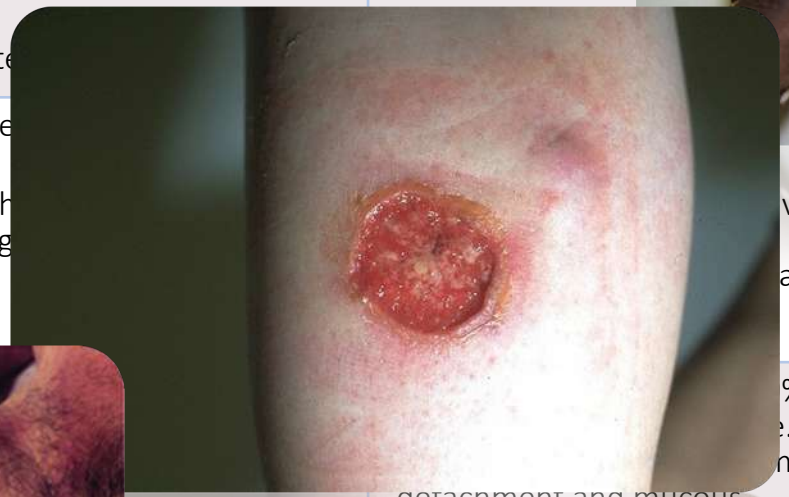
AE = adverse event; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events version 4.03; N/A = not applicable.

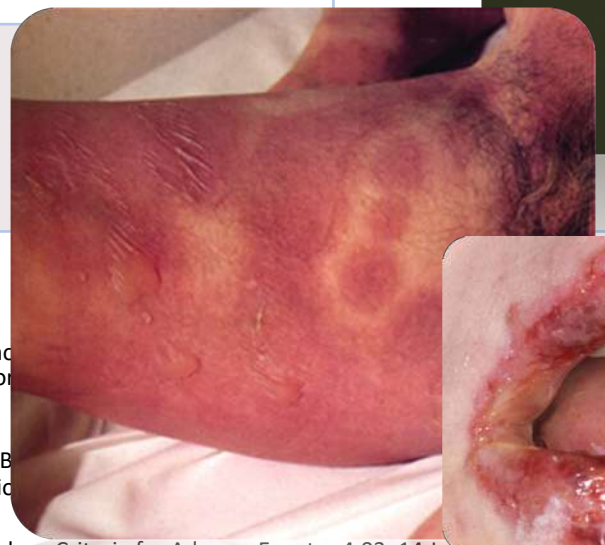
1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

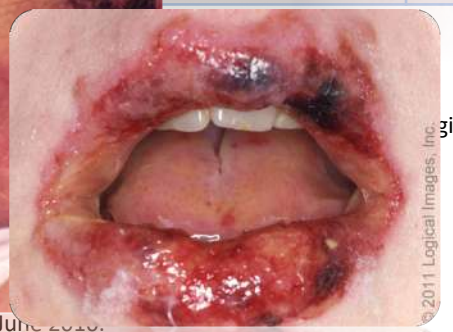
CTCAE v4.03 Definitions
Skin Disorders (3 of 4)

AE[a]	Grade 1	Grade 2	Grad	
Skin hypopigmentation	• Hypopigmentation or depigmentation covering <10% BSA **or** • No psychosocial impact	• Hypopigmentation or depigmentation covering >10% BSA **or** • Associate	• N/A	
Skin ulceration	• Combined area of ulcers <1 cm **or** • Non-blanchable erythema of intact skin with associated warmth or edema	• Combine **or** • Partial th involving fat	ving ay	ve destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss
Stevens-Johnson syndrome	• N/A		% .g. nal detachment and mucous membrane detachment)	• Skin sloughing covering 10–30% BSA with associated signs (e.g. erythema, purpura, epidermal detachment and mucous membrane detachment)









[a]AEs have been selected based on those most commo gimens.
*Grade 5 definition: death. Grade 5 not applicable fo

AE = adverse event; B
Adverse Events versio

1. Common Terminology Criteria for Adverse Events v4.03. 14 Jun

CTCAE v4.03 Definitions
Skin Disorders (4 of 4)

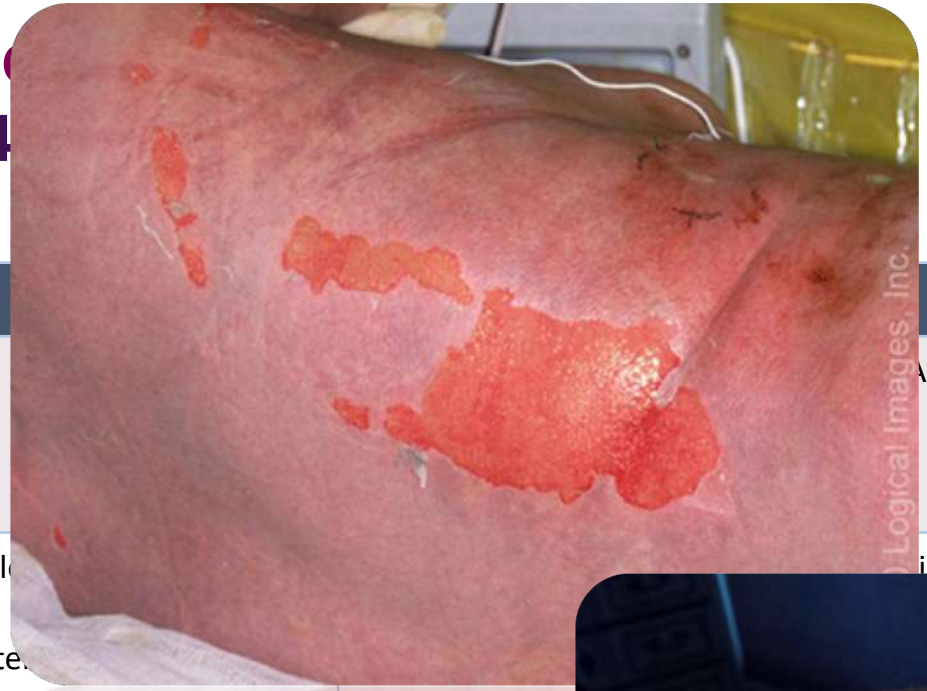
AE[a]	Grade 1	Grade 2	Grade 3	Grade 4
Toxic epidermal necrolysis	• N/A	• N/A	• N/A	• Skin sloughing covering ≥30% BSA with associated symptoms (e.g. erythema, purpura, or epidermal detachment)
Urticaria	• Urticarial lesions covering <10% BSA **or** • Topical intervention indicated	• Urticarial lesions covering 10–30% BS **or** • Oral intervention indicated	• Urticarial lesions covering >30% BSA **or** • IV intervention indicated	• N/A

[a]AEs have been selected based on those most commonly observed with durvalumab and tremelimumab monotherapy and combination regimens.
*Grade 5 definition: death. Grade 5 not applicable for urticaria.

AE = adverse event; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events version 4.03; IV = intravenous; N/A = not applicable.

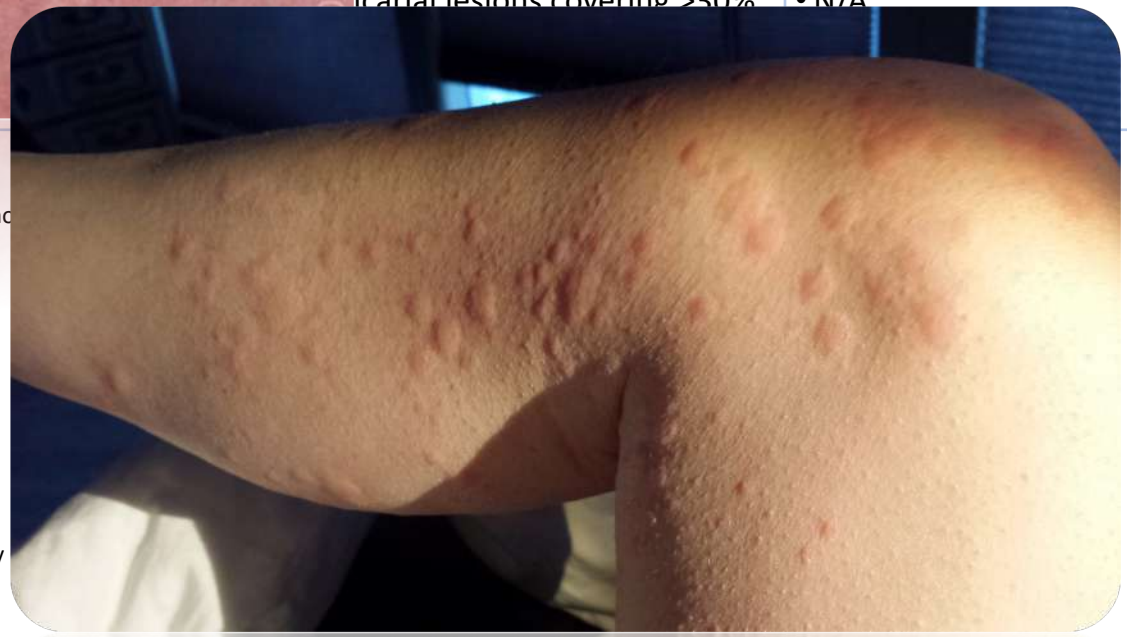
1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

CTCAE v4.03 D
Skin Disorders (4



AE[a]		Grade 3	Grade 4
Toxic epidermal necrolysis	• N/A	A	• Skin sloughing covering ≥30% BSA with associated symptoms (e.g. erythema, purpura, or epidermal detachment)
Urticaria	• Urticarial l BSA **or** • Topical inte	icarial lesions covering ≥30%	• N/A

[a]AEs have been selected based on those most commonly observed with durvalumab and tremelimumab monc
*Grade 5 definition: death. Grade 5 not applicable for urticaria.



AE = adverse event; BSA = body surface area; CTCAE = Common Terminology Adverse Events version 4.03; IV = intravenous; N/A = not applicable.

1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

Toxicity Management
Skin Disorders

- Monitor for signs and symptoms of dermatitis (rash and pruritus)
- If there is any bullous formation, contact study physician and discontinue study drug

Grade 1

- Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).

Grade 2

- Obtain dermatology consult.
- Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
- Consider moderate-strength topical steroid.
- If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
- Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.

Grade 3 or 4

- Consult dermatology.
- Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.
- Consider hospitalization.
- Monitor extent of rash (Rule of Nines).[a]
- Consider skin biopsy (preferably more than 1) as clinically feasible.
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.[b]
- Discuss with study physician.

[a]Burge S, et al. Oxford Handbook of Medical Dermatology, 2010; [b]Refer to current National Comprehensive Cancer Network guidelines for treatment of cancer-related infections (category 2B recommendation).

IV = intravenous; PO = orally. PJP = pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Dose Modifications
Skin Disorders

Grade 1	Grade 2	Grade 3	Grade 4

• No dose modification.	• For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline.
	  ○ If toxicity worsens, treat as Grade 3.
	  ○ If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (see Toxicity Management).
		• Hold study drug/study regimen until resolution to Grade ≤1 or baseline.
		• If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen.
			• Permanently discontinue study drug/study regimen.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Case #3

Patient History

- 55 year old gentleman who was diagnosed with a T2 N0 p16 negative SCC of the floor of the mouth
- Treated with radiation with relapse 1.5 years later. Salvage resection not successful
- 1st line carboplatin plus paclitaxel – 1st cycle sepsis, 2nd cycle coronary vasospasm
- Enrolled in a phase I clinical trial of pembrolizumab plus novel anti-lag3
- 2 cycles of I/O results in 10% reduction in disease burden

Problems Begin To Emerge…

- Presents at cycle 4 with vague abdominal pain, anorexia and malaise (12 weeks)
- LFTs were abnormal – AST 292, ALT 1318, ALP 138, GGT 713, normal bilirubin (grade 4 transaminitis)
- Initiated immediately on oral prednisone 1.5 mg/kg
- LFTs immediately began to fall with measurements every twice weekly with normalization in 2 weeks
- Continued on steroids for 2 months, then taper with no relapse
- Disease remains stable to date off of therapy

Signs and Symptoms
Hepatobiliary Disorders

Signs and Symptoms[1-5]

- Mainly asymptomatic elevations in serum levels of hepatic enzymes
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Total bilirubin is rarely elevated
- Sometimes accompanied by fever
- Typically emerges 8-12 weeks into therapy
- Antibodies typically absent

•The relevant clinical study protocol should always be consulted for specific study-related information.

1. Naidoo J, et al. *Ann Oncol*. 2015;26(12):2375-2391.
2. Postow MA. *Am Soc Clin Oncol. Educ Book.* 2015;76-83.
3. Michot JM, et a. *Eur J Cancer*. 2016;54:139-148.
4. Spain L, et al. *Cancer Treat Rev*. 2016;44:51-60.
5. Fecher LA, et al. *Oncologist*. 2013;18(6):733-743.

CTCAE v4.03 Definitions
Hepatobiliary Disorders

AE[a]	Grade 1	Grade 2	Grade 3	Grade 4
ALT increased	>ULN–3.0 x ULN	>3.0–5.0 x ULN	>5.0–20.0 x ULN	>20.0 x ULN
ALP increased	>ULN–2.5 x ULN	>2.5–5.0 x ULN	>5.0–20.0 x ULN	>20.0 x ULN
AST increased	>ULN–3.0 x ULN	>3.0–5.0 x ULN	>5.0–20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	>ULN–1.5 x ULN	>1.5–3.0 x ULN	>3.0–10.0 x ULN	>10.0 x ULN

[a]AEs have been selected based on those most commonly observed with durvalumab and tremelimumab monotherapy and combination regimens.

*Grade 5 not applicable for increased ALT, AST, ALP or blood bilirubin.

1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

Toxicity Management
Hepatobiliary Disorders

- ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase.

Any Grade
• Infliximab should not be used for management of immune-related hepatitis. • Monitor and evaluate liver function tests: AST, ALT, ALP, and total bilirubin. • Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Management
Hepatobiliary Disorders

Grade 1	Grade 2	Grade 3 or 4
• Continue LFT monitoring per protocol.	• Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. • If no resolution to Grade ≤1 in 1 to 2 days, discuss with study physician. • If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. • If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.[a]	• Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. • If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** • Perform hepatology consult, abdominal workup, and imaging as appropriate. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.[a]

[a]Refer to current National Comprehensive Cancer Network guidelines for treatment of cancer-related infections (category 2B recommendation).

IV = intravenous; LFTs = liver function tests; PJP = pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia); PO = orally.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Dose Modifications
Hepatobiliary Disorders

Grade 1	Grade 2	Grade 3	Grade 4
• No dose modifications. ○ If it worsens, then treat as Grade 2 event.	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. ○ If toxicity worsens, then treat as Grade 3 or Grade 4. ○ If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper (see Toxicity Management).	• For elevations in transaminases ≤8 x ULN, or elevations in bilirubin ≤5 x ULN: ○ Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline. ○ Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. ○ Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days. • For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria[a] and in the absence of any alternative cause.	• Permanently discontinue study drug/study regimen.

[a]AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated ALP).

ALP = alkaline phosphatase; ALT = alanine transaminase;
AST = aspartate transaminase; ULN = upper limit of normal.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Case #4 Mr DF

67M – melanoma of upper chest dx 2014

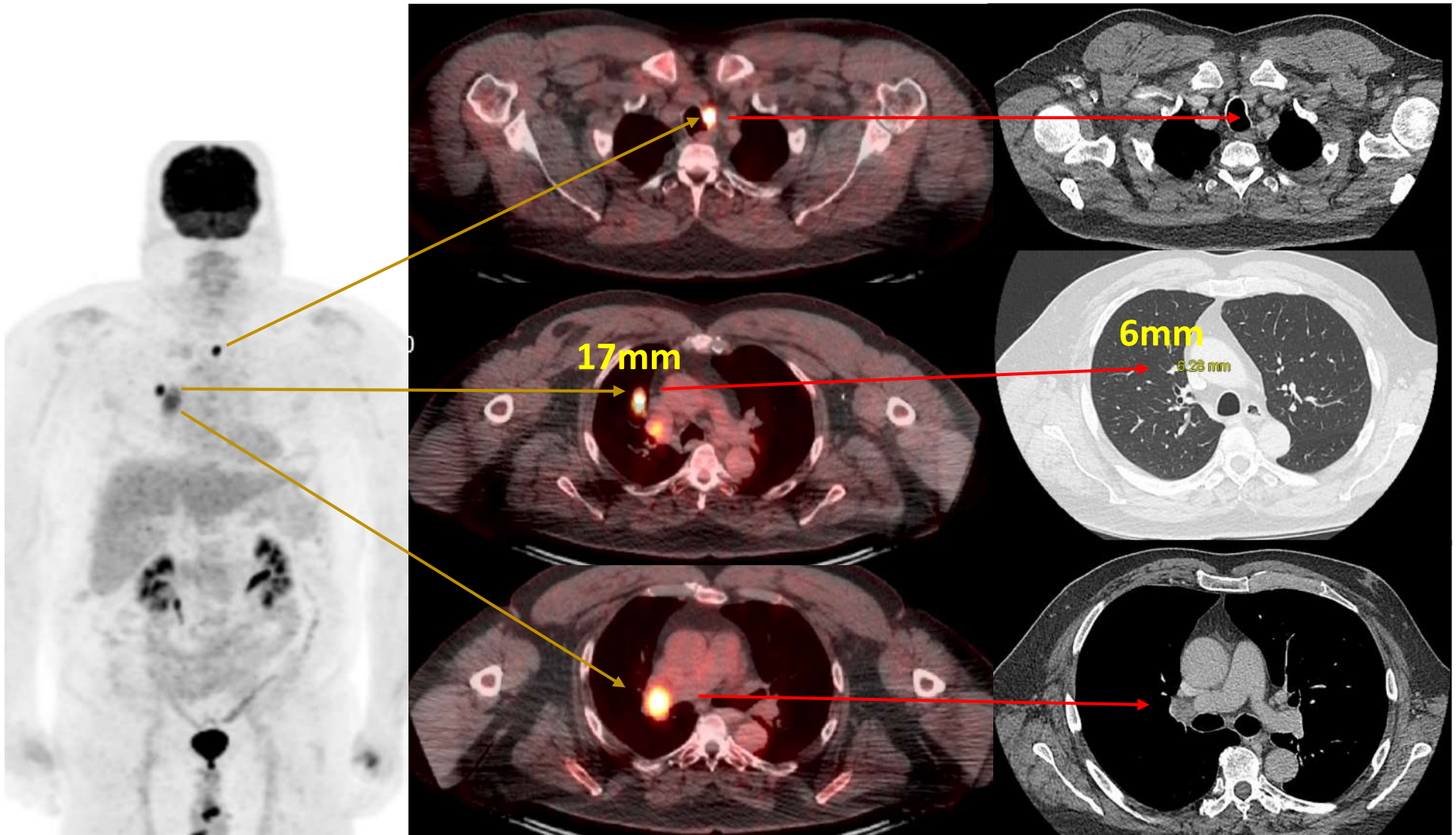
PMHx: Prostate Ca (prostatectomy), DSL, OSA

March 2016 – metastases in lung and LN

April 2016 – starts concurrent Nivolumab + Ipilimumab

Mr. DF

April 2016 **Nov 2016**



Problems Emerge…

Date	AM Cortisol
June 15	423
July 7	119
July 26	32

ACTH also critically low

- Pt didn’t feel overly unwell but could not perform as well at the gym as usual
- Started immediately on Hydrocortisone at replacement doses
- Other affected axes: prolactin, gonadotropins
- Concerning for hypophysitis

Hypophysitis: Treatment

- No clear guidelines
- Some sources suggest high-dose steroids with taper, down to physiologic but not beyond that as recovery is rare

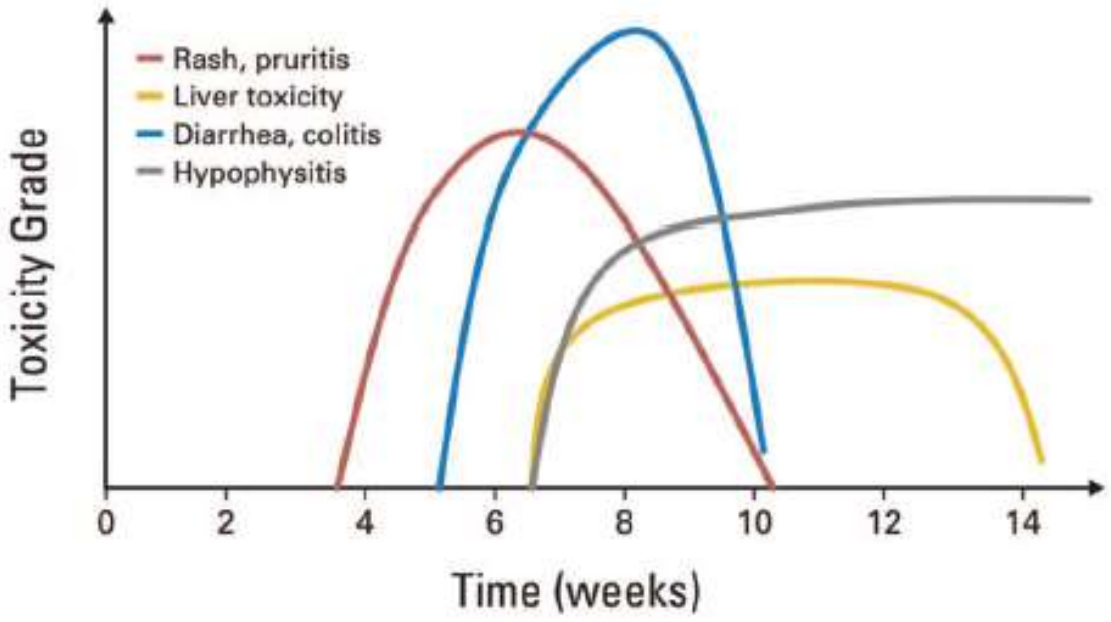


Figure 14: Kinetics of appearance of immune-related adverse events.

Postow. 2015 ASCO Educational Book

Hypophysitis: ?Steroids

- Faje et al.
  - 17 pts developed hypophysitis post Ipilimumab trx
  - 16/17 pts treated with high dose steroids (Prednisone 60) with taper over 6-8 weeks
  - 1/17 pts recovered adrenal function
  - F/U had median of 11.5mo and range up to 36mo

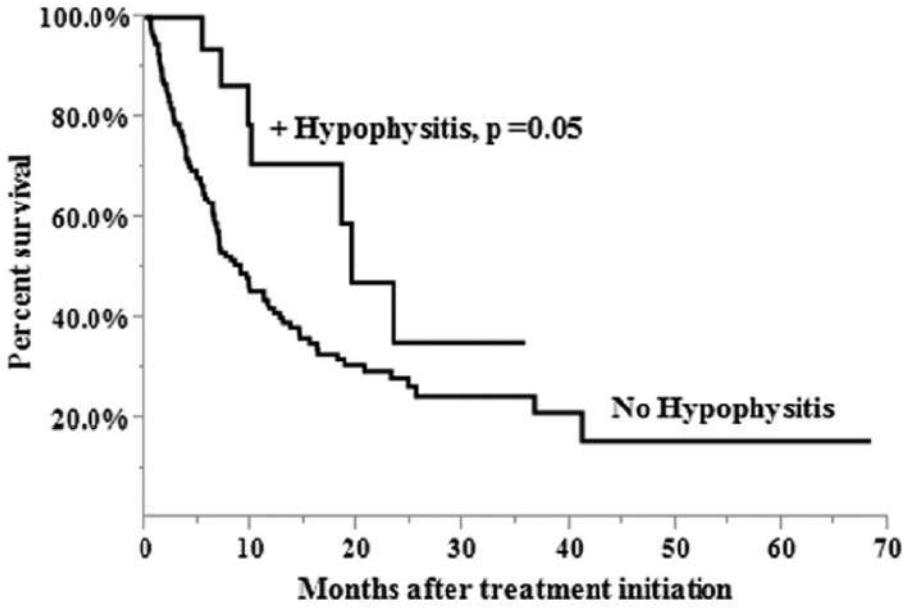


Figure 15: Kaplan-Meier plots for survival in metastatic melanoma patients, with and without hyophysitis, after the initiation of Ipilimumab.

Faje et al. JCEM 2014: 99(11): 4078

Hypophysitis: Treatment

- Monitor AM cortisol regularly in patients who are not on steroids
  - Cortisol peaks in the AM, that is when we are best able to detect deficiency
- If AM cortisol low:
  - Get AM cortisol and ACTH level
  - Start **Hydrocortisone 20mg qAM + 10mg qPM** immediately
  - Refer to Endocrinology urgently
  - Order MRI on first diagnosis or if symptomatic to rule-out metastases or other process
  - *Advise on sick day management

Hypophysitis: Treatment

OTHER DYSFUNCTION

- Central hypothyroidism (T4 low, TSH low or normal)
  - Treat with levothyroxine – full dose (1.6µg/kg) in pts with no cardiac dysfunction
  - Titrate every 6 weeks to attain normal T4 (do not follow TSH)
- Central hypogonadism: consider replacement for quality of life*
- DI: very rare, watch for symptoms
- Consult Endocrinology

Other Key Endocrine Disorders

- Autoimmune thyroiditis
- Type 1 diabetes

Toxicity Case #5

Mr. Reaction

- Receiving anti-PD1 + anti-CTLA4 for melanoma
- On assessment prior to cycle 3 of combination treatment:
  - New cough
  - Green sputum
  - Nasal congestion
  - Sort throat
  - Hot/cold intolerance
- Vital signs
  - BP 114/68
  - HR 110 (normal 70)
  - Temp 38.1 deg Celsius
  - O2 sat 93% at rest, 92% with exertion
- Examination
  - No wheeze or crackles, normal heart sounds but tachycardic

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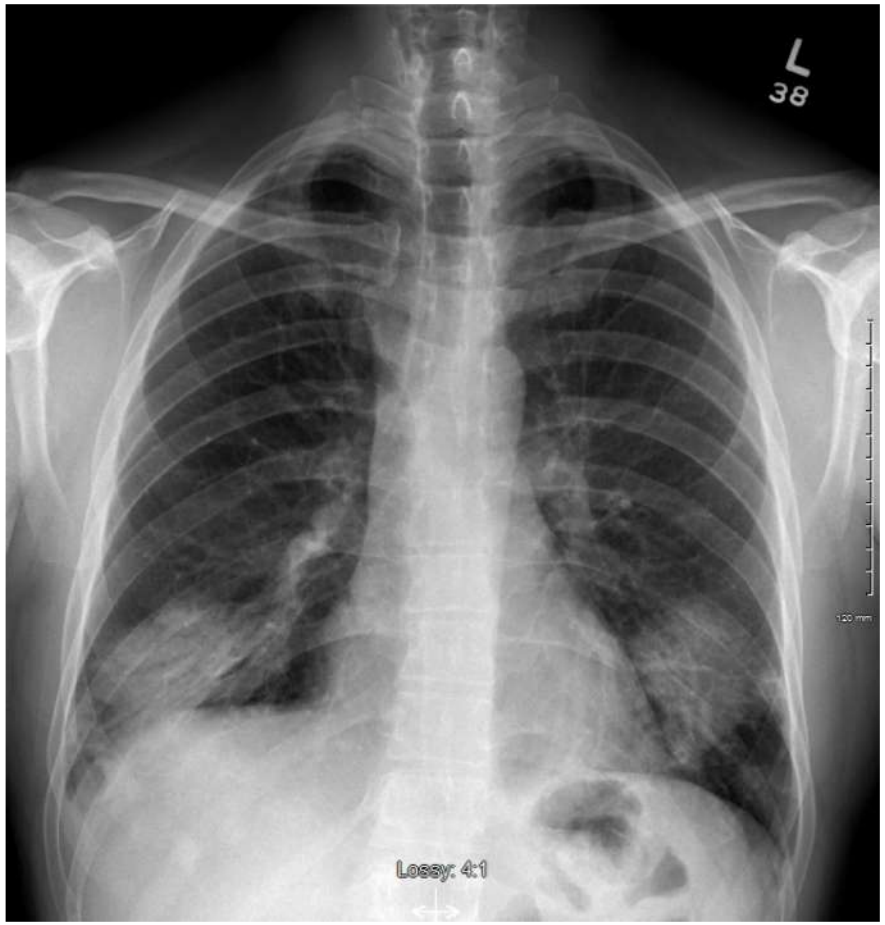
Durvalumab and Tremelimumab are investigational drugs and are not approved for use in Canada

Mr. Reaction



- CXR performed:
  - Confluent mass-like opacity seen in both lower lobes, infective or inflammatory process
- Rx'd levofloxacin, sent to respirology with CT scan ordered

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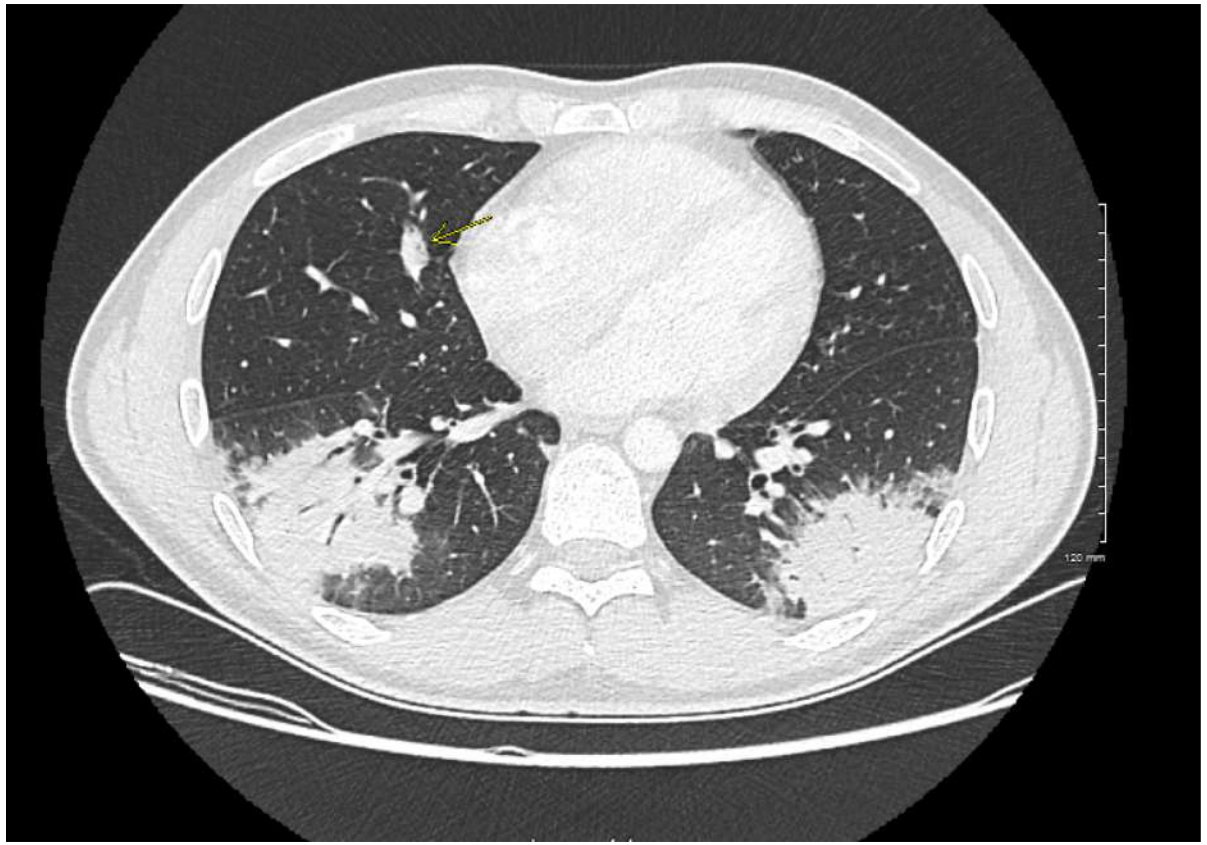
Mr. Reaction



- CT report
  - Air space consolidation subpleural in both lower lobes
  - There are multiple small areas of nodular consolidation bilaterally and larger areas in the bases of the lungs.
  - The appearance is classic for organizing pneumonia since there is some central sparing in some of these confluent airspace opacities.

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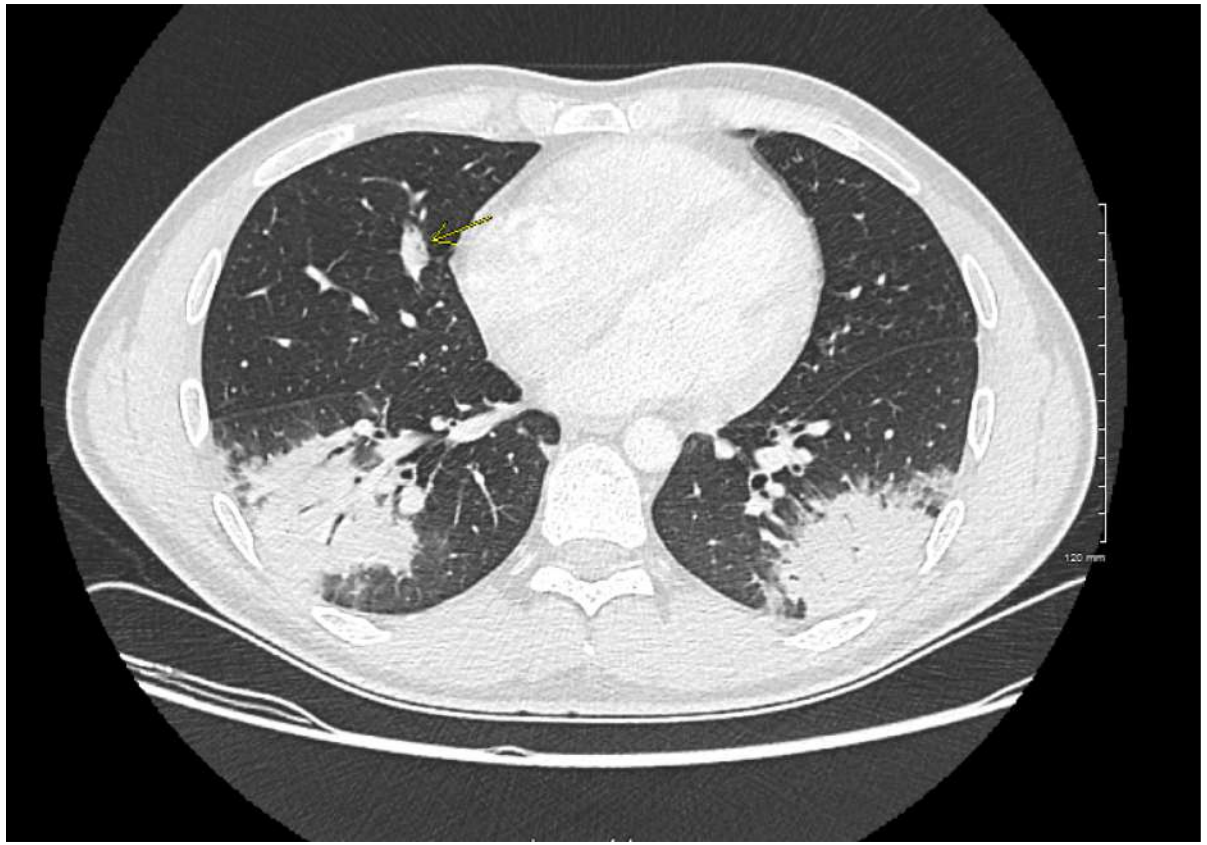
Mr. Reaction



- Respirology opinion
  - BOOP-like organizing pneumonia secondary to anti-CTLA4.
  - This drug is well known to cause organizing pneumonia.
  - "I do not suspect infection"
- Prednisone 1mg/kg, with slow taper

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Durvalumab and Tremelimumab are investigational drugs and are not approved for use in Canada

Signs and Symptoms
Respiratory Disorders

Signs and Symptoms[1-3]

- Dry cough
- Progressive shortness of breath
- Fine inspiratory crackles
- Tachypnea
- Hypoxia
- Radiographic changes on X-ray or CT scan
- Fever
- Chest pain

•**The relevant clinical study protocol should always be consulted for specific study-related information.**

1. Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.
2. Chow LQ. *Am Soc Clin Oncol Educ Book*. 2013. doi:10.1200/EdBook_AM.2013.33.e280.
3. Naidoo J, et al. *Ann Oncol*. 2015:26(12):2375-2391.

CT = computed tomography.

Key Tests to Confirm the Diagnosis
Respiratory Disorders

Imaging: Chest x-ray and CT scan[1,2]	▪ Ground-glass opacities (GGO); often seen in lung cancer patients ▪ Cryptogenic organizing pneumonia (COP)-like; commonly present in patients with melanoma ▪ Hypersensitivity-type pneumonitis ▪ Interstitial-type pneumonitis
Pulmonary function tests[3,4]	▪ Arterial oxygen saturation via oximetry ▪ Lung diffusion (DLCO) testing ▪ Spirometry
Bronchoscopy and histology	▪ Bronchoscopy with bronchoalveolar lavage and lung tissue will help distinguish infections ▪ Varied histological features[1,3,5,6]

DLCO = diffusing capacity of the lung for carbon monoxide.

•The study-related relevant clinical study protocol should always be consulted for specific information.

1. Naidoo J. Pneumonitis with anti–PD-1/PD-L1 therapy [presentation]. ECC 2015..
2. Naidoo J, et al. ECC 2015. Abstract 503.
3. Michot JM, et al. Eur J Cancer. 2016;54:139-148.
4. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.
5. Chow LQ. Am Soc Clin Oncol Educ Book. 2013. doi:10.1200/EdBook_AM.2013.33.e280.
6. Peng B, et al. BMC Cancer. 2015;15:895.

Toxicity Management
Respiratory Disorders

- CT = computed tomography; ILD = interstitial lung disease.

Any Grade
• Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. • Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high-resolution CT scan.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Management
Respiratory Disorders

Grade 1	Grade 2	Grade 3 or 4
• Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. • Consider pulmonary and infectious disease consult.	• Monitor symptoms daily and consider hospitalization. • Promptly start systemic steroids (e.g. prednisone 1 to 2 mg/kg/day PO or IV equivalent). • Reimage as clinically indicated. • If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. • If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment.[a] • Consider pulmonary and infectious disease consult. • Consider, as necessary, discussing with study physician.	• Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. • Obtain pulmonary and infectious disease consult. • Hospitalize the patient. • Supportive care (eg, oxygen). • If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment.[a]

[a]Refer to current National Comprehensive Cancer Network guidelines for treatment of cancer-related infections (category 2B recommendation).

CT = computed tomography; ILD = interstitial lung disease; IV = intravenous; PJP = pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia); PO = orally; TNF = tumour necrosis factor.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Dose Modifications
Respiratory Disorders

Grade 1	Grade 2	Severe (Grade 3-4)
• No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. ○ If toxicity worsens, then treat as Grade 3 or Grade 4. ○ If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	• Permanently discontinue study drug/study regimen.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Neurologic Disorders

Symptoms
Nervous System Disorders

Myasthenia Gravis and Guillain-Barré Symptoms[a,1]

- Prominent dysphagia
- Rapidly progressive weakness
- Respiratory insufficiency
- Autonomic insufficiency

Other Symptoms[b,1]

- Headache
- Nausea
- Vertigo
- Behavior changes
- Weakness

[a]Seminal symptoms of a potential decompensation; [b]Including but not limited to limbic encephalitis, autonomic neuropathy, and excluding Myasthenia Gravis and Guillain-Barré.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Management

Nervous System Disorders: Myasthenia Gravis and Guillain-Barré

Any Grade

- Prompt diagnosis of immune-mediated peripheral neuromotor symptoms is important as some patients may experience acute decompensation. Monitor for certain sentinel symptoms, such as prominent dysphagia, rapidly progressive weakness, and signs or respiratory insufficiency or autonomic instability.
- Evaluate for alternative etiology, such as disease progression, infection, metabolic syndromes, or medications.
- Diagnosis of immune-mediated peripheral neuromotor syndromes can be challenging in patients with underlying cancer because of the confounding effects of cancer and its treatments. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consultation.
- Neurophysiological testing is routinely indicated and best facilitated through a neurology consultation.
- Use of corticosteroids as the primary treatment of Guillain-Barré is not typically considered effective. Patients should start treatment with IV IG followed by plasmapheresis if not responsive.

IG = immunoglobulin; IV = intravenous.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Management

Nervous System Disorders: Myasthenia Gravis

Grade 1

- Discuss with the study physician.
- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described on the previous slide.
- Obtain a neurology consult.

Grade 2

- Discuss with the study physician.
- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.
- Obtain a neurology consult
- Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine).
- Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.
- Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.
- If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

Grade 3 or 4

- Discuss with study physician.
- Recommend hospitalization.
- Monitor symptoms and obtain neurological consult.
- Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.
- Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.
- If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

AChE = acetylcholine esterase; IG = immunoglobulin; IV = intravenous.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Management

Nervous System Disorders: Guillain-Barré

Grade 1	Grade 2	Grade 3 or 4
• Discuss with the study physician. • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. • Obtain a neurology consult.	• Discuss with the study physician. • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. • Obtain a neurology consult. • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). • It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. • Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.	• Discuss with study physician. • Recommend hospitalization. • Monitor symptoms and obtain neurological consult. • It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. • Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

IG = immunoglobulin; IV = intravenous.

Other Concerning Neurologic Syndromes

- Encephalitis
- Meningitis

Renal Disorders

Clinical Characteristics and Distinguishing Features

Renal Disorders

Infectious etiologies[1,2]	▪ Systemic symptoms such as high fever, chilling, nausea and vomiting ▪ Positive urine cultures or viral serology
Physical obstruction of the kidney[3]	▪ Hydronephrosis on renal ultrasonography
Tumor progression and/or metastatic disease[4]	▪ Radiographic changes are typical
Acute kidney injury induced by alternative medications[1,3]	▪ Temporal association between exposure to the causative agent and onset ▪ Can be associated with rash, fever, arthralgias, or combination of these symptoms
Autoimmune disease[3]	▪ Circulating autoantibodies (e.g. ANAs, double-stranded DNA antibody) often present
Vascular etiologies[3]	▪ May be associated with livedo reticularis, abdominal bruits and funduscopic abnormalities

Immune-mediated nephritis[1,5]

- **Asymptomatic impairment of renal function** associated with mild proteinuria and gradually increasing creatinine levels
- Associated rash may be indicative of a systemic illness (DRESS)

ANA = antinuclear antibody; DNA = deoxyribonucleic acid; DRESS = drug rash with eosinophilia and systemic symptoms.

- **The relevant clinical study protocol should always be consulted for specific study-related information.**

1. Kodner CM, et al. *Am Fam Physician.* 2003;67(12):2527-2534, 2. Lee DG, et al. *J Korean Med Sci.* 2009;24(2):296-301, 3. Rahman M, et al. *Am Fam Physician.* 2012;86(7):631-639, 4. Kawamoto S, et al. *Semin Ultrasound CT MR.* 2009;30(2):67-77, 5. Izzedine H, et al. *Invest New Drugs.* 2014;32(4):769-773.

Key Tests to Confirm the Diagnosis

Renal Disorders

Laboratory tests[1–3]	▪ CMP (comprehensive metabolic panel with assessment of GFR) ▪ Urinalysis (spot and 24-hour measures) ▪ CBC (complete blood count) ▪ Urine cultures and viral serology (e.g. CMV, EBV)
Radiological tests[4]	▪ Can detect inflammatory cortical renal enlargement ▪ CT scan can rule out other etiologies
Histological analysis[5-8]	▪ Granulomatous nephritis ▪ Lymphocytic nephritis

CMV = cytomegalovirus; EBV = Epstein-Barr virus; GFR = glomerular filtration rate.

- **The relevant clinical study protocol should always be consulted for specific study-related information.**

1. Dusenbury SM, White A, eds. The Washington Manual of Pediatrics. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:359-373. 2. Kodner CM, et al. Am Fam Physician. 2003;67(12):2527-2534. 3. Lee DG, et al. J Korean Med Sci. 2009;24(2):296-301. 4. Forde PM, et al. Anticancer Res. 2012;32(10):4607-4608. 5. Naidoo J, et al. Ann Oncol. 2015;26(12):2375-2391. 6. Izzedine H, et al. Invest New Drugs. 2014;32(4):769-773. 7. Thajudeen B, et al. Am J Ther. 2015;22(3):e84-e87. 8. Voskens CJ, et al. PLoS One. 2013;8(1):e53745.

CTCAE v4.03 Definitions

Renal Disorders

AE[a]	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine Increased	• >1 to 1.5 × baseline • >ULN to 1.5 × ULN	• >1.5 to 3 × baseline • >1.5 to 3 × ULN	• >3 × baseline • >3 to 6 × ULN	• >6 × ULN

[a]AEs have been selected based on those most commonly observed with durvalumab and tremelimumab monotherapy and combination regimens.
Grade 5 not applicable to creatinine increased.

AE = adverse event; ULN = upper limit of normal

1. Common Terminology Criteria for Adverse Events v4.03. 14 June 2010.

Toxicity Management

Renal Disorders

Any Grade
• Consult with a nephrologist. • Monitor for signs and symptoms that may be related to changes in renal function, (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). • Patients should be thoroughly evaluated to rule out any alternative etiology, such as disease progression or infections. • Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

BUN = blood urea nitrogen

•**The relevant clinical study protocol should always be consulted for specific study-related information.**

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Toxicity Management

Renal Disorders

Grade 1	Grade 2	Grade 3 or 4
• Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. • Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.	• Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. • Carefully monitor serum creatinine every 2-3 days and as clinically warranted. • Consult nephrologist and consider renal biopsy if clinically indicated. • If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.[a] • When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.	• Carefully monitor serum creatinine on a daily basis. • Consult nephrologist and consider renal biopsy if clinically indicated. • Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.[a]

[a]Refer to current National Comprehensive Cancer Network guidelines for treatment of cancer-related infections (category 2B recommendation).
IV = intravenous; PJP = pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia); PO = orally.

•The relevant clinical study protocol should always be consulted for specific study-related information.

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Dose Modifications

Renal Disorders

Grade 1	Grade 2	Grade 3 or Grade 4

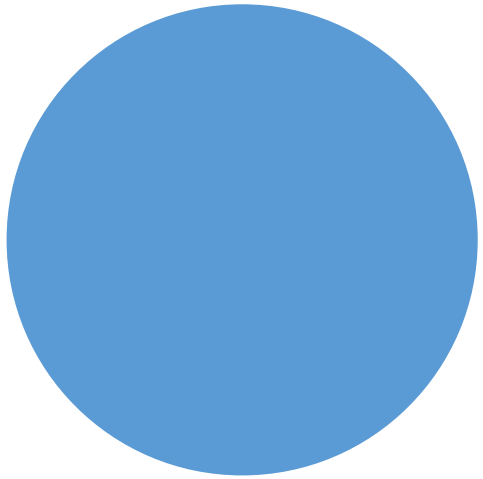
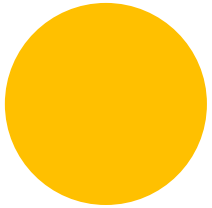
• No dose modification.	• hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline.
	  • If toxicity worsens, then treat as Grade 3 or 4.
	  • If toxicity improved to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (see Toxicity Management).
		• Permanently discontinue study drug/study regimen.

•**The relevant clinical study protocol should always be consulted for specific study-related information.**

1. Dosing Modification and Toxicity Management Guidelines 1 November 2017 Version.

Conclusions

- I/O therapy can result in unique toxicities involving all major organs
- Detection can be subtle
- Potentially high risk if not detected early as toxicity can rapidly escalate
- If an autoimmune syndrome exists, I/O therapy can cause it
- WHEN IN DOUBT, GIVE THE ANTIDOTE

Thank you for your attention