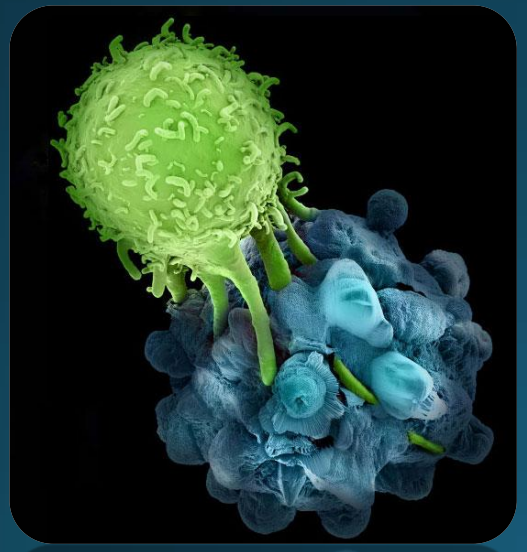
Immunotherapy and the 'itis' es



March 18, 2021

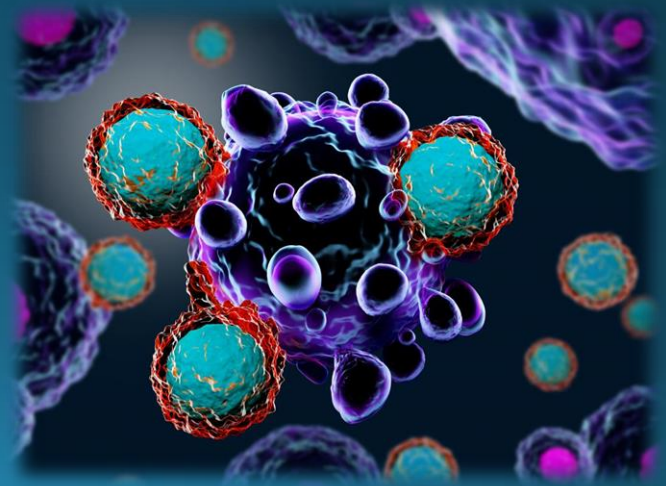
Dr. Suzana Gilmour
Medical Oncologist at BC Cancer Abbotsford Centre

Objectives

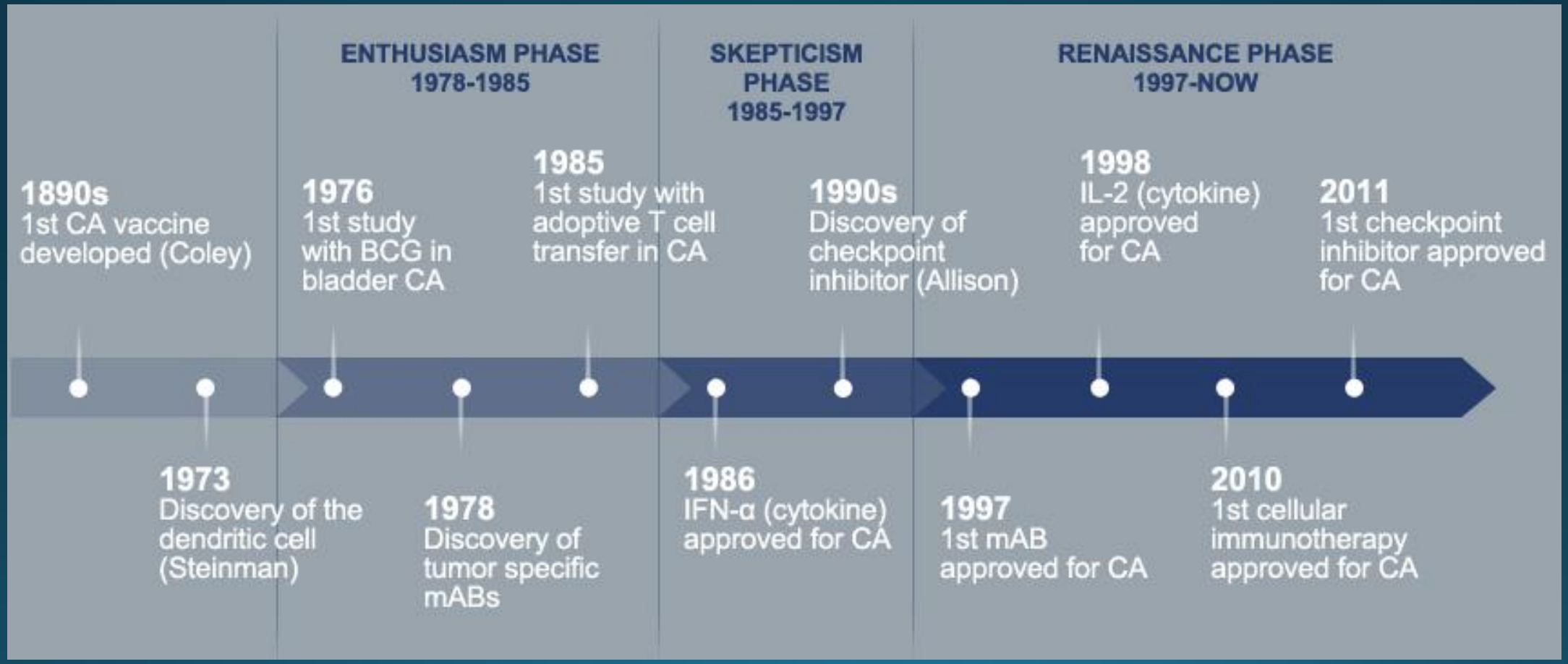
1) Introduce immunotherapy and mechanism of action
2) Review adverse event profile of immunotherapy
3) Provide resources for immunotherapy management

Cancer and the Immune System

- Cancer cells are able to avoid detection and destruction by the immune system through multiple mechanisms
- Cancer cells may…
  - Reduce the expression of tumor antigens on their surface, making it harder for the immune system to detect them
  - Express proteins on their surface that inhibit immune cell activation
  - Induce cells in the microenvironment to release substances that suppress immune responses
  - Secrete substances themselves that downregulate the immune system



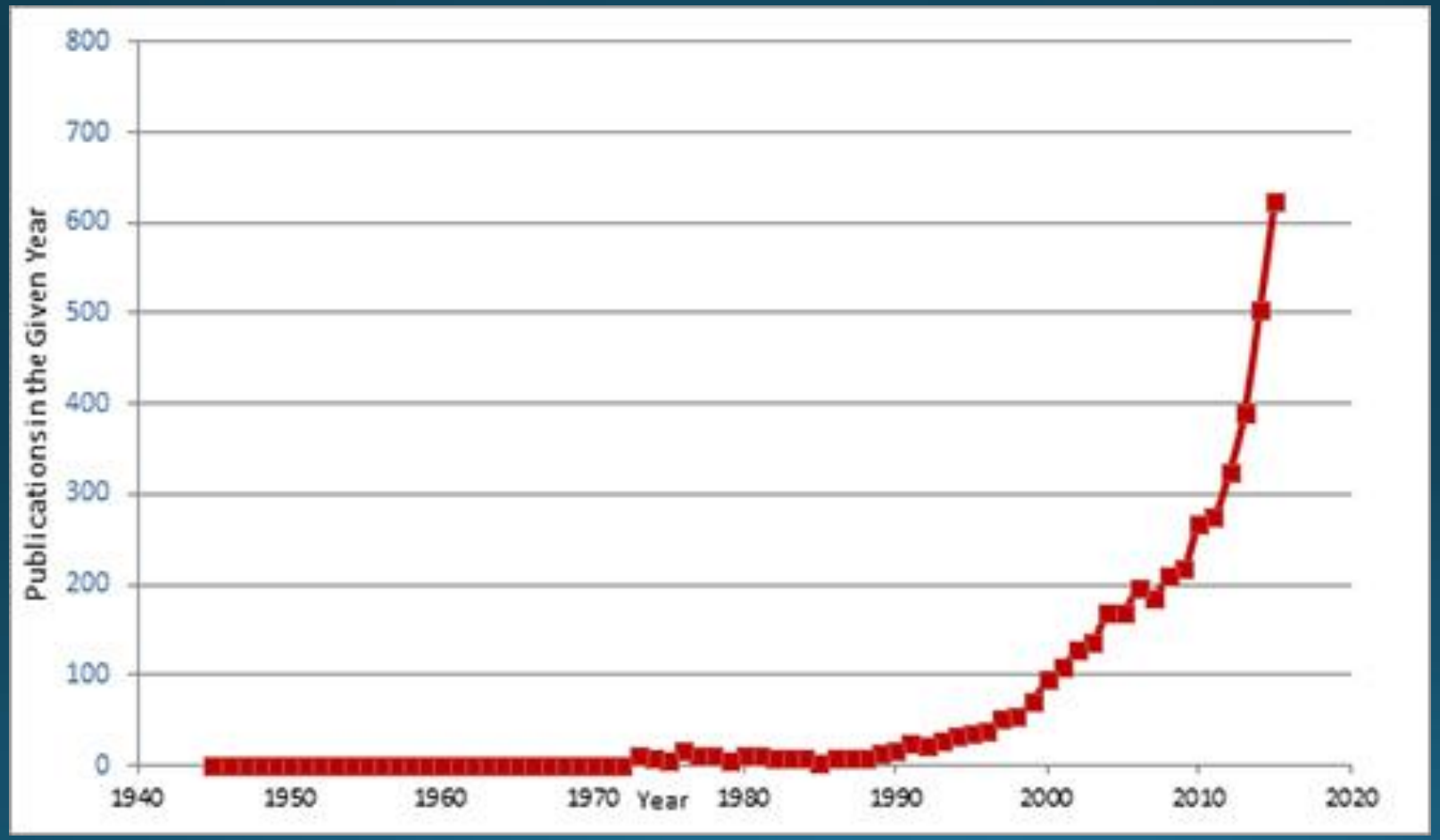
Immunotherapy



Source: Lesterhuis, et al. Nat Rev Drug Discov. 2011. 10(8):591-600.

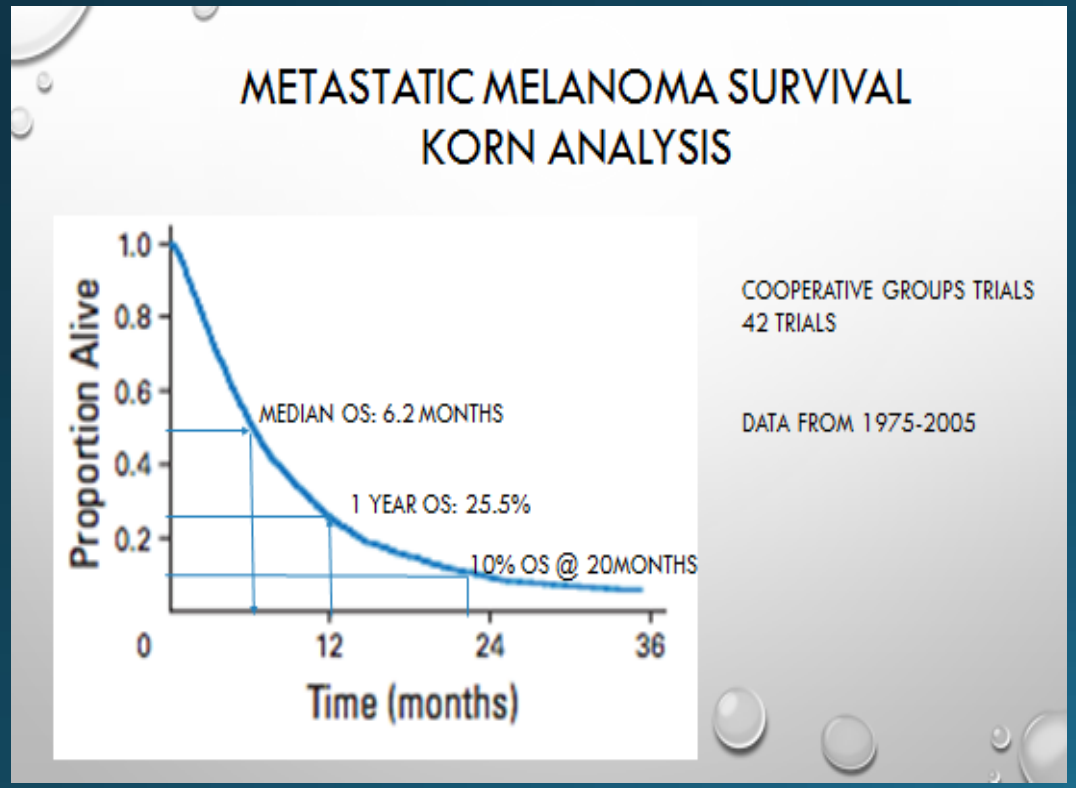
A Paradigm Shift

The number of publications on cancer immunotherapy in the given year

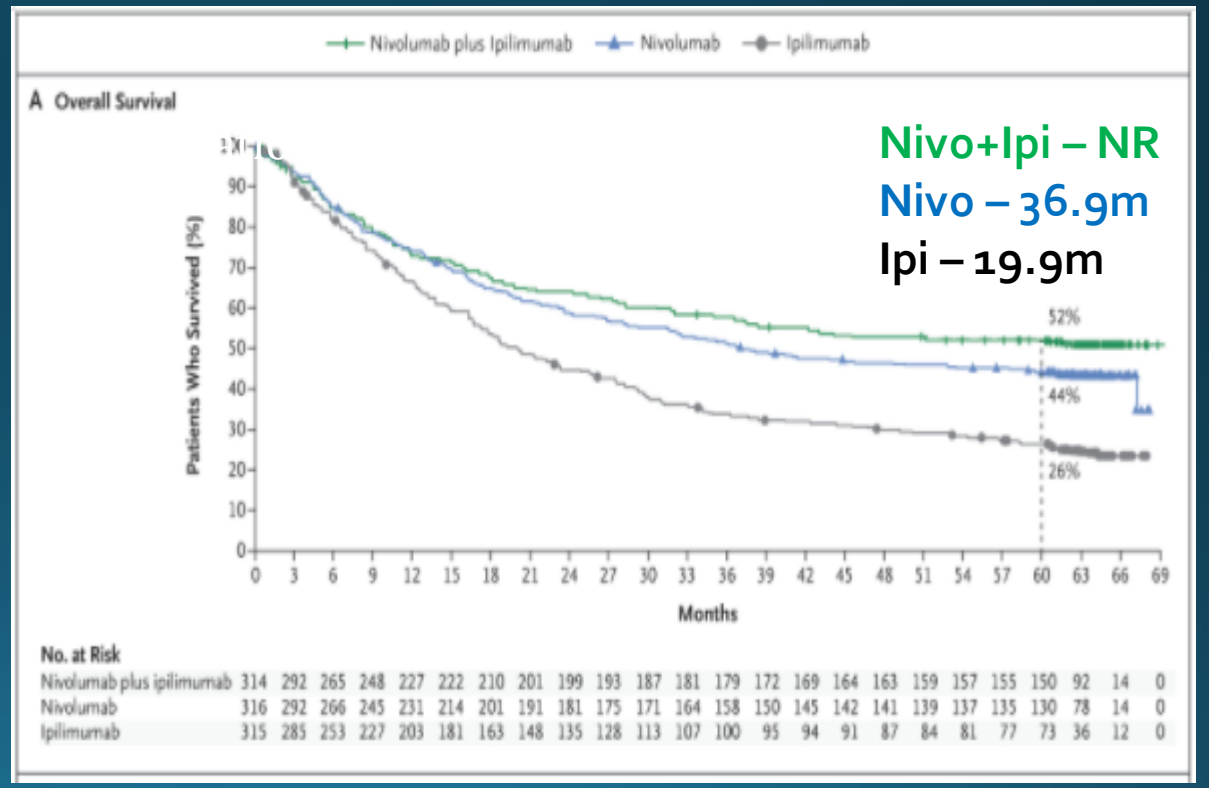


Source: Razvi E and Oosta G. GEN. March 2016

Metastatic Melanoma – 2019 updates

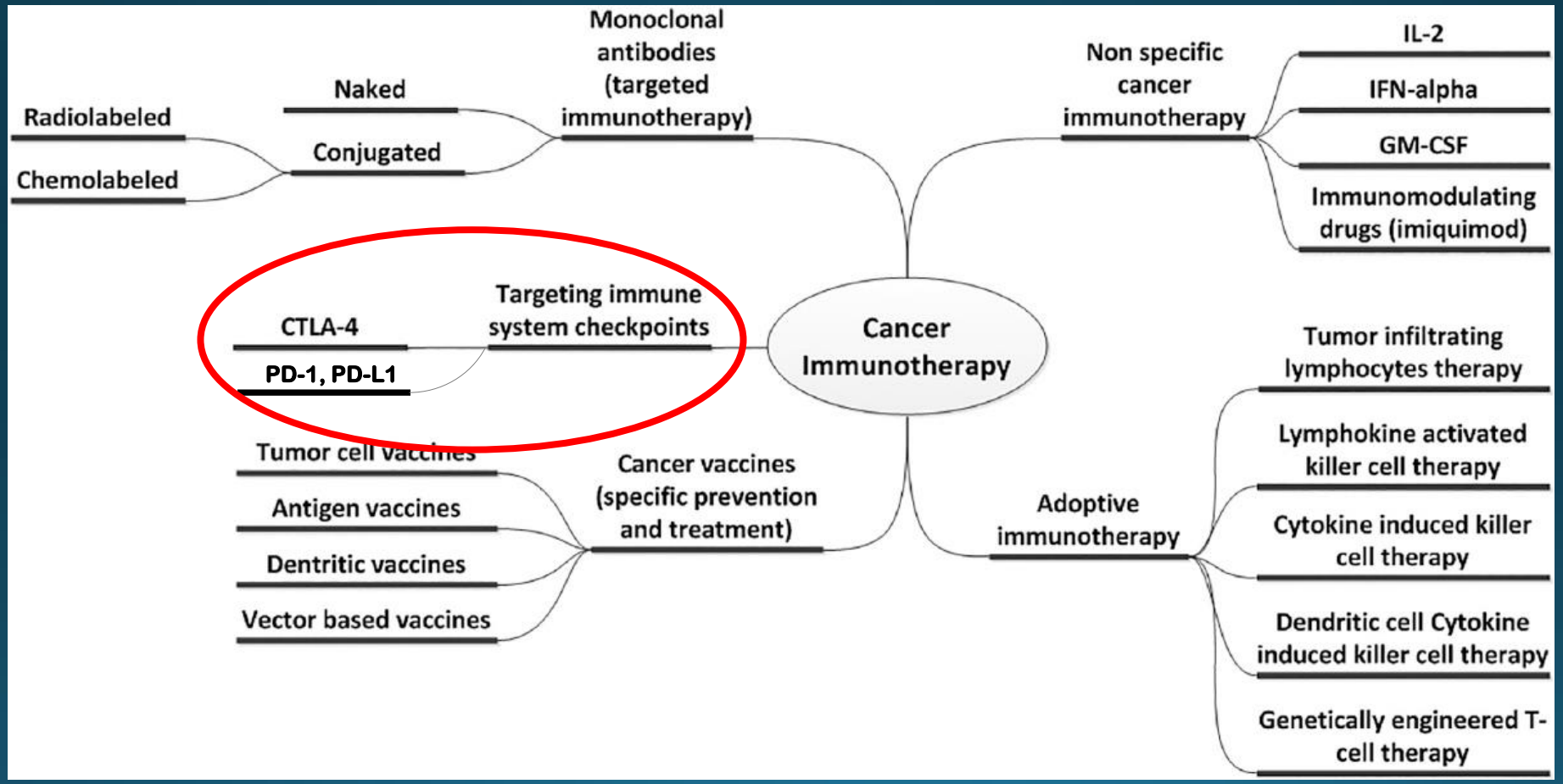


CHECKMATE 067 - 5Y OVERALL SURVIVAL DATA



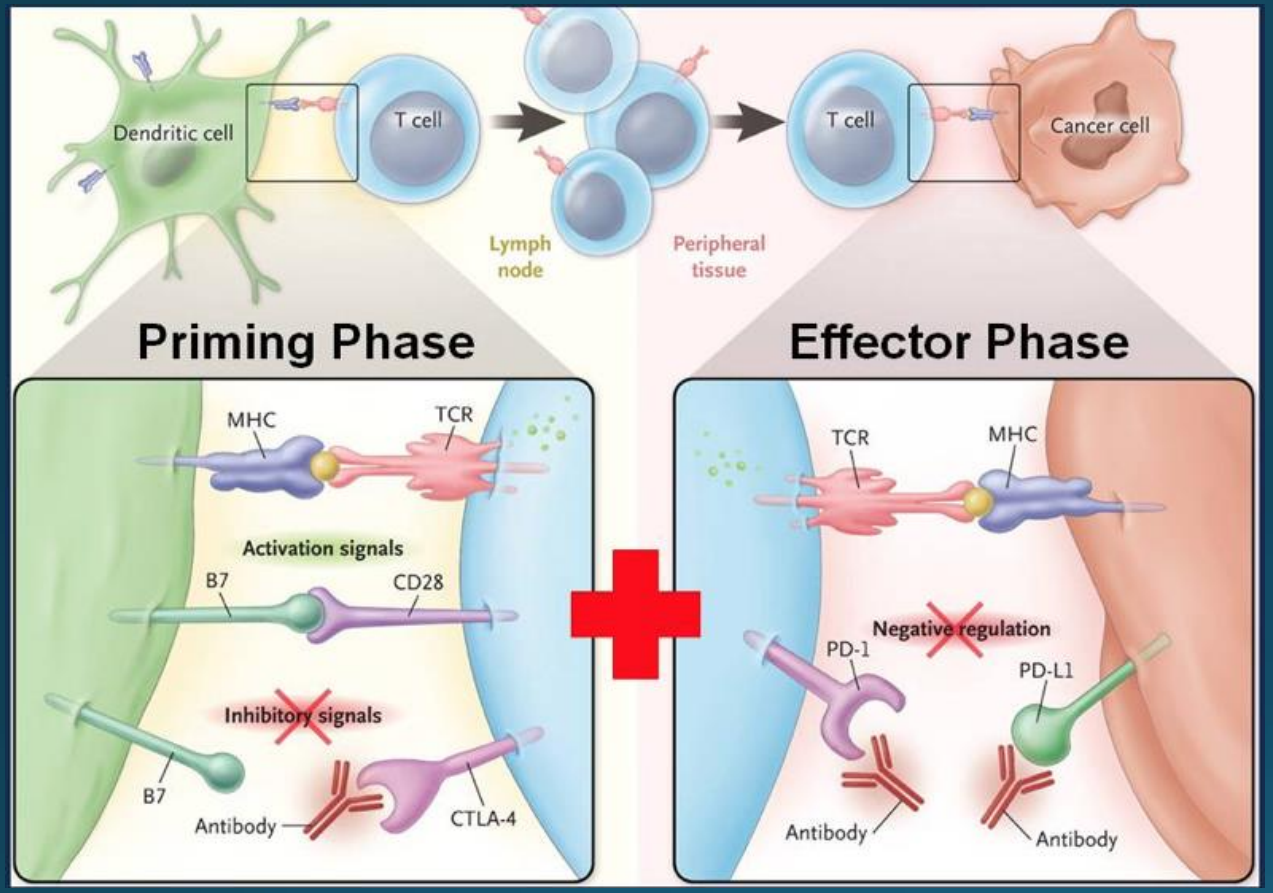
Source: Larkin et al. N Engl J Med. 2019. 381:1535-1546.

Immunotherapy



Source: Kalanjiam V and Murali Gopika Manoharan GV. SRM J Res Dent Sci. 2015. 6:175-80.

Immune Checkpoint Inhibitors



<u>CTLA-4 inhibitor</u>

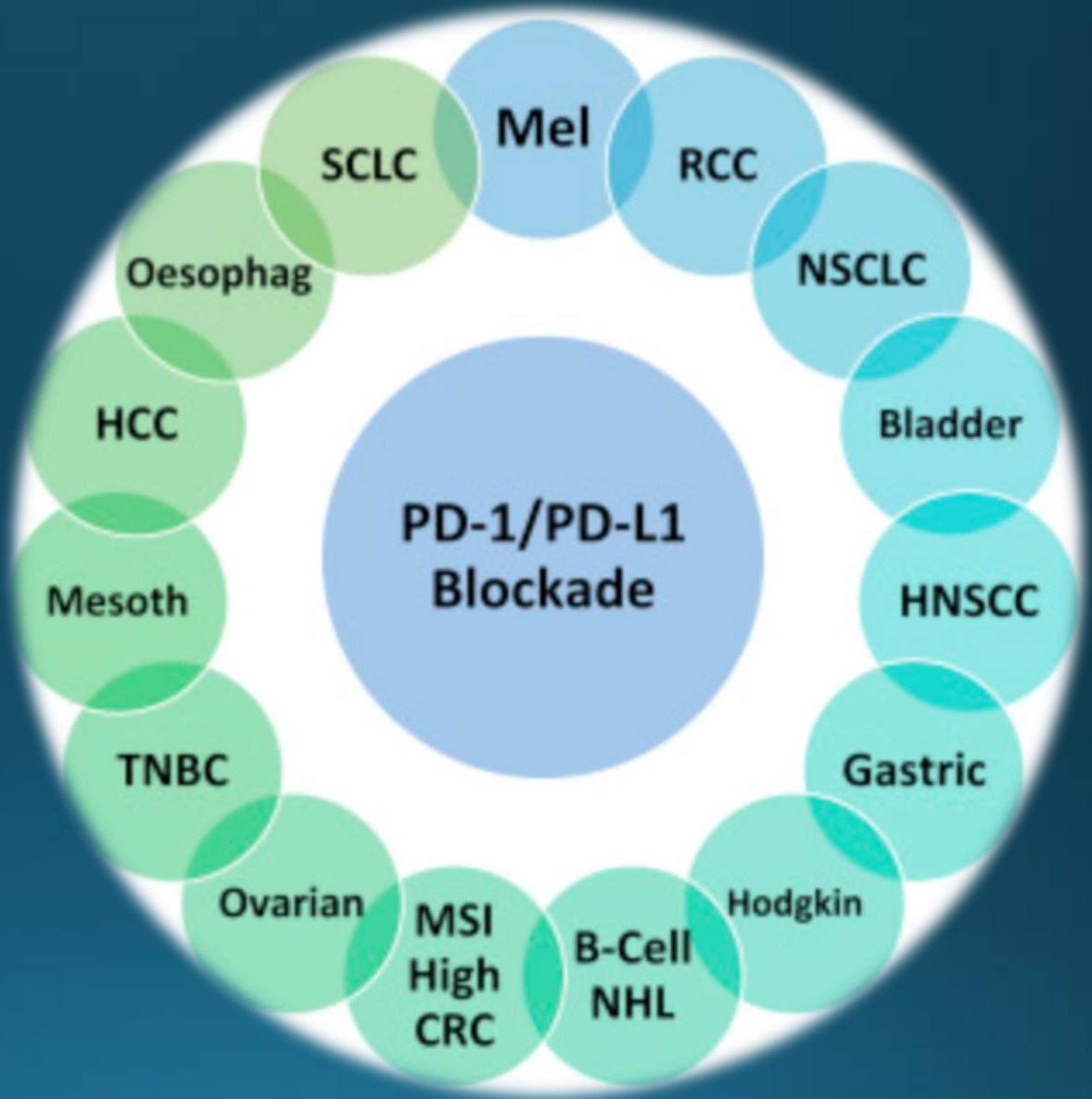
- Ipilimumab
- Tremelimumab

<u>PD-1 and PD-L1 inhibitors</u>

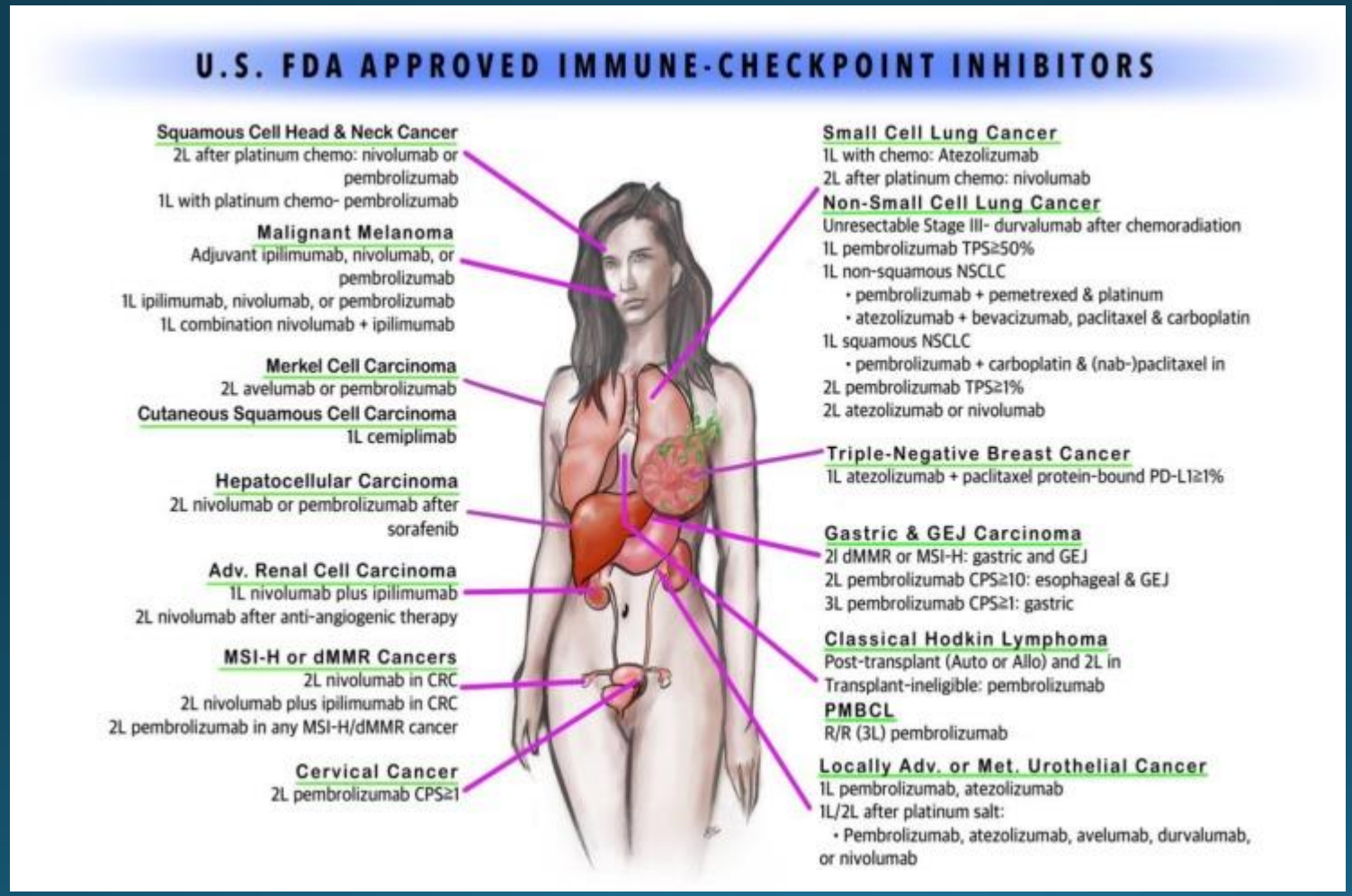
- PD-1: Nivolumab, pembrolizumab
- PD-L1: Atezolizumab, duravulmab, avelumab

Source: Heger M. *Nature*. 2012. 18(7):993.

They're everywhere....



Current approved indications



Source: Vaddepally RK, et al. Cancers 2020. 12(3):738

Currently at the BC Cancer

- Stage IV Melanoma:
  - Ipilimumab + Nivolumab (USMAVIPNI)
  - Pembrolizumab (SMAVPEM, SMAVPEM6)
  - Nivolumab (SMAVNIV, SMAVNIV4)
  - Ipilimumab (SMAVIPI , SMAVIPI)
  - *Avelumab for Merkel Cell (SMMCCAVE)*
  - *Cemiplimab for SCC (USMAVCEM)*

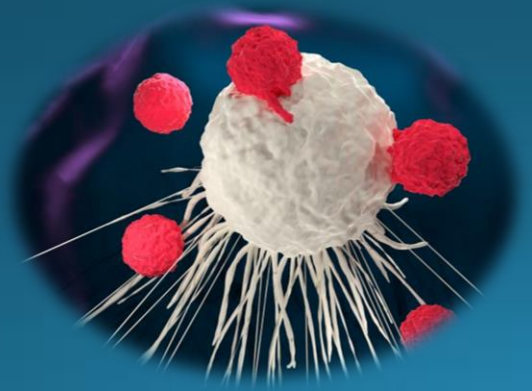
- Stage IV RCC:
  - Ipilimumab + Nivolumab (UGUAVIPNI)
  - Nivolumab (GUAVNIV or GUAVNIV4)
  - Pembrolizumab (UGUAVPEM or UGUAVPEM6)
  - Pembrolizumab + Axitinib (GUAVPEMAX)

- Stage IV H&N:
  - Nivolumab (UHNAVNIV or UHNAVNIV4)

- Stage IIIB/C/IV NSCLC:
  - Pembrolizumab (ULUAVPMBF, ULUAVPMBF6)
  - Pembrolizumab, Paclitaxel + Carboplatin (ULUAVPCPMB)
  - Pembrolizumab, Platinum + Gemcitabine (ULUAVPGPMB)
  - Pembrolizumab, Platinum + Pemetrexed (ULUAVPPPMB)
  - Pembrolizumab (ULUAVPMB, ULUAVPMB6, LUAVPMBM, ULAVPMBM6)
  - Pembrolizumab + Pemetrexed (LUAVPPMBM)
  - Nivolumab (ULUAVNIV, ULUAVNIV4)
  - Durvalumab (ULULADUR, ULULADUR4)

- Hodgkin Lymphoma (Relapsed/Refractory):
  - Pembrolizumab (LYPEM, LYPEM6)
  - Nivolumab (LYNIV, LYNIV4)

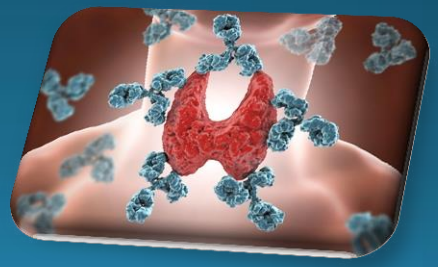
- PLUS … several clinical trials looking at immunotherapy combined with other agents



BC Cancer Agency
CARE + RESEARCH

Checkpoint inhibitor toxicity

- Checkpoint inhibitors have a unique spectrum of toxicity due to their mechanism of action
- Chemotherapy interferes with cell cycle function and affects rapidly dividing cells, thereby affecting cancer cells but also impacting other cells in the body with a high turnover rate
  - i.e. Hair → alopecia, Bone marrow → febrile neutropenia, Gut mucosa → stomatitis, N/V, diarrhea
- Checkpoint inhibitors 'turn on' the immune system and adverse events related to immune system over-activity and autoimmunity
  - Any 'itis' you can think of!!



Tolerability of oncology therapies

Chemotherapy

- **Target:** rapidly dividing tumour and normal cells
- **Adverse Events:** diverse due to non-specific nature of therapy

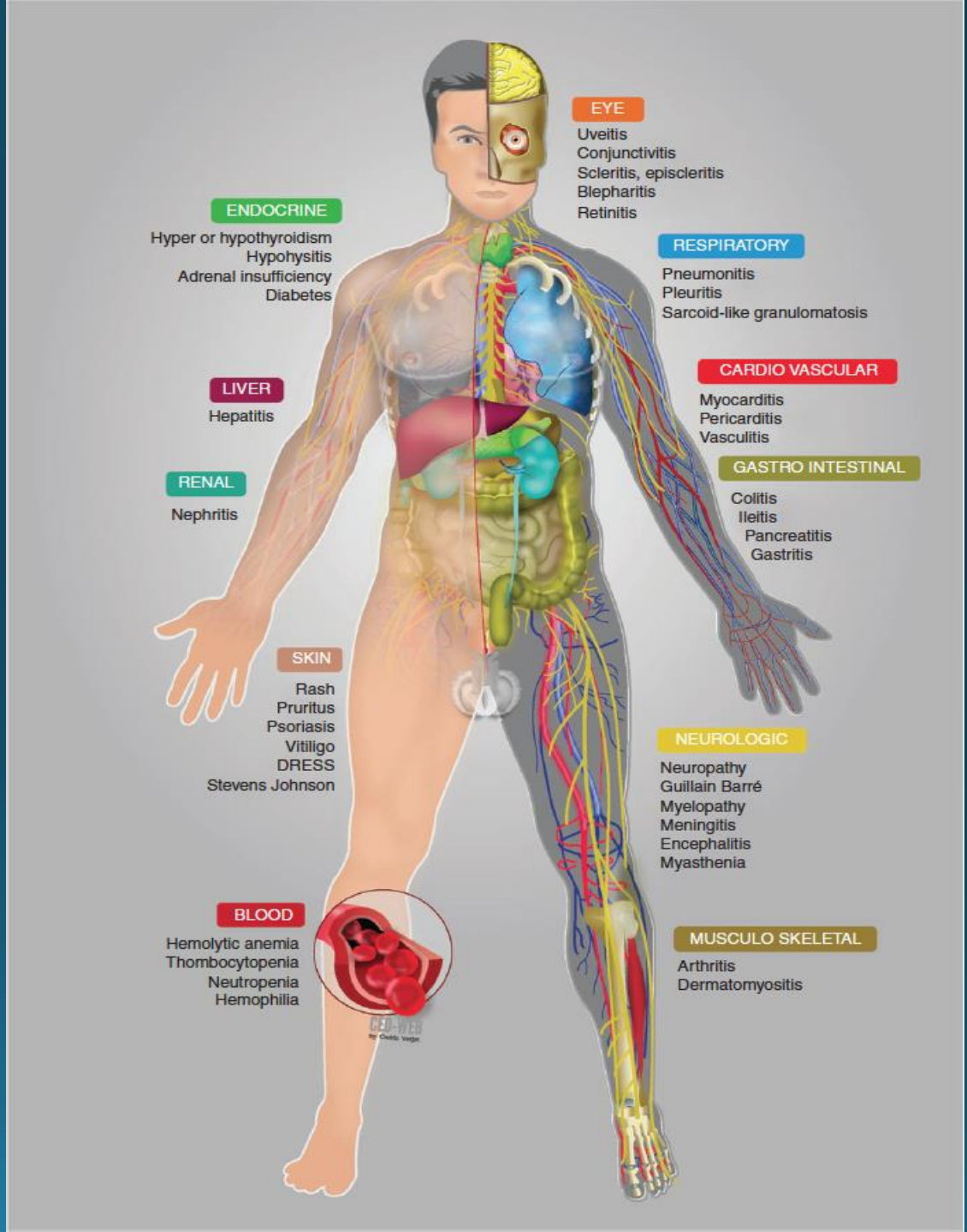
Immunotherapy

- **Target:** immune system
- **Adverse Events:** unique events can occur as a result of immune-system activity

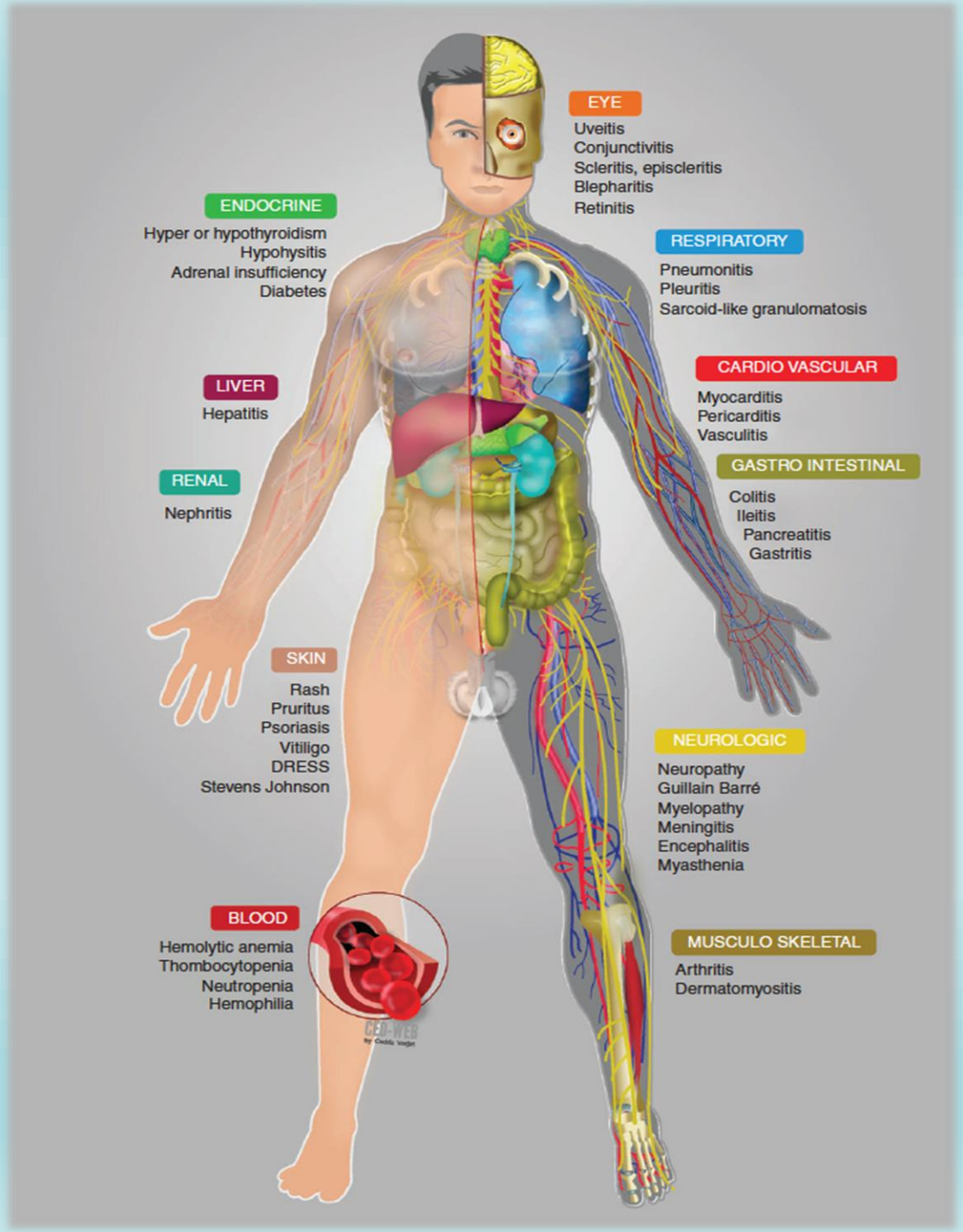
Different spectrum of adverse events but with potentially similar presentations

Immune-related Adverse Events (irAEs)

Just add "itis"



Source: Champiat et al. Annals of Oncology. 2016. 27:559-574.


EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis
ENDOCRINE
Hyper or hypothyroidism
Hypohysitis
Adrenal insufficiency
Diabetes
RESPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis
CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis
LIVER
Hepatitis
GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis
RENAL
Nephritis
SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson
NEUROLOGIC
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia
BLOOD
Hemolytic anemia
Thombocytopenia
Neutropenia
Hemophilia
MUSCULO SKELETAL
Arthritis
Dermatomyositis

Some of the things we have seen so far…

- Rash
- Psoriasis
- Vitiligo
- Ophthalmopathy
- Hypo/hyperthyroidism
- Hypophysitis
- Diabetic ketoacidosis
- New onset of T1DM
- Arthritis/myositis
- Encephalitis
- Myasthenia gravis
- Febrile illness NYD
- Pneumonitis
- Sarcoidosis x 2
- Hepatitis (requiring MMF)
- Erosive esophagitis/gastritis
- Colitis (requiring infliximab)
- Protein-losing enteropathy
- *Psychosis - unclear etiology on combination immunotherapy*

POLL – How familiar are you with immunotherapy?

1. Very familiar
2. Somewhat familiar
3. Neutral
4. Somewhat unfamiliar
5. Not familiar at all

POLL – Have you managed/seen any patients on immunotherapy?

1. Yes – more than 10
2. Yes – 1-10
3. Unsure
4. No

Case 1 – Ms. AS

- ID – 74 year old woman with metastatic melanoma
- PMHx – none
- History of Presenting Illness:
  - 1991 – Cutaneous R shoulder melanoma treated with excision
  - Well until screening mammogram in 2014 showed mass in L breast that was biopsied & found to be melanoma
  - July 2014 - PET showed involvement of R arm, cardiophrenic LNs, multiple abdominal LNs, sacrum & R tibial plateau
  - *Options* - Dacarbazine chemotherapy vs BRAF inhibitor if BRAF mutation identified. Ipiliumumab available after progression on dacarbazine.

Case 1 – Ms. AS

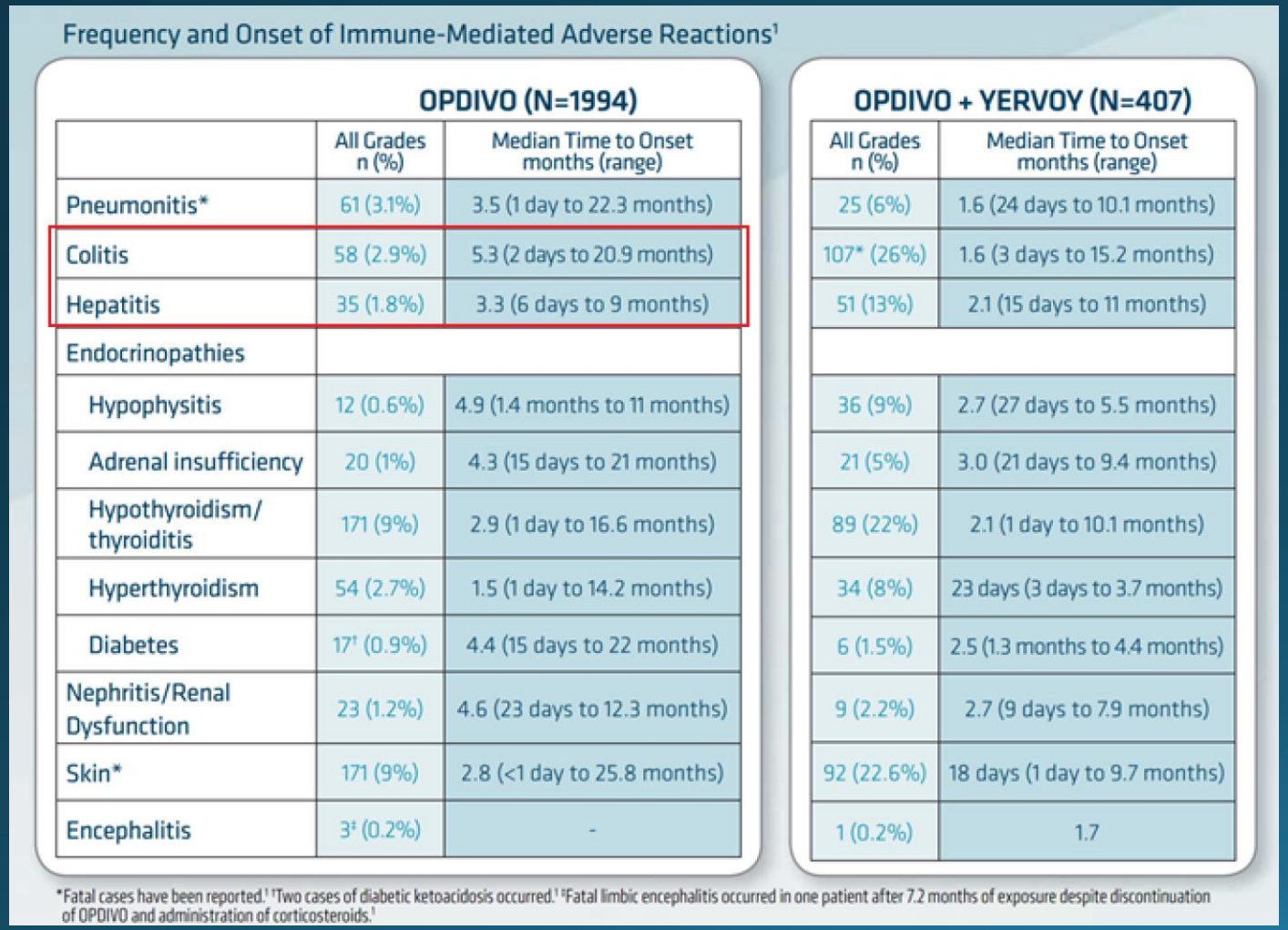
- BUT BRAF mutation neg so started dacarbazine Sept 2014
- 1 cycle of dacarbazine complicated by neutropenia so switched to ipilimumab Oct 2014
- 3 cycles that were well tolerated but then diarrhea (6-8x per day) Dec 2014
  - Started on prednisone 75mg x 10 days (1mg/kg) then dropped to 50mg daily x 2 weeks however worsening with decrease in steroids requiring admission Jan 2015
  - Had flex sig showing mild inflammation & hydrocortisone 100mg IV initiated (no need for infliximab as per GI)
  - Stepped down to oral steroids and fully recovered by Feb 2015

Gastrointestinal irAE

- Important because more grade 3/4 toxicity and may lead to admission
- Terminology of AE:
  - *Diarrhea* – frequent & watery bowel movements
  - *Colitis* – inflammation of the colon
  - *Enteritis* – inflammation of the small bowel
  - *Enterocolitis* – inflammation of the small & large bowel
  - *Hepatitis* – inflammation of the liver
- Any '*itis*' → esophagitis, gastritis, enteritis, colitis, pancreatitis, hepatitis
- GI irAEs can wax and wane (especially in colitis/hepatitis)
- Prompt identification and management essential!

Weber JS, et al. *The Oncologist*. 2016; 21:1230-40.
U.S.D.o.H.a.H. CTCAE Version 4.0, 2009.

Frequency and Timing



Frequency and Onset of Immune-Mediated Adverse Reactions[1]

	OPDIVO (N=1994)		OPDIVO + YERVOY (N=407)	
	All Grades n (%)	Median Time to Onset months (range)	All Grades n (%)	Median Time to Onset months (range)
Pneumonitis*	61 (3.1%)	3.5 (1 day to 22.3 months)	25 (6%)	1.6 (24 days to 10.1 months)
Colitis	58 (2.9%)	5.3 (2 days to 20.9 months)	107* (26%)	1.6 (3 days to 15.2 months)
Hepatitis	35 (1.8%)	3.3 (6 days to 9 months)	51 (13%)	2.1 (15 days to 11 months)
Endocrinopathies				
Hypophysitis	12 (0.6%)	4.9 (1.4 months to 11 months)	36 (9%)	2.7 (27 days to 5.5 months)
Adrenal insufficiency	20 (1%)	4.3 (15 days to 21 months)	21 (5%)	3.0 (21 days to 9.4 months)
Hypothyroidism/ thyroiditis	171 (9%)	2.9 (1 day to 16.6 months)	89 (22%)	2.1 (1 day to 10.1 months)
Hyperthyroidism	54 (2.7%)	1.5 (1 day to 14.2 months)	34 (8%)	23 days (3 days to 3.7 months)
Diabetes	17† (0.9%)	4.4 (15 days to 22 months)	6 (1.5%)	2.5 (1.3 months to 4.4 months)
Nephritis/Renal Dysfunction	23 (1.2%)	4.6 (23 days to 12.3 months)	9 (2.2%)	2.7 (9 days to 7.9 months)
Skin*	171 (9%)	2.8 (<1 day to 25.8 months)	92 (22.6%)	18 days (1 day to 9.7 months)
Encephalitis	3‡ (0.2%)	-	1 (0.2%)	1.7

*Fatal cases have been reported.[1] †Two cases of diabetic ketoacidosis occurred.[1] ‡Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids.[1]

Source: OPDIVO Adverse Reactions Management Guide. BMS.

Immune-related Adverse Events

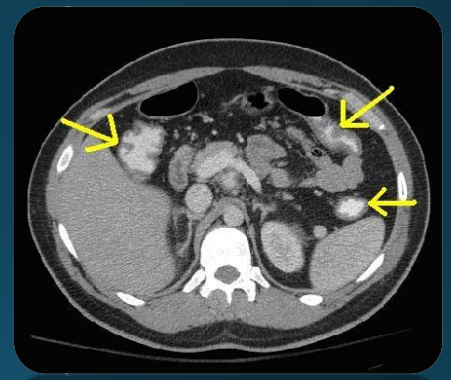
Table 1. Incidence of treatment-related AEs of interest associated with immune checkpoint inhibitors

	Patients reporting event, %							
	NIVO[a,b]		NIVO + IPI[a,c]		IPI[a,d]		Pembro[e,f]	
AE	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3-5
Pruritus	18.8	0	33.2	1.9	35.4	0.3	14.1	0
Rash	25.9	0.6	40.3	4.8	32.8	1.9	13.4	0
Diarrhea	19.2	2.2	44.1	9.3	33.1	6.1	14.4	1.1
Colitis	1.3	0.6	11.8	7.7	11.6	8.7	2.9	1.8
Elevated ALT	3.8	1.3	17.6	8.3	3.9	1.6	1.4	0.4
Elevated AST	3.8	1.0	15.3	6.1	3.5	0.6	2.2	0.4
Hypothyroidism	8.6	0	15.0	0.3	4.2	0	7.6	0
Hypophysitis	0	0	0.3	0	0	0	0.4	0.4
Pneumonitis	1.3	0.3	6.4	1.0	1.6	0.3	1.8[g]	0.4[g]

Source: Weber JS, et al. *The Oncologist*. 2016; 21:1230-40.

Colitis Work Up

- History, physical
  - R/O other causes common in cancer patients → medication–related, disease progression, *C. difficile*, other bacterial/viral pathogens
- Bloodwork including CRP, LEs
- Stool culture , *C. difficile* toxin
- Imaging – AXR, CT
- Colonoscopy & biopsy if persistent ≥ grade 2 diarrhea



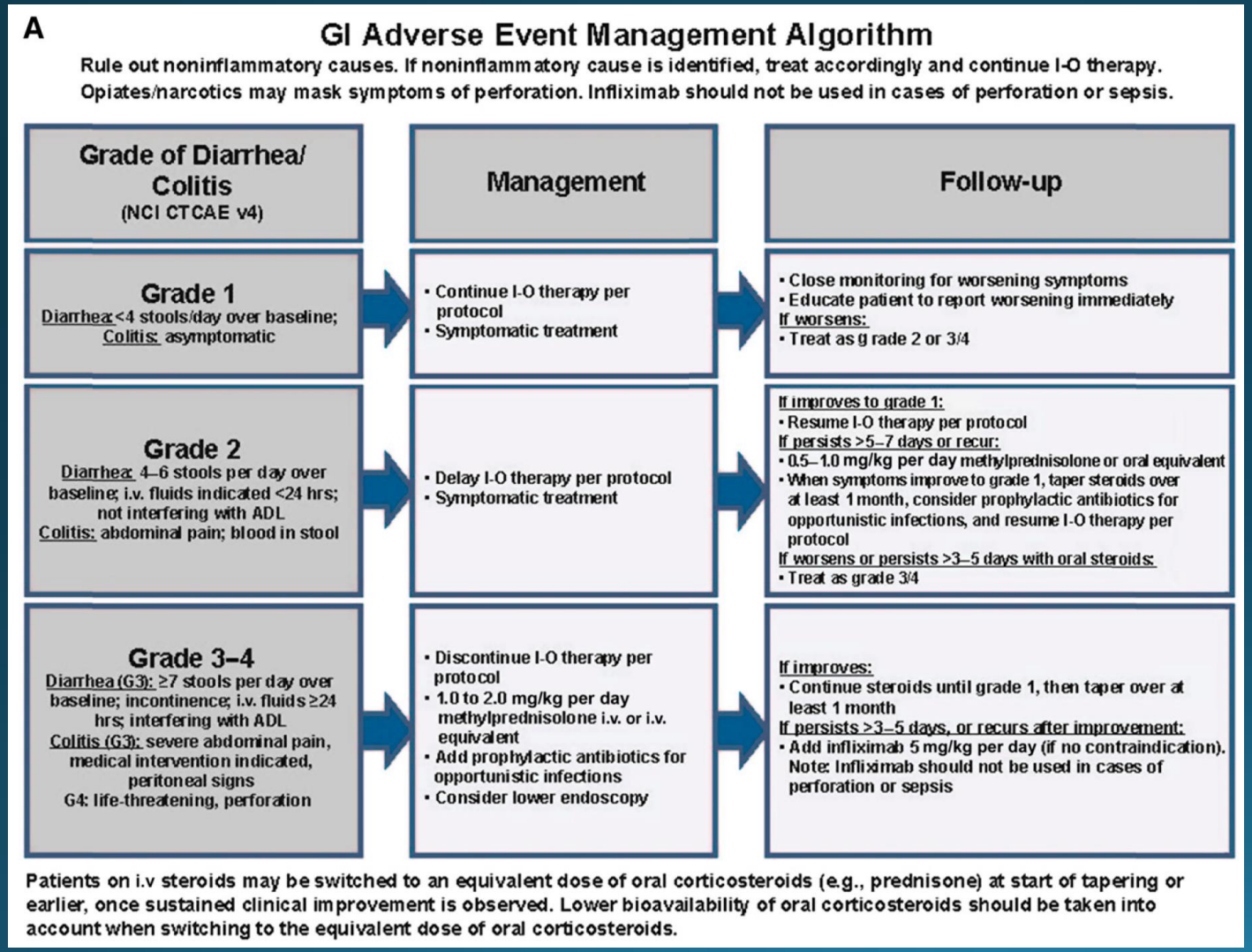
Eigentler TK, et al. *Cancer Treatment Reviews.* 2016; 45:7-18.

Colonoscopy Findings

(A) Colonoscopic view of bowel edema and ulceration in the descending colon of patient 29, who experienced autoimmune colitis.
(B) Histopathologic analyses revealed focal active colitis (left panel) with crypt destruction, loss of goblet cells, and neutrophilic infiltrates in the crypt epithelium (right panel) (original magnification: left panel, ×20; right panel, ×60).

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

Diarrhea/Colitis Management



A

GI Adverse Event Management Algorithm

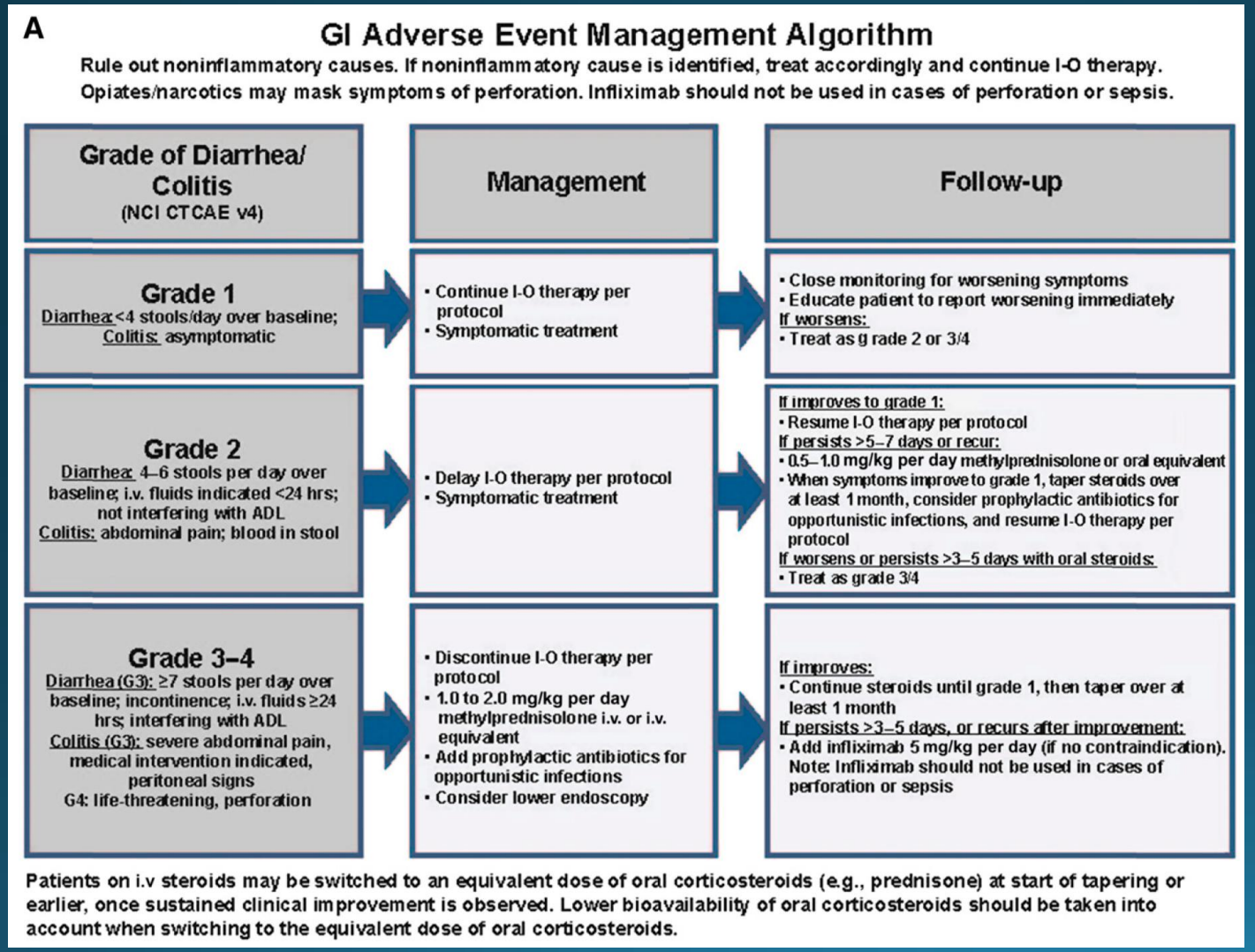
Rule out noninflammatory causes. If noninflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as grade 2 or 3/4
Grade 2 Diarrhea: 4–6 stools per day over baseline; i.v. fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists >5–7 days or recur: • 0.5–1.0 mg/kg per day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol If worsens or persists >3–5 days with oral steroids: • Treat as grade 3/4
Grade 3–4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; i.v. fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg per day methylprednisolone i.v. or i.v. equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists >3–5 days, or recurs after improvement: • Add infliximab 5 mg/kg per day (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on i.v steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Weber JS, et al. *The Oncologist*. 2016; 21:1230-40.

Diarrhea/Colitis Management



A

GI Adverse Event Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as grade 2 or 3/4
Grade 2 Diarrhea: 4–6 stools per day over baseline; i.v. fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists >5–7 days or recur: • 0.5–1.0 mg/kg per day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol If worsens or persists >3–5 days with oral steroids: • Treat as grade 3/4
Grade 3–4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; i.v. fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg per day methylprednisolone i.v. or i.v. equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists >3–5 days, or recurs after improvement: • Add infliximab 5 mg/kg per day (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on i.v steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

If ongoing → may need other immunosuppressants such as tacrolimus or mycophenolate mofetil in steroid & infliximab refractory. Colectomy may be needed (involve surgery early).

Weber JS, et al. *The Oncologist*. 2016; 21:1230-40.
Spain L, Diem S, Larkin J. *Cancer Treatment Reviews*. 2016; 44:51-60.

Enterocolitis

Monitoring
Diarrhea, abdominal pain, mucus or blood in stools- with or without fever, ileus, peritoneal signs

Grade 1
Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis

- Physician notified of assessment
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Antidiarrheal treatment
- Book nursing follow up call for next business day and/or create care plan if BC Cancer nurse unable to follow up

Grade 2
Diarrhea of 4 to 6 stools per day over baseline, IV fluids less than 24 h , normal daily activities, abdominal pain, mucus or blood in stool.

- Physician notified and collaborative symptom management initiated
- **Withhold checkpoint inhibitors**
- Antidiarrheal treatment
- If persists beyond 3-5 days* or recur, start predniSONE 0.5 to 1 mg/kg/day PO
- Patient education of steroid use
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

* 1-2 days if combination check-point inhibitors

Improvement to Grade 1 or less
- Resume checkpoint inhibitors
- If steroid used, taper over at least 1 month BEFORE resuming checkpoint inhibitors
- Consider prophylactic antibiotics for opportunistic infections
- Patient education of steroid tapering per physician order

Grade 3 or 4
Grade 3: diarrhea of 7 or more stools per day over baseline, incontinence, IV fluids for 24 h or more, impaired daily activities; colitis with severe abdominal pain, requiring medical interventions, peritoneal signs of bowel perforation
Grade 4: life-threatening colitis, perforation

- Physician notified and collaborative symptom management initiated
- **Withhold (if Grade 3) or discontinue (if Grade 4 or persistent Grade 3) checkpoint inhibitors**
- Gastroenterology consultation
- Rule out bowel perforation; if bowel perforation is present, DO NOT administer corticosteroids
- Consider endoscopic evaluation
- predniSONE 1 to 2 mg/kg/day PO
- Prophylactic antibiotics for opportunistic infections
- Patient education of steroid use
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

Improvement to Grade 1 or less
- Taper predniSONE over at least 1 month before resuming checkpoint inhibitors
- Patient education of steroid tapering per physician order

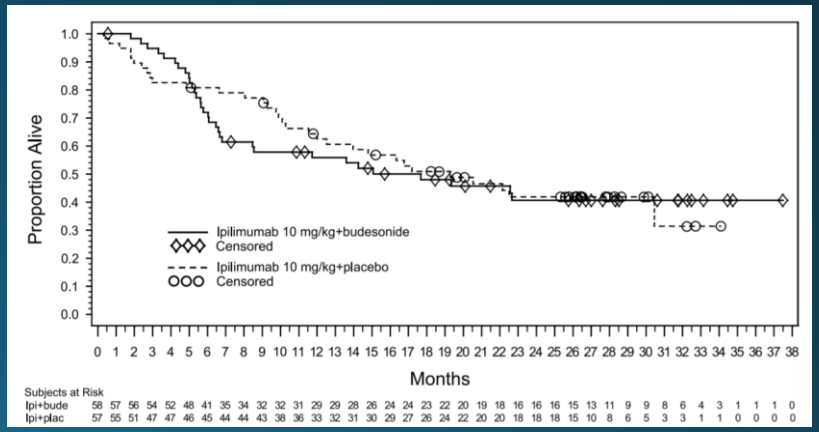
If no response within 5 days or recur
- Consider treatment with inFLIXimab; if refractory to inFLIXimab, consider mycophenolate
- Continually evaluate for evidence of gastrointestinal perforation or peritonitis
- Consider repeat endoscopy

Prophylaxis for Diarrhea?

- 115 stage III/IV melanoma patients
  - Ipilimumab + budesonide vs ipilimumab + placebo
    - Q3 weeks x 4 doses with daily budesonide (9mg daily) which was tapered down by week 16; maintenance ipilimumab at weeks 24, 26, 48 & q 12 weeks thereafter

Table 2. Rate of grade ≥2 diarrhea in patients given ipilimumab with or without prophylactic budesonide

Patients with grade ≥2 diarrhea*	Ipilimumab + budesonide (group A; *n* = 58)	Ipilimumab + placebo (group B; *n* = 57)	Total (*N* = 115)
Grade 2, *n* (%)	11 (19.0)	10 (17.5)	21 (18.3)
Grade 3, *n* (%)	6 (10.3)	10 (17.5)	16 (13.9)
Grade 4, *n* (%)	2 (3.4)	0	2 (1.7)
Grade ≥2 diarrhea rate, *n* (%)	19/58 (32.7)	20/57 (35.0)	39/115 (33.9)
95% CI†	21.0-46.3	22.9-48.8	—
Difference in rate of grade ≥2 diarrhea, %‡	2.3		
95% CI§	-15.2 to 19.9		



Weber J, et al. *Cancer Therapy: Clinical.* 2009; 15(17):5591-8.

Colitis & Checkpoint Inhibitors

- Immune-related diarrhea/colitis less frequent with PD-1 inhibitors vs anti-CTLA-4 inhibitors
  - Diarrhea 14-19% vs 33%; colitis 1-3% vs 12%
- Can safely treat with anti-PD1 post anti-CTLA4 related GI toxicity
- Resolution of diarrhea occurred in ~90% of patients with median time to resolution of 1-2 weeks (with nivolumab)

Eigentler TK, et al. *Cancer Treatment Reviews*. 2016; 45:7-18.
Weber JS, et al. *The Oncologist*. 2016; 21:1230-40.

Back to our case…Ms. AS

- Diarrhea resolved
- BUT biochemical progression Feb 2015 (LDH 983 → 2047)
- CT showing new liver lesions & calvarial, L-spine lesions but other lesions stable or improved
- Started nivolumab Apr 2015
  - Grade 2 diarrhea off/on
  - LDH normalized, CT showing mixed response after 6 cycles
  - Cycle 7 delayed for diarrhea & upper abdominal pain in July 2015
    - LEs increased (AST, ALT 2x ULN; ALP slightly elevated, bilirubin N, LDH N)
    - Repeat CT showing mixed response & distended gallbladder (?acalculus cholecysitits)

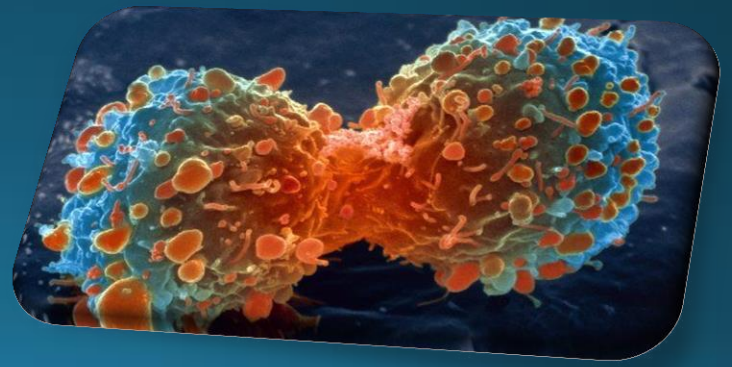
Case 1 – Ms. AS

Bilirubin Panel Bilirubin, Total	**20**	**A**	<20	umol/L
Albumin	37		35-50	g/L
Alanine Aminotransferase	**573**	**A**	<50	U/L
Aspartate Aminotransferase	**306**	**A**	<35	U/L
Alkaline Phosphatase	**628**	**A**	42-116	U/L
Gamma Glutamyl Transferase	**878**	**A**	<59	U/L
Lactate Dehydrogenase	**512**	**A**	260-494	U/L

- VGH ED⟶ general surgery ⟶ GI
  - Abdominal ultrasound showed no evidence of biliary dilatation or other abnormalities
  - Admitted under general surgery for presumed acalculous cholecystitis
  - General surgery did HIDA scan which was negative
  - GI involved given ongoing elevation in liver enzymes for further work up
  - Bloodwork for hepatitis including viral & autoimmune causes was negative
  - Upper endoscopy showing mild gastritis (not explaining extent of abdominal pain)

Case 1 – Ms. AS

- After ruling out other causes, diagnosed with drug-induced hepatitis secondary to nivolumab
  - Nivolumab permanently discontinued (after completing 6 cycles) and prednisone initiated with slow taper (40mg daily initially)
- Resolution over time with LEs followed weekly
- Surveillance…



Immune-related Adverse Events

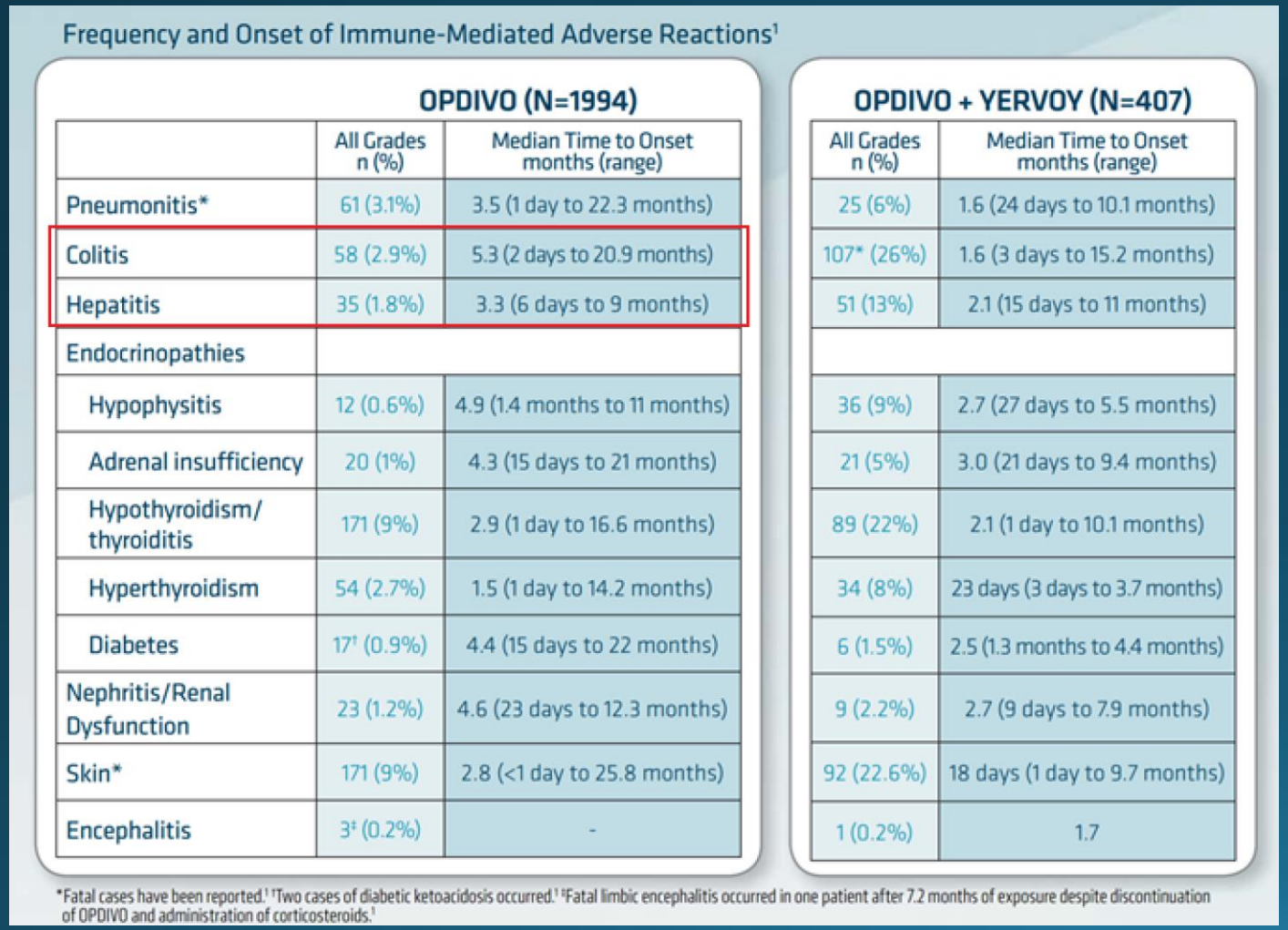
Table 1. Incidence of treatment-related AEs of interest associated with immune checkpoint inhibitors

	Patients reporting event, %							
	NIVO[a,b]		NIVO + IPI[a,c]		IPI[a,d]		Pembro[e,f]	
AE	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3-5
Pruritus	18.8	0	33.2	1.9	35.4	0.3	14.1	0
Rash	25.9	0.6	40.3	4.8	32.8	1.9	13.4	0
Diarrhea	19.2	2.2	44.1	9.3	33.1	6.1	14.4	1.1
Colitis	1.3	0.6	11.8	7.7	11.6	8.7	2.9	1.8
Elevated ALT	3.8	1.3	17.6	8.3	3.9	1.6	1.4	0.4
Elevated AST	3.8	1.0	15.3	6.1	3.5	0.6	2.2	0.4
Hypothyroidism	8.6	0	15.0	0.3	4.2	0	7.6	0
Hypophysitis	0	0	0.3	0	0	0	0.4	0.4
Pneumonitis	1.3	0.3	6.4	1.0	1.6	0.3	1.8[g]	0.4[g]

[a]Based on data from the phase 3 study CheckMate 067 [6]. Incidence of hypophysitis and pneumonitis is based on unpublished data from CheckMate 067.
[b]One treatment-related death (neutropenia) was reported.
[c]No treatment-related deaths were reported.
[d]One treatment-related death (cardiac arrest) was reported.
[e]Based on data from the phase 3 study KEYNOTE-006 every 3 week dosing group [4].
[f]No treatment-related deaths were reported.
[g]AE of special interest, regardless of attribution of study drug.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IPI, ipilimumab; NIVO, nivolumab; Pembro, pembrolizumab.

Source: Weber JS, et al. *The Oncologist*. 2016; 21:1230-40.

Frequency and Timing



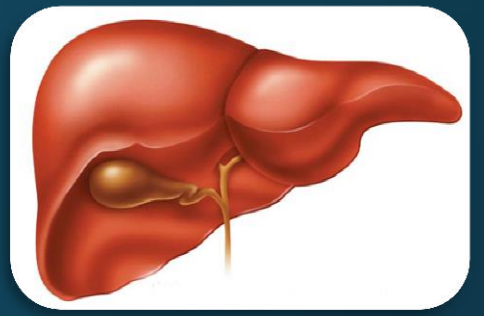
Frequency and Onset of Immune-Mediated Adverse Reactions[1]

	OPDIVO (N=1994)		OPDIVO + YERVOY (N=407)	
	All Grades n (%)	Median Time to Onset months (range)	All Grades n (%)	Median Time to Onset months (range)
Pneumonitis*	61 (3.1%)	3.5 (1 day to 22.3 months)	25 (6%)	1.6 (24 days to 10.1 months)
Colitis	58 (2.9%)	5.3 (2 days to 20.9 months)	107* (26%)	1.6 (3 days to 15.2 months)
Hepatitis	35 (1.8%)	3.3 (6 days to 9 months)	51 (13%)	2.1 (15 days to 11 months)
Endocrinopathies				
Hypophysitis	12 (0.6%)	4.9 (1.4 months to 11 months)	36 (9%)	2.7 (27 days to 5.5 months)
Adrenal insufficiency	20 (1%)	4.3 (15 days to 21 months)	21 (5%)	3.0 (21 days to 9.4 months)
Hypothyroidism/ thyroiditis	171 (9%)	2.9 (1 day to 16.6 months)	89 (22%)	2.1 (1 day to 10.1 months)
Hyperthyroidism	54 (2.7%)	1.5 (1 day to 14.2 months)	34 (8%)	23 days (3 days to 3.7 months)
Diabetes	17† (0.9%)	4.4 (15 days to 22 months)	6 (1.5%)	2.5 (1.3 months to 4.4 months)
Nephritis/Renal Dysfunction	23 (1.2%)	4.6 (23 days to 12.3 months)	9 (2.2%)	2.7 (9 days to 7.9 months)
Skin*	171 (9%)	2.8 (<1 day to 25.8 months)	92 (22.6%)	18 days (1 day to 9.7 months)
Encephalitis	3‡ (0.2%)	-	1 (0.2%)	1.7

*Fatal cases have been reported.[1] †Two cases of diabetic ketoacidosis occurred.[1] ‡Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids.[1]

Source: OPDIVO Adverse Reactions Management Guide. BMS.

Hepatitis



- History, physical
  - Often asymptomatic elevation of AST, ALT (rarely bilirubin) but can have associated fever, malaise, nausea; fulminant hepatitis has been reported with ipilimumab
  - Most common onset between 8-14 weeks
  - R/O other etiology – viral, medication, alcohol, disease progression
- Labs – LEs, bilirubin, albumin, INR/PTT, glucose, hepatitis B/C serology, autoimmune W/U
- Imaging – CT scan to R/O disease progression, abdominal U/S
- Consult hepatology +/- biopsy

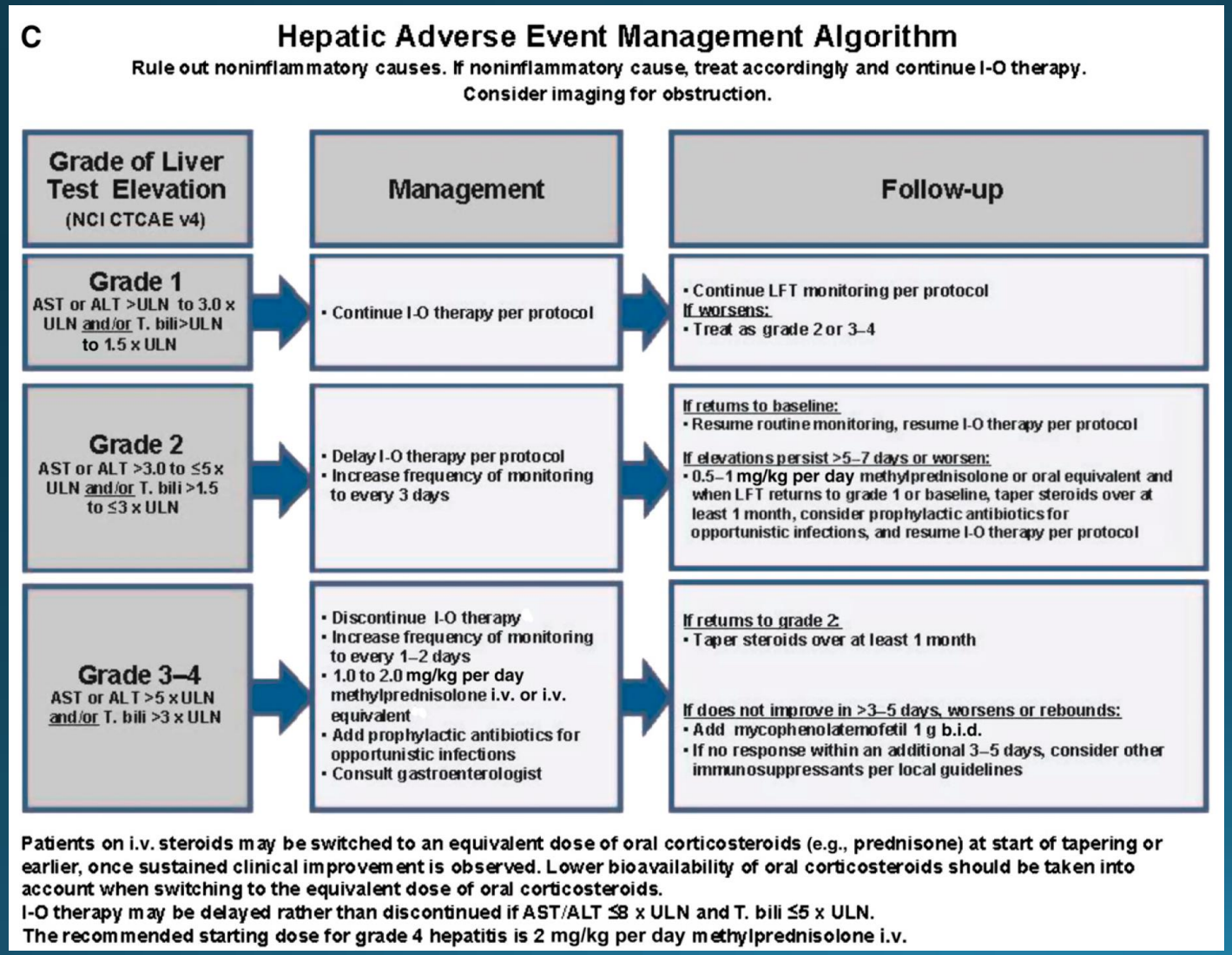
Spain L, Diem S, Larkin J. *Cancer Treatment Reviews*. 2016; 44:51-60.

Hepatitis

- More common with nivo + ipi combo vs single agent PD1 (14% vs 1-2%)
- Generally reversible and able to be retreated however some may need permanent discontinuation
- Use with caution in patients with significant liver disease or elevated serum transaminases
  - Assess LEs at baseline & prior to each cycle

Spain L, Diem S, Larkin J. *Cancer Treatment Reviews*. 2016; 44:51-60.

Hepatitis



C **Hepatic Adverse Event Management Algorithm**

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT >ULN to 3.0 x ULN and/or T. bili>ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as grade 2 or 3–4
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or T. bili >1.5 to ≤3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: • Resume routine monitoring, resume I-O therapy per protocol If elevations persist >5–7 days or worsen: • 0.5–1 mg/kg per day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3–4 AST or ALT >5 x ULN and/or T. bili >3 x ULN	• Discontinue I-O therapy • Increase frequency of monitoring to every 1–2 days • 1.0 to 2.0 mg/kg per day methylprednisolone i.v. or i.v. equivalent • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3–5 days, worsens or rebounds: • Add mycophenolatemofetil 1 g b.i.d. • If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines

Patients on i.v. steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
I-O therapy may be delayed rather than discontinued if AST/ALT ≤8 x ULN and T. bili ≤5 x ULN.
The recommended starting dose for grade 4 hepatitis is 2 mg/kg per day methylprednisolone i.v.

Weber JS, et al. *The Oncologist*. 2016; 21:1230-40

Case 1 – Ms. AS

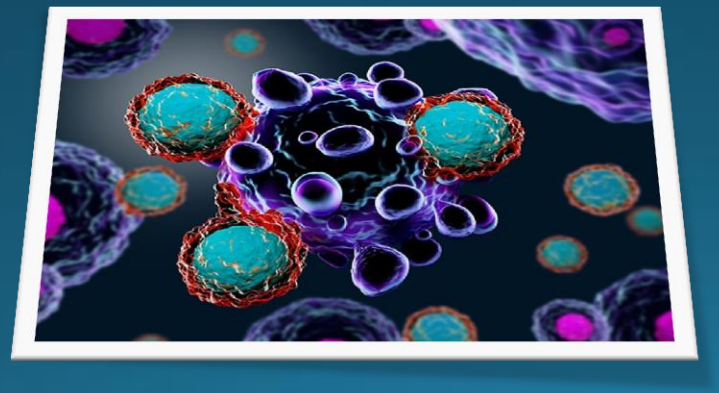
- LDH increasing and CT showing evidence of disease progression in Nov 2015
- Progression of symptoms with pain
- LEs improved & off steroids
- Chemotherapy offered but patient declined. Offered pembrolizumab which she started…

Case 1 – Ms. AS

- 3 cycles of pembrolizumab (LDH 4401 ⟶ 1830)
- LEs remaining normal but progression of disease
- Pembrolizumab stopped
- Patient passed away

Takeaway Points

- Patient had toxicity but early recognition and management allowed to get treated for adverse events and continue being treated for melanoma
- She was able to be on all three available checkpoint inhibitors successfully despite previous toxicity



Case 2 – Mr. JT

- ID – 56 year old man with metastatic melanoma
- PMHx – otherwise healthy
- History of Presenting Illness:
  - 1996 - Stage 2a (pT3a) cutaneous melanoma of the right arm, treated with excision
  - 2010 – Relapsed with right axillary mass (biopsy confirmed), managed with right ALND and adjuvant IFN
  - 2013 – Recurrence with metastatic disease
    - PET scan: FDG-avid deposits in liver and left biceps muscle and FDG-avid portocaval LAD
    - US guided biopsy of liver: metastatic melanoma, BRAF wild-type

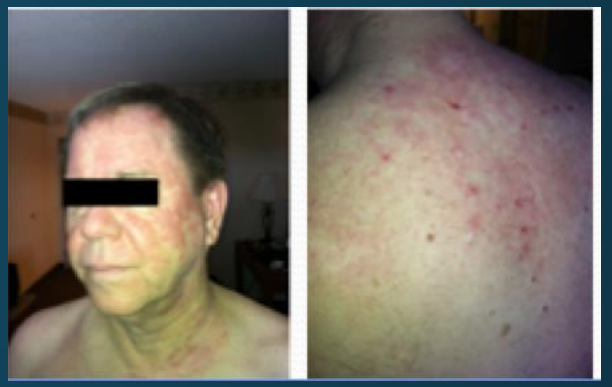
Case 2 – Mr. JT

- Started on ipilimumab 3mg/kg IV q3 weeks (given for up to four cycles)

- Developed a rash one week after cycle 1
  - Pruritic erythematous, scaly eruption affecting the upper torso

Skin Toxicity

- One of the most common immune-related adverse events seen with checkpoint inhibitors

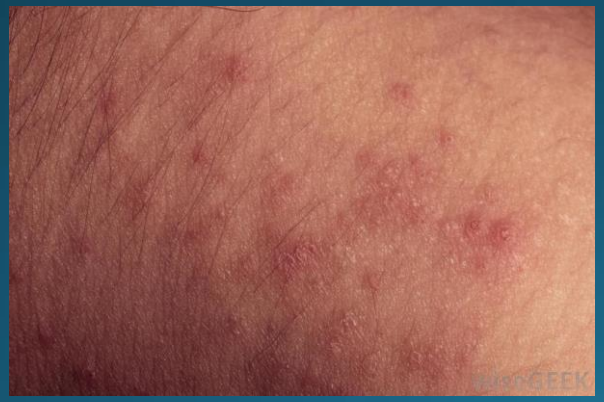


Source: BMS Ipilimumab product monograph

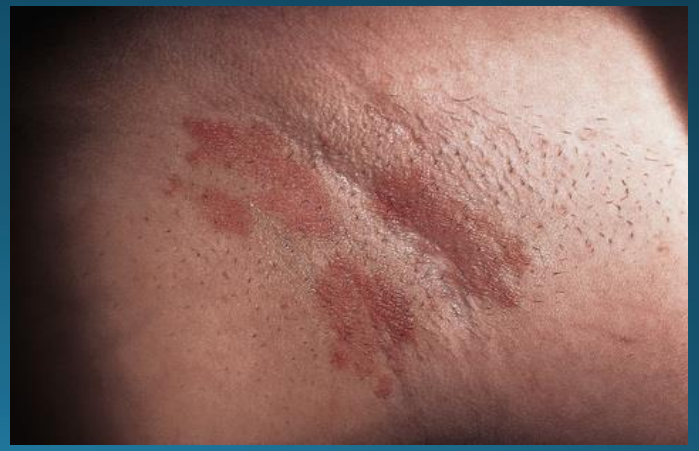
Incidence	>20%
Manifestations	Rash typically focal with a maculopapular appearance occurring on the trunk, back or extremities
Management	Symptomatic management • Topical corticosteroids for rashes • Anti-histamines for pruritus
Note	Some skin reactions can be severe/life-threatening and require hospitalization

Skin Toxicity

- Ipilimumab:
  - Dermatitis, vitiligo, Grover's disease, dermatomyositis
  - Timing: typically starts within weeks of treatment starting
- PD-1 inhibitors:
  - Lichenoid dermatitis, pruritus, vitiligo, inverse psoriasiform eruption, bullous pemphigoid, sarcoidosis (cutaneous nodules)
  - Timing: usually takes longer to onset, and can occur anytime in treatment course

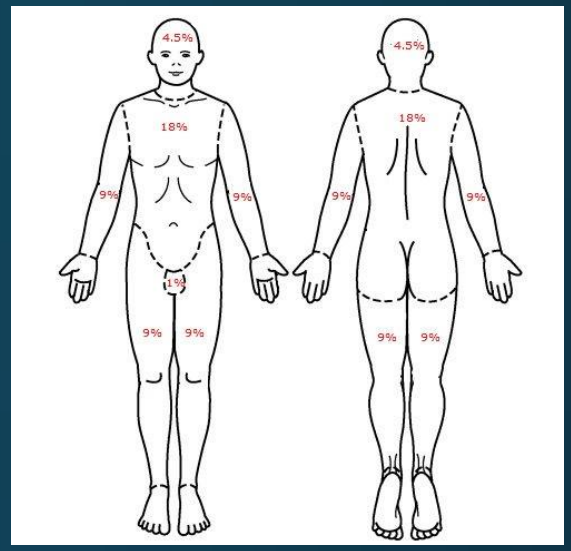


Lichenoid dermatitis



Inverse psoriasiform rash

Skin Toxicity



Grade 1-2 (Covering ≤ 30% of BSA)

Management:

- Symptomatic therapy (e.g. antihistamines, topical steroid creams)
- Continue immunotherapy

If persists >1-2 wks:

- Consider skin biopsy
- Delay immunotherapy
- Consider 0.5-1mg/kg/day prednisone or equivalent.

Grade 3-4 (Covering > 30% of BSA or life-threatening)

Management:

- Delay or discontinue immunotherapy
- 1mg/kg/day Prednisone (or equivalent)
- Consider skin biopsy, dermatology consult

If improves to Grade 1:

- Taper steroids over at least 1 month
- Consider resuming immunotherapy

BSA: Body Surface Area

Case 2 - Mr JT

- Seen by dermatologist → ipilimumab-related rash
- Managed with steroid cream with good effect
  - Rx: betamethasone valerate 0.1% cream BID
- Received 4 cycles of ipilimumab, then observation
- Several months after completing ipilimumab, evidence of progression on CT scan

Case 2 - Mr JT

- Started on PD1 inhibitor pembrolizumab
- Issues with recurrent AP and N/V, but CT scan showed regression in metastases after just 1 cycle of pembrolizumab
- Received cycles 2-9
- Worsening fatigue, weight loss, ongoing N/V
- Repeat CT Oct 2014 showed further reduction in tumor burden

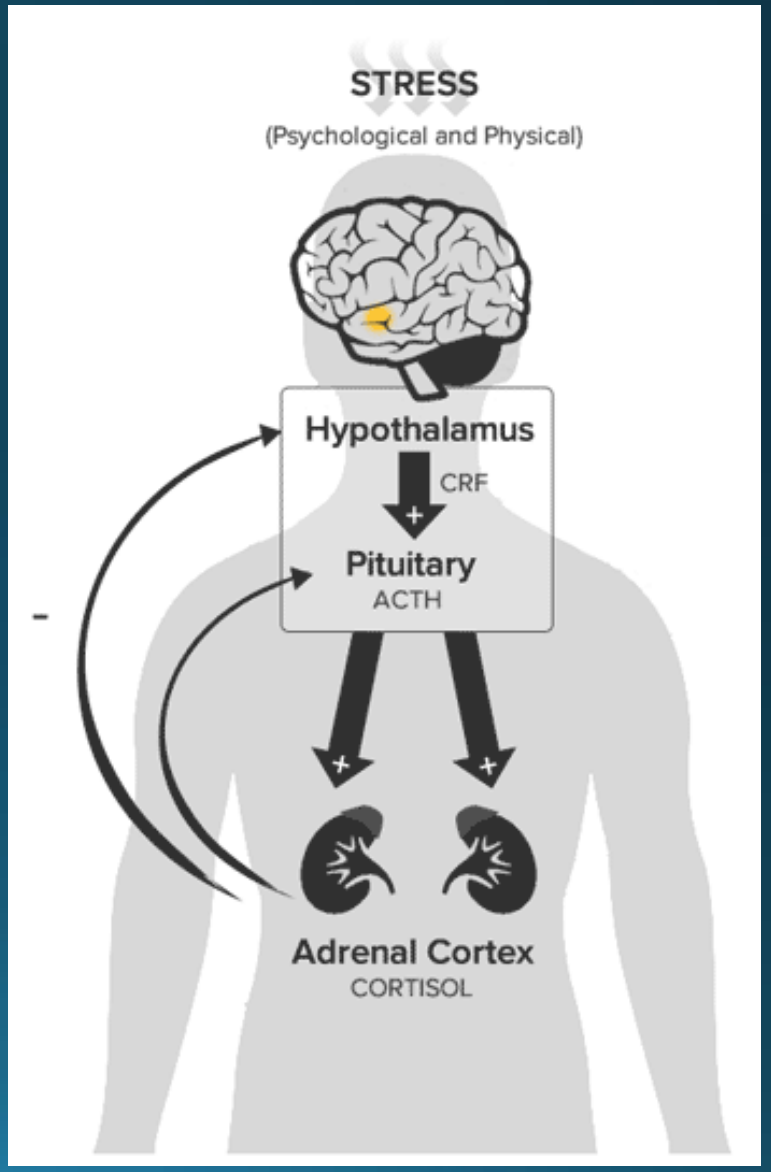
Case 2 - Mr JT

- ??immune-related endocrine toxicity
- Serum cortisol 93 (120-620)
- ACTH undetectable

→ Central adrenal insufficiency

Endocrine Immune-Related Adverse Events - Adrenal Insufficiency

- Low levels of cortisol secreted by the adrenal glands
  - 1° Adrenal insufficiency – failure of adrenal glands
    - Low cortisol, High ACTH (hyperpigmentation, electrolyte abnormalities)
  - 2° Adrenal insufficiency – failure of the pituitary gland
    - Low cortisol, Low ACTH
- Presents with non-specific, insidious symptoms
  - Fatigue, anorexia, weight loss, GI symptoms, myalgias
- Adrenal crisis
  - Life-threatening medical emergency
  - Shock, delirium, hypoglycemia, electrolyte abnormalities, GI distress
  - Typically precipitated by abrupt withdrawal of exogenous glucocorticoids, or acute illness/stress that body isn't able to respond to by increasing cortisol production



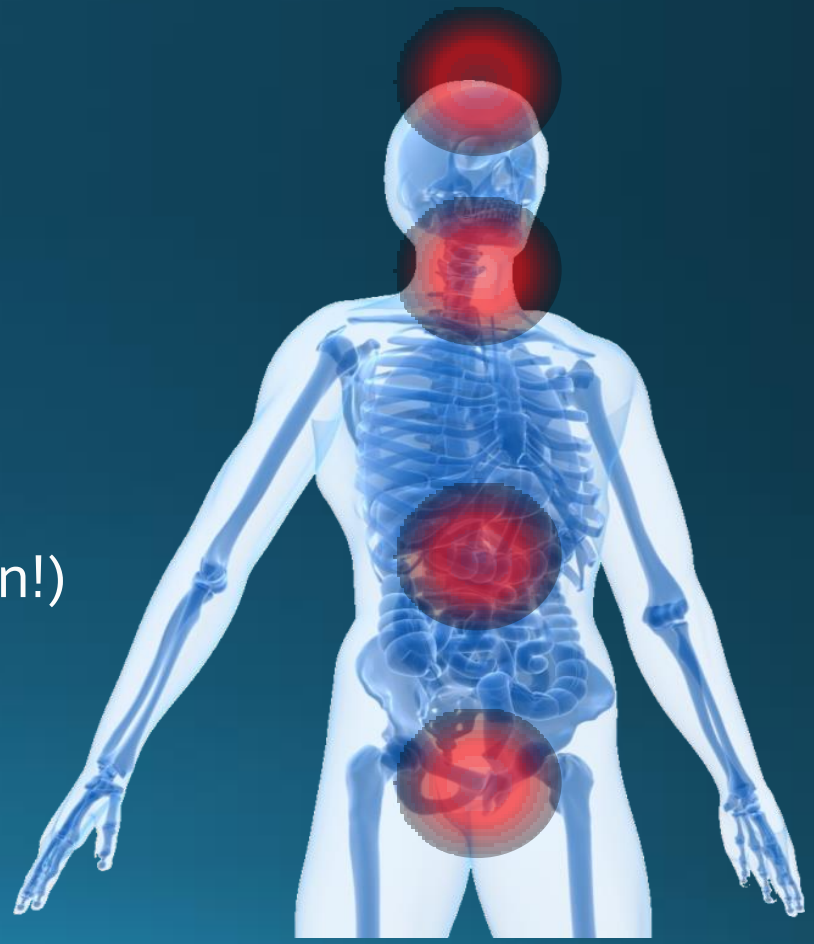
Adrenal Insufficiency

- **Diagnosis:**
  - AM cortisol
    - >415 nmol/L – normal
    - <275 nmol/L – Sn 62%, Sp 77%
    - <138 nmol/L – Sn 36%, Sp 99%
  - ACTH stimulation test
    - Cosyntropin 250mcg IV, measure cortisol at 0, 30, 60 mins
    - Normal: cortisol level doubles to an absolute value > 500 nmol/L
- **Treatment:**
  - Hydrocortisone, dosed to mimic endogenous cortisol secretion (20mg qAM, 10mg qPM)
  - Patient education important – 3x3 rule, Medic Alert

Baseline AM cortisol can be helpful

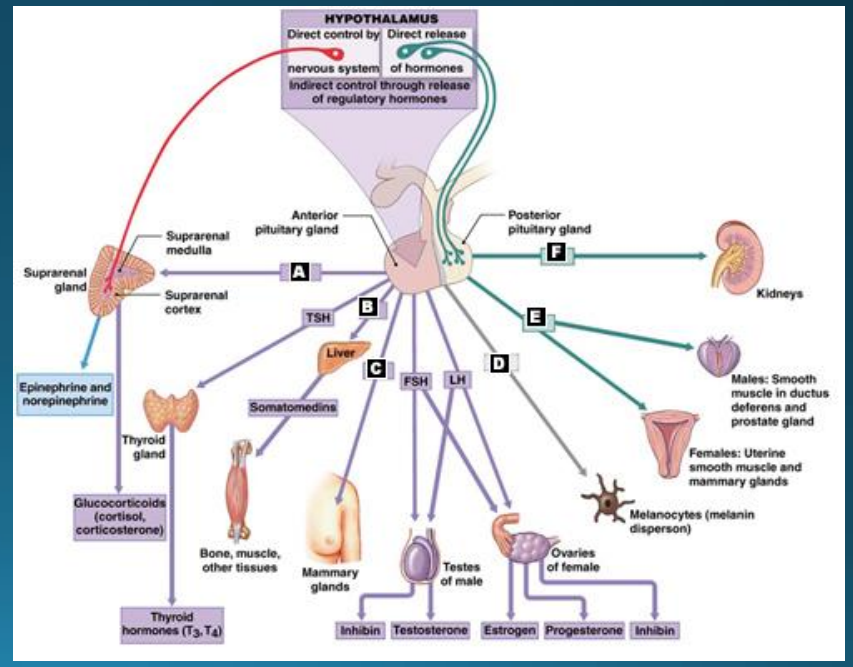
Endocrine irAEs

- Autoimmune endocrinopathies can affect any organ in the endocrine system
- This includes:
  - Pituitary gland
    - Hypophysitis
    - Adrenal insufficiency
  - Thyroid gland
    - Hypo or hyperthyroidism (VERY common!)



Hypophysitis

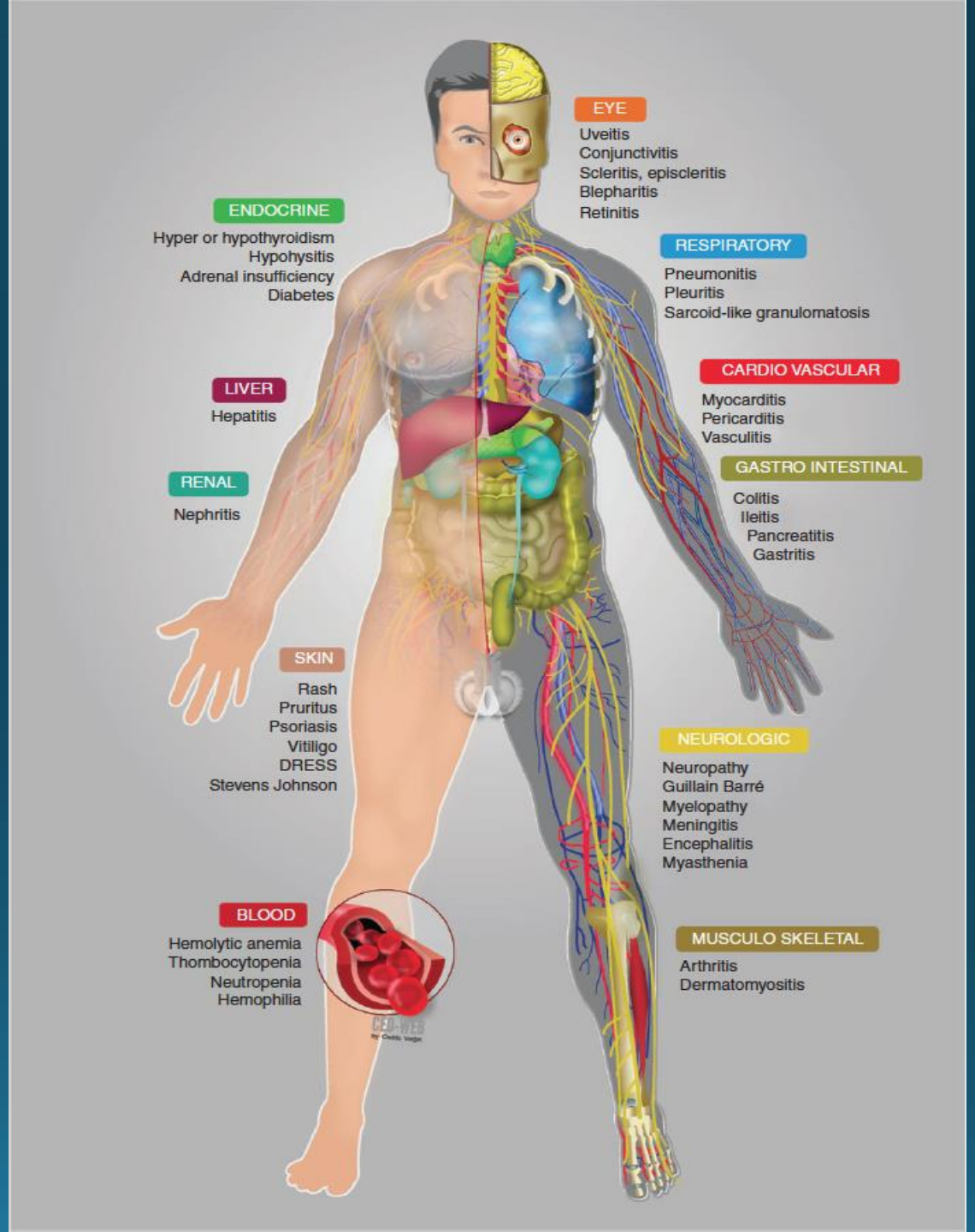
- Hypophysitis is a rare, yet serious complication of checkpoint inhibitors
- Inflammation of the pituitary gland
- Manifests clinically as adrenal insufficiency, hypothyroidism and hypogonadism
- Non-specific symptoms- clues: lethargy, N/V, headaches, visual change
- Diagnosed based on MRI showing pituitary swelling (CT can be normal)
- Need to check all pituitary hormones
  - LH, FSH, cortisol, IGF, free T3 and T4, testosterone
- Management:
  - Endocrinology referral
  - Systemic glucocorticoids – Prednisone 1mg/kg/day
    - +/- stress dose steroids if evidence of adrenal crisis
  - Hormone replacement
  - Long-term monitoring



Case 2 - Mr JT

- Endocrinology referral
- Started on Hydrocortisone
- Marked improvement in energy level and general well-being
- Other pituitary hormone levels checked – all within normal limits
- Remained on pembrolizumab for a total of 2 years

Immune-related Adverse Events



Source: Champiat et al. *Annals of Oncology*, 2016; 27: 559-574.

Baseline Assessment

Table 2. Recommended monitoring for patients on PD-1 inhibitors

Toxicity	Baseline testing	Suggested ongoing monitoring[a]
Endocrine	• TSH,T3, and T4 • No other baseline hormonal testing needed	• TSH every 4–6 weeks (every other dose) • No routine monitoring of other hormones needed
Hepatotoxicity	• LFTs • Hepatitis B surface antigen (HBsAg) • Hepatitis B surface antibody (anti-HBs) • Hepatitis B core antibody (anti-HBc) • Anti-HCV	• LFTs prior to each cycle
Pneumonitis	• Chest radiograph • High-resolution chest CT scan with and without injection of contrast	• Chest imaging every 4–6 weeks (every other dose) • If symptoms, resting and exertion pulse oximetry and high-resolution chest CT scan (consider spirometry with measurement of carbon monoxide-diffusing capacity)

[a]Immune-related adverse events' surveillance should be continued every 12 weeks up to 1 year after discontinuation of immunotherapy.
Abbreviations: CT, computed tomography; HCV, hepatitis C virus; LFTs, liver function tests; PD-1, programmed cell death protein-1; TSH, thyroid-stimulating hormone.

Source: O'Kane, GM et al. *The Oncologist*, 2016; 22:70-80.

Immune-related Adverse Events

Table 1. Incidence of treatment-related AEs of interest associated with immune checkpoint inhibitors

	Patients reporting event, %							
	NIVO[a,b]		NIVO + IPI[a,c]		IPI[a,d]		Pembro[e,f]	
AE	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3-5
Pruritus	18.8	0	33.2	1.9	35.4	0.3	14.1	0
Rash	25.9	0.6	40.3	4.8	32.8	1.9	13.4	0
Diarrhea	19.2	2.2	44.1	9.3	33.1	6.1	14.4	1.1
Colitis	1.3	0.6	11.8	7.7	11.6	8.7	2.9	1.8
Elevated ALT	3.8	1.3	17.6	8.3	3.9	1.6	1.4	0.4
Elevated AST	3.8	1.0	15.3	6.1	3.5	0.6	2.2	0.4
Hypothyroidism	8.6	0	15.0	0.3	4.2	0	7.6	0
Hypophysitis	0	0	0.3	0	0	0	0.4	0.4
Pneumonitis	1.3	0.3	6.4	1.0	1.6	0.3	1.8[g]	0.4[g]

Source: Weber JS, et al. The Oncologist. 2016; 21:1230-40.

Immunotherapy vs Chemotherapy

Table 2. Incidence and RR of summary toxicity endpoints, including 95% CI and number of trials in each analysis

Summary AE endpoints	No. of trials	PD-1/PD-L1 inhibitor incidence % (95% CI)	Chemotherapy incidence % (95% CI)	RR (95% CI)	*p* value
Any all-grade AEs	7	67.6 (64.2–70.8)	82.9 (78.9–86.2)	0.82 (0.76–0.88)	<.001
Any high-grade AEs	7	11.4 (9.9–13.1)	35.7 (26.0–46.8)	0.32 (0.22–0.45)	<.001
Treatment discontinuation	7	4.5 (3.5–5.7)	11.1 (8.5–14.3)	0.44 (0.33–0.57)	<.001
Treatment-related deaths	3	0.6 (0.3–1.1)	1.4 (0.7–2.5)	0.42 (0.16–1.13)	.09

Abbreviations: AE, adverse event; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; RR, relative risk.

Source: Nishijima, et al. The Oncologist. 2017. 22:470-479.

Ipilimumab (CTLA-4 inhibitor)

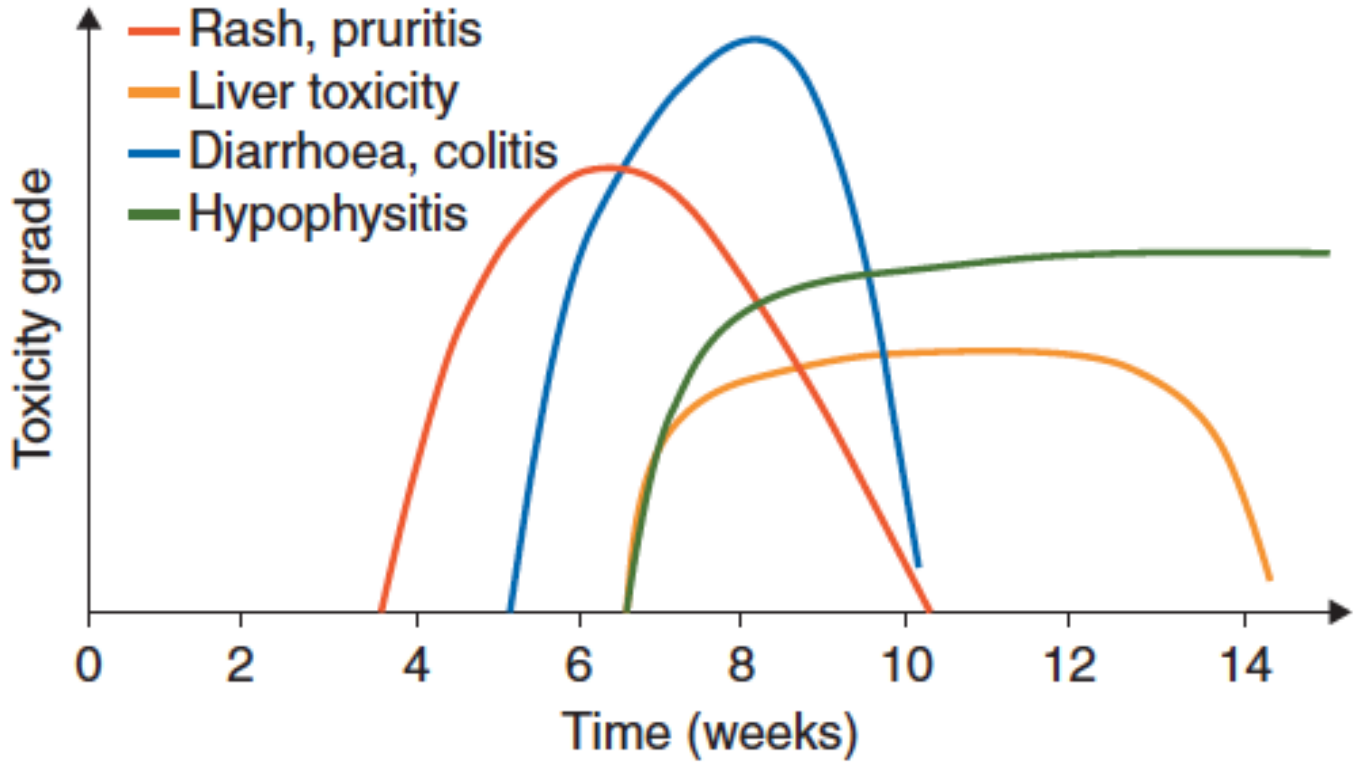
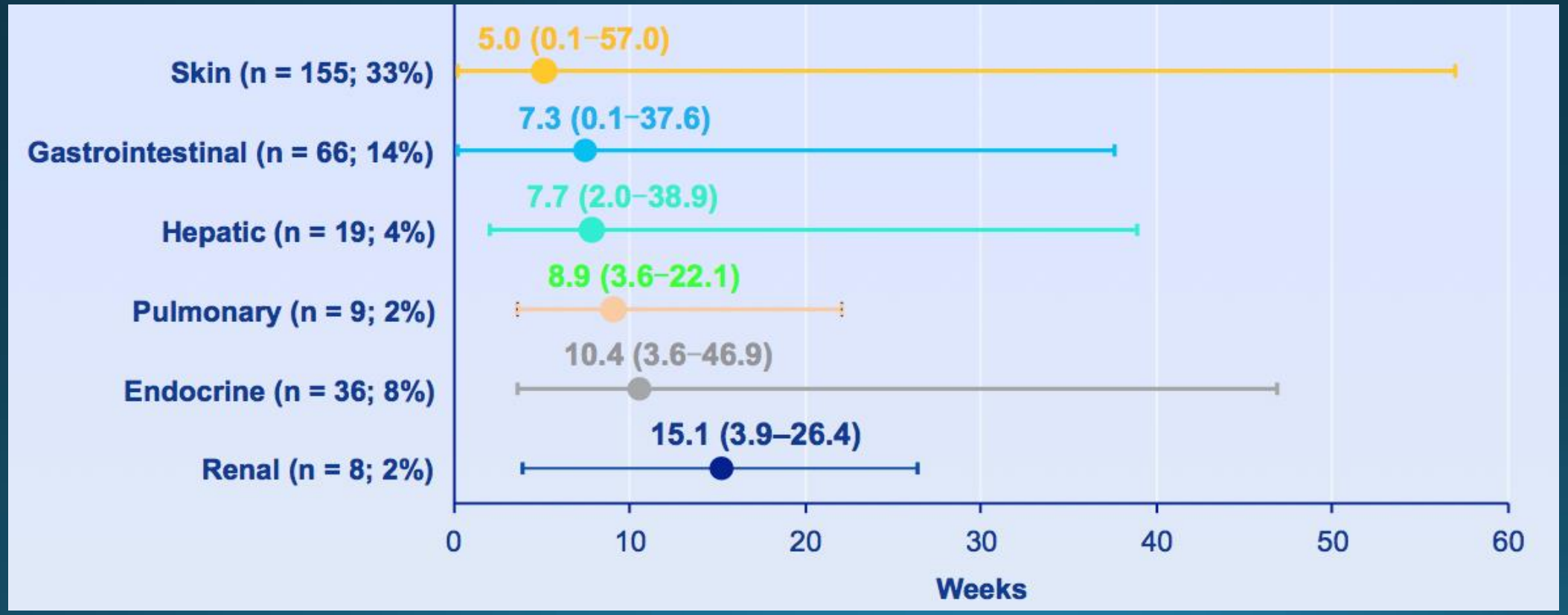


Figure 1. Timing of occurence of immune-related adverse events following ipilimumab treatment.

Source: Haanen JG, et al. Annals of Oncol. 2017. 28(4):119-142

Nivolumab (PD-1 Inhibitor)

Time to onset of select treatment-related irAEs seen with Nivolumab
(Any grade, N = 474)



Source: Webber J. Pooled Analysis. Abstract 9018. ASCO 2015

The Common	The Life Threatening	The Weird & Wonderful
• Fatigue • Rash • Pruritus • Diarrhea • Endocrinopathies - Thyroid (hyper or hypo)	• Pneumonitis • Colitis • Hepatitis • Nephritis • Type 1 Diabetes and DKA • Pancreatitis • Hypophysitis - Adrenal insufficiency	Neurologic irAEs • Guillain-Barre Syndrome • Inflammatory myopathies • Aseptic meningitis • CIPD • PRES • Peripheral neuropathy <u>Mimickers of progression</u> • Pseudoprogression • Sarcoidosis

Awareness and Education is important

- irAEs are typically low grade and easily managed, but early recognition is important to prevent significant morbidity and mortality
- Patient and care team education is required to help with diagnosis of immune-related adverse events, which can present with non-specific, insidious symptoms
- The cornerstone of treatment is systemic glucocorticoids and withholding or permanent discontinuation of the immunotherapy

Also, not everything is an immune-related AE….
And not everyone needs steroids…

ASSESS AND ASK THE PATIENT ABOUT THE FOLLOWING SIGNS OR SYMPTOMS

GASTROINTESTINAL

- Any changes in normal bowel habits or changes from baseline (eg, last week, last visit)
  - Diarrhea
  - Abdominal pain
  - Blood or mucus in stool with or without fever
  - Peritoneal signs consistent with bowel perforation
  - Ileus

LIVER

- Elevations in liver function tests
  - AST >2.5 times upper limit of normal (ULN)
  - ALT >2.5 times ULN
  - Total bilirubin >1.5 times ULN

NOTE: Always check lab values prior to each infusion.

SKIN

- Pruritus
- Rash

NEUROLOGIC

- Monitor for symptoms of motor and sensory neuropathy
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paresthesia

ENDOCRINE

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

Source: KEYTRUDA Product Monograph. Merck Canada Inc. May 19, 2015.

BC Cancer Agency
CARE & RESEARCH

MEDICAL ALERT

NAME _____

has received

NIVOLUMAB: Immune-Mediated Adverse Reactions

ALWAYS CARRY THIS CARD AND SHOW TO PHYSICIANS INCLUDING ANESTHETISTS

SEVERE IMMUNE-MEDIATED ADVERSE REACTIONS

Including enterocolitis, intestinal perforation, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, endocrinopathy, pneumonitis and toxicities in other organ systems. Duration of risk after treatment is unknown.

FOR MORE INFORMATION:

Abbottsford - Abbotsford Centre..... 604-851-4710
Kelowna - Centre for the Southern Interior..... 250-712-3900
Prince George - Centre for the North..... 250-645-7300
Surrey - Fraser Valley Centre..... 604-930-4055
Vancouver - Vancouver Centre..... 604-877-6000
Victoria - Vancouver Island Centre..... 250-519-5500

www.bccancer.bc.ca/health-professionals/professional-resources/cancer-drug-manual

Rev 1 March 2017

BC Cancer Agency
CARE & RESEARCH

To Whom It May Concern:

RE: _____

Medical Oncologist _____
Immunotherapy Regimen _____

This patient is receiving **immunotherapy** at the BCCA and is at risk of **immune-related toxicities** which may be life threatening and require urgent management.

Immunotherapy toxicities are different from those encountered with standard chemotherapy or targeted therapies. The immune system may become dysregulated during immunotherapy treatment, leading to symptoms and findings which mimic autoimmune disorders. Adverse events can occur during or following treatment and can be life threatening. Any organ system in the body is at risk including, but not limited to:

Lungs (pneumonitis, pleuritis, sarcoidosis)
Gastrointestinal (colitis, ileitis, pancreatitis)
Liver (hepatitis)
Skin (rash, Stevens-Johnson syndrome)
Endocrine (hypophysitis, adrenal insufficiency, hypo/hyperthyroidism, type 1 diabetes mellitus)
Renal (interstitial nephritis)
Blood (hemolytic anemia, thrombocytopenia, neutropenia)
Neurologic (encephalitis, Guillain-Barré syndrome, meningitis, myasthenia gravis, neuropathy)
Musculoskeletal (myositis, arthritis)
Cardiovascular (pericarditis, myocarditis, vasculitis)
Ophthalmologic (uveitis, scleritis, episcleritis, conjunctivitis, retinitis)

Management of immune-related toxicities necessitates prompt coordination with a medical oncologist with prompt initiation of **high dose corticosteroids**. Referral to the appropriate subspecialty. If you suspect your patient is presenting with immune-related toxicity, please contact the patient's medical oncologist directly or if after hours contact the on-call physician. For additional information on immunotherapy toxicity treatment algorithms, located at the end of the above posted protocol at www.bccancer.bc.ca.

Resources and Education

Guidelines:

- "Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" – *Annals of Oncology*, 2017 (https://www.annalsofoncology.org/article/S0923-7534(19)42153-4/pdf)
- "Management of immunotherapy-related toxicities" –*NCCN Clinical Practice Guidelines in Oncology, 2021 (https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf → you do need to log in but it's free to sign up)*
- *"Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline." – Journal of Clinical Oncology, 2018 (https://ascopubs.org/doi/pdf/10.1200/JCO.2017.77.6385)*

Drug Monographs:

- Nivolumab (https://www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf)
- Pembrolizumab (https://www.merck.ca/static/pdf/KEYTRUDA-PM_E.pdf)

Articles:

- "Management of adverse events following treatment with anti-PD 1 Agents" – *The Oncologist,* 2016
- "Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper" – *Annals of Oncology*, 2016
- "Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy: a Meta-Analysis" – *Oncologist*, 2017
- "Monitoring and management of immune-related AEs associated with PD-1 axis inhibitors in lung cancer" – *The Oncologist*, 2016

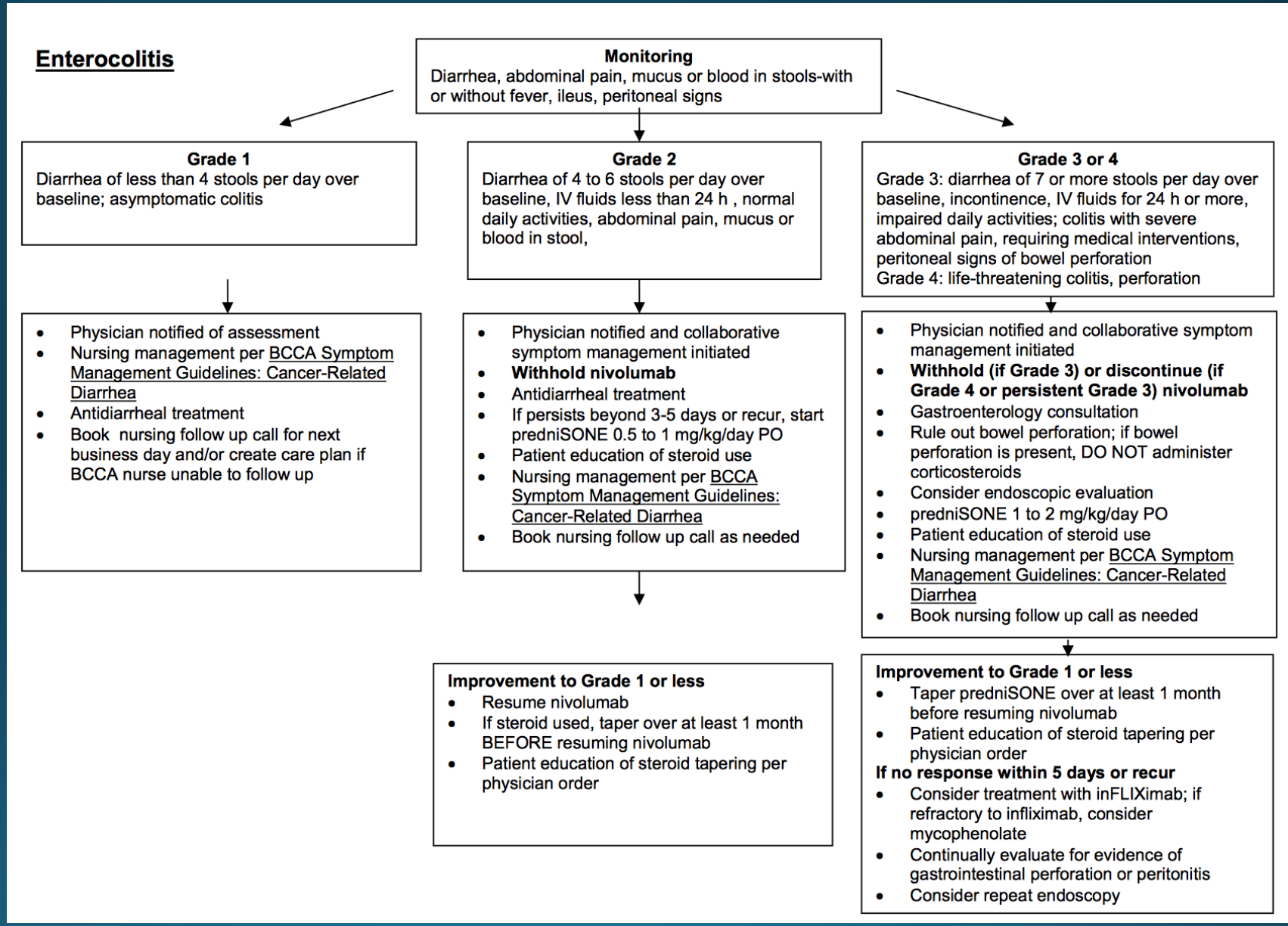
Protocols:

- BC Cancer protocols: BC Cancer website → Health Professionals →Chemotherapy Protocols → Immunotherapy →SCIMMUNE Protocol

Call your local medical oncologist for advice…

- These drugs can cause any 'itis' and toxicity can present in a myriad of ways
- Call us for patients on these drugs if you suspect potential toxicity
- AND don't forget the usual suspects in patients including infection, other drug toxicity, progressive malignancy etc.

SCIMMUNE Protocol



http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf

Conclusions

- Checkpoint inhibitors are immunomodulatory agents that are used to amplify T-cell mediated immunity and allow the patient to mount an effective anti-tumor immune response
- Checkpoint inhibitors have improved the prognosis for patients in a number of different disease sites
- These agents are associated with unique immune-related toxicities, with skin and the GI tract being most commonly affected
- CTLA-4 inhibitors are associated with higher rates of immune-related adverse events than PD-1 inhibitors, with combination immunotherapy showing significantly increased risk of Grade 3 or 4 toxicity
- Overall, however, immunotherapy is better tolerated than chemotherapy

Conclusions

- Immune-related adverse events are typically low grade and easily managed, but require early recognition to prevent significant morbidity and mortality
- Patient and care team education is required to help with the diagnosis of immune-related adverse events, which can present with non-specific, insidious symptoms
- The cornerstone of treatment is systemic glucocorticoids and withholding or permanent discontinuation of the immunotherapy

Also, not everything is an immune-related AE….

POLL – How comfortable would you feel seeing a patient on IO?

1. Very comfortable
2. Somewhat comfortable
3. Neutral
4. Somewhat uncomfortable
5. Not comfortable at all


Questions?