MedEd ON THE GO Oncology

Recognizing and Managing Immunotherapy Related Adverse Events

Various Speakers

MedEd ON THE GO Oncology

Cancer Immunotherapy Related Colitis

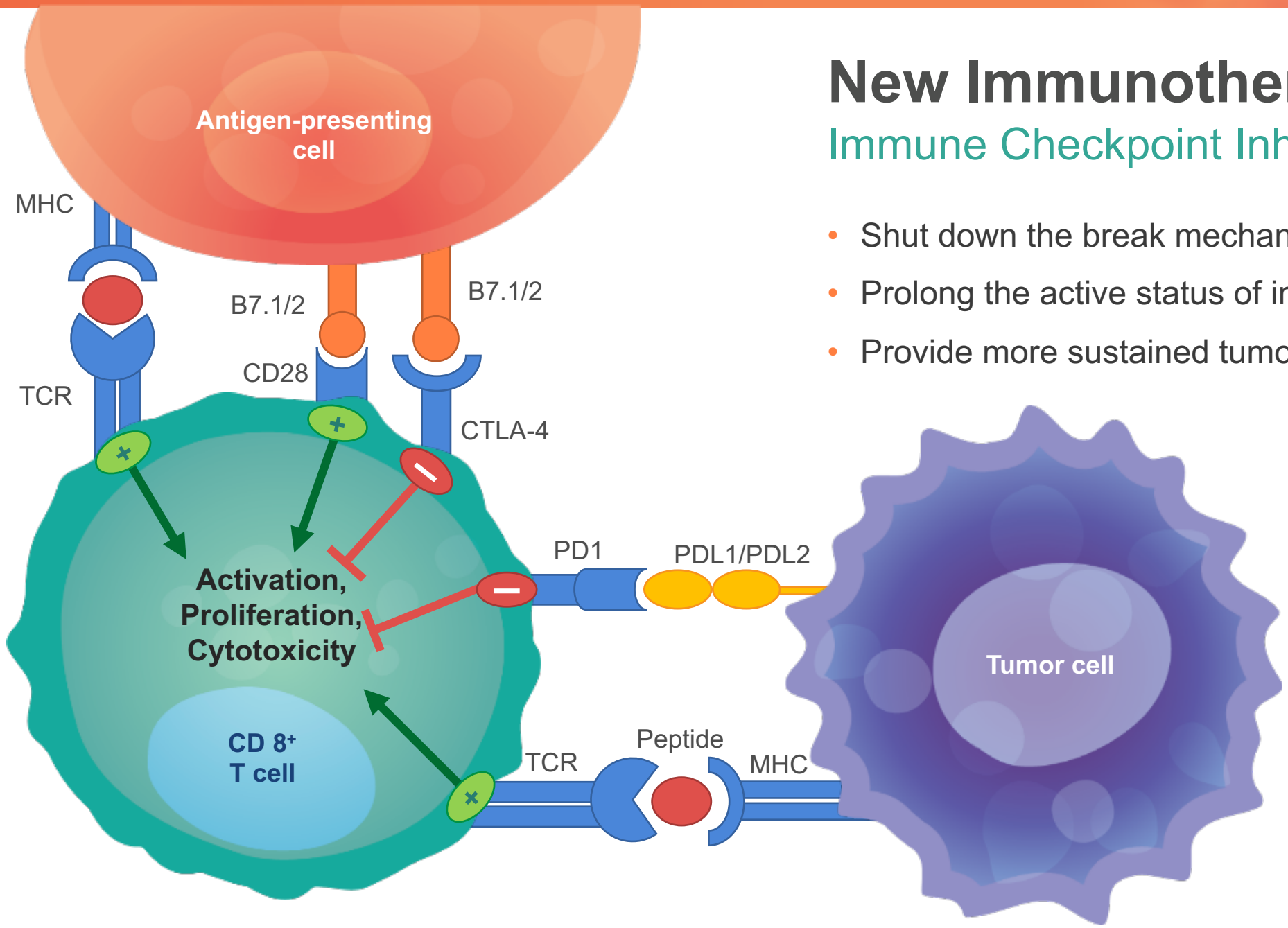
Yinghong Wang, MD, PhD

Director of Medication-Induced Colitis and Enteritis
Director of Fecal Microbiota Transplantation
Assistant Professor, Department of Gastroenterology, Hepatology & Nutrition
The University of Texas MD Anderson Cancer Center, Houston, TX

New Immunotherapy

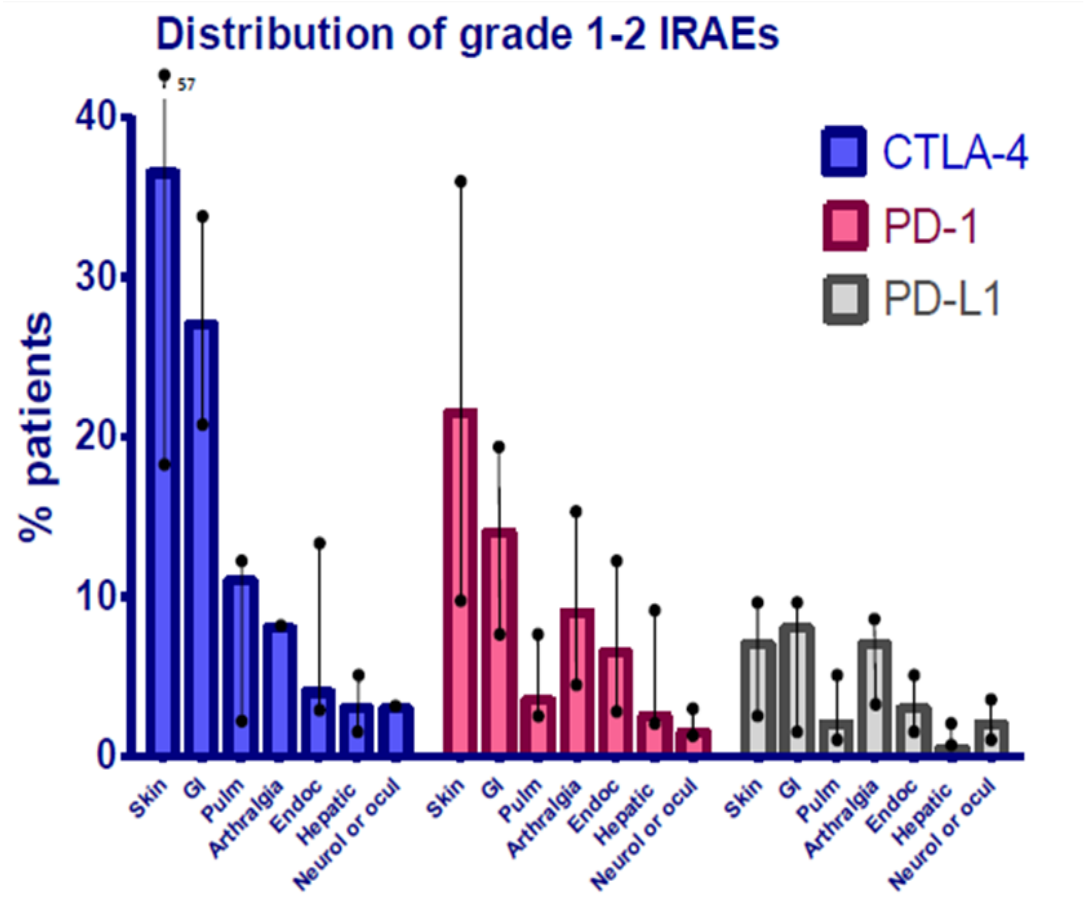
Immune Checkpoint Inhibitor: ICI

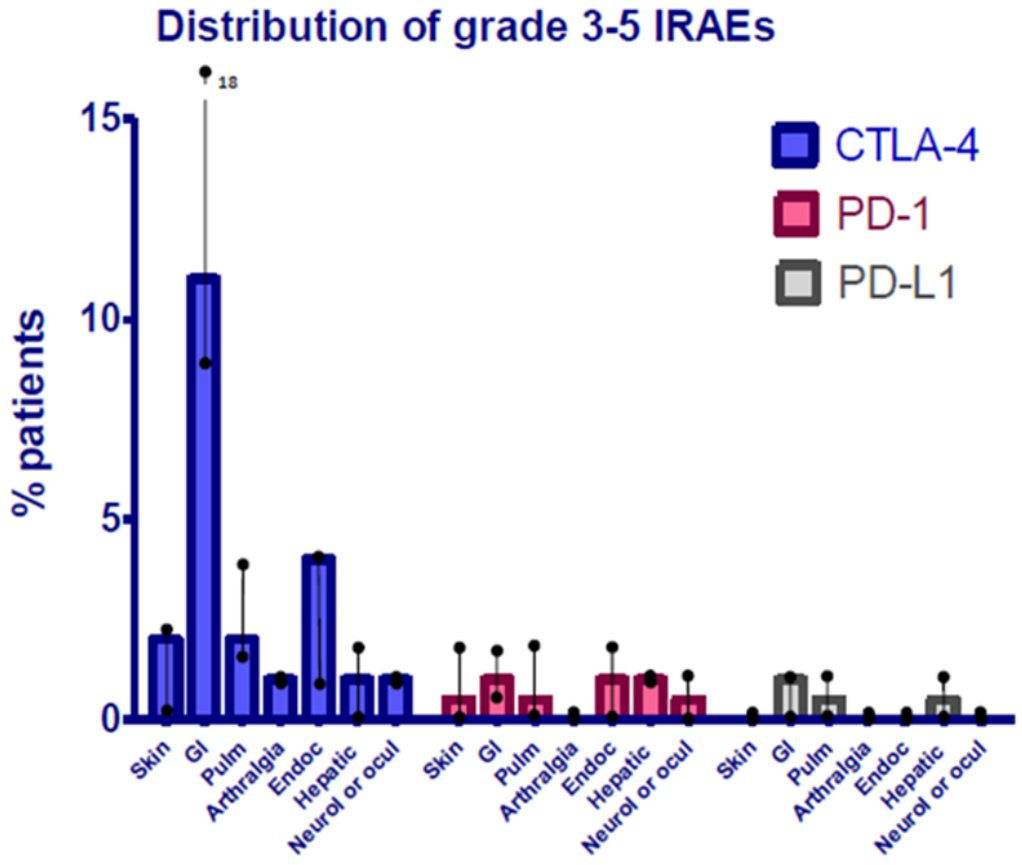
- Shut down the break mechanism of immune cells
- Prolong the active status of immune cells
- Provide more sustained tumor cell eradication



Adapted from Santarpia M et al. *Cancer Biol Med.* 2015;12(2):74.

Distribution of irAEs

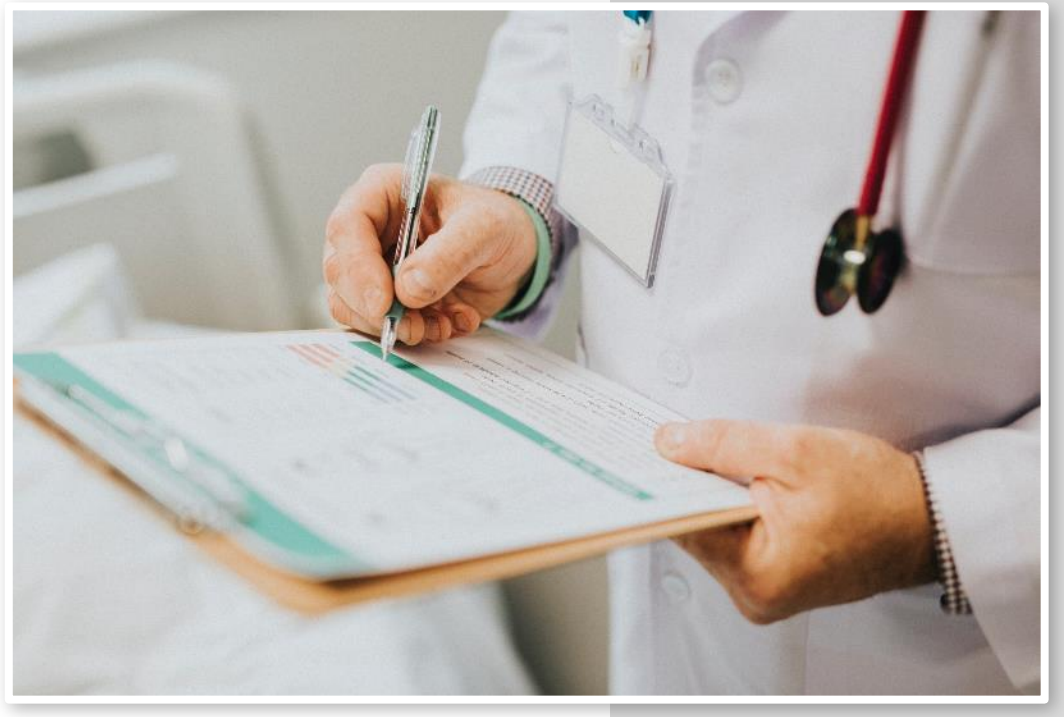




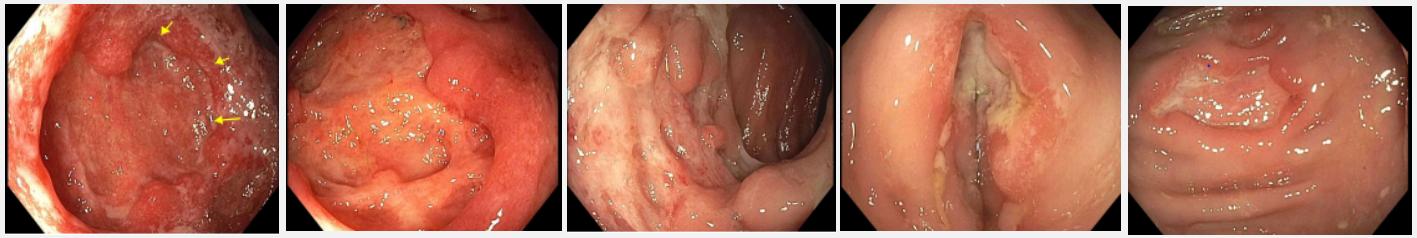
Michot JM, et al. *Eur J Cancer.* 2016;54:139-148.

Common Colitis Symptoms

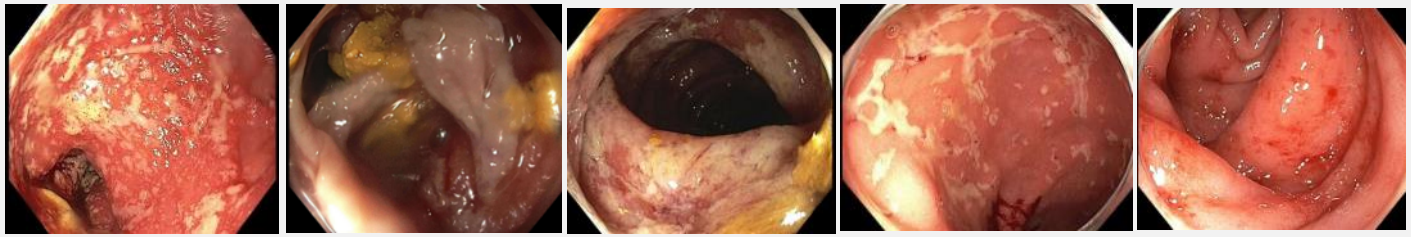
- ✓ Diarrhea
- ✓ Bleeding
- ✓ Mucus
- ✓ Abdominal pain
- ✓ Fever



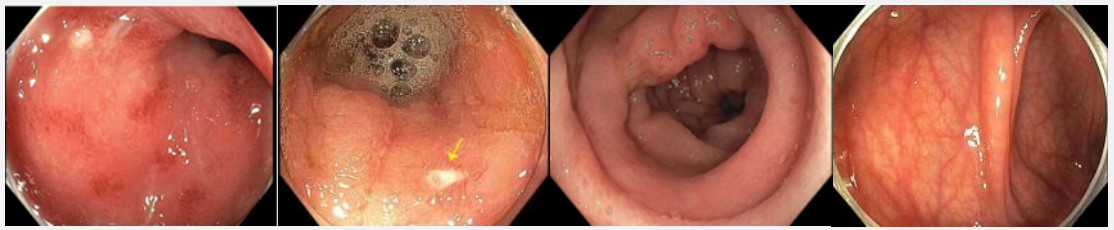
Endoscopy Presentations



Severe inflammation with large deep ulcerated mucosa



Moderate to severe inflammation with diffuse/patchy erythema, superficial ulcers, exudate, LOV



Mild inflammation with mild patchy erythema, aphtha, edema or normal mucosa

Wang Y et al. *Inflamm Bowel Dis*. 2018 Jul 12;24(8):1695-1705.

Stool Biomarkers and Its Sensitivity

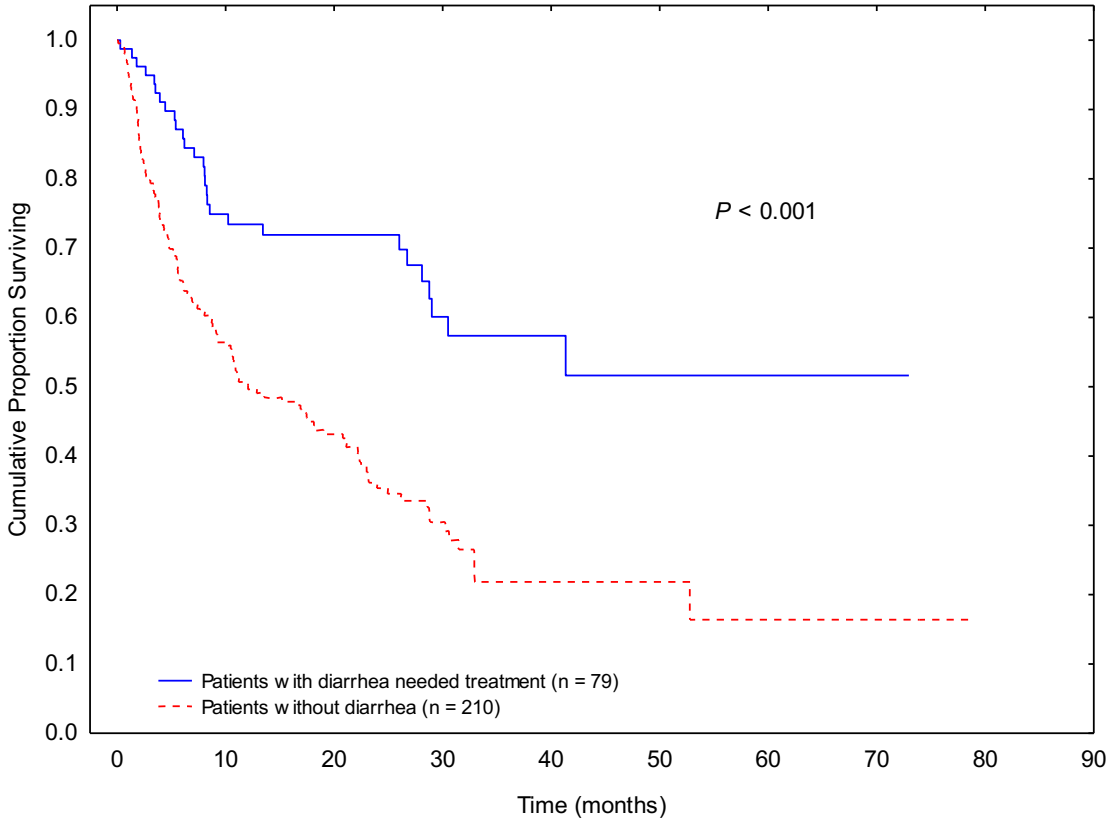
	Lactoferrin (+) N (%)	Lactoferrin (-) N (%)
Abnormal Scope	42 (70)	4 (36)
Normal Scope	18 (30)	7 (64)
Abnormal Histology	54 (90)	3 (27)
Normal Histology	6 (10)	8 (73)

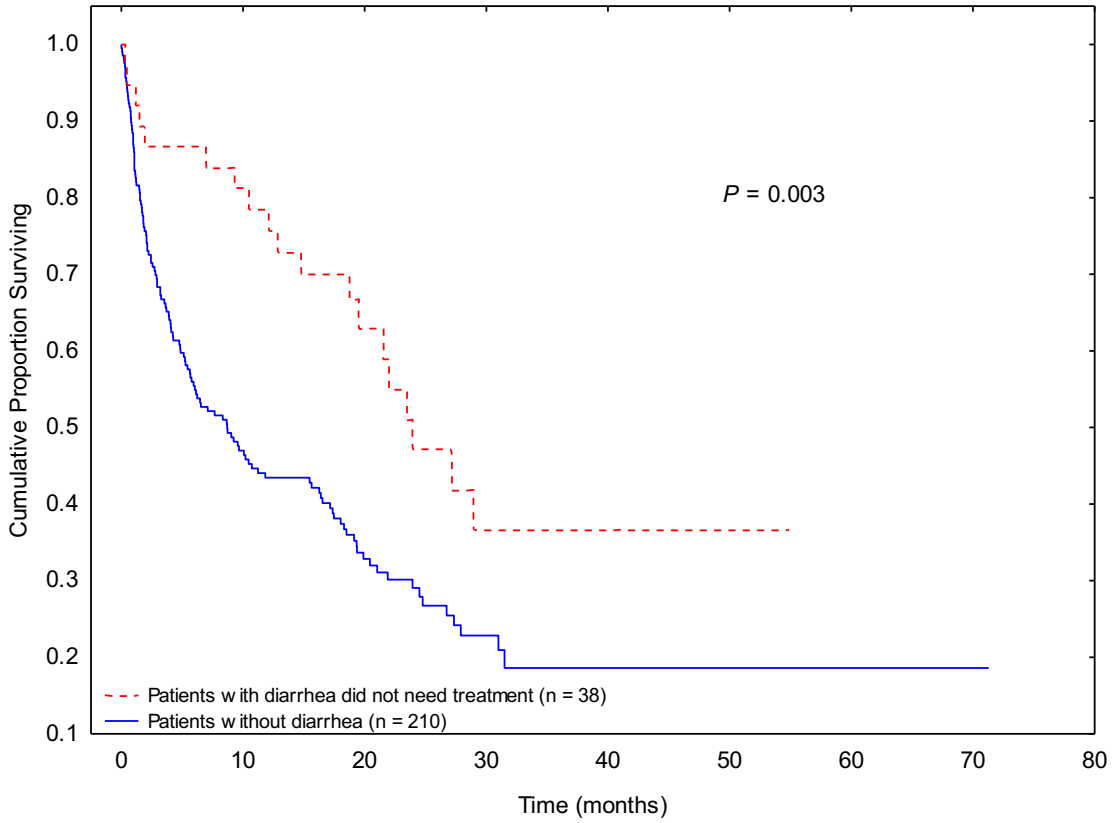
Scope Findings	Calprotectin (SD)
Ulcers	465 (363)
Non-Ulcer Inflammation	213 (184)
Normal	152 (133)
P	0.006

Sensitivity of lactoferrin for endoscopic inflammation is **70%**
Sensitivity of lactoferrin for histologic inflammation is **90%**

Abu-Sbeih H, et al. *J Immunother Cancer.* 2018 Sep 25;6(1):95

Overall Survival with GI Toxicity





Wang et al *J Immunother Cancer.* 2018 May 11;6(1):37.

Endoscopic Features and Outcomes

Characteristic	High-risk Features N = 71	No high-risk Features N = 111	*P* value
Duration of symptoms (days, SD)	41 (106)	27 (60)	0.301
IV steroids, n (%)	41 (66.1)	42 (58.3)	0.378
Infliximab/vedolizumab, n (%)	30 (46.2)	12 (15.8)	**< 0.001**
Mean duration from dx to first recurrence (days, SD)	140 (147)	144 (121)	0.902
Outcomes, n (%)			
Hospitalization	58 (81.7)	74 (66.7)	**0.028**
Duration of hospitalization (days, SD)	9 (8)	6 (5)	**0.016**
Recurrence	20 (28.2)	31 (27.9)	1.000
Repeat Endoscopy	18 (25.4)	18 (16.2)	0.181

[a]High-risk endoscopic features; deep ulcers > 2 mm in depth, large ulcers > 1 cm, multiple ulcers, extensive involvement

Abu-Sbeih H, et al. *J Immunother Cancer.* 2018 Sep 25;6(1):95

Timing of Endoscopy and Clinical Outcomes

Characteristic	> 7 days of onset N = 89	≤ 7 days of onset N = 93	*P* value
IV steroids, n (%)	46 (66.7)	37 (56.9)	0.287
Duration of symptoms (days, SD)	47 (104)	19 (47)	**0.026**
Duration of steroid (days, SD)	74 (90)	49 (43)	**0.053**
Infliximab/vedolizumab, n (%)	26 (29.2)	27 (29.0)	1.000
Duration from onset to first infliximab/vedolizumab dose (days, SD)	23 (17)	14 (17)	0.154
Outcomes, n (%)			
Hospitalization	58 (65.2)	74 (79.6)	**0.032**
Duration of hospitalization (days, SD)	9 (7)	6 (7)	**0.068**
ICU admission	4 (4.5)	3 (3.2)	0.856
Recurrence	60 (67.4)	60 (67.4)	0.191

Abu-Sbeih H, et al. *J Immunother Cancer.* 2018 Sep 25;6(1):95.

Timing of Endoscopy and Clinical Outcomes

Characteristic	>30 days of onset N = 40	≤30 days of onset N = 142	*P* value
IV steroids, n (%)	23 (57.5)	60 (42.3)	**0.054**
Duration of symptoms (days, SD)	54 (92)	26 (77)	**0.062**
Duration of steroid (days, SD)	87 (120)	53 (41)	**0.019**
Infliximab/vedolizumab, n (%)	8 (22.9)	34 (32.1)	0.395
Duration from onset to first infliximab/vedolizumab dose (days, SD)	31 (23)	15 (14)	**0.030**
Outcomes, n (%)			
Hospitalization	27 (67.5)	105 (73.9)	0.428
Duration of hospitalization (days, SD)	9 (7)	7 (6)	0.138
ICU admission	4 (10)	3 (2.1)	**0.072**
Recurrence	20 (50.0)	31 (21.8)	**0.001**

Abu-Sbeih H, et al. *J Immunother Cancer.* 2018 Sep 25;6(1):95.

Timing of SIT and Clinical Outcomes of ICI Colitis

Covariate	≤ 10 days of onset N = 44	> 10 days of onset N = 40	*P* value
High-risk endoscopic features initially, n (%)	17 (55)	23 (70)	0.302
Duration of symptoms, mean days (SD)	25 (32)	50 (40)	**0.002**
Multiple hospitalization, n (%)	13 (30)	22 (55)	**0.026**
Duration of hospitalization, mean days, (SD)	10 (8)	12 (8)	0.321
Failed steroid taper after SIT, n (%)	9 (23)	19 (49)	**0.033**
# of attempts at steroids taper, median (IQR)	1 (1-4)	2 (1-4)	**< 0.001**
Overall duration of steroids, mean days (SD)	64 (38)	82 (51)	0.092
Recurrent diarrhea, n (%)	8 (18)	8 (20)	1.000
Infectious adverse events, n (%)	16 (36)	9 (23)	0.233

SIT: Selected immunosuppressive therapy (infliximab or vedolizumab)

Abu-Sbeih H, et al. *J Immunother Cancer*. 2019;7(1):93.

Univariate Analysis for Recurrence

Characteristics	Odds Ratio (95% CI)	*P*
Colitis grade 3-4	1.79 (0.59-3.38)	0.299
Multiple hospitalization	26.25 (3.22-213.82)	**0.002**
Failed steroid tapering after SIT	4.07 (1.29-12.88)	**0.017**
Infliximab	12.57 (1.57-100.57)	**0.017**
No. of SIT infusions ≥3	0.09 (0.01-0.72)	**0.023**
Endoscopic remission	0.15 (0.03-0.79)	**0.025**
Histologic remission	0.18 (0.04-0.88)	**0.033**
Number of steroids tapering attempts	3.35 (1.68-6.69)	**0.001**
Duration from onset to SIT	1.00 (0.98-1.03)	0.774
Overall duration of steroids	1.01 (1.00-1.03)	**0.022**
Calprotectin after SIT	1.01 (1.00-1.01)	**0.014**
Duration of hospitalization	1.14 (1.05-1.23)	**0.001**
Duration of symptoms	1.02 (1.01-1.03)	**0.008**

Abu-Sbeih H, et al. *J Immunother Cancer.* 2019;7(1):93.

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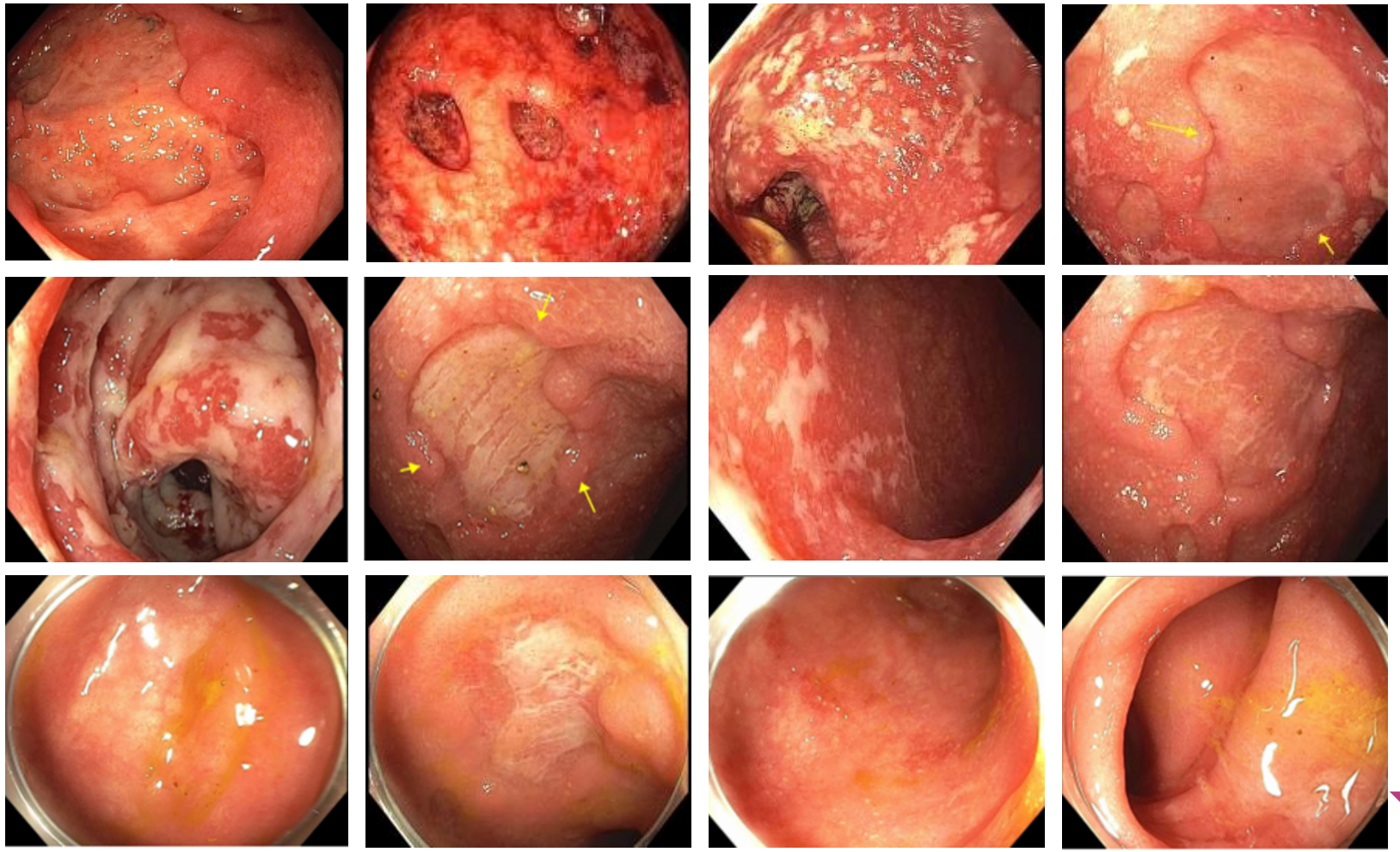
Abu-Sbeih H, et al. *J Immunother Cancer.* 2019;7(1):93.

Fecal Microbiota Transplantation (FMT)



1 Original colonoscopy at the diagnosis

2 After steroid+2 doses infliximab + 1 dose of vedolizumab (3 months)

3 4 weeks after the FMT treatment

Wang Y et al. *Nature Medicine*. 2019;25:188; Wang Y et al. *Nature Medicine.* 2018;24:1804-1808.

Take Home Message

- Stool **lactoferrin**→ good screening marker
- Early **endoscopy**→ severity measurement
- Visible mucosal **ulcers**→
  - steroid refractory
  - require early potent immunosuppressant treatment
- Early **infliximab or vedolizumab regardless of steroid response** → early symptoms resolution and shorter duration of steroid exposure
- **Repeat endoscopy** and biopsy → essential to confirm complete remission
- Presence of **organ toxicities** predicts a better OS, the more severe, the better outcome
- Overall immunosuppressant treatment → safe for long term survival
- **FMT** is effective treating IMS refractory ICI colitis

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Cancer Immunotherapy Related Toxicities in Upper GI Tract, Pancreas and Gallbladder

Yinghong Wang, MD, PhD

Director of Medication-Induced Colitis and Enteritis
Director of Fecal Microbiota Transplantation
Assistant Professor, Department of Gastroenterology, Hepatology & Nutrition
The University of Texas MD Anderson Cancer Center, Houston, TX

ICI Related Upper GI Toxicity

Clinical Symptoms

- Nausea and vomiting
- Abdominal pain
- Dyspepsia
- Diarrhea
- GI bleed

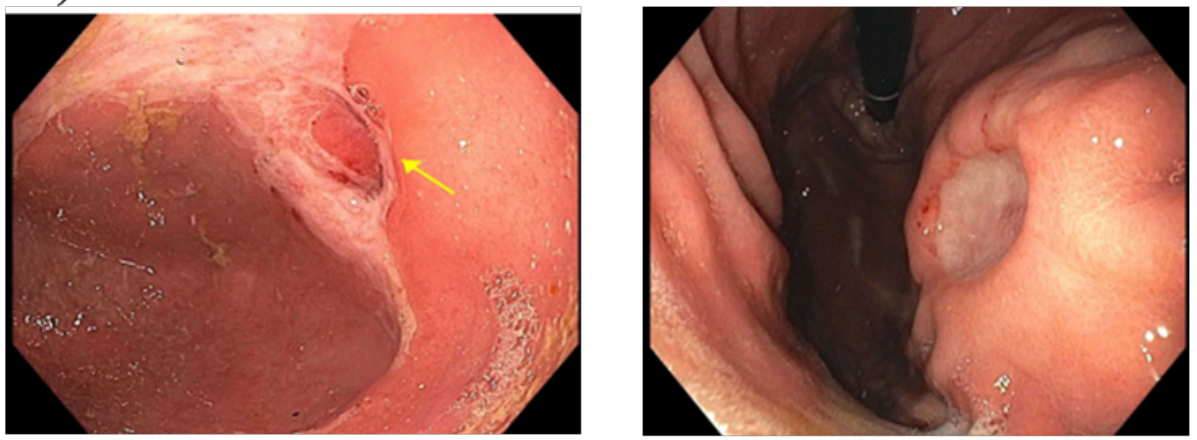
Onset

- ~4-9 months after ICI initiation
- Can occur concurrently with colitis
- Incidence unclear

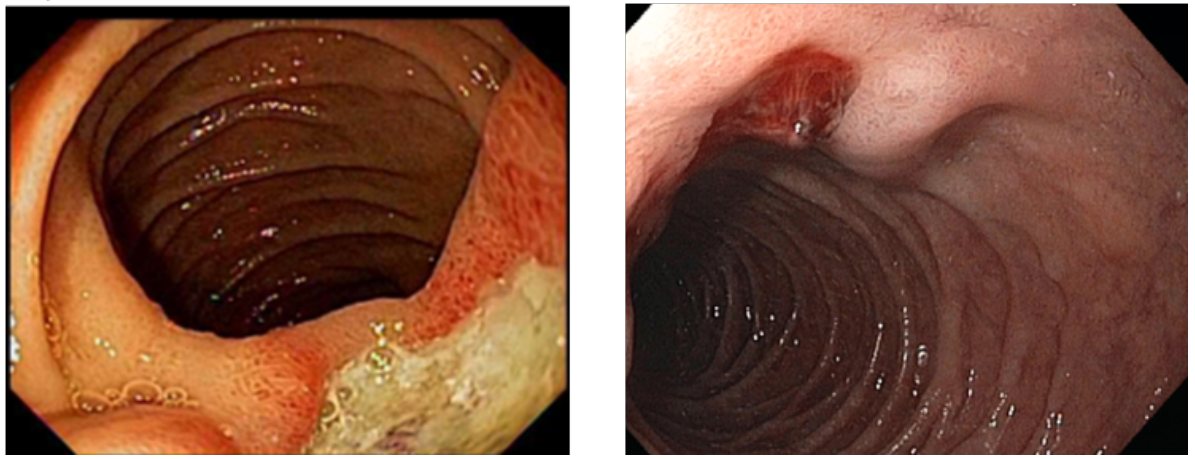
Tang T, et al. *Scand J Gastroenterol*. 2019;54(5):538-45;
Shi Y et al. *Eur J Cancer*. 2017;84:367–369.

Endoscopic Images of Upper GI Toxicity

A)

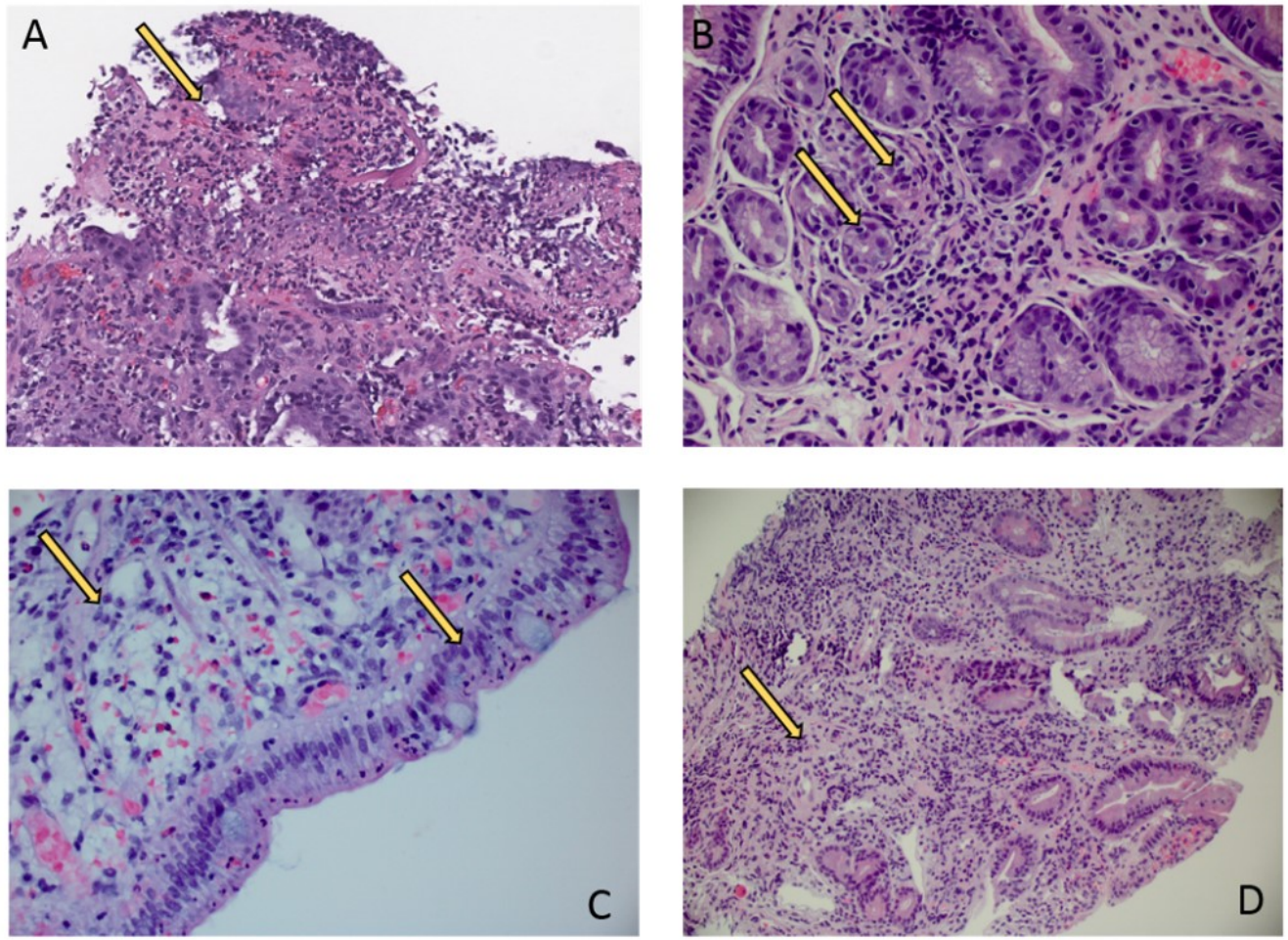


B)



Tang T, et al. *Scand J Gastroenterol*. 2019;54(5):538-45

Histological Features of Upper GI Toxicity



Tang T, et al. *Scand J Gastroenterol*. 2019;54(5):538-45.; Gonzalez RS et al. *Histopathology.* 2017;70(4):558-6.; Bavi P et al. *Histopathology.* 2017;71(3):494-6.

Management for ICI Related Gastroenteritis

- **The appropriate treatment is still unclear**
- **The reported medical treatments:**
  - Proton pump inhibitors
  - Histamine$_2$ blockers
  - Corticosteroids
  - Vedolizumab

Puzanov I et al. *J Immunother Cancer.* 2017;5:95; Tang T, et al. *Scand J Gastroenterol*. 2019;54(5):538-45.

ICI Related Cholecystitis

Clinical Symptoms

- Fever
- Abdominal pain
- Nausea/vomiting

Onset

- ~6 months after ICI initiation
- Usually symptoms last for 5 days
- Incidence: 0.6% (> non-ICI=0.2%)
- anti–CTLA-4 > other ICI agents

Abu-Sbeih H et al. *J Immunother Cancer*. 2019:7(1):118

Management for ICI Related Cholecystitis

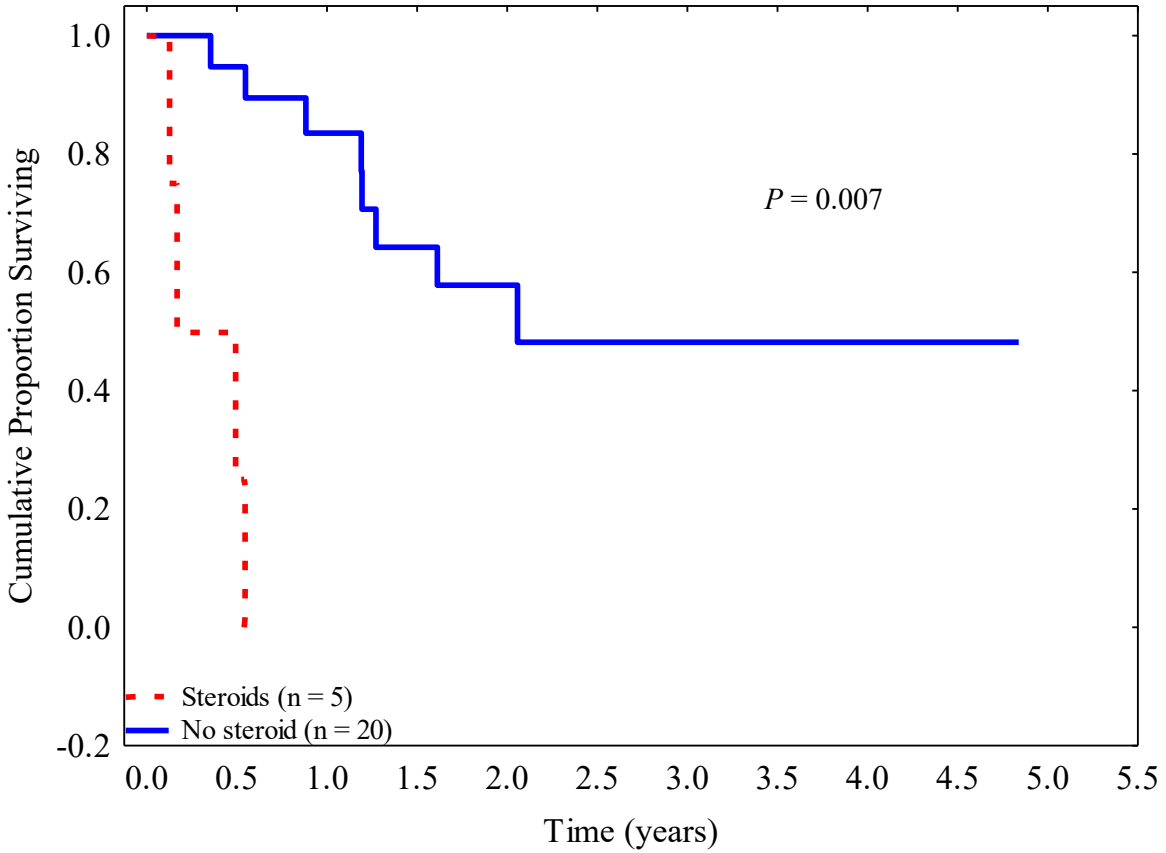
Treatment as Traditional Acute Cholecystitis

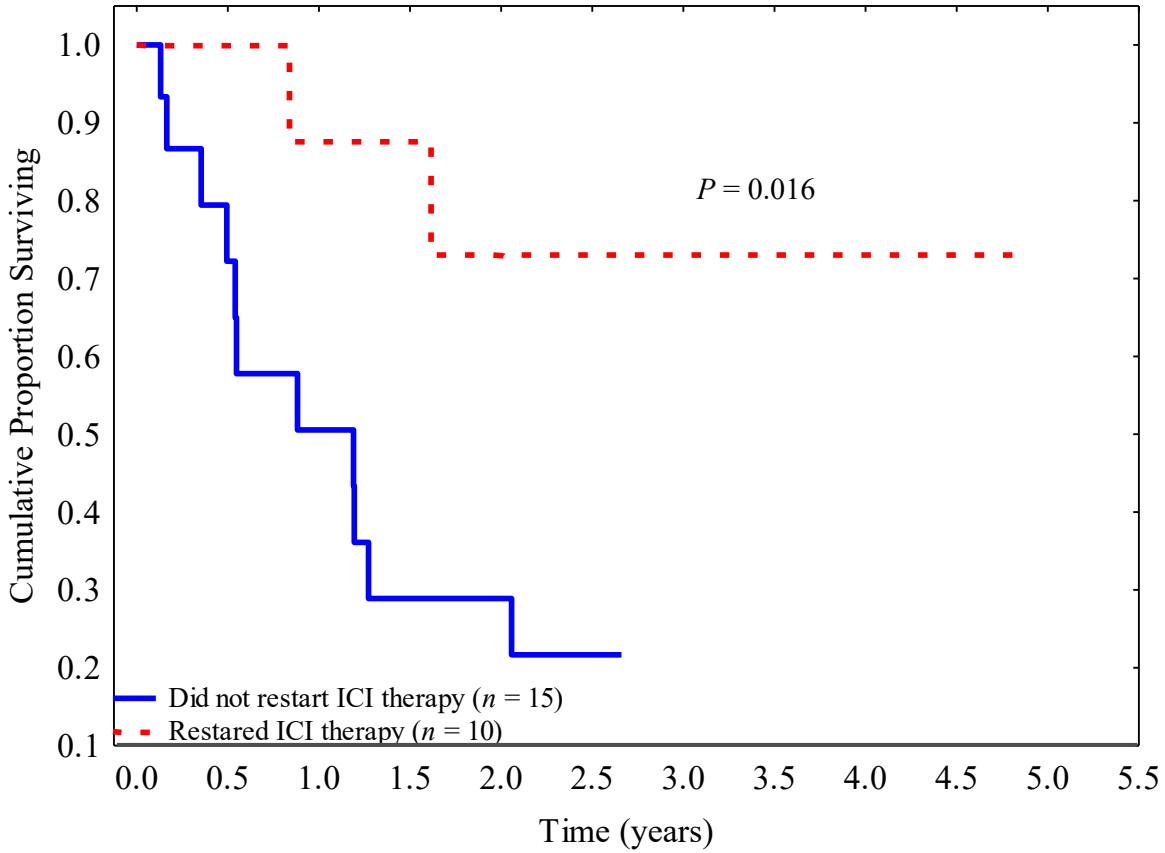
- IV fluid
- Antibiotics
- Steroids?
- Cholecystectomy
- Percutaneous drainage

Complications

- Sepsis
- Perforation

Overall Survival in Patients with ICI Cholecystitis





Abu-Sbeih H et al. *J Immunother Cancer.* 2019:7(1):118

ICI Related Pancreatic Injury

Clinical Symptoms

- Fever
- Abdominal pain
- Nausea/vomiting
- Dyspnea
- Asymptomatic

Onset

- ~3-4 months after ICI initiation
- Usually symptoms last for 5 days
- Elevation in lipase/amylase
- Incidence 0.6% to 4%

Abu-Sbeih H et al. *J Immunother Cancer.* 2019;7:31.

Management for ICI Related Pancreatic Injury

Treatment as Traditional Acute Pancreatitis

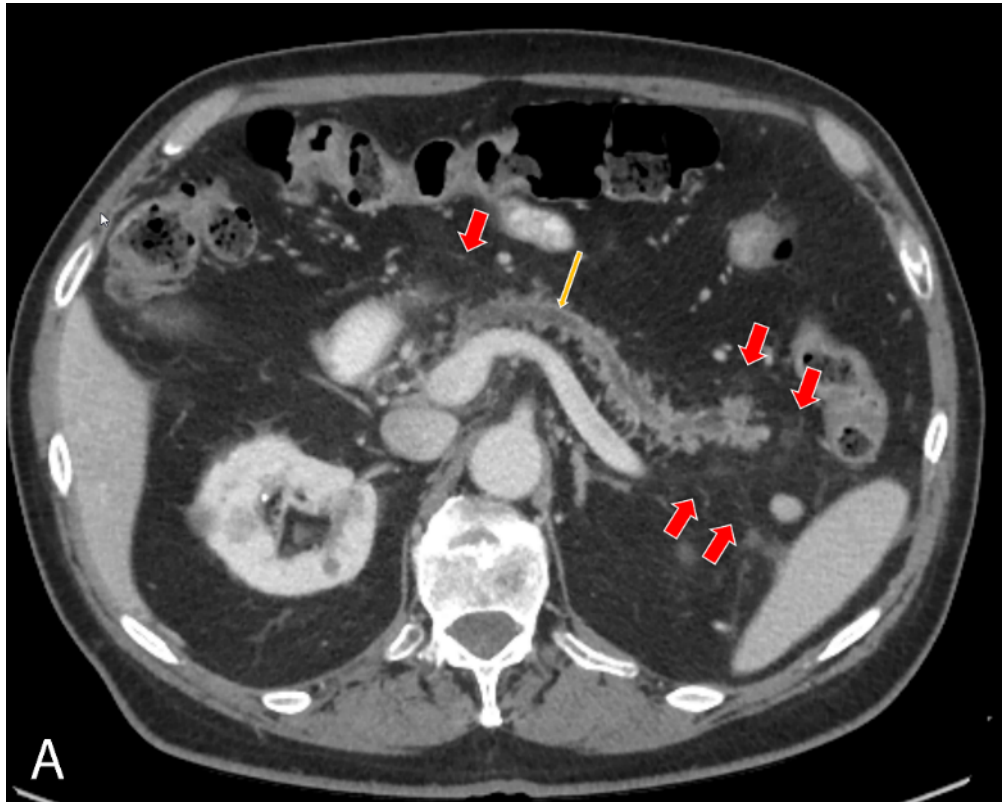
- IV fluid and pain control (decrease the long term adverse outcome)
- Role of steroid is unclear

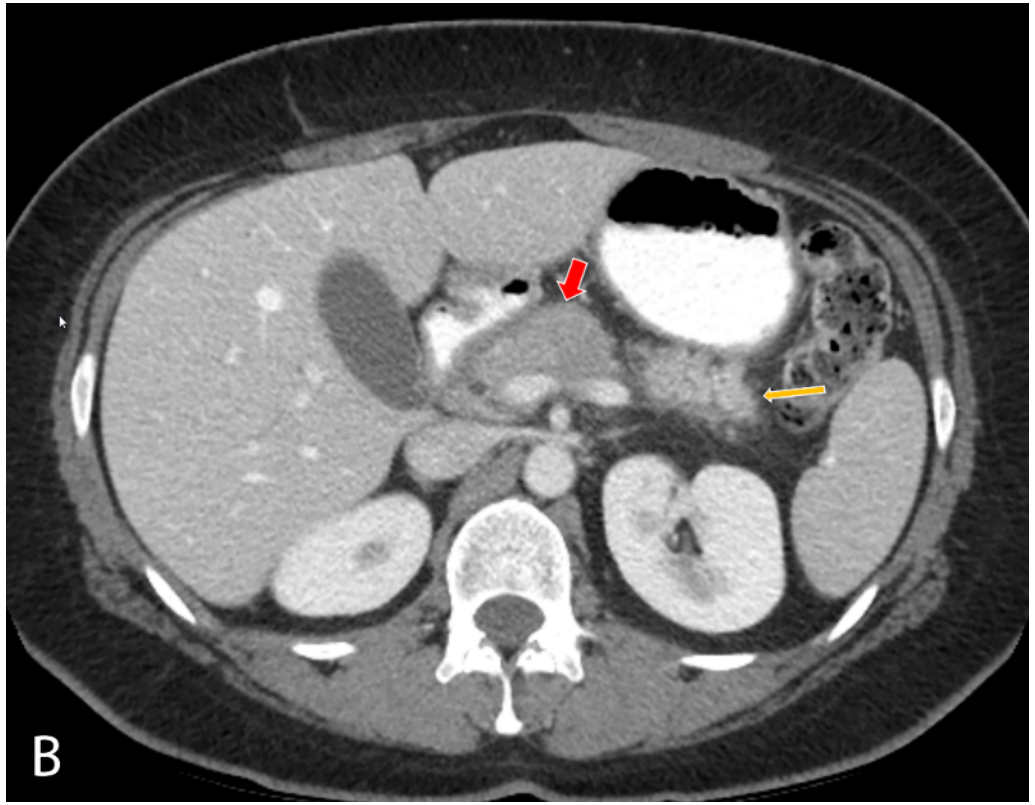
Long Term Adverse Outcomes

- Diabetes mellitus
- Chronic pancreatitis
- Recurrent pancreatitis

Abu-Sbeih H et al. *J Immunother Cancer.* 2019;7:31.

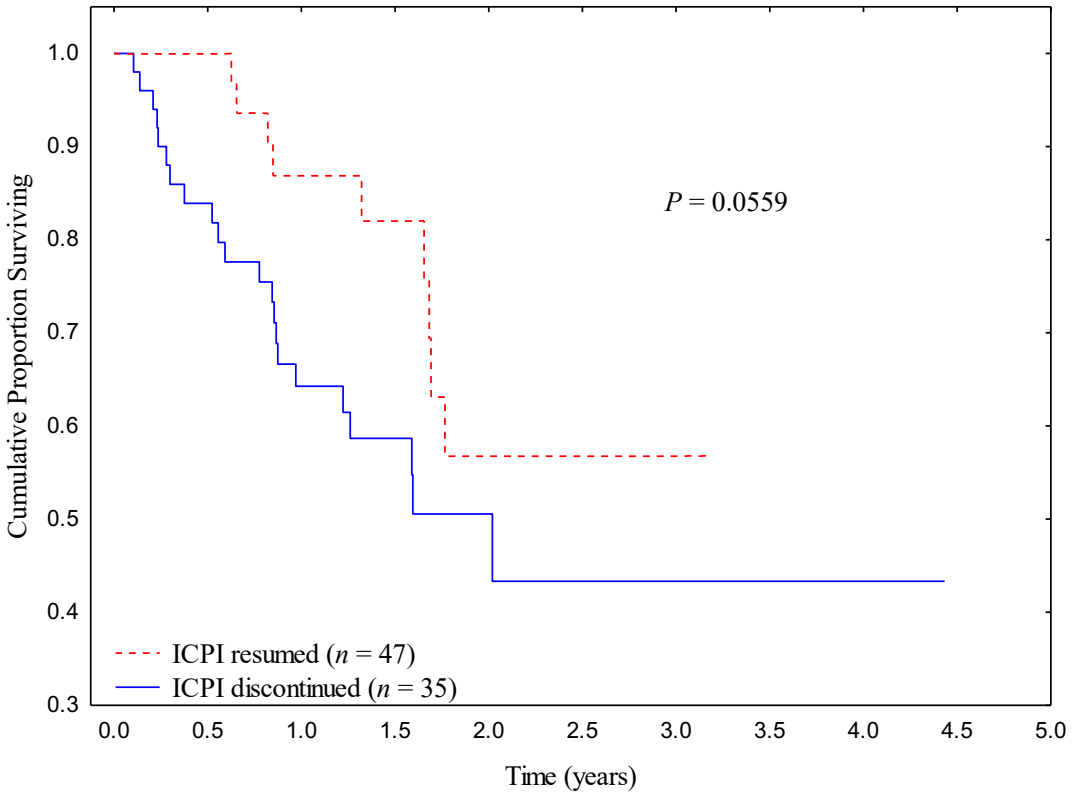
ICI Pancreatitis

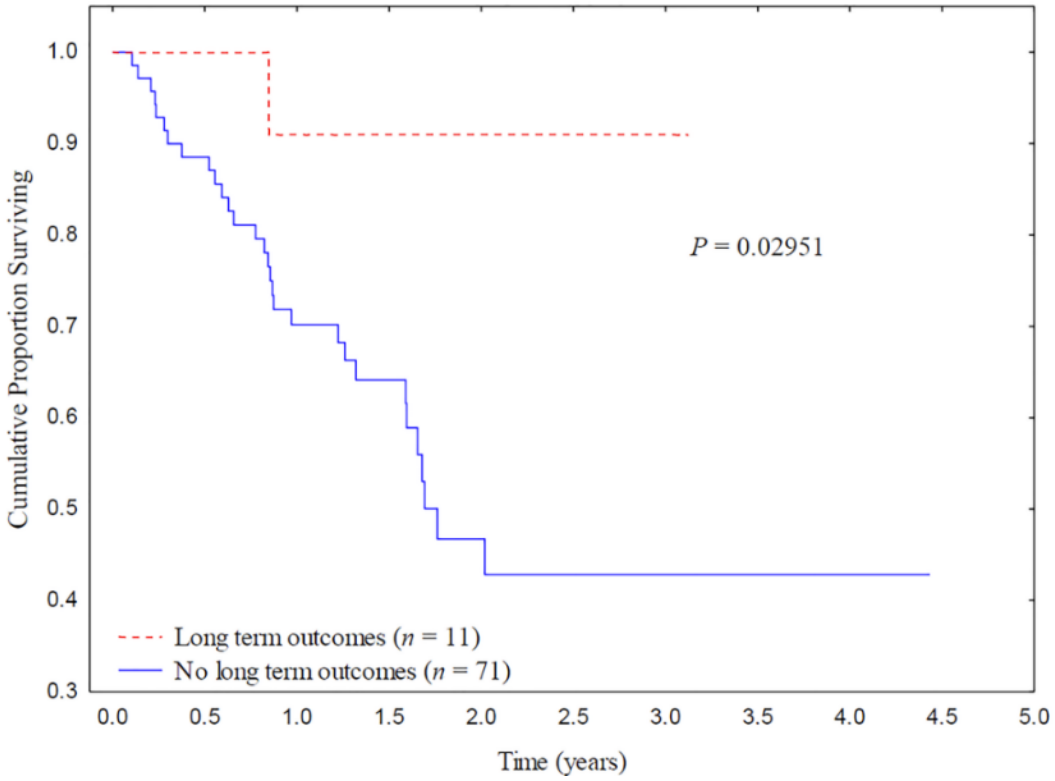




Abu-Sbeih H et al. *J Immunother Cancer.* 2019;7:31.

Overall Survival of ICI Pancreatitis





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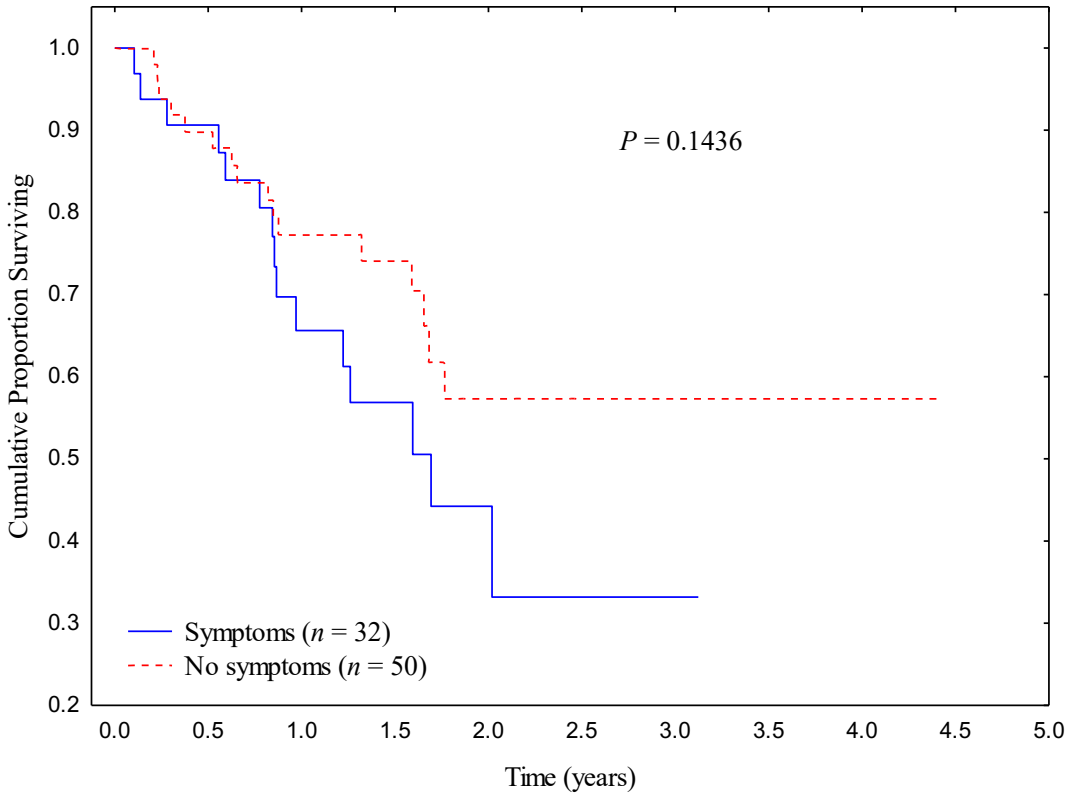

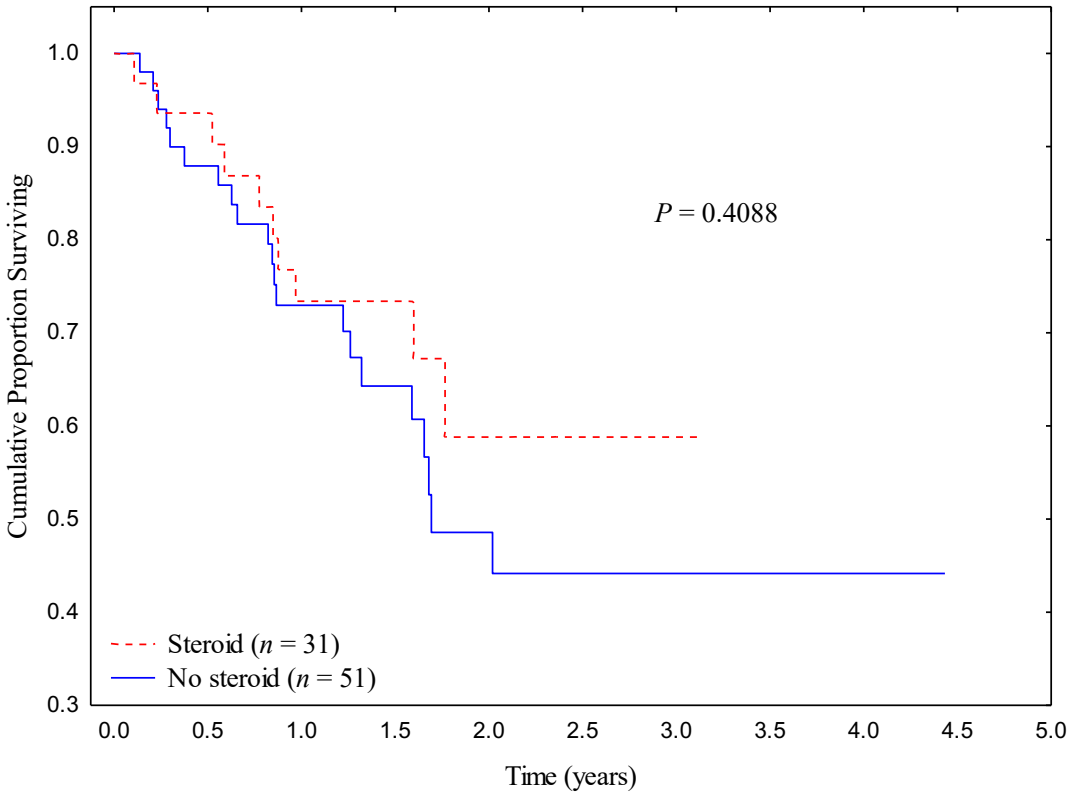

Abu-Sbeih H et al. *J Immunother Cancer.* 2019;7:31.

Take Home Message

- ICI can cause toxicity in upper GI tract, pancreas and gallbladder.
- Overall incidence is not clear.
- Symptoms can be overlapping and nonspecific.
- Endoscopy and body imaging can be useful evaluation tools.
- Management is mainly symptomatic support. Immunosuppressant use for these indications still need further studies.

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Cancer Immunotherapy Related Hepatitis

Yinghong Wang, MD, PhD

Director of Medication-Induced Colitis and Enteritis
Director of Fecal Microbiota Transplantation
Assistant Professor, Department of Gastroenterology, Hepatology & Nutrition
The University of Texas MD Anderson Cancer Center, Houston, TX

Incidence

- Anti-PD-(L)1: 5-10%
- Anti-CTLA-4: 15%
- Combination: up to 30%
- **Grade 3-4 hepatitis:**
  - 1-3% monotherapy
  - 8-14% combination anti-PD-1 and anti-CTLA-4 therapy

Topalian SL et al. *J Clin Oncol.* 2014;32:1020-30.
Bernardo SG et al. *Melanoma Res.* 2013;23:47-54.
Larkin J et al. *N Engl J Med*. 2015;373:23-34.
Boutros C et al. *Nat Rev Clin Oncol.* 2016;13:473-86.

ICI Related Hepatitis Symptoms

- Malaise
- Jaundice
- Abdominal pain
- Asymptomatic

Kim KW et al. *Invest New Drugs.* 2013;31(4):1071-7.

ICI Related Hepatitis

- 2-3 months after ICI initiation
- Elevation of AST, ALT, total bilirubin, alkaline phosphatase
- The most common injury pattern: hepatocellular and panlobular
- Fulminant hepatitis can occur

Kim et al. *Invest New Drugs* 2013;31:1071-7.

Diagnosis

- **Exclusion of other causes of liver injury:**
  - Concomitant medications
  - Autoimmune type of hepatitis (ANA, AMA, ASMA, ALKM-1, ceruloplasmin, iron)
  - Viral infection (Hep A, B, C, CMV, EBV, HSV, HIV)
  - Alcohol

Tirumani SH et al. *Cancer Immunol Res.* 2015;3(10):1185-92.; Kim KW et al. *Invest New Drugs.* 2013;31(4):1071-7.

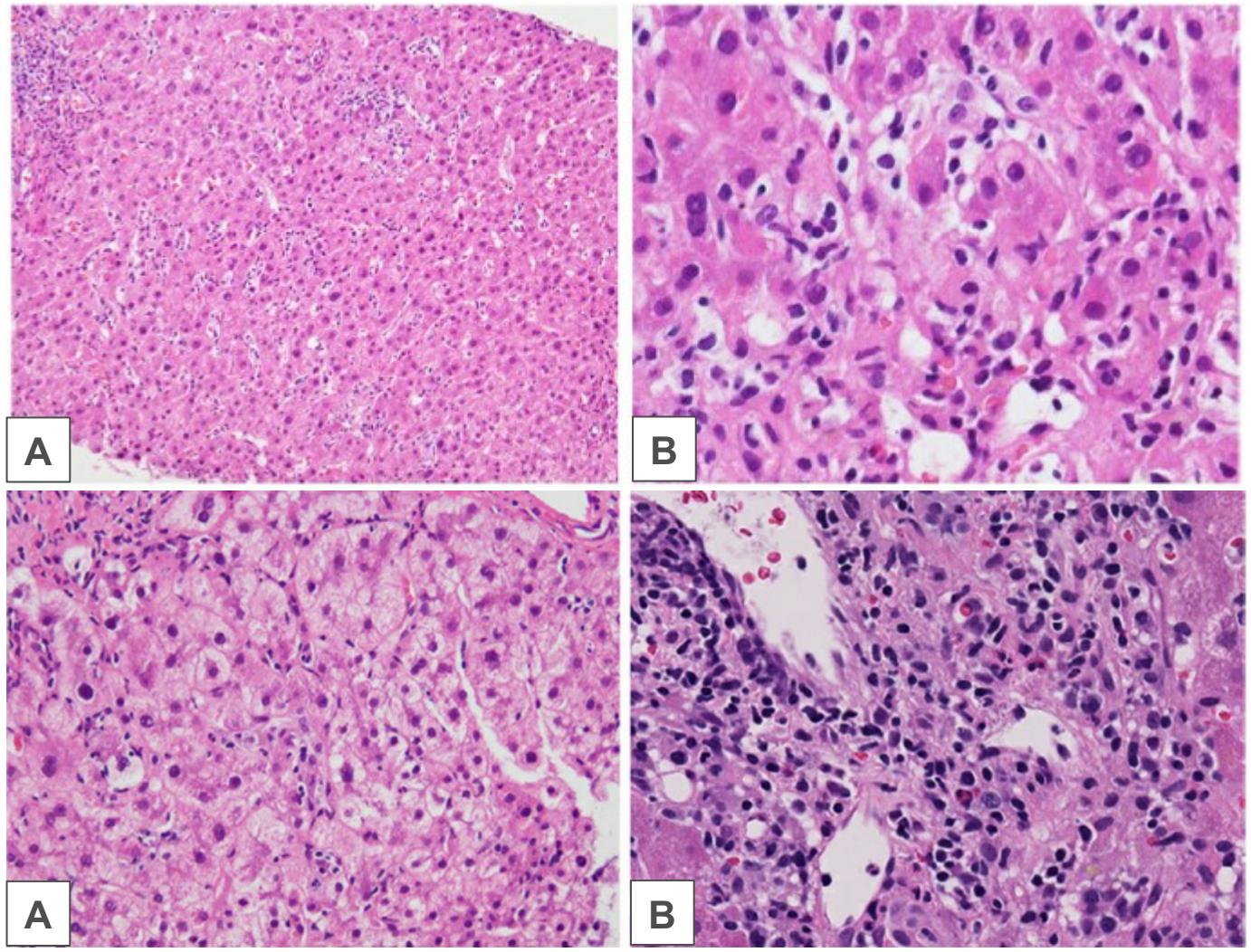
Diagnosis

- **Abdominal imaging might be considered:**
  - Rule out liver metastasis and thromboembolic event
  - Normal morphology
  - Periportal edema, hepatomegaly, attenuated liver parenchyma, and enlarged periportal lymph nodes in severe hepatitis.

- **Liver biopsy:** severe persistent cases, or when the diagnosis is uncertain.

Kim et al. *Invest New Drugs* 2013;31:1071-7.
Tirumani et al. *Cancer Immunol Res* 2015;3:1185-92.

Pathology Images of ICI Hepatitis

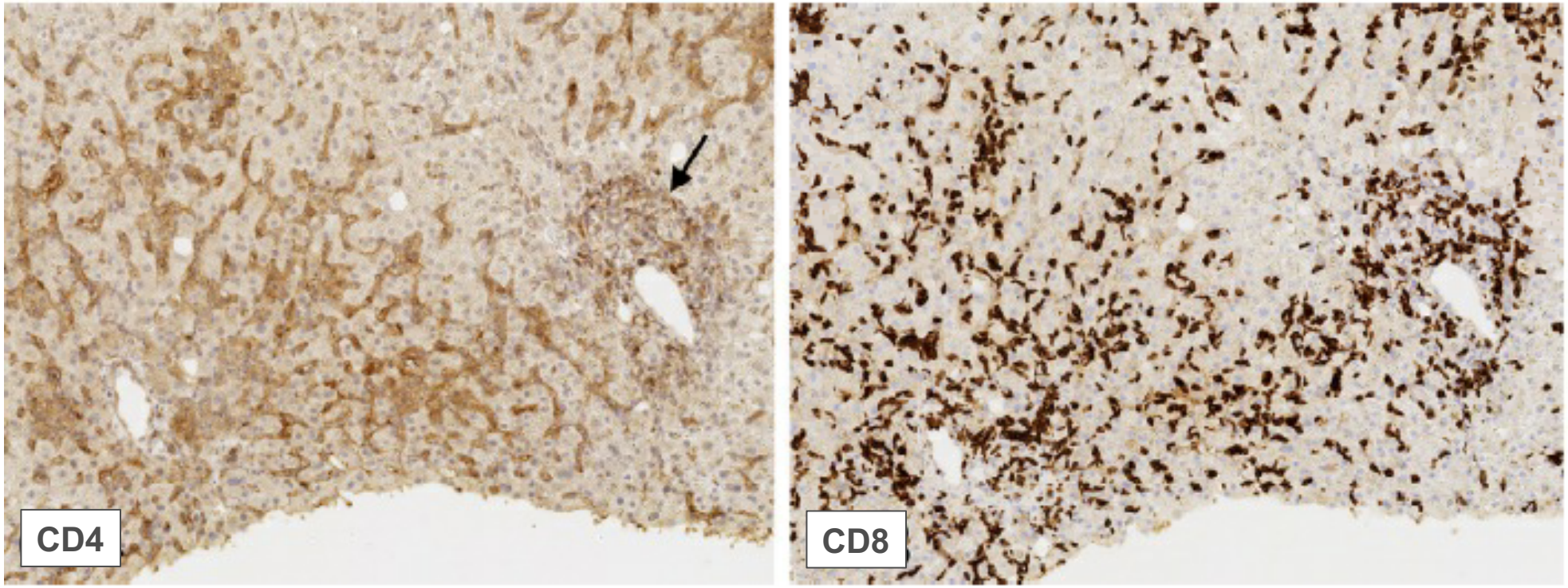


A. Foci of focal necrosis are scattered in the liver parenchyma.

B. Hepatocytes show lytic necrosis with lymphocytic infiltration.

Zen Y, Yeh MM. *Semin Diagn Pathol*. 2019 Jul 24; doi: 10.1053/j.semdp.2019.07.009.

Pathology Images of ICI Hepatitis



Zen Y, Yeh MM. *Semin Diagn Pathol*. 2019 Jul 24; doi: 10.1053/j.semdp.2019.07.009.

Manage of ICI Related Hepatitis

- Closely monitor LFTs
- May need to hold ICI until grade 1 toxicity achieved
- Steroid can be started once toxicity level reaches grade 2
- Ideal duration of steroid is unclear
- Other steroid sparing agents are reported (e.g. mycophenolate mofetil, azathioprine)
- Permanent discontinuation of ICI for grades 3 and 4 hepatitis should be considered
- Rebound enzymes elevation can occur after initial treatment

Puzanov I et al. *J Immunother Cancer.* 2017;5:95

Take Home Message

- ICI-induced hepatotoxicity can occur in 5-30%.
- ICI-induced hepatitis often occurs 2-3 months after the initiation of ICI therapy.
- The presentation is usually asymptomatic elevations of AST, ALT and total bilirubin, but may be accompanied with fever, malaise, and even death in rare cases.
- The diagnosis of ICI-induced hepatitis is usually made after the exclusion of other etiologies of hepatitis.
- When the diagnosis of ICI-induced hepatitis is made, ICI treatment should be discontinued, and corticosteroids should be started.
- Resumption of ICI therapy might be considered in patients with grade 1 or 2 hepatotoxicity.

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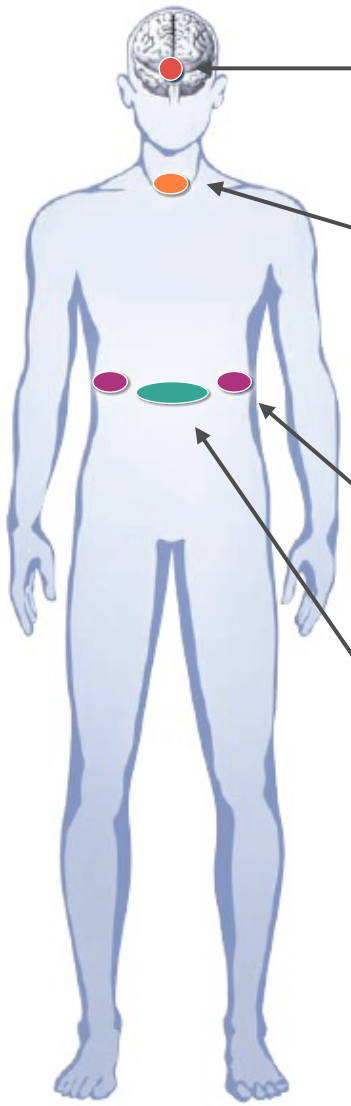
Endocrinopathies Associated With Immune Checkpoint Inhibitor Therapy

Monica Girotra, MD

Associate Clinical Member
Memorial Sloan Kettering Cancer Center
New York, NY

Endocrinopathies With Immune Checkpoint Inhibitors[1,2]

- Two main endocrinopathies
  1. **Hypophysitis**, typically induced by CTLA-4 antibodies
  2. **Primary thyroid dysfunction**, induced by PD-1/PD-L1 or CTLA-4 antibodies
- Symptoms can **be non-specific and endocrinopathies often are long lasting**
- *Pancreas and adrenal glands are less commonly affected*



Pituitary gland
- **Hypophysitis**

Thyroid gland
- **Thyrotoxicosis**
- **Hypothyroidism**

(usually from thyroiditis)

Adrenal glands (rare)
- Primary adrenal insufficiency

Pancreas (rare)
- Diabetes mellitus

1. Byun DJ et al. *Nat Rev Endocrinol*. 2017;13(4):195-207.
2. Image adapted from Yervoy® (ipilimumab) Risk Evaluation and Mitigation Strategy (REMS). http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_Full.pdf.

CTLA-4 Associated Hypophysitis

- Incidence of hypophysitis estimated at ~ 10% *(many studies lacked specific endocrine data; rare with anti-PD-1 therapy alone)*
- Onset of symptoms can range from **6 to 12 weeks after treatment**, but patients may present as early as week 4 and as late as week 16
- Most common symptoms include: **Headache, fatigue and/or muscle weakness**; non-specific, may be misattributed to general symptoms related to cancer
- Less frequent: *Nausea, anorexia, weight loss, visual changes, alterations in mental status, temperature intolerance and arthralgia*
- *Low levels of sodium have also been reported, with some studies reporting hyponatremia in approximately 50% of patients*

Faje AT, et al. *J Clin Endocrinol Metab.* 2014;99(11):4078-85. Ryder M, et al. *Nat Rev Endocrinol.* 2017;13(4):195-207.

Hypophysitis

- Morbidity predominantly related to **secondary adrenal insufficiency, which may be life-threatening if not treated**
- Levothyroxine used to treat secondary hypothyroidism
  - In patients with both ACTH and TSH deficiency, *glucocorticoid replacement should be initiated prior or at the same time as thyroid hormone replacement in order to prevent precipitating adrenal crisis*
- Hyponatremia is typically temporary and improves after adrenal and thyroid hormone replacement
- Testosterone may be used in men who develop hypogonadism; estrogen in premenopausal women
- Diabetes insipidus is uncommon

Byun DJ et al. *Nat Rev Endocrinol*. 2017;13(4):195-207.

Hypophysitis: Steroid Dosing

- **Reserve high-dose steroids** for:
  - ***Severe illness, significant hyponatremia, severe headache, visual abnormalities or significant pituitary enlargement***
  - In a retrospective studies, *high-dose steroids do not seem to reverse hypopituitarism*
  - Concern that the immunosuppressant effect of high-dose steroids could negatively affect anti-tumor efficacy
- Glucocorticoids can decrease pituitary size gradually and relieve symptoms
  - *Low-dose glucocorticoids can alleviate fatigue and headache; used to treat adrenal insufficiency;* e.g. Hydrocortisone 10-20 mg in the AM and 5-10 mg in the pm (equivalent to prednisone 4-7.5 mg QD)
  - Adrenal insufficiency teaching for increasing steroid doses during illness or for surgical procedures.
  - Majority did not show signs of HPA axis recovery at long term follow-up and remained on physiologic dose of steroids and levothyroxine if needed

Byun DJ et al. *Nat Rev Endocrinol*. 2017;13(4):195-207. Min L, et al. *Clin Cancer Res.* 2015;21:749-755. Faje AT, et al. *Cancer*. 2018;124(18):3706-14. Sinha AG et al. *Endocr Rev.* 2018;39(2).

Hypophysitis

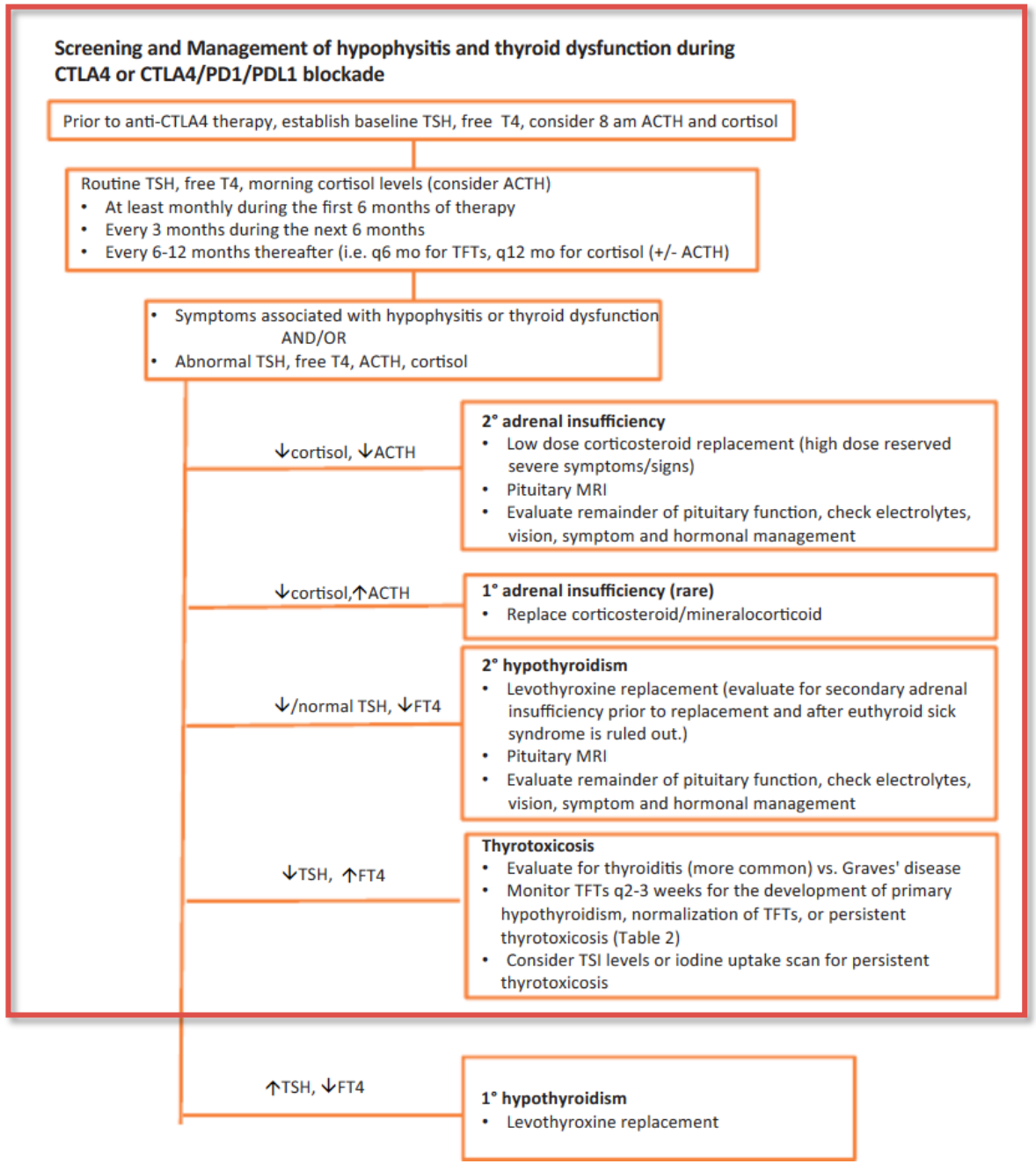
- Screening for secondary adrenal insufficiency is often not a component of routine monitoring during CTLA-4 blockade
- Consider routine monitoring with early-morning ACTH & cortisol + TSH, FT4 at baseline and during treatment (i.e. monthly during the first 6 months)

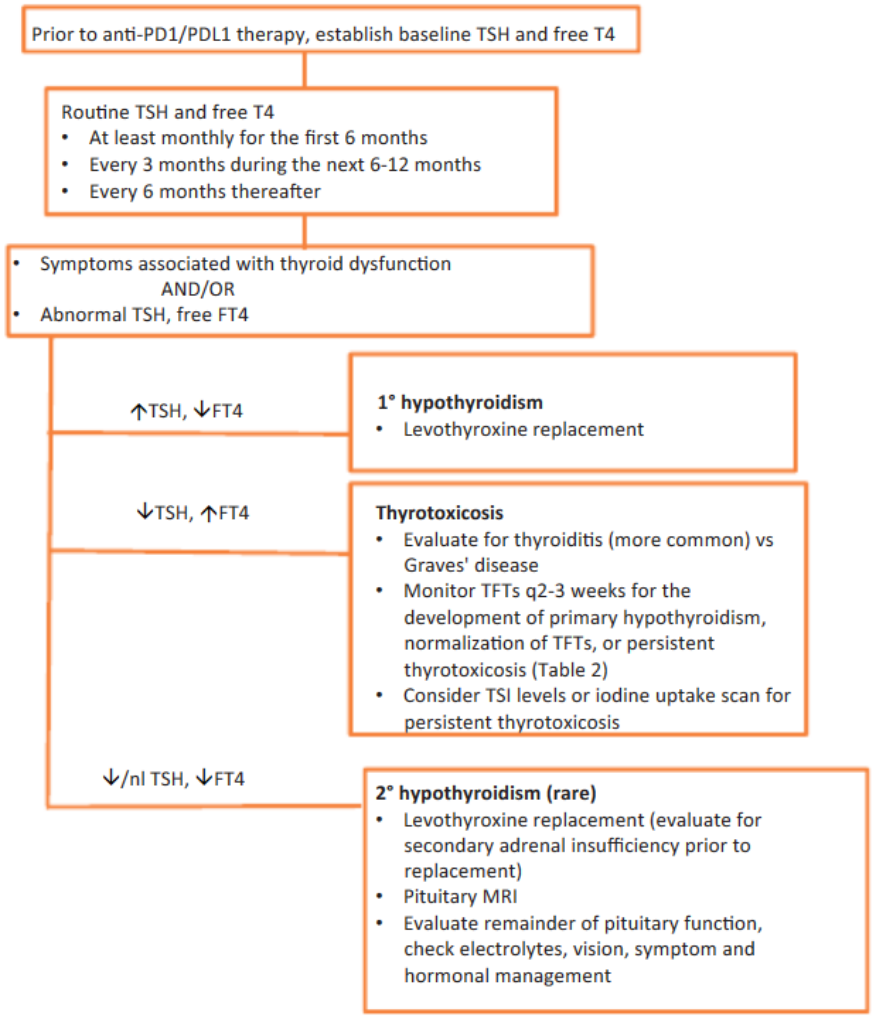
If results are normal and patient is asymptomatic	→	test every 3 months for the next 6 to 12 months, followed by further testing every 6-12 months thereafter
If signs of hypophysitis or hypopituitarism	→	prompt evaluation including early-morning ACTH, cortisol, TSH and FT4

  - Cosyntropin stimulation test not very useful in diagnosing early secondary adrenal insufficiency
- **In patients with hypophysitis/hypopituitarism:**
  - MR pituitary
  - Assess levels of gonadotropins and sex hormones

FT4 = free thyroxine; TFTs = thyroid function tests.

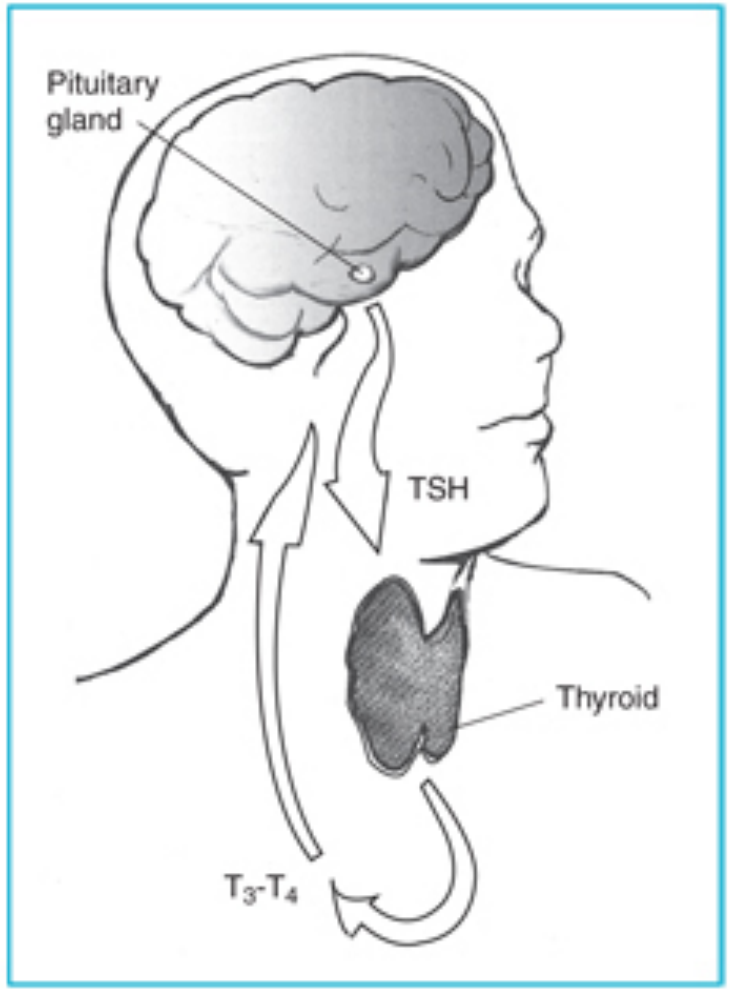
Byun DJ, et al. *Nat Rev Endocrinol*.2017;13(4):195-207.





Girotra M, et al. *JNCI Cancer Spectr.* 2018;2(3).

Primary Thyroid Dysfunction



- *Thyroiditis*: Thyroid **inflammation → leak thyroid hormones** (*thyrotoxicosis)* → can result in permanent **damage to thyroid** (hypothyroidism) *Graves disease less common*
- Important to distinguish primary thyroid dysfunction from thyroid dysfunction secondary to hypophysitis
  - Primary hyperthyroidism or thyrotoxicosis: Elevated-normal FT4/T3 suppress pituitary TSH
  - Primary hypothyroidism: Low-to-normal FT4 or T3 which elevates TSH section from the pituitary
  - Hypothyroidism secondary to pituitary dysfunction: Low-to-mid-normal levels of TSH → low FT4
- T3 levels in patients with acute illness can be inaccurate

Byun DJ, et al. *Nat Rev Endocrinol*. doi: 10.1038/nrendo.2016.205.
Image from: https://www.niddk.nih.gov/health-information/health-topics/endocrine/hashimotos-disease/Pages/fact-sheet.aspx

Primary Thyroid Dysfunction & CTLA-4 Blockade

- **Primary hypothyroidism** reported in **5.6% of patients (5.2% to 5.9%)**
- In a **review of clinical trials using ipilimumab without PD1 blockade, primary hypothyroidism presented after 5 months to 3 years**

Byun DJ, et al. *Nat Rev Endocrinol.* doi: 10.1038/nrendo.2016.205. Faje AT, et al. *J Clin Endocrinol Metab*. 2014;99:4078-4085.
Ryder M, et al. *Endocr Relat Cancer*. 2014;21:371-381.

Thyroid Dysfunction with PD-1/PD-L1 Antibodies

- Initial studies:
  - Hypothyroidism: ~5 – 8 %
  - Hyperthyroidism: ~3 %
- In **detailed recent studies looking specifically at thyroid dysfunction, may occur in 14 – 20 %** of pts

Study		Cohort		Endocrinopathy					
		Age (range)	*n*	Hypothyroidism	Hyperthyroidism	Adrenal insufficiency	Hypophysitis	Other thyroid*	T1DM
PD1 antibodies									
Nivolumab	Topalian *et al.* (2012)[12]	63 (29–85)	296	7†	3	NR	2§	NR	NR
	Topalian *et al.* (2014)[11]	61 (29–85)	107	6†	2	NR	1	1	NR
	Motzer *et al.* (2015)[109‖]	61 (SD 9)	168	10†	NR	NR	NR	NR	NR
	Gettinger *et al.* (2015)[67¶]	65 (38–85)	129	NR	NR	NR	NR	NR	NR
	Rizvi *et al.* (2015)[113]	65 (57–71)	117	3†	NR	1†	NR	1	NR
	Brahmer *et al.* (2015)[114]	62 (39–85)	135	5†	NR	NR	NR	NR	NR
	Robert *et al.* (2015)[107]	64 (18–86)	210	9†	7†	NR	1	NR	1
	Larkin *et al.* (2015)[132]	59 (25–90)	316	27†	13†	NR	2	NR	NR
Pembrolizumab	Robert *et al.* (2014)[66]	59 (18–88)	173	7†	3†	NR	2	NR	NR
	Robert *et al.* (2015)[115]	61–63 (18–89)	556	52†	27†	NR	3	NR	2
	Garon *et al.* (2015)[116]	64 (28–93)	495	34†	9†	NR	NR	NR	NR
Total‡			2,702	160/2,573 (5.9%)	71/2,153 (3.3%)	2/117 (1.7%)	10/1,658 (0.6%)	3/224 (1.3%)	3/766 (0.4%)
PDL1 antibodies									
MDX-1105	Brahmer *et al.* (2012)[26]	63 (29–83)	207	6†	NR	2†	NR	2	NR
Atezolizumab	McDermott *et al.* (2016)[117]	61 (33–81)	70	6†	NR	NR	NR	NR	NR
Total‡			277	12/277 (4.3%)	NA	2/207 (1.0%)	NA	2/207 (1.0%)	NA

Byun DJ, et al. *Nat Rev Endocrinol.* 2017;13(4):195-207. Osorio JC, et al. *Ann Oncol*. 2017;28:583-589.

Primary Thyroid Dysfunction With Anti-PD-1 Treatment

Typical of **onset** after the initiation of anti-PD1 treatment:

Thyrotoxicosis that Progresses to Hypothyroidism	Hypothyroidism	Isolated Thyrotoxicosis
3 weeks (range 3–21 wks)	**6 weeks** (range 3–40 wks)	**8.6 weeks** (range 6–11 wks)

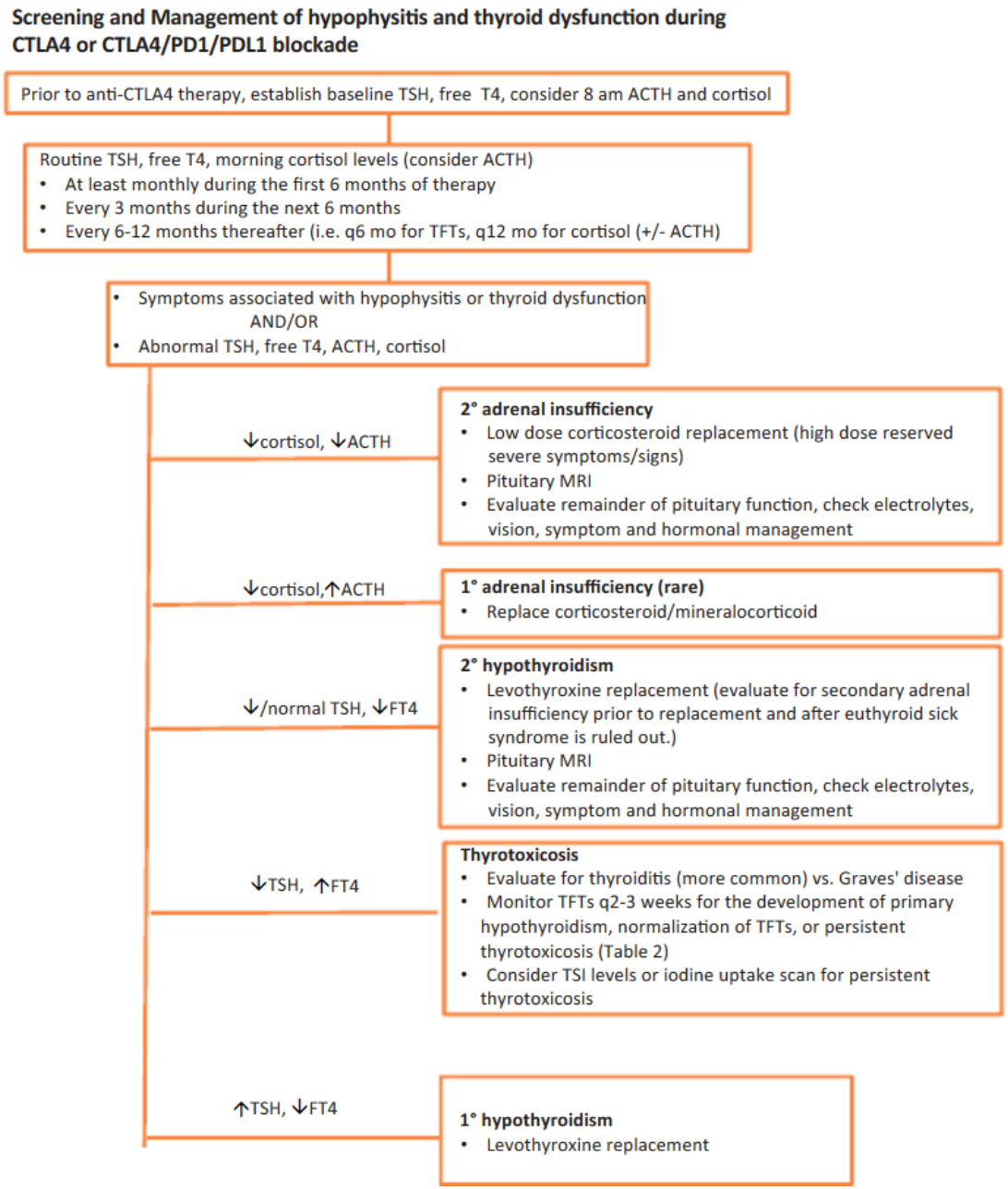
de Filette J, et al. *J Clin Endocrinol Metab*. 2016;101:4431-4439.

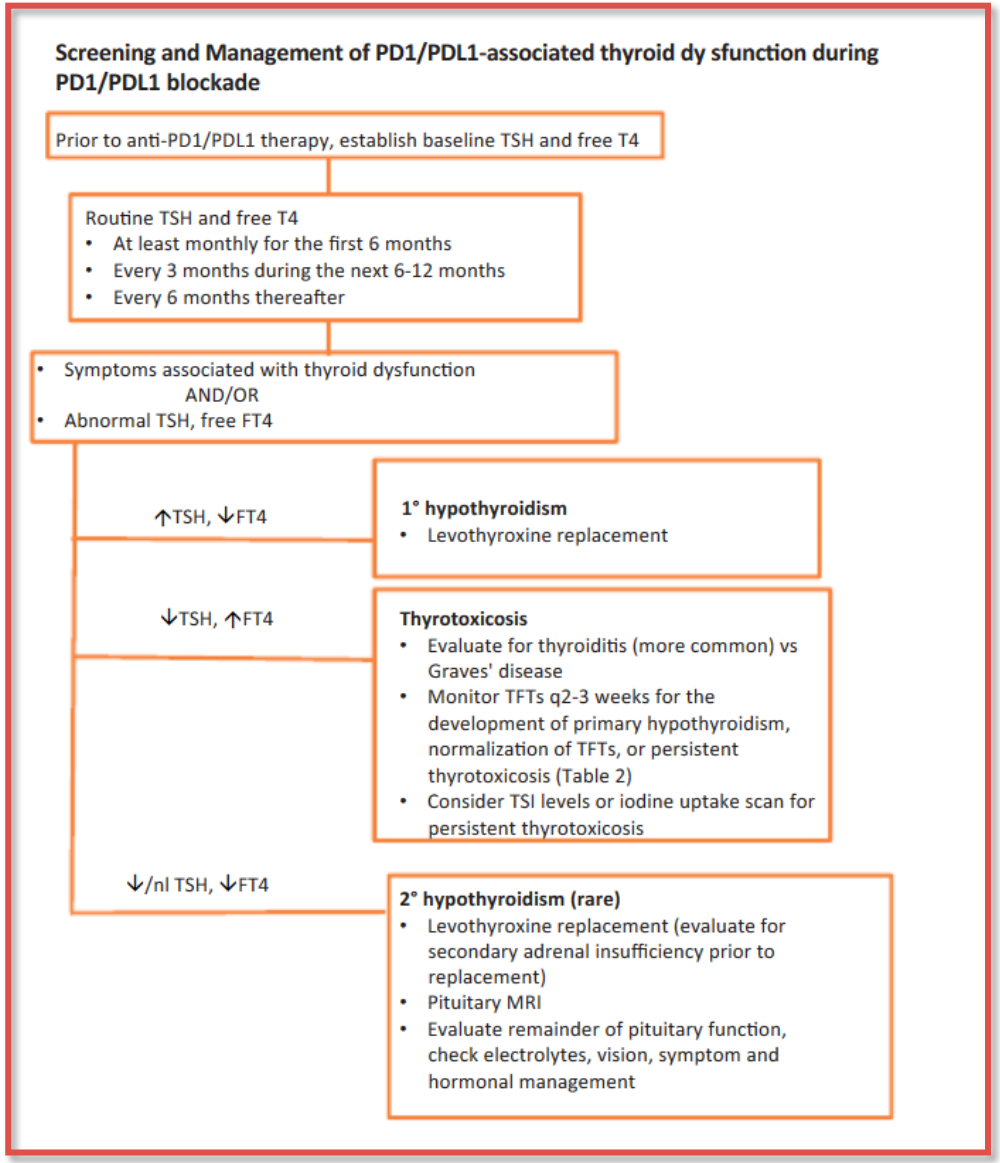
Primary Thyroid Dysfunction

- Can be subclinical and detected only via laboratory tests
  - **Hypothyroidism:** *Fatigue, muscle weakness, cold intolerance and bradycardia*
  - **Thyrotoxicosis:** *Tremor, weight loss, palpitations, heat intolerance*
- Thyrotoxicosis usually transient and can be managed conservatively
  - β-blockers can be useful for treating symptoms such as tremor and tachycardia
  - Majority of patients relatively asymptomatic
- Hypothyroidism replaced with thyroid hormone
- Monitor patients for symptoms/signs of hypothyroidism or thyrotoxicosis

- In addition to baseline TFTs, such as serum TSH & FT4, before initial therapy, subsequent TFTs should be measured (i.e. monthly during the first 6 months, then q3 months for 6 to12 months, then q6 months thereafter)

Byun DJ, et al. *Nat Rev Endocrinol.* 2017;13(4):195-207.





Girotra M, et al. *JNCI Cancer Spectr.* 2018;2(3).

Checkpoint Inhibitor Induced Insulin-Dependent Diabetes

- Incidence: estimated at ≤ 1 %
- Associated with *both anti-PD-1 and anti-PD-L1 agents*
- Rare with CTLA-4 blockade alone
- < 1 month - 12 months after drug exposure
- Given the morbidity related to DKA and hyperglycemia, clinicians managing patients undergoing anti-PD-1 or anti-PDL-1 therapy should carefully monitor patients for hyperglycemia.

Kapke J, et al. *Case Rep Oncol.* 2017;10(3):897-909. Barroso-Sousa, R, et al. J*AMA Oncol.* 2018;4(2):173-82.
Herold KC, NIH Conference on Cancer, Autoimmunity, & Immunology March 2018.

Checkpoint Inhibitor Induced Insulin-Dependent Diabetes

- New onset hyperglycemia or DKA
  - (polyuria/polydipsia; generalized weakness; abdominal pain, nausea or vomiting; blurry vision)
- Insulin dependent
- Low c-peptide values
- May or may not have autoantibodies
  - ~ 40% cases + autoantigens from pancreatic islets *(GAD65, insulin, insulinoma-associated protein 2 (IA-2), zinc transporter ZnT8)*
- 40-60% with elevated amylase/lipase; role of pancreatic inflammation
- Remain insulin dependent over time

Kapke J, et al. *Case Rep Oncol*. 2017;10(3):897-909. Barroso-Sousa, R, et al. *JAMA Oncol.* 2018;4(2):173-82.
Herold KC, NIH Conference on Cancer, Autoimmunity, & Immunology March 2018.

Summary

I. Immune-related endocrine events with these agents *most commonly affect the pituitary and thyroid glands*, but other target organs may be affected

II. There is an *increased susceptibility to hypophysitis in patients treated with anti-CTLA-4 therapy*

III. *Anti-PD-1/PDL1 treatment* has been predominately linked to *primary thyroid dysfunction and less commonly IDDM*

IV. Immune-related endocrine events are often *irreversible; management typically requires hormone replacement*

MedEd ON THE GO Oncology

Introduction and Clinical Indications for Immune Effector Cell Therapy

Loretta J. Nastoupil, MD

Associate Professor
Department of Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center
Houston, TX

Objectives

I. Review the clinical development of immune effector cell therapy, i.e., CAR T-cell therapy

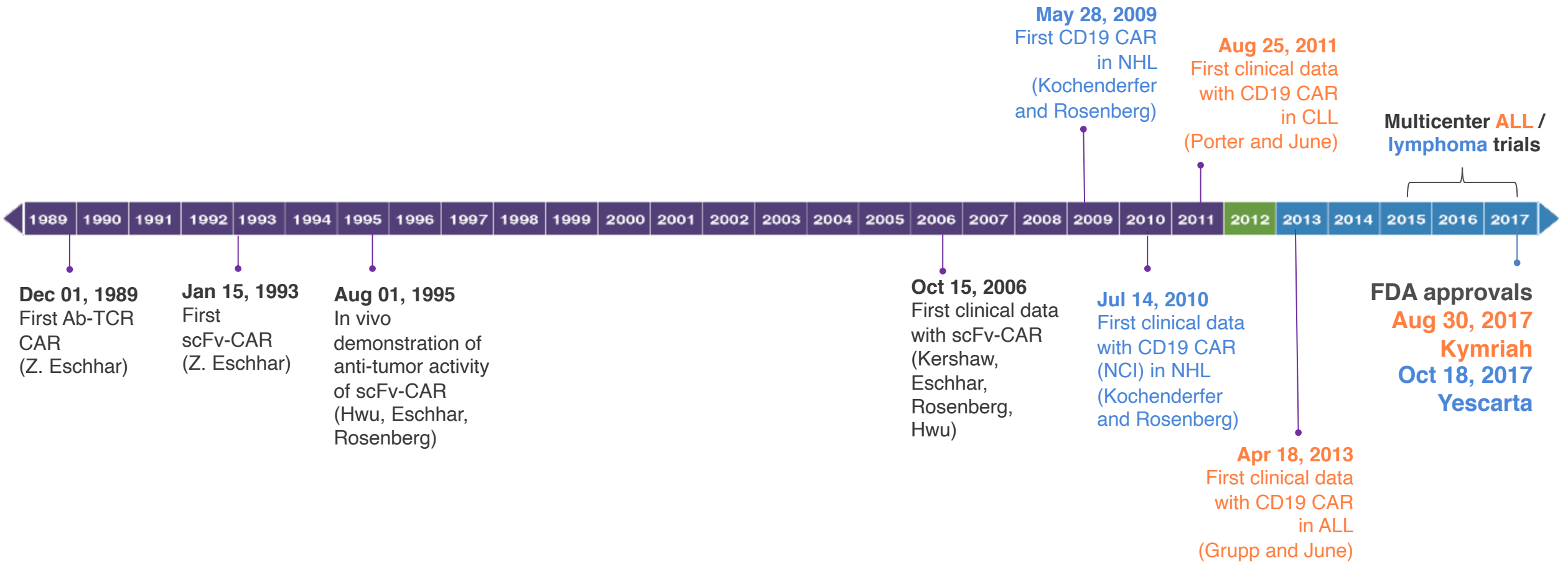
II. Describe the clinical situation in which CAR T-cell therapy is currently approved

III. Review the unique side effects associated with CAR T-cell therapy

CAR T Development

From Discovery to FDA Approval

Discovery to FDA approval ~25 years



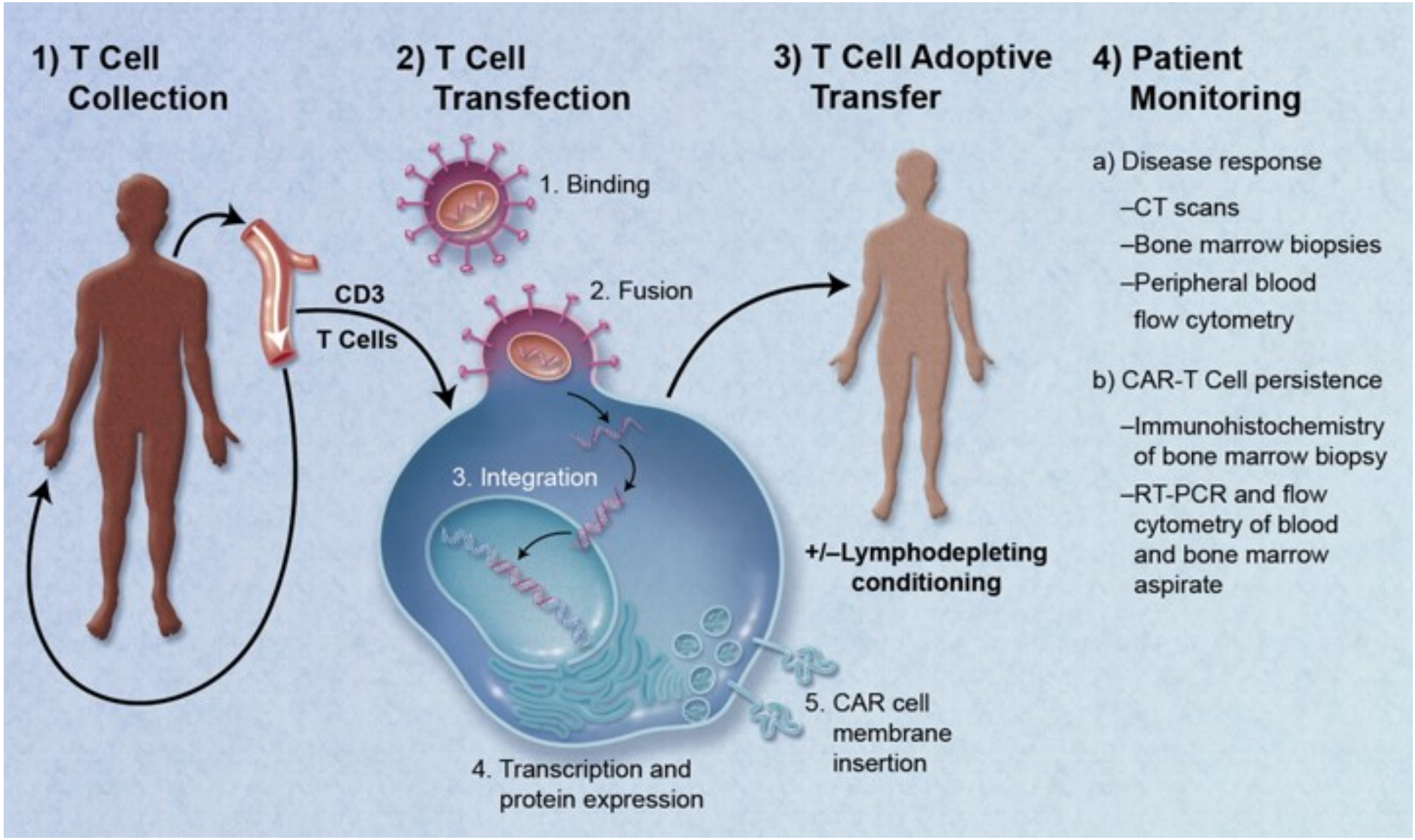
What Makes a Good CAR T-cell Candidate?

Tumor antigen that is present on all, or most, of the cancer cells and is necessary for that cancer cell's survival

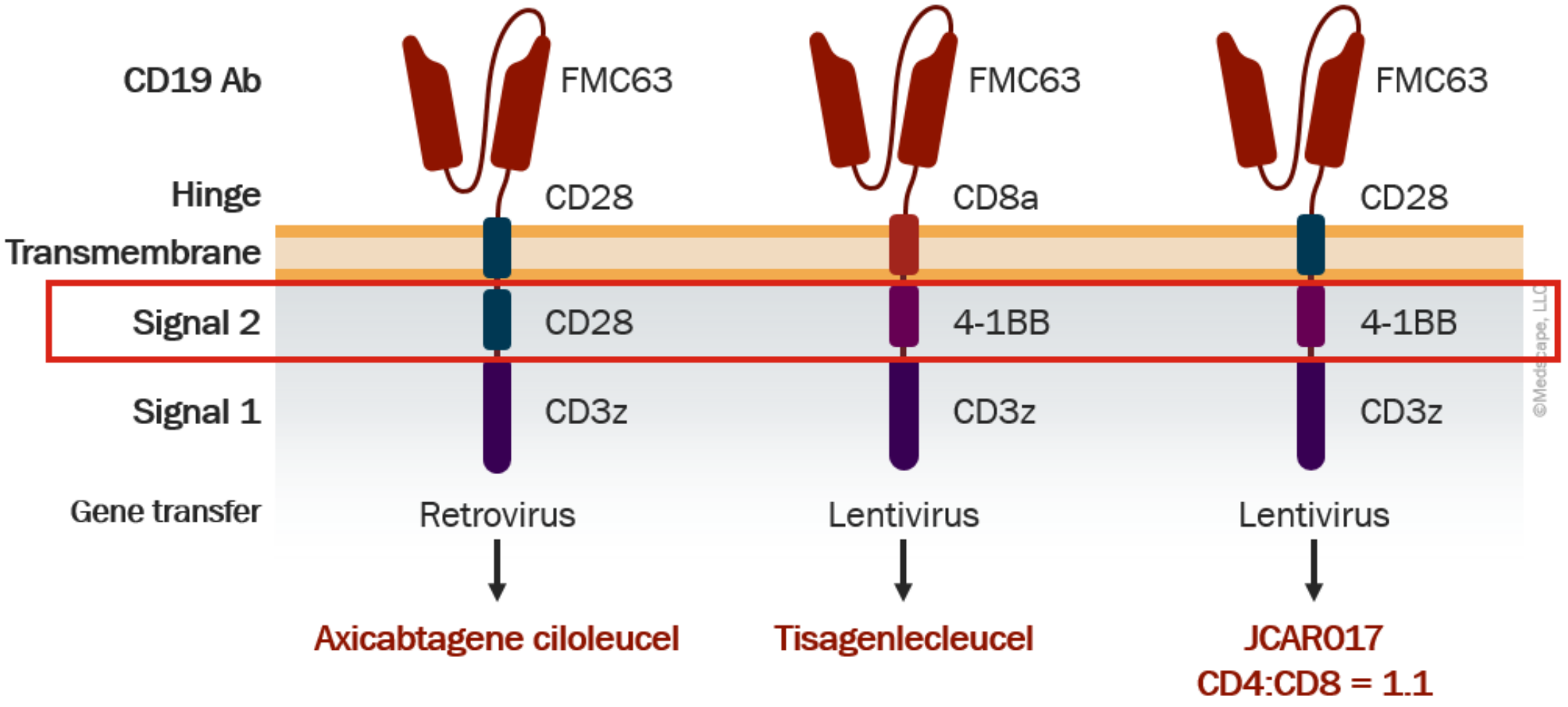
Tumor antigen that is not present on normal healthy cells such that immune attack on those normal healthy cells would lead to an unacceptable toxicity

A Good CAR T-cell Candidate

CAR T-cell Manufacturing Process



CD19 CAR T-cell Therapy in Pivotal Trials



FDA Approved Indications for CAR T-cell therapy

- **Tisagenlecleucel is indicated for[1]**
  - Adult patients with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy
  - Patients ≤ 25 years with B-cell precursor ALL refractory or after second relapse

- **Axicabtagene ciloleucel is indicated for[2]**
  - Adult patients with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy

1. Kymriah™ [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018.
2. Yescarta® [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2019.

CAR T-cell Administration and Timing Considerations

- **Special considerations:**
  - Can the patient wait: tumor burden and/or potential for organ function compromise
  - Performance status
  - Risk of bleeding
  - Cardiac, renal and/or pulmonary reserve
  - Prior history or current CNS involvement
  - History of autoimmune disease or neurologic conditions
  - Insurance coverage
- Eligibility criteria will be center dependent
- Timing matters! Best to refer at the time of relapse, before salvage chemotherapy

Summary

I. There are two FDA approved CD19 targeted CAR-T products for the treatment of relapsed refractory large B-cell lymphoma

II. They differ in terms of their costimulatory molecules, which may also lead to differences in terms of onset of acute toxicity and persistence

III. Both CAR-T treatment strategies appear equivalent in terms of efficacy, with about 40% of patients resulting in durable remissions, and this could be definitive therapy for those patients

MedEd ON THE GO Oncology

Identification and Management of Toxicity Associated with Immune Effector Cells

Loretta J. Nastoupil, MD

Associate Professor
Department of Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center
Houston, TX

CAR T-cell Toxicity- Acute

Cytokine Release Syndrome

- **Cause:** activation/expansion of CAR T-cells and increased levels cytokines (IL-6, IL-15, INF-γ, GM-CSF, others)
  - Monocytes and macrophages are a source of some of these cytokines
- **Onset:** variable; 1-3 days CD28; 3-5 days 4-1BB
- **Duration:** 3 – 5 days
- **Risk:** variable up to 30% grade 3
  - Disease burden
  - Peak CAR T-cell levels
  - Pre-treatment and peak cytokine levels

Neurotoxicity

- **Cause:** mechanism less well understood
  - Impaired vascular/BBB integrity
    - High ANG2:ANG1; High vWF levels, low vWF:ADAMSTS13; markers of DIC
  - High CSF:blood cytokine levels
  - CAR+ and CAR- T-cells in CSF
- **Onset:** 5 – 7 days; later than CRS
- **Duration:** 5 – 10 days
  - Fully reversible except in cases of fatal cerebral edema
- **Risk:** variable, up to 40% grade 3
  - Disease burden
  - Peak CAR T-cell levels
  - Early and high grade CRS
  - Pre-treatment and peak cytokine levels
  - DIC

Identification and Management of Acute Toxicity Associated with Immune Effector Cells

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

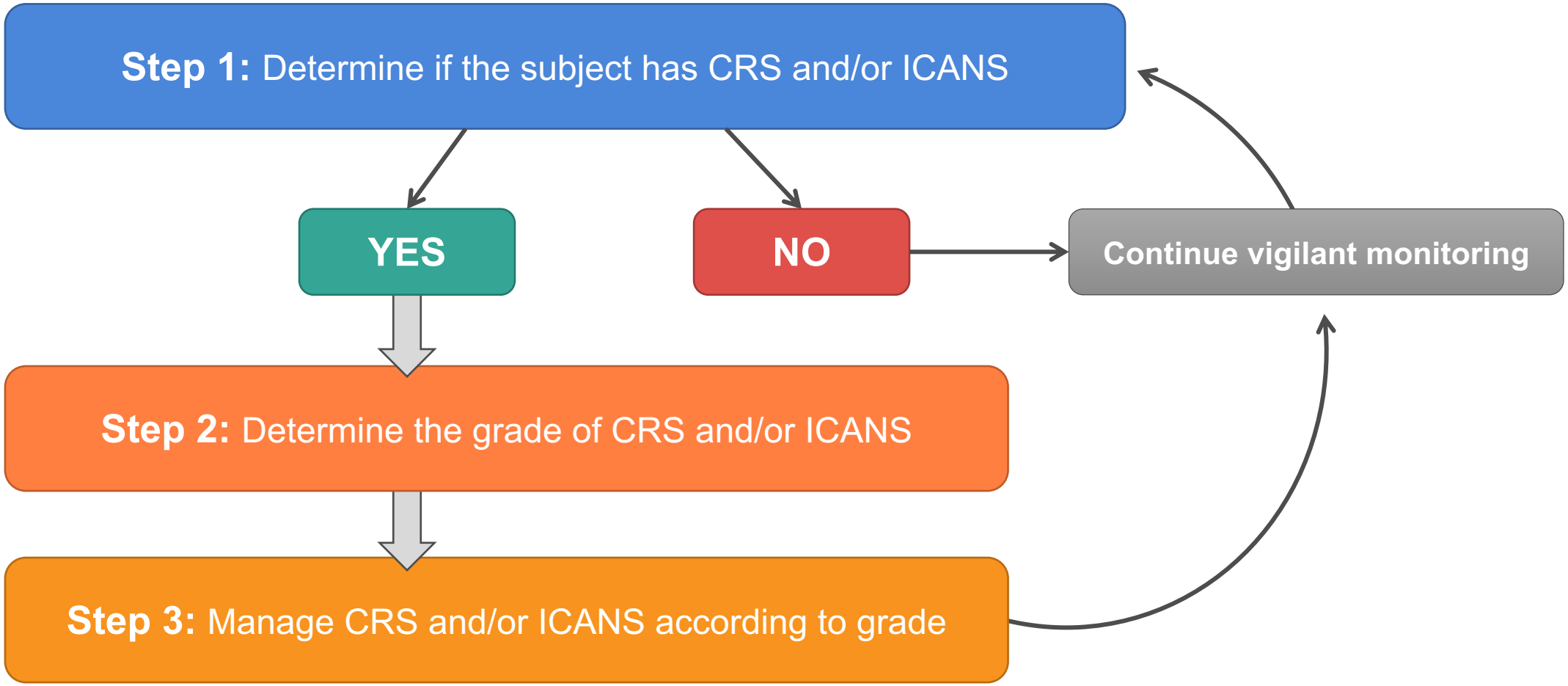
Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Step Approach to IEC-Associated Toxicity Assessment and Management



CRS – Cytokine Release Syndrome; ICANS - Immune effector cell (IEC)-Associated Neurotoxicity Syndrome
MD Anderson Cancer Center

ASTCT Definition of CRS

- CRS is “a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset and may include hypotension, capillary leak (hypoxia) and end organ dysfunction.”

- CRS should be applied to any immune effector cell engaging therapy, not just CAR T cells

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

ASTCT Consensus Grading of CRS

CRS Parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever#†	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
		With either:		
Hypotension#	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And / or‡		
Hypoxia#	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

#Not attributable to any other cause

†In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity

‡CRS grade is determined by the more severe event

^Low-flow nasal cannula is ≤ 6 L/min and high-flow nasal cannula is > 6 L/min

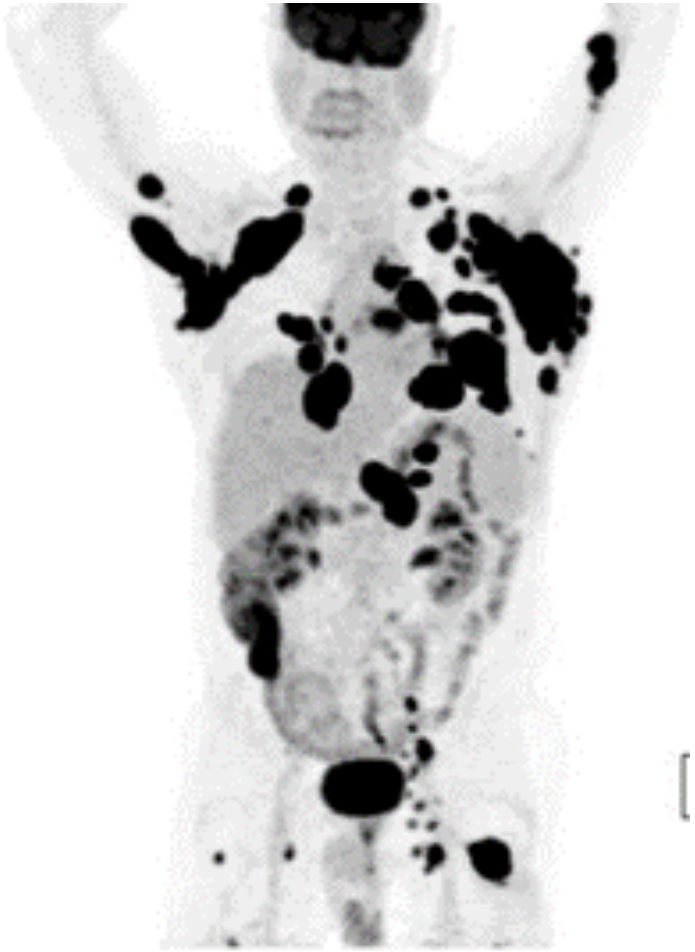
*Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Clinical Case – CRS

- 62 y/o M with a h/o refractory DLBCL, non-GCB, s/p 4 lines of therapy undergoes anti-CD19 autologous CAR T cell therapy. On day 1 he has fever, Tmax 39.4, blood pressure is normal, O2 sats > 95%. Despite best supportive care, fever persists and on day 3 he develops hypotension (80/60), mild tachycardia HR 110, O2 sats 95% on RA.

- **What is the next step in management?**
- He initially responds to 500mL NS IV fluid bolus with improvement in BP (110/64), HR 95, O2 sats 94% on RA.
- 6 hours later you are notified by RN with the following vital signs: T 39.1, HR 110, BP 94/72, O2 sats 90% on 2 L NC
- What is the next step in management?



CARTOX– Management of CRS

*** High risk for severe CRS: Bulky disease, co-morbidities, early onset CRS (<3 days)**

CRS Grade	Symptom or Sign	Management
Grade 1	Fever or grade 1 organ toxicity	• Acetaminophen and hypothermia blanket as needed for fever • Ibuprofen may be used as second option for fever if not contraindicated • Assess for infection with blood and urine cultures, and chest x-ray • Empiric broad-spectrum antibiotics and filgrastim if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider IL-6 antagonist for persistent (> 3 days) or refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500 – 1000 mL normal saline • May give a second IV fluid bolus if SBP remains < 90 mm Hg • Consider IL-6 antagonist for hypotension refractory to fluid bolus • If hypotension persists after two fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, and obtain ECHO and initiate other methods of hemodynamic monitoring • In patients at high-risk* or if hypotension persists after IL-6 antagonist, may use dexamethasone 10mg IV q 6h • Manage fever and constitutional symptoms as in grade 1 CRS
	Hypoxia	• Supplemental oxygen • IL-6 antagonist +/- corticosteroids and supportive care as in hypotension
	Grade 2 organ toxicity	• Symptomatic management of organ toxicity as per standard guidelines • Use IL-6 antagonist +/- corticosteroids and supportive care as in hypotension

Maximum of one siltuximab dose per patient

Neelapu. *Nat Rev Clin Oncol.* 2018;15(1):47-62

CARTOX– Management of CRS

CRS Grade	Symptom or Sign	Management
Grade 3	**Hypotension**	• IV fluid boluses as needed as in grade 2 • IL-6 antagonist as in grade 2 if not administered previously • Vasopressors as needed • Transfer to ICU, ECHO and hemodynamic monitoring as in grade 2 • Start dexamethasone 10mg IV q 6h; increase to 20 mg IV every 6h if refractory • Manage fever and constitutional symptoms as in grade 1
	Hypoxia	• Supplemental oxygen including high flow oxygen delivery and non-invasive positive pressure ventilation • IL-6 antagonist + corticosteroids and supportive care as above
	Grade 3 organ toxicity or grade 4 transaminitis	• Symptomatic management of organ toxicity as per standard guidelines • IL-6 antagonist + corticosteroids and supportive care as above
Grade 4	**Hypotension**	• IV fluids, IL-6 antagonist, vasopressors, and hemodynamic monitoring as in grade 3 • High-dose corticosteroids (e.g. Methylprednisolone IV 1g/day x 3 days followed by rapid taper at 250mg q12 h x 2 days, 125mg q12 h x 2 days, and 60mg q12 h x 2 days); taper of corticosteroids may be individualized • Manage fever and constitutional symptoms as in grade 1
	Hypoxia	• Mechanical ventilation • IL-6 antagonist + corticosteroids and supportive care as above
	Grade 4 organ toxicity excluding transaminitis	• Symptomatic management of organ toxicities as per standard guidelines • IL-6 antagonist + corticosteroids and supportive care as above

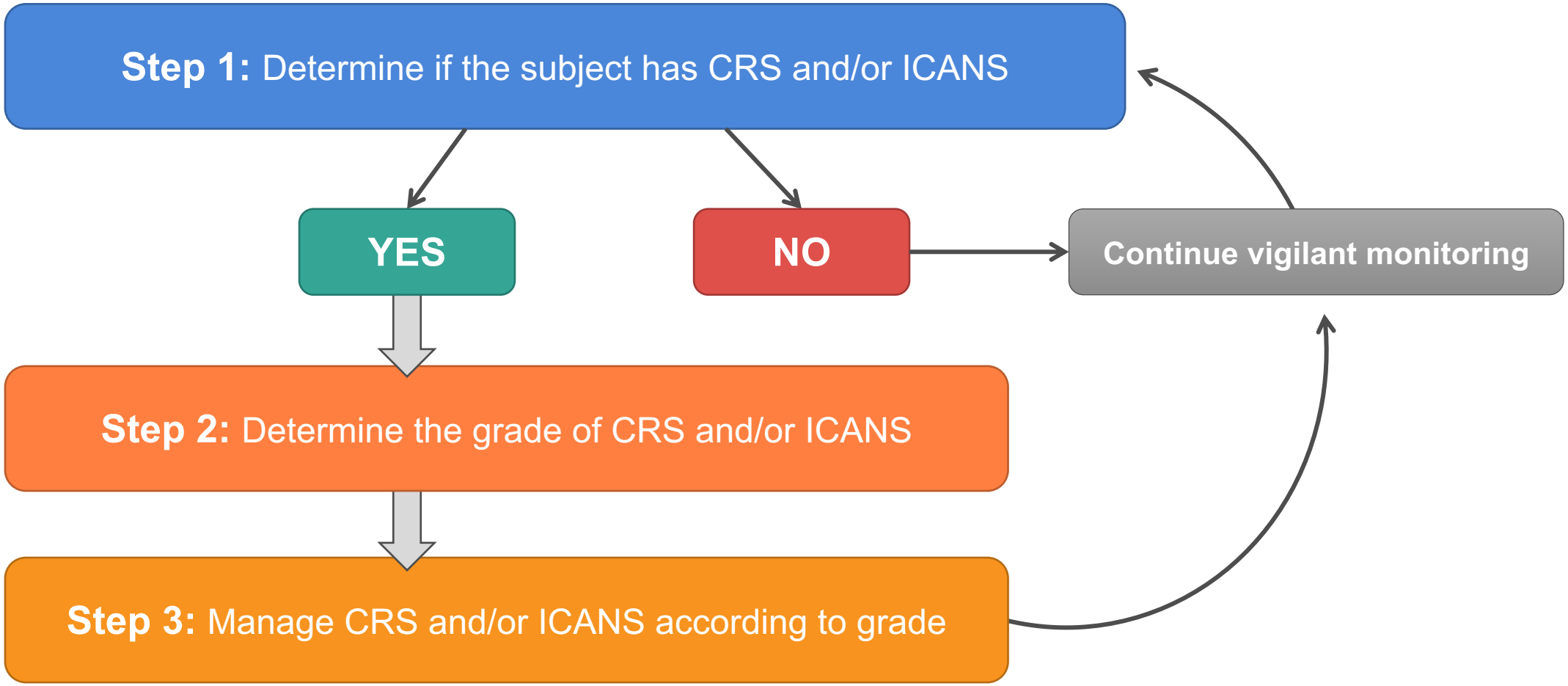
Neelapu. *Nat Rev Clin Oncol.* 2018;15(1):47-62

Back to Our Case

- 62 y/o M is day 6 following CD19 CAR T-cell therapy
- On day 3, he developed grade 2 CRS. He received 2 doses of tocilizumab. He is currently afebrile, on room air with adequate sats, HR and BP.
- However, you are notified by the bedside RN that he is disoriented, cannot provide his location or date. Family are also alarmed that he is slow to respond to questions and is providing inaccurate responses.

- What is the next step in management?

Step Approach to IEC-Associated Toxicity Assessment and Management



CRS – Cytokine Release Syndrome; ICANS - Immune effector cell (IEC)-Associated Neurotoxicity Syndrome
MD Anderson Cancer Center

ASTCT Definition of ICANS

(IEC-Associated Neurotoxicity Syndrome)

- ICANS is “a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.”
- Similar to CRS, ICANS should be applied to any immune effector cell engaging therapy, not just CAR T cells.

Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-638.

ASTCT Encephalopathy Assessment Tool

Immune-Effector Cell-Associated Encephalopathy (ICE) Tool	
Orientation	Orientation to year, month, city, hospital: 4 points
Naming	Ability to name 3 objects (eg, point to clock, pen, and button): 3 points
Following commands	Ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point
Writing	Ability to write a standard sentence (eg, “Our national bird is the bald eagle): 1 point
Attention	Ability to count backwards from 100 by ten: 1 point

- You ask the bedside RN for his ICE score and she reports a score of 4, he can follow commands (1 point) and can name 3 objects (3 points).
- He is not oriented, sentence is ineligible, and he fails twice to count backwards.

Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-638.

ASTCT Consensus Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score^	7 – 9	3 – 6	0 – 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness❖	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimulation to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings§	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging#	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

^ A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
❖ Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
§ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
# Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-638.

CARTOX– Management of Neurotoxicity

Grade	Management
Grade 1	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids and assess swallowing • Convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam (0.25-0.5mg IV every 8h) or haloperidol (0.5mg IV every 6h) may be used for agitated patients with careful monitoring • Neurology consultation • Fundoscopic exam to assess for papilledema • MRI brain with and without contrast; diagnostic lumbar puncture with opening pressure; MRI spine if focal peripheral neurological deficits; CT scan of brain may be performed if MRI brain is not feasible • Daily 30 min EEG until toxicity symptoms resolve; if no seizures on EEG, continue levetiracetam 750 mg every 12h • If EEG shows non-convulsive status epilepticus, treat as per algorithm in Appendix 4 • Consider IL-6 antagonist if associated with concurrent CRS
Grade 2	• Supportive care and neurological work-up as per grade 1 • If associated with concurrent CRS symptoms, IL-6 antagonist • If NOT associated with CRS, dexamethasone 10mg IV every 6h or methylprednisolone 1mg/kg IV every 12h or if refractory to IL-6 antagonist • Consider ICU transfer if associated with grade 2 or greater CRS

Maximum of one siltuximab dose per patient

Neelapu. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

CARTOX– Management of Neurotoxicity

Grade	Management
Grade 3	• Supportive care and neurological work-up as per grade 1 • ICU transfer is recommended • IL-6 antagonist if associated with concurrent CRS as per grade 2 and if not administered previously • If NOT associated with CRS, corticosteroids as above or for worsening symptoms despite anti-IL-6 therapy; Continue corticosteroids until improvement to grade 1 and then taper • Stage 1 or 2 papilledema with CSF op < 20mmHg, treat as per algorithm in Appendix 6 • Consider repeat neuro-imaging (CT or MRI) q 2-3 days if persistent neurotoxicity ≥ grade 3 CRES
Grade 4	• Supportive care and neurological work-up as per grade 1 • ICU monitoring; Consider mechanical ventilation for airway protection • IL-6 antagonist and repeat neuro-imaging as per grade 3 • High-dose corticosteroids (e.g. methylprednisolone IV 1 g/day x 3 days followed by rapid taper at 250mg q12 h x 2 days, 125mg q12 h x 2 days, and 60mg q12 h x 2 days); Continue corticosteroids until improvement to grade 1 and then taper • For convulsive status epilepticus, treat as per algorithm in Appendix 5 • Stage 3, 4, or 5 papilledema, CSF op ≥ 20mmHg, or cerebral edema, treat as per algorithm in Appendix 6

Neelapu. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

Case Conclusion

62 y/o M, s/p CAR T-cell therapy with grade 2 CRS on day 6. He is evaluated with brain imaging and EEG. No cerebral edema, no seizure activity. No evidence of papilledema. He is started on Keppra for seizure prophylaxis. Neurology is following closely.

- He initiates dexamethasone 10mg IV q 6 hrs and continues this for 2 days. ICE score is now 10, steroids are tapered over the next several days.
- He fully recovers within 2 weeks.

He returns at month 3 with moderate pancytopenia. IgG level is 288. He is now experiencing late toxicity (prolonged cytopenias and B-cell aplasia). He is supported with growth factors, transfusion as indicated and IVIG. No evidence of MDS on bone marrow eval.

He is now 2 years out with no evidence of recurrent lymphoma. IgG 580. ANC 1.5.

Summary

I. This is an example of a case of a patient who had grade two cytokine release syndrome, grade two ICANS, had a full recovery.

II. His light toxicity was pancytopenia that ultimately did recover, and B-cell aplasia with hypogammaglobulinemia.

III. This also demonstrates the durability of responses that we see in about 40% of patients as he remains without disease relapse two years out.

MedEd ON THE GO Oncology

Recognizing and Managing Central Nervous System Toxicities

Chelsea C. Pinnix, MD, PhD

Associate Professor
Associate Residency Program Director
Department of Radiation Oncology, Hematologic Malignancies Section
The University of Texas MD Anderson Cancer Center
Houston, TX

Neurotoxicities Affecting the CNS

- Seizures (CAR T-cell therapy, blinatumomab)[1]
- Headache
- Acute encephalopathy (CAR T-cell therapy, blinatumomab)[1,2]
- Chronic encephalopathy
  - Progressive multifocal leukoencephalopathy (PML)
- Stroke
- Posterior reversible encephalopathy syndrome (PRES)
- Radiation necrosis
- Myelopathy

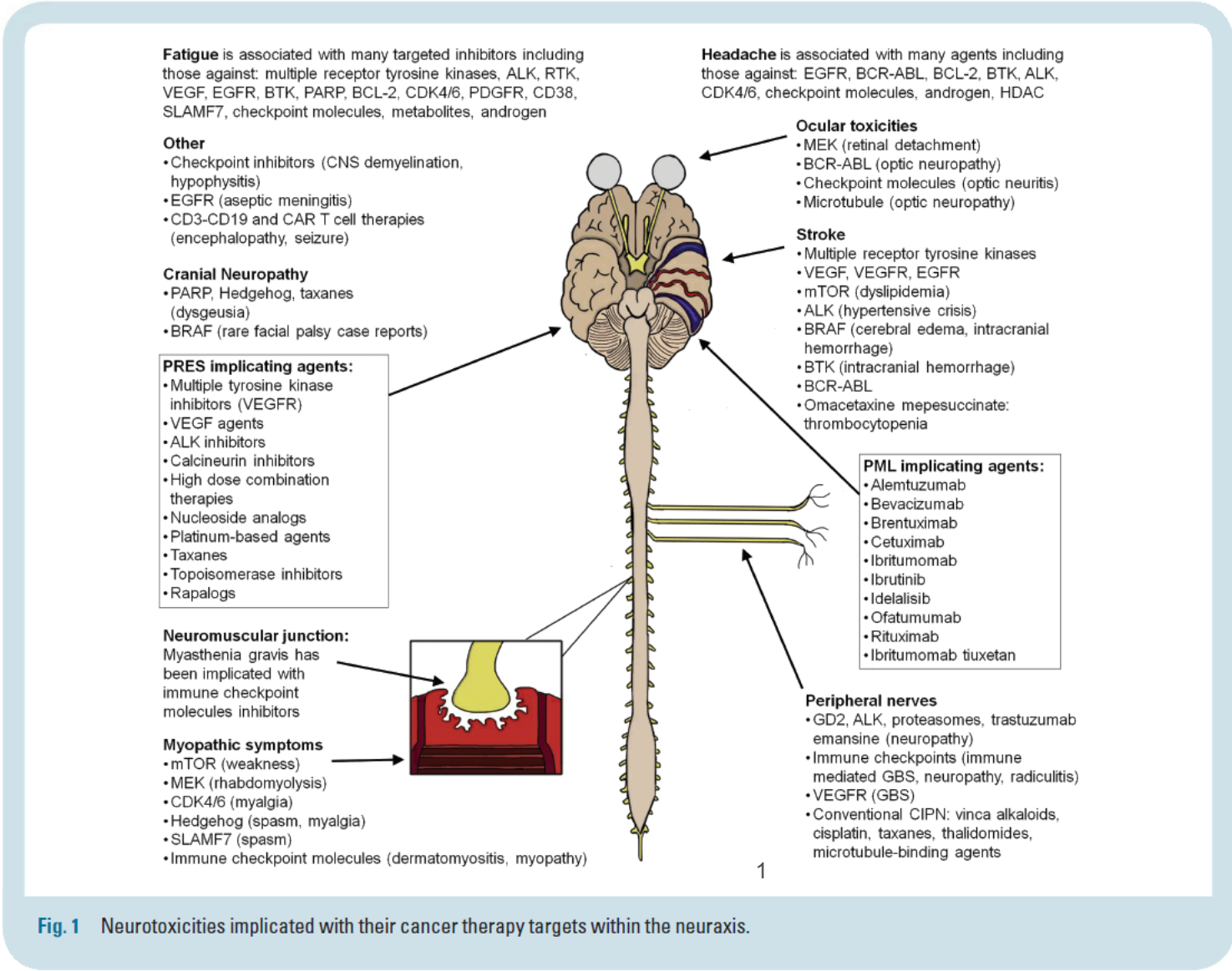


Fig. 1 Neurotoxicities implicated with their cancer therapy targets within the neuraxis.

[1]Magge RS & DeAngelis LM. *Blood Rev.* 29, 93-100 (2015).
[2]Neelapu SS, et al. *Hematol Oncol.* 2019;37 Suppl 1:48-52.
[3]Zukas AM, Schiff D. *Neuro Oncol*. 2018 Jan 10;20(1):24-36.

Neurotoxicity Related to CAR T-cell Therapy

- After cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) is the second most common acute toxicity observed after CAR T cell therapy[1]
- Significantly elevated LDH observed among patients that experience severe neurotoxicity[2]
- Severity of neurotoxicity seems to be associated with cytokines and the degree of CAR T-cell expansion
- **Clinical Presentation:** aphasia, confusion that can progress to seizures, coma, motor weakness and cerebral edema
- Severe neurotoxicity has been associated with inferior OS[2]

1. Lee DW, Santomasso BD, Locke FL et al. *Biol Blood Marrow Transplant.* 2019; 25(4):625-638.
2. Karschnia P, Jordan JT, Forst DA et al. *Blood.* 2019;133(20):2212-2221.

Immune Effector Cell-Associated Encephalopathy (ICE) Score

ICE	
Orientation	Orientation to year, month, city, hospital: 4 points
Naming	Ability to name 3 objects (eg, point to clock, pen, and button): 3 points
Following commands	Ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point
Writing	Ability to write a standard sentence (eg, “Our national bird is the bald eagle): 1 point
Attention	Ability to count backwards from 100 by 10: 1 point

Scoring	
10	No impairment
7 – 9	Grade 1 ICANS
3 – 6	Grade 2 ICANS
0 – 2	Grade 3 ICANS
0	Due to patient unarousable and unable to perform ICE assessment, Grade 4 ICANS

Goal: Provide objectivity for grading across all FDA approved CART products

Lee DW, Santomasso BD, Locke FL et al. *Biol Blood Marrow Transplant.* 2019 Apr;25(4):625-638.

ICANS Consensus Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7 – 9	3 – 6	0 – 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimulation to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

- ICANS grade is determined by the most severe event among the neurotoxicity domains that is not attributable to other causes
- A patient with a ICE score of 3 who has a generalized seizure would be classified as grade 3 ICANS

Lee DW, Santomasso BD, Locke FL et al. *Biol Blood Marrow Transplant.* 2019 Apr;25(4):625-638.

Management of ICANS

- **Essential components of therapy**
  - Early recognition of toxicity → prompt intervention
  - Supportive care, close monitoring
  - Many centers use prophylactic levetiracetam on day of CAR T-cell infusion
  - Diagnostic EEG
  - Brain imaging to exclude cerebral edema
- **Role of Steroids**
  - Considered in grade 2 ICANS
  - Grade 3 ICANS: dexamethasone 10-20 mg q6 hours
  - Grade 4 ICANS: high dose methylprednisolone up to 1000 mg/day
- Patients with cerebral edema require measures to lower ICP
- Grade 4 ICANS patients typically in ICU and intubated

ASBMT ICANS Grade	Management
Grade 1	• Aspiration precautions and IV hydration • Seizure prophylaxis with levetiracetam • EEG • Imaging of brain • Consider tocilizumab if there is concurrent CRS
Grade 2	• Supportive care as in grade 1 • Consider dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in grade 1 • Dexamethasone 10-20 mg IV q 6 hours or its equivalent of methylprednisolone • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide • High-dose methylprednisolone 1000 mg/day for focal/local edema
Grade 4	• Supportive care as in grade 1 • High-dose methylprednisolone 1000 mg/day • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide • Imaging of spine for focal motor weakness • Lower ICP by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema

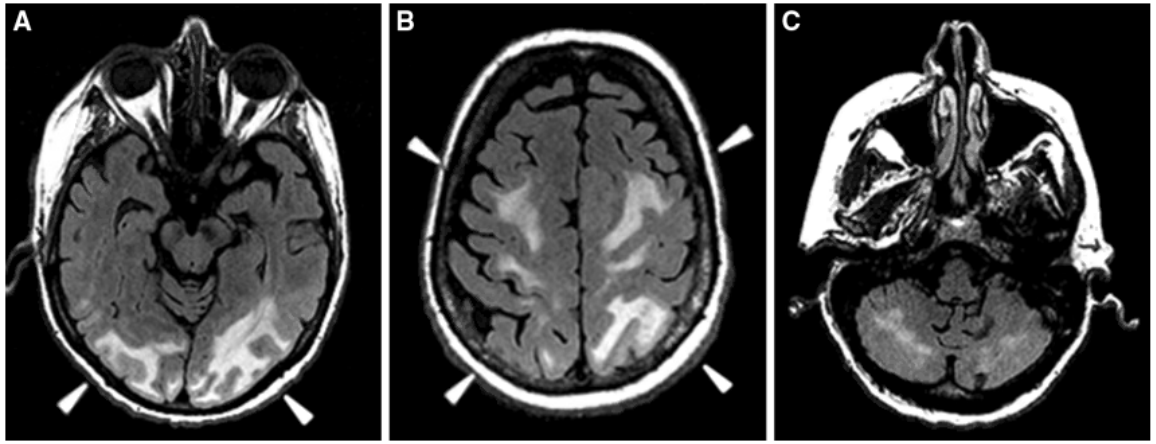
Neelapu SS, et al. *Hematol Oncol.* 2019 Jun;37 Suppl 1:48-52.

Posterior Reversible Encephalopathy Syndrome (PRES)

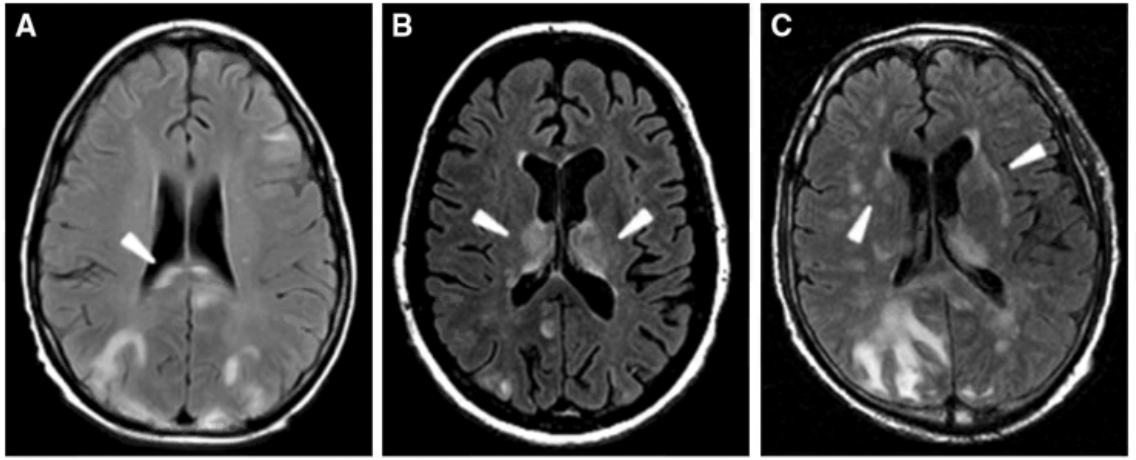
- Disorder characterized by a range of neurological symptoms in the setting of characteristic neurologic findings
- **Clinical presentation:** HA, visual changes, confusion, seizures
- Often seen in setting of acute hypertension
- Hypothesized etiology: failed cerebral blood pressure autoregulation coupled with endothelial dysfunction
- No single anti-neoplastic agent has been consistently associated with PRES however multiple agents are linked:
  - Several chemotherapy agents (cisplatin, cytarabine, gemcitabine)
  - Immunomodulatory agents (tacrolimus)
  - Targeted therapies (bevacizumab, ipilimumab, sorafenib, sunitnib and rituximab)

PRES: Imaging Findings

- Imaging: on MRI T2 FLAIR sequences bilateral white matter lesions, predominating in the posterior circulation
- Additional lobar involvement often appreciated among cancer patients
  - In MDACC study of 69 patients with PRES, 61% of patients had atypical MRI findings[1]



Typical MRI Findings



Atypical MRI Findings

1. Kamiya-Matsuoka C, Paker AM, Chi L et al. *J Neurooncol.* 2016 May;128(1):75-84.

PRES: Therapy, Management and Outcomes

DIAGNOSIS

Imaging, LP to exclude other diagnoses, EEG for detection of non-convulsive seizures

THERAPY

Discontinuation of the triggering agent, maintenance of normal BP, anticonvulsive therapy

OUTCOMES

Most often neurological manifestations are reversible however residual neurological deficits can be observed (especially among patients with intracranial hemorrhage and thrombocytopenia)[1]

1. Kamiya-Matsuoka C, Paker AM, Chi L et al. *J Neurooncol.* 2016 May;128(1):75-84.

Progressive Multifocal Leukoencephalopathy (PML)

- Among patients with systemic immunosuppression, John Cunningham virus (JCV) infection of the CNS can cause PML
- In the general population JCV seropositivity is prevalent (ranging from 33-91% based on the population and country studied) and asymptomatic
- Among patients with chronically decreased cellular T lymphocytic immunosurveillance of the CNS, PML can occur
  - HIV
  - Hematologic malignancy
  - Monoclonal antibody therapy (natalizumab, rituximab, alemtuzumab, brentuximab)

Table 2. Incidence of PML in Different Populations.[1]

Clinical Entity	Incidence (Post 1996)
General population	1 per 200 000
HIV	1.3 per 1000
Natalizumab (HIV negative)	1 per 1000
Rituximab (HIV negative)	1 per 32 000

Abbreviation: PML, progressive multifocal leukoencephalopathy.

1. Bohra C, Sokol, Dalia S. *Cancer Control*. 2017 Oct-Dec; 24.

PML: Presentation and Diagnosis

Table 1. Clinical and Pathological Features of PML.

Clinical features
- Hemiparesis, visual impairment, and altered mentation
- Headache, vertigo, and seizures
- Parkinson's and aphasia
- Others depending on site of lesion

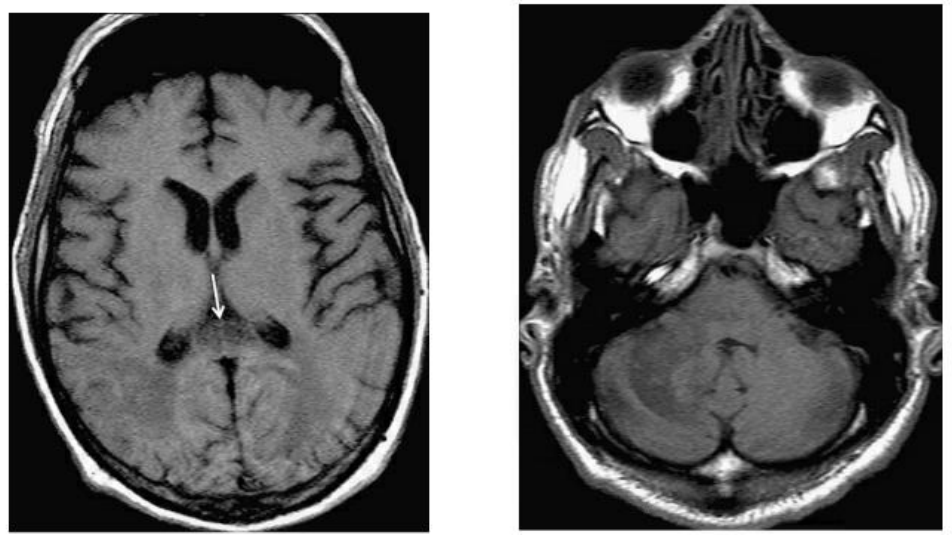
Radiological features
- Most likely subcortical lesion
- No ring enhancing
- CT scan demonstrates nonenhancing, subcortical hypodensities; MRI scan shows altered signal from the subcortical lesions

Laboratory features of PML
- EEG shows focal slowing; CSF may show mild elevation of protein or an increased cell count, viral antigen detection, viral DNA detection, and demonstration of viral pathogens in the lymphocytic cells

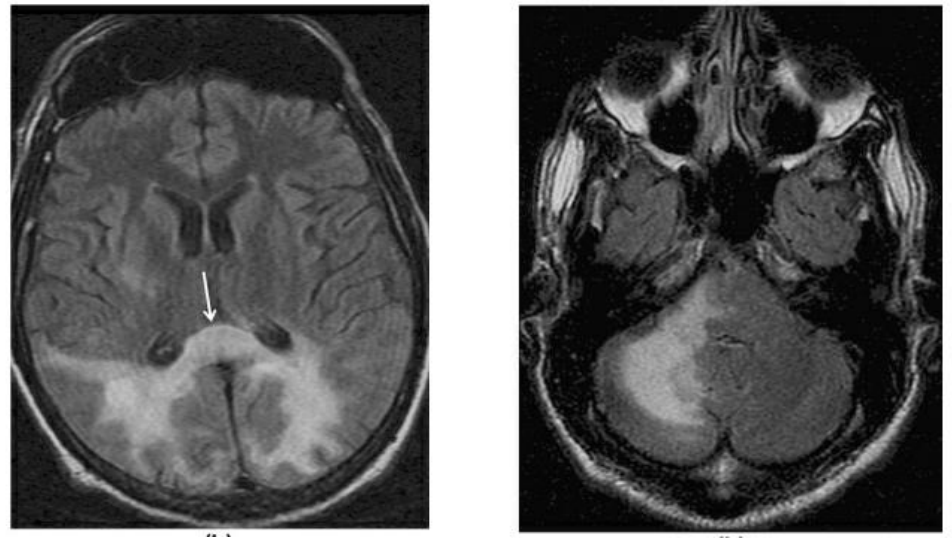
Pathological features
- The microscopic hallmark of the disease is intranuclear basophilic or eosinophilic inclusions within the swollen nuclei of oligodendrocytes, often at the periphery of lesions. Large, occasionally multinucleated astrocytes with prominent processes are another characteristic feature

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy.

T1



T2 FLAIR



Shah R, Bag AK, Chapman PR, Curé JK. *Clin Radiol*. 2010 Jun;65(6):431-9.
Bohra C, Sokol , Dalia S. *Cancer Control*. 2017 Oct-Dec; 24.

PML: Treatment and Prognosis

- No definite therapy
- High rates of mortality
  - Among pts with underlying hematologic malignancy mortality 74-90%[1]
- Recent data suggest that PD-1 blockade may result in reduction of JC viral load and increased CD4+ and CD8+ activity against the JC virus[2-4]
- BK virus-specific T cell therapy[5]

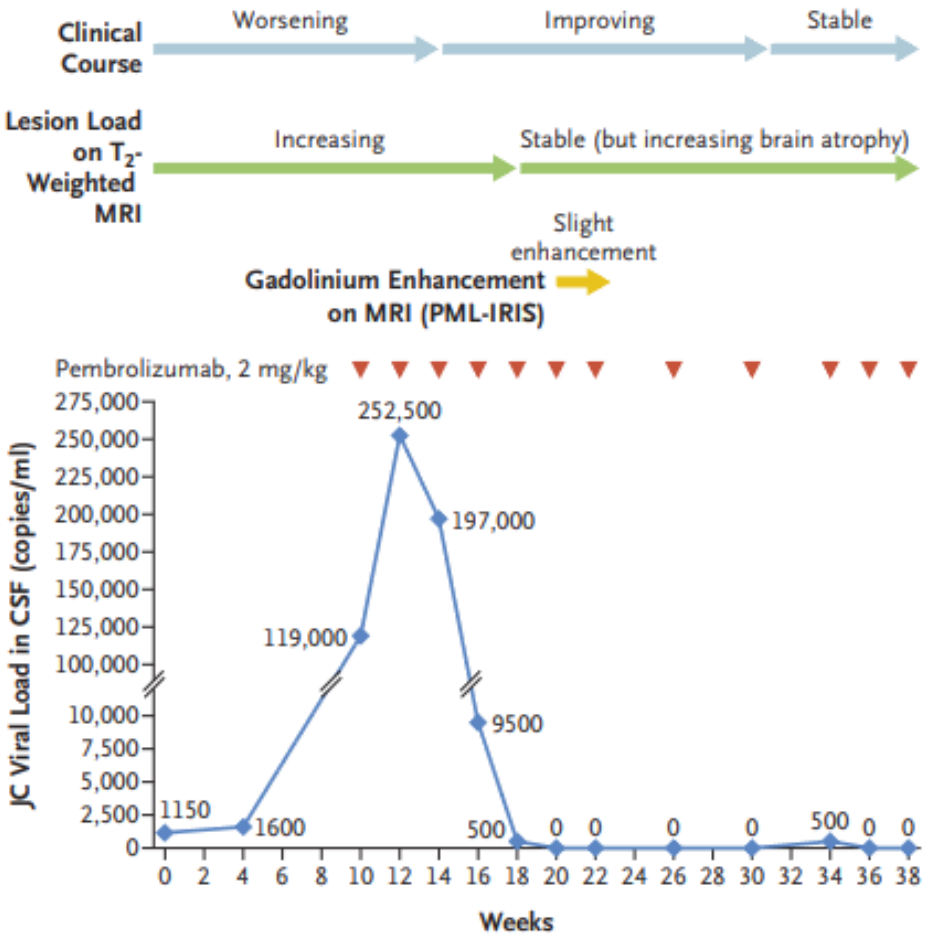


Figure 1. Pembrolizumab Treatment, JC Viral Load in CSF, Clinical Course, and Lesions on T_2-Weighted MRI over a 38-Week Period.

The management of progressive multifocal leukoencephalopathy in this patient, including diagnostic workup, began in November 2017, and the treatment period with pembrolizumab began in February 2018. CSF denotes cerebrospinal fluid, and PML-IRIS progressive multifocal leukoencephalopathy–immune reconstitution inflammatory syndrome.

1. Adrianzen Herrera D, Ayyappan S, Jasra S et al. *Leuk Lymphoma*. 2019 Feb;60(2):395-401.
2. Cortese I, Muranski P, Enose-Akahata Y, et al. *N Engl J Med.* 2019;380:1597-1605.
3. Rauer S, Marks R, Urbach H, et al. *N Engl J Med.* 2019;380:1676-1677.
4. Walter O, Treiner E, Bonneville F, et al. *N Engl J Med.* 2019;380:1674-1676.
5. Muftuoglu M, Olson A, Marin D. *N Engl J Med.* 2018; 379:1443-1451

Conclusions

I. Neurotoxicity due to cancer therapy is a diagnosis of exclusion and must be distinguished from CNS disease involvement

II. Biological and immunological therapies have distinctive mechanisms of CNS neurotoxicity

III. Early recognition of neurotoxicity and cessation of offending agent is critical to avoid added neurological injury

MedEd ON THE GO Oncology

Recognizing and Managing Muscle and Peripheral Nervous System Toxicities

Chelsea C. Pinnix, MD, PhD

Associate Professor
Associate Residency Program Director
Department of Radiation Oncology, Hematologic Malignancies Section
The University of Texas MD Anderson Cancer Center
Houston, TX

Neuromuscular Toxicity of Novel Cancer Therapies

- The Peripheral Nervous System (PNS) is not protected by the blood-brain barrier, making it susceptible to toxicity from systemic agents
- New immunotherapies and targeted therapies may result in undesired engagement of the immune system against host tissues resulting in neuromuscular adverse events
- Neurological treatment complications may be challenging to differentiate from cancer progression → recognizing and distinguishing toxicity from tumor is imperative for proper patient care

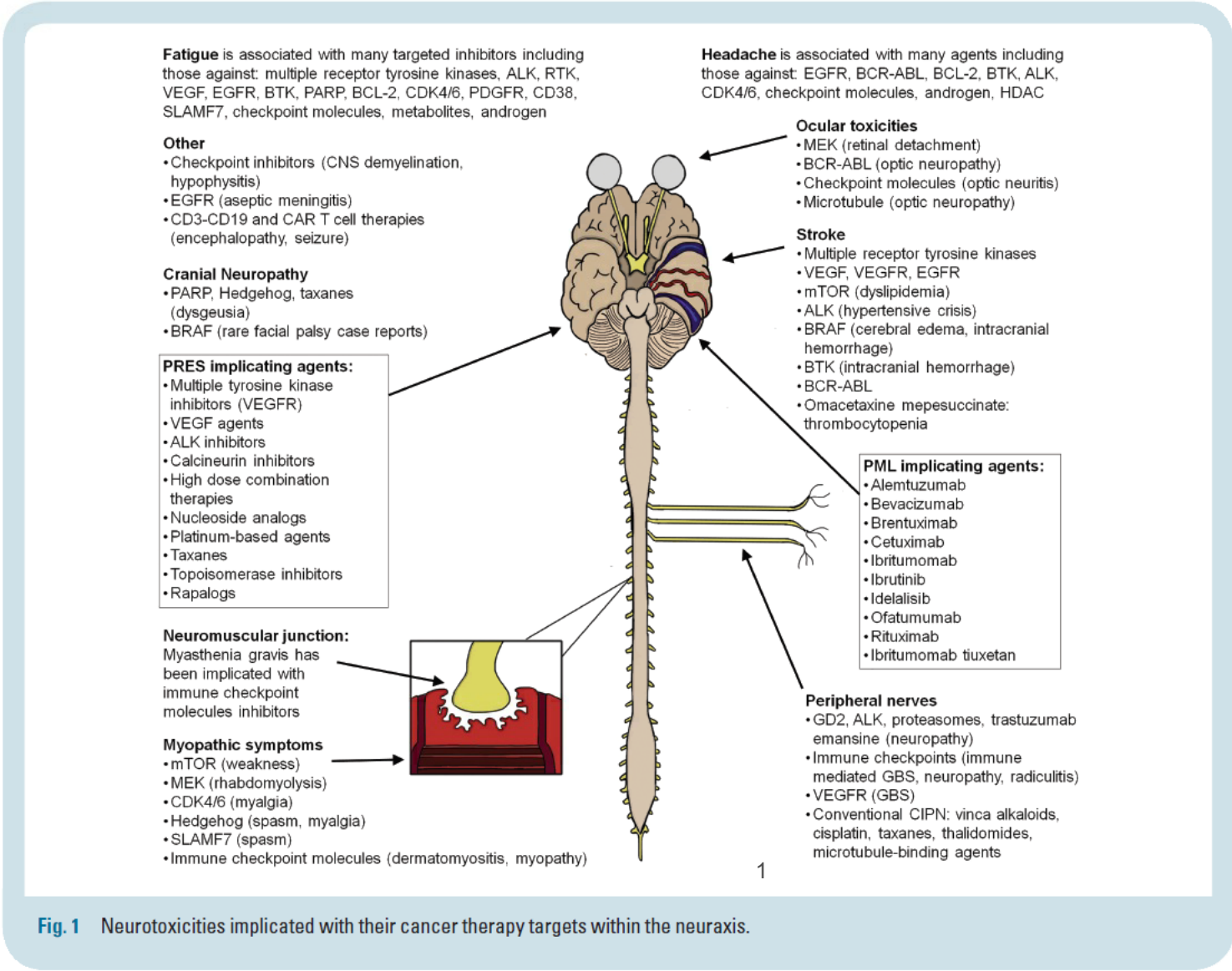


Fig. 1 Neurotoxicities implicated with their cancer therapy targets within the neuraxis.

1. Zukas AM, Schiff D. *Neuro Oncol.* 2018 Jan 10;20(1):24-36.

Peripheral Neuropathy (PN)

- Peripheral neuropathy is the most common neurological complication of cancer therapy
- Many traditional chemotherapeutic agents cause peripheral neuropathy (platinum-based agents, vinca alkaloids, taxanes, alkylators, anti-metabolites)
- **Targeted Agents:**
  - Proteosome inhibitors (bortezomib, carfilzomib)
  - Biological agents: brentuximab
  - Immunotherapy: PN is a rare complication with anti-CTLA4 and/or anti-PD1/PD-L agents (<3% pts)[1]

NCI CTCAE v5.0 Neurotoxicity[2]					
Adverse event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL*		
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL*	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL*	Life-threatening consequences; urgent intervention indicated	

1. Touat M, Talmasov D, Ricard D, Psimaras D. *Curr Opin Neurol*. 2017 Dec;30(6):659-668.
2. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Proteosome Inhibitor-related Peripheral Neuropathy

- Bortezomib can cause PN in 60-75% of patients presentation that are treated with twice weekly therapy[1]
  - Grade 3 or 4 among 15% - 30% of patients
- **Etiology:** dorsal root ganglia damage
- **Clinical Presentation:** painful, distal sensory neuropathy, mild LE weakness less common (~10%), autonomic symptoms
- **Diagnostic findings:** demyelinating or mixed axonal-demyelinating neuropathy on nerve conduction studies
- **Treatment:** glucocorticoids or IV immunoglobulins, discontinuation of therapy
- Carfilzomib associated with much less severe neuropathy

1. Argyriou AA, Iconomou G, Kalofonos HP. *Blood*. 2008 Sep 1;112(5):1593-9.

Brentuximab-related Peripheral Neuropathy

- PN occurs in 3-53% of patients and is severe in 10-14%*
- **Clinical Presentation:**
  - Predominantly sensory
- Within 3 months of treatment discontinuation 50% of patients experience complete resolution
- Treatment often continued at a lower dose once the neuropathy improves to grade 1

*Stone JB, DeAngelis LM. *Nat Rev Clin Oncol.* 2016 Feb;13(2):92-105.

Immune Demyelinating Polyradiculoneuropathy

- Rare complication of anti-PD1 and/or anti-CTLA4 agents[1,2]
- **Resembles Guillain-Barre syndrome:** progressive sensory symptoms, ascending weakness and respiratory insufficiency
- **CSF evaluation:** elevated protein levels without pleocytosis (or only mild lymphocytosis); normal glucose levels
- Nerve conduction studies demonstrate demyelinating features
- **Treatment:** glucocorticoids to combat the T-cell response; intravenous immunoglobulin or plasmapheresis
- Ipilimumab can rarely cause chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Can resolve with treatment cessation and plasmapheresis

1. Stone JB, DeAngelis LM. *Nat Rev Clin Oncol.* 2016 Feb;13(2):92-105.
2. Touat M, Talmasov D, Ricard D, Psimaras D. *Curr Opin Neurol.* 2017 Dec;30(6):659-668

Myasthenia Gravis and Necrotizing Myositis

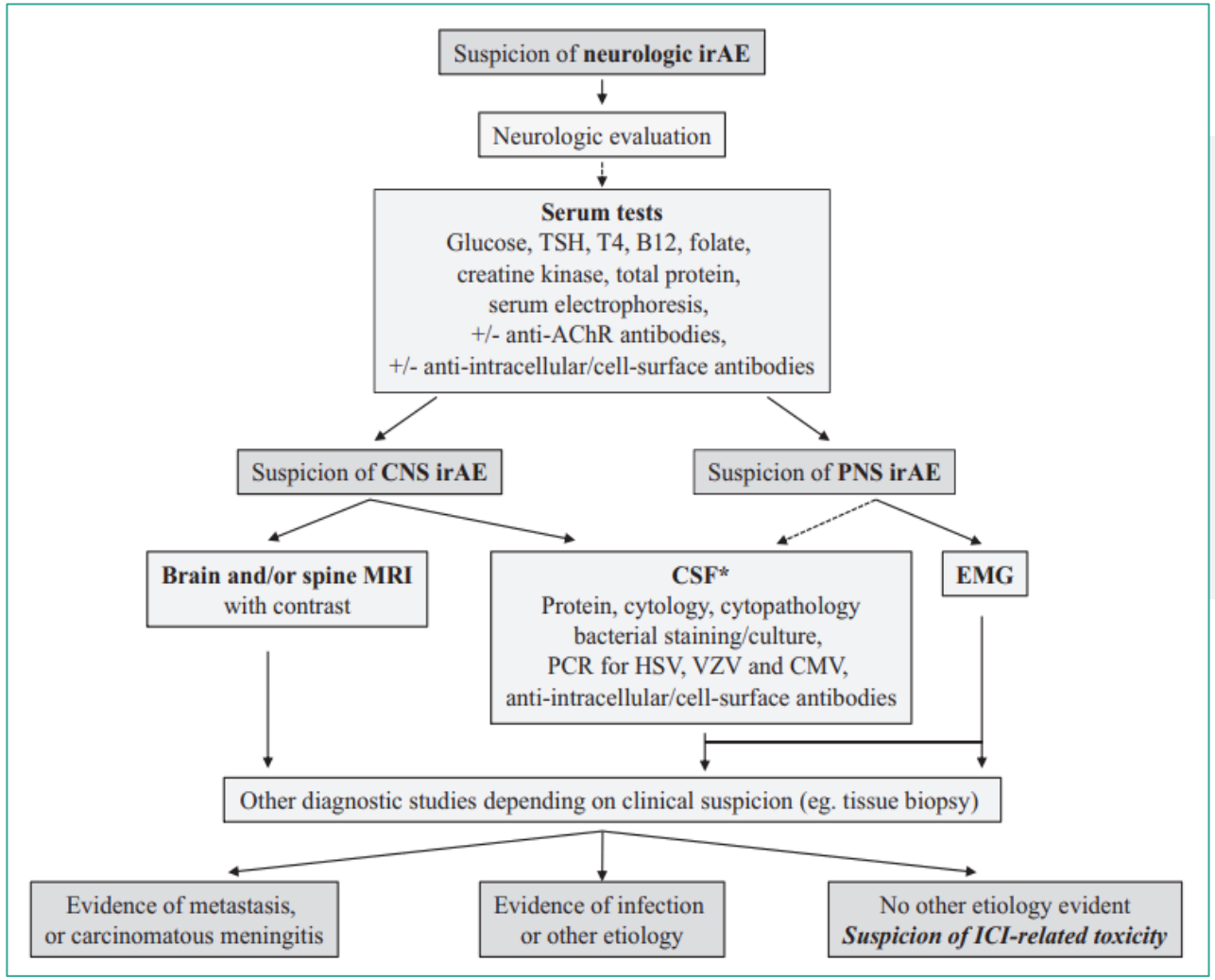
- **Myasthenic-type syndrome** affecting the neuromuscular junction can be a rare complication of IFN-a, IL-2 and immune checkpoint inhibitors[1,2]
  - **Presentation:** ptosis, diploplia, weakness, respiratory difficulty that worsens with repetitive activity
  - **Treatment:** discontinuation of offending agent, plasmapheresis, IVIG, symptom therapy with pyridostigmine

- **Necrotizing myositis** is a rare complication predominantly reported among patients receiving immune checkpoint inhibitors
  - Clinical presentation similar to myasthenia gravis
  - Muscle biopsy shows multifocal necrosis with rare T-cell infiltrates
  - Most cases respond to corticosteroids

1. Stone JB, DeAngelis LM. *Nat Rev Clin Oncol.* 2016 Feb;13(2):92-105.
2. Touat M, Talmasov D, Ricard D, Psimaras D. *Curr Opin Neurol.* 2017 Dec;30(6):659-668

Simplified Diagnostic Algorithm

for the Investigation of Neurological Immune-related Adverse Events.[1]



After exclusion of disease progression and infection, treatment-related toxicity should remain prominent on the differential when patients present with neurologic symptoms

AChR, acetylcholine receptor; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; ENMG, electromyography; PNS, peripheral nervous system.
*CSF analysis is not required for neuromuscular immune-related adverse events.

1. Touat M, Talmasov D, Ricard D, Psimaras D. *Curr Opin Neurol*. 2017 Dec;30(6):659-668.

Conclusions

I. The mechanisms of neurotoxicity continue to evolve with the introduction of novel cancer therapies

II. The peripheral nervous system is subject to treatment-related toxicity from traditional chemotherapy as well as newer target agents and immunotherapy

III. Recognition of toxicity is key as drug discontinuation can prevent further injury or in many cases restore normal function