Emerging Toxicities and Management

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Advances in Cancer Immunotherapy

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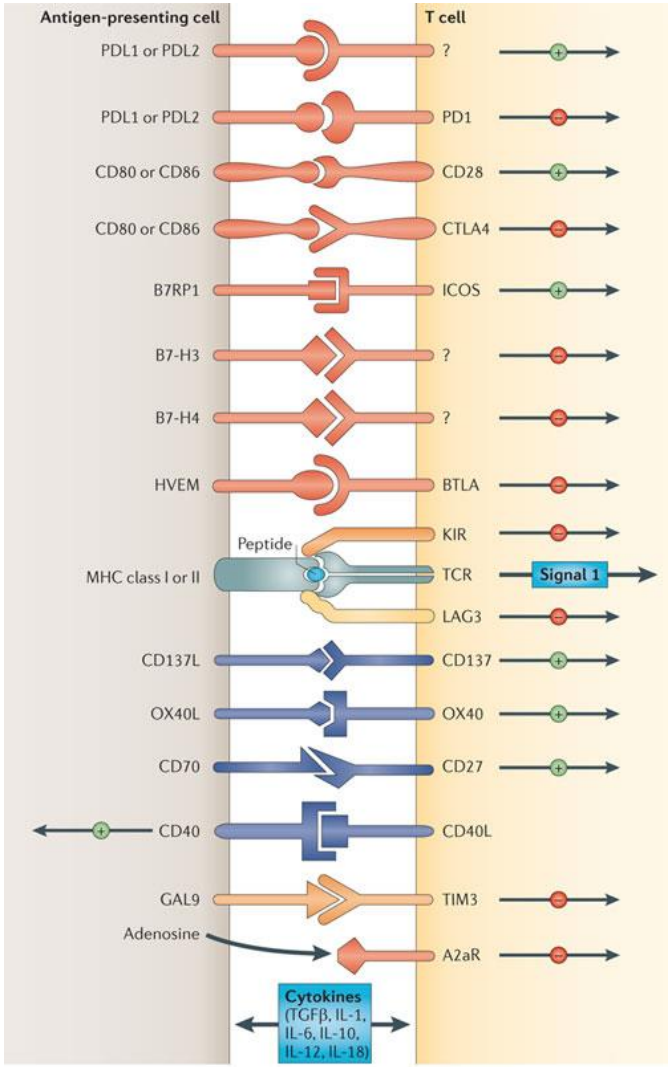
Disclosure and Conflict of Interest

- Consulting Fees: BMS, Eisai, Merck, Eli Lilly, QED, Zymeworks, Adaptiimmune, Imvax, CytomX

- Contracted Research: BMS, Eli Lilly, Pfizer, Novartis, Yiviva, Loxo, Polaris, Zymeworks, BI

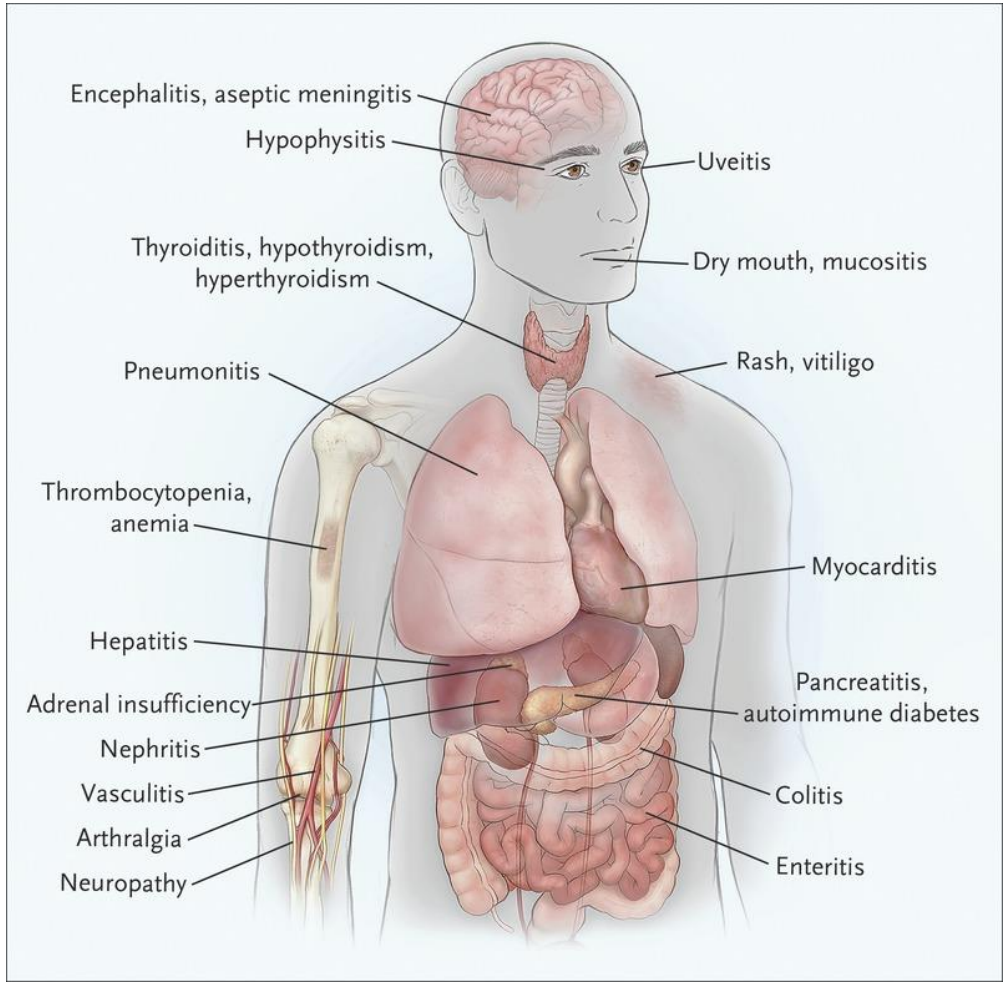
Targeting the immune synapse leads to on target toxicity



Pardoll et al. *Nature* 2012

Immune Related Adverse Events (irAE)

- Mechanism-based toxicities associated with checkpoint blockade.
- Typically thought to reflect inflammation of non-tumor (normal tissues).
- Can range in severity from mild to very serious (fatal).
- Typically reversible with appropriate treatment.



Postow et al. NEJM 2018

Why do these events occur?

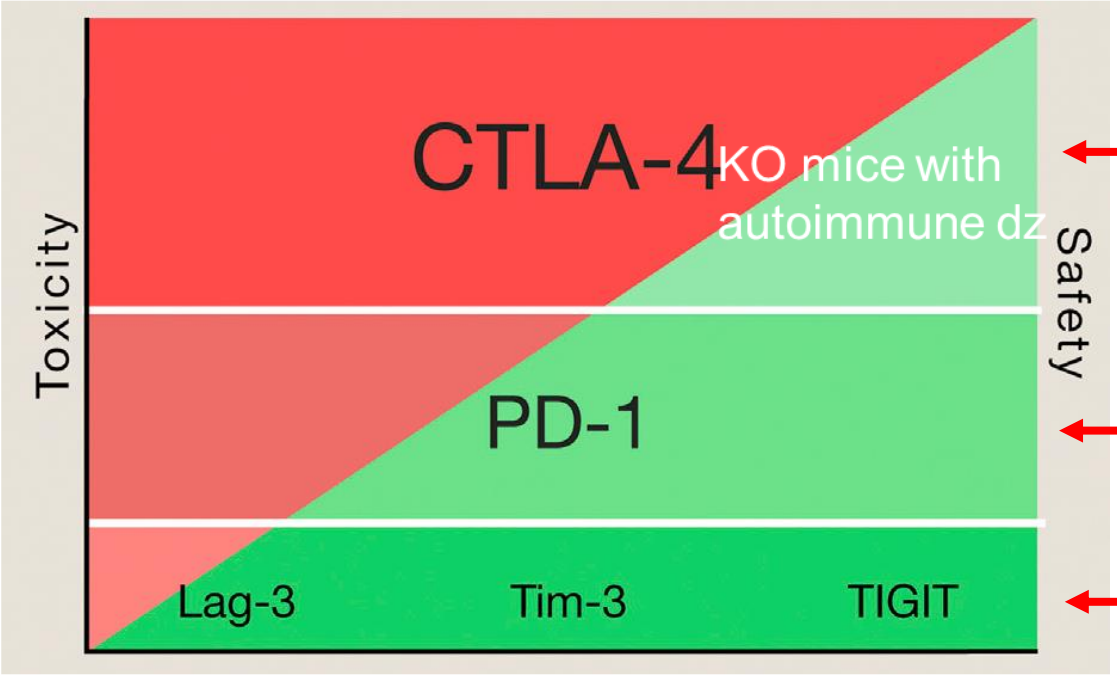
CTLA-4 and PD-1 polymorphisms are linked with autoimmune diseases

Autoimmune disease	Polymorphism	Ethnic group	Referred studies
Thyroiditis, Graves' disease and Hashimoto's disease	CTLA-4	European	Ueda, Nature 2003 [8] Vaidya, Rheumatology 2002 [72]
Diabetes mellitus	CTLA-4	European Asian	Ueda, Nature 2003 [8] Zhernakova, Hum Genet, 2005 [73] Zalloua PA, Hum Immunol 2004 [10] Jin, P of Endocrinol Investig, 2014 [74]
Celiac disease	CTLA-4	European	Zhernakova, Hum Genet, 2005 [73] Song, Hum Immunol, 2013 [75]
Myasthenia gravis	CTLA-4	South American	Fernández-Mestre, Hum. Immunol. 2009 [76]
Systemic lupus erythematosus	CTLA-4	Asian	Hudson, Hum Genet, 2002 [77]
	PD-1	European and Mexicans	Prokunina, Nat Gene, 2002 [9] Bertsias, Arthritis Rheum. 2009 [78]
Rheumatoid arthritis	CTLA-4	European	Vaidya, rheumatology 2002 [72]
	PD-1	European and Asian	Lee, Z. Rheumatol. 2015 [79]
Addison's disease	CTLA-4	European	Blomhoff, J Clin Endocrinol Metabol 2004 [8]

CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; PD-1: programmed cell death protein.

Michot et al. Eur J Cancer 2018

Hierarchy of Immune-mediated Toxicity Based on Immune Checkpoint Molecule



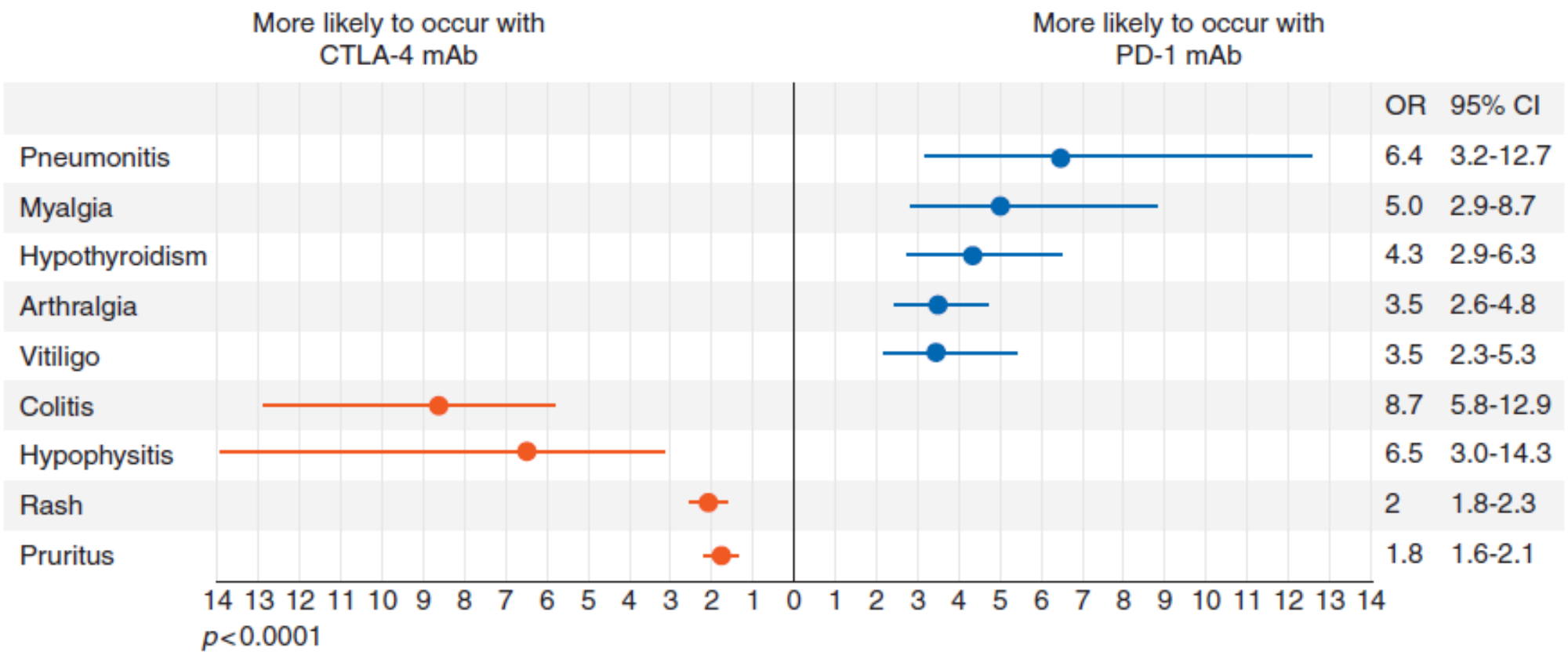
KO mice = death from lymphoproliferative disease

KO mice = autoimmune disease

KO mice = No phenotype

Anderson A, Immunity 2016;44:989-1005

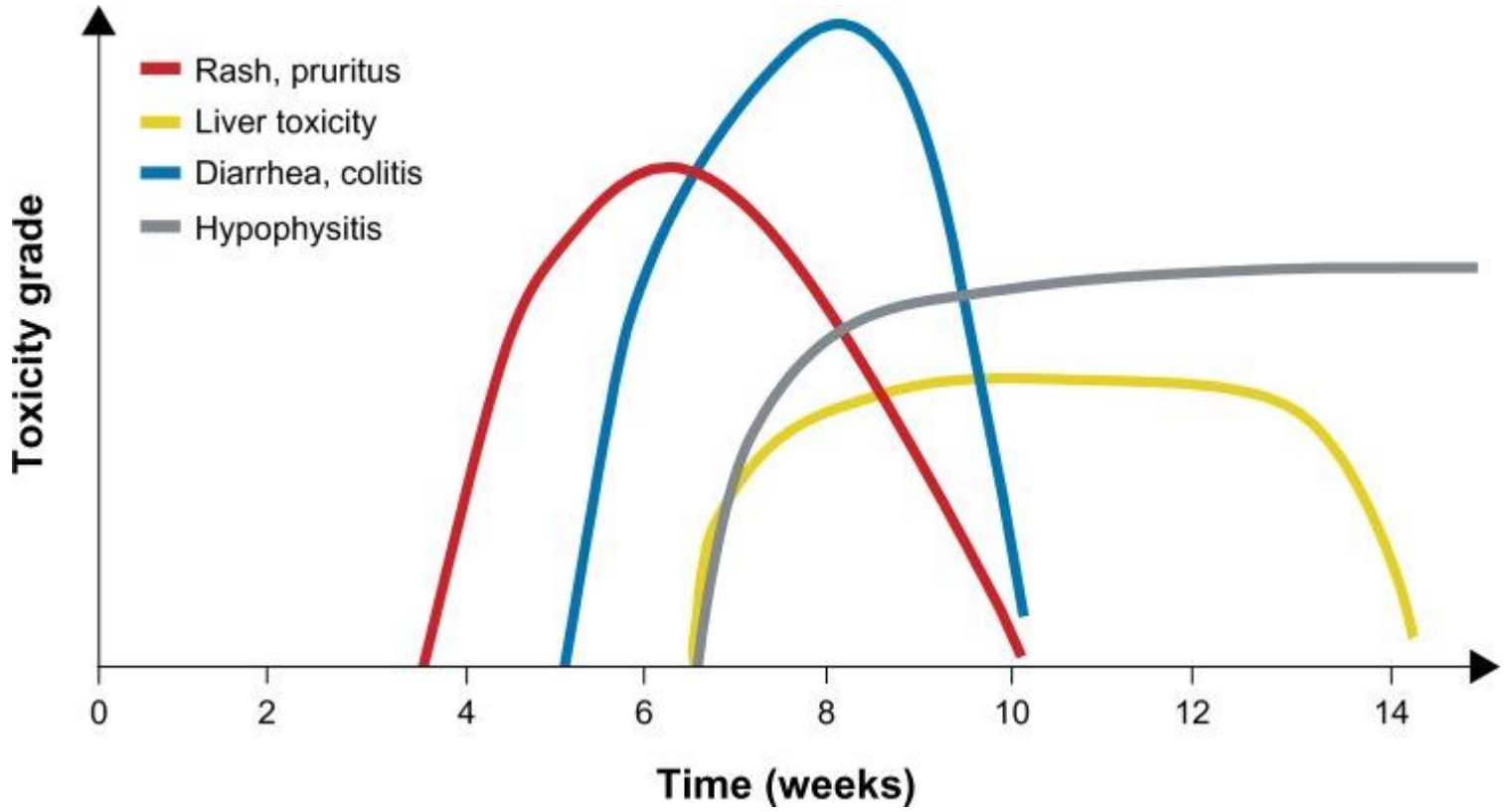
CTLA-4 versus PD-1 – overlapping, but unique toxicities



Khoja et al. Annals of Oncology 2017

irAEs are often not immediate and exhibit different kinetics

Time course with anti-CTLA 4 based treatment



Weber JS. el al. J Clin Oncol. 2012;30(21):2691–2697.8

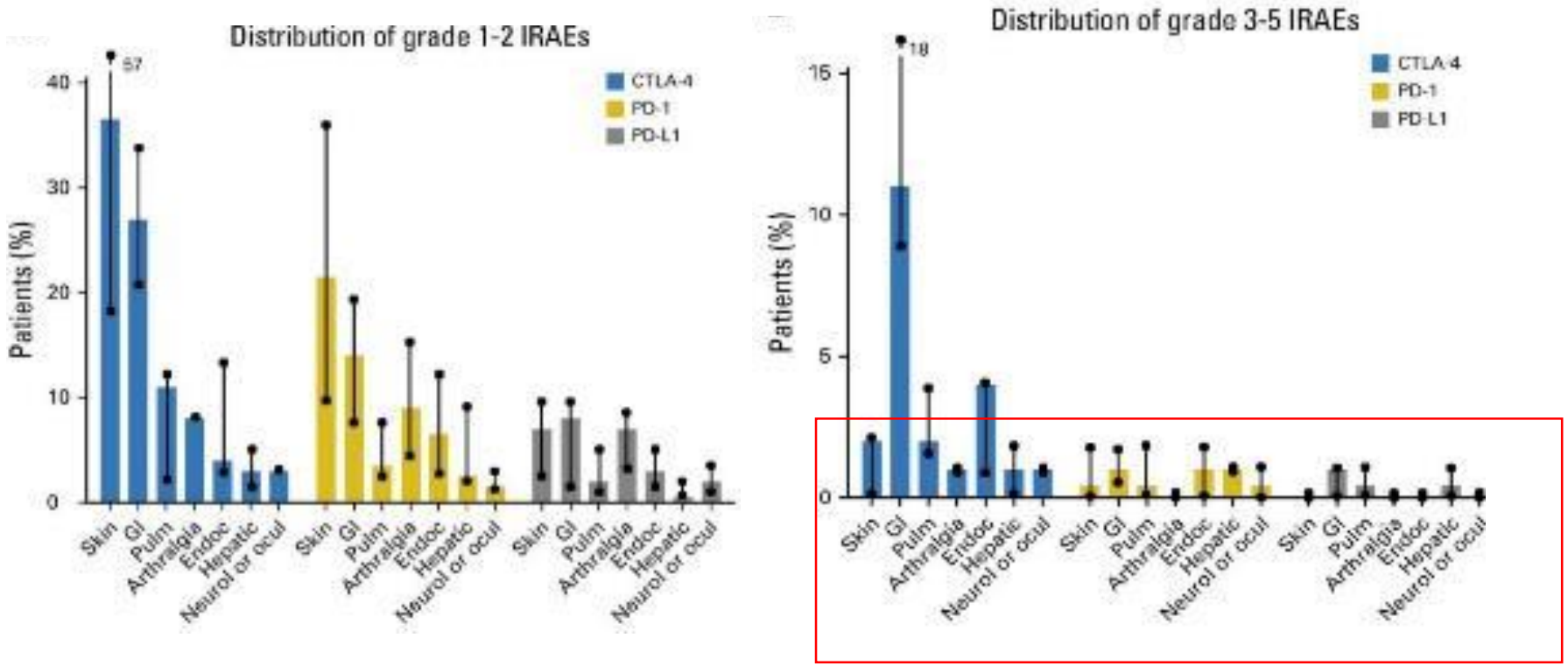
Dose and schedule matters for anti-CTLA4 based treatment

TABLE 2. Common trAEs (≥ 5% in Any Group)[a]

	T300 + D (n = 74), No. (%)		Durvalumab (n = 101), No. (%)		Tremelimumab (n = 69), No. (%)		T75 + D (n = 82), No. (%)	
AE	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Patients with any trAE	61 (82.4)	28 (37.8)	61 (60.4)	21 (20.8)	58 (84.1)	30 (43.5)	58 (70.7)	20 (24.4)
Pruritus	24 (32.4)	0	11 (10.9)	0	19 (27.5)	1 (1.4)	13 (15.9)	0
Rash	24 (32.4)	2 (2.7)	7 (6.9)	0	15 (21.7)	2 (2.9)	11 (13.4)	0
AST increased	12 (16.2)	9 (12.2)	8 (7.9)	3 (3.0)	10 (14.5)	6 (8.7)	12 (14.6)	7 (8.5)
ALT increased	11 (14.9)	3 (4.1)	5 (5.0)	0	7 (10.1)	3 (4.3)	8 (9.8)	2 (2.4)
Amylase increased	11 (14.9)	5 (6.8)	2 (2.0)	1 (1.0)	3 (4.3)	0	6 (7.3)	1 (1.2)
Lipase increased	9 (12.2)	5 (6.8)	1 (1.0)	0	9 (13.0)	4 (5.8)	4 (4.9)	4 (4.9)
Fatigue	8 (10.8)	0	9 (8.9)	1 (1.0)	11 (15.9)	0	8 (9.8)	0
Diarrhea	7 (9.5)	1 (1.4)	9 (8.9)	1 (1.0)	14 (20.3)	6 (8.7)	10 (12.2)	1 (1.2)
Alkaline phosphatase increased	6 (8.1)	3 (4.1)	7 (6.9)	1 (1.0)	1 (1.4)	0	1 (1.2)	0
Hyperthyroidism	6 (8.1)	0	2 (2.0)	0	0	0	4 (4.9)	1 (1.2)
Hypothyroidism	6 (8.1)	0	10 (9.9)	0	2 (2.9)	0	7 (8.5)	0
Bilirubin increased	4 (5.4)	1 (1.4)	3 (3.0)	0	2 (2.9)	0	5 (6.1)	0
Abdominal pain	2 (2.7)	0	0	0	5 (7.2)	0	4 (4.9)	0
Rash maculopapular	2 (2.7)	1 (1.4)	2 (2.0)	0	7 (10.1)	0	5 (6.1)	0

Kelley et al. JCO 2021

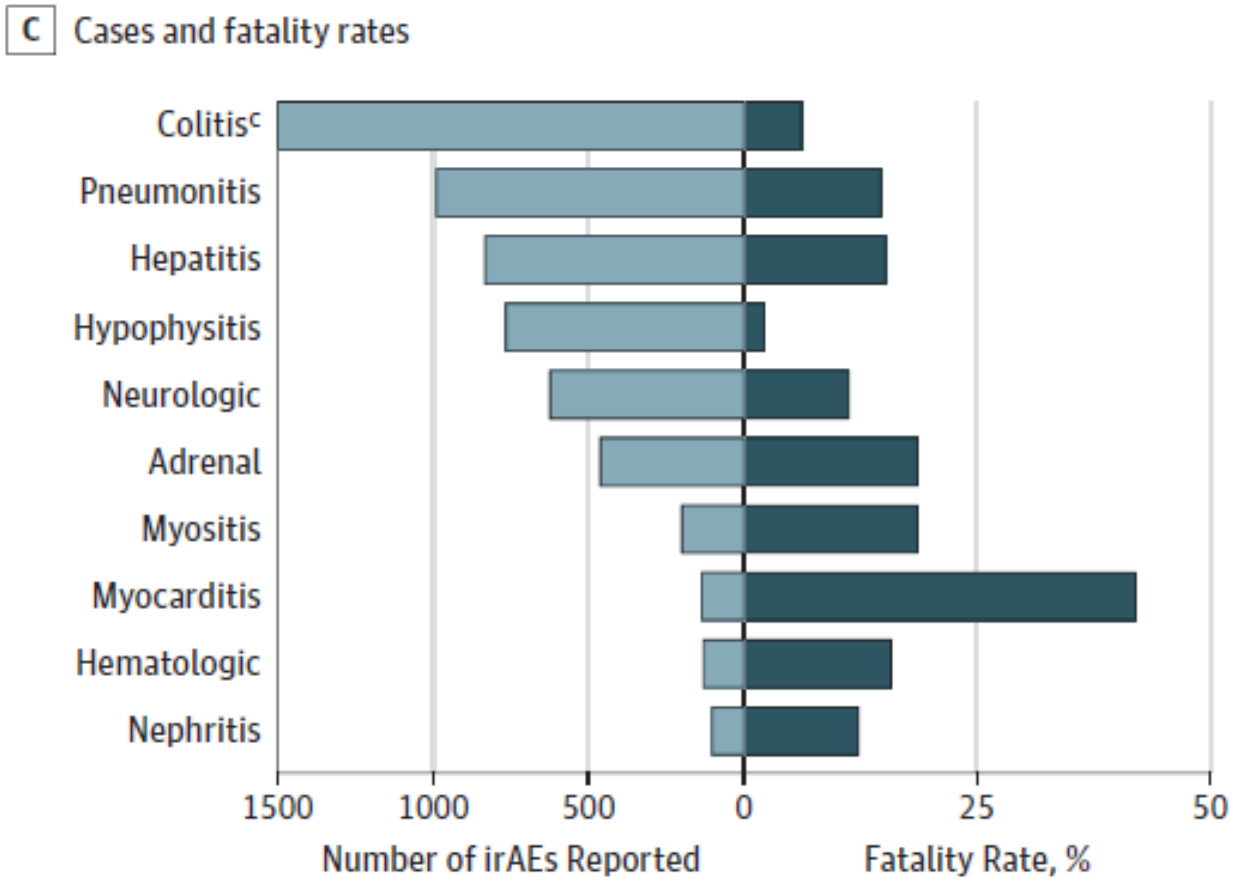
Spectrum of Severity



Severe irAEs are infrequent

Michot et al, *Eur J Cancer* 2016

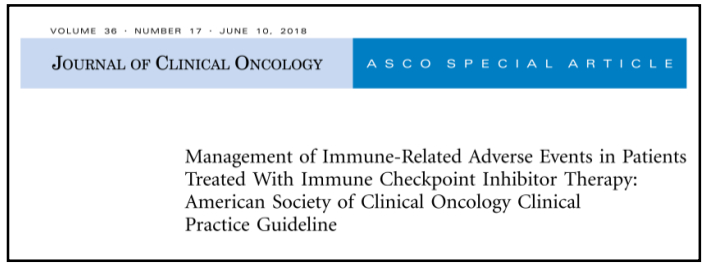
Rare but Potentially Serious Events



General Approach to Management

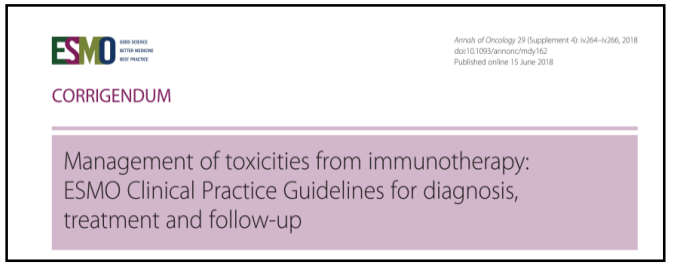
- Review publicly available management guidelines
- Rapid diagnostic testing to rule out other causes
- Rapid treatment of Grade ≤ 2
- Hold immune based treatment for Grade ≥ 3 events
- Subspeciality consultation
- Immune suppression
  - Systemic corticosteroids
  - Novel Agents
- Risk of recurrence with re-challenge

Corticosteroids remain a cornerstone of treatment


VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline


ESMO

CORRIGENDUM

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up


NCCN National Comprehensive Cancer Network®

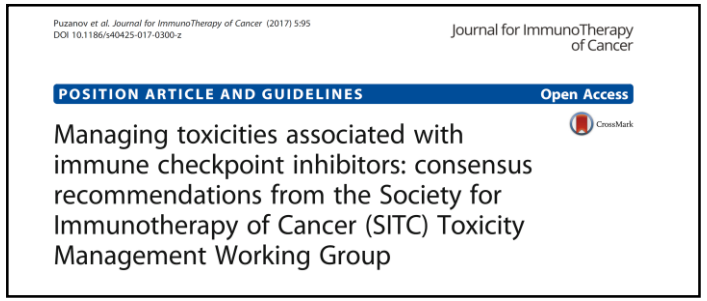
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) in partnership with the American Society of Clinical Oncology (ASCO)

Management of Immunotherapy-Related Toxicities

(Immune Checkpoint Inhibitor-Related Toxicities)

Version 1.2018 — February 14, 2018

NCCN.org

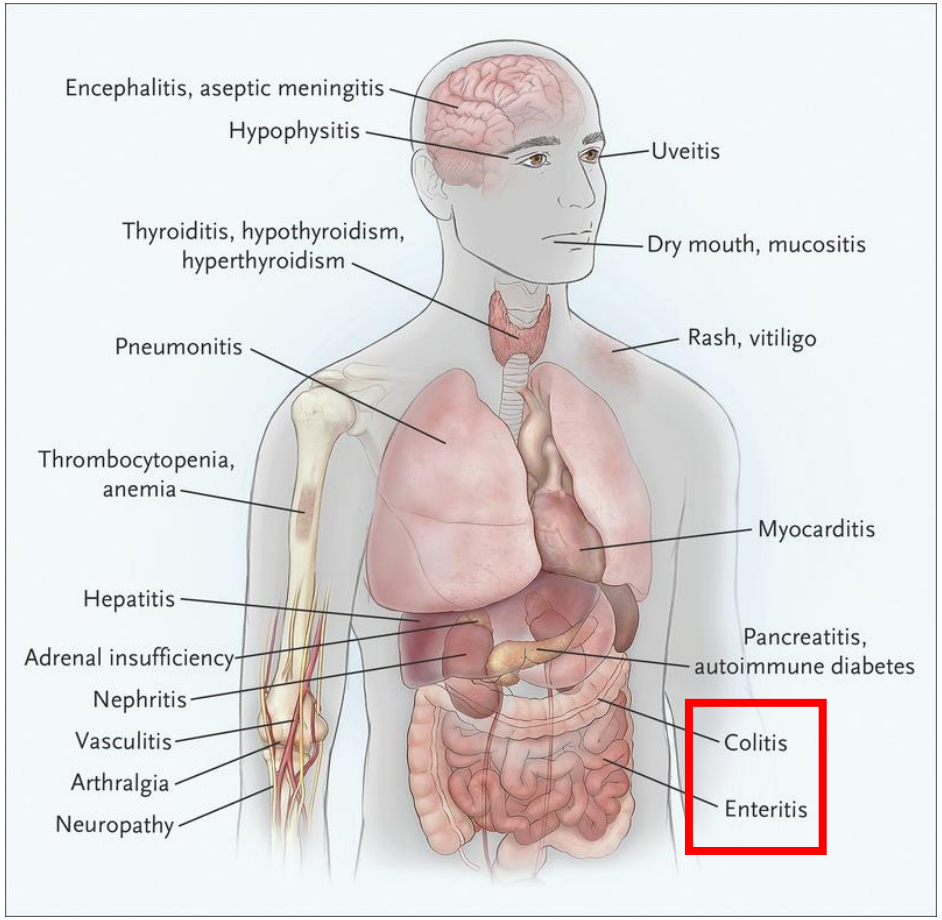

Journal for ImmunoTherapy of Cancer

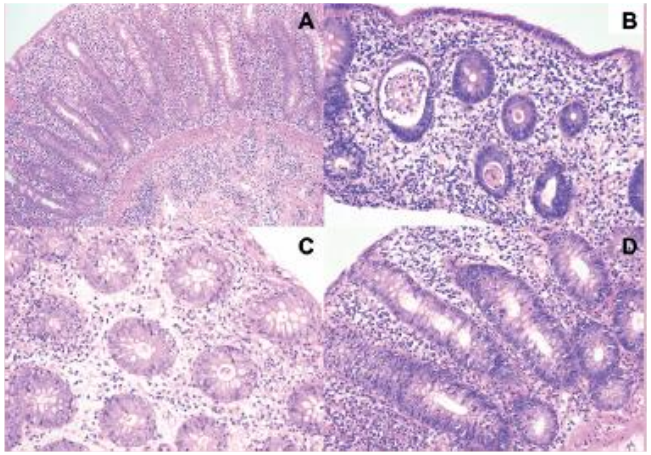
POSITION ARTICLE AND GUIDELINES | Open Access

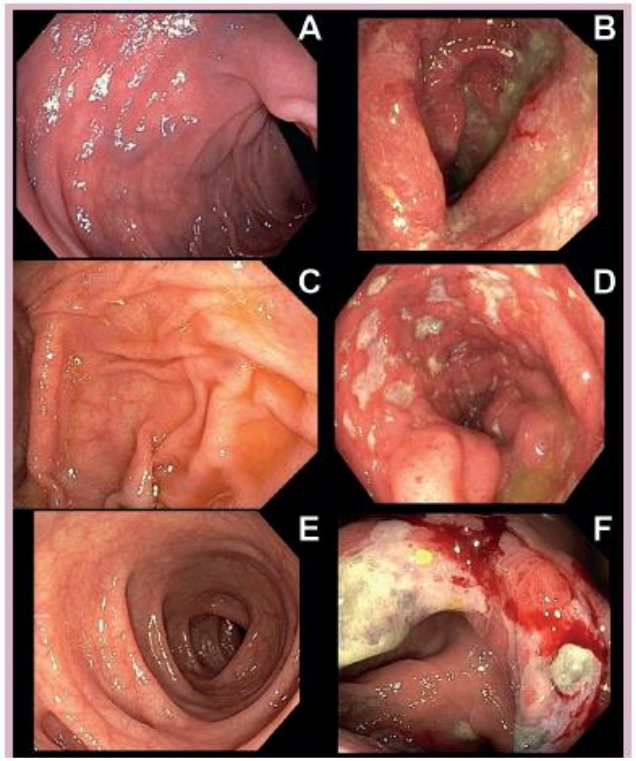
Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

Though other immune modulate agents are employed in refractory cases

Immune Mediate Colitis



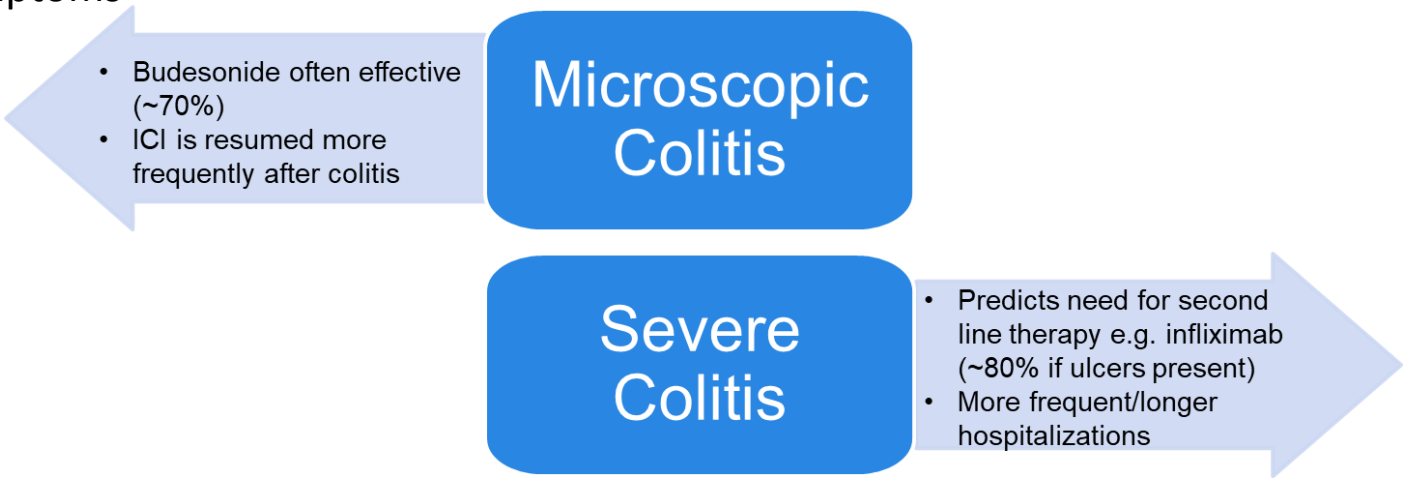




Role of Endoscopic Evaluation for immune mediated Colitis

Confirm diagnosis: 15-30% of patients may have alternative diagnoses / non-inflammatory diarrhea

Prognosticate: endoscopy and histology are better predictors of disease course than symptoms



Guide therapy: steroids are only effective in ~60% of cases and rapid evaluation allows for early introduction of steroid alternatives

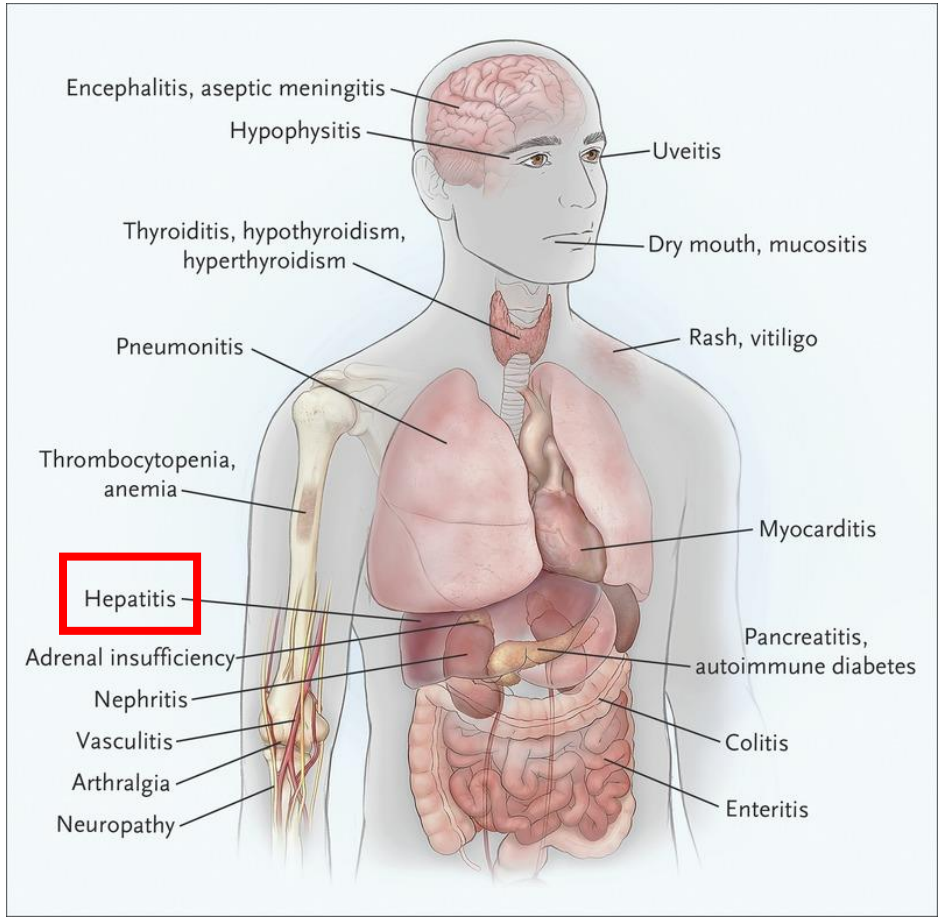
Curtesy David Falchek. Hughes et al. JITC 2019; Foppen et al. ESMO Open 2018; Abu-Sbeih et al. JITC 2018 Ibraheim et al. APT 2020, Johnson et al. JITC 2018

Biologics in irColitis

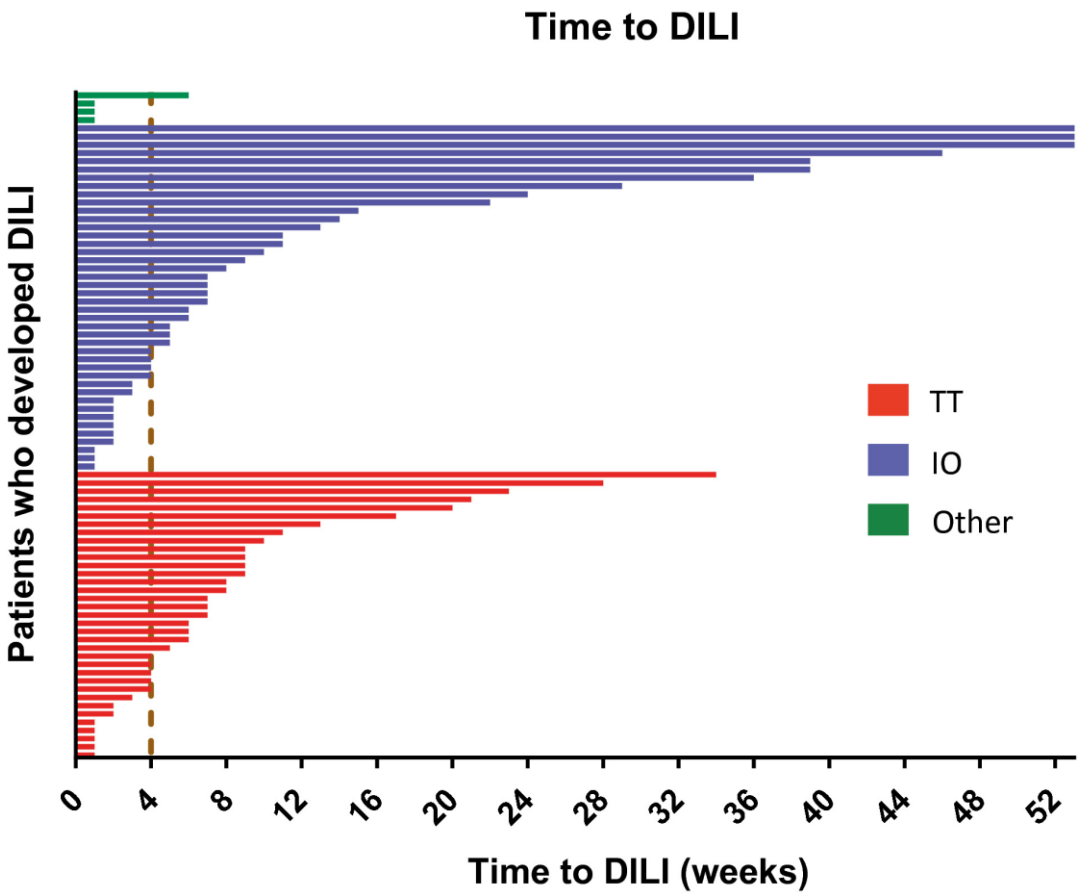
	Infliximab	Vedolizumab
Mechanism	Anti-TNF-α	Anti-integrin (α4β7) [*gut selective*]
Dose	5 (to 10) mg/kg IV at 0/2/6 weeks	300mg IV at 0/2/6 weeks
Efficacy in steroid-refractory irColitis	72-97%	75-89% (~70% if prior IFX failure)
Pros	Rapid onset Most experience	Excellent safety Less likely to interfere with anti-tumor effect (theoretical)
Cons	Infection risk ?Impact on anti-tumor effect	Slower onset
Additional Considerations	Consider avoiding if high risk for immunosuppression or concomitant hepatitis	Consider avoiding if GI cancer or GI metastases

Zou, Faleck et al. JITC 2021 (accepted); Horvat et al. JCO 2015; Johnson et al. JITC 2018;
Abu-Sbeih et al. JITC 2018; Harris & Faleck, DDW 2020; Ibraheim et al. APT 2020

Drug Induced Liver Injury/ Immune Mediated Hepatitis



Median onset 6-8 weeks, wide range



Mondaca et al Cancer 2020

Factors that predispose to immune mediate hepatitis and liver injury?

ARTICLE

https://doi.org/10.1038/s41467-021-21572-y OPEN

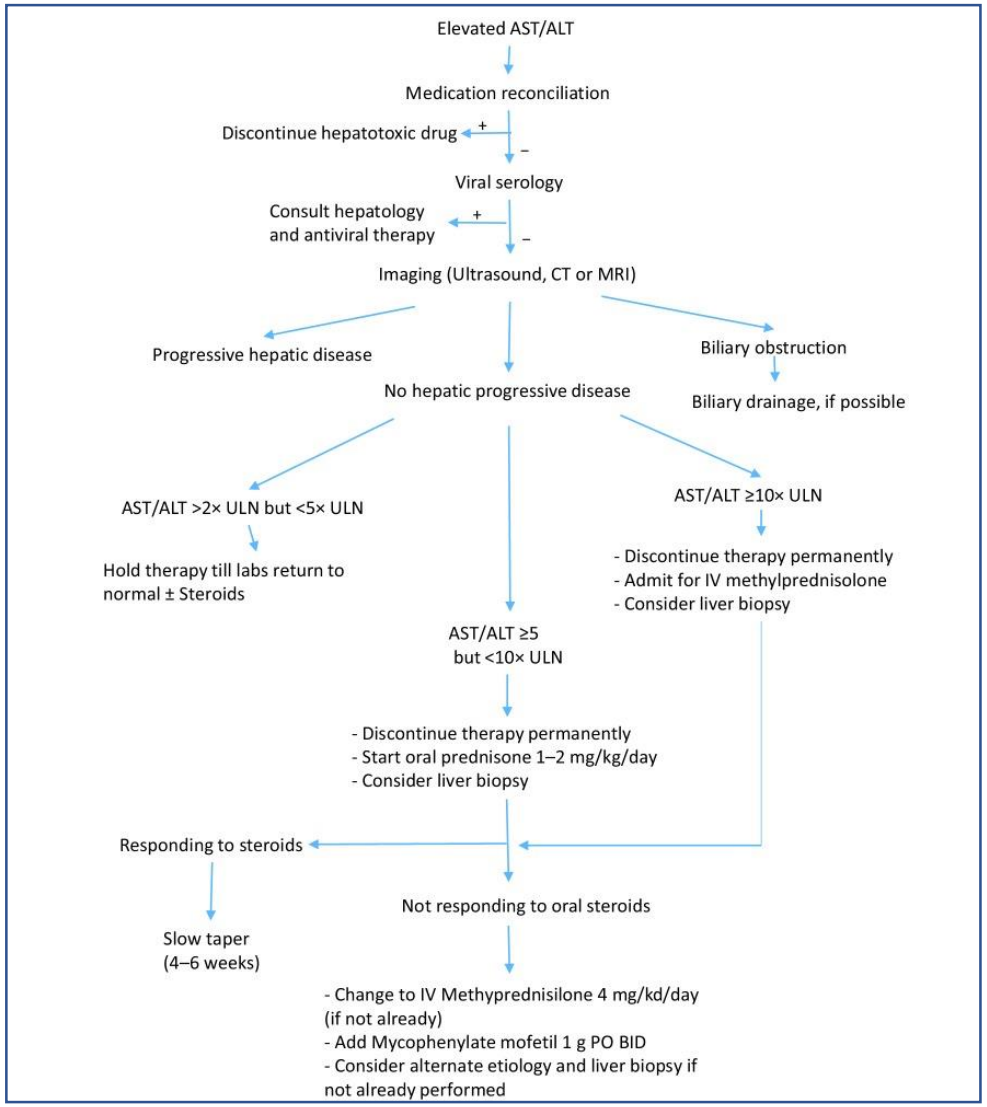
Virus-specific memory T cell responses unmasked by immune checkpoint blockade cause hepatitis

James A. Hutchinson[1✉], Katharina Kronenberg[1], Paloma Riquelme[1], Jürgen J. Wenzel[2], Gunther Glehr[3], Hannah-Lou Schilling[1], Florian Zeman[4], Katja Evert[5], Martin Schmiedel[6], Marion Mickler[7], Konstantin Drexler[7], Florian Bitterer[1], Laura Cordero[1], Lukas Beyer[8], Christian Bach[9], Josef Koestler[2], Ralph Burkhardt[10], Hans J. Schlitt[1], Dirk Hellwig[6], Jens M. Werner[1], Rainer Spang[3], Barbara Schmidt[2], Edward K. Geissler[1,11] & Sebastian Haferkamp[7]

Checkmate-40 AEs	Uninfected (N =57)		HCV (N = 50)		HBV (N= 51)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
TRAE	40(70)	7(12)	40 (80)	15 (30)	35 (69)	3 (6)
AST increase	3 (5)	2 (4)	6 (12)	5 (10)	1 (2)	0
ALT increase	3 (5)	2 (4)	7(14)	3 (6)	3 (6)	0

El-Khoueriy et al. Lancet 2017

Diagnosis/Management Approach for liver function abnormalities on immune based treatment



J Gastrointest Oncol. 2018 Feb; 9(1): 220–224

Endocrinopathies

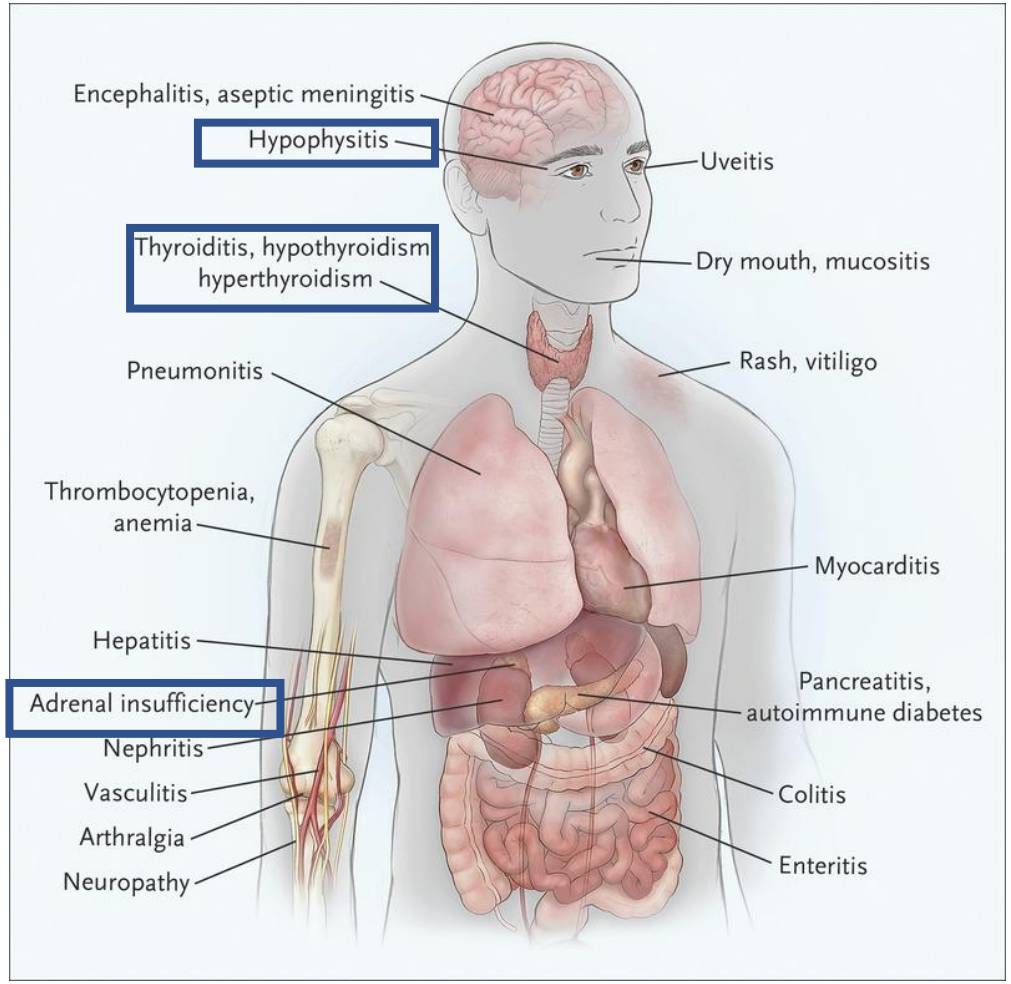


Table 3. Incidence rates of IRAEs endocrine sequelae. (data from Barroso-Sousa et al[47])

	Hypophysitis incidence rate (95% CI)	Hypothyroidism incidence rate (95% CI)	Hyperthyroidism incidence rate (95% CI)	Primary adrenal insufficiency N of pts with PAI/ total n of pts (%)*	N of pts with DM1/ total n of pts (%)
Anti-CTLA4	0.0 (0.0-6.7) - 6.5 (1.4-17.9)	0.0 (0.0-45.9) - 15.2 (6.3-28.9)	0.0 (0.0-45.9) - 2.3 (0.9-5.0)		
Anti-PDL1	0.0 (0.0-5.9) - 3.0 (0.1-15.8)	0.0 (0.0-1.2) - 5.6 (2.5-10.8)	0.0 (0.0-1.2) - 0.7 (0.2-1.8)	43/5831 (0.7%)**	
Anti-PD1		0.0 (0.0-30.8) - 40.0 (19.1-63.9)	0.0 (0.0-9.0) - 7.7 (1.6-20.9)		13/5831 (0.2%)***
Combination	3.8 (0.5-13.0) - 11.7 (6.0-20.0)	3.8 (0.5-13.0) - 16.0 (9.2-25.0)	3.8 (0.5-13.0) - 9.9 (6.8-13.8)	11/262 (4.2%)	

*number of patients with primary adrenal insufficiency as adverse event following immune check point inhibitors therapy/total number of patients who received ICIs therapy.
** Refers to pts taking Anti-CTLA4/Anti-PDL1/Anti-PD1; *** Refers to pts taking Anti-CTLA4/Anti-PDL1/Anti-PD1 or combination of them.
PAI: primary adrenal inufficiency; DM1: diabetes mellitus type 1.

Cardiomyopathy and myositis

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Table 1. Incidence of Myocarditis and Myositis in Patients Receiving Nivolumab or Ipilimumab plus Nivolumab.

Characteristic	Nivolumab (N=17,620)	Nivolumab plus Ipilimumab (N=2974)
	no. (%)	
Myocarditis		
Any*	10 (0.06)	8 (0.27)
Fatal events	1 (<0.01)	5 (0.17)
Myositis		
Any	27 (0.15)	7 (0.24)
Fatal events	2 (0.01)	1 (0.03)

* The number of patients with myocarditis includes six patients with concurrent myocarditis and myositis.

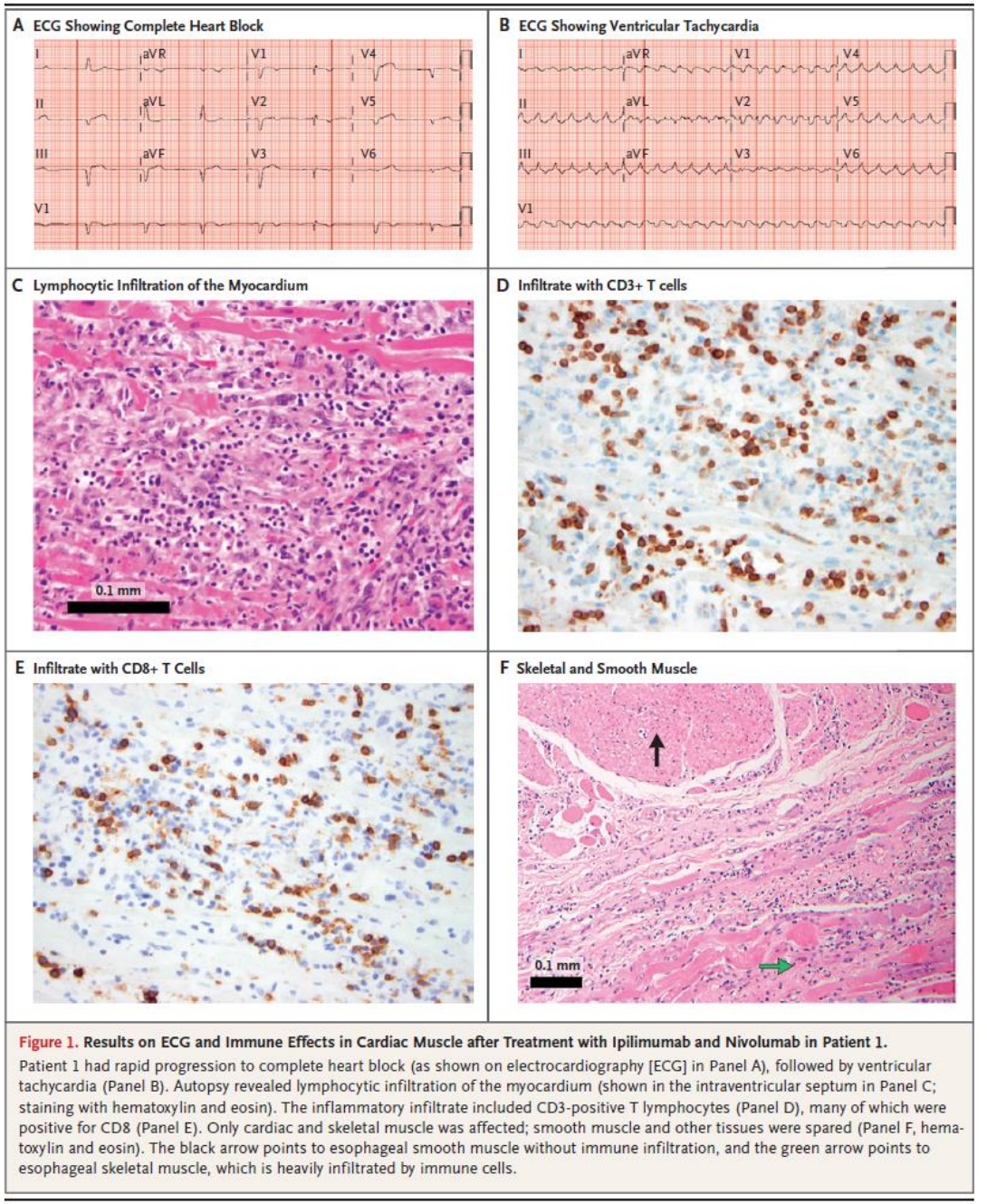
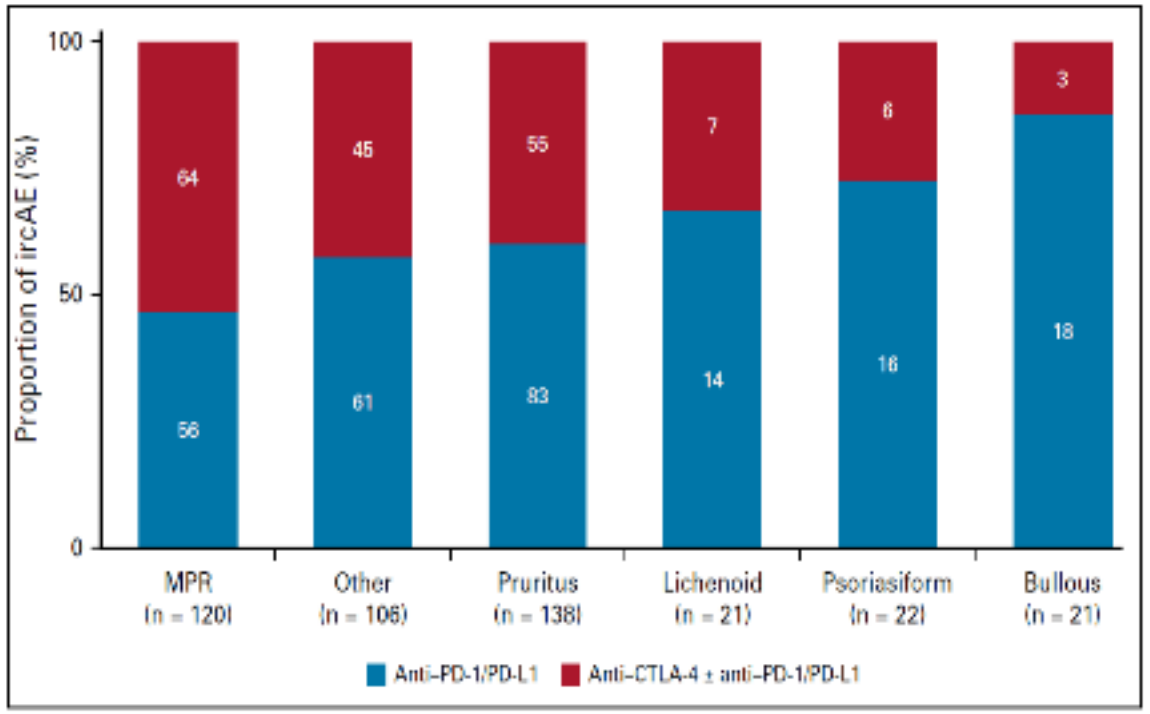


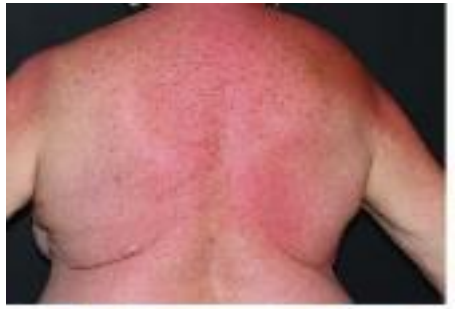
Figure 1. Results on ECG and Immune Effects in Cardiac Muscle after Treatment with Ipilimumab and Nivolumab in Patient 1.
Patient 1 had rapid progression to complete heart block (as shown on electrocardiography [ECG] in Panel A), followed by ventricular tachycardia (Panel B). Autopsy revealed lymphocytic infiltration of the myocardium (shown in the intraventricular septum in Panel C; staining with hematoxylin and eosin). The inflammatory infiltrate included CD3-positive T lymphocytes (Panel D), many of which were positive for CD8 (Panel E). Only cardiac and skeletal muscle was affected; smooth muscle and other tissues were spared (Panel F, hematoxylin and eosin). The black arrow points to esophageal smooth muscle without immune infiltration, and the green arrow points to esophageal skeletal muscle, which is heavily infiltrated by immune cells.

Dermatologic Evaluation Yields Various Phenotypes

Immune-related cutaneous AE Phenotype
(n=427)

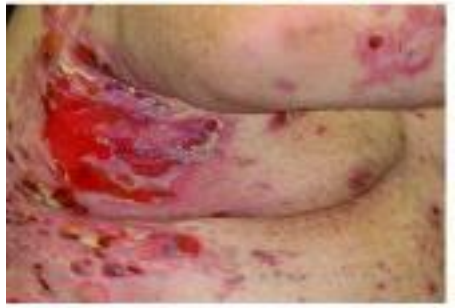


Maculopapular rash

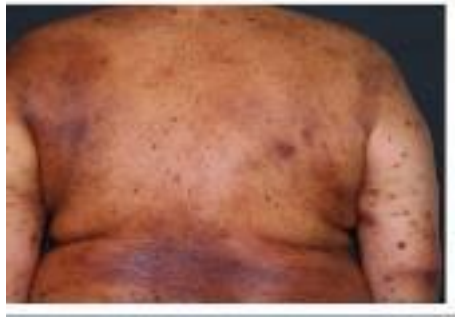


Psoriasiform rash

Bullous pemphigoid



Eczematous rash



Slide curtesy Mario Lacouture. Phillips and Wu,et al, *J Clin Oncol* 2019; Geisler et al, *J Am Acad Dermatol* 2020

Effects of Long-Term Corticosteroids and Immunosuppression

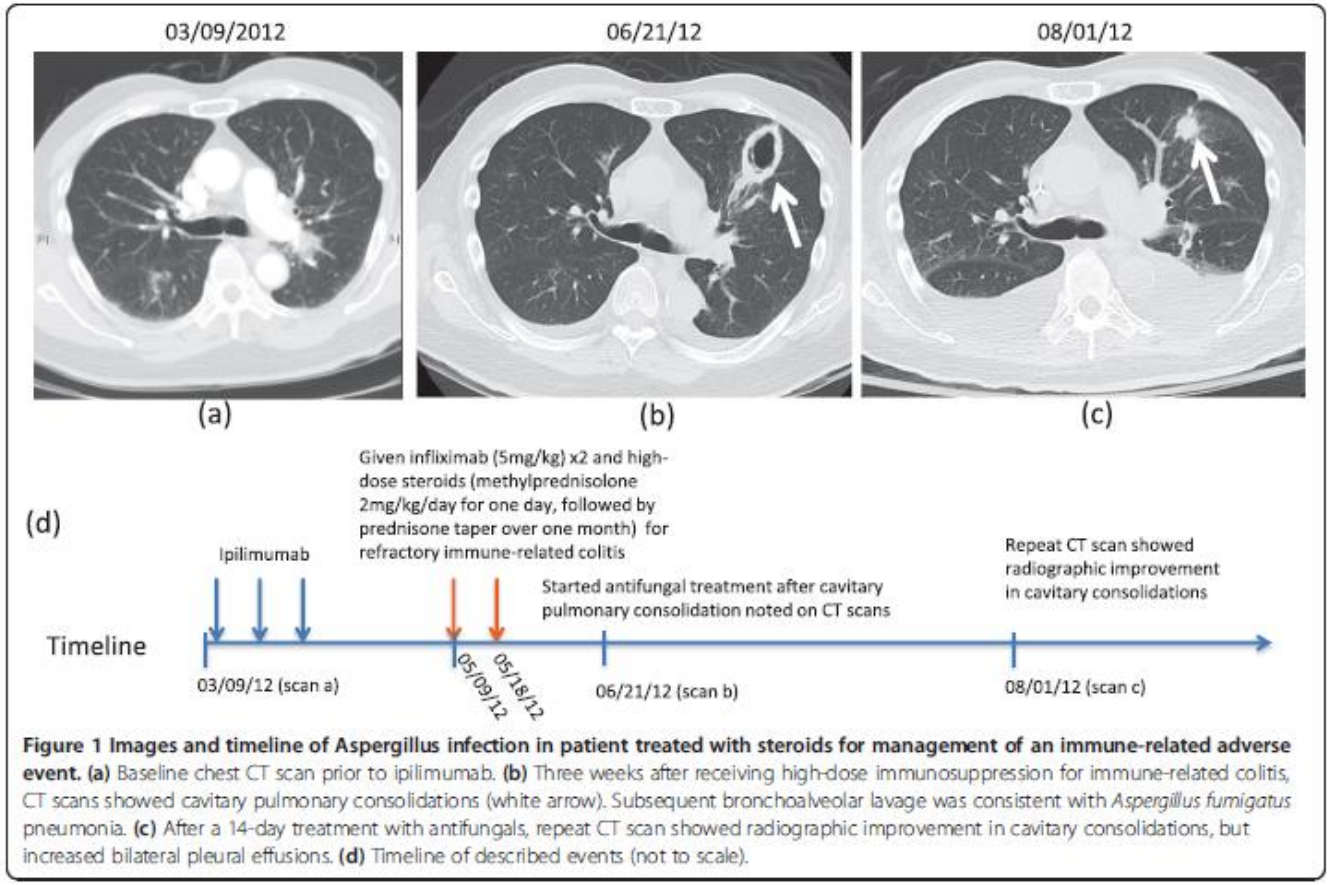
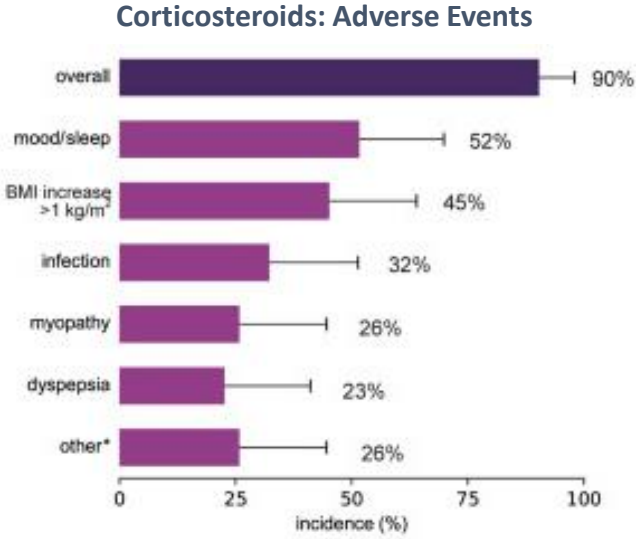


Figure 1 Images and timeline of Aspergillus infection in patient treated with steroids for management of an immune-related adverse event. (a) Baseline chest CT scan prior to ipilimumab. **(b)** Three weeks after receiving high-dose immunosuppression for immune-related colitis, CT scans showed cavitary pulmonary consolidations (white arrow). Subsequent bronchoalveolar lavage was consistent with *Aspergillus fumigatus* pneumonia. **(c)** After a 14-day treatment with antifungals, repeat CT scan showed radiographic improvement in cavitary consolidations, but increased bilateral pleural effusions. **(d)** Timeline of described events (not to scale).



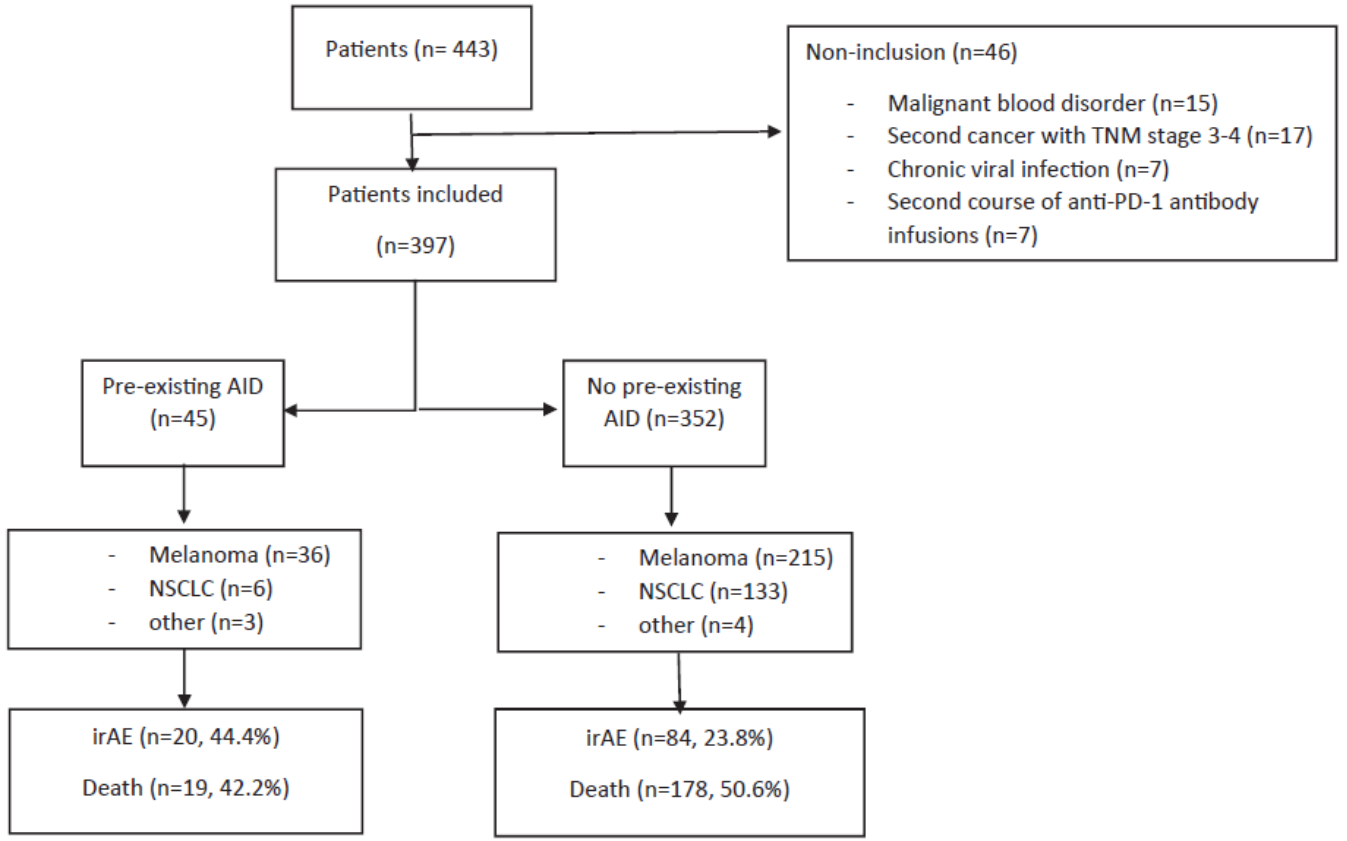
Immunotherapy in patients with autoimmune diseases must be used with caution

HCC in the context of autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) ***Incidence 3-18 cases per 1000 patient year***

Co-occurring autoimmune disease (AID) **Incidence unknown**

All Prospective Studies in HCC and IO have excluded thus limitation in data

REISAMIC Registry for Patient Autoimmune Disease (AID)



irAE 44% for those with AID vs 23.8% for those without AID

Danlos et al. European Journal of Cancer 2018

Immunotherapy following liver transplant is contraindicated in routine practice

Change in liver function in 7 patient following IO treatment in prior liver transplant recipient

ID	Change in Child Pugh	Change in MELD	Change in AFP (ng/mL)	Change in albumin (g/dL)	Change in Tbili (mg/dL)	Change in AST (U/L)	Change in ALT (U/L)	Change in INR
1	0	+5	+1,000	−0.3	0	+162	+84	+0.08
2	0	0	N/A	+0.3	+0.1	−4	−7	−0.2
3	+1	0	+214,082	−0.1	0	+3	+26	+0.08
4	+1	+1	+8,480	−0.3	+0.1	+7	0	+0.08
5	0	+1	+206.1	+1.5	−0.1	+11	+1	+0.45
6	+2	+5	+64.6	−1.1	+0.2	+900	+846	0.18
7	+2	+6	+44,767	−0.1	+0.8	169	+151	+0.1
Median	+1	+1	+1,000	−0.3	+0.1	+11	+26	+0.08

ID, patient identification; MELD, model for end stage liver disease; AFP, alpha-fetoprotein; Tbili, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; ng/Ml, nanograms per milliliter; g/dL, grams per deciliter; mg/dL, milligrams per deciliter; U/L, units per liter.

7 patients with advanced solid tumors and prior liver transplant- 5 with HCC

2 of 7 (29%) patients with prior liver transplant treated with IO developed acute rejection

0 of 5 HCC patients had clinical benefit

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Conclusions

- Immunotherapy with checkpoint inhibitors has revolutionized cancer care
- Several agents are now approved with GI cancers based on pivotal phase 3 data indicating survival advantage over prior standards
- On-target toxicity serves to activate the immune response leading to immune related adverse events
- Although most toxicity are mild, severe or fatal toxicity may occur
- Most societies have established guidelines to help mange patients' patients
- Immunosuppression is often required and, in most cases, effectively resolve underlying toxicity