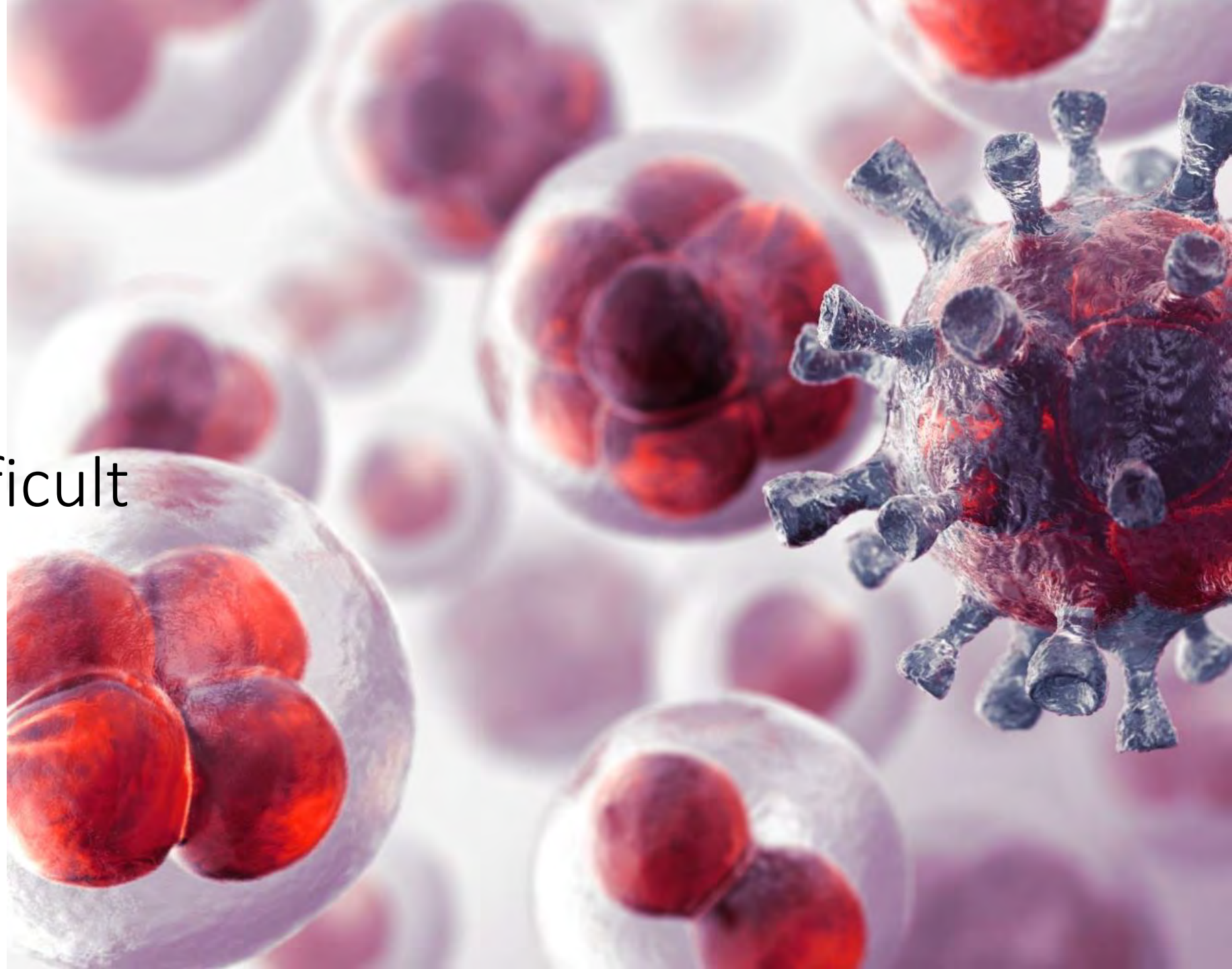
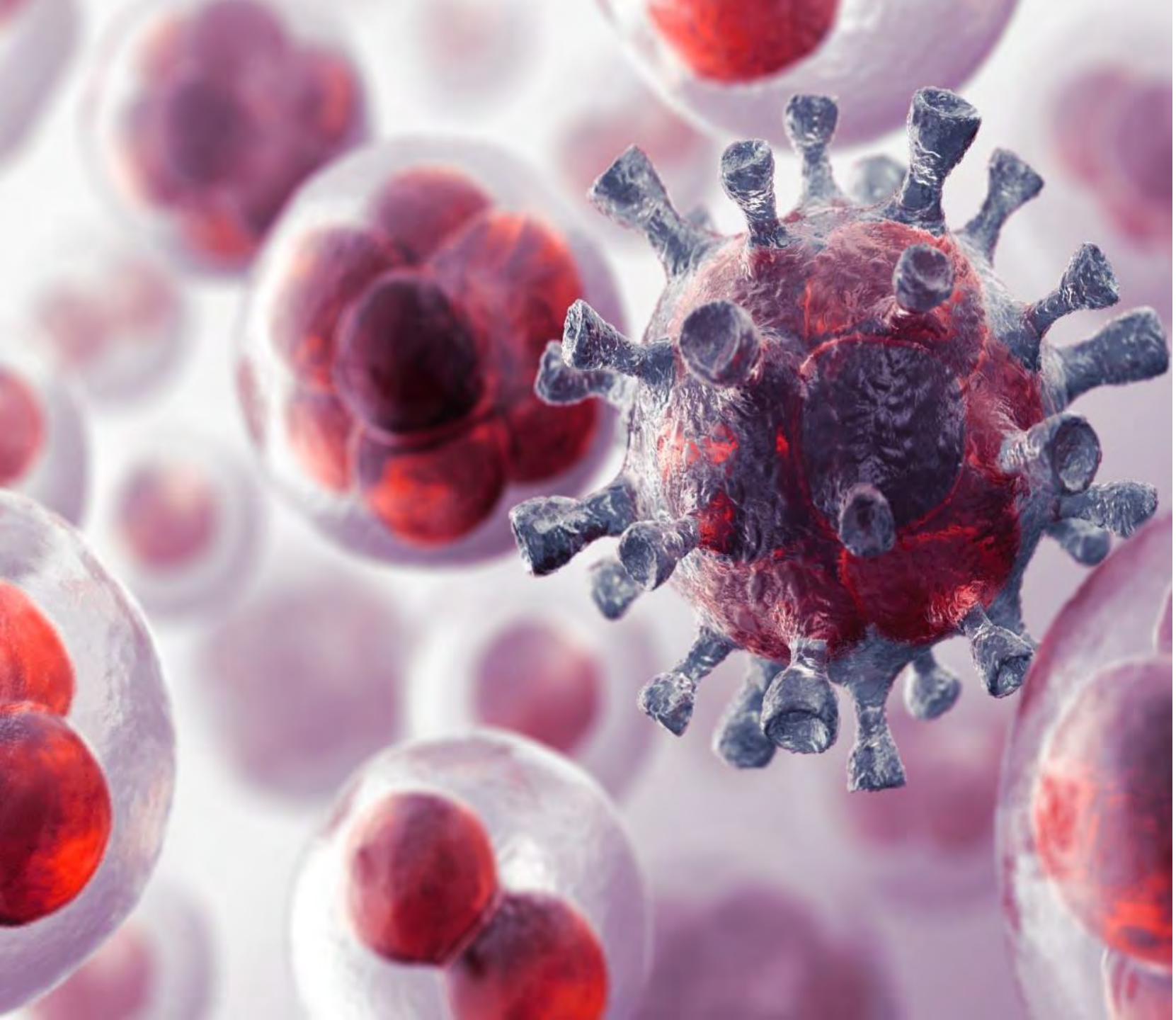
Immune Checkpoint Inhibitors Managing Difficult Toxicities

FLASCO Spring Congress

April 5, 2025

Jeanelle King, PA-C

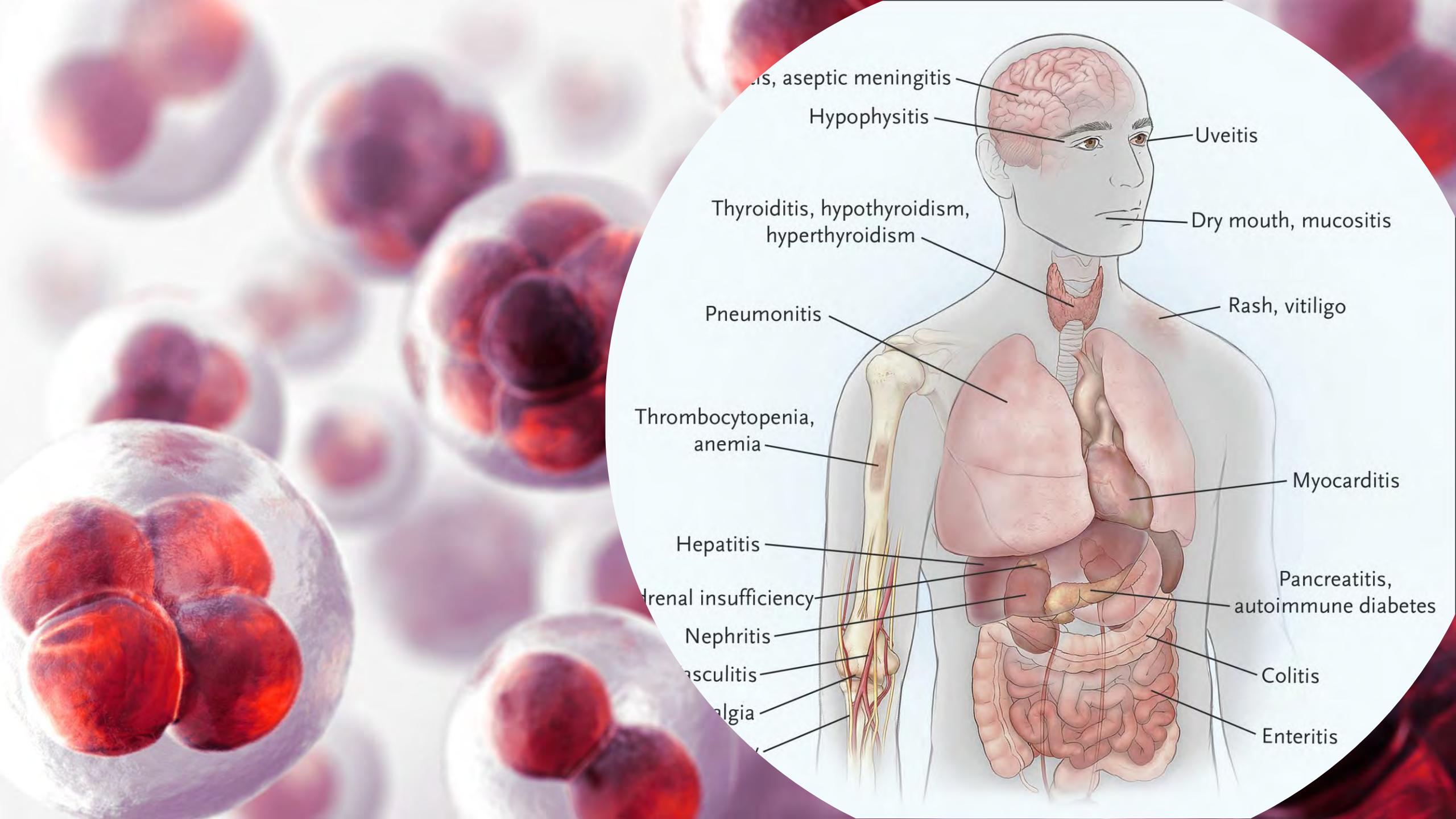




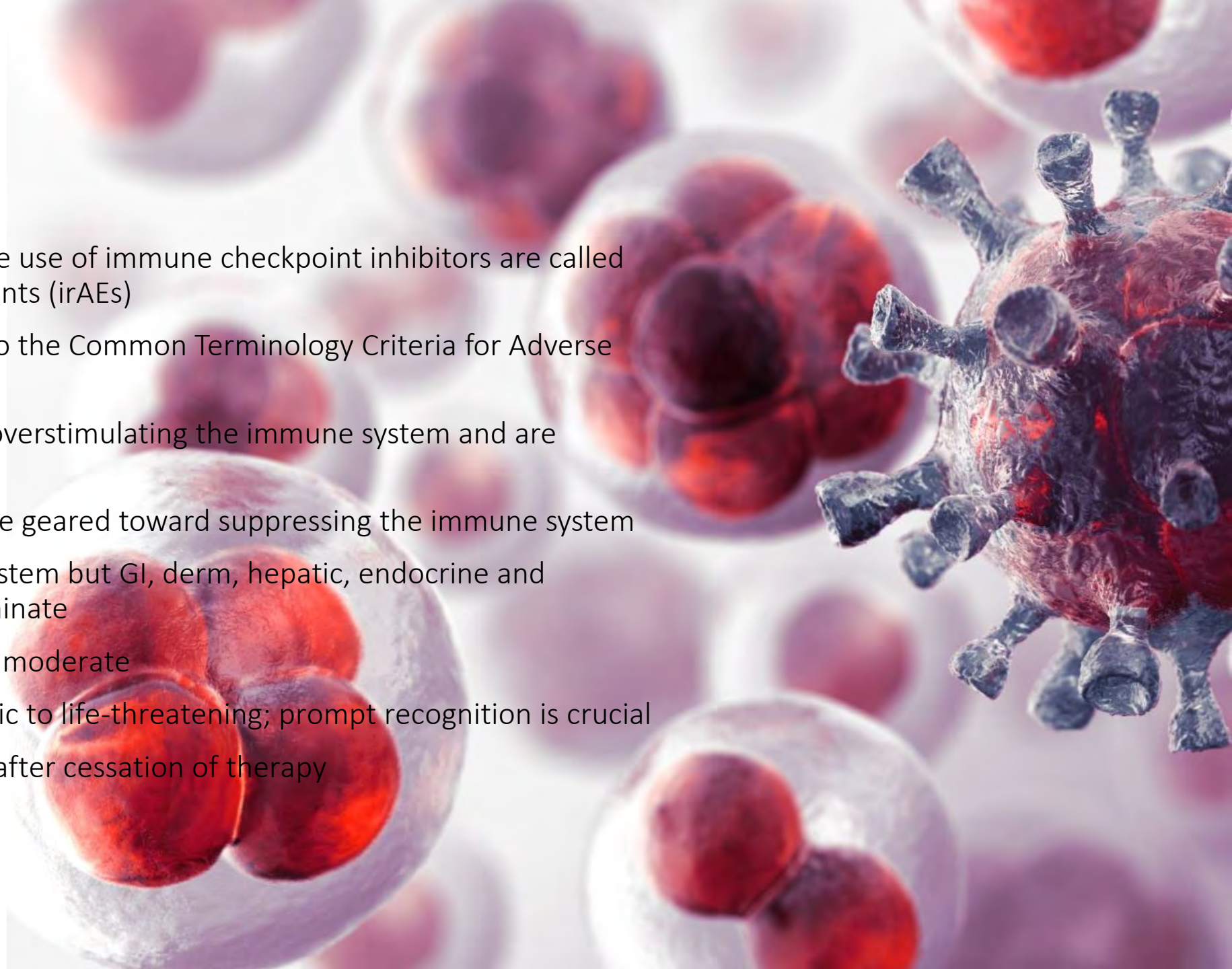
Disclosures

Speaker's bureau for *Regeneron, Pfizer*, *BMS*, and *Merck*

- **i3 Health and FLASCO have mitigated all relevant financial relationships**

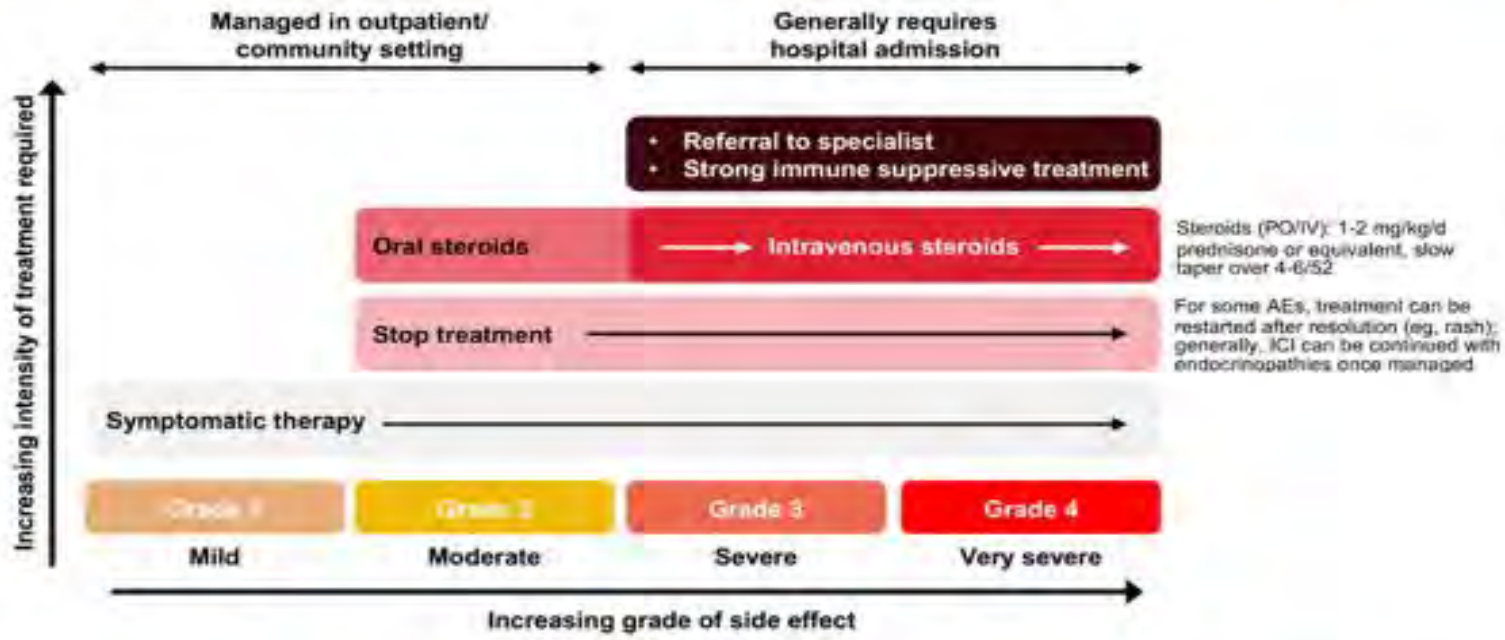

is, aseptic meningitis
Hypophysitis
Uveitis
Thyroiditis, hypothyroidism,
hyperthyroidism
Dry mouth, mucositis
Pneumonitis
Rash, vitiligo
Thrombocytopenia,
anemia
Myocarditis
Hepatitis
Pancreatitis,
autoimmune diabetes
drenal insufficiency
Nephritis
asculitis
Colitis
algia
Enteritis

Basic Principles



- Adverse events related to the use of immune checkpoint inhibitors are called immune-related adverse events (irAEs)
- irAEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE)
- irAEs are usually a result of overstimulating the immune system and are inflammatory in nature
- Most treatments for irAEs are geared toward suppressing the immune system
- irAEs can affect any organ system but GI, derm, hepatic, endocrine and pulmonary toxicities predominate
- Majority of irAEs are mild to moderate
- Severity can be asymptomatic to life-threatening; prompt recognition is crucial
- Onset is variable; can occur after cessation of therapy

eneral Recommendations for Treatment of irAEs[1]



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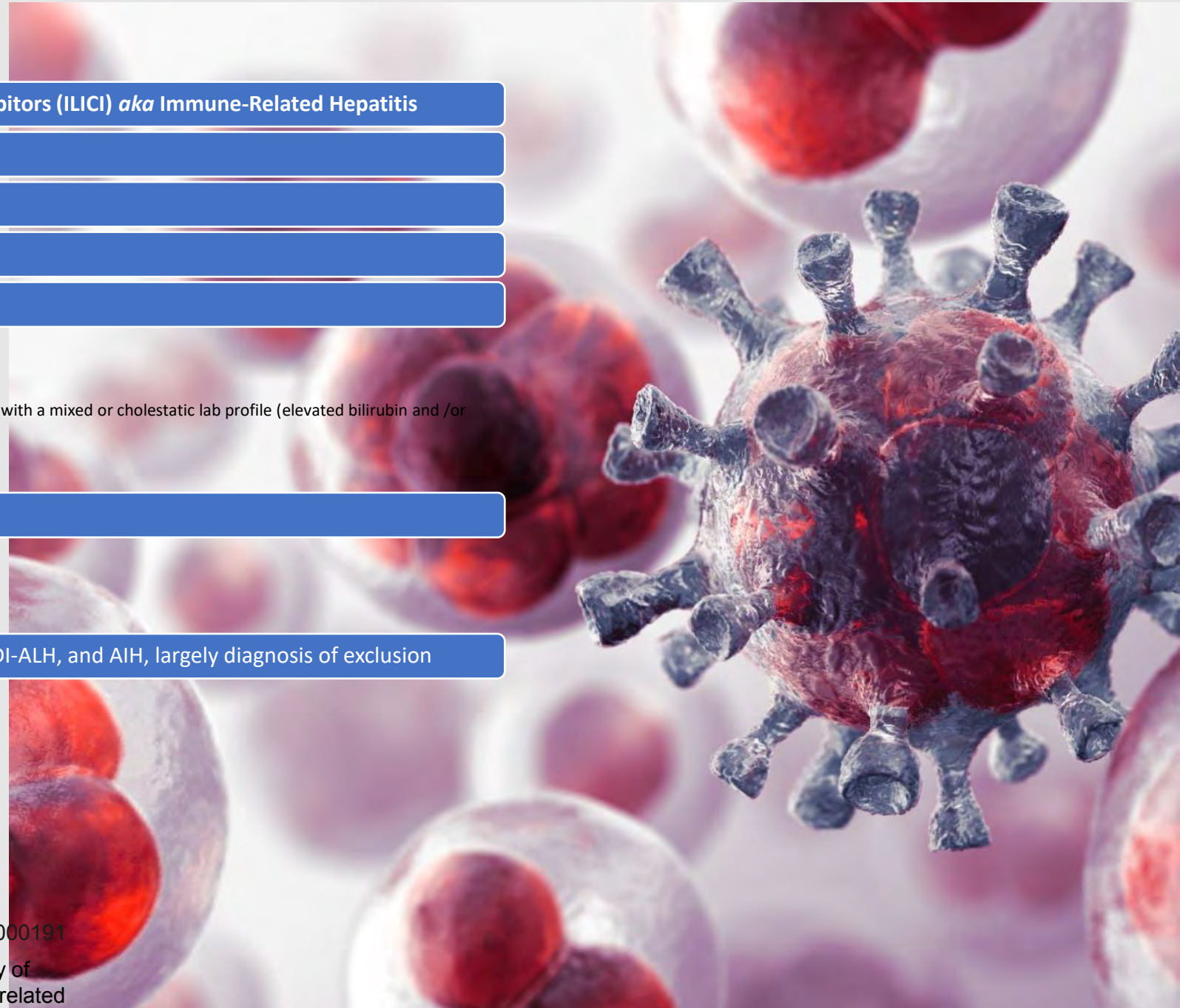
Immune-Mediated Liver Injury Caused by Immune Checkpoint Inhibitors (ILICI) *aka* Immune-Related Hepatitis

- A specific type of hepatic Immune-Related AE (irAE)
- Preceded and/or accompanied by other irAEs
- Incidence: 5-19% (Single ICI < Combination ICIs; higher in HCC)
- Clinical Features:
  - - Onset 1-15 weeks after ICI
  - - Usually asymptomatic, acute elevation ALT/AST
  - -Rarely presents with frank liver failure
  - -The laboratory profile is hepatocellular in 40%–50% of patients, while others present with a mixed or cholestatic lab profile (elevated bilirubin and /or Alk phosphatase).
  - -Severe 2-3%, especially with CLDs, cirrhosis with HCC
  - - Imaging: Hepatomegaly, periportal edema, lymphadenopathy (non-specific)
- Histology: Necroinflammation (panlobular vs. zone 3 >> zone 1)
  - -Pathogenesis not well understood
  - - Infiltrates: CD8>>CD4 T cells, plasma cells, eosinophils, MACs
  - - Granulomas with CTLA-4 agents
  - - Rare biliary injury: Acute cholangitis, VBDS (PD-1)
- Differential Diagnosis: Preexisting CLDs, viral hepatitis, ArLD, DILI, DI-ALH, and AIH, largely diagnosis of exclusion



Swanson LA, Hawa F, Fontana RJ. Immune-mediated liver injury from checkpoint inhibitors: Best practices in 2024. *Clin Liver Dis (Hoboken)*. 2024;23(1):e0191. Published 2024 Jun 5. doi:10.1097/CLD.0000000000000191

Brahmer JR, Abu- Sbeih H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related

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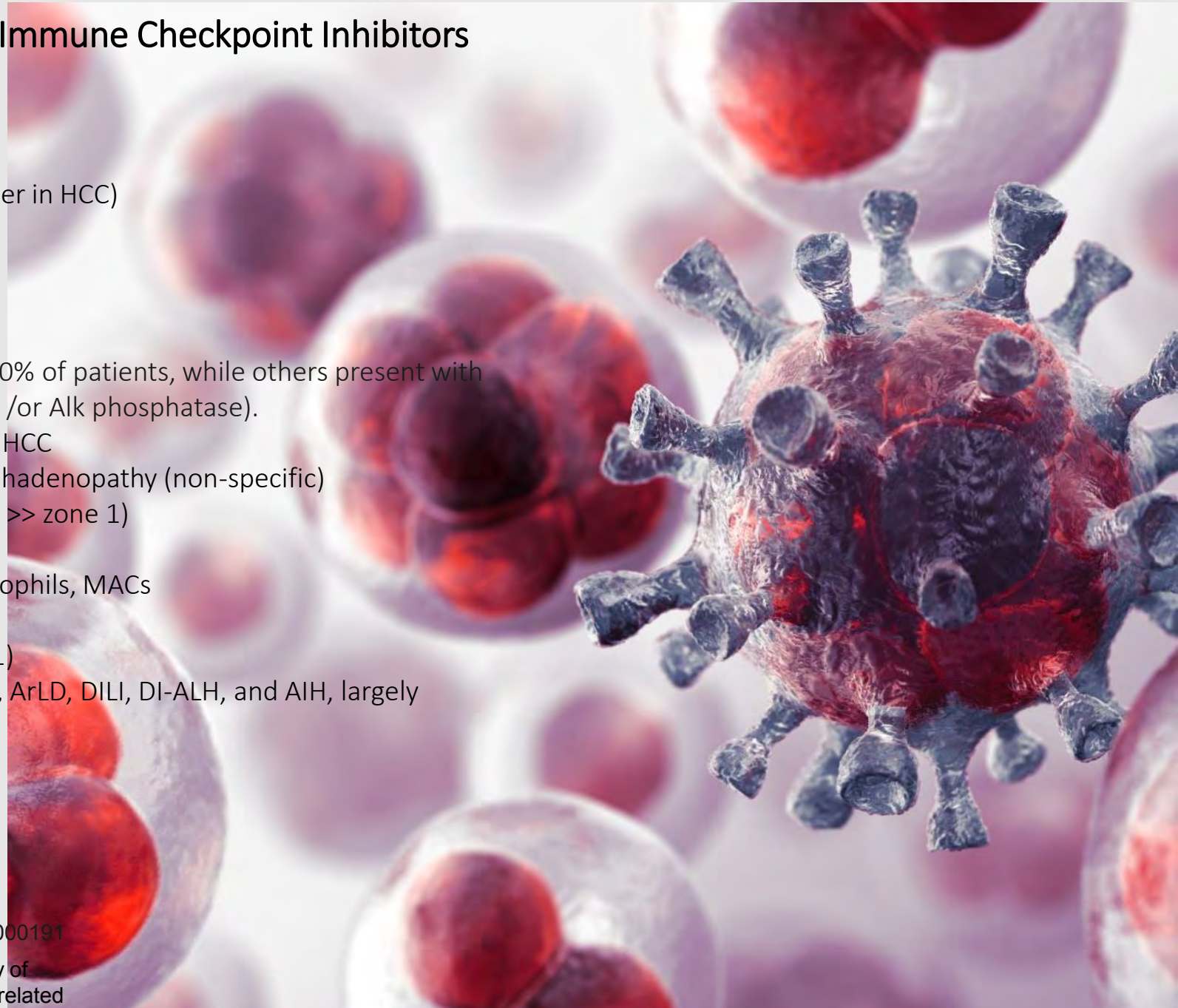

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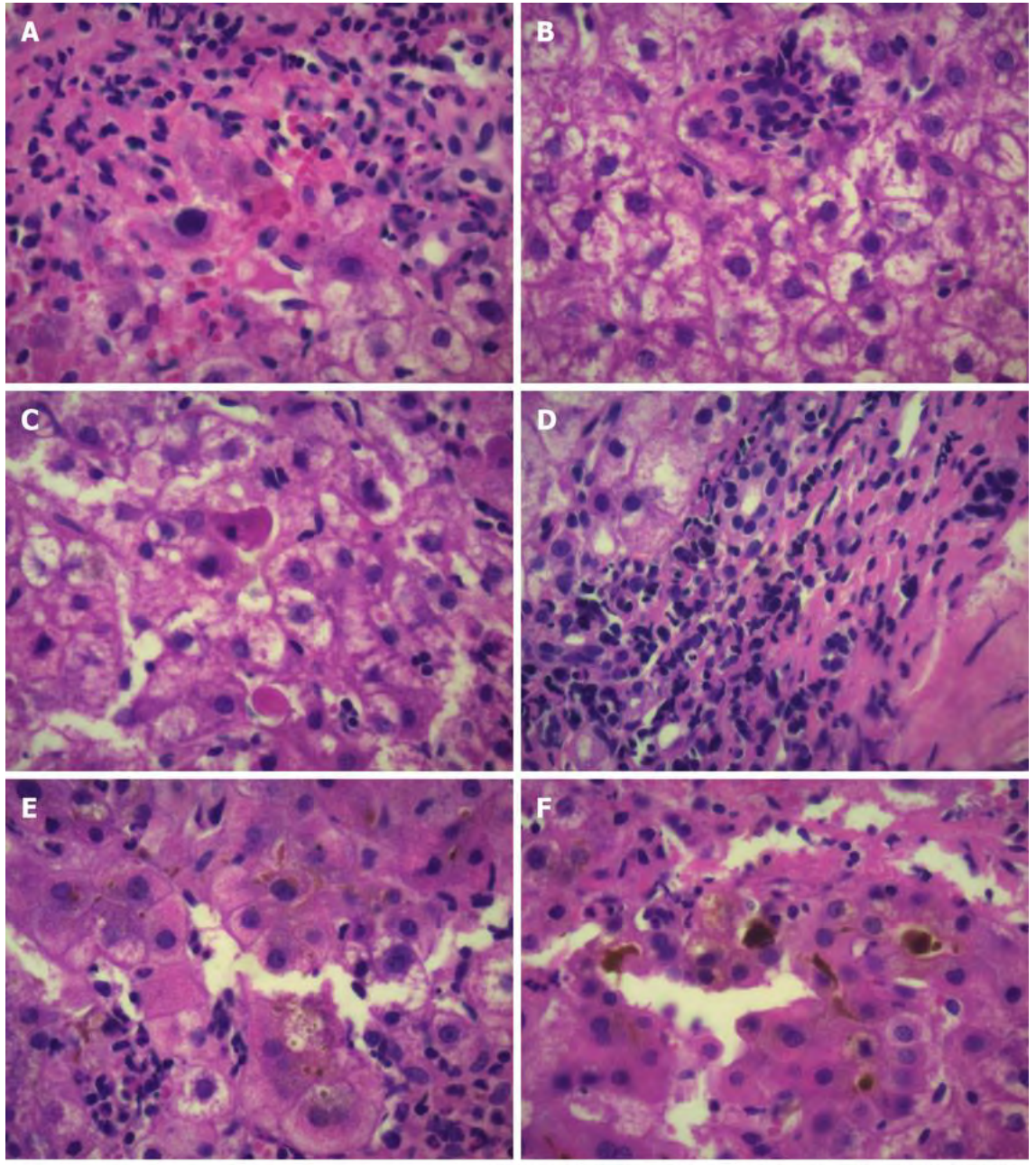
So why does this happen?

Epitope spreading is a phenomenon in which an immune response initially directed against a specific epitope (a small, recognizable part of an antigen) gradually expands to target other epitopes



Pathological changes of drug-induced liver injury -induced by atezolizumab used for treatment of hepatocellular carcinoma (H&E 40×). A: Portal inflammation and interfase hepatitis; B: Focal lobular necrosis; C: Frequent lobular acidophilic bodies; D: Ductal damage and migration of inflammatory cells into ductal epithelium; E: Hepatocyte rosettes as a result of liver regeneration; F: Hepatocanalicular cholestasis and biliary plugs.

Vanderlugt, CJ, Miller, SD. Epitope Spreading. Current Opinion in Immunology. 1996;8 (6) 831-836.

https://doi.org/10.1016/S0952-7915(96)80012-4.

Bessone, Fernando & Bjornsson, Einar. (2022). Checkpoint inhibitor-induced hepatotoxicity: Role of liver biopsy and management approach. World Journal of Hepatology. 14. 1269-1276. 10.4254/wjh.v14.i7.1269.

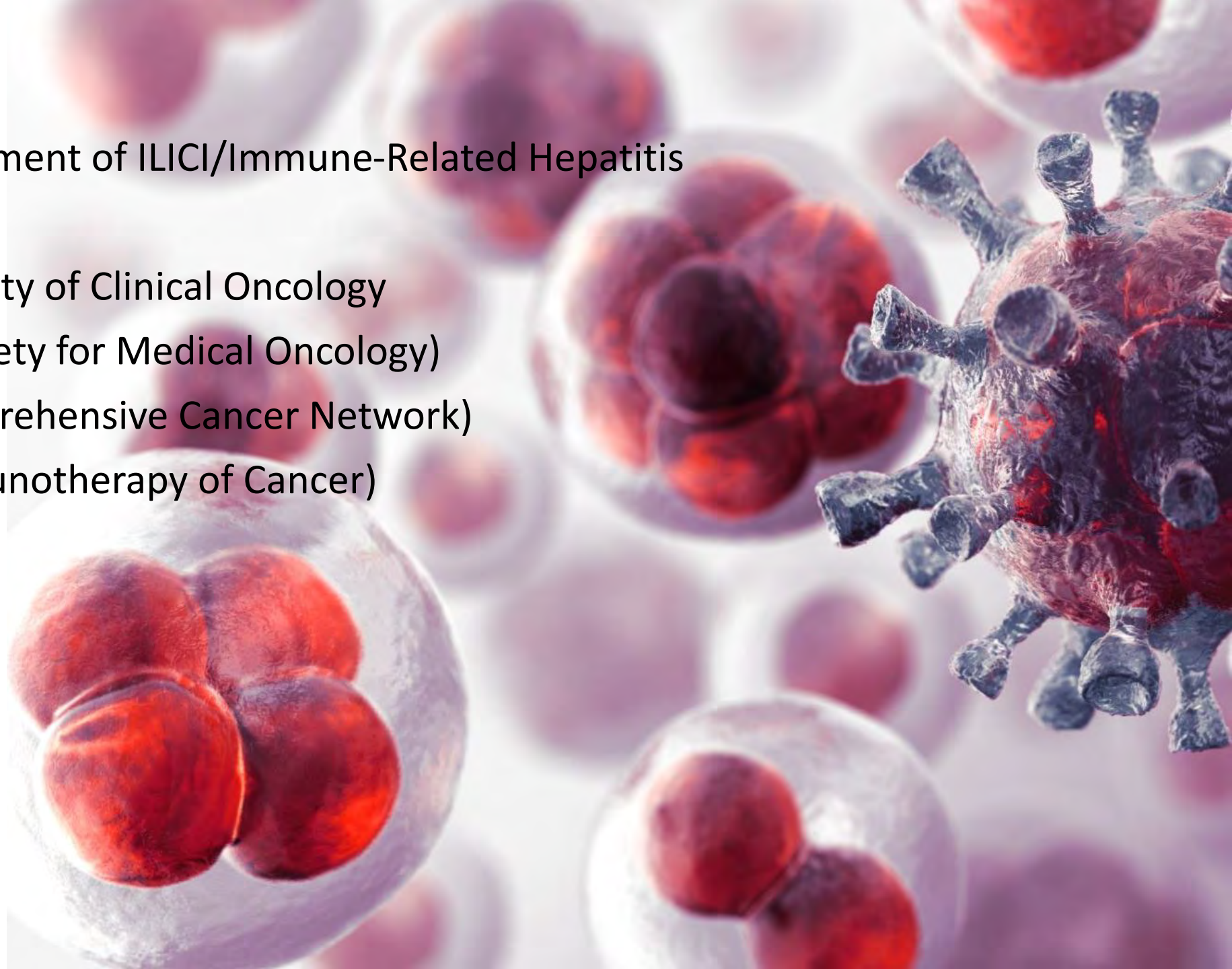
Comparison of the clinicopathologic features of hepatic injury due to ICIs, DILI, and AI

Feature	ICIs	DILI	AIH
Autoimmune antibody	Absent	ANA, SMA, pANCA	ANA, Anti LKM1, SMA
Histology	PD-1/L1: Lobular, non-granulomatous hepatitis CTLA-4: Central vein endothelialitis, granulomatous hepatitis with fibrin ring deposits[21]	Cholestasis and bile duct injury non-caseating granulomas, mild lobular and portal inflammation[51]	Lymphoplasmacytic interface hepatitis, emperipolesis, and hepatocyte rosettes[52]
Type of immune cells	Eosinophilic infiltration and plasmacytosis less frequently with significantly fewer $CD20^-$ or $CD4^+$ lymphocytes	Prominent intra-acinar lymphocyte Prominent port neutrophils[53]	Prominent intra-acinar plasma cell and eosinophils[53]

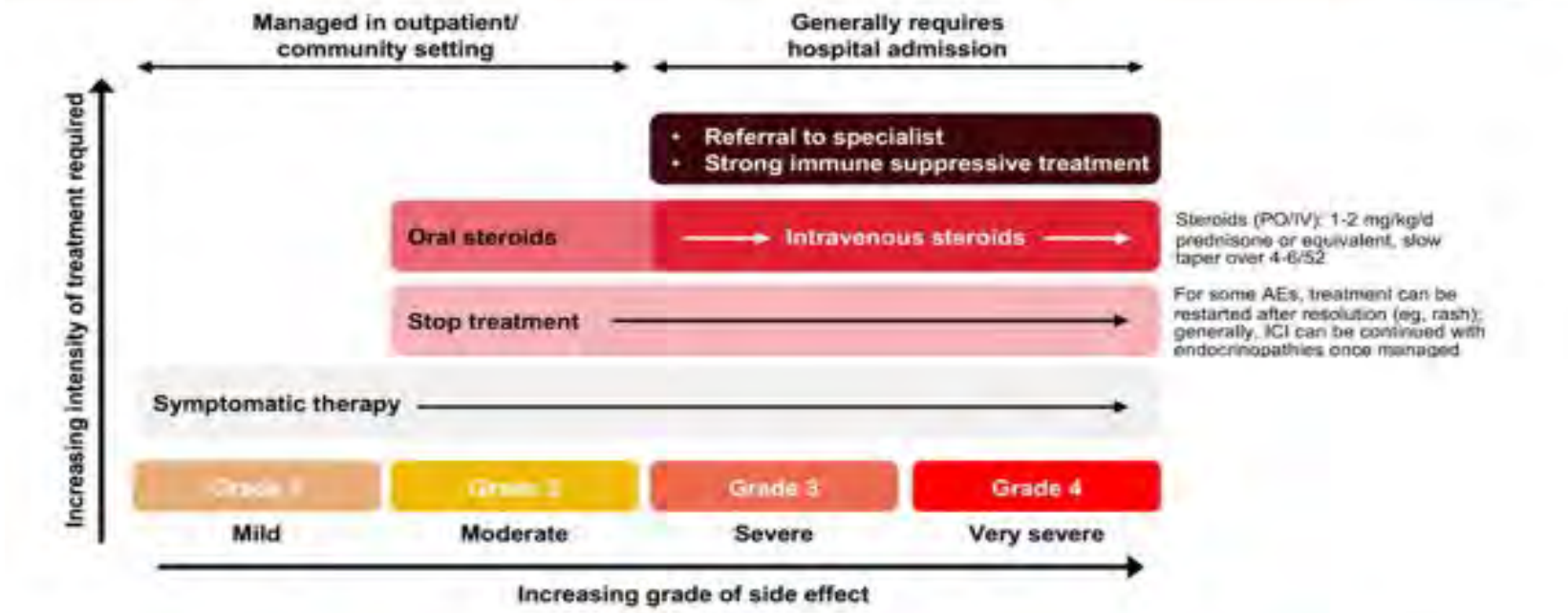
Abbreviations: ICI, Immune checkpoint inhibitors; DILI, Drug-induced liver injury; AIH, Autoimmune hepatitis; ANA, Antinuclear antibodies; SMA, Smooth muscle antibodies; pANCA, Perinuclear antineutrophil cytoplasmic antibodies; LKM1, Liver kidney microsomal type 1.

Guidelines for management of ILICI/Immune-Related Hepatitis

- ASCO (American Society of Clinical Oncology
- ESMO (European Society for Medical Oncology)
- NCCN (National Comprehensive Cancer Network)
- SITC (Society for Immunotherapy of Cancer)



eneral Recommendations for Treatment of irAEs[1]



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MAYO CLINIC

3 weeks post cycle 1 Ipi/Nivo (pre-cycle 2 outpatient visit)

- Maculopapular rash and arthralgias
- AST 560 (10x ULN) and ALT 268 (5x ULN) → **Grade 3 elevation**
  - US liver: negative
  - Viral hepatitis screen: negative
- Started prednisone 1 mg/kg with slow taper for ICI-related hepatitis and dermatitis
- Cycle 2 placed on hold

Courtesy of Nayef Abdel-Razeq, M.D.
Hematology/Oncology Fellow
Mayo Clinic Comprehensive Cancer Center

ASCO

2.0. Gastrointestinal Toxicities

Additional Considerations:

- May consider fecal microbiota transplant,[4,5] JAK inhibitor tofacitinib[6] or IL-12 blocking antibody ustekinumab[7] in patients who are refractory to the previous immunosuppressants.
- Patients with both irAE-related hepatitis and irAE-related colitis are less common, and management may include permanently discontinuing ICPi and offering other immunosuppressant agents (e.g., prednisone and mycophenolate) that work systemically for both conditions. Infliximab is contraindicated for hepatic irAE.
- Currently, enteritis and/or gastritis alone as the cause of gastrointestinal toxicity is uncommon and endoscopy with biopsy is recommended as the evaluation tool. It may be managed similarly to colitis including steroid and/or biologics etc.

2.2. Hepatitis

Workup and Evaluation:

- Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or consider weekly if grade 1 LFT elevations. No treatment is recommended for grade 1 LFT abnormality.
- Review medications and supplements that may cause hepatotoxicity and rule out abnormal liver enzymes from development or progression of liver metastases.
- Liver biopsy should be considered if the patient is steroid refractory or if concern for other differential diagnoses that would alter medical management.

For grade ≥2:

- Work up for other causes of elevated liver enzymes (e.g. viral hepatitis, alcohol history, iron studies, thromboembolic event, or potential liver metastasis from primary malignancy) by doing blood work and imaging (ultrasound and cross-sectional imaging). If suspicion for primary autoimmune hepatitis is high, can consider ANA/ASMA/ANCA. If patients with elevated ALKP alone, GGT should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies.

Grading	Management
G1: Asymptomatic (AST or ALT >ULN to 3.0× ULN and/or total bilirubin >ULN to 1.5× ULN)	• Continue ICPi with close monitoring; consider alternate etiologies. • Consider monitoring labs 1 to 2 times weekly. • Manage with supportive care for symptom control.
G2: Asymptomatic (AST or ALT >3.0 to ≤5× ULN and/or total bilirubin >1.5 to ≤3× ULN)	• Hold ICPi temporarily. • Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs. Temporarily hold other potentially hepatotoxic oncologic agents. • For grade 2 hepatic toxicity, may administer steroid (0.5-1mg/kg day prednisone) or equivalent if no improvement is seen after 3-5 days. • Increase frequency of monitoring to every 3 days. • If inadequate improvement after 3 days, consider adding mycophenolate mofetil. • May initiate steroid taper when symptoms improve to ≤ G1 and may resume ICPi treatment when steroid ≤ 10mg/d. Taper over at least 1 month. • Consider hepatology consult for G2 and above. • May resume if recover to ≤ G1 on prednisone ≤ 10mg/d.

ASCO

2.0. Gastrointestinal Toxicities	
G3: AST or ALT 5-20× ULN and/or total bilirubin 3-10× ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	• Follow G2 recommendations as listed, with the following additions for G3: • Consider permanently discontinuing ICPi if asymptomatic; permanently discontinue if symptomatic. • Immediately start steroid 1-2 mg/kg methylprednisolone or equivalents. • If steroid refractory, consider liver biopsy to rule out NASH, tumor, cholestatic variants, other drug-related hepatic inflammation, infection, or other autoimmune entity and consider adding azathioprine[B] or mycophenolate[C] if infectious cause is ruled out. • Labs daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated total bilirubin 3 × > ULN. • If no improvement is achieved with steroid or for patients on ICPi therapy combined with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis. • Steroid taper can be attempted around 4-6 weeks when ≤ G1, re-escalate if needed, optimal duration unclear. • Consider transfer to tertiary care facility if necessary.
G4: AST or ALT >20× ULN and/or total bilirubin >10× ULN OR decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	• Follow G3 recommendations as listed, with the following additions for G4: • Administer 2 mg/kg/d methylprednisolone equivalents.
Additional considerations: • Infliximab is contraindicated for immune-related hepatitis.	

[A] High-risk endoscopic features include large deep ulceration, multiple ulcers, and extensive colitis beyond left colon.[1,2]
[B] Anecdotal experience suggests azathioprine may be beneficial in steroid-refractory immune-related hepatitis. If using azathioprine, should test for thiopurine methyltransferase (TPMT) deficiency.
[C] A case study reports use of mycophenolate mofetil in steroid-refractory immune-related hepatitis with some success.[8]

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

J. Haanen, M. Obeid, L. Spain, F. Carbonnel, Y. Wang, C. Robert, A.R. Lyon, W. Wick, M. Kostine, S. Peters, K. Jordan, J. Larkin

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Volume 33 Issue 12 Pages 1217-1238 (December 2022)
DOI: 10.1016/j.annonc.2022.10.001

ESMO

General guidance for immunosuppression

irAE management generally consists of four sequential steps: (i) diagnosis and grading of irAEs, (ii) ruling out differential diagnoses and pre-immunosuppression work-up, (iii) selecting the appropriate immunosuppression strategy for grade ≥2 events and (iv) active evaluation at 72 h to adapt treatment. See Supplementary Table S2 and Section 1 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

To minimise the occurrence of CS-induced AEs, the following general guidance is proposed[2]:

- The lowest effective CS dose should be prescribed for the shortest possible duration, which, in general will be several weeks for grade ≥3 irAEs, including tapering
- CS therapy tapering or discontinuation only on medical advice
- Lifestyle adaptations to minimise the risk of CS-induced AEs

Annals of Oncology 2022 331217-1238DOI: (10.1016/j.annonc.2022.10.001)

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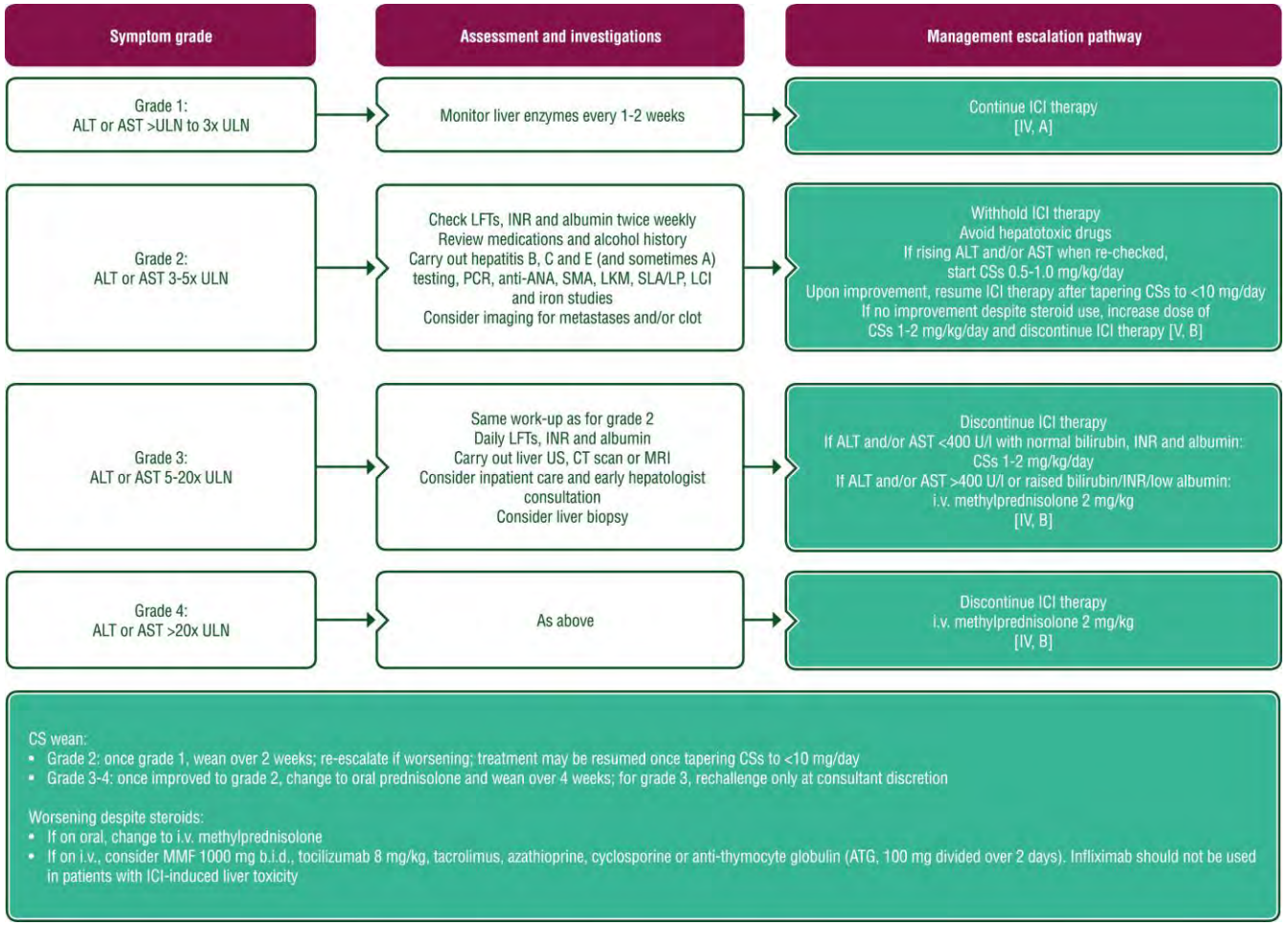

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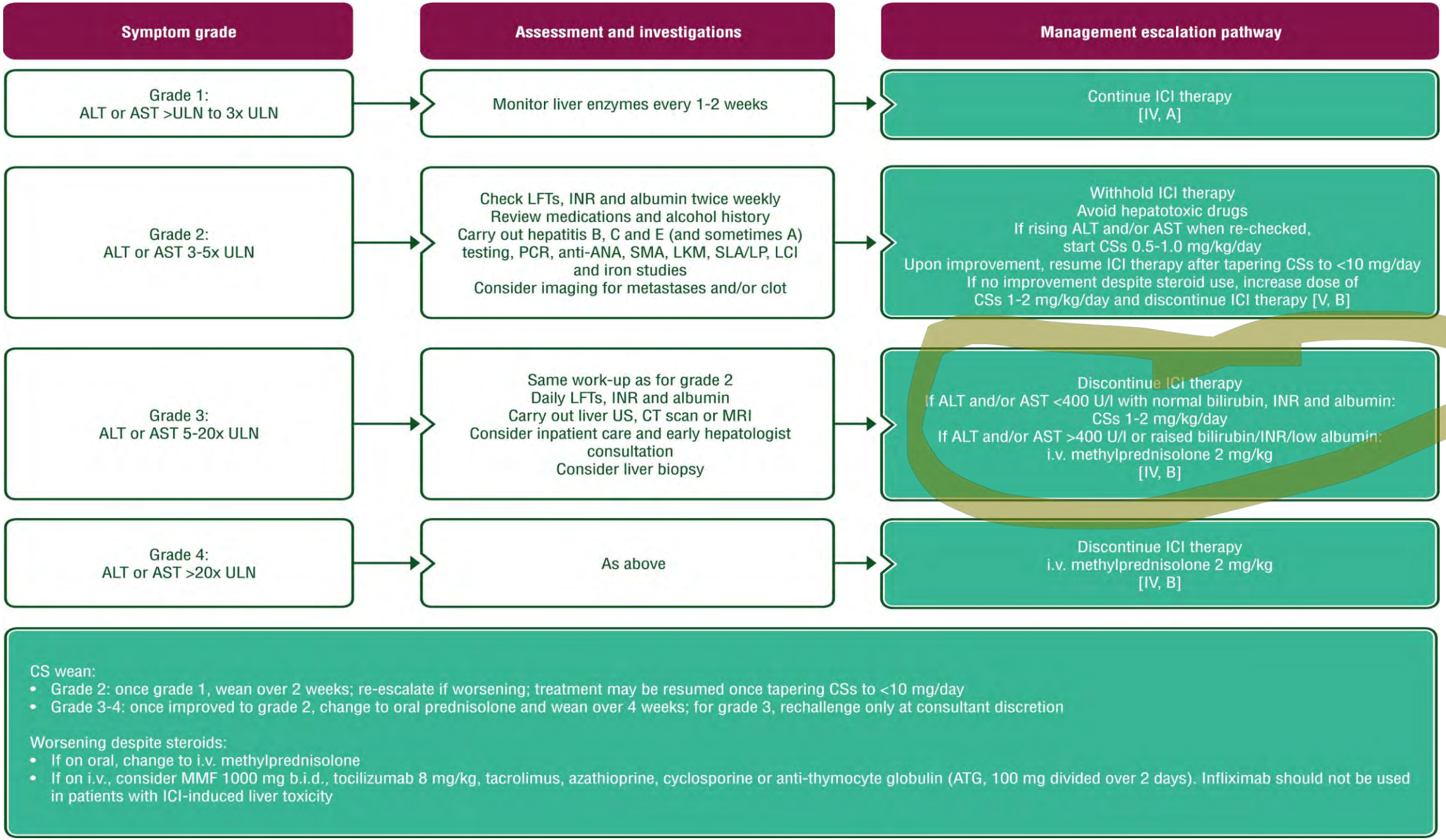

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PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Patient and relevant family history of any autoimmune/ organ-specific disease, endocrinopathy, or infectious disease (ID) • Neurologic examination • Bowel habits (typical frequency/consistency) • ID screening (human immunodeficiency virus [HIV]; hepatitis A, B, C) as indicated	Clinical examination at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General blood work • Complete blood count (CBC) (with differential if indicated) • Comprehensive metabolic panel (CMP)	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Consider dermatology referral. Monitor affected skin and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (FT4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	ICI_ENDO-2 and ICI_ENDO-3

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related AEs (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B). For guidance on general recommendations for vaccination in patients with cancer, see NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections.

[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Pituitary/Adrenal (ICI_ENDO-4) • Consider serum cortisol (morning preferred) and thyroid function as above	Consider repeating every 4–6 weeks during immunotherapy (immuno-oncology [IO]-only regimens[c]), then follow-up every 12 weeks as indicated	Morning serum cortisol, adrenocorticotropic hormone (ACTH), TSH, FT4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol (premenopausal individuals), and cosyntropin stimulation test only as indicated
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Consider pulmonary function tests (PFTs) with diffusion capacity for patients who are high risk (eg, interstitial lung disease on imaging, chronic obstructive pulmonary disease [COPD], previous suspected treatment-related lung toxicity) • In the absence of prior imaging, consider a chest x-ray	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes
Cardiovascular (ICI_CARDIO-1) • Consider baseline electrocardiogram (ECG) • Consider high-sensitivity troponin and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms[d]	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine kinase (CK)

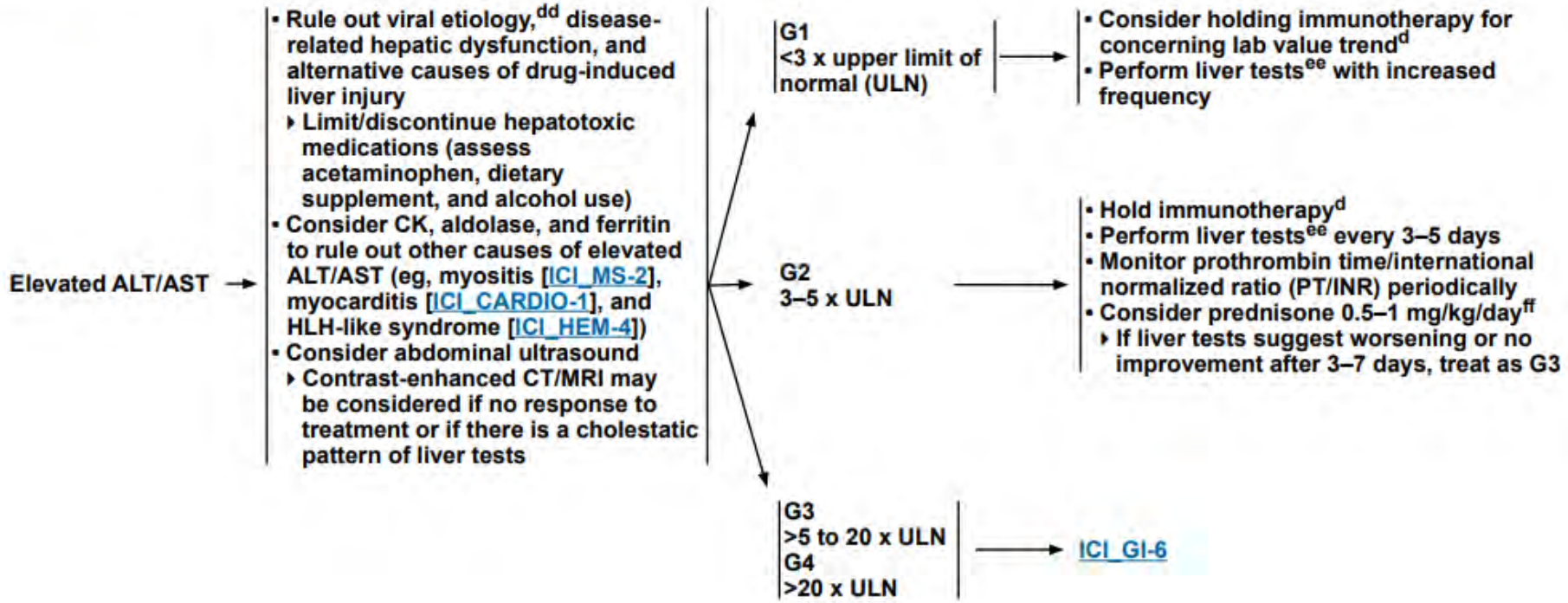
[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of irAEs. See Principles of Immunotherapy Patient Education (IMMUNO-B). For guidance on general recommendations for vaccination in patients with cancer, see NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections.

[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

[c] For regimens that require steroid premedication, routine surveillance is not recommended.

[d] For individuals with a high-risk profile (eg, receiving immune checkpoint inhibitor [ICI] combination therapy regimens, including those with LAG-3), consider checking high-sensitivity troponin every cycle for the first 3 cycles (which corresponds with the median time to onset of myocarditis), and then every 3 months.

Note: All recommendations are category 2A unless otherwise indicated.



[d] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[o] Principles of Immunosuppression (IMMUNO-A).
[bb] Consider initiating steroids while waiting for results in cases of G4 ALT/AST elevations.
[cc] Hyperbilirubinemia of hepatic origin is generally of conjugated predominance (or conjugated hyperbilirubinemia).
[dd] Consider testing for viral infections based on liver test pattern, viral risk factors, and clinical presentation including hepatitis B surface antigen (HBsAg).
[ee] ALT, AST, alkaline phosphatase, bilirubin (total and direct), and albumin.
[ff] When liver tests show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.

Note: All recommendations are category 2A unless otherwise indicated.

NCCN Guidelines Version 1.2025
Management of Immune Checkpoint Inhibitor-Related Toxicities

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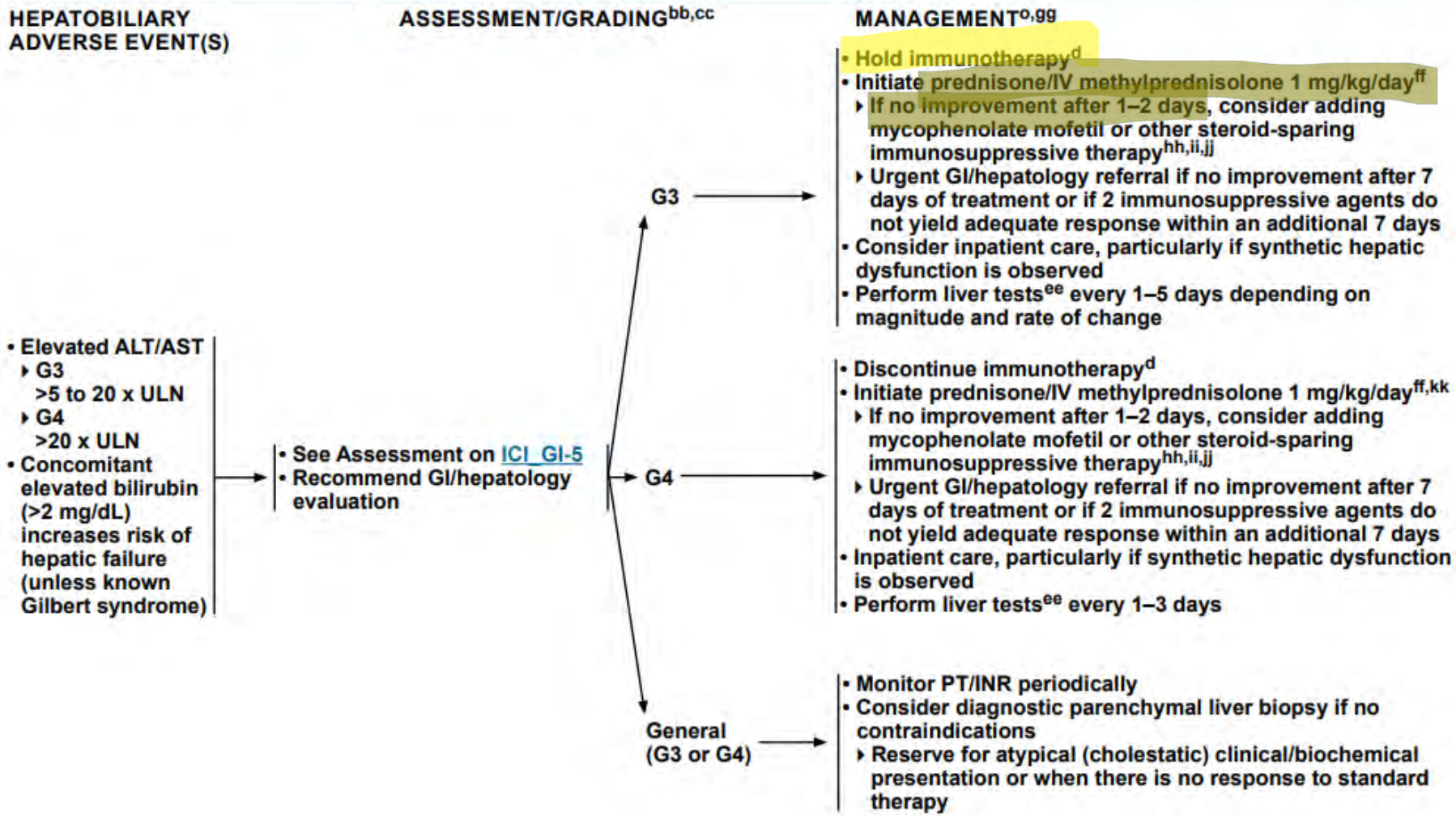

Footnotes on ICI_GI-6A

Note: All recommendations are category 2A unless otherwise indicated.

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,[1] Hamzah Abu-Sbeih,[2] Paolo Antonio Ascierto ,[3] Jill Brufsky,[4] Laura C Cappelli,[5] Frank B Cortazar,[6,7] David E Gerber,[8] Lamya Hamad,[9] Eric Hansen,[10] Douglas B Johnson,[11] Mario E Lacouture,[12] Gregory A Masters,[13] Jarushka Naidoo,[1,14] Michele Nanni,[10] Miguel-Angel Perales,[12] Igor Puzanov,[10] Bianca D Santomasso,[15] Satish P Shanbhag,[5,16] Rajeev Sharma,[10] Dimitra Skondra,[17] Jeffrey A Sosman,[18] Michelle Turner,[1] Marc S Ernstoff [19]

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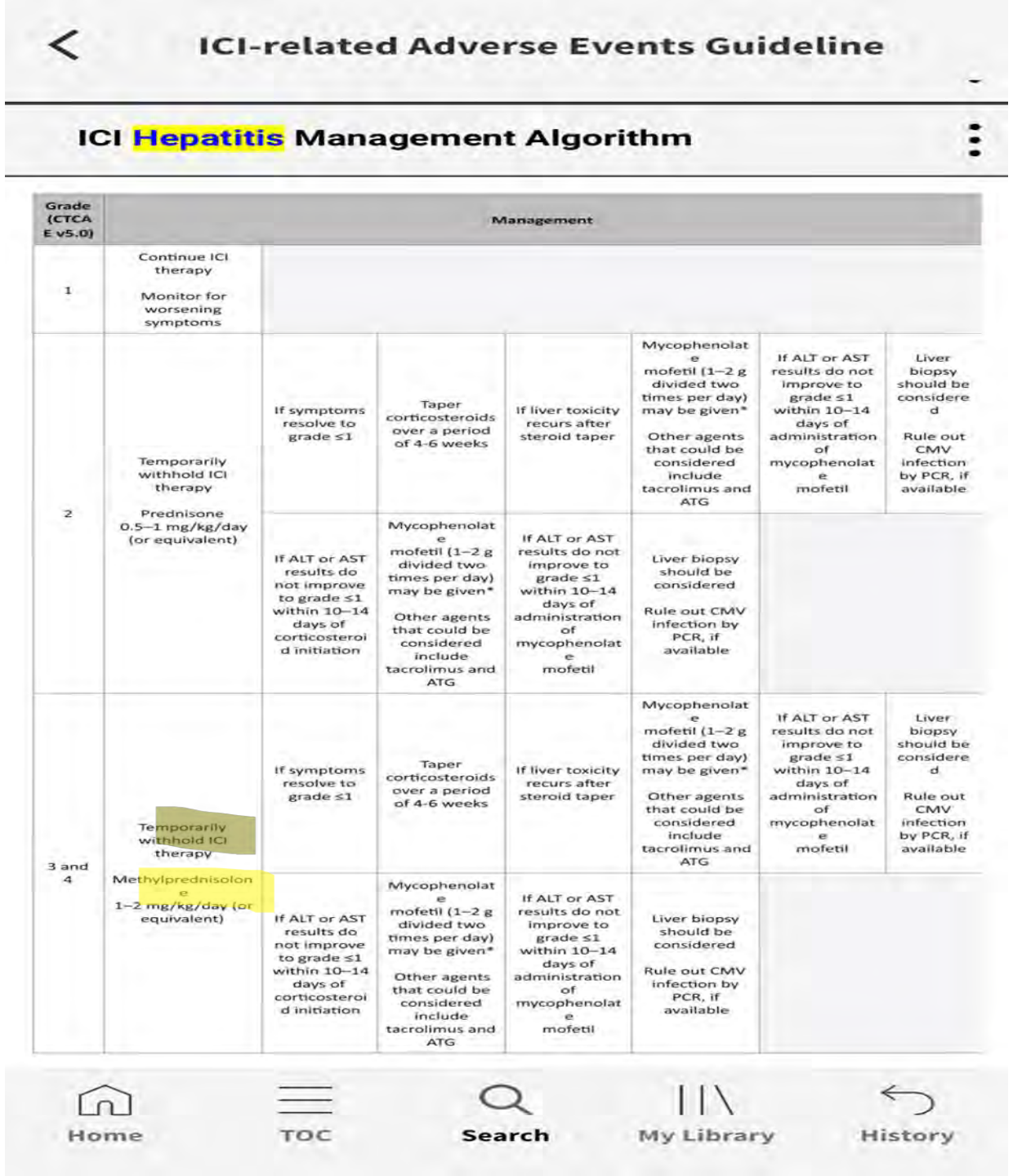
Accepted 24 March 2021

ABSTRACT

Immune checkpoint inhibitors (ICIs) are the standard of care for the treatment of several cancers. While these immunotherapies have improved patient outcomes in many clinical settings, they bring accompanying risks of toxicity, specifically immune-related adverse events (irAEs). There is a need for clear, effective guidelines for the management of irAEs during ICI treatment, motivating the Society for Immunotherapy of Cancer (SITC) to convene an expert panel to develop a clinical practice guideline. The panel discussed the recognition and management of single and combination ICI irAEs and ultimately developed evidence- and consensus-based recommendations to assist medical professionals in clinical decision-making and to improve outcomes for patients.

a wide variety of cancer types. A study of ICI usage estimated that in 2018, 44% of patients with metastatic solid or hematological tumors in the US were eligible for treatment with ICIs.[2] ICIs are also a focus of active drug development, and a number of ongoing trials are evaluating novel antibodies or testing approved ICIs in combination with other treatment modalities including chemotherapies or targeted agents. The use of ICIs as adjuvant therapy has been approved for high-risk melanoma and esophageal and gastro-esophageal junction (GEJ) cancers, and studies of peri-operative checkpoint blockade (including in the neoadjuvant setting) are

SITC



ICI-related Adverse Events Guideline

ICI Hepatitis Management Algorithm

Grade (CTCAE v5.0)	Management						
1	Continue ICI therapy Monitor for worsening symptoms						
2	Temporarily withhold ICI therapy Prednisone 0.5–1 mg/kg/day (or equivalent)	If symptoms resolve to grade ≤1	Taper corticosteroids over a period of 4-6 weeks	If liver toxicity recurs after steroid taper	Mycophenolate mofetil (1–2 g divided two times per day) may be given* Other agents that could be considered include tacrolimus and ATG	If ALT or AST results do not improve to grade ≤1 within 10–14 days of administration of mycophenolate mofetil	Liver biopsy should be considered Rule out CMV infection by PCR, if available
		If ALT or AST results do not improve to grade ≤1 within 10–14 days of corticosteroid initiation	Mycophenolate mofetil (1–2 g divided two times per day) may be given* Other agents that could be considered include tacrolimus and ATG	If ALT or AST results do not improve to grade ≤1 within 10–14 days of administration of mycophenolate mofetil	Liver biopsy should be considered Rule out CMV infection by PCR, if available		
3 and 4	Temporarily withhold ICI therapy Methylprednisolone 1–2 mg/kg/day (or equivalent)	If symptoms resolve to grade ≤1	Taper corticosteroids over a period of 4-6 weeks	If liver toxicity recurs after steroid taper	Mycophenolate mofetil (1–2 g divided two times per day) may be given* Other agents that could be considered include tacrolimus and ATG	If ALT or AST results do not improve to grade ≤1 within 10–14 days of administration of mycophenolate mofetil	Liver biopsy should be considered Rule out CMV infection by PCR, if available
		If ALT or AST results do not improve to grade ≤1 within 10–14 days of corticosteroid initiation	Mycophenolate mofetil (1–2 g divided two times per day) may be given* Other agents that could be considered include tacrolimus and ATG	If ALT or AST results do not improve to grade ≤1 within 10–14 days of administration of mycophenolate mofetil	Liver biopsy should be considered Rule out CMV infection by PCR, if available		

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Guidelines for grade 3 Immune-related Hepatitis

	ASCO	ESMO	NCCN	SITC
Treatment	Hold CPI	Discontinue CPI	Hold CPI	Hold CPI
Steroids	IV methylprednisolone	IV methylprednisolone IF AST and/or ALT >400 U/L	Oral or IV	Oral or IV
2nd line Immunosuppression	“When steroid refractory”	“Worsening despite steroids”	“If no improvement after 1-2 days”	“If AST or ALT do not improve to < or = grade 1 after 10-14 days”

Corticosteroids for Immune-Related Adverse Events and Checkpoint Inhibitor Efficacy: Analysis of Six Clinical Trials

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ABSTRACT

PURPOSE Retrospective studies suggest that immunosuppressive treatment of immune-related adverse events (irAEs) impairs survival in patients with melanoma who received immune checkpoint inhibitors. Here, we study this association across tumor types using data from six international phase II/III registrational trials.

METHODS A post hoc analysis was performed on individual patient data from the anti–programmed cell death-1 (anti–PD-1) + anti–cytotoxic T lymphocyte–associated protein-4 (anti–CTLA-4) treatment arms of six clinical trials (CheckMate-067, -142, -214, -648, -743, and -9LA). Among patients who received systemic immunosuppression for treatment-related adverse events (trAEs), associations of peak and cumulative corticosteroid dose, and use of second-line immunosuppression with overall survival (OS) and progression-free survival (PFS) were assessed using multilevel Cox regression with adjustment for age and sex.

RESULTS Of the 1,959 patients who received anti–PD-1 ± anti–CTLA-4 therapy, 834 patients who were treated with immunosuppression for trAEs were included. Eight hundred and thirty-two patients (100%) received corticosteroids and 81 patients (10%) received second-line immunosuppressants. High corticosteroid peak dose was associated with worse PFS: adjusted hazard ratio (HR_{adj}), 1.15 (95% CI, 1.02 to 1.29) for 1 versus 0.5 mg/kg prednisolone and HR_{adj}, 1.43 (95% CI, 1.05 to 1.96) for 2 versus 0.5 mg/kg. Similar effects were observed for OS: HR_{adj}, 1.21 (95% CI, 1.06 to 1.39) and HR_{adj}, 1.66 (95% CI, 1.17 to 2.37) for 1 and 2 versus 0.5 mg/kg, respectively. Cumulative corticosteroid dose was not associated with survival. HR_{adj} of use of second-line immunosuppression was 1.23 (95% CI, 0.90 to 1.68) for PFS and 1.25 (95% CI, 0.88 to 1.77) for OS.

CONCLUSION Higher corticosteroid peak dose for trAEs is associated with worse survival across tumor types, while cumulative dose is not. Too few patients received second-line immunosuppressants to confirm or reject an association with survival. These data argue for a reconsideration of irAE management approaches, starting with lower corticosteroid dose whenever feasible.

ACCOMPANYING CONTENT

Data Supplement

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