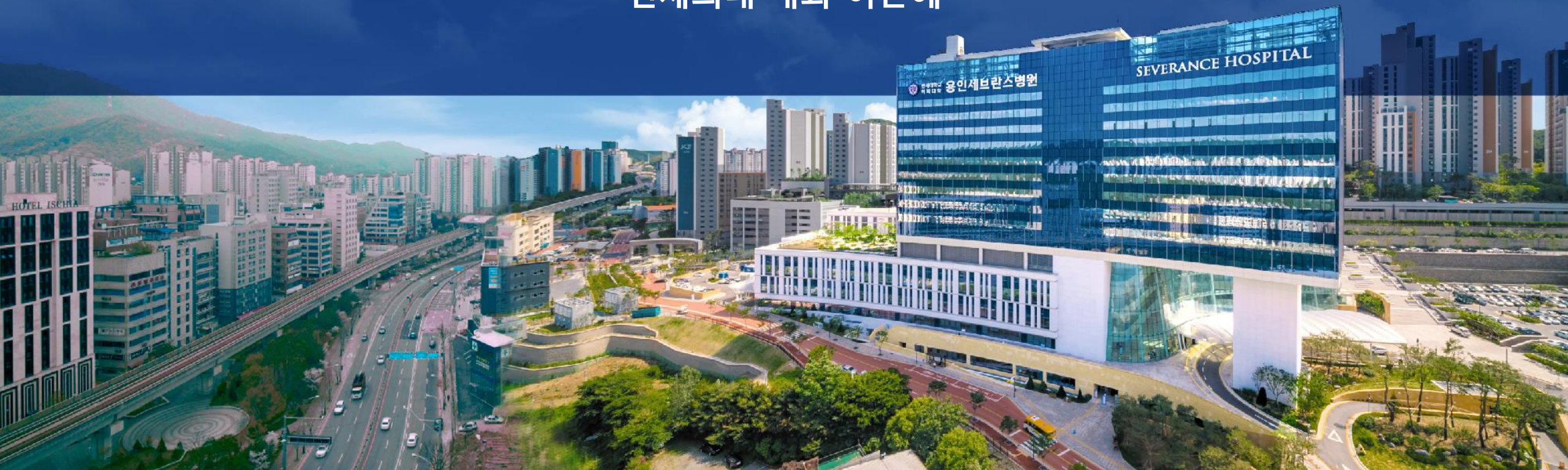
세브란스 SEVERANCE | 용인세브란스병원 YONGIN SEVERANCE HOSPITAL

Lung Cancer School 2022

Management of Steroid-Refractory Immune-Related Adverse Events

연세의대 내과 이은혜



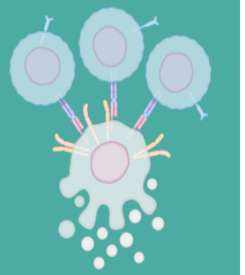
목차

- Mechanism of immune-related adverse events (imAEs)
- Incidence and onset of imAEs for Immune check point inhibitors
- Management of steroid refractory imAEs
- Summary

목차

Chemotherapy, Targeted Therapy, and ICI Therapy Have Different MoAs That May Lead to Different Toxicity Profiles

Chemotherapy 	▪ Acts on **rapidly dividing cells**, including tumor cells and some normal cells ▪ Prevents or slows cell growth and division
Targeted Therapy 	▪ Targets **proteins** that regulate cell growth, division, and spread

IO Therapy 	▪ Helps the body's own immune system fight cancer
	▪ Modulates immune inhibitory mechanisms to reactivate antitumor immunity
	  ▪ By **modulating the immune system**, IO may be effective in a broad range of tumors, independent of tumor histology or driver mutations
	  ▪ However, IO therapy may also affect normal, healthy cells

Immune Checkpoint Inhibitors

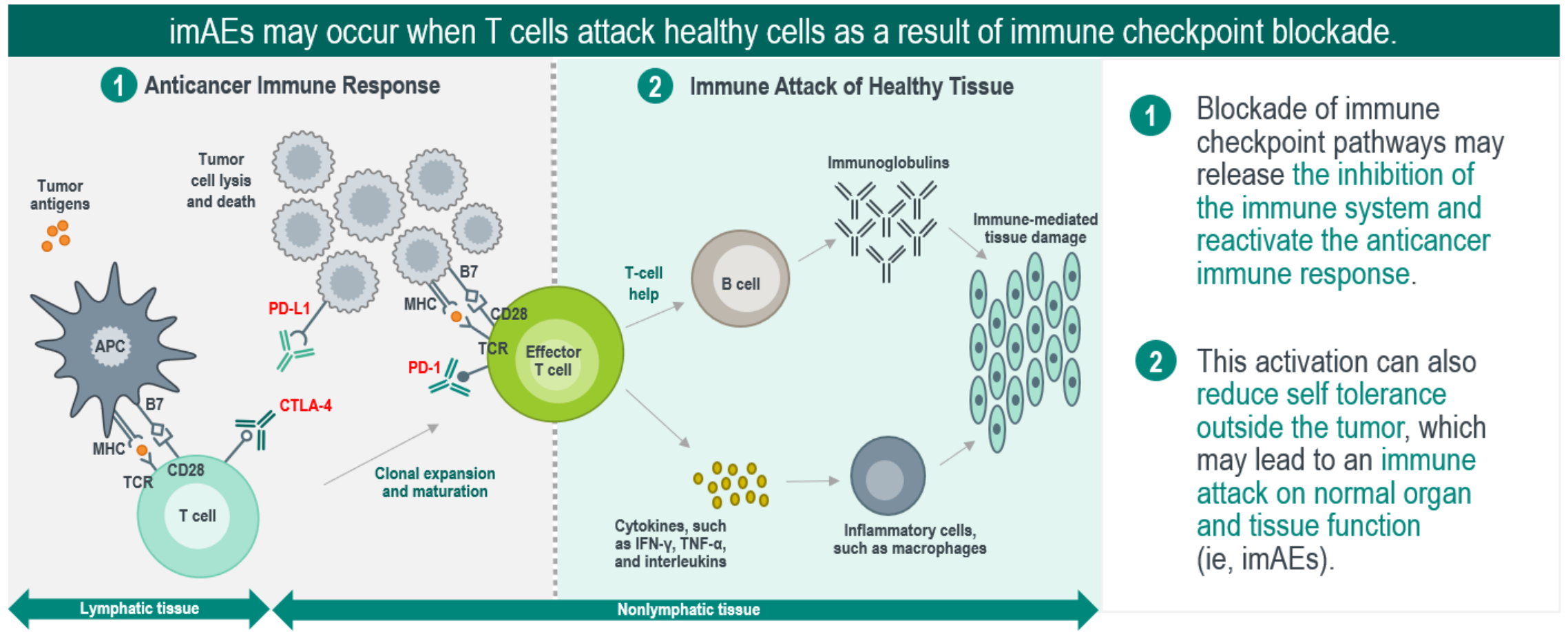
Table 1 | Checkpoint inhibitor approved indications

Drug	Month/year of first FDA approval	Month/year of first EMA approval	Indications
CTLA-4 blockers			
Ipilimumab	March 2011	July 2011	Melanoma; renal cell carcinoma; dMMR/MSI-H; colorectal cancer
PD-1 blockers			
Pembrolizumab	September 2014	July 2015	Melanoma; NSCLC; HNSCC; Hodgkin's lymphoma; bladder cancer; dMMR/MSI-H; gastric cancer, cervical cancer, large B cell lymphoma, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, small cell lung cancer, esophageal cancer, endometrial cancer
Nivolumab	December 2014	June 2015	Melanoma; NSCLC; renal cell carcinoma; Hodgkin's lymphoma; head and neck squamous cell cancer; bladder cancer; dMMR/MSI-H; colorectal cancer; hepatocellular carcinoma; small cell lung cancer
Cemiplimab	September 2018	June 2019	Cutaneous squamous cell cancer
PD-L1 blockers			
Atezolizumab	May 2016	September 2017	Bladder cancer; NSCLC; breast cancer; small cell lung cancer
Avelumab	March 2017	September 2017	Merkel cell; bladder cancer; renal cell cancer
Durvalumab	May 2017	September 2018	Bladder cancer; NSCLC

FDA=United States Food and Drug Administration; EMA=European Medicines Agency

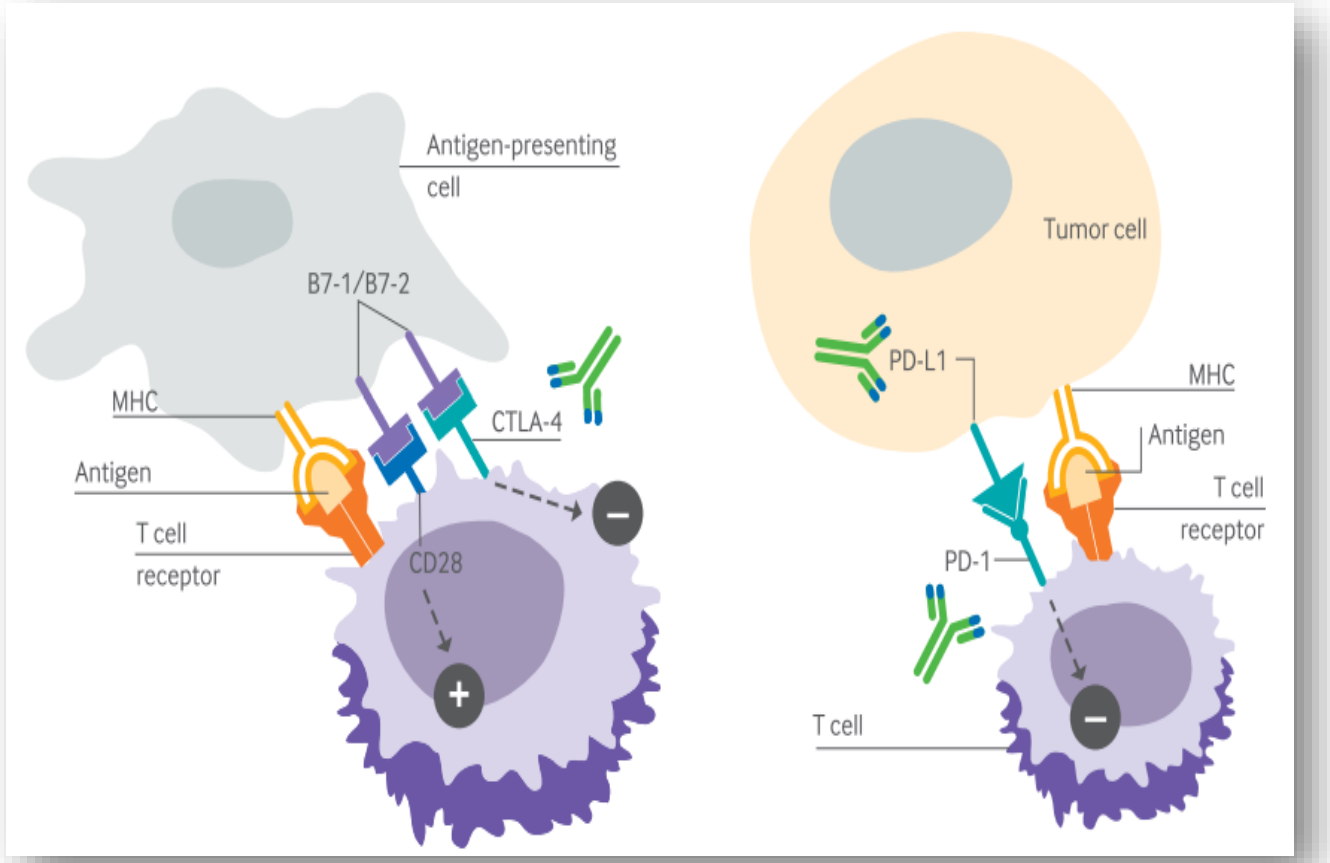
Chan KK, Bass AR. Autoimmune complications of immunotherapy: pathophysiology and management. Bmj. 2020;369:m736.

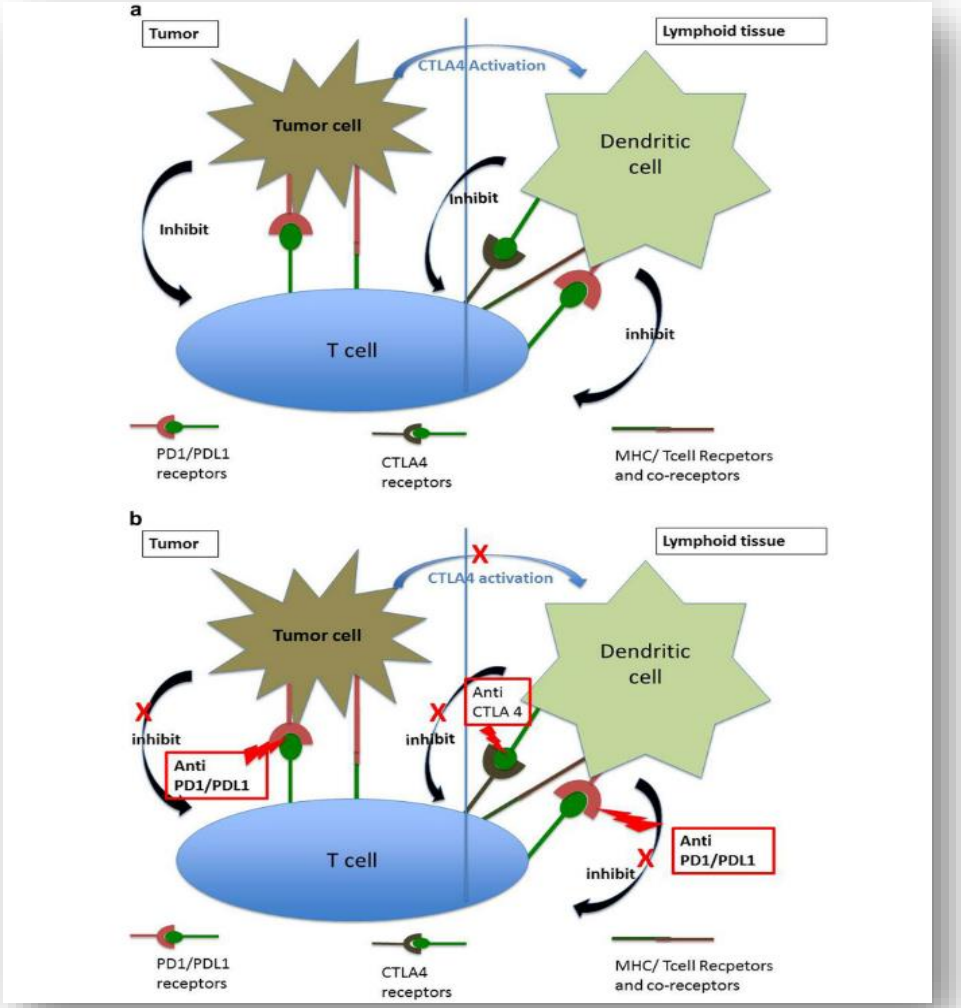
Immune Checkpoint Blockade and imAEs



Ribas A. N Engl J Med. 2012;366(26):2517–2519; Day D, Hansen AR. BioDrugs. 2016;30(6):571–584. Boutros C et al. Nat Rev Clin Oncol. 2016;13(8):473–486.

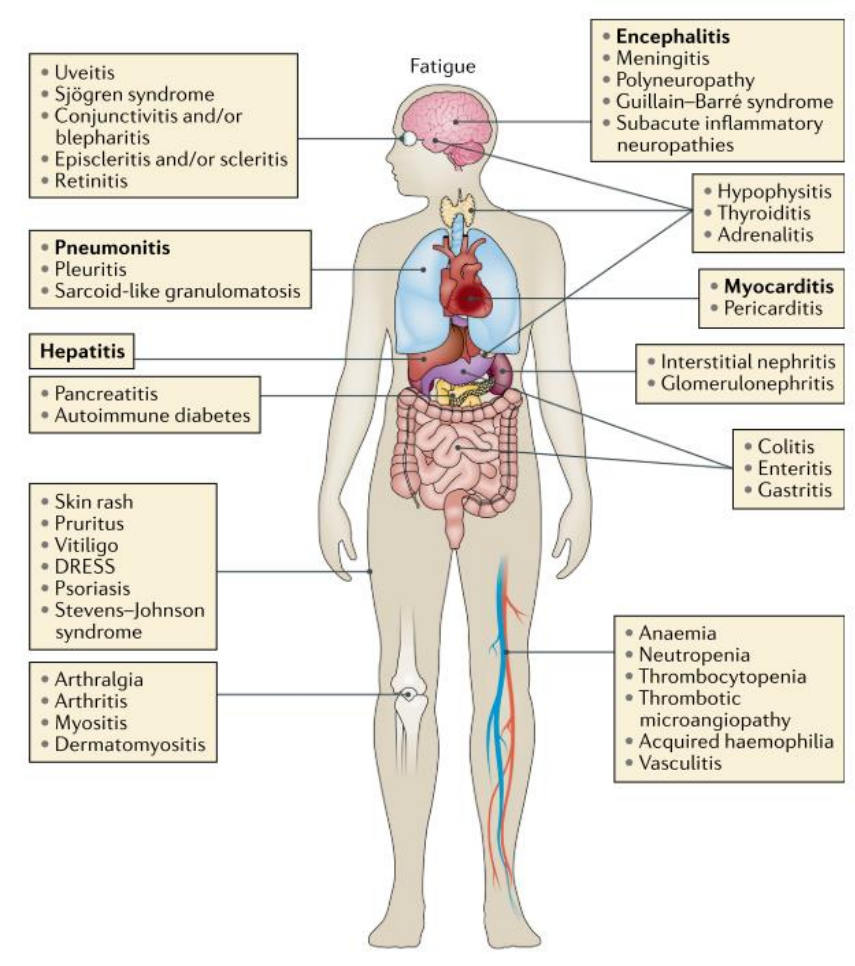
Immune Checkpoint Blockade and imAEs





Chan KK et al. pathophysiology and management. Bmj. 2020;369:m736; Lemiale et al. Ann Intensive Care. 2019;9:25.

Immune-mediated Adverse Events (imAEs)



Organ System (imAE)	Signs and Symptoms
LUNG (pneumonitis)	Shortness of breath, fatigue, chills, weakness, cough, headache
GASTROINTESTINAL (colitis)	Diarrhea, abdominal pain, nausea, cramping, blood or mucus in stool, changes in bowel habits, fever, abdominal distention, obstipation, constipation
LIVER (hepatitis)	Jaundice of the skin or sclera, nausea, vomiting, abdominal pain, fatigue, dark urine, anorexia
ENDOCRINE (thyroid, pituitary, adrenal glands, pancreas)	Palpitations, weight loss or gain, fatigue, diarrhea/constipation, cold/heat intolerance, tremors, hair loss, depression/anxiety, headache, vision changes, weakness, dizziness, confusion, high urine output, anorexia, nausea, vomiting, abdominal pain
KIDNEY (nephritis, kidney failure)	Decreased urine output, blood in the urine, peripheral edema, anorexia
SKIN (rash, Stevens–Johnson syndrome)	Rash, blistering, erythema, skin sloughing, purpura, epidermal or mucous membrane detachment
CARDIAC (myocarditis, pericarditis, arrhythmias)	Shortness of breath, chest pain, arrhythmia, pleural effusion, fatigue, palpitations, weakness, dizziness, nausea, vomiting
OCULAR (uveitis)	Blurred vision, change in color vision, photophobia, distortion, blind spots or partial vision loss, visual field changes, double vision, tenderness, pain with eye movement, eyelid swelling, protrusion of the eyeball
CNS (encephalitis, neuropathy)	Confusion, altered behaviour, headache, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality, numbness, tingling with or without pain, sensory ataxia, hyporeflexia or areflexia

- imAEs affecting the skin, endocrine system, GI tract, and lungs are most commonly encountered.
- More rarely, neurologic, ocular, cardiovascular, hematologic, and renal imAEs can occur.

Postow MA et al. N Engl J Med. 2018;378:158-68; Martins F et al. Nat Rev Clin Oncol. 2019;16:563-80; Daniels GA et al. Emerg Med J. 2019;36(6):369–377.

목차

Incidence of imAEs for ICIs and Combination Therapy

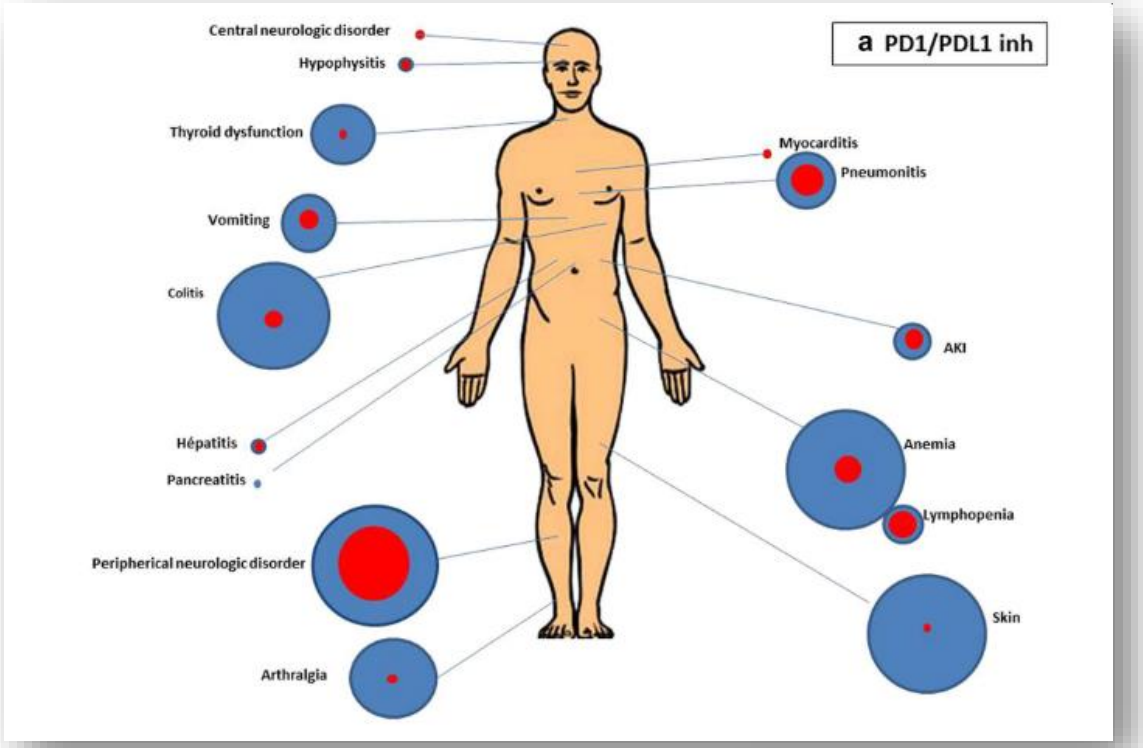
Table 2 | Incidence of organ specific autoimmune side effects from checkpoint inhibitors (Adapted with permission)[12]

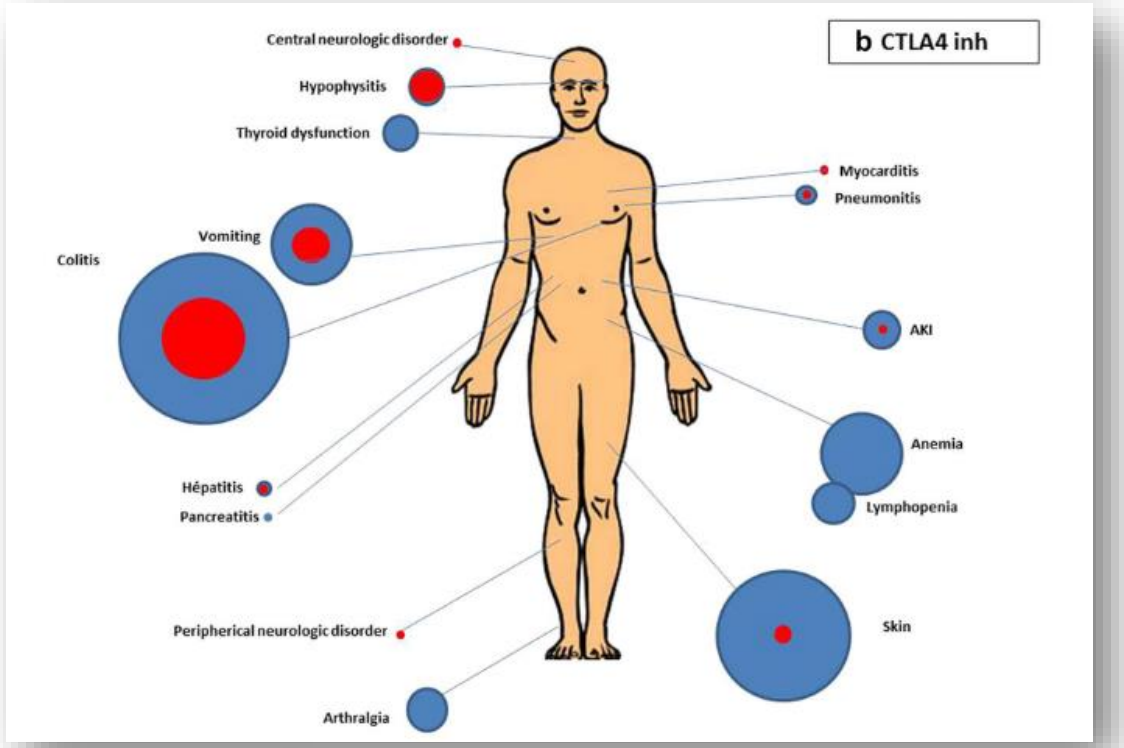
Adverse effect	anti-CTLA-4 incidence	anti-PD-1 or PD-(L)1 incidence	Combination incidence
Pruritis			
All grades	25% (21-29)	15% (12-17)	34% (29-38)
Grade ≥3	1% (0-1)	0% (0-2)	2% (1-4)
Rash			
All grades	23% (19-27)	10% (8-13)	41% (36-45)
Grade ≥3	1% (1-2)	0% (0-1)	5% (3-7)
Colitis			
All grades	8% (6-10)	1% (1-2)	16% (10-25)
Grade ≥3	5% (4-6)	1% (0-1)	11% (6-19)
Elevated aspartate transaminase or alanine aminotransferase			
All grades	5% (2-9)	5% (4-7)	19% (15-23)
Grade ≥3	2% (1-4)	1% (1-2)	9% (6-12)
Hypothyroidism			
All grades	3% (2-5)	8% (7-9)	15% (12-19)
Grade ≥3	0% (0-0)	0% (0-0)	0% (0-2)
Hypophysitis			
All grades	4% (2-7)	1% (0-1)	–
Grade ≥3	2% (1-3)	0% (0-1)	–
Pneumonitis			
All grades	1% (0–2)	4% (2-6)	–
Grade ≥3	1% (0–1)	1% (1-2)	–
Arthralgia			
All grades	5% (3-9)	8% (7-11)	11% (8-14)
Grade ≥3	0% (0-1)	0% (0-0)	0% (0-2)

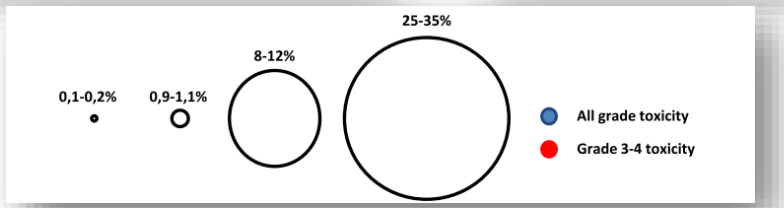
- Medline and Cochrane Reviews from 2000.1~2019.7, A large systematic review and meta-analysis of 35 randomized controlled trials including 16485 patients
- Incidence of any irAEs with anti-CTLA-4 antibodies : 72%, high grade irAEs 24%
- Incidence of any irAEs with anti-PD-1 or anti-PD-L1 antibodies: 74%, high-grade irAEs, 14%
- Risk of fatal AEs : 0.3%–1.3%
- Colitis and hypophysitis : more frequent with anti-CTLA-4 treatment
- thyroiditis and pneumonitis: more common with anti-PD-(L)1 treatment

Chan KK, Bass AR. Bmj. 2020;369:m736.

Incidence of imAEs for ICIs and Combination Therapy

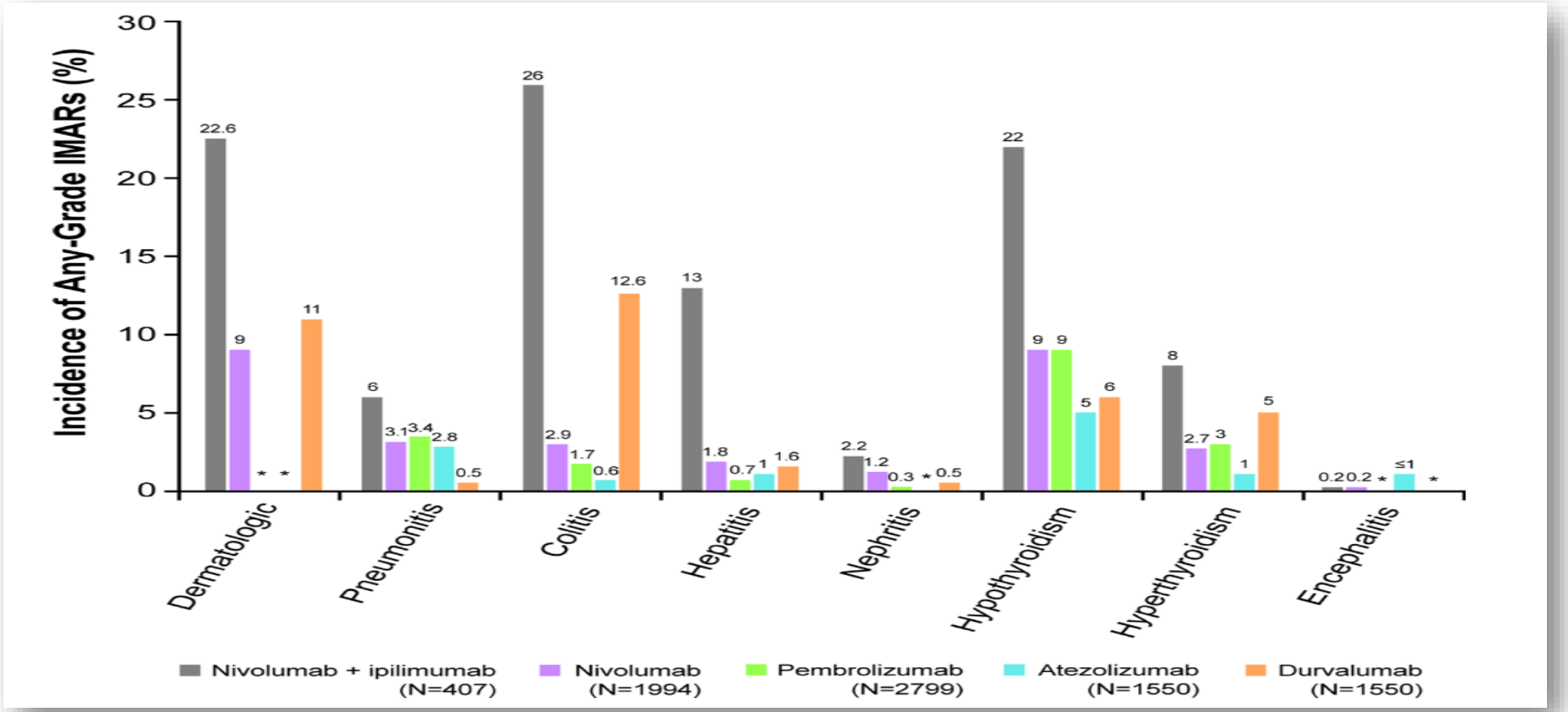






Lemiale et al. Ann Intensive Care. 2019;9:25.

Incidence of Any-grade imAEs for ICIs and Combination Therapy



Daniels GA et al. Emerg Med J. 2019;36:369-77.

Incidence of steroid-refractory imAEs for ICIs

IASLC

BRIEF REPORT

Beyond Steroids: Immunosuppressants in Steroid-Refractory or Resistant Immune-Related Adverse Events

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Abstract

Introduction

The optimal management for immune-related adverse events (irAEs) in patients who do not respond or become intolerant to steroids is unclear. Guidelines suggest additional immunosuppressants on the basis of case reports and expert opinion.

Methods

We evaluated patients with lung cancers at Memorial Sloan Kettering Cancer Center treated with immune checkpoint blockade from 2011 to 2020. Pharmacy records were queried to identify patients who received systemic steroids and an additional immunosuppressant (e.g., tumor necrosis factor-α inhibitor, mycophenolate mofetil). Patient records were manually reviewed to evaluate baseline characteristics, management, and outcomes.

Luo J et al. J Thorac Oncol. 2021;16:1759-64.

Incidence of steroid-refractory imAEs for ICIs

Table 1. Baseline Patient Characteristics and Treatment Details

Characteristics	Patients (N = 51)
Median age [IQR], y	64 [59-71]
Sex, n (%)	
Female	29 (57)
Male	22 (43)
Cigarette smoking status, n (%)	
Former or current	43 (84)
Never	8 (16)
Lung cancer histology, n (%)	
Adenocarcinoma	36 (71)
Nonadenocarcinoma	8 (16)
Small cell lung cancer	7 (14)[a]
PD-L1 expression by TPS, n/N (%)	
0%	11/33 (33)
1%-49%	7/33 (21)
≥50%	15/33 (45)[a]
Unknown or not applicable	18
Line of therapy, n (%)	
1 or early stage	28 (55)
2	13 (25)
3 or higher	10 (20)
Past medical history, n (%)	
Autoimmune condition[b]	7 (14)
Previous thoracic radiation therapy	11 (22)
Treatment, n (%)	
Anti-PD-(L)1 monotherapy	25 (49)
Anti-PD-(L)1+CTLA-4 combination	19 (37)
Anti-PD-(L)1+chemotherapy	5 (10)
Anti-PD-(L)1+other (non-chemotherapy)	2 (4)

[a]Percentages may not add up to 100 owing to rounding.
[b]Autoimmune condition including thyroiditis (n = 3), inflammatory bowel disease (n = 2), psoriasis (n = 2), reactive airways disease (n = 1), and type 2 diabetes (n = 1).
IQR, interquartile range; PD-(L)1, programmed cell death protein (ligand) 1; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Results

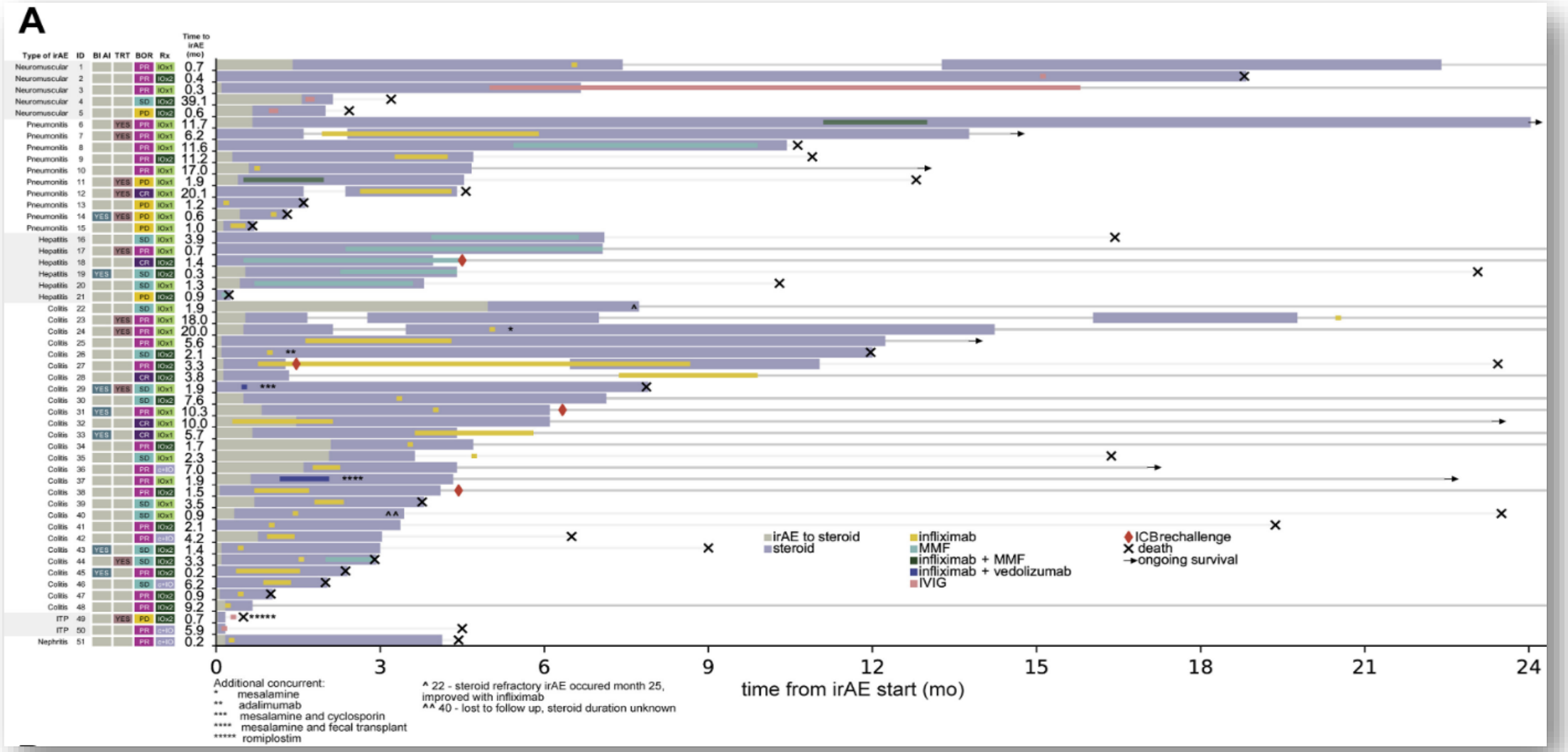
Among 2750 patients with lung cancers treated with immune checkpoint blockade, 51 (2%) received both steroids and an additional immunosuppressant for a severe irAE (tumor necrosis factor-α inhibitor (73%), mycophenolate mofetil (20%)). The most common events were colitis (53%), pneumonitis (20%), hepatitis (12%), and neuromuscular (10%). At 90 days after the start of an additional immunosuppressant, 57% were improved from their irAE, 18% were unchanged, and 25% were deceased. Improvement was more common in hepatitis (five of six) and colitis (18 of 27) but less common in neuromuscular (one of five) and pneumonitis (3 of 10). Of the patients who died, 8 of 13 were attributable directly to the irAE and 4 of 13 were related to toxicity from immunosuppression (three infection-related deaths, one drug-induced liver injury leading to acute liver failure).

Conclusions

Steroid-refractory or resistant irAEs events are rare. Although existing treatments help patients with hepatitis and colitis, many patients with other irAEs remain refractory or experience toxicities from immunosuppression. A more precise understanding of the pathophysiology of specific irAEs is needed to guide biologically-informed treatments for severe irAEs.

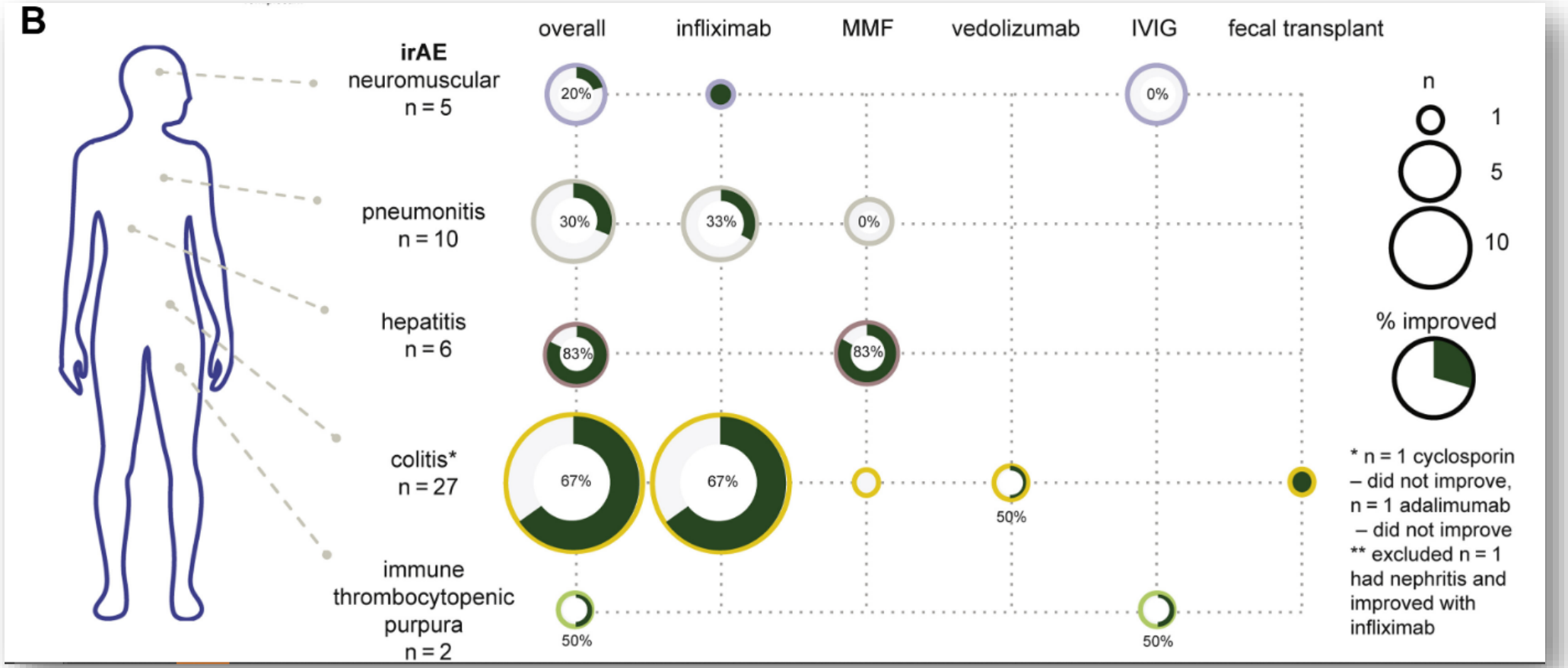
Luo J et al. J Thorac Oncol. 2021;16:1759-64.

Steroid refractory or resistant irAEs – 51 patients



Luo J et al. J Thorac Oncol. 2021;16:1759-64.

Steroid refractory or resistant irAEs



- The proportion of patients who improved from their steroid refractory irAE at 90 days after the start of the second immunosuppressant grouped by type of irAE

Luo J et al. J Thorac Oncol. 2021;16:1759-64.

Onset and Duration of imAEs

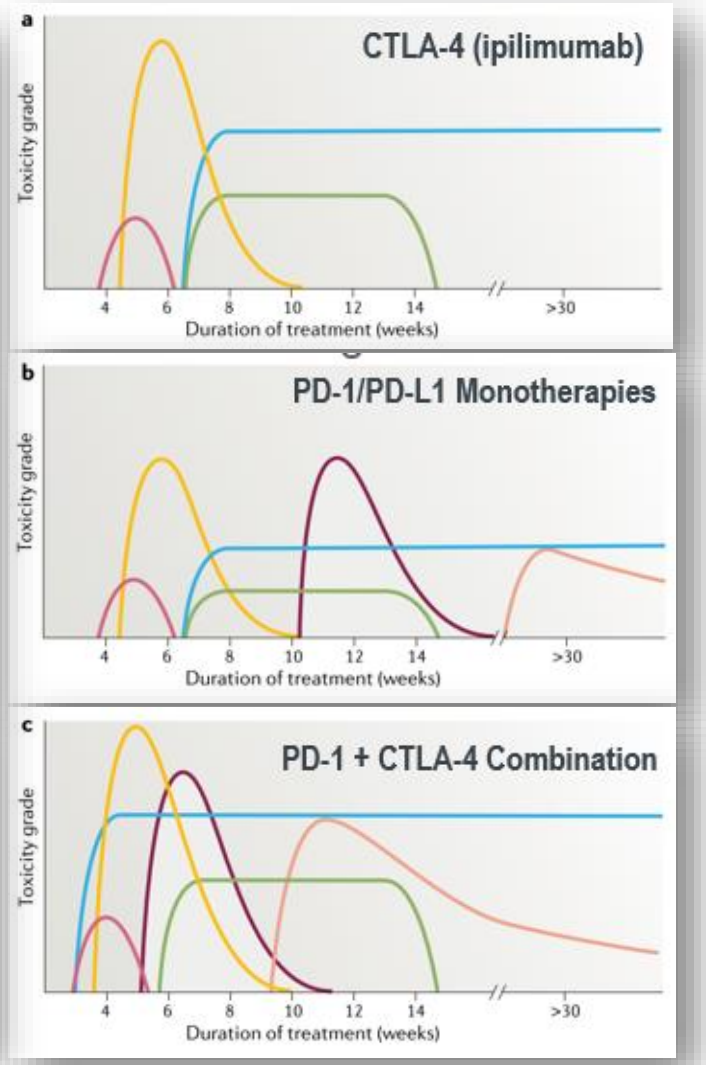
imAEs may occur at any time during treatment.

- Most imAEs will occur within the first few weeks or months (median onset is usually 2–16 weeks) after treatment initiation.
- PD-1 inhibitors may have a slightly later onset compared with CTLA-4 inhibitors.
- Overall, imAEs in patients receiving combination ICIs appear to have an earlier onset than the same imAEs in those receiving monotherapies.

The pattern of onset may vary by organ system.

- Dermatologic imAEs commonly are the first to emerge.

Occurrence of different imAEs can be simultaneous or can emerge one after another, and imAEs may persist beyond cessation of treatment.



- **Median time onset of irAEs**
  - **Skin: 3 weeks**
  - **GI : 7.1 weeks**
  - **Liver: 8.4 weeks**
  - **Endocrine: 11.4 weeks**
  - **Lungs: 9.4 weeks**
  - **Kidneys: 16.3 weeks**

Martins F et al. Nat Rev Clin Oncol. 2019;16:563-80. Chan KK, Bass AR. Bmj. 2020;369:m736.

Incidence and Severity of imAEs

Frequency and timing of imAEs differ between ICIs, dosing schedule and regimen, and cancer type.

- PD-1/PD-L1 inhibitors may be associated with lower overall incidence of imAEs and lower incidence of Grade ≥3 imAEs compared with CTLA-4 inhibitors.
- Combination therapy with 2 ICIs is associated with both earlier imAE onset and higher levels of immune-mediated toxicity than either one alone.

Most imAEs are reversible and manageable but have the potential for life-threatening or fatal outcomes.

- Because less-common toxicities may be life threatening and initial presentation may be mild, with nonspecific symptoms, prompt diagnosis and treatment are required.
- Risk of fatal AEs associated with therapy may be lower with ICIs (estimated incidence, 0.3%–1.3%) than with conventional treatments.

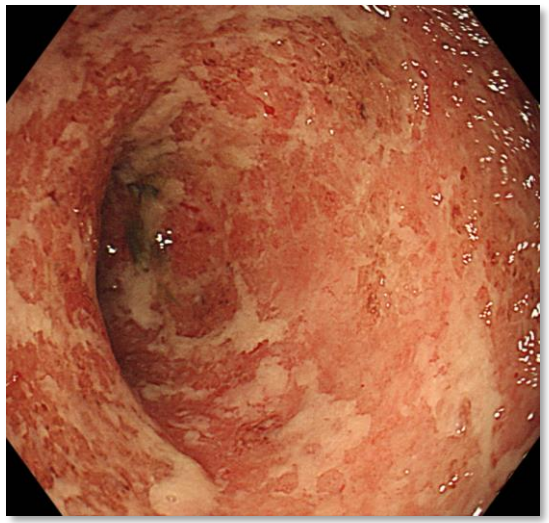
imAEs related to ICIs may present similarly to those related to chemotherapy (eg, diarrhea and colitis) but may have different underlying causes and require different diagnostic procedures, workup, and management.

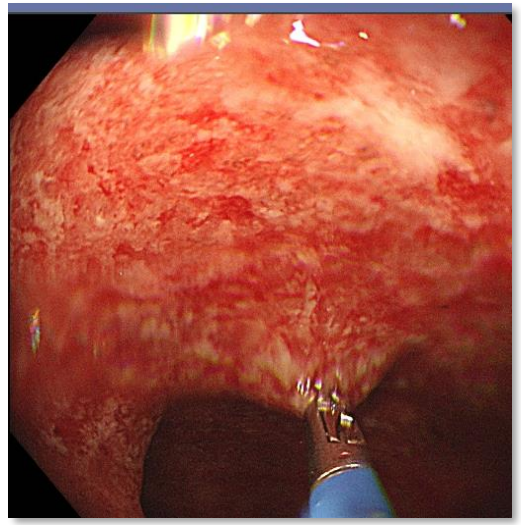
Daniels GA et al. Emerg Med J. 2019;36(6):369–377; Martins F et al. Nat Rev Clin Oncol. 2019;16(9):563–580. Sosa A et al. Ther Adv Med Oncol. 2018;10:1758835918764628.

목차

Case 1 imAEs, colitis after Pembrolizumab

- M/57
  - NSCLC (Sqcc), cT2N2M0 IIIA, PD-L1 (sp263) 60%
  - s/p neoadj CCRTx -> disease progression with pericardial effusion (2020.5), stage IV
  - s/p 1st-13th pembrolizumab (2020.6.18 -2021.5.17)
  - 2021.5.24 G3 diarrhea, hematochezia 로 adm





<2021.5.25 sigmoidoscopy>

- 전반적으로 erythema +++, edema +++, exudate +++, mucoal friability, hemorrhage, granularity 소견 보임
- Imp: r/o immune related colitis, Bx at DC*2(A), SC*2(B), Rectum*2(C)
- Pathology: chronic colitis, active, CMV immunostaining result: negative (#A,B); positive (#C)

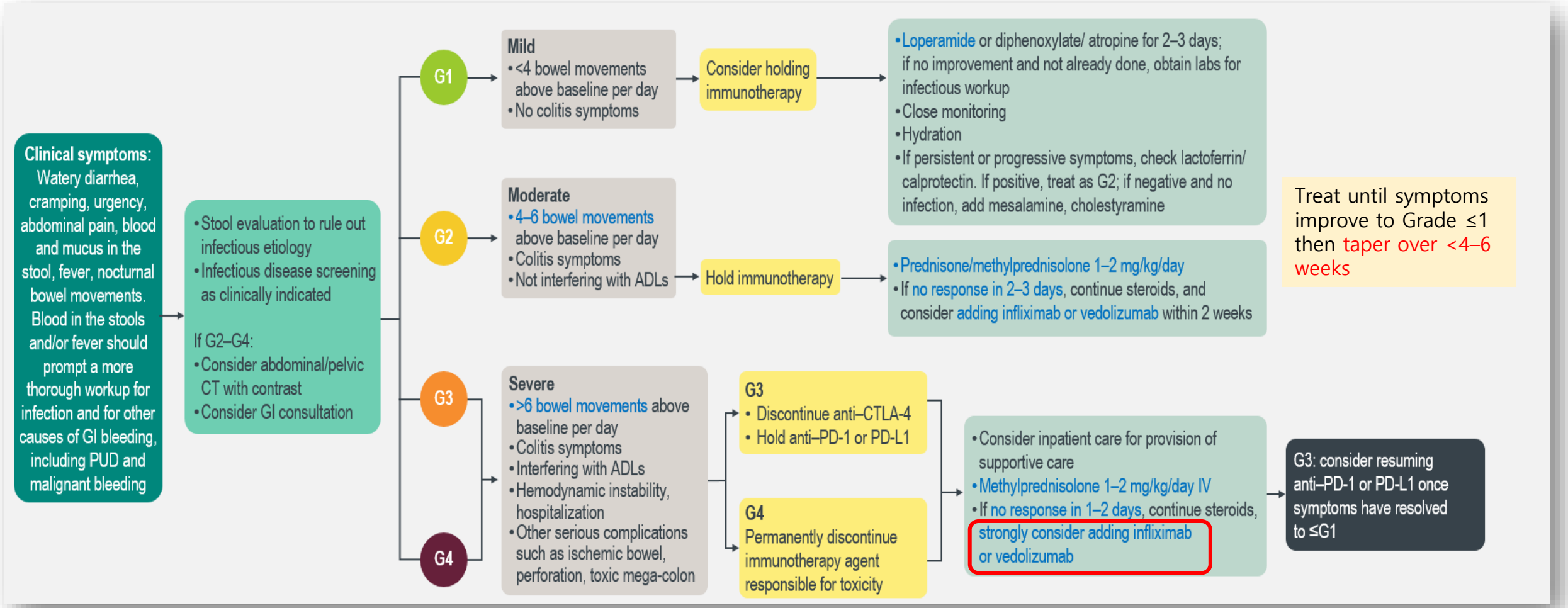
Ref from Severance Hospital

Case 1 imAEs, colitis after Pembrolizumab

- Patient progress
  - Treatment
    - Steroid: MP 62.5mg (1mg/kg) for 1 week → 31.25 (0.5mg/kg) for 1 week -> 이후 po 로 tapering (total 4주 사용) 후 중단
    - 감염내과 consult: CMV colitis 에 준하여 ganciclovir 5mg/kg BID 로 IV infusion 2-3주 유지: ganciclovir 375mg bid for 2 weeks -> po Valganciclovir PO 900mg bid for 1 week
    - 소화기내과 consult: mesalazine 1200mg 4T (4800mg) S1 + Pentasa suppo S1 지속유지
  - Progress
    - Symptom improved, Pembrolizumab stop, steroid stop (total 4주 사용)
    - Mesalazine 4.8g + pentasa suppo 유지

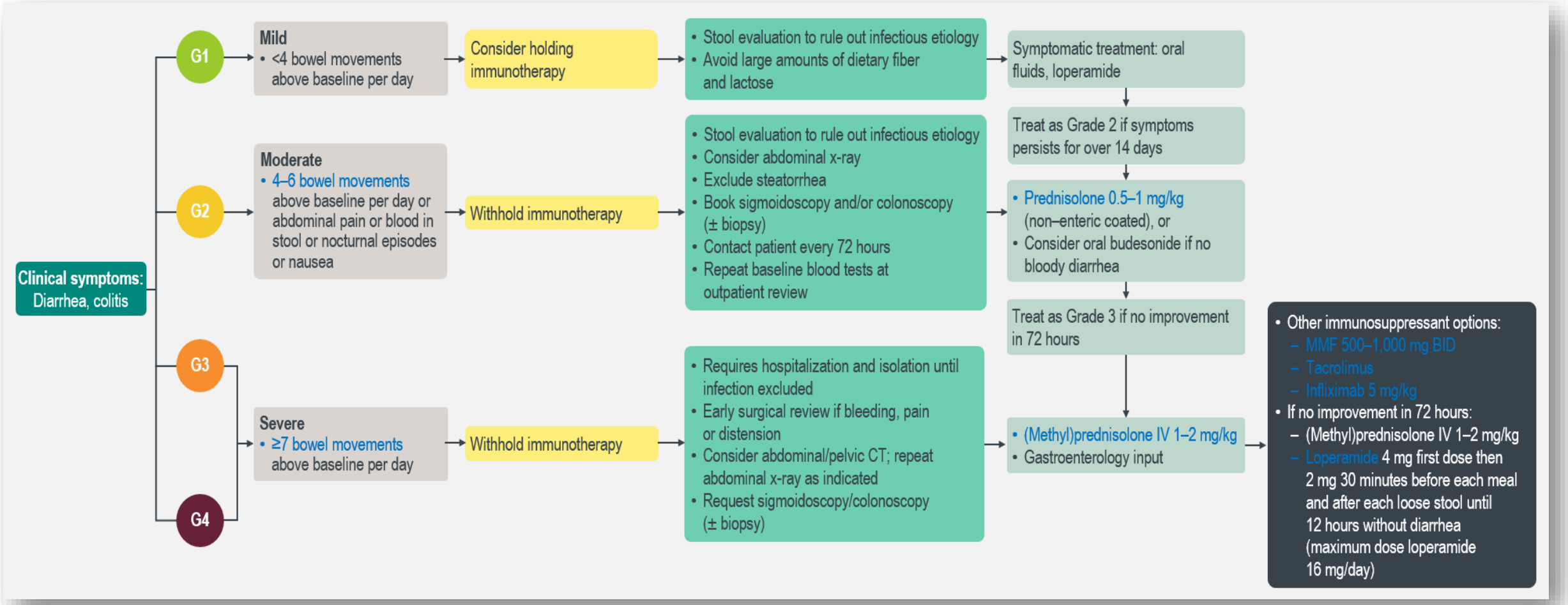
Ref from Severance Hospital

imAEs: Gastrointestinal: Colitis - NCCN & ASCO



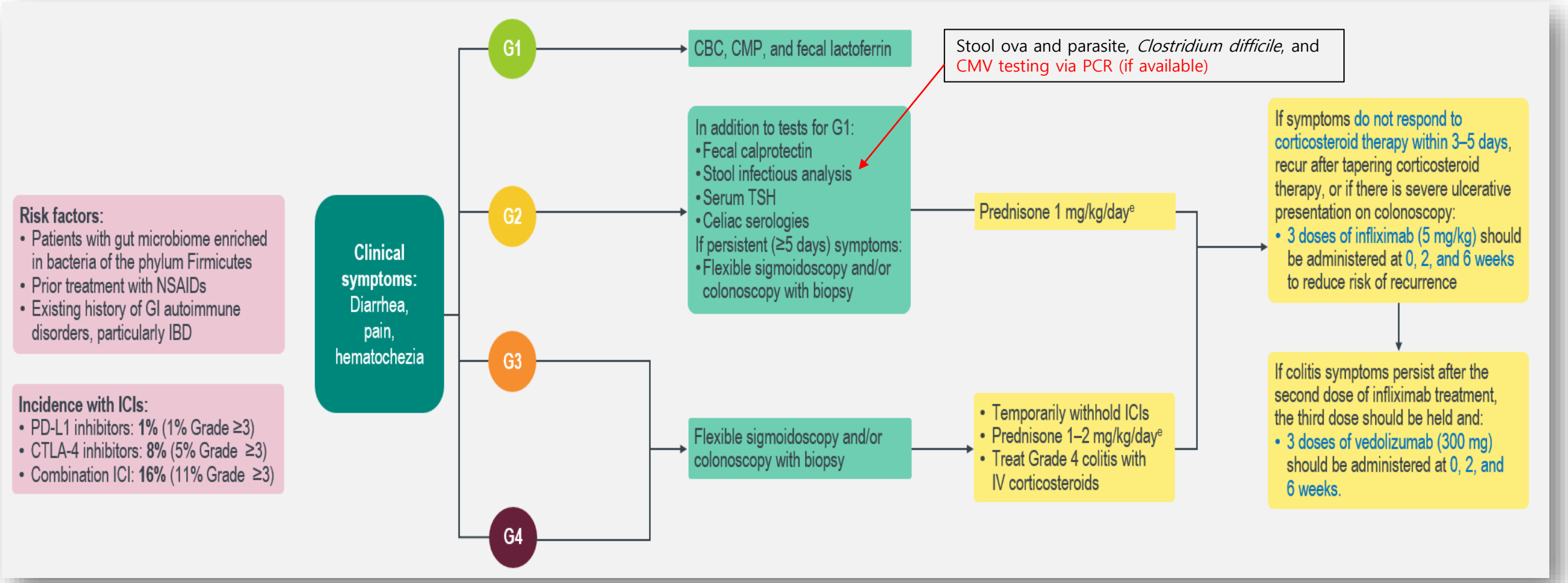
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-related Toxicities V.4.2021
Schneider BJ et al. J Clin Oncol. 2021;39(35):3978–3992; Daniels GA et al. Emerg Med J. 2019;36(6):369–377.

imAEs: Gastrointestinal: Colitis - ESMO



Haanen JBAG et al. Ann Oncol. 2017;28(suppl 4):iv119–iv142

imAEs: Gastrointestinal: Colitis -SITC (society for immunotherapy of cancer)



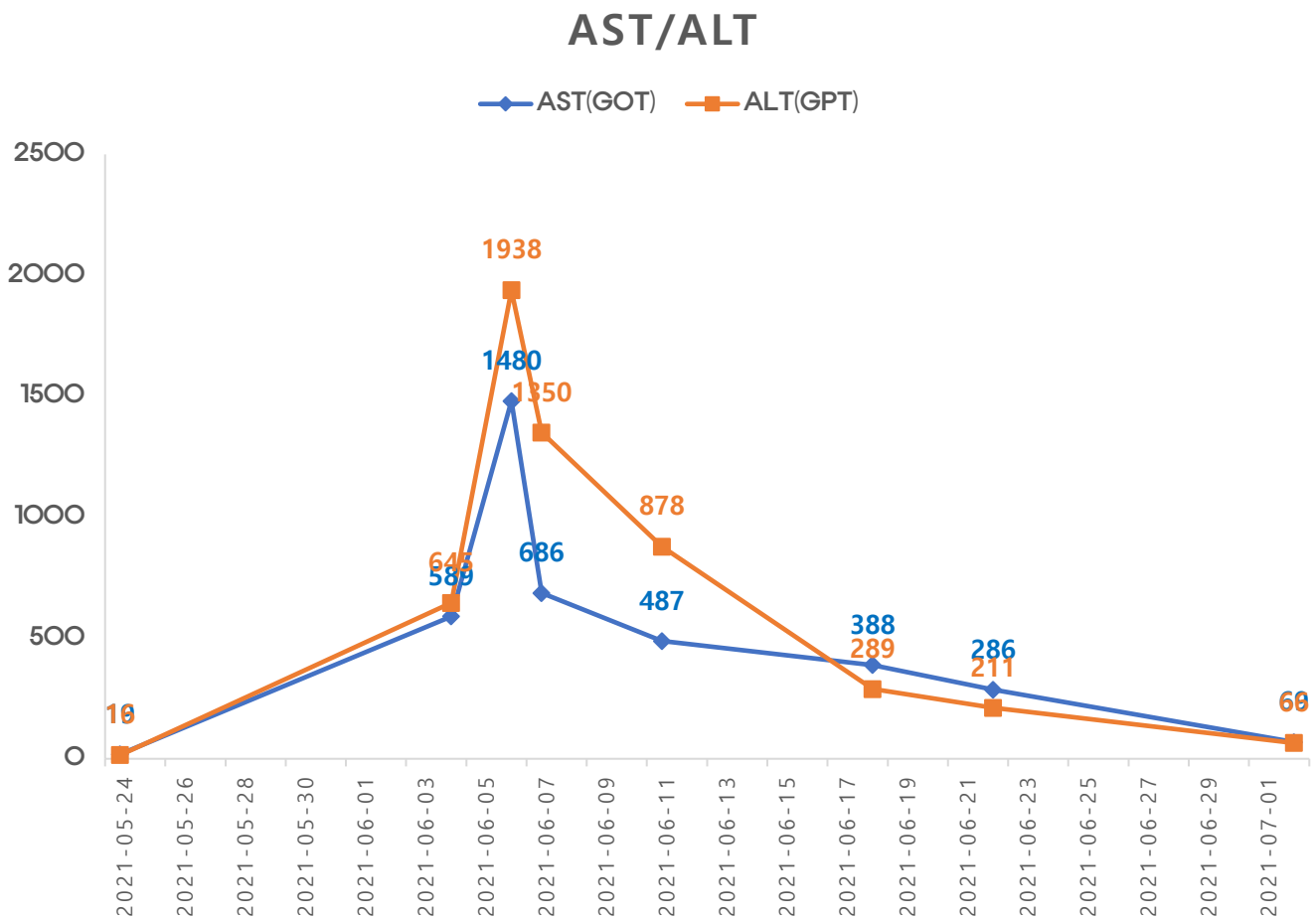
Brahmer JR et al. J Immunother Cancer. 2021;9(6):e002435.

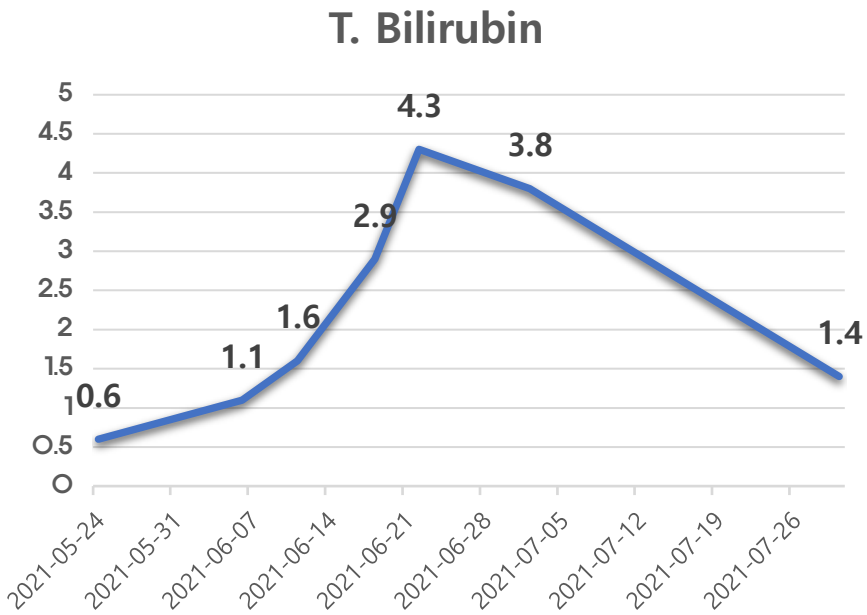
Case 2 imAEs, hepatitis after Durvalumab

- M/78
  - NSCLC (adeno), cT4N2M0 IIIB
  - EGFR wild, PD-L1 (sp263) : 20%
  - PHx: Chronic hepatitis B
  - 항암시작전 prophylactic anti-viral (entecavir, Baraclude®) 2021.4.1~
  - s/p def CCRTx 55Gy/25Fx (2021.4.9-2021.5.14)
  - 1st Durvalumab 2021.5.28
  - 2021.6.4 mild fever, chill 로 시행한 lab 상 AST/ALT (589/645) 상승 소견으로 adm

Ref from GangNam Severance Hospital

Case 2 imAEs, hepatitis after Durvalumab





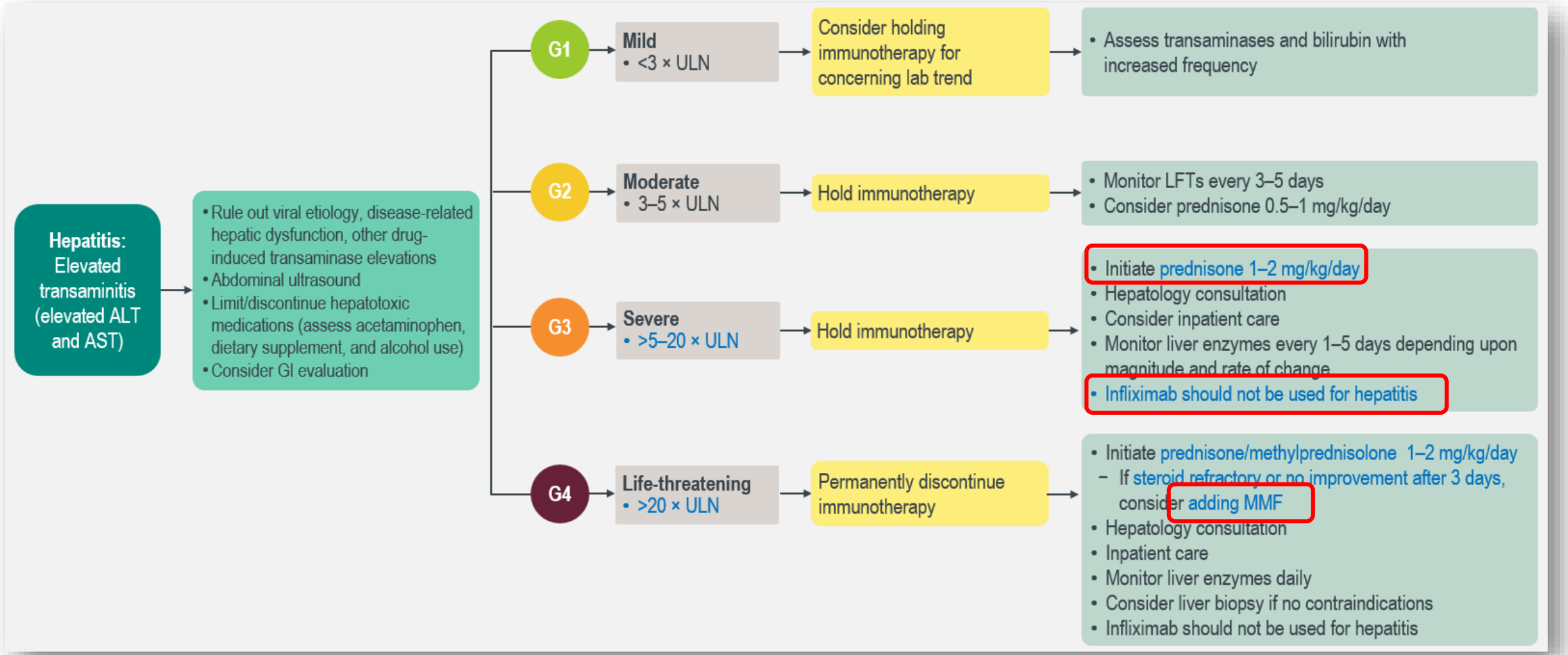
Ref from GangNam Severance Hospital

Case 2 imAEs, hepatitis after Durvalumab

- Patient progress
  - Treatment
    - Steroid: MP 100mg (1.5mg/kg) for 1 week → 80mg (1mg/kg) for 1 week -> 60mg for 1 week → 이후 po 로 tapering (total 6주 사용) 후 중단 + septrin prophylaxis
    - 소화기내과 consult: HBV DNA titer 낮고 (200) B viral flare up 가능성은 낮은 상태이며, r/o immune related hepatitis 준하여 steroid 치료, LFT f/u 권고
  - Progress
    - Symptom improved, Durvalumab 영구중단, steroid stop (steroid total 6주 사용함)
    - Anti viral (entecavir, Baraclude®) 유지

Ref from GangNam Severance Hospital

imAEs: Gastrointestinal: Hepatitis-NCCN & ASCO



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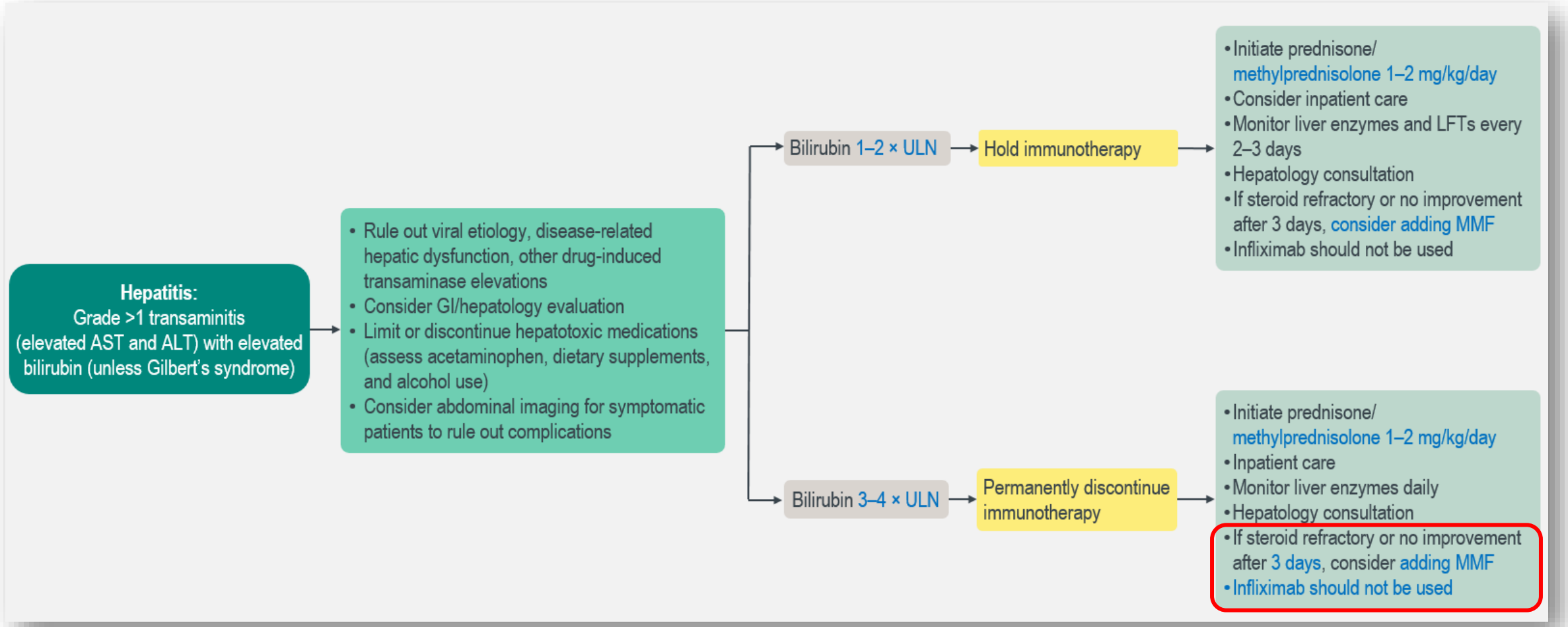
imAEs: Gastrointestinal: Hepatitis-NCCN & ASCO



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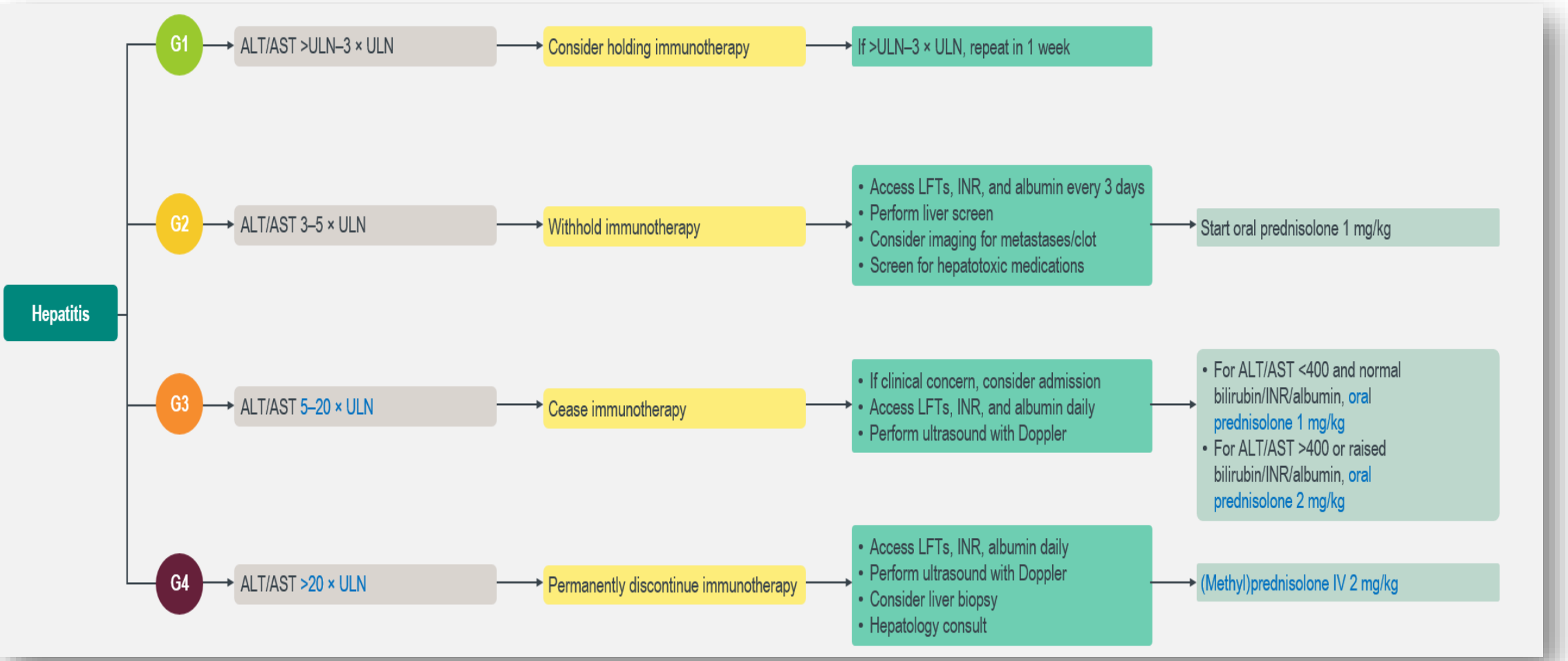
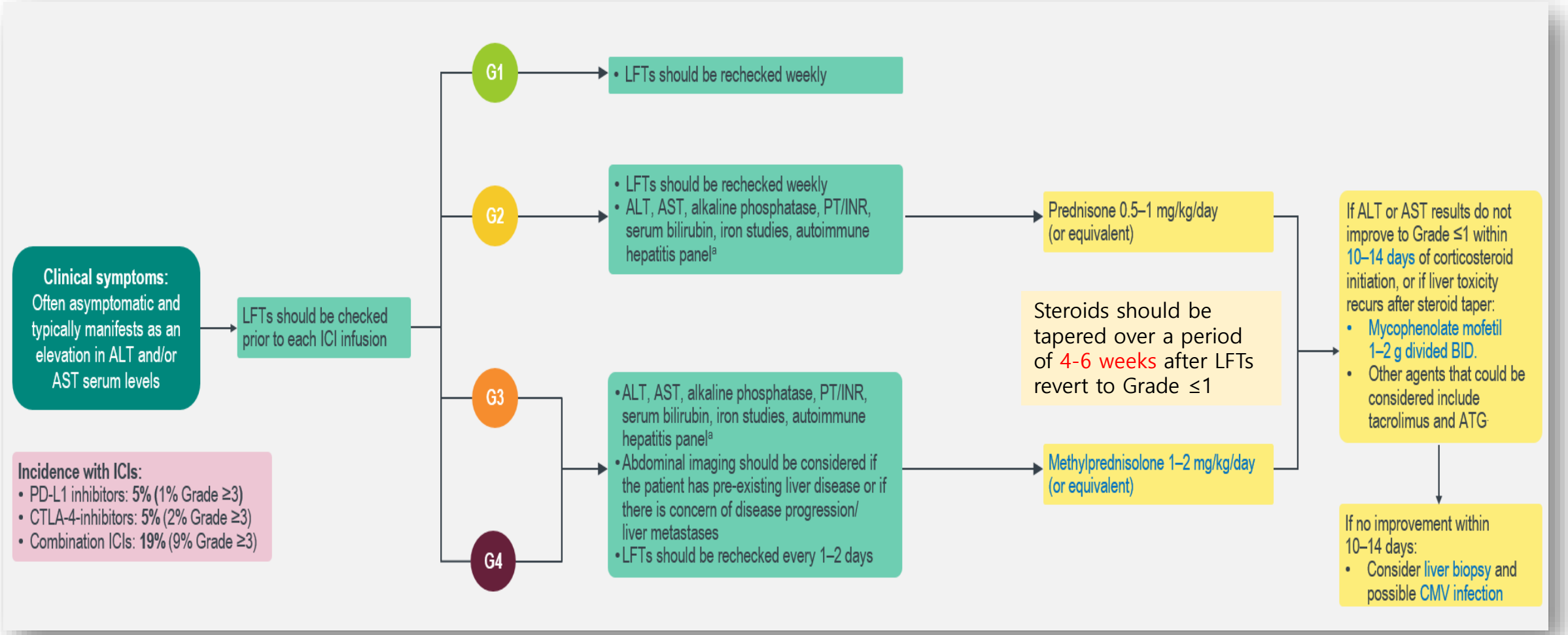
imAEs: Gastrointestinal: Hepatitis - ESMO



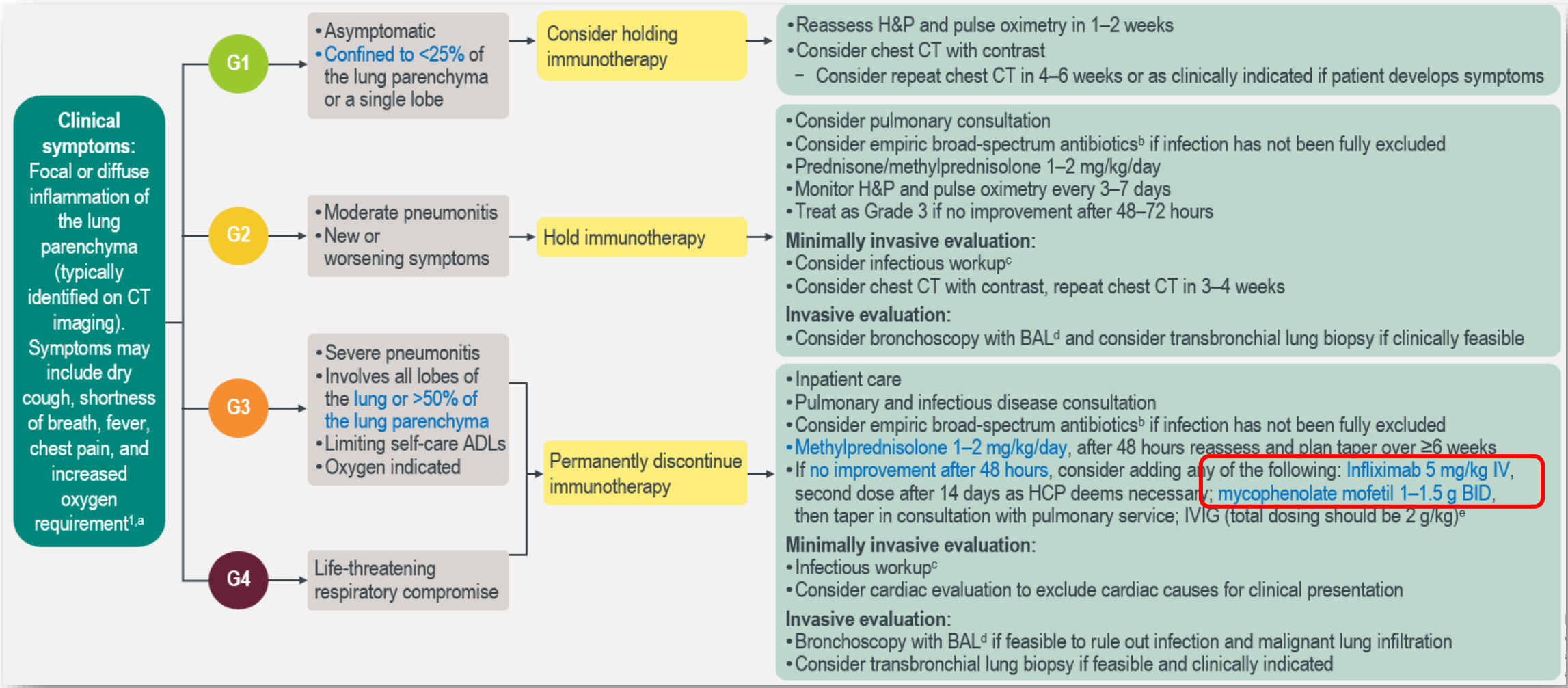
Haanen JBAG et al. Ann Oncol. 2017;28(suppl 4):iv119–iv142

imAEs: Gastrointestinal: Hepatitis - SITC



Brahmer JR et al. J Immunother Cancer. 2021;9(6):e002435.

Pulmonary: Pneumonitis - NCCN & ASCO



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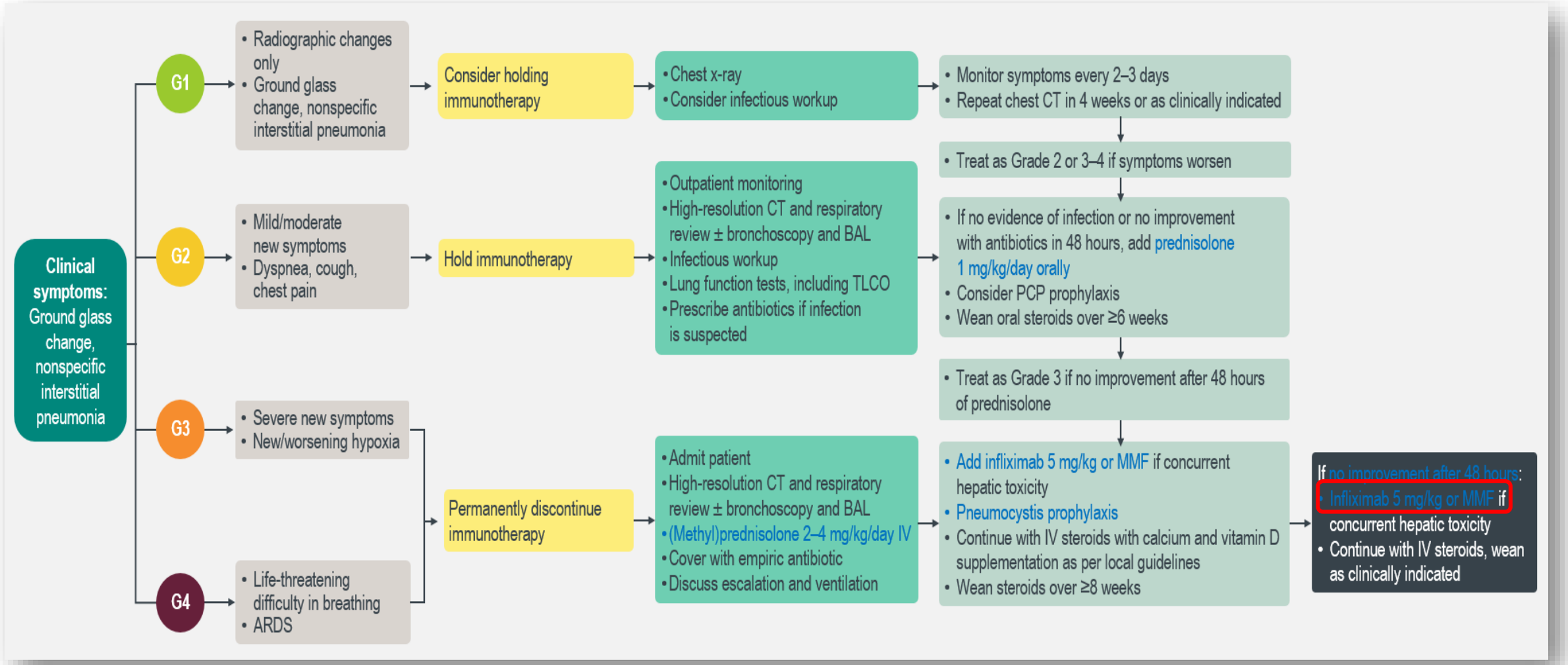
Pulmonary: Pneumonitis - ESMO



Haanen JBAG et al. Ann Oncol. 2017;28(suppl 4):iv119–iv142

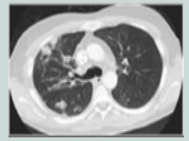
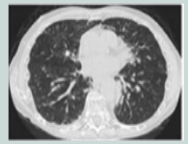
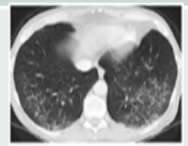
Pulmonary: Pneumonitis - SITC

Risk factors:
- Patients with NSCLC or RCC have higher risk of developing ICI-associated pneumonitis compared with patients with melanoma
- Prior curative-intent radiotherapy
- Squamous tumor histology
- Active or former smokers
- Underlying lung condition and asthma[a]

Clinical symptoms: Dyspnea, persistent cough, chest pain, fever, and hypoxia (potentially leading to respiratory failure)

- Pre-existing autoimmune ILD → Refer to specialist prior to ICI therapy for risk assessment; Consider PFTs
- Suspected pneumonitis → High-resolution chest CT; If negative CT result, consider PFTs
- G2 → Prednisone 1–2 mg/kg/day (or equivalent) tapering over 4–6 weeks
- ≥G3 → Methylprednisolone 1–2 mg/kg/day IV (or equivalent) tapering over 4–6 weeks

Incidence with ICIs:
- PD-L1 inhibitors: **4%** (1% Grade ≥3)
- CTLA-4 inhibitors: **1%** (1% Grade ≥3)
- Combination ICIs: **7%** (2% Grade ≥3)

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n=5, 19%)		• Discrete patchy or confluent consolidation with or without air bronchograms • Predominantly peripheral or subpleural distribution
Ground-glass opacities (n=10, 37%)		• Discrete focal areas of increased attenuation • Preserved bronchovascular markings
Interstitial (n=6, 22%)		• Increased interstitial markings • Interlobular septal thickening • Peribronchovascular infiltration, subpleural reticulation • Honeycomb pattern in severe patient cases
Hypersensitivity (n=2, 7%)		• Centrilobular nodules • Bronchiolitis-like appearance • Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n=4, 15%)		• Mixture of nodular and other subtypes • Not clearly fitting into other subtype classifications

Brahmer JR et al. J Immunother Cancer. 2021;9(6):e002435.

imAEs: Endocrinopathies: Adrenal, Pituitary, and Thyroid - NCCN & ASCO

Signs and Symptoms

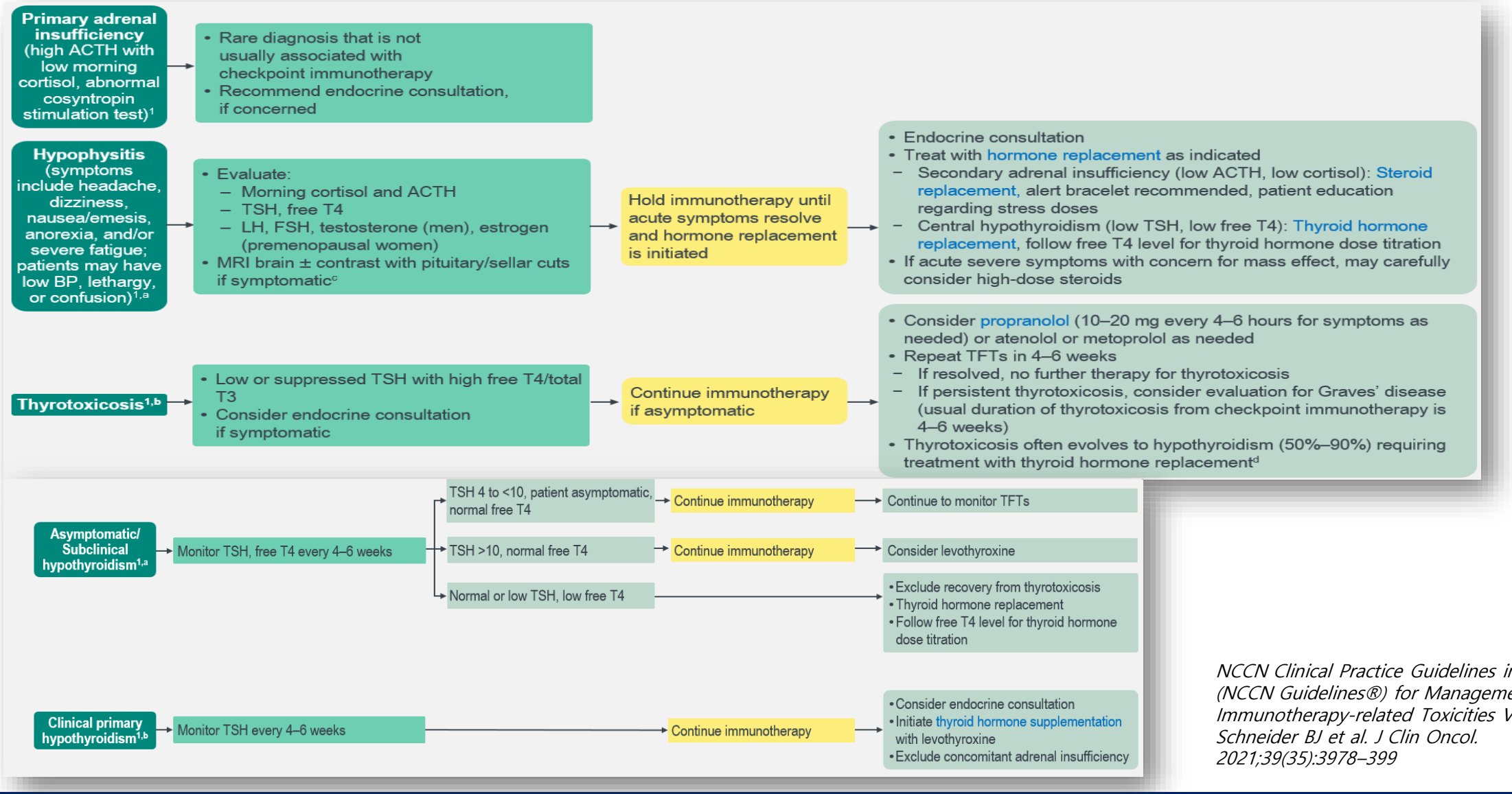
- Headache
- Visual changes
- Cold/heat intolerance
- Dry skin
- Constipation
- Weight gain/loss
- Fatigue
- Palpitations
- Insomnia
- Frequent bowel movements
- Nausea or vomiting
- Lightheadedness or orthostasis or syncope
- Polyuria or polydipsia
- Abdominal pain
- Nausea or vomiting

Monitoring

- Monitor TSH and FT4 for primary hypothyroidism and thyrotoxicosis
- Consider TSH receptor Ab testing if Graves' disease is suspected
- Evaluate AM levels of ACTH and cortisol level, basic metabolic panel, renin and aldosterone, ACTH stimulation test, infection, and adrenal CT for metastasis or hemorrhage for primary adrenal insufficiency
- Evaluate ACTH and cortisol (AM), TSH, free T4, and electrolytes for hypophysitis

imAE[2]	Grade 1	Grade 2	Grade 3	Grade 4
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hypophysitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate iADLs[b]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; self-care ADLs[c] limited	Life-threatening consequences; urgent intervention indicated
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy is indicated; limiting iADLs[b]	Severe symptoms; limiting self-care ADLs[c]; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement therapy is indicated; limiting iADLs[b]	Severe symptoms; limiting self-care ADLs[c]; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

imAEs: Endocrinopathies – Adrenal, Pituitary, and Thyroid - NCCN & ASCO



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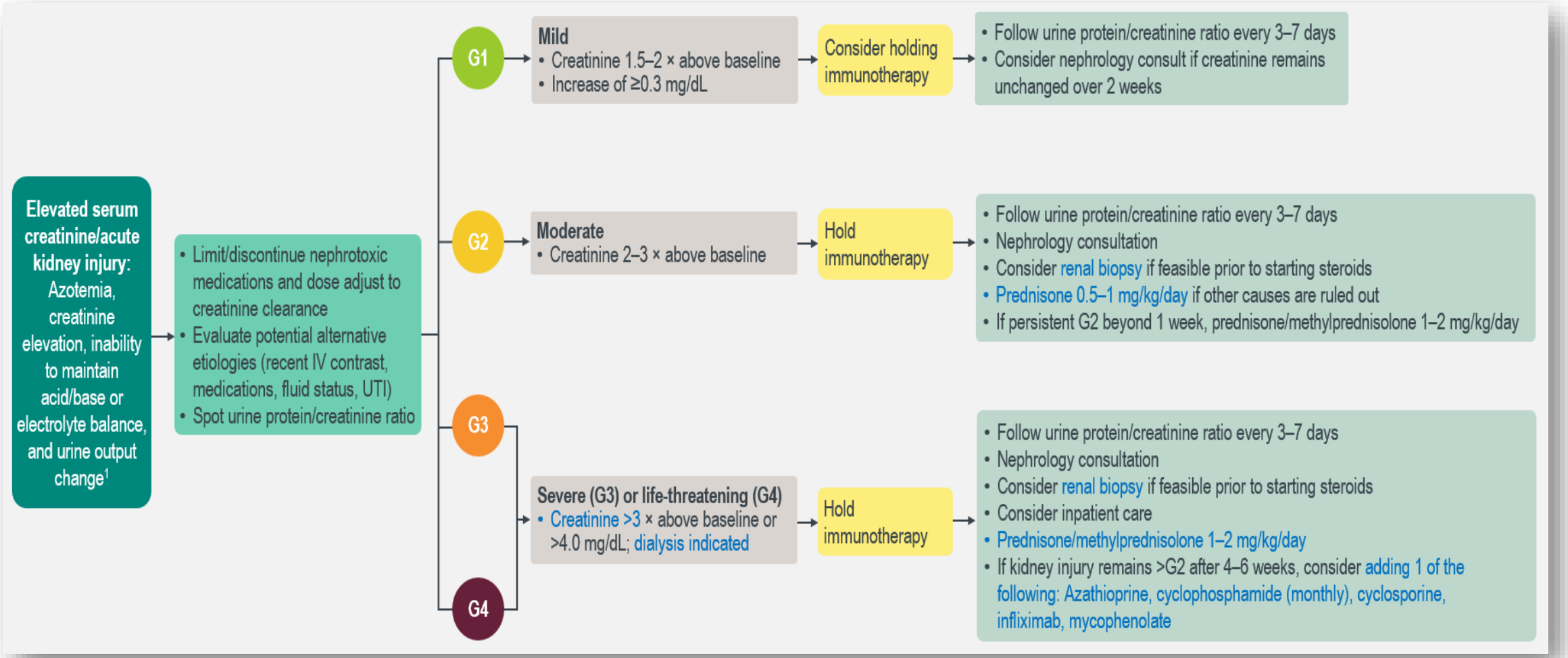
imAEs: Nephritis - NCCN & ASCO



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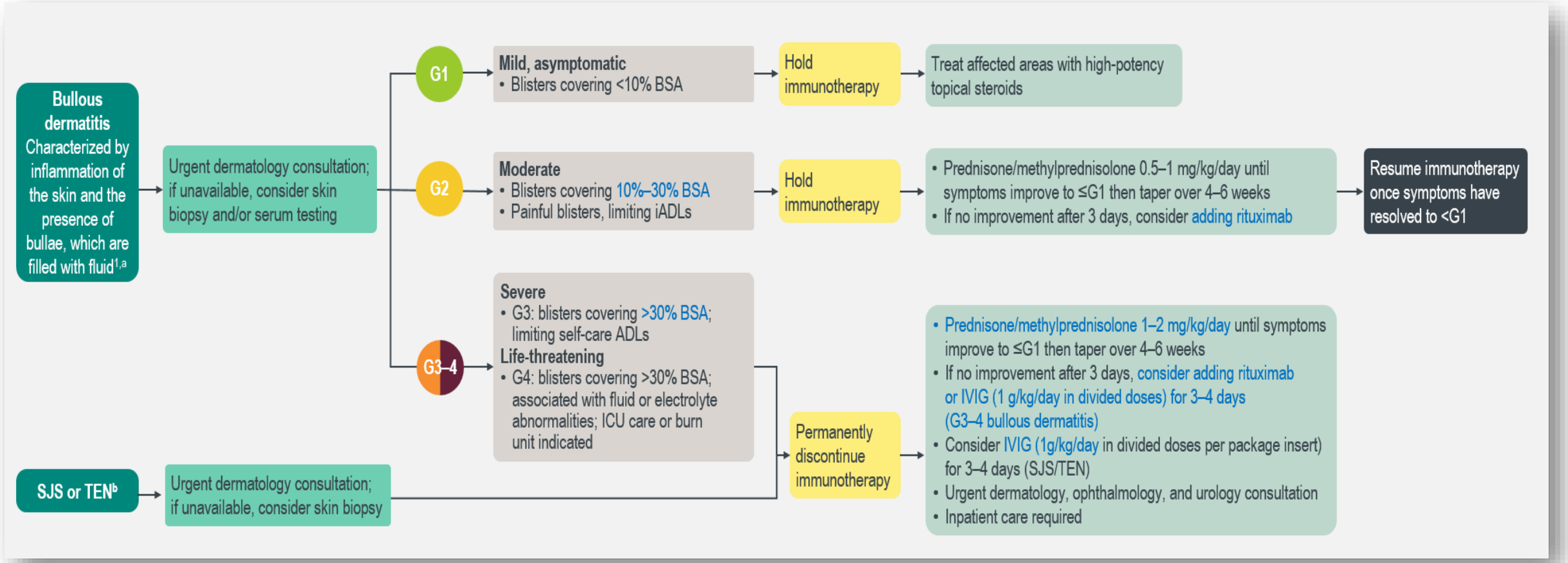
imAEs: Dermatologic reactions-Bullous Dermatitis and SJS/TEN- NCCN & ASCO



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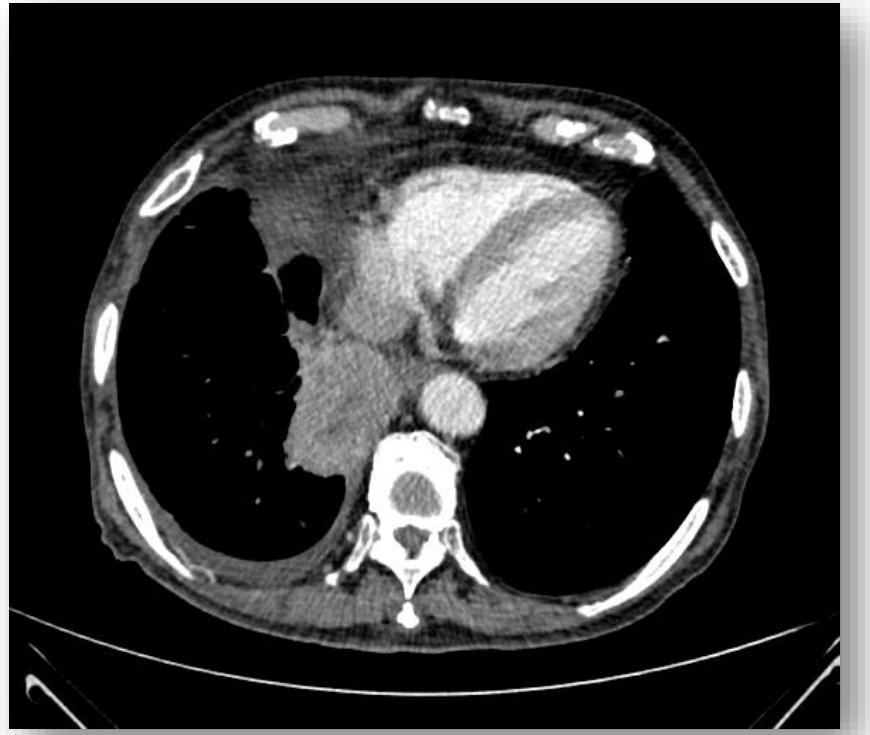
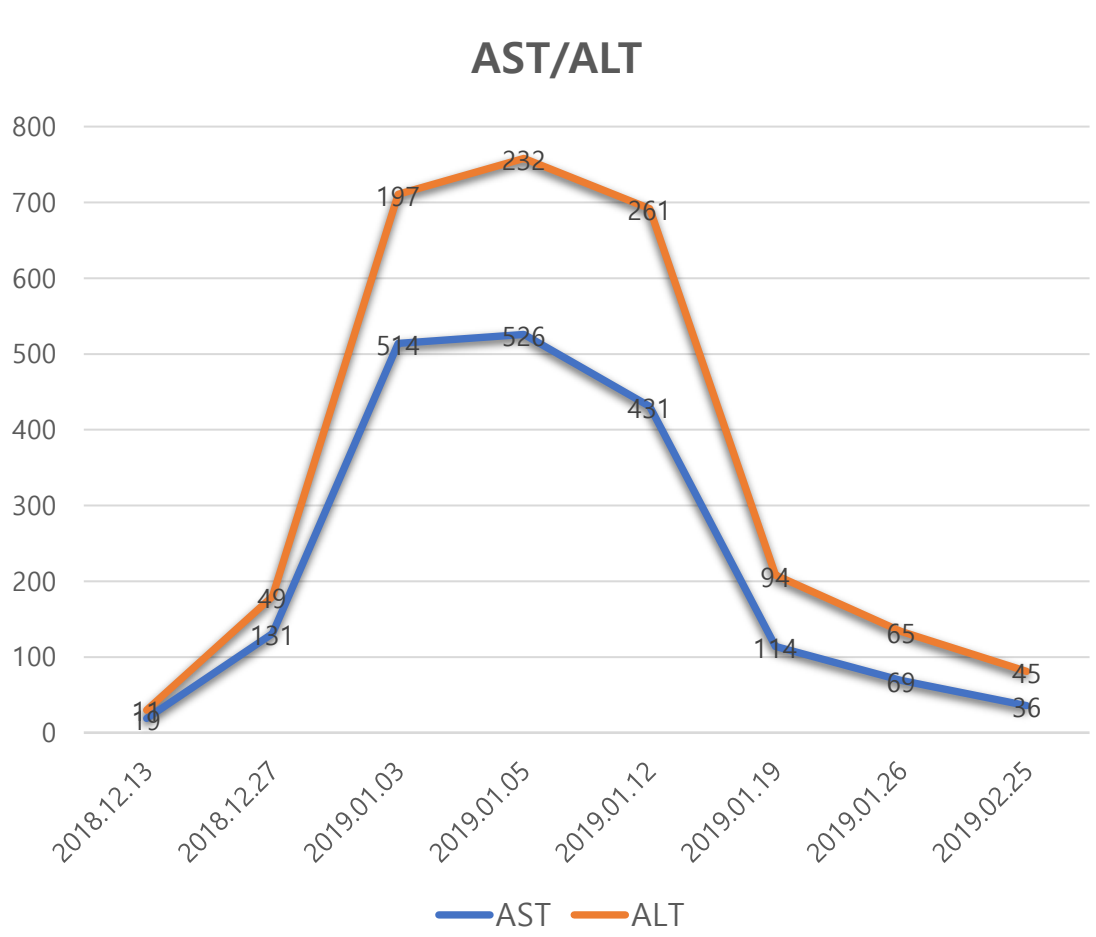
Case 3 imAEs, polymyositis after Nivolumab

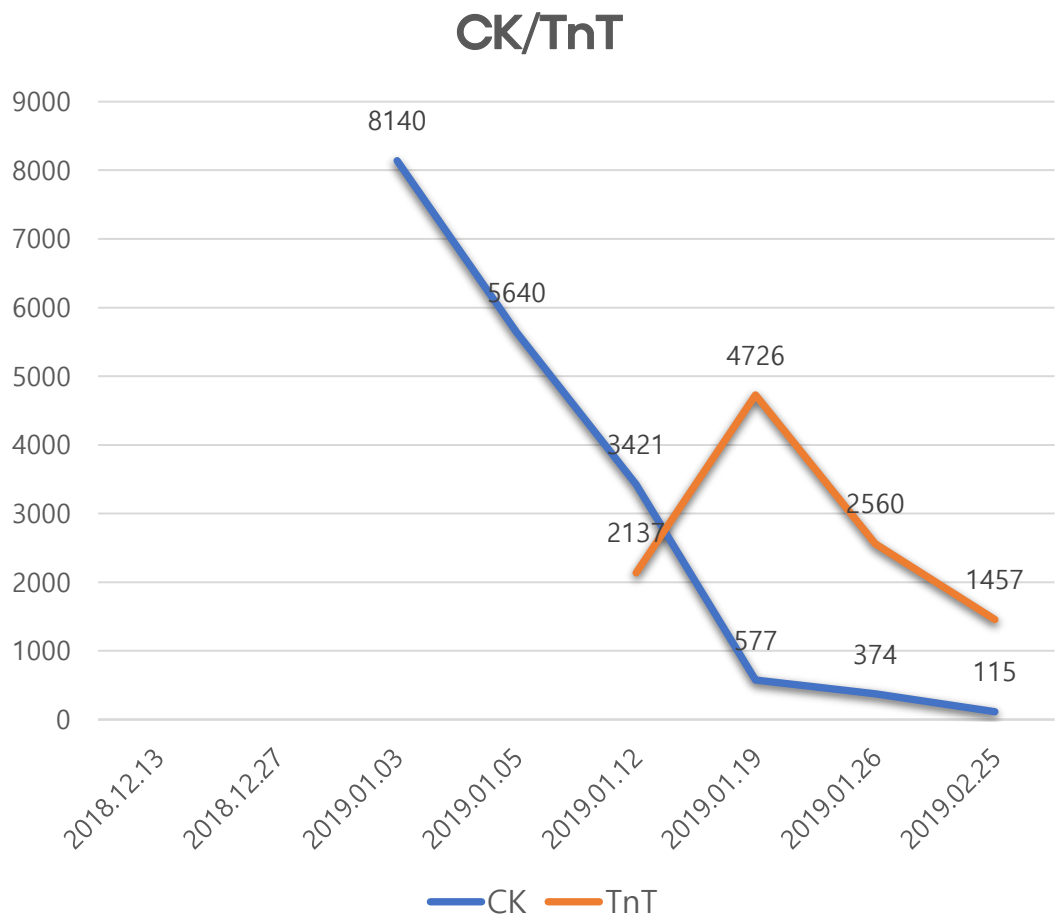
- M/82
  - NSCLC (Adenoca), stage IV, EGFR: wild 2018.3.22
  - ex-smoker (60세 quit, 1/2p*35yr)
  - 1L Pemetrexed/cisplatin 2018.4-2018.6
  - Pemetrexed maintenance 2018.7 -2018.11
  - Disease progression
  - 2L 1st~2nd nivolumab 2018.11.27 / 2018.12.13
  - 2018.12.27 onset: General weakness
  - 2019.1.3 adm: AST/ALT elevation, CK elevation
  - Imp : r/o polymyositis, r/o drug-induced hepatitis



Ref from Severance Hospital

Case 3 imAEs, polymyositis after Nivolumab





Ref from Severance Hospital

Case 3 imAEs, polymyositis after Nivolumab

- Patient progress
  - Treatment
    - Steroid: MP 500mg for 5 days → MP 62.5 mg (1mg/kg) for 3 weeks -> MP 31.25 (0.5mg/kg) for 3 weeks → PL 20mg → PL 10mg → PL 5mg 사용 후 tapering out (total 3개월 사용)
    - Brain MRI, EMG, NCV 시행
    - 신경과 consult: immune-related polymyopathy, neuropathy imp 으로 steroid treatment 권고
  - Progress
    - 입원 10일째 intubation → ventilator 3일째 extubation 후 re-intubation → weaning failure, 3개월 입원치료 후 home ventilator 유지하여 장기요양병원전원
    - Nivolumab 영구중단, steroid 중단 (total 3개월 정도 사용)
    - 2022.7 현재 disease progression 소견없이 f/u

Ref from Severance Hospital

imAEs: Musculoskeletal

Signs and Symptoms

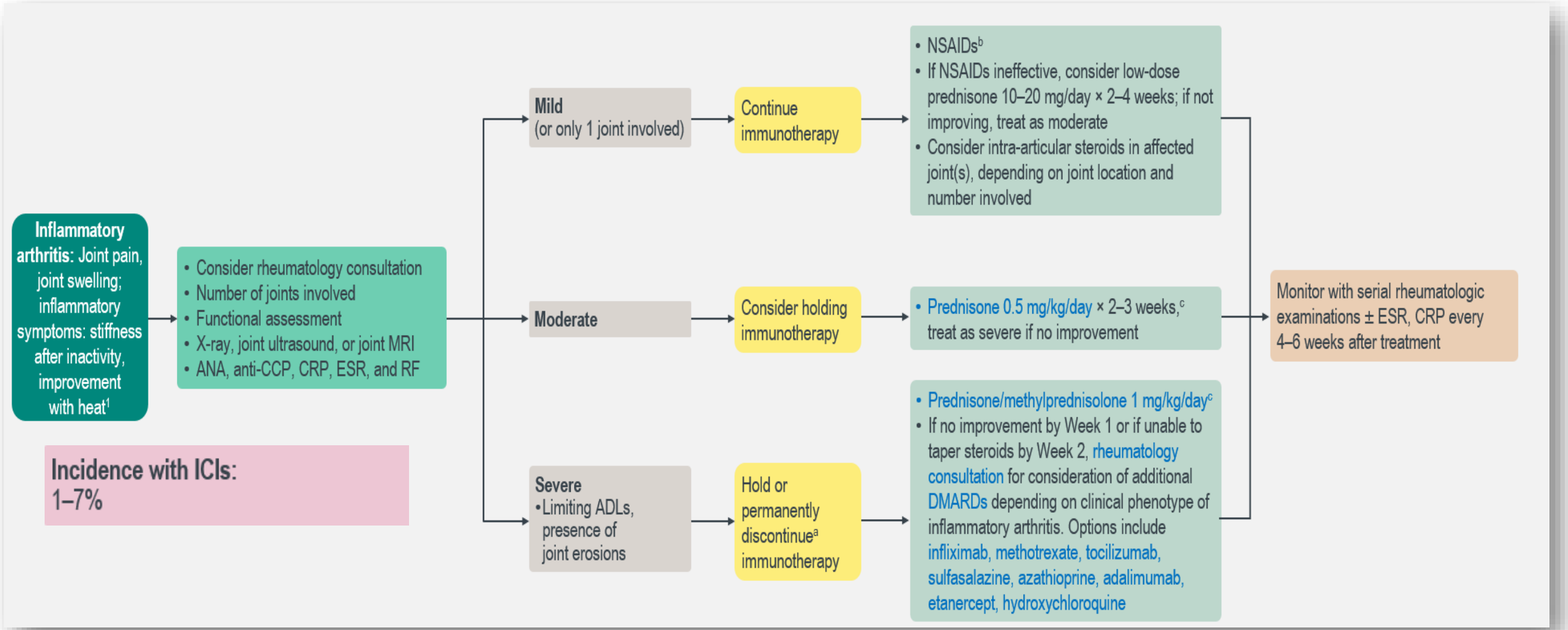
- Inflammatory arthritis
  - Joint pain, joint swelling; inflammatory symptoms: stiffness after inactivity, improvement with heat
- Myalgia/myositis
  - Marked discomfort sensation originating from a muscle or group of muscles (myalgia)
  - Characterized by inflammation and/or weakness involving the skeletal muscles (myositis)
- PMR/GCA
  - Fatigue and/or muscle and joint pain (PMR)
  - Headache, scalp tenderness, jaw claudication, visual symptoms (GCA)

Monitoring

- Monitor patients with inflammatory arthritis with serial rheumatologic examinations, including inflammatory markers, every 4–6 weeks after initiation of treatment
- Monitor patients with myositis for CK, ESR, CRP, and aldolase if CK has not been elevated
- Monitor patients with polymyalgia-like syndrome for ESR and CRP

imAE	Grade 1	Grade 2	Grade 3	Grade 4
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting iADLs[a]	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADLs[b]	—
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting iADLs	Pain associated with severe weakness; limiting self-care ADLs	Life-threatening consequences; urgent intervention indicated
Polymyalgia-like syndrome	Mild stiffness and pain	Moderate stiffness and pain, limiting age-appropriate iADLs	Severe stiffness and pain, limiting self-care ADL (G3–4)	Severe stiffness and pain, limiting self-care ADL (G3–4)

imAEs: Musculoskeletal- NCCN & ASCO



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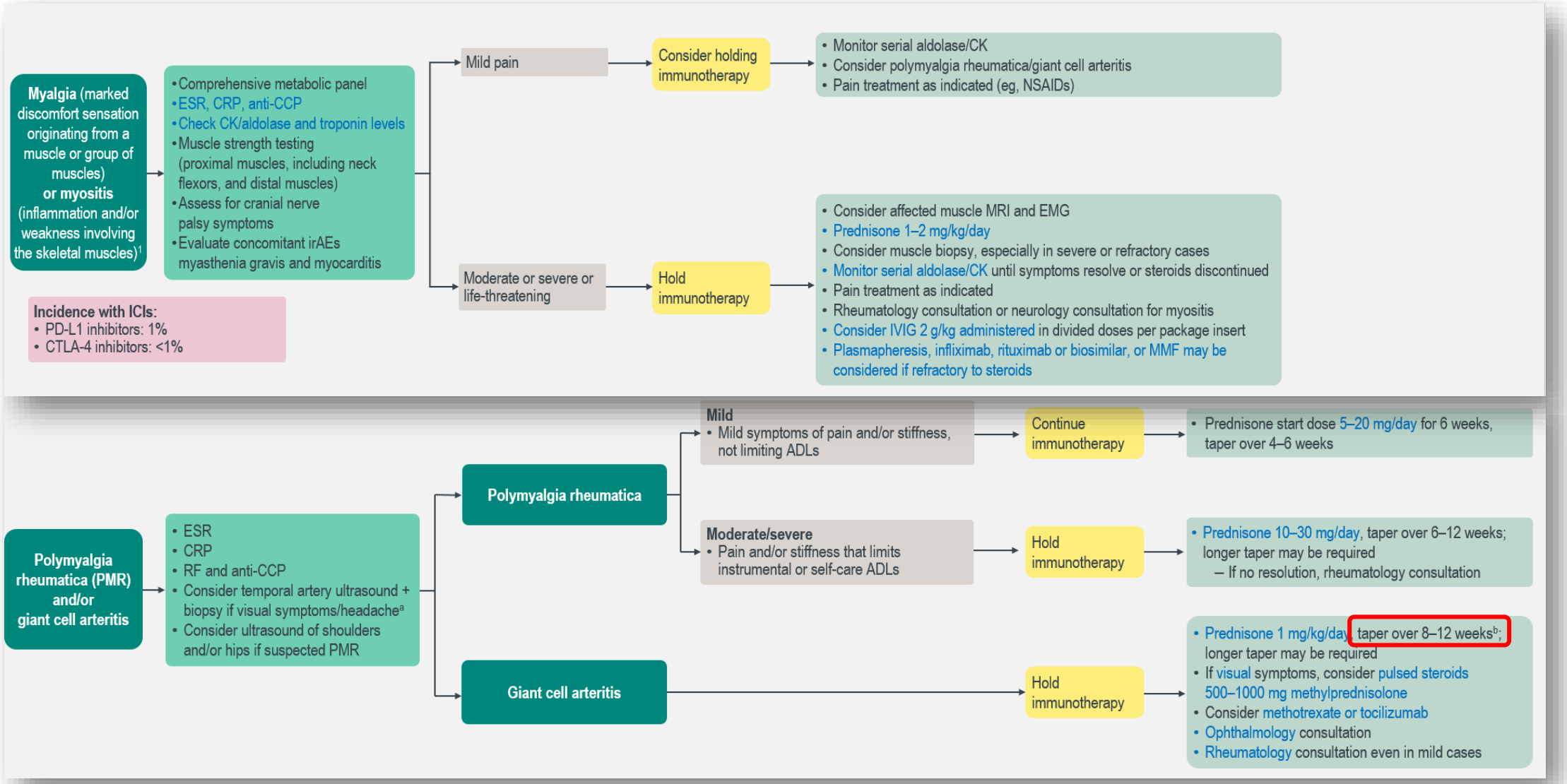
imAEs: Musculoskeletal- NCCN & ASCO



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imAEs: Neurologic

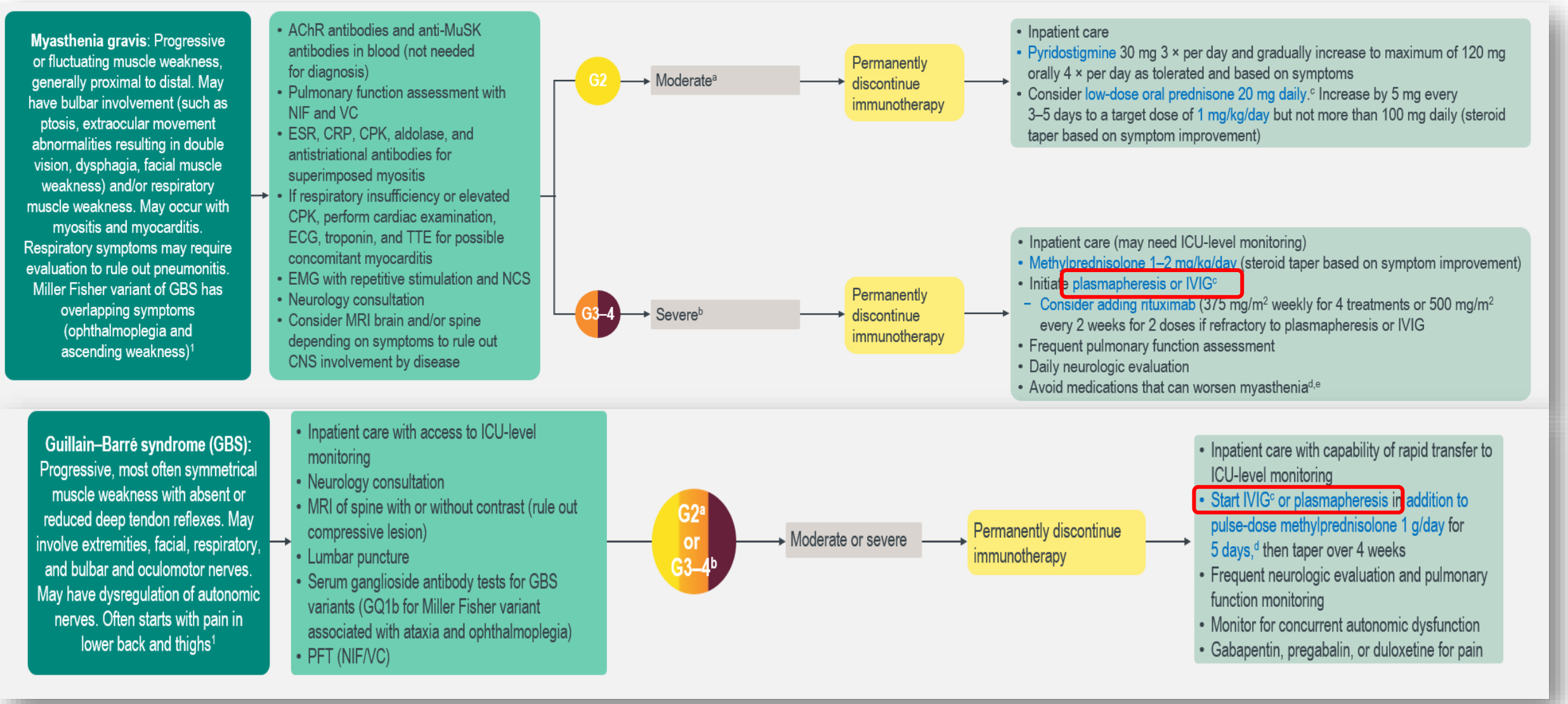
Signs and Symptoms

- **Myasthenia gravis:**
  - Progressive or fluctuating muscle weakness, generally proximal to distal; may have bulbar involvement[a] and/or respiratory muscle weakness[b]
- **Guillain-Barre (GBS):**
  - Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes; may involve extremities, facial, respiratory, and bulbar and oculomotor nerves; may have dysregulation of autonomic nerves[c]
- **Peripheral neuropathy:**
  - Asymmetric or symmetric sensory-motor deficit. Sensory deficit may be painful or painless paresthesias or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit[d]
- **Aseptic meningitis:**
  - Headache, photophobia, and neck stiffness, often afebrile but may be febrile; there may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis)
- **Encephalitis:**
  - Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality
- **Transverse myelitis:**
  - Acute or subacute weakness or sensory changes bilaterally, often with increased deep tendon reflexes

Monitoring

- Brain and/or spine MRI with and without contrast
- Lumbar puncture with CSF analysis including cytology
- Nerve conduction studies and EMG
- Electroencephalogram to rule out seizure activity in cases of encephalopathy
- Pulmonary function assessment (NIF and VC)
- Neurologic consultation

imAEs: Neurologic-NCCN & ASCO



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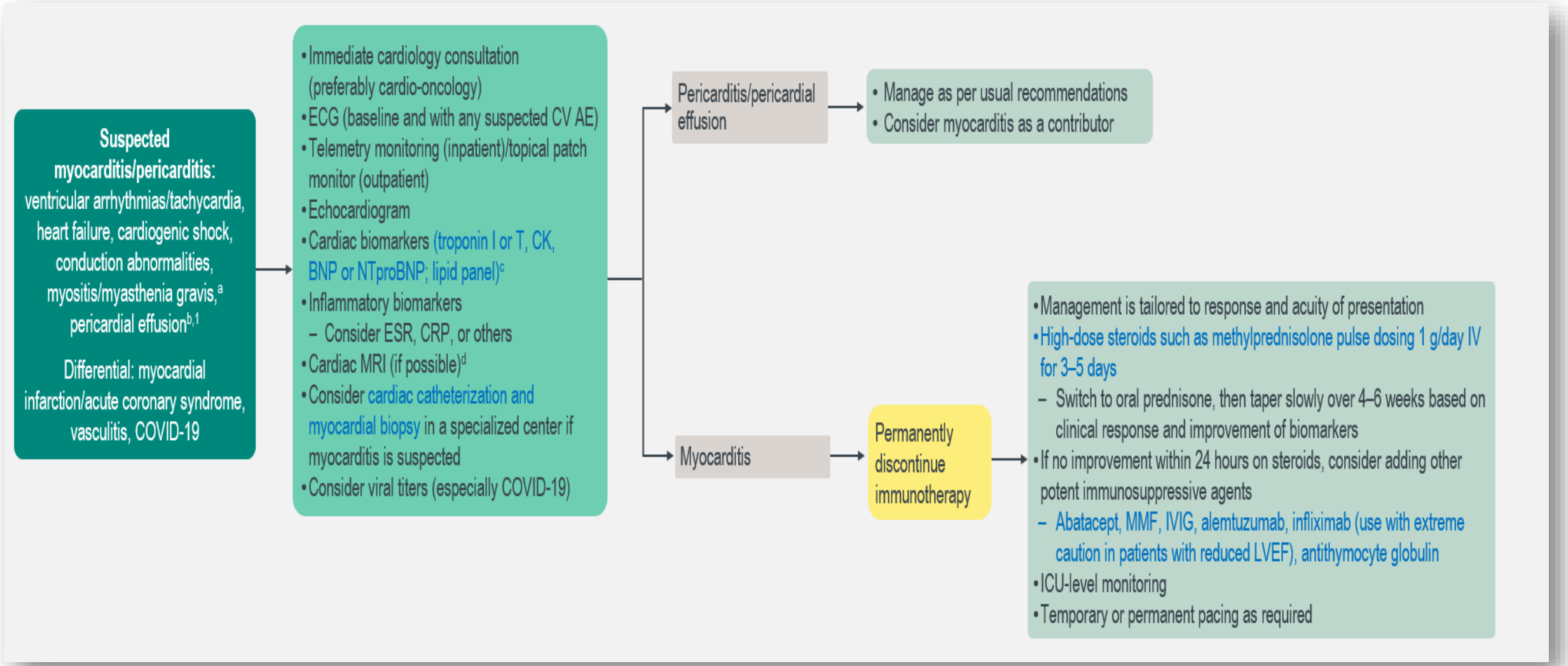
imAEs: Cardiovascular: Myocarditis/Pericarditis – NCCN & ASCO



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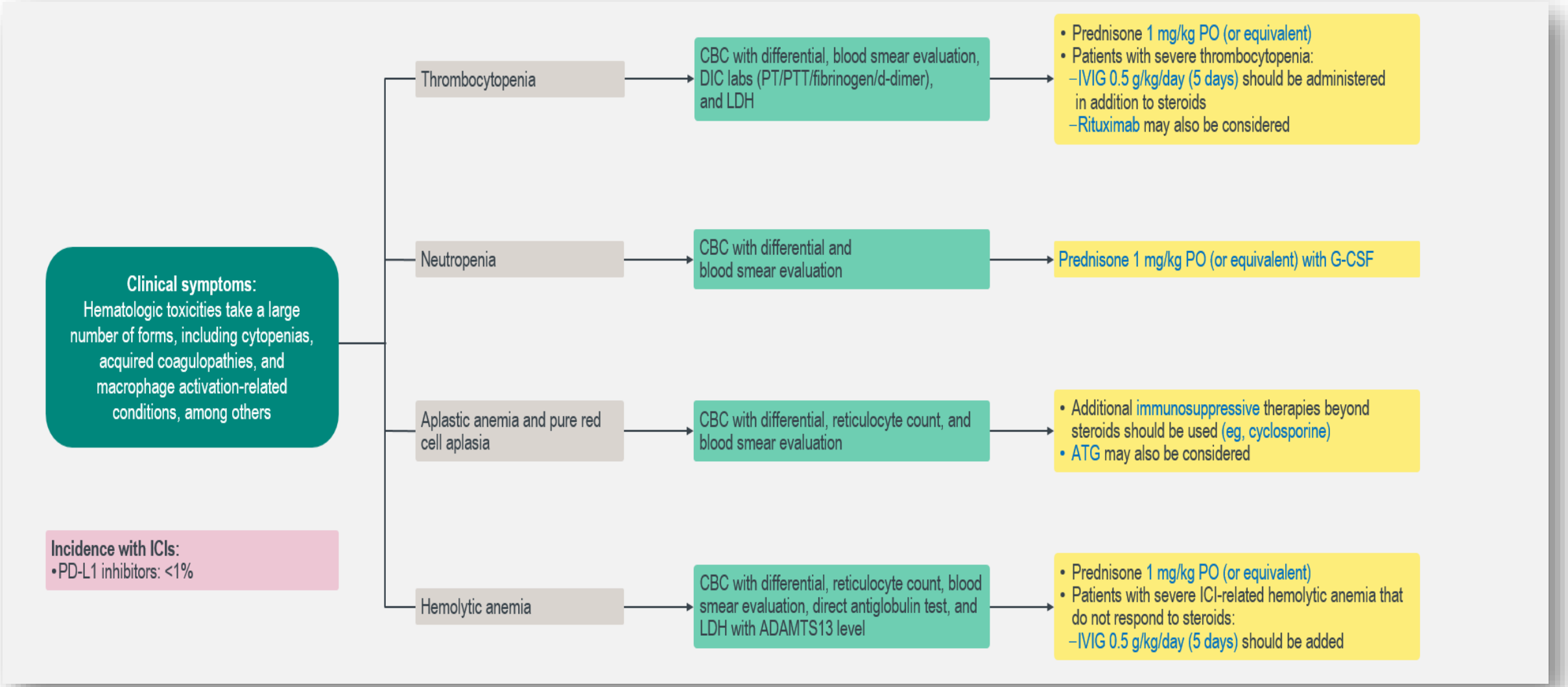
imAEs: Hematologic-SITC



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Management of fatal imAEs

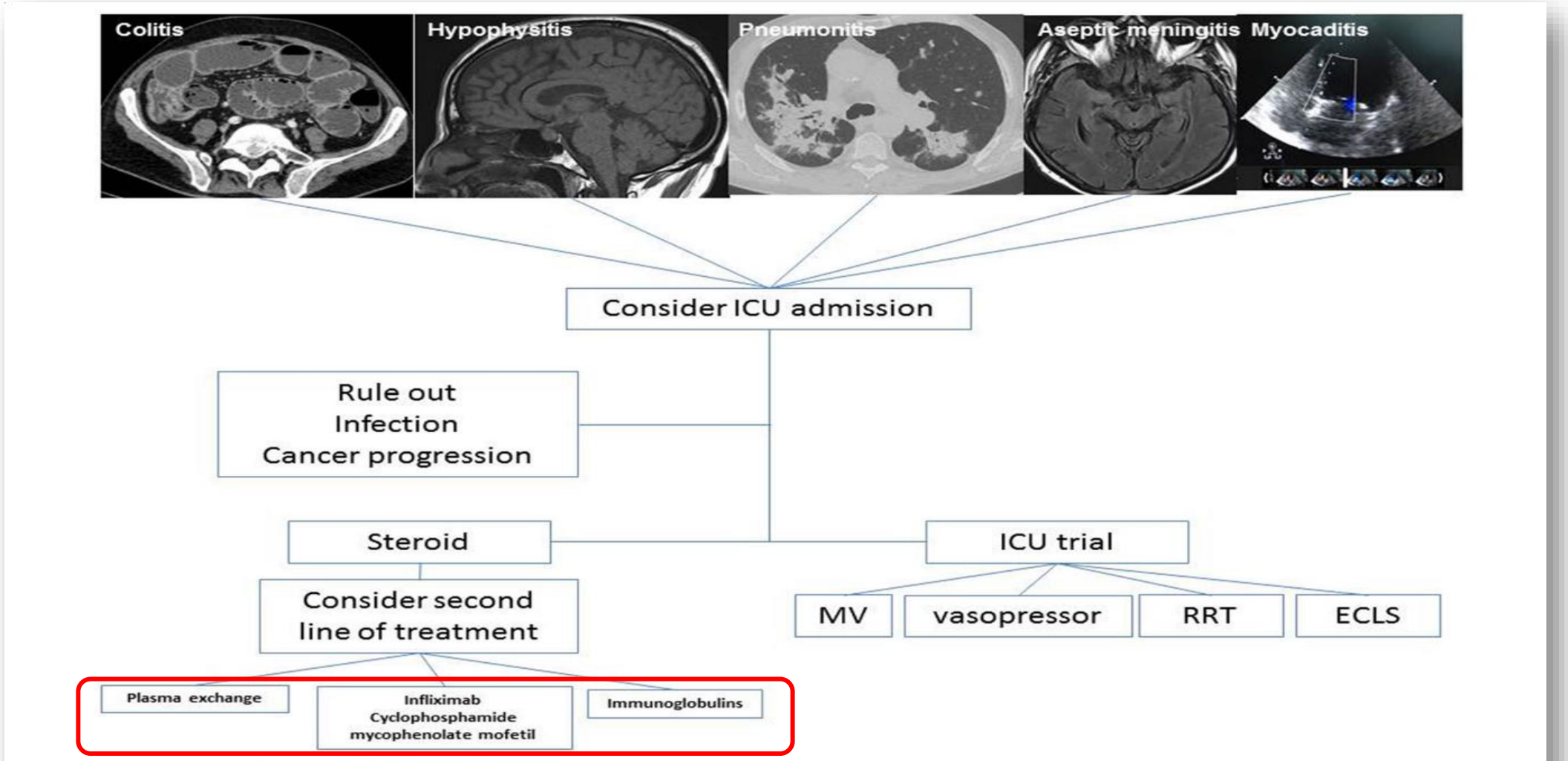

Fig. 6 Management of the most frequent IrAEs in the ICU. *ICU* intensive care unit, *MV* mechanical ventilation, *RRT* renal replacement therapy, *ECLS* extracorporeal life support

Lemiale et al. Ann Intensive Care. 2019;9:25.

Before Beginning Therapy With ICIs

Pretherapy Assessment	Monitoring Frequency	Evaluation for Abnormal Findings or Symptoms
General bloodwork • CBC (with differential if indicated) • Comprehensive metabolic panel	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated
Thyroid • TSH, free T4	Every 4–6 weeks during immunotherapy, then follow up every 12 weeks as indicated	Total T3 and free T4 if abnormal thyroid function suspected
Adrenal/pituitary • Consider serum cortisol (morning preferred) and thyroid function as per previous slide	Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow up every 6–12 weeks as indicated	LH, FSH, testosterone (men), estradiol (women), ACTH, and serum cortisol
Pulmonary • Oxygen saturation (resting and with ambulation) • Consider PFTs with diffusion capacity for high-risk patients (eg, interstitial lung disease on imaging, COPD, previous suspected treatment-related lung toxicity)	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with BAL if needed to exclude other causes
Cardiovascular • Consider baseline ECG • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal • 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 CRP, ESR, or CPK

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Summary

- ICIs are commonly associated with autoimmune toxicities, including high grade toxicity in up to a half of patients and fatal toxicities in 0.3%-1.3%, depending on the ICI regimen
- Most AEs occur 2-9 weeks after ICI initiation, but AE can be seen as late as two years after
- Commonly affected organ systems: skin, gastrointestinal tract, lungs, and endocrine system
- Colitis and hypophysitis are more frequent with anti-CTLA-4 treatment, and thyroiditis and pneumonitis are more common with anti-PD-(L)1 treatment
- Treatment of high-grade ICI related toxicity with high dose corticosteroids and early intervention with a targeted biologic, other immunosuppressants could be helpful
- The management of imAEs is best accomplished with early recognition and team-based approach between medical oncologists and medical subspecialists

감사합니다

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