HOSPITAL MEDICINE™ SUMMIT

The Role of the Hospitalist: A Focus on Oncology Treatment Adverse Events

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Learning Objectives

- Identify the grade ≥3 treatment-related adverse events (trAEs) associated with immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), and cellular therapies
- Devise an initial diagnostic and treatment plan for serious trAEs

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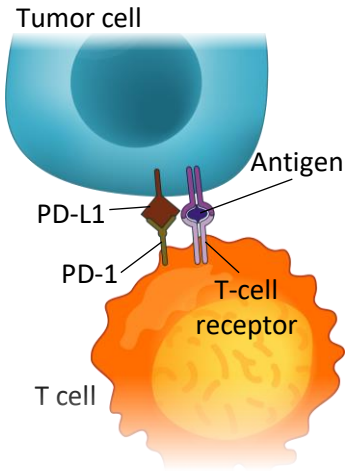
Introduction to Oncology Therapies

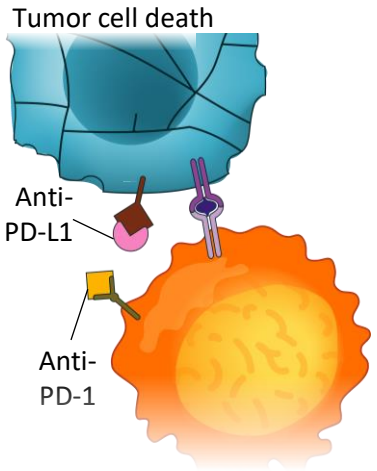
Immune Checkpoint Inhibitors: Mechanism of Action

PD-1/PD-L1

PD-L1 binds to PD-1 and inhibits T-cell killing of tumor cell



Blocking PD-L1 or PD-1 allows T-cell killing of tumor cell

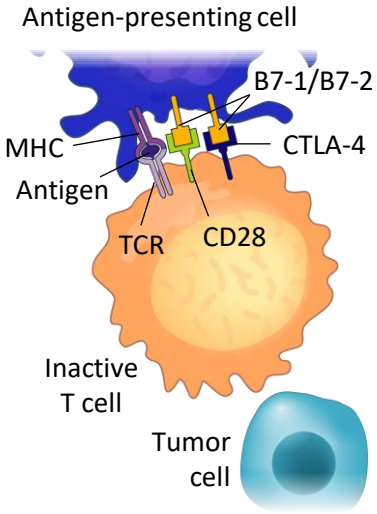


PD-1 inhibitors: pembrolizumab, nivolumab, cemiplimab

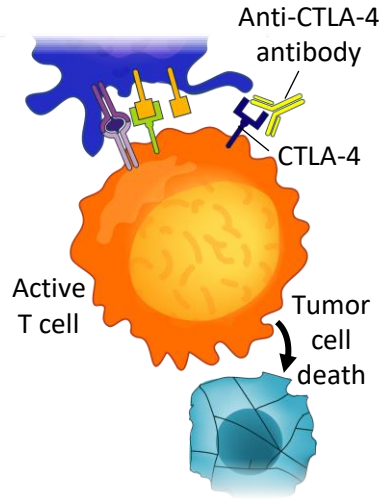
PD-L1 inhibitors: atezolizumab, avelumab, durvalumab

CTLA-4

CTLA-4/B7 binding inhibits T-cell activation



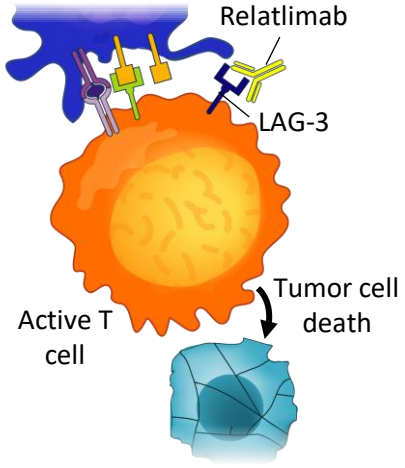
Blocking CTLA-4 allows T-cell killing of tumor cell



CTLA-4 inhibitor: ipilimumab

LAG-3

Blocking LAG-3 allows T-cell killing of tumor cell

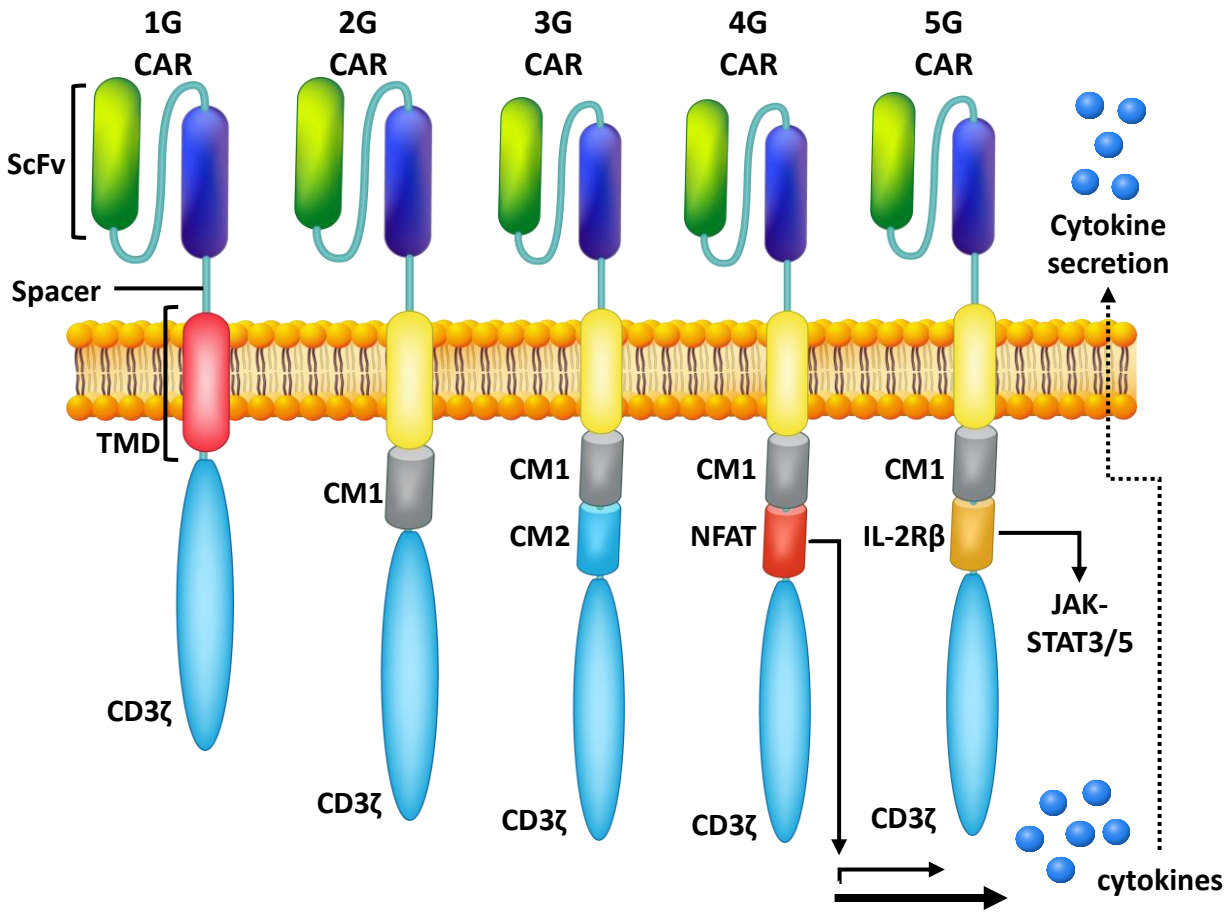


LAG-3 inhibitor: relatlimab

CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associate protein 4; LAG-3, lymphocyte-activation gene 3; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.

Centanni M, et al. *Clin Pharmacokinet.* 2019:58,835–857.

CAR-T: Mechanism of Action

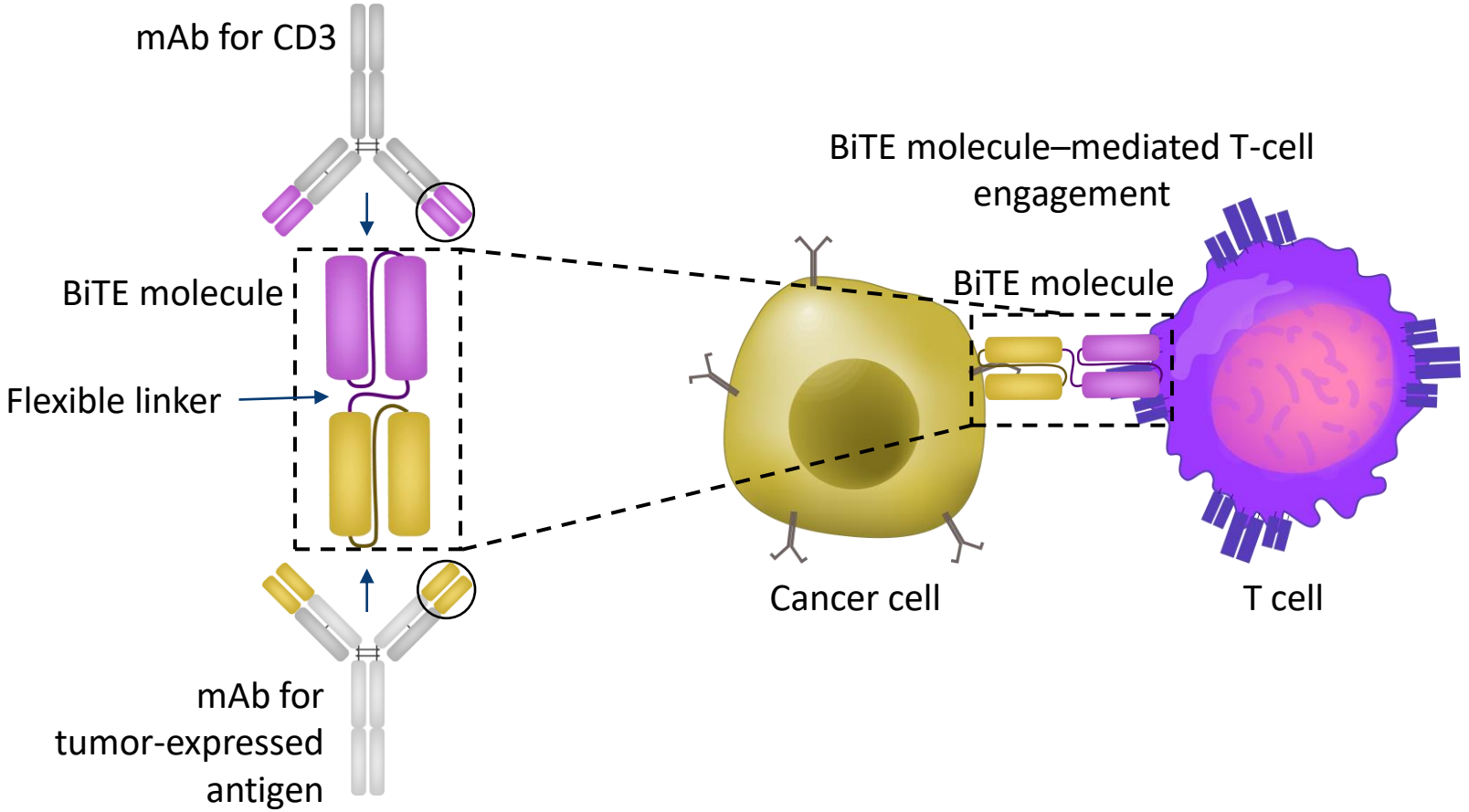


- Tisagenlecleucel
- Axicabtagene ciloleucel
- Brexucabtagene autoleucel
- Lisocabtagene maraleucel
- Idecabtagene vicleucel
- Ciltacabtegene autoleucel

CAR-T, chimeric antigen receptor T cells; IL, interleukin; JAK, Janus kinase; NFAT, nuclear factor of activated T cells; ScFv, single-chain variable fragment; STAT, signal transducer and activators of transcription.

American Cancer Society. CAR T-cell therapy and its side effects. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/car-t-cell1.html

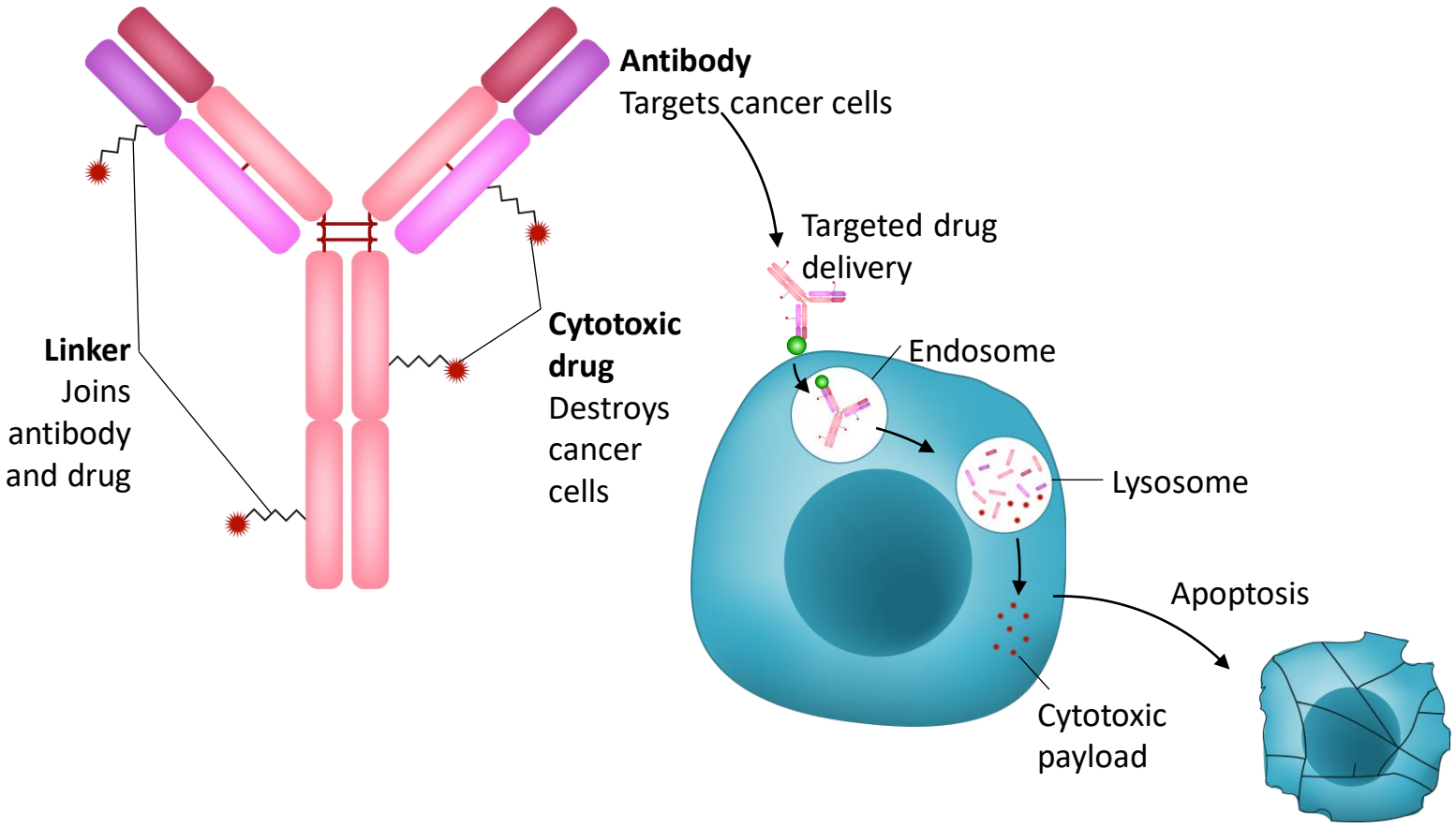
Bispecific T-cell engagers (BITEs) Mechanism of Action



BiTE, bispecific T cell engager; mAb, monoclonal antibody.

Viardot A, et al. *Ann Hematol.* 2020;99(10):2215-2229.

Antibody Drug Conjugate – Mechanism of Action



Gemtuzumab ozogamicin	Ado-trastuzumab emtansine
Brentuximab vedotin	Enfortumab vedotin
Inotuzumab ozogamicin	Fam-trastuzumab deruxtecan
Moxetumomab pasudotox	Sacituzumab govitecan
Polatuzumab vedotin	Cetuximab sarotalocan
Belantamab mafodotin	Disitamab vedotin
Loncastuximab tesirine	Tisotumab vedotin

Fu Z, et al. *Sig Transduct Target Ther.* 2022;7:93.

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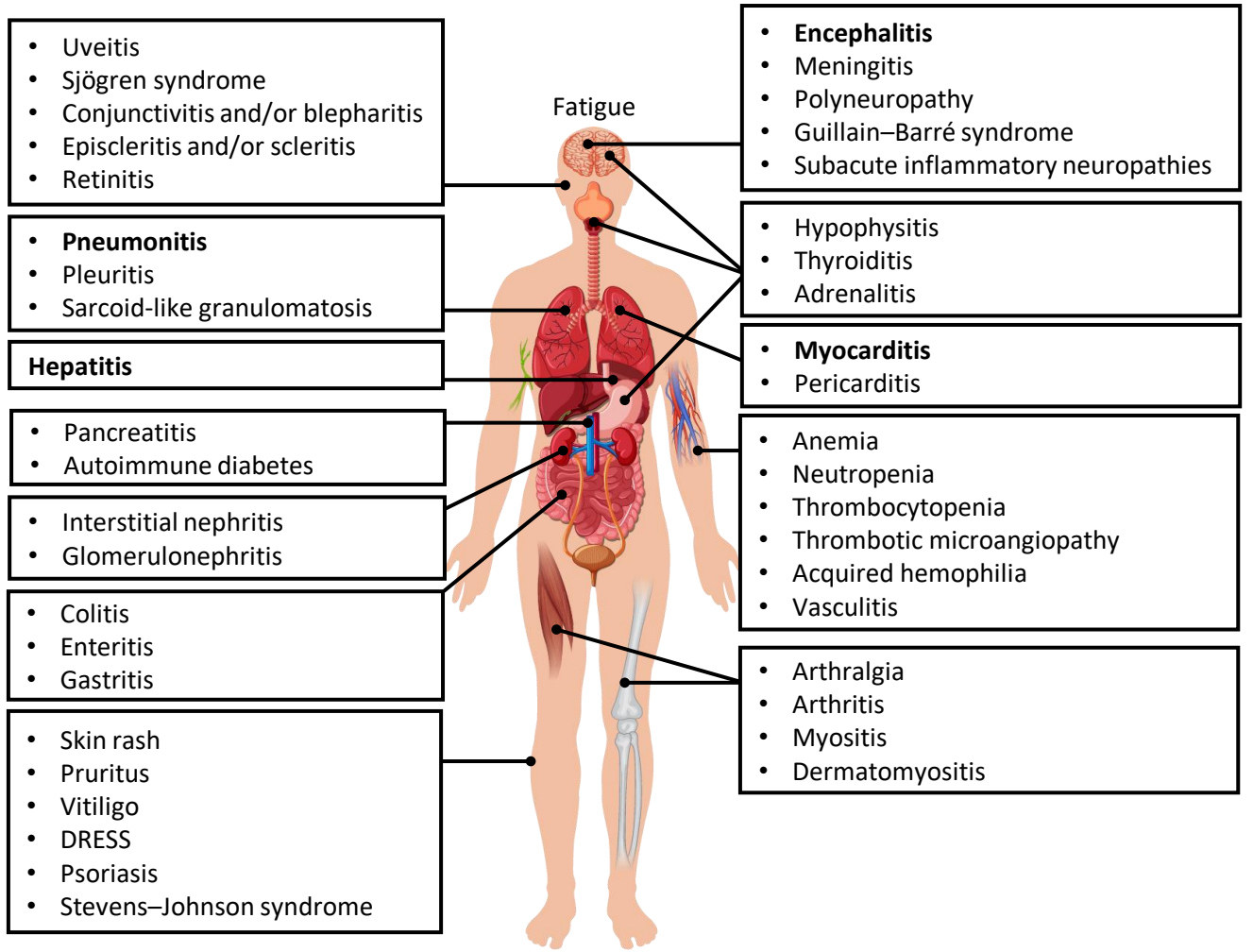
Introduction to Treatment Related Adverse Events

Estimated Frequencies of Common Any-Grade Immune-Related Adverse Events (irAEs)

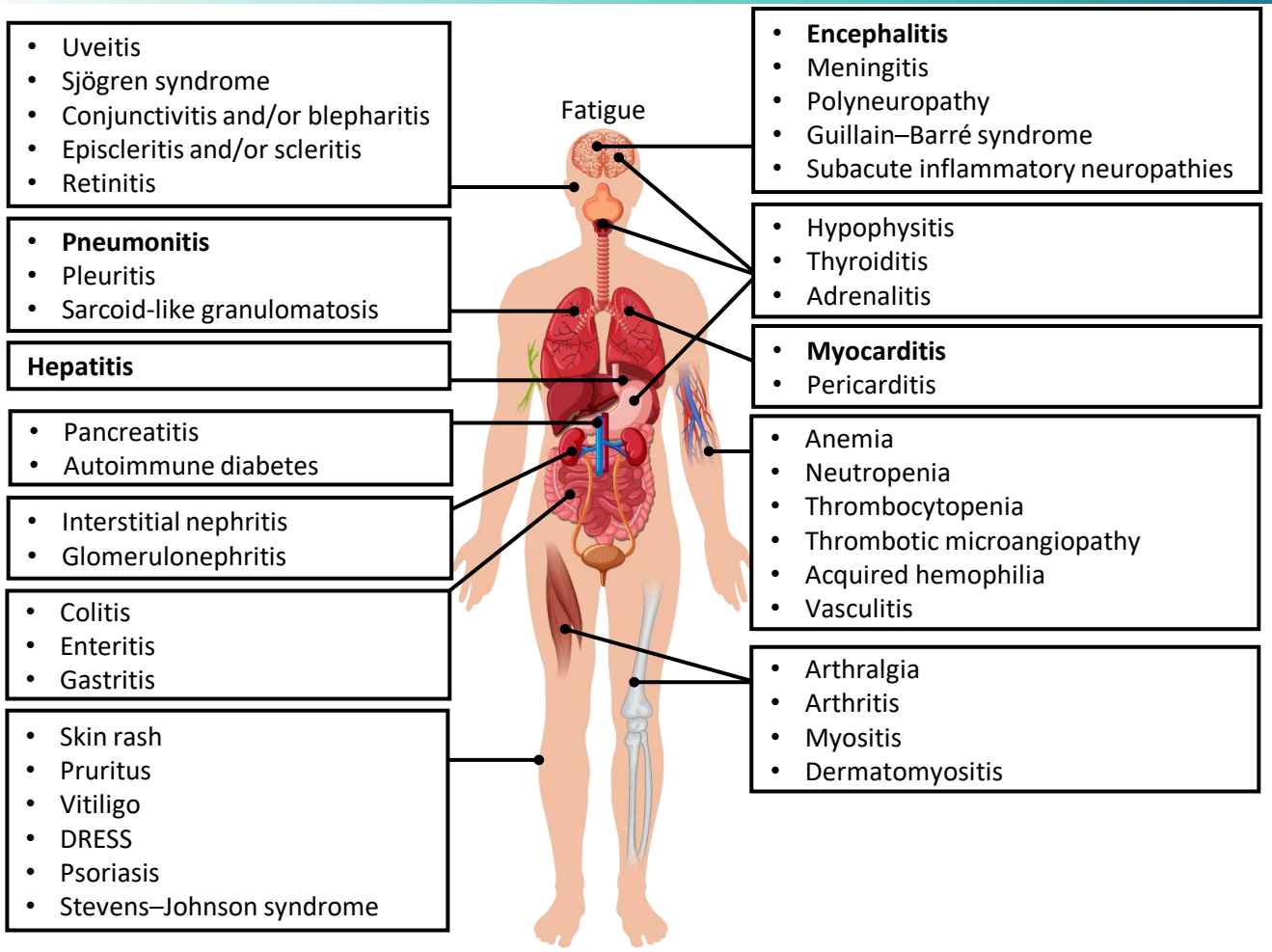
	CTLA-4 Inhibitors	PD-1/PD-L1 Inhibitors
Rash	24%	15%
Colitis	8%-22%	1%-2%*
Pneumonitis	Very Low**	2%-4%
Hepatic	5%-10%	5%-10%
Hyper/hypothyroidism	1%-5%	5%-10%
Hypophysitis	1%	Very Low**

*Grade 3/4 only; **Very Low = irAEs less than 1%.



Fink J. Identifying and managing immune-related adverse events. Targeted Oncology. https://www.targetedonc.com/view/identifying-and-managing-immunerelated-adverse-events. Accessed November 4, 2022; Martins F, et al. *Nat Rev Clin Oncol.* 2019;16(9):563-580.

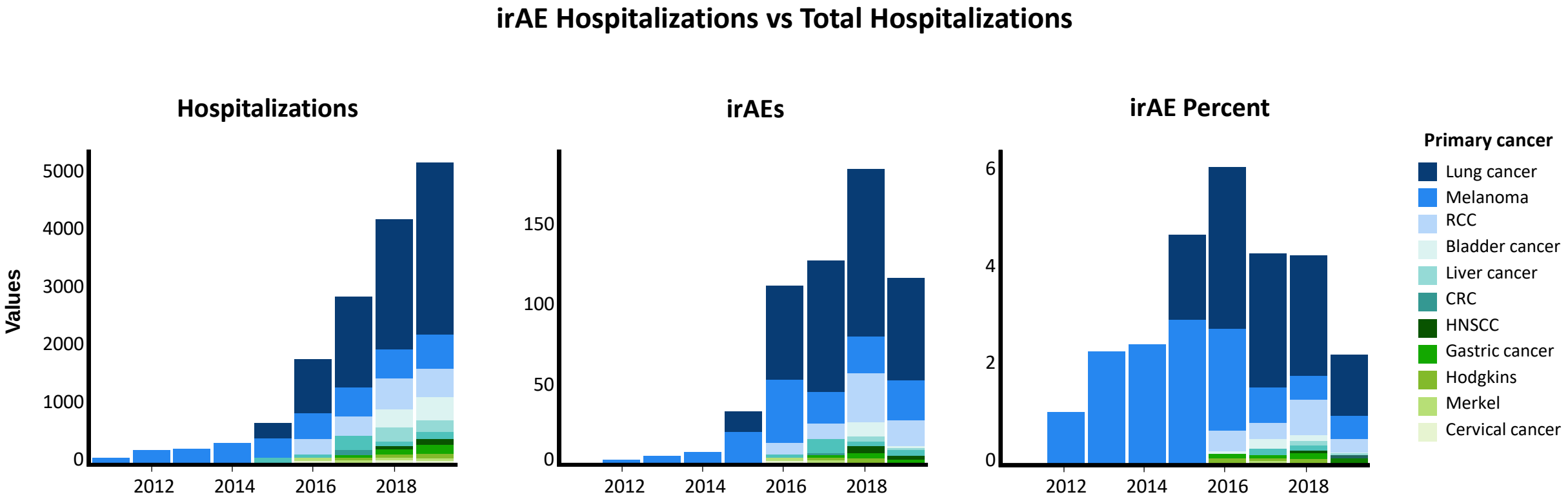
irAEs Commonly Associated With ICI Therapy



- Frequency of irAEs depends on:
  - The agents used
  - Exposure time
  - Administered dose
  - Patient's intrinsic risk factors

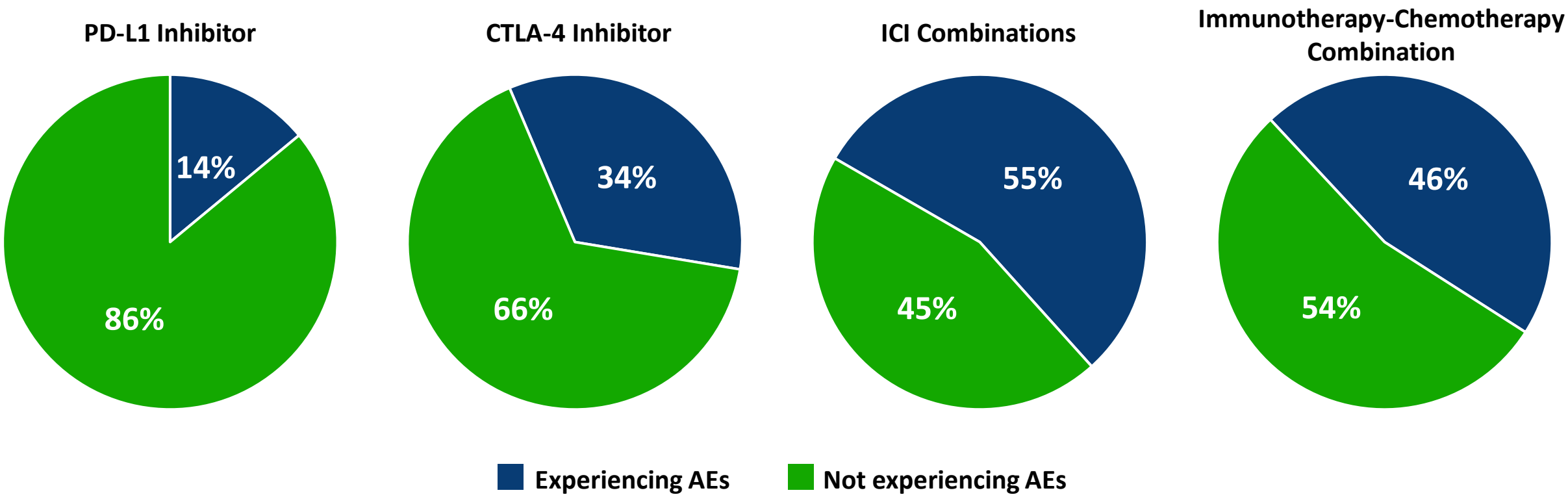
Martins F, et al. *Nat Rev Clin Oncol.* 2019;16(9):563-580.

Incidence of irAE Hospitalizations and Total Hospitalizations in Patients on ICI Therapy



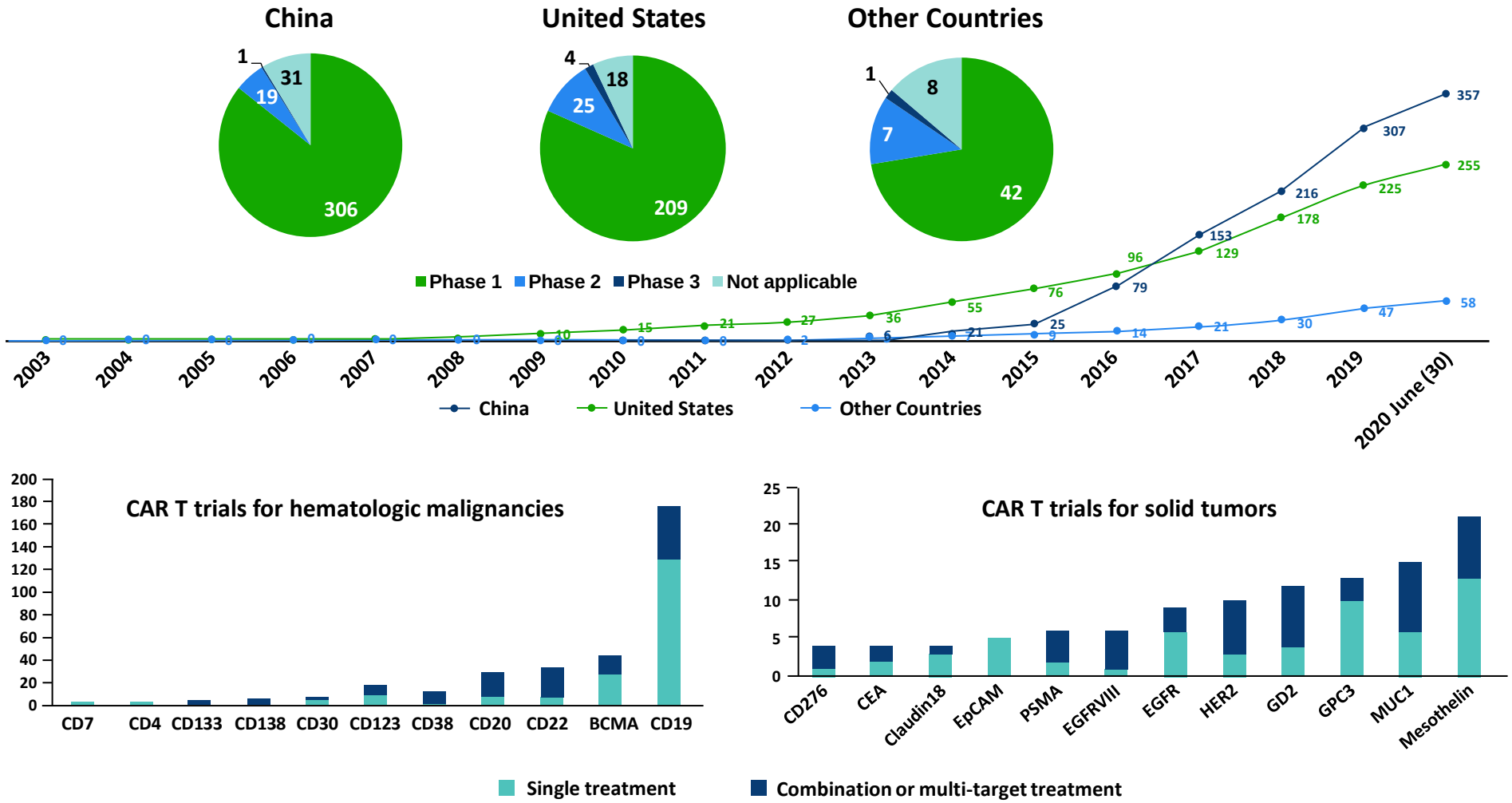
Kalinich M, et al. *J ImmunoTher Cancer*, 2021;9(3):e001935.

Frequency of Grade ≥3 AEs



Arnaud-Coffin P, et al. *Int J Cancer*. 2019;145(3):639-648.

The Increased Use of Adaptive Cell Therapies



Wei J, et al. *Cell Mol Immunol.* 2021;18:792–804.

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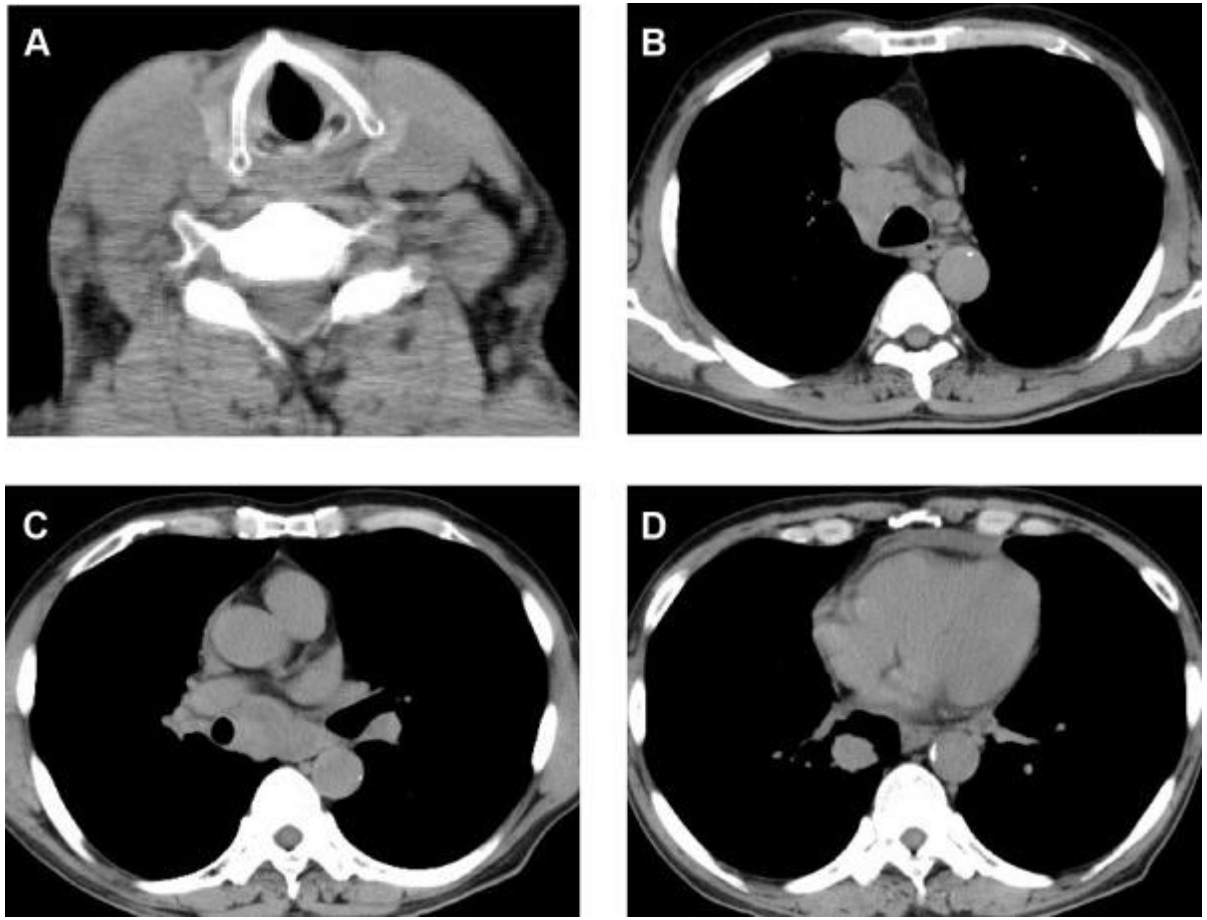
Adverse Events

Cytokine Release Syndrome (CRS)

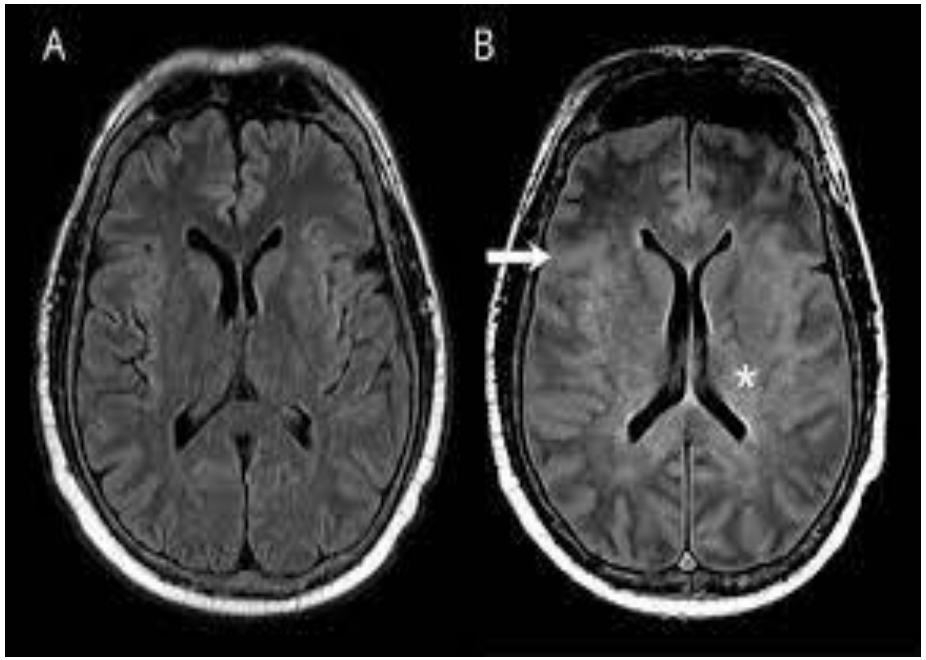
- Symptomology: fever, hypotension, tachycardia, hypoxia, and chills
- Serious events: hypotension, hypoxia, atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, and HLH/MAS
- Typical time to onset: 2-3 days (can occur hours after infusion to 15 days post-infusion)
- Typical duration: 7-8 days



HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome.
NCCN. Management of CAR T-cell-related toxicities (Version 1.2022) Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Symptomology: delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder, anxiety, agitation and signs of psychosis
- Serious events: seizures, depressed level of consciousness, as well as fatal and serious cases of cerebral edema
- Typical time to onset: 4-10 days
- Typical duration: 14-17 days



Guha-Thakurta N, et al. *Neurology*. 2018;91(18):843.
NCCN. Management of CAR T-cell-related toxicities (Version 1.2022) Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

ADC and Their Adverse Events

Payload	Drugs Using This Payload	Adverse Events
Ozogamicin	• Gemtuzumab ozogamicin • Inotuzumab ozogamicin	VOD, myelosuppression
Vedotin	• Brentuximab vedotin • Polatuzumab vedotin • Enfortumab vedotin • Disitamab vedotin • Tisotumab vedotin	Neuropathy, myelosuppression
Pasudotox	Moxetumomab pasudotox	Capillary leak syndrome, HUS

HUS, hemolytic uremic syndrome; VOD, veno-occlusive disease.

Mylotargtm. Package insert. Pfizer; 2000; Besponsa. Package insert. Pfizer; 2017; Adcetris. Package insert. Seagen; 2022; Polivy. Package insert. Genetech; 2019; Padcev. Package insert. Astellas; 2022;Tivdak. Package insert. Seagen; 2022; Lumoxiti. Package insert. AZ; 2021

ADC and Their Adverse Events

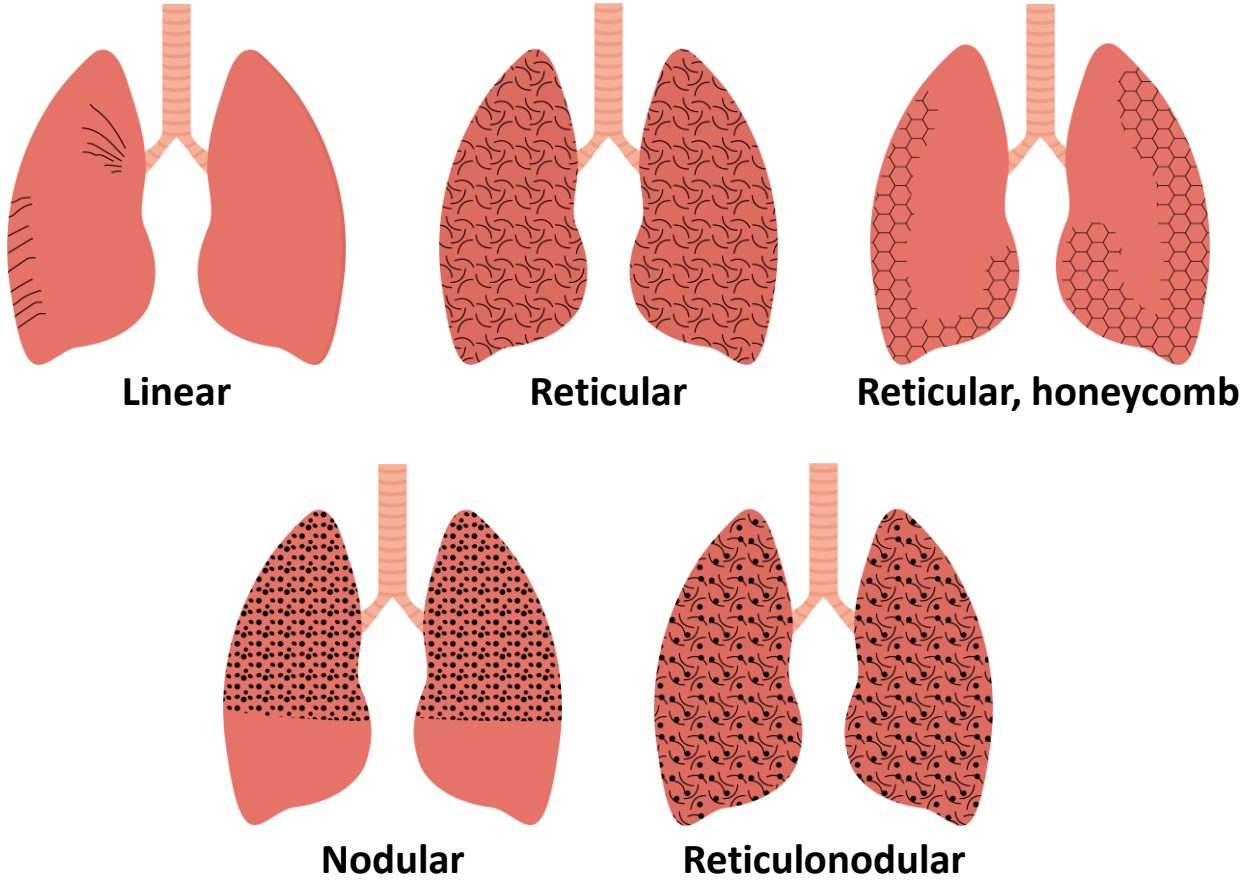
Payload	Drugs Using This Payload	Adverse Events
Mafodotin	Belantamab mafodotin	Keratopathy
Tesirine	Loncastuximab tesirine	Effusions (pleural, pericardial), myelosuppression
Govitecan	Sacituzumab govitecan	Diarrhea, myelosuppression
Deruxtecan	Fam-trastuzumab deruxtecan	ILD, myelosuppression, cardiotoxicity
Emtansine	Ado-trastuzumab emtansine	Peripheral neuropathy, ILD, myelosuppression, cardiotoxicity

ILD; Interstitial lung disease

Blenrep. Package insert. GSK; 2022. Zynlonta. Package insert. ADC; 2022. TRODELVY. Package insert. Gilead Science; 2022. Enhertu. Package insert. AZ; 2022. Kadcyla. Package insert. Genentech; 2022.

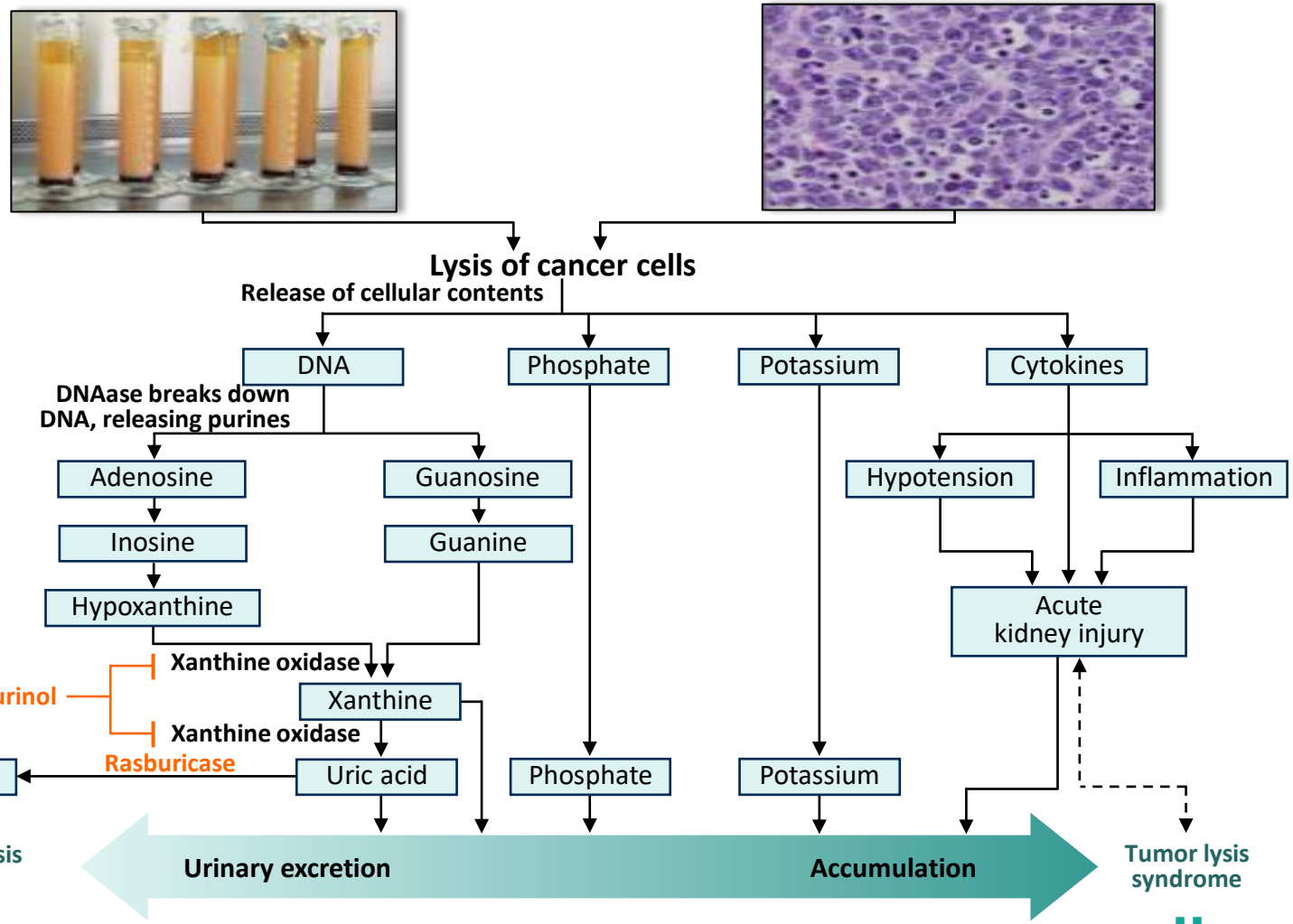
ILD and Pneumonitis

- Symptomatic patients:
  - Fatigue
  - Shortness of breath
  - Dyspnea
  - Dry cough
  - Chest Pain
  - Fever
  - Skin Rash



Tarantino P, et al. *JAMA Oncol*. 2021;7(12):1873-1881.
Radiology Key. Interstitial lung disease. Available at: https://radiologykey.com/interstitial-lung-disease-2/

Tumor Lysis Syndrome



DNA, deoxyribonucleic acid.

Howard SC, et al. *N Engl J Med*. 2011;364(19):1844-1854.

Tumor Lysis Syndrome

Definitions of Laboratory and Clinical Tumor Lysis Syndrome*

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 µmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/liter) in adults or >6.5 mg/dL (2.1 mmol/liter) in children	
Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/liter) or ionized calcium <4.5 mg/dL (1.12 mmol/liter)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hr

*In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.
†The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 – albumin in grams per deciliter).
‡Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injury are from Levin et al.

Howard SC, et al. *N Engl J Med*. 2011;364(19):1844-1854.

Risk Stratification of Tumor Lysis Syndrome and Prophylaxis Recommendations

Risk category	Malignant Disease	Prophylaxis
Low-risk disease	Solid tumor Multiple myeloma CML CLL Indolent NHL Hodgkin lymphoma AML (WBC <25,000/mL and LDH <2 ULN)	• Monitoring (daily laboratory tests) • Intravenous hydration • Consider allopurinol
Intermediate-risk disease	AML (WBC 25,000-100,000/mL) AML (WBC <25,000/mL and LDH ≥2 ULN) Intermediate-grade NHL (LDH ≥2 ULN) ALL (WBC <100,000/mL and LDH <2 ULN) Burkitt lymphoma (LDH <2 ULN) Lymphoblastic NHL (LDH <2 ULN)	• Monitoring (laboratory tests every 8 to 12 hours) • Intravenous hydration • Allopurinol for up to 7 days
High-risk disease	ALL (WBC 100,000/mL and/or LDH ≥2 ULN) Burkitt lymphoma (stages III/IV and/or LDH ≥2 ULN) Lymphoblastic NHL (stages III/IV and/or LDH ≥2 ULN) IRD with renal dysfunction and/or renal involvement IRD with elevated uric acid, potassium, and/or phosphate	• Monitoring (laboratory tests every 6 to 8 hours) Intravenous hydration • Rasburicase

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; IRD, intermediate-risk disease; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma; ULN, upper limit of normal; WBC, white blood cell count.

Halfdanarson TR, Hogan WJ, Madsen BE. *Mayo Clin Proc*. 2017;92(4):609-641.

Initial Evaluation of Fever and Neutropenia

Fever:

- Single temperature equivalent to ≥38.3°C orally

or

- Equivalent to ≥38.3°C orally over 1-hour period

Neutropenia:

- ≤500 neutrophils/mcL

or

- ≤1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 hours

→

- Complete H&P including supplemental history:
  - Major comorbid illness
  - Type and time since last chemotherapy
  - Prior documented infections in the last 3 months
  - Recent antibiotic therapy/prophylaxis
  - Medications
  - Use of devices
- Epidemiologically relevant exposures (eg, marijuana or cigarette smoking, vaping, injection drug use)
- Laboratory/radiology assessment:
  - CBC with differential, comprehensive metabolic panel
  - Consider chest x-ray and urinalysis

→

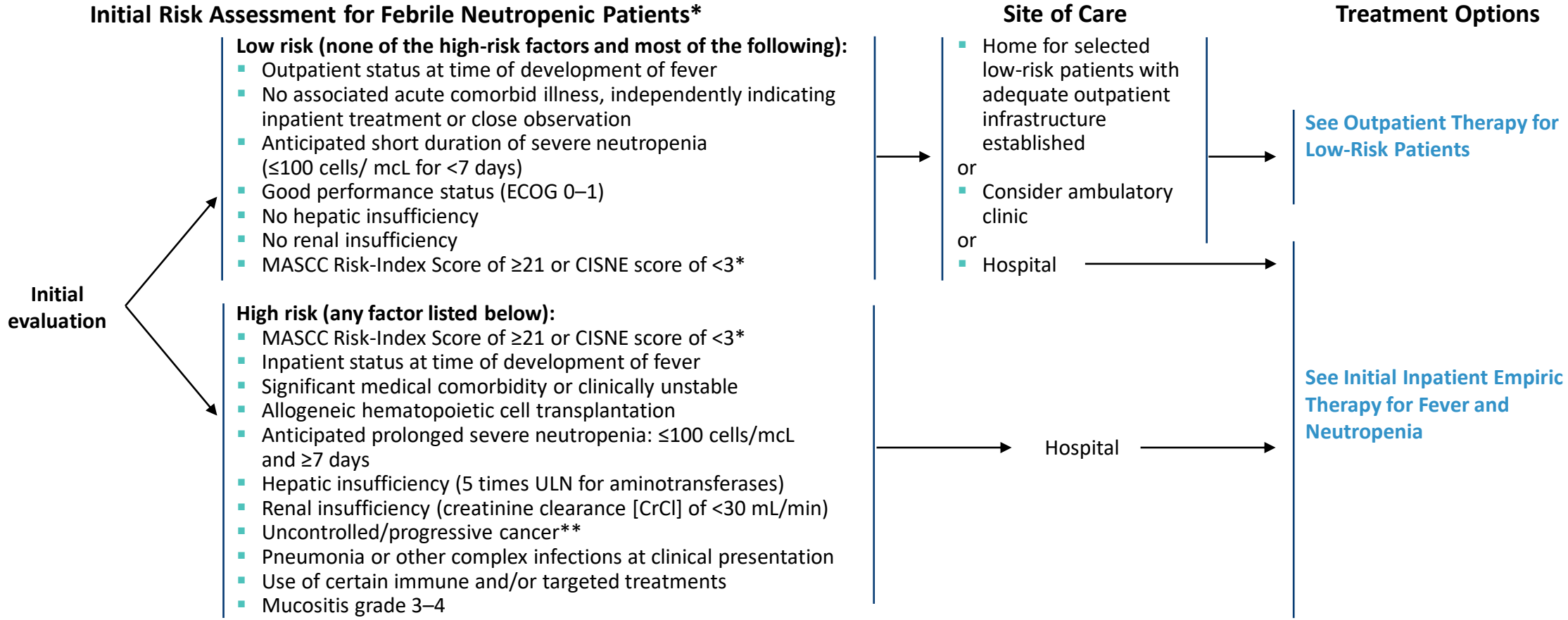
- Blood culture × 2 sets (one set = 2 bottles)
  - One peripheral + one catheter (preferred)
- Urine culture (only if patient has symptoms or abnormal urinalysis; exercise caution in interpreting results if urinary catheter is present)
- Site-specific diagnostics:
  - Diarrhea (*Clostridioides difficile* [*C difficile*] assay, enteric pathogen screen)
  - Skin (aspirate/biopsy of skin lesions or drainage)
- Viral diagnostics:
  - PCR- and/or direct fluorescence antibody (DFA)-based tests for vesicular/ulcerated lesions on skin or mucosa
  - Throat or nasopharynx for respiratory virus symptoms, especially during outbreaks

→ **See initial Risk Assessment**

CBC, complete blood count; H&P, history and physical exam; PCR, polymerase chain reaction.

NCCN. Prevention and Treatment of Cancer-Related Infections (Version 3.2022). Available at: http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

Initial Risk Assessment For Febrile Neutropenic Patients



*Risk categorization refers to risk of serious complications, including mortality, in patients with neutropenic fever. Risk stratification is validated in adults; no generalizable, cross-validated, risk-stratified management exists for pediatric patients with febrile neutropenia. See Risk Assessment Resources (FEV-D); **Uncontrolled/progressive cancer is defined as any patients with leukemia not in compete remission, or patients with other cancers and evidence of disease progression after more than 2 courses of chemotherapy.

ECOG, Eastern Cooperative Oncology Group; CISNE, Clinical Index of Stable Febrile Neutropenia

National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections (Version 3.2022). http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed November 4, 2022.

Management Tools

NCCN Management Tool for irAEs

Interactive Decision Support Tool

NCCN® Managing irAEs Tool

Enter Patient Details

Which organ system if primary affected?

- ◯ Cardiovascular: suspected myocarditis/pericarditis
- ◯ Dermatologic
- ◯ Endocrine
- ◯ Gastrointestinal, hepatic, or pancreatic
- ◯ Musculoskeletal
- ◯ Neurologic or ocular
- ◯ Other: fatigue
- ◯ Other: infusion-related reactions
- ◯ Pulmonary: pneumonitis
- ◯ Renal: elevated serum creatinine/acute kidney injury

SUBMIT (AFTER COMPLETING QUESTIONS ABOVE)

Enter Patient Details

Which organ system if primary affected? Endocrine [Change]

Which endocrine adverse event is the patient experiencing?
Asymptomatic/subclinical hypothyroidism [Change]

Which best describes the asymptomatic/subclinical hypothyroidism?

- ◯ TSH between 4 and <10, patient asymptomatic, normal free T4
- ◯ Elevated TSH (>10), normal free T4
- ◯ Normal or low TSH, low free T4

SUBMIT (AFTER COMPLETING QUESTIONS ABOVE)

Recommendations

- Continue immunotherapy
- Consider endocrine consultation
- Initiate thyroid hormone supplementation with levothyroxine*; repeat TSH in 4-6 weeks to guide dosing changes
- Exclude concomitant adrenal insufficiency (morning cortisol level)

*Levothyroxine oral daily approximately 1.6 mcg/kg with goal of getting TSH to ge or age-appropriate range; reduce dose by 10% to avoid n in patient populations that may be sensitive to thyroid on (eg, older patients or patients with comorbidities). For young s with TSH >10 with low free T4, a full replacement dose is estimated This dose can be reduced 10% or more in older patients, those with disease (CAD) and/or per provider recommendations. Alternatively, s or those with comorbidities, including CAD, starting doses of 50-100 considered with follow-up TSH levels at 4-6 weeks and further dose achieve TSH in reference range. For subclinical hypothyroidism tients or in patients with underlying CAD, TSH >10 with normal free therapy may include the above dosing options, alternatively, as these ntact thyroid function, most often empiric supplemental levothyroxine ximately 50-100 mcg may be considered rather than weight-based

TSH, thyroid-stimulating hormone.

NCCN. CCO - Clinical Care Options. https://www.clinicaloptions.com/oncology/programs/ici-based-therapy/irae-decision-support-tool/idst/page-1

Management of CAR-T Related CRS

CRS Grade	Anti-IL-6 Therapy	Corticosteroids	Additional Supportive Care
Grade 1 Fever (≥38°C)	For prolonged CRS (<3 days) in patients or those with significant symptoms, comorbidities and/or are elderly, consider 1 dose of tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)	For idecabtagene and lisocabtagene, consider dexamethasone 10 mg IV every 24 hours for early-onset CRS (<72 hours after infusion)	• Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat in 8 hours if no improvements; no more than 3 doses in 24 hours, with a maximum of 4 doses total	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Consider dexamethasone 10 mg IV every 12-24 hours depending on product	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, EKG, troponin, and BNP if persistent tachycardia • Manage per Grade 3 if no improvement within 24 hours starting anti-IL-6 therapy • Symptomatic management of organ toxicities
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula, face mask, nonrebreather mask, or Venturi mask	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours. If refractory, management as grade 4	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation)	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours. If refractory, consider 3 doses of methylprednisolone 1000 mg/day IV; if refractory, consider dosing every 12 hours	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

BNP, brain natriuretic peptide; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; EKG, electrocardiogram; ICU, intensive care unit; IV, intravenous.

NCCN. Management of CAR T-cell-related toxicities (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Management of ICANS

Neurotoxity 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 stimuli to arose. 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 (>5 min); 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

ICE, Immune Effector Cell-Associated Encephalopathy (ICE) score; ICP, increased intracranial pressure

*Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted; **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); ****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(4):625-638; National Comprehensive Cancer Network. Management of CAR T-cell-related toxicities (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed October 13, 2022.

Management Approach to ICANS

CAR T-CELL-RELATED NEUROTOXICITY TREATMENT

Assessment and Supportive Care Recommendations (all grades)

- Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness
- MRI of the brain with and without contrast (or brain CT if MRI is not feasible) for ≥ grade 2 neurotoxicity
- Neurology consultation at first sign of neurotoxicity
- Conduct electroencephalogram (EEG) for seizure activity for grade ≥2 neurotoxicity
- Aspiration precautions; IV hydration
- Use caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment)

Treatment by Grade	No Concurrent CRS[x]	Additional Therapy if Concurrent CRS
Grade 1[v]	• Supportive care	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose)[aa,†]
Grade 2	• Supportive care • 1 dose of dexamethasone 10 mg IV and reassess. Can repeat every 6–12 hours, if no improvement	Anti-IL-6 therapy as per Grade 1[aa] Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS
Grade 3[w]	• ICU care is recommended • Dexamethasone 10 mg IV every 6 hours or methylprednisolone, 1 mg/kg IV every 12 hours[k,y] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity	Anti-IL-6 therapy as per Grade 1[aa]
Grade 4[w]	• ICU care, consider mechanical ventilation for airway protection • High-dose corticosteroids[k,z] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity	Anti-IL-6 therapy as per Grade 1[aa]

[†]Under conditions of limited tocilizumab availability, consider one of the following conservation strategies:

- Limit tocilizumab use to a maximum of 2 doses during a CRS episode
- Consider using steroids more aggressively during a CRS episode
- If necessary, consider replacing second dose of tocilizumab with siltuximab or anakinra, although there is very limited evidence to support this approach.

[k]Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

[v]For lisocabtagene maraleucel or idecabtagene vicleucel, if ICANS develops <72 hours after infusion, consider dexamethasone 10 mg IV every 12-24 hours ×2 doses and reassess.

[w]Patients should undergo assessment for papilledema or other signs of elevated intracranial pressure. If intracranial pressure is excluded, a diagnostic lumbar puncture may be considered for patients with grade 3-4 neurotoxicity.

[x]If dexamethasone is used for prophylaxis of CRS, there may be an increased risk of grade 4 and prolonged neurologic toxicities.

[y]For axicabtagene ciloleucel or brexucabtagene autoleucel, methylprednisolone 1 g daily for 3-5 days may be preferable.

[z]For example, methylprednisolone IV 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.

[aa]Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

CT, computed tomography; MRI, magnetic resonance imaging.

NCCN. Management of CAR T-cell-related toxicities (Version 1.2022). Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf . Accessed October 13, 2022.

Management of ILD and Pneumonitis

For Asymptomatic ILD (Grade 1)	For Symptomatic ILD (Grade 2 or greater)
• Consider corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent) • Interrupt trastuzumab deruxtecan until resolved to Grade 0, then: – If resolved in 28 days or less from date of onset, maintain dose – If resolved in greater than 28 days from date of onset, reduce dose one level	• Promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) – Continue for at least 14 days followed by gradual taper for at least 4 weeks • Permanently discontinue trastuzumab deruxtecan in patients who are diagnosed with any symptomatic ILD/pneumonitis

Any Grade ILD or Pneumonitis with Trastuzumab Emtansine	Permanently Discontinue

ILD and Pneumonitis | ENHERTU® (fam-trastuzumab deruxtecan-nxki). www.enhertuhcp.com. Accessed October 17, 2022. https://www.enhertuhcp.com/en/her2-low-breast/manage-potential-risks/ild-and-pneumonitis
Kadcyla. Package insert. Genetech; 2022.

Management of Tumor Lysis Syndrome (TLS)

- All patients:
  - Allopurinol 300 mg daily
  - Strict ins and outs
  - IV isotonic fluids at 100-200 mL/hr with target 2L urine output per day
  - Monitor on telemetry
  - Check TLS labs (BMP, phosphorous, uric acid):
    - Low risk patients – every 12 hours
    - High risk patients – every 6-8 hours
  - If high risk and/or uric acid >8, then give rasburicase
  - Only treat SYMPTOMATIC hypocalcemia

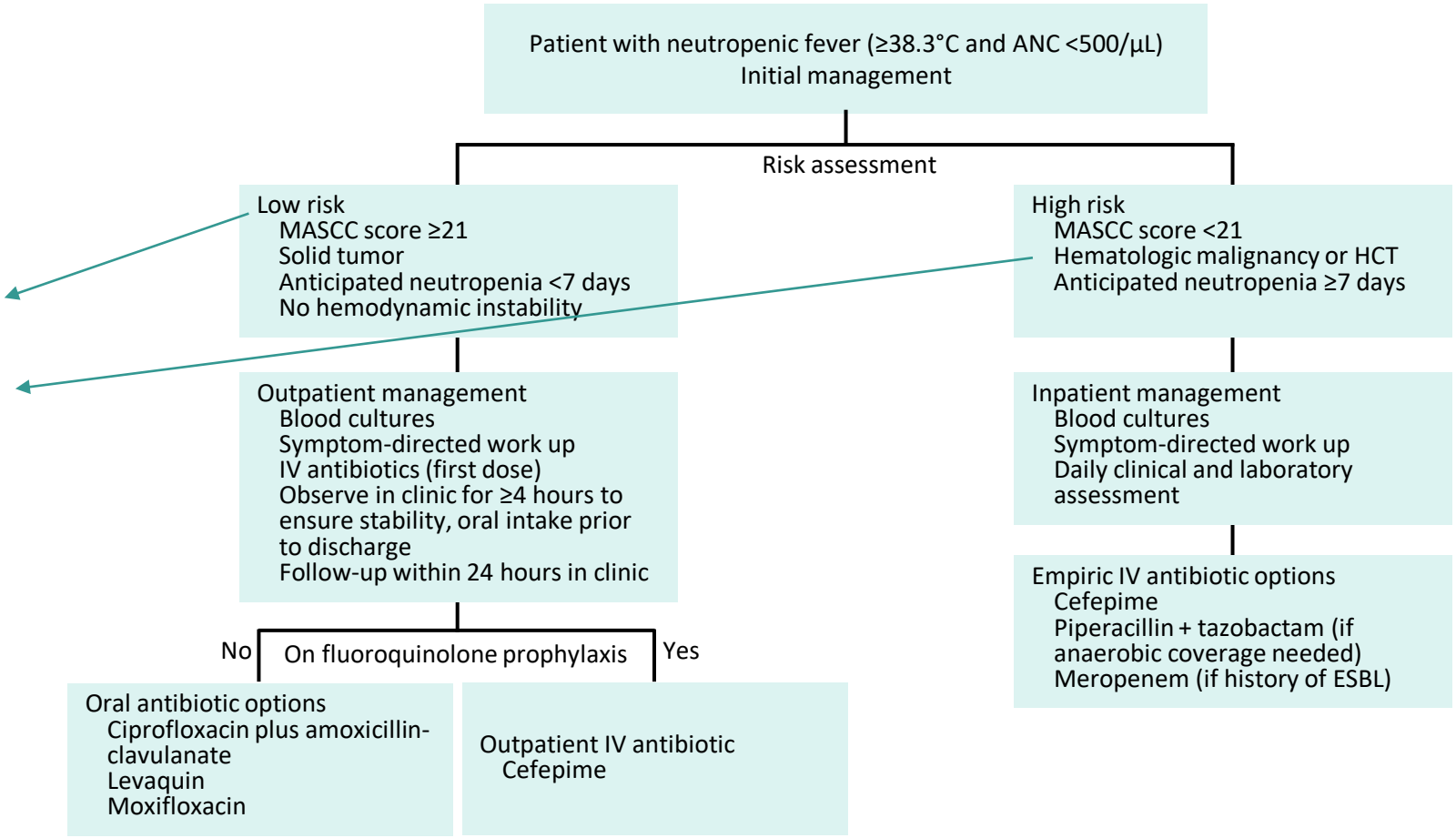
BMP, basic metabolic panel.

Howard SC, et al. *N Engl J Med.* 2011:364(19):1844-1854.

Management of Neutropenic Fever in Patients With Cancer

MASCC Risk-Index Score/Model

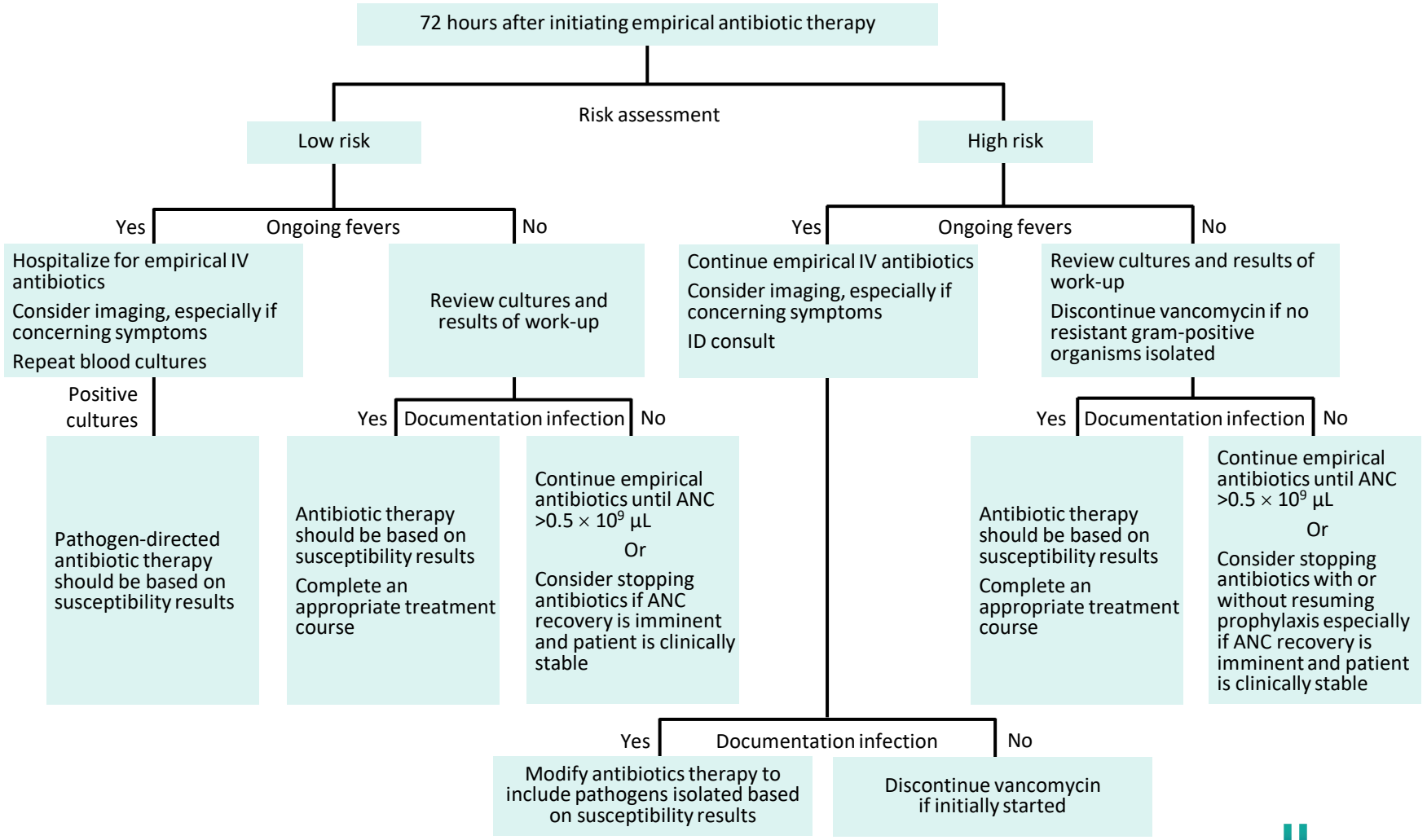
Characteristic	Weight
• Burden of illness	
– No or mild symptoms	5
– Moderate symptoms	3
• No hypotension	5
• No COPD	4
• Solid tumor or hematologic malignancy with no previous fungal infection	4
• No dehydration	3
• Outpatient status	3
• Age <60 years	2



COPD, chronic obstructive pulmonary disease; ESBL, extended spectrum beta-lactamase; ANC, absolute neutrophil count.

Zimmer A, et al. *J Oncol Pract.* 2019;15(1):19-24.

Management of Neutropenic Fever in Patients with Cancer



ID, infectious disease.

Zimmer A, et al. *J Oncol Pract.* 2019;15(1):19-24.

Case #1 – Tom

Tom is a 67-year-old male patient with non-small cell lung cancer on pembrolizumab (first treatment 6 months ago, last treatment 2 weeks ago) who presents with 4 days of watery diarrhea. He is now having 9-10 loose stools per day and has significantly decreased his oral intake without improvement in his diarrhea.

- Labs:
  - WBC of 15 with left shift
  - Creatinine 1.9 (baseline 0.8)
  - K = 3.1
  - HCO3 = 19
  - Cl = 110

Cl, chloride; HCO3, bicarbonate; K, potassium; WBC, white blood cell.

Case # 1 Question

What is the best next step in the management of this patient?

A. Start loperamide 2 mg after each loose stool, maximum 16 mg over 24 hours
B. Check bacterial stool culture and start piperacillin-tazobactam
C. Check stool ova & parasites (O&P) and start empiric ivermectin
D. **Check *C difficile* stool PCR and consult GI for endoscopy**

Case #1 Continued – Tom

- *C difficile* PCR is negative
- GI is consulted but unable to perform colonoscopy for 2 days due to weekend

Case # 1 Question

What is the next best step in management?

A. **Start IV methylprednisolone 1 mg/kg daily**
B. Start loperamide while awaiting the results of the endoscopy
C. Obtain a CT of the abdomen and pelvis
D. Start IV piperacillin-tazobactam

NCCN Management Tool for Colitis

Enter Patient Details

Which organ system if primary affected?

- ◯ Cardiovascular: suspected myocarditis/pericarditis
- ◯ Dermatologic
- ◯ Endocrine
- ● Gastrointestinal, hepatic, or pancreatic
- ◯ Musculoskeletal
- ◯ Neurologic or ocular
- ◯ Other: fatigue
- ◯ Other: infusion-related reactions
- ◯ Pulmonary: pneumonitis
- ◯ Renal: elevated serum creatinine/acute kidney injury

Which gastrointestinal, hepatic, or pancreatic adverse event is the patient experiencing?

- ◯ Diarrhea or colitis
- ◯ Elevated transaminitis
- ◯ Grade >1 transaminitis with elevated bilirubin (unless Gilbert syndrome)
- ◯ Elevation in amylase/lipase (asymptomatic)
- ◯ Acute pancreatitis

Interactive Decision Support Tool

NCCN® Managing irAEs Tool

Enter Patient Details

Which organ system if primary affected?
Gastrointestinal hepatic, or pancreatic [Change]

Which gastrointestinal, hepatic, or pancreatic adverse event is the patient experiencing? Diarrhea or colitis [Change]

What grade is the diarrhea or colitis?

- ◯ Mild (grade 1)
- ◯ Moderate (grade 2)
- ◯ Severe (grade 3/4)

SUBMIT (AFTER COMPLETING QUESTIONS ABOVE)

Recommendations

- Grade 3: Discontinue anti–CTLA-4; consider resuming anti–PD-1/PD-L1 after resolution of toxicity
- Grade 4: Permanently discontinue immunotherapy agent responsible for toxicity
- Consider inpatient care for provision of support care
- IV methylprednisolone (1-2 mg/kg/day); if no response in 1-2 days, continue steroids, strongly consider adding infliximab or vedolizumab

NCCN. CCO - Clinical Care Options. https://www.clinicaloptions.com/oncology/programs/ici-based-therapy/irae-decision-support-tool/idst/page-1

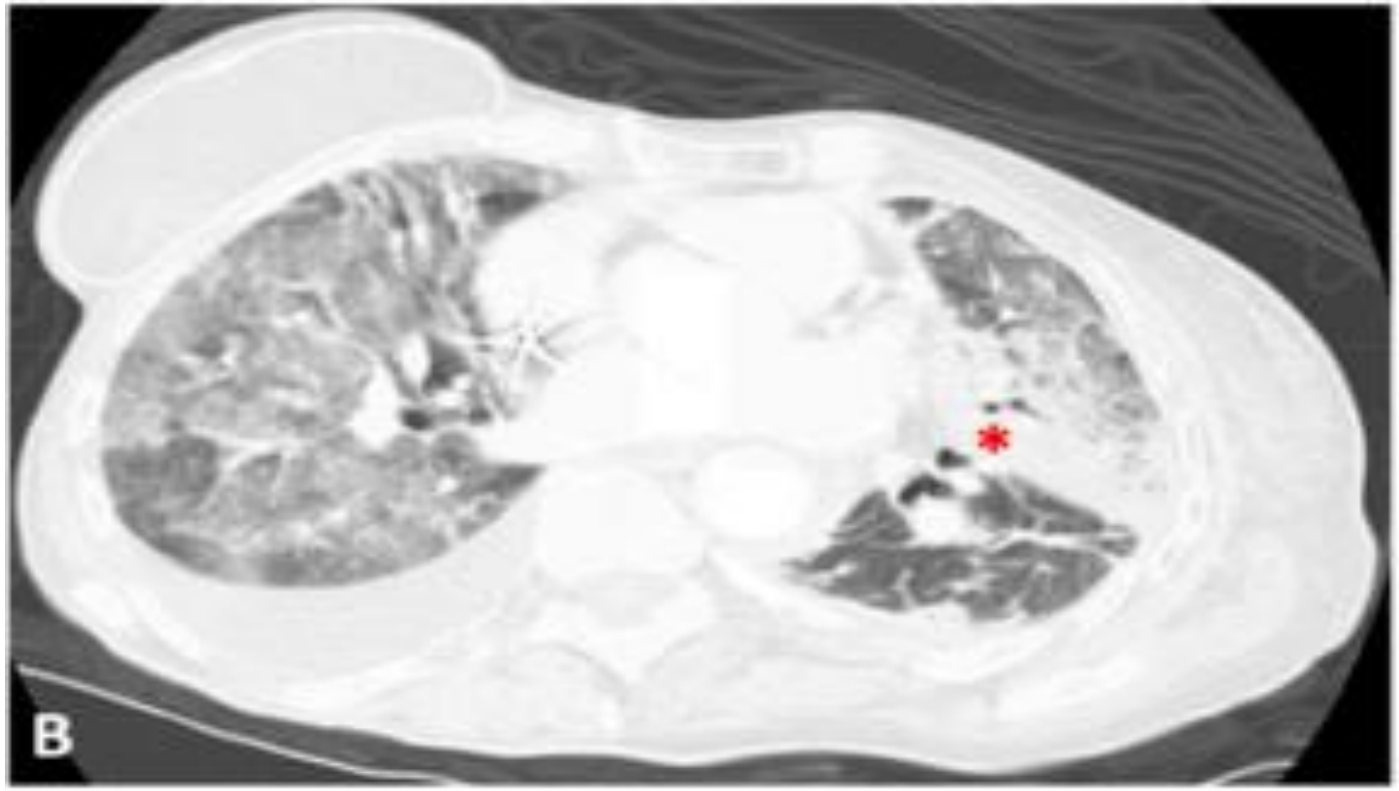
Case #2 - Sarah

Sarah is a 48-year-old female with a history of metastatic HER2-positive breast cancer who presents with a 1-week history of progressive shortness of breath on exertion and a dry cough. She is currently receiving trastuzumab deruxtecan under the care of her oncologist; her last dose was 2 weeks ago.

- Exam: SaO_2 93% on 4L, RR 28, bibasilar inspiratory crackles on exam
- Labs: WBC 19 with left shift, normal creatinine, normal NT-BNP

SaO2, oxygen saturation; NT-BNP, N-terminal b-type natriuretic peptide; RR, respiration rate.

Case #2: CT Scan



Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378.

Case # 2 Question

What is the best next step in the management of this patient?

A. Order an echocardiogram and start IV furosemide
B. Order blood and sputum cultures and start empiric levofloxacin
C. Consult pulmonary for bronchoscopy with bronchioalveolar lavage and start posaconazole
D. **Start IV methylprednisolone 1 g daily**

Case #3 - John

John is a 52-year-old male with relapsed diffuse large B-cell lymphoma who was admitted to your hospital for infusion of axicabtagene ciloleucel.

On day 4 after receiving his CAR-T cells, he develops fever to 102° and a decrease in blood pressure to 92/52.

Case #3 Question

What is the next best step in management?

A. **Draw blood cultures, obtain a CXR, and start empiric cefepime and vancomycin and IV fluid bolus**
B. Start methylprednisolone 1 g daily
C. Order IV tocilizumab 8 mg/kg × 1
D. Start anakinra 100 mg x 1

John: Case Continued....

You administer a fluid bolus and start empiric broad-spectrum antibiotics. His blood pressure does not response to 2L of IV lactated Ringer's and decreases to 84/54. His lactic acid is 4 mmol/L.

Case #3 Question

What is the next best step in management?

A. Add ambisome to his antimicrobial regimen
B. Start methylprednisolone 1 g daily
C. **Order IV tocilizumab 8 mg/kg × 1**
D. Start vasopressors and continue the same antibiotics

Summary and Discussion

- ICI-related adverse events are different than those of traditional chemotherapy
  - Can present in ANY organ system and require recognition of the agent received and a high index of suspicion to ensure early and appropriate therapy
  - Usually occur within months of initiation of therapy
  - NCCN guidelines can help to guide assessment and initial management
- ADCs are a form of chemotherapy and their toxicities are dependent on the drug that is linked to them
- Cellular therapies include CAR-T cells and BITEs and can cause CRS and ICANS

Clinical Pearls

- Ask your cancer patients what therapies they are receiving and look them up
  - If they are receiving ICIs, consider:
    - CT chest for shortness of breath or dry cough
    - Do not ignore elevated AST/ALT
    - irAEs can involve ANY organ system and may be the cause of an unexplained presentation, especially if patient is not responding to usual standard of care
  - Fluids and close lab monitoring are critical in prevention and management of TLS
  - Not every patient with neutropenic fever needs vancomycin empirically
  - When in doubt, call the oncologist on call or the treating oncologist
    - Know patient's malignancy, therapy, and date of last treatment

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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Thank you!

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