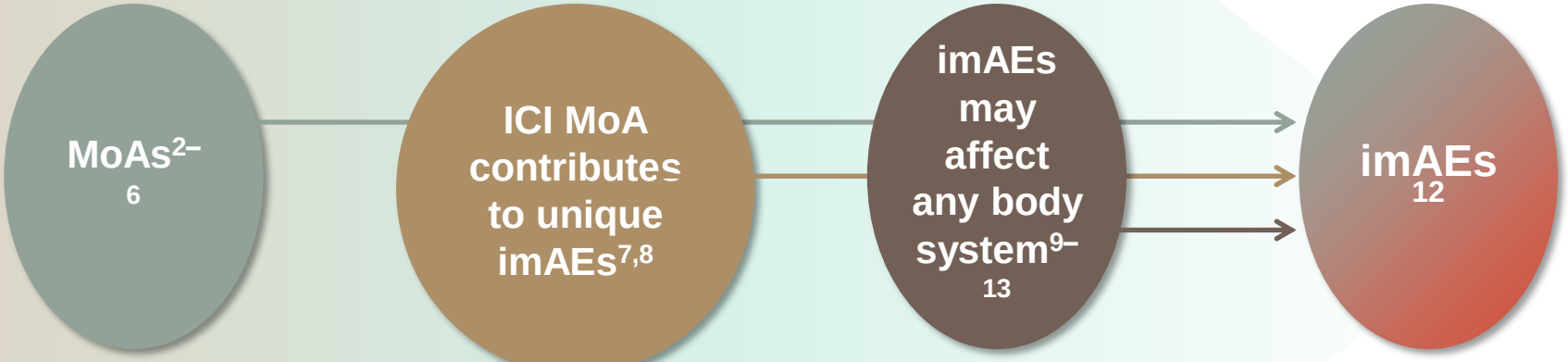
MANAGING TOXICITIES OF IMMUNOTHERAPY – TIPS AND TRICKS

DR RIDU KUMAR
MBBS, MD, DM Medical Oncology
Bone Marrow Transplant Specialist
Consultant Medical Oncology
MAGADH CANCER CENTRE , Patna

- ICIs have a unique set of immune-related adverse events (IRAEs), which differ from standard chemotherapy toxicities due to their **immune-based origin**
- The exact pathophysiology underlying the occurrence of IRAEs is not clear.
- They are believed to be associated with the role that immune checkpoints play in maintaining immunologic homeostasis.
- **Disinhibition of T-cell function** by ICIs may lead to IRAEs.

Immune-mediated Adverse Events and Immune Checkpoint Blockade

Immune-mediated adverse events (imAEs) associated with immune checkpoint blockade are multifocal in development and presentation.[1]



Unique MoAs may lead to differing toxicity profiles associated with chemotherapy, targeted therapies, and ICIs.

ICIs act on the immune system and may facilitate immune function.

However, facilitating immune function can also reduce self tolerance outside the tumor, which may lead to imAEs affecting other body systems and possibly being fatal.

imAEs may occur at any time during treatment and may persist long after cessation of treatment.

1. Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-related Toxicities V.4.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed 24 January 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. **2.** National Cancer Institute. Chemotherapy to Treat Cancer. cancer.gov/about-cancer/treatment/types/chemotherapy. Accessed 24 January 2022. **3.** National Cancer Institute. Targeted Therapy to Treat Cancer. cancer.gov/about-cancer/treatment/types/targeted-therapies. Accessed 24 January 2022. **4.** Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264. **5.** Eigentler TK et al. *Cancer Treat Rev*. 2016;45:7–18. **6.** Boutros C et al. *Nat Rev Clin Oncol*. 2016;13(8):473–486. **7.** Day D, Hansen AR. *BioDrugs*. 2016;30(6):571–584. **8.** Chen DS, Mellman I. *Immunity*. 2013;39(1):1–10. **9.** Ribas A. *N Engl J Med*. 2012;366(26):2517–2519. **10.** Champiat S et al. *Ann Oncol*. 2016;27(4):559–574. **11.** Daniels GA et al. *Emerg Med J*. 2019;36(6):369–377. **12.** Brahmer JR et al. *J Immunother Cancer*. 2021;9(6):e002435. **13.** Haanen JBAG et al. *Ann Oncol*. 2017;28(Suppl 4):iv119–iv142.

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

IO therapy differs from conventional anticancer treatments.

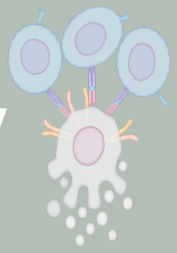
Chemotherapy[1]

- Acts on **rapidly dividing cells**, including tumor cells and some normal cells
- Prevents or slows cell growth and division

Targeted Therapy[2]

- Targets **proteins** that regulate cell growth, division, and spread

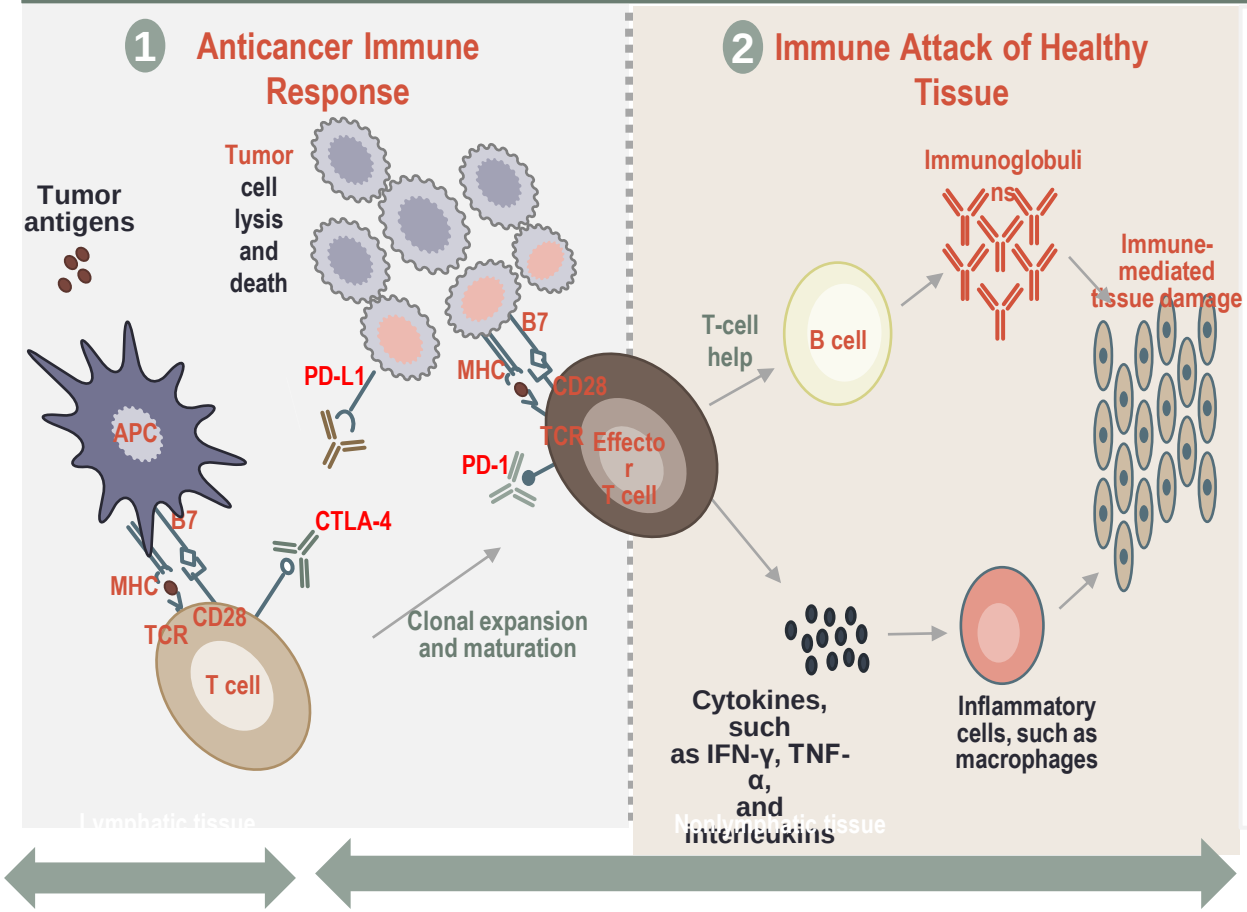
IO Therapy



- 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 Blockade and imAEs

imAEs may occur when T cells attack healthy cells as a result of immune checkpoint blockade.[1]



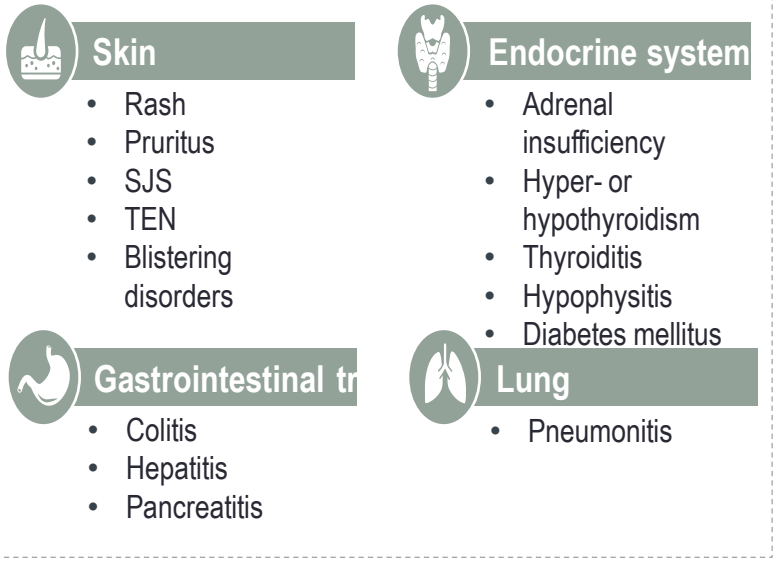
1. Blockade of immune checkpoint pathways may release the inhibition of the immune system and reactivate the anticancer immune response.

2. This activation can also reduce self tolerance outside the tumor, which may lead to an immune attack on normal organ and tissue function (ie, imAEs)

Immune-mediated Adverse Events (imAEs)

imAEs are a unique spectrum of toxicities associated with ICIs and can affect virtually any organ system.[1]

- Overall, imAEs affecting the skin, endocrine system, GI tract, and lungs are most commonly encountered.[2]
- More rarely, neurologic, ocular, cardiovascular, hematologic, and renal imAEs can occur.[2]



Incidence and Severity of imAEs

Frequency and timing of imAEs differ between ICIs, dosing schedule and regimen, and cancer type.[1]

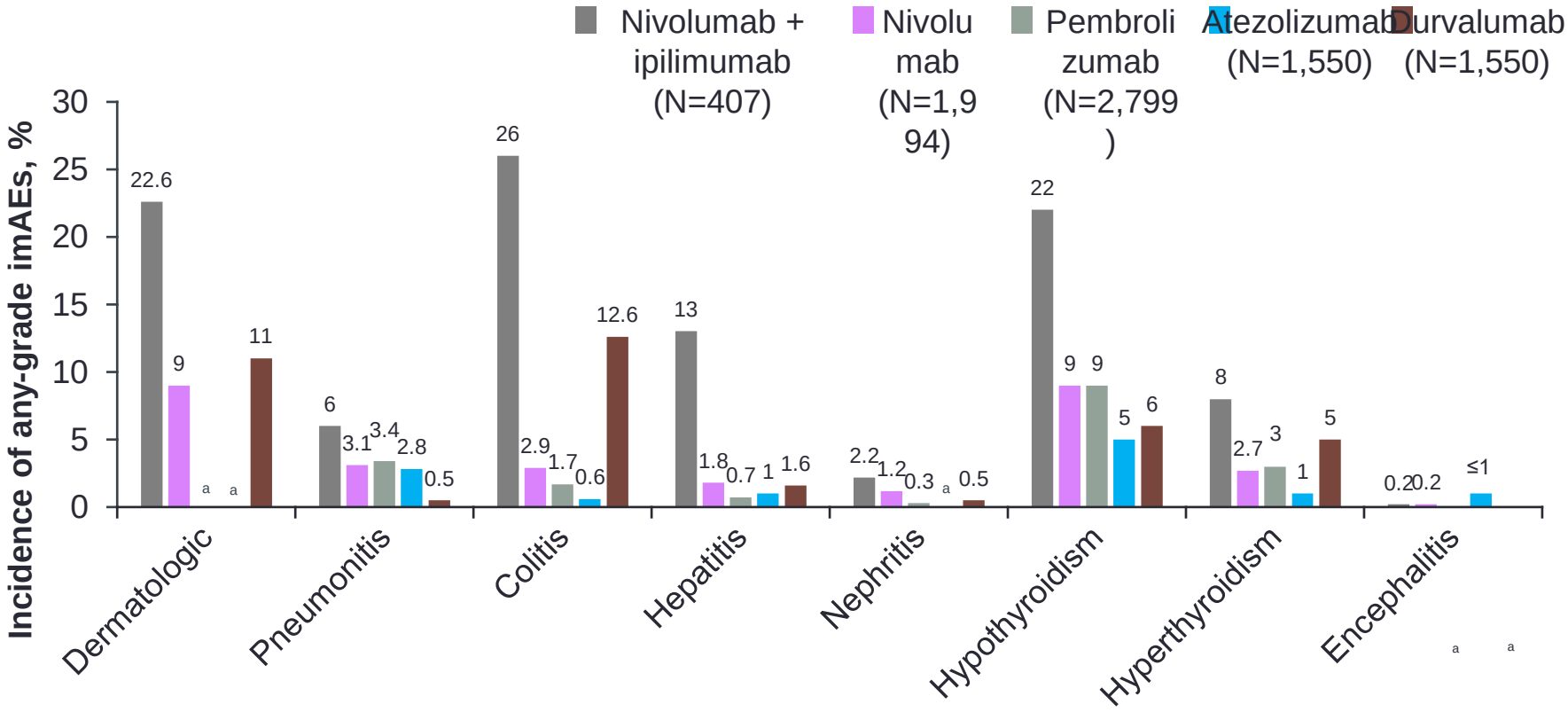
- PD-1/PD-L1 inhibitors may be associated with lower overall incidence of imAEs and lower incidence of Grade ≥3 imAEs compared with CTLA-4 inhibitors.[2]
- Combination therapy with 2 ICIs is associated with both earlier imAE onset and higher levels of immune-mediated toxicity than either one alone.[1,2]

Most imAEs are reversible and manageable but have the potential for life-threatening or fatal outcomes.[3]

- Because less-common toxicities may be life threatening and initial presentation may be mild, with nonspecific symptoms, prompt diagnosis and treatment are required.[1]
- Risk of fatal AEs associated with therapy may be lower with ICIs (estimated incidence, 0.3%–1.3%) than with conventional treatments.[2]

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.[1]

Incidence of Select Any-grade imAEs for Specific ICIs and Combination Therapy



[a]Data not available.

Daniels GA et al. *Emerg Med J*. 2019;36(6):369–377.

Onset and Duration of imAEs

imAEs may occur at any time during treatment.[1]

- 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.

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.

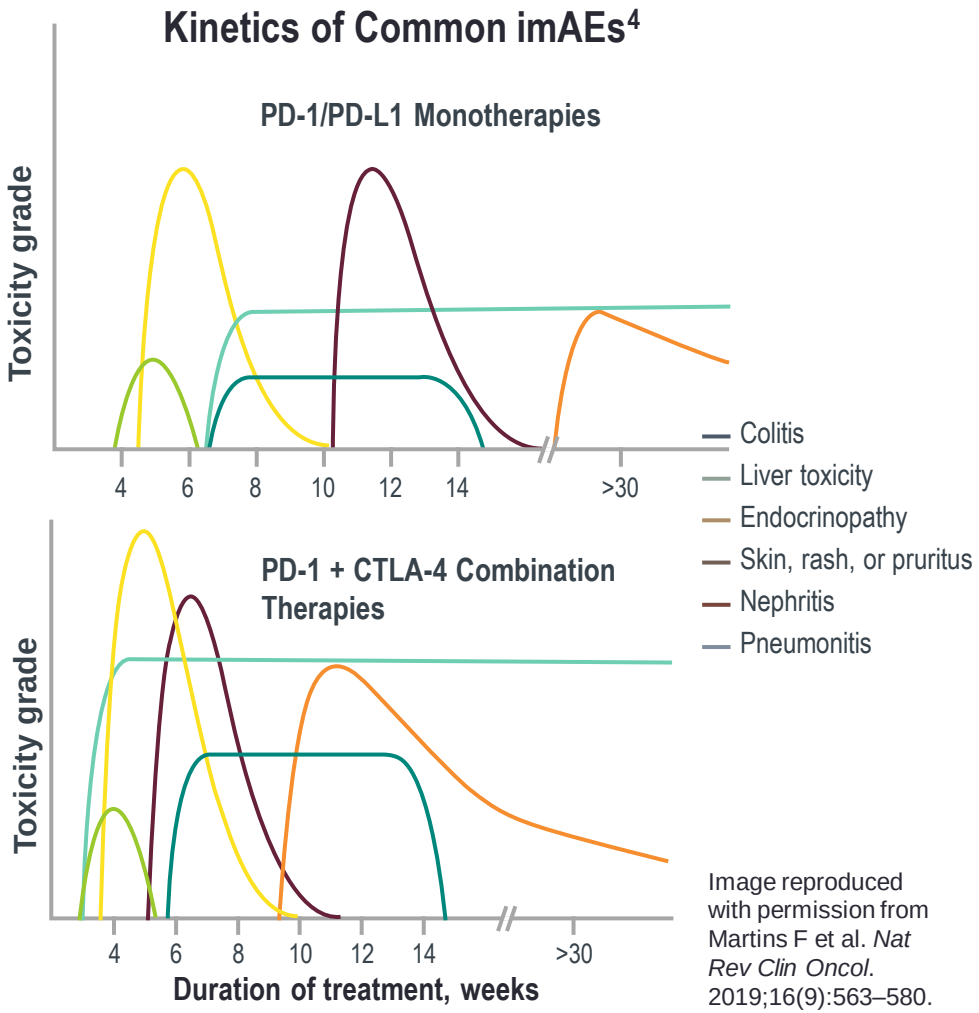


Image reproduced with permission from Martins F et al. *Nat Rev Clin Oncol*. 2019;16(9):563–580.

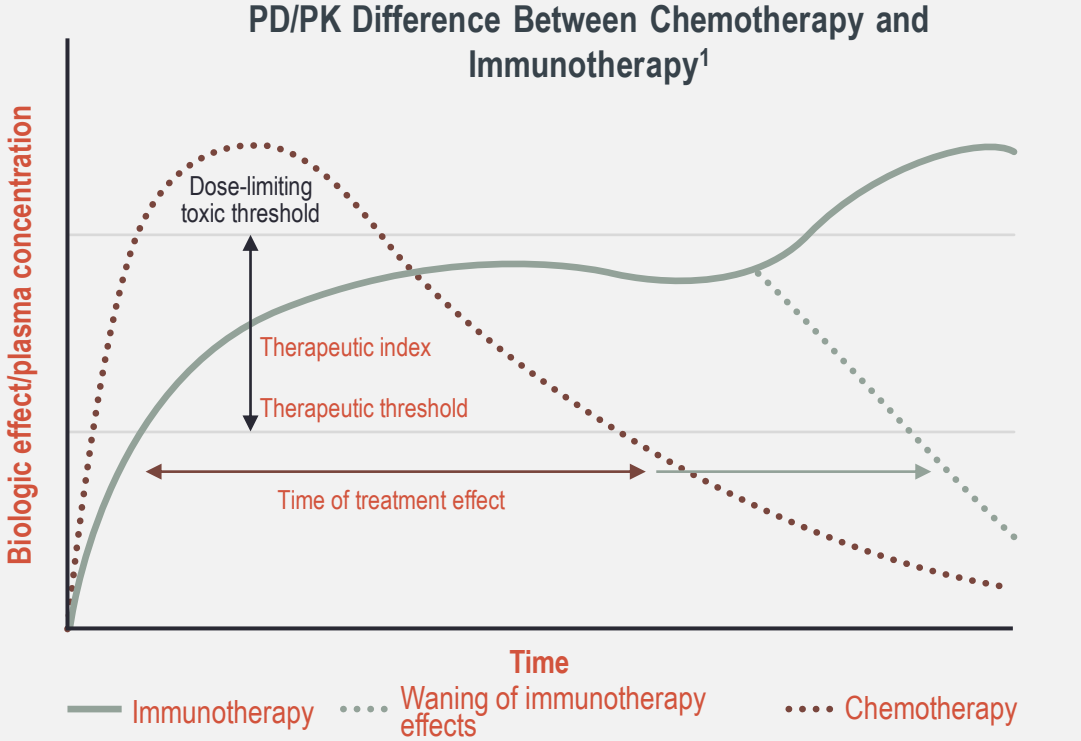
ICI Exposure and imAEs

imAEs from immunotherapy can have a delayed onset and prolonged duration, in part due to PK/PD differences in comparison with chemotherapy.[1]

- Moreover, the relationship between imAEs and dose/exposure remains to be fully established.

imAE risk can vary with ICI dose.

- imAE risk appears to be dose independent with PD-1 inhibitors.[2]
- Risk appears to be dose dependent with CTLA-4 inhibitors.[3]



Reproduced from Puzanov et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *Journal for ImmunoTherapy of Cancer* 2017. Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Before Beginning Therapy

IRAE management

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

Before Beginning Therapy With ICIs: Patient Counseling Recommendations

Prior to starting immunotherapy:

Assess patients':

- Understanding of disease and recommendations for treatment
- Ability to monitor and report potential irAEs. Engagement of caregiver may be necessary
- Need for home care support service during therapy

Document:

- All underlying medical conditions affecting any organ system (eg, pulmonary, cardiac, neurologic, musculoskeletal)
- History of any autoimmune diseases
- All medications, including over-the-counter medications and herbal supplements

Advise patients:

- Of reproductive age to use effective birth control during and for at least 5 months after the final dose of immunotherapy[a]
- That breastfeeding is contraindicated during and for at least 5 months after the final dose of immunotherapy

Educate patients about:

- The mechanism of action and rationale for use of ICIs
- The potential toxicity profile of ICI therapy, including presenting symptoms and timing
- Existing educational resources

Provide patients:

- With and instruct them to carry a wallet card that outlines the type of immunotherapy they are receiving, potential irAEs, and contact numbers for their oncology health care team

Instruct patients to notify the oncology health care team if:

Any new signs or symptoms develop, including severe fatigue, headache, rash, cough, shortness of breath, chest pain, abdominal bloating, change in bowel pattern, weight loss, vision changes or eye pain, severe muscle weakness, severe muscle or joint pains, and/or mood changes

They are evaluated by other HCPs or admitted to the hospital

Any new medications are prescribed or prior to receiving any **immunizations or vaccinations**

- Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. Because of the lack of clarity regarding live vaccine use, it is not recommended during ICI therapy

irAEs can occur after completion of therapy. Patients should monitor symptoms for at least 2 years following the conclusion of immunotherapy

Before Beginning Therapy With ICIs: Pre-therapy Assessments (1 of 2)

Pretherapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings or Symptoms
Clinical • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening (HIV; hepatitis A, B, C) as indicated	Clinical examination at each visit with 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 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

Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data become available.

Before Beginning Therapy With ICIs: Pre-therapy Assessments (2 of 2)

Pretherapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings or Symptoms
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
Pancreatic • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis
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

Monitoring and Identifying imAEs

Recognizing Signs and Symptoms of 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,

Infusion-related Reactions Signs and Symptoms

Infusion (IV) Reactions Symptoms	
Fever, chills, rigors	Shortness of breath
Urticaria, pruritus	Cough, wheezing
Angioedema	Hypoxemia
Flushing, headache	Dizziness, syncope
Hypertension	Sweating
Hypotension	Arthralgia, myalgia

TREATMENT

- Temporary Immunosuppression with oral corticoids, high dose steroid therapy (oral prednisolone 1–2 mg/kg/day or IV equivalent),

or additional immunosuppressants in more severe cases

- For steroid-refractory cases, including patients with severe IRAEs that are not responsive to steroids within 48–72 h, early initiation of additional immunosuppressants or plasmapheresis can be considered with close guidance from a disease-specific subspecialist

Immunomodulatory Agents

- Tumor Necrosis Factor Inhibitors (TNFI) (infliximab)
- Mycophenolate Mofetil (MMF)
- Antithymocyte Globulin (ATG)
- Calcineurin Inhibitors
- Methotrexate
- intravenous gammaglobulin (IVIG)
- CD20 Mab- Rituximab ,obinutuzumab
- Anti-IL6 - tocilizumab

- **Grade 1 IRAEs** - ICI treatment can be continued with close monitoring (with the exception of some neurologic, hematologic and cardiac toxicities)
- **Grade 2** IRAEs- steroid treatment with 0.5–1 mg/kg prednisone/equivalent is recommended and ICI therapy should be held until toxicity resolves to Grade ≤ 1.
- **Grade 3** IRAEs- ICI treatment should be held, and dose adjustment is not recommended. Cautious retreatment with ICIs can be considered when IRAEs revert to Grade ≤ 1. Patients should be treated with high dose steroids (oral prednisolone 1–2 mg/kg/day or IV equivalent) until resolution to ≤ Grade 1, at which point steroid treatment should taper slowly over 4–6 weeks.
- If there is no improvement with steroids in 1–3 days, other immunosuppressant and immunomodulatory agents can be considered.
- All patients who experience **GRADE 4 IRAES** should permanently discontinue ICI therapy, with the exception of patients with grade 4 endocrinopathies controlled by hormone replacement.

THANK YOU

Glossary: Before Beginning Therapy

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AE	Adverse event
BAL	Bronchoalveolar lavage
BSA	Body surface area
CBC	Complete blood count
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CRP	C-reactive protein
CT	Computed tomography
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
FSH	Follicle-stimulating hormone
HbA1c	Hemoglobin A1c

Abbreviation	Definition
HCP	Health care provider
HIV	Human immunodeficiency virus
ICI	Immune checkpoint inhibitor
imAE	Immune-mediated adverse event
irAE	Immune-related adverse event
LH	Luteinizing hormone
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network® (NCCN®)
PFT	Pulmonary function test
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid-stimulating hormone

Glossary: General Considerations

Abbreviation	Definition
AE	Adverse event
APC	Antigen-presenting cell
CTLA-4	Cytotoxic T-lymphocyte–associated protein 4
GCA	Giant cell arteritis
GI	Gastrointestinal
ICI	Immune checkpoint inhibitor
IFN-γ	Interferon gamma
imAE	Immune-mediated adverse event
IO	Immuno-oncology
MHC	Major histocompatibility complex

Abbreviation	Definition
MoA	Mechanism of action
NCCN	National Comprehensive Cancer Network® (NCCN®)
PD	Pharmacodynamic
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PK	Pharmacokinetic
SJS	Stevens–Johnson syndrome
TCR	T-cell receptor
TEN	Toxic epidermal necrolysis
TNF-α	Tumor necrosis factor alpha