# Monitoring and Managing Toxicities Associated with Immune-Checkpoint Inhibitors

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# Disclosure

## Speaker for Bristol Myers Squibb

# Learning Objectives

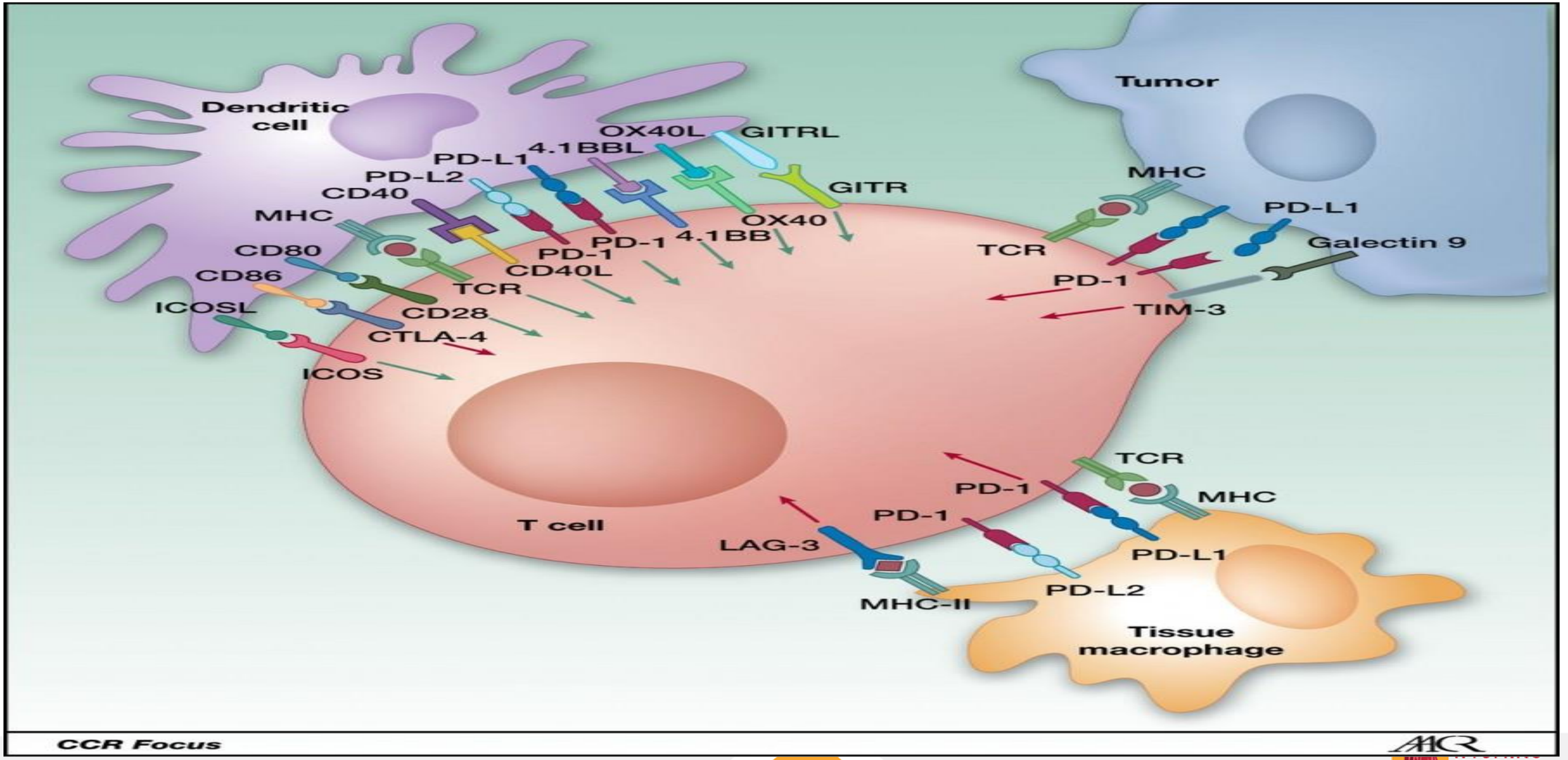
1. Review the current FDA-Approved for Immune Checkpoint Inhibitors (ICI) therapy in Oncology & Mechanism of Action

1. Discuss Principles/Process & Grading of Immune-Mediated Adverse Reactions/(IMARS)/ Immune-Mediated Adverse Events, (irAE's) with emphasis on Early Recognition

3. Implement Prompt Evidence-Based Interventions to Treat IMARS/irAE's

4. Discuss Principles of Patient Education and Supportive Patient Care Interventions to minimize Morbidity and Mortality

# Mechanism of Action of Immunotherapies



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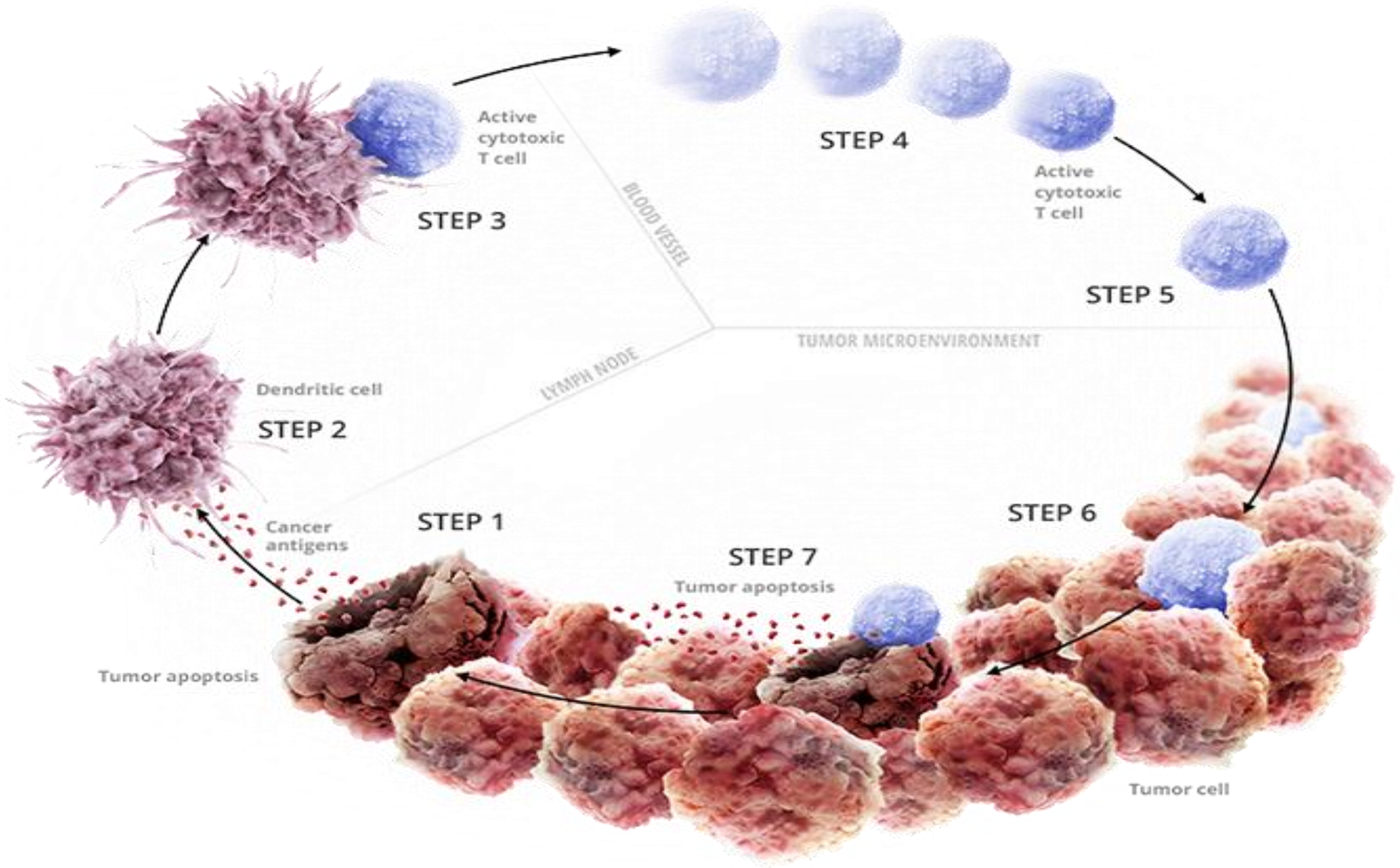


## STEPS 1-3: INITIATING AND PROPAGATING ANTICANCER IMMUNITY[1]

- Oncogenesis leads to the expression of neoantigens that can be captured by dendritic cells
- Dendritic cells can present antigens to T cells, priming and activating cytotoxic T cells to attack the cancer cells

## STEPS 4-5: ACCESSING THE TUMOR[1]

- Activated T cells travel to the tumor and infiltrate the tumor microenvironment

## STEPS 6-7: CANCER-CELL RECOGNITION AND INITIATION OF CYTOTOXICITY[1]

- Activated T cells can recognize and kill target cancer cells
- Dying cancer cells release additional cancer antigens, propagating the cancer immunity cycle

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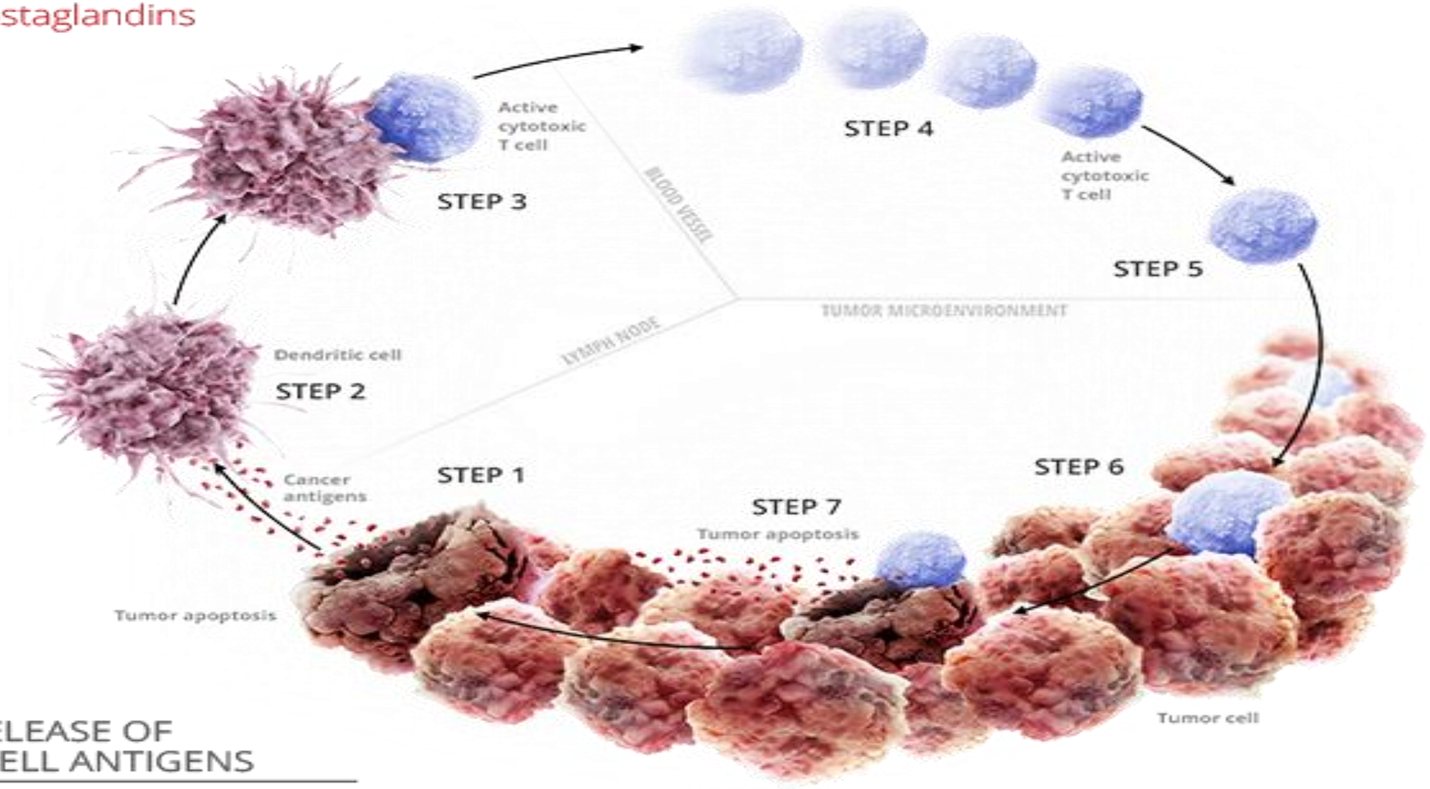
# Mechanism of Action of Immunotherapies

**STEP 3:** PRIMING AND ACTIVATION

- CD28/B7.1
- CD137/CD137L
- **OX40/OX40L***
- **CD27/CD70***
- HVEM
- GITR
- **IL-2***
- IL-12
- CTLA4/B7.1
- **PD-L1/B7.1***
- **PD-L1/PD-1***
- Prostaglandins

**STEP 4:** TRAFFICKING OF T CELLS TO TUMORS

- CX3CL1
- CXCL9
- CXCL10
- CCL5




**STEP 5:** INFILTRATION OF T CELLS INTO TUMORS

- LFA1/ICAM1
- Selectins
- **VEGF***
- Endothelin B receptor

**STEP 2:** CANCER ANTIGEN PRESENTATION

- TNFα
- IL-1
- IFNα
- **CD40L/CD40***
- CDN
- ATP
- HMGB1
- TLR
- IL-10
- IL-4
- IL-13

**STEP 6:** RECOGNITION OF CANCER CELLS BY T CELLS

- **T-cell receptor***
- Reduced pMHC on cancer cells

**STEP 1:** RELEASE OF CANCER CELL ANTIGENS

- Immunogenic cell death
- Tolergenic cell death

**STEP 7:** KILLING OF CANCER CELLS

- IFNγ
- T-cell granule content
- **PD-L1/B7.1***
- **PD-L1/PD-1***
- **IDO***
- TGFβ
- BTLA
- TIM-3/phospholipids
- LAG-3
- Arginase
- MICA-MICB
- B7-H4
- VISTA

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# Current List of FDA-Approved Immune Checkpoint Inhibitors

1.**Atezolizumab (TECENTRIQ)-** is a programmed death-ligand 1 (PD-L1) blocking antibody/Multiple Indications

**2. Avelumab (BAVENCIO)-**is a programmed death-ligand 1 (PD-L1) blocking antibody/Multiple Indications

**3. Cemiplimab-rwlc (LIBTAYO**)- is a programmed death receptor-1 (PD-1) blocking antibody/Multiple Indications

**4. Dostarlimab-gxly(JEMPERLI)-**is a programmed death-ligand 1 (PD-L1) blocking antibody/Multiple Indications

**5.Durvalumab (IMFINZI)-** is a programmed death-ligand 1 (PD-L1) blocking antibody/Multiple Indications

# Current List of FDA-Approved Immune Checkpoint Inhibitors

**5. Ipilimumab (YERVOY)-** is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody/Multiple Indications

**6. Nivolumab (OPDIVO)-** is a programmed death receptor-1 (PD-1) blocking antibody/Multiple Indications
***Also available in combination as **OPDUALAG,** (**nivolumab and relatinib-rmbw**) -a lymphocyte activation gene-3, (LAG) blocking antibody. (2022)

**7. Pembrolizumab (KEYTRUDA)-** is a programmed death receptor-1 (PD-1) blocking antibody/Multiple Indications

**8. Retifanlimab-dlwr (ZYNYZ)**-is a programmed death receptor-1 (PD-1) blocking antibody for the treatment of metastatic or recurrent locally advanced adult Merkel cell carcinoma

**9. Tremelimumab (Imjuno)-**is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-blocking antibody. Indicated for use with durvalumab, for adult patients with unresectable hepatocellular carcinoma

# Strategies for Early Recognition & Prompt Interventions for Immunotherapy-Related Toxicity

- Comprehensive Baseline Assessment of the Patient's Current Emotional, Physical and Spiritual Status
- Comprehensive Baseline Physical Assessment
- Social Determinants of Health
- Financial Toxicity
- Gravity of Current Malignancy
- Comprehensive Patient & Significant Other(s) Education

NCCN. Clinical Practice Guidelines in Oncology. Management of immuno-related toxicities Accessed 2024; Walker S et al. *Guide to Cancer immunotherapy.* 2018.

## Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 Publish Date: November 27, 2017

**Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
**Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
**Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
**Grade 4:** Life-threatening consequences; urgent intervention indicated.
**Grade 5:** Death related to AE.

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, 2017.

# Strategies for Early Recognition & Prompt Interventions for Immunotherapy-Related Toxicity

## Diarrhea

**Grade 1**: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline

**Grade 2**: Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL

**Grade 3:** Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL

**Grade 4:** Life-threatening consequences; urgent intervention indicated

**Grade 5:** Death related to AE.

Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Publish Date: November 27, 2017.

# Strategies for Early Recognition & Prompt Interventions for Immunotherapy-Related Toxicity

## Adverse Reactions vs IMARS-Must Differentiate these toxicities!
## Chemo-related? Radiation therapy related? Or from Immuno-Oncology Agents?

- **Immune-Mediated Adverse Reactions (IMARS) can occur in any organ system**
- **IMARS have varying onset and can appear within the first 1-2 weeks, the first 12 weeks, vary in every patient**
- **IMARS can recur 22+ months after the completion of I-O therapy**
- **Each I-O manufacturer reports varying occurrence percentages of each of IMARS, their onset and duration**

NCCN. Clinical Practice Guidelines in Oncology. Management of immuno-related toxicities Accessed 2024;
Walker S et al. *Guide to Cancer immunotherapy*. 2018.

# Strategies for Early Recognition & Prompt Interventions for Immunotherapy-Related Toxicity

## Adverse Reactions vs IMARS?

## Must Differentiate other Oncologic Therapy Related Toxicities & Benign Disease Issues!

**Chemotherapy-related? I-O Combination Regimens?**
**Radiation therapy related? Concurrent I-O?**
**Disease Progression?**
**Comorbidities?**

## Or from Immuno-Oncology Agents?

NCCN. Clinical Practice Guidelines in Oncology. Management of immuno-related toxicities Accessed 2024;
Walker S. et al. *Guide to Cancer immunotherapy*. 2018.

# Strategies for Early Recognition & Prompt Interventions for Immunotherapy-Related Toxicity

## Immune-Mediated Adverse Reactions (IMARS)
## More Common Symptoms:

- **fatigue/asthenia, musculoskeletal pain**
- **decreased appetite, diarrhea, nausea/vomiting, pyrexia**
- **cough, dyspnea, constipation, abdominal pain**
- **pruritus/rash, peripheral neuropathy**
- **mucosal inflammation, alopecia, and stomatitis**

NCCN. Clinical Practice Guidelines in Oncology. Management of immuno-related toxicities. Accessed 2024.

# Strategies for Early Recognition & Prompt Interventions for Immunotherapy-Related Toxicity

## Immune-Mediated Adverse Reactions on Organ Systems Include:

- **Pneumonitis**
- **Colitis**
- **Hepatitis**
- **Encephalitis**
- **Endocrinopathies- Hypophysitis-inflammation of the pituitary gland-pituitary-hypothalamic, pituitary-thyroid, pituitary-gonadal, pituitary-adrenal systems-visual disturbance, confusion, memory loss, hallucinations, Adrenal insufficiency, Hyper/Hypothyroidism, Type 1 diabetes mellitus**
- **Dermatologic adverse reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)**
- **Nephritis and Renal Dysfunction**
- **Solid Organ Transplant Rejection**
- **Infusion-Related Reactions**
- **Embryo-Fetal toxicity**

NCCN. Clinical Practice Guidelines in Oncology. Management of immuno-related toxicities Accessed 2024.

# Implementation of Prompt Evidence-Based Interventions to Treat IMARS

## Adverse Reaction Severity & Dose Modification

- **Each Manufacturer has IMAR Guidelines for Severity, Dose Modification and Discontinuation**
  - **The Range of IMAR Onset and Duration is Different for Each I-O Agent**

**Colitis:**

**Grade 2 diarrhea or colitis**- Withhold dose till return to baseline

**Grade 3 diarrhea or colitis**-Withhold dose when I-O administered as a single agent

**Grade 4 diarrhea or colitis-** Permanently discontinue

**Pneumonitis:**

**Grade 2 pneumonitis-** Withhold dose till return to baseline

**Grade 3 or 4 pneumonitis**- Permanently discontinue

NCCN. Clinical Practice Guidelines in Oncology. Management of immuno-related toxicities Accessed 2024.

# Implementation of Prompt Evidence-Based Interventions to Treat IMARS

## Inspire Hope!

- **Patient and Caregiver Education that is Understood is Key!**
- **Social Determinants of Health Considerations are CRITICAL!!!**
- **Through Informed consent is Critical to Patient Participation and Understanding**
- **Comprehensive assessment of reported IMAR.  Related to I-O or not?**
- **Grade the IMAR and call HCP STAT**
- **Consider Comorbidities in all aspects of interventions e.g. The Geriatric Patient**
  **Unsafe living conditions? Might require emergency hospitalization**

NCCN. Clinical Practice Guidelines in Oncology. Management of immuno-related toxicities Accessed 2024.

# Implementation of Prompt Evidence-Based Interventions to Treat IMARS

## Pharmacological Interventions

- Corticosteroids
- Infliximab (Remicade)
- Mycophenolate mofetil (Cellcept)
- Intravenous Immunoglobulin Therapy (IVIG)
- Rituximab (Rituxan)
- Methotrexate
- Cyclophosphamide

- Plasmapheresis-has also been used

## Use Approved Supportive Therapies as per HCP & Follow Institutional Policies

NCCN. Clinical Practice Guidelines in Oncology. Management of immuno-related toxicities Accessed 2024.

# Implementation of Prompt Evidence-Based Interventions to Treat IMARS

## Pharmacological Interventions

- **Corticosteroids-**Have variable effects on all T lymphocytes. Corticosteroids enter the cellular membrane and attach to the glucocorticoid receptor. Corticosteroids then bind to/interrupts DNA. This binding them suppresses inflammation by:
- Reducing the number of T cells  in circulation, especially immature CD4+ T cells
- Reduces memory T cells, T helper type 17+ (Th17+) T cells, and CD8+ effector T cells,.
- High dose corticosteroids, (doses >1 mg/kg per day in children or >40 mg daily in adults), rapidly destroys most circulating T cells by inhibiting IL2-responsible for T cell growth, impairs release of T cells from the lymph system

- **Infliximab (Remicade)**- Is a monoclonal antibody that binds to Tumor Necrosis Factor-α and disrupts the pro-inflammatory cascade.
- Once TNF-a is blocked, downregulation of local and systemic pro-inflammatory cytokines (i.e. IL-1, IL-6), occurs.
- This reduces and inhibits lymphocyte and leukocyte migration to sites of inflammation and induces cell death of induction of TNF-producing cells such as activated monocytes and T lymphocytes.

# Implementation of Prompt Evidence-Based Interventions to Treat IMARS

## Pharmacological Interventions

- **Mycophenolate mofetil (MMF, CellCept(R))-** is a precursor of mycophenolic acid (MPA). It inhibits inosine monophosphate dehydrogenase (IMPDH). T and B-lymphocytes need this pathway to survive. MPA is incredibly lethal to lymphocytes than on other cell types.

- **Intravenous Immunoglobulin Therapy (IVIG)-**IVIG has many actions and competitive interactions in the human immune system, not all of which are completely understood.

- IVIG inactivates T-cells by competing for and interrupting their interaction of binding with antigen presenting cells and notably, expansion of the regulatory T cell population.

- Additionally, IVIG induces anti-inflammatory cytokines from innate cells and leads to decreased macrophage responsiveness to interferon.

# Implementation of Prompt Evidence-Based Interventions to Treat IMARS

## Pharmacological Interventions

- **Rituximab (Rituxan) -**Is a monoclonal antibody who's mechanisms of action are still not fully understood.
- In IMAR's, Rituxan binds to the CD4+ receptor in T's cells leading to apoptosis.
- Research on rheumatoid arthritis led to research in use with IMAR's in checkpoint inhibitor therapies.

- **Methotrexate-**Is an antifolate antimetabolite cancer chemotherapeutic agent.
- It causes depriviation of a form of folic acid, that in turn prevents DNA synthesis, thereby being cytotoxic.
- However, methotrexate has a different mechanism of action in the treatment of IMAR's. Methotrexate is used in IMAR's and autoimmune diseases because it inhibits the enzyme AICAR transformylase.
- This lack of enzyme suppresses adenosine and guanine metabolism which leads to Adenosine accumulation. Adenosine is a powerful anti-inflammatory that suppresses T-cells.

- **Cyclophosphamide-** is a non-cell cycle specific cancer chemotherapy. It is a type of nitrogen mustard drug that damages normal DNA production and inhibiting protein synthesis, leading to cell death.
- Additionally, Cyclophosphamide's cytotoxicity targets T cells, and specific damage to T regs.

# Discuss Principles of Patient Education and Supportive Patient Care Interventions to Minimize Morbidity and Mortality

**Potential for untoward morbidity and mortality related to I-O induced (IMARS) Assessment/Planning/Implementation & Evaluation Include:**

- Reinforcement of evidence-based individualized patient education concerning IMARS.
- Know your patient's coping mechanisms & support systems!
- Urge STAT provider notification of any untoward reaction
- Urge compliance of all IMAR interventions and supportive teaching compliance

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# Discuss Principles of Patient Education and Supportive Patient Care Interventions to Minimize Morbidity and Mortality

**Potential for untoward morbidity and mortality related to I-O induced (IMARS) Assessment/Planning/Implementation & Evaluation Include:**

- Provide on-going ECOG status, vital signs monitoring, laboratory/radiological assessments
- Provide ongoing physical, emotional and spiritual assessments
- Provide ongoing healthcare and supportive care interventions
- Ongoing assessment of patient compliance and participation and potential IMARS

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# What Does the Future Hold?

## STEP 3: PRIMING AND ACTIVATION

- CD28/B7.1
- CD137/CD137L
- **OX40/OX40L***
- **CD27/CD70***
- HVEM
- GITR
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- IL-12
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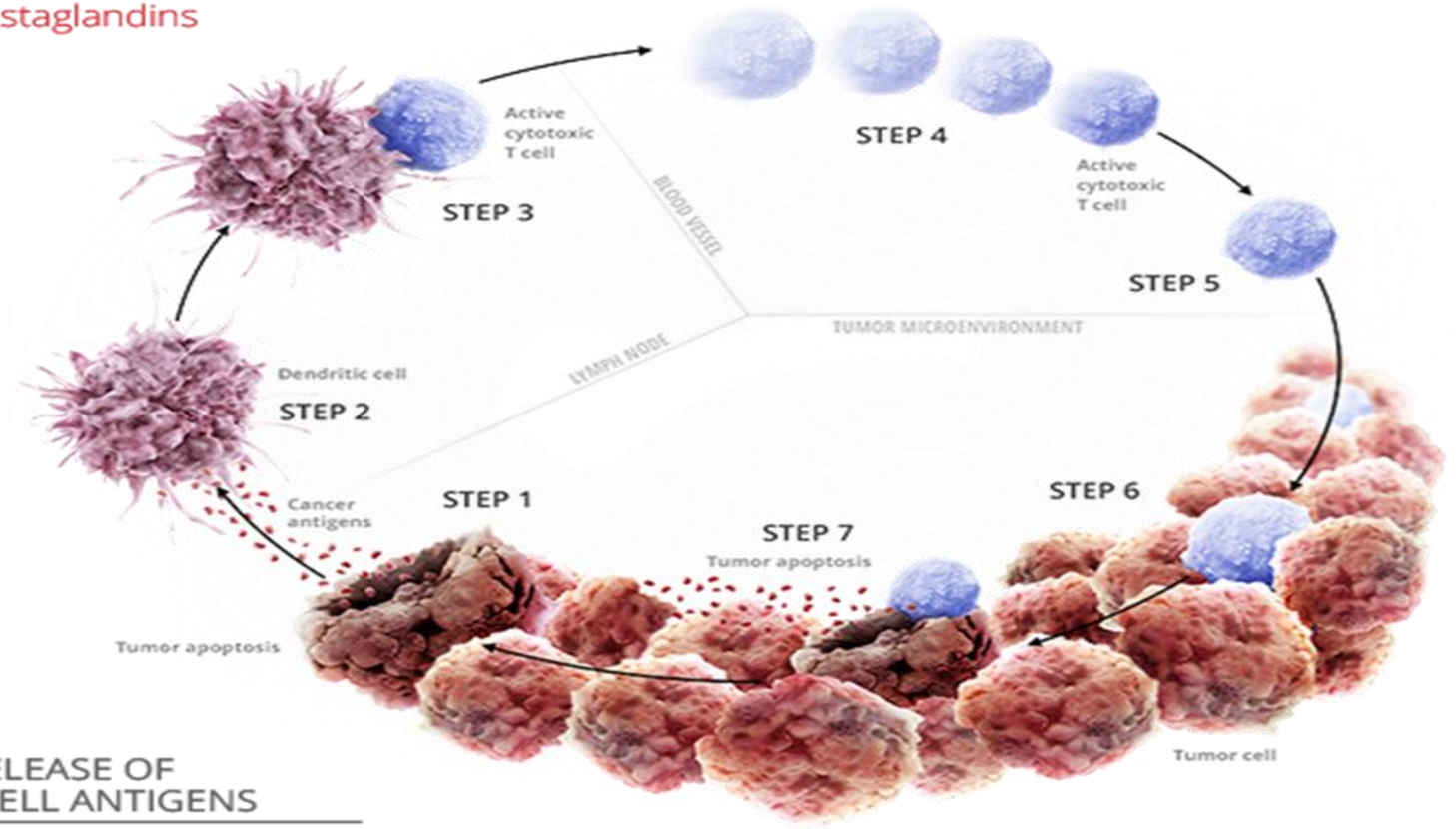


## STEP 5: INFILTRATION OF T CELLS INTO TUMORS

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- Selectins
- **VEGF***
- Endothelin B receptor

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- IFNα
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## STEP 6: RECOGNITION OF CANCER CELLS BY T CELLS

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- Reduced pMHC on cancer cells

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- Immunogenic cell death
- Tolergenic cell death

## STEP 7: KILLING OF CANCER CELLS

- IFNγ
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- Arginase
- MICA-MICB
- B7-H4
- VISTA

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# Thank You!

## Do You Have Any Questions?

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