CANCER IMMUNOTHERAPY AND TOXICITIES

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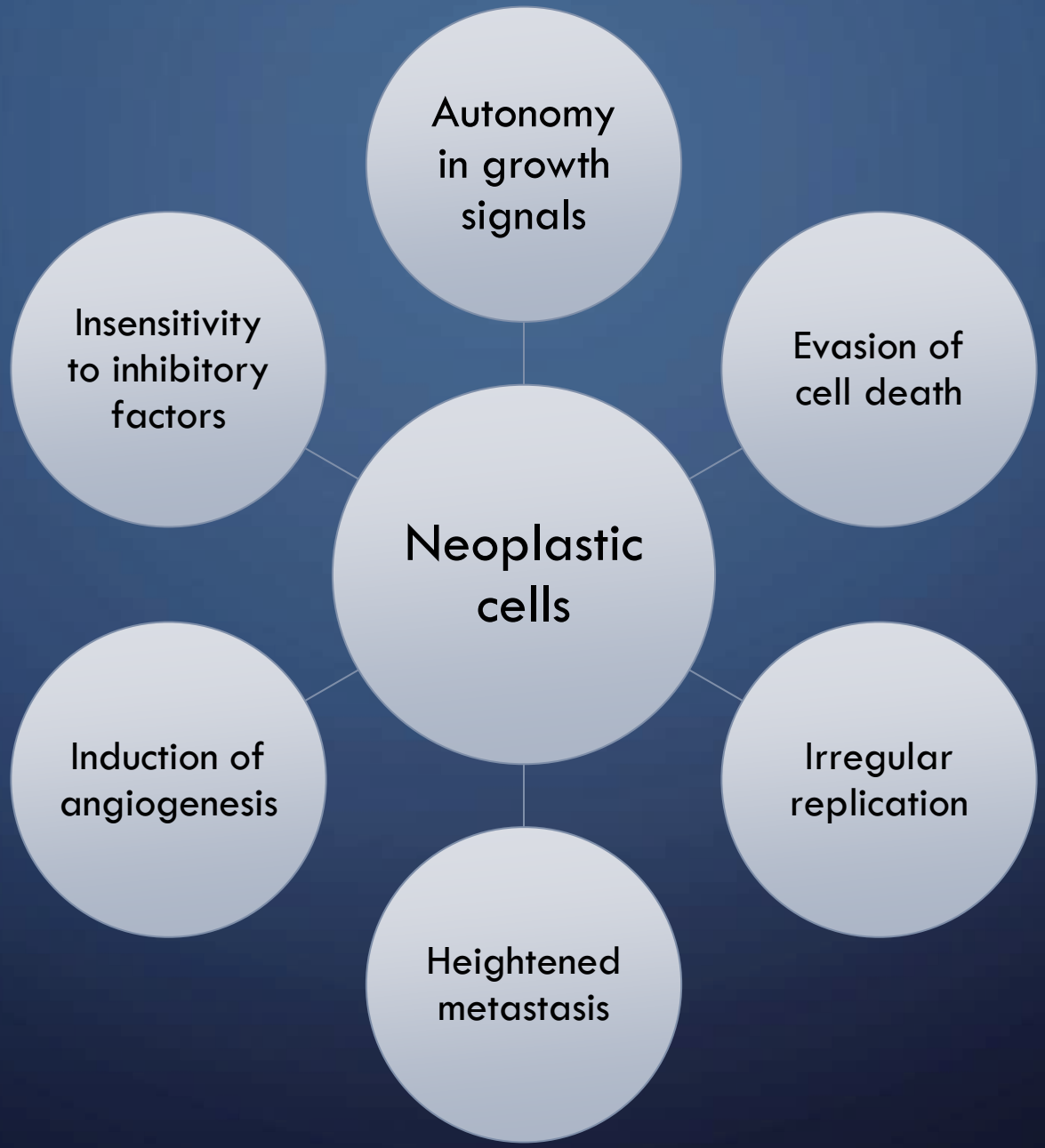
MD, MSc, PhD


Autonomy in growth signals
Insensitivity to inhibitory factors
Evasion of cell death
Neoplastic cells
Induction of angiogenesis
Irregular replication
Heightened metastasis

Era of personalized medicine

Chemotherapy

Targeted therapy

Immunotherapy

THE IDEA OF CANCER IMMUNOEDITING

THE THREE E's

Elimination (immunosurveillance)

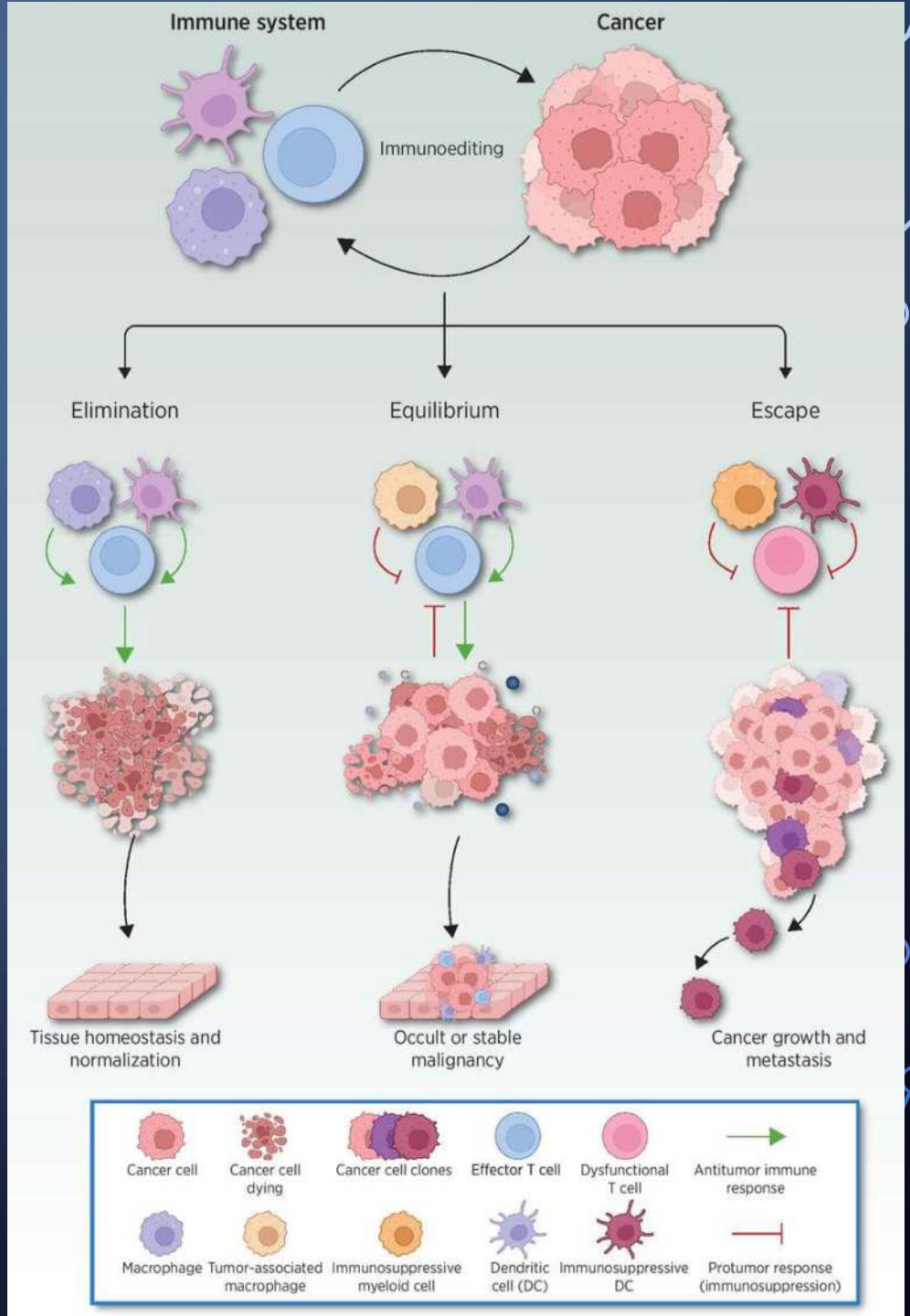
The host's immune system recognize and respond to tumor-specific antigens

Equilibrium (tumor dormancy)

Some tumor cells survive and enter the next phase. Occult or stable malignancy

Escape (tumor progress)

Tumor cells develop resistance and escape. Cancer growth and metastasis



Cancer immunotherapies were developed based on studies of the mechanisms of tumor escape

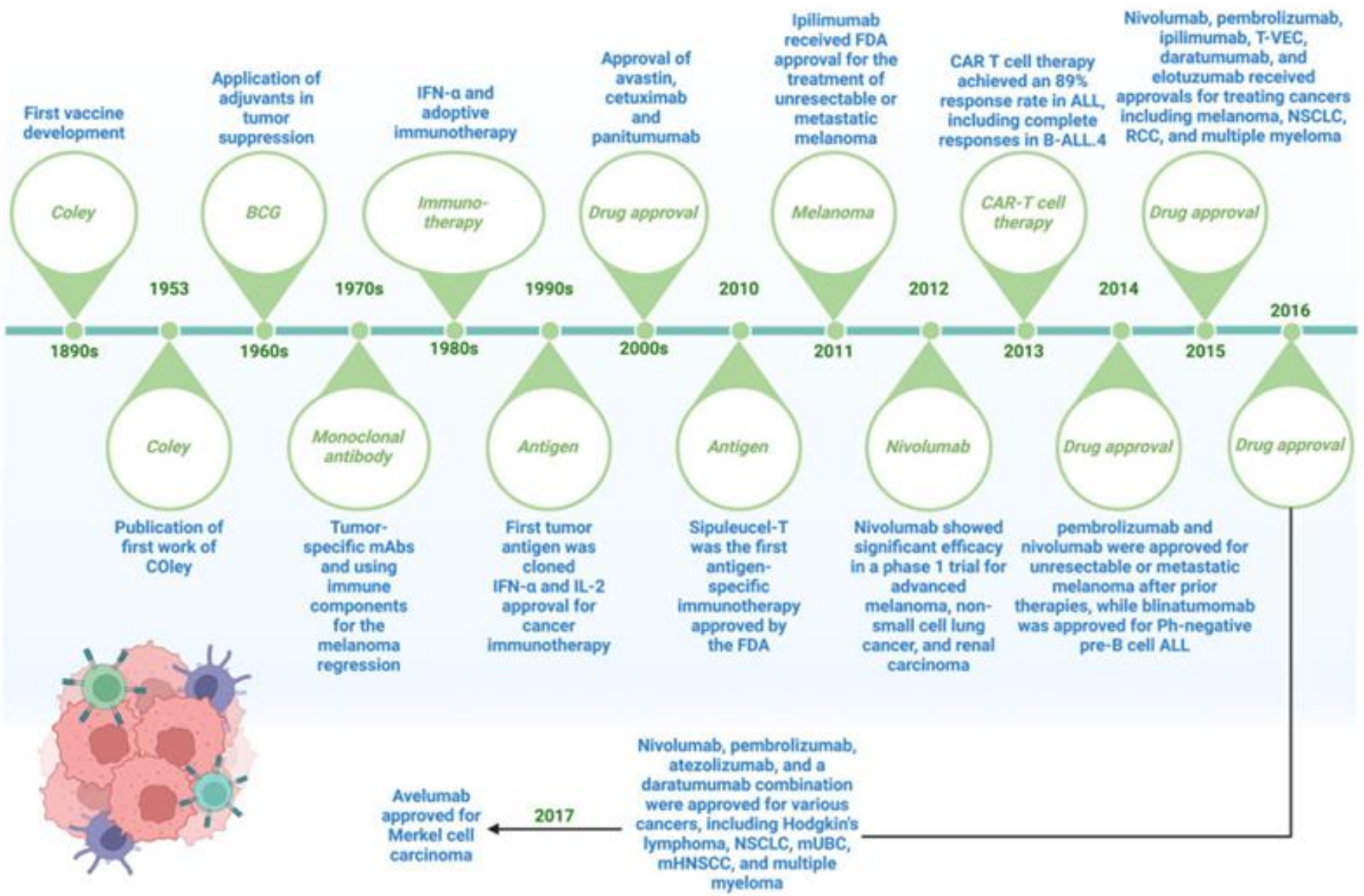
- Alteration or loss of antigens
- Manipulation of cytokine expression
- Upregulation of immune checkpoint proteins

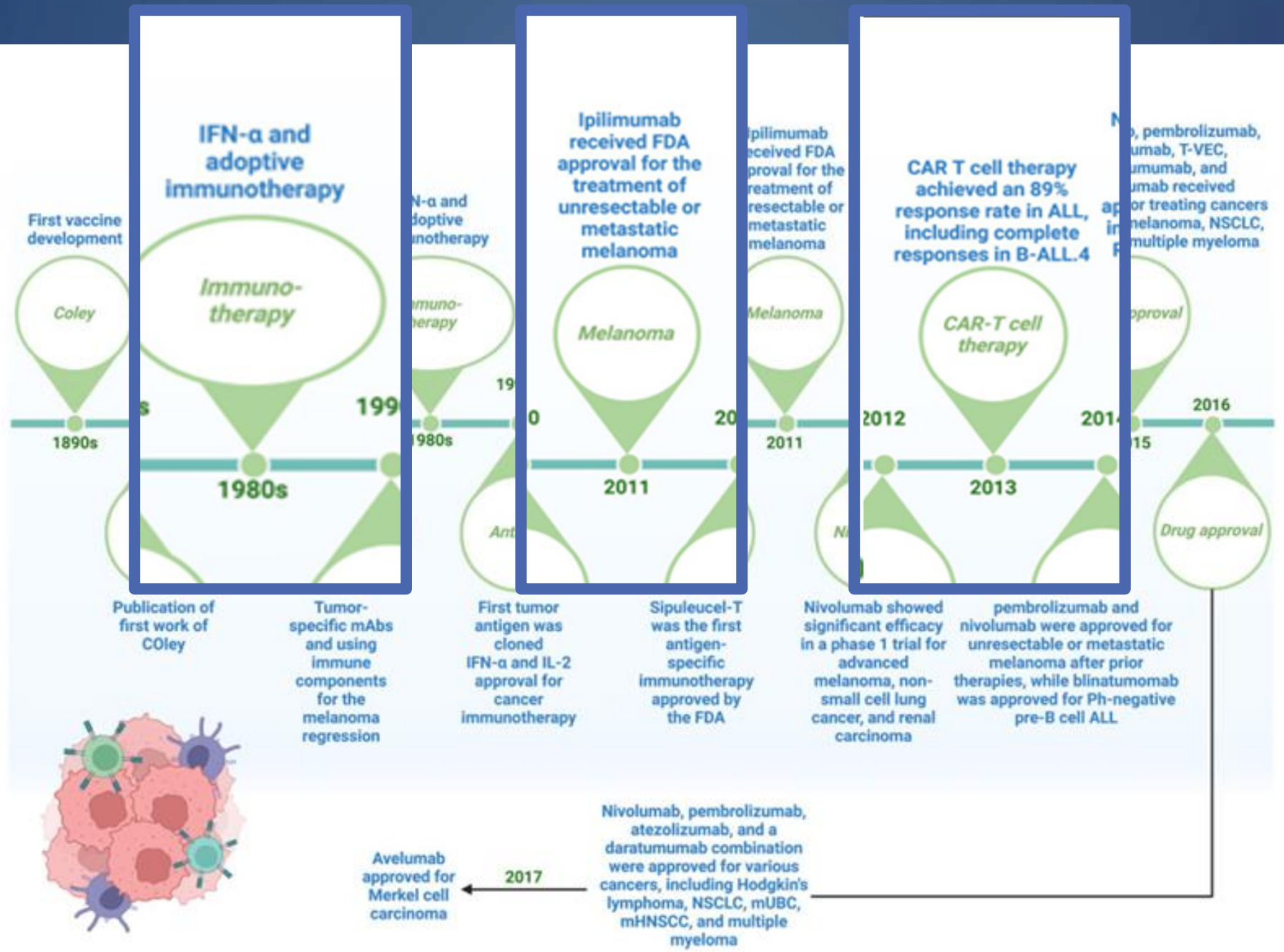
Significance and clinical implications

Understanding the specific antigens lost during the "editing" process can guide the development of **personalized** treatment

Cancer immunoediting is a major reason for **resistance** to immunotherapies

Immunoscore: researchers use the intensity of T-cell infiltration as a key prognostic marker for patient survival (higher infiltration indicates better immune control)


First vaccine development
Coley
1890s
Coley
Publication of first work of COley
1953
Application of adjuvants in tumor suppression
BCG
1960s
Monoclonal antibody
Tumor-specific mAbs and using immune components for the melanoma regression
1970s
IFN-α and adoptive immunotherapy
Immuno-therapy
1980s
Antigen
First tumor antigen was cloned IFN-α and IL-2 approval for cancer immunotherapy
1990s
Approval of avastin, cetuximab and panitumumab
Drug approval
2000s
Antigen
Sipuleucel-T was the first antigen-specific immunotherapy approved by the FDA
2010
Ipilimumab received FDA approval for the treatment of unresectable or metastatic melanoma
Melanoma
2011
Nivolumab
Nivolumab showed significant efficacy in a phase 1 trial for advanced melanoma, non-small cell lung cancer, and renal carcinoma
2012
CAR T cell therapy achieved an 89% response rate in ALL, including complete responses in B-ALL.4
CAR-T cell therapy
2013
Drug approval
pembrolizumab and nivolumab were approved for unresectable or metastatic melanoma after prior therapies, while blinatumomab was approved for Ph-negative pre-B cell ALL
2014
Nivolumab, pembrolizumab, ipilimumab, T-VEC, daratumumab, and elotuzumab received approvals for treating cancers including melanoma, NSCLC, RCC, and multiple myeloma
Drug approval
2015
Drug approval
2016
Nivolumab, pembrolizumab, atezolizumab, and a daratumumab combination were approved for various cancers, including Hodgkin's lymphoma, NSCLC, mUBC, mHNSCC, and multiple myeloma
2017
Avelumab approved for Merkel cell carcinoma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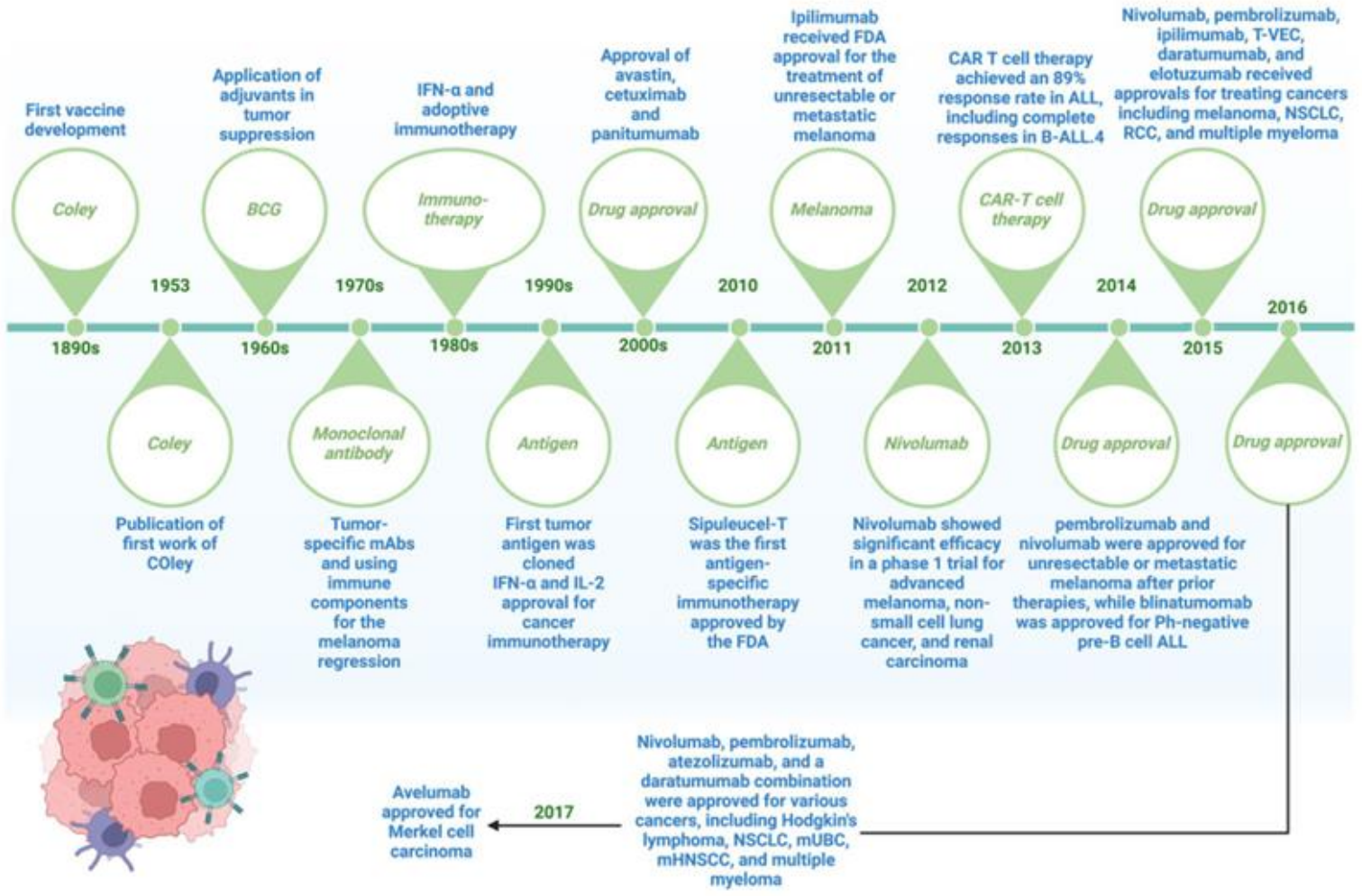
First approaches based on cancer growth in immunocompromised patients

Early approaches targeted cytokines to affect immune cell function. Short half-life, narrow therapeutic window, toxicity risks



IMMUNOTHERAPY

1. Immune checkpoint inhibitors (ICIs)

2. Adoptive cell transfer (ACT) (TIL, TCR, CAR-T cell)

3. Oncolytic virus therapy

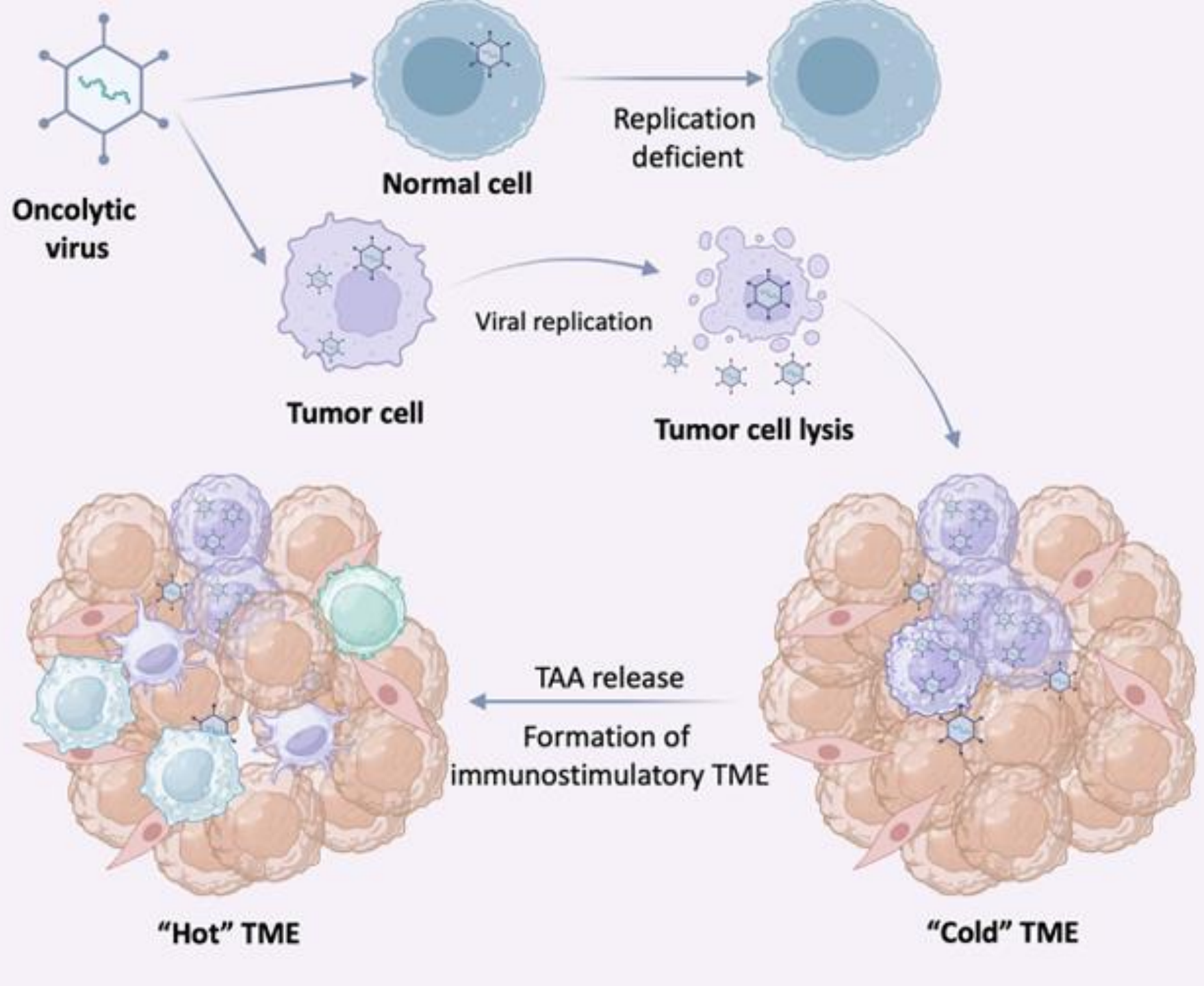
4. Cancer vaccines

4. Cancer vaccines

- Designed to train the immune system to recognize and attack cancer cells, acting as either **prevention** or **treatment**
- Preventive vaccines: HPV
- mRNA Technology: similar to COVID-19 vaccines
- Current Approvals for treatment: BCG vaccine for bladder cancer and Sipuleucel-T (Provenge) for prostate cancer
- **Tumor heterogeneity!**

3. Oncolytic virus therapy

- Replication-specific viruses that directly infect and **lyse tumor cells in situ**
- OVs can enter both normal and cancer cells, but the inherent abnormalities in the cancer cells provide a selective advantage for viral replication, allowing replication within tumor cells and direct lysis
- T-VEC is a genetically modified type 1 herpes simplex virus (HSV-1) which is the first approved oncolytic virus for the treatment of advanced melanoma by the US FDA
- OVs are administered to patients **intratumorally**, basic limitation

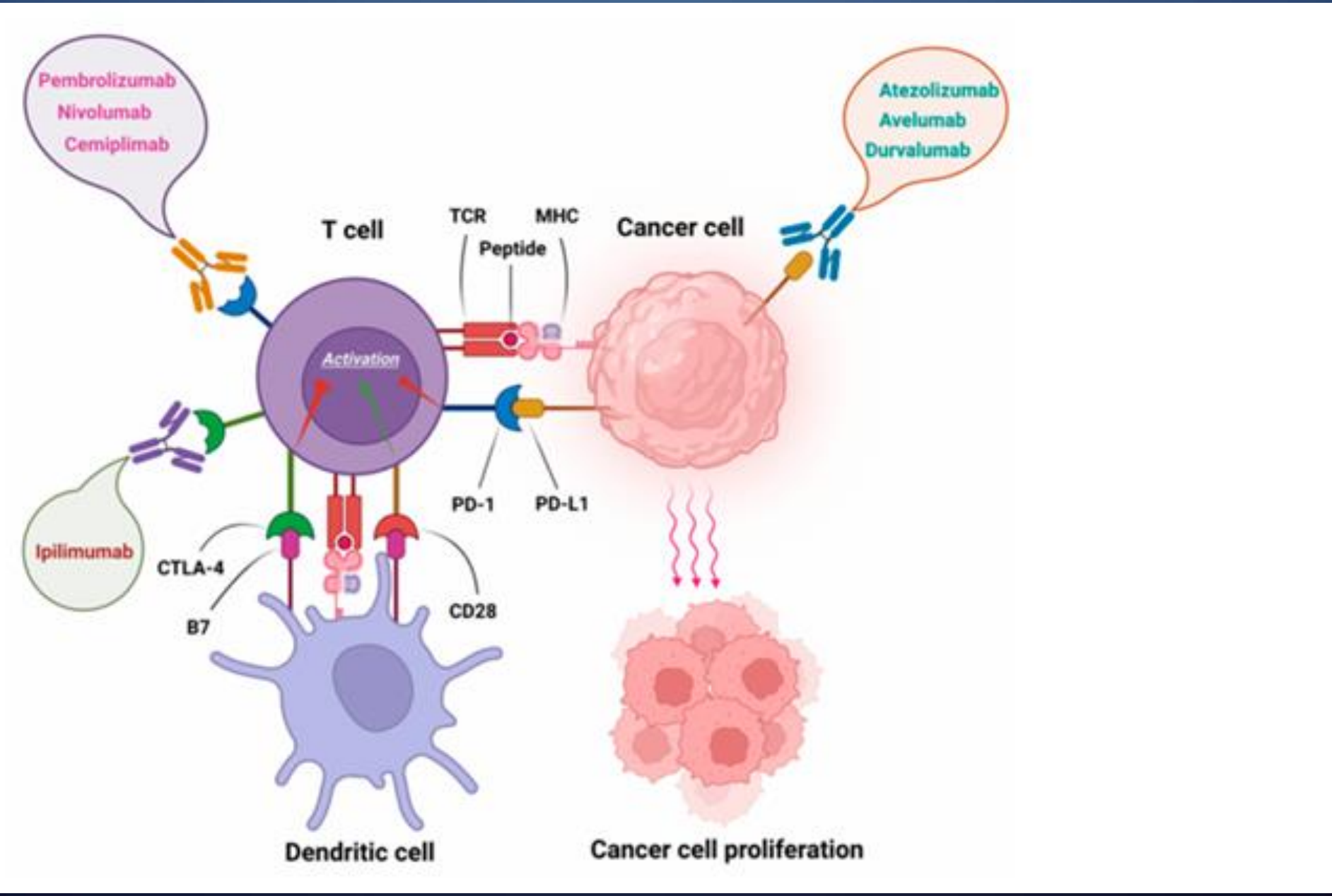

Oncolytic virus
Normal cell
Replication deficient
Tumor cell
Viral replication
Tumor cell lysis
TAA release
Formation of immunostimulatory TME
"Hot" TME
"Cold" TME

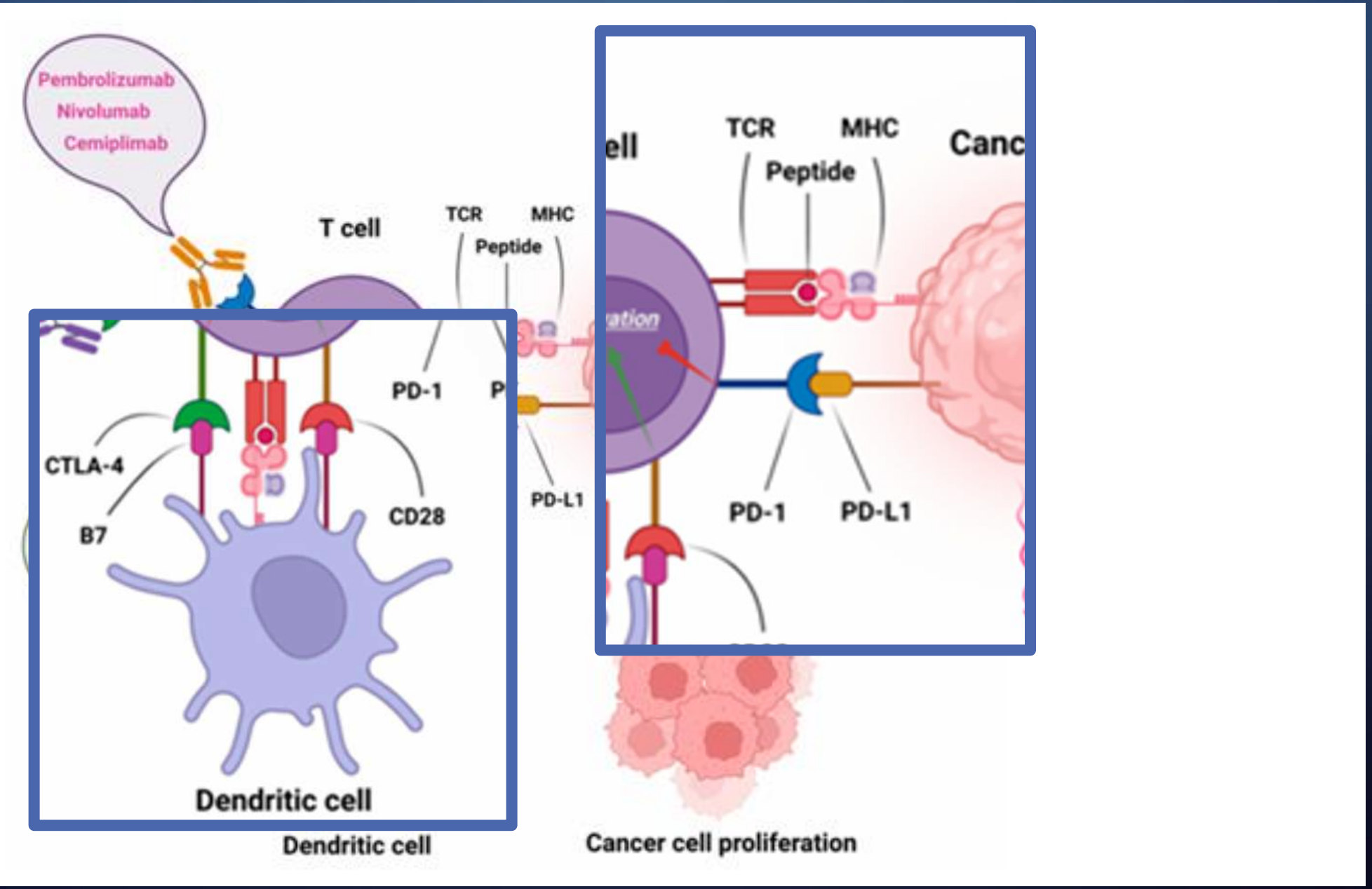
2. Adoptive cell transfer (ACT) (TIL, TCR, CAR-T cell)

- **Ex vivo** modification of patient T cells to generate specific antitumor reactivity
- Chimeric antigen receptor **(CAR) T cells** are used to treat hematologic malignancies and are being investigated in multiple solid tumors
- Current clinical use of CAR-T cells targets CD19, the pan–B-cell antigen, in the treatment of hematologic malignancies
- The most common toxicities are cytokine release syndrome (**CRS**) and immune effector cell associated neurotoxicity syndrome (**ICANS**)

1. Immune checkpoint inhibitors (ICIs)

PD-1 (programmed cell death-1) inhibitors	PDL-1 inhibitors	CTLA-4 (cytotoxic T lymphocyte antigen 4) inhibitors
• Nivolumab • Pembrolizumab • Cemiplimab	• Atezolizumab • Durvalumab • Avelumab	• Ipilimumab


Pembrolizumab
Nivolumab
Cemiplimab
Atezolizumab
Avelumab
Durvalumab
T cell
TCR
MHC
Peptide
Cancer cell
Activation
PD-1
PD-L1
Ipilimumab
CTLA-4
B7
CD28
Dendritic cell
Cancer cell proliferation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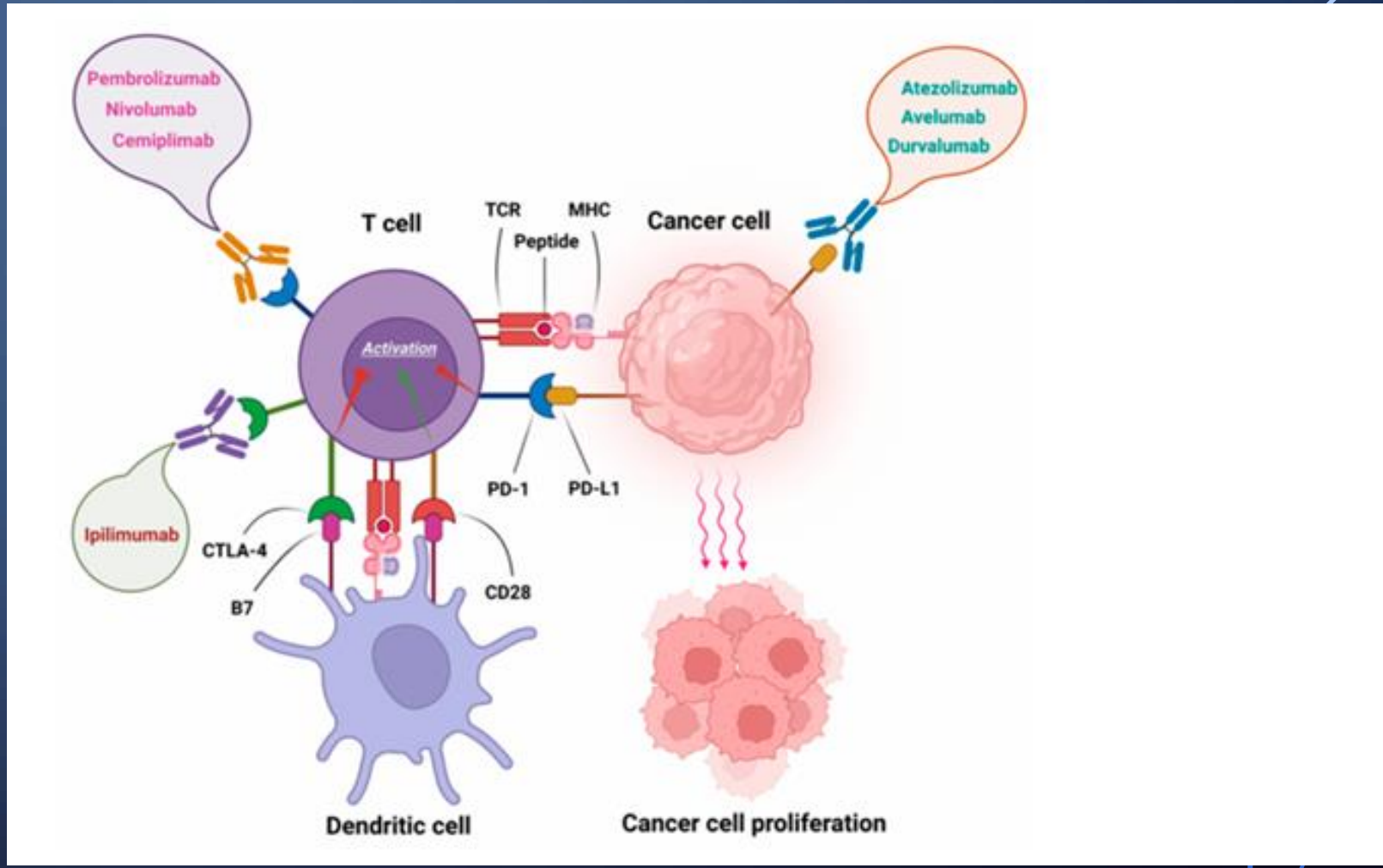
PD-1
PD-L1
Cancer cell proliferation

CTLA-4 is expressed on the surface of CD4+ and CD8+ lymphocytes

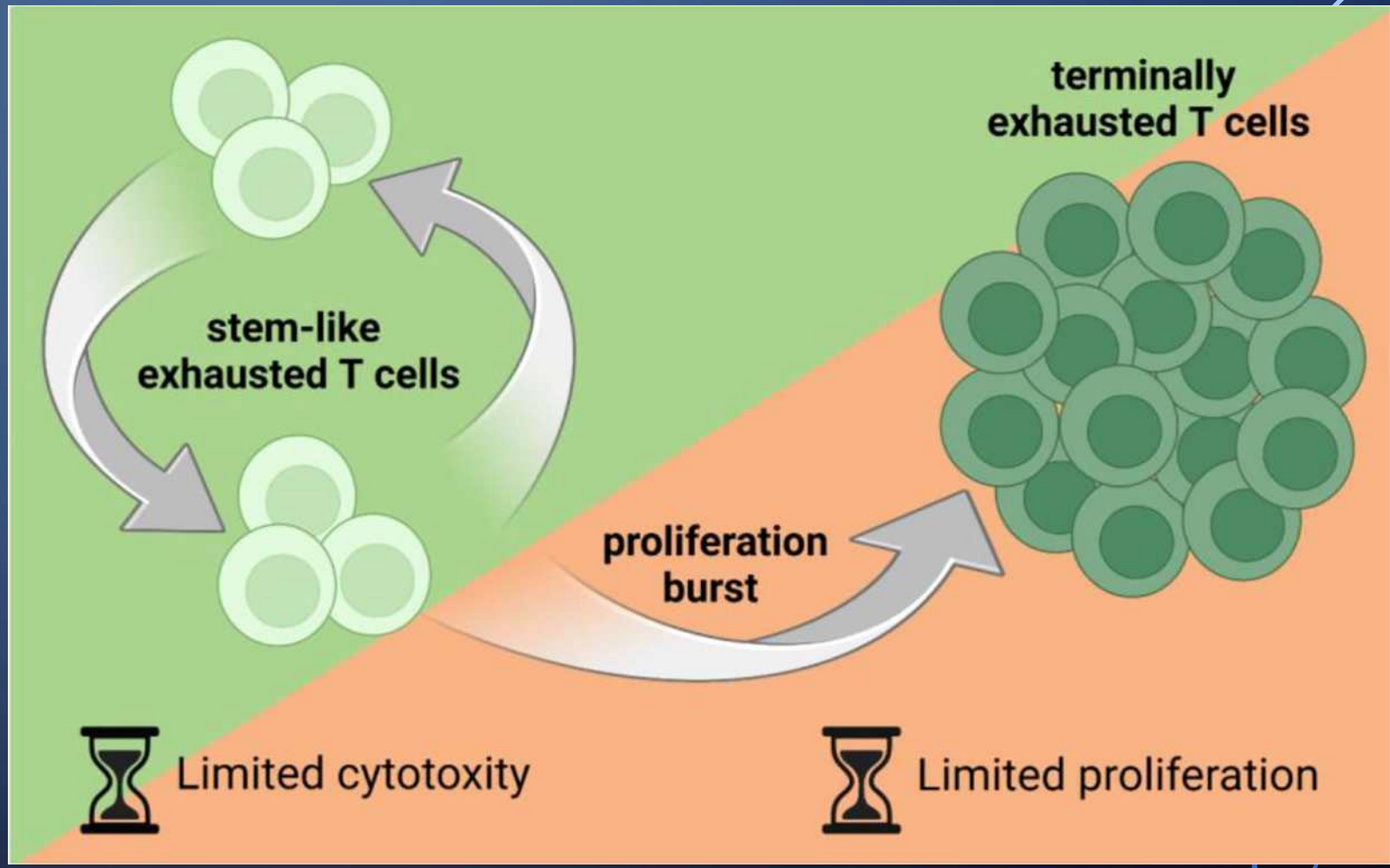
PD-1 is a cell-surface receptor expressed on multiple immune cell types (T, B, NK cells) and binds to the ligands PD-L1 and PD-L2

PD-L1 is expressed on multiple tissue types, including tumor cells.
PD-L2 is expressed primarily on hematopoietic cells



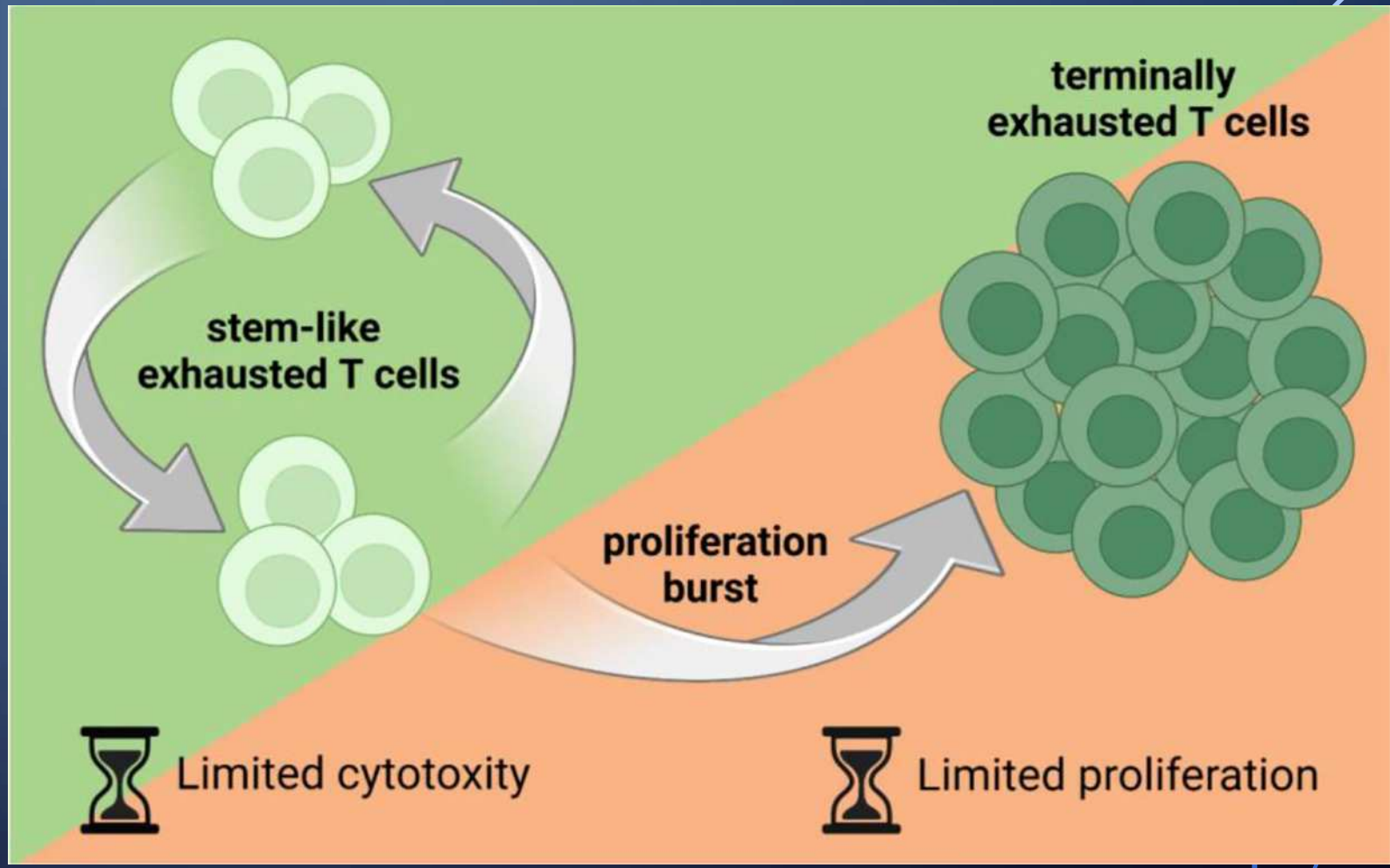
Immune checkpoint proteins, including PD-1 and CTLA 4, initiate signaling pathways that **suppress T-cell function**

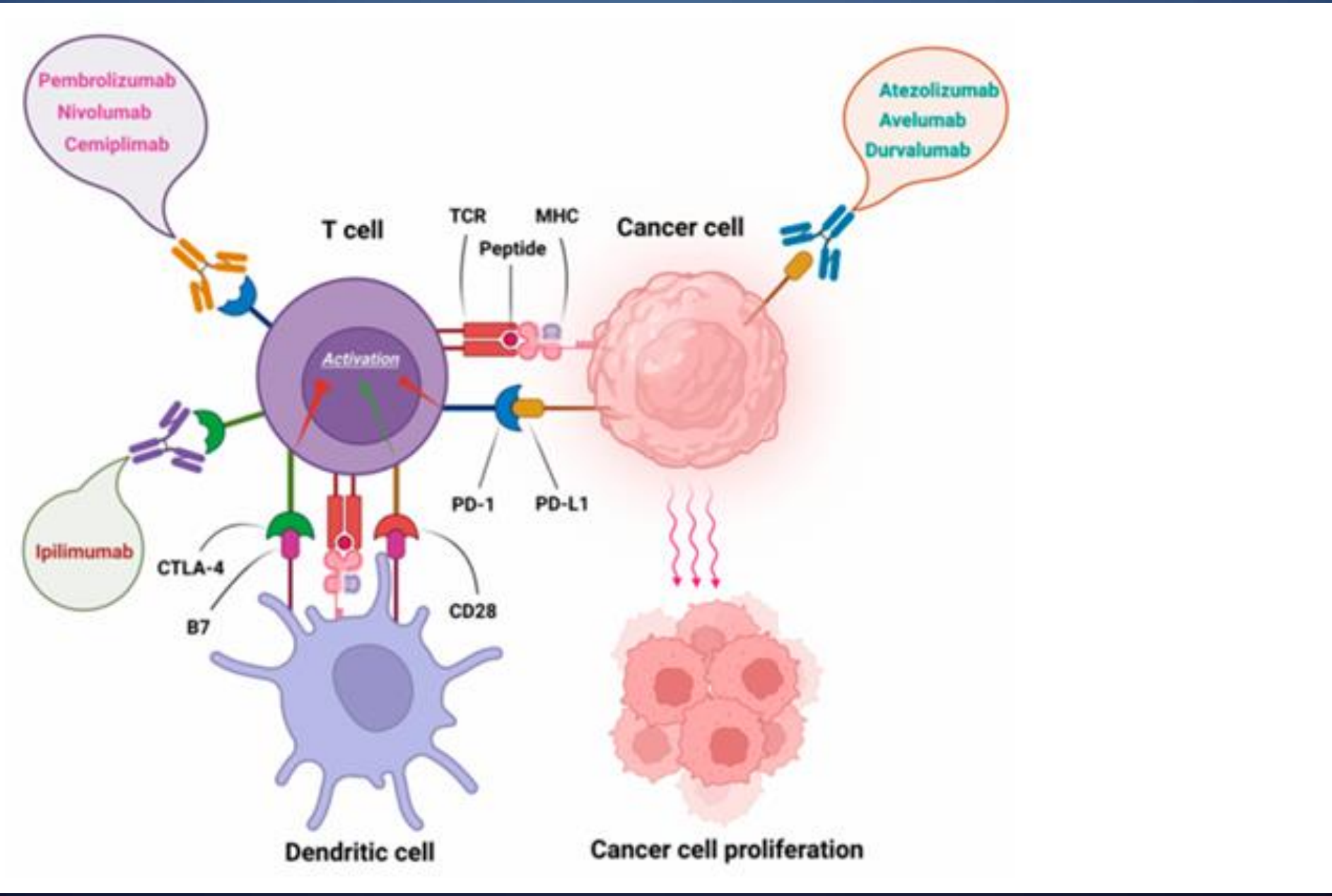
Tumor cells use checkpoint protein signaling, to evade immune response and establish a TME that permits tumor growth



Upregulation of the PD-1 pathway can promote **T-CELL EXAUSTION** (reduced T-cell effector function and proliferation)

Exhausted T cells highly express immune checkpoints (CTLA-4, PD-1, LAG-3, TIGIT) that effectively prevent T cell activation

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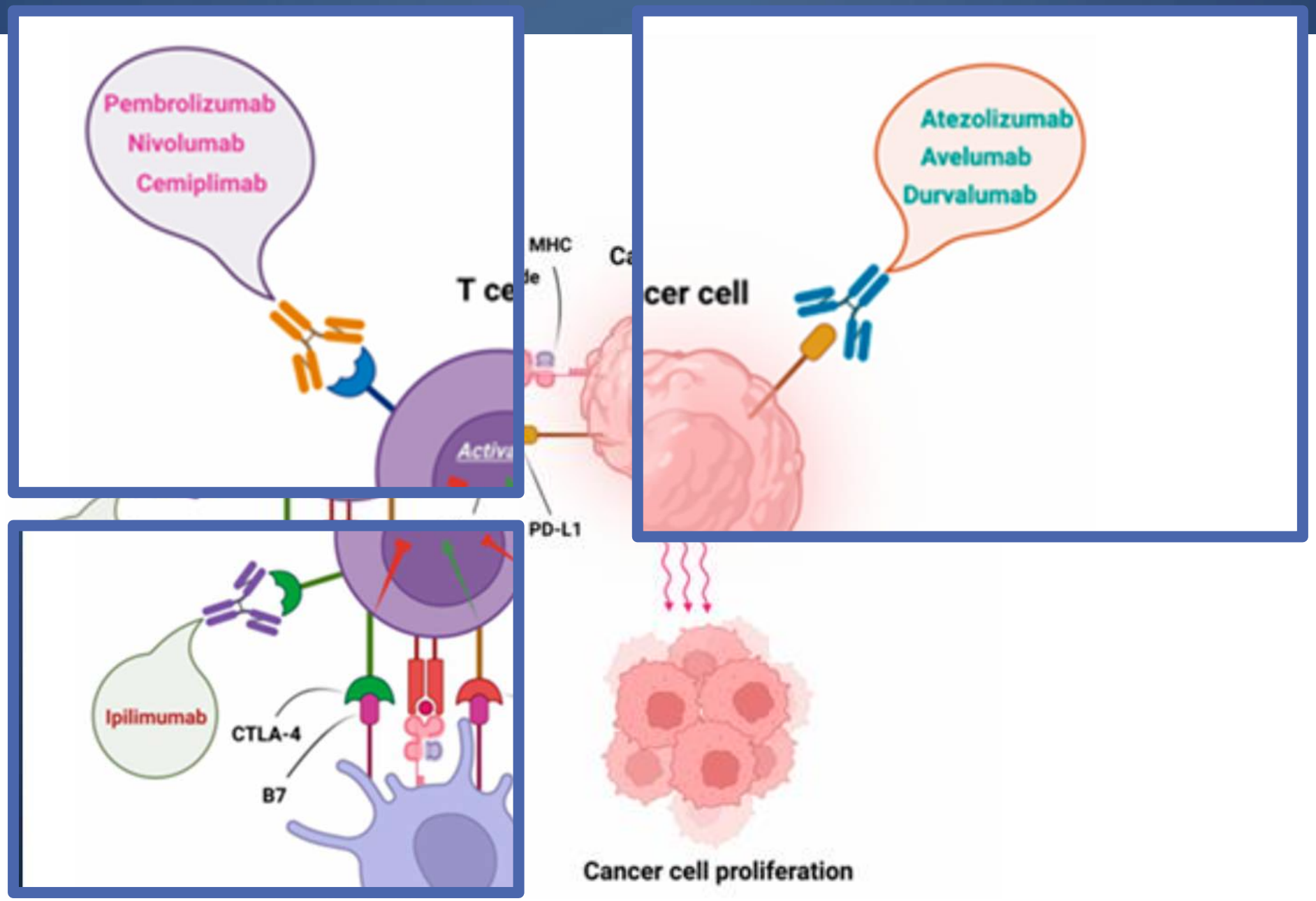
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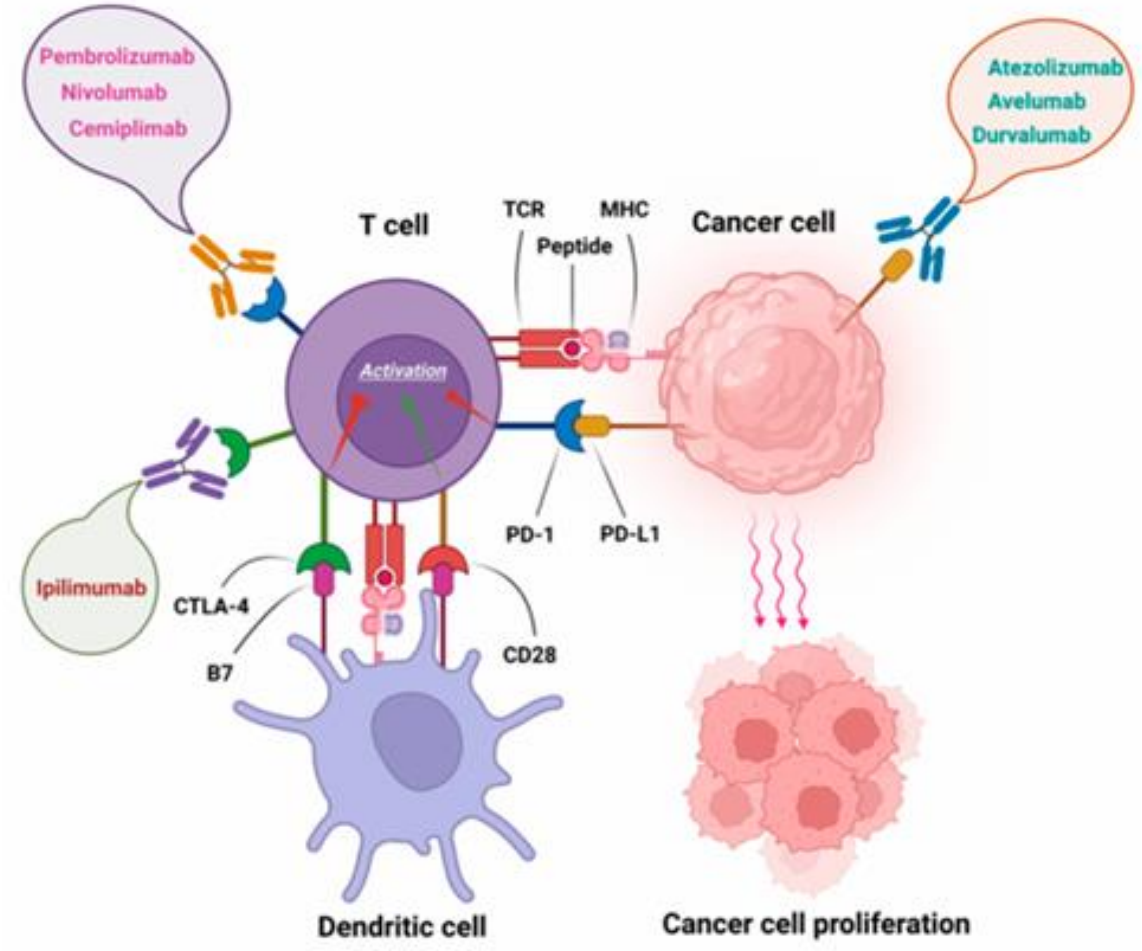
CTLA-4
B7
Cancer cell proliferation

ICIs bind to immune checkpoint proteins to over come this tumor-mediated effect

Checkpoint inhibitors have transformed treatment algorithms with ongoing expanded indications



2011–2014 (Foundations)

Ipilimumab (2011) – First CTLA-4 inhibitor

Pembrolizumab (2014) – First PD-1 therapy

Nivolumab (2014) – PD-1 inhibitor

2016–2018 (Expansion)

Atezolizumab (2016) – First PD-L1 inhibitor

Avelumab (2017) – PD-L1 (Merkel cell)

Durvalumab (2017) – PD-L1 (bladder)

Cemiplimab (2018) – PD-1 (cSCC)

2021–2026 (Next-gen & Formulations)

Dostarlimab (2021) – PD-1 (dMMR endometrial)

Relatlimab-rmbw (2022) – First LAG-3 inhibitor

Toripalimab (2023) – PD-1 (NPC)

Tislelizumab (2024) – PD-1 (ESCC)

Atezolizumab and hyaluronidase-tqjs (2024) – Subcutaneous PD-L1

Nivolumab and hyaluronidase-nvhy (2024) – Subcutaneous PD-1

Pembrolizumab plus berahyaluronidase alfa-pmph (2026) – SC formulation (ovarian)

SIGNIFICANT DEVELOPMENTS AND COMBINATIONS

2017: Pembrolizumab granted the first tumor-site **agnostic approval** (MSI-H or dMMR solid tumors)

2025-2026: **subcutaneous** formulations (atezolizumab, nivolumab, pembrolizumab)

Novel immunotherapy combinations

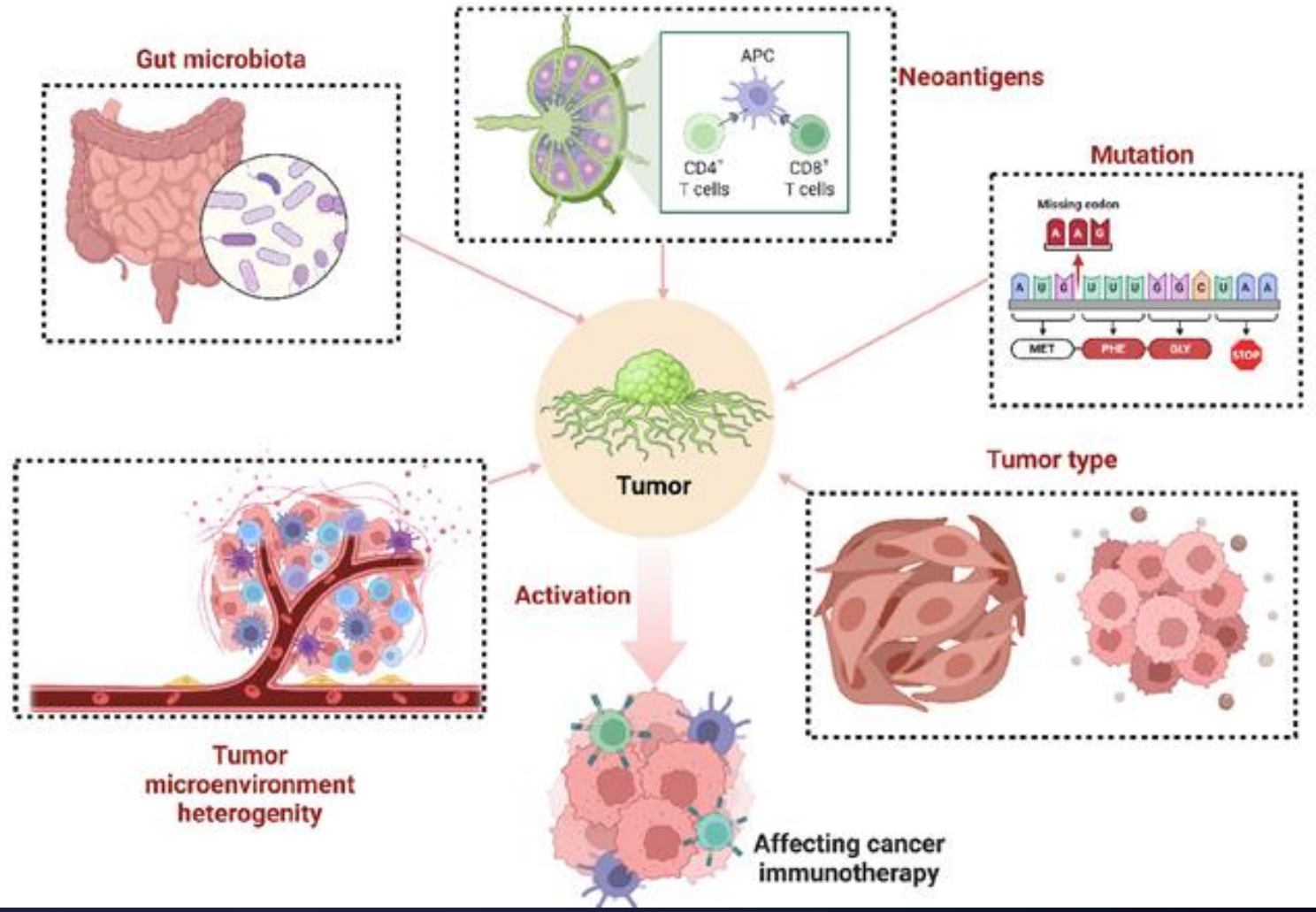
KEY NOVEL IMMUNOTHERAPY COMBINATIONS

Neoadjuvant and adjuvant setting, immunotherapy + chemotherapy as 1st line,

Immune Checkpoint Inhibitors + Anti-angiogenic Agents: anti PD1 with anti VEGF

Dual Checkpoint Inhibition: CTLA-4 with PD-1/PD-L1 inhibitors

FACTORS AFFECTING CANCER IMMUNOTHERAPY



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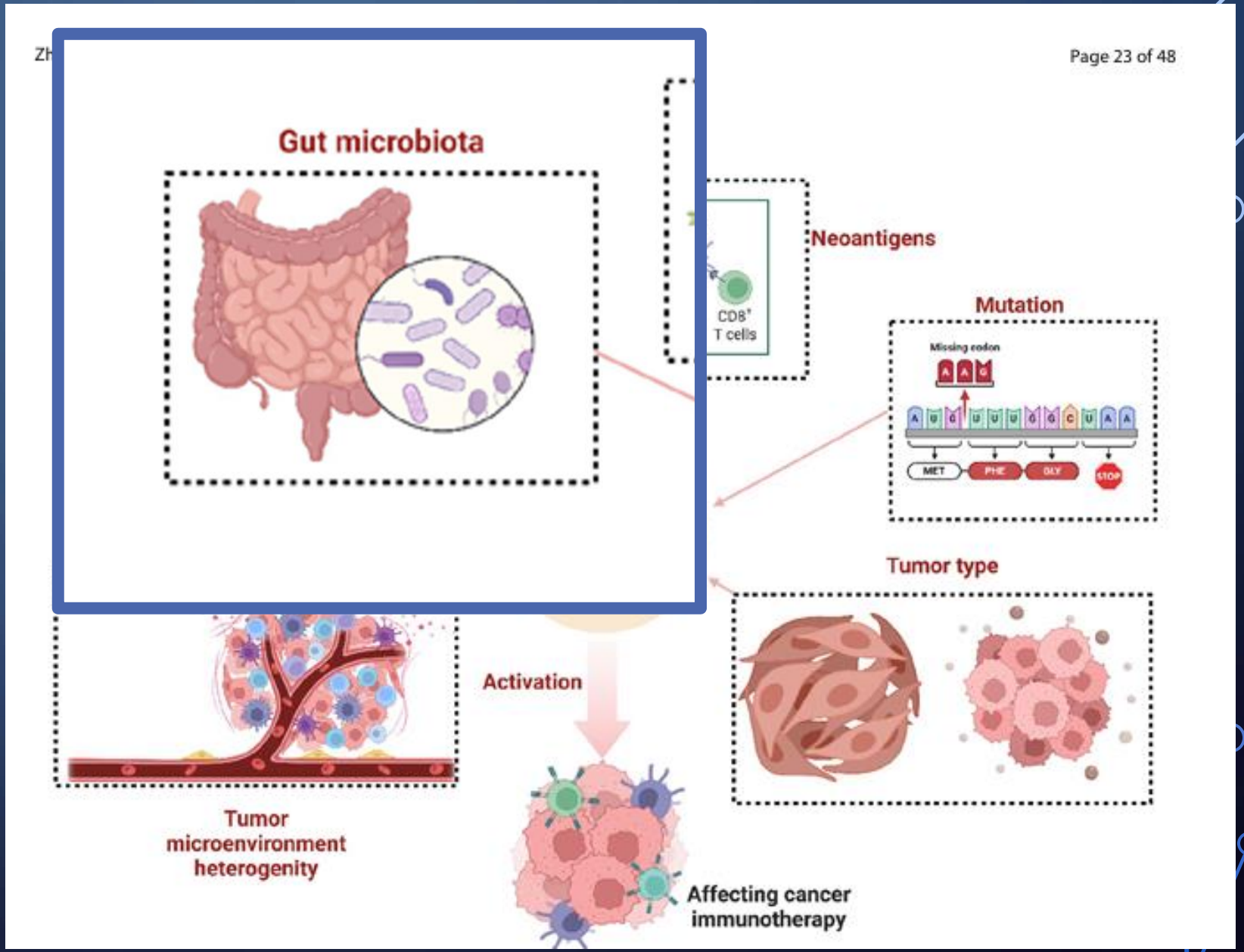


The role of the gut microbiota in tumor, immunity, and immunotherapy

Yuyan Xie and Fang Liu*

REVIEW Open Access

Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies

Yuting Lu[1], Xiangliang Yuan[2], Miao Wang[1], Zhihao He[1], Hongzhong Li[3], Ji Wang[4*] and Qin Li[1*]

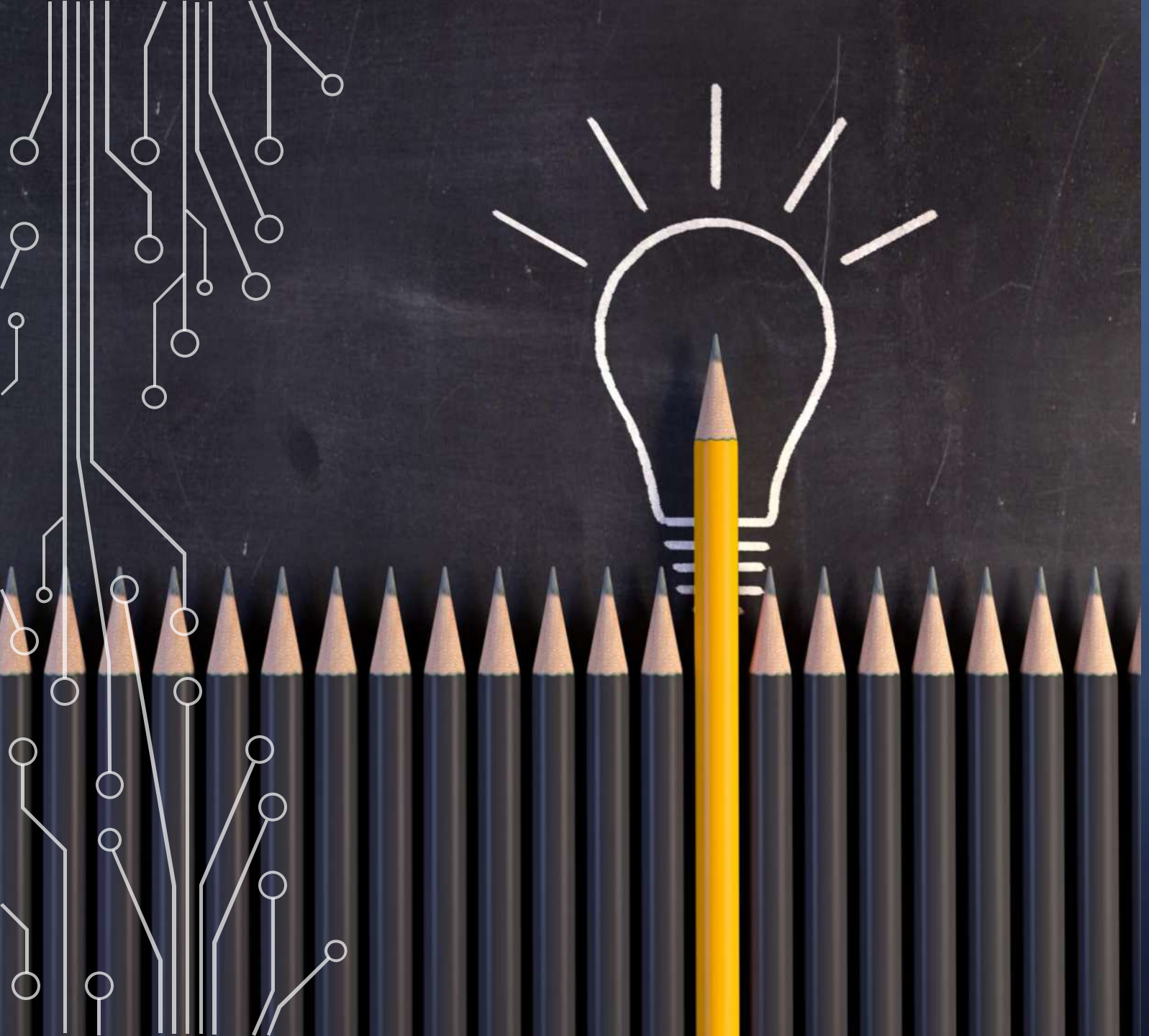
REVIEW Open Access

Critical role of the gut microbiota in immune responses and cancer immunotherapy

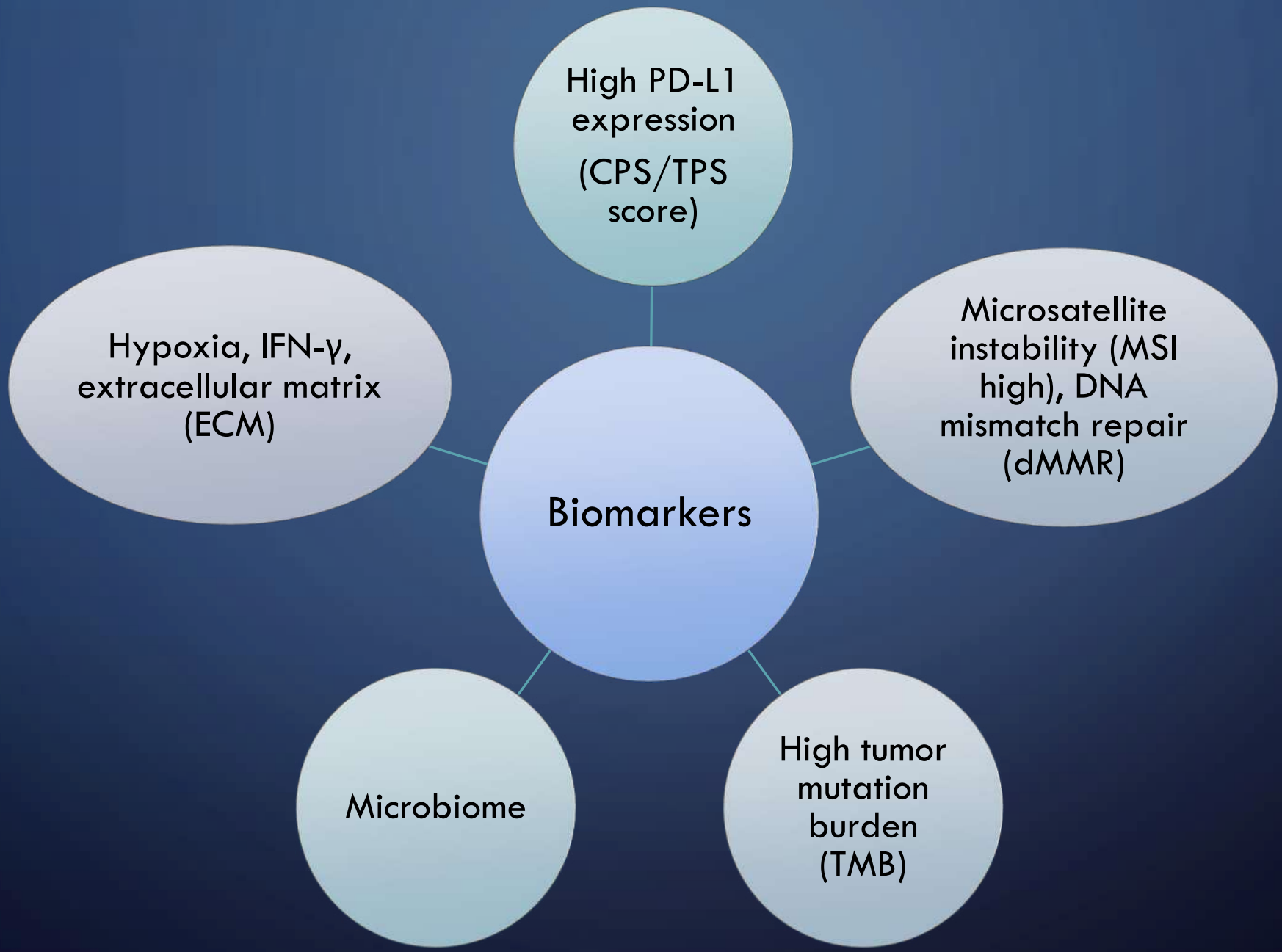
Zehua Li[1,2†], Weixi Xiong[3,4†], Zhu Liang[2,5†], Jinyu Wang[6], Ziyi Zeng[7], Damian Kołat[8,9], Xi Li[10], Dong Zhou[3,4], Xuewen Xu[1] and Linyong Zhao[11*]

Gut Microbiota and Immune Checkpoint Inhibitors–Based Immunotherapy

Mingming Tian [1], Si Zhang [2], Yujen Tseng [3], Xizhong Shen [1], Ling Dong [1], Ruyi Xue [1]



is immunotherapy beneficial for everyone?


High PD-L1 expression (CPS/TPS score)
Hypoxia, IFN-γ, extracellular matrix (ECM)
Microsatellite instability (MSI high), DNA mismatch repair (dMMR)
Biomarkers
Microbiome
High tumor mutation burden (TMB)

BIOMARKERS IN IMMUNOTHERAPY

Real world data!!!

Burden?

Aid?

PROs

Patient Selection: 20-30% of patients likely to respond to ICIs

Approval & Standardization: Validated markers such as PD-L1 expression, MSI-H, dMMR are integral to clinical guidelines for selecting first-line therapy

Tissue-Agnostic Options: MSI-H/dMMR and High TMB allow for approval of therapies based on molecular features rather than just tumor origin

Real-Time Monitoring: liquid biopsies like circulating tumor DNA (ctDNA) allow for non-invasive monitoring of treatment efficacy and early detection of relapse

CONs

Imperfect Predictors: A single biomarker is rarely sufficient. Many patients with high PD-L1 do not respond, while some with negative PD-L1 do

Assay Heterogeneity: Variability between testing platforms inconsistent results across laboratories and studies

Tumor Heterogeneity: Tumors are dynamic; a single biopsy may not represent the whole tumor or its evolution during treatment

Accessibility and Cost: Advanced diagnostics (NGS, Whole Exome Sequencing) are expensive and require infrastructure not always available

Hyper-progression Risks: In some cases, checkpoint inhibitors can accelerate tumor growth, a phenomenon that current biomarkers fail to reliably predict

IMMUNE RELATED ADVERSE EVENTS

irAEs

Common Terminology Criteria for Adverse Events (CTCAE)

v6.0 (MedDRA 28.0)

Published July 22, 2025

Cancer Therapy Evaluation Program
Division of Cancer Therapy and Diagnosis
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

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 instrumental ADL or mild/moderate impact on age-appropriate normal daily activity
Grade 3	Severe or medically significant but **NOT IMMEDIATELY LIFE-THREATENING**; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL or severe impact on age-appropriate normal daily activity
Grade 4	**LIFE-THREATENING** consequences; urgent intervention indicated
Grade 5	Death related to AE

Immunotherapies have transformed treatment landscape for multiple solid and hematologic malignancies

irAEs: disinhibition of T-cell function by ICIs can lead to organ-specific inflammatory side effects with unique toxicity profiles, variable depending on the type of immunotherapy

Pathophysiology: not yet fully understood, combination of pathways involving autoreactive T cells, autoantibodies, and cytokines

- 72% with ipilimumab monotherapy
- 66% with anti–PD-1/anti–PD-L1 monotherapy
- **Higher incidence with dual blockade**

Bertrand *et al. BMC Medicine* (2015) 13:211
DOI 10.1186/s12916-015-0455-8

BMC Medicine

RESEARCH ARTICLE Open Access

Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis

JAMA Oncol. 2019 Apr 25;5(7):1008–1019. doi: 10.1001/jamaoncol.2019.0393

Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials

A Systematic Review and Meta-analysis

Published in final edited form as:
N Engl J Med. 2017 October 05; 377(14): 1345–1356. doi:10.1056/NEJMoa1709684.

Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.-J. Grob, C.L. Cowey, C.D. Lao, J. Wagstaff, D. Schadendorf, P.F. Ferrucci, M. Smylie, R. Dummer, A. Hill, D. Hogg, J. Haanen, M.S. Carlino, O. Bechter, M. Maio, I. Marquez-Rodas, M. Guidoboni, G. McArthur, C. Lebbé, P.A. Ascierto, G.V. Long, J. Cebon, J. Sosman, M.A. Postow, M.K. Callahan, D. Walker, L. Rollin, R. Bhore, F.S. Hodi, and J. Larkin

JAMA Oncol. 2017 Aug 17;4(1):98–101. doi: 10.1001/jamaoncol.2017.2391

Measuring Toxic Effects and Time to Treatment Failure for Nivolumab Plus Ipilimumab in Melanoma

Alexander N Shoushtari [1,2,✉], Claire F Friedman [1,2], Pedram Navid-Azarbaijani [1,2], Michael A Postow [1,2], Margaret K Callahan [1,2], Parisa Momtaz [1,2], Katherine S Panageas [3], Jedd D Wolchok [1,2], Paul B Chapman [1,2]

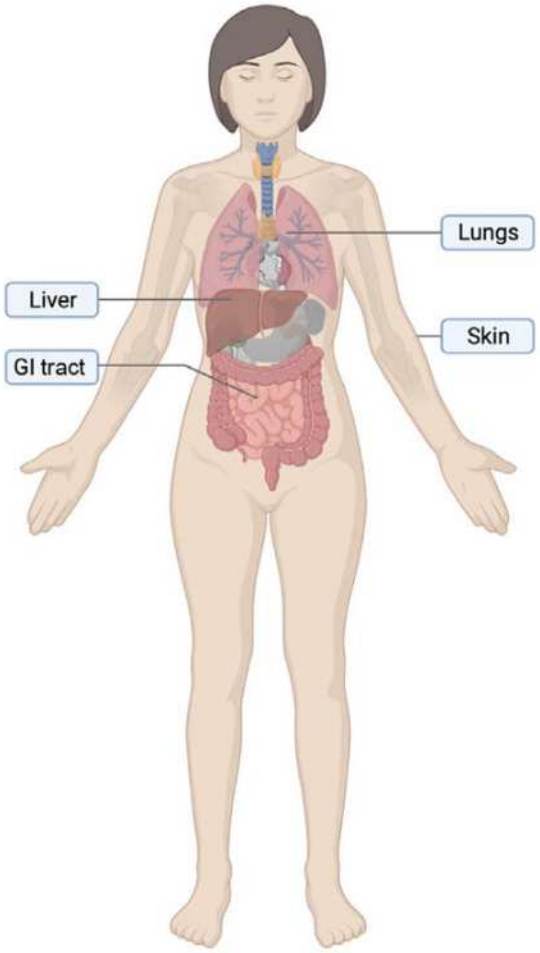
JAMA Oncol. 2018 Sep 13;4(12):1721–1728. doi: 10.1001/jamaoncol.2018.3923

Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors

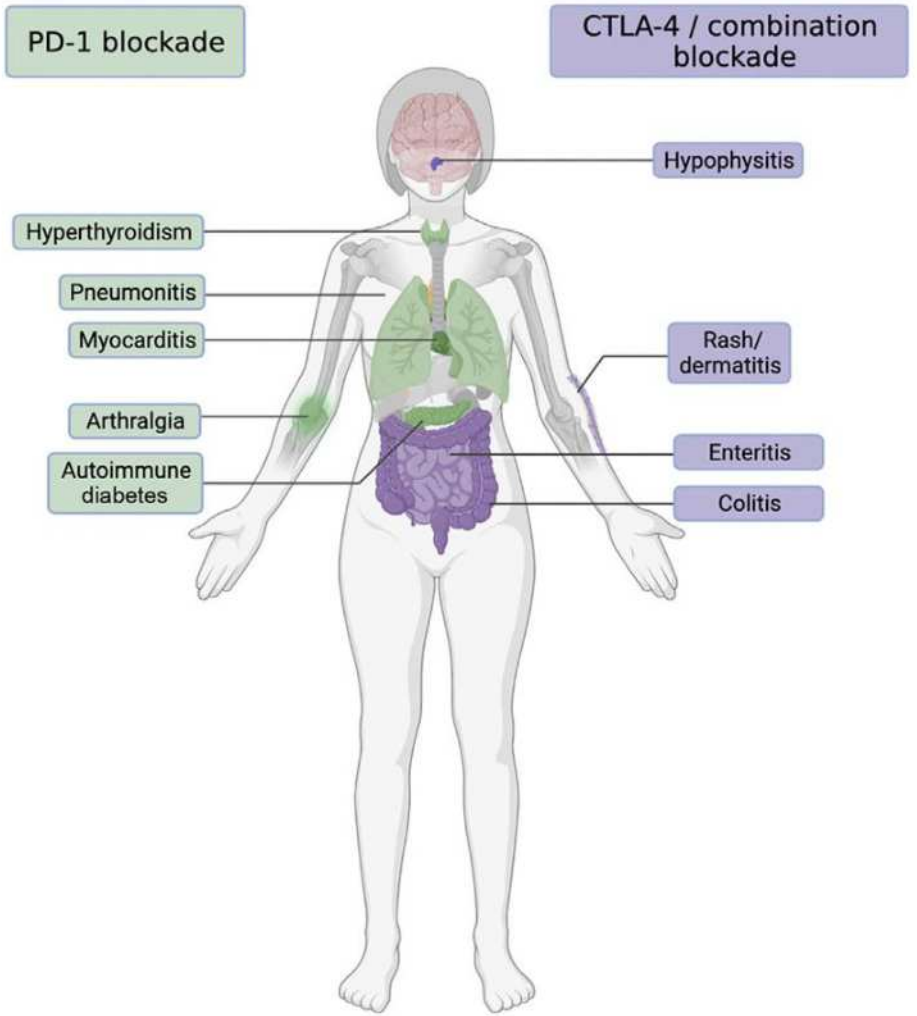
A Systematic Review and Meta-analysis

Daniel Y Wang [1], Joe-Elie Salem [1,2,3], Justine V Cohen [4], Sunandana Chandra [5], Christian Menzer [6], Fei Ye [7], Shilin Zhao [7], Satya Das [1], Kathryn E Beckermann [1], Lisa Ha [5], W Kimryn Rathmell [1], Kristin K Ancell [1], Justin M Balko [1], Caitlin Bowman [5], Elizabeth J Davis [1], David D Chism [1], Leora Horn [1], Georgina V Long [8,9,10,11], Matteo S Carlino [8,9,12,13], Benedicte Lebrun-Vignes [2,3], Zeynep Eroglu [14], Jessica C Hassel [6], Alexander M Menzies [8,9,12,13], Jeffrey A Sosman [5], Ryan J Sullivan [4], Javid J Moslehi [1], Douglas B Johnson [1,✉]

- 0.36% with anti–PD-1
- 0.38% with anti–PD-L1
- 1.08% with anti–CTLA-4
- 1.23% with combined anti–PD-1 / anti–PD-L1 and CTLA-4
- **Colitis (70%) with anti–CTLA-4 therapy**

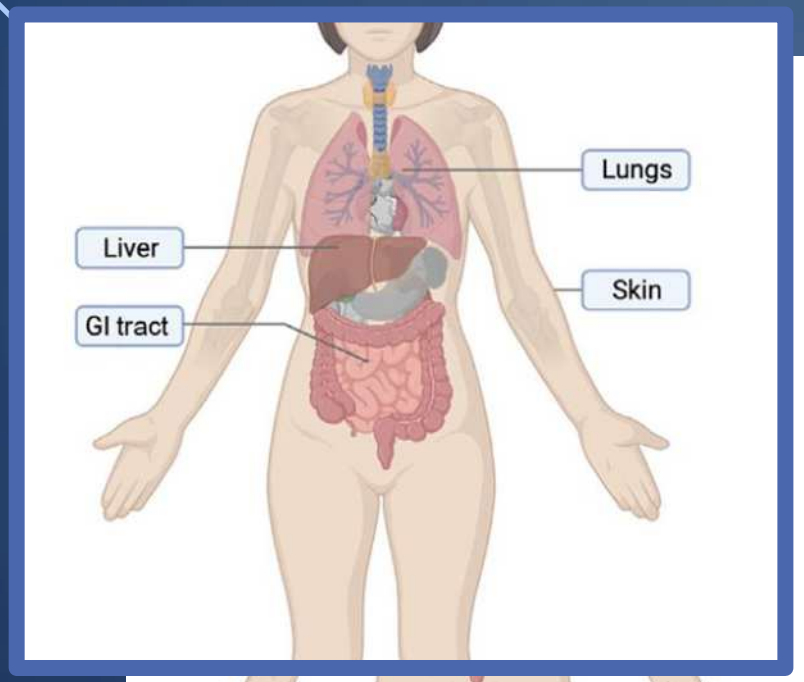


Major barrier organs

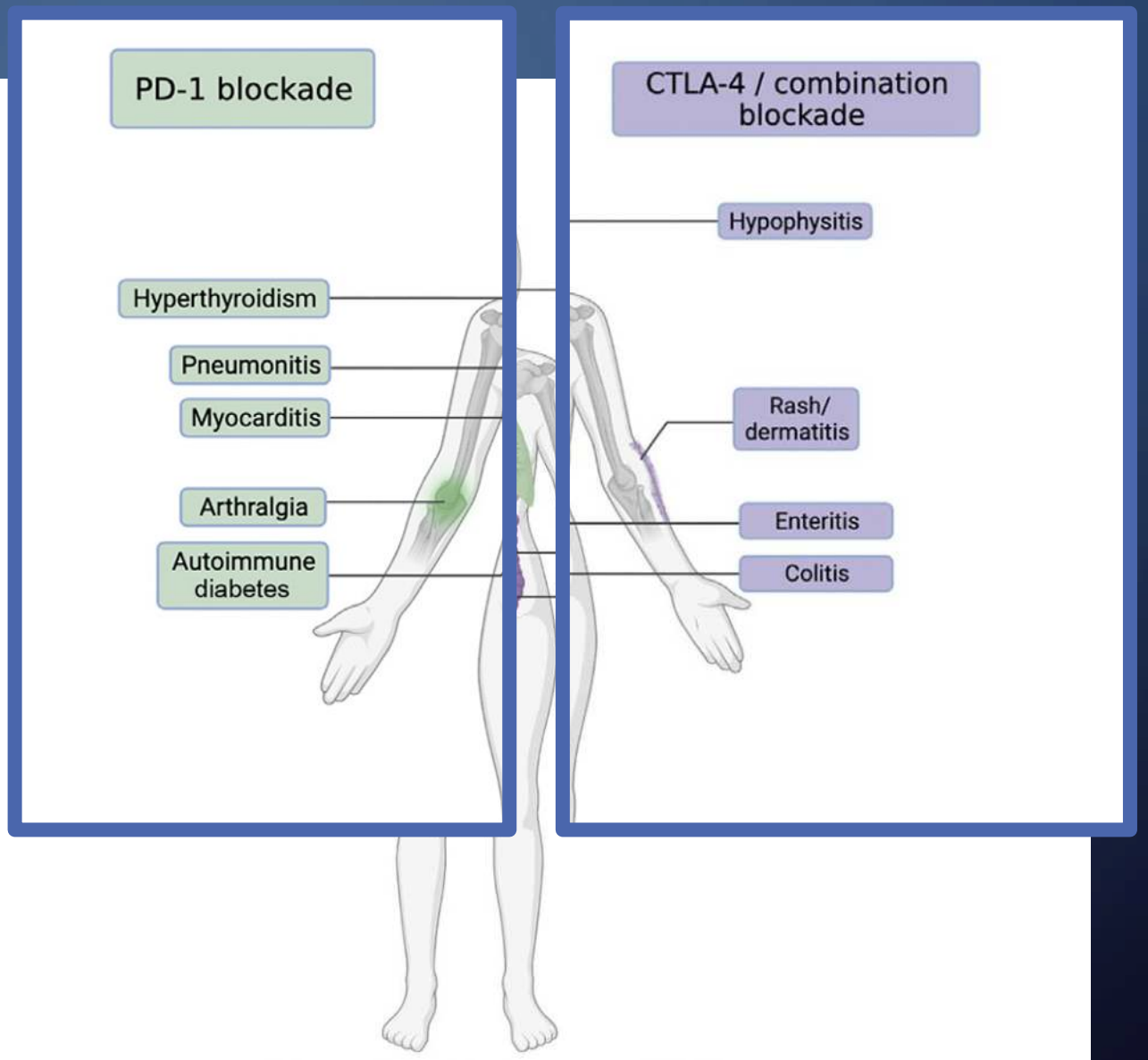


Most clinically important irAE

Trends in Cancer



Major barrier organs



Most clinically important irAE

Trends in Cancer

irAEs BASIC FEATURES

Variable in onset, kinetics, presentation, often require specific management
irAEs can affect any organ system in the body. Most toxicities occur at **barrier organs** including the skin, G.I. tract, liver, lungs
Most toxicities are mild, but severe toxicities in any of these organs can be life threatening
The fact that barrier organs are so commonly involved suggests that the antigenic targets may be the **commensal microbiome** (not yet demonstrated)
Distribution, severity, and frequency of irAEs related to the class of ICI used

irAEs BASIC FEATURES

CTLA-4 blockade leads to more frequent and severe toxicities than PD-1 blockade
Colitis and **hypophysitis** is more common with CTLA-4blockade than with either PD-1 or PD-L1 inhibitors
PD-1 blockade is more frequently associated with **thyroiditis** and **pneumonitis**
Combination immunotherapy is considerably more toxic, **additive rather than synergistic risk**
Treatment dependent on the organ involved and the severity of the inflammation, rather than on the class of checkpoint inhibitor that was used

DERMATOLOGIC TOXICITY

irCAEs (ir cutaneous AEs): Most common irAE in patients treated with CTLA-4 or PD-1/ PD-L1 blockade
All-grade toxicity: 30% to 40% of patients treated with PD-1/PD-L1 blockade and 50% of patients treated with ipilimumab
Most of the dermatologic toxicity is grade 1 or 2
Diverse presentation: from maculopapular or papulopustular to severe toxicities such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) or DRESS syndrome (mainly with a combination ICI)

DERMATOLOGIC TOXICITY

Most common cutaneous toxicities are maculopapular rash, pruritis, and vitiligo

Vitiligo: only in patients with melanoma (7.5% of patients treated with nivolumab, 8.3% of patients treated with pembrolizumab)

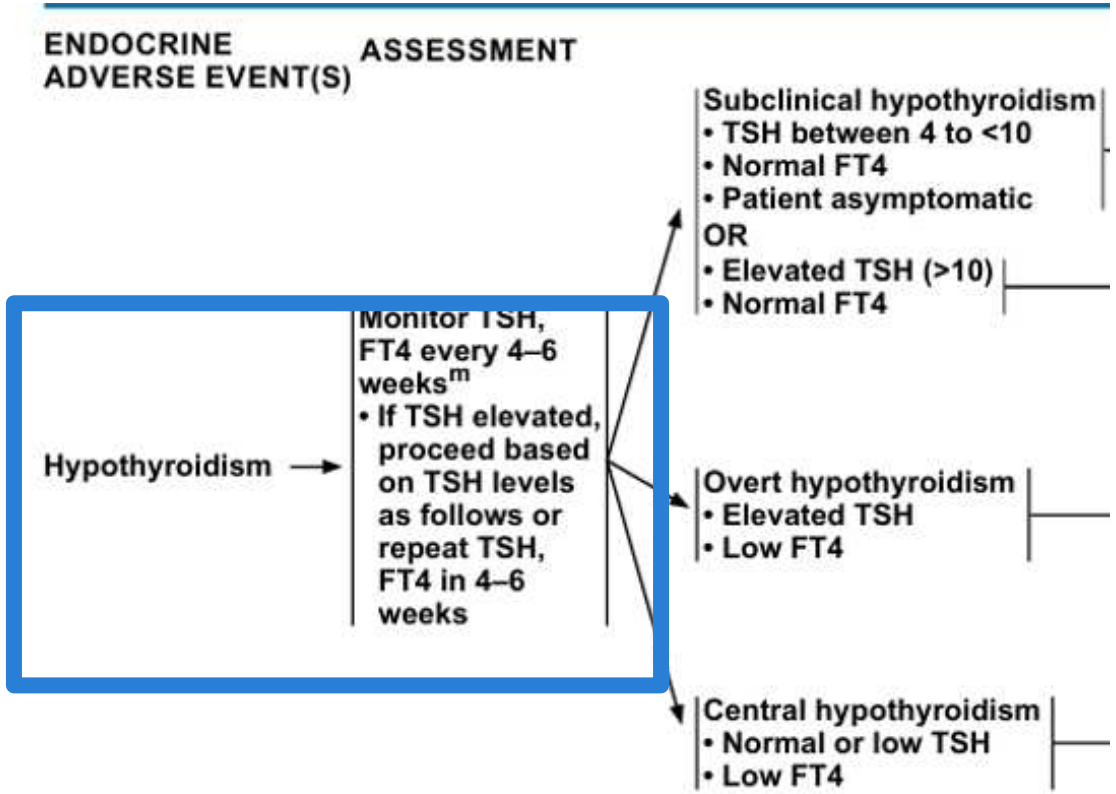
The development of vitiligo and dermatitis have been associated with **improved outcomes**!

ENDOCRINOPATHIES

Hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, primary adrenal insufficiency, insulin-dependent DM
Variable by agent, highest incidence after combination therapy
Presentation may be **nonspecific**, including nausea, fatigue, headache, or weakness
Unlike other irAEs, which resolve with treatment, endocrinopathies are almost always permanent and require **lifelong hormone replacement**

ENDOCRINOPATHIES THYROID DYSFUNCTION

Hypothyroidism is the most common endocrinopathy with ICI therapy
Thyroid storm and myxedema crisis have rarely been reported
Hypothyroidism more common with anti–PD-1 monotherapy than with anti–CTLA-4
Median onset of thyroid dysfunction occurs 4 weeks after starting therapy
Guidelines recommend checking **TSH** and free thyroxine levels at baseline and routinely during ICI therapy



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ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT
Hypothyroidism	Monitor TSH, FT4 every 4–6 weeks[m] • If TSH elevated, proceed based on TSH levels as follows or repeat TSH, FT4 in 4–6 weeks	
	Subclinical hypothyroidism • TSH between 4 to <10 • Normal FT4 • Patient asymptomatic	• Continue immunotherapy • Continue to monitor thyroid function tests (TFTs)
	OR • Elevated TSH (>10) • Normal FT4	• Continue immunotherapy • Consider levothyroxine if elevated TSH persists. If patient becomes symptomatic, treat as overt hypothyroidism
	Overt hypothyroidism • Elevated TSH • Low FT4	• Consider endocrine consultation • Check serum cortisol to exclude coexistent adrenal insufficiency prior to treatment • Initiate thyroid hormone supplementation with levothyroxine[n] ‣ Repeat TSH in 4–6 weeks to guide dosing changes • Continue immunotherapy once adrenal insufficiency is ruled out and replacement endocrine therapy has started
	Central hypothyroidism • Normal or low TSH • Low FT4	Hypophysitis/Central hypothyroidism (ICI_ENDO-3); exclude recovery from thyrotoxicosis and non-thyroidal illness
Thyrotoxicosis[o,p]	• Low or suppressed TSH with high FT4/total T3 • Consider endocrine consultation if symptomatic	• Continue immunotherapy if asymptomatic • Consider propranolol (10–20 mg every 4–6 hours for symptoms as needed) or atenolol or metoprolol as needed for symptoms until thyrotoxicosis resolves • Repeat TFTs in 4–6 weeks ‣ If resolved, no further therapy for thyrotoxicosis. Thyrotoxicosis often evolves to hypothyroidism (50%–90%) requiring treatment with thyroid hormone replacement (see Overt hypothyroidism above for levothyroxine dosing) ‣ If persistent thyrotoxicosis, consider evaluation for Graves' disease.[q]

ENDOCRINOPATHIES HYPOPHYSITIS

The highest incidence of hypophysitis occurs with anti **CTLA-4** monotherapy and combination therapy
Dose-dependent: 1%-4% with ipilimumab 3 mg/kg and 16% with 10 mg/kg
Deficiency of at least 1 pituitary hormone with **MRI** abnormality or deficiency of ≥2 pituitary hormones in the presence of symptoms
Adrenal insufficiency secondary to ICI-induced hypophysitis is usually permanent and requires **lifelong hormone replacement**
If adrenal insufficiency and hypothyroidism are both present, steroids should be started **before** thyroid hormone replacement to prevent **adrenal crisis**

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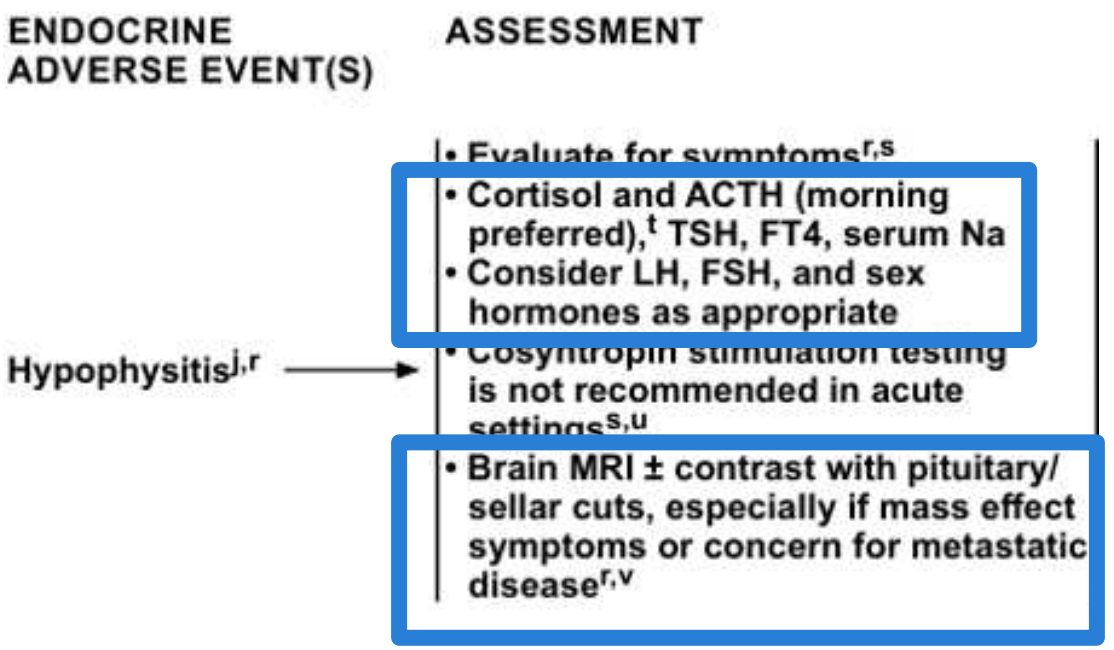
ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT
Hypophysitis[j,r]	• Evaluate for symptoms[r,s] • Cortisol and ACTH (morning preferred),[t] TSH, FT4, serum Na • Consider LH, FSH, and sex hormones as appropriate • Cosyntropin stimulation testing is not recommended in acute settings[s,u] • Brain MRI ± contrast with pituitary/sellar cuts, especially if mass effect symptoms or concern for metastatic disease[r,v]	• Endocrine consultation and patient education • Hold immunotherapy[k] until acute symptoms resolve and hormone replacement is initiated • If severe symptoms with concern for mass effect, may consider high-dose steroids[w] • Treat with physiologic hormone replacement[x,y,z] • Secondary adrenal insufficiency (low ACTH, low cortisol) ▸ Physiologic steroids in ambulatory patients and stress dosing for acute illness or surgery/procedures[j,x] • Central hypothyroidism (normal or low TSH, low FT4) ▸ Thyroid hormone replacement, titrate to FT4 level[y]
Primary adrenal insufficiency (high ACTH with low morning cortisol, abnormal cosyntropin stimulation test)	• Rare diagnosis that is not usually associated with checkpoint immunotherapy • If there is concern for this diagnosis, recommend endocrine consultation	



G.I. TOXICITY COLITIS

Diarrhea is a common complication, higher incidence in patients treated with CTLA-4 antibodies
Highest incidence of colitis in **dual** CTLA-4/PD-1 blockade, also increased risk of grade 3 and 4
In anti–CTLA-4 monotherapy, average onset after 3rd infusion, symptoms may occur since 1st infusion
Diarrhea or colitis may **recur** after discontinuation of therapy, presentation like chronic inflammatory bowel disease

G.I. TOXICITY COLITIS

Early flexible rectosigmoidoscopy or ileocolonoscopy with biopsies in patients with suspected IR enterocolitis of grade >1 is strongly recommended.
In ≥grade 2 ICI should be stopped and systemic **corticosteroids** started
If there is no response within 3 to 5 days, **infliximab** should be considered; a single 5-mg/kg dose is usually sufficient (also, shorter time to symptom resolution and shorter duration of steroid use)
Deep ulcerations and extensive inflammation above the left colon are predictive of **CS-refractory disease** and requirement for immunosuppressant treatment

oint Inhibitor-Related

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MANAGEMENT[p]

- Hydration
- Close monitoring[q]
- Dietary modifications[r]
- Consider loperamide or diphenoxylate/atropine for 2–3 days as an adjunct for symptom relief
  - If no improvement and not already done, obtain lab tests for infectious workup
  - Caution is warranted to avoid masking symptoms; discontinue antidiarrheals if diarrhea persists, to assess response to immunosuppressive therapy
- If persistent or progressive symptoms, check lactoferrin/calprotectin
  - If positive, treat as G2
  - If negative and no infection, continue G1 management and consider adding mesalamine and/or cholestyramine

GRADE 1

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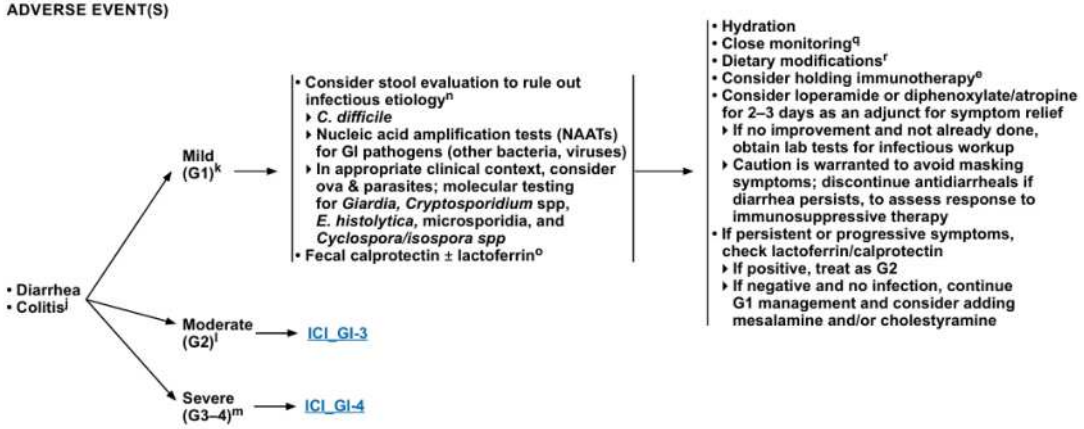

int Inhibitor-Related

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GRADE 2

- Hold immunotherapy[e]
- For pathologically confirmed microscopic colitis, consider budesonide 9 mg daily prior to systemic steroids[t]
- Prednisone/IV methylprednisolone[u,v] (1–2 mg/kg/day)[w]
- If no response to oral steroids after 3 days, consider IV steroids:
  - If colonoscopy or flexible sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis on histology,[x] consider adding infliximab[g,h,i,y] or vedolizumab[h,y,z]
    - ◊ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[aa]
- For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease)
- For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise

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GASTROINTESTINAL ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[p]
• Diarrhea • Colitis[j] Moderate (G2)[l]	• Stool evaluation to rule out infectious etiology[n] ▸ *C. difficile* ▸ NAATs for GI pathogens (other bacteria, viruses) ▸ In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia*, *Cryptosporidium* spp, *E. histolytica*, microsporidia, and *Cyclospora/isospora spp* • Fecal calprotectin ± lactoferrin[o] • Consider abdominal/pelvic CT with contrast[s] • Consider GI consultation ▸ Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy[o]	• Hold immunotherapy[e] • For pathologically confirmed microscopic colitis, consider budesonide 9 mg daily prior to systemic steroids[t] • Prednisone/IV methylprednisolone[u,v] (1–2 mg/kg/day)[w] • If no response to oral steroids after 3 days, consider IV steroids: ▸ If colonoscopy or flexible sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis on histology,[x] consider adding infliximab[g,h,i,y] or vedolizumab[h,y,z] ◊ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[aa] • For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease) • For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise

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GRADE 3-4

- G3: If using combination IO therapy, discontinue current therapy[e]
- G4: Discontinue immunotherapy agent responsible for toxicity[e]
- Consider inpatient care for provision of supportive care
- IV methylprednisolone[v] (1–2 mg/kg/day)[w]
- If no response in 1–2 days or unable to transition to oral steroids, additional immunosuppression required
  - If colonoscopy or flexible sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis on histology,[x] continue steroids and strongly consider adding infliximab[g,h,i,y] or vedolizumab[h,y,z,aa]
    - ◊ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[aa]
- For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease)
- For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise

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GRADING

- Diarrhea
- Colitis
  Severe (G3–4)[m]

ASSESSMENT/GRADING

- Stool evaluation to rule out infectious etiology[n]
  - *C. difficile*
  - NAATs for GI pathogens (other bacteria, viruses)
  - In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia, Cryptosporidium* spp, *E. histolytica,* microsporidia, and *Cyclospora/isospora spp*
- Fecal calprotectin ± lactoferrin[o]
- Consider abdominal/pelvic CT with contrast[s]
- Recommend GI consultation
  - Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy[o]

MANAGEMENT[p]

- G3: If using combination IO therapy, discontinue current therapy[e]
- G4: Discontinue immunotherapy agent responsible for toxicity[e]
- Consider inpatient care for provision of supportive care
- IV methylprednisolone[v] (1–2 mg/kg/day)[w]
- If no response in 1–2 days or unable to transition to oral steroids, additional immunosuppression required
  - If colonoscopy or flexible sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis on histology,[x] continue steroids and strongly consider adding infliximab[g,h,i,y] or vedolizumab[h,y,z,aa]
    - ◊ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[aa]
- For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease)
- For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Start infliximab at 5 mg/kg.
[h] Perform ID screening (HIV; hepatitis A, B, C), and TB blood test (eg, T-Spot/QuantiFERON-TB Gold) (depending on facility), preferably before administering first dose of infliximab or vedolizumab. In urgent situations, treatment does not need to be held for results.
[i] Infliximab antibody testing is generally not recommended and should not delay switch of therapy.
[m] More than 6 bowel movements above baseline per day, colitis symptoms, interference with

G.I. TOXICITY HEPATOTOXICITY

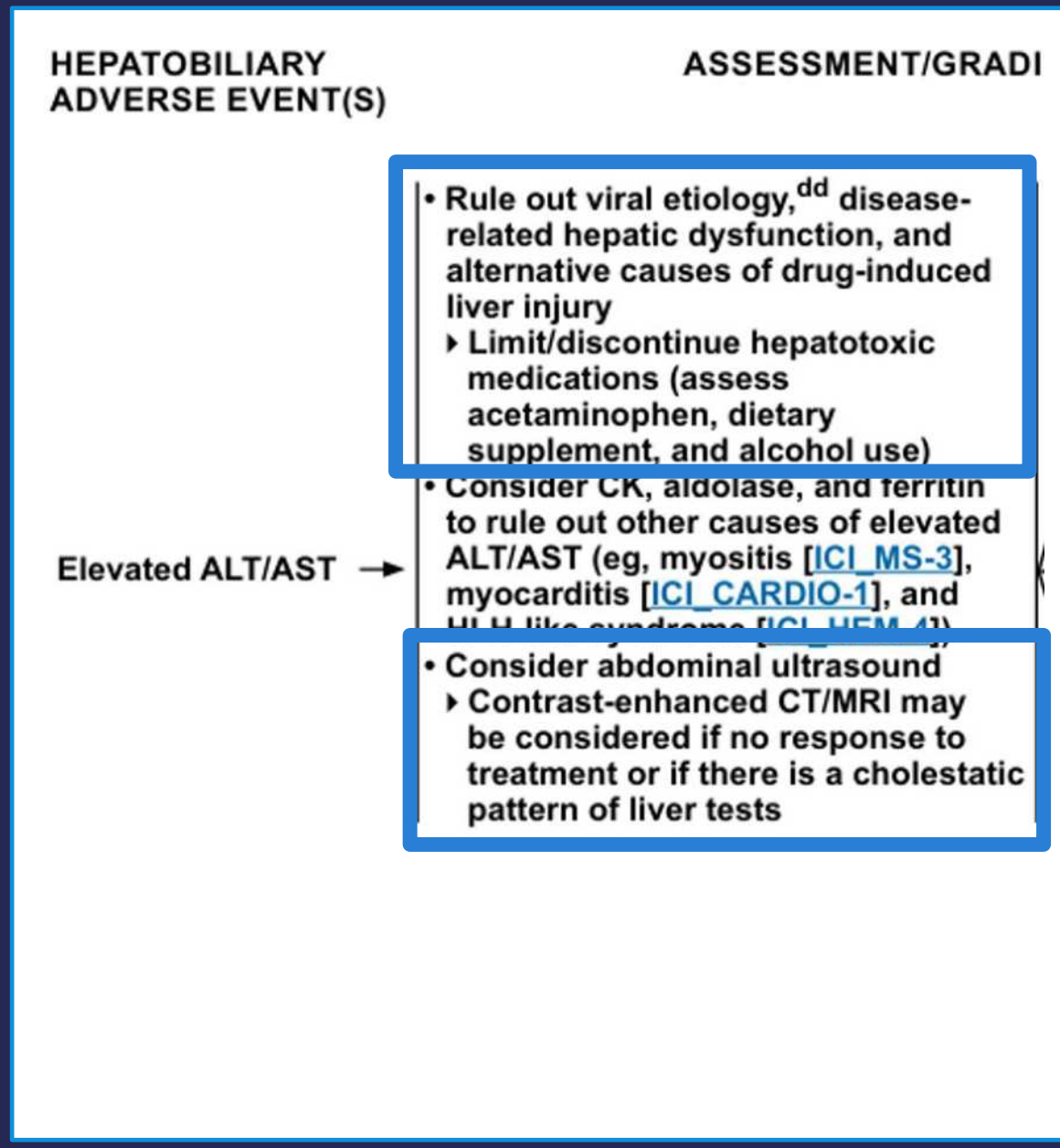
Estimated incidence **3% to 9%** in patients treated with ipilimumab and 1% to 2% in those treated with anti PD-1/anti–PD-L1 antibodies
The incidence of ipilimumab-induced hepatitis is **dose-dependent**
Most often asymptomatic elevations of AST and ALT with or without hyperbilirubinemia
Transaminase elevation is observed between 6 and 14 weeks after the initiation of treatment

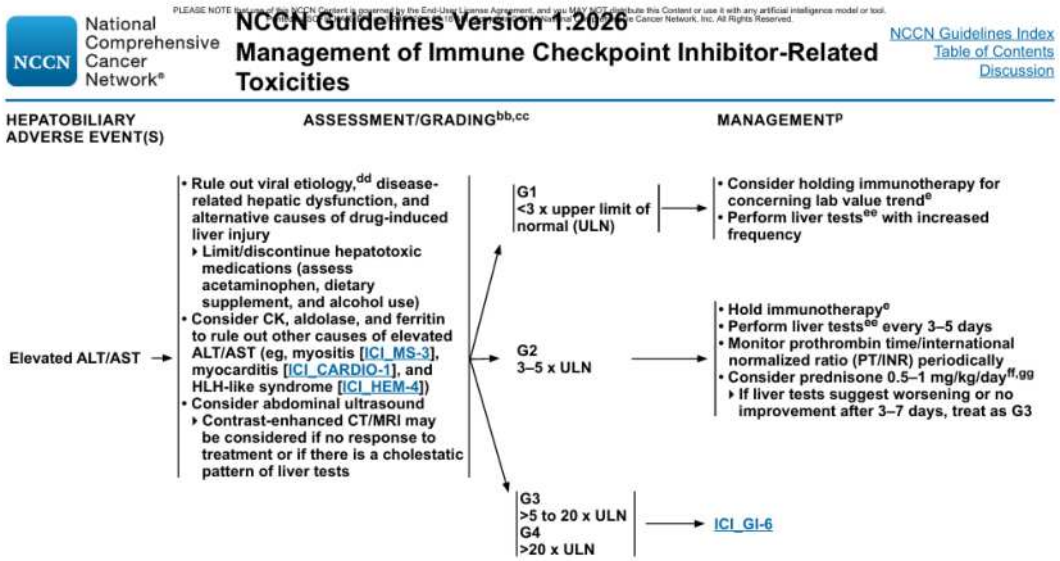
G.I. TOXICITY HEPATOTOXICITY

Most cases resolve with treatment discontinuation, but multiple reports of acute liver failure have been published

In grade 2 toxicity, ICI should be held and liver function tests monitored; therapy can be resumed when there is resolution to grade 1, and **corticosteroids** should be started if there is no improvement

Rare cases are refractory to high-dose steroids, and then **mycophenolate mofetil** or **tacrolimus** or **tocilizumab** should be considered. **Infliximab is contraindicated** according to some guidelines given concerns about hepatotoxicity


HEPATOBILIARY ADVERSE EVENT(S)
ASSESSMENT/GRADI
• Rule out viral etiology,dd disease-related hepatic dysfunction, and alternative causes of drug-induced liver injury
▸ Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)
Elevated ALT/AST
• Consider CK, aldolase, and ferritin to rule out other causes of elevated ALT/AST (eg, myositis [ICI_MS-3], myocarditis [ICI_CARDIO-1], and
• Consider abdominal ultrasound
▸ Contrast-enhanced CT/MRI may be considered if no response to treatment or if there is a cholestatic pattern of liver tests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HEPATOBILIARY ADVERSE EVENT(S)
ASSESSMENT/GRADINGbb,cc
MANAGEMENTp
Elevated ALT/AST
• Rule out viral etiology,dd disease-related hepatic dysfunction, and alternative causes of drug-induced liver injury
▸ Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)
• Consider CK, aldolase, and ferritin to rule out other causes of elevated ALT/AST (eg, myositis [ICI_MS-3], myocarditis [ICI_CARDIO-1], and HLH-like syndrome [ICI_HEM-4])
• Consider abdominal ultrasound
▸ Contrast-enhanced CT/MRI may be considered if no response to treatment or if there is a cholestatic pattern of liver tests
G1
<3 x upper limit of normal (ULN)
• Consider holding immunotherapy for concerning lab value trende
• Perform liver testsee with increased frequency
G2
3–5 x ULN
• Hold immunotherapye
• Perform liver testsee every 3–5 days
• Monitor prothrombin time/international normalized ratio (PT/INR) periodically
• Consider prednisone 0.5–1 mg/kg/dayff,gg
▸ If liver tests suggest worsening or no improvement after 3–7 days, treat as G3
G3
>5 to 20 x ULN
G4
>20 x ULN
ICI_GI-6

GRADE 3-4

MANAGEMENT[p,hh]

- Monitor PT/INR weekly or more often if clinically indicated based on liver tests and patient condition
- Consider diagnostic parenchymal liver biopsy if no contraindications
  - Reserve for atypical (cholestatic) clinical/biochemical presentation or when there is no response to standard therapy

- Hold immunotherapy[e]
- Initiate prednisone/IV methylprednisolone 0.5–1 mg/kg/day[ff,g]
  - If no improvement after 1–2 days, consider adding mycophenolate mofetil or tacrolimus[ii]
    - ◊ If refractory to mycophenolate mofetil or tacrolimus, consider tocilizumab or other steroid-sparing immunosuppressive therapy[jj,kk]
  - Urgent GI/hepatology referral if no improvement after 7 days of treatment or if 2 immunosuppressive agents do not yield adequate response within an additional 7 days
- Consider inpatient care, particularly if synthetic hepatic dysfunction is observed[ll]
- Perform liver tests[ee] every 1–5 days depending on magnitude and rate of change

- Discontinue immunotherapy[e]
- Initiate prednisone/IV methylprednisolone 0.5–1 mg/kg/day[ff,gg,mm]
  - If no improvement after 1–2 days, consider adding mycophenolate mofetil or tacrolimus[ii]
    - ◊ If refractory to mycophenolate mofetil or tacrolimus, consider tocilizumab or other steroid-sparing immunosuppressive therapy[jj,kk]
  - Urgent GI/hepatology referral if no improvement after 7 days of treatment or if 2 immunosuppressive agents do not yield adequate response within an additional 7 days
- Inpatient care, particularly if synthetic hepatic dysfunction is observed[ll]
- Perform liver tests[ee] every 1–3 days

Footnotes on ICI_GI-6A

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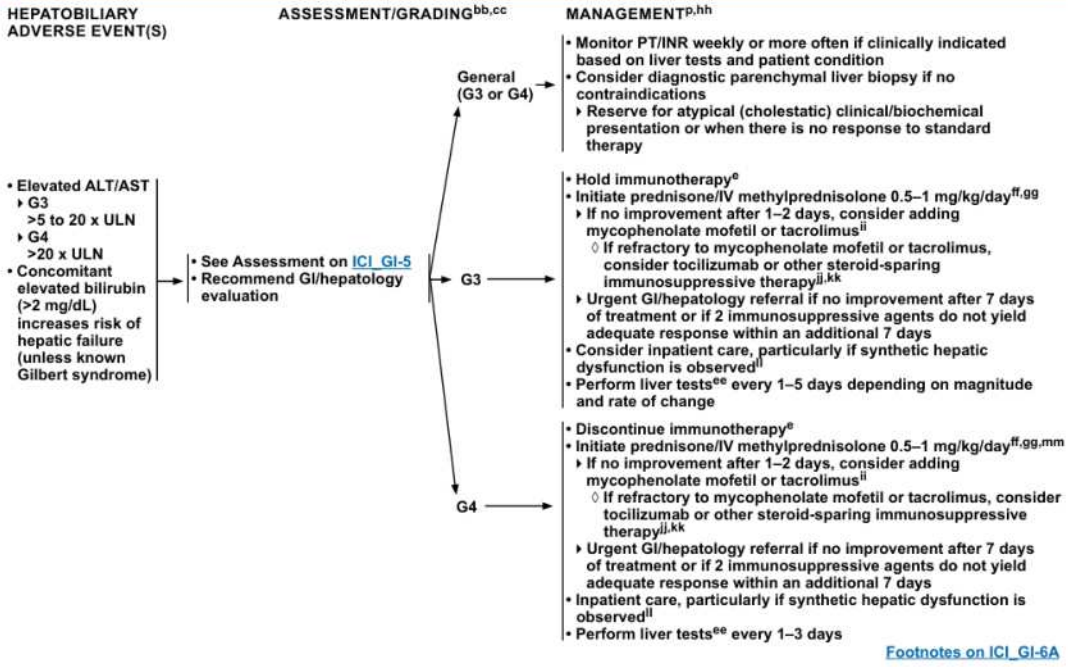

PNEUMONITIS

The most common pulmonary toxicity of ICI therapy
Low overall incidence but **potentially life-threatening** and should be considered in any patient who develops new respiratory symptoms
A meta-analysis of fatal AEs of ICI found that 35% of anti–PD-1/anti–PD-L1–related fatalities resulted from pneumonitis
Incidence slightly higher with **PD-1** monotherapy vs CTLA-4 monotherapy and increases with dual checkpoint inhibition
More common and more severe in patients who have **NSCLC** compared to melanoma and RCC (underlying lung pathology, including COPD and pulmonary fibrosis)

PNEUMONITIS

Presentation varies in severity and acuity of onset
Cough, chest pain, wheezing, shortness of breath, new hypoxia, or fatigue
Some are **asymptomatic,** with a diagnosis made incidentally on imaging studies
High index of suspicion should be maintained in patients on ICI therapy who develop respiratory symptoms
Baseline pulmonary function tests can be considered in patients who are at high risk

PNEUMONITIS

Concurrent **broad-spectrum antibiotics** and immunosuppression during workup because of the potential for overlapping presentation of pneumonitis and infection
In grade ≥2 pneumonitis, ICI should be withheld, pulmonology should be consulted for bronchoscopy with bronchoalveolar lavage, high-dose **steroids** should be started, and hospitalization may be needed
Limited data exist regarding the management of **steroid- refractory** pneumonitis
Additional immunosuppression with **infliximab**, **cyclophosphamide**, or **mycophenolate mofetil** can be considered

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PULMONARY ADVERSE EVENT(S)	GRADING	MANAGEMENT[f]
Pneumonitis[a]	Mild (G1)[b]	• Consider holding immunotherapy[g] • Reassess in 1–2 weeks ▸ History and physical (H&P) ▸ Pulse oximetry (resting and with ambulation) • Consider chest CT with contrast[h,i] ▸ Consider repeat chest CT in 4–6 weeks or as clinically indicated if patient develops symptoms
	Moderate (G2)[c,d]	• Hold immunotherapy[g] • Consider pulmonary consultation • Minimally invasive evaluation ▸ Consider infectious workup: ◊ Nasal swab for potential viral pathogens[j] ◊ Sputum culture (including bacterial, fungal, and acid-fast bacilli [AFB]), blood culture, and urine antigen test (eg, *pneumococcus*, *legionella*) ▸ Chest CT with contrast[h,i] and repeat chest CT in 3–4 weeks • Invasive evaluation ▸ Consider early bronchoscopy with BAL (send for institutional immunocompromised panel[k]) and consider transbronchial lung biopsy if clinically feasible to evaluate for progressive malignancy, fungal infections, or steroid responsive ILD • Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded • Prednisone/IV methylprednisolone 1–2 mg/kg/day[l] ▸ Consider mycophenolate mofetil as a steroid-sparing immunosuppressant for steroid-dependent pneumonitis at the time of steroid tapering[m] • Monitor every 3–7 days with[n]: ▸ H&P and pulse oximetry (resting and with ambulation) • If no improvement after 48–72 hours of steroids,[o] treat as grade 3
	Severe (G3–4)[e]	ICI_PULM-2

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GRADING	MANAGEMENT[f]
Mild (G1)[b]	• Consider holding immunotherapy[g] • Reassess in 1–2 weeks ▸ History and physical (H&P) ▸ Pulse oximetry (resting and with ambulation) • Consider chest CT with contrast[h,i] ▸ Consider repeat chest CT in 4–6 weeks or as clinically indicated if patient develops symptoms
Moderate (G2)[c,d]	• Hold immunotherapy[g] • Consider pulmonary consultation • Minimally invasive evaluation ▸ Consider infectious workup: ◊ Nasal swab for potential viral pathogens[j] ◊ Sputum culture (including bacterial, fungal, and acid-fast bacilli [AFB]), blood culture, and urine antigen test (eg, *pneumococcus*, *legionella*) ▸ Chest CT with contrast[h,i] and repeat chest CT in 3–4 weeks • Invasive evaluation ▸ Consider early bronchoscopy with BAL (send for institutional immunocompromised panel[k]) and consider transbronchial lung biopsy if clinically feasible to evaluate for progressive malignancy, fungal infections, or steroid responsive ILD • Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded • Prednisone/IV methylprednisolone 1–2 mg/kg/day[l] ▸ Consider mycophenolate mofetil as a steroid-sparing immunosuppressant for steroid-dependent pneumonitis at the time of steroid tapering[m] • Monitor every 3–7 days with[n]: ▸ H&P and pulse oximetry (resting and with ambulation) • If no improvement after 48–72 hours of steroids,[o] treat as grade 3

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ASSESSMENT/ GRADING

Severe (G3–4)[e] pneumonitis[a] →

MANAGEMENT[f]

- Hold immunotherapy[g]
- Inpatient care
- Pulmonary and ID consultation
- Minimally invasive evaluation
  - Infectious workup:
  - Consider that the patient may be immunocompromised
    - ◊ Nasal swab for potential viral pathogens[j]
    - ◊ Sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (eg, *pneumococcus*, *legionella*)
    - ◊ Consider cardiac evaluation to exclude cardiac causes for clinical presentation
- Invasive evaluation
  - Bronchoscopy with BAL (send for institutional immunocompromised panel[k]) if feasible to rule out infection, malignant lung infiltration, or steroid responsive ILD and consider transbronchial lung biopsy if feasible and clinically indicated
- Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
- IV methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks[f]
- Consider adding any of the following if no improvement after 48 hours:
  - Preferred:
    - ◊ IVIG[p]
    - ◊ Tocilizumab[q]
  - Other recommended:
    - ◊ Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service[m]
      - – Consider mycophenolate mofetil as a steroid-sparing immunosuppressant for steroid-dependent pneumonitis at the time of steroid tapering[m]
    - ◊ Infliximab[r] 5 mg/kg, a second dose may be repeated 14 days later at the discretion of the treating provider

RENAL TOXICITY

Rare, estimated incidence of 2% with ICI monotherapy and 5% with combination therapy
Presentation varies, worsening hypertension, electrolyte imbalance, altered urinary output, or rising creatinine
Renal toxicity occurs earlier with **ipilimumab** therapy (2-3 months) compared with anti–PD-1 therapy (3-10 months)
Acute interstitial nephritis (**AIN**) is the most commonly reported pathology
Workup includes urinalysis, renal ultrasound, **biopsy** if needed

RHEUMATOLOGIC TOXICITY

Incidence not well characterized, difficulty in distinguishing between these irAEs and other musculoskeletal complaints
Variable presentations including arthritis, with symptoms persisting **beyond cessation** of checkpoint blockade
Grade 1: nonsteroidal anti-inflammatory drugs, followed by **prednisone** if no improvement occurs
Grade ≥2: prednisone or even methotrexate, sulfasalazine, leflunomide, or anticytokine therapy in steroid-refractory cases

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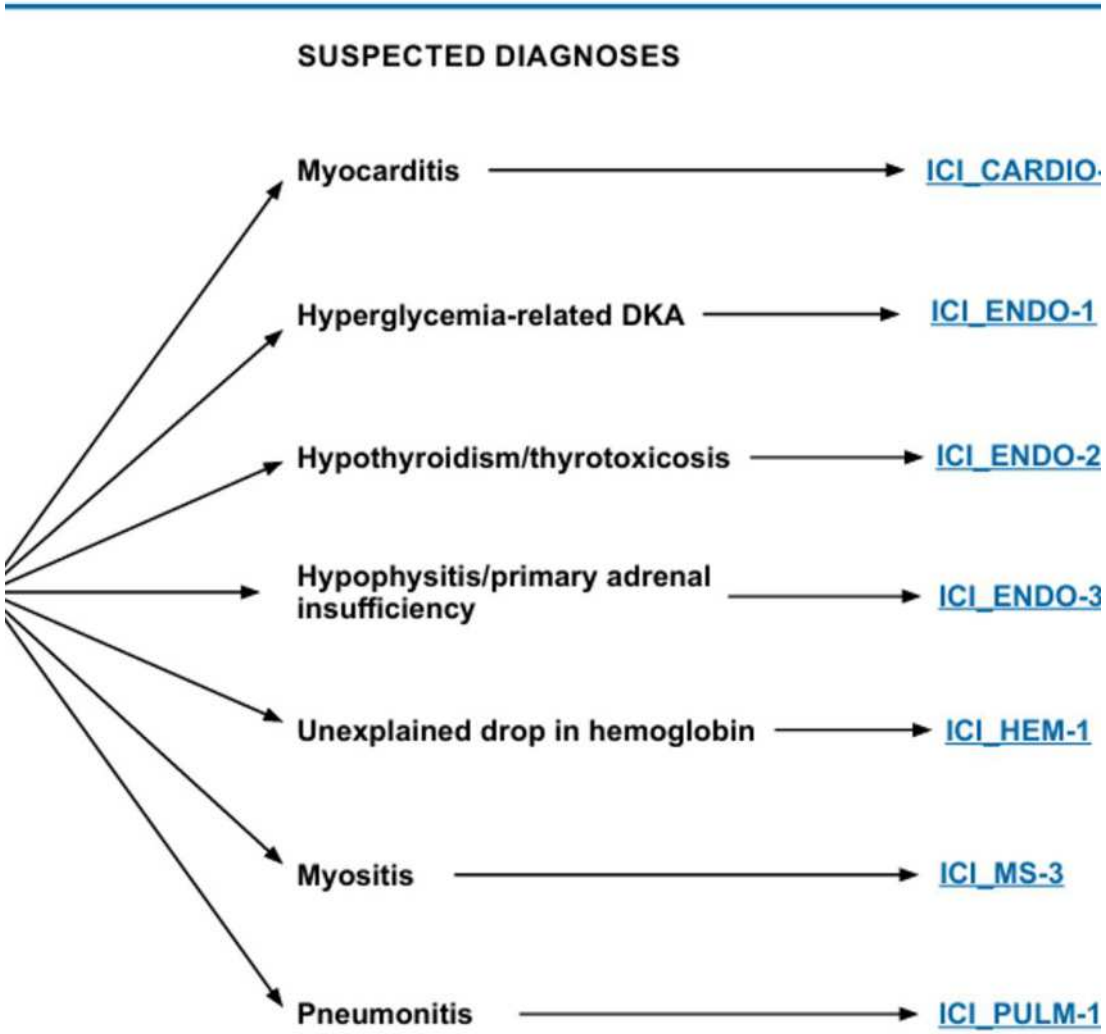
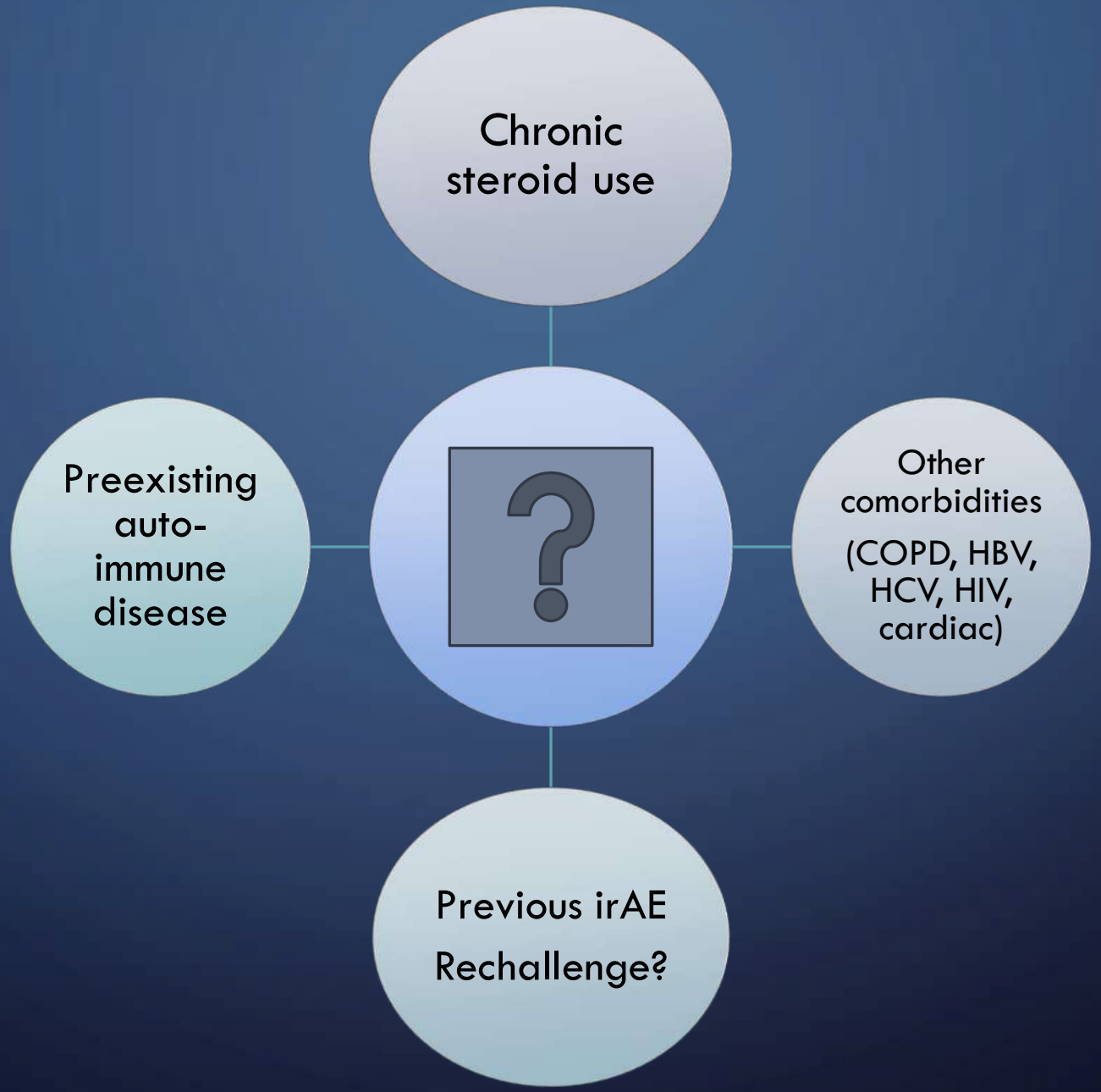
Management
Toxicities

SE (S)	ASSESSMENT
FATIGUE	• Evaluate for and rule out other non-ICI–related etiologies of fatigue • Physical exam including vital signs (weight, temperature, heart rate, respiratory rate [RR], blood pressure, oxygen saturation [rest and walking]) • Lab tests ▸ CBC ▸ CMP ▸ TSH, FT4 (if not done recently) ▸ Morning cortisol ▸ Morning ACTH (if morning cortisol subnormal) ▸ Morning testosterone ▸ CK and cardiac enzymes • Medication review • Assess for depression (consider PHQ-9)[a]




Chronic steroid use
Preexisting auto-immune disease
?
Other comorbidities (COPD, HBV, HCV, HIV, cardiac)
Previous irAE Rechallenge?


OncoDaily io
Steroids and Immunotherapy
Friend or Enemy ?

Cancer-related symptoms

- Edema related to tumor or metastasis (e.g. brain edema)
- Tumor compression
- Bone or neuropathic pain
- Fatigue, anorexia and cachexia
- Peritoneal carcinosis with bowel obstruction

Treatment of drug-related adverse events

- Chemotherapy-induced nausea or vomiting
- Hypersensitivity reactions
- Immune-related adverse events
- Drug- and radiation-induced adverse events

CORTICOSTEROIDS

Symptoms related to comorbidities

- Chronic obstructive pulmonary disease
- Autoimmune disease
- Paraneoplastic syndrome

Anti-cancer treatment

- B- and T-cell non-Hodgkin lymphoma
- Multiple myeloma
- B- and T-cell acute lymphoid leukemia

Prevention of adverse drug reactions

- Nausea
- Hypersensitivity reactions

STEROIDS AND IMMUNOTHERAPY

Dosing and timing!

Most prospective clinical trials have excluded patients receiving doses of steroids above physiologic levels (e.g., prednisone 7.5mg or more)

>10mg/day of prednisone was independently associated with poorer clinical outcomes after adjusting for covariates, such as smoking history, performance status, and history of brain metastases

STEROIDS AND IMMUNOTHERAPY

ICI requires an intact and robust immune response; the **immunosuppressive** properties of steroids have led to a widespread concern they may interfere with antitumor responses

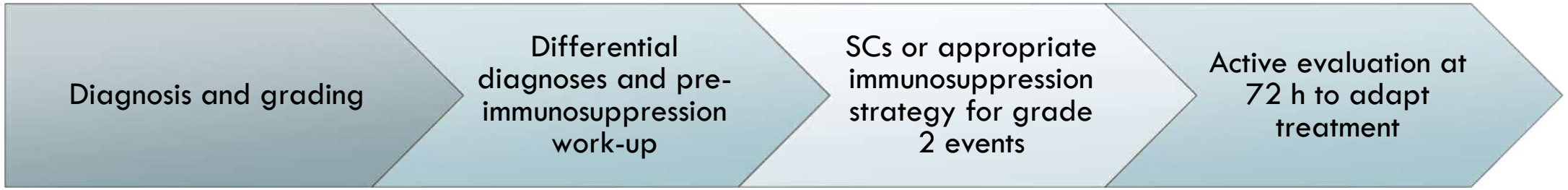
Steroid use **shortly** after starting therapy intuitively could pose a heightened risk of adverse clinical outcomes compared with **later use,** potentially by forestalling a developing anti-tumor immune response

AUTOIMMUNE HISTORY OR PRIOR IRAE

In patients with **preexisting autoimmune** disease there is a risk of exacerbation of autoimmunity
In patients with **prior irAEs,** there is a risk of redevelopment of prior irAEs, or development of de novo irAEs with ICI therapy
These populations were excluded from **trials** leading to FDA approval
Diverse spectrum of disease pathophysiology and severity, long-term prospective studies are needed to clarify the optimal approach

RECHALLENGE?

Permanent discontinuation of ICI after **grade 4** irAEs, except for endocrine toxicity, which is managed with physiologic hormone replacement, and after **grade 3** toxicity with a high risk of morbidity and mortality
Nature and severity of the autoimmune disease or irAE, the organ system affected, goals of treatment, therapeutic alternatives, and the expected clinical benefit of additional ICI
Multidisciplinary teams (MDTs), **case by-case basis**


Diagnosis and grading
Differential diagnoses and pre-immunosuppression work-up
SCs or appropriate immunosuppression strategy for grade 2 events
Active evaluation at 72 h to adapt treatment

	PROs	CONs
chemotherapy	• Not expensive • No need for biomarkers • Fast results	• Targets rapidly dividing cells (both healthy and malignant) • Resistance • Toxicities, hair loss • Limited number of cycles
immunotherapy	• Uses host immune system against cancer • Greater specificity • Long lasting results • Lower toxicity profile • Combination therapies	• Autoimmune side effects (irAEs) • Expensive • Biomarkers not always reliable • Resistance
targeted therapy	• Targets specific proteins required for cancer growth • Long lasting results • Lower toxicity profile • Combination therapies	• Side effects • Resistance • Lab quality methods