Clinical aspects of immune related side effects of CPI

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ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ
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ΙΑΤΡΙΚΗ ΣΧΟΛΗ

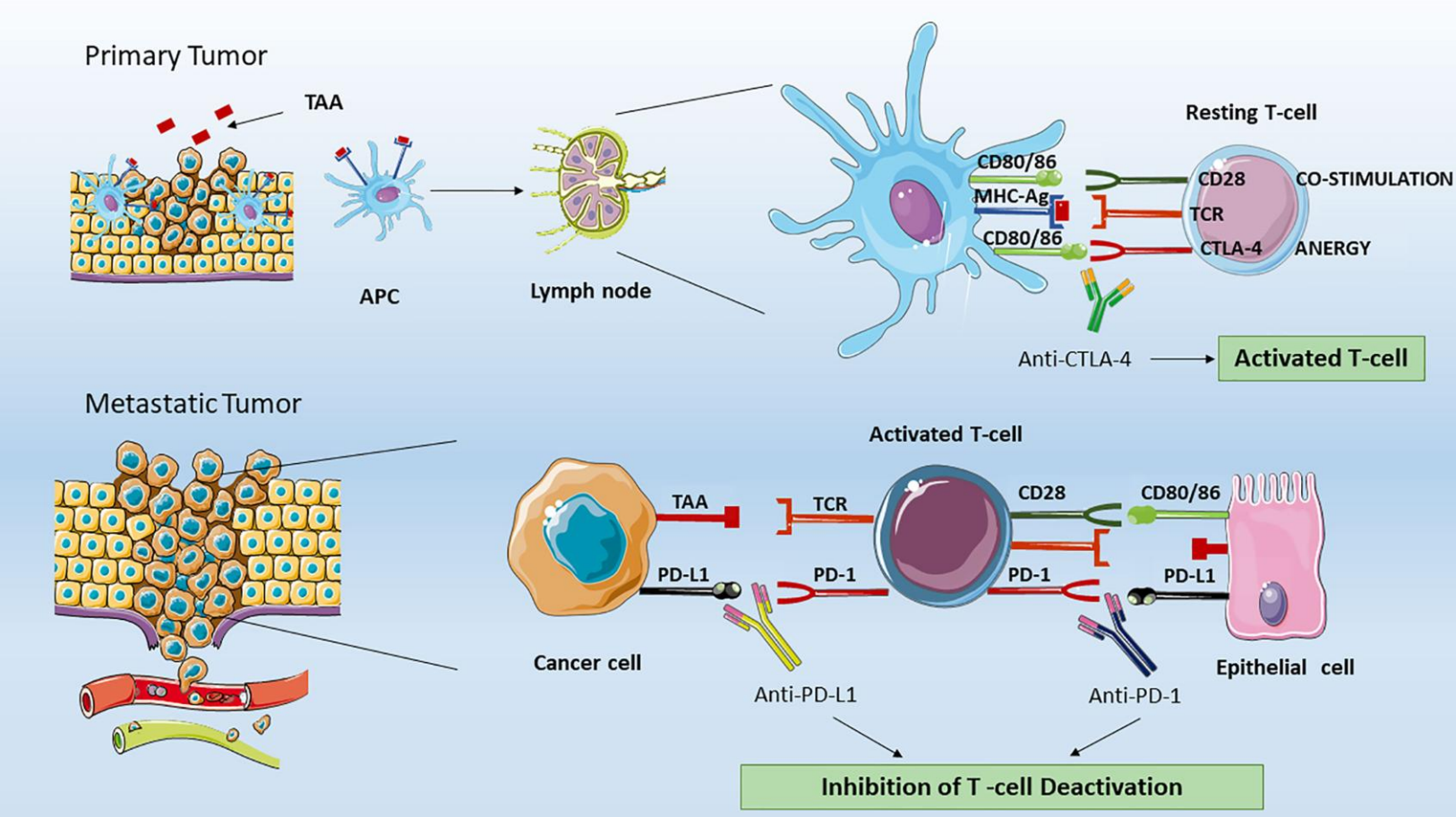
OUTLINE

- **Immune related side effects of Immune check point inhibitors (ICI)**

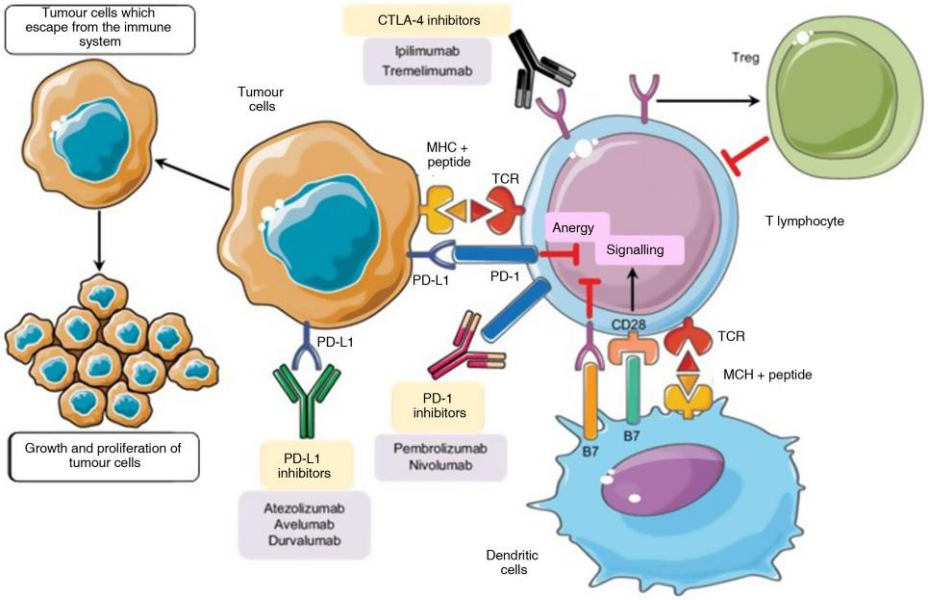
  - Prevalence and frequency
  - Difference among drugs acting on different targets
  - Time of onset
  - Patients With Preexisting Autoimmune Disease
    - Safety
    - Efficacy

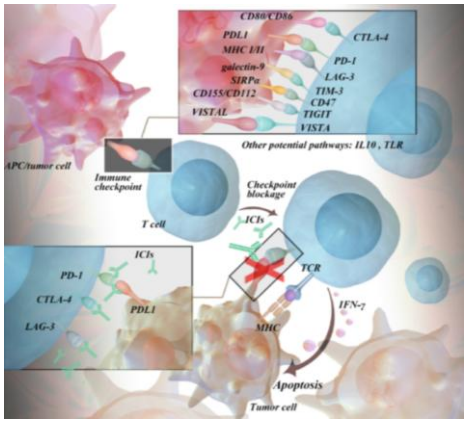
  - Prognosis

Immune check point inhibitors



Immune check point inhibitors





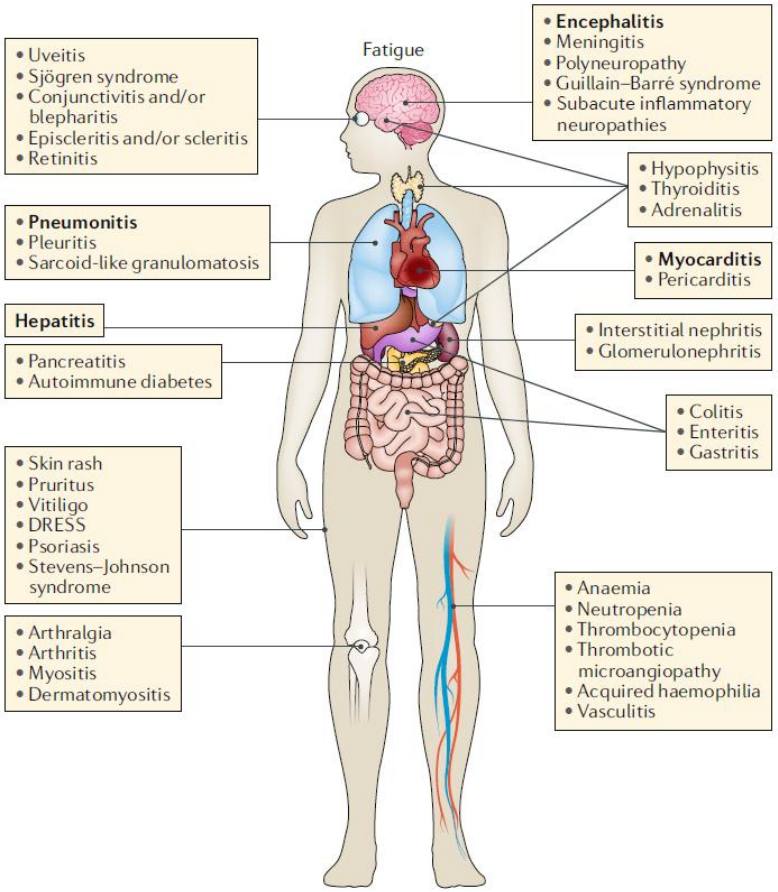
LAG-3 (lymphocyte activation gene 3)

Relatlimab

OUTLINE

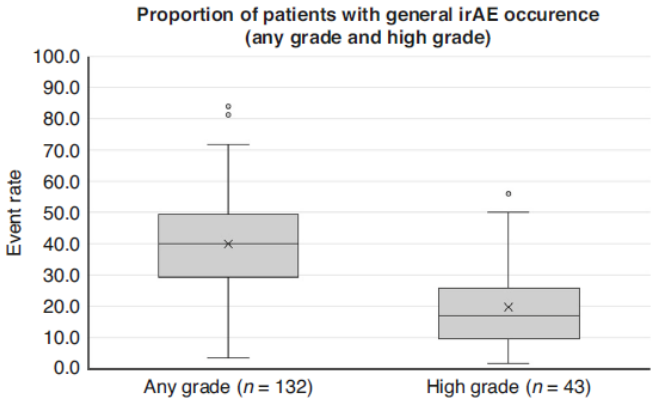
- Immune related side effects of Immune check point inhibitors (ICI)
  - Prevalence and frequency

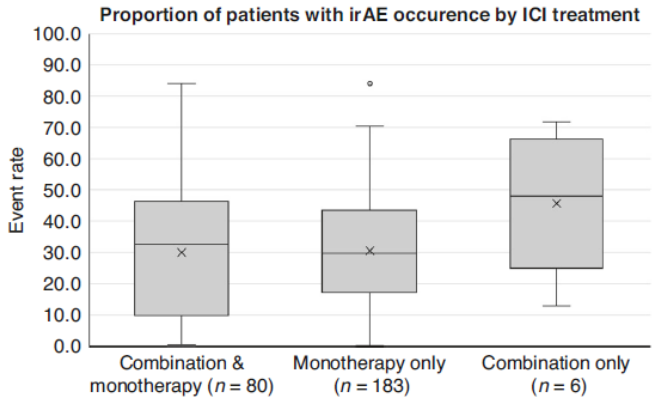
Immune-related adverse events (irAE)



Martins F, et al Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019.

40% of the patients developed irAEs across any grade

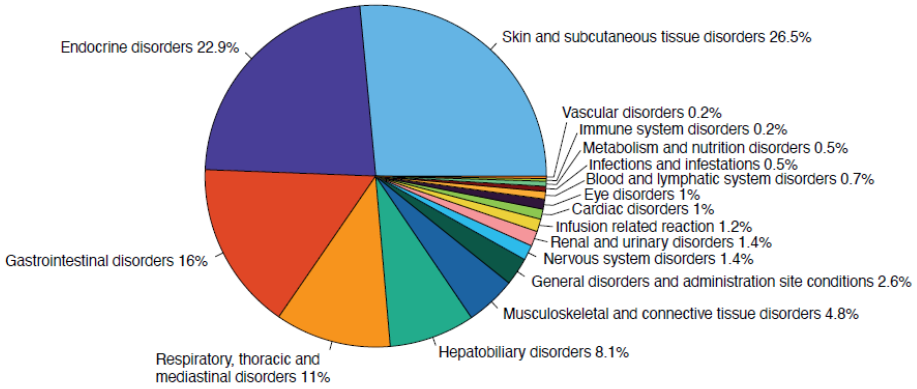


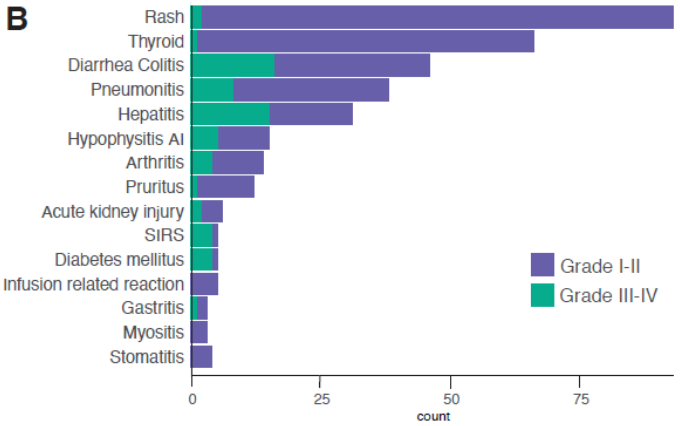


Patients receiving anti- PD-1 or anti- PD-L1 antibodies have a lower incidence of any- grade irAEs than those receiving anti- cytotoxic T lymphocyte antigen 4 (CTL A-4) antibodies[2]

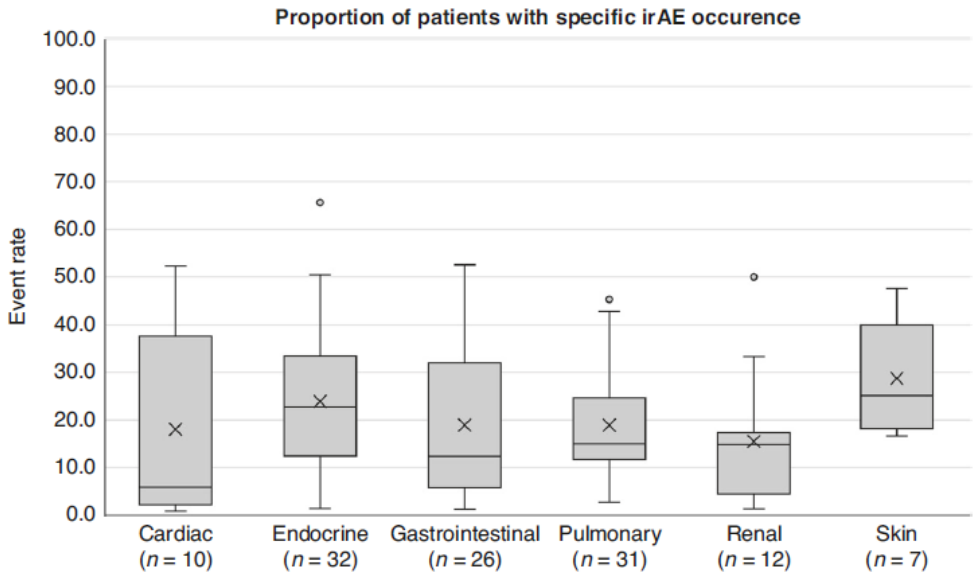
1.Jayathilaka B, et al a systematic review. Br J Cancer. 2025 Jan
2. Martins F, et al Nat Rev Clin Oncol. 2019

Skin,endocrine system, gastrointestinal tract and lung: most frequently observed irAEs



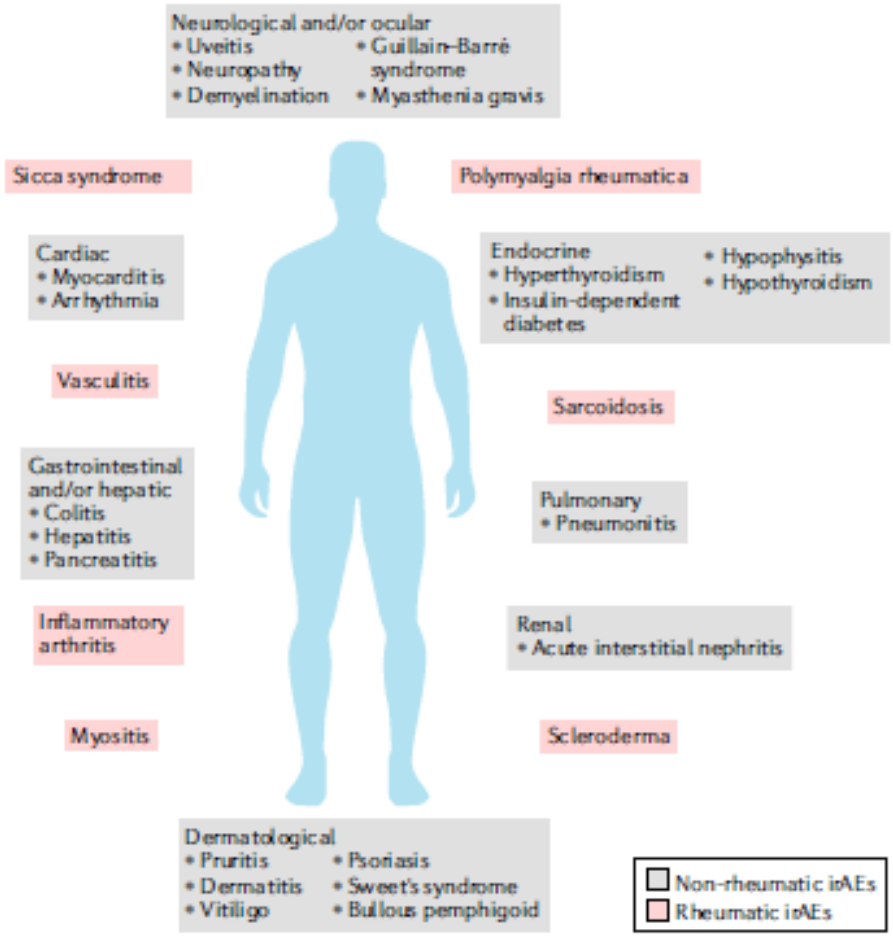


Quandt Z, et al Associations between immune checkpoint inhibitor response, immune-related adverse events, and steroid use in RADIOHEAD: a prospective pan-tumor cohort study. J Immunother Cancer. 2025 May



Jayathilaka B, et al Cancer and treatment specific incidence rates of immune-related adverse events induced by immune checkpoint inhibitors: a systematic review. Br J Cancer. 2025 Jan

Rheumatic Manifestations and Diseases From Immune Checkpoint Inhibitors



- Mild to moderate
- Late onset
- Arthralgia : 40%

Calabrese et al Nat Rev Rheumatol. 2018 Oct

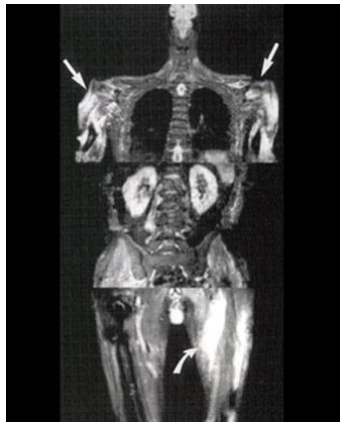
Rheumatic Manifestations and Diseases From Immune Checkpoint Inhibitors

- **No predictive markers**
  - classic HLA associations
  - perturbations of peripheral B cells
  - Cytokines
  - signature autoantibodies

- **Inflammatory Arthritis**
  - More often (4%)
  - anti-CTLA-4 , anti-PD-1/PD-L1 and combination therapy
  - usually mild or moderate
- **PMR**
  - r/o temporal arteritis
- **Vasculitis**
  - Rare
  - Melanoma
- **SLE**
- **Sjogren syndrome**

Shen P, et alRheumatic 2021 Nov.

Myositis



- 2-18%
- Muscle weakness in the proximal limbs and muscle
- 1-2 months of ICI initiation
- Strongly associated with **myocarditis** (11.3%) and **myasthenia** (11.9%),resulting in increased mortality
- Paraneoplastic myositis is difficult to distinguish from ICI-induced myositis
- **CK levels do not perfectly reflect disease severity** in patients
  - Severity of muscle weakness
  - CK levels
  - extra-skeletal muscle organ complications

Shen P, et alRheumatic 2021 Nov.

TABLE 1 | Manifestations and management of selected rheumatic irAEs.

Rheumatic irAEs	Differences from classic rheumatic disease	Testing
Arthritis	1. Can manifest as mono-, oligo- or polyarthritis 2. Myofasciitis may be prominent early in the course of disease 3. RF and CCP are often negative 4. DMARDs are needed when relapse occurs during steroid tapering	ANA, CCP, RF ESR, CRP
PMR	1. Some patients are not responsive to low-dose prednisone, higher doses of steroids may be needed and patients always have not increased inflammatory markers 2. Involvement of joints, such as the knees and hand joints	RF, ESR, CRP, CCP
Myositis	1. Autoantibodies are usually absent 2. High-dose steroids are usually required 3. Increased frequency of concurrent myasthenia and/or cardiac involvement 4. Can manifest as myalgia and oculomotor symptoms	CK, EMG, MRI, muscle biopsy troponin, transaminases, ESR, CRP, anti-striated Muscle, acetylcholine receptor, and myositis Antibody panel Echocardiogram and EKG to screen for concomitant myocarditis
Vasculitis	Inflammatory markers are commonly increased, but autoantibodies are rare	RF, ESR, CRP, CCP, ANCA
SS	1. Dry mouth is the most prominent symptom 2. Autoantibodies, including anti-Ro and anti-La antibodies, are rare 3. Rare parotitis	ANA, RF, ESR, CRP, anti-Ro, anti-La antibodies
SLE	1. Patients are always older 2. No striking female predominance 3. Autoantibodies are usually absent	ANA, anti-dsDNA antibodies, ESR, CRP, C3, C4.

- Autoantibodies are usually absent
- Not typical manifestations

Shen P, et alRheumatic 2021 Nov.

OUTLINE

- **Immune related side effects of Immune check point inhibitors (ICI)**

  - **Difference among drugs acting on different targets**

irAEs varied among drugs acting on different targets

Targets	General	Distinct
CTLA-4	Colitis, pituitary inflammation and rash are commonly caused. Neurotoxicity (meningitis), hepatotoxicity, cardiotoxicity, hematotoxicity, and ocular toxicity are rare.	HLH is a fatal systemic inflammatory syndrome reported as a rare irAE in patients receiving nivolumab, ipilimumab, and/or pembrolizumab. Neuromuscular junction dysfunction (myasthenia gravis) was over-reported in patients treated with anti-PD-1/PD-L1 compared with anti-CTLA-4. Currently, 5 cases of acquired hemophilia A related to ICIs have been reported, including: ipilimumab, nivolumab, and atezolizumab. Camrelizumab: RCCEP, mainly manifesting as facial telangiectasia and the appearance of red blood streaks. Pembrolizumab: autoimmune polyendocrine syndrome.
PD-1/PD-L1	Cutaneous toxicity is the most common, followed by immune pneumonia, hypothyroidism, joint and muscle pain. PD-L1 inhibitor has a higher overall incidence of colitis. Myocarditis, immune nephritis and pituitary inflammation are rare yet serious.	
LAG-3	The main ones are colitis, immune hepatitis, rash, neuropathy, and endocrine toxicity.	

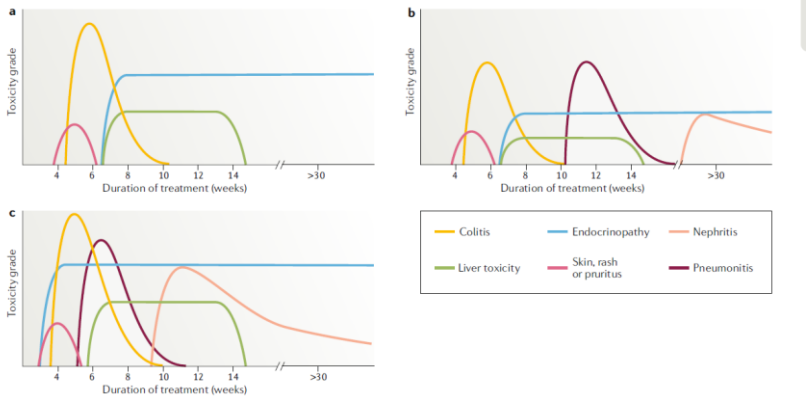
RCCEP, reactive cutaneous capillary endothelial proliferation; HLH, Hemophagocytic lymphohistiocytosis.

Yin Q, et al. Front Immunol. 2023 May

OUTLINE

- **Immune related side effects of Immune check point inhibitors (ICI)**
  - **Time of onset**

The majority of irAEs occur within 6 months of treatment



	Duration of treatment (weeks)
Ipilimumab induced colitis	4 -8
Hypophysitis	6-14
Abnormalities in thyroid function	4-7
Hepatitis	1-14
Neurological irAEs	1-7
Acute interstitial nephritis (AIN)	2-12
Rheumatic irAEs	7 (>50)
Pneumonitis	2-8 (24)

irAEs in patients receiving combination immune- checkpoint inhibitors (ICIs) have an earlier onset than the same irAEs in those receiving monotherapies

Martins F, et al Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019.

Late onset irAEs

Table 2. Immune-Related Adverse Event Diagnoses by Time of Admission

	Events, No. (%)			
Organ system	All	Early (0-6 mo)	Intermediate (>6-12 mo)	Late (>12 mo)
No.	898	679	128	91
Gastrointestinal	233 (25.9)	183 (78.5)	29 (12.4)	21 (9.0)
Pulmonary	128 (14.3)	91 (71.1)	21 (16.4)	16 (12.5)
Hepatic	120 (13.4)	96 (80.0)	14 (11.7)	10 (8.3)
Endocrine	115 (12.8)	91 (79.1)	17 (14.8)	7 (6.1)
Neurologic	86 (9.6)	70 (81.4)	12 (13.9)	4 (4.7)
Cardiac	64 (7.1)	53 (82.8)	7 (10.9)	4 (6.3)
Dermatologic	53 (5.9)	36 (67.9)	10 (18.9)	7 (13.2)
Kidney	32 (3.6)	18 (56.2)	4 (12.5)	10 (31.3)
Rheumatologic	26 (2.9)	17 (65.4)	5 (19.2)	4 (15.4)
Hematologic	23 (2.6)	12 (52.2)	6 (26.1)	5 (21.7)
Other[a]	18 (2.0)	12 (66.7)	3 (16.7)	3 (16.7)

- Retrospective observational cohort study included patients who received ICIs and were hospitalized with irAEs
- The **kidney and hematologic** organ systems exhibit a higher propensity to manifest later
- **Melanoma**, followed by lung and **genitourinary** cancers
- Patients treated with **anti–PD-L1**–based therapies were more likely to present later compared with those receiving combination ICI therapy

Durbin SM, et al Late-Onset Immune-Related Adverse Events After Immune Checkpoint Inhibitor Therapy. JAMA Netw Open. 2025 Mar

OUTLINE

- **Immune related side effects of Immune check point inhibitors (ICI)**

  - **Patients With Preexisting Autoimmune Disease**
    - **Safety**
    - **Efficacy**

Annals of Internal Medicine REVIEW

Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease

A Systematic Review

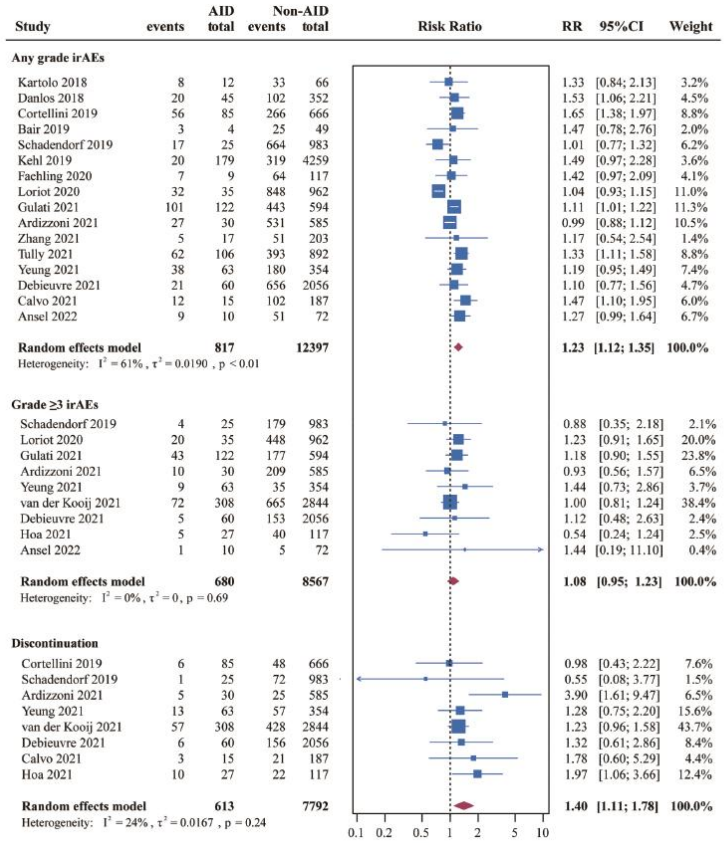
Noha Abdel-Wahab, MD, PhD; Mohsin Shah, MD; Maria A. Lopez-Olivo, MD, PhD; and Maria E. Suarez-Almazor, MD, PhD

- **75% of patients**
  - Exacerbation of preexisting autoimmune disease (50%)
  - De novo irAEs
  - Both

- No differences in frequency of adverse events in patients with active versus inactive preexisting autoimmune disease
- Receiving immunosuppressive therapy at initiation of CPI therapy seemed to have fewer adverse events than those not receiving therapy

Abdel-Wahab N, et al A Systematic Review. Ann Intern Med. 2018

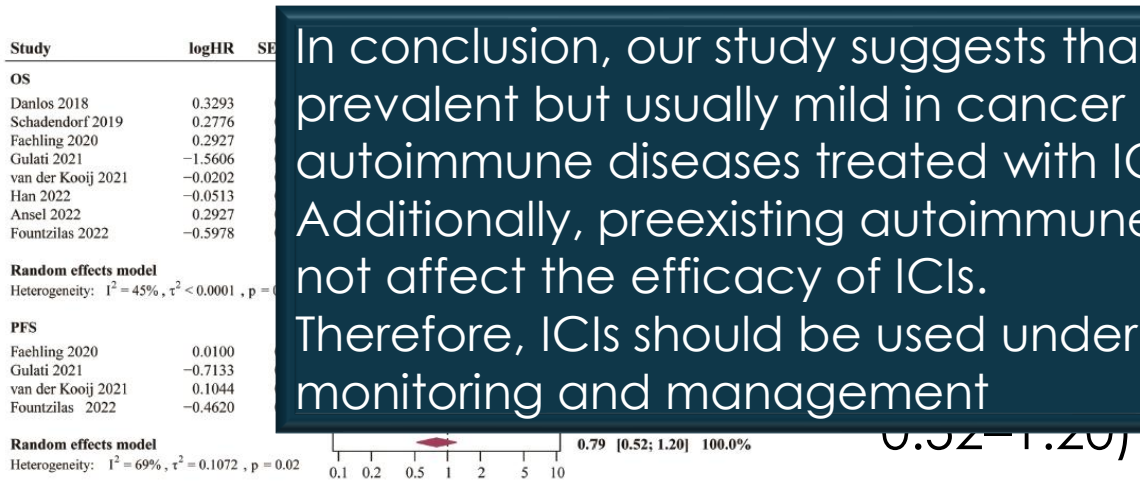
Cancer patients with autoimmune disease have increased risk of irAEs



- Cancer patients with autoimmune disease had a 23% increased overall risk of any grade compared with patients without autoimmune disease (risk ratio **1.23**, 95% CI: 1.12–1.351)
- The overall risk ratio was **1.08** (95% CI: 0.95–1.23) for grade≥ 3 irAEs
- The overall risk ratio was **1.40** (95% CI: 1.11–1.78) for discontinuation due to immunotoxicity.

Le J, et al. Hum Vaccin Immunother. 2025

No significant difference between cancer patients with and without autoimmune disease in OS and PFS



In conclusion, our study suggests that irAE is prevalent but usually mild in cancer patients with autoimmune diseases treated with ICIs. Additionally, preexisting autoimmune diseases do not affect the efficacy of ICIs. Therefore, ICIs should be used under rigorous monitoring and management

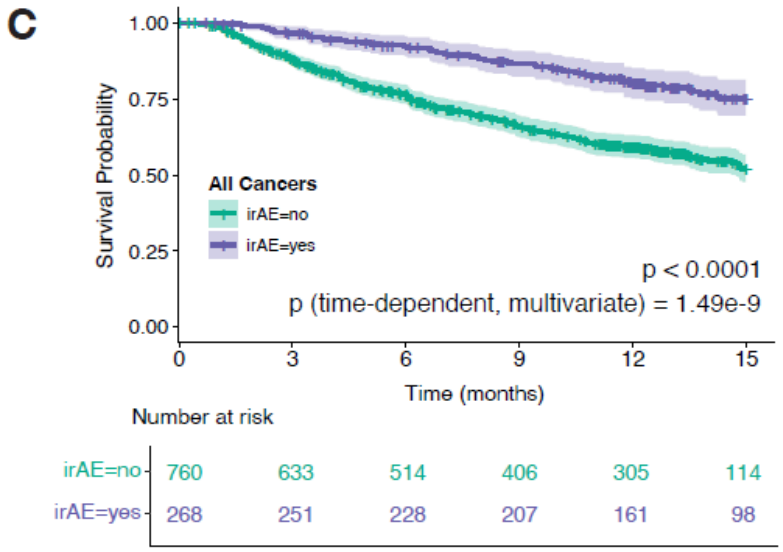
Le J, et al. Hum Vaccin Immunother. 2025

OUTLINE

- **Immune related side effects of Immune check point inhibitors (ICI)**

  - **Prognosis**

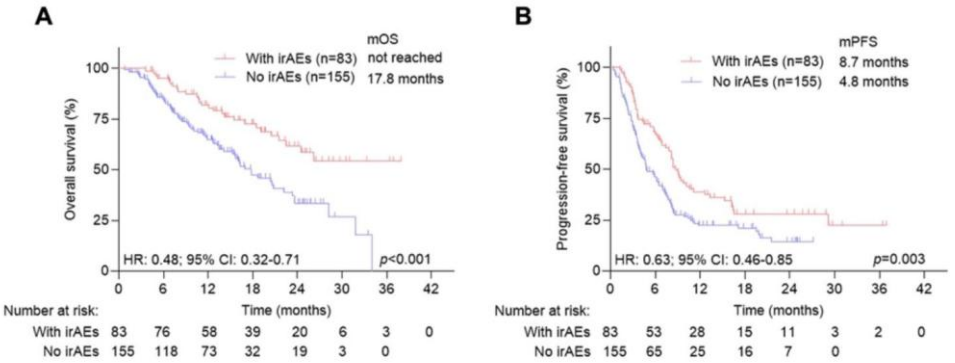
irAEs and prognosis



- Improved real-world overall survival (rwOS) HR=0.4
  - adjusting for age, sex, and metastatic disease

Quandt Z, et al Associations between immune checkpoint inhibitor response, immune-related adverse events, and steroid use in RADIOHEAD: a prospective pan-tumor cohort study. J Immunother Cancer. 2025 May

irAEs and prognosis



- 238 patients /83 patients
- There was a significant association with longer **Overall Survival** (OV) (HR: 0.52, P = 0.015) and **Progression free survival** (PFS) (HR: 0.63, P = 0.025) for patients with irAEs than for patients without irAEs

Han X,.et al Organ-specific immune-related adverse events and prognosis in cancer patients receiving immune checkpoint inhibitors. BMC Cancer. 2025 Jan

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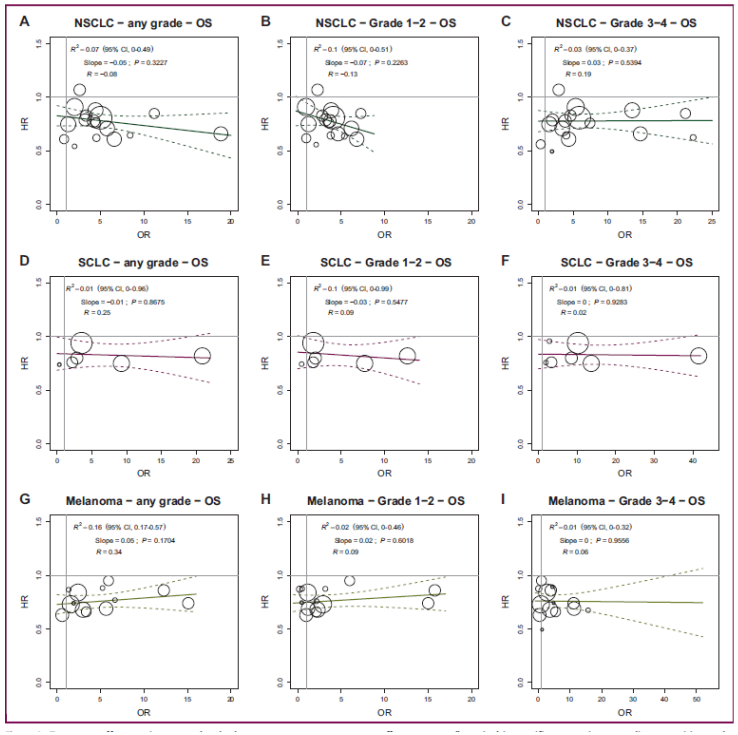
REVIEW

Immune-related adverse events as potential surrogates of immune checkpoint inhibitors' efficacy: a systematic review and meta-analysis of randomized studies

V. Amoroso[1*†], F. Gallo[2†], A. Alberti[1], D. Paloschi[1], W. Ferrari Bravo[1], A. Esposito[1], D. Cosentini[1], S. Grisanti[1], R. Pedersini[1], F. Petrelli[3] & A. Berruti[1]



- Sixty-two randomized trials 42 247 patients
- No significant association between the treatment effects for overall grade 1-2 or grade 3-4 irAE rates or specific (skin, gastrointestinal, endocrine) irAE rates

Amoroso V et l. ESMO Open. 2023 Apr

Take home messages

- 40% of the patients developed irAEs across any grade
- irAEs develop more often within the first 6 months of treatment
  - Late onset
- Cancer patients with autoimmune disease have increased risk of irAEs
  - 75%
  - mild
- Preexisting autoimmune diseases do not affect the efficacy of ICIs
- irAEs – prognosis?