

# Clinical aspects of immune related side effects of CPI



ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΝΟΣΟΚΟΜΕΙΟ ΗΡΑΚΛΕΙΟΥ Αργυρώ Ρέπα Επιμελήτρια Α Ρευματολογική Κλινική ΠΑΓΝΗ Ηράκλειο 31/5/2025



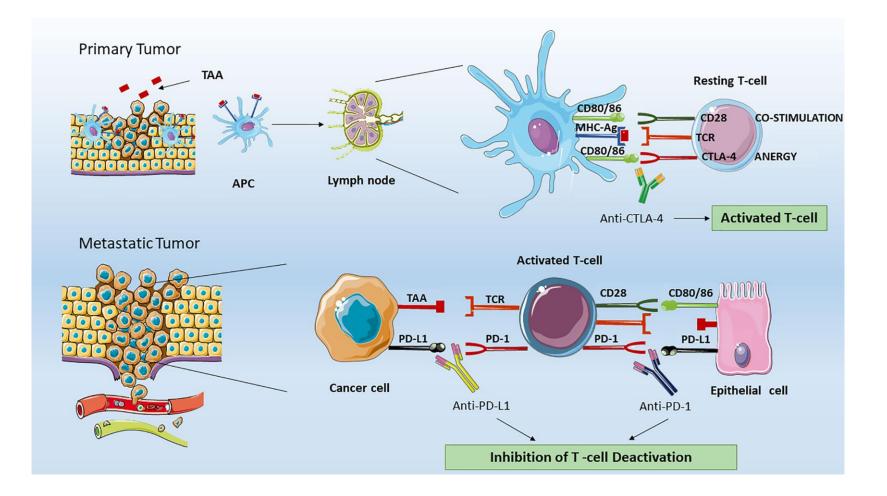
# OUTLINE



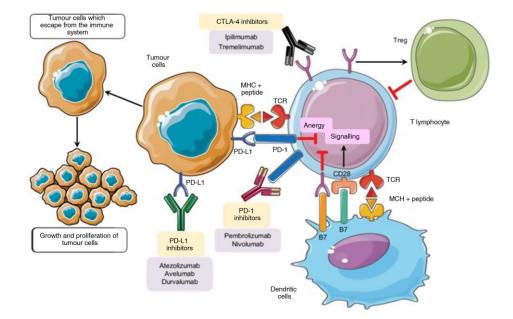
- Immune related side effects of Immune check point inhibitors (ICI)
  - Prevalence and frequency
  - Difference among drugs acting on different targets
  - ➤Time of onset
  - ➢Patients With Preexisting Autoimmune Disease
    - Safety
    - ≻Efficacy

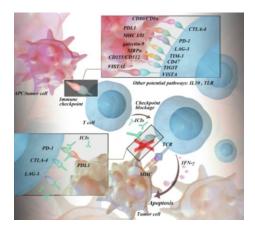
➢ Prognosis

## Immune check point inhibitors



# Immune check point inhibitors





LAG-3 (lymphocyte activation gene 3)

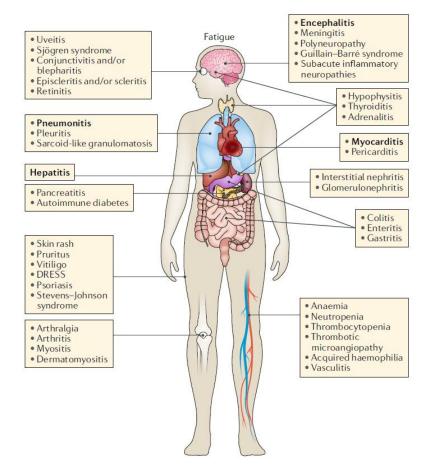
Relatlimab





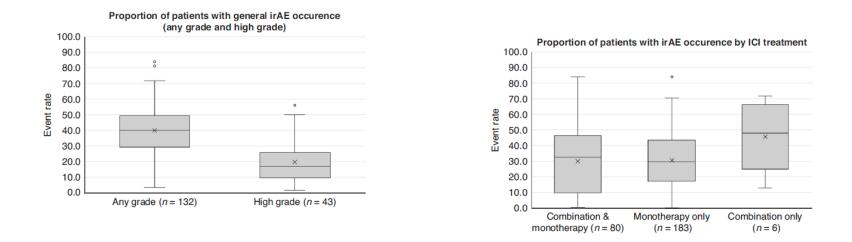
- Immune related side effects of Immune check point inhibitors (ICI)
  - Prevalence and frequency

### Immune-related adverse events (irAE)



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

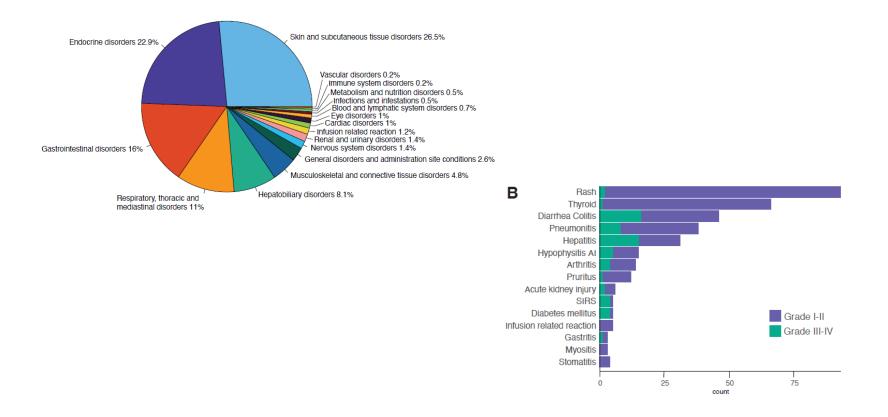
# 40% of the patients developed irAEs across any grade



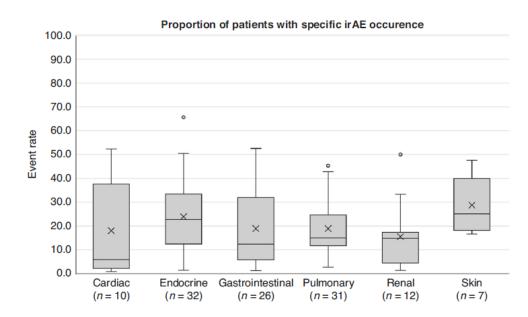
Patients receiving anti- PD-1 or anti- PD-L1 antibodies have a lower incidence of any- grade irAEs than those receiving anti- cytotoxic T lymphocyte antigen 4 (CTL A-4) antibodies<sup>2</sup>

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 ir AEs

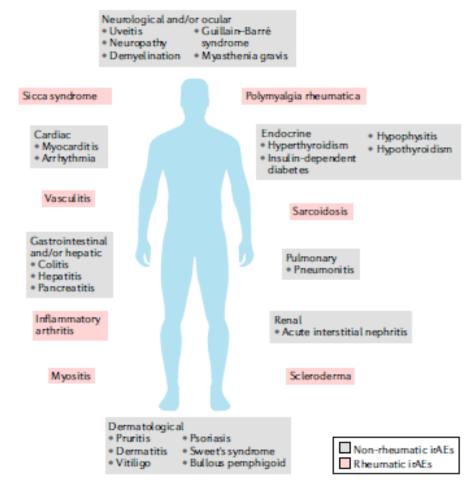


Quandt Z, et al Associations between immune checkpoint inhibitor response, immunerelated adverse events, and steroid use in RADIOHEAD: a prospective pan-tumor cohort study. J Immunother Cancer. 2025 May



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

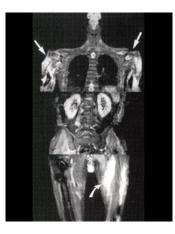
## Rheumatic Manifestations and Diseases From Immune Checkpoint Inhibitors

### 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

# **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 ICIinduced 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	<ol> <li>Can manifest as mono-, oligo- or polyarthritis</li> <li>Myofasciitis may be prominent early in the course of disease</li> <li>RF and CCP are often negative</li> <li>DMARDs are needed when relapse occurs during steroid tapering</li> </ol>	ANA, CCP, RF ESR, CRP
PMR	<ol> <li>Some patients are not responsive to low-dose prednisone, higher doses of steroids may be needed and patients always have not increased inflammatory markers</li> <li>Involvement of joints, such as the knees and hand joints</li> </ol>	RF, ESR, CRP, CCP
Myositis	<ol> <li>Autoantibodies are usually absent</li> <li>High-dose steroids are usually required</li> <li>Increased frequency of concurrent myasthenia and/or cardiac involvement</li> <li>Can manifest as myalgia and oculomotor symptoms</li> </ol>	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
Vasculitis	Inflammatory markers are commonly increased, but autoantibodies are rare	myocarditis RF, ESR, CRP, CCP, ANCA
SS	<ol> <li>Dry mouth is the most prominent symptom</li> <li>Autoantibodies, including anti-Ro and anti-La antibodies, are rare</li> <li>Rare parotitis</li> </ol>	ANA, RF, ESR, CRP, anti-Ro, anti-La antibodies
SLE	<ol> <li>Patients are always older</li> <li>No striking female predominance</li> <li>Autoantibodies are usually absent</li> </ol>	ANA, anti-dsDNA antibodies, ESR, CRP, C3, C4.

 Autoantibodies are usually absent

• Not typical manifestations

#### Shen P, et alRheumatic 2021 Nov.





 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
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.	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.
LAG-3	The main ones are colitis, immune hepatitis, rash, neuropathy, and endocrine toxicity.	

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

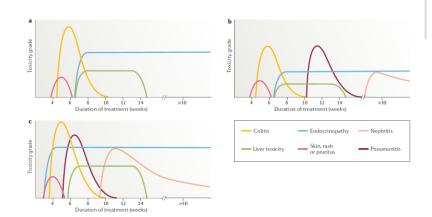




 Immune related side effects of Immune check point inhibitors (ICI)

Time of onset

# The majority of irAEs occur within 6 months of treatment



those receiving monotherapies

			Duration of treatment (weeks)
a A	b	Ipilimumab induced colitis	4 -8
oxicity grade	origin grade	Hypophysitis	6-14
$\frac{1}{4} \frac{1}{6} \frac{1}{10} \frac{1}{12} \frac{1}{14} \frac{1}{1} \frac{1}{50} \frac{1}{50}$	4 6 8 10 12 14 >30 Duration of treatment (weeks)	Abnormalities in thyroid function	4-7
Ity grade	Colitis Endocrinopathy Nephritis     Liver toxicity Skin, rash     or pruritus Pneumonitis	Hepatitis	1-14
poor		Neurological irAEs	1-7
4 6 8 10 12 14 - >30 Duration of treatment (weeks)		Acute interstitial nephritis (AIN)	2-12
irAEs in patients	receiving combine	atippointing yare-ch	neçkpoint
inhibitors (ICIs) h those receiving	ave an earlier ons	et than the same	irAEs in 2-8 (24)

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

# Late onset ir AEs

	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 <sup>a</sup>	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





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

# Patients With Preexisting Autoimmune Disease Safety Efficacy

### **Annals of Internal Medicine**



### 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

# Cancer patients with autoimmune disease have increased risk of irAEs

Study	events	AID total	Noi events	n-AID total	Risk Ratio	RR	95%CI	Weight
Any grade irAEs								
Kartolo 2018	8	12	33	66		1.33	[0.84; 2.13]	3.2%
Danlos 2018	20	45	102	352		1.53	[1.06; 2.21]	4.5%
Cortellini 2019	56	85	266	666	-	1.65	[1.38; 1.97]	8.8%
Bair 2019	3	4	25	49		1.47	[0.78; 2.76]	2.0%
Schadendorf 2019	17	25	664	983		1.01	[0.77; 1.32]	6.2%
Kehl 2019	20	179	319	4259		1.49	[0.97; 2.28]	3.6%
Fachling 2020	7	9	64	117		1.42	[0.97; 2.09]	4.1%
Loriot 2020	32	35	848	962		1.04	[0.93; 1.15]	11.0%
Gulati 2021	101	122	443	594		1.11	[1.01; 1.22]	11.3%
Ardizzoni 2021	27	30	531	585		0.99	[0.88; 1.12]	10.5%
Zhang 2021	5	17	51	203		1.17	[0.54; 2.54]	1.4%
Tully 2021	62	106	393	892		1.33	[1.11; 1.58]	8.8%
Yeung 2021	38	63	180	354	<b>*</b>	1.19	[0.95; 1.49]	7.4%
Debieuvre 2021	21	60	656	2056		1.10	[0.77; 1.56]	4.7%
Calvo 2021	12	15	102	187	:- <b>-</b> -		[1.10; 1.95]	6.0%
Ansel 2022	9	10	51	72	-	1.27	[0.99; 1.64]	6.7%
Random effects mode	el	817		12397	•	1.23	[1.12; 1.35]	100.0%
Heterogeneity: $I^2 = 619$	$\%, \tau^2 = 0.01$	90 , p <	0.01					
Grade ≥3 irAEs								
-	4	25	179	983		0.88	[0 35: 2 18]	2.1%
Schadendorf 2019	4 20	25 35	179 448	983 962		0.88		
Schadendorf 2019 Loriot 2020	20	35	448	962		1.23	[0.91; 1.65]	20.0%
Schadendorf 2019 Loriot 2020 Gulati 2021	20 43	35 122	448 177	962 594		1.23 1.18	[0.91; 1.65] [0.90; 1.55]	20.0% 23.8%
Schadendorf 2019 Loriot 2020 Gulati 2021 Ardizzoni 2021	20 43 10	35 122 30	448 177 209	962 594 585		1.23 1.18 0.93	[0.91; 1.65] [0.90; 1.55] [0.56; 1.57]	20.0% 23.8% 6.5%
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Schadendorf 2019 Loriot 2020 Gulati 2021 Ardizzoni 2021 Yeung 2021 van der Kooij 2021 Debieuvre 2021 Ansel 2022 Random effects mod Heterogeneity: 1 <sup>2</sup> = 09 Viscontinuation Cortellini 2019 Schadendorf 2019 Schadendorf 2019 Yeung 2021 van der Kooij 2021 Debieuvre 2021	$\begin{array}{c} 20\\ 43\\ 10\\ 9\\ 72\\ 5\\ 5\\ 1\\ 1\\ 6\\ 6\\ 7\\ 6\end{array}$	35 122 30 63 308 60 27 10 680 = 0.69 855 255 300 63 308 60	448 177 209 35 665 153 40 5 40 5 42 25 57 428 156	962 594 585 354 2844 2056 117 72 <b>8567</b> 6666 983 585 354 2844 2056		1.23 1.18 0.93 1.44 1.00 1.12 0.54 1.44 <b>1.08</b> 0.98 0.55 3.90 1.28 1.23 1.32	[0.91; 1.65] [0.90; 1.55] [0.56; 1.57] [0.73; 2.86] [0.81; 1.24] [0.48; 2.63] [0.42; 1.24] [0.48; 2.63] [0.42; 1.24] [0.95; 1.23] [0.95; 1.23] [0.05; 1.23] [0.05; 2.20] [0.96; 1.58] [0.61; 2.86]	20.0% 23.8% 6.5% 3.7% 38.4% 2.4% 2.5% 0.4% 100.0% 7.6% 1.5% 6.5% 15.6% 43.7% 8.4%
Schadendorf 2019 Loriot 2020 Gulati 2021 Ardizzoni 2021 Yan der Kooij 2021 Debieuvre 2021 Hoa 2021 Ansel 2022 Random effects mod Heterogeneity: 1 <sup>2</sup> = 0? Discontinuation Cortellini 2019 Schadendorf 2019 Ardizzoni 2021 Yeung 2021 Debieuvre 2021 Calvo 2021	$\begin{array}{c} 20\\ 43\\ 10\\ 9\\ 72\\ 5\\ 5\\ 1\\ 1\\ 6\\ 7\\ 6\\ 1\\ 3\\ 57\\ 6\\ 3\end{array}$	$35 \\ 122 \\ 30 \\ 63 \\ 308 \\ 60 \\ 27 \\ 10 \\ 680 \\ = 0.69 \\ 85 \\ 25 \\ 30 \\ 63 \\ 308 \\ 60 \\ 15 \\ 15 \\ 15 \\ 15 \\ 10 \\ 15 \\ 10 \\ 10$	448 177 209 35 665 153 40 5 5 40 5 5 7 428 156 57 428 156 21	962 594 585 354 2844 2056 117 72 <b>8567</b> 6666 983 585 354 2846 2056 187		1.23 1.18 0.93 1.44 1.00 1.12 0.54 1.44 <b>1.08</b> 0.98 0.55 3.90 1.28 1.23 1.32 1.78	[0.9]; 1.65] [0.90; 1.55] [0.56; 1.57] [0.73; 2.86] [0.81; 1.24] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.22] [0.69; 1.23] [0.69; 5.12] [0.67; 5.20] [0.57; 2.20] [0.57; 5.20] [0.57; 5.20] [0.66; 5.28] [0.66; 5.28]	20.0% 23.8% 6.5% 3.7% 38.4% 2.4% 2.5% 0.4% 100.0% 7.6% 1.5% 6.5% 15.6% 43.7% 8.4%
Schadendorf 2019 Loriot 2020 Gulati 2021 Ardizzoni 2021 Yeung 2021 van der Kooij 2021 Debieuvre 2021 Ansel 2022 Random effects mod Heterogeneity: 1 <sup>2</sup> = 09 Discontinuation Cortellini 2019 Schadendorf 2019 Schadendorf 2019 Yeung 2021 van der Kooij 2021 Debieuvre 2021	$\begin{array}{c} 20\\ 43\\ 10\\ 9\\ 72\\ 5\\ 5\\ 1\\ 1\\ 6\\ 6\\ 7\\ 6\end{array}$	35 122 30 63 308 60 27 10 680 = 0.69 855 255 300 63 308 60	448 177 209 35 665 153 40 5 40 5 42 25 57 428 156	962 594 585 354 2844 2056 117 72 <b>8567</b> 6666 983 585 354 2844 2056		1.23 1.18 0.93 1.44 1.00 1.12 0.54 1.44 <b>1.08</b> 0.98 0.55 3.90 1.28 1.23 1.32	[0.9]; 1.65] [0.90; 1.55] [0.56; 1.57] [0.73; 2.86] [0.81; 1.24] [0.48; 2.63] [0.24; 1.24] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.63] [0.48; 2.22] [0.08; 3.77] [1.61; 9.47] [0.75; 2.20] [0.96; 1.58] [0.61; 2.86] [0.60; 5.29]	20.0% 23.8% 6.5% 3.7% 38.4% 2.4% 2.5% 0.4% 100.0% 7.6% 1.5% 6.5% 15.6% 43.7%

- 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

Study	logHR SE	In conclusion, our study suggests that irAE is	d
OS Danlos 2018 Schadendorf 2019	0.3293	prevalent but usually mild in cancer patients with	
Faehling 2020 Gulati 2021	0.2927 -1.5606 -0.0202	autoimmune diseases treated with ICIs.	S
Ansel 2022	-0.0513 0.2927 -0.5978	Additionally, preexisting autoimmune diseases do	
<b>Random effects model</b> Heterogeneity: $I^2 = 45\%$ , $\tau^2$	< 0.0001 , p = (	not affect the efficacy of ICIs.	$\mathcal{DS}$
PFS Faehling 2020	0.0100	Therefore, ICIs should be used under rigorous	8)
van der Kooij 2021	-0.7133 0.1044 -0.4620	monitoring and management	
<b>Random effects model</b> Heterogeneity: $I^2 = 69\%$ , $\tau^2$	= 0.1072 , p = 0	0.02  0.1  0.2  0.5  1  2  5  10  0.79  [0.52; 1.20]  100.0%  0.02  1  .20	

#### Le J, et al. Hum Vaccin Immunother. 2025

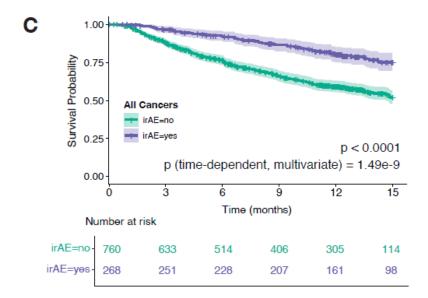




 Immune related side effects of Immune check point inhibitors (ICI)

**Prognosis** 

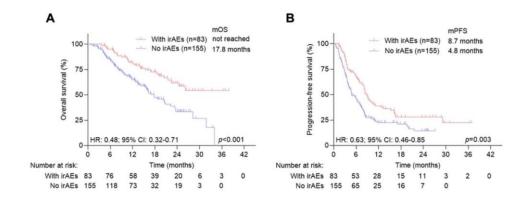
## irAEs and prognosis



- 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, immunerelated 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

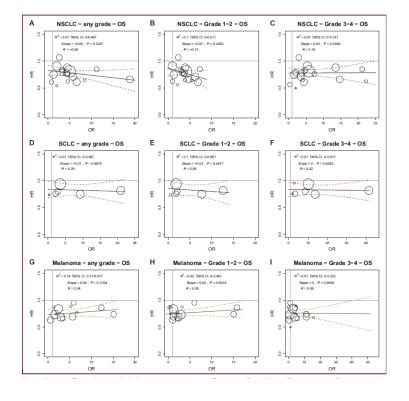




#### REVIEW

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

V. Amoroso<sup>1\*†</sup>, F. Gallo<sup>2†</sup>, A. Alberti<sup>1</sup>, D. Paloschi<sup>1</sup>, W. Ferrari Bravo<sup>1</sup>, A. Esposito<sup>1</sup>, D. Cosentini<sup>1</sup>, S. Grisanti<sup>1</sup>, R. Pedersini<sup>1</sup>, F. Petrelli<sup>3</sup> & A. Berruti<sup>1</sup>



- 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



### 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?