La gestione della tossicità da immunoterapia

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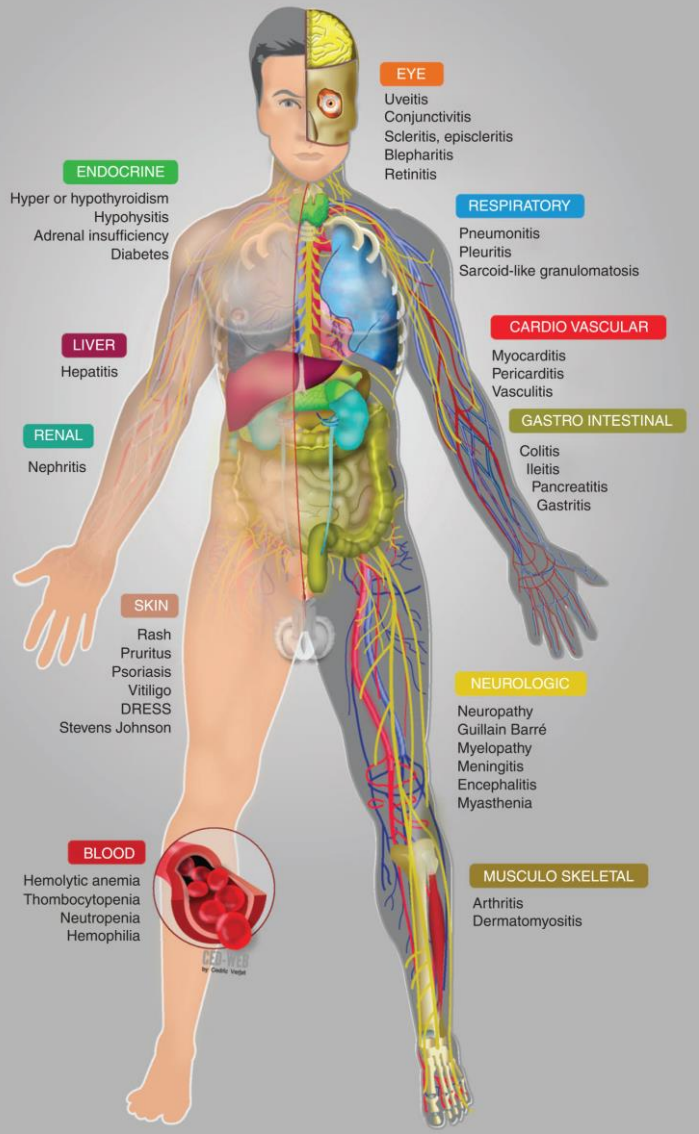
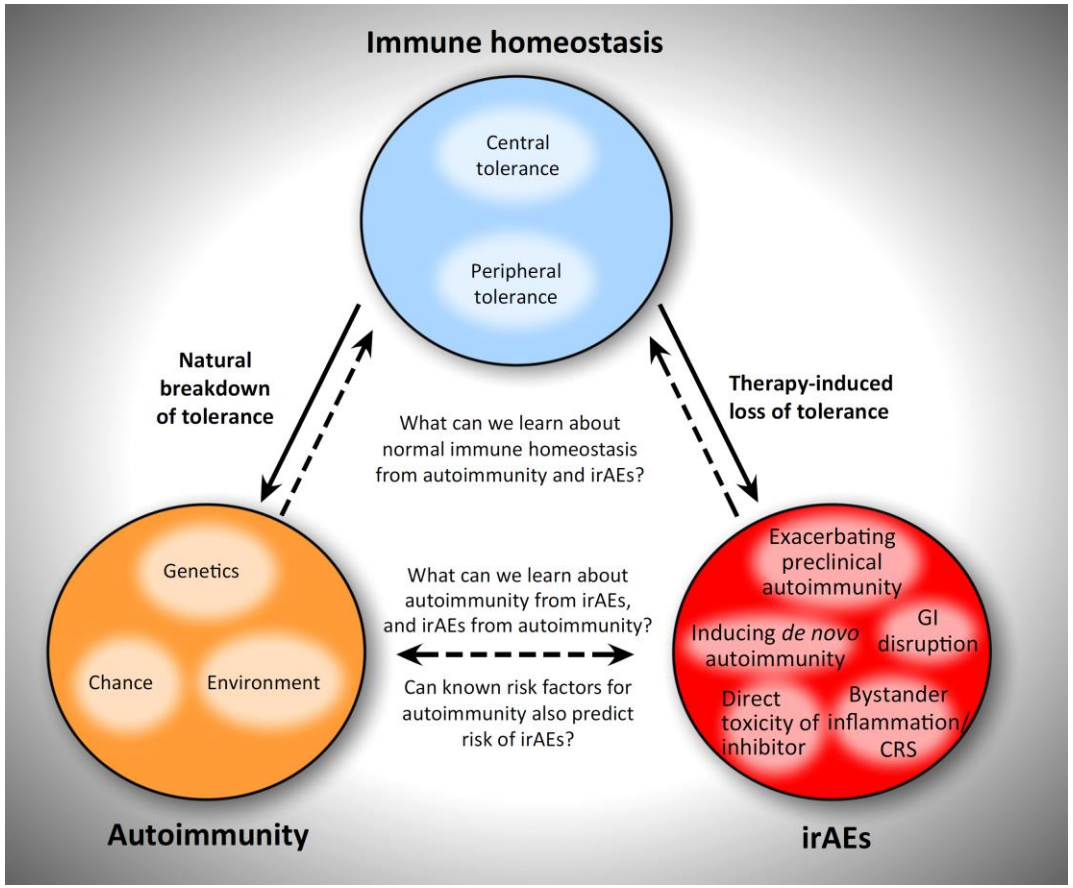
Eventi avversi immuno-correlati (irAEs)

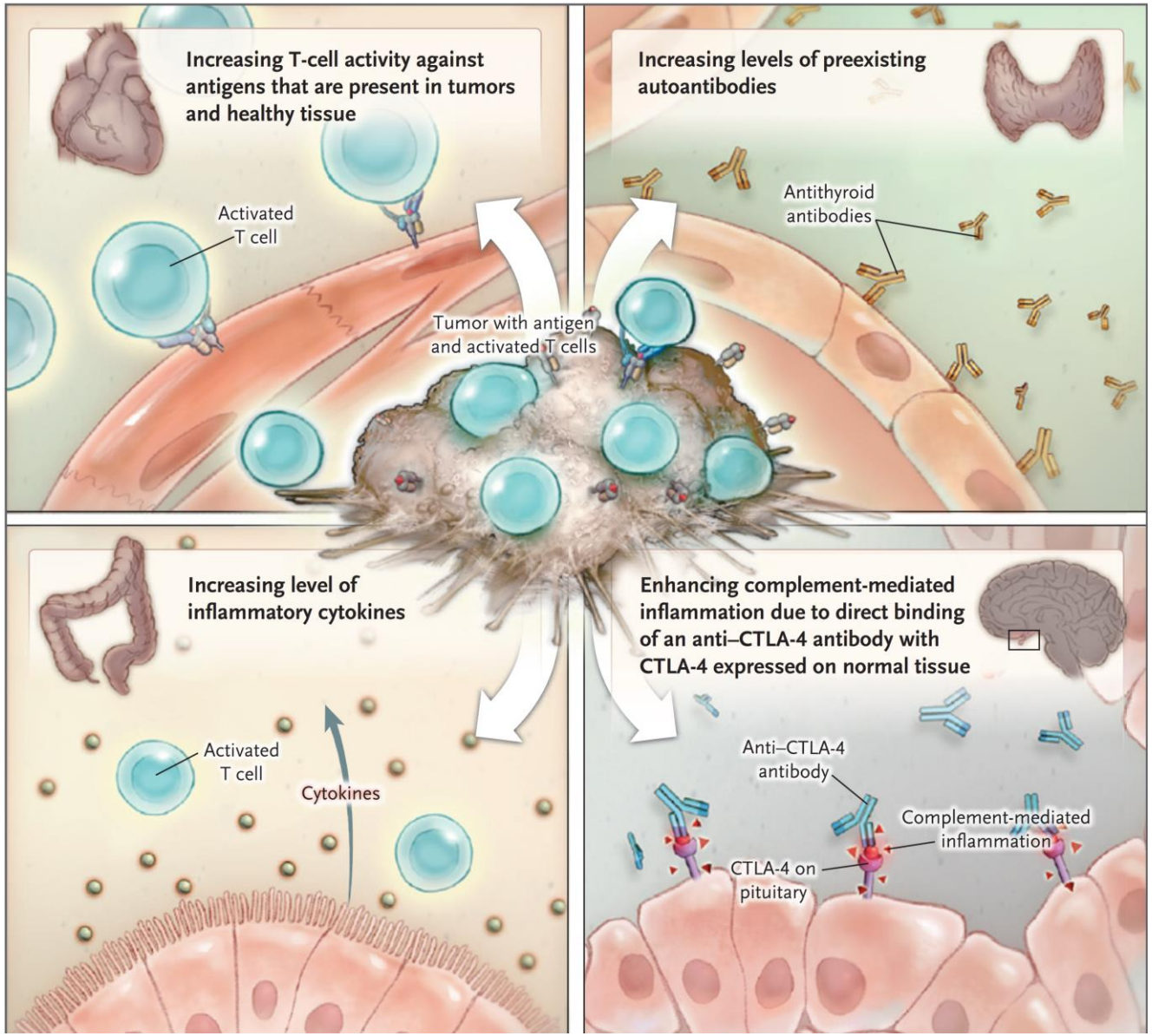


irAEs
may potentially affect
any organ/system

Champiat S et al. Ann Oncol 2016;27:559-74

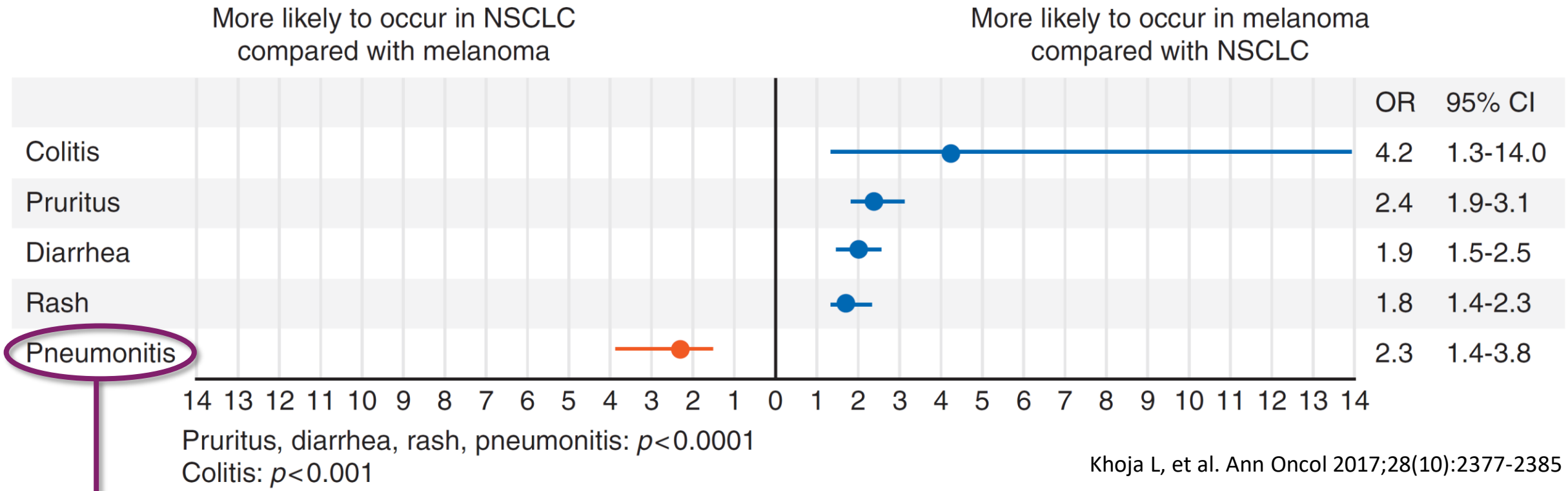
Patogenesi degli irAEs





Pauken KE et al. Trends Immunol 2019;40(6):511-523. Postow MA, et al. N Engl J Med 2018;378(2):158-168

Pattern degli irAEs in relazione al tumore primitivo



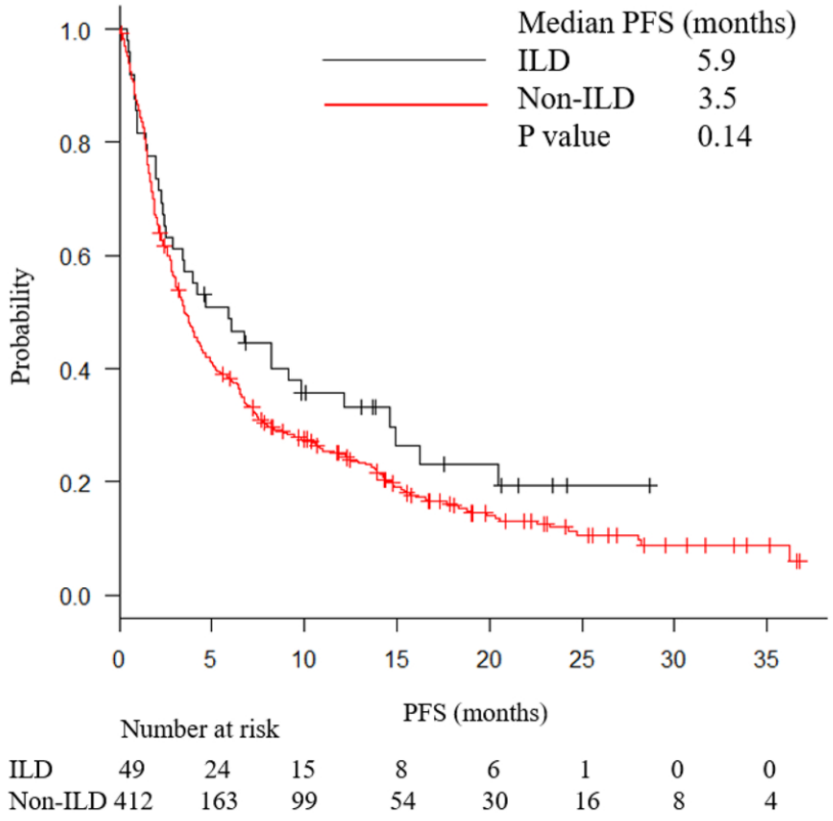
Khoja L, et al. Ann Oncol 2017;28(10):2377-2385

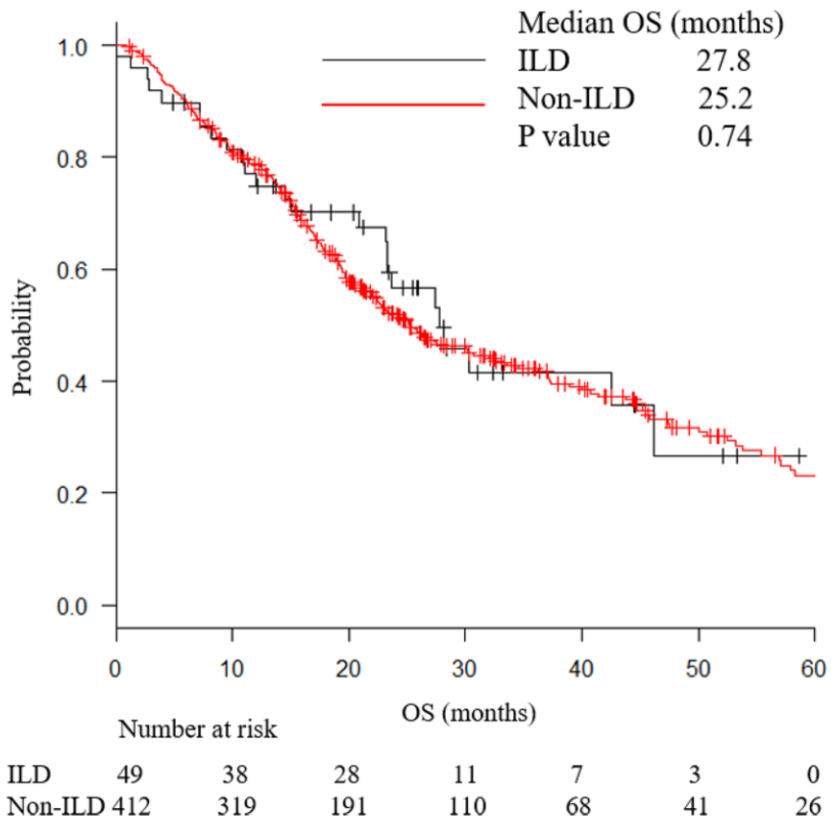
Polmonite immunocorrelata nel NSCLC:

- Incidenza 3-5% negli studi clinici con anti-PD1[1]
- Fino al 19% in esperienze «real-life»[2]

1. Berti A, et al. Crit Rev Oncol Hematol 2021;162:103351. 2. Suresh K, et al. J Thorac Oncol 2018;13:1930-1939

Rischio di polmonite nel NSCLC: pre-esistente interstiziopatia

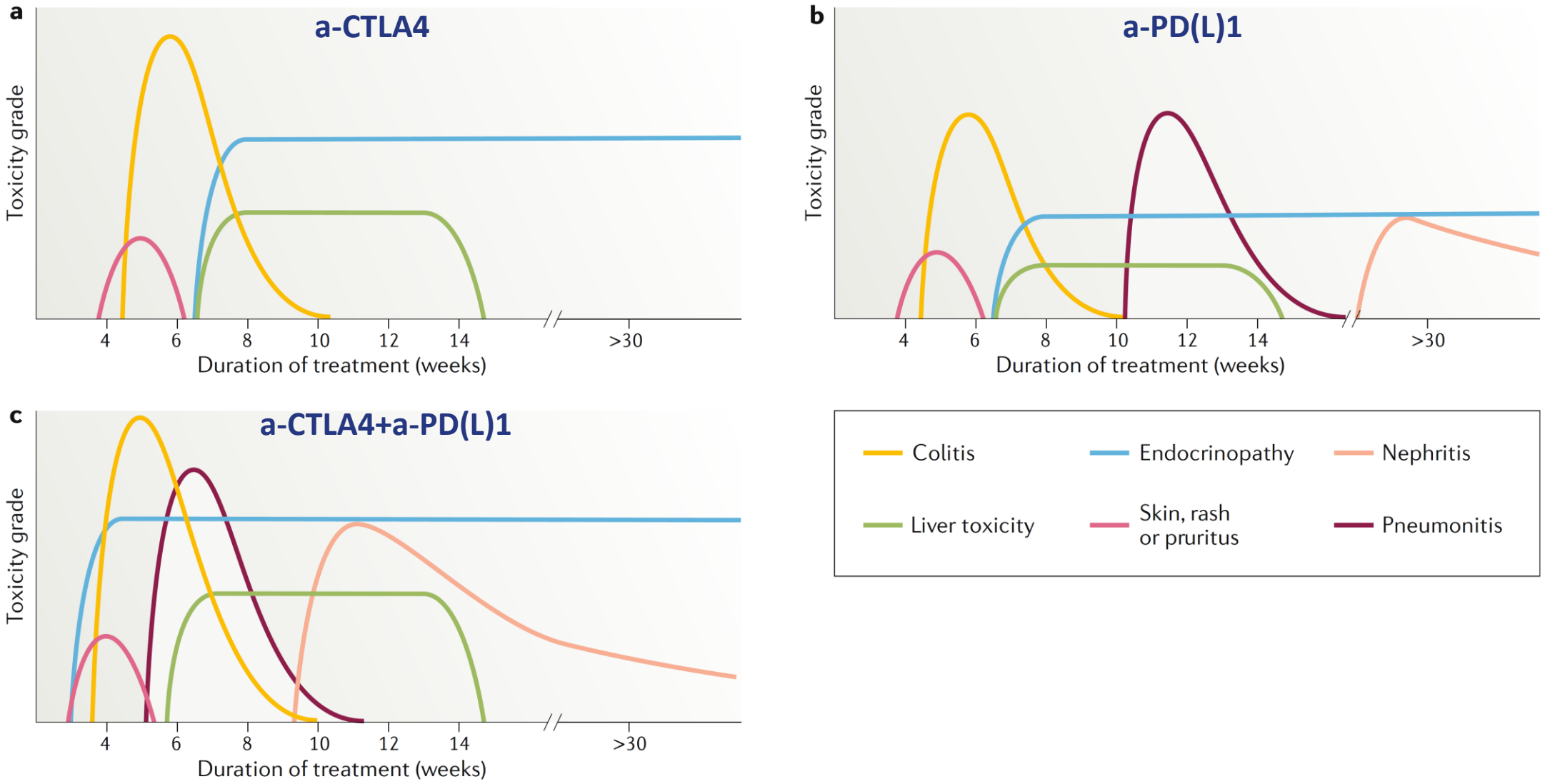




	Any grade				≥ G3				G5			
	All	Non-ILD	ILD	P value	All	Non-ILD	ILD	P value	All	Non-ILD	ILD	P value
All adverse effect	164 (35.6)	131 (31.8)	33 (67.3)	<0.01	51 (11.1)	36 (8.7)	15 (30.6)	<0.01	7 (1.5)	4 (0.97)	3 (6.1)	<0.01
Pneumonitis	54 (11.7)	39 (9.5)	15 (30.6)	<0.01	23 (5.0)	15 (3.6)	8 (16.3)	<0.01	7 (1.5)	4 (0.97)	3 (6.1)	<0.01

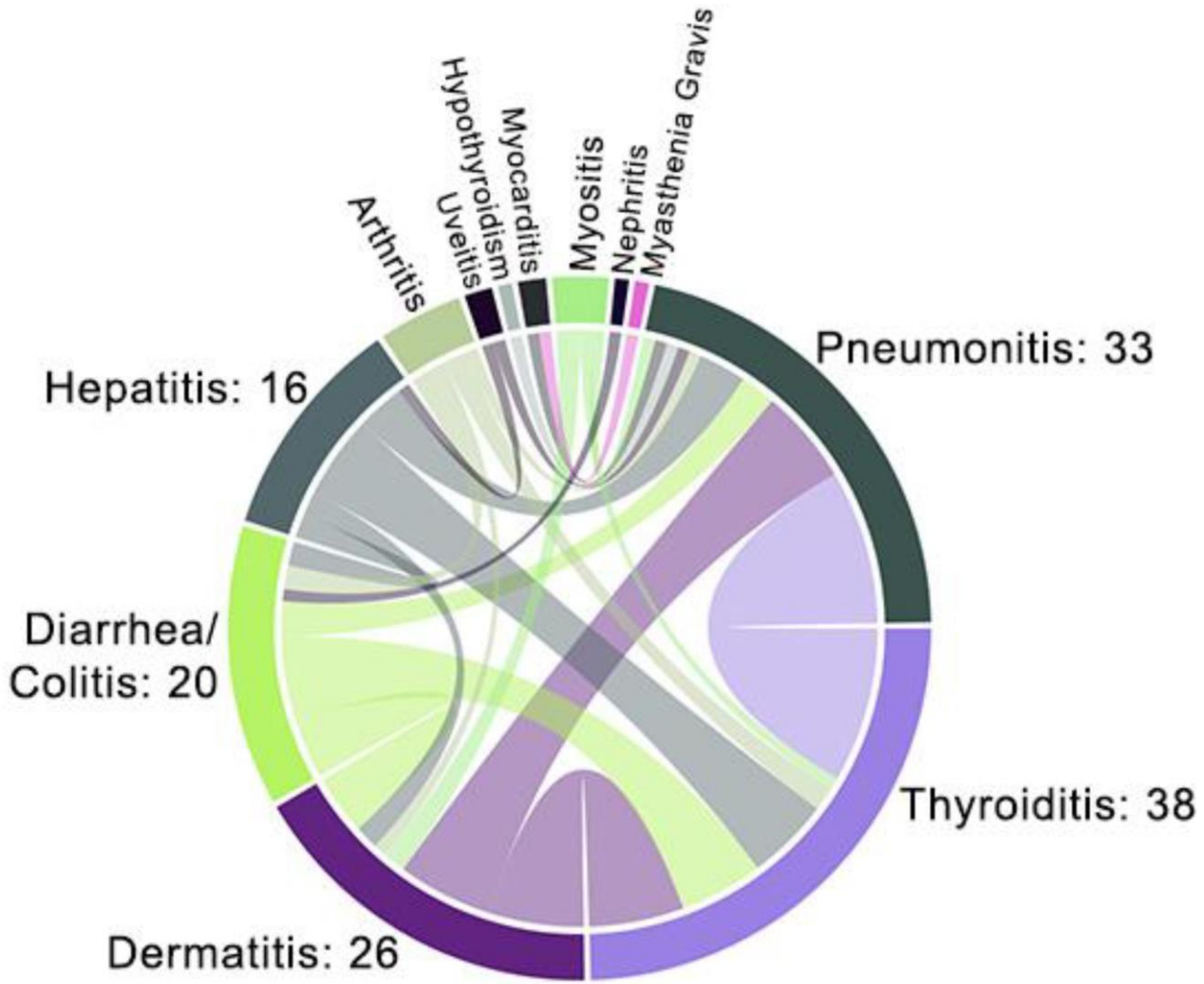
Tasaka Y et al. Lung Cancer 2021;155:120-126.

Cinetica degli irAEs



Postow MA, et al. N Engl J Med 2018;378(2):158-168

IrAEs multipli nel NSCLC



n=623

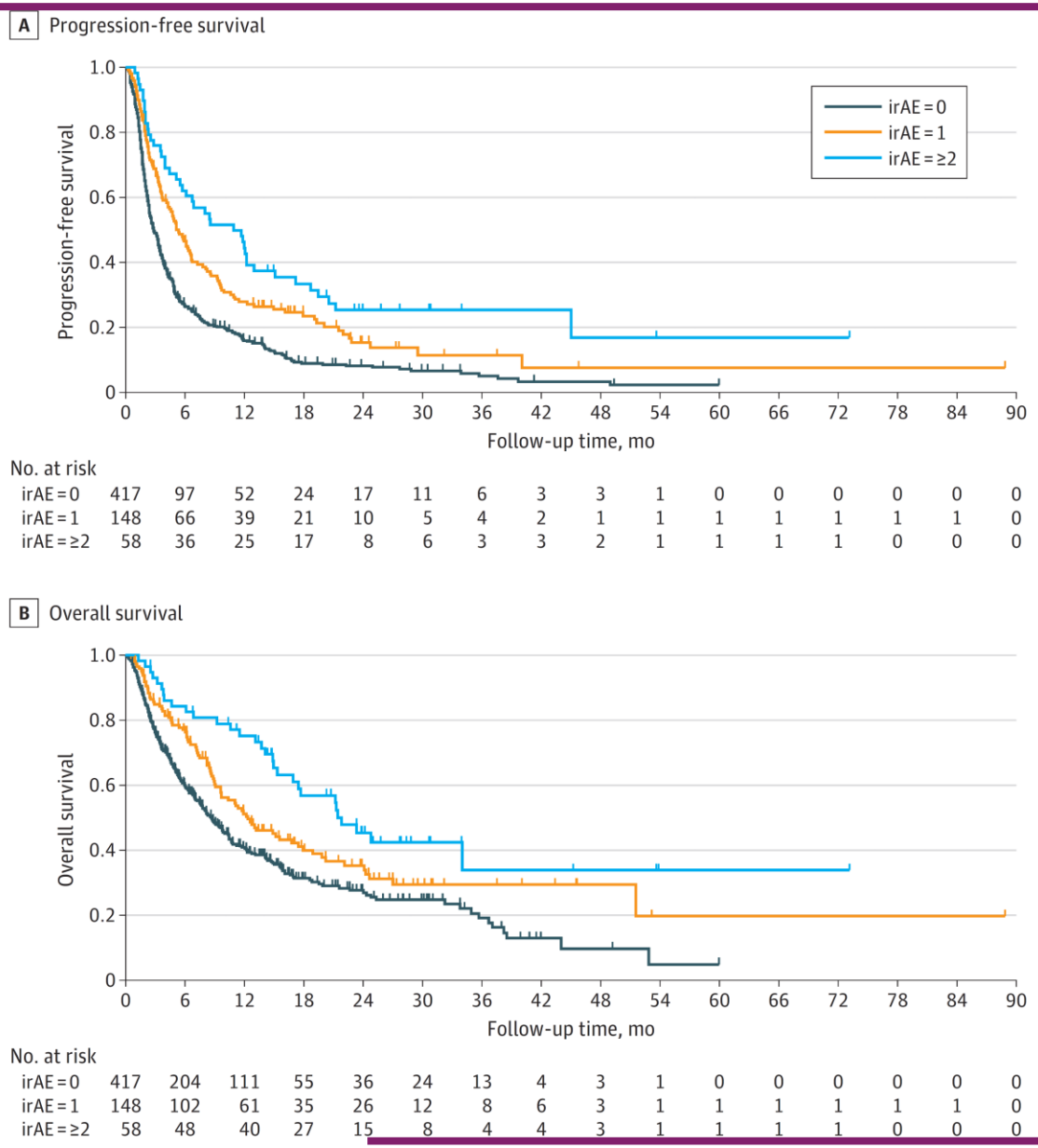
Multiple irAEs: 58 (9.3%)

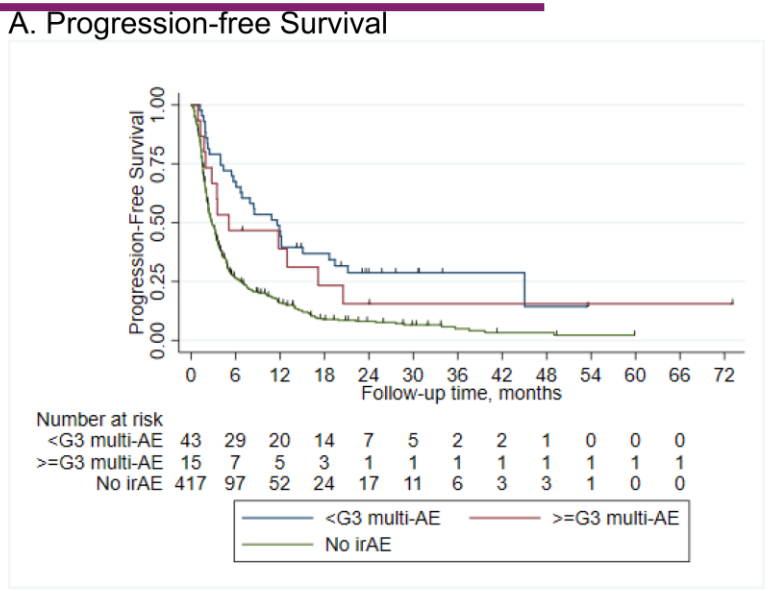
Most common multisystem patterns:

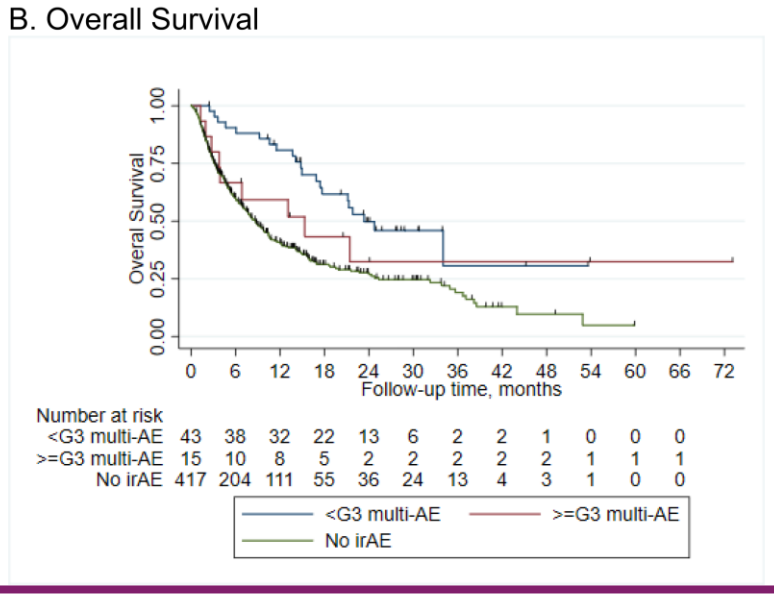
Pneumonitis	Thyroiditis	(14%)
Hepatitis	Thyroiditis	(10%)
Dermatitis	Pneumonitis	(10%)
Dermatitis	Thyroiditis	(8%)

Shankar B, et al. JAMA Oncol 2020;6(12):1952-1956.

Impatto prognostico degli irAEs nel NSCLC





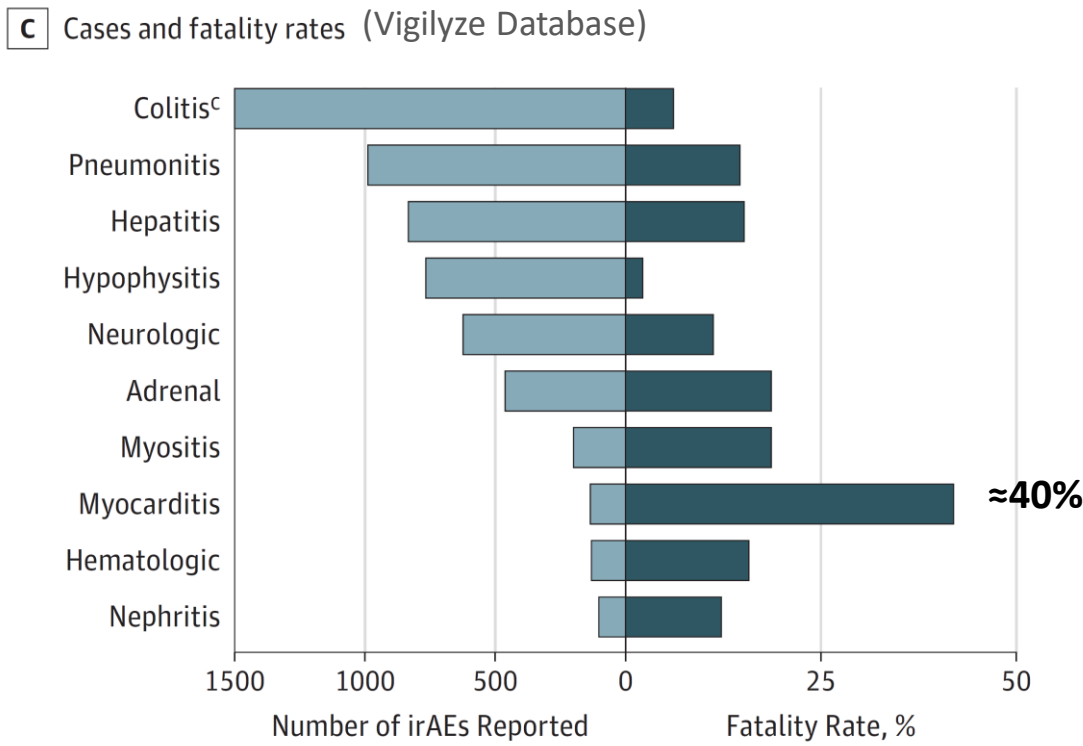


Shankar B, et al. JAMA Oncol 2020;6(12):1952-1956.

Mortalità degli irAEs

Table 2. Incidence and Types of Immune Checkpoint Inhibitor-Related Fatalities From Systematic Review and Meta-analysis

Variable	Anti-CTLA-4 (n = 5368)	Anti-PD-1 (n = 9136)	Anti-PD-L1 (n = 3164)	Anti-PD-1/PD-L1 Plus CTLA-4 (n = 1549)
Deaths, No. (%)	58 (1.08)	33 (0.36)	12 (0.38)	19 (1.23)
Type of fatal toxic effect				
Colitis	23 (40)	2 (6)	0	2 (11)
Pneumonitis	3 (5)	14 (42)	5 (42)	4 (21)
Hepatitis	5 (9)	0	1 (8)	2 (11)
Cardiac	9 (16)	4 (12)	3 (25)	4 (21)
Neurologic	1 (2)	1 (3)	0	3 (16)
Nephritis	1 (2)	0	0	1 (5)
Hematologic	2 (4)	2 (6)	0	2 (11)
Infectious	8 (14)	5 (15)	2 (18)	3 (16)
Hemorrhagic/thrombotic	2 (4)	1 (3)	0	1 (5)
Electrolyte imbalance	1 (2)	2 (6)	0	0
Multiorgan failure	3 (5)	0	0	0
Other	1 (2)	2 (6)	1 (8)	0



Wang DY et al. JAMA Oncol 2018;4(12):1721-1728.

Cronicizzazione degli irAEs

Table 2. Incidence of Chronic Immune-Related Adverse Events (irAEs)

Chronic irAEs	Patients, No. (%)	
	With chronic irAEs	Ongoing chronic irAE at last follow-up
Total chronic irAEs	167 (100)	NA
Required steroids	55 (32.9)	NA
Symptomatic	82 (49.1)	NA
Resolved	24 (14.4)	NA
≥Grade 2	90 (53.9)	NA
Grade 3-5	6 (3.6)	NA
irAE Type[a]		
Adrenal insufficiency	12 (3.1)	12 (100)
Arthritis/arthralgias	22 (5.7)	22 (100)
Colitis/diarrhea	6 (1.6)	2 (33.3)
Dermatitis/pruritus	19 (6.6)	17 (89.5)
Xerostomia[b]	9 (2.3)	8 (88.9)
Hypophysitis	8 (2.1)	8 (100)
Neuropathy	3 (1.8)	1 (33.3)
Ocular toxic effect[c]	5 (1.3)	5 (100)
Other neurotoxicity[d]	8 (2.1)	5 (63.0)
Pneumonitis	6 (1.6)	4 (66.7)
Thyroiditis/hypothyroid	54 (14.0)	54 (100)

Abbreviation: NA, not applicable.

[a] Greater than 1% observation frequency.

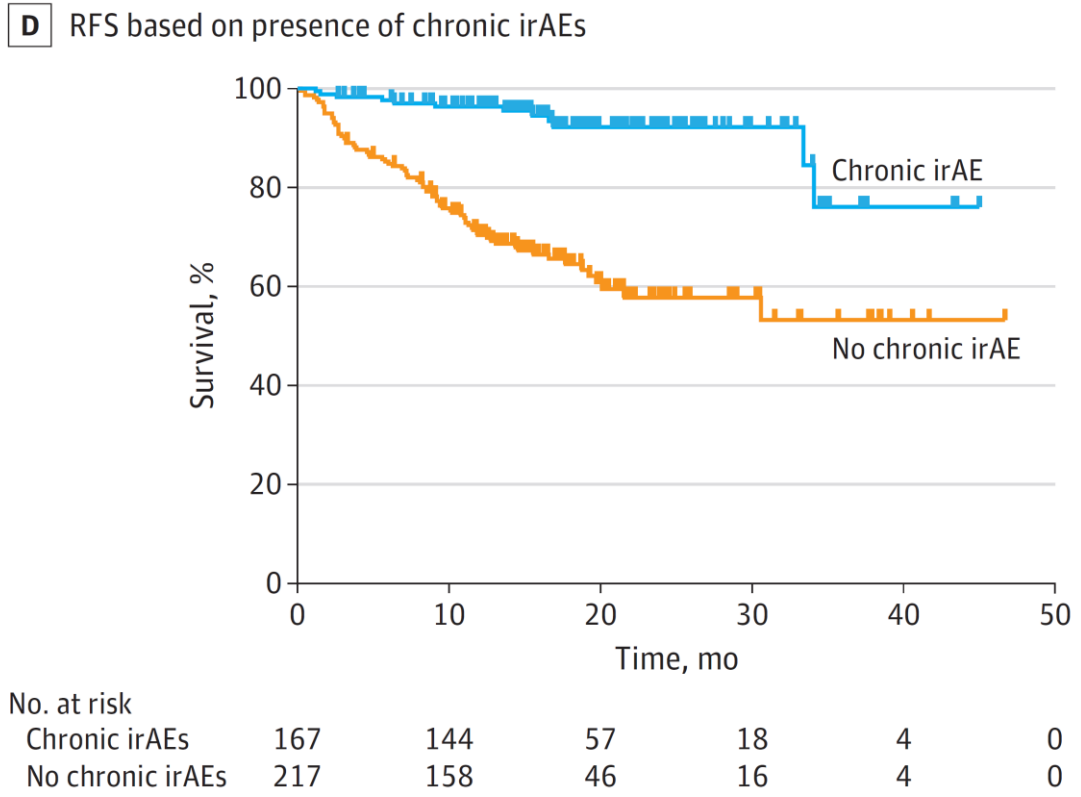
[b] Dry mouth (n = 6), Sicca syndrome (n = 2), and Sjogren syndrome (n = 1).

[c] Conjunctivitis (n = 1), uveitis (n = 1), retinal vasculitis (n = 1), nonischemic optic neuropathy (n = 1), and blurred vision (n = 1).

[d] Guillain-Barré syndrome (n = 2), Bell palsy (n = 1), parkinsonian gait (n = 1), myasthenia gravis (n = 1), autonomic neuropathy (n = 1), tremors (n = 1), and transverse myelitis (n = 1).

n=387 pts with stage III-IV melanoma treated with adjuvant anti-PD-1

43.2% had chronic irAEs



Chronic irAEs defined as irAEs persisting ≥ 12 wks after ICI cessation

Patrinely JR Jr, et al. JAMA Oncol 2021;7(5):744-748

Complicanze a lungo termine delle endocrinopatie

Type 1 Diabetes Mellitus[1]

Swedish retrospective, matched cohort study (n=36869; ctrl=184110)

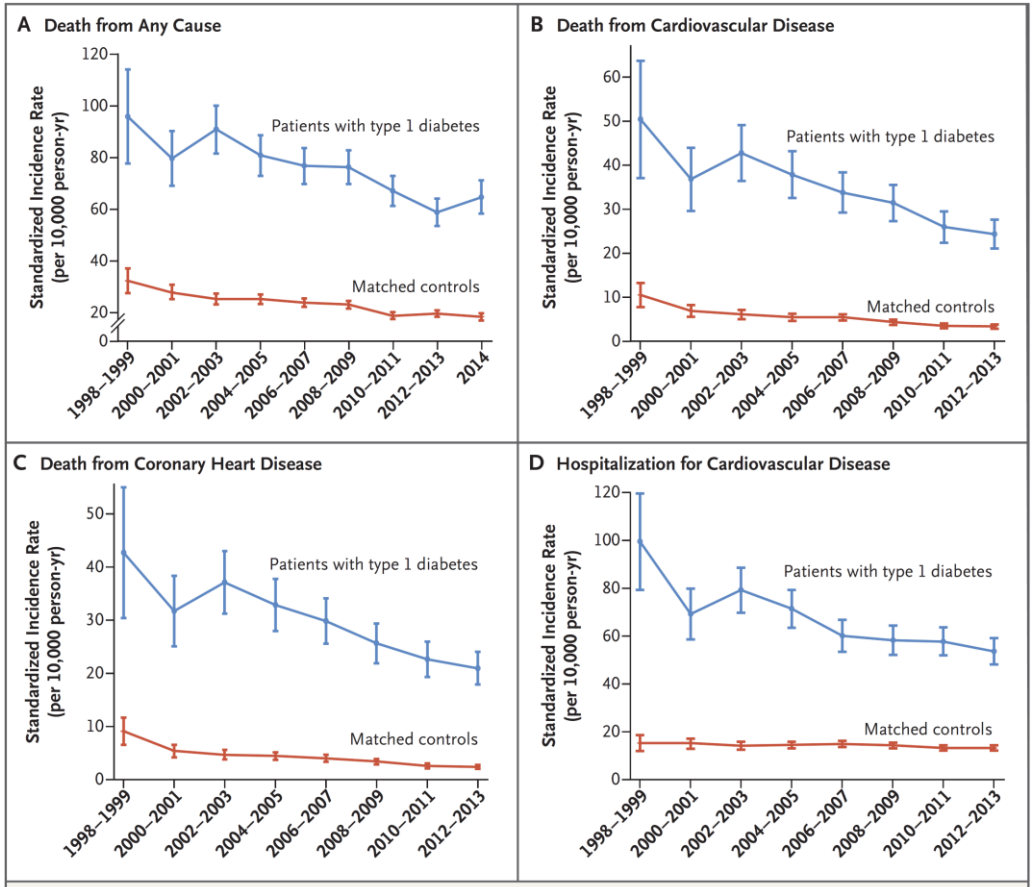
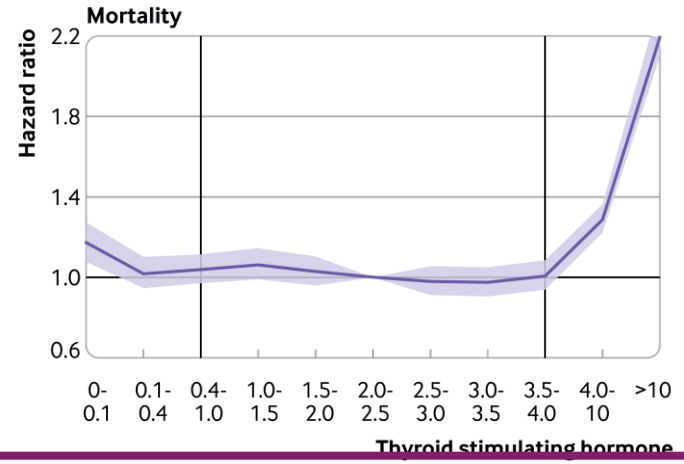


Figure 1. Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

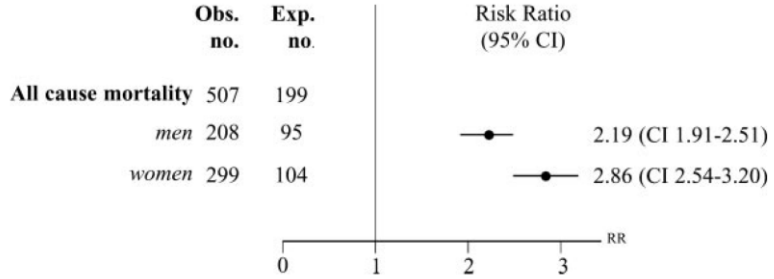
Hypothyroidism[2]

Retrospective, cohort study (n=162 369)



Addison Disease[3]

Population-based, retrospective observational study (n=1675)



1. Rawshani A, et al. N Engl J Med 2017;376:1407-1418. 2. Thayakaran R, et al. BMJ 2019;366:l4892. Bergthorsdottir R, et al. J Clin Endocrinol Metab 2006;91:4849-53.

Linee guida sulla gestione della tossicità da immunoterapia

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): i119–i142, 2017
doi:10.1093/annonc/mdx225

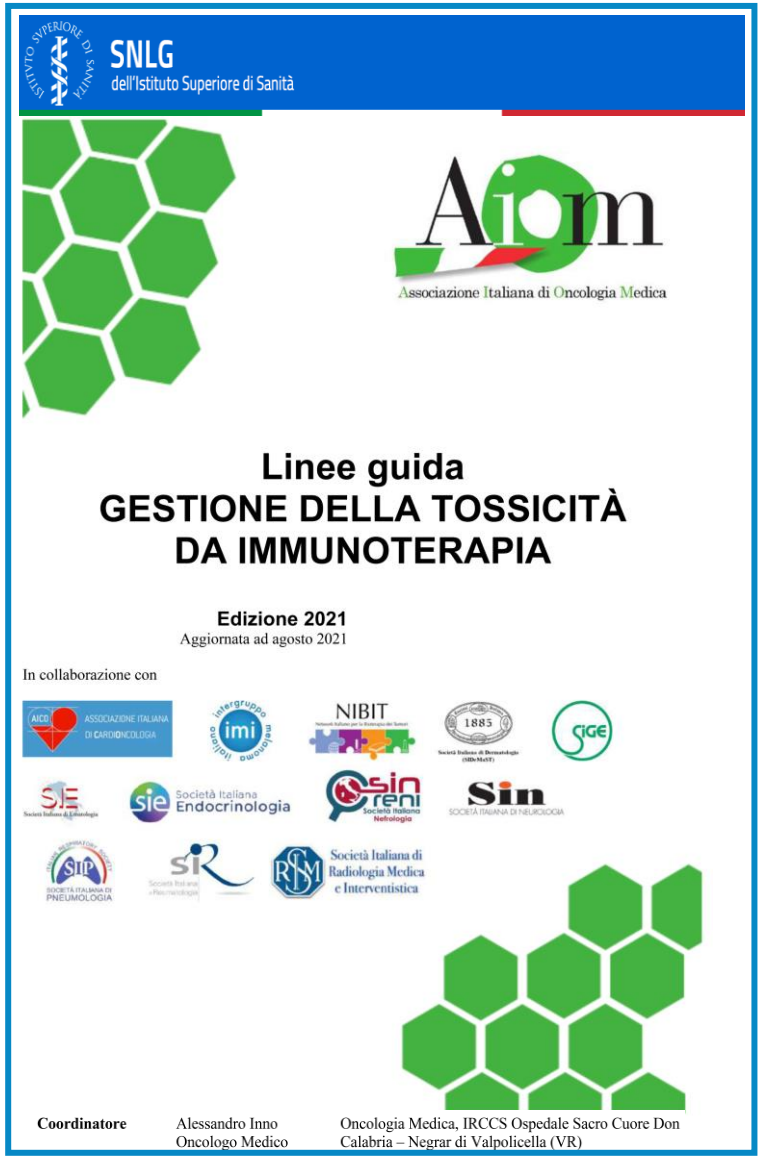
CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Open access — Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events



Schneider BJ, et al. J Clin Oncol 2021;39(36):4073-4126. Haanen JBAG, et al. Ann Oncol 2018;29(Suppl 4):iv264-iv266.
Brahmer JR, et al. J Immunother Cancer 2021;9(6):e002435. https://snlg.iss.it/wp-content/uploads/2021/12/LG-200_Tox-da-immunoterapia_agg2021.pdf

Gestione della tossicità: principi generali

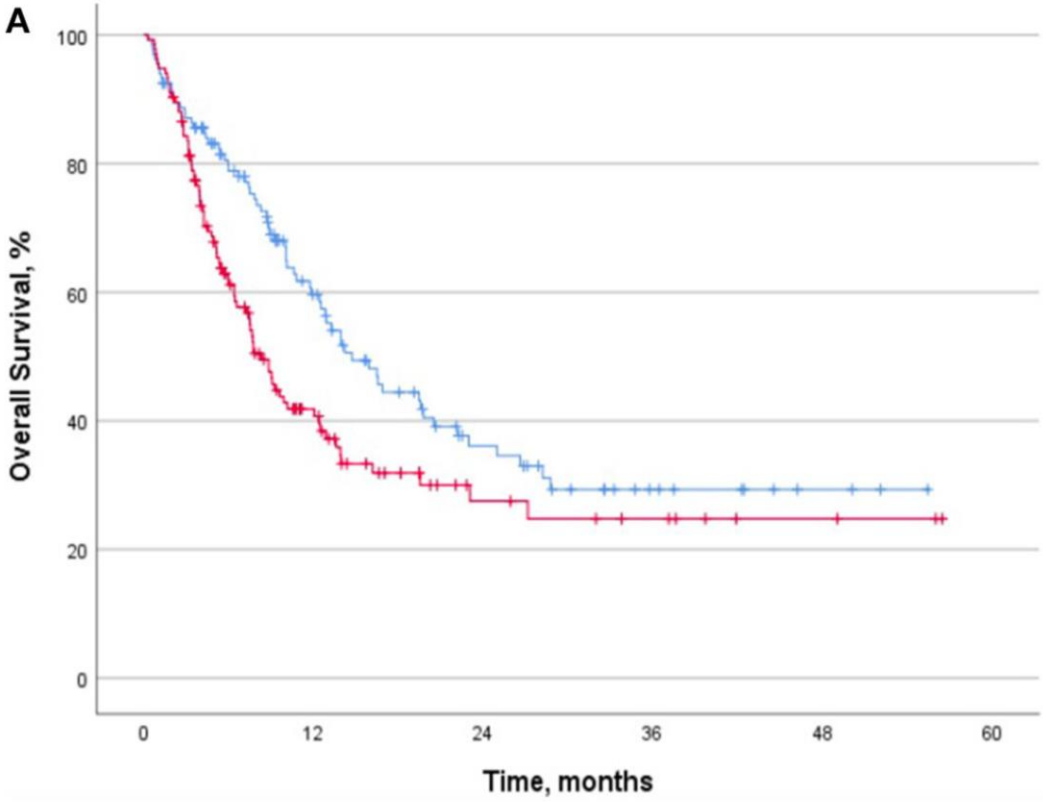
It is recommended that clinicians manage toxicities as follows:

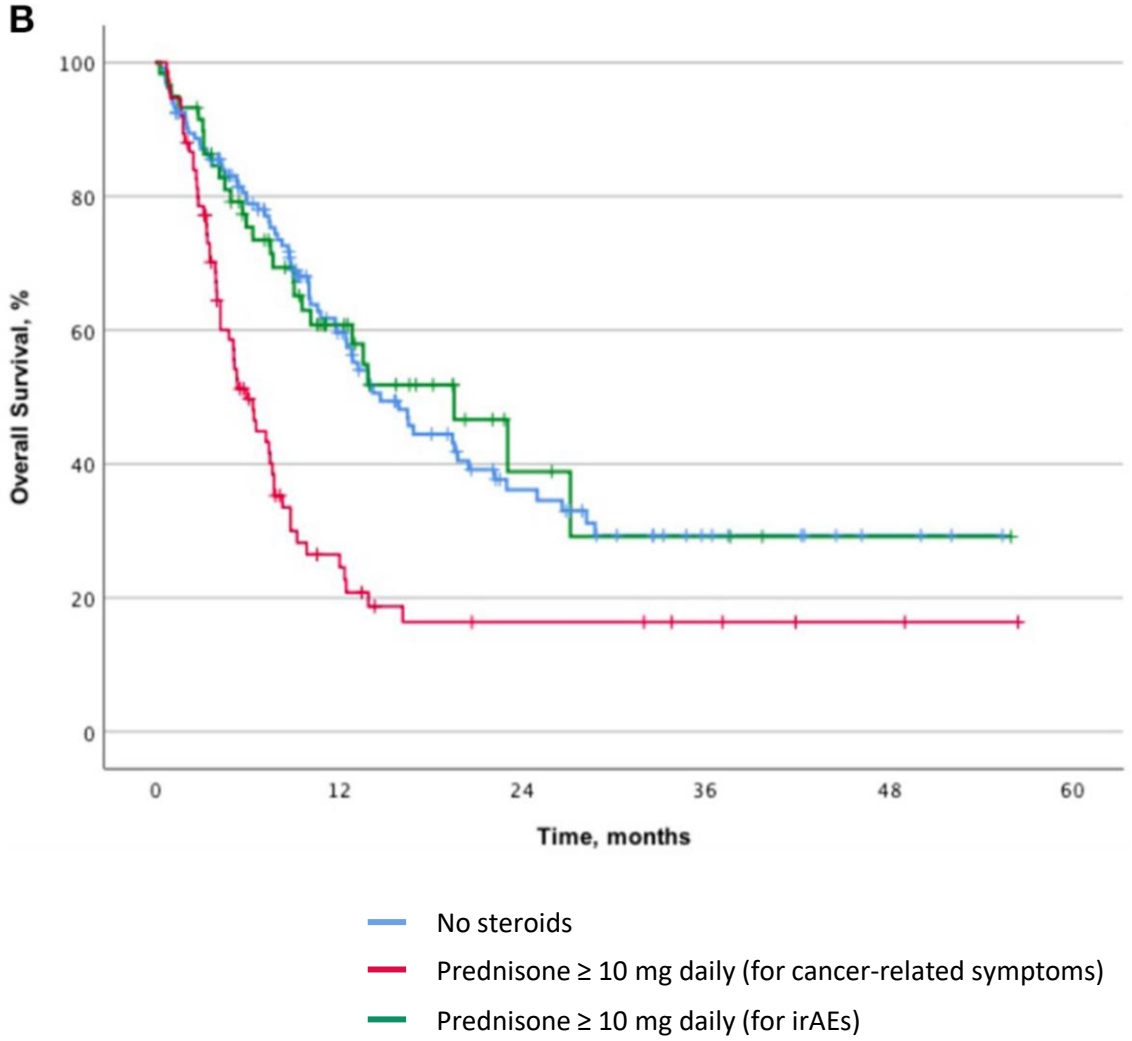
- Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs before initiating therapy and throughout treatment and survivorship.
- There should be a high level of suspicion that new symptoms are treatment-related.
- In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities.
- Consider holding ICPis for most grade 2 toxicities and resume when symptoms and/or laboratory values revert ≤ grade 1. Corticosteroids (initial dose of 0.5-1 mg/kg/d of prednisone or equivalent) may be administered.
- Hold ICPis for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent). Corticosteroids should be tapered over the course of at least 4-6 weeks. If symptoms do not improve with 48-72 hours of high-dose steroid, infliximab may be offered for some toxicities.
- When symptoms and/or laboratory values revert ≤ grade 1, rechallenging with ICPis may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended. Rechallenge with PD-1/PD-L1 monotherapy may be offered in patients with toxicity from combined therapy with a CTLA-4 antagonist once recovered to ≤ grade 1.
- In general, grade 4 toxicities warrant permanent discontinuation of ICPis, except for endocrinopathies that have been controlled by hormone replacement.

Schneider BJ, et al. J Clin Oncol 2021;39(36):4073-4126

Impatto prognostico degli steroidi

n=267 NSCLC pts treated with anti-PD(L)1 drugs





Riudavets M et al. Front Oncol 2020;10:1677

Tapering dello steroide

Characteristics	No recurrent pneumonitis (*n* = 13), *n* (%)	Recurrent unprovoked pneumonitis (*n* = 3), *n* (%)
Treatment		
Anti-PD-1	10 (77)	3 (100)
Ipi-nivo	3 (23)	0 (0)
BRAF ^{V600} mutant	1 (8)	1 (33)
Onset of first event (median, range), wk[a]	26.4 (3.6–123.7)	12.4 (12.3–22.1)
Additional organ classes involved with irAEs		
0 (only pneumonitis)	4 (31)	1 (33)
1 or more	9 (69)	2 (67)
Grade of first event		
G1	5 (38)	1 (33)
G2	7 (54)	1 (33)
G3	0 (0)	1 (33)
G4	1 (8)	0 (0)
Grade of recurrent event		
G1	n/a	0 (0)
G2	n/a	1 (33)
G3	n/a	2 (67)
Duration of steroid treatment at first event, median (range), wk	10.0 (4.6–26)	5.1 (5.1–8)
Disease control		
Yes	12 (92)	2 (67)
No	1 (8)	1 (33)

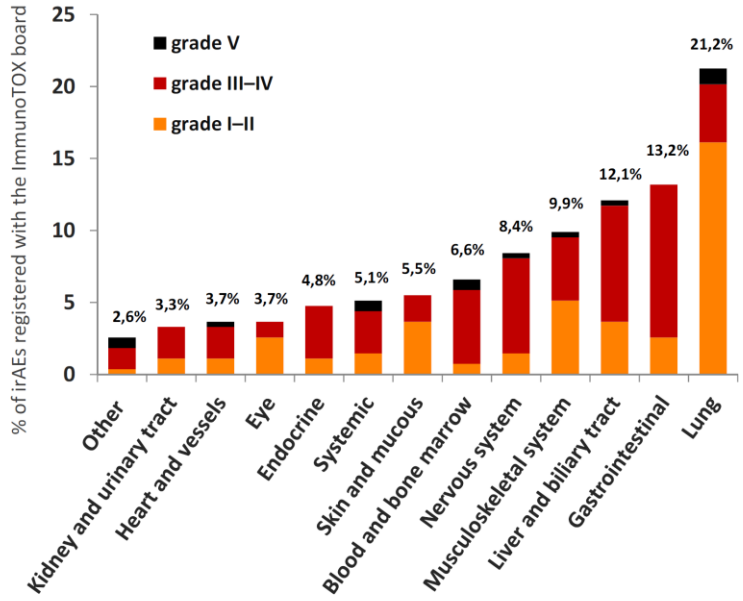
Asher N, et al. Oncologist 2019;24(5):640-647.

Gestione della tossicità da immunoterapia: approccio multidisciplinare

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com

Original Research

The 2016–2019 ImmunoTOX assessment board report of collaborative management of immune-related adverse events, an observational clinical study



Vantaggi di board multidisciplinari per gestione di tossicità immunorelate

- Ottimizzazione del management
- Identificazione di nuove e rare tossicità
- Incremento di conoscenza tramite **cross-contamination**
- Raccolta di dati clinici e traslazionali
- Network building con altri istituti e figure professionali

Michot JM, et al. Eur J Cancer. 2020;130:39-50.

Take Home Message

- L’immunoterapia è ben tollerata
- La maggior parte degli irAEs è reversibile, ma alcuni eventi possono essere fatali (miocardite, polmonite) e altri cronici/persistenti (endocrinopatie)
- Necessaria adeguata informazione al paziente e ai caregivers
- Elevata attenzione da parte del medico a sintomi/segni di sospetto
- Trattamento secondo linee guida (introduzione tempestiva dello steroide quando indicato)
- Approccio multidisciplinare

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