Progetto CANOA

CARCINOMA MAMMARIO:
QUALI NOVITA' PER IL 2024?

''Saper leggere'' uno studio clinico
per migliorare la pratica clinica

Gestione della tossicità da immunoterapia

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Disclosures

- Consulting activity: MSD, AstraZeneca
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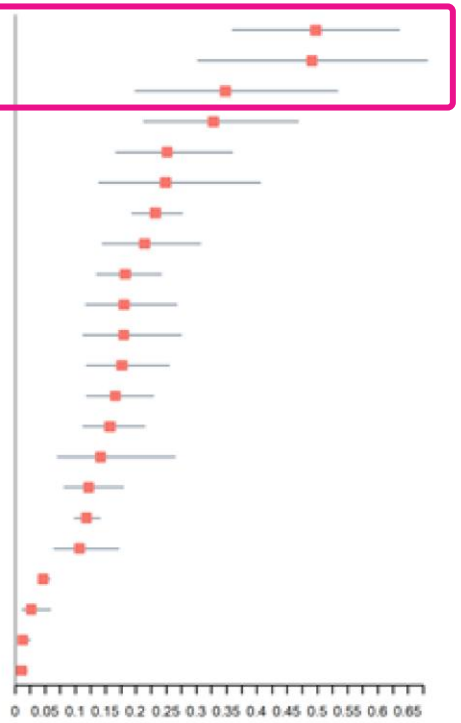
Tossicità IO/CTx nel carcinoma mammario

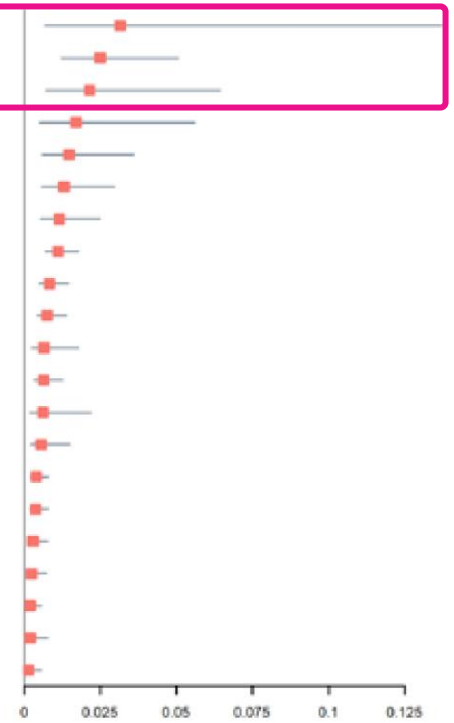
Grade 1-2 AEs

Adverse Event	Incidence(%) (95%CI)
Nausea	49.70 (35.90-63.55)
Fatigue	49.10 (30.24-68.21)
Anemia	34.74 (19.91-53.28)
Diarrhoea	32.77 (21.25-46.81)
Headache	25.14 (16.72-35.97)
Arthralgia	24.88 (13.87-40.52)
Constipation	23.20 (19.27-27.65)
Voimting	21.43 (14.39-30.67)
Fever	18.24 (13.49-24.18)
ALT elevation	18.05 (11.73-26.74)
AST elevation	17.98 (11.26-27.45)
Rash	17.64 (11.83-25.48)
Dyspnea	16.59 (11.75-22.92)
Pruritus	15.70 (11.26-21.47)
Neutropenia	14.15 (7.02-26.47)
Back pain	12.17 (8.12-17.85)
Hypothyroid	11.77 (9.83-14.04)
Abdominal Pain	10.65 (6.43-17.11)
Hyperthyroid	4.67 (3.79-5.73)
Pneumonitis	2.65 (1.18-5.88)
Colitis	1.27 (0.64-2.51)
Adrenal insufficiency	1.08 (0.58-2.00)



Grade ≥ 3 AEs

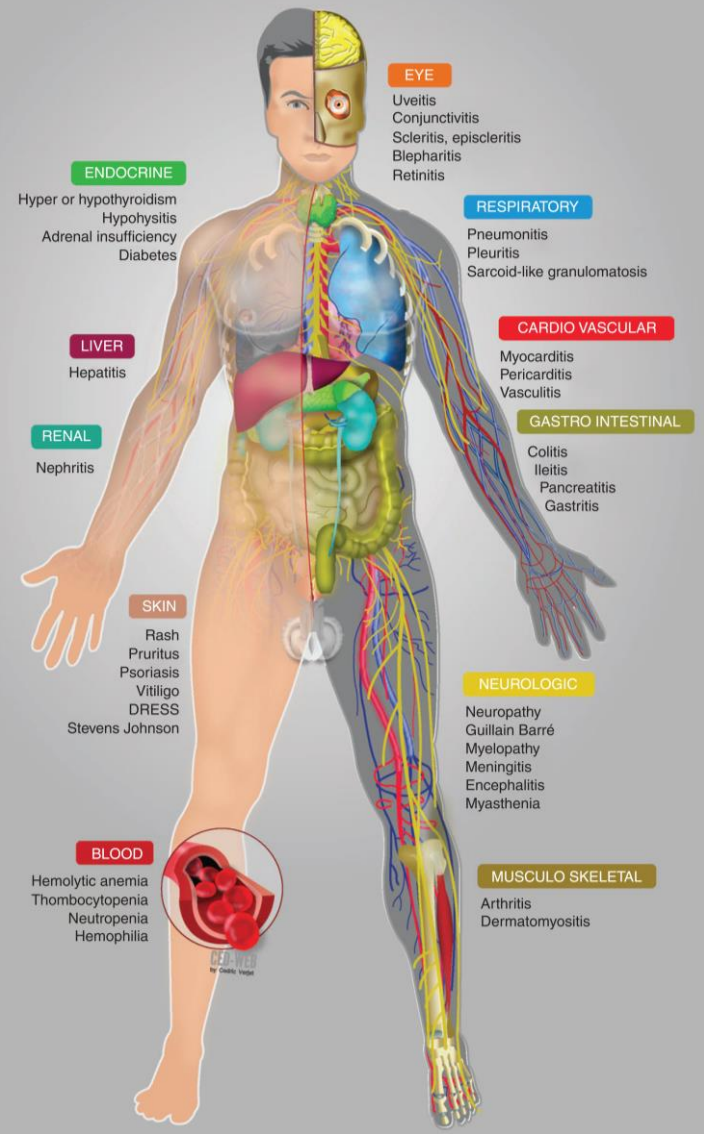
Adverse Event	Incidence(%) (95%CI)
Neutropenia	3.15 (0.66-13.72)
Fatigue	2.50 (1.22-5.05)
Anemia	2.16 (0.70-6.45)
Adrenal insufficiency	1.70 (0.50-5.61)
ALT elevation	1.47 (0.60-3.60)
Diarrhoea	1.31 (0.57-2.98)
Nausea	1.16 (0.53-2.50)
Fever	1.11 (0.68-1.81)
Dyspnea	0.84 (0.47-1.46)
Pneumonitis	0.76 (0.42-1.38)
AST elevation	0.65 (0.24-1.80)
Rash	0.64 (0.32-1.28)
Arthralgia	0.62 (0.18-2.20)
Voimting	0.57 (0.21-1.51)
Colitis	0.40 (0.20-0.80)
Hypothyroid	0.38 (0.18-0.79)
Headache	0.29 (0.11-0.78)
Constipation	0.24 (0.08-0.74)
Hyperthyroid	0.21 (0.08-0.57)
Abdominal Pain	0.20 (0.05-0.79)
Back pain	0.15 (0.04-0.58)



In una meta-analisi di 9 studi con anti-PD(L)1 (n=1) e combinazioni di anti-PD(L)1 e chemioterapia (n=8)
in 2941 pazienti con carcinoma mammario triplo-negativo
la **tossicità più frequente** è stata quella correlata alla **chemioterapia**

Zhang Y et al. Life (Basel) 2022;12(12):1990.

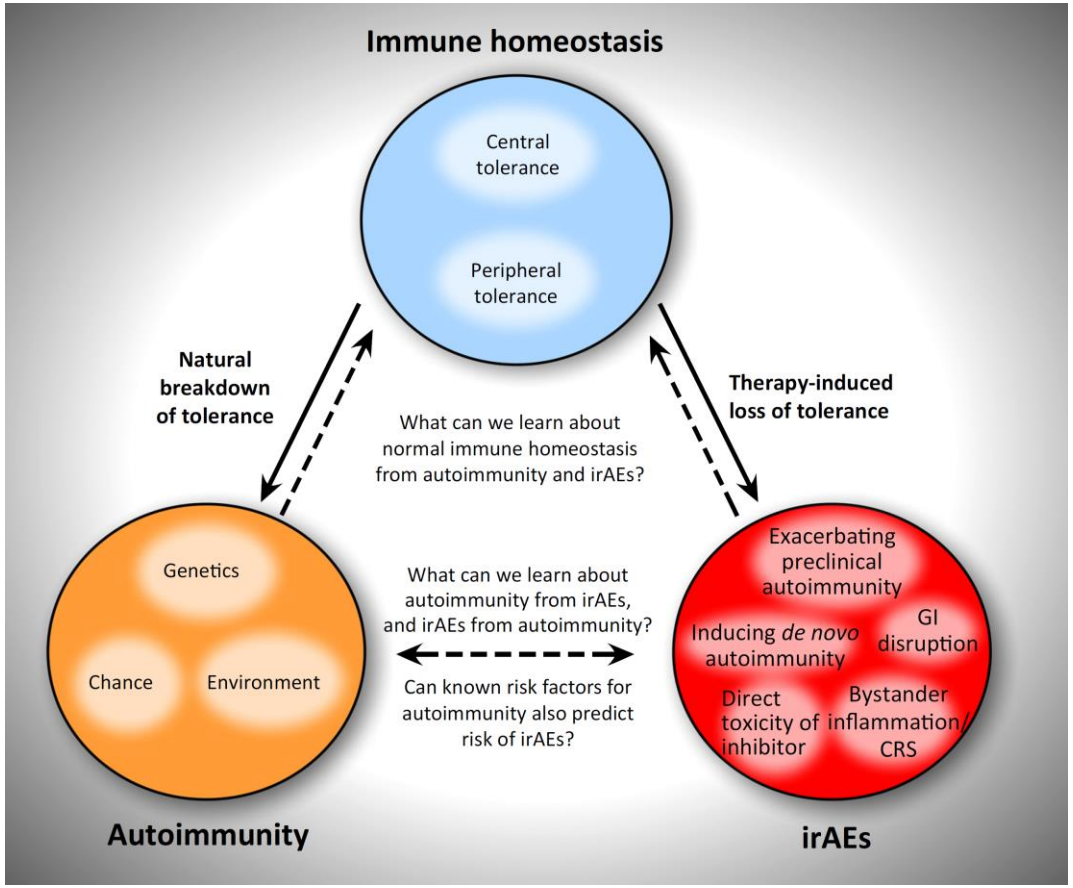
Eventi avversi immuno-correlati (irAEs)

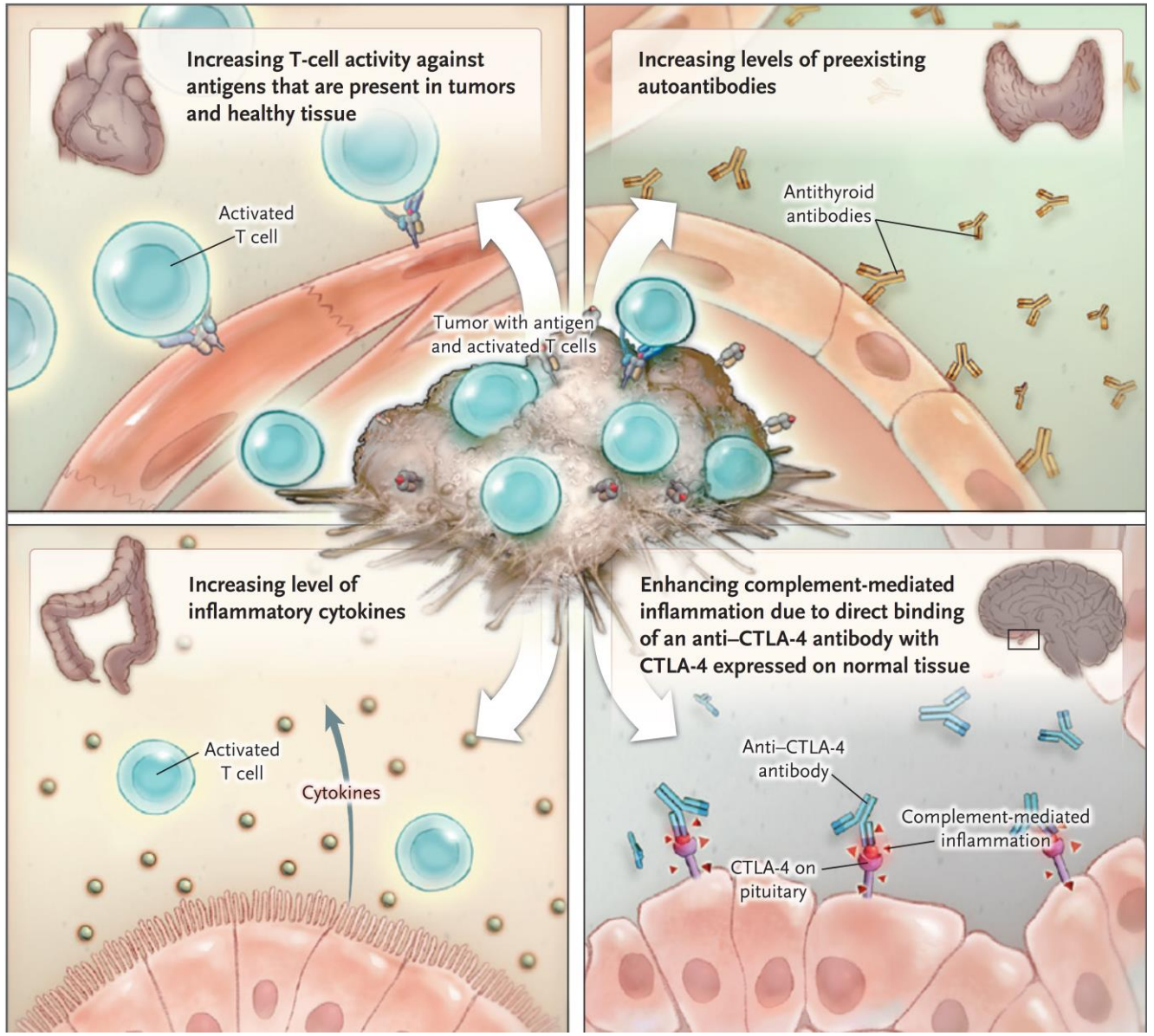


Gli irAEs
possono colpire
potenzialmente qualsiasi
organo/apparato

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

Patogenesi degli irAEs



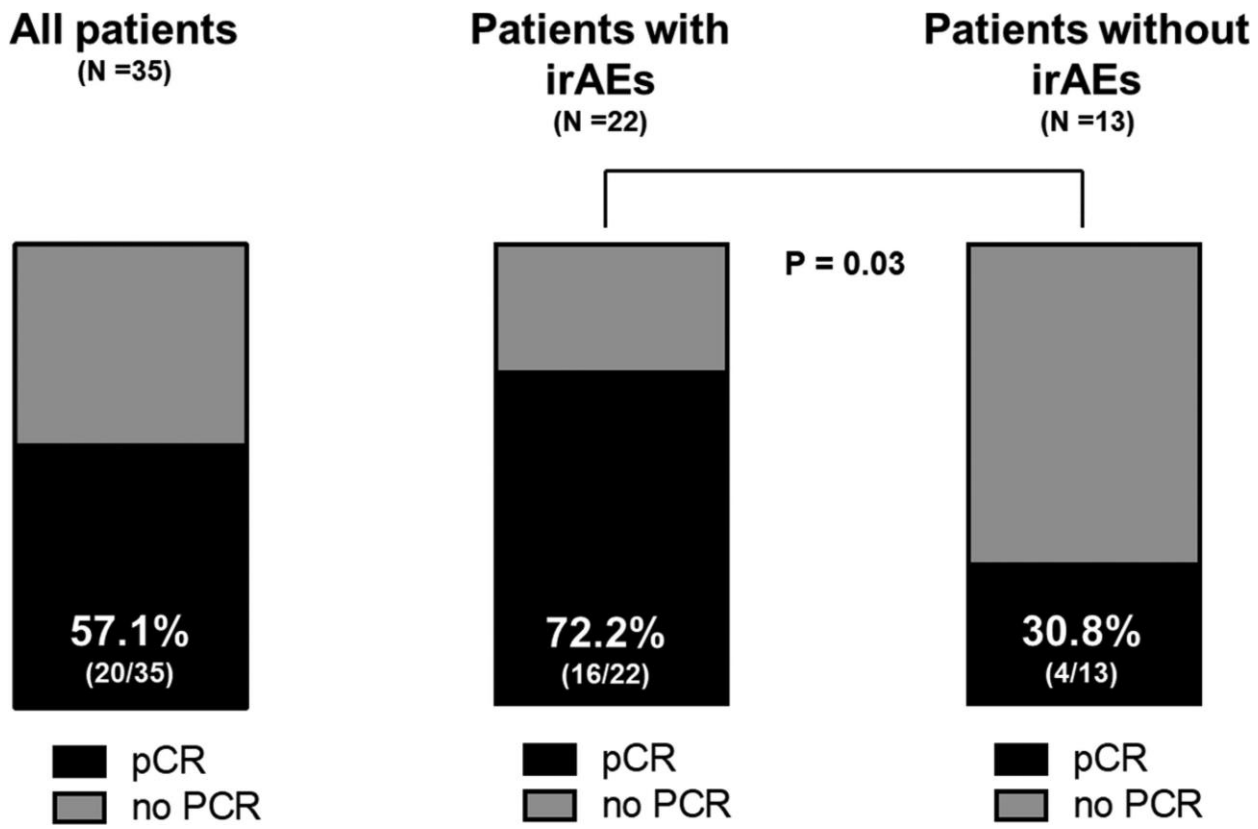


Pauken KE et al. Trends Immunol 2019;40(6):511-523. Postow MA, et al. N Engl J Med 2018;378(2):158-168

Impatto prognostico: irAEs e risposta patologica completa nel TNBC

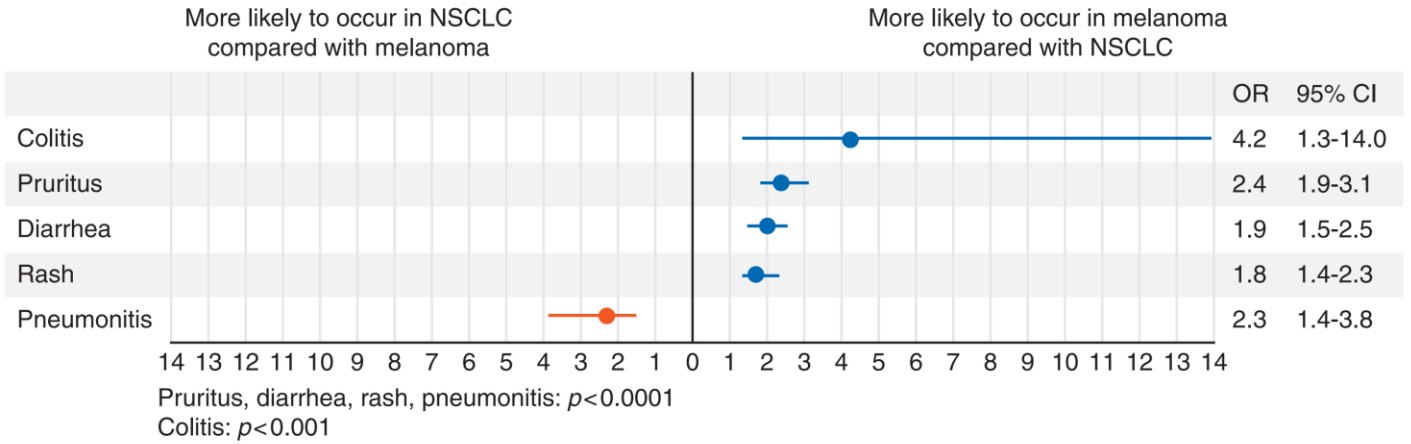
Table 4. Incidence and types of irAEs observed in the study population. Of note, 22 patients (62.9%) experienced at least one irAE, with investigators reporting a total of 25 irAEs. Most (77.3%) irAEs occurred during the neoadjuvant treatment phase. Treatment of irAEs mainly involved the use of corticosteroids (in 68.2% of cases), and pembrolizumab was discontinued in most (81.8%) of patients experiencing irAEs.

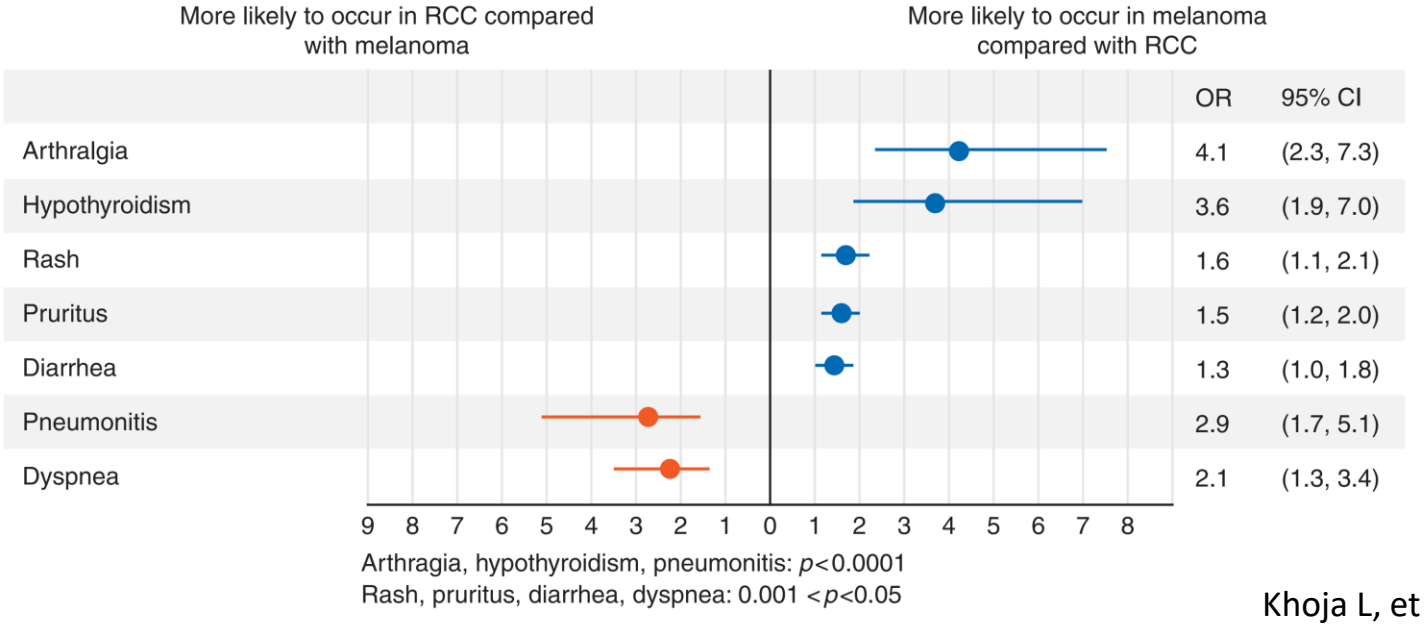
Type of irAE – no. (%)	
Hypothyroidism	7 (20.0)
Arthritis	3 (8.6)
Hepatitis	3 (8.6)
Pneumonitis	3 (8.6)
Dermatitis	2 (5.7)
Myokarditis	2 (5.7)
Eosinophilia	1 (2.9)
Hyperthyroidsm	1 (2.9)
Hypophysitis	1 (2.9)
ITP	1 (2.9)
Nephritis	1 (2.9)
	Total iAEs observed (*n*=25)
	Patients with irAEs (*N*=22)
Steroid Use yes–no. (%)	15 (68.2)
Use of other immunosuppression yes–no. (%)	1 (4.5)
Discontinuation of Pembrolizumab yes–no. (%)	18 (81.8)



Marhold M et al. Oncoimmunology 2023;12(1):2275846.

Pattern degli irAEs in relazione alla neoplasia primitiva





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

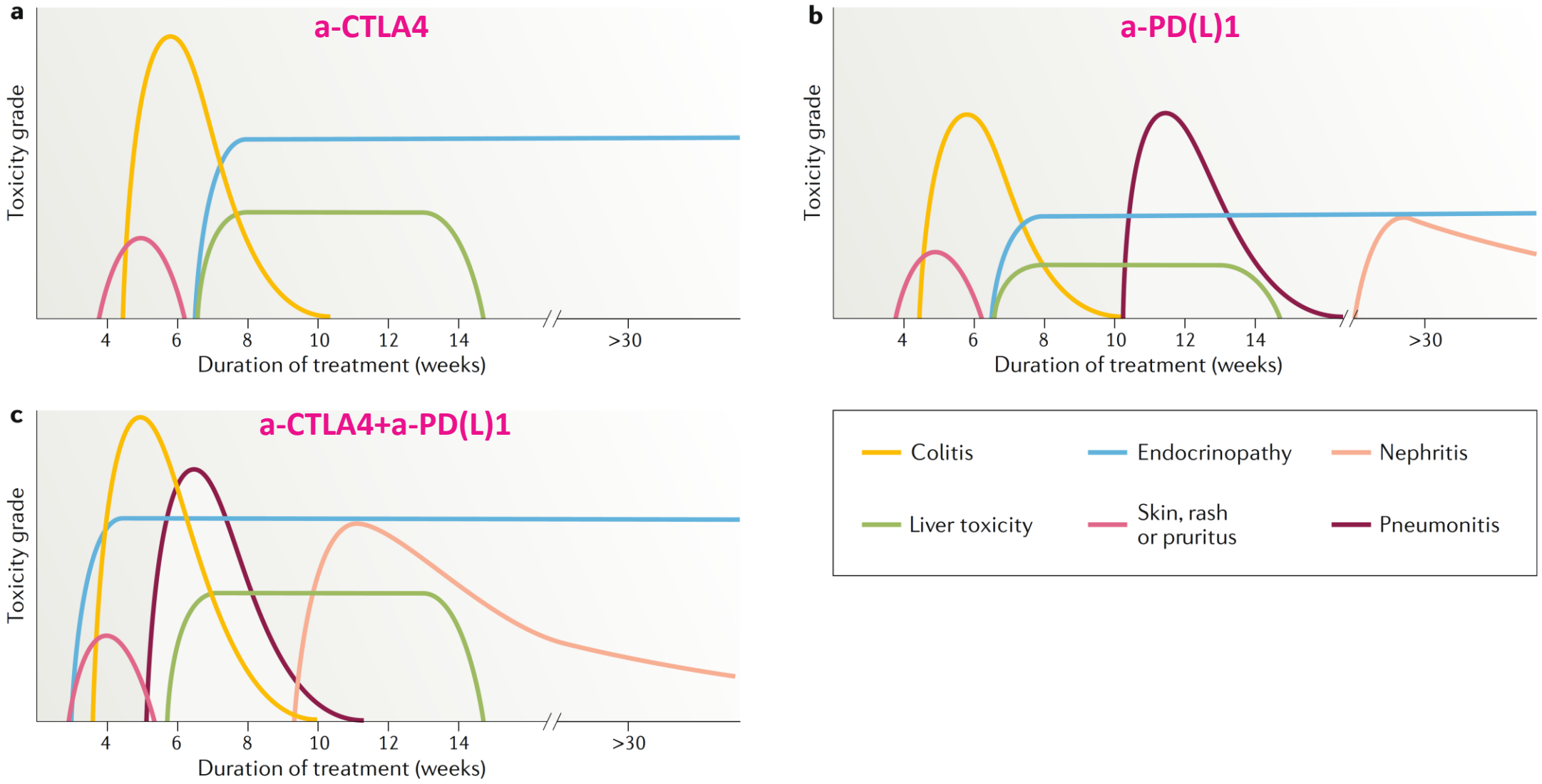
Incidenza degli irAEs nel TNBC

	Any Grade (%)	G 3-5 (%)
Overall	**35.7**	**8.5**
Rash	37.8	1.1
Hypothyroidism	12.2	0.4
Infusion reactions	12.0	1.6
Hyperthyrodism	4.5	0.3
Pneumonitis	1.8	0.6
Hypophysitis	1.7	-
Hepatitis	1.6	1.0
Adrenal Insufficiency	1.1	0.6
Colitis	0.9	0.4
Thyroiditis	0.7	0.2
Nephritis	0.7	0.4
Myositis	0.5	1.0
T1DM	0.3	0.3
Encephalitis	0.2	0.2

In una meta-analisi di 9 studi su 4697 pazienti con carcinoma mammario trattati con ICI, gli irAEs più frequenti sono stati la **tossicità cutanea**, la **tossicità tiroidea** e le **reazioni infusionali**.

Balibegloo M et al. Int Immunopharmacol 2021;96:107796.

Cinetica degli irAEs

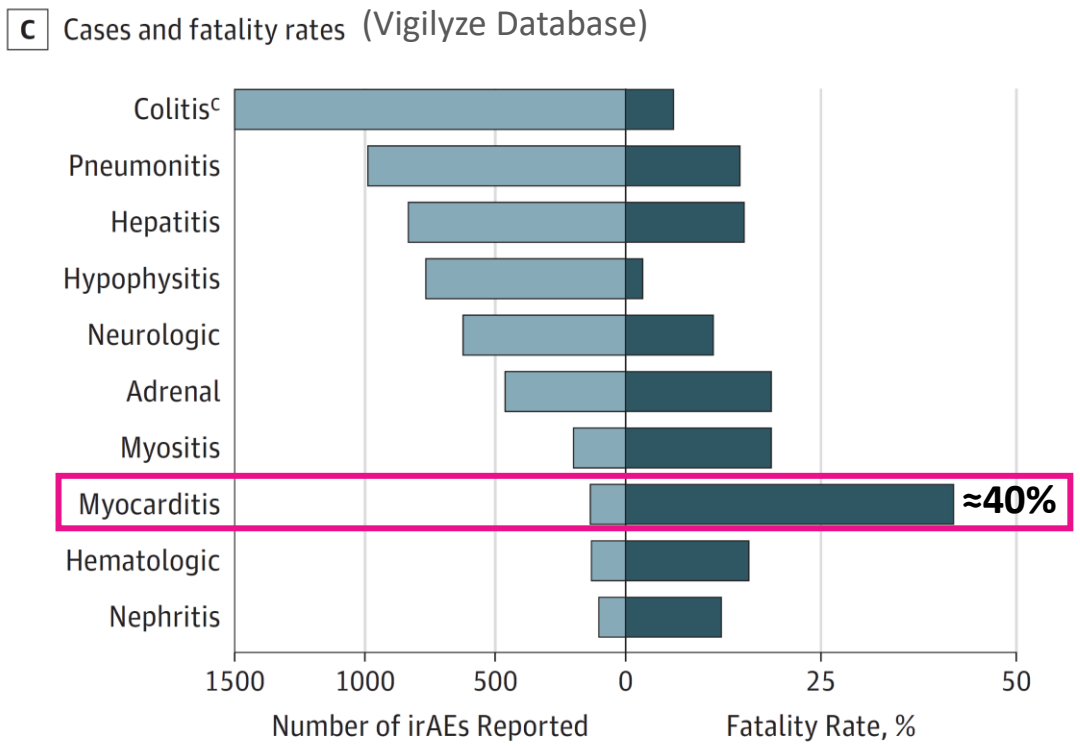


Postow MA, et al. N Engl J Med 2018;378(2):158-168

IrAEs fatali

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

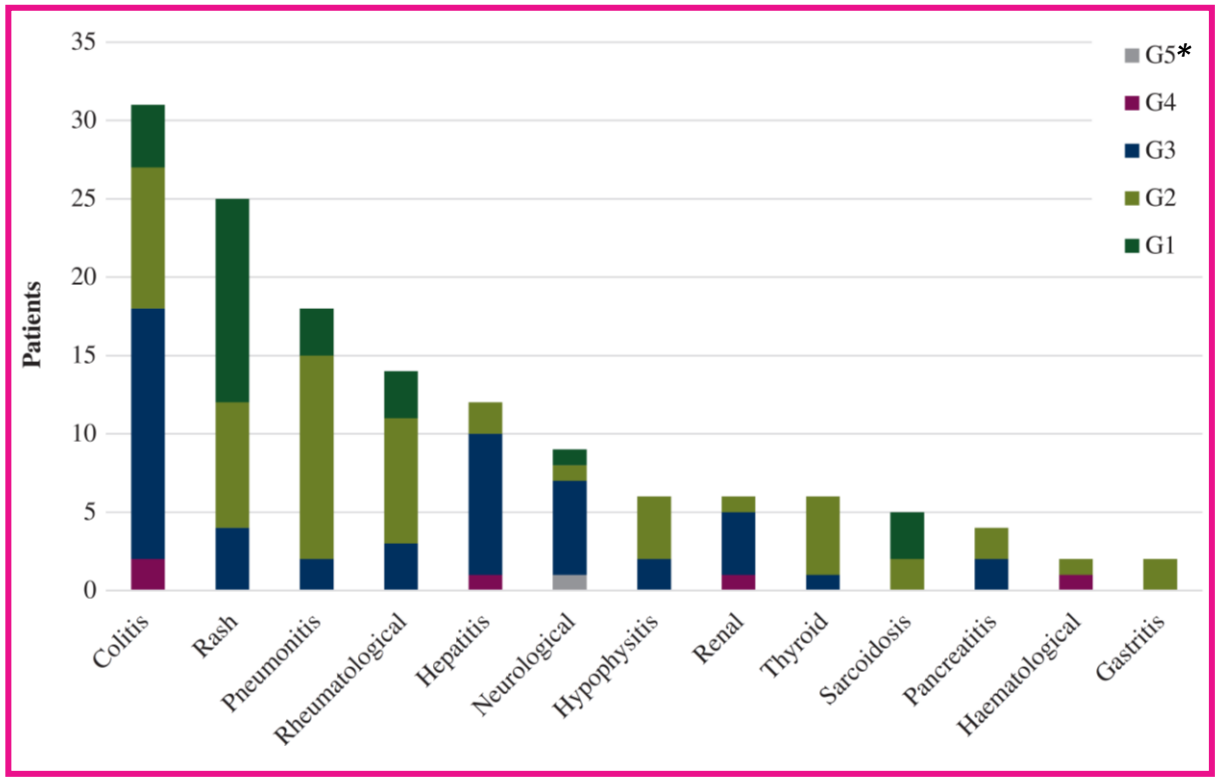


Wang DY et al. JAMA Oncol 2018;4(12):1721-1728.

IrAEs tardivi

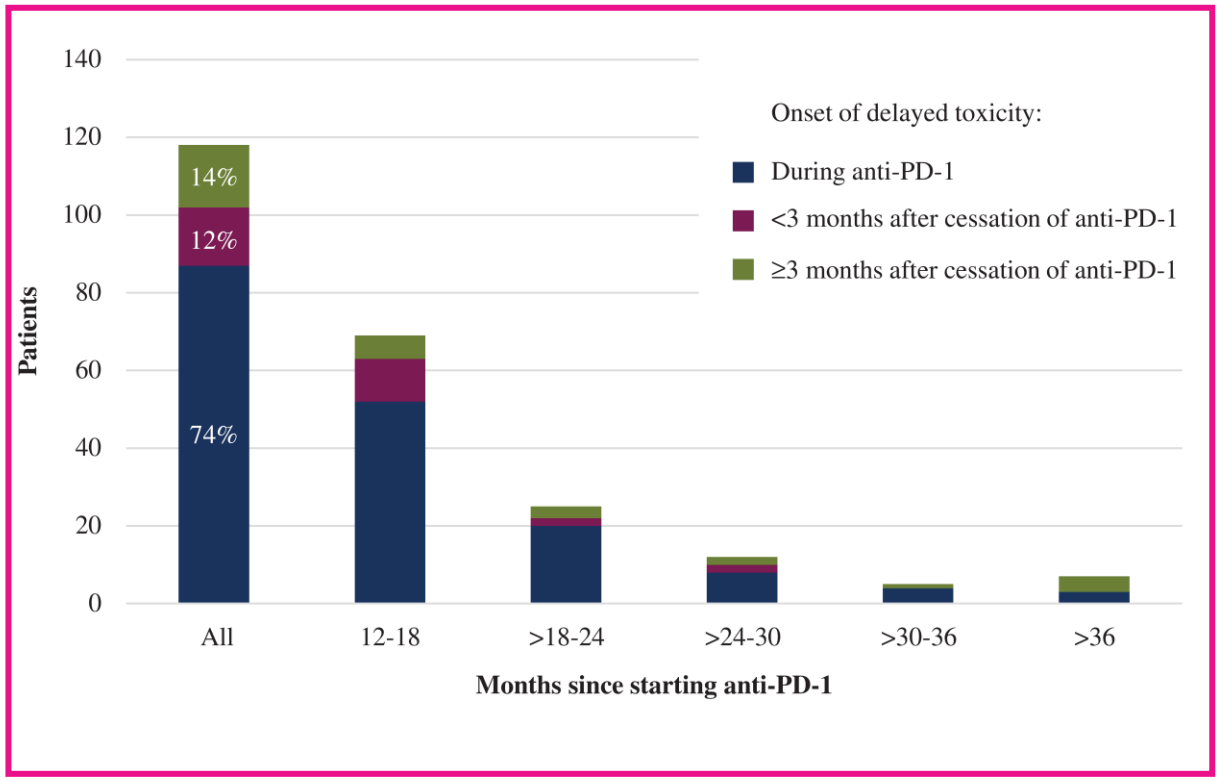
- 999 melanoma pts treated with immunotherapy surviving > 1 year (retrospective data)
- **Incidence** of delayed irAEs (occurring >1 year after immunotherapy initiation): **5.3%**; may be high-grade and can lead to death
- 58% also had a previous irAEs, often affecting a different organ (86%)

N. of delayed toxicity cases by irAE subtype and grade



**1 case of G5 encephalitis and 1 case of multi-organ irAE*

Onset of delayed IrAEs in relation to anti-PD-1 therapy.



Owen CN, et al. Ann Oncol 2021;32(7):917-925.

IrAEs cronici

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

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).

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

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://www.iss.it/-/snlg-tossicita-immunoterapia

Gestione della tossicità: principi generali

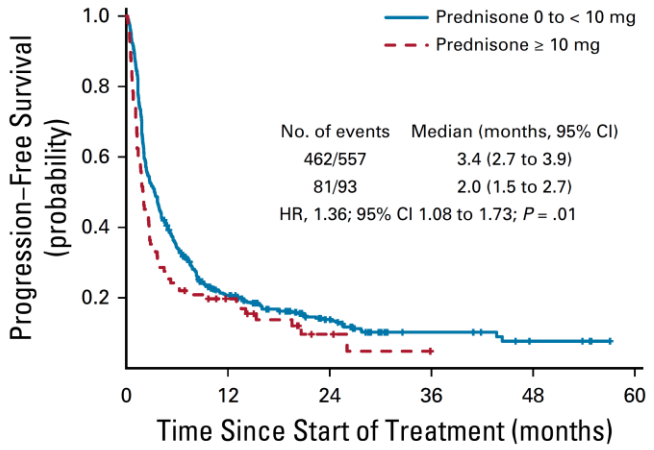
It is recommended that clinicians manage toxicities as follows:

- 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

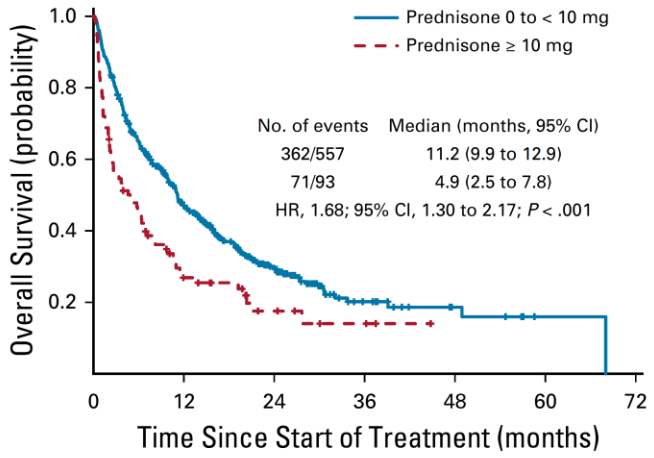
Impatto prognostico dello steroide nella gestione della tossicità

n=650 NSCLC pts treated with anti-PD(L)1 drugs



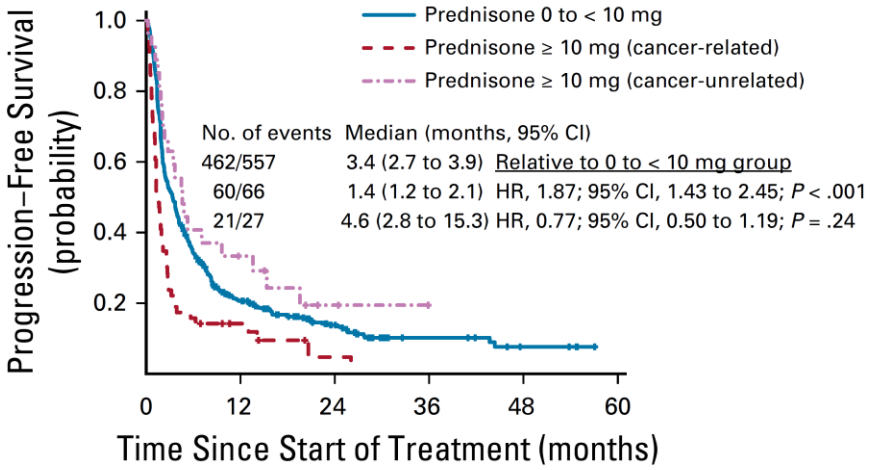
No. at risk:

Prednisone 0 to < 10 mg	557	91	35	10	4	0
Prednisone ≥ 10 mg	93	14	3	0	0	0



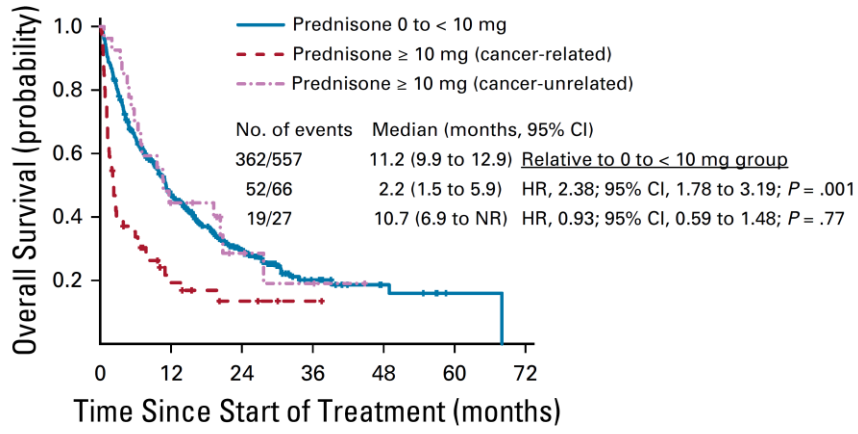
No. at risk:

Prednisone 0 to < 10 mg	557	213	75	17	7	1	0
Prednisone ≥ 10 mg	93	19	7	3	0	0	0



No. at risk:

Prednisone 0 to < 10 mg	557	91	35	10	4	0
Prednisone ≥ 10 mg (cancer-related)	66	6	1	0	0	0
Prednisone ≥ 10 mg (cancer-unrelated)	27	8	2	0	0	0



No. at risk:

Prednisone 0 to < 10 mg	557	213	75	17	7	1	0
Prednisone ≥ 10 mg (cancer-related)	66	8	3	1	0	0	0
Prednisone ≥ 10 mg (cancer-unrelated)	27	11	4	2	0	0	0

Ricciuti B, et al. J Clin Oncol 2019;37(22):1927-1934.

Tapering dello steroide

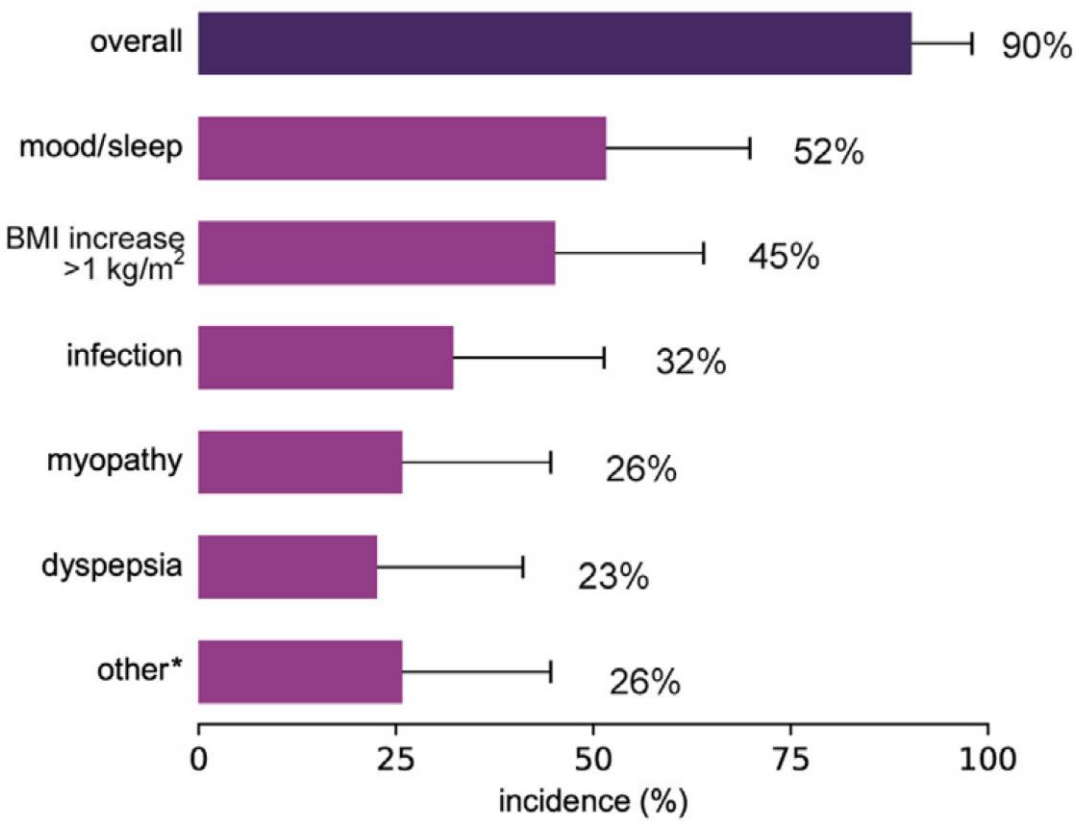
n=16 melanoma pts with ICI-related pneumonitis

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.

Eventi avversi dello steroide

Adverse effects of systemic steroids reported by lung cancer patients who received treatment for at least 30 days (n = 31)



Other adverse effects included hyperglycemia without diabetes (n=3), hypertension (n=2), bruising (n=2), symptomatic compression fracture (n=1), and acne (n=1).

Preventing the adverse events associated with corticosteroids

SIX KEY MEASURES

1 rule out infections before initiating corticosteroids (e.g. perform a bronchoalveolar lavage for pneumonitis). Protect against the main opportunistic infections, as follows:

Drug	Opportunistic Infection	Population of patients involved
Sulfametoxazole	Pneumocystis	All patients
Ivermectin or albendazole (one dose)	Strongyloidiasis	Patients living in or having travelled in the tropics
Aciclovir or Valaciclovir	Varicella zoster virus	Elderly patients
Rifampicin and INH or INH alone	Tuberculosis	Patients with a history of tuberculosis

2 Electrolytes imbalance

3 Decompensation of diabetes

4 Mood disorders

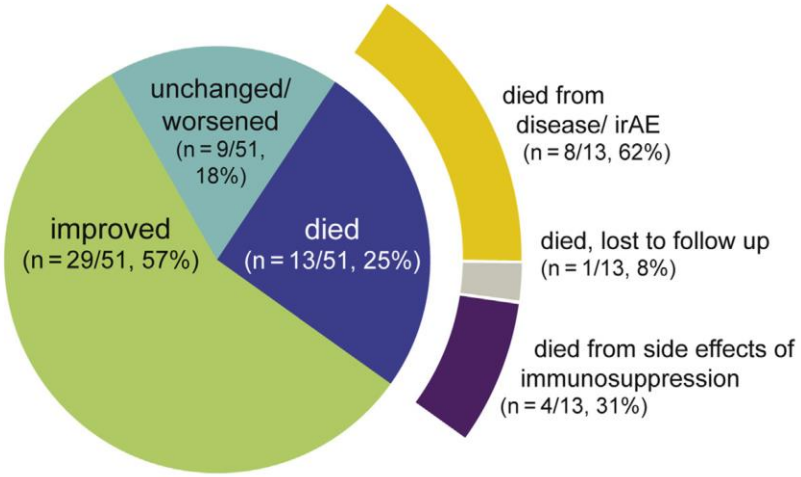
5 Adrenal insufficiency

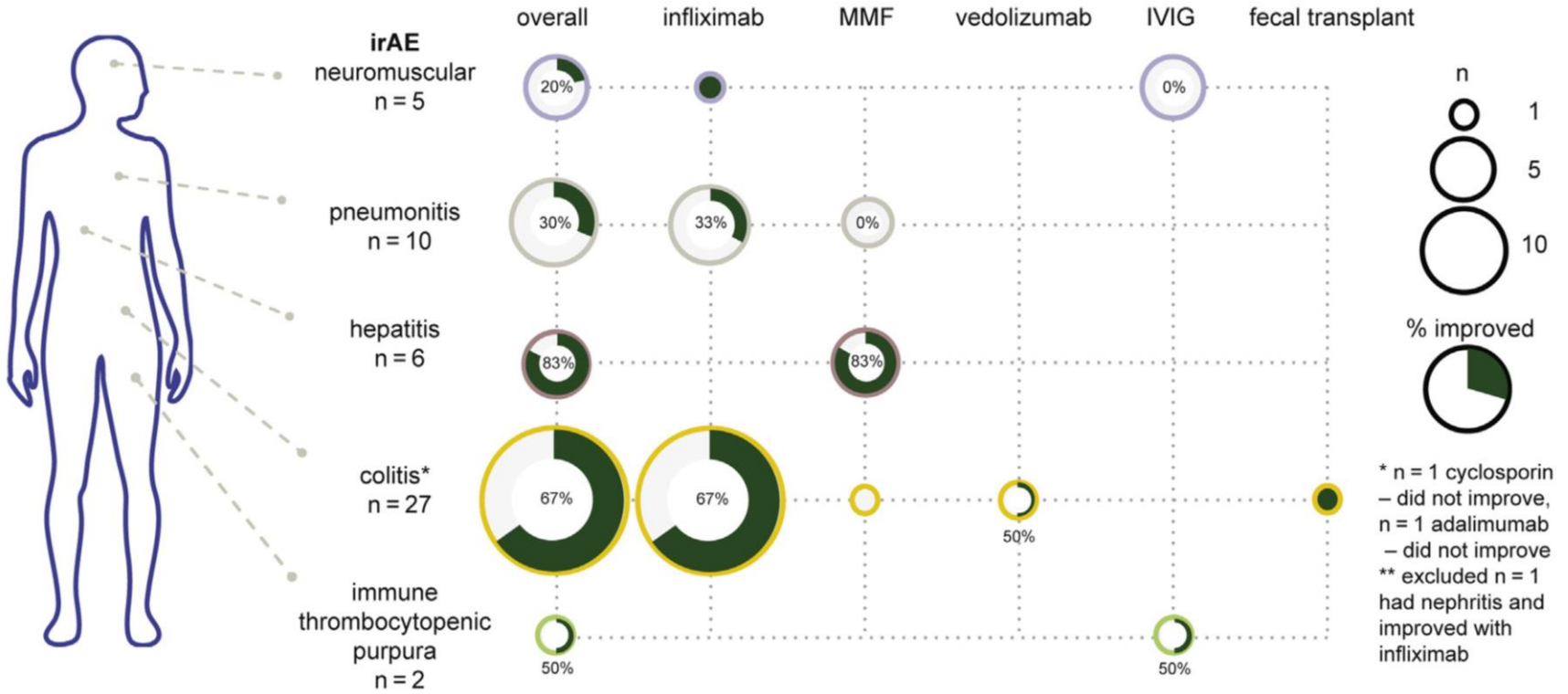
6 Bone growth and osteoporosis

Luo J, et al. J Thorac Oncol 2021;16(10):1759-1764.
Aldea M, et al. Eur J Cancer. 2020;141:239-251.

Trattamento delle tossicità steroido-refrattarie

n= 51 (2%) out of 2750 lung cancer pts treated with steroids + an additional immunosuppressant for severe irAEs





Luo J, et al. J Thorac Oncol 2021;16(10):1759-1764

Timing di inizio dell'immunosoppressore

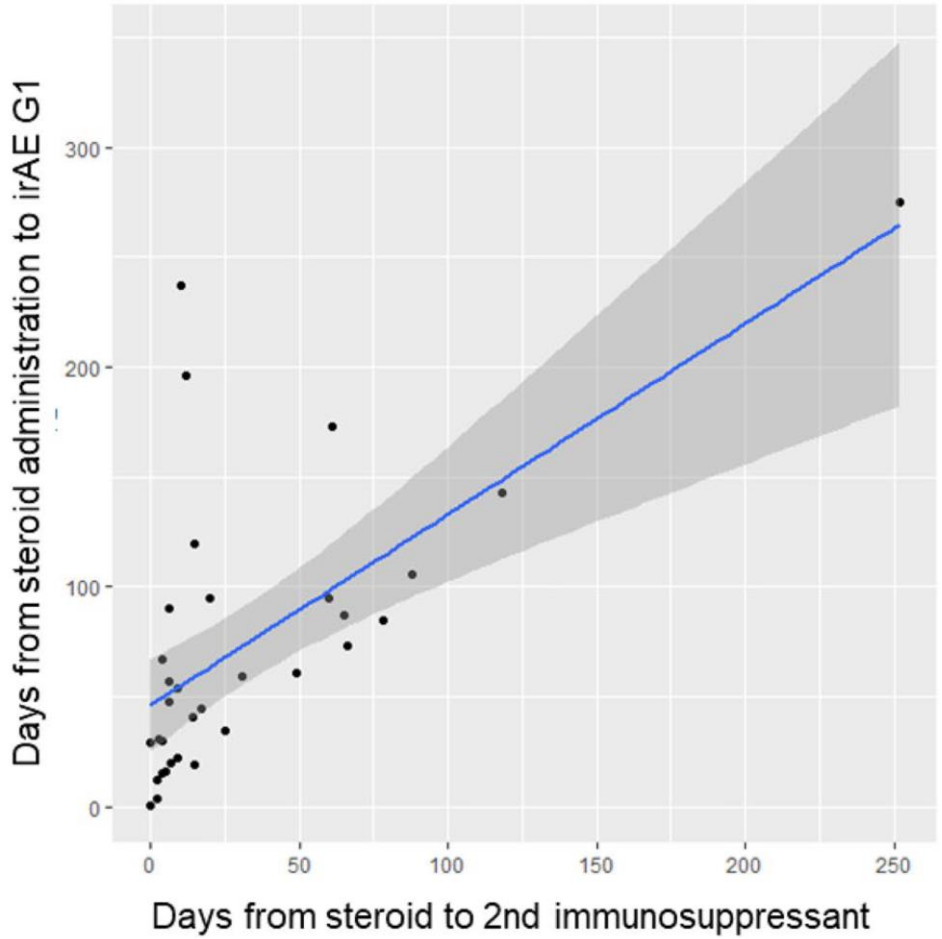
Retrospective study on 84 pts with immune-related colitis receiving selective immunosuppressive therapy[1]

Table 1 Clinical characteristics stratified by the timing of selective immunosuppressive therapy initiation (SIT)

Covariate	≤ 10 days of onset *N* = 44	> 10 days of onset *N* = 40	*P*
ICI type, No. (%)			0.687
Anti-CTLA-4 monotherapy	11 (25)	10 (25)	
Anti-PD-1/L1 monotherapy	19 (43)	14 (35)	
Combination	14 (32)	16 (40)	
Diarrhea grade, No. (%)			0.668
1–2	8 (18)	6 (15)	
3	28 (64)	29 (73)	
4	8 (18)	5 (13)	
Colitis grade, No. (%)			0.603
1–2	24 (56)	22 (55)	
3	16 (37)	17 (43)	
4	3 (7)	1 (3)	
Endoscopic features, No. (%)			0.739
Ulcer	13 (42)	17 (52)	
Non-ulcerative inflammation	12 (39)	11 (33)	
Normal	6 (19)	5 (15)	
High-risk endoscopic features initially, No. (%)[a]	17 (55)	23 (70)	0.302
Overall duration of steroids, mean days (SD)	64 (38)	82 (51)	0.092
Duration of hospitalization, mean days (SD)	10 (8)	12 (8)	0.321
Duration of symptoms, mean days (SD)	25 (32)	50 (40)	0.002
Follow-up duration, mean months (SD)	5 (3)	4 (3)	0.875
Number of steroids tapering attempts, median (IQR)	1 (1–4)	2 (1–4)	< 0.001
Multiple hospitalization, No. (%)	13 (30)	22 (55)	0.026
Failed steroid tapering after SIT, No. (%)[b]	9 (23)	19 (49)	0.033
Recurrent IMC, No. (%)	8 (18)	8 (20)	1.000
Infectious adverse events, No. (%)	16 (36)	9 (23)	0.233

[a]High-risk features are ulcers deeper than 2 mm or wider than 1 cm, and extensive endoscopic inflammation involving the colon proximal to the splenic flexure
[b]Available for the 79 patients who received steroids
Abbreviation: SIT, selective immunosuppressive therapy

Retrospective study on 73 NSCLC pts with steroid-refractory irAEs receiving second-line immunosuppressive therapy[2]



1. Abu-Sbeih H, et al. J Immunother Cancer 2019;7(1):93.
2. Ogusu S, et al. Cancer Immunol Immunother 2023;72(11):3765-3772.

Definizione di steroido-refrattarietà

Steroid-unresponsive irAEs include:

⇒ irAEs in which there is no clinical improvement after a standard time frame of guideline-based irAE-directed steroid therapy.

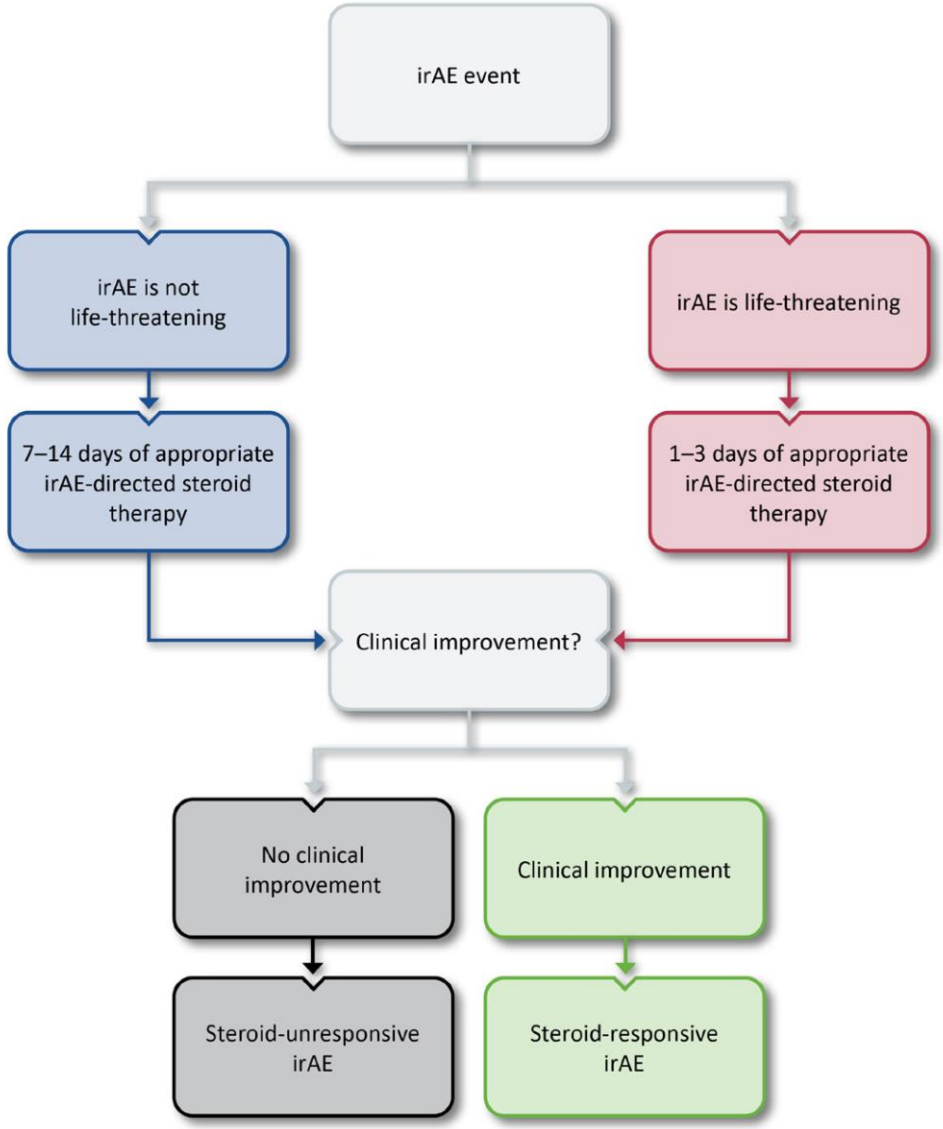
⇒ Steroid-refractory irAEs are those that derived no clinical benefit with steroids.

⇒ Steroid-resistant irAEs derived some clinical benefit without resolution of the event.

Life-threatening versus non-life-threatening irAEs:

⇒ For life-threatening irAEs (eg, pneumonitis, myocarditis, colitis), steroid-unresponsive irAEs are those in which there is no clinical improvement after 1–3 days of appropriate irAE-directed steroid therapy.

⇒ For non-life-threatening irAEs (eg, arthritis), steroid-unresponsive irAEs are those in which there is no clinical improvement after 7–14 days of appropriate irAE-directed steroid therapy.



Naidoo J, et al. J Immunother Cancer 2023;11(3):e006398.

Ripresa dell'immunoterapia dopo irAEs

Summary of retrospective studies on rechallenge ICIs after irAEs

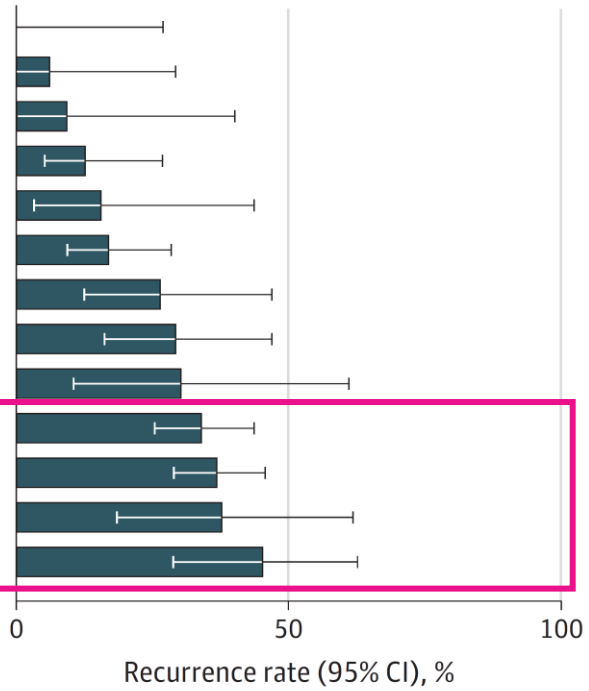
	Santini[1]	Simonaggio[2]	Abu-Sbeih[3]	Naidoo[4]	Pollack[5]	Delaunay[6]
N irAEs	68 various	93 various	167 colitis	43 pneumonitis	80 various	64 pneumonitis
tumor	NSCLC	Multiple	Multiple	Multiple	Melanoma	Multiple
Retreat.	38	40	167	12	80	10
New/Recurr.	52% (40% G≥3)	55% (60% G≥3)	34% (10% G≥3)	25% (0% G≥3)	18% (0% G≥3)	30% (0% G≥3)

≈20-50% New/Recurrent irAEs

Pharamcovigilance study (VigiBase)[7]
Data on 452 informative rechallenge

Figure 2. Rate of Recurrence According to the Initial Immune-Related Adverse Event

Adverse drug reaction	No. of cases	Recurrence rate (95% CI), %
Diabetes	13	0 (0-27)
Neurologic	17	6 (0-29)
Uveitis	11	9 (0-40)
Adrenal	40	12 (5-27)
Pancreatitis	13	15 (3-43)
Thyroiditis	60	17 (9-28)
Hypophysitis	23	26 (12-47)
Hepatitis	31	29 (16-47)
Hematologic	10	30 (10-61)
Pneumonitis	101	34 (25-43)
Colitis	123	37 (29-45)
Skin	16	38 (18-61)
Arthritis	29	45 (28-62)



1. Santini FC, et al. Cancer Immunol Res 2018;6(9):1093-1099. 2. Simonaggio A, et al. JAMA Oncol 2019;5(9):1310–7.
3. Abu-Sbeih H, et al. J Clin Oncol 2019;37(30):2738-2745. 4. Naidoo J, et al. J Clin Oncol 2017;35(7):709-717. 5. Pollack MH, et al. Ann Oncol 2018;29(1):250-255.
6. Delaunay M, et al. Eur Respir J 2017;50(2):1700050. 7. Dolladille C, et al. JAMA Oncol 2020;6(6):865-871.

Principali criticità nella gestione della tossicità da immunoterapia

Emerging physician awareness	Diagnostic complexity
Inconsistent awareness across patients	Lack of widespread evidence

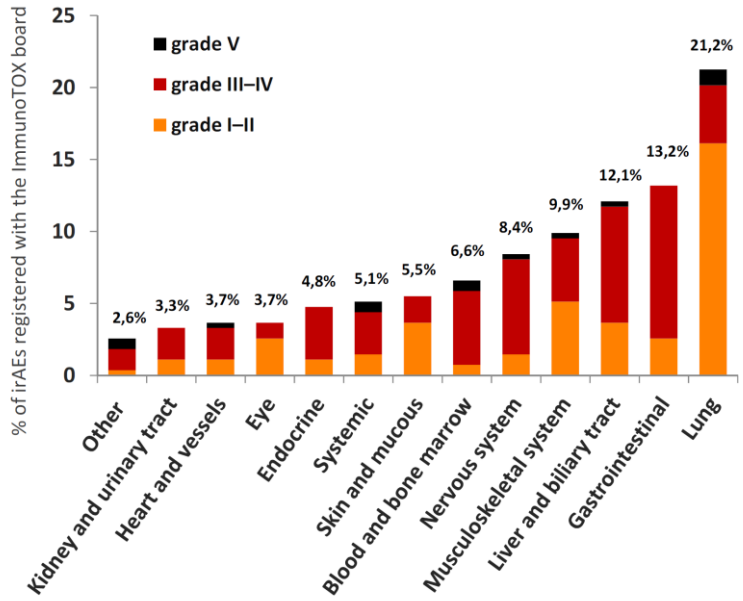
Johnson DB, et al. Lancet Oncol 2020;21(8):e398-e404.

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 tossicità rare
- 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 Messages

- L’immunoterapia è un trattamento ben tollerato
- La maggior parte degli irAEs è precoce e reversibile, ma esistono anche eventi tardivi, cronici o fatali
- Necessaria adeguata informazione a paziente e caregivers
- Necessario elevato livello di attenzione da parte del medico
- Diagnosi differenziale / di esclusione
- Trattamento secondo linee guida: introduzione tempestiva dello steroide quando indicato, lento tapering, profilassi degli eventi avversi correlati allo steroide, impiego di altri agenti immunosoppressivi nelle tossicità steroido-refrattarie
- Approccio interdisciplinare
- Necessaria formazione degli operatori sanitari
- Necessario maggior sforzo nella ricerca (di base, traslazionale, clinica) per generare evidenze

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