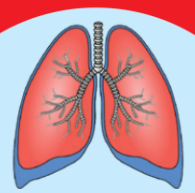

La gestione della tossicità da immunoterapia

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IRCCS Ospedale Sacro Cuore Don Calabria
Negrar di Valpolicella (VR)

Tossicità: immunoterapia vs chemioterapia

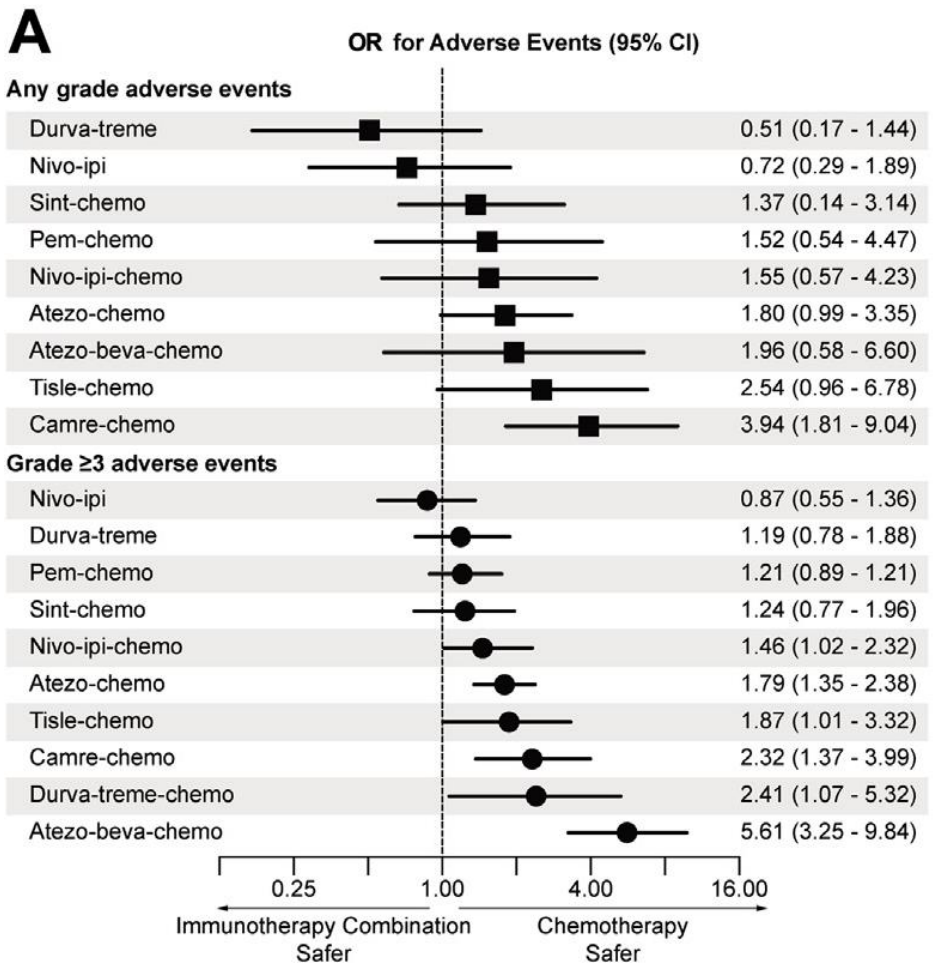
Meta-analysis (22 trials, >12k pts)

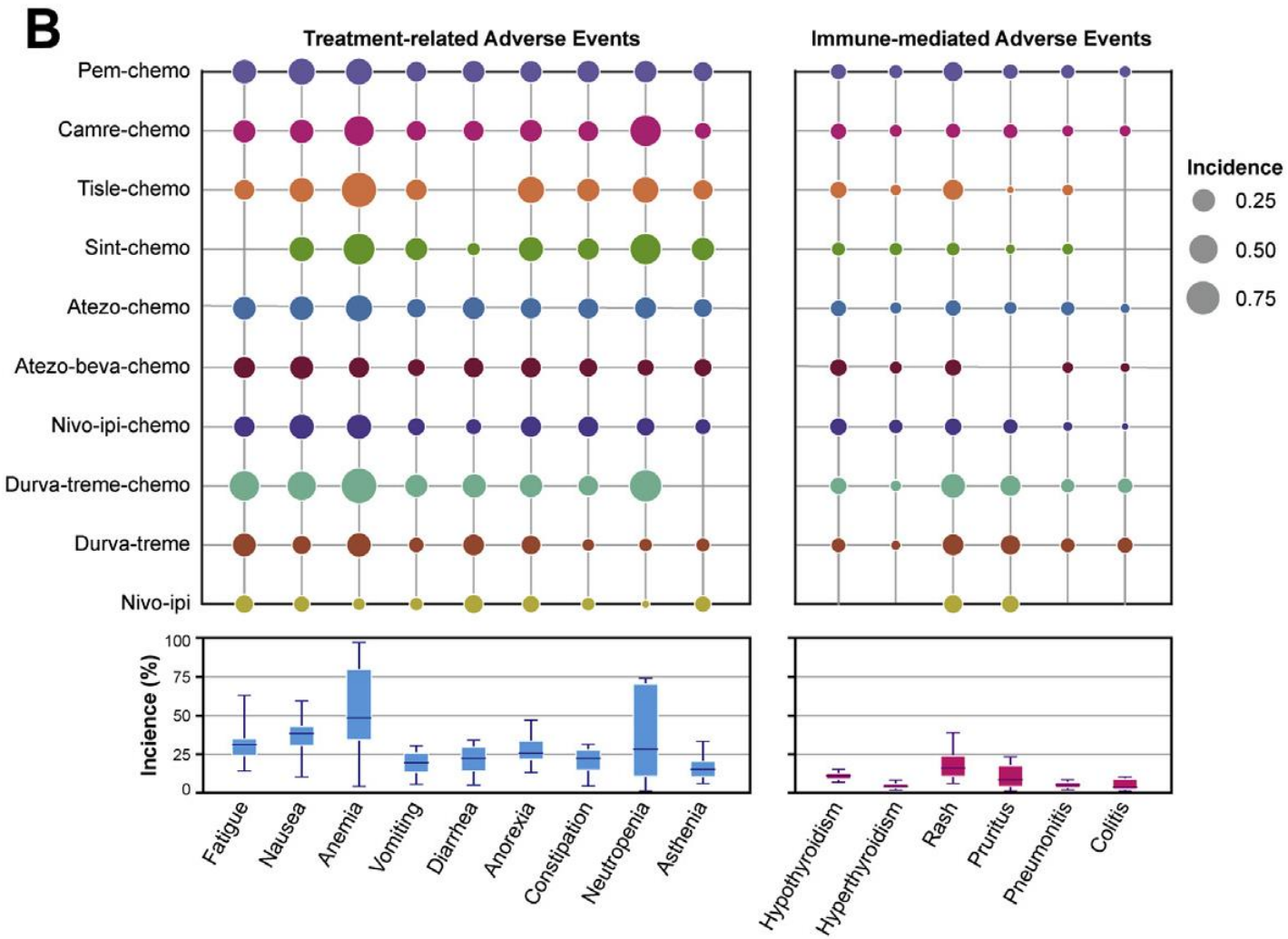
	ICI	*vs*	Chemo	OR
Any grade AEs	65.82%	*vs*	85.19%	0.35
Grade ≥ 3 AEs	16.56%	*vs*	41.09%	0.26
Treatment discontinuation	6.41%	*vs*	10.75%	0.55
Toxic deaths	0.87%	*vs*	1.28%	0.67

Magee DE, et al. Ann Oncol 2020;31:50-60

Tossicità delle combinazioni

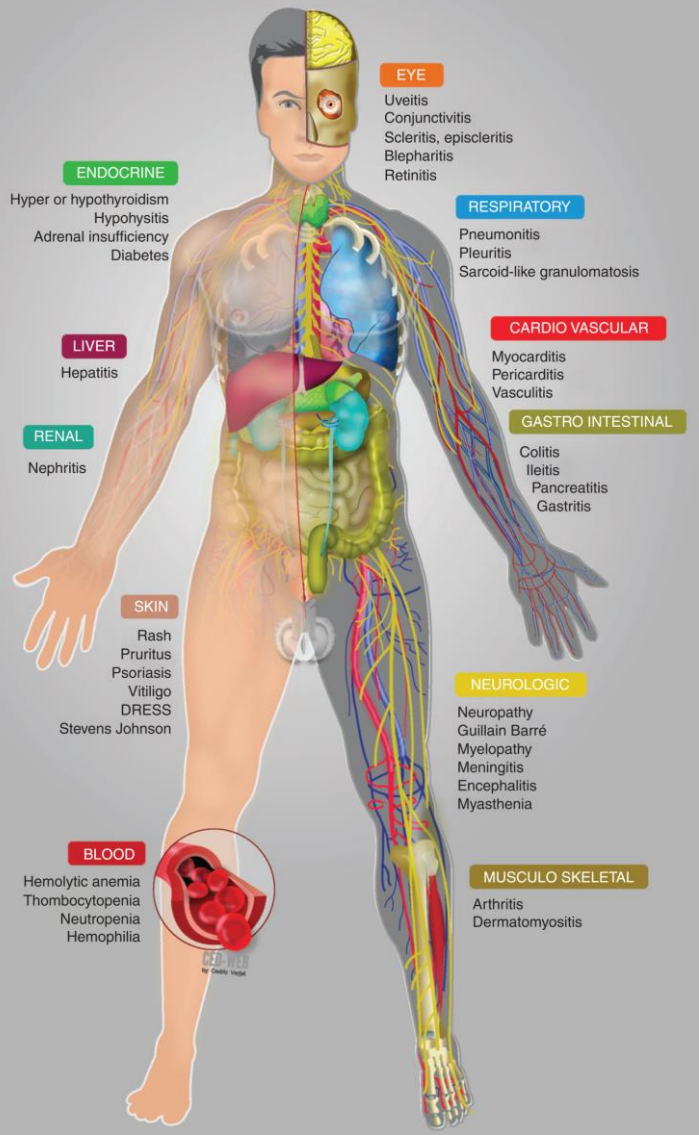
Network meta-analysis (16 studies, >8k pts)





Liu L, et al. J Thorac Oncol 2021;16(7):1099-1117

Eventi avversi immuno-correlati



irAEs
may potentially affect
any organ/system

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

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

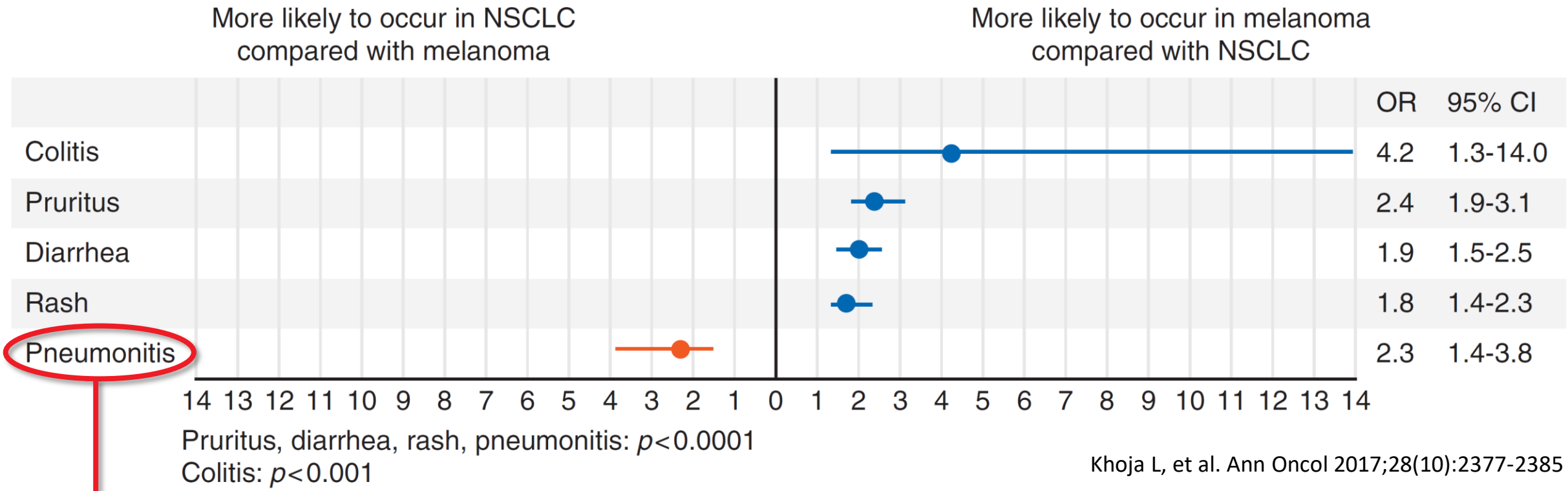
Gestione della tossicità: principi generali

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

Pattern di tossicità immuno-correlata nel NSCLC



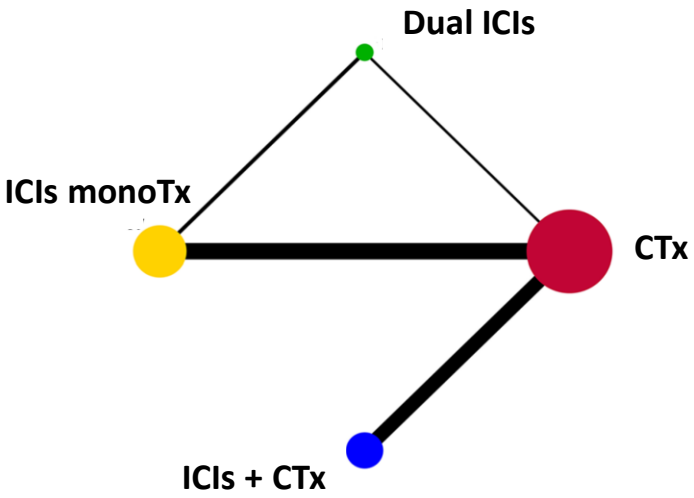
Khoja L, et al. Ann Oncol 2017;28(10):2377-2385

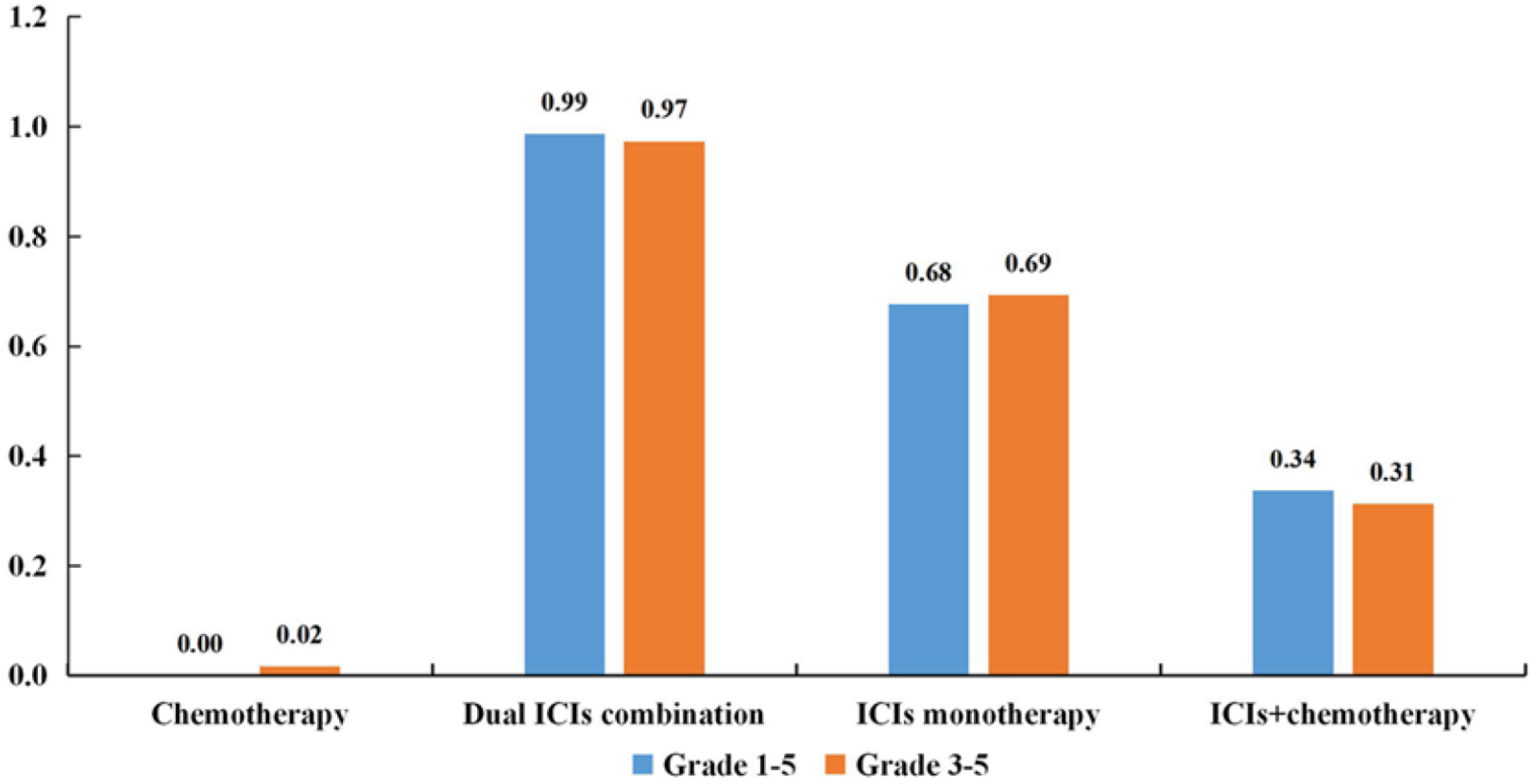
Polmonite immunocorrelata nel NSCLC:

- 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

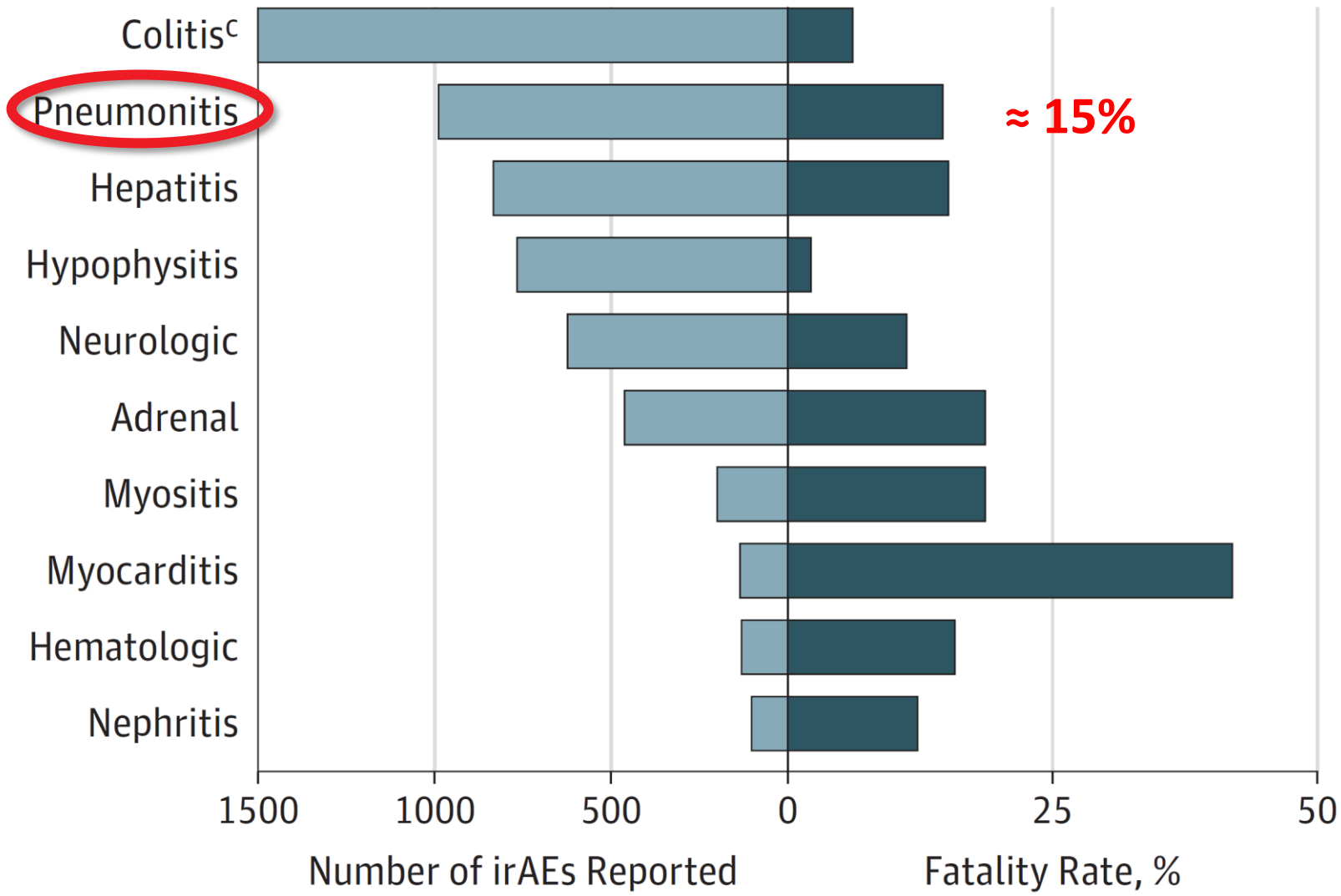
Rischio di polmonite nel NSCLC: una network meta-analysis





Chen X et al. J Immunother Cancer 2020; 8(2):e001170.

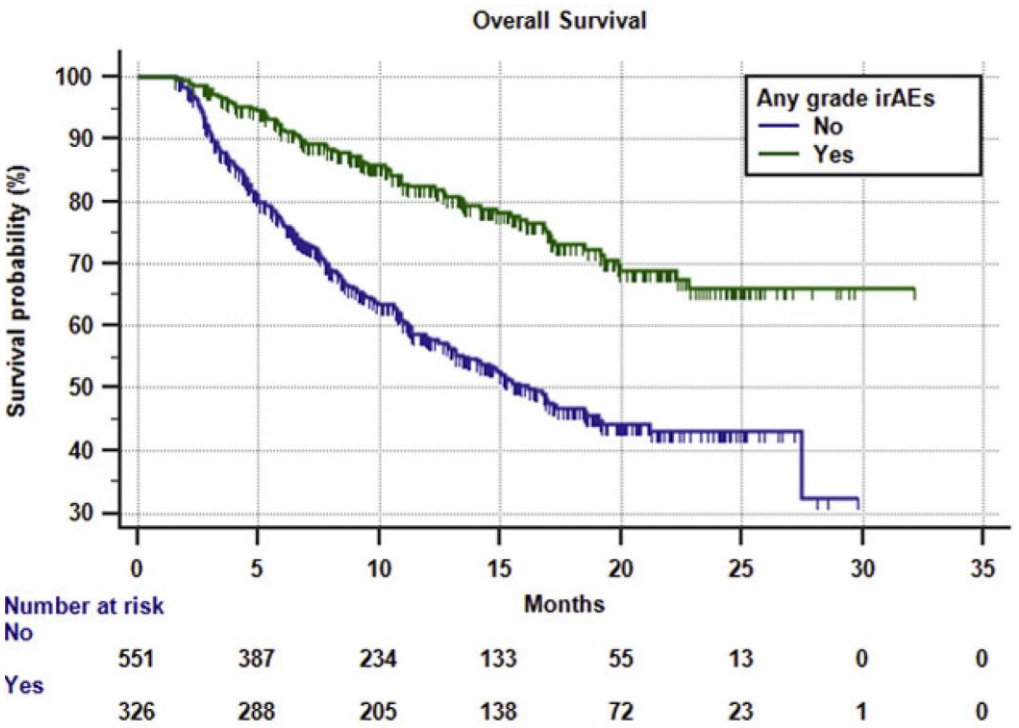
Mortalità degli irAEs



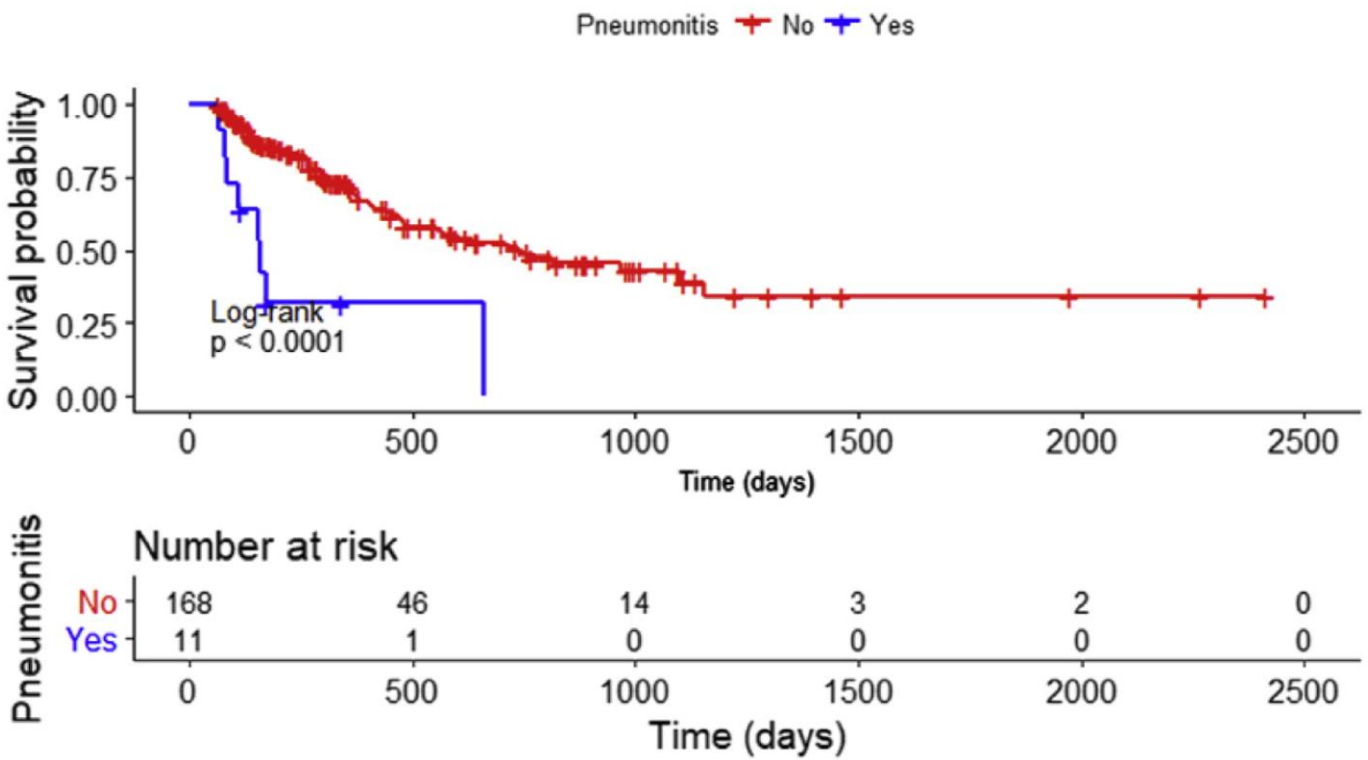
Wang DY et al. JAMA Oncol 2018;4(12):1721-1728.

Impatto prognostico degli irAEs e della polmonite immuno-correlata

irAEs vs no irAEs[1]



Pneumonitis vs no Pneumonitis[2]



1. Cortellini A et al. Clin Lung Cancer 2020;21(6):498-508. 2. Suresh K, Naidoo J. Clin Lung Cancer 2020;21(3):e169-e170

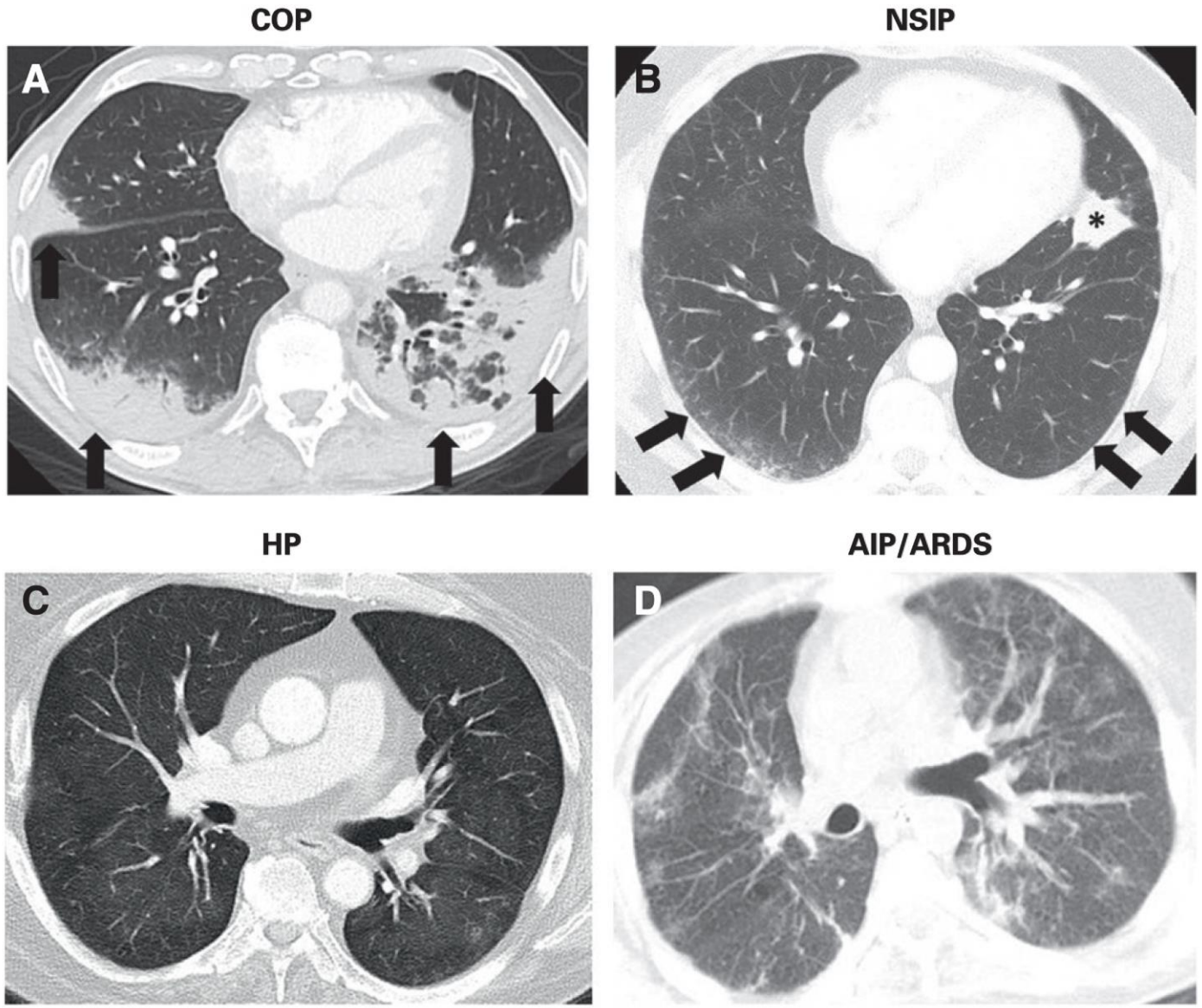
Pattern radiologici di polmonite immuno-correlata

A. Polmonite criptogenica organizzata (COP)

B. Polmonite interstiziale aspecifica (NSIP)

C. Polmonite da ipersensibilità (HP)

D. Polmonite interstiziale acuta / Sindrome da distress respiratorio acuto (AIP/ARDS)



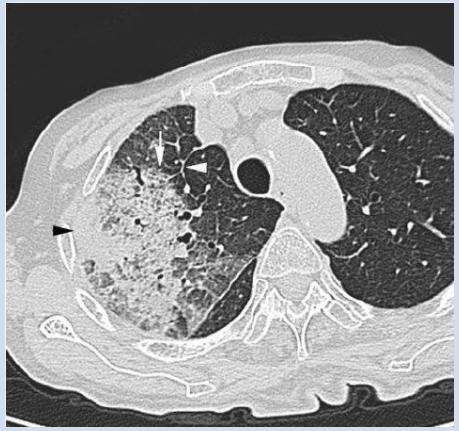
➡ *Aree GGO e addensamenti reticolari*

* *Massa tumorale*

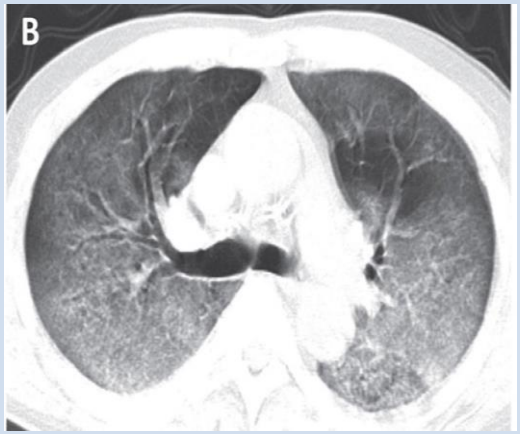
Nishino M, et al. JCO Precis Oncol 2017;1:PO.17.00026

Diagnosi differenziale della polmonite immuno-correlata

Polmonite infettiva

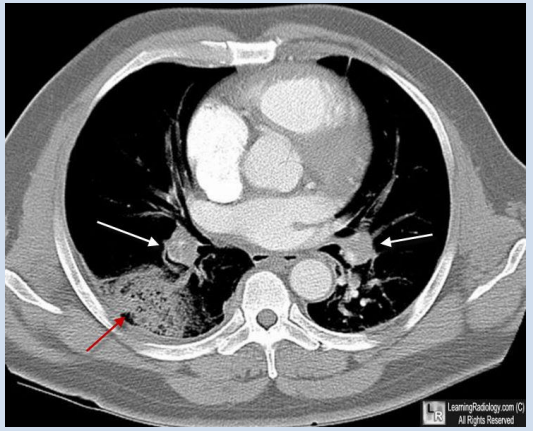


Polmonite da Klebsiella



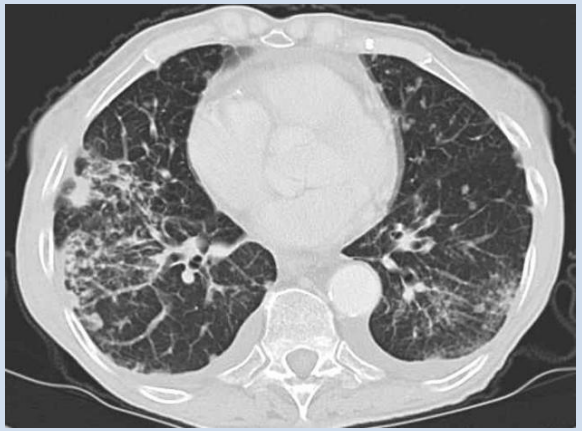
Polmonite da SARS-CoV-2

Embolia polmonare



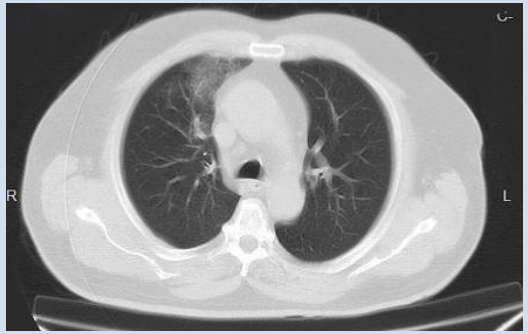
TEP in entrambe le a. polmonari con infarto polmonare

Progressione tumorale



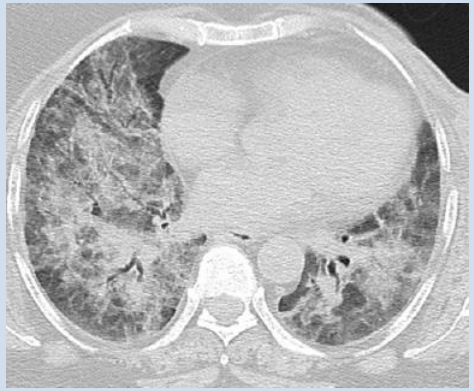
Linfangite carcinomatosa

Tossicità da radioterapia

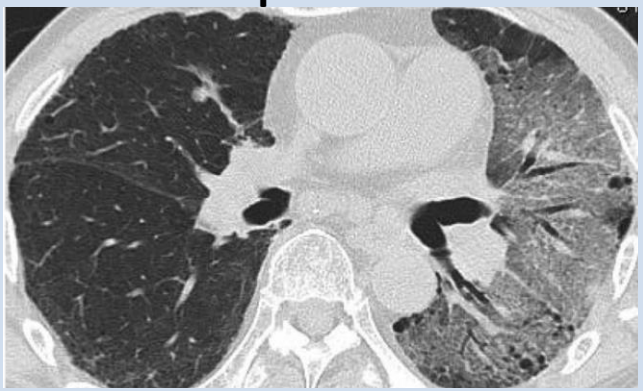


Polmonite attinica

Tossicità da chemioterapia



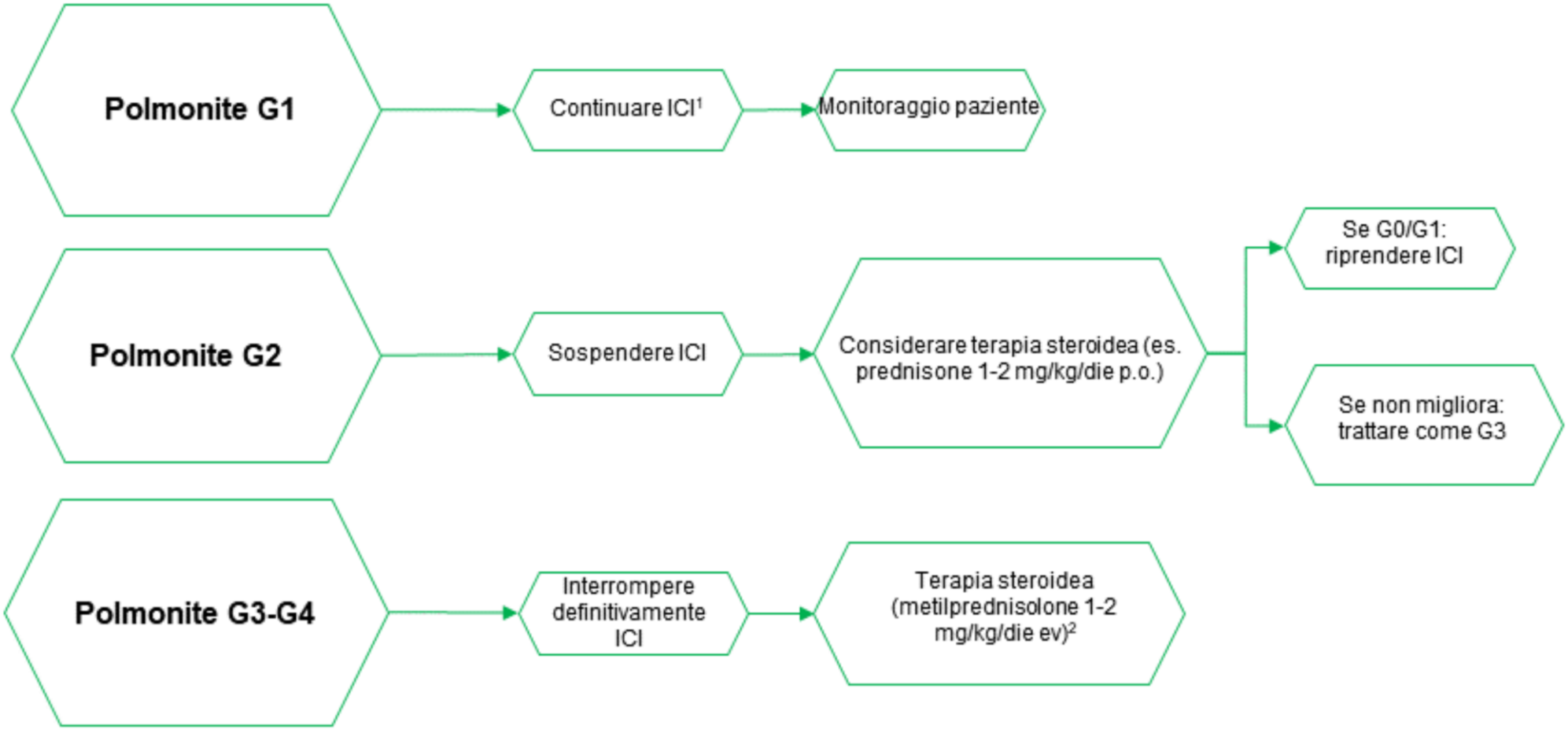
Paclitaxel



Pemetrexed

Gestione della polmonite immuno-correlata

Grado 1
Asintomatica; solo osservazione clinico-diagnostica; intervento non indicato
Grado 2
Sintomatica; indicato intervento medico; limitazione nelle ADL strumentali
Grado 3
Sintomi severi; limitazione nelle ADL primarie; indicata ossigenoterapia
Grado 4
Compromissione respiratoria potenzialmente letale; indicato intervento urgente (es. intubazione, tracheostomia)

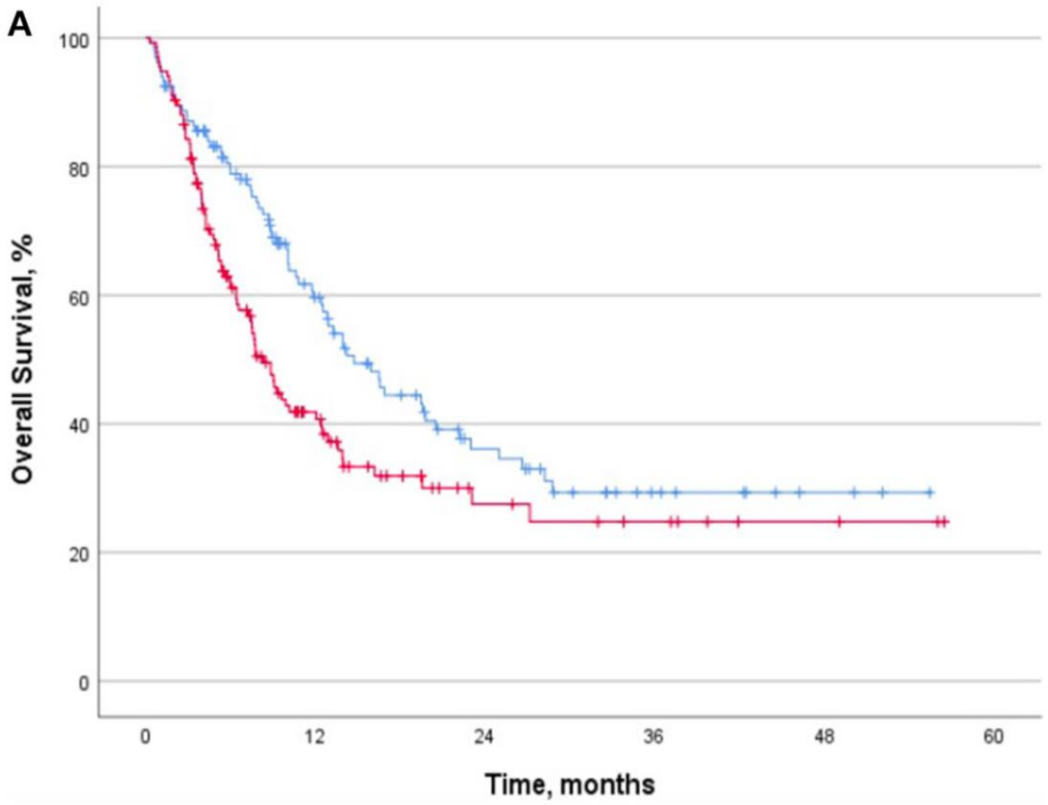


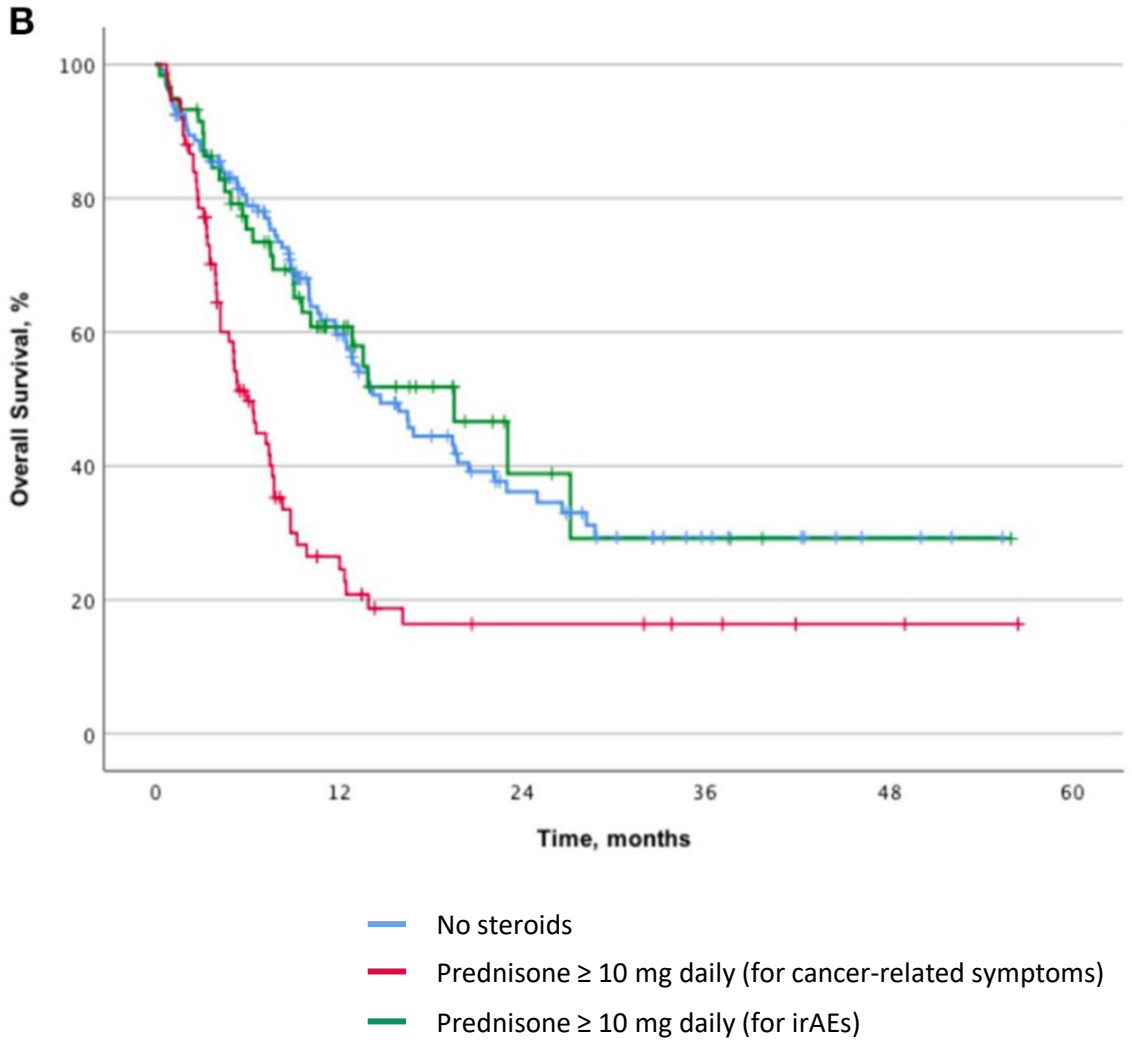
1. Considerare sospensione temporanea in casi selezionati (pazienti con infiltrato infiammatorio esteso oltre un lobo del polmone o oltre il 25% del parenchima polmonare, o pazienti con concomitanti patologie polmonari che sono a maggior rischio di sviluppare insufficienza respiratoria)
2. Vi sono evidenze a sostegno dell'utilizzo in pazienti steroido-refrattari di altri farmaci immunosoppressori (infliximab, micofenolato, ciclofosfamide, IGIV, tocilizymab). Tali farmaci al momento della stesura della presente linea guida non sono indicati in Italia per il trattamento di polmonite immunocorrelata da ICI, per cui il loro impiego in questa indicazione è da considerarsi off-label

https://snlg.iss.it/wp-content/uploads/2021/12/LG-200_Tox-da-immunoterapia_agg2021.pdf

Impatto prognostico degli steroidi

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





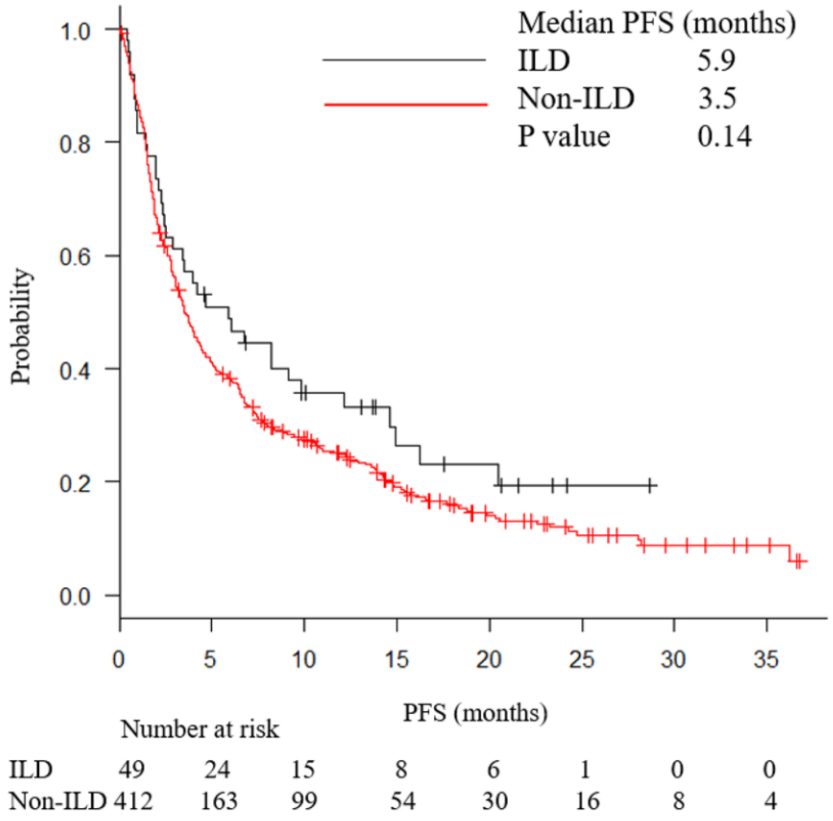
Riudavets M et al. Front Oncol 2020;10:1677

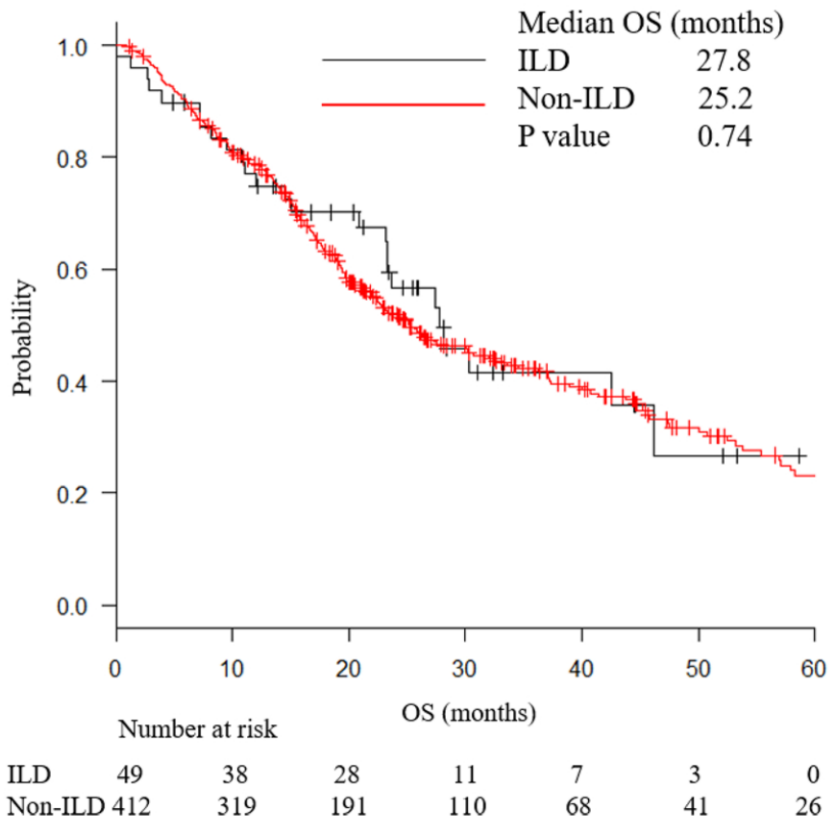
Tapering dello steroide

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.

IO in pazienti con ILD

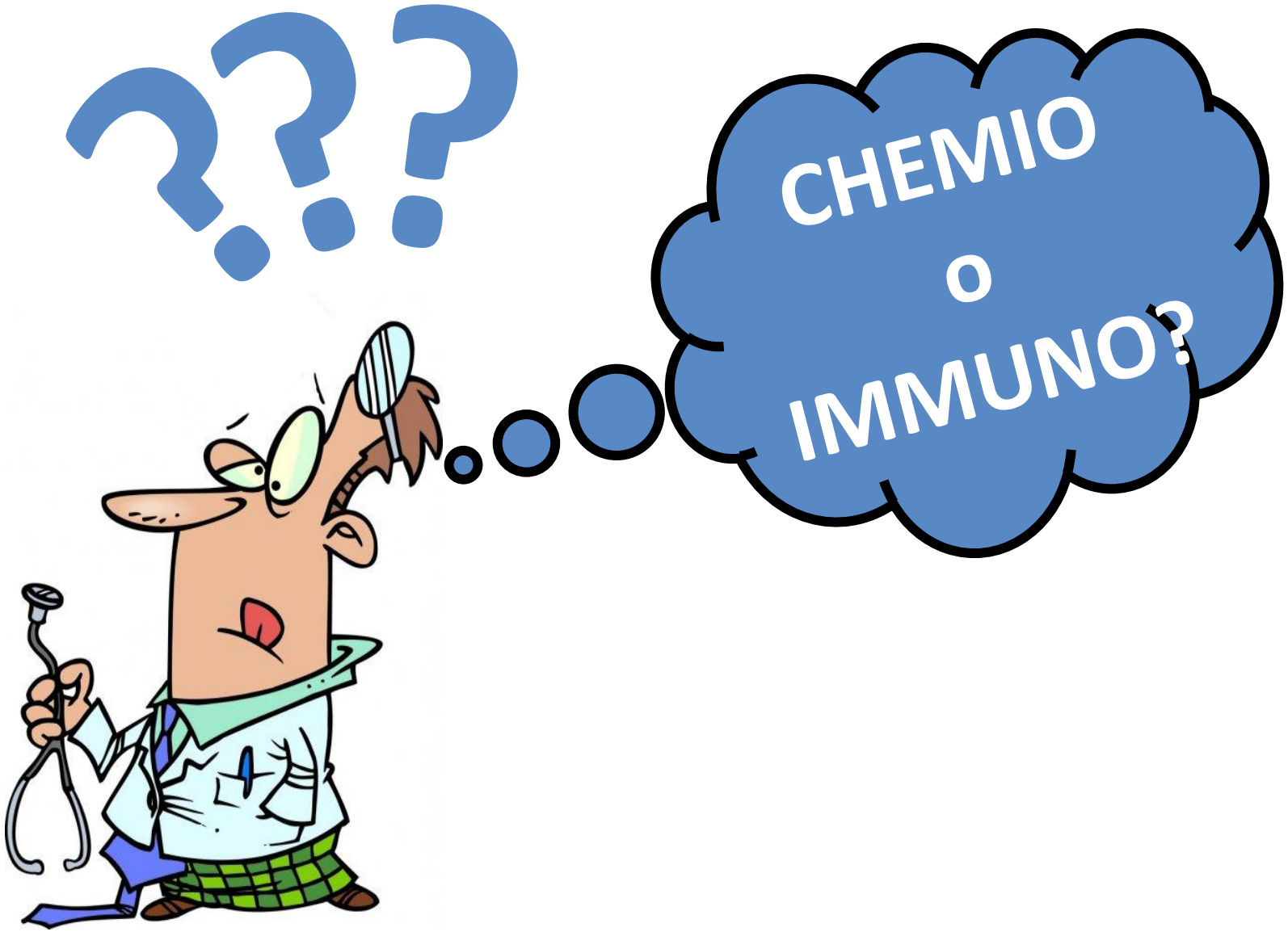




	Any grade				≥ G3				G5			
	All	Non-ILD	ILD	P value	All	Non-ILD	ILD	P value	All	Non-ILD	ILD	P value
All adverse effect	164 (35.6)	131 (31.8)	33 (67.3)	<0.01	51 (11.1)	36 (8.7)	15 (30.6)	<0.01	7 (1.5)	4 (0.97)	3 (6.1)	<0.01
Pneumonitis	54 (11.7)	39 (9.5)	15 (30.6)	<0.01	23 (5.0)	15 (3.6)	8 (16.3)	<0.01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

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

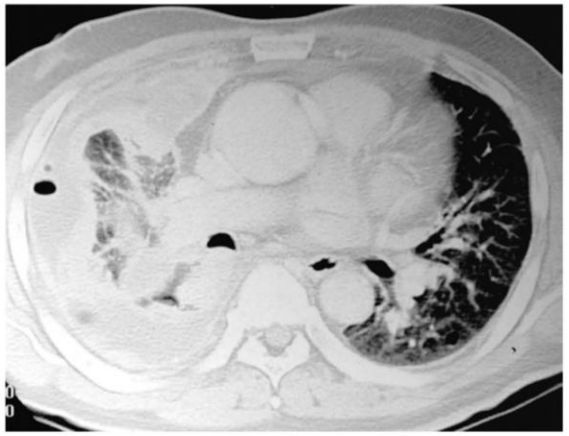
Tossicità delle combinazioni IO/CTx



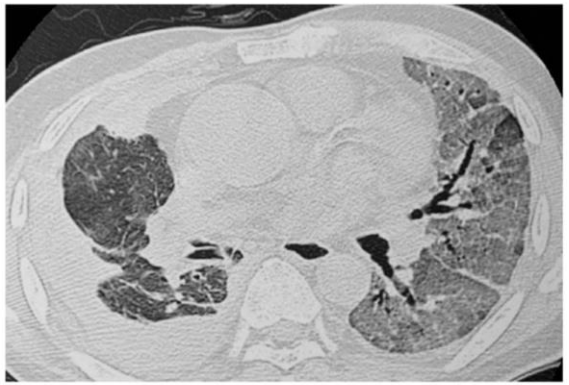
Polmonite interstiziale da pemetrexed

Incidenza : 2.6%

Background: 70's, Male, MPM biphasic type, stage IV, 1st line treatment, PS1 at starting of pemetrexed treatment, presence of pre-existing ILD and exposure to asbestos, no smoking history.
Outcome: Recovering from ILD/died on day-28 due to disease progression

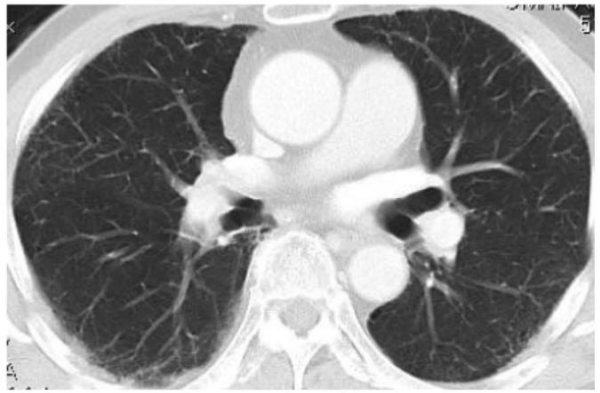


Before pemetrexed treatment (5mm)

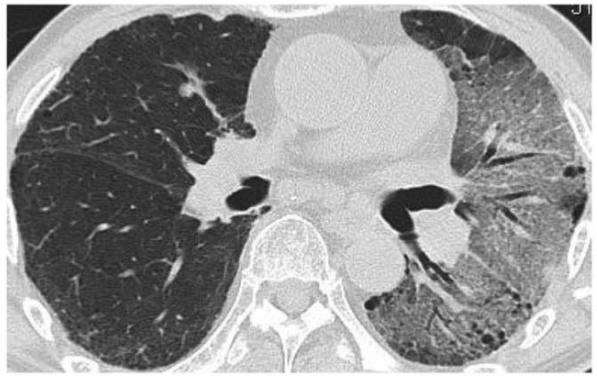


On the day of ILD onset: 8 days after the first treatment (day-8 of 1st course) (1.25mm)

Background: 60's, Male, adenocarcinoma, stage IV, 1st line treatment, PS1 at starting of pemetrexed treatment, no pre-existing ILD, presence of smoking history.
Outcome: Death/ died on day16 from ILD onset.

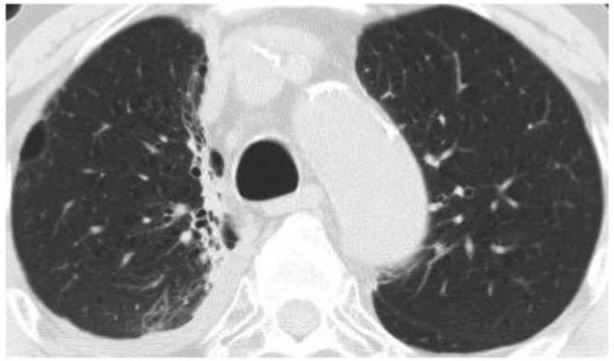


Before pemetrexed treatment

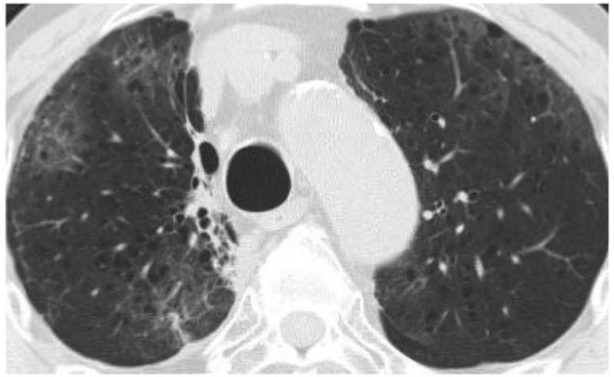


On the day of ILD onset: 126 days after the first treatment (day 56 of fourth course)

Background: 70's, Male, NSCLC adenocarcinoma, stage IV, 3rd line treatment, PS1 at starting of pemetrexed treatment, presence of pre-existing ILD and smoking history.
Outcome: Recovering from ILD.



Before Pemetrexed treatment



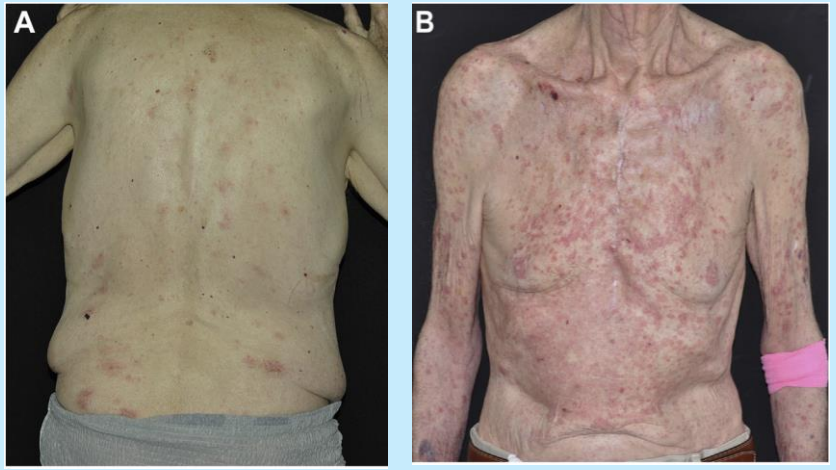
On the day of ILD onset: 79 days after the first treatment (day-9 of fourth course)

Tomii K, et al. Jpn J Clin Oncol 2017;47(4):350-356

Tossicità cutanea da immunoterapia

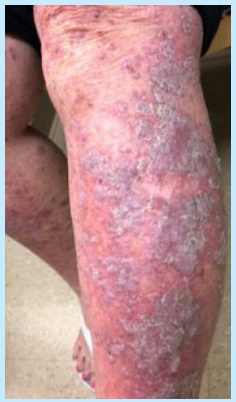
Molto frequente	Frequente	Rara
Rash maculo-papulare e lichenoide	Psoriasi	Alopecia areata
Prurito	Pemfigoide bolloso	Alopecia
Vitiligine	Lesioni granulomatose	Morfea
		Sindrome di Sweet
		Sindrome di Grover
		Sindrome di Stevens-Johnson /
		Necrolisi epidermica tossica
		Cheratosi seborroica flogosata
		Lichen sclero-atrofico
		Eruzioni acneiformi
		Dermatomiosite
		Fascite eosinofila
		Cheratoacantomi multipli
		Cheratosi lichenoidi
		Pemfigo
		Vasculiti cutanee
		Sarcoidosi
		Capelli ondulati o arricciati
		Eritema nodoso

Rash maculo-papulare

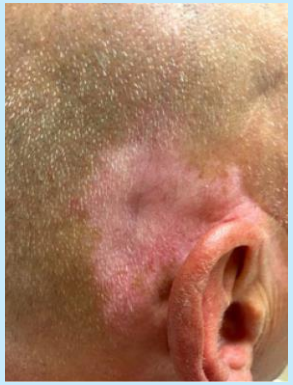


Grado 2 *Grado 3*

Rash Lichenoide



Vitiligo

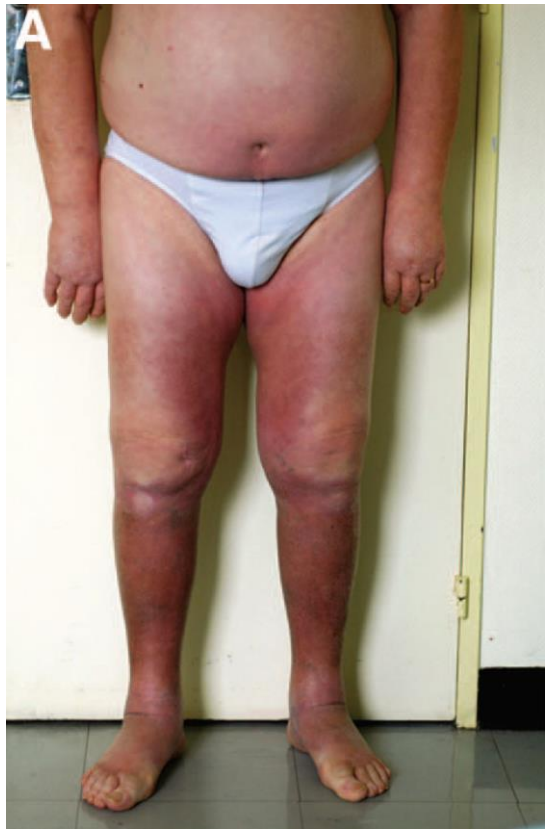


Belum VR, et al. Eur J Cancer. 2016;60:12-25

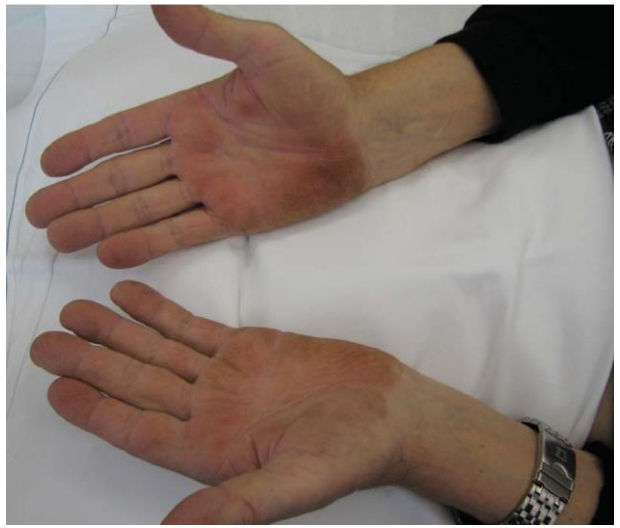
Tossicità cutanea da pemetrexed

Incidenza: 14%

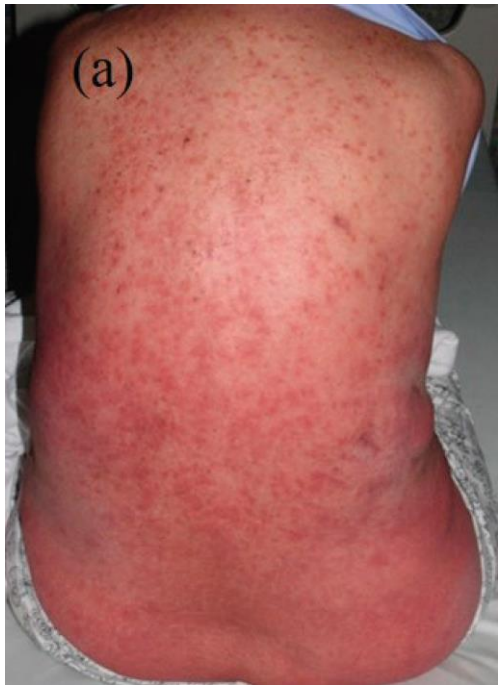
Eritema/edema



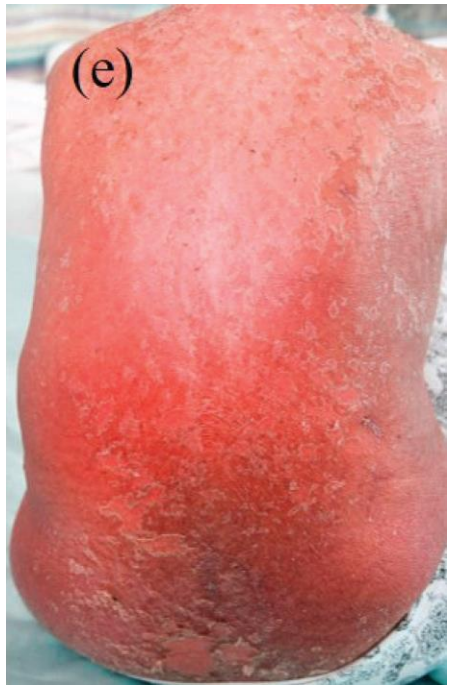
Iperpigmentazione



Rash maculo-papulare



Necrolisi epidermica tossica



Eguia B, et al. J Thorac Oncol 2011;6:2083-9. Schallier D, et al. Anticancer Res 2011;31:1753-5. Eichhoff G. Ecancermedicalscience 2020;14:1010.

Gestione della tossicità cutanea

Grado 1

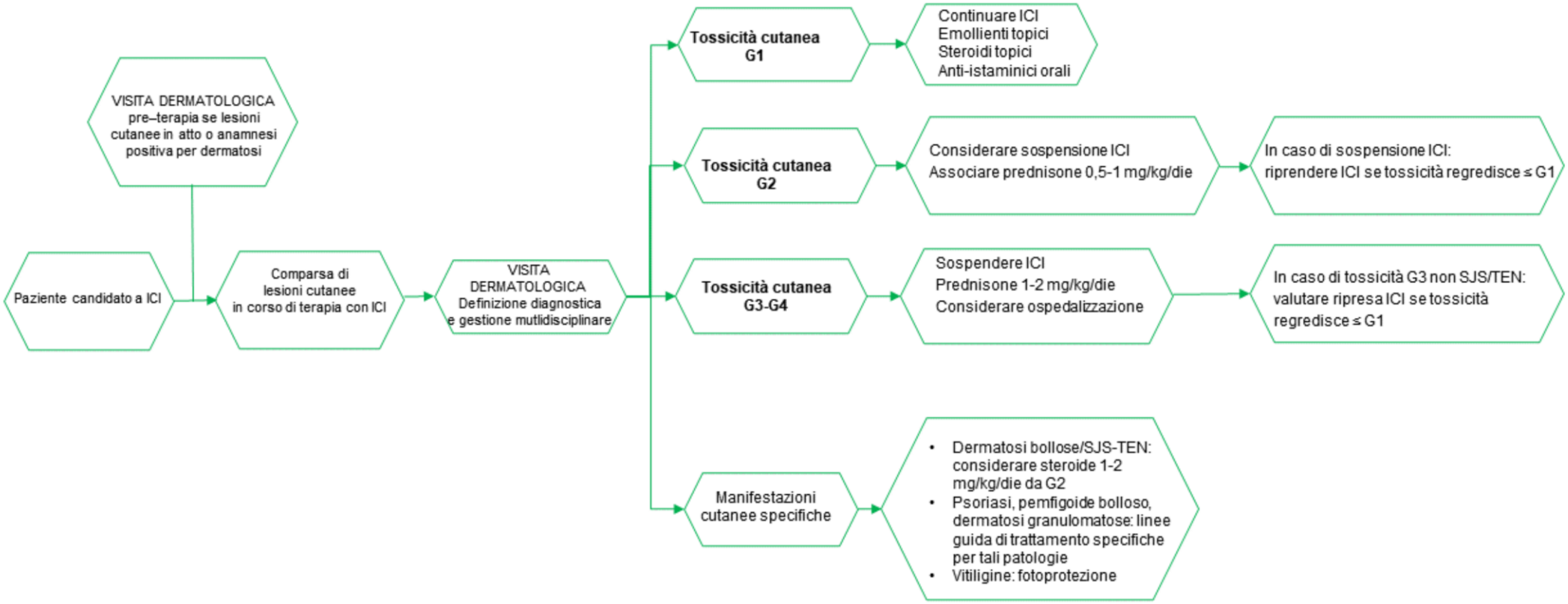
Macule/papule che ricoprono <10% della superficie corporea con o senza sintomi (es. prurito, bruciore, senso di tensione)

Grado 2

Macule/papule che ricoprono 10 - 30% della superficie corporea con o senza sintomi (es. prurito, bruciore, senso di tensione); limitazione delle ADL strumentali

Grado 3-4

Macule/papule che ricoprono >30% della superficie corporea, con o senza sintomi associati; limitazione delle ADL primarie

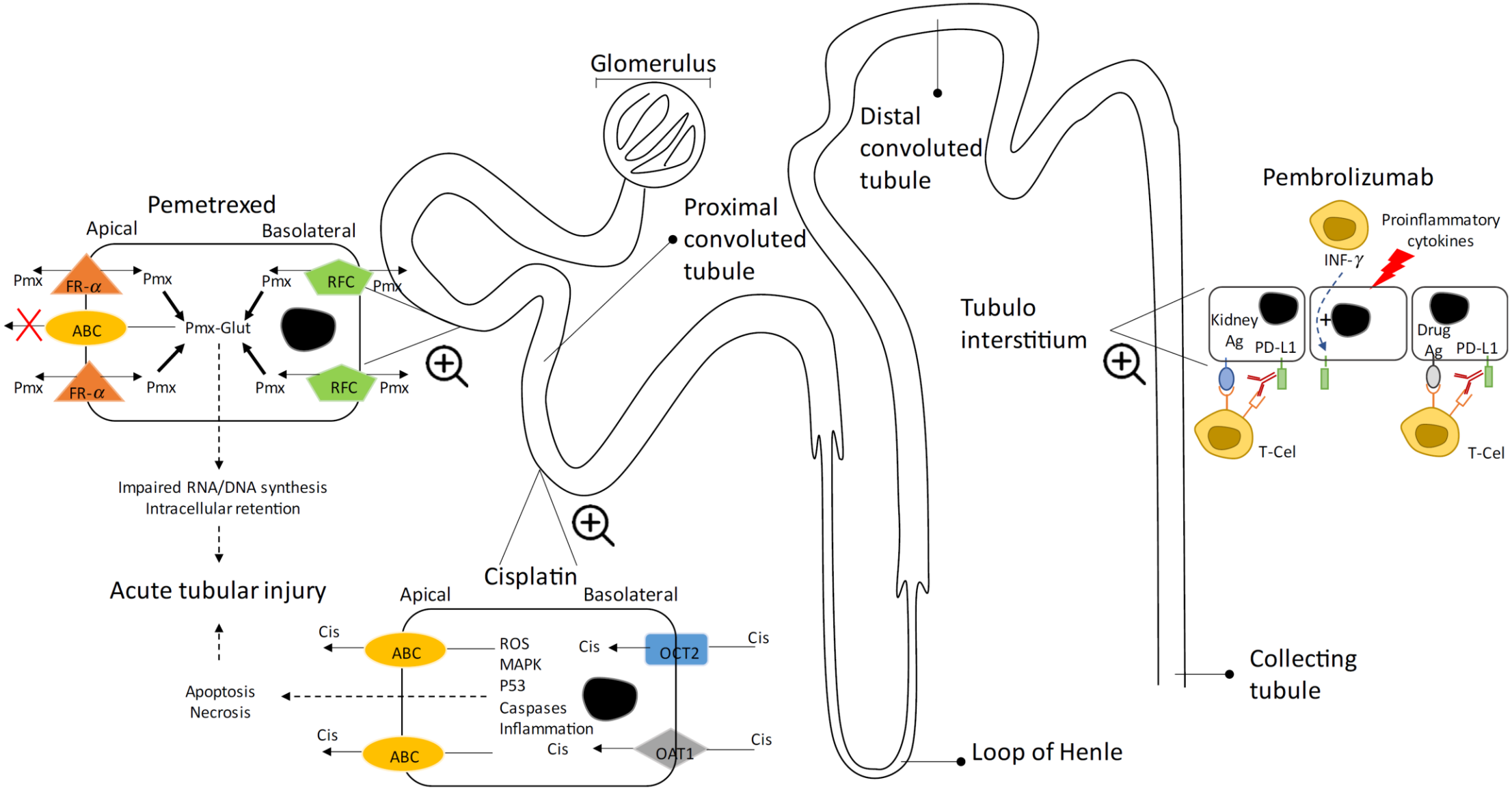


SJS/TEN= sindrome di Stevens-Johnson, Toxic Epidermic Necrolysis

1. Per la gestione del prurito vi sono evidenze a supporto dell'uso di GABA agonisti, aprepitant o omalizumab; tali farmaci tuttavia non hanno in Italia specifica indicazione a trattamento di tossicità cutanea da ICI, e il loro utilizzo con questa indicazione è da considerarsi off-label

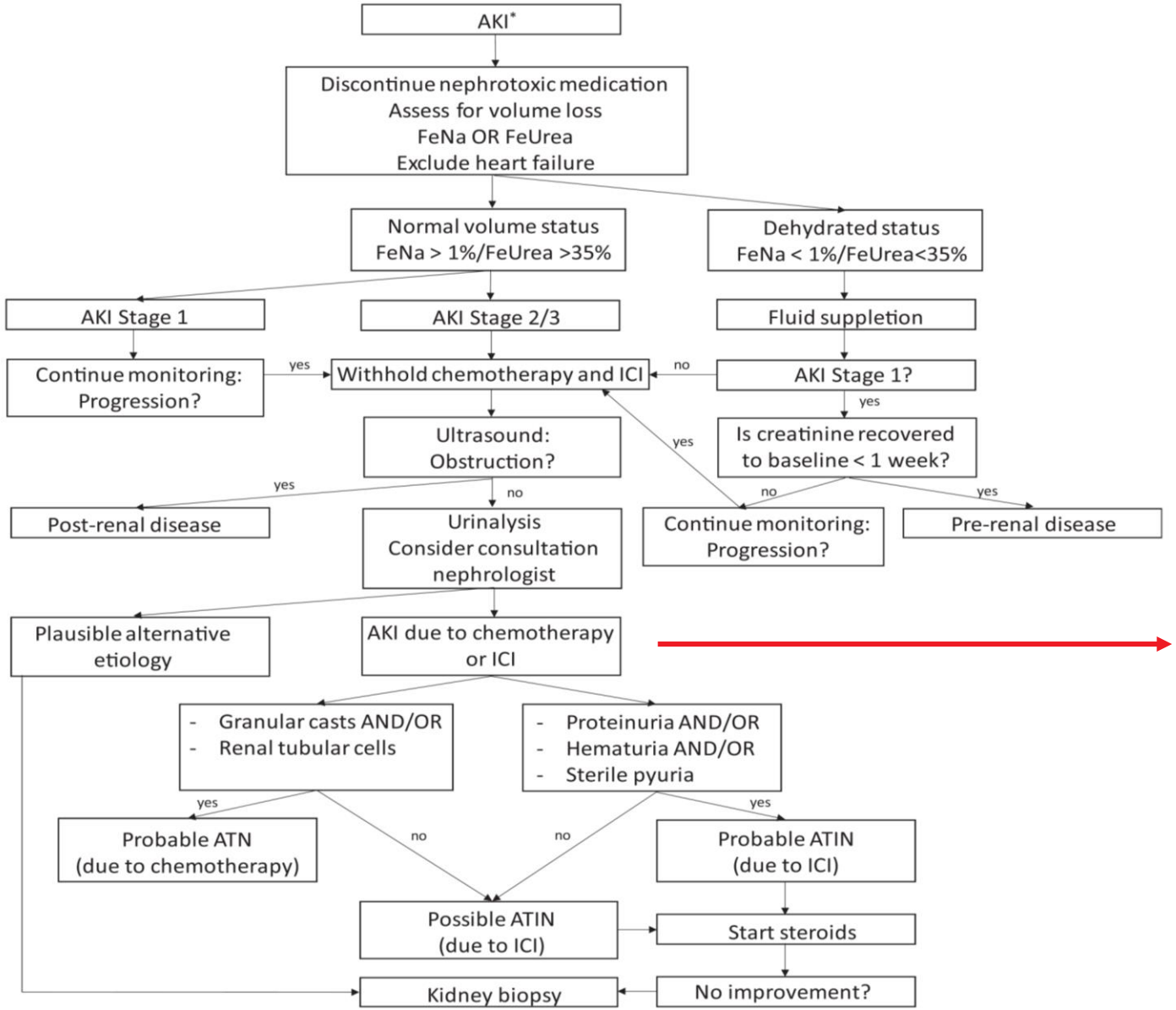
https://snlg.iss.it/wp-content/uploads/2021/12/LG-200_Tox-da-immunoterapia_agg2021.pdf

Tossicità renale da chemio-immunoterapia: patogenesi



Dumoulin DW, et al. J Thorac Oncol 2020;15(9):1472-1483.

Tossicità renale da chemio-immunoterapia: iter diagnostico



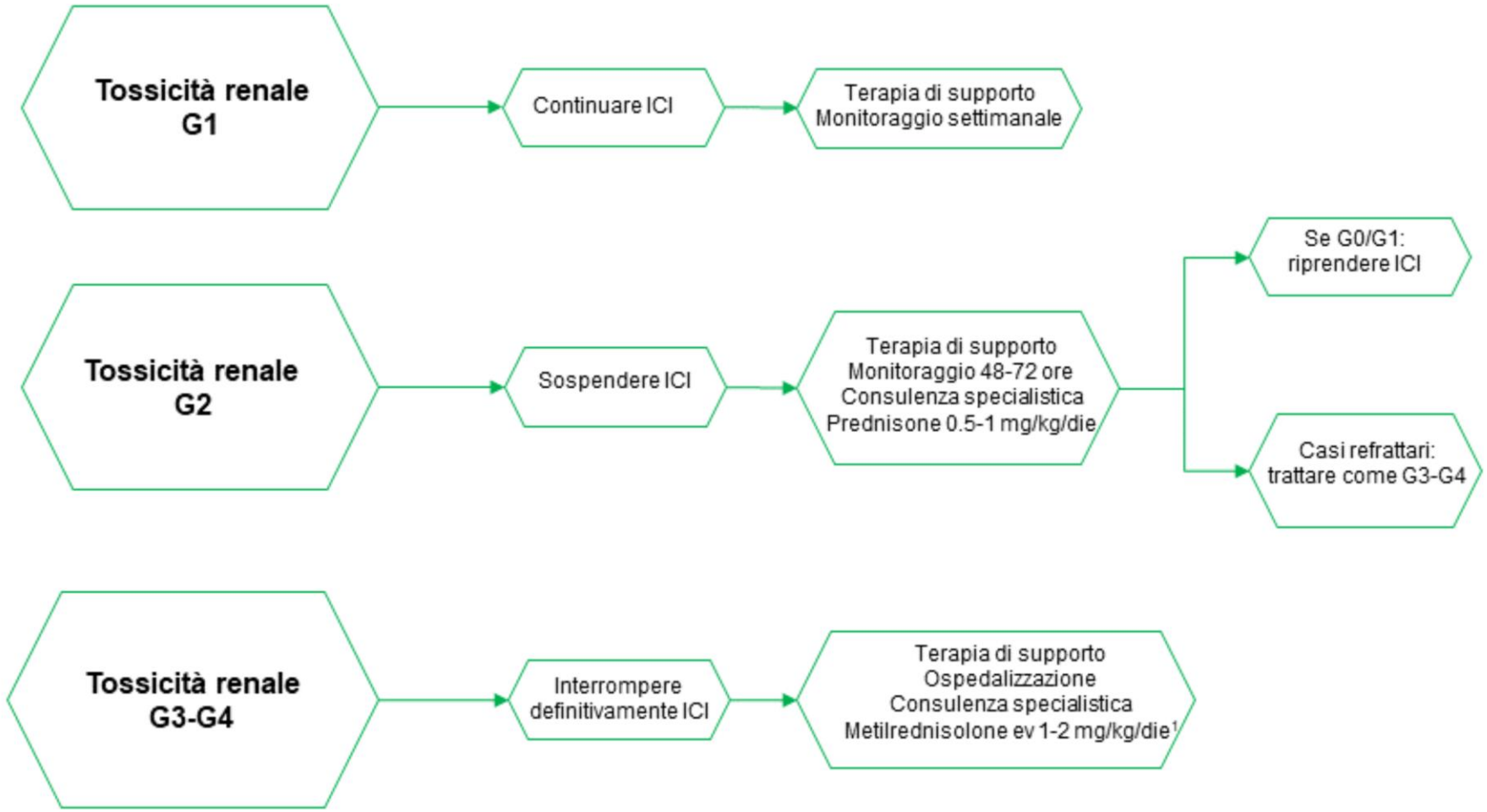
Urinanalysis in ATIN and ATN

	ATIN	ATN
WBC	+[a]	0
WBC casts	+	0
RBC	+	0
Protein	+	±
Renal tubular cell casts	±	+
Granular casts	0	+

Dumoulin DW, et al. J Thorac Oncol 2020;15(9):1472-1483.

Gestione della tossicità renale

Grado 1
Aumento creatinina compreso tra limite superiore della norma e ≤ 1.5 volte il limite superiore della norma
Grado 2
Aumento compreso tra > 1.5 volte il limite superiore della norma e 3 volte il limite superiore della norma; aumento compreso tra >1.5 volte e 3 volte il limite superiore della norma o baseline
Grado 3
Aumento > 3 volte il baseline; aumento compreso tra > 3 volte il limite superiore della norma e ≤ 6 volte il limite superiore della norma
Grado 4
Aumento > 6 volte il limite superiore della norma



1. Vi sono evidenze a sostegno dell'utilizzo in pazienti steroido-refrattari di altri farmaci immunosoppressori (azatioprina, ciclofosfamide, ciclosporina, infliximab o micofenolato). Tali farmaci al momento della stesura della presente linea guida non sono indicati in Italia per il trattamento di nefrite immunocorrelata da ICI, per cui il loro utilizzo per questa indicazione è da considerarsi off-label

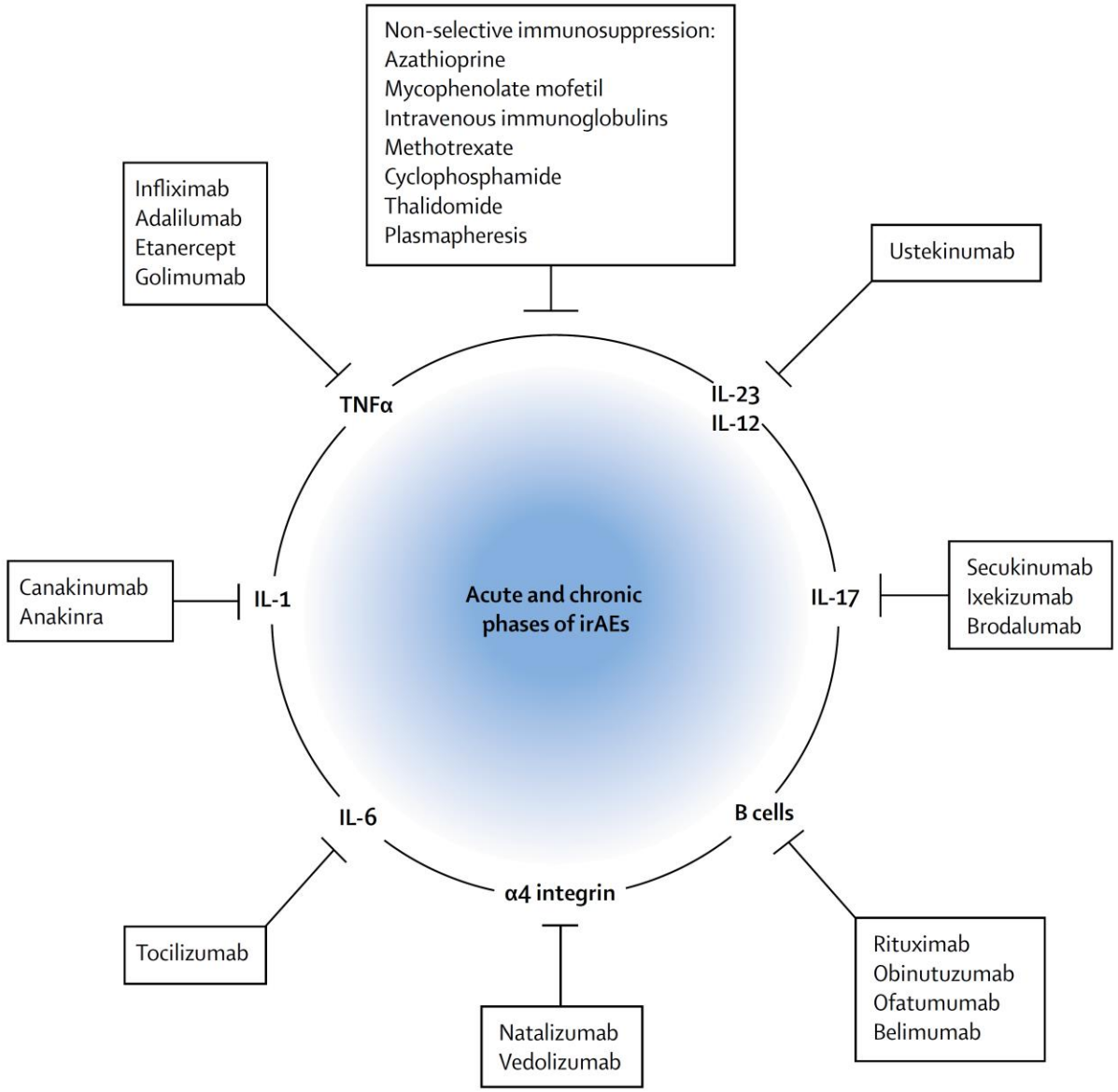
https://snlg.iss.it/wp-content/uploads/2021/12/LG-200_Tox-da-immunoterapia_agg2021.pdf

Gestione della tossicità da immunoterapia: prospettive future

	irAE indications
Anti-IL-1 blockade	Severe irAE during acute phase; severe or refractory arthritis; chronic inflammatory; demyelinating polyradiculoneuritis; psoriasis-like reactions; psoriasis exacerbation; severe and anti-TNFα refractory colitis; myasthenia gravis; encephalitis; aseptic meningitis; myocarditis; pneumonitis
Anti-IL-6 blockade	Severe irAE during acute phase; severe or refractory arthritis; large vessel vasculitis; uveitis; myocarditis; pneumonitis; myasthenia gravis
Intravenous immunoglobulins	Guillain-Barré syndrome; subacute and chronic inflammatory demyelinating polyradiculoneuritis; subacute and chronic inflammatory neuropathies; immune neutropenia; immune thrombocytopenia; facial nerve palsy; myasthenia gravis; transverse myelitis; enteric neuropathy; encephalitis; aseptic meningitis
Anti-CD20 depletion	Systemic lupus erythematosus; severe Sjögren's syndrome; ANCA-associated vasculitis; cutaneous vasculitis; autoimmune autonomic ganglionopathy; sensory ganglionopathy; nephritis; myasthenia gravis; transverse myelitis; enteric neuropathy; encephalitis; aseptic meningitis; hepatitis
Anti-IL-17 blockade	Severe colitis and anti-TNFα refractory colitis; severe or refractory arthritis; anti-IL-6 refractory irAEs
Anti-TNFα blockade	Severe colitis; hepatitis; severe or refractory arthritis; nephritis; uveitis; pneumonitis; myocarditis
Anti-integrin 4 blockade	Limbic encephalitis
Anti-IL-23 and anti-IL-12 blockade	Acute phase, severe, or anti-TNFα refractory colitis; severe or anti-TNFα refractory psoriasis; severe or refractory arthritis
Janus kinase inhibitor	Severe or refractory arthritis

irAE=immune-related adverse event; IL=interleukin type; ANCA=antineutrophil cytoplasmic antibody.

Table: **New therapeutic perspectives for the management of immune-related adverse events**



Martins F et al. Lancet Oncol 2019;20(1):e54-e64.

Take Home Messages

- Adeguata informazione al paziente e ai caregivers
- Elevata attenzione da parte del medico a sintomi/segni di sospetto
- Diagnosi differenziale con altre condizioni
- Identificazione dell'agente causale (chemioterapico vs immunoterapico)
- Trattamento secondo linee guida (terapia steroidea quando indicata)
- Approccio multidisciplinare

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