CARCINOMA DEL POLMONE NON MICROCITOMA:
QUALI NOVITÀ PER IL 2016?

Immunoterapia
Quadri clinici e gestione della tossicità: quale impatto nella pratica clinica?

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REVIEW ARTICLE

Toxicities of Immunotherapy for the Practitioner

Jeffrey S. Weber, James C. Yang, Michael B. Atkins, and Mary L. Disis

MICHAEL A. POSTOW

2015 ASCO EDUCATIONAL BOOK | asco.org/edbook

Managing Immune Checkpoint-Blocking Antibody Side Effects

Michael A. Postow, MD

Optimal management of immune-related toxicities associated with checkpoint inhibitors in lung cancer

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Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper

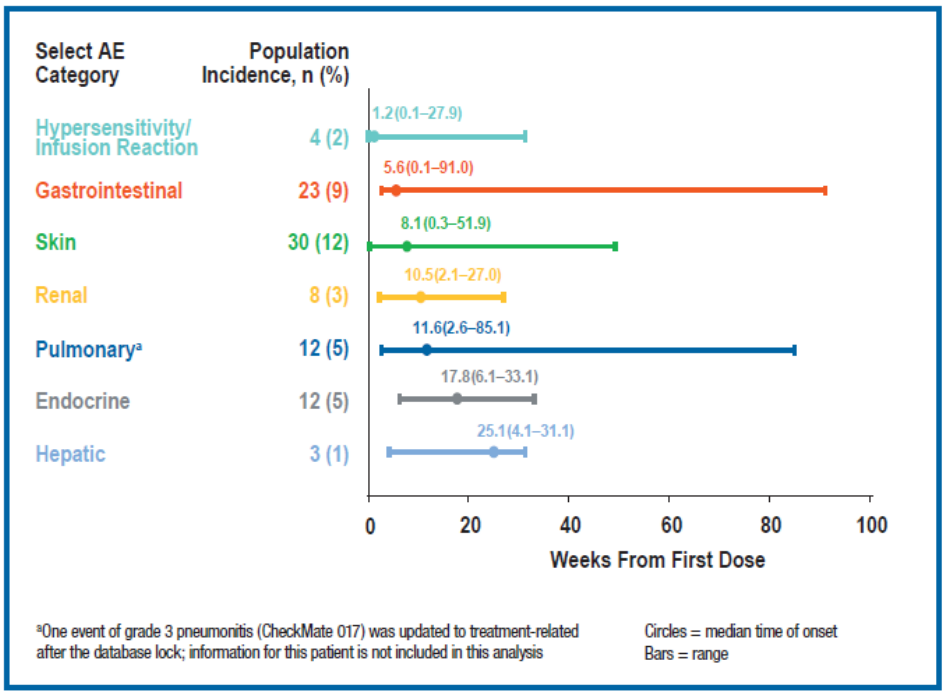
Annals of Oncology 27: 559–574, 2016
doi:10.1093/annonc/mdv623
Published online 28 December 2015`

S. Champiat[1,2], O. Lambotte[3,4,5,6], E. Barreau[7], R. Belkhir[8], A. Berdelou[9], F. Carbonnel[10], C. Cauquil[11], P. Chanson[12,13,14], M. Collins[10], A. Durrbach[15], S. Ederhy[16], S. Feuillet[17,18], H. François[15], J. Lazarovici[19], J. Le Pavec[17,18,20], E. De Martin[21,22], C. Mateus[23], J.-M. Michot[1], D. Samuel[21,22], J.-C. Soria[1,2], C. Robert[2,23], A. Eggermont[24] & A. Marabelle[1,24,25*]

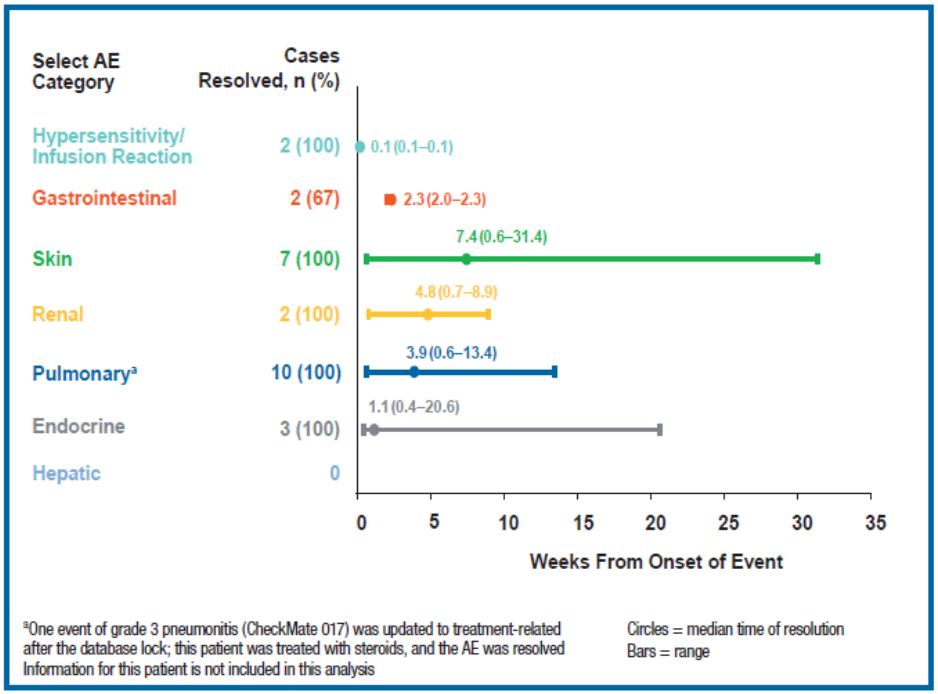
Incidenza, cinetica e reversibilità della tossicità immuno-correlata

Pooled analysis degli studi Checkmate 017 e 063 (298 pazienti)

Time to onset of treatment-related select AEs (any grade)



Time to resolution of treatment-related select AEs with IMs (any grade)



Gettinger S et al. ESMO 2015

Mortalità per polmonite immuno-correlata negli studi con nivolumab

Treatment-related events	Phase 1 (NSCLC)[1,2] N=129	Phase 2 (Squamous NSCLC)[3] N=117	Phase 3 (Squamous NSCLC)[4] N=131	Phase 3 (Non-Squamous) NSCLC[5] n=287
Pneumonitis (any grade)	8 (7%)	6 (5%)	6 (5%)	8 (3%)
Pneumonitis G3-4	3 (2%)	4 (3%)	0 (0%)	3 (1%)
Deaths due to pneumonitis	3 (2%)*	1 (1%)	0 (0%)	0 (0%)

*= 2 of the 3 deaths occurred early in the trial
(before pneumonitis was recognized as a toxicity of treatment with nivolumab)

1. Topalian SL et al. N Eng J Med 2012; 366:2443-54
2. Gettinger SN et al. J Clin Oncol 2015;33
3. Rizvu NA et al. Lancet Oncol 2015;16:257-65
4. Brahmer J et al. N Engl J Med 2015;373:123-35
5. Borghaei H et al. N Engl J Med 2015;373:1627-39

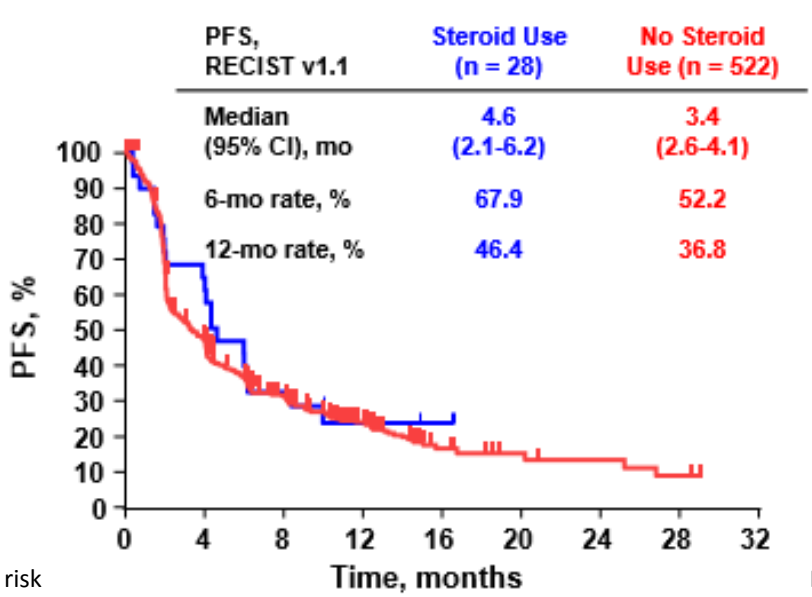
Algoritmo generale per la gestione della tossicità immuno-relata

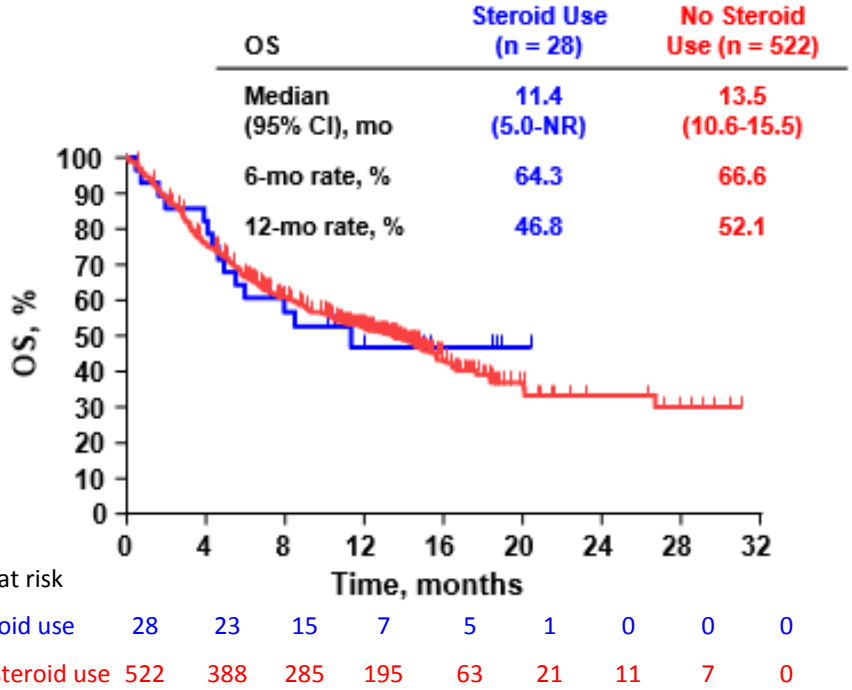
CTCAE grade	Management
1	• Supportive treatment • Increased monitoring of symptoms • Exclude infection • Patient education
2	As per grade 1 but in addition: • Withhold immunotherapy until toxicity has resolved to grade 1 or less • Consider oral steroids if persistent symptoms > 5 days
3	• Supportive therapy • Commence IV steroids (typical dose 1-2 mg/kg methylprednisolone) • If not resolving within 48 h consider addition of other immunosoppressants • Consider system specific investigations • Seek expert opinion of relevant speciasist • Withold immunotherapy, consider restarting if toxicity grade 1 or less on individual basis • Steroids will need to be tapered over 3-6 weeks
4	As for grade 3 but permanently discontinue immunotherapy

Howell M et al. Lung Cancer 2015;88:117-23

Terapia steroidea e outcome

KEYNOTE-001 - NSCLC cohorts n = 550





No clear relationship between steroid use and continued efficacy of anti-PD1 antibody

Leighl et al. WCLC 2015

Polmonite

For suspected immune-mediated adverse reactions, exclude other causes.
Evaluate with imaging and pulmonary consultation if changes in respiratory status occur.

	Grade 1 (Radiographic changes only)	**Grade 2** (Mild-to-moderate symptoms; worsens from baseline)	**Grade 3-4** (Severe symptoms; new/worsening hypoxia; life-threatening); **hospitalize**
I-O Treatment	**Consider delay**	**Delay**	**Permanently discontinue**
Monitoring	2-3 days	Daily	Daily
Consult	Consider pulmunary and ID consult	Pulmunary and ID consult	Pulmunary and ID consult
Steroids	-	1 mg/kg/day methylprednisolone IV or oral equivalent	2-4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactc antibiotics for opportunistic infections
Pulmunary tests	-	Consider bronchoscopy, lung biopsy	Consider bronchoscopy, lung biopsy

Follow-up

Re-image at least every 3 weeks	**Re-image every 1-3 days**	
If improved Resume treatment if withheld, when stable	**If improved to baseline** Taper steroids over at least 1 month and then resume treatment	**If improved to baseline** Taper steroids over at least 6 weeks
If worsens Treat as grade 2 or 3-4	**If not improving after 2 weeks or worsening:** Treat as grade 3-4	**If not improving after 48 hours or worsening:** Add additional immunosuppression (e.g. infliximab, cyclophosphamide, IVIG, or mycophenolate)

Robert C, et al. N Engl J Med 2015;372:320-30 (Suppl Appendix)

Diarrea/Colite

For suspected immune-mediated adverse reactions, exclude other causes (Clostridium difficile or other pathogens).

	Grade 1 (Diarrhea: <4 stools per day over baseline; Colitis: asymptomatic)	**Grade 2** (Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL; Colitis: abdominal pain, blood in stool)	**Grade 3-4** (Diarrhea [G3]: ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL; Colitis [G3]: severe abdominal pain, medical intervention indicated, peritoneal signs; [G4] life-threatening, perforation)
I-O Treatment	**Continue**	**Delay**	**Discontinue**
Symptomatic treatment	Administer	Administer	-
Steroids	-	-	1-2 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactc antibiotics for opportunistic infections
GI tests	-		Consider lower GI endoscopy

Follow-up

Close monitoring for worsening symptoms **Educate patient to report worsening immediately**	**If improved to grade 1** Resume treatment	**If improved from Grade 3** When at Grade 1, taper steroids over at least 1 month before resuming treatment
If symptoms worsen or persist Treat as Grade 2 or 3-4	**If symptoms persist >5 days or recur** 0.5 to 1 mg/kg/day methylprednisolone or oral equivalents **If symptoms worsen or persist >3 to 5 days with oral steroids** Treat as Grade 3-4	**If symptoms persist ≥ 3 to 5 days or recur after improvement** Add infliximab (if no contraindication)

Robert C, et al. N Engl J Med 2015;372:320-30 (Suppl Appendix)

Rash

For suspected immune-mediated adverse reactions, exclude other causes

	Grade 1-2 (Covering ≤30% BSA)	**Grade 3-4** (Covering >30% BSA; life-threatening consequences)
I-O Treatment	**Continue**	**Grade 3: delay** **Grade 4: permanently discontinue**
Sypmtomatic treatment	Administer antihistamines	-
Consult	-	Dermatology
Steroids	Topical steroids	1-2 mg/kg/day methylprednisolone IV or IV equivalent
Skin test	-	Consider skin biopsy

Follow-up

If symptoms persist >1-2 weeks or recur Consider skin biopsy Withhold treatment Consider 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent. Once improving, taper steroids over at least 1 month, and resume treatment	**If improves to Grade 1** Taper steroids over at least 1 month before resuming treatment
If worsens Treat as Grade 3-4	

Robert C, et al. N Engl J Med 2015;372:320-30 (Suppl Appendix)

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The key to successful management of checkpoint antibody toxicities is:

- **Early diagnosis**
- **High suspicion**
- **Excellent patient-provider communication**
- **Rapid and aggressive use of corticosteroids and other immune suppressants for irAEs**

Sacro Cuore Don Calabria

Cancer Care Center Negrar - Verona

Cancer Care Center

Numero Verde

800 143 143

Numero per la Cura del Tumore

GRAZIE

PER L'ATTENZIONE

Epatite

For suspected immune-mediated adverse reactions, exclude other causes (viral infection, metastases). Consider imaging to rule out obstruction.

	Grade 1 (AST or ALT >ULN to 3.0x ULN and/or T. bili >ULN to 1.5x ULN)	**Grade 2** (AST or ALT >3.0 to ≤5x ULN and/or T. bili >1.5 to ≤3x ULN)‡	**Grade 3-4 (AST or ALT >5x ULN and/or T. bili >3x ULN)**
I-O Treatment	**Continue**	**Delay**	**Permanently discontinue**
Monitoring	Monitor LFTs prior to and periodically during treatment	Increase frequency of monitoring to every 3 days	Increase frequency of monitoring to every 1 to 2 days-
Consult	-	-	Gastroenterology
Steroids	-		1-2 mg/kg/day methylprednisolone IV or IV equivalent Add profilactic antibiotics for opportunistic infections

Follow-up

Continue monitoring LFTs	**If improves to Grade 1 or baseline** Resume treatment Resume routine LFT monitoring	**If improves to <Grade 2** Taper steroids over at least 1 month
If worsens Treat as Grade 2 or 3-4	**If elevation persist >5-7 days or worsen** 0.5 to 1 mg/kg/day methylprednisolone or oral equivalents and when LFT returns to grade 1 or baseline taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume treatment	**If does not improve in >3-5 days, worsen, or rebound** Add mycophenolate 1g BID

Robert C, et al. N Engl J Med 2015;372:320-30 (Suppl Appendix)

Tossicità renale

For suspected immune-mediated adverse reactions, exclude other causes

	Grade 1 (Creatinine >ULN and >baseline but ≤1.5x baseline)	**Grade 2-3** (Creatinine >1.5x to ≤6x ULN or >1.5x baseline)	**Grade 4** (Creatinine >6x ULN)
I-O Treatment	**Continue**	**Delay**	**Permanently discontinue**
Monitoring	Monitor creatinine prior to and weekly during Treatment	Monitor creatinine every 2-3 days	Monitor creatinine daily
Consult	-	-	Nefrology
Steroids	-	0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent	1-2 mg/kg/day methylprednisolone IV or IV equivalent
Renal tests	-	Consider renal biopsy	Consider renal biopsy

Follow-up

If improved to baseline Resume routine creatinine Monitoring	**If improves to grade 1:** Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume treatment and routine creatinine monitoring	**If improves to grade 1:** Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections
If worsens Treat as Grade 2-3 or 4	**If elevation persist >7 days or worsen** Treat as Grade 4	

Robert C, et al. N Engl J Med 2015;372:320-30 (Suppl Appendix)

Endocrinopatia

For suspected immune-mediated adverse reactions, exclude other causes.
Consider visual field testing, endocrinology consultation, and imaging.

	Asymptomatic TSH Elevations (eg, hypothyroidism, hyperthyroidism)	**Symptomatic Endocrinopathy** (eg, hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)	**Suspicion of Adrenal Crisis** (eg, severe dehydration, hypotension, shock out of proportion to current illness)
I-O Treatment	**Continue**	**Delay or discontinue**	**Delay or discontinue**
Monitoring	If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated	Evaluate endocrine function. Consider pituitary scan. Repeat labs in 1 to 3 weeks/MRI in 1 month if symptoms persist but normal lab/pituitary scan	Rule out sepsis
Consult	Consider Endocrinology	Consider Endocrinology	Endocrinology
Steroids	-	1-2 mg/kg/day methylprednisolone IV or oral equivalent	Stress-dose of IV steroids with mineralocorticoid activity
Clinical management	-	Initiate appropriate hormone thrapy	Administer IV fluids
Follow-up	**Continue standard monitoring**	**If improved (with or without hormone replacement)** Resume treatment **Continue standard monitoring** Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component Taper steroids over at least 1 month before resuming treatment†	**When adrenal crisis ruled out** Treat as Symptomatic Endocrinopathy

Robert C, et al. N Engl J Med 2015;372:320-30 (Suppl Appendix)

Tossicità neurologica

For suspected immune-mediated adverse reactions, exclude other causes.
Evaluation may include but may not be limited to consultation with a neurologist, brain MRI, and lumbar puncture.

	Grade 1 (Asymptomatic or mild symptoms)	**Grade 2** (New onset moderate symptoms, limiting instrumental ADL)	**Grade 3-4** (New onset severe symptoms, limiting self-care ADL, life-threatening)
I-O Treatment	**Continue**	**Delay**	**Permanently discontinue**
Symptomatic treatment	-	Treat symptoms per local guidelines	Treat symptoms per local guidelines
Consult	-	-	Neurology
Steroids	-	Consider 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent	1-2 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections

Follow-up

Continue to monitor the patient	**If improves to baseline** Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections Resume treatment	**If improves to grade 2** Taper steroids over at least 1 month
If worsens Treat as Grade 2 or 3-4	**If worsens** Treat as Grade 3-4	**If worsens tor atypical presentation:** Consider IVIG or other immunosuppressive therapies

Robert C, et al. N Engl J Med 2015;372:320-30 (Suppl Appendix)