Identificação e manejo dos efeitos colaterais associados ao tratamento imunoterápico

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Declaração de Conflitos de Interesse

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96/2008 da ANVISA, declaro que:

- Honorários por aulas ministradas: Astellas, Bayer, Ferring, Zodiac
- Auxílio para congressos: Bayer, Janssen, Pfizer, Sanofi, Zodiac, Roche
- Subinvestigadora de estudos clínicos: AstraZeneca, BMS, Janssen, MSD, Roche

Introdução

- Imunoterapia: revolução no tratamento do câncer
- Perfil de eventos adversos (imuno-relacionados, irAE) peculiar
- Maioria de grau leve a moderado
- Potencial para eventos graves e fatais
  - Mortes relacionadas ao tratamento: até 2%
  - Alto grau de suspeição!
  - Reconhecimento e tratamento precoces
- Recomendações: consenso clínico entre especialistas

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Ke
Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallme
Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, I
Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santo
Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wo
collaboration with the National Comprehensive Cancer Network

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
in partnership with the American Society of Clinical Oncology (ASCO)

Management of Immunotherapy-Related Toxicities

e Checkpoint Inhibitor-Related Toxicities)

Version 1.2018 — February 14, 2018

NCCN.org

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

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

POSITION ARTICLE AND GUIDELINES Open Access

CrossMark

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

Puzanov et al. J Immunother Cancer 2017 Nov 21;5(1):95
Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]
Haanen et al. Ann Oncol 2017 Jul 1;28(suppl_4):iv119-iv142
NCCN Guidelines v1.2018 Management of Immunotherapy-Related Toxicities

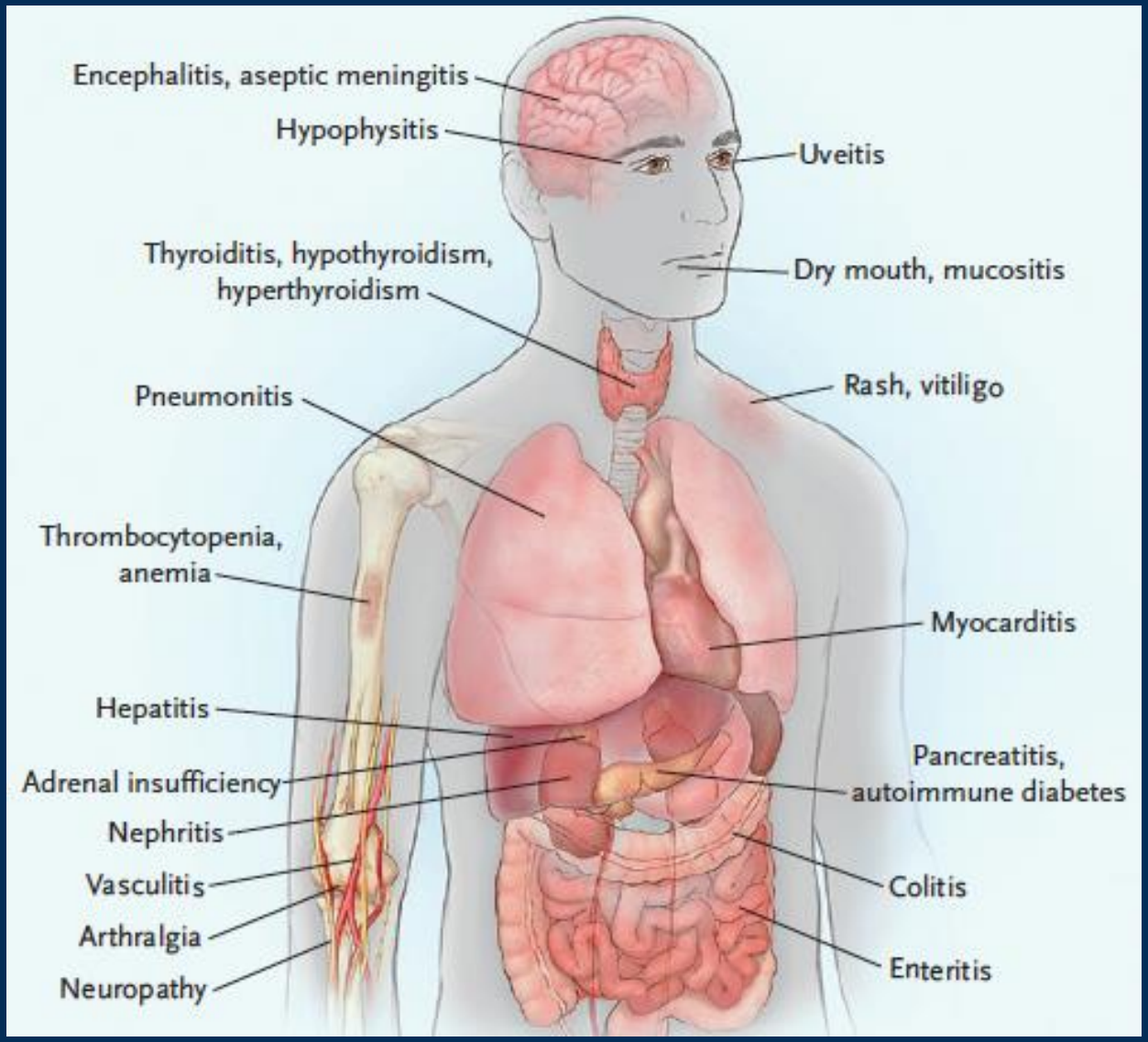


Figure 1. Organs Affected by Immune Checkpoint Blockade.

Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

Postow et al. N Engl J Med 2018;378:158

Mecanismos possíveis associados a irAE

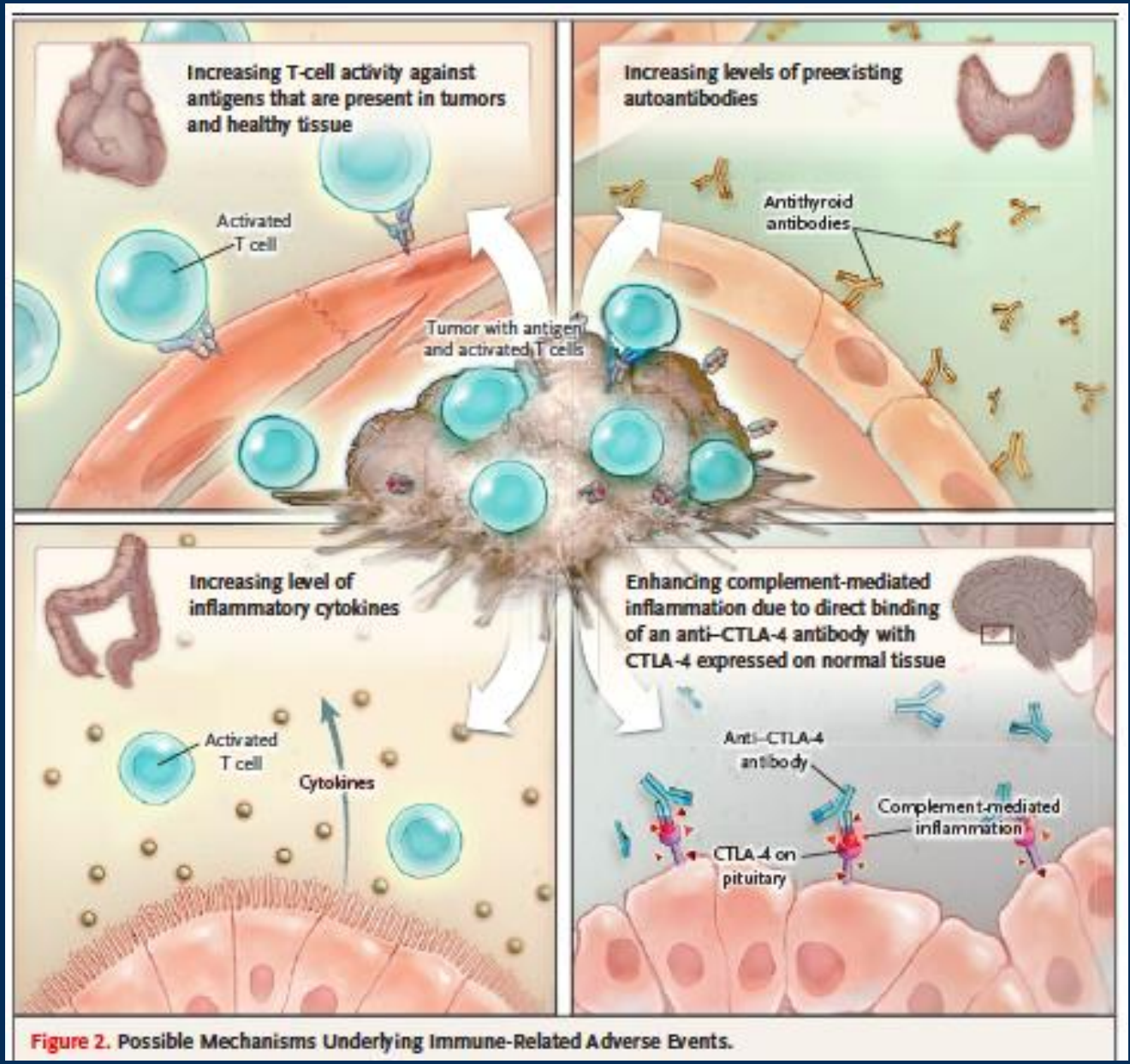


Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

Postow et al. N Engl J Med 2018;378:158

Incidência

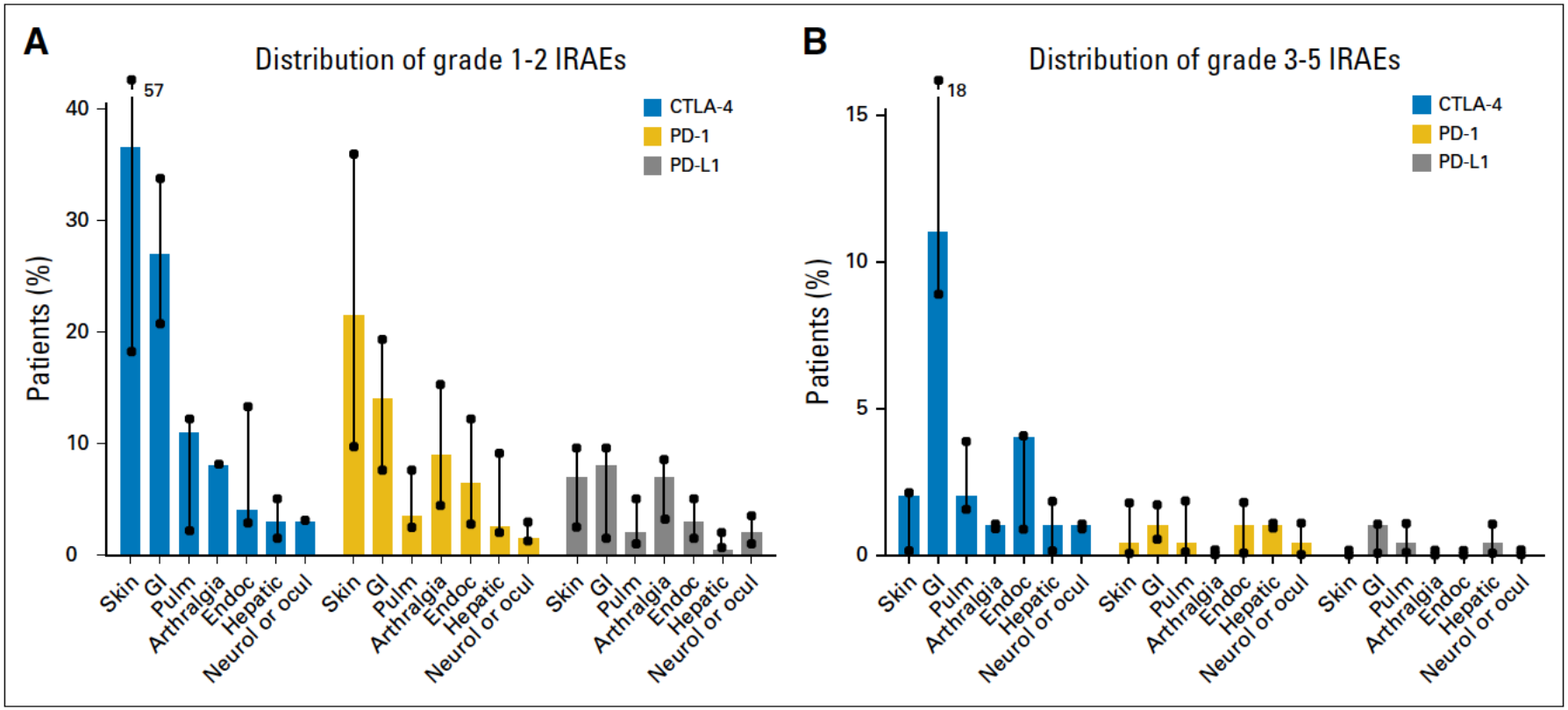
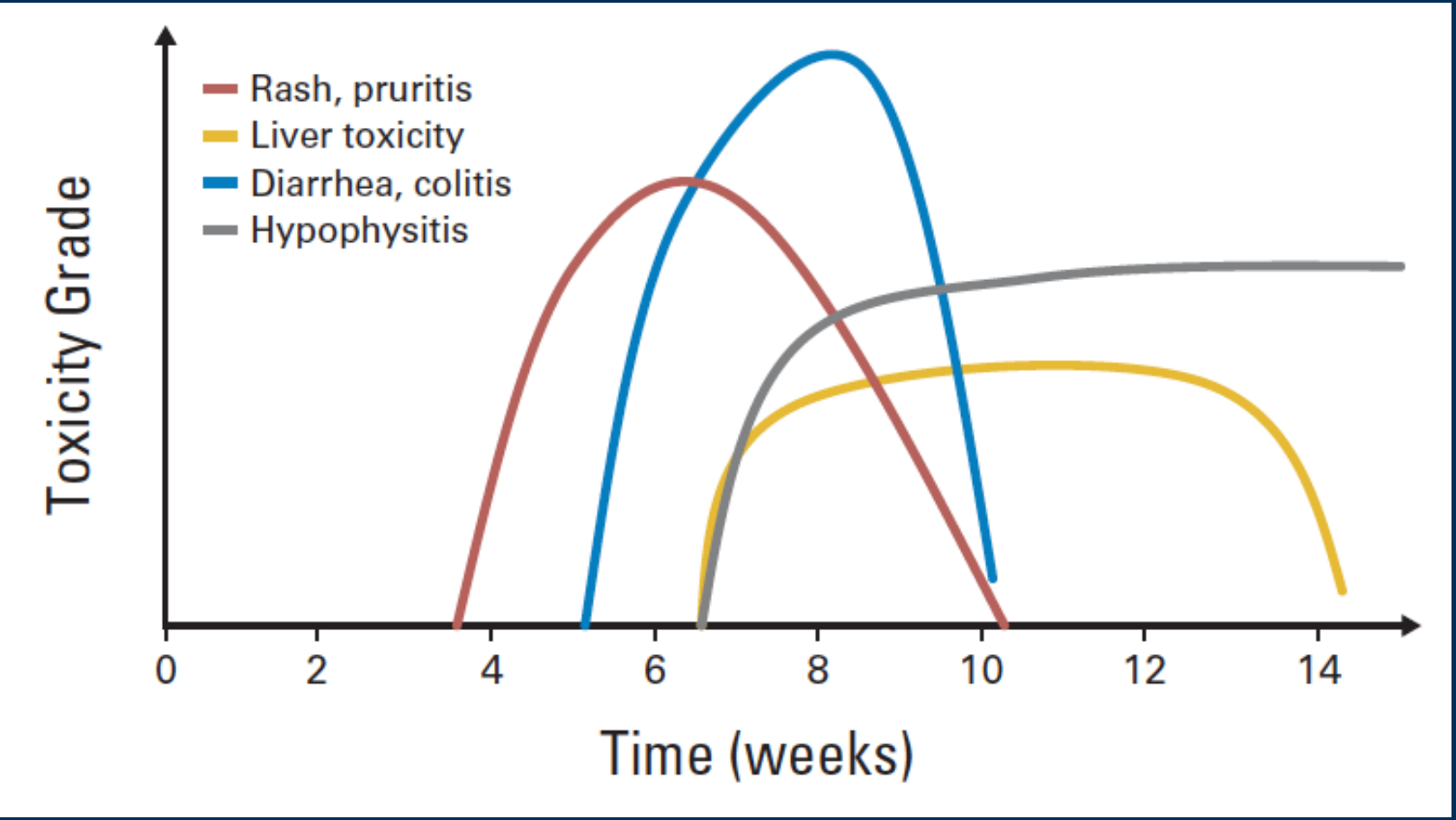


Fig A1. Distribution of (A) grade 1 to 2 and (B) grade 3 to 5 immune-related adverse events (irAEs) for all tumor types in the main clinical trials with anti– cytotoxic T-cell lymphocyte-4 (anti–CTLA-4), anti–programmed death 1 (PD-1), or anti–PD ligand 1 (PD-L1) antibodies as single therapies. The values quoted are the median (range) irAE rates for the set of clinical trials as a whole. Adapted from European Journal of Cancer, Vol 54, J.M. Michot et al, Immune-Related Adverse Events With Immune Checkpoint Blockade: A Comprehensive Review, 139-149, Copyright 2016, with permission from Elsevier. Endoc, endocrinology; Neurol, neurology; ocul, ocular; Pulm, pulmonary.

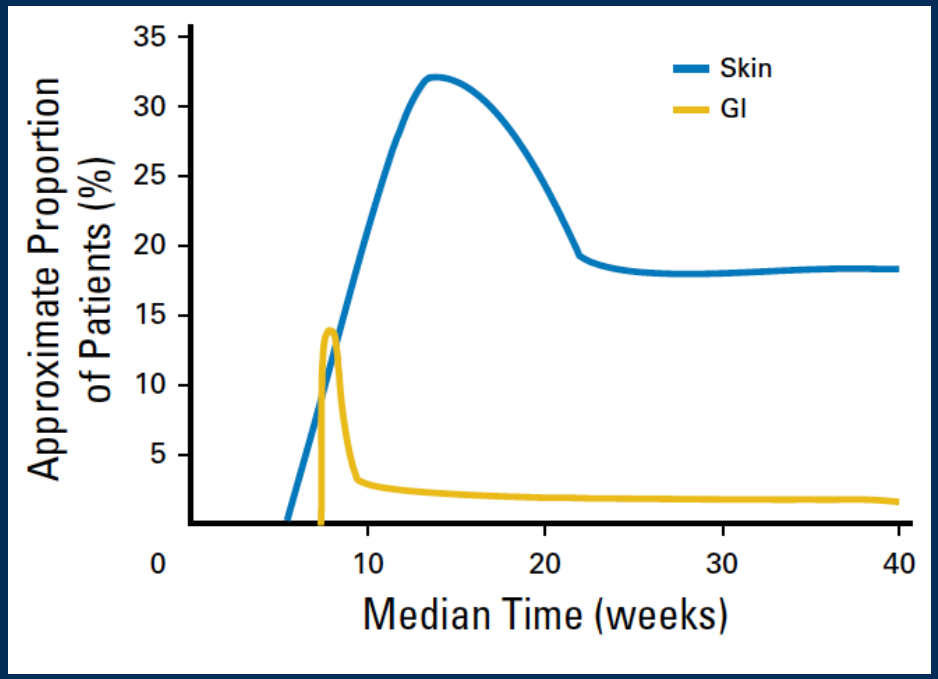
Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

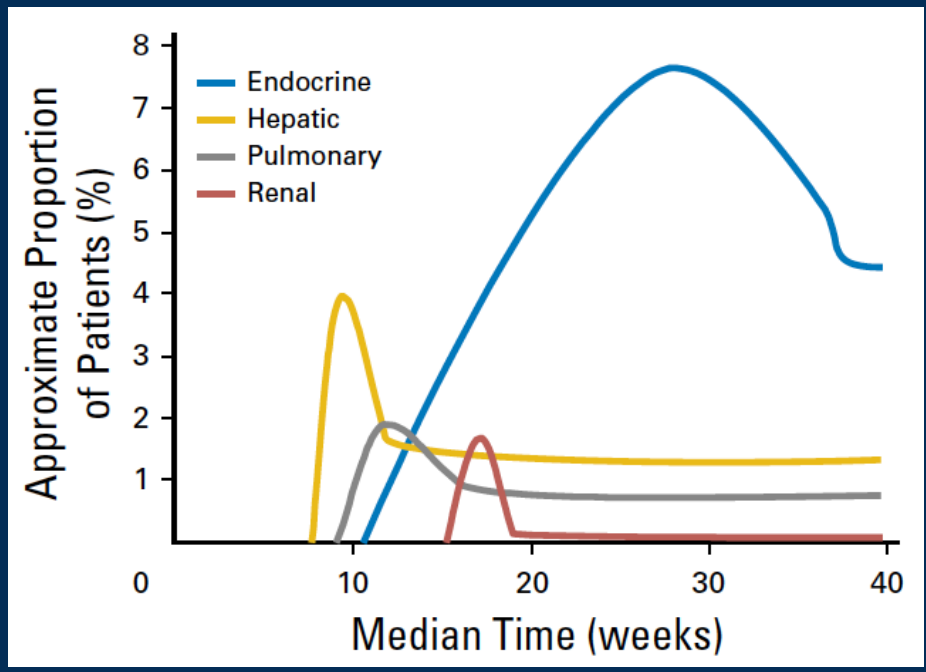
Cinética dos Eventos Adversos: Ipilimumabe



Weber et al. J Clin Oncol 2012; 30: 2691

Cinética dos Eventos Adversos: Nivolumabe





Weber et al. J Clin Oncol 2017; 35: 785

Toxicidade e eficácia

Nivolumabe em Melanoma

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy and PFS

		Any-Grade Treatment-Related Select AEs				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
	All Patients (N = 576)	Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P		< .001		< .0001*	< .001*	1.00		.736	

Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate; PFS, progression-free survival.
*Versus no treatment-related select AEs.

Weber et al. J Clin Oncol 2017 Mar;35(7):785

Toxicidade e eficácia

- Dados disponíveis conflitantes
- EA específicos (ex: vitiligo em pacientes com melanoma) podem estar mais claramente associados a eficácia da terapia

Postow et al. N Engl J Med 2018;378:158

Segurança da Imunoterapia em pacientes com doença auto-immune prévia

- Dados limitados – população excluída dos estudos clínicos prospectivos
- Estudos retrospectivos sugerem que tais pacientes podem ser tratados seguramente e eficazmente com iCPI

Postow et al. N Engl J Med 2018;378:158

Toxicidade cutânea

- Mais comum e a mais precoce a acontecer
- 30 - 50% dos pacientes tratados com inibidores de checkpoints imunes (iCPI)

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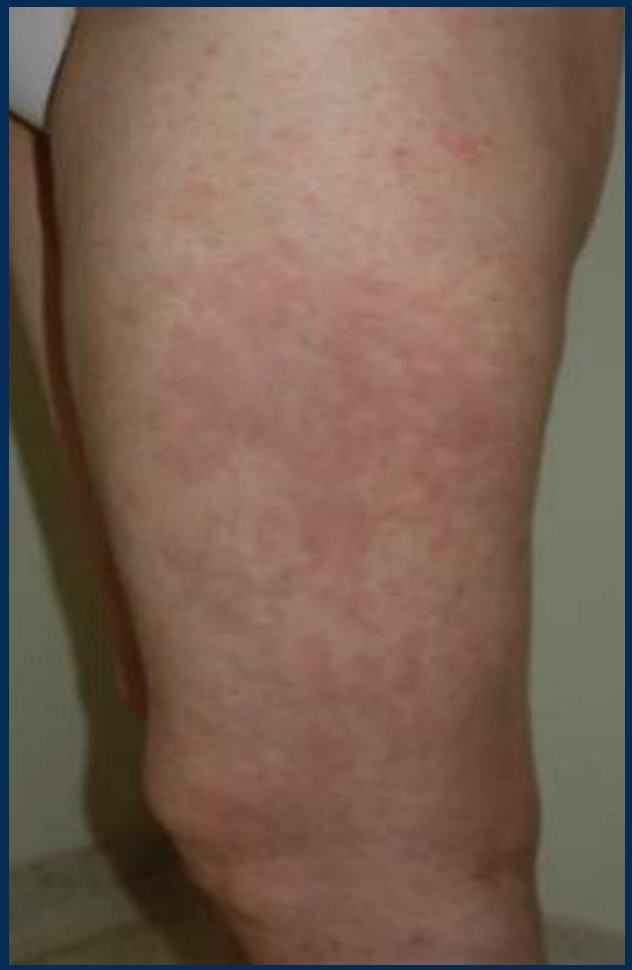
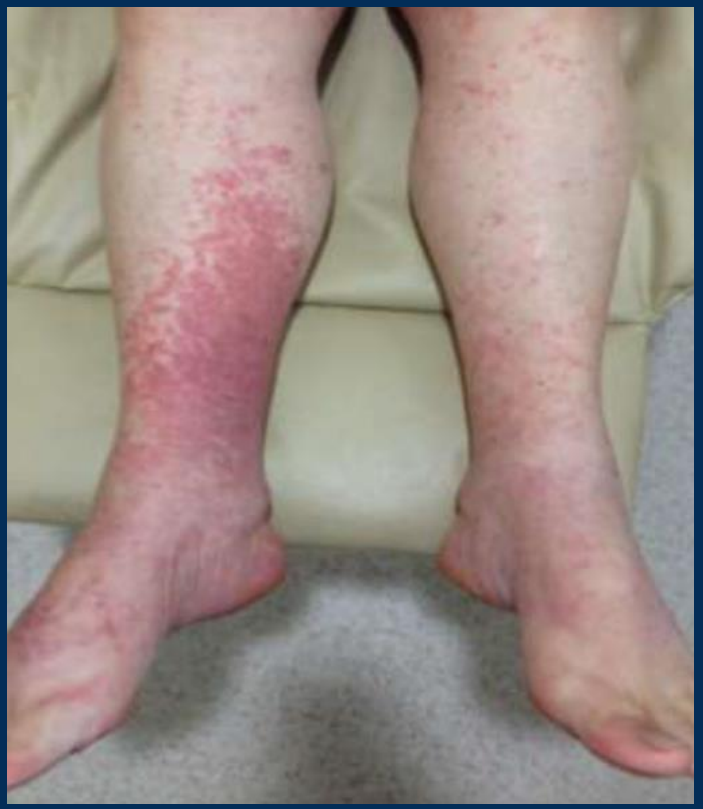
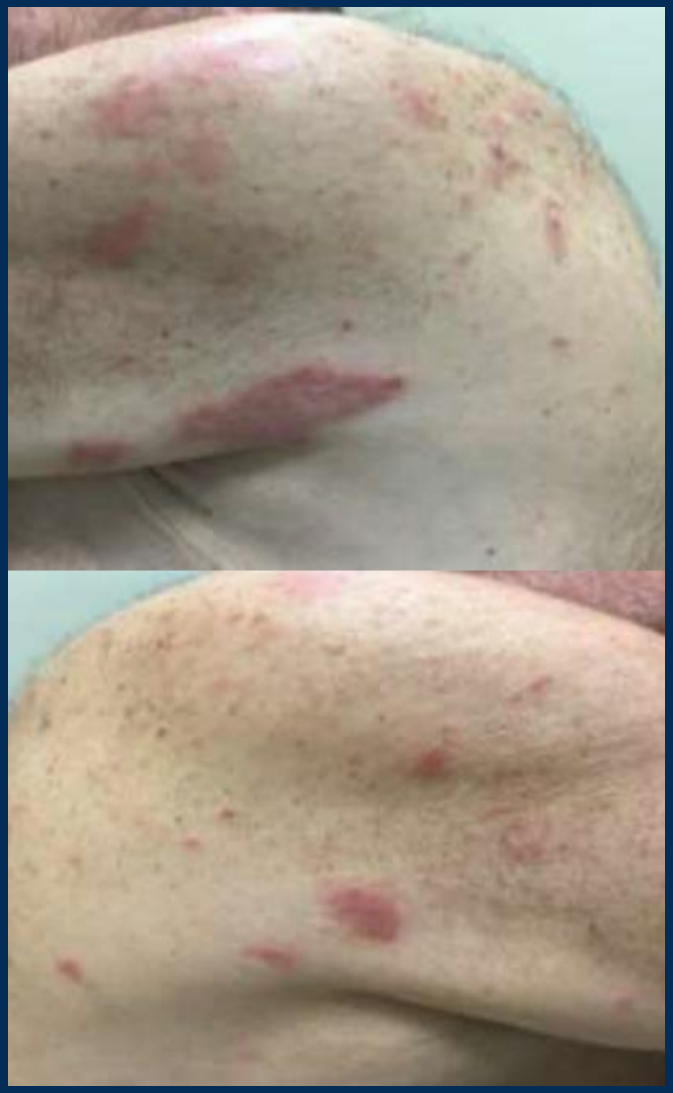
Toxicidade cutânea



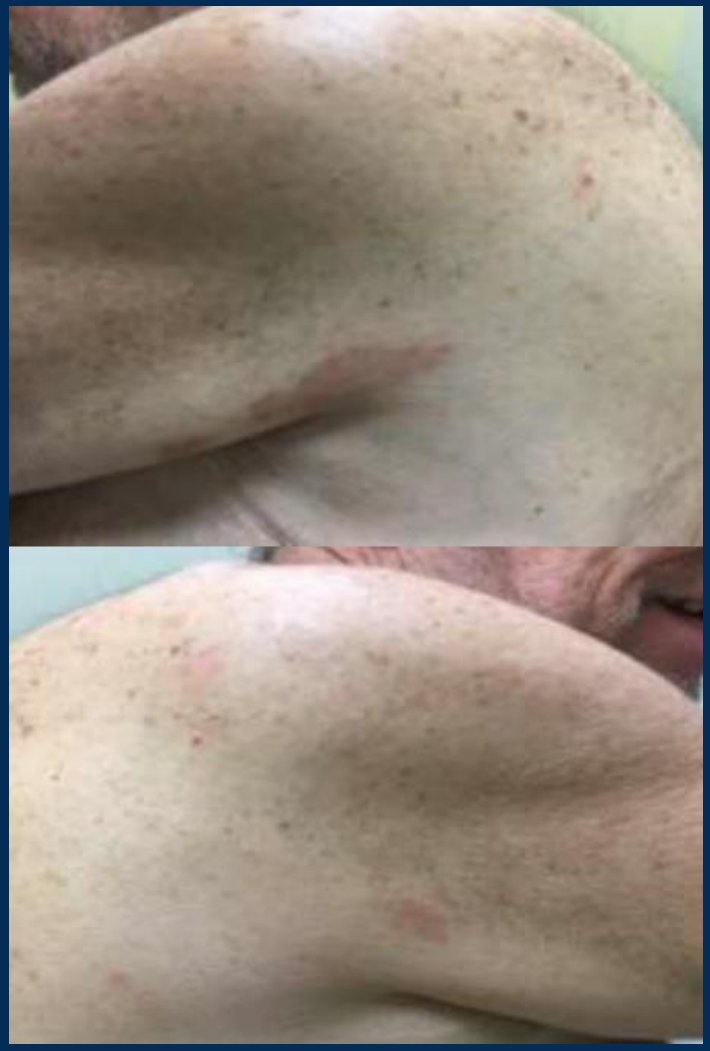


Cortesia: dr Rafael Schmerling

Dermatite com Nivolumabe

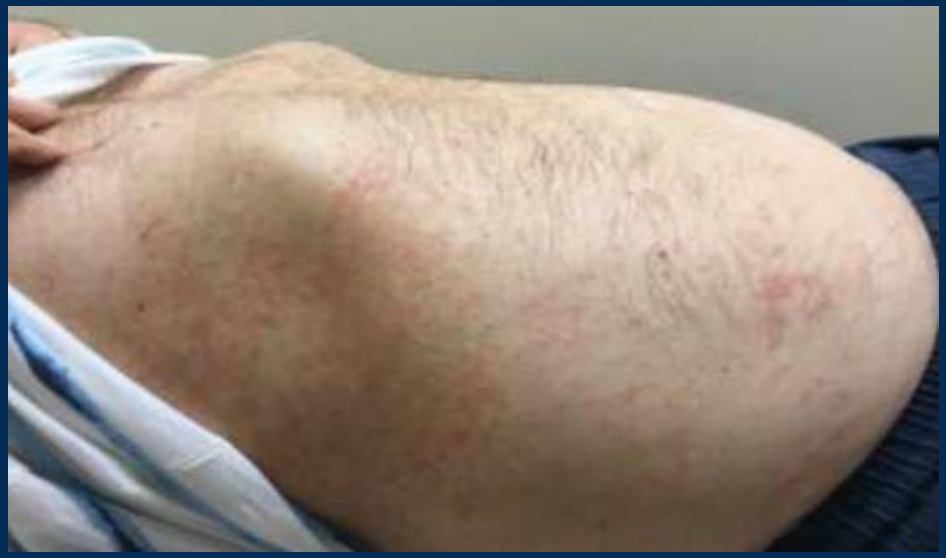


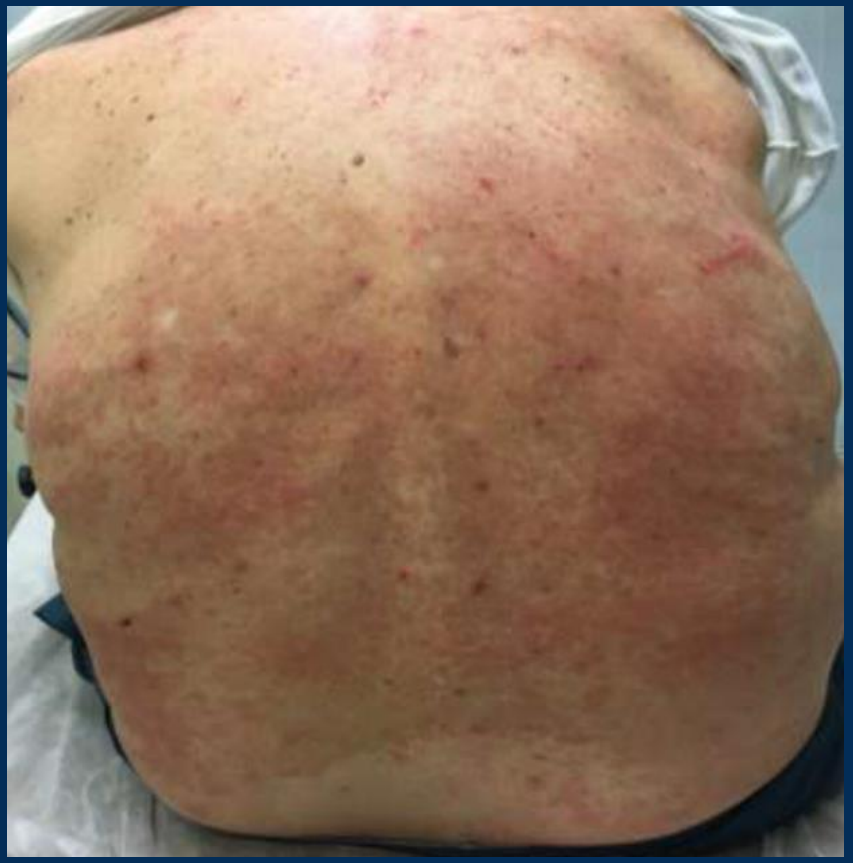
Prednisona



Cortesia: dr Rafael Schmerling

Dermatite com Pembrolizumabe





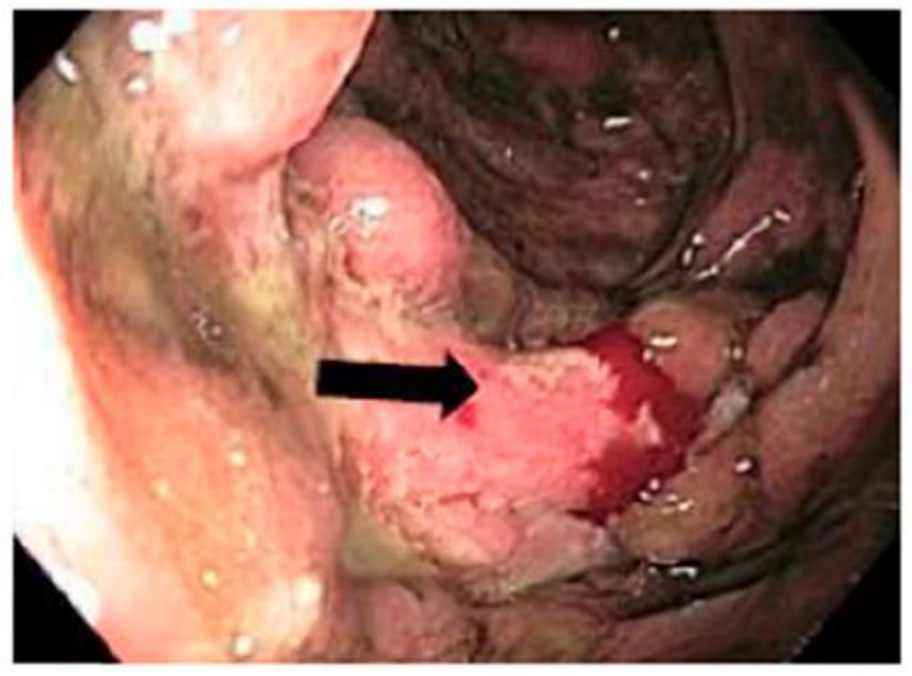
Cortesia: dr Rafael Schmerling

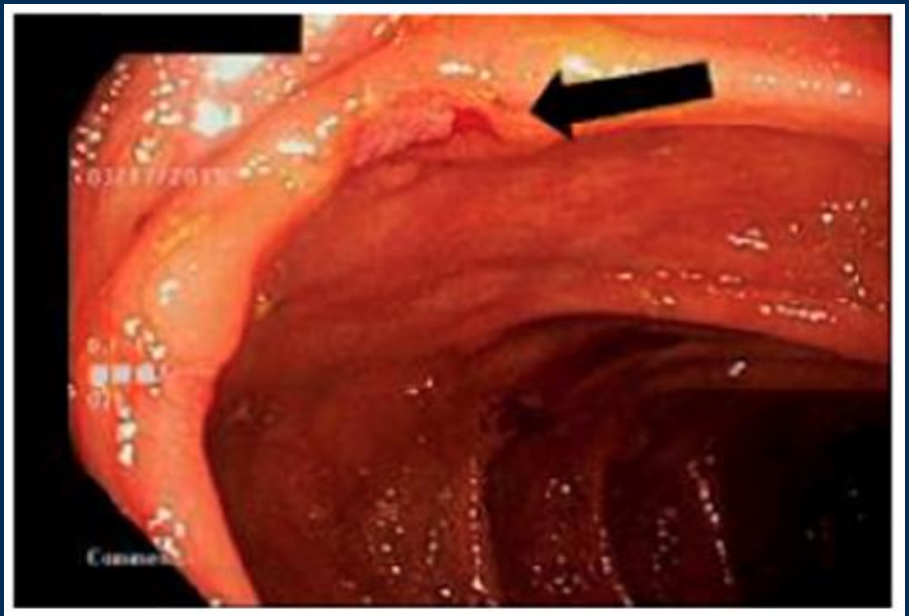
Toxicidade gastrointestinal

- Frequência:
  - Colite: 8 – 27%
  - Diarréia:
    - Anti-CTLA-4: 54%
    - Anti-PD-1: ≤ 19%
- Alta incidência de EA G3/4 comparado aos outros órgãos/sistemas.
  - Obstrução, perfuração, megacolon tóxico
- Sintomas:
  - 5 – 10 semanas após o início do iCPI
  - Pode ocorrer/recorrer meses após o término da imunoterapia

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]
Weber et al. The Oncologist 2016;21:1

Toxicidade gastrointestinal





Weber et al. The Oncologist 2016;21:1

Toxicidade gastrointestinal

Hepatite

- 2 – 10% dos paciente em monoterapia
- 25 – 30% com combinação
- Exclusão de outras etiologias
- Casos corticóide-refratários: micofenolato mofetil (infliximabe: não recomendado, pelo potencial hepatotóxico)

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Toxicidade pulmonar

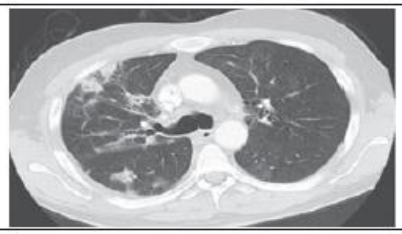
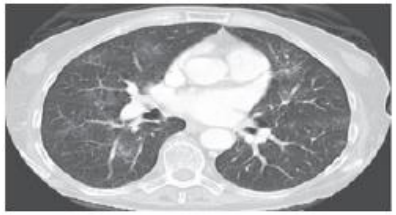
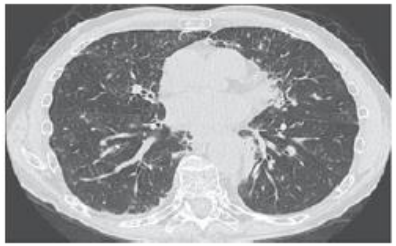
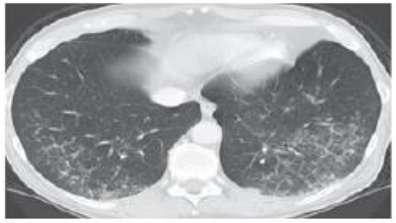
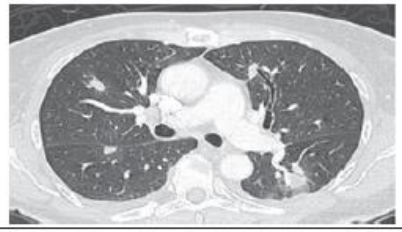
- Incomum, mas potencialmente grave.
- Incidência:
  - Anti-PD-1/PD-L1: 2,7%
  - Anti-CTLA-4: < 1%
  - Combinação (10%) > monoterapia (3%)
- Relação com o sítio do tumor primário incerto
- Relação com tabagismo:
  - Ativo/prévio: 56%
  - Nunca fumaram: 44%
- RT torácica: sem diferença nas taxas de pneumonite.

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Toxicidade pulmonar

- Imagem: variável - comumente opacidades em vidro fosco ou infiltrados nodulares, predominantemente em lobos inferiores.
- Biópsia pulmonar: pode ser útil para descartar outras etiologias.

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Naidoo et al. J Clin Oncol 2017 Mar;35(7):709

Toxicidade endócrina

- 10% dos pacientes
- Distinção entre insuficiência endócrina primária x secundária

- Hipotireoidismo
- Hipertireoidismo
- Insuficiência adrenal
- Hipofisite
- Diabetes

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Outras toxicidades

Toxicidade músculo-esquelética

- Sintomas: em até 40% dos pacientes
- Frequência: anti-PD-1/PD-L1 > anti-CTLA-4 e combinação > monoterapia
- Mais comuns:
  - Artrite inflamatória;
  - Miosite;
  - Síndrome polimialgia reumática-like.

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Outras toxicidades

Toxicidade renal

- IRA: incomum com iCPI
  - Monoterapia: 1-2% qualquer grau; < 1% G3/4
  - Nivolumabe + Ipilimumabe: 4,5% qualquer grau; 1,6% G3/4
- Biópsia renal: nefrite tubulointersticial aguda; microangiopatia trombótica.

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Outras toxicidades

Toxicidade em sistema nervoso

- Incidência:
  - Anti-CTLA-4: 3,8%
  - Anti-PD-1: 6,1%
  - Combinação: até 12%
  - G3/4: < 1%
- Mais comuns: cefaléia e neuropatia periférica sensorial.

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Outras toxicidades

Toxicidade em sistema nervoso

- Miastenia grave
- Síndrome de Guillain-Barré
- Neuropatia periférica
- Neuropatia autonômica
- Meningite asséptica
- Encefalite
- Mielite transversa

- Exclusão de progressão de doença em SNC, convulsão, infecção e distúrbios metabólicos.
- Avaliação inicial: RM crânio e/ou coluna + LCR.

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Outras toxicidades

Toxicidade hematológica

- Anemia hemolítica auto-immune
- Púrpura trombocitopênica trombótica adquirida
- Síndrome hemolítico-urêmica
- Anemia aplásica
- Linfopenia
- Trombocitopenia imune
- Hemofilia adquirida

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

Outras toxicidades

Toxicidade cardiovascular

- < 0,1% dos pacientes
- Miocardite, pericardite, arritmia, insuficiência cardíaca e vasculite
  - Suspensão do iCPI: recomendada em todos os graus
  - Infliximabe: associado a insuficiência cardíaca (IC) – contra-indicado em IC moderada-grave
- Tromboembolismo venoso

Toxicidade ocular

- Uveíte/irite
- Episclerite
- Blefarite

Brahmer *et al.* J Clin Oncol 2018 Feb 14 [Epub ahead of print]

NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF ROUTINE MONITORING

Baseline Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/ Symptoms
Clinical: • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency)	Clinical exam at each visit with AE symptom assessment	Follow-up testing based on findings, symptoms
Imaging: • CT imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork: • CBC with differential • Comprehensive metabolic panel • Infectious disease screening as indicated	Repeat every 2–3 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated.
Thyroid • Thyroid-stimulating hormone (TSH), free thyroxine (T4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 if abnormal thyroid function suspected. TPO antibodies if TSH is high, TRAbs if TSH is low.
Adrenal/Pituitary • Adrenal: Morning adrenocorticotropic hormone (ACTH) and cortisol • Pituitary: TSH, free T4, and total T3	Every 2–3 weeks during immunotherapy, then follow-up every 6–12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone
Pulmonary • Oxygen saturation (resting and with ambulation) • Pulmonary function tests (PFTs)	Repeat oxygen saturation tests based on symptoms	Chest CT to evaluate for pneumonitis, biopsy if needed to exclude other causes
Cardiovascular • ECG and total CK • Cardiac biomarkers (ie, troponin I or T) if risk factors present	Consider periodic testing for those with abnormal baseline or symptoms	Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)
Pancreatic • Baseline amylase/lipase	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal imaging for suspected pancreatitis
Musculoskeletal • Joint examination/functional assessment as needed for patients with pre–existing disease	No routine monitoring needed if asymptomatic	N/A

Abordagem geral

Table 2 General guidance for corticosteroid management of immune-related adverse events

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

Puzanov et al. J Immunother Cancer 2017 Nov 21;5(1):95

Rechallenge

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Skin	• Maculopapular rash and/or pruritus: consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/ localized with only topical intervention indicated). • Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN.
GI	• PD-1/PD-L1 agents: After grade 2–3 colitis, consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. In rare circumstances in which the patient cannot completely taper off steroids, immunotherapy may be resumed while patient is still on ≤10 mg steroid daily. • CTLA-4 agents: permanently discontinue if irAE is grade 2 or above.
Liver	• Transaminitis without elevated bilirubin: following a grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg daily. • Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 3–4) hepatitis.
Pancreas	• Grade 2 pancreatitis: consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase. Consider consultation with relevant pancreas specialist regarding resumption. • Permanent discontinuation is warranted for severe (grade 3–4) pancreatitis.

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Rechallenge

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Endocrine	• Thyroid: no discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs. • Primary adrenal insufficiency: after appropriate replacement endocrine therapy is instituted, immunotherapy may continue. • Hypophysitis manifested by deficiency of TSH/ACTH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction): hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms are controlled on <10-mg daily steroid dose. • T1DM with DKA: consider resuming once DKA has been corrected and glucose level has stabilized.
Lung	• Progressive grade 1 pneumonitis requiring a hold: consider resuming upon radiographic evidence of improvement. • Grade 2: resume once pneumonitis has resolved to ≤ grade 1. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) pneumonitis.
Kidney	• Grade 1–2 renal irAE: hold immunotherapy per guidelines; upon resolution to ≤ grade 1, consider resuming concomitant with steroid if creatinine is stable. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) proteinuria.
Eye	• Grade 2 irAE: hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology upon resolution to ≤ grade 1. • Permanent discontinuation of immunotherapy is warranted in the setting of severe (grade 3–4) uveitis or episcleritis.
Nervous System	• Myasthenia gravis: consider resuming immunotherapy after moderate (grade 2) AE based on steroid responsiveness. Permanently discontinue immunotherapy after grade 3–4 AE. • GBS: permanently discontinue immunotherapy for any grade GBS. • Peripheral neuropathy: following hold for grade 1–2 AE, consider resuming if symptoms resolve to ≤ grade 1 or if patient has well-controlled isolated painful sensory neuropathy. • Aseptic meningitis: consider resuming following mild to moderate AE if symptoms resolve to grade 0. • Encephalitis: permanent discontinuation is warranted in the setting of moderate to severe encephalitis (grade 2–4). • Transverse myelitis: discontinuation of immunotherapy following any-grade transverse myelitis.
Cardiovascular	• Grade 1 myocarditis: consider resuming upon resolution of symptoms. • Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.
Musculoskeletal	• Inflammatory arthritis (moderate to severe irAE requiring hold): resume upon stabilization or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis that significantly impairs ADLs and quality of life.

Mensagens finais

irAE:

- Alto grau de suspeição
  - Detecção precoce -> manejo adequado
- Corticóide: peça principal do tratamento
- Educação do paciente e de sua família
- Acompanhamento multidisciplinar

Obrigada!