Toxicidade dos Inibidores de Checkpoint Imunes

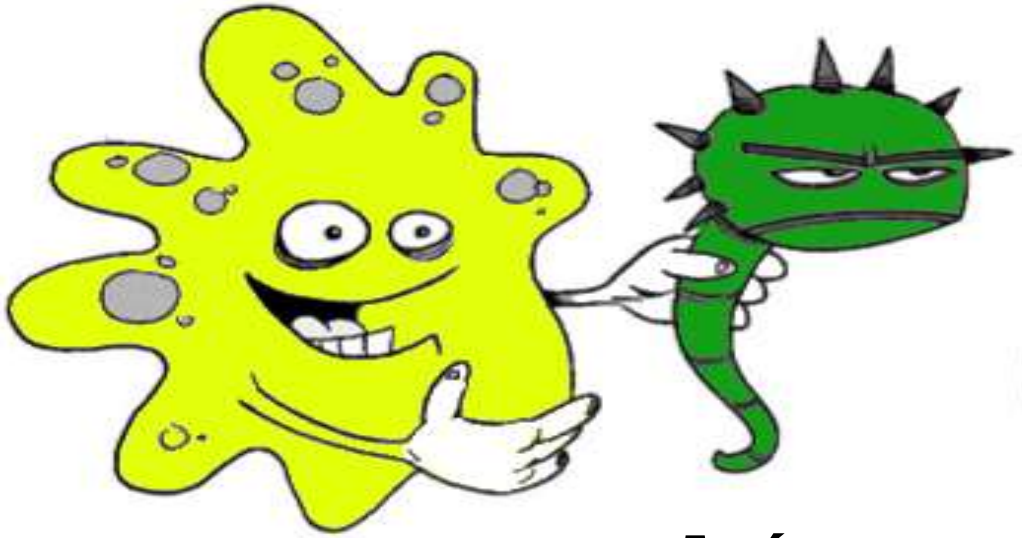
Rafael Aron Schmerling

A Beneficência
Portuguesa
de São Paulo

Potenciais Conflitos de Interesse

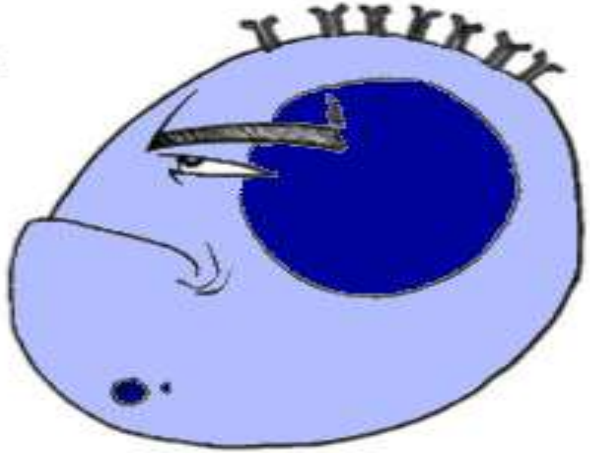
Bristol-Myers Squibb	Consultoria, honorários, pesquisa, patrocínio
Eurofarma	Consultoria
Merck Sharp & Dome	Consultoria, honorários, patrocínio
Novartis	Consultoria, pesquisa
Pierre-Fabre/Array	Consultoria, honorários, pesquisa
PROVECTUS	Consultoria, honorários
ROCHE	Consultoria, honorários, pesquisa
Sanofi	Honorários
UNITED Medical	Honorários

Checkpoints Imunológicos



Célula Apresentadora de Antígeno

Antígeno



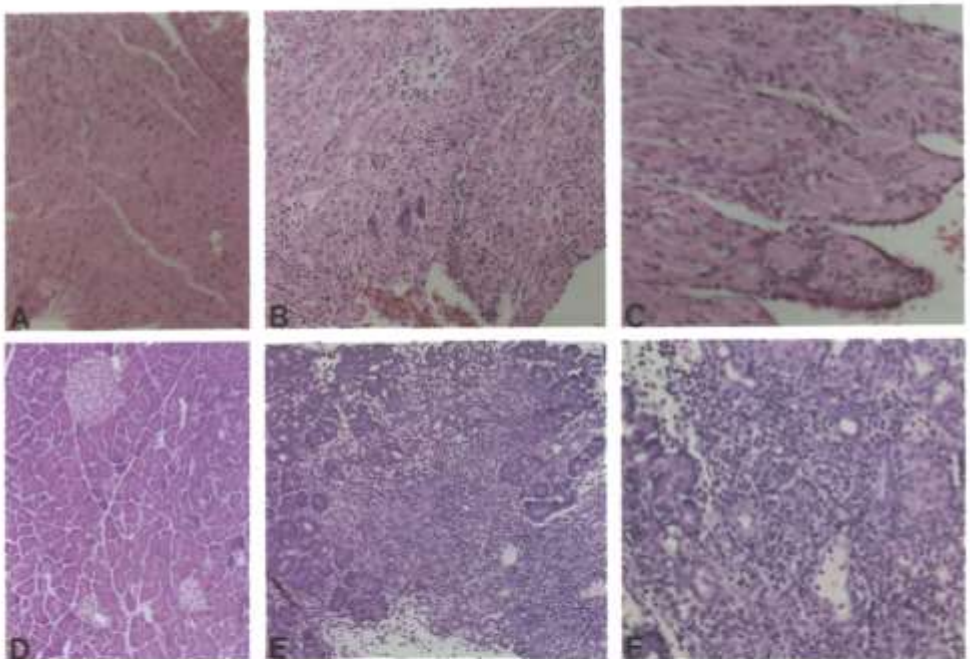
Linfócito T

Camundongo deficiente de CTLA-4

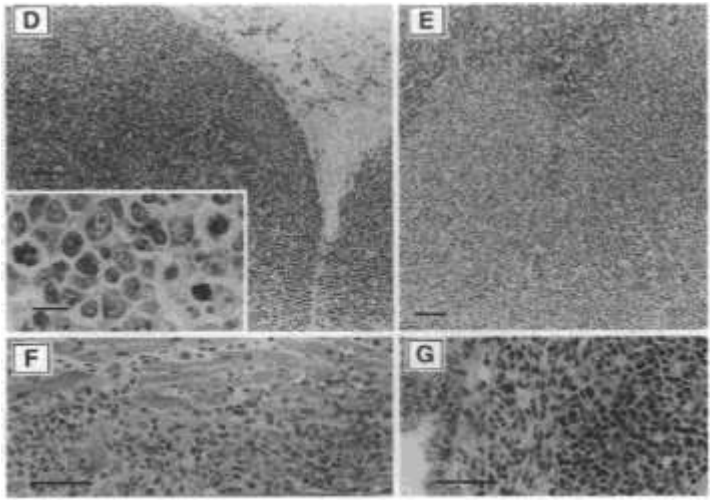
wt 50x -/- 50x -/- 100x

miocardio

pâncreas



Timo Baço

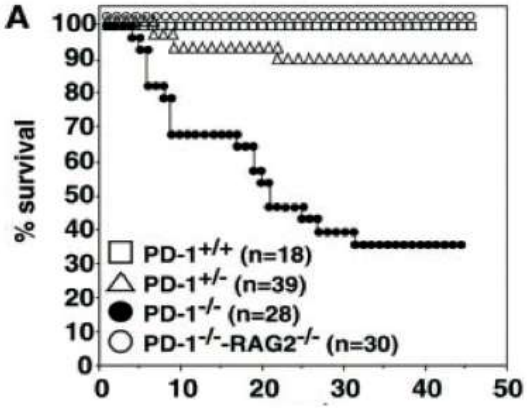


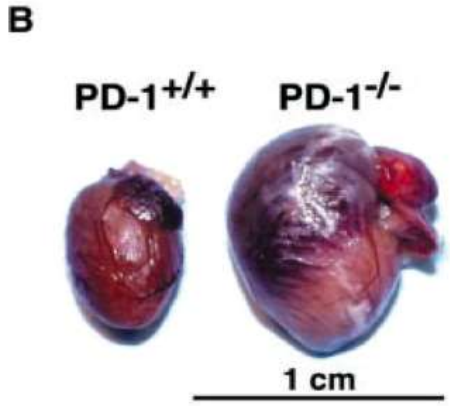
Miocardio Pulmão

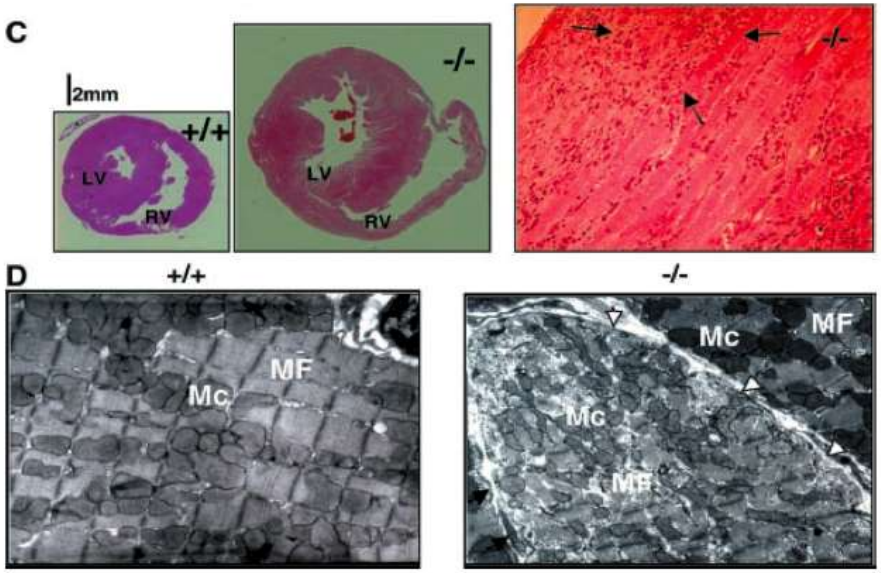
Waterhouse et al, Science 1995

Tivoli et al, *Immunity 1995*

Camundongo deficiente de PD1







Nishimura et al, Science 2001; 291:319-22

Ipilimumabe – Toxicidade

	Ipilimumabe 10mg/kg			Ipilimumabe 3mg/kg		
	G1-2	G3	G4	G1-2	G3	G4
Qualquer evento	45%	27%	7%	45%	16%	2%
Rash	25%	1%	0	13%	1%	0
Prurido	22%	1%	0	22%	1%	0
Diarreia	27%	10%	<1%	17%	6%	0
Colite	4%	5%	<1%	3%	2%	0
Fadiga	10%	1%	0	8%	1%	0
AST/ALT	4/4%	2/2%	1/1%	1/1%	<1/<1%	<1%/0
Hipofisite	4%	2%	<1%	1%	1%	1%

Ascierto et al, *Lancet Oncol 2017*

Ipilimumabe – Toxicidade

	Ipilimumabe 10mg/kg			Ipilimumabe 3mg/kg		
	G1-2	G3	G4	G1-2	G3	G4
Qualquer evento	45%	27%	7%	45%	16%	2%
Rash	25%	1%	0	13%	1%	0
Prurido	22%	1%	0	22%	1%	0
Diarreia	27%	10%	<1%	17%	6%	0
Colite	4%	5%	<1%	3%	2%	0
Fadiga	10%	1%	0	8%	1%	0
AST/ALT	4/4%	2/2%	1/1%	1/1%	<1/<1%	<1%/0
Hipofisite	4%	2%	<1%	1%	1%	1%

Ascierto et al, *Lancet Oncol 2017*

anti-PD1 – Toxicidade em Melanoma

	Nivolumabe (CM-67)		Pembrolizumabe (KN006)	
	Total	G3-5	Total	G3-4
Qualquer evento	86%	21%	77%	17%
Fadiga	36%	1%	23%	1%
Prurido	21%	<1%	20%	0
Diarreia	21%	3%	17%	1%
Rash	23%	<1%	17%	0
Hipotireoidismo	11%	0	8%	0
Artralgia	10%	<1%	14%	0
AST/ALT	4%/4%	1%/1%	2%	2%
Pneumonite	2%	<1%	2%	<1%
Vitiligo	9%	<1%	11%	0

Wolchok et at *N Engl J Med 2017*; Robert et al *N Engl J Med 2015*; Schachter et al, *Lancet 2017*

anti-PD1 – Toxicidade em Pulmão

	Nivolumabe (CM-57)		Pembrolizumabe (KN001,024)	
	Total	G3-5	Total	G3-5
Qualquer evento	71%	18%	74%	27%
Fadiga	19-21%	1%	10-19%	1%
Prurido	11%	0	11%	0
Diarreia	8-14%	<1%	8-14%	1-4%
Rash	10%	1%	10%	<1%
Hipotireoidismo	7%	<1%	7-14%	<1%
Pirexia	4%	<1%	4-10%	<1%
AST/ALT	3%	<1%	3%/2%	<1%
Pneumonite	4%	2%	4-6%	2-3%
Vitiligo	NR	NR	NR	NR

Carbone et al *N Engl J Med 2017; Borghaei N Engl J Med 2016;* Garon et at *N Engl J Med 2015*; Reck et al *N Engl J Med 2016*

anti-PD1 – Toxicidade em Rim e Bexiga

	Nivolumabe (CM-25 - RIM)		Pembrolizumabe (KN045, Bexiga)	
	Total	G3-5	Total	G3-5
Qualquer evento	79%	19%	61%	15%
Fadiga	33%	2%	14%	1%
Prurido	14%	0	20%	0
Diarreia	12%	1%	9%	1%
Rash	10%	<1%	NR	NR
Hiporexia	12%	0	NR	NR
Edema	4%	0	NR	NR
Anemia	8%	2%	4%	1%
Pneumonite	4%	1%	4%	2%
Hipotireoidismo	NR	NR	6%	0

Motzer et al *N Engl J Med 2015* ; Bellmunt et al *N Engl J Med 2017*

anti-PDL1 – Toxicidade

	Atezolizumab (urotelial)		Durvalumab (Ph1)		Avelumab	
	Total	G3-5	Total	G3*	Total	G3-4
Qualquer evento	69%	16%	64%	5%		
Fadiga	30%	2%	13%	0	24%	0
Prurido	10%	<1%				
Diarreia	8%	<1%	10%	0	9%	0
Rash	7%	<1%			7%	0
Hiporexia	12%	<1%	9%	0	6%	0
AST/ALT	3%	1%			1%	1%
Anemia	3%	<1%				
Pneumonite	2%	1%				
Hipotireoidismo					3%	0

Ferhenbarcher et al. *Lancet 2016;* Massardet al. *J Clin Oncol 2016;* Kaufman *et al. Lancet Oncol*, 2016

anti-PD1 vs anti-PD-L1

Metanálise NSCLC

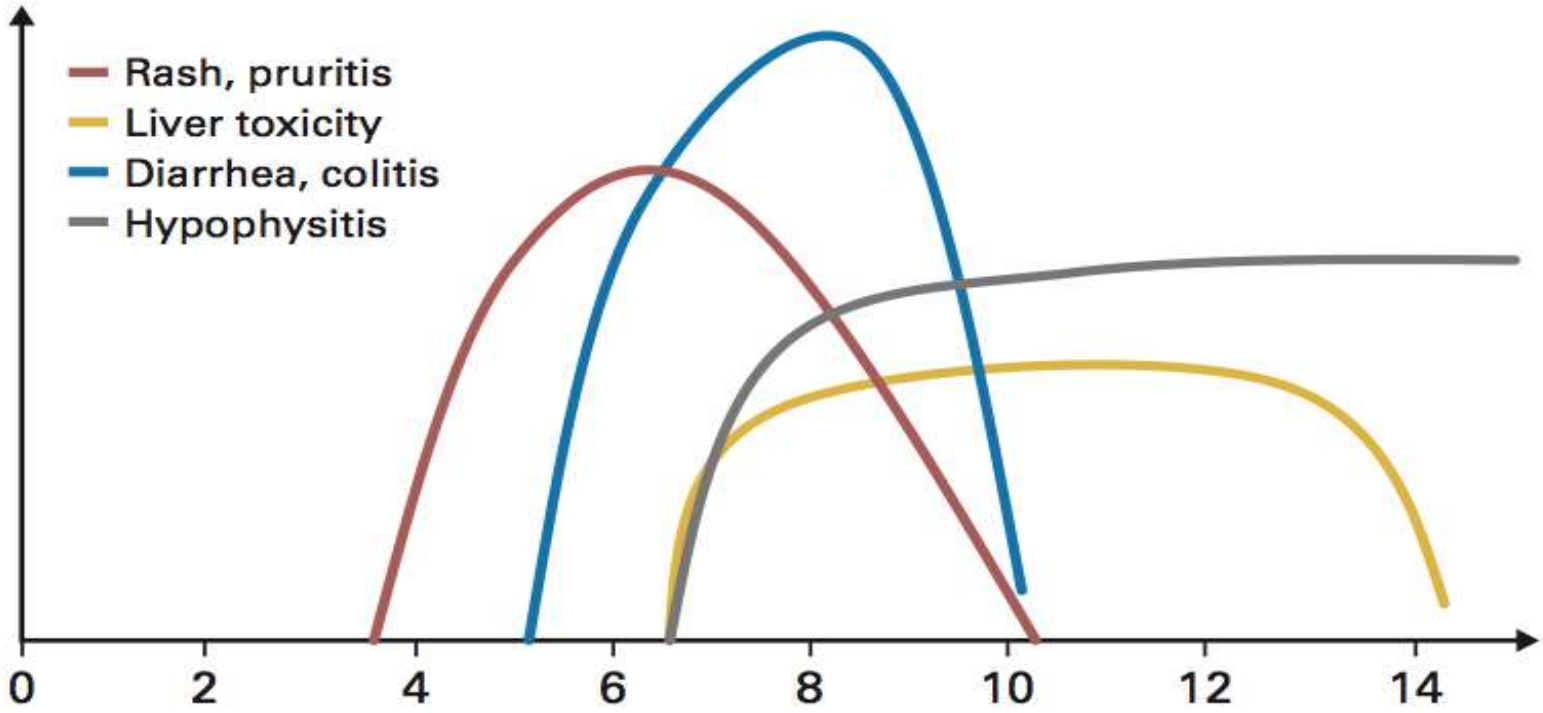
Study	Drug
Gettinger 2015[17]	Nivolumab at a dose of 1, 3, or 10 mg/kg
Rizvi 2015[18]	Nivolumab at dose of 3 mg/kg
Brahmer 2015[8]	Nivolumab at a dose of 3 mg/kg
Borghaei 2015[9]	Nivolumab at dose of 3 mg/kg
Garon 2015[16]	Pembrolizumab at a dose of 2 or 10 mg/kg
Sakai 2015[19]	Nivolumab at dose of 3 mg/kg
Bauer 2015[20]	Nivolumab at dose of 3 mg/kg
Herbst 2016[10]	Pembrolizumab at dose of 2 mg/kg
Herbst 2016[10]	Pembrolizumab at dose of 10 mg/kg
Goldberg 2016[21]	Pembrolizumab at dose of 10 mg/kg
Gettinger 2016[22]	Nivolumab at dose of 3 mg/kg
Socinski 2016[23]	Nivolumab at dose of 3 mg/kg
Reck 2016[12]	Nivolumab at dose of 3 mg/kg
Brahmer 2014[24]	Durvalumab
Rizvi 2015[25]	Durvalumab
Spigel 2013[26]	Atezolizumab
Horn 2015[27]	Atezolizumab
Spigel 2015[28]	Atezolizumab
Besse 2015[29]	Atezolizumab
Fehrenbacher 2016[11]	Atezolizumab
Verschraegen 2016[30]	Avelumab
Gulley 2015[31]	Avelumab
Antonia 2016[32]	Durvalumab
Barlesi 2016[33]	Atezolizumab

Drug	AE Rate, %
Nivolumab	62
Pembrolizumab	67.5
Atezolizumab	65
Durvalumab	75
Avelumab	67

	PD-1 Inhibitors N = 3284	PD-L1 Inhibitors N = 2460	*P*
Overall AEs, %	64	66	.8
Grade 3-5 AEs, %	13	21	.15
Fatigue of any grade, %	19	21	.4
Diarrhea of any grade, %	9	12	.4
Rash of any grade, %	9	7	.8
IRAEs, %	16	11	.07
Grade 3-5 IRAEs, %	3	5	.4
Hypothyroidism of any grade, %	6.7	4.2	.07
Pneumonitis of any grade, %	4	2	.01
Colitis of any grade, %	1.7	1	.4
Overall response rate, %	19	18.6	.17

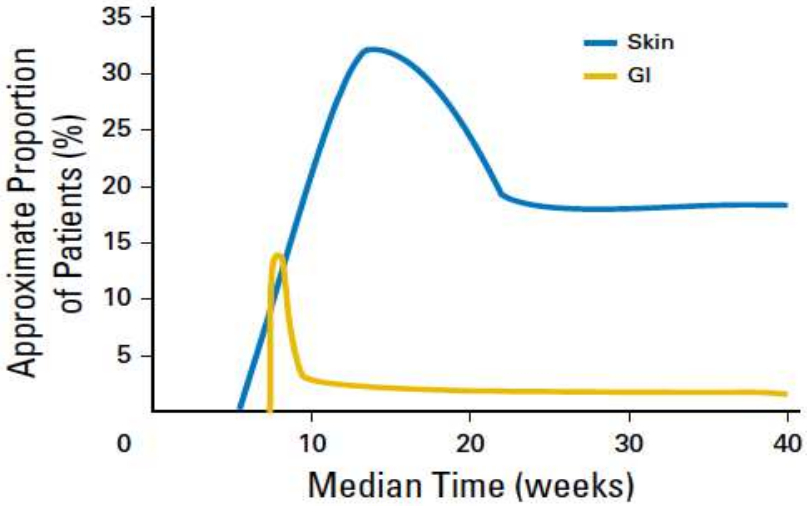
Pilai et al. *Cancer 2017*

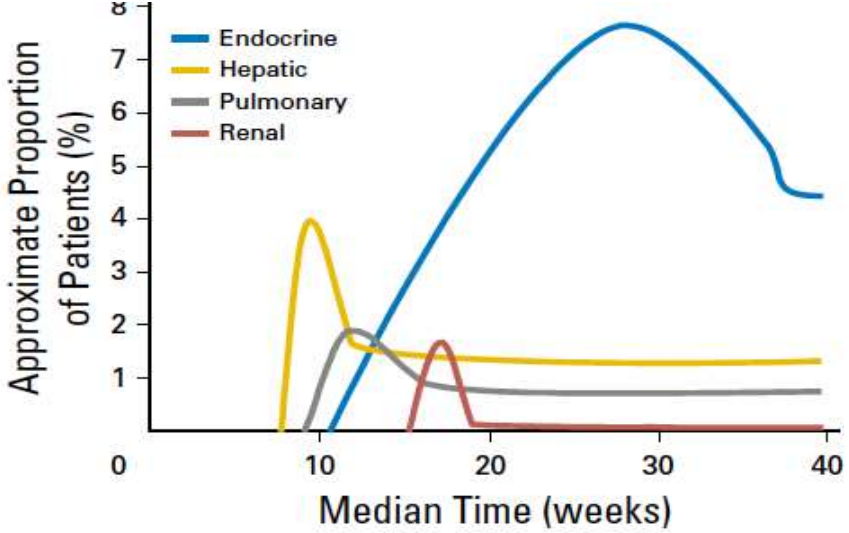
Cinética dos Efeitos Adversos Imunes



Weber et al, *J Clin Oncol 30; 2691, 2012*

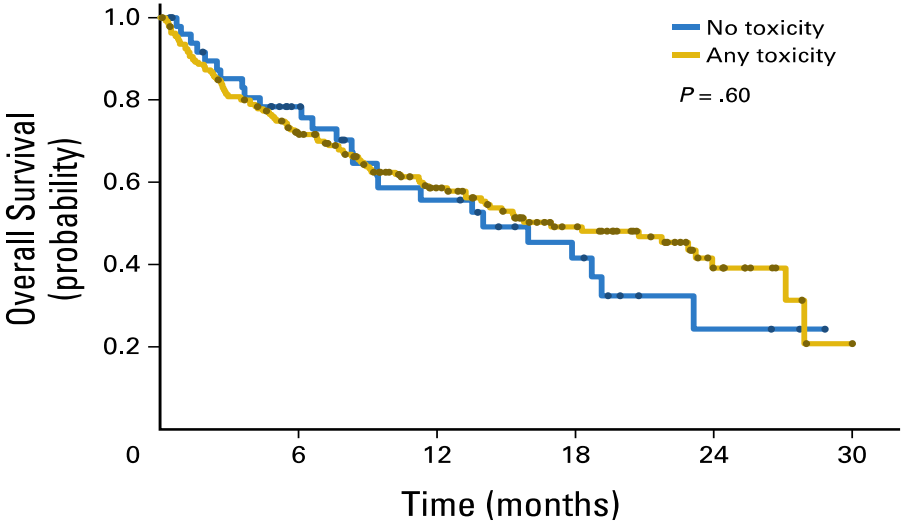
Cinética dos Efeitos Adversos Imunes



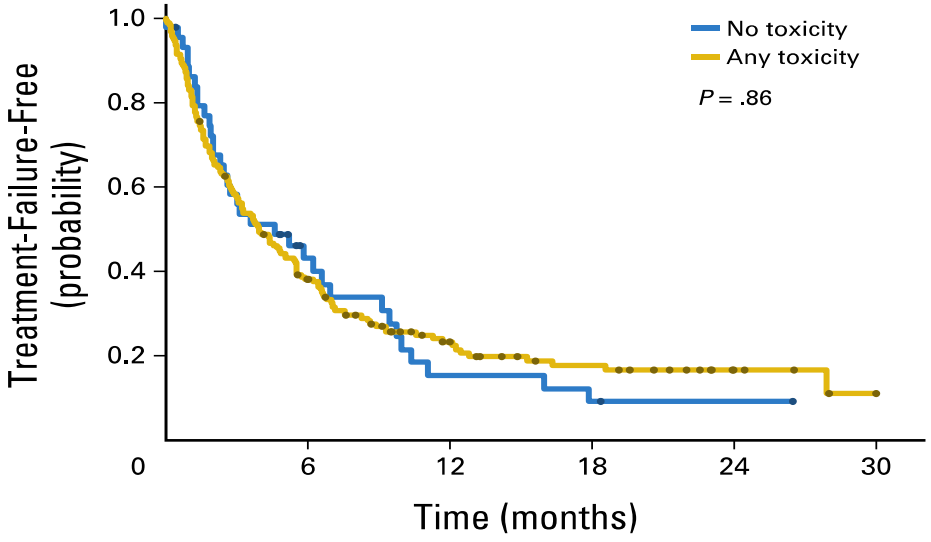


Weber J et al. J Clin Oncol 2017; 35:785-92

Toxicidade e Eficácia



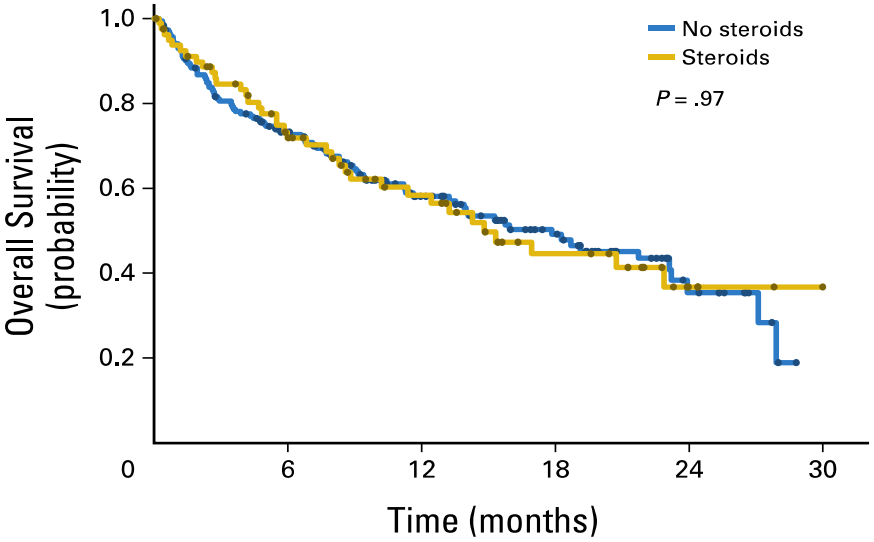
No. at risk					
No toxicity	49	31	20	12	4
Any toxicity	213	136	82	47	15



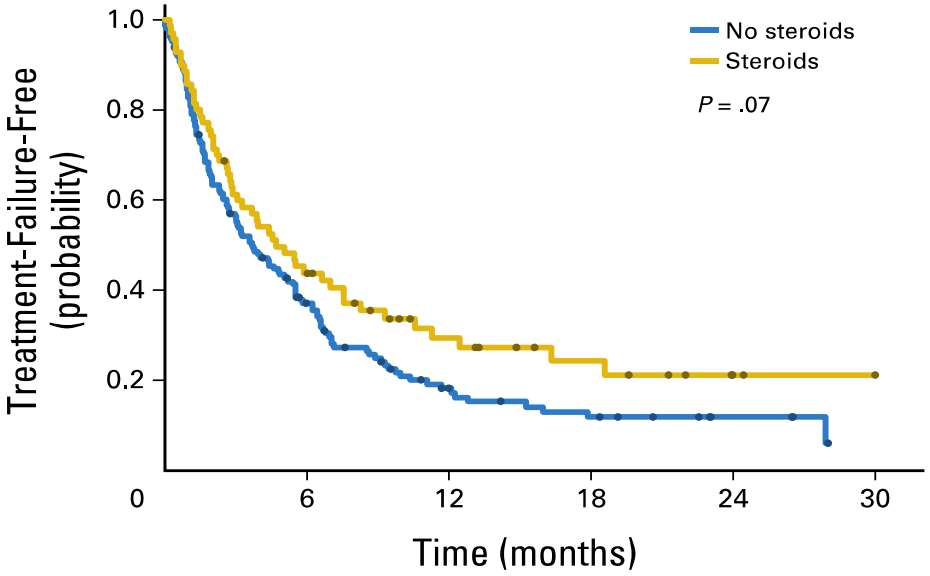
No. at risk						
No toxicity	45	15	6	4	2	1
Any toxicity	188	66	28	17	6	1

Horvat et al. J Clin Oncol 33:3193, 2015

Toxicidade e Eficácia



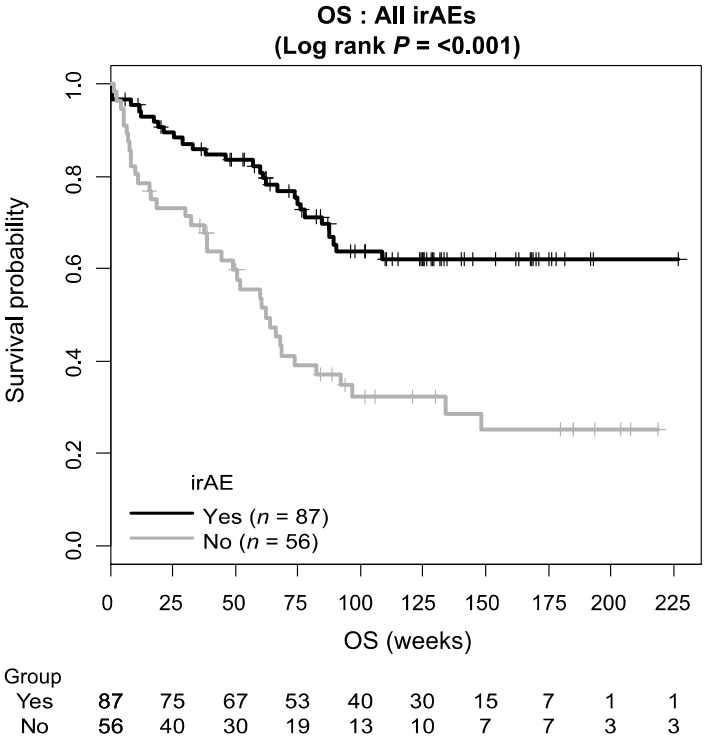
No. at risk						
No steroids	182	117	71	42	13	1
Steroids	80	50	31	17	6	1

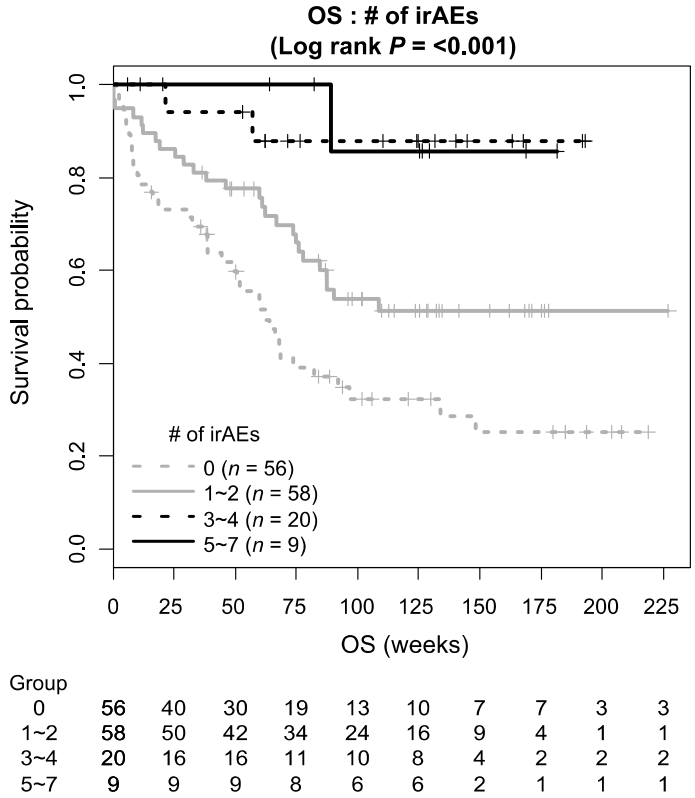


No. at risk						
No steroids	163	51	19	12	5	1
Steroids	70	30	15	9	3	1

Horvat et al. J Clin Oncol 33:3193, 2015

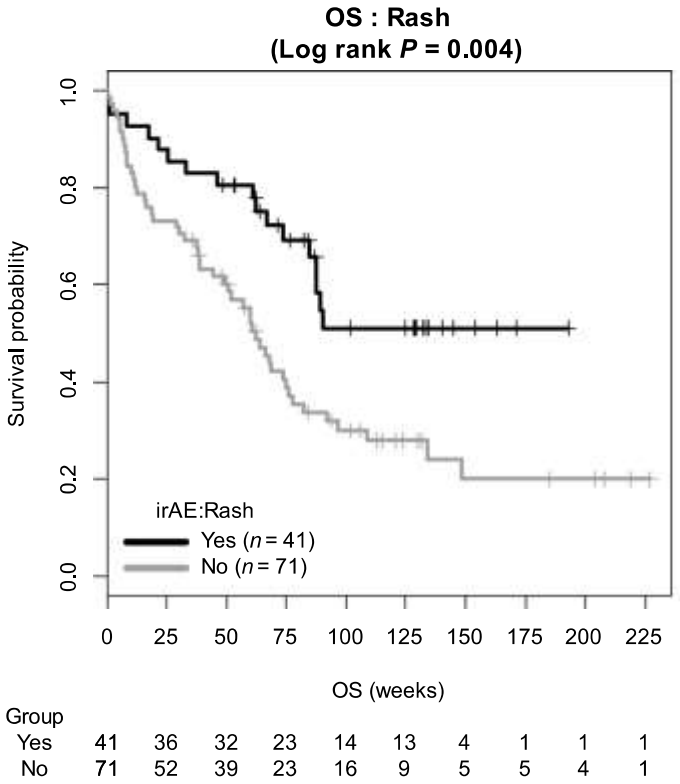
Toxicidade e Eficácia – anti PD1

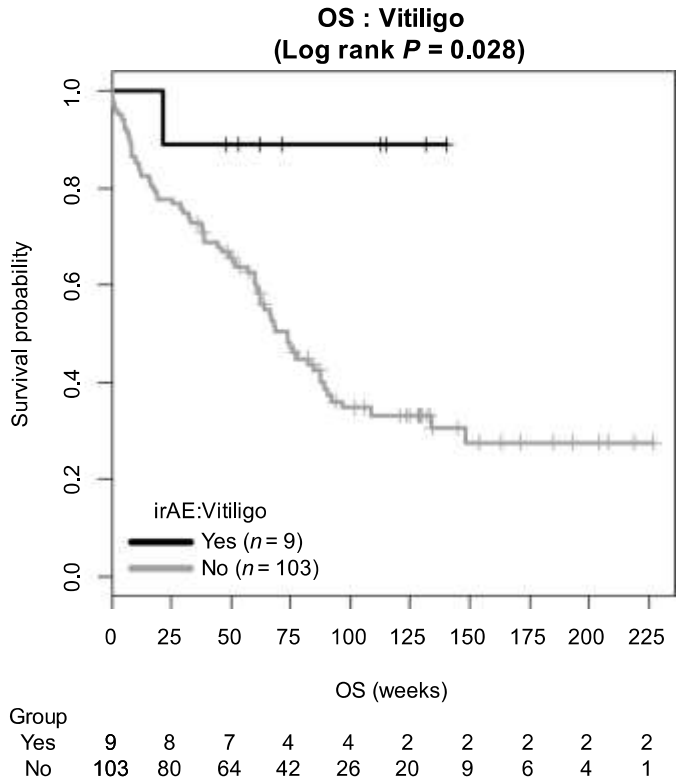




Freeman-Keller M et al. Clin Cancer Res 2015; 22:886-94

Toxicidade e Eficácia - Vitiligo

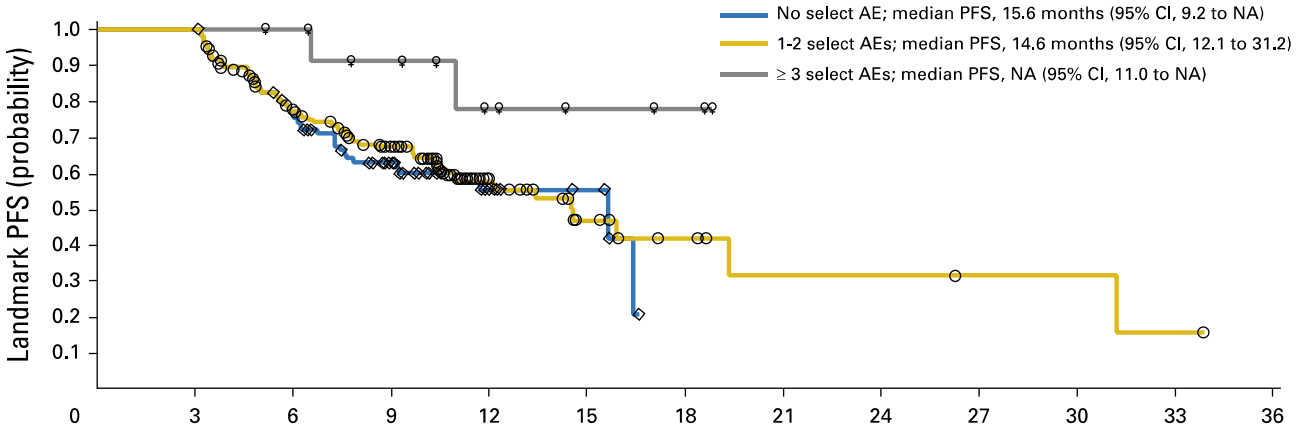




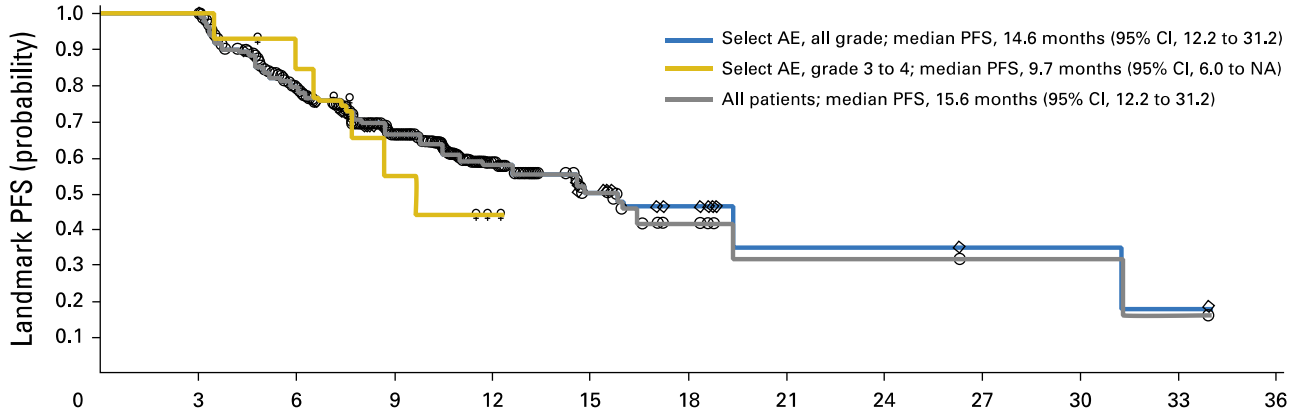
Freeman-Keller M et al. Clin Cancer Res 2015; 22:886-94

Toxicidade e Eficácia – anti PD1

Número de eventos



Gravidade dos eventos



Weber J et al. J Clin Oncol 2017; 35:785-92

Toxicidade e Eficácia

		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	

Weber J et al. J Clin Oncol 2017; 35:785-92

Ipilimumabe e Autoimunidade prévia

Patient No.	Baseline Condition	Autoimmune Exacerbation	Treatment	Immune-Related Adverse Event	Treatment	Outcome Notes
2	Sarcoidosis	…	…	Glaucoma	Ocular steroids	
3	RA	Joint pain	As for hypophysitis	Hypophysitis	Prednisone 1 mg/kg tapered over 6 wk; now receiving 7.5 mg	Durable CR
4	RA	…	…	Thyroiditis	Prednisone 1 mg/kg tapered over 2 wk	
5	Psoriasis	Worsening plaques	As for colitis	Colitis	Methylprednisolone 2 mg/kg tapered over 6 wk	After 1 dose
6	Psoriasis, Graves disease	…	…	Hypophysitis	Prednisone 30 mg ×1 wk, transition to hydrocortisone over 5 d	PR
8	RA, polymyalgia rheumatica	Joint pain, myalgias	Prednisone 30 mg/d tapered over 1 mo	…	…	After 3 d
9	RA	Joint pain	Prednisone 15 mg/d down to 10 mg	…	…	After 7 mo
11	Transverse myelitis	…	…	Colitis	Prednisone 1 mg/kg tapered over 8 wk	
12	Crohn disease	…	…	Colitis	Methylprednisolone 1 mg/kg tapered over 8 wk	After 1 dose
14	Ulcerative colitis	Diarrhea, disease flare	Infliximab, dexamethasone 2 mg daily[a]	…	…	PR
15	Inflammatory arthritis[b]	Joint pain	As for colitis	Colitis	Prednisone 1 mg/kg tapered over 4 wk, infliximab	…
20	Psoriasis	…	…	Hypophysitis	Prednisone 50 mg ×1 dose, then 5 mg daily	…
23	Sarcoidosis	Hypercalcemia, renal insufficiency	Prednisone 25 mg/d, tapered to 20 mg after 4 wk	…	…	Ongoing SD
24	RA	Joint pain	Prednisone 10 mg/d, now receiving 8 mg/d	…	…	Ongoing PR
28	Psoriasis	…	…	Presumed colitis grade 5	Methylprednisolone 1 mg/kg	Patient died

Johnson et al. JAMA Oncol 2:234-40, 2016

Anti PD-1 e Auto-Imunidade Prévia

FLARE em Autoimunidade prévia (n:52)		
Reumático	52%	AR, PM, SCL, Sjg, Art.Psor
Dermatológico	38%	Psoríase
Gastro-Intestinal	0	
Neurológico	0	
Endócrino	25%	Graves
Respiratório	0	
Hematológico	100%	PTI

FLARE conforme status	
Ativo	60%
Inativo	30%
Com Imunossupressor	50%
Sem Imunossupressor	10%

Toxicidade Habitual	
Não	71%
Sim	29%
G1-2	20%
G3	10%

FLARE conforme Medicação	
Corticoesteróides	21%
Outros Imunossupressores	12%
Corticóides + outros	4%
Ig IV	2%

Menzies et al. *Ann Oncol*, 2016

Anti PD-1 e Toxicidade prévia a Ipilimumab

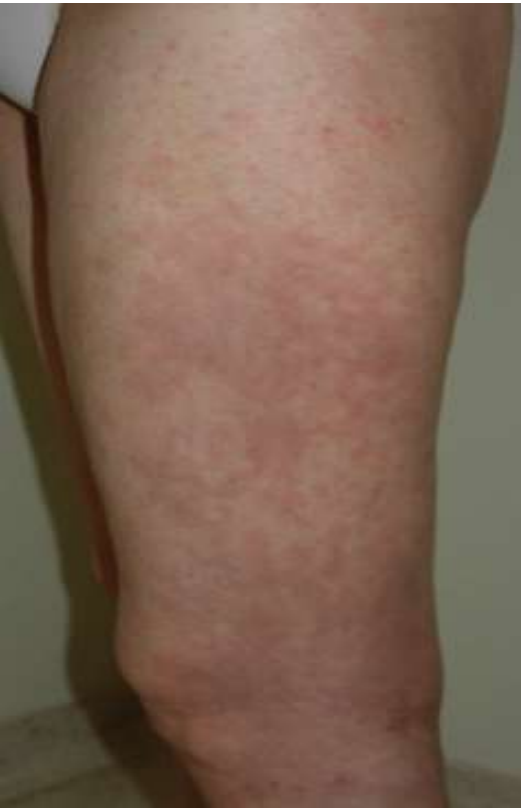
Recorrência (N:67)	
Não	97%
Sim	3%

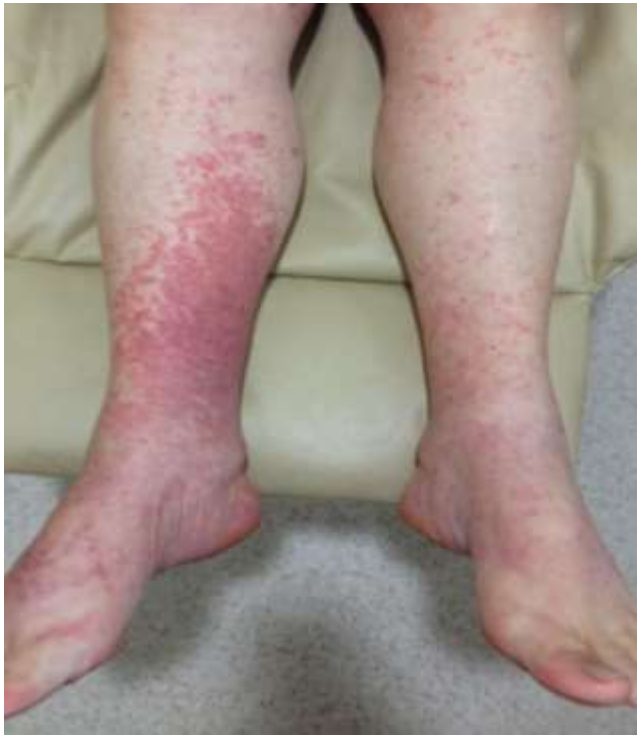
Tratamento Necessário	
Sintomáticos	9%
Corticoesteróide oral	15%
Outros Imunossupressores	1%
Corticoesteróide IV	6%
Corticoesteróide + Outros	3%

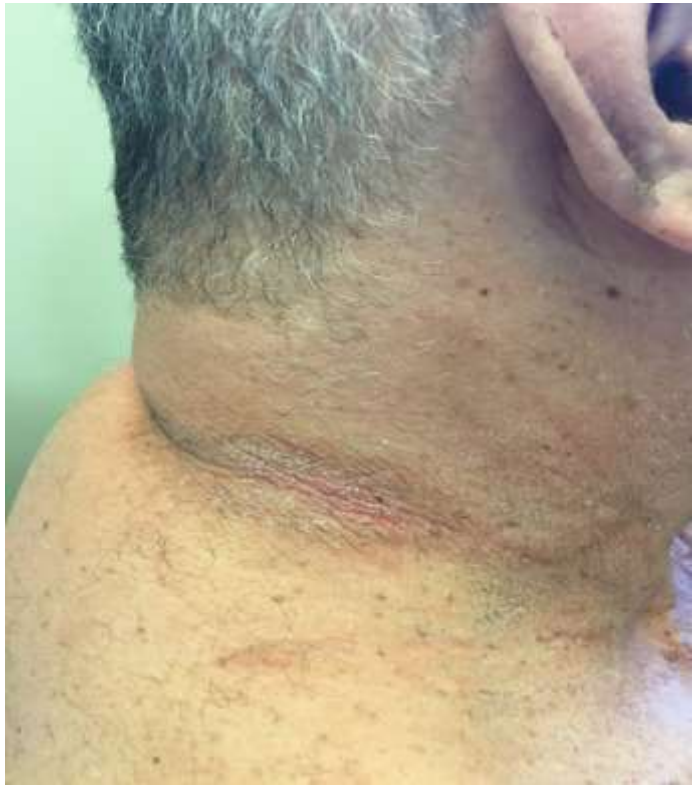
Outros EA	
Não	66%
Sim	34%
G1-2	13%
G3	18%
G4	3%

Menzies et al. *Ann Oncol*, 2016

Toxicidade Cutânea







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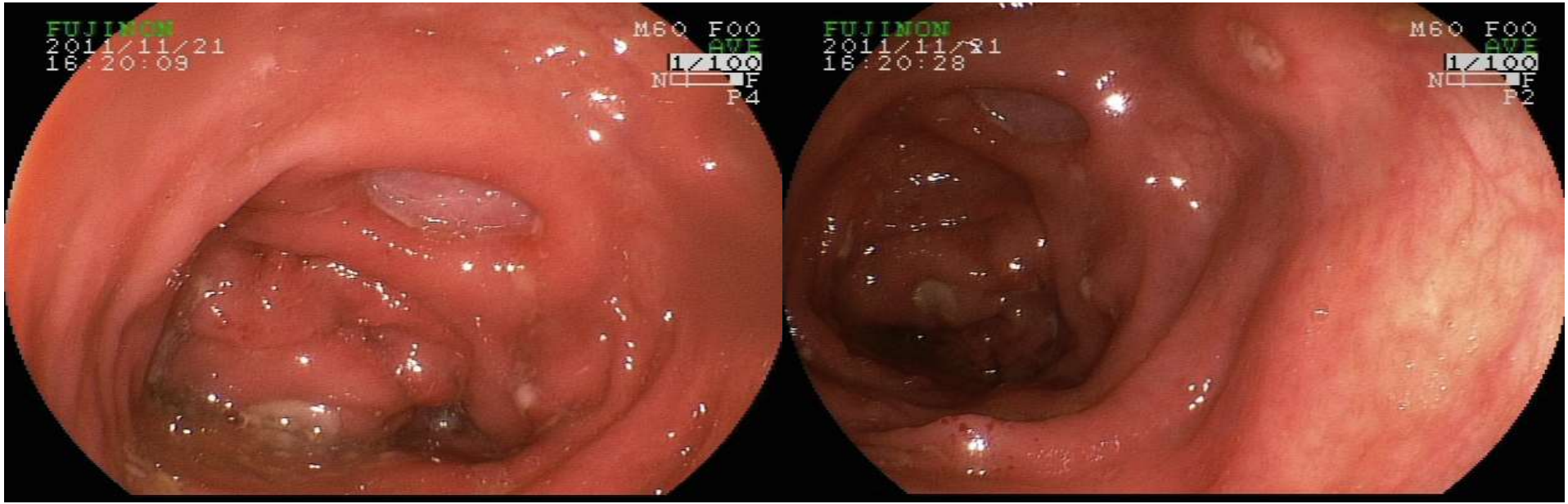
Toxicidade Gastrointestinal



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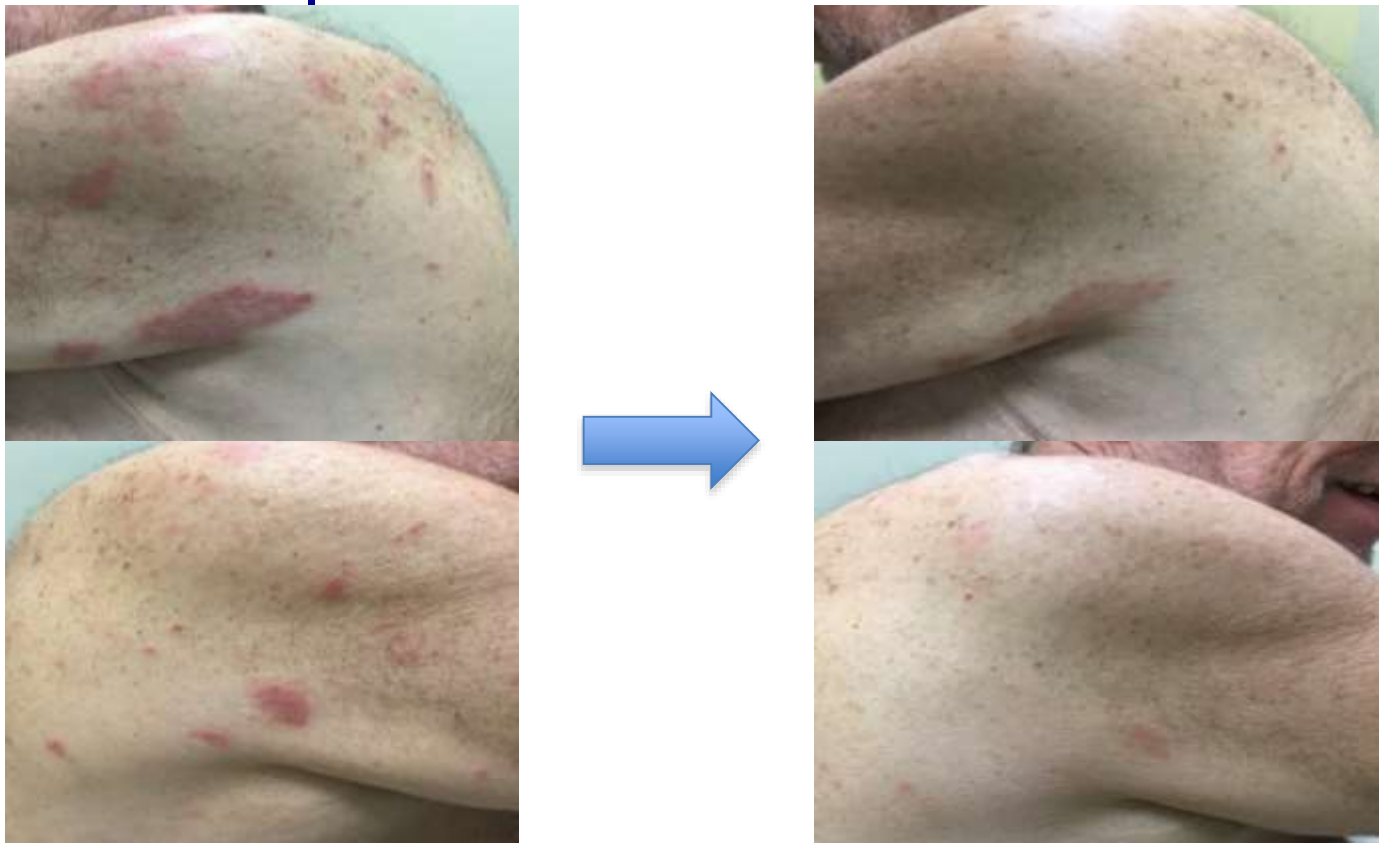
Dermatite com Nivolumab

tratado com prednisona



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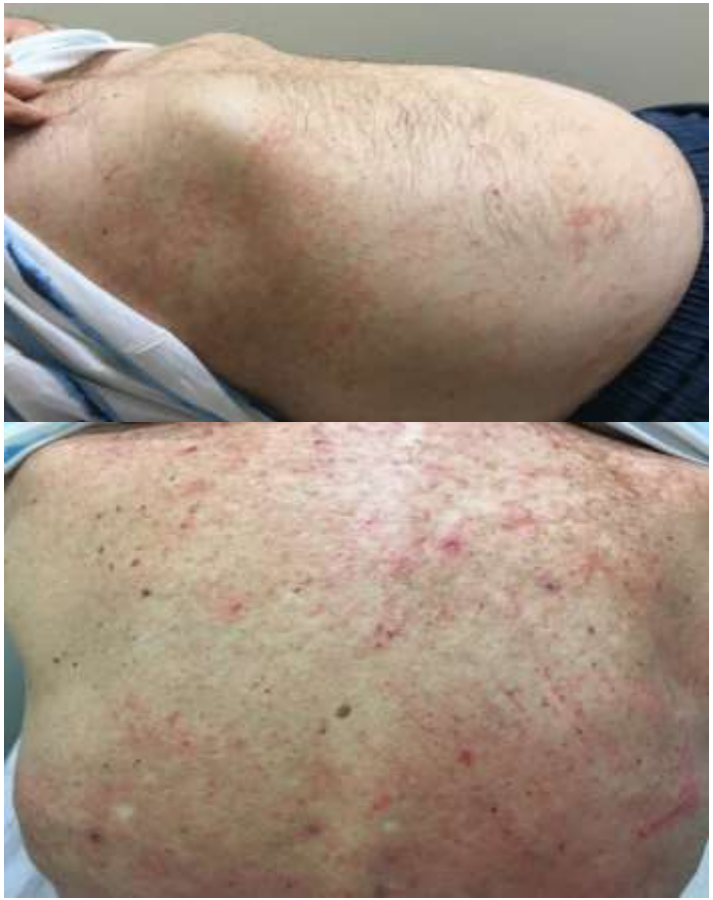
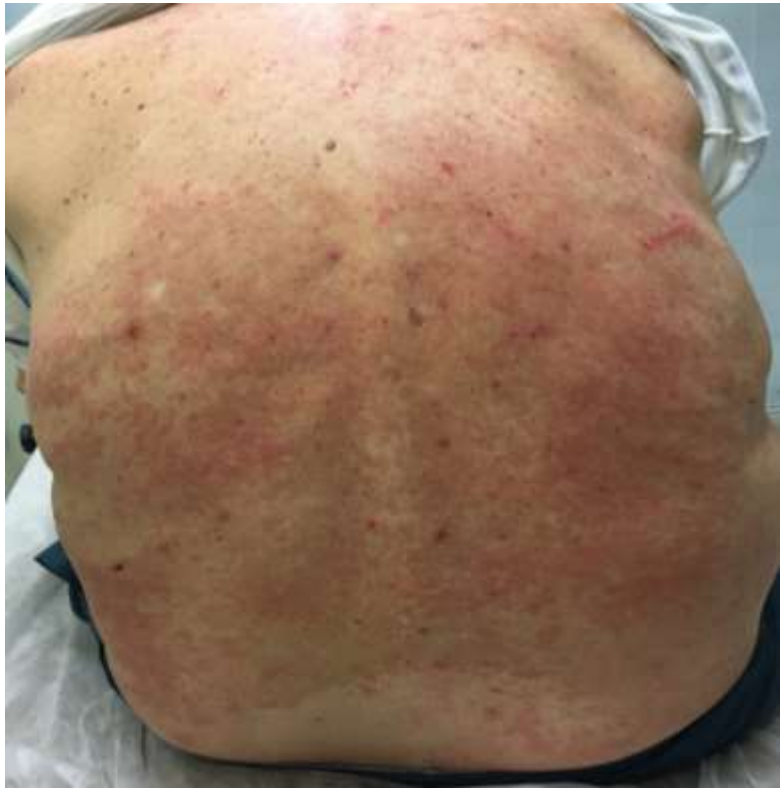
Dermatite com Pembrolizumab





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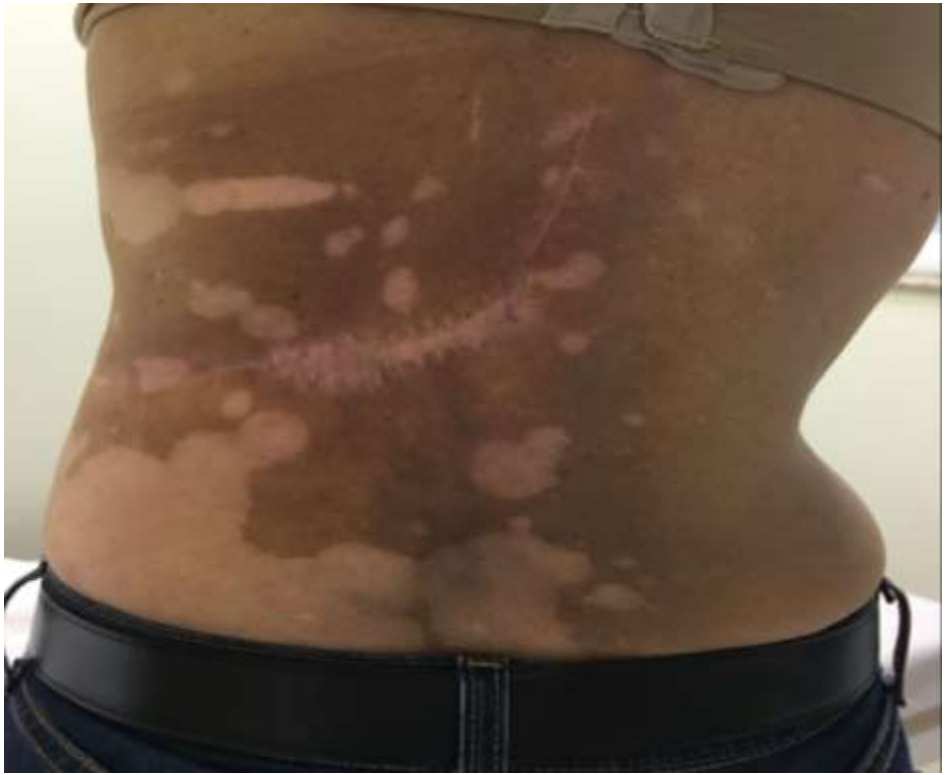
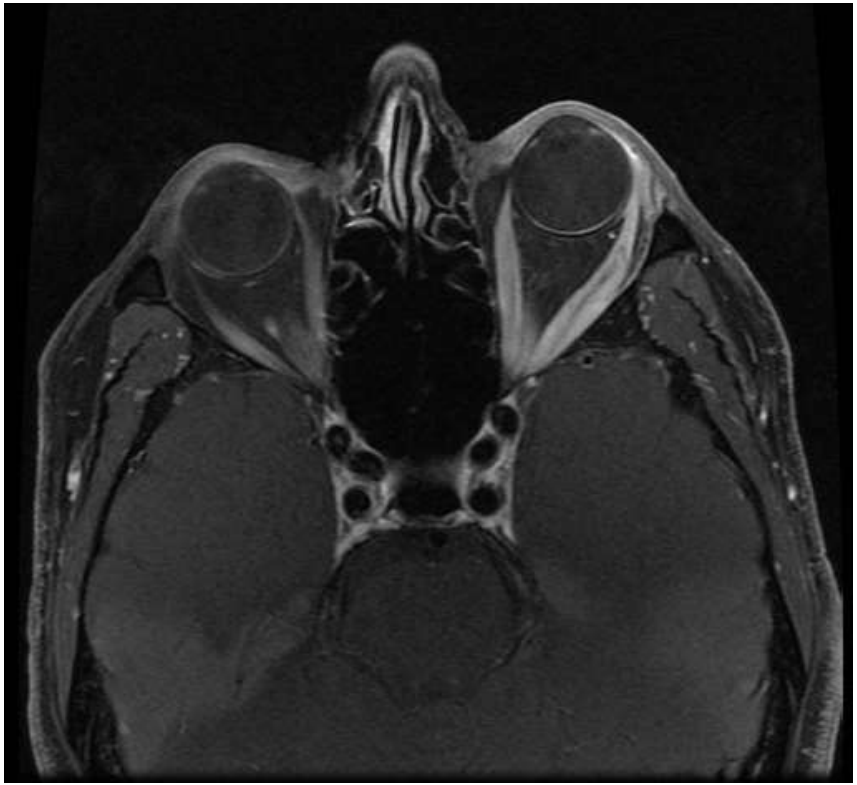
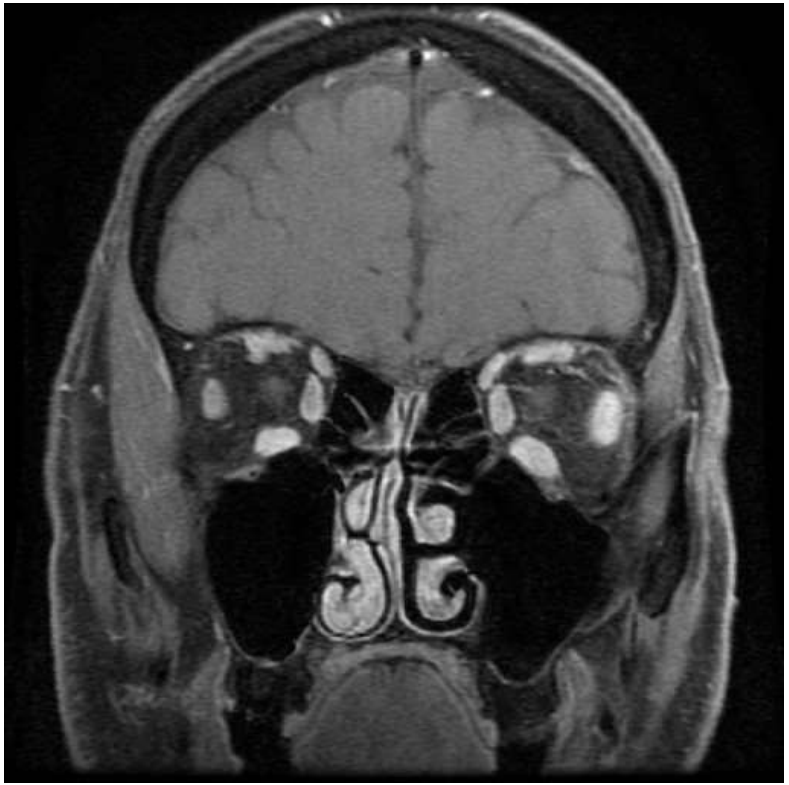
Vitiligo



Rafael Schmerling

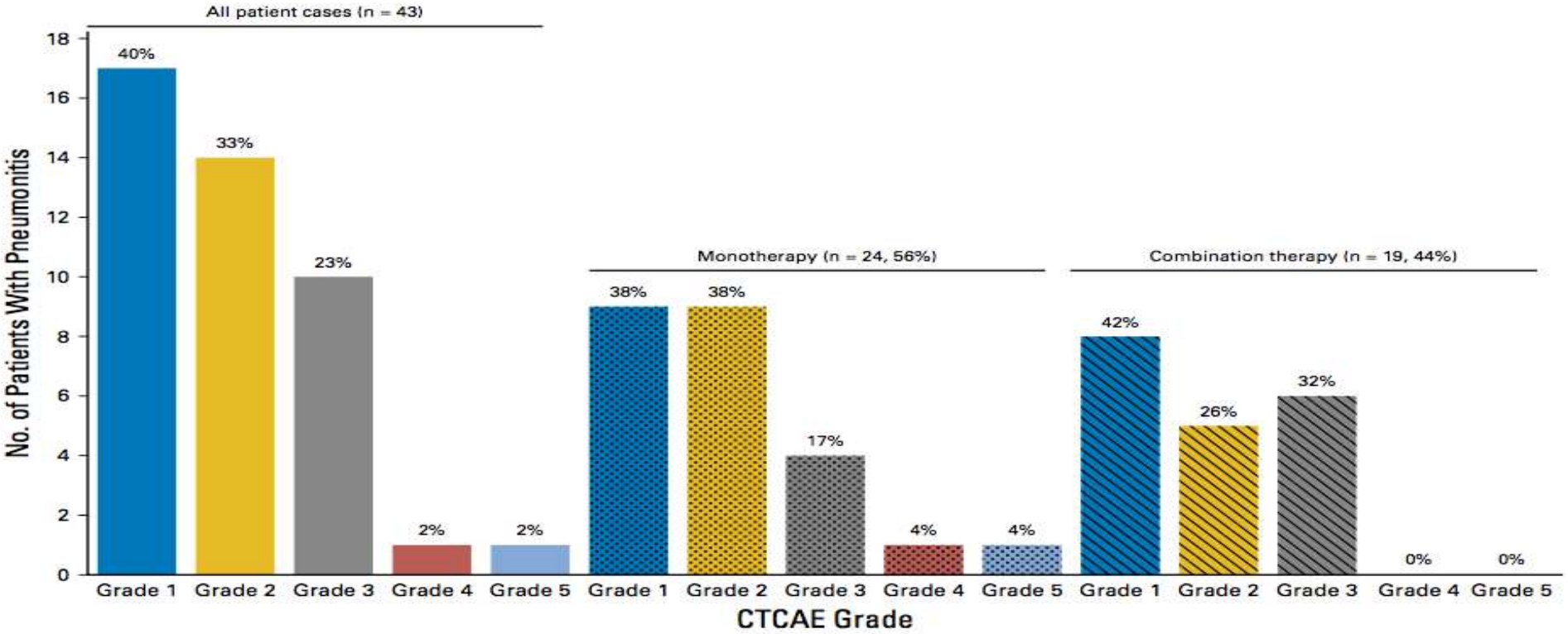
Miosite do m. reto ocular lat E





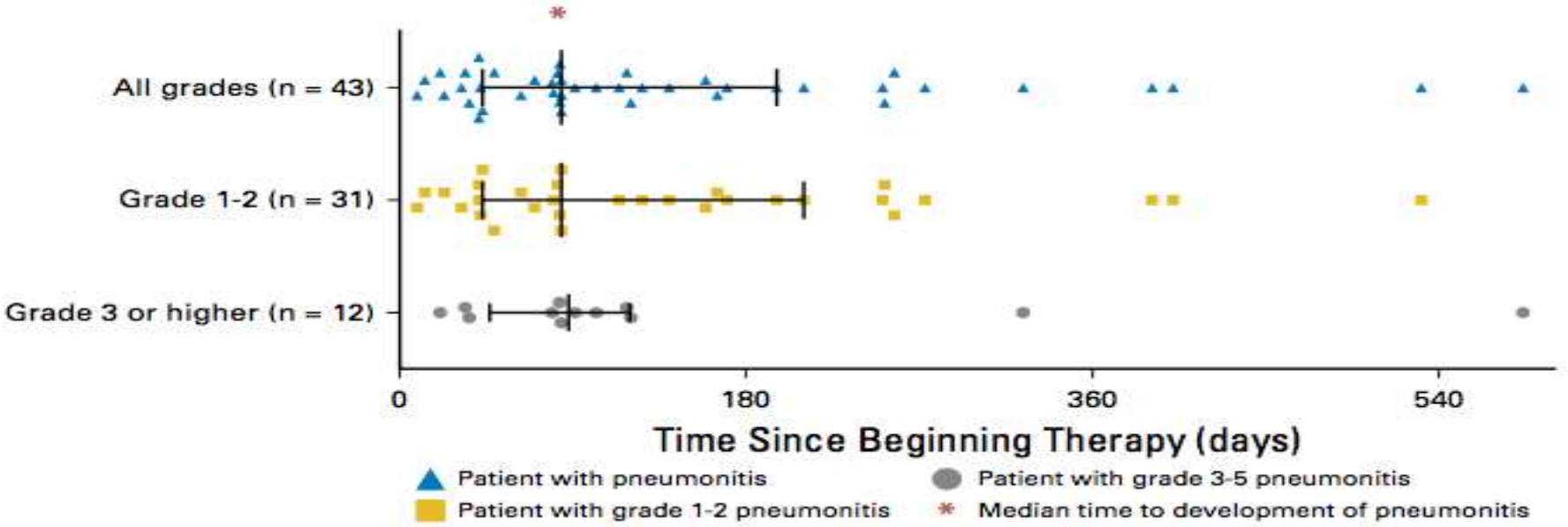
Cortesia Dr Buzaid

Pneumonite



Naidoo et al. *J Clin Oncol epub, ahead of print*, 2016

Pneumonite



Naidoo et al. *J Clin Oncol epub, ahead of print*, 2016

Pneumonite

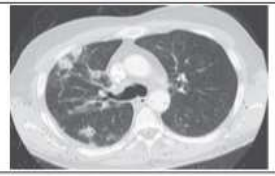
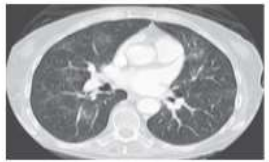
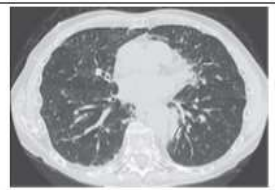
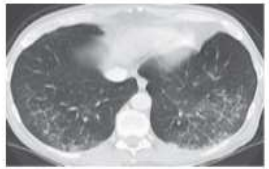
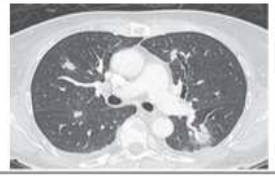
Diagnóstico		Incidência
Pulmão	20%	3,3%
Melanoma	60%	3,6%
Hemato	9%	
Bexiga	2%	
Mama	2%	
Cab/Pesc	2%	
Pancreas	2%	

Incidência		
	MSKCC	MIA
Não	551 (95%)	312 (95%)
Sim	27 (5%)	16 (5%)

Características		
História de Fumo	56% Sim	44% Não
Doenças Pulmonares	37% Sim	63% Não
RT	37% Sim	63% Não
Combinação	44% Combo	56% Isolado
Resposta	25 RC/RP	
	2 PD	
	14 SD	

Naidoo et al. *J Clin Oncol*, 2016

Pneumonite

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

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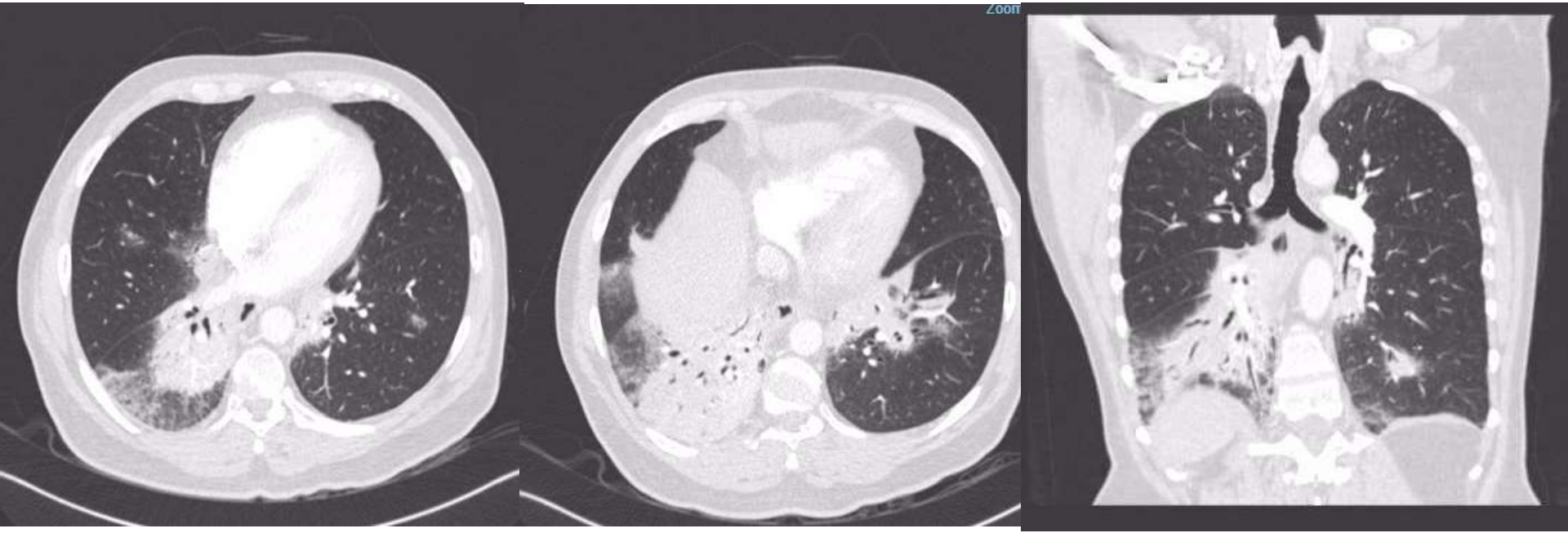
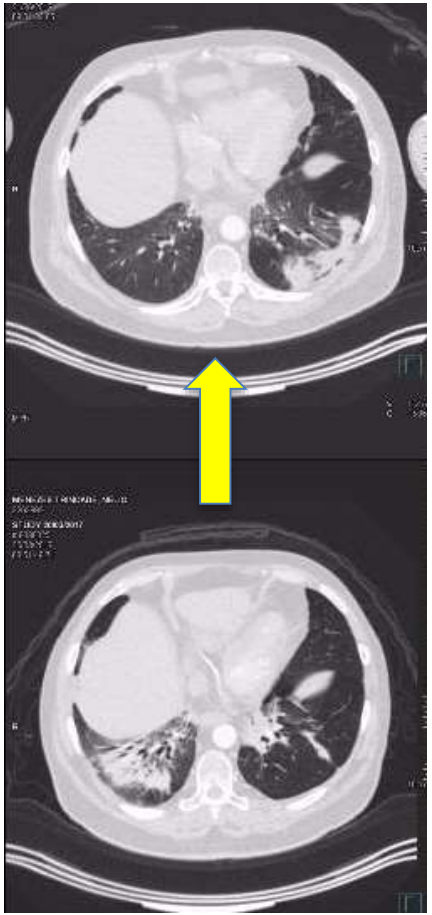
Pneumonite

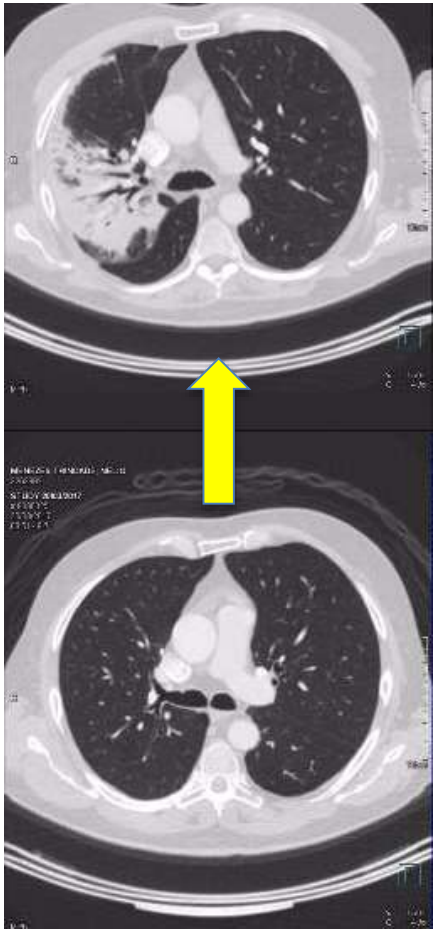


Cortesia Carolina Kawamura-Haddad

Pneumonite

Corticoterapia



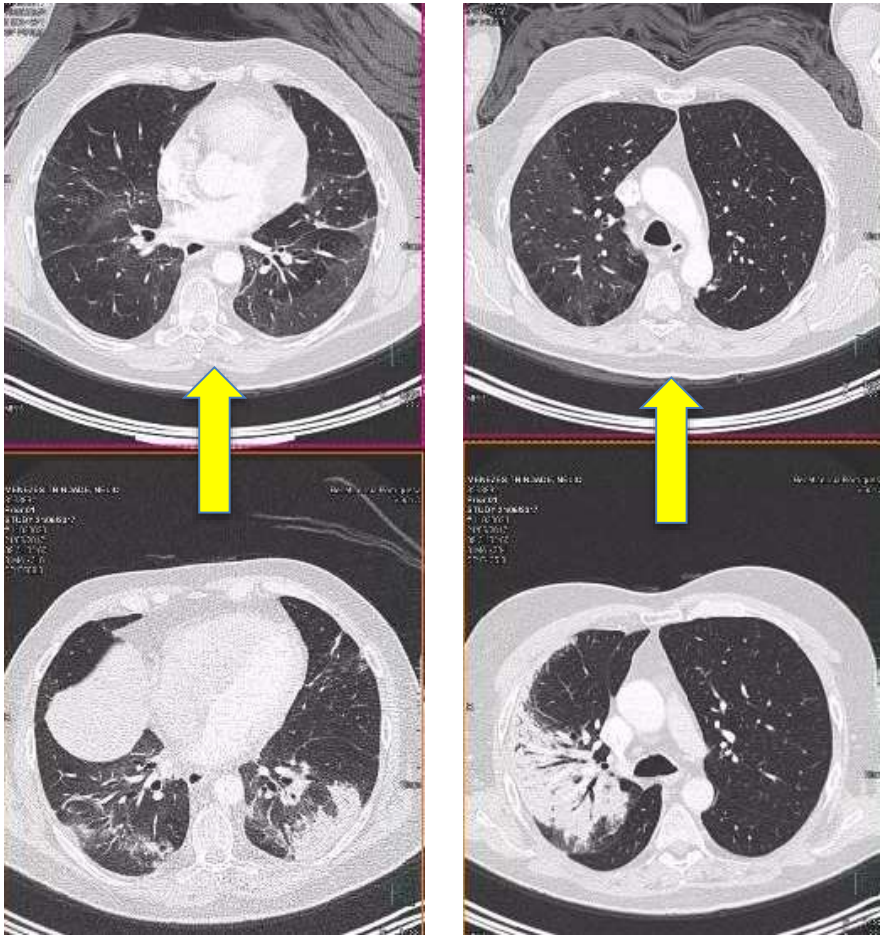


Cortesia Carolina Kawamura-Haddad

Pneumonite

Diagnóstico de CMV

Tratamento com antiviral



Cortesia Carolina Kawamura-Haddad

Outras toxicidades

Renal – padrão de nefrite

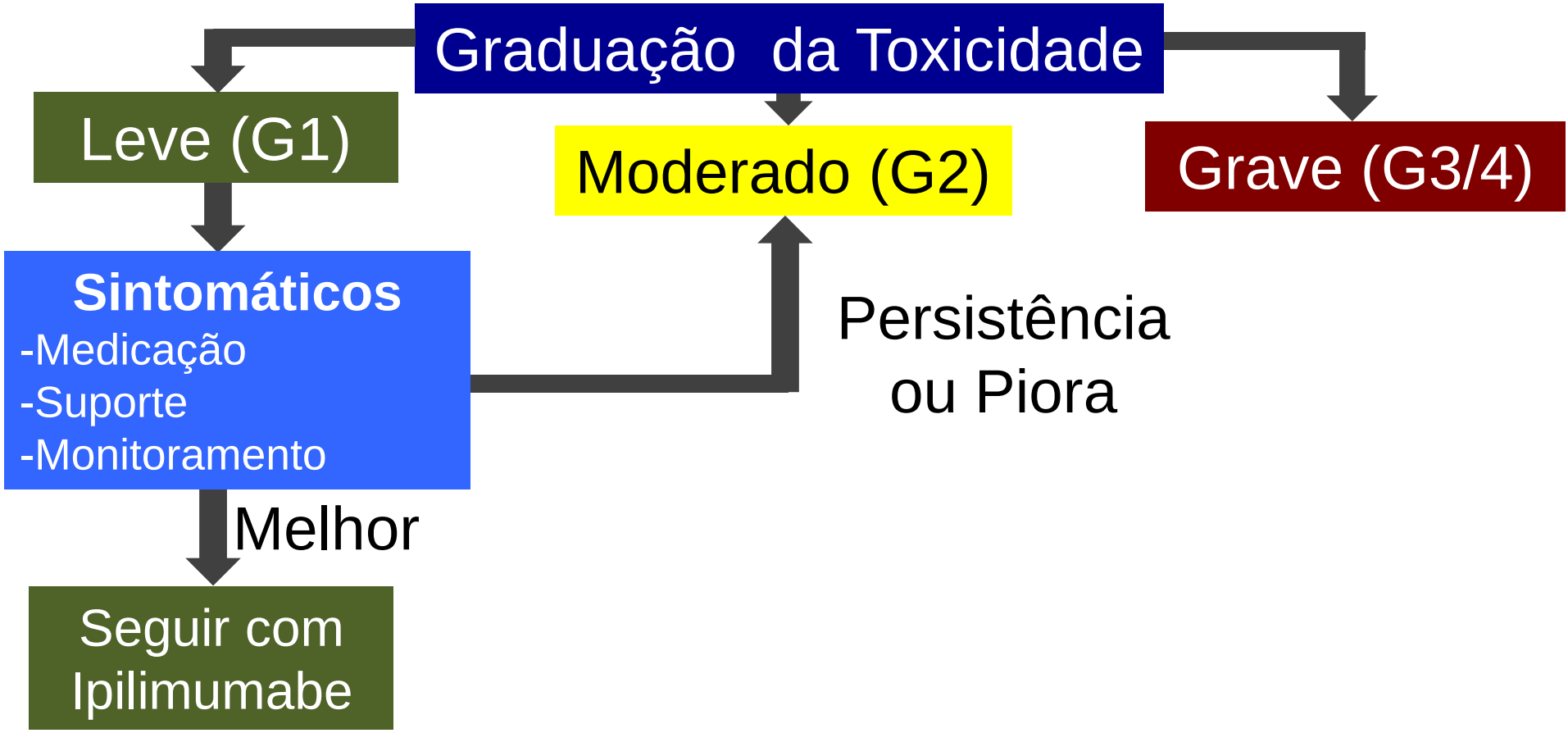
Hepático – não utilizar infliximabe; se preciso, Micofenolato

Endócrino – priorizar a reposição hormonal

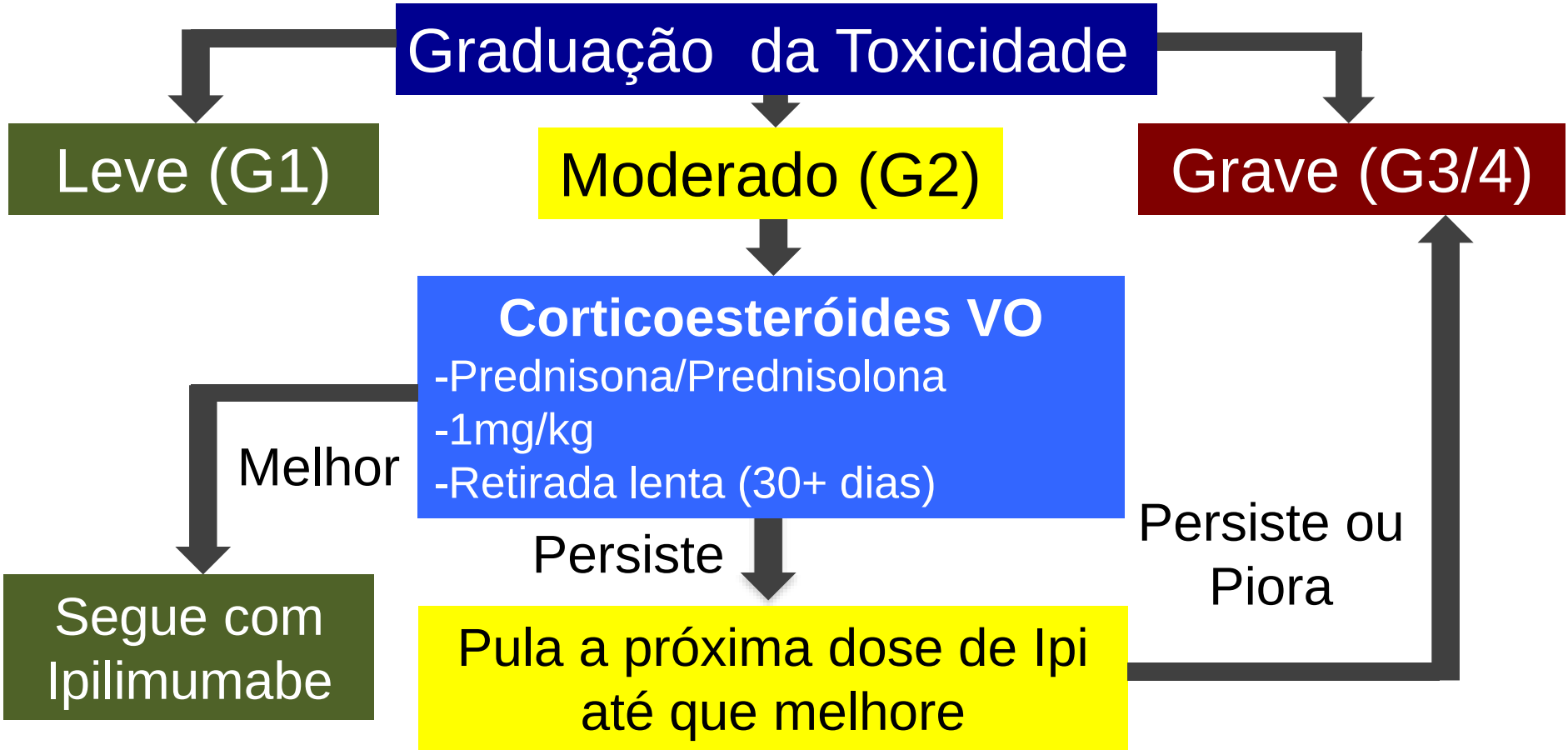
Neurológico – acompanhamento conjunto

Cardíaca – acompanhamento conjunto

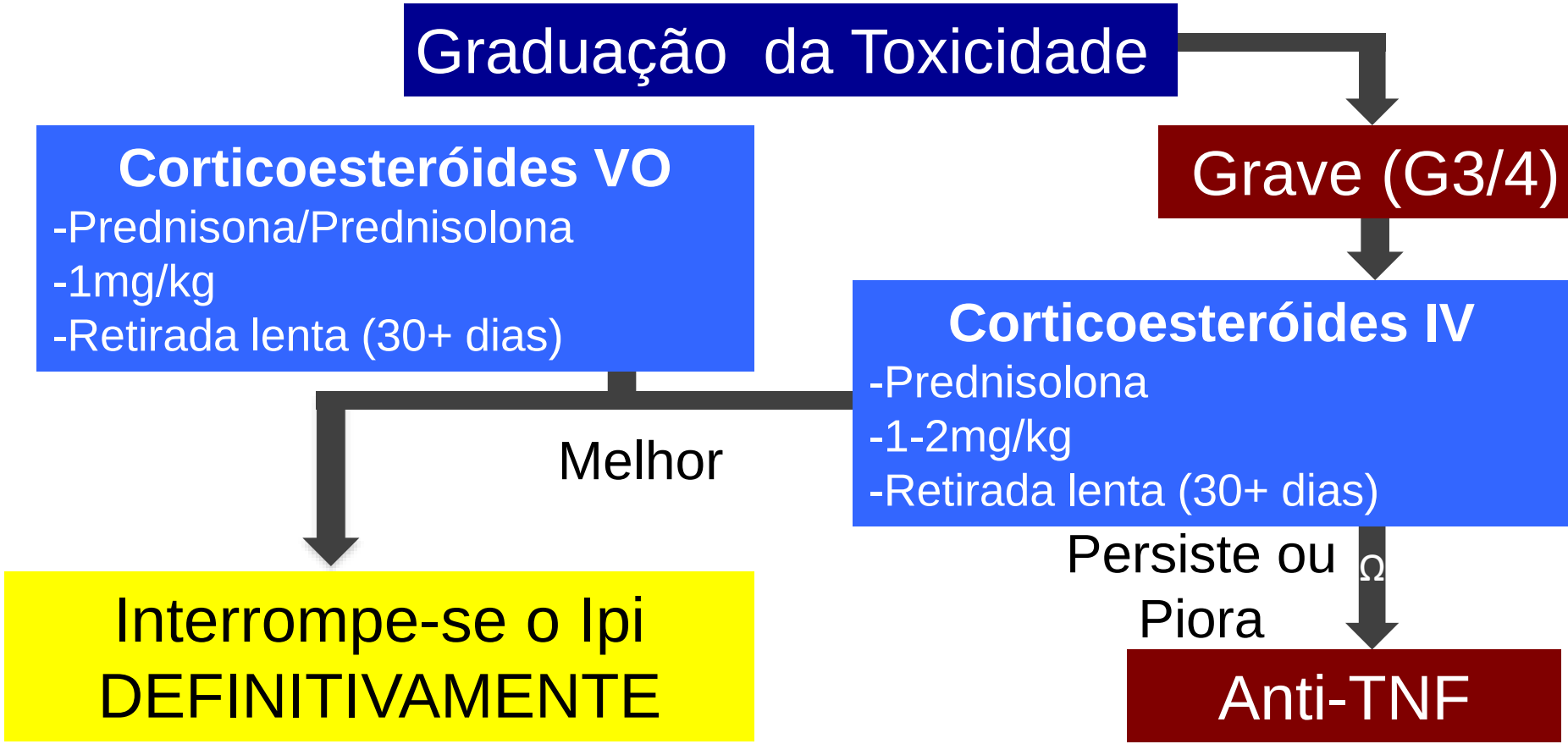
Guia Geral de Manejo de Efeitos Adversos



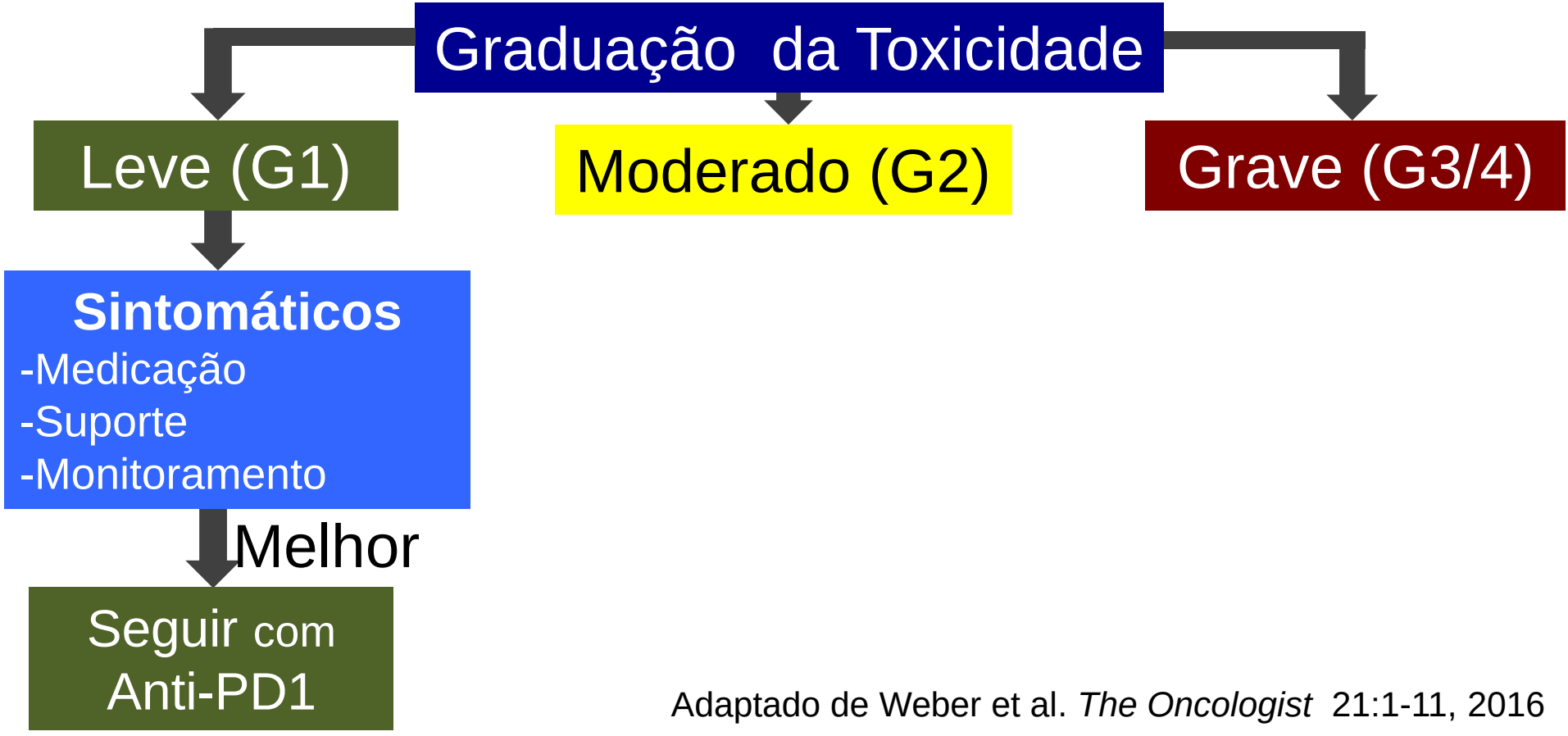
Guia Geral de Manejo de Efeitos Adversos



Guia Geral de Manejo de Efeitos Adversos

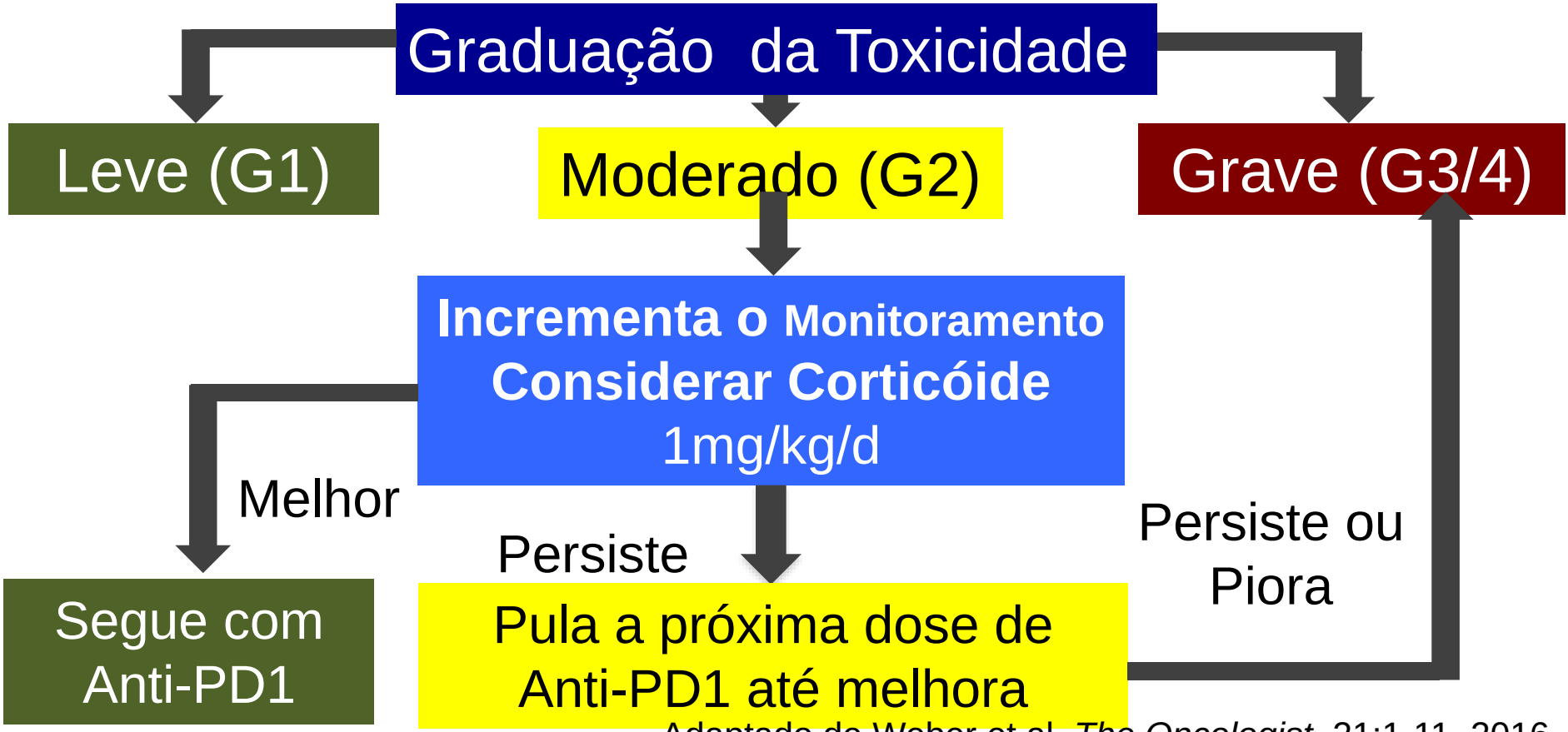


Guia Geral de Manejo de Efeitos Adversos



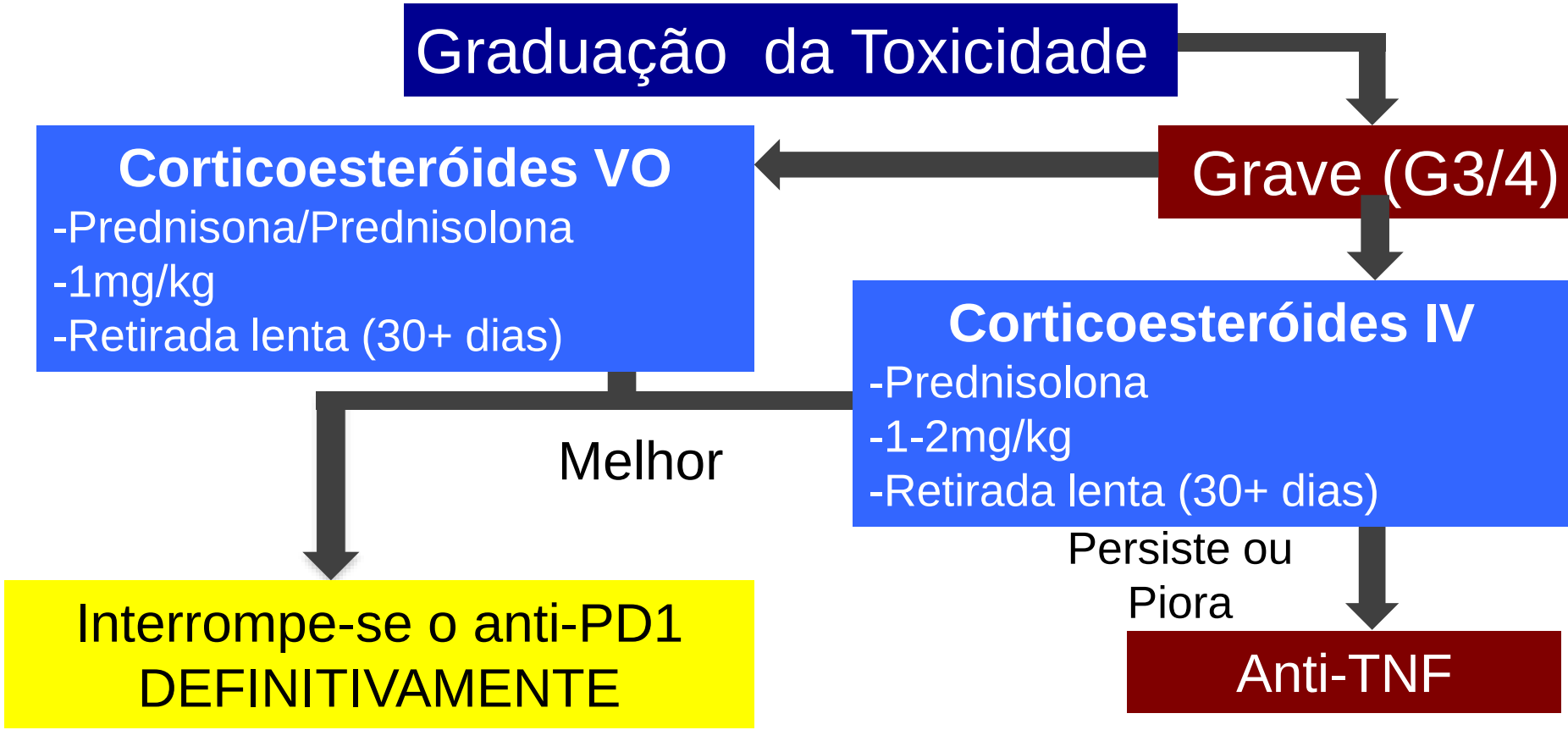
Adaptado de Weber et al. *The Oncologist* 21:1-11, 2016

Guia Geral de Manejo de Efeitos Adversos



Adaptado de Weber et al. *The Oncologist* 21:1-11, 2016

Guia Geral de Manejo de Efeitos Adversos



Adaptado de Weber et al. *The Oncologist* 21:1-11, 2016

Conclusões – Inibidores de Checkpoints

Toxicidade Previsível, para a maior parte dos pacientes

Educação da equipe e do paciente

O aprendizado com o manejo de ipilimumabe facilitou o tratamento das complicações de anti-PD1.

Sítio da doença pode ter influência na toxicidade

Não hesitem em usar esteróides!!!

Obrigado!

@MelanomaSarcoma