Eventos adversos & QOL em Imunoterapia: O que mudou e com o que devemos nos preocupar?

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Potenciais conflitos de interesse

✓ Honorários recebidos por esta atividade: MSD

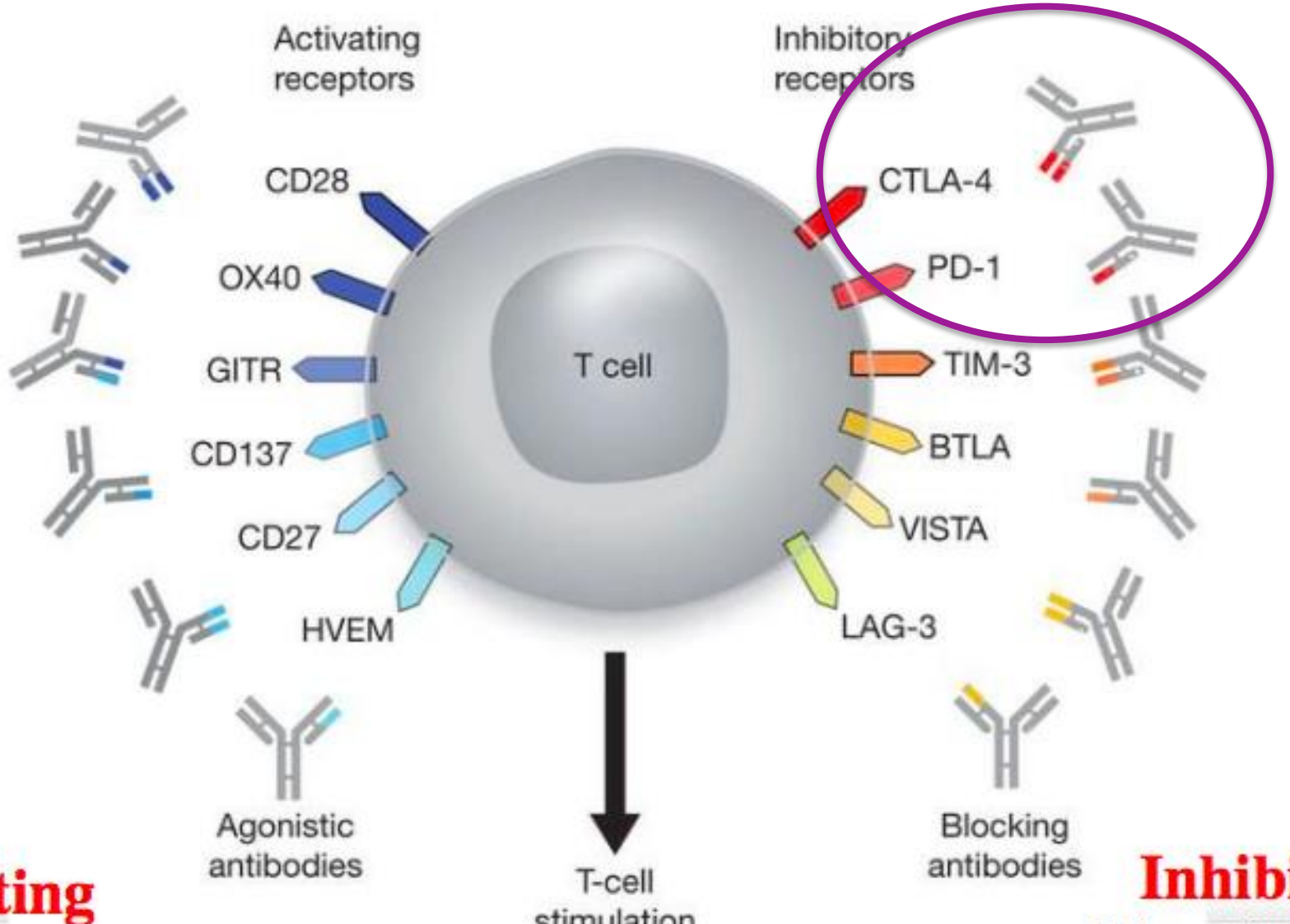
✓ Participação em Advisory Board:
Astellas, Bayer, Janssen, Roche, Sanofi

A aula foi preparada com base em estudos publicados ou apresentados em congressos e pautada pelo melhor nível de evidência encontrado.

Features of Cancer Immunotherapy

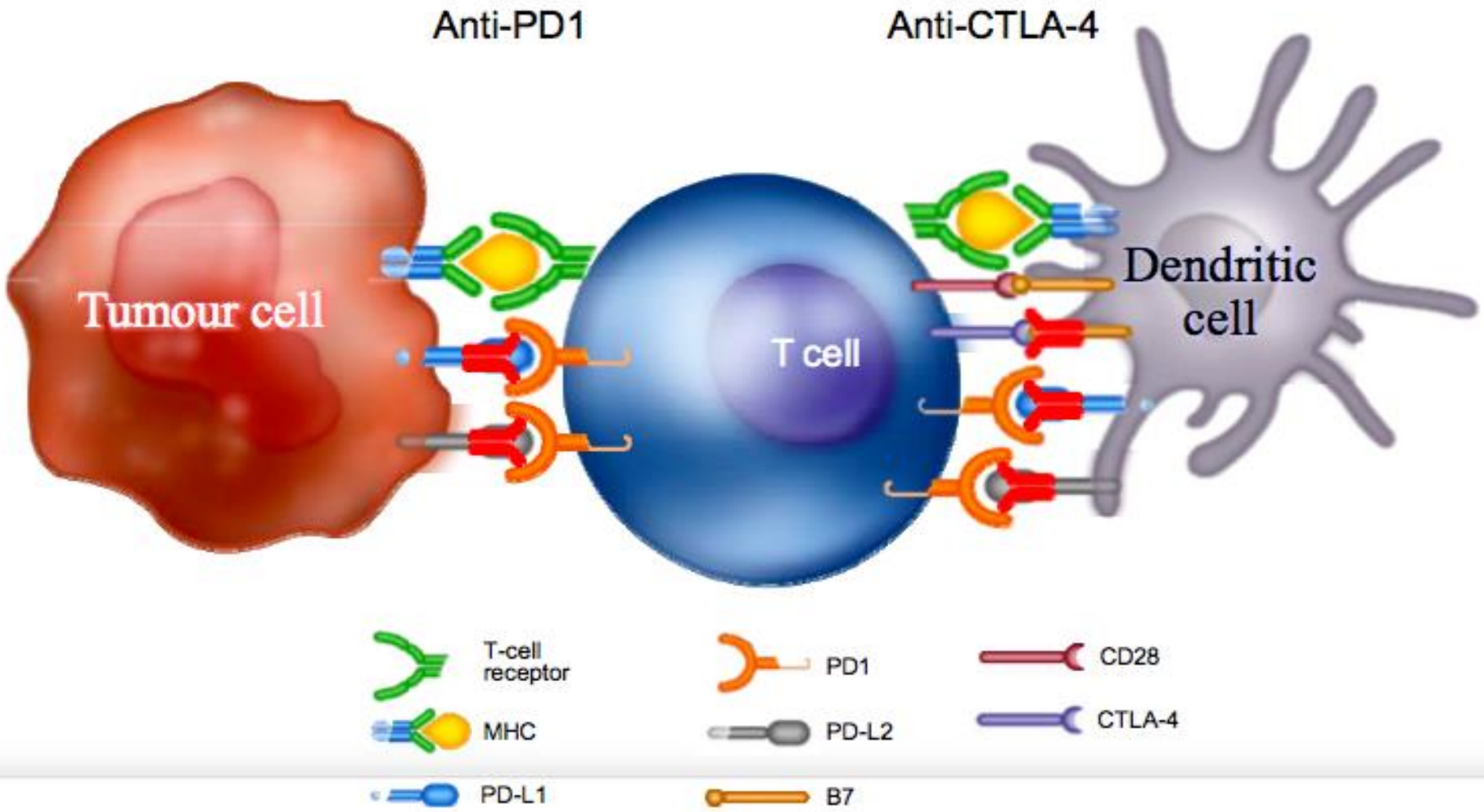
Adaptable	**Ability to adapt the response beyond the initially targeted antigen**
Specific	**Ability to recognize and target only tumor cells**
Long Lasting	**Capacity for memory can result in durability of tumor responses**
Universal	**Potentially applicable to all cancers**

Immune Modulatory Receptors



Mellman, *Nature*, 2011

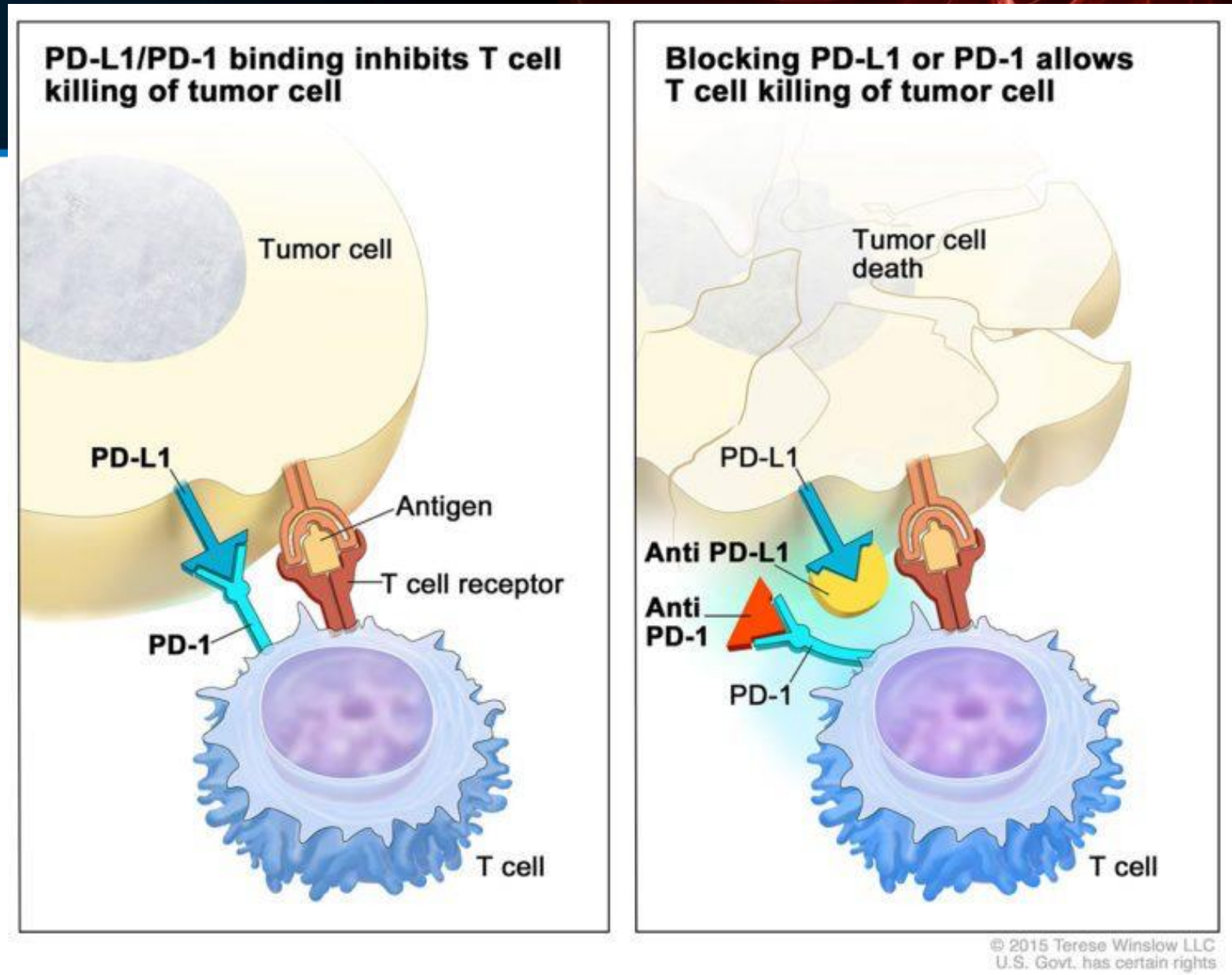
Immune-checkpoint inhibition



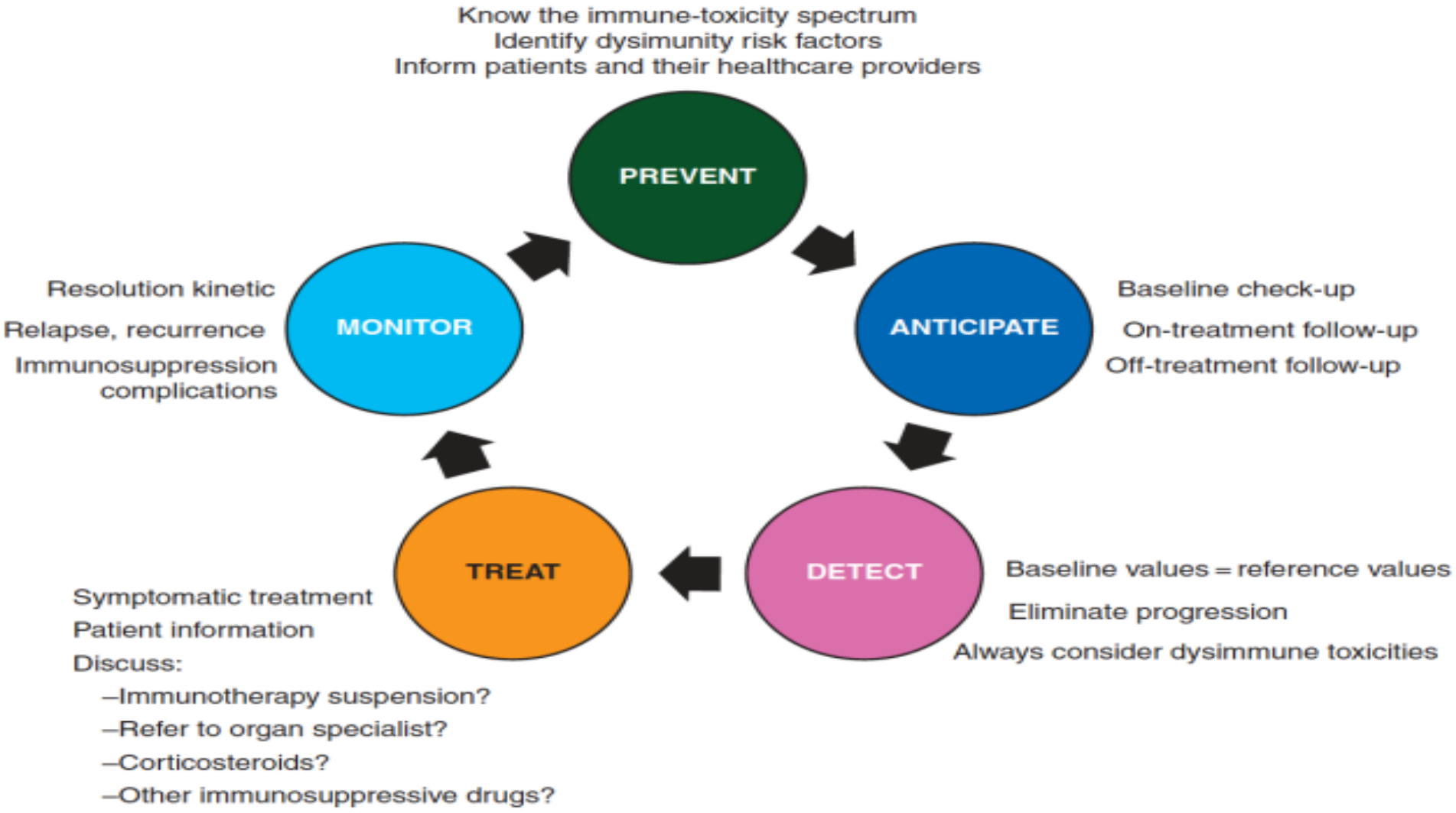
Adapted from Sznol M, et al. Presented at ASCO 2013: oral presentation CRA9006

Anti-PD-1 ou Anti-PD-L1

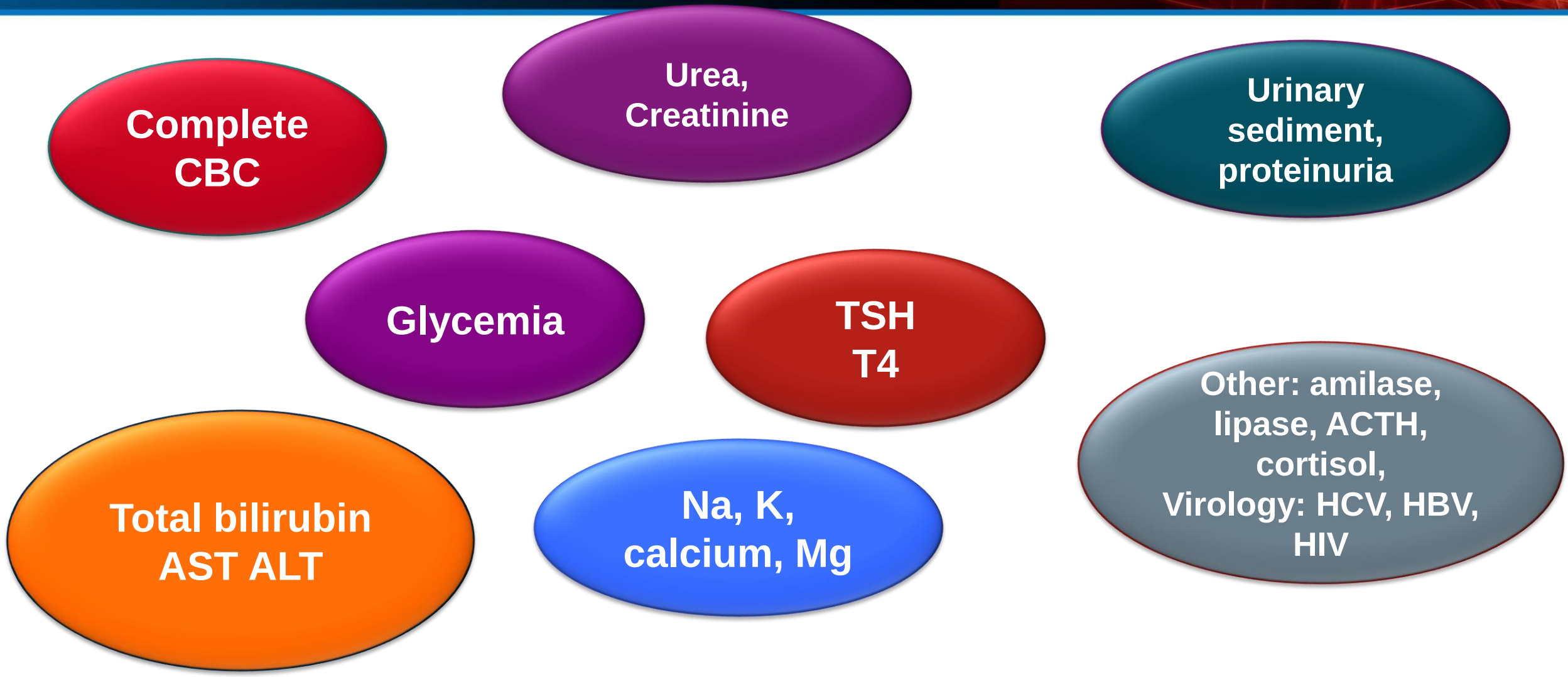
- PD1 suprime a atividade de células T no microambiente tumoral.
- O bloqueio de PD1 permite a ativação dessas células, para reconhecimento dos antígenos tumorais.



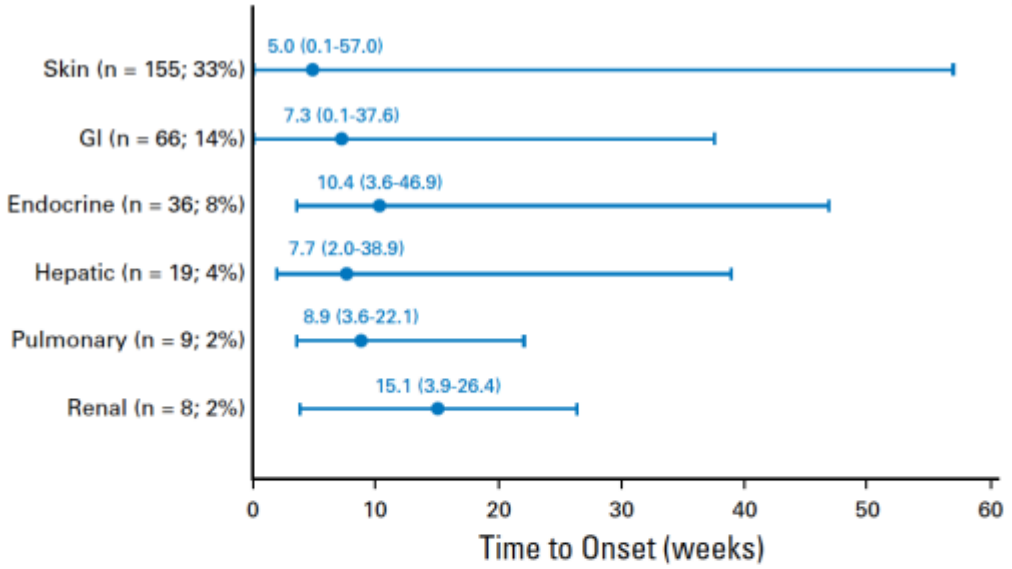
Pilares do manejo da toxicidade da Imunoterapia

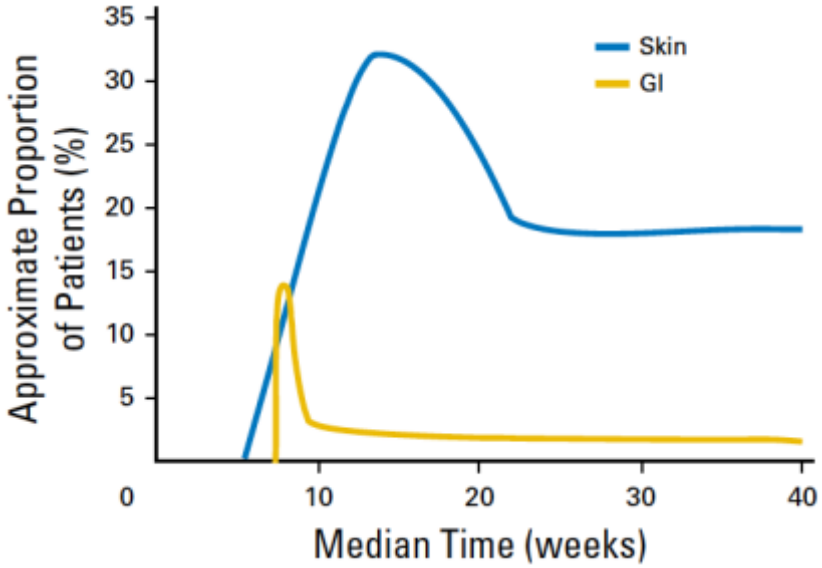


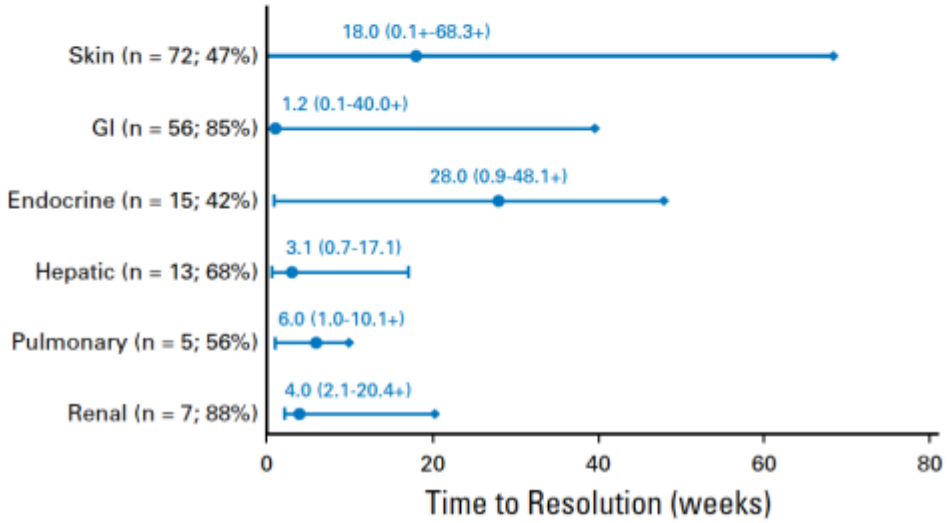
Check list de exames iniciais (além de imagens recentes)

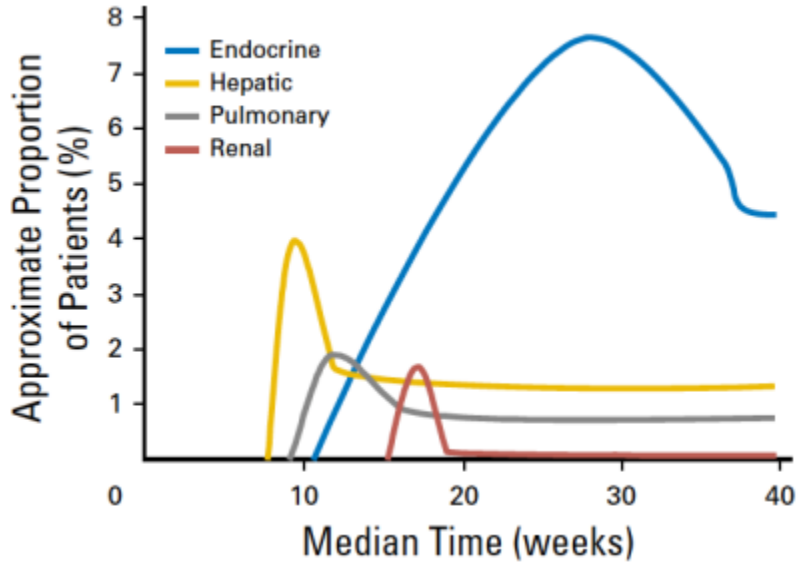


Timeline dos eventos adversos (anti-PD-1 Monoterapia)





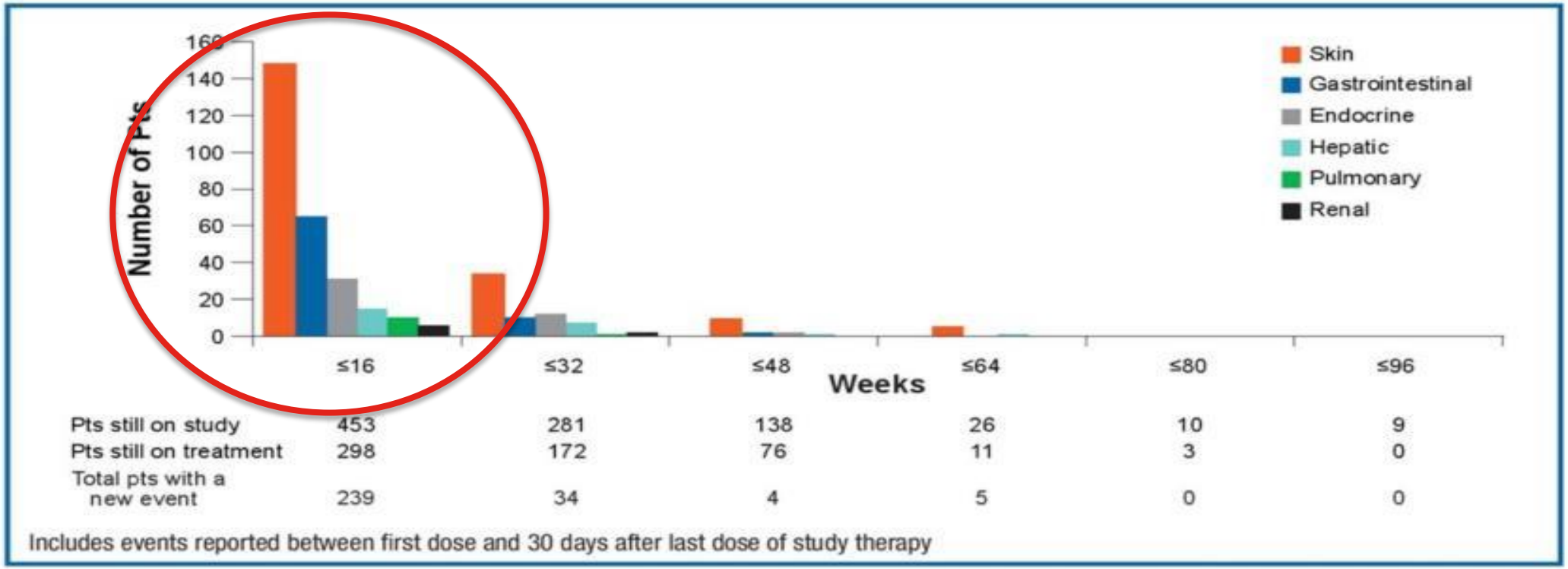




Weber JS, et al. *J Clin Oncol.* 2015;29. Abstract 9018

In the patients who experienced new AEs, 85% did so within the first 16 weeks

Figure 2. New treatment-related select AEs over time (any grade; N = 576)



Weeks	≤16	≤32	≤48	≤64	≤80	≤96
Pts still on study	453	281	138	26	10	9
Pts still on treatment	298	172	76	11	3	0
Total pts with a new event	239	34	4	5	0	0

Includes events reported between first dose and 30 days after last dose of study therapy

- In the 282 pts who experienced new treatment-related select AEs, 85% did so within the first 16 weeks of treatment

Weber JS, et al. *J Clin Oncol.* 2015;29. Abstract 9018

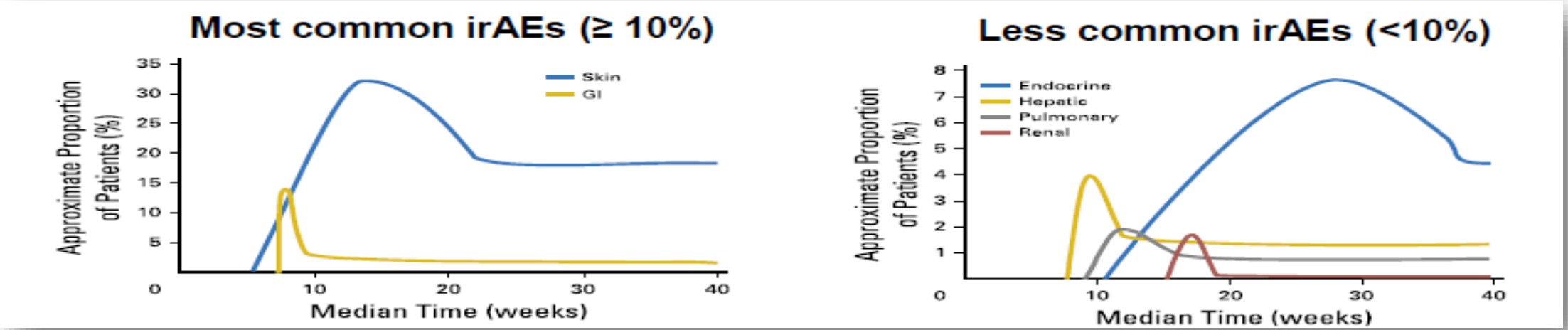
Anti-PD-1/PD-L1

Toxicidade G3-4

- Melanoma: 10-20%
- CPNPC CEC*: 7-58%
- CPNPC Não CEC*: 10-69%
- Tumor Renal**: 19-79%

Tumores Uroteliais
Qquer Grau 60%
G3-5 15%

(*) pós Platina
(**) pós TKI



Haanen JBAG. Ann Oncol. 2017 Jul 1;28(suppl_4):iv119-iv142.

Webwe J Clin Oncol 2016

ASCO *Guidelines* – Distribuição dos eventos

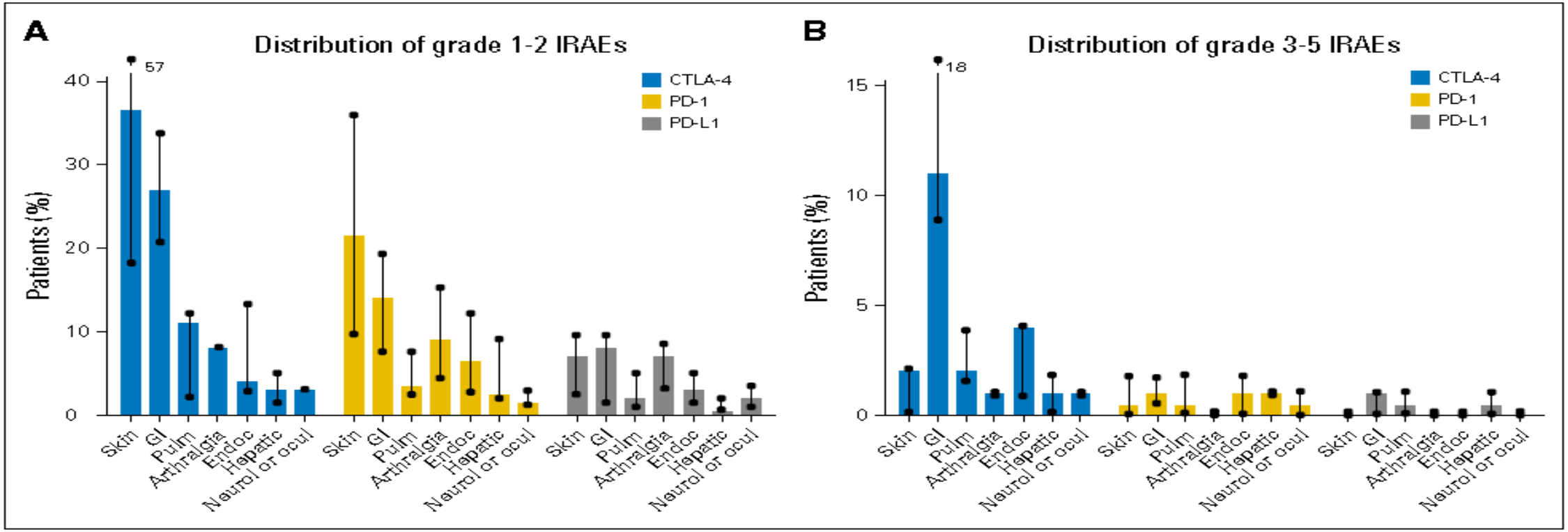
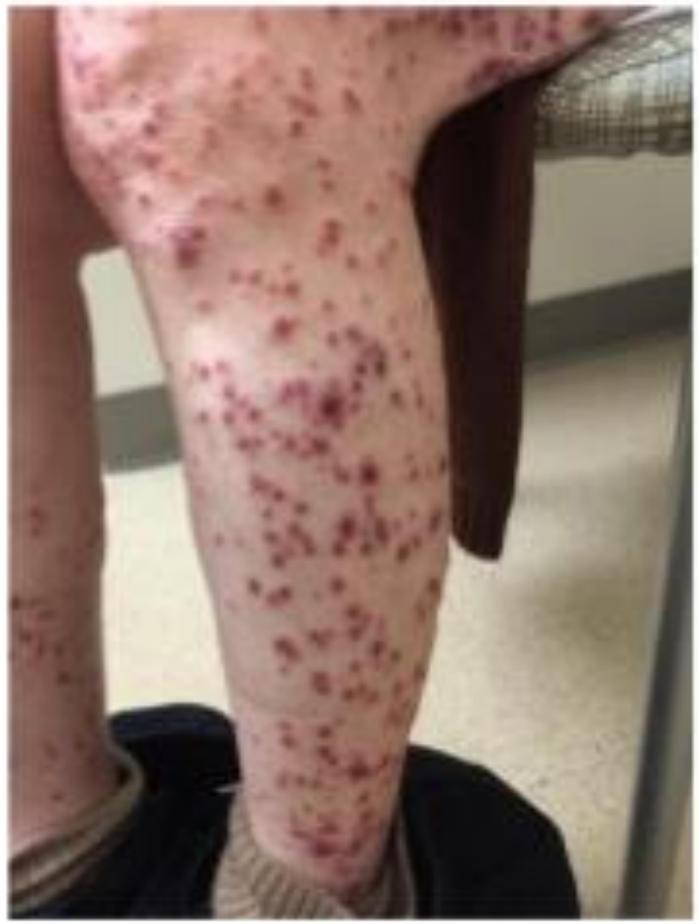


Fig A1. Distribution of (A) grade 1 to 2 and (B) grade 3 to 5 immune-related adverse events (irAEs) for all tumor types in the main clinical trials with anti– cytotoxic T-cell lymphocyte-4 (anti–CTLA-4), anti–programmed death 1 (PD-1), or anti–PD ligand 1 (PD-L1) antibodies as single therapies. The values 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 Management of Immune-Related Adverse Events in Patients
Treated With Immune Checkpoint Inhibitor Therapy: ASCO Clinical Practice Guideline. JCO 2018

Immune-Mediated Dermatitis

- Reported in up to 40% of pts with anti–CTLA-4 and anti–PD-1 agents
- Occasionally severe rashes
- Onset within a few wks of starting or several wks/mos into therapy
- Severity driven by symptoms
- Rule out other etiologies
- Generally not infusion related

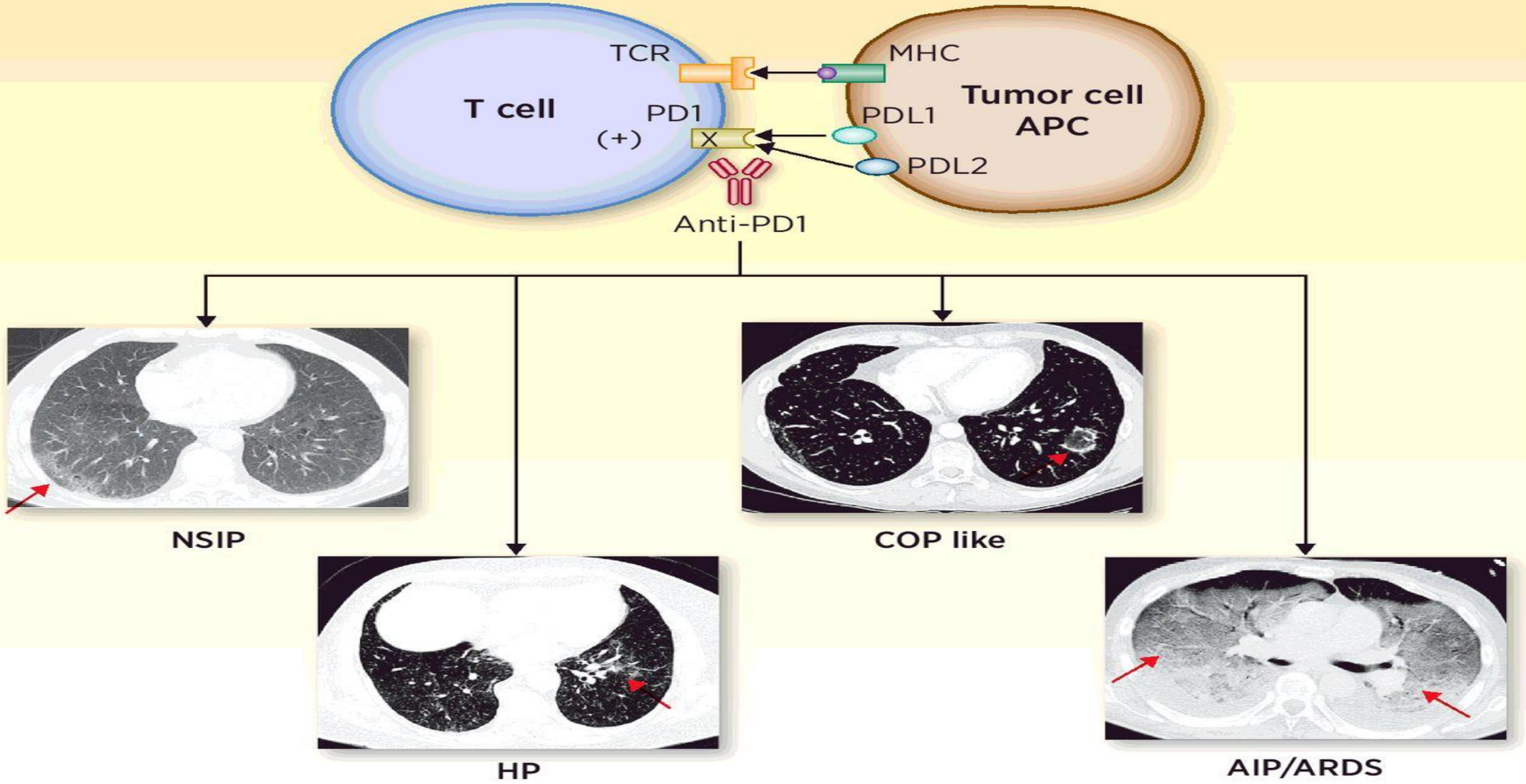


Hodi FS, et al. N Engl J Med. 2010;363:711-723.
Image courtesy Matthew M. Burke, MBA, RN, MSN, APRN-BC.

Toxicidade Pulmonar- Pneumonite

Grading	Management
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks

Brahmer et al Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Clinical Practice Guideline. JCO 2018



DIRETRIZES

Diretrizes brasileiras de manejo de toxicidades imunomediadas associadas ao uso de bloqueadores de correceptores imunes

Brazilian guidelines for the management of immune-related adverse events associated with checkpoint inhibitors

Grupo de Trabalho da Sociedade Brasileira de Oncologia Clínica[1]

RESUMO

Nos últimos anos, assistimos à consolidação da "imunoterapia" como uma forma efetiva e viável de se tratar o câncer. Em particular, a manipulação terapêutica de moléculas envolvidas na modulação da resposta imune com o uso de anticorpos monoclonais, ou bloqueadores de correceptores imunes, viabilizou uma nova realidade para pacientes com melanoma, câncer de pulmão e diversas outras neoplasias. Como exemplos, bloqueadores do cytotoxic T lymphocyte associated antigen 4 (CTLA-4) e programmed cell death protein 1 (PD-1) foram recentemente incorporados à prática clínica após aprovações por agências reguladoras no Brasil e em inúmeros outros países, e novas modalidades e combinações para a mobilização do sistema imunológico estão em estudo. Todavia, essa ativação imune, particularmente de linfócitos T, leva ao risco do desenvolvimento de respostas direcionadas a tecidos sadios que se manifestam clinicamente como eventos adversos imunomediados. Nesse contexto, o conhecimento do perfil de segurança desses fármacos e dos passos para o tratamento eficaz desses eventos adversos é fundamental, e ganhará ainda mais importância nos próximos anos, frente ao crescimento de indicações dos bloqueadores de correceptores imunes, do número de pacientes tratados com esses agentes e à sua incorporação à prática da oncologia. Com esse foco, a presente diretriz se propõe a discutir o espectro de toxicidades relacionadas ao uso de bloqueadores de correceptores imunes e as estratégias destinadas a permitir o seu diagnóstico precoce e manejo adequado.

1. Grupo de Trabalho da Sociedade Brasileira de Oncologia Clínica

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Conflitos de interesse: Potenciais conflitos de interesse dos autores envolvidos na elaboração das diretrizes estão pormenorizados no quadro 1. (Material Suplementar).

Fontes de financiamento: O presente projeto foi conduzido mediante patrocínio educacional da Merck Sharp & Dohme (MSD)

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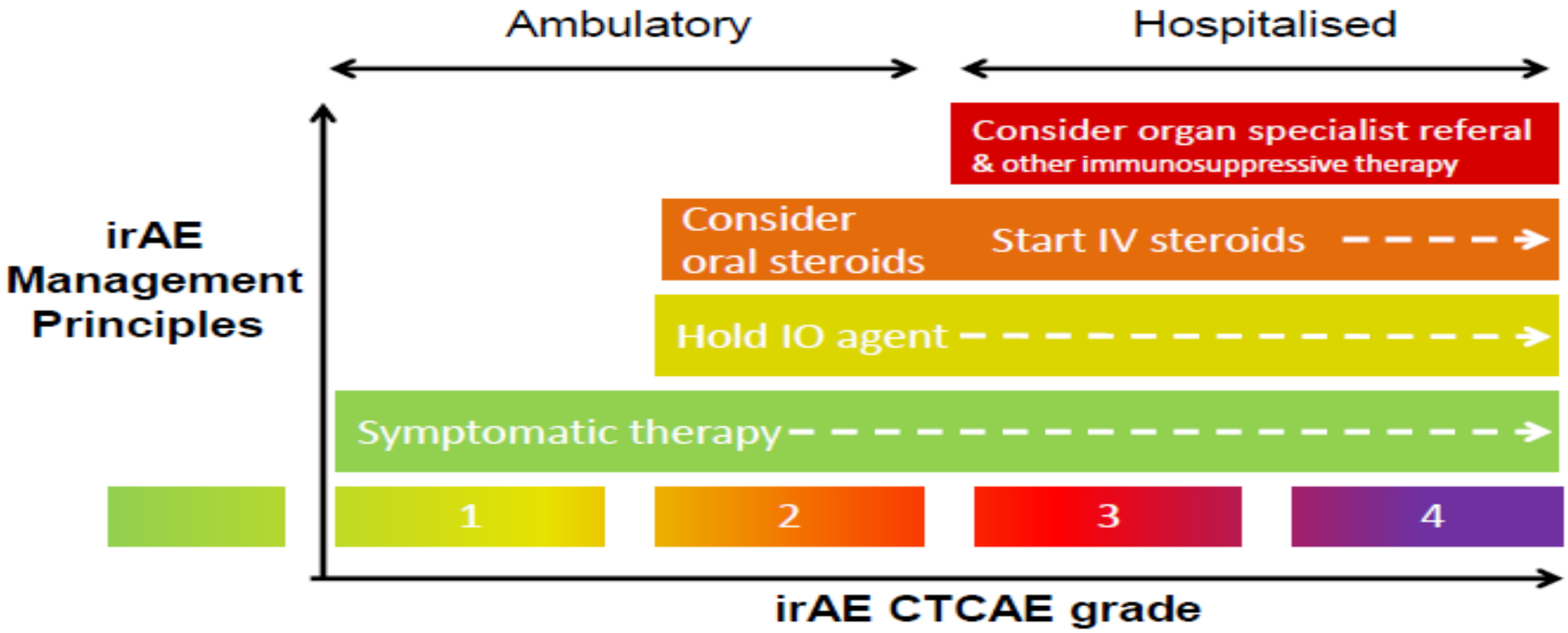
http://brazilianjournalofoncology.com.br/diretrizes-brasileiras-de-manejo-de-toxicidades-imunomediadas-associadas-ao-uso-de-bloqueadores-de-correceptores-imunes/

Estratégias de Manejo Geral de irAEs



Champiat S and Besse B, Sep, ESMO 2017

Análises de Qualidade de Vida
QLQ-C30 *Structure*

Global health status / QoL:
Global health status / QoL

Functioning scales:
Physical functioning
Role functioning
Emotional functioning
Cognitive functioning
Social functioning

Symptom scales / single items:
Fatigue
Nausea and vomiting
Pain
Dyspnoea
Insomnia
Appetite loss
Constipation
Diarrhoea
Financial difficulties

QLQ-C30

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4

Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about ☑
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self-care ☑
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☑
- I am unable to perform my usual activities ☐

Pain/Discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☑

Anxiety/Depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☑
- I am extremely anxious or depressed ☐

VAS (Visual Analog Scale)

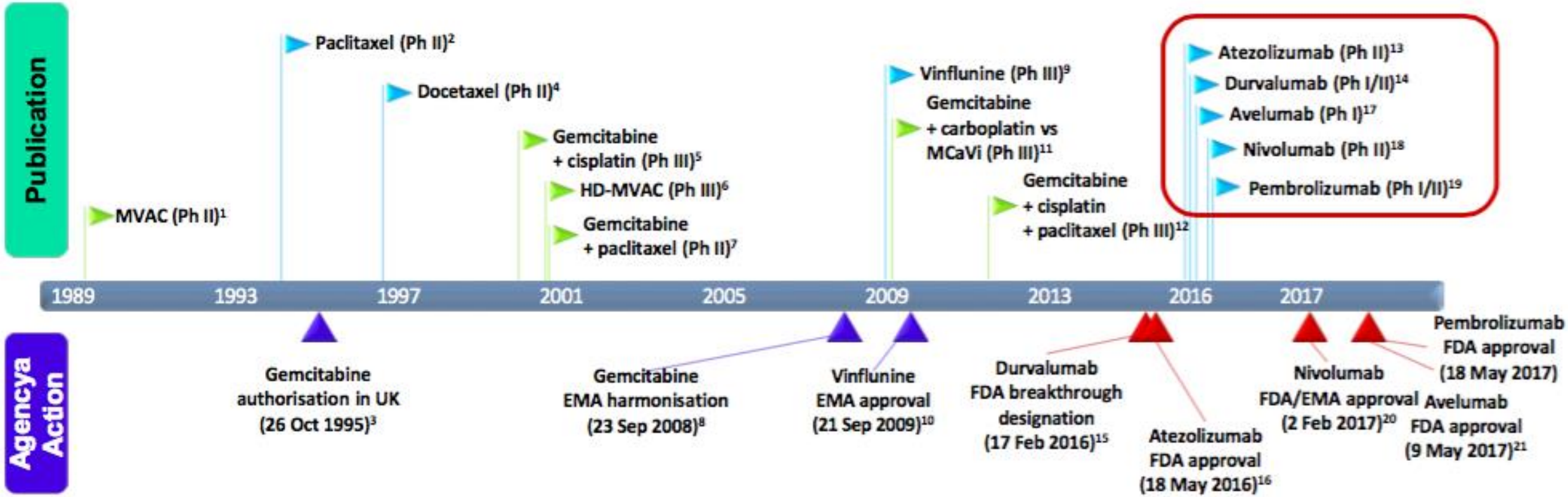
Best imaginable health state

Worst imaginable health state

Nos tumores uroteliais…

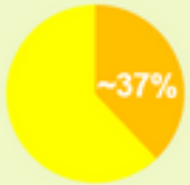
Dados de toxicidade e qualidade de vida…

Evolution of systemic therapy for urothelial cancer to 2017



1. Sternberg CN et al. Cancer 1989;64:2448–2458; 2. Roth BJ et al. J Clin Oncol 1994;12:2264–2270; 3. Eli Lilly. SmPC Gemzar® 01 Jul 2014. Available at: http://www.medicines.org.uk; 4. McCaffrey JA et al. J Clin Oncol 1997;15:1853–1857; 5. Von der Maase H et al. J Clin Oncol 2000;18:3068–3077; 6. Sternberg CN et al. J Clin Oncol 2001;19:2638–2646; 7. Meluch AA et al. J Clin Oncol 2001;19:3018–3024; 8. EMA. EMEA/CHMP/512295/2008; 24 Sep 2008. Available at: http://www.ema.europa.eu; 9. Bellmunt J et al. J Clin Oncol 2009;27:4454–4461; 10. EMA. EMEA/H/C/000983; 2012. Available at: http://www.ema.europa.eu; 11. De Santis M et al. J Clin Oncol 2009;27:5634–5639; 12. Bellmunt J et al. J Clin Oncol 2012;30:1107–1113; 13. Rosenberg JE et al. Lancet 2016;387:1909–1920; 14. Massard C et al. ASCO 2016. Abstract #4502 and oral presentation; 15. AstraZeneca. Press release 17 Feb 2016. Available at: http://www.astrazeneca.com; 16. FDA. Press release 18 May 2016. Available at: http://www.fda.gov); 17. Apolo AB et al. ASCO 2016. Abstract #4514 and poster; 18. Galsky MD et al. ESMO 2016. Abstract #LBA31_PR; 19. Balar A et al. ESMO 2016. Abstract #LBA32_PR; 20. FDA. Press release 2 Feb 2017. Available at http://www.fda.gov; 21. FDA. Press release 9 May 2017. Available at http://www.fda.gov. All links accessed Sept 2017.

Immune checkpoint inhibitors licensed in metastatic urothelial cancer.

Immunotherapy (IO)	Atezolizumab[1,2]	Nivolumab[3]	Pembrolizumab	Durvalumab[5]	Avelumab[6]
Target for inhibition	PD-L1	PD-1	PD-1	PD-L1	PD-L1
Studies performed	Phase 1-3	Phase 1 and 2	Phase 1 and 3	Phase 1b	Phase 1b
Cell types scored for PD-L1 status	IC	TC	TC + IC	IC + TC	IC + TC
FDA + EMA Licence	Platinum refractory and platinum ineligible.	Platinum refractory	Platinum refractory and platinum ineligible	Platinum refractory	Platinum refractory
Estimated PD-L1 prevalence in urothelial cancer trials					

- IC, immune cells; IHC, immunohistochemistry; IO, immuno-oncology; PD-L1, programmed death ligand-1; TC, tumour cells.
- 1. Rosenberg JE et al. *Lancet* 2016;387:1909–1920; 2. Hoffman-Censits JH et al. *J Clin Oncol* 2016;34(Suppl. 2S):Abstract 355; 3. Sharma P et al. *J Clin Oncol* 2016;34(Suppl.):Abstract 4501; 4. Bellmunt J et al. *N Engl J Med* 2017;376:1015–1026; 5. Powles C et al. *J Clin Oncol* 2016;34:3119–3125; 6. Apolo AB et al. *J Clin Oncol* 2016;34(Suppl.):Abstract 4514.

Presented by T. Powles. ASCO GU 2018

KEYNOTE 045

KEYNOTE-045: Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

Open-label 2-arm, multi-centre, international, randomised (1:1) Phase III trial

Key Eligibility Criteria

- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1-2 lines of platinum-based chemo or recurrence within 12 mo of perioperative platinum-based therapy
- ECOG PS 0-2
- Provision of tumor sample for biomarker assessment

Stratification Factors

- ECOG PS (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 mo)

R (1:1)
N = 542

N = 270 → Pembrolizumab 200 mg IV Q3W for 2 years

N = 272 → Paclitaxel 175 mg/m² Q3W
OR
Docetaxel 75 mg/m² Q3W
OR
Vinflunine 320 mg/m² Q3W

Key End Points

Primary: OS and PFS in total and PD-L1 CPS ≥10% populations

Secondary: ORR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

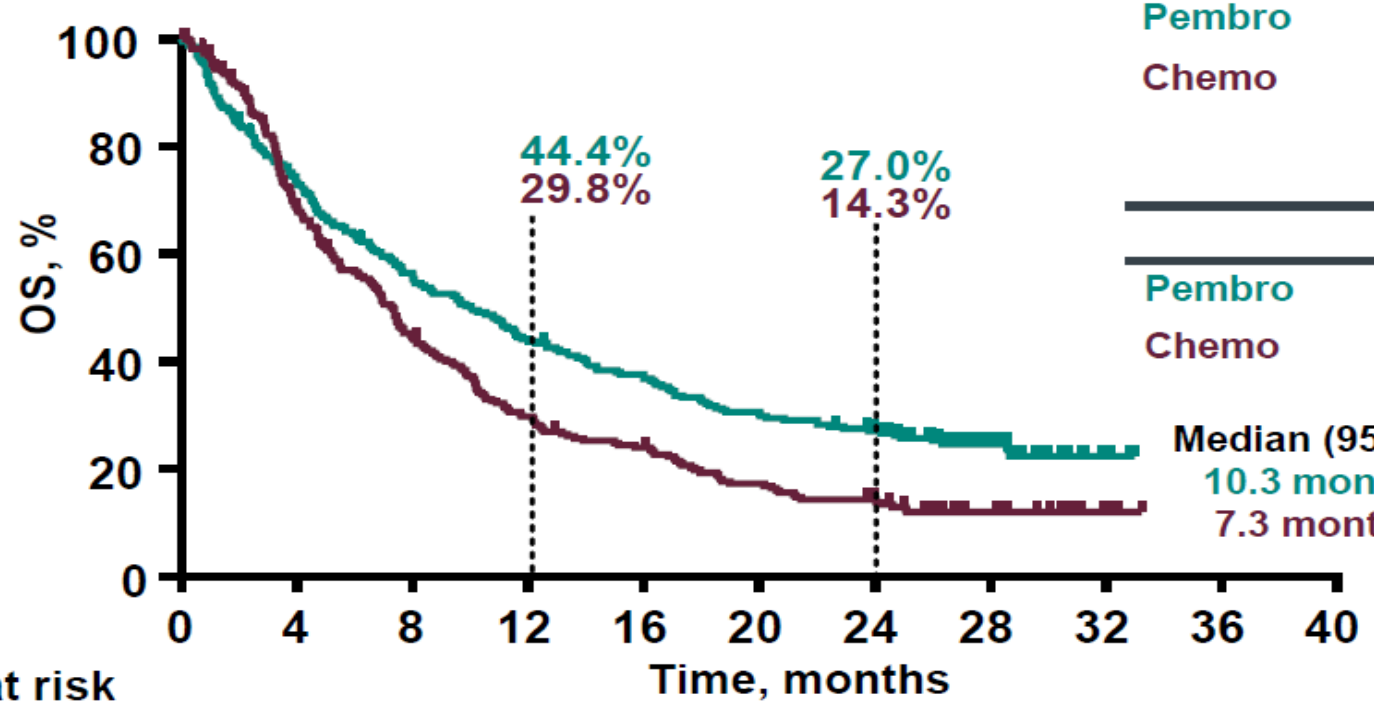
CPS = combined positive score.

Necchi A. ECCO 2017

Bellmunt J. N Engl J Med. Mar 16;376(11):1015-1026, 2017

Anti – PD1 x Quimioterapia (KN045, fup 24 meses)

Overall Survival: Total



No. at risk

Pembro	270	194	147	116	98	80	67	32	6	0	0
Chemo	272	173	109	73	58	41	33	18	4	0	0

14.1 months of follow-up[1]

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	155	0.73 (0.59-0.91)	0.0022
Chemo	179		

27.7 months of follow-up

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	199	0.70 (0.57–0.85)	0.00017
Chemo	218		

Median (95% CI):
10.3 months (8.0–12.3)
7.3 months (6.1–8.1)

60.6% at 24 months in the chemotherapy arm received an immunotherapeutic agent, including those who received pembrolizumab as part of the cross over.

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.
1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

Bellmunt J., ASCO GU, 2018.

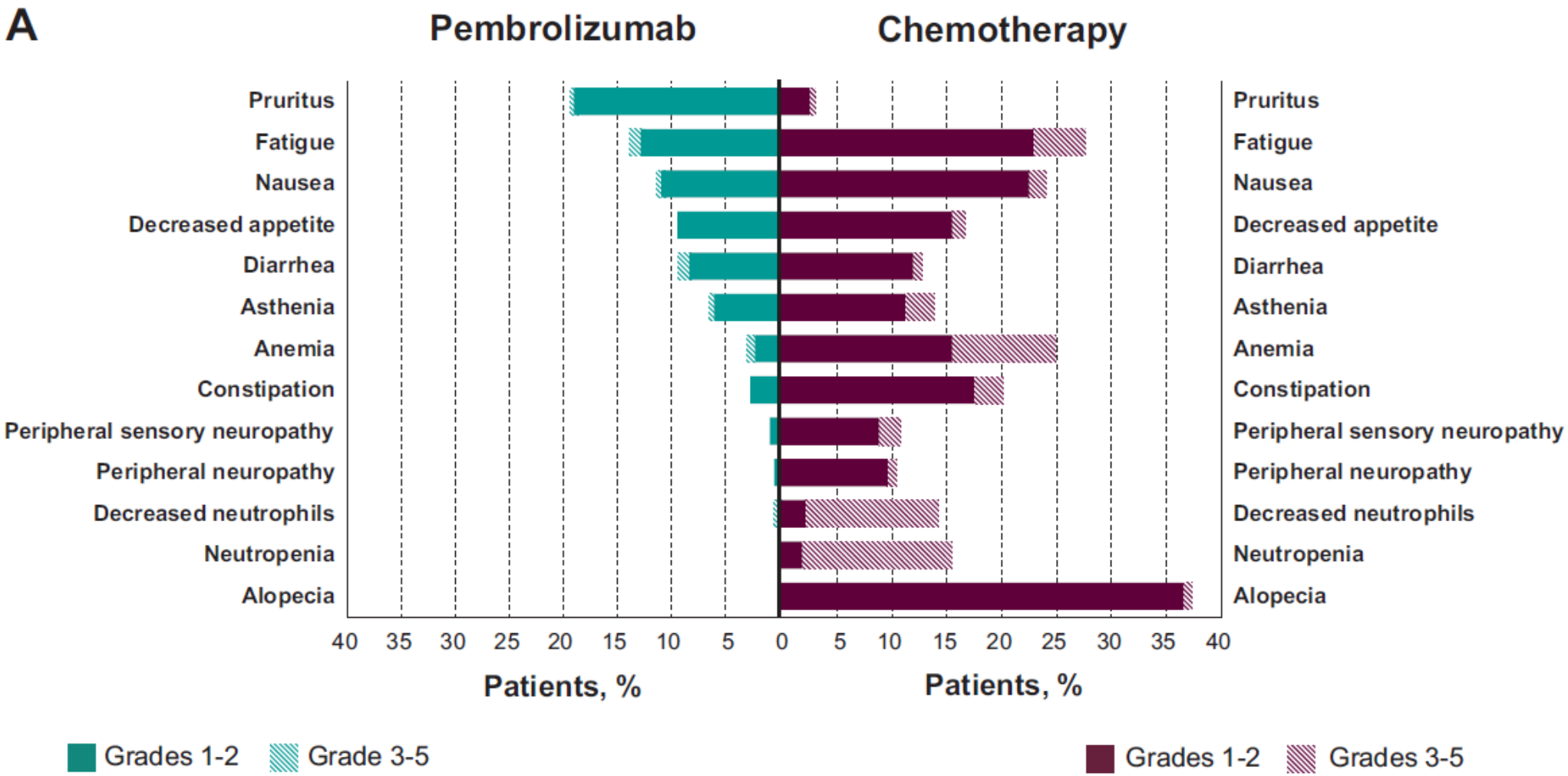
Tempo de Exposição ao Tratamento Eventos Adversos - KEYNOTE 045

	Pembrolizumab N = 266	Chemotherapy N = 255
Exposure, median (range)	3.5 mo (0.03-20.0)	1.5 mo (0.03-14.2)
Treatment-related AEs, n (%)	162 (60.9)	230 (90.2)
Grade 3-5	40 (15.0)	126 (49.4)
Serious	27 (10.2)	57 (22.4)
Discontinuation	15 (5.6)	28 (11.0)
Grade 5	4 (1.5)	4 (1.6)

Seguimento desta segunda analise interina foi de 14.meses.
18% ainda recebendo pembro e 1.2% QT no momento desta analise
4 MORTES do Pembro: Pneumonite, PD, Obstrução Urinaria, Não especificada
4 MORTES QT: sepse em 2 , choque séptico 1, Não especificada em 1

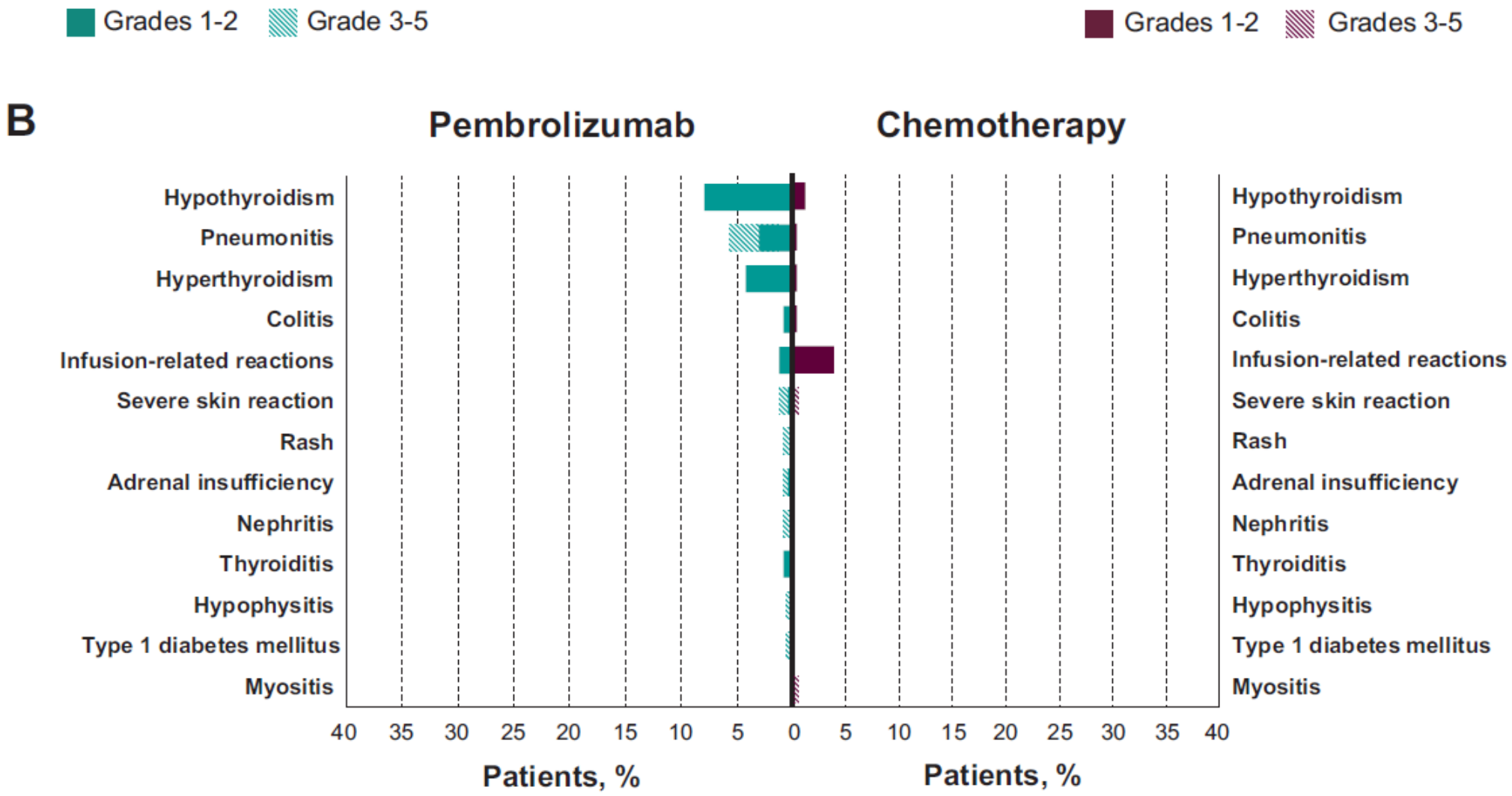
Necchi A. ECCO 2017
Bellmunt J. N Engl J Med. Mar 16;376(11):1015-1026, 2017

Anti – PD1 x Quimioterapia (KN045, fup 24 meses)
AEs ocorrendo em ≥ 10% dos pacientes



Bellmunt J., ASCO GU, 2018.

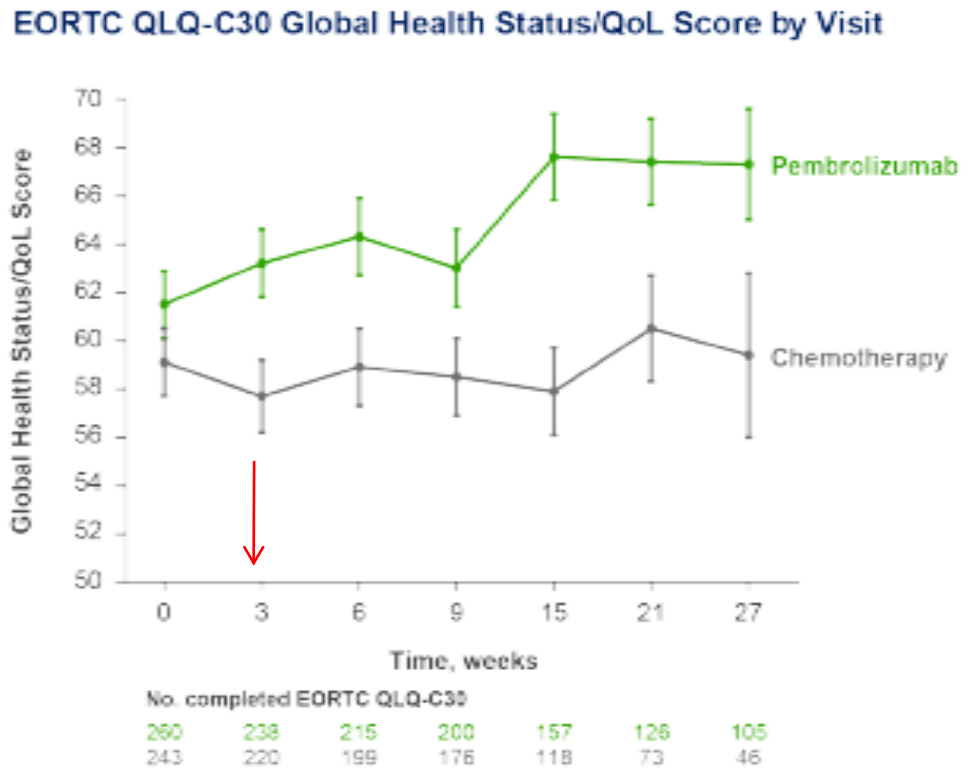
Anti – PD1 x Quimioterapia (KN045, fup 24 meses)
AEs ocorrendo em ≥ 1pacientes

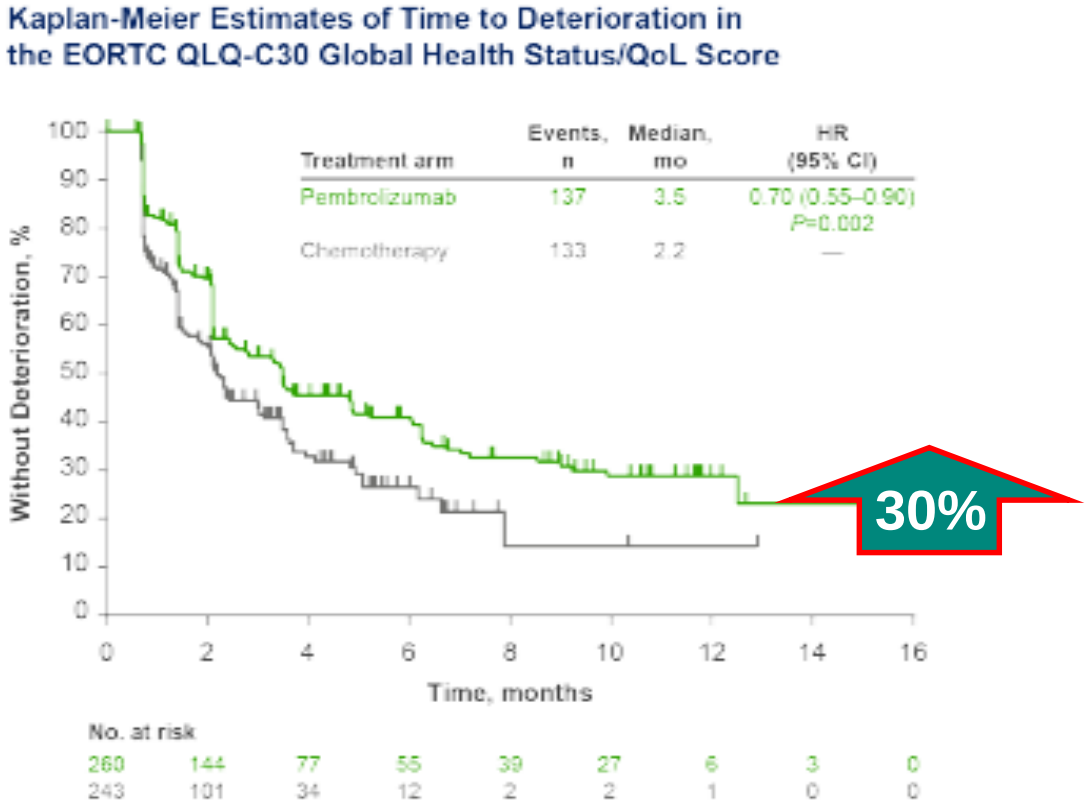


Bellmunt J., ASCO GU, 2018.

KEYNOTE -045
Dados de Qualidade de Vida

- Compliance: 95% Baseline / 88% Week 15
- N=520



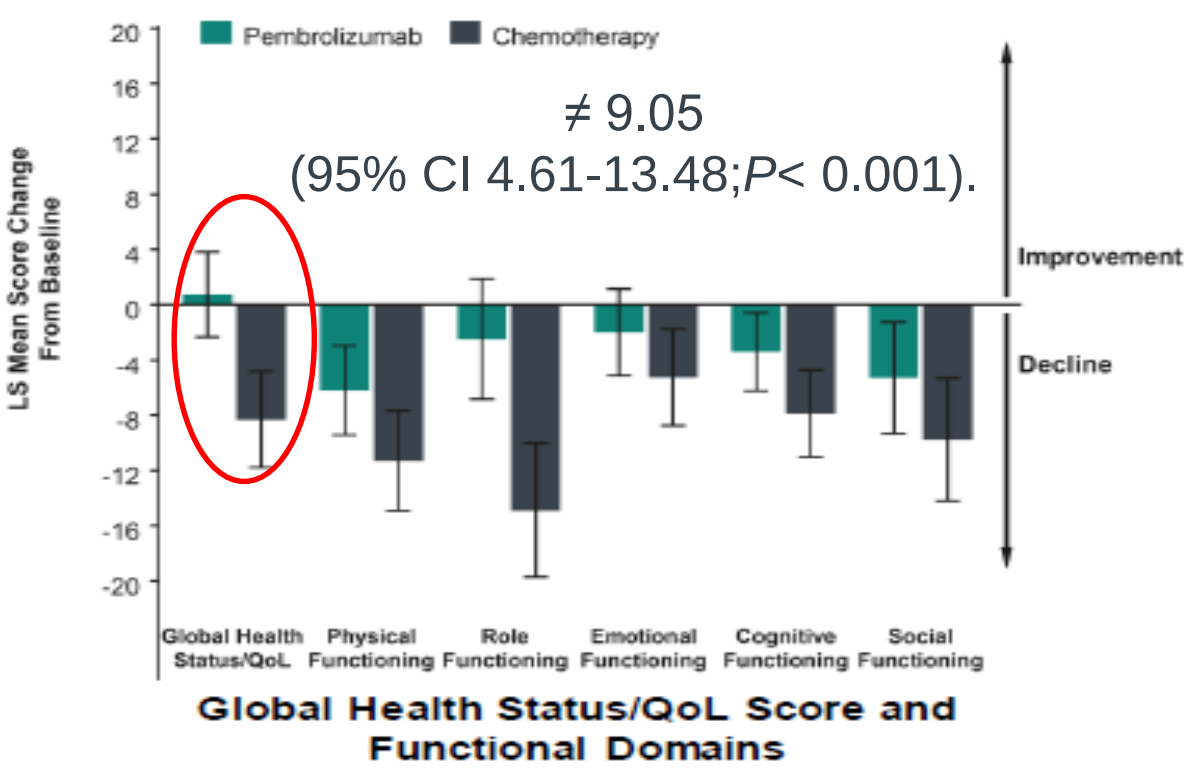


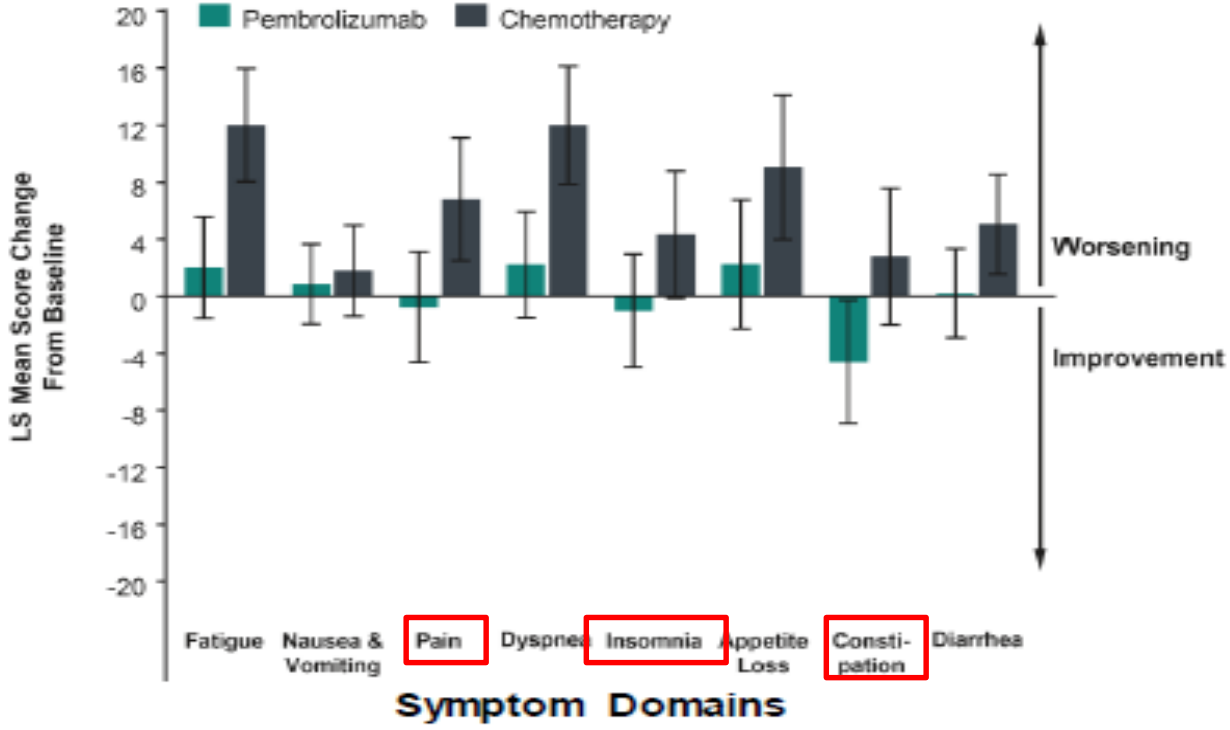
Wit R. J Clin Oncol 35, 2017 (suppl; abstr 4530)

KEYNOTE – 045

Change from Baseline to Week 15 in the Individual EORTC QLQ-C30

- Patients in the pembrolizumab arm had minimal change from baseline in the mean scores of the individual QLQ-C30 functional and symptom domains at week 15, whereas patients in the chemotherapy arm experienced worsening scores for almost all domains





Wit R. J Clin Oncol 35, 2017 (suppl; abstr 4530)

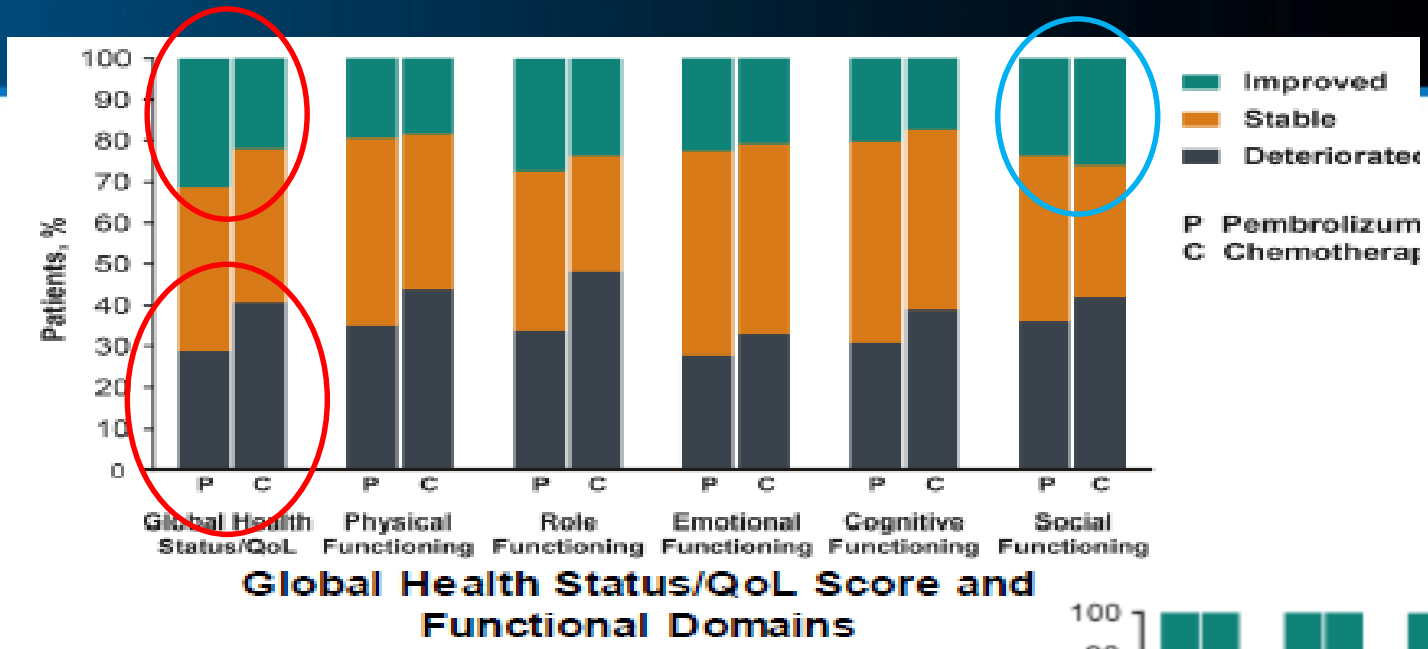
KEYNOTE – 045

Change, LS mean (95% CI)[a]	Pembrolizumab N = 266	Chemotherapy N = 254
Without disease progression	+5.97 (+2.48 to +9.46)	–4.31 (–8.02 to –0.60)
With disease progression	–3.54 (–6.95 to –0.13)	–13.95 (–17.75 to –10.15)

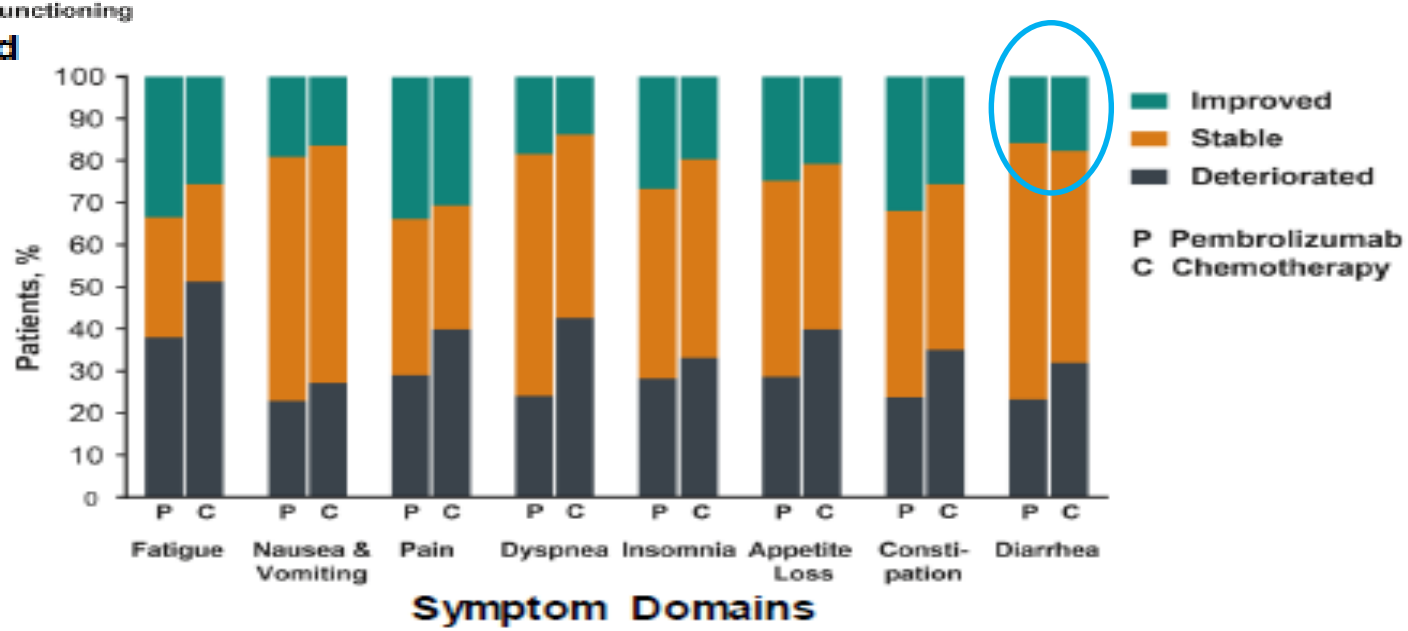
[a]Based on a constrained longitudinal data analysis model with the global health status/QoL score as the response variable, treatment by study visit interaction, disease progression status and disease progression status by treatment arm as covariates, and stratification by the randomization stratification factors (ie, ECOG performance status 0/1 vs 2, presence vs absence of liver metastases, hemoglobin ≥10 g/dL vs <10 g/dL, and time from completion of most recent chemotherapy ≥3 months vs <3 months).

Vaughn DJ. J Clin Oncol 35, 2017 (suppl 6S; abstract 282)

KEYNOTE – 045



Global Health Status/QoL Score and Functional Domains



Symptom Domains

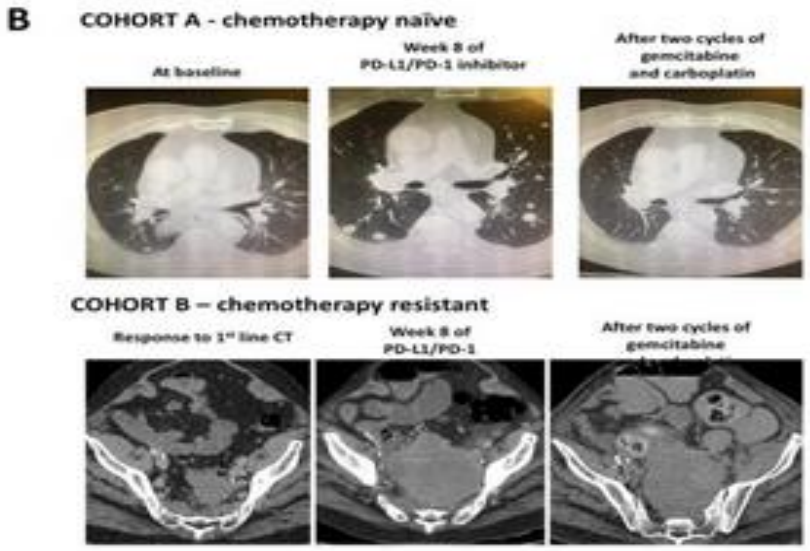
EORTC QLQ-C30 Global
Improved: 31.2% x 22.0%
Deterioration: 28.9% x 40.6%

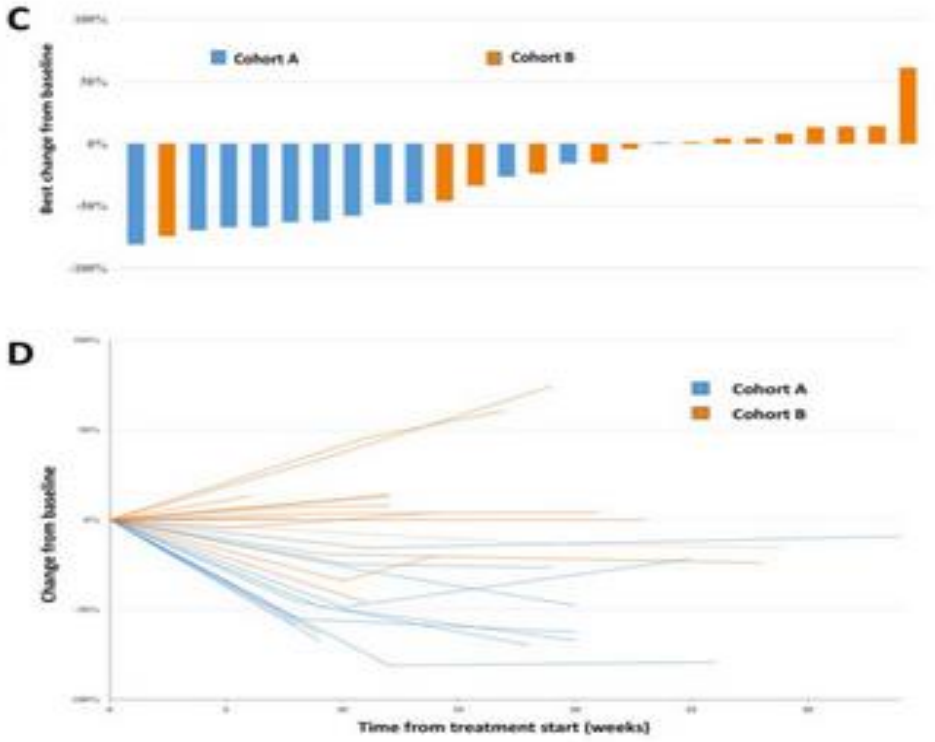
Wit R. J Clin Oncol 35, 2017 (suppl; abstr 4530)

E se a Imunoterapia não funcionar afinal…?

Chemotherapy is active in patients who have failed front line immune therapy (blue).

Cohort A: Prior IO only
Cohort B: Prior Chemo then IO





Szabados et al Eur Urol in press 2017

Qualidade de Vida

- Qualidade de Vida em carcinoma urotelial pós platina, Pembrolizumabe x QT :
  - Melhor HRQoL
  - > Tempo para Deterioração na HRQoL
  - > Sobrevida global
  - < Eventos Adversos

- **Pembrolizumabe é o novo padrão-ouro para carcinoma urotelial avançado platina-refratário.**
- **Única imunoterapia com ganho de SG em estudo randomizado fase 3.**

Conclusões e orientações

- Imunoterapia é eficiente do ponto de vista clínico e com melhor perfil de segurança
- Atenção para as *“**ITES**”*….
- Acompanhamento precoce com especialistas (G3-G4)
- Não ter medo do uso de corticóide quando indicado
- Não ter pressa para retirar corticóide (mínimo de 4 semanas)
- Não se reduz dose de Inibidores de *checkpoint*
  - Posterga ou Suspende
- Efeitos podem aparecer ou mesmo durar semanas após interrupção


Obrigado