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IV SIMPÓSIO MULTIPROFISSIONAL DE URO-ONCOLOGIA

1 a 3 de Março de 2018

SHERATON SÃO PAULO WTC HOTEL





# AVALIAÇÃO DE RESPOSTA COM OS IMUNOTERÁPICOS

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# Armas Disponíveis para Tratar o Câncer

- Cirurgia
- Quimioterapia
- Radioterapia
- Hormonioterapia
- Terapia Alvo Específico
- **IMUNOTERAPIA**

# Cancer Immunotherapy: Imaging Assessment of Novel Treatment Response Patterns and Immune-related Adverse Events<sup>1</sup>

*Jennifer J. Kwak, MD*

*Sree Harsha Tirumani, MD*

*Annick D. Van den Abbeele, MD*

*Phillip J. Koo, MD*

*Heather A. Jacene, MD*

**Abbreviations:** CTLA-4 = cytotoxic T-lymphocyte antigen-4, FDA = U.S. Food and Drug Administration, FDG = fluorodeoxyglucose, MIP = maximum intensity projection

**RadioGraphics** 2015; 35:424-437

**Published online** 10.1148/rg.352140121

**Content Codes:** GI MI NM OI

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Cancer immunotherapy is changing the imaging evaluation of cancer treatment response and treatment-related toxic effects. New emerging patterns of treatment response and treatment-related toxic effects after treatment with immunomodulating agents have been observed. Treatment response after immunomodulatory therapy can be associated with significantly delayed decrease in tumor size, and new or enlarging tumors observed soon after completion of treatment may not reflect disease progression. In addition, activation of the immune system to fight cancer may lead to unwanted autoimmune-mediated toxic effects that could be mistaken for metastatic disease or misdiagnosed as a non-treatment-related process and delay appropriate clinical management. Radiologists must recognize the novel treatment response patterns and the wide range of autoimmune toxic effects, which should not be mistaken for treatment failure or metastatic disease progression.

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## IMAGEM EM IMUNOTERAPIA

RADIOGRAPHICS 2015; 35: 424-437



## **Cancer Therapy: Clinical**

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# **Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria**

Jedd D. Wolchok,<sup>1</sup> Axel Hoos,<sup>2</sup> Steven O'Day,<sup>3</sup> Jeffrey S. Weber,<sup>4</sup> Omid Hamid,<sup>3</sup> Celeste Lebbé,<sup>5</sup> Michele Maio,<sup>6</sup> Michael Binder,<sup>7</sup> Oliver Bohnsack,<sup>8</sup> Geoffrey Nichol,<sup>9</sup> Rachel Humphrey,<sup>2</sup> and F. Stephen Hodi<sup>10</sup>

**Abstract** **Purpose:** Immunotherapeutic agents produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. Resulting clinical response patterns extend beyond those of cytotoxic agents and can manifest after an initial increase in tumor burden or the appearance of new lesions (progressive disease). Response Evaluation Criteria in Solid Tumors or WHO criteria, designed to detect early effects of cytotoxic agents, may not provide a complete assessment of immunotherapeutic agents. Novel criteria for the evaluation of antitumor responses with immunotherapeutic agents are required.

**Experimental Design:** The phase II clinical trial program with ipilimumab, an antibody that blocks CTL antigen-4, represents the most comprehensive data set available to date for an immunotherapeutic agent. Novel immune therapy response criteria proposed, based on the shared experience from community workshops and several investigators, were evaluated using data from ipilimumab phase II clinical trials in patients with advanced melanoma.

**Results:** Ipilimumab monotherapy resulted in four distinct response patterns: (a) shrinkage in baseline lesions, without new lesions; (b) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (c) response after an increase in total tumor burden; and (d) response in the presence of new lesions. All patterns were associated with favorable survival.

**Conclusion:** Systematic criteria, designated immune-related response criteria, were defined in an attempt to capture additional response patterns observed with immune therapy in advanced melanoma beyond those described by Response Evaluation Criteria in Solid Tumors or WHO criteria. Further prospective evaluations of the immune-related response criteria, particularly their association with overall survival, are warranted. (Clin Cancer Res 2009;15(23):7412–20)

# IMUNOTERAPIA



- Estratégia desenhada para atacar o TU através do sistema imune
- O tratamento não ataca a célula tumoral diretamente,
- Através de uma estimulação do sistema imune
- Melanoma, pulmão, cólon, rim, bexiga urinária, hematológico, mama.

55 a, masc, tabagista

T2b X T3a

CA vesical



# CISTOPROSTATECTOMIA RADICAL, LINFADENECTOMIA, RECONSTRUÇÃO ORTOTÓPICA

Axial Volume 1

A 155

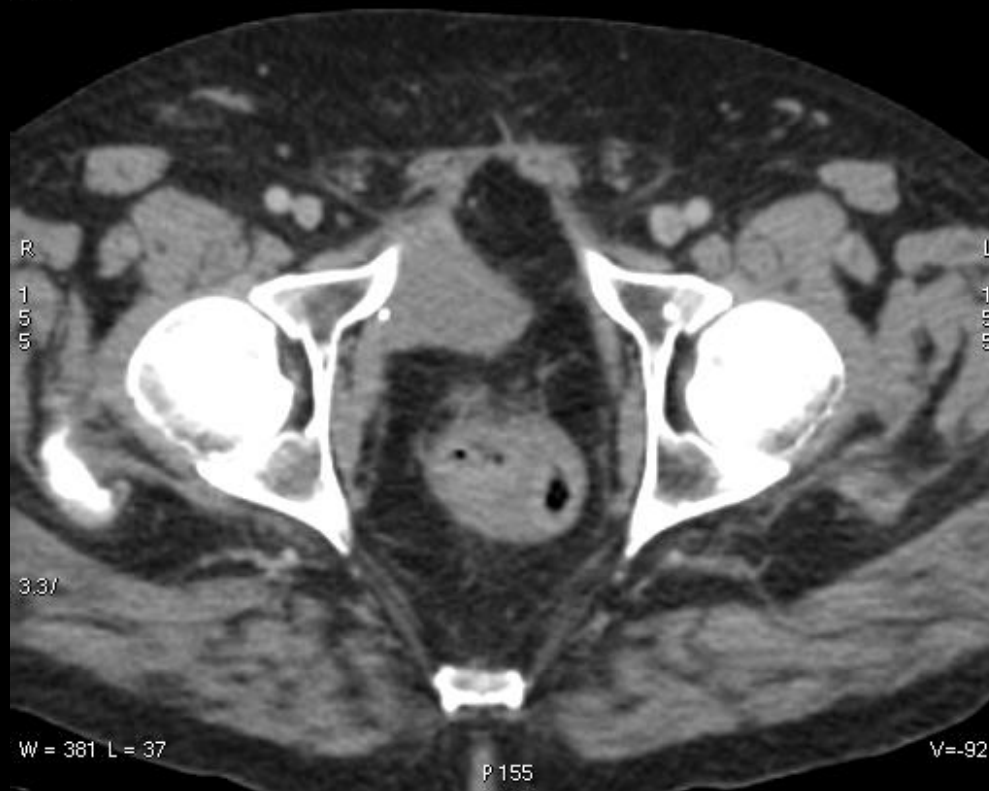
....

I: 729.7

Im: 261

DFOV 31.0cm

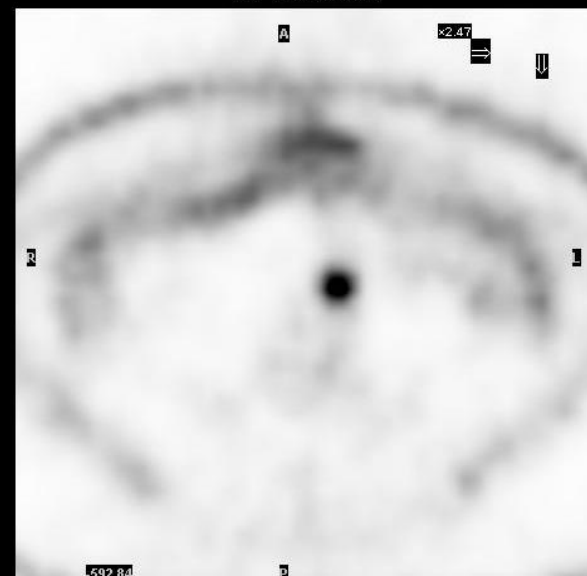
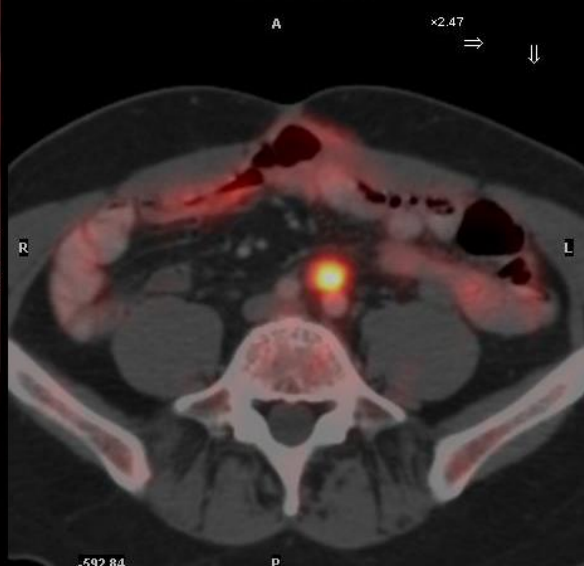
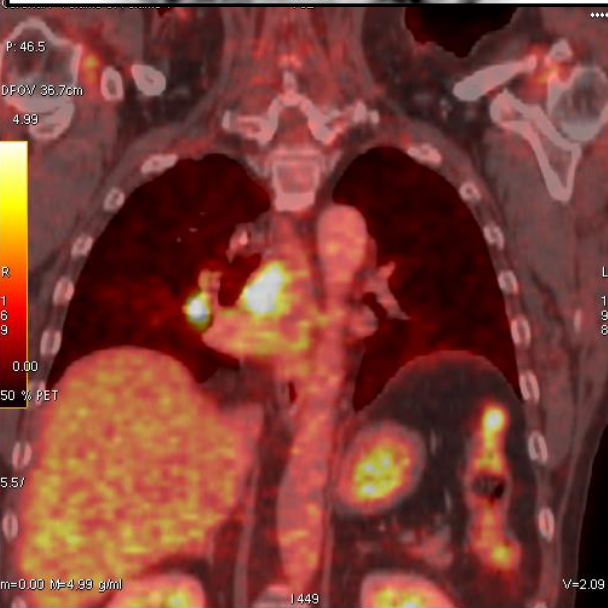
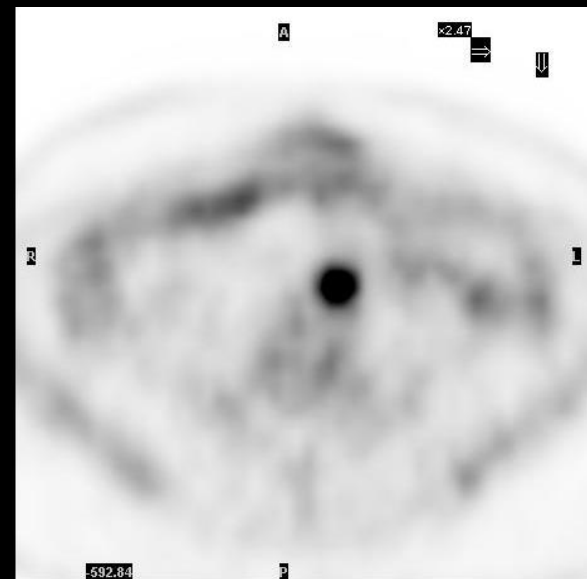
STND



DIAG. Invasão Colo vesical = T3  
CA céls. TRANSICIONAIS



# 06 MESES APÓS CISTECTOMIA

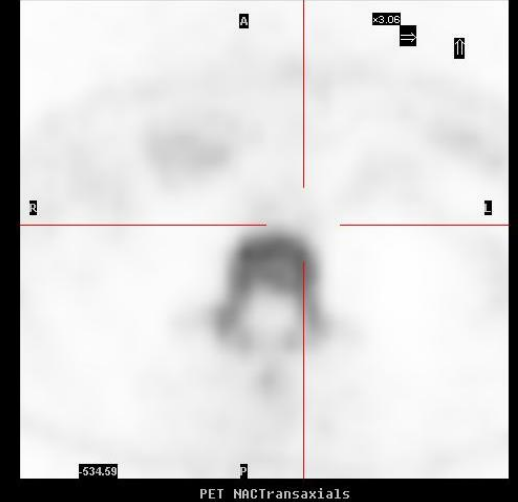
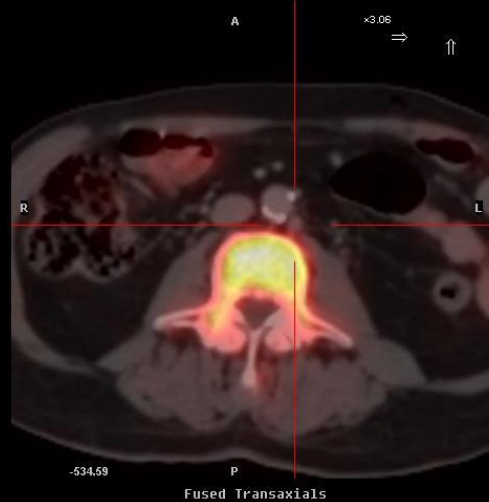
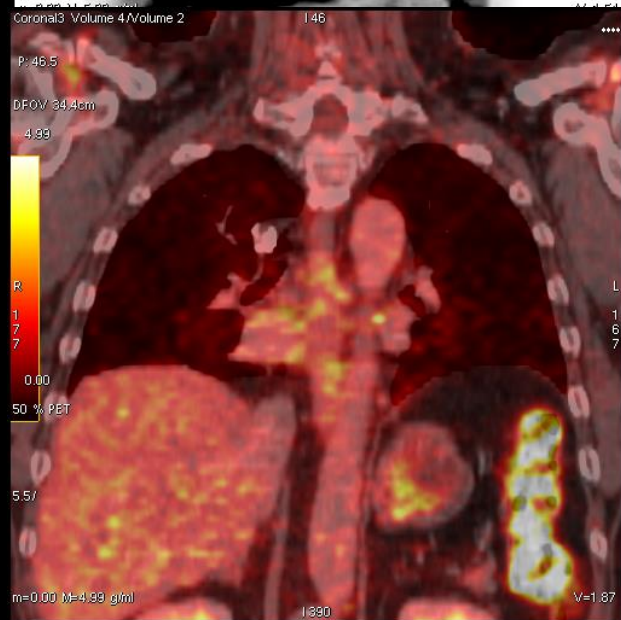
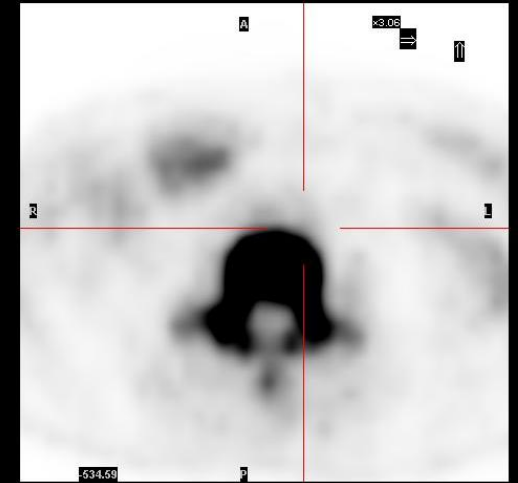


CT Transaxials

PET Transaxials

# IMUNOTERAPIA

## 08 SEMANAS



# Primórdios da Imunoterapia Tumoral

CONTRIBUTION TO THE KNOWLEDGE OF  
SARCOMA.<sup>1</sup>

By WILLIAM B. COLEY, M.D.,

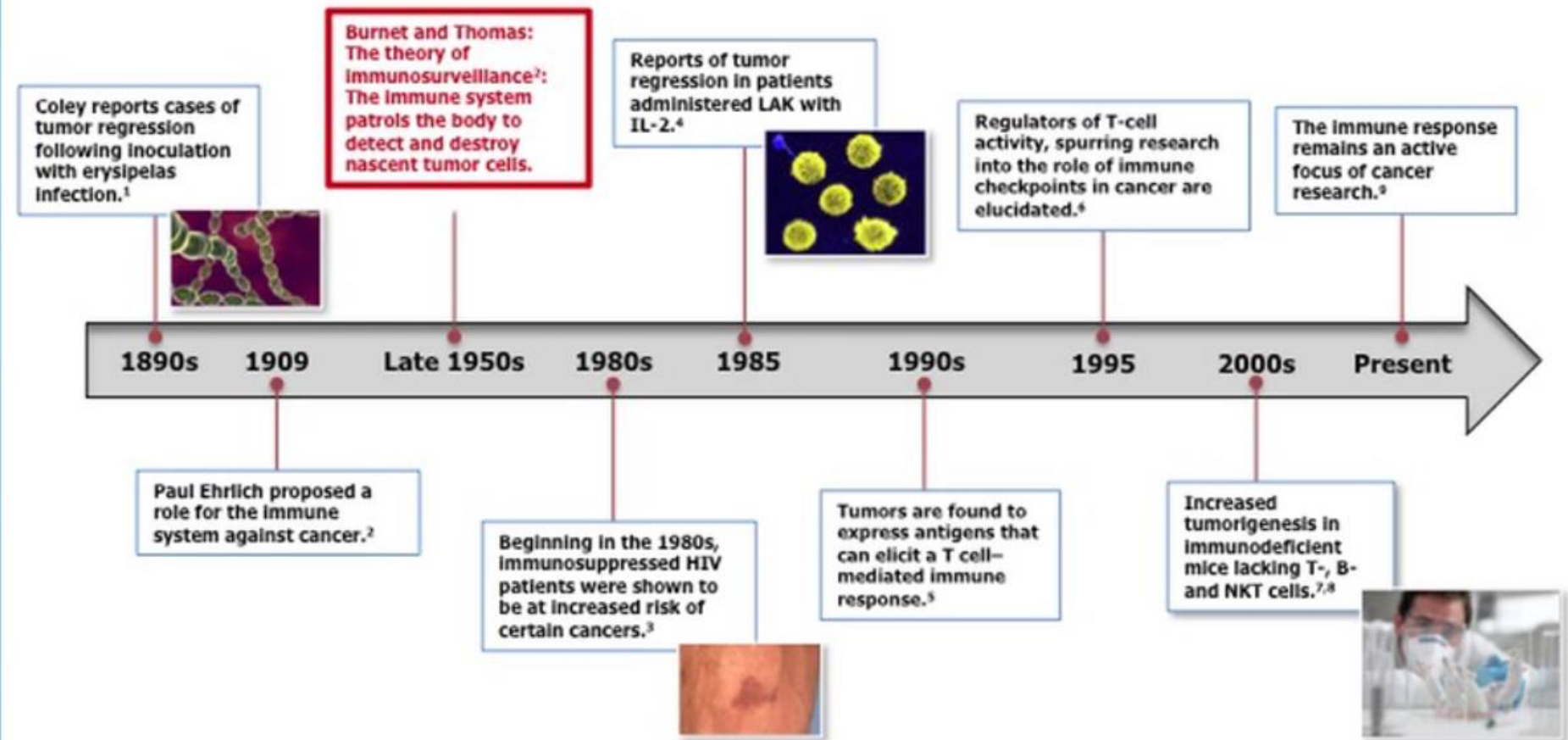
Annals of Surgery 14: 199-220, 1981

- William B. Coley, 1862-1936
- Chefe da Bone Sarcoma Unit no Memorial Hospital – New York
- 1891 – primeira injeção de *Streptococcus pyogenes* em paciente com sarcoma
- 1893 – injeção de *Streptococcus pyogenes* e *Serratia marcescens* inativados por calor
- Mais de mil pacientes com sarcomas e carcinomas foram tratados por ele.





# What Have We Learned About the Role of the Immune System in Oncology ?



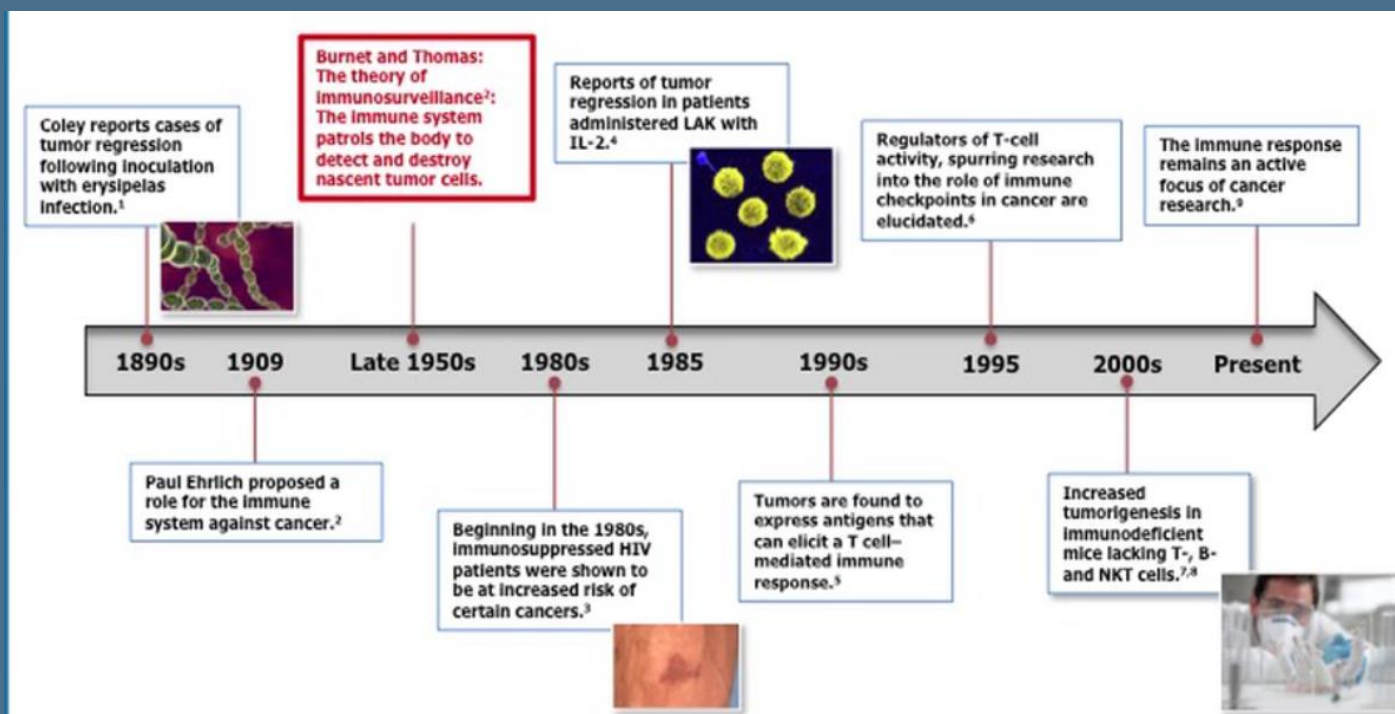
HIV = human immunodeficiency virus;  
LAK = lymphokine-activated killer;  
IL-2 = interleukin-2;  
NKT = natural killer T.

1. Coley WB. *Am J Med Sci.* 1893;105:487–511. 2. Ichim CV. *J Transl Med.* 2005;3:8.  
3. Levine AM et al. *Curr Probl Cancer.* 1987;11:209–55. 4. Rosenberg SA et al. *N Engl J Med.* 1985;313:1485–1492. 5. van der Bruggen P et al. *Science.* 1991;254:1643–1647. 6. Tivol EA. et al. *Immunity.* 1995;3:541–547. 7. Vesely MD et al. *Annu Rev Immunol.* 2011;29:235–271. 8. Shankaran V. et al. *Nature.* 2001;410:1107–1111. 9. Drake CG et al. *Nat. Rev. Clin. Oncol.* 2014;11: 24–37.

# INTERLEUCINA 2



- **1985** – IMUNOTERAPIA
- IL-2 : estimula as células imunes a aumentarem em número para combater o tumor





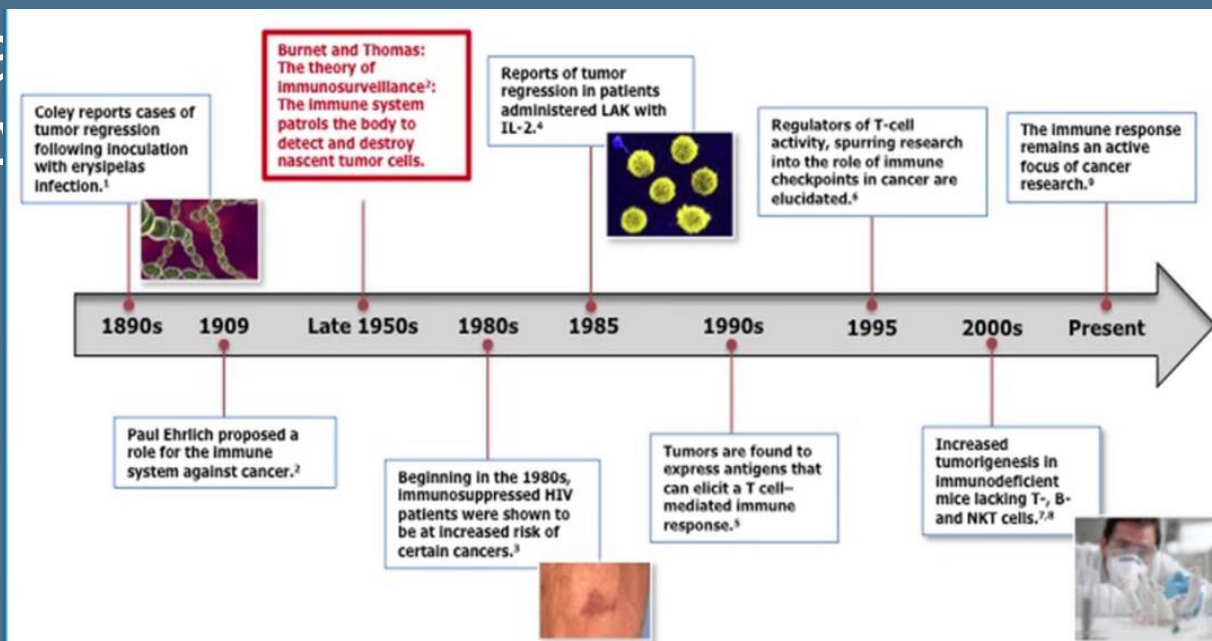
# CHECK POINT



(ponto de controle do sistema imune)

- **1995** – Como o sistema imune faz a checagem ?
- O sistema imune tem que ter um “ FREIO ” ...
- Não pode ficar ativo o tempo todo !!
- Consequência  
IMUNOMEDIA

*James P. Allison*  
 MD. ANDERSON  
 CANCER CENTER

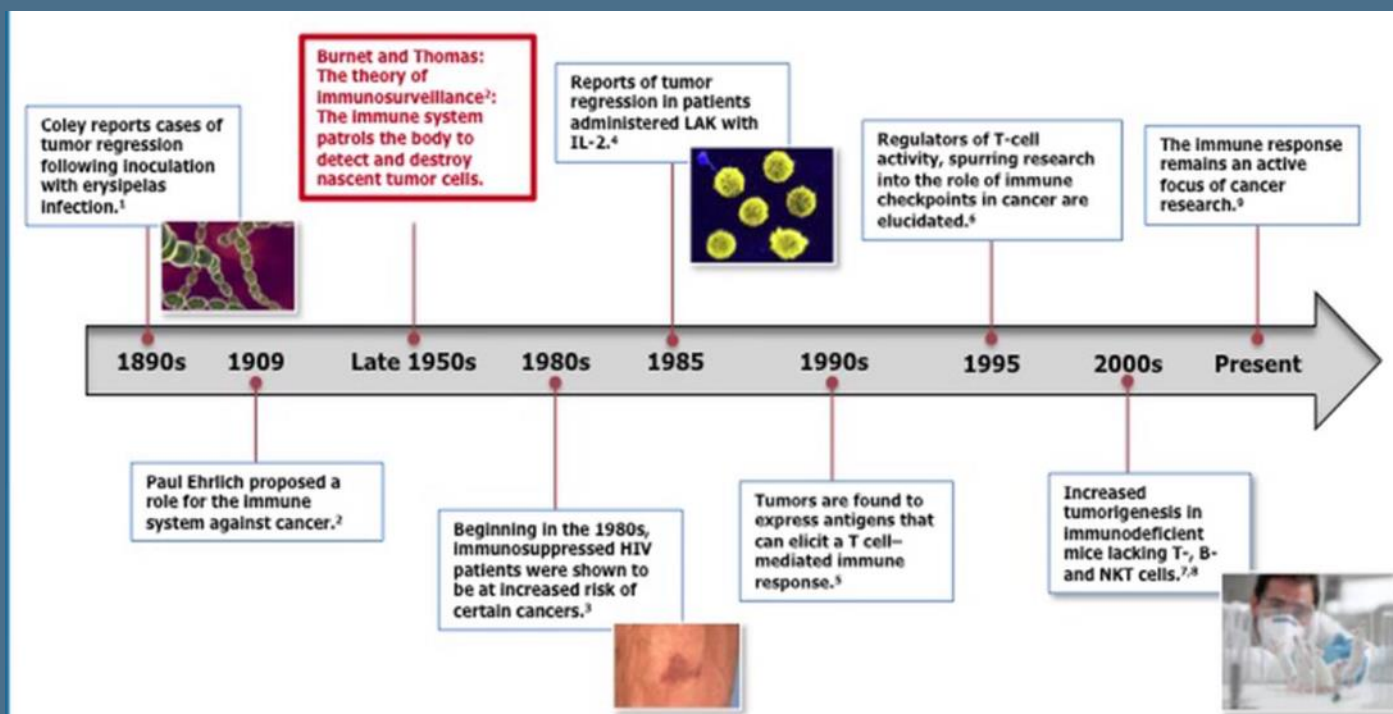


# CTLA – 4

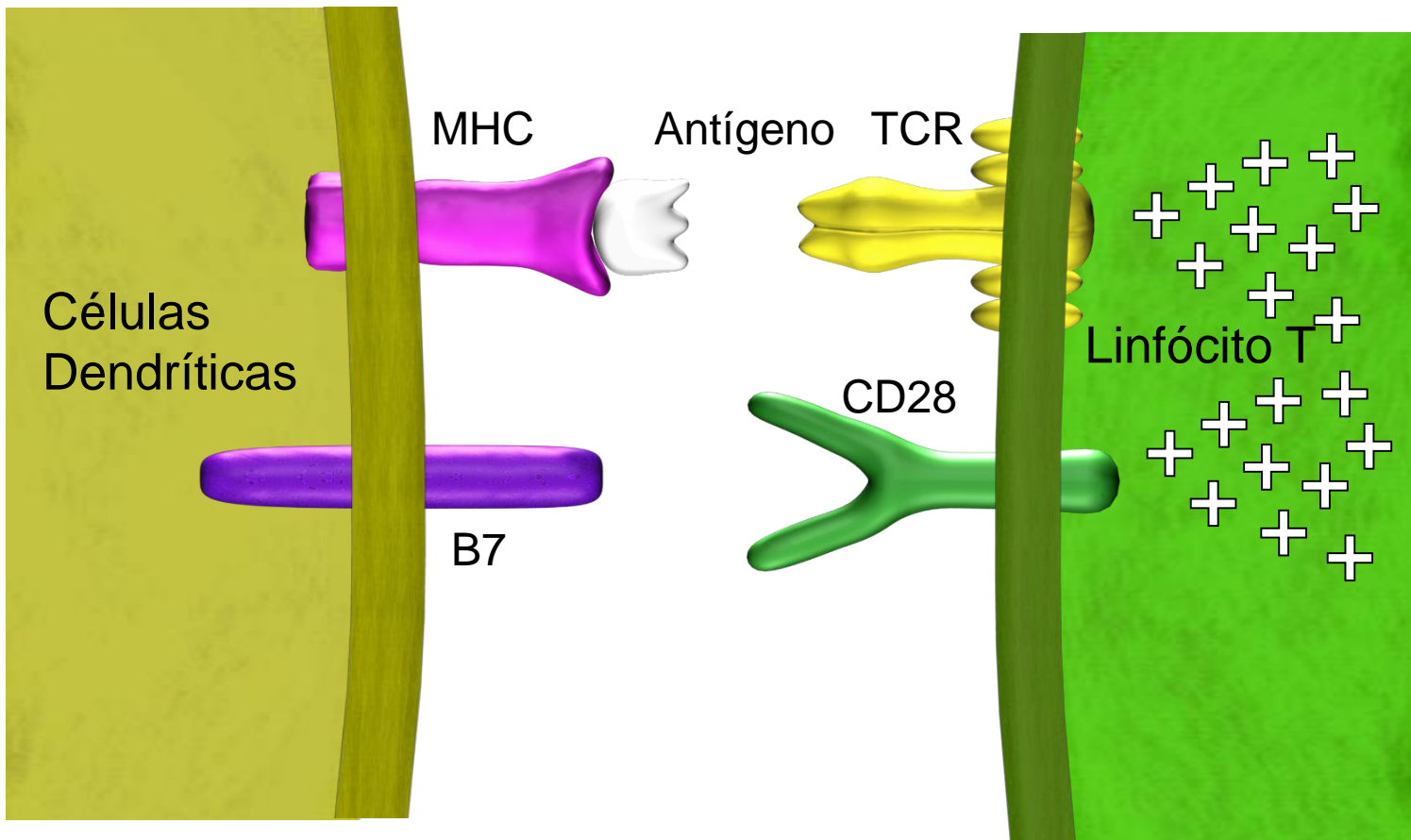


## (Cytotoxic T-Lymphocyte-associated protein 4)

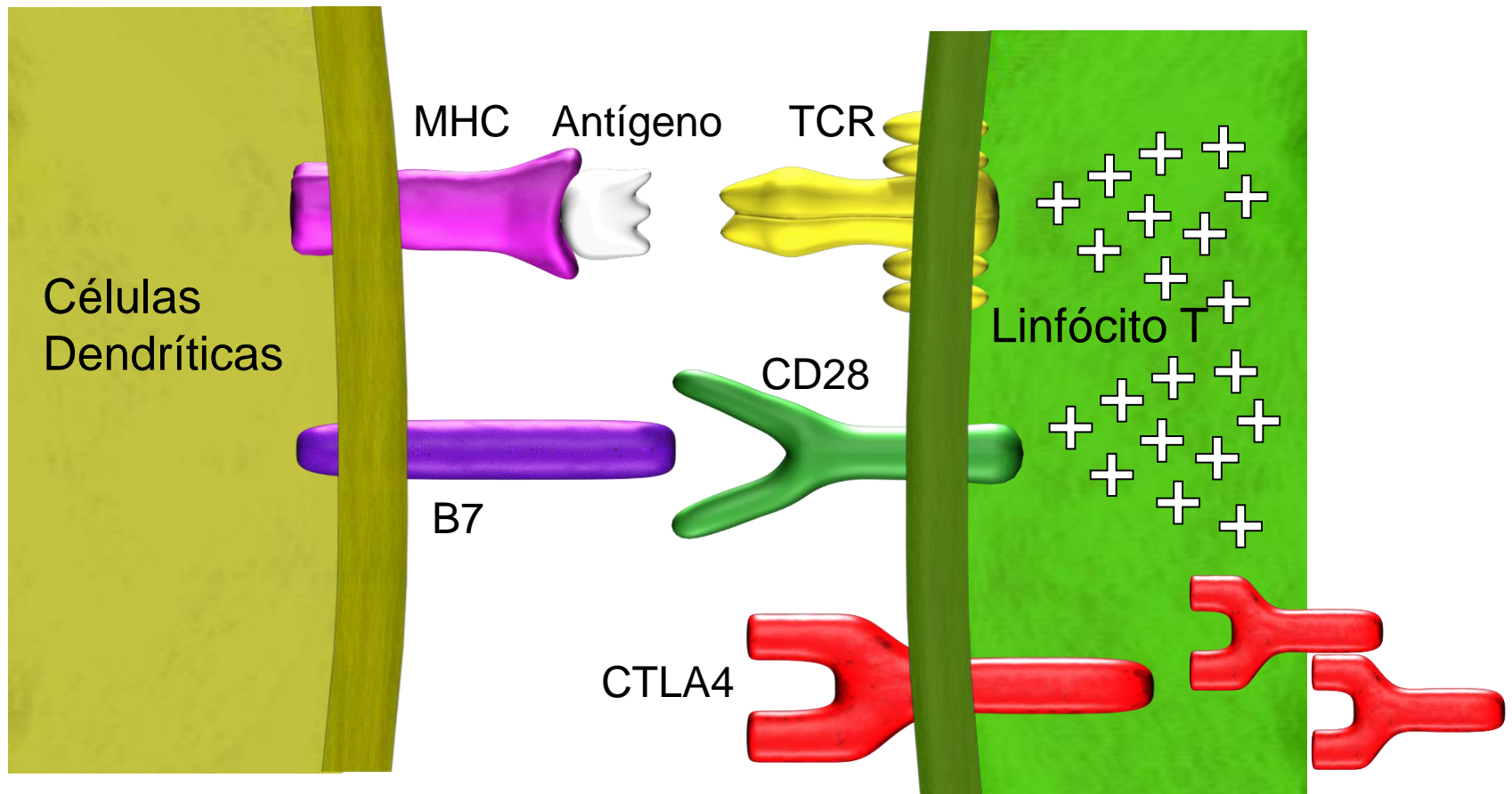
- *Check point*
- **1995** – Início da imunoterapia moderna



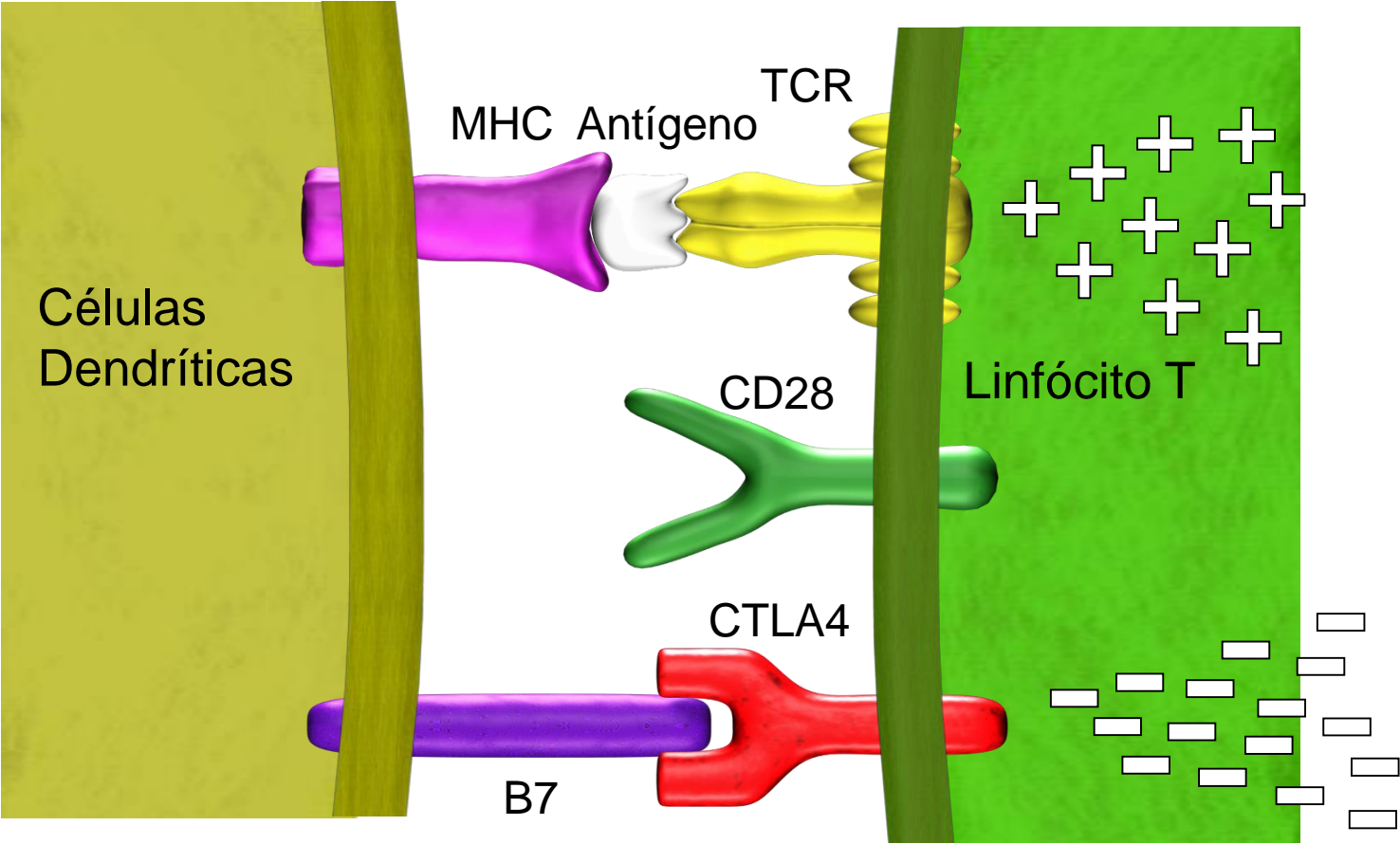
# Apresentação do Antígeno (TU) pela Célula Dendrítica (APC)



# Receptores CTLA4 “Up-Regulated” depois da ativação do linfócito T

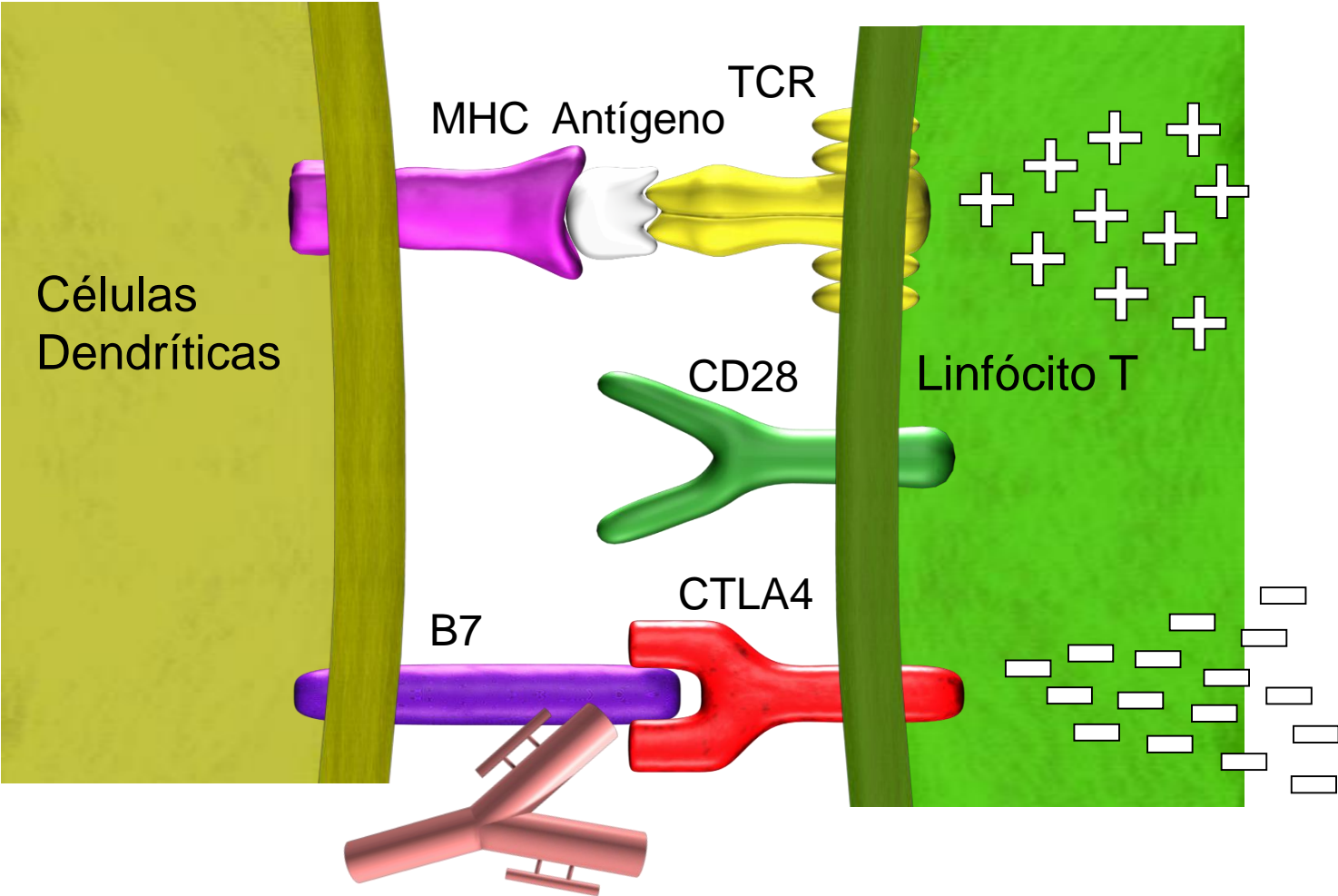


# CTLA4 Modula Negativamente a Activação de Linfócito T



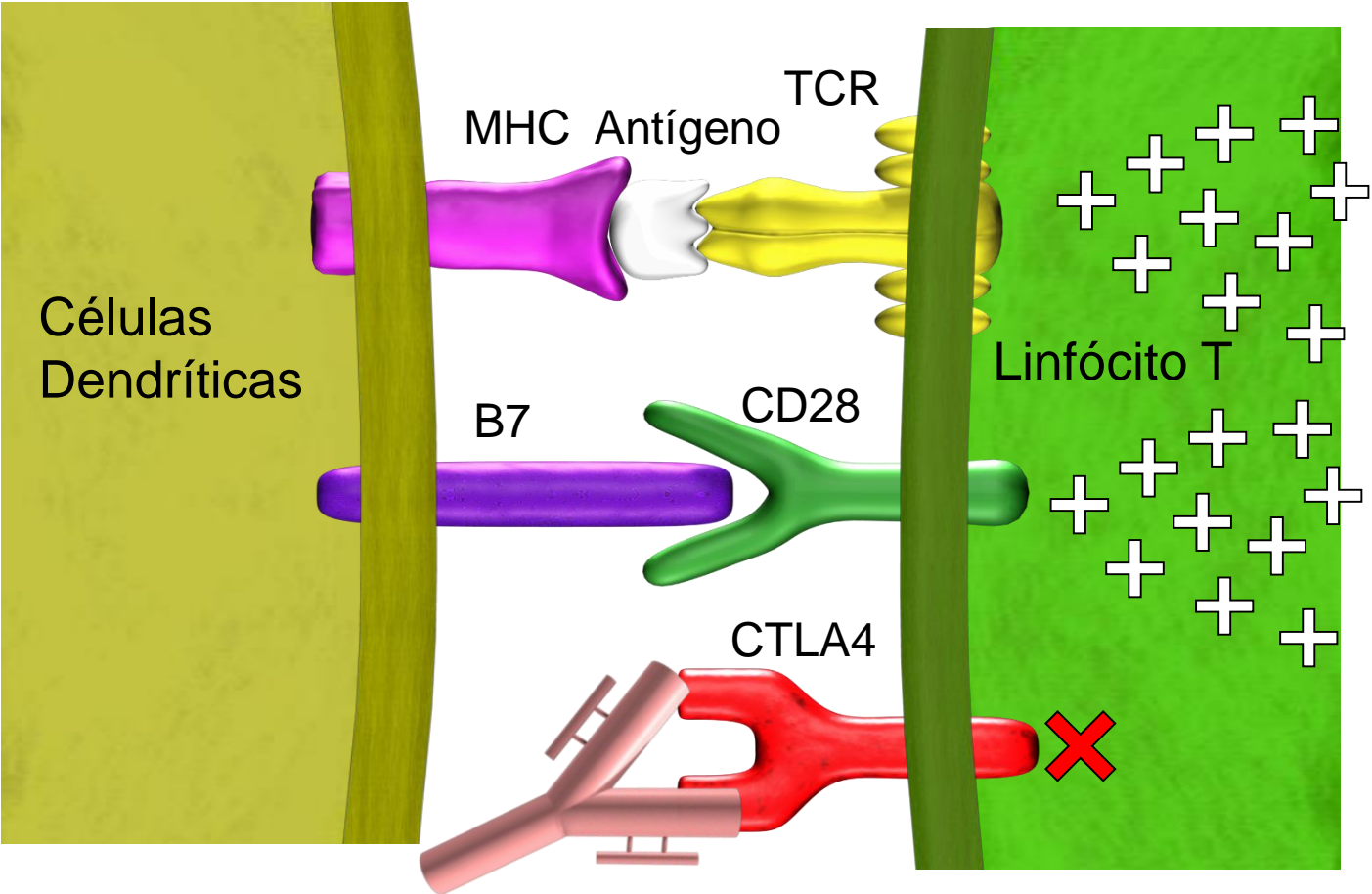


# Bloqueio do CTLA4: elimina o “freio” da ativação do linfócito T



Anti CTLA 4 evita interação com o B7.

# Bloqueio do CTLA4: elimina o “freio” da ativação do linfócito T



# IMUNOTERAPIA



- CTLA – 4: antígeno citotóxico de linfócitos T,  
evita que o Linfócito T agrida o  
sistema imune

- Inibidor de *check point*:  
**Anti CTLA 4** = IPILIMUMABE

“ não deixa o linfócito T dormir ... ”

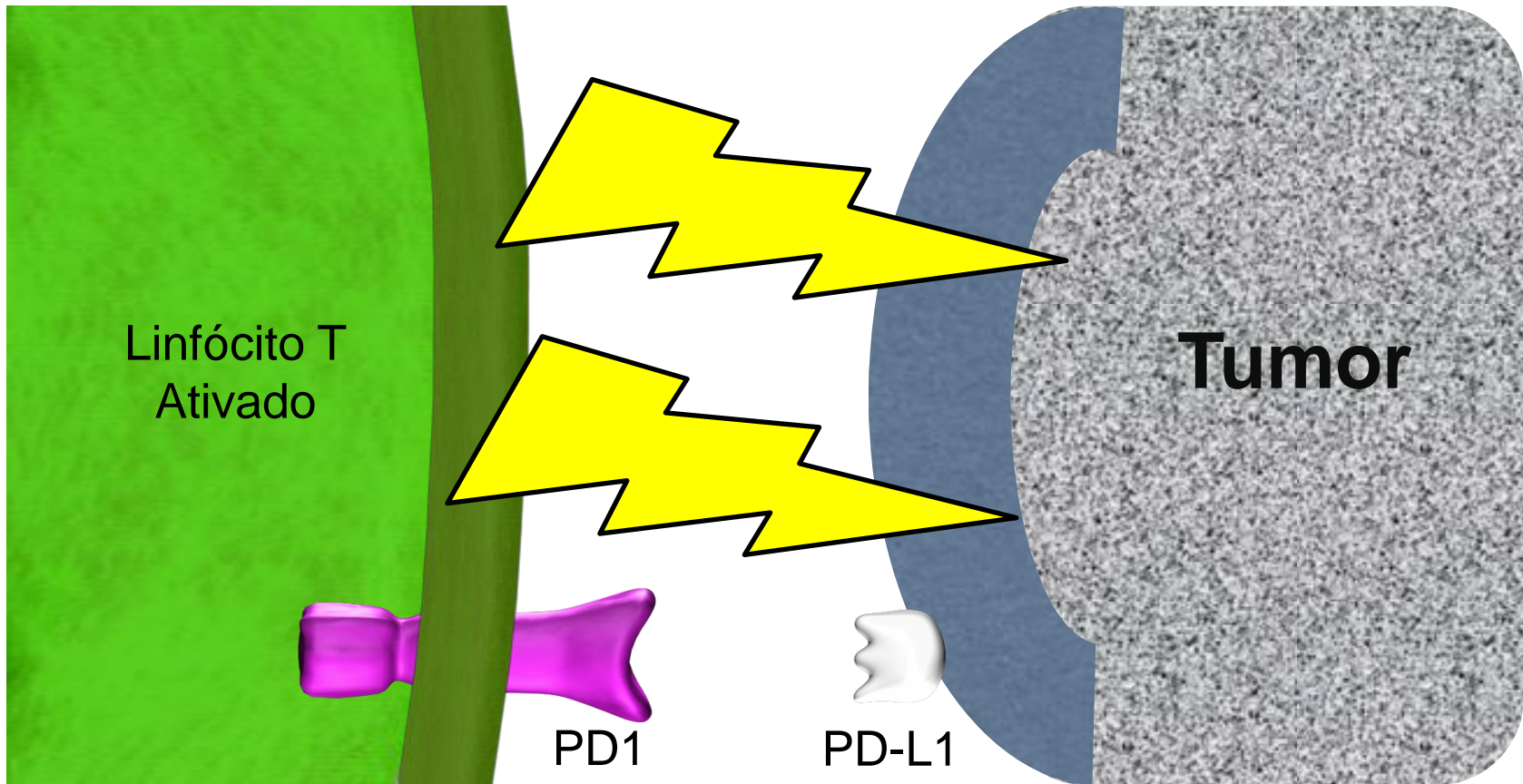
# IMUNOTERAPIA

## ponto de controle do sistema imune



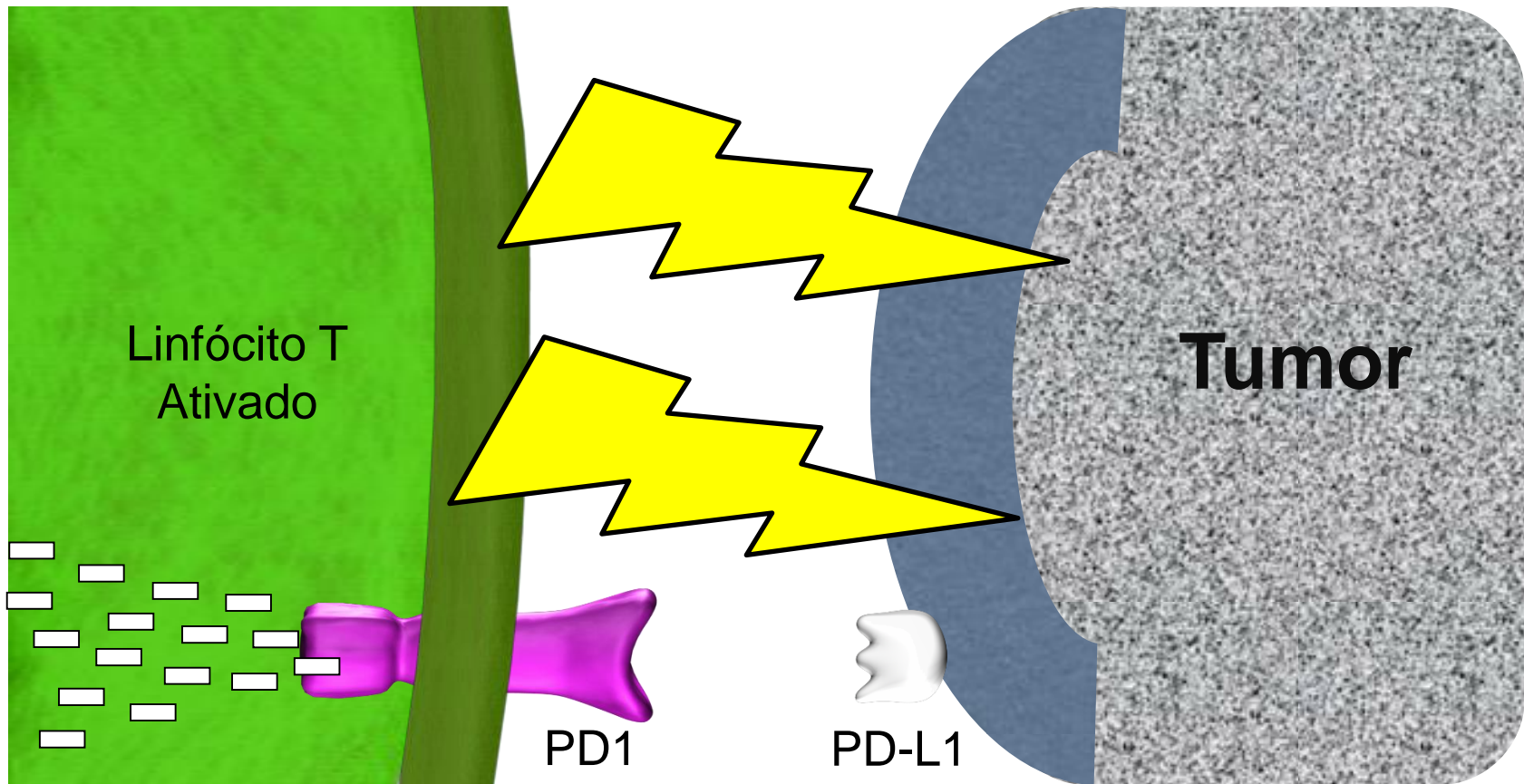
*Check point* **PD 1/PD L1** : marcadores de superfície;  
receptores de programação de morte celular na superfície do Linfócito T

# Evasão do sistema imune mediada pelo PD1/PDL1

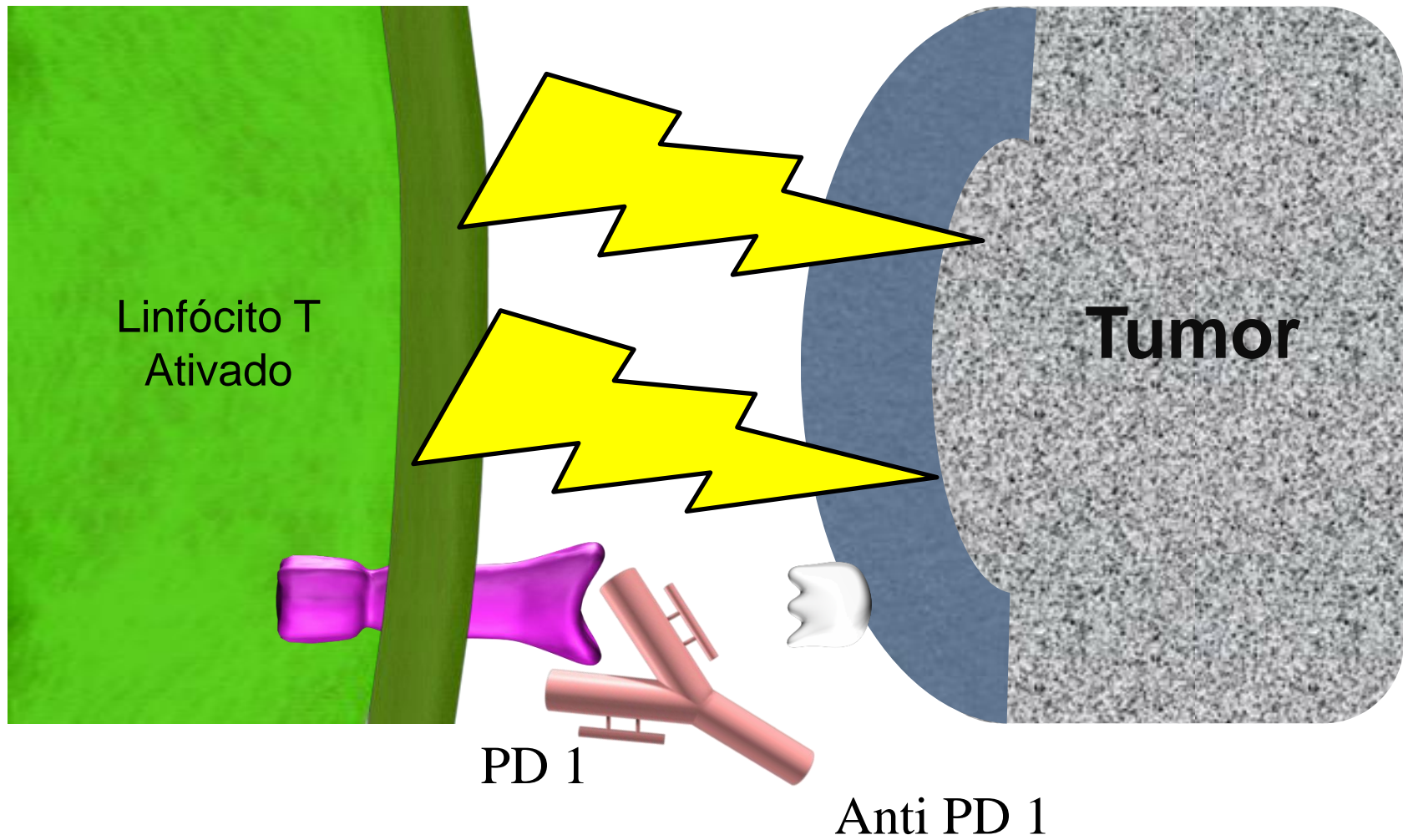




# Evasão do sistema imune mediada pelo PD1/PDL1



# Evasão do sistema imune mediada pelo PD1/PDL1





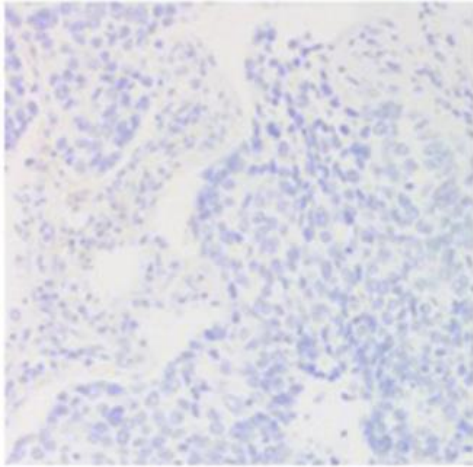
# Inibidores de *check point*

- **Anti – PD 1** (ex: NIVOLUMABE, PEMBROLIZUMABE)

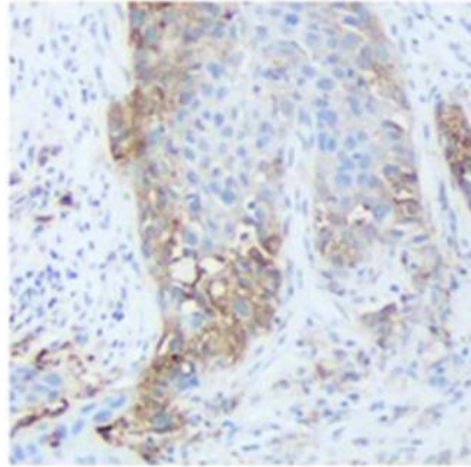
“ bloqueia o PD L1 que freiaria e paralisaria o linfócito T...”

# IHQ – EXPRESSÃO PDL-1 (BIOMARCADOR no TU)

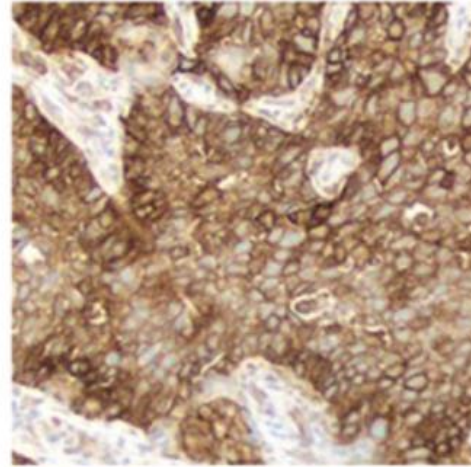
PS <1%



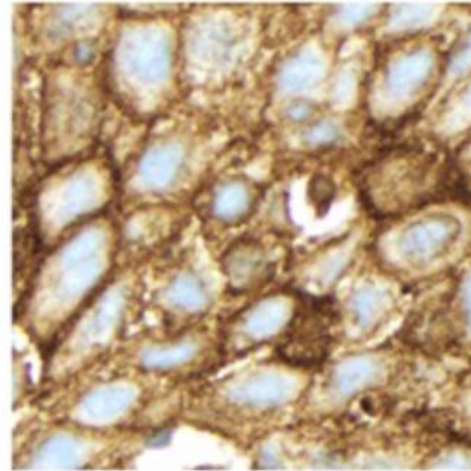
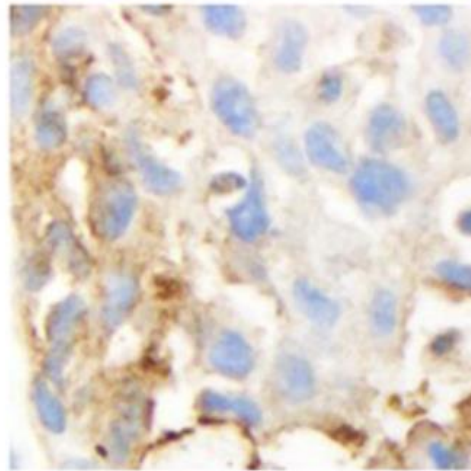
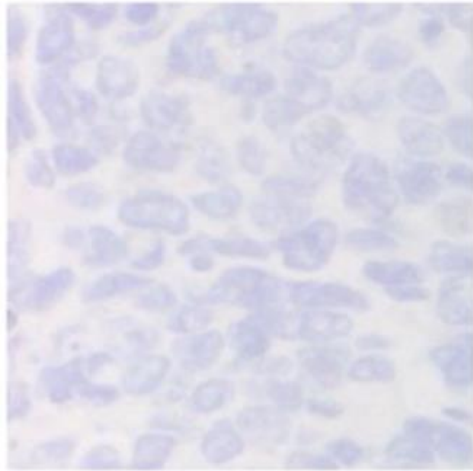
PS 1-49%



PS ≥50%



5x  
magnification



40x  
magnification

Brown chromogen: PD-L1 staining.  
Blue color: hematoxylin counterstain.

Garon\_AACR 2015\_19Apr15

ponto de corte



# IMUNOTERAPIA



## PROBLEMA GRAVE !!!

- Alguns tipos não atuam no SNC
- IL - 2

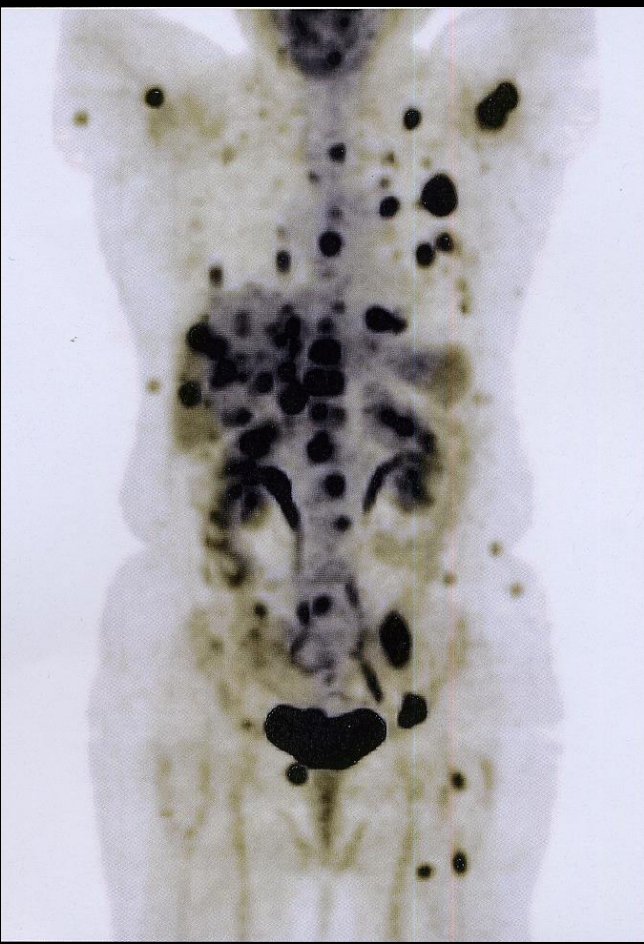


# MELANOMA METASTÁTICO

26/09/2006

17/01/2007

04/03/2017

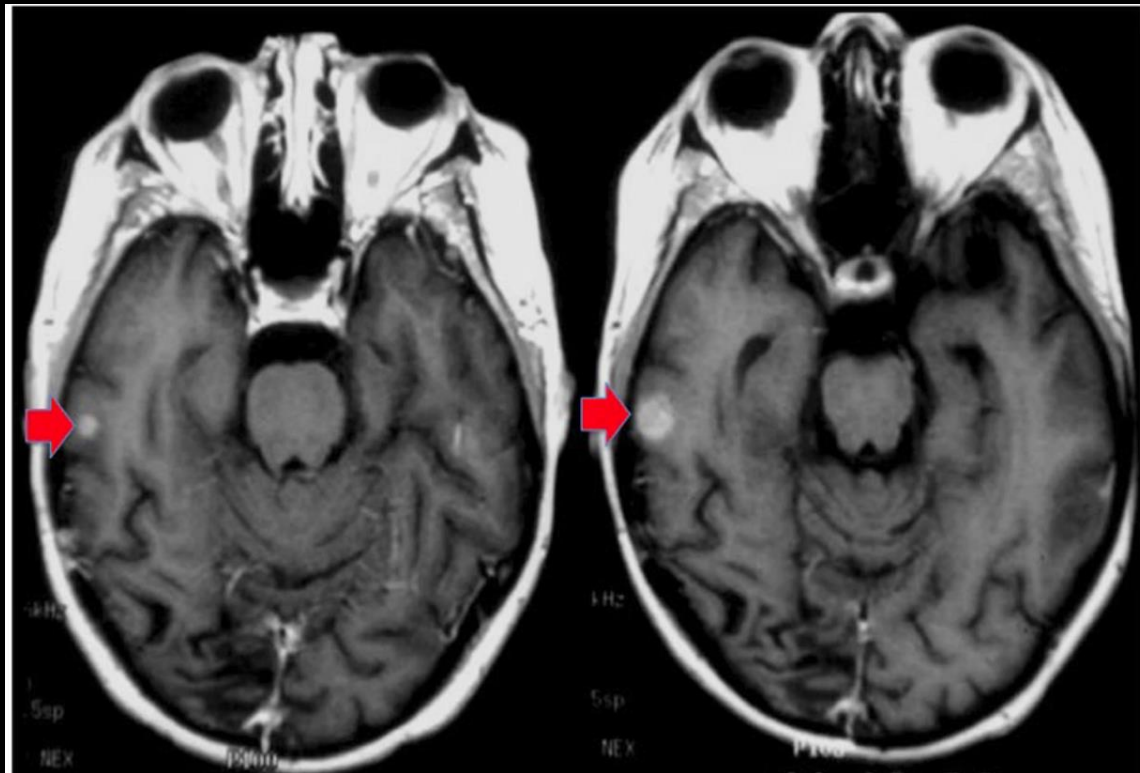


IMUNOTERAPIA IL - 2

# IMUNOTERAPIA

PROBLEMA GRAVE !!!

- Não atua no SNC



17/01/2007

04/03/2007

# IMUNOTERAPIA

## **irRC** – *Immune related response criteria*

- Proporciona uma caracterização mais rigorosa das formas de resposta atípica
- Previne interrupção prematura do tratamento

*Proc Natl Acad Sci USA 2008; 105:3005–3010*

*Clin Cancer Res 2009; 15(23)*

*Journal of Clinical Oncology 2016; 34: 1510-1517*

*Radiographics 2015; 35: 424-437*

# IMUNOTERAPIA - IrRC

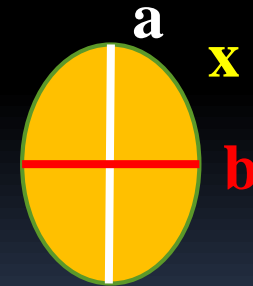
## Seguimento

- 03 exames consecutivos (baseline e F up)
- Intervalo até 12 semanas após tratamento
- Avaliação **CARGA TUMORAL**
- PD  $\geq$  25 % aumento carga tumoral
- RP  $\geq$  50 % diminuição carga tumoral

# IMUNOTERAPIA - IrRC

## Seguimento

- 5 lesões/órgão até 10 lesões viscerais (**lv**)
- 5 lesões cutâneas (**lc**)
- Máximo 15 lesões alvo
- Lesões novas (**ln**  $\geq 0,5 \times 0,5$  cm)
- Medida bidimensional (SPD)

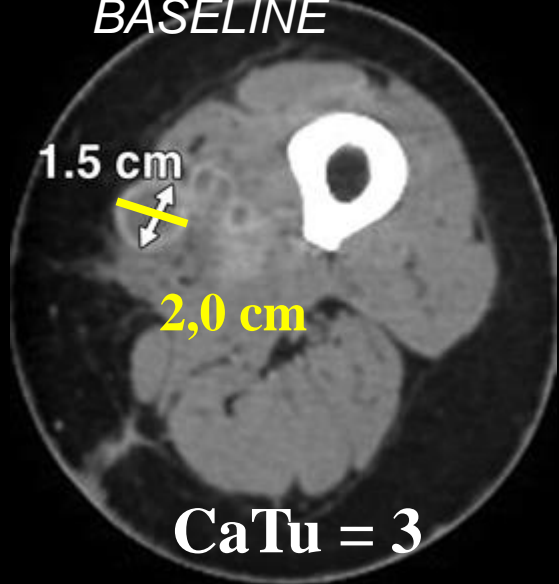


- **Carga tu = SPD (lv e lc) + SPD (ln)**



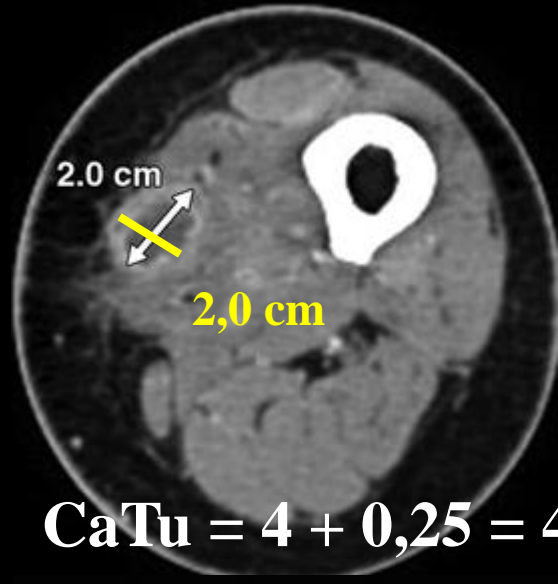
# Carga tumoral (CaTu)

15/ FEV / 2011  
BASELINE



12 SEMANAS

15/ MAI/ 2011



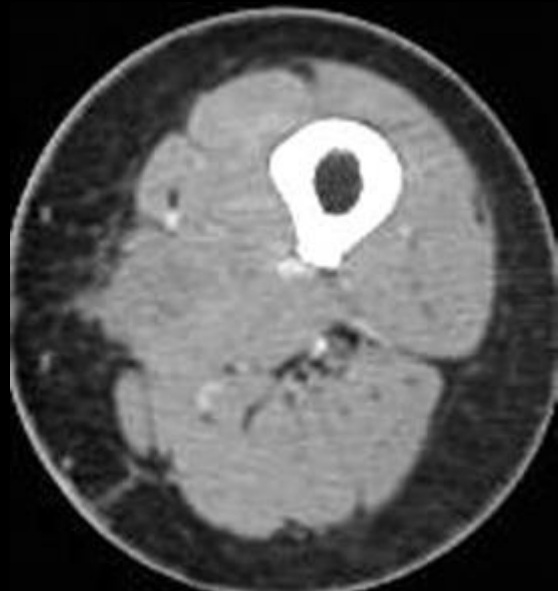
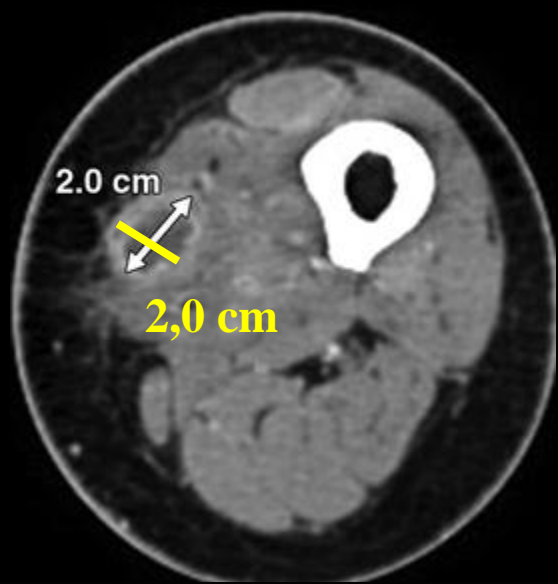
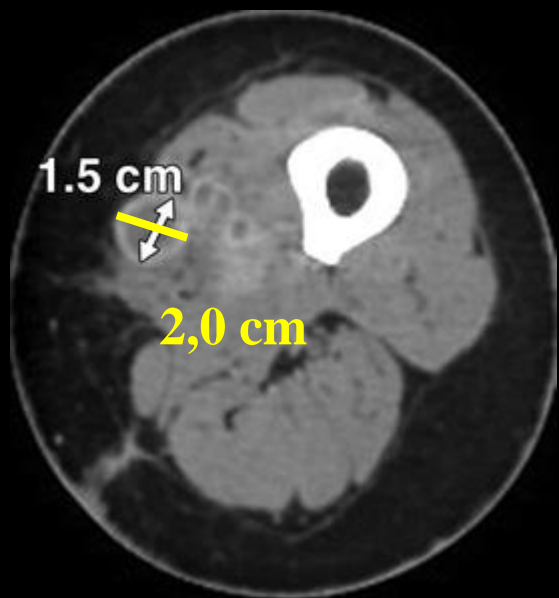
MELANOMA METASTÁTICO

CaTu = 3  $\Rightarrow$  4,25 (42%)

15/ FEV / 2011

15/ MAI / 2011

15/ JUN / 2011



MELANOMA METASTÁTICO

*Proc Natl Acad Sci USA 2008; 105:3005–3010*

# IMUNOTERAPIA - IrRC

## 04 Tipos de resposta

**TIPO 1** - Diminuição tumoral

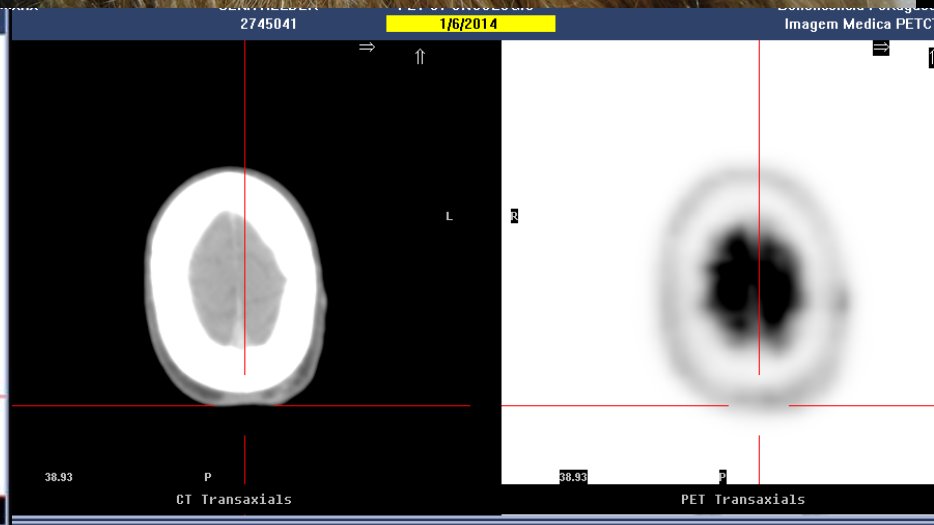
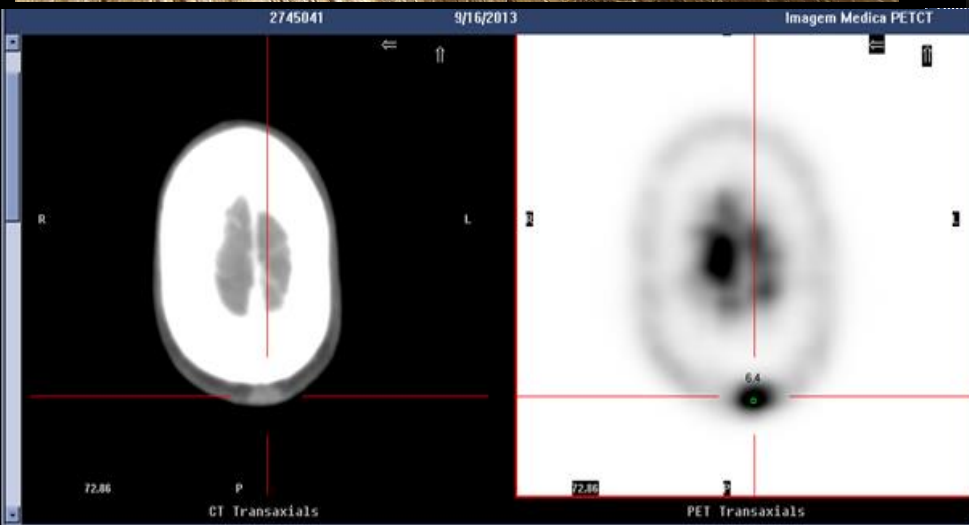
**TIPO 2** - Doença estável

*Proc Natl Acad Sci USA 2008; 105:3005–3010*  
*Clin Cancer Res 2009; 15(23)*  
*Radiographics 2015; 35: 424-437*



# IMUNOTERAPIA

IrRC - Tipo 01 de resposta (regressão)



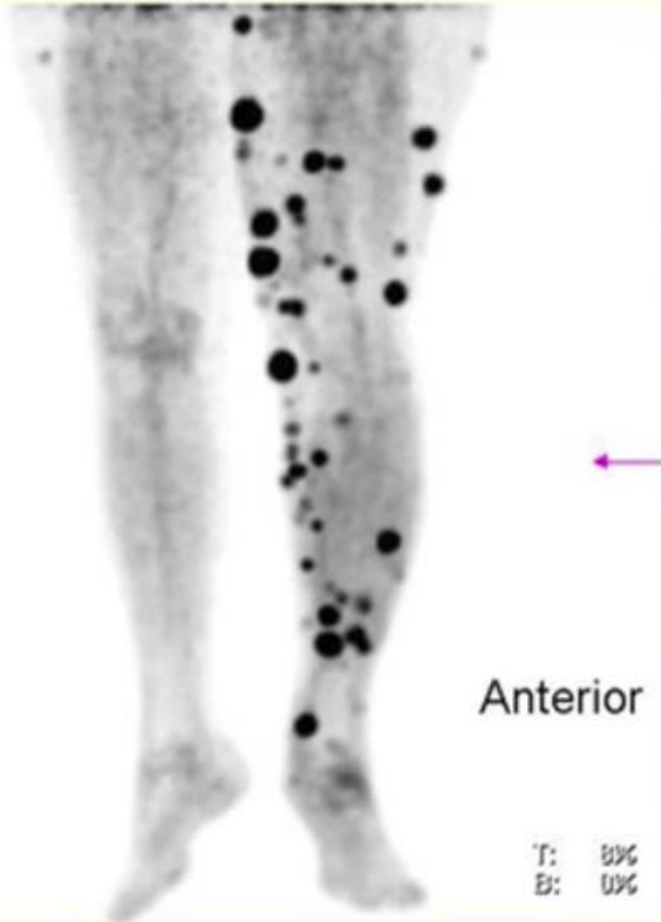
**PRÉ**

**PÓS**

# IMUNOTERAPIA

## IrRC - Tipo 02 de resposta (dça estável)

Pré-Tratamento



03 meses

Pós-Ipilimumab



Menos de 50 % diminuição carga tumoral



# IMUNOTERAPIA - IrRC

## Tipos de resposta

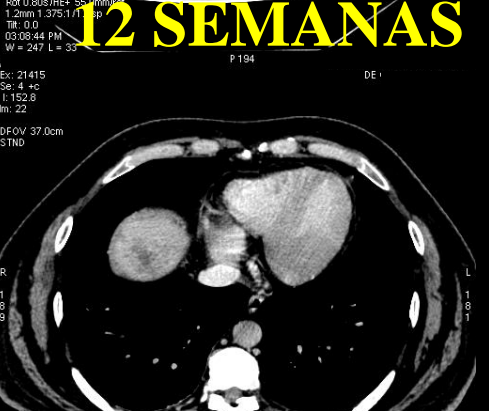
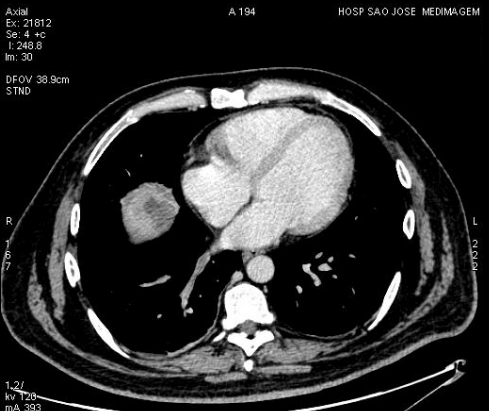
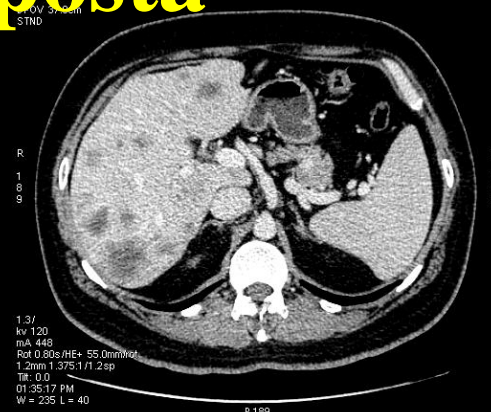
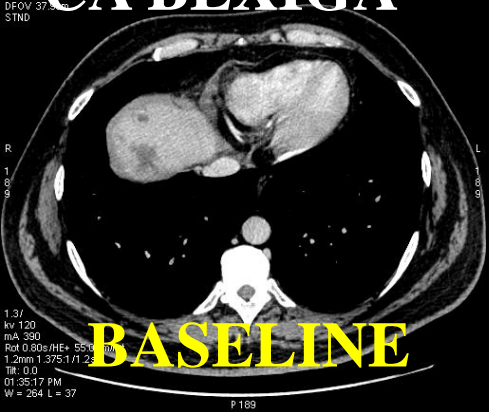
**TIPO 3** - Retardo na resposta da lesão, após aumento inicial da carga tu.

*Proc Natl Acad Sci USA 2008; 105:3005–3010*

*RADIOGRAPHICS 2015; 35: 424-437*

# CA BEXIGA

# IrRC - Tipo 03 de resposta

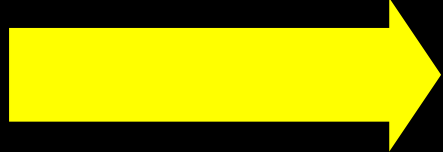


MELANOMA METASTÁTICO  
TRATAMENTO: IMUNOTERAPIA - IPIILIMUMABE

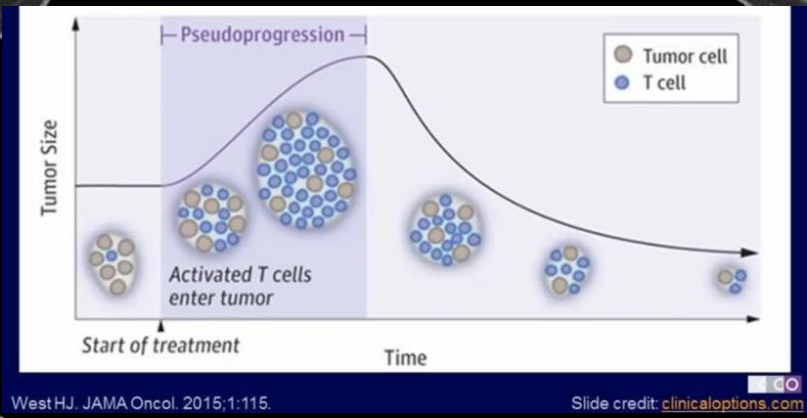
# IrRC - Tipo 03 de resposta



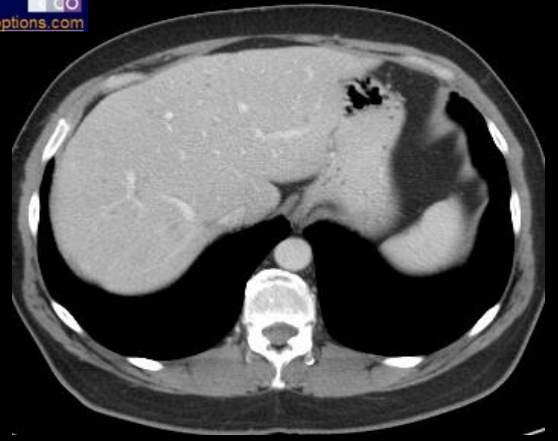
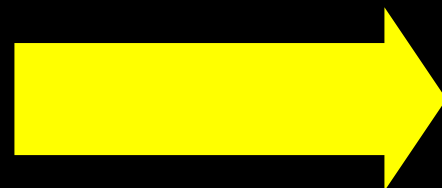
10/ AGO / 2012



20/ SET / 2012



20/ OUT / 2012



21/ DEZ / 2012

# IrRC - Tipo 03 de resposta



BASELINE

12 SEMANAS  
IMUNOTERAPIA

36 SEMANAS



# IMUNOTERAPIA - IrRC

## Tipos de resposta

**TIPO 3** - Retardo na resposta da lesão, após aumento inicial da carga tu.

- “aumento contínuo do tu enquanto o organismo prepara uma resposta imune adequada...”

- “aumento transitório no tamanho tu devido à infiltração céls. imunes com edema...”

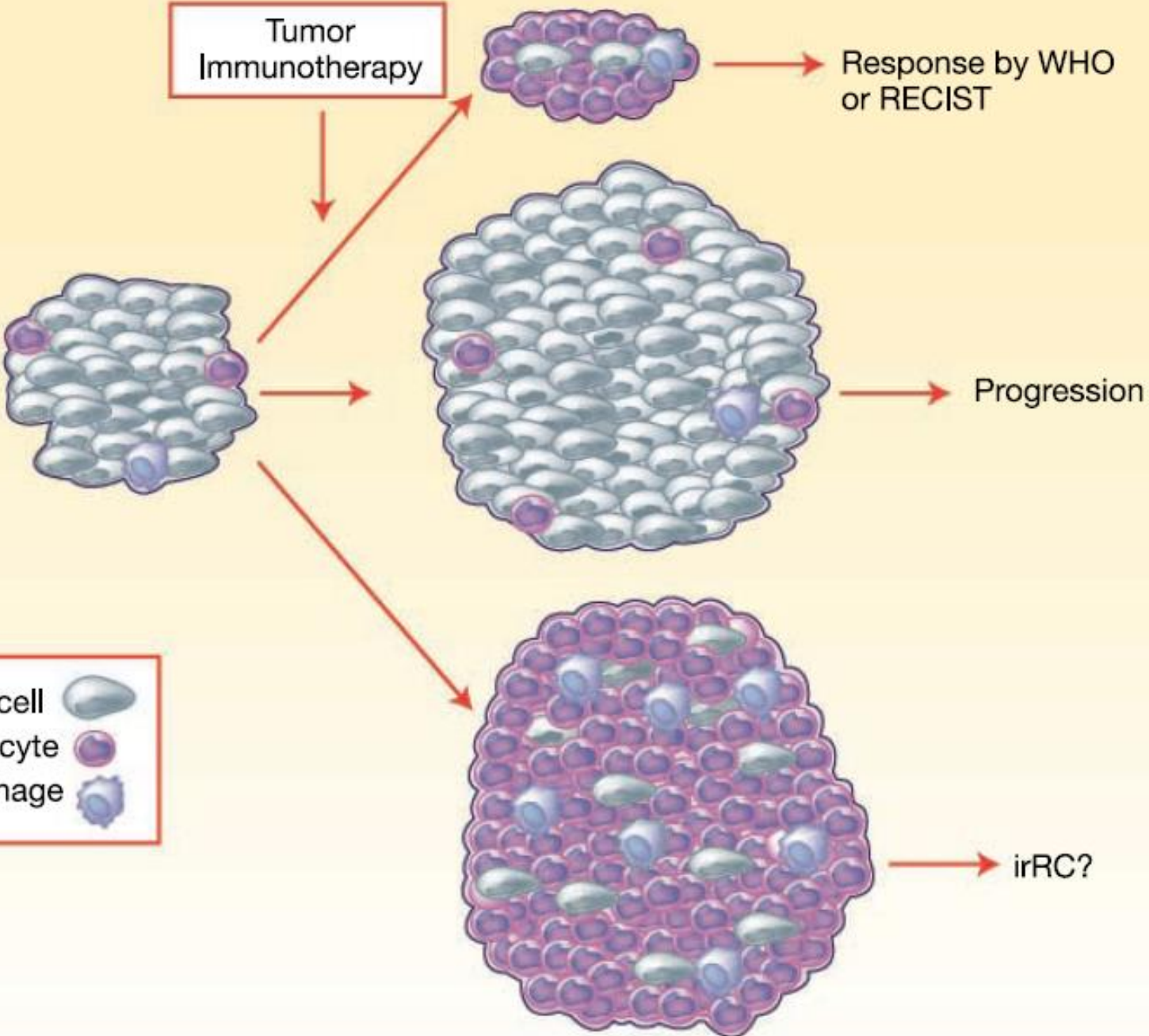
*RADIOGRAPHICS 2015; 35: 424-437*




*Proc Natl Acad Sci USA 2008; 105:3005–3010*

*Clin Cancer Res 2009; 15(23)*



Tumor Immunotherapy



Cancer cell   
Lymphocyte   
Macrophage 

## Depigmentação na Borda das Lesões com IL-2 em Dose Alta

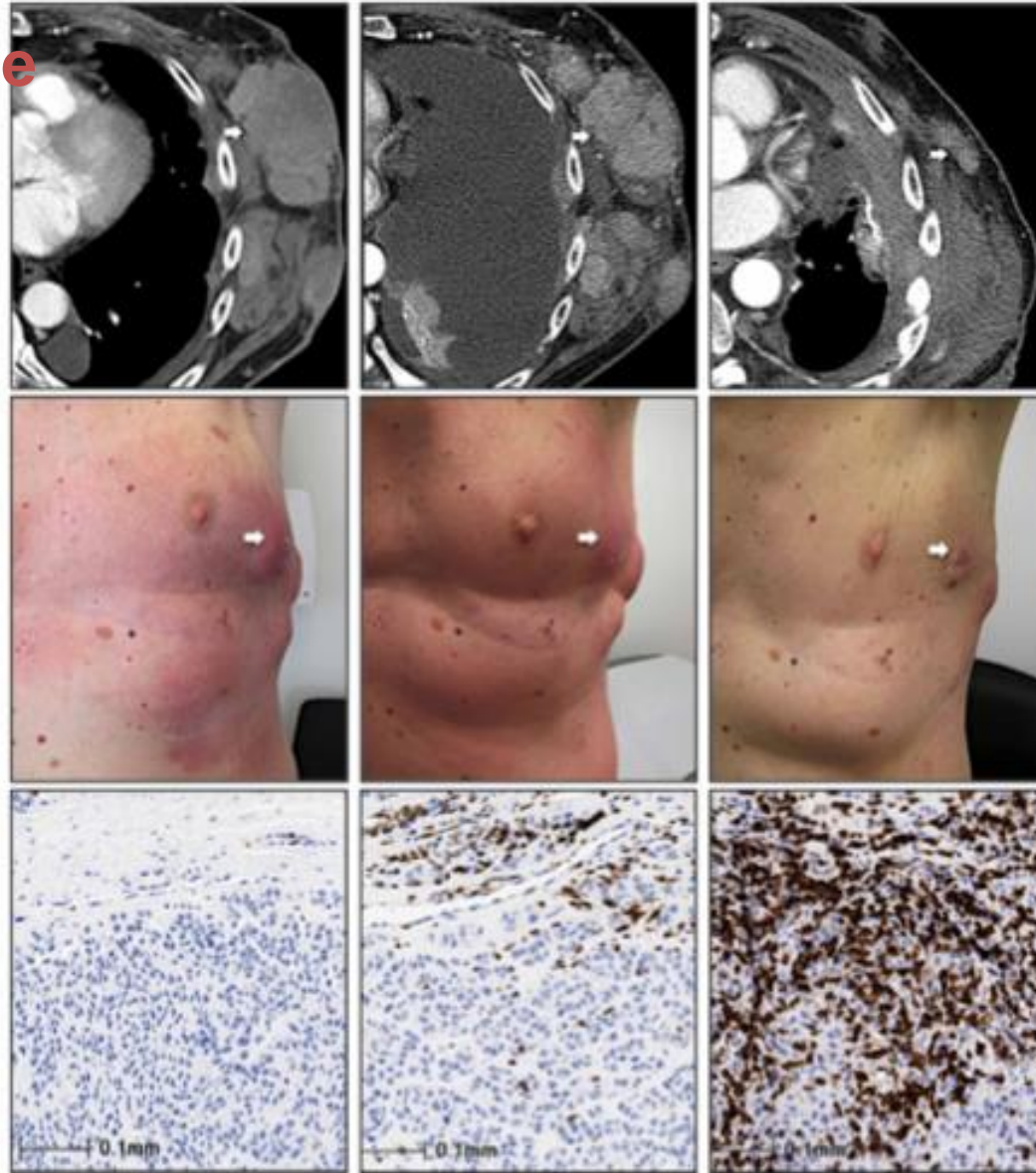


ÁREA ONDE O SISTEMA IMUNE ATUA

*Buzaid, AC*

# Infiltrado inflamatório e resposta tumoral

Pembrolizumabe



CD8+

Before Tx

Day +27

Day +130

Tumeh *et al.* Nature 2014.

# IMUNOTERAPIA - IrRC

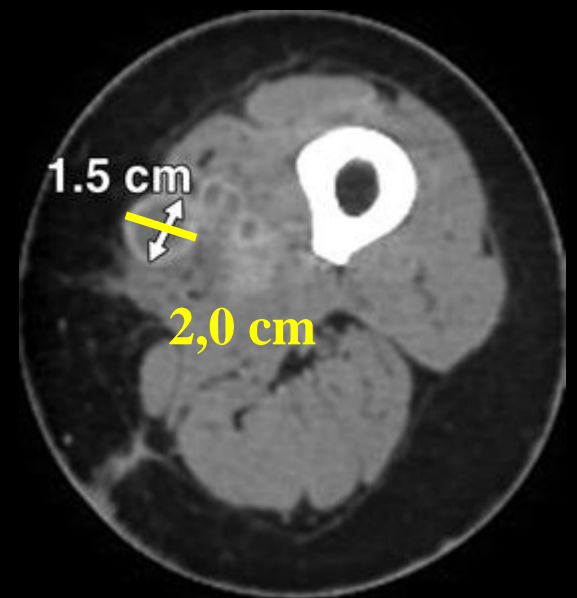
## Tipos de resposta

**TIPO - 4** Nova lesão após trat. completo, precedendo a diminuição da carga tumoral.

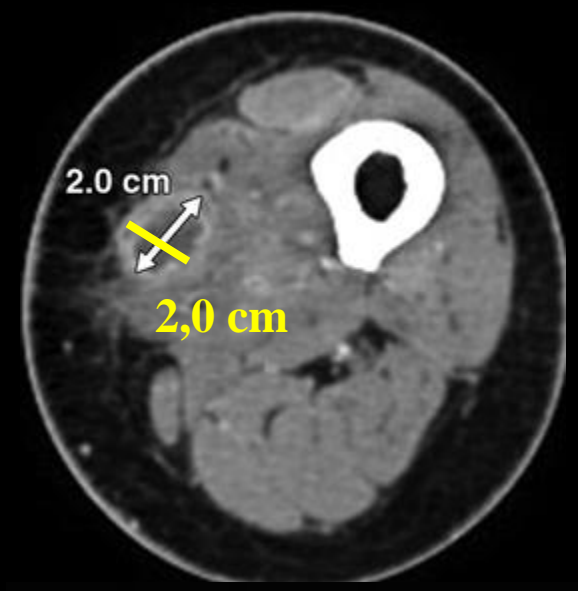


# IMUNOTERAPIA: IPILIMUMAB IrRC-Tipo 04 de resposta

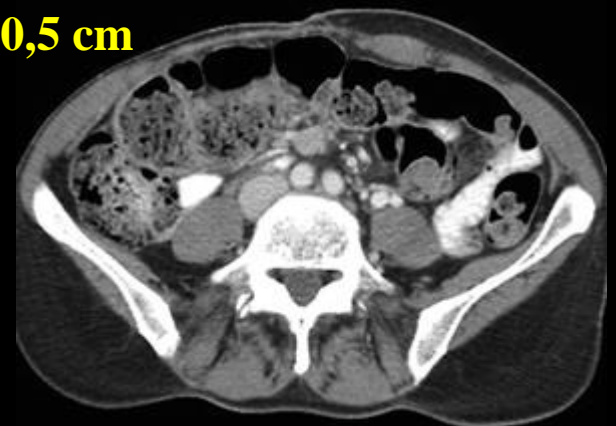
15/ FEV / 2011



15/ MAI/ 2011



15/ JUN/ 2011



MELANOMA METASTÁTICO

Proc Natl Acad Sci USA 2008; 105:3005–3010



# IrRC-Tipo 04 de resposta

## Ipilimumabe

**Screening (Nov,2007)**



**Sem 12: inflamação & progressão**



**Sem 14: melhora**



**Sem 16: melhora contínua**



**Sem 72: remissão completa**



**Dez 2010: remissão completa**



Hoos et al, *J Natl Cancer Inst* 2010; 102:1388-1397

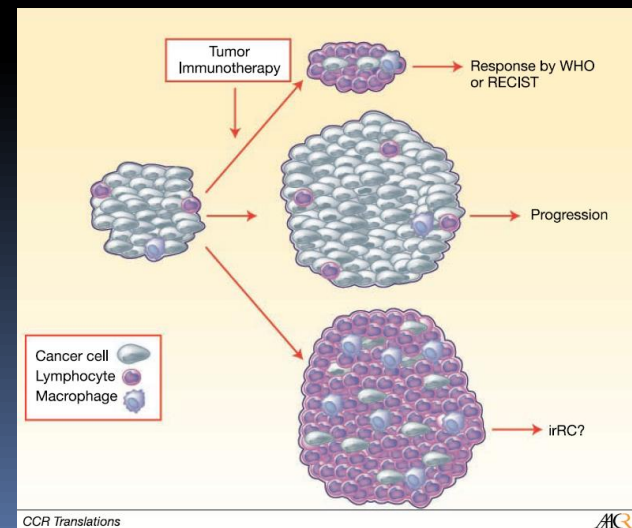
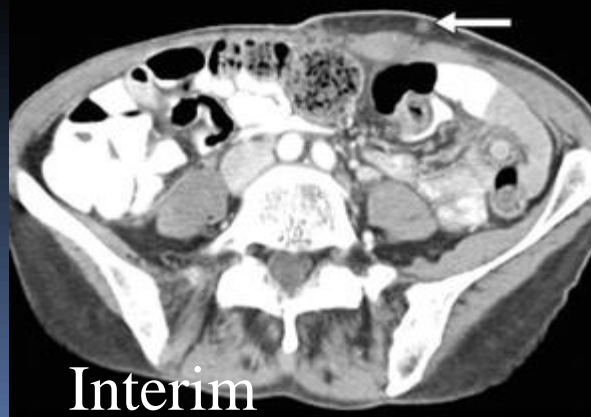
**Cortesia de Buzaid, A.C.**

# IMUNOTERAPIA - IrRC

## Tipos de resposta

**TIPO 4** Nova lesão após trat completo, precedendo a diminuição da carga tumoral.

- “ aumento no tamanho das micrometástases não vistas ao exame prévio, por infiltração de céls imunes (T) no tu...”



# EFEITO ABSCOPAL

(abs = *off* ; copal = *target*)



The NEW ENGLAND  
JOURNAL of MEDICINE

## Abscopal Effect in a Patient with Melanoma

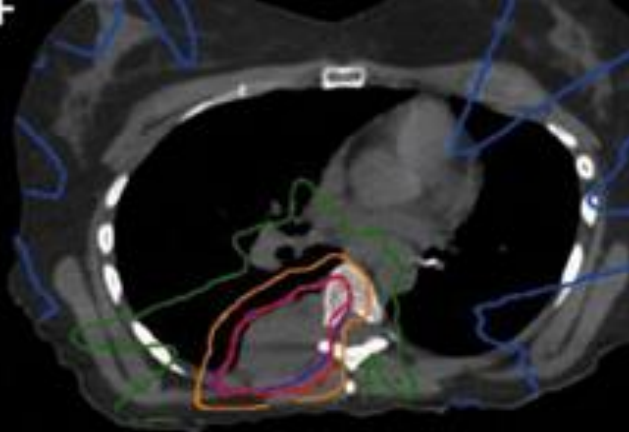
N Engl J Med 2012; 366:2035-2036 | May 24, 2012

“Fenômeno raro de regressão tumoral de uma lesão metastática distante do sítio primário irradiado”.

Estímulo da resposta imune anti-tumor

Melanoma, pulmão, linfoma e CCR.

The word "abscopal" is derived from the Latin prefix "ab," meaning "away from," and the Greek word "skopos," meaning "target."



RTX interim  
Anti CTLA 4



MELANOMA  
METASTÁTICO

**EFEITO ABSCOPAL**  
Estímulo da resposta  
imune anti-tumor

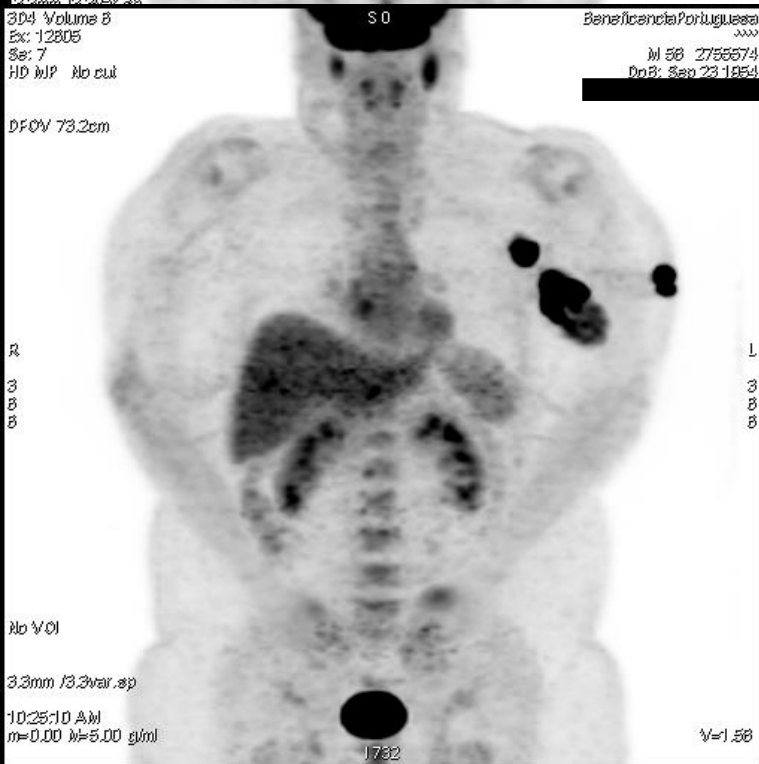




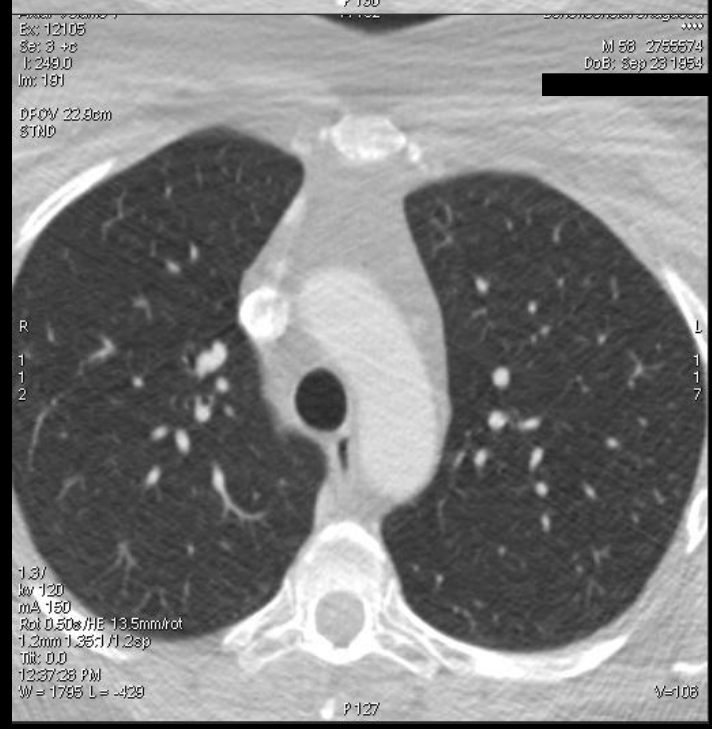
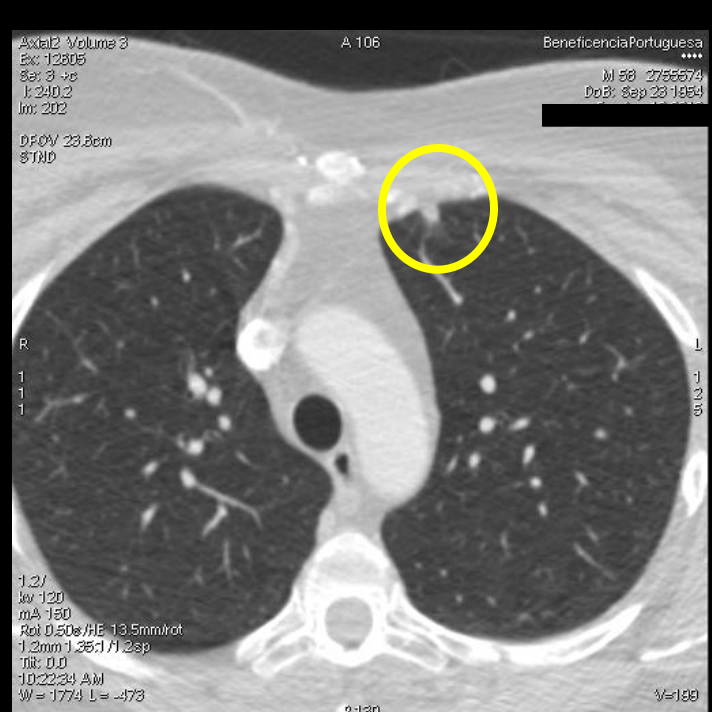


# MELANOMA METASTÁTICO

IPILIMUMABE  
+  
RTx axila esquerda



06 semanas após  
RTx





# A RETROSPECTIVE ANALYSIS OF THE ABSCOPAL EFFECT WITH ANTI-PD1 THERAPY IN PATIENTS WITH METASTATIC SOLID TUMORS

## Authors:

Jéssica Ribeiro Gomes,<sup>1</sup> Rafael Aron Schmerling,<sup>1</sup> Carolina Kawamura Haddad,<sup>1</sup> Douglas Jorge Racy,<sup>2</sup> Robson Ferrigno,<sup>3</sup> Erlon Gil,<sup>4</sup> Pedro Zanuncio,<sup>4</sup> Antônio Carlos Buzaid<sup>5</sup>

## Experiência do Centro Oncológico Antônio Ermírio de Moraes

- ✓ Estudo retrospectivo
- ✓ 23 pacientes com melanoma metastático
- ✓ Imunoterapia + RTx hipofracionada
- ✓ 05 receberam RT junto com o início das drogas
- ✓ 18 pacientes receberam RT após PD / IMUNOTERAPIA (análise de efeito abscopal)
- ✓ 12: Nivolumab; 3: Pembrolizumab, 3: Ipilimumab

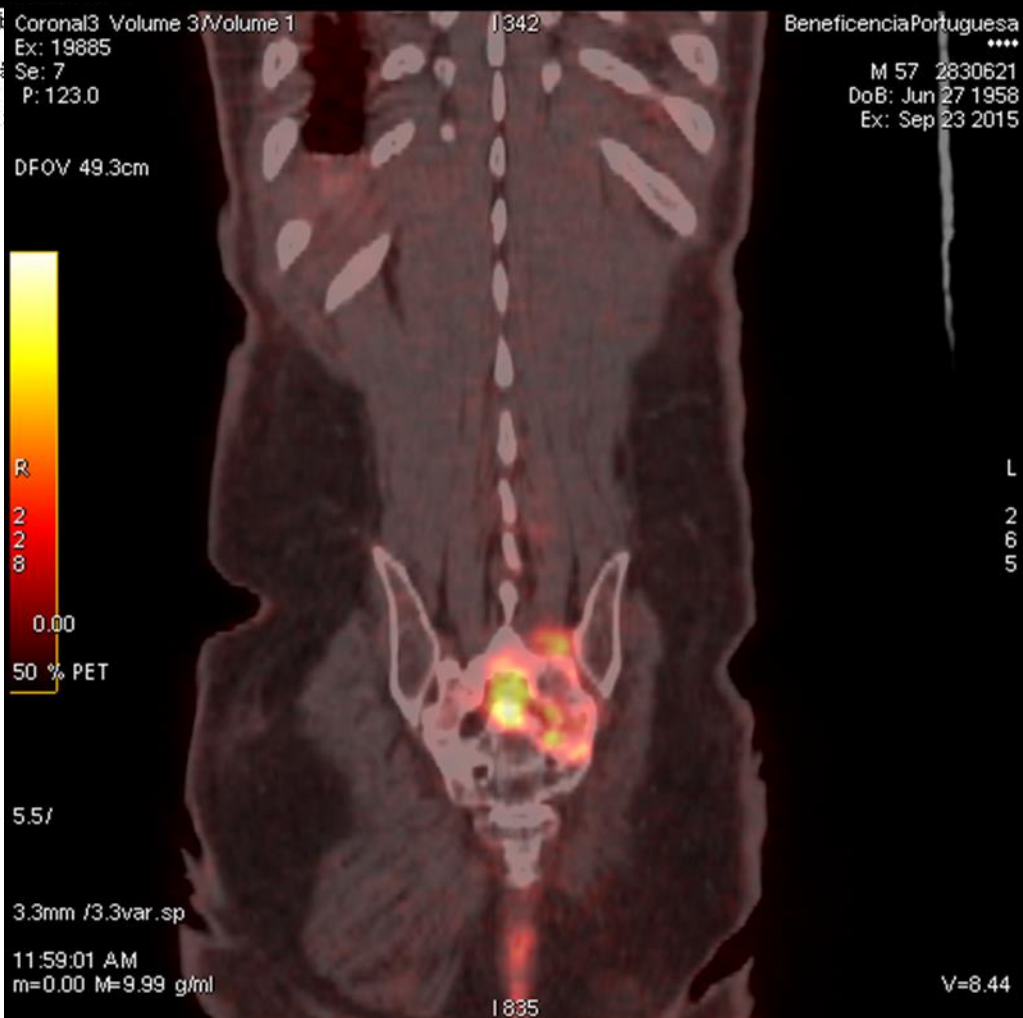


# Experiência do Centro Oncológico Antônio Ermírio de Moraes

- ✓ Seguimento mediano: 06 meses
- ✓ 6 pacientes (33,3%) RP ou RC da área irradiada e dos outros sítios **(efeito abscopal)**
- ✓ 8 pacientes (44,4%) obtiveram controle do local irradiado e sem resposta sistêmica
- ✓ Exacerbação do efeito local: 14/18 (77,8%)
- ✓ 4 pacientes (22,2 %) não responderam
- ✓ Seguimento maior e maior número de pacientes são necessários para verificar a real chance e duração do **efeito abscopal**

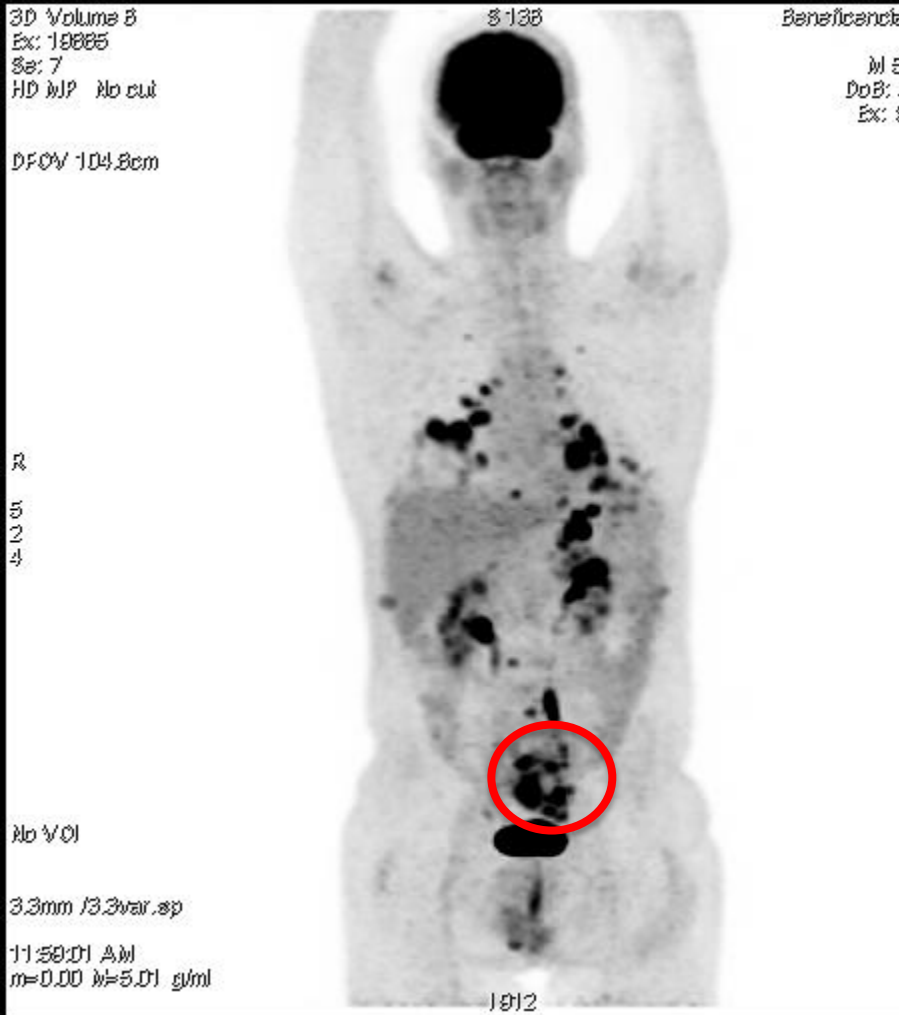
**ASTRO 2016**

# Adenoca de cárdia; IMUNOTERAPIA Anti PD 1



**RT<sub>x</sub> (APÓS 4 CICLOS de IMUNOTERAPIA)**

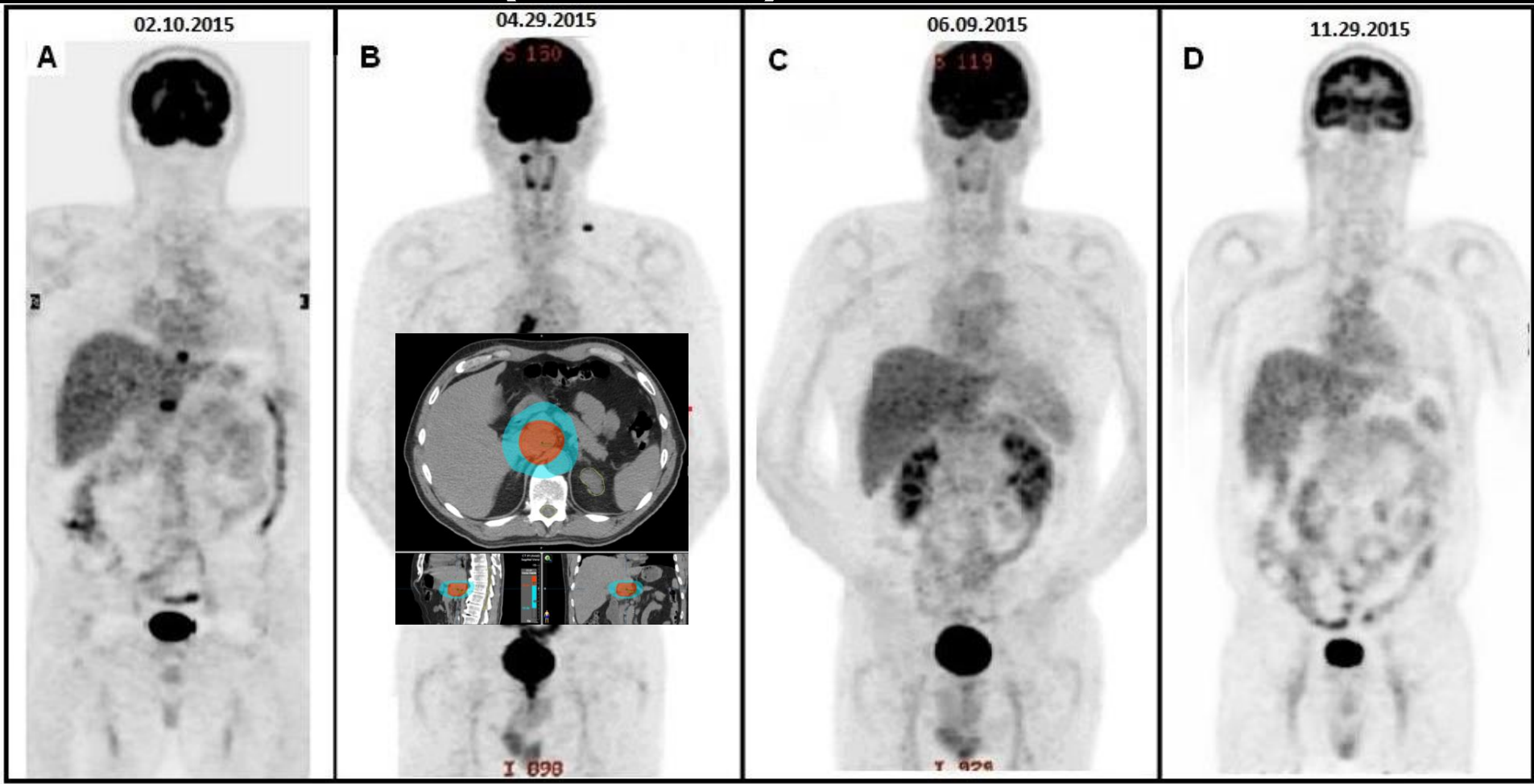
# Imunoterapia



**RTx (APÓS 4 CICLOS IMUNO) Efeito abscopal**

# Melanoma metastático

PD após 05 doses  
de Nivolumabe (Anti – PD1)



PD RTx

RC





Critical Review

## Combinations of Radiation Therapy and Immunotherapy for Melanoma: A Review of Clinical Outcomes

Christopher A. Barker, MD,\* and Michael A. Postow, MD<sup>†</sup>

*\*Department of Radiation Oncology and <sup>†</sup>Department of Medicine, Melanoma and Sarcoma Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, New York*

Received Jul 16, 2013, and in revised form Aug 19, 2013. Accepted for publication Aug 26, 2013

RT **AUMENTA** a visibilidade dos TU pelo sistema imune  
RT é **IMUNOGÊNICA**  
RT e IMUNOTERAPIA (**SINERGISMO**)



MED IMAGEM

Diagnósticos Médicos por Imagem



CENTRO ONCOLÓGICO

**ANTÔNIO ERMÍRIO DE MORAES**

**BENEFICÊNCIA PORTUGUESA DE SÃO PAULO**



Mirante

