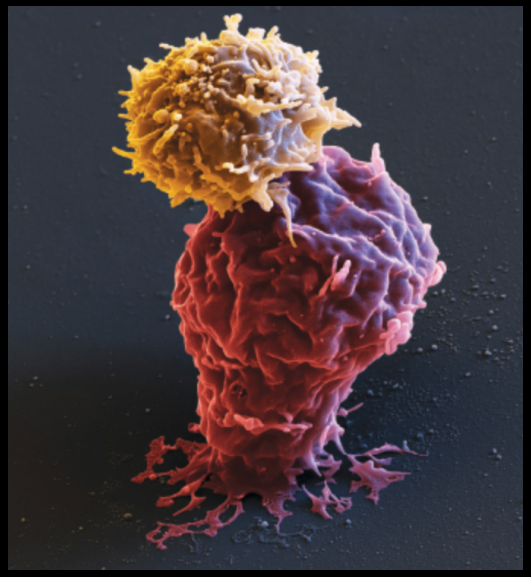
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Making Cancer History®

Atual papel da imunoterapia na Oncologia I



Alexandre A. A. Jácome, MD, PhD
Postdoctoral Fellow no Departamento de Oncologia Clinica Gastrointestinal
MD Anderson Cancer Center

Imunoterapia

- ✓ Mecanismos de evasão imune
- ✓ Mecanismos de ação dos inibidores de checkpoint
- ✓ Eficácia
- ✓ Eventos adversos imuno-relacionados
- ✓ Avaliação de resposta
- ✓ Biomarcadores preditivos
- ✓ Perspectivas

Imunoterapia

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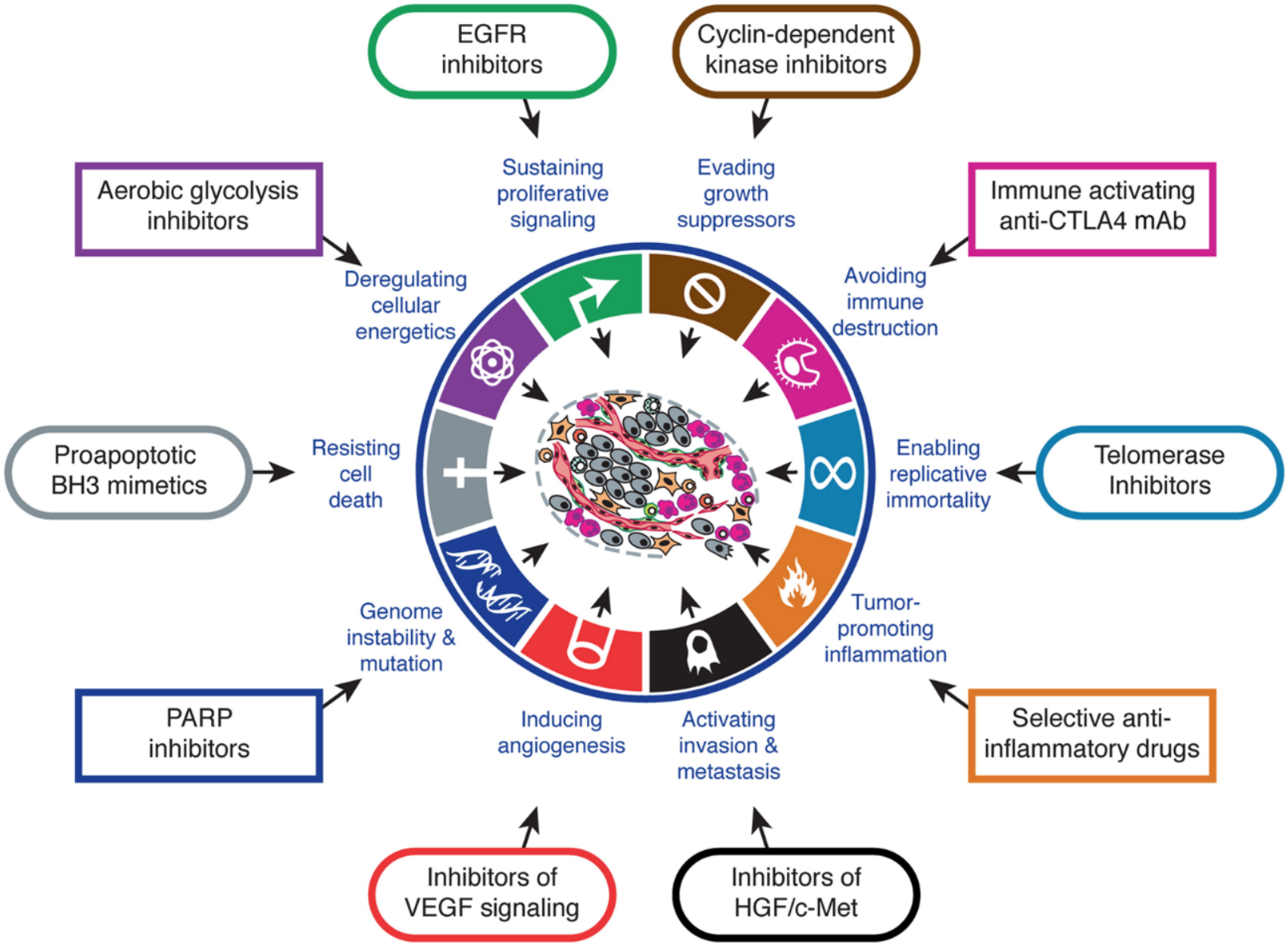
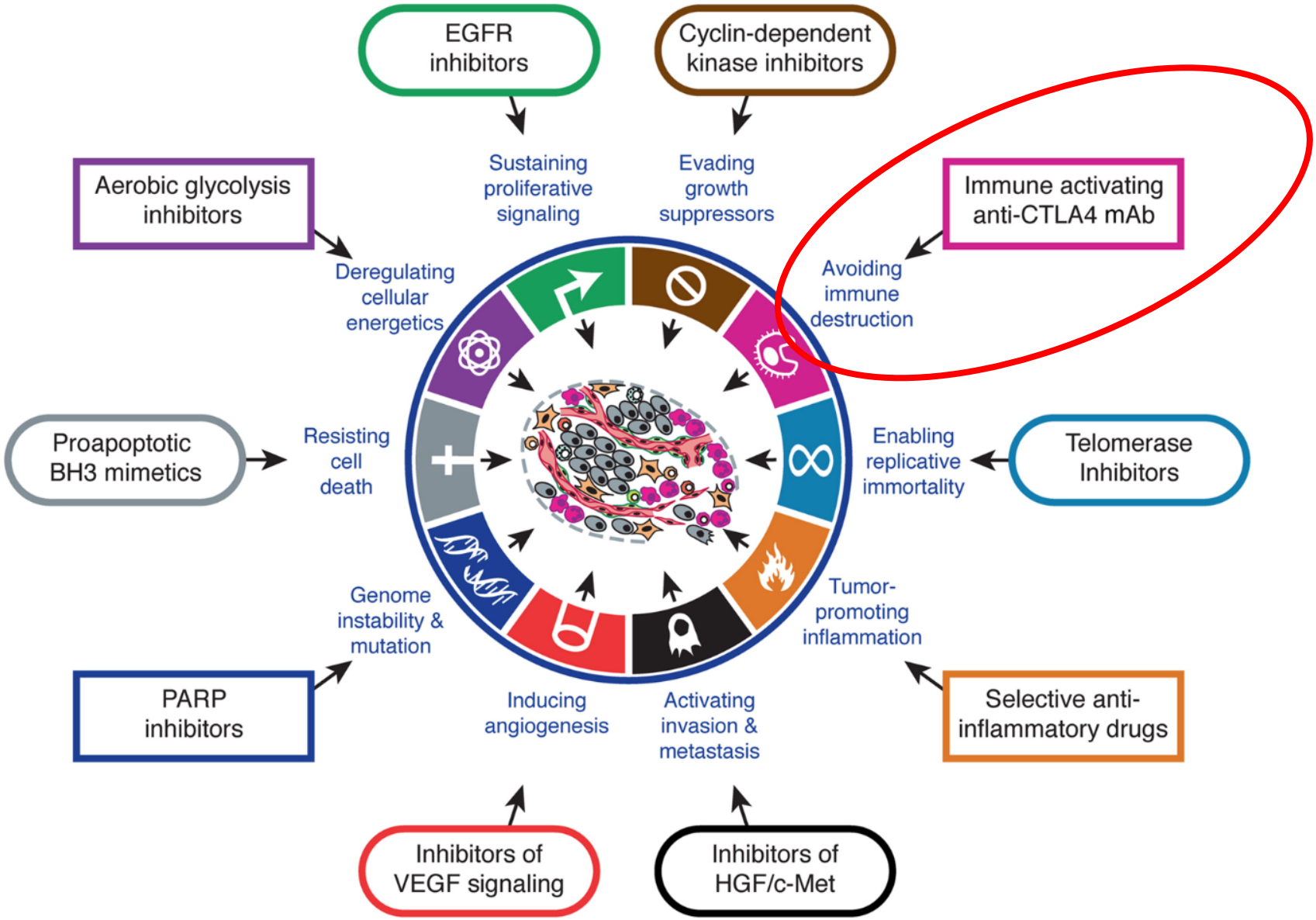
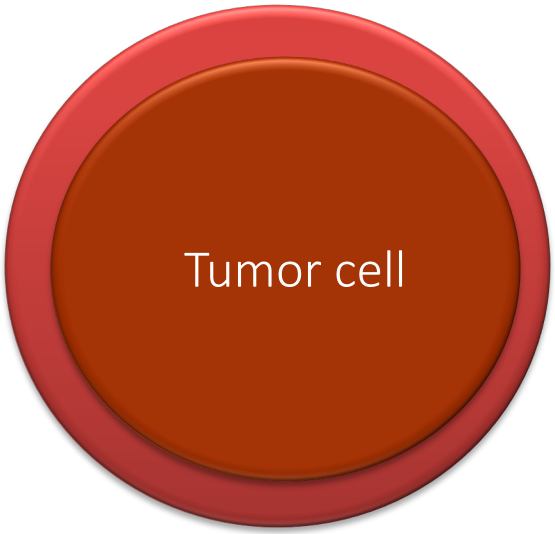
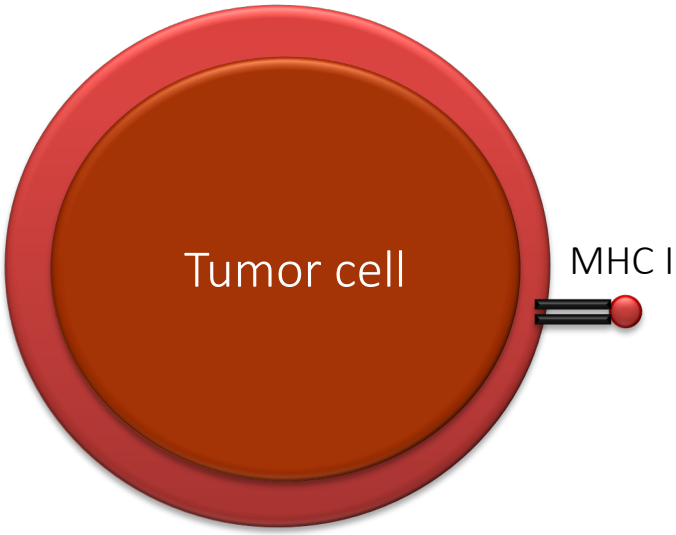


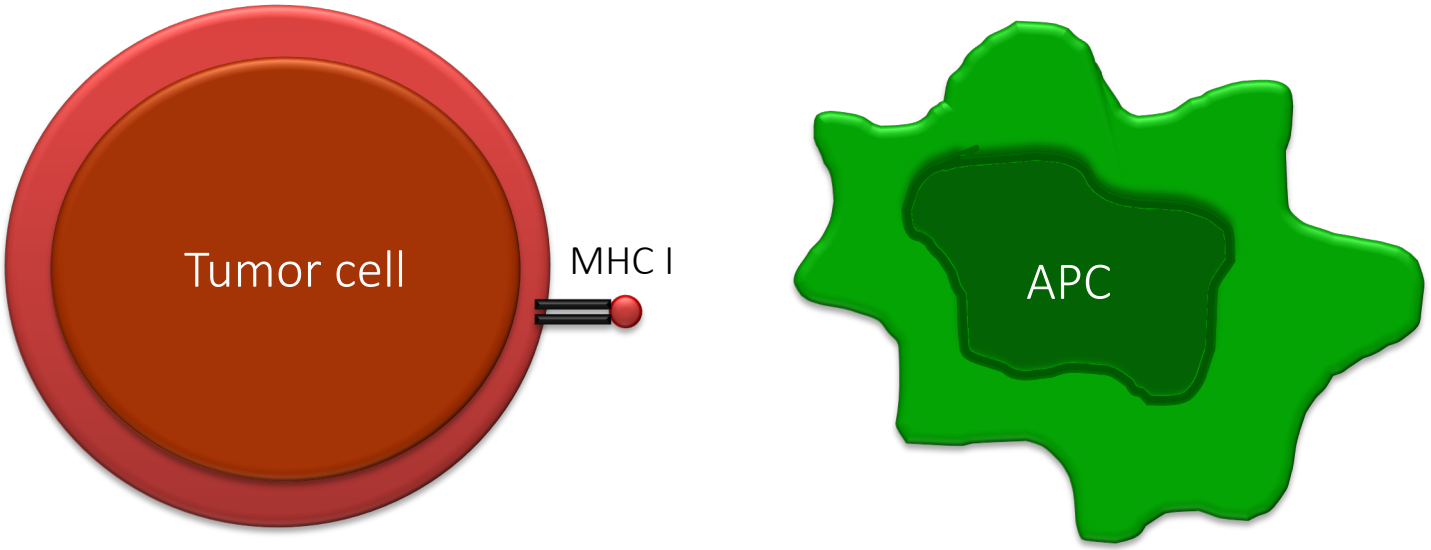
Extraido de Hanahan et al. Cell 2011

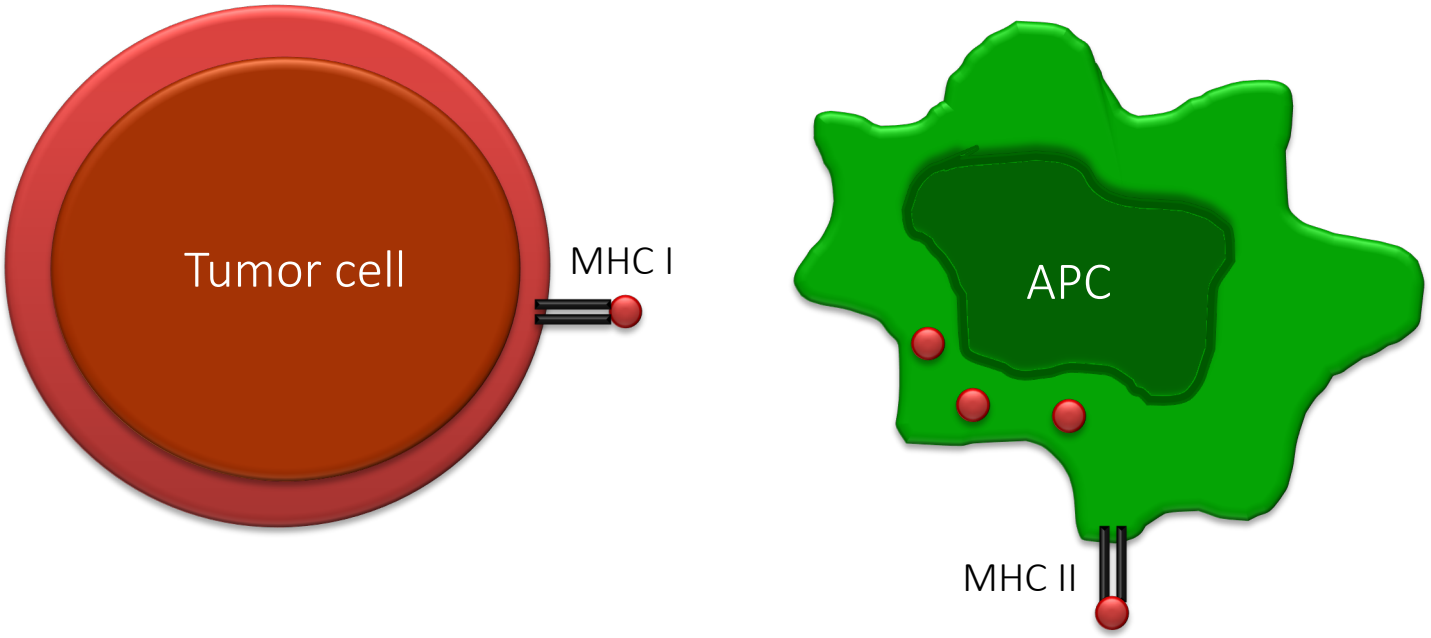


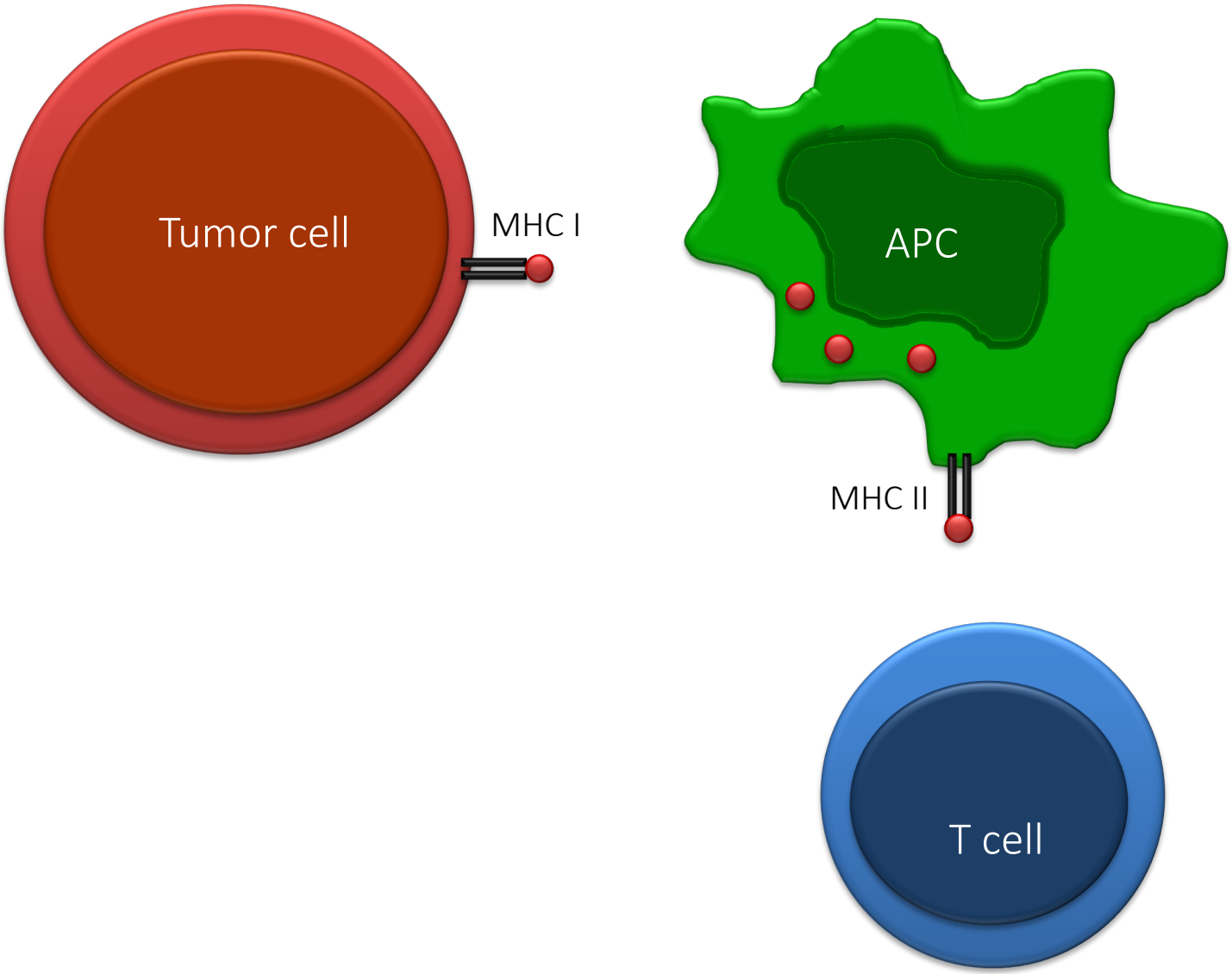
Extraido de Hanahan et al. Cell 2011

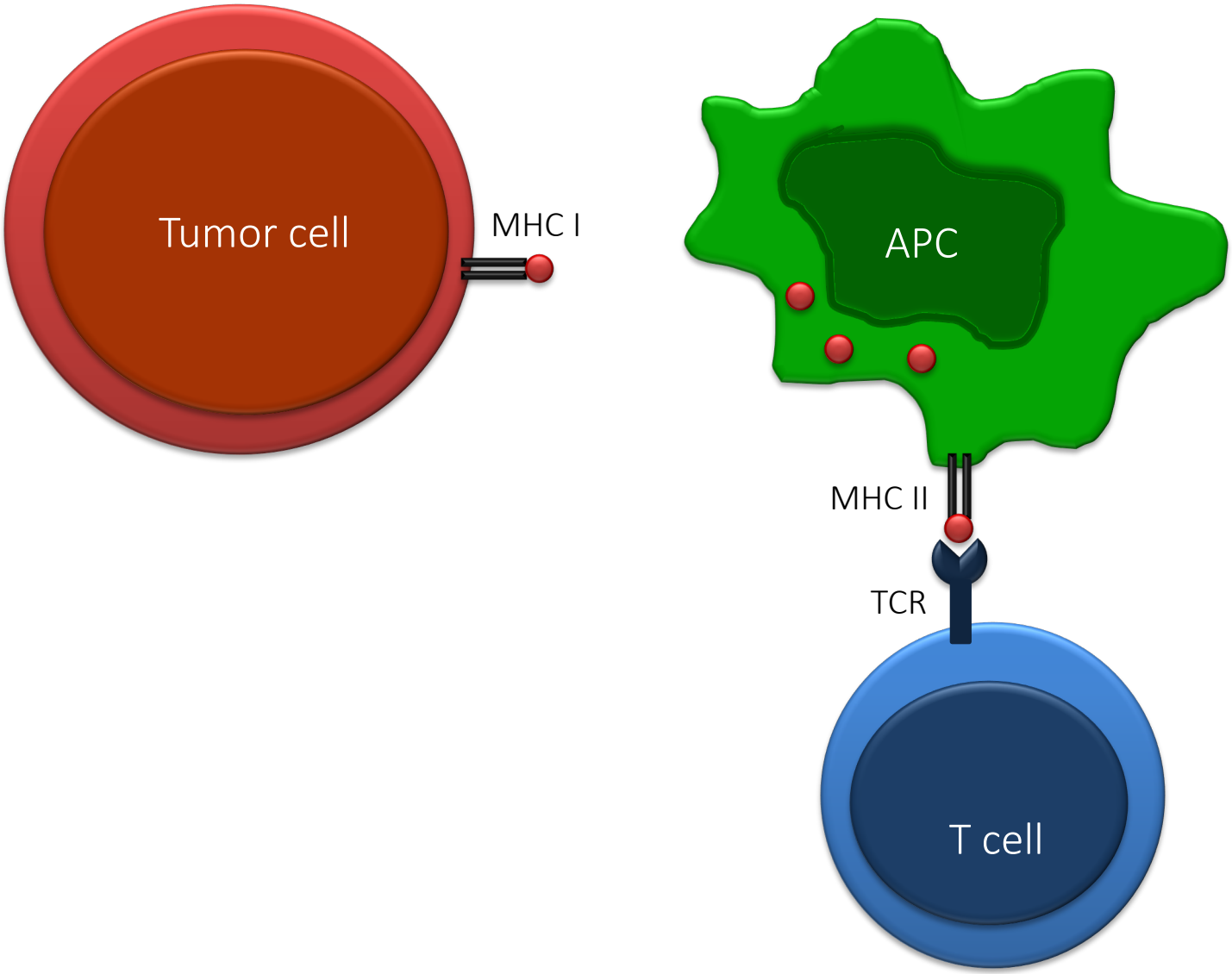

Tumor cell

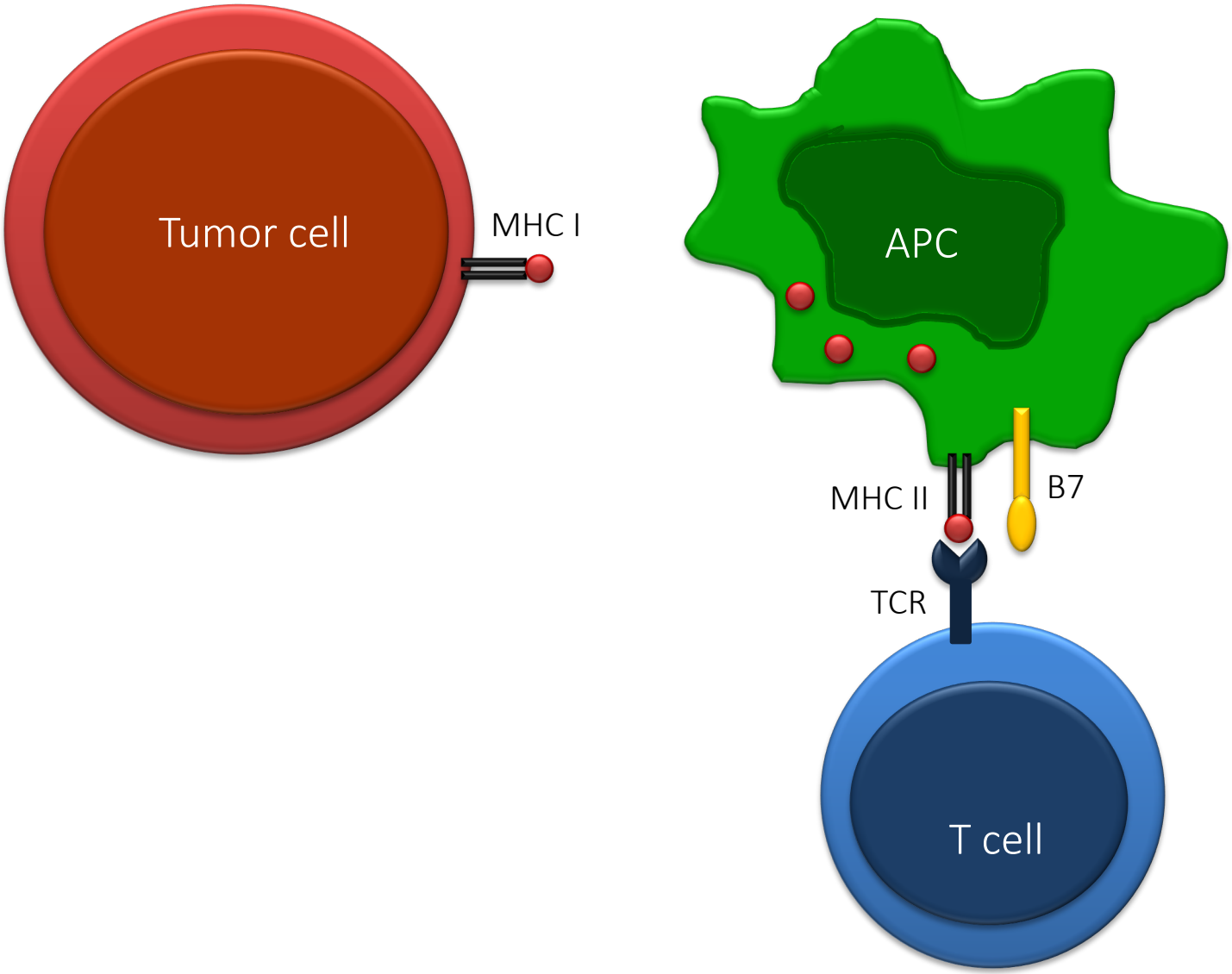

Tumor cell
MHC I

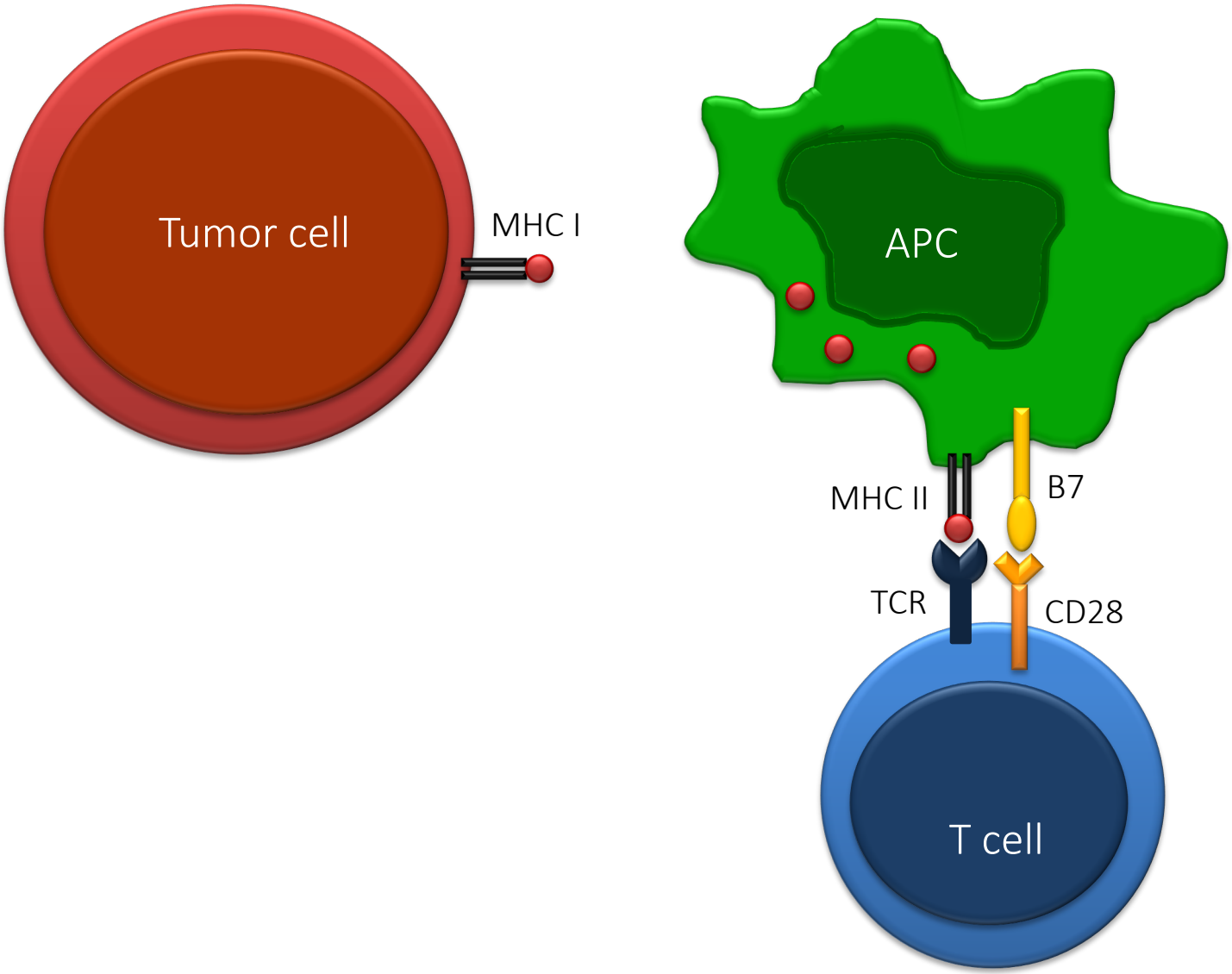

Tumor cell
MHC I
APC

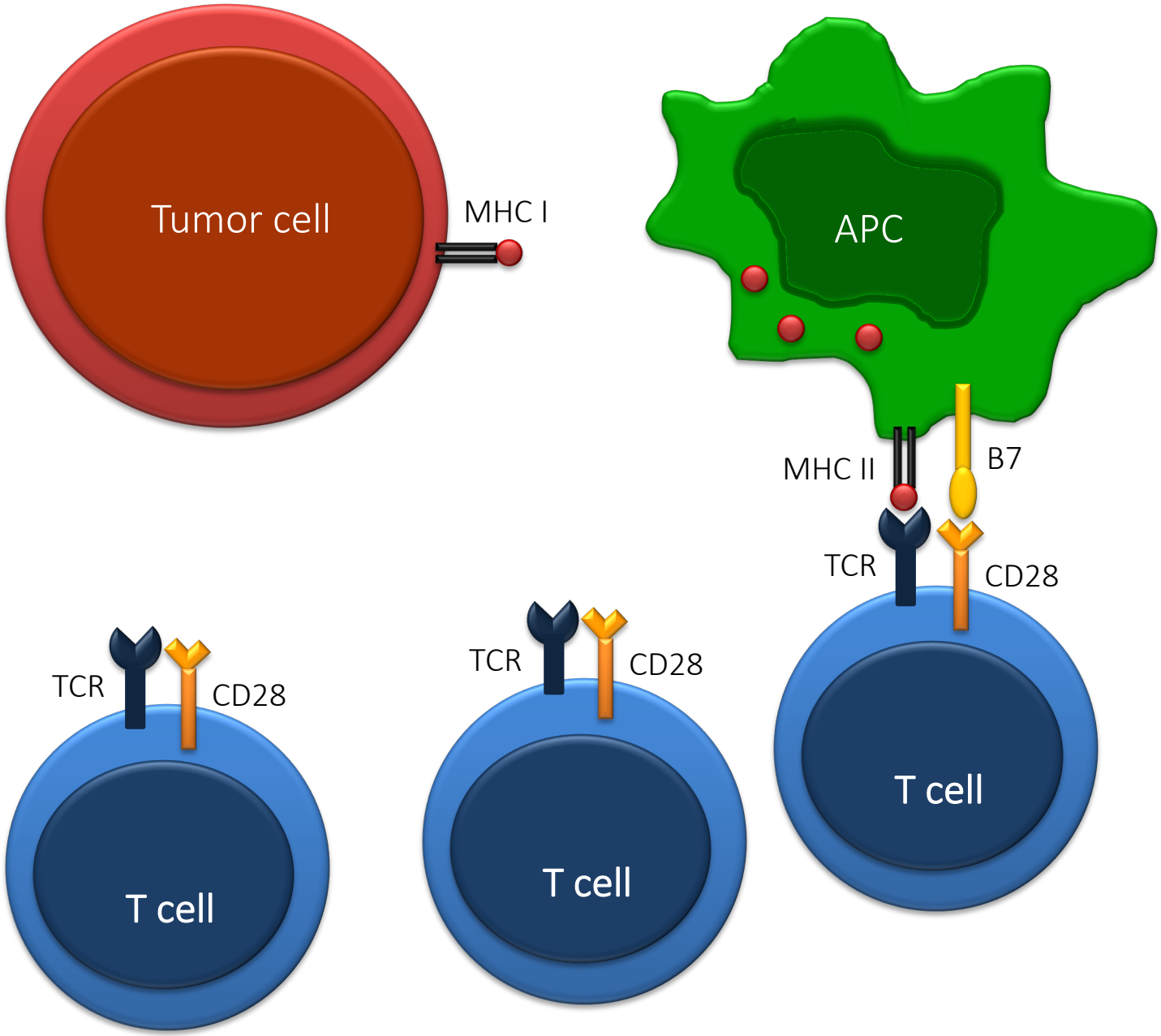

Tumor cell
MHC I
APC
MHC II

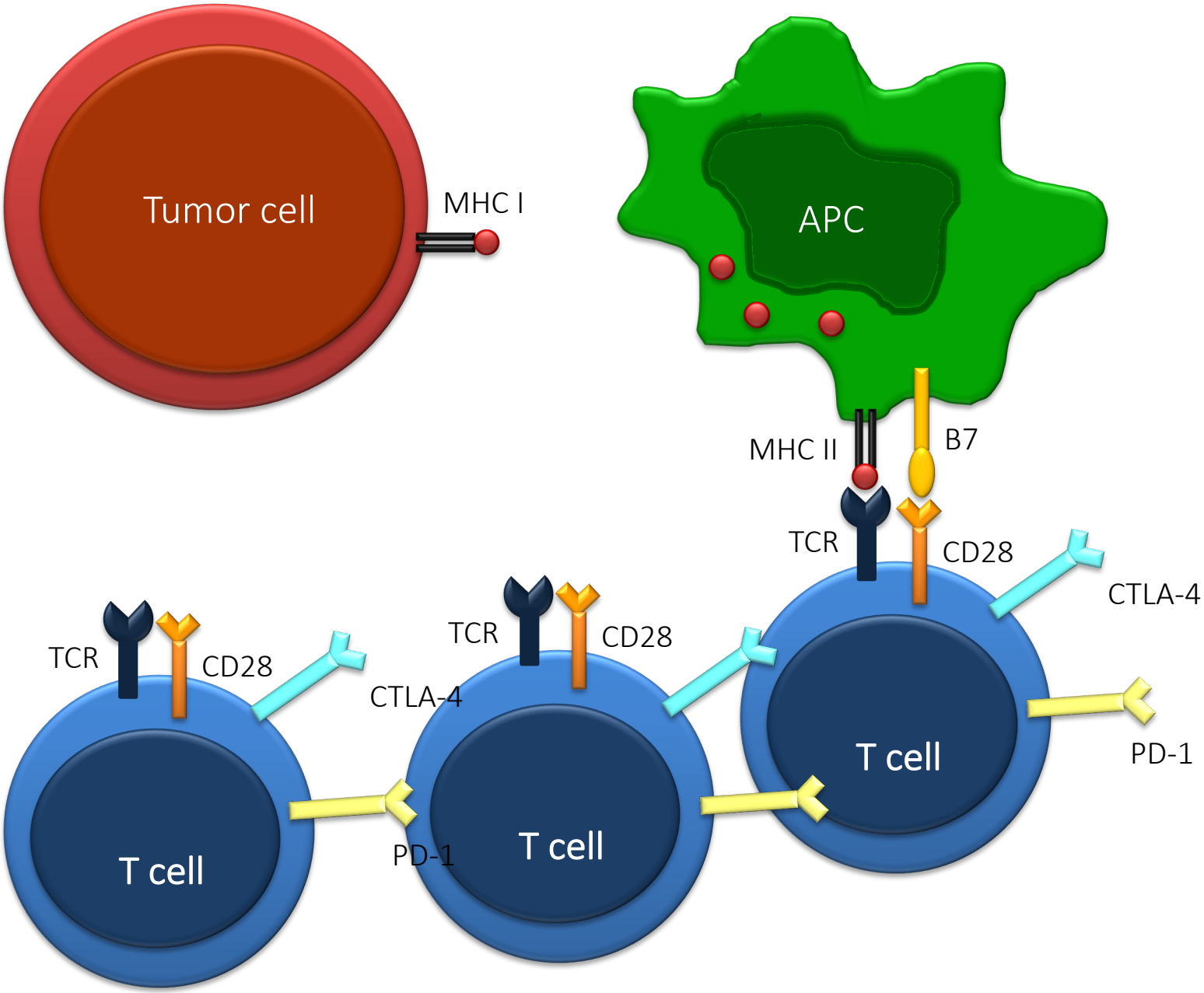

Tumor cell
MHC I
APC
MHC II
T cell

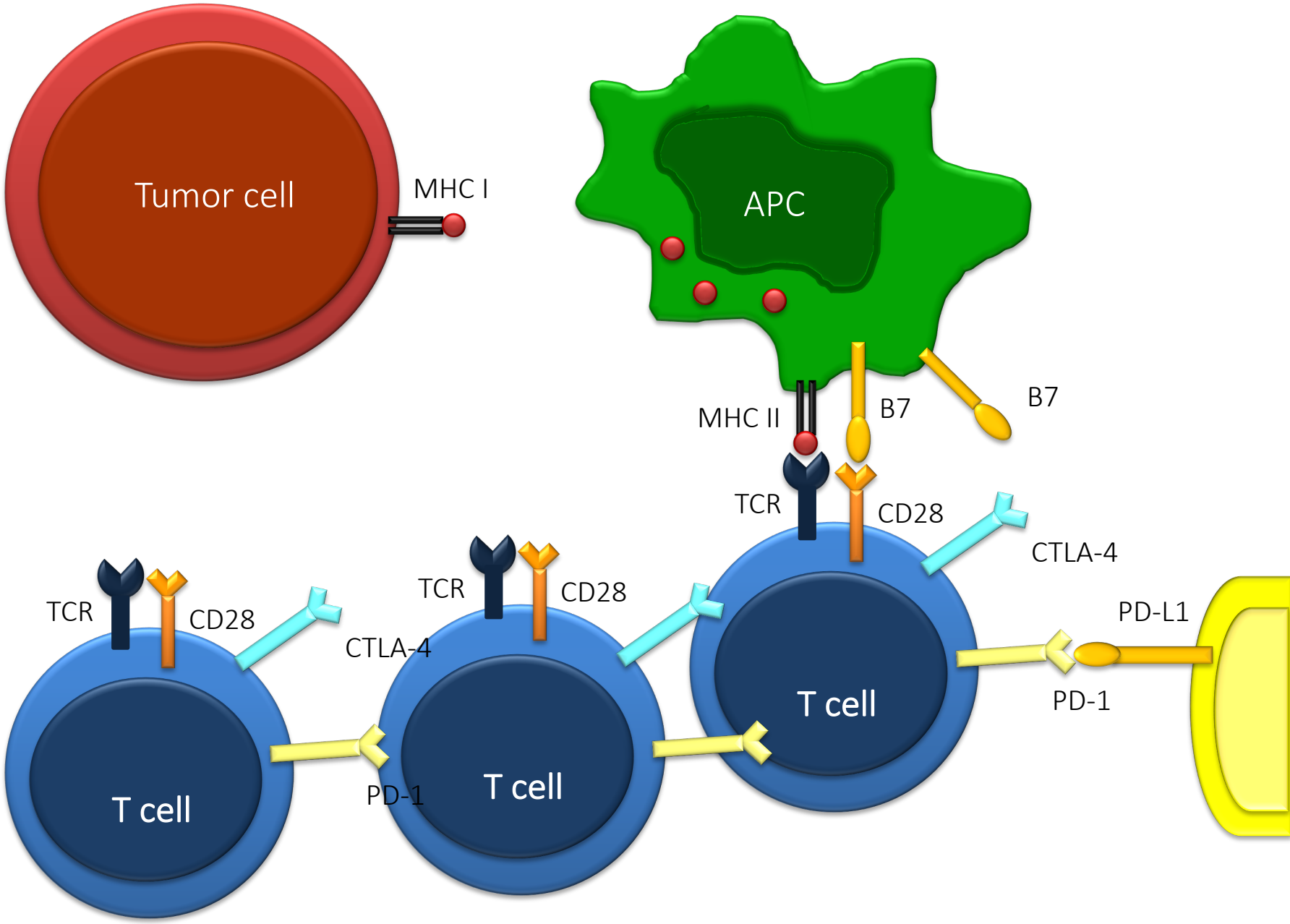

Tumor cell
MHC I
APC
MHC II
TCR
T cell

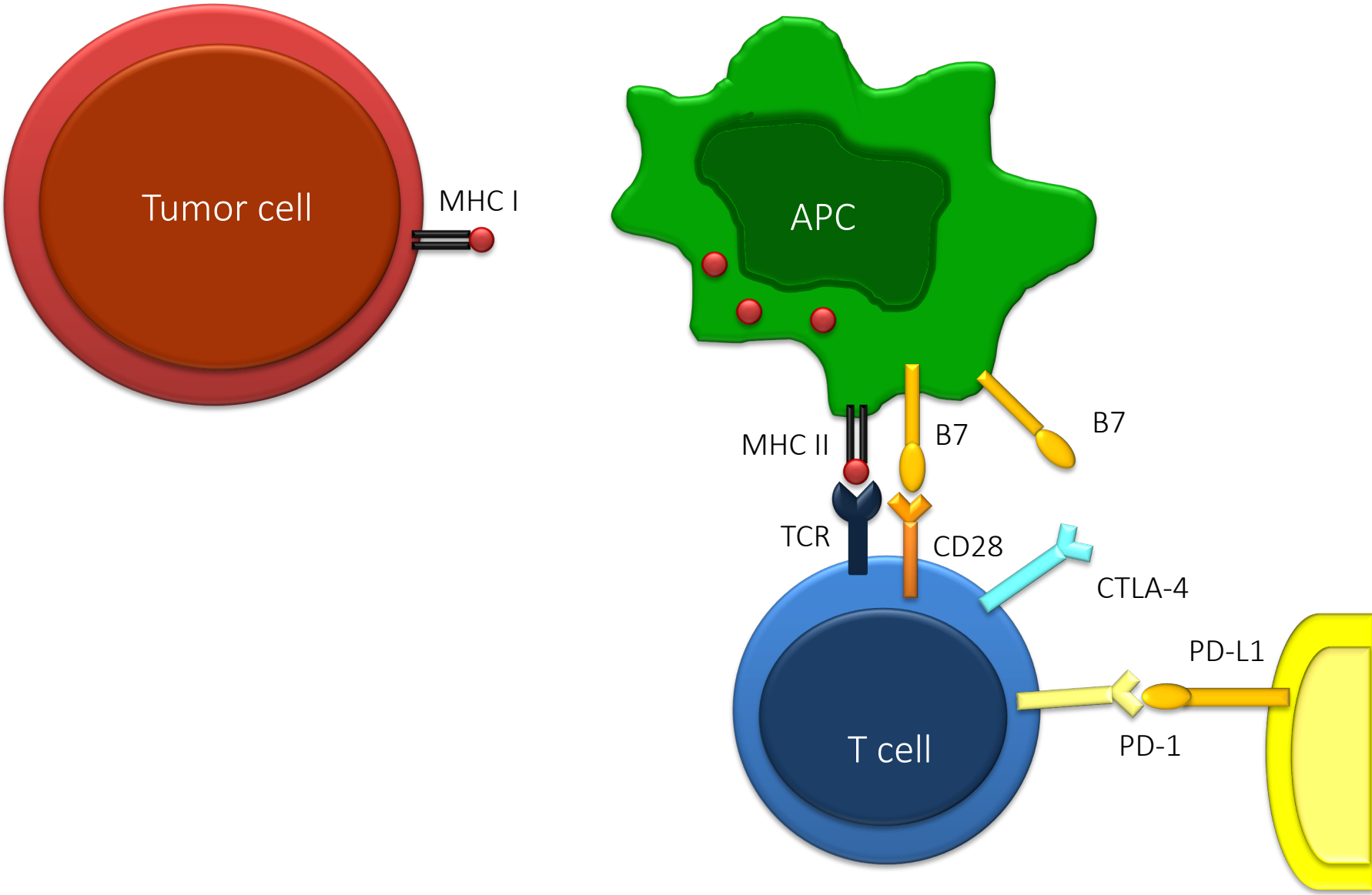

Tumor cell
MHC I
APC
MHC II
B7
TCR
T cell

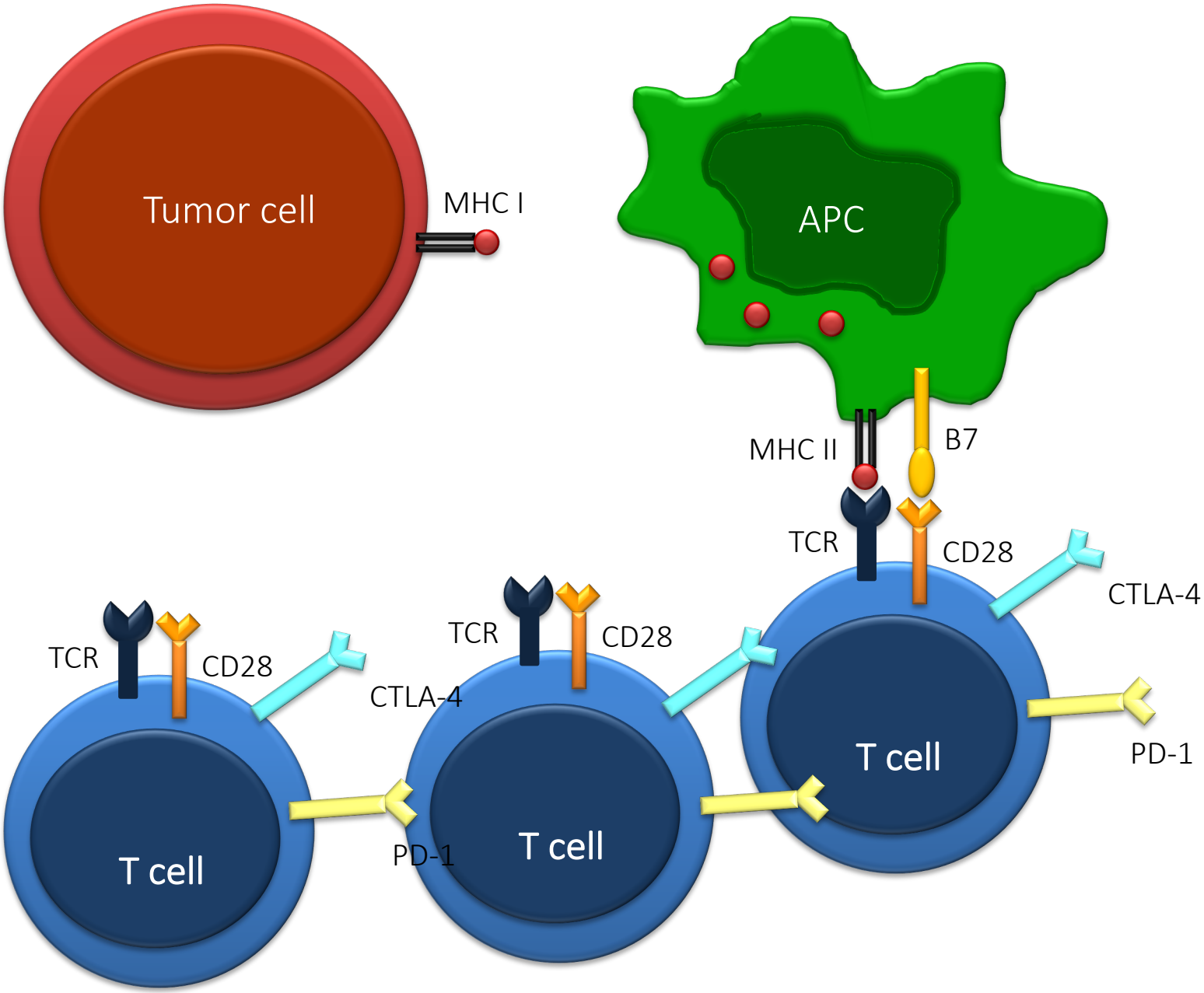

Tumor cell
MHC I
APC
MHC II
B7
TCR
CD28
T cell

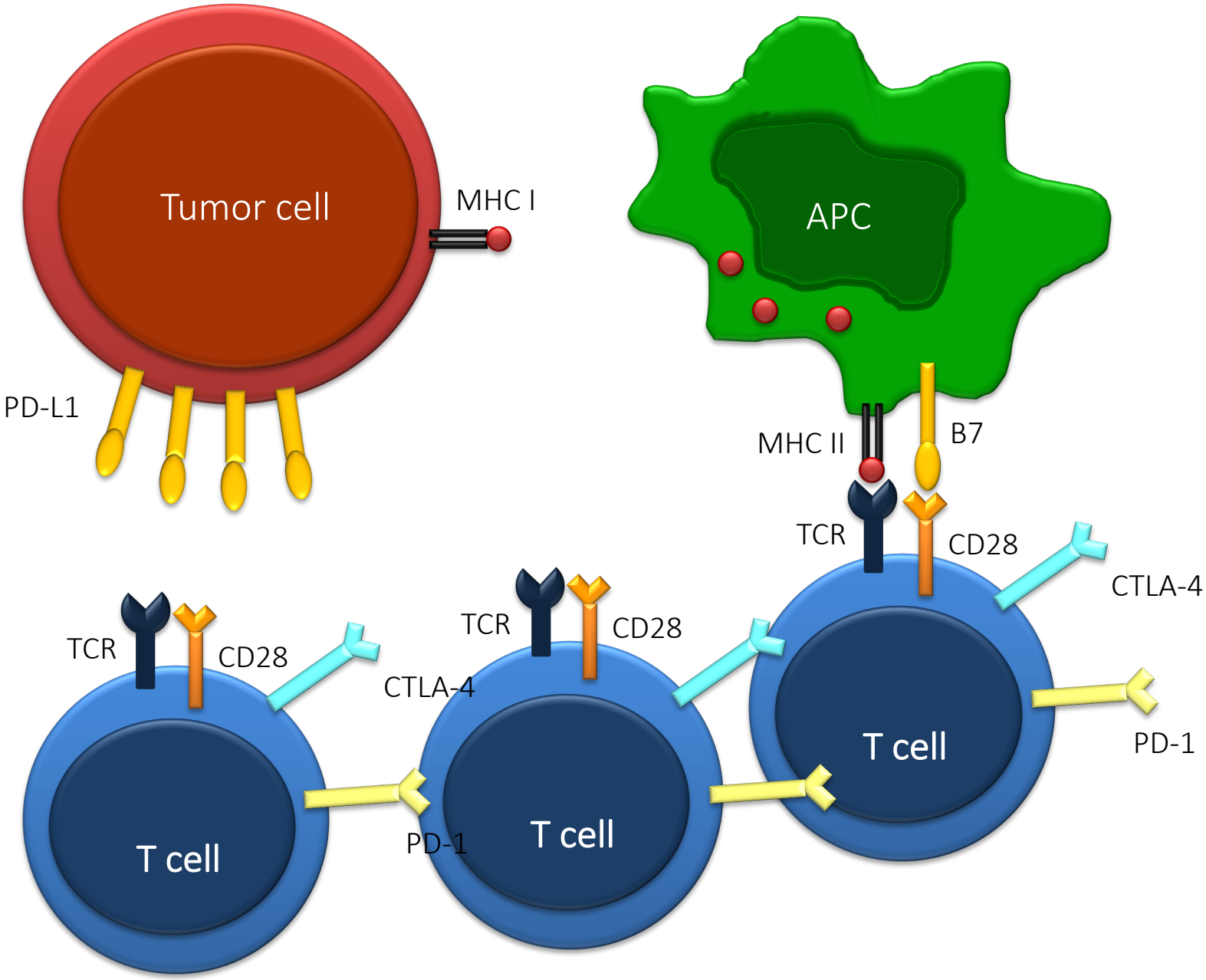

Tumor cell
MHC I
APC
MHC II
B7
TCR
CD28
TCR
CD28
T cell
TCR
CD28
T cell
T cell

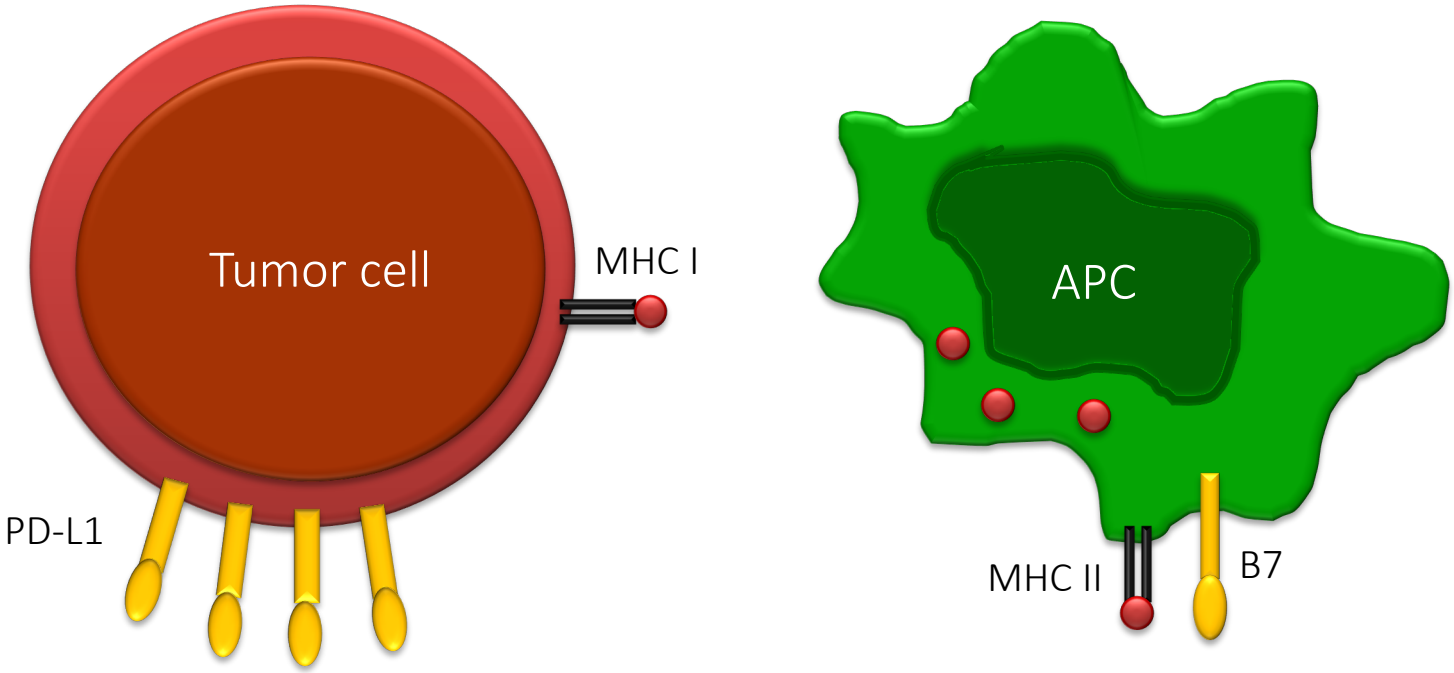

Tumor cell
MHC I
APC
MHC II
B7
TCR
CD28
CTLA-4
TCR
CD28
CTLA-4
TCR
CD28
T cell
PD-1
T cell
T cell
PD-1

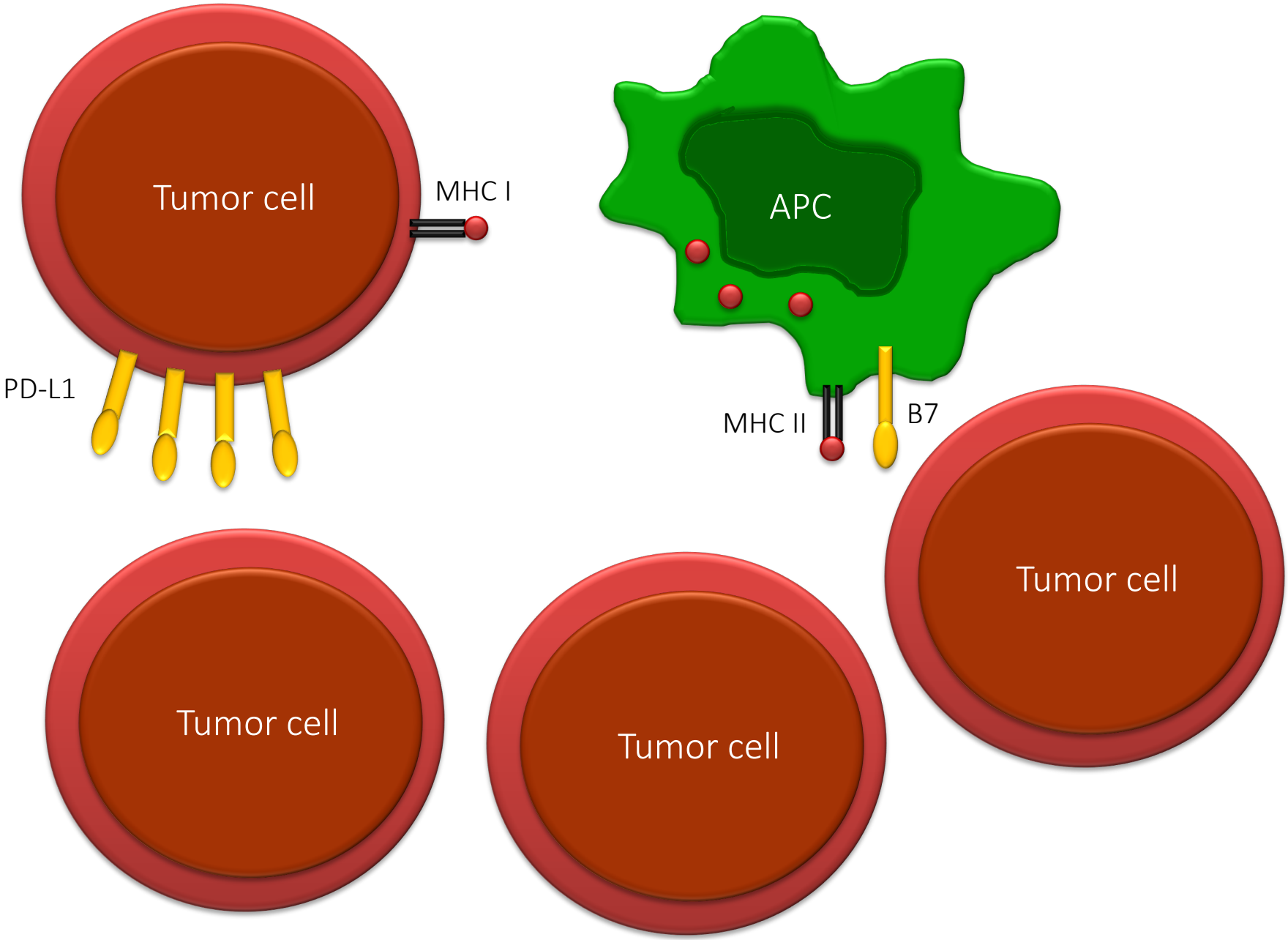

Tumor cell
MHC I
APC
MHC II
B7
B7
TCR
CD28
CTLA-4
PD-L1
PD-1
TCR
CD28
CTLA-4
PD-1
TCR
CD28
T cell
T cell
T cell


Tumor cell
MHC I
APC
MHC II
B7
B7
TCR
CD28
CTLA-4
PD-L1
T cell
PD-1


Tumor cell
MHC I
APC
MHC II
B7
TCR
CD28
CTLA-4
TCR
CD28
CTLA-4
TCR
CD28
T cell
PD-1
T cell
T cell
PD-1


Tumor cell
MHC I
PD-L1
APC
MHC II
B7
TCR
CD28
CTLA-4
PD-1
T cell
T cell
T cell

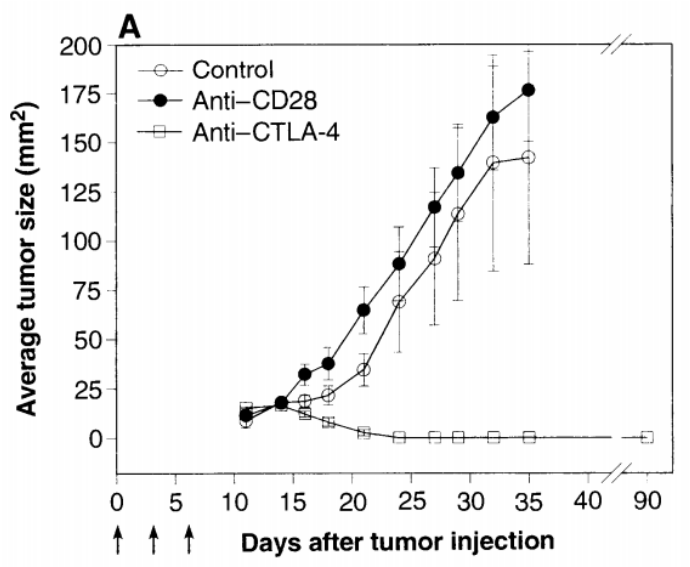

Tumor cell
MHC I
PD-L1
APC
MHC II
B7


Tumor cell
MHC I
PD-L1
APC
MHC II
B7
Tumor cell
Tumor cell
Tumor cell

Enhancement of Antitumor Immunity by CTLA-4 Blockade

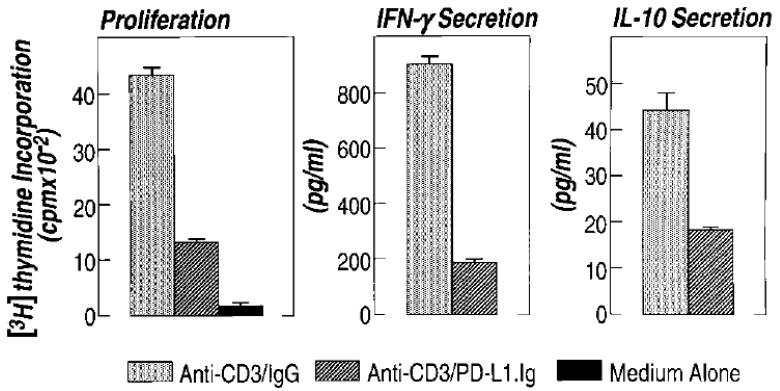
Dana R. Leach, Matthew F. Krummel, James P. Allison*

One reason for the poor immunogenicity of many tumors may be that they cannot provide signals for CD28-mediated costimulation necessary to fully activate T cells. It has recently become apparent that CTLA-4, a second counterreceptor for the B7 family of costimulatory molecules, is a negative regulator of T cell activation. Here, in vivo administration of antibodies to CTLA-4 resulted in the rejection of tumors, including preestablished tumors. Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.



Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation

By Gordon J. Freeman,* Andrew J. Long,‡ Yoshiko Iwai,§ Karen Bourque,‡ Tatyana Chernova,* Hiroyuki Nishimura,§ Lori J. Fitz,‡ Nelly Malenkovich,* Taku Okazaki,§ Michael C. Byrne,‡ Heidi F. Horton,‡ Lynette Fouser,‡ Laura Carter,‡ Vincent Ling,‡ Michael R. Bowman,‡ Beatriz M. Carreno,‡ Mary Collins,‡ Clive R. Wood,‡ and Tasuku Honjo§



Extraido de Leach DR et al. Science 1996; Freeman GJ et al. J Exp Med 2000

"for their discovery of cancer therapy by inhibition of negative immune regulation"

"this year's Nobel Laureates have established an entirely new principle for cancer therapy"

Jim Allison

Tasuko Honjo

Extraido de www.nobelprize.org

Imunoterapia

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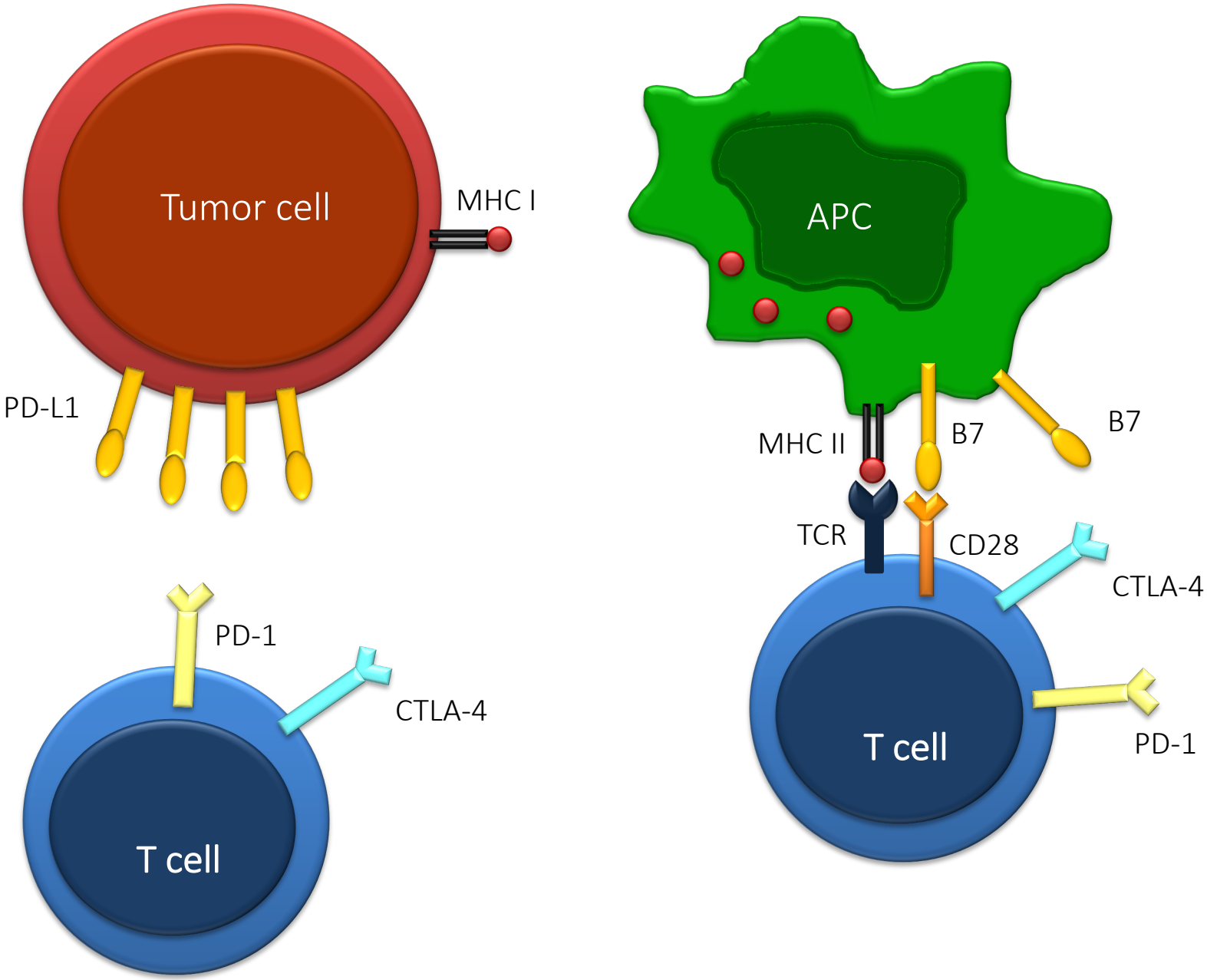
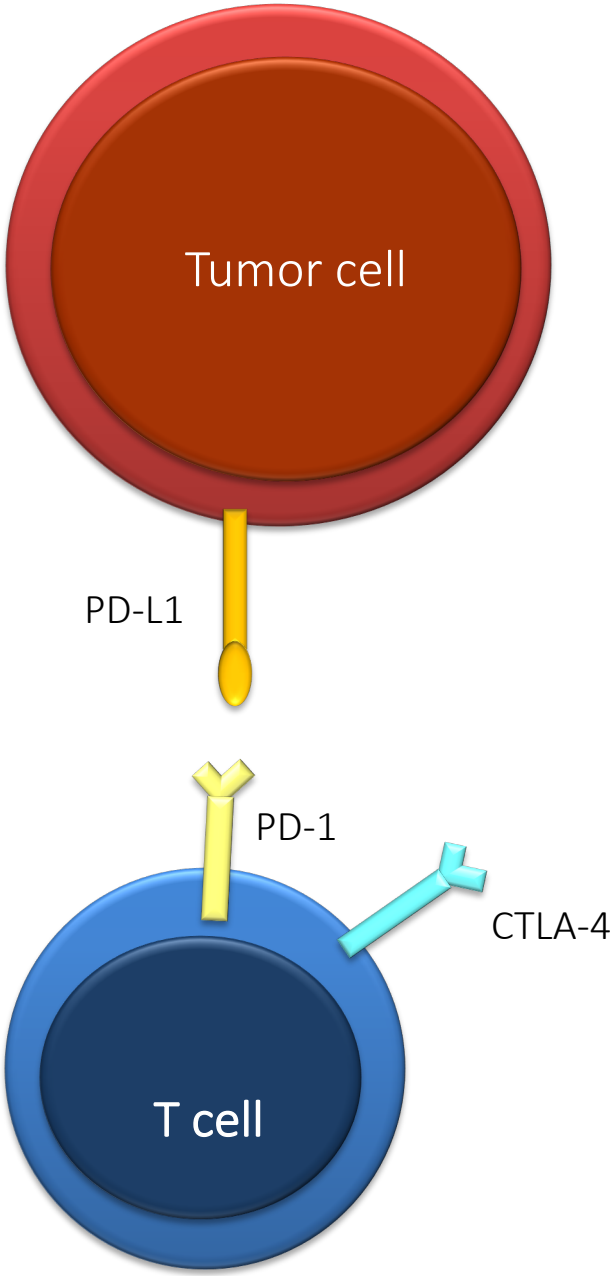
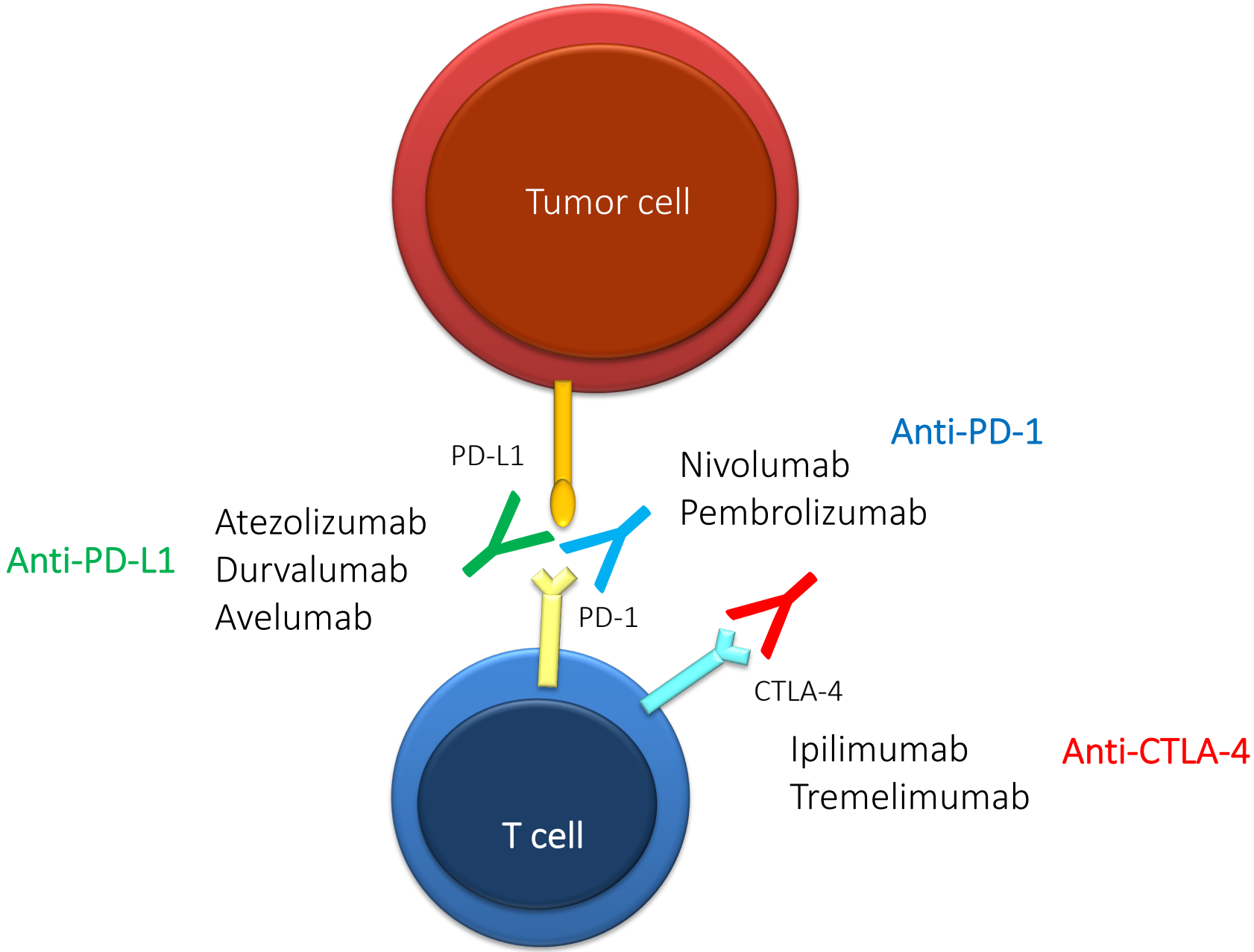

Tumor cell
MHC I
PD-L1
APC
MHC II
B7
B7
TCR
CD28
CTLA-4
PD-1
T cell
PD-1
CTLA-4
T cell


Tumor cell
PD-L1
PD-1
CTLA-4
T cell


Tumor cell
PD-L1
Anti-PD-1
Nivolumab
Pembrolizumab
Atezolizumab
Durvalumab
Avelumab
Anti-PD-L1
PD-1
CTLA-4
Ipilimumab
Tremelimumab
Anti-CTLA-4
T cell

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Como dizer que uma droga está sendo benéfica ao paciente?

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Melhora de sintomas?

Redução tumoral?

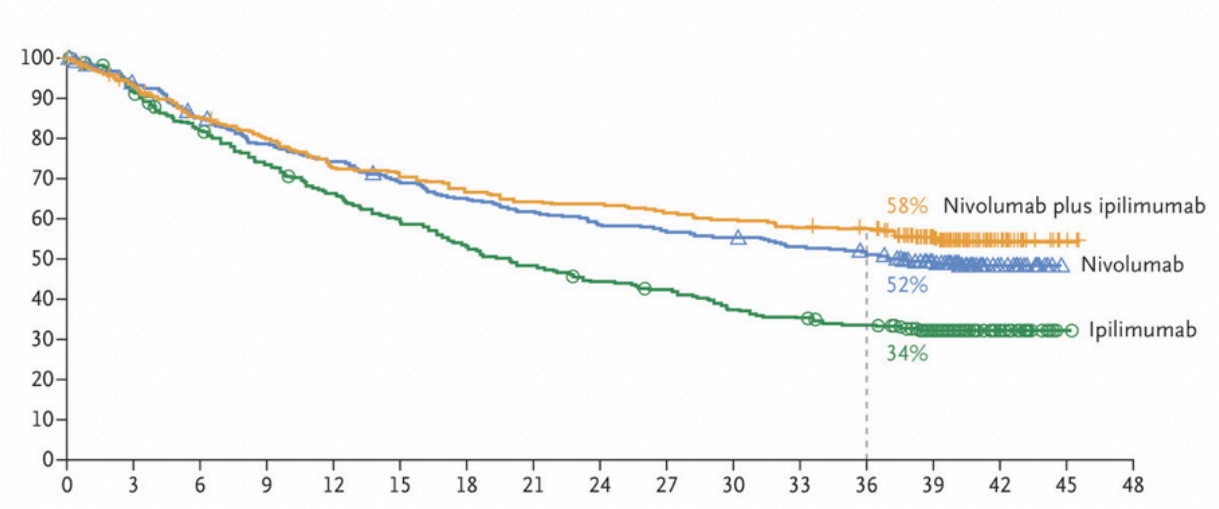
Aumento de sobrevida?

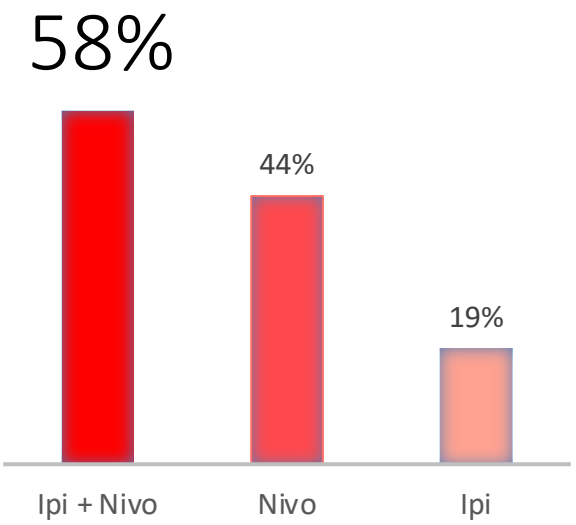
Melhora em qualidade de vida?

Cura?

Qual endpoint enxergar para avaliar o benefício da imunoterapia?

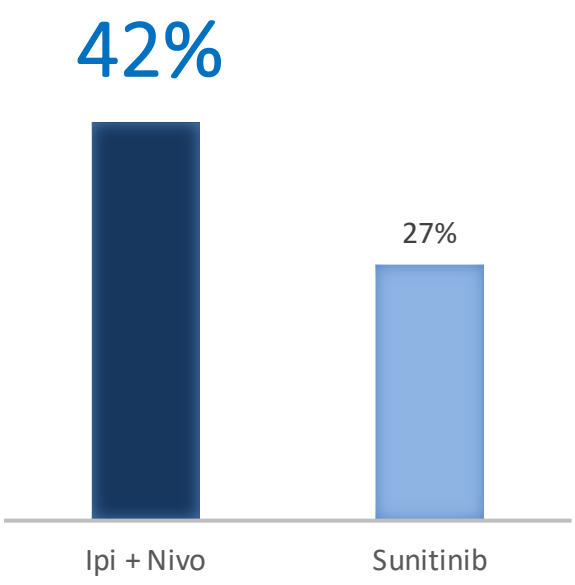
Melanoma

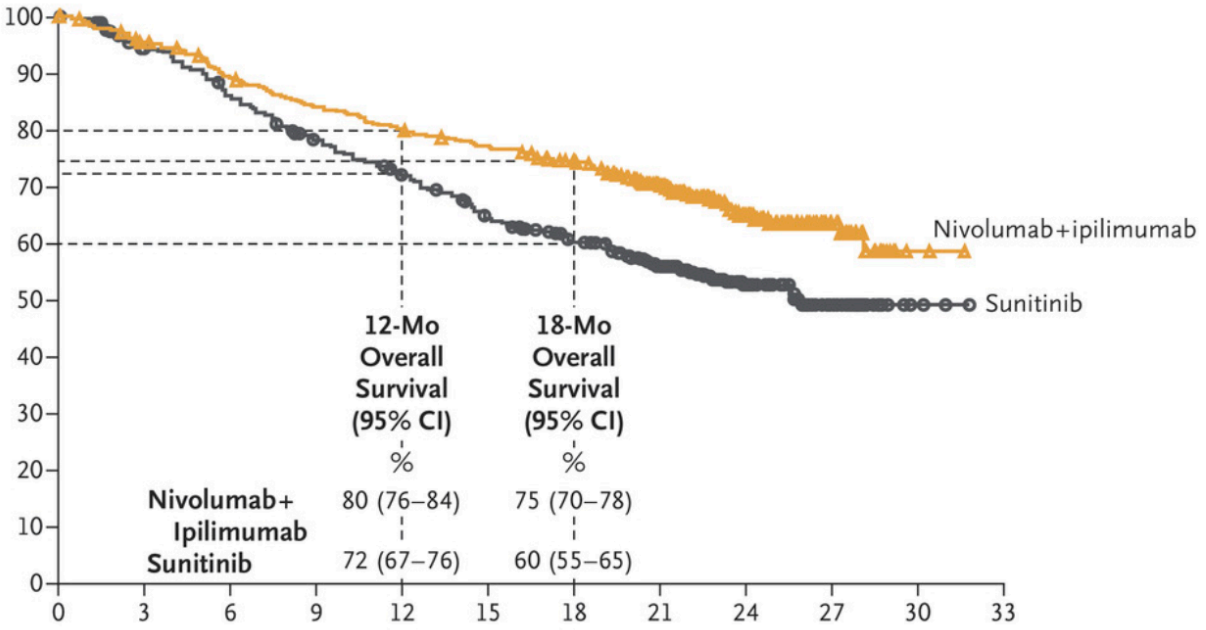




Extraido de Wolchok et al. N Engl J Med 2017

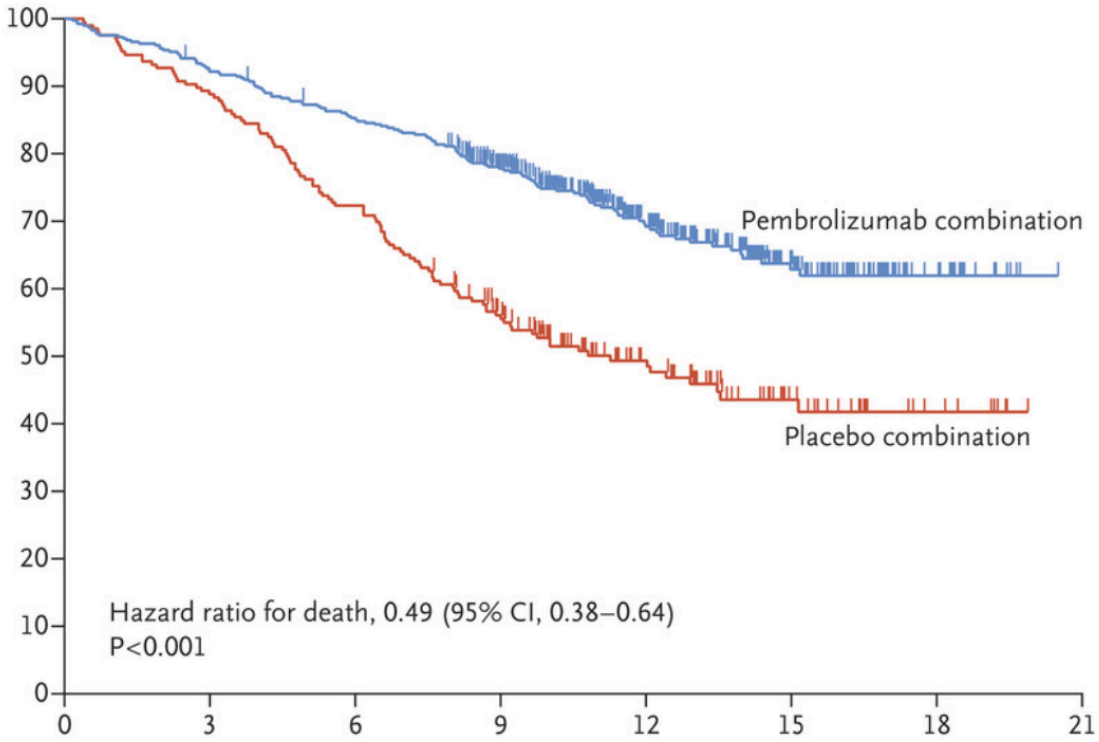
Rim





Extraido de Motzer et al. N Engl J Med 2018

Pulmão (Histologia não-escamosa)

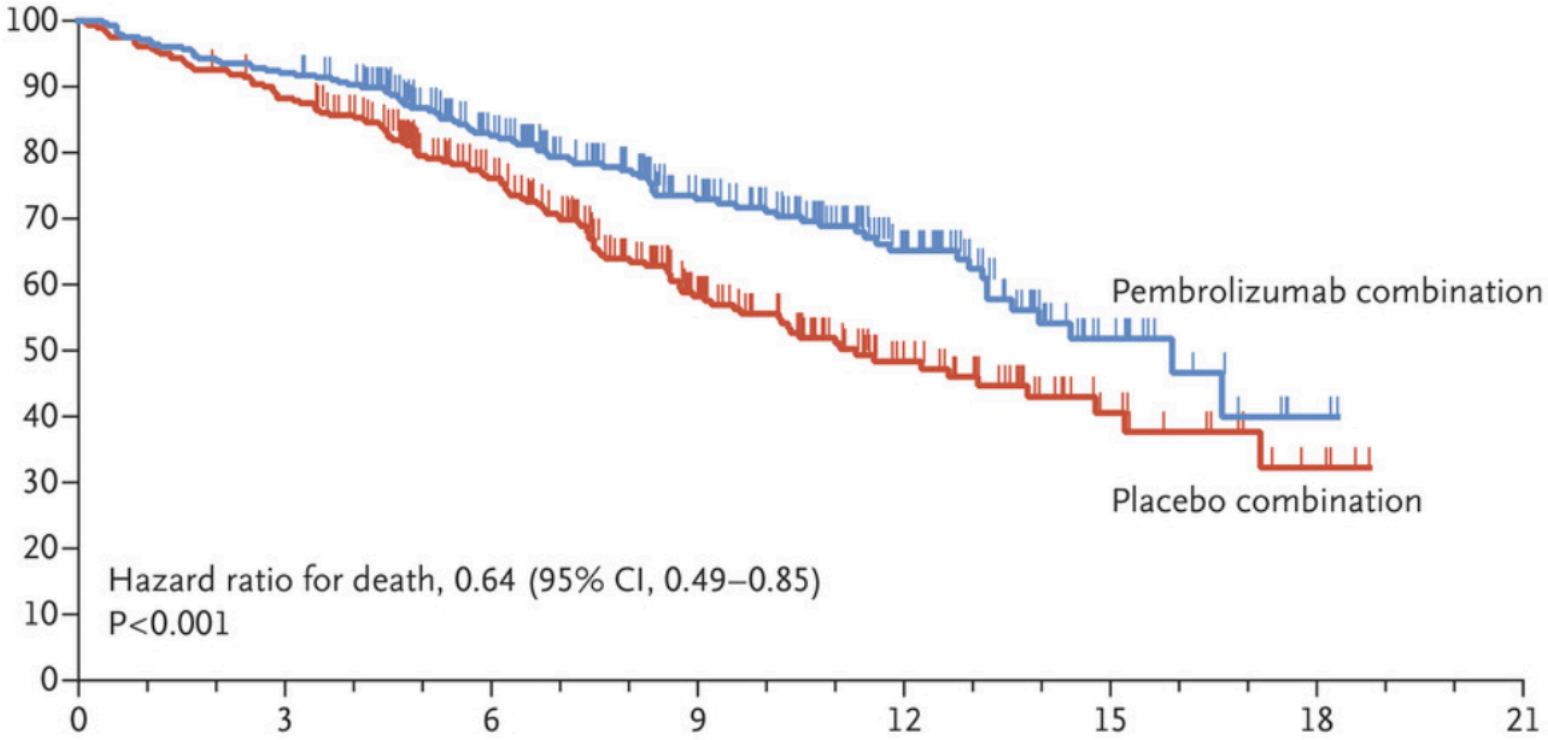


Taxa de resposta:

48% vs 19%

Extraido de Gandhi et al. N Engl J Med 2018

Pulmão (Histologia escamosa)

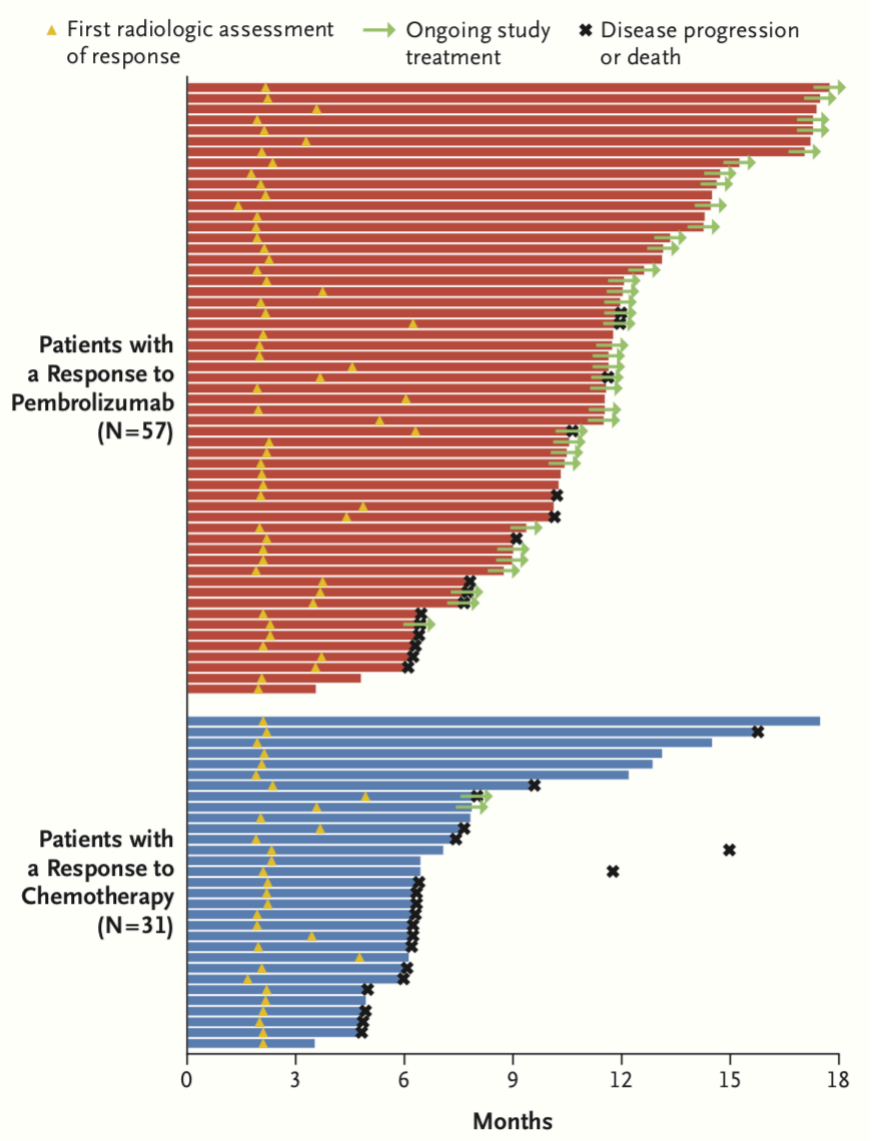


Taxa de resposta:

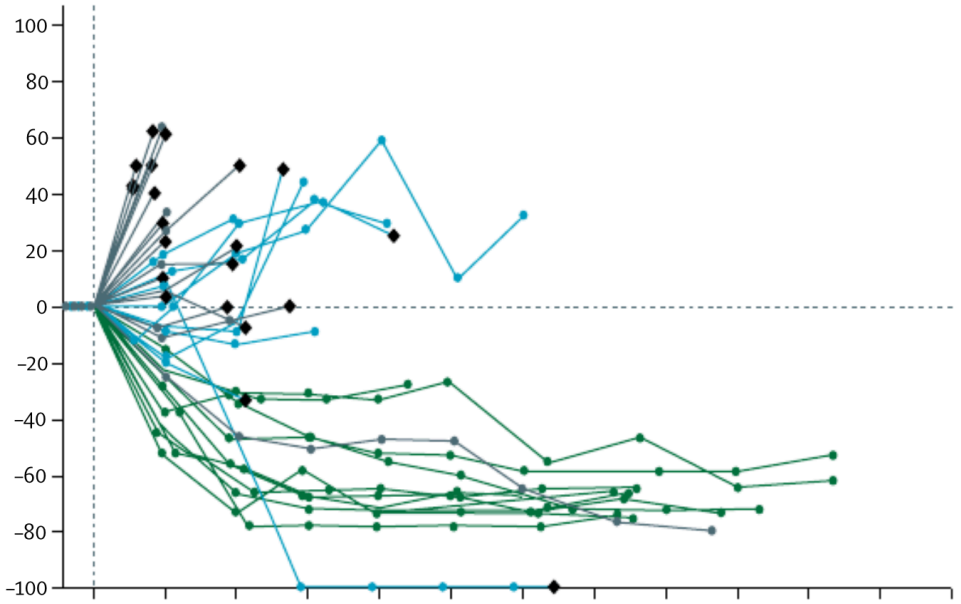
58% vs 38%

Extraido de Gandhi et al. N Engl J Med 2018

Carcinoma urotelial



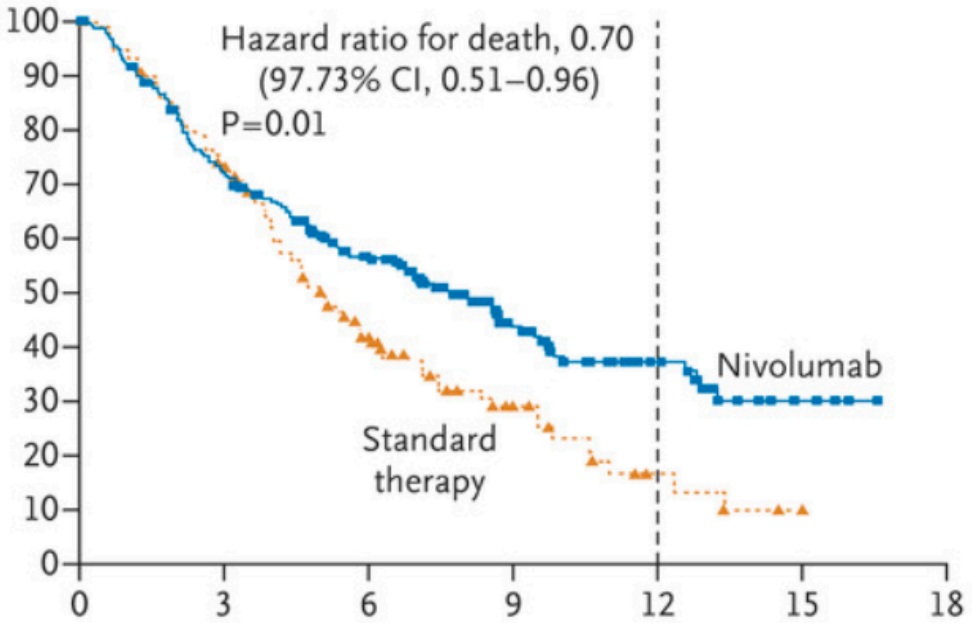
1ª linha – Fase II



2ª linha – Fase III

Extraido de Bellmunt et al. N Engl J Med 2017; Balar et al. Lancet 2017

Cabeça e Pescoço



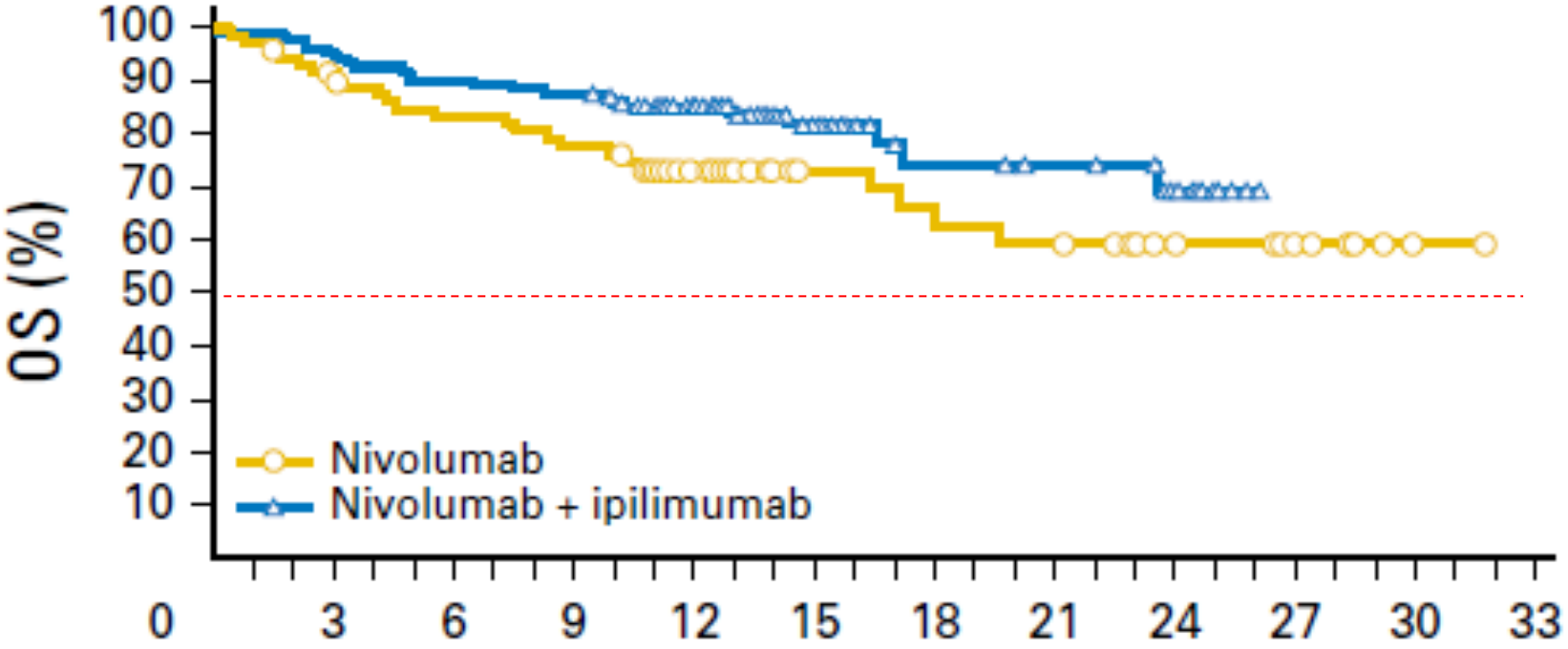
2ª linha – Fase III

ESMO 2018
PD-L1 + / CPS > 20

	QT	Pembro	Combo
SG	10.7m	14.9m	13.0m
DR	4.5m	20.9m	-
TR	36%	23%	36%

Extraido de Ferris et al. N Engl J Med 2016; Balar et al. Lancet 2017

Coloretal MSI-H



Extraído de Overman M et al. J Clin Oncol 2018

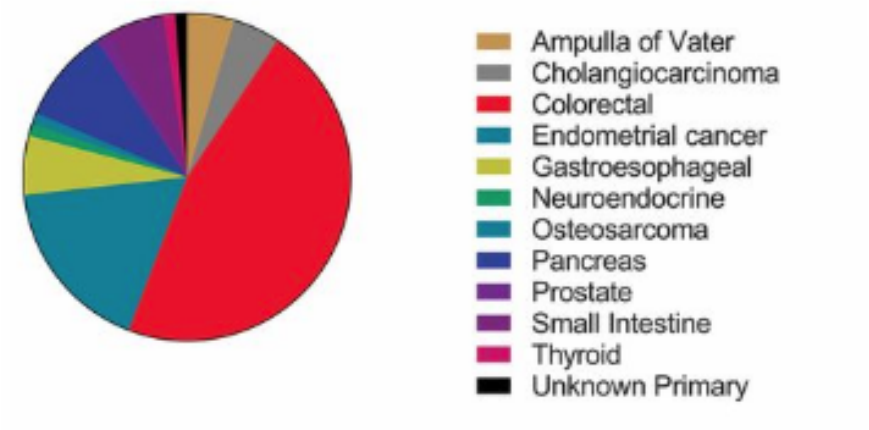
Coloretal MSI-H

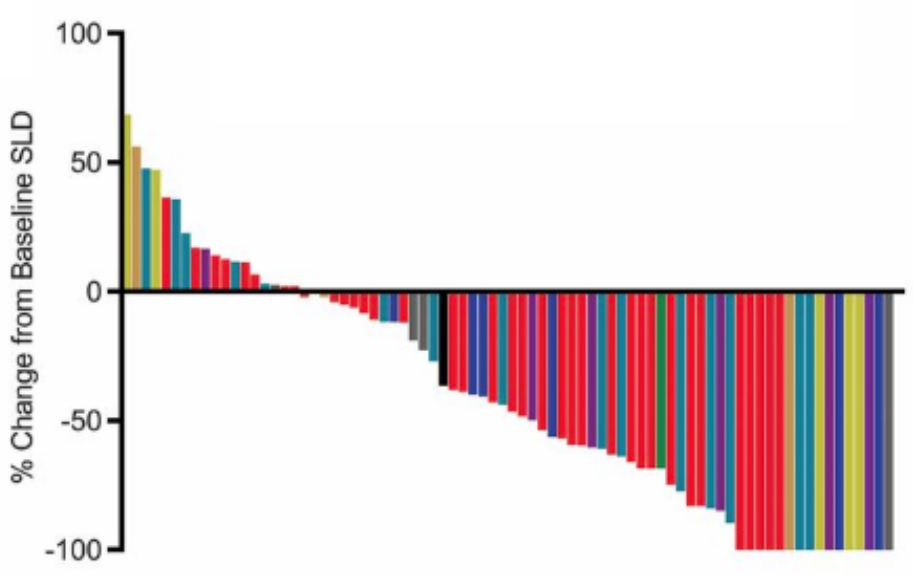
ESMO 2018
CheckMate 142
Dados de primeira-linha de tratamento
Endpoint primário: Taxa de resposta

	Ipilimumab + Nivolumab
Taxa de resposta	60%
Resposta completa	7%
Taxa de controle de doença	84%

Extraido de Ferris et al. N Engl J Med 2016; Balar et al. Lancet 2017

MSI-H não-coloretal





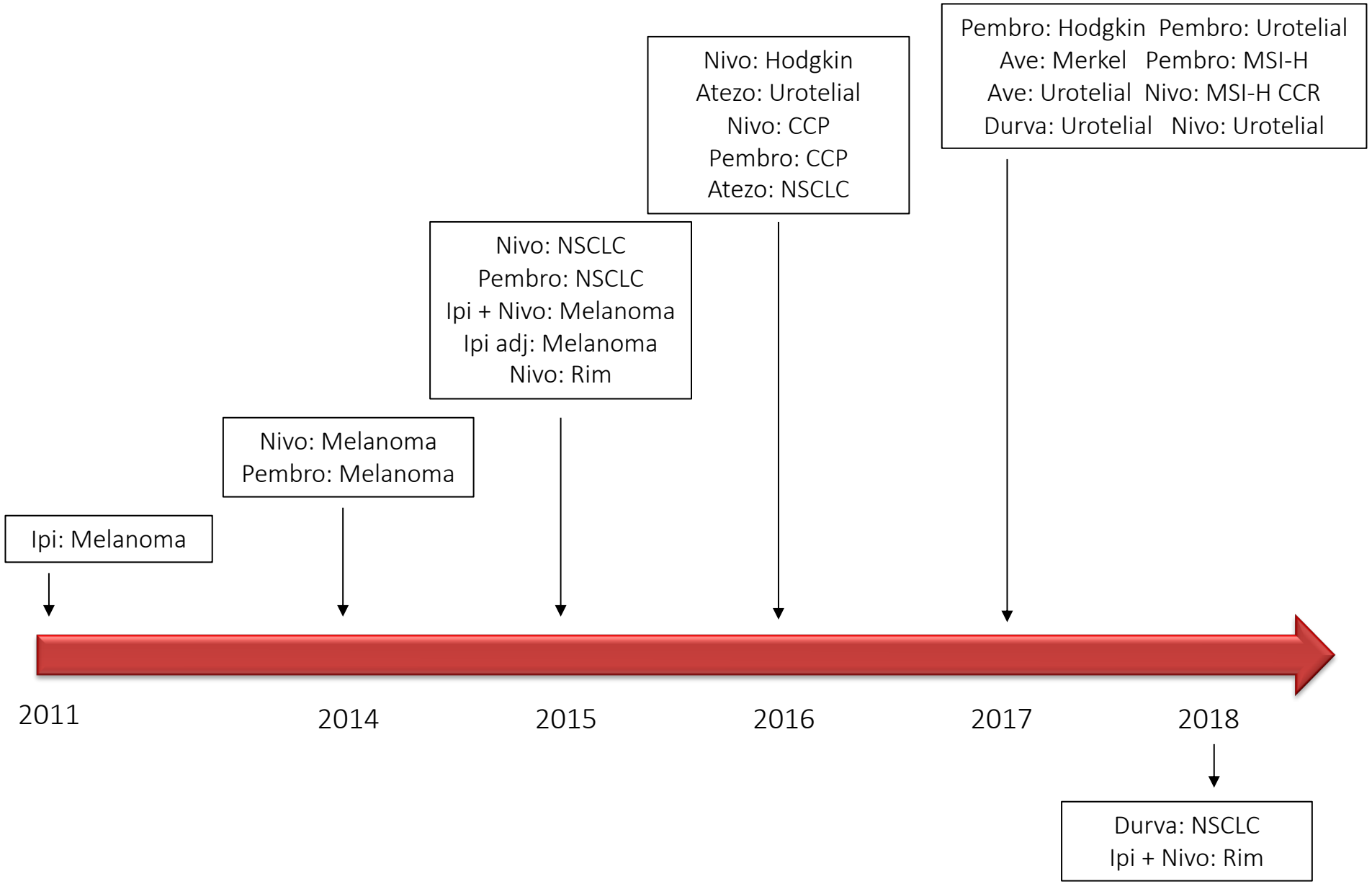
Extraido de Le DT et al. Science 2017

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

Listen to the FDA D.I.S.C.O. podcast about this approval

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Extraído de www.fda.gov



Extraido de Wei SC et al. Cancer Disc 2018

Brasil / ANVISA

- ✓ Melanoma:
  - ✓ Ipilimumabe + Nivolumabe
  - ✓ Nivolumabe
  - ✓ Pembrolizumabe
  - ✓ Ipilimumabe
- ✓ Rim:
  - ✓ Ipilimumabe + Nivolumabe
  - ✓ Nivolumabe
- ✓ Pulmão
  - ✓ Nivolumabe
  - ✓ Pembrolizumabe
  - ✓ Atezolizumabe
  - ✓ Durvalumabe

Brasil / ANVISA

- ✓ Cabeça e Pescoço:
  - ✓ Nivolumabe
- ✓ Urotelial:
  - ✓ Pembrolizumabe
  - ✓ Atezolizumabe
  - ✓ Durvalumabe
  - ✓ Nivolumabe
- ✓ Gástrico:
  - ✓ Pembrolizumabe
- ✓ Carcinoma de células de Merkel
  - ✓ Avelumabe
- ✓ Hodgkin:
  - ✓ Nivolumabe

Imunoterapia

- ✓ Mecanismos de evasão imune
- ✓ Mecanismos de ação dos inibidores de checkpoint
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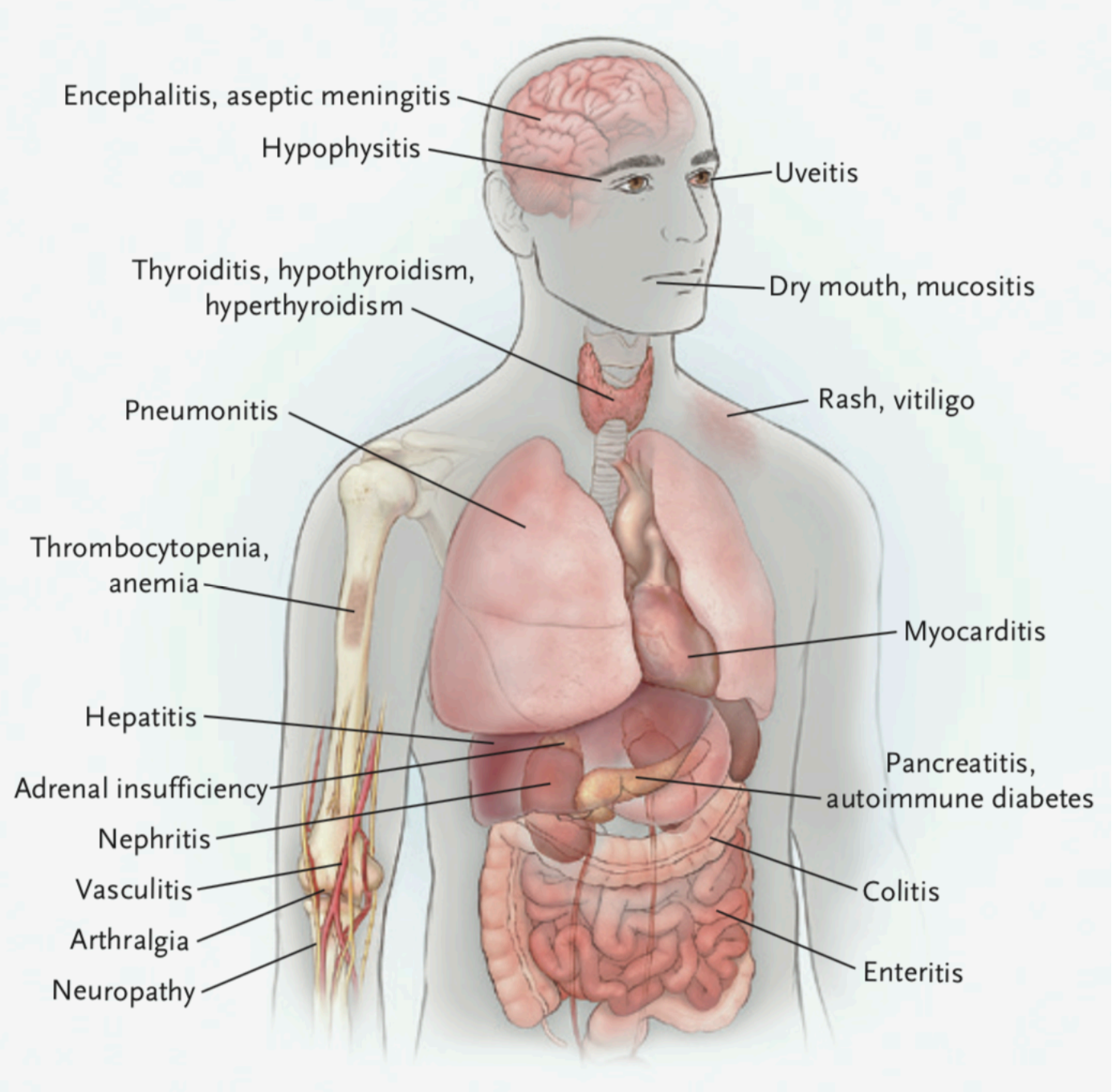
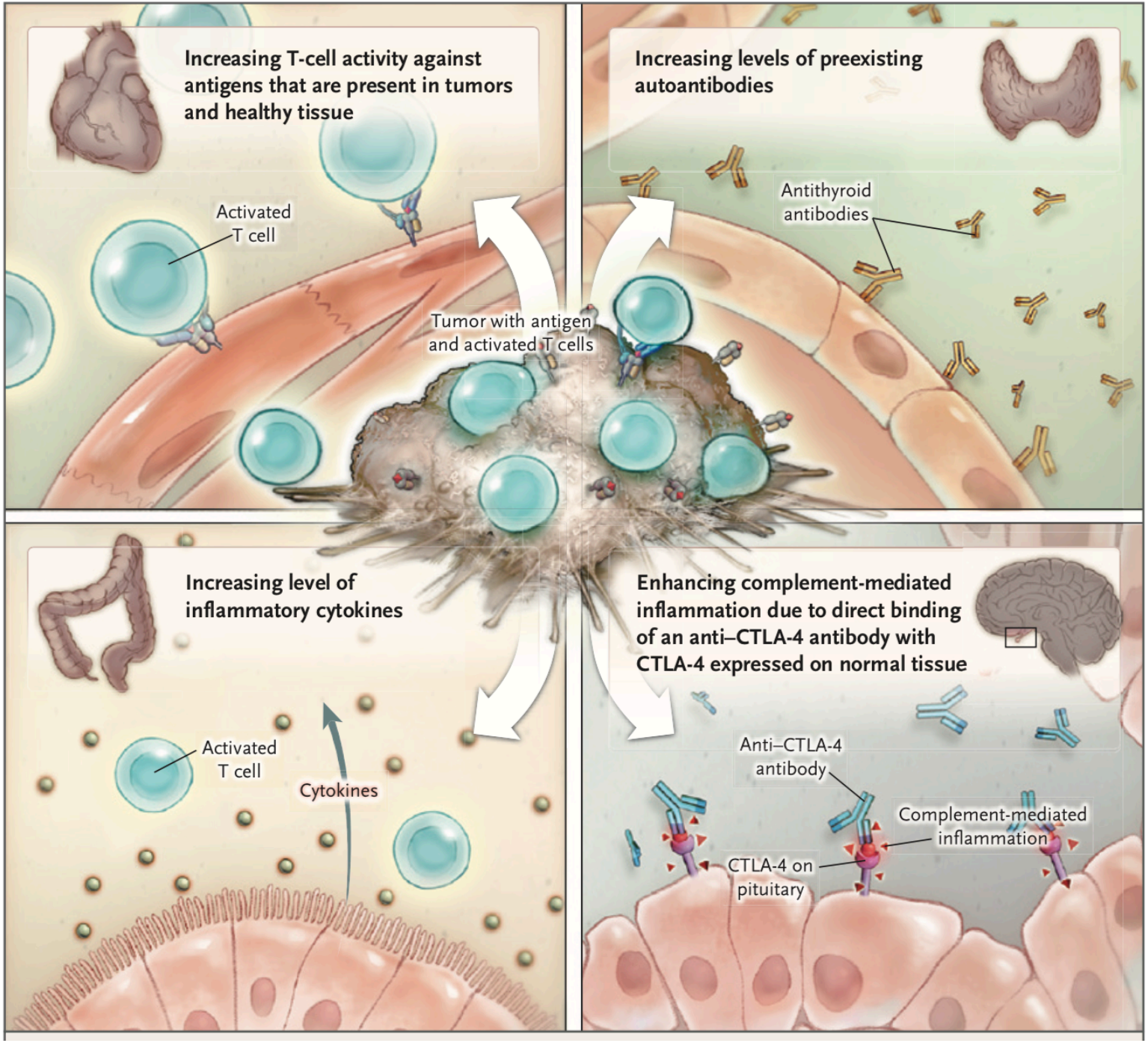
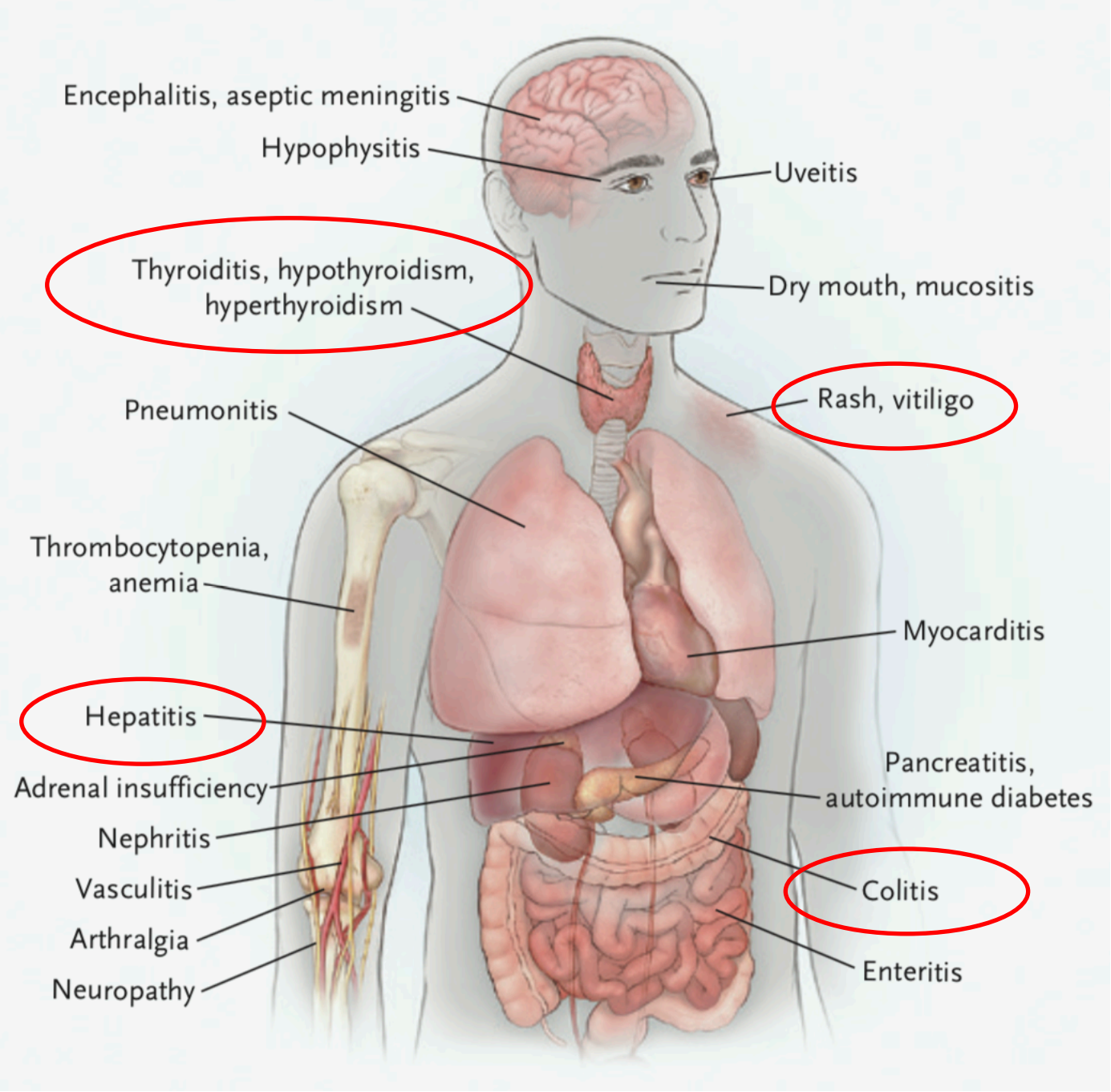


Extraído de Postow M N Engl J Med 2018



Extraído de Postow M N Engl J Med 2018



Extraído de Postow M N Engl J Med 2018

Eventos adversos

	Ipi + Nivo		Ipi		Nivo	
	Total	G3-4	Total	G3-4	Total	G3-4
Diarreia	45%	9%	34%	6%	21%	3%
Rash	30%	3%	22%	2%	23%	< 1%
ALT / AST	19%	9%	4%	2%	4%	1%
Pneumonite	7%	1%	2%	< 1%	2%	< 1%
Descontinuação	39%	30%	16%	14%	12%	8%

Wolchok JD et al. N Engl J Med 2017

Eventos adversos

	Ipi + Nivo		Ipi		Nivo	
	Total	G3-4	Total	G3-4	Total	G3-4
Diarreia	45%	9%	34%	6%	21%	3%
Rash	30%	3%	22%	2%	23%	< 1%
ALT / AST	19%	9%	4%	2%	4%	1%
Pneumonite	7%	1%	2%	< 1%	2%	< 1%
Descontinuação	39%	30%	16%	14%	12%	8%

Wolchok JD et al. N Engl J Med 2017

Eventos adversos

	Ipi + Nivo	Ipi	Nivo	Pembro
	G3-4	G3-4	G3-4	G3-4
Diarreia	9%	6%	3%	4%
Rash	3%	2%	< 1%	4%
ALT / AST	9%	2%	1%	< 1%
Pneumonite	1%	< 1%	< 1%	3%
Descontinuação	30%	14%	8%	5%

Wolchok JD et al. N Engl J Med 2017; Reck M et al. N Engl J Med 2016