

Imunoterapia em câncer colorectal: Esperança para quem?



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Introdução

- ✓ Há mais de 10 anos não observamos surgimento de novas terapias no manejo do câncer coloretal.
- ✓ Com exceção dos anticorpos anti-EGFR, não haviam tratamentos que consideravam a heterogeneidade molecular da doença.
- ✓ A imunoterapia tem se apresentado revolucionária em alguns tumores e promissora em inúmeros outros.
- ✓ Busca-se subgrupos de pacientes com câncer coloretal que possam usufruir desta nova modalidade terapêutica.

Satélites

TGCTATGC**COLORECTALCANCERIMMUNOTHERAPY**

Satélites

TGCTATGC**COLORECTALCANCERIMMUNOTHERAPY**COLORECTALCANCERIMMU
NOTHERAPY

Satélites

TGCTATGC**COLORECTALCANCERIMMUNOTHERAPYCOLORECTALCANCERIMMU
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Satélites

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NOTHERAPYCOLORECTALCANCERIMMUNOTHERAPYGCATTAGCATTATCGAGCTA
C

Satélites

TGCTATGC**COLORECTALCANCERIMMUNOTHERAPYCOLORECTALCANCERIMMU**
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C



Satélites (> 100bp)

Satélites

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C




Satélites (> 100bp)

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Satélites


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 Satélites (> 100bp)


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 Satélites (> 100bp)

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 Minisatélites (10 – 100bp)

Satélites

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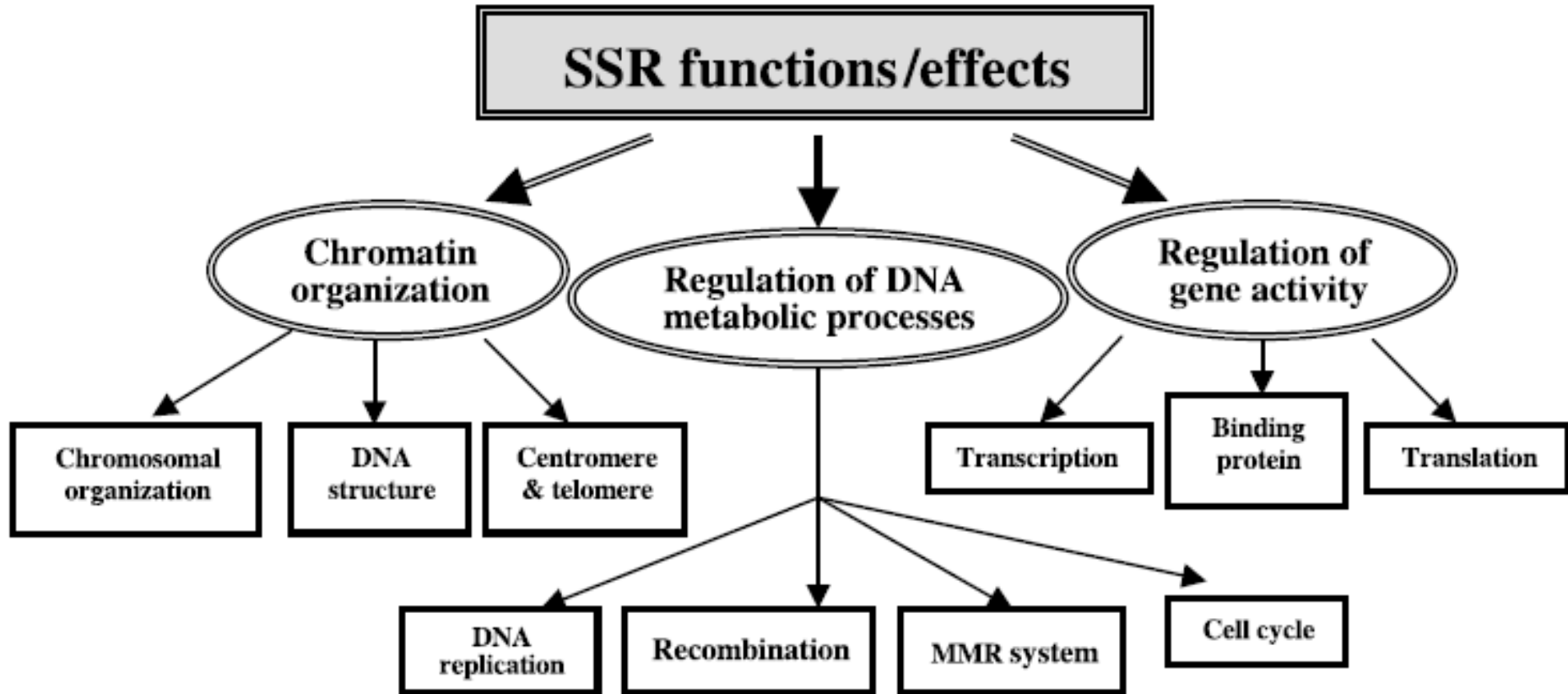
 Satélites (> 100bp)

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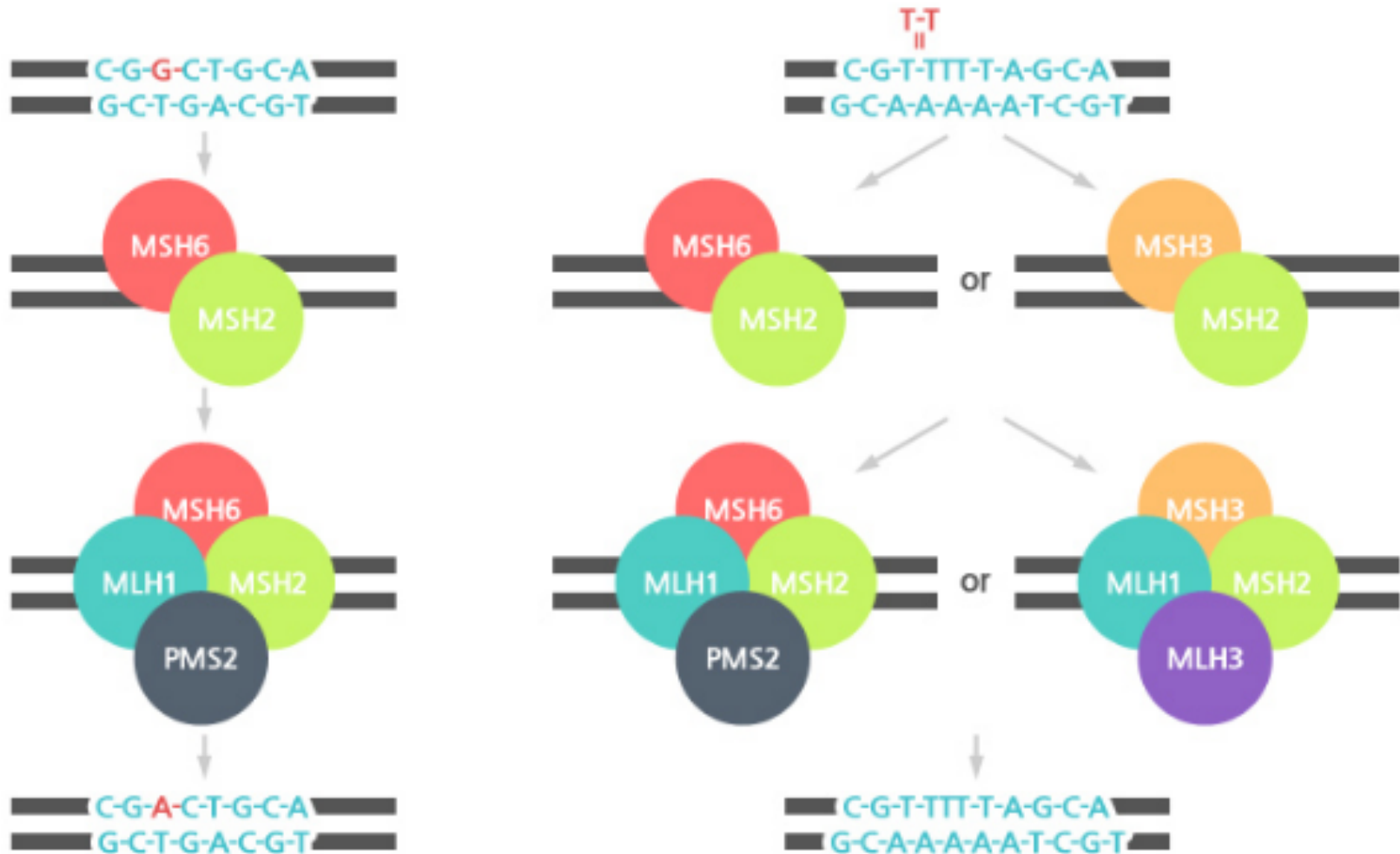
 Minisatélites (10 – 100bp)

TGCTATGCCOLO

Função dos microsátélites



Microsatélites e neoantígenos

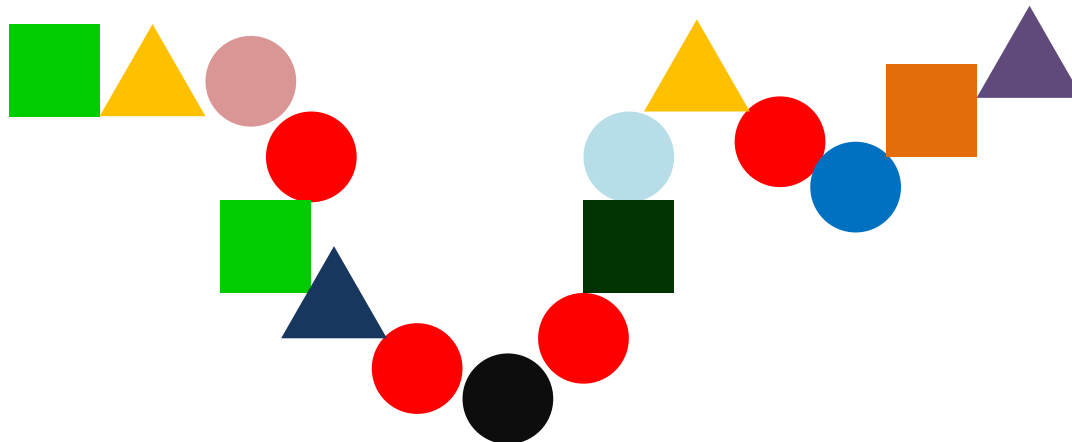


Microsatélites e neoantígenos

TGCTATGCCO T COLOC A LO A OLOC G LOCOL G COLO A OLOCO C OCOLO A O L
O COL T COLO C OLOCO C OCOL T COLOC CA OCO T O G OLOCO T O ATCGAGCT
AC

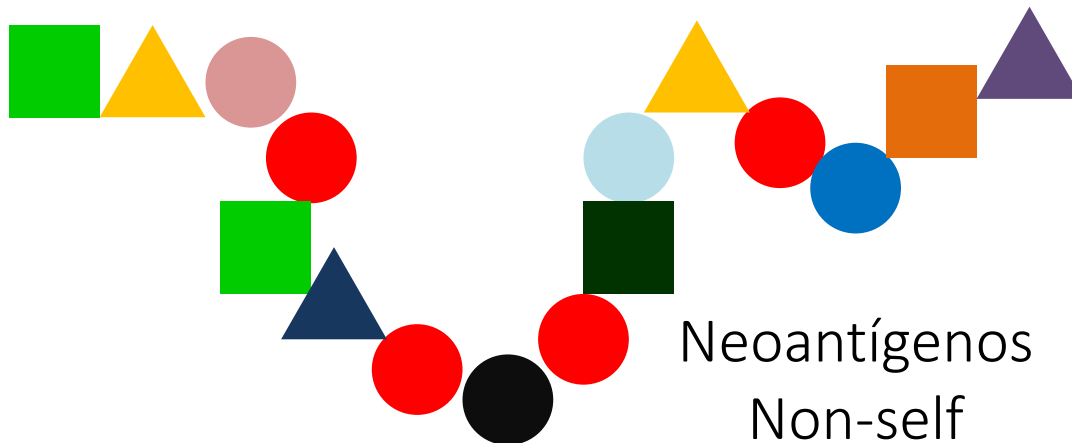
Microsatélites e neoantígenos

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O COL T COLO C OLOCO C OCOL T COLOC CA OCO T O G OLOCO T O ATCGAGCT
AC



Microsatélites e neoantígenos

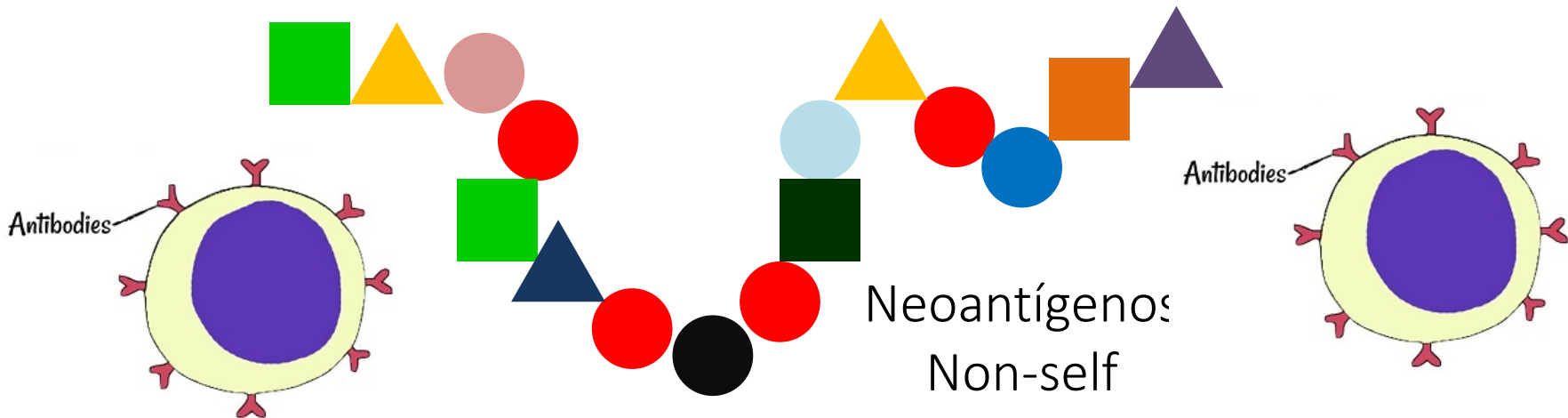
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COL T COLO C OLOCO C OCOL T COLOC CA OCO T O G OLOCO T O ATCGAGCT
AC



Neoantígenos
Non-self

Microsatélites e neoantígenos

TGCTATGCCO T COLOC A LO A OLOC G LOCOL G COLO A OLOCO C COLO A OL
OCOL T COLO C OLOCO C OCOL T COLOC CA OCO T O G OLOCO T OATCGAGCT
AC





dMMR



S. Lynch

Germinativa

MLH1 / MSH2 /
MSH6 / PMS2

1/3

dMMR



S. Lynch

Germinativa

Somática

MLH1 / MSH2 /
MSH6 / PMS2

1/3

2/3

Metilação MLH1

dMMR



S. Lynch

Germinativa

Somática

MLH1 / MSH2 /
MSH6 / PMS2

1/3

2/3

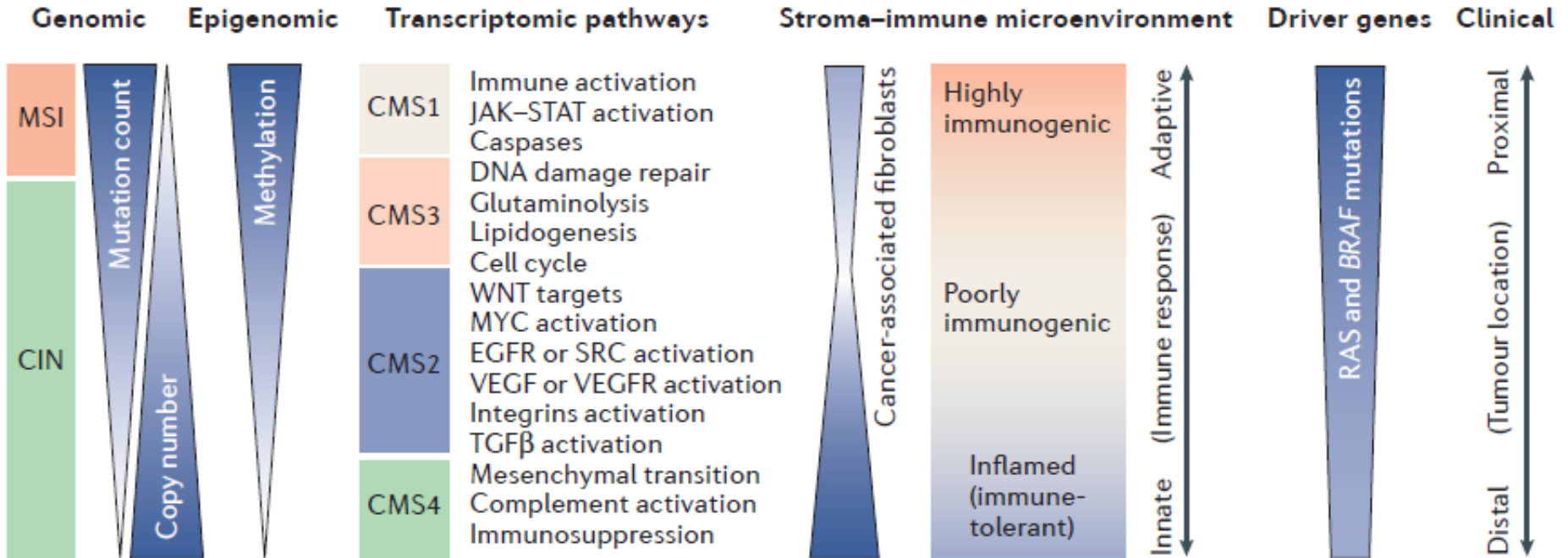
Metilação MLH1

dMMR

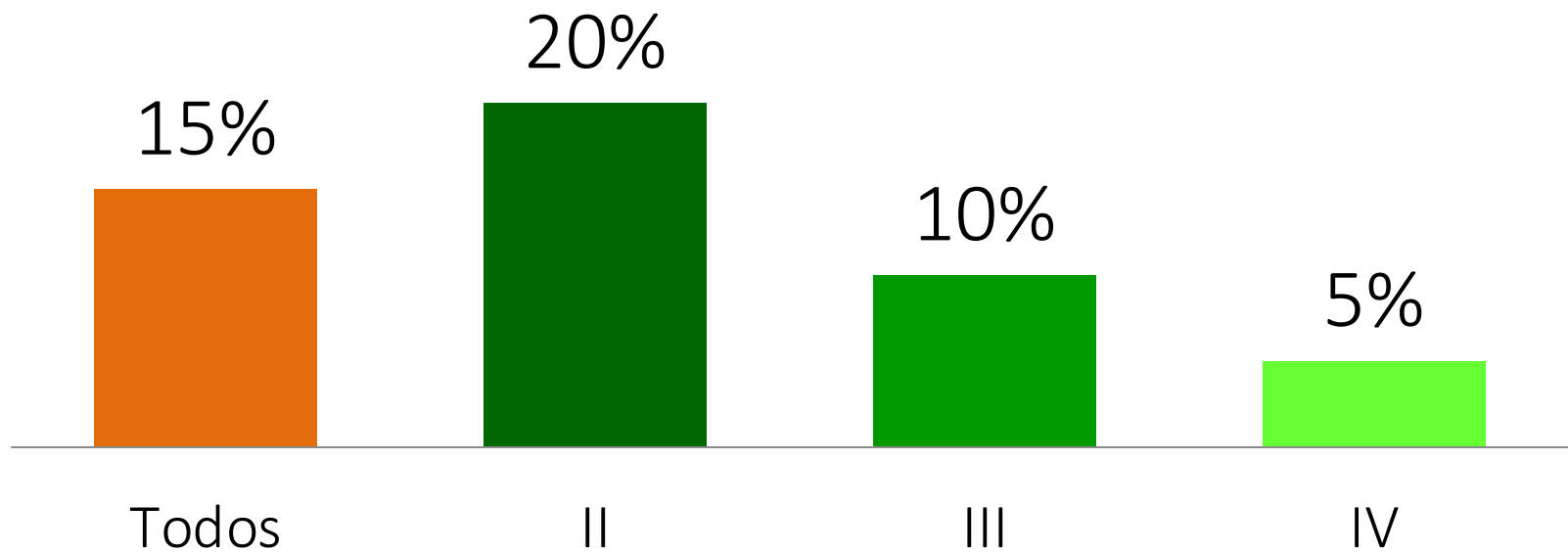


MSI-H

Caracterização molecular do CRC



Incidência de MSI-H



dMMR = MSI-H

↑ mutações

dMMR = MSI-H

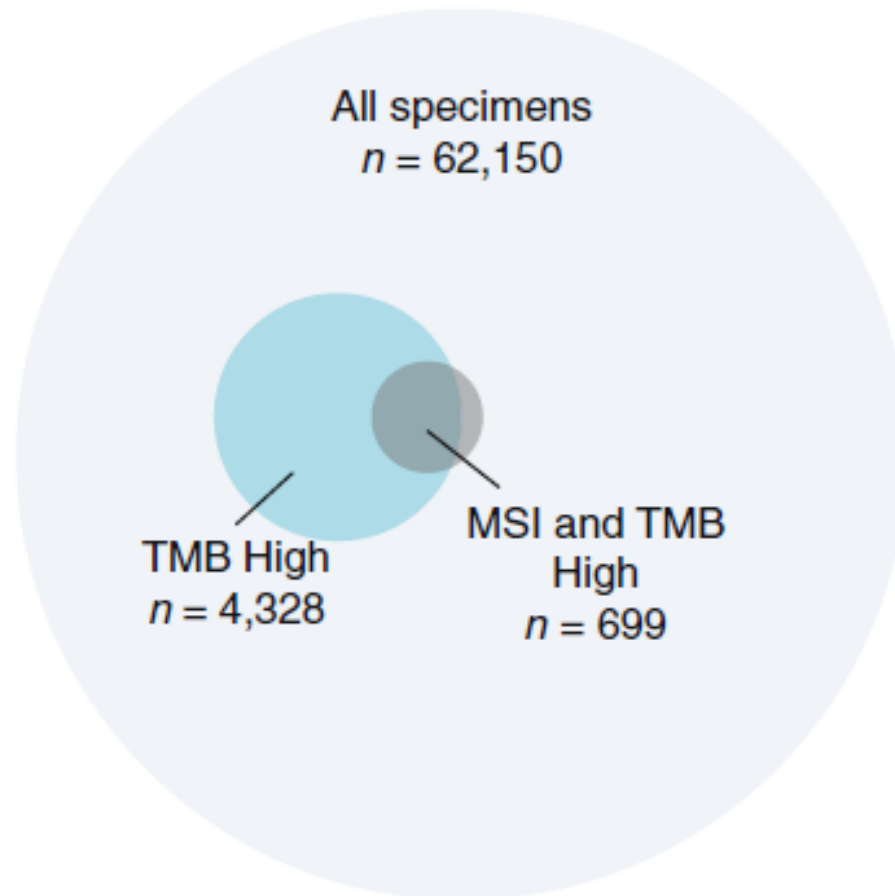
↑ mutações



↑ TMB

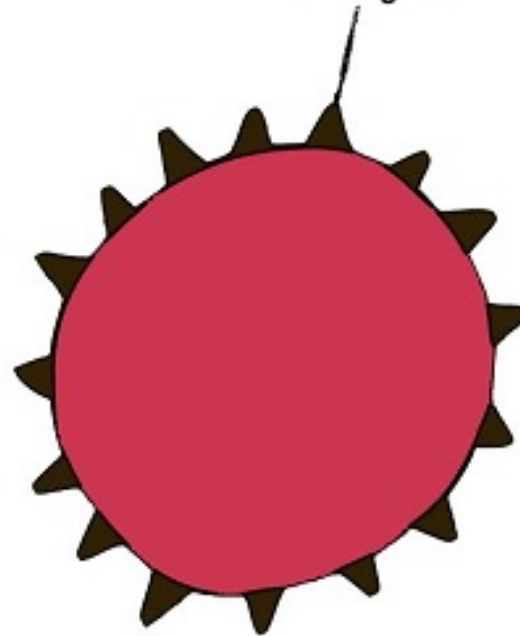
(Tumor mutational burden)

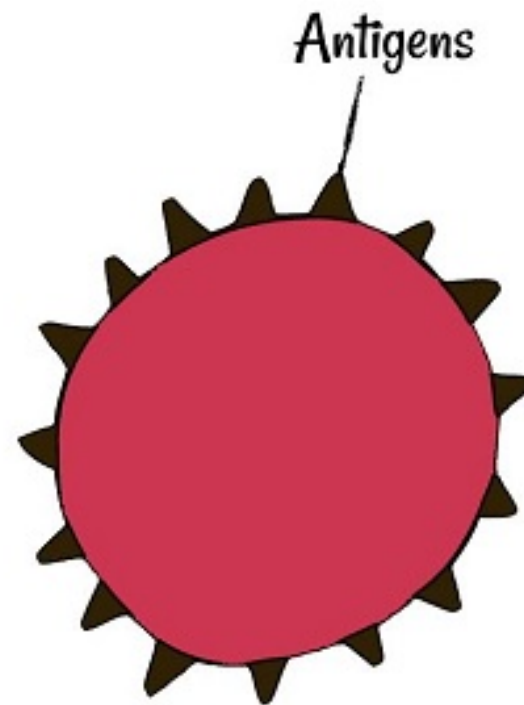
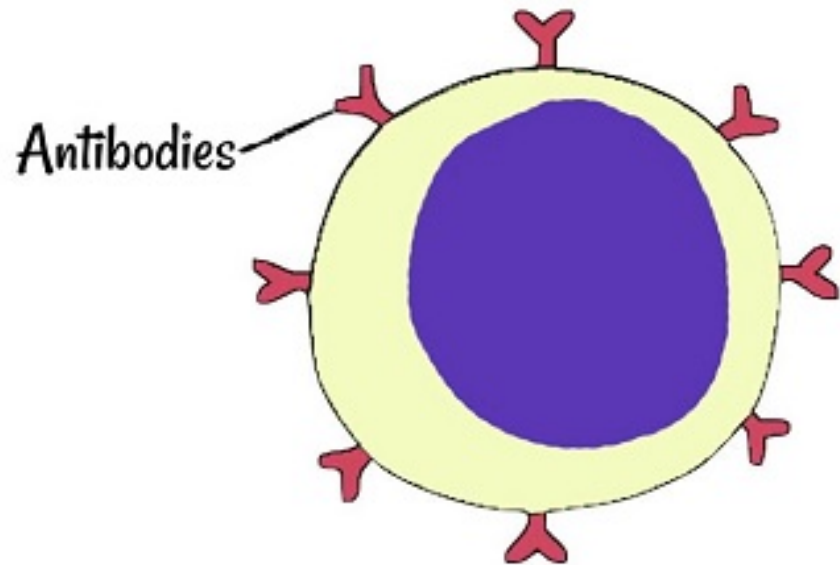
MSI-H vs TMB

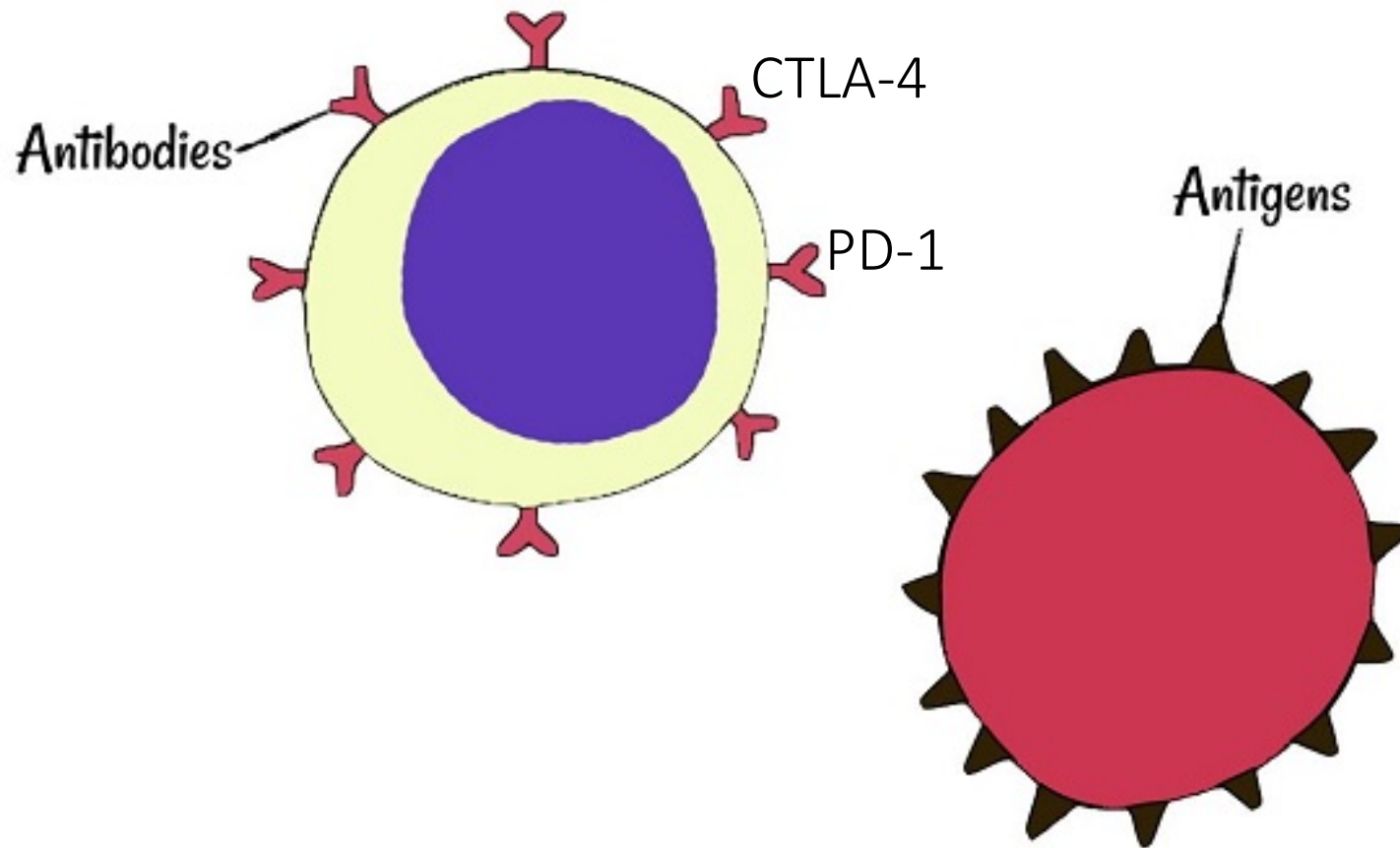


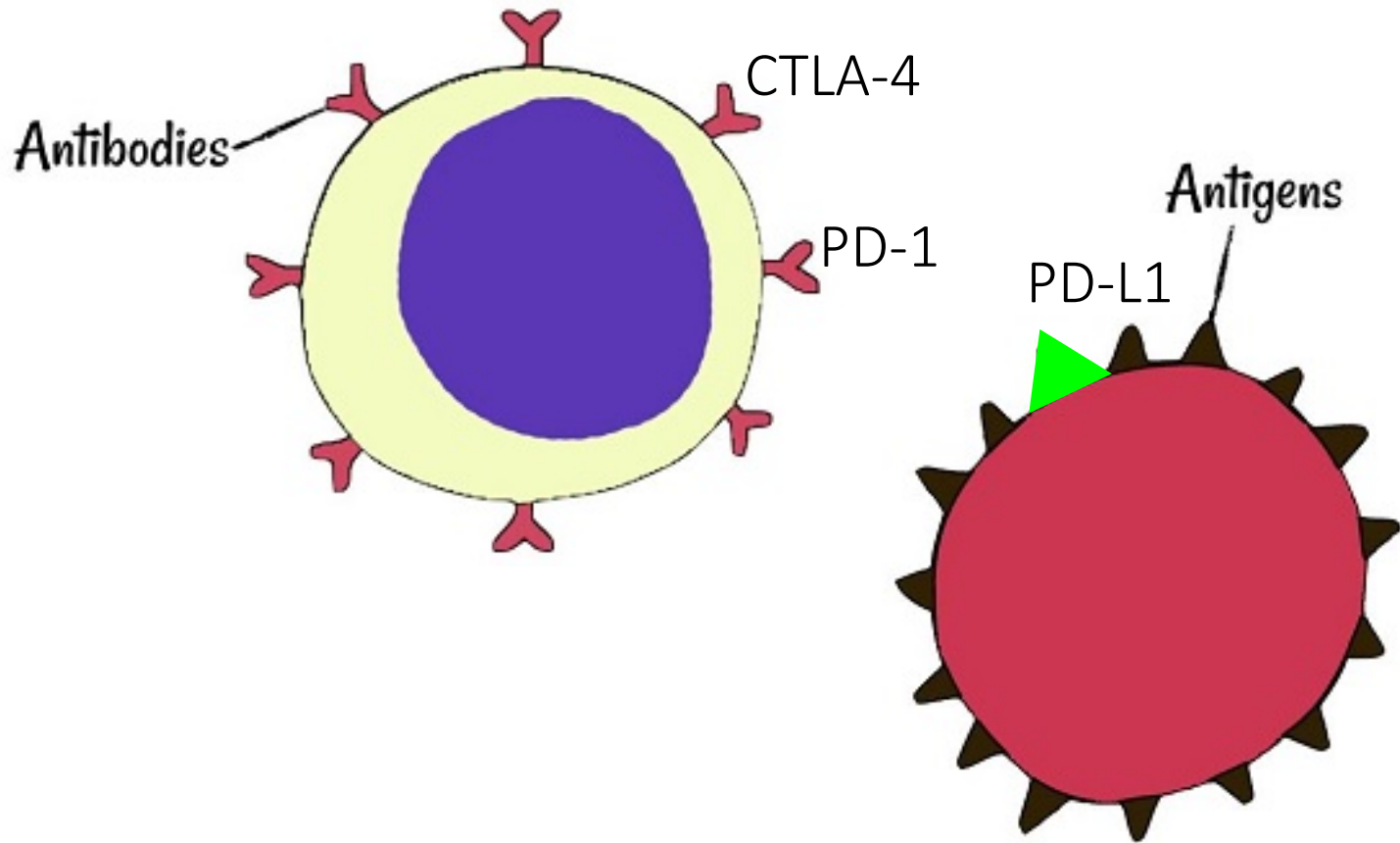
Há estreita correlação entre altos níveis de TMB e MSI-H

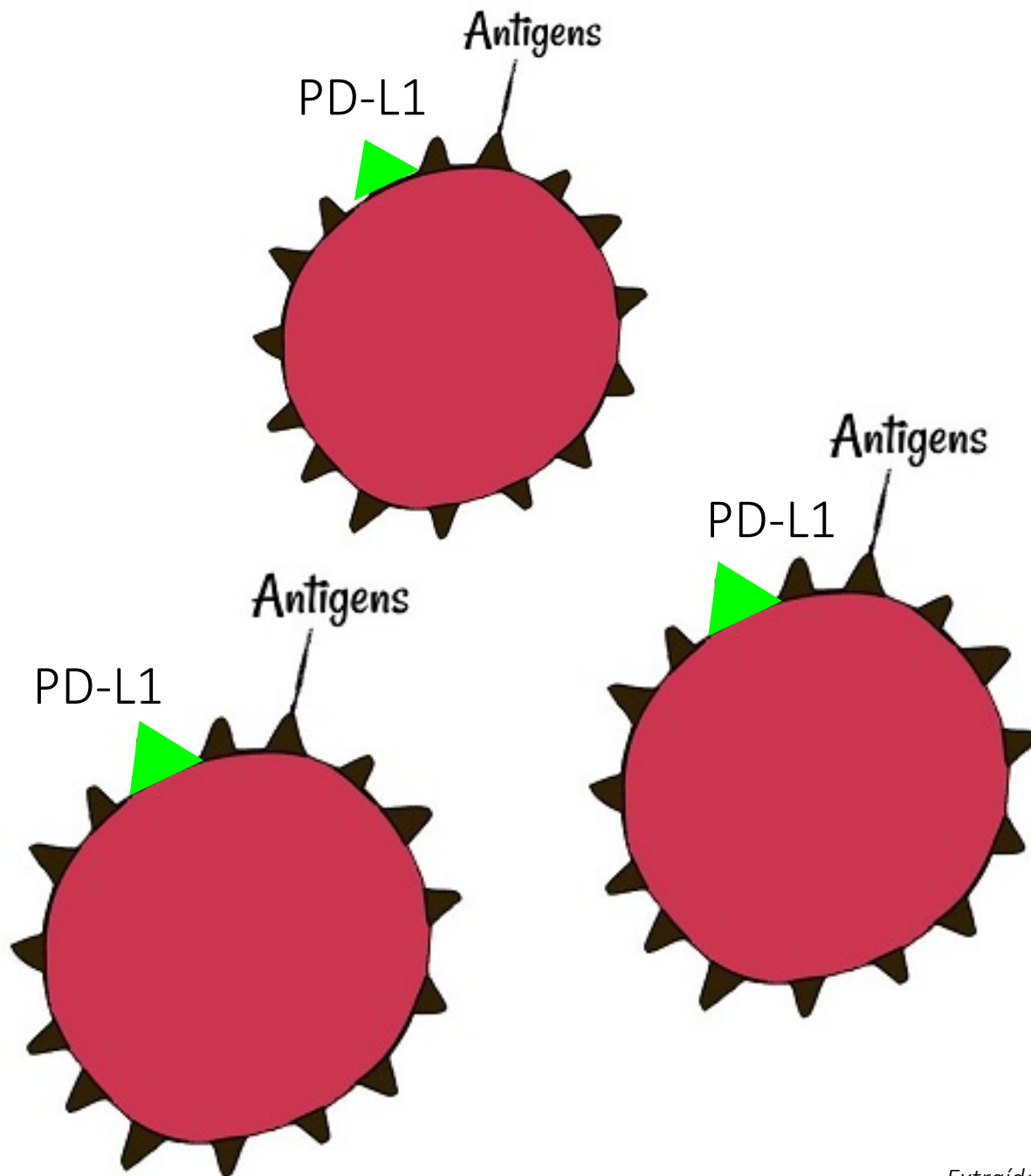
Antigens

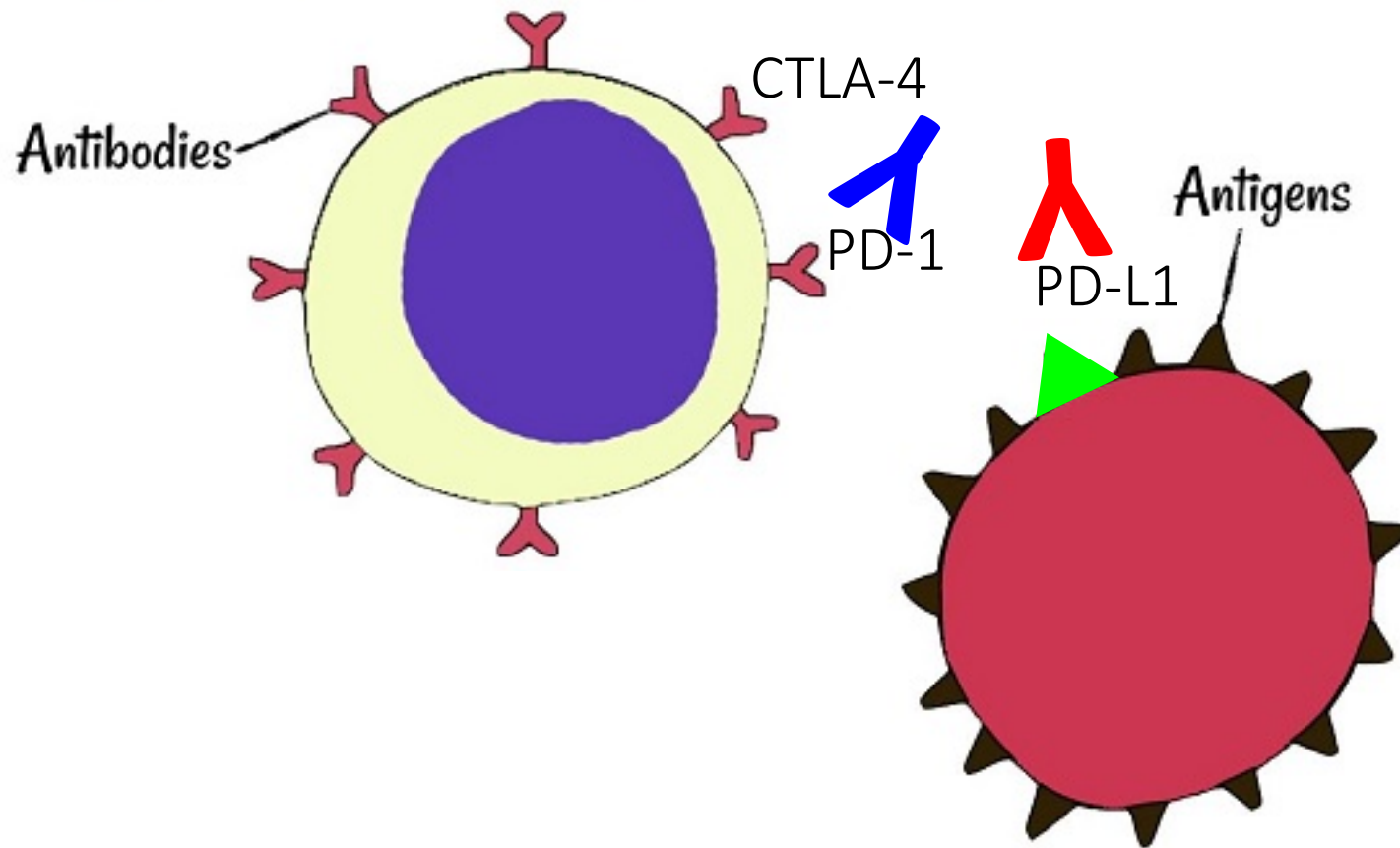


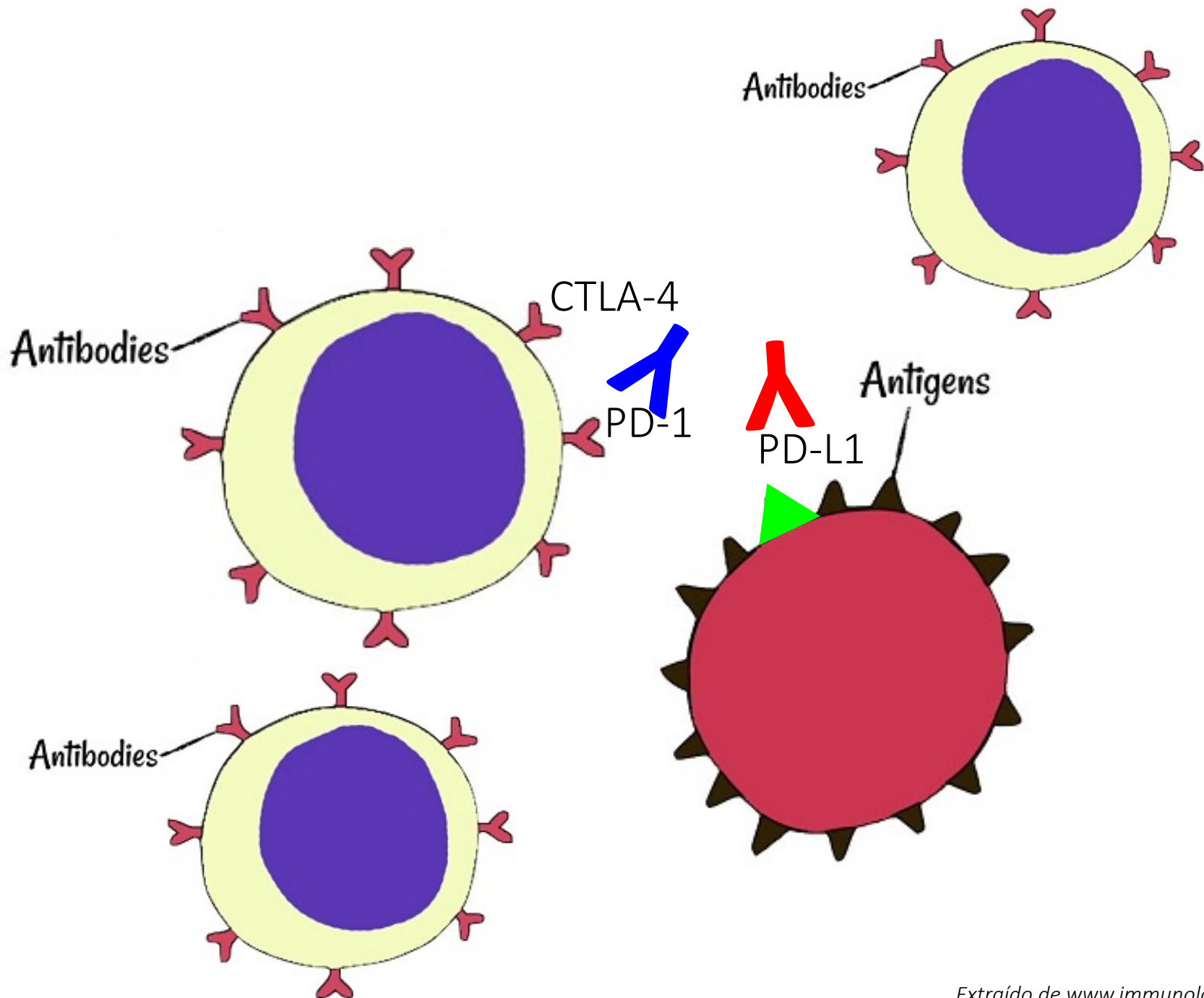








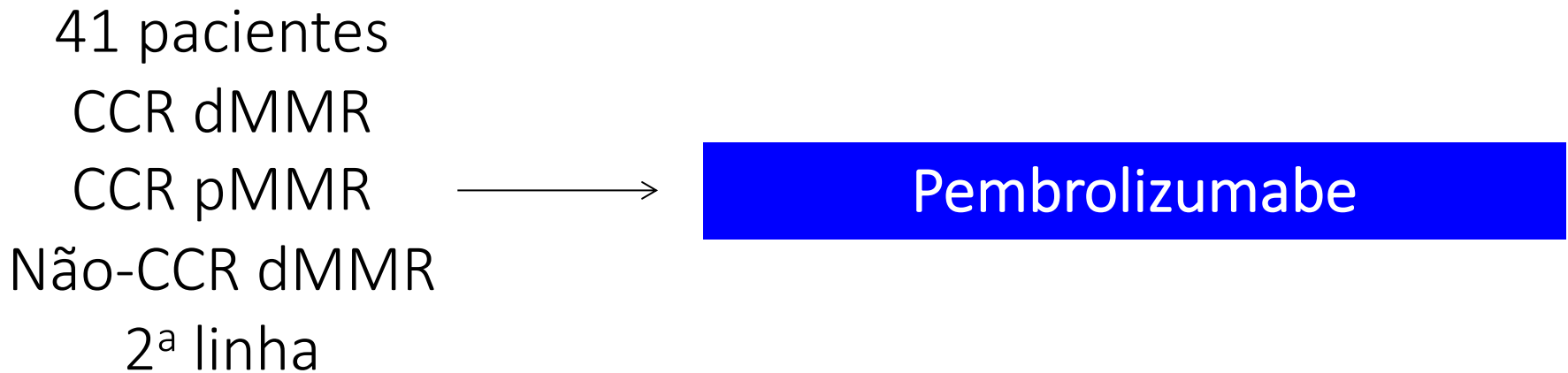




Imunoterapia vs MSI-H

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

The NEW ENGLAND JOURNAL of MEDICINE

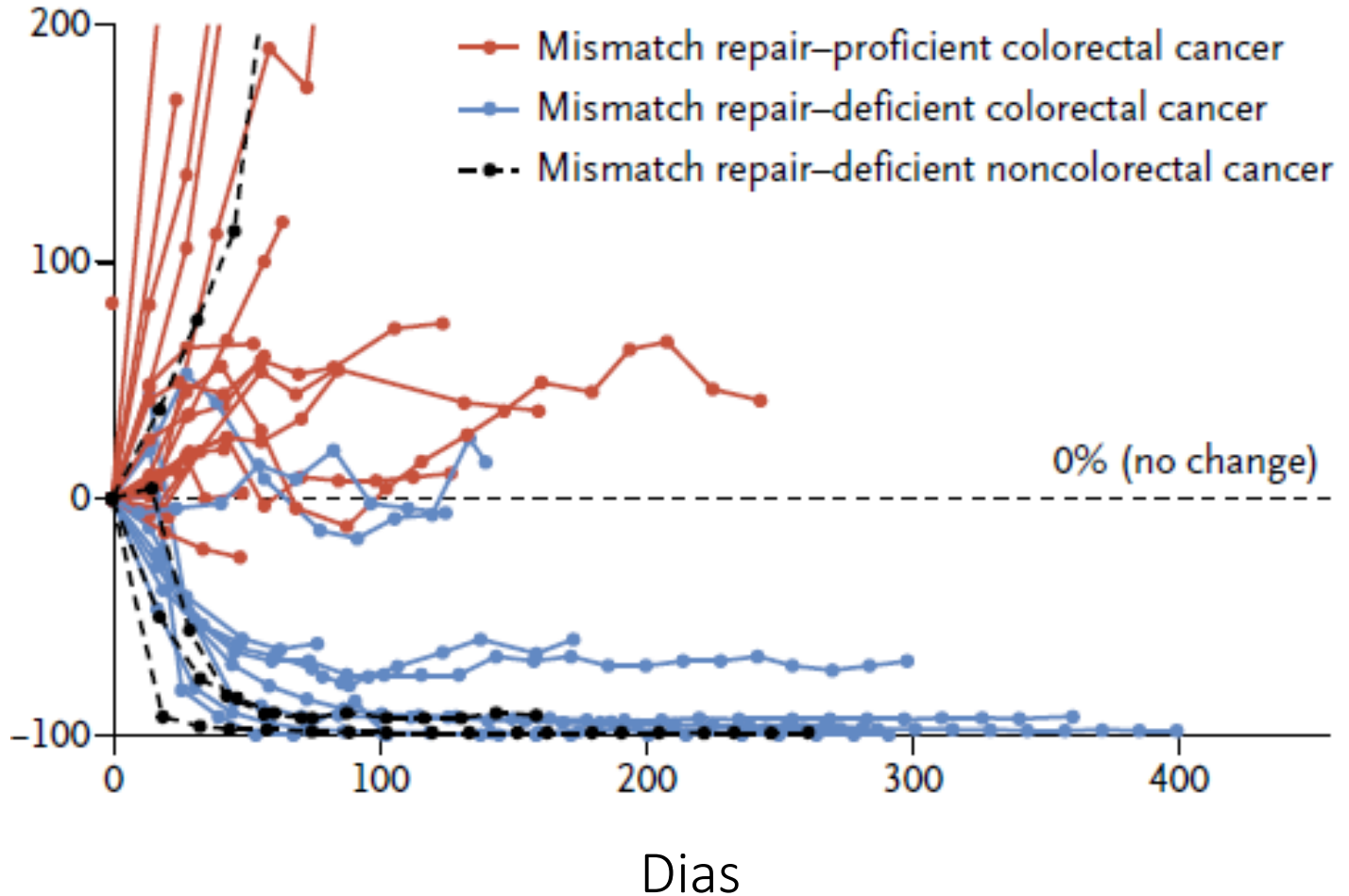


Endpoint primário: Resposta objetiva e PFS em 20 sem

Imunoterapia vs MSI-H

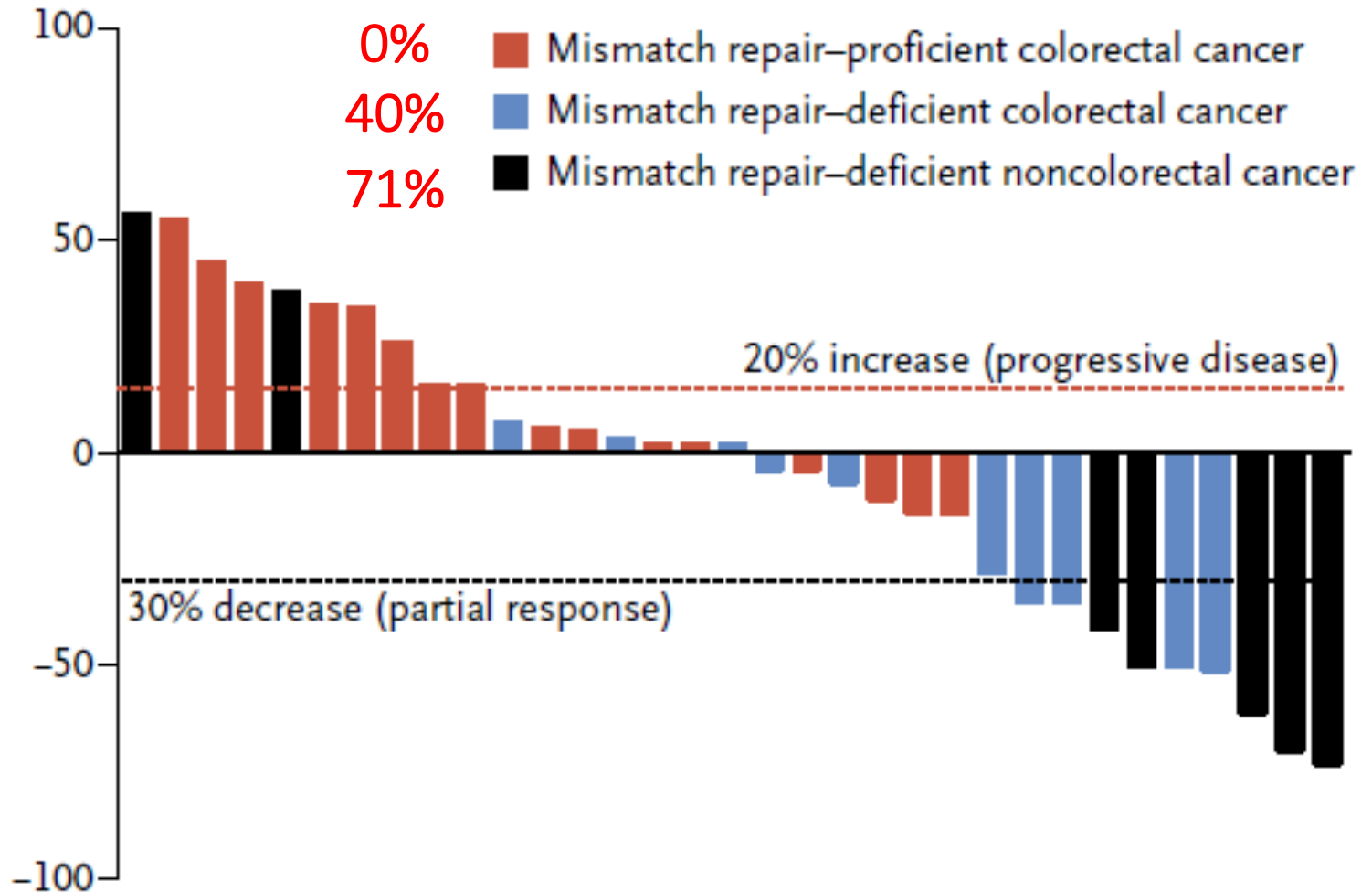
Resposta
bioquímica

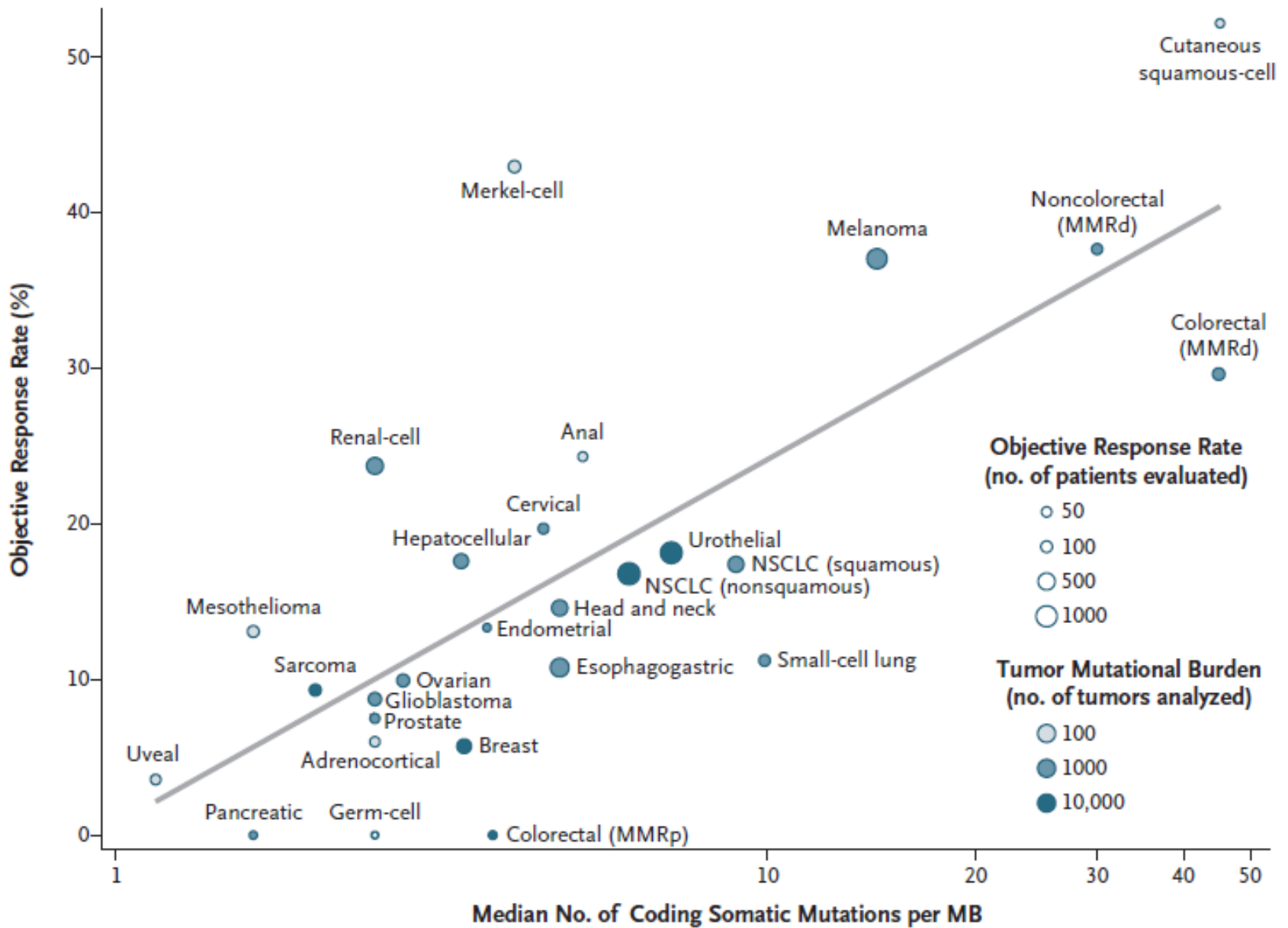
Marcador
tumoral



Imunoterapia vs MSI-H

Resposta radiológica

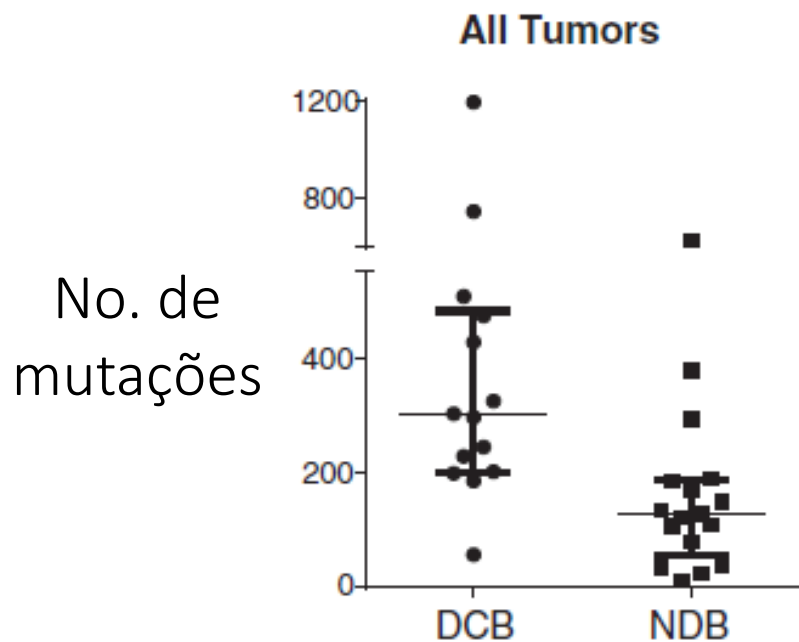






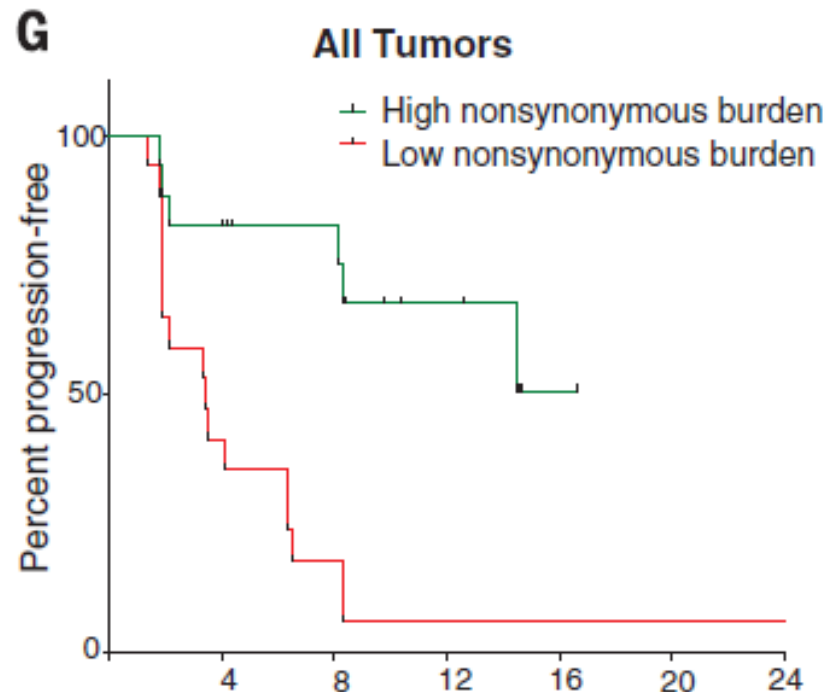
TMB e resposta a imunoterapia

34 pacientes com CPNPC submetidos a Pembrolizumabe



DCB: RP ou DE > 6 meses

NCB: Benefício clínico não-durável

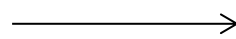


Checkmate 142

Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study

Michael J Overman, Ray McDermott, Joseph L Leach, Sara Lonardi, Heinz-Josef Lenz, Michael A Morse, Jayesh Desai, Andrew Hill, Michael Axelson, Rebecca A Moss, Monica V Goldberg, Z Alexander Cao, Jean-Marie Ledeine, Gregory A Maglinte, Scott Kopetz, Thierry André**

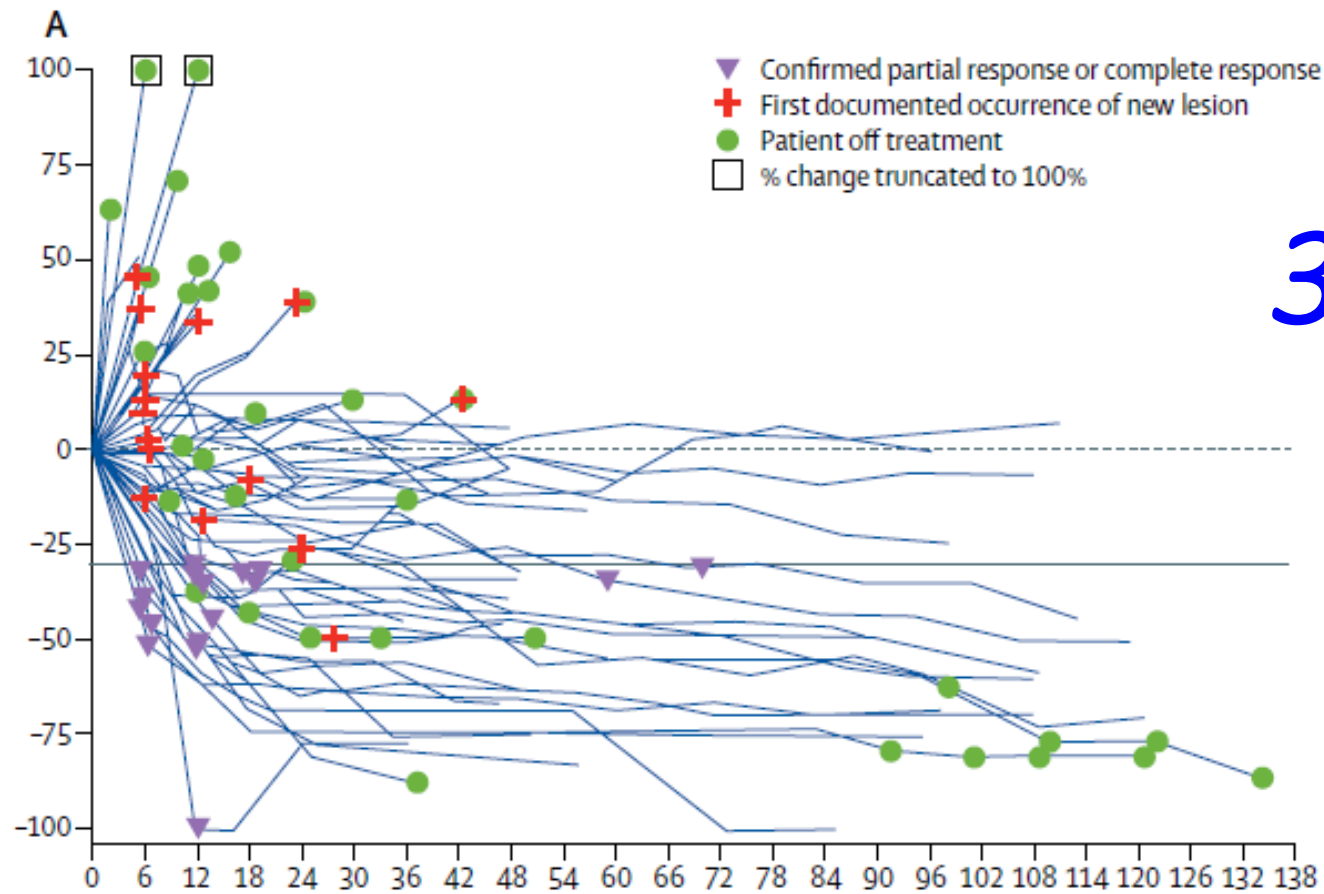
74 patients
CCRm MSI-H
2ª linha



Nivolumabe

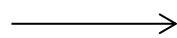
Endpoint primário: Resposta objetiva

Checkmate 142



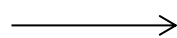
Keynote-164 e Keynote-158

61 pacientes
CCRm MSI-H
3ª linha



Pembrolizumabe

77 pacientes
Não-CCRm MSI-H
2ª linha

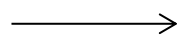


Pembrolizumabe

Endpoint primário: Resposta objetiva

Keynote-164 e Keynote-158

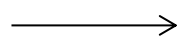
61 pacientes
CCRm MSI-H
3ª linha



Pembrolizumabe

28%

77 pacientes
Não-CCRm MSI-H
2ª linha



Pembrolizumabe

38%

Endpoint primário: Resposta objetiva


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


 SHARE

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 EMAIL

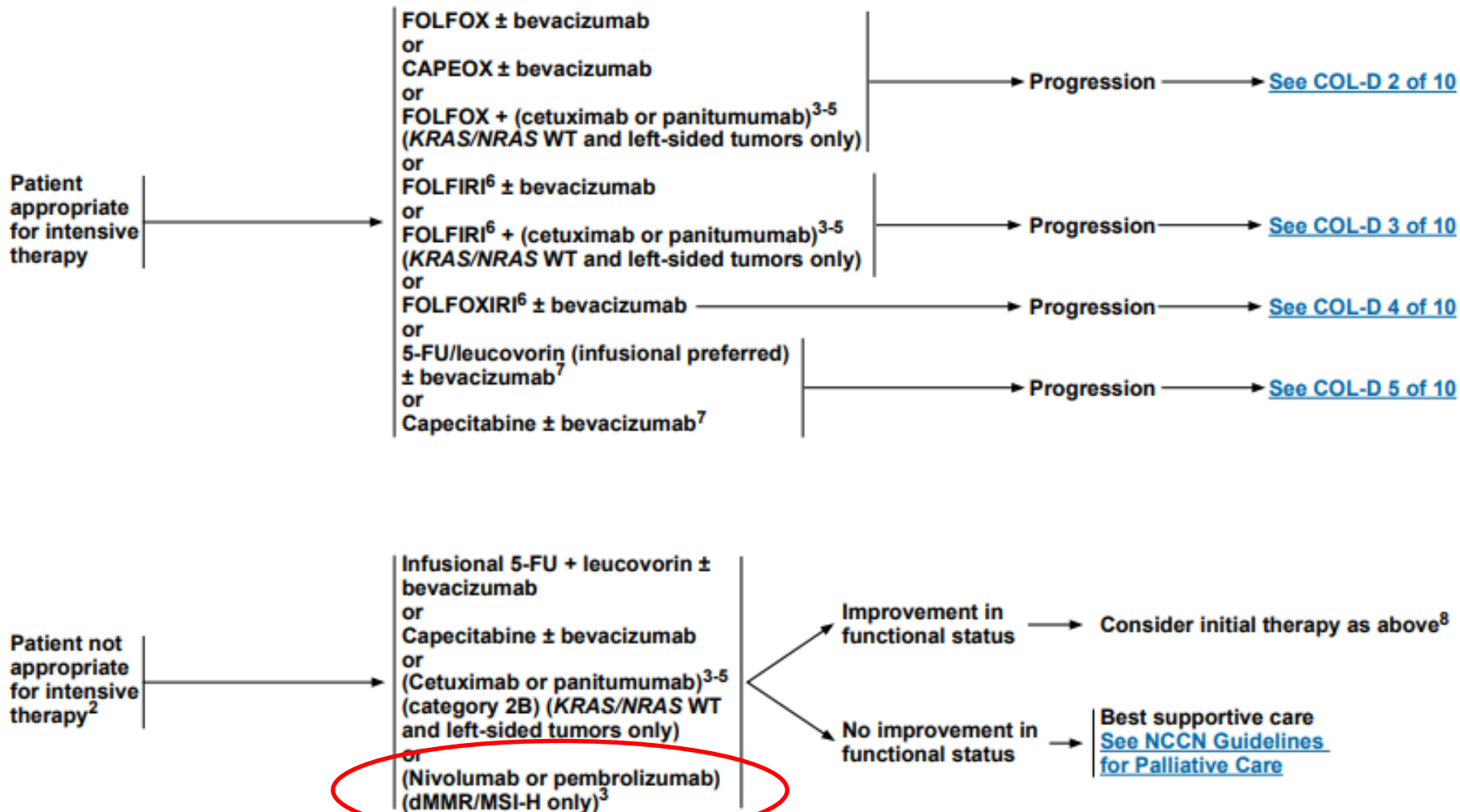
 PRINT

[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.

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE¹

INITIAL THERAPY²



[See footnotes COL-D 6 of 10](#)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Checkmate 142

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

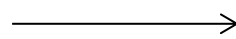
Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlish, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

119 pacientes

CCRm MSI-H

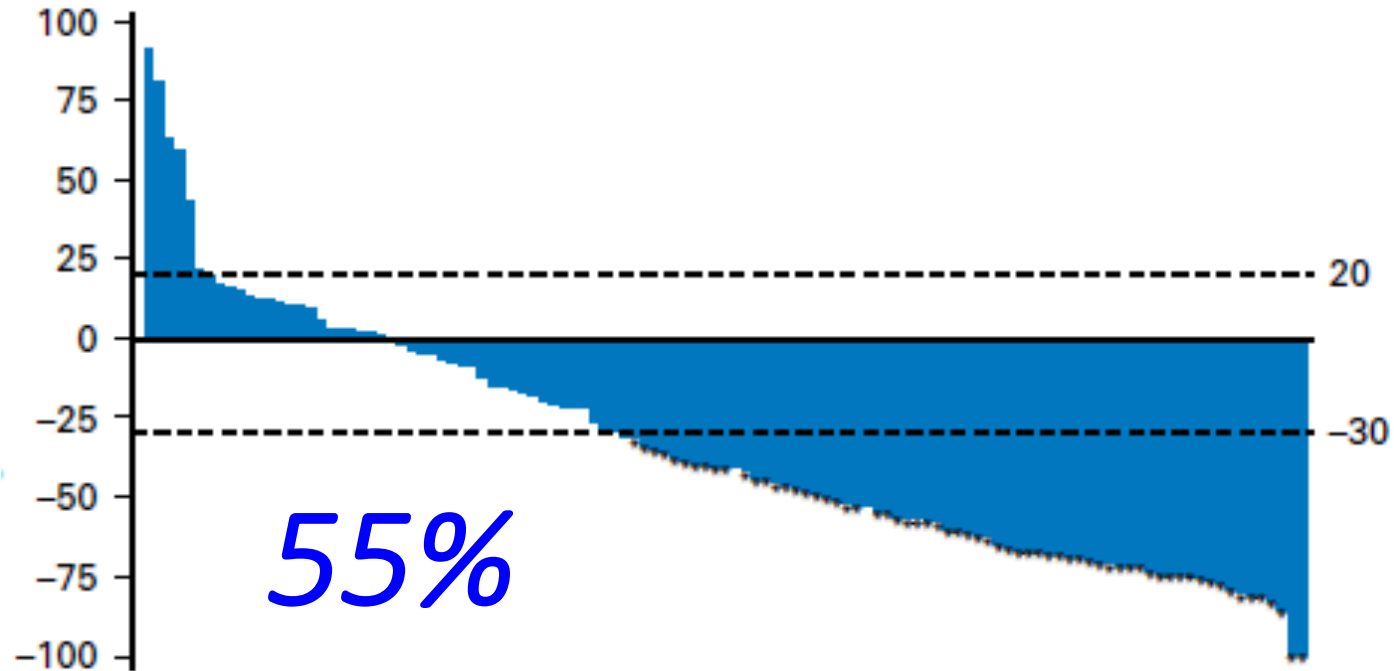
2ª linha



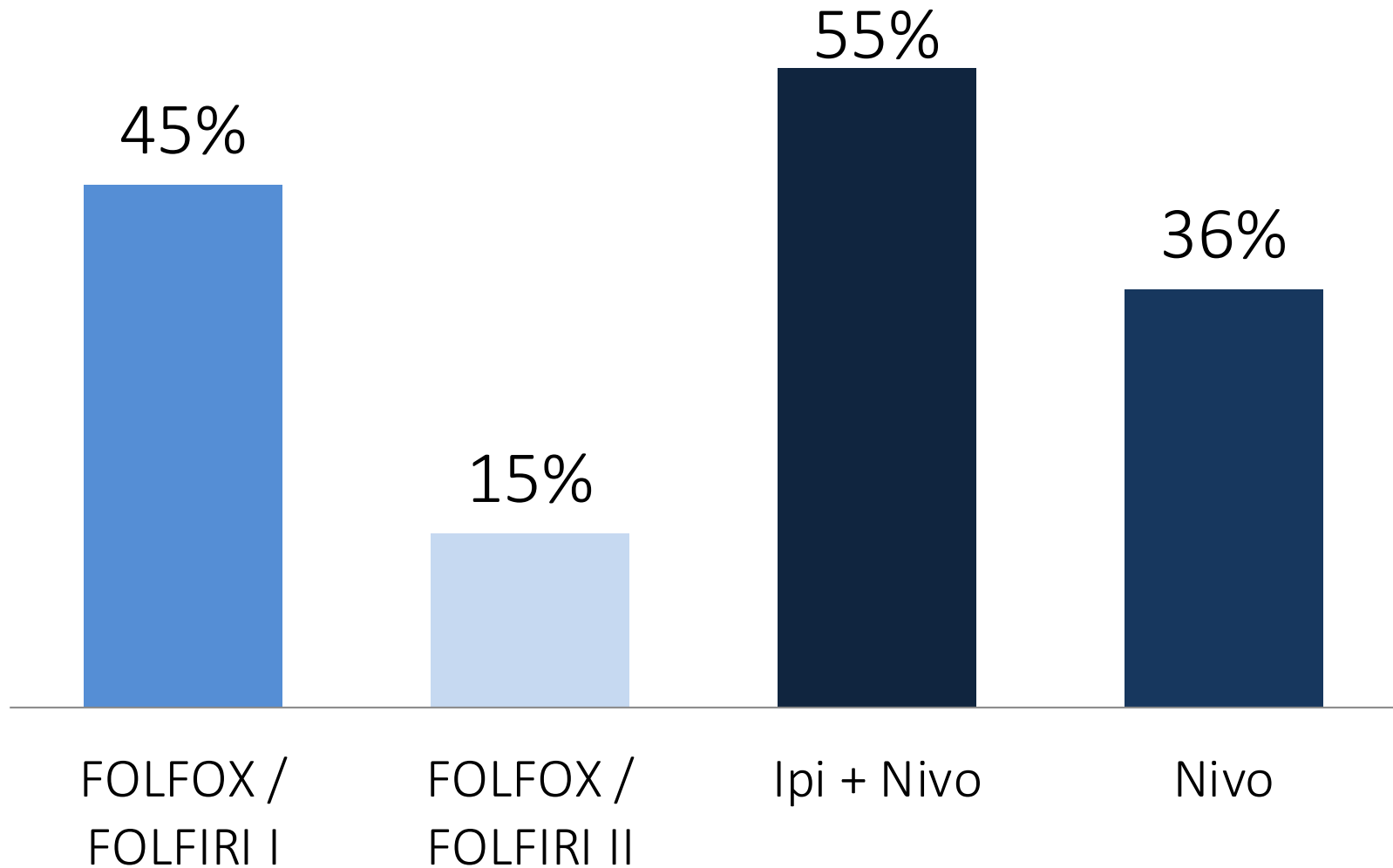
Ipilimumabe + Nivolumabe

Endpoint primário: Resposta objetiva

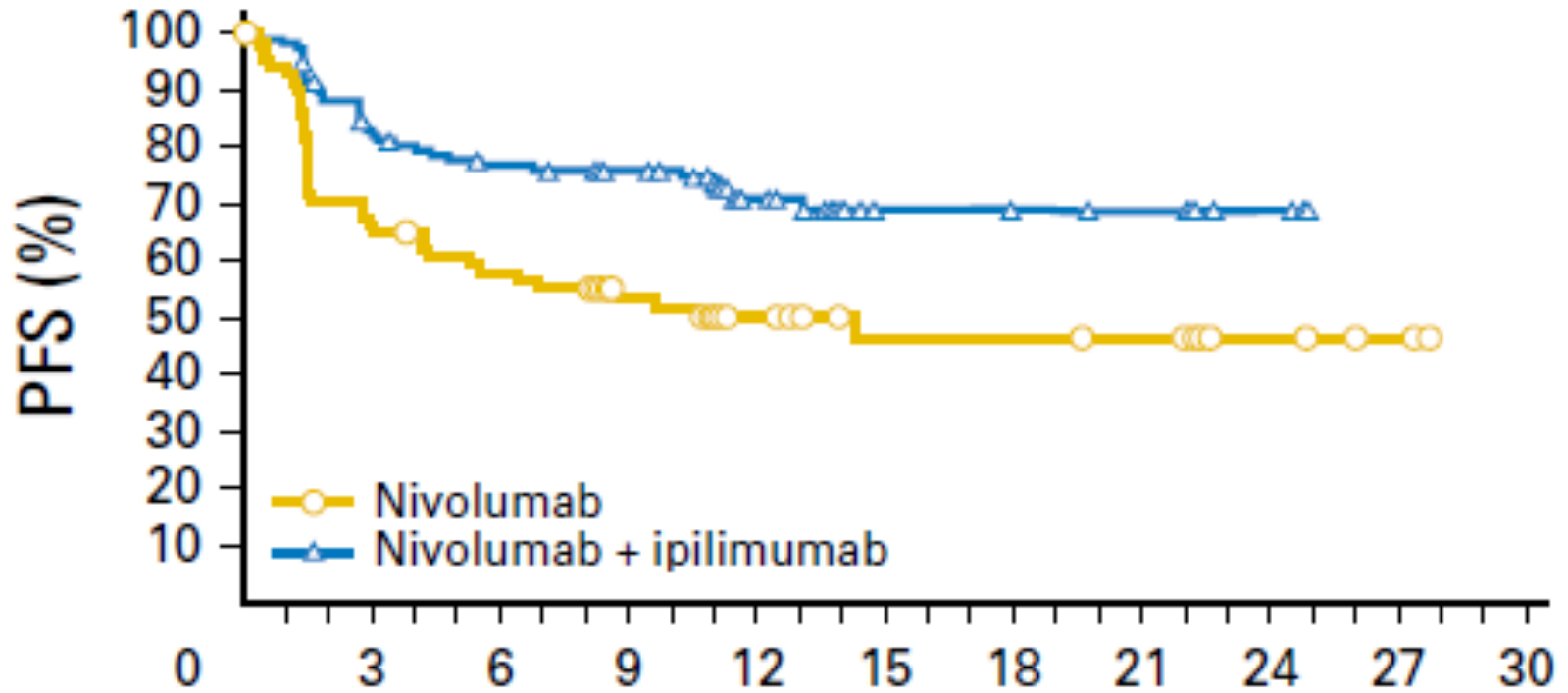
Checkmate 142



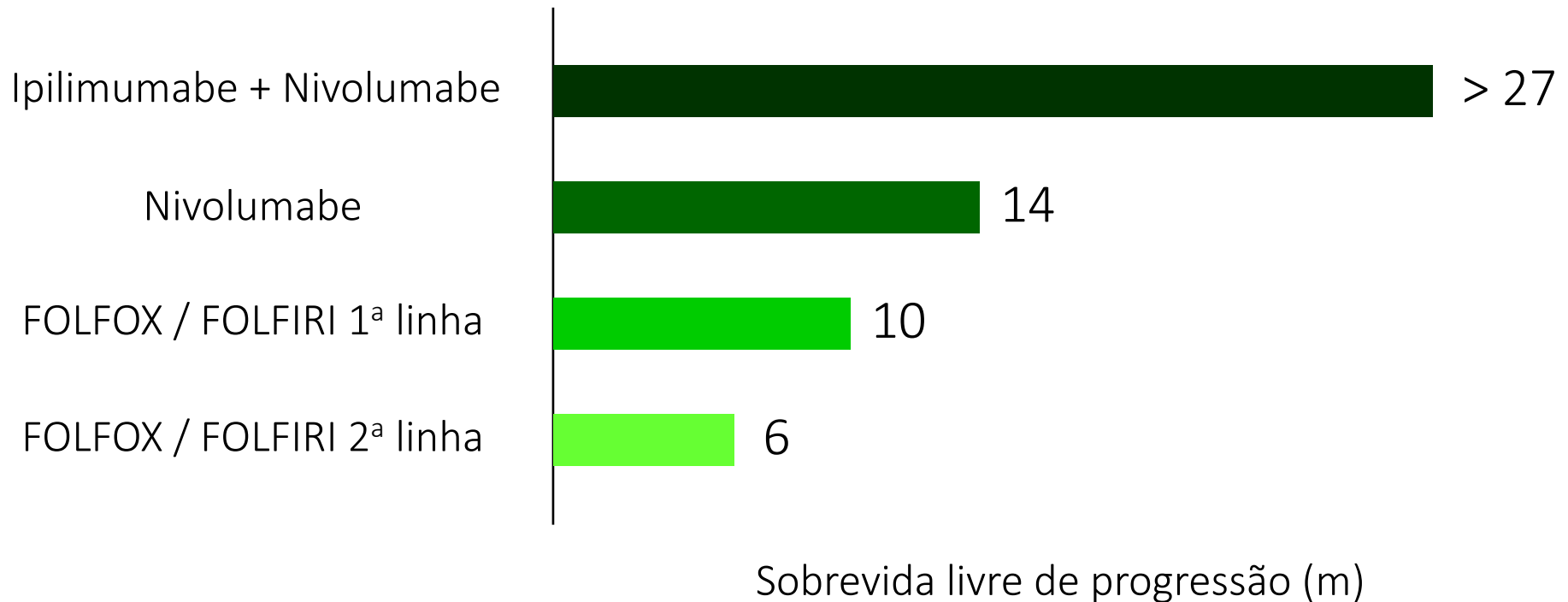
Checkmate 142



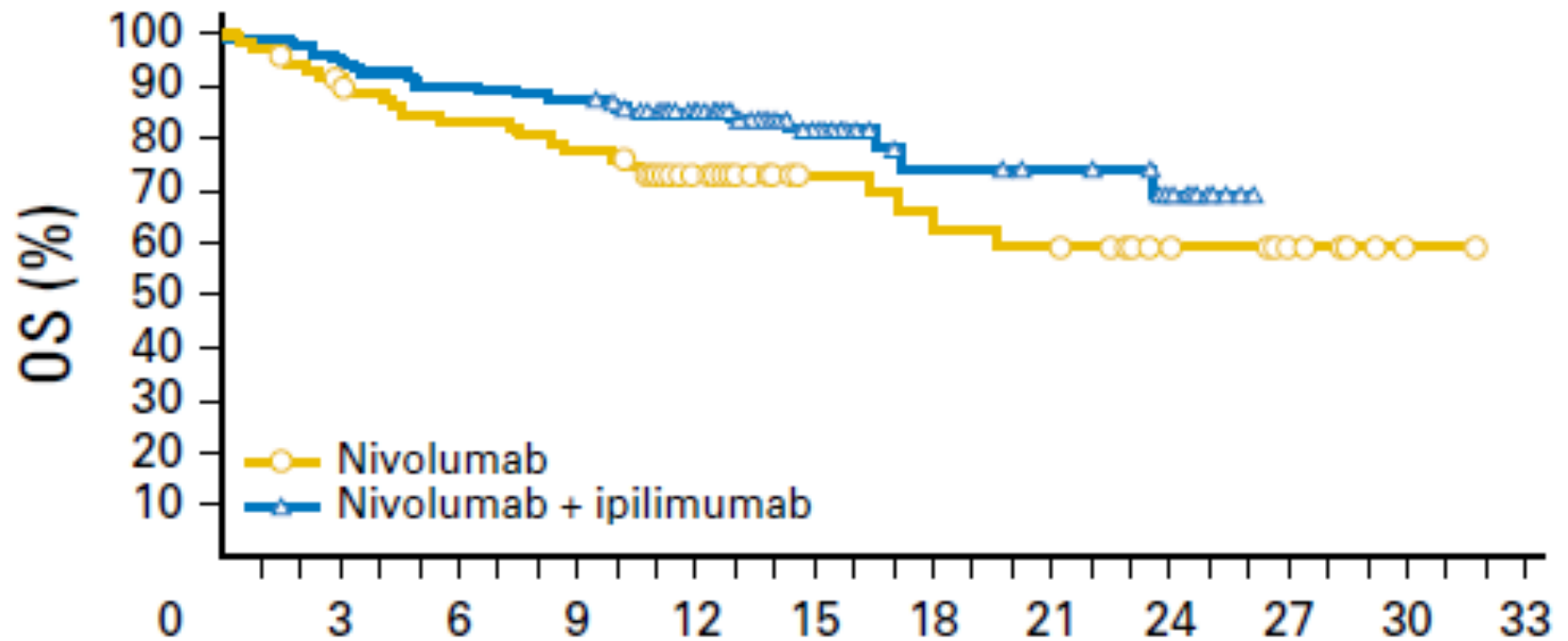
Checkmate 142



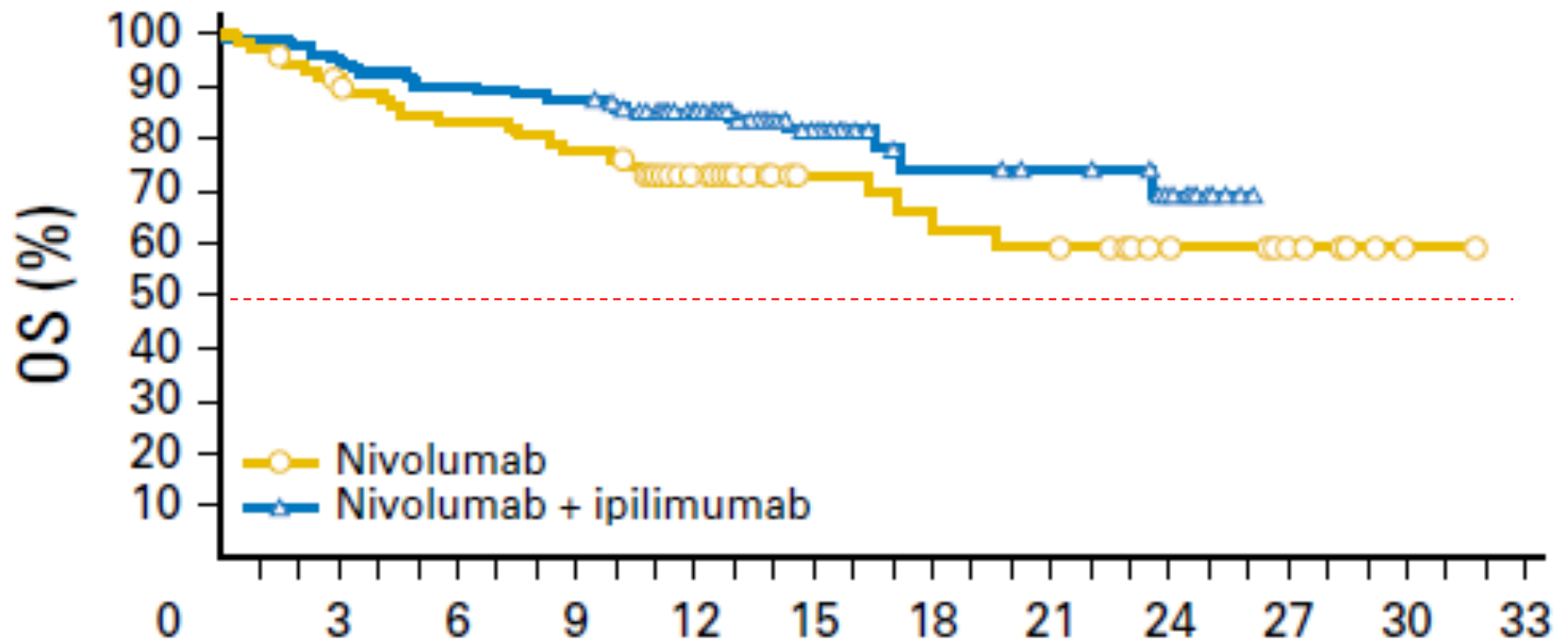
Checkmate 142



Checkmate 142



Checkmate 142



Imunoterapia em câncer
colorectal:

Esperança para quem?

Imunoterapia em câncer
colorectal:

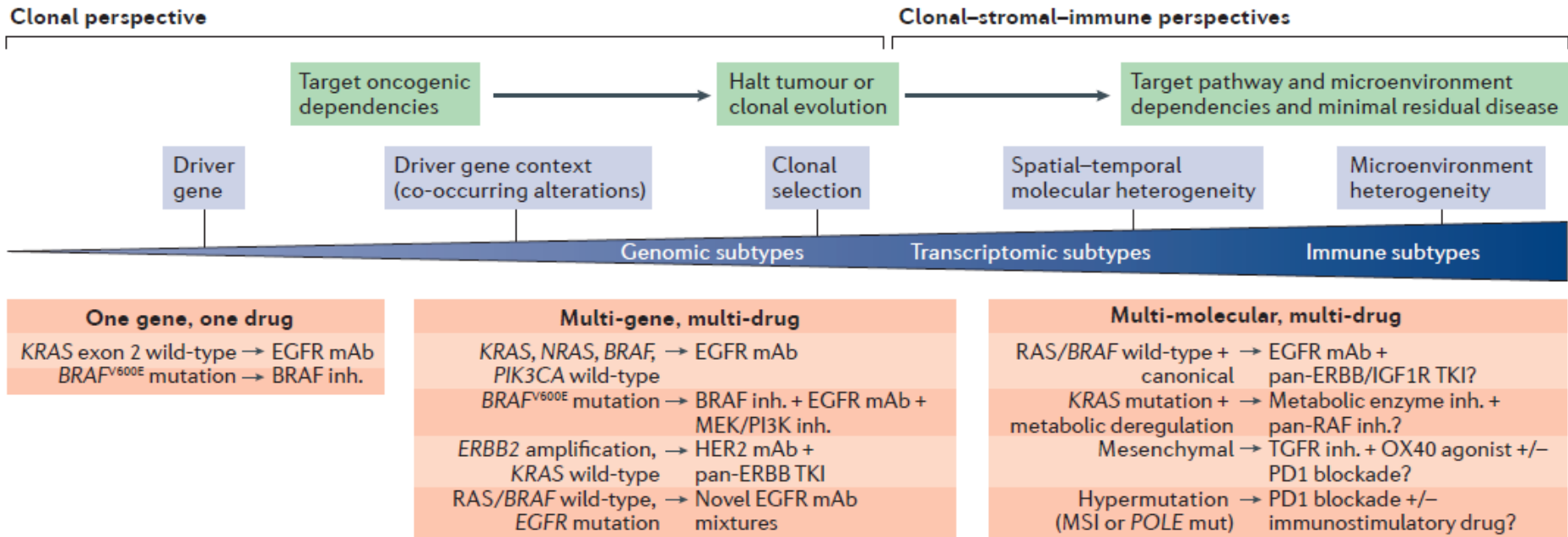
Esperança para quem?

Pacientes dMMR / MSI-H

Perspectivas

- ✓ Terapia de conversão em metástases hepáticas de ressecção borderline?
- ✓ Tratamento neoadjuvante do câncer de reto?
- ✓ Associação com quimioterapia ou terapia-alvo?

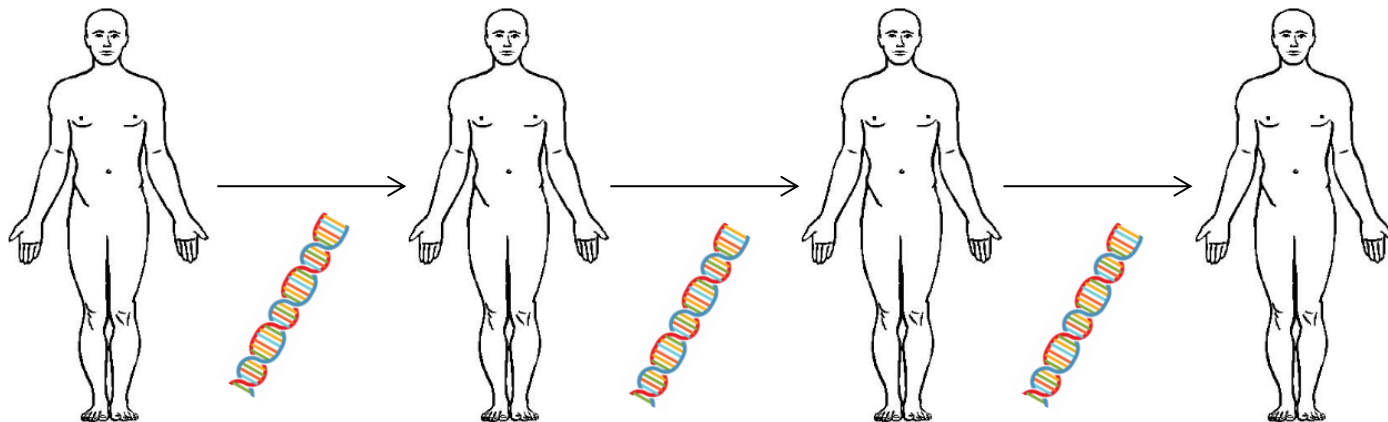
Perspectivas



APOLLO

RESEARCH PLATFORM FOR
THE MOON SHOTS PROGRAM

Adaptive Patient-Oriented Longitudinal Learning and Optimization



Conclusões

- ✓ Os pacientes com câncer coloretal com instabilidade de microsátélites representam um subgrupo com elevada carga mutacional.
- ✓ Os estudos fase II realizados até o momento são motivos de enorme otimismo quanto à aplicabilidade de imunoterapia nesta população de pacientes.
- ✓ É possível que a combinação de imunoterápicos torne-se a primeira linha de tratamento em câncer coloretal dMMR / MSI-H em breve.
- ✓ Abre-se uma enorme perspectiva de aplicabilidade desta nova modalidade terapêutica em diversos cenários clínicos no câncer coloretal.