Charles University
1st Faculty of Medicine
General Hospital

Imunoterapie v léčbě lymfomů

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CLSG KLS
Czech Lymphoma Study Group
Kooperativní Lymfomová Skupina

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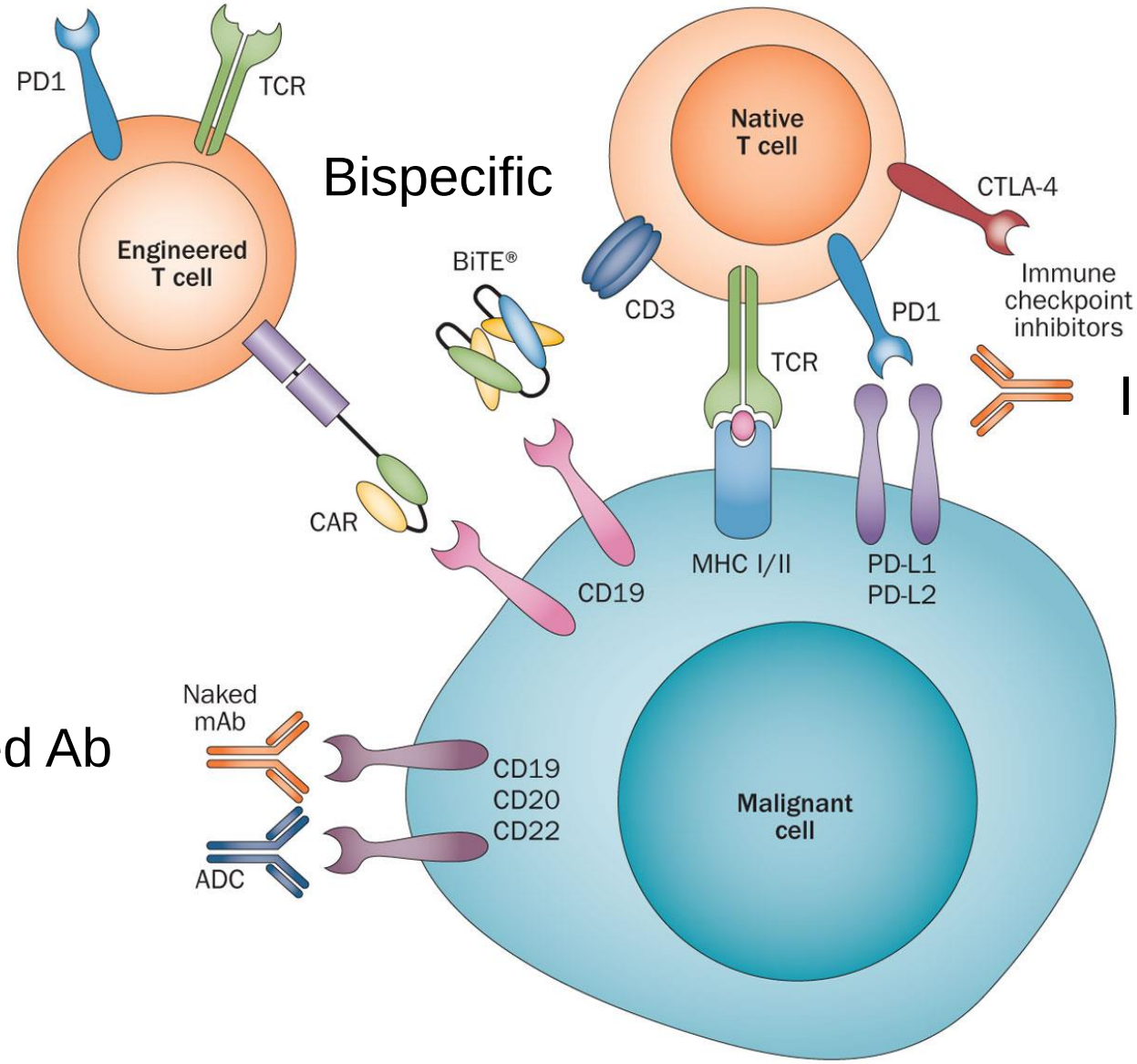
Immune system targeting

CAR T Cells

Bispecific

Immune Checkpoint

Ingeneered naked Ab



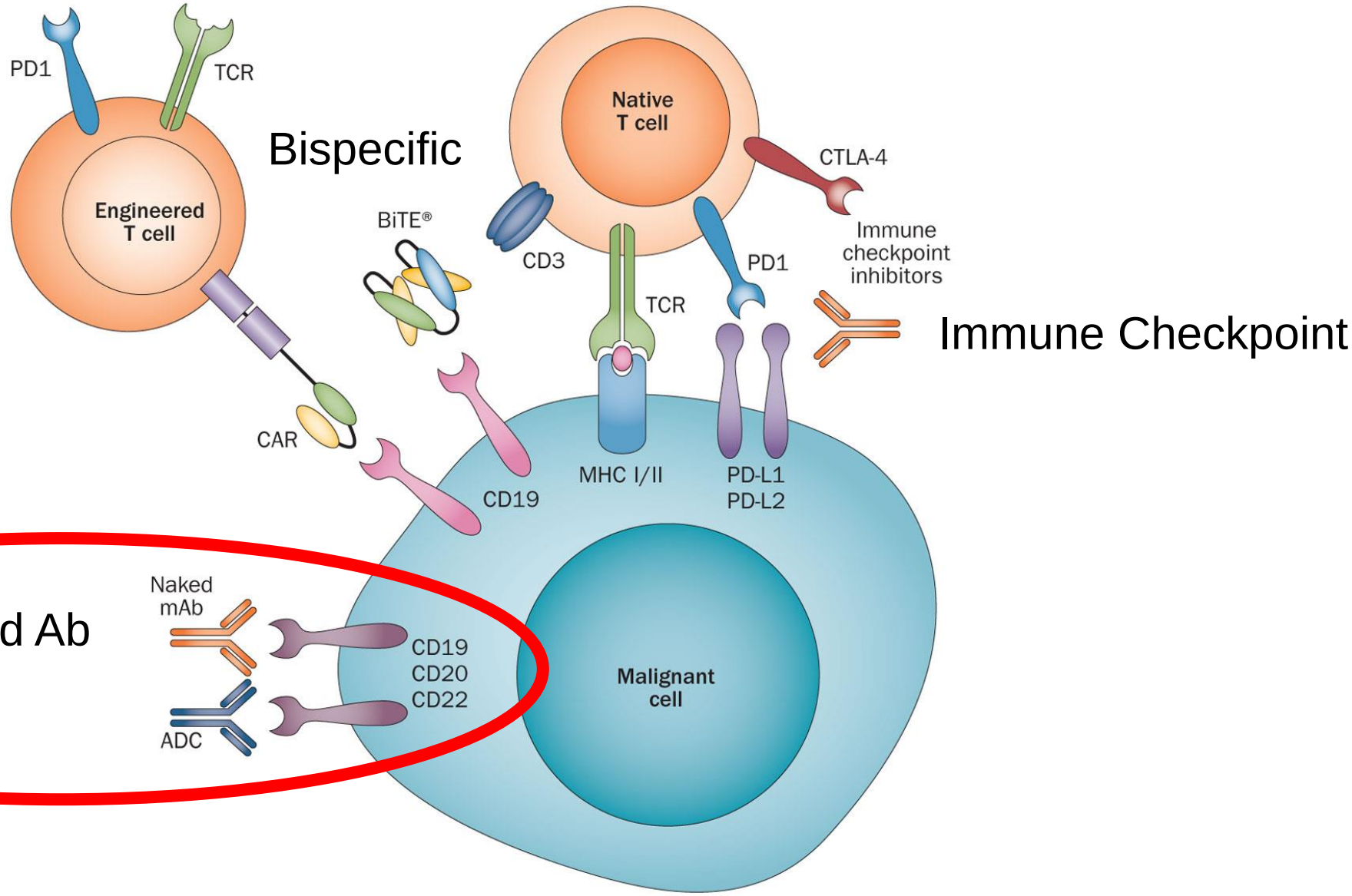
Ingeneered antibodies

CAR T Cells

Bispecific

Immune Checkpoint

Ingeneered naked Ab



Antibodies +/- combination with other - lenalidomide

	Type	Glycoengeneered
antiCD20		
• rituximab	I	NO
• rituximab s.c.		
• rituximab biosimilars		
• ofatumumab	I	NO
• obinutuzmab	II	YES
• ublituximab	I	YES
antiCD19		
• MOR208		YES

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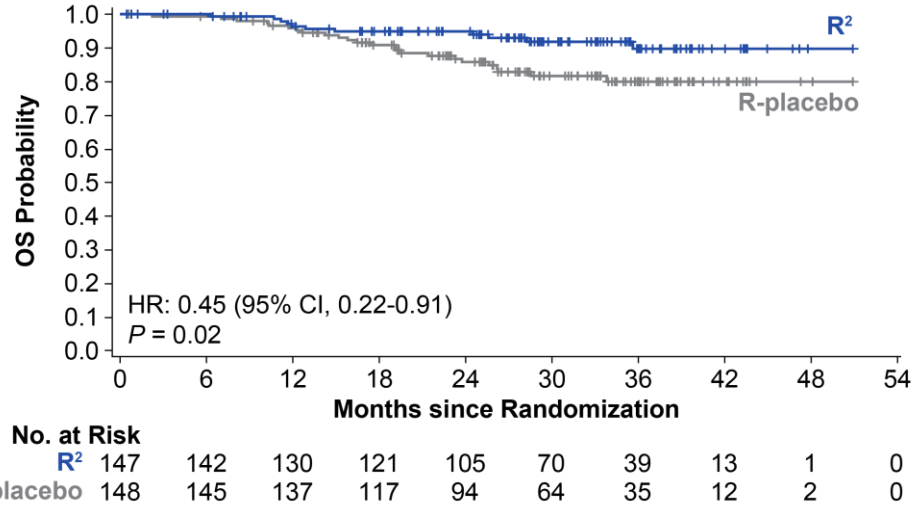
• ofatumumab	I	NO
• obinutuzmab	II	YES
• ublituximab	I	YES
antiCD19		
• MOR208		YES

R^2 – lenalidomide (Revlimid) + Rituximab



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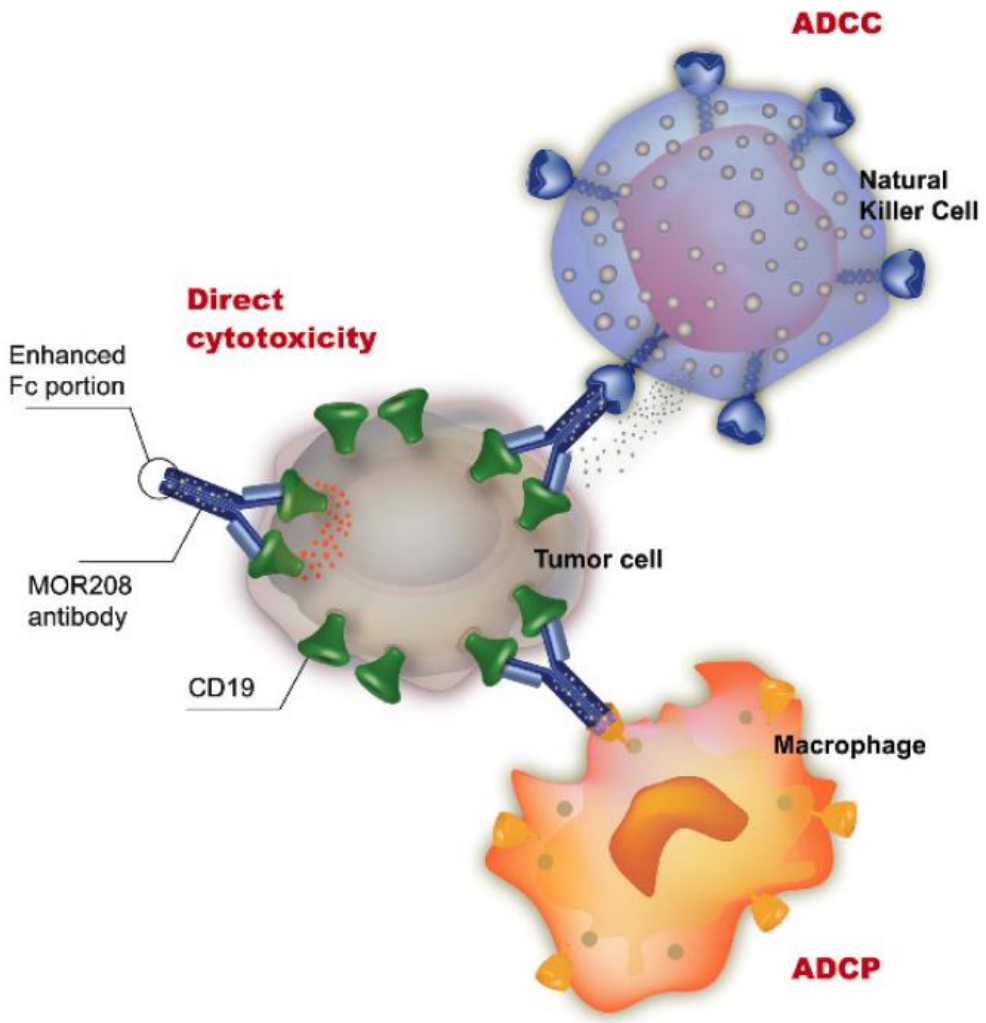
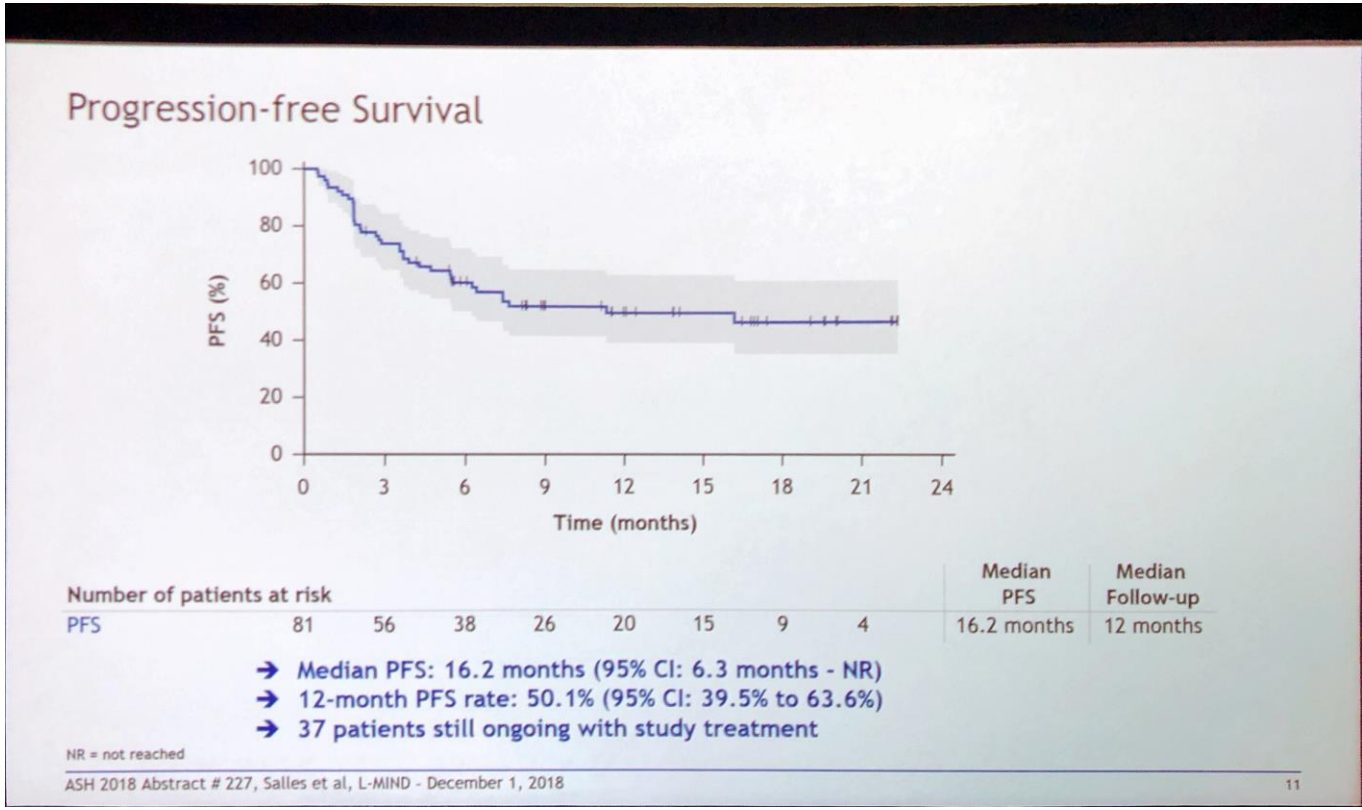
Leonard J, Trneny M et al ASH 2018

MOR 208 - antiCD19 Ab



L-MIND study combination: lenalidomide + MOR208

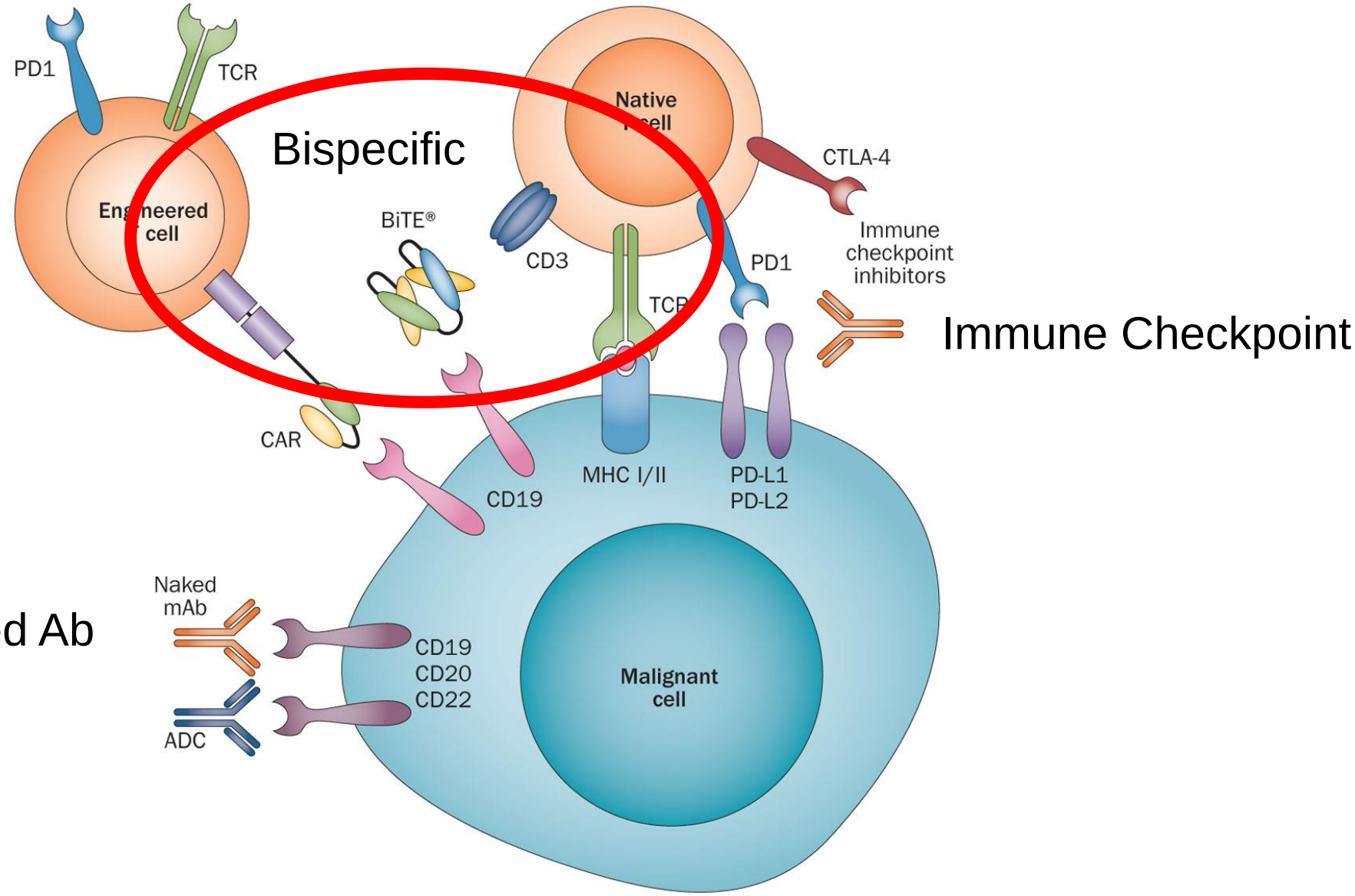


Blum KA et al, ASH 2014, abstr 3089
Jurczak W et al, Annals of Oncology Published online 9 February 2018
Salles G et al ASH 2018

Bispecific antibodies

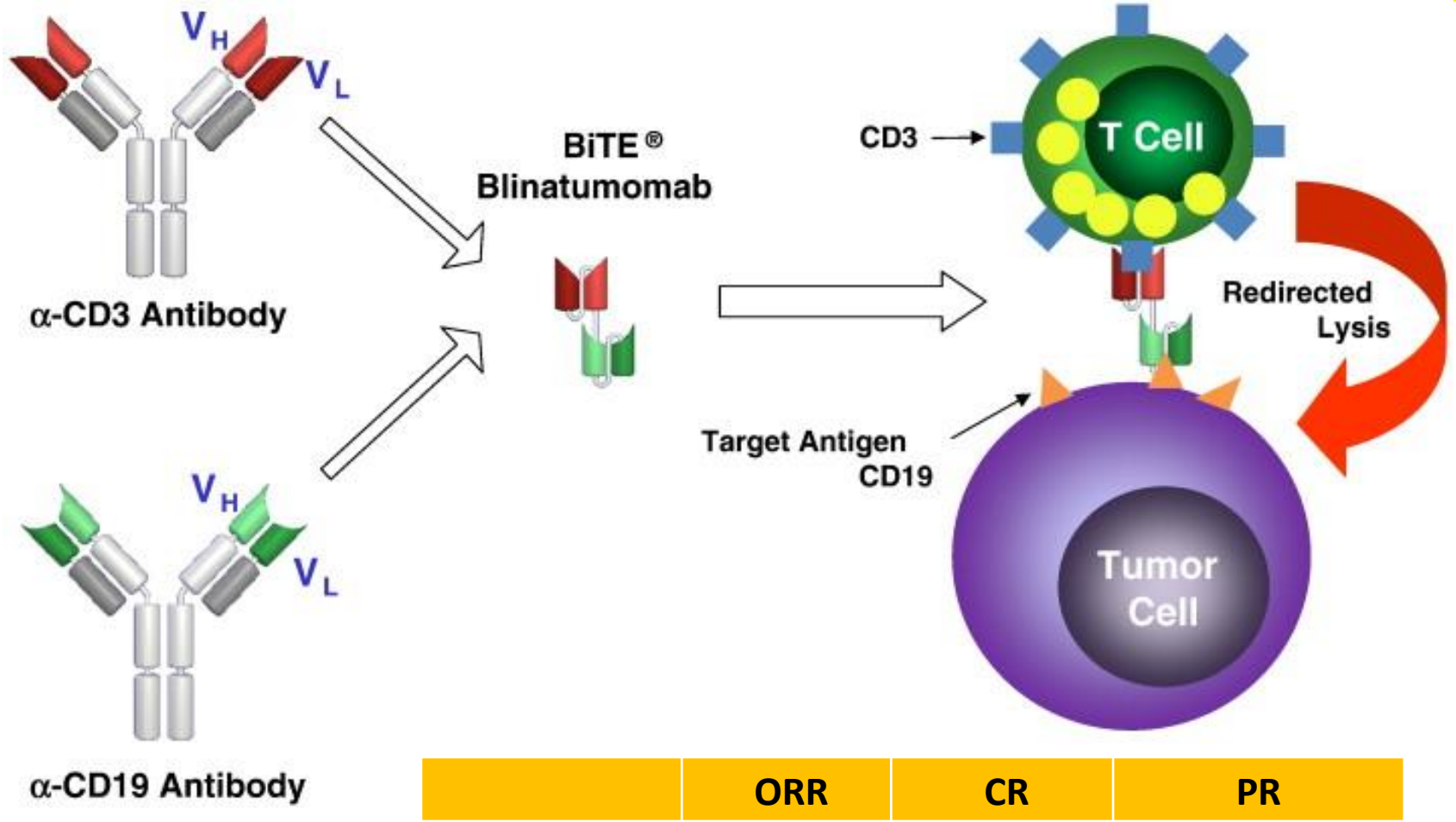
CAR T Cells

Ingeneered naked Ab



Immune Checkpoint

Bispecific antibodies BiTe - blinatumomab



Problems:
- **mode of administration**
- **toxicity**
- **response durability**

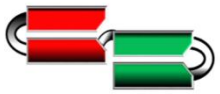
	ORR	CR	PR
DLBCL (n 11)	6 (55%)	4 (18%)	2 (18%)
FL (n 15)	12 (80%)	6 (40%)	6 (40%)
MCL (n 7)	5 (71%)	3 (43%)	2 (28%)
DLBCL (21)	9 (43%)	4 (19%)	5 (24%)

Goebeler ME et al, JCO, February 16, 2016
Viardot A et al Blood. 2016;127(11):1410-1416

Bispecific antibodies

CD19xCD3

Blinatumomab

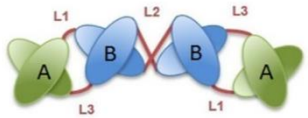


Bispecific
Bivalent

Size 54 kDA
Half-life 2 h

Amgen

AFM11

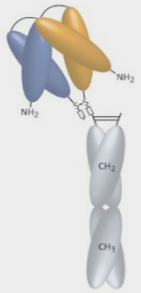


Bispecific
Tetravalent

Size 105 kDA
Half-life 20 h
CD3 affinity ↑

Affimed

MGD011



Bispecific
Bivalent *

Size 110 kDA
Half-life
340-460h

Macrogenics

AMG562

bispecific
Bivalent

Half-life
extended

Amgen

CD20xCD3

FBTA05 (Lymphomun)

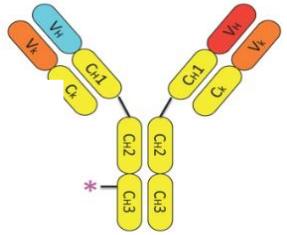
*

ended IgG >150 k

DVD-IgG*
200 kDa

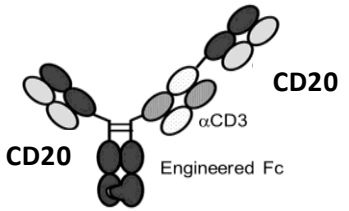
Trion/Fresenius

RGN1979



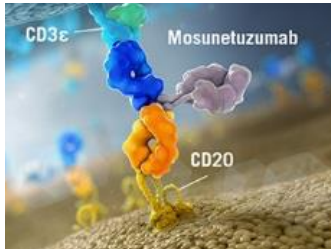
Regeneron

RG6026 „TCB“



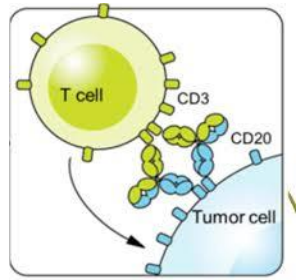
Roche/Genentech

RG7828 „TDB“
Mosunetuzumab



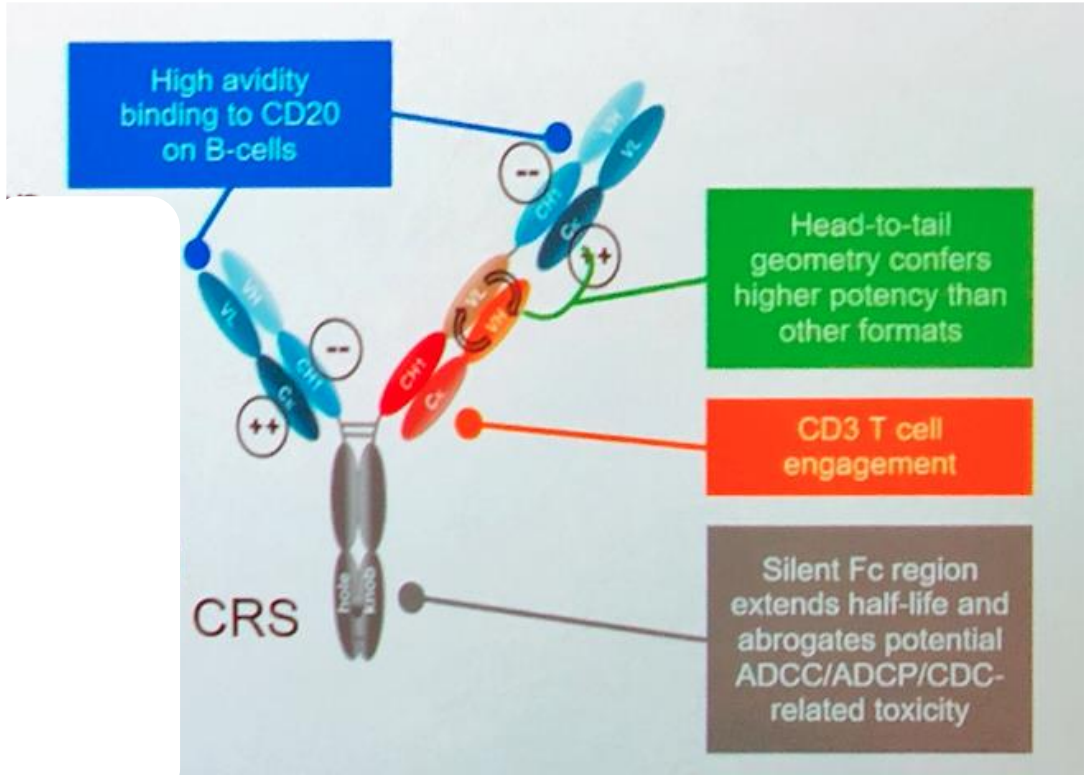
Genentech/Roche

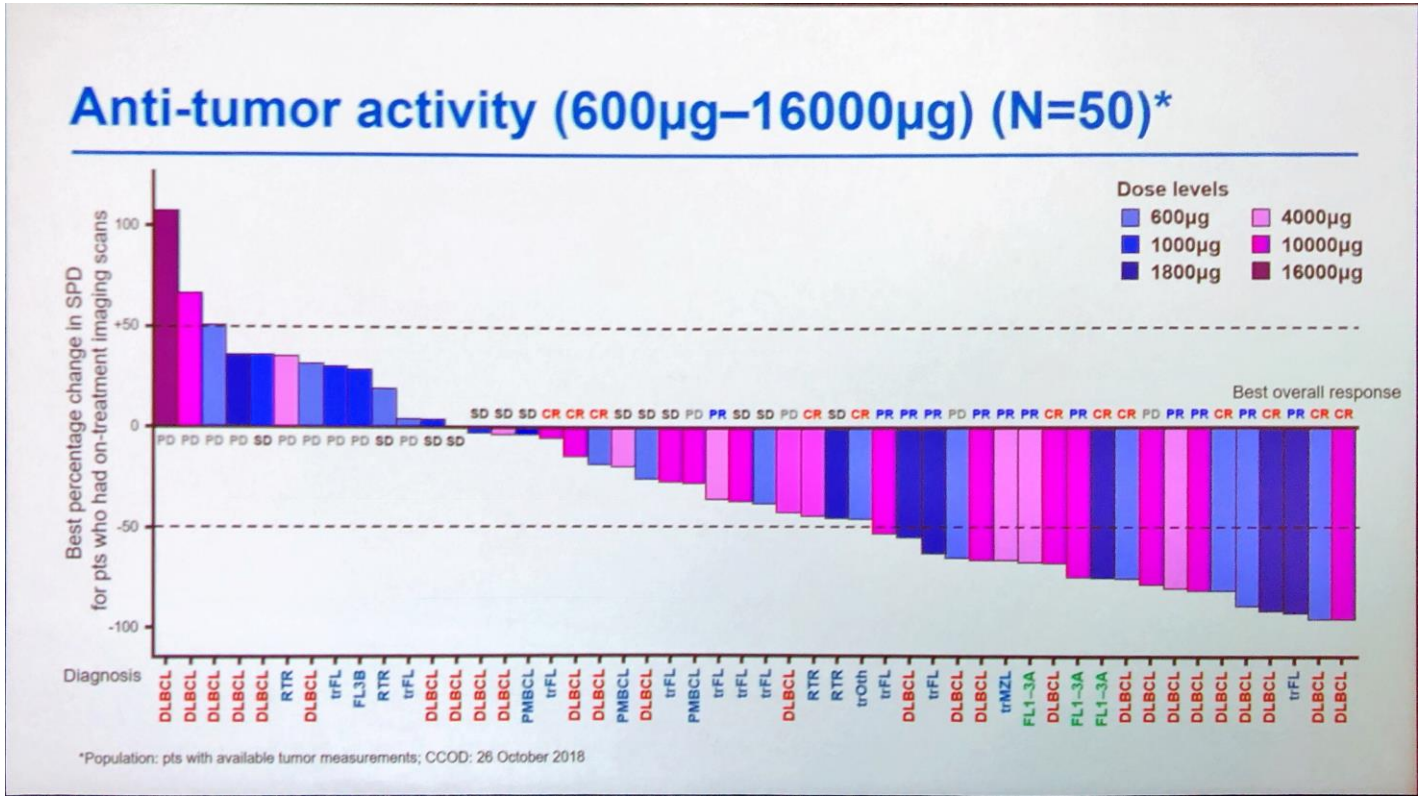
GEN3013



Genmab

RG6026





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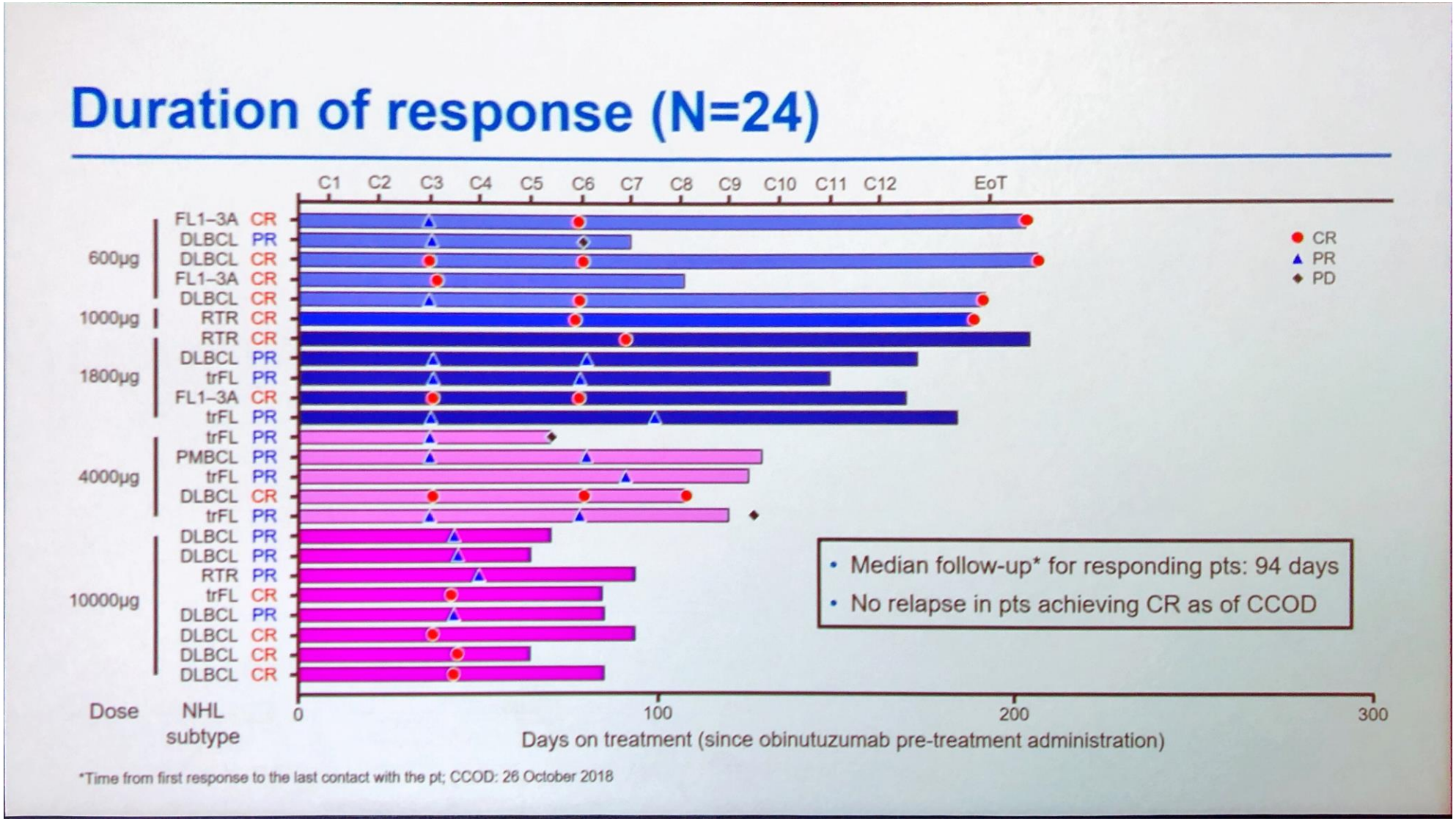
Hutchings M et al, kASH 2018



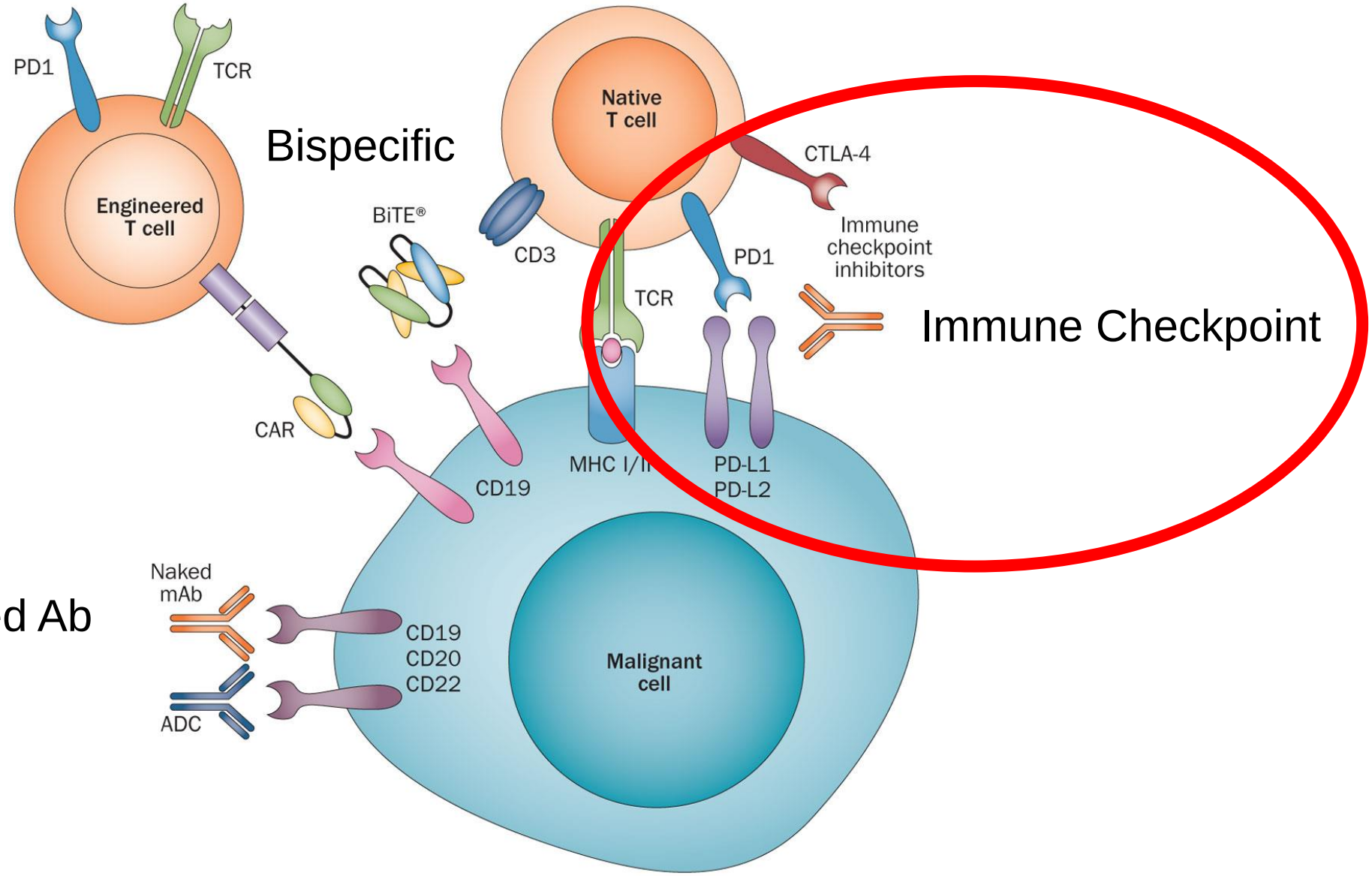
Hutchings M et al, kASH 2018

Immune Checkpoint Inhibition

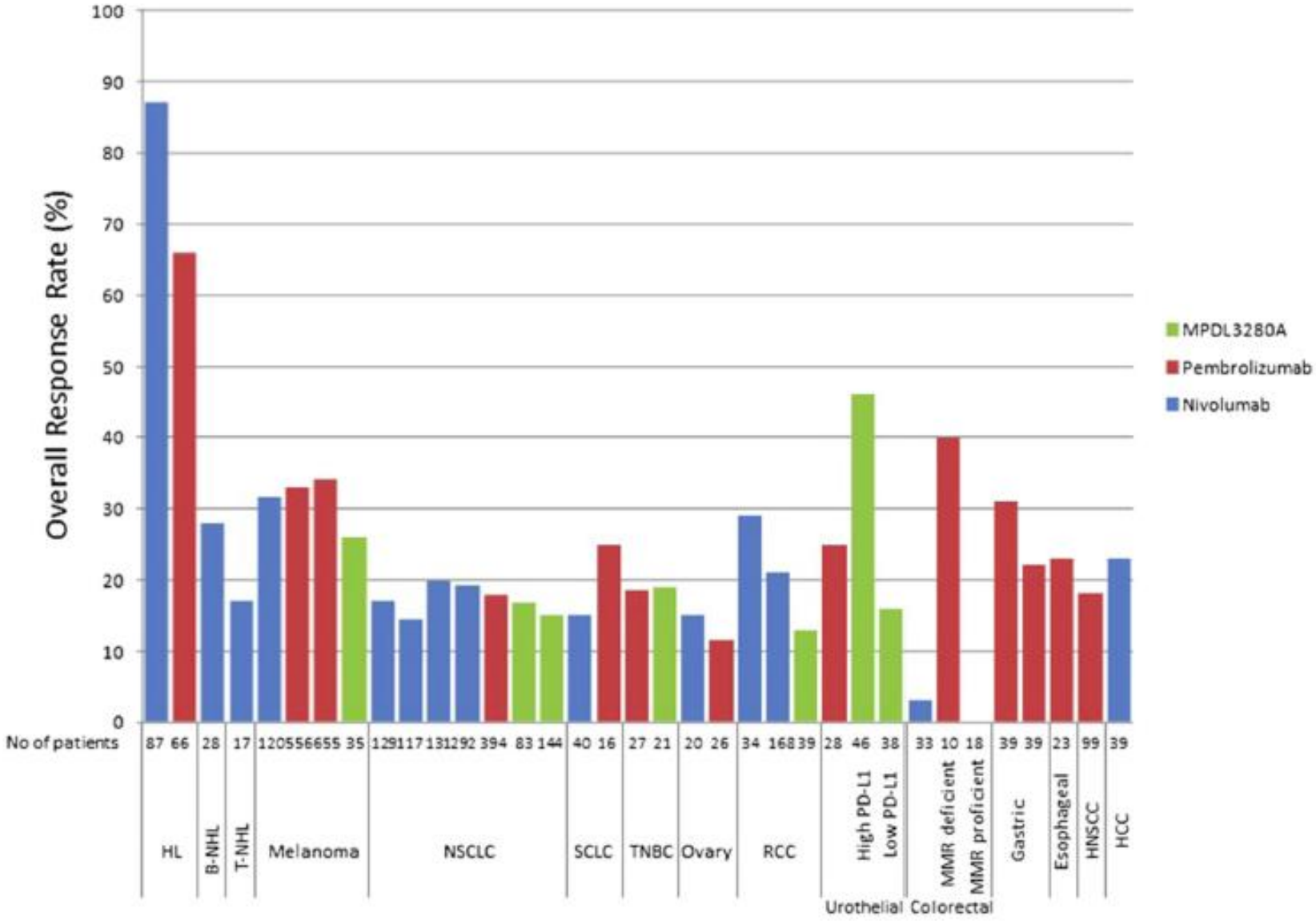
CAR T Cells

Bispecific

Ingeneered naked Ab



Odpověď nádorů na “immune checkpoint” inhibici



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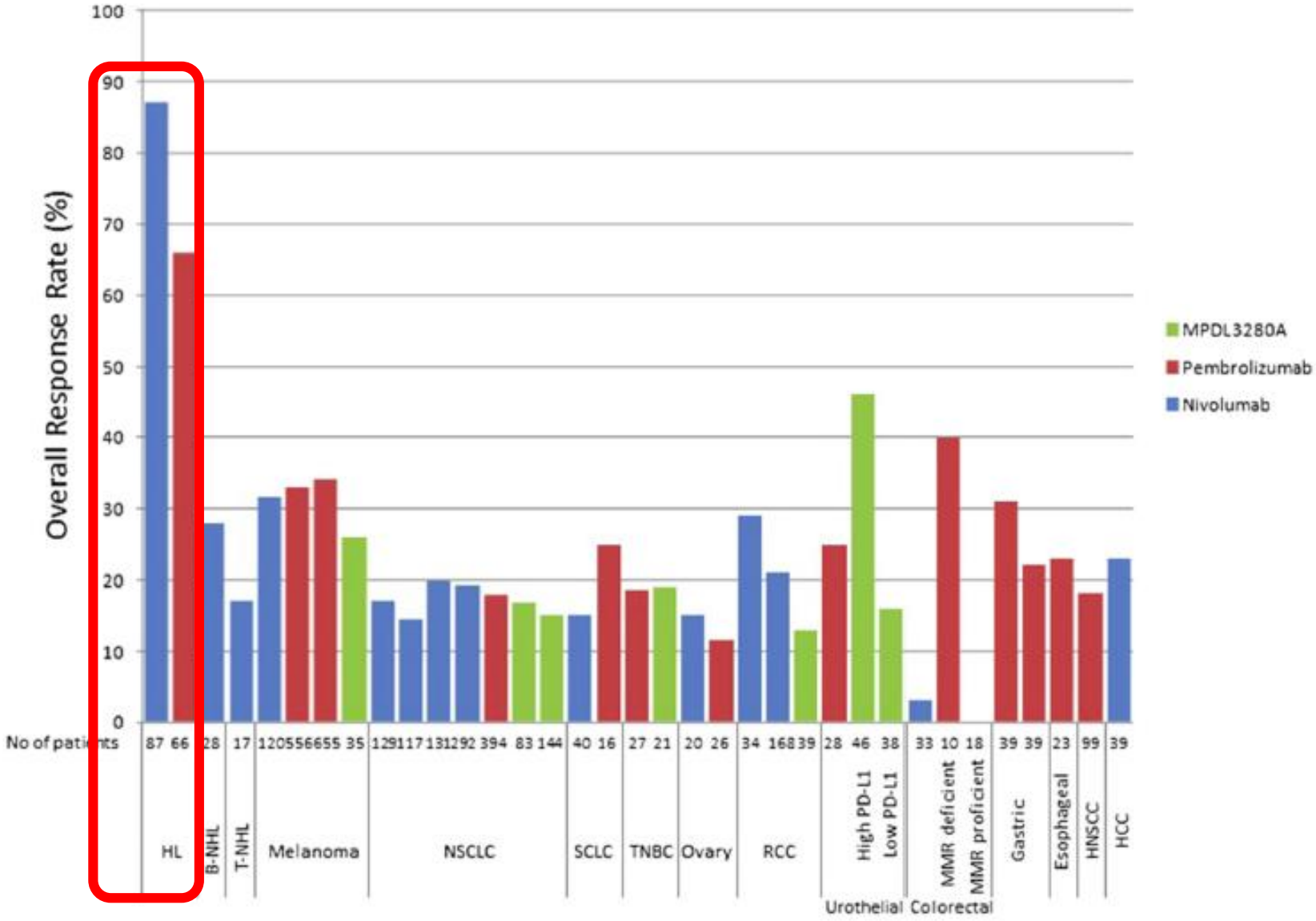
Matsuki E & Younes A; Curr Treat Options Oncol. 2016 June ; 17(6): 31

Odpověď nádorů na "immune checkpoint" inhibici



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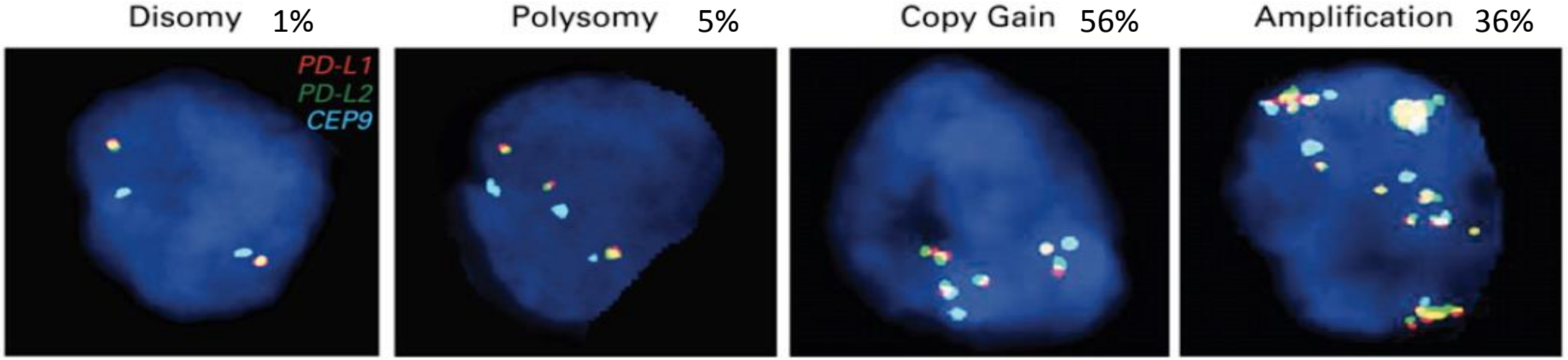
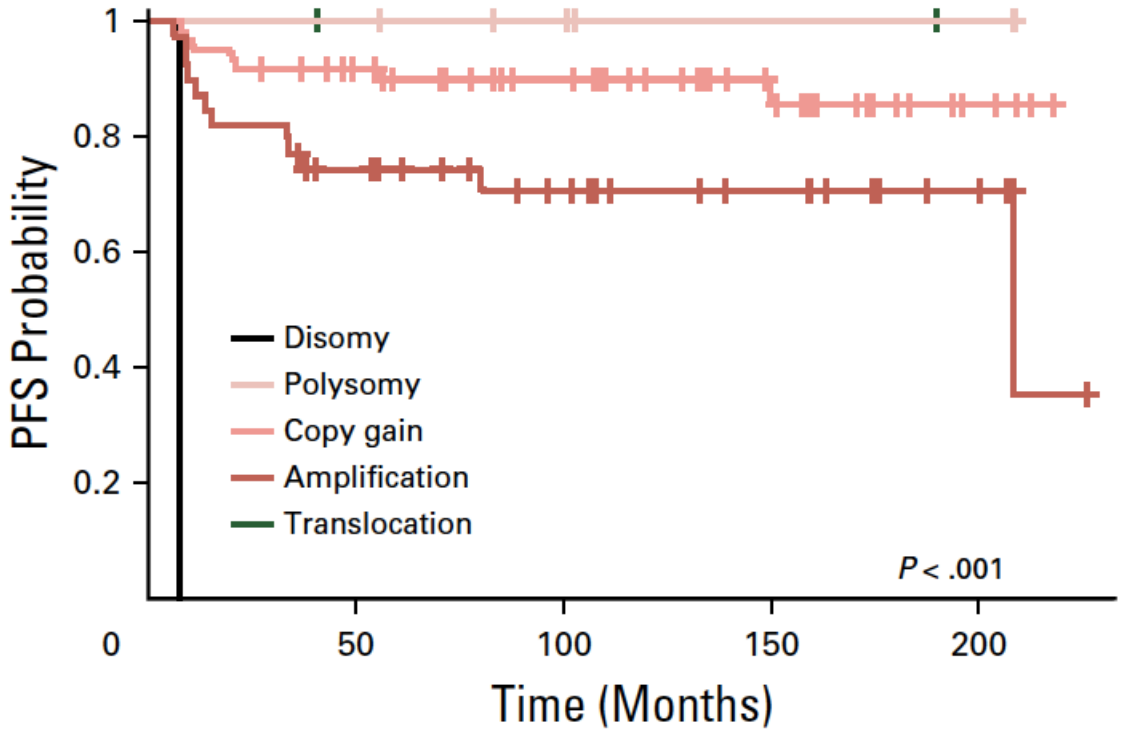
9p24.1 Alterations and PD-1 Ligand Expression





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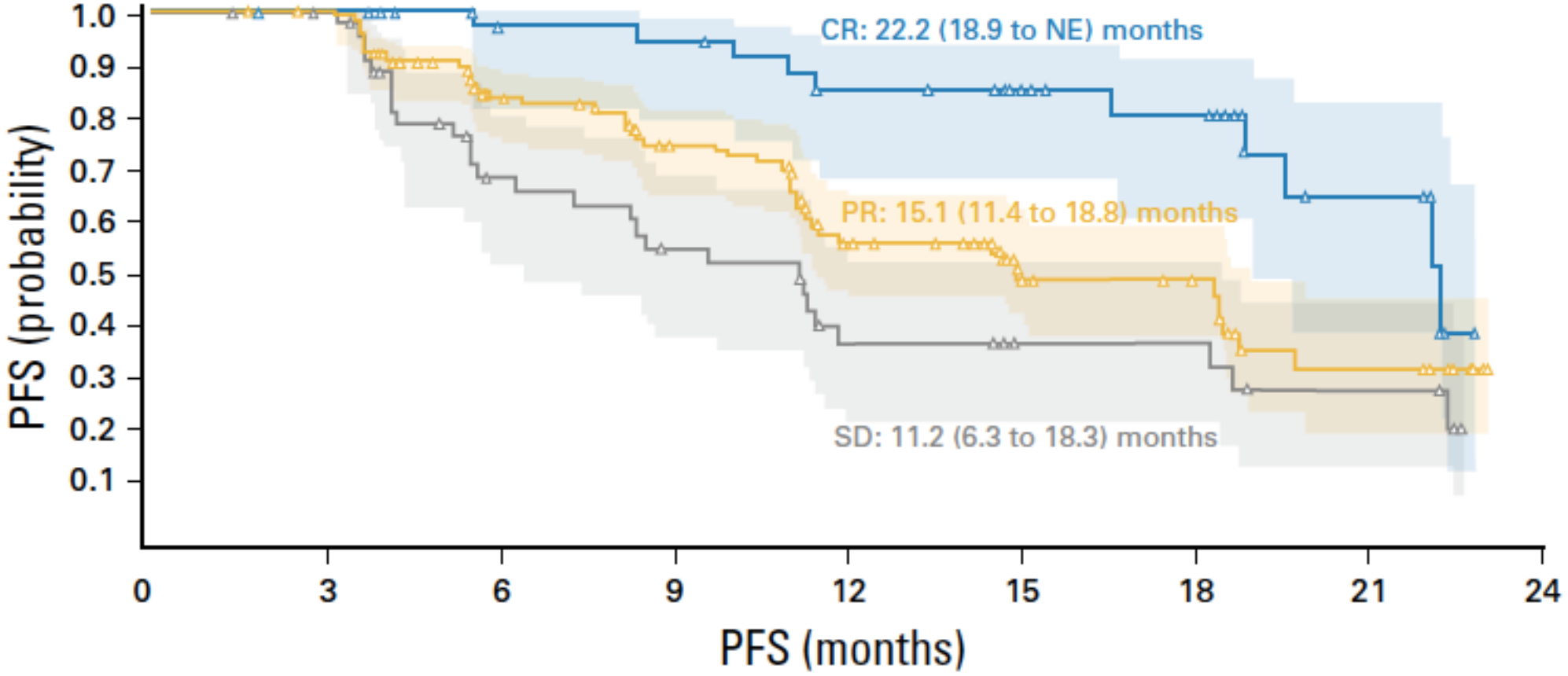
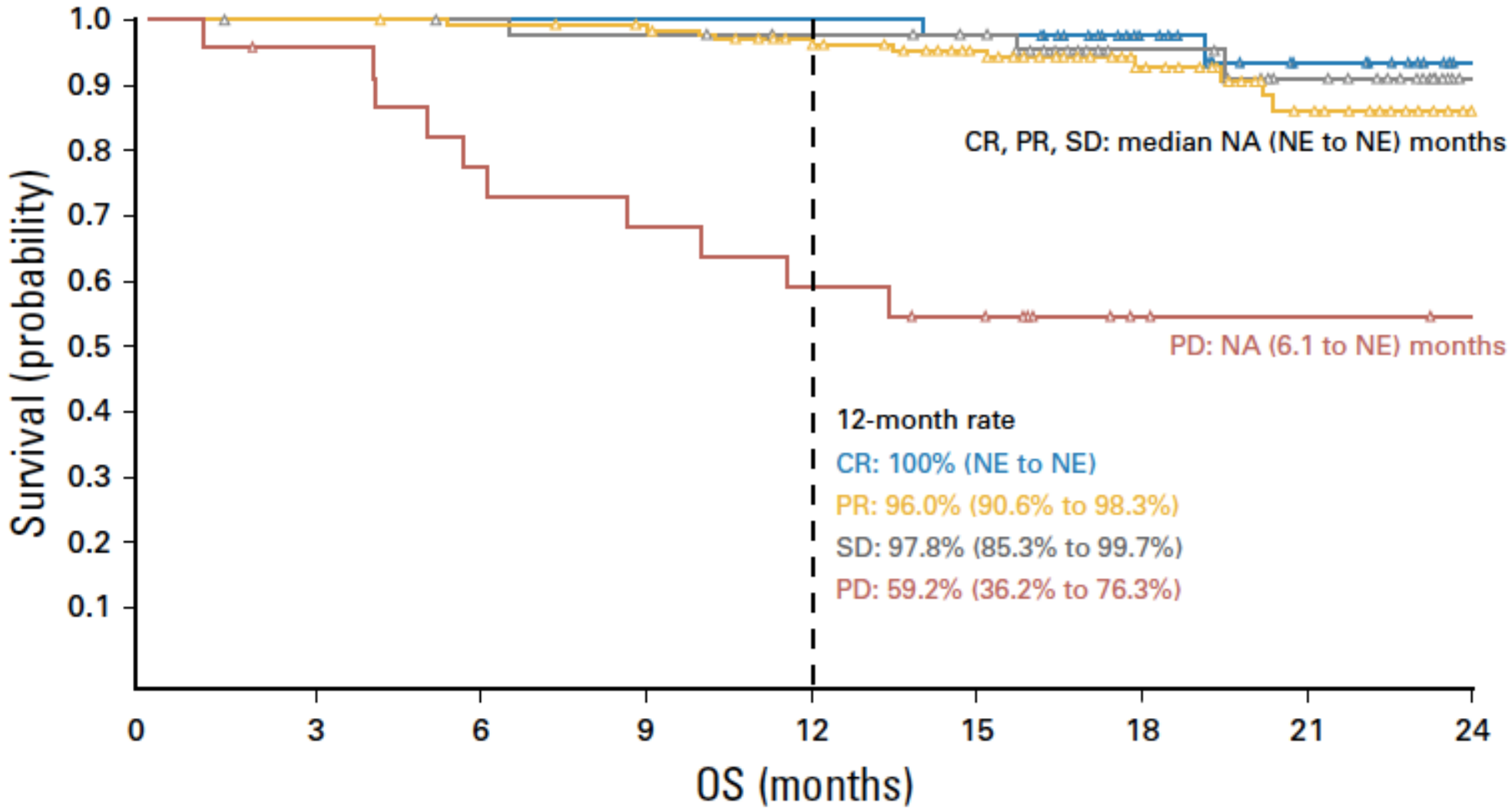
Carey CD et al, Blood. 2017;130(22):2420-2430

Checkmate 205: PFS according to response



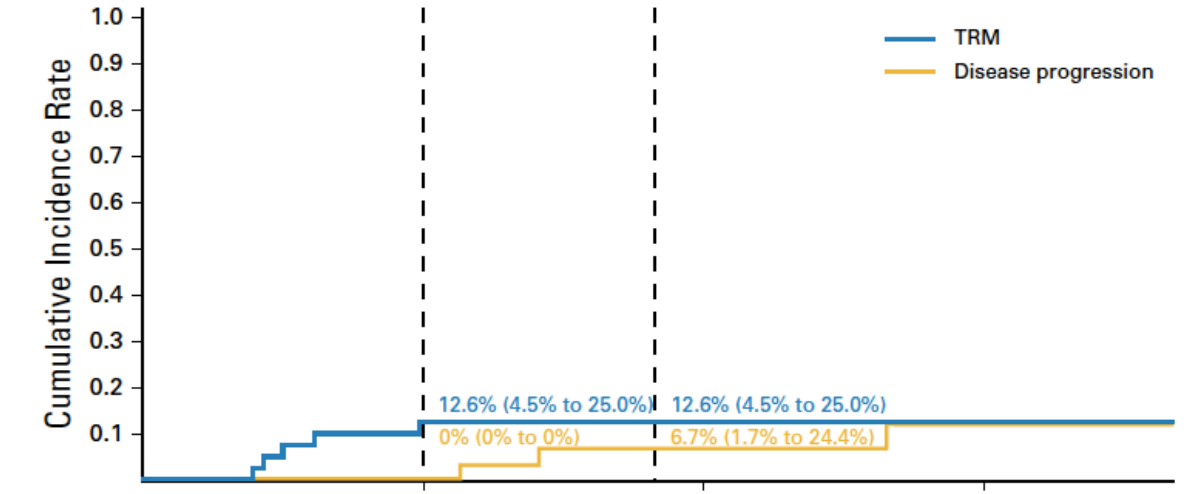
Armand P et al, J Clin Oncol 2018 36:1428-1439

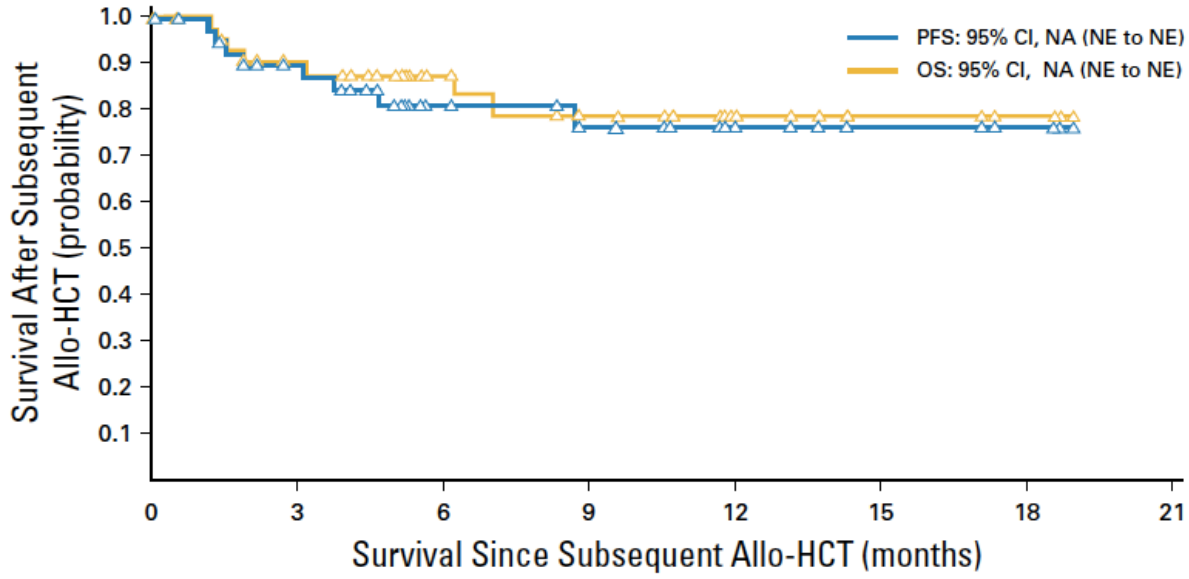
Checkmate 205: OS according to response



Armand P et al, J Clin Oncol 2018 36:1428-1439

Allogeneic Stem Cell Transplantation





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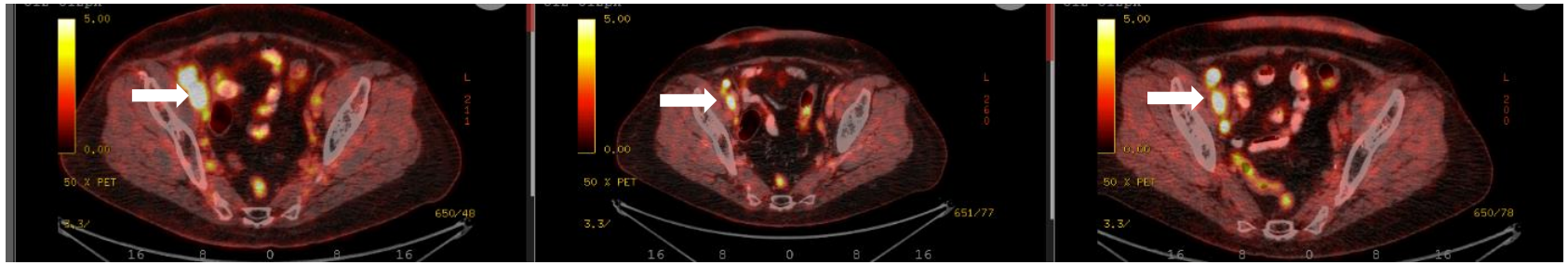
Armand P et al, J Clin Oncol 2018 36:1428-1439

Treatment beyond progression

17.12.2014 | 27.4.2015 – 3m | 17.9.2015 – 9m



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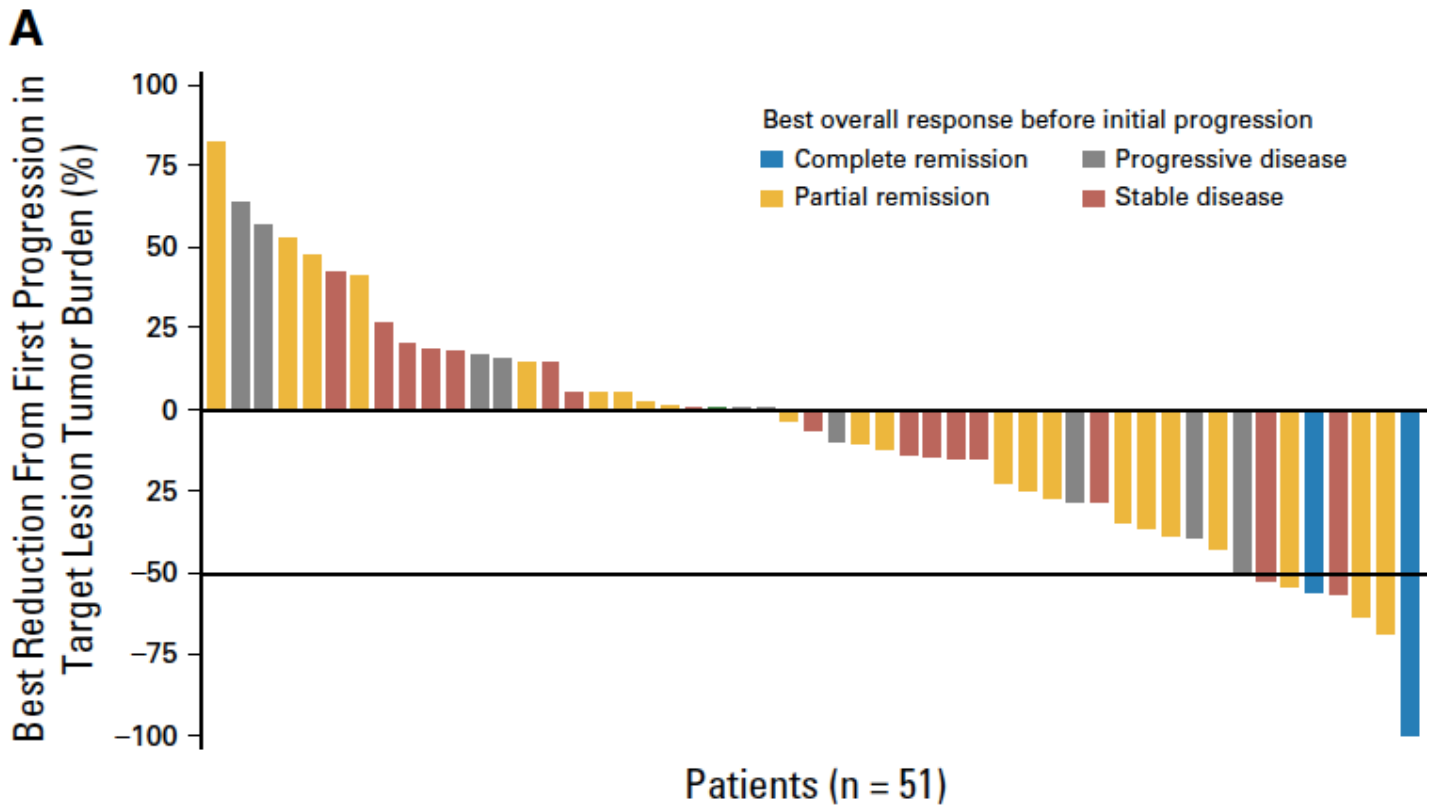

LYRIC kritéria

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Case report
Armand P et al, J Clin Oncol 2018 36:1428-1439
Cheson B et al. Blood 2016 128:2489-2496

Immune check-point inhibitors in othe B-cell lymphomas

	DLBCL		PTL	EBV⁻ PCNSL	PMBL
PD-1 Ligand Deregulation					
9p24.1/*PD-L1*^{gain} and/or *PD-L2*^{gain}	6% (11/180)[a]	7% (4/55)[a]	54% (26/50)[h]	52% (33/63)[p]	55% (6/11)
PD-L1 or *PDL-2* translocation	NA	NA	4% (2/50)[j]	6% (4/66)[q]	20% (25/125)[r]

Chapuy B et al, Blood. 2016;127(7):869-881

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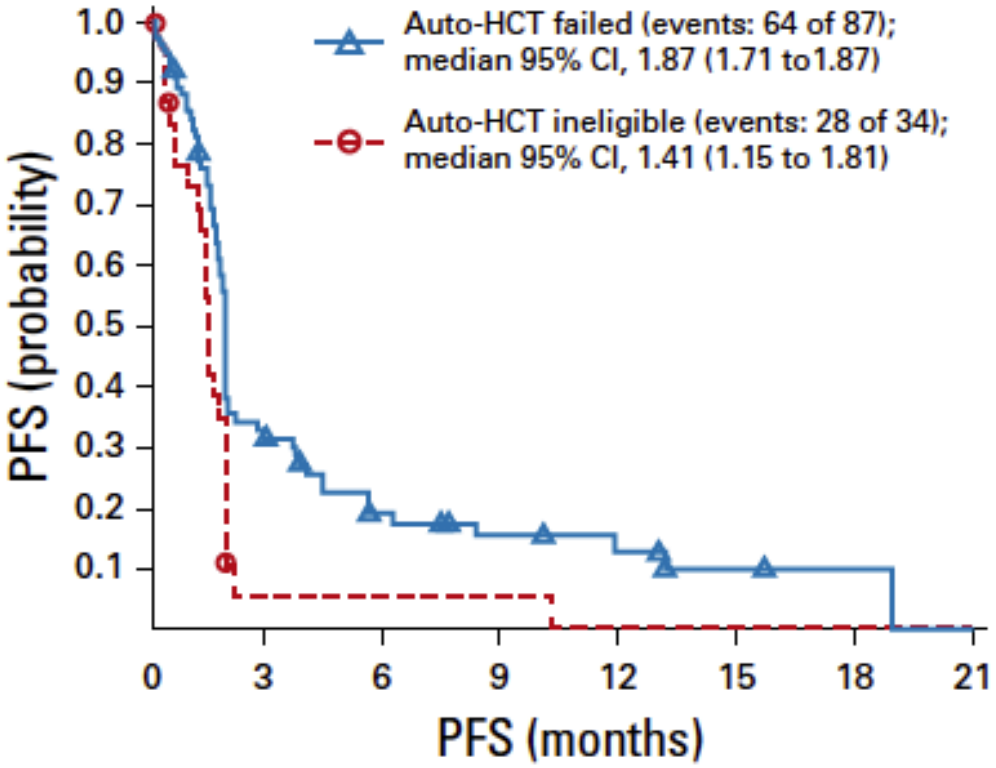

Chapuy B et al, Blood. 2016;127(7):869-881
Ansell S et al, JCO January 8, 2019 online

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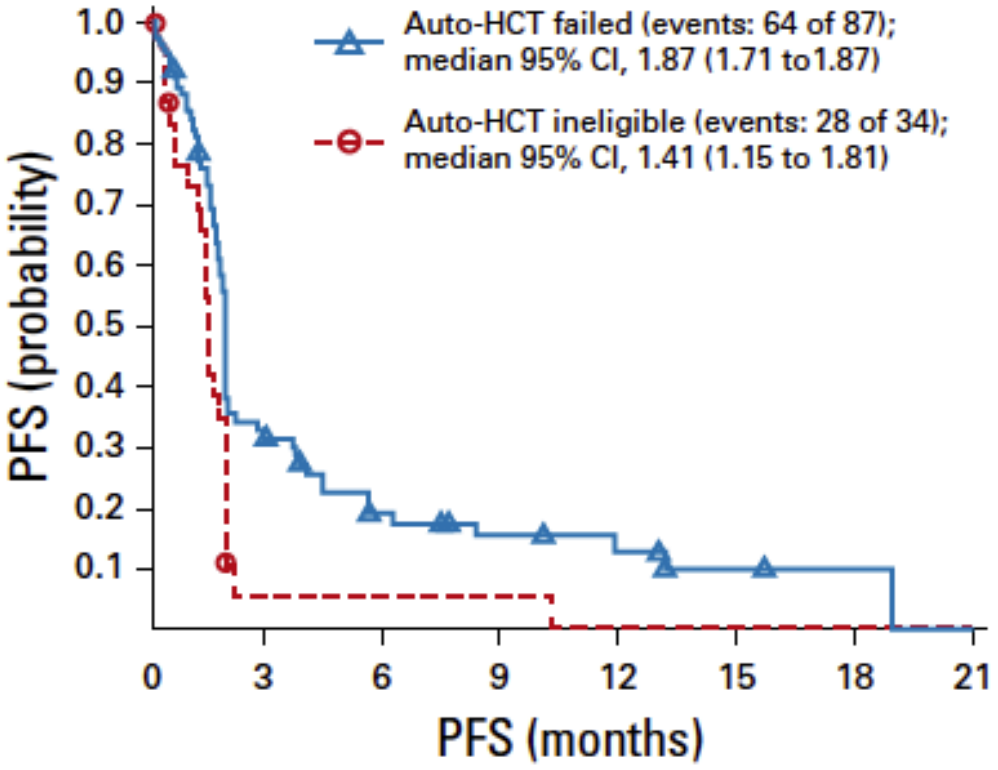
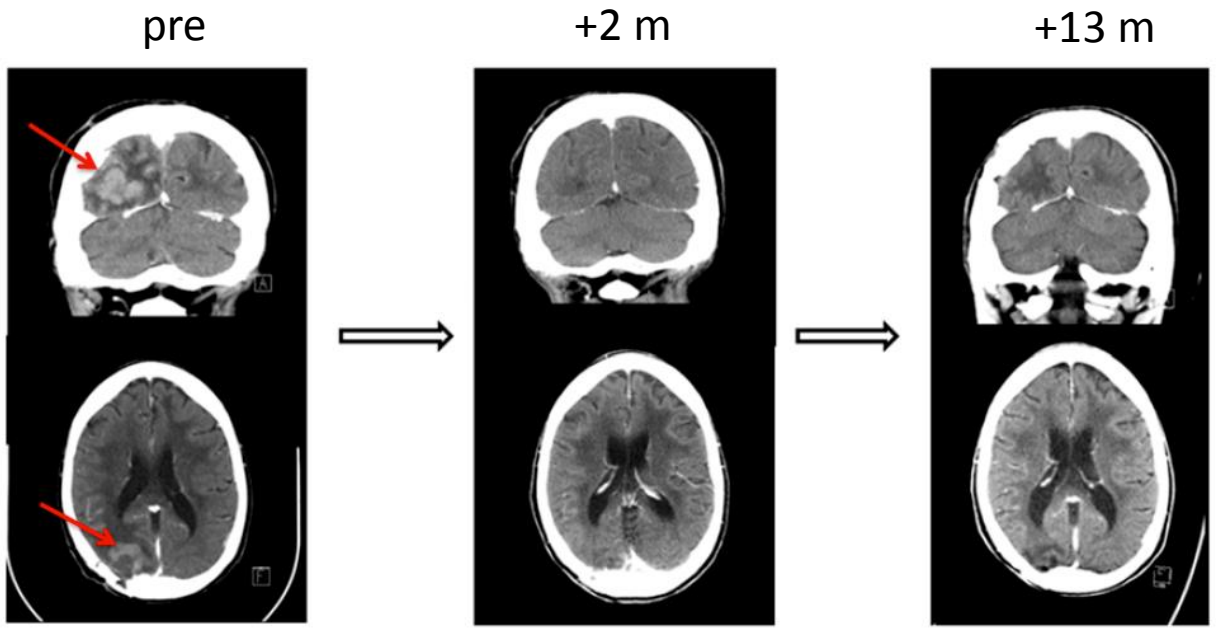
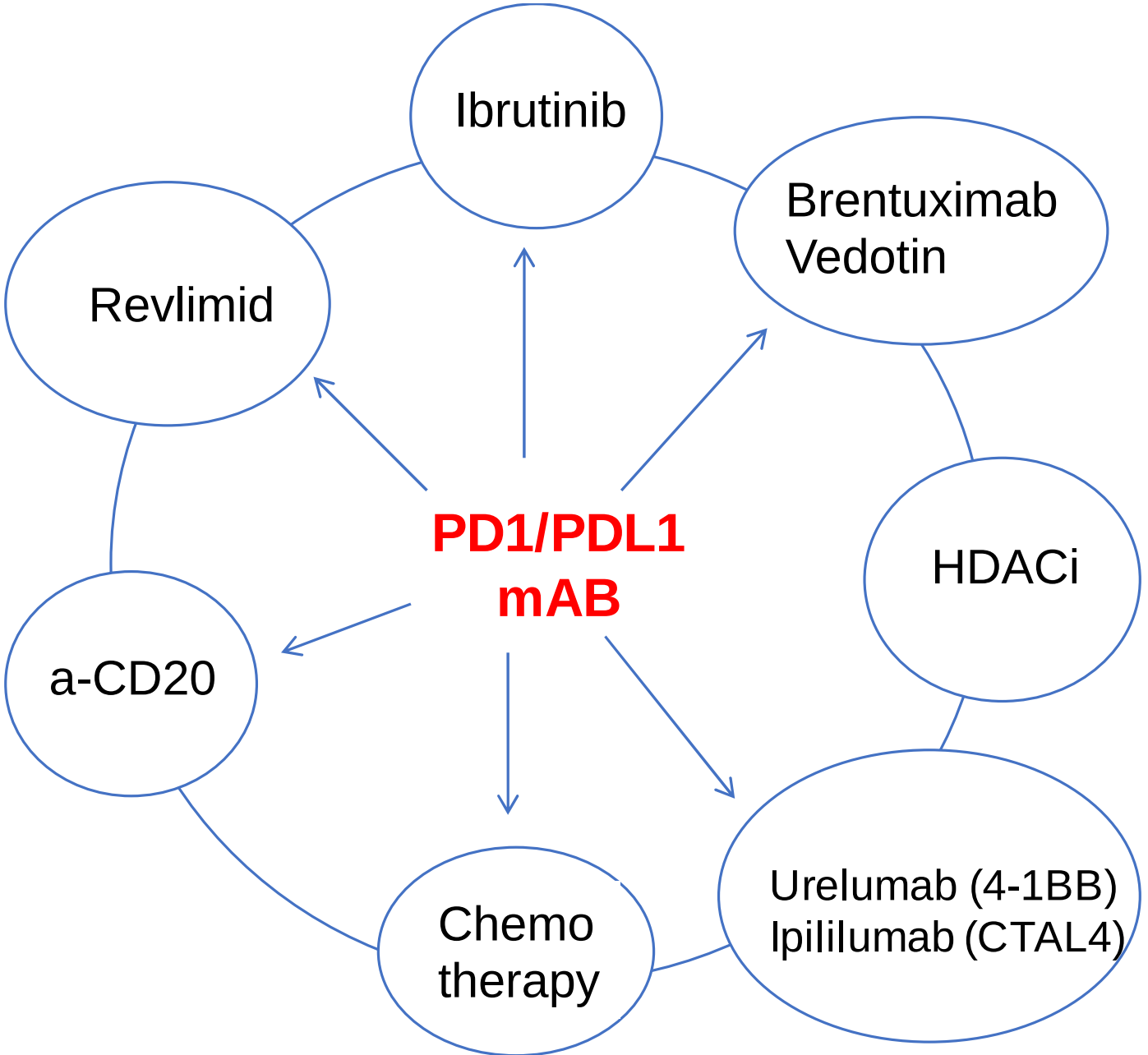


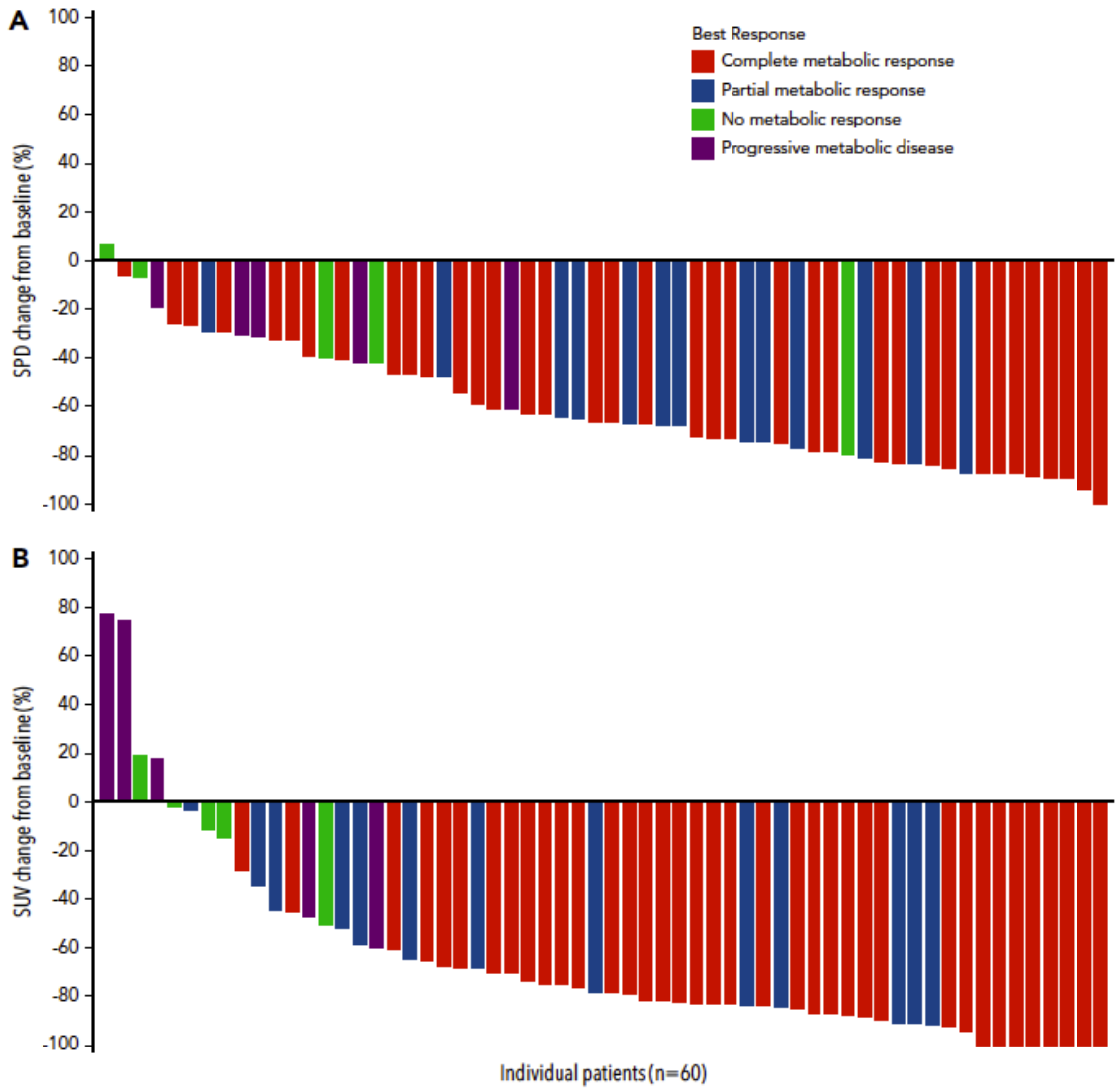


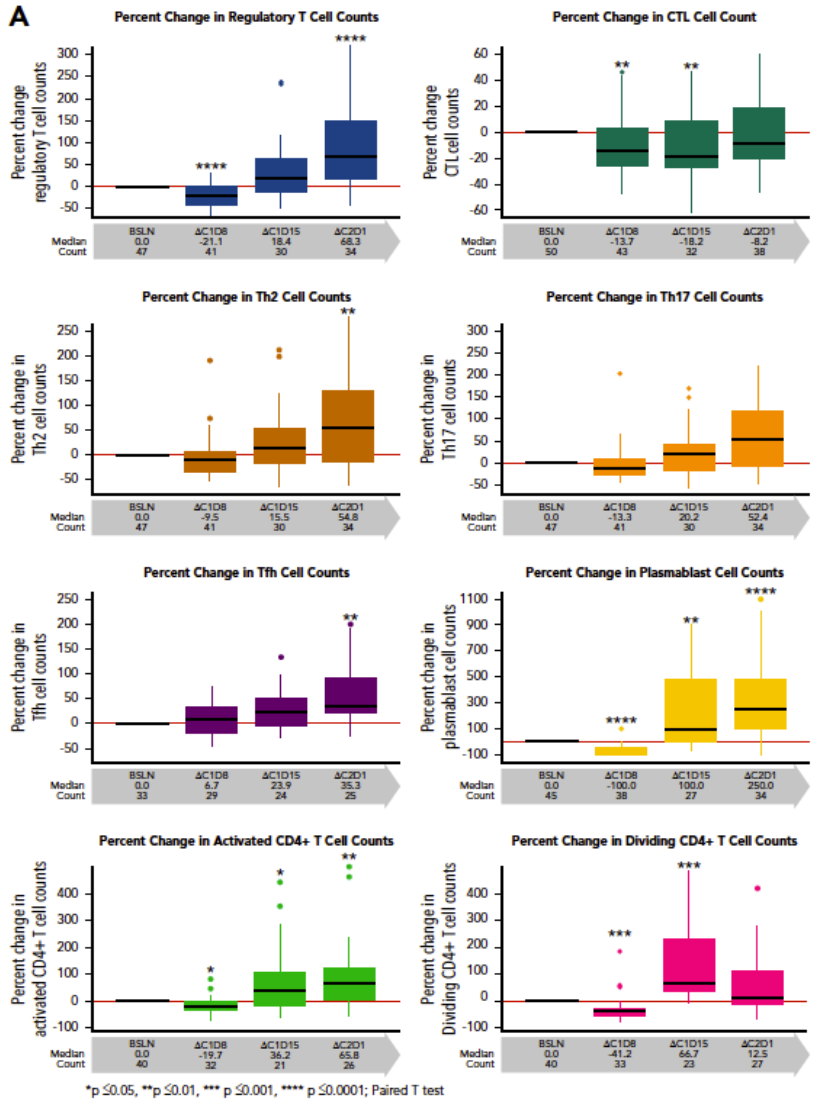
Nayak L et al, Blood. 2017;129(23):3071-3073
Chapuy B et al, Blood. 2016;127(7):869-881
Ansell S et al, JCO January 8, 2019 online

Combinations



Nivolumab and Brentuximab vedotin





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Herrera AF et al, Blood. 2018;131(11):1183-1194

Progression on PD-1/PD-L1 inhibitors?

Rapid Progression of Adult T-Cell Leukemia–Lymphoma after PD-1 Inhibitor Therapy

N ENGL J MED 378;20 NEJM.ORG MAY 17, 2018

Lee Ratner, M.D., Ph.D.
Washington University School of Medicine
St. Louis, MO
lratner@wustl.edu

We initiated a phase 2 trial of nivolumab (ClinicalTrials.gov number, NCT02631746) in patients with ATLL who had an increased mutational load and overexpression of PD-L1. Here, we describe treatment of the first three patients, which resulted in rapid progression of disease in all three after a single dose of nivolumab.

Our patients had the chronic, smoldering, and acute subtypes of ATLL (Table 1). The first

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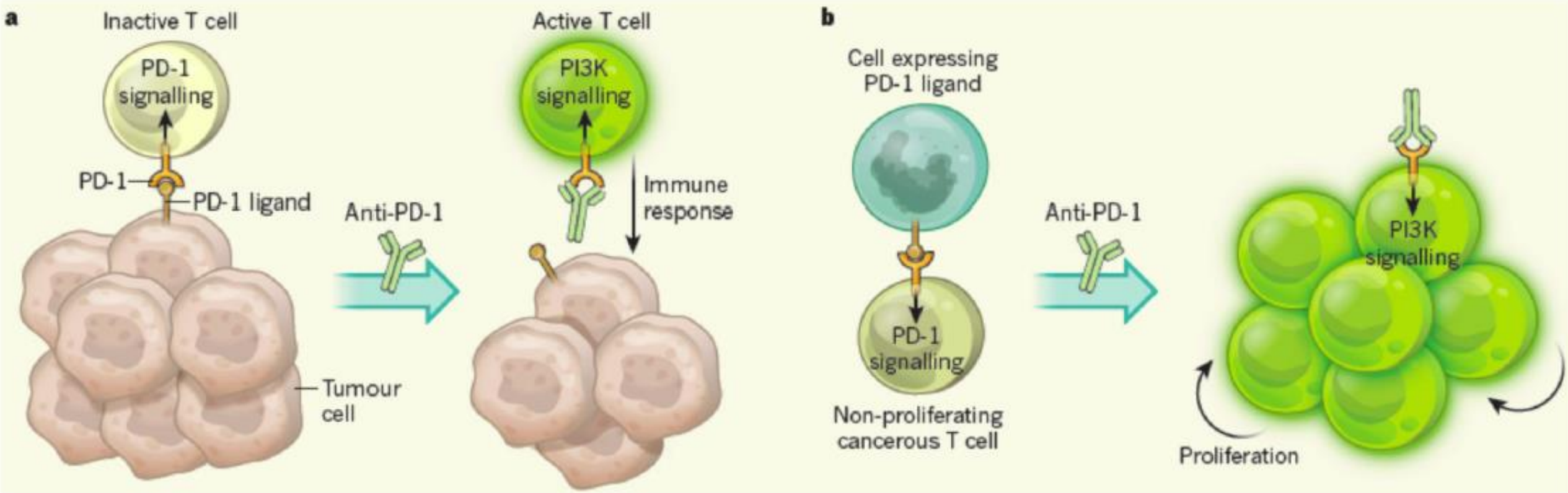
Dual role of PD-1 inhibition



Ludin A & Zon LI, Nature. 2017 December 07; 552(7683): 41–42.

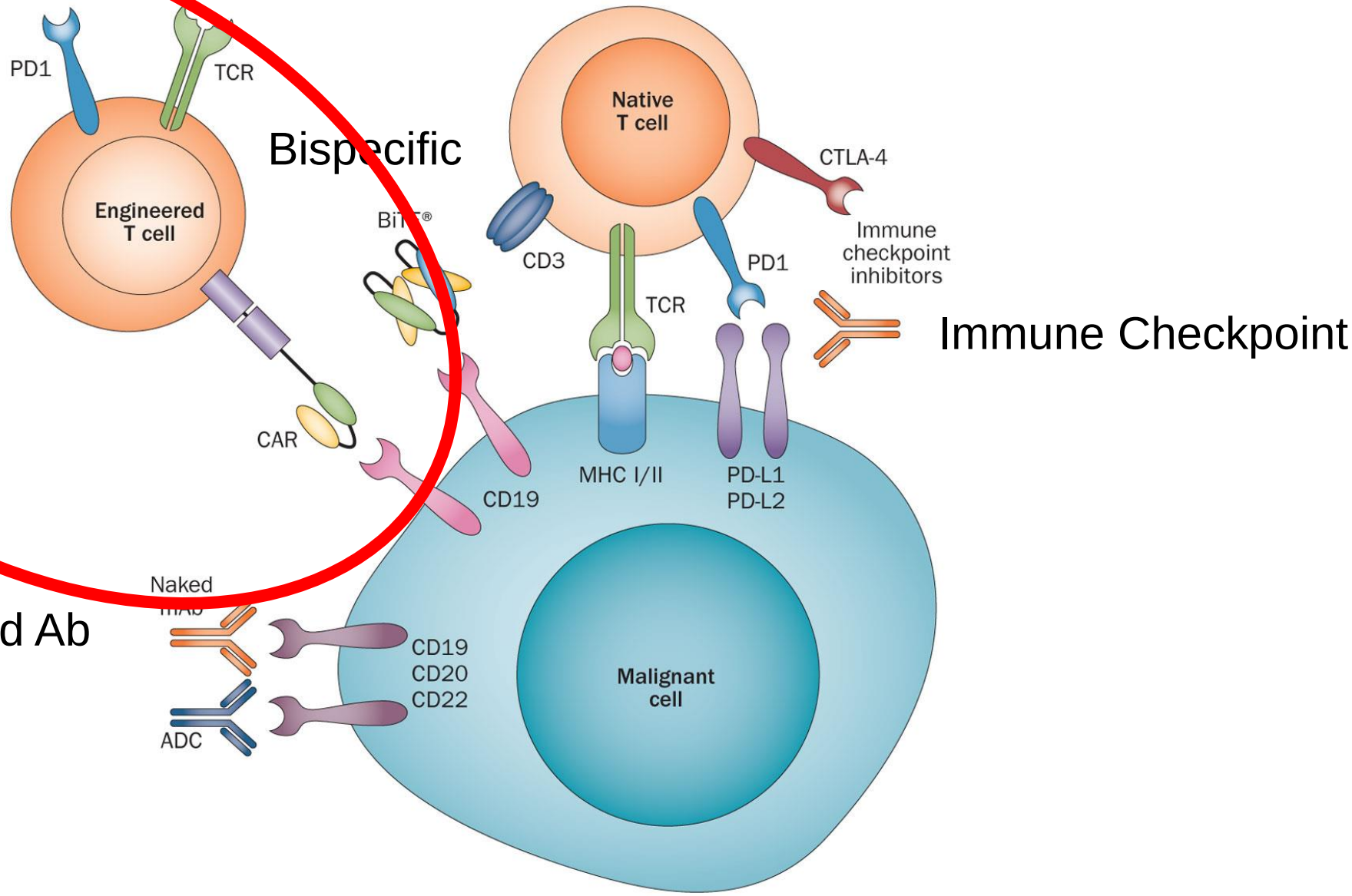
CAR T Cells

CAR T Cells

Bispecific

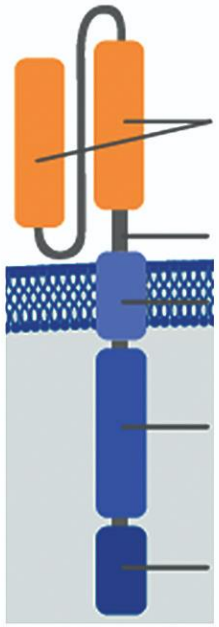
Ingeneered naked Ab

Immune Checkpoint



CAR T Cell

CAR: Modular Design



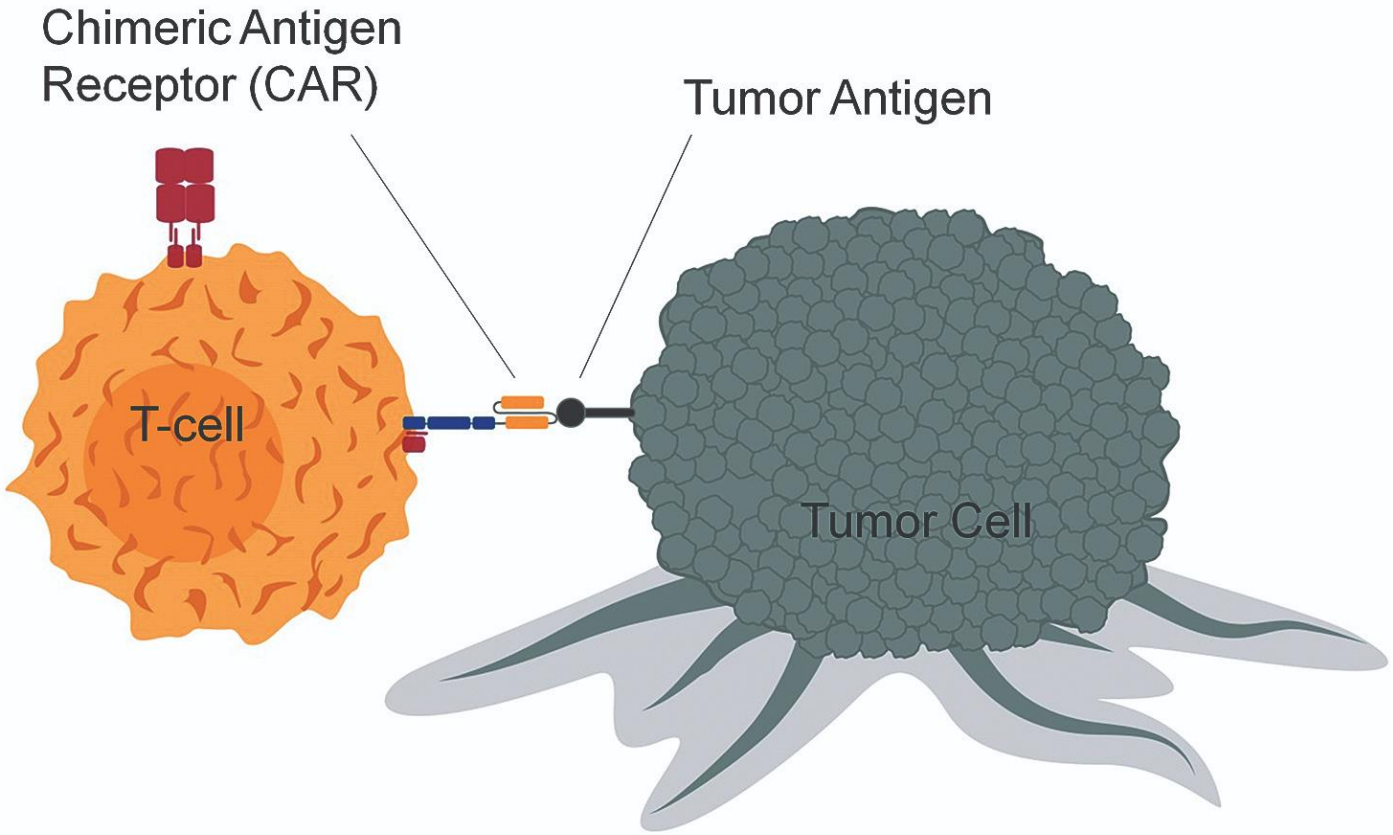
Targeting Element (scFv)

Spacer

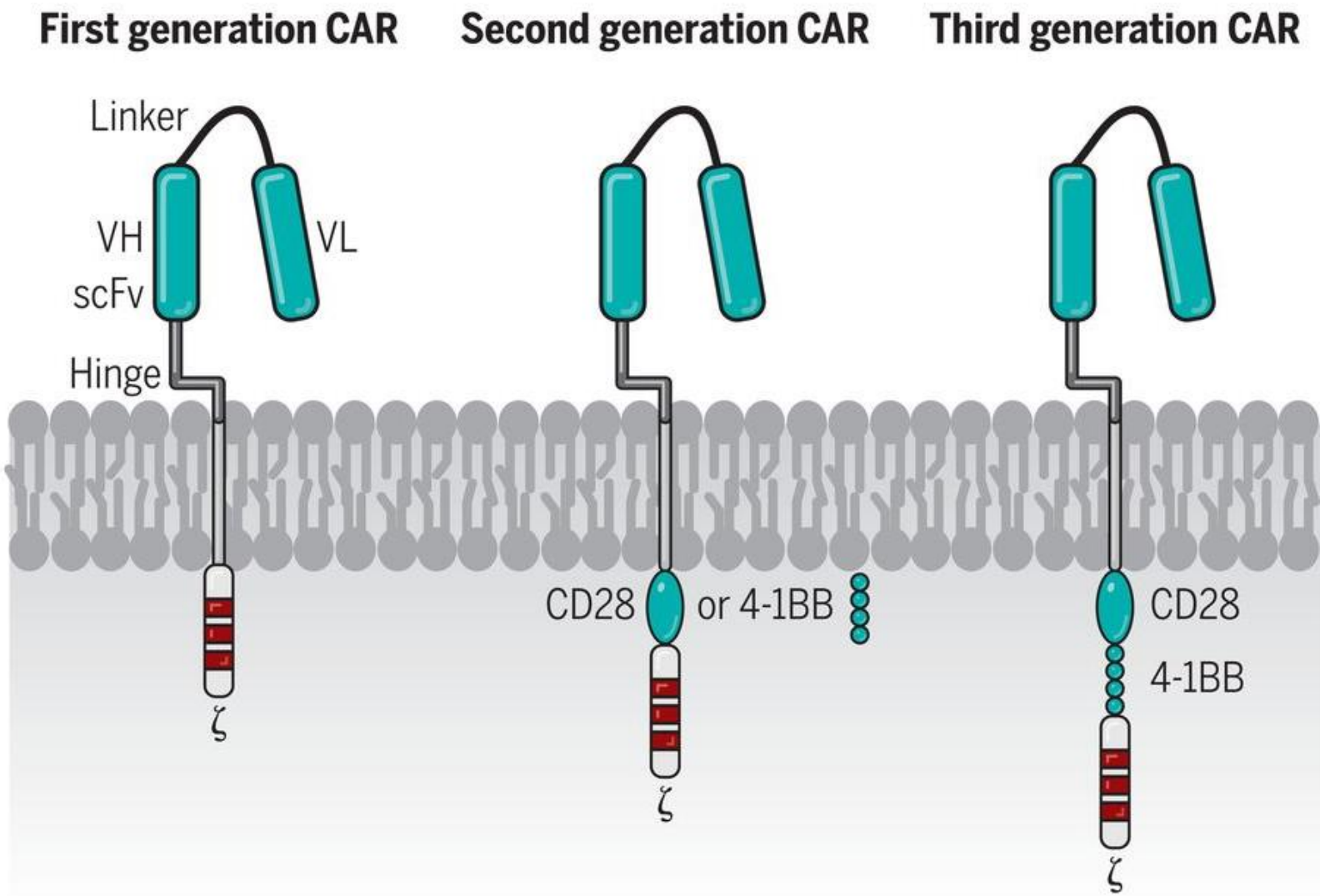
Transmembrane Domain

Co-stimulatory Domain
(e.g. CD28 or 4-1BB)

Signaling Domain
CD3z



CAR T Cells Generation



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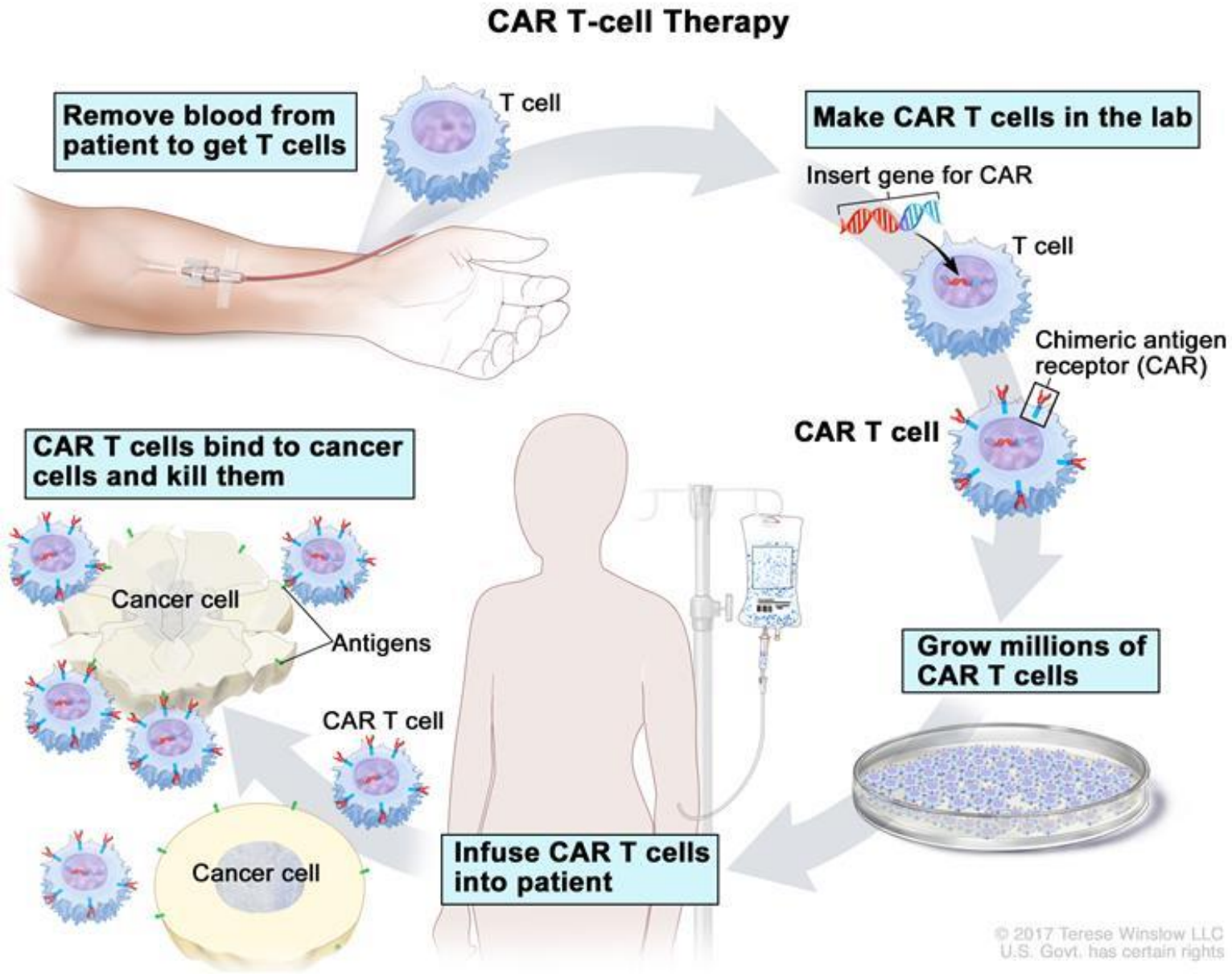
June K et al: Science 2018 359 (6382), 1361-1365.

CAR T cells production

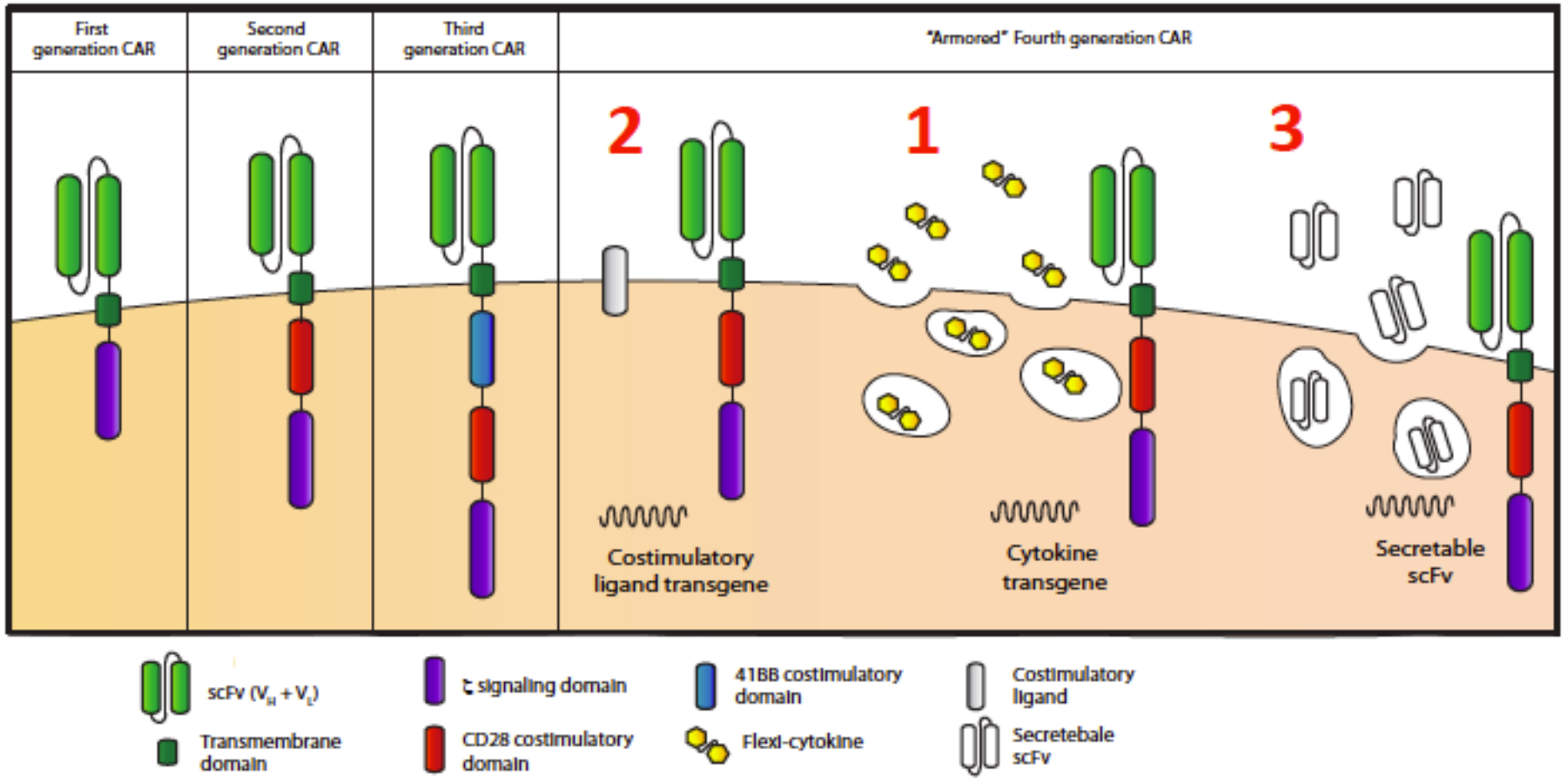


CAR T cells in different studies

Study	ZUMA-1 (Neelapu, 2017)	JULIET (Schuster, 2017)	TRANSCEND (Abramson, 2017)
No of patients enrolled (treated)	111 (101)	141 (99)	NR (91) 67 in CORE
Median age, range	58 (23–76)	56 (24–75)	61 (29–82)
Median follow-up	15.4 months	5.6 months	6.3 months
Costimulatory domain	CD28	4-1BB	4-1BB
Bridging chemotherapy	Not allowed	Allowed	Allowed
CART dose	2.0×10^6 cells/kg	Median, 3.1×10^8	DL1 5.0×10^7 cells[a] DL2 1.0×10^8 cells
Conditioning regimen	Flu 30 mg/m^2 x3d Cy 500 mg/m^2 x3d	Flu 25/m^{2}x 3d Cy 250 mg/m^2 x3d or B 90 mg/m^2 x 2d	Flu 30 mg/m^2 x3d Cy 300 mg/m^2 x3d
Efficacy			
%ORR (%CR)	82 (54)	59 (43)	84 (61)
3-mo %ORR (%CR)	44 (39)	45 (37)	65 (53)
mDOR	11.1 months	NR	9.2 months

Neelapu SS et al, N Engl J Med. 2017 Dec 28;377:2531-2544
Schuster JS et al, N Engl J Med. 2017 Dec 28;377(26):2545-2554
Abramson JS et al, J Clin Oncol 2017, 15:7513

Armored CAR T cells



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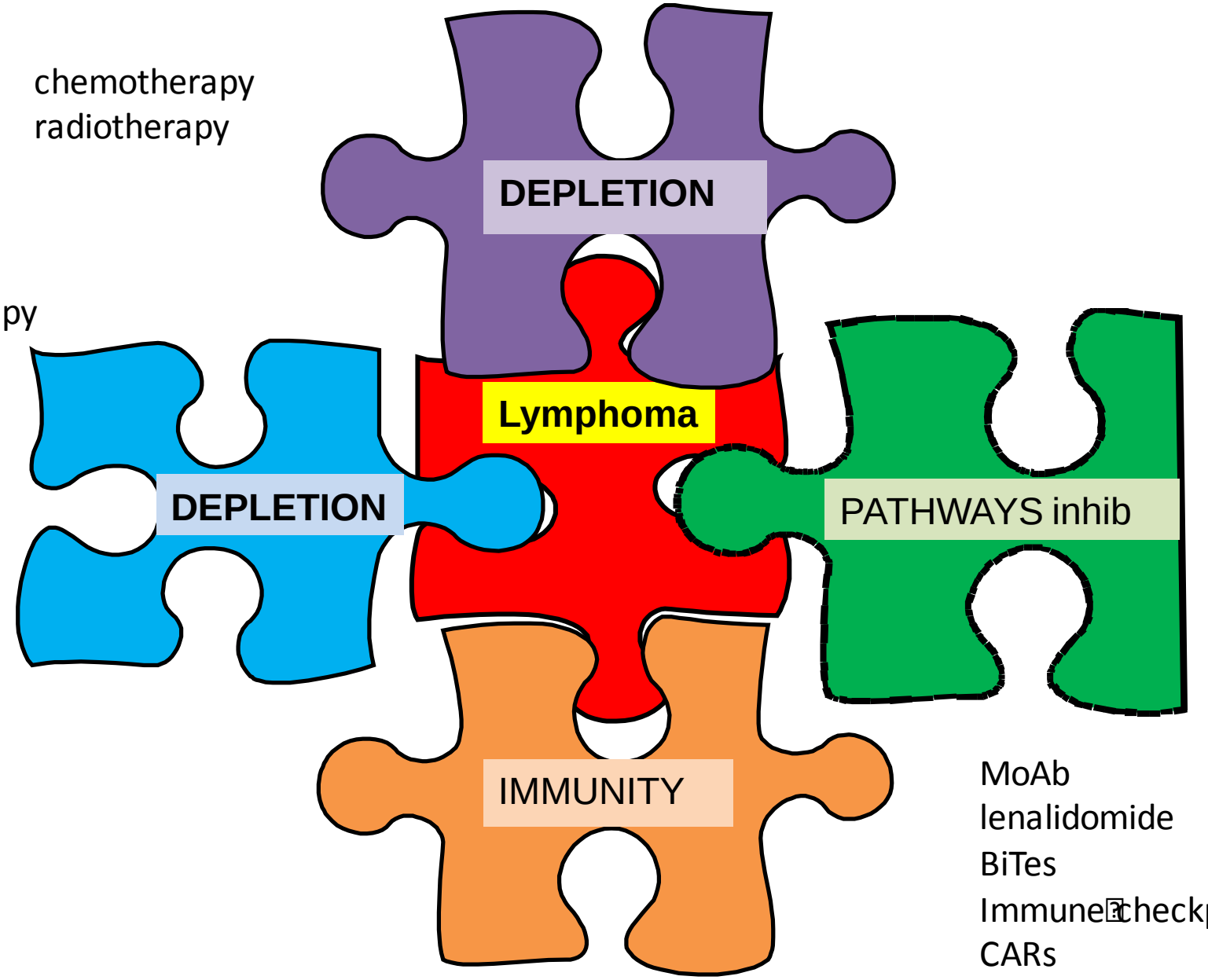
courtesy by R. Brentjens

Conclusion: Rational approach - combinations

chemotherapy
radiotherapy

radioimmunotherapy
antibody-drug conjugates



PI3k kinases
SYK
BTK
EZH2 epigenetic
ABT199 apoptosis

MoAb
lenalidomide
BiTes
Immune checkpoint inhib
CARs

Charles University
1st Faculty of Medicine
General Hospital

Thank you

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