CAR T/BI-Specific Antibodies for Lymphomas

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City of Hope

Disclosures

- Consultant for PepPromene Bio, Inc. and Trillium Therapeutics, Inc.
- Stock/Shareholder of PepPromene Bio, Inc. and Trillium Therapeutics, Inc.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

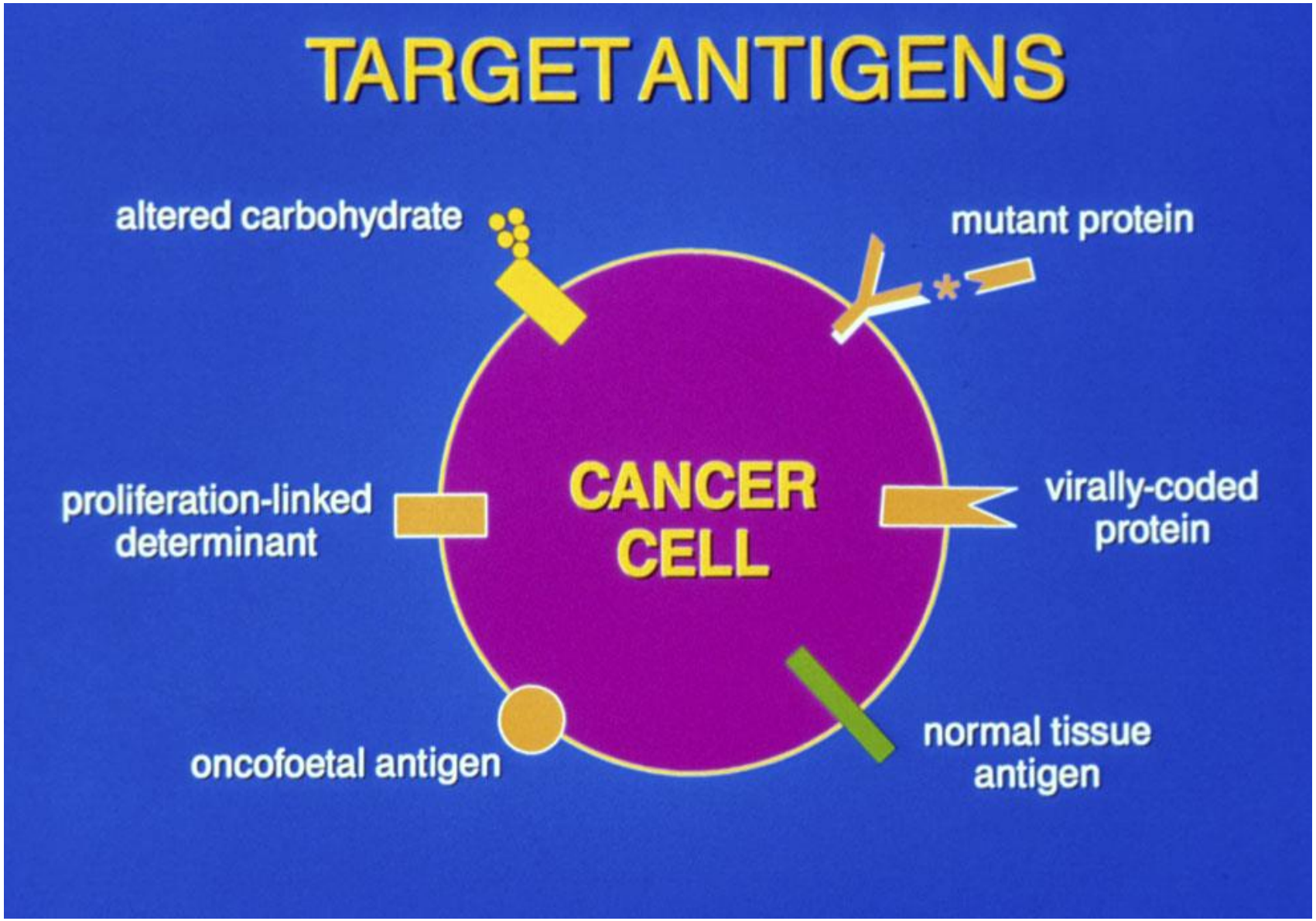
The following CLC & IB components will be addressed in this presentation:

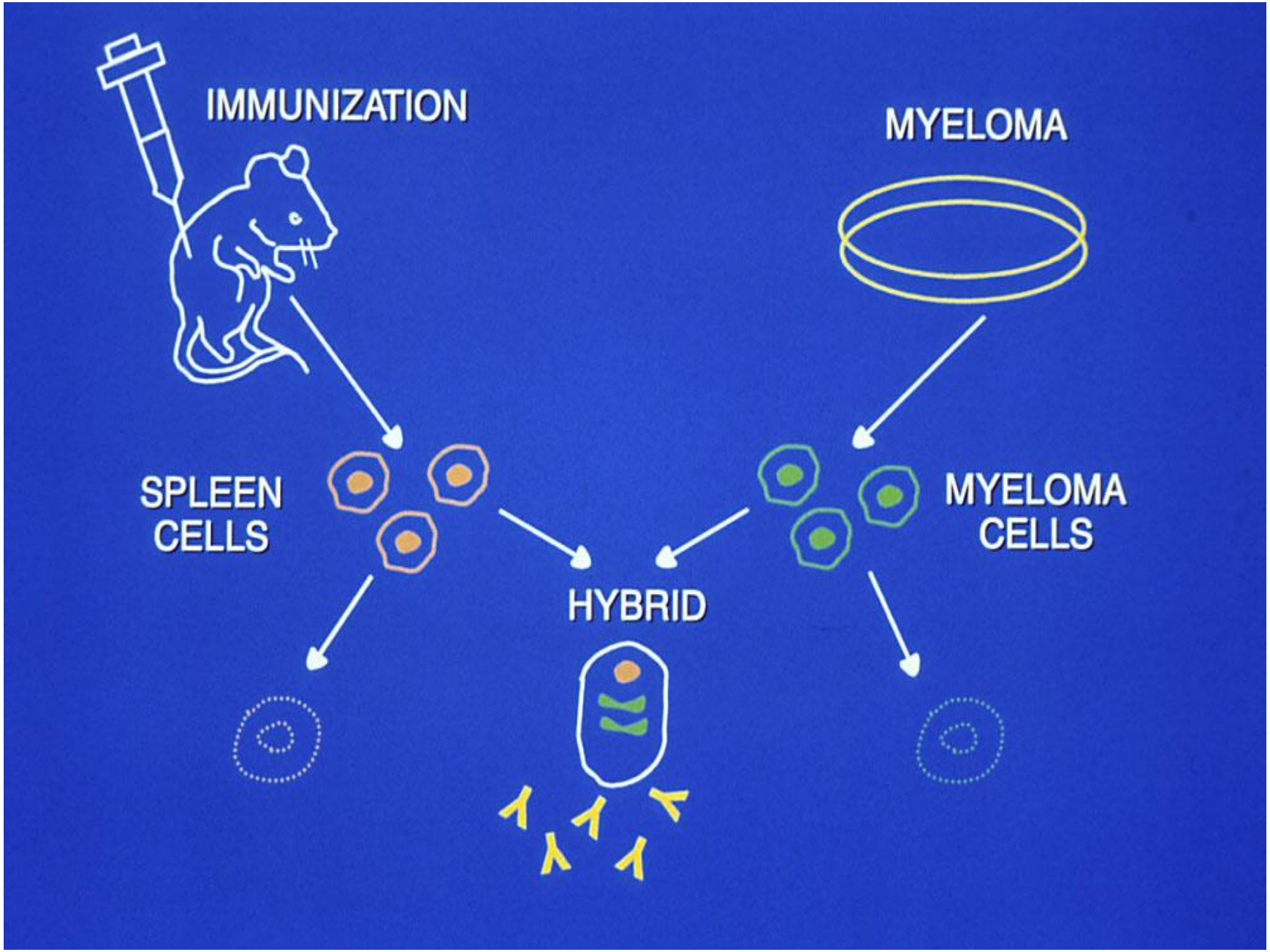
- *Expand therapy to all at risk groups.*
- *Expand access through knowledge of options.*

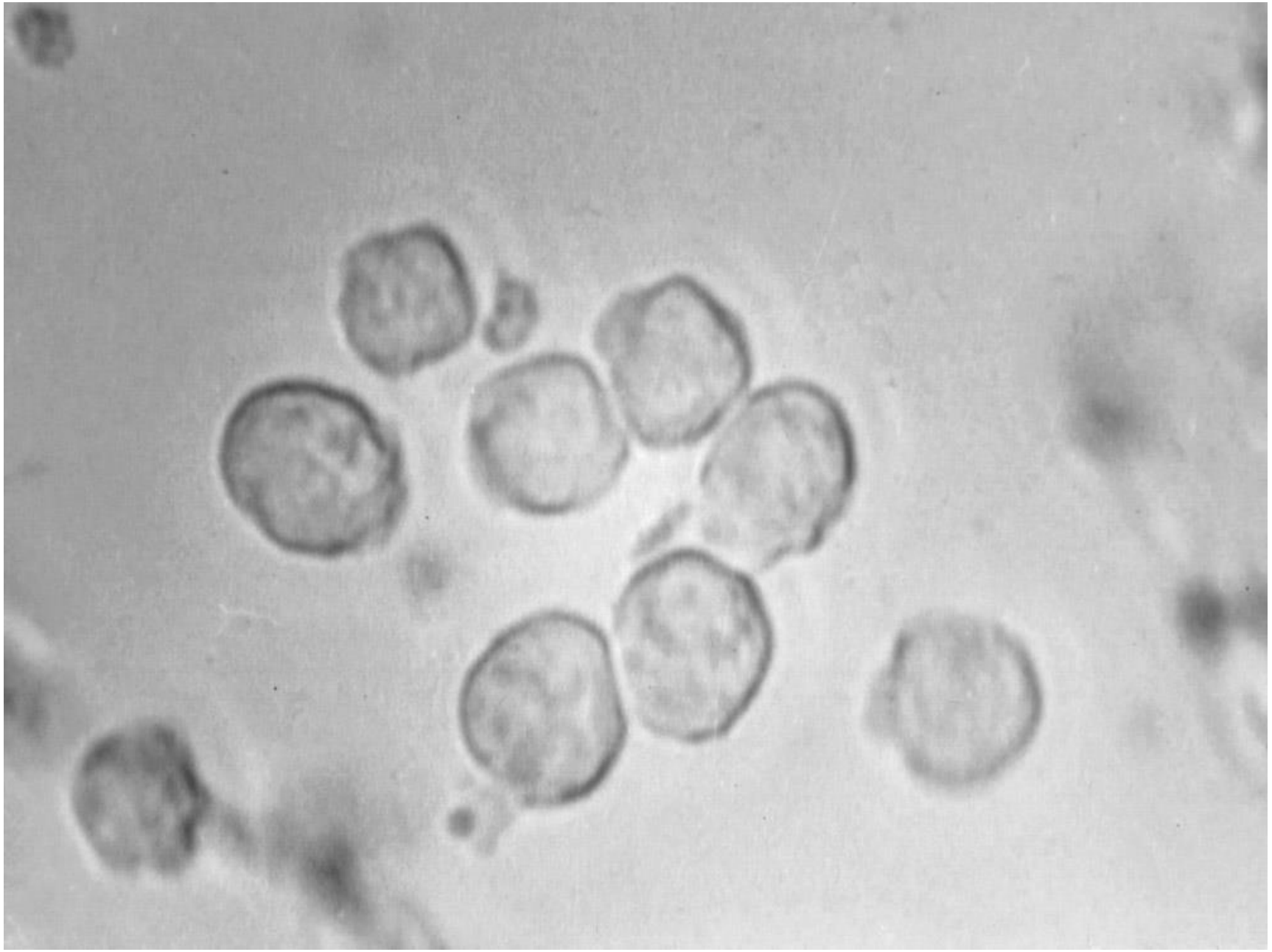
City of Hope

Multidisciplinary Approaches to Cancer Symposium
CAR T/BiSpecific Antibodies for Lymphomas
November 11, 2022

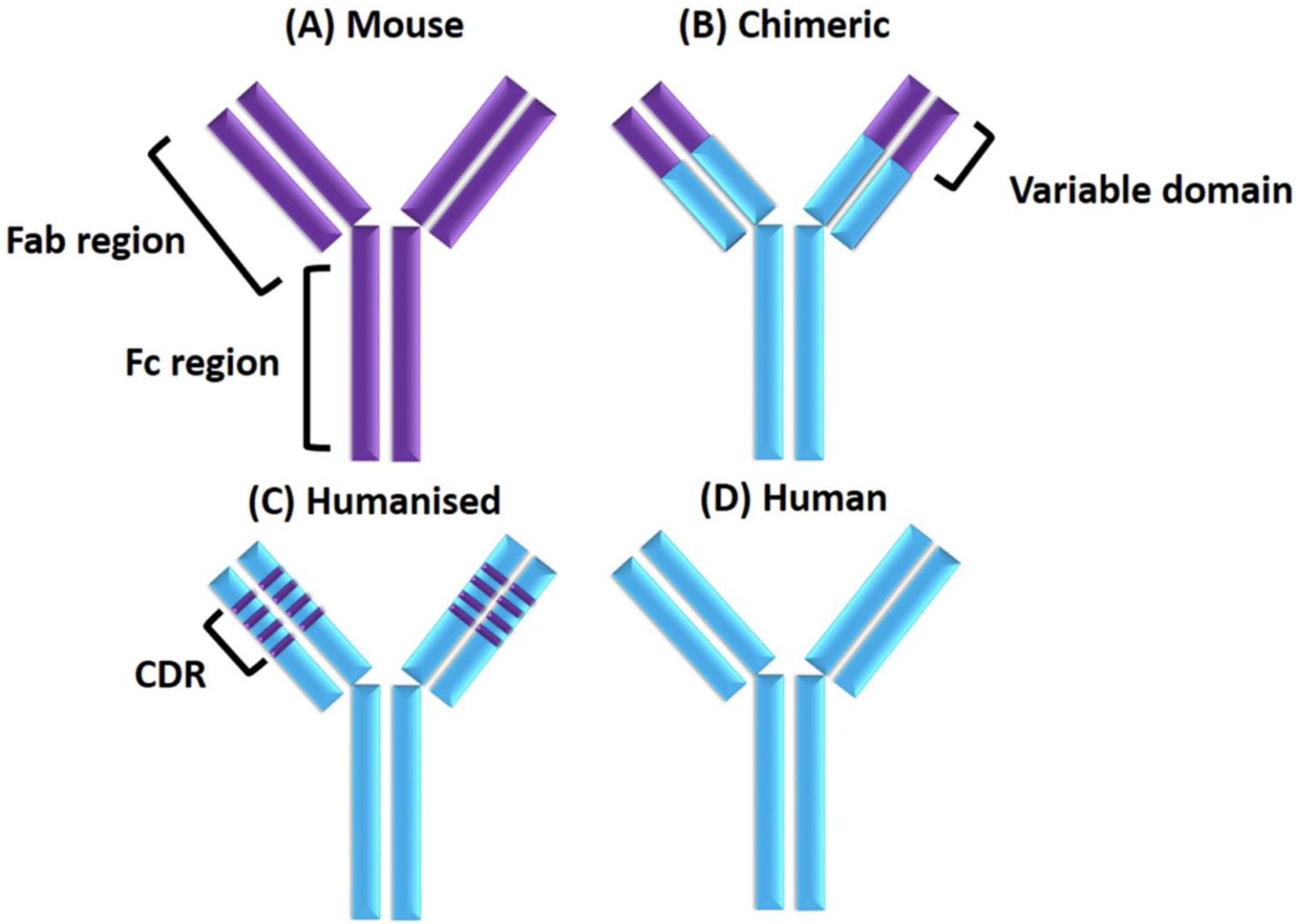
Target Antigens




IMMUNIZATION
MYELOMA
SPLEEN CELLS
MYELOMA CELLS
HYBRID

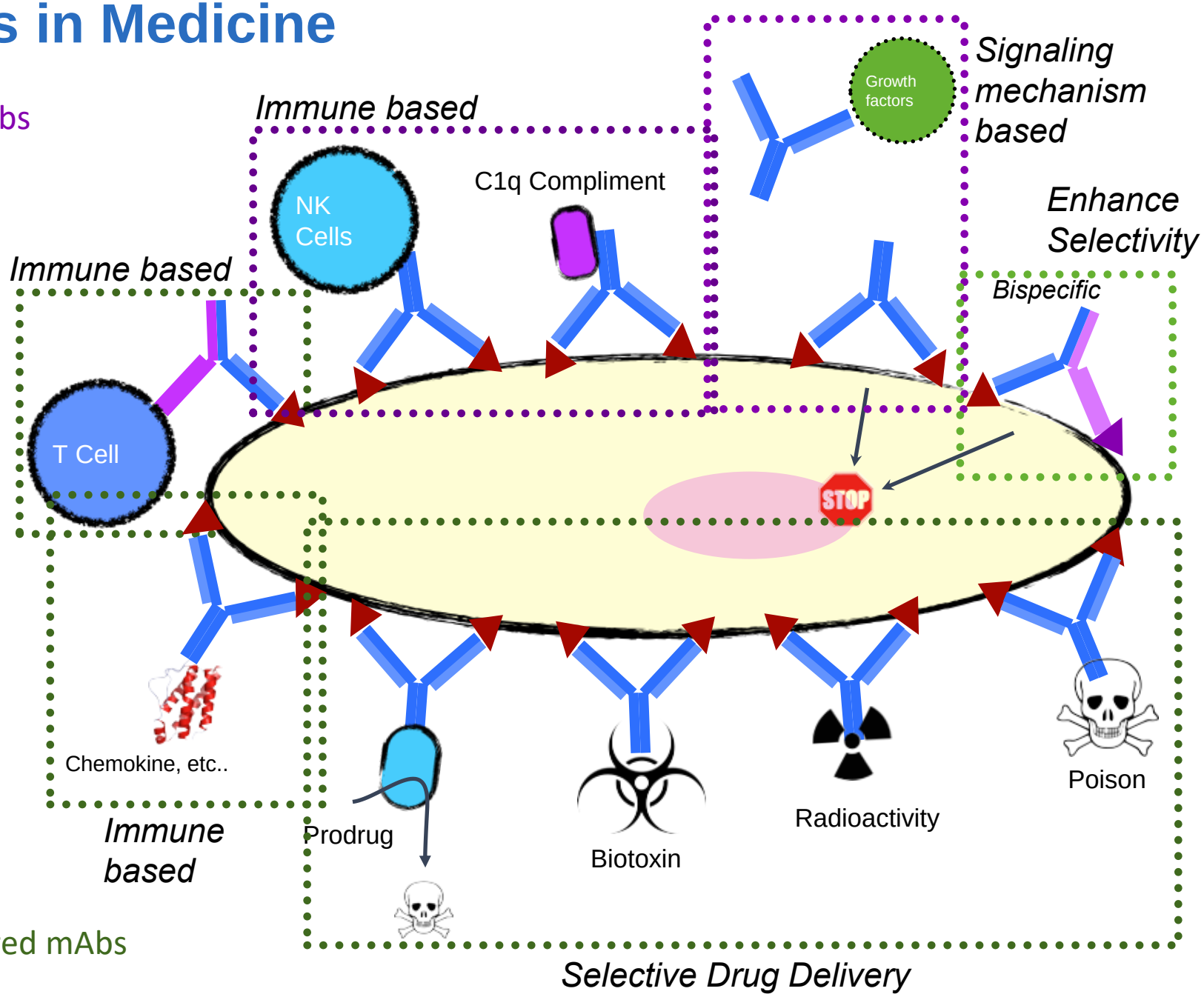


MOUSE-HUMAN RECOMBINANT ANTIBODIES



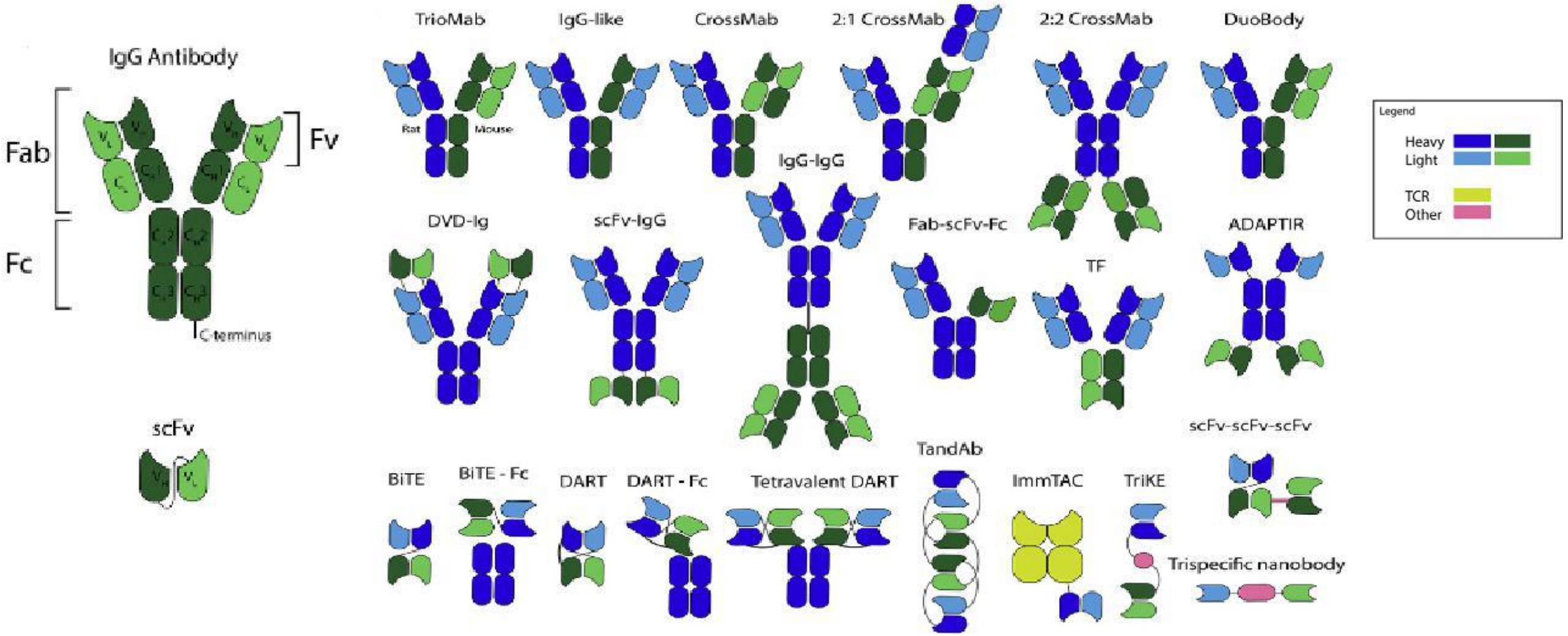
Antibodies in Medicine

Naked mAbs



Engineered mAbs

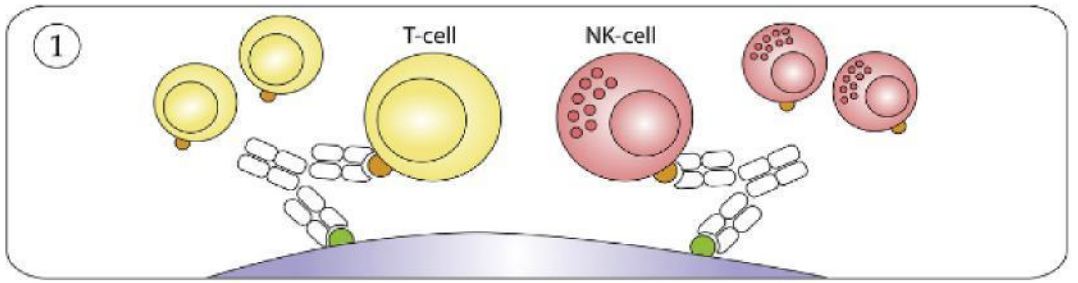
Bispecific Antibody Constructs



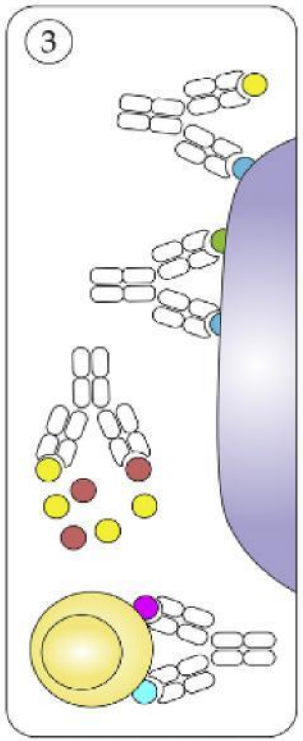
Suurs et. al. Pharmacology & Therapeutics. 2019

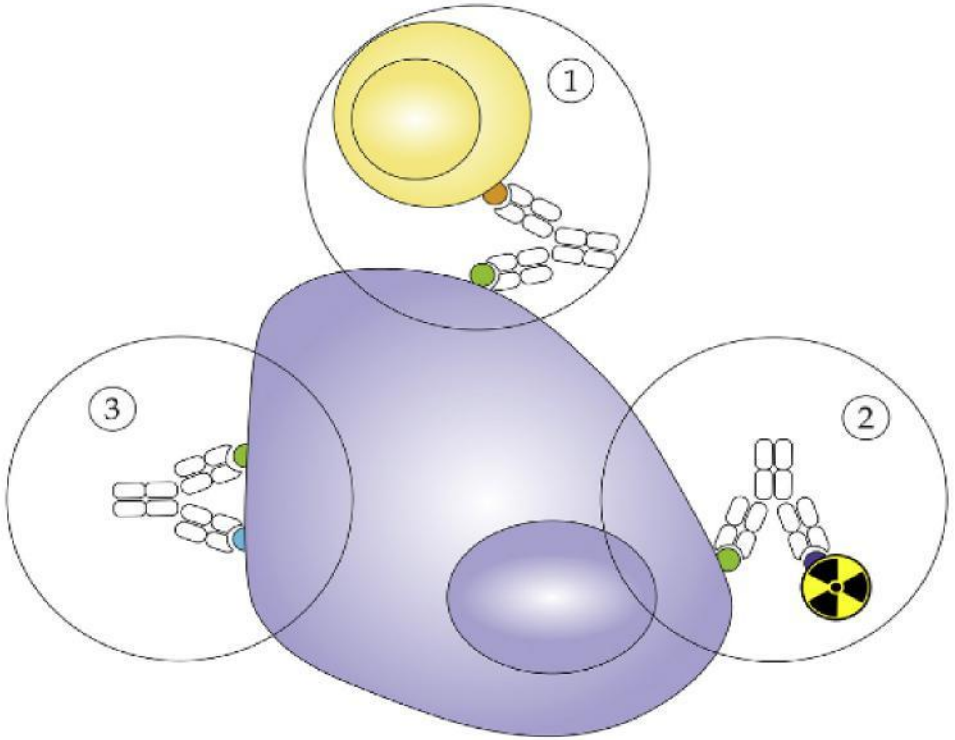
Mechanisms of action of bispecific Abs

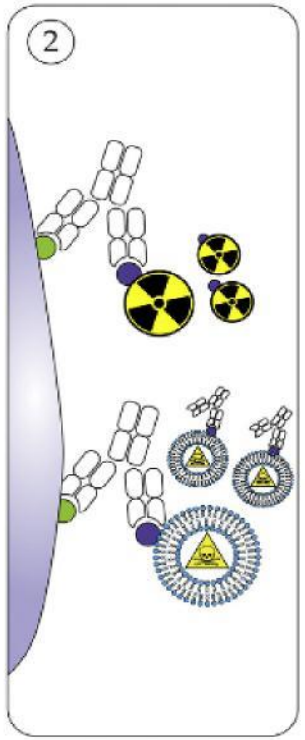
1) Engagement of immune cells to the tumor cell



3) Blocking signaling







2) Targeted delivery of payloads

Suurs, et al. Pharmacology & Therapeutics, 2019

Bispecific antibodies (CD3/CD20) in development for B-NHL

		Odronextamab (Regeneron)	**Mosunetuzumab** (Roche/Genentech)	**Glofitamab** (Roche)	**Plamotamab** (Xencor)	**Epcoritamab** (AbbVie/Genmab)
	Study Phase	**Phase 1/2**	**Phase 1/1b**	**Phase 1b**	**Phase 1**	**Phase 1/2**
	Study Population	R/R B-NHL patients with aggressive disease after at least 2 prior therapies	R/R NHL patients with at least 2 prior therapies	R/R NHL patients with aggressive disease after at least 1 prior systemic therapy	Transplant ineligible R/R NHL patients	R/R DLBCL and aggressive NHL patients after anti-CD20 treatment and/or ASCT
	Construct	IgG4 “Reduced FC binding”	IgG1	IgG “Double Binding”	No FcyR Binding	IgG1
	Administration	IV q2W	IV q3W	IV q3W	IV Weekly	SC q28d
	Sample Size	DLBCL = 71 FL = 37	DLBCL = 119 FL = 62	DLBCL = 85 FL = 18 (fixed dosing)	DLBCL = 18 FL = 5	DLBCL = 46 FL = 12
Efficacy	**DLBCL: ORR, CR, mDoR/DoCR**	60% ORR, 60% CR mDOR 10.3 mo mDoCR 9.5 mo	35% ORR, 19% CR	49% ORR, 34% CR mDoCR NR	39% ORR, 28% CR	68% ORR, 46% CR (dose 12-60 mg)
Efficacy	**FL: ORR, CR, mDoR/DoCR**	93% ORR, 75% CR mDOR 7.7 mo mDoCR 8.1 mo	68% ORR, 50% CR mDoR 20.4 mo	67% ORR, 50% CR mDoR NR	ORR N/A, 20% CR	80% ORR, 60% CR (dose 12-48 mg)
Safety	**All CRS**	62%	28.4% (Group B) 23% (FL population)	56%	56%	59%
Safety	**Grade 3+ CRS**	7%	1.4%; 6%	2%	4%	0%

CD20 x 3 bispecific Ab (mosunetuzumab) use in post CAR T nonresponders

69 yo with double expressor DLBCL
Prior therapies: RCHOP x6 (2006), RCHOP x6 + XRT (2012), cyclophosphamide (10/2018), axi-cel

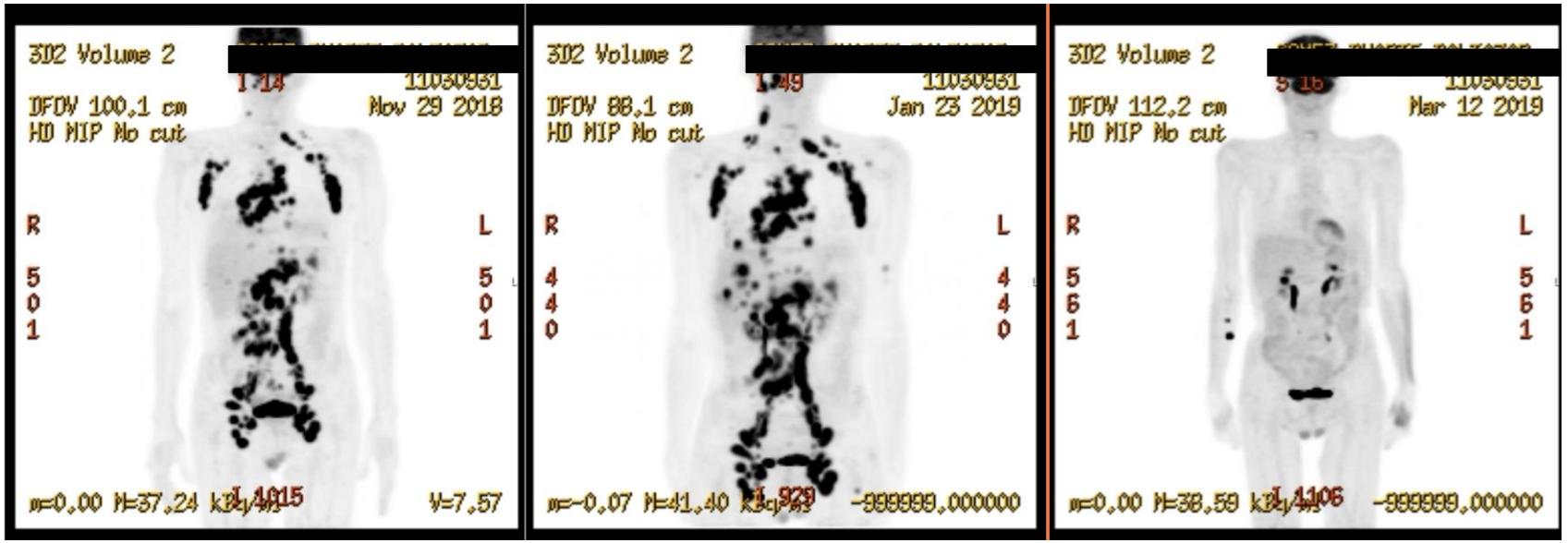
D0 Axi-cel

IRB#15391
D1C1 Mosun/TDB

Pre Axi-Cel, Day -7

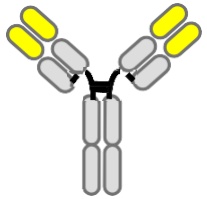
Post Axi-Cel D+38

D37 Mosun/TDB



New Kid On The Block
IgM: Next-Generation Antibody-Based Therapies

IgG

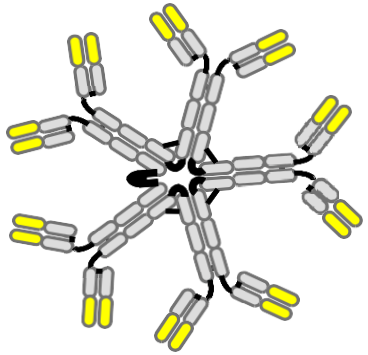


Conventional therapeutic antibodies are IgG

Limitations:

- 2 binding sites
- Difficult targets
- Rare targets
- Cross-linking receptors

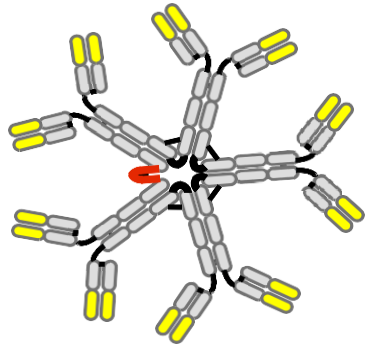
IgM



Advantages:

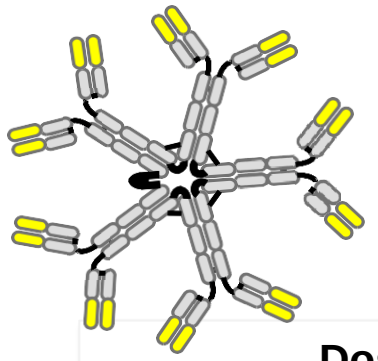
- 10 binding sites
- Binds difficult targets
- Binds rare targets
- Cross-links agonist receptors
- Joining (J) chain

Next-Generation IgMs



Breakthroughs:

- Improved:
  - Affinity & specificity
  - Half-life
- Bispecific format with:
  - Higher avidity
  - Better safety



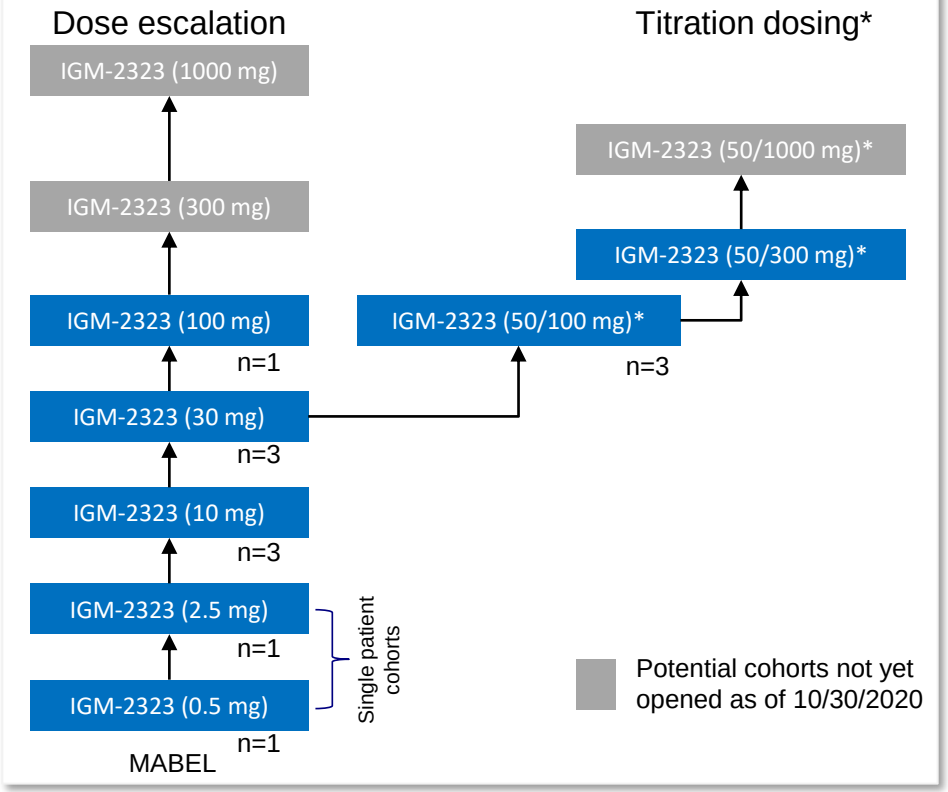
Study IGM-2323-001: Phase I study design

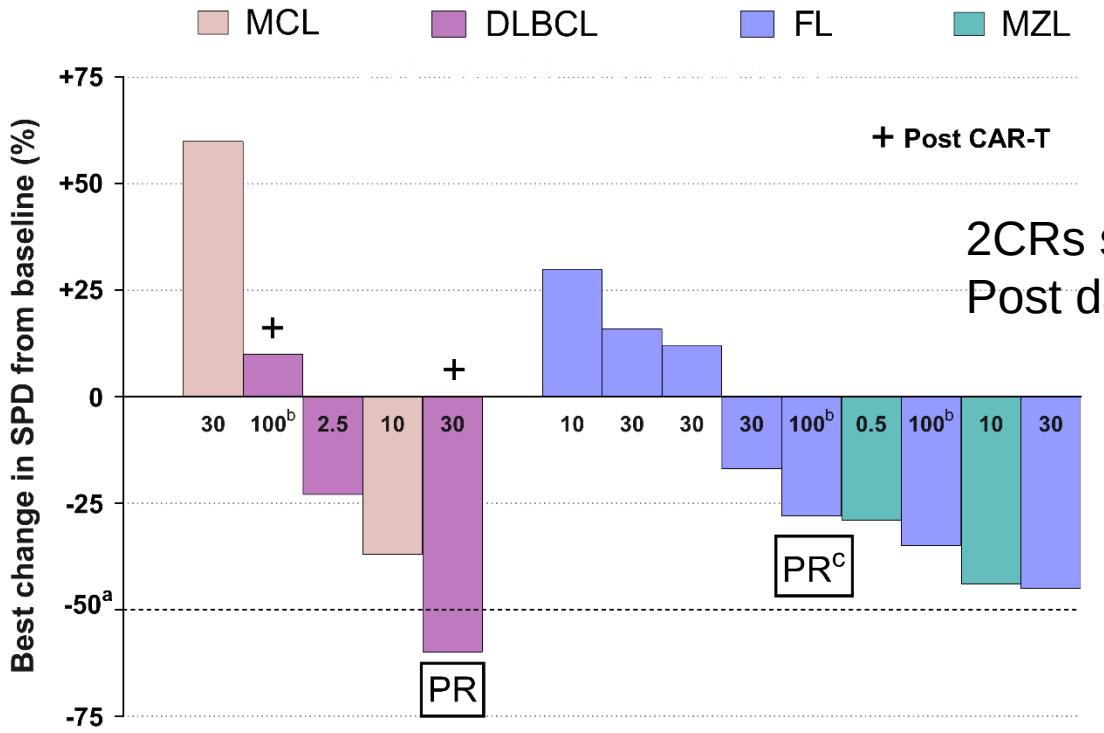
- IGM-2323 IV weekly therapy
  - (1 cycle = 21 days)

Key eligibility criteria

- CD20-positive NHL
- R/R DLBCL, FL, MCL, or MZL
- ≥2 prior lines of therapy (must have included an anti-CD20 mAb combined with an alkylating agent)
- Post CAR-T eligible if not refractory

Dose escalation phase



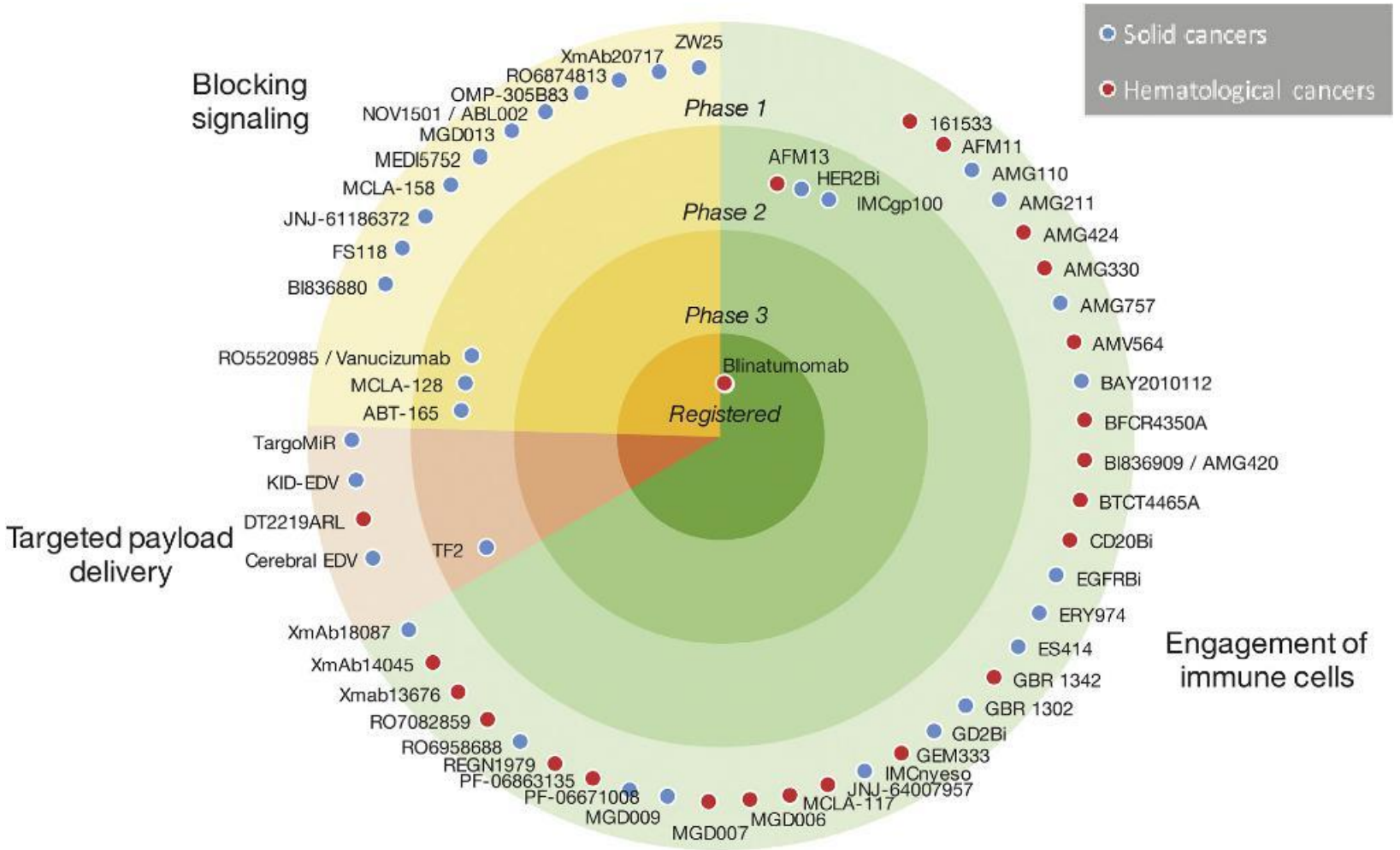


2CRs seen
Post data cut off

Data cut-off: October 30, 2020

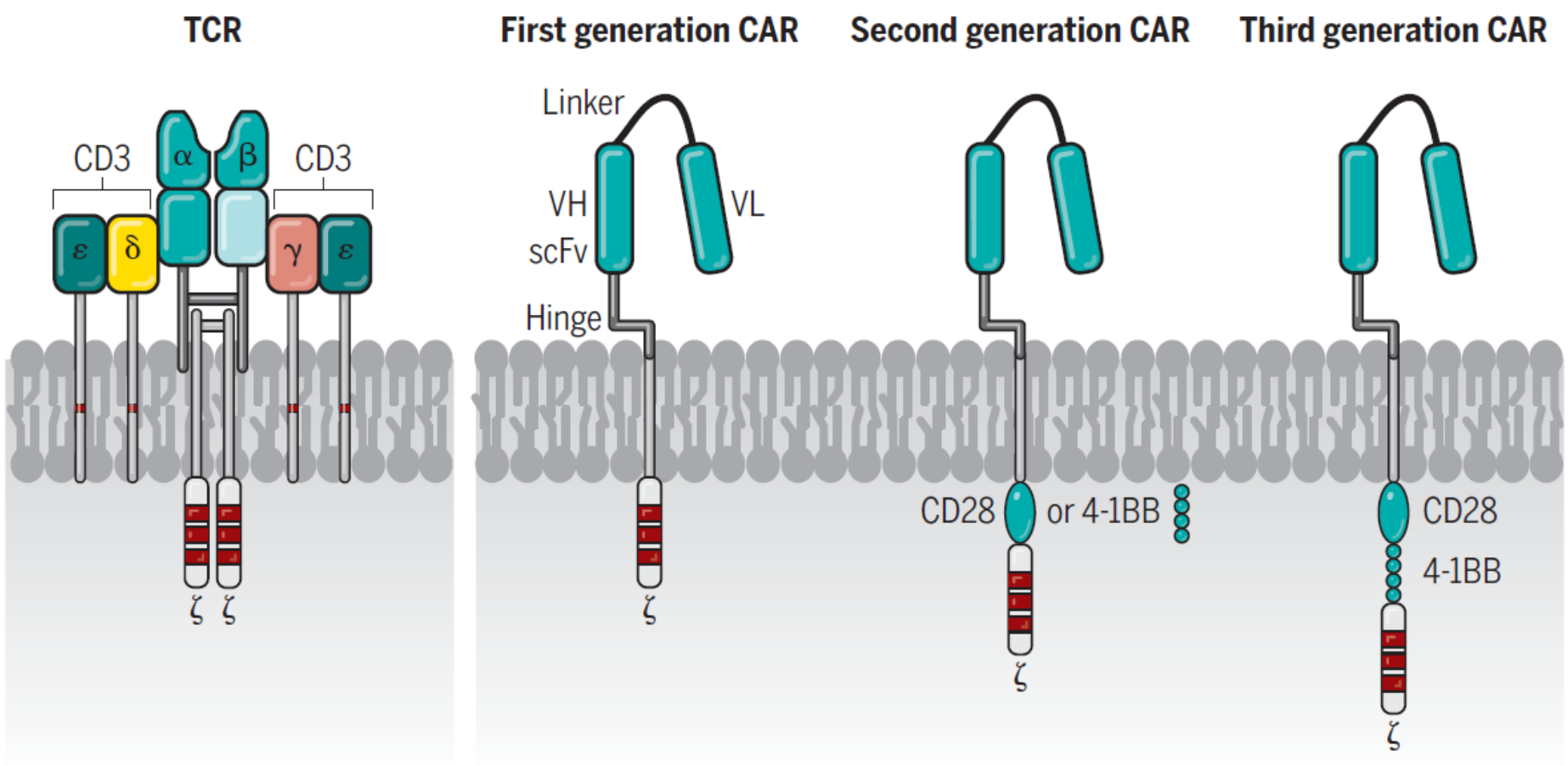
ClinicalTrials.gov Identifier: NCT04082936. CAR-T: chimeric antigen receptor T cell; DLBCL: diffuse large B-cell lymphoma; DLT: dose-limiting toxicity; FL: follicular lymphoma; IV, intravenous; mAb: monoclonal antibody; MABEL: minimally active biologic effect level; MCL: mantle cell lymphoma; MTD: maximum tolerated dose; MZL: marginal zone lymphoma; NHL: non-Hodgkin's lymphoma; PK: pharmacokinetics; QW: every week; R2PD: recommended Phase II dose; R/R: relapsed/refractory; SD: stable disease; ⁺patient has only received 50 mg dose as of the data cut-off

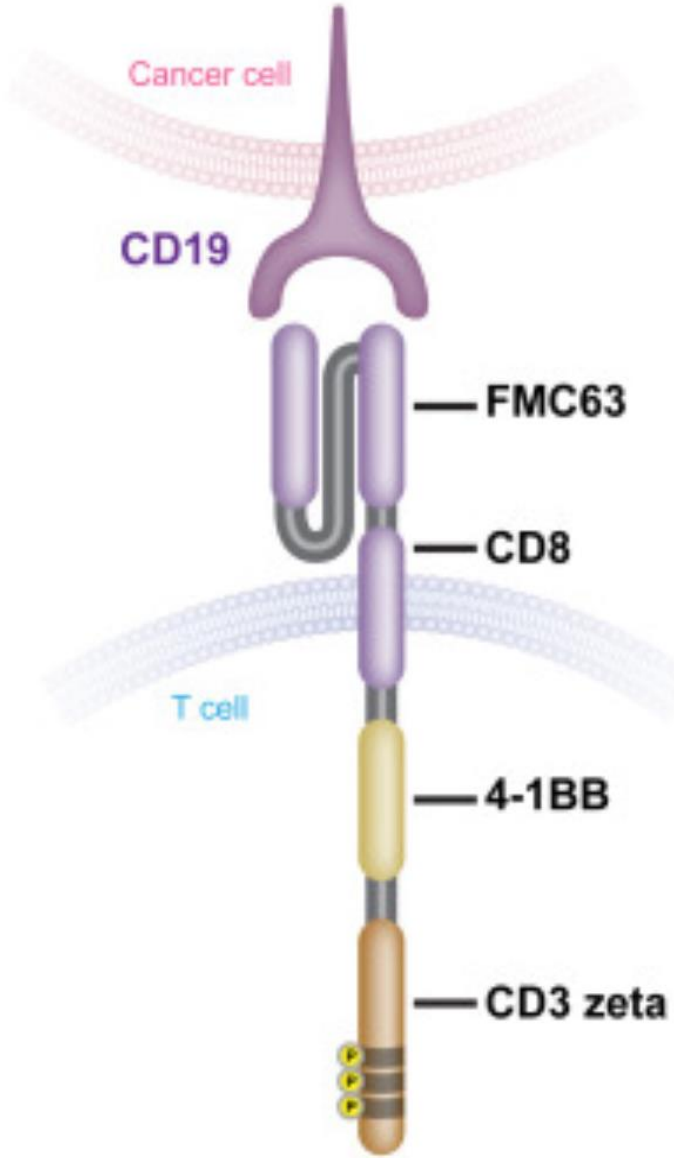
Bispecific Abs in Development

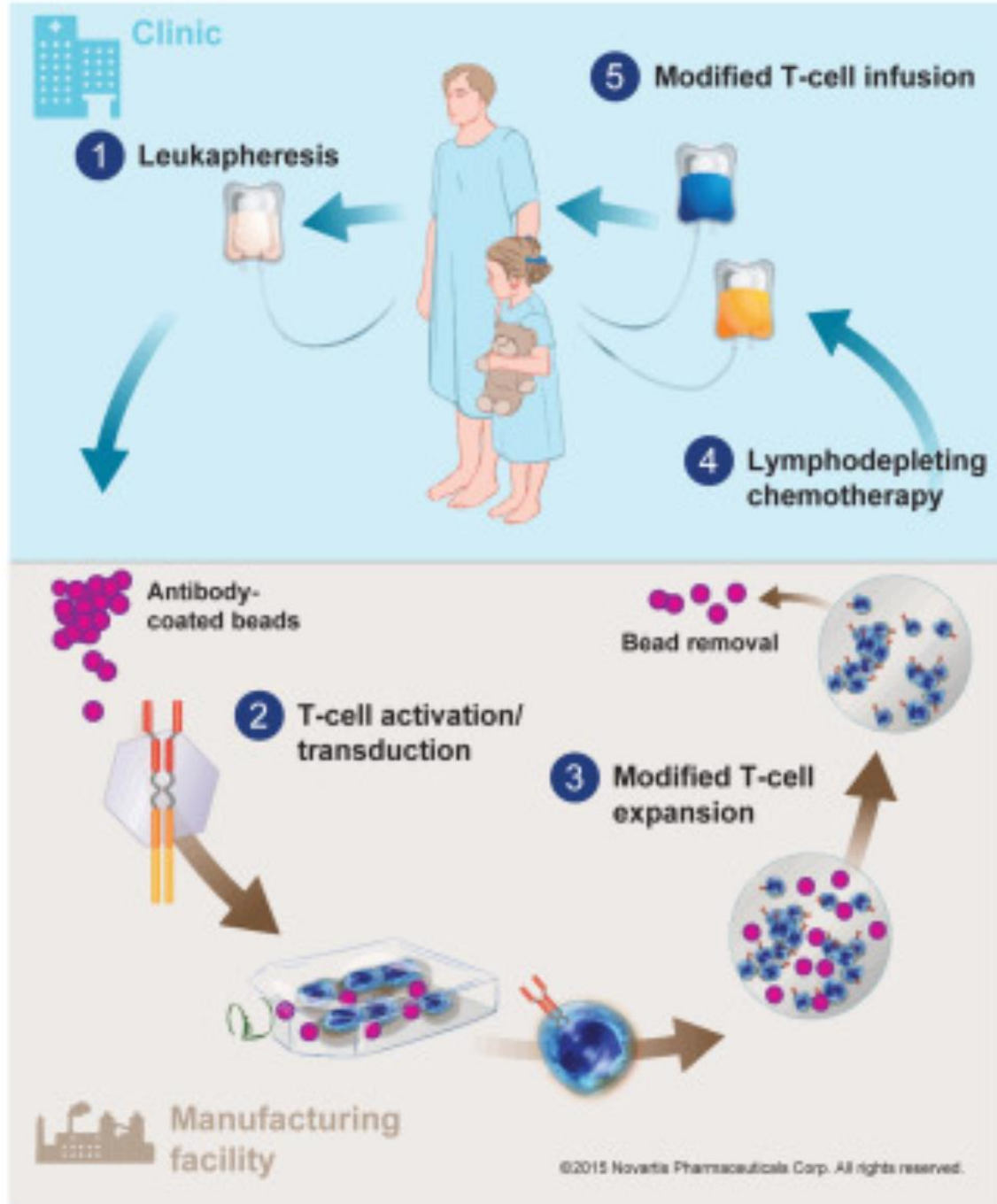


Suurs, et al. Pharmacology & Therapeutics. 2019.

Chimeric Antigen Receptor T-cell Therapy




Cancer cell
CD19
FMC63
CD8
T cell
4-1BB
CD3 zeta


Clinic
1 Leukapheresis
5 Modified T-cell infusion
4 Lymphodepleting chemotherapy
Antibody-coated beads
Bead removal
2 T-cell activation/ transduction
3 Modified T-cell expansion
Manufacturing facility
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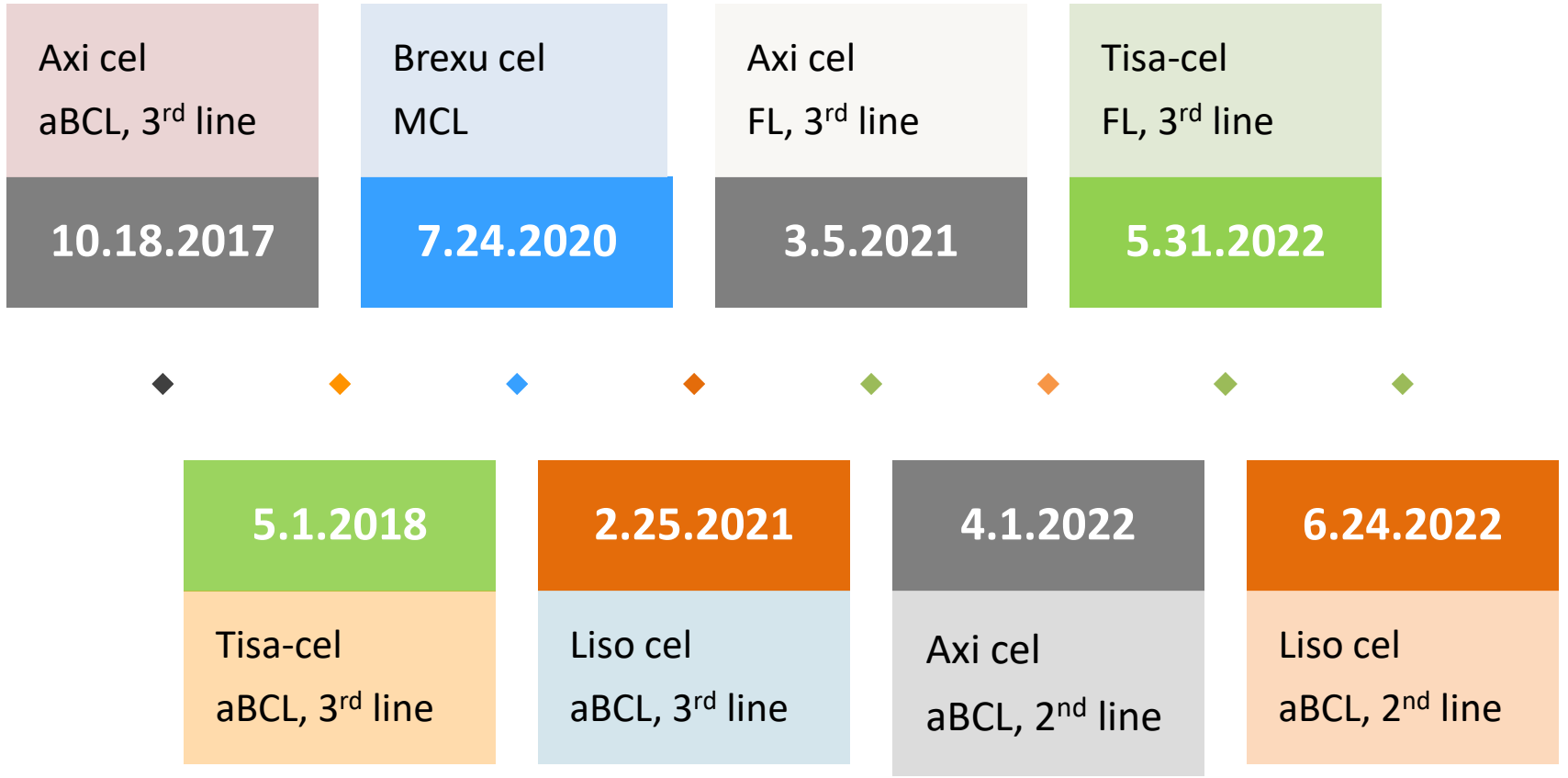
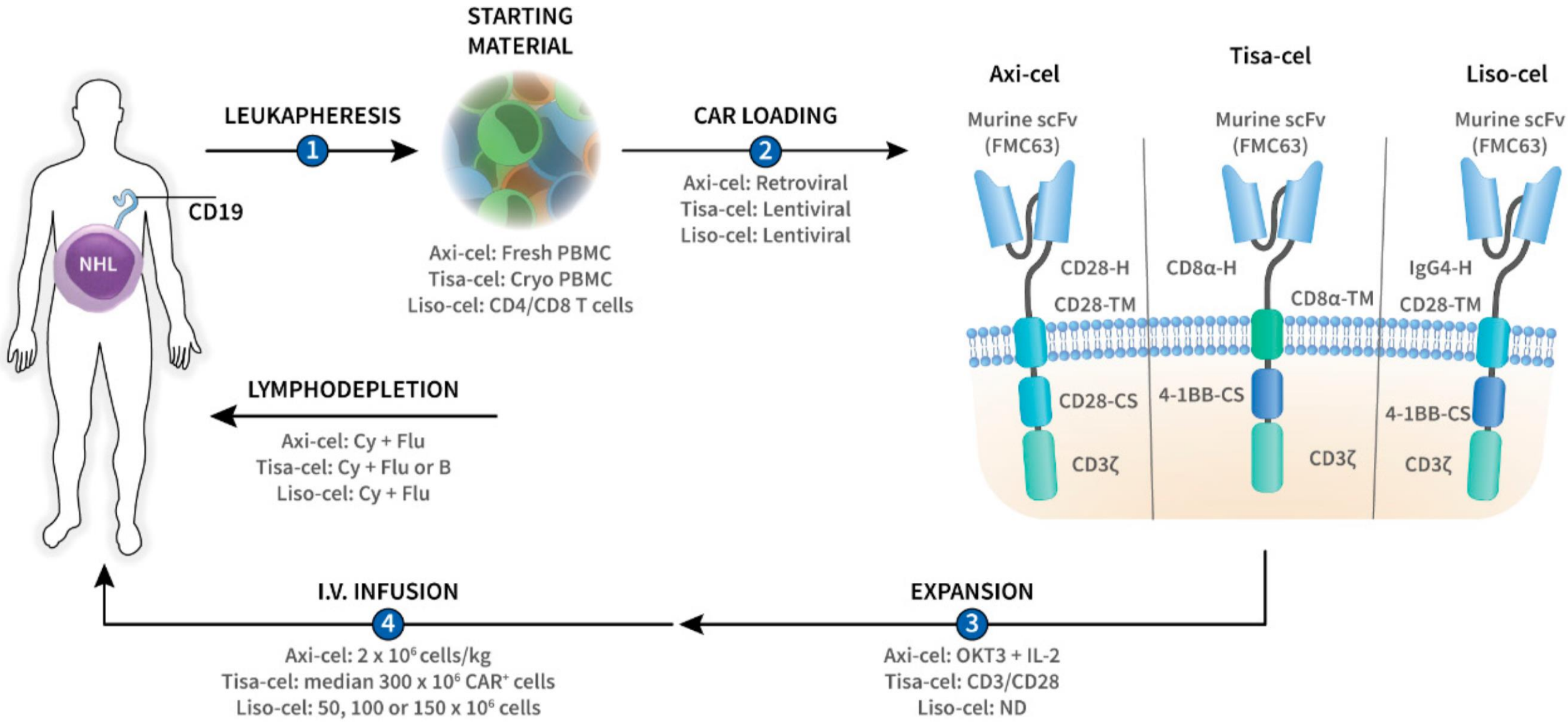
FDA Approved CAR T Cell Therapy for Lymphoma

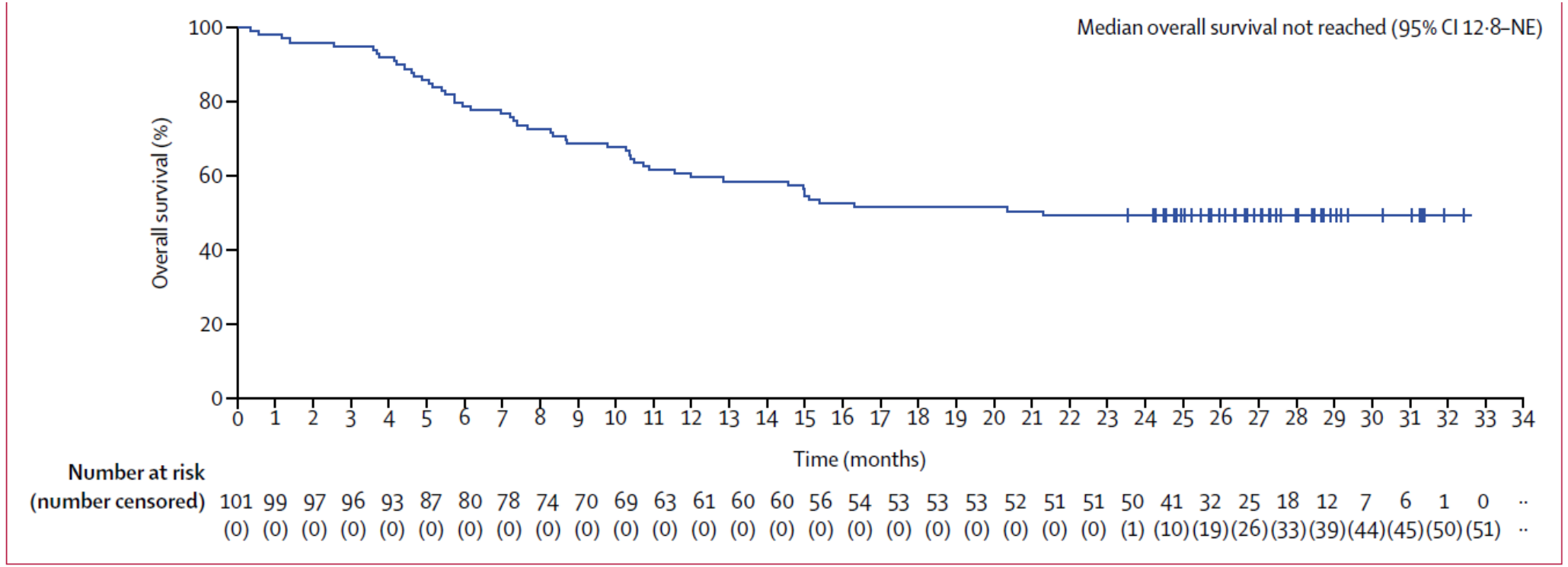


Axi cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Brexu cel: brexucabtagen autoleucel;
Liso cel: lisocabtagene maraleucel;


STARTING MATERIAL
LEUKAPHERESIS
1
CD19
NHL
Axi-cel: Fresh PBMC
Tisa-cel: Cryo PBMC
Liso-cel: CD4/CD8 T cells
CAR LOADING
2
Axi-cel: Retroviral
Tisa-cel: Lentiviral
Liso-cel: Lentiviral
Axi-cel
Tisa-cel
Liso-cel
Murine scFv (FMC63)
Murine scFv (FMC63)
Murine scFv (FMC63)
CD28-H
CD28-TM
CD28-CS
CD3ζ
CD8α-H
CD8α-TM
4-1BB-CS
CD3ζ
IgG4-H
CD28-TM
4-1BB-CS
CD3ζ
LYMPHODEPLETION
Axi-cel: Cy + Flu
Tisa-cel: Cy + Flu or B
Liso-cel: Cy + Flu
I.V. INFUSION
4
Axi-cel: 2 x 10⁶ cells/kg
Tisa-cel: median 300 x 10⁶ CAR⁺ cells
Liso-cel: 50, 100 or 150 x 10⁶ cells
EXPANSION
3
Axi-cel: OKT3 + IL-2
Tisa-cel: CD3/CD28
Liso-cel: ND

	Tisa-Cel	Axi-Cel	Liso-Cel
Trial Leading to Approval	Juliet	Zuma-1	Transcend
n	93	119	344
Target	CD19		
Disease	DLBCL, tFL	DLBCL, tFL, PMBCL	DLBCL, tLGL, FL3B
LDP	Flu+Cy or B	Flu+Cy	Flu+Cy
Bridging	No	No	Yes
ORR	64%	83%	73%
CR	52%	58%	53%
CRS	22%	11%	2%
Neurotox	12%	32%	10%
Neutropenia	NR	39%	60%
Infections	22%	28%	12%

Cart-T Cell Therapy for DLBCL

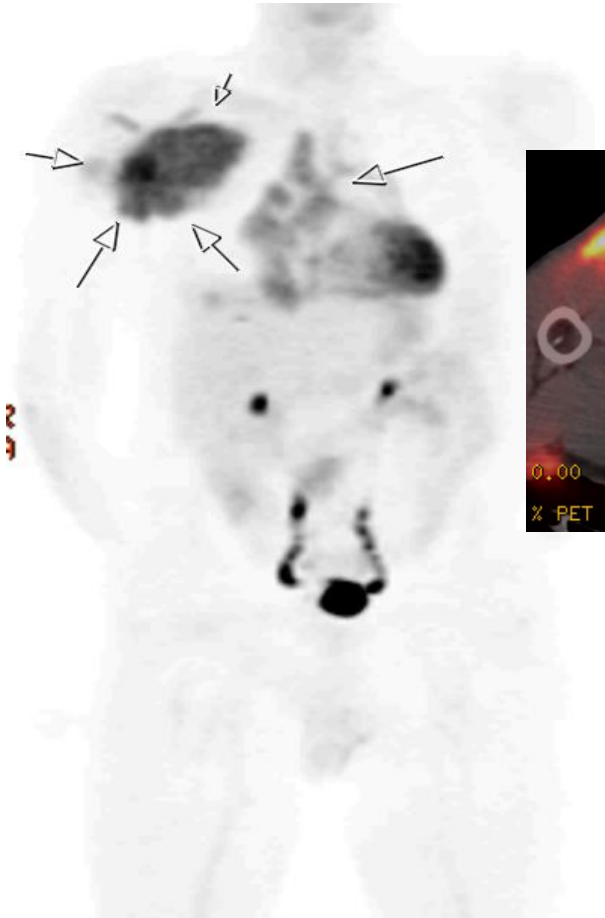


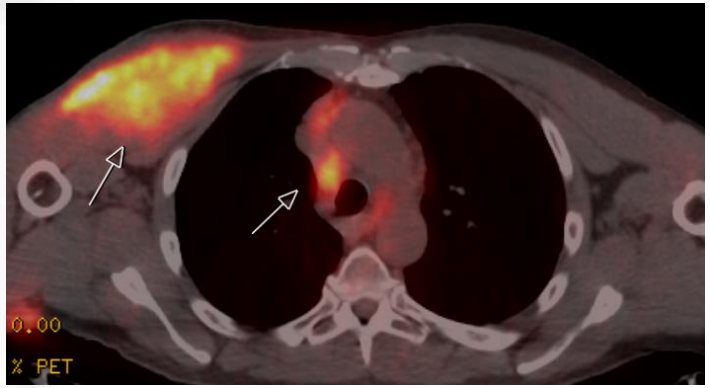
Kaplan-Meier estimates of investigator-assessed duration of response (A), progression-free survival (B), and overall survival (C)

All 101 patients assessable for activity in phase 2 are shown. The x-axis shows time since infusion of chimeric antigen receptor T cells. NE=not estimable.

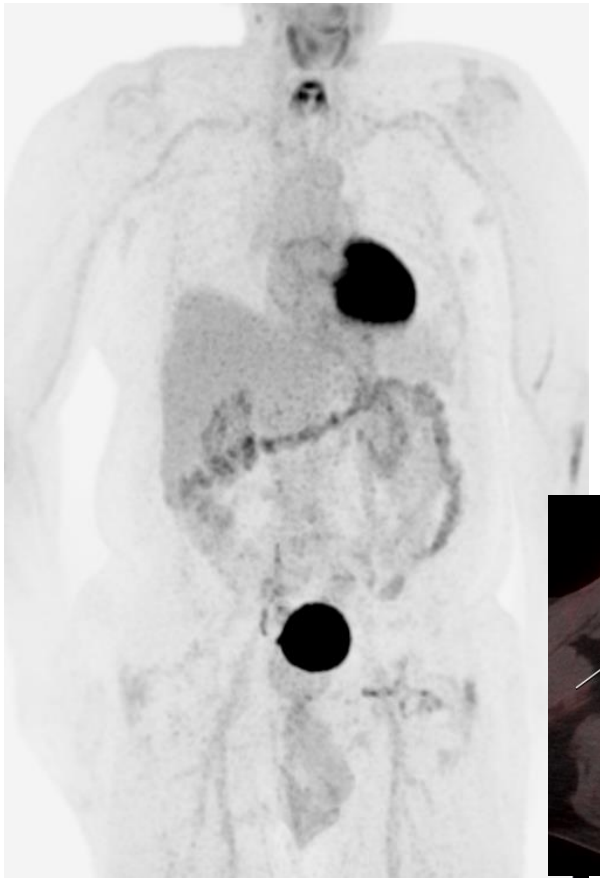
Axi-Cel CART DLBCL Patient

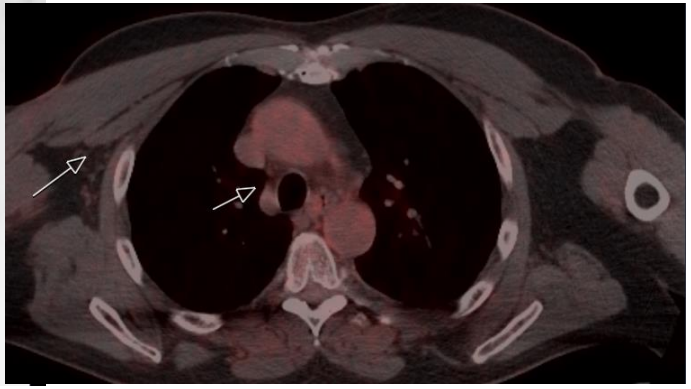
Pre-treatment





Post-treatment





~~CAR T~~ therapy in the 2nd line: CAR is better than SOC (chemo+ASCT)

Three phase 3 clinical trials

Randomized LBCL pts with no response or relapse within 12 months from the first line treatment) to either CD19CAR T or standard of care chemo followed auto transplant

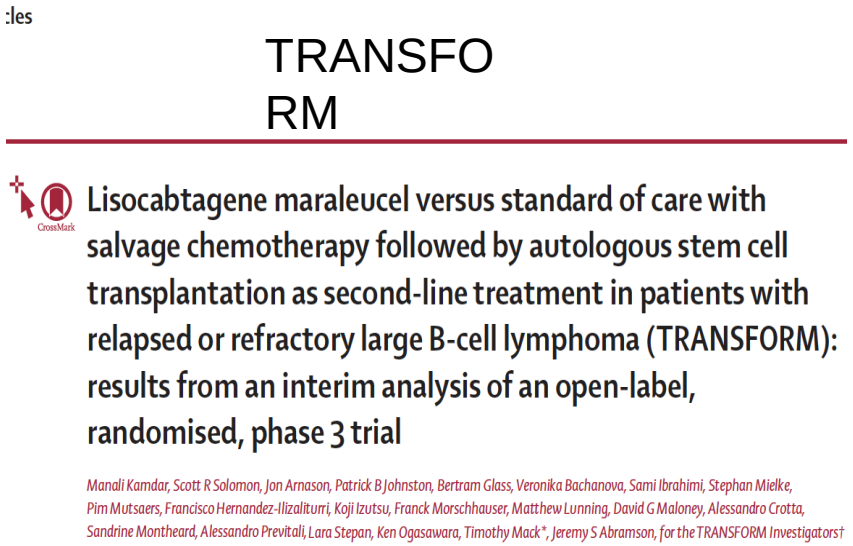

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

F.L. Locke, D.B. Miklos, C.A. Jacobson, M.-A. Perales, M.-J. Kersten, O.O. Oluwole, A. Ghobadi, A.P. Rapoport, J. McGuirk, J.M. Pagel, J. Muñoz, U. Farooq, T. van Meerten, P.M. Reagan, A. Sureda, I.W. Flinn, P. Vandenberghe, K.W. Song, M. Dickinson, M.C. Minnema, P.A. Riedell, L.A. Leslie, S. Chaganti, Y. Yang, S. Filosto, J. Shah, M. Schupp, C. To, P. Cheng, L.I. Gordon, and J.R. Westin, for All ZUMA-7 Investigators and Contributing Kite Members*

ZUMA-7


:les

TRANSFORM

Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

Manali Kamdar, Scott R Solomon, Jon Arnason, Patrick B Johnston, Bertram Glass, Veronika Bachanova, Sami Ibrahimi, Stephan Mielke, Pim Mutsaers, Francisco Hernandez-Ilizaliturri, Koji Izutsu, Franck Morschhauser, Matthew Lunning, David G Maloney, Alessandro Crotta, Sandrine Montheard, Alessandro Previtali, Lara Stepan, Ken Ogasawara, Timothy Mack*, Jeremy S Abramson, for the TRANSFORM Investigators†


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

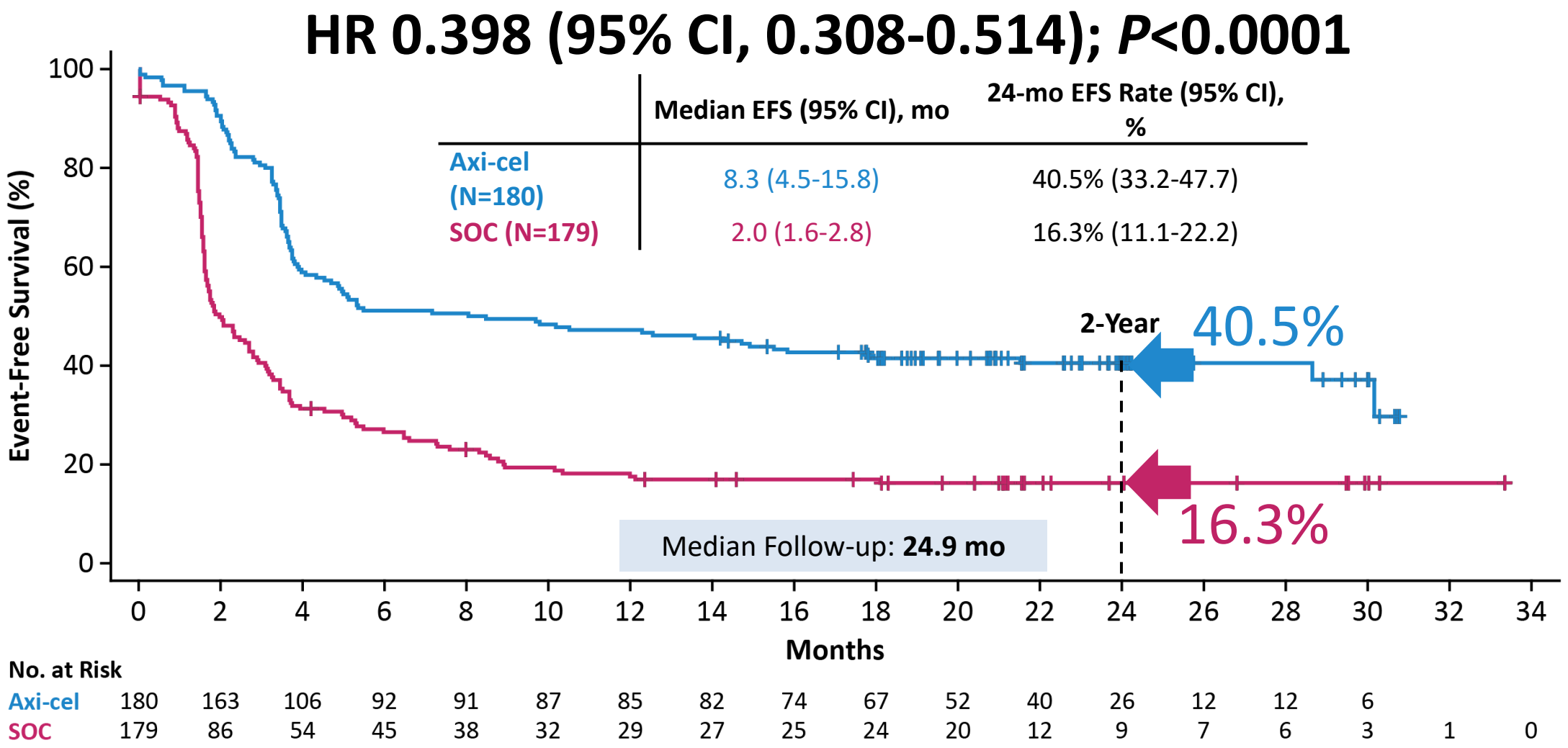
Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

M.R. Bishop, M. Dickinson, D. Purtill, P. Barba, A. Santoro, N. Hamad, K. Kato, A. Sureda, R. Greil, C. Thieblemont, F. Morschhauser, M. Janz, I. Flinn, W. Rabitsch, Y.-L. Kwong, M.J. Kersten, M.C. Minnema, H. Holte, E.H.L. Chan, J. Martinez-Lopez, A.M.S. Müller, R.T. Maziarz, J.P. McGuirk, E. Bachy, S. Le Gouill, M. Dreyling, H. Harigae, D. Bond, C. Andreadis, P. McSweeney, M. Kharfan-Dabaja, S. Newsome, E. Degtyarev, R. Awasthi, C. del Corral, G. Andreola, A. Masood, S.J. Schuster, U. Jäger, P. Borchmann, and J.R. Westin

BELINDA

Locke et al. NEJM 2021; Bishop et al. NEJM 2021; Kamda et. al. Lancet 2021

Primary EFS Endpoint: Axi-Cel Is Superior to SOC

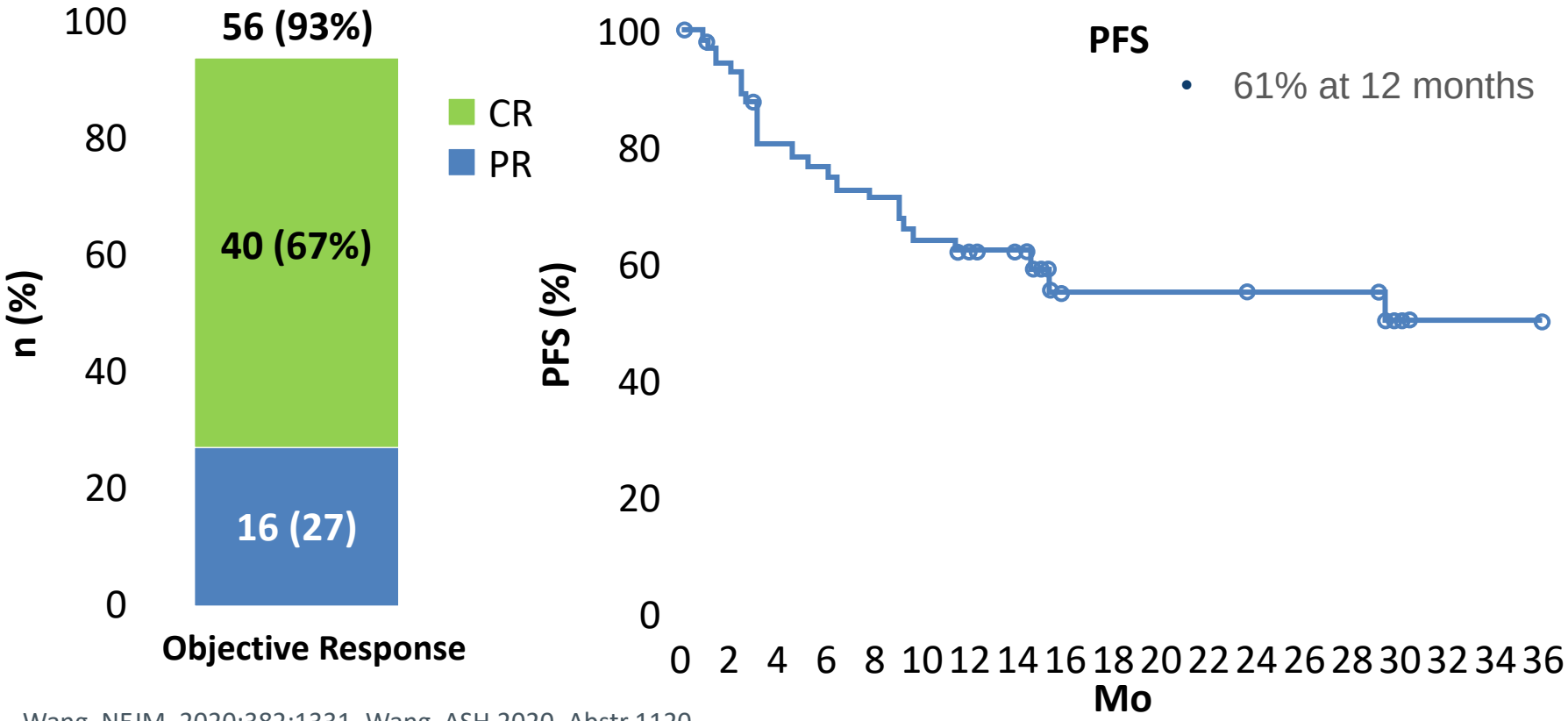


Locke F et al., NEJM 2021

ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Relapsed/Refractory MCL

Multicenter, single-arm, open-label phase II trial of brexucabtagene autoleucel for adults with relapsed/refractory mantle cell lymphoma (N = 74 enrolled, 68 received agent)

After failure of BTKi and up to 5 prior therapies; bridging steroid ± BTKi permitted (37%)



- CRS grade ≥ 3: 15%
- Neurotoxicity grade ≥ 3: 31%
- Tocilizumab: 59%
- 1 gr 4 cerebral edema
- 2 gr 5 events (PNA and infection)

Wang. NEJM. 2020;382:1331. Wang. ASH 2020. Abstr 1120.

CART-T Cell Therapy for R/R Follicular Lymphomas (Zuma-5)

- ORR – 93%
- CR – 80%
- Median DOR – 20.8 months
- Median PFS – 23.5 months
- 12-month OS – 93.4%

CAR T Cell Therapy: Complications

Commonly reported important adverse events

- On target off tumor effects, i.e. B cell aplasia (CD19CAR)
- Lymphodepletion chemo-related toxicity
- Tumor lysis syndrome
- Macrophage activation syndrome (HLH/MAS)
- Coagulopathy
- Cytokine release syndrome
- Neurotoxicity
- Infection

Cytokine Release Syndrome (CRS)

Findings: fever, hypoxemia, hypotension, electrolyte abnormalities, cytopenias, elevated inflammatory markers, coagulopathy

Treatment:
Supportive care
Tocilizumab (IL-6 receptor blocker)
Corticosteroids

Neurotoxicity (ICANS)

- Not fully understood
- Systemic inflammation and circulating cytokines result in endothelial cell activation, disruption of the blood-brain barrier, leading to an inflammatory cascade in the CNS
- Findings: headache, confusion, tremor, progressive encephalopathy, dysgraphia, seizures, cerebral edema, coma
- Treatment: corticosteroids

CAR T-cell therapy and bispecific antibodies for R/R DLBCL

	CAR T-Cell Therapy			Bispecifics			
	Axi-cel (Gilead/Kite)	**Tisa-cel** (Novartis)	**Liso-cel** (BMS)	**Glofitamab** (Roche)	**Odronextamab** (Regeneron)	**Mosunetuzumab** (Roche/Genentech)	**Epcoritamab** (AbbVie/Genmab)
Patient Population	R/R DLBCL patients after ≥ 2 prior therapies	R/R DLBCL patients after ≥ 2 prior therapies	R/R large B-cell lymphoma patients after ≥ 2 prior therapies	R/R aggressive NHL patients after ≥ 1 prior therapies	R/R aggressive DLBCL patients after ≥ 2 prior therapies	R/R NHL patients with at least 2 prior therapies	R/R DLBCL and aggressive NHL patients after anti-CD20 treatment and/or ASCT
Trial, Phase (P)	NCT02348216 ZUMA-1, P1/2	NCT02445248 JULIET, P2	NCT02631044 TRANSCEND NHL-001, P1	NCT03075696 NP30179, P1	NCT02290951, P1	NCT02500407 GO29781, P1/1b	NCT03625037 P1/2
Efficacy	CR: 51% ORR: 72% mDOR: 9.2 mo	CR: 32% ORR: 50% mDOR not reached at 1 4 mo	54% CR 73% ORR mDOR: 16.7 mo	CR: 34% ORR: 49%	CR: 60% ORR: 60%	CR: 19% ORR: 35%	CR: 68% ORR: 46% (dose:12-60 mg)
Safety (Severe AEs)	CRS: 94% (13% grade 3+) Neutropenia: 31%	CRS: 74% (grade 3+:23%) Grade 3+ Neutropenia: 17%	CRS: 46% (grade 3+: 4%) Grade 3+ Neutropenia: 76%	CRS: 56.4% Neutropenia: 30.8%	CRS: 62.2% (7.1% grade 3+) Gr 3 neurologic AEs : 4%	CRS: 28.4% (Total population in Group B of study)	CRS: 59% (Total population); no Grade ≥ 3 CRS events

FDA Approved Therapies

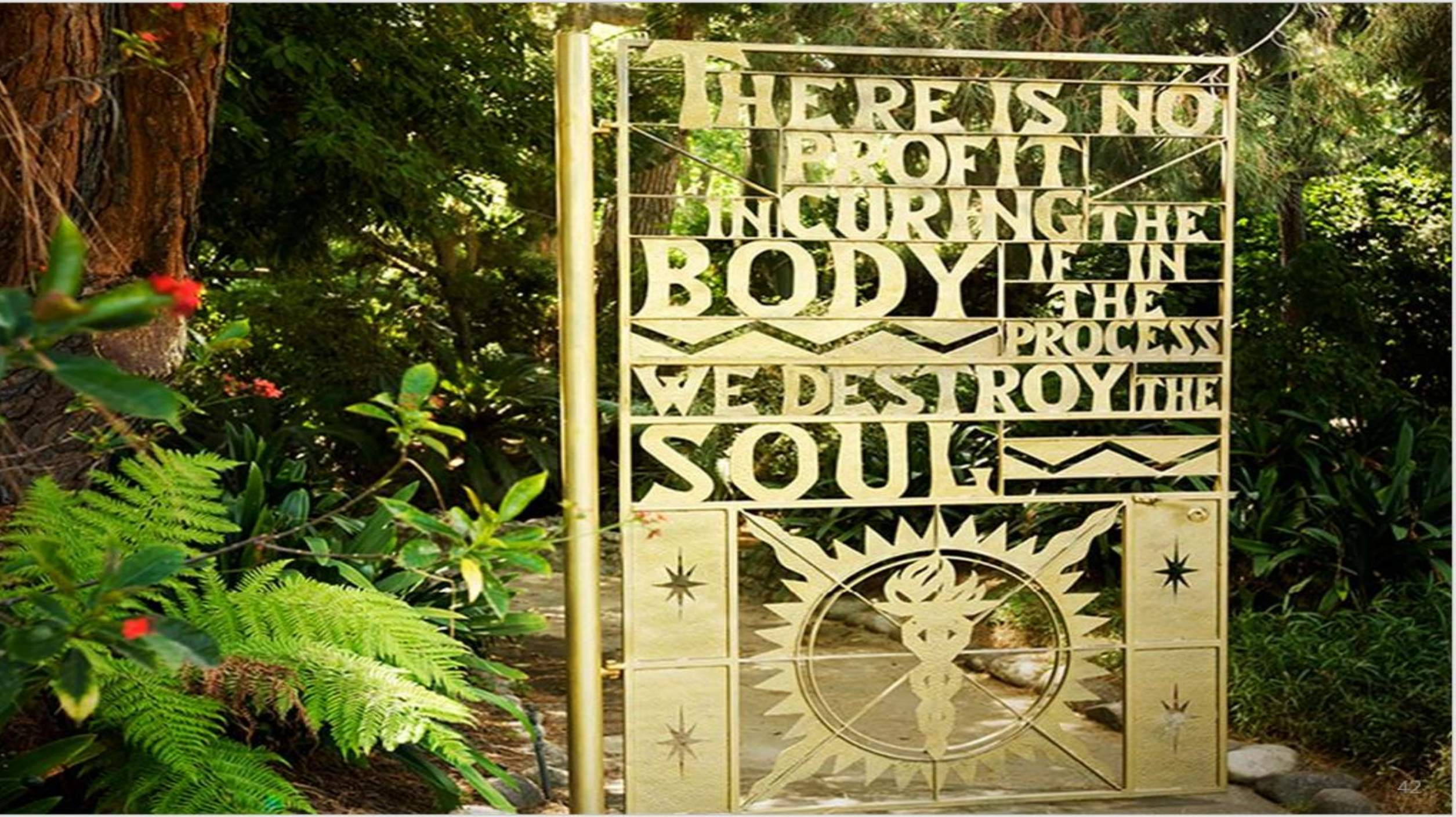
Investigational

Summary

- Bispecific antibodies against CD20 show promise in B cell lymphomas but have not yet been FDA approved
- CAR T cell therapy is an efficacious treatment strategy for B cell lymphomas that otherwise have very poor prognosis
- CAR T therapy is associated with predictable and treatable toxicities

Future Directions

- Bispecific Antibodies/CAR-T Cell Therapies in earlier lines of therapy
- Bispecific Antibodies/CAR-T Cell Therapies in combination with other treatments
- Bispecific Antibodies/CAR-T Cell Therapies targeting a broader spectrum of antigens
- Allogeneic CAR-T Cell Therapies
- CAR - Natural Killer (NK) Cell Therapies


THERE IS NO
PROFIT
IN CURING THE
BODY IF IN
THE
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WE DESTROY THE
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