癌症標靶治療藥物
Bispecific antibodies
（單株抗體發展史與臨床應用）

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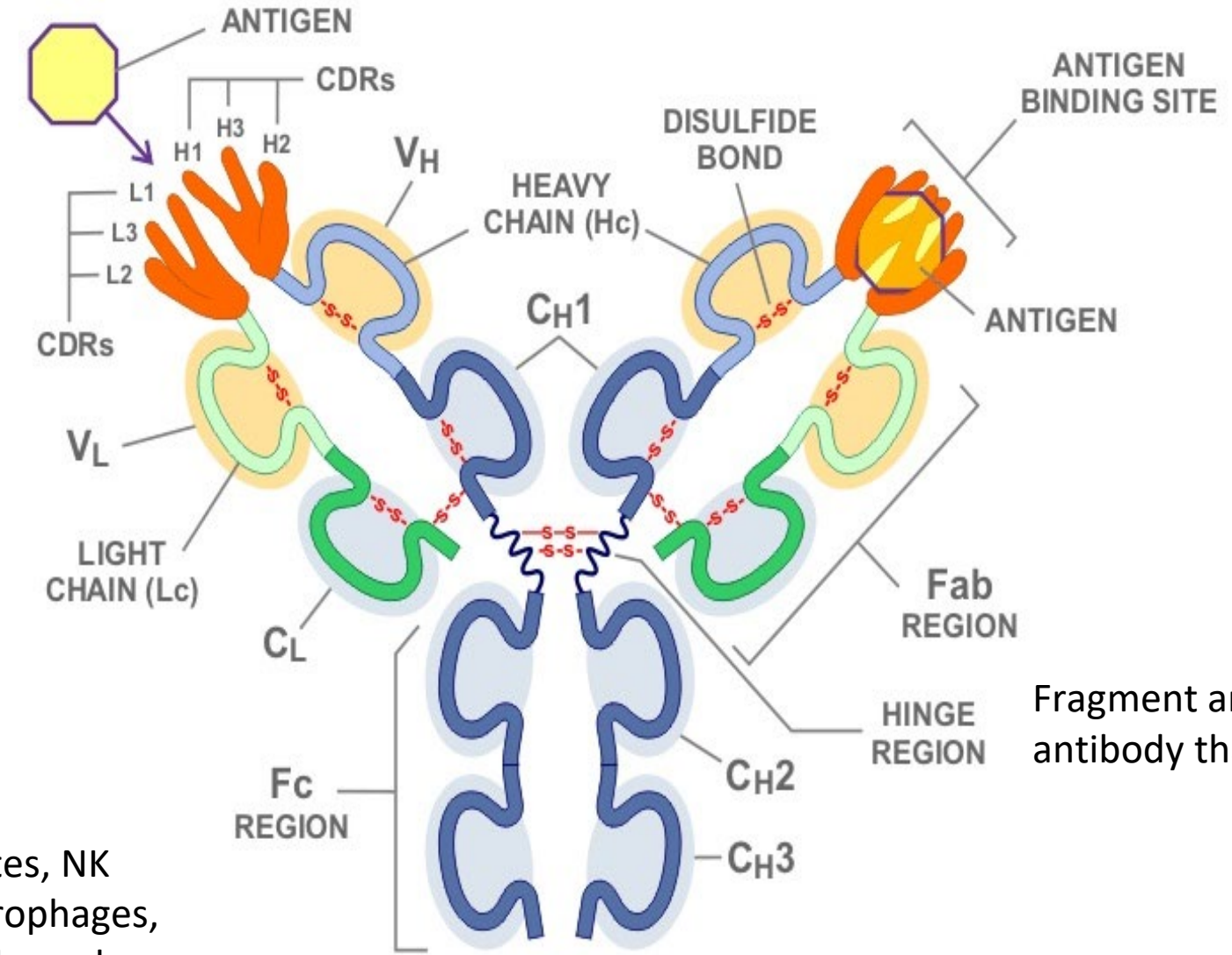
大綱

- 標靶治療誕生： 在1975年，柯勒(Kohler)與麥爾斯坦(Milstein)將B細胞與骨髓瘤細胞(myeloma cells)成功地合成融合瘤細胞，這劃時代的創舉，便開啟了應用單株抗體的新紀元。
- 單株抗體開啟在癌症與免疫治療的新紀元
- 單株抗體的藥物命名
- 單株抗體的演化
  - 單株抗體變型
  - 雙特異性抗體 (bispecific T-cell Enganger,BiTE)-> Bispecific antibody
  - 抗體藥物複合體(antibody-drug conjugate, ADC)
  - 三功能性抗體(Trifunctional Antibody)
- 單株抗體在癌症的應用歷史與療效
  - Anti-HER2 inhibitor： Pertuzumab, Trastuzumab
  - Anti-CD20 inhibitors : Rituximab/ CD20, Obinutuzumab CD20, Ofatumumab CD20
  - VEGF inhibitors : Bevacizumab

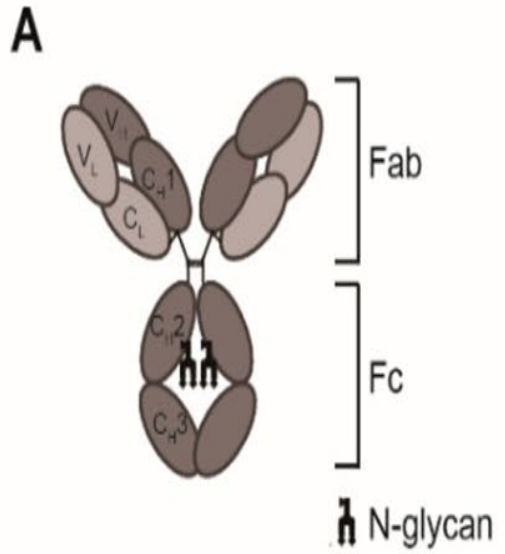
Complementarity determining regions (CDRs 互補決定區)

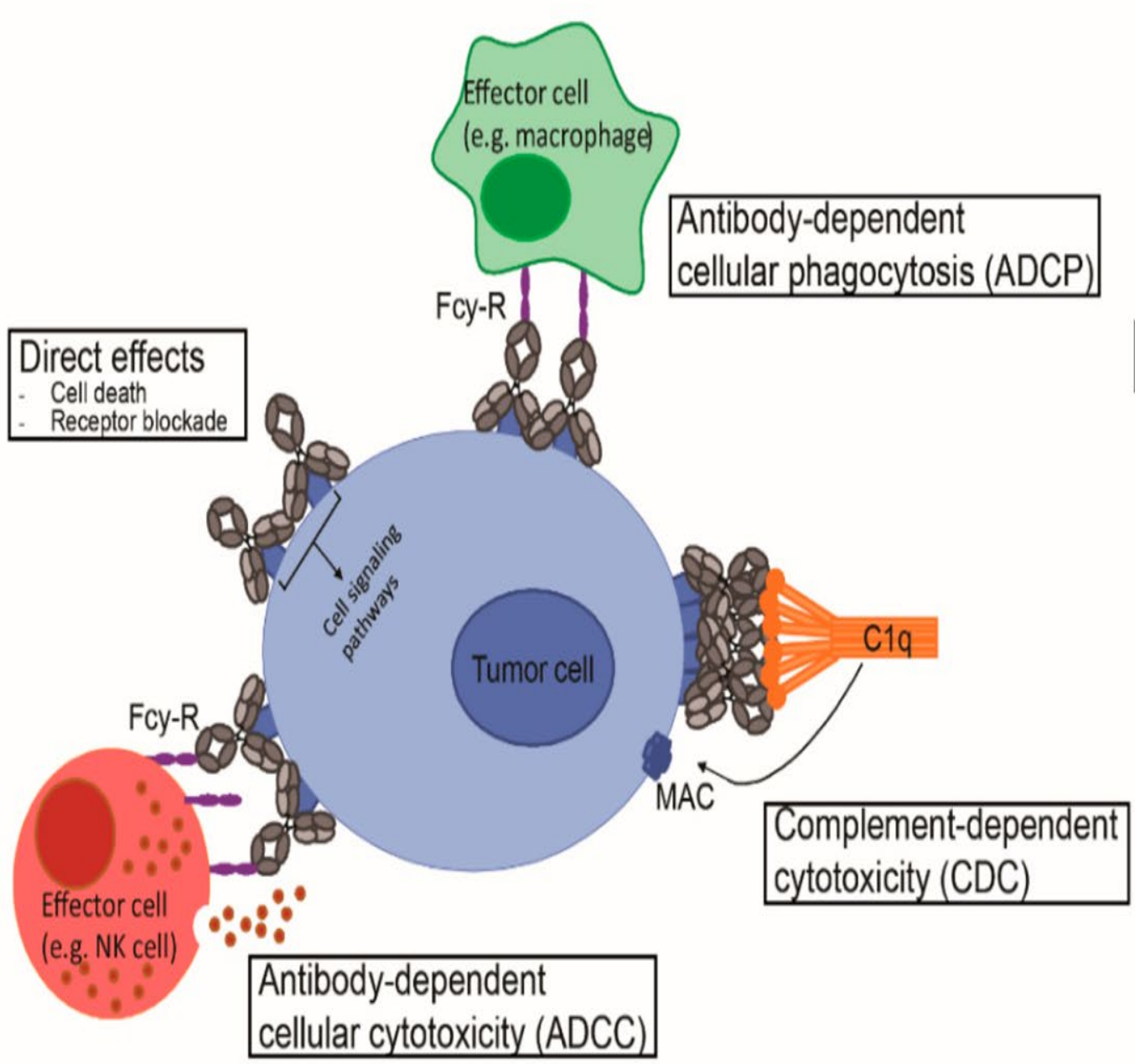


Fragment antigen-binding (Fab) is a region on an antibody that binds to antigens

FcR: B lymphocytes, NK cells, macrophages, neutrophils, and mast cells.

Fc domain





Function of Fc receptor

macrophages and monocytes, neutrophils, eosinophils and lymphocytes of the innate immune system (natural killer cells) or adaptive immune system (e.g., B cells). Activation of phagocytes is the most common function attributed to Fc receptors.

The birth of monoclonal antibodies : hybridoma

César Milstein and Georges Köhler together in 1984, the year they were awarded the Nobel Prize in physiology or medicine, jointly with Niels Jerne. Photo reproduced courtesy of the Celia Milstein and the MRC Laboratory of Molecular Biology, Cambridge, UK.

1975, Nature published a three page report by César Milstein and Georges J. F. Köhler describing a method for generating large amounts of monoclonal antibodies of a predefined specificity.

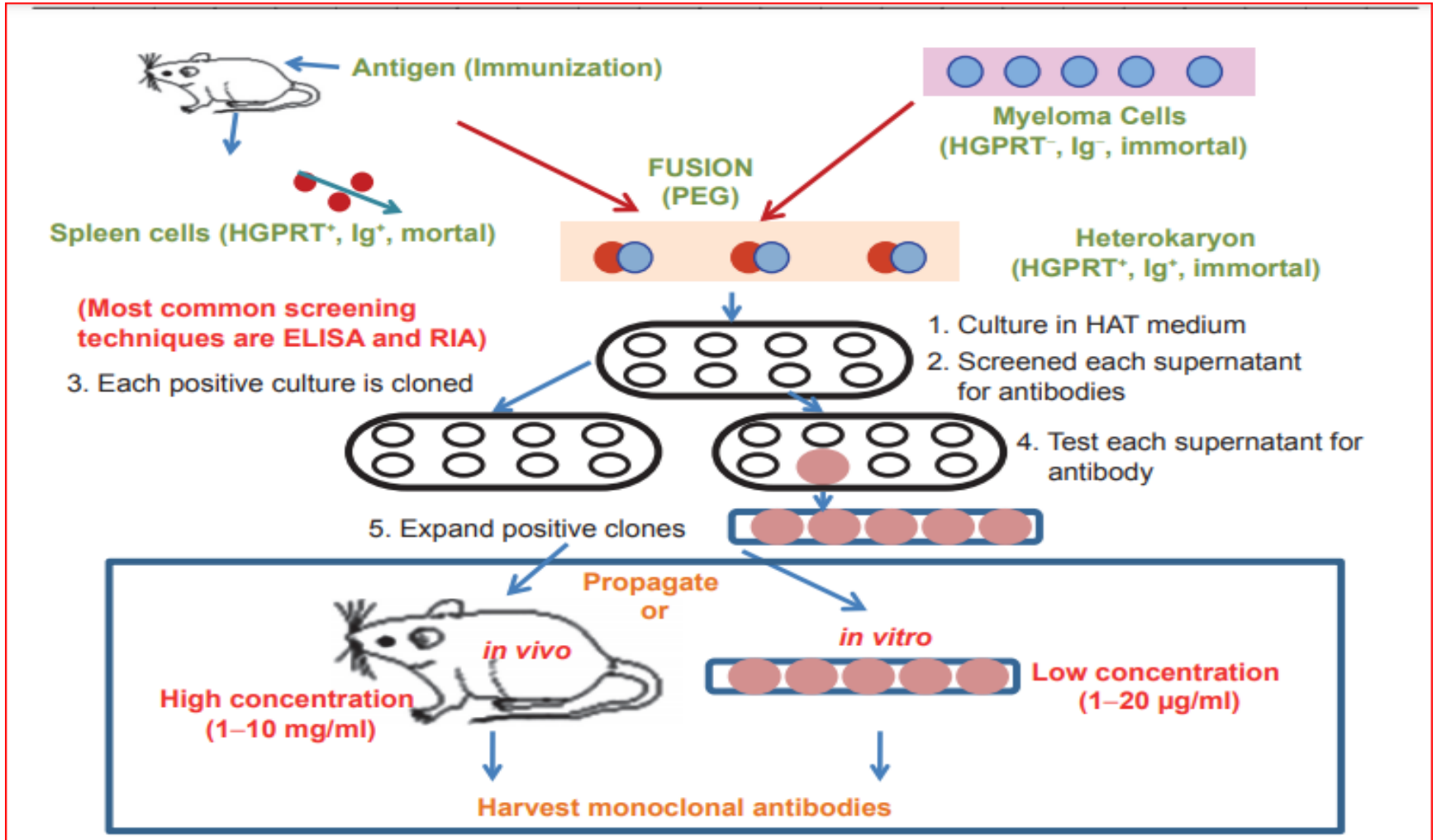
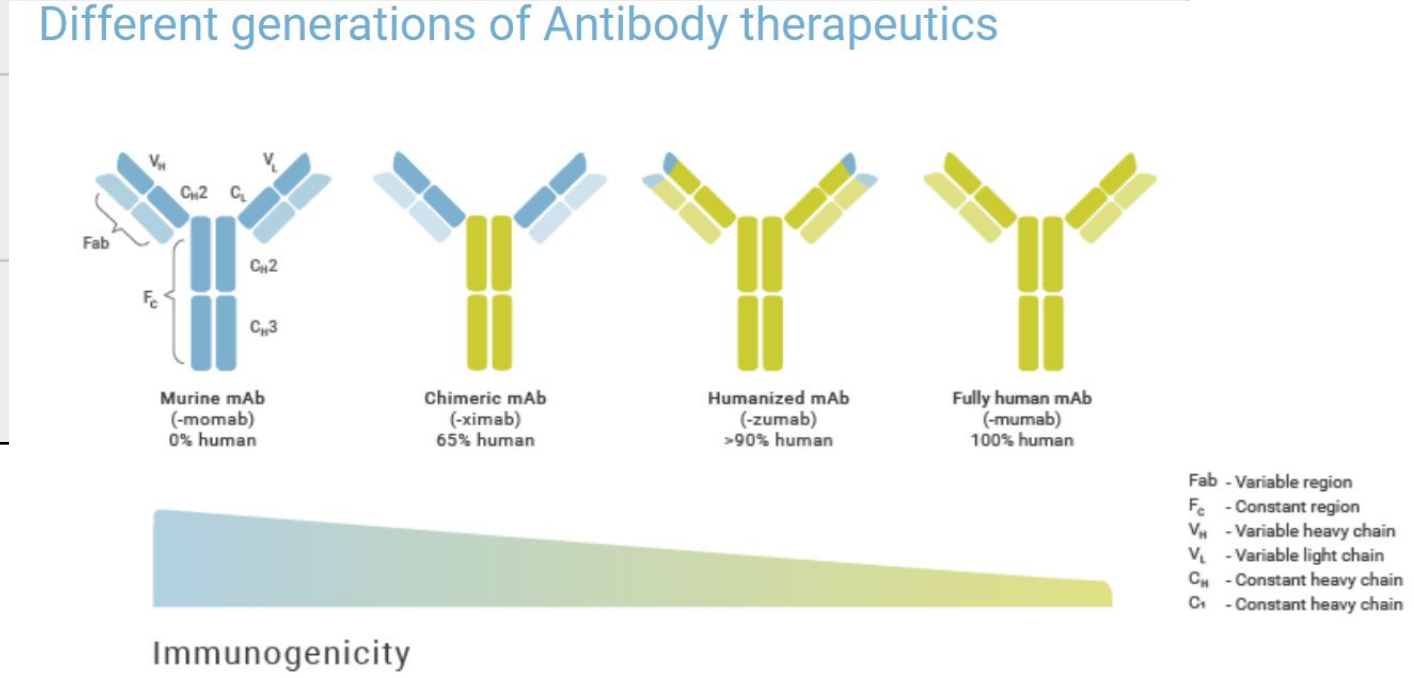


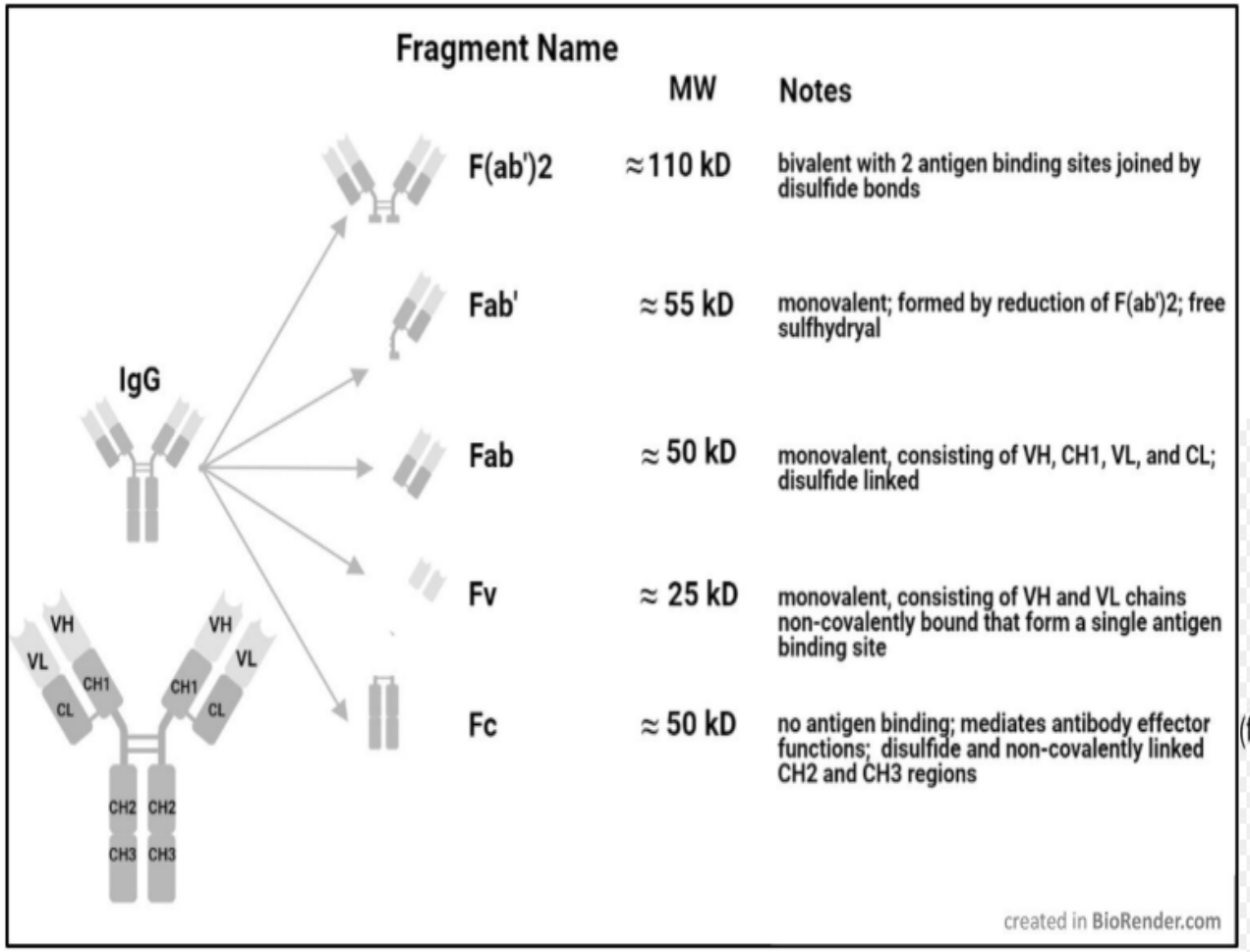
Figure 1. Production of monoclonal antibody by hybridoma technology. The hybridoma technology outline involves the isolation of spleen cells from immunized mice, their fusion with immortal myeloma cells and the production and further propagation of monoclonal antibodies from the hybrid cells.[2]

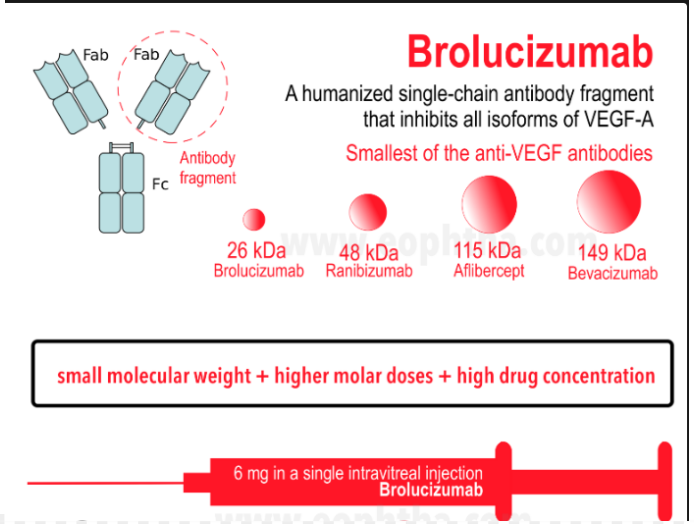
Indian Journal of Clinical Medicine 2013:4 9–21

Monoclonal antibodies (單株抗體)會以人源化的程度與靶點來命名	
人源化程度	
-xi-	嵌合
-tuxi-	嵌合-人源化腫瘤（rituximab（CD20),cetuximab）
-zu- atezolizumab	人源化
-u- Ramucirumab	全人類

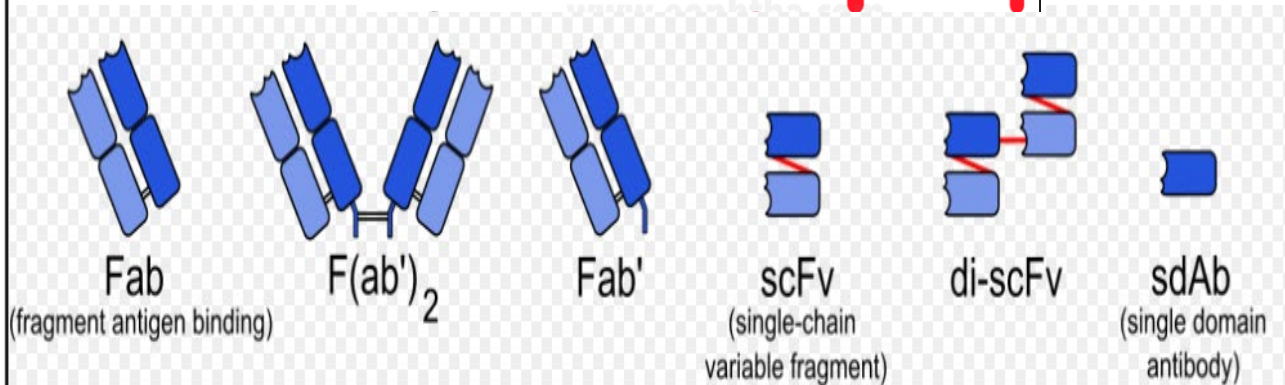


標靶點	
-b/ba/bac	細菌感染 ibalizumab (HIV) , Raxibacumab (anthrax)
-am(i)	Serum amyloidosis protein
-ci/c-	心血管, 全身循環 Alirocumab (降血脂, 全人) Idarucizumab (reversal of dabigatran), bevacizumab, caplacizumab (anti-Von willebrand factor), Ramucirumab
-f(u)/fung-	真菌感染
-gros-	Skeletal muscle mass related growth factor/receptor
-ki-	白介素 canakinumab (interleukin 1), Guselkumab (intreleukin-23治療乾癬), Ixekizumab (interleukin 17A) , Risankizumab (interleukin-23), Secukinumab (interleukin 17A) : ankylosing spondylitis, psoriasis),Tildrakizumab (interleukin-23), Ustekinumab (interleukin 12 and interleukin 23, psoriatic arthritis)
-le/les-	炎症病變 : alemtuzumab (CD52 B, T cells CELL)
-li/l-	免疫調解 : adalimumab (TMF), basilixumab, Belimumab, Brodalumab (IL-17receptor), daclizumab (interleukine 2) , Dupilumab (interleukin-4)receptor , Eculizumab (complement inhibitor), Golimumab (TNF), infliximab (TNF), Lanadelumab (kallikrein),Ocrelizumab (CD20), Ravulizumab (complement inhibitor), Sarilumab (interleukin 6 receptor), Vedolizumab (selective adhesion-molecule), nivolumab, pembrolizumab, atezolizumab, cemiplimab, Durvalumab, Ipilimumab,
-ne/n-	神經系統
-so/os/s	骨科 : Denosumab,
-tox/toxa-	毒素 Bezlotoxumab (clostridioides), Obiltoxaximab (anthrax) 解毒劑
-tu/t-	腫瘤 rituximab (CD20),cetuximab (EGFR), ofatumumab, teprotumumab (thyroid Ca), blinatumomab (CD/19/CD3), daratumumab (CD38), Elotuzumab (SLAM-7), Dinutuximab (GD2), Gemtuzumab, ibrutumomab (CD20-zevalin Y-90), Inotuzumab (CD22), Sacituzumab (Trop-2)
-vi/v-	病毒 palivizumab (RSV), REGEN-COV (Casirivimab/imdevimab)
例外	Ranibizumab (AMD) 相關性黃斑部退化 (age related macular degeneration, AMD

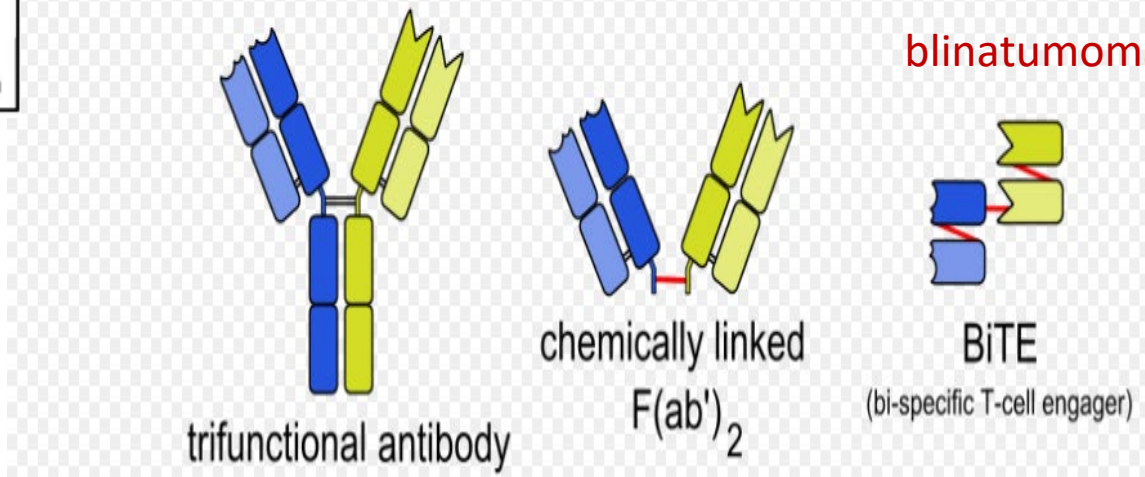




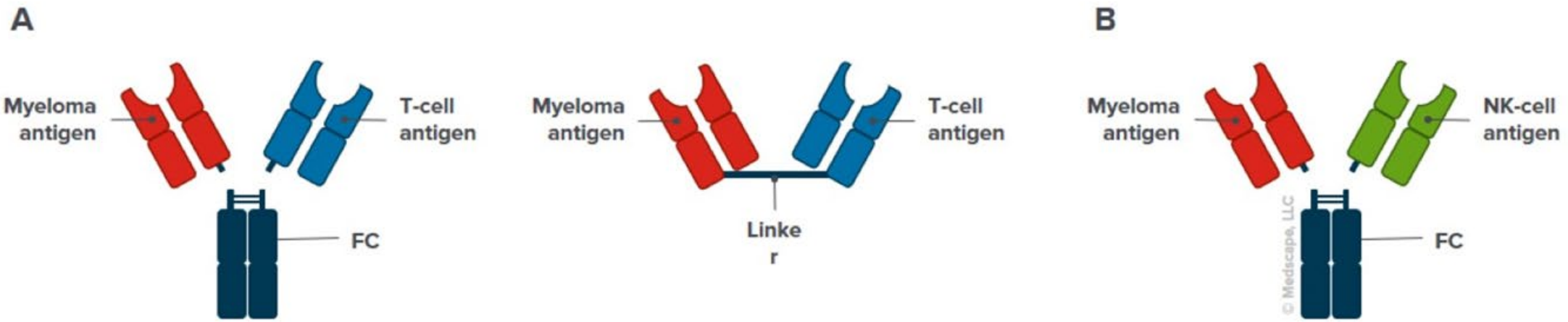
Brolucizumab



blinatumomab



Bispecific antibodies

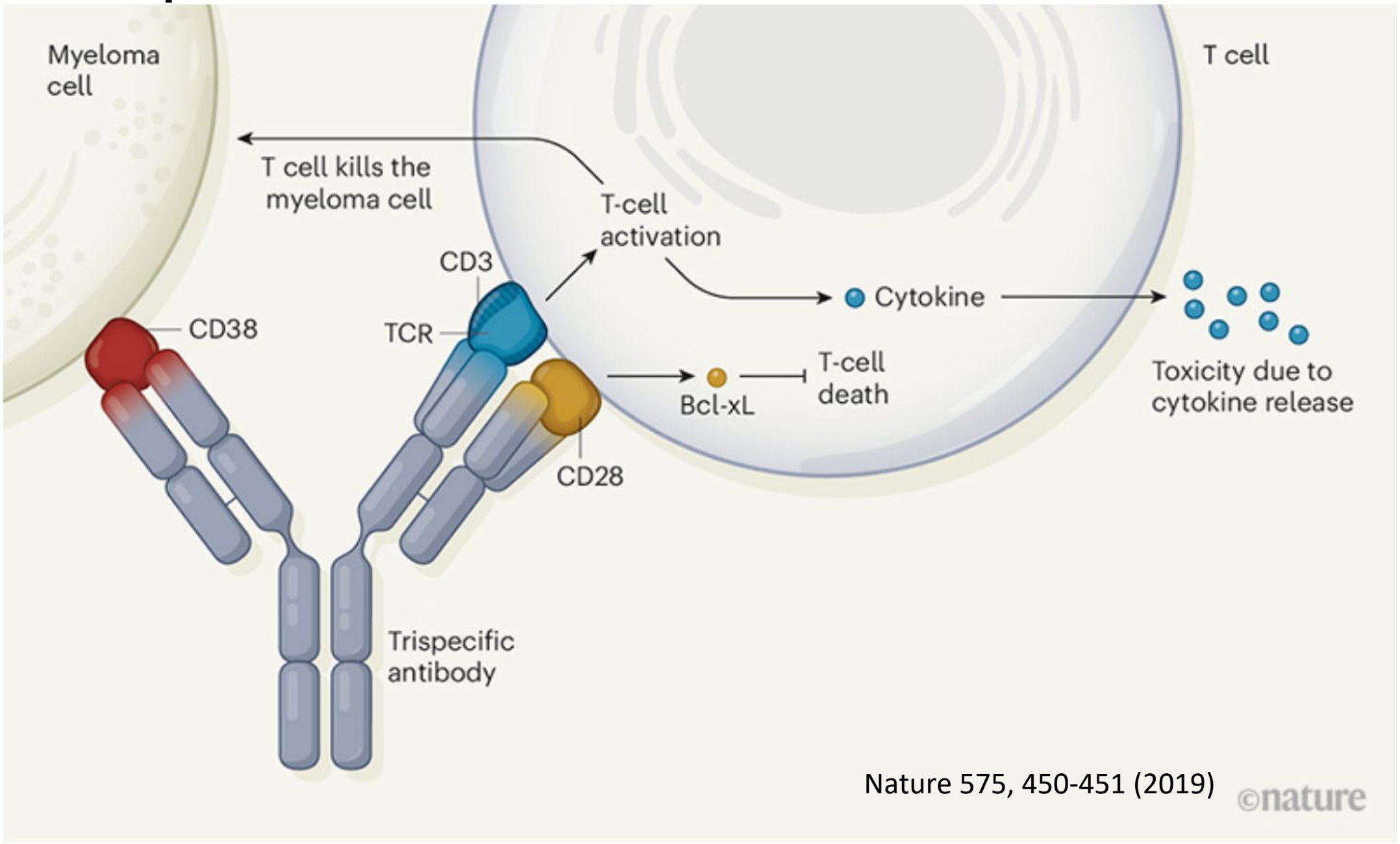


- Constructs vary in antigen-binding domains and dimerization (homodimers vs heterodimers) resulting in differences in antigen-binding sites (valency), size, geometry, and flexibility
  - Fc portion provides stability in circulation allowing for intermittent (instead of continuous) dosing, it can also promote ADCC and complement activation
  - These variables bestow different pharmacokinetic and pharmacodynamic properties
- T cells brought to close proximity in cells expressing MM antigen, form an immunologic synapse and promote cell-mediated cytotoxicity via release of perforin and granzymes
- Bispecific NK-cell engagers are currently in development

Images are representative schematics only.

Lancman G, et al. *Hematology Am Soc Hematol Educ Program.* 2020:264-271.

Trispecific antibodies



Nature 575, 450-451 (2019)

Efficacy will depend

- Cancer Driven gene
- Fc function
- Properties of human IgG subclasses.

	IgG1		IgG2		IgG3		IgG4	
General								
Molecular mass (kD)	146		146		170		146	
Amino acids in hinge region	15		12		62[a]		12	
Inter-heavy chain disulfide bonds	2		4[b]		11[a]		2	
Mean adult serum level (g/l)	6.98		3.8		0.51		0.56	
Relative abundance (%)	60		32		4		4	
Half-life (days)	21		21		7/~21[a]		21	
Placental transfer	++++		++		++/++++[a]		+++	
Antibody response to:								
Proteins	++		+/–		++		++[e]	
Polysaccharides	+		+++		+/–		+/–	
Allergens	+		(–)		(–)		++	
Complement activation								
C1q binding	++		+		+++		–	
Fc receptors								
FcγRI	+++[c]	65[d]	–	–	++++	61	++	34
$Fc\gamma RIIa_{H131}$	+++	5.2	++	0.45	++++	0.89	++	0.17
$Fc\gamma RIIa_{R131}$	+++	3.5	+	0.10	++++	0.91	++	0.21
FcγRIIb/c	+	0.12	–	0.02	++	0.17	+	0.20
$Fc\gamma RIIIa_{F158}$	++	1.2	–	0.03	++++	7.7	–	0.20
$Fc\gamma RIIIa_{V158}$	+++	2.0	+	0.07	++++	9.8	++	0.25
FcγRIIIb	+++	0.2	–	–	++++	1.1	–	–
FcRn (at pH < 6.5)	+++		+++		++/+++[a]		+++	

Front Immunol. 2014; 5: 520.

Bispecific antibody design

- Simultaneously target two different antigens, enhancing their effectiveness against cancer.
- With or without an Fc region. IgG-like bispecifics contain an Fc region, allowing them to activate immune cells via mechanisms like ADCC and ADCP, but they may face limitations in tissue penetration and can cause off-target effects.
- Non-IgG-like bispecifics, lacking an Fc region, are smaller and offer better tissue penetration, though they require frequent dosing due to shorter half-lives.
- Various designs, including trivalent and multispecific formats, improve tumor specificity by targeting multiple antigens or activating immune pathways.
- Modulating affinity and valency : Adjusting affinities for CD3 or tumor-associated antigens (TAAs) further optimizes therapeutic potential and reduces off-target toxicity.
- To enhance specificity, tumor penetration, and the ability to modulate the tumor microenvironment, marking an exciting future for bispecific antibody therapies.
- >200 bispecific antibodies, with increasingly diverse designs and mechanisms of action, are currently in preclinical or clinical development

雙特異性抗體給藥的共同特徵

- 雙特異性抗體（bsAbs）是一類創新的治療藥物，能同時靶向兩種不同的抗原或表位。儘管其設計和作用機制各異，但在給藥方式上通常具有以下共同特徵：
- 1. 靜脈輸注（IV Infusion）：大多數雙特異性抗體通過靜脈輸注給藥，因為其分子結構較大且複雜，這樣可以確保最佳的生物利用度和即時的治療效果。
- 2. 漸進式劑量增加（Step-Up Dosing）：為了減少細胞因子釋放綜合症（CRS）等不良反應，通常採用漸進式劑量增加方案：初始劑量較低。隨後逐漸增加劑量，直至達到治療劑量。初始劑量的輸注時間可能較長（如2–6小時），以減少輸注相關反應的風險。耐受性建立後，後續劑量的輸注時間可能縮短。
- 3. 初始劑量需住院監測：在首次幾次給藥期間，患者通常需在醫院監測以應對可能的輸注相關反應（IRRs）或CRS。
- 4. 預防性用藥：通常需要使用預防性藥物，如類固醇、抗組胺藥及退燒藥，以預防或處理輸注相關反應和CRS。

Bispecific and multispecific antibodies in oncology

Bispecific T cell engager

- CD20 × CD3 Odronextamab (RR FL, RR DLBCL)
- BCMA × CD3 Linvoseltamab (RR MM)

Dual signalling pathway inhibition

- HER2 × HER2 (advanced and/or metastatic HER2-amplified biliary tract cancer BTC)

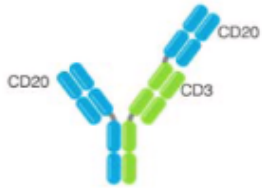
Bispecific NK cell engager

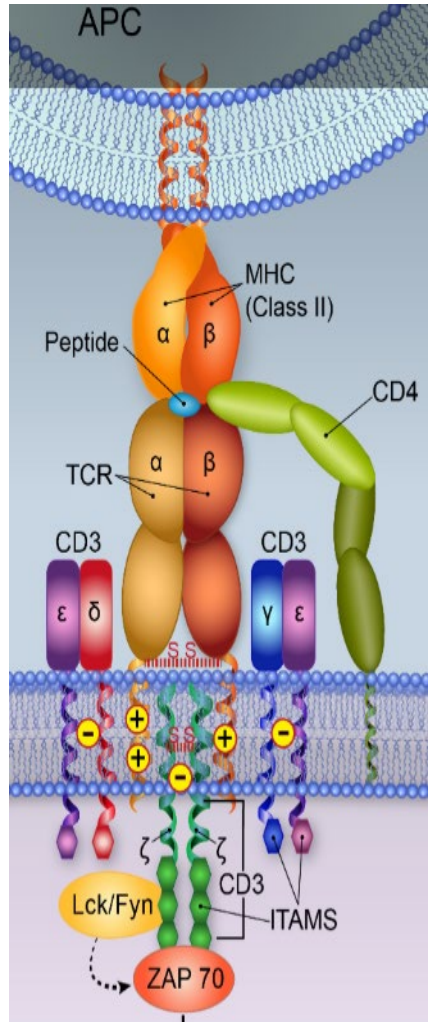
- CD30 × CD16 (NHL)

Dual checkpoint inhibition

- PD-1 × CTLA4 (ccRCC, clear-cell renal cancer, NSCLC, TNBC)
- PD-1 × VEGF (advanced-stage EGFR/ALK wild type NSCLC)

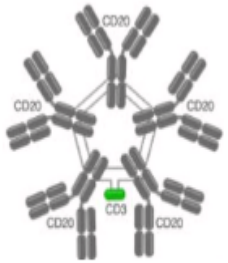
Comparative characteristics of CD20XCD3 BsAb currently in development

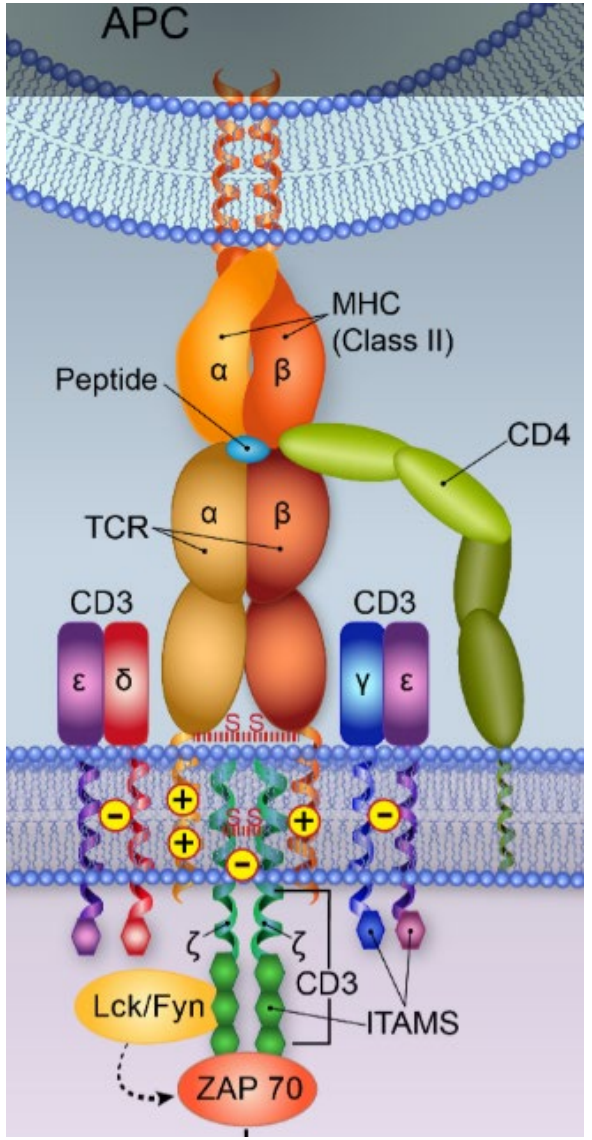
Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab[18]		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1	SP34-der. (CD3ε)	By-L1 (type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (no FcγR binding)
Epcoritamab[16]		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.) (CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (no FcγR,C1q binding)
Odronexamab[17]		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumomab)	Modified IgG4 (no FcγRIII binding)
Plamotamab[90]		IgG1	Fab-Fc x scFv-Fc	1:1	α-CD3_H1.30 (SP34-der.) (CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (no FcγR binding)



Blood (2023) 141 (5): 467–480.

Comparative characteristics of CD20XCD3 BsAb currently in development

IgM 2323[19]		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No



Blood (2023) 141 (5): 467–480.

Agent	Target	Indication and activity	Common grade ≥3 adverse events	Year of approval
Blinatumomab	CD3 × CD19	RR B-ALL: CR/CRh in 43–44%, mRFS 5.9 months, mOS 6.1–6.9 months	Neutropenia (37.8–41%), infection (34.1%), elevated circulating liver enzymes (6–12.7%), neurological events (9.4–11%), CRS (4.9%)	2014[a], 2017 (FDA); Subsequently, MRD^+ B-ALL
Mosunetuzumab	CD3 × CD20	RR FL: CRR 60%, ORR 80%, mPFS 17.9 months, mOS NR	Neutropenia or reduced neutrophil count (26%), hypophosphataemia (17%), anaemia (8%), increased serum ALT (5%), CRS (2%)	2022[a] (EMA), 2022[a] (FDA)
Tebentafusp	CD3 × gp100–HLA-A*02:01	HLA-A*02:01-positive uveal melanoma: ORR 11%, mPFS 3.4 , mOS 21.6 months	Rash (19%), elevated circulating liver enzymes (10%), pyrexia (5%), pruritus (5%), CRS (1%)	2022 (FDA), 2022 (EMA)
Teclistamab	CD3 × BCMA	RR MM: CRR 39.4%, ORR 63%, mPFS 11.3 months, mOS 18.3 months	Neutropenia (64.2%), anaemia (37.0%), lymphopenia (32.7%), thrombocytopenia (21.2%), CRS (0.6%)	2022[a] (FDA), 2022[a] (EMA)
Glofitamab	CD3 × CD20	RR DLBCL: CRR 39%, ORR 52%, mPFS 4.9 months, mOS 12 months	Neutropenia (27%), thrombocytopenia (8%), anaemia (6%), CRS (4%)	2023[a] (FDA), 2023[a] (EMA), 2023[a] (NMPA)
Epcoritamab	CD3 × CD20	RR DLBCL: CRR 38.9%, mPFS 4.4 months, mOS NR	Neutropenia (14.6%), anaemia (10.2%), thrombocytopenia (5.7%), CRS (2.5%)	2023[a] (FDA) 2023[a] (EMA)
Elranatamab	CD3 × BCMA	RR MM: ORR 61%, estimated 15-month PFS 50.9%, estimated 15-month OS 56.7%	Neutropenia (48.8%), anaemia (37.4%), lymphopenia (25.2%), thrombocytopenia (23.6%)	2023[a] (FDA), 2024[a] (EMA)
Talquetamab	CD3 x PRC5D	RR MM: ORR 72%, mDOR 9.5 months, mPFS NR	Lymphopenia (47%), anaemia (33%), neutropenia (26%), leukopenia (16%)	2023[a] (FDA)
Tarlatamab	CD3 x DLL3	RR SCLC: ORR 40%, mDOR 9.7 months, mPFS 4.9 months	CRS (26%), neutropenia (8%)	2024[a] (FDA)
Amivantamab	EGFR × MET	Advanced-stage NSCLC (EGFR exon 20 insertion mutations (in combination with chemotherapy): ORR 73%, mPFS 11.4 months, mOS NR	Neutropenia (33%), rash (11%), leukopenia (11%), anaemia (11%), thrombocytopenia (10%)	2021[a] (FDA)
Cadonilimab	PD-1 × CTLA4	Advanced-stage cervical cancer: ORR 32.3%, mPFS 3.7 months, mOS NR	Anaemia (5%), reduced appetite (4%), dyspnoea (2%)	2022 (NMPA)

Relapsed or refractory (R/R) B-cell lymphoma

Relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)

- Platinum-based combinations followed by high-dose therapy and autologous stem cell support (ASCS) as 2nd line therapy, with an 15%–20% cure rate in the rituximab era
- Advent of targeted agents
  - polatuzumab vedotin (CD79b), tafasitamab(CD19), loncastuximab(CD19) have resulted in incremental benefits for patients with R/R DLBCL
- T-cell-based immunotherapies
  - CAR- T cells (axicabtagene ciloleucel and lisocabtagene maraleucel): durable remissions 30%–40% (limited access outside large tertiary care centers, complex insurance approval processes, high costs, limited manufacturing capability, and poten-tially long product turnaround, among others.)
- Bispecific antibodies (BsAbs)
  - off-the-shelf T-cell redirecting drugs with promising activity in B-cell non- Hodgkin lymphoma and the potential to play a major role in the treatment of R/R DLBCL.

Antibody	Obinutuzumab	Rituximab	Ofatumumab
Trade name (EU)	Gazyvaro	MabThera	Arzerra
Manufacturer	Roche	Roche	GlaxoSmithKline
Antibody type	II	I	I
IgG subclass	IgG1	IgG1	IgG1
Structure	Humanized	Chimeric	Fully human
Binding to CD20 epitope	Large loop	Large loop	Large and small loop
Binding to lipid rafts	–	++	++++
ADCC	++++	++	++
CDC	+	++	++++
Direct cell death induction	++++	+	+

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; I Ig, immunoglobulin.

Comparison of commercially available anti-CD20 antibodies

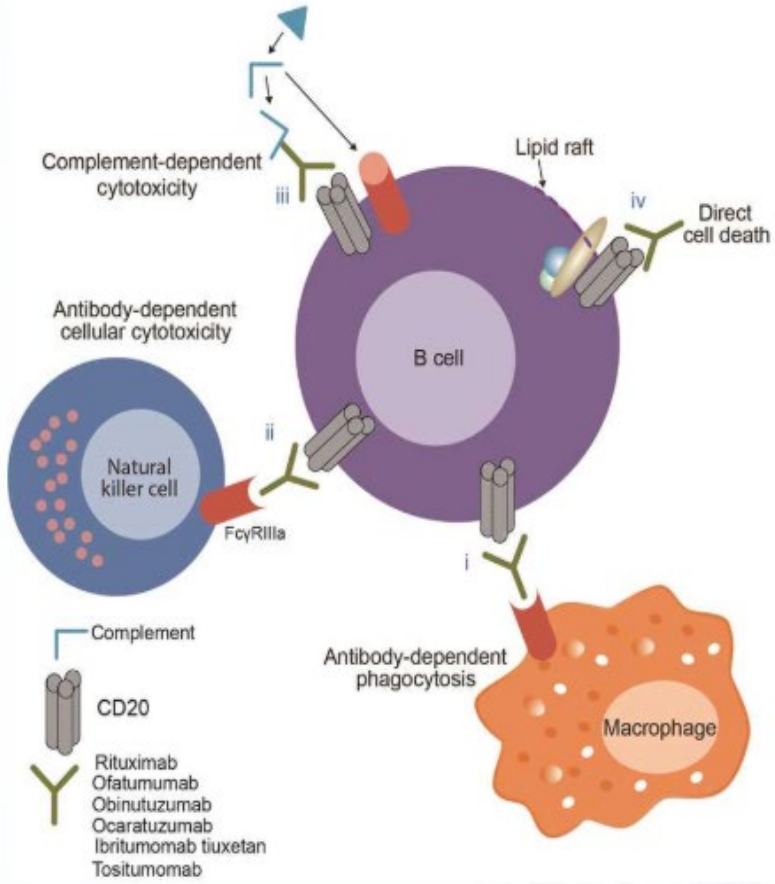


Fig.1 Mechanism of action of obinutuzumab

February 2015Pharmacogenomics and Personalized Medicine 8(default):1-7

Conclusion

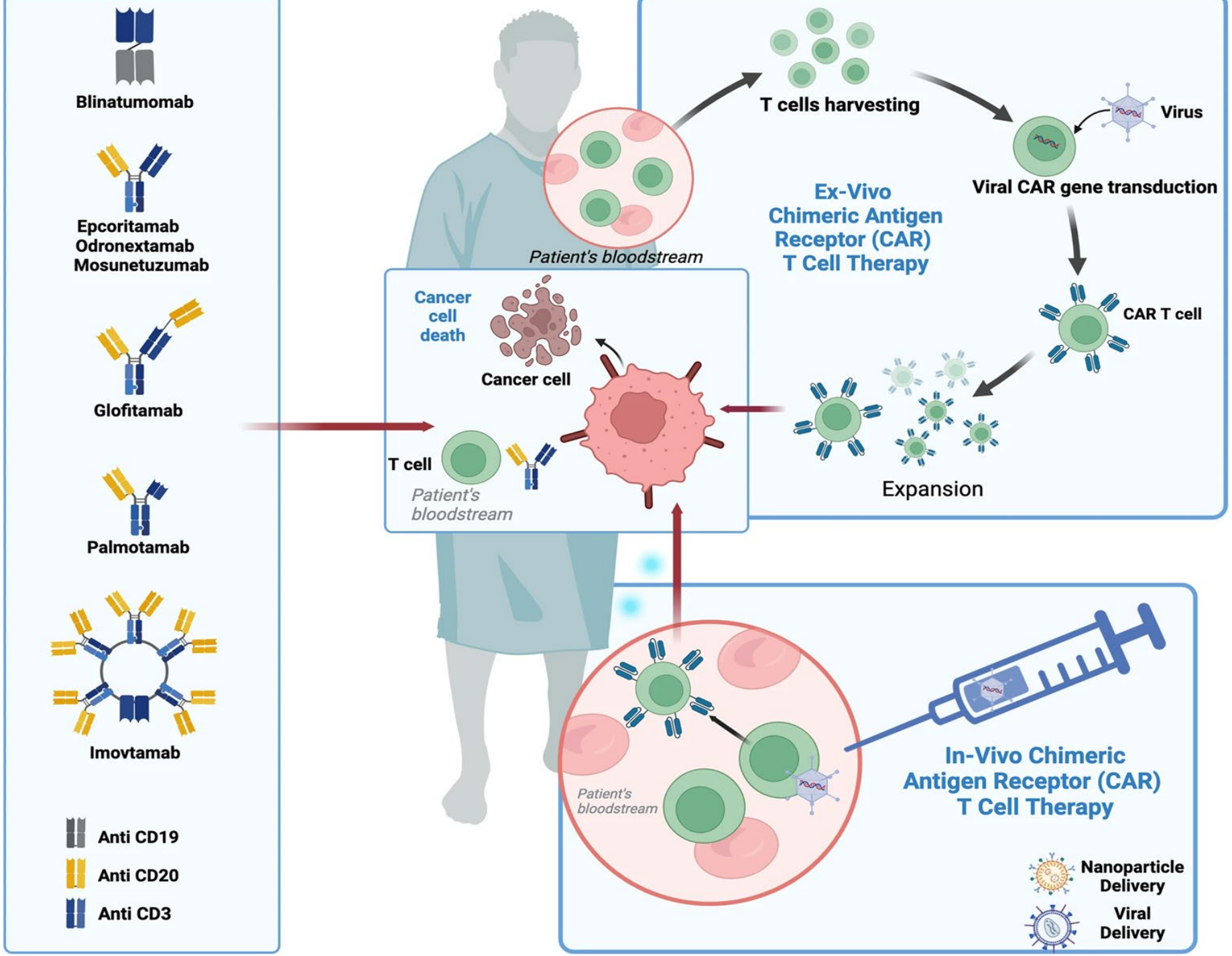
- Obinutuzumab : signifcant improvement in PFS
  - No improvements in OS, ORR and CRR, and an increment in the incidences of AEs.
- Ofatumumab comparable results in PFS, OS and CRR
  - a lower ORR and higher incidences of AEs.
- 131-tositumomab
  - similar results with rituximab regarding PFS, OS, ORR and CRR but was associated with higher incidences of AEs.
- 90Y-ibritumomab achieved a higher ORR, similar PFS, OS and CRR
  - higher incidences of AEs.

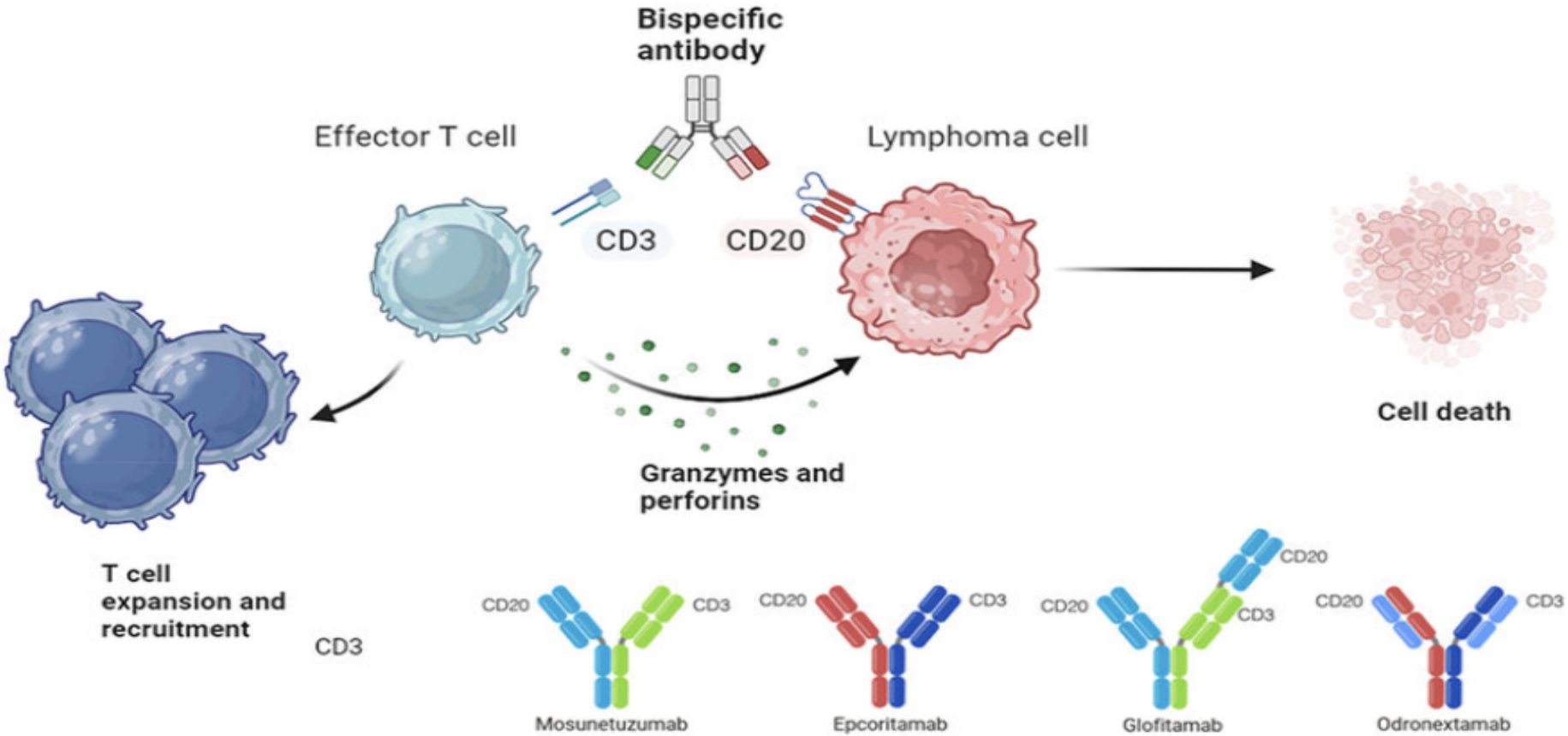
Sci Rep 11, 3255 (2021).

Landscape of effector cellular therapy for DLBCL therapy.

Bispecific T cell engagers (left) include BiTEs like blinatumomab, fused full-length antibodies like the DLBCL-approved products epcoritamab and glofitamab, and multivalent constucts like imovtamab. Approved CAR-19 therapies (top right) are manufactured ex vivo from each patient's T cells, requiring 20–40 days. Viral or nanoparticle delivery of CAR genes (bottom right) in vivo is one of many investigational ways to potentially accelerate targeted cell therapy delivery.

Blood Cancer J. 14, 27 (2024).





Mechanism of action of antiCD20 and antiCD3 bispecific antibodies. Mosunetuzumab, IgG1 ab with a rituximab-like antiCD20 domain; epcoritamab, IgG1 ab with an ofatumumab-like antiCD20 domain; glofitamab, IgG1 ab with a ratio 2:1 CD20:CD3 and an obinutuzumab-like antiCD20 domain; odronextamab, IgG4 ab with an ofatumumab-like antiCD20 domain.Illustration created with biorender-individual version.

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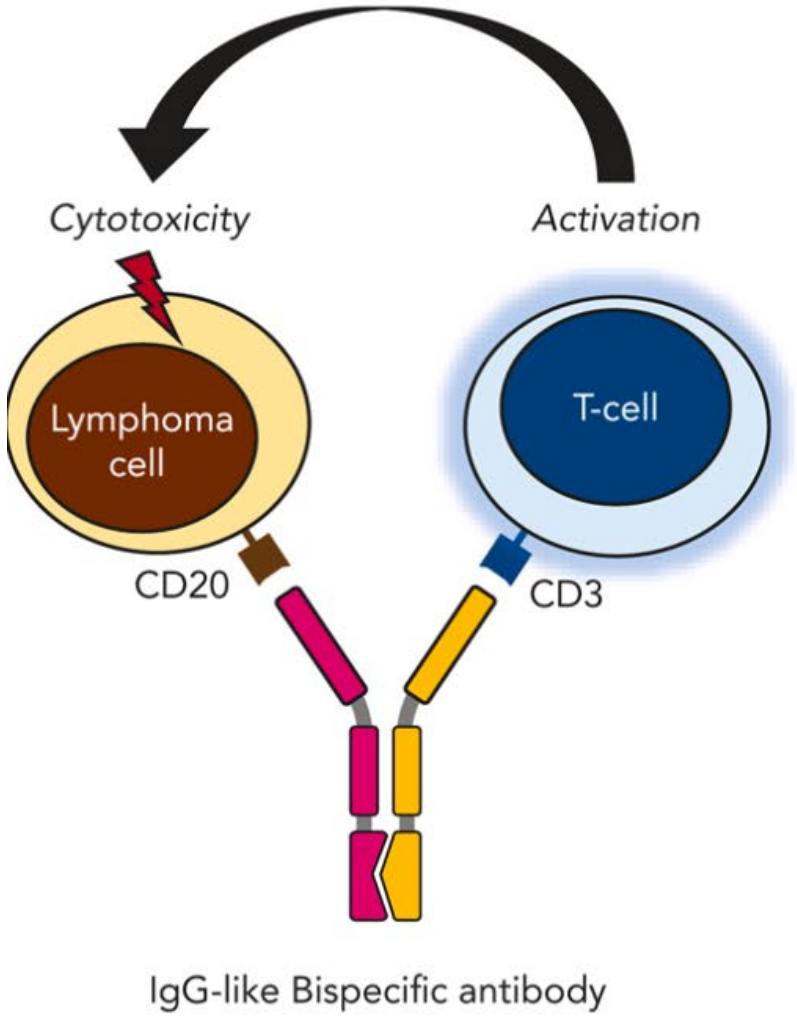
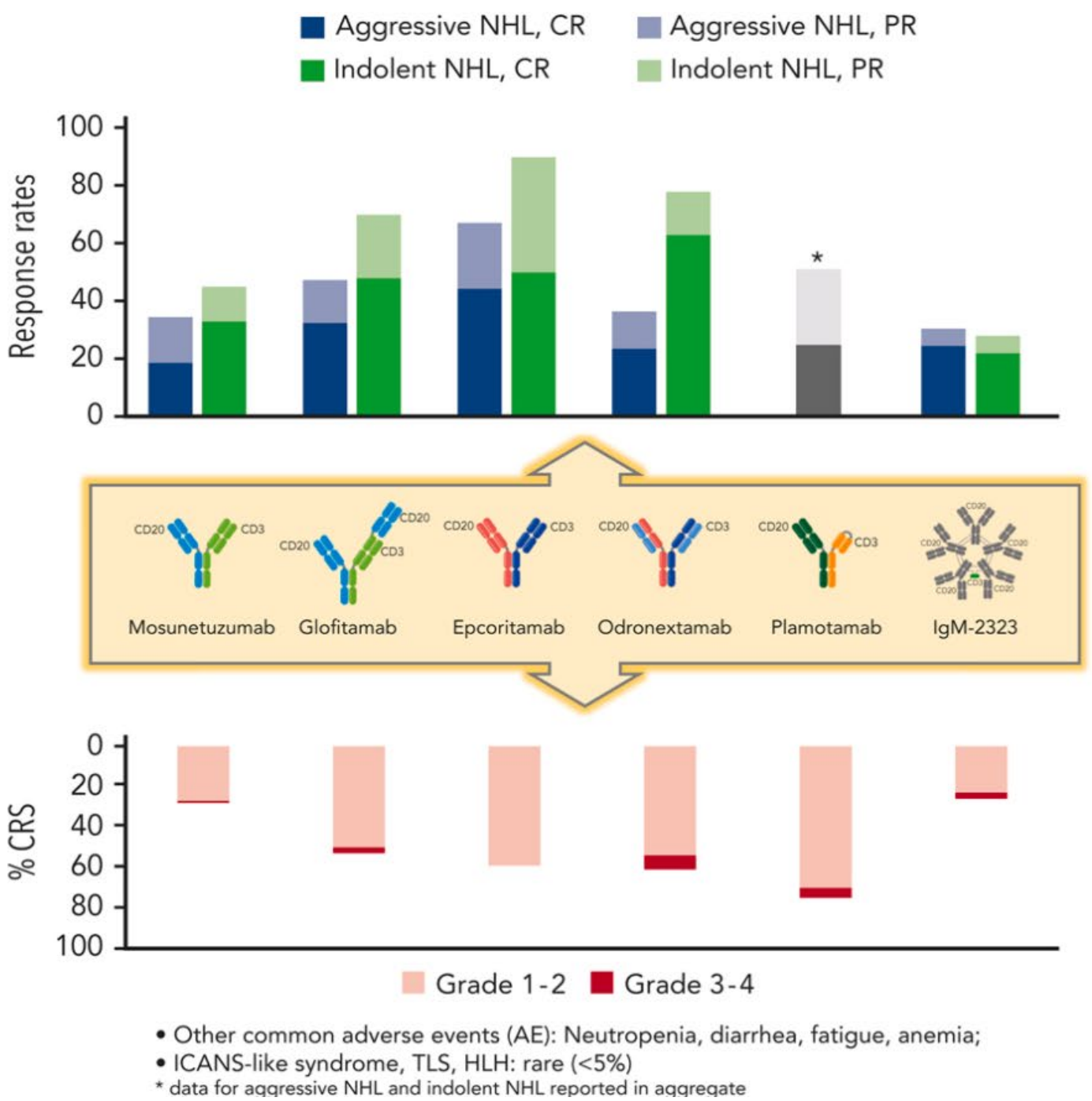
2024, VOL. 13, NO. 1, 2321648

Currently Approved Indications

- **Glofitamab:** Adult relapsed/refractory DLBCL, not otherwise specified or large B-cell lymphoma arising from FL who have received 2 or more prior lines of systemic therapies (2023, June approved)
- **Epcoritamab:**
  - Adults with relapsed/refractory DLBCL and high-grade DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, after 2 or more lines of systemic therapy (2023, May approved)
  - Adult patients with relapsed or refractory FL after 2 or more lines of systemic therapy (2024, June approved)

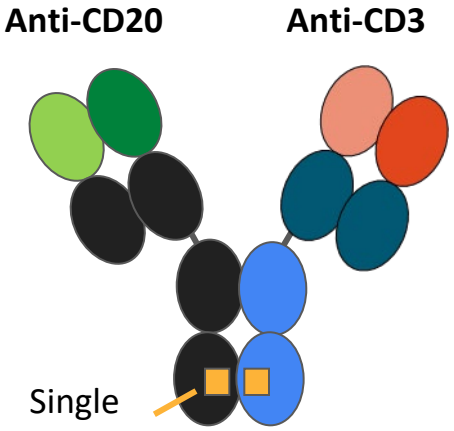




Blood (2023) 141 (5): 467–480.

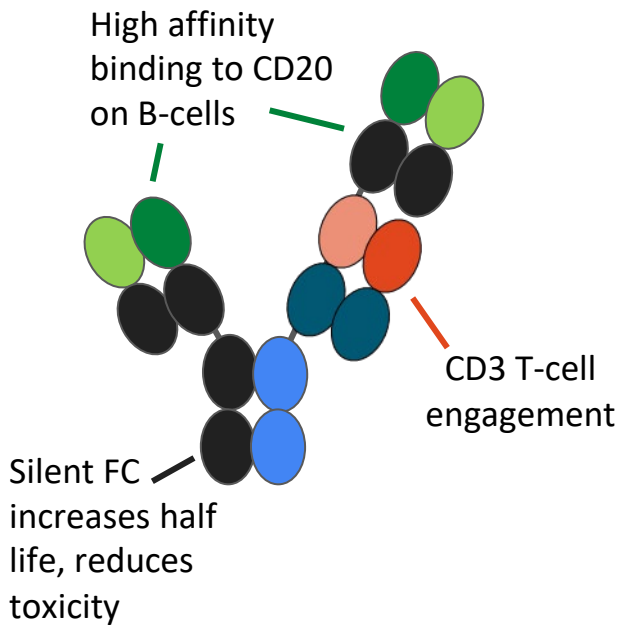
CD20/CD3 Bispecific Antibodies in B-Cell Lymphomas

Humanized mouse IgG1-based mAb



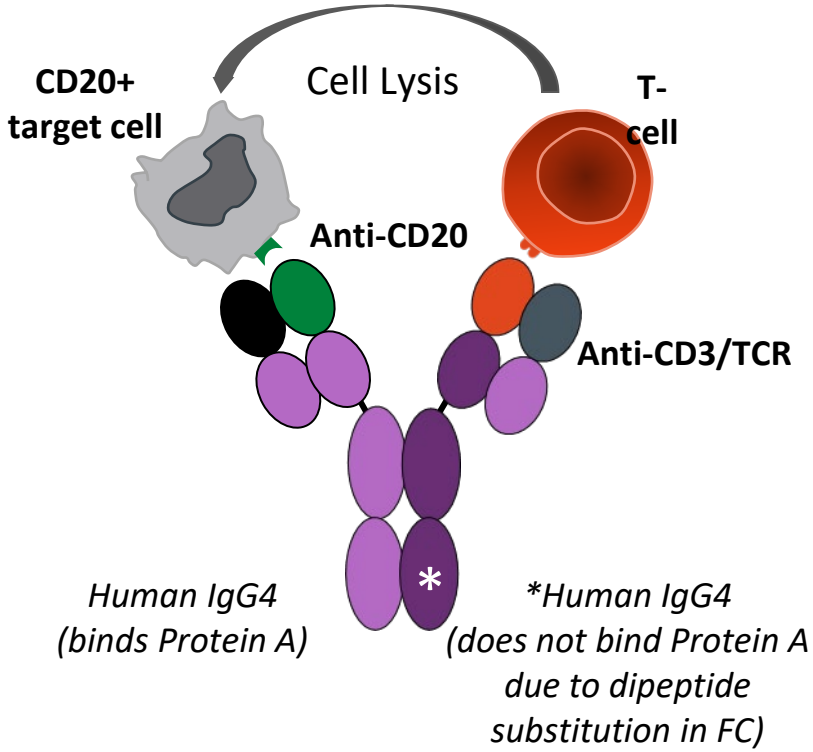
Epcoritamab (SC)

3L+ R/R DLBCL



Glofitamab (IV)

3L+ R/R DLBCL



Odronextamab (IV)

Approval Status: Priority Review for 3L+ R/R FL and DLBCL

Castaneda-Puglianni. Drugs Context. 2021;10:2021. Bannerji. ASH 2020. Abstr 42. Budde. ASH 2018. Abstr 399. Hutchings. Lancet. 2021;398:1157. Engelberts. eBioMedicine. 2020;52:102625. Hutchings. JCO. 2021;39:1959. Epcoritamab PI. Glofitamab PI.

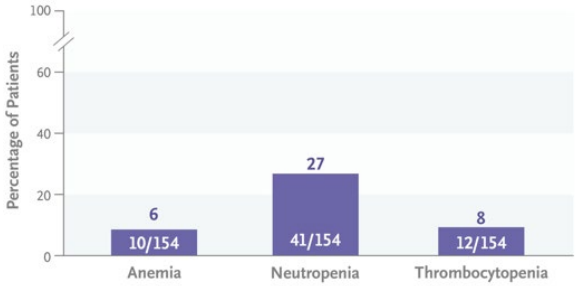
Antibody Name	Trial Name (Pt Number)	Indication	ORR	PFS	Overall Survival (OS)	Adverse Events	Source of Journal
Mosunetuzumab (Rituximab)	GO29781 (90 pts)	R/R Follicular Lymphoma after at least two prior therapies	ORR : 77.8% CR : 60 % Median DOR : NR; 79.5% of complete responders at least 24 months	24-month PFS: 51.4%	Not yet mature in published data	CRS, Neutropenia, Fatigue	Blood. 2022;140(suppl 1):1467-1470.
Glofitamab (obinutuzumab)	NP30179 (155 pts)	R/R Diffuse Large B-Cell Lymphoma (DLBCL) after at least two prior therapies	ORR :52% CR : 39% CR (CAR-T) : 35%. The median time to a complete response : 42 days	The 12-month PFS : 37%) At 12 months CR : 78%		CRS, Neutropenia, Infections	N Engl J Med 2022;387:2220-2231
Epcoritamab (Ofatumumab)	EPCORE NHL-1 (157 pts)	R/R DLBCL after prior therapies	ORR 63.1% and CR39.5%,	The mDoCR : 20.8 mo Median time to CR : 2.7 mo;	mOS : 18.5 mo	CRS, Pyrexia, Neutropenia	JCO Volume 41, Number 16_suppl
Odronextamab (Ofatumumab)	ELM-2 (375 pts) (across five cohorts)	R/R DLBCL and FL	DLBCL (CAR T-cell naive): ORR: 50.8; CR: 31.6%; FL: ORR: 80%; CR: 73.4%	DLBCL: mDCR : 36.3 months FL: Median DCR : 25.1 months mPFS: 20.7 months	FL: m OS: Not reached	CRS, pyrexia, anemia, neutropeni a;	Annals of Oncology, 2024 Nov;35(11):1039-1047 Blood (2024) 144 (Supplement 1): 3118.

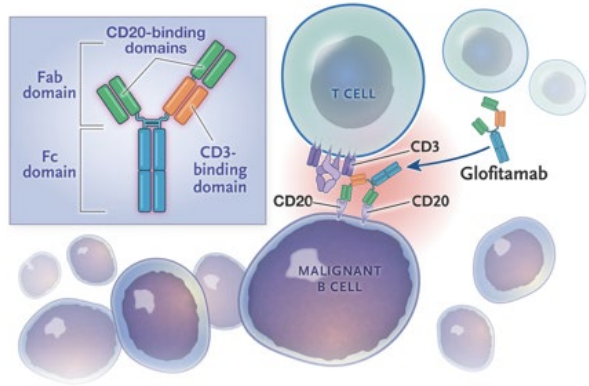
Single-agent clinical efficacy (Mosunetuzumab)

- Indication : with R/R FL after ≥2 prior lines of therapy
- Among 197 subjects, 43 were treated at a target dose of 13.5 mg, and 154 at 30 mg.
  - 1/3 follicular lymphoma (FL), 2/3 B-NHL (aNHL).
  - The median number of prior therapies : 3.
  - CAR T-cell therapy : 10%
  - aNHL : ORR, CR, mDOR (35%, 19%, and 7.6 months), mPFS : 1.4 months
  - indolent NHL : ORR, CR, mDOR, mPFS (66%, 48%, 16.8 months, and 11.8 months)
- IV or SC formulations
- 90 pts (the target dose of 30 mg)
  - R/R FL
  - ORR : 80% , CR : 60%.
  - The median DOR and PFS (22.8 months and 17.9 months), 18-month OS rate : 90%

J Clin Oncol, 40 (5) (2022), pp. 481-491Lancet Oncol, 23 (8) (2022), pp. 1055-1065

Glofitamab



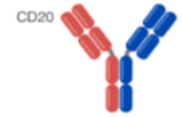


- Indication: R/R diffuse large B-cell lymphoma not otherwise specified or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of therapy.
- 171 pts with CD20 (+) B-NHL previously a median of 3 prior lines of therapy
  - a single 1000 mg dose of pretreatment obinutuzumab followed by fixed or step-up dosing IV glofitamab every 2 or 3 weeks.
    - Dose-dependent clinical activity starting at 0.6 mg, and at doses ≥10 mg the ORR among patients with aNHL was 61%, including 49% CR.
- 155 pts with aNHL treated with glofitamab (target dose of 30 mg) NP30179
  - ORR and CR (52% and 39%), CR rate : CAR T-cell therapy (35%) and not CAR-T (42%).
  - Median follow-up of 12.6 months, the median DOR was 18.4 months, the PFS was 4.9 months, and the OS was 11.5 months.
- R/R FL
  - Deep tumor volume reductions were observed regardless of obinutuzumab administration.
- R/R mantle cell lymphoma
  - ORR (81%) , CR (67%) regardless of prior Bruton tyrosine kinase inhibitor therapy.

NEJM 2022;387:2220-2231

J Clin Oncol, 39 (18) (2021), pp. 1959-1970
J Clin Oncol, 40 (16_suppl) (2022), p. 7500

Epcoritamab

Epcoritamab[16]		IgG1	Controlled Fab-arm exchange	1:1

- Indication
  - R/R follicular lymphoma after 2 or more lines of therapy.
  - R/R third-line diffuse large B-cell lymphoma (DLBCL). (SC)
- 73 pts with R/R B-NHL at doses ranging from 0.0128 to 60 mg.
  - SC initially weekly, then every 2 weeks, then every 28 days.
  - 22 pts with aNHL treated at doses between 12 mg (the minimum clinically active dose) and 60 mg, the ORR (68%) and CR (45%) . At a median follow-up of 9.2 months, 75% remained relapse-free for at least 6 months.
- 157 pts R/R aNHL
  - ORR and CR (63% and 39%)
  - CAR-T–naïve (ORR, 69%; CR, 42%) vs CAR-T–exposed (ORR, 54%; CR, 34%) individuals.
  - At the 12-month mark, 80% of CRs were maintained, and 67% of patients were alive.
- 127 pts Phase 1/2 EPCORE NHL-1 study (R/R) follicular lymphoma (FL)
  - ORR : 82% with CR : 60%. mPFS : 15.4 months, mDOR, duration of CR, and OS were not reached, minimal residual disease (MRD) negativity was associated with improved PFS.

European Hematology Association, Session Presidential Symposium
(11 June 2022)
Vienna, Austria

Blood. 2023;142(Suppl 1):1655.

Odronextamab (Ofatumumab)

- Indication
  - R/R follicular lymphoma and R/R diffuse large B-cell lymphoma (DLBCL), both after 2 or more lines of systemic therapy.
- 127 pts ELM-2 trial R/R DLBCL
  - ORR : 52% (naive to CAR T) , CR : 31.5%, and mDOR : 10.2 months
  - ORR : 33.3% and CR : 26.7%. (CART)
  - At 24 months, the CR rate was maintained in 47%
- 121 pts ELM-2 trial R/R follicular lymphoma (median follow-up of 22 months)
  - ORR : 82% and CR : 75%. Duration of CR: 20.5 months, mPFS : 20 months , OS not yet reached

Blood. 2023;142(1):436.

Deciding Between Available Bispecific Antibodies and Other 3L+ Treatments for R/R DLBCL

- **How do bispecific antibodies compare to other therapies?**
  - "Off the shelf" option (availability): means we can give right away whereas therapies like CAR T-cells require adequate cell collection, manufacturing time, etc
  - **Safety profiles:**
    - Lower toxicity risks/safer: including for patients not good candidate for CAR T-cell therapy
    - Shorter hospitalization times
    - Different targets (CD20 vs CD19) which means that CAR T-cell does not preclude bispecific antibody and vice versa
- **What are the advantages for bispecific antibodies over chemotherapy?**
  - Improved efficacy, potentially better safety and/or improved QoL

Deciding Between Available Bispecific Antibodies: Which One Is Best for Each Patient?

Choosing Between Glofitamab vs Epcoritamab for DLBCL

- Safety and efficacy were similar in pivotal trials
- Inpatient observation recommended for both
- Glofitamab has a fixed duration (21-day cycle x 12) and less frequent administration
- Glofitamab *does not require steroids* for CRS mitigation
- Epcoritamab does *not require obinutuzumab* use for tumor volume reduction

Epcoritamab-bysp PI. Glofitamab-gxbm PI.

Comparison of structure, administration, CRS, and neurotoxicity associated with CD3×CD20 BsAbs in NHL

Drug	Mosunetuzumab	Epcoritamab	Glofitamab	Odronextamab
Structure	Fully humanized IgG1 CD3×CD20 BsAb with 1:1 CD3:CD20 ratio of Fab arms	IgG-like anti-CD3×CD20 BsAb. Proprietary format, with point mutations in the Fab portion of the Fc of the antibody and heterodimerization.	Humanized mouse-derived BsAb with 1:2 CD3:CD20 ratio of Fab arms	Fully humanized IgG4 anti-CD3×CD20 BsAb developed using an Fc domain with a mutation in the protein A of the Fc portion
Route of administration	IV	SC	IV	IV
Dosing schedule	C1: days 1, 8, 15; C2+: day 1, every 21 d, for up to 8 cycles in CR or up to 17 cycles for PR or SD	C1-3: days 1, 8 ,15, and 22; C4-9: days 1 and 15; C10+: day 1, every 28 d until progression	C1: obin, day 1; glofit, days 8 and 15; C2-12: day 1, every 21 d	C1: days 1, 2, 8, 9, 15, 16 of a 21-d cycle; C2-4: days 1, 8, 15 of a 21-d cycle; C5+: day 1, every 14 d; If CR for at least 9 mo: day 1, every 28 d
CRS mitigation				
Step-up dosing	C1D1: 1 mg C1D8: 2 mg C1D15: 60 mg C2D1: 60 mg C3+D1: 30 mg	C1D1: 0.16 mg C1D8: 0.8 mg C1D15: 48 mg C1D22: 48 mg C2D1+: 48mg	C1D1: obin 1000 mg C1D8: 2.5 mg C1D15: 10 mg C2D1+: 30 mg	C1D1: 0.2 mg, C1D2: 0.5 mg C1D8: 2 mg, C1D9: 2 mg C1D15: 10 mg, C1D16: 10 mg C2-C4: 80 mg (FL) or 160 mg (DLBCL) C5+: 160 mg (FL) or 320 mg (DLBCL)

Blood (2024) 143 (16): 1565–1575.

Drug	Mosunetuzumab					Epcoritamab					Glofitamab					Odronextamab				
Premedications	• A/P 500-1000 mg, 30 min prior, for C1 and C2 • Diphenhydramine 50-100 mg, 30 min prior, for C1 and C2 • Dexamethasone 20 mg or MP 80 mg, 1 h prior, for C1 and C2. Continue all premedications if CRS with prior dose.					• A/P 650-1000 mg, 30-120 min before C1 treatments • Diphenhydramine 50 mg, 30-120 min before C1 treatments • Dexamethasone 15 mg, 30-120 min before C1 treatments and for 3 consecutive days after. Continue dexamethasone thereafter if G2 or G3 CRS with prior dose.					• A/P 500-1000 mg, 30 min before all treatments • Diphenhydramine 50 mg, 30 min before all infusions • Dexamethasone 20 mg, 1 h before treatment on C1D8, C1D15, C2D1, and C3D1. Continue if CRS with prior dose.					• A/P 650 mg, 30-60 min before all treatment • Diphenhydramine 25 mg, 30-60 min prior before all infusion • Dexamethasone 10 mg orally, 12-24 h before split dose, 20 mg IV on day of dosing, 10 mg orally on the day after step-up dosing. Following first full dose, dexamethasone 10 mg before dosing; continue if CRS with prior dose.				
住院	Optional					C1D15: 24-h admission					C1D8: 24-h admission					Performed during step-up dosing				
CRS grading	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
	26%	17%	1%	1%	0%	34%	15%	3%	0%	0%	47%	12%	3%	1%	0%	35%-39%	13%	0%	0%	0%
	Time course for CRS onset			Median time (h) to CRS onset		Time course for CRS onset			Median time (h) to CRS onset		Time course for CRS onset			Median time (h) to CRS onset		Time course for CRS onset			Median time (h) to CRS onset	
	C1D1: 23.3% C1D8: 5.6% C1D15: 36.4% C2D1: 10.3% C3+D1: 2.4%			C1D1: 5 C1D8: 20 C1D15: 27 C2D1: 38		C1D1: 5.8% C1D8: 11.8% C1D15: 42.8% C1D22: 4.9% C3+ 3%			All doses: 24 C1D15: 20		C1D8: 42.8% C1D15: 25.2% C2: 26% C3+: 0.9%			C1D8: 13.5 (range: 6-52)		C1D1/2: 22%-24% C1D8/9: 27%-32% C1D15/16: 21%-35% C2D1: 14%-17% C2D8+: 9%-14%			All doses: 18-20	
Median duration of CRS	3 d (1-29 d)					2 d (range: 1-27 d)					30.5 h (range, 0.5-317 h)					8-10 h (range, 0.1-190 h)				
Neurotoxicity	G 1-2		G3	G4	G5	G1	G2	G3	G4	G5	G 1-2		G 3-4		G5	G 1-2		G 3-4		G5
	3%		0%	0%	0%	4.5%	1.3%	0%	0%	0.6%	5%		3%		0%	4% (DLBCL)		0%		0%

Glofitamab: Dosing and Administration

- Intravenously administered in 21-day cycles for 12 cycles
- **CD20 antibody obinutuzumab given prior to first dose** to reduce risk of toxicity by decreasing tumor burden
- Hospitalization recommended for 24 hr after step-up dose 1 and if CRS with prior dose

Treatment Cycle	Day	Dose	Infusion Duration	Premedication
Cycle 1	1	Obinutuzumab 1000 mg at 50-400 mg/hr (deplete circulating B-cells)		▪ N/A
▪ Step-up dose 1 ▪ Step-up dose 2	8 15	2.5 mg IV 10 mg IV	4 hr 4 hr†	▪ IV dexamethasone* 20 mg completed ≥1 hr before infusion ▪ PO/IV diphenhydramine 50 mg (or an equivalent) and PO acetaminophen 500-1000 mg ≥30 min before infusion
Cycle 2	1	30 mg IV	4 hr†	▪ Same as cycle 1 Day 8 and 15 guidance
Cycle 3	1	30 mg IV	2 hr‡	▪ Same as cycle 1 Day 8 and 15 guidance
Cycle 4-12	1	30 mg IV	2 hr‡	▪ PO/IV diphenhydramine 50 mg (or an equivalent) and PO acetaminophen 500-1000 mg ≥30 min before infusion ▪ *If CRS occurred with previous dose,* add IV dexamethasone* 20 mg completed ≥1 hr before infusion

*If dexamethasone unavailable, administer IV prednisone 100 mg, prednisolone 100 mg, or methylprednisolone 80 mg. †Infusion time may be extended to up to 8 hr, if CRS occurred with previous dose. ‡Infusion time should be kept at 4 hr, if CRS occurred with previous dose.

Glofitamab-gxbm PI.

Epcoritamab Dosing and Administration

- Subcutaneous injection
- Administered in 28-day cycles for ≥10 cycles total
- Hospitalization recommended for 24 hr after Cycle 1 Day 15 dose

Treatment Cycle	Day	Dose	Premedication
Cycle 1 ▪Step-up dose 1 ▪Step-up dose 2 ▪Step-up dose 3 (first full dose) ▪Target dose	 1 8 15 22	 0.16 mg SC 0.8 mg SC 48 mg SC 48 mg SC	▪ PO/IV prednisolone 100 mg or dexamethasone 15 mg (or an equivalent) for 30-120 min before weekly administration *and* for 3 consecutive days after each dose ▪ PO/IV diphenhydramine 50 mg and PO acetaminophen 650-1000 mg for 30-120 min before weekly administration
Cycle 2-3	1, 8, 15, 22	48 mg SC	▪ *For grade 2/3 CRS with prior dose:* PO/IV prednisolone 100 mg or dexamethasone 15 mg (or an equivalent) for 30-120 min before weekly administration *and* for 3 consecutive days after dose
Cycle 4-9	1, 15	48 mg SC	▪ Same as cycle 2-3
Cycle 10 and beyond	1	48 mg SC	▪ Same as cycle 2-3

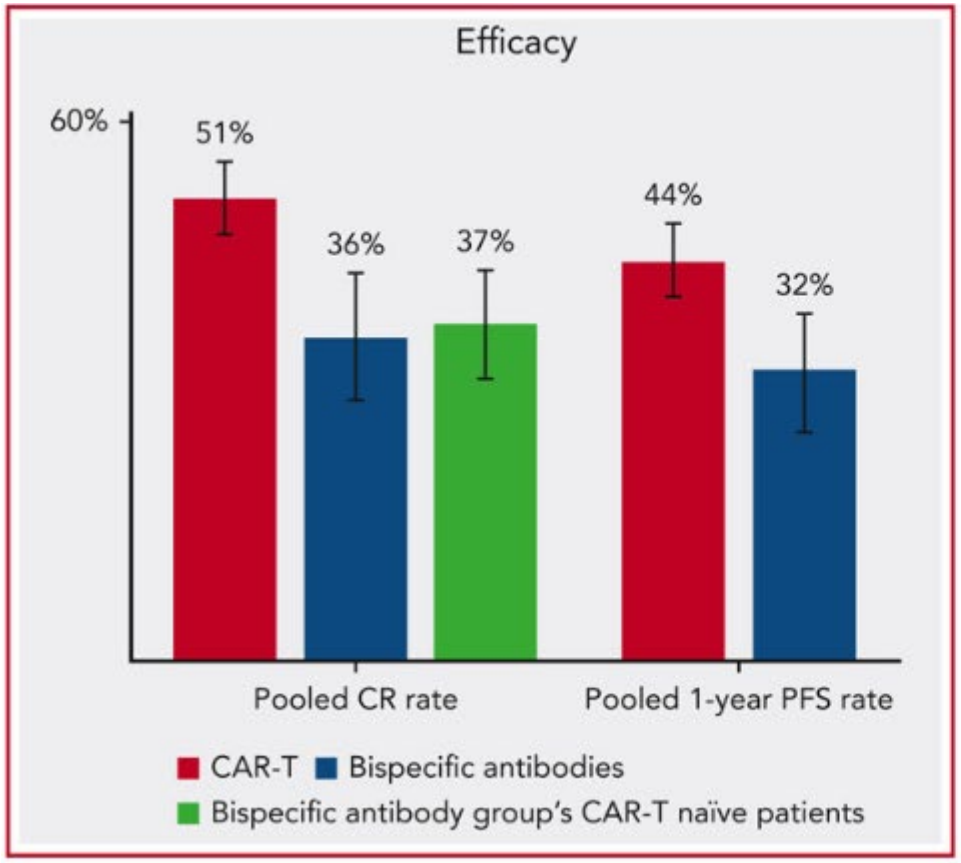
Epcoritamab-bysp PI.

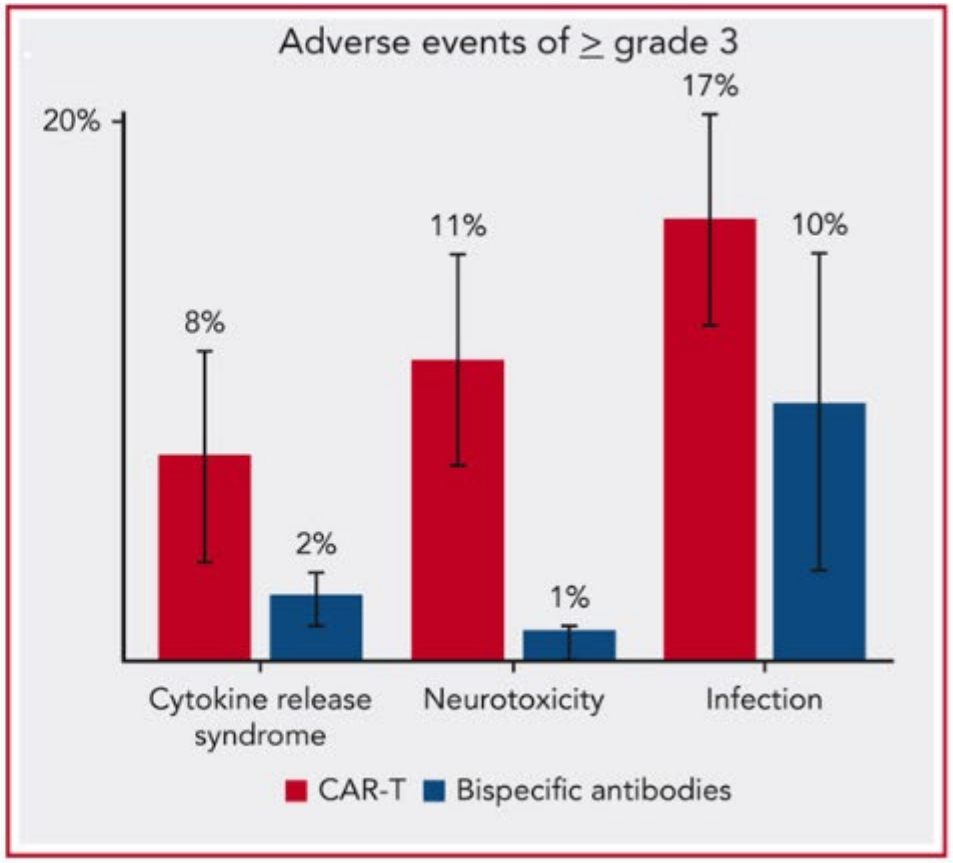
Glofitamab and Epcoritamab: Clinical Trial Data Efficacy and Safety Summary

Bispecific	ORR	CR	Median DoR	Median PFS	Median Time to CR	CRS Incidence	ICANS Incidence	Cytopenias Grade 3/4	Serious Infections
Glofitamab	51.6%	39.4%	26.9 mo	12.1 mo	43.0 days	G1: 48% G2: 12% G3: 3% G4: 1%	G1/2: 5.0% G3/4: 3.0%	Neut: 26% Anemia: 8% Thromb: 8% Lymph: 83%	G3/4: 16.0% Fatal: 4.8%
Epcoritamab	63.0%	39.0%	15.5 mo	4.4 mo	2.7 mo	G1: 32% G2: 16% G3: 3% G4: 0%	G1: 4.5% G2: 1.3% G3: 0% G4: 0%	Neut: 32% Anemia: 12% Thromb: 12%	G3/4: 15.0% Fatal: 1.3%

Bacac. Clin Cancer Res. 2018;24:4785. Falchi. ASCO 2023. Abstr 7550. Dickinson. NEJM. 2022;387:2220. Glofitamab-gxbm PI. Karimi. ASCO 2023. Abstr 7525. Thieblemont. EHA 2022. Abstr LBA 2364. Thieblemont. JCO. 2023;41:223.

Comparison of CAR-T cell therapy and Bispecific antibodies as 3-line or later treatment for diffuse large B-cell lymphoma: A meta- analysis





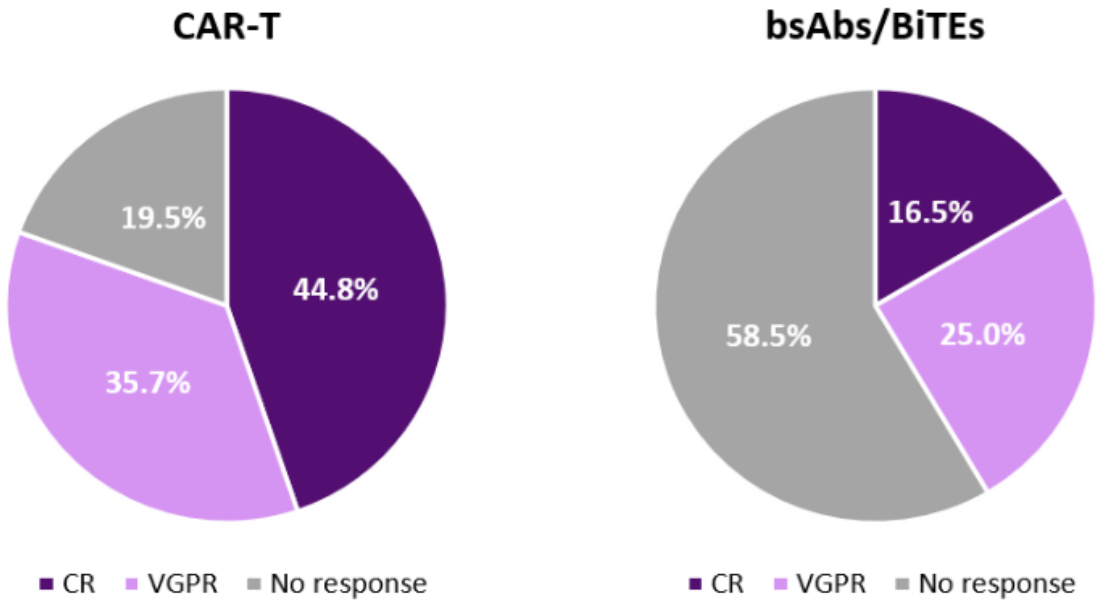
Blood (2024) 144 (6): 629–638

Comparison of CAR T-cell and bispecific antibody as third-line or later-line treatments for multiple myeloma: a meta-analysis

Journal for ImmunoTherapy of Cancer
2024;12:e010064.

- Results CAR-T-cell therapy achieved significantly higher pooled CR rate (0.54 (95% CI 0.42–0.69) vs bispecific antibodies 0.35 (0.30–0.41), p<0.01) and pooled ORR (0.83 (0.76–0.90) vs 0.65 (0.59–0.71), p<0.01).

Figure 1. Response rates reported with BCMA CAR-T and bsAbs/BiTEs[1]



1. Session V. 3rd European CAR-T cell Meeting; Feb 5, 2021; Virtual.

AE Identification and Management and/or Addressing Barriers to Treatment

Selected risk-adapted strategies to mitigate CRS

- **Analyses of factors that define the risk of CRS**
  - Antibody format
  - Modulating CD3 binding domains and their affinity
  - Clinical dosing strategies (such as use of priming doses or step-up dosing)
  - Quantitative cytokine modelling (using induced cytokine levels to guide subsequent dosing)
  - Route of administration (intravenous versus subcutaneous)
  - Composition of the redirected effector cell population (pan-T cell populations versus $CD8^+$ T cells or tissue-resident T cells, NK cells and/or macrophages)
  - Indication (haematological malignancies or solid tumours expressing specific targets)
  - Tumour burden
- **Strategies to prevent severe CRS**
  - Pre-infusion risk assessment
  - Pre-infusion risk mitigation (such as debulking to reduce the size of the antigen compartment)
  - Pre-emptive strategies: early tocilizumab or steroids in patients with low-grade CRS
  - Optimize supportive care (including the use of intravenous fluids)
- **Pharmacological approaches to treat CRS**
  - Treatment interruption or discontinuation
  - Glucocorticoids
  - Cytokine-targeted strategies
    - IL-6R/IL-6 inhibitors (tocilizumab, siltuximab)
    - IL-1 inhibitors (anakinra)
    - Inhibitors of TNF (for example, etanercept) or IFNγ (emapalumab)
- **Innovative approaches to prevent CRS**
  - Pretreatment with antibodies competing for the same targets
  - Restricting T cell activation to the tumour site (for example, using masking strategies for conditional activation of T cell engagers)

CRS, cytokine release syndrome; NK, natural killer.

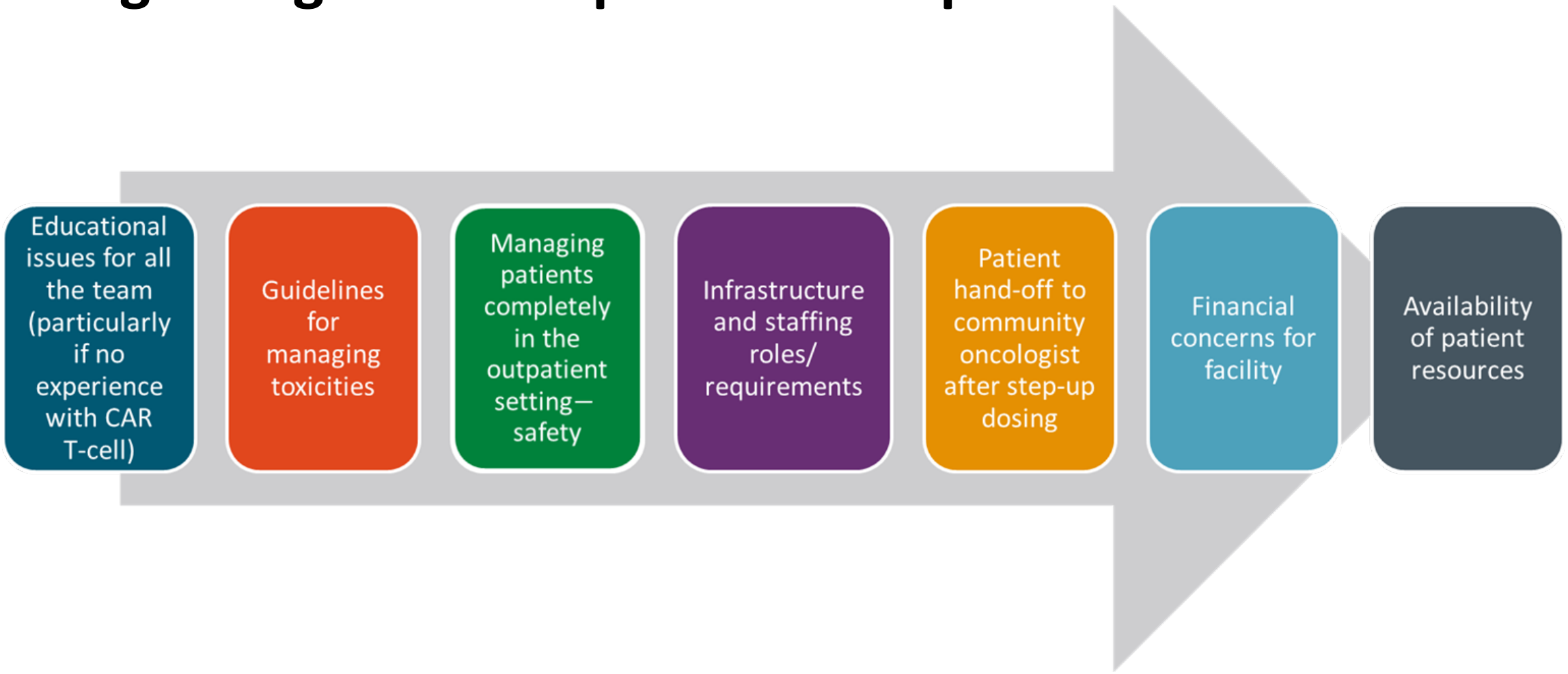
Nature Reviews Clinical Oncology volume 21, pages 539–560 (2024

Summary of Key AEs With Bispecific Antibodies

- **CRS**
  - ASTCT grading
  - Incidence and timing of onset vary by disease subtype, product, administration route, and dosing schedule
  - Incidence across products: 40%-65% with majority occurring with the first step-up doses
    - Grade 1/2: 43%-70%
    - Grade 3/4: 2%-4%
  - CRS Onset (most grade 1-3/grade 4-5): Cycle 1 Day 15 / between Cycle 1 Day 15 and Cycle 2 Day 1
- **Neurotoxicity: ICANS**
  - ASTCT grading
  - Incidence across products: 1%-8%
- Cytopenias/infections
- Tumor flare (with FL and DLBCL FDA-approved bispecific antibodies)
- Hypersensitivity reactions
- ICANS onset: N/A

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Ongoing Healthcare Professionals Challenges Regarding Novel Bispecific Therapies



ASTCT Consensus Grading of CRS

CRS Parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever[*†]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
	With either:			
Hypotension[*]	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
	And/ or[‡]			
Hypoxia[*]	None	Requiring low-flow nasal cannula (low-flow nasal cannula is ≤6 L/min and high-flow nasal cannula is >6 L/min)	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

[*]Not attributable to any other cause. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
[†]In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity.
[‡]CRS grade is determined by the more severe event.

Lee. Biol Blood Marrow Transplant. 2019;25:625.

激素釋放症候群 Cytokine Release Syndrome (CRS) 評估及建議治療措施

(通常發生時間: 開始治療後 2-3 天 (但可能在幾小時內，也可能延後到10-15天）。通常持續時間: 7–8 天，根據藥物會有差異)

CRS的等級	Anti-IL-6 therapy	類固醇	建議措施
第1級 體溫≥38°C，無影響血壓或血氧	對於CRS持續時間超過3天，且患者有顯著症狀、合併症和/或年齡超過65歲，考慮給予單劑Tocilizumab 8 mg/kg(不超過 800mg) 靜脈輸注1小時	可考慮給予單劑dexamethasone 10 mg 並評估是否需要下一劑量	● Fever workup並使用考慮使用廣效經驗性抗生素 ● 如果嗜中性白血球低下，考慮使用G-CSF。 ● 給予IV fluid ● 評估是否有Organ dysfunction ● 觀察決定是否暫停給藥 ● 給予退燒藥做症狀治療
第2級 體溫≥38°C，並有下列任一種情形： 1. 低血壓，對輸液有反應，且不須使用升壓劑 2. 低血氧，須使用低流量氧氣(鼻導管或面罩)	給予Tocilizumab 8 mg/kg(不超過800mg) 靜脈輸注1小時 *若無改善，則視需要每8時重複投予tocilizumab。24小時內最多投予3劑；最多共可投予4劑。	如果在開始投予1-2劑tocilizumab後24小時內血壓未獲改善，則給予methylprednisolone 1mg/kg Q12H 或 dexamethasone 10 mg Q24H to Q6H *持續使用類固醇治療，直到副作用降至第1級或更低，然後在3天內逐步減量。	● 暫停給藥 ● 給予IV fluid resuscitation，對於兩次IV fluid resuscitation和開始tocilizumab後仍持續性頑固性低血壓者，開始使用升壓藥，並考慮轉至ICU ● 若在開始tocilizumab治療後24小時內沒有改善，進入第三級治療。 ● 治療Organ dysfunction
第3級 體溫≥38°C，並有下列任一種情形： 1. 低血壓，只須使用一種升壓劑 2. 低血氧，須使用高流量鼻導	同第2級治療，並給予methylprednisolone 1mg/kg Q12H 或dexamethasone 10 mg Q12H to Q6H		● 轉至ICU以進行連續性血液動力學監測 ● 必要時進行插管及呼吸器治療。 ● 排除其他造成休克的原因 ● 治療Organ dysfunction ● 通常需永久停用藥物

激素釋放症候群 Cytokine Release Syndrome (CRS) 評估及建議治療措施

第3級 體溫≥38°C，並有下列任一種情形： 1. 低血壓，只須使用一種升壓劑 2. 低血氧，須使用高流量鼻導管、非再吸入型面罩	同第2級治療，並給予methylprednisolone 1mg/kg Q12H 或dexamethasone 10 mg Q12H to Q6H	• 轉至ICU以進行連續性血液動力學監測 • 必要時進行插管及呼吸器治療。 • 排除其他造成休克的原因 • 治療Organ dysfunction • 通常需永久停用藥物
第4級 體溫≥38°C，並有下列任一種情形： 1. 低血壓，須使用兩種以上升壓劑 2. 低血氧，須使用高正壓呼吸器或插管	同第2級治療，並給予 dexamethasone 10 mg Q6H 或methylprednisolone 1-2g / daily * 3 days 考慮後線免疫抑制劑如:Anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, intrathecal chemotherapy, or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT)	

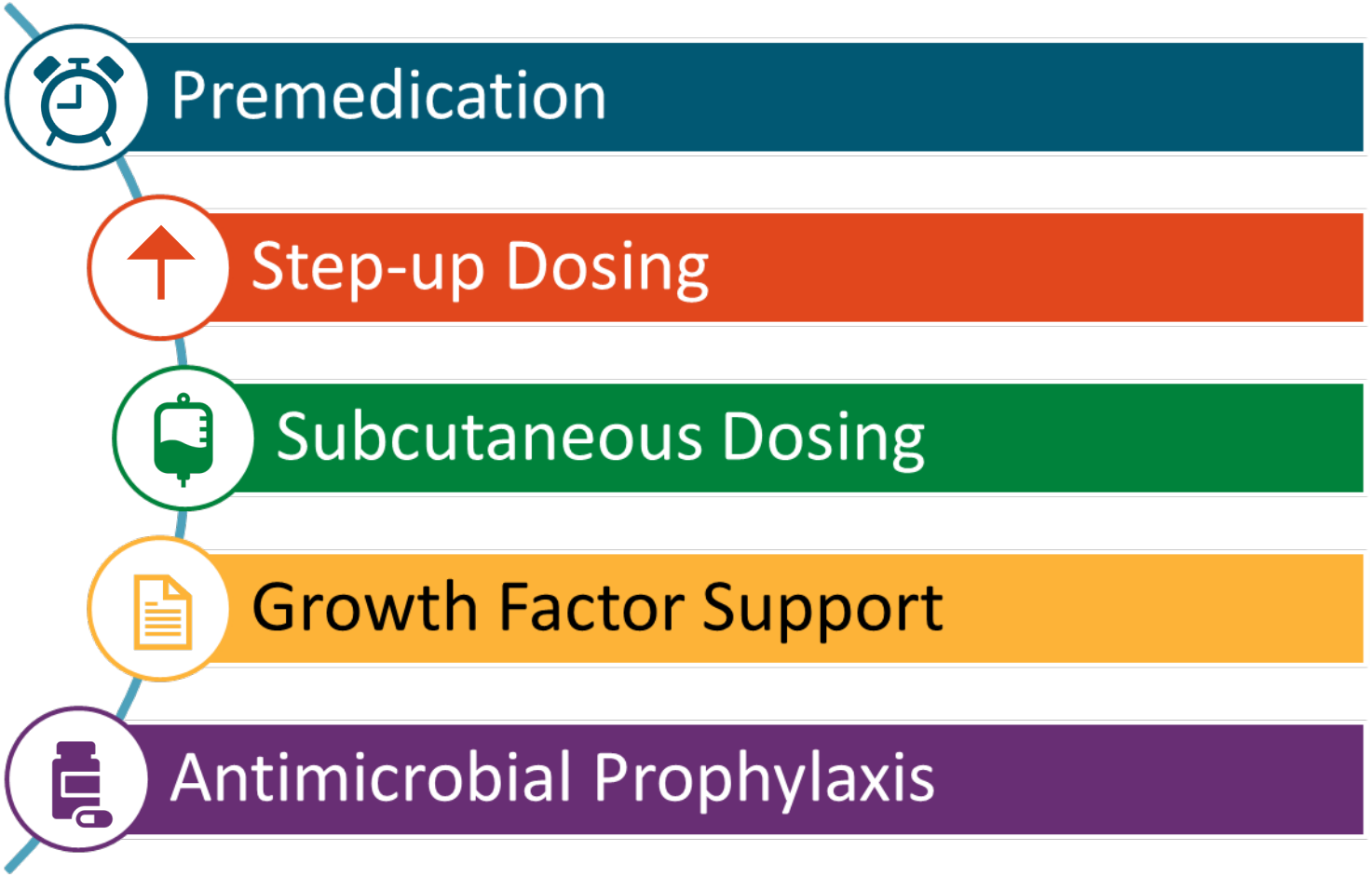
Crombie. Blood. 2024;143:1565.

ICANS：免疫作用細胞相關神經毒性症候群 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) 評估及建議治療措施 (通常發生時間: 開始治療後 4-10 天 。通常持續時間: 14-17 天

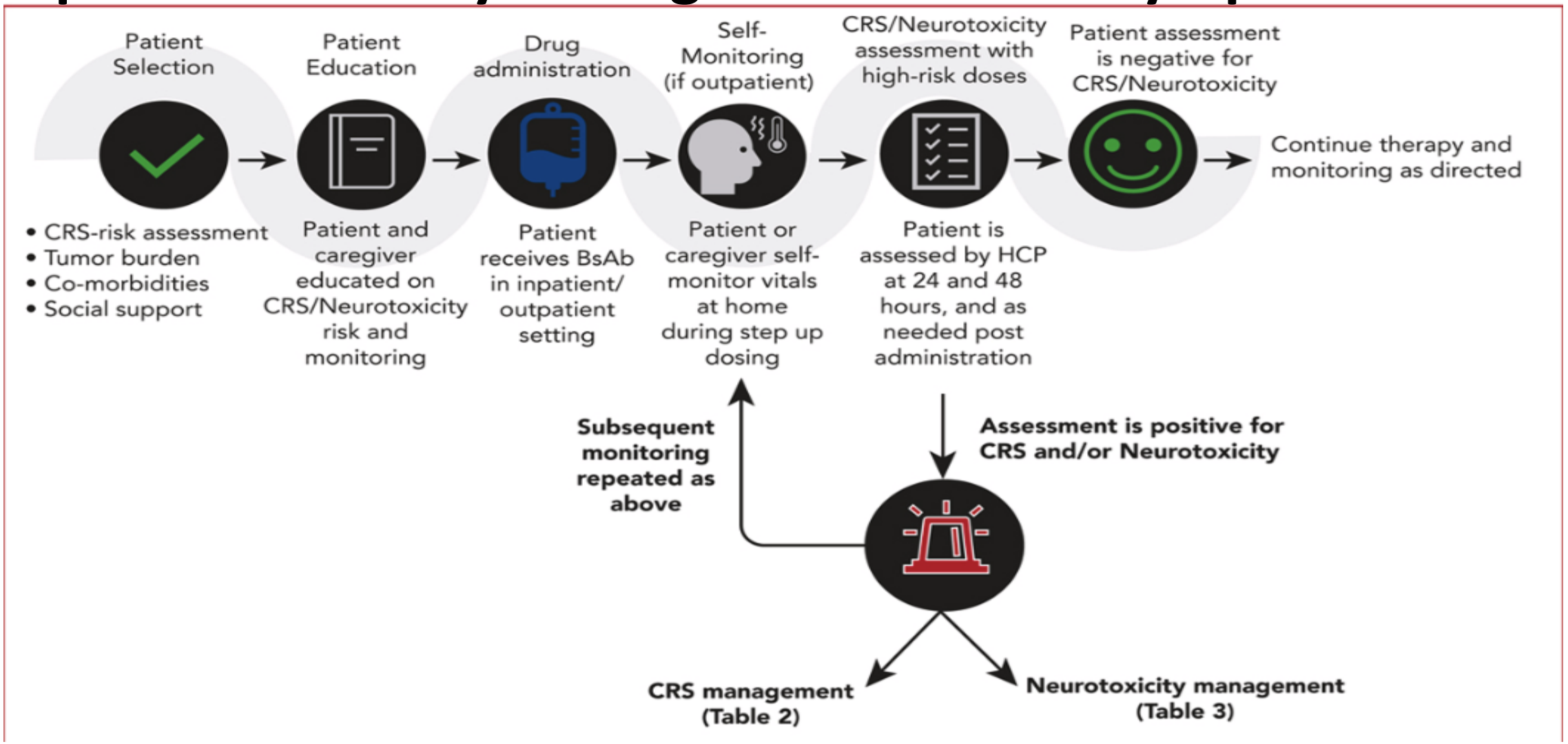
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unarousable)
Depressed consciousness	Awakens spontaneously	Awakens to voice	Awakens to tactile stimuli only	Unarousable or needs vigorous/repetitive tactile stimuli, stupor, or coma
Seizure	N/A	N/A	Clinical seizure that is focal or generalized, resolves rapidly; nonconvulsive seizures via EEG, resolves with intervention	Prolonged seizure (>5 min) that is life-threatening *or* clinical or electrical seizures that are repetitive and do not return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness (ie, hemiparesis or paraparesis)
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema via neuroimaging	Diffuse cerebral edema via neuroimaging; decerebrate/decorticate posturing; papilledema, cranial nerve VI palsy, or Cushing triad

ICE
▪ **Orientation:** Orientate to current mo, yr, city, hospital (4 points) 定向能力: 對年份、月份、城市、醫院的定向能力（4 分）
▪ **Naming:** Name 3 objects, such as a clock, pen, or button (3 points) 命名能力：能夠命名三個物體（如時鐘、筆、鈕扣）（3 分）
▪ **Following commands:** Follow simple commands, such as “show me 2 fingers” (1 point) : 遵從指令能力：能夠遵從簡單指令（如“給我看兩根手指”或“閉上眼睛並伸出舌頭”）（1 分）
▪ **Writing:** Write a standard sentence, such as “Our national bird is a bald eagle” (1 point) 寫作能力：能夠寫出一個標準句子（如“我要趕快康復”）（1 分
▪ **Attention:** Count backward by 10, starting at 100 (1 point) : 注意力：能夠倒數，從 100 開始每次減 10（1 分）

Toxicity Mitigation



Bispecific Antibody management in B cell lymphoma



Blood (2024) 143 (16): 1565–1575.

Monitoring and Managing Cytopenias

- Monitor CBC at baseline and periodically during treatment
- Withhold agent if severe anemia, thrombocytopenia, and neutropenia per PI
- Severe and long-lasting neutropenia poses increased infection risk
  - Administer appropriate infection prophylaxis
- Administer growth factor support per institutional guidelines

Crombie. Blood. 2024;143:1565. Ludwig. Lancet Oncol. 2023;24:e255.

Infection Prophylaxis and Vaccinations

- Complete outstanding vaccinations ≥2 wk prior to therapy start (eg, influenza, pneumococcal, COVID-19)
  - Delay postinfusion vaccinations for 3-6 mo after bispecific antibody therapy
- Optimal prophylaxis duration has not been established, but recommended for up to 6 mo following treatment
- Monitor immunoglobulin levels

Antibacterial Prophylaxis	Antiviral Prophylaxis	Antifungal Prophylaxis
Recommend for patients at high risk of infection	HSV/VZV prophylaxis in all patients	▪ PJP prophylaxis recommended ▪ Other antifungal prophylaxis recommended for patients at high risk of fungal infection

Crombie. Blood. 2024;143:1565. Ludwig. Lancet Oncol. 2023;24:e255. Raje. Blood Ca J. 2023;13:116.

Managing Infections Associated With Bispecific Antibodies

- Withhold until resolution; consider permanent discontinuation for grade 4 infections
- Manage infections in accordance with institutional policies and susceptibility patterns
  - Consult with infectious disease specialist
- Utilize targeted therapy if the infectious organism can be identified
- Consider IVIG for recurrent infections in accordance with institutional policies

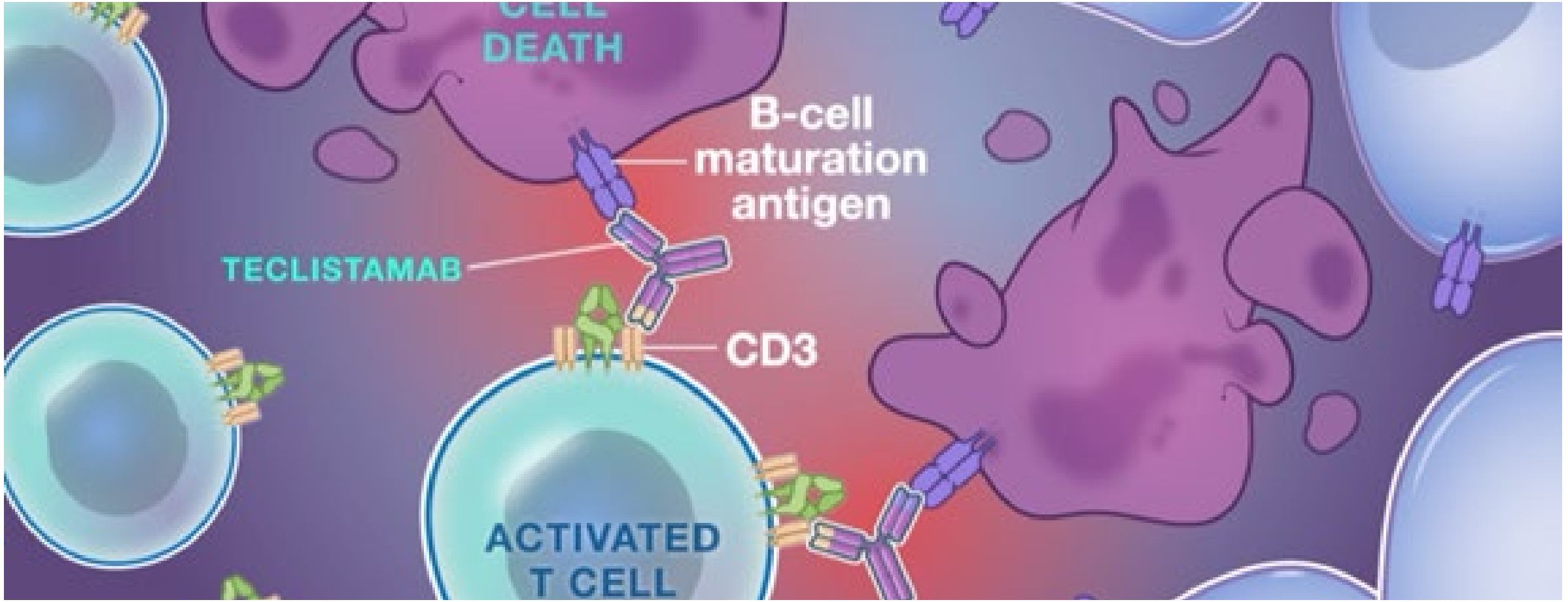
Bacterial Infections	Viral Infections	Fungal Infections
▪ Empiric antibacterial agents based on infection site ▪ Concomitant neutropenia: broad spectrum agents (third- or fourth-generation cephalosporin or carbapenem) ▪ Reserve vancomycin for specific indications	▪ Management based on type of virus and institutional protocol ▪ Examples include influenza, VZV, CMV, EBV, RSV, COVID-19	▪ Localized candidiasis: fluconazole ▪ Invasive candidiasis: echinocandin ▪ PJP: trimethoprim-sulfamethoxazole or atovaquone or primaquine with sulfonamide

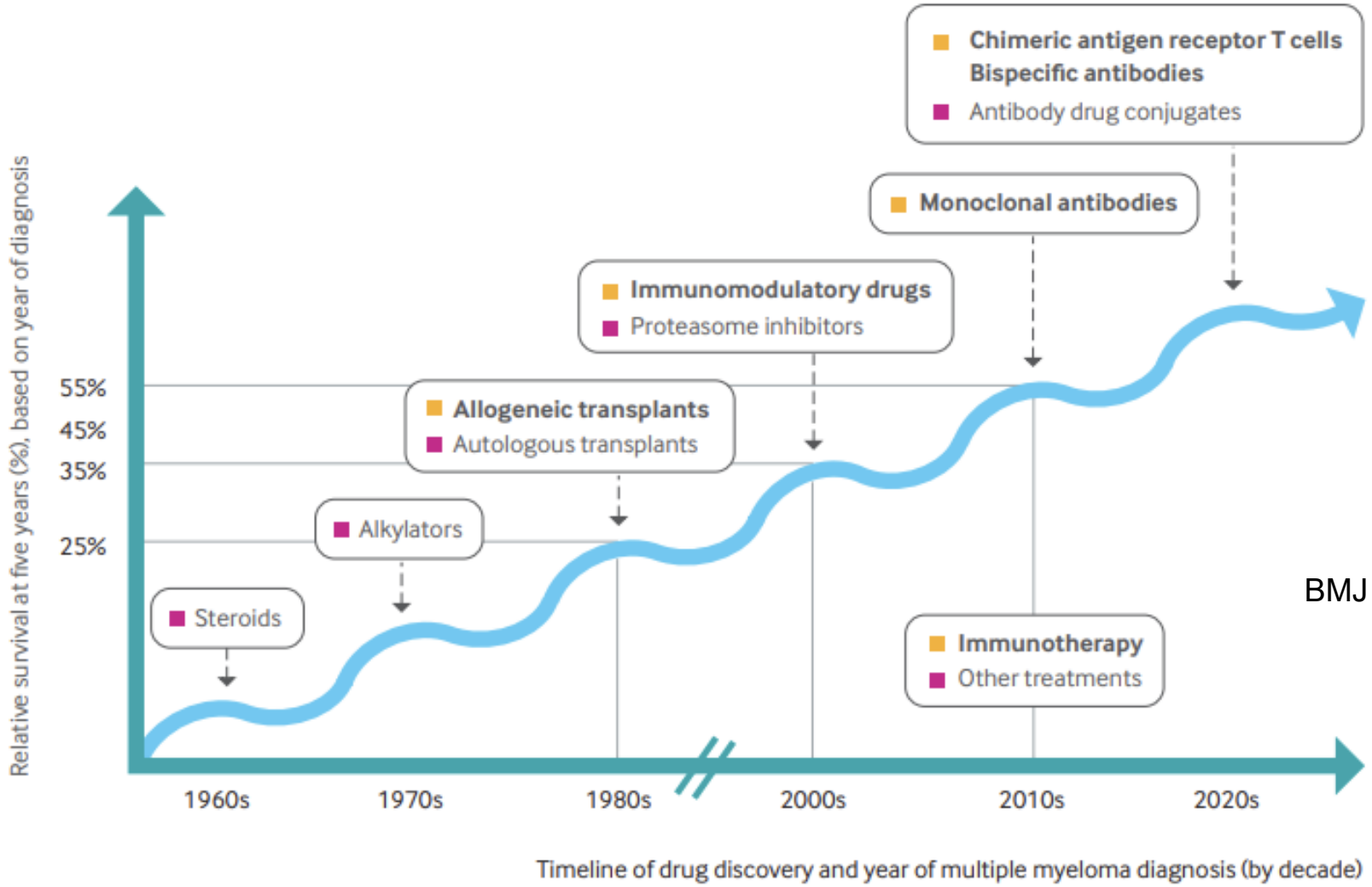
Crombie. Blood. 2024;143:1565. Ludwig. Lancet Oncol. 2023;24:e255. Raje. Blood Ca J. 2023;13:116.

B-cell precursor ALL with CD19 (+)
Philadelphia chromosome (-)
Blinatumomab (CD3 × CD19)

US FDA 適應症	試驗設計/適用病人	試驗結果	用法劑量
B-cell acute lymphoblastic leukemia, Relapsed or refractory, CD19 (+) disease NEJM 2017; 376:836-847	405 pts (TOWER) blinatumomab (271 pts) or chemotherapy (134 ps), 376 pts received at least one dose. mOS : 7.7 (blinatumomab group) vs 4.0 months (chemotherapy) P=0.01).	CR : (34% vs. 16%, P<0.001) P<0.001). Blinatumomab vs chemotherapy EFS : (6-month estimates, 31% vs. 12%; P<0.001), mDOR (7.3 vs. 4.6 months). A total of 24% underwent allogeneic stem-cell transplantation. ADR ≧ grade 3, (87% vs 92% chemotherapy group.)	≧45 kg (continuous IV infusion) Induction cycle 1: 9 mcg/day IV on days 1-7 and 28 mcg/day IV on days 8- 28, followed by 2 wks of off ≧45 kg Induction cycle 2: 28 mcg/day on days 1-28 followed by 2 wks of no treatment ≧45 kg Consolidation cycles 3 - 5: 28 mcg/day days 1 - 28 followed by 2 wks of no treatment ≧45 kg Continued therapy cycles 3- 9: 28 mcg/day on days 1 - 28 followed by 8 wks of no treatment
Treatment of adult and pediatric patients with B-cell precursor ALL in first or second complete remission with MRD ≥ 0.1% Clin Cancer Res (2019) 25 (2): 473–477	BLAST; NCT01207388) Pts: 86 >3 chemotherapy blocks of standard ALL therapy (e.g., induction, intensification, and consolidation), were in morphologic CR	Single-arm trial with 86 pts in CR1 or CR2 with MRD ≥ 0.1% CR1: 85.2% ; CR2: 72.0% Relapse-Free Survival (RFS): CR1: 35.2 months; CR2: 12.3 months ADR : pyrexia, infusion-related reactions, headache, infections, tremor, and chills.	Continuous intravenous infusion over 4 weeks, followed by a 2-week treatment-free interval. 15 μg/m2/day (equivalent to the recommended dosage of 28 μg/day for patients > 45 kg) 每次前導性或鞏固性治療的療程包含四週的連續輸注加上兩週的無治療期間，在臨床試驗當中，病人可以在第一次治療後任何時間點進行移植。
adult and pediatric patients >1 month with CD19 (+) Philadelphia chromosome (-) B-cell precursor acute lymphoblastic leukemia in the consolidation phase of multiphase chemotherapy. NEJM 2024;391:320-333	RCT phase 3 (1:1) Pt: 224 (age 30-70) BCR: ABL1 (-) indicating fusion) who had MRD (-) <0.01% after induction and intensification chemotherapy to receive 4 cycles of blinatumomab as consolidation chemotherapy	Adding Blinatumomab+chemotherapy vs chemotherapy The 3-year OS : 84.8% vs 69% The hazard ratio [HR] for OS : 0.42 . In a later analysis the 5-year OS : 82.4 % vs 62.5 %, HR : 0.44	two cycles of blinatumomab at a dose of 28 μg per day for 4 weeks with a 2-week interval between cycles, followed by four cycles of chemotherapy and two additional cycles of blinatumomab

Multiple myeloma





BMJ 2020;370:m3176

Fig 1 | Multiple myeloma treatments—timeline of drug discovery and five year relative survival (using data from the Surveillance, Epidemiology, and Ends Results program).

Data for year of diagnosis and relative survival are: 1975, 26.5% (observed); 1980, 26.0% (observed); 1985, 27.4% (observed); 1990, 29.9% (observed); 1995, 33.5% (observed); 2000, 34.6% (observed); 2005, 47.1% (observed); 2010, 53.6% (observed); 2015, 55.3% (modelled)

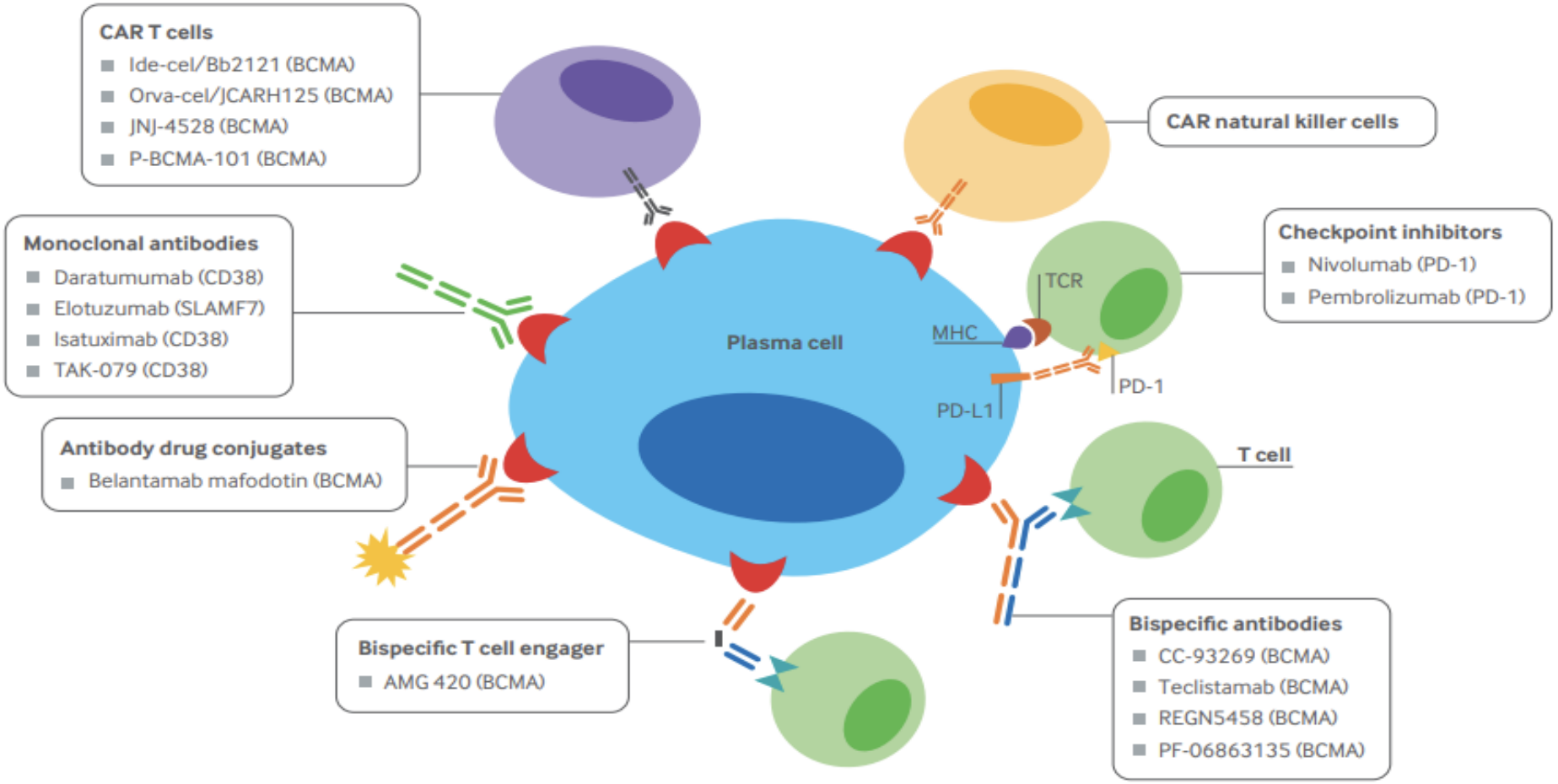
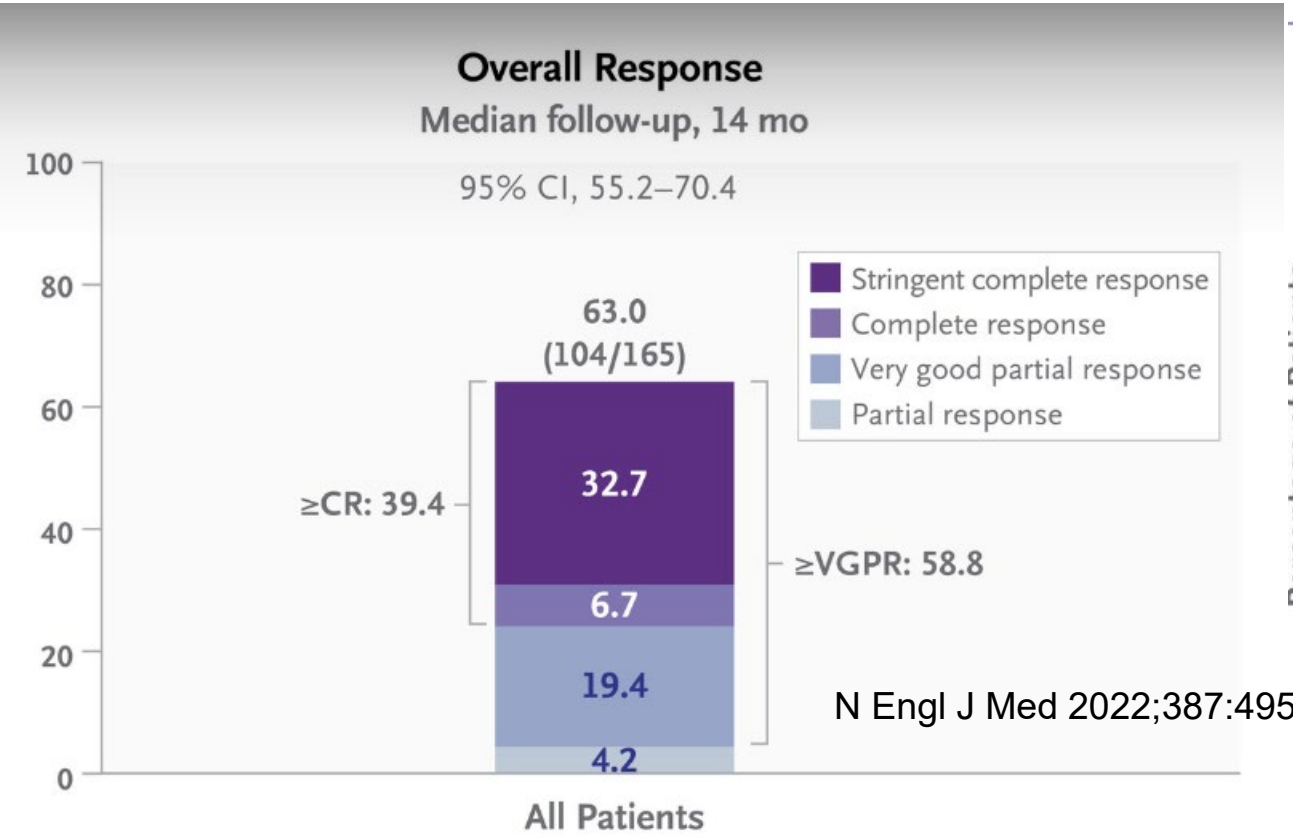
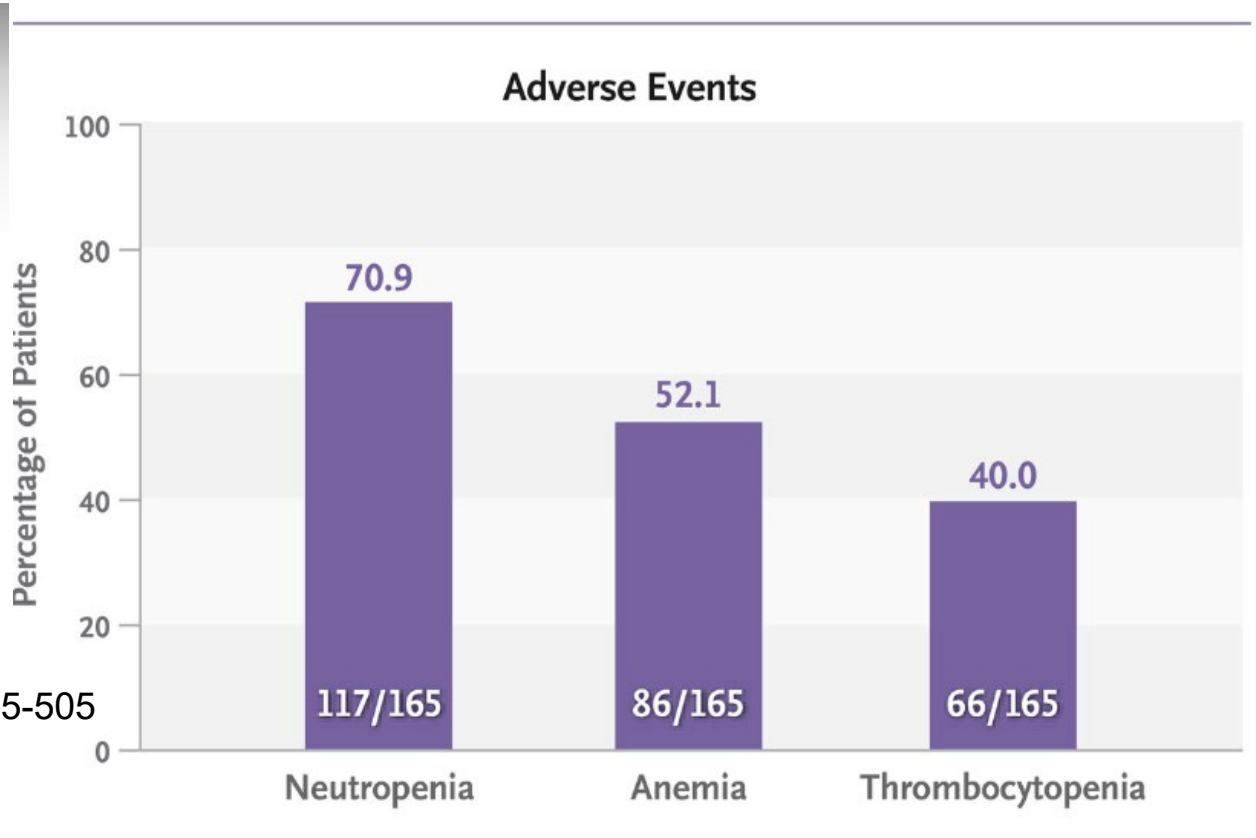


Fig 2 | Recent immunotherapeutic approaches to treat multiple myeloma. CAR=chimeric antigen receptor; TCR=T cell receptor; MHC=major histocompatibility complex; BCMA=B cell maturation antigen; PD-L1=programmed death-ligand 1; PD-1=programmed cell death protein 1

BMJ 2020;370:m3176

Antibody Name	Trial Name (Study Patient Number)	Patients	Result	ADR
Teclistamab CD3 × BCMA	MajesTEC-1 (165 pts) Dose : 1.5 mg/kg after receiving step-up doses	R/R Multiple Myeloma triple-class (immunomodulator, proteasome inhibitor, AntiCD38 inhibitor) refractory disease (median, five previous therapy lines)	ORR : 63% mDOR: 18.4 months mDOPFS : 11.3 months .	72.1% , neutropenia (grade 3/4, 64.2%), anemia (grade 3/r 4, 37.0%), and thrombocytopenia (grade 3/ 4, 21.2%). Infections (grade 3/4, 44.8%). ICAN (3.0%; all grade 1 or 2).





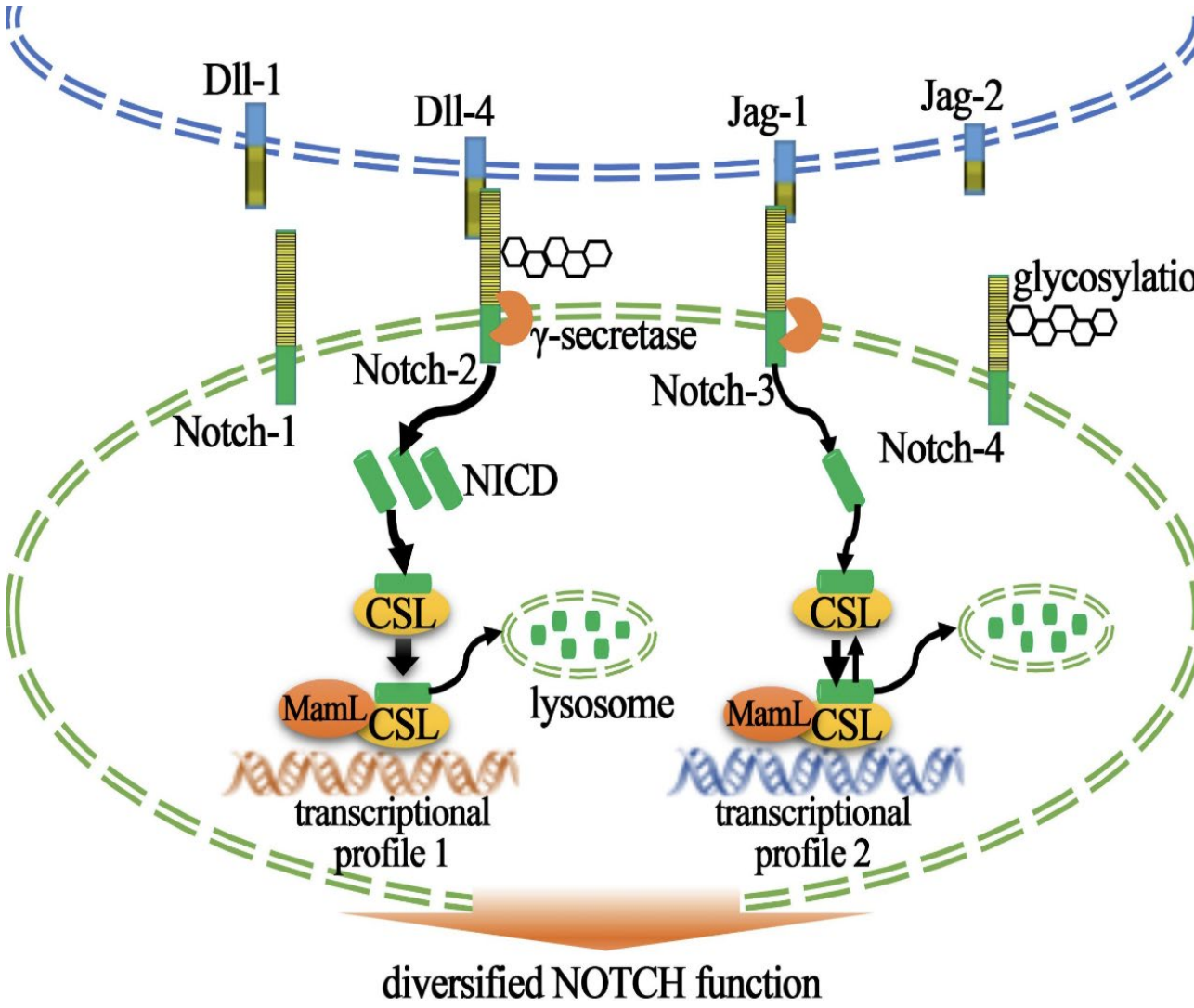
N Engl J Med 2022;387:495-505

Small cell lung cancer

- is an aggressive, high-grade, neuroendocrine carcinoma (NEC) that annually contributes to 13%–15% of lung cancer diagnoses
- 5-year survival rate: 27% (localized disease) to 3% (metastatic disease)
- Transient responses to current standard-of-care (SOC) therapies that are almost always followed by the development of drug resistance and relapse
- No targeted therapy for SCLC has proven to be better than existing therapies

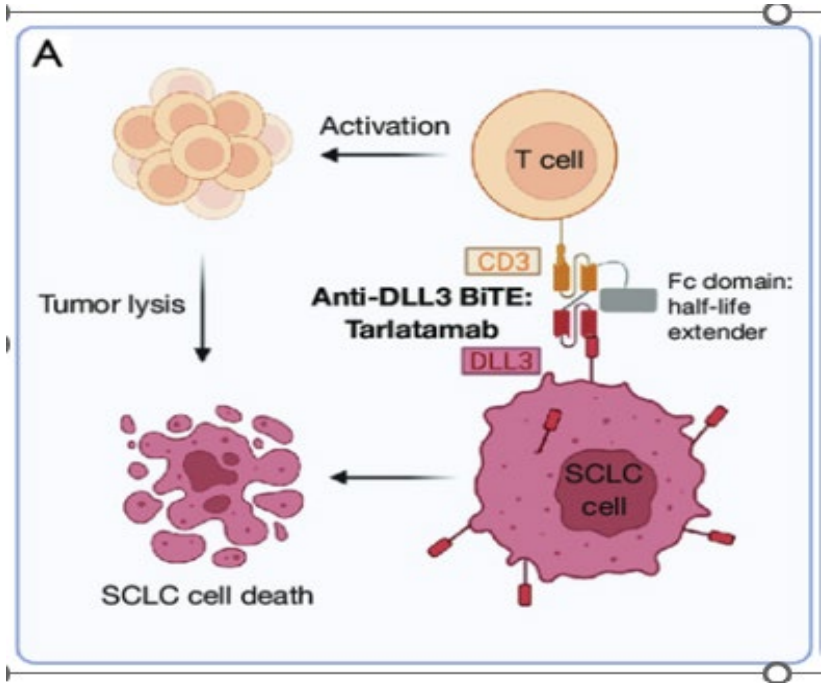
Mechanism of Notch Signaling

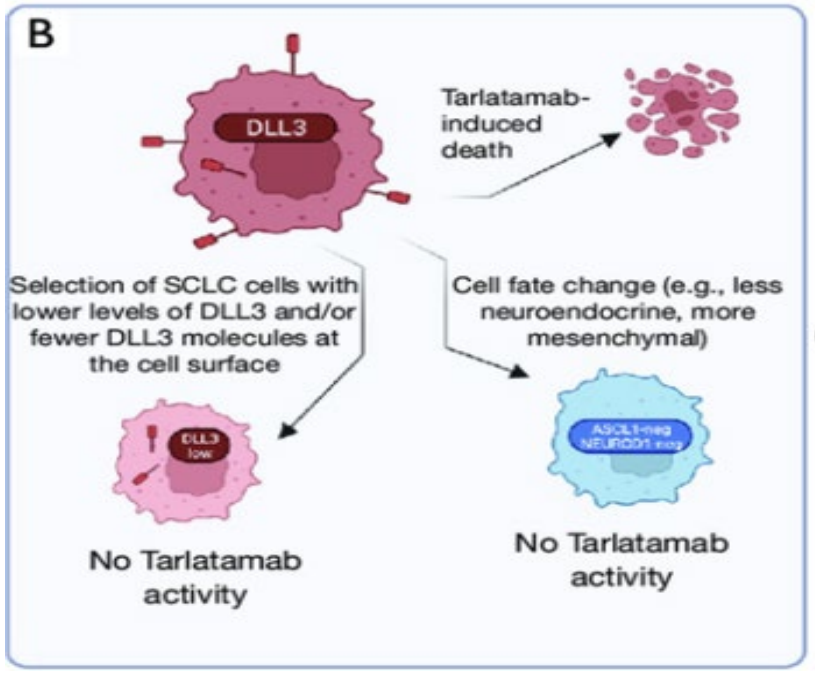
- The Notch signaling pathway operates through direct **cell-to-cell interactions** via the following steps
  - **Ligand Binding**
    - Ligands (e.g., Delta-like [DLL] and Jagged families) on one cell bind to Notch receptors (Notch1-4) on an adjacent cell.
  - **Receptor Activation and Cleavage**
    - the Notch receptor undergoes proteolytic cleavage by **gamma-secretase**, releasing the Notch intracellular domain (NICD).
  - **Nuclear Translocation:核轉位：**
    - The NICD translocates to the nucleus and interacts with transcription factors to regulate gene expression.
  - **Target Gene Activation**
    - Genes involved in cell differentiation, proliferation, and apoptosis are activated, including **Hes and Hey family genes**, which regulate downstream cellular responses.



DLL3 and the Notch Pathway

- Delta-like ligand 3 (DLL3) is an atypical Notch ligand that acts as a negative regulator of Notch signaling in SCLC.
- DLL3 is **highly expressed** on the surface of SCLC tumor cells but **not in normal tissues**
- Due to the suppression of Notch signaling, SCLC cells often rely on DLL3 to maintain their neuroendocrine phenotype.
  - **Antibody-drug conjugates (ADCs):抗體藥物偶聯物(ADCs)**：
    - **Rovalpituzumab tesirine (Rova-T):**
      - A DLL3-targeting ADC that initially showed promise in clinical trials but was later discontinued due to toxicity and limited efficacy.
  - **Bispecific T-cell engagers (BiTEs):雙特異性 T 細胞接合劑（BiTEs）**：
  - **CAR-T Cell Therapy:CAR-T 細胞療法**





Transl Lung Cancer Res 2023 | https://dx.doi.org/10.21037/tlcr-23-230

Small cell lung cancer : extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

Antibody Name	Trial Name (Study Patient N)	Indication	Dosing	Comparative ORR/mOS	mDOR	Overall Survival (mOS)	Adverse Events	Source of Journal
Tarlatamab CD3 x DLL3	**DeLLphi-300 (152 pts)**	**R/R Small Cell Lung Cancer (SCLC) with DLL3 expression**	**tarlatamab ≥10 mg dose q2 wks , once q3 wks, or once on day 1 and once on day 8 of a 21-day cycle**	**ORR :25%** mOS :17.5 months (once d1, d8 a 21 cycles mOS 20.3 months (10mgq 2 wks)	mDOR : 11.2 months CNS tumor shrinkage of ≥30% was observed in 62.5% of patients with baseline CNS lesion of ≥10 mm	**17 pts (10 mg Q2 wks , ORR 35.3%, the mDOR was 14.9 months , mOS : 20.3 months and 29.4% had sustained disease control with time on treatment ≥52 weeks**	**Cytokine release syndrome, Anemia, Dyspnea**	J Clin Oncol . 2024 Oct 10;42(29):3392-3399

Amivantamab (EGFR × MET) : Patients with Non–Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations

- EGFR mutations, 85 % of all mutations (exon19 deletions and exon 21 L858R point mutations)
- The third most common EGFR mutations: insertions in exon 20 (EGFR Ex20Ins)
- EGFR exon 20 insertion mutations does not respond well to treatment with currently approved EGFR tyrosine kinase inhibitors
- MET(Mesenchymal-Epithelial Transition Factor) amplification or overactivation is a common mechanism of resistance in cancers initially responsive to EGFR inhibitors

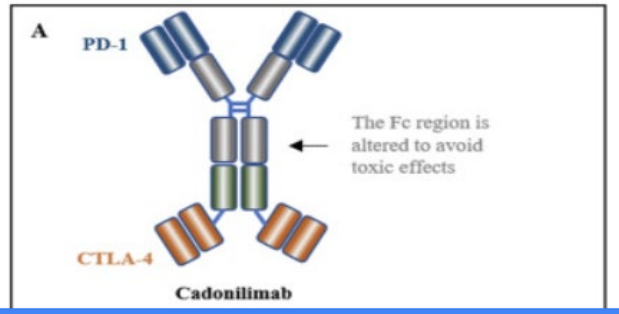
Amivantamab	EGFR × MET	Advanced-stage NSCLC (EGFR exon 20 insertion mutations (in combination with chemotherapy): ORR 73%, mPFS 11.4 months, mOS NR	Neutropenia (33%), rash (11%), leukopenia (11%), anaemia (11%), thrombocytopenia (10%)	2021[a] (FDA)

Amivantamab (EGFR x MET)

Trial name	Pts	Indication	Comparative Protocol	Comparative ORR	Comparative PFS	Comparative OS	Adverse Events
CHRYSALIS J Clin Oncol 39:3391-3402	81	Locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, post-platinum-based chemotherapy	Amivantamab monotherapy	ORR: 40%	mDOR : 11.1 months mPFS : 8.3 months		Common: rash, infusion-related reactions, paronychia; Serious: interstitial lung disease, pneumonitis
PAPILLON N Engl J Med 2023;389:2039-2051	308 phase3	First-line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations	Amivantamab + carboplatin/pemetrexed vs. carboplatin/pemetrexed alone	73% vs 47%	PFS : 11.4 vs 6.7 months At 18 months, PFS : 31% vs 3%		
MARIPOSA N Engl J Med 2024;391:1486-1498	1074 pts (429 to amivantamab–lazertinib, 429 to osimertinib, and 216 to lazertinib)	Non–small cell lung cancer, locally advanced or metastatic, with EGFR exon 19 deletion or exon 21 L858R substitution mutation, first-line treatment	Amivantamab + lazertinib vs. Osimertinib	ORR : 86% vs 85%	mDOR: 25.8 vs 16.8 months	The incidence of discontinuation 10% vs 3%	

Week 1: IV: 1,050 mg split over days 1 and 2 (350 mg on day 1 and 700 mg on day 2). Weeks 2 to 5: IV: 1,050 mg once weekly. Subsequent infusions (starting at week 7): IV: 1,050 mg once every 2 weeks until disease progression or unacceptable toxicity.

Cadonilimab (PD-1 × CTLA4)



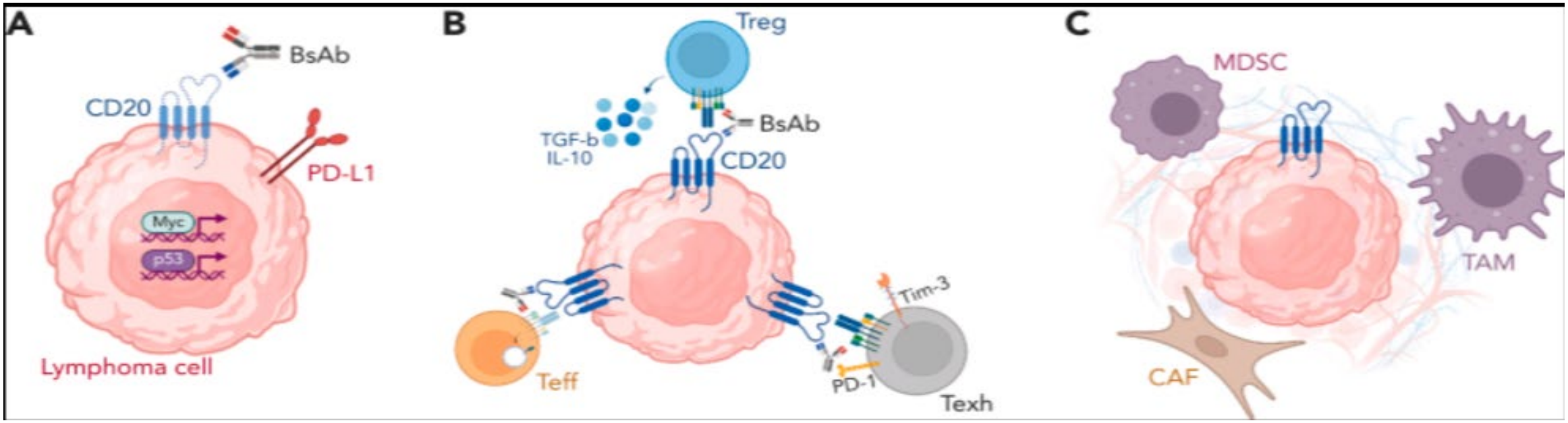
Trial Name	Study Patient Number	Indication	Comparative Protocol	Comparative ORR	Comparative PFS	Comparative OS	Adverse Events	Dosing
Phase 3 Clinical Study **Lancet . 2024 Oct 26;404(10463): 1668-1676**	COMPASSION-16 445 pts	Cadonilimab plus platinum-based chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer	Cadonilimab+ chemotherapy vs chemotherapy	ORR: 33.0%	PFS : 12·7 VS 8·1 months	Median OS: 27 vs 22·8 months	Common: anemia, hypoalbuminemia, decreased white blood cell count; Serious: interstitial lung disease, pneumonitis	cadonilimab (10 mg/kg) every 3 weeks for six cycles, followed by maintenance therapy every 3 weeks for up to 2 years.
AK104-302 (COMPASSION-15) **2024 AACR Annual Meeting; April 5-10, 2024; San Diego, CA.**	610	First-line treatment for unresectable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (GC/GEJC)	Cadonilimab + XELOX (capecitabine/oxaliplatin) vs. placebo + XELOXCadonilimab + XELOX	ORR: 65.2% (Cadonilimab arm) vs. 48.9% (Placebo arm)	Median PFS: 7 months (Cadonilimab arm) vs. 5.3 months (Placebo arm)	Median OS: 15 months (Cadonilimab arm) vs. 10.8 months (Placebo arm)	Common: rash, infusion-related reactions, paronychia; Serious: interstitial lung disease, pneumonitis	

Mechanism of resistance

(A) tumor cell–intrinsic mechanisms,

(B) T-cell intrinsic mechanisms,

(C) T-cell extrinsic mechanisms,



Antigen loss and activation of immune-evasive gene expression programs,

Activation of regulatory T-cells, downregulation of the T-cell receptor, and development of T-cell exhaustion,

Recruitment of immunosuppressive myeloid and/or stromal cells. CAF, cancer-associated fibroblast; IL-10, interleukin-10; MDSC, myeloid-derived suppressor cell

PD-1, programmed death 1; PD-L1, programmed death ligand 1; TAM, tumor-associated macrophage; Teff, effector T cell; Texh, exhausted T cell; TGF-b, transforming growth factor beta; Tim-3, T-cell immunoglobulin mucin-3; Treg, regulatory T cell.

Blood (2023) 141 (5): 467–480.

Can we do better

- Targeting when tumor burden low (MRD)
- Bring treatment to earlier lines before resistance
- Combination therapy : Chemotherapy, immunomodulatory, targeted
- Manage T cell exhaustion

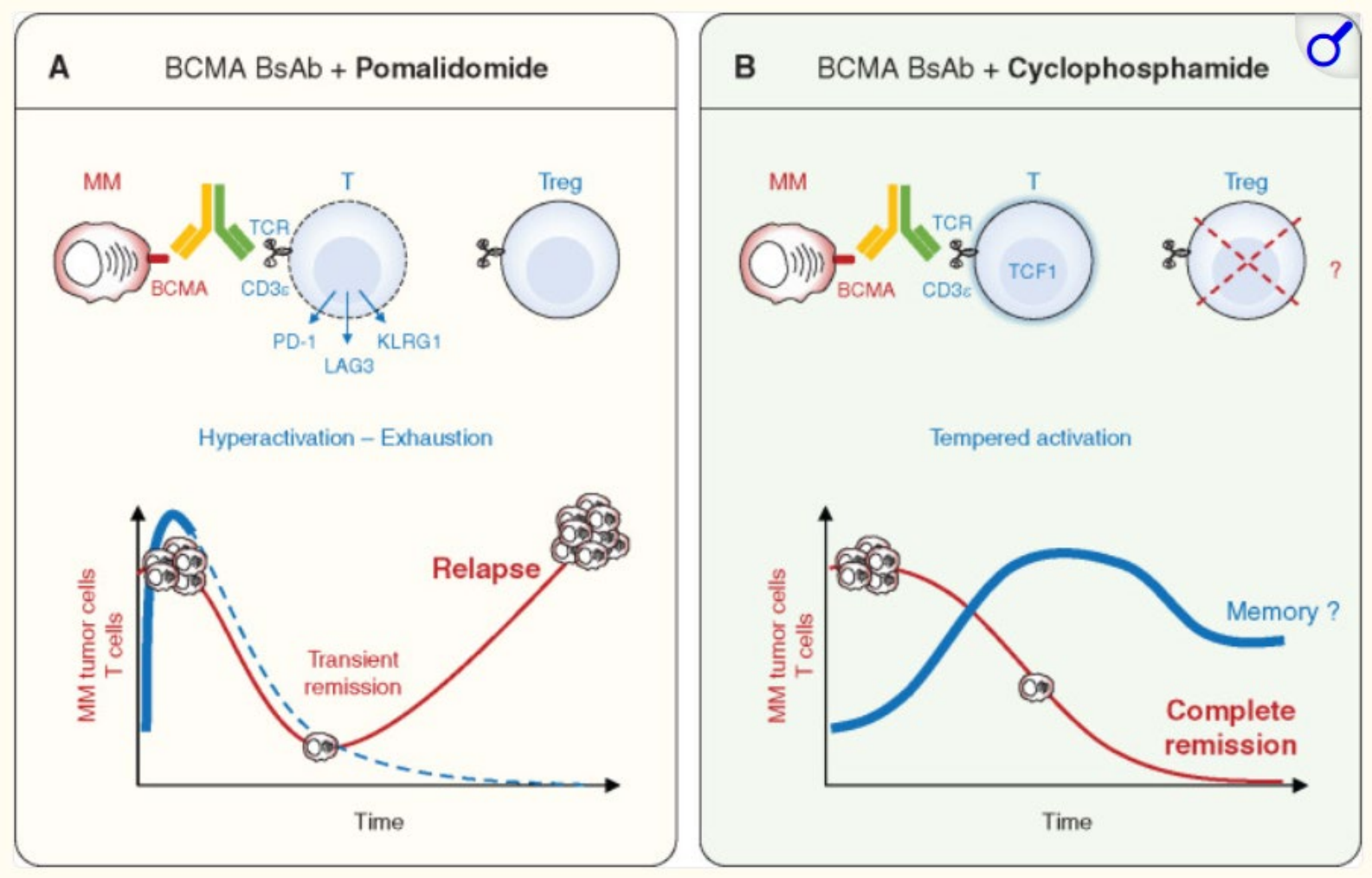
Optimal combinations

最佳的治療組合策略以達成 BCMA/CD3ε 雙特異性抗體（BsAb）在多發性骨髓瘤（MM）中持久的療效

A. IMiD 藥物 Pomalidomide 對骨髓瘤細胞（細胞毒性作用）及免疫細胞（刺激作用）產生多方面的影響。然而，矛盾的是，Pomalidomide 在 BsAb 治療過程中會促進 T 細胞的過度活化及衰竭，最終導致腫瘤復發。

B. Cyclophosphamide 是一種烷化劑，具有腫瘤減量的效果，同時也是一種淋巴耗竭劑。在與 BCMA/CD3ε BsAb 聯合使用時，能夠適度調控 T 細胞的活化，減輕 T 細胞衰竭，改變腫瘤微環境，並獨特地誘導持久的抗多發性骨髓瘤免疫反應。

Treg：調節性 T 細胞。



Blood Cancer Discov. 2021 Jun 4;2(4):297–299.

Conclusion

- Bispecific antibodies represent a transformative advancement in oncology, offering promising new treatment options, particularly for hematologic malignancies and select solid tumors.
- T cell engagers need Step-Up Dosing, monitor Cytokine Release Syndrome /Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- To find Optimal combinations are on going
- T-cell exhaustion is a significant challenge in bispecific antibody (bsAb) therapies

Thank you for listening