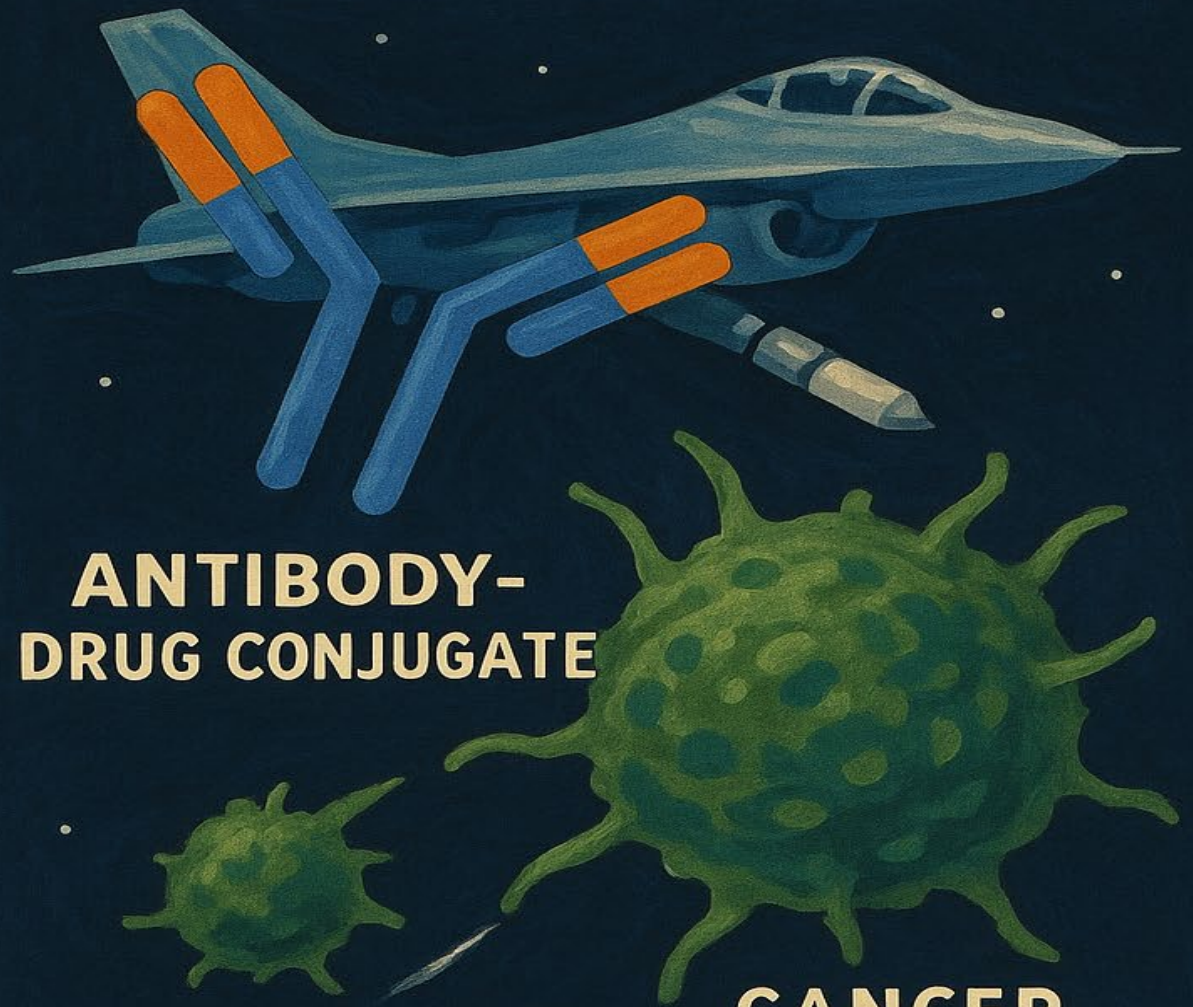
Chemotherapy 2.0 & Antibody 2.0
（化療2.0與抗體2.0）
精準腫瘤醫學的新時代

臨床藥師：方麗華

MIDNIGHT HAMMER



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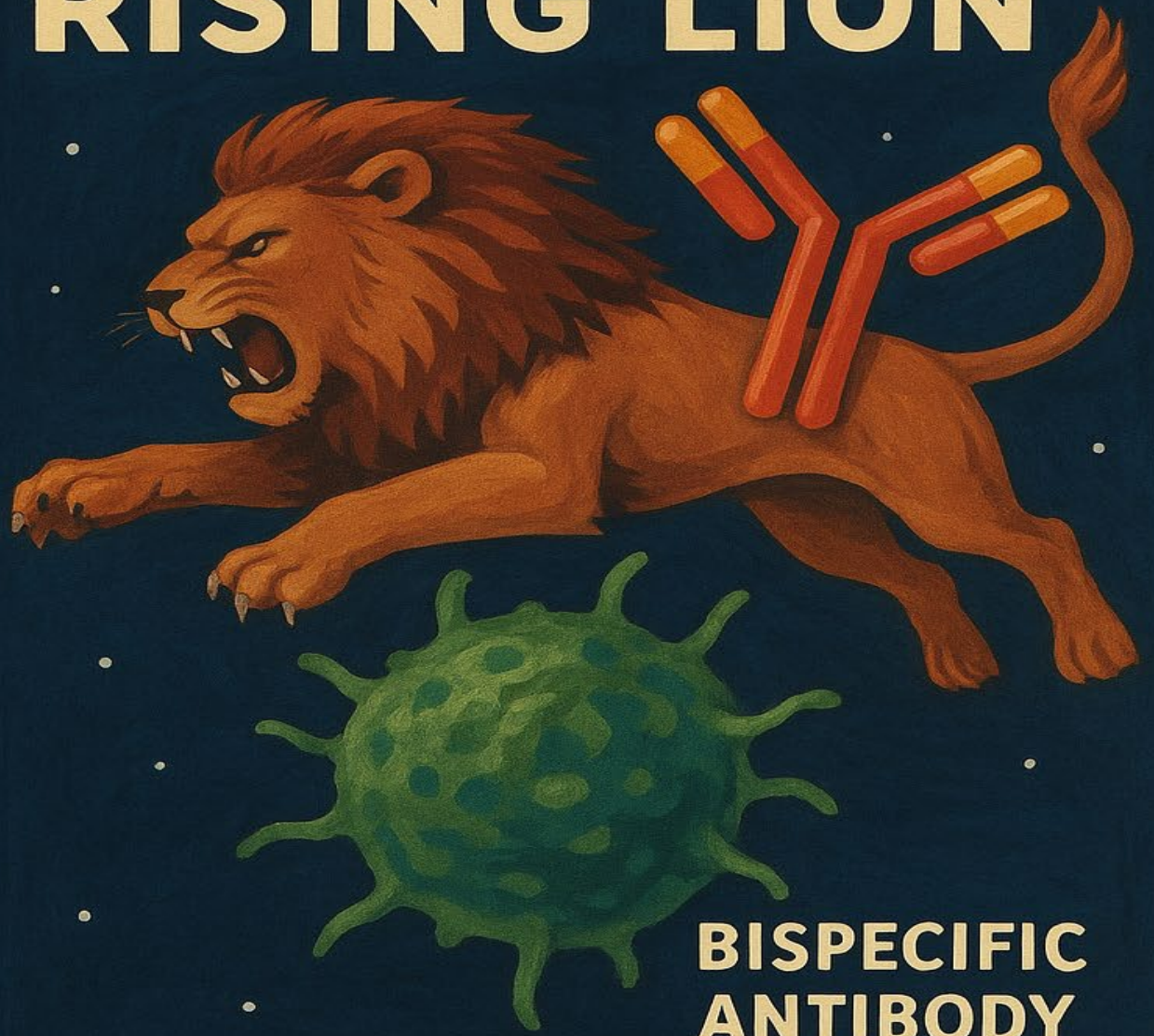


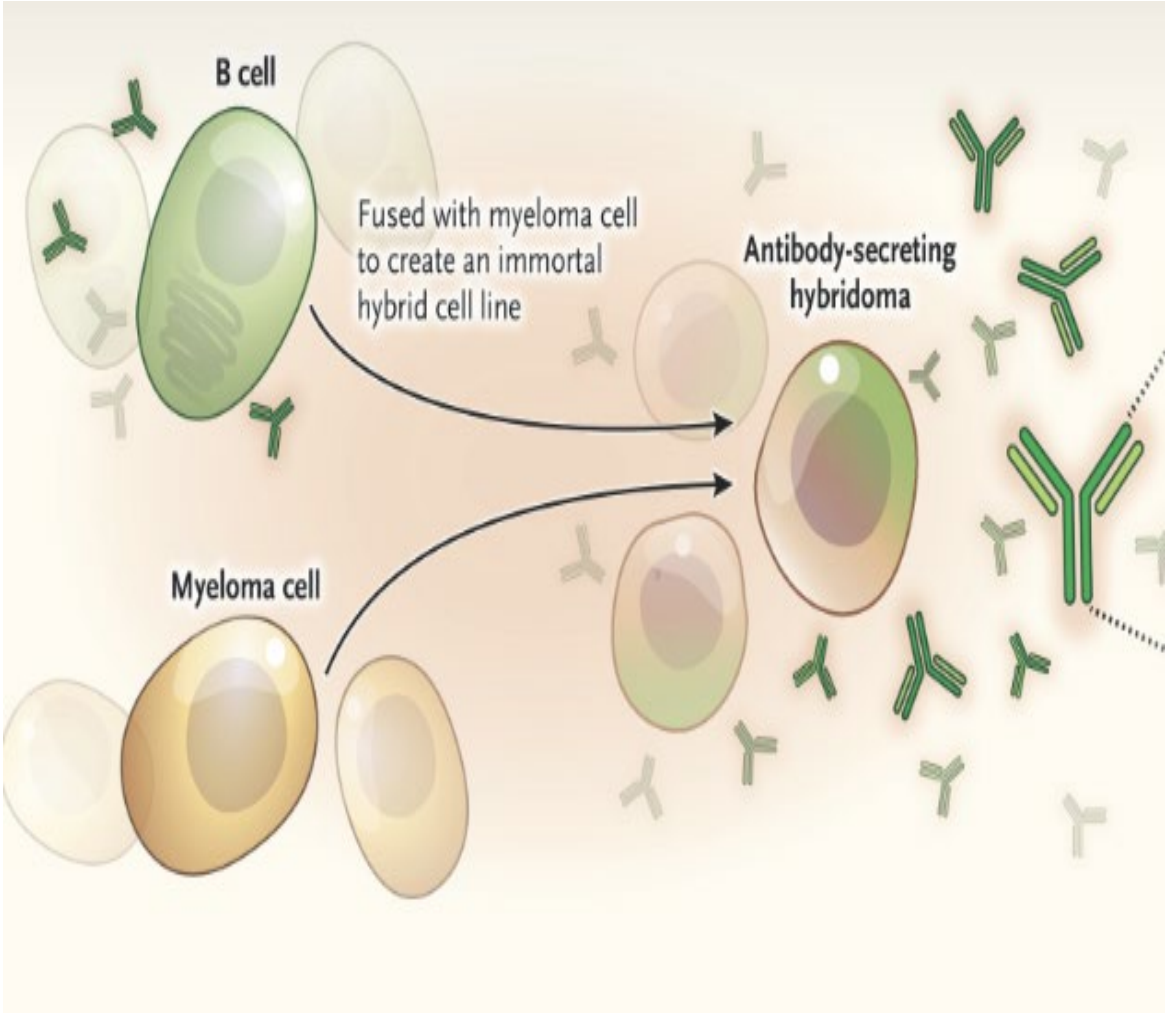
大綱

- 簡介
  - 定義“2.0”概念: 從傳統至標靶
- Antibody 1.0
  - 1975: Köhler 和 Milstein 發展雜交瘤技術（Hybridoma technology），這項技術可用來生產單株抗體（monoclonal antibodies），是免疫學與生物製藥領域的重要突破。
  - 1997: FDA-批准第一個單株抗體 – Rituximab (anti-CD20)
  - 限制: Resistance, immunogenicity, limited tumor penetration
- Antibody 2.0: 工程化抗體Engineered antibodies (ADCs & BsAbs)
- 重要研究 (The impact studies)

歷史背景：傳統化療（Chemotherapy 1.0）

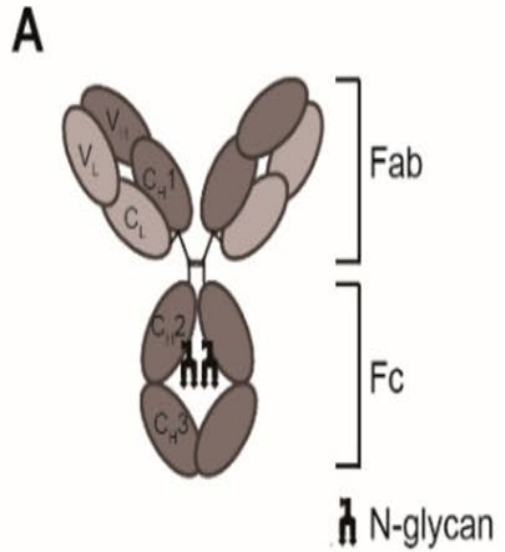
- **傳統化療的發展與侷限**
- **簡史**：源於二戰後發現氮芥類對癌細胞的作用，1940年代開始應用於淋巴瘤治療；此後興起各類化療藥物（如抗代謝物、生物鹼等），1960-70年代多種藥物組合提高治癒率（例如兒童急性白血病、霍奇金淋巴瘤）。
- **作用機制**：大多針對快速分裂細胞的 DNA 或細胞分裂機制，**但缺乏選擇性**，無法區分癌細胞與正常增殖細胞。
- **侷限性**：副作用嚴重（如骨髓抑制、脫髮、噁心嘔吐），治療劑量受正常組織耐受度限制；某些腫瘤細胞對化療藥物天生或後天產生抗藥性，導致療效下降。傳統化療被形容為「**地毯式轟炸**」，有效但伴隨大量「附帶傷害」。

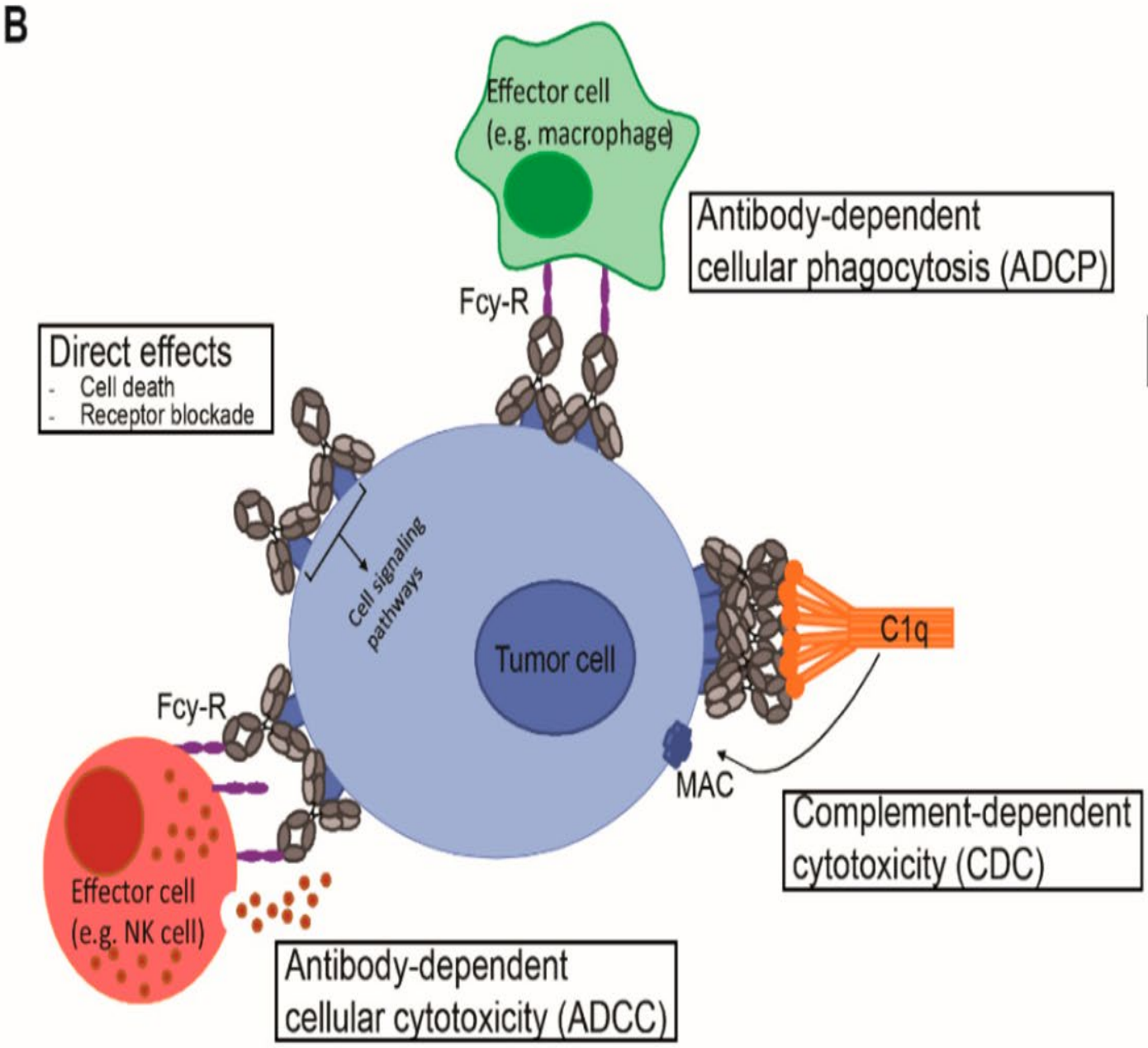
第一代單株抗體療法的發展與侷限性



- 1975年Köhler與Milstein發明雜交瘤技術製備單株抗體；1997年首個治療性抗癌單株抗體Rituximab獲批，此後Herceptin等陸續問世。
- 單株抗體成為標靶治療的開端，能專一辨識癌細胞表面抗原攻擊腫瘤。
- 作用機制：透過結合腫瘤相關抗原發揮療效，例如阻斷致癌訊號（如Herceptin阻斷HER2受體）、標記癌細胞讓免疫細胞清除（ADCC作用）或引發細胞凋亡。
- 侷限性：只能鎖定單一靶點，難以應對腫瘤的複雜性與多樣性
- 此外，早期鼠源抗體易產生免疫原性（human anti-mouse antibody response反應），需經人源化技術改良。由於單一抗體作用有限，常須與化療等併用才能達到理想療效。

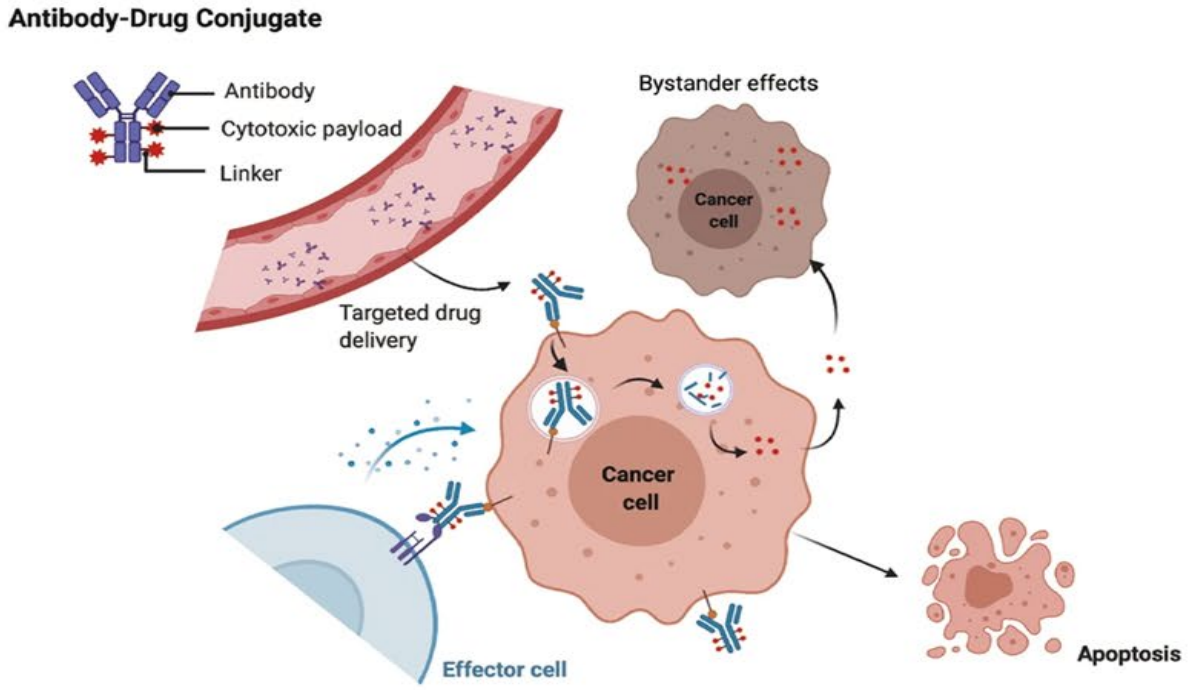
Fc domain

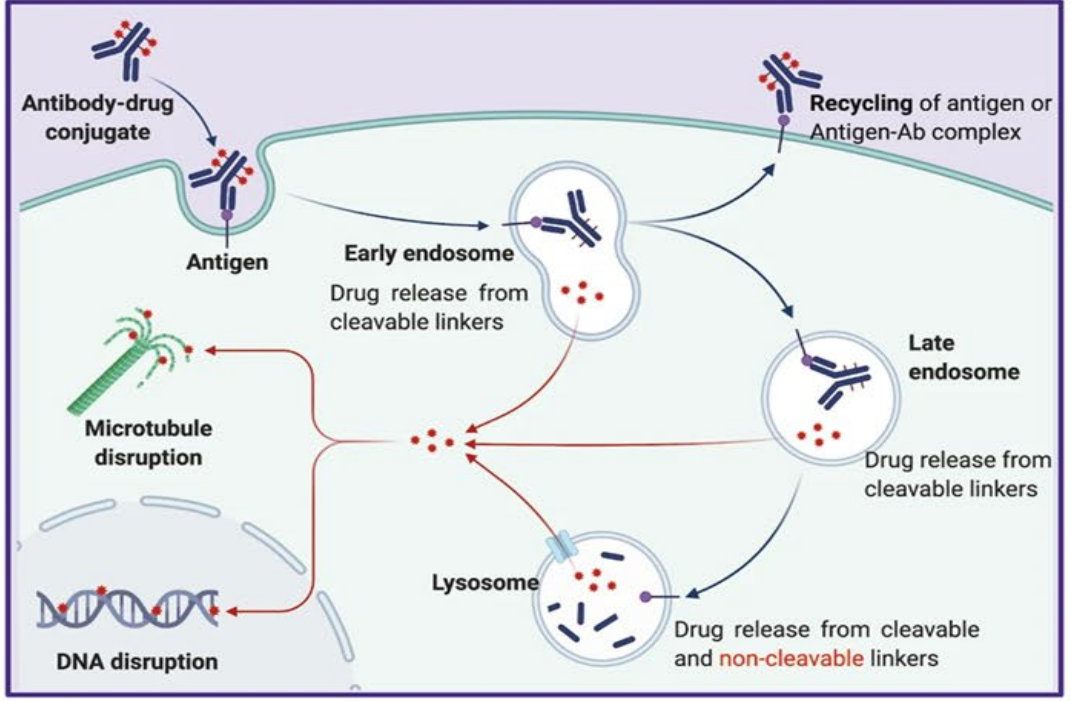


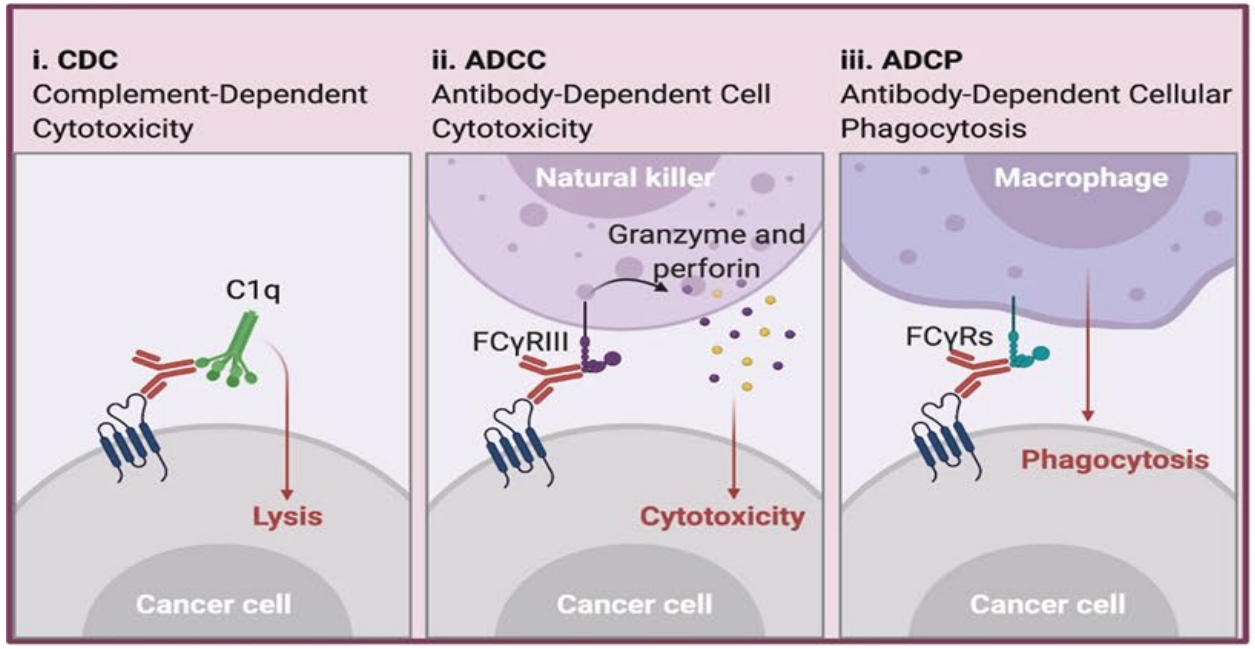


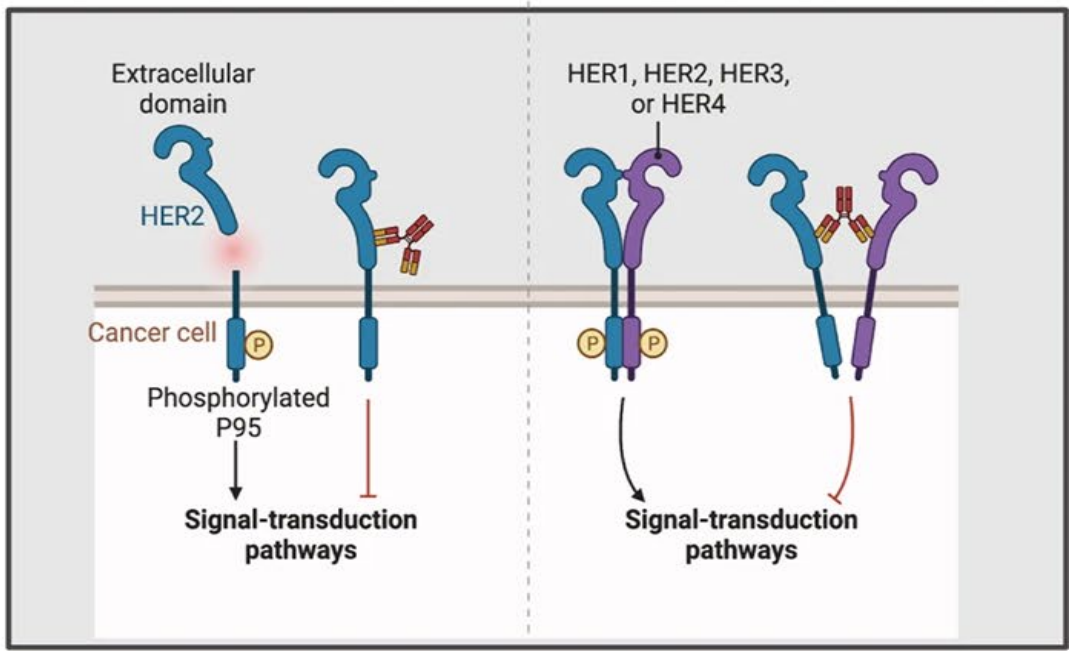
Function of Fc receptor

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.









Sig Transduct Target Ther 7, 93 (2022).

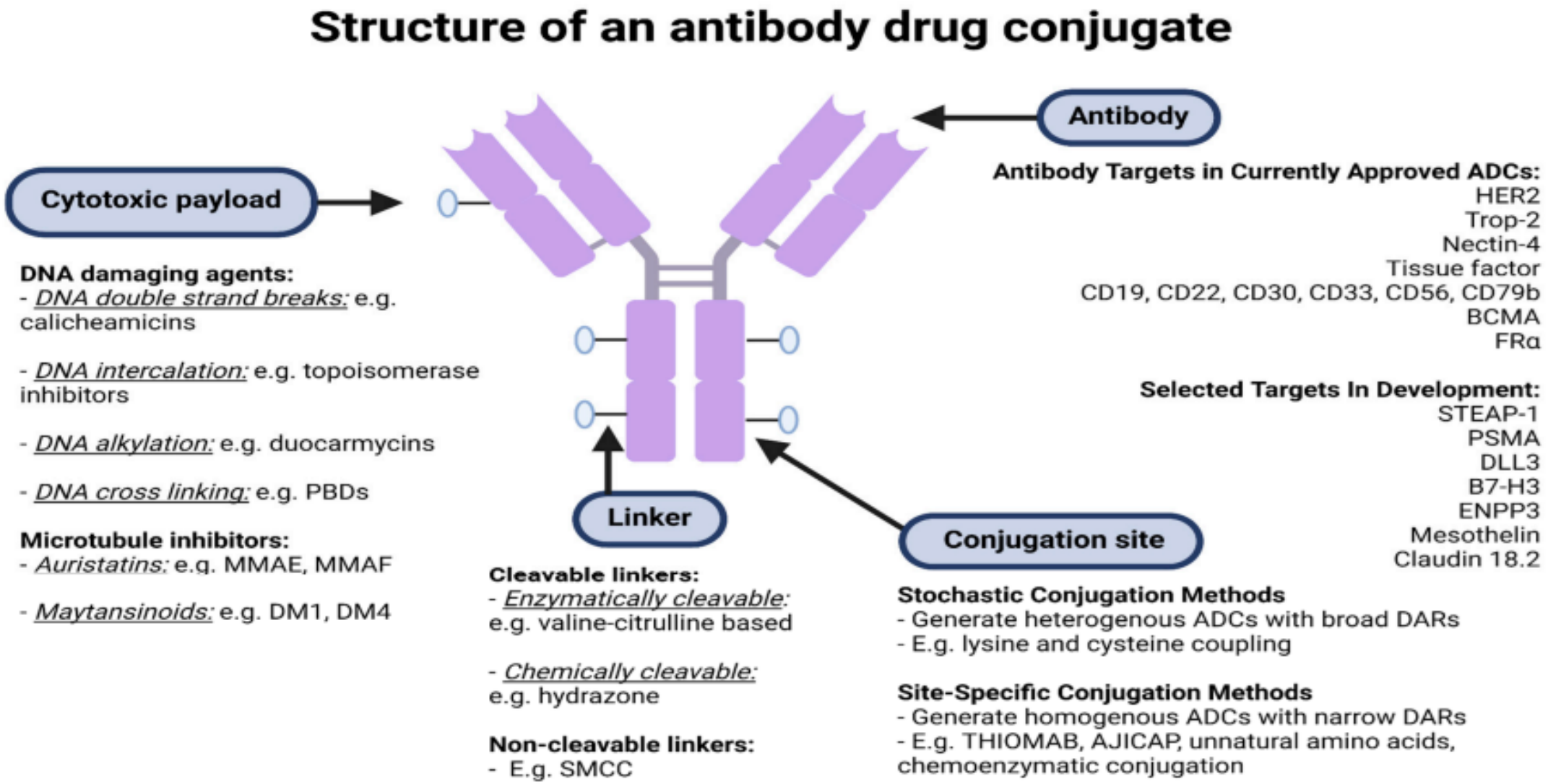
Properties of human IgG subclasses

Subclass	Serum Abundance (Normal %)	Main Function	Fc Receptor Binding	Complement Activation	Hinge Region	Half-life
IgG1	~60–65%	Strong response to **proteins**, viruses, bacteria	High	**Strong** (via C1q)	Moderate	~21 days
IgG2	~20–25%	Response to **polysaccharides** (e.g., bacterial capsules)	Low	Weak	Short	~21 days
IgG3	~5–10%	Strong complement activation, **early immune response**	Highest	**Very strong**	Long, flexible	~7 days
IgG4	~3–6%	Involved in **chronic antigen exposure**, allergic responses, **anti-inflammatory** role	Intermediate	**Minimal/None**	Short	~21 days

Chemotherapy 2.0（化療2.0）
Targeted Delivery via Antibody-Drug Conjugates (ADCs)

- **A. 概念 & 設計**
  - 基本結構：ADC由三部分構成—單株抗體、連接子、細胞毒藥物。
  - 抗體部分提供對靶抗原的專一性，例如HER2、CD30等通常在癌細胞表面高表達的分子；理想靶抗原須為膜表面且與抗體結合後易內化，以利ADC帶藥物進入癌細胞。連接子是一段化學鍵結，將藥物「栓」在抗體上，在血液中保持穩定，並設計於特定條件（如溶酶體低pH或特定酶）下斷裂釋放藥物。細胞毒藥物（載荷）常選用傳統化療藥中威力最強者，如微管抑制劑MMAE/DM1或拓撲異構酶抑制劑Deruxtecan等。經由抗體帶領，這些毒物可定向輸送至腫瘤細胞並在局部高濃度發揮作用。
- **作用機轉**：ADC像「**智慧導彈**」，利用抗體導航至癌細胞表面的靶抗原，形成抗原-抗體複合體後**內吞**進入細胞內部。當ADC進入腫瘤細胞的溶酶體/內體環境時，連接子受到酸性或酶作用而斷裂，**釋放細胞毒藥物**，後者在細胞內部造成DNA損傷或微管破壞，導致癌細胞死亡。由於藥物主要在目標細胞內釋放，對周圍正常細胞影響較小。值得一提的是，某些ADC具「**旁觀者效應**」，即釋放的活性藥物可以瀰散至鄰近細胞發揮殺傷作用。這對於腫瘤中靶抗原表達不均的情況特別有利：即使部分癌細胞靶標低表達，旁觀者效應仍能讓藥物殺死鄰近的這些癌細胞。

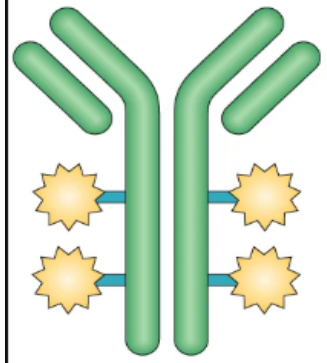
Antibody–Drug Conjugates



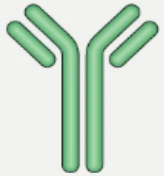
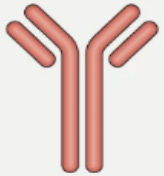
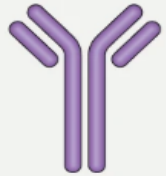
Pharmaceutics 2023, 15, 2017

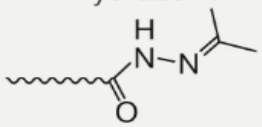
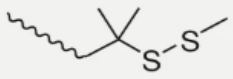
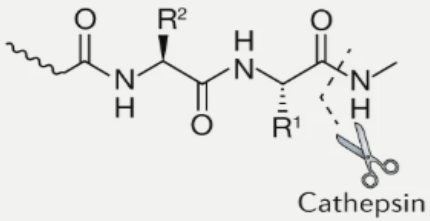
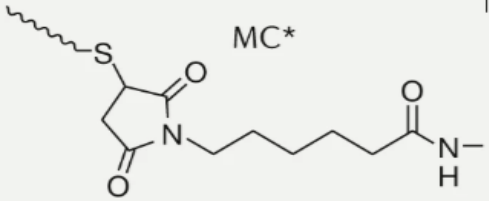
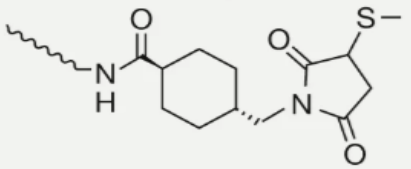
Chemotherapy 2.0：抗體藥物複合體（ADCs）

- **第一代 ADC**：早期概念於1980年代提出，將細胞毒藥物透過化學連接鍵偶聯至單株抗體，期望抗體將「毒藥」**專一運送**至癌細胞。
  - ozogamicin（Mylotarg），用於急性骨髓性白血病。第一代ADC多使用**不穩定連接子**和鼠源/人源化抗體，藥物如Calicheamicin毒性強但易脫落；因此療效未顯著優於單獨化療藥，且免疫原性和非預期毒性事件頻發。Mylotarg因毒性問題於2010年撤市。
- **第二代 ADC**：透過改良抗體類型（多採用穩定的IgG1而非IgG4）、更穩定的**可斷鍵連接子**，以及引入高效**細胞毒載荷**（如**auristatin類**MMAE、**maytansinoid類**DM1），提升ADC效力
  - Brentuximab vedotin（Adcetris，抗CD30）
  - Trastuzumab emtansine（T-DM1/Kadcyla，抗HER2）。這些ADC具更佳的血中穩定性，載藥量（DAR值）提高且均一，臨床療效和安全性明顯改善。然而部分問題仍存在：若DAR過高（>6）會增加抗體疏水性造成清除加速、毒性增加，顯示需進一步優化。
- **第三代 ADC**：重點突破在**定點偶聯技術**，使小分子藥物在抗體上特定位點鍵結，獲得**均一的DAR**和更穩定的構型。
  - 同時開發更先進連接子（只在腫瘤內部環境裂解）以及創新載荷（如**拓撲異構酶抑制劑** Deruxtecan、PBD二聚體等超強細胞毒），實現更高的治療指數。
    - Polatuzumab vedotin（Polivy，抗CD79b，用於大型B細胞淋巴瘤）、Enfortumab vedotin（Padcev，抗Nectin-4，用於尿路上皮癌）和 Trastuzumab deruxtecan（Enhertu，抗HER2）。



Nature Reviews Clinical Oncology volume 18, pages327–344 (2021)

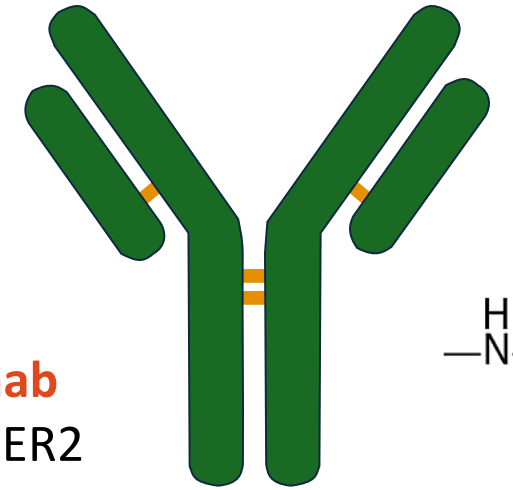
	IgG1	IgG2	IgG3	IgG4
Antibodies				
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

	Cleavable			Non-cleavable
Linkers	Hydrazone 	Disulfide 	Dipeptide  Cathepsin	MC*  MCC* 
	Acid cleavable	Reducible	Protease cleavable	

Payloads	 Auristatins	 Maytansinoids	 Calicheamicins	 Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition

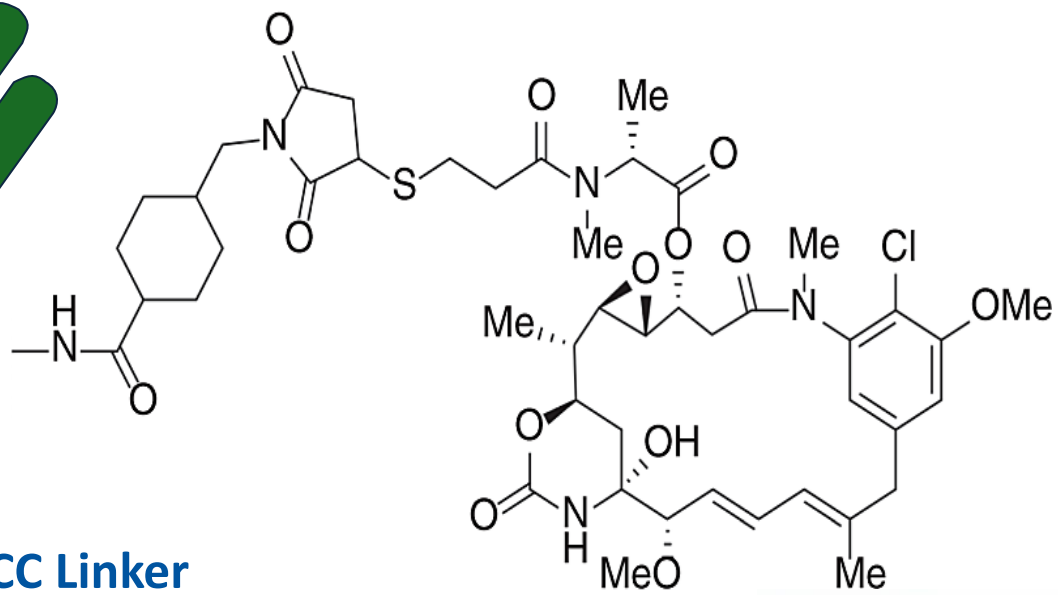
Monomethyl auristatin E : (Synonyms: MMAE; Vedotin) : 200 times that of vinblastine, another antimitotic drug used for Hodgkin lymphoma as well as other types of cancer. Maytansine binds tubulin at the vinca-binding site, similar to vinca alkaloids,

Trastuzumab Emtansine(T-DM1): HER2-Targeted ADC



Trastuzumab

- Targets HER2
- Humanized IgG1



DM1 Payload

- Maytansine derivative
- Microtubule inhibitor

MCC Linker

- DAR ~3.5:1
- Noncleavable thioether linker
- Lysosomal proteolytic degradation releases Lys-MCC-DM1 into the cell

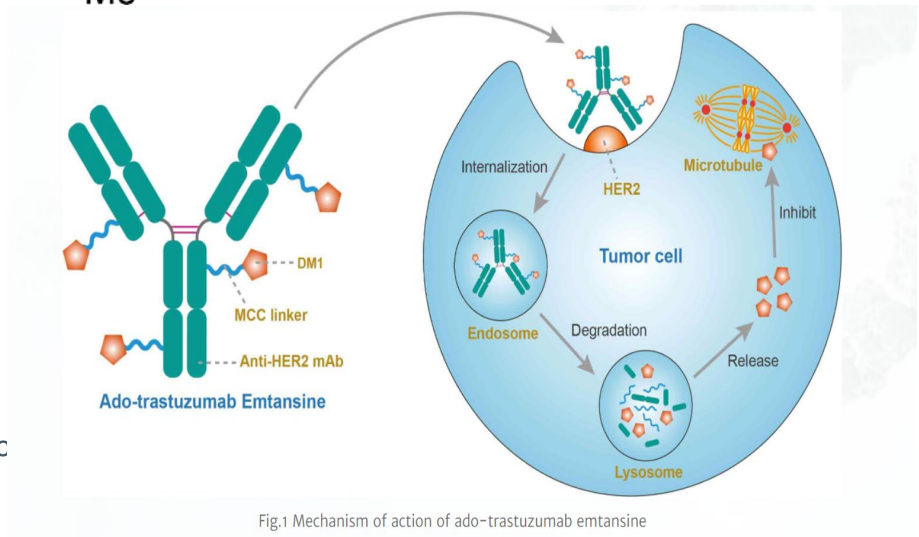


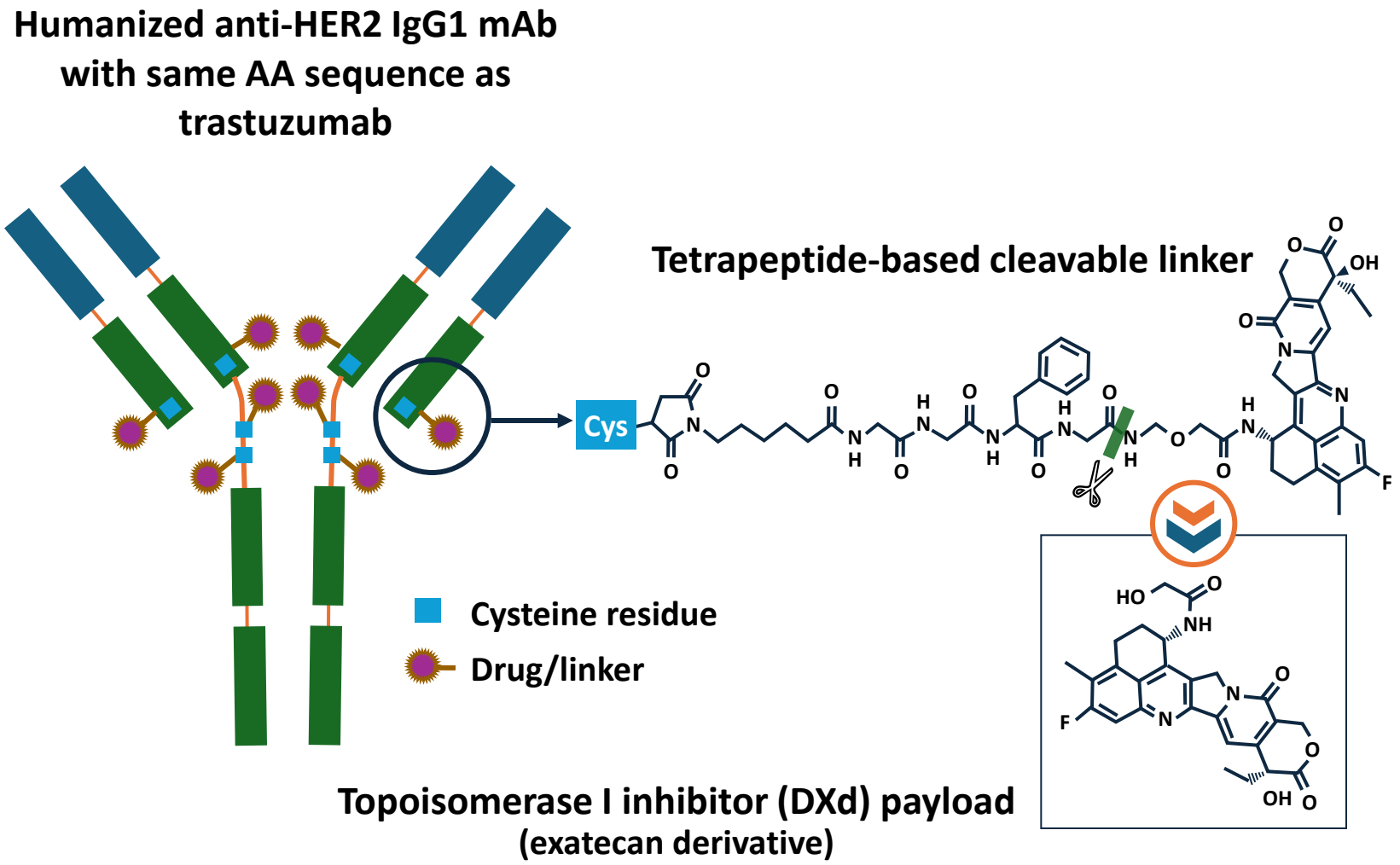
Fig.1 Mechanism of action of ado-trastuzumab emtansine

T-DM1: 2 FDA-Approved Indications

	HER2+ MBC	HER2+ EBC (Adjuvant)
Trial	EMILIA: T-DM1 vs lapatinib + capecitabine	KATHERINE: T-DM1 vs trastuzumab
ORR, %	44 vs 31	--
PFS or iDFS	**mPFS:** 9.6 vs 6.4 mo (HR: 0.65; 95% CI: 0.55-0.77; *P* <.001)	**7-yr iDFS:** 80.8% vs 67.1% (HR: 0.54; 95% CI: 0.44-0.66; nominal *P* <.0001)
OS	**mOS:** 30.9 vs 25.1 mo (HR: 0.68; 95% CI: 0.55-0.85; *P* <.001)	**7-yr OS:** 89.1% vs 84.4% (HR: 0.66; 95% CI: 0.51-0.87; *P* = .0027)
FDA approval	February 2013 (full)	May 2019 (full)
Indication	HER2+ MBC previously treated with trastuzumab and a taxane, separately or in combination, with either: ▪ Prior tx for metastatic disease ▪ Disease recurrence during/within 6 mo of completing adjuvant tx	Adjuvant treatment of HER2+ EBC with residual invasive disease after neoadjuvant taxane and trastuzumab-based tx

Trastuzumab emtansine PI. Verma. NEJM. 2012;367:1783. Loibl. SABCS 2023. Abstr GS03-12.
NCCN. Clinical practice guidelines in oncology: breast cancer. v.1.2024. nccn.org.

HER2-Targeted ADC: Trastuzumab Deruxtecan (Enhertu)

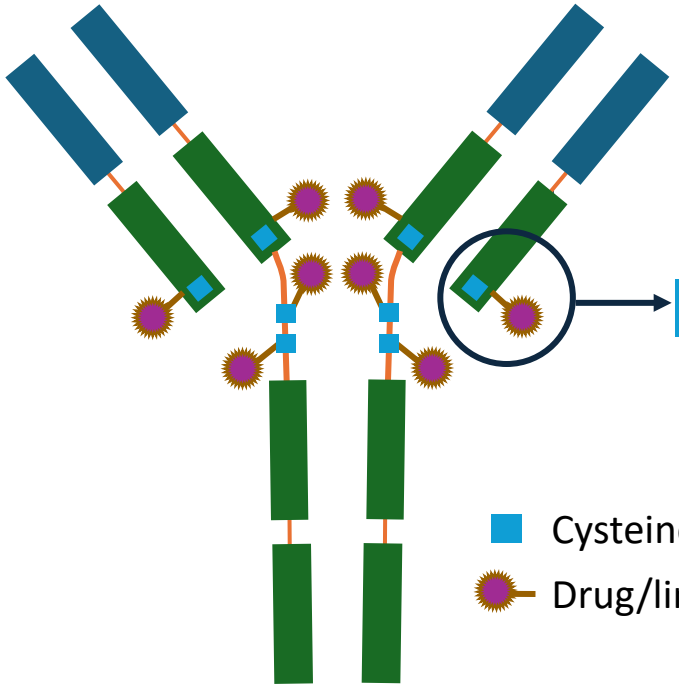


- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

Slide credit: clinicaloptions.com

Trastuzumab Deruxtecan (Enhertu): HER2-Targeted ADC

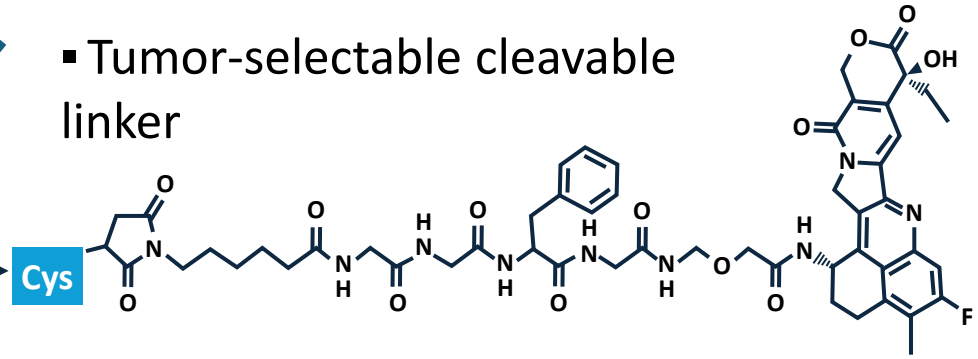


Anti-HER2 mAb

- Same AA sequence as trastuzumab
- Humanized IgG1

Tetrapeptide-Based Linker

- DAR ~8:1
- Tumor-selectable cleavable linker



DXd Payload

- Exatecan derivative
- Topoisomerase I inhibitor
- Membrane permeable
- Short systemic half life
- **Bystander killing effect**

FDA approved in advanced settings for:

- HER2+ MBC
- HER2-low MBC
- HER2+ gastric/GEJ adenocarcinoma
- *HER2*-mutated NSCLC

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Ogitani. Clin Cancer Res. 2016;22:5097.

T-DXd: 2 FDA-Approved Indications in Breast Cancer

	HER2+ MBC	HER2-Low MBC
Trial	DESTINY-Breast03: T-DXd vs T-DM1	DESTINY-Breast04: T-DXd vs physician's choice
ORR, %	79 vs 35	52.3 vs 16.3
mPFS, mo (HR; 95% CI)	28.8 vs 6.8 (0.33; 0.26-0.43; *P* <.0001)	10.1 vs 5.4 (0.51; *P* <.001)
mOS, mo (HR; 95% CI)	NR vs NR (0.64; 0.47-0.87; *P* = .0037)	23.4 vs 16.8 (0.64; 0.49-0.84; *P* = .001)
FDA approval	December 2019 (accelerated) May 2022 (full)	August 2022 (full)
Indication	Unresectable or metastatic HER2+ BC after a HER2-based regimen in either metastatic setting or neo/adjuvant setting with recurrence during/within 6 mo of completing tx	Unresectable or metastatic HER2-low BC after prior CT in metastatic setting or had recurrence during/within 6 mo of completing adjuvant CT

HER2+ = IHC3+ or IHC2+/ISH+
(In situ hybridization (ISH).

HER2 low = IHC 1+ or IHC 2+/ISH-

Trastuzumab deruxtecan PI. Hurvitz. Lancet. 2023;401:105. Modi. ASCO 2022. LBA3. Modi. NEJM. 2022;387:9.

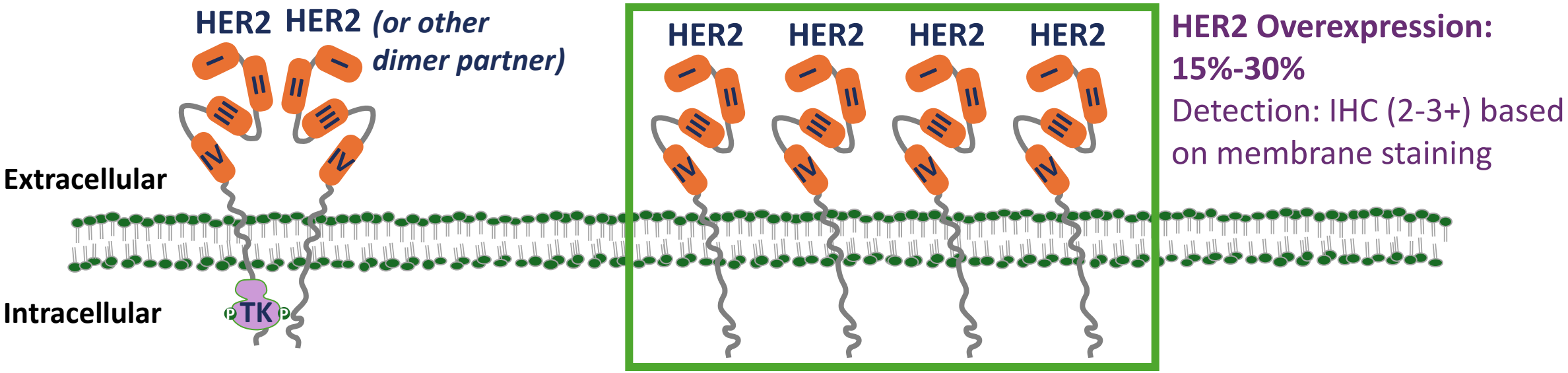
T-DXd: FDA-Approved Indication in HER2+ Gastric/GEJ Adenocarcinoma

- **HER2 positivity in gastric/GEJ adenocarcinoma** defined as:
  - *HER2* gene amplification and/or HER2 protein overexpression
  - IHC 3+ *or* IHC 2+/ISH+

	HER2+ Gastric/GEJ Adenocarcinoma
Trial	DESTINY-Gastric01: T-DXd vs physician's choice
ORR, %	51 vs 14
mPFS, mo (HR; 95% CI)	5.6 vs 3.5 (0.47; 0.31-0.71)
mOS, mo (HR; 95% CI)	12.5 vs 8.9 (0.60; 0.42-0.86)
FDA approval	January 2021 (full)
Indication	LA or metastatic HER2+ gastric/GEJ adenocarcinoma after trastuzumab-based regimen

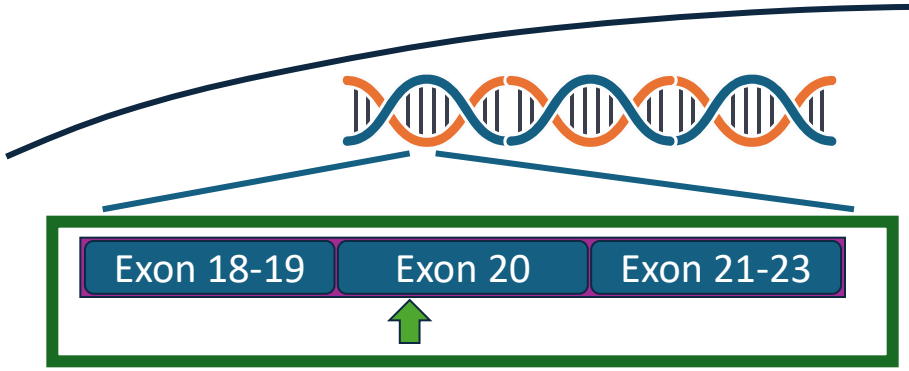
Trastuzumab deruxtecan PI. Shitara. Lancet Oncol. 2019;20:827. Shitara. NEJM. 2020;382:2419. Yamaguchi. ASCO GI 2022. Abstr 242.

HER2-Positive NSCLC



HER2 Overexpression: 15%-30%

Detection: IHC (2-3+) based on membrane staining



***HER2* Gene Mutation: 1%-3%**

Detection: NGS (activating *HER2*/*ERBB2* mutation)

***HER2* Amplification: 2%-5%**

Detection: FISH (*HER2*/*CEP17* ratio >2 and/or HER2 copy number >6)

Yu. Front Oncol. 2022;12:860313.

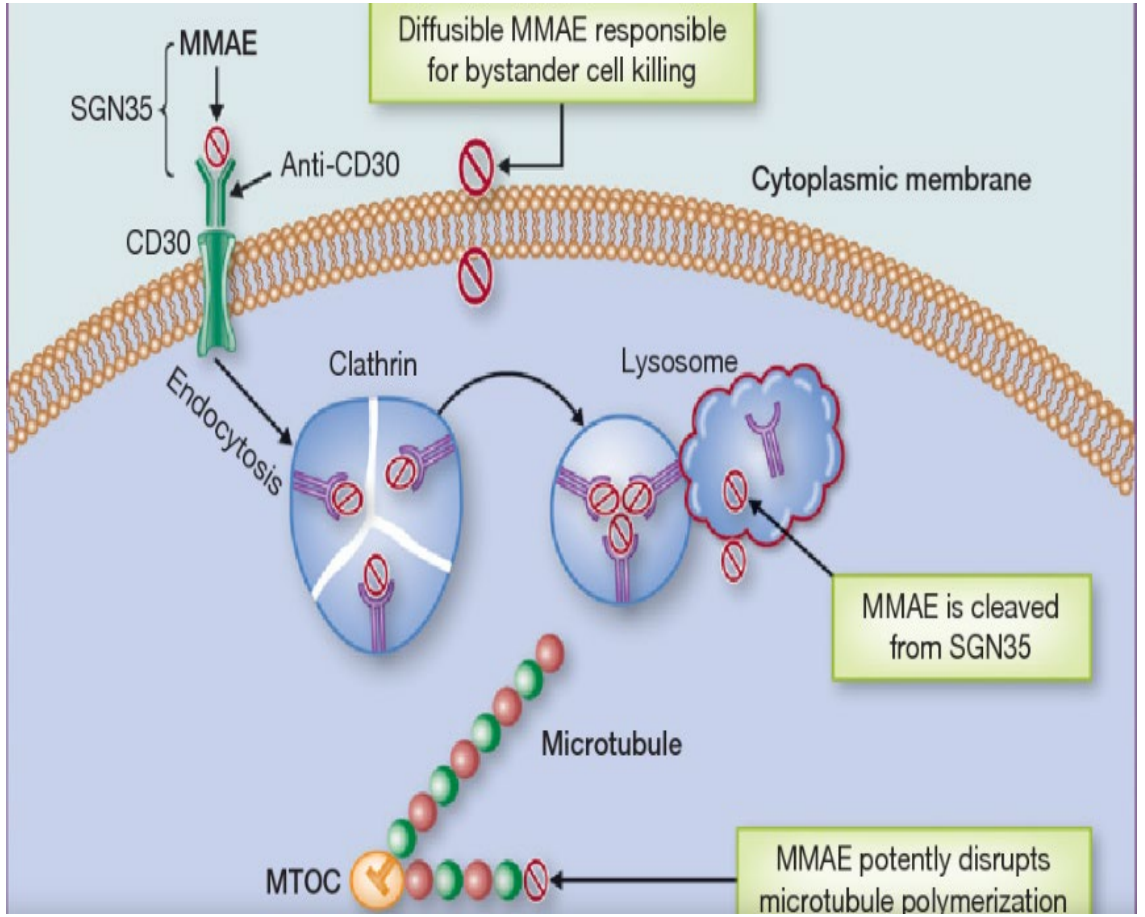
T-DXd: FDA-Approved Indication in *HER2*-Mutated NSCLC

	***HER2*-Mutated NSCLC**
Trial	DESTINY-Lung02: T-DXd
ORR, %	49
mPFS, mo (HR; 95% CI)	9.9 --
mOS, mo (HR; 95% CI)	19.5 --
FDA approval	August 2022 (accelerated)
Indication	Unresectable or metastatic *HER2*-mutated NSCLC with a prior systemic tx

Trastuzumab deruxtecan PI. Goto. JCO. 2023;41:4852. Jänne. WCLC 2023. Abstr MA13.10.

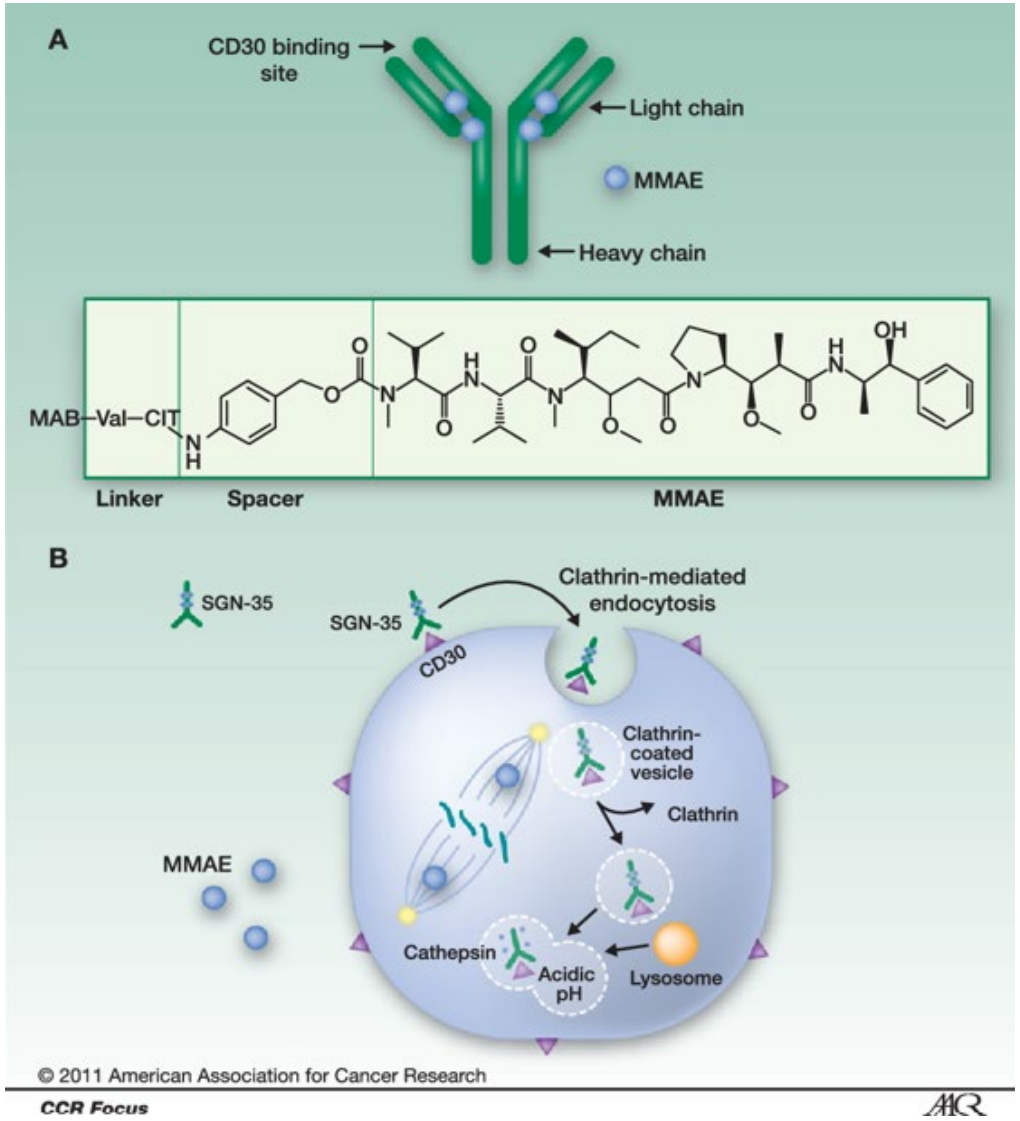
ADC : payload with vedotin

- Brentuximab Vedotin (Adcetris): Target: CD30
  - Uses: Primarily used for Hodgkin lymphoma and systemic anaplastic large cell lymphoma.
- Polatuzumab Vedotin (Polivy): Target: CD79b
  - Use: Used in combination with other chemotherapies for the treatment of diffuse large B-cell lymphoma (DLBCL).
- Tisotumab Vedotin (Tissue factor) : Target : TF (tissue factor)
  - Recurrent or metastatic cervical cancer
- Enfortumab Vedotin (Padcev): Target: Nectin-4
  - Bladder cancer and other urothelial cancers
- Belantamab mafodotin : target (B-Cell Maturation antigen)



Brentuximab Vedotin (Adcetris): Target: CD30

- Study : ECHELON
  - AVD vs ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) : untreated advanced classical Hodgkin lymphoma.
  - Brentuximab Vedotin plus CHP (cyclophosphamide, doxorubicin, and prednisone) versus CHOP : untreated CD30-positive peripheral T-cell lymphoma (PTCL), including systemic anaplastic large cell lymphoma (sALCL).
- Study : ALCANZA
  - Brentuximab Vedotin versus physician‘s choice (methotrexate or bexarotene) : CD30 (+) cutaneous T-cell lymphoma (CTCL). CD30 (+) mycosis fungoides (MF) or primary cutaneous anaplastic large-cell lymphoma (C-ALCL).

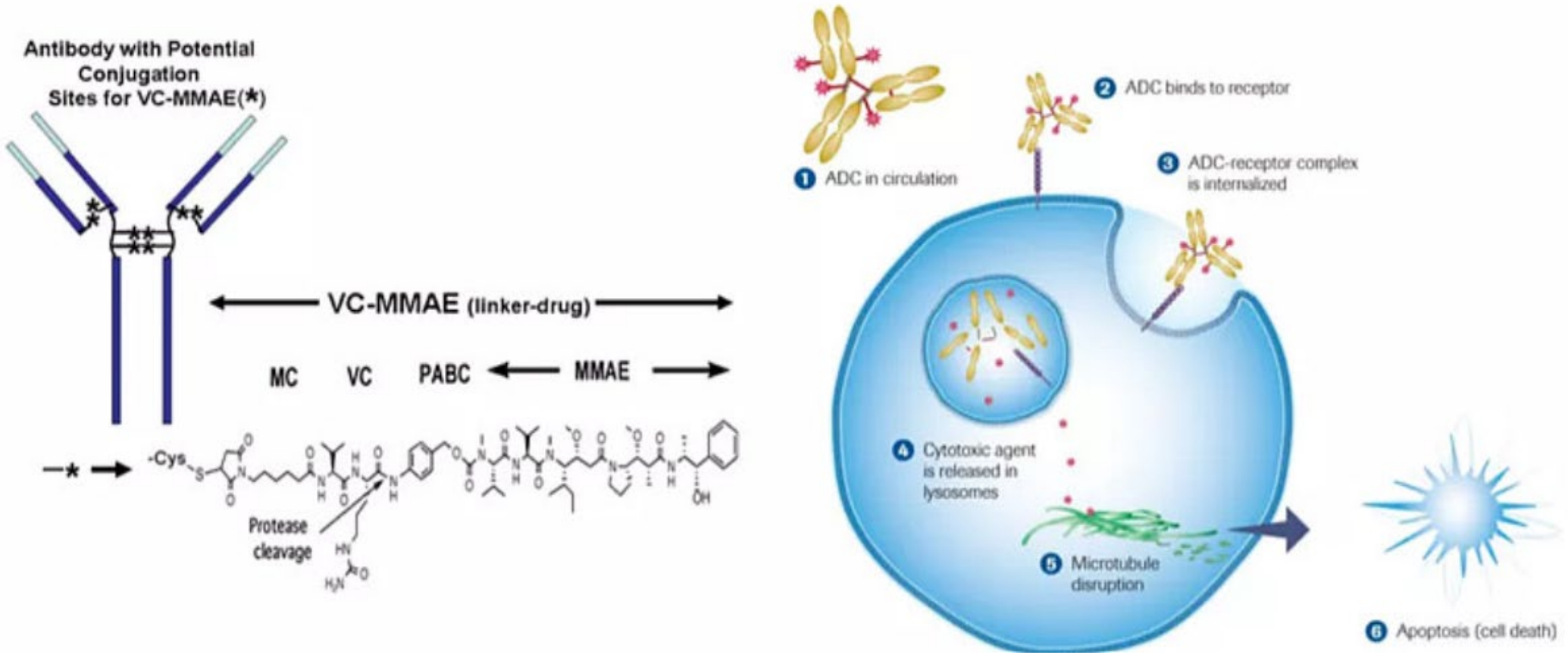


Brentuximab Vedotin	SG035-0003 CD30	AETHERA CD30	ALCANZA CD 30
Indication	Relapsed or refractory Hodgkin lymphoma (HL) (post auto-SCT, phase 2)	HL patients at high risk of relapse post-auto-HSCT (phase 3) consolidation	brentuximab vedotin vs physician's choice in cutaneous T-cell lymphoma (phase 3) (previously treated)
Comparative Regimens	Single-arm study	Brentuximab Vedotin vs. Placebo	Brentuximab Vedotin vs vs physician's choice:
Overall Response Rate (ORR)	75%, CR : 34%		ORR; 54.7% vs 12.5% (P < .001); CR 17.2% vs 1.6% (P = .002)
Median Progression-Free Survival (PFS)	Median 5.6 months	42.9 months vs 24.1 months At 5 yrs : 59% vs 41%	16.7 months vs 3.5 months (P < .001)
Overall Survival (OS)	Durable CR: 2 years		3-y OS, 64.4 months vs 61.9 (HR for OS, P =0.31)
Adverse Reactions	Peripheral neuropathy, fatigue, nausea, neutropenia, diarrhea	Peripheral sensory neuropathy, neutropenia, upper respiratory tract infection	Peripheral sensory neuropathy, fatigue, nausea, diarrhea
Source	Younes, A., et al. J Clin Oncol. 2012. (Link)	Moskowitz, CH., et al. Lancet. 2015. (Link) Blood (2018) 132 (25): 2639–2642	Blood Adv . 2021 Dec 14;5(23):5098-5106

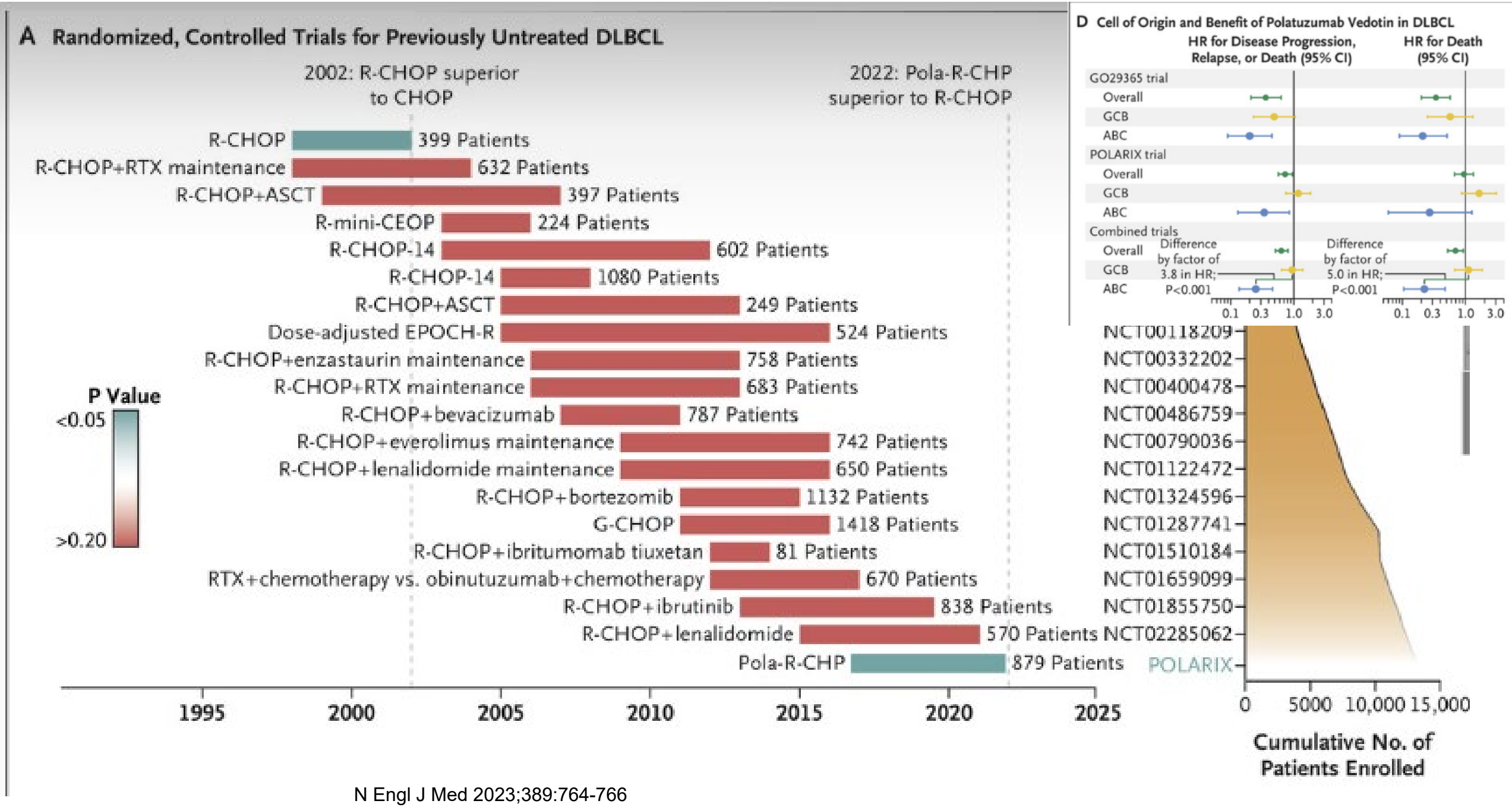
Brentuximab Vedotin	ECHELON-1 CD 30	ECHELON-2 CD 30
Indication	Previously untreated advanced III or IV classical Hodgkin's lymphoma	phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma
Comparative Regimens	Brentuximab Vedotin + AVD vs. ABVD	A+CHP vs CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) 6-8 cycles
Overall Response Rate (ORR)		59% vs 50%
Median Progression-Free Survival (PFS)	82.1% vs 77.2% (at 2 yrs) Brentuximab + AVD vs ABVD: longer	5-year PFS rates were 51.4% vs 43.0% (CHOP) (hazard ratio = 0.70),
Overall Survival (OS)	The 6-year overall survival 93.9% (A+AVD) vs 89.4% (ABVD)	5-year OS : 70.1% (A+CHP) vs 61.0%
Adverse Reactions	peripheral neuropathy, febrile neutropenia. fewer second cancers were reported with A+AVD	Peripheral neuropathy was resolved or improved in 72% of patients in the A+CHP arm and 78% in the CHOP arm.
Source	NEJM 2022;387:310-320 NEJM 2018;378:331-344	Ann Oncol . 2022 Mar;33(3):288-298.

Polatuzumab Vedotin

Figure 1. Polatuzumab Vedotin Mechanism of Action.



Category	Polatuzumab Vedotin (Polivy) CD79b	Polatuzumab Vedotin (Polivy) CD79b
Indication	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	phase 3 trial, (untreated intermediate-risk or high-risk DLBCL.
Comparative Drug(s)	Bendamustine and rituximab (BR) vs. Polatuzumab Vedotin with BR (Pola-BR)	modified regimen of pola-R-CHP vs standard R-CHOP
Overall Response Rate (ORR)	CR : Pola-BR: 45%; BR: 18%	
Median Progression-Free Survival (PFS)	Pola-BR : 9.5 months BR: 3. 7 months	76.7% vs. 70.2% (p=0.02) at 2 years;
Median Overall Survival (OS)	Pola-BR: 12.4 months vs BR: 4.7 months	at 2 years did not differ significantly (88.7% pola-R-CHP vs 88.6% R-CHOP ; P = 0.75).
Adverse Effects	Thrombocytopenia, neutropenia, anemia, fatigue, peripheral neuropathy, diarrhea	The safety profile was similar in the two groups.
Source	J Clin Onco 2019 38:155-165.	J Clin Onco 2019 38:155-165.



N Engl J Med 2023;389:764-766

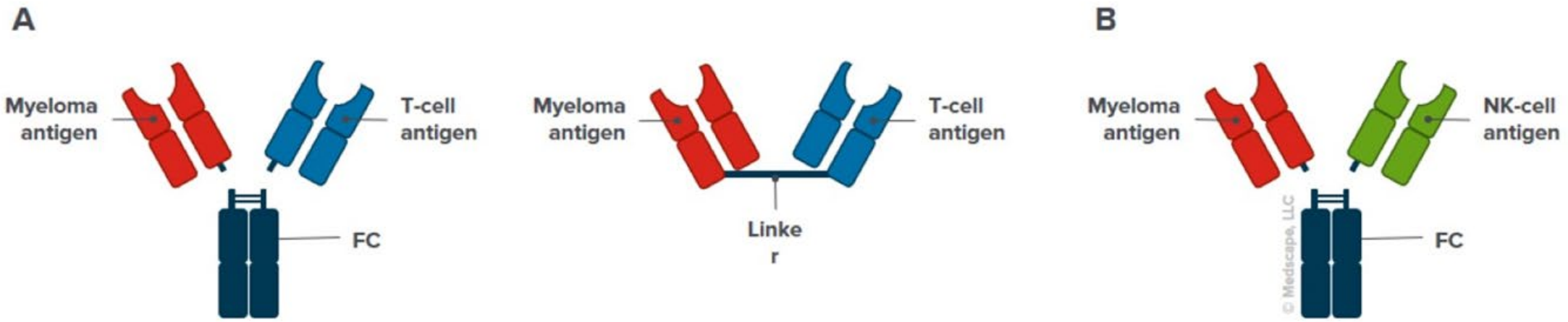
挑戰與副作用

- **靶點選擇受限**：ADC理想靶抗原須在腫瘤中高表達且不外泌，正常組織中表達極低，並且與抗體結合後易內化。可滿足這些條件的抗原並不多見，限制了ADC的適用癌種。研發時需慎選靶標以避免**脫靶毒性**，例如抗原若有可溶形式或在關鍵正常細胞表達，可能引發嚴重副作用。
- **治療視窗與毒性**：儘管ADC較傳統化療更精準，仍可能出現嚴重副作用。連接子若不夠穩定，在血中**過早釋放**載藥會攻擊正常細胞，造成**意料外的毒性**。例如第一代ADC因連接子在生理pH下緩慢水解，出現全身性毒性。常見ADC相關不良反應包括骨髓抑制（如中性球低下）、肝功能異常和周邊神經病變等，需要嚴密監控。儘管整體副作用少於全身化療，但某些ADC仍有特殊毒性：如Enfortumab和Brentuximab因MMAE可能導致周邊神經炎，Belantamab mafodotin（抗BCMA ADC）會造成角膜毒性等。
- **抗藥性機制**：腫瘤細胞可透過多種途徑對ADC產生抗性。例如**降低靶抗原表達**或改變抗原內循環途徑，令ADC難以發揮作用；或者過度表現**藥物外排幫浦**，在毒物釋放前即將其泵出細胞。一些血癌患者在接受抗CD19或CD33的治療後出現靶抗原陰性的復發，即是癌細胞調控抗原逃避免疫的例子。為克服此問題，可考慮同時瞄準多個抗原的治療策略（如雙靶或多靶ADC）來降低逃逸風險。
- **藥物動力學與製造挑戰**：早期ADC採用胺基酸隨機偶聯，導致同一製劑內部抗體連接的藥物數目（DAR）不一致，為一群異質性分子混合物。DAR的不均會影響ADC的藥代動力學和療效，且高DAR的ADC易聚集、清除快、毒性高。新一代定點偶聯技術改善了DAR均一性，但生產工藝仍複雜昂貴。每種ADC都需克服抗體表達、藥物偶聯、純化等技術難題，製造成本遠高於小分子藥物。

Antibody 2.0 (抗體2.0) : Bispecific Antibodies (BsAbs)

- **A. 概念**
  - 一種抗體，兩個結合位點：通常一端結合腫瘤抗原，另一端結合免疫效應細胞（例如 CD3）。
  - 功能：引導免疫細胞攻擊腫瘤。
  - 雙重靶向，突破單靶侷限
- **B. 重要型態**
  - **BiTEs (Bispecific T-cell engagers)** – e.g., *Blinatumomab (CD19/CD3)*
  - **Full-length bispecifics** – e.g., *Mosunetuzumab (CD20/CD3)*
- **C. 臨床應用**
- Hematologic malignancies: ALL, NHL (CD19/CD3, CD20/CD3)
- Solid tumors under investigation: PSMA/CD3, HER2/CD3, EGFRxMET
- Advantages: Off-the-shelf immunotherapy
- Challenges: CRS, neurotoxicity, short half-life (for some formats)

Bispecific antibodies

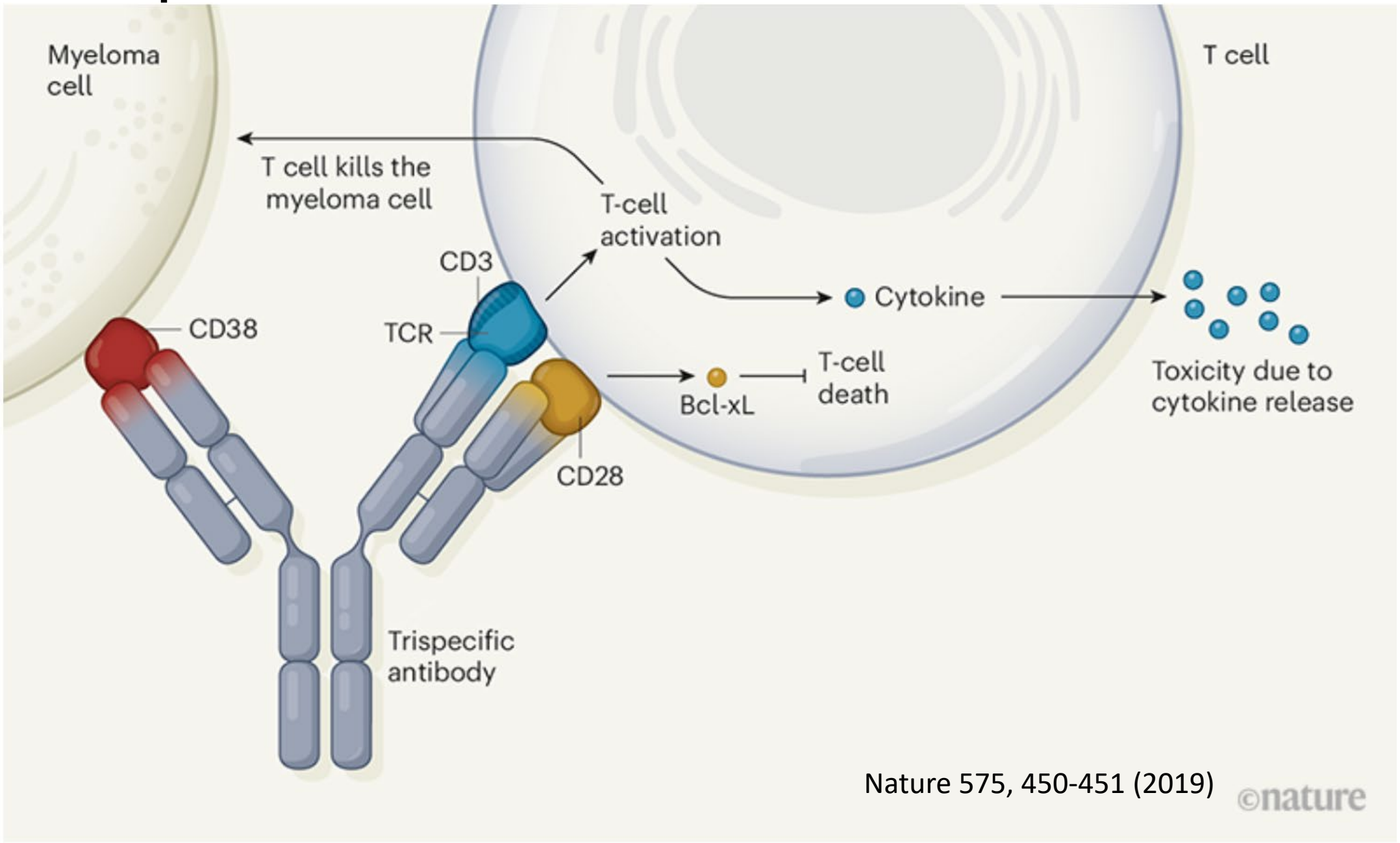


- Constructs vary in antigen-binding domains and dimerization (homodimers vs heterodimers) resulting in differences in antigen-binding sites (valency), size, geometry, and flexibility
  - Fc portion provides stability in circulation allowing for intermittent (instead of continuous) dosing, it can also 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

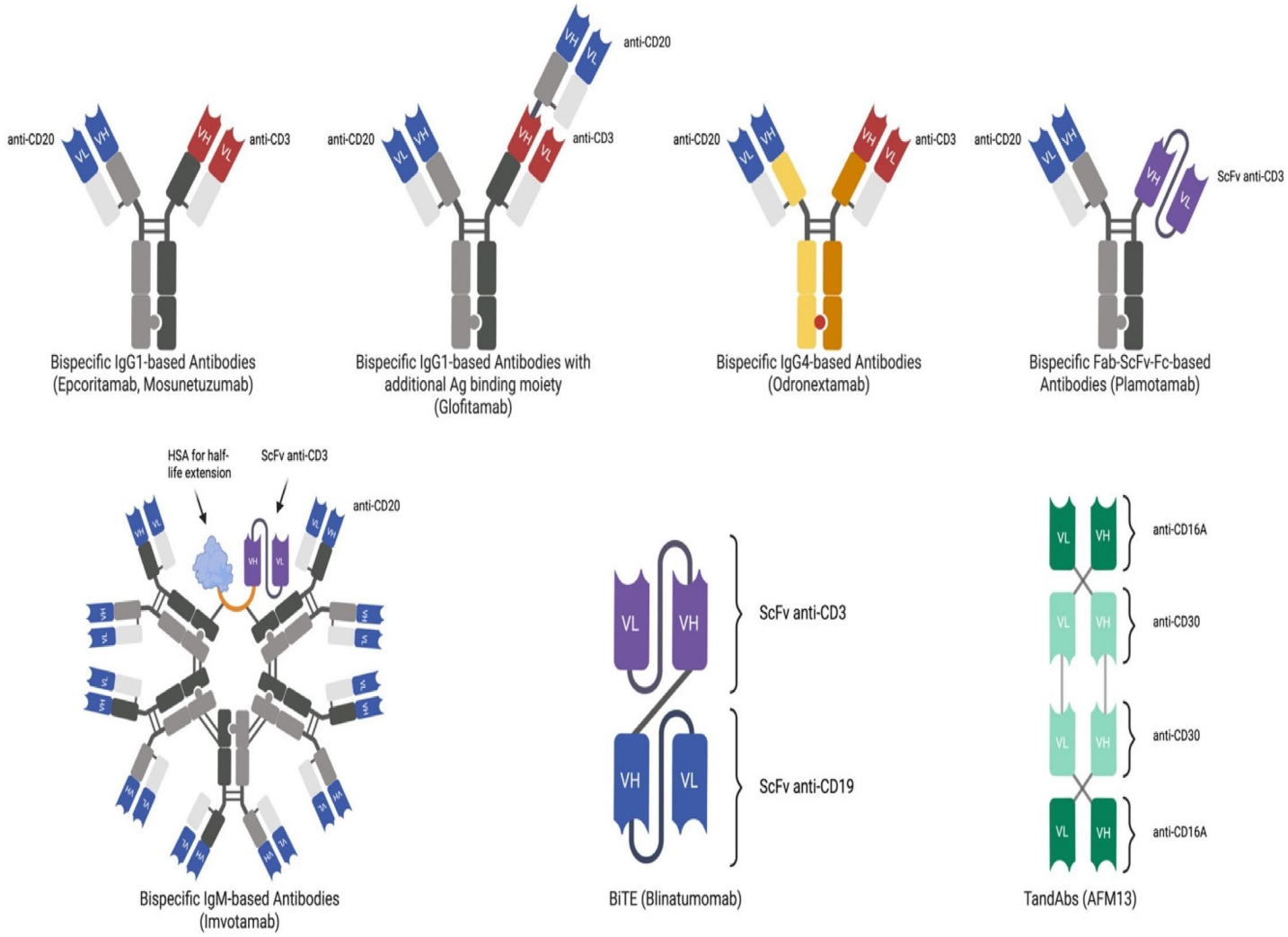


Nature 575, 450-451 (2019)

多樣的工程平台

- **雙特異性T細胞接合抗體（T cell engager，如BiTE平台）**：由兩個單鏈可變片段(scFv)串聯而成的小型抗體片段，分子量小且不含Fc段。典型代表是**Blinatumomab**，一端結合T細胞CD3、另一端結合腫瘤細胞抗原（CD19），將T細胞直接拉至腫瘤細胞旁啟動殺傷。BiTE類因缺乏Fc介導的長效機制，血中半衰期短，需要連續輸注給藥，但能有效啟動免疫細胞，適合急性癌症的治療。

- 全長IgG型雙抗：利用基因工程解決重鏈/輕鏈錯配問題，製造出的完整IgG雙特異性抗體。這類雙抗保留IgG的長半衰期和Fc功能，可每幾週給藥一次。代表如Mosunetuzumab（CD20×CD3，全長IgG1抗體）和Teclistamab（BCMA×CD3，人源化IgG4抗體）。



Bispecific and multispecific antibodies in oncology

Bispecific T cell engager

- CD20 × CD3 Odronextamab (RR FL, RR DLBCL)
- BCMA × CD3 Linvoseltamab (RR MM)
- DLL3 (Delta-like ligand 3)x CD3 Tarlatamab (small cell lung cancer)

Dual signalling pathway inhibition

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

Bispecific NK cell engager

- CD30 × CD16 (NHL)

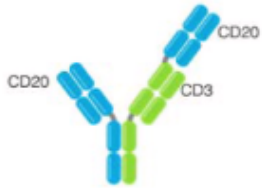
Dual checkpoint inhibition

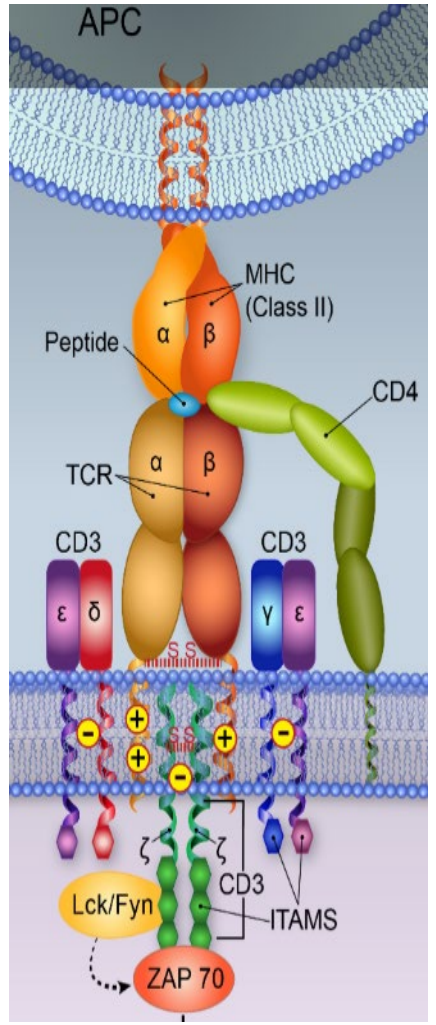
- PD-1 × CTLA4 (ccRCC, clear-cell renal cancer, NSCLC, TNBC)
- PD-1 × VEGF (advanced-stage EGFR/ALK wild type NSCLC)

代表性藥物與作用機轉

- **Blinatumomab** ：全球首款獲批的雙特異性T細胞接合抗體（屬BiTE架構）。它同時結合B細胞表面的CD19和T細胞上的CD3，將患者自身的T細胞直接「牽引」到帶有CD19的白血病細胞旁，誘導T細胞釋放穿孔素、顆粒酶殺死白血病細胞。Blinatumomab於2014年獲FDA批准用於復發難治性B細胞急性淋巴性白血病(ALL)，後來擴大至微小殘留病灶陽性的ALL。它在臨床上顯著提高了ALL的完全緩解率，特別是清除微小殘留病的能力，為傳統化療後仍有殘存腫瘤的患者提供了新的治癒途徑。
- **Mosunetuzumab**：羅氏開發的全長IgG型雙抗，靶向CD20（在B淋巴瘤細胞）和CD3（在T細胞）。用意類似Blinatumomab，透過一端結合T細胞、一端結合惡性B細胞，將T細胞引導去殺死CD20陽性的淋巴瘤。因為是完整抗體架構，Mosunetuzumab半衰期較長，可間歇給藥。臨床試驗在經多線治療失敗的非何杰金淋巴瘤（如濾泡性淋巴瘤）中取得約60%的總體反應率，部分患者達長期完全緩解。該藥於2022年底獲FDA批准用於二線後復發的濾泡淋巴瘤。
- **Teclistamab**：靶向B細胞成熟抗原**BCMA**（骨髓瘤細胞表面）與CD3（T細胞）。用於治療多發性骨髓瘤，特別是經多種療法後仍復發的難治患者。Teclistamab將T細胞導向帶有BCMA的骨髓瘤細胞，誘發T細胞殺傷作用。在臨床試驗中顯示出約63%的總反應率（包括大量深度緩解），為晚期骨髓瘤帶來突破性療效，FDA已於2022年批准其上市。

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.

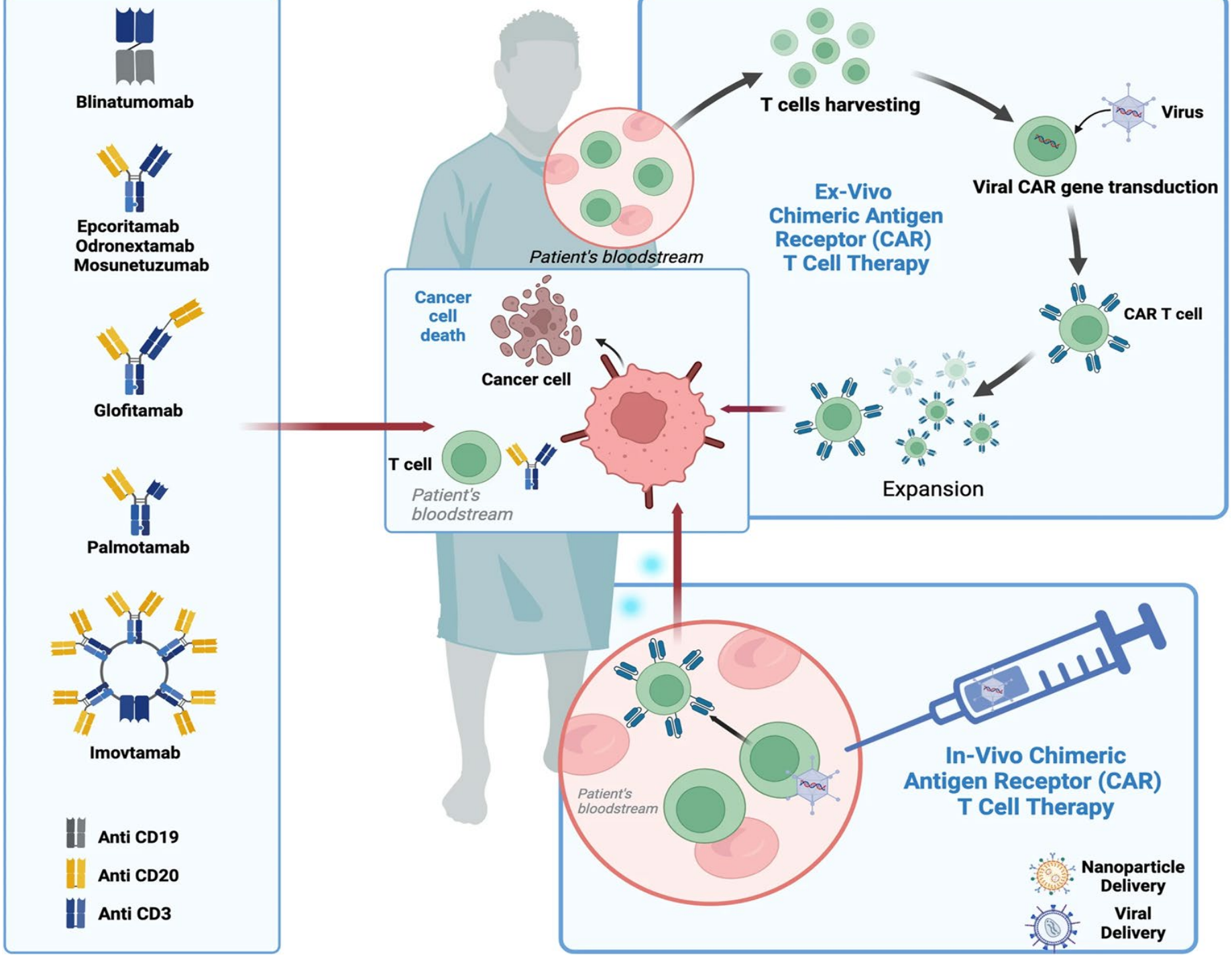
代表性藥物與作用機轉

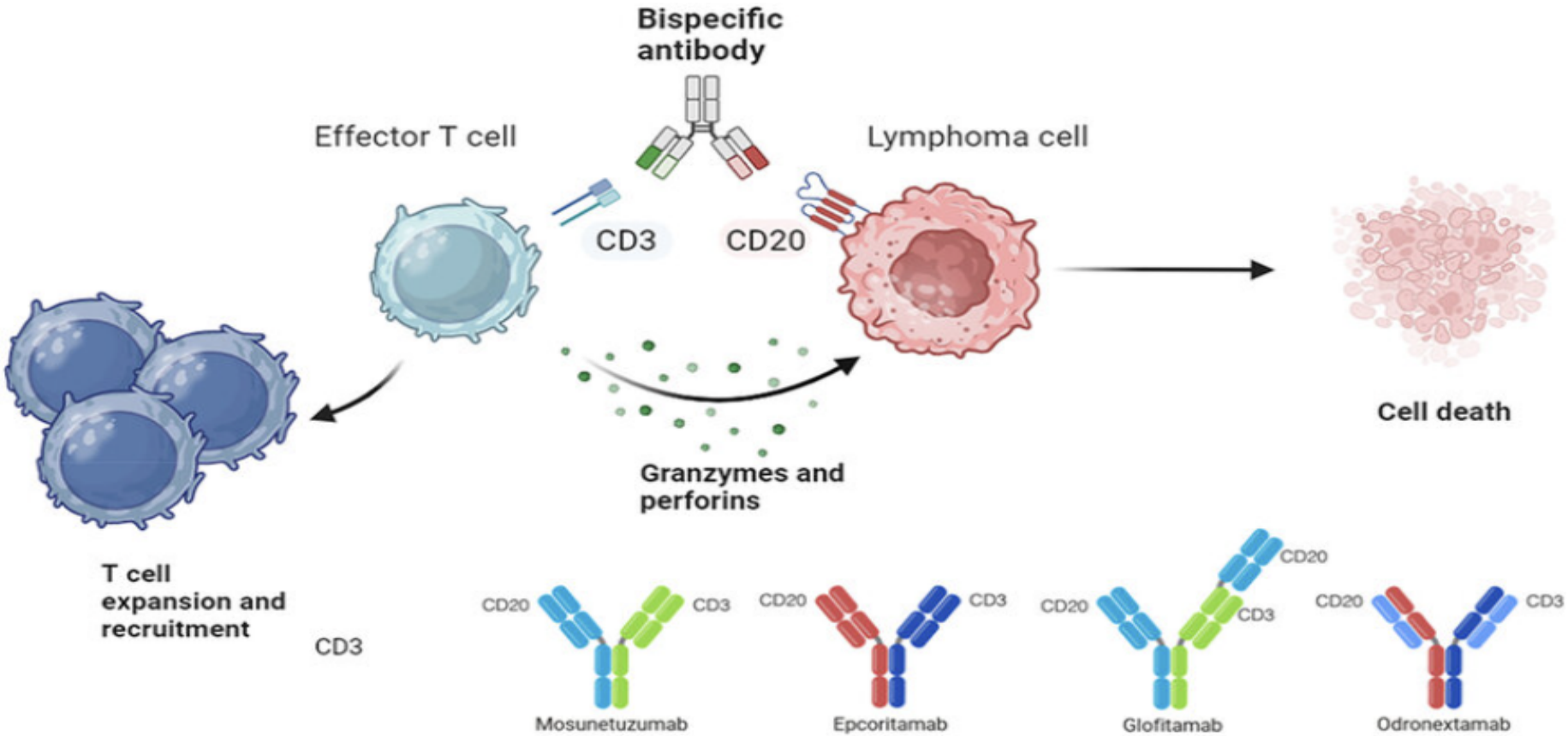
- Epcoritamab: 與Mosunetuzumab類似，靶向CD20×CD3，於2023年獲批用於復發性diffuse large B cell lymphoma 。特點是皮下注射給藥，提高便利性
- Glofitamab: 羅氏另一款針對CD20×CD3的雙抗，採用2:1結構（雙價結合CD20，一價結合CD3）增強對腫瘤細胞的親和，多用於臨床試驗中並與Mosunetuzumab競逐類似適應症。
- Amivantamab: 靶向EGFR×cMet的雙抗，用於非小細胞肺癌EGFR Exon20插入突變患者。透過同時封鎖EGFR及其旁路路徑cMet，克服腫瘤對EGFR-TKI的抗藥性。
- Cadonilimab (AK104): 中國康方生物開發的PD-1×CTLA-4雙抗，結合兩種免疫檢查點，2022年在中國批准用於治療晚期宮頸癌。它等同於PD-1抑制劑＋CTLA-4抑制劑的功能合一，在提升免疫療效的同時降低兩藥聯用的毒性疊加。

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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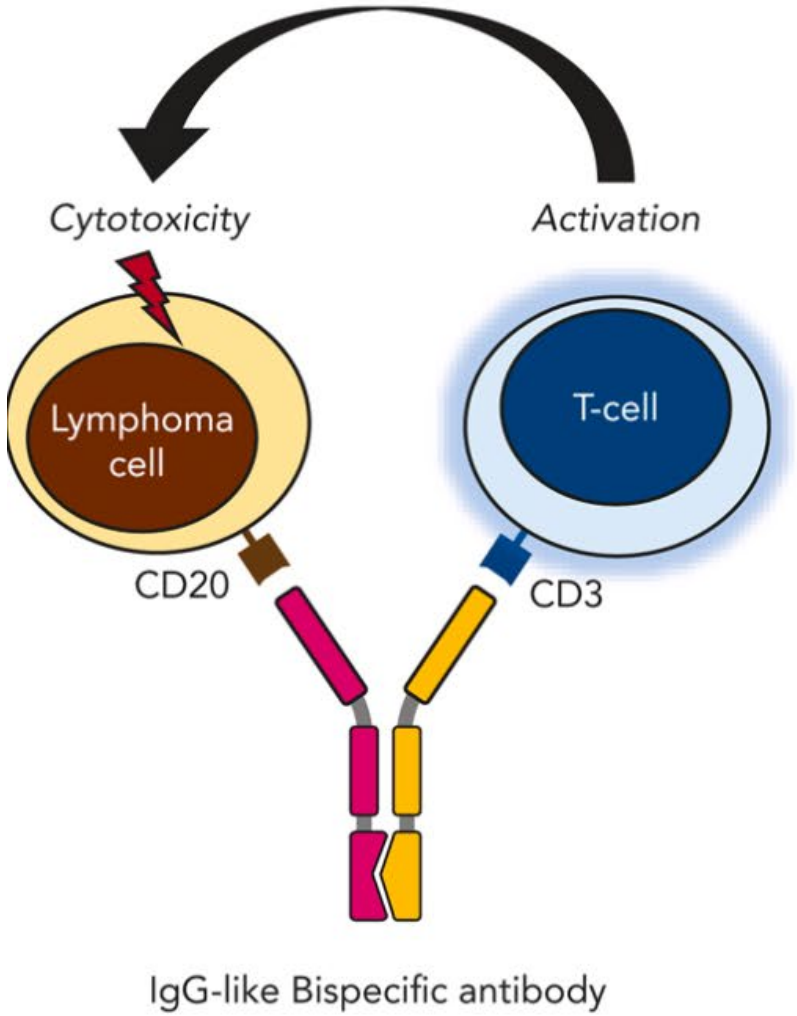
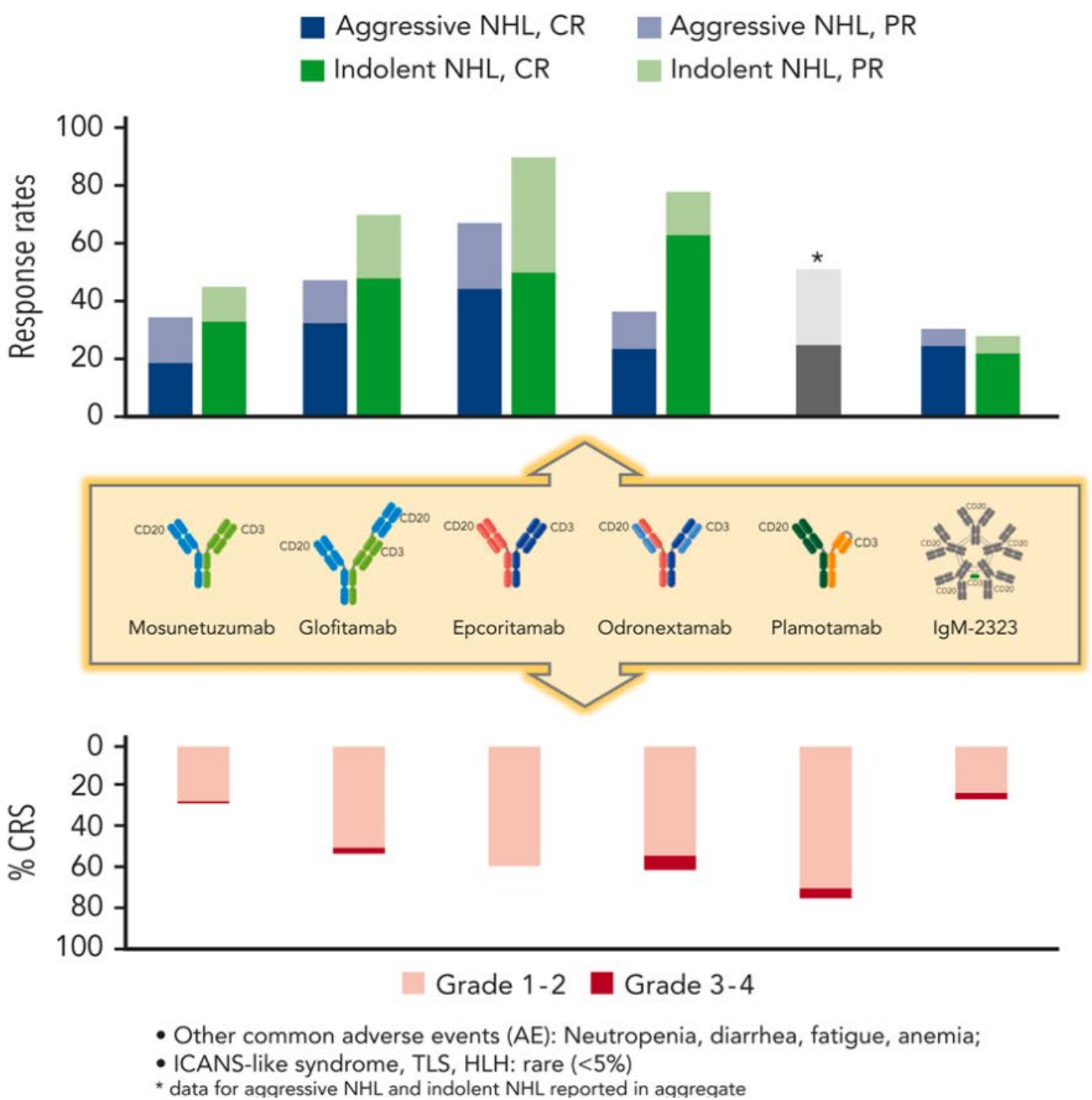
2024, VOL. 13, NO. 1, 2321648

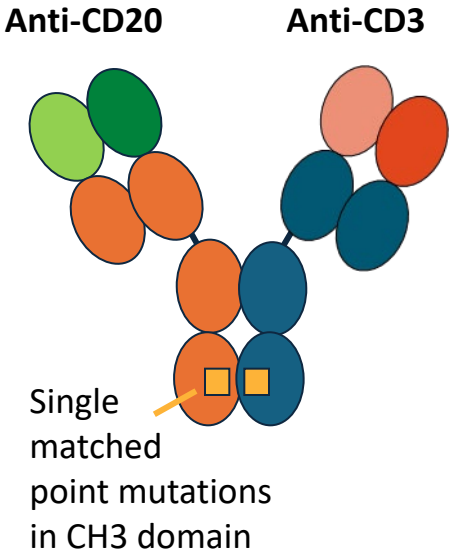




Blood (2023) 141 (5): 467–480.

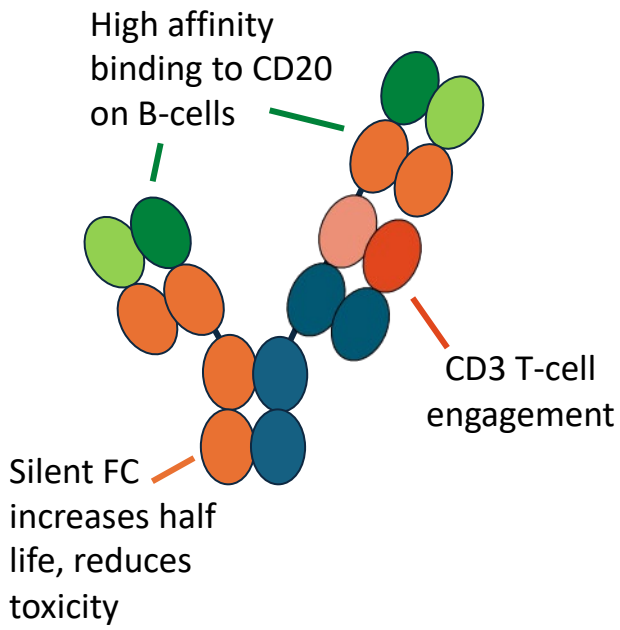
CD20/CD3 Bispecific Antibodies in B-Cell Lymphomas

Humanized mouse IgG1-based mAb



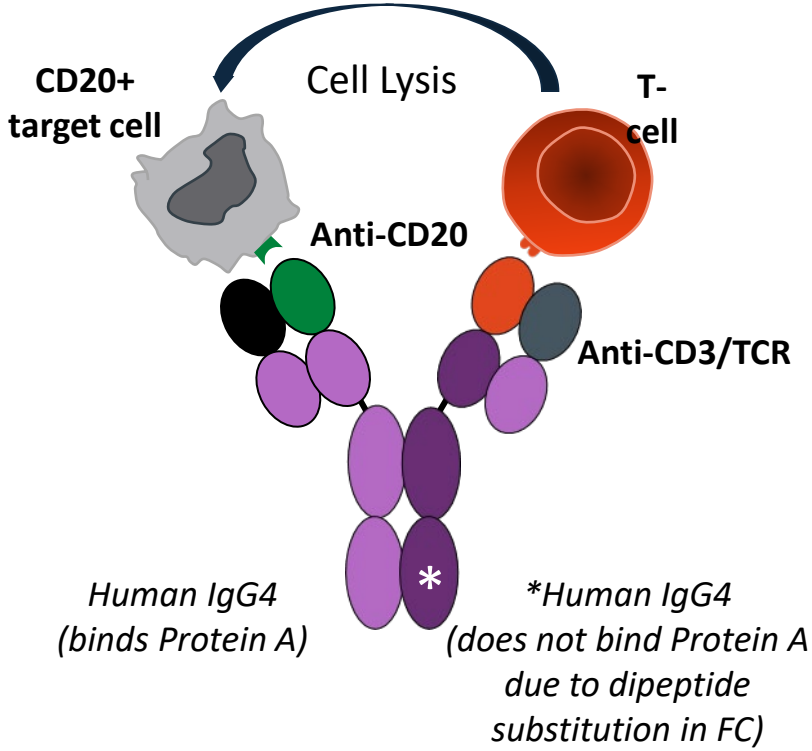
Epcoritamab (SC)

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.

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。

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.

在多次治療失敗後的復發／難治型 DLBCL（R/R DLBCL）中，雙特異性抗體間的選擇或其他三線以上治療的考量雙特異性抗體與其他療法相比如何？

- 現成可用off the shelf）的治療選項：表示可以立即給藥，不像 CAR-T 細胞治療需先收集細胞、製造等候時間等程序。
  - 安全性
    - 毒性風險較低／相對安全，尤其適合不適合接受 CAR-T 細胞治療的病人
    - 住院時間較短
    - 攻擊標靶不同（如 CD20 vs CD19）：代表接受 CAR-T 細胞治療並不排除未來使用雙特異性抗體的可能性，反之亦然。
  - 雙特異性抗體相較化學治療的優勢為何？
    - 療效提升，可能帶來更佳的安全性和／或生活品質的改善（QoL）。

選擇可用的雙特異性抗體：哪一種最適合每位病人？

在 Glofitamab vs Epcoritamab for DLBCL選擇

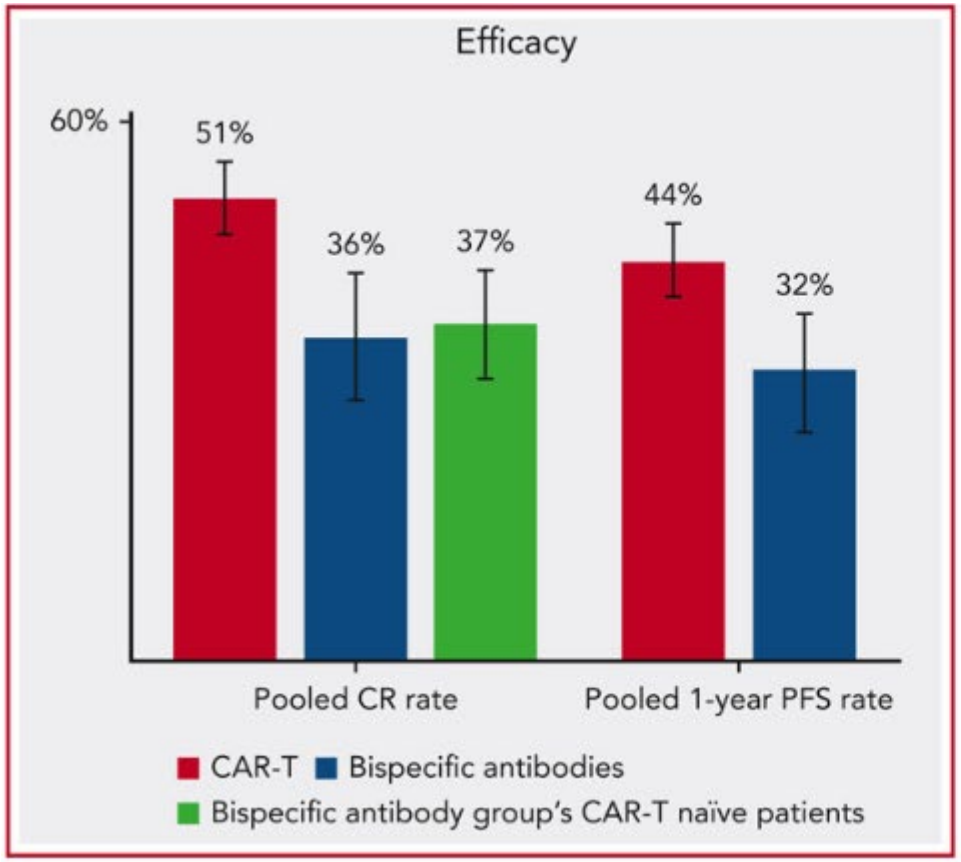
- 在pivotal trials ，安全性與有效性相當
- 都需住院觀察
- Glofitamab has a fixed duration (21-day cycle x 12) and less frequent administration
- Glofitamab *does not require steroids* for CRS mitigation
- Epcoritamab does *not require obinutuzumab* use for tumor volume reduction

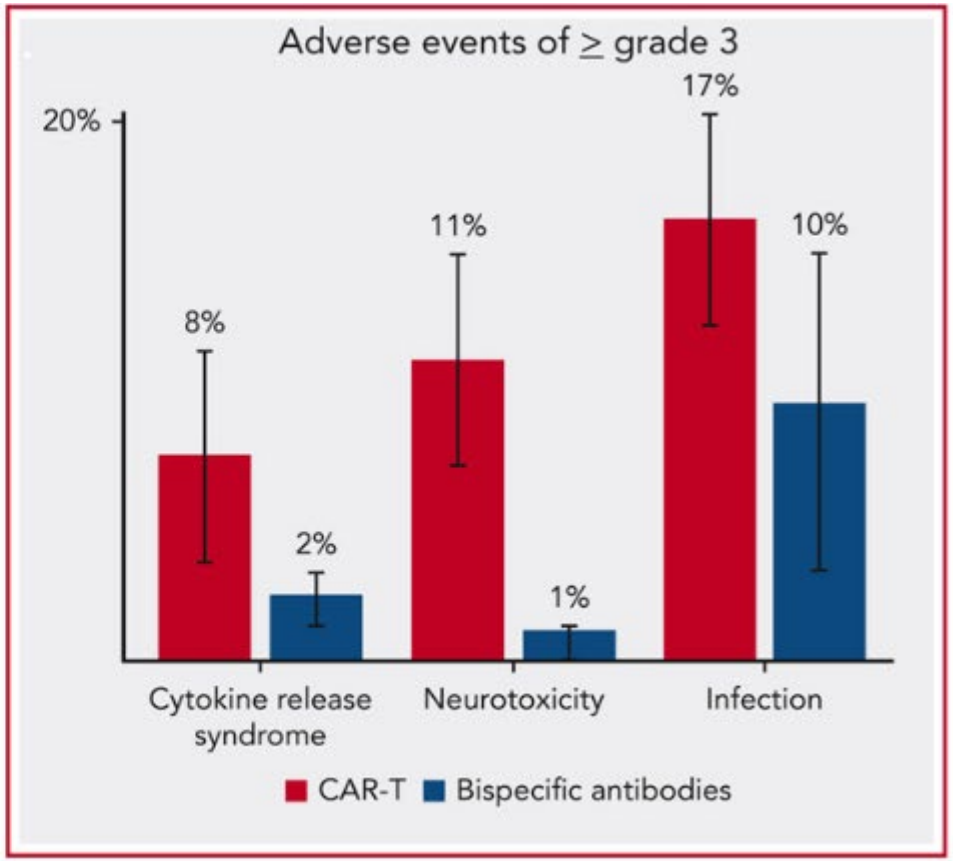
Epcoritamab-bysp PI. Glofitamab-gxbm PI.

Hutchings et al., NEJM, 2022

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%

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





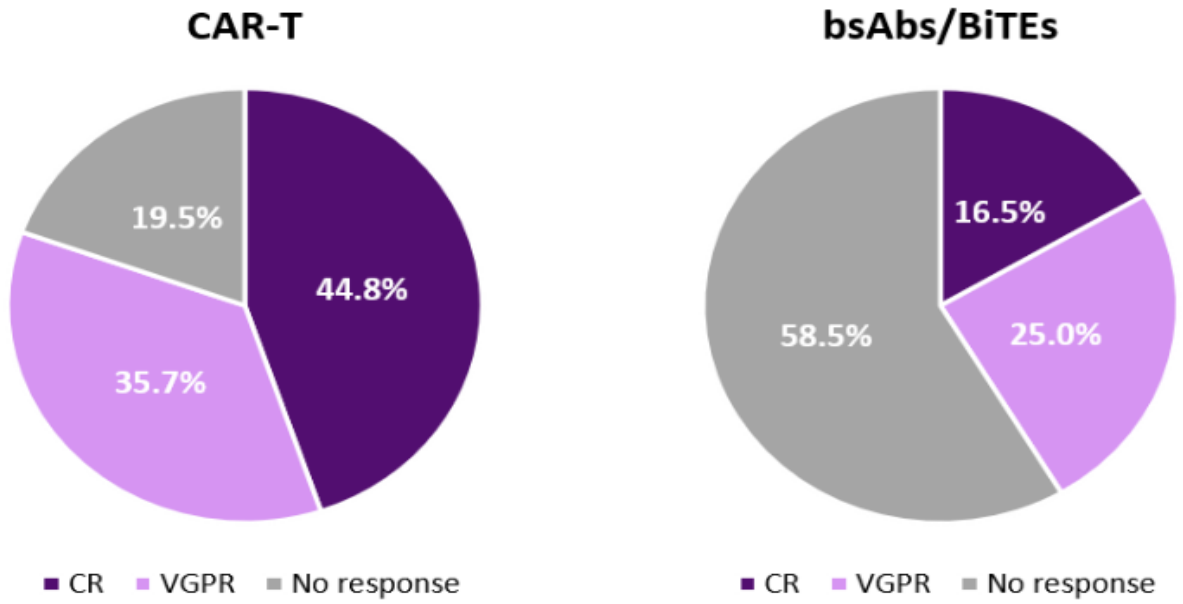
Blood (2024) 144 (6): 629–638

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.

結論 :整合與比較

比較項目	ADC（化療 2.0）	雙特異性抗體（抗體 2.0）
作用機轉	運送細胞毒素至腫瘤	引導免疫細胞攻擊腫瘤
標靶對象	腫瘤抗原	腫瘤抗原 + CD3（或其他）
殺傷方式	細胞毒素	免疫細胞介導殺傷
適應症	實體瘤與血液腫瘤	血液腫瘤與實體腫瘤
主要安全性考量	非標靶毒性	CRS、神經毒性
給藥方式	間歇性靜脈注射（如每三週）	通常為連續或每週給藥

Take home message： Chemotherapy 2.0

- 抗體藥物複合體（ADC）自 2000 年代以來在腫瘤治療領域展現卓越成果，結合單株抗體的專一性與化療藥物的殺傷力，實現「精準化療」的目標。
- **FDA 核准藥物超過 15 項**： Trastuzumab emtansine（T-DM1）、Trastuzumab deruxtecan（T-DXd）、Sacituzumab govitecan、Enfortumab vedotin 等，廣泛應用於乳癌、非小細胞肺癌、泌尿道上皮癌、淋巴瘤等。
- **突破標靶限制**：T-DXd 等具「旁觀者效應」的 ADC，能攻擊異質性高或抗原表現不均的腫瘤，提高治療成功率。
- **顯著延長無惡化存活期（PFS）與總存活期（OS）**：
  - DXd 對 HER2 陽性轉移性乳癌 PFS 中位數達 **28.8 個月**，顯著優於 T-DM1。
  - EV-301：Enfortumab vedotin 在膀胱癌中顯示總生存期明顯改善。
- **毒性相對可控**：ADC 副作用以血液學、間質性肺炎、肝功能異常等為主，透過嚴密監控多數可管理。
- **正進一步擴展至早期疾病與聯合療法**：如 T-DXd 應用於早期乳癌輔助治療階段，或與免疫檢查點抑制劑聯合使用，進一步提升療效。

Take home message :Antibody 2.0 (Bispecific Antibody)

- 正在將腫瘤治療從廣泛的細胞毒性，轉變為量身打造的智慧型治療方式。
- 雙抗療法在血液腫瘤領域已有重大成果，特別是對復發/難治病例帶來希望。例如，在復發性 Diffuse Large B cell lymphoma ，傳統治療完全緩解率僅約17.5%，而加入CD3xCD20雙抗後，完全緩解率提升到40%以上，幾乎提高了兩倍，且顯著延長病人存活。這些亮眼數據使雙抗有望成為經標準療法後復發淋巴瘤的新標準治療。
- 雙抗也正在實體瘤中展開研究，如針對肺癌、胃癌的雙抗臨床試驗等。如果成功，雙抗將拓展至更多癌種，進一步改寫治療指引。
- 「現成」免疫治療的優勢：相較於需為每位患者量身定製的CAR-T細胞療法，雙特異性抗體屬於開啟「off-the-shelf」療法，可大量製備、隨時給藥且可根據情況隨時停止或調整。這讓臨床運用更加靈活，醫師能像開單株抗體或化療藥一樣開立雙抗，免除了複雜的細胞採集與工程改造流程。
- 主要副作用：細胞激素釋放症候群(CRS)、神經毒性ICANS）。
- 腫瘤逃逸與耐受這持續的演進是由更先進的科學、技術與病人篩選所驅動。