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Anticuerpos Biespecíficos: Desarrollo farmacológico

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Anticuerpos Biespecíficos: Desarrollo farmacológico

- INTRODUCCIÓN
- CLASIFICACIÓN
  - FUNCIONAL
  - ESTRUCTURAL
- RETOS
  - BIOMARCADORES
  - VIA DE ADMINISTRACIÓN
  - DOSIFICACIÓN
  - TOXICIDAD
- CONCLUSIONES

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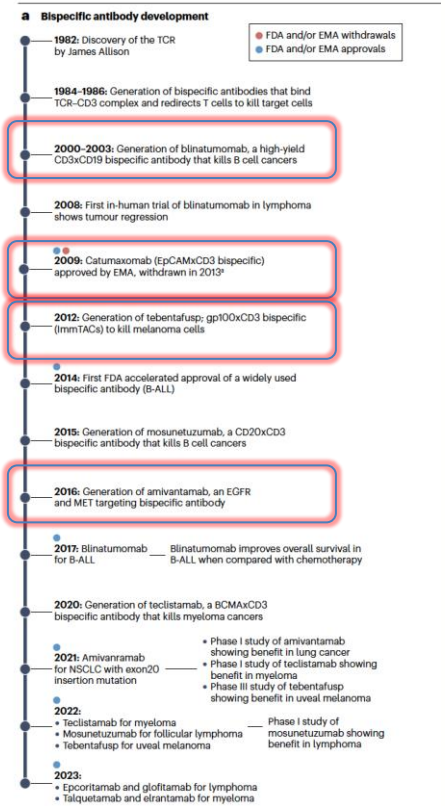

Table 1 | Approved bispecific antibodies for cancer therapy

bsAb	International non-proprietary name	Targets	MoA	Format	Year of first approval/ region[a]	Indications	Company
Removab	Catumaxomab	EpCAM×CD3ε	TDCC	Quadroma mouse/rat 1+1	2009 Withdrawn EU 2013	Ovarian ascites, intraperitoneal	Trion Pharma/ Fresenius
Blincyto	Blinatumomab	CD19×CD3ε	TDCC	BiTE 1+1	2014 United States/EU, Japan	ALL	Amgen
Rybrevant	Amivantamab	EGFR×MET	Signalling inhibition, ADCC	Duobody 1+1	2021 United States/EU	NSCLC EGFR exon 20 insert mutation	J&J
KIMMTRAK	Tebentafusp	gp100-HLA-A*02×CD3ε	TDCC	scFv-TCR fusion 1+1	2022 United States/EU	Uveal melanoma	Immunocore
Lunsumio	Mosunetuzumab	CD20×CD3ε	TDCC	KiH 1+1 IgG	2022 United States/EU	Relapsed/refractory follicular NHL	Roche group
Kaitanni	Cadonilimab	PD1×CTLA4	Dual checkpoint inhibition	IgG-scFv tetrabody 2+2	2022 China	Hepatocellular carcinoma	Akeso Bio
Tecvayli	Teclistamab	BCMA×CD3ε	TDCC	Duobody 1+1	2022 United States/EU	Relapsed/refractory multiple myeloma	J&J
Columvi	Glofitamab	CD20×CD3ε	TDCC	CrossMAb 2+1	2023 United States/EU	Relapsed/refractory DLBCL	Roche group
(T)Epkinly	Epcoritamab	CD20×CD3ε	TDCC	Duobody 1+1	2023 United States/EU, Japan	Relapsed/refractory DLBCL	Genmab, Abbvie
Talvey	Talquetamab	GPRC5D×CD3ε	TDCC	Duobody 1+1	2023 United States/EU	Relapsed/refractory multiple myeloma	J&J
Elrexfio	Elranatamab	BCMA×CD3ε	TDCC	bsAb 1+1	2023 United States/EU	Relapsed/refractory multiple myeloma	Pfizer

ADCC, antibody-dependent cellular cytotoxicity; ALL, acute lymphocytic leukaemia; BCMA, B cell maturation antigen; BiTE, bispecific T cell engager; bsAb, bispecific antibody; DLBCL, diffuse large B cell lymphoma; EGFR, epidermal growth factor receptor; EpCAM, epithelial cellular adhesion molecule; GPRC5D, G-protein-coupled receptor class C group 5 member D; MoA, mechanism of action; NSCLC, non-small cell lung cancer; NHL, non-Hodgkin lymphoma; scFv, single-chain variable fragment; TCR, T cell receptor; TDCC, T cell-dependent cellular cytotoxicity. [a]Region of approval limited to the United States, the European Union (EU), Japan and China; products may also be approved in other countries. Status as of end of 2023.

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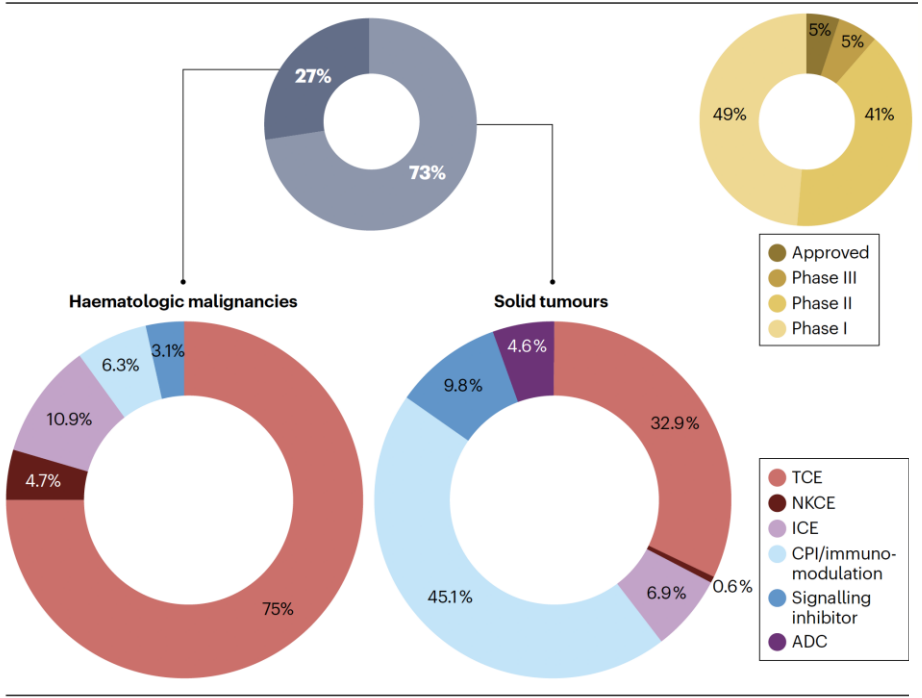
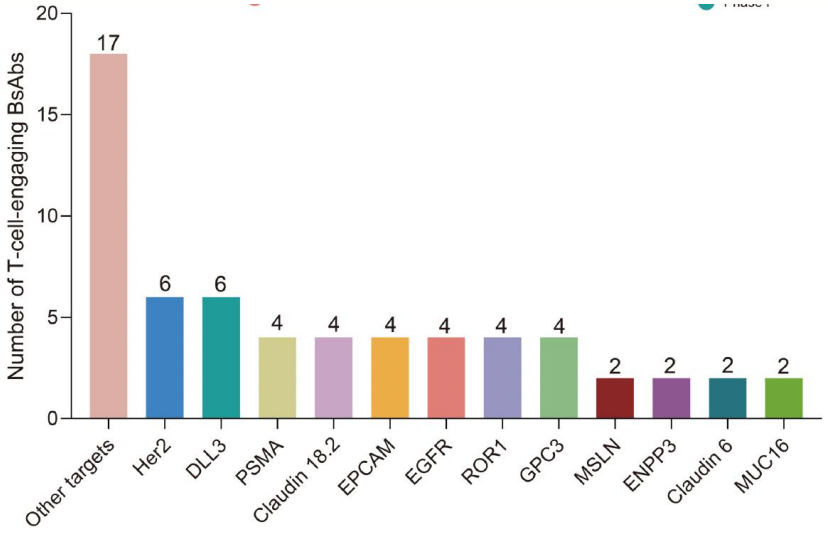
Aprox 200 compuestos en desarrollo



90% en EC fase I/II



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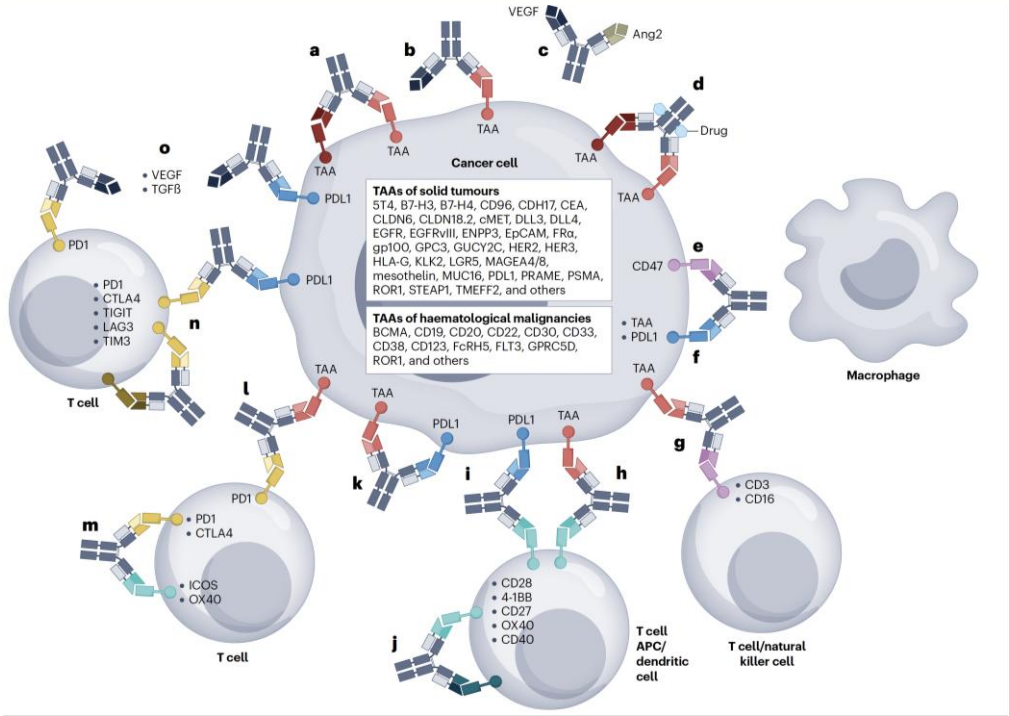
- Dual Immune-chekpoints blockade
  - Co-inhibitory
  - Co-stimulatory

- Oncogenic Pathway inhibition



- IMMUNE CELL ENGAGERS
  - T cell engagers
  - NK cell engagers
  - Innate cell engagers:
    - Macrophages
    - Fibroblasts

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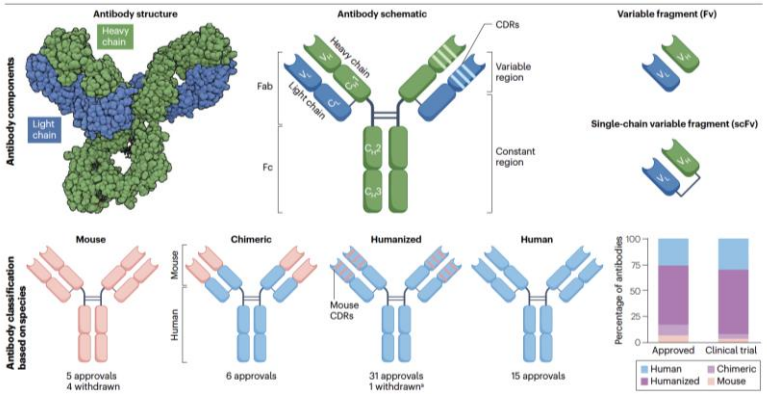

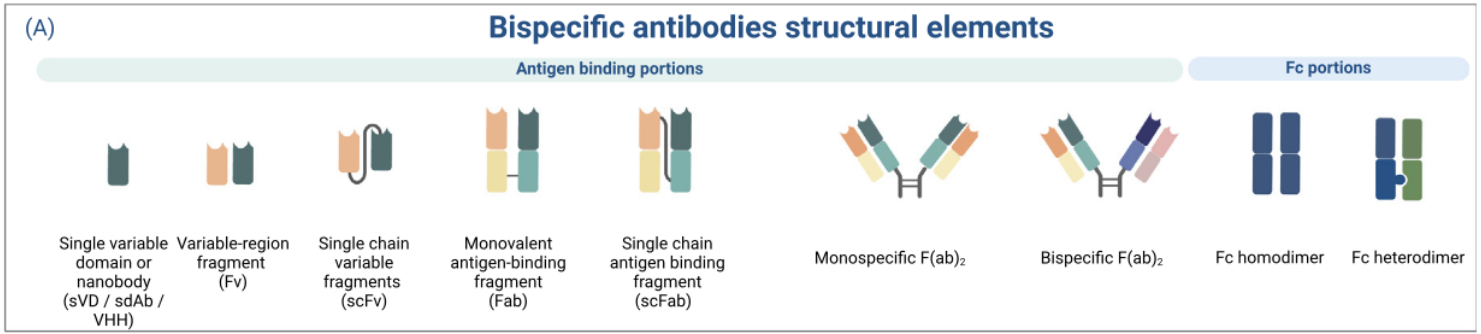

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Herrera et al. Trends in Cancer. 2024

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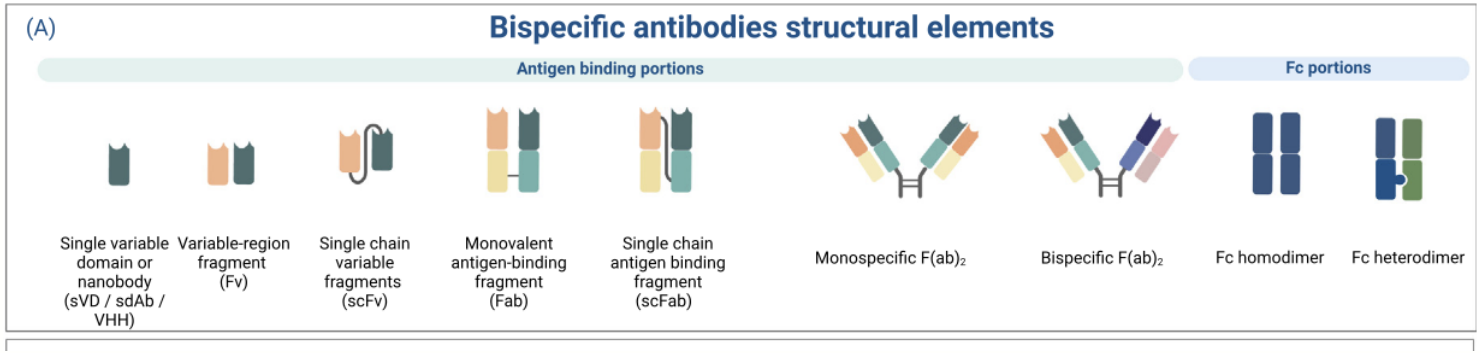

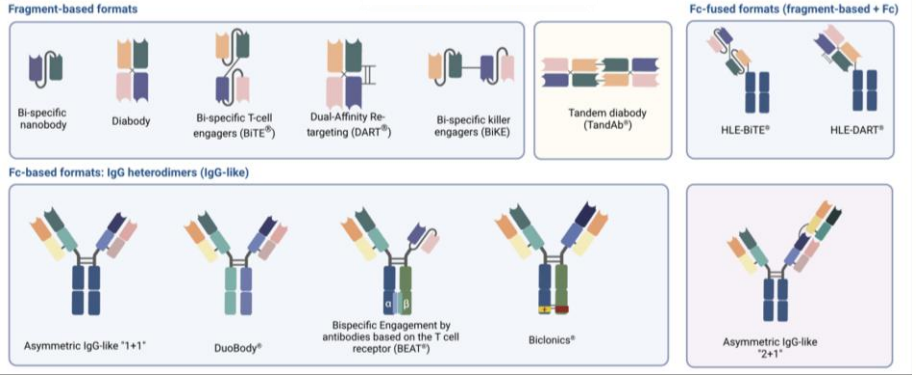

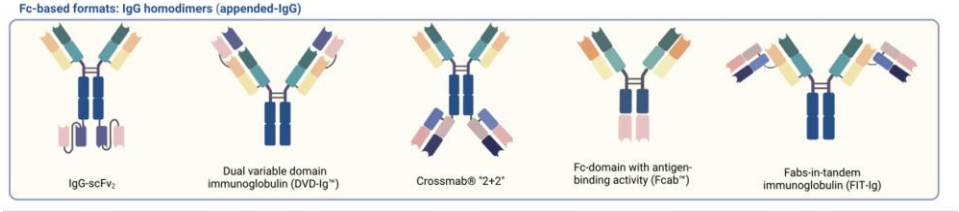

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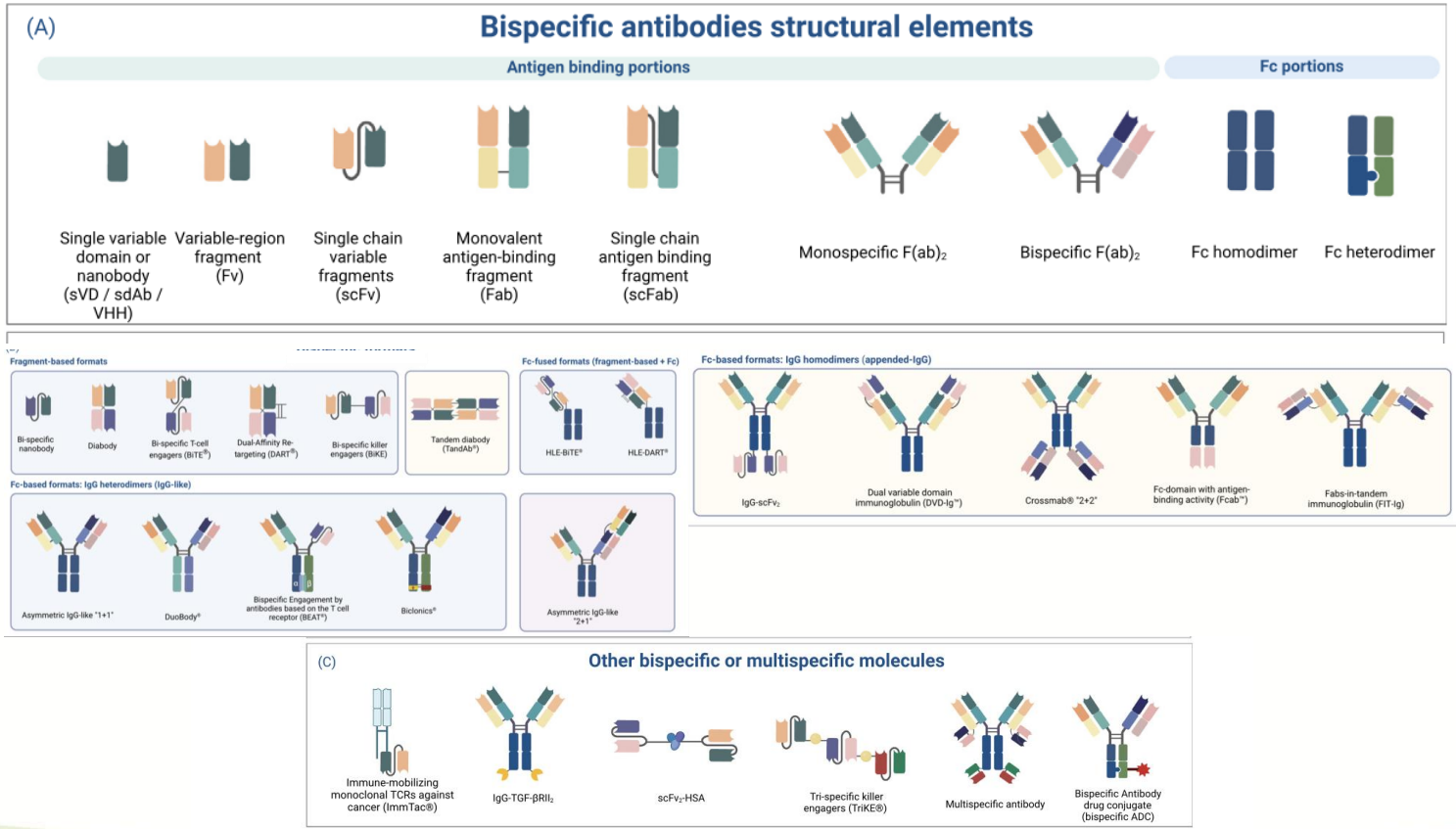

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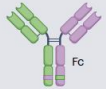
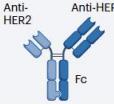
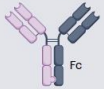
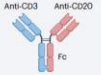
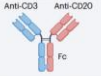
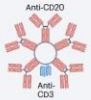
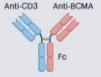
Table 2 (continued) | Bispecific antibodies approved or nearing approval by the FDA and EMA

Target	Antibody	Structure	Format	Major indications	Adverse effects
Receptor blockers					
EGFRxcMET	Amivantamab	Anti-EGFR Anti-cMET 	IgG1 (half-life extension) Fc afucosylation (enhanced ADCC) K409R, F405L mutation (for Fab exchange) ~146 kDa	Lung cancer	Skin rash Stomatitis Muscle pain Cytopenia Electrolyte abnormality Embryo–fetal toxicity
Her2xHer2	Zanidatamab (in clinical trial)	Anti-HER2 Anti-HER2 	Two anti-HER2 scFvs (bind two distinct HER2 epitopes) IgG1 (half-life extension) ~125 kDa	HER2⁺ cancers	Diarrhoea Infusion reaction Cardiac failure
PD1xCTLA4	Volrustomig MEDI5752 (in clinical trial)	Anti-PD-1 Anti-CTLA-4 	IgG1 (half-life extension) L234F, L235E, P331S mutation (reduced FcγR binding) ~145 kDa (estimated)	Multiple solid tumours	Checkpoint inhibitor-associated irAEs: Diarrhoea Thyroid disorders Skin rash Hepatotoxicity

ADCC, antibody-dependent cellular cytotoxicity; ALL, acute lymphoblastic leukaemia; CRS, cytokine release syndrome; Ig, immunoglobulin; irAEs, immune-related adverse events; IV, intravenous; kDa, kilodalton; scFv, single-chain variable fragment; TLS, tumour lysis syndrome. Fc-bearing bispecific antibodies also carry Fc mutations that enable pairing of the heterogenous heavy chains (not shown).

Table 2 | Bispecific antibodies approved or nearing approval by the FDA and EMA

Target	Antibody	Structure	Format	Major indications	Adverse effects
T cell engagers					
CD19xCD3	Blinatumomab	Anti-CD19 scFv	Lacks Fc (short half-life ~2 h) ~54 kDa	B cell precursor ALL	CRS Neurotoxicity Infection Cytopenia TLS
CD20xCD3	Mosunetuzumab	Anti-CD3 Anti-CD20 	IgG1 Fc (half-life extension) N297G mutation (aglycosylation and reduced ADCC) ~146 kDa	Lymphoma	CRS Neurotoxicity Infection Cytopenia Embryo–fetal toxicity
	Epcoritamab	Anti-CD3 Anti-CD20 	IgG1 Fc (half-life extension) L234F, L235E, D265A mutation (reduced ADCC) ~146 kDa	Lymphoma	CRS Neurotoxicity Infection Cytopenia TLS
	Glofitamab	Anti-CD20 Anti-CD20 	Two anti-CD20 scFvs linked with one anti-CD3 scFv IgG1 Fc (half-life extension) P329G, L234A, L235A mutation (reduced ADCC) ~194 kDa	Lymphoma	CRS Neurotoxicity Infection Cytopenia
	Imvotamab (in clinical trial)	Anti-CD20 	IgM pentamer (ten CD20-binding sites) Albumin fusion (half-life extension) ~960 kDa	Lymphoma	CRS Cytopenia Hypophosphatemia
BCMAxCD3	Teclistamab	Anti-CD3 Anti-BCMA 	IgG4 Fc (half-life extension) S228P (hinge stabilization), and F234A and L235A mutation (reduced FcγR binding) ~143 kDa	Multiple myeloma	CRS Neurotoxicity Infection Cytopenia Hepatotoxicity Embryo–fetal toxicity
	Elranatamab	Anti-CD3 Anti-BCMA 	IgG2 Fc (half-life extension) ~145 kDa	Multiple myeloma	CRS Neurotoxicity Cytopenia
GPRC5DxCD3	Talquetamab	Anti-CD3 Anti-GPRC5D 	IgG4 Fc (half-life extension) S228P (hinge stabilization), and F234A and L235A mutation (reduced FcγR binding) ~147 kDa	Multiple myeloma	CRS Neurotoxicity Cytopenia Skin rash Hepatotoxicity Embryo–fetal toxicity
GP100xCD3	Tebentafusp	Anti-gp 100 TCR 	Lacks Fc, MW above renal filtration cut-off (half-life 6–8 h) ~75–77 kDa	Melanoma	CRS Skin rash Hepatotoxicity Embryo–fetal toxicity

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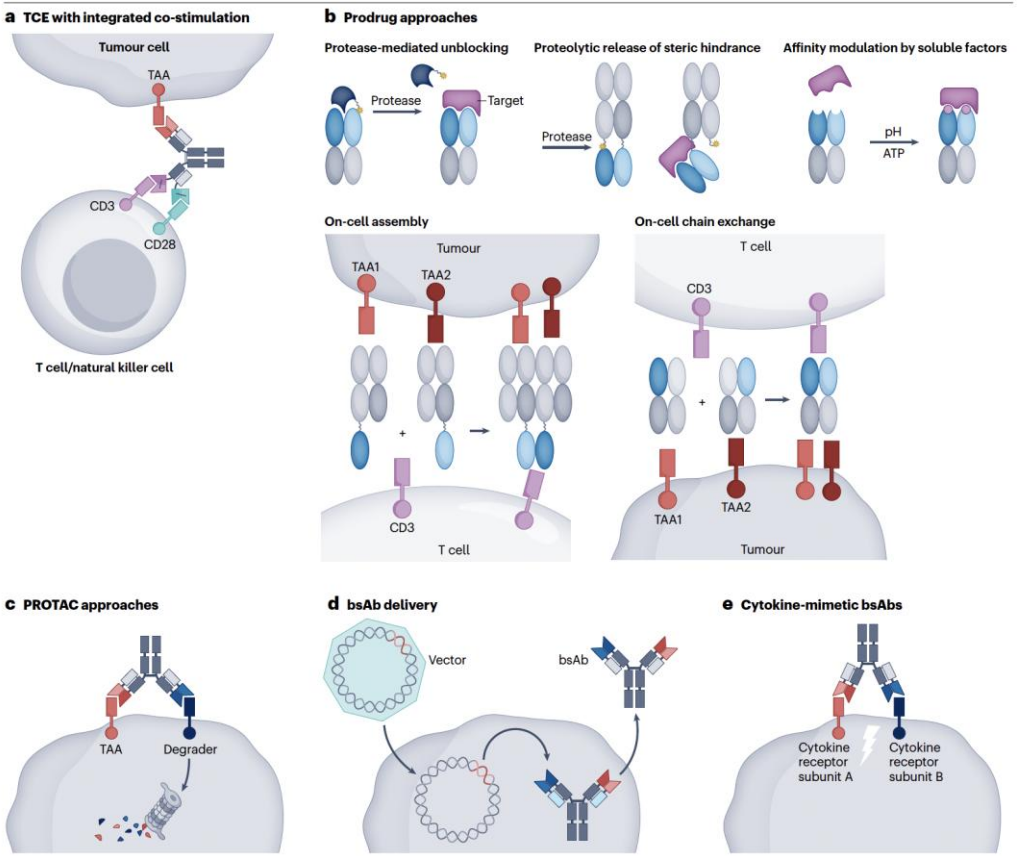

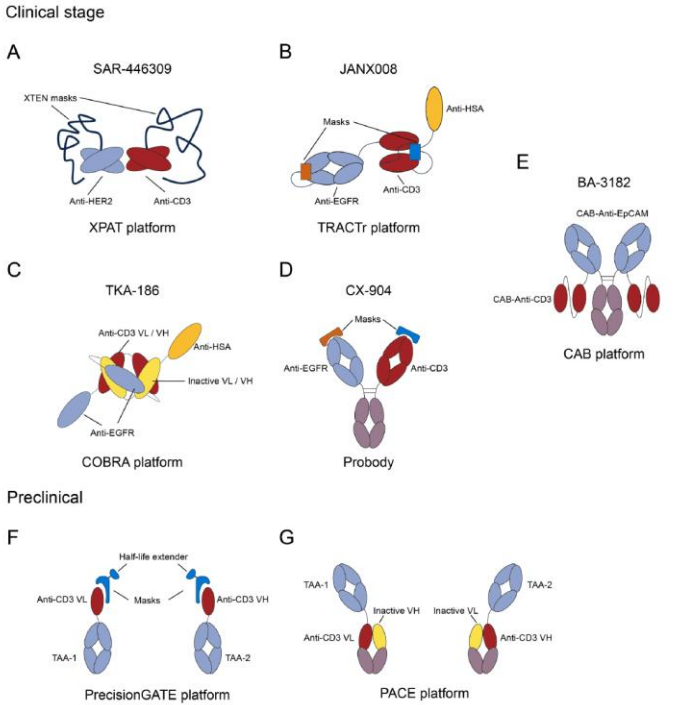

Fig. 4. Exploring Conditional Activation of TCBs: Various strategies for selectively activating T-cell engagers are currently under exploration. In the field of solid tumors, clinical trials are underway for TCBs developed from five platforms, while two platform based on the principle of half-antibody are in the preclinical stage. **A** XPAT platform: XTEN-ylated protease-activated TCB targeting Her2; **B** TRACTr platform: Tumor activated t-cell engager (TRACTr) targeting EGFR to enhance tumor-specific activation. **C** COBRA platform: Conditional bispecific redirected activation TCB is engineered to target EGFR. **D** Probody platform: Probody TCB targeting EGFR. **E** CBA platform: conditionally active biologic targeting EpCAM. **F** PrecisionGATE platform: Precision Guided Antibody Tumor Engager platform. **G** PACE platform: Prodrug-Activating Chain Exchange platform.

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Table 2 (*continued*)

Molecular	Target	Valency	Format	Company	Disease Area	Clinical Developmental Phase
AMG-794	Claudin 6 × CD3	1 + 1	Tandem scFv-scFc (HLE-BiTE)	Amgen	Cancer (SCLC, ovarian)	I
Xmab-541	Claudin 6 × CD3	2 + 1	Tandem Fab-scFv-Fc × Fab-Fc (XmAb)	Xencor	Cancer (ovarian; unspecified Solid Tumor)	I
Ubamatamab	MUC16 × CD3	1 + 1	Hetero Fab-Fc, (Common LC)	Regeneron	Cancer (fallopian tube, ovarian, peritoneal)	II
LBL-033	MUC16 × CD3	2 + 1	Tandem Fab − scFv − Fc × Fab − Fc	Leads Biolabs	Cancer (solid)	II
Umizortamig (GNC-039)	EGFRvIII × PD-L1 × 4-1BB × CD3	2 + 2 + 2 + 2	Tandem scFv-Fab-Fc-scFv (GNC)	Biokin Pharmaceutical	Cancer (brain, solid)	I
BA-1202	CEA × CD3	2 + 2	IgG-[L]-scFv	Luye Pharma Group	Cancer (solid)	I
TAK-280 (MVC-280)	B7-H3 × CD3	4 + 2	Tandem sdAb-scFv (COBRA)	Takeda/Maverick Therapeutics	Cancer (solid)	II
GEN-1047	B7-H4 × CD3	1 + 1	Hetero Fab-Fc (Duobody)	Genmab	Cancer (solid)	II
BI-765049	B7-H6 × CD3	1 + 1	Hetero scFab-Fc	Boehringer Ingelheim	Cancer (solid)	I
JNJ-78278343	KLK2 × CD3	Undisclosed	Undisclosed	Johnson & Johnson/ Zymeworks	Cancer (prostate)	I
QL-335	LY6G6D × CD3	2 + 1	Tandem Fab-scFv-Fc × Fab-Fc	QLSF Biotherapeutics	Cancer (colorectal)	I
CBA-1535	5 T4 × CD3	2 + 1	Tandem scFv-Fab (Tribody)	Chiome Bioscience	Cancer (lung)	I
ANJ-564 (TTX-564)	CD33 × CD3	Undisclosed	Undisclosed	Anji Pharmaceuticals	Cancer (solid)	I
Cabotamig (ARB-202)	CDH17 × CD3	2 + 2	IgG-[H]-scFv	Arbele	Cancer (gastrointestinal)	II
ASP-2074	TSPAN8 × CD3	1 + 1	Hetero Fab-Fc × scFv-Fc	Astellas	Cancer (solid)	I
JNJ-70218902	TMEFF2 × CD3	1 + 1	Hetero Fab-Fc (Duobody)	Johnson & Johnson/Genmab	Cancer (solid)	I
AMG-509 (Xaluritamig)	STEAP1 × CD3	2 + 1	Tandem Fab-scFv-Fc × Fab-Fc (XmAb)	Amgen/Xencor	Cancer (prostate)	I
IMA-401	MAGE-A4/A8 × CD3	1 + 1	Hetero scFv-Fc × TCR-Fc	Immatics Biotechnologies	Cancer (solid)	I
IMA-402	PRAME × CD3	1 + 1	Hetero scFv-Fc × TCR-Fc	Immatics Biotechnologies	Cancer (solid)	II
IMC-F106C	PRAME × CD3	1 + 1	Tandem TCR-scFv	Immunocore	Cancer (melanoma, NSCLC)	III

* The clinical information was collected from ClinicalTrials.gov, Citeline Clinical, and Synapse.

Table 2
*Overview of Clinical-stage TCBs for Solid Tumor Treatment.

Molecular	Target	Valency	Format	Company	Disease Area	Clinical Developmental Phase
Ruminotamab (RG-6194)	Her2 × CD3	1 + 1	Hetero Fab-Fc	Roch	Cancer (breast)	I
M-02	Her2 × CD3	1 + 1	Hetero Fab-Fc × scFv-Fc	Wuhan YZY Biopharma	Cancer (breast, gastrointestinal, stomach, ovarian)	I
SAR-446309 (AMX-818)	Her2 × CD3	1 + 1	Tandem scFV (XPAT)	Sanofi/Amunix	Cancer (solid)	I
SAR-443216	Her2 × CD28 × CD3	1 + 1 + 1	Tandem domain-exchanged Fv × Fab-Fc (CODV-Ig)	Sanofi	Cancer (gastrointestinal, stomach)	I
EX-101	Her2 × CD3	1 + 1	Hetero Fab-Fc (ExMab)	Excelmab	Cancer (breast, gastrointestinal, stomach)	I
BC-004	Her2 × CD3	Undisclosed	Undisclosed	Buchang Shenzhou Pharmaceutical	Cancer (solid)	I
BI-764532 (OBT-620)	DLL3 × CD3	1 + 1	Hetero scFab-Fc	Boehringer Ingelheim/ Oxford BioTherapeutics	Cancer (SCLC, Neuroendocrine)	II
HPN-328	DLL3 × CD3	1 + 1	Tandem sdAb-sdAb-scFv (TriTAC)	Harpoon Therapeutics	Cancer (SCLC, Neuroendocrine)	II
ZG-006	DLL3 × CD3	2 + 1	Tandem scFv-Fc × Fab-Fc	Suzhou Zelgen Biopharmaceuticals	Cancer (SCLC, Neuroendocrine)	II
RG-6524	DLL3 × 4-1BB × CD3	1 + 2	Tandem scFab-Fc × Fab-Fc (Dual/LINC-Ig)	Roche	Cancer (SCLC, Neuroendocrine, solid)	I
QLS-31904	DLL3 × CD3	1 + 1	Tandem Fab-scFv	Qilu Pharmaceutical	Cancer (solid)	I
REGN-4336	PSMA × CD3	1 + 1	Hetero Fab-Fc, (Common LC)	Regeneron	Cancer (prostate, renal)	II
JNJ-80038114	PSMA × CD3	Undisclosed	Undisclosed	Johnson & Johnson	Cancer (prostate)	I
JANX007	PSMA × CD3	1 + 1	Tandem Fab-scFv-sdAb (TRACTr)	Janux Therapeutics	Cancer (prostate)	I
CC-1	PSMA × CD3	2 + 2	IgG-[L]-scFv	German Cancer Research Center	Cancer (prostate)	I
HBM-7022 (AZD-5863)	Claudin 18.2 × CD3	2 + 1	Tandem saAb-Fc × Fab-Fc (HBICE)	AstraZeneca/Harbour Biomed	Cancer (solid)	II
IBI-389	Claudin 18.2 × CD3	Undisclosed	Undisclosed	Innovent Biologics	Cancer (solid)	I
ASP-2138	Claudin 18.2 × CD3	2 + 1	Tandem Fab-scFv-Fc × Fab-Fc (XmAb)	Astellas Pharma/Xencor	Cancer (Esophageal, Gastric, Pancreas)	I
QLS-31905	Claudin 18.2 × CD3	2 + 1	Tandem Fab-Fc-scFv × Fab-Fc	Qilu Pharmaceuticals	Cancer (solid)	II
Catumaxomab	EpCAM × CD3	1 + 1	Hetero Fab-Fc	LintonPharm/ Fresenius	Cancer (bladder, breast, colorectal)	III
M-01	EpCAM × CD3	1 + 1	Hetero Fab-Fc × scFv-Fc	Wuhan YZY Biopharma	Cancer (breast, colorectal, stomach)	III
BA-3182	EpCAM × CD3	2 + 2	IgG-[L]-scFv (CAB technology)	BioAtla	Cancer (breast, colorectal)	I
A-337	EpCAM × CD3	2 + 1	Tandem ScFv-Fab (iTAb)	ITabMed/Yifan Pharmaceutical	Cancer (solid)	I
SMET-12	EGFR × CD3	1 + 1	Tandem Fab-Fc (HbiAb)	Zhejiang Shimai Pharmaceutical	Cancer (solid)	II
TAK-186 (MVC-101)	EGFR × CD3	4 + 2	Tandem sdAb-scFv (COBRA)	Takeda/Maverick Therapeutics	Cancer (colorectal, head and neck)	II
JANX008	EGFR × CD3	1 + 1	Tandem Fab-scFv-sdAb	Janux Therapeutics	Cancer (colorectal, head and neck, SCLC)	I
CX-904	EGFR × CD3	1 + 1	Hetero Fab-Fc (Probody)	Amgen/CytomX Therapeutics	Cancer (colorectal, solid)	I
EMB-07	ROR1 × CD3	1 + 1	Tandem Fab-Fc (MAT-Fab)	EpimAb	Cancer (solid)	I
GNC-035	ROR1 × PD-L1 × 4-1BB × CD3	2 + 2 + 2 + 2	Tandem scFv-Fab-Fc-scFv (GNC)	SystImmune	Cancer (breast, stomach)	II
NVG-111	ROR1 × CD3	1 + 1	Tandem scFv	NovalGen	Cancer (SCLC)	I
NM32-2668	ROR1 × CD3	1 + 1	Tandem scFv (scMATCH3)	Numab	Cancer (solid)	I
CM-350	GPC3 × CD3	1 + 1	Hetero Fab-Fc	Chengdu KeyMed Biosciences	Cancer (solid)	II
CMD-011	GPC3 × CD3	1 + 1	Tandem Fab-Fc (HbiAb)	Zhejiang Shimai Pharmaceutical	Cancer (liver)	II
SAR-444200	GPC3 × CD3	Undisclosed	Tandem sdAb (Nanobody)	Sanofi	Cancer (solid)	II
ERY-974	GPC3 × CD3	1 + 1	Hetero Fab-Fc (TRAB)	Chugai (Roche)	Cancer (gastrointestinal, stomach, liver)	I
JNJ-79032421	MSLN × CD3	Undisclosed	Undisclosed	Johnson & Johnson	Cancer (solid)	I
AMG-305	MSLN × CDH3 × CD3	1 + 1 + 2	Tandem scFv-Fc-scFv	Amgen	Cancer (solid)	I
JNJ-87890387	ENPP3 × CD3	Undisclosed	Undisclosed	Johnson & Johnson	Cancer (solid)	I
XmAb-819	ENPP3 × CD3	2 + 1	Tandem Fab-scFv-Fc × Fab-Fc (XmAb)	Xencor	Cancer (renal)	I

(continued on next page)

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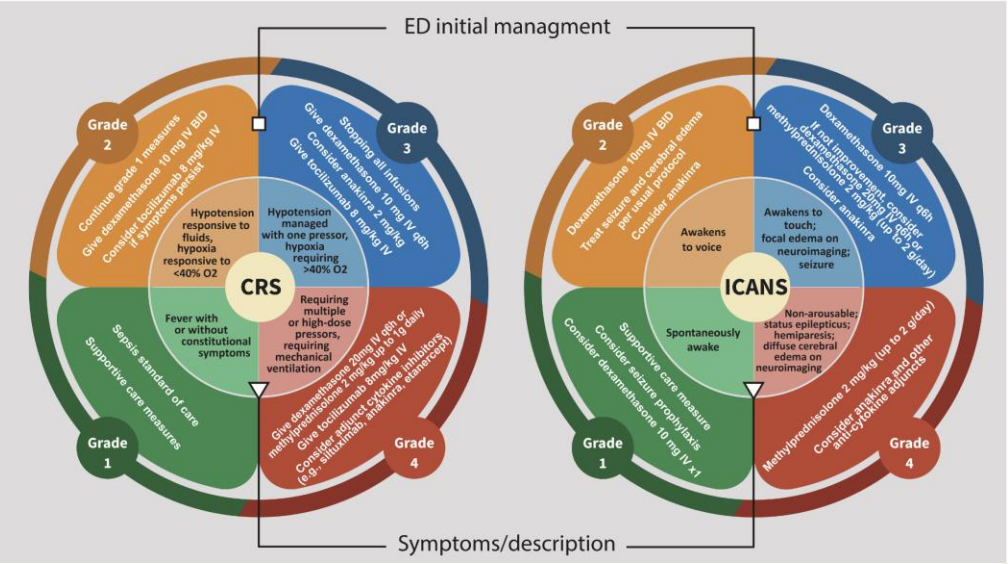

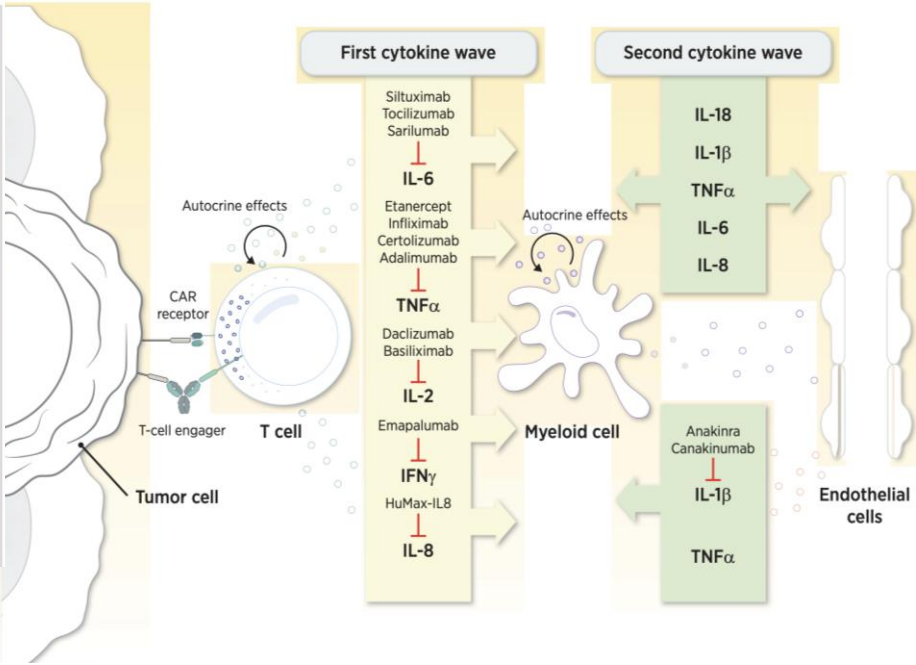

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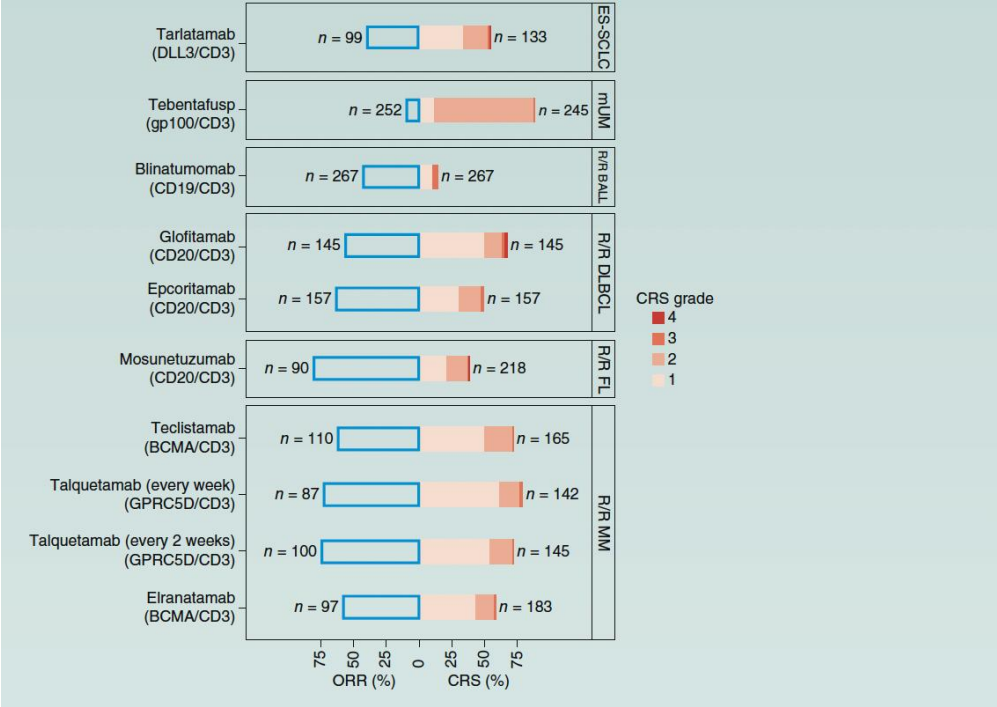

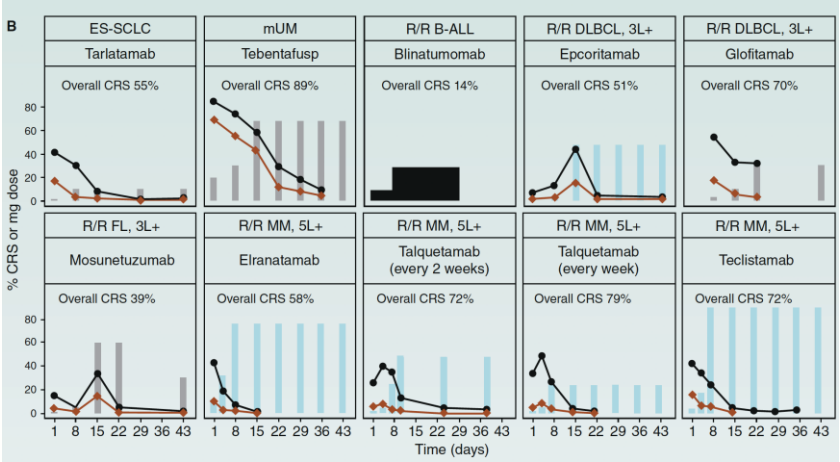

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Table 1. Examples of T-BiSp dose-finding strategies used related to CRS mitigation.

Category	Strategy, example
Step-up dose optimization	Increasing the number of steps with higher target dose levels during dose ranging: • Teclistamab dose escalation included one-step, two-step, and three-step regimens for intravenous and subcutaneous cohorts, in which more steps were initiated at higher target doses. A two-step subcutaneous once-weekly regimen and a three-step intravenous once-weekly regimen were selected for phase I dose expansion (14). • Epcoritamab dose-ranging trials used single-step at target doses <1.5 and double-step at target doses 1.5–60 mg (17) Testing multiple priming schedules per target dose: • Teclistamab dose ranging included different steps with the same target dose (0.02/0.8, 0.02/0.0576/0.8; mg/kg), the same steps with different target doses (0.01/0.06/0.18, 0.01/0.06/0.27; mg/kg), and the same steps with different maintenance dosing (2/6/30/150 once weekly and 2/6/30/300 every 2 weeks; mg; ref. 73). • Two SUD schedules for each epcoritamab target dose ≥6 mg were evaluated (e.g., 0.04/0.5/6 and 0.08/0.5/6), altering either SUD1 or SUD2 or both (17) Splitting step doses: • Elranatamab tested one priming dose (44 mg) in phase I. This single-step dose was converted to a double-step approach in a phase II trial by splitting the dose into 12 and 32 mg administered on days 1 and 4, respectively, and CRS was reduced by 8% (NCT04649359; NCT03269136; ref. 74). • Odronextamab split the administration of each of two step doses over 2 days (i.e., the SUD1 dose of 1 mg was administered as two 0.5 mg doses on separate days). They used split dosing after three escalations of SUD1 (1 mg+) and three escalations of SUD2 (20 mg+). Their selected RP2D regimen included a new SUD schedule with two untested SUDs and an additional third step (0.7/4/20), all administered as split doses (75) Flexible step-dose timing based on CRS: • Cevostamab evaluated a 0.3/3.3/160 regimen administered on day 1, days 2–4 (depending on the emergence and resolution of CRS), and day 8 (76) Single step for continuous infusion: • Initiating blinatumomab at 9 mcg/day (the lowest dose at which B-cell depletion was observed) for 1 week prior to escalating to the target dose (28 mcg/day) reduced CRS events occurring with the first dose [BLA 125557: Blincyto (blinatumomab)]

Table 1. Examples of T-BiSp dose-finding strategies used related to CRS mitigation. (Cont'd)

Category	Strategy, example
Route of administration development	First filing in intravenous with parallel or sequential subcutaneous development: • Mosunetuzumab—subcutaneous dose escalation and expansion arms were added to the phase I/II trial in 2018, 4 years prior to intravenous filing (NCT02500407). • Glofitamab—a subcutaneous dose escalation trial was registered in 2021, 2 years prior to intravenous filing (ISRCTN17975931). • Blinatumomab—phase I/II study of subcutaneous blinatumomab in B-ALL began in 2020 (NCT04521231), 6 years after authorization of the continuous intravenous infusion formulation. Expansion to NHL indications began in 2017, evaluating both intravenous (phase II/III; NCT02910063) and subcutaneous (phase Ib; NCT02961881) First filing in intravenous with no planned subcutaneous development: • Tebentafusp—intravenous approval received in 2021. No trials of subcutaneous formulations are registered. • Tarlatamab—an intravenous infusion product for small cell lung cancer was recently approved by FDA in 2024. • Linvoseltamab—filing application with an intravenous product is under FDA and EMA in 2024 First filing in subcutaneous: • Teclistamab—conducted intravenous dose ranging, then subcutaneous dose ranging, and proceeded with subcutaneous dose expansion only (80). • Elranatamab—proceeded with subcutaneous dose expansion after concurrent intravenous and subcutaneous dose ranging (74). • Epcoritamab—only subcutaneous dose ranging and expansion were sought, which was supported by an *in vivo* study in cynomolgus monkeys demonstrating a similar degree of prolonged B-cell depletion with subcutaneous and intravenous administration (17) Parallel intravenous/subcutaneous development with unknown filing plan: • Alnuctamab—pivoted from intravenous to subcutaneous, reducing CRS from 76% to 56% (81, 82). A phase III trial is listed without formulation specification (NCT06232707). • Plamotamab—subcutaneous dose expansion was added after arms of intravenous dose ranging (NCT02924402). • ABBV-383—after completing intravenous dose ranging with three dose-expansion cohorts (NCT03933735; refs. 20, 40, 60), a new phase Ib study with a subcutaneous formulation was announced (NCT06223516)

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Muchas gracias

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