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REVIEW – CLINICAL ONCOLOGY

T cell-redirecting bispecific antibodies in cancer immunotherapy: recent advances

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Abstract

Purpose Globally, cancer is a critical illness which seriously threatens human health. T-cell-based cancer immunotherapy for some patients has demonstrated impressive achievements including chimeric antigen receptor T cells, immune checkpoint inhibitors and T cell-redirecting bispecific antibodies (TRBAs). TRBAs recruit T cells to lyse cancer cells bypassing the antigen presentation through the major histocompatibility complex pathways. In this review we summarized the TRBAs formats, biophysical characteristics, the preclinical and clinical trial results, as well as the challenges faced by TRBAs in tumour therapy.

Methods Herein the relevant literature and clinical trials from the PubMed and ClinicalTrials.gov database.

Results The advances in protein engineering technology have generated diverse TRBAs format which can be classified into two categories: IgG-like TRBAs and non-IgG-like TRBAs. Multiple applications of TRBAs showed encouraging curative effect and entered clinical trials for lymphoid malignancy and solid tumour.

Conclusions TRBA is a powerful tool for the cancer treatment and the clinical studies showed potent anti-tumour efficacy in hematologic malignancies. Although the clinical outcomes of TRBAs in solid tumours are less satisfied than hematologic malignancies, many preclinical antibodies and combination therapies are being evaluated

Keywords Cancer immunotherapy · Bispecific antibodies · Redirected T cell · Lymphoid malignancy · Solid tumour

Abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
ALL	Acute lymphoblastic leukemia
AML	Acute myelocytic leukemia
APCs	Antigen-presenting cells
ATC	Activated T cells
BiTE	Bispecific T-cell engagers
BsAb	Bispecific antibody
CAR-T	Chimeric antigen receptor T cells
CDC	Complement-dependent cytotoxicity
CEA	Carcinoembryonic antigen
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRh	Complete response with partial hematopoietic recovery
DART	Dual-affinity re-targeting
DLBCL	Diffuse large B-cell lymphoma
EpCAM	Epithelial cell adhesion molecule
FAE	Fab-arm exchange
Fab	Fragment of antigen binding
FcγR	Fc-gamma receptors
Fv	Variable fragments
HER	Human epidermal growth factor receptor
ImmTAC	Immune-mobilising monoclonal T cell receptors against cancer
KiH	Knobs-into-holes
mCR	Macroscopic complete remission
MDS	Myelodysplastic syndrome
MHC	Major histocompatibility complex
MM	Multiple myeloma
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NETs	Neuroendocrine tumours
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate

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OS	Overall survival
Ph−	Philadelphia chromosome negative
Ph+	Philadelphia chromosome positive
PSMA	Prostate-specific membrane antigen
ScFv	Single chain antibody variable fragments
SSTR2	Somatostatin receptor 2
SOC	Standard of care chemotherapy
TCR	T cell receptor
TRBAs	T cell-redirecting bispecific antibodies

Introduction

Cancer is a leading cause of death worldwide and conventional therapeutic procedures have not prevented tumour recurrence or drug resistance (Housman et al. 2014; Oldhafer et al. 2014). However in recent years, there have been several major breakthroughs for cancer treatment by deploying monoclonal antibodies (Shepard et al. 2017), bi- or multi-specific antibody (Thakur et al. 2018), immune checkpoint inhibitors (Byun et al. 2017), chimeric antigen receptor T cell (CAR-T) therapy (Fraietta et al. 2018) or vaccines (Banchereau and Palucka 2018). In particular, bispecific antibody recognizing two different epitopes with a broad range of applications is attracting increasing attention as a novel strategy for cancer immunotherapy (Fan et al. 2015).

T cell-redirecting bispecific antibodies (TRBAs) are amongst the most used approaches in cancer treatment and the first report in which TRBAs specifically engaged CD3 on T cells on one side and the antigens of cancer cells independent of their T cell receptor (TCR) on the other side, was published 30 years ago (Staerz et al. 1985), which specifically engaged CD3 on T cells in one side and on another side to antigens of cancer cells independent of their T cell receptor (TCR). TRBAs have made considerable progress in hematological malignancies (Klausen et al. 2018) and solid tumour treatments (Yu et al. 2017) in the past 10 years. Catumaxomab is the first TRBA-targeting epithelial cell adhesion molecule (EpCAM) and CD3, which was approved in Europe for the treatment of malignant ascites in 2009 (Seimetz et al. 2010). This discovery was followed by another successful TRBA targeting CD19 and CD3 (Blinatumomab), which was given marketing permission by the Food and Drug Administration (FDA) for relapsed or refractory precursor B-cell acute lymphoblastic leukemia (ALL) treatment in 2014 (Przepiorka et al. 2015). At present, although many patients benefit from Blinatumomab, there are a number of TRBAs with different formats and characteristics showing potential anti-tumour efficacy in clinical studies (Table 1), some of which are discussed in this review.

Formats and key characteristics of bispecific T cell-redirecting antibodies

The therapeutic clinical usage of bispecific antibodies was hampered by manufacturing problems of low yields and instability, as well as patient's immunogenicity in the past (Fan et al. 2015). The development of various formats or structures has led to less immunogenic, which are also easier to produce and more stable. TRBAs, with one arm targeted to CD3 of T cells and another to specific cancer cell epitope, can be roughly divided into two categories: IgG-like TRBAs and non-IgG-like TRBAs (Fig. 1). A comparison of main TRBA formats is summarized in Table 2.

IgG-like TRBAs

Triomab was created by Quadroma technology which is to fuse two antibodies producing hybridoma together to generate a bispecific antibody (BsAb) with one binding to cancer epitope and another to CD3, the two bispecific antibodies were connected together through intra-chain disulfide bonds in the core hinge region. To avoid random non-functional antibody assembling, two antibodies producing hybridomas from two species were fused together to guarantee the functional heavy chain and light chain assemble. Triomab retains their original Fc-mediated effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (Chelius et al. 2010). Additionally, the Fc region of BsAbs favors industrial scale purification and improves solubility, stability and serum half-lives (Spiess et al. 2015). Mostly, Triomab format of TRBAs is composed of half anti-CD3 rat IgG2b antibody to recognize T cells, while another half is antigen binding site to specific cancer epitope from mouse IgG2a isotype which is exchangeable. For example, catumaxomab is binding to EpCAM and CD3 antigens, the first bispecific antibody in market for EpCAM-positive carcinomas with malignant ascites treatment (Seimetz et al. 2010). Several further Triomab antibodies have been developed binding to tumour-associated antigens including FBTA05(CD20/CD3) (Stanglmaier et al. 2008), ertumaxomab (HER2/CD3) (Kiewe et al. 2006) and ektomun (GD2/GD3).

IgG–ATC is another form of bispecific antibody [the activated T cells (ATC) format bispecific antibodies], conjugated together by a chemical process in vitro, such as by utilizing reagent 2-iminothiolane HCl and sulphosuccinimidyl 4-(*N*-maleimidomethy cyclohexane-1-carboxylate) to link an ATC-activated antibody (anti-CD3, OKT3

Table 1 Clinical trials of T cell-redirecting bispecific antibodies in malignancy

Name	Targets	Formats	Diseases	Clinical phase	Status	Identifier	References
Blinatumomab	CD19/CD3	BiTE	ALL		Approved in USA		Przepiorka et al. (2015)
MGD011	CD19/CD3	DART	Relapsed or refractory B-cell malignancies	I	Active, not recruiting	NCT02454270	Liu et al. (2017)
AFM11	CD19/CD3	TandAb	CD19-positive B-cell NHL	I	Recruiting	NCT02106091	Reusch et al. (2015)
			B-precursor ALL	I	Recruiting	NCT02848911	
BTCT4465A	CD20×CD3	IgG1	NHL, CLL	I	Recruiting	NCT02500407	Ferl et al. (2018) and Sun et al. (2015)
XmAb13676	CD20/CD3	XmAb	CD20-expressing hematologic malignancies	I	Recruiting	NCT02924402	Chu et al. (2014a)
REGN1979	CD20×CD3	IgG–cLC	B-cell malignancies	I	Recruiting	NCT02290951	Bannerji et al. (2016)
			Lymphoma	I	Recruiting	NCT02651662	Topp et al. (2017)
FBTA05	CD20/CD3	Triomab	B-cell lymphoma	I/II	Terminated	NCT01138579	Buhmann et al. (2013)
MGD006 (S80880)	CD123/CD3	DART	AML	I	Recruiting	NCT02152956	Al-Hussaini et al. (2016)
JNJ-63709178	CD123/CD3	DuoBody	Relapsed or refractory AML	I	Suspended	NCT02715011	Gaudet et al. (2016)
XmAb14045	CD123/CD3	XmAb	CD123-expressing hematologic malignancies	I	Recruiting	NCT02730312	Chu et al. (2014b)
APVO436	CD123/CD3	ADAPTIR	AML, MDS	I	Not yet recruiting	NCT03647800	Godwin et al. (2017)
AMG330	CD33/CD3	BiTE	Relapsed or refractory AML	I	Recruiting	NCT02520427	Aigner et al. (2013)
AMV564	CD33/CD3	TandAb	AML	I	Recruiting	NCT03144245	Han et al. (2018)
			MDS	I	Recruiting	NCT03516591	Cheng et al. (2017)
MCLA-117	CLEC12A/CD3	IgG-cLC	AML	I	Recruiting	NCT03038230	Van Loo et al. (2015)
BI836909	BCMA/CD3	BiTE	MM	I	Recruiting	NCT02514239	Hipp et al. (2017)
JNJ-64007957	BCMA/CD3	DuoBody	Relapsed or refractory MM	I	Recruiting	NCT03145181	Pillarisetti et al. (2016)
AMG424	CD38/CD3	BiTE	Relapsed or refractory MM	I	Not yet recruiting	NCT03445663	de Zafra et al. (2017)

Table 1 (continued)

Name	Targets	Formats	Diseases	Clinical phase	Status	Identifier	References
GBR 1342	CD38/CD3	BEAT	MM	I	Recruiting	NCT03309111	Ryan Richter et al. (2018)
Catumaxomab	EpCAM/CD3	Triomab	Malignant ascites		Withdrawn		Seimetz et al. (2010)
MT110	EpCAM/CD3	BiTE	Solid tumour	I	Completed	NCT00635596	Fiedler et al. (2012) and Herrmann et al. (2010)
Ertumaxomab	HER2/CD3	Triomab	Her2/Neu-positive advanced solid tumours	I/II	Terminated	NCT01569412	Haense et al. (2016)
HER2Bi-aATC	HER2/CD3	IgG-ATC	Ovarian cancer	I	Withdrawn	NCT02470059	Lum et al. (2015)
GBR1302	HER2/CD3	BEAT	HER2 expressing solid tumours	I	Recruiting	NCT02829372	Wermke et al. (2017)
EGFRBi-aATC	EGFR/CD3	IgG-ATC	Recurrent or refractory glioblastoma	I/II	Withdrawn	NCT02521090	Zitron et al. (2013)
MEDI-565 (AMG211)	CEA/CD3	BiTE	Gastrointestinal adenocarcinomas	I	Completed	NCT01284231	Oberst et al. (2014) and Pishvaian et al. (2016)
			Relapsed/refractory gastrointestinal adenocarcinoma	I	Completed	NCT02291614	Vries et al. (2015)
RG7802	CEA/CD3	IgG-Crossmab	Advanced and/or metastatic CEA-positive solid tumours	I	Active, not recruiting	NCT02324257	Bacac et al. (2016) and Lehmann et al. (2016)
			Advanced and/or metastatic CEA-positive solid tumours	I	Active, not recruiting	NCT02650713	
BAY2010112	PSMA/CD3	BiTE	Prostate neoplasms	I	Active, not recruiting	NCT01723475	Friedrich et al. (2012)
ES414 (MOR209)	PSMA/CD3	ADAPTIR	Prostate cancer	I	Recruiting	NCT02262910	Hernandez-Hoyos et al. (2016)
IMCgp100	gp100	ImmTAC	Uveal melanoma	II	Recruiting	NCT03070392	Hassan et al. (2014)
			Uveal melanoma	I/II	Recruiting	NCT02570308	
			Malignant melanoma	I/II	Recruiting	NCT02535078	
MGD009	B7H3/CD3	DART	Unresectable or metastatic B7-H3-expressing neoplasms	I	Recruiting	NCT02628535	Tolcher et al. (2016)
			Advanced solid tumours	I	Recruiting	NCT03406949	
MGD007	gpA33/CD3	DART-Fc	Relapsed/refractory metastatic colorectal carcinoma	I	Recruiting	NCT02248805	Moore et al. (2018)

Table 1 (continued)

Name	Targets	Formats	Diseases	Clinical phase	Status	Identifier	References
			Relapsed/refractory metastatic colorectal carcinoma	I	Recruiting	NCT03531632	
GD2Bi-aATC	GD2/CD3	IgG-ATC	Neuroblastoma, osteosarcoma	I	Recruiting	NCT02173093	Yankelevich et al. (2012)
XmAb18087	SSTR2/CD3	XmAb	Neuroendocrine tumour; gastrointestinal neoplasm	I	Recruiting	NCT03411915	Lee et al. (2017b)
			Advanced solid tumours	I	Recruiting	NCT03406949	
ERY974	Glypican 3/CD3	IgG4	Advanced solid tumours	I	Recruiting	NCT02748837	Ishiguro et al. (2017)
PF-06671008	P-cadherin/CD3	DART	Neoplasms	I	Recruiting	NCT02659631	Fisher et al. (2018)

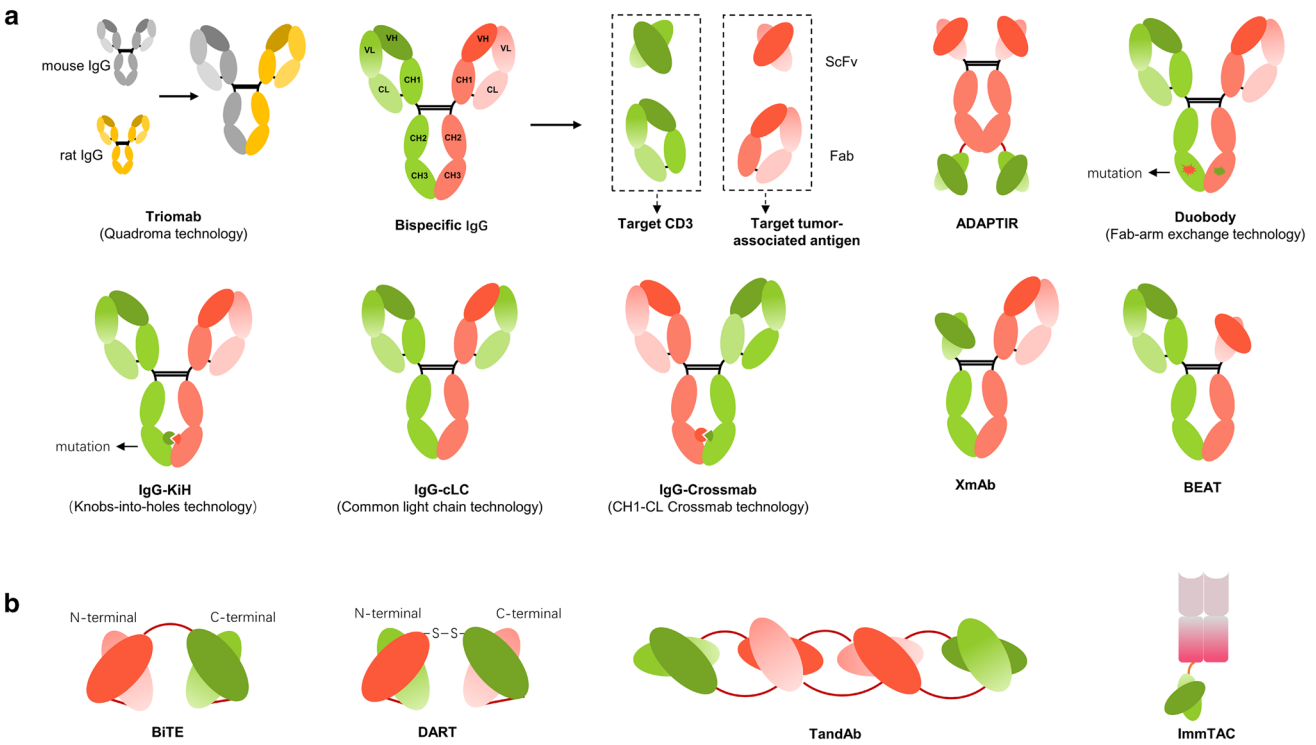

Fig. 1 Formats of T cell-redirecting bispecific antibodies (TRBAs). **a** IgG-like TRBAs. **b** Non-IgG-like TRBAs

antibody) with a HER2/neu-specific antibody (9184) to treat HER2/neu + breast tumours (Sen et al. 2001). This strategy takes advantage of anti-CD3 antibody to activate T-cell expansion and direct those T-cells to specifically kill cancer cells in patient. Another example was: IgG–ATC bispecific antibodies were designed to target CD3 and GD2 for neuroblastoma treatment (Yankelevich et al. 2012).

The idea of Duobody construction originated from human IgG4 Fab-arm exchange (FAE) that occurs naturally in vivo (Labrijn et al. 2013). It had been identified that site-directed mutagenesis at residues S228 and R409 of IgG4 blocked FAE process and introducing the two residues enabled IgG1 molecules to engage in FAE (Labrijn et al. 2011). Because of IgG1 containing a stable hinge, IgG1 CH3 domain at residues K409R and F405L mutations facility 2-MEA-mediated

Table 2 Comparison of different TRBA formats

TRBA formats	Advantages	Disadvantages
Triomab	Full length: long serum half-life Eliminate VH and VL mispairing ADCC, CDC	Mouse-derived: highly immunogenic FcγR binding: potential cytokine storm
Duobody	Full length: long serum half-life Controlled Fab-arm exchanged: stable heterodimer ADCC, CDC	FcγR binding: potential cytokine storm
IgG–cLC	Full length: long serum half-life Common light chain: eliminate light-chain mispairing	Challenge to find the identical light chain
IgG–Crossmab	Full length: long serum half-life Exchange the CH1 and CL: eliminate mispairing Introduce KiH technology: heavy-chain heterodimerization	Not mentioned
XmAb	Full length: long serum half-life Eliminate light-chain and heavy-chain mispairing	Not mentioned
BEAT	Full length: long serum half-life Eliminate light-chain and heavy-chain mispairing IgG1 and IgG3 Fc domain: unique heterodimer for purification	Not mentioned
ADAPTIR	Full length: long serum half-life Bivalently bind to two targets Few side products	Not mentioned
BiTE	Lack of Fc domain: reduce the potential for nonselective T cell activation Simple manufacturing processes Low weight: enhanced tissue penetration	Short serum half-life Antibody aggregation
DART	Lack of Fc domain: reduce the potential for nonselective T cell activation Low weight: enhanced tissue penetration Introduce intra-chain disulfide bonds: stable, less aggregation	Short serum half-life
TandAb	Lack of Fc domain: reduce the potential for nonselective T cell activation Longer serum half-life Bivalently bind to two targets	Not mentioned

FAE process to efficiently generate a DuoBody. DuoBody ensures a proper in vivo half-life and good manufacturability while retaining Fc-mediated effector functions (Labrijn et al. 2013). Some Duobodies such as CD123/CD3 and BCMA/CD3 antibody demonstrated superior anti-tumour activity (Gaudet et al. 2016; Pillarisetti et al. 2016).

In human full-length bispecific antibodies' production, the formations of undesirable homodimers and mispaired molecules limit the yield, stability or biological activity. To overcome those problems of undesirable heavy–heavy chain pairing, the CH3 domains of two Ig heavy chains were modified to form "knobs-into-holes" structure by employing a "knob" mutation (T366W) and pairing "hole" mutations (T336S, L368A, Y407V). The knobs-into-holes (KiH) technology achieves noncovalent interactions for two distinct monoclonal antibodies (IgG-KiH), along with disulfide bridges in the hinge region, drive the assembly formation of bispecific hetrodimers (Ridgway et al. 1997; Shatz et al. 2013). BTCT4465A (Mosunetuzumab, CD20/CD3) is a full-length, fully humanized IgG1 antibody with KiH modification to target CD20 positive non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL) (Sun et al. 2015). Sometimes, KiH method could result light chain mispairing problems.

Common light chain (cLC) bispecific antibodies (IgG-cLC) have the advantage of preventing mispairing of heavy and light chains for full-length IgG format during production process. There are several TRBAs based on native IgG benefitting from the usage of same selected anti-CD3 light chains which own excellent biophysical characteristics (Smith et al. 2015; Van Loo et al. 2015). Nevertheless, it is a challenge to find the identical light chains that recognize different antigens or do not contribute significantly to antigens binding.

As mentioned earlier, IgG–KiH bispecific antibodies still maintain the possibility of a total of four pairings of heavy and light chains. Based on heavy chain CH3 "knobs-into-holes" structure of IgG–KiH bispecific antibodies, additionally there is sequence exchange between heavy and light chain CH1 regions of the antibody to form IgG–Crossmab which solves light-chain mispairing problems and retains the original antigen-binding affinity (Schaefer et al. 2011). For example, CH1 of CD3 antibody heavy and light chain were exchanged (crossover) to produce CD3-binding antibody in combining with KiH technology to generate a bispecific antibody against CEA with great potent anti-tumour activity (Bacac et al. 2016).

The main characteristic of XmAbs fomat is to graft one ScFv (single chain antibody variable fragments) on to one

of the hinge domains of another antibody to generate an asymmetric bispecific IgG antibody. In practice, the anti-human CD3 ScFv domain is transplanted onto the hinge domain of an anti-tumour associated antibody. XmAb format with original Fc scaffold, one normal heavy chain and one light chain, one heavy-binding region and one light-binding region prevents light chain and heavy chain mispairing during production and purification. So far, there are two studies demonstrating XmAbs stimulating T cell-mediated anti-tumour activities (Chu et al. 2014a, b).

BEAT format is similar to XmAb, but anti-tumour ScFv is grafting on the hinge domain of anti-CD3 antibody to form BEAT bispecific antibodies. Moreover, the production and purification of heterodimeric BEATs are done uniquely using IgG3 Fc domain to remove undesirable formations (Moretti et al. 2013). Briefly, the BEAT platform is designed with a missing protein A-binding site on the heavy chain (IgG3 Fc region) of the molecule and thus the unwanted monospecific IgG contaminants can separate by protein A purification as the molecules exhibiting a different affinity for protein A. This strategy obtains the BEATs with purity of 97% (Moretti et al. 2013). GBR1302, a BEAT format TBRA, was reported to effectively recruit cytotoxic T cells against HER2-positive breast cancer cells including the trastuzumab-resistant breast cancer cell lines (Wermke et al. 2017).

A portion of bispecific antibodies is designed for both targets of T cell recruitment mono and another antigen with limited distance and space between monovalent binding domains. ADAPTIR platform contains four ScFv binding domains connected to the CH2 and CH3 domains of IgG1 by flexible linkers. This optimal structure creates therapeutics with increased stability, reduced cytokine release and longer half-life for treatment of cancer and autoimmune diseases (Blankenship et al. 2016; Pellerin et al. 2018). The ES414 bispecific antibody with ADAPTIR format binds bivalently to both PSMA and CD3, yet does not cross-link and activate T cells without target present (Hernandez-Hoyos et al. 2016).

Non-IgG-like TRBAs

Bispecific T-cell Engagers (BiTE) format is developed by recombinant expression of two cross-linked different Fv (variable fragments) with linkers, which simultaneously bind the invariant CD3 expressed on T cells and cell-surface tumour-associated antigens. Blinatumomab, the first BiTE with the domain arrangement as VLCD19-VHCD19-VHCD3-VLCD3, using a 5-amino acid (GGGGS) and 15-amino acid (GGGGS)3 linkers to connect Fv and ScFv fragments (Loffler et al. 2000). In addition, the short linker prevents inter-chain mispairing of the VH and the VL domains, and the long linker makes two ScFvs more flexible to bind target antigens. This platform is widely applied in various cancers for immunotherapy.

BiTE with two individual VL–VH chain interactions of ScFv has a limited serum stability and antibody aggregation (Yuraszeck et al. 2017). Thus, a novel Fv-derived format based on a covalently linked bispecific antibody structure (BiTE) and extra intra-chain disulfide bonds between ScFv to form dual-affinity re-targeting (DART) structure (Johnson et al. 2010). The first DART antibody, MGD006(CD19/CD3) (Moore et al. 2011), displayed favourable biological properties, stability and optimal redirect T-cell killing of tumour cells, and DARTs (MGD007, MGD009,MGD011) are all in clinic study right now.

Four ScFv domains targeted two antigens are joined together by disulfide bonds and GS linkers to generate a bispecific tandem diabody (TandAb) (Ellwanger et al. 2017; McAleese and Eser 2012). A TandAb targeting CD19/CD3 had similarly close apposition of the tumour target and effector cell membranes and possessed a long serum half-life of almost 20 h (Reusch et al. 2015).

Immune-mobilising monoclonal T cell receptors against cancer (ImmTAC) is an extraordinary class of bispecific antibody that drives recruitment of polyclonal T cells for mediating an effective and durable anti-tumour response in patients. For the ImmTAC, soluble specific TCRs (anti-human leucocyte antigen-restricted tumour-associated antigens) with non-transmembrane domains and an artificial disulfide bond, linked to a humanized anti-CD3 ScFv domain via a flexible linker to recognize, and subsequently present the cancer cells to killer T cells (Bossi et al. 2014; Oates et al. 2015).

Action mechanism of T cell-redirecting bispecific antibodies

For cancer immunotherapy, the key point is to direct the patient's own immune system to recognize and destroy cancer cells, based on the activation and expansion of immune effector cells, such as CD8+ T cells, CD4+ T cells or NK cells. To activate T cells for the effective killing of cancer cells in the immune recognition system, there are two requirements: (1) tumour antigens or epitopes present on the major histocompatibility complex (MHC) by antigen-presenting cells (APCs) for TCR recognition; and (2) the binding of the costimulatory surface molecules B7 of APCs with CD28 molecules of T cells (necessary for T cell activation) (Wang et al. 2014) (Fig. 2a). However, tumour cells may escape immune elimination by losing immunogenicity, antigenicity, or orchestrating an immunosuppressive microenvironment (Beatty and Gladney 2015). Currently, checkpoint inhibitors, CAR-T and some bispecific antibodies are widely used in the clinic to overcome immune suppression

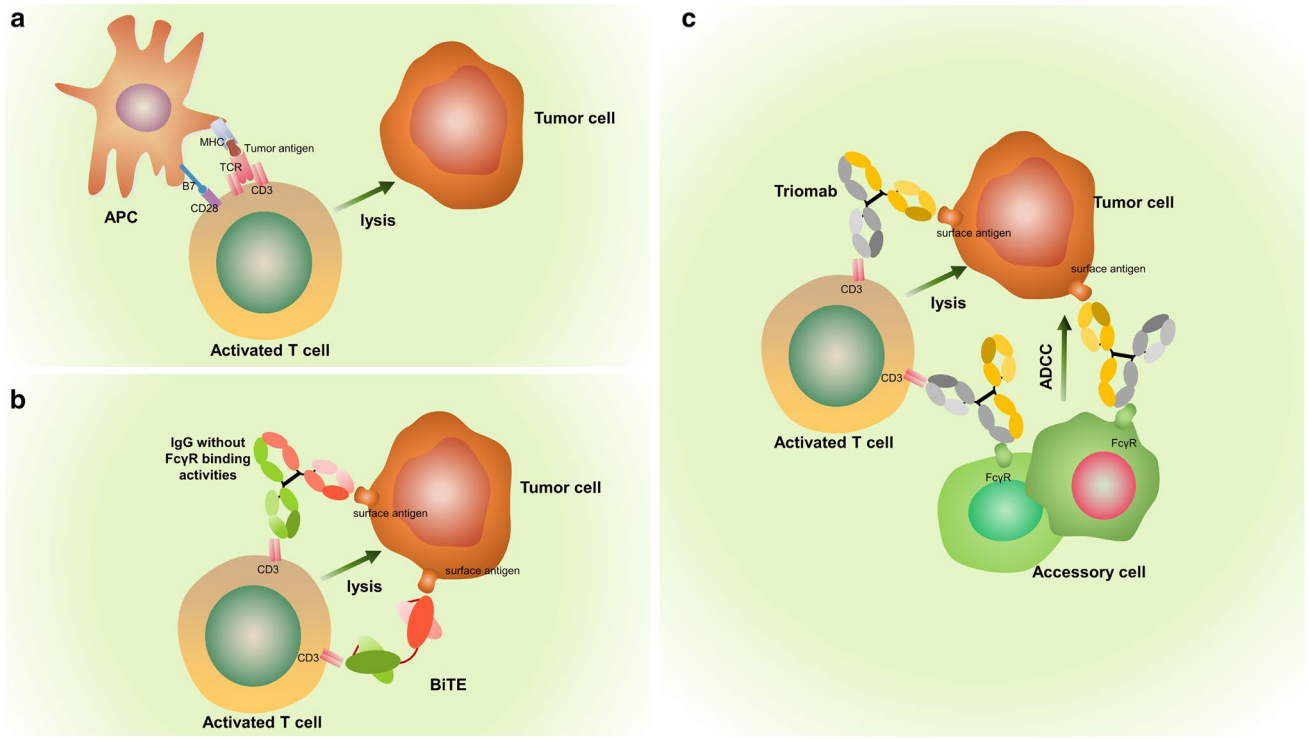

Fig. 2 Mechanism of T cell killing in cancer immunotherapy. **a** T-cell recognition mechanisms. T cell activated by tumour antigens presented on APC to kill tumour cells. **b** BiTE antibody and IgG-like TRBAs without Fc ADCC redirecting T cells to tumour cells. **c** Triomabs simultaneously recruit T cells and induces ADCC for tumour cells lysis

and potential T cell depletion (Cameron et al. 2011; Poole 2014; Prasad 2018; Yuraszeck et al. 2017). The first bispecific antibody on the market, Blinatumomab targeting the CD3 epsilon domain of TCRs and CD19, a surface antigen of B-cells, is used to treat acute lymphoblastic leukemia (Przepiorka et al. 2015). Although, TRBAs have different formats, the essential aim is to direct CD3 T cells to target tumour cells. Non-IgG-like TRBAs such as those of the BiTE format, directly target CD3 molecules on the surface of CD8+ and CD4+ T cells to connect to tumor-specific antigens, e.g.CD19, and then release cytotoxic granules such as perforin and granzymes to kill CD19+ tumour cells, at same time, they transiently increase the levels of the cytokines IFN-γ, TNF-α, IL-2, IL-4, IL-6, and IL-10 (Yuraszeck et al. 2017) (Fig. 2b). IgG-like TRBAs can be divided into two sub-types based on Fc-gamma receptors (FcγR), which induce antibody-dependent cell-mediated cytotoxicity (ADCC). For example, Triomab can simultaneously recruit T cells and induce ADCC by binding to FcγR on accessory cells such as natural killer cells and macrophages (Seimetz et al. 2010) (Fig. 2c). However, ERY974 bispecific antibodies with mutations in the Fc region do not have ADCC activities to avoid glypican 3-independent cytokine release (Ishiguro et al. 2017). Increasing clinical IgG-like TRBAs markedly reduce or eliminate FcγR and complement binding to prevent strong cytokine release syndrome (Bacac et al. 2016; Hernandez-Hoyos et al. 2016; Moore et al. 2018).

Clinical application in lymphoid malignancies

Lymphoid malignancies are a large group of heterogeneous malignancies that arise from different stages of lymphocyte development and remain difficult to treat. The main treatments are designed to control and eliminate tumour cells in patients. The personalized therapy and combination of bispecific antibodies with immune checkpoint inhibitors and others are very important. After recovery, restoring the functional immune system is becoming a priority to maintain health by bone morrow transplantation (Klausen et al. 2018). Bispecific antibody immunotherapy is a potential effective method for lymphoid neoplasms.

CD19-positive neoplasms

CD19 is a B-cell-specific molecule of the immunoglobulin superfamily and is expressed from early B-cell development (pro-B stage) to the last differentiation stage including some plasma cells. CD19 is an excellent target for B-cell

malignancy treatment, such as acute lymphoblastic leukemias (ALLs) and CD19-positive NHL (Watkins and Bartlett 2018). The first approved BiTE bispecific antibody, Blinatumomab, specific for CD3 and CD19, was approved in 2014 by FDA to treat Philadelphia chromosome-negative (Ph−) relapsed or refractory precursor B-cell ALL. The basis for the approval resulted from a single-arm trial with a 32% complete remission rate and a minimal residual disease (MRD) response (31%) in all patients treated with Blinatumomab; cytokine release syndrome was reported initially in 11% of patients, but it was rarely life threatening or fatal (Przepiorka et al. 2015). More significantly, the approval for Blinatumomab for the treatment of Ph− relapsed or refractory precursor B-cell ALL has been extended based on two clinical trials, TOWER and ALCANTARA in 2017. Complete remission rates were 34% for patients receiving blinatumomab and 16% for those receiving standard-of-care chemotherapy in the TOWER trial, and the complete remission rate was 31% in ALCANTARA. All adverse events were similar to those observed previously in Ph-relapsed or refractory ALL including cytokine release syndrome and some neurological events (Pulte et al. 2018). Currently, 51 clinical trials of Blinatumomab are being carried out for ALL (39 trials), NHL (10 trials), multiple myeloma (1 trial) and lymphoid cancer with Richter's transformation (1 trial) (Table 3). However, Blinatumomab suffers from a main drawback because of its short serum half-life (2.11 h, due to the relatively small molecule and simple structure with a molecular weight of 50–60 kDa), and patients require continuous intravenous infusion (Yuraszeck et al. 2017). MGD011, a DART format of TRBAs also targeting CD19, is engineered with improved serum circulating half-life (6.7 days), which shows potent anti-tumour activity in mouse leukemia/lymphoma models and displays prolonged pharmacokinetics in cynomolgus monkeys (Liu et al. 2017). Another TRBA, tetravalent bispecific CD19/CD3 TandAb (AFM11) elicited more B-cell lysis in vitro with lower effector-to-target ratios than BiTE. After intravenous administration of AFM11 in mice, the half-life ranged from 18.4 to 22.9 h (Reusch et al. 2015). MGD011 and AFM11 have completed preclinical evaluation and are underway in clinical trials for treatment of CD19 positive malignancies. So far, there is only one

Table 3 Blinatumomab in clinical trials (selected)

Diseases	Clinical phase identifier	Results	Main adverse events	References
Relapsed/refractory Ph+ B-precursor ALL	II, NCT02000427	45 participants CR/CRh, 36% OS, 7.1 months	Pyrexia, 58% Febrile neutropenia, 40% Headache, 31%	Martinelli et al. (2017)
Relapsed/refractory ALL	III, NCT02013167	405 participants CR, 34% (Blinatumomab), 16% (SOC) Median OS, 7.7 months (Blinatumomab), 4.0 months (SOC)	Neutropenia, 37.8%(Blinatumomab), 57.8% (SOC) Infection, 34.1%(Blinatumomab), 52.3% (SOC)	Kantarjian et al. (2017)
B-precursor ALL	II, NCT01207388	116 participants MRD response, 78% Median OS, 36.5 months	Neurologic events, 13%	Gokbuget and Dombret (2018)
Relapsed/refractory B-precursor ALL	I/II, NCT01471782	93 participants MTD, 15 μg/m^2/day CR, 39% MRD response, 52%	Anemia, 36% Thrombocytopenia, 21% Hypokalemia, 17%	von Stackelberg et al. (2016)
Relapsed/refractory B-precursor ALL	II, NCT01466179	225 participants CR/CRh, 43% Mean OS, 76.1 months	Neutropenia, 25% Anaemia, 14%	Barlev et al. (2017) and Topp et al. (2015)
Relapsed/refractory B-precursor ALL	II, NCT01209286	36 participants CR/CRh, 69% Median OS, 9.8 months MRD response, 88%	Pyrexia, 81%	Topp et al. (2014)
Relapsed/refractory B-precursor ALL	II, NCT00560794	21 participants MRD response, 80%	Lymphopenia, 29%	Klinger et al. (2012)
Relapsed/refractory DLBCL	II, NCT01741792	25 participants CR, 19% ORR, 43%	Tremor, 48% Pyrexia, 44% Fatigue, 26% Edema, 26%	Viardot et al. (2016)
Relapsed NHL	I, NCT00274742	MTD, 60 μg/m^2/day OR, 69%	Neurologic events, 22%	Goebeler et al. (2016)

anti-CD19/CD3 bispecific antibody (Blinatumomab) on the market for hematologic malignancies, many TRBAs are being developed in trials and are expected to be more effective in relapsed or refractory diseases.

CD20-positive neoplasms

CD20 is highly expressed on normal and malignant B-cells, and anti-CD20 bispecific antibodies are also being explored for the treatment of B-cell leukemias and lymphomas (Esteban et al. 2018). BTCT4465A, targeting CD20/CD3 full-length bispecific antibody, is highly active in killing CD20-expressing B-cells (Sun et al. 2015) and is in clinical trials for ALL and NHL therapies (NCT02500407). Moreover, the preclinical pharmacokinetic and pharmacodynamic data of BTCT4465A from a mixed-effects nonhuman primate model can be scaled to the human clinical perspective (Ferl et al. 2018). Based on the redirected T cell-cytotoxicity mechanism, bispecific antibody XmAb13676 is generated to kill CD20 positive B-cell leukemias and lymphomas with an extended serum half-life in mice of 6.7 days. Data from an evaluation in cynomolgus monkeys showed strongly activated and stimulated depletion of over 97% of circulating CD40-positive B-cells within 4 h after dosing (Chu et al. 2014a). REGN1979 is designed with an IgG-cLC format to target CD20 and CD3 molecules. Treatment with REGN1979 prevented the growth of B-cell tumours in mice and caused the depletion of B-cells with a long half-life of approximately 14 days in cynomolgus monkeys (Smith et al. 2015; Varghese et al. 2014). Preliminary phase 1 results of REGN1979 demonstrated an acceptable safety profile at flat doses of 0.03–3 mg in 25 patients with CD20 positive B-Cell malignancies, and dose escalation and treatment schedule optimization is continuing (Bannerji et al. 2016). Another clinical study showed that combinations of REGN1979 and the anti-PD1 antibody REGN2810 were well tolerated in 69 patients with lymphoma, and higher doses were under evaluation, and the most common treatment-related adverse events, such as cytokine release syndrome (89%) and pyrexia (67%), were similar to single agent studies of REGN1979 (Topp et al. 2017).

CD123-positive neoplasms

CD123 is differentially overexpressed in a large proportion of patients (40–93%) with acute myeloid leukemia (AML) blasts (Munoz et al. 2001). A DART format antibody (MGD006/S80880) binding to CD123 and CD3 was designed to mediate the target-effector cell association, T-cell activation and proliferation in a dose-dependent treatment of AML cells and primary AML blasts in vitro and the suppression of tumour growth with continuous administration in a mouse model (Al-Hussaini et al. 2016). In nonhuman primates, MGD006 showed the killing of CD123-expressing target cells and was well tolerated when the primates were continuously infused with doses that escalated weekly to up to 1 mg/kg per day for approximately 4 weeks (Chichili et al. 2015). Based on the preclinical data of MGD006, the first in-human phase I study for AML patients is currently underway. The new bispecific anti-CD123/CD3 molecule, APVO436, induced significantly lower levels of several T cell cytokines (IFNγ, IL-2, and TNFα) than MGD006 and inhibited tumour growth in subcutaneous tumour models; as a potential treatment option, it is in an advanced stage of clinical testing for AML (Comeau et al. 2018). However, another TRBA targeting CD123 (JNJ-63709178) was suspended because of serious adverse events in the clinic (Gaudet et al. 2016).

CD33-positive neoplasms

The expression of CD33 is restricted in normal myelopoiesis, and yet leukemic stem cells in patients with AML express CD33, indicating that this molecule is a promising target for AML treatment (Hauswirth et al. 2007). AMG330 and AMV564, CD33/CD3-bispecific antibodies emerged as appropriate candidates to activate and redirect AML patient-derived T-cells for the lysis of blasts (Aigner et al. 2013; Han et al. 2018). AMG330 with the BiTE format was sufficient to induce an efficient and specific lysis of AML cell lines (KG-1 and U937 cells) at very low concentrations (1.8 pM). In vitro studies demonstrated that AMV564 anti-tumour activity, with EC50 values of approximately 0.7–3 pM, and the preclinical pharmacokinetic and pharmacodynamic model data showed the potential for a wide therapeutic index of AMV564 for patients with AML. Because myelodysplastic syndromes (MDS) are associated with AML progression, AMV564 is also applied to treat patients with intermediate-2 or high-risk MDS (Cheng et al. 2017; Han et al. 2018). After AMV564 treatment was combined with anti-PD-1 antibodies, MDS-specific immune responses increased, resulting in the depletion of MDS cells and the improvement of hematopoiesis.

Others

Multiple myeloma (MM) is the second most common hematologic malignancy with an increasing incidence and prevalence. For MM immunotherapy, which is a common hematological malignancy characterized by an uncontrolled proliferation of monoclonal plasma cells in the bone, several bispecific antibodies [BMCA/CD3 (BI836909, JNJ-64007957) and CD38/CD3 (AMG424, GBR1342)] have completed preclinical evaluation and are now in clinical trials. Administration of BI836909 significantly prolonged the survival of the mice at dose levels of 0.005 mg/kg/day,

and also significantly prolonged survival of the orthotopic xenograft in animals; moreover, it led to the depletion of BCMA-positive plasma cells in the bone marrow in a cynomolgus monkey study with dose levels ranging from 0.08 to 0.3 ng/ml (Hipp et al. 2017). AMG424 inhibited 98% of tumour growth in tumour-bearing mice and depleted peripheral CD38-expressing target cells in nonhuman primates (de Zafra et al. 2017).

Clinical application in solid tumour

At present, several bispecific antibodies redirecting the activity of T cells have entered clinical trials for solid tumour treatment. Despite the numerous positive results of TRBAs against fluid (hematologic) cancers, formidable challenges still remain in solid tumour therapy because of numerous physical and biological barriers (Thakur et al. 2018).

EpCAM-positive neoplasms

The trifunctional antibody Catumaxomab targeting EpCAM and CD3 was used to investigate the efficacy of systemic chemotherapy for gastric cancer with peritoneal carcinomatosis in a phase 2 study (NCT01504256). Patients were treated Catumaxomab combined with chemotherapeutic agents (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel, FLOT, arm A) or FLOT alone (arm B), and the rate of macroscopic complete remission (mCR) was 27% in arm A and 19% in arm B. Nonetheless, the median overall survival (OS) was 13.2 months and 13.0, respectively, with no statistical significance in the Catumaxomab group (Knodler et al. 2018). However, Catumaxomab was approved in the EU in 2009 for the treatment of malignant ascites in adults and had been withdrawn from the market in 2017 for commercial reasons. MT110 is another bispecific antibody that directs CD3-expressing T cells to kill EpCAM-positive tumour cells. In a safety and pharmacology phase I study, a total of 23 patients were treated with MT110 doses of up to 24 µg/day and tolerated the treatment with only a few and mild clinical adverse events. Mean steady-state serum concentrations of MT110 were dose-dependent reaching up to 1.4 ng/ml at 24 µg/day and evaluation at higher doses is needed (Fiedler et al. 2010). Another phase I trial of MT110 concomitant dexamethasone indicated that a dose of 48 µg/day was tolerable and showed PD evidence of anti-tumour activity (Fiedler et al. 2012). However, a recent study reported that MT110 was associated with dose-limiting toxicities, including severe diarrhoea and increased liver enzymes, which precluded dose escalation to potentially therapeutic levels (Kebenko et al. 2018).

HER-positive neoplasms

Human epidermal growth factor receptor (HER) family members such as HER2 and EGFR (HER1), are considered attractive immunotherapy targets for solid tumours or glioblastoma. However, a phase I trial of ertumaxomab was undesirable in patients with advanced solid tumours. Single doses of up to 300 µg were well tolerated but many adverse events were also observed, such as fatigue (100%), pain (93%), cephalgia (86%), chills (79%), nausea (57%), fever (50%), emesis (50%) and diarrhoea (36%) (Haense et al. 2016).While other TRBAs targeting HER molecules are currently suspended in clinical trials, only GBR1302 is enrolling adults with progressing HER2-positive solid tumours for which no standard or curative treatment is available and aims to determine the safety and tolerability of monotherapy in subjects (Wermke et al. 2016). The preliminary PD data in the phase I study indicated changes in peripheral T-cell populations and inflammatory cytokines (IL-2, IL-6, IL-10, IFN-γ, TNF-α) following GBR1302 treatment with doses ranging from 30 to 100 ng/kg and dose escalation (Wermke et al. 2018).

CEA-positive neoplasms

Nevertheless, some TRBAs obtained encouraging clinical activity in solid tumours. Carcinoembryonic antigen (CEA) is overexpressed in a variety of cancers, including microsatellite stable (MSS) metastatic colorectal cancers (mCRC). The CEA-TCB antibody is a novel TRBA being investigated for the treatment of CEA-expressing solid tumours (Lehmann et al. 2016). More recently, the preliminary results of a phase I study (NCT02324257) demonstrated encouraging anti-tumour activity of CEA-TCB as a monotherapy, which was further enhanced in combination with Atezolizumab. Fourteen patients (45%) with mCRC showed either a partial response or stable disease in the monotherapy with doses of 60 mg or above. For the combination treatment with doses of 5–160 mg of CEA-TCB, 11 patients (44%) were shown to induce tumour lesion inflammation at 80 and 160 mg doses, and 9 patients (82%) had partial response or stabilization. In addition, favourable pharmacokinetics and a manageable safety profile were observed in both therapy strategies (Tabernero et al. 2017). MEDI-565 is a BiTE antibody specifically bound to normal and malignant tissues in a CEA-specific manner, and kills CEA-positive cells (Oberst et al. 2014). The phase 1 dose escalation study of MEDI-565 showed that the maximum tolerated dose was 5 mg on days 1 through 5 every 28 days with dexamethasone in 39 adults with gastrointestinal adenocarcinoma (Pishvaian et al. 2016). A clinical study of MEDI-565 as a continuous intravenous infusion for relapsed/refractory gastrointestinal (GI)

adenocarcinoma has been completed (NCT02291614) but no results have been reported yet.

PSMA-positive neoplasms

Prostate-specific membrane antigen (PSMA) is a potential biomarker and ideal therapeutic target of prostate cancer (PC) (Ghosh and Heston 2004). BAY2010112, the first bispecific for PSMA and CD3 single-chain antibody was developed to induce target cell-dependent activation and cytokine release of T cells, and efficiently redirect T cells for the lysis of PC cells on the basis of preclinical results (Friedrich et al. 2012), but no clinical data have been reported yet. Another TRBA ES414 targeting PSMA also completed the preclinical trial and is being evaluated in a phase 1 study of patients with metastatic castration-resistant prostate cancer (NCT02262910). To improve serum stability, ES414 fuses the Fc region and does not cross-link T cells or target cells through Fcγ, such as CD16 or CD64. This novel bispecific antibody redirects T cell cytotoxicity and drives serial lysis and multiple rounds of T cell proliferation in vitro and in vivo (Hernandez-Hoyos et al. 2016).

IMCgp100-positive neoplasms

IMCgp100 is a bispecific agent of the ImmTAC format consisting of a soluble, affinity-enhanced T cell receptor (TCR) specific for the melanoma-associated antigen gp100, fused to an anti-CD3 ScFv for malignant melanoma treatment in clinical trials (Hassan et al. 2014). Phase I was conducted in 31 patients with advanced melanoma who received doses from 5 to 900 ng/kg, and the maximum tolerated dose (MTD) was determined to be 600 ng/kg. Pharmacodynamic effects of chemokine/cytokine release and lymphocyte infiltration into tumours were observed over 2 days post-dose. The most frequently related adverse events include rash (100%), pruritus (64%), pyrexia (50%), and periorbital oedema (46%). In general, IMCgp100 has a favourable safety profile and durable responses in melanoma (Middleton et al. 2016). In another active clinical trial (NCT02570308), an acceptable safety profile and preliminary efficacy were observed with a 50% increase in the dose of IMCgp100 above what was administered in the first-in-human phase 1 trial for UM patients Considering the encouraging progress-free survival (PFS) in this trial, a phase 2 cohort and separate pivotal study of IMCgp100 is ongoing for advanced UM (Sato et al. 2017).

Others

B7-H3 protein expression is extremely limited in normal human tissues but is overexpressed in a variety of solid tumours (Picarda et al. 2016). Anti-B7-H3 and CD3 DART antibody (MGD009) is designed to redirect T cells to kill B7-H3 expressing tumour cells (Tolcher et al. 2016). Preliminary observations of the MGD009 phase I ongoing trial indicate evidence of PD-1 upregulation on both peripheral CD4 and CD8 T-cells. Thus, MGA012 is an anti-PD-1 antibody combined with MGD009 to recruit cytotoxic and helper T cells for relapsed or refractory cancer treatment (Shankar et al. 2018).

Therapies for neuroendocrine tumours (NETs) with somatostatin analogues and radionuclides suffer from short half-life, modest efficacy, and toxicities due to the inhibition of somatostatin receptor 2 (SSTR2), which is highly expressed in NETs (Hallet et al. 2015). XmAb18087, a humanized XmAb antibody stimulated peripheral T cell activation, extravasation, and cytokine induction at doses of both 1 and 10 μg/kg, then mediated the depletion of SSTR2-positive tumour cells in a monkey clinical assessment (Lee et al. 2017a). As SSTR2 is also overexpressed in small-cell lung cancer cells, XmAb18087 is being evaluated for safety and tolerability in clinical trials of small-cell lung cancer patients.

The therapeutic target and its antibody selection for TRBAs are critical, and several TRBAs targeting new antigens, such as glypican 3 and P-cadherin, were recently generated for solid tumour treatment and have been tested in clinical trials (Fisher et al. 2018; Ogita et al. 2018).

Conclusion and perspectives

TRBA therapy, which does not require an endogenous TCR cancer-specific MHC peptide complex, can redirect CD3 T cells to engage in the serial lysis of tumour cells. To improve their stability and productivity, a diverse format of TRBAs was generated. However, many complications still exist and need to be resolved, such as the short serum half-life, unwanted aggregations or immunogenicity.

The preclinical and clinical studies of TRBAs showed their potent anti-tumour efficacy, but the clinical outcome in solid tumours is less satisfactory than haematologic malignancies as well as CAR-T therapy. Treatments of lymphoid malignancies with TRBAs are impressive and expected to minimize adverse effects and have manageable clinical toxicity profiles. Regarding the targeted immunotherapies that have produced unprecedented responses in leukemia, a minor group of patient relapses have occurred due to the emergence of antigen loss variants. Another strategy is CAR-T cells with dual specificities to handle this challenging clinical scenario of when one of the antigens is lost from the cell surface (Ruella et al. 2016). In solid tumours, the redirection of T cell cytotoxicity and induction of potent immune effects by TRBAs is a potential way to treat tumours. However, many patients lack an immunotherapeutic response due to a failure of effector T cells to reach into tumours; for example, the

vascular membrane and tumour inner environmental barriers developed by tumours (Melero et al. 2014) dampen the efficacy of activated T cells by TRBAs. In addition, immunosuppressive leukocytes such as macrophages in the tumour microenvironment (Beatty and Gladney 2015) lead to the inhibition of effective T cells. We believe that, in near future, scientists and clinicians can develop even better formats and procedures to redirect endogenous killer T-cells in cancer patient therapy and to overcome many side effects, specially in TRBAs therapy in combination with immune check point inhibitors will result in a remarkable outcome for patient.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no competing interests associated with the manuscript.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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