MABS
2024, VOL. 16, NO. 1, 2321635
https://doi.org/10.1080/19420862.2024.2321635

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A pivotal decade for bispecific antibodies?

Marlena Surowka and Christian Klein

Roche Innovation Center Zurich, Roche Pharma Research & Early Development, Roche Glycart AG, Schlieren, Switzerland

ABSTRACT

Bispecific antibodies (bsAbs) are a class of antibodies that can mediate novel mechanisms of action compared to monospecific monoclonal antibodies (mAbs). Since the discovery of mAbs and their adoption as therapeutic agents in the 1980s and 1990s, the development of bsAbs has held substantial appeal. Nevertheless, only three bsAbs (catumaxomab, blinatumomab, emicizumab) were approved through the end of 2020. However, since then, 11 bsAbs received regulatory agency approvals, of which nine (amivantamab, tebentafusp, mosunetuzumab, cadonilimab, teclistamab, glofitamab, epcoritamab, talquetamab, elranatamab) were approved for the treatment of cancer and two (faricimab, ozoralizumab) in non-oncology indications. Notably, of the 13 currently approved bsAbs, two, emicizumab and faricimab, have achieved blockbuster status, showing the promise of this novel class of therapeutics. In the 2020s, the approval of additional bsAbs can be expected in hematological malignancies, solid tumors and non-oncology indications, establishing bsAbs as essential part of the therapeutic armamentarium.

ARTICLE HISTORY
Received 23 January 2024
Revised 15 February 2024
Accepted 16 February 2024

KEYWORDS
bsAb; bsADC; CD3ε; CPI; IgG; mab; TCE

Introduction

Since the discovery of monoclonal antibodies, bispecific versions that could be used as therapeutics have been of intense interest.[1–5] However, development was slowed due to challenges with the generation and production of bispecific antibodies (bsAbs) for clinical trials and the biological understanding of the more complicated mechanisms of action (MOAs). The first bsAb, the EpCAM/CD3ε T cell engager catumaxomab, was finally approved in 2009 as a treatment of patients with malignant ascites (Figure 1).[6] This bsAb was subsequently withdrawn 2013 from the market, likely related to the fact that it could only be administered intraperitoneally, as patients had severe infusion reactions when administered intravenously, and the high immunogenicity due to its rat-mouse chimeric quadrome design with a fully functional Fc portion.[6] From 2009 to 2020, only two additional bsAbs were approved: (1) in 2014, the Fc-free tandem single-chain variable fragment (scFv)-based CD19/CD3ε bispecific T cell engager (BiTE) blinatumomab (Amgen) for the treatment of acute lymphoblastic leukemia (ALL),[7–9] and (2) in 2017, the humanized hetero-dimeric coagulation factor IXa/X bispecific ART-Ig emicizumab (Roche group), which acts as a Factor VIII mimetic for the treatment of hemophilia A (Figure 1).[10,11]

Due to the intense interest in these molecules and advances in the technologies used to develop them during the past two decades, hundreds of bsAbs have been described, engineered using various different technologies and developed preclinically.[1–5] Of these, over 100 bsAbs have reached clinical trials.[1,3,5] Based on this major effort in developing novel bsAb formats, novel target combinations and bispecific lead molecules, the landscape has substantially changed recently and bsAb approvals are becoming frequent since 2021. In the past three years alone (2021–2023), 11 novel bsAbs were approved by health authorities in the US, Europe, Japan and/or China for use in patients (Figure 1, Table 1). Of these 11 bsAbs, nine were approved for treatment of cancer: (1) the EGFR/c-MET bsAb amivantamab (Johnson & Johnson (J&J)) for the treatment of non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations,[12,13] (2) the gp100-pMHC/CD3ε bsAb tebentafusp (Immunocore) for the treatment of unresectable or metastatic uveal melanoma,[14,15] (3) the CD20/CD3ε T cell engager (TCE) mosunetuzumab (Roche group) for the treatment of relapsed/refractory (R/R) follicular lymphoma,[16,17] (4) the PD-1/CTLA-4 bsAb cadonilimab (Akeso) for treatment of patients with relapsed or metastatic cervical cancer,[18,19] (5) the BCMA/CD3ε TCE teclistamab (J&J) for the treatment of R/R multiple myeloma,[20,21] (6) the CD20/CD3ε TCE glofitamab (Roche group) for the treatment of R/R diffuse large B cell lymphoma (DLBCL),[22,23] (7) the CD20/CD3ε TCE epcoritamab (AbbVie/Genmab) for the treatment of R/R DLBCL,[24,25] (8) the GPRC5D/CD3ε TCE talquetamab (J&J) for the treatment of R/R multiple myeloma[26,27] and (9) the BCMA/CD3ε TCE elranatamab (Pfizer) for the treatment of R/R multiple myeloma.[28,29] Two additional bsAbs were approved for non-oncology indications, the VEGF-A/Ang-2 bsAb faricimab (Roche group) for the treatment of wet age-related macular degeneration, diabetic macular edema, and macular edema following retinal vein occlusion,[30–33] which was the first bsAb approved for use in ophthalmology, and the TNF/human serum albumin (HSA) bsAb ozoralizumab (Taisho) for the treatment of inadequately managed rheumatoid arthritis.[34–36] The Roche group with Chugai is currently

CONTACT Christian Klein christian.klein.ck1@roche.com Roche Innovation Center Zurich, Roche Pharma Research & Early Development, Roche Glycart AG, Wagistrasse 10, Schlieren 8952, Switzerland

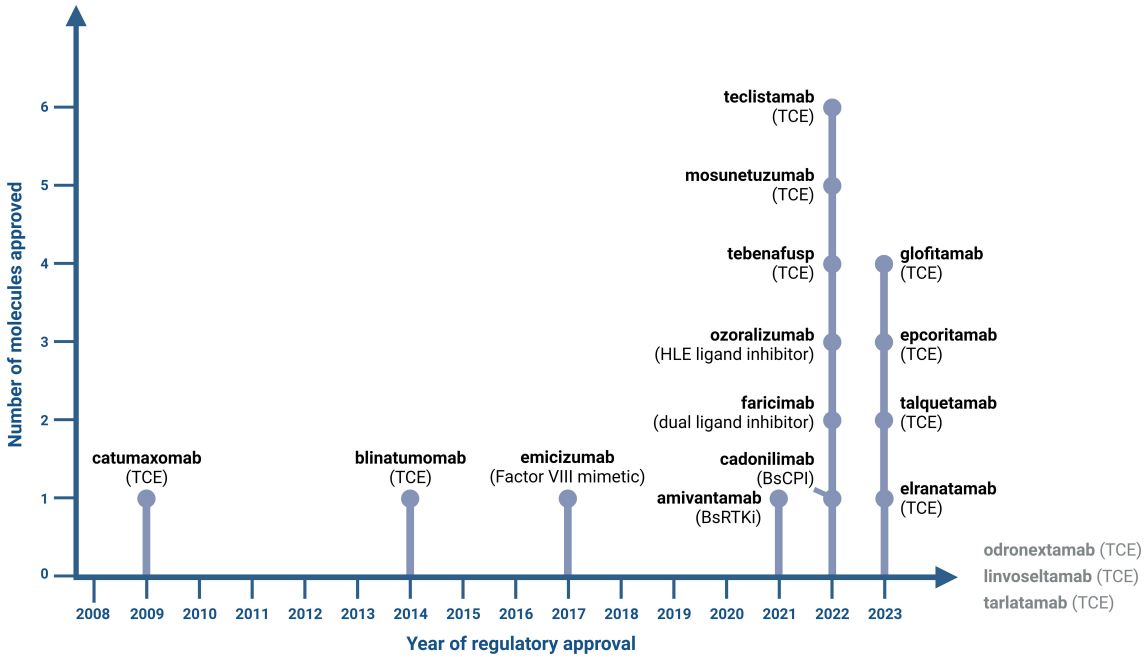

Figure 1. Timeline of regulatory approval of bsAbs with their respective MOA. Linvoseltamab, odronextamab and tarlatamab are currently under regulatory review with a decision anticipated in 2024. Created with Biorender.com.

leading the field with four approved bsAbs, followed by J&J with three approved bsAbs. Notably, of the 13 currently approved bsAbs, two, emicizumab and faricimab, have already achieved blockbuster status with annual sales exceeding four and two billion dollars, respectively, underlining the commercial promise of this novel class of therapeutics.

Bispecific antibody formats

The variety of bispecific antibody formats developed reflects the diversity of technologies applied in these approved bsAbs (Figure 2). The respective bsAb formats cover non-IgG-like bsAbs, with 1) Amgen's short half-life tandem-scFv-based BiTE format applied in blinatumomab,[37,38] 2) Immunocore's T cell receptor (TCR)-scFv fusion-based ImmTac format applied in tebentafusp[39,40] and 3) Ablynx's trivalent bispecific tandem nanobody format with half-life extension via HSA binding applied in ozoralizumab.[41] Most bsAbs, however, are IgG-like molecules with pharmacokinetics that are similar to antibodies due to the presence of an Fc. Five asymmetric 1 + 1 IgG-like bsAbs are derived from either controlled Fab arm exchange, based on Duobody technology applied in amivantamab,[42] teclistamab,[43] epcoritamab,[44] and talquetamab,[45] or related chain exchange technology by Pfizer[46] applied in elranatamab.[47] Alternatively, correct chain association is enforced via Chugai's ART-Ig technology[48] applied in the asymmetric 1 + 1 IgG-like bsAb emicizumab[49,50] together with common light chains. Correct heavy chain association can also be ensured in asymmetric 1 + 1 IgG-like bsAbs using knobs-into-holes technology applied together with in vitro assembly in mosunetuzumab,[51] or together with CrossMab technology to enforce correct light chain association in the 1 + 1 IgG-like bsAb faricimab[52] or the trivalent 2 + 1 bsAb glofitamab.[53] Finally, Akeso's cadonilimab comprises a symmetric tetravalent 2 + 2 C-terminal IgG-scFv fusion.[54] Among the approved bsAbs, four apply Genmab's Duobody technology,[55,56] three apply Genentech's knobs-into-holes[57,58] and two apply Roche pRED's CrossMab technology.[59–61] The diversity of formats available suggests that "standardized" bsAbs are unlikely to arise, but recent approvals underpin a focus on classical heterodimeric IgG-like bsAb formats. These bsAbs typically show IgG-like pharmacokinetics and low incidence of anti-drug antibodies.

MOAs for approved bsAbs

TCEs are bispecific antibodies that bind with one specificity to a cell surface tumor antigen, and with the second specificity to a subunit of the TCR complex, so that, upon simultaneous binding to the tumor antigen and the TCR, the T cell is subsequently activated to kill the tumor cell, secrete cytokines and start to proliferate.[62] Apparently, T cell engagement strictly relies on bispecificity and cannot be achieved by the combination of two conventional mAbs. For the treatment of cancer, the pre-dominant MOA is T cell engagement, with the largest number of bsAbs approved and in clinical trials being TCEs.[5] Figure 2a shows an overview of the evolution of approved TCE bsAb formats. This class of molecules includes TCEs for the treatment of relapsed/refractory hematological cancers: 1) CD19/CD3ε blinatumomab for the treatment of ALL,[7–9] 2) the CD20/CD3ε TCEs mosunetuzumab for the treatment of R/R non-Hodgkin's lymphoma (NHL),[51] and glofitamab[53] and epcoritamab[44] for the treatment of R/R DLBCL, and 3) the BCMA/CD3ε TCEs teclistamab[43] and elranatamab,[47] and GPRC5D/CD3ε talquetamab,[45] for the treatment of R/R multiple myeloma. While generally T cell engagement for the treatment of solid tumors appears to be more challenging,[63] the soluble gp100-peptideMHC/CD3ε -

Table 1. Approved bsAbs and bsAbs under regulatory review.

	Trade name	INN	Targets	MOA	Format	Indications	Year	1st Approval	Company
Discontinued									
1	Removab	Catumaxomab	EpCAM/CD3ε	T cell engager	1+1 Quadroma	Ovarian ascites (intraperitonael)	2009	Europe	Trion Pharma
Approved									
1	Blincyto	Blinatumomab	CD19/CD3ε	T cell engager	1+1 (scFv)2 BiTE	Acute lymphocytic leukemia	2014	US	Amgen
2	Hemlibra	Emicizumab	factor IXa/factor X	Factor VIII mimetic	1+1 ART-Ig	Haemophilia A	2017	US	Roche group
3	Rybrevant	Amivantamab	EGFR/c-Met	Dual signaling inhibitor + ADCC	1+1 Duobody	Non-Small Cell Lung Cancer, EGFR exon 20 mutated	2021	US	Johnson & Johnson
4	Kimmtrak	Tebentafusp	gp100-HLA-A*02 /CD3ε	T cell engager	1+1 TCR-scFv	Uveal melanoma	2022	US	Immunocore
5	Vabysmo	Faricimab	Ang-2/VEGF	Dual ligand inhibitor	1+1 CrossMab	wAMD, DME, RVO	2022	US	Roche group
6	Lunsumio	Mosunetuzumab	CD20/CD3ε	T cell engager	1+1 IgG-KiH	Relapsed/refractory fNHL	2022	Europe	Roche group
7	Kaitanni	Cadonilimab	PD-1/CTLA-4	Dual checkpoint inhibitor	2+2 IgG-scFv Tetrabody	Cervical cancer	2022	China	Akeso
8	Tecvayli	Teclistamab	BCMA/CD3ε	T cell engager	1+1 Duobody	Relapsed/refractory multiple myeloma	2022	Europe	Johnson & Johnson
9	Nanozora	Ozoralizumab	TNFa/HSA	Ligand inhibitor	2+1 Nanobody	Rheumatoid arthritis	2022	Japan	Taisho Pharmaceutical, Ablynx
10	Columvi	Glofitamab	CD20/CD3ε	T cell engager	2+1 CrossMab	Relapsed/refractory DLBCL	2023	Canada	Roche group
11	(T)Epkinly	Epcoritamab	CD20/CD3ε	T cell engager	1+1 Duobody	Relapsed/refractory DLBCL	2023	US	Genmab, AbbVie
12	Talvey	Talquetamab	GPRC5D/CD3ε	T cell engager	1+1 Duobody	Relapsed/refractory multiple myeloma	2023	US	Johnson & Johnson
13	Elrexfio	Elranatamab	BCMA/CD3ε	T cell engager	1+1 bsAb	Relapsed/refractory multiple myeloma	2023	US	Pfizer
Under regulatory review									
1	n.a.	Linvoseltamab	BCMA/CD3ε	T cell engager	1+1 Veloci-Bi	Relapsed/refractory multiple myeloma	n.a	Pending US	Regeneron
2	n.a.	Odronextamab	CD20/CD3ε	T cell engager	1+1 Veloci-Bi	Relapsed/refractory DLBCL	n.a.	Pending US	Regeneron
3	n.a.	Tarlatamab	DLL3/CD3ε	T cell engager	1+1 Fc-(scFv)2 Fc-BiTE	Relapsed advanced small cell lung cancer	n.a.	Pending US	Amgen
4	n.a.	Zanidatamab	HER2/HER2	Dual signaling inhibitor + ADCC + CDC	1+1 Azymetric	Biliary tract cancer	n.a.	Pending US	Zymeworks/Jazz Pharmaceuticals
5	n.a.	Ivonescimab	PD-1/VEGF	Dual checkpoint/ligand inhibitor	2+2 IgG-scFv Tetrabody	Non-Small Cell Lung Cancer	n.a.	Pending China	Akeso

ADCC, antibody-dependent cellular cytotoxicity; ART-Ig, bispecific antibody manufacturing technology; BiTE, bispecific T cell engager; CDC, complement-dependent cytotoxicity; DLBCL, diffuse large b cell lymphoma; DME, diabetic macular edema; fNHL, follicular non-Hodgkin's lymphoma; KIH, knobs-into-holes; n.a., not applicable; RVO, Retinal vein occlusion; scFv, single-chain Fv fragment; TCR, T cell receptor; wAMD, wet age-related macular degeneration.

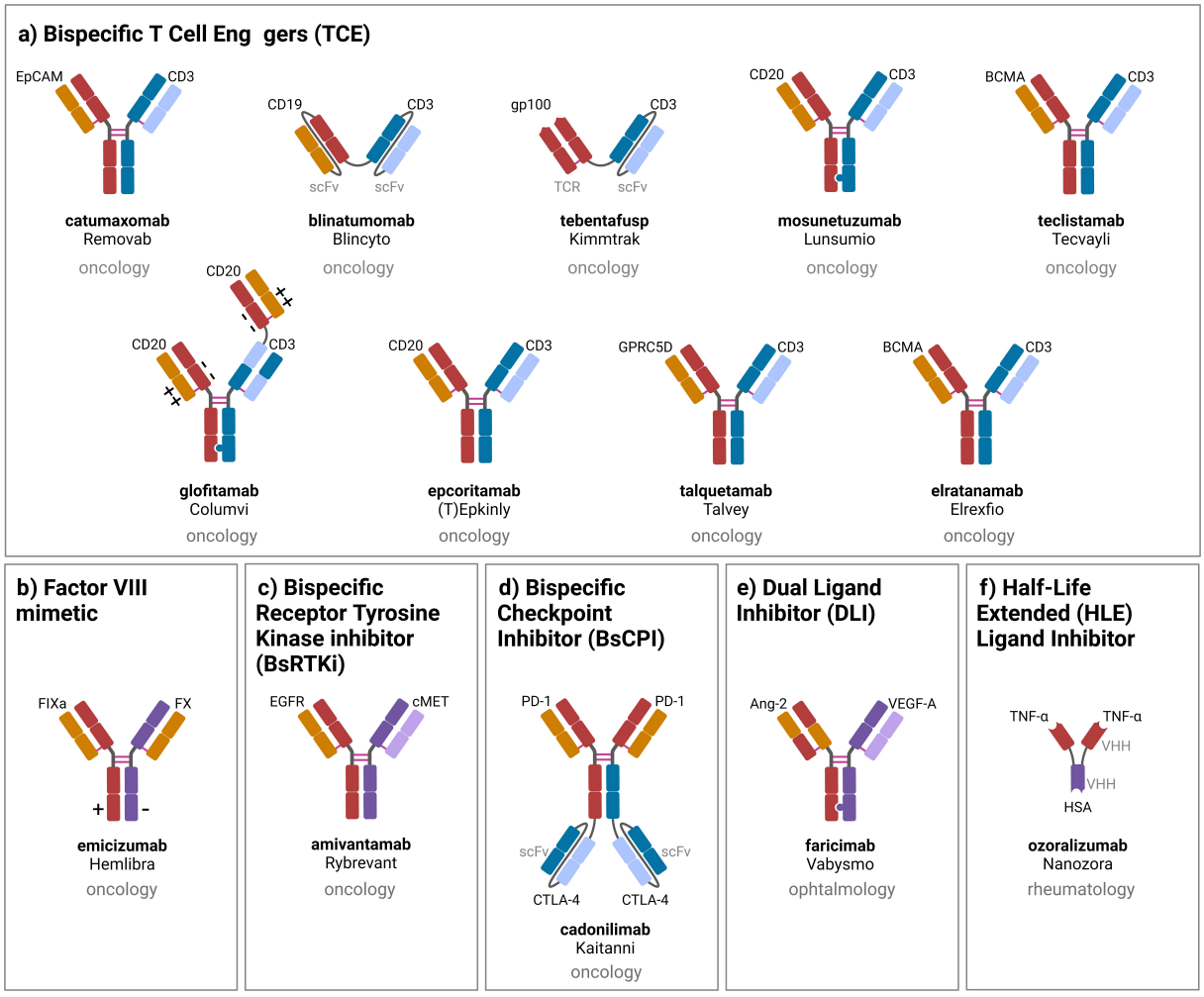

Figure 2. Schematic representation, indication and mechanism of action of approved bsAbs: a) T cell engagers (TCE), b) factor VIII mimetic, dual signaling inhibition: c) bispecific receptor tyrosine kinase (RTK) inhibitor (BsRtki), d) bispecific checkpoint inhibitor (BsCPI), e) dual ligand inhibitor (DLI), f) half-life extended (HLE) ligand inhibitor. Created with Biorender.com.

specific TCR-scFv fusion tebentafusp was the first TCE to be approved for the treatment of uveal melanoma, providing evidence for use outside of hematological tumors.

Hemophilia A is a hereditary bleeding disorder characterized by the lack of blood coagulation Factor VIII. While recombinant Factor VIII can be administered to patients, this is related to challenges such as Factor VIII production, short half-life with frequent administration and the development of neutralizing antibodies.[64] For this purpose, Chugai designed and optimized the IXa/X bsAb emicizumab so that it mimics the function of blood coagulation Factor VIII by bringing the enzyme Factor IXa and the substrate Factor X into close proximity while exhibiting IgG-like extended pharmacokinetics[49,50] (Figure 2b).

Monospecific receptor tyrosine kinase blocking mAbs, such as anti-EGFR cetuximab and panitumumab or anti-HER2 trastuzumab and pertuzumab, have revolutionized cancer therapy.[65] While there has been little progress in targeting additional RTKs, EGFR/c-Met bsAb amivantamab, a first bsAb targeting two RTKs simultaneously, was recently approved for a specific subset of NSCLC patients with EGFR exon 20 insertion mutations.[12,13] In addition to its dual signaling inhibitor function, both via blocking the ligand binding sites and via receptor downregulation, amivantamab also contains an afucosylated Fc portion to mediate enhanced antibody-dependent cellular toxicity (ADCC) for NK cell and macrophage/monocyte engagement[42] (Figure 2c).

During the past decade, approved immune checkpoint inhibitory antibodies, including those targeting PD-1 (nivolumab, pembrolizumab, cemiplimab), PD-L1 (atezolizumab, avelumab, durvalumab), and CTLA-4 (ipilimumab, tremelimumab), have revolutionized the field of cancer therapy and established cancer immunotherapy.[66] Based on this experience, the dual PD-1/CTLA-4 checkpoint inhibitory bsAb cadonilimab was designed with the goal of specifically, and ideally simultaneously, binding and inhibiting PD-1 and CTLA-4 on antigen-specific T cells to overcome checkpoint inhibition[54] (Figure 2d).

The pro-angiogenic ligands VEGF-A and Ang-2 contribute to vision loss by fostering retinal angiogenesis and destabilizing blood vessels causing leakiness and subsequent edema and inflammation.[67,68] Faricimab was specifically designed to block VEGF-A and Ang-2 in the eye to interfere with angiogenesis, stabilize vessels and reduce leakage and inflammation[52,69] (Figure 2e). In order to minimize peripheral activity and

abolish FcγR engagement, it was designed with an engineered Fc portion with Triple A FcRn and P329G LALA mutations.[52]

Notably, bispecificity is a major benefit when considering intraocular administration. For the TNF ligand inhibitor ozoralizumab, it should be noted that functionally, this nanobody construct functions like a monospecific antibody blocking TNF, with the second single domain specificity solely required to enable IgG-like pharmacokinetics by binding to HSA in the absence of an Fc portion, enabling FcRn recycling[41] (Figure 2f).

Outlook for the future

In this decade, 11 bsAbs have already been approved, and the approval of additional bsAbs with medical practice-changing potential can be expected in the coming years. In oncology, the development of differentiated dual RTK signaling inhibitors with bsAb co-targeting different cell surface receptors remains an area of active and advanced clinical research. Selected examples are: EGFR/LGR5 like petosemtamab,[70] HER2/HER3 like zenocutuzumab[71] or bi-paratopic bsAbs targeting HER2 like zanidatamab[72] which is currently under regulatory review in the US.[73–75] Another very important area to watch in this context is the use of bsAbs for the generation of bispecific antibody-drug conjugates (bsADCs),with several bsADCs being investigated in advanced clinical trials,[76–78] including bi-paratopic monospecific bsAbs targeting HER2 like zanidatamab zovodotin (ZW49) or c-MET with REGN5093.[79]

The development of TCEs for the treatment of different hematological malignancies will remain a major area of research in the field of synthetic immunity approaches, as this class of therapeutics already has proven its benefit. To date, the asymmetric 1 + 1 TCEs odronextamab (CD20/CD3ε)[80] and linvoseltamab (BCMA/CD3ε) based on Regeneron's VelociBi technology are currently under regulatory review that may result in approval in 2024, and various additional TCEs are in advanced clinical development in NHL, multiple myeloma and AML.[75] Importantly, emerging data support the idea that TCEs may in the future also find broader application in solid tumors. In fact, recently promising clinical data have been published for Amgen's 1 + 1 DLL3/CD3ε Fc-BiTE tarlatamab for the treatment of R/R small cell lung cancer,[81,82] which is currently under regulatory review, and for Xencor/Amgen's 2 + 1 STEAP1/CD3ε XmAb xaluritamig for the treatment of R/R prostate cancer.[83,84] These data support the view that solid tumor targets that are sufficiently tumor specific to achieve potent anti-tumor efficacy while limiting on-target off-tumor toxicity are available. In this context, tumor activation mechanisms like protease activation aim to increase the therapeutic window of solid tumor-directed TCEs.[85–89] Based on the mechanism of action of TCEs that provide the TCR signal 1 to T cells, rapid clinical adoption of CD28- or 4-1BB/CD137-targeted costimulatory bsAbs to provide the signal 2 to T cells, resulting in sustained and more durable T cell responses,[90,91] is now occurring.

In the field of boosting endogenous or preexisting immunity, another major area of research remains the development of dual-targeted checkpoint inhibitory bsAbs targeting, for example, PD-1 and CTLA-4[92,93] or LAG-3 (tebotelimab).[94] Several of these dual checkpoint inhibitors are currently in advanced clinical trials and results will show whether they are superior in terms of efficacy and/or safety compared to the respective combinations of PD-1/PD-L1 mAbs with CTLA-4 or LAG-3 mAbs. Notably, the dual-targeted PD-1/VEGF inhibitory bsAb ivonescimab is currently under regulatory review by the National Medicinal Product Administration in China for treatment of NSCLC.[75,95]

Finally, given the versatility of bsAbs and the potential to mediate completely novel MOAs, the field of bsAbs is poised to see novel emerging approaches and candidates enter the clinic, hopefully providing pivotal data in the years to come, both in oncology and in non-oncology indications, including applications in infection/virology, autoimmunity, metabolism, neurology and ophthalmology. These novel concepts include different approaches as described recently,[5] including the development of: 1) effector cell engagers different from TCEs, engaging, e.g., myeloid, NK or γδ-T cells,[96–98] 2) *in situ* assembly concepts to specifically activate bsAbs on dual target-expressing cells[99,100] or in the tumor microenvironment,[101] 3) PROTAC-like approaches resulting in internalization and degradation of membrane proteins,[102] 4) antibody-based cytokine mimetics to trigger cytokine receptors,[103,104] and 5) unique solutions for delivery of bsAbs beyond barriers such as the blood-brain-barrier,[105] which may have applications for the treatment of neurodegenerative and other diseases.[106]

Disclosure statement

MS declares employment and patents with Roche, CK declares employment, patents/royalties and stock ownership with Roche.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Marlena Surowka http://orcid.org/0009-0007-2113-9692
Christian Klein http://orcid.org/0000-0001-7594-7280

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