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Review Article

Structure and function of therapeutic antibodies approved by the US FDA in 2023

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ABSTRACT

In calendar year 2023, the United States Food and Drug Administration (US FDA) approved a total of 55 new molecular entities, of which 12 were in the class of therapeutic antibodies. Besides antibody protein drugs, the US FDA also approved another five non-antibody protein drugs, making the broader class of protein drugs about 31% of the total approved drugs. Among the 12 therapeutic antibodies approved by the US FDA, 8 were relatively standard IgG formats, 3 were bivalent, bispecific antibodies and 1 was a trivalent, bispecific antibody. In 2023, no new antibody–drug conjugates, immunocytokines or chimeric antigen receptor-T cells were approved. Of the approved antibodies, two targeted programmed cell death receptor-1 (PD-1) for orphan indications, two targeted CD20 for diffuse large B cell lymphoma, two targeted different receptors (B-cell maturation antigen [BCMA] and G-coupled protein receptor class C, group 5, member D [GPRC5D]) for treatment of multiple myeloma, and one each that targeted amyloid-β protofibrils for Alzheimer's disease, neonatal Fc receptor alpha-chain for myasthenia gravis, complement factor C5 for CD55 deficiency with hyper-activation of complement, angiopathic thrombosis and severe protein-losing enteropathy disease, interleukin (IL)-23p19 for severely active ulcerative colitis, IL-17A-F for plaque psoriasis and respiratory syncytial virus (RSV)-F protein for season-long RSV prophylaxis in infants.

Statement of Significance: Structural insights into the 12 novel therapeutic antibodies approved by the US FDA in 2023.

KEYWORDS: therapeutic antibodies; bispecific antibodies; new molecular entities; US FDA

INTRODUCTION—ANTIBODIES APPROVED BY UNITED STATES FOOD AND DRUG ADMINISTRATION IN 2023

In the calendar year of 2023, the United States Food and Drug Administration (US FDA) approved a total of 55 new molecular entities (NMEs), including 38 small-molecule drugs (includes peptide- and oligonucleotide-based molecules), five non-antibody biologics and 12 antibody-based (i.e., any biologic containing one or more antibody domains) biologics [1]. Figure 1 shows a comparison of these 2023 approvals with previous years, indicating that 2023 was a strong year both for novel drug approvals in the USA in general and for antibody-based drugs. The 12 antibody-based drugs approved in 2023 (Table 1) ties for the highest number of antibodies approved by the US FDA in a calendar year ever, equaling 2020 (Fig. 1). Many of the antibodies approved by the US FDA in 2023 had previously been flagged as "Antibodies to Watch in 2023" [2]. Further information on antibodies approved during the 2023 calendar year, including antibodies approved by regulatory authorities outside the USA, can be found in Crescioli et al. [3].

Thirty-seven years ago, in 1986, the US FDA approved muromonab CD3 (Orthoclone OKT3), the first monoclonal antibody (mAb) drug, for treatment of organ rejection during transplantation [29]. With the 12 new US FDA antibody approvals in 2023, that brings the total of novel antibodies and antibody-based drugs approved by the FDA from 19 June 1986 to 31 December 2023 to 145, an average of ca. 3.9 antibody approvals/year. This number includes 96 immunoglobulin G (IgG)–based antibodies, six antibody fragments, 13 Fc fusions or Fc-based proteins,

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Table 1. Antibodies and antibody-like molecules approved by the US FDA in 2023

#	Trade name (generic name)	Sponsor/ partner(s)	Date FDA approved	Molecular target	Approved indication	Dosing	Structure description	Refs
1	Leqembi® (lecanemab-irmb)	Biogen/ Eisai	1/6/23 (accelerated approval); 7/6/23 (full approval)	Amyloid protofibrils	AD	10 mg/kg Q2W IV	Humanized IgG1κ (from murine mab 158).	[5, 6]
2	Zynyz® (retifanlimab-dlwr)	Incyte Corp./ Macrogenics	3/22/23 (accelerated approval)	PD-1	MCC	500 mg Q4W IV	Humanized IgG4κ S227P, ΔK445.	[1, 7, 8]
3	Epkinly™ (epcoritamab-bysp)	Abbvie/ Genmab	5/19/23 (accelerated approval)	CD20 × CD3	DLBCL	QW step-up dosing to steady state 48 mg QW SC	Bispecific "Duobody"; Human/chimeric heterodimeric, bivalent bispecific IgG1λ/κ; IgG1λ mouse/human chimeric HC1 (454aa) L242F, L243E, D273A, F413L, ΔK454 targets CD3ε; IgG1κ human HC2 (451aa) L239F, L240E, D270A, K414R, ΔK451 targets CD20.	[9, 10]
4	Columvi™ (glofitamab-gxbm)	Roche	6/15/23 (accelerated approval)	CD20 × CD3	R/R DLBCL; LBCL (arising from FL)	QW step up dosing to 30 mg steady state QW IV	Humanized heterodimeric, trivalent bispecific ("2:1") IgG1λ/κ lambda/kappa with domain crossover and silenced Fc; Four chains: HC1 (674aa; VH (119aa, targeting CD20)-CH1-tetraglycylseryl$_2$ linker-Vλ (111aa, targeting CD3ε)-IgG1 CH1-hinge-CH2-CH3) K149E, K215E, L461A, L462A, P556G, S581C, targets both CD20 and CD3ε; LC1 × 2 (κ, 219aa, targeting CD20) E128R, Q129K; HC2 (449aa) K149E, K215E, L236A, L237A, P331G, Y351C, T368S, L370A, Y409V; LC2 (crossover VH, Cκ, 232aa, targeting CD3ε) T127S.	[11, 12]
5	Rystiggo® (rozanolixizumab-noli) (UCB7665)	UCB	6/26/23 (full approval)	FcRn alpha chain	gMG	Weight based ca. 7–10 mg/kg QW SC	Humanized IgG4κ S225P.	[13, 14]
6	Beyfortus™ (nirsevimab-alip)	Astrazeneca/ Sanofi	7/17/23 (full approval)	RSV F-protein	Prophylaxis against RSV in infants	Weight based 10–20 mg/kg single dose IM	Human IgG1κ, M261Y, S263T, T265E ("YTE" for half-life extension).	[15, 16]
7	Talvey™ (talquetamab-tgvs)	Janssen R&D	8/9/23 (accelerated approval)	GPRC5D × CD3	MM	SC Q3D step-up dosing to 0.8 mg/kg steady state SC Q2W or 0.4 mg/kg QW SC	Bispecific "Duobody"; Humanized heterodimeric, bivalent bispecific IgG4κ/λ; IgG4κ HC1 (445aa) S226P, F232A, L233A, targets GPRC5D; IgG4λ HC2 (452aa) S233P, F239A, L240A, F410L, R414K, targets CD3ε.	[17, 18]

(*Continued*)

Table 1. Continued

#	Trade name (generic name)	Sponsor/ partner(s)	Date FDA approved	Molecular target	Approved indication	Dosing	Structure description	Refs
8	Elrexfio™ (elranatamab-bcmm)	Pfizer	8/14/23 (accelerated approval)	BCMA × CD3	MM	Step-up dosing Q4D to 76 mg steady state QW leading to Q2W SC (after 25 weeks dosing)	Humanized/human heterodimeric, bivalent bispecific IgG2κ. Human IgG2κ HC1 (441aa) C218E, P223E, D259A, A324S, P325S, L362E with human κLC1 (215aa), targets BCMA; Humanized IgG2κ HC2 (447aa) L116T, C224R, E226R, P229R, D265A, A330S, P331S, K409R with humanized κLC2 (219aa) Q105S, targets CD3ε.	[19, 20]
9	Veopoz™ (pozelimab-bbfg)	Regeneron	8/18/23 (full approval)	C5	CHAPLE disease	Loading dose 30 mg/mg IV, followed by 10-12 mg/kg QW SC	Human IgG4κ S228P.	[21, 22]
10	Bimzelx® (bimekizumab-bkzx)	UCB	10/17/23 (full approval)	IL-17A and IL-17F	Moderate to severe PsO	320 mg SC Q4W to 16 weeks, then Q8W SC	Humanized IgG1κ (bifunctional, two targets with single combining site).	[23, 24]
11	Omvoh™ (mirikizumab-mrkz)	Eli Lilly	10/26/23 (full approval)	IL-23p19	Severely active UC	300 mg IV Q4W to 12 weeks induction, then 200 mg SC Q4W maintenance	Humanized IgG4κ S223P, F229A, L230A; ΔK441.	[25, 26]
12	Loqtorzi™ (toripalimab-tpzi) (JS001)	Coherus BioSciences	10/27/23 (full approval)	PD-1	ANPC	3 mg/kg Q2W IV (alternative: with cisplatin and gemcitabine, 240 mg Q3W IV)	Humanized IgG4κ S233P.	[27, 28]

Abbreviations: aa, amino acid residues; ANPC, advanced nasopharyngeal carcinoma; BCMA, B-cell maturation antigen; CHAPLE, CD55 deficiency with hyper-activation of complement, angiopathic thrombosis and severe protein-losing enteropathy; DLBCL, diffuse large B-cell lymphoma; FcRn, neonatal receptor; FL, follicular lymphoma; gMG, general Myasthenia gravis; GPRC5D, G-coupled protein receptor class C, group 5, member D; HC, heavy chain; IL, interleukin; IM, intramuscular; IV, intravenous; LC, light chain; mAb, monoclonal antibody; LBCL, large B-cell lymphoma; MCC, Merkel cell carcinoma; MM, multiple myeloma; PD, programmed cell death protein; PsO, plaque psoriasis; Q4D, dosing every 4 days; QW, Q2W, Q3W, Q4W, Q8W, weekly, every other week, every third week, every fourth week and every eighth week dosing, respectively; Refs, references; RSV, respiratory syncytial virus; SC, subcutaneous; UC, ulcerative colitis.

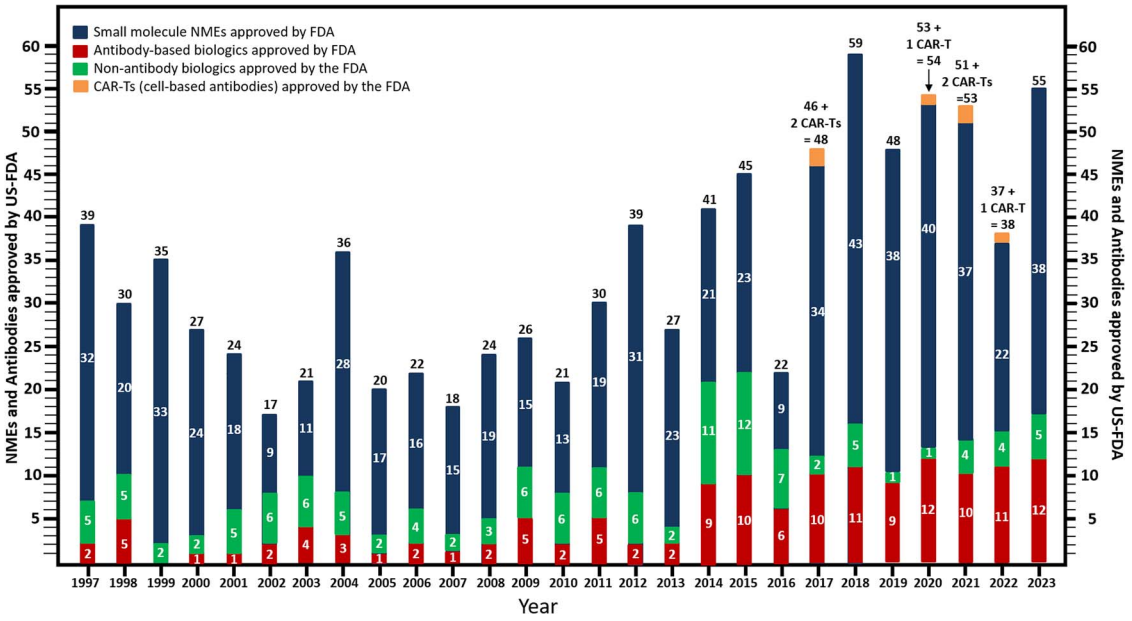

Figure 1. FDA approvals In the last 27 years. Number of small molecules, antibody-based biologics, non-antibody biologics and chimeric antigen receptor-T cells (CAR-Ts) approved on an annual basis from 1997 to 2023. These data are derived from references 1 and 4.

13 antibody–drug conjugates (ADCs), 12 bispecific antibodies, two antibody mixtures, two radioimmunoconjugates (RICs) and one emergency approval [30].

Figure 1 shows that the number of new antibody-based biologics approvals annually has increased substantially over the past decade. From 1997 to 2013, the average number of newly FDA approved novel antibodies was 2.35 per year. From 2014 to 2023, the last 10 years, that number has increased to 10 new, novel antibody–based drugs approved by the FDA per year. That translates to 100 newly FDA approved, novel antibodies in the past decade, more than doubling the total number of previously approved antibodies. In roughly that same time period, 2012–22, the worldwide value of antibodies increased from $64.6 billion (US) to $243 billion (US) [31, 32] (Fig. 2), nearly a four-fold increase in value. Of course, the antibody sales figure is a multi-year lagging indicator as compared with newly approved antibodies. To that end, it has been predicted that the value of marketed antibodies worldwide will increase to nearly $500 billion (US) by 2030, representing an approximate 10% forward compound annual growth rate (CAGR) [33].

OVERVIEW OF 2023 FDA-APPROVED ANTIBODIES

Most of the dozen antibodies approved in 2023 targeted well-known targets and pathways, while just a few others represented forays into truly novel targets for known diseases. In the category of well-known approaches, there were two anti-programmed cell death protein-1 (PD-1) antibodies, two T-cell engager (TCE) antibodies targeting CD20, a new, highly differentiated anti-respiratory syncytial virus (RSV) mAb, the second antibody to be approved targeting amyloid-β for treatment of Alzheimer's disease (AD), the second antibody-based biologics to target the neonatal receptor (FcRn) (albeit using a new mechanism of action), the second bispecific TCE antibody to target B-cell maturation antigen (BCMA) (a third altogether, the third being an anti-BCMA-ADC that has since been withdrawn from marketing in the USA [43]) and antibodies targeting the well-known TH17 pathway cytokines interleukin (IL)-23p19 and IL-17AF. The novelty on this last one is the co-targeting of IL-17F with IL-17A, which improves the efficacy due to the partially differentiated IL-17F biology [44]. Finally, one of the newly approved antibodies targets the well-known protein complement C5.

One of the aspects driving differentiation of those antibodies approved this year was the engineered features incorporated into many of them, as noted in Table 1 and as follows. In 2023, four bispecific TCE antibodies were approved—this significantly adds to the five bispecific TCEs previously approved by the FDA from 1997 to 2022 [30], demonstrating the strength of this approach and the wider acceptance of the technology to solve certain disease issues. Glofitamab represents the second use of the CrossMab technology [45] to be approved by the US FDA, but the first to use it to generate a 2:1 design [46].

From a novel biology standpoint, this group of 12 FDA-approved antibodies contains only two truly novel targets, the first of which is GPRC5D, a G-coupled protein receptor (GPCR) found highly expressed in multiple myeloma (MM) cells targeted by the TCE, talquetamab [47]. The second novel target is IL-17F, a member of the IL-17 family not previously targeted for treatment of PsO. Bimekizumab combines binding of a well-validated target (IL-17A) with a second, related cytokine, IL-17F, using the same combining site (thus, dual specificity rather than bispecificity) [48]. Binding to IL-17F provides

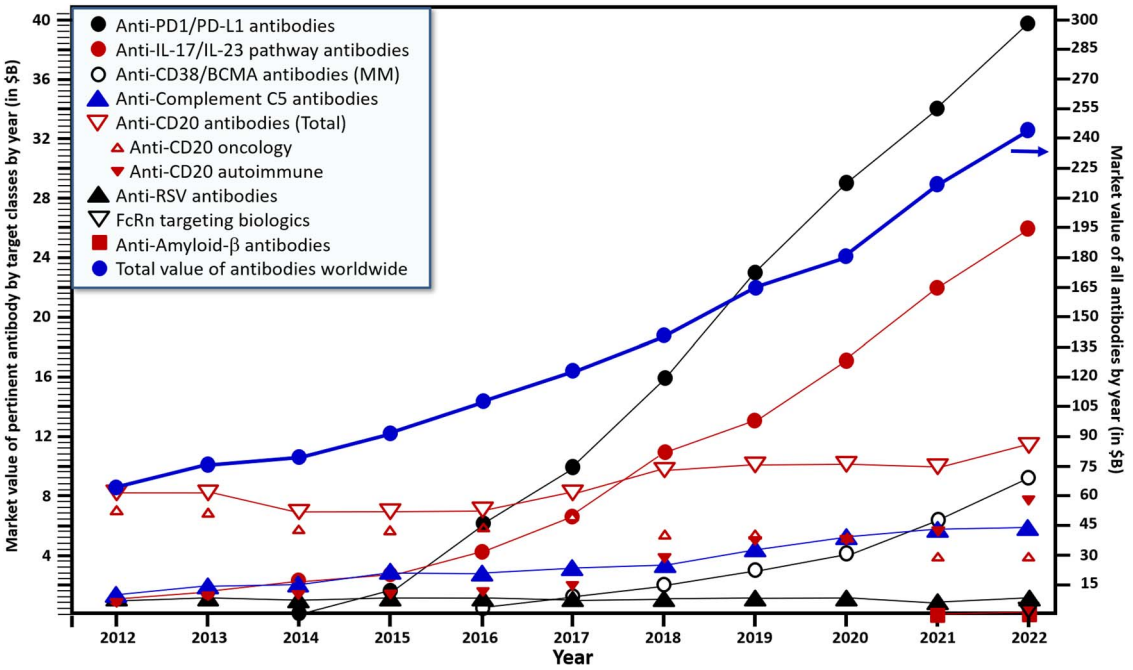

Figure 2. The historical value of markets for antibodies approved in 2023. These include anti-programmed cell death protein-1 (PD-1)/programmed cell death protein ligand-1 (PD-L1) mAbs, mAbs with targets in the TH17 pathway, antibodies targeting multiple myeloma, anti-C5 (complement) mAbs, anti-CD20 antibodies (subdivided into market for targeting B-cells for cancer vs the market for targeting B-cells for autoimmune disorders), anti-respiratory syncytial virus (RSV) mAbs, biologics targeting FcRn, anti-amyloid-β mAbs (all on left side numbers) and the total value of antibody-based biologics worldwide (right side numbers). These data are derived from references (31, 32, 34–42).

additional potential efficacy in an effort to compete in a highly crowded field (bimekizumab is the 12th biologic approved for a PsO-related indication) [48].

The other 10 antibodies approved by the US FDA in 2023 offer (i) new and more potent approaches to older targets (e.g., the anti-CD20 TCEs, glofitamab, epcoritamab); (ii) targeting of a specific phase in the disease progression (e.g., lecanemab for AD); (iii) a novel mechanistic approach (e.g., using the rozanolixizumab IgG CDRs to target FcRn α-subunit, a recently validated target); (iv) a currently novel approach to a highly popular, validated target (elranatamab TCE for MM, as opposed to CAR-T and ADC approaches against the same target); and (v) vast improvement of pharmacokinetics–pharmacodynamics (PK-PD) of a well-validated target (RSV F-protein targeted by the long-lasting nirsevimab to allow for RSV season-long protection).

Finally, several antibodies approved by the FDA in 2023 will likely help to improve the sponsors' portfolios, but do not (at least yet) appear to provide significant differentiation over currently approved antibodies from other sponsors across multiple indications. Some of them will, however, meet significant unmet medical needs. These include the two anti-PD-1 antibodies (toripalimab, retifanlimab), the anti-C5 mAb (pozelimab) and the anti-IL-23p19 mAb (mirikizumab). Typically, these kinds of antibodies are targeted by their sponsors for initial approval in novel disease types and/or smaller markets, which allows them to secure their initial approvals without having to run large head-to-head comparison clinical trials with long-standing approved and competitive drugs. Examples of this approach include (i) FDA approval in 2023 of toripalimab for nasopharyngeal carcinoma (NPC) [49], an indication for which neither pembrolizumab (Keytruda®) or nivolumab (Opdivo®) are yet approved, and (ii) FDA approval of the new anti-C5 antibody, pozelimab, for treatment of the ultra-rare "CD55 deficiency with hyper-activation of complement, angiopathic thrombosis and severe protein-losing enteropathy" (CHAPLE) disease [50], an indication for which neither of the currently approved anti-C5 mAbs, Soliris® and Ultomoris® is approved. Another antibody approved by the FDA in 2023 was retifanlimab (Zynyz®), which was approved for Merkel cell carcinoma (MCC), an indication for which both of the anti-PD-1 standard bearers, Keytruda® and Opdivo®, are FDA-approved, thus entering a highly competitive situation. Finally, in some cases in which a new biologic is entering a highly competitive space, FDA approval is sought and granted to provide a novel mechanism of action to a well-treated medical indication. In this case, the anti-IL-23p19 mAb, mirikizumab (Omvoh™), which is now the fourth anti-IL-23p19 and the ninth addition to the IL-17/IL-23 pathway inhibitors in general [30], was approved for treatment of severely active ulcerative colitis (SA-UC), an indication dominated by the anti-tumor necrosis factor (TNF)-α antibodies and also featuring the approved anti-IL-12/IL-23p40 bifunctional antibody, ustekinumab (Stelara®). While mirikizumab efficacy in this indication may not allow it to supplant the anti-TNF antibodies, it does provide an excellent alternative for those patients who fail anti-TNF therapy for SA-UC.

STRUCTURAL FEATURES OF THE 12 NEWLY APPROVED ANTIBODIES

Amino acid sequences for all of the newly US FDA–approved antibodies are available from the World Health Organization (WHO) who oversees the naming process and provide direction for choosing the generic names (or International Nonproprietary Names, INNs) of therapeutics [51]. As a side note, there is a significant change in the naming convention of antibodies [52] that has not impacted antibodies covered in this review, but will impact future antibodies. The WHO collects, catalogues and publishes in their biannual reports the structures of all "named" molecules, including the sequences of monoclonal antibodies and all biologics, which can be accessed on the WHO website under "INN Lists" [51]. The "INN Recommended Lists" (currently at List 90) contains the information on all the antibodies covered in this review (among all the drugs approved in the past and drugs in clinical trials with WHO "approved" names), while the "INN Proposed Lists" (currently at List 129) contains information on drug candidates currently in late-stage clinical trials with proposed names filed at the WHO. These documents significantly help to wade through the confusion or lack of specific information often found in the literature over the exact sequences of antibodies, particularly those that are highly engineered (e.g., glofitamab, discussed in this paper, falls into that category) [51]."

Of the 12 novel antibodies approved by the US FDA in 2023, three are canonical IgG1κ antibodies (Table 1; Fig. 3). Two of these (bimekizumab and lecanemab) had no additional modifications outside of the complementarity determining regions (CDRs), whereas the third, nirsevimab, has incorporated the now-well known "YTE" (M252Y/S254T/T256E) mutations [53, 54] to increase circulating half-life through modulated pH-dependent binding of the Fc to the neonatal receptor (FcRn), which serves, among many functions, to recycle antibodies captured through pinocytosis back into circulation [55] (Table 1). Five of the newly approved antibodies (mirikizumab, rozanolixizumab, pozelimab, retifanlimab, toripalimab) are of the IgG4κ isotype containing the hinge-stabilizing S/P mutation first described by Angal et al. in 1993 [56] (Fig. 3). Additional publications in more recent years have demonstrated the stabilizing capability of this single mutation to the hinge of the human IgG4 [57, 58], which explains its wide use. More recently, it also has been demonstrated that additional mutations can further stabilize the IgG4 hinge, so these may be expected to be featured in future IgG4-based therapeutic antibodies [58]. Of these human and humanized IgG4 antibodies, one (mirikizumab) was additionally modified to significantly reduce FcγR binding and interaction. Many forms of IgG Fc silencing have been introduced over the past 15–20 years or so [59–62], and these have proven to be very popular to reduce the potential for unwanted interactions with the immune system and the possible toxicities that might accompany them [59–62].

Previous to 2023, the FDA had approved eight therapeutic bispecific antibodies, five of which were TCEs linking the T-cell receptor (TCR) component CD3ε to the tumor surface antigen of choice to promote synapse-dependent, T-cell-mediated killing [30, 63]. Note that this number includes tebentafusp (Kimmtrak®), which is a soluble TCR (targeting major histocompatibility complex [MHC] receptor–loaded gp100 peptide; i.e., tumor antigen) × anti-CD3ε [64]. In 2023 alone, the number of TCEs approved by the US FDA increased from 5 to 8, and the total number of FDA-approved therapeutic bispecific antibodies increased from 8 to 12 [30].

One of the newly approved antibodies, elranatamab, is a heterobispecific, bivalent TCE antibody built off of the IgG2κ framework (Fig. 3) [65, 66]. This antibody has mutations in the CH3 domain of each Fc half [19] that promote heterodimerization over homodimerization, pushing the formation of the two Fc halves into heterospecificity [65, 66]. The light chain specificity issue [63] is handled by two compensating mutations, one each in CH1 and CL of the CD3ε binding half (Table 1). Elranatamab is Fc-silenced (Table 1), as mentioned above.

Two of the antibodies approved by the US FDA in 2023 (epcoritamab, talquetamab) are further variations on the heterobispecific, bivalent TCE antibody structure [3, 9, 17]. Epcoritamab is an IgG1κ/λ, Fc-silenced heterobispecific antibody with mutations in the CH3 (Fc' F413L, Fc" K414R) [9], as expected, to drive formation of the heterodimeric Fc over the homodimeric pairing [67] (Table 1). The light chain pairing issue is resolved in this antibody by use of the Duobody-controlled Fab-arm exchange process in which each parental antibody is produced separately, followed by chemical treatment to separate the half Fcs and then reconstitute the heterodimeric bispecific antibody for further purification as described previously [67]. Note that possession of both the κ vs λ light chains in this mAb does not, in itself, ensure the desired light chain specificity. Talquetamab is an IgG4κ/λ S/P stabilized hinge-bivalent, bispecific TCE antibody also produced using the Duobody-controlled Fab-arm exchange process [68]. Talquetamab shares with epcoritamab the use of λ vs κ light chains and Fc-silencing modifications, the latter of which is incorporated into most TCE antibodies [30] (Table 1).

By far the most complex of the newly US FDA–approved antibodies is glofitamab (Columvi™). Glofitamab not only incorporates many of the technologies described above, but also includes the CrossMab technology developed at Roche [45, 46]. That technology allows for the construction of a "2:1" style trivalent, bispecific (e.g., two combining sites for CD20, one for CD3ε) (Table 1, Fig. 3), giving glofitimab a higher avidity on CD20 than found with any of the other FDA-approved IgG-based bivalent bispecific antibodies (Fig. 3).

LEQEMBI® (LECANEMAB-IRMB) (BIOGEN/EISAI)

The first novel antibody approved by the US FDA in 2023 was lecanemab-irmb (Leqembi®), sponsored by Biogen in collaboration with Eisai, for treatment of AD. In January, Leqembi® was granted accelerated approval by the US FDA based on biomarker data from a Phase 2 trial [69].

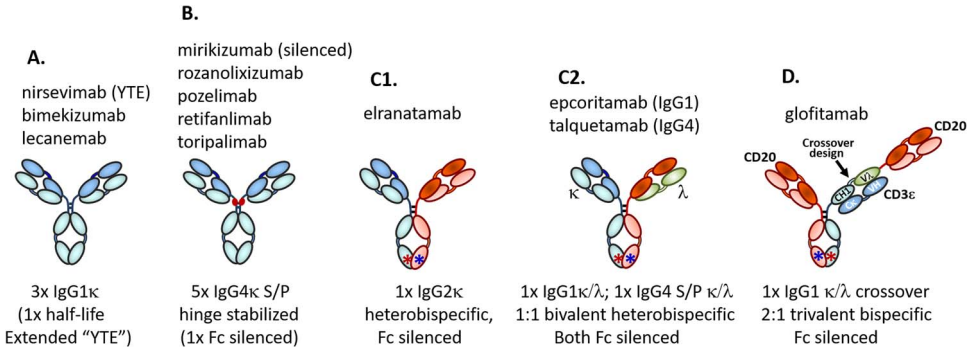

Figure 3. Cartoon showing the generalized structures of the 12 new antibodies approved by the US FDA in 2023. (A) Three of the antibodies are essentially normal IgG1κ types, one of which incorporates the YTE long half-life technology [53]. (B) Five of the new antibodies are of the hinge-stabilized IgG4 isotype, one of which is Fc-silenced; (C) 1. One antibody is a heterodimeric IgG2κ bivalent bispecific antibody; 2. Two antibodies are heterodimeric bivalent bispecific antibodies that incorporate both κ and λ light chains. (D) One antibody is a trivalent heterodimeric, bispecific antibody incorporating Roche's CrossMab technology [45].

By shortly after mid-year, the accelerated approval was upgraded to traditional full approval, based on the results of a Phase 3 confirmatory trial, in which both the primary and secondary endpoints were achieved [70].

AD is the most common form of dementia, resulting in a progressive cognitive and behavioral impairment, most widely found in people over 65 years of age [71]. Since 1991, one of the most prevalent explanations for the pathogenesis of AD has been the "amyloid hypothesis" [72], which can be summarized by the accumulation of amyloid-β (Aβ) peptides (Aβ40 and Aβ42) that develop into neurotoxic senile plaques, additionally promoting the development of tau pathology, the combination of which lead to neuronal cell death and neurodegeneration [72].

In normal subjects, Aβ is generated from amyloid precursor protein (APP) via cleavage by beta and gamma secretases, resulting in the generation of extracellular Aβ peptides of 40 and 42 amino acid lengths [71, 72]. Normally, these peptides are degraded and do not accumulate, but in individuals carrying certain mutations or in older people who have lost the ability to degrade the peptides, they accumulate and ultimately cause disease [71, 72].

The first antibody to be approved by the US FDA for treatment of AD was Aduhelm® (aducanumab), which was approved on 7 June 2021 [73] (Table 2). Aducanumab targets residues 3–7 of Ab [74] and tends to bind the more complex Aβ plaques (Fig. 4) [75], resulting in reduction of plaque volume. As an indication of the expectations for success of Leqembi®, Biogen announced the discontinuation of Aduhelm® on 31 January 2024 to focus its resources on the newly approved Leqembi®. Aduhelm® was originally approved against the advisory committee opinion even though the risk/benefit ratio was not well established. Hopefully, with Aduhelm® being discontinued and replaced by Leqembi®, treatment of AD by anti-Aβ antibodies will start to be improved.

In 2023, lecanemab (trade name, Leqembi®) became the second antibody targeting the amyloid-beta (Aβ) pathway to be approved by the US FDA for treatment of AD. Lecanemab is a humanized IgG1κ antibody derived from Mab 158, which targets residues 1–15 of Aβ42 [74] (Fig. 4). As differentiated from virtually all other clinical stage anti-Aβ mAbs, lecanemab demonstrates preferential binding to the toxic forms of Aβ, including Aβ oligomers and soluble Aβ protofibrils [76] (Fig. 4). Lecanemab binds these toxic oligomers and protofibrils about 10–15-fold greater than its binding to Aβ fibrils and existing plaques [69] and as much as 100-fold over Aβ monomers [78]. This differentiates it significantly from solanezumab, which primarily binds monomers, and aducanumab and gantenerumab, which tend to bind plaques and mature fibrils more avidly (Fig. 4). As illustrated in Fig. 4, It now has become clear that two parameters are key to the success of anti-Aβ antibodies, the first being the actual epitope on Aβ to which the antibody binds and the second, the form of pathogenic Aβ to which the antibody binds *in vivo* [74, 79].

The mouse antibody Mab 158 was derived at the Uppsala University in Sweden as part of the study on the "Arctic" mutation in amyloid-beta precursor protein (APP), which was found to lead to the accumulation of abnormally high levels of toxic amyloid-beta protofibrils [81]. Eisai licensed the antibody and humanized it under the name BAN2401 [82]. In 2014, Eisai signed a collaboration deal with Biogen for the development of lecanemab.

Specifically, Leqembi® was approved for the treatment of patients with mild cognitive impairment or who possess mild dementia [6, 83]. Lecanemab is dosed via the intravenous (IV) route of administration at 10 mg/kg over about an hour of infusion time. With a terminal half-life of 5–7 days and a clearance of 0.434 L/day, lecanemab is dosed every 2 weeks, with steady-state concentrations reached after about 6 weeks [6].

In randomized, double-blinded phase 3 clinical trials, patients suffering from mild dementia treated with Leqembi® achieved statistically significant scores as compared with placebo controls for slowing cognitive decline over an 18-month period, including scores for "Clinical Dementia Rating–Sum of Boxes" (CDR-SB), "Alzheimer's Disease Composite Score" (ADCOMS), "Alzheimer's Disease Assessment Scale" (ADAScog14) and "Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment" (ADCS-MCI-ADL) [84].

Table 2. Examples of anti-amyloid antibodies either FDA approved or in late-stage clinical trials

Antibody	Sponsor	Current status[#]	Specific target	Disease state targeted	Format	Refs
Aduhelm® Aducanumab (BIIB037)	Biogen/ Neurimmune	FDA approved 6/7/21; Discontinued by Biogen on 1/31/24	Aβ 3–7; preferably binds parenchymal Ab over vascular Ab	AD, in patients with mild cognitive impairment or mild dementia	Human IgG1κ	[74, 76]
Leqembi® Lecanemab-irmb BAN2401	Biogen/Eisai Co	FDA approved 1/6/23	Aβ 1–16 preferably binds soluble protofibrils	AD, in patients with mild cognitive impairment or mild dementia	Humanized IgG1κ from MAb 158	[74]
Donanemab	Eli Lilly	Phase 3 (NCT05026866, NCT05508789)	Aβ (p3–42)*	Patients at risk for cognitive and functional decline of AD (presymptomatic)	Humanized IgG1κ from mouse mE8	[74]
Gantenerumab (RG-1450)	Roche/MorphoSys	Phase 2/3 (NCT01760005)	Conformational epitope on Aβ2–11 and Aβ18–27; Amyloid-β fibrils; prodromal AD	Familial AD, early onset AD caused by mutation	Human IgG1κ	[74]
Solanezumab	Eli Lilly	Phase 3 (NCT01760005)	Aβ 16–26; binds mostly Ab monomers	Familial AD, early onset AD caused by mutation; failed large trial in 2020	Humanized IgG1κ	[74, 77]
Remternetug	Eli Lilly	Phase 3 (NCT05463731)	Aβ (N3pG-42)	Early symptomatic AD	Human IgG1κ	None

Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; Refs, references.
*Targets pyroglutamate-3 form of amyloid-β sequence [74]. [#]Example active clinical trials provided for non-approved candidates.

As an example, using the ADAS-Cog14 scoring system, Q2W treatment with 10 mg/kg lecanemab reduced a clinical decline of 47% over an 18-month period as compared with placebo [84]. Concomitant with these cognition measures, patients treated with Leqembi® also showed reductions in brain amyloid burden [84] as well as the rate of development of tau pathology [74]. Leqembi® does not work for everyone. One significant limitation for the use of Leqembi® in treating AD patients is that it does not slow the cognitive decline in patients carrying the APOE4 mutation (in fact, it appears to enhance decline in homozygous APOE4 patients) [85]. Additionally, in one trial, Leqembi® did not slow the cognitive decline in women. These limitations will need to be teased out with additional studies and real-world data analyses.

From a safety perspective, similar to most anti-amyloid-β antibodies, Leqembi® can cause adverse events (AEs) known as "amyloid-related imaging abnormalities-edema" (ARIA-E; brain swelling) and deposition of hemosiderin (ARIA-H; brain hemorrhage) [6, 85]. In one Leqembi® study, symptomatic ARIA occurred in 5/161 (3%) of patients, although symptoms associated with ARIA typically self-resolved in 80% of ARIA-positive patients during the period of observation. The safety profile for Leqembi® is considered manageable [6]. At this point in time, however, it is difficult to say whether Leqembi® will prove over time to provide significant benefit for a wide range of AD patients considering the risks and seemingly narrow range of current clinically meaningful outcomes [85, 86].

EPCORITAMAB AND GLOFITAMAB, CD20 × CD3 BISPECIFIC ANTIBODIES

Diffuse large B-cell lymphoma

Non-Hodgkin lymphoma (NHL) is a malignant disease of the lymph system that can either be indolent, or slowly progressing, or aggressive. Diffuse large B-cell lymphoma (DLBCL) is an aggressive form of NHL that comprises ca. 25–30% of all diagnosed NHL cases. DLBCL typically (e.g., ca. 70% of the time) presents as a fast-growing mass of malignant B cells forming enlarged lymph nodes, although DLBCL also can form in extranodal sites [87].

Treatment of DLBCL has historically included the use of chemotherapy including cyclophosphamide, doxorubicin HCl (hydroxydaunorubicin), vincristine sulfate (Oncovin®) and prednisone (combined, known as "CHOP"). Rituximab (Rituxan®), an anti-CD20 mAb that was approved in 1997 for the treatment of slow growing or indolent NHL [88], was later approved in 2006 by the US FDA to be combined with CHOP (R-CHOP) for treatment of DLBCL [89]. While R-CHOP has become the standard of care for

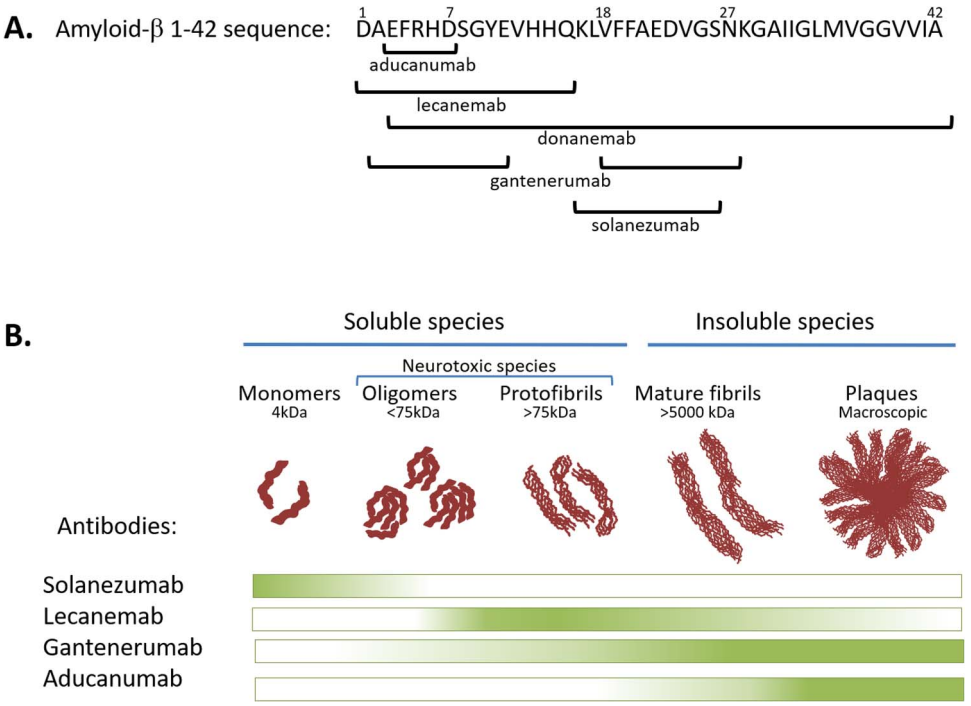

Figure 4. Amyloid structures targeted by anti-Amyloid-β antibodies. (A) The primary amino acid sequence of Aβ1–42 with the epitopes to which leading anti-Aβ mAbs bind. (B) Amyloid quaternary structures to which leading anti-Aβ mAbs bind. Adapted from Lannfelt [80], Soderberg [81] and Loeffler [74].

DLBCL, it also has been recognized that newer treatments were needed both for R-CHOP failures, which can reach 50% [89] and to improve response rates.

Since the first approval of rituximab, the US FDA has now approved a total of 10 novel anti-CD20 antibodies, 7 of them monospecific and 3 (including the two described here) bispecific TCE antibodies [30]. The anti-CD20 × CD3ε TCE antibodies (Table 3), which first burst onto the clinical scene around 2015 [90], represent a true next-generation approach to treatment of B-cell malignancies, which should help revive the market for anti-CD20 cancer antibodies. Both epcoritamab (Epkinly™) and glofitamab (Columvi™) were approved in 2023 for treatment of DLBCL in patients who have failed multiple previous treatments.

The two new anti-CD20 antibodies approved by the US FDA in 2023, epcoritamab and glofitamab, are being approved into a fully mature, albeit not "hot" marketplace. As shown in Fig. 2, the market for anti-CD20 antibodies has been relatively stable, led by the sales of rituximab (Rituxan®), which is now also available as a biosimilar [32, 39–42] and ocrelizumab (Ocrevus®). A noteworthy twist to the anti-CD20 market is that the market for B-cell-depleting oncology mAbs has decreased slightly over the past 5 years, while the overall CD20 market has increased, boosted by the relatively newer use of anti-CD20 antibodies such as rituximab and ocrelizumab in autoimmune diseases [91] (Fig. 2). This trend appears like it might continue, with two of the CD20 × CD3ε TCE antibodies shown in Table 3, mosunetuzumab (NCT05155345) and imvotamab (NCT06041568, NCT06087406), already being tested in clinical autoimmune disease settings.

Table 3 shows clinical examples of CD20 × CD3ε antibodies, including epcoritamab and glofitamab, which were approved for marketing by the FDA in 2023. Of the six antibodies shown in Table 3, half of them are now approved by the FDA. From a structural point of view, mosunetuzumab, epcoritamab and odronextamab are heterodimeric, bivalent bispecific IgGs and plamotamab is a variation of that theme by incorporating an scFV as one arm to help avoid light chain mispairing issues [92]. These antibodies are all monovalent on both the CD20 target side and CD3ε side. Glofitamab, which has the 2:1 structure described earlier, is differentiated significantly from those other antibodies due to its inherent avidity on CD20. Another anti-CD20 × CD3ε antibody differentiated by avidity is imvotamab, which is an IgM bispecific antibody with 10 CD20 binding sites and one CD3ε binding site [93].

These six TCE antibodies (Table 3) represent a highly competitive landscape for next-generation antibodies targeting CD20 [95, 96, 99]. Some of them, such as mosunetuzumab (Lunsumio®), appear to be more efficacious against indolent heme malignancies such as follicular lymphoma (FL), while others, such as glofitamab (Columvi™) and epcoritamab (Epkinly™), have demonstrated better results against aggressive lymphomas such as DLBCL [95, 96] (Table 3).

Epcoritamab

Epcoritamab (GEN3013), marketed under the brand name of Epkinly™ in the USA, is an asymmetric bivalent, bispecific, Fc-silenced human/chimeric IgG1κ/λ Duobody [67]. The structure and reference to the sequence of epcoritamab

Table 3. Advanced CD20 × CD3ε antibodies for B-cell malignancies

Antibody	Sponsor	Status	Primary indications	Dose	DLBCL/ LBCL	R/R FL	Potential AEs	Structure	Refs
Lunsumio® mosunetuzumab-axgb (RG7828)	Genentech/ Roche	FDA approved 12/22/22	R/R FL approved; SLE (Ph 1)	FL: step up to 60 mg SS IV	*N* = 98 ORR = 38% CR = 20%	*N* = 90 ORR 80% CR 60% PR 20% MDOR 22.8 mo	CRS total 39% (grd 3–4, 2.5%); ICANS 1% of patients total; grd 3–4 neutropenia 38%	Asymmetric bivalent, bispecific, Fc silenced IgG1k	[94]
Epkinly™ Epcoritamab-bysp (GEN3013)	Abbvie/- Genmab	FDA approved 5/19/23	R/R DLBCL approved; FL (Ph 3)	DLBCL: step up to 48 mg SC, QW, SS to Q2W; FL: 48 mg + R^2	*N* = 148 ORR 61% CR 38% PR 23% MDOR 15.6 mo	*N* = 101 Epcor + R^2 ORR 97% CMR 86%	CRS total 51% -gr3–4, 2.5%; ICANS 6% mostly grade 1–2; grade 3–4 neutropenia 32%	Asymmetric bivalent, bispecific, Fc silenced human/chimeric IgG1κ/λ	[10, 95]
Columvi™ Glofitamab (RG6026)	Roche	FDA approved 6/15/23	R/R DLBCL NOS, LBCL arising from FL approved	DLBCL: step up to 30 mg IV Q3W SS	*N* = 132 ORR 56% CR 43% PR 13% MDOR 18.4 mo	*N* = 24 ORR 79% CR 71%	CRS total 70% (grade 3–4 = 4%) ICANS 4.8% of all patients; grade 3–4 neutropenia 26%	Asymmetric trivalent, bispecific (2:1), Fc silenced humanized IgG1κ/λ	[12]
Odronex-tamab (REGN1979)	Regeneron	Phase 3	Oncology (NHL, CLL)	R/R DLBCL: step up and split dosing to 160 mg QW	*N* = 140 ORR 49% CR 31% MDOR 17.9 mo	*N* = 131 ORR 82% CR 75% MDOR 20.2 mo	CRS total 55%; neutropenia 40%; pyrexia 31%	Asymmetric bivalent, bispecific, Fc-silenced human IgG4κ	[95, 96]
Plamotamab (Xmab13676)	Janssen/ Xencor	Phase 1	Oncology (CLL; WM)	Step up protocol with dosing not defined	*N* = 25 ORR 47% CMR/CR 26%	*N* = 6 ORR 100% CMR/CR 50%	CRS total 57%; grd 3+ neutropenia 7%	Asymmetric bivalent, bispecific, Fc silenced IgG1-like with FAb on CD20 binding arm, scFv on the anti-CD3ε side	[97]
Imvotamab (IGM2323)	IGM Biosciences	Phase 1/2	RA, SLE	100 or 300 mg plateau dose	*N* = 6 ORR = 50% CR = 50%	*N* = 3 ORR = 66% CR = 66%	CRS total 19%; grd 3+ neutropenia 0%	IgM with 10 CD20-binding arms and a single anti-CD3ε binding arm	[98]

Abbreviations: CLL, chronic lymphocytic leukemia; CMR, complete metabolic response; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ICANS, immune effector cell–associated neurotoxicity syndrome; IV, intravenous infusion; LBCL, large B-cell lymphoma (arising from FL); MDOR, median duration of response; NHL, non-Hodgkin lymphoma (all forms); NOS, not otherwise specified; ORR, overall response rate; Ph, clinical phase; R^2, rituximab plus lenalidomide; RA, rheumatoid arthritis; Refs, references; SC, subcutaneous; SLE, systemic lupus erythematosus; SS, steady state; WM, Waldenström macroglobulinemia. Rounded to the nearest whole number. Abstracted from drug prescription information documents, Jin et al. [95], Russler-Germain et al. [96], Davis et al. [99] and others as referenced.

are provided in Table 1. This antibody, which was discovered at Genmab [67], is assembled after upstream production by a process known as controlled Fab arm exchange (FAE) as noted above [67]. For FAE, each parental antibody, one anti-CD20 and the other anti-CD3ε, is oxidized individually, the two antibodies are mixed and then reduced, with the mutations in CH3 (F413L on the CD3ε side, K414R on the CD20 side; see Table 1) driving heterologous Fc formation over parental IgG reformation [67].

As shown in Table 3, epcoritamab (Epkinly™) has been granted accelerated approval by the US FDA for treatment of relapsed or refractory (R/R) DLBCL, based on an objective response rate (ORR) of 61% and a complete remission (CR) rate of 38% such as achieved in clinical trial EPCOR NHL-1, which a median duration of response (MDOR) of 15.6 months [10]. Additional trials achieved similar results [95]. These efficacy data compare favorably with the other CD20 × CD3ε antibodies (Table 3). Full approval for Epkinly™ will require continued efficacy in confirmatory trials currently underway.

For treatment of FL, epcoritamab + R^2 (rituximab and lenalidomide) resulted in very promising ORR of 97% with a CMR of 86%. Phase 3 clinical trials testing treatment of FL with epcoritamab with or without R2 are continuing (e.g., NCT05409066) [100].

From a safety standpoint, patients treated with epcoritamab had a total rate of cytokine release syndrome (CRS) of 51%, with 2.5% of patients experiencing grade-3+ CRS (Table 3) [10]. Neurotoxicity, as evidenced by immune effector cell-associated neurotoxicity syndrome (ICANS), occurred in a total of 6.1% of patients, mostly at grades 1–2. Grades 3–4 leukopenia also occurred in 32% of all patients dosed (Table 3) [10]. The AEs were considered manageable, with CRS being managed at least in part by the step-up dosing used at the initiation of the dosing regimen.

Epcoritamab is dosed via the subcutaneous route of administration with a T_{max} of 4 days after the first dose and 2.3 days after the end of dose cycle 3 [10]. SC dosing of epcoritamab may give it a dosing convenience advantage over glofitamab, which is currently approved only for IV dosing. The half-life in the terminal elimination phase for epcoritamab was 22 days after the third cycle of dosing, with a clearance (CL) of 0.53 L/d [10], which is a significantly longer half-life than observed with most antibodies with a CL that high [101]. Anti-drug antibody (ADA) response was low at about 2.6% [10].

Glofitamab

Glofitamab (Columvi™), also known as RG6026, is a trivalent, bispecific IgG1κ/λ-based antibody with two combining sites targeting CD20 and one targeting CD3ε [87, 91] (Fig. 3). This configuration, with proper cognate heavy/light chain pairing, is achieved via cross-over, chain-swapping technology [45, 46, 87, 102] combined with an asymmetric Fc generated using a modified version of knobs-into-holes technology [104]. The structure and reference to the sequence of glofitamab are provided in Table 1.

As shown in Table 3, glofitamab (Columvi™) has been granted accelerated approval by the US FDA for treatment of relapsed or refractory (R/R) DLBCL, based on an ORR of 56% and CR of 39–43%, exemplified by Study NP30179, with an MDOR of 18.4 months [12]. Additional trials achieved similar results [95, 103] and, similar to epcoritamab, these efficacy data compare favorably with the other CD20 × CD3ε antibodies (Table 3). Full approval for Columvi™ will require continued efficacy in confirmatory trials currently underway.

Patients treated with glofitamab had a total rate of CRS of 63–70%, with 4% of patients experiencing grade-3+ CRS (Table 3) [12, 103]. ICANS occurred in a total of 4.8% of patients, mostly at grades 1–2. Grades 3–4 leukopenia also occurred in 26% of all patients dosed (Table 3) [12]. The AEs were considered manageable, with CRS being managed at least in part by the step-up dosing used at the initiation of the dosing regimen.

Glofitamab is dosed via the IV route of administration [12]. The half-life in the terminal elimination phase for glofitamab was 7.6 days, significantly shorter than epcoritamab [10], with a volume of distribution of 5.6 L and a relatively high CL rate of 0.617 L/d [12]. ADA response was low at about 1.1% [12].

ZYNYZ® (RETIFANLIMAB-DLWR) AND LOQTORZI™ (TORIPALIMAB-TPZI) (ANTI-PD-1)

General for PD-1

PD-1, first described in detail in 1992 [105], is a checkpoint receptor found on activated T- and B-lymphocytes that binds the ligand PD-L1 typically expressed on antigen-presenting cells [106] as well as tumor cells [107]. In its normal role, PD-1 acts as a brake on immune response by suppressing inflammatory T-cell activity to help prevent autoimmune reactions [106]. Unfortunately, many forms of cancer have co-opted the PD-1/PD-L1 regulatory axis by over-expressing PD-L1 to prevent T cells from killing the cancer cells [107]. The importance of this T-cell evasion pathway (as well as the CTLA4 pathway) has been exemplified by the awarding of the 2018 Nobel Prize in Medicine to Tasuko Honjo and James P Allison for their discoveries of cancer therapy by inhibition of negative immune regulation pathways [108].

Pembrolizumab (Keytruda®), sponsored by Merck and Co., was the first anti-PD-1 inhibitory mAb approved by the FDA when it was approved for the treatment of metastatic melanoma on 4 September 2014 [109, 110]. Shortly thereafter, nivolumab (Opdivo®), a second anti-PD-1 mAb sponsored by Bristol-Myers Squibb (BMS), was also approved by the US FDA for treatment of metastatic melanoma [103, 105]. Since then, indications approved for both Keytruda and Opdivo® have been expanded significantly [110, 111].

By the beginning of 2023, four anti-PD-1 and three anti-PD-L1 antibodies had been approved by the US FDA for various cancer indications [30]. Retifanlimab (Zynyz®) and toripalimab (Loqtorzi™), both approved in 2023 (Table 1), represent the fifth and sixth anti-PD-1 inhibitor mAbs approved by the US FDA. Additionally, there are at least 19 additional monospecific or bispecific anti-PD-1 antibodies in late-stage (Phase IIb, Phase III) clinical trials [30], many

of which will likely be submitted for approval within the next few years. As can be seen in Fig. 2, these new anti-PD-1 antibodies are entering a very hot market, i.e., significant well-embedded competition, that is currently valued at about $40 billion/year gross worldwide sales, making up ca. 16% of all antibody sales worldwide.

Retifanlimab (Zynyz®) and toripalimab (Loqtorzi™) are both hinge-stabilized (S/P; 56) IgG4κ isotype antibodies (Table 1), which is currently the preferred IgG format for anti-PD-1 antibodies (e.g., nivolumab [BMS], pembrolizumab [Merck], cemiplimab [Regeneron] and sintilimab [Innovent] are internationally approved anti-PD-1 IgG4 S/P antibodies) [112]. The current thinking is that Fcγ receptor activity is likely not to be an asset in therapeutically blocking PD-1 and may be a liability [112].

Zynyz®

Retifanlimab (Zynyz®), previously known as Macrogenics MGA012 (aka INCMGA00012), binds to the PD-1 receptor, blocking interaction with its ligands PD-L1 and PD-L2, which potentiates T-cell activity [113]. Retifanlimab was granted accelerated approval based on results from the POD1UM-201 trial (NCT03599713) for the treatment of metastatic or recurring MCC, a rare (e.g., 2000–3000 new cases are diagnosed each year in the USA) but aggressive neuroendocrine form of skin cancer [114]. American folk singer Jimmy Buffett died of MCC in 2023 after battling the disease for 4 years.

In the POD1UM-201 open-label, single-arm clinical trial evaluating 65 patients, retifanlimab (Zynyz®) achieved an ORR of 52%, a CR of 18% and a partial response (PR) of 34%. A formal MDOR was not achieved in that trial, but over 50% of the patients treated had a DOR of >12 months [8].

The half-life in the terminal elimination phase for retifanlimab was 19 days, with a clearance of 0.24 L/d, the half-life of which is consistent with other approved antibodies (e.g., siltuximab, pertuzumab) with clearance rates in that range [101]. ADA response was low at about 3%. SAEs occurred in 22% of patients receiving retifanlimab [8].

Toripalimab (Loqtorzi™)

Toripalimab-tpzi (Loqtorzi™), also known as JS001, binds PD-1 and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of T-cell activation [115]. Toripalimab, which possesses an unusually long-heavy-chain complimentary determining region-3 (CDR-H3), binds PD-1 in the FG loop in a PD-1-glycosylation-independent manner [116]. This epitope differentiates toripalimab from both prembrolizumab and nivolumab, which bind to the C'D loop and N-terminal loop epitopes, respectively [116].

Toripalimab (Loqtorzi™), sponsored in the USA by Coherus BioSciences, was granted full approval in the USA for treatment of metastatic or with recurrent, locally advanced NPC, a relatively rare (0.7% of all cancers, with 133,354 new cases worldwide in 2020) but malignant-prone cancer [117]. NPC has significantly higher incidence rates in Asian, particularly Chinese, populations, which account for over 70% of new cases [117]. Loqtorzi® is approved for first-line therapy in combination with cisplatin and gemcitabine and as a single agent for later lines [28, 118]. In the POLARIS-02 open label, multicohort clinical trial of 172 NPC patients (NCT02915432), single-agent Loqtorzi® achieved an ORR of 21%, a CR of 2.3% and a PR of 19%, with an MDOR of 14.9 months [28, 118].

The half-life in the terminal elimination phase for toripalimab was 10 days for the first dose and 18 days at steady state, with a CL of 0.36 L/d, which is a significantly higher CL rate and terminal shorter half-life than observed with either pembrolizumab or nivolumab, the leading anti-PD-1 antibodies [101]. ADA response was low at about 3.4–3.7% [28].

Toripalimab had previously been approved by the China National Medical Products Administration in 2018 for treatment of melanoma [119]. Importantly, Loqtorzi™ is the first innovative antibody drug discovered and developed in China to be approved for marketing in the USA.

BIMZELX® (BIMEKIZUMAB) (ANTI-IL-17AF)

Plaque psoriasis and IL-17 cytokines

Plaque psoriasis (PsO) is a relatively common chronic autoimmune disease of the skin that affects ca. 2–5% of the adult population, ca. 20% of which is in the moderate-to-severe category [120, 121]. PsO is characterized by itchy, scaly patches of thick, reddish skin, and while PsO is not considered a life-threatening disease, it is very uncomfortable and can significantly affect quality of life. The first biologic approved to treat PsO was alefacept (Amevive®), an Fc fusion protein containing the CD2-binding domain of lymphocyte function–associated antigen-3 (LFA-3) [122]. This was followed by approval of the anti-TNF-α biologics, in 2003 and 2004, respectively, etanercept (Enbrel®) and infliximab (Remicade®), for treatment of PsO, followed later by other anti-TNFs, the anti-IL-12/23 mAb, ustekinumab (Stelara®) in 2009 and finally, the anti-IL-17 mAbs. The first anti-IL-17A mAb to be approved in the USA for treatment of PsO was secukinumab (Cosentyx®), approved in 2015. Prior to 2023, at least 14 biologics, mostly in the anti-TNF, anti-IL-17 and anti-IL-23 families, have been approved in the USA for treatment of PsO [121], with a total of $26B in sales in 2022 (see Fig. 2), making this area a hot and highly competitive market for new entries (see Fig. 2).

The IL-17 family of pro-inflammatory cytokines has six structurally related members, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (aka IL-25) and IL-17F, that play a significant role in resistance to infection, particularly fungal infection [123]. IL-17A, the prototype of the family also referred to as "IL-17," is generated by a subset of activated CD4-positive T-cells, called TH17 cells, under inflammatory conditions. IL-17A and IL-17F share about 55% sequence identity at the amino acid level [124]. IL-17A is produced primarily by TH17 T cells, whereas IL-17F is produced by T cells, innate immune cells and epithelial cells (broader distribution) [125]. IL-17A and IL-17F each can form homodimers,

but also can form IL-17AF heterodimers, which is unique among the IL-17 family members [126]. IL-17A, IL-17F and IL-17AF heterodimers all signal through the same multimeric receptor, which includes the IL-17 receptor A (IL-17RA) subunit and the IL-17RC subunit [127]. IL-17A has a higher affinity than IL-17F for IL-17RA, which is widely expressed and expressed largely in lymphocytes and induces the expression of proinflammatory cytokines, whereas IL-17F binds better to IL-17RC, a receptor predominantly expressed in non-hematopoietic cells [126, 127].

IL-17F levels have been demonstrated to be as much as 30-fold higher than IL-17A levels in psoriatic tissues [128], and antibodies directed against IL-17F, but not IL-17A, suppressed development of colitis in animal models [128], demonstrating some potential differences in their contribution to pathology. Currently FDA-approved anti-IL-17A antibodies such as secukinumab (Cosentyx®) and ixekizumab (Taltz®), both of which are approved for treatment of PsO, block only IL-17A homodimer, and they would also be expected to block the IL-17AF heterodimer, but neither would block the IL-17F homodimer, which may lead to undertreatment considering the high levels of IL-17F in psoriatic tissues. One pre-2023 approved antibody, brodalumab (Siliq®), binds to IL-17RA and blocks the binding of both IL-17A and IL-17F to that receptor [120, 129]. In *in vitro* preclinical studies, bimekizumab, originally known as UCB4940, demonstrated better control of cytokine release and neutrophil migration than blocking either IL-17A or IL-17F alone [130].

Bimzelx®

Bimekizumab (Bimzelx®) was granted full approval in the USA for treatment of PsO based on data from several clinical trials including BE ABLE 1, BE ABLE 2, BE READY, BE VIVID, BE SURE and BE RADIANT [48]. Across multiple trials with over 1300 patients of different weights, psoriasis area and severity index (PASI) 90 and PASI 100 scores for bimekizumab (Bimzelx®) averaged ca. 87% and 62%, respectively [24]. At week 52 of treatment in the BE VIVID study (NCT03370133), patients treated with bimekizumab achieved significantly higher response rates (PASI 90/100, 81.6%, 64.2%, respectively) than those treated with ustekinumab (PASI 90/100, 55.8%, 38%) ustekinumab, $p < 0.001$, respectively) [131, 132]. Additionally, in a recent meta-analysis of clinical trials for biologics treating PsO, bimukizumab (Bimzelx®, anti-IL-17AF), infliximab (Remicade®, anti-TNF-α), ixekizumab (Taltz®, anti-IL-17A) and risankizumab (Skyrizi®, IL-23p19) were found to be the four most effective biologics tested, while maintaining similar levels of serious AEs (SAEs) [129].

Bimekizumab had a good safety profile, with mostly mild-to-moderate infections (36% in treated vs 22.5% in untreated patients) being the most relevant side effect. Bimekizumab is administered SC with a bioavailability of ca. 70% and a T_{max} of 72–96 h [24], both values of which are typical for SC-delivered mAbs [101]. The half-life in the terminal elimination phase for bimekizumab was 23 days, with a CL of 0.337 L/d. ADA response was fairly significant, with nearly half (45%) of all patients administered with the drug experiencing at least some ADA response. Of those, 34% had neutralizing antibodies (NADA), although no apparent NADA-related change in efficacy, PK or safety was observed in those patients [24].

OMVOH™ (MIRIKIZUMAB-MRKZ)—IL-23P19

Ulcerative colitis

Ulcerative colitis (UC) is a chronic, autoimmune-related inflammatory bowel disease (IBD) that results in inflammation and formation of ulcers in the digestive tract [133]. While ulcerative colitis is not typically considered a fatal disease, it is a serious disease that can severely decrease quality of life. Additionally, complications as a result of having severe UC can be life-threatening. In 2005, the first biologic approved for the treatment of ulcerative colitis was infliximab (Remicade®), an anti-TNF-α mAb originally approved by the US FDA in 1998 for treatment of Crohn's disease (CD). There are currently five biologics approved for treatment of UC and severe acute UC (SA-UC), including three anti-TNF-α antibodies (infliximab [Remicade®], adalimumab [Humira®] and golimumab [Simponi®]) (and their biosimilars), an integrin receptor antagonist, vedolizumab (Entyvio®) and the anti-IL-12/23 dual antagonist, ustekinumab (Stelara®) [133]. No IL-23p19 mAbs have been approved prior to 2023 for treatment of UC or SA-UC [133].

IL-23, a member of the IL-12 four-helix bundle family of cytokines, is a heterodimeric cytokine comprised of a novel p19 subunit bound to IL-12p40 that functions to promote expansion of T helper type 17 (TH17) cells [134]. IL-23 binds to a heterodimeric receptor comprised of its cognate IL-23R subunit and IL-12Rβ1, the latter of which is also shared with IL-12 [135]. Research in animal models has shown that pharmacologic inhibition of IL-23p19 can ameliorate intestinal inflammation. Blocking IL-23 has been demonstrated to have therapeutic effects for autoimmune diseases such as PsO, inflammatory bowel disease and rheumatoid arthritis. Previous to 2023, there is one FDA- approved therapeutic antibody that bind both IL-12 and IL-23 via the p40 subunit (Ustekinumab [Stelara®], approved in 2009 [136]) and three approved antibodies binding to IL-12p19, including guselkumab (Tremfya®, approved 2017 [137]), tildrakizumab (Ilumya®, approved 2018 [138]) and risankizumab (Skyrizi®, approved 2019 [139]). Current indications approved for the anti-IL-23p19 antibodies include: Ilumya®, for treatment of moderate-to-severe PsO [138], Tremfya®, for treatment of PsO and active psoriatic arthritis (APsA) [137] and Skyrizi®, for treatment of PsO, APsA and moderate-to-severely active CD [139]. Stelara®, which targets both IL-12 and IL-23, is approved for treatment of PsO, APsA and CD, as well as moderate to severely active UC [136].

Omvoh™

Mirikizumab-mrkz (Omvoh™) is a humanized, silenced IgG4 mAb (Table 1) that is directed against the p19

subunit of IL-23 [140]; as with the other IL-23p19-targeted mAbs, it does not bind IL-12. It was approved by the FDA for the treatment of moderately to severely active ulcerative colitis (SA-UC). As mentioned earlier, the only IL-23 binder previously approved for this indication is the IL-12/23 dual binder, Stelara®. Thus, mirikizumab offers an IL-23-specific alternative for TNF failures in SA-UC.

Safety and efficacy of mirikizumab (Omvoh™) for treatment of SA-UC patients who had failed previous tofacitinib and biologic treatments were evaluated in two randomized, double-blinded, placebo-controlled clinical trials, an induction study, Lucent-1 (NCT03518086), and a maintenance study, Lucent-2 (NCT03524092) [141]. Scores for clinical remission, clinical response, endoscopic improvement and histologic-endoscopic mucosal improvement were 10%, 22%, 14% and 11% over placebo control scores at 12 weeks, respectively [26]. While these response rates cannot be compared directly with the response rates achieved by the other biologics used to treat SA-UC, there are clinical trials planned (LUCENT-ACT) or underway (VIVID-1) to assess head-to-head efficacy vs vedolizumab and ustekinumab, respectively.

Mirikizumab had a good safety profile, with infection rates only slightly higher than placebo controls [26]. A few patients experienced nasopharyngitis or arthralgia, although the incidence of these AEs was only slightly higher than placebo controls.

Mirikizumab is administered SC with a bioavailability of ca. 44%, which is rather low for SC-administered mAbs, and an average T_{max} of 5 days [26]. The half-life in the terminal elimination phase for mirikizumab was 9.3 days, with a CL of 0.55 L/d [26], both of which are significantly poorer than other anti-IL-23 mAbs such as risankizumab (>21d $T_{1/2}$) [142] and guselkumab (ca. 15d $T_{1/2}$) [143]. ADA response was moderate, with ca. 23% of all patients (88/378 total patients) administered with mirikizumab in the UC-1 and UC-2 trials experiencing at least some ADA response. Of these, 38% had what was considered to be "high titer" responses and 10 patients experienced systemic drug loss apparently due to ADAs [26].

NEW FDA-APPROVED ANTIBODIES TARGETING MULTIPLE MYELOMA (TALVEY™ AND ELREXFIO™)

Antibody treatments for multiple myeloma

Multiple myeloma (MM), also known historically as Kahler's disease, accounts for ca. 1.8% of all human cancers, with ca. 32,000 new patients in the USA in 2020 [144]. MM, which is rising in incidence, is a B-cell malignancy caused by uncontrolled expansion of plasma cells in the bone marrow. MM cells produce what is known as M proteins, monoclonal antibodies or fragments thereof that have no specific function [144]. The earliest stage of plasma cell differentiation into MM is called monoclonal gammopathy of undetermined significance (MGUS), which can develop into smoldering (or asymptomatic) MM, which can lead to MM. In MM, the expanding MM cells crowd out both normal red and white blood cells in the bone marrow, leading to anemia and infections, respectively [130]. The accumulation of MM cells in bone marrow also leads to bone pain, fractures (especially of the spine) and loss [145]. MM cells also produce copious quantities of IgG or IgM M protein, which can cause lead to anemia, infections, peripheral neuropathy, renal failure and other symptoms [145].

Since its approval in 2015, the anti-CD38 antibody daratumumab (Darzalex®) has been the standard in antibody treatment of MM [146]. While daratumumab has been a significant addition to the armament for treatment of MM, many patients are either resistant to the drug or become resistant to it. Additionally, daratumumab is known to cause fratricide of healthy NK and T cells, which can, at least theoretically, reduce its effectiveness [147]. Thus, there has been a significant effort to find alternative antibody targets for treatment of MM. Over recent years, such targets have included BCMA, CD33 and GPRC5D. In 2023, two new bispecific, TCE antibodies were approved by the US FDA for treatment of MM, Elrexfio™ (elranatamab-bcmm), a BCMA × CD3ε TCA and Talvey™ (talquetamab-tgvs), a GPRC5D × CD3ε TCE (Tables 1 and 4; Fig. 3).

Elrexfio (elranatamab-bcmm) BCMA × CD3 MM

B-cell maturation antigen (BCMA), also known as tumor necrosis factor receptor superfamily 17 (TNFRS17) [148], is preferentially expressed on long-lived plasma cells and memory B cells, as well as MM cells. The expression of BCMA on MM cells has made it a target of interest for MM for several years. As its name suggests, it is expressed primarily on mature B lymphocytes and functions as the receptor for B-cell activating factor (BAFF, aka CD257, TNFSF138, BLyS) [149]. A second BCMA ligand, a proliferation-inducing ligand (APRIL, aka CD256, TNFSF13), also has been identified that is highly elevated in MM [149]. Previous anti-BCMA antibodies approved for treatment of MM include belantamab mafodotin (Blenrep®), an antibody-drug conjugate (ADC) comprised of an afucosylated anti-BCMA IgG antibody conjugated via a noncleavable linker to monomethyl-auristatin F (J6M0-mcMMAF) approved in 2020 [150], and teclistamab-cqyv (Tecvayli®), a bispecific T-cell engager (TCE) approved in 2022 [151]. Additionally, many other anti-BCMA antibodies, TCEs and CAR-Ts are currently being tested in clinical trials for treatment of MM [152, 153], demonstrating the importance of this antigen as a target for MM.

Elranatamab-bcmm (Elrexfio™), also known as PF-06863135, is a humanized, Fc-silenced IgGκ-based bivalent, bispecific BCMA × CD3 TCE. Elranatamab is derived from two "parental" monoclonal antibodies (mAbs), an anti-BCMA mAb and an anti-CD3ε mAb [154]. Both sides of the heterodimeric Fc have been mutated to dampen the ability of the antibody to bind Fc receptors and complement (Table 1) [154]. Elranatamab, which had been granted Breakthrough Therapy Designation as well as Orphan Drug Designation, was granted accelerated approval by the US FDA based on the results of a single-arm Phase 2 trial called the MagnetisMM-3 (NCT04649359) trial [20, 154]. As with all accelerated

Table 4. Approved and clinical late-stage antibodies for multiple myeloma

Antibody	Sponsor	Specific target	Current status*	Clinical response	SAEs	Format	Refs
Darzelex® Daratumumab	J&J/ Genmab	CD38	FDA approved 11/16/15	D-VMP (N = 350) vs VMP (N = 356) ORR: DVMP 91% vs 74% VMP alone MRD: DVMP 78% vs VMP 22%	NA	Human IgG1κ	[155]
Empliciti® Elotuzumab	BMS/ Abbvie	SLAMF7	FDA approved 11/30/15	ELD (N = 321) vs LD (N = 325) ORR: ELD 78.5% vs LD 65.5% mPFS: ELD 19.4 mo vs LD 14.9 mo	NA	Humanized IgG1κ	[156]
Sarclisa® Isatuximab-irfc	Sanofi	CD38	FDA approved 03/02/20	IsaPD (N = 154) vs PD alone (N = 153) ORR: IsaPD 60% vs 35% PD alone mPFS: IsaPD 12 mo vs 6 mo PD alone	NA	Chimeric IgG1κ	[157]
Tecvayli® Teclistamab-cqyv	J&J	BCMA × CD3ε	FDA approved 10/25/22	N = 110 ORR: 62% CR: 28% MDOR: 9 mo	CRS: 72% all grades NT: 25% all grades	Bivalent, bispecific IgG4 S/P-AA	[47, 158, 159]
Elrexfio™ Elranatamab-bcmm	Pfizer	BCMA × CD3ε	FDA approved 8/14/23	N = 97 ORR: 58% CR: 26% MDOR: NR, 74% at 12 mo mPFS: 57% at 12 mo	CRS: 58% all grades NT: 59% all grades ICANS: 3.3%	Humanized/human heterodimeric, bivalent bispecific IgG2κ	[20, 47, 159]
Talvey™ Talquetamab-tgvs	J&J	GPRC5D × CD3ε	FDA approved 8/9/23	N = 100 ORR: 74% sCR + CR: 33% Combined PR: 41% MDOR: 9.5 mo	CRS: 75–79% all grades	Humanized heterodimeric, bivalent bispecific IgG4κ/λ S/P	[18, 47, 159]
Linvoseltamab (REGN5458)	Regeneron	BCMA × CD3ε	Phase 3 (NCT05730036)	N = 252 ORR: 64% (200 mg dose) CR: NA MDOR: NR	CRS: 37% all grades	Human heterodimeric, bivalent bispecific IgG4κ S/P	[159]
Alnuctamab (BMS-986349; CC-93269)	Celgene	BCMA × CD3ε	Phase 3 (NCT06232707; not yet recruiting)	N = 26 (at 30 mg target dose) ORR: 65% CR: 19% MDOR: 33.6 mo (all doses and ROAs)	CRS: 76% all grades	Asymmetric trivalent, bispecific (2:1) design	[160, 161]
ABBV-383 (formerly TNB-383B)	Abbvie (Teneo-Bio)	BCMA × CD3ε	Phase 3 (NCT06158841; not yet recruiting)	N = 122 ORR: 68% (doses ≥40 mg) VGPR: 43% MDOR: NA	CRS: 57% all grades and all doses	Human IgG-like bispecific with one Fab arm (CD3ε) and two VHH (BCMA) on the other arm	[162, 163]

Note: Tapia-Galisteo et al. [153] provide a more in-depth look at earlier stage molecules. Abbreviations: BCMA, B-cell maturation antigen; CR, complete response; CRS, cytokine release syndrome; D-VMP, Darzalex® in combination with bortezomib, melphalan, and prednisone; ELD, Empliciti® in combination with lenalidomide and dexamethasone; FDA, (US) Food and Drug Administration; ICANS, immune effector cell-associated neurotoxicity syndrome; IsaPD, Sarclisa®, pomalidomide and dexamethasone; LD, lenalidomide and dexamethasone alone; MDOR, median duration of response; N, number of patients evaluated; mo, months; NA, not applicable; NT, neurotoxicity; ORR, overall response; PD, pomalidomide, and dexamethasone; PFS, progression-free survival; PR, partial response; Refs, references; ROAs, route of administration; sCR, stringent CR; S/P, IgG4 modified stabilized hinge (as described in text); VGPR, very good partial response; VHH, single heavy-chain domain antibody; VMP, bortezomib, melphalan and prednisone alone.
*Example active clinical trials provided for non-approved candidates.

approvals, continued approval will be based on the results of confirmatory clinical trials.

Table 4 shows high-level clinical data obtained with the various antibody therapeutics for treatment of MM. The anti-CD38 antibody data shown are differentials between standard of care (SOC) and SOC plus the anti-CD38, so those data are not directly comparable to the elranatamab data. The three BCMA × CD3ε bispecific antibodies, including elranatamab, all have ORRs ranging from 58% to 64% (Table 4). Treatment with teclistamab and elranatamab resulted in 28% and 26% CRs, respectively. Treatment with elranatamab resulted in 58% CRS, 59% neurotoxicities and 3.3% ICANS, in line with, or better than, the other approved MM bispecific antibodies (Table 4). Because of the risk due to the SAEs associated with the use of elranatamab to treat MM, Elrexfio™ is available only through a restricted program called the ELREXFIO Risk Evaluation and Mitigation Strategy (REMS).

ADAs against elranatamab were observed in about 9% of patients dosed in clinical trials, with about 60% of those being neutralizing, although the effect of the ADAs on PK and PD is as yet unknown [20]. Elranatamab is dosed at 76 mg by the subcutaneous route of administration with a systemic bioavailability of ca. 56% and a T_{max} of 7 days [20]. The volume of distribution at steady state (Vss) was 7.76 L, and the CL was 0.324 L/day, resulting in a terminal phase half-life of 22 days [20], all within the "average" range for therapeutic antibodies [101].

Talvey™ (talquetamab-tgvs) GPRC5D × CD3 MM

A relatively new target for MM on the horizon was identified in 2013 by profiling gene expression in MM cells versus cells from other hematological malignancies [164]. The new target, G protein-coupled receptor class C group 5 member D (GPRC5D), is a member of the 7-pass membrane spanning G protein-coupled receptor (GPCR) family [165]. Even in MM cells, GPRC5D is expressed at low levels, e.g., 191–1271 receptors per cell [165], which would make this a relatively poor target for antibody-dependent cellular cytotoxicity (ADCC)/compliment-dependent cytotoxicity (CDC)/antibody-dependent cellular phagocytosis (ADCP)-based approaches similar to the use of daratumumab to target CD38. On the other hand, highly sensitive approaches such as TCE [165] and CAR-T [166] approaches would still be able to target this low-expressed antigen. One significant advantage of GPRC5D over other MM targets is that, by nature of it being a GPCR, it is not shed from the membrane like many other cell surface targets such as BCMA [165]. To date, only a few CAR-T cell approaches (e.g., CAR-GPRC5D, BCMA-GPCRC5D CAR-T, MCARH109, OriCAR-017) [167] and four antibodies (i.e., talquetamab, QLS32015, BMS-986393, AZD0305) have been in clinical trials for treatment of MM by targeting GPRC5D, either alone or with BCMA.

Talquetamab-tgvs (Talvey™) is a bivalent, bispecific TCE antibody that binds to the CD3ε receptor expressed on the surface of T-cells with one Fab arm, with the other Fab arm binding GPRC5D expressed on the surface of MM cells and non-malignant plasma cells, as well as healthy tissues such as epithelial cells in keratinized tissues of the skin and tongue [168]. Talvey™, which had previously been granted Orphan Drug Designation, was granted accelerated approval by the US FDA for treatment of MM. As with all accelerated approvals, continued approval will be based on the results of confirmatory clinical trials.

As can be seen in Table 4, the patient group treated with talquetamab achieved an ORR of 74% and a stringent CR (sCR) of 20%, with an MDOR of 9.5 months. Additionally, CRs, very good PRs and PRs were achieved in 13%, 25% and 16% of patients treated. These data are consistent with results obtained with BCMA × CD3ε TCEs (Table 4).

SAEs occurred in 47% of patients who received talquetamab, including CRS (13%), bacterial infection (8%) including sepsis and pyrexia (4.7%), ICANS (3.8%), SARS-CoV2 infection (2.7%), neutropenia (2.1%) and upper respiratory tract infection (2.1%) [18]. Because of the risk due to the SAEs associated with the use of talquetamab to treat MM, Talvey is available only through a restricted program called the Talvey Risk Evaluation and Mitigation Strategy (REMS).

ADAs against talquetamab were observed in about 18–25% of patients dosed in clinical trials, although there did not appear to be any clinical manifestations (e.g., changes in PK, PD, efficacy, safety) of the ADA responses [18].

After step-up dosing, talquetamab is dosed at 0.8 mg/kg mg Q2W by the subcutaneous route of administration with a systemic bioavailability of ca. 59% and a T_{max} of 3.7 days [18]. The Vss was 10.1 L, and the clearance was 0.9 L/day, resulting in a terminal phase half-life of 8.4 days [18]. The CL ranks among the highest for IgG-like antibodies [101], suggesting that target-mediated clearance may possibly be involved.

RYSTIGGO® (ROZANOLIXIZUMAB-NOLI)—FCRN-ALPHA SUBUNIT

A subset of autoimmune diseases is characterized by the presence of autoantibodies against specific human (self) proteins. These antibody-mediated autoimmune diseases include generalized myasthenia gravis (gMG), which is characterized by the presence of pathogenic antibodies binding the acetylcholine receptor (AChR) [169], neuromyelitis optica spectrum disorder (NOSD, anti-aquaporin-4 autoantibodies), idiopathic immune thrombocytopenic purpura (ITP, anti-GPIIb/IIIa or GPIb/IX autoantibodies), pemphigus vulgaris (anti-Dsg1 or Dsg-2 autoantibodies), Graves' disease (agonist anti-thyrotropin receptor autoantibodies) and systemic lupus erythematosus (SLE, anti-dsDNA autoantibodies), to name a few [170, 171]. While historically, at least some of these diseases were treated with high-dose intravenous immunoglobulin (IVIg) [172], until recently, there has been a paucity of approaches to treat these diseases with specific drugs.

FcRn maintains the homeostasis of endogenous IgG, contributing significantly to the elongated (nominally, 21 days) half-life of circulating human IgG1, IgG2 and IgG4 isotypes, as well as human serum albumin (HSA) [173]. This is accomplished by FcRn-binding pinocytosed

IgG at acidic pH, protecting it from the lysosomal degradation pathway, followed by transporting the bound IgG back to the cell surface whereby, at neutral pH, it is exocytosed back into circulation [173].

FcRn is a member of the MHC class I receptor family as evidenced by its α-1,2,3 domains sharing a high degree of homology with MHC class I receptors and its non-covalent interaction with β2-microglobulin to form a heterodimer [173]. Different from MHC class I receptors, however, FcRn, the peptide binding groove found in other MHC class I receptors, is occluded in FcRn, so it is not involved in Class I presentation. Historically, FcRn was stated to be expressed on cells of the reticuloendothelial system, including endothelial and epithelial cells, hepatocytes and myeloid cells), but it is now known that FcRn expression is significantly broader, including in most organs (e.g., lung, stomach, liver, kidney, bladder, muscle, skin) and other tissues [173].

Human FcRn β2m and α1 domains bind the CH2 and CH3 domains, respectively, of human IgG1,2,4 isotypes in such a manner that the Fab arms of the IgG are situated "upside down" in a membrane proximal position [173]. This binding only occurs in endosomes at lower pH such as pH 5–6, wherein the histidines H310, H433, H435 in the Fc are charged, allowing for binding to residues E115 and D130 of FcRn. At neutral pH and above (e.g., pH 7.4), the charge is lost and the ability of FcRn to bind the IgGs is eliminated [173].

FcRn has long intrigued medical scientists as a potential target to reduce pathogenic IgG autoantibodies produced in autoimmune diseases [174]. The concept is simple: since FcRn is the IgG recycle receptor, either antagonism of that receptor, or overwhelming competition for the receptor, should decrease its ability to recycle serum IgGs, including those that are pathogenic [174]. For example, one of the hypotheses for the success of IVIg treatment for various antibody-driven autoimmune disorders is that the supraphysiological levels of exogenous IgG achieved after IVIg dosing results in endogenous IgGs, including the pathogenic forms, being outcompeted, resulting in degradation instead of recycling [175].

FcRn is encoded by the *FCGRT* gene, which has multiple variants based on the variable number of tandem repeats (VNTRs) in its promoter region, a factor which affects its expression. Homozygous VNTR3/VNTR3 is found in 84% of the population, VNTR2/VNTR3 in 13% and other VNTRs in fewer (~3% or less) individuals [173]. VNTR3/VNTR3 results in highest expression of FCGRT, increased binding of IgG at acidic pH [173], whereas the VNTR2/VNTR3 polymorphism has been associated with decreased effectiveness of IVIg treatment for MG [172]. Thus, it is clear that VNTR polymorphisms have the ability to affect the efficacy of anti-FcRn blocking agents, the details of which are still being worked out.

The first agent entry in the field of FcRn modulation is efgartigimod alfa (Vyvgart®), which was approved by the US FDA in 2021 for treatment of generalized myasthenia gravis (gMG) in patients who are positive for the anti-acetylcholine receptor (AChR) antibody (Table 4) [171]. Efgartigimod alfa is a 51 kDa IgG1-based mutated (M32Y, S34T, T36E, H213K, N214F) Fc fragment that binds human FcRn competitively and lowers overall serum IgG levels. Across the various FcRn inhibiting therapeutics, it appears that they are broadly capable of reducing overall circulating IgG levels by 25–50% at effective doses [176]. This reduction appears to be enough to inhibit IgG immune complex-mediated immune responses.

Rozanolixizumab-noli (Rystiggo®) (aka UCB7665), sponsored by UCB, is an IgG4κ FcRn receptor blocking antibody that was granted full approval by the US FDA for the treatment of gMG in adult patients who have autoantibodies against either AChR or muscle-specific tyrosine kinase (MuSK) [14]. Rozanolixizumab and its Fab fragment (1510.g57) bind to the alpha subunit of human FcRn with high affinity at both pH 6.0 (23 pM K_D) and pH 7.4 (34 pM K_D) and competes directly with IgG binding to the receptor [177]. Rozanolixizumab was demonstrated to inhibit IgG recycling *in vitro*, with an IC_{50} of 410 pM, and induced a rapid decline in plasma IgG *in vivo* in both a human FcRn transgenic mouse model and in cynomolgus monkeys [177].

In Phase II (NCT03052751) and Phase III MycarinG (NCT03971422) clinical trials to test the ability of rozanolixizumab to treatment gMG, rozanolixizumab demonstrated strong efficacy by reducing pathogenic antibodies by 78%, competitive with plasma exchange procedures, IVIg treatment [178, 179] and other FcRn-targeting biologics (Table 5) [173]. Other than rozanolixizumab (Rystiggo®), three other FcRn inhibitors are either approved (e.g., Vyvgart) or in late-stage clinical trials (nipocalimab and batoclimab) [173]. In single ascending-dose clinical trials, the typical reduction for most of these molecules dosed at 7–10 mg/kg is in the range of 40–55%. After multiple doses and achievement of steady state, those numbers improve to about 75–85% reduction in overall IgG levels [173].

In the Phase III MycarinG clinical trial for treatment of gMG with rozanolixizumab, all primary and secondary endpoints were met at both 7 and 10 mg/kg doses, indicating strong efficacy [179]. The most common AE was headaches, found in 38–45% of patients treated. Additionally, due to the substantial lowering of plasma IgG, 48% of patients reported infections, of which 4% were serious [14].

Rozanolixizumab is dosed by subcutaneous infusion with a T_{max} of about 2 days. The volume of distribution was 6.6 L, and the clearance was high at 0.89 L/d [14]. Because rozanolixizumab inhibits FcRn the terminal half-life would be expected to be shortened from a normal therapeutic IgG, and while the half-life in humans has apparently not been reported for this molecule, the clearance data as compared with other therapeutic antibodies [101] indicate that it would indeed be short.

ADAs against rozanolixizumab were observed in about 37% of patients dosed in clinical trials, with slightly over half of those being neutralizing antibodies. While some of the patients with ADAs experienced up to a 60% decrease in trough as compared with placebo control patients, there did not appear to be any other clinical manifestations (e.g., changes in efficacy, safety) of the ADA responses [14]. Based on the mechanism of action, it is expected that ADAs would also be lowered significantly, along with other circulating antibodies.

Table 5. Approved and clinical late-stage FcRn antagonists

Molecule	Sponsor	Current status*	Approved or lead indication(s)	Format	Dosing	Refs
Vyvgart® Efgartigimod alfa-fcab (ARGX-113)	arGEN-X	FDA approved 12/17/21	MG; ITC, CIDP	Human IgG1 (YTE)-Fc (51 kDa)	10 mg/kg IV infusion QW for 4 weeks	[173, 180]
Rystiggo® Rozanolixizumab-noli (UCB7665)	UCB	FDA approved 6/26/23	MG	Human IgG4κ	Weight-based ~8–10 mg/kg SC infusion QW for 6 weeks	[14, 173]
Nipocalimab (M281)	Janssen R&D (Momenta)	Phase 3 (NCT05912517)	MG, HDFN, RA, SLE, wAIHA	Human IgG1λ R120K, N296A, ΔK445	IV infusion Q2W	[173, 181]
Batoclimab (IMVT-1401)	Immunovant Sciences GmbH	Phase 3 (NCT05403541)	MG, GD	Human IgG1λ L238A, L239A, ΔK450 (Fc silenced)	SC QW or Q2W	[173, 182]

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; FcRn, neonatal receptor; GD, Graves' disease; HDFN, hemolytic disease of the fetus and newborn; ITP, immune thrombocytopenia; kDa, kilodaltons; MG, myasthenia gravis; PC-POTS, post-COVID-19 postural orthostatic tachycardia syndrome; PV, pemphigus vulgaris; QW, Q2W, weekly and every other week dosing, respectively; RA, rheumatoid arthritis; Refs, references; SLE, systemic lupus erythematosus; wAIHA, warm autoimmune hemolytic anemia. Additional sources: Evaluate Pharma, clinicaltrials.gov, individual company press releases.
*Example active clinical trials provided for non-approved candidates.

VEOPOZ™ (POZELIMAB-BBFG)—COMPLEMENT FACTOR C5

Complement-mediated diseases and treatments

The complement system is a fast-acting protein–protein interaction cascade that plays a significant role in innate immune response to both sterile and infective immune insults [183]. The complement cascade can be activated via three different pathways, the classical pathway, the alternative pathway and the lectin pathway [183]. All three of these pathways all converge on the terminal complement pathway that is initiated by the cleavage of complement factor C5 by C5 convertase (C4bC2aC3b) into C5a and C5b. Once formed, C5b becomes a building block, recruiting C6, C7, C8 and C9, to form the cylinder-shaped membrane attack complex (MAC) [183].

While in homeostasis, the complement cascade provides a vital set of innate immune responses, however, when homeostasis is disrupted, components of the complement cascade can become pathogenic. C5a, the other cleavage product of C5, is an anaphylatoxin that promotes cell differentiation and recruitment [184]. Dysregulation of C5a binding to its cognate receptor, the GPCR C5aR1, is known to lead to inflammatory disorders including sepsis and acute respiratory distress syndrome (ARDS) [184]. As part of its pathology, C5a causes neutrophils to produce tissue factor which initiates the clotting cascade and can activate platelets, especially those that are downmodulated for CD55 and CD59 expression, to cause paroxysmal nocturnal hemoglobinuria (PNH) [185].

Anti-C5 antibody, eculizumab (Soliris®), which blocks the cleavage of C5 to C5a and C5b, was first approved by the US FDA in 2007 and is used today for treatment of two complement-mediated inflammatory diseases, PNH, to reduce hemolysis and atypical hemolytic uremic syndrome (aHUS), to inhibit complement-mediate thrombotic microangiopathy [186]. The approval of Soliris® was followed recently by the FDA approval of ravulizumab (Ultomiris®), an extended half-life version of Soliris® that is now indicated for treatment of aHUS and PNH, as well as the new indications of gMG and neuromyelitis optica spectrum disorder (NMOSD) [187].

Pozelimab-bbfg (Veopoz™)

CHAPLE syndrome is an ultra-rare, inherited genetic disorder characterized by overactivation of the complement pathway, resulting in severe gastrointestinal pain and diarrhea [188, 189]. CHAPLE syndrome, which is diagnosed in less than 100 patients per year, can be life-threatening. Until 2023, no medicines had been approved in the USA to treat this rare disorder.

Pozelimab-bbfg (Veopoz™) is a human, hinge-stabilized IgG4k antibody directed against the terminal complement protein C5 that inhibits terminal complement activation by blocking cleavage of C5 into C5a (anaphylatoxin) and C5b, thereby blocking the formation of the membrane-attack complex (C5b-C9, a structure mediating cell lysis) [190].

Pozelimab-bbfg (Veopoz™), which previously had been granted Rare Pediatric Disease designation, Orphan Disease designation and Fast Track designation, was granted full approval by the US FDA for the treatment of adult and pediatric patients over 1 year of age for CHAPLE disease [22, 50]. As noted above, Veopoz™ is the first treatment approved in the USA for CHAPLE disease.

Pozelimab functions by binding to complement factor C5, thereby inhibiting its conversion into C5a and C5b,

effectively blocking the terminal complement activation pathway. Safety and efficacy of pozelimab in patients with CHAPLE syndrome and associated hypoalbuminemia (<3.2 g/dL) were evaluated in a single-arm clinical study of ten patients (NCT04209634) [22, 189]. After a single 30 mg/kg IV dose of pozelimab followed by weekly 10–12 mg/kg subcutaneous doses, albumin levels were normalized (to levels of >3.5 g/dL) in all patients by 15.5 days; by 12 weeks, albumin levels in all patients reached a normalized steady state that was maintained for the full 72-week study period [22].

Pozelimab is dosed as a 30 mg/kg loading dose followed by weekly 10 mg/kg maintenance doses administered by subcutaneous infusion. The bioavailability after SC dosing was 51%, slightly on the low side for mAbs, and T_{max} was achieved in about 7 days. The volume of distribution was 6 L (300 mg single dose) to 8.6 L (600 mg dose), and the median terminal half-life in healthy subjects was 13.5–14.1 days [22], slightly higher than the 11 d average half-life for Soliris® [186], but significantly shorter than the 49 d circulating half-life exhibited by Ultomiris® [187]. ADAs against pozelimab were not observed [22].

Because pozelimab blocks the terminal pathway for complement activation, it presents a significant risk for infection by encapsulated bacteria such as *Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae* (type b) and, to a lesser extent, *Neisseria gonorrhoeae*. Thus, one of the precautions taken was that all patients taking pozelimab received meningococcal vaccination prior to dosing [22].

BEYFORTUS™ (NIRSEVIMAB-ALIP)—RSV F PROTEIN

Respiratory syncytial virus

Respiratory syncytial virus (RSV), a negative-sense, single-stranded virus, is a common seasonal respiratory virus that is one of the most common causes of lower respiratory tract infections. RSV is particularly dangerous for elderly adults with risk factors, as well as for the very young, i.e., infants. RSV is the major cause of respiratory illness in young children, with a global incidence of 9.5% and a mortality rate of 2.2% [191]. The mortality rate is even higher for those infants who are immunosuppressed or who have other risk factors. RSV is also differentiated from many other viruses in that it can re-infect individuals, even within the same season, making it particularly insidious.

The initial efforts to protect infants from RSV infection were based on the use of RSV-specific IVIg, which was provided for children less than 24 months of age who were born prematurely or with breathing problems or other high-risk factors [192]. This approach, which was ultimately demonstrated to be non-efficacious [192], led to the concept of developing a highly potent, highly specific mAb that could be used as a prophylactic against RSV infection.

Pavilizumab (Synagis®), a highly potent antibody targeting the A-antigenic site of RSV-F protein, was the sixth ever antibody to be approved in the USA (approved in 1998) [193]. Pavilizumab is indicated as a prophylactic antibody given Q4W by the intramuscular (IM) route of administration during an RSV-high season for prevention of serious lower respiratory tract disease in infants at high risk for RSV infection [193]. For years, the sponsor of Synagis®, AstraZeneca, has tried to develop a more potent, longer lasting version of that antibody, but until recently, success had proven elusive [194].

Nirsevimab

Nirsevimab-alip (Beyfortus®) is an anti-RSV mAb developed by AstraZeneca in collaboration with Sanofi and granted full approval by the US FDA that is indicated for the prevention of lower respiratory tract disease caused by RSV in neonates and infants during their first RSV season [16]. Nirsevimab is dosed at 10–20 mg/kg via the IM route of administration with an 84% bioavailability. Nirsevimab contains the long half-life mutations known as YTE [54, 195], which increases it circulating half-life; the terminal half-life of nirsevimab in infants is 71 d [16], more than three-fold the *in vivo* half-life of a typical therapeutic antibody [54, 101]. This allows it to be dosed once at the beginning of the RSV season with sustained efficacy for the entire season.

Nirsevimab-alip (Beyfortus®), previously known as MEDI8897 [54], targets a conserved epitope in antigenic site Ø on the prefusion F protein of RSV [54, 195]. Nirsevimab binds at high affinity, with KD values of 0.12 and 1.22 nM for RSV subtype A and B strains, respectively [16], resulting in EC_{50} values of 21 pM for RSV A and 19 pM for RSV B, respectively [16]. Nirsevimab neutralizes RSV by inhibiting conformation changes in the F protein that are required for fusion of the viral and cellular membranes, which blocks viral entry [54]. The neutralization of RSV viruses *in vitro* by nirsevimab falls into the range of <1.0 ng/mL to ca. 20 ng/mL, more than 10-fold more potent than palivizumab [54]. While nirsevimab possesses some Fc functionality associated with an IgG1, the binding to Fcγ receptors is somewhat muted due to the presence of the YTE mutations required for elongated half-life [196]. Additionally, the Fc functions are not apparently required for optimal prophylactic activity and protection, as determined in preclinical models [196].

Nirsevimab is dosed by IM injection, with a bioavailability of 84% and a T_{max} of 6 days [16]. Treatment of infants with nirsevimab in clinical trials resulted in neutralizing antibody (NAb) titers of more than 140-fold higher than baseline by the end of the first month. NAbs remained at least 50-fold higher than baseline through 5 months and more than seven-fold above baseline after a full year [197]. Modeling of the PK profiles suggested that serum concentrations of nirsevimab should remain above the EC_{90} value of 6.8 μg/mL for at least 150 days (ca. 5 months) [54]. These increases in titers resulted in efficacy as compared with standard of care (SOC) of 83% for hospitalization related to RSV-associated lower respiratory tract infection [178], and an efficacy of about 74.5% for incidence of very severe RSV-associated lower respiratory tract infection [198, 199], without a significant difference in AEs between treatment and placebo arms [191, 199].

As with all biologics, nirsevimab can provoke an anti-antibody response. In three separate clinical trials utilizing the recommended dose regimen, 3.3–7.0% of the subjects

tested positive for ADAs. Interestingly, >94% of those responses were targeted against the YTE mutations in the Fc, whereas there were few ADA responses against the variable sequences of the antibody [16].

SUMMARY

In 2023, 12 new antibodies were approved by the US FDA for 10 different indications. These 12 newly approved antibodies represent a tie with 2020 for the most ever approved by the FDA in a single calendar year. One key factor that stands out is the approval of four new bispecific antibodies, all of which are TCE, also representing the greatest number of TCEs approved in a single calendar year. Considering all of the antibodies in late stage and/or registrational clinical trials [2, 3], we should see another large cohort of novel antibodies approved by the US FDA in 2024.

AUTHOR CONTRIBUTIONS

William Strohl (Writing—original draft, Writing—review & editing-[equal])

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None.

CONFLICT OF INTEREST STATEMENT

WRS is the sole owner and employee of BiStro Biotech Consulting, an independent consulting company. WRS also serves as an independent Director for IGM Biosciences. WRS also serves on the Scientific Advisory Boards of GlycoEra and two other unnamed small biotechnology companies. WRS is an editorial board member of Antibody Therapeutics, but is blinded from reviewing or making decisions for this manuscript.

DATA AVAILABILITY STATEMENT

Data supporting the information provided here are all from the public literature or public websites.

ETHICS AND CONSENT

Consent was not required.

ANIMAL RESEARCH

Not applicable.

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