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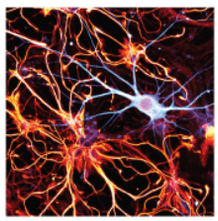

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Antibodies to watch in 2025

Silvia Crescioli[a], Hélène Kaplon[b], Lin Wang[c], Jyothsna Visweswaraiah[d], Vaishali Kapoor[e], and Janice M. Reichert[a]

[a]Business Intelligence Research, The Antibody Society, Inc., Framingham, MA, USA; [b]Translational Medicine Department, Institut de Recherches Internationales Servier, Gif-sur-Yvette, France; [c]Regeneron Formulation Development, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [d]Drug Creation, Seismic Therapeutic, Watertown, MA, USA; [e]Department of Radiation Oncology, Washington University in St. Louis School of Medicine, St. Louis, MO, USA

ABSTRACT

The commercial development of antibody therapeutics is a global enterprise involving thousands of biopharmaceutical firms and supporting service organizations. To date, their combined efforts have resulted in over 200 marketed antibody therapeutics and a pipeline of nearly 1,400 investigational product candidates that are undergoing evaluation in clinical studies as treatments for a wide variety of diseases. Here, we discuss key events in antibody therapeutics development that occurred during 2024 and forecast key events related to the late-stage clinical pipeline that may occur in 2025. In particular, we report on 21 antibody therapeutics granted a first approval in at least one country or region during 2024, including bispecific antibodies tarlatamab (IMDELLTRA®), zanidatamab (Ziihera®), zenocutuzumab (BIZENGRI®), odronextamab (Ordspono®), ivonescimab (依達方®), and antibody–drug conjugate (ADC) sacituzumab tirumotecan (佳泰萊®). We also discuss 30 investigational antibody therapeutics for which marketing applications were undergoing review by at least one regulatory agency, as of our last update on December 9, 2024, including ADCs datopotamab deruxtecan, telisotuzumab vedotin, patritumab deruxtecan, trastuzumab botidotin, becotatug vedotin, and trastuzumab rezetecan. Of 178 antibody therapeutics we include in the late-stage pipeline, we summarize key data for 18 for which marketing applications may be submitted by the end of 2025, such as bi- or multispecific antibodies denecimig, sonelokimab, erfonrilimab, and anbenitamab. Key trends in the development and approval of antibody formats such as bispecifics and ADCs, as well as clinical-phase transition and global approval success rates for these antibody formats, are reported.

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Introduction

Since 2010, the Antibodies to Watch article series[1] has provided annual updates on commercial clinical development and marketing approvals of antibody therapeutics. Each report focuses on three categories, defined by the development stage of the molecules: 1) the late-stage clinical pipeline (i.e., molecules in pivotal Phase 2, Phase 2/3 or Phase 3 studies); 2) investigational antibody therapeutics with marketing applications undergoing review by regulatory agencies; and 3) antibody therapeutics granted their first marketing approval during the past calendar year. For antibody therapeutics in late-stage clinical studies, due to the substantial increase in the number over the past 16 years (from 26 reported in Antibodies to Watch in 2010 to 178 included in this report), we now provide summaries of recent development only for late-stage antibody therapeutics for which marketing applications may be submitted soon, as suggested by public disclosures from the companies developing the molecules.

To enable analyses of trends, the Antibody Society also collects data for antibody therapeutics in the early stages of clinical development. These pipeline data have been included in multiple analyses of development trends and approval success rates for antibody therapeutics reported in Antibodies to Watch articles.[2–7] For example, we previously reported an increase in the proportion of antibodies in late-stage studies with non-canonical formats designed to enhance the biological activity of the molecule.[3] Here, we analyzed trends and the success rates for different antibody formats, classifying the molecules according to: 1) specificity (i.e., monospecific or bispecific/multispecific); 2) conjugation status (i.e., antibody-drug conjugates (ADCs, limited here to antibodies conjugated to cytotoxic drugs), radioimmunotherapy (including radioimmunoconjugates (RIC) and antibody chelator conjugates), and immunoconjugates (i.e., antibody conjugates that are not included in the ADC or radioimmunotherapy groups or that are composed of an antibody fused to non-immunoglobulin derived protein domains); and 3) composition (i.e., one molecule or a mixture). For our analyses, each molecule is represented only once and classified based on how greatly the modification alters the molecular properties. Thus, the ADC group includes bispecific ADCs, the Radioimmunotherapy group includes bispecific radioimmunotherapeutics, and the Immunoconjugate group includes immunoconjugate mixtures.

Most of the recombinant monoclonal antibodies currently marketed are canonical naked monospecific antibodies, but

CONTACT Janice M. Reichert janice.reichert@antibodysociety.org Business Intelligence Research, The Antibody Society, Inc., 247 Prospect Street, Framingham, MA 01701 USA

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since 2019 there has been an increase in the approval of ADCs, bispecifics, immunoconjugates, and antibody mixtures (Figure 1a). These non-canonical formats account for ~25% of the antibody products approved in 2024 (as of November) and ~30% of investigational antibody therapeutics currently in regulatory review (Figure 1a). This trend is likely be a consequence of an increase in the number of antibodies with non-canonical formats, particularly ADCs, bispecifics and immunoconjugates, entering clinical studies (Figure 1b). Our analysis shows that since 2010 there has been a steady increase of antibody therapeutics with non-canonical format entering clinical studies, and since 2021 these have accounted for ~50% of the antibodies entering clinical studies each year (Figure 1b).

We also evaluated differences in clinical-phase transition and global success rates of antibodies with different formats (Figure 2). We analyzed a cohort of 1,373 antibodies entering clinical studies during 2000–2019, stratified by general molecular category as described above, and assigned each molecule to its most advanced phase of development, choosing one of the nine possible phases of development (Phase 1, 2, or 3 clinical study; regulatory review; approved; all development terminated at Phase 1, 2, 3, or during regulatory review). We evaluated global success, defined as the first marketing approval in any country; no subsequent supplemental approvals were included in calculations. Final fates (i.e., approved or all development terminated) were known for 67% of the Naked monospecific, 76% of the ADC, 61% of the Bispecific/multispecific, 73% of the Immunoconjugate, 79% of the Mixture, and 73% of the Radioimmunotherapy groups. It should be noted that rates may vary as the final fates of molecules still in development are decided in the future.

For most formats, phase transition rates show an overall pattern typical of drug development, with Phase 2 to 3 transition having the lowest rate and the marketing application submission to approval transition having the highest rate.[2] Exceptions are seen, however, for the ADC and Radioimmunotherapy formats. For the ADC group, the Phase 1 to 2 transition rate is the lowest, which is consistent with the elevated toxicity reported for first-generation ADCs. The Radioimmunotherapy group also has a low Phase 1 to 2 transition rate, the lowest compared to the other groups, likely due to the reported toxicity of RICs. Moreover, this group has a marketing application submission to approval transition rate

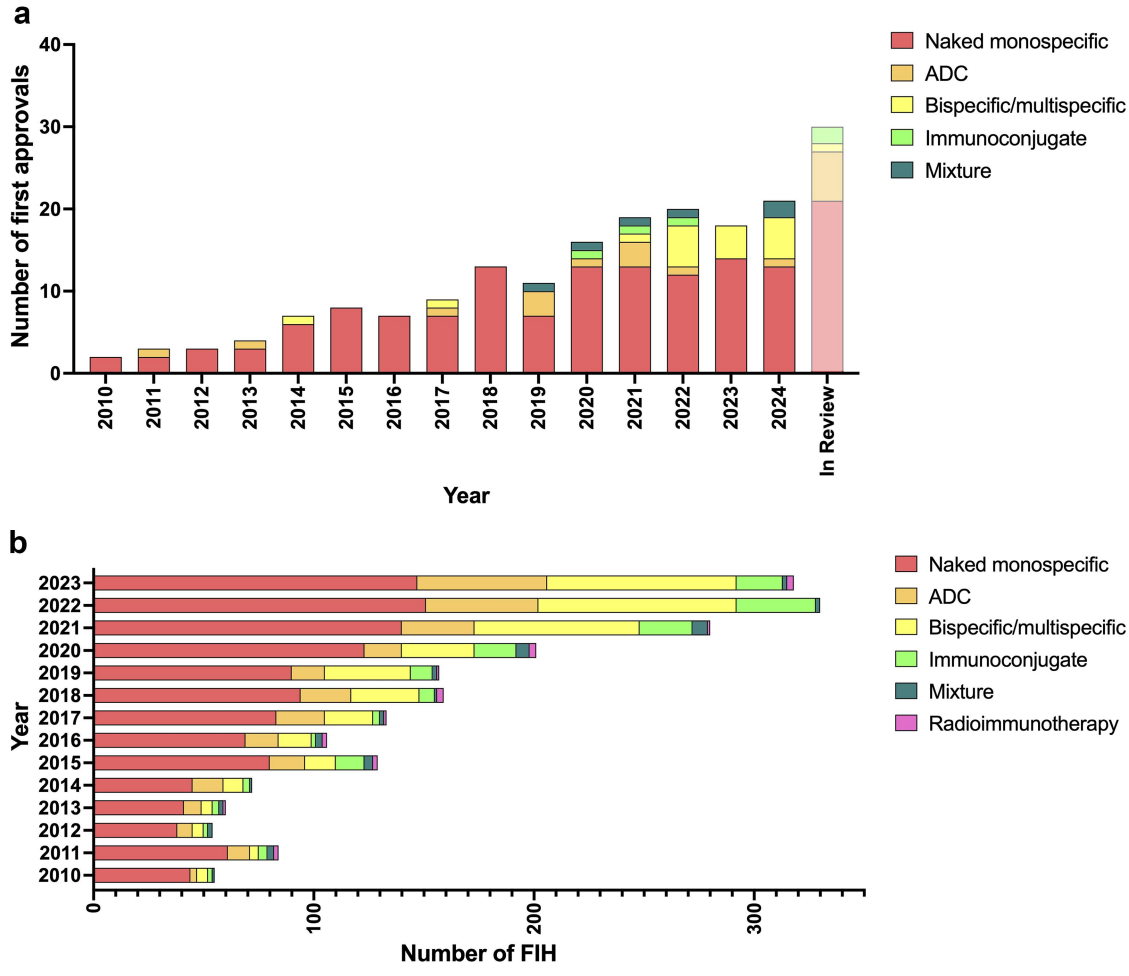

Figure 1. Trends in antibody formats. (a) Trends in first approvals of antibody therapeutics in any country and antibodies currently in regulatory review stratified by general molecular category. (b) Trends in first-in-human studies of antibody therapeutics stratified by general molecular category. 2024 data are as of December 7, 2024. Molecules are counted only once and categorized as: naked monospecific (canonical format); antibody – drug conjugate (ADC) (when conjugated to a cytotoxic drug, including bispecific ADC); bispecific/multispecific (naked); immunoconjugates (antibodies conjugated to molecules (excluding cytotoxic drugs, radioisotopes and chelators); or fused to non-immunoglobulin derived protein domains, including immunoconjugate mixtures); mixture; radioimmunotherapy (including radioimmunoconjugates (RIC) and antibody chelator conjugates).

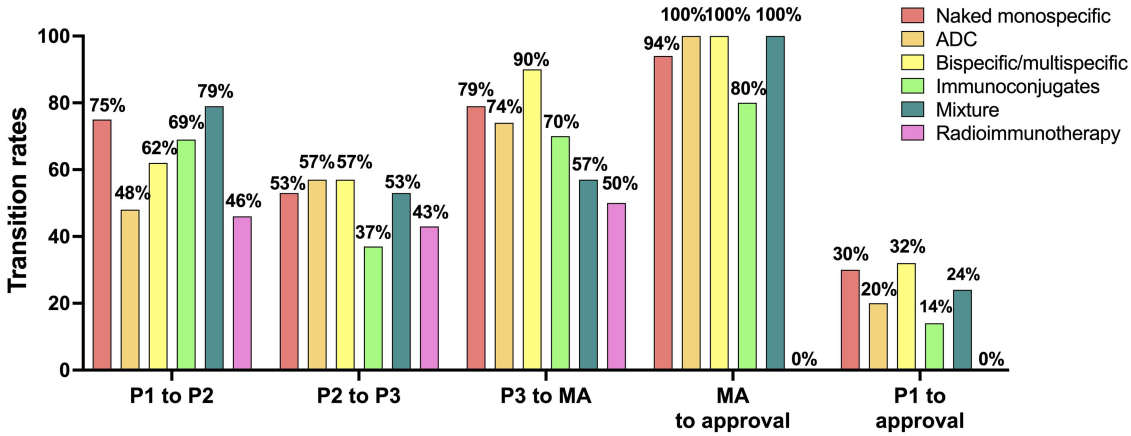

Figure 2. Clinical phase transition and global success rates for different antibody formats. Clinical phase transition and global approval success rates for antibody therapeutics that entered clinical study during 2000–2019, stratified by molecular category. Red bars, naked monospecific. Orange bars, ADC. Yellow bars, bispecific/multispecific. Light green bars, immunoconjugate. Dark green bars, antibody mixture. Pink bars, antibody for radioimmunotherapy (including RIC and antibody chelator conjugates). Cohorts included only novel antibody therapeutics in clinical studies sponsored by commercial firms; biosimilars were excluded. Final fates (approval or termination) are known for 67% of the naked monospecific, 76% of the ADC, 61% of the bispecific/multispecific, 73% of the immunoconjugate, 79% of the mixture, and 73% of the radioimmunotherapy groups. Mabs in phase 1/2 studies were classified as Phase 2; mAbs that advanced to Phase 2/3 were classified as Phase 3. Transitions occurring between Phase 1 to 2 and Phase 2 to 3 clinical studies conducted world-wide were included. Global approval refers to a first approval granted in any country or region; supplemental approvals of any kind were not included. Single-step transition rates were calculated as the number of antibody therapeutics that transitioned from a given phase to the next divided by the sum of the number that transitioned and the number that were terminated at that phase at the time of the calculation. Phase 1 to approval rates were calculated by multiplying the four relevant single-step transition rates. Data as of December 7, 2024.

of 0% because development of the only RIC that transitioned to regulatory review, Iodine-131 omburtamab, was terminated.

Our analysis shows that the global approval success rates for the different antibody formats vary substantially (0–32%). The Radioimmunotherapy group currently has the lowest rate (0%). It should be noted that, while two RICs, Iodine-131 tositumomab (Bexxar) and Yttrium-90 ibritumomab tiuxetan (Zevalin), were granted marketing approvals, both molecules first entered clinical study well before 2000, and so were not included in our success rate analysis. Interestingly, despite the low success rate of RIC, we observe an increase in the number of antibodies for radioimmunotherapy entering clinical studies during both 2015–2019 and 2020–2024 compared to the previous 5-year period (2010–2014), although the numbers are small, i.e., <10 in any of these periods. This nascent trend could be related to advancements in RIC technology and the use of next-generation isotope payloads, such as alpha emitters (Actinium-225, Thorium-227, Boron-10) which have a short tissue penetration range and high linear energy transfer and a potential for more targeted delivery, reducing damage to surrounding healthy tissue.

Immunoconjugates had the second lowest approval success rate (14%). This group includes a variety of antibody molecules with very different characteristics in terms of structure and mechanism of action, including immunocytokines, immunotoxins, bispecific immunoconjugates, unconventional ADCs, and PEGylated antibodies. Due to the heterogeneity and the small number of the molecules included, analyses of molecules stratified by their subcategory would likely not yield meaningful results. As immunoconjugates have entered clinical studies in increasing numbers during 2020–2024, we expect that such analyses will be possible in the future.

The ADC group's global approval success rate was 20%, below that of both canonical (i.e., naked, monospecific) antibodies (30%) and bispecific/multispecifics (32%) (Figure 2). Because our data is limited to antibody therapeutics entering clinical studies during 2000–2019, the ADC group includes a substantial number of first-generation molecules, which had toxicity issues.[8,9] Advancements in their design have yielded next-generation ADCs with improvements in the structure, linker, and payload. In a preliminary analysis of the ADC group stratified by payload type, we detected a higher success rate for ADCs that incorporated topoisomerase I inhibitors vs. tubulin inhibitors or DNA binding agents (data not shown). While fewer than a dozen topoisomerase I inhibitor-based ADC were included in the data we analyzed, the current early-stage pipeline includes nearly 100 such ADCs. We look forward to reporting success rates for these ADCs in the future.

As a group, bispecific and multispecific antibodies had the highest approval success rate (32%). Interestingly, when stratified by therapeutic area, i.e., cancer and non-cancer indications, the Bispecific/multispecifics for cancer had a substantially higher success rate (35%) than those for non-cancer indications (23%) (Supplemental Figure S1). This result, which is likely due in part to the success of the T-cell engaging bispecifics, shows that success can depend not just on the format, but also on the target and mechanism of action, highlighting the complexity of antibody therapeutics development.

In the remainder of this installment of the Antibodies to Watch article series, we provide details for 21 antibody therapeutics granted a first approval in 2024, as of December 4, and 30 product candidates for which marketing applications are under consideration. We also discuss 18 investigational antibody therapeutics that are forecast to enter regulatory review by the end of 2025. Due to the large volume of information available for the molecules, only publications and other disclosures made public between January and November 2024 are cited in the summaries below.

Antibody therapeutics granted a first approval in any country in 2024

As of December 4, a total of 21 antibody therapeutics were granted a first approval in at least one country or region during 2024 (Table 1). Some of these were subsequently approved in additional countries or regions in 2024. Of the 21 approved products, the majority were approved in China, with 9/21 (43%) approved in the US or the EU. Eleven (55%) were approved for non-cancer indications, while 10 were approved for cancer. Key details for the approved products are provided in the summaries below, which appear in the same order as in Table 1.

First marketing approvals granted in the US or EU in 2024

Donanemab (Eli Lilly and Company)

Donanemab (Kisunla™, donanemab-azbt, LY3002813) is a humanized IgG1κ monoclonal antibody designed to target Aβ (p3–42), a pyroglutamate variant of amyloid beta found in aggregated amyloid plaques. The FDA granted donanemab Breakthrough Therapy designation for the treatment of Alzheimer's disease.

On July 2, 2024, the US Food and Drug Administration (FDA) approved Kisunla™ (donanemab-azbt) for treating adults with early symptomatic Alzheimer's disease, including those with mild cognitive impairment (MCI) or mild dementia and confirmed amyloid pathology.[10] The recommended dosage of KISUNLA is 700 mg every 4 weeks (Q4W) for three doses, then 1400 mg Q4W, administered as a ~ 30-min intravenous (IV) infusion. Kisunla™ therapy is supported by evidence for discontinuing treatment once amyloid plaques are cleared. In September and October 2024, Eli Lilly announced that Kisunla™ had been granted approvals in Japan and Great Britain, respectively.[11,12] The European Medicines Agency (EMA) started evaluating a marketing application for donanemab in August 2023; as of November 2024, the application is still undergoing evaluation.

The approvals were supported by results from the pivotal Phase 3 TRAILBLAZER-ALZ 2 trial (NCT04437511).[13] This trial involved 1,736 patients with early symptomatic Alzheimer's disease who had amyloid and low to medium or high tau pathology. Participants were randomly assigned in a 1:1 ratio to receive either IV donanemab (700 mg for the first 3 doses and 1400 mg thereafter) ($n = 860$) or a placebo ($n = 874$) Q4W for 72 weeks. The primary outcome of this study was the change in the integrated Alzheimer's Disease Rating

Table 1. Commercially sponsored monoclonal antibody therapeutics granted a first approval in any country during 2024.

INN (Brand name)	Target(s); Format	Indication first approved	Country/region of approval in 2024*
Donanemab (Kisunla®)	Amyloid β; Humanized IgG1κ	Early Alzheimer's disease	US, Japan, UK [EU review]
Axatilimab (Niktimvo®)	CSF-1 R; Humanized IgG4κ	Graft vs. host disease	US
Marstacimab (HYMPAVZI®)	TF pathway inhibitor; Human IgG1λ	Hemophilia	US, EU
Crovalimab (派圣凯®, PiaSky®)	Complement C5; Humanized IgG1κ	Paroxysmal nocturnal hemoglobinuria	US, EU, Japan, China
Zolbetuximab (VYLOY)	Claudin 18.2; Chimeric IgG1κ	HER2-negative gastric or gastroesophageal junction adenocarcinoma	US, EU, Japan, UK, [China review]
Tarlatamab (IMDELLTRA®)	DLL3, CD3; scFv-scFv-scFc bispecific	Small cell lung cancer	US
Zanidatamab (Ziihera®)	HER2; Humanized biparatopic bispecific fragment (Fab-h-CH2-CH3 × scFv-h-CH2-CH3)	HER2-positive biliary tract cancer	US [EU, China review]
Zenocutuzumab (BIZENGRI®)	HER2, HER3; Humanized IgG1κ ; Bispecific	NRG1+ pancreatic ductal adenocarcinoma or NSCLC	US
Odronextamab (Ordspono®)	CD20, CD3; Human IgG4κ bispecific	Diffuse large B-cell lymphoma	EU
Mazorelvimab, Zamerovimab (克瑞毕®)	Rabies virus glycoprotein; Humanized IgG1κ, mixture of 2 monospecific antibodies	Rabies, post-exposure prophylaxis	China
Vunakizumab (安达静®)	IL-17A; Humanized IgG1κ	Psoriasis	China
Xeligekimab (金立希®)	IL-17A; Human IgG4κ	Psoriasis	China
Stapokibart (Kangyueda®, 康悦达®)	IL-4 R alpha; Humanized IgG4κ	Atopic dermatitis	China
Ebronucimab (伊喜宁®)	PCSK9; Human IgG1λ	Primary hypercholesterolemia and mixed hyperlipidemia, heterozygous familial hypercholesterolemia	China
Ongericimab (君适达®)	PCSK9; Humanized IgG4κ	Hypercholesterolemia	China
Enlonstobart (Enshuxing ®, 恩舒幸®)	PD-1; Human IgG4k	Cervical cancer	China
Iparomlimab, Tuvonralimab (齐倍安®)	PD-1, CTLA-4; mixture 2 monospecific antibodies	Cervical cancer	China
Benmelstobart (Andewei®)	PD-L1; Humanized IgG1κ	Small cell lung cancer	China
Ivonescimab (依達方®)	PD-1, VEGF-A; IgG1κ-[scFv]2 bispecific	Lung cancer	China
Sacituzumab tirumotecan (佳泰莱®)	TROP-2; Humanized IgG1κ ADC	Triple-negative breast cancer, NSCLC	China
Seniprutug (Tribuvia®)	TCR Vbeta9; Humanized IgG1κ	Axial spondyloarthritis	Russia

*Subsequent approvals that occurred in 2024 in other countries are noted; table includes information found in the public domain as of December 4, 2024. Abbreviations: CSF-1 R, colony-stimulating factor-1 receptor; DLL3, Delta-like ligand 3, EU, European Union; IL, interleukin; NSCLC, non-small cell lung cancer; PCSK9, proprotein convertase subtilisin/kexin type 9; PD-L1, programmed cell death protein ligand 1; scFv, single-chain variable fragment; TCR, T cell receptor; VEGF, vascular endothelial growth factor. Further data for approved antibody therapeutics available at: https://www.antibodysociety.org/antibody-therapeutics-product-data/.

Scale (iADRS) from baseline to 76 weeks. The results showed that donanemab significantly slowed cognitive and functional decline by 22% based on the iADRS. Notably, certain subgroups of patients experienced an even greater benefit. For example, in patients with low to medium levels of tau (n = 1182), donanemab treatment slowed decline by 35% on the iADRS.[13]

On October 29, 2024, Eli Lilly and Company announced positive results from the TRAILBLAZER-ALZ 6 (NCT05738486) Phase 3b study, showing a reduction in amyloid-related imaging abnormalities with edema/effusion (ARIA-E) at the 24-week primary endpoint in participants receiving a slightly modified titration of donanemab.[14] Lilly is in discussions with global regulators regarding the study results, with plans to submit for a potential label update for Kisunla™. Lilly is conducting several clinical trials of donanemab, including TRAILBLAZER-ALZ 3, which focuses on reducing the risk of progression to symptomatic Alzheimer's in individuals with preclinical Alzheimer's disease, and TRAILBLAZER-ALZ 5, a registration trial for early symptomatic Alzheimer's disease currently enrolling participants in China, Korea, Taiwan, and other locations.

Axatilimab (Syndax Pharmaceuticals)

Axatilimab (Niktimvo, axatilimab-csfr, SNDX-6352, UCB6352, INCA034176) is a humanized, hinge-stabilized (S228P) IgG4κ antibody targeting the colony-stimulating factor 1 receptor (CSF-1 R), which is expressed in monocytes and macrophages. UCB granted Syndax an exclusive worldwide license for development of axatilimab in 2016. In 2021, Syndax and Incyte entered into an exclusive worldwide co-development and co-commercialization license agreement for axatilimab in chronic graft-vs-host disease (cGVHD) and any future indications. Niktimvo will be co-commercialized by Incyte and Syndax Pharmaceuticals in the US. Incyte has exclusive commercialization rights for Niktimvo outside of the US. Axatilimab was granted Orphan Drug designation by the FDA for the treatment of patients with cGVHD.

On August 14, 2024, the FDA approved axatilimab-csfr (Niktimvo) for the treatment of cGVHD after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg.[15] The recommended dosage of Niktimvo is 0.3 mg/kg (maximum 35 mg) every 2 weeks (Q2W) in adult and pediatric patients weighing 40 kg and above administered as an IV infusion over 30 minutes.[16] Axatilimab is the first anti-CSF-1 R antibody to be granted a marketing approval. The FDA's approval was based on results from the pivotal Phase 2 AGAVE-201 study (NCT04710576), which evaluated the safety and efficacy of 3 dose levels of Niktimvo in a total of 241 adult and pediatric patients with refractory cGVHD who received at least two prior lines of systemic therapy. Patients were IV administered 0.3 mg/kg Q2W (0.3-mg dose group), 1 mg/kg Q2W, or 3 mg/kg Q4W. The efficacy of Niktimvo was based on the overall response rate through Cycle 7 Day 1. The trial met the primary endpoint across all cohorts receiving Niktimvo. Of the patients who received Niktimvo at the approved dose of 0.3 mg/kg Q2W (n = 80), 74% achieved an overall response rate within the first 6 months of treatment, with a median time to response of 1.5 months.[17]

Marstacimab (Pfizer, Inc.)

Marstacimab (HYMPAVZI™, marstacimab-hncq, PF-06741086) is a human IgG1λ antibody targeting the Kunitz 2 domain of tissue factor pathway inhibitor. The target is a naturally occurring anticoagulation protein that prevents the formation of blood clots. Marstacimab, which is being developed as a prophylactic to prevent or reduce the frequency of bleeding in people with hemophilia, was granted Fast Track designation for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A with inhibitors or hemophilia B with inhibitors and Orphan Drug designation for treatment of hemophilia A and hemophilia B patients with or without inhibitors by FDA. EMA has granted Orphan Medicinal Product designation to marstacimab for treatment of hemophilia. Marstacimab was approved for hemophilia in both the US and the EU in 2024.

On October 11, 2024, the FDA approved HYMPAVZI™ (marstacimab-hncq) for the treatment of adults and adolescents with hemophilia A or B without inhibitors. The recommended dosage of HYMPAVZI includes a loading dose of 300 mg (two 150 mg SC injections), which after 1 week is followed by maintenance dosing of 150 mg Q1W by subcutaneous (SC) injection on the same day each week, at any time of day. The approval is based on results from the Phase 3 BASIS trial (NCT03938792), which demonstrated substantial bleed reduction compared to routine prophylaxis and on-demand treatment. In the study, HYMPAVZI reduced the annualized bleeding rate for treated bleeds by 35% and 92% after a 12-month active treatment period compared to routine prophylaxis and on-demand treatment, respectively, in patients with hemophilia A or B without inhibitors. The safety profile for HYMPAVZI was consistent with Phase 1/2 results. HYMPAVZI is the first Q1W SC prophylactic treatment for eligible people living with hemophilia B, and the first to be administered via a pre-filled pen or syringe for eligible people living with hemophilia A or B.[18]

The European Commission approved marstacimab in November 2024 for routine prophylaxis of bleeding episodes in patients 12 years of age and older weighing at least 35 kg with severe hemophilia A (congenital factor VIII [FVIII] deficiency, FVIII < 1%) without FVIII inhibitors or severe hemophilia B (congenital factor IX [FIX] deficiency, FIX < 1%) without FIX inhibitors. The marketing authorization in the EU was also based on results from the pivotal Phase 3 BASIS study.[19]

Crovalimab (Chugai Pharmaceuticals, Genentech, F. Hoffmann-La Roche Ltd.)

Crovalimab ('派圣凯®, PiaSky, crovalimab-akkz, SKY59, RG6107, RO7112689) is a complement C5-inhibiting, humanized IgG1κ antibody engineered with M428L/N434A modifications to enhance affinity to the neonatal Fc receptor at acidic pH, thereby extending its plasma half-life. Developed by Chugai Pharmaceuticals, crovalimab lacks effector

functions and is intended as a treatment for paroxysmal nocturnal hemoglobinuria (PNH). Crovalimab, developed with Chugai's Recycling Antibody® technology, is engineered to repeatedly bind its antigen, allowing for sustained complement inhibition at a low, SC dose administered Q4W. Unlike existing antibody drugs, crovalimab targets a different epitope on C5, offering a potential alternative for patients with PNH who have a specific C5 gene mutation.

On February 6, 2024, SC crovalimab received its first approval in China for the treatment of adolescents and adults (aged ≥12 years) with PNH who have not previously been treated with complement inhibitors. This approval was based on positive results from the Phase 3 studies COMMODORE 2 (NCT04434092) and COMMODORE 3 (NCT04654468) in patients with PNH.[20] Crovalimab was subsequently approved in Japan in March 2024 for treating both treatment-naïve and previously treated patients with PNH, based on positive results from the phase 3 studies COMMODORE 1 (NCT04432584) and COMMODORE 2,[21] as well as in the US and the EU in June and August 2024, respectively.

The global Phase 3 COMMODORE 1 and 2 studies evaluated the efficacy and safety of crovalimab compared to eculizumab in participants with PNH. COMMODORE 1 focused on C5 inhibitor-experienced patients, while COMMODORE 2 involved patients not previously treated with complement inhibitors. COMMODORE 1 assessed the safety, pharmacokinetics (PK), pharmacodynamics (PD), and exploratory efficacy of crovalimab. The data from this study support crovalimab's favorable benefit–risk profile, highlighting the convenience of SC administration with the option for self-administration.[22] Data from the COMMODORE 2 study showed that SC crovalimab administered Q4W was non-inferior to IV eculizumab given Q2W in controlling disease, with comparable safety for patients who had not previously received C5 inhibitors.[23]

COMMODORE 3 was a multicenter, single-arm trial conducted in China that evaluated crovalimab in C5 inhibitor-naive PNH patients ($n = 51$). Patients received a weight-based dosing schedule, with an initial loading phase (IV on Days 1 and 4, weekly SC starting Day 2) and maintenance SC Q4W from Week 5 onward. Treatment was extended beyond 24 weeks for patients with clinical benefits. The co-primary endpoints of hemolysis control and transfusion avoidance (TA) were met: 78.7% achieved hemolysis control (Weeks 5–25), and the TA rate increased from 0.0% pre-treatment to 51.0% post-treatment ($p < .0001$).[21]

Zolbetuximab (Astellas Pharma Inc.)

Zolbetuximab (VYLOY, zolbetuximab-clzb) is a chimeric IgG1κ antibody targeting Claudin 18.2 (CLDN18.2) that was originally developed by Ganymed Pharmaceuticals AG. Astellas acquired Ganymed in 2016. CLDN18.2 is a tight-junction molecule of the gastric epithelium that becomes accessible on the tumor cell surface during malignant transformation. The protein is also ectopically expressed in other cancers including pancreatic cancer. CLDN18.2 has become an attractive target for cancer immunotherapy, as evidenced by the over 40 anti-CLDN18.2 antibodies in currently clinical study, including some in bispecific and ADC formats.

On March 26, 2024, Japan's Ministry of Health, Labour and Welfare (MHLW) approved VYLOY™ (zolbetuximab) for patients with CLDN18.2-positive, unresectable, advanced, or recurrent gastric cancer. Zolbetuximab was subsequently approved for untreated CLDN18.2-positive, human epidermal growth factor receptor 2 (HER2)-negative unresectable advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma in the UK, the EU, and the US[24] in August, September, and October 2024, respectively. Zolbetuximab is the first anti- CLDN18.2 antibody granted marketing approval.

The marketing approvals were based on data from the Phase 3 SPOTLIGHT (NCT03504397) and GLOW clinical trials (NCT03653507). Both were randomized (1:1), double-blind, multicenter trials that included patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma. The SPOTLIGHT trial included 565 patients randomized to receive either zolbetuximab (800 mg/m^2 loading dose administered IV followed by 600 mg/m^2 once every 3 weeks (Q3W) plus mFOLFOX6 chemotherapy (283 patients) or placebo plus mFOLFOX6 (282 patients). The GLOW study evaluated zolbetuximab plus capecitabine and oxaliplatin as first-line treatment in 507 patients.

In the SPOTLIGHT study, the median progression-free survival (PFS) was 10.6 months (95% CI: 8.9, 12.5) in the zolbetuximab-clzb/chemotherapy arm and 8.7 months (95% CI: 8.2, 10.3) in the placebo/chemotherapy arm (hazard ratio [HR] 0.751 [95% CI: 0.598, 0.942]; 1-sided p-value = .0066). Median overall survival (OS) was 18.2 months (95% CI: 16.4, 22.9) and 15.5 months (95% CI: 13.5, 16.5), respectively (HR 0.750 [95% CI: 0.601, 0.936]; 1-sided p-value = .0053).[24]

In the GLOW study, the median PFS was 8.2 months (95% CI: 7.5, 8.8) in the zolbetuximab-clzb/chemotherapy arm and 6.8 months (95% CI: 6.1, 8.1) in the placebo/chemotherapy arm (HR 0.687 [95% CI: 0.544, 0.866]; 1-sided p-value = .0007). Median OS was 14.4 months (95% CI: 12.3, 16.5) and 12.2 months (95% CI: 10.3, 13.7), respectively (HR 0.771 [95% CI: 0.615, 0.965]; 1-sided p-value = 0.0118).[24]

Tarlatamab (Amgen)

Tarlatamab (IMDELLTRA™, tarlatamab-dlle, AMG 757) is an extended half-life anti-Delta-like ligand 3 (DLL3) × anti-CD3 bispecific T cell engaging antibody developed by Amgen. It binds to DLL3 on tumor cells and CD3 on T cells, activating T cells to target and kill DLL3-expressing small cell lung carcinoma (SCLC) cells.

On May 16, 2024, the FDA granted accelerated approval to IMDELLTRA™ (tarlatamab-dlle) for the treatment of adult patients with extensive-stage (ES) SCLC who have disease progression following platinum-based chemotherapy.[25] Tarlatamab is the first antibody targeting DLL3 to be granted a marketing approval. This approval was based on promising response rates and duration of response (DoR) observed in clinical trials. The approval was supported by results from the Phase 2 DeLLphi-301 (NCT04471727) trial, which evaluated IMDELLTRA in patients who had failed two or more prior

lines of treatment and received the 10 mg Q2W dosing regimen. The study found that IMDELLTRA at this dose ($n = 99$) demonstrated a significant objective response rate (ORR) of 40% (95% CI: 31, 51) and a median DoR of 9.7 months (CI: 2.7, 20.7+). The median OS was 14.3 months, with final survival data still pending.[26] The safety profile was manageable, with cytokine release syndrome (CRS) being the most common adverse event. In September 2024, Amgen presented the extended follow-up data from the DeLLphi-301 Phase 2 study demonstrating sustained anticancer activity and a manageable safety profile with IMDELLTRA in patients with ES-SCLC previously treated with platinum-based chemotherapy.[27]

Tarlatamab is being investigated in multiple studies including DeLLphi-303 (NCT05361395), a Phase 1b study investigating tarlatamab in combination with standard of care (SOC) therapies in first-line ES-SCLC; DeLLphi-304 (NCT05740566), a randomized Phase 3 trial comparing tarlatamab monotherapy with SOC chemotherapy in second-line treatment of SCLC; DeLLphi-305 (NCT06211036), a randomized Phase 3 trial comparing tarlatamab in combination with durvalumab versus durvalumab alone as first-line maintenance treatment in ES-SCLC; DeLLphi-306 (NCT06117774), a randomized placebo-controlled Phase 3 trial of tarlatamab following concurrent chemoradiotherapy in limited-stage SCLC; and DeLLpro-300, a Phase 1b study of tarlatamab in de novo or treatment-emergent neuroendocrine prostate cancer.

Zanidatamab (BeiGene, Jazz Pharmaceuticals Plc, Zymeworks Inc)

Zanidatamab (ZW25) is a humanized, biparatopic, bispecific IgGκ assembled from half-antibodies (Fab-h-CH2-CH3 × scFv-h-CH2-CH3) that targets two non-overlapping epitopes of HER2. In 2022, Zymeworks licensed the development and commercialization rights across all indications in the United States, Europe, Japan, and all other territories, except for those Asia/Pacific territories previously licensed by Zymeworks, to Jazz Pharmaceuticals. BeiGene acquired exclusive development and commercial rights to zanidatamab, in Asia (excluding Japan), Australia, and New Zealand in 2018. The FDA granted Breakthrough Therapy designation for zanidatamab in patients with previously treated HER2 gene-amplified BTC, Fast Track designation for zanidatamab as a single agent for refractory BTC, and Orphan Drug designation for zanidatamab in refractory BTC.

On November 20, 2024, Jazz Pharmaceuticals announced that the FDA granted accelerated approval of Ziihera® (zanidatamab-hrii) 50 mg/mL for injection for IV use for the treatment of adults with previously treated, unresectable, or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test.[28] A confirmatory, randomized Phase 3 trial (HERIZON-BTC -302; NCT06282575) evaluating zanidatamab in combination with SOC therapy versus SOC therapy alone in the first-line setting for patients with HER2-positive BTC initiated in July 2024 is currently recruiting patients.

The approval was based in part on the results of the single-arm, phase 2b trial (HERIZON-BTC-01; NCT04466891) of zanidatamab in patients with HER2-amplified, unresectable, locally advanced, or metastatic BTC with disease progression on previous gemcitabine-based therapy.[28,29] Patients ($n = 87$) received zanidatamab 20 mg/kg IV Q2W. Patients were assigned into cohorts based on HER2 immunohistochemistry (IHC) score: Cohort 1 (IHC 2+ or 3+; HER2-positive) and cohort 2 (IHC 0 or 1+). The primary endpoint was confirmed objective response rate in Cohort 1 as assessed by independent central review (ICR). The median duration of the follow-up was 12.4 months (interquartile range 9.4–17.2). Confirmed objective responses were observed in 33 patients in cohort 1 (41.3% (95% CI 30.4–52.8)), but none of the HER2-low patients in cohort.

Marketing applications for zanidatamab as a treatment for BTC were also submitted in the European Union and China. Beigene anticipates approval by NMPA for zanidatamab as second-line treatment of HER2+ BTC in the second half of 2025.

In addition to BTC, zanidatamab is being evaluated in Phase 3 studies as a treatment for HER2+ breast cancer (NCT06435429) and gastric cancer (NCT05152147).

Zenocutuzumab (Merus N.V.)

Zenocutuzumab (MCLA-128) is a humanized, ADCC-enhanced, bispecific IgG1κ antibody that simultaneously targets the growth factor receptors HER2 and HER3, thereby blocking signal transduction caused by the binding of HER3 with its ligand neuregulin 1 (NRG1) or NRG1-fusion proteins. The antibody is in development by Merus as a treatment for patients with solid tumors harboring NRG1 gene fusions (NRG1+ cancer), who typically have suboptimal responses to conventional systemic treatment. The FDA granted Breakthrough Therapy Designation for zenocutuzumab for the treatment of patients with advanced unresectable or metastatic NRG1+ pancreatic cancer following progression with prior systemic therapy or who have no satisfactory alternative treatment options, as well as Fast Track Designation for the treatment of patients with metastatic NRG1+ cancer that have progressed on SOC therapy and Orphan Drug Designation for the treatment of patients with pancreatic cancer.

On December 4, 2024, Merus N.V. announced the FDA-approved BIZENGRI® (zenocutuzumab-zbco) as a treatment indicated for adults with pancreatic adenocarcinoma or NSCLC that are advanced unresectable or metastatic and harbor a NRG1 gene fusion who have disease progression on or after prior systemic therapy.[30] The approval was based on data from the open-label Phase 1/2 eNRGy trial (NCT02912949), which evaluated the safety and anti-tumor activity of zenocutuzumab monotherapy in NRG1+ NSCLC, PDAC, and other solid tumors. The study consisted of three patient cohorts: 1) NRG1+ NSCLC, 2) NRG1+ PDAC, and 3) other NRG1+ solid tumors. In the dose expansion period of the eNRGy study, participants received IV infusions of 750 mg of zenocutuzumab Q2W.[31,32] Response rates were measured using RECIST v1.1 as assessed by blinded ICR. The ORR was 33% (95% CI, 22%–46%) and 40% (95% CI, 23%–59%) in the NRG1+

NSCLC ($n = 64$) and NRG1+ PDAC ($n = 30$) cohorts, respectively, and the median DOR was 7.4 months (95% CI, 4.0–16.6) in the NRG1+ NSCLC cohort and ranged from 3.7 months to 16.6 months in the NRG1+ PDAC cohorts.[30]

Odronextamab (Regeneron Pharmaceuticals, Inc)

Odronextamab (Ordspono™, REGN1979) is a human, hinge-stabilized, anti-CD20×CD3 bispecific IgG4κ antibody. The Fc region was engineered (E233P, F234V, L235A, G236del) to reduce effector functions. Regeneron's VelocImmune® technology and Veloci-Bi® platform were used to create the antibody, which is being developed by the company for the treatment of RR B-cell NHL, including FL and DLBCL. Odronextamab received Fast Track designation from the FDA and Orphan Drug and Orphan Medicinal Product designations by the FDA and EMA, respectively, for the treatment of patients with follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). Marketing applications for odronextamab for FL and DLBCL were submitted by Regeneron in both the US and the EU.

Based on a positive opinion from EMA, the European Commission approved odronextamab in August 2024 for the treatment of adults with relapsed/refractory (R/R) FL or R/R DLBCL, after two or more lines of systemic therapy. The approval was supported by results from the Phase 1 ELM-1 (NCT02290951) and pivotal Phase 2 ELM-2 (NCT03888105) trials, which demonstrated robust, durable response rates and an acceptable safety profile of odronextamab in adults with R/R FL or R/R DLBCL. In R/R FL patients enrolled in the ELM-2 study ($n = 128$), the ORR was 80%; of the 73% that achieved a complete response, the median DoR was 25 months. In chimeric antigenic receptor T cell therapy-naïve, R/R DLBCL patients enrolled in the ELM-2 ($n = 127$) study, the ORR was 52%, with 31% achieving a CR. Among complete responders, the median DoR was 18 months.[33]

In March 2024, the FDA issued complete response letters (CRLs) for the biologics license applications (BLAs) for odronextamab in R/R FL and in R/R DLBCL, each after two or more lines of systemic therapy. The sole approvability issue relates to the enrollment status of the confirmatory trials. Regeneron is sponsoring multiple Phase 3 trials of odronextamab in lymphoma patients as part of the OLYMPIA program. The FDA required that the trials include both dose-finding and confirmatory portions. While enrollment in the dose-finding portion has begun, the CRLs indicate that the confirmatory portions of these trials should be underway and that the timelines to completion be agreed prior to resubmission.[34] As of early November 2024, Regeneron had not publicly disclosed updates regarding these timelines.

First marketing approvals granted in only China or Russia in 2024

Mazorelvimab, Zamerovimab (Synermore Biologics Co. Ltd.)

Mazorelvimab and zamerovimab (克瑞毕®, SYN-023) is a 1:1 mixture of two humanized IgG1κ antibodies, CTB-011 and CTB-012, that bind non-overlapping epitopes of the rabies outer envelope glycoprotein. In June 2024, China's National Medical Products Administration (NMPA) approved the mixture of mazorelvimab and zamerovimab for post-exposure prophylaxis treatment of rabies.

The mazorelvimab and zamerovimab mixture was compared to human rabies immune globulin (HRIG) as post-exposure prophylaxis of rabies in adults with Category 3 rabies exposure risks in a randomized Phase 3 study (NCT04644484). The study, which was conducted in China, enrolled 1,000 participants who were administered a Chinese-licensed rabies vaccine in conjunction with the interventions, i.e., either the investigational antibody mixture or the control agent, HRIG. Interventions were administered by direct injection into the wound or, when this was not possible, by SC or intramuscular (IM) injection.

Results of the Phase 2 NCT03961555 clinical study, which also evaluated the effects of mazorelvimab and zamerovimab mixture and had a study design similar to that of the NCT04644484 study, were recently reported.[35] The NCT03961555 study enrolled 448 participants who were randomized to receive either 0.3 mg/kg SYN023 or 0.133 mL/kg HRIG as well as rabies vaccine within 54 hours of potential rabies exposure. The anti-rabies immune response with the mazorelvimab and zamerovimab mixture and rabies vaccine (RabAvert/Rabipur) was found to be non-inferior to that of HRIG and vaccine. No probable/confirmed rabies cases occurred in any patient and the safety profile of the mazorelvimab and zamerovimab mixture was acceptable.

Vunakizumab (Jiangsu Hengrui Pharmaceuticals Co., Ltd.)

Vunakizumab (SHR-1314, 夫那奇珠单抗, 安达静®) is a humanized IgG1κ monoclonal antibody that binds to IL-17A, a cytokine that plays a critical role in the inflammatory processes associated with various autoimmune disorders. On August 20, 2024, vunakizumab was approved by the NMPA for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[36]

The approval of vunakizumab was based on a multicenter, randomized, double-blind, parallel, placebo-controlled Phase 3 clinical study (SHR-1314-301). A total of 690 adult patients with moderate-to-severe plaque psoriasis were enrolled and randomly assigned in a 2:1 ratio to either the vunakizumab group (240 mg Q2W followed by 240 mg Q4W) or the placebo group (switching to vunakizumab 240 mg treatment at Week 12, with dosing Q2W at Weeks 12, 14, and 16, then Q4W thereafter). The co-primary endpoints were the proportion of subjects achieving Psoriasis Area and Severity Index 90 (PASI 90) at Week 12 and the proportion of subjects achieving a static Physician's Global Assessment (sPGA) score of 0/1 at Week 12. Key secondary endpoints included the proportion of subjects achieving PASI 75/PASI 100 at Week 12 and the proportion of subjects with an sPGA score of 0. At Week 12, the PASI 90 response rate was 76.8% in the vunakizumab group versus 0.9% in the placebo group. Similarly, the sPGA 0/1 response rate was 71.8% compared to 0.4% in the placebo group. Additional key measures also showed strong differences: PASI 75 was 93.6% versus 4.0%, PASI

100 reached 36.6% versus 0.0%, and the sPGA 0 response rate was 38.2% versus 0.0%. Efficacy was maintained through week 52 in the vunakizumab group, with PASI 100 and sPGA 0 response rates reaching 63.1% and 63.3%, respectively. The clinical response to vunakizumab had a rapid onset, with a mean percentage reduction in PASI of >50% by Week 2. By Week 4, 56.6% of participants had already achieved a PASI 75 response. During the 12-week induction phase, the overall occurrence and severity of adverse effects were similar between subjects treated with vunakizumab and those receiving a placebo.[37]

Xeligekimab (Chongqing Genrix Biopharmaceutical Co., Ltd.)

Xeligekimab (GR1501, 赛立奇单抗, 金立希®) is a human, hinge-stabilized IgG4κ antibody targeting interleukin-17A (IL-17A), a cytokine involved in several immune-mediated inflammatory diseases. On August 27, 2024, Genrix Bio announced that xeligekimab had been approved for market authorization by the NMPA for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[38] An NDA for xeligekimab for the indication of radiographic axial spondyloarthritis was accepted by the NMPA in January 2024.[39]

The approval of xeligekimab was based on a randomized, double-blind, placebo-controlled, multicenter Phase 3 clinical study (CTR20210246/ChiCTR2100043223) of patients with moderate-to-severe plaque psoriasis. Patients were randomized to 200 mg xeligekimab administered SC Q2W (n = 281) or placebo (n = 139) for the first 12 weeks, followed by an extension of the treatment schedule to xeligekimab Q4W for further 40 weeks. By Week 12, 90.7% of participants in the xeligekimab group achieved at least a 75% improvement from baseline compared to 8.6% in the placebo group. Additionally, 74.4% of patients in the treatment group achieved clear or almost clear skin (PGA 0/1) by Week 12, compared to 3.6% in the placebo group. The primary endpoint was successfully met. Furthermore, secondary clinical endpoints were also achieved, with a PASI 90 response rate of 74.4% at Week 12. The PASI 75/90 and PGA 0/1 responses were maintained up to week 52, demonstrating significant and lasting efficacy.[40]

Stapokibart (Keymed Biosciences Inc.)

Stapokibart (康悦达®, Kangyueda, CM310) is a humanized, hinge-stabilized IgG4κ monoclonal antibody developed by Keymed Biosciences that targets Interleukin-4 receptor alpha (IL-4 Rα), blocking both IL-4 and IL-13 signaling, ultimately reducing Type 2 inflammation. On September 12, 2024, Keymed Biosciences announced that the NMPA had approved stapokibart for the treatment of moderate-to-severe atopic dermatitis.[41] Keymed is also pursuing supplemental approvals. In June 2024, stapokibart's NDA for treating chronic rhinosinusitis with nasal polyps (CRSwNP) was accepted by the NMPA and granted priority review. In April 2024, the NMPA accepted an NDA for stapokibart targeting seasonal allergic rhinitis. Keymed also collaborates with CSPC Pharmaceutical Group to develop and commercialize stapokibart for the treatment of moderate-to-severe asthma, chronic obstructive pulmonary disease, and other respiratory diseases in China.

NMPA's approval was based on the results of a multicenter, randomized, double-blind, placebo-controlled Phase 3 confirmatory clinical study (CM310AD005). This trial evaluated the efficacy, safety, PK/PD, and immunogenicity of stapokibart in patients with moderate-to-severe atopic dermatitis. A total of 500 eligible patients were randomized in a 1:1 ratio to receive either stapokibart (600–300 mg Q2W) or a placebo. The co-primary endpoints were the proportion of subjects achieving ≥75% improvement in Eczema Area and Severity Index (EASI-75) from baseline and the proportion of subjects with an IGA score of 0 or 1 and a deduction of ≥2 points from baseline at Week 16 of treatment. The results showed that after 16 weeks of treatment with stapokibart, the proportion of subjects who achieved EASI-75 reached 66.9%, while 44.2% achieved an IGA score of 0 or 1 with a reduction of ≥2 points from baseline, both of which surpassed those of the placebo group (25.8% and 16.1%, respectively), with both differences being statistically significant ($p < 0.0001$). The two co-primary endpoints were both met successfully. At Week 52 of the maintenance treatment period, the EASI-75 achievement rates were 92.5% for the stapokibart group and 88.7% for those who switched from placebo to stapokibart. The rates for attaining an IGA score of 0 or 1 with a reduction of ≥2 points from baseline were 67.3% and 64.2%, respectively.[42]

Ebronucimab (Akeso Biopharma, Inc.)

Ebronucimab (AK102, 伊喜宁®) is a human anti-PCKS9 IgG1λ monoclonal antibody treatment for hypercholesterolemia jointly developed by Akeso Biopharma, Inc. and AD Pharmaceuticals. In September 2024, the NMPA approved ebronucimab for the treatment of primary hypercholesterolemia and mixed hyperlipidemia and heterozygous familial hypercholesterolemia (HeFH).[43]

The approval was based on results from four randomized pivotal studies, including three studies that evaluated ebronucimab vs. placebo as a treatment of primary hypercholesterolemia and mixed hyperlipidemia (CTR20212815 (450 mg Q4W dosing), CTR20213363 (450 mg or 600 mg Q6W dosing), CTR20212466 (450 mg Q4W or 150 mg Q2W)) and one for the treatment of HeFH (CTR20191935 (450 mg Q4W, 300 mg Q4W, or 150 mg Q2W dosing). The efficacy results of ebronucimab were consistent across studies and the different indication populations, showing that ebronucimab can significantly reduce low-density lipoprotein cholesterol (LDL-C) levels from baseline, with a maximum reduction of more than 65% in each dosing cycle.[44] The results of the Phase 3 CTR20212466 study (NCT05255094), which enrolled patients with primary hypercholesterolemia, including HeFH, or mixed dyslipidemia, showed that ebronucimab had a notable LDL-C-lowering effect in Chinese patients who received either the 450 mg Q4W or 150 mg Q2W dose.[45]

Ongericimab (Shanghai Junshi Biosciences Co., Ltd.)

Ongericimab (JS002, 昂戈瑞西单抗, 君适达®) is a humanized, hinge-stabilized anti-PCSK9 IgG4κ monoclonal antibody

developed by Junshi Biosciences. On October 11, 2024, it received approval from the NMPA for the treatment of primary hypercholesterolemia and mixed dyslipidemia (in combination with statins). Additionally, two sNDAs are currently under review by the NMPA. These include one for the treatment of heterozygous familial hypercholesterolemia, and another for patients with primary hypercholesterolemia and mixed dyslipidemia in which statins are not tolerated or contraindicated (as a single agent).[46]

The approval was primarily based on two pivotal Phase 3 clinical trials, both multicenter, randomized, double-blind, and placebo-controlled: JS002–003 (NCT04781114) and JS002–006 (NCT05532800). The JS002–003 study evaluated the efficacy and safety of SC ongericimab injections for treating primary hypercholesterolemia and mixed dyslipidemia in China, enrolling 806 participants. Results from this trial showed that SC injections of ongericimab, administered at doses of 150 mg Q2W or 300 mg Q4W, led to a significant reduction in LDL cholesterol levels – over 60% compared to placebo. These reductions were sustained over the 52-week treatment period. Additionally, ongericimab significantly improved other lipid measures, including non-HDL cholesterol, apolipoprotein B (ApoB), and total cholesterol. The safety profile of ongericimab was favorable, with no new safety concerns emerging during the study.

The JS002–006 study was designed to evaluate the efficacy and safety of ongericimab delivered via two different SC injection devices, a pre-filled syringe and an autoinjector, in treating primary hypercholesterolemia and mixed dyslipidemia. This trial enrolled 255 participants. Findings revealed that both methods of ongericimab administration showed significant lipid-lowering effects. After 12 weeks of treatment at a dose of 150 mg Q2W, patients experienced significant reductions in LDL cholesterol levels, with a 72.7% decrease in the pre-filled syringe group and a 71.1% decrease in the autoinjector group, compared to placebo, both showing favorable safety profiles.

Enlonstobart (CSPC Pharmaceutical Group Ltd.)

Enlonstobart (SG001, Enshuxing, 恩朗苏拜单抗, 恩舒幸®) is a human, hinge-stabilized anti-PD-1 IgG4κ monoclonal antibody that blocks the PD-1 pathway, which allows immune cells to target and destroy cancer cells more effectively. Enlonstobart was initially developed by Hangzhou Sumgen Biotech Co., Ltd. In November 2018, Sumgen Biotech entered into a strategic collaboration with CSPC Pharmaceutical Group for the development of enlonstobart. In June 2024, enlonstobart was granted conditional marketing approval by the NMPA for the treatment of recurrent or metastatic cervical cancer patients with positive PD-L1 (combined positive score (CPS)≥1) expression who previously failed to respond to platinum-based chemotherapy.[47,48]

The approval of enlonstobart is primarily based on data from a pivotal Phase 2 trial (NCT04886700), which demonstrated a significant improvement in the ORR for advanced cervical cancer treatment. In this multicenter, single-arm, open-label study, a total of 107 cervical cancer patients were enrolled, each receiving 240 mg of enlonstobart Q2W, with a maximum treatment duration of 24 months, or until disease progression, intolerable toxicities, or other criteria for study discontinuation were met. The trial results showed an ORR of 29%, as evaluated by an independent imaging review committee, with two patients achieving a complete response and 29 patients experiencing partial responses. The median DoR was 16.6 months. Furthermore, enlonstobart exhibited a favorable safety profile.[49]

An ongoing Phase 3 clinical trial (NCT05715840/CTR20230132) is assessing the efficacy of enlonstobart in combination with platinum-based chemotherapy, with or without bevacizumab, as a first-line treatment for recurrent or metastatic cervical cancer in patients with positive PD-L1 expression (CPS ≥ 1). Additionally, several other clinical studies are underway to explore enlonstobart's potential in combination with nanomedicines, antibody drugs, ADCs, and small-molecule therapies for the treatment of various solid tumors.

Iparomlimab, tuvonralimab (Qilu Puget Sound Biotherapeutics)

Iparomlimab and tuvonralimab (齐倍安®), which are anti-PD-1 and anti-CTLA-4 mAbs, respectively, are the components of the two-antibody mixture PSB205, also known as QL1706, developed by Qilu Puget Sound Biotherapeutics. The mixture is produced by a single cell line via the company's proprietary MabPair technology. Iparomlimab is a hinge-stabilized IgG4κ monoclonal antibody, while tuvonralimab is an IgG1κ monoclonal antibody carrying mutations in both heavy and light chain to allow efficient pairing of the correct chains.

In September 2024, the NMPA granted accelerated approval to PSB205 for the treatment of recurrent or metastatic cervical cancer.[50] The approval was based on results from the pivotal, single-arm Phase 2 DUBHE-C-206 study (NCT05557565) conducted by Qilu Pharma in China, which included 148 immune checkpoint inhibitors naïve patients with recurrent or metastatic cervical cancer who failed first-line platinum-based chemotherapy with or without bevacizumab. Patients received iparomlimab and tuvonralimab 5.0 mg/kg administered IV Q3W. The study's primary endpoint was the ORR evaluated by the independent review committee (IRC) and assessed up to 2 years. The ORR was 33.8%, the disease control rate (DCR) was 64.9%, and the median PFS was 5.4 months.[51] An ongoing, randomized, double-blind, placebo-controlled Phase 3 trial (NCT05446883) evaluating iparomlimab and tuvonralimab plus chemotherapy as first-line treatment for persistent, recurrent, or metastatic cervical cancer has a primary completion date in September 2024.

The iparomlimab and tuvonralimab mixture is also being investigated as a treatment for nasopharyngeal carcinoma (NPC) and non-small cell lung cancer (NSCLC). In NPC, results from a single-arm Phase 2 study (NCT05576272) of 29 patients who were administered QL1706 (5 mg/kg IV) in combination with chemotherapy (gemcitabine and cisplatin) were recently reported. The primary endpoint was safety and tolerability, and secondary endpoints included ORR, PFS, and OS. With a median follow-up of 15.5 months, the median ORR and PFS were 82.1% and 12.5 months, respectively, while the

median OS was not reached.[52] In NSCLC, results of an open-label, multicohort Phase 2 study (NCT05329025) assessing the efficacy and safety of QL1706 in combination with bevacizumab, paclitaxel or pemetrexed, and carboplatin in 91 patients with advanced epidermal growth factor receptor (EGFR) wild-type (60 patients) and EGFR mutant (31 patients) NSCLC were recently reported. All drugs were given IV on Day 1 Q3W at protocol-defined doses, with QL1706 dosed at 5 mg/kg. For patients with EGFR wild-type NSCLC, the ORR was 45%, and the median PFS was 6.8 months. In patients with EGFR-mutant NSCLC that progressed after EGFR-tyrosine kinase inhibitor (TKI) therapy, the ORR was 54.8% and the median PFS was 8.5 months.[53]

Benmelstobart (Sino Biopharmaceutical Ltd.)

Benmelstobart (Andewei, TQB2450) is a humanized anti-PD-L1 IgG1κ monoclonal antibody with an Fc engineered to reduce effector function (D265A) in development by Sino Biopharmaceutical's subsidiary Chia Tai Tianqing Pharmaceutical.

On April 29, 2024, benmelstobart was approved for marketing by NMPA in combination with anlotinib, carboplatin, and etoposide for the first-line treatment of ES-SCLC based on the results from randomized, double blinded, placebo controlled, multicenter Phase 3 ETER701 (NCT04234607) trial.[54] The study compared benmelstobart and anlotinib plus etoposide/carboplatin (EC; $n = 246$), placebo/anlotinib plus EC ($n = 245$) or double placebo/EC alone ($n = 247$). Benmelstobart (1,200 mg IV) was administered on Day 1 of each 21-day cycle. The benmelstobart and anlotinib plus EC treatment arm showed a significantly improved median OS (19.3 months) compared to the chemotherapy alone (etoposide/carboplatin) arm (OS 11.9 months; HR 0.61, $p < 0.05$), while the improvement of OS was not statistically significant with anlotinib plus EC (13.3 versus 11.9 months; HR 0.86; $p = 0.1723$). Compared with the EC alone group, the median IRC-assessed PFS was significantly longer in both the benmelstobart and anlotinib plus EC group (6.9 months (95% CI 6.2–8.3) versus 4.2 months (95% CI 4.17–4.24); HR 0.32 (95% CI 0.26–0.41); $p < 0.0001$) and in the anlotinib plus EC group (5.6 months (95% CI 5.6–6.8) versus 4.2 months (95% CI 4.17–4.24); HR 0.44 (95% CI 0.36–0.55); $p < 0.0001$).[55]

As of July 2024, the NMPA is reviewing marketing applications for benmelstobart for two additional indications: 1) in combination with anlotinib for the treatment of recurrent or metastatic endometrial cancer that has been previously treated by a first- or second-line chemotherapy regimen that was either unsuccessful or not tolerated and 2) in combination with anlotinib for the first-line treatment of advanced unresectable or metastatic renal cell carcinoma.[54] Benmelstobart is also undergoing evaluation in Phase 3 clinical trials for other indications, including maintenance treatment after radiotherapy and chemotherapy for NSCLC and first-line NSCLC.

Ivonescimab (Akeso, Summit Therapeutics)

Ivonescimab (依达方®) is a tetravalent, bispecific antibody targeting PD-1 and human vascular endothelial growth factor (VEGF) that was engineered to have impaired effector functions (L234A, L235A). By targeting these two antigens, the molecule combines cancer immunotherapy with an anti-angiogenesis mechanism of action. Akeso has out-licensed development and commercialization rights to ivonescimab in certain territories, including the United States, Canada, Europe, Japan, Latin America, Africa, and the Middle East, exclusively to Summit Therapeutics. To date, late-stage clinical studies of ivonescimab have focused on NSCLC indications. NMPA has granted three Breakthrough Therapy Designations for ivonescimab for treatment of NSCLC in various settings and patient populations.

In May 2024, the NMPA approved ivonescimab, combined with chemotherapy, for the treatment of EGFR-mutated locally advanced or metastatic non-squamous NSCLC patients who have progressed after treatment with EGFR TKIs. Ivonescimab is the first antibody targeting the combination of PD-1 and VEGF to be granted a marketing approval. The approval was based on results from the randomized, double-blinded Phase 3 hARMONi-A study (AK112–301, NCT05184712, CTR20213079), which was conducted in China.[56] Patients were randomized 1:1 to receive IV ivonescimab (20 mg/kg) plus pemetrexed (500 mg/m^2) and carboplatin (AUC 5) ($n = 161$) or IV placebo plus chemotherapy ($n = 161$) Q3W for four cycles. The primary endpoint was PFS assessed by IRC per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in the intention-to-treat (ITT) population. The median follow-up time was 7.89 months. The median PFS in the ivonescimab group was 7.1 (95% CI, 5.9–8.7) months vs 4.8 (95% CI, 4.2–5.6) months for placebo (difference, 2.3 months; HR, 0.46 [95% CI, 0.34–0.62]; $p < 0.001$). The ORR was 50.6% (95% CI, 42.6%–58.6%) with ivonescimab and 35.4% (95% CI, 28.0%–43.3%) with placebo (difference, 15.6% [95% CI, 5.3%–26.0%]; $p = 0.006$).

In July 2024, Akeso submitted a supplemental BLA for ivonescimab as a monotherapy for first-line treatment of PD-L1-positive (PD-L1 TPS ≥ 1%) locally advanced or metastatic NSCLC to the NMPA. The supplemental BLA is based on results from the Phase 3 hARMONi-2 (AK112–303, NCT05499390) study, which evaluated the efficacy and safety of ivonescimab compared to anti-PD-1 pembrolizumab (Keytruda®) as first-line treatment of advanced NSCLC patients whose tumors have a programmed cell death-ligand 1 (PD-L1) Tumor Proportion Score (TPS) greater than or equal to 1%. Patients (total $n = 398$) were randomly assigned to receive IV ivonescimab at a selected dose or IV pembrolizumab at 200 mg Q3W. The primary endpoint of the study was PFS assessed by IRRC per RECIST v1. Positive top-level results of a pre-specified interim analysis of data from the HARMONi-2 study were reported in September 2024.[57] In the ITT population, the median PFS for the ivonescimab group was 11.14 months vs. 5.82 months with pembrolizumab, while the ORR for the ivonescimab group was 50.0% vs. 38.5% with pembrolizumab. In addition, ivonescimab outperformed pembrolizumab across factors, such as age, sex, PD-L1 expression, histological type, and the presence of liver or brain metastases, in subgroup analyses.

Sacituzumab tirumotecan (Sichuan Kelun Pharmaceutical Co., Ltd., Merck & Co.)

Sacituzumab tirumotecan (佳泰莱®, SKB264, MK-2870) is a humanized, IgG1κ ADC targeting TROP2 with a proprietary cytotoxic, belotecan-derived payload. This ADC has an average drug-to-antibody ratio (DAR) of 7.4 and includes a hydrolytic linker that enables extracellular pH-sensitive cleavage and intracellular enzymatic cleavage to release the membrane-permeable payload. Kelun Pharmaceutical granted development rights to sacituzumab tirumotecan in territories outside Greater China (including Mainland China, Hong Kong, Macao, and Taiwan) to Merck & Co. in 2022. Sacituzumab tirumotecan has received three Breakthrough Therapy designations from the NMPA for: 1) locally advanced or metastatic triple-negative breast cancer (TNBC), 2) locally advanced or metastatic HR-positive and HER2− breast cancer which has received at least second-line systemic therapy, and 3) locally advanced or metastatic EGFR-mutated NSCLC which has failed EGFR- TKI therapy.

On November 21, 2024, the NMPA granted marketing authorization in China for sacituzumab tirumotecan for adult patients with unresectable locally advanced or metastatic TNBC who have received at least two prior systemic therapies, with at least one of them for advanced or metastatic setting. The approval is based on the positive results from the Phase 3 OptiTROP-Breast01 study.[58]

Results of the Phase 3 OptiTROP-Breast01 study (NCT05347134) in which sacituzumab tirumotecan monotherapy demonstrated statistically significant and clinically meaningful PFS and OS benefits over chemotherapy were recently reported.[59] In this study, patients with locally recurrent or metastatic TNBC who had received two or more prior therapies including at least one for metastatic setting were randomly assigned (1:1) into the experiment group ($n = 130$) and control group ($n = 133$), stratified by number of previous treatment lines (2–3 vs. >3). The effects of sacituzumab tirumotecan (5 mg/kg, IV on day 1 and Day 15 of each 28-day cycle) were then compared with the control, which was the physician's choice of chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine). The primary endpoint was progression-free survival (PFS) by blinded ICR. The TROP2 expression was determined by immunohistochemistry (IHC) using the semi-quantitative H-score method. The primary endpoint of PFS was met based on interim analysis (data cut-off: Jun 21, 2023) with a 69% reduction in risk of progression or death (HR 0.31; 95% CI, 0.22 to 0.45; $p < 0.00001$). The median PFS assessed by blinded ICR was 5.7 months (95% CI, 4.3 to 7.2) and 2.3 months (95% CI, 1.6 to 2.7) with sacituzumab tirumotecan and with chemotherapy, respectively, with PFS at 6 months 43.4% vs. 11.1%, respectively. In the subset of patients with TROP2 h-score of >200, the median PFS was 5.8 months with SKB264 and 1.9 months with chemotherapy (HR 0.28; 95% CI, 0.17 to 0.48). As assessed by the blinded ICR, the objective response rate was 43.8% and 12.8% with SKB264 and with chemotherapy, respectively.

Two supplemental marketing applications are undergoing review by NMPA. In August 2024, the NMPA accepted a marketing application for sacituzumab tirumotecan for the treatment of patients with locally advanced or metastatic EGFR-mutant NSCLC who failed after treatment with an EGFR-TKI and platinum-based chemotherapy. Another application for treatment of adult patients with locally advanced or metastatic NSCLC with EGFR mutations who have progressed after EGFR-TKI therapy was accepted by NMPA in October 2024.[58]

The marketing application for sacituzumab tirumotecan for treatment of patients with locally advanced or metastatic EGFR-mutant NSCLC who failed after treatment with an EGFR-TKI and platinum-based chemotherapy was based on the results of the OptiTROP-Lung03 study. This randomized, pivotal clinical study evaluated sacituzumab tirumotecan monotherapy (5 mg/kg, IV Q2W) versus docetaxel for the treatment of patients with locally advanced or metastatic EGFR-mutant NSCLC who failed after treatment with EGFR-TKI therapy and platinum-based chemotherapy. At a pre-specified analysis, sacituzumab tirumotecan monotherapy demonstrated a statistically significant and clinically meaningful improvement in ORR and PFS compared with docetaxel.[58]

Merck has initiated 10 Phase 3 clinical trials evaluating sacituzumab tirumotecan. Five studies are recruiting NSCLC patients (NCT06074588, NCT06170788, NCT06312137, NCT06305754, and NCT06422143), while one each is recruiting patients with endometrial cancer (NCT06132958), HR +/HER2− unresectable locally advanced or metastatic breast cancer (NCT06312176), cervical cancer (NCT06459180), TNBC (NCT06393374), and gastroesophageal cancer (NCT06356311).

Seniprutug (BIOCAD)

Seniprutug (Tribuvia®, BCD-180) is a humanized anti-T cell receptor Vbeta9 IgG1 monoclonal antibody developed by BIOCAD and scientists from the Pirogov Russian National Research Medical University. In April 2024, the Ministry of Health of the Russian Federation registered seniprutug (Tribuvia®) for the treatment of patients with radiological axial spondyloarthritis (axSpA).[60] Seniprutug is the first antibody targeting TCR Vbeta9 to be granted a marketing approval.

The effects of a fixed dose of seniprutug were compared with adalimumab and placebo in patients with active axSpA in the 5-arm Phase 3 LEVENTA study (NCT06333210). The study, which was conducted in Belarus and the Russian Federation, included HLA-B27+ patients with radiographic axSpA and non-radiographic axSpA who had no response to prior therapy with non-steroidal anti-rheumatic drugs (NSAIDs), had not received biologic disease-modifying anti-rheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), and those with insufficient efficacy and/or loss of efficacy on bDMARDs and/or tsDMARDs. Interventions in the study arms were: 1) IV seniprutug; 2) IV placebo; 3) IV seniprutug + SC placebo; 4) IV + SC placebo; 5) IV placebo + SC adalimumab. The primary outcome measures were the proportion of subjects who achieved ASAS40 among bDMARDs and tsDMARD-naive and among bDMARDs and/or tsDMARD-experienced

subjects at Week 24. An ASAS40 (Assessment in SpondyloArthritis 40%) response is defined as a ≥ 40% improvement in three of the four areas of a scoring system designed to rate the severity of axSpA.

Seniprutug demonstrated superiority over placebo in the Phase 2 ELEFTA study (NCT05445076), which evaluated two doses of seniprutug in comparison with placebo in patients with active radiographic axSpA.[61] The study included HLA-B27+ patients with radiographic axSpA who had no response to prior therapy with NSAIDs, have not received biologic therapy or tDMARDs. A total of 260 patients were randomized into three groups and were administered seniprutug at doses of 5 mg/kg or 7 mg/kg, or placebo. Seniprutug was administered at Weeks 0–12–36. Patients in the placebo group were switched to seniprutug at a dose of 5 mg/kg at Week 24 and continued therapy at Week 36. The primary outcome measure was the proportion of subjects who achieved ASAS40 at Week 24. The proportion of patients who were administered seniprutug at the dose of 7 and 5 mg/kg and achieved ASAS40 at Week 24 was 51.4% and 40.8%, respectively, compared with 24% in the placebo group ($p = 0.0012$ and $p = 0.0417$, respectively). The tolerability of seniprutug therapy was deemed acceptable.

Antibody therapeutics undergoing first regulatory review

We identified 30 investigational (i.e., not approved for marketing in any country) antibody therapeutics for which marketing applications, which include BLAs submitted in the US, marketing authorization applications submitted in the EU, and new drug applications (NDAs) submitted in China, were undergoing review by at least one regulatory agency, as of our last update on December 9, 2024 (Table 2). Of these applications, 13 were undergoing review in either the US or the EU and possibly other countries, while 17 were undergoing review solely in China. Sixteen applications were for non-cancer indications, while 14 were for cancer. Relevant details for these molecules are summarized below, in the order they appear in Table 2.

Antibodies with marketing applications in review: non-cancer indications

Bentracimab (SFJ Pharmaceuticals, SERB Pharmaceuticals)

Bentracimab (PB2452; formerly MEDI2452) is a human antibody Fab that binds to and neutralizes Brilinta®/Brilique® (ticagrelor), thereby reversing the antiplatelet effects of ticagrelor and its active metabolite. Ticagrelor is an oral $P2Y_{12}$ platelet inhibitor with a product label that includes a black box warning regarding bleeding risk. The FDA and EMA have granted bentracimab Breakthrough Therapy and PRIME designations, respectively. SERB Pharmaceuticals acquired exclusive US rights to bentracimab from SFJ Pharmaceuticals. The FDA accepted a BLA for bentracimab, with priority review and a target action date in the first quarter of 2025.[62]

The BLA submission was based on the results of the single-arm, open-label trial Phase 3 REVERSE-IT trial (NCT04286438), which evaluated the effects of bentracimab in ticagrelor-treated patients requiring urgent surgery or other invasive procedures or who have major bleeding. An interim analysis indicated that bentracimab reversed the ticagrelor's antiplatelet effects within 5 to 10 minutes and the effect was sustained for over 24 hours.[63] The BLA also includes results of the planned second interim analysis of the REVERSE-IT trial data.[62]

Garadacimab (CSL Ltd.)

Garadacimab (CSL312) is a hinge-stabilized, human anti-Factor XIIa IgG4λ antibody developed as a treatment for hereditary angioedema (HAE). An unusually long CDR-H3 of garadacimab binds the beta-chain of FXIIa, thereby inhibiting its proteolytic activity and the subsequent activation of procoagulant and proinflammatory pathways.[64] Garadacimab was granted Orphan Drug and Orphan Medicinal Product designations for hereditary angioedema in the US and the EU, respectively.

Marketing applications for garadacimab as a once-monthly, autoinjector-administered, prophylactic treatment for HAE are undergoing review in the EU, US, Japan, and Canada. These applications include data from Phase 2, pivotal Phase 3, and open-label extension studies, which demonstrated that garadacimab provides durable protection against HAE attacks and has a safety profile suitable for long-term use.[65,66] CSL anticipates approvals for garadacimab for HAE in the EU, the US, and Japan in the first half of 2025.[67]

Nipocalimab (Johnson & Johnson)

Nipocalimab (JNJ-80202135, M281) is a human-aglycosylated IgG1λ monoclonal antibody targeting the neonatal Fc receptor (FcRn), a protein responsible for regulating the levels of IgG antibodies in the bloodstream. As demonstrated in preclinical models, blocking FcRn nipocalimab increases circulating levels of IgG antibodies, thereby reducing immune system overactivity in auto-immune diseases. Nipocalimab is being developed by Johnson & Johnson as a treatment for diseases driven by pathogenic IgG antibodies, such as generalized myasthenia gravis (gMG) and hemolytic disease of the fetus and newborn (HDFN).

Nipocalimab was granted US Fast Track and Orphan Drug designations for gMG and HDFN, US Breakthrough Therapy designation for HDFN, as well as Orphan Medicinal Product designation for HDFN in the EU. The drug has additional regulatory agency designations for warm autoimmune hemolytic anemia, fetal neonatal alloimmune thrombocytopenia, and chronic inflammatory demyelinating polyneuropathy. Johnson & Johnson has submitted marketing applications to the FDA and EMA for nipocalimab for the treatment of gMG patients.[68,69]

The marketing application submissions were based on the positive data from the double-blind placebo-controlled Phase 3 Vivacity-MG3 trial (NCT04951622). In this study, 153 seropositive adult gMG patients with insufficient response (MG-Activities of Daily Living (MG-ADL) score ≥6) to ongoing SOC were randomized 1:1 to receive nipocalimab (30 mg/kg IV loading dose followed by 15 mg/kg every 2 weeks) plus current SOC or placebo plus current SOC. The study results demonstrate sustained disease control over 24 weeks in

Table 2. Commercially sponsored investigational monoclonal antibody therapeutics with marketing applications in regulatory review in any country.

INN or drug code	Target; Format	Indication(s) under review	Country/region of review
Bentracimab	Ticagrelor; Human IgG1λ Fab	Reversal of the antiplatelet effects of ticagrelor	US
Garadacimab	Factor XIIa; Human IgG4λ	Hereditary angioedema	EU, US, Japan, Canada
Nipocalimab	FcRn; Human IgG1λ	Generalized myasthenia gravis	EU, US
Vilobelimab	Complement C5a; Chimeric IgG4κ	Septic acute respiratory distress syndrome induced by SARS-CoV-2	EU
Sipavibart	SARS-CoV-2; Human IgG1λ	Prophylaxis of COVID-19	EU, Japan
Clesrovimab	RSV (F glycoprotein); Human IgG1κ	Prevention of RSV infection	EU
Narsoplimab	MASP-2; Human IgG4λ	Hematopoietic stem cell transplant-associated thrombotic microangiopathy	US (2nd cycle)
Recaticimab	PCSK9; Humanized IgG1κ	Hypercholesterolemia	China
Suciraslimab	CD22; Chimeric IgG1κ	Rheumatoid arthritis	China
TNM002	Tetanus toxin; Human	Prophylaxis of *C. tetani* infection	China
Gensci-048	IL-1 beta	Acute gouty arthritis	China
IBI311	IGF-1 R	Thyroid eye disease	China
Batoclimab	FcRn; Human IgG1λ	Generalized myasthenia gravis	China (resubmission)
Ebdarokimab	IL-12/23p40; Humanized IgG1κ	Psoriasis	China
Picankibart	IL-23p19; Human IgG1κ	Psoriasis	China
SSGJ-608, 608	IL-17A	Psoriasis	China
Cosibelimab	PD-L1; Human IgG1λ	Squamous cell carcinoma	US (resubmission)
Datopotamab deruxtecan	TROP-2; Humanized IgG1κ, ADC	HR+/HER2- breast cancer, NSCLC	EU, US, Japan, Canada
Telisotuzumab vedotin	cMET, Humanized IgG1κ, ADC	NSCLC	US
Patritumab deruxtecan	HER3; Human IgG1κ, ADC	NSCLC	US (2nd cycle)
Linvoseltamab	BCMA, CD3; Human IgG4κ, Bispecific	Multiple myeloma	EU, US (2nd cycle)
Bifikafusp alfa, Onfekafusp alfa	Fibronectin EDB; Human immunoconjugate mixture (scFv-IL2, scFv-TNF)	Melanoma	EU
Trastuzumab botidotin (舒泰莱®)	HER2; Humanized IgG1κ ADC	HER2+ breast cancer	China
Tagitanlimab (科泰莱®)	PD-L1; Humanized IgG1κ	Nasopharyngeal cancer, solid tumor indications	China
Becotatug vedotin	EGFR; Humanized IgG1κ ADC	Nasopharyngeal cancer	China
Iparomlimab	PD-1; Humanized/chimeric IgG4κ	Cancer	China
Finotonlimab	PD-1; Humanized IgG4κ	Head and neck squamous cell carcinoma, hepatocellular carcinoma	China
Suvemcitug (ENZESHU)	VEGF-A; Humanized IgG1κ	Epithelial ovarian, fallopian tube, or primary peritoneal cancer.	China
Trastuzumab rezetecan	HER2; Humanized IgG1κ ADC	NSCLC	China
Retlirafusp-α	PD-L1, TGF beta; Human IgG4κ bispecific immunoconjugate	Gastric and gastroesophageal junction adenocarcinoma	China

Table includes information found in the public domain as of December 9, 2024. Abbreviations: ADC, antibody–drug conjugate; BCMA, B cell maturation antigen; EDB, extra-domain B; HER, human epidermal growth factor receptor; IL, interleukin; MASP, mannan-binding lectin-associated serine protease; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; scFv, single-chain variable fragment; TNF, tumor necrosis factor; TROP-2, trophoblast cell-surface antigen 2. Monthly lists of medicines for human use under evaluation by EMA available at: https://www.ema.europa.eu/en/medicines/medicines-human-use-under-evaluation. Further data for antibody therapeutics undergoing review available at: https://www.antibodysociety.org/antibody-therapeutics-product-data/.

antibody-positive adult patients who received nipocalimab. During the double-blind phase, 31.2% (24/77) of patients receiving nipocalimab and 13.2% (10/76) of those in the placebo arm achieved the pre-specified endpoint of minimal symptom expression, defined as an MG-ADL total score of 0 or 1, at any point.[70]

Ongoing late-stage clinical studies are also evaluating the efficacy and safety of nipocalimab in: 1) children with gMG (Phase 2/3 NCT05265273 study); 2) adults with pregnancies at risk for HDFN (Phase 3 AZALEA trial (NCT05912517)); 3) patients with warm autoimmune hemolytic anemia (Phase 2/3 ENERGY study (NCT04119050)); 4) adults with chronic inflammatory demyelinating polyneuropathy (Phase 2/3 NCT05327114 study); and 5) adults with pregnancies at risk of fetal and neonatal alloimmune thrombocytopenia (Phase 3 FREESIA-1 study (NCT06449651)). As of November 2024, these studies are recruiting participants.

Vilobelimab (InflaRx N.V.)

Vilobelimab (Gohibic), a chimeric IgG4κ antibody, blocks complement system-mediated inflammatory responses by binding to one component of the system, complement C5a. InflaRx N.V. is developing vilobelimab as a treatment for SARS-CoV-2-induced septic acute respiratory distress syndrome (ARDS) and ulcerative pyoderma gangrenosum, which are diseases in which C5a signaling plays a key role. Vilobelimab was granted Fast Track and Orphan Drug designations by the FDA, and Orphan Medicinal Product designation by EMA, for the treatment of ulcerative pyoderma gangrenosum.

In August 2023, the EMA started the evaluation of a marketing application for vilobelimab. On November 14, 2024, EMA's Committee for Medicinal Products for Human Use adopted a positive opinion, recommending approval of Gohibic for the treatment of adults with SARSCoV2induced acute respiratory distress syndrome (ARDS) who are receiving

systemic corticosteroids.[71] The European Commission's decision will normally be issued 67 days from adoption of an opinion.

The application included results of the Phase 2/3 PANAMO trial ($n = 368$; NCT04333420), which evaluated vilobelimab plus SOC vs placebo plus SOC for the treatment of COVID-19 related severe pneumonia. SOC included concomitant corticosteroids (97%) and anti-thrombotic agents (98%), as well as immunomodulators (~20%), predominantly tocilizumab over baricitinib. A post-hoc subgroup analysis of 61 patients administered tocilizumab in the vilobelimab plus SOC and placebo plus SOC groups indicated that co-administration of vilobelimab and tocilizumab may result in a synergistic survival benefit in such critically ill ARDS patients.[72]

Sipavibart (AstraZeneca)

Sipavibart (AZD3152) is a human IgG1λ antibody that targets the spike protein of SARS-CoV-2. Derived from B-cells of patients after SARS-CoV-2 infection, sipavibart was optimized for reduced Fc effector function (L234F, L235E, P331S), which minimizes the risk of antibody-dependent enhancement of infections, and extended half-life (M252Y, S254T, T256E). Sipavibart was licensed by AstraZeneca from RQ Biotechnology in May 2022. AstraZeneca submitted a marketing application to EMA for sipavibart for the pre-exposure prophylaxis of COVID-19 in immunocompromised patients.[73] EMA's evaluation of the application, which was accepted under an accelerated assessment procedure, started in June 2024. AstraZeneca has also submitted a marketing application for sipavibart for the pre-exposure prophylaxis of COVID-19 in immunocompromised patients in Japan.

The marketing applications included data from the Phase 1/3 SUPERNOVA trial (NCT05648110) of sipavibart vs tixagevimab/cilgavimab (EVUSHELD) or placebo in preventing COVID-19 in immunocompromised patient population. The study included an open-label Phase 2 sub-study to evaluate the safety, PK, and neutralizing activity of AZD3152 for pre-exposure prophylaxis of COVID-19. AZD3152 was IM administered as 300 mg doses on Day 1 and Day 181 of the SUPERNOVA trial. In total, 1,669/3,335 participants received sipavibart and 1,666/3,335 received comparator. Positive high-level results from the trial showed sipavibart demonstrated a statistically significant reduction in the incidence of symptomatic COVID-19 compared to control (tixagevimab/cilgavimab or placebo) in an immunocompromised patient population. The trial met both dual primary endpoints: 1) relative risk reduction of symptomatic COVID-19 caused by any SARS-CoV-2 variant and 2) relative risk reduction of infections caused by SARS-CoV-2 variants not containing the F456L mutation.[74]

Clesrovimab (Merck Sharp & Dohme LLC (MSD))

Clesrovimab (MK-1654) is a human monoclonal IgG1κ antibody developed by Merck (MSD) for the prevention of respiratory syncytial virus (RSV) infections, particularly in infants and vulnerable populations such as older adults. The mechanism of action involves neutralizing RSV by targeting the virus' F protein, which is essential for viral entry into host cells. Incorporation of YTE mutations (M252Y, S254T, T256E) extend its half-life to allow for dosing once every RSV season. EMA began the evaluation of a marketing application for clesrovimab on November 28, 2024.

In October 2024, Merck announced positive topline results from its double-blind, randomized Phase 2b/3 clinical trial (MK-1654-004, NCT04767373) comparing the safety and efficacy of a single 105 mg dose of clesrovimab administered IM vs placebo in 3,632 healthy preterm and full-term infants. All prespecified endpoints of the study were met. The reduction in incidence of RSV-associated medically attended lower respiratory infections requiring ≥1 indicator of lower respiratory infection or severity compared to placebo through Day 150 (5 months) post-dose, which was the primary efficacy endpoint, was 60.4% (95% CI: 44.1, 71.9, $p < 0.001$). In addition, RSV-associated hospitalizations (secondary endpoint) and RSV-associated lower respiratory tract infection hospitalizations (tertiary endpoint) through Day 150 were reduced by 84.2% (95% CI: 66.6, 92.6, $p < 0.001$) and 90.9% (95% CI: 76.2, 96.5), respectively, in participants who received clesrovimab vs. placebo.[75]

Merck is evaluating the effects IM clesrovimab vs IM palivizumab in infants and children at increased risk for severe RSV disease in the Phase 3 MK-1654-007 trial (NCT04938830). An estimated 1000 participants were enrolled in this study, which is active, but not enrolling as of October 2024. The study's primary completion date is in April 2025.

Narsoplimab (Omeros Corporation)

Narsoplimab (OMS721) is a human anti-mannan-binding lectin-associated serine protease-2 (MASP-2) antibody. The target is an effector enzyme of the lectin pathway of the complement system. The FDA granted narsoplimab Breakthrough Therapy designation in patients who have high-risk hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA), and Orphan Drug designation for the prevention of complement-mediated TMAs and for the treatment of TA-TMA. Narsoplimab has also been designated an Orphan Medicinal Product for treatment in hematopoietic stem cell transplantation in the EU.

Omeros Corporation's rolling submission of the BLA for narsoplimab as a treatment for TA-TMA was completed in late 2020. After receiving a CRL from the FDA concerning issues with the BLA, Omeros has engaged in ongoing discussions with the agency regarding: 1) an analysis plan to assess already existing clinical trial data, existing data from an historical control population available from an external source, data from the narsoplimab expanded access (i.e., compassionate use) program, and data directed to the mechanism of action of narsoplimab; and 2) the FDA's requirements for resubmission of the BLA. The company has revised and resubmitted the statistical analysis plan and the FDA has now responded with additional recommendations on the analysis plan. Following data preparation, if the results of primary and secondary efficacy analyses support resubmission, the company intends to finalize and resubmit the BLA as soon as possible.[76] Moreover, the company plans to submit a marketing application to EMA in the first half of 2025.

Omeros's clinical pipeline also includes OMS1029, which is a long-acting, next-generation MASP-2 inhibitor being evaluated in Phase 1 studies, and zaltenibart (OMS906), which is an anti-MASP-3 antibody evaluated in Phase 2 studies of patients with PNH. Omeros plans to initiate a Phase 3 program for zaltenibart in PNH by the end of 2024.

Recaticimab (Jiangsu Hengrui pharmaceuticals Co., Ltd.)

Recaticimab (SHR-1209, 瑞卡西单抗) is a long-acting, humanized IgG1κ monoclonal antibody that selectively targets PCSK9. The Fc region was mutated (M252Y, S254T, T256E) to extend the serum half-life of the antibody. In June 2023, Hengrui announced that the NDA for recaticimab was accepted by the NMPA. This submission was based on three multicenter, randomized, double-blind, placebo-controlled Phase 3 clinical trials (SHR-1209-301, SHR-1209-302, and SHR-1209-303), each investigating different indications.

The SHR-1209-301 study (REMAIN-1, NCT04849000) evaluated the efficacy and safety of SHR-1209 as a monotherapy in patients with non-familial hypercholesterolemia and mixed hyperlipidemia. The primary endpoint measured the percentage change in LDL-C from baseline to Week 12 for the 150 mg Q4W and 450 mg Q12W dosing regimens, and to Week 16 for the 300 mg Q8W. A total of 703 patients were randomized to receive either recaticimab at doses of 150 mg Q4W ($n = 157$), 300 mg Q8W ($n = 156$), or 450 mg every 12 weeks ($n = 155$), or placebo ($n = 78$, 79, and 78, respectively). Recaticimab further lowered patients' LDL-C levels compared to placebo, achieving reductions of 49.6% (95% CI: 44.2%–54.9%) at 150 mg Q4W, 52.8% (95% CI: 48.3%–57.2%) at 300 mg Q8W, and 45.0% (95% CI: 41.0%–49.0%) at 450 mg Q12W ($p < 0.0001$ for all comparisons). The safety profile of recaticimab was comparable to that of placebo. After 12 or 16 weeks of treatment, patients on recaticimab continued until Week 24, while those initially on placebo were switched to recaticimab following the same dosing regimen. Both the 24-week recaticimab regimen and the 12- or 8-week recaticimab treatment after placebo showed continued efficacy.[77]

SHR-1209-302 study (REMAIN-2, NCT04885218) examined the efficacy and safety of SHR-1209 as an add-on therapy for patients with non-familial hypercholesterolemia (non-FH) and mixed hyperlipidemia, with the enrollment of 689 participants. Patients were randomized to receive recaticimab (150 mg Q4W, 300 mg Q8W, and 450 mg Q12W) or a placebo for 48 weeks. The primary efficacy endpoint was defined as the percentage change in calculated LDL-C levels from baseline to Week 24. Results showed a significant and dose-dependent reduction in LDL-C levels with recaticimab compared to placebo, with treatment differences of −62.2%, −59.7%, and −53.4% for the respective dosages. At Week 24, 85.8% to 94.5% of patients treated with recaticimab reached the LDL-C target levels, with these reductions maintained over the 48-week trial.[78]

The SHR-1209-303 study evaluated the efficacy and safety of SHR-1209 in combination with other lipid-lowering therapies for patients with heterozygous familial hypercholesterolemia. A total of 143 patients were randomized to receive either recaticimab ($n = 95$) or placebo ($n = 48$). By Week 12, the recaticimab group showed a mean LDL-C reduction of 54.4% (95% CI: −57.9% to −50.8%), compared to a 4.5% reduction in the placebo group (95% CI: −9.4% to 0.3%). The treatment difference was −49.8% (95% CI: −55.8% to −43.9%; $p < 0.0001$), demonstrating the significant impact of recaticimab.[79]

Suciraslimab (SinoMab BioScience Limited)

Suciraslimab (SM03, 舒西利单抗) is a chimeric anti-CD22 IgG1κ antibody developed by SinoMab BioScience for the treatment of rheumatoid arthritis. Suciraslimab binds specifically to a conformational epitope of CD22, which facilitates the conversion of CD22 from cis-ligand to trans-ligand binding, and trans-ligand bound CD22 can suppress BCR-elicited immune response against autologous cells.[80] In September 2023, the NMPA accepted the BLA for suciraslimab as a treatment for rheumatoid arthritis, and, as of June 2024, it was in the final review stage. SinoMab plans to further develop suciraslimab as a treatment for systemic lupus erythematosus (SLE), MCI due to Alzheimer's disease, as well as Alzheimer's disease.[81]

TNM002 (Zhuhai Trinomab Biotech Co., Ltd.)

TNM002 is a human monoclonal antibody that targets the tetanus neurotoxin (TeNT), offering a novel therapeutic approach for preventing or treating tetanus. Developed through Trinomab's proprietary HitmAb® technology platform, TNM002 works by binding to the TeNT toxin, neutralizing its effects on the nervous system, and is designed for IM administration. On December 6, 2023, Trinomab announced that the NDA for TNM002 was accepted by the NMPA and granted priority review for emergency tetanus prevention.[82]

A multicenter, randomized, double-blind, parallel, and positive-controlled Phase 3 clinical trial (CTR20223067/NCT05664750) evaluated IM administration of TNM002 vs human tetanus immunoglobulin (HTIG) as prophylaxis against tetanus. The primary endpoint was an increase in tetanus-neutralizing antibody titers compared to baseline after administration. TNM002 achieved protective levels of anti-tetanus antibodies, outperforming the standard 250 IU HTIG in both efficacy and antibody duration. TNM002 demonstrated good safety, tolerability, and low immunogenicity, with an adverse event rate comparable to placebo or HTIG in Phase 1–3 trials.[82]

Gensci-048 (Changchun GeneScience Pharmaceutical Co., Ltd.)

Gensci-048 (genakumab, 金纳单抗) is a humanized monoclonal antibody targeting the interleukin-1β (IL-1β) pathway. IL-1β is a key pro-inflammatory cytokine that plays a role in various inflammatory diseases. By specifically blocking the binding of IL-1β to its receptor, genakumab can inhibit inflammation. In April 2024, GenSci announced that the marketing application for genakumab had been accepted by the NMPA for the treatment of acute gouty arthritis. Genakumab is also undergoing clinical research for other indications, such as systemic juvenile idiopathic arthritis and interstitial lung disease.[83]

GenSci conducted a prospective, randomized, multicenter, active-controlled Phase 3 study (GUARD-1, CTR20223136)

involving Chinese adult patients with gout flares, featuring a 48-week treatment period followed by a 12-week safety follow-up. Patients were randomized (1:1) to receive a single dose of genakumab 200 mg SC ($n = 157$) or betamethasone 7 mg IM ($n = 156$), with re-dosing administered on demand in case of new episodes in intervals >2 weeks. The study demonstrated that genakumab effectively reduced pain and delayed new episodes compared to betamethasone. The co-primary endpoints included the change in pain intensity for the most affected joint at baseline, assessed 72 hours post-treatment using the 0–100 mm Visual Analog Scale (VAS), and the time to the first new gout episode within 12 weeks. Genakumab demonstrated non-inferiority in reducing pain intensity at 72 hours compared to betamethasone, with a mean difference in pain scores of −3.32 mm (95% CI: −7.56 to 0.91) in the Full Analysis Set and −2.21 mm (95% CI: −6.49 to 2.07) in the Per Protocol Set. Additionally, genakumab significantly extended the median time to the first new gout episode compared to betamethasone, which had a median time of 45 days (with data for genakumab not estimable).[84]

IBI311 (Innovent Biologics, Inc)

IBI311 is a recombinant anti-insulin-like growth factor 1 receptor (IGF-1 R) antibody developed by Innovent to treat thyroid eye disease (TED). By binding to IGF-1 R, a receptor overexpressed in orbital fibroblasts (OFs), B cells, and T cells in TED patients, IBI311 blocks IGF-1 R signaling, reducing the activation of inflammatory pathways. This action helps decrease the production of hyaluronic acid and other glycosaminoglycans associated with OF activation, alleviating symptoms such as proptosis, diplopia, and ocular congestion. In May 2024, the NMPA accepted the NDA for IBI311 for TED treatment.[85]

This NDA was accepted based on the positive results of a multicenter, randomized, double-masked, placebo-controlled Phase 2/3 clinical study RESTORE-1 (CTR20223393). Phase 3 results showed that the primary endpoint was successfully met, demonstrating significant improvements in proptosis, disease activity, and quality of life in patients treated with IBI311 compared to placebo. At Week 24, the proportion of participants experiencing a reduction in proptosis of ≥2 mm from baseline in the study eye, without deterioration ≥2 mm increase in the fellow eye, was significantly greater in the IBI311 group compared to the placebo group. The responder rates for those receiving IBI311 and placebo were 85.8% and 3.8%, respectively, showing a significant difference of 81.9% (95% CI: 69.8% to 93.9%, $p < 0.0001$). IBI311 also showed significant improvements compared to placebo in key secondary endpoints, such as overall response rate (the percentage of subjects with a reduction in proptosis of ≥2 mm from baseline and an improvement in clinical activity score of ≥2 in the study eye), the percentage of subjects with a clinical activity score (CAS) of 0 or 1, and the mean change in proptosis from baseline in the study eye. The overall safety profile of IBI311 was favorable with no serious adverse events reported.[86]

Batoclimab (Harbour BioMed (Guangzhou) Co. Ltd., Roivant sciences Ltd., HanAll Biopharma)

Batoclimab (HBM9161, IMVT-1401, 巴托利单抗) is a human IgG1λ anti-FcRn monoclonal antibody with an Fc engineered for reduced effector function (L234A, L235A) initially developed by HanAll Biopharma as a treatment for IgG-mediated autoimmune diseases, including generalized myasthenia gravis (gMG) and Grave's disease. HanAll Biopharma licensed batoclimab to Harbour Biomed, which subsequently entered into an agreement with NBP Pharma, a wholly owned subsidiary of the CSPC Group, to co-develop batoclimab in Greater China. HanAll also licensed batoclimab development rights to Roivant Sciences for North America, Latin America, Switzerland, and North Africa, as well as the EU, UK, and the Middle East. Batoclimab received Breakthrough Therapy designation from NMPA for the treatment of adult patients with MG.

In June 2023, Harbour BioMed submitted a marketing application to NMPA for the treatment of gMG, then resubmitted the application with additional safety data in June 2024.[87] The submission was based on positive results from a placebo-controlled Phase 3 study (NCT05039190) conducted in China, which showed that weekly SC batoclimab (680 mg dose) demonstrated efficacy for both primary and secondary endpoints in gMG. Patients ($n = 131$) who tested positive for antibodies received placebo or SC batoclimab (680 mg dose) weekly. Each treatment cycle consisted of a 5-week treatment period in which patients received six doses of placebo or drug, followed by a 4-week observation period (9 weeks in total). In patients who received placebo, the rate of sustained Myasthenia Gravis Activities of Daily Living Scale (MG-ADL) improvement in the first cycle in antibody-positive patients was 31.3% (20 of 64), whereas the MG-ADL improvement was 58.2% (39 of 67) in the batoclimab group (odds ratio, 3.45; 95% CI, 1.62–7.35; $p = .001$).[88]

Roivant Sciences' subsidiary Immunovant has prioritized the development of IMVT-1402, a next-generation anti-FcRn antibody, that could have a more favorable overall therapeutic profile due to its unique binding to FcRn, which avoids a reduction in albumin and the subsequent increase in cholesterol levels caused by batoclimab. Nevertheless, Immunovant is currently conducting Phase 3 studies of batoclimab in patients with gMG (NCT05403541), thyroid eye disease (NCT05524571, NCT05517421, NCT05517447), and Phase 2 studies in chronic inflammatory demyelinating polyneuropathy (NCT05581199) and Graves' disease (NCT05907668).

Ebdarokimab (Akeso Biopharma, Inc.)

Ebdarokimab (AK101, 依若奇单抗) is a human anti-IL-12/23p40 IgG1κ monoclonal antibody developed by Akeso Biopharma. By targeting the p40 subunit common to both IL-12 and IL-23, ebdarokimab inhibits the signaling of these cytokines, which are involved in inflammatory responses. Ebdarokimab is being developed to treat moderate-to-severe plaque psoriasis.

The NMPA is reviewing a marketing application for ebdarokimab for the treatment of moderate-to-severe plaque psoriasis that was submitted in mid-2023. The long-term safety and efficacy of ebdarokimab were evaluated in a single arm, Phase 3 study (CTR20220206) of Chinese patients with moderate-to-severe plaque psoriasis. The study included three groups: 1) patients treated with ebdarokimab in a previous 16-week, double-blind, placebo-controlled study (CTR20212660)

continued to receive ebdarokimab 135 mg at Week 16, followed by maintenance treatment every 12 weeks and follow-up until Week 52; 2) patients from the placebo group in the previous study received ebdarokimab 135 mg at Week 16/Week 20 in this study, followed by maintenance treatment every 12 weeks, and follow-up until Week 52; and 3) patients who directly participated in this study received ebdarokimab 135 mg treatment at Week 0/4 followed by maintenance treatment every 12 weeks, and follow-up until Week 52. As reported at the 2024 European Academy of Dermatology and Venereology Congress in Amsterdam,[89] the ≥75% improvement in Psoriasis Area and Severity Index (PASI75) and Static Physicians Global Assessment (sPGA) 0/1 response rates of group 1 at Week 16 were 80.5% and 66.0%, respectively. The improvement in PASI75 and sPGA0/1 response rates of group 1 patients was consistently maintained until Week 52. After switching to ebdarokimab at Week 16, the PASI score of patients in group 2 decreased. The response rates of PASI75 and sPGA0/1 at Week 32 were 81.4% and 71.1%, respectively, and the response rates were maintained until Week 52. The response rates of PASI75 and sPGA0/1 at Week 16 of group 3 were 69.5% and 59.1%, respectively, which were consistent with the results from group 1.

Picankibart (Innovent Biologics, Inc.)

Picankibart (IBI112) is an anti-IL-23p19 IgG1κ monoclonal antibody developed by Innovent Biologics, Inc. to treat patients with psoriasis or other autoimmune diseases. The molecule neutralizes the p19 subunit of IL-23, thereby preventing IL-23 binding to cell-surface receptors and consequent downstream signaling, which blocks IL-23-induced IL-17 production. Picankibart is Fc engineered with YTE mutations (M252Y, S254T, T256E) to extend half-life. In September 2024, Innovent Biologics, Inc. announced that an NDA for picankibart for the treatment of moderate-to-severe plaque psoriasis was accepted by the NMPA.[90]

Acceptance of the NDA was based on positive results from the randomized, double-blind, placebo-controlled Phase 3 CLEAR-1 study (NCT05645627), which evaluated the efficacy and safety of IBI112 in different dose regimens for the treatment of subjects with moderate-to-severe plaque psoriasis. The trial enrolled a total of 500 patients who were randomized (1:2:2 ratio) to receive placebo or picankibart 200 mg Q4W at Weeks 0, 4, and 8, followed by 200 mg or 100 mg every 12 weeks. The primary endpoints of the study were the percentage of patients achieving more than 90% improvement from baseline Psoriasis Area and Severity Index score (PASI 90) at Week 16 and the percentage of patients achieving a static Physician's Global Assessment (sPGA) score of clear (0) or almost clear (1) at Week 16. Both primary endpoints were successfully met, with a significantly higher proportion of patients receiving picankibart achieving PASI 90 and sPGA 0 or 1 compared to those receiving placebo (80.3% vs. 2.0% for PASI 90 and 93.5% vs. 13.1% for sPGA 0/1, both $p < 0.0001$). Picankibart also showed a favorable safety profile and met all key secondary endpoints, with high level of skin clearance maintained through one year.[91]

SSGJ-608 (Sunshine Guojian Pharmaceutical (Shanghai) Co. Ltd., 3SBio Inc.)

SSGJ-608 (608), a humanized monoclonal antibody that targets IL-17A, was developed by 3SBio and Sunshine Guojian Pharmaceutical (Shanghai) Co. Ltd. to treat patients with autoimmune and inflammatory diseases. 3SBio submitted an NDA to the NMPA for SSGJ-608 for moderate-to-severe plaque psoriasis in November 2024.

The Phase 3 SSGJ-608-PsO-III-01 study (NCT05536726) in Chinese patients with moderate-to-severe plaque psoriasis has successfully met all primary and secondary endpoints. The randomized, double-blind, placebo-controlled, parallel-group SSGJ-608-PsO-III-01 study evaluated the effect of two dose regimens of SSGJ-608 versus placebo in Chinese participants with moderate-to-severe plaque psoriasis. Participants received: 1) SSGJ-608 160 mg at Week 0 + 80 mg Q2W (6 cycles) +80 mg Q4W during maintenance period, 2) SSGJ-608 160 mg Q4W (3 cycles) +160 mg Q8W during maintenance period, or placebo at pre-specified time points to maintain blinding. The study consisted of an induction dosing period with dosing for 12 weeks and the primary endpoint measured at 12 weeks, followed by a randomized, double-blind, 40-week maintenance dosing period. During the maintenance dosing period, the maintenance of response/remission, as well as relapse following treatment were evaluated. The Psoriasis Area and Severity Index (PASI) 75, indicating the percentage of participants achieving a ≥ 75% improvement, at Week 12 was 95.1% in patients who received the 160 mg Q4W +160 mg regimen and 93.4% in those who received the 160 mg Q4W regimen. The primary efficacy data at 12 weeks showed rapid response rate and efficacy advantages. In the maintenance treatment period, the 608 dosing interval was extended to Q4W or Q8W, and the efficacy remained high.[92]

SSGJ-608 is also being investigated in clinical studies in patients with ankylosing spondylitis and nonradiographic axial spondylitis.

Antibodies with marketing applications in review: cancer indications

Cosibelimab (Checkpoint Therapeutics, Inc.)

Cosibelimab (CK-301) is a human IgG1λ antibody that binds the immune checkpoint PD-L1, thereby inhibiting interactions with its receptor PD-1. This blockade removes the suppressive effects of PD-L1 on anti-tumor T-cells to restore the cytotoxic T-cell response. Moreover, cosibelimab's functional Fc domain may induce antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) against tumor cells. Checkpoint Therapeutics is developing cosibelimab as a treatment for cutaneous squamous cell carcinoma (cSCC).

The company announced in January 2023 that they had submitted a BLA for the approval of cosibelimab for the treatment of patients with metastatic or locally advanced cSCC to the FDA. In December 2023, the company announced the FDA issued a CRL for the cosibelimab BLA that cited inspection findings that arose during a multisponsor inspection of Checkpoint's third-party contract manufacturing organization as approvability issues to address in a resubmission.

Checkpoint resubmitted its BLA for cosibelimab that was accepted by the FDA as of July 2024. The FDA's target date for an action on the BLA is December 28, 2024. Checkpoint anticipates additional potential submissions in markets worldwide, including Europe.[93,94]

Datopotamab deruxtecan (AstraZeneca, Daiichi Sankyo Co., Ltd.)

Datopotamab deruxtecan (Dato-DXD) is an anti- trophoblast cell-surface antigen 2 (TROP2) ADC in development as a treatment for breast and lung cancer. The payload, a topoisomerase I inhibitor, is conjugated to a humanized IgG1κ antibody via a cleavable linker. Daiichi Sankyo maintains exclusive rights for this ADC in Japan but has an agreement with AstraZeneca to jointly develop and commercialize datopotamab deruxtecan in the rest of the world.

In March 2024, the EMA started evaluating two marketing applications for datopotamab deruxtecan for two types of cancer. One application is for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have progressed on and are not suitable for endocrine therapy and received at least one additional systemic therapy. The other application is for the treatment of adult patients with locally advanced or metastatic nonsquamous NSCLC who require systemic therapy following prior treatment. Both applications remain under evaluation by the EMA as of early December 2024.

Also in March 2024, Daiichi Sankyo submitted a marketing application to Japan's MHLW for datopotamab deruxtecan for the treatment of adult patients with HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) unresectable or recurrent breast cancer after prior chemotherapy. The submission is based is based on Phase 3 TROPION-Breast01 (NCT05104866) clinical trial results.

In April 2024, AstraZeneca announced that the FDA accepted a BLA for datopotamab deruxtecan for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior systemic therapy for unresectable or metastatic disease. The BLA is based on results from the Phase 3 TROPION-Breast01 trial. The FDA's target date for an action on the BLA is January 29, 2025.[95]

In November 2024, Daiichi Sankyo and AstraZeneca announced that they submitted a BLA to the FDA for accelerated approval for datopotamab deruxtecan for the treatment of adult patients with locally advanced or metastatic EGFR-mutated NSCLC who have received prior systemic therapies, including an EGFR-directed therapy. This BLA includes pooled analyses from three clinical studies: 1) Phase 2 TROPION-Lung05, Phase 3 TROPION-Lung01, and 3) Phase 1 TROPION-PanTumor01. Simultaneously, the companies announced that a BLA previously submitted for nonsquamous NSCLC, which was based on results from the Phase 3 TROPION-Lung01 trial, was voluntarily withdrawn.[96]

Results from the randomized, open-label Phase 3 TROPION-Lung01 (NCT04656652) trial were recently reported.[97] Patients received datopotamab deruxtecan 6 mg/kg ($n = 299$) or docetaxel 75 mg/m^2 ($n = 305$) Q3W in this study. The dual primary endpoints were PFS and OS. The median PFS was 4.4 months (95% CI, 4.2 to 5.6) and 3.7 months (95% CI, 2.9 to 4.2) for patients who received datopotamab deruxtecan vs. docetaxel, respectively (HR, 0.75 (95% CI, 0.62 to 0.91); $p = 0.004$). The median OS results numerically favored datopotamab deruxtecan compared to docetaxel (12.9 versus 11.8 months) but did not reach statistical significance (HR 0.94; 95% confidence interval [CI] 0.78–1.14; $p = 0.530$). In the prespecified subgroup of patients with nonsquamous NSCLC, the median PFS was 5.5 versus 3.6 months (HR, 0.63 (95% CI, 0.51 to 0.79)), and datopotamab deruxtecan showed a 2.3-month improvement in OS compared to docetaxel (14.6 versus 12.3 months; HR 0.84; 95% CI 0.68–1.05). In patients with squamous NSCLC, the median PFS was 2.8 versus 3.9 months (HR, 1.41 (95% CI, 0.95 to 2.08)) and the median OS was 7.6 versus 9.4 months (HR, 1.32 (95% CI, 0.91 to 1.92)).[97] AstraZeneca and Daiichi Sankyo are evaluating datopotamab deruxtecan in multiple additional Phase 3 studies of patients with NSCLC.

Results from the Phase 3 TROPION-Breast01 trial (NCT05104866) of datopotamab deruxtecan compared to the investigator's choice of chemotherapy in patients with in HR-positive/HER2-negative (HR+/HER2–) breast cancer, who have progressed on and are not suitable for endocrine therapy per investigator assessment and have received at least one additional systemic therapy for unresectable or metastatic disease, showed a statistically significant and clinically meaningful improvement in PFS, but did not achieve statistical significance in the final OS analysis in patients with inoperable or metastatic HR-positive, HER2-low or -negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer previously treated with endocrine-based therapy and at least one systemic therapy.[98] AstraZeneca and Daiichi Sankyo are also evaluating datopotamab deruxtecan alone and with immunotherapy in patients with triple-negative or HR-low, HER2-negative breast cancers in the Phase 3 TROPION-Breast02, TROPION-Breast03, TROPION-Breast04 and TROPION-Breast05 trials.

Telisotuzumab vedotin (AbbVie)

Telisotuzumab vedotin (Teliso-V, ABBV-399) is an ADC composed of a humanized IgG1κ antibody that targets cMET conjugated to monomethyl auristatin E (MMAE) via a cleavable valine-citrulline linker. cMet overexpression, which is found across various tumor types, is associated with poor prognoses. The antibody portion, hz224G11, was discovered at Pierre Fabre and originally developed by AbbVie as a naked molecule (ABT-700). The FDA granted Breakthrough Therapy designation for Teliso-V for treatment of patients with advanced/metastatic EGFR wild type, NSCLC with high levels of c-Met overexpression whose disease has progressed on or after platinum-based therapy.

In September 2024, AbbVie announced the submission of a BLA to the FDA for Teliso-V for approval as monotherapy in patients with previously treated cMet overexpressing, EGFR wild-type locally advanced or metastatic NSCLC cancer. The BLA, which is supported by data from the Phase 2 LUMINOSITY trial, will be evaluated under the Oncology Center of Excellence Real-Time Oncology Review program.[99]

Results of the open-label, single-arm Phase 2 LUMINOSITY trial (M14–239, NCT03539536), which aimed to identify NSCLC populations that overexpress c-Met best suited for Teliso-V monotherapy in the second line or third-line setting and then to expand the groups to evaluate efficacy in the selected populations, were recently reported.[100] Teliso-V (1.9 mg/kg) was administered via IV infusion Q2W to 172 patients until disease progression, intolerable toxicity, or other study discontinuation criteria were met. The study's primary endpoint, ORR determined by ICR, was 28.6% (95% CI, 21.7 to 36.2; c-Met high, 34.6% [95% CI, 24.2 to 46.2]; c-Met intermediate, 22.9% [95% CI, 14.4 to 33.4]). The median DoR was 8.3 months (95% CI, 5.6 to 11.3; c-Met high, 9.0 [95% CI, 4.2 to 13.0]; c-Met intermediate: 7.2 [95% CI, 5.3 to 11.5]), the median OS was 14.5 months (95% CI, 9.9 to 16.6; c-Met high, 14.6 [95% CI, 9.2 to 25.6]; c-Met intermediate, 14.2 [95% CI, 9.6 to 16.6]), and the median PFS was 5.7 months (95% CI, 4.6 to 6.9; c-Met high, 5.5 [95% CI, 4.1 to 8.3]; c-Met intermediate: 6.0 [95% CI, 4.5 to 8.1]).

AbbVie is sponsoring the ongoing randomized Phase 3 TeliMET NSCLC-01 trial (NCT04928846), which is evaluating the effects of Teliso-V versus docetaxel in subjects with previously treated cMET overexpressing, EGFR wildtype, locally advanced/metastatic nonsquamous NSCLC. An estimated 698 participants will receive IV Teliso-V Q2W or docetaxel Q3W until meeting study drug discontinuation criteria. The study's primary completion date is in March 2028.

Patritumab deruxtecan (Daiichi Sankyo, Merck & Co.)

Patritumab deruxtecan (HER3-DXd, U3–1402) is an ADC consisting of a human IgG1κ monoclonal antibody targeting HER3 conjugated to the topoisomerase I inhibitor payload DXd/DX-8951 via a stable tetrapeptide (GGFG)-based cleavable linker. Daiichi Sankyo and Merck are collaborating on the development of patritumab deruxtecan.

In December 2023, the companies announced that the FDA accepted and granted Priority Review to a BLA for accelerated approval of patritumab deruxtecan for the treatment of adult patients with locally advanced or metastatic EGFR-mutated NSCLC previously treated with two or more systemic therapies. The BLA was based on the results of the pivotal Phase 2 hERTHENA-Lung01 study (NCT04619004), which evaluated patritumab deruxtecan, administered IV as either a fixed dose (5.6 mg/kg Q3W) and up-titrated, in patients with advanced EGFR-mutated NSCLC previously treated with EGFR TKI therapy and platinum-based chemotherapy.[101] In June 2024, the FDA issued a CRL for this BLA, which referred to findings related to an inspection of a third-party manufacturing facility. No issues with the efficacy or safety data submitted were identified in the CRL. The companies plan to address the FDA's feedback as quickly as possible.[102]

In September 2024, Daiichi Sankyo and Merck announced the Phase 3 hERTHENA-Lung02 trial (NCT05338970), which evaluated patritumab deruxtecan administered IV at 5.6 mg/kg Q3W to patients with locally advanced or metastatic EGFR-mutated NSCLC who received prior EGFR TKI treatment, met its primary endpoint of PFS, demonstrating a statistically significant improvement versus platinum plus pemetrexed induction chemotherapy followed by pemetrexed maintenance chemotherapy. The companies indicated that the HERTHENA-Lung02 trial data will be shared with regulatory agencies.[103]

Linvoseltamab (Regeneron Pharmaceuticals, Inc.)

Linvoseltamab (REGN5458) is a hinge-stabilized, bispecific IgG4κ antibody targeting B-cell maturation antigen (BCMA) and CD3 developed by Regeneron as a treatment for multiple myeloma (MM). The antibody, which was Fc engineered to reduce effector function, enables T cell-mediated killing of cancer cells by bringing BCMA-expressing cancer cells into the proximity of CD3-expressing T cells. The FDA granted linvoseltamab Fast Track designation for MM.

In February 2024, Regeneron announced that the FDA accepted for Priority Review a BLA for linvoseltamab as a treatment for adult patients with R/R MM that has progressed after at least three prior therapies.[104] The EMA also accepted a marketing application for linvoseltamab in the same indication and this application remains under evaluation as of November 2024.

In August 2024, Regeneron announced that the FDA issued a CRL for the BLA for linvoseltamab that identified an approvability issue related to findings from a pre-approval inspection at a third-party fill/finish manufacturer for another company's product candidate.[105] Resolution of this issue will be required for regulatory approvals in both the US and the EU.

The marketing applications are supported by data from an open-label Phase 1/2 trial (LINKER-MM1) investigating linvoseltamab in R/R MM patients who have received at least three prior lines of therapy or are triple refractory. Two doses of IV-administered linvoseltamab, 50 mg ($n = 104$) or 200 mg ($n = 117$), both given Q1W for 3 cycles followed by Q2W dosing onwards, were evaluated in Part 2 of the study. Dosing was reduced to Q4W from cycle 6 onwards for patients in the 200 mg group who achieved at least a very good partial response (VGPR). The study's primary endpoint was ORR. In patients treated with 50 mg at a median follow-up of 7.4 months, the ORR was 48%, with 21% achieving ≥CR. In patients treated with 200 mg at a median follow-up of 14.3 months, the ORR was 71%, with 50% achieving ≥ CR and 63% achieving a VGPR or better, as determined by an IRC.[106]

Regeneron is sponsoring an open-label, randomized Phase 3 study (LINKER-MM3, NCT05730036) of linvoseltamab vs the combination of elotuzumab, pomalidomide, and dexamethasone in patients with R/R MM. The study, which will enroll an estimated 380 patients, started in September 2023 and has an estimated primary completion date in December 2032.

Bifikafusp alfa, onfekafusp alfa (Philogen SpA)

Bifikafusp alfa and onfekafusp alfa are the components of Nidlegy™, an immunocytokine mixture also known as Daramun, developed by Philogen as a treatment for skin cancers. Both of these immunocytokines incorporate L19, a single-chain variable fragment (scFv) antibody that targets

the extra-domain B (EDB) of fibronectin. In bifikafusp alfa, L19 is fused to IL2, while in onfekafusp alfa L19 is fused to tumor necrosis factor (TNF). Philogen and Sun Pharma have a distribution, license, and supply agreement to commercialize Nidlegy in Europe, Australia, and New Zealand as a skin cancer treatment. The companies submitted a marketing application to EMA for Nidlegy™ for the treatment of locally advanced fully resectable melanoma in the neoadjuvant setting, which was validated in June 2024.[107]

The marketing application includes data from the open-label, randomized Phase 3 PIVOTAL trial (NCT02938299), which evaluated Nidlegy as a neoadjuvant intralesional therapy for resectable, locally advanced Stage III melanoma. In this study, a total of 256 patients were randomized 1:1 to a treatment (neoadjuvant Nidlegy followed by surgery) and a control arm (surgery). Patients in the treatment arm (n = 127) were administered Nidlegy (13 Mio IU of L19IL2 + 400 µg of L19TNF, Q1W for up to 4 weeks) distributed among all injectable tumor lesions. The primary endpoint of the study was recurrence-free survival (RFS), assessed by investigators and confirmed by retrospective blinded ICR of PET/CT scans. The HR between the RFS of the treatment and the control arm was 0.59 (95% CI 0.41–0.86; log-rank $p = 0.005$) as per the blinded ICR assessment and 0.61 (0.41–0.92; $p = 0.018$) as per investigator assessment (power = 85%; two-sided $\alpha = 0.05$). Median RFS was 16.7 and 6.9 months in the treatment and in the control arms, respectively, as per the blinded ICR.[108]

Trastuzumab botidotin (Sichuan Kelun-Biotech Biopharmaceutical Co Ltd, Sorrento Therapeutics, Inc.)

Trastuzumab botidotin (A166, 博度曲妥珠单抗, 舒泰莱®) is a humanized, IgG1κ anti-HER2 ADC created using Levena Biopharma's proprietary tubulin inhibitor Duo-5 toxin, cleavable linker and site-specific K-Lock™ conjugation chemistry. The ADC is in development as a treatment for HER2-positive solid tumors. The NMPA accepted a marketing application sponsored by Sichuan Kelun-Biotech Biopharmaceutical Co Ltd. for trastuzumab botidotin for third-line+, HER2-positive breast cancer in May 2023. If approved, the company aims to launch trastuzumab botidotin in China in the second half of 2024 or the first half of 2025.[109,110]

Tagitanlimab (Sichuan Kelun Pharmaceutical Co., Ltd.)

Tagitanlimab (A167, KL-A167, HBM9167, 泰特利单抗, 科泰莱®) is a humanized anti-PD-L1 IgG1κ monoclonal antibody Fc engineered to reduce effector functions (L234A, L235A, G237A) developed by Sichuan Kelun Pharmaceutical Co., Ltd. Harbour BioMed acquired the global rights to develop and commercialize tagitanlimab, excluding the Greater China region, through a licensing agreement with Kelun-Biotech. In November 2021, the NMPA accepted a marketing application for tagitanlimab as a third-line or later treatment for relapsed or metastatic NPC. Additionally, in May 2024, the NMPA accepted an NDA for A167, based on a Phase 3 registrational study, for use as a first-line treatment of NPC. If approved, the company aims to launch tagitanlimab in China in the second half of 2024 or the first half of 2025.[109,110]]

The randomized, double-blind, placebo-controlled Phase 3 study (NCT05294172) efficacy of KL-A167 combined with cisplatin and gemcitabine vs placebo combined with cisplatin and gemcitabine in the treatment of recurrent or metastatic NPC. The study included 295 patients who received tagitanlimab 1200 mg Q3W, cisplatin 80 mg/m^2 on Day 1 of each 21-day cycle, 4–6 cycles, gemcitabine 1000 mg/m^2, Day 1 and Day 8 of each 21-day cycle, 4–6 cycles or placebo with matching cisplatin and gemcitabine therapy. As of October 2024, study results have not been reported.

The results of a Phase 2 trial were reported in 2022.[110] In this study, patients received IV doses of tagitanlimab at 900 mg every 2 weeks, continuing treatment until confirmed disease progression, intolerable toxicity, or withdrawal of informed consent. The primary endpoint was the ORR, evaluated by the IRC by RECIST v1.1. A total of 153 patients were treated, with 132 included in the full analysis set (FAS) for efficacy evaluation. As of the data cutoff on July 13, 2021, the median follow-up duration was 21.7 months (95% CI: 19.8–22.5). Among the FAS population, the ORR as assessed by the IRC was 26.5% (95% CI: 19.2–34.9%), while the disease control rate (DCR) was 56.8% (95% CI: 47.9–65.4%). The median PFS was 2.8 months (95% CI: 1.5–4.1). The median DoR was 12.4 months (95% CI: 6.8–16.5), and the median OS for this group was 16.2 months (95% CI: 13.4–21.3).[111]

Becotatug vedotin (Shanghai Miracogen, Lepu Biopharma Co., Ltd.)

Becotatug vedotin (MRG003) is a humanized anti-EGFR IgG1κ antibody conjugated to the microtubule disrupting agent MMAE via a cleavable valine-citrulline linker. Developed by Shanghai Miracogen and Lepu Biopharma, MRG003 was granted Breakthrough Therapy, Orphan Drug, and Fast Track designation by the FDA for the treatment of recurrent or metastatic NPC. MRG003 has also been granted Breakthrough Therapy designation by the Center for Drug Evaluation in China for the treatment of recurrent or metastatic NPC. In September 2024, Lepu Biopharma announced that the NMPA had accepted an NDA for becotatug vedotin for the treatment of recurrent or metastatic NPC and granted the application a priority review.[112]

The 2-part, pivotal Phase 2 MRG003–005 study (NCT05126719, CTR20210995) is assessing the effects of becotatug vedotin in patients with recurrent metastatic NPC. Part A is an open-label, single arm, multicenter study in patients with inoperable, radiotherapy ineligible recurrent or metastatic NPC who have failed (or are intolerable) at least 1 prior line platinum-based systemic chemotherapy and PD-1 (L1) inhibitors. In Part A, patients are IV administered either 2.0 mg/kg or 2.3 mg/kg becotatug vedotin Q3W for up to 24 months. Part B is an open-label, randomized, multicenter study to compare the efficacy and safety of becotatug vedotin versus capecitabine/docetaxel in patients with recurrent or metastatic NPC who have failed at least two prior lines of systemic chemotherapy and PD-1 (L1) inhibitors. In Part B, patients receive either 2.3 mg/kg becotatug vedotin Q3W IV or capecitabine tablets/docetaxel injection for up to 60 months. The primary outcome measure is the ORR by IRC as determined from baseline to disease progression, intolerable drug-related toxicities, withdrawal of consent, or study discontinuation for any reason (up to 24 months). The target enrollment is

238 patients, and the primary completion date is in October 2024.

Becotatug vedotin is also being evaluated in a Phase 3 trial (CTR20223356) as a second or third line of therapy for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). This trial, which aims to compare the efficacy and safety of becotatug vedotin versus the standard treatment of cetuximab/methotrexate, has a primary completion date in August 2025.

Iparomlimab (Qilu Pharmaceutical Co. Ltd)

Iparomlimab (QL1604, 艾帕洛利单抗) is a highly selective, humanized, hinge-stabilized, anti-PD-1 IgG4κ monoclonal antibody developed for the treatment of solid tumors. In September 2023, the NMPA accepted an NDA for iparomlimab. Iparomlimab is the anti-PD1 component of QL1706 [iparomlimab + anti-CTLA-4 tuvonralimab]; an NDA for QL1706 is also undergoing review by the NMPA.

Results for a Phase 2 pivotal clinical study (NCT04326829) for iparomlimab for the treatment of patients with unresectable or metastatic deficient mismatch repair/microsatellite instability high solid tumors were recently reported. In the study, 120 patients received IV administration of iparomlimab at a fixed dose of 200 mg (or 3 mg/kg for patients under 40 kg) Q3W, with treatment continuing for up to 2 years or until disease progression, intolerable toxicities, initiation of new anti-tumor therapy, death, withdrawal of consent, or other specified reasons. The primary endpoint of the study was the objective response rate, evaluated by the Independent Radiological Review Committee (IRRC) based on RECIST version 1.1. As of January 20, 2024, the ORR were 48.3% (58/120; 95% CI: 39.1–57.6%) and 50.0% (30/60; 36.8–63.2%) in the intention to treat (ITT) and full analysis set (FAS), respectively. In colorectal cancer patients, the ORR per IRRC was 46.3% (37/80) and 57.9% (22/38) in the ITT and FAS, respectively.[113]

Finotonlimab (Sinocelltech Ltd.)

Finotonlimab (SCT-I10A) is a humanized, hinge-stabilized IgG4κ monoclonal antibody targeting the immune checkpoint protein PD-1 that is being developed by Sinocelltech primarily for solid tumors. The NMPA is reviewing an NDA accepted on November 30, 2023, for finotonlimab for head and neck squamous cell carcinoma, as well as an NDA accepted on January 17, 2024, for finotonlimab for patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

The effects of finotonlimab (200 mg IV Q3W) plus standard chemotherapy (cisplatin +5-fluorouracil) vs. placebo plus standard chemotherapy were evaluated in a randomized, double-blinded Phase 3 study (NCT04146402) of patients with first-line recurrent/metastatic head and neck squamous cell carcinoma. The primary endpoint was OS is defined as the time from the first dose of finotonlimab until the date of death from any cause. In the group administered finotonlimab plus chemotherapy ($n = 247$), OS was 14.1 months (95% confidence interval (CI) 11.1–16.4), compared with 10.5 months (95% CI 8.1–11.8) in the placebo plus chemotherapy group.[114]

The effects of finotonlimab combined with SCT510, a bevacizumab biosimilar antibody, were compared to sorafenib as a first-line treatment for advanced HCC in a Phase 3 study (NCT04560894). Patients received finotonlimab (200 mg Q3W) plus SCT510 (15 mg/kg Q3W) or sorafenib (400 mg orally twice daily) until no clinical benefit or unacceptable toxicity. At an interim analysis (November 2, 2023), a total of 346 patients were enrolled and received at least one dose (finotonlimab plus SCT510 group, $n = 230$; sorafenib group, $n = 116$), and the median follow-up was 19.7 months. The median OS of the finotonlimab plus SCT510 group was significantly longer than that of the sorafenib group (22.1 vs. 14.2 months, respectively; HR 0.60; 95% confidence interval [CI]: 0.44, 0.81; $p = 0.0008$). Median PFS in the SCT-I10A plus SCT510 group compared to the sorafenib group was significantly prolonged (7.1 vs. 2.9 months, respectively; HR 0.50; 95% CI: 0.38, 0.65; $p < 0.0001$). The ORR was also higher in the finotonlimab plus SCT510 group (32.8% [75/229]) compared to the sorafenib group (4.3% [5/116]).[115]

Suvemcitug (Simcere Zaiming Pharmaceutical Co., Ltd., Apexigen, Inc.)

Suvemcitug (BD0801, ENZESHU, 苏维西塔单抗) is a humanized, rabbit-derived, IgG1κ antibody that targets VEGF that inhibits tumor angiogenesis by selectively binding to VEGFA and blocking its interaction with VEGFR1 and VEGFR2. On March 15, 2024, Simcere Zaiming announced that the NDA for suvemcitug injection was accepted by the NMPA for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.[116] Co-developed by Simcere and Apexigen, Inc., Simcere Zaiming currently holds the exclusive rights to develop and commercialize this product in Greater China.

The SCORES Study (NCT04908787) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of suvemcitug in combination with chemotherapy for platinum-resistant ovarian cancer, enrolling 421 patients across 55 sites in China. After initial treatment with chemotherapy, patients were randomly assigned (2:1) to either suvemcitug (1.5 mg/kg Q2W) or placebo combined with chemotherapy until progression or unacceptable toxicity. The primary endpoint for this study was PFS determined by a blinded IRC and OS was the key secondary endpoint. Suvemcitug significantly extended PFS, with the experimental arm ($n = 281$) achieving a median PFS of 5.49 months compared to 2.73 months in the control arm ($n = 140$, HR 0.46, $p < 0.0001$). Positive PFS results were consistent across all subgroups, such as various age groups, Eastern Cooperative Oncology Group (ECOG) performance status, prior therapies, and platinum-refractory status. 50.1% of participants had received prior VEGF-targeted therapy, and 48.9% had been treated with PARP inhibitors, with suvemcitug in combination with chemotherapy showing significant PFS improvement in these patients. Preliminary data showed a trend toward a survival benefit in the experimental arm with a median OS of 16.07 months, compared to 14.88 months in the control group (HR 0.79, $p = 0.1244$). The experimental group also outperformed in various other secondary efficacy measures such as ORR and DCR. Additionally, suvemcitug

combined with chemotherapy was well-tolerated, with no new safety concerns relative to other drugs in the same class.[117]

Trastuzumab rezetecan (Jiangsu HengRui Medicine Co. Ltd., Suzhou Suncadia Biopharmaceuticals Co. Ltd.)

Trastuzumab rezetecan (SHR-A1811) is an ADC composed of the anti-HER2 antibody trastuzumab conjugated to a payload, SHR9265, that acts as a topoisomerase I inhibitor. The DAR is an average of 5.3 to 6.4. The NMPA has granted trastuzumab rezetecan Breakthrough Therapy Designations for three indications: 1) HER2-mutant, advanced NSCLC after platinum-based chemotherapy; 2) HER2-positive, recurrent, or metastatic breast cancer; 3) HER2-low, recurrent, or metastatic breast cancer. In September 2024, Suzhou Suncadia Biopharmaceuticals Co. Ltd. submitted a marketing application to the NMPA for trastuzumab rezetecan as a treatment for HER2-mutant NSCLC in September 2024.[118]

Trastuzumab rezetecan was evaluated in an open-label, dose-escalation, and expansion Phase 1/2 study (NCT04818333) of patients with advanced NSCLC who have HER2 expression, amplification, or mutation, and who had previously failed or were intolerant of platinum-based chemotherapy. Patients were IV administered trastuzumab rezetecan at doses of 3.2 to 8.0 mg/kg Q3W, with 4.8 mg/kg as the recommended dose for expansion. The primary efficacy endpoint was ORR. Based on data available as of April 11, 2023, the 4.8 mg/kg cohort showed an ORR of 41.9% (95% CI 27.0–57.9), while the median DoR and PFS were 13.7 and 8.4 months, respectively.[119]

Jiangsu HengRui Medicine Co., Ltd. is sponsoring a randomized, open-label, multicenter Phase 3 study (NCT06430437, CTR20241861) of trastuzumab rezetecan for first-line treatment in subjects with HER2-mutated advanced or metastatic NSCLC that is not yet recruiting as of early December 2024. Trastuzumab rezetecan is also being evaluated in Phase 3 studies as a treatment for advanced colorectal cancer (NCT06199973), recurring or metastatic breast cancer (NCT05814354), and HER2-positive advanced gastric cancer or gastroesophageal junction adenocarcinoma (NCT06123494) that are enrolling patients, as of early December 2024.

Retlirafusp (Jiangsu HengRui Medicine Co. Ltd., Suzhou Suncadia Biopharmaceuticals Co., Ltd.)

Retlirafusp alfa (SHR-1701) is a bifunctional immunoconjugate composed of a human anti-PD-L1 IgG4 antibody fused at the C-terminus of both heavy chains to the N-terminal-truncated extracellular domain of human-transforming growth factor (TGF)-β receptor II via a peptidyl linker. By binding PD-L1 and TGFβ, the molecule can simultaneously block two immunosuppressive signaling pathways commonly used by cancer cells. On September 19, 2024, the NMPA accepted Hengrui Pharmaceutical's marketing application for retlirafusp alfa, which seeks approval for its use in combination with chemotherapy (fluorouracil and platinum-based drugs) for the first-line treatment of locally advanced unresectable, recurrent, or metastatic G/GEJ adenocarcinoma.

Results of a randomized, placebo-controlled Phase 3 study (NCT04950322) of retlirafusp alfa administered to previously untreated patients with a pathologically confirmed diagnosis of locally advanced unresectable or metastatic G/GEJ adenocarcinoma that was HER2-overexpression or -amplification negative were recently reported.[119] In part 1 of the study, the recommended dose of retlirafusp alfa was determined to be 30 mg/kg, when administered in combination with oxaliplatin and capecitabine (CAPOX). In part 2 of the study, 731 patients were randomized (1:1) to receive CAPOX plus either retlirafusp alfa (n = 365; 30 mg/kg, iv, Q3W) or matching placebo (n = 366). Randomization was stratified by PD-L1 CPS (≥5 vs <5), ECOG performance status (0 vs 1), and peritoneal metastasis (yes vs no). The study's primary endpoint was OS, assessed in the population with PD-L1 CPS ≥ 5 and in the ITT population. As of May 20, 2024, median follow-up was 8.5 months (interquartile range 5.6–13.2). The median OS was significantly prolonged in patients with PD-L1 CPS ≥ 5 administered the combination of retlirafusp alfa and CAPOX vs placebo and CAPOX (16.8 vs 10.4 months; HR, 0.53 (95% CI 0.40–0.68). A statistically significant and clinically meaningful benefit in OS was also observed in the overall population administered the retlirafusp alfa and CAPOX combination, regardless of PD-L1 level.[120]

Antibodies to watch in 2025: non-cancer indications

Here, the phrase "Antibodies to Watch" refers to antibody therapeutics that may be the subject of a marketing application by the end of 2025. Our forecasts are based on the totality of the evidence, comprising public disclosures by the sponsoring company or companies, including the release of top-level clinical study data, and projected primary completion dates of ongoing clinical studies. Of the antibody therapeutics we identified as in late-stage clinical studies for non-cancer indications, we project that marketing applications for 13 may be submitted by the end of 2025 (Table 3). Key details for these molecules are given below, with the summaries ordered according to our estimated marketing application submission dates. Additional data for these molecules can be found in Supplemental Table S1.

Depemokimab (GSK)

Depemokimab (GSK3511294) is a humanized monoclonal IgG1κ antibody targeting interleukin-5 (IL-5), a cytokine responsible for the growth, activation, and survival of eosinophils, but also for type 2 inflammation, typically detected by raised blood eosinophil count. M252Y, S254T, T256E (YTE) mutations in the Fc provide extended half-life and allow twice-yearly dosing. Developed by GSK, depemokimab is being studied as a treatment for severe eosinophilic asthma. Depemokimab was granted Orphan Drug designation for the treatment of hypereosinophilic syndrome. GSK plans regulatory submissions in the US for depemokimab in severe asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) by the end of 2024, which will be followed by regulatory submissions in the EU, China, and Japan. The company anticipates a dual indication launch in 2025.[121]

The 52-week, randomized, double-blind, placebo-controlled Phase 3 SWIFT-1 (NCT04719832) and SWITF-2

Table 3. Commercially sponsored investigational monoclonal antibodies in late-stage clinical studies for non-cancer indications, with regulatory submission anticipated during 2024–2025.

INN or drug code	Target(s); Format	Indication of relevant* late-stage study (est. submission year, country#)	Most advanced clinical phase
Depemokimab	IL-5; Humanized IgG1κ	Eosinophilic asthma, chronic rhinosinusitis with nasal polyps (2024, US)	Phase 3
Apitegromab	Myostatin; Human IgG4λ	Spinal muscular atrophy (2025Q1, EU, US)	Phase 3
ANX005	Complement C1q; Humanized IgG4κ	Guillain-Barré syndrome (2025H1, US)	Phase 3
Sibeprenlimab	APRIL; Humanized IgG2κ	Immunoglobulin A nephropathy (2025H1)	Phase 3
Denecimig	Factor IXa, Factor X; Human IgG4κ; Bispecific	Hemophilia (2025)	Phase 3
Astegolimab	IL-33 R; Human IgG2κ	COPD (2025)	Phase 3
Cendakimab	IL-13; Humanized IgG1κ	Eosinophilic esophagitis (2025)	Phase 3
SSGJ-613	IL-1 beta; Humanized	Psoriasis (2025, China)	Phase 3
Itepekimab	IL-33; Human IgG4κ	COPD (2025H2, EU, US)	Phase 3
Veligrotug	IGF-1 R; Humanized IgG1κ	Thyroid eye disease (2025H2)	Phase 3
Anselamimab	Amyloid; Chimeric IgG1κ	Amyloid light chain amyloidosis (~2025)	Phase 3
Sonelokimab	IL-17A, IL17F, albumin; Humanized VHH-VHH'-VHH; Trispecific	Hidradenitis suppurativa (~2025H2)	Phase 3
Ersodetug	Insulin receptor; Human IgG2κ	Congenital hyperinsulinism (~2025H2)	Phase 3

*Indication for which a regulatory submission is anticipated. #First marketing application submission dates and country are estimates based on company announcements and pivotal trial completion dates. Table includes information found in the public domain as of December 1, 2024. Abbreviations: APRIL, a proliferation inducing ligand; Fab, antigen-binding fragment; IL, interleukin; RSV, respiratory syncytial virus. See Supplemental Table S1 for more details about each antibody. Additional data for investigational antibody therapeutics in late-stage clinical studies also available at: https://www.antibodysociety.org/antibodies-in-late-stage-clinical-studies/.

(NCT04718103) studies assessed the efficacy and safety of depemokimab in adults and adolescents with severe asthma with type 2 inflammation. Study participants (total $n = 762$) were randomly assigned (2:1) to receive 100 mg SC depemokimab or placebo at Weeks 0 and 26, in addition to SOC treatment. The primary endpoint was the annualized rate of clinically significant exacerbations over 52 weeks. In both trials, depemokimab induced a 54% reduction of exacerbations.[122]

In October 2024, GSK announced positive top-line results from the replicate randomized, double-blind Phase 3 ANCHOR-1 (NCT05274750) and ANCHOR-2 (NCT05281523) studies, which evaluated the efficacy and safety of 100 mg SC depemokimab in CRSwNP patients.[123] ANCHOR-1 included 143 patients who were administered depemokimab and 128 who received a placebo, while in ANCHOR-2, 129 patients received depemokimab and 128 received a placebo. Both trials met their co-primary endpoints: 1) change from baseline in total endoscopic nasal polyp score at 52 weeks and 2) change from baseline in mean nasal obstruction score from Weeks 49 to 52.

GSK is also conducting other Phase 3 studies of depemokimab with data readouts expected in 2025. Patients who were previously enrolled in one of the SWIFT trials could join the Phase 3 AGILE study (NCT05243680), an open-label 12-month extension study to characterize the long-term safety, efficacy, and immunogenic profile of depemokimab adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype. The study's estimated primary completion date is in May 2025. The randomized, double-blind, non-inferiority Phase 3 NIMBLE study (NCT04718389) is assessing exacerbation rate, additional measures of asthma control, and safety in approximately 1700 adult and adolescent severe asthmatic participants with an eosinophilic phenotype treated with depemokimab compared with mepolizumab or benralizumab. The study's primary completion date is in May 2025. In addition, depemokimab is being investigated in 160 adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) receiving SOC therapy in the Phase 3 OCEAN study (NCT05263934), which has a primary completion date in October 2025.

Apitegromab (Scholar Rock)

Apitegromab (SRK-015) is a hinge-stabilized IgG4λ monoclonal antibody developed by Scholar Rock to inhibit myostatin (growth differentiation factor 8), a negative regulator of muscle growth. The drug is primarily in development for treating spinal muscular atrophy (SMA), a condition marked by motor neuron loss and progressive muscle wasting, and is also being explored for preserving lean muscle mass in obese patients. The FDA has granted Fast Track, Orphan Drug and Rare Pediatric Disease designations, and the EMA has granted Priority Medicines (PRIME) and Orphan Medicinal Product designations, to apitegromab for the treatment of SMA. Scholar Rock expects to submit marketing applications in the US and the EU in the first quarter of 2025.[124]

Results were recently reported for the Phase 2 TOPAZ study (NCT03921528), which assessed the safety and efficacy of IV apitegromab administered Q4W in patients with later-onset Type 2 and Type 3 SMA.[125,126] A total of 58 participants (mean age 9.4 years) were divided into three cohorts. Cohort 1 ($n = 23$) included ambulatory participants who received apitegromab 20 mg/kg alone or with nusinersen; Cohort 2 ($n = 20$) included non-ambulatory patients receiving apitegromab and nusinersen at the same doses as those in Cohort 1; and Cohort 3 ($n = 20$) evaluated two doses of apitegromab (2 mg/kg, 20 mg/kg) combined with nusinersen. The primary endpoint, improvement in motor function, was measured by changes in the Hammersmith Functional Motor Scale-Expanded (HFMSE). At Month 12, the most significant improvements were observed in Cohort 3, with mean score increases of 5.3 and 7.1 points for the 2 mg/kg and 20 mg/kg doses, respectively.[124] Benefits observed at 12 months were sustained at 36 months, based on results of the open-label extension of

the study, during which patients received apitegromab 20 mg/kg by IV infusion Q4W.[125]

Insights from the TOPAZ study informed the design of the randomized, double-blind, placebo-controlled, 5-arm Phase 3 SAPPHIRE study (NCT05156320), which enrolled patients (n = 188) with later-onset SMA who were receiving approved survival motor neuron upregulator therapy (nusinersen or risdiplam). Type 2 and non-ambulatory Type 3 SMA patients in the age 2–12 y/o main efficacy population are administered IV apitegromab 10 mg/kg, 20 mg/kg, or placebo Q4W for 52 weeks. Patients in the exploratory subpopulation (ages 13–21 years old at screening) are randomized to receive apitegromab 20 mg/kg or placebo for up to 52 weeks. As announced in October 2024, the primary endpoint of the study, mean HFMSE change from baseline at 12 months, was met.[123] In the main efficacy population, the mean difference in change from baseline in HFMSE was 1.8 points (p = 0.0192) for all patients receiving apitegromab 10 mg/kg and 20 mg/kg (n = 106) compared to placebo (n = 50). Patients receiving 20 mg/kg of apitegromab (n = 53) showed a 1.4-point mean difference compared to placebo (p = 0.1149).[126] The long-term safety and efficacy of apitegromab administered IV at 20 mg/kg Q4W in patients with SMA who completed TOPAZ or SAPPHIRE are being evaluated in an open-label Phase 3 extension study (ONYX, NCT05626855), which has a 104-week treatment period.

ANX005 (Annexon Biosciences, Inc.)

ANX005 is a humanized anti-C1q IgG4κ antibody developed by Annexon Biosciences. By inhibiting C1q, ANX005 aims to prevent the activation of the complement cascade, which can lead to inflammation, cell damage, and neurodegeneration. This inhibition is intended to mitigate complement-mediated damage in muscular disorders such as Guillain–Barré syndrome (GBS). ANX005 has been granted Fast Track and Orphan Drug designations from the FDA, as well as Orphan Medicinal Product designation by the EMA, for treatment of GBS. Annexon plans to submit a BLA to the FDA in the first half of 2025.[127,128]

Annexon reported positive topline results from a randomized, placebo-controlled Phase 3 trial (NCT04701164) that evaluated the effects of either 30 mg/kg or 75 mg/kg IV doses of ANX005 vs placebo in 241 GBS patients. The study was conducted in Bangladesh and the Philippines, which are regions with high GBS prevalence and limited access to the SOC (IV immunoglobulin). The results showed that a single infusion of ANX005 30 mg/kg achieved the study's primary endpoint, with a 2.4-fold improvement of the GBS disability scale (GBS-DS) at Week 8. ANX005 also led to an early reduction in neurofilament light chain levels, a biomarker for nerve damage, showing an 11.2% reduction relative to placebo between Weeks 2 and 4.[127,128]

Following feedback from the FDA, Annexon initiated a real-world evidence (RWE) protocol with the International Guillain–Barré Syndrome Outcomes Study (IGOS, NCT01582763) to compare the results obtained with the Phase 3 study participants with those from Western patients. The company expects initial topline data from the RWE comparability protocol by the end of 2024.

Sibeprenlimab (Otsuka Pharmaceutical Co., Ltd.)

Sibeprenlimab (VIS649) is a humanized IgG2κ antibody targeting the antigen a proliferation inducing ligand (APRIL), which is implicated in the pathogenesis of immunoglobulin A nephropathy (IgAN). By binding APRIL, the antibody blocks signaling through its receptors, BCMA and transmembrane activator calcium modulator and cyclophilin ligand interactor, thereby interfering with downstream activities, such as B cell proliferation, IgA production, and terminal B-cell survival. The FDA granted Breakthrough Therapy designation for sibeprenlimab for the treatment of IgAN. Based on positive results from the Phase 3 VISIONARY study, Otsuka plans to submit a BLA to the FDA for sibeprenlimab for the treatment of IgAN in adults in the first half of 2025.[129]

The randomized, double-blind, placebo-controlled Phase 3 VISIONARY study (NCT05248646) is evaluating the effects of sibeprenlimab (400 mg administered SC Q4W) compared to placebo in approximately 530 patients with IgAN who were receiving SOC therapy. The study's primary endpoint is the relative change from baseline in the urinary protein-to-creatinine ratio (uPCR) in 24-hour urine collections after 9 months of treatment. As announced in October 2024, the study met its primary endpoint at prespecified interim analysis.[130]

Denecimig (Novo Nordisk)

Denecimig (NN-7769, NNC0365–3769, Mim8), a human, hinge-stabilized IgG4κ bispecific antibody derived from Genmab's Duobody technology is being developed to treat blood clotting and coagulation disorders. Created by Novo Nordisk, denecimig promotes the assembly of activated coagulation Factors IXa (FIXa) and X (FX) on platelet membranes, mimicking Factor VIII, making it a potential treatment for hemophilia A, which is caused by mutations in the F8 gene encoding Factor VIII. Denecimig received Orphan Drug designation from the FDA for treatment of hemophilia A. Novo Nordisk plans to submit marketing applications for denecimig to regulatory agencies in 2025.[131]

Novo Nordisk's Phase 3 FRONTIER clinical program is evaluating denecimig as a preventative treatment for hemophilia A with or without inhibitors. The program includes FRONTIER 2 in people aged 12 years and older (NCT05053139), FRONTIER 3 in pediatric patients (NCT05306418), FRONTIER 4 (NCT05685238) open-label extension study to collect long-term safety data following participation in the FRONTIER Phase 2 and Phase 3 studies, and FRONTIER 5 (NCT05878938) investigating the effects of switching from emicizumab to denecimig in people with hemophilia A.

In May 2024, Novo Nordisk announced that the 26-week open-label, randomized FRONTIER 2 Phase 3 study met its co-primary endpoints, demonstrating that both once-weekly and once-monthly doses of denecimig significantly reduced the number of treated bleeding episodes in patients aged 12

years and older with hemophilia A. For those without prior prophylaxis treatment, weekly denecimig reduced treated bleeds by 97%, and monthly doses by 99%. Furthermore, 86% of patients on the weekly regimen and 95% on the monthly regimen experienced zero treated bleeds, compared to none in the group without prophylaxis. In patients who were already on coagulation factor prophylaxis, weekly doses of denecimig reduced treated bleeds by 48%, and monthly doses led to a 43% reduction. Furthermore, 66% of the patients on the weekly regimen and 65% on the monthly regimen reported no treated bleeds, demonstrating the superiority of denecimig over previous prophylaxis methods.[132]

Astegolimab (Hoffmann-La Roche, Amgen)

Astegolimab (RO7187807, MSTT1041A, RG6149, AMG282) is a human monoclonal IgG2κ antibody that targets and inhibits the IL-33 receptor, which is also known as ST2. IL-33 is a cytokine involved in inflammatory responses and is implicated in various immune-mediated diseases such as asthma and chronic obstructive pulmonary disease (COPD). In 2016, Amgen licensed exclusive global rights to astegolimab to Genentech, an independent subsidiary of Roche, which plans regulatory submission(s) in COPD in 2025.[133]

Roche is conducting two Phase 3 studies of astegolimab in COPD. The randomized, double-blind, placebo-controlled ARNASA study (NCT05595642) is evaluating the efficacy and safety of astegolimab in 1290 COPD patients. In the 3-arm study, participants receive SC astegolimab Q2W, SC astegolimab Q4W or SC placebo Q2W. The primary study endpoint is the annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period. The estimated primary completion date is in June 2025.

The Phase 3 open-label extension ALNASA study (NCT05878769) aims to assess the long-term safety and further explore the efficacy of astegolimab in COPD patients who have completed the 52-week placebo-controlled treatment period in the Phase 3 ARNASA or Phase 2b ALIENTO (NCT05037929) studies. An estimated 2000 patients will receive SC astegolimab Q2W until the end of the study. The primary outcome measure is the incidence of all adverse events up to 12 weeks after the last dose of study treatment. The estimated primary completion date is in June 2027.

Cendakimab (Bristol Myers Squibb)

Cendakimab (CC-93538, RPC4046; ABT-308, 13C5.5, BMS-986355) is a humanized IgG1κ antibody blocking the binding of IL-13, which prevents IL-13 from binding to its two receptors, IL-13 Rα1 and IL-13 Rα2. The Fc of the antibody was engineered to reduce Fc-mediated effector function (L234A, L235A). Cendakimab has been developed for immune-mediated disorders by multiple companies. In 2013, AbbVie licensed cendakimab to receptors, which was acquired by Celgene in 2015. Celgene was then acquired by Bristol Myers Squibb (BMS) in 2019. A Phase 3 trial evaluating the efficacy and safety of cendakimab in patients with eosinophilic esophagitis (EoE) met both co-primary endpoints,[134] allowing the possibility for marketing submissions in 2025.

The efficacy and safety of cendakimab in adult and adolescent patients with EoE were evaluated in a randomized, double-blind, placebo-controlled induction and long-term controlled Phase 3 study (NCT04753697). The study had three arms: 1) cendakimab 360 mg administered SC once weekly for 24 weeks followed by cendakimab 360 mg SC once weekly for 24 weeks; 2) cendakimab 360 mg SC once weekly for 24 weeks followed by cendakimab 360 mg SC once every other week for 24 weeks, with matching placebo will be administered once every other week on alternate weeks during the maintenance phase to maintain the blind; and 3) matching placebo SC once weekly for 24 weeks followed by matching placebo SC once weekly for 24 weeks. The study met the co-primary endpoints, change in dysphagia day clinical response and eosinophil histologic response at 24 weeks, demonstrating statistically significant reductions versus placebo in symptoms (dysphagia days) and esophageal eosinophil counts after 24 weeks of treatment.[134]

SSGJ-613 (Sunshine Guojian Pharmaceutical (Shanghai) Co. Ltd., 3SBio)

SSGJ-613 is a humanized monoclonal antibody targeting IL-1β, a key mediator of acute gouty flares. The molecule, developed by Sunshine Guojian Pharmaceutical (Shanghai) Co. Ltd. and 3SBio, is currently in clinical studies for the treatment of gout and gouty arthritis. 3SBio is planning to submit an NDA to the NMPA for the treatment of acute gout arthritis by the end of 2025.[91]

Positive results of an active-controlled Phase 2 study in Chinese patients with acute gout arthritis were recently reported.[135] In this study, which enrolled a total of 90 participants, eligible patients were randomized 1:1:1 receive a single dose (200 or 300 mg SC) of SSGJ-613 or betamethasone (1 mL IM). The study demonstrated that a single injection of SSGJ-613 at either dose could achieve rapid pain relief similar to that of steroids and provide effective prophylaxis against flares.

In January 2024, Sunshine Guojian Pharmaceutical initiated an active-controlled Phase 3 study (CTR20233982, NCT06169891, SSGJ-613-AG-III-01) evaluating the efficacy and safety of SSGJ-613 antibody injection in Chinese patients with acute gout. Randomized patients receive one SC injection of SSGJ-613 (200 mg) and placebo (0.9% sodium chloride) matching the active control betamethasone (IM injection) once, or betamethasone and placebo matching SSGJ-613, on Day 1. The estimated enrollment is 500 participants. The primary outcome measures include the change in pain intensity in the target joint from baseline to 72 hours post dose (as measured on a 0–100 mm Visual Analog Scale (VAS)) and the time to first new flare (measured within 12 weeks after the first administration).

Itepekimab (Sanofi, Regeneron)

Itepekimab (SAR440340, REGN3500) is a human IgG4κ monoclonal antibody developed using Regeneron's proprietary VelocImmune technology. The antibody binds to and inhibits the signaling of IL-33, an initiator and amplifier of airway inflammation. Jointly developed by Regeneron and Sanofi, itepekimab is under investigation for the treatment of respiratory diseases. The lead indication for itepekimab is

COPD for which Sanofi plans marketing application submissions in the US and the EU in the second half of 2025.[136]

Itepekimab is under investigation in two randomized, double-blind, placebo-controlled Phase 3 studies, AERIFY-1 and 2 (NCT04701983 and NCT04751487, respectively).[137] The three-arm AERIFY-1 study was designed to assess the efficacy and safety of SC itepekimab vs placebo in former smokers with moderate-to-severe chronic obstructive pulmonary disease (COPD). Participants were randomized 1:1:1 to receive SC administration of itepekimab 300 mg Q2W, itepekimab 300 mg Q4W with alternating matching placebo at the 2-week interval between itepekimab dosing, or matching placebo (Q2W) for up to 52 weeks. The AERIFY-2 study design is the same, but current as well as former smokers with moderate-to-severe COPD were included. Estimated enrollment is 960 and 1210 participants for AERIFY-1 and 2, respectively. The primary endpoint of both studies is the annualized rate of moderate or severe acute exacerbation of COPD (AECOPD), measured over a placebo-controlled treatment period. The estimated primary completion dates for AERIFY-1 and 2 are June 27 and May 30, 2025, respectively.

The long-term safety and tolerability of Itepekimab is being evaluated in the double-blind, 2-arm Phase 3 AERIFY-4 study (NCT06208306). This extension study, which will recruit an estimated 700 subjects from those who had participated in the AERIFY-1 and 2 studies, is designed to generate additional safety data, assess the durability of treatment response, and provide additional PK and immunogenicity assessments of both itepekimab SC Q2W or itepekimab SC Q4W. The estimated primary completion date for AERIFY-4 is in December 2026.

Veligrotug (Viridian Therapeutics, Inc.)

Veligrotug (VRDN-001, AVE-1642) is a humanized IgG1κ mAb targeting the insulin-like growth factor 1 receptor (IGF-1 R) extracellular domain. Initially developed by ImmunoGen in collaboration with Sanofi-Aventis, worldwide rights to develop and commercialize VRDN-001 for all non-oncology indications that do not use radiopharmaceuticals were exclusively licensed by Viridian from ImmunoGen, Inc. Viridian anticipates submitting a BLA for veligrotug for the treatment of thyroid eye disease (TED) in the second half of 2025.

In September 2024, Viridian Therapeutics announced positive top-level results of the placebo-controlled Phase 3 THRIVE study (NCT05176639), which first evaluated the effects of multiple ascending doses (MAD) of veligrotug in healthy volunteers and participants with moderate-to-severe active TED, then evaluated a single dose level of veligrotug in TED participants.[138] In the MAD portion of the study, participants were randomized to receive 30-min IV infusions of veligrotug ranging from 3 mg/kg to 20 mg/kg ($n = 75$) or placebo ($n = 38$). Participants with TED were then randomized to receive IV Infusions of 10 mg/kg veligrotug or placebo every 3 weeks. The study's primary endpoint was the proptosis responder rate at Week 6 for MAD TED participants and Week 15 for Phase 3 study subjects. The study met the primary and all secondary endpoints at 15 weeks after five infusions of veligrotug, showing highly statistically significant ($p < 0.0001$) improvements on all of the measured signs and symptoms of TED. Of patients receiving veligrotug, the proptosis responder rate was 70% and 67% achieved an overall response, while, of those who received placebo, the proptosis responder rate was 5% and 5% achieved an overall response.

A randomized, double-masked, placebo-controlled Phase 3 study of veligrotug, THRIVE-2 (NCT06021054), in patients with chronic TED has exceeded enrollment. In this study, patients will receive 5 Infusions of 10 mg/kg veligrotug. Topline data readout is expected by the end of 2024.

Anselamimab (AstraZeneca)

Anselamimab (CAEL-101, 11-1F4) is a chimeric monoclonal IgG1κ antibody designed to target amyloid fibrils that form from misfolded light-chain proteins produced by plasma cells in the bone marrow and mediate phagocytosis by macrophages and neutrophils. These fibrils accumulate in tissues and organs, causing a condition known as light chain (AL) amyloidosis. This rare disease leads to the deposition of amyloid in critical organs such as the heart, kidneys, and liver, progressively impairing their function and causing significant organ damage over time.

Caelum Biosciences, a subsidiary of Fortress Biotech, Inc., secured exclusive worldwide license rights to anselamimab from Columbia University and subsequently collaborated with Alexion Pharmaceuticals, Inc. in the clinical development of the molecule. AstraZeneca acquired both Alexion and Caelum Biosciences in 2021. Anselamimab has received Orphan Drug and Orphan Medicinal Product designations from the FDA and EMA, respectively, as a potential therapy for patients with AL amyloidosis. The FDA also granted Fast Track designation to anselamimab for AL amyloidosis. AstraZeneca anticipates readouts of key Phase 3 studies of anselamimab in AL amyloidosis in 2025, which could allow regulatory submissions for anselamimab for AL amyloidosis in 2025.[139,140]

AstraZeneca's Alexion division is currently evaluating anselamimab in the Cardiac Amyloid Reaching for Extended Survival (CARES) program, which aims to assess its efficacy vs placebo in AL amyloidosis patients in two Phase 3 studies. The primary endpoint for both studies is time from first dose of trial drug until death or end of trial. The randomized, blinded Phase 3 NCT04512235 study evaluates the efficacy and safety of IV anselamimab or placebo combined with SOC for plasma cell dyscrasia in 281 treatment-naïve patients with Mayo Stage IIIa AL amyloidosis. The estimated primary completion date of the study is April 2025. The Phase 3 NCT04504825 study has the same design, but includes 125 Mayo Stage IIIb patients. The estimated primary completion date of the study is May 2025.

Sonelokimab (Merck Serono, MoonLake Immunotherapeutics AG)

Sonelokimab (M1095, ALX-0761) is a trispecific antibody fragment targeting IL-17A, IL17F, and albumin. The molecule is composed of three nanobodies, which are camelid-derived heavy-chain-only single-domain antibodies covalently linked by flexible glycine-serine spacers. A domain specific for IL-17F and one specific for both IL-17A and IL-17F are separated by a domain targeting albumin to facilitate enrichment of the

nanobody at sites of inflammatory edema. In 2021, MoonLake Immunotherapeutics AG in-licensed sonelokimab from Merck KGaA, which had acquired full, exclusive rights to sonelokimab through a global development and commercialization agreement with Ablynx (now Ablynx, a Sanofi Company) in 2013.

MoonLake Immunotherapeutics is developing sonelokimab for the treatment of hidradenitis suppurativa (HS) and psoriatic arthritis (PSA), as well as other indications in dermatology and rheumatology. Following positive top-line results from the global Phase 2 MIRA trial announced in 2023, the company initiated the Phase 3 VELA program, which is expected to enroll 800 patients with moderate-to-severe HS. The readout of the primary endpoint is anticipated in mid-2025; positive study outcomes could potentially enable marketing application submissions by the end of 2025.

The VELA program consists of two Phase 3 trials, VELA-1 (NCT06411899) and VELA-2 (NCT06411379), which are global, randomized, double-blind, placebo-controlled studies identical in design, evaluating the efficacy and safety of SC sonelokimab compared to placebo in adult participants with moderate-to-severe HS. Patients randomized to the sonelokimab arm will receive 120 mg Q2W sonelokimab from Weeks 0 to 6, then 120 mg Q4W starting at Week 8 up to Week 48. Those in the placebo arm will receive placebo Q2W from Weeks 0 to 6 then Q4W starting at Week 8 up to Week 16, after which they will receive sonelokimab 120 mg Q2W for 4 doses from Weeks 16 to 22 then Q4W from Week 24 up to Week 48. The primary endpoint is the higher measure of clinical response, HS Clinical Response (HiSCR) 75, defined as at least a 75% reduction from baseline in abscess and inflammatory nodule (AN) count, with no increase from baseline in abscess or draining fistula count, and is measured at Week 16. Each study has an estimated enrollment of 400 patients and a primary completion date in June 2025.

Solenokimab is also being investigated in PSA, with the Phase 2 ARGO trial having met primary and key secondary endpoints and Phase 3 trial (NCT06641076, NCT06641089) initiation anticipated in Q4 2024. Phase 2 trials are expected to be initiated in palmo-plantar pustulosis and in radiographic and non-radiographic axSpA by the end of 2024.[141]

Ersodetug (Rezolute, Inc.)

Ersodetug (RZ358, XOMA 358) is a human IgG2κ monoclonal antibody targeting insulin receptor. The antibody binds to an allosteric site on the insulin receptor at target tissues such as liver, fat, and muscle, modulating insulin's binding, signaling, and activity to restore glucose levels to a normal range. Ersodetug has been shown to induce whole-body insulin resistance and reverse insulin-stimulated hypoglycemia in both mice and healthy humans and has the potential to be effective at treating hypoglycemia caused by any form of hyperinsulinism (HI), which is a rare, genetic, pediatric endocrine disorder that has congenital and acquired forms.

Rezolute, Inc., which licensed the global development and commercialization rights for ersodetug from XOMA Corporation in 2017, is developing the molecule as a treatment of hyperinsulinism (HI). Ersodetug has received Orphan Drug and Orphan Medicinal Product designation in the US and the EU, respectively, and Pediatric Rare Disease designation in the US. The Phase 3 sunRIZE study of ersodetug in patients with congenital HI has an estimated primary completion date in April 2025. Top-line data is expected by the second half of 2025.[142]

The randomized, double-blind, placebo-controlled, parallel-arm Phase 3 sunRIZE trial (NCT06208215) is evaluating the efficacy and safety of ersodetug in patients with congenital HI, as add-on to SOC therapy compared to SOC therapy alone over 24 weeks and the longer-term safety and efficacy of ersodetug during a subsequent open-label extension period. The study will enroll an estimated 48 participants (≥1 year to ≤45 years of age) to be randomized in a 1:1 ratio into 2 dosing arms (5 or 10 mg/kg). Participants within each dosing level will be further randomized in a 2:1 ratio to receive ersodetug as add-on to SOC or placebo as add-on to SOC. An additional open-label arm will be conducted in parallel for participants who are ≥3 months to <1 year old and will enroll 8 participants. Upon completion of the pivotal treatment period (24-weeks), patients may roll-over to the open-label extension period. The primary endpoint is the change in average weekly hypoglycemia events from baseline by point-of-care self-monitoring blood glucose.

Antibodies to watch in 2025: cancer indications

Based on the totality of evidence available as of November 2024, we project that marketing applications for only five of the antibody therapeutics we identified as in late-stage clinical studies for cancer may be submitted by the end of 2025 (Table 4). Key details for these molecules are given below, with the summaries ordered according to our estimated marketing application submission dates. Additional data for these molecules can be found in Supplemental Table S1.

Erfonrilimab (Jiangsu Alphamab Biopharmaceuticals Co., Ltd)

Erfonrilimab (KN046) is a humanized bispecific antibody with a 2 + 2 symmetric design (VHH-VHH')2-Fc)) that targets the immune system checkpoint proteins PD-L1 and CTLA-4. Jiangsu Alphamab is developing erfonrilimab for various solid tumors and has engaged in partnerships relating to erfonrilimab with several companies, including Pfizer, Zelgen (泽璟), Sunny Lake (东阳光), Kintor Pharmaceutical (开拓), Sinovent (信诺维), and InxMed. Erfonrilimab received Orphan Drug designation from the FDA for thymic epithelial tumors and biliary tract cancer. Jiangsu Alphamab anticipates final OS analysis for first-line treatment of squamous (sq) NSCLC, and, if results are positive, may submit an NDA to the NMPA in 2024.[143]

Results from the open-label Phase 2 KN046–202 trial (NCT04054531) of erfonrilimab in combination with chemotherapy as first-line therapy for metastatic NSCLC were recently reported.[144] The study included two arms: 1) patients with non-sq-NSCLC who received pemetrexed with KN046 (5

Table 4. Commercially sponsored investigational monoclonal antibodies in late-stage clinical studies for cancer indications, with regulatory submission anticipated during 2024–2025.

INN or drug code	Target(s); Format	Indication of relevant* late-stage study (est. submission year, country#)	Most advanced clinical phase
Erfonrilimab	PD-L1, CTLA-4; Humanized/chimeric IgG1, Bispecific	NSCLC (2024, China)	Phase 3
Anbenitamab	HER2; Humanized IgG1κ; biparatopic bispecific	NSCLC (2025, China)	Phase 3
Nofazinlimab	PD-1; Humanized; IgG4κ	Hepatocellular carcinoma (2025, China)	Phase 3
Cobolimab	TIM3; Humanized IgG4κ	NSCLC (2025H1, US, EU)	Phase 3
Tiragolumab	TIGIT; Human IgG1κ	NSCLC (2025)	Phase 3

*Indication for which a regulatory submission is anticipated. #First marketing application submission dates and country are estimates based on company announcements and pivotal trial completion dates. Table includes information found in the public domain as of December 1, 2024. Abbreviations: ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule-5; CTLA-4, cytotoxic T lymphocyte antigen-4; HER, human epidermal growth factor receptor; PD-L1, programmed cell death protein ligand 1; TIGIT, T-cell Immunoreceptor with Ig and ITIM domains; TIM-3, T cell immunoglobulin and mucin-domain containing-3. See Supplemental Table S1 for more details about each antibody. Additional data for investigational antibody therapeutics in late-stage clinical studies also available at: https://www.antibodysociety.org/antibodies-in-late-stage-clinical-studies/.

mg/kg IV Q3W) and carboplatin ($n = 51$) and 2) patients with sq-NSCLC who receive paclitaxel with KN046 (5 mg/kg IV Q3W) and carboplatin ($n = 36$). After four cycles, maintenance therapy includes KN046 with pemetrexed for non-sq-NSCLC and KN046 for sq-NSCLC. The primary endpoints were confirmed ORR and median DoR. The confirmed ORR was 43.1% and 50.0% in the non-sq-NSCLC and sq-NSCLC cohorts, respectively. The median DOR was 9.7 (95% CI: 4.01–20.73) and 7.3 (95% CI: 3.52-NR) months in the non-sq-NSCLC and sq-NSCLC cohorts, respectively. The median PFS was 5.8 (95% CI: 4.80–7.16) and 5.7 (95% CI: 4.17–8.71) months in the non-sq-NSCLC and sq-NSCLC cohorts, respectively. The median OS was 27.2 (95% CI: 15.18-NR) months in the non-sq-NSCLC cohort and 26.6 (95% CI: 12.19-NR) months in the sq-NSCLC cohort.

The randomized, placebo-controlled Phase 3 ENREACH-LUNG-01 study (NCT04474119, CTR20201294) aims to verify the efficacy and safety of KN046 in combination with platinum-containing chemotherapy in first-line treatment for advanced sq-NSCLC patients. In this 2-arm study, patients receive carboplatin, paclitaxel, and IV KN046 5 mg/kg Q3W for the first 12 weeks of the double-blind period, then IV KN046 5 mg/kg Q2W during the crossover period or patients receive carboplatin, paclitaxel, and placebo. Initiated in September 2020, the study's estimated enrollment is 482 patients. The primary endpoint is PFS according to RECIST 1.1 criteria and the secondary endpoint is OS during the evaluation period (3 years).

Anbenitamab (Shanghai JMT-Bio Technology Co., Ltd., Jiangsu Alphamab Biopharmaceuticals Co. Ltd)

Anbenitamab (KN026) is a humanized, biparatopic bispecific IgG1κ monoclonal antibody targeting two non-overlapping epitopes of HER2. The antibody has been designed with common light chain and heavy chains engineered with knob-in-hole and electrostatic steering mutations to enable heterodimerization. By blocking HER2, anbenitamab inhibits tumor cell growth and promotes antibody-dependent cell-mediated cytotoxicity (ADCC).

In 2021, Shanghai JMT-Bio obtained from Jiangsu Alphamab the exclusive development and commercialization license rights to anbenitamab as a single agent and in combination with KN046, a bispecific antibody targeting the immune system checkpoint proteins PD-L1 and CTLA-4, for breast cancer and gastric cancer indications in mainland China. Anbenitamab combined with chemotherapy was granted Breakthrough Therapy designation by the NMPA for the treatment of patients with HER2-positive gastric cancer who have failed first-line standard treatment and the FDA granted Orphan Drug designation for anbenitamab in combination with KN046 for the treatment of HER2-positive or low-expressing G/GEJ cancer. An NDA for anbenitamab is expected to be submitted in 2025.[145]

Shanghai JMT-Bio is conducting pivotal trials assessing the efficacy of anbenitamab in gastric and breast cancers. KN026–001 (NCT05427383, CTR20213458) is a two-stage randomized, Phase 2/3 clinical study to evaluate the efficacy of IV anbenitamab at 30 mg/kg Q3W in combination with chemotherapy (paclitaxel/docetaxel/irinotecan) vs placebo and chemotherapy in an estimated 286 patients with HER2-positive advanced unresectable or metastatic gastric cancer, including adenocarcinoma of the gastro-esophageal junction, who have failed first-line therapy. The study's primary endpoints are PFS and OS up to 2.5 years. The estimated primary completion date of the study is November 2025.

Shanghai JMT-Bio is also conducting a randomized, controlled, open-label Phase 3 KN026–001 trial (NCT05838066, CTR20231442) evaluating the efficacy and safety of anbenitamab in combination with HB1801 (albumin-bound docetaxel) versus trastuzumab + pertuzumab + docetaxel in the first-line treatment of patients with HER2-positive recurrent or metastatic breast cancer. The primary study endpoint is PFS. The study's estimated primary completion date is in July 2026.

Nofazinlimab (CStone Pharmaceuticals, 3SBio Inc.)

Nofazinlimab (CS1003) is a humanized, hinge-stabilized IgG4κ monoclonal antibody targeting human PD-1 derived from CStone Pharmaceuticals's proprietary hybridoma platform. Nofazinlimab cross-reacts with both human and murine PD-1, facilitating efficacy tests in homologous mouse tumor models. The molecule is currently being developed by CStone and 3SBio for immunotherapy of various tumors, with 3SBio controlling rights to develop, register, manufacture, and

commercialize nofazinlimab in mainland China and CStone retaining these rights outside mainland China. Nofazinlimab was granted US Orphan Drug Designation for the treatment of patients with HCC. 3SBio plans to submit an NDA to the NMPA for nofazinlimab for HCC in 2025.[91]

The double-blind, randomized Phase 3 CS1003–305 study (NCT04194775, CTR20192524) is evaluating the efficacy and safety of IV nofazinlimab in combination with lenvatinib, which is an SOC TKI, compared to placebo and lenvatinib as a first-line treatment for patients with advanced HCC. Participants are administered 200 mg nofazinlimab Q3W with lenvatinib or placebo and lenvatinib until disease progression or intolerable toxicity occurs or withdrawal from the study due to other reasons. The primary endpoint of the study is OS. The enrollment is 534 patients; final OS analysis is expected in the first half of 2025.

Cobolimab (GSK)

Cobolimab (GSK4069889, TSR-022) is a humanized, hinge-stabilized IgG4κ monoclonal antibody directed against the immune checkpoint T cell immunoglobulin and mucin containing protein-3 (TIM-3), which is associated with suppressed anti-tumor responses. By inhibiting TIM-3, cobolimab activates immune system functions and its activity is enhanced when combined with PD-1 agents. Cobolimab was discovered and initially developed by TESARO, which was acquired by GSK in 2019. GSK is planning regulatory submissions in the US and the EU for cobolimab in second-line NSCLC patients in the first half of 2025.[121]

The randomized, open-label, three-arm Phase 2/3 COSTAR Lung trial (NCT04655976) is designed to compare the effects of 1) cobolimab combined with anti-PD-1 dostarlimab + docetaxel, 2) dostarlimab + docetaxel and 3) docetaxel alone. The study has enrolled 758 patients with advanced NSCLC who have progressed on prior anti-PD-(L)1 therapy and chemotherapy randomized 2:1:1 to the 3 study arms, respectively. The study's primary endpoint is OS in participants receiving combinations versus docetaxel alone up to 44 months. Data readout is expected in the first half of 2025.[121]

Tiragolumab (Hoffmann LaRoche)

Tiragolumab (RO7092284, RG6058, MTIG7192A) is a human IgG1κ antibody targeting an immune checkpoint protein, T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), which is found on activated T cells, natural killer cells, and regulatory T cells and acts as an inhibitor of immune system functions. Dual blockade of TIGIT and PD-1/PD-L1 has shown enhanced anti-cancer effects in some preclinical and clinical studies.[146] Roche is evaluating combinations of tiragolumab and anti-PD-L1 atezolizumab (Tecentriq®) in multiple late-stage studies of patients with lung cancer, esophageal cancer, and HCC.

As of Q3 2024, Roche anticipated possible marketing application submissions in 2025 for the combination tiragolumab and atezolizumab for patients with Stage III unresectable NSCLC who have received at least two cycles of concurrent platinum-based chemoradiotherapy and have not had radiographic disease progression based on the SKYSCRAPER-03 study (NCT04513925) and for first-line treatment of patients with locally advanced unresectable or metastatic PD-L1-selected NSCLC with no EGFR mutation or anaplastic lymphoma kinase translocation based on the placebo-controlled Phase 3 SKYSCRAPER-01 study (NCT04294810).[132] However, the SKYSCRAPER-01 study did not meet its primary endpoints of PFS or OS.

In July 2024, Genentech, a member of the Roche Group, reported that the placebo-controlled Phase 2/3 SKYSCRAPER-06 study (NCT04619797) of tiragolumab in combination with atezolizumab and chemotherapy as a first-line treatment for non-squamous NSCLC failed to meet primary endpoints of PFS at its primary analysis and OS at its first interim analysis. The company indicated that they intend to terminate the study.[147]

Ongoing late-stage studies are also evaluating tiragolumab in combination with other therapies as first-line treatments for esophageal cancer (SKYSCRAPER-07 (NCT04543617), SKYSCRAPER-08 (NCT04540211)) and HCC patients (SKYSCRAPER-14, NCT05904886). The placebo-controlled Phase 3 SKYSCRAPER-08 study conducted in China is evaluating tiragolumab in combination with atezolizumab and chemotherapy as a first-line treatment in patients with unresectable locally advanced, unresectable recurrent, or metastatic esophageal cancer. Eligible patients were randomized (1:1) to one of the two study arms to receive: 1) tiragolumab 600 mg + atezolizumab 1200 mg + chemotherapy, or 2) placebo + chemotherapy. The study met both primary endpoints of independent review facility-assessed PFS and OS, with median PFS 6.2 vs 5.4 months and median OS 15.7 vs 11.1 months for treatment arm that included tiragolumab vs placebo, respectively.[148]

Outlook for the future

Overall, 2024 was a very good year for antibody therapeutics, as demonstrated by the substantial increase in the number of molecules in late-stage clinical development (178 reported here) compared to that reported in Antibodies to Watch in 2010–2024 (range 26–138).[1] Moreover, here we report slightly higher numbers for antibody therapeutics undergoing regulatory review and granted a first approval compared to the 2024 version of Antibodies to Watch.

With this positive news, we have, however, also noted an area of concern relating to the higher percentage of BLAs that are not approved by the FDA on a first cycle, which delays patient access to the therapies. Four of the nine investigational antibodies (i.e., those not approved elsewhere) in regulatory review in the US are currently in a second cycle of review following receipt of a CRL from the FDA (Table 2). The FDA is also currently reviewing applications for another four antibody therapeutic products that received first approval in another country, and therefore not included in Table 2, and three of these received a CRL, bringing the total number of molecules in FDA review to 13, with seven (54%) in the second cycle of review (Supplemental Table S2). We have recently noted an increase in CRLs issued by the FDA, especially those

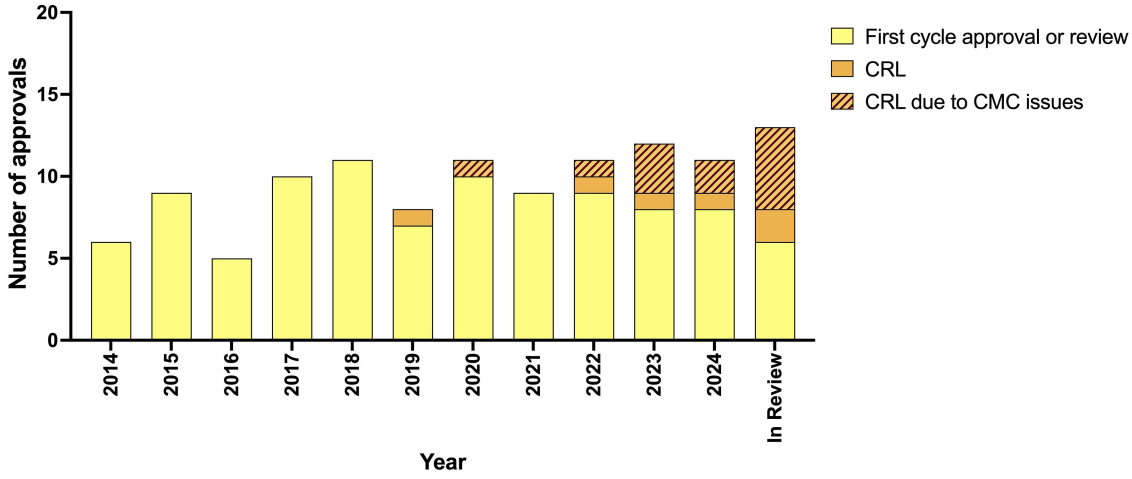

Figure 3. Trends in issuance of complete response letters by the US food and drug administration. Yellow sections, antibody therapeutics approved after a first review or currently undergoing a first review. Orange section, complete response letter (CRL) issued by the FDA. Striped orange section, CRL issued by the FDA due to Chemistry, Manufacturing, and Controls (CMC) issues. Data for 2024 is as of December 7, 2024.

due to CMC concerns (Figure 3). CRLs are issued by the FDA when the agency has concerns regarding a marketing application. These concerns must be addressed by the sponsoring company in a resubmitted BLA that must be further reviewed by the FDA, which can delay approval of a product by 6 months or more. Notably, the majority of CRLs were issued due to CMC deficiencies rather than concerns relating to safety or efficacy, highlighting the need for sponsors and their third-party manufacturing partners to be proactive and ensure that manufacturing sites meet FDA requirements for current good manufacturing practices.[149]

As in the past, we will continue to track the progress of antibody therapeutics as they enter late-stage clinical studies and progress toward marketing approvals. We look forward to reporting further trends and documenting the successes of these molecules in 'Antibodies to Watch' articles in the future.

Disclosure statement

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ORCID

Silvia Crescioli http://orcid.org/0000-0002-1909-5957
Hélène Kaplon http://orcid.org/0000-0002-5597-2195
Lin Wang http://orcid.org/0009-0005-7958-9894
Jyothsna Visweswaraiah http://orcid.org/0000-0002-6181-2438
Vaishali Kapoor http://orcid.org/0000-0002-7581-1487
Janice M. Reichert http://orcid.org/0000-0003-0400-1951

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Abbreviations

Aβ	amyloid beta
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
AML	acute myeloid leukemia
Ang-2	angiopoietin-2
ANGPTL3	angiopoietin-like protein 3
ASCO	American Society of Clinical Oncology
axSpA	axial spondyloarthritis
BCMA	B cell maturation antigen
BLA	biologics license application
BTC	biliary tract cancer
CDC	complement-dependent cytotoxicity
CI	confidence interval
CLDN18.2	claudin 18.2
CLL	chronic lymphocytic leukemia
CMC	Chemistry, Manufacturing, and Controls
COVID-19	coronavirus disease 2019
CPS	combined positive score
CR	complete response
CRSwNP	chronic rhinosinusitis with nasal polyps
cSCC	cutaneous squamous cell carcinoma
CTLA-4	cytotoxic T lymphocyte antigen-4
DLBCL	diffuse large B-cell lymphoma
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EpCAM	epithelial cell adhesion molecule
EU	European Union
Fab	antigen-binding fragment
Fc	crystallizable fragment
FcγR	receptor for IgG Fc
FcRn	neonatal Fc receptor
FDA	US Food and Drug Administration
FL	follicular lymphoma
G/GEJ	gastric or gastroesophageal junction
GvHD	graft-vs-host disease
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2

HLA	human leukocyte antigen
HoFH	homozygous familial hypercholesterolemia
HR	hazard ratio
iADRS	Integrated AD Rating Scale
IFN	interferon
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
IM	intramuscular
ITT	intention-to-treat
ICR	independent central review
IRC	independent review committee
IV	intravenous
LAG-3	lymphocyte-activation gene 3
LDL	low-density lipoprotein
LM	leptomeningeal metastases
mAb	monoclonal antibody
MASP-2	mannan-binding lectin-associated serine protease-2
MCI	mild cognitive impairment
MET	mesenchymal epithelial transition factor
MHLW	Ministry of Health, Labour and Welfare
MM	multiple myeloma
MMAE	monomethyl auristatin E
NDA	new drug application
NHL	non-Hodgkin's lymphoma
NK	natural killer
NMPA	National Medical Products Administration
NPC	nasopharyngeal carcinoma
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PNH	paroxysmal nocturnal hemoglobinuria
PK	pharmacokinetics
PR	partial response
PRIME	Priority Medicines
Q2W	every 2 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
R/R	relapsed or refractory
RSV	respiratory syncytial virus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
scFv	single-chain variable fragment
SOC	standard of care
TCR	T cell receptor
TIGIT	T-cell Immunoreceptor with Ig and ITIM domains
TIM-3	T-cell immunoglobulin and mucin-domain domain-containing molecule-3
TKI	tyrosine kinase inhibitor
TMAs	thrombotic microangiopathies
TNF	tumor necrosis factor
UK	United Kingdom
US	United States
VEGF	human vascular endothelial growth factor
VHH	variable heavy chain single domain antibodies

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