




REPORT

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## Antibodies to watch in 2022

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### ABSTRACT

In this 13th annual installment of the annual 'Antibodies to Watch' article series, we discuss key events in commercial antibody therapeutics development that occurred in 2021 and forecast events that might occur in 2022. Regulatory review of antibody therapeutics that target the SARS-CoV-2 coronavirus proceeded at an unprecedented pace in 2021, resulting in both emergency use authorizations and full approvals for sotrovimab, regdanvimab, REGEN-COV2, as well as others, in numerous countries. As of November 1, a total of 11 antibody therapeutics had been granted first approvals in either the United States or European Union in 2021 (evinacumab, dostarlimab, loncastuximab, tesirine, amivantamab, aducanumab, tralokinumab, anifrolumab, bimekizumab, tisotumab vedotin, regdanvimab, REGEN-COV2). The first global approvals of seven products, however, were granted elsewhere, including Japan (pabinafusp alfa), China (disitamab vedotin, penpulimab, zimberelimab), Australia (sotrovimab, REGEN-COV2), or the Republic of Korea (regdanvimab). Globally, at least 27 novel antibody therapeutics are undergoing review by regulatory agencies. First actions by the Food and Drug Administration on the biologics license applications for faricimab, sutimlimab, tebentafusp, relatlimab, sintilimab, ublituximab and tezepelumab are expected in the first quarter of 2022. Finally, our data show that, with antibodies for COVID-19 excluded, the late-stage commercial clinical pipeline of antibody therapeutics grew by over 30% in the past year. Of those in late-stage development, marketing applications for at least 22 may occur by the end of 2022.

### ARTICLE HISTORY

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### KEYWORDS

antibody therapeutics; cancer; COVID-19; Food and Drug Administration; European Medicines Agency; immune-mediated disorders; SARS-CoV-2

## Introduction

The 'Antibodies to Watch' article series endeavors to document recent approvals of novel monoclonal antibody (mAb) therapeutic products, candidate products in regulatory review, and the late-stage commercial clinical pipeline on an annual basis. Since the first publication in 2010,<sup>1</sup> the number of approved products has substantially grown, exceeding 100 in the United States (US),<sup>2</sup> and, as described below, record numbers of antibody therapeutics are undergoing regulatory review. We analyzed data for products in these two categories, and found that nearly half (45%) were treatments for cancer, 27% for immune-mediated disorders, 8% for infectious diseases, 7% for cardiovascular/hemostasis disorders, with products for other therapeutics areas comprising 5% or less of the total (Figure 1).

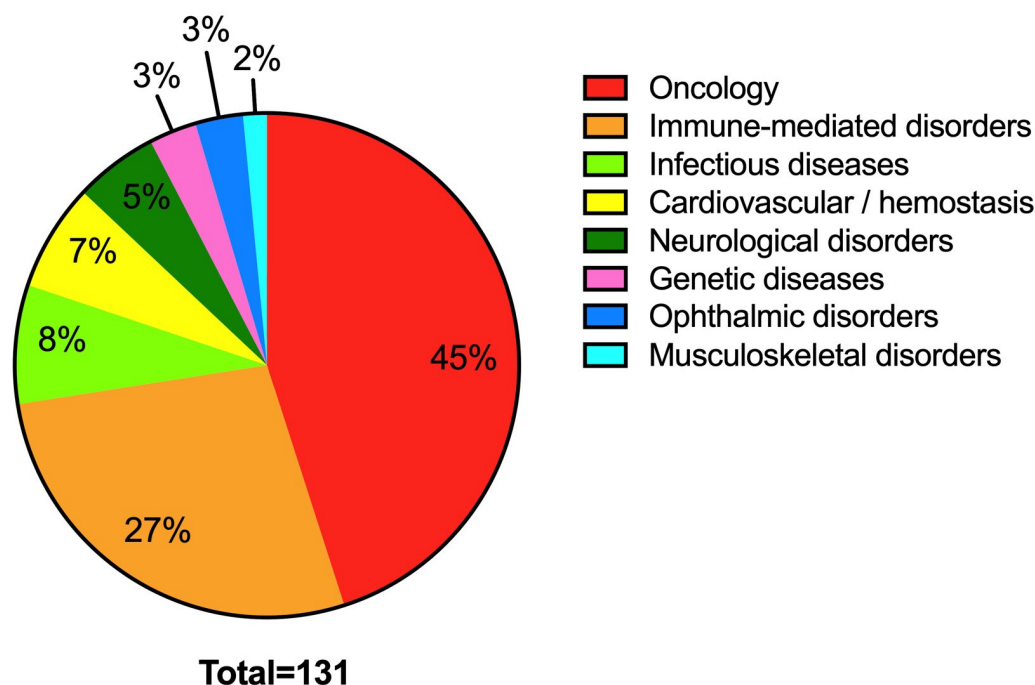
Of those for cancer ( $n = 59$ ), the most frequent targets include programmed cell death protein 1 (PD-1), CD20, and human epidermal growth factor receptor 2 (HER2) (Figure 2). Of those for diseases other than cancer ( $n = 72$ ), the most frequent targets include tumor necrosis factor (TNF), amyloid beta, IL-23 p19 subunit, and calcitonin gene-related peptide (Figure 3).

The 'Antibodies to Watch' article series primarily focuses on first approvals that occur in the US or EU, thereby excluding approvals for any supplemental indications that are granted to marketed products. In the past, first approvals in these 2 regions were typically also the first global approval, but, as we

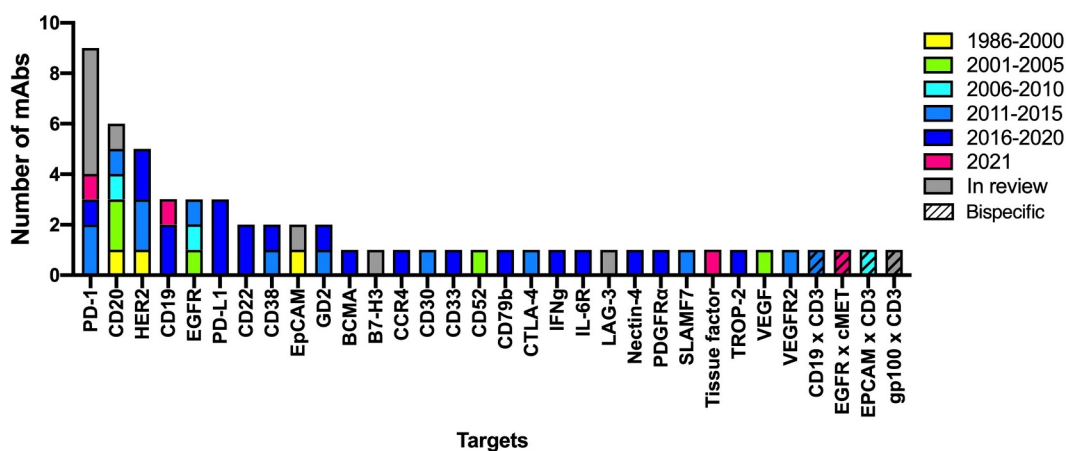
also discuss below, an increasing number of first global approvals are being granted in other regions, most notably in China.

Despite the development of vaccines, the coronavirus pandemic remains a serious global concern in 2021, although there are signs that the rate of infections may abate in 2022. To enable and facilitate comparison with data published in past 'Antibodies to Watch' articles, data for antibody therapies for coronavirus disease 2019 (COVID-19) and our discussion of this data are segregated from the traditional topics, i.e., recently approved antibody products, antibody therapeutics in regulatory review, and those that may transition to regulatory review soon.

Forecasts of future events, particularly the submission of marketing applications for antibody therapeutics in late-stage clinical studies, is a key feature of the 'Antibodies to Watch' articles. We include such forecasts here for 22 of 115 antibody therapeutics in late-stage clinical studies. However, while past articles have included tables listing all relevant antibody therapeutics in late-stage development (i.e., pivotal clinical studies) in the body of the paper, data for the 115 antibodies included in 'Antibodies to Watch in 2022' are in Supplemental Tables provided as a single Excel file. Antibody therapeutics undergoing evaluation for cancer and noncancer indications can be found in Supplemental Tables S1 and S2, respectively. Since the size of the tables was no longer a concern, we expanded the data presented to include light chain, Fc mutations, and fused



**Figure 1.** Primary indications for antibody therapeutics approved or in regulatory review in the United States or European Union. Figure based on data publicly available as of November 15, 2021. Total = 131 and includes products that were approved but subsequently withdrawn from the market. Each product is included once; supplemental approvals are not included. Biosimilar and Fc fusion protein products were excluded. Antibodies granted emergency use authorizations (EUAs) or in review for EUAs are not included. Immune-mediated disorders category includes asthma; the genetic disorders are Muckle-Wells syndrome, X-linked hypophosphatemia, hereditary angioedema attacks, and homozygous familial hypercholesterolemia. A searchable table of the figure data is available at [www.antibodysociety.org/antibody-therapeutics-product-data/](http://www.antibodysociety.org/antibody-therapeutics-product-data/)



**Figure 2.** Targets for antibody therapeutics approved or in regulatory review in the United States or European Union for cancer. Figure based on data publicly available as of November 15, 2021. Total = 59 and includes products that were approved but subsequently withdrawn from the market. Bars with hash marks represent bispecific antibodies. Antibodies granted emergency use authorizations (EUAs) or in review for EUAs are not included. Biosimilar and Fc fusion protein products were excluded. A searchable table of the figure data is available at [www.antibodysociety.org/antibody-therapeutics-product-data/](http://www.antibodysociety.org/antibody-therapeutics-product-data/). Abbreviations: BCMA, B-cell maturation antigen; CTLA-4, cytotoxic T lymphocyte antigen-4; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; PD-1 programmed cell death protein-1; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor.

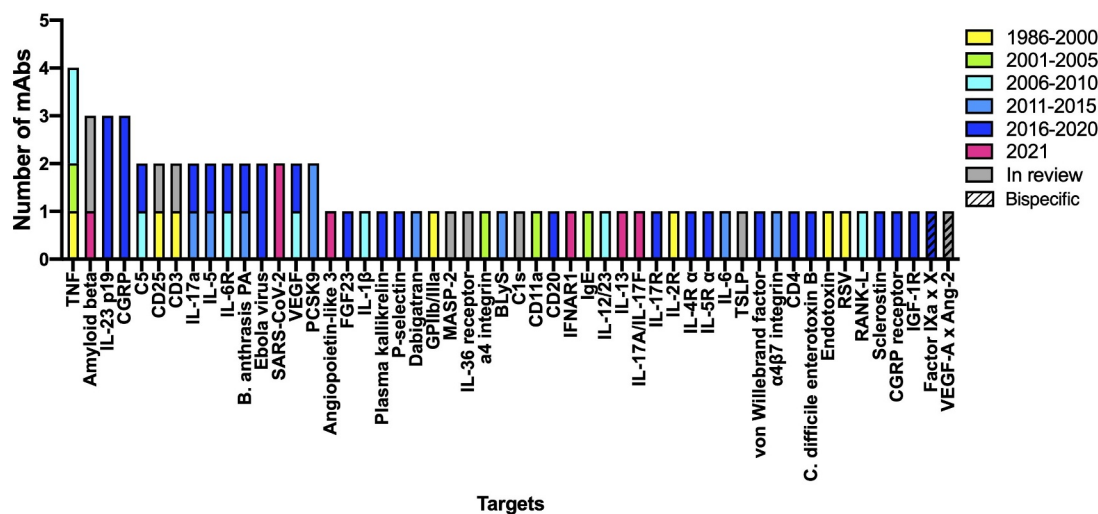
or conjugated components, while also providing the traditional information, such as sponsoring company, international non-proprietary and code names, basic molecular format (e.g., sequence source, isotype), target, most advanced phase of clinical development, and the relevant indications.

Data presented here were collected and analyzed during mid-August through mid-November 2021. While we also aimed to continuously update data throughout this 3-month period, we cannot guarantee that we captured data for all

events. Due to the large volume of literature for the molecules, we focused on publications and other disclosures made public during January to mid-November 2021.

### COVID-19 interventions

As has been widely reported, the initial cases of infection with SARS-CoV-2 were first observed in China in late 2019, and this highly transmissible and often deadly coronavirus triggered



**Figure 3.** Targets for antibody therapeutics approved or in regulatory review in the United States or European Union for noncancer indications. Figure based on data publicly available as of November 15, 2021. Total = 72 and includes products that were approved but subsequently withdrawn from the market. Bars with hash marks represent bispecific antibodies. Antibodies granted emergency use authorizations (EUAs) or in review for EUAs are not included. Biosimilar and Fc fusion protein products were excluded. A searchable table of the figure data is available at [www.antibodysociety.org/antibody-therapeutics-product-data/](http://www.antibodysociety.org/antibody-therapeutics-product-data/). Abbreviations: Ang, angiopoietin; Blys, B lymphocyte stimulator; CGRP, calcitonin gene-related peptide; FGF, fibroblast growth factor; GP, glycoprotein; IGF, insulin-like growth factor; IL, interleukin; MASP-2, mannan-binding lectin-associated serine protease-2; TNF, tumor necrosis factor; RSV, respiratory syncytial virus; VEGF, vascular endothelial growth factor.

a global pandemic that remains in effect 2 y later. When [accessed in early November 2021, the Johns Hopkins University of Medicine Coronavirus Research Center ([coronavirus.jhu.edu/map.html](http://coronavirus.jhu.edu/map.html)) indicated that nearly 250 million people located world-wide have been infected and over 5 million of these have died. Cases of infection in the US exceed 45 million, and approximately 725,000 of the infected people have died. The virus has mutated multiple times, resulting in the so-called variants of concern, some of which are more transmissible than the original virus. Such variants of concern include (1) alpha (B.1.1.7 (501Y.V1)), which contains an N501Y mutation in the spike protein; (2) beta (B.1.351 (501Y.V2)), which has nine mutations (L18F, D80A, D215G, Δ242-244, K417N, E484K, N501Y, D614G, and A701V); (3) gamma (P.1 (501Y.V3)), which shares mutations with the Beta variant; and (4) delta (B.1.617.2), which contains a substantial number of mutations and is more than twice as transmissible as the original strain.<sup>3,4</sup>

In response to the pandemic, many organizations mobilized, and in some cases combined, their resources to discover and develop antibody therapeutics for the prevention and treatment of COVID-19. As of early November 2021, seven antibody products that targeted the virus, developed as either monotherapy or a combination of anti-SARS-CoV-2 mAbs, had been granted approvals or emergency use authorizations (EUAs) or such authorizations had been requested (Table 1). Due to the substantial and immediate medical need, the first products granted EUAs, bamlanivimab and REGN-COV2, were developed as intravenous (IV) treatments for high-risk outpatients with SARS-CoV-2 infection. However, other formulations and products using subcutaneous (SC) or intramuscular (IM) administration for prevention or treatment of COVID-19 are now, or may soon be, available.

Our discussion of antibody-based COVID-19 interventions focuses on those reviewed in the US or European Union (EU) in 2021 and those the sponsoring company has indicated might

soon enter regulatory review in these regions. While we are tracking the global development of investigational antibody therapeutics, limited information is available for markets outside the US or EU, e.g., China, where a product's status regarding emergency use is difficult to ascertain. In the US, multiple products have EUAs, but these authorizations will terminate when the pandemic is over, as declared by the Secretary of the Department of Health and Human Services.<sup>5</sup> It seems likely that full approvals will be sought in the US for products that are granted EUAs, provided that data supports their further use. In the EU, the European Medicines Agency (EMA) may review COVID-19 medicines in a rolling review process to speed up the assessment. Their opinions of the data are intended to support national decision-making on the possible use of medicines for COVID-19 before a formal EU-wide authorization is issued.<sup>6,7</sup> As in the US, full approvals will also be sought in the EU for medicines that receive positive opinions.

### Antibodies for COVID-19 granted EUAs or approvals, or undergoing review in the US or EU in 2021

The biopharmaceutical industry made substantial advances in the development of anti-SARS-CoV-2 antibody therapeutics in 2021, expanding the number of antibodies available, as well as the patient populations and routes of administration (Table 1). Numerous countries have granted authorizations for the emergency use of anti-SARS-CoV-2 antibodies, but full approvals have also been requested or already granted in the cases of regdanvimab in the Republic of Korea and sotrovimab and REGN-COV2 in Australia. Details are provided below for antibody therapeutics for COVID-19 that are being considered for emergency use or approval, and those for which such a request might be made, i.e., adintrevimab (ADG20) and lenzilumab.

**Table 1.** Monoclonal antibodies in late-stage clinical studies or marketed for COVID-19.

INN, code or brand name	Molecular format	Status for COVID-19	COVID-19 indication(s)
Etesevimab + bamlanivimab	SARS-CoV-2; Human mAbs	EUA granted	Treatment and prevention of COVID-19
Sotrovimab (Xevudy®)	SARS-CoV-2; Human IgG1	Approved in Australia; EUA granted; EMA rolling review <sup>b</sup>	Mild-to-moderate COVID-19
Regdanvimab (Regkirona)	SARS-CoV-2; Human IgG1	Approved in ROK and EU	Mild-to-moderate COVID-19 in adults
Casirivimab + imdevimab (REGEN-COV2, Ronapreve™)	SARS-CoV-2; Human mAbs	Approved in Australia and EU; EUA granted and BLA in review in US	Treatment and prevention of COVID-19
Tocilizumab <sup>a</sup> (Actemra)	IL-6 R; Humanized IgG1	EUA granted; MAA in review	Hospitalized patients receiving systemic corticosteroids who require supplemental oxygen, mechanical ventilation, or ECMO
Tixagevimab + cilgavimab (AZD7442, Evusheld)	SARS-CoV-2; Human IgG1	EUA, CMA requested	Pre-exposure prophylaxis (NCT04625725); Post-exposure prophylaxis (NCT04625972)
Amubarvimab + romlusevimab (BRIL-196 + BRIL-198)	SARS-CoV-2; Human mAbs	EUA requested	Symptomatic non-hospitalized adults with COVID-19 (NCT04518410); Hospitalized patients with COVID-19 (NCT04501978)
Adintrevimab (ADG20)	SARS-CoV-2; Human mAb	Phase 2/3	Prevention of COVID-19 (NCT04859517); Mild-to-moderate COVID-19 (NCT04805671)
TY027	SARS-CoV-2; Human mAb	Phase 3	Early COVID-19 (NCT04649515)
MAD0004J08	SARS-CoV-2; Human mAb	Phase 2/3	Asymptomatic to moderately severe COVID-19 (NCT04952805)
MW33	SARS-CoV-2; Human mAb IgG1	Phase 2/3	Mild-to-moderate COVID-19 (NCT04627584)
C144-LS and C-135-LS	SARS-CoV-2; mAb	Phase 2/3	Confirmed COVID-19 outpatients (NCT04518410)
Upanovimab (SCTA01)	SARS-CoV-2; Humanized mAb	Phase 2/3	Hospitalized patients with severe COVID-19 (NCT04644185)
Lenzilumab	GM-CSF; Human IgG1	Phase 3	COVID-19 pneumonia (NCT04351152)
Leronlimab	CCRS5; Humanized IgG4	Phase 3	COVID-19 pneumonia (NCT04901676, NCT04901689 (not yet recruiting))
Vilobelimab	C5; Chimeric IgG4	Phase 2/3	Severe COVID-19 pneumonia (NCT04333420)
Meplazumab	CD147; Humanized IgG2	Phase 2/3	Hospitalized adults with COVID-19 (NCT04586153)
Plonmarlimab	GM-CSF; Humanized IgG1	Phase 2/3	Severe COVID-19 (NCT04341116)
Mavrilimumab	GM-CSFR; Human IgG4	Phase 2/3	COVID-19 pneumonia and hyper-inflammation (NCT04447469)
EB05	Toll-like receptor 4; Humanized IgG1	Phase 2/3	Hospitalized patients with COVID-19 (NCT04401475)

Data collected during August 1 to November 15, 2021. <sup>a</sup>Previously approved for another indication. <sup>b</sup>Medicine can be used in the EU to treat COVID-19, after EMA's CHMP completed its review under Article 5(3) of Regulation (EC) No 726/2004. Abbreviations: BLA, biologics license application; ECMO, extracorporeal membrane oxygenation; CMA, conditional marketing authorisation; EU, European Union; EUA, emergency use authorization in the US; MAA, marketing authorization application; ROK, Republic of Korea.

### **Bamlanivimab + etesevimab (Eli Lilly and Company)**

On February 9, 2021, the US Food and Drug Administration (FDA) issued an EUA for anti-SARS-CoV-2 antibodies bamlanivimab and etesevimab administered together for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients who test positive for SARS-CoV-2 and who are at high risk for progressing to severe COVID-19.<sup>8</sup> On September 16, 2021, the FDA revised the EUA for the bamlanivimab and etesevimab combination to include emergency use as post-exposure prophylaxis for COVID-19 in adults and pediatric patients (12 y of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.<sup>9</sup> An EUA that FDA issued in November 2020 for bamlanivimab administered as monotherapy was revoked in April 2021 due to the increase of SARS-CoV-2 viral variants resistant to bamlanivimab alone.<sup>10</sup>

An assessment report issued in March 2021 by EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that bamlanivimab monotherapy and combination therapy of bamlanivimab/etesevimab might

provide a therapeutic option for the treatment of confirmed COVID-19 in patients aged 12 y and older that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19 in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions of use.<sup>11</sup> This assessment enables national decision-making on the possible use of these medicines before a formal authorization is issued. An application for use of the bamlanivimab and etesevimab combination was withdrawn in October 2021 because the company was not able to generate data required for the review at that time.<sup>12</sup>

Etesevimab (LY-CoV016, LY3832479) is a recombinant human IgG1 $\kappa$  antibody with low effector function due to the introduction of point mutations (L234A, L235A) in the Fc. Initially co-developed by Junshi Biosciences and the Institute of Microbiology of the Chinese Academy of Sciences, the antibody was licensed to Lilly for development outside of Greater China. Bamlanivimab (LY-CoV555, LY3819253), a human IgG1 $\kappa$  antibody, was discovered by Abcellera and is now developed with Eli Lilly and Company.



The first EUA, granted in February 2021, was based on a randomized, double-blind, placebo-controlled clinical trial (BLAZE-1, NCT04427501) in 1,035 non-hospitalized adults with mild-to-moderate COVID-19 symptoms who were at high risk for progressing to severe COVID-19. Of these patients, 518 received a single infusion of bamlanivimab (2800 mg) and etesevimab (2800 mg) together, and 517 received placebo. The primary endpoint was COVID-19 related hospitalizations or death by any cause during 29 d of follow-up. Hospitalization or death occurred in 11 (2.1%) patients treated with the combination of mAbs vs. 36 (7%) patients who received placebo. By D 29, none of the patients who received bamlanivimab plus etesevimab had died, and 10 of the 517 patients who received placebo had died.<sup>13</sup>

The expanded EUA granted in September 2021 was based on data from Part 1 of the randomized, double-blind, placebo-controlled Phase 3 BLAZE-2 study (NCT04497987), which evaluated the risk of contracting symptomatic COVID-19 among residents and staff of long-term care facilities.<sup>9</sup> In this trial, 965 participants negative for the SARS-CoV-2 virus at baseline were randomized to receive IV administration of either 4,200 mg of bamlanivimab or placebo. After all participants reached 8 weeks of follow-up, results showed a significantly lower frequency of symptomatic COVID-19 in the bamlanivimab treatment arm versus placebo (odds ratio 0.43,  $P = 0.00021$ ). Moreover, the risk of contracting COVID-19 was 80% lower in a prespecified subgroup of nursing home residents.<sup>14</sup> While the BLAZE-2 study only evaluated dosing with bamlanivimab alone, FDA concluded that it is reasonable to expect that bamlanivimab and etesevimab together may be safe and effective for post-exposure prophylaxis because bamlanivimab and etesevimab administered together will provide an advantage over bamlanivimab alone against certain SARS-CoV-2 viral variants.

Only the combination of bamlanivimab and etesevimab, which target overlapping regions of the SARS-CoV-2 spike protein, is authorized for emergency use in patients infected with SARS-CoV-2; the individual antibodies are currently not authorized or approved for any use. The authorized treatment dosage is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as a single IV infusion as soon as possible after a positive viral test for SARS-CoV-2 and within 10 d of symptom onset. With revision of the EUA, the authorized post-exposure prophylaxis dosage is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as a single IV infusion as soon as possible after exposure to an individual infected with SARS-CoV-2, and the exposure meets close contact criteria per the Centers for Disease Control and Prevention. FDA has defined some limits to the emergency use of bamlanivimab and etesevimab. For example, use of the combination is not authorized in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.<sup>15</sup>

## Sotrovimab (Xevudy®, VIR biotechnology, GlaxoSmithKline)

On March 27, 2021, the FDA issued an EUA for sotrovimab (VIR-7831; GSK4182136) for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death.<sup>16</sup> Sotrovimab is a human anti-SARS-CoV-2 IgG1 $\kappa$  antibody derived from the B cell of a COVID-19 survivor. An application for the use of sotrovimab for COVID-19 is under rolling review in the EU. EMA's CHMP issued a positive scientific opinion on emergency use of sotrovimab for COVID-19 in May 2021. Sotrovimab has also been authorized for emergency use in other areas, including Japan. VIR and GSK plan to submit a Biologics License Application (BLA) to the FDA in the first half of 2022.

On August 20, 2021, the Australian Therapeutic Goods Administration (TGA) granted Xevudy a provisional approval for the treatment of adults and adolescents (aged 12 y and over and weighing at least 40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progression to hospitalization or death. The TGA's decision was made based on short-term efficacy and safety data, and continued approval depends on the evidence of longer evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.<sup>17</sup>

The application to the TGA included data from the randomized, double-blind, placebo-controlled Phase 1/2/3 COMET-ICE trial (NCT04545060), which evaluated the effects of sotrovimab in non-hospitalized adults with mild-to-moderate COVID-19 symptoms and a positive SARS-CoV-2 test result. Patients received a single IV dose of 500 mg sotrovimab ( $n = 528$ ) or placebo ( $n = 529$ ). The study's primary endpoint was progression of COVID-19 (defined as hospitalization for greater than 24 h for acute management of any illness or death from any cause) through D 29. The D 29 analysis data cutoff was April 27, 2021. Analysis of the available data indicated that treatment with sotrovimab resulted in a statistically significant reduction in the risk of severe and/or critical respiratory COVID-19 through D 29 when compared with placebo (adjusted relative risk reduction: 74% (95% CI: 41–88%);  $P = 0.002$ ). There were no deaths in the sotrovimab arm and 2 deaths in the placebo arm of the study as of the data cutoff date.<sup>17</sup> An interim analysis of the COMET-ICE trial that included an intention-to-treat population of 583 patients (291 in the sotrovimab group and 292 in the placebo group) was published in October 2021.<sup>18</sup> Disease progression leading to hospitalization or death occurred in 3 patients (1%) in the sotrovimab group vs. 21 patients (7%) in the placebo group (relative risk reduction, 85%; 97.24% confidence interval (CI), 44 to 96;  $P = 0.002$ ).

Sotrovimab is administered as a 500-mg single IV dose given over 30 min by health care providers. The product has, however, also been formulated for IM administration. In the randomized, open-label COMET-TAIL Phase 3 trial, which achieved its primary endpoint, IM administration of sotrovimab was non-inferior to IV administration for the early treatment of mild-to-moderate COVID-19 in high-risk, non-hospitalized adults and adolescents (12 y of age and older).

### **Regdanvimab (Regkirona; Celltrion Group)**

On September 18, 2021, Celltrion announced that the Korean Ministry of Food and Drug Safety (MFDS) had approved regdanvimab (CT-P59, Regkirona) for the treatment of mild-to-moderate COVID-19. The MFDS had authorized it for emergency use only in February 2021. Regdanvimab, a human IgG1 $\lambda$  antibody that targets the SARS-CoV-2 viral spike protein,<sup>19</sup> is available for emergency use in Brazil and Indonesia. Celltrion has submitted or plans to submit requests for provisional authorization in other countries, including Australia, Canada, and the US.

In March 2021, EMA's CHMP issued a positive scientific opinion for regdanvimab, which can be used to support national advice on regdanvimab's possible use before a marketing authorization is issued in the EU. On October 5, 2021, Celltrion announced that they submitted a marketing authorization application (MAA) to EMA seeking approval of regdanvimab for the treatment of confirmed COVID-19 in adults ( $\geq 18$ ) who do not require supplemental oxygen therapy and who are at increased risk of progressing to severe COVID-19.<sup>20</sup> On November 12, 2021, the European Commission (EC) approved Regkirona for the treatment of adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

The approvals are based in part on results from Part 1 of a 3-arm, randomized, placebo-controlled Phase 2/3 study (NCT04602000; EudraCT: 2020-003369-20) that evaluated 2 different doses of regdanvimab in outpatients with mild-to-moderate COVID-19. Patients received a single dose of either 40 mg CT-P59 ( $n = 101$ ) or 80 mg CT-P59 ( $n = 103$ ) administered via IV infusion over  $90 \pm 15$  min, or placebo ( $n = 103$ ). Compared to placebo treatment, fewer patients treated with regdanvimab were hospitalized or received oxygen therapy up to D 28 due to SARS-CoV-2 infection (4/101 (4.0%), 5/103 (4.9%) and 9/103 (8.7%) patients in the 40 mg/kg CT-P59, 80 mg/kg CT-P59 and placebo groups, respectively). There were no deaths. Data from Part 1 did not establish an effect on the duration of symptoms, and the median (95% CI) time to negative conversion by RT-qPCR was similar in the regdanvimab groups compared to the placebo group. As no dose-response relationship was observed, the 40 mg/kg dose of regdanvimab was selected for evaluation in Part 2 of this ongoing study.<sup>21</sup>

As approved in the Republic of Korea, the recommended dosage of regdanvimab is 40 mg/kg administered as a single IV infusion over 60 min. An inhaled formulation of regdanvimab developed by Inhalon Biopharma, Inc. is being evaluated in a Phase 1 clinical study.

### **Casirivimab + imdevimab (Regeneron, Roche Registration GmbH)**

In August 2021, Regeneron submitted a BLA for casirivimab + imdevimab (REGEN-COV2, Ronapreve™) that included data on the efficacy and safety of REGEN-COV to treat and prevent SARS-CoV-2 infection in non-hospitalized people, which was accepted for priority review status by FDA. The company expects to complete a second BLA submission that focuses on hospitalized COVID-19 patients by the end of 2021. REGEN-

COV was first authorized by FDA for emergency use as a treatment for high-risk outpatients with COVID-19 in November 2020, and its use was extended to include certain post-exposure prophylaxis settings in July 2021.<sup>22</sup> The authorized dose for both treatment of mild-to-moderate COVID-19 and post-exposure prophylaxis is 600 mg casirivimab and 600 mg imdevimab administered IV or SC.

FDA is also reviewing a request to extend authorization for REGEN-COV2 as a treatment for COVID-19 in hospital settings. This request is based on results from a randomized, double-blind, placebo-controlled Phase 2/3 trial that evaluated REGEN-COV in hospitalized adult patients with COVID-19. Patients ( $n = 1,197$ ) were randomized 1:1:1 to receive a one-time infusion of 2,400 mg or 8,000 mg REGEN-COV, or placebo. The study's primary endpoint was met, showing REGEN-COV significantly reduced viral load within 7 d of treatment. Patients administered REGEN-COV experienced a 36% reduced risk of dying within 29 d of receiving treatment, and the risk was reduced by 56% for patients who were seronegative at baseline. Similar efficacy was observed with both doses evaluated in the study.<sup>23</sup>

In August 2020, Regeneron announced details of a collaborative agreement in which Roche will be primarily responsible for certain aspects of clinical development and commercialization of Ronapreve, including securing regulatory approvals outside the US, following the initial EMA approval. In February 2021, EMA's CHMP issued a positive opinion regarding the use of casirivimab and imdevimab for the treatment of confirmed COVID-19 in patients that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19. EU member states can use the positive opinion when making national decisions about use of the antibody cocktail, prior to a potential future EMA market authorization. On October 11, 2021, EMA announced that they started evaluating an MAA for Ronapreve submitted by Roche Registration GmbH.<sup>24</sup> On November 12, 2021, the EC approved Ronapreve for treatment of COVID-19 in adults and adolescents aged 12 y and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, and for prevention of COVID-19 in adults and adolescents aged 12 y and older weighing at least 40 kg.

In December 2020, Chugai obtained development and exclusive commercialization rights in Japan from Roche. Chugai obtained Ronapreve's Special Approval for Emergency use in Japan for the treatment of SARS-CoV-2 infection in July 2021. In November 2021, Chugai announced that authorization had also been granted for IV or SC administration of Ronapreve to treat unvaccinated or inadequately vaccinated individuals who have been in close contact with COVID-19 patients or have tested positive for asymptomatic COVID-19 and are at high risk for progression to severe COVID-19. In addition, SC administration was authorized for the treatment of SARS-CoV-2 infection when IV administration is not feasible due to unavoidable circumstances.

In October 2021, Australia's TGA provisionally approved the use of Ronapreve for the treatment and prevention of COVID-19 in specific target populations: (1) treating adults and adolescents aged 12 y and older and weighing at least 40 kg

who do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe COVID-19 and (2) prevention of COVID-19 in patients of the same age and weight as for treatment who have been exposed to SARS-CoV-2 and who either have a medical condition making them unlikely to respond to or be protected by vaccination, who have not been vaccinated against COVID-19. The approval was granted to Roche Products Pty Limited.<sup>25</sup>

### **Tocilizumab (Actemra®, RoActemra; Genentech Inc.)**

On June 24, 2021, the FDA issued an EUA for Actemra® (tocilizumab) administered IV for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 y of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.<sup>26</sup> The EUA was issued to Genentech Inc. EMA is evaluating an MAA for RoActemra (tocilizumab) to extend its use to include treatment of hospitalized adult patients with severe COVID-19 who are already receiving treatment with corticosteroids and require extra oxygen or mechanical ventilation.

Actemra is a recombinant humanized IgG1κ mAb that inhibits inflammation by selectively binding to both soluble and membrane-bound human IL-6 receptors and subsequently inhibiting IL-6-mediated signaling through these receptors. The data supporting Actemra's EUA are derived from four clinical trials, the randomized, controlled, Phase 3 platform RECOVERY trial (NCT04381936) and three randomized, double-blind, placebo-controlled trials (EMPACTA (NCT04372186), COVACTA, and REMDACTA). The RECOVERY and EMPACTA trials contributed the most important scientific evidence on the potential benefit of Actemra in the enrolled patients.

In the RECOVERY trial, 4,116 hospitalized patients with severe COVID-19 pneumonia were randomized to receive either Actemra with standard care (2,022 patients) or standard care alone (2,094 patients). The primary endpoint of the study, death through 28 d of follow-up, was met. The probabilities of death by d 28 were estimated to be 30.7% for patients receiving Actemra and 34.9% for patients receiving standard care alone. The median times to hospital discharge were 19 d and >28 d for patients receiving Actemra and patients receiving standard care alone, respectively.<sup>27</sup>

In the EMPACTA trial, 389 hospitalized, non-ventilated patients with COVID-19 pneumonia were randomized to receive Actemra (249 patients) or placebo (128 patients). Patients received one infusion of either 8 mg/kg Actemra, with a maximum dose of 800 mg, or placebo. If clinical signs or symptoms worsened or did not improve, one additional infusion of blinded treatment of Actemra or placebo could be given 8–24 h after the initial infusion. The primary endpoint, the need for mechanical ventilation or death through 28 d of follow-up was met. Of patients receiving Actemra, the proportion who progressed to mechanical ventilation or death (12.0%) was significantly reduced compared to those who received placebo (19.3%).<sup>27</sup>

Tocilizumab was jointly developed by Osaka University and Chugai in the 1990s and licensed by Hoffmann-La Roche in 2003. Tocilizumab was granted its first marketing approval in 2005 in Japan for Castleman's disease and was subsequently approved in the EU and the US for a variety of inflammatory disorders. According to the current label, Actemra is FDA approved for rheumatoid arthritis, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome.

### **Antibodies to Watch: COVID-19 interventions**

While numerous companies are sponsoring late-stage studies of antibodies for COVID-19 (Table 1), few companies have explicitly stated that they have submitted or are planning to submit an EUA request. Such public disclosures have been made by AstraZeneca for tixagevimab + cilgavimab (AZD7442), Bria Biosciences for amubarvimab and romlusevimab, Adagio Therapeutics for adintrevimab (ADG20), and Humanigen for lenzilumab.

### **Tixagevimab + cilgavimab (AstraZeneca)**

AZD7442, comprising the combination of two human anti-SARS-CoV-2 IgG1κ antibodies (tixagevimab + cilgavimab, Evusheld), was derived from B cells from convalescent patients after infection with SARS-CoV-2. Discovered by Vanderbilt University Medical Center, the antibodies bind to distinct sites on the SARS-CoV-2 spike protein. These antibodies were licensed to AstraZeneca in June 2020, and then engineered with mutations that extend half-life (YTE) and reduce Fc receptor and complement C1q binding (L234F, L235E, P331S). In October 2021, AstraZeneca submitted an EUA request for AZD7442 to FDA based on prophylaxis use data derived from the PROVENT and STORM CHASER trials, and they expect a US regulatory decision, as well as a conditional marketing authorization regulatory decision in the EU, by the end of 2021.<sup>28</sup>

The randomized, placebo-controlled Phase 3 PROVENT trial (NCT04625725) is assessing the safety and efficacy of a single 300 mg dose of AZD7442 compared to placebo for the prevention of COVID-19. A total of 5,197 participants who did not have SARS-CoV-2 infection at baseline (i.e., pre-exposure setting) were randomized in a 2:1 ratio to receive AZD7442 ( $n = 3,460$ ) or saline placebo ( $n = 1,737$ ), with each administered in two separate, sequential IM injections. The primary outcome measure was the first case of any SARS-CoV-2 RT-PCR positive symptomatic illness occurring post dose prior to d 183. Subjects will continue to be followed for 15 months. At the primary analysis, the study data showed AZD7442 reduced the risk of developing symptomatic COVID-19 by 77% (95% CI: 46–90), compared to placebo.<sup>29</sup>

The placebo-controlled Phase 3 STORM CHASER study (NCT04625972) evaluated AZD7442 for post-exposure prophylaxis of COVID-19 in adults. Patients in this study also received a single 300 mg dose of AZD7442 or placebo;



however, the trial's primary endpoint, post-exposure prevention of symptomatic COVID-19 with AZD7442 compared to placebo, was not met.

AZD7442 is being evaluated as a treatment for COVID-19 outpatients in the Phase 3 TACKLE study (NCT04723394). Patients receive a single dose (as separate IM injections) of 600 mg AZD7442 or saline placebo on D 1. The efficacy primary outcome measure is a composite of either severe COVID-19 or death from any cause through D 29 in outpatients who had been symptomatic for 7 d or less. The trial met the primary endpoint, with the risk of developing severe COVID-19 or death (from any cause) reduced by 50% in the AZD7442 study arm compared to the placebo arm. Among participants who received treatment within 5 d of symptom onset, the risk of developing severe COVID-19 or death (from any cause) was reduced by 67% in the AZD7442 study arm compared to the placebo arm.<sup>30</sup>

### **Amubarvimab + romlusevimab (Brii Biosciences)**

Amubarvimab and romlusevimab (BRII-196 and BRII-198) are human IgG1 antibodies that target distinct epitopes of the SARS-CoV-2 spike protein. Developed by Brii Biosciences, the antibodies were engineered for half-life extension (YTE mutations) for longer duration of protection and have been shown to retain activity against viral variants of concern.<sup>31</sup> On October 8, 2021, Brii Biosciences announced that they submitted an EUA application to the FDA for the amubarvimab and romlusevimab combination as a treatment for COVID-19 based on interim results from the Phase 2/3 ACTIV-2 trial. Data to support the EUA request will be submitted to the FDA on a rolling basis.<sup>32</sup>

Sponsored by the National Institutes of Health (NIH), the ACTIV-2 study (NCT04518410) is a master protocol designed to evaluate the safety and efficacy of multiple investigational agents in COVID-19-positive adult outpatients. Patients ( $n = 837$ ) were administered one dose comprising 1000 mg (BRII-196) and 1000 mg (BRII-198) combination therapy by consecutive IV infusions or placebo. In an interim analysis, the combination of the two antibodies demonstrated a statistically significant reduction of 78% in the combined endpoint of hospitalization and death compared with placebo (relative risk [95% CI]: 0.22 [0.05–0.86],  $P < 0.00001$  (nominal, one-sided)). Results were similar for those treated within 5 d compared to those treated within 6–10 d; in both cases, 2% of antibody-treated patients progressed to hospitalization or death compared with 11% in the placebo group.<sup>32</sup>

The combination of BRII-196 and BRII-198 was also evaluated in NIH's ACTIV-3 study (NCT04501978), but did not meet the inclusion criteria for further enrollment in the trial, due to futility. The ACTIV-3 study evaluated investigational agents compared to placebo in adults hospitalized with COVID-19.<sup>33</sup>

### **Adintrevimab (Adagio Therapeutics, Inc.)**

Adintrevimab (ADG20) is a human anti-SARS-CoV-2 IgG1 $\lambda$  antibody derived from memory B cells of a 2003 SARS survivor. The antibody targets a highly conserved epitope in the receptor binding domain of the virus and can neutralize the

original SARS-CoV-2 strain, as well as all known variants of concern. Adintrevimab is formulated at high concentrations, enabling IM administration, and was engineered to have a long half-life (M428L/N434A mutations). Adagio Therapeutics is developing adintrevimab for both prevention and treatment of COVID-19. The company anticipates that data from ongoing clinical studies may support an EUA request in the second quarter of 2022.<sup>34</sup>

The safety and efficacy of adintrevimab are being evaluated in the single-dose, placebo-controlled Phase 2/3 clinical trials, STAMP (NCT04805671) and EVADE (NCT04859517). The STAMP trial is evaluating adintrevimab as a treatment for high-risk individuals with mild or moderate COVID-19, while the EVADE trial is evaluating adintrevimab as post-exposure prophylaxis and pre-exposure prophylaxis of COVID-19. Data from a Phase 1 study informed the 300 mg IM dose selection, and also confirmed the extended half-life of adintrevimab, which approached 100 d based on data for this dose given as a single injection.<sup>34</sup> The estimated enrollment for the STAMP and EVADE studies are 1,084 and 6,412 participants, respectively, and the estimated primary completion dates are in January 2022 and July 2022, respectively.

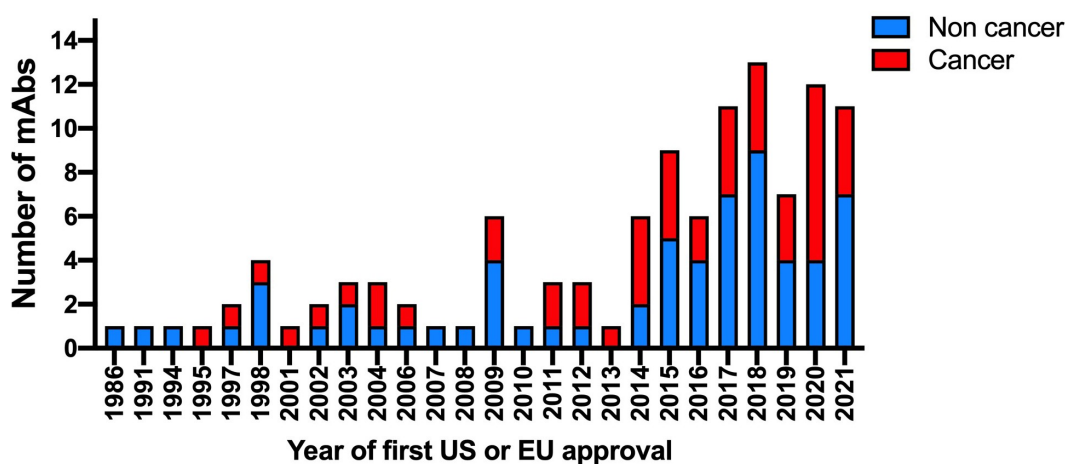
### **Lenzilumab (Humanigen, Inc.)**

Lenzilumab is a Humaneered® IgG1 $\kappa$  mAb that targets GM-CSF. Humaneering® is a proprietary technology developed by KaloBios, which can be used to convert antibodies with non-human sequences into human antibodies. KaloBios changed its company name to Humanigen in 2017. Humanigen is developing lenzilumab as a treatment for COVID-19-associated hyperinflammatory immune response, i.e., acytokine storm, which is characterized by GM-CSF-mediated activation and trafficking of myeloid cells. The company sponsored the randomized, placebo-controlled Phase 3 LIVE-AIR study (NCT04351152) of lenzilumab in hospitalized patients with severe and critical COVID-19 pneumonia. Additionally, lenzilumab is included in the Phase 2/3 NIH-sponsored ACTIV 5/BET B study (NCT04583969) of agents for COVID-19.

In May 2021, based on data available at the time, Humanigen requested an EUA in the US for lenzilumab to treat newly hospitalized COVID-19 patients. FDA declined this request, but invited the submission of additional data as it becomes available. Such data may be derived either from the LIVE-AIR or ACTIV 5/BET B studies. As of September 2021, Humanigen had completed the submission of a Conditional Marketing Authorization for lenzilumab in hospitalized COVID-19 patients to the Medicines and Healthcare products Regulatory Agency in the UK,<sup>35</sup> and indicated that data from the ACTIV-5/BET B study, as designed, may support EUA and BLA submissions.<sup>36</sup>

Initiated in May 2020 and completed in March 2021, the LIVE-AIR trial assessed the potential for lenzilumab to improve the likelihood of ventilator-free survival beyond standard supportive care in hospitalized subjects with severe COVID-19.<sup>37</sup> The study enrolled 520 adult patients who experienced blood oxygen saturation of less than or equal to 94%, or required low-flow supplemental oxygen, or high-flow oxygen support, or non-invasive positive pressure ventilation;





**Figure 4.** Antibody therapeutics first approved in the United States or European Union each year during 1997–2021. Figure based on data publicly available as of November 15, 2021. Products that were approved but subsequently withdrawn from the market are included in the totals. Antibodies granted emergency use authorizations (EUAs) or in review for EUAs are not included. Biosimilar and Fc fusion protein products were excluded. A searchable table of the figure data is available at [www.antibodysociety.org/antibody-therapeutics-product-data/](http://www.antibodysociety.org/antibody-therapeutics-product-data/)

and were hospitalized but did not require invasive mechanical ventilation. Patients were randomized to receive three infusions of either 600 mg lenzilumab or placebo, with each 1-h infusion separated by 8 h over a 24-h period. All patients received standard of care, including dexamethasone (or other steroids) and/or remdesivir. The study's primary endpoint, survival without ventilation measured through d 28 following treatment, was met (hazard ratio (HR): 1.54; 95% CI: 1.02–2.32,  $P = 0.0403$ ). The Kaplan–Meier estimates for invasive mechanical ventilation and/or death in the lenzilumab vs. placebo arms were 15.6% (95% CI: 11.5–20.9) vs. 22.1% (95% CI: 17.4–27.9), respectively.<sup>37</sup>

ACTIV-5/BET-B (NCT04583969) is a platform trial comprising a series of randomized, double-blind, placebo-controlled trials using common assessments and endpoints in hospitalized adults diagnosed with COVID-19, with the goal of determining which agents should be moved quickly into larger studies. Initiated by NIH in October 2020, the study is evaluating lenzilumab plus remdesivir vs. placebo plus remdesivir in adult hospitalized patients who need medical care for COVID-19 pneumonia. Patients are randomized (1:1) to receive a 200-mg IV remdesivir loading dose on D 1, followed by a 100-mg once-daily IV maintenance dose up to a 10-d total course while hospitalized and 600-mg IV lenzilumab or placebo infusion every 8 h starting on D 1 for a total of 3 doses. The primary outcome measure of the study is the time to ventilation or death in patients with a baseline score of 5 or 6 within D 1 through D 29. The estimated primary completion date is December 2021.

### Antibody therapeutics granted a first approval in the US or EU in 2021

As of November 15, a total of 11 antibody therapeutics had been granted first approvals in either the US or EU in 2021, which is within the range of 6–13 product approvals that have occurred each year since 2014 (Figure 4). Details for 9 of the 11 products, evinacumab, dostarlimab loncastuximab tesirine, amivantamab,

aducanumab, tralokinumab, anifrolumab, bimekizumab, and tisotumab vedotin, are summarized below; regdanvimab and the combination of casirivimab and imdevimab were discussed in the section on 'COVID-19 interventions.' Of the 11 products (Table 2), 7 were approved in the US; BLAs for two mAbs, tralokinumab and bimekizumab, have been submitted but seem unlikely to be approved for reasons explained in the summaries for the respective molecules below. The FDA granted accelerated approval to five of the seven products, dostarlimab (dostarlimab-gxly), loncastuximab tesirine (loncastuximab tesirine-lpyl), amivantamab (amivantamab-vmjw), aducanumab (aducanumab-awwa), and tisotumab vedotin (tisotumab vedotin-tftv). The accelerated approval pathway enables FDA to approve products based on the drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, but a required post-approval trial is needed to verify that the drug provides the expected clinical benefit.

In the EU, EMA's CHMP evaluates MAAs for recombinant biologics submitted under the centralized procedure and issues an opinion that is considered by the EC, which then may grant an approval. Of the 11 first US or EU approvals granted in 2021, 6 were approved in the EU as of November 12, 2021 (Table 2). It should be noted, however, that the EC granted approvals in 2021 for four antibody therapeutic products, moxetumomab pasudotox, [fam-]trastuzumab deruxtecan, tafasitamab, and satralizumab, that were first approved by FDA prior to 2021. In addition, sacituzumab govitecan, which was approved by FDA in 2020, received a positive opinion and is under consideration for approval by the EC. These molecules are not discussed here because our focus is on only the first approval for innovative antibody-based products. As they are not innovative, approvals of biosimilar products are also excluded from our discussion.

### Evinacumab (Evkeeza; Regeneron Pharmaceuticals, Inc.)

On February 11, 2021, the FDA approved Evkeeza (evinacumab-dgnb) injection as an add-on treatment for patients aged 12 y and older with homozygous familial hypercholesterolemia

**Table 2.** Antibody therapeutics granted first approvals in the European Union or the United States during 2021.

INN; Brand name	Target; Format	Indication first approved	Date of first EU approval	Date of first US approval
Evinacumab; Evkeeza	Angiotensin-like protein 3; Human IgG4	Hypercholesterolemia	6/17/2021	2/11/2021
Dostarlimab; Jemperli	PD-1; Humanized IgG4	Deficient mismatch repair endometrial cancer	4/21/2021	4/22/2021
Loncastuximab tesirine; Zynlonta	CD19; Humanized IgG1 ADC	Diffuse large B-cell lymphoma	In review	4/23/2021
Amivantamab; Rybrevant	EGFR, cMet; Human IgG1 bispecific	Non-small cell lung cancer	Positive opinion	5/21/2021
Aducanumab; Aduhelm	Amyloid beta; Human IgG1	Early Alzheimer's disease	In review	6/7/2021
Tralokinumab; Adtralza	IL-13; Human IgG4	Atopic dermatitis	6/17/2021	In review (2nd cycle)
Anifrolumab; Saphnelo	IFN $\alpha$ , $\beta$ , $\omega$ receptor 1; Human IgG1	Systemic lupus erythematosus	In review	7/30/2021
Bimekizumab; Bimzelx	IL-17A and IL-17 F; Humanized IgG1	Psoriasis	8/20/2021	In review
Tisotumab vedotin; TIVDAK	Tissue factor; Human IgG1 ADC	Cervical cancer	NA	9/20/2021
Regdanvimab; Regkirona	SARS-CoV-2; Human IgG1	SARS-CoV-2 infection	11/12/2021	NA
Casirivimab + imdevimab; Ronapreve, REGEN-COV2	SARS-CoV-2; Mixture of 2 human IgG1	SARS-CoV-2 infection	11/12/2021	In review

Table includes information publicly available as of November 1, 2021. Abbreviations: ADC, antibody-drug conjugate; EGFR, epidermal growth factor receptor; IFN, interferon; IgG, immunoglobulin; IL, interleukin; NA, not applicable; PD-1, programmed cell death protein 1.

(HoFH), a rare genetic condition that causes severely high cholesterol.<sup>38</sup> Evkeeza received FDA's Orphan Drug and Breakthrough Therapy designations for this indication, and the biological license application (BLA) received a priority review.

On June 17, 2021, Evkeeza was also authorized in the EU as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 y and older with HoFH, which occurs in ~1 in 300,000 people in the EU. Due to the rarity of the disease, comprehensive data on the efficacy and safety of the medicine under normal conditions of use could not be provided by the applicant, and Evkeeza was thus authorized under exceptional circumstances, which requires annual reassessment of the risk–benefit balance.

Developed by Regeneron, Evkeeza is a human IgG4 $\kappa$  antibody engineered with a mutation (S228P) in the hinge region that minimizes half-antibody formation. The antibody binds, and thereby inhibits, the activity of angiotensin-like protein 3, which regulates the metabolism of plasma lipids such as LDL-C. The recommended dose is 15 mg/kg administered by IV infusion over 60 min once monthly.

The product approvals were based in part on data from the ELIPSE clinical trial (NCT03399786). In this Phase 3 study, a total of 65 patients were randomized to receive either IV administration of evinacumab 15 mg/kg every 4 weeks ( $n = 43$ ) or placebo ( $n = 22$ ), plus other lipid-lowering therapies. The primary endpoint, percent change from baseline in the LDL-C level at Week 24, was met. At baseline, LDL-C was 260 mg/dL in the evinacumab group and 247 mg/dL in the placebo group. Relative to baseline, the LDL-C level at Week 24 was reduced by 47.1% in the patients administered evinacumab, but increased 1.9% in the placebo group.<sup>39</sup>

### **Dostarlimab (Jemperli; GlaxoSmithKline)**

On April 21, 2021, the EC issued a conditional marketing authorization valid throughout the EU for Jemperli (dostarlimab-gxly) monotherapy for the treatment of adult patients

with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen. The conditional marketing authorization was recommended by the EMA, because the Jemperli addresses an unmet medical need, and the benefit of immediate availability outweighed the risk from less comprehensive data than normally required.<sup>40</sup>

On April 22, 2021, the FDA granted an accelerated approval to Jemperli for treating patients with recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing chemotherapy and whose cancers are deficient in their ability to repair DNA inside the cell, as determined by an FDA-approved test. The FDA granted dostarlimab Breakthrough Therapy designation for this indication, and the BLA was given a priority review. To continue approval, the FDA requires a final report and datasets from a clinical trial evaluating overall response rate and duration of response to verify and describe the clinical benefit of dostarlimab in patients with dMMR, recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen in a sufficient number of patients or from a randomized Phase 3 clinical trial that verifies and describes the clinical benefit of dostarlimab in patients with recurrent or primary advanced endometrial cancer.<sup>41</sup>

On August 17, 2021, the FDA granted an additional accelerated approval for Jemperli for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. This approval was based on tumor response rate and durability of response.

Dostarlimab is a humanized IgG4 $\kappa$  antibody that binds PD-1 on T cells and blocks interactions with its ligands PD-L1 and PD-L2, thereby activating immune responses. To prevent formation of half-antibodies, each heavy chain of the antibody contains a mutation (S228P) to promote stabilization of disulfide bonds between the two heavy chains.<sup>42</sup> The

recommended dose is 500 mg every 3 weeks (Q3W) for Dose 1 through 4, with subsequent doses of 1,000 mg every 6 weeks beginning 3 weeks after Dose 4 (Dose 5 onwards). Doses are administered as an IV infusion over 30 min.

The product approvals were based in part on the Phase 1 GARNET clinical trial (NCT02715284), which was the first trial to test a 6-week anti-PD-1 dosing regimen in patients. This dose escalation and cohort expansion study included patients with recurrent or advanced solid tumors who had limited available treatment options. Cohort A1 from part 2B recruited patients with MSI-H endometrial cancer, who had progressed on or after at least one, but no more than two lines of anticancer therapy (of which, at least one must be a platinum-based therapy). In this cohort of 108 patients, the objective response rate was 43.5% as assessed based on RECIST v1.1. (47/108; 95% CI: 34.0–53.4, with 10.2% complete responses (CRs) (11/108), and 33.3% partial responses (36/108). In addition, 89.4% of responders had an ongoing response at the time of data cutoff.<sup>40</sup>

### ***Loncastuximab tesirine (Zynlonta; ADC Therapeutics SA)***

On April 23, 2021, the FDA granted accelerated approval to Zynlonta (loncastuximab tesirine-lpyl) for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. The drug received Orphan Drug designation from the FDA for this indication. The marketing application for Zynlonta was granted priority review, and the review used the Assessment Aid, a voluntary submission from the applicant to facilitate FDA's assessment. A marketing application for loncastuximab tesirine for the treatment of relapsed or refractory DLBCL was validated by EMA by October 2021.

Zynlonta is an antibody–drug conjugate (ADC) composed of an anti-CD19 humanized IgG1 $\kappa$  antibody conjugated via a linker to pyrrolbenzodiazepine-dimer toxin that induces the killing of CD19-expressing malignant B cells. The drug is administered as an IV infusion over 30 min on D 1 of each cycle (Q3W), with the recommended dosage 0.15 mg/kg Q3W for 2 cycles and 0.075 mg/kg Q3W for subsequent cycles.

FDA's approval was based on data from the open-label, single-arm Phase 2 LOTIS 2 study (NCT03589469), which evaluated the safety and efficacy of loncastuximab tesirine for the treatment of patients with relapsed or refractory DLBCL following  $\geq 2$  lines of prior systemic therapy. In this study, loncastuximab tesirine was administered as an IV infusion over 30 min on D 1 of each cycle (Q3W) at a dose of 0.15 mg/kg Q3W for 2 cycles and 0.075 mg/kg Q3W for subsequent cycles for up to 1 y or until disease progression, unacceptable toxicity, or other discontinuation criteria. A total of 145 patients received at least one dose of the drug. The study results indicated the drug had an acceptable safety profile and substantial single-agent anti-tumor activity.<sup>43</sup> As of the March 1, 2021, cutoff date, the overall response rate was 48.3%, the CR rate was 24.8%, and the median duration of response was 13.4 months for the responders, with durable responses in high-risk subgroups.<sup>44</sup> To continue approval, the

company must conduct a randomized, Phase 3 clinical trial to verify and describe the clinical benefit of loncastuximab tesirine-lpyl in patients with relapsed or refractory large B-cell lymphoma.<sup>45</sup>

### ***Amivantamab (Rybrevant; Janssen Research & Development, LLC)***

On May 21, 2021, the FDA granted accelerated approval to Rybrevant (amivantamab-vmjw) for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. The drug received Breakthrough Therapy designation for this indication, and the application received Priority Review. FDA's review was conducted under Project Orbis, which provides a framework for concurrent submission and review of oncology drugs among international partners. For the review of amivantamab, the FDA collaborated with the Brazilian Health Regulatory Agency and United Kingdom's Medicines and Healthcare products Regulatory Agency.<sup>46</sup> A marketing application submitted to EMA received a positive opinion in October 2021.

Amivantamab is a human bispecific antibody targeting EGFR and mesenchymal epithelial transition factor (MET) created using Genmab's DuoBody controlled Fab-arm exchange platform. The IgG1-based drug contains low fucose and has been shown in relevant in vivo models to function through multiple mechanisms of action, including antibody-dependent cell-mediated cytotoxicity (ADCC), receptor down-modulation, and trogocytosis.<sup>47</sup> The recommended dosage of Rybrevant is based on baseline body weight and administered as an IV infusion after dilution.

FDA's approval of Rybrevant was based in part on results from 81 patients with NSCLC and EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy, who participated in the Phase 1 CHRYSALIS study (NCT02609776). In the trial population in which all patients received the drug, the overall response rate was 40% and the median duration of response was 11.1 months, with 63% of patients having a duration of response of 6 months or more. As a condition of the approval, the sponsor must submit a final report to FDA that includes datasets for progression-free survival, overall response rate, duration of response, and overall survival from a randomized clinical trial to verify and confirm the clinical benefit of Rybrevant for its approved indication, which may be derived from an ongoing Phase 3 study.<sup>46</sup>

### ***Aducanumab (Aduhelm; Biogen Inc., Eisai, Co., Ltd.)***

On June 7, 2021, the FDA granted an accelerated approval to Aduhelm (aducanumab-avwa) for the treatment of Alzheimer's disease (AD) based on reduction in amyloid  $\beta$  (A $\beta$ ) plaques observed in patients treated with the drug. Aducanumab had been granted Fast Track designation for this indication, and the BLA received a Priority review. FDA's approval was controversial because most members of

their Peripheral and Central Nervous System Drugs Advisory Committee voted that study data did not support the drug's efficacy during an advisory meeting held in November 2020. The drug label was modified as of July 7, 2021, to indicate that treatment with Aduhelm should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, which was the population included in clinical trials. No data currently available shows that initiating treatment at earlier or later stages of the disease is effective. Aducanumab was accepted into EMA's PRiority MEDicines (PRIME) program, and EMA has accepted for review, following a standard timetable, an MAA for aducanumab for AD.

Aducanumab is a human IgG1 $\kappa$  antibody that targets aggregated forms of A $\beta$ , including soluble oligomers and insoluble fibrillar forms. After an initial series of seven doses that increase from 1 to 10 mg/kg, the recommended dosage of Aduhelm is 10 mg/kg. The drug is administered as an IV infusion over approximately 1 h every 4 weeks and at least 21 d apart.

The late-stage development program for Aduhelm consisted of two Phase 3 clinical trials with identical designs conducted in patients with mild-cognitive impairment due to AD and mild AD dementia with a positive amyloid PET scan. One study (NCT02484547, 221AD302, EMERGE), initiated in September 2015, showed positive results for the 10 mg/kg dose group, specifically a reduction in the baseline- and placebo-corrected primary efficacy endpoint, Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) scores during the 78-week treatment period. CDR-SB is a dementia-staging instrument used in making or excluding a diagnosis of dementia in people with mild cognitive deficits. However, the second trial (NCT02477800, 221AD301, ENGAGE), initiated in August 2015, did not meet the primary endpoint. FDA documents indicate that, based on the data presented to them, their review team found clear exposure–efficacy and dose–response relationships for aducanumab, a consistent pharmacodynamic effect (A $\beta$  plaque reduction) in clinical studies, and a clear relationship between A $\beta$  plaque reduction and clinical endpoint CDR-SB for aducanumab.<sup>48</sup> The reduction in amyloid plaque is considered a surrogate for a reduction in clinical decline. A post-approval trial must be conducted to verify that the drug provides the expected clinical benefit.<sup>49</sup>

### **Tralokinumab (Adtralza<sup>®</sup>, LEO Pharma Inc.)**

On June 17, 2021, the EC authorized the marketing of Adtralza<sup>®</sup> (tralokinumab) for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy. The EC decision is valid in all EU Member States, Iceland, Norway, and Liechtenstein. The EMA's CHMP had adopted a positive opinion, recommending this authorization, in April 2021.

Tralokinumab is a human IgG4 $\lambda$  antibody that interferes with IL-13-mediated signaling by blocking its interactions with both IL-13 receptor  $\alpha$ 1 and IL-13 receptor  $\alpha$ 2. The hinge region was not modified to limit half-antibody formation.<sup>50</sup> The dose recommended is 300 mg every 2 weeks, with a loading dose of

600 mg on D 1, and the dose of 300 mg every 4 weeks for patients who achieve clear or almost clear skin after 16 weeks of treatment.

The EC marketing authorization was supported by data from two Phase 3 monotherapy efficacy and safety studies (ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885)), as well as a Phase 3 combination therapy efficacy and safety study (ECZTRA 3 (NCT03363854)). These studies included over 1900 patients who received either an initial dose of 600 mg tralokinumab (four 150 mg injections) on D 1, followed by 300 mg every 2 weeks up to Week 16, or they received matching placebo. Patients who responded to tralokinumab were re-randomized at Week 16 and administered tralokinumab maintenance SC injection regimen every 4 weeks for 36 weeks. In the ECZTRA 3 study, patients received concomitant topical corticosteroids on active lesions as needed. Tralokinumab was administered by SC injection in the studies. Although the primary endpoints, the proportion of patients with eczema area and severity index-75 at Week 16 and the proportion of patients with an Investigator's Global Assessment score of 0 or 1 at Week 16 were met in the three pivotal studies, EMA noted that the majority of patients enrolled in the two monotherapy studies did not respond to treatment.<sup>51</sup>

LEO Pharma's BLA for tralokinumab for the treatment of adults with moderate-to-severe atopic dermatitis also included data from the ECZTRA 1, 2 and 3 studies. After the first cycle review period, FDA issued a Complete Response letter requesting additional data relating to a device component of tralokinumab. This FDA action was announced by the company on April 29, 2021.<sup>52</sup>

### **Anifrolumab (Saphnelo; AstraZeneca)**

On July 30, 2021, the FDA approved AstraZeneca's Saphnelo (anifrolumab-fnia) for the treatment of adult patients with moderate-to-severe systemic lupus erythematosus (SLE) who are receiving standard therapy.<sup>53</sup> The FDA granted anifrolumab Fast Track designation for SLE. Saphnelo is undergoing regulatory review for SLE in the EU and Japan.

Anifrolumab is an interferon (IFN) alpha receptor 1 (IFNAR1)-specific human IgG1 $\kappa$  antibody. It blocks the action of several type I IFNs (IFN- $\alpha$ , IFN- $\beta$  and IFN- $\omega$ ) implicated in the pathogenesis of SLE. The antibody's Fc-mediated effector functions are reduced due to the incorporation of three mutations in the Fc region (L234F, L235E, and P331S). The recommended dosage is 300 mg administered as an IV infusion over a 30-min period every 4 weeks.

FDA's approval was based in part on efficacy and safety data from three 52-week treatment period, randomized, double-blind, placebo-controlled studies (Phase 2 study NCT01438489; Phase 3 studies NCT02446912 and NCT02446899) of anifrolumab in SLE patients who also received standard of care. In the Phase 2 study, 305 patients were randomized (1:1:1) to receive anifrolumab-fnia, 300 or 1000 mg, or placebo. The Phase 3 NCT02446912 study included 457 patients who were randomized (1:2:2) to receive



anifrolumab-fnia 150 mg, 300 mg, or placebo, while the Phase 3 NCT02446899 study randomized 362 patients (1:1) who received anifrolumab-fnia 300 mg or placebo. In these trials, more patients treated with Saphnelo experienced a reduction in overall disease activity across organ systems, including skin and joints, and achieved sustained reduction in oral corticosteroid use compared to placebo.<sup>54</sup>

### **Bimekizumab (Bimzelx; UCB Pharma S.A.)**

On August 20, 2021, the EC authorized marketing of Bimzelx (bimekizumab) in the EU for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. Bimekizumab is a humanized IgG1κ antibody that selectively inhibits IL-17A and IL-17 F by binding regions common to these pro-inflammatory cytokines, which share ~50% sequence identity and are expressed as homodimers and IL-17A/F heterodimers. Bimekizumab is approved at a recommended dose of 320 mg, administered by two SC injections every 4 weeks to week 16 and every 8 weeks thereafter.<sup>55</sup>

Regulatory reviews of marketing applications for bimekizumab are underway in Australia, Canada, Switzerland, Japan, and the US. An action on the BLA submitted to FDA was expected in October 2021, but UCB was notified that the FDA requires on-site inspections of the European manufacturing facilities for bimekizumab before they can approve the application and they were unable to conduct these inspections due to COVID-19-related restrictions on travel. Action on the application has thus been deferred until the inspections can be completed.<sup>56</sup>

The decision to grant a marketing approval in the EU was supported by results from three Phase 3 studies that included an active comparator arm, ustekinumab (Stellara®; BE VIVID study; NCT03370133), adalimumab (Humira®; BE SURE study; NCT03412747), or secukinumab (Cosentyx®; BE RADIANT study; NCT03536884). All three pivotal studies met their coprimary endpoints at Week 16, demonstrating superiority of bimekizumab over the active comparator in certain defined measures (e.g., Psoriasis Area and Severity Index). Clinical responses achieved with bimekizumab at week 16 were maintained for up to 1 y.<sup>57–60</sup> Coprimary endpoints were also met in the Phase 3 BE READY study (NCT03410992), which investigated the efficacy and safety of bimekizumab in patients with moderate-to-severe plaque psoriasis compared to placebo.<sup>60</sup>

### **Tisotumab vedotin (Tivdak; Genmab A/S; Seagen, Inc)**

On September 20, 2021, the FDA granted accelerated approval to Tivdak<sup>TM</sup> (tisotumab vedotin-tftv) for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. The BLA for Tivdak for this indication was given a Priority review. Tivdak's approval was based on tumor response and the durability of the response; verification and description of clinical benefit in confirmatory trials may be necessary for continued approval for this indication.

Tivdak is an ADC comprising Genmab's human IgG1κ antibody targeting tissue factor conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable linker using

Seagen's ADC technology. The companies are co-developing the product. The recommended dose of Tivdak is 2 mg/kg (up to a maximum of 200 mg) given as an IV infusion over 30 min Q3W until disease progression or unacceptable toxicity.

FDA's approval was based on results of the pivotal single-arm Phase 2 innovaTV 204 study (NCT03438396), which included 101 patients with recurrent or metastatic cervical cancer who had received no more than two prior systemic regimens in the recurrent or metastatic setting, including at least one prior platinum-based chemotherapy regimen. Patients received tisotumab vedotin 2.0 mg/kg IV Q3W until progression or toxicity. The major efficacy outcome measures were confirmed objective response rate as assessed by an independent review committee using RECIST v1.1 criteria and duration of response. The objective response rate was 24% [95% CI: 15.9–33.3%], including 7 patients (7%) with a CR and 17 patients (17%) with a partial response, and the median duration of response was 8.3 months (95% CI: 4.2, not reached).<sup>61</sup>

### **Antibody therapeutics first approved or undergoing regulatory review outside the US or EU in 2021**

Although antibody therapeutics are typically granted a first approval in the US or EU, this is not always the case. In 2021, 7 antibody therapeutics were granted their first global approval in Japan, China, Australia, or the Republic of Korea (Table 3). Three of the products, sotrovimab, REGN-COV2, and regdanvimab, were previously discussed. Summaries for the four other products, pabinafusp alfa, disitamab vedotin, penpulimab and zimberelimab, are provide in the following sections. In addition, we also discuss eight antibody therapeutics with marketing applications undergoing review in China (cadonilimab, geptanolimab, serplulimab, envafohimab, sugemalimab, ripertamab, socazolimab) or Japan (ozoralizumab). All the antibody therapeutics approved in China in 2021 and those currently being reviewed by China's National Medical Products Administration (NMPA) are for cancer, suggesting the existence of substantial unmet medical need in this area. For completeness, we have included discussion of felzartamab because I-Mab has indicated that the submission of an NDA for felzartamab for third-line treatment of multiple myeloma (MM) is on track for the fourth quarter of 2021.

### **Pabinafusp alfa (IZCARGO; JCR Pharmaceuticals Co., Ltd.)**

Pabinafusp alfa (IZCARGO®; JR-141) is an immunoconjugate composed of human iduronate-2-sulfatase (IDS) fused to the C terminus of the heavy chain of an anti-human transferrin receptor (hTfR) IgG1κ antibody. After binding hTfR, the drug crosses the blood-brain barrier by transcytosis to deliver IDS to the brain. Pabinafusp alfa thus acts as targeted enzyme replacement therapy. JCR Pharmaceuticals Co., Ltd developed pabinafusp alfa as a treatment for mucopolysaccharidosis II (MPS-II, Hunter syndrome), which is caused by IDS deficiency.

JCR Pharmaceuticals announced in March 2021 that Japan's Ministry of Health, Labour and Welfare (MHLW) approved IZCARGO® for the treatment of MPS-II.<sup>62</sup> Pabinafusp alfa

received SAKIGAKE designation in Japan; it has also been granted Fast Track designation by FDA and Orphan Drug designation by the EMA. The approval in Japan was supported by the results from a single-arm Phase 2/3 study (NCT03568175) of 28 Japanese patients with mucopolysaccharidosis II who were administered 2.0 mg/kg of pabinafusp alfa once per week for 52 weeks. The primary outcome measure was the change from baseline in heparan sulfate levels, a biomarker for effectiveness against central nervous system (CNS) symptoms, in cerebrospinal fluid. Significant reductions in heparan sulfate concentrations were observed in all patients, and positive changes in neurocognitive developments were observed in 21 of the 28 patients.<sup>63</sup>

JCR Pharmaceuticals has filed a marketing application in Brazil and will sponsor a standard of care-controlled study Phase 3 study (NCT04573023) that will enroll an estimated 50 patients with MPS-II. Patients will receive 2.0 mg/kg/week pabinafusp alfa IV or idursulfase (ELAPRASE®) as the standard of care. The study's estimated primary completion date is August 2024.

#### **Disitamab vedotin (Aidixi; RemeGen Co., Ltd./Seagen, Inc.)**

Disitamab vedotin (Aidixi; vedicitumumab, RC48-ADC) is composed of a humanized anti-HER2 IgG1κ antibody linked to MMAE, a synthetic antineoplastic agent, via a protease cleavable linker. RemeGen Co., Ltd. developed this ADC, then entered into an exclusive worldwide licensing agreement with Seagen, Inc. to develop and commercialize it, as announced in August 2021.<sup>64</sup> Disitamab vedotin received FDA Breakthrough Therapy designation for use in second-line treatment of patients with HER2-expressing, locally advanced or metastatic urothelial cancer who have previously received platinum-containing chemotherapy.

RemeGen Co., Ltd. announced in June 2021 that the NMPA conditionally approved disitamab vedotin for the treatment of patients with locally advanced or metastatic gastric cancer (including gastroesophageal junction (GEJ) adenocarcinoma) who have received at least two types of systemic chemotherapy.<sup>65</sup> This approval is supported by data from a single-arm, pivotal Phase 2 clinical trial (NCT03556345) of disitamab vedotin in patients with HER2-positive locally advanced or metastatic gastric cancer. Patients ( $n = 127$ ) received 2.5 mg/kg of the drug via IV infusions every 2 weeks until investigator-assessed loss of clinical benefit, unacceptable toxicity, investigator or participant decision to withdraw from therapy, or death. For all patients, the investigator-assessed confirmed objective response rate was 18.1% (95% CI: 11.8–25.9%), the median progression-free survival (PFS) was 3.8 months (95% CI: 2.7–4.0, 89 events [70.1%]) and the median overall survival was 7.6 months (95% CI: 6.6–2, 52 events [40.9%]).<sup>66</sup>

RemeGen submitted, and the NMPA has accepted, a New Drug Application for disitamab vedotin for use in metastatic urothelial cancer. The company is also sponsoring Phase 2 or Phase 3 studies evaluating disitamab vedotin in patients with biliary tract cancer, gynecological malignancies, and breast cancer.

#### **Penpulimab (Akesobio/Chia Tai-Tianqing Pharmaceutical Group Co., Ltd)**

Penpulimab is a humanized IgG1κ mAb that targets a unique epitope of PD-1 and includes an Fc region modified to remove Fc receptor and complement-mediated effector functions. Penpulimab has a lower antigen-binding dissociation rate, resulting in a higher receptor occupancy compared to marketed anti-PD-1 antibody therapeutics.<sup>67</sup> These characteristics may allow penpulimab to be more effective and have an improved safety profile. Penpulimab is being developed and commercialized by Akesobio and Chia Tai-Tianqing Pharmaceutical Group Co., Ltd., a subsidiary of Sino Biopharmaceutical Limited.

Akeso announced in August 2021 that penpulimab received an approval in China for treatment of patients with relapsed or refractory classic Hodgkin's lymphoma after at least second-line systemic chemotherapy treatment.<sup>68</sup> This approval is supported by data from a single-arm, open-label pivotal clinical trial (NCT03722147) in which patients were administered 200 mg penpulimab IV every 2 weeks until progression or unacceptable toxicity. In 85 patients evaluable for efficacy the objective response rate was 89.4% (95% CI: 80.8–95.0%) after a median follow-up of 15.8 months; 40 patients (47%) achieved a CR.<sup>67</sup>

As of August 2021, NMPA is reviewing marketing applications for penpulimab in combination with chemotherapy for first-line treatment of locally advanced or metastatic squamous NSCLC and for third-line treatment of metastatic nasopharyngeal carcinoma. In addition, FDA is reviewing a BLA for third-line treatment of metastatic nasopharyngeal carcinoma (Table 4). Chia Tai-Tianqing Pharmaceutical Group Co., Ltd. is pursuing development of penpulimab for other types of cancer, including advanced gastric and GEJ adenocarcinoma and advanced hepatocellular carcinoma (HCC).

#### **Zimberelimab (Gloria Biosciences)**

Zimberelimab (GLS-010, AB122) is a human monoclonal IgG4λ antibody targeting PD-1 derived from Ligand's transgenic rat platform, OmniRat®. GloriaBio has a sublicense agreement with Ligand's licensee Wuxi Biologics Ireland Limited for zimberelimab's development and commercialization rights in China. Arcus Biosciences, Inc. holds worldwide rights to zimberelimab excluding China and Thailand, and has licensed rights to commercialize zimberelimab in Japan and certain other territories in Asia (excluding China) to Taiho Pharmaceutical Co., Ltd.

Gloria Biosciences submitted a marketing application for zimberelimab to China's NMPA for the treatment of recurrent or refractory classical Hodgkin's lymphoma and announced the drug's approval for this indication in August 2021. The approval was supported by the results of a single-arm Phase 2 clinical study (NCT03655483) that enrolled 85 patients with recurrent or refractory classical Hodgkin's lymphoma after two or more lines of therapy. Patients were administered 240 mg zimberelimab IV once every 2 weeks until progression, death, unacceptable toxicity, or consent withdrawal. Of the 85 patients enrolled, 77 (90.6%; 95% CI: 82.3–95.9) had an

**Table 3.** Antibody therapeutics first approved or undergoing regulatory review outside the US or EU in 2021.

INN, Brand name	Target; Format	Indication first approved or in review	Status
Pabinafusp alfa, IZCARGO®	Transferrin receptor; Immunoconjugate	Mucopolysaccharidosis II	Approved in Japan (Mar 2021)
Disitamab vedotin, Aidixi	HER2; Humanized IgG1 ADC	Gastric cancer, including gastroesophageal junction adenocarcinoma	Approved in China (Jun 2021)
Penpulimab	PD-1; Humanized IgG1	Hodgkin's lymphoma	Approved in China (Aug 2021)
Zimberelimab	PD-1; Human IgG4I	Hodgkin's lymphoma	Approved in China (Aug 2021)
Sotrovimab, Xevudy	SARS-CoV-2; Human IgG1	SARS-CoV-2 infection	Approved in Australia (Aug 2021)
Casirivimab + imdevimab (REGEN-COV2, Ronapreve™)	SARS-CoV-2; Human mAbs	SARS-CoV-2 infection	Approved in Australia (Oct 2021)
Regdanimab, Regkirona	SARS-CoV-2; Human IgG1	SARS-CoV-2 infection	Approved in Republic of Korea (Sep 2021)
Cadonilimab	PD-1, CTLA-4; Humanized IgG1 bispecific	Cervical cancer	Regulatory review in China
Geptanolimab	PD-1; Humanized IgG4k	Peripheral T-cell lymphoma	Regulatory review in China
Serplulimab	PD-1; Humanized IgG4k	MSI-high/dMMR solid tumors	Regulatory review in China
Envafohimab	PD-L1; Humanized VH-Fc	MSI-high/dMMR solid tumors	Regulatory review in China
Sugemalimab	PD-L1; Humanized IgG4I	Non-small cell lung cancer (Stage 3 and 4)	Regulatory review in China
Ripertamab	CD20; Chimeric IgG1	Non-Hodgkin's lymphoma	Regulatory review in China
Socazolimab	PD-L1; Human IgG1	Cervical cancer	Regulatory review in China
Ozoralizumab	TNF, albumin; Humanized bispecific nanobody	Rheumatoid arthritis	Regulatory review in Japan

Table includes information publicly available as of November 1, 2021. Abbreviations: CTLA-4, cytotoxic T lymphocyte antigen-4; dMMR, mismatch repair deficient; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability-high; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TNF, tumor necrosis factor.

objective response as assessed by an independent radiology review committee (IRRC). The CR, 12-month PFS and overall survival rates were 32.9% ( $n = 28$ ), 78% (95% CI: 67.5–85.6) and 99% (95% CI: 91.9–99.8), respectively.<sup>69</sup>

In collaboration with Gilead Sciences, Arcus Biosciences is conducting Phase 1 and Phase 2 trials to evaluate the safety and tolerability of zimberelimab in patients with various types of cancer. The company initiated the global registrational Phase 3 ARC-10 trial (NCT04736173) in February 2021 to evaluate zimberelimab monotherapy or in combination with Arcus' anti-TIGIT antibody (domvanalimab, AB154) in patients with PD-L1-positive locally advanced or metastatic NSCLC. Participants in the active comparator arm receive carboplatin, pemetrexed, and paclitaxel. The estimated enrollment is 625 patients, and the study's estimated primary completion date is December 2025.

The Phase 2 ARC-7 study (NCT04262856) is intended to provide data supportive of ARC-10. The ARC-7 study has three arms: Arm 1 (zimberelimab monotherapy): 360 mg by IV infusion Q3W; Arm 2 (domvanalimab + zimberelimab): domvanalimab 10 mg/kg by IV infusion every 2 weeks + zimberelimab 240 mg by IV infusion every 2 weeks; and Arm 3 (domvanalimab + zimberelimab + AB928): domvanalimab 10 mg/kg by IV infusion Q3W + zimberelimab 240 mg by IV infusion every 2 weeks + AB928 150 mg orally once daily.<sup>70</sup> The estimated enrollment is 150 patients, and the study's estimated primary completion date is March 2022.

### Cadonilimab (Akeso Inc.)

Cadonilimab (AK104) is a humanized tetravalent IgG1 $\kappa$  bispecific antibody targeting PD-1 and CTLA-4 developed by Akesobio for the treatment of relapsed or metastatic cervical cancer, as well as other malignancies such as gastric and GEJ

adenocarcinoma and NSCLC. Mutations in the Fc region (L234A, L235A, G237A) reduce the antibody's Fc effector functions. The FDA granted Fast Track and Orphan Drug designations to cadonilimab for the treatment of relapsed or metastatic cervical cancer after the failure of platinum-based chemotherapy treatment. Cadonilimab also received Breakthrough Therapy designation from China's NMPA for treatment of patients with recurrent or metastatic cervical cancer after standard therapies. In September 2021, Akeso, Inc. announced the NMPA accepted a new drug application (NDA) for cadonilimab for the treatment of relapsed or metastatic cervical cancer, which will be evaluated under priority review.<sup>71</sup>

The NDA includes data from the pivotal, single-arm, open-label Phase 2 study (NCT04380805) that evaluated the effects of cadonilimab administered to patients with recurrent or metastatic cervical cancer. All patients received AK104 as a single agent at a dose of 6 mg/kg on D 1 and 15 of each 28-d treatment cycle via IV infusion. The study's primary endpoint, the objective response rate assessed by IRRC, was met. As of the data cutoff date in July 2020, with 21 patients evaluable for efficacy, the objective response rate was 47.6% and the disease control rate was 66.7%.<sup>72</sup>

Akeso initiated a Phase 3 trial (NCT04982237) evaluating cadonilimab plus platinum-containing chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer. The trial will enroll an estimated 440 participants. The estimated primary completion date is April 1, 2025.

### Geptanolimab (Genor Biopharma Co., Inc.)

Geptanolimab (GB226, APL-501, CBT 501) is a humanized, hinge-stabilized anti-PD-1 IgG4 $\kappa$  mAb being developed in China by Genor Biopharma Co., Inc for the treatment of

**Table 4.** Investigational antibody therapeutics in regulatory review in the European Union or the United States.

International non-proprietary name	Target; Format	Indication under review	Status in EU	Status in US
Faricimab	VEGF-A, Ang-2; Human/humanized IgG1 /λ bispecific	Diabetic macular edema and neovascular age-related macular degeneration	In review	In review
Sutimlimab	C1s; Humanized IgG4	Cold agglutinin disease	NA	In review (2nd cycle)
Tebentafusp	gp100, CD3; Bispecific immunconjugate	Metastatic uveal melanoma	NA	In review
Relatlimab	LAG-3; Human IgG4	Melanoma	In review	In review
Sintilimab	PD-1; Human IgG4	Non-small cell lung cancer	NA	In review
Ublituximab	CD20; Chimeric IgG1	Chronic lymphocytic leukemia and small lymphocytic lymphoma; Multiple sclerosis	NA	In review
Tezepelumab	Thymic stromal lymphopoietin; Human IgG2	Severe asthma	In review	In review
Penpulimab	PD-1; Humanized IgG1	Metastatic nasopharyngeal carcinoma	NA	In review
Tislelizumab	PD-1; Humanized IgG4	Esophageal squamous cell carcinoma	NA	In review
Lecanemab	Amyloid beta protofibrils; Humanized IgG1	Early Alzheimer's disease	NA	Rolling BLA in review
Toripalimab	PD-1; Humanized IgG4	Nasopharyngeal carcinoma	NA	In review
Inolimomab	CD25; Murine IgG1	Acute graft-vs-host disease	NA	In review
Omburtamab	B7-H3; Murine IgG1	CNS/leptomeningeal metastasis from neuroblastoma	In review	NA
Spesolimab	IL-36 receptor; Humanized IgG1	Generalized pustular psoriasis	In review	NA
Teplizumab	CD3; Humanized IgG1	Type 1 diabetes	NA	In review (2nd cycle)
Retifanlimab	PD-1; Humanized IgG4	Carcinoma of the anal canal	In review	In review (2nd cycle)
Oportuzumab monatox	EpCAM; Humanized scFv immunotoxin	Bladder cancer	MAA withdrawn	In review (2nd cycle)
Narsoplimab	MASP-2; Human IgG4	Hematopoietic stem cell transplant-associated thrombotic microangiopathy	NA	In review (2nd cycle)
Donanemab	Amyloid β; Humanized IgG1	Early Alzheimer's disease	NA	In review

Table includes information publicly available as of November 1, 2021. Abbreviations: BLA, biologics license application; CNS, central nervous system; MAA, marketing authorization application; NA, Not applicable or available.

relapsed/refractory peripheral T cell lymphoma (PTCL) and other cancers. Outside of China, Apollomics, Inc. (previously CBT Pharmaceuticals, Inc.) is developing geptanolimab as APL-501 (previously CBT-501).

In August 2020, Genor announced that NMPA had granted priority review status to its NDA for geptanolimab for PTCL.<sup>73</sup> Efficacy and safety data from the single-arm Phase 2 Gxplore-002 study (NCT03502629) of geptanolimab administered to PTCL patients were recently published. Eligible patients with r/r PTCL received 3 mg/kg geptanolimab IV every 2 weeks until disease progression or intolerable toxicity. The primary endpoint was the objective response rate assessed by the IRRC. With a median follow-up of 4.06 (range: 0.30–22.9) months, 36 of 89 patients in the full analysis set had achieved objective response (40.4%, 95% CI: 30.2–51.4), and the median duration of response was 11.4 months (95% CI: 4.8 to not reached). The benefit of geptanolimab treatment was significantly greater in patients with PD-L1 expression ≥50% (objective response rate 53.3%; median PFS 6.2 months) compared to those with PD-L1 expression less than 50% (objective response rate 25.0%; median PFS 1.5 months).<sup>74</sup>

### Serplulimab (Shanghai Henlius Biotech Inc.)

Serplulimab (HLX10) is a humanized, hinge-stabilized anti-PD-1 IgG4κ antibody in development by Shanghai Henlius Biotech Inc. as a monotherapy and in combination with other agents for the treatment of cancer. The company granted PT Kalbe Genexine Biologics exclusive rights to develop and commercialize serplulimab in relation to its first monotherapy

and two combination therapies in certain Southeast Asian countries. NDAs for serplulimab for the treatment of MSI-H/dMMR solid tumors and the first-line treatment of locally advanced or metastatic squamous NSCLC in combination with carboplatin and albumin-bound paclitaxel have been accepted by China's NMPA.

In April 2021, Shanghai Henlius Biotech announced NMPA's acceptance of serplulimab's NDA for the treatment of MSI-H solid tumors,<sup>75</sup> which was granted a priority review. The application included results from the single-arm pivotal Phase 2 study (NCT03941574), which enrolled 108 patients with unresectable or metastatic MSI-H/dMMR solid tumors who have progressed on or been intolerant to standard therapies. Patients received 3 mg/kg serplulimab IV every 2 weeks for up to 2 y until disease progression, unacceptable toxicity, or patient withdrawal. The primary endpoint was the objective response rate assessed by IRRC. Among 68 patients included in the main efficacy analysis population, with a median follow-up duration of 7.7 (range: 1.1–16.4) months, the IRRC and investigator-assessed objective response rates were 38.2% (95% CI: 26.7–50.8%; 2 CR) and 35.3% (95% CI: 24.1–47.8%), respectively.<sup>76</sup>

In September 2021, Shanghai Henlius Biotech announced NMPA's acceptance of serplulimab's NDA for the treatment of squamous NSCLC, which was granted a priority review.<sup>77</sup> This NDA includes results from the randomized, double-blind, multicenter Phase 3 clinical trial (NCT04033354) evaluating serplulimab in combination with chemotherapy (carboplatin and albumin-bound paclitaxel) versus chemotherapy alone in patients with locally advanced or metastatic squamous NSCLC.



Shanghai Henlius Biopharma is also sponsoring ongoing late-stage clinical studies of serplulimab as monotherapy or in combination with other agents as a treatment for gastric cancer, esophageal squamous cell carcinoma, and small cell lung cancer. Phase 3 studies of serplulimab in HCC, metastatic colorectal cancer, cervical cancer, and triple-negative breast cancer patients are planned.

### **Envafohimab (Alphamab Oncology)**

Envafohimab (KN035) is composed of a humanized anti-PD-L1 nanobody fused to a human IgG1 Fc (VH-h-CH2-CH3 gamma1 chain dimer). The Fc region contains two mutations that alter ADCC and complement-dependent cytotoxicity (CDC) effector functions. Invented by Alphamab Oncology, envafohimab is in development as a treatment for MSI-H cancer, biliary tract, and soft sarcoma cancers. Alphamab Oncology has collaborative or partnership agreements with TRACON Pharmaceuticals, 3D Medicines Inc., and Simcere Pharmaceutical Group regarding development of envafohimab in specific indications and designated geographical regions. FDA has granted envafohimab Orphan Drug designation for advanced biliary tract cancer and soft tissue sarcoma. An NDA submitted by Alphamab Oncology in November 2020 for envafohimab for the treatment of MSI-H advanced colorectal cancer and gastric cancer/dMMR advanced solid tumors that have failed previous standard of care was accepted for priority review by China's NMPA.<sup>78</sup>

The NDA includes results from a pivotal Phase 2 clinical trial (NCT03667170) evaluating envafohimab as monotherapy for the treatment of MSI-H/dMMR advanced solid tumors. Patients receive 150 mg envafohimab SC on D 1, 8, 15, 22 of every 4-week cycle. The primary endpoint is the objective response rate, as assessed by a blinded independent review committee. Results for 103 Chinese patients with advanced MSI-H/dMMR solid tumors who failed first-line or above systemic treatment enrolled in the study were recently reported.<sup>79</sup> With a median follow-up of 11.5 months, the objective response rate was 42.7% (95% CI: 33.0–52.8), and the median PFS was 11.1 months (95% CI: 5.5 to not evaluable). Overall survival at 12 months was 74.6% (95% CI: 64.7–82.1).

TRACON Pharmaceuticals is sponsoring the pivotal Phase 2 ENVASARC study (NCT04480502) in patients with locally advanced, unresectable or metastatic undifferentiated pleomorphic sarcoma or myxofibrosarcoma who have progressed on one or two lines of prior therapy. Patients are administered 300 mg envafohimab Q3W by SC injection (cohort A;  $n = 80$ ) or 300 mg envafohimab Q3W by SC injection combined with 1 mg/kg ipilimumab Q3W IV for four doses (cohort B;  $n = 80$ ).<sup>80</sup> The company expects Interim efficacy data from the ENVASARC study by end of 2021; the estimated primary completion date of the study is July 2022.

### **Sugemalimab (CStone Pharmaceuticals)**

Sugemalimab (CS1001), a hinge-stabilized, human anti-PD-1 IgG4 $\lambda$  antibody, was derived from Ligand's OmniRat<sup>®</sup> transgenic animal platform by CStone Pharmaceuticals. The company has strategic collaboration agreements with Pfizer and EQRx for the development and commercialization of sugemalimab in mainland China and outside of Greater China, respectively. Sugemalimab is being evaluated in late-clinical trials of patients with Stage III and IV NSCLC, lymphoma, gastric cancer, and esophageal cancer. The FDA granted Orphan Drug designation to sugemalimab for the treatment of T-cell lymphoma. The FDA and NMPA have granted Breakthrough Therapy designation for relapsed or refractory extranodal natural killer/T-cell lymphoma (ENKTL). As of September 2021, NDAs are undergoing review by NMPA for sugemalimab as treatment for Stage IV and Stage III NSCLC. The company plans regulatory submissions in other countries, including the US, in the future.<sup>81</sup>

In November 2020, the NMPA accepted the NDA of sugemalimab plus chemotherapy for the first-line treatment of patients with Stage IV squamous and non-squamous NSCLC. The safety and efficacy of sugemalimab with or without platinum-containing chemotherapy in patients with Stage IV NSCLC was evaluated in the placebo-controlled Phase 3 GEMSTONE-302/CS1001-302 study (NCT03789604). Patients received chemotherapy (Carboplatin on D 1 of each 21-d cycle; Pemetrexed on D 1 of each 21-d cycle; Paclitaxel on D 1 of each 21-d cycle) with or without 1200 mg sugemalimab by IV infusion Q3W, for up to 24 months. The primary outcome measure was PFS in patients with PD-L1  $\geq 1\%$  and PFS in all patients evaluated by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. In patients with both squamous and non-squamous NSCLC, the investigator-assessed PFS was 9.0 vs. 4.9 months, the median overall survival was 22.8 vs. 17.7 months, the 12-month PFS rate was 36.4% vs. 14.8%, and 24-month overall survival rate was 47.1% vs. 38.1% for patients in the sugemalimab plus chemotherapy versus placebo plus chemotherapy groups, respectively. PFS benefits were observed in all PD-L1 expression levels.<sup>82</sup>

In September 2021, the NMPA accepted the NDA of sugemalimab in patients with unresectable Stage III NSCLC without disease progression after concurrent or sequential chemoradiotherapy. The NDA was based on results from the placebo-controlled Phase 3 GEMSTONE-301 trial (NCT03728556) of sugemalimab as consolidation treatment in subjects with locally advanced/unresectable (Stage III) NSCLC that has not progressed after prior concurrent/sequential chemoradiotherapy. Patients received CS1001 mAb by IV infusion Q3W, for up to 24 months.

The study met its primary endpoint of PFS. In the sugemalimab arm, the median PFS was 9.0 months vs. 5.8 months in the placebo arm (HR = 0.64,  $P = 0.0026$ ). Moreover, median overall survival was not reached for sugemalimab vs. 24.1 months for placebo (HR = 0.44), and sugemalimab demonstrated clinical benefit in all subgroup analyses regardless of whether patients received concurrent or sequential chemoradiotherapy prior to sugemalimab.<sup>83</sup>

**Ripertamab (CSPC Pharmaceutical Group Ltd.)**

Ripertamab (SCT400) is a recombinant, human-mouse chimeric anti-CD20 IgG1 $\kappa$  mAb produced by Sinocelltech Ltd. SCT400 differs from rituximab by only one amino acid (V219A in the CH1 domain of the heavy chain).<sup>84</sup> In 2018, CSPC Pharmaceutical Group Ltd. signed a licensing and commercialization agreement with Sinocelltech to advance the development of SCT400 as a treatment for hematological malignancies, including non-Hodgkin's lymphoma (NHL). As of July 2021, Sinocelltech's pipeline (accessed via [www.sinocelltech.com](http://www.sinocelltech.com)) indicated that a marketing application had been submitted.

**Socazolimab (Lee's Pharmaceutical Holdings Limited)**

Socazolimab (ZKAB001, STI-A1014) is a human anti-PD-L1 IgG1 $\lambda$ 2 mAb identified by Sorrento Therapeutics, Inc. using its proprietary G-MAB™ library platform, then licensed exclusive rights to develop and commercialize the antibody for Greater China, which includes Mainland China, Hong Kong, Macau, and Taiwan, to China Oncology Focus Limited, an affiliate of Lee's Pharmaceutical Holdings Limited. Socazolimab was granted Breakthrough designation by the NMPA. In November 2021, Sorrento announced that China Oncology Focus Limited submitted an NDA for socazolimab to treat recurrent or metastatic cervical cancer that was accepted by NMPA.<sup>85</sup>

Socazolimab has been evaluated as a treatment for various cancers, including recurrent or metastatic cervical cancer, maintenance therapy for high-grade osteosarcoma after adjuvant chemotherapy, locally advanced and metastatic urothelial carcinoma, extensive small cell lung cancer in combination with carboplatin and etoposide, advanced urothelial carcinoma in combination with albumin-bound paclitaxel and esophageal carcinoma.

**Ozoralizumab (Taisho Pharmaceutical Co., Ltd.)**

Ozoralizumab (TS-152, ATN-103) is a VHH-based, humanized, trivalent bispecific Nanobody® containing two domains that bind TNF and one domain that binds serum albumin, which extends the half-life of the molecule. Ablynx discovered and performed the initial clinical studies of ozoralizumab in rheumatoid arthritis (RA) patients. The company licensed rights to develop and commercialize it in Japan and Greater China to Taisho Pharmaceutical and Eddingpharm, respectively, before being acquired by Sanofi in 2018.

In March 2021, Taisho Pharmaceutical announced that they applied for approval to manufacture and market Japan's MHLW for the planned indication of RA not inadequately managed by the currently available treatments. The marketing application is based on the results of the randomized, placebo-controlled Phase 2/3 TS152-3000-JA study in Japan, which enrolled patients with active RA who have had an inadequate response to methotrexate (MTX) treatment. In this study, ozoralizumab was SC administered to patients with RA in combination with MTX once every 4 weeks. Patients who received ozoralizumab showed a statistically significant improvement over placebo group on ACR20 improvement

rate. A similar efficacy was observed in the Phase 3 TS152-3001-JA study in Japan, which did not include the administration of MTX.<sup>86</sup>

Taisho Pharmaceutical is also sponsoring a Phase 3 extension study (NCT04077567) of RA patients who completed the TS152-3000-JA or TS152-3001-JA studies). The study, which is active but not recruiting, has enrolled 401 patients who receive either 30 mg or 80 mg ozoralizumab SC every 4 weeks. The primary outcome measure related to efficacy is the percentage of subjects who meet the American College of Rheumatology 20% (ACR20) criteria from baseline of the previous study. The study's estimated primary completion date is December 2022.

**Felzartamab (I-Mab, MorphoSys)**

Felzartamab (TJ202, MOR202) is a human anti-CD38 IgG1 $\kappa$  antibody derived from MorphoSys HuCAL library. I-Mab licensed development, manufacturing, and commercialization rights for felzartamab in China, Macau, Hong Kong and Taiwan from MorphoSys in 2017. Felzartamab is being developed for the treatment of MM, as well as autoantibody-mediated autoimmune diseases. I-Mab is conducting two parallel registrational trials of felzartamab, with the goal of registration in Greater China; the submission of an NDA for felzartamab for third-line treatment of MM is on track for the fourth quarter of 2021.<sup>87</sup>

In August 2021, I-Mab announced that topline data of the registrational trial for felzartamab for third-line treatment of MM met the primary and secondary endpoints and the data confirmed clinical advantages of felzartamab, such as its lower infusion-related reaction rate and shorter infusion time for outpatient administration. The company is also evaluating the combination of felzartamab and lenalidomide in a Phase 3 registrational for second-line MM. The company expects to complete patient enrollment in September 2021. Data from this study may allow submission of an NDA for the felzartamab and lenalidomide combination in 2023.<sup>87</sup>

**Antibody therapeutics undergoing first regulatory review in the US or EU**

Based on information available as of November 15, 2021, marketing applications for 19 investigational antibody therapeutics were undergoing regulatory review by either the FDA or EMA (Table 4). It should be noted that EMA issues monthly reports listing the MAAs under review, while the FDA does not routinely disclose such information unless the BLA will be the subject of an FDA advisory committee meeting. The FDA may act on the BLA for faricimab in late 2021 or early 2022. The FDA's first actions on the BLAs for sutimlimab, tebentafusp, relatlimab, sintilimab, ublituximab, tezepelumab are expected in the first quarter of 2022. The timelines for progress on an additional four applications, for teplizumab, retifanlimab, oportuzumab monatox, and narsoplimab, depend on the timing of the re-submission of BLAs by the sponsoring companies, and whether these revised BLAs meet the FDA's expectations. Summaries for these investigational antibody therapeutics in review are provided in the following sections.

### **Faricimab (Genentech/F. Hoffmann-La Roche Ltd.)**

Faricimab (RO6867461, RG7716) is an anti-vascular endothelial growth factor-A (VEGF-A) and anti-angiopoietin-2 (Ang-2) bispecific antibody derived from Roche's CrossMab technology. Genentech and Roche developed the antibody as a treatment for ophthalmic disorders. In July 2021, Genentech announced that a BLA for faricimab for the treatment of wet, or neovascular, age-related macular degeneration (AMD) and diabetic macular edema (DME) had been accepted by FDA and granted Priority Review. The FDA also accepted the company's submission for diabetic retinopathy. An MAA for faricimab for wet AMD and DME was also validated by EMA.<sup>88</sup>

The marketing applications include results from four Phase 3 studies in wet AMD and DME. The randomized, double-masked, and active comparator-controlled TENAYA (NCT03823287) and LUCERNE (NCT03823300) studies evaluated the effects of faricimab (6.0 mg administered at fixed intervals of every 2, 3, or 4 months) and aflibercept (Eylea®) (2.0 mg administered at fixed two-month intervals) in wet AMD patients. The primary endpoint of the studies, average change in best-corrected visual acuity (BCVA) from baseline through week 48, was met in both studies. The average vision gains from baseline in the faricimab arms were +5.8 and +6.6 letters, compared to +5.1 and +6.6 letters in the aflibercept arms, in the TENAYA and LUCERNE studies, respectively, demonstrating the non-inferiority of faricimab compared to aflibercept. The study also showed that faricimab's treatment interval could be longer than that of aflibercept – nearly 80% of patients treated with faricimab were able to go 3 months or longer between treatments during the first year.<sup>88</sup>

The 3-arm, randomized, double-masked, active comparator-controlled YOSEMITE (NCT03622580) and RHINE studies (NCT03622593) compared the effects of faricimab (6.0 mg administered at personalized treatment intervals (PTI) of up to 4 months or 6.0 mg administered at fixed 2-month intervals) to those of aflibercept (2.0 mg administered at fixed two-month intervals) in DME patients. The primary endpoint, average change in BCVA score from baseline at 1 y, was met, with faricimab again showing non-inferiority in visual acuity gains compared to aflibercept. In the YOSEMITE study, the average vision gains from baseline were +11.6, +10.7, and +10.9 letters eye chart letters in the faricimab PTI, faricimab 2-month, and aflibercept arms, respectively. The average vision gains from baseline were +10.8, +11.8, and +10.3 letters in the faricimab PTI, faricimab 2-month, and aflibercept arms, respectively, in the RHINE study.<sup>88</sup>

### **Sutimlimab (Sanofi)**

Sutimlimab, a hinge-stabilized, humanized IgG4κ antibody that targets and inhibits complement component 1s (C1s), was developed as a treatment of hemolysis in adult patients with cold agglutinin disease (CAD). A mutation in the Fc region (L235E) reduces the effector functions of the antibody. This rare autoimmune disorder is characterized by hemolysis caused by activation of the classic complement pathway.

Sutimlimab received FDA's Breakthrough Therapy and Orphan Drug designations for CAD, and Orphan Drug designation in the EU for this indication.

In May 2020, Sanofi announced the FDA had granted priority review to its BLA for sutimlimab for the treatment of hemolysis in adult patients with CAD. The BLA was based on data from the CARDINAL open-label, single-arm study (NCT03347396), which enrolled 24 adult patients with CAD who received a recent blood transfusion. In this study, sutimlimab administration rapidly halted hemolysis, increased hemoglobin levels, and reduced fatigue.<sup>89</sup> In November 2020, Sanofi announced that FDA issued a Complete Response letter describing deficiencies identified by FDA during a pre-license inspection of a third-party facility responsible for manufacturing. In October 2021, Sanofi announced that the FDA accepted the resubmission of the BLA for sutimlimab, and the BLA was granted priority review with a target action date of February 5, 2022.<sup>90</sup>

Efficacy data from Part A of the Phase 3 Cadenza trial (NCT03347422) of patients with primary CAD without a recent history of blood transfusion were presented at the European Hematology Association's 2021 Congress. The purpose of Part A was to determine whether sutimlimab administration results in a  $\geq 1.5$  g/dL increase in hemoglobin level and avoidance of transfusion in participants. A total of 42 patients were enrolled and randomized to either sutimlimab ( $n = 22$ ) or placebo ( $n = 20$ ). Of patients treated with sutimlimab, 73% ( $n = 16$ ) met the primary composite endpoint compared to 15% ( $n = 3$ ) in the placebo group. The data also showed a statistically significant improvement in fatigue in patients treated with sutimlimab compared to the placebo group.<sup>91</sup>

### **Tebentafusp (Immunocore Holdings Plc)**

Tebentafusp (IMCgp100) is a bispecific fusion protein composed of (1) a T cell receptor (TCR) recognizing a human leukocyte antigen (HLA)-A\*02:01 complexed with a peptide derived from gp100 antigen expressed by melanoma cells and (2) an antibody single-chain variable fragment that binds CD3 present on T cells. Developed by Immunocore, this molecule creates a bridge between tumor cells and immune cells, and thus facilitates tumor-cell killing by T cells. As the TCR domain recognizes a peptide presented on HLA-A\*02:01, tebentafusp can only be used to treat patients expressing this HLA type.<sup>92</sup> Tebentafusp has been granted Breakthrough Therapy, Fast Track, and Orphan Drug designations by the FDA.

In August 2021, Immunocore announced that the EMA and FDA have each accepted applications for the approval of tebentafusp (IMCgp100) for the treatment of HLA-A\*02:01-positive adult patients with metastatic uveal melanoma.<sup>93</sup> The FDA has granted Priority Review to the BLA, which has an expected target action date of February 23, 2022. The BLA will be reviewed under FDA's Real-Time Oncology Review pilot program and their Project Orbis initiative, which enables concurrent review by the health authorities in partner countries. The MAA will receive accelerated assessment by EMA, which has a timeframe for review of the MAA of 150 d (excluding clock-stops).



The marketing applications are based on a late-stage clinical trial (NCT03070392) that enrolled 378 patients with advanced uveal melanoma who were HLA-A\*0201-positive. In the study, patients were randomized 2:1 to receive tebentafusp or investigator's choice of therapy (either pembrolizumab, ipilimumab, or dacarbazine). Tebentafusp was administered at a dose of 20 µg on cycle 1 D 1, then 30 µg on cycle 1 D 8, then 68 µg on cycle 1 D 15 and weekly thereafter by IV infusion over 15 min until confirmed disease progression or unacceptable toxicity. The primary outcome measure is overall survival. As reported in April 2021, the overall survival was superior for the tebentafusp arm versus the investigator's choice arm with an HR of 0.51 (95% CI: 0.36–0.71;  $P < 0.0001$ ) in the intention-to-treat population. Moreover, the 1-y survival rate was 73.2% for patients in the experimental arm vs. 57.5% in the investigator's choice arm.<sup>94</sup>

### **Relatlimab (Bristol Myers Squibb, Ono Pharmaceutical Co., Ltd.)**

Relatlimab (BMS-986016, ONO4482) is a human IgG4κ antibody that targets LAG-3, which, like PD-1, is an immune checkpoint. Bristol Myers Squibb (BMS) and Ono have a strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea, and Taiwan. An MAA is undergoing evaluation by EMA.

In September 2021, the FDA accepted for priority review the BLA for relatlimab and anti-PD-1 Opdivo® (nivolumab), as a fixed-dose combination administered as a single infusion, for the treatment of adult and pediatric patients (12 y and older and weighing at least 40 kg) with unresectable or metastatic melanoma. FDA's first action on the application is expected by March 19, 2022.<sup>95</sup> BMS announced on October 1, 2021, that EMA had validated an MAA for the relatlimab and nivolumab fixed-dose combination for first-line treatment of adult and pediatric patients (12 y and older and weighing at least 40 kg) with advanced (unresectable or metastatic) melanoma.

The BLA included data from the Phase 2/3 RELATIVITY-047 trial (NCT03470922), which evaluated the effects of relatlimab combined with nivolumab versus nivolumab in a total of 714 patients with previously untreated metastatic or unresectable melanoma. Patients were randomized 1:1 and administered a fixed-dose combination of 160 mg relatlimab and 480 mg nivolumab or 480 mg nivolumab by IV infusion every 4 weeks until disease recurrence, unacceptable toxicity or withdrawal of consent. The study's primary endpoint was PFS by blinded independent central review. As reported during the American Society of Clinical Oncology (ASCO) Annual Meeting in June 2021, after a median follow-up of 13.2 months, the median PFS in the group that received both relatlimab and nivolumab was significantly longer (10.1 months [95% CI: 6.4–15.7]) than in the group that received nivolumab only (4.6 months [95% CI: 3.4–5.6]; HR: 0.75 [95% CI: 0.6–0.9];  $P = 0.0055$ ).<sup>96</sup>

BMS is also sponsoring the Phase 3 RELATIVITY-098 study (NCT05002569) of adjuvant immunotherapy with relatlimab and nivolumab fixed-dose combination versus nivolumab monotherapy after complete resection of Stage III–IV melanoma. The study's estimated enrollment is 1050 patients. Due to start in September 2021, the study's estimated primary completion date is July 2025.

### **Sintilimab (Innovent Biologics, Eli Lilly and Company)**

Sintilimab (Tyvyt®, IBI308) is a human monoclonal IgG4κ antibody directed against PD-1. The PD-1 blockade disrupts the binding of PD-1 to its ligands PD-L1 and PD-L2, leading to the reinvigoration of T cells and enhancement of anti-tumor responses.<sup>97</sup> Innovent Biologics and Eli Lilly and Company are co-developing and commercializing the drug as a treatment for various tumor types. In May 2021, the companies jointly announced that a BLA was accepted for review by the FDA for sintilimab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of non-squamous NSCLC.<sup>98</sup> FDA plans to hold an Advisory Committee meeting to discuss the BLA. The FDA's first action date for the application is in March 2022.

Sintilimab was first approved in 2018 by China's National Medical Products Administration of (NMPA) for the treatment of relapsed and refractory classical Hodgkin's lymphoma after at least two lines of systemic chemotherapy. Supplemental approvals granted by NMPA for sintilimab in combination with pemetrexed and platinum chemotherapy as first-line therapy for people with non-squamous NSCLC and for sintilimab in combination with gemcitabine and platinum chemotherapy as first-line therapy for people with unresectable locally advanced or metastatic squamous NSCLC were announced in February and June 2021, respectively.

NMPA's approval of sintilimab for non-squamous NSCLC is based on data from the randomized, placebo-controlled Phase 3 ORIENT-11 study (NCT03607539), and results from this study were included in the BLA submitted to FDA. In ORIENT-11, a total of 397 patients with previously untreated, locally advanced or metastatic non-squamous NSCLC without sensitizing EGFR or anaplastic lymphoma kinase genomic aberration were administered pemetrexed plus platinum chemotherapy with sintilimab ( $n = 266$ ) or without sintilimab ( $n = 131$ ). The median PFS in the sintilimab combination arm was 8.9 (95% CI: 7.1–11.3) months vs. 5.0 (95% CI: 4.8–6.2) months in the placebo combination arm, and the confirmed objective response rate was 51.9% in the sintilimab-combination group vs. 29.8% in the placebo-combination group.<sup>99</sup>

NMPA is reviewing regulatory submissions for sintilimab in combination with BYVASDA® (bevacizumab injection) for the first-line treatment of HCC and for the second-line treatment of squamous NSCLC, and for sintilimab in combination with chemotherapy (cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil) for the first-line treatment of esophageal squamous cell carcinoma. Sintilimab is also being evaluated in combination with oxaliplatin and capecitabine for the first-line treatment of unresectable, locally advanced, recurrent or



metastatic gastric or GEJ adenocarcinoma in the placebo-controlled Phase 3 ORIENT-16 study (NCT03745170), which met its predefined primary endpoint of overall survival. A supplemental NDA submission to the NMPA based on the study results is planned.<sup>100</sup>

### **Ublituximab (TG Therapeutics, Inc.)**

Ublituximab (TG-1101) is a chimeric anti-CD20 IgG1 $\kappa$  antibody with low fucose content in its Fc region, which enhances its effector functions. TG Therapeutics licensed ublituximab from LFB Group, and is developing it as a treatment for chronic lymphocytic leukemia (CLL) and multiple sclerosis (MS). The combination of ublituximab and Ukoniq<sup>®</sup> (umbralisib), a small-molecule inhibitor of PI3K-delta and casein kinase CK1-epsilon, was granted Fast Track and Orphan Drug designations by FDA for the treatment of CLL patients. Ukoniq<sup>®</sup> is FDA-approved as a treatment for several types of NHL.

In May 2021, TG Therapeutics announced that FDA had accepted a BLA for ublituximab in combination with Ukoniq<sup>®</sup> as a treatment for patients with CLL and small lymphocytic lymphoma. The BLA included results from the Phase 3 UNITY-CLL trial (NCT02612311), which included both treatment-naïve and relapsed or refractory patients.<sup>101</sup> In September 2021, TG Therapeutics submitted a BLA for ublituximab for the treatment of patients with relapsing forms of multiple sclerosis, based on positive results from the Phase 3 ULTIMATE I (NCT03277261) and II (NCT03277248) trials.<sup>102</sup> Patients (ULTIMATE I,  $N = 549$ ; ULTIMATE II,  $N = 545$ ) were randomized (1:1) to receive either 450 mg ublituximab via a 1-h IV infusion every 24 weeks (following D 1 infusion of 150 mg) or 14 mg oral teriflunomide once-daily, throughout a 96-week treatment period. The primary endpoint, annualized relapse rate, was met in both studies, with 60% and 50% reductions in the annualized relapse rate over teriflunomide observed in ULTIMATE I and II, respectively.<sup>103</sup> The FDA's first actions on both BLAs are expected by March 25, 2022.

### **Tezepelumab (AstraZeneca/Amgen)**

Tezepelumab (AMG157, MEDI-9929) is a human IgG2 $\lambda$  antibody that targets a cytokine, thymic stromal lymphopoietin, that plays a key role in asthma inflammation. The drug was developed by Amgen in collaboration with AstraZeneca for the treatment of asthma. In May 2021, Amgen announced the submission of a BLA to FDA for tezepelumab as a treatment for severe asthma. FDA had previously granted Breakthrough Therapy designation for tezepelumab for this indication. The BLA was granted a Priority Review, and FDA's first action date is in the first quarter of 2022. A marketing application for tezepelumab as a treatment for severe asthma is also undergoing review by EMA under standard timelines.

The marketing applications included data from the randomized, placebo-controlled Phase 3 NAVIGATOR study (NCT03347279), which evaluated the effects of tezepelumab in adults and adolescents with severe uncontrolled asthma. In this study, patients received tezepelumab (210 mg;  $n = 529$ ) or placebo ( $n = 532$ ) SC every 4 weeks for 52 weeks. The primary

outcome measure of the study, the annualized asthma exacerbation rate from baseline to Week 52, was met. For the tezepelumab group, the annualized rate of asthma exacerbations was 0.93 (95% CI: 0.80–1.07), while the rate was 2.10 (95% CI: 1.84–2.39) with placebo (rate ratio, 0.44; 95% CI: 0.37–0.53;  $P < 0.001$ ). Overall, data from the study indicated that, compared to those administered placebo, patients who received tezepelumab had fewer exacerbations and better lung function, asthma control, and health-related quality of life.<sup>104</sup> A pre-specified exploratory analysis showed that tezepelumab reduced the annualized asthma exacerbation rate in patients with nasal polyps by 86% (95% CI: 70–93) and 52% (95% CI: 42–61) in those without nasal polyps over 52 weeks compared to placebo given with standard of care.<sup>105</sup>

### **Penpulimab (Akesbio/Chia Tai-Tianqing Pharmaceutical Group Co., Ltd)**

Penpulimab (AK105) is a humanized anti-PD-1 $\kappa$  IgG1 antibody approved in China in 2021 for patients with relapsed or refractory classic Hodgkin's lymphoma after at least second-line systemic chemotherapy treatment, as discussed in a previous section. The FDA granted penpulimab Breakthrough Therapy and Fast Track designations for third-line treatment of metastatic nasopharyngeal carcinoma. In May 2021, Akeso and Sino Biopharmaceutical Limited jointly announced the BLA submission to the FDA for penpulimab as a third-line treatment of metastatic nasopharyngeal carcinoma. The FDA will review the BLA under the Real-Time Oncology Review program, which aims to accelerate the process of drug approval relative to a priority review.<sup>106</sup>

The BLA is supported by data from the single-arm, open-label Phase 2 AK105-202 study (NCT03866967) of metastatic nasopharyngeal carcinoma patients with disease progression after  $\geq 2$  prior lines of therapy including platinum-containing chemotherapy. Patients received 200 mg penpulimab IV once every 2 weeks until disease progression or unacceptable toxicity. In patients ( $N = 111$ ) assessed by an independent review committee, the objective response rate was 27% (39.5% in PD-L1+ patients; 19.7% in PD-L1- patients) after median follow-up of 7.9 (range: 0.9–16.9) months.<sup>107</sup>

Akeso is sponsoring the ongoing randomized, placebo-controlled Phase 3 AK105-304 study (NCT04974398) of penpulimab combined with chemotherapy (cisplatin and gemcitabine) versus placebo combined with chemotherapy in the first-line treatment of recurrent or metastatic nasopharyngeal carcinoma. Patients in the treatment arm will receive penpulimab (200 mg, administered on D 1 of each cycle, once Q3W) + cisplatin (80 mg/m<sup>2</sup>, administered on D 1 of each cycle, Q3W, up to 6 cycles) + gemcitabine (1000 mg/m<sup>2</sup>, administered on D 1 and 8 of each cycle, Q3W, up to 6 cycles), 3 weeks per treatment cycle. Penpulimab will then be used for maintenance treatment (200 mg, administered on D 1 of each cycle, Q3W). The primary outcome measure is PFS, and the estimated enrollment is 278 patients. Initiated in August 2021, the study has an estimated primary completion date in July 2023.

### **Tislelizumab (BeiGene, Novartis Pharmaceuticals Corporation)**

Tislelizumab (BGB-A317) is a hinge-stabilized, humanized anti-PD-1 IgG4 $\kappa$  mAb specifically designed to minimize binding to Fc $\gamma$ R on macrophages. In January 2021, BeiGene and Novartis entered into a collaboration and license agreement granting Novartis rights to develop, manufacture, and commercialize tislelizumab in major markets outside of China. Orphan Drug designations were granted for tislelizumab for the treatment of esophageal cancer by the EMA and FDA. In September 2021, BeiGene announced that FDA accepted for review a BLA for tislelizumab as a treatment for patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma after prior systemic therapy. The FDA's target date for a first action on the application is July 12, 2022.<sup>108</sup>

The BLA includes clinical results from the Phase 3 RATIONALE 302 trial (NCT03430843) of tislelizumab compared to chemotherapy in previously treated patients with advanced or metastatic esophageal squamous carcinoma, which were presented at the 2021 American Society of Clinical Oncology Annual Meeting. The study met its primary endpoint, improved overall survival compared with chemotherapy in the intent to treat population. For patients in the tislelizumab vs. chemotherapy arms, the median overall survival was 8.6 vs. 6.3 months (HR 0.70, 95% CI: 0.57–0.85,  $P = 0.0001$ ). In PD-L1+ patients who received tislelizumab, the median overall survival was 10.3 months vs. 6.8 months for those who received chemotherapy (HR 0.54, 95% CI: 0.36–0.79,  $P = 0.0006$ ).<sup>109</sup>

Tislelizumab was first approved in China in December 2019. As of September 2021, NMPA has granted tislelizumab conditional marketing approvals for three indications, classical Hodgkin's lymphoma; urothelial carcinoma; HCC, and full approvals for two additional indications, squamous NSCLC, and non-squamous NSCLC.<sup>110</sup> In addition, NMPA is reviewing three supplemental applications for tislelizumab: (1) as second- or third-line treatment of patients with locally advanced or metastatic NSCLC who progressed on prior platinum-based chemotherapy; (2) for patients with previously treated, locally advanced unresectable or metastatic MSI-H or dMMR solid tumors; and (3) for the treatment of patients with locally advanced or metastatic esophageal squamous cell carcinoma who have disease progression following or are intolerant to first-line standard chemotherapy.

The NMPA approval of tislelizumab for classical Hodgkin's lymphoma is based on the clinical results from a single-arm, multicenter, pivotal Phase 2 trial (NCT03209973). Among the patients who were evaluable for responses, the objective response rate was 76.9% and the CR rate was 61.5%. In April 2020, NMPA granted tislelizumab an approval for treatment of patients with locally advanced or metastatic urothelial carcinoma with PD-L1 high expression whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.<sup>111</sup> The approval was based on a single-arm, multicenter Phase 2 trial (NCT04004221). Among 104 efficacy-evaluable patients, the

confirmed objective response rate was 24.8% and the CR rate was 9.9%. The median progression-free survival and overall survival times were 2.1 and 9.8 months, respectively.<sup>112</sup>

In January 2021, NMPA's approved tislelizumab as first-line treatment for patients with advanced squamous NSCLC in combination with chemotherapy.<sup>113</sup> The approval was based on results from a Phase 3 trial (NCT03594747) where the PFS in tislelizumab + chemotherapy arm was 7.6 months vs. 5.5 months with chemotherapy alone.<sup>114</sup> In June 2021, NMPA granted tislelizumab an approval for first-line treatment of patients with advanced non-squamous NSCLC and a conditional approval for the treatment of patients with HCC who have been previously treated with at least one systemic therapy.<sup>115</sup> In NSCLC, the approval of tislelizumab for the first-line treatment of patients with advanced non-squamous NSCLC was supported by clinical results from a Phase 3 trial (NCT03663205) of tislelizumab in combination with pemetrexed and platinum chemotherapy (either carboplatin or cisplatin) in patients with stage IIIB or stage IV non-squamous NSCLC, compared to pemetrexed and platinum alone. In HCC, NMPA's conditional approval of tislelizumab in patients with HCC who have received at least one systemic therapy is based on clinical results from a single-arm, open-label, multicenter, global pivotal Phase 2 trial (NCT03419897) in which the objective response rate was 13.3% (95% CI: 9.3–18.1). Median overall survival was 13.2 months (95% CI: 10.8, 15.0) and PFS was 2.7 months (95% CI: 1.4–2.8).

### **Lecanemab (Eisai Co., Ltd., Biogen Inc.)**

Lecanemab (BAN2401), a humanized anti-A $\beta$  protofibril IgG1 $\kappa$  antibody for the treatment of early AD, was developed through a collaboration between BioArctic and Eisai that started in the mid-2000s. In 2014, Eisai and Biogen entered into a collaboration to develop and commercialize lecanemab. In June 2021, lecanemab was granted FDA's Breakthrough Therapy designation for the treatment of AD, and in September 2021, Eisai initiated a rolling BLA to the FDA for lecanemab for the treatment of early AD.<sup>116</sup> The BLA was submitted under the accelerated approval pathway, which allows drugs for serious diseases to be approved based on the results of a surrogate endpoint (e.g., A $\beta$  levels) that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.

The BLA for lecanemab includes results of the placebo-controlled Phase 2 Study 201 (NCT01767311) in 856 patients with mild cognitive impairment due to AD and mild AD with confirmed presence of amyloid pathology. Several dose levels and intervals (2.5, 5, or 10 mg lecanemab every 2 weeks; 5 or 10 mg lecanemab monthly; all administrations are via 60-min IV infusion) were evaluated, and eligible participants have the option to participate in the Extension phase to receive 10 mg/kg lecanemab every 2 weeks for up to 60 months. The study endpoints were selected to evaluate the effect of lecanemab treatment on reducing brain A $\beta$  and clinical decline. The primary outcome measure was the change from baseline in the AD Composite Score (ADCOMS) at 12 months, and key secondary endpoints included amyloid pathophysiology as

measured by amyloid positron emission tomography at 18 months. Study 201 did not meet the 12-month primary endpoint, but reduction in brain amyloid was observed, along with a consistent reduction of clinical decline across several of the clinical and biomarker endpoints.<sup>117</sup>

The ongoing placebo-controlled Phase 3 Clarity AD study (NCT03887455) of lecanemab in patients with early AD may serve as a confirmatory study to verify the clinical benefit of lecanemab. The study includes 1,795 patients and has completed its enrollment.<sup>116</sup> In the core phase of the study, patients are administered 10 mg/kg lecanemab IV once every 2 weeks or placebo, and the primary outcome measure is change from baseline in the Clinical Dementia Rating-Sum-of-Boxes at 18 months. In an extension phase, patients receive 10 mg/kg lecanemab IV once every 2 weeks. The primary completion date of the study is in September 2022.

### **Toripalimab (Tuoyi®, Shanghai Junshi Biosciences)**

Toripalimab (Tuoyi®) a humanized IgG4κ mAb specific for human PD-1 developed by Shanghai Junshi Biosciences Co., Ltd., which licensed rights to develop and commercialize toripalimab in the US and Canada to Coherus BioSciences, Inc. Toripalimab was granted two Breakthrough Therapy designations: (1) as monotherapy for recurrent or metastatic nasopharyngeal carcinoma with disease progression on or after platinum-containing chemotherapy and (2) in combination with gemcitabine and cisplatin as a first-line treatment for patients with recurrent or metastatic nasopharyngeal carcinoma. The FDA has also granted toripalimab Orphan Drug designations for nasopharyngeal carcinoma, mucosal melanoma and soft tissue sarcoma, and Fast Track designation for the treatment of mucosal melanoma.

In November 2021, Coherus BioSciences, Inc. and Shanghai Junshi Biosciences Co., Ltd. announced that the FDA accepted for review the BLA for toripalimab in combination with gemcitabine and cisplatin for the first-line treatment for patients with advanced recurrent or metastatic nasopharyngeal carcinoma and toripalimab monotherapy for the second-line or above treatment of recurrent or metastatic nasopharyngeal carcinoma after platinum-containing chemotherapy. The FDA has granted Priority Review designation for the toripalimab BLA and set a date for a first action on the BLA in April 2022.<sup>118</sup>

Toripalimab was first approved in China for the second-line treatment of metastatic melanoma in December 2018. The drug subsequently received conditional approvals in China for the third-line treatment of recurrent or metastatic nasopharyngeal carcinoma and for locally advanced or metastatic urothelial carcinoma who failed platinum-containing chemotherapy or progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Toripalimab's approval in China for nasopharyngeal carcinoma was based on data from the single-arm Phase 2 POLARIS-02 study (NCT02915432), and results from this study were included in the BLA submitted to the FDA. In the POLARIS-02 study, patients with recurrent or metastatic nasopharyngeal carcinoma received 3 mg/kg toripalimab IV once every 2 weeks until confirmed disease progression or unacceptable toxicity. For all 190 patients, the objective response rate

was 20.5%, the median PFS was 1.9 months, and the median overall survival was 17.4 months. Toripalimab demonstrated survival benefits regardless of PD-L1 expression, with an objective response rate of 23.9% in the 92 patients with recurrent or metastatic nasopharyngeal carcinoma after failure of at least two lines of prior systemic chemotherapy.<sup>119</sup>

The BLA submission to the FDA is also supported by the results of the randomized, placebo-controlled Phase 3 JUPITER-02 trial (NCT03581786). In the JUPITER-02 study, patients with advanced nasopharyngeal carcinoma with no prior chemotherapy in the r/m setting were randomized (1:1) to receive 240 mg toripalimab ( $n = 146$ ) or placebo ( $n = 143$ ) in combination with gemcitabine 1000 mg/m<sup>2</sup> and cisplatin 80 mg/m<sup>2</sup> Q3W for up to 6 cycles, followed by monotherapy with toripalimab or placebo Q3W until disease progression, intolerable toxicity, or completion of 2 y of treatment. The combination of toripalimab + chemotherapy significantly improved the PFS compared to the placebo arm, with median PFS of 11.7 vs. 8.0 months (HR = 0.52 (95% CI: 0.36–0.74),  $P = 0.0003$ ) and 1-y PFS rates of 49% and 28%, respectively. The overall response rate was 77.4% in the toripalimab arm vs. 66.4% in the placebo arm.<sup>120</sup>

Shanghai Junshi Biosciences is also sponsoring late-stage clinical studies of toripalimab for other cancers, including renal cell carcinoma, HCC, small cell lung cancer, triple-negative breast cancer, intrahepatic cholangiocarcinoma, neuroendocrine carcinoma of the bladder, gastric cancer, esophageal cancer, and NSCLC. Based on positive results of the randomized, placebo-controlled Phase 3 CHOICE-01 study (NCT03856411) evaluating toripalimab plus chemotherapy as first-line treatment of advanced squamous or non-squamous NSCLC, Junshi Biosciences and Coherus plan to meet with the FDA to discuss the potential submission of a BLA for toripalimab for this indication.<sup>121</sup>

### **Inolimomab (ElsaLys Biotech SA)**

Inolimomab (Leukotac) is a murine anti-IL-2 receptor IgG1κ licensed by ElsaLys Biotech and developed as a treatment of acute graft-versus-host disease (aGvHD). FDA and EMA granted inolimomab Orphan Drug designation for aGvHD. In July 2020, ElsaLys announced the submission of a BLA to FDA for inolimomab for treatment of steroid-refractory aGvHD in grade II–IV adult patients. As of December 2020, early access to inolimomab to adults and pediatric patients over 28 d of age for the treatment of steroid-refractory or steroid-dependent aGvHD was granted by the French National Agency for the Medicines and Health Products Safety via a Temporary Authorisation for Use, which was renewed in April 2021. ElsaLys plans to submit early access applications in other European countries, while they continue to work gaining marketing approval in Europe and the US.<sup>122</sup>

### **I-131 Omburtamab (Y-mAbs Therapeutics, Inc.)**

Omburtamab is a murine IgG1κ anti-B7H3 antibody 8H9 licensed by Y-mAbs Therapeutics from Memorial Sloan Kettering Cancer Center. Y-mAbs is developing this intraventricular CNS administered, I-131-labeled antibody as



a treatment for relapsed or refractory neuroblastoma with CNS or leptomeningeal metastasis (CNS/LM). The FDA granted omburtamab Breakthrough Therapy, Orphan and Rare Pediatric designations for this indication. In April 2021, Y-mAbs announced that an MAA had been submitted to EMA for omburtamab for treatment of pediatric patients with CNS/LM from neuroblastoma.<sup>123</sup>

The company completed a rolling BLA submission for omburtamab for the treatment of CNS/LM from neuroblastoma in pediatric patients in August 2020, but announced in October 2020 that FDA refused to file the BLA due to deficiencies in the Chemistry, Manufacturing and Control (CMC) and Clinical modules. As announced in November 2021, Y-mAbs Therapeutics requested a pre-BLA meeting with FDA, which may be held in January 2022. Pending a positive meeting, the company aims to initiate resubmission of the omburtamab BLA shortly thereafter.<sup>124</sup>

### **Spesolimab (Boehringer Ingelheim)**

Spesolimab (BI 655130) is a humanized IgG1 $\kappa$  antibody that blocks activation of the IL-36 receptor, which is involved in the pathogenesis of neutrophilic skin diseases such as generalized pustular psoriasis (GPP),<sup>125</sup> palmoplantar pustulosis (PPP) and hidradenitis suppurativa (HS). The FDA granted spesolimab Orphan Drug designation for the treatment of GPP in October 2018. In October 2021, Boehringer Ingelheim announced that their MAA for the treatment of flares in GPP had been validated and is under evaluation with the EMA.<sup>126</sup>

The MAA includes data from the 12-week randomized, placebo-controlled Phase 2 Effisayil-1 trial (NCT03782792). The study evaluated the efficacy, safety, and tolerability of single 900 mg dose of IV administered spesolimab, with the option of a second dose if symptoms persisted on D 8 in 53 patients experiencing a GPP flare.<sup>127</sup> The superiority of treatment with spesolimab over placebo in pustular clearance after 1 week of treatment was demonstrated in the Effisayil-1 trial.<sup>126</sup>

Two additional Phase 2 studies of GPP patients are recruiting participants. The Effisayil 2 study (NCT04399837) is a randomized, placebo-controlled, dose-finding study to evaluate the efficacy and safety of subcutaneous spesolimab compared with placebo in the prevention of GPP flares in patients with a history of GPP, while NCT03886246 is a 5-y open-label extension study.

Spesolimab is also being evaluated in a total of 5 Phase 2 clinical studies of patients with Crohn's disease, PPP or HS. Two of these studies have primary completion dates in 2022. The NCT04762277 study, which is a randomized, double-blind, placebo-controlled, study of spesolimab in an estimated 45 patients with moderate-to-severe HS, has a primary completion date in January 2022, and the NCT03752970 study, which is evaluating the mechanism of action and clinical effect of spesolimab in an estimated 45 patients with fistulizing Crohn's disease, has a primary completion date in April 2022.

### **Teplizumab (Provention Bio, Inc.)**

Teplizumab (PRV-031; proposed trade name TZIELD) is a humanized IgG1 $\kappa$  antibody that targets an epitope of the CD3-epsilon chain expressed on mature T lymphocytes, and thereby

expands regulatory T-cells and re-establishes immune tolerance. Mutations in the Fc region (L234A, L235A) reduce the effector functions of the antibody. The FDA granted teplizumab Breakthrough Therapy designation for the prevention or delay of clinical Type 1 diabetes (T1D).

Submission of a rolling BLA for teplizumab for the delay of clinical T1D in at-risk individuals was completed by November 2020. In May 2021, FDA's Endocrinologic and Metabolic Drugs Advisory Committee considered the question of whether the teplizumab's benefits outweighed the risks in delaying the onset of clinical T1D, and voted 10–7 to support approval. Among other data, the committee considered results from the Phase 2 'At-Risk' study (TN-10; NCT01030861). In this study, high-risk autoantibody-positive non-diabetic relatives of patients with T1D received IV infusions of teplizumab given for 14 consecutive days ( $n = 44$ ) or placebo ( $n = 32$ ). The total dose of teplizumab was  $\sim 9034 \mu\text{g}/\text{m}^2$ .<sup>128</sup> The study was found to have successfully demonstrated the treatment effect of teplizumab in delaying T1D diagnosis in at-risk patients, with median times to T1D diagnosis of 49.5 vs. 24.9 months in the teplizumab and placebo groups, respectively.

The committee briefing document noted that the planned commercial drug product and the study drug used in the clinical trials are not manufactured in the same facility, and a single-dose PK bridging study in healthy volunteers failed to demonstrate PK comparability between the two products.<sup>128</sup> The mean Area Under the Curve (AUC)<sub>0-inf</sub> for the commercial product was less than half (48.5%, 90% CI: 43.6–54.1) that for the drug used in the primary efficacy study, which may have been caused by faster clearance of the drug from circulation.

FDA issued a Complete Response letter, received by Provention Bio on July 2, 2021, stating that the company needed to establish PK comparability appropriately between the intended commercial product and the clinical trial product or provide other data that adequately justify why PK comparability is not necessary.<sup>129</sup> Considerations related to product quality and certain deficiencies conveyed during a recent general inspection, not specific to teplizumab, at a fill/finish manufacturing facility were also cited in the letter. Provention Bio plans to work with FDA to address the concerns expressed in the letter.

### **Retifanlimab (Incyte Corporation)**

Retifanlimab (INCMGA00012, MGA012) is a humanized, hinge-stabilized IgG4 $\kappa$  antibody targeting PD-1. Incyte Corporation licensed the molecule from MacroGenics in 2017, although MacroGenics retained the right to develop its pipeline assets in combination with retifanlimab. Incyte is sponsoring clinical studies evaluating retifanlimab monotherapy as a treatment for MSI-H endometrial cancer, Merkel cell carcinoma and squamous cell carcinoma of the anal canal (SCAC).

In January 2021, Incyte announced that the FDA accepted its BLA for retifanlimab as a potential treatment for adult patients with locally advanced or metastatic SCAC who have progressed on, or who are intolerant of, platinum-based chemotherapy. Retifanlimab had been granted Fast Track and Orphan Drug designations by the FDA for this indication.



The BLA submission was based on data from the single-arm Phase 2 POD1UM-202 trial (NCT03597295), which enrolled 94 patients. Retifanlimab monotherapy resulted in an objective response rate of 14%.<sup>130</sup>

In June 2021, FDA's Oncologic Drug Advisory Committee voted 13 to 4 for the deferral of the FDA approval of retifanlimab's BLA until further data are available from clinical trial POD1UM-303 (NCT04472429), an ongoing placebo-controlled, double-blind, randomized Phase 3 study in platinum-naïve advanced SCAC initiated in November 2020.<sup>131</sup> In July 2021, Incyte received a Complete Response letter from FDA based on their determination that additional data are needed to demonstrate the clinical benefit of retifanlimab in SCAC.<sup>132</sup> Incyte plans to work with FDA to address the concerns expressed in the letter.

### **Oportuzumab monatox (Sesen Bio, Inc.)**

Oportuzumab monatox (Vysyneum™, Vicineum®, VB4-845) is a humanized single-chain variable fragment (scFv) targeting epithelial cell adhesion molecule fused to *Pseudomonas aeruginosa* exotoxin A (ETA(252–608)). Sesen Bio is developing the drug, administered intravesically or intratumorally, as a treatment of high-risk non-muscle invasive bladder cancer (NMIBC) that is unresponsive to treatment with bacillus Calmette-Guérin (BCG). Oportuzumab monatox was granted FDA's Fast Track designation for the treatment of NMIBC.

Sesen Bio's rolling BLA submission for oportuzumab monatox for the treatment of BCG-unresponsive NMIBC was completed in December 2020, and accepted by FDA and granted Priority Review in February 2021. On August 13, 2021, the company announced that it received a Complete Response letter from the FDA in which the agency provided recommendations specific to additional clinical and statistical data and analyses, as well as CMC issues. Sesen Bio plans to work with FDA to address the concerns expressed in the letter. If another clinical trial is required, the company projects resubmitting the BLA in 2023.<sup>133</sup>

Sesen Bio submitted an MAA to the EMA for oportuzumab monatox for the treatment of high-risk, BCG-unresponsive NMIBC in March 2021, but withdrew the application in August 2021.<sup>134</sup>

### **Narsoplimab (Omeros Corporation)**

Narsoplimab (OMS721), a human IgG4λ anti-mannan-binding lectin-associated serine protease-2 (MASP-2) antibody, inhibits complement activation that occurs through the lectin pathway, and thereby can reduce thrombotic microangiopathy (TMA) plasma-mediated microvascular endothelial cell injury. Omeros is developing narsoplimab as a treatment for hematopoietic stem cell transplant (HSCT)-associated TMA, which is induced by factors, such as conditioning regimens and graft-vs-host disease, that are associated with stem cell transplantation. Narsoplimab was granted FDA's Breakthrough Therapy and Orphan Drug designations for HSCT-TMA, and Orphan Drug designation for HSCT in the EU. In October 2019, Omeros announced that they had initiated submission of a rolling BLA for narsoplimab for

HSCT-TMA. On October 18, 2021, Omeros announced that the company received a Complete Response letter regarding this BLA. Omeros had previously announced that the FDA notified them of deficiencies the agency had identified during the BLA review that precluded discussion of labeling and post-marketing requirements/commitments at that time.<sup>135</sup>

The effects of narsoplimab were evaluated in an uncontrolled, three-stage, dose-escalation cohort Phase 2 pivotal trial (NCT02222545) that included adults with thrombotic microangiopathies. The study's primary endpoints were improvement in laboratory markers and clinical status, as well as safety and tolerability. Data on 28 patients were shared on June 11, 2021, at the 26th Congress of the European Hematology Association.<sup>136</sup> Most (61%) patients responded to narsoplimab, with 74% showing improvement in any organ function and 67% showing improvement specifically in kidney function, and narsoplimab was well tolerated.

### **Donanemab (Eli Lilly)**

Donanemab (LY3002813) is a humanized IgG1κ antibody targeting Aβ, the main component of the extracellular plaques found in the brain of patients with AD. Donanemab binds specifically to N-terminally truncated pyroglutamate-modified Aβ (Aβ<sub>pE</sub>), also known as N3pG Aβ, a form of Aβ found in cerebral plaques only. Donanemab received FDA's Breakthrough Therapy designation for the treatment of AD based on results from the Phase 2 TRAILBLAZER-ALZ study. In the third quarter of 2021, Lilly initiated rolling submission of a BLA for donanemab for accelerated approval in early Alzheimer's disease.

Results from the placebo-controlled TRAILBLAZER-ALZ Phase 2 clinical trial (NCT03367403), which assessed the safety and efficacy of donanemab in patients with early AD, were published in May 2021.<sup>137</sup> Donanemab (700 mg for the first three doses and 1400 mg thereafter) was given IV every 4 weeks for up to 76 weeks to 131 patients, while 126 received placebo. The study's primary endpoint, change from baseline in the Integrated AD Rating Scale (iADRS) score in a time frame from baseline to 18 months, was met. The change from baseline in the iADRS score at 76 weeks was -6.86 for patients who received donanemab vs. -10.06 for those who received placebo (difference, 3.20; 95% CI: 0.12–6.27;  $P = 0.04$ ).<sup>137</sup>

Donanemab is currently undergoing safety and efficacy evaluation in two placebo-controlled Phase 3 studies, TRAILBLAZER-ALZ 2 (NCT04437511) in early, symptomatic AD patients and TRAILBLAZER-ALZ 3 (NCT05026866), which will enroll patients with preclinical AD and evaluate whether treatment with donanemab can slow or prevent the clinical progression of AD. The estimated enrollments for TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ 3 are 1,500 and 3,300 patients, respectively, and the estimated primary completion dates are in February 2023 and September 2027, respectively. The 2-arm Phase 3 TRAILBLAZER-ALZ 4 study (NCT05108922), which is investigating amyloid plaque clearance with donanemab compared with aducanumab-avwa in participants with early symptomatic AD, started in November 2021.

## Late-stage commercial clinical pipeline

As defined here, the late-stage commercial clinical pipeline includes novel antibody therapeutics that are currently undergoing evaluation in one or more pivotal Phase 2, Phase 2/3, or Phase 3 clinical studies sponsored by commercial firms, but have not transitioned to regulatory review or been approved in any country. Our assignment of clinical status is derived from information found on company websites and clinical trial registries. As mentioned above, to enable and facilitate comparison with data published in past ‘Antibodies to Watch’ articles, we have excluded data for antibody therapies for COVID-19 from the analyses and discussions below.

Even with molecules in development for COVID-19 excluded, our data show that the number of antibodies in late-stage development grew by over 30% in the past year, from 88 reported in ‘Antibodies to watch in 2021’,<sup>138</sup> to 115 as reported here (Supplemental Tables S1, S2). The indications most frequently studied were cancer (53%), immune-mediated disorders (22%) and cardiovascular/hemostasis disorders (10%), with all other indications comprising 5% or less each (Figure 5). As with the products that have advanced to regulatory review or are already approved in the US or EU, the late-stage antibody therapeutics pipeline is concentrated in two areas, cancer, and immune-mediated disorders, which comprise about three-quarters of the totals in both cases (Figures 1, 5).

Of those in late-stage clinical studies as treatments for cancer ( $n = 61$ ), the most frequently targeted antigens include the immune checkpoints PD-1, CTLA-4, PD-L1, TIGIT, as well as HER2, for monospecific antibodies and the combinations of CD20xCD3 and BCMAxCD3 for bispecific antibodies (Figure 6). PD-1 and HER2 are also frequent targets of the antibodies in review or approved in the US or EU (Figure 2). Notably, this group includes innovative antibodies that target at least 28 tumor-associated antigens or combinations of such antigens that are not represented among the antigens targeted by antibodies approved or in review in the US or EU and a substantial number of bispecific antibodies, half of which are T-cell engaging molecules, i.e., antibodies that target a tumor-associated antigen and CD3.

Of the antibodies in late-stage studies as treatments for noncancer indications ( $n = 54$ ), the most frequent targets include FcRn and PCSK9 (Figure 7). The targets are diverse, reflecting the broad range of diseases for which the antibodies are being studied as possible treatments.

### Antibodies to watch in 2022: noncancer indications

Based on the information publicly available as of November 1, 2021, 54 antibody therapeutics are in late-stage clinical studies for noncancer indications other than COVID-19 (Supplemental Table S2). Of these, BLA or MAA submissions for at least six (Table 5) are planned in 2022 (bentracimab, crovalimab, etrolizumab, gantenerumab, ligelizumab, nirsevimab).

#### Bentracimab (PhaseBio Pharmaceuticals, Inc.)

Bentracimab (PB2452) is a recombinant human antigen-binding fragment (Fab) (CH1(IgG1)/ $\lambda$ ) designed to reverse ticagrelor’s antiplatelet activity in patients who have major

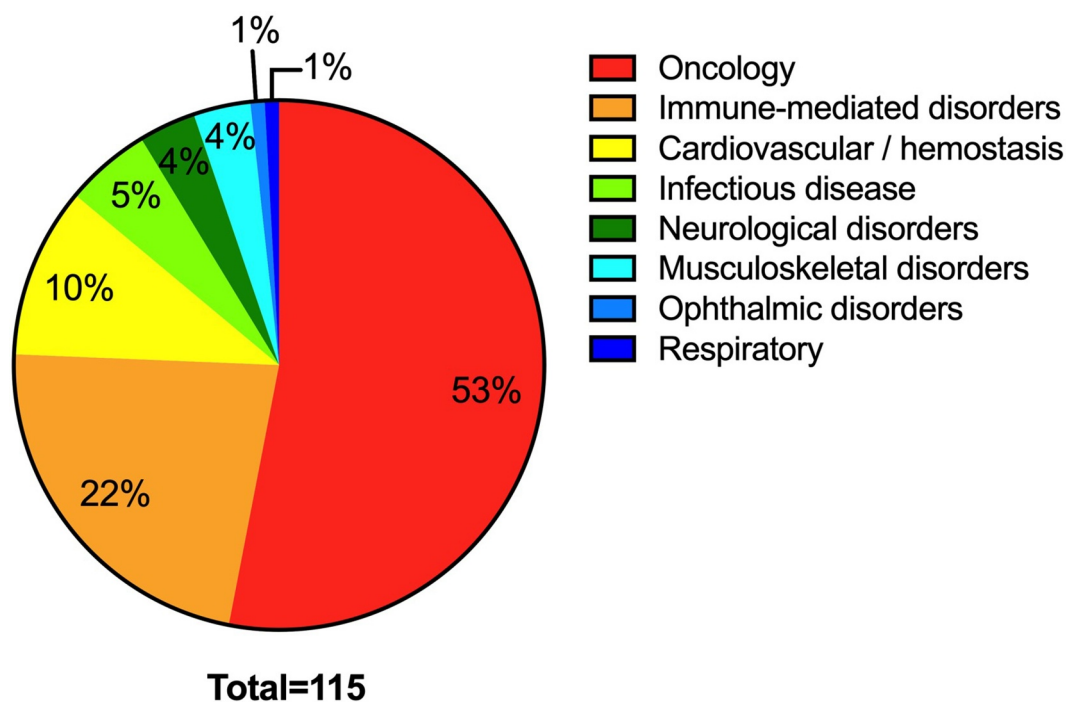
bleeding or need urgent surgery. Ticagrelor (Brilinta®) binds to the P2Y<sub>12</sub> receptor on platelets, preventing adenosine diphosphate (ADP)-induced platelet aggregation; bentracimab binds and sequesters free ticagrelor, favoring the drug’s clearance from the bloodstream, restoring ADP’s ability to bind the P2Y<sub>12</sub> receptor and induce platelet aggregation. Antibodies designed for small-molecule drug clearance are uncommon, with only one antibody, idarucizumab (Praxbind; Boehringer Ingelheim), approved for therapeutic use. If approved, bentracimab would thus be the second antibody marketed for this type of target.

PhaseBio in-licensed bentracimab from MedImmune in 2018, and then licensed rights to commercialize the drug in 49 European countries and other markets to Alfasigma S.p. A. in 2021. FDA has granted Breakthrough Therapy designation to bentracimab in 2019. Bentracimab was granted a PRIME designation by the EMA in 2020 for reversal of the antiplatelet effects of ticagrelor in patients with uncontrolled major or life-threatening bleeding or requiring urgent surgery or an invasive procedure. PhaseBio plans to submit a BLA for bentracimab to FDA by mid-2022.<sup>139</sup>

To support a BLA for bentracimab, PhaseBio is conducting the Phase 3 REVERSE-IT (Rapid and SustainEd ReVERSal of TicagrElor – Intervention Trial) trial (NCT04286438), a single-arm trial in which bentracimab is assessed in patients who present with uncontrolled major or life-threatening bleeding (Cohort 1) or who require urgent surgery or an invasive procedure (Cohort 2). Patients in the trial receive an initial IV bolus of 6 g infused over 10 min for rapid reversal, followed immediately by a 6 g IV loading infusion over 4 h and then a 6 g IV maintenance infusion over 12 h. In the case of patients with potential drug interaction from recent concomitant use of moderate or strong CYP3A inhibitors with ticagrelor, the dose may be increased to 36 g bentracimab administered over an active treatment period of 24 h and 10 min. The REVERSE-IT trial sites have completed enrollment in the surgery cohort, and shifted focus are enrolling patients with uncontrolled major or life-threatening bleeding events. The study achieved the primary reversal endpoint with immediate and sustained reversal of the antiplatelet effects of ticagrelor in both surgical and bleeding populations.<sup>139</sup>

#### Crovalimab (Chugai Pharmaceuticals, Roche)

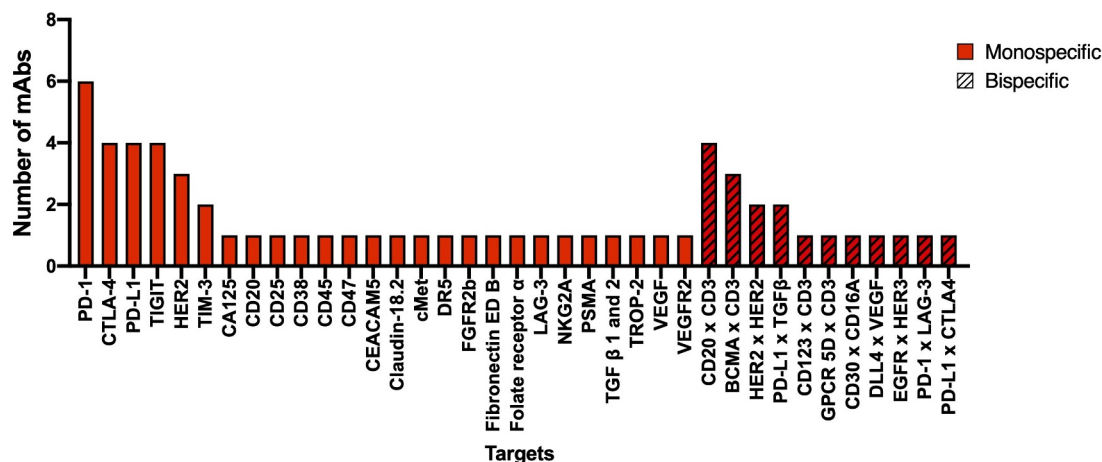
Crovalimab (RG6107, RO7112689, SKY59) is a humanized anticomplement C5 IgG1 $\kappa$  mAb designed to inhibit complement activation by blocking the cleavage of C5 into C5a and C5b. Crovalimab was developed by Chugai Pharmaceuticals using their Recycling Antibody® technology,<sup>140</sup> which allows a single antibody molecule to bind to antigen multiple times. The antibody is engineered to dissociate from the antigen in acidic conditions within the cell and to be recycled by FcRn while the antigen is transferred to lysosomes and degraded. In addition, crovalimab has been engineered to enhance FcRn binding and eliminate effector functions. As of a July 2021 update, Roche indicated that regulatory submissions for crovalimab as a treatment for paroxysmal nocturnal hemoglobinuria (PHN) may occur in 2022.<sup>141</sup>



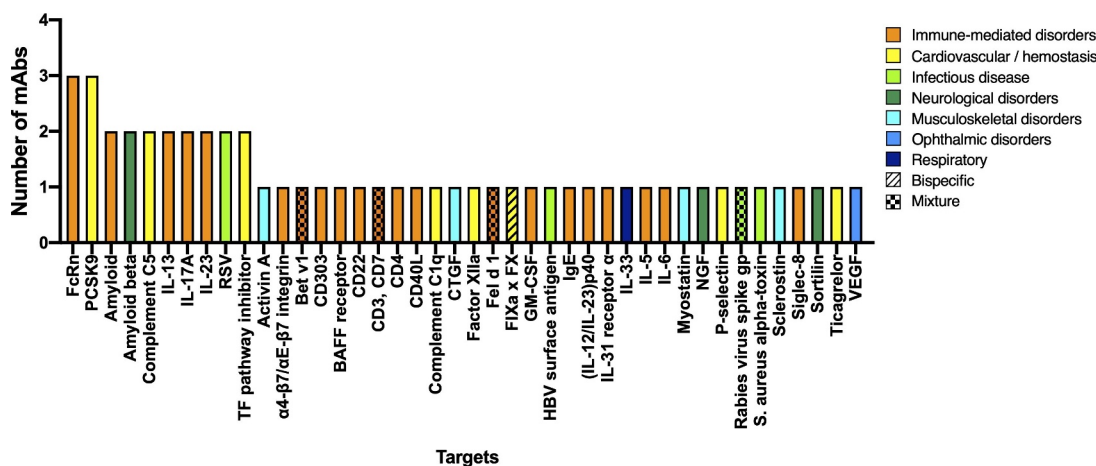
**Figure 5.** Primary indications for antibody therapeutics in late-stage clinical studies sponsored by commercial firms. 'Late-stage' is defined as pivotal Phase 2, Phase 2/3, or Phase 3 studies. Figure based on data publicly available as of November 15, 2021. Immune-mediated disorders category includes allergy and asthma; respiratory includes chronic obstructive pulmonary disease. Antibody therapeutics that have transitioned to regulatory review or been approved in any country, antibody therapeutics for COVID-19, biosimilar antibodies and Fc fusion proteins were excluded.

Crovalimab is currently undergoing evaluation in three Phase 3 clinical trials, COMMODORE 1, 2, 3 (NCT04432584, NCT04434092, NCT04654468, respectively), of patients with PHN. COMMODORE 1 and 2 are randomized, active-controlled trials evaluating the efficacy and safety of crovalimab versus eculizumab (SOLIRIS®) in children or adults with PNH. COMMODORE 1 is currently treated (COMMODORE 1) or not previously treated (COMMODORE 2) with complement inhibitors. COMMODORE 3 is a single-arm study evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of crovalimab in patients with PNH, not previously treated with

complement inhibitors. Crovalimab is administered at a dose of 1000 mg IV (for participants with body weight between 40 and 100 kg) or 1500 mg IV (for participants with body weight  $\geq 100$  kg) on Week 1 D 1. On Week 1 D 2 and on Weeks 2, 3 and 4, it will be administered at a dose of 340 mg SC. For Week 5 and Q4W thereafter, it will be administered at a dose of 680 mg SC (for participants with body weight between 40 and 100 kg) or 1020 mg SC (for participants with body weight  $\geq 100$  kg). Patients in the COMMODORE 1 and 2 active-control arm will be administered at eculizumab a dose of 900 mg every 2 weeks. The COMMODORE 1 primary



**Figure 6.** Targets for antibody therapeutics in late-stage clinical studies for cancer indications sponsored by commercial firms. 'Late-stage' is defined as pivotal Phase 2, Phase 2/3, or Phase 3 studies. Figure based on data publicly available as of November 15, 2021. Antibody therapeutics that have transitioned to regulatory review or been approved in any country, biosimilar antibodies and Fc fusion proteins were excluded. Abbreviations: BCMA, B-cell maturation antigen; CTLA-4, cytotoxic T lymphocyte antigen-4; DLL4, Delta-like ligand 4; GPCR, G-protein coupled receptor; HER, human epidermal growth factor receptor; PD-1 programmed cell death protein-1; PSMA, prostate-specific membrane antigen; TGF, transforming growth factor. See Supplemental Table S1 for additional information about the antibodies.



**Figure 7.** Targets for antibody therapeutics in late-stage clinical studies for noncancer indications sponsored by commercial firms. ‘Late-stage’ is defined as pivotal Phase 2, Phase 2/3, or Phase 3 studies. Figure based on data publicly available as of November 15, 2021. Antibody therapeutics that have transitioned to regulatory review or been approved in any country, antibody therapeutics for COVID-19, biosimilar antibodies and Fc fusion proteins were excluded. Abbreviations: HBV, hepatitis B virus; GM-CSF, granulocyte-macrophage colony-stimulating factor; NGF, nerve growth factor; PCSK9, proprotein convertase subtilisin/kexin; TF, tissue factor; VEGF, vascular endothelial growth factor. See Supplemental Table S2 for additional information about the antibodies.

**Table 5.** Investigational monoclonal antibodies in late-stage clinical studies for noncancer indications, with regulatory submission anticipated during 2021–2022.

INN	Target; Format	Indication of relevant late-stage study <sup>a</sup>	Status
Benracimab	Ticagrelor; Human IgG1 Fab	Reversal of the antiplatelet effects of ticagrelor	Phase 3
Crovalimab	Complement C5; Humanized IgG1	Paroxysmal nocturnal hemoglobinuria	Phase 3
Etolizumab	α4-β7/αE-β7 integrin receptor; Humanized IgG1	Crohn’s disease	Phase 3
Gantenerumab	Amyloid β; Human IgG1	Alzheimer’s disease	Phase 3
Ligelizumab	IgE; Humanized IgG1	Chronic spontaneous urticaria	Phase 3
Nirsevimab	RSV; Human IgG1	RSV infection	Phase 2/3

<sup>a</sup>Indication for which a regulatory submission is anticipated. See Supplemental Table S2 for more details about each antibody. Table includes information publicly available as of November 1, 2021. Abbreviation: RSV, respiratory syncytial virus.

endpoint is the non-inferiority of crovalimab compared with eculizumab based on mean percentage change in Lactate Dehydrogenase (LDH) levels (time frame: Baseline through Week 25), while the COMMODORE 2 and 3 primary end-points are based on the percentage of participants who achieve transfusion avoidance (Baseline through Week 25) and percentage of participants with hemolysis control (Week 2 through Week 25). The estimated primary completion dates for the COMMODORE 1 and 2 studies are in July 2022, and in December 2022 for COMMODORE 3.

Crovalimab is also undergoing evaluation in the Phase 3 COMMUTE-a (NCT04861259) and COMMUTE-p (NCT04958265) clinical trials of patients with atypical hemolytic uremic syndrome (aHUS). COMMUTE-a includes adolescent and adult (12 y and older) patients, while COMMUTE-p includes pediatric (up to 17 y old) patients. The primary completion date of the COMMUTE-a, which has an estimated enrollment of 90 patients, is March 2024. The COMMUTE-p study will enroll an estimated 35 patients and has an estimated primary completion date in December 2025.

### Etolizumab (Hoffmann-La Roche)

Etolizumab (RO5490261, rhuMAb beta7, RG7413, PRO 145223) is a humanized IgG1κ antibody that targets the β7 subunit common to the integrins α4-β7 and αE-β7 that was developed by Genentech, a member of the Roche Group.

Etolizumab was undergoing evaluation in Phase 3 studies in patients with ulcerative colitis (HIBISCUS I and II (NCT02163759 and NCT02171429), HICKORY (NCT02100696) and LAUREL (NCT02165215)), but results of the studies were inconsistent. As of a July 2021 update, Roche is considering etolizumab for Crohn’s disease as a possible regulatory submission in 2022.<sup>142</sup> The FDA granted etolizumab Orphan Drug designation for pediatric Crohn’s disease.

The placebo-controlled Phase 3 BERGAMOT study (NCT02394028) evaluated etolizumab as an induction and maintenance treatment in adult patients with moderate-to-severely active Crohn’s disease with and without prior anti-TNF treatment. The study had three arms: (1) Etolizumab SC 210 mg (induction only); (2) Etolizumab SC 105 mg and maintenance; and (3) Placebo. The BERGAMOT study enrolled 1150 patients and was completed in September 2021.

Recruitment for an open-label extension and safety monitoring study for BERGAMOT, JUNIPER (NCT02403323), is ongoing. Patients are administered 105 mg etolizumab SC every 4 weeks. The estimated enrollment for the JUNIPER study is 900 patients, and the estimated primary completion date is May 2026.

### Gantenerumab (Roche)

Gantenerumab (RO4909832, RG1450) is a human IgG1κ mAb directed against a conformational epitope of Aβ that includes both N terminal and central amino acids. The antibody



preferentially binds aggregated forms of A $\beta$ , such as oligomers and plaques, removing them via microglia-mediated phagocytosis. Gantenerumab was generated by MorphoSys using their HuCAL technology, and, under a licensing agreement, Roche is responsible for clinical development and commercialization. Gantenerumab was granted FDA's Breakthrough Therapy designation for the treatment of AD. Roche is planning to submit marketing applications in 2022.

Unlike aducanumab (Aduhelm), which was recently approved by FDA for AD, gantenerumab is formulated for SC administration. Gantenerumab demonstrated the capacity to lower brain amyloid plaques in patients with prodromal-to-moderate AD in the Phase 3 SCARlet RoAD (NCT01224106) and Marguerite RoAD (NCT02051608) open-label extension (OLE) studies, with continuous reduction of amyloid plaque levels below the amyloid positivity threshold at 36 months.<sup>143</sup> Patients received SC doses of up to 1200 mg gantenerumab every 4 weeks in the OLE studies, and the results informed the design of the GRADUATE 1 and 2 studies (NCT03444870 and NCT03443973, respectively), which are two parallel, global, placebo-controlled and randomized Phase 3 trials evaluating the safety and efficacy of gantenerumab in patients with early (prodromal to mild) AD. The primary endpoint of the studies is the change from baseline to Week 116 in Global Outcome, as measured by Clinical Dementia Rating-Sum of Boxes. The primary completion dates of GRADUATE 1 and 2 are in May and September 2022, respectively.

Gantenerumab and an anti-A $\beta$  antibody developed by Eli Lilly and Company, solanezumab, were evaluated in patients with dominantly inherited AD in the placebo-controlled Phase 2/3 DIAN-TU-001 study (NCT01760005), which was sponsored by Washington University School of Medicine and included Hoffmann-La Roche and Eli Lilly and Company as collaborators. No beneficial effect on cognitive measures was observed in either the gantenerumab ( $n = 52$ ) or the solanezumab study arms ( $n = 52$ ) when compared to the placebo arm ( $n = 40$ ), but gantenerumab significantly reduced amyloid plaques. Improvement in downstream biomarkers in patients treated with gantenerumab support the possibility of preventing or slowing AD progression via amyloid lowering, especially at the early stages of the disease.<sup>144</sup>

### **Ligelizumab (Novartis Pharmaceuticals Corporation)**

Ligelizumab (QGE031) is a humanized anti-IgE IgG1 $\kappa$  antibody in development for chronic spontaneous urticaria (CSU). The FDA granted ligelizumab Breakthrough Therapy designation for the treatment of CSU in patients who have an inadequate response to H1-antihistamine treatment. Novartis is planning to file regulatory submissions for ligelizumab for CSU in 2022.<sup>145</sup>

The safety and efficacy of ligelizumab compared with omalizumab (XOLAIR®) are currently being investigated in ongoing Phase 3 clinical trials, including PEARL 1 and PEARL 2 (NCT03580369 and NCT03580356). PEARL 1 and PEARL 2 are active- and placebo-controlled studies with four arms (72 mg or 240 mg ligelizumab; 300 mg omalizumab; or placebo, with dosing once every 4 weeks). Omalizumab is FDA-approved for CSU, with a recommended dose of 150 or

300 mg SC every 4 weeks. For both studies, the primary outcome measure is the absolute change from baseline in the Urticaria Activity Score 7 at Week 12. The enrollments for PEARL 1 and PEARL 2 were 1072 and 1079 patients, respectively, and the primary completion dates were in July and June 2021, respectively. Read-out from these studies is expected in the second half of 2021.<sup>145</sup>

### **Nirsevimab (AstraZeneca, Sanofi)**

Nirsevimab (MEDI8897) is an anti-respiratory syncytial virus (RSV) human IgG1 $\kappa$  antibody with an Fc that was modified using AstraZeneca's proprietary YTE half-life extension technology. Developed by AstraZeneca and Sanofi, nirsevimab is administered as a single dose to infants experiencing their first RSV season, and infants with congenital heart disease or chronic lung disease entering their first and second RSV seasons, to prevent RSV infection. Nirsevimab has received numerous regulatory agency designations intended to facilitate development and review, including Promising Innovative Medicine designation from the UK Medicines and Healthcare Products Regulatory Agency; Breakthrough Therapy designation from China's NMPA; FDA's Breakthrough Therapy designation for the prevention of lower respiratory tract infection caused by RSV, and EMA's PRIME designation for the same indication.

Under the terms of an agreement announced in March 2017, AstraZeneca leads all development and manufacturing activities and Sanofi will lead commercialization activities and record revenues. AstraZeneca also has an agreement with Swedish Orphan Biovitrum AB regarding certain rights to payments relating to milestones and US profits or losses for nirsevimab. AstraZeneca has indicated that they plan regulatory submissions in 2022 for nirsevimab based on results of the Phase 3 MELODY and Phase 2/3 MEDLEY clinical trials.

The placebo-controlled Phase 3 MELODY trial (NCT03979313) is evaluating the safety and efficacy of nirsevimab for the prevention of medically attended RSV lower respiratory tract infections in healthy late preterm and term infants (i.e., born at 35 weeks 0 d or greater gestational age). Participants up to 1 y of age were included. After randomized (2:1), the infants received a single 50 mg (<5 kg body weight) or 100 mg (>5 kg body weight) IM injection of nirsevimab or placebo. Approximately 1,500 infants were dosed with either nirsevimab or placebo between July 2019 and February 2021. In April 2021, AstraZeneca announced that the study met its primary endpoint of a statistically significant reduction in the incidence of medically attended lower respiratory tract infections caused by RSV compared to placebo in trial participants during their first RSV season.<sup>146</sup>

The active-controlled Phase 2/3 MEDLEY study (NCT03959488) evaluated the safety and tolerability of nirsevimab compared to palivizumab when administered to preterm infants entering their first RSV season and children with CLD and CHD entering their first and second RSV season. Participants up to 1 y of age were included. Safety is assessed by monitoring the occurrence of treatment-emergent adverse events or treatment-emergent serious adverse events through 360 d post-dose. Approximately 925 infants entering their first

RSV season were included in the study. In June 2021, AstraZeneca announced that the monitored safety signals were similar between the two study arms.<sup>147</sup>

### Antibodies to watch in 2022: cancer indications

Based on the information publicly available as of November 1, 2021, 61 antibody therapeutics are in late-stage clinical studies for cancer indications (Supplemental Table S1). Of these, BLA or MAA submissions for at least 16 are planned (Table 6). In particular, marketing applications for mosunetuzumab and tremelimumab may be submitted by the end of 2021, and regulatory submissions for magrolimab, mirvetuximab soravtansine, glofitamab, zolbetuximab, tiragolumab, zanidatamab, REGN5458, talquetamab, teclistamab, odronextamab, sabatolimab, cosibelimab, apamistamab-I-131, and erfonrilimab may occur during 2022.

#### Mosunetuzumab (Genentech)

Mosunetuzumab (RG7828, BTCT4465A) is an aglycosylated (N297G) humanized IgG1 $\kappa$  bispecific antibody constructed using knobs-into-holes technology. The antibody targets CD20 and CD3, and redirects T cells to eliminate malignant B cells while avoiding the destruction of engaged T cells. In July 2020, the FDA granted Breakthrough Therapy designation for mosunetuzumab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies. Roche plans to file a regulatory application for mosunetuzumab as a treatment (3 L+) for FL by the end of 2021.

The safety and efficacy of mosunetuzumab as a single agent or in combination with other agents is being evaluated in 4 Phase 1/2 studies of patients with lymphomas. Preliminary results for patients with relapsed or refractory FL who participated in the Phase 1/2 GO29781 study (NCT02500407) were reported in November 2020. In this study, patients received mosunetuzumab via IV or SC injection as a single-agent or in combination with atezolizumab at 1200 mg (IV). For all patients ( $n = 62$ ), the overall response rate was 68%, with 31 patients (50%) achieving CR.<sup>148</sup>

Early data from the ongoing Phase 1/2 GO40516 study (NCT03671018) of mosunetuzumab in combination with polatuzumab vedotin in patients with B-cell NHL showed promising efficacy and an acceptable safety profile. The median follow-up duration was 9.6 (0.7–23.7) months. For all patients ( $n = 22$ ), the overall response rate and CR were 68.2% and 54.5%, respectively, but both rates were 100% for patients with FL ( $n = 3$ ).<sup>149</sup>

Mosunetuzumab is also being investigated in combination with lenalidomide vs. rituximab + lenalidomide in relapsed or refractory FL in a Phase 3 trial (GO42909, NCT04712097). An estimated 400 patients will be randomized to receive IV mosunetuzumab or rituximab IV in combination with oral lenalidomide. The primary outcome measure is PFS. Initiated in July 2021, the estimated primary completion date is May 2029.

#### Tremelimumab (AstraZeneca)

Tremelimumab (CP-675,206) is a human IgG2 $\kappa$  antibody targeting CTLA-4 originally developed by Pfizer. In 2011, AstraZeneca's subsidiary MedImmune gained global development rights to tremelimumab, but Pfizer retained the rights for use in certain combination therapies. By modulating an immune checkpoint, tremelimumab may find application as a treatment for numerous types of cancer, and it has been evaluated as part of combination therapy in late-stage clinical studies of patients with NSCLC, HCC, small cell lung cancer, bladder cancer, and renal cell carcinoma. Tremelimumab and anti-PD-L1 durvalumab (Imfinzi®, MEDI-4736) were granted Orphan Drug designations in the US for the treatment of HCC, and tremelimumab was also granted Orphan designation for HCC in the EU. AstraZeneca reported that they plan regulatory submissions for tremelimumab in combination with durvalumab as first-line therapy of NSCLC and HCC in Q4 2021 and H1 2022, respectively.<sup>28</sup>

Positive results from the 3-arm, randomized Phase 3 POSEIDON trial (NCT03164616), which evaluated the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for first-line treatment in patients with Stage 4 NSCLC, were presented at the World Conference on Lung Cancer held September 8–14, 2021. Treatment-naïve patients with EGFR/anaplastic large-cell lymphoma kinase (ALK) wild-type metastatic NSCLC were randomized (1:1:1) to receive (1) durvalumab (1500 mg) + chemotherapy Q3W for 4 cycles followed by durvalumab (1500 mg) every 4 weeks until progression; (2) durvalumab (1500 mg) + tremelimumab (75 mg) concurrently with chemotherapy Q3W for up to 4 cycles, followed by durvalumab (1500 mg) every 4 weeks until progression, with one additional dose of tremelimumab post chemotherapy (5th dose); or (3) chemotherapy Q3W for up to 6 cycles. Standard of care chemotherapy options included platinum + pemetrexed, platinum + gemcitabine or carboplatin + nab-paclitaxel, with the selection based on the patients' histology. Both overall survival and PFS were statistically significantly improved with the combination of durvalumab + tremelimumab and chemotherapy versus chemotherapy alone. The median overall survival was 14.0 months versus 11.7 months and the median PFS was 6.2 months versus 4.8 months for the combination vs. chemotherapy alone, respectively.<sup>28</sup>

Positive results have also been reported for the 4-arm Phase 3 HIMALAYA trial (NCT03298451), which evaluated durvalumab plus tremelimumab as first-line treatment of unresectable HCC.<sup>28</sup> One arm of the study evaluated the STRIDE regimen, comprising a single priming dose of 300 mg tremelimumab added to durvalumab (1500 mg) followed by durvalumab every 4 weeks. The other three study arms were as follows: (1) durvalumab only; (2) sorafenib only; and (3) an alternate regimen of the durvalumab plus tremelimumab combination. The primary endpoint, overall survival from the date of randomization until death due to any cause assessed up to 4 y, of the study was met. A single, high priming dose of tremelimumab added to Imfinzi demonstrated a statistically significant and clinically meaningful overall survival benefit versus sorafenib

**Table 6.** Investigational monoclonal antibodies in late-stage clinical studies for cancer indications, with regulatory submission anticipated during 2021–2022.

INN	Target(s); Format	Indication of relevant <sup>a</sup> late-stage study	Status
Mosunetuzumab	CD20, CD3; Humanized IgG1 bispecific	Follicular lymphoma	Phase 3
Tremelimumab	CTLA-4; Human IgG2	Non-small cell lung cancer	Phase 3
Magrolimab	CD47; Humanized IgG4	Myelodysplastic syndrome	Phase 3
Mirvetuximab soravtansine	FR $\alpha$ ; Humanized IgG1 ADC	Ovarian cancer	Phase 3
Gloftamab	CD20, CD3e; IgG1 bispecific	Diffuse large B-cell lymphoma	Phase 3
Zolbetuximab	Claudin-18.2; Chimeric IgG1	Gastric and gastro-esophageal junction adenocarcinoma	Phase 3
Tiragolumab	TIGIT; Human IgG1	Small cell lung cancer	Phase 3
Zanidatamab	HER2, HER2; Humanized IgG1 bispecific	Biliary tract cancer	Pivotal Phase 2
REGN5458	BCMA, CD3; Human bispecific	Multiple myeloma	Pivotal Phase 2
Talquetamab	GPRC5D, CD3; Humanized IgG4 bispecific	Multiple myeloma	Pivotal Phase 2
Teclistamab	BCMA, CD3; Humanized/human IgG4 bispecific	Multiple myeloma	Phase 3 pending
Odronextamab	CD20, CD3; Human IgG4 bispecific	Non-Hodgkin's lymphoma	Pivotal Phase 2
Sabatolimab	TIM-3; Humanized IgG4	Myelodysplastic syndrome	Phase 3
Cosibelimab	PD-L1; Human IgG1	Squamous cell carcinoma	Phase 3
Iodine (131I) apamistamab	CD45; Murine IgG1, radiolabeled	Acute myeloid leukemia	Phase 3
Efonrilimab	PD-L1, CTLA-4; Humanized/chimeric IgG1 bispecific	Non-small cell lung cancer	Phase 3

<sup>a</sup>Indication for which a regulatory submission is anticipated. See Supplemental Table S1 for more details about each antibody. Table includes information publicly available as of November 1, 2021. Abbreviations: BCMA, B-cell maturation antigen; CTLA-4, cytotoxic T lymphocyte antigen-4; FR, folate receptor; GPRC5D, G protein-coupled receptor class C group 5 member D; HER2, human epidermal growth factor receptor 2; 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 domain-containing molecule-3.

as a first-line treatment for patients not eligible for localized treatment. Durvalumab alone demonstrated non-inferior overall survival to sorafenib.

### Magrolimab (Gilead Sciences, Inc.)

Magrolimab (Hu5F9-G4) is a humanized IgG4 $\kappa$  antibody blocking CD47, a macrophage immune checkpoint and 'don't eat me' signal expressed by leukemic cells. Blocking the CD47/SIRP $\alpha$  interaction inhibits the negative phagocytic signal leading to engulfment and elimination of leukemic cells. Originally developed at Stanford University, the antibody was licensed by Forty Seven, Inc., which was acquired by Gilead in 2020. FDA has granted magrolimab Breakthrough Therapy designation for four hematologic malignancies: myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), relapsed/refractory diffuse large B cell lymphoma (DLBCL) and FL. Magrolimab was also granted Orphan Drug designation by the FDA for MDS and AML and by the EMA for MDS. Gilead anticipates a potential BLA submission for magrolimab for accelerated approval in MDS in the first quarter of 2022.<sup>150</sup>

Magrolimab is currently being studied in a randomized, double-blind, placebo-controlled, multicenter Phase 3 trial (ENHANCE; NCT04313881) to evaluate its efficacy in combination with azacitidine vs. azacitidine plus placebo in previously untreated patients with intermediate-/high-/very high-risk MDS. In this study, participants were randomized to receive either magrolimab IV for three cycles (Cycle 1: 1 mg/kg priming dose on D 1 and 4; 15 mg/kg on D 8; and 30 mg/kg on D 11, 15, and 22; Cycle 2: weekly doses of 30 mg/kg on D 1, 8, 15, and 22; Cycle 3 and onward: 30 mg/kg every 2 weeks on D 1 and 15) or placebo in combination with azacitidine. The primary outcome measures are the proportion of participants with CR and overall survival. The primary completion date is August 2022.

Magrolimab is also being evaluated in a late-stage clinical study as a potential treatment for patients with AML. A Phase 3, randomized, open-label study (ENHANCE-2,

NCT04778397) evaluating the safety and efficacy of magrolimab in combination with azacitidine versus physician's choice of venetoclax in combination with azacitidine or intensive chemotherapy in previously untreated patients with tp53 mutant AML was initiated in July 2021. The primary completion date is September 2023. Another Phase 3 study in AML patients (ENHANCE-3, NCT05079230) has an estimated study start date in December 2021.

### Mirvetuximab soravtansine (ImmunoGen, Inc.)

Mirvetuximab soravtansine (IMGN853), comprising a humanized folate receptor alpha (FR $\alpha$ ) IgG1 $\kappa$  antibody conjugated to the maytansinoid drug DM4 via a cleavable disulfide linker, is being developed by ImmunoGen as a treatment for epithelial malignancies, including ovarian cancer adenocarcinoma. The drug has been granted US and EU Orphan Drug designations for ovarian cancer, as well as FDA's Fast Track designation for a specific subset of patients with medium to high FR $\alpha$ -positive platinum-resistant ovarian cancer who received at least one, but no more than three prior systemic treatment regimens, and for whom single-agent chemotherapy is appropriate as the next line of therapy. ImmunoGen anticipates submission of a BLA in the first quarter of 2022, with potential accelerated approval in 2022.<sup>151</sup>

Data from the treatment arms of the Phase 1b/2 FORWARD II study (NCT02606305) that evaluated mirvetuximab in combination with Avastin® (bevacizumab) in patients with medium and high FR $\alpha$ -expressing recurrent ovarian cancer for whom a non-platinum-based combination regimen is appropriate were presented at the 2021 American Society of Clinical Oncology Virtual Annual Meeting.<sup>152</sup> A total of 60 patients (32 with platinum-resistant and 28 with platinum-sensitive disease) received mirvetuximab soravtansine (6 mg/kg; adjusted ideal body weight) and bevacizumab (15 mg/kg) on D 1 of a 21-d cycle. The confirmed overall response rate was 64%, and the median duration of response and median PFS were 11.8 months and 10.6 months, respectively, in patients



with high FRa recurrent ovarian cancer, regardless of platinum status. For all patients, the confirmed overall response rate was 47%, and the median duration of response and median PFS were 9.7 months and 8.3 months, respectively.

ImmunoGen has completed accrual in the pivotal Phase 3 SORAYA study (NCT04296890) and further enrolled patients in the confirmatory MIRASOL study (NCT04209855). The single-arm SORAYA trial is evaluating the efficacy and safety of mirvetuximab soravtansine in patients with platinum-resistant high-grade serous epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer, whose tumors express a high-level of FRa, who receive mirvetuximab soravtansine (6 mg/kg adjusted ideal body weight) administered on D 1 of every 3-week cycle. ImmunoGen expects to release top-line data from the SORAYA study in the fourth quarter of 2021.<sup>151</sup>

### **Glofitamab (Hoffmann-La Roche)**

Glofitamab (RO7082859, CD20-TCB, RG6026) is a full-length IgG1 $\lambda$ / $\kappa$ , asymmetric 2:1 CrossMab.<sup>153</sup> Like mosunetuzumab, which is also being developed by Roche, glofitamab is a bispecific T-cell engaging antibody that targets CD20 and CD3. The two molecules, however, are structurally distinct. While mosunetuzumab includes two antigen-binding fragments (Fabs), one targeting CD20 and another that targets CD3, glofitamab has a total of 3 Fabs, two that targeting CD20 (derived from the Type II CD20 IgG1 obinutuzumab), with one of the CD20 Fabs fused to an anti-CD3 $\epsilon$  Fab via a flexible linker. It also has an engineered heterodimeric Fc region with LALAPG mutations, which abolishes binding to Fc $\gamma$  Rs and C1q.<sup>154</sup> Roche has indicated that they may submit marketing applications for glofitamab as a treatment for diffuse large B-cell lymphoma (DLBCL, 3 L+) in 2022.

Roche is currently sponsoring seven Phase 1 or Phase 1/2 studies of glofitamab in lymphoma patients. Preliminary results of the first-in-humans study NP30179 (NCT03075696) have been reported.<sup>155</sup> This study is evaluating the safety, efficacy, tolerability, and pharmacokinetics of escalating doses of glofitamab as a single agent and in combination with obinutuzumab (Gazyva®/Gazyvaro™) administered after a fixed, single-dose pretreatment of obinutuzumab in patients with relapsed/refractory B-cell NHL. Results were reported for only the monotherapy part of the study. All patients were pretreated with 1 g obinutuzumab, and then received up to 25 mg glofitamab administered IV. Among patients with aggressive disease, the overall response rate and CR were 48.0% (61/127) and 33.1% (42/127), respectively, including 41.1% (30/73) and 28.8% (21/73) in DLBCL patients. Clinical activity increased with increasing doses. At doses of 10 mg or more, the overall response rate and CR were 60.9% (42/69) and 49.3% (34/69), respectively, including 55.3% (21/38) and 42.1% (16/38) for DLBCL patients.

Glofitamab is undergoing evaluation in a randomized, open-label, multicenter Phase 3 study (NCT04408638) of glofitamab or rituximab in combination with gemcitabine + oxaliplatin (GemOx) for the treatment of patients with relapsed or refractory DLBCL. In this study, participants will receive up to 8 cycles of glofitamab IV or rituximab IV in combination with

GemOx IV followed by up to 4 cycles of glofitamab monotherapy. The primary outcome measure is the overall survival. The estimated primary completion date is March 2022.

### **Zolbetuximab (Astellas)**

Zolbetuximab (IMAB362) is a chimeric IgG1 $\kappa$  antibody targeting claudin 18.2 (CLDN18.2), developed by Astellas. In normal tissue, the expression of CLDN18.2 is confined to tight junctions of the gastric mucosa, but in malignant cells, due to changes in cell polarity, the epitopes of CLDN18.2 are exposed on the cancer cell surface. Preclinical data showed that zolbetuximab triggers tumor cell death via ADCC and CDC mechanisms.<sup>156</sup> Zolbetuximab was originally developed by Ganymed Pharmaceuticals AG, which was acquired by Astellas in 2016. Astellas expects to submit marketing applications for zolbetuximab as a treatment for gastric and GEJ adenocarcinoma during the 2022 fiscal year, which starts in April 2022. Orphan drug designation was granted to zolbetuximab for this indication in the EU.

Preliminary results were recently reported for two Phase 2 studies (FAST, ILUSTRO) that evaluated zolbetuximab in combination with chemotherapy in patients with CLDN18.2-positive advanced gastric/GEJ cancer. In the FAST study (NCT01630083), zolbetuximab was evaluated in combination with epirubicin, oxaliplatin, and capecitabine.<sup>156</sup> Zolbetuximab was administered as a loading dose of either 800 or 1000 mg/m<sup>2</sup>, then 600 mg/m<sup>2</sup> Q3W. PFS (HR = 0.44; 95% CI: 0.29–0.67;  $P < 0.0005$ ) and overall survival (HR = 0.55; 95% CI: 0.39–0.77;  $P < 0.0005$ ) were significantly improved in patients who received zolbetuximab. In the ILUSTRO study (NCT03505320), zolbetuximab is being evaluated as monotherapy, in combination with modified FOLFOX6 (mFOLFOX6) (with or without nivolumab) and in combination with pembrolizumab. In cohort 2 of the study, patients received zolbetuximab 800 mg/m<sup>2</sup> IV on Cycle 1 D 3 then 600 mg/m<sup>2</sup> Q3W, as well as the mFOLFOX6 chemotherapy. Of 19 evaluable patients, 12 had confirmed partial responses, the median PFS was 13.7 months (95% CI: 7.4–not estimable) and the 12-month PFS rate was 58%.<sup>157</sup>

Zolbetuximab is now being investigated for the treatment of locally advanced unresectable gastric and GEJ adenocarcinoma in two Phase 3 studies (SPOTLIGHT, GLOW) with primary completion dates in February and June 2022, respectively. The randomized, double-blind, multicenter Phase 3 SPOTLIGHT trial (NCT03504397) is studying the efficacy and safety of zolbetuximab plus mFOLFOX6 with placebo plus mFOLFOX6 in patients with unresectable or metastatic CLDN18.2-positive, HER2-negative gastric/GEJ cancer. In the study, ~550 participants will receive zolbetuximab 800 mg/m<sup>2</sup> IV on Cycle 1 D 1 (loading dose), then 600 mg/m<sup>2</sup> IV Q3W or placebo. Additionally, participants will receive up to 12 treatments of mFOLFOX6 (or components of mFOLFOX6 if some components are discontinued due to toxicity) over 4 or more cycles (each cycle is approximately 42 d) in which mFOLFOX6 is administered on D 1, 15 and 29. The primary outcome measure is PFS.



The Phase 3 GLOW trial (NCT03653507) is comparing zolbetuximab + capecitabine/oxaliplatin (CAPOX) vs. placebo + CAPOX in the same patient population. Zolbetuximab will be administered as an 800-mg/m<sup>2</sup> IV loading dose followed by 600 mg/m<sup>2</sup> Q3W. The ~500 participants will also receive CAPOX (capecitabine/oxaliplatin) treatment until disease progression or a total of 8 treatments. Oxaliplatin is administered on D 1 of each cycle, whereas capecitabine is taken twice daily on D 1 through 14. As in SPOTLIGHT trial, the primary outcome measure is PFS.

### **Tiragolumab (Genentech, a member of the Roche Group)**

Tiragolumab (MTIG7192A, RO7092284, RG6058) is a human IgG1κ mAb targeting T-cell Immunoreceptor with Ig and ITIM domains (TIGIT). TIGIT is an inhibitory immune check-point expressed on activated and exhausted T cells, regulatory T cells, and natural killer (NK) cells, making it a relevant target in multiple cancers. Blocking TIGIT's binding to its ligand, poliovirus receptor (CD155), enhances T and NK cell functionality.<sup>158</sup> Roche has indicated that they may submit marketing applications for tiragolumab in combination with anti-PD-L1 atezolizumab (Tecentriq®) as first-line treatment of small cell lung cancer in 2022.

The combination of tiragolumab and atezolizumab is currently being evaluated in two Phase 3 studies (SKYSCRAPER-02, SKYSCRAPER-02 C) of patients with untreated extensive-stage small cell lung cancer. SKYSCRAPER-02 (NCT04256421) is a randomized, double-blind, placebo-controlled study of atezolizumab plus carboplatin and etoposide with or without tiragolumab in patients with untreated extensive-stage small cell lung cancer. Participants receive either tiragolumab 600 mg in IV infusion Q3W or placebo in combination with atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W + carboplatin and etoposide by IV on a 21-d cycle for 4 cycles. Following the induction phase, participants will continue maintenance therapy with tiragolumab plus atezolizumab or atezolizumab plus placebo. SKYSCRAPER-02 C (NCT04665856) has the same design, but study sites are located only in China. The primary outcome measures are PFS and overall survival. Both studies were initiated in February 2020 and have estimated primary completion dates in September 2023.

Tiragolumab is also under investigation in the SKYSCRAPER-01 trial (NCT04294810), which was designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in participants with previously untreated locally advanced, unresectable or metastatic PD-L1-selected NSCLC, with no EGFR mutation or ALK translocation. The participants receive atezolizumab 1200 mg by IV infusion followed by tiragolumab 600 mg IV or placebo Q3W on D 1 of each 21-d cycle until disease progression, loss of clinical benefit or unacceptable toxicity. Initiated in March 2020, the estimated primary completion date in August 2022. The FDA granted Breakthrough Therapy designation for tiragolumab in combination with anti-PD-L1 atezolizumab for first-line treatment of people with metastatic NSCLC whose tumors have high PD-L1 expression with no EGFR or ALK genomic tumor aberrations.

### **Zanidatamab (Zymeworks Inc., BeiGene)**

Zanidatamab (ZW25) is a humanized anti-HER2 bispecific IgG1-like antibody derived from the proprietary Azymetric platform. Developed by Zymeworks, the antibody is biparatopic, simultaneously binding different epitopes of HER2 (ECD4, the trastuzumab binding domain, and ECD2, the pertuzumab binding domain), which is overexpressed in many cancers. The FDA granted Breakthrough Therapy designation for zanidatamab for biliary tract cancer (BTC), as well as two Fast Track designations, one for previously treated or recurrent HER2-positive BTC and another for first-line gastroesophageal adenocarcinoma in combination with standard of care chemotherapy. Zanidatamab also received Orphan Drug designation for the treatment of BTC, gastric and ovarian cancers from the FDA and for gastric cancer from the EMA. Zymeworks is targeting BLA submission for zanidatamab for BTC in 2022.

BeiGene acquired exclusive development and commercial rights to zanidatamab in Asia (excluding Japan), Australia, and New Zealand in 2018. The companies are collaborating on joint global development for selected indications.

Preliminary results of an ongoing first-in-human, 3-part study (NCT02892123) to investigate the effects of zanidatamab as monotherapy and combined with selected chemotherapy agents in patients with locally advanced (unresectable) and/or metastatic HER2-expressing cancers indicated that zanidatamab is well tolerated and has durable antitumor activity in patients with HER2-overexpressing BTC. In this study, zanidatamab is administered at 20 mg/kg every 2 weeks. As of the data cutoff date (Jul 28, 2020), 20 patients with BTC had been treated with zanidatamab, with 17 evaluable for response. Among these, the confirmed objective response rate was 47% ( $n = 8$ ; 95% CI: 23–72), the disease control rate was 65% ( $n = 11$ ; 95% CI: 38–86) and the median duration of response was 6.6 months (95% CI: 3.2–not estimable).<sup>159</sup>

Zymeworks and BeiGene initiated a pivotal Phase 2b study (HERIZON-BTC-01, NCT04466891) to evaluate the antitumor activity of zanidatamab in patients with HER2-amplified, inoperable and advanced or metastatic BTC, including gallbladder cancer and cholangiocarcinoma. In this multicenter, open-label, single-arm trial, patients will receive 20 mg/kg zanidatamab IV every 2 weeks until one of the treatment discontinuation criteria is met. The primary endpoint of the study is the confirmed objective response rate. The estimated primary completion date is July 2022.

In September 2021, Zymeworks announced data from a Phase 2 study (NCT03929666) of zanidatamab plus combination chemotherapy in HER2-expressing gastrointestinal cancers, including gastroesophageal adenocarcinoma (GEA), biliary tract cancer, and colorectal cancer, showing an encouraging confirmed objective response rate (75% overall and 93% for the proposed Phase 3 regimen of zanidatamab + CAPOX/FP). The median duration of response and median PFS were 16.4 months and 12 months, respectively.<sup>160</sup> Based on these results, Zymeworks and BeiGene initiated a randomized, Phase 3 study (HERIZON-GEA-01) that will evaluate zanidatamab plus chemotherapy (CAPOX or FP) with or without

tislelizumab, versus standard of care (trastuzumab plus chemotherapy), for first-line treatment of locally advanced, unresectable, or metastatic HER2-positive GEA.

### **REGN5458 (Regeneron Pharmaceuticals, Inc.)**

REGN5458 is a human, T-cell engaging IgG4 bispecific antibody derived from Regeneron's VelocImmune® 'human antibody mouse' technology and its VelociBi™ platform. The antibody contains a mutation (S228P) to stabilize the hinge region, substitutions to minimize Fc effector functions, and, to assist purification, binding to Protein A was limited via a mutation on the CD3 Fc (Supplemental Table S1). The molecule is designed to bind to B-cell maturation antigen (BCMA) overexpressed on MM cells and CD3 on T cells in order to bring the tumor cell and T cell into proximity, thus facilitating tumor cell killing by T cells.<sup>161</sup> Regeneron is developing REGN5458 as a therapy for relapsed or refractory MM, and plans to submit a BLA for REGN5458 in this indication in 2022.

The safety and antitumor activity of REGN5458 are being assessed in patients with relapsed or refractory MM in an ongoing first-in-human Phase 1/2 study (NCT03761108) initiated in January 2019. REGN5458 was administered IV to patient cohorts at six dose levels (3–96 mg) the first part of the study. Following the dose escalation phase of the study to determine a recommended phase 2 dose regimen of REGN5458 as monotherapy, treatment consists of weekly doses of REGN5458, followed by a maintenance phase administered every 2 weeks. Preliminary results as of June 15, 2020, data cutoff have been reported.<sup>162</sup> For 45 patients treated with REGN5458, the objective response rate was 35.6% across all dose levels and 60% in the cohort receiving the highest dose level. Of responders, 81.3% achieved at least a very good partial response, and 43.8% and 18.8% had a duration of response >4 months and >8 months, respectively.

The Phase 2 portion of the NCT03761108 trial of REGN5458 is potentially pivotal, i.e., the study may yield efficacy data sufficient to support a marketing application. The estimated enrollment is 200 patients and the estimated primary completion date of the study is in December 2022. Regeneron also plans to evaluate REGN5458 in earlier lines of MM and in combinations with standard of care and novel agents in MM patients.<sup>163</sup>

### **Talquetamab (Janssen Research & Development, LLC)**

Talquetamab (JNJ-64407564) is a humanized IgG4κ/λ T-cell engaging bispecific antibody developed by Janssen using Genmab's DuoBody® technology for the treatment of relapsed or refractory MM. The molecule targets G protein-coupled receptor class C group 5 member D (GPCR5D) and CD3, thus facilitating the interaction of T cells and GPCR5D-expressing malignant cells. GPCR5D is normally expressed only in cells that produce hard keratin (e.g., hair), but a recent study demonstrated that GPCR5D mRNA and protein are expressed in plasma cells in bone marrow from patients with MM.<sup>164</sup> Talquetamab received a PRIME designation from the EMA for treatment of adult patients with relapsed or

refractory MM, who previously received ≥3 prior lines of therapy. Selective highlights as of October 19, 2021, of a Janssen pipeline update indicate that the company plans to submit marketing applications for talquetamab in MM between 2021 and 2023.

Talquetamab is being evaluated in four ongoing Phase 1 studies and one potentially pivotal Phase 2 study of MM patients. Preliminary results were reported for the Phase 1, first-in-human, open-label, dose escalation and dose expansion study (NCT03399799) of talquetamab in patients with relapsed or refractory MM.<sup>165</sup> Eligible patients received talquetamab IV (range: 0.5–180 µg/kg) or SC (range: 5.0–800 µg/kg) weekly or biweekly. In the first part of the study, the recommended Phase 2 dose (RP2D) was identified as weekly SC 405 µg/kg, with 10.0 and 60.0 µg/kg step-up doses. As of February 8, 2021, 174 patients had received talquetamab, with 28 receiving the RP2D. In response-evaluable patients ( $n = 24$ ), the overall response rate at the RP2D was 63%, with 50% reaching very good partial response or better. The median time to first confirmed response at the RP2D was 1.0 (range: 0.2–3.8) months and the responses were durable (median follow-up 6.2 [range: 2.7–9.7+] months. Initiated in December 2017, the estimated primary completion date of the study is in April 2022.

The ongoing Phase 2 study (NCT04634552) will evaluate the effects of talquetamab in patients with relapsed or refractory MM. The study includes three cohorts that will enroll participants with MM who have previously received ≥ 3 prior lines of therapy. Cohort A will include patients who have not been exposed to T cell redirection therapies, and they will receive talquetamab SC at the RP2D. Cohort B will include patients who have been exposed to T cell redirection therapies, and they will receive talquetamab SC at the RP2D. Cohort C will include patients who have not been exposed to T cell redirection therapies, and they will receive talquetamab SC at the RP2D biweekly. The estimated enrollment is 201 participants. Initiated in January 2021, the estimated primary completion date of the study is in August 2023.

### **Teclistamab (Janssen Research & Development, LLC)**

Teclistamab (JNJ-64007957) is an IgG4λ T-cell redirecting antibody derived from Ligand's transgenic mouse (OmniAb) and Genmab's DuoBody technology. The antibody selectively targets BCMA and CD3. Teclistamab was granted Breakthrough Therapy designation for the treatment of relapsed or refractory MM by the FDA, and EMA's PRIME designation for treatment of adult patients with relapsed or refractory MM who previously received ≥3 prior lines of therapy in 2021. Teclistamab had previously been granted Orphan Drug designations for MM in both the US and EU. Selective highlights as of October 19, 2021, of a Janssen pipeline update indicate that the company plans to submit marketing applications for teclistamab in MM between 2021 and 2023.

Teclistamab is under investigation in five Phase 1 studies and one Phase 2 study, and the start of a Phase 3 study is pending. Preliminary results were recently reported for an ongoing first-in-human dose escalation and dose expansion clinical study (NCT03145181) to assess the efficacy of teclistamab in patients with relapsed or refractory MM.<sup>166</sup> In the dose

escalation part of the study, teclistamab was administered IV (range: 0.3–19.2 µg/kg [once every 2 weeks] or 19.2–720 µg/kg [once per week]) or subcutaneously (range: 80–3000 µg/kg [once per week]) in different cohorts, with step-up dosing for 38.4 µg/kg or higher doses.<sup>166</sup> Based on the dose escalation data, the RP2D selected for teclistamab was once per week SC administration of teclistamab at 1500 µg/kg, after 60 µg/kg and 300 µg/kg step-up doses. For 40 patients administered the RP2D, the overall response rate in response-evaluable patients was 65% (95% CI: 48–79), and 58% achieved a very good partial response or better. The median duration of response for these patients was not reached. The primary completion date of the study is February 2022.

In the follow-on dose expansion Phase 2 trial (NCT04557098), the efficacy of teclistamab at the RP2D in patients with relapsed or refractory MM is being evaluated. The estimate enrollment is 185 patients, and the primary outcome measure is the overall response rate. The estimated primary completion date of the study is in April 2023.

A Phase 3 study (NCT05083169) started in October 2021 will compare teclistamab in combination with daratumumab SC (Darzalex®) versus daratumumab SC, pomalidomide, and dexamethasone or daratumumab SC, bortezomib, and dexamethasone in patients with relapsed or refractory MM. The estimate enrollment is 560 patients, and the primary outcome measure is PFS. The estimated primary completion date of the study is in January 2025.

### **Odronextamab (Regeneron Pharmaceuticals, Inc.)**

Odronextamab (REGN1979) is T-cell engaging, hinge-stabilized human bispecific antibody based on an IgG4κ isotype modified to reduce Fc effector functions. The antibody targets CD20 and CD3, and it is in development by Regeneron Pharmaceuticals for the treatment of relapsed or refractory B-cell NHL. The FDA granted REGN1979 Orphan Drug designation for the treatment of FL and diffuse large B-cell lymphoma, which are two types of NHL. In 2020, Regeneron Pharmaceuticals and Zai Lab entered into a strategic collaboration for the development and commercialization of REGN1979 in mainland China, Hong Kong, Taiwan, and Macau. If results from a potentially pivotal clinical study are positive, Regeneron may submit marketing applications for odronextamab in B-cell NHL in 2022.

The ongoing ELM-1 Phase 1 study (NCT02290951) is evaluating the safety and tolerability of odronextamab in patients with CD20 + B-cell malignancies previously treated with CD20-directed antibody therapy. Patients with diffuse large B-cell lymphoma, FL, mantle cell lymphoma, marginal zone lymphoma, and other B-cell NHLs were included. Preliminary results were reported in December 2020.<sup>167</sup> As of June 25, 2020, 127 patients with relapsed or refractory B-cell NHL had been treated with odronextamab IV at doses in the 0.03–320 mg range. Premedication with dexamethasone mitigated the risk of the development of cytokine release syndrome. In FL patients treated at doses of ≥5 mg ( $n = 28$ ), the objective response rate was 92.9%, and the CR rate was 75.0%. The median duration of response was 7.7 (range: 0+–20.9+) months, with 13 of 21 CRs ongoing at last tumor assessment, and the median duration of

CR was 8.1 (range: 0+ to 19.9+) months. In DLBCL patients who had not received prior CAR-T therapy and were treated at odronextamab doses ≥80 mg ( $n = 10$ ), the objective response rate and CR rate were 60%. The median observed duration of response was 10.3 (range: 2.9–18.6+) months, with four of 6sixCRs ongoing at last tumor assessment. The median duration of CR was 9.5 (range: 2.9–18.6+) months. The estimated primary completion date of this study is December 2025.

Odronextamab is also being evaluated in the potentially pivotal, ongoing, non-randomized ELM-2 Phase 2 study (NCT03888105) of NHL patients. The study has five arms, with patients assigned according to their diagnosis: Arm 1, FL patients; Arm 2, DLBCL patients; Arm 3, in mantle cell lymphoma patients; Arm 4, marginal zone lymphoma Grade 1–3a patients; and Arm 5 for B-cell NHL patients other than those with FL Grade 1–3a, DLBCL, MCL, MZL and Waldenström macroglobulinemia. Odronextamab is administered using a step-up dose schedule consisting of an initial dose at Week 1, an intermediate dose at Week 2, and thereafter, a fixed weekly dose until Week 12 followed by maintenance dosing every 2 weeks until progression or discontinuation. The dose for indolent B-cell NHL is 80 mg weekly followed by 160 mg every 2 weeks, and for aggressive B-cell NHL is 160 mg weekly followed by 320 mg every 2 weeks. All patients with durable CRs of 9 months will transition from every 2- to every 4-week dosing.<sup>168</sup> The primary outcome measure is the objective response rate. The estimated primary completion date is January 2025.

### **Sabatolimab (Novartis Pharmaceuticals Corporation)**

Sabatolimab (MBG453) is a humanized anti-T-cell immunoglobulin and mucin-domain domain-containing molecule-3 (TIM-3) IgG4κ (S228P) antibody. Novartis is developing the antibody for the treatment of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). The FDA granted Fast Track designation for sabatolimab (MBG453) for the treatment of adult patients with MDS defined with a revised international prognostic scoring system risk category of high or very high risk in combination with hypomethylating agents, and the EC has granted Orphan Drug designation for sabatolimab to treat MDS. Novartis has identified sabatolimab for high-risk MDS as a filing opportunity in 2022/2023, based on PFS and/or overall survival outcomes from a dual approach based on parallel Phase 2 and Phase 3 trials.<sup>169</sup>

The efficacy and safety of sabatolimab are being evaluated in three clinical studies of patients with MDS, STIMULUS MDS-1 (NCT03946670), STIMULUS-MDS2 (NCT04266301), and STIMULUS-MDS3 (NCT04812548). STIMULUS MDS-1 and STIMULUS MDS-3 are Phase 2 studies. The placebo-controlled STIMULUS MDS-1 is evaluating IV sabatolimab added to hypomethylating agents azacitidine and decitabine in adults with intermediate-, high- or very high-risk MDS, while the single-arm STIMULUS MDS-3 study is evaluating sabatolimab in combination with azacitidine and venetoclax in this same patient population. The primary completion dates for STIMULUS MDS-1 and STIMULUS MDS-3 are October 2023 and October 2025, respectively.



STIMULUS-MDS2 is a randomized, double-blind, placebo-controlled Phase 3 study evaluating the clinical effects of sibatolimab in combination with azacitidine in adult patients with intermediate-, high-, or very high-risk MDS or chronic myelomonocytic leukemia-2. In this 2-arm study, patients receive either sibatolimab 800 mg every 4 weeks + azacitidine 75 mg/m<sup>2</sup> or azacitidine 75 mg/m<sup>2</sup> + placebo. Overall survival is the primary outcome measure for the study, which has a primary completion date in January 2027.

### **Cosibelimab (Checkpoint Therapeutics, Inc.)**

Cosibelimab (CK-301) is a human anti-PD-L1 IgG1 $\lambda$  antibody in development by Checkpoint Therapeutics, Inc., which is majority controlled by Fortress Biotech. Licensed from Dana-Farber Cancer Institute, the molecule was optimized at Adimab. If results of a registration-enabling study in are positive, Checkpoint Therapeutics may submit a BLA for cosibelimab for metastatic cutaneous squamous cell carcinoma (cSCC) in 2022.<sup>170</sup>

In the registration-enabling Phase 1 (NCT03212404) trial, the safety, tolerability, and efficacy of cosibelimab when administered IV as a single agent is being evaluated in patients with selected recurrent or metastatic cancers. The study includes pivotal cohorts (~75 patients) in metastatic and locally advanced cSCC. Patients are treated with fixed doses (800 mg every 2 weeks; 1200 mg Q3W). The company expects to report top-line results of the study in the 4<sup>th</sup> quarter of 2021.

Checkpoint Therapeutics plans to initiate a Phase 3 study (NCT04786964) of cosibelimab in combination with platinum +pemetrexed chemotherapy in patients with first-line metastatic NSCLC. An estimated 560 participants will be randomized to receive either (1) cosibelimab 1200 mg IV plus pemetrexed 500 mg/m<sup>2</sup> IV (with vitamin supplementation) and cisplatin 75 mg/m<sup>2</sup> IV or carboplatin AUC 5 IV on D 1 of every 3-week cycle for 4 cycles, followed by cosibelimab 1200 mg IV plus pemetrexed 500 mg/m<sup>2</sup> IV Q3W until progression or (2) the active control therapy (platinum+pemetrexed chemotherapy). Due to start in September 2021, the study was listed on ClinicalTrials.gov as not yet recruiting as of early November 2021. The estimated primary completion date is May 2024.

### **Apamistamab-I-131 (Actinium Pharmaceuticals, Inc.)**

Apamistamab-I-131 (Iomab-B) is a radiolabeled (iodine-131) IgG1 $\kappa$  antibody that targets CD45, which is expressed on leukemia, lymphoma, and normal immune cells, including those in bone marrow. Actinium Pharmaceuticals, Inc. is developing the antibody as a conditioning agent used prior to an allogeneic bone marrow transplant (BMT) for patients with active, relapsed or refractory AML, who are age 55 or older. Iomab-B was granted Orphan Drug designations for this indication by both EMA and FDA. The company expects have topline data to support the submission of BLA with the FDA during 2021–2022.<sup>171</sup>

Data from the SIERRA trial (NCT02665065) of Iomab-B were presented at the 2021 Society of Nuclear Medicine and Molecular Imaging Annual Meeting, held virtually from

June 11–14, 2021.<sup>172</sup> This study is evaluating the efficacy of Iomab-B prior to HSCT vs. conventional care in older patients with active, relapsed or refractory AML. Of patients receiving the therapeutic dose of Iomab-B, 100% underwent BMT and successfully engrafted, compared to 18% of patients who received physician's choice of salvage therapy on the control arm. In evaluable patients, the 100-d non-relapse transplant-related mortality rate was 5% in the Iomab-B arm vs. 20% for those who achieved CR and received standard of care HCT. The study, which was fully enrolled as of September 2021,<sup>171</sup> has a primary completion date in December 2021.

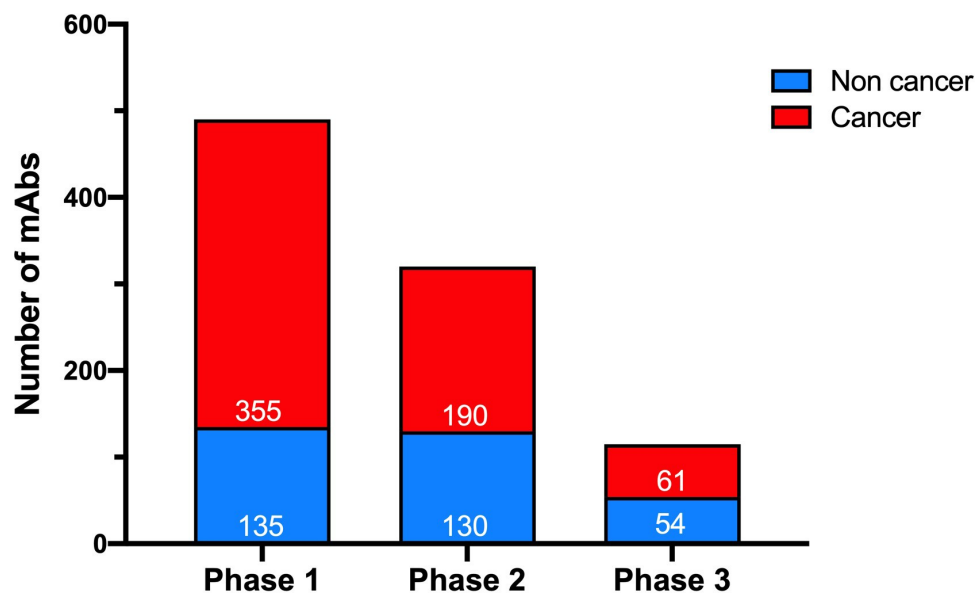
### **Erfonrilimab (Alphamab Oncology)**

Erfonrilimab (KN046), a humanized bispecific antibody that targets the immune checkpoints PD-L1 and CTLA-4, is being developed as a treatment for cancer by Jiangsu Alphamab Biopharmaceuticals Co., Ltd, a wholly owned subsidiary of Alphamab Oncology. As of August 2021, KN046 is being evaluated in 8 Phase 2 studies recruiting patients with NSCLC, thymic carcinoma, esophageal squamous cell carcinoma, gastrointestinal tumors, or breast cancer, including triple-negative breast cancer, and a Phase 3 study (NCT04474119) in squamous NSCLC patients. KN046 was granted an Orphan Drug designation by the FDA for the treatment of thymic epithelial tumors, and the combination of KN026 (anti-HER2 bispecific antibody) with KN046 was granted an Orphan Drug designation by the FDA for the treatment of HER2-positive or low expressing gastric or GEJ cancer. Alphamab Oncology is preparing to submit a BLA for KN046 in China in mid-2022.<sup>173</sup>

Preliminary results for a Phase 2 study (NCT04054531) of KN046 plus platinum-based doublet chemotherapy as a first-line therapy for advanced NSCLC patients were recently reported.<sup>174</sup> Patients in study arm 1 received KN046 5 mg/kg IV Q3W + carboplatin AUC5 IV Q3W  $\times$  4 cycles + paclitaxel 500 mg/m<sup>2</sup> IV Q3W  $\times$  4 cycles, while patients in study arm 2 received KN046 5 mg/kg IV Q3W + carboplatin AUC5 IV Q3W  $\times$  4 cycles + pemetrexed 500 mg/m<sup>2</sup> IV Q3W  $\times$  4 cycles. The median treatment time was 21 weeks. In the efficacy evaluable patients ( $n = 81$ ), the overall objective response rate was 50.6% (95% CI: 39.3–61.9%) and the disease control rate (DCR) was 87.7% (95% CI: 78.5–93.9%). For evaluable patients with non-squamous NSCLC ( $n = 48$ ), the overall objective response rate and DCR were 45.8% (95% CI: 31.4–60.8%) and 89.6% (95% CI: 77.3–96.5%), respectively, while these rates were 57.6% (95% CI: 39.2–74.5%) and 84.8% (95% CI: 68.1–94.9%) for evaluable patients with squamous NSCLC ( $n = 33$ ), respectively.

KN046 in combination with chemotherapy (carboplatin and paclitaxel) is being evaluated for first-line treatment of advanced squamous NSCLC in the placebo-controlled Phase 3 ENREACH-LUNG-01 study (NCT04474119). Patients in the experimental study arm will receive KN046 5 mg/kg Q3W in addition to chemotherapy. Initiated in September 2020, the study completed patient enrollment ( $n = 482$ ) in October 2021. The study's estimated primary completion date is August 2022.





**Figure 8.** Global commercial clinical pipeline of innovative antibody therapeutics. Figure based on data publicly available as of November 15, 2021. Antibody therapeutics that have transitioned to regulatory review or been approved in any country, biosimilar antibodies and Fc fusion proteins were excluded.

### Notable set-backs

The biopharmaceutical industry advanced a substantial number of new antibodies into late-stage clinical studies within the past year, and continued to submit marketing applications for investigational antibody therapeutics to regulatory agencies in the US, EU, Japan, and China, as well as other countries, at a rapid pace (Tables 3, 4). However, we note that the outcome of the US regulatory review process in 2021 has been irregular, most particularly in the unprecedented number of the BLAs that received a Complete Response letter after a first review and entered a second cycle for various reasons, including issues with comparability of clinical trial and intended commercial products, and insufficient clinical data. In one case, FDA delayed action on bimekizumab's BLA due to their inability to travel to Europe to conduct inspections. Agenus' decision to withdraw the BLA for balstilimab was also unusual, although the withdrawal resulted from changes in the medical treatment landscape and was recommended by FDA.<sup>175</sup> No single cause explains the recent spate of irregularities, but various stresses on companies and FDA due to the pandemic have undoubtedly contributed. We, and likely the rest of the world, look forward to living in less interesting times.

Finally, we would like to acknowledge the (apparent) demise of tanezumab (PF-04383119, Raylumis), a humanized IgG2 $\kappa$  antibody targeting nerve growth factor developed by Pfizer and Eli Lilly and Company as a treatment of pain, including osteoarthritis (OA) pain and chronic lower back pain. After an epic journey that included evaluation in clinical studies that spanned an ~17-y period, Pfizer and Lilly discontinued the global clinical development program in October 2021 following receipt of a Complete Response letter from the FDA for tanezumab's BLA for OA pain and a negative opinion adopted by the EMA on tanezumab's MAA in OA pain.<sup>176–178</sup> Tanezumab was included in the first 'Antibodies to Watch' article, published in 2010,<sup>1</sup> and one of us (JMR) will miss writing about the adventures of this intrepid molecule.

### Outlook for the future

As 2021 draws to a close, the pandemic caused by the SARS-CoV-2 virus continues to disrupt the daily lives of people and the functions of organizations located across the globe. No workers, companies, or government agencies have been unaffected. Although the vaccines now available have the potential to greatly reduce infection, vaccine hesitancy and uneven distribution of the vaccines have hampered efforts to stop the spread of the virus. In 2021, biopharmaceutical companies made progress in their development of anti-SARS-CoV-2 antibodies for both prophylactic and therapeutic use, and have expanded the routes of administration to include subcutaneous and IM injections, which are more convenient for patients. Numerous anti-SARS-CoV-2 antibodies have been granted short-term EUAs as well as full approvals, which will ensure the products remain available to patients after the pandemic has officially ended. In the US, that will occur on the date that the Department of Health and Human Services declares the public health emergency is over. We look forward to such declarations from all governments in the near future.

The number of novel antibody therapeutics undergoing a first regulatory review is currently at a record level because applications have continued to be submitted while the number approved has not kept pace. Typically, antibody therapeutics are approved after a first review cycle, but deficiencies of various sorts were identified in some applications. As a consequence, the opportunity in 2021 to exceed the all-time record number of EU and US approvals (13) set in 2018 was missed, but the opportunity remains in 2022 due to the substantial numbers in regulatory review (19) and queued to enter regulatory review as of November 2021. Although it has been only 1 y since 'Antibodies to watch in 2021'<sup>138</sup> was written, the late-stage clinical pipeline of novel antibody therapeutics has grown by over 30%, suggesting many new products may be available to patients in need in the near future. The long-term

outlook also seems promising, as the early-stage commercial pipeline now includes over 800 novel antibody therapeutics (Figure 8). We look forward to documenting progress made in the development of these therapeutics in future ‘Antibodies to Watch’ articles.

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## List of Abbreviations

A $\beta$ , amyloid beta; ACR20, American College of Rheumatology 20%; AD, Alzheimer’s disease; ADC, antibody–drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; ADP, adenosine diphosphate; aGvHD, acute graft-vs-host disease; ALK, anaplastic large-cell lymphoma kinase; AMD, age-related macular degeneration; AML, acute myeloid leukemia; Ang-2, angiopoietin-2; ANGPTL3, angiopoietin-like protein 3; ASCO, American Society of Clinical Oncology; BCG, bacillus Calmette-Guérin; BCMA, B cell maturation antigen; BCVA, Best-corrected visual acuity; BLA, biologics license application; BMS, Bristol Myers Squibb; BMT, bone marrow transplant; BTC, biliary tract cancer; CAD, cold agglutinin disease; CAPOX, capecitabine/oxaliplatin; CAR-T, chimeric antigenic receptor – T cell; CDC, complement-dependent cytotoxicity; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; CLDN18.2, claudin 18.2; CLL, chronic lymphocytic leukemia; CMC, Chemistry, Manufacturing and Controls; CNS, central nervous system; COVID-19, coronavirus disease 2019; CR, complete response; CSCC, cutaneous squamous cell carcinoma; CSU, chronic spontaneous urticaria; CTLA-4, cytotoxic T lymphocyte antigen-4; DCR, disease control rate; DLBCL, diffuse large B-cell lymphoma; DM4, N2’-deacetyl-N2’-(4-mercapto-4-methyl-1-oxopentyl) maytansine; DME, diabetic macular edema; dMMR, deficient mismatch repair; EC, European Commission; ECMO, extracorporeal membrane oxygenation; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ENKTL, extranodal natural killer/T-cell lymphoma; EpCAM, epithelial cell adhesion molecule; ESMO, European Society for Medical Oncology; EU, European Union; EUA, Emergency use authorization; Fab, antigen-binding fragment; Fc, crystallizable fragment; Fc $\gamma$ R, Receptors for IgG Fc; FcRn, neonatal Fc receptor; FDA, US Food and Drug Administration; FL, follicular lymphoma; FR $\alpha$ , folate receptor alpha; GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; GM-CSF, granulocyte-macrophage colony stimulating factor; GPP, generalized pustular psoriasis; GPRC5D, G Protein-Coupled Receptor

Class C Group 5 Member D; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; HoFH, homozygous familial hypercholesterolemia; HR, hazard ratio; HS, hidradenitis suppurativa; HSCT, hematopoietic stem cell transplant; hTfR, anti-human transferrin receptor; iADRS, Integrated AD Rating Scale; IDS, iduronate-2-sulfatase; IFN, interferon; IFNAR1, interferon alpha receptor 1; IGA, Investigator’s Global Assessment; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; IM, intramuscular; INN, International Nonproprietary Names; IRRC, independent radiology review committee; IV, intravenous; LAG-3, Lymphocyte-activation gene 3; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LM, leptomeningeal metastases; MAA, marketing authorisation application; mAb, monoclonal antibody; MASP-2, mannan-binding lectin-associated serine protease-2; MDS, myelodysplastic syndrome; MET, mesenchymal epithelial transition factor; MFDS, Korean Ministry of Food and Drug Safety; MHLW, Ministry of Health, Labour and Welfare; MM, multiple myeloma; MMAE, monomethyl auristatin E; MMR, mismatch repair; MPS-II, mucopolysaccharidosis II; MS, multiple sclerosis; MSI, microsatellite instability; MTX, methotrexate; NDA, new drug application; NHL, non-Hodgkin’s lymphoma; NIH, National Institutes of Health; NK, natural killer cells; NMIBC, non-muscle invasive bladder cancer; NMPA, China’s National Medical Products Administration; NSCLC, non-small cell lung cancer; OA, osteoarthritis; OR, overall response; OS, overall survival; 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; PHN, paroxysmal nocturnal hemoglobinuria; PPP, palmoplantar pustulosis; PR, partial response; PRIME, Priority Medicines; PTCL, peripheral T cell lymphoma; PTL, personalized treatment intervals; Q3W, every 3 weeks; RA, rheumatoid arthritis; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; ROK, Republic of Korea; RSV, respiratory syncytial virus, RT-qPCR, Quantitative reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; SCAC, squamous cell carcinoma of the anal canal; scFv, single-chain variable fragment; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; TCR, T cell receptor; TGA, Australian Therapeutic Goods Administration; TIGIT, T-cell Immunoreceptor with Ig and ITIM domains; TIM-3, T-cell immunoglobulin and mucin-domain domain-containing molecule-3; 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

## References

- Reichert JM. Antibodies to watch in 2010. *MAbs*. 2010;2:84–100. doi:10.4161/mabs.2.1.10677.
- Mullard A. FDA approves 100th monoclonal antibody product. *Nat Rev Drug Discov*. 2021;20(7):491–95. doi:10.1038/d41573-021-00079-7.
- Ryu DK, Song R, Kim M, Kim YI, Kim C, Kim JI, Kwon KS, Tijssma AS, Nuijten PM, van Baalen CA, et al. Therapeutic effect of CT-P59 against SARS-CoV-2 South African variant. *Biochem Biophys Res Commun*. 2021;566:135–40. doi:10.1016/j.bbrc.2021.06.0162.
- Centers for Disease Control and Prevention. SARS-CoV-2 Variant classifications and definitions. [Updated 2021 Oct 4 [accessed 2021 Nov 1]. [www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html](http://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html).
- U.S. Food and Drug Administration. Emergency use authorization. [Updated 2021 Oct 29 accessed 2021 Nov 1]. [www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization](http://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization).
- European Medicines Agency. COVID-19 treatments. [accessed 2021 Nov 1]. [www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments](http://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments).
- European Medicines Agency. COVID-19 treatments: article 5 (3) reviews. [accessed 2021 Nov 1]. [www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-covid-19/covid-19-treatments-article-53-reviews](http://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-covid-19/covid-19-treatments-article-53-reviews).

8. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19. 2021 Feb 9 press release [accessed 2021 Nov 1]. [www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0](http://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0).
9. U.S. Food and Drug Administration. FDA authorizes bamlanivimab and etesevimab monoclonal antibody therapy for post-exposure prophylaxis (prevention) for COVID-19. 2021 Sept 16 press release [accessed 2021 Nov 1]. [www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-bamlanivimab-and-etesevimab-monoclonal-antibody-therapy-post-exposure-prophylaxis](http://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-bamlanivimab-and-etesevimab-monoclonal-antibody-therapy-post-exposure-prophylaxis).
10. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for monoclonal antibody bamlanivimab. 2021 Apr 16. press release [accessed 2021 Nov 1]. [www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab](http://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab).
11. European Medicines Agency. EMA/177113/2021 assessment report: procedure under article 5 (3) of regulation (EC) No 726/2004 Eli Lilly and company limited use of bamlanivimab and etesevimab for the treatment of COVID-19. 2021 Mar 16 [accessed 2021 Nov 1]. [www.ema.europa.eu/en/documents/referral/eli-lilly-company-limited-antibody-combination-bamlanivimab-etesevimab-covid19-article-53-procedure-assessment-report\\_en.pdf](http://www.ema.europa.eu/en/documents/referral/eli-lilly-company-limited-antibody-combination-bamlanivimab-etesevimab-covid19-article-53-procedure-assessment-report_en.pdf).
12. Eli Lilly and Company Limited. Withdrawal of rolling review for bamlanivimab (EMA/H/C/005836/0000) and etesevimab. 2021 Oct 29 letter [accessed 2021 Nov 3]. [www.ema.europa.eu/en/documents/withdrawal-letter/withdrawal-letter-bamlanivimab-etesevimab\\_.pdf](http://www.ema.europa.eu/en/documents/withdrawal-letter/withdrawal-letter-bamlanivimab-etesevimab_.pdf).
13. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, Hebert C, Perry R, Boscia J, Heller B, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med*. 2021;385(15):1382–92. doi:10.1056/NEJMoa2102685.
14. Eli Lilly and Company. Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. 2021 Jan 20 press release [accessed 2021 Nov 3]. [investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented](http://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented).
15. U.S. Food and Drug Administration. Emergency use authorization (EUA) for bamlanivimab 700 mg and etesevimab 1,400 mg. center for drug evaluation and research (CDER) review. [accessed 2020 Nov 1]. [www.fda.gov/media/152756/download](http://www.fda.gov/media/152756/download).
16. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes additional monoclonal antibody for treatment of COVID-19. 2021 May 26 press release [accessed 2021 Nov 1]. [www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19](http://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19).
17. Therapeutic Goods Administration. Australian public assessment report for sotrovimab, proprietary product name: xevudy; sponsor: glaxoSmithKline Australia Pty Ltd. [accessed 2021 Nov 1]. [www.tga.gov.au/sites/default/files/auspar-sotrovimab-210820.pdf](http://www.tga.gov.au/sites/default/files/auspar-sotrovimab-210820.pdf).
18. Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, Sarkis E, Solis J, Zheng H, Scott N, et al. COMET-ICE investigators. early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385(21):1941–50. doi:10.1056/NEJMoa2107934.
19. Kim C, Ryu DK, Lee J, Kim YI, Seo JM, Kim YG, Jeong JH, Kim M, Kim JI, Kim P, et al. A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. *Nat Commun*. 2021;12(1):288. doi:10.1038/s41467-020-20602-5.
20. Celltrion Group. Celltrion submits marketing authorisation application to the European medicines agency for regdanvimab (CT-P59). 2021 Oct 5 press release [accessed 2021 Nov 3]. [www.celltrionhealthcare.com/en-us/board/newsdetail?modify\\_key=529&pagenumber=1&keyword=&keyword\\_type=](http://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=529&pagenumber=1&keyword=&keyword_type=)
21. European Medicines Agency. EMA/192245/2021 assessment report: procedure under article 5 (3) of regulation (EC) no 726/2004 celltrion use of regdanvimab for the treatment of COVID-19. 2021 Mar 25 [accessed 2021 Nov 1]. [www.ema.europa.eu/en/documents/referral/regdanvimab-treatment-covid-19-celltrion-covid-19-article-53-procedure-assessment-report\\_en.pdf](http://www.ema.europa.eu/en/documents/referral/regdanvimab-treatment-covid-19-celltrion-covid-19-article-53-procedure-assessment-report_en.pdf).
22. U.S. Food and Drug Administration. Emergency use authorization (EUA) for casirivimab and imdevimab. [accessed 2021 Nov 1]. [www.fda.gov/media/151863/download](http://www.fda.gov/media/151863/download).
23. Regeneron Pharmaceuticals, Inc. New REGEN-COV™ (casirivimab and imdevimab) data show supportive results in patients hospitalized with COVID-19. 2021 Sep 30 press release [accessed 2021 Nov 3]. [investor.regeneron.com/news-releases/news-release-details/new-regen-covtm-casirivimab-and-imdevimab-data-show-supportive](http://investor.regeneron.com/news-releases/news-release-details/new-regen-covtm-casirivimab-and-imdevimab-data-show-supportive).
24. European Medicines Agency. EMA receives application for marketing authorisation for ronapreve (casirivimab/imdevimab) for treatment and prevention of COVID-19. 2021 Oct 11 press release [accessed 2021 Nov]. [www.ema.europa.eu/en/news/ema-receives-application-marketing-authorisation-ronapreve-casirivimab-imdevimab-treatment](http://www.ema.europa.eu/en/news/ema-receives-application-marketing-authorisation-ronapreve-casirivimab-imdevimab-treatment).
25. Therapeutic Goods Administration. Australian product information: ronapreve® (casirivimab and imdevimab). [accessed 2021 Nov 1]. [www.tga.gov.au/sites/default/files/ronapreve-pi.pdf](http://www.tga.gov.au/sites/default/files/ronapreve-pi.pdf).
26. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes drug for treatment of COVID-19. 2021 June 24 press release [accessed 2021 Nov 3]. [www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19](http://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19).
27. U.S. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Actemra® (tocilizumab). [accessed 2021 Nov 3]. [www.fda.gov/media/150321/download](http://www.fda.gov/media/150321/download).
28. AstraZeneca. Year to date and Q3 2021 results. 2021 Nov 12 press release [accessed 2021 Nov 12]. [www.astrazeneca.com/content/dam/az/PDF/2021/q3/Year-to-date\\_and\\_Q3\\_2021\\_results\\_announcement.pdf](http://www.astrazeneca.com/content/dam/az/PDF/2021/q3/Year-to-date_and_Q3_2021_results_announcement.pdf).
29. AstraZeneca. AZD7442 PROVENT phase III prophylaxis trial met primary endpoint in preventing COVID-19. 2021 Aug 20 press release [accessed 2021 Nov 3]. [www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html](http://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html).
30. AstraZeneca. AZD7442 reduced risk of developing severe COVID-19 or death in TACKLE phase III outpatient treatment trial. 2021 Oct 11 press release [accessed 2021 Nov 3]. [www.astrazeneca.com/media-centre/press-releases/2021/azd7442-phiii-trial-positive-in-covid-outpatients.html](http://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-phiii-trial-positive-in-covid-outpatients.html).
31. Bria Biosciences. Corporate presentation. 2021 Oct [accessed 2021 Nov 3]. [www.briibio.com/upload/BriaBio-Corporate-Presentation.pdf](http://www.briibio.com/upload/BriaBio-Corporate-Presentation.pdf).
32. Bria Biosciences. Bria bio initiates submission of emergency use authorization filing to U.S. FDA for BRII-196/BRII-198, its monoclonal antibody combination therapy for non-hospitalized COVID-19 patients at high risk of clinical progression to severe disease. 2021 Oct 9 press release [accessed Nov 3 2021]. [www.briibio.com/news-detail.php?id=370#news](http://www.briibio.com/news-detail.php?id=370#news).
33. National Institutes of Health. NIH-Sponsored ACTIV-3. Clinical trial closes enrollment into two sub-studies. 2021 Mar 4 press release [accessed Nov 3, 2021]. [www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies](http://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies).
34. Adagio Therapeutics, Inc. Adagio Therapeutics provides update for ADG20 COVID-19 antibody program and reports third quarter 2021 financial results. 2021 Nov 15 [accessed 2021 Nov 15]. [investors.adagiotx.com/news-releases/news-release-details/adagio-therapeutics-provides-update-adg20-covid-19-antibody](http://investors.adagiotx.com/news-releases/news-release-details/adagio-therapeutics-provides-update-adg20-covid-19-antibody).
35. Humanigen, Inc. Humanigen submits all planned modules for potential conditional marketing authorization from the UK's MHRA. 2021 Oct 1 press release [accessed 2021 Nov 3]. [s28.q4cdn.com/539885110/files/doc\\_news/Humanigen-Submits-All-Planned-Modules-for-Potential-Conditional-Marketing-Authorization-from-the-UKs-MHRA-2021.pdf](http://s28.q4cdn.com/539885110/files/doc_news/Humanigen-Submits-All-Planned-Modules-for-Potential-Conditional-Marketing-Authorization-from-the-UKs-MHRA-2021.pdf).



36. Humanigen, Inc. Humanigen presentation. 2021 Sept [accessed 2021 Nov 3]. [s28.q4cdn.com/539885110/files/doc\\_presentations/2021/September/HGEN-Corporate-Deck-presented-at-Oppenheim-Fall-Summit-Sep.-22-2021.pdf](https://s28.q4cdn.com/539885110/files/doc_presentations/2021/September/HGEN-Corporate-Deck-presented-at-Oppenheim-Fall-Summit-Sep.-22-2021.pdf).
37. Temesgen Z, Burger CD, Baker J, Polk C, Libertin C, Kelley C, Marconi VC, Orenstein R, Durrant C, Chappell C, et al. Lenzilumab efficacy and safety in newly hospitalized covid-19 subjects: results from the live-air phase 3 randomized double-blind placebo-controlled trial. medRxiv. 2021 May 5 preprint posted doi:10.1101/2021.05.01.21256470.
38. U.S. Food and Drug Administration. BLA 761181 approval letter. 2021 Feb 11 [accessed 2021 Nov 1]. [www.accessdata.fda.gov/drug\\_satfda\\_docs/appletter/2021/761181Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drug_satfda_docs/appletter/2021/761181Orig1s000ltr.pdf).
39. European Medicines Agency. Evkeeza assessment report EMA/250315/2021. [accessed 2021 Nov 1]. [www.ema.europa.eu/en/documents/assessment-report/evkeeza-h-c-5449-0000-epar-assessment-report\\_en.pdf](http://www.ema.europa.eu/en/documents/assessment-report/evkeeza-h-c-5449-0000-epar-assessment-report_en.pdf).
40. European Medicines Agency. Jemperli assessment report EMA/176464/2021. [accessed 2021 Nov 1]. [www.ema.europa.eu/en/documents/assessment-report/jemperli-epar-public-assessment-report\\_en.pdf](http://www.ema.europa.eu/en/documents/assessment-report/jemperli-epar-public-assessment-report_en.pdf).
41. U.S. Food and Drug Administration. BLA 761174 approval letter. 2021 Apr 22 [accessed 2021 Nov 1]. [www.accessdata.fda.gov/drug\\_satfda\\_docs/appletter/2021/761174Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drug_satfda_docs/appletter/2021/761174Orig1s000ltr.pdf).
42. Kumar S, Ghosh S, Sharma G, Wang Z, Kehry MR, Marino MH, Neben TY, Lu S, Luo S, Roberts S, et al. Preclinical characterization of dostarlimab, a therapeutic anti-PD-1 antibody with potent activity to enhance immune function in in vitro cellular assays and in vivo animal models. *MABs*. 2021;13(1):1954136. doi:10.1080/19420862.2021.1954136.
43. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, Kahl BS, Radford J, Solh M, Stathis A. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2021;22(6):790–800. doi:10.1016/S1470-2045(21)00139-X.
44. ADC Therapeutics SA. ADC therapeutics reports second quarter 2021 financial results and provides business updates. 2021 Aug 3 press release [accessed 2021 Nov 3]. [ir.adctherapeutics.com/press-releases/press-release-details/2021/ADC-Therapeutics-Reports-Second-Quarter-2021-Financial-Results-and-Provides-Business-Updates/default.aspx](http://ir.adctherapeutics.com/press-releases/press-release-details/2021/ADC-Therapeutics-Reports-Second-Quarter-2021-Financial-Results-and-Provides-Business-Updates/default.aspx).
45. U.S. Food and Drug Administration. BLA 761196 approval letter. 2021 Apr 23 [accessed 2021 Nov 1]. [www.accessdata.fda.gov/drug\\_satfda\\_docs/appletter/2021/761196Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drug_satfda_docs/appletter/2021/761196Orig1s000ltr.pdf).
46. U.S. Food and Drug Administration. NDA/BLA multi-disciplinary review and evaluation: BLA 761210; RYBREVANT, amivantamab-vmjw. [accessed 2021 Nov 1]. [www.accessdata.fda.gov/drug\\_satfda\\_docs/nda/2021/761210Orig1s000MultidisciplineR.pdf](http://www.accessdata.fda.gov/drug_satfda_docs/nda/2021/761210Orig1s000MultidisciplineR.pdf).
47. Neijssen J, Cardoso RMF, Chevalier KM, Wiegman L, Valerius T, Anderson GM, Moores SL, Schuurman J, Parren PWHI, Strohl WR, et al. Discovery of amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR and MET. *J Biol Chem*. 2021;296:100641. doi:10.1016/j.jbc.2021.100641.
48. U.S. Food and Drug Administration. ADUHELM™ application number 761178Orig1s000: clinical pharmacology and biopharmaceutics review(s). [www.accessdata.fda.gov/drug\\_satfda\\_docs/nda/2021/761178Orig1s000ClinPharm\\_Redacted.pdf](http://www.accessdata.fda.gov/drug_satfda_docs/nda/2021/761178Orig1s000ClinPharm_Redacted.pdf).
49. U.S. Food and Drug Administration. BLA 761178 approval letter. 2021 Jun 7 [accessed 2021 Nov 4]. [www.accessdata.fda.gov/drug\\_satfda\\_docs/appletter/2021/761178Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drug_satfda_docs/appletter/2021/761178Orig1s000ltr.pdf).
50. Dumet C, Pottier J, Gouilleux-Gruart V, Watier H. Insights into the IgG heavy chain engineering patent landscape as applied to IgG4 antibody development. *MABs*. 2019;11(8):1341–50. doi:10.1080/19420862.2019.1664365.
51. European Medicines Agency. EMA/266138/2021 assessment report: adtralza. 2021 Apr 22 [accessed 2021 Nov 4]. [www.ema.europa.eu/en/documents/assessment-report/adtralza-h-c-5255-0000-epar-assessment-report\\_en.pdf](http://www.ema.europa.eu/en/documents/assessment-report/adtralza-h-c-5255-0000-epar-assessment-report_en.pdf).
52. LEO Pharma A/S. Update on U.S. FDA review of LEO pharma's biologics license application for tralokinumab for the treatment of adults with moderate-to-severe atopic dermatitis. 2021 Apr 29 press release [accessed 2021 Nov 4]. [www.leo-pharma.us/Files/Billeder/leo-us/Press%20Release\\_FDA\\_Review\\_tralokinumab.pdf](http://www.leo-pharma.us/Files/Billeder/leo-us/Press%20Release_FDA_Review_tralokinumab.pdf).
53. AstraZeneca. Saphnelo (anifrolumab) approved in the US for moderate to severe systemic lupus erythematosus. 2021 Aug 2 press release [accessed 2021 Nov 4]. [www.astrazeneca.com/media-centre/press-releases/2021/saphnelo-approved-in-the-us-for-sle.html](http://www.astrazeneca.com/media-centre/press-releases/2021/saphnelo-approved-in-the-us-for-sle.html).
54. U.S. Food and Drug Administration. Highlights of prescribing information: SAPHNELO (anifrolumab-fnia) injection, for intravenous use. [Revised 2021 Jul 21 accessed 2021 Nov 4]. [www.accessdata.fda.gov/drug\\_satfda\\_docs/label/2021/761123s000lbl.pdf](http://www.accessdata.fda.gov/drug_satfda_docs/label/2021/761123s000lbl.pdf).
55. European Medicines Agency. EMA/393532/2021 assessment report: bimzelx. 2021 Jun 24 [accessed 2021 Nov 4]. [www.ema.europa.eu/en/documents/assessment-report/bimzelx-epar-public-assessment-report\\_en.pdf](http://www.ema.europa.eu/en/documents/assessment-report/bimzelx-epar-public-assessment-report_en.pdf).
56. UCB. Update on U.S. FDA review of biologics license application (BLA) for bimekizumab. 2021 Oct 16 press release [accessed 2021 Nov 4]. [www.ucb.com/stories-media/Press-Releases/article/Update-on-U-S-FDA-Review-of-Biologics-License-Application-BLA-for-bimekizumab](http://www.ucb.com/stories-media/Press-Releases/article/Update-on-U-S-FDA-Review-of-Biologics-License-Application-BLA-for-bimekizumab).
57. Reich K, Papp KA, Blauvelt A, Langley RG, Armstrong A, Warren RB, Gordon KB, Merola JF, Okubo Y, Madden C, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial. *Lancet*. 2021;397(10273):487–98. doi:10.1016/S0140-6736(21)00125-2.
58. Warren RB, Blauvelt A, Bagel J, Papp KA, Yamauchi P, Armstrong A, Langley RG, Vanvoorden V, De Cuyper D, Cioffi C, et al. Bimekizumab versus adalimumab in plaque psoriasis. *N Engl J Med*. 2021;385(2):130–41. doi:10.1056/NEJMoa2102388.
59. Reich K, Warren RB, Lebwohl M, Gooderham M, Strober B, Langley RG, Paul C, De Cuyper D, Vanvoorden V, Madden C, et al. Bimekizumab versus secukinumab in plaque psoriasis. *N Engl J Med*. 2021;385(2):142–52. doi:10.1056/NEJMoa2102383.
60. Gordon KB, Foley P, Krueger JG, Pinter A, Reich K, Vender R, Vanvoorden V, Madden C, White K, Cioffi C, et al. Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial. *Lancet*. 2021;397(10273):475–86. doi:10.1016/S0140-6736(21)00126-4.
61. U.S. Food and Drug Administration. Highlights of prescribing information TIVDAK™ (tisotumab vedotin-tftv) for injection, for intravenous use. Revised 2021 Sept [accessed 2021 Nov 4]. [www.accessdata.fda.gov/drug\\_satfda\\_docs/label/2021/761208s000lbl.pdf](http://www.accessdata.fda.gov/drug_satfda_docs/label/2021/761208s000lbl.pdf).
62. JCR Pharmaceuticals Co., Ltd. JCR pharmaceuticals announces approval of IZCARGO® (pabinafusp alfa) for treatment of MPS II (hunter syndrome) in Japan. 2021 Mar 23 press release [accessed 2021 Nov 4]. [ssl4.eir-parts.net/doc/4552/tdnet/1946438/00.pdf](https://ssl4.eir-parts.net/doc/4552/tdnet/1946438/00.pdf).
63. Okuyama T, Eto Y, Sakai N, Nakamura K, Yamamoto T, Yamaoka M, Ikeda T, So S, Tanizawa K, Sonoda H, et al. A Phase 2/3 Trial of pabinafusp alfa, IDS fused with anti-human transferrin receptor antibody, targeting neurodegeneration in MPS-II. *Mol Ther*. 2021;29(2):671–79. doi:10.1016/j.ymthe.2020.09.039.
64. Seagen Inc. Seagen and remeGen announce exclusive worldwide license and co-development agreement for disitamab vedotin. 2021 Aug 9 press release [accessed Nov 4, 2021]. [investor.seagen.com/press-releases/news-details/2021/Seagen-and-RemeGen-Announce-Exclusive-Worldwide-License-and-Co-Development-Agreement-for-Disitamab-Vedotin/default.aspx](http://investor.seagen.com/press-releases/news-details/2021/Seagen-and-RemeGen-Announce-Exclusive-Worldwide-License-and-Co-Development-Agreement-for-Disitamab-Vedotin/default.aspx).
65. RemeGen Co., Ltd. China ushered in the first self-developed ADC new drug vidicuzumab for gastric cancer indications approved for marketing. 2021 June 10 press release [accessed 2021 Nov 4]. [www.remegen.cn/Invest2.aspx?ID=342](http://www.remegen.cn/Invest2.aspx?ID=342).

66. Peng Z, Liu T, Wei J, Wang A, He Y, Yang L, Zhang X, Fan NF, Luo S, Gong, J, et al. A phase II study of efficacy and safety of RC48-ADC in patients with locally advanced or metastatic HER2-overexpressing gastric or gastroesophageal junction cancers. *J Clin Oncol.* 2020;38(15\_suppl):Abstr 4560. doi:10.1200/JCO.2020.38.15\_suppl.4560.
67. Song Y, Zhou K, Jin C, Qian Z, Hou M, Fan L, Li F, Ding K, Zhou H, Li X, et al. A phase II study of penpulimab, an anti-PD-1 antibody, in patients with relapsed or refractory classic Hodgkin lymphoma (cHL). *Journal of Clinical Oncology.* 2021;39(15\_suppl):7529–7529. doi:10.1038/s41591-021-01444-0.
68. Akeso, Inc. Penpulimab monoclonal antibody (PD-1) obtains marketing approval in China. 2021 Aug 5 press release [accessed 2021 Nov 6]. [www.akesobio.com/en/media/akeso-news/2021-8-5/](http://www.akesobio.com/en/media/akeso-news/2021-8-5/).
69. Lin N, Zhang M, Bai H, Liu H, Cui J, Ke X, Zhang H, Liu L, Yan D, Jiang Y, et al. Efficacy and safety of GLS-010 (zimberelimab) in patients with relapsed or refractory classical Hodgkin lymphoma: a multicenter, single-arm, phase II study. *Eur J Cancer.* 2021; S0959-8049(21):00479–2. doi:10.1016/j.ejca.2021.07.021.
70. Chaudhry A, Johnson M, Colburn D, Gilbert H, Garofalo A, Paoloni M, Krishnan K. ARC-7: a phase II study to evaluate the safety and efficacy of zimberelimab alone, AB154 in combination with zimberelimab, and AB154 in combination with zimberelimab and AB928 in front-line, PD-L1 expressing, non-small cell lung cancer (NSCLC). *Annals Oncol.* 2020;31(SUPPLEMENT 4):S897. doi:10.1016/j.annonc.2020.08.1733.
71. Akeso, Inc. New drug application for cadonilimab (PD-1/CTLA-4 bi-specific antibody) for the treatment of relapsed or metastatic cervical cancer accepted by NMPA. 2021 Sept 24 press release [accessed 2021 Nov 6]. [www.akesobio.com/en/media/akeso-news/210924/](http://www.akesobio.com/en/media/akeso-news/210924/).
72. Akeso, Inc. 2020 annual results presentation. 2021 Mar [accessed 2021 Nov 5]. [www.akesobio.com/media/1404/akesoplus2020plu sarpluspresentation\\_ve-website.pdf](http://www.akesobio.com/media/1404/akesoplus2020plu sarpluspresentation_ve-website.pdf).
73. Genor Biopharma Co., Inc. Untitled. 2020 Aug 5 press release [accessed 2021 Nov 4]. [www.genorbio.com/en/media/corporate-news/nmpa-granted-priority-review-status-to-geptanolimab/](http://www.genorbio.com/en/media/corporate-news/nmpa-granted-priority-review-status-to-geptanolimab/).
74. Shi Y, Wu J, Wang Z, Zhang L, Wang Z, Zhang M, Cen H, Peng Z, Li Y, Fan L, et al. Efficacy and safety of geptanolimab (GB226) for relapsed or refractory peripheral T cell lymphoma: an open-label phase 2 study (gxplore-002). *J Hematol Oncol.* 2021;14:12. doi:10.1186/s13045-021-01033-1.
75. Shanghai Henlius Biotech Inc. The NDA of the novel anti-PD-1 serplulimab of henlius accepted by NMPA and proposed to be granted priority review. 2021 Apr 22 press release [accessed 2021 Nov 5]. [www.henlius.com/en/NewsDetails-3031-26.html](http://www.henlius.com/en/NewsDetails-3031-26.html).
76. Qin S, Li J, Zhong H, Jin C, Chen L, Yuan X, Fan Q, Chen K, Cao P, Xiao J, et al. Efficacy and safety of HLX10, a novel anti-PD-1 antibody, in patients with previously treated unresectable or metastatic microsatellite instability-high or mismatch repair-deficient solid tumors: a single-arm, multicenter, phase 2 study. *J Clin Oncol.* 2021;39(15\_suppl):2566–2566. doi:10.1200/JCO.2021.39.15\_suppl.2566.
77. Shanghai Henlius Biotech, Inc. The NDA of henlius novel anti-PD-1 mab serplulimab for first-line treatment of sqNSCLC accepted by China's NMPA, phase 3 MRCT met its primary endpoint. 2021 Sept 17 press release [accessed 2021 Nov 5]. [www.prnewswire.com/news-releases/the-nda-of-henlius-novel-anti-pd-1-mab-serplulimab-for-first-line-treatment-of-sqnsclc-accepted-by-chinas-nmpa-phase-3-mrct-met-its-primary-endpoint-301379340.html](http://www.prnewswire.com/news-releases/the-nda-of-henlius-novel-anti-pd-1-mab-serplulimab-for-first-line-treatment-of-sqnsclc-accepted-by-chinas-nmpa-phase-3-mrct-met-its-primary-endpoint-301379340.html).
78. Alphamab Oncology. Alphamab Oncology reports full year 2020 financial results and business highlights. 2021 Mar 23 press release [accessed 2021 Nov 5]. [www.alphamabonc.com/en/html/news/2217.html](http://www.alphamabonc.com/en/html/news/2217.html).
79. Li J, Deng Y, Zhang W, Zhou AP, Guo W, Yang J, Yuan Y, Zhu L, Qin S, Xiang S, et al. Subcutaneous envafolelimab monotherapy in patients with advanced defective mismatch repair/microsatellite instability high solid tumors. *J Hematol Oncol.* 2021;14(1):95. doi:10.1200/JCO.2021.39.15\_suppl.5504.
80. D'Angelo SP, Robinson SI, Lam J, Adams BJ, Freddo JL, Theuer CP, Maki RG. ENVASARC: a pivotal trial of envafolelimab, and envafolelimab in combination with ipilimumab, in patients with advanced or metastatic undifferentiated pleomorphic sarcoma or myxofibrosarcoma who have progressed on prior chemotherapy. *J Clin Oncol.* 2021;39(15\_suppl):TPS11581. doi:10.1200/JCO.2021.39.15\_suppl.TPS11581.
81. CStone Pharmaceuticals. CStone announces China's NMPA has accepted its new drug application for sugemalimab in the treatment of stage III NSCLC. 2021 Sept 2 press release [accessed 2021 Nov 5]. [www.cstonepharma.com/en/html/news/2645.html](http://www.cstonepharma.com/en/html/news/2645.html).
82. CStone Pharmaceuticals. CStone presents updated data from registrational clinical study of sugemalimab in patients with stage IV NSCLC in an oral presentation at IASLC 2021 WCLC. 2021 Sept 14 press release [accessed 2021 Nov 5]. [www.cstonepharma.com/en/html/news/2652.html](http://www.cstonepharma.com/en/html/news/2652.html).
83. CStone Pharmaceuticals. CStone will present registrational clinical study data of sugemalimab in patients with stage III non-small cell lung cancer in an oral presentation at ESMO congress. 2021 Sept 17 press release [accessed 2021 Nov 5]. [www.cstonepharma.com/en/html/news/2656.html](http://www.cstonepharma.com/en/html/news/2656.html).
84. Gui L, Han X, He X, Song Y, Yao J, Yang J, Liu P, Qin Y, Zhang S, Zhang W, et al. Phase I study of chimeric anti-CD20 monoclonal antibody in Chinese patients with CD20-positive non-Hodgkin's lymphoma. *Chin J Cancer Res.* 2016;28:197–208. doi:10.21147/j.issn.1000-9604.2016.02.07.
85. Sorrento Therapeutics, Inc. Sorrento's license partner, Lee's pharmaceutical announces NDA filing acceptance by NMPA for anti-PD-L1 antibody socazolimab for treatment of recurrent or metastatic cervical cancer. 2021 Nov 1 press release [accessed 2021 Nov 2]. [investors.sorrentotherapeutics.com/news-releases/news-release-details/sorrento-license-partner-lees-pharmaceutical-announces-nda](http://investors.sorrentotherapeutics.com/news-releases/news-release-details/sorrento-license-partner-lees-pharmaceutical-announces-nda).
86. Taisho Pharmaceutical Co., Ltd. Notification of application for approval to manufacture and market anti-tnfa multivalent NANOBODY® compound (ozoralizumab) in Japan. 2021 Mar 22 press release [accessed 2021 Sept 13]. [www.taisho.co.jp/global/news/2021/20210322000753.html](http://www.taisho.co.jp/global/news/2021/20210322000753.html).
87. I-Mab. I-Mab advances late-stage development of its differentiated CD38 antibody felzartamab (TJ202) in China. 2021 Oct 13 press release [accessed 2021 Nov 5]. [www.i-mabbiopharma.com/en/article-700.aspx](http://www.i-mabbiopharma.com/en/article-700.aspx).
88. Genentech. FDA accepts application for genentech's faricimab for the treatment of wet age-related macular degeneration (AMD) and diabetic macular edema (DME). 2021 July 28 press release [accessed 2021 Nov 5]. [www.gene.com/media/press-releases/14923/2021-07-28/fda-accepts-application-for-genentechs-f](http://www.gene.com/media/press-releases/14923/2021-07-28/fda-accepts-application-for-genentechs-f).
89. Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, Kuter DJ, Jilma B, Tvedt THA, Fruebis J, et al. Sutimlimab in cold agglutinin disease. *N Engl J Med.* 2021;384(14):1323–34. doi:10.1056/NEJMoa2027760.
90. Sanofi. Strong Q3 performance drives guidance upgrade to around 14% business EPS growth at CER. 2021 Oct 28 press release [accessed 2021 Nov 6]. [www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2021/Press\\_Release\\_Q3\\_2021\\_EN.pdf](http://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2021/Press_Release_Q3_2021_EN.pdf).
91. Sanofi. New pivotal data at EHA 2021 reinforces sutimlimab as a first-in-class investigational c1s inhibitor with the potential to be the first approved treatment for hemolysis in people with CAD, a serious and chronic autoimmune hemolytic anemia. 2021 June 11 press release [accessed 2021 Nov 6]. [www.sanofi.com/en/media-room/press-releases/2021/2021-06-11-09-00-00-2245658](http://www.sanofi.com/en/media-room/press-releases/2021/2021-06-11-09-00-00-2245658).
92. Damato BE, Dukes J, Goodall H, Carvajal RD. Tebentafusp: t cell redirection for the treatment of metastatic uveal melanoma. *Cancers (Basel).* 2019;11(7):971. doi:10.3390/cancers11070971.
93. Immunocore Holdings Plc. Immunocore announces that U.S. Food and Drug Administration and European Medicines Agency accept biologics license application and marketing authorization application for tebentafusp in metastatic uveal melanoma. 2021

- Aug 24 press release [accessed 2021 Nov 5]. [ir.immunocore.com/news-releases/news-release-details/immunocore-announces-us-food-and-drug-administration-and](https://www.immunocore.com/news-releases/news-release-details/immunocore-announces-us-food-and-drug-administration-and).
94. Piperno-Neumann S, Hassel JC, Rutkowski P, Baurain J-F, Butler MO, Schlaak M, Sullivan RJ, Ochsenreither S, Dummer R, Kirkwood JM, et al. CT002 - Phase 3 randomized trial comparing tebentafusp with investigator's choice in first line metastatic uveal melanoma. American Association for Cancer Research virtual annual meeting. 2021 Apr 10; [www.abstractsonline.com/pp8/#!/9325/presentation/5133](https://www.abstractsonline.com/pp8/#!/9325/presentation/5133).
  95. Bristol Myers Squibb. U.S. Food and drug administration accepts for priority review Bristol Myers Squibb's application for LAG-3-blocking antibody relatlimab and nivolumab fixed-dose combination as treatment for patients with unresectable or metastatic melanoma. 2021 Sept 20 press release [accessed 2021 Nov 5]. [news.bms.com/news/corporate-financial/2021/U.S.-Food-and-Drug-Administration-Accepts-for-Priority-Review-Bristol-Myers-Squibbs-Application-for-LAG-3-Blocking-Antibody-Relatlimab-and-Nivolumab-Fixed-Dose-Combination-as-Treatment-for-Patients-with-Unresectable-or-Metastatic-Melanoma/default.aspx](https://www.bms.com/news/corporate-financial/2021/U.S.-Food-and-Drug-Administration-Accepts-for-Priority-Review-Bristol-Myers-Squibbs-Application-for-LAG-3-Blocking-Antibody-Relatlimab-and-Nivolumab-Fixed-Dose-Combination-as-Treatment-for-Patients-with-Unresectable-or-Metastatic-Melanoma/default.aspx).
  96. Lipson EJ, Tawbi HA-H, Schadendorf D, Ascierto PA, Matamala L, Gutiérrez EC, Rutkowski P, Gogas H, Lao CD, Janoski de Menezes J, et al. Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase III results from RELATIVITY-047 (CA224-047). *J Clin Oncol*. 2021;39(15\_suppl):9503–9503. doi:10.1200/JCO.2021.39.15\_suppl.9503.
  97. Zhang L, Mai W, Jiang W, Geng Q. Sintilimab: a promising anti-tumor PD-1 antibody. *Front Oncol*. 2020;10:594558. doi:10.3389/fonc.2020.594558.
  98. Innovent Biologics, Inc. U.S. FDA accepts regulatory submission for sintilimab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of people with nonsquamous non-small cell lung cancer. 2021 May 18 press release [accessed 2021 Nov 5]. [www.prnewswire.com/news-releases/us-fda-accepts-regulatory-submission-for-sintilimab-in-combination-with-pemetrexed-and-platinum-chemotherapy-for-the-first-line-treatment-of-people-with-nonsquamous-non-small-cell-lung-cancer-301293152.html](https://www.prnewswire.com/news-releases/us-fda-accepts-regulatory-submission-for-sintilimab-in-combination-with-pemetrexed-and-platinum-chemotherapy-for-the-first-line-treatment-of-people-with-nonsquamous-non-small-cell-lung-cancer-301293152.html).
  99. Yang Y, Wang Z, Fang J, Yu Q, Han B, Cang S, Chen G, Mei X, Yang Z, Ma R. Efficacy and safety of sintilimab plus pemetrexed and platinum as first-line treatment for locally advanced or metastatic nonsquamous NSCLC: a randomized, double-blind, phase 3 study (oncology pProgram by innovENT anti-PD-1-11). *J Thorac Oncol*. 2020;15(10):1636–46. doi:10.1016/j.jtho.2020.07.014.
  100. Innovent Biologics, Inc. Innovent announces sintilimab in combination with chemotherapy meets the primary endpoint of overall survival in the phase 3 ORIENT-16 study for the first-line treatment of advanced or metastatic gastric or gastroesophageal junction adenocarcinoma. 2021 Aug 15 press release [accessed 2021 Nov 5]. [www.prnewswire.com/news-releases/innovent-announces-sintilimab-in-combination-with-chemotherapy-meets-the-primary-endpoint-of-overall-survival-in-the-phase-3-orient-16-study-for-the-first-line-treatment-of-advanced-or-metastatic-gastric-or-gastroesophageal-juncti-301355470.html](https://www.prnewswire.com/news-releases/innovent-announces-sintilimab-in-combination-with-chemotherapy-meets-the-primary-endpoint-of-overall-survival-in-the-phase-3-orient-16-study-for-the-first-line-treatment-of-advanced-or-metastatic-gastric-or-gastroesophageal-juncti-301355470.html).
  101. TG Therapeutics, Inc. TG therapeutics announces FDA acceptance of biologics license application for ublituximab in combination with UKONIQ® (umbralisib) as a treatment for patients with chronic lymphocytic leukemia and small lymphocytic lymphoma. 2021 May 25 press release [accessed 2021 Nov 5]. [ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-announces-fda-acceptance-biologics-license](https://www.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-announces-fda-acceptance-biologics-license).
  102. TG Therapeutics, Inc. TG therapeutics submits biologics license application to the U.S. Food and Drug Administration for ublituximab as a treatment for patients with relapsing forms of multiple sclerosis. 2021 Sept 30 press release [accessed 2021 Nov 5]. [ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-submits-biologics-license-application-us-food](https://www.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-submits-biologics-license-application-us-food).
  103. Steinman L, Fox E, Hartung H-P, Enrique Alvarez E, Qian P, Wray S, Robertson D, Huang D, Selmaj K, Wynn D, et al. Phase 3 results of the ULTIMATE I & II global studies: ublituximab versus teriflunomide in relapsing multiple sclerosis. European Committee for Treatment and Research in Multiple Sclerosis; 2021 Oct 13-15 Virtual presentation [accessed 2021 Nov]. [www.tgtherapeutics.com/wp-content/uploads/2021/10/Steinman-ORAL-ECTRIMS-2021-PH3-ULTIMATE-I-II-10.13.21.pdf](https://www.tgtherapeutics.com/wp-content/uploads/2021/10/Steinman-ORAL-ECTRIMS-2021-PH3-ULTIMATE-I-II-10.13.21.pdf).
  104. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, Brightling CE, Griffiths JM, Hellqvist Å, Bowen K, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800–09. doi:10.1056/NEJMoa2034975.
  105. Amgen. New tezepelumab data show 86% reduction in exacerbations in patients with severe asthma and comorbid nasal polyps. 2021 Sept 5 press release [accessed 2021 Nov 6]. [www.amgen.com/newsroom/press-releases/2021/09/new-tezepelumab-data-show-86-reduction-in-exacerbations-in-patients-with-severe-asthma-and-comorbid-nasal-polyps](https://www.amgen.com/newsroom/press-releases/2021/09/new-tezepelumab-data-show-86-reduction-in-exacerbations-in-patients-with-severe-asthma-and-comorbid-nasal-polyps).
  106. Akeso, Inc. Akeso penpulimab monoclonal antibody (PD-1) submitted BLA in the United States. 2021 May 24 press release [accessed 2021 Nov 4]. [www.akesobio.com/en/media/akeso-news/21-5-24/](https://www.akesobio.com/en/media/akeso-news/21-5-24/).
  107. Chen X, Wang W, Zou Q, Li J, Hu C, Hu C, Lin Q, Zhu X, Jiang Y, Sun Y, et al. 804 A phase II study of the anti-programmed cell death-1 (PD-1) antibody penpulimab in patients with metastatic nasopharyngeal carcinoma (NPC) who had progressed after two or more lines of chemotherapy. *Journal for ImmunoTherapy of Cancer*. 2020;8(Suppl 3):A853–A853. doi:10.1136/jitc-2020-SITC2020.0804.
  108. BeiGene, Ltd. BeiGene announces U.S. FDA acceptance of biologics license application for tislelizumab in esophageal squamous cell carcinoma. 2021 Sept 13 press release [accessed 2021 Sept 13]. [ir.beigene.com/news-details/?id=5c97c078-8ee7-4a4e-aba3-19d5a9dac715](https://ir.beigene.com/news-details/?id=5c97c078-8ee7-4a4e-aba3-19d5a9dac715).
  109. Shen L, Kato K, Kim S-B, Ajani JA, Zhao K, He Z, Yu X, Shu Y, Luo Q, Wang J, et al. RATIONALE 302: randomized, phase 3 study of tislelizumab versus chemotherapy as second-line treatment for advanced unresectable/metastatic esophageal squamous cell carcinoma. *J Clin Oncol*. 2021;39(15\_suppl):4012–4012. doi:10.1200/JCO.2021.39.15\_suppl.4012.
  110. BeiGene, Ltd. China national medical products administration approves beigene's tislelizumab for patients with classical hodgkin's lymphoma who have received at least two prior therapies. 2019 Dec 27 press release [accessed 2021 Nov 6]. [ir.beigene.com/news-details/?id=e524da7d-6573-4abb-8c9a-dc5672ea87aa](https://ir.beigene.com/news-details/?id=e524da7d-6573-4abb-8c9a-dc5672ea87aa).
  111. BeiGene, Ltd. China national medical products administration approves beigene's tislelizumab for patients with previously treated locally advanced or metastatic urothelial carcinoma. 2020 Apr 10 press release [accessed 2021 Nov 6]. [ir.beigene.com/news-details/?id=9d7cfa84-81fd-44e1-b8dc-f5d82068095a](https://ir.beigene.com/news-details/?id=9d7cfa84-81fd-44e1-b8dc-f5d82068095a).
  112. Ye D, Liu J, Zhou A, Zou Q, Li H, Fu C, Hu H, Huang J, Zhu S, Jin J, et al. Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. *Cancer Science*. 2021 Jan;112(1):305–13. doi:10.1111/cas.14681.
  113. BeiGene, Ltd. China national medical products administration approves tislelizumab in combination with chemotherapy in first-line advanced squamous non-small cell lung cancer. 2021 Jan 13 press release [accessed 2021 Nov 6]. [ir.beigene.com/news-details/?id=bafd0e50-64fe-4313-9f63-a58be0fc2c54](https://ir.beigene.com/news-details/?id=bafd0e50-64fe-4313-9f63-a58be0fc2c54).
  114. Wang J, Lu S, Yu X, Hu Y, Sun Y, Wang Z, Zhao J, Yu Y, Hu C, Yang K, et al. Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. 2021;7:709–17. doi:10.1001/jamaoncol.2021.0366.
  115. BeiGene, Ltd. China NMPA approves tislelizumab in non-small cell lung cancer and hepatocellular carcinoma. 2021 June 23 press release [accessed 2021 Nov 6]. [ir.beigene.com/news-details/?id=06abb5cf-b5fa-405e-9d3b-e800e1106b99](https://ir.beigene.com/news-details/?id=06abb5cf-b5fa-405e-9d3b-e800e1106b99).



116. Eisai Co., Ltd., Biogen Inc. Eisai initiates rolling submission to the U.S. FDA for biologics license application of lecanemab (BAN2401) for early Alzheimer's disease under the accelerated approval pathway. 2021 Sept 28 press release [accessed 2021 Nov 6]. [www.eisai.com/news/2021/pdf/enews202177pdf.pdf](http://www.eisai.com/news/2021/pdf/enews202177pdf.pdf).
117. Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, Lannfelt L, Bradley H, Rabe M, Koyama A, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-A $\beta$  protofibril antibody. *Alzheimers Res Ther.* 2021;13(1):80. doi:10.1186/s13195-021-00813-8.
118. Coherus BioSciences, Inc. Shanghai Junshi Biosciences Co., Ltd. Coherus and Junshi Biosciences announce FDA acceptance of BLA filing for toripalimab for treatment of nasopharyngeal carcinoma. 2021 Nov 1 press release [accessed 2021 Nov 6]. [investors.coherus.com/news-releases/news-release-details/coherus-and-junshi-biosciences-announce-fda-acceptance-bla](http://investors.coherus.com/news-releases/news-release-details/coherus-and-junshi-biosciences-announce-fda-acceptance-bla).
119. Wang FH, Wei XL, Feng J, Li Q, Xu N, Hu XC, Liao W, Jiang Y, Lin XY, Zhang QY, et al. Efficacy, safety, and correlative biomarkers of toripalimab in previously treated recurrent or metastatic nasopharyngeal carcinoma: a phase II clinical trial (POLARIS-02). *J Clin Oncol.* 2021;39(7):704–12. doi:10.1200/JCO.20.02712.
120. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi YR, Jin F, Xu R, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. *Nat Med.* 2021;27(9):1536–43. doi:10.1038/s41591-021-01444-0.
121. Coherus BioSciences, Inc. Coherus and Junshi Biosciences announce positive interim results of CHOICE-01, a phase 3 clinical trial evaluating toripalimab in combination with chemotherapy as first-line treatment for non-small cell lung cancer. 2021 Aug 18 press release [accessed 2021 Nov 6]. [investors.coherus.com/news-releases/news-release-details/coherus-and-junshi-biosciences-announce-positive-interim-results/](http://investors.coherus.com/news-releases/news-release-details/coherus-and-junshi-biosciences-announce-positive-interim-results/).
122. ElsaLys Biotech SA. While ElsaLys continues to work on the filing of marketing approval in Europe and the U.S. for inolimomab, the company confirms the renew of its cohort ATU in France and compassionate use programs submissions in several other countries. 2021 Apr 14 press release [accessed 2021 Nov 6]. [www.elsalysbiotech.com/node/118](http://www.elsalysbiotech.com/node/118).
123. Y-mAbs Therapeutics, Inc. Y-mAbs submits omburtamab marketing authorization application to the European medicines agency. 2021 Apr 27 press release [accessed 2021 Nov 6]. [ir.ymabs.com/news-releases/news-release-details/y-mabs-submits-omburtamab-marketing-authorization-application](http://ir.ymabs.com/news-releases/news-release-details/y-mabs-submits-omburtamab-marketing-authorization-application).
124. Y-mAbs Therapeutics, Inc. Y-mAbs announces third quarter financial results and recent corporate developments. 2021 Nov 4 press release [accessed 2021 Nov 5]. [ir.ymabs.com/news-releases/news-release-details/y-mabs-announces-third-quarter-financial-results-and-recent](http://ir.ymabs.com/news-releases/news-release-details/y-mabs-announces-third-quarter-financial-results-and-recent).
125. Samotij D, Szczęch J, Reich A. Generalized pustular psoriasis: divergence of innate and adaptive immunity. *Int J Mol Sci.* 2021;22(16):9048. doi:10.3390/ijms22169048.
126. Boehringer Ingelheim. Boehringer Ingelheim announces European Medicines Agency's filing acceptance and validation of marketing authorization application for spesolimab in generalized pustular psoriasis. 2021 Oct 29 press release [accessed 2021 Nov 6]. [www.boehringer-ingelheim.com/press-release/ema-filing-acceptance-and-validation-spesolimab](http://www.boehringer-ingelheim.com/press-release/ema-filing-acceptance-and-validation-spesolimab).
127. Choon SE, Leibold MG, Marrakchi S, Burden AD, Tsai T-F, Morita A, Navarini AA, Zheng M, Xu J, Turki H, et al. Study protocol of the global Effisayil 1 phase II, multicentre, randomised, double-blind, placebo-controlled trial of spesolimab in patients with generalized pustular psoriasis presenting with an acute flare. *BMJ Open.* 2021 11(3):e043666. doi:10.1136/bmjopen-2020-043666.
128. U.S. Food and Drug Administration. FDA briefing document, endocrinologic and metabolic drugs advisory committee meeting: teplizumab BLA 761183. 2021 May 27 [accessed 2021 Nov 5]. [www.fda.gov/media/149388/download](http://www.fda.gov/media/149388/download).
129. Provention Bio, Inc. Provention bio receives complete response letter (CRL) to biologics license application (BLA) for teplizumab for the delay of clinical type 1 diabetes (T1D) in at-risk individuals. 2021 July 6 press release [accessed 2021 Nov 6]. [investors.proventionbio.com/2021-07-06-Provention-Bio-Receives-Complete-Response-Letter-CRL-to-Biologics-License-Application-BLA-for-Teplizumab-for-the-Delay-of-Clinical-Type-1-Diabetes-T1D-in-At-risk-Individuals](http://investors.proventionbio.com/2021-07-06-Provention-Bio-Receives-Complete-Response-Letter-CRL-to-Biologics-License-Application-BLA-for-Teplizumab-for-the-Delay-of-Clinical-Type-1-Diabetes-T1D-in-At-risk-Individuals).
130. U.S. Food and Drug Administration. FDA briefing document, oncologic drugs advisory committee meeting: retifanlimab-dlwr infusion BLA 761209. 2021 June 24 [accessed 2021 Nov 5]. [www.fda.gov/media/150251/download](http://www.fda.gov/media/150251/download).
131. Incyte Corporation. Incyte announces outcome of FDA Oncologic Drugs Advisory Committee (ODAC) meeting reviewing retifanlimab as a treatment for patients with squamous cell carcinoma of the anal canal (SCAC). 2021 June 24 press release [accessed 2021 Nov 6]. [investor.incyte.com/press-releases/press-releases/2021/Incyte-Announces-Outcome-of-FDA-Oncologic-Drugs-Advisory-Committee-ODAC-Meeting-Reviewing-Retifanlimab-as-a-Treatment-for-Patients-with-Squamous-Cell-Carcinoma-of-the-Anal-Canal-SCAC/default.aspx](http://investor.incyte.com/press-releases/press-releases/2021/Incyte-Announces-Outcome-of-FDA-Oncologic-Drugs-Advisory-Committee-ODAC-Meeting-Reviewing-Retifanlimab-as-a-Treatment-for-Patients-with-Squamous-Cell-Carcinoma-of-the-Anal-Canal-SCAC/default.aspx).
132. Incyte Corporation. Incyte provides regulatory update on retifanlimab for the treatment of certain patients with squamous cell carcinoma of the anal canal (SCAC). 2021 July 23 press release [accessed 2021 Nov 6]. [investor.incyte.com/press-releases/press-releases/2021/Incyte-Provides-Regulatory-Update-on-Retifanlimab-for-the-Treatment-of-Certain-Patients-with-Squamous-Cell-Carcinoma-of-the-Anal-Canal-SCAC/default.aspx](http://investor.incyte.com/press-releases/press-releases/2021/Incyte-Provides-Regulatory-Update-on-Retifanlimab-for-the-Treatment-of-Certain-Patients-with-Squamous-Cell-Carcinoma-of-the-Anal-Canal-SCAC/default.aspx).
133. Sesen Bio, Inc. Business update call. 2021 2021 Aug 16 [accessed 2021 Nov 6]. [ir.sesenbio.com/static-files/cb6d46da-104c-4721-bfc3-f38c18711b71](http://ir.sesenbio.com/static-files/cb6d46da-104c-4721-bfc3-f38c18711b71).
134. Sesen Bio, Inc. United States securities and exchange commission form 8-K. 2021 Aug 20 [accessed 2021 Nov 6]. [ir.sesenbio.com/static-files/4b10acb3-3750-4995-b9ce-48a820549f0b](http://ir.sesenbio.com/static-files/4b10acb3-3750-4995-b9ce-48a820549f0b).
135. Omeros Corporation. Omeros provides regulatory update on biologics license application for narsoplimab in the treatment of HSCT-TMA. 2021 Oct 1 press release [accessed 2021 Nov 5]. [investor.omeros.com/news-releases/news-release-details/omeros-provides-regulatory-update-biologics-license-application](http://investor.omeros.com/news-releases/news-release-details/omeros-provides-regulatory-update-biologics-license-application).
136. Perales M-A, Cairo MS, Duarte RF, Giral S, Ho -VT-V, Laurence J, Leung N, Penack O, Rambaldi A, Scordo M, et al. Narsoplimab (OMS721) treatment contributes to improvements in organ function in adult patients with high-risk transplant-associated thrombotic microangiopathy. *European Hematology Association*; 2021 June 11 [accessed 2021 Nov 5]. [investor.omeros.com/static-files/bcb7c499-95e8-4a21-a4f9-4fe64df750d8](http://investor.omeros.com/static-files/bcb7c499-95e8-4a21-a4f9-4fe64df750d8).
137. Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, Shcherbinin S, Sparks J, Sims JR, Brys M, et al. Donanemab in early Alzheimer's disease. *N Engl J Med.* 2021;384(18):1691–704. doi:10.1056/NEJMoa2100708.
138. Kaplon H, Reichert JM. Antibodies to watch in 2021. *MABS.* 2021;13(1):1860476. doi:10.1080/19420862.2020.1860476.
139. PhaseBio Pharmaceuticals, Inc. PhaseBio announces interim results from pivotal REVERSE-IT phase 3 trial of bentracimab for the reversal of antiplatelet effects of ticagrelor in patients requiring urgent surgery or experiencing uncontrolled major or life-threatening bleeding. 2021 Nov 15 press release [accessed 2021 Nov 16]. [investors.phasebio.com/news-releases/news-release-details/phasebio-announces-interim-results-pivotal-reverse-it-phase-3](http://investors.phasebio.com/news-releases/news-release-details/phasebio-announces-interim-results-pivotal-reverse-it-phase-3).
140. Chugai Pharmaceuticals. Chugai's strategy for drug discovery research. 2019 Dec 9 presentation [accessed 2021 Nov 6]. [www.chugai-pharm.co.jp/cont\\_file\\_dl.php?f=FILE\\_1\\_85.pdf&src=\[%0\],\[%1\]&rep=139,85](http://www.chugai-pharm.co.jp/cont_file_dl.php?f=FILE_1_85.pdf&src=[%0],[%1]&rep=139,85).
141. Roche. Roche pharma day 2021. 2021 Sept 14 presentation [accessed 2021 Nov 6]. [www.roche.com/dam/jcr:178db2c0-31b1-4ad1-aaea-e7eff839bcf6/en/irp20210914.pdf](http://www.roche.com/dam/jcr:178db2c0-31b1-4ad1-aaea-e7eff839bcf6/en/irp20210914.pdf).
142. Roche. H2 2021 results. 2021 July 22 [accessed 2021 Nov 6]. [www.roche.com/dam/jcr:a1437516-3f73-4112-a483-40c8b1c3836e/en/irp210722.pdf](http://www.roche.com/dam/jcr:a1437516-3f73-4112-a483-40c8b1c3836e/en/irp210722.pdf).

143. Klein G, Delmar P, Kerchner GA, Hofmann C, Abi-Saab D, Davis A, Voyle N, Baudler M, Fontoura P, Doody R. Thirty-six-month amyloid positron emission tomography results show continued reduction in amyloid burden with subcutaneous gantenerumab. *J Prev Alzheimers Dis.* 2021;8(1):3–6. doi:10.14283/jpad.2020.68.
144. Salloway S, Farlow M, McDade E, Clifford DB, Wang G, Llibre-Guerra JJ, Hitchcock JM, Mills SL, Santacruz AM, Aschenbrenner AJ, et al. A trial of gantenerumab or solanezumab in dominantly inherited alzheimer's disease. *Nat Med.* 2021;27(7):1187–96. doi:10.1038/s41591-021-01369-8.
145. Novartis Pharmaceuticals Corporation. Q2 2021 results. Investor presentation; [accessed 2021 Nov 6]. [www.novartis.com/sites/www.novartis.com/files/q2-2021-investor-presentation.pdf](http://www.novartis.com/sites/www.novartis.com/files/q2-2021-investor-presentation.pdf).
146. AstraZeneca. Nirsevimab MELODY phase III trial met primary endpoint of reducing RSV lower respiratory tract infections in healthy infants. 2021 Apr 26 press release [accessed 2021 Oct 10]. [www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/nirsevimab-phase-iii-trial-met-primary-endpoint.html](http://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/nirsevimab-phase-iii-trial-met-primary-endpoint.html).
147. AstraZeneca. Nirsevimab MEDLEY phase II/III trial demonstrated favourable safety and tolerability profile in infants at high risk of RSV. 2021 June 28 press release [accessed 2021 Nov 5]. [www.astrazeneca.com/media-centre/press-releases/2021/nirsevimab-phii-iii-trial-confirms-safety-profile.html](http://www.astrazeneca.com/media-centre/press-releases/2021/nirsevimab-phii-iii-trial-confirms-safety-profile.html).
148. Assouline SE, Kim WS, Sehn LH, Schuster SJ, Cheah CY, Nastoupil LJ, Shadman M, Yoon S-S, Matasar MJ, Diefenbach C, et al. Mosunetuzumab shows promising efficacy in patients with multiply relapsed follicular lymphoma: updated clinical experience from a phase I dose-escalation trial. *Blood.* 2020;136(Supplement 1):42–44. doi:10.1182/blood-2020-135839.
149. Budde LE, Ghosh N, Chavez JC, Lossos IS, Mehta A, Dorritie KA, Kamdar MK, Negricea R, Pham S, Hristopoulos M, et al. Promising tolerability and efficacy results from dose-escalation in an ongoing phase Ib/II study of mosunetuzumab (M) with polatuzumab vedotin (pola) in patients (pts) with relapsed/refractory (R/R) B-cell non-hodgkin's lymphoma (B-NHL). *J Clin Oncol.* 2021;39(15\_suppl):7520–7520. doi:10.1200/JCO.2021.39.15\_suppl.7520.
150. Gilead Sciences, Inc. Q3 21 financial results. 2021 Oct 28 [accessed 2021 Nov 6]. [investors.gilead.com/static-files/cf9f2815-947e-4d97-adcc-7d50ee064075](http://investors.gilead.com/static-files/cf9f2815-947e-4d97-adcc-7d50ee064075).
151. ImmunoGen, Inc. ImmunoGen reports recent progress and third quarter 2021 financial results. 2021 Oct 29 press release [accessed 2021 Nov 7]. [investor.immunogen.com/news-releases/news-release-details/immunogen-reports-recent-progress-and-third-quarter-2021](http://investor.immunogen.com/news-releases/news-release-details/immunogen-reports-recent-progress-and-third-quarter-2021).
152. O'Malley DM, Oaknin A, Matulonis UA, Mantia-Smaldone G, Lim PC, Castro CM, Provencher DM, Memarzadeh S, Zweidler-mckay PA, Wang J, et al. Mirvetuximab soravtansine, a folate receptor alpha (FR $\alpha$ )-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-agnostic ovarian cancer: final analysis. *J Clin Oncol.* 2021;39(15\_suppl):5504–5504. doi:10.1200/JCO.2021.39.15\_suppl.5504.
153. Surowka M, Schaefer W, Klein C. Ten years in the making: application of CrossMab technology for the development of therapeutic bispecific antibodies and antibody fusion proteins. *MAbs.* 2021;13(1):1967714. doi:10.1080/19420862.2021.1967714.
154. Cremasco F, Menietti E, Speziale D, Sam J, Sammicheli S, Richard M, Varol A, Klein C, Umana P, Bacac M, et al. Cross-linking of T cell to B cell lymphoma by the T cell bispecific antibody CD20-TCB induces IFN $\gamma$ /CXCL10-dependent peripheral T cell recruitment in humanized murine model. *PLoS One.* 2021;16(1):e0241091. doi:10.1371/journal.pone.0241091.
155. Hutchings M, Morschhauser F, Iacoboni G, Carlo-Stella C, Offner FC, Sureda A, Salles G, Martínez-Lopez J, Crump M, Thomas DN, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *J Clin Oncol.* 2021 39(18):1959–70. doi:10.1200/JCO.20.03175.
156. Sahin U, Türeci Ö, Manikhas G, Lordick F, Rusyn A, Vynnychenko I, Dudov A, Bazin I, Bondarenko I, Melichar B. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. *Annals Oncol.* 2021;32(5):609–19. doi:10.1016/j.annonc.2021.02.005.
157. Klempner SJ, Lee K-W, Metges J-P, Catenacci DVT, Loupakis F, Ilson DH, Shah MA, Shitara K, Arozullah A, Park JW, et al. Phase 2 study of zolbetuximab plus mFOLFOX6 in claudin 18.2-positive locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (G/GEJ): ILUSTRO cohort 2. *J Clin Oncol.* 2021;39(15\_suppl). doi:10.1200/JCO.2021.39.15\_suppl.e16063.
158. Harjunpää H, Guillerey C. TIGIT as an emerging immune checkpoint. *Clin Exp Immunol.* 2020;200(2):108–19. doi:10.1111/cei.13407.
159. Meric-Bernstam F, Hanna DL, El-Khoueiry AB, Kang Y-K, Oh DY, Chaves JM, Rha SY, Hamilton EP, Pant S, Javle MM, et al. Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): results from a phase I study. *J Clin Oncol.* 2021;39(3\_suppl):299–299. doi:10.1200/JCO.2021.39.3\_suppl.299.
160. Zymeworks Inc. Zanidatamab phase 2 clinical trial demonstrates promising response rate and durability in first-line HER2-positive gastroesophageal adenocarcinoma (GEA) at the European Society for Medical Oncology (ESMO) annual congress. 2021 Sept 16 press release [accessed 2021 Nov 7]. [ir.zymeworks.com/news-releases/news-release-details/zanidatamab-phase-2-clinical-trial-demonstrates-promising](http://ir.zymeworks.com/news-releases/news-release-details/zanidatamab-phase-2-clinical-trial-demonstrates-promising).
161. DiLillo DJ, Olson K, Mohrs K, Meagher TC, Bray K, Sineshchekova O, Startz T, Kuhnert J, Retter MW, Godin S. A BCMAXCD3 bispecific T cell-engaging antibody demonstrates robust antitumor efficacy similar to that of anti-BCMA CAR T cells. *Blood Advances.* 2021;5(5):1291–304. doi:10.1182/bloodadvances.2020002736.
162. Madduri D, Rosko A, Brayer J, Zonder J, Bensinger WI, Li J, Xu L, Adriaens L, Chokshi D, Zhang W, et al. REGN5458, a BCMA x CD3 bispecific monoclonal antibody, induces deep and durable responses in patients with relapsed/refractory multiple myeloma (RRMM). American Society of Hematology 62<sup>nd</sup> Annual Meeting and Exposition; 2020 Dec 5-8. [ash.confex.com/ash/2020/webprogram/Paper139192.html](http://ash.confex.com/ash/2020/webprogram/Paper139192.html).
163. Regeneron Pharmaceuticals, Inc. Regeneron corporate presentation. 2021 Nov [accessed 2021 Nov 7]. [investor.regeneron.com/static-files/fe9d17bb-38cc-4a2c-b96c-dbc4a79d072e](http://investor.regeneron.com/static-files/fe9d17bb-38cc-4a2c-b96c-dbc4a79d072e).
164. Smith EL, Harrington K, Staehr M, Masakayan R, Jones J, Long TJ, Ng KY, Ghoddusi M, Purdon TJ, Wang X. GPRC5D is a target for the immunotherapy of multiple myeloma with rationally designed CAR T cells. *Sci Transl Med.* 2019;11:eaa07746. doi:10.1126/scitranslmed.aau7746.
165. Berdeja JG, Krishnan AY, Oriol A, van de Donk NW, Rodríguez-Otero P, Askari E, M-v M, Monique C, Minnema CLJ, Verona R, et al. Updated results of a phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM). *J Clin Oncol.* 2021;39(suppl 15):abstr 8008. doi:10.1200/JCO.2021.39.15\_suppl.8008.
166. Usmani SZ, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, Rosinol L, Chari A, Bhutani M, Karlin L. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. *Lancet.* 2021;398(10301):665–74. doi:10.1016/S0140-6736(21)01338-6.
167. Bannerji R, Allan JN, Arnason JE, Brown JR, Advani R, Ansell SM, O'Brien SM, Duell J, Martin P, Joyce RM, et al. Odronebamab (REGN1979), a human CD20 x CD3 bispecific antibody, induces durable, complete responses in patients with highly refractory B-cell non-Hodgkin lymphoma, including patients refractory to

- CAR T therapy. American Society of Hematology 62<sup>nd</sup> Annual Meeting and Exposition; 2020 Dec 5-8. [ash.confex.com/ash/2020/webprogram/Paper136659.html](http://ash.confex.com/ash/2020/webprogram/Paper136659.html).
168. Kim TM, Alonso A, Prince M, Taszner M, Cho S-G, Stevens DA, Poon M, Lim F, Le Gouill S, Carpio C, et al. A phase 2 study of odronextamab (REGN1979), a CD20 x CD3 bispecific antibody, in patients with relapsed/refractory B-cell non-Hodgkin lymphoma. American Society of Hematology 62<sup>nd</sup> Annual Meeting and Exposition; 2020 Dec 5-8. [ash.confex.com/ash/2020/webprogram/Paper136344.html](http://ash.confex.com/ash/2020/webprogram/Paper136344.html).
  169. Novartis. Q3 2021 results: investor presentation. [accessed 2021 Nov 19]. [prod1.novartis.com/sites/novartis\\_com/files/q3-2021-investor-presentation.pdf](http://prod1.novartis.com/sites/novartis_com/files/q3-2021-investor-presentation.pdf).
  170. Checkpoint Therapeutics, Inc. Checkpoint therapeutics reports third quarter 2021 financial results. 2021 Nov 4 press release [accessed 2021 Nov 6]. <https://ir.checkpointtx.com/news-events/press-releases/detail/75/checkpoint-therapeutics-reports-third-quarter-2021>.
  171. Actinium Pharmaceuticals, Inc. Actinium completes enrollment in the pivotal phase 3 SIERRA trial of Iomab-B. 2021 Sept 15 press release [accessed 2021 Nov 7]. [ir.actiniumpharma.com/press-releases/detail/401/actinium-completes-enrollment-in-the-pivotal-phase-3-sierra](http://ir.actiniumpharma.com/press-releases/detail/401/actinium-completes-enrollment-in-the-pivotal-phase-3-sierra).
  172. Actinium Pharmaceuticals, Inc. Pivotal Phase 3 SIERRA trial data showing 100% bone marrow transplant engraftment in patients treated with Iomab-B presented at the 2021 virtual SNMMI conference. 2021 June 15 press release [accessed 2021 Nov 7]. [ir.actiniumpharma.com/press-releases/detail/398/pivotal-phase-3-sierra-trial-data-showing-100-bone-marrow](http://ir.actiniumpharma.com/press-releases/detail/398/pivotal-phase-3-sierra-trial-data-showing-100-bone-marrow).
  173. Alphamab Oncology. Completion of patient enrollment in a phase III clinical trial of kn046 in combination with chemotherapy in the treatment of advanced unresectable or metastatic squamous NSCLC. 2021 Oct 15 press release [accessed 2021 Nov 6]. [www1.hkexnews.hk/listedco/listconews/sehk/2021/1015/2021101501156.pdf](http://www1.hkexnews.hk/listedco/listconews/sehk/2021/1015/2021101501156.pdf).
  174. Yang Y, Fang W, Huang Y, Li X, Huang S, Wu J, Li Y, Chang B, Hu S, Yang S, et al. A phase 2, open-label, multicenter study to evaluate the efficacy, safety, and tolerability of KN046 in combination with chemotherapy in subjects with advanced non-small cell lung cancer. *J Clin Oncol.* 2021;39(15\_suppl):9060-9060. doi:10.1200/JCO.2021.39.15\_suppl.9060.
  175. Agenus. Agenus provides update on balstilimab development. 2021 Oct 22 press release [accessed 2021 Nov 7]. [investor.agenusbio.com/news-releases/news-release-details/agenus-provides-update-balstilimab-development](http://investor.agenusbio.com/news-releases/news-release-details/agenus-provides-update-balstilimab-development).
  176. Pfizer Inc., Eli Lilly and Company. Joint FDA advisory committee votes on application for tanezumab for the treatment of osteoarthritis pain. 2021 Mar 25 press release [accessed 2021 Nov 7]. [www.pfizer.com/news/press-release/press-release-detail/joint-fda-advisory-committee-votes-application-tanezumab](http://www.pfizer.com/news/press-release/press-release-detail/joint-fda-advisory-committee-votes-application-tanezumab).
  177. European Medicines Agency. EMA/512898/2021, EMEA/H/C/005189/0000: refusal of the marketing authorisation for raylumis (tanezumab). 2021 Sept 17 [accessed 2021 Nov 7]. [www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-raylumis-tanezumab\\_en.pdf](http://www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-raylumis-tanezumab_en.pdf).
  178. Pfizer Inc. Pfizer reports third-quarter 2021 results. 2021 Nov 2 press release [accessed 2021 Nov 7] [s21.q4cdn.com/317678438/files/doc\\_financials/2021/q3/Q3-2021-PFE-Earnings-Release.pdf](http://s21.q4cdn.com/317678438/files/doc_financials/2021/q3/Q3-2021-PFE-Earnings-Release.pdf).