


## Antibodies to watch in 2019

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### ABSTRACT

For the past 10 years, the annual 'Antibodies to watch' articles have provided updates on key events in the late-stage development of antibody therapeutics, such as first regulatory review or approval, that occurred in the year before publication or were anticipated to occur during the year of publication. To commemorate the 10th anniversary of the article series and to celebrate the 2018 Nobel Prizes in Chemistry and in Physiology or Medicine, which were given for work that is highly relevant to antibody therapeutics research and development, we expanded the scope of the data presented to include an overview of all commercial clinical development of antibody therapeutics and approval success rates for this class of molecules. Our data indicate that: 1) antibody therapeutics are entering clinical study, and being approved, in record numbers; 2) the commercial pipeline is robust, with over 570 antibody therapeutics at various clinical phases, including 62 in late-stage clinical studies; and 3) Phase 1 to approval success rates are favorable, ranging from 17–25%, depending on the therapeutic area (cancer vs. non-cancer). In 2018, a record number (12) of antibodies (ereunumab (Aimovig), fremanezumab (Ajovy), galcanezumab (Emgality), burosumab (Crysvida), lanadelumab (Takhzyro), caplacizumab (Cablivi), mogamulizumab (Poteligeo), moxetumomab pasudodox (Lumoxiti), cemiplimab (Libtayo), ibalizumab (Trogarzo), til-drakizumab (Ilumetri, Ilumya), emapalunab (Gamifant)) that treat a wide variety of diseases were granted a first approval in either the European Union (EU) or United States (US). As of November 2018, 4 antibody therapeutics (sacituzumab govitecan, ravulizumab, risankizumab, romosozumab) were being considered for their first marketing approval in the EU or US, and an additional 3 antibody therapeutics developed by Chinese companies (tislelizumab, sintilimab, camrelizumab) were in regulatory review in China. In addition, our data show that 3 product candidates (leronlimab, bro-lucizumab, polatuzumab vedotin) may enter regulatory review by the end of 2018, and at least 12 (eptinezumab, teprotumumab, crizanalizumab, satralizumab, tanezumab, isatuximab, spartalizumab, MOR208, oportuzumab monatox, TSR-042, enfortumab vedotin, ublituximab) may enter regulatory review in 2019. Finally, we found that approximately half (18 of 33) of the late-stage pipeline of antibody therapeutics for cancer are immune checkpoint modulators or antibody-drug conjugates. Of these, 7 (tremelimumab, spartalizumab, BCD-100, omburtamab, mirvetuximab soravtansine, trastuzumab duocarmazine, and depatuxizumab mafodotin) are being evaluated in clinical studies with primary completion dates in late 2018 and in 2019, and are thus 'antibodies to watch'. We look forward to documenting progress made with these and other 'antibodies to watch' in the next installment of this article series.

### ARTICLE HISTORY

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## Introduction

The rise in the importance of monoclonal antibody (mAb) therapeutics to medical care over the past 30 years has been extraordinary. During this time, a plethora of scientific and technological advances both large and small have facilitated the discovery and development of mAb therapeutics, over 80 of which have been granted marketing approvals. In 2018, scientists responsible for two advances critical to antibody discovery, phage display and immune checkpoint modulation, were awarded Nobel prizes. George P. Smith and Sir Gregory P. Winter were jointly awarded Nobel Prizes in Chemistry for phage display of peptides and antibodies.<sup>1</sup> George Smith first described the use of phage display in 1985,<sup>2</sup> and the proof of concept for phage-displayed peptide libraries in 1990.<sup>3</sup> Also in 1990, Sir Gregory Winter and colleagues reported the display of a folded and fully functional antibody fragment on filamentous phage. Since then, this technology has been used for

research and development of antibodies by organizations located world-wide,<sup>4,5</sup> yielding over 80 antibodies that entered clinical study. Of these, more than 10 have been granted marketing approvals. In 2002, adalimumab became the first mAb therapeutic derived from phage display to be granted a marketing approval. It has since become the most successful mAb on the market, and is currently prescribed for a wide variety of immune-mediated disorders (rheumatoid arthritis, juvenile rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, axial spondyloarthritis, ulcerative colitis, uveitis, hidradenitis suppurativa and Behçet syndrome).

Compared to phage display, the discovery of immune system checkpoints in the 1990s appeared to be less directly related to the field of antibody research and development, but it is arguably now equally important. In acknowledgement of the value of this work, the 2018 Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo

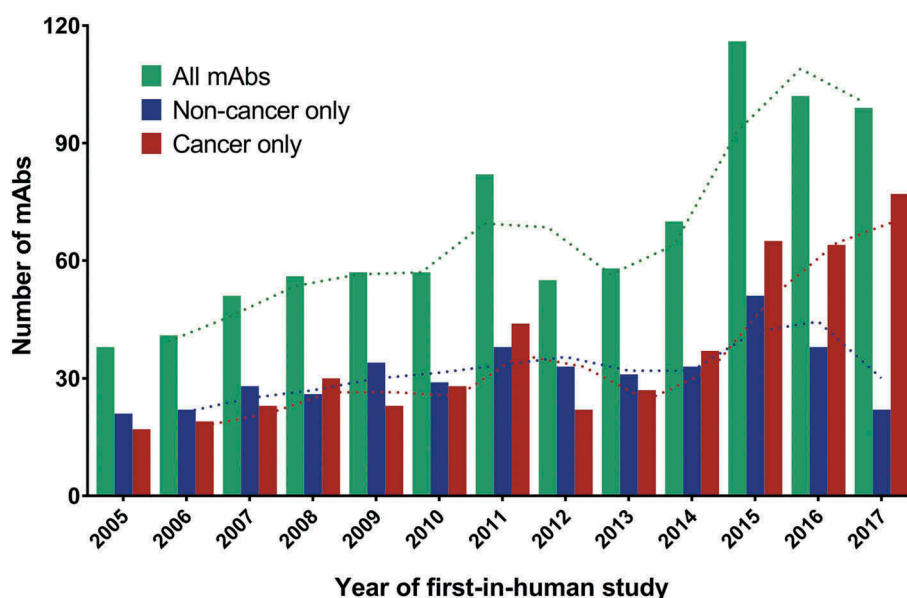
for their discovery of cancer therapy by inhibition of negative immune regulation.<sup>6</sup> Tasuku Honjo and colleagues first described the programmed cell death 1 (PD-1) protein in 1992,<sup>7</sup> and James Allison and colleagues reported in 1996<sup>8</sup> that blocking CTLA-4's inhibitory effects improved immune responses directed toward tumor cells. Since then, the number of proteins known to function as either stimulatory or inhibitory checkpoints of the immune system has dramatically expanded,<sup>9</sup> and numerous antibody therapeutics targeting PD-1 (cemiplimab, nivolumab, pembrolizumab), the ligand for PD-1 (PD-L1; durvalumab, avelumab, atezolizumab) or CTLA-4 (ipilimumab) have been granted marketing approvals. Because these therapeutics act by enhancing the immune system response rather than targeting a tumor antigen, they are used to treat many types of cancers, including melanoma, non-small-cell lung cancer, renal cell cancer, urothelial carcinoma, hepatocellular cancer, gastric cancer, colorectal cancer, head and neck cancer, Merkel cell carcinoma and Hodgkin's lymphoma. Remarkably, there are ~120 antibody immune checkpoint modulators currently in clinical studies, together comprising ~20% of the total commercial clinical pipeline of antibody therapeutics. MABs in the clinical pipeline target CTLA-4, PD-1 and PD-L1, but also other immune system checkpoints such as CD40, GITR, LAG-3, OX40, TIGIT and TIM-3.

Numerous scientific discoveries, including phage display and immune checkpoint modulation, technological advances, and substantial efforts by a multitude of researchers and medical professionals enabled the increase in the number of commercially sponsored first-in-human clinical studies of antibody therapeutics from ~12 per year in the early 1990s to ~30 per year by the mid-2000s,<sup>10</sup> and then to ~70 per year in 2014 (Figure 1). During 2015 to 2017, however, the number of antibody therapeutics entering a first Phase 1 study each year did not gradually increase, but rather

soared upward, averaging just over 100 per year over the 3-year period. Data from this 3-year period also shows a remarkable trend toward development of antibody therapeutics for cancer at the expense of the development of such therapeutics for non-cancer indications. It remains to be seen whether these trends continue into the future.

The comparatively high approval success rates for mAbs may be one reason for the growing interest in the development of these therapeutics. As reported by Hay et al.,<sup>11</sup> biologics such as mAbs have a likelihood of approval of near 1 in 4 compared to that of new molecular entities, which approach 1 in 8. Simply put, mAbs are granted marketing approvals at twice the rate of small molecule drugs.

To verify results reported in Hay et al., and to provide additional details about clinical phase transition and approval success rates for mAbs, we collected data in the public domain for over 680 antibody therapeutics that entered clinical studies sponsored by commercial firms between January 1, 2000 and December 31, 2014. The data was collected from various websites, and included sources such as company pipelines and press releases, clinical trials registries, and an open-access database of therapeutic antibodies (IMGT/mAb-DB, <http://www.imgt.org/mAb-DB/>). The available data was cross-checked against several commercial databases (Beacon Targeted Therapies, Therapeutic Antibody Database, BioMedTracker). Antibody therapeutics developed solely by non-commercial organizations, e.g., National Institutes of Health, and all biosimilar antibodies were excluded. Molecules with at least one binding site derived from an antibody gene were included, but Fc fusion proteins were excluded. We defined success as a first marketing approval in either the US or EU. Each molecule was assigned one therapeutic category and one of 9 possible phases of development (Phase 1, 2 or 3 clinical study; regulatory review in the US or EU; approved in the US or EU; all development terminated at Phase 1, 2 or 3, or terminated



**Figure 1.** Number of antibody therapeutics entering first-in-human studies per year, 2005–2017.

Green bars, all antibody therapeutics. Blue bars, antibody therapeutics for non-cancer indications only. Red bars, antibody therapeutics for cancer only. Dotted lines, 2-year moving averages. Totals include only antibody therapeutics sponsored by commercial firms; those sponsored solely by government, academic or non-profit organizations were excluded. Biosimilar antibodies and Fc fusion proteins were also excluded.

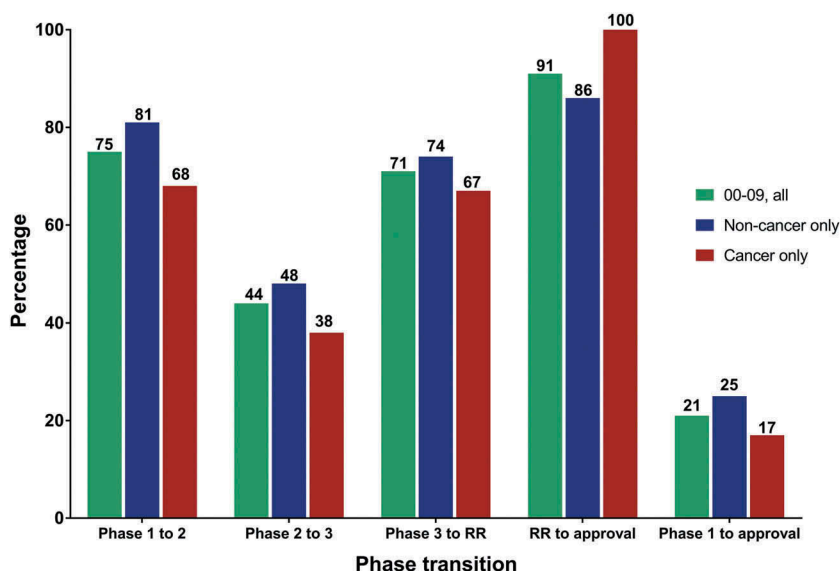
in regulatory review in the US or EU). The phase of development was determined from the data available for the most advanced phase of the molecules. For example, a molecule in Phase 3 studies was assigned to Phase 3 regardless of whether Phase 1 or Phase 2 studies were also in progress. Molecules were considered terminated if they were not listed in the relevant company pipeline or no development had recently been reported, regardless of whether the molecule was described as a licensing opportunity. Our dataset appears to be substantially larger than the mAb subset of Hay et al.; the method we used to calculate success rates was most closely aligned with their 'lead indications' approach.

We analyzed our data when stratified by time (entry into clinical study during 2000–2009 and 2005–2014) and by therapeutic category (non-cancer and cancer) (Figures 2 and 3). For all mAbs that entered clinical study during 2000–2009 ( $n = 357$ ), the Phase 1 to 2, Phase 2 to 3, Phase 3 to regulatory review and regulatory review to approval transition rates were 75%, 44%, 71% and 91%, respectively, with an overall (Phase 1 to approval) success rate of 21% (Figure 2). These results are nearly identical to those reported by Hay et al., for their biologics data analyzed by lead indications (75.1%, 44.0%, 71.7% and 88.0% for phase transitions in the order listed above, with an overall success rate of 20.8%). Our data for mAbs entering clinical studies during 2000–2009 indicated that mAbs developed for cancer indications had lower phase transition rates and a lower overall approval success rate compared to those developed for non-cancer indications. This trend toward lower success rates for oncology drugs was also reported by Hay et al. It should be noted that approximately one-quarter of the mAbs were in clinical

studies or regulatory review at the time we calculated the success rates shown in Figure 2, and thus the rates may vary somewhat when the final fates (approval or termination) for all molecules in the cohort become known.

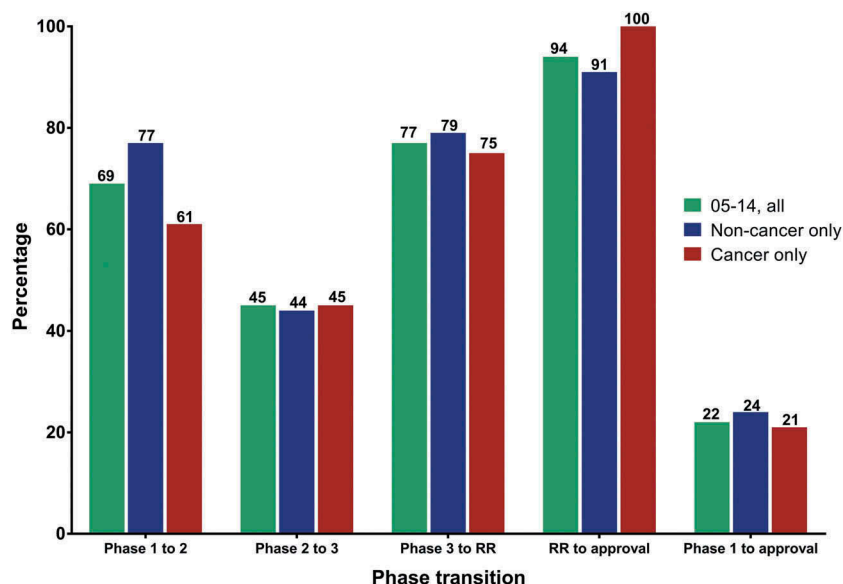
For all mAbs that entered clinical study during 2005–2014 ( $n = 569$ ), the Phase 1 to 2, Phase 2 to 3, Phase 3 to regulatory review, and regulatory review to approval transition rates were 69%, 45%, 77% and 94%, respectively, with an overall success rate of 22% (Figure 3). The overall approval success rates for the two periods is thus very similar, although there was some variability in phase transition rates. Our data for this cohort also showed that approval success rates were lower for mAbs developed for cancer vs non-cancer indications, but the difference (21 vs 24%, respectively) was less pronounced compared to the rates for mAbs that entered clinical study during 2000–2009 (17% vs 25%, respectively). Nearly half of the mAbs that entered clinical study during 2005–2014 were still in clinical study or regulatory review at the time of our analysis. We look forward to reporting updated success rates for this cohort when the final fates of more molecules become known in the future.

The success of antibody therapeutics has motivated hundreds of companies to engage in the development of these molecules. Collectively, companies are currently sponsoring clinical studies of more than 570 mAbs. Of these, ~90% are undergoing early-stage studies designed to assess the safety (Phase 1) or safety and preliminary efficacy (Phase 1/2 or Phase 2) of the molecules in various patient populations (Figure 4). Reflecting the recent substantial increase in the number of anti-cancer antibodies entering clinical study, most (~70%) of the mAbs at Phase 1 are for cancer. The numbers



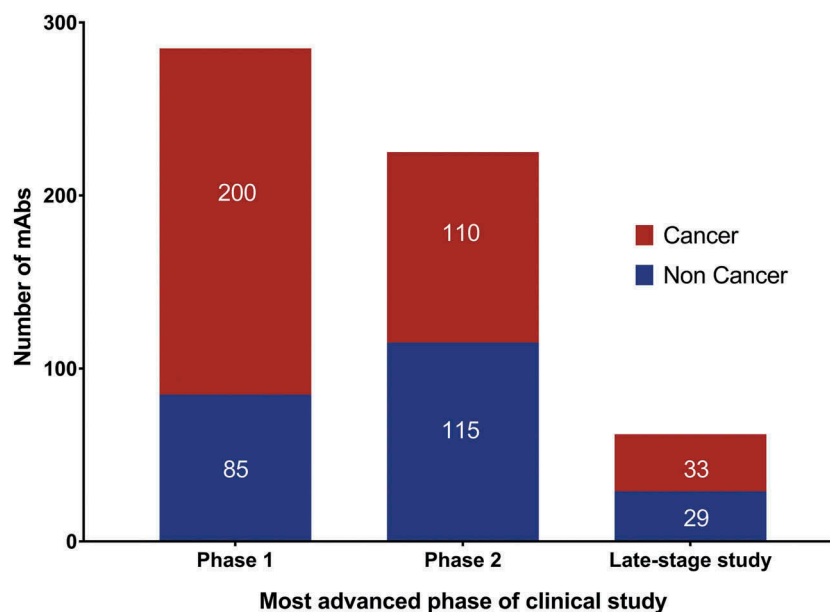
**Figure 2.** Clinical phase transition and approval success rates for antibody therapeutics that entered clinical study during 2000–2009.

Green bars, all antibody therapeutics. Blue bars, antibody therapeutics for non-cancer indications only. Red bars, antibody therapeutics for cancer only. Cohorts included only antibody therapeutics sponsored by commercial firms; those sponsored solely by government, academic or non-profit organizations were excluded. Number of molecules that entered clinical study during 2000–09: all,  $n = 357$ ; non-cancer only,  $n = 181$ ; cancer only,  $n = 176$ . Final fates (approval or termination) are known for 76%. MAbs that had advanced to Phase 1/2 were classified as Phase 2; mAbs that had advanced to Phase 2/3 were classified as Phase 3. Two mAbs with first approvals outside the US/EU regions (italizumab (Alzumab) and Rabishield approvals in India) were classified as Phase 3. Phase transition percentages were calculated as follows: the number of antibody therapeutics that completed a given phase and transitioned to the next was divided by the arithmetic difference between the number that entered the phase and the number that remained in the phase at the time of the calculation. Phase transitions occurring between clinical studies conducted world-wide were included. Approval success were defined as a first US or EU approval; supplemental approvals were not included. Abbreviation RR, regulatory review.



**Figure 3.** Clinical phase transition and approval success rates for antibody therapeutics that entered clinical study during 2005–2014.

Green bars, all antibody therapeutics. Blue bars, antibody therapeutics for non-cancer indications only. Red bars, antibody therapeutics for cancer only. Cohorts included only antibody therapeutics sponsored by commercial firms; those sponsored solely by government, academic or non-profit organizations were excluded. Number of molecules that entered clinical study during 2005–14: all,  $n = 569$ ; non-cancer only,  $n = 295$ ; cancer only,  $n = 274$ . Final fates (approval or termination) are known for 58%. MAb that had advanced to Phase 1/2 were classified as Phase 2; mAbs that had advanced to Phase 2/3 were classified as Phase 3. Two mAbs with first approvals outside the US/EU regions (italizumab (Alzumab) and Rabishield approvals in India) were classified as Phase 3. Phase transition percentages were calculated as follows: the number of antibody therapeutics that completed a given phase and transitioned to the next was divided by the arithmetic difference between the number that entered the phase and the number that remained in the phase at the time of the calculation. Transitions occurring between clinical studies conducted world-wide were included. Approval success were defined as a first US or EU approval; supplemental approvals were not included. Abbreviation RR, regulatory review.

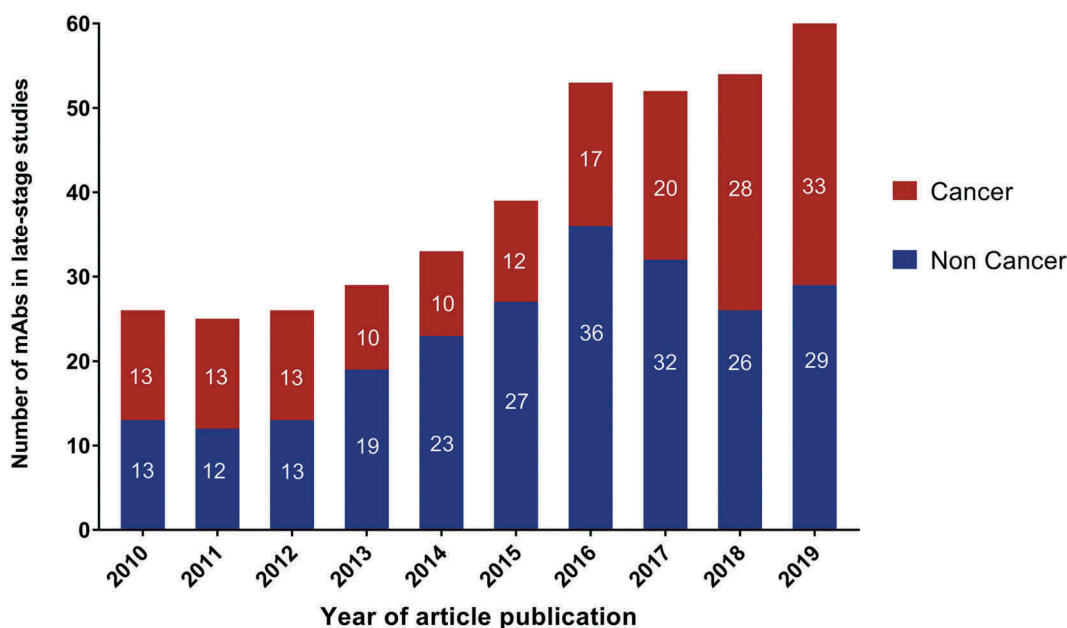


**Figure 4.** Clinical phases for antibody therapeutics in development.

Data as of November 2018. Totals include only antibody therapeutics sponsored by commercial firms; those sponsored solely by government, academic or non-profit organizations were excluded; biosimilars and Fc fusion proteins were excluded. Phase 1/2 included with Phase 2; late-stage studies include pivotal Phase 2, Phase 2/3 and Phase 3. Tables of mAbs in late-stage studies are available at [www.antibodysociety.org](http://www.antibodysociety.org).

of mAbs intended to treat cancer vs non-cancer indications are similar for mAbs currently at Phase 2 and late-stage clinical studies (pivotal Phase 2, Phase 2/3 or Phase 3). The ‘Antibodies to watch’ article series has documented the substantial increase in the number of mAbs in late-stage studies

that has occurred over the past 10 years (Figure 5).<sup>12–20</sup> The 62 mAbs currently undergoing evaluation in late-stage studies represent the largest number at this stage to date, with the increase, at least in part, due to the advancement of mAbs developed by companies based in China.



**Figure 5.** Antibodies to watch in 2010–2019.

Data from ‘Antibodies to watch’ articles published in *mAbs*. 2019 data as of November 2018. Totals include only antibody therapeutics sponsored by commercial firms; those sponsored solely by government, academic or non-profit organizations were excluded. Tables of mAbs in late-stage studies are available at [www.antibodysociety.org](http://www.antibodysociety.org).

Following in the tradition of the ‘Antibodies to watch’ article series, we provide here updates on recent and anticipated events relevant to antibody therapeutics clinical development. We describe the antibody therapeutics that were approved in either the US or EU during 2018, and those undergoing regulatory review in these two regions as of November 2018. In acknowledgment of the rapid progress in the development of novel antibody therapeutics in China, we also discuss several antibody immune checkpoint inhibitors undergoing regulatory review by China’s National Medical Products Administration (NMPA). Finally, we provide an overview of antibody therapeutics in late-stage clinical

study that may progress to regulatory review in late 2018 or 2019, based on public disclosures by the sponsoring companies.

### Antibody therapeutics approved in the US or EU in 2018

A total of 12 new antibodies were granted approvals in either the US or EU during 2018 (Table 1). Perhaps reflecting the higher approval success rate for antibodies that are treatments for non-cancer indications, the majority (75%) of the products

**Table 1.** Antibody therapeutics granted first approvals in the European Union or the United States during 2018\*.

International non-proprietary name#	Brand name	Target; Format	Indication first approved	Date of first EU approval	Date of first US approval
Erenumab	Aimovig	CGRP receptor; Human IgG2	Migraine prevention	7/26/2018	5/17/2018
Fremanezumab	Ajovy	CGRP; Humanized IgG2	Migraine prevention	In review	9/14/2018
Galcanezumab	Emgality	CGRP; Humanized IgG4	Migraine prevention	11/14/2018	9/27/2018
Burosumab	Crysvita	FGF23; Human IgG1	X-linked hypophosphatemia	2/19/2018	4/17/2018
Lanadelumab	Takhzyro	Plasma kallikrein; Human IgG1	Hereditary angioedema attacks	11/22/2018	8/23/2018
Caplacizumab	Cablivi	von Willebrand factor; Humanized Nanobody	Acquired thrombotic thrombocytopenic purpura	8/31/2018	In review
Mogamulizumab	Poteligeo	CCR4; Humanized IgG1	Mycosis fungoides or Sézary syndrome	11/22/2018	8/8/2018
Moxetumomab pasudodox	Lumoxiti	CD22; Murine IgG1 dsFv immunotoxin	Hairy cell leukemia	NA	9/13/2018
Cemiplimab	Libtayo	PD-1; Human mAb	Cutaneous squamous cell carcinoma	In review	9/28/2018
Ibalizumab	Trogarzo	CD4; Humanized IgG4	HIV infection	In review	3/6/2018
Tildrakizumab	Ilumetri, Ilumya	IL-23 p19; Humanized IgG1	Plaque psoriasis	9/17/2018	3/20/2018
Emapalumab	Gamifant	IFN $\gamma$ ; Human IgG1	Primary hemophagocytic lymphohistiocytosis	In review	11/20/2018

Data available as of November 30, 2018. \*Biosimilar products were excluded. #INN assigned by the World Health Organization; US product names in alphabetical order are burosumab-twza, cemiplimab-rwlc, emapalumab-lzsg, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, ibalizumab-uyyk, lanadelumab-flyo, mogamulizumab-kpkc, moxetumomab pasudotox-tdfk, tildrakizumab-asmn. Abbreviations: CD, cluster of differentiation; CGRP, calcitonin gene-related peptide; dsFv, disulfide-stabilized variable fragment; EU European Union; FGF23, fibroblast growth factor 23; IgG, immunoglobulin G; NA, not applicable; PD-1 programmed cell death 1; US, United States.

are for such diseases, including 3 for migraine prevention and 1 for human immunodeficiency virus (HIV) infection.

### **Erenumab (Novartis)**

On May 17, 2018, the US Food and Drug Administration (FDA) approved erenumab-aooe (Aimovig) for the preventive treatment of migraine in adults. Erenumab is a human IgG2 mAb that targets calcitonin gene-related peptide (CGRP) receptor, thereby blocking the activity of CGRP, which is involved in migraine attacks. The treatment is given by once-monthly subcutaneous (SC) injections. The approval was based on data from three clinical trials that compared erenumab-aooe to placebo. Over 2000 participants were included in the studies. In the first study (STRIVE, NCT02456740), which included 955 participants with a history of episodic migraine, patients administered erenumab-aooe experienced, on average, one to two fewer monthly migraine days than those on placebo over a 6-month period. In the second study (ARISE, NCT02483585), which included 577 patients with a history of episodic migraine, patients administered erenumab-aooe experienced, on average, one fewer migraine day per month than those on placebo over a 3-month period. In the third study (NCT02066415), which evaluated 667 patients with a history of chronic migraine, patients treated with erenumab-aooe experienced, on average, 2.5 fewer monthly migraine days than those receiving placebo over a 3-month period.<sup>21</sup> On July 26, 2018, erenumab was issued a marketing authorization in the EU for prophylaxis of migraine in adults who have at least 4 migraine days per month.

### **Fremanezumab (Teva Pharmaceuticals)**

On September 14, 2018, the FDA approved fremanezumab-vfrm (Ajovy<sup>TM</sup>) for the preventive treatment of migraine in adults. The drug may be administered as either 225 mg monthly, or 675 mg quarterly, SC doses.<sup>22</sup> Fremanezumab-vfrm is a humanized mAb that binds to CGRP, thereby blocking the binding of this ligand to its receptor. In a Phase 3 study (NCT02629861) of patients with migraines administered fremanezumab, mean migraine days per month decreased from 8.9 days to 4.9 days in the fremanezumab 225 mg dosing group, from 9.2 days to 5.3 days in the fremanezumab 675 mg dosing group, and from 9.1 days to 6.5 days in the placebo group, as assessed from baseline to 12 weeks.<sup>23</sup> A marketing authorization application for fremanezumab is undergoing review by the European Medicines Agency (EMA).

### **Galcanezumab (Eli Lilly & Company)**

On September 27, 2018, the FDA approved galcanezumab-gnlm (Emgality<sup>®</sup>) for the preventive treatment of migraine in adults, making Emgality the third antibody therapeutic approved by FDA in 2018 for this indication. Like fremanezumab, galcanezumab is a humanized mAb that binds to CGRP. The recommended dosage of Emgality is 240 mg loading dose (administered as two consecutive injections of 120 mg each), followed by monthly doses of 120 mg. The efficacy and safety of Emgality was demonstrated in two Phase 3 clinical trials in patients with episodic migraine

(EVOLVE-1 (NCT02614183), EVOLVE-2 (NCT02614196)) and one Phase 3 clinical trial in patients with chronic migraine (REGAIN (NCT02614261)). In all three studies, patients were randomized to receive once-monthly placebo, Emgality 120 mg after an initial loading dose of 240 mg, or Emgality 240 mg. In EVOLVE-1, the mean change from baseline (days) was -4.7 days (n = 210) for Emgality 120 mg compared to -2.8 days (n = 425) for placebo (p < 0.001), while in EVOLVE-2, the mean change from baseline (days) was -4.3 days (n = 226) for Emgality 120 mg compared to -2.3 days (n = 450) for placebo (p < 0.001). In the REGAIN study, the mean change from baseline (days) was -4.8 days (n = 273) for Emgality 120 mg compared to -2.7 days (n = 538) for placebo (p < 0.001).<sup>24</sup> In November 2018, the European Commission (EC) granted marketing authorization for Emgality<sup>®</sup> for the prophylaxis of migraine in adults who have at least four migraine days per month.

### **Burosumab (KRN23; Kyowa Hakko Kirin Co. Ltd, Ultragenyx Pharmaceutical Inc.)**

On February 19, 2018, the EC issued a conditional marketing authorization in the EU for burosumab (Crysvita) as a treatment for X-linked hypophosphatemia (XLH) in children 1 year of age and older, and adolescents with growing skeletons. Burosumab is a human IgG1 mAb that binds to and inhibits the activity of fibroblast growth factor 23, thereby reducing loss of phosphate from the kidney and other metabolic abnormalities, and ameliorating bone changes that are a hallmark of the disease.<sup>25</sup> In a double-blind, placebo-controlled, Phase 3 study of symptomatic adults with XLH administered SC burosumab 1 mg/kg (n = 68) or placebo (n = 66) every 4 weeks, across midpoints of dosing intervals, 94.1% of burosumab-treated participants attained mean serum phosphate concentration above the lower limit of normal compared with 7.6% of those receiving placebo (p < 0.001).<sup>26</sup> Burosumab was granted Orphan Drug designations in the EU and US, and FDA granted the drug Breakthrough Therapy designation for pediatric XLH. Burosumab-twza was approved by the FDA on April 17, 2018.<sup>27</sup>

### **Lanadelumab (Shire)**

On August 23, 2018, the FDA approved lanadelumab-flyo (Takhzyro<sup>TM</sup>) injection for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years of age and older. This rare, genetic, and potentially life-threatening disorder can result in recurrent attacks of severe swelling in various parts of the body, including the throat. HAE affects people with low levels of, or poorly functioning, C1 esterase inhibitor proteins, which act by inhibiting plasma kallikrein and preventing spontaneous activation of the complement system. Takhzyro is a human mAb that targets plasma kallikrein, and thereby helps prevent attacks of edema. FDA's approval of Takhzyro was based in part on data from the multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 HELP study (NCT02586805), which included 125 patients with HAE. In this study, Takhzyro reduced the number of monthly HAE attacks an average of 87% (n = 27) or 73% (n = 29) vs. placebo (n = 41) when administered SC at 300 mg every two weeks or at 300 mg

every four weeks, respectively (adjusted  $P < 0.001$ ).<sup>28</sup> The FDA had previously granted Takhzyro Breakthrough Therapy and Orphan Drug designations. The biologics license application (BLA) for the drug was granted a priority review. Takhzyro, which was designated as an orphan medicinal product in the EU in 2015, was reviewed under EMA's accelerated assessment program. In November 2018, the EC granted marketing authorization for Takhzyro SC injection for the routine prevention of recurrent attacks of HAE in patients aged 12 years and older.

### **Caplacizumab (Sanofi)**

On August 31, 2018, the EC issued a marketing authorization for caplacizumab (Cablivi™), a bivalent single-domain nanobody targeting von Willebrand factor, as a treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP). During episodes of this rare, life-threatening blood clotting disorder, microclots can form, leading to low platelet counts, ischemia and organ dysfunction in aTTP patients. Caplacizumab was granted Fast Track designation in the US and Orphan Drug designations in the US and EU for the treatment of aTTP. The BLA for caplacizumab is undergoing a priority review at the FDA. A first action on the application is expected by February 6, 2019.<sup>29</sup> Caplacizumab was developed by Ablynx, a Sanofi company. The approval of caplacizumab in the EU was based in part on the Phase 3 HERCULES study (NCT02553317), a placebo-controlled, randomized study to evaluate the efficacy and safety of caplacizumab in more rapidly restoring normal platelet counts as a measure of the prevention of further microvascular thrombosis. Positive results from this study were presented at the 59th Annual Meeting of the American Society of Hematology in December 2017.<sup>30</sup> The HERCULES study recruited 145 patients with an acute episode of aTTP who were randomized 1:1 to receive either caplacizumab or placebo in addition to standard-of-care treatment, which was daily plasma exchange (PEX) and immunosuppression. Patients were administered a single intravenous (IV) bolus of 10 mg caplacizumab or placebo followed by daily SC dose of 10 mg caplacizumab or placebo until 30 days after the last daily PEX. Depending on the response, the treatment could be extended for additional 7-day periods up to a maximum of 28 days. The primary endpoint (time to platelet count response) and several secondary endpoints of HERCULES study were met. In particular, caplacizumab provided faster resolution of an aTTP episode with significantly shorter time to platelet count response, clinically relevant reduction in aTTP-related death, exacerbation of aTTP, or a major thromboembolic event, and prevention of aTTP relapses when treatment is extended until resolution of underlying disease.<sup>30</sup> A 3-year Phase 3 follow-up study (NCT02878603) of patients who completed the HERCULES study is in progress.

### **Mogamulizumab (Kyowa Hakko Kirin)**

On August 8, 2018, the FDA approved Poteligeo® (mogamulizumab-kpkc) for IV use for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy. The diseases are

subtypes of cutaneous T-cell lymphoma (CTCL), which is a rare and difficult-to-treat type of non-Hodgkin's lymphoma. The FDA had previously granted mogamulizumab Breakthrough Therapy and Orphan Drug designations, and the BLA for mogamulizumab received a priority review. FDA's approval was based on an open-label, multi-center, randomized Phase 3 clinical trial (NCT01728805) of 372 patients with relapsed MF or SS who received either mogamulizumab or vorinostat. Study sites were located in the US, Europe, Japan and Australia. Median progression-free survival (PFS) was 7.6 months for patients administered mogamulizumab compared to 3.1 months for patients taking vorinostat in this clinical trial.<sup>31</sup> Poteligeo was designated as an orphan medicinal product in the EU in 2016. The EC granted a marketing authorization to Poteligeo® for the treatment of adult patients with MF or SS who have received at least one prior systemic therapy in November 2018.

Developed by Kyowa Kirin, mogamulizumab is a humanized glyco-engineered mAb that binds to CC chemokine receptor type 4 on cancer cells.<sup>32</sup> Mogamulizumab was produced using Kyowa Hakko Kirin's proprietary POTELLIGENT® platform, which produces antibodies with low/no fucose content. Such antibodies have increased affinity to FcγRIIIa (CD16), and enhanced antibody-dependent cell-mediated cytotoxicity activity. Mogamulizumab's first approval, in 2012, was granted by the Japanese Ministry of Health, Labour and Welfare for treatment of patients with relapsed or refractory CCR4-positive adult T-cell leukemia-lymphoma.

### **Moxetumomab pasudotox (Astrazeneca)**

On September 13, 2018, the FDA approved moxetumomab pasudotox-tdfk (Lumoxiti) for the treatment of adult patients with relapsed or refractory hairy cell leukemia who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog. The drug is a recombinant immunotoxin targeting CD22 composed of a single-chain variable fragment (scFv) fused to a truncated form of *Pseudomonas* exotoxin PE38.<sup>33</sup> In a pivotal, multi-center, open-label study (NCT01829711) of moxetumomab pasudotox involving 80 patients (79% males; median age, 60.0 years), the durable complete response rate was 30%, the complete response rate was 41%, and the objective response rate (complete and partial response) was 75%.<sup>34</sup> Due to the severity and rarity of the disease, the FDA granted the application Fast Track and Priority Review designations, and moxetumomab pasudotox received US Orphan Drug designation.

### **Cemiplimab (Sanofi)**

On September 28, 2018, the FDA approved cemiplimab-rwlc (Libtayo) for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Cemiplimab-rwlc is the third antibody therapeutic targeting PD-1 to be granted an FDA approval, but it is the first drug to be approved in the US specifically for advanced CSCC. FDA's approval of Libtayo was based on a combined analysis of data from an open-label, multi-center, non-randomized Phase 2 trial known as EMPOWER-CSCC-1

(Study 1540) and two advanced CSCC expansion cohorts from a multi-center, open-label, non-randomized Phase 1 trial (Study 1423). A total of 108 patients (75 with metastatic disease and 33 with locally-advanced disease) were included in the efficacy evaluation. The confirmed objective response rate for all patients treated with Libtayo was 47%.<sup>35</sup> FDA granted cemiplimab Breakthrough Therapy designation status for advanced CSCC in 2017, and the drug's BLA was granted a priority review. A marketing authorization application for cemiplimab is undergoing EMA review.

### **Ibalizumab (Theratechnologies, Inc)**

On March 6, 2018, the FDA approved ibalizumab-uiyk (Trogarzo) for adult patients infected with HIV who were previously treated with multiple HIV medications and whose HIV infections are resistant to currently available therapies.<sup>36</sup> Ibalizumab-uiyk, a humanized IgG4 mAb, is a CD4 domain 2-directed post-attachment HIV-1 inhibitor. The BLA was granted Breakthrough Therapy, Fast Track and Priority Review designations, and ibalizumab was granted an Orphan Drug designation by FDA. Theratechnologies Inc. and TaiMed Biologics, Inc. have an agreement to market and distribute Trogarzo in the US and Canada. The product is IV administered as a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks after dilution in 250 mL of 0.9% sodium chloride. The safety and efficacy of ibalizumab-uiyk were evaluated in the Phase 3 TMB-301 study (NCT02475629), which was a single arm, multicenter clinical trial conducted in 40 heavily treatment-experienced HIV-infected patients with multidrug resistant HIV-1.<sup>37</sup> At week 25, viral load <50 was achieved in 43% of patients, while 55% and 48% of patients had a  $\geq 1$  log<sub>10</sub> reduction in viral load and a  $\geq 2$  log<sub>10</sub> reduction in viral load, respectively. The most common adverse reactions reported in at least 5% of subjects were diarrhea, dizziness, nausea, and rash. In total, 292 patients with HIV-1 infection were exposed to ibalizumab-uiyk IV infusion during clinical studies.<sup>38</sup> A marketing authorization application for ibalizumab is undergoing EMA review.

### **Tildrakizumab (Sun Pharma)**

On March 20, 2018, the FDA approved tildrakizumab-asmn (Ilumya) for treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Tildrakizumab, a humanized IgG1 kappa mAb, targets IL-23p19 and blocks the interaction of IL-23 with its receptor, thereby inhibiting release of pro-inflammatory cytokines and chemokines. FDA approval was supported by results from two Phase 3 trials (reSURFACE 1 and 2) in which patients were randomized to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo (2:2:1; reSURFACE 1), or to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg (2:2:1:2; reSURFACE 2). In these trials, the tildrakizumab 200 mg and 100 mg doses were well tolerated and found to be efficacious compared with placebo and etanercept in the treatment of patients with moderate-to-severe chronic

plaque psoriasis. The results of both studies were published in *The Lancet* in July 2017.<sup>39</sup> In a pooled analysis of three randomized controlled trials that included over 2000 patients, tildrakizumab therapy for up to 64 weeks was well tolerated, with low rates of serious treatment-emergent adverse events (AEs), discontinuations due to AEs, and AEs of clinical interest.<sup>40</sup> An EU-wide marketing authorization for tildrakizumab (Ilumetri) was issued to Almirall S.A. on September 17, 2018. In the EU, Ilumetri is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.

### **Emapalumab (Novimmune/Swedish Orphan Biovitrum AB)**

On November 20, 2018, the FDA approved emapalumab-lzsg (Gamifant) for the treatment of pediatric (newborn and above) and adult patients with primary hemophagocytic lymphohistiocytosis (HLH) who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.<sup>41</sup> Developed by Novimmune SA, emapalumab is a human IgG1 antibody that targets interferon  $\gamma$ . Emapalumab received a variety of designations intended to facilitate the development of drugs for rare, serious or life-threatening diseases, including Breakthrough Therapy, Rare Pediatric Disease, and Orphan Drug designations in the US, and Priority Medicines and Orphan Drug designations in the EU. The FDA's approval was based in part on a clinical study of 27 pediatric patients with suspected or confirmed primary HLH with either refractory, recurrent or progressive disease during conventional HLH therapy or who were intolerant of conventional HLH therapy. Results from this study showed that 63% of patients experienced a response and 70% were able to proceed to stem cell transplant. A marketing application for emapalumab is undergoing evaluation by EMA.

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

As of November 2018, a total of 4 antibody therapeutics (sacituzumab govitecan, ravulizumab, risankizumab, romosozumab) are being considered for their first marketing approvals in the US or EU (Table 2). Reflecting the diversity of mAbs in clinical development, the product candidates are for diseases in a variety of therapeutic areas, such as cancer, cardiovascular/hemostasis, immune-mediated disorders, and bone/skeletal diseases.

#### **Sacituzumab govitecan (Immunomedics)**

This antibody-drug conjugate (ADC) is composed of a humanized anti-Trop-2 antibody conjugated to SN38 (active metabolite of the topoisomerase I inhibitor irinotecan). A BLA for approval of sacituzumab govitecan as third-line therapy for metastatic triple-negative breast cancer was granted Priority Review by the FDA, and the action date is January 18, 2019.<sup>42</sup> Immunomedics is planning clinical studies of the ADC in other cancers. Patients are being recruited for a pivotal Phase 2 study of sacituzumab govitecan as a treatment for metastatic urothelial cancer after failure of



**Table 2.** Investigational antibody therapeutics in regulatory review in the European Union or the United States\*.

International non-proprietary name	Brand name proposed	Target; Format	Indication	Status in EU	Status in US
Sacituzumab govitecan	(Pending)	TROP-2; humanized IgG1 ADC	Triple-negative breast cancer	NA	In review
Ravulizumab (ALXN1210)	(Pending)	C5; humanized IgG2/4	Paroxysmal nocturnal hemoglobinuria	In review	In review
Risankizumab	(Pending)	IL-23 p19; Humanized IgG1	Plaque psoriasis	In review	In review
Romosozumab	EVENITY	Sclerostin; Humanized IgG2	Osteoporosis in postmenopausal women at increased risk of fracture	In review	In review

Data available as of November 30, 2018. \*Antibody therapeutics not previously approved in the EU or US for any indication; biosimilar products were excluded. Abbreviations: ADC, antibody-drug conjugate; EU, European Union; C5, complement component 5; IgG, immunoglobulin G; IL, interleukin; NA, not applicable; TROP-2, trophoblast cell-surface antigen 2; US, United States.

platinum-based regimen or anti-PD-1/PD-L1 based immunotherapy (NCT03547973) and a Phase 2 study of the ADC in patients with metastatic castration-resistant prostate cancer who have progressed on second generation androgen receptor-directed therapy (NCT03725761).

### **Ravulizumab (Alexion Pharmaceuticals)**

Also known by the drug code ALXN1210, ravulizumab is a humanized mAb targeting complement component 5 (C5). A BLA for approval of ravulizumab for treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) is undergoing review at FDA. The BLA's action date is February 18, 2019, following an expedited eight-month review, instead of the standard 12-month review, which was allowed by Alexion's use of a rare disease priority review voucher.<sup>43</sup> Ravulizumab is also undergoing regulatory review in the EU. The mAb was granted Orphan Drug designation in both the US and EU for the treatment of patients with PNH. In a Phase 3 study, ravulizumab demonstrated non-inferiority to Soliris® (anti-C5 eculizumab) in complement inhibitor treatment-naïve patients with PNH.<sup>44</sup> Also developed by Alexion Pharmaceuticals, Soliris® was first approved for PNH in 2007.

### **Risankizumab (Abbvie)**

Like the recently approved products Tremfya (guselkumab) and Ilumya (tildrakizumab), risankizumab targets IL-23p19 and it was evaluated as a treatment for plaque psoriasis. The BLA for risankizumab is supported by data from four Phase 3 studies, ultIMMA-1, ultIMMa-2, IMMhance and IMMvent, that evaluated the safety and efficacy of risankizumab in more than 2,000 patients with moderate-to-severe chronic plaque psoriasis. In these four studies, all co-primary and ranked secondary outcome measures were met and no new safety signals were observed.<sup>45</sup> Results of the UltIMMa-1 (NCT02684370) and UltIMMa-2 (NCT02684357) studies were reported in *The Lancet*.<sup>46</sup> Assuming the BLA receives a standard review, FDA may make a decision in April 2019. Risankizumab is also undergoing regulatory review in the EU.

### **Romosozumab (Amgen/UCB Pharma)**

This humanized IgG2 mAb, which targets sclerostin, has been evaluated as a treatment for osteoporosis in women and men.

A BLA for romosozumab as a treatment of osteoporosis in postmenopausal women at high risk for fracture was submitted to the FDA in July 2016, but additional safety and efficacy data was requested in the FDA's complete response letter, as announced by collaborators Amgen and UCB in July 2017.<sup>47</sup> In July 2018, Amgen and UCB announced that the BLA had been resubmitted,<sup>48</sup> thus starting a second review cycle. In addition to data from early-stage clinical studies, the original BLA included data from the Phase 3 placebo-controlled FRAME study, including 7,180 postmenopausal women with osteoporosis. The resubmitted BLA includes results from the more recent Phase 3 ARCH study, an alendronate-active comparator trial including 4,093 postmenopausal women with osteoporosis who experienced a fracture, and the Phase 3 BRIDGE study, which included 245 men with osteoporosis. Romosozumab is also undergoing regulatory review in the EU.

### **Antibody therapeutics undergoing regulatory review in China**

A decade ago, when the 'Antibodies to watch' article series was started, the innovative antibodies in late-stage clinical studies were developed primarily by companies based in the US or EU. Since then, the Chinese biopharmaceutical industry has made substantial strides in the clinical development of antibody therapeutics, with the aim of gaining marketing approvals not only in China, but also globally. Chinese companies are engaging with FDA, and developing their product candidates according to the standards of the FDA and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ([www.ich.org](http://www.ich.org)).<sup>49</sup> In particular, Chinese companies have progressed multiple antibodies targeting PD-1 into late-stage studies and regulatory review in China, including tislelizumab, sintilimab and camrelizumab.

### **Tislelizumab (BGB-A317; Beigene Ltd.)**

This humanized IgG4 mAb binds to PD-1, but does not bind human FcγRI or mediate crosslinking between PD-1 and FcγRI. Interactions with FcγRI were reported to have a negative effect on anti-cancer activity of antibodies targeting PD-1.<sup>50</sup> In August 2018, BeiGene announced that China's NMPA accepted a new drug application (NDA) for tislelizumab for the treatment of relapsed or refractory Hodgkin's lymphoma.<sup>51</sup> The NDA, which was granted a priority review,

included results from a pivotal Phase 2 study (NCT03209973) of 70 Chinese patients showing an overall response rate of 85.7%, including 61.4% complete response, with a minimum of 24 weeks of follow-up and a median follow-up time of 7.85 months at the data cutoff. Tislelizumab is also being evaluated in Phase 3 studies of patients with non-small cell lung cancer, hepatocellular carcinoma and esophageal squamous cell carcinoma.

### **Sintilimab (IBI308; Innovent Biologics)**

Innovent Biologics and Eli Lilly and Company are jointly developing sintilimab, a human IgG4 antibody targeting PD-1, in China. In April 2018, the NDA for sintilimab for relapsed and refractory classical Hodgkin's lymphoma was submitted in China and granted priority review status. In the Phase 2 registrational study ORIENT-1 (NCT03114683) that assessed the efficacy and safety profile of sintilimab, the overall response rate was 79.2%, with disease control rate of 97.9%, among the 96 patients with a minimum 24-week follow-up.<sup>52</sup> Sintilimab is also being evaluated as first-line treatment for patients with non-squamous non-small cell lung cancer (NCT03607539 Phase 3 ORIENT-11 study) and as first-line treatment for patients with previously untreated squamous non-small cell lung cancer (NCT03629925 Phase 3 ORIENT-12 study).

### **Camrelizumab (SHR-1210; Jiangsu Hengrui Medicine Co., Ltd.)**

An NDA for camrelizumab, a humanized IgG4 antibody targeting PD-1, for relapsed/refractory classic Hodgkin's lymphoma submitted by Hengrui to China's NMPA was accepted in April 2018, and is currently under review.<sup>53</sup> Hengrui has partnered with Incyte Corporation to further develop camrelizumab. In two Phase 1/2 studies (NCT02961101, NCT03250962) of camrelizumab with or without decitabine, the addition of decitabine increased the complete response rate of patients with relapsed/refractory classic Hodgkin's lymphoma, and significantly reversed the resistance of anti-PD-1 therapy.<sup>54</sup> The safety profile of the combination therapy was deemed acceptable. Camrelizumab is undergoing evaluation as a treatment for other types of cancer, and results have been reported for early-phase clinical studies of camrelizumab in patients with advanced non-squamous non-small cell lung cancer,<sup>55</sup> advanced hepatocellular carcinoma, gastric or esophagogastric junction cancer,<sup>56</sup> nasopharyngeal carcinoma,<sup>57</sup> advanced esophageal carcinoma,<sup>58</sup> and advanced solid tumors.<sup>59</sup>

### **Antibodies to watch in 2019: non-cancer indications**

As of November 2018, 29 novel antibody therapeutics were in late-stage clinical studies for non-cancer indications (Table 3). No single therapeutic area predominated, although, at ~40% of the total, antibodies for immune-mediated disorders were the largest group. Of the 29 product candidates, two (leronlimab, brolocizumab) may enter regulatory review by the end of 2018, and at least five (eptinezumab, teprotumumab, crizanlizumab, satralizumab, tanezumab) may enter regulatory review in 2019.

### **Leronlimab (PRO140; CytoDyn)**

The chemokine receptor CCR5 is the principal HIV co-receptor, but it has potential as a drug target for other diseases, such as cancer and immune-mediated disorders.<sup>60</sup> Leronlimab, a humanized IgG4 mAb that blocks CCR5, was granted FDA's Fast Track drug designation for the treatment of HIV infection. This designation allows a 'rolling' BLA submission, i.e., the BLA can be submitted in sections, which may be in progress, as CytoDyn has indicated that they made progress toward filing a BLA for leronlimab as a combination therapy for HIV and are confident that two-thirds of the BLA submission (i.e., clinical and non-clinical sections) will be completed by the end of 2018 and the last section, Chemistry, Manufacturing and Controls, by the first quarter of 2019.<sup>61</sup> Leronlimab is undergoing evaluation in late-stage clinical studies that include treatment-experienced HIV-infected patients with CCR5-tropic virus who demonstrate evidence of HIV-1 replication despite ongoing antiretroviral therapy (ART) with documented genotypic or phenotypic resistance to ART drugs within three drug classes (or within two or more drug classes with limited treatment options). The primary efficacy endpoint of a pivotal 25-week study (NCT02483078), 0.5log reduction in viral load after one week of therapy with leronlimab in combination with the patient's failing drug regimen, was met. An open-label extension of this study is continuing to enroll patients. The successful results of this trial may serve as the basis for the BLA submission. CytoDyn is also developing leronlimab as a treatment for graft-vs.-host disease and triple-negative breast cancer.

### **Brolocizumab (RTH258; Novartis)**

This ~26 kDa humanized scFv targets all isoforms of vascular endothelial growth factor-A, and it is undergoing evaluation as a treatment for neovascular age-related macular degeneration (nAMD). Novartis has indicated that regulatory submissions for brolocizumab may occur in December 2018.<sup>62</sup> In October 2018, Novartis released 96-week results from the Phase 3 HAWK (NCT02307682) and HARRIER (NCT02434328) studies that reaffirmed positive 48-week findings.<sup>63</sup> The two studies included more than 1,800 patients in comparing the efficacy and safety of intravitreal injections of 6 mg brolocizumab or 3 mg brolocizumab (HAWK study only) versus 2 mg aflibercept in patients with nAMD. The primary efficacy endpoint of the studies, non-inferiority to aflibercept (EYLEA®) in mean change in best-corrected visual acuity (BCVA) at week 48, was met. The 96-week results indicate patients administered brolocizumab maintained robust visual gains, with mean change in BCVA of 5.9 letters for brolocizumab 6 mg versus 5.3 letters for aflibercept in the HAWK study, and 6.1 letters versus 6.6 letters, respectively, in the HARRIER study. Superior reductions in retinal fluid and central subfield thickness (CST) demonstrated at 48 weeks were reaffirmed at 96 weeks. The percentage of patients with nAMD that had intra-retinal fluid and/or sub-retinal fluid was 24% for brolocizumab 6 mg vs. 37% for aflibercept in HAWK ( $p = 0.0001$ ) and 24% vs. 39%, respectively, in the HARRIER study ( $P < 0.0001$ ). Absolute reductions in CST from baseline were -175  $\mu\text{m}$  for brolocizumab 6 mg versus -149  $\mu\text{m}$  for aflibercept in HAWK

**Table 3.** Investigational monoclonal antibodies in late-stage clinical studies for non-cancer indications.

Primary sponsoring company	INN or code name	Molecular format	Target(s)	Most advanced phase	Pivotal Phase 2, Phase 2/3 or 3 indications
Omeros Corporation	OMS721	Human mAb	MASP-2	Phase 3	Atypical hemolytic uremic syndrome
Novartis	Ligelizumab	Human IgG1	IgE	Phase 3	Chronic spontaneous urticaria
Bioerativ	Sutimlimab, BIVV009	Humanized mAb	C1s	Phase 3	Cold agglutinin disease
Regeneron Pharmaceuticals	Evinacumab	Human mAb	Angiopoietin-like 3	Phase 3	Homozygous familial hypercholesterolemia
Novartis	Crizanlizumab	Humanized IgG2	CD62 (aka P-selectin)	Phase 3	Sickle cell disease
UCB	Bimekizumab	Humanized IgG1	IL-17A, F	Phase 3	Ankylosing spondylitis, psoriasis
Biocad	BCD-085	Humanized mAb	IL-17	Phase 3	Ankylosing spondylitis, psoriasis
AstraZeneca/ MedImmune LLC	Tralokinumab	Human IgG4	IL-13	Phase 3	Atopic dermatitis
Novartis	Ianalumab (VAY736)	Human IgG1	BLYS/BAFF/TACI/BCMA receptor	Phase 2/3	Autoimmune hepatitis
R-Pharm	Olokizumab	Humanized IgG4	IL-6	Phase 3	Rheumatoid arthritis
AstraZeneca/ MedImmune LLC	Anifrolumab	Human IgG1	IFN $\alpha$ , $\beta$ , $\omega$ receptor 1	Phase 3	Systemic lupus erythematosus
Genentech	Etolizumab	Humanized IgG1	a4-b7/aE-b7 integrin receptor	Phase 3	Ulcerative colitis; Crohn's disease
Boehringer Ingelheim	BI655130	Human IgG1	IL-36R	Phase 2/3	Ulcerative colitis
Eli Lilly & Co.	Mirikizumab	Humanized IgG4	IL-23p19	Phase 3	Ulcerative colitis, psoriasis
Shire	SHP-647	Human IgG2	Mucosal addressin cell adhesion molecule	Phase 3	Ulcerative colitis; Crohn's disease
AstraZeneca/ MedImmune LLC	Tezepelumab	Human IgG2	Thymic stromal lymphopoietin	Phase 3	Severe uncontrolled asthma
CytoDyn	Leronlimab (PRO140)	Humanized IgG4	CCR5	Phase 2/3	HIV infection
GC Pharma	Lenvirozumab (GC1102)	Humanized IgG1	Hepatitis B virus surface antigen	Phase 2/3	Hepatitis B virus-associated liver transplant
Biogen	Aducanumab	Human IgG1	Amyloid beta	Phase 3	Alzheimer's disease
Genentech	Crenezumab	Humanized IgG4	Amyloid beta	Phase 3	Alzheimer's disease
Hoffmann-La Roche	Gantenerumab	Human IgG1	Amyloid beta	Phase 3	Alzheimer's disease
Hoffmann-La Roche	Faricimab	Bispecific CrossMab	VEGF-A, Ang2	Phase 3	Diabetic macular edema
Novartis	Brolucizumab	Humanized scFv	VEGF-A	Phase 3	Neovascular age-related macular degeneration
Vieila Bio	Inebilizumab	Humanized IgG1	CD19	Phase 2/3	Neuromyelitis optica and neuromyelitis optica spectrum disorders
Chugai Pharmaceuticals/ Roche	Satralizumab	Humanized IgG2	IL-6R	Phase 3	Neuromyelitis optica and neuromyelitis optica spectrum disorders
Horizon Pharma USA	Teprotumumab	Human IgG1	IGF-1R	Phase 3	Thyroid eye disease
Alder	Eptinezumab	Humanized IgG1	CGRP	Phase 3	Episodic migraines
Biopharmaceuticals	Fasinumab	Human IgG4	Nerve growth factor	Phase 3	Pain due to osteoarthritis of knee or hip, low back pain
Regeneron Pharmaceuticals	Tanezumab	Humanized IgG2	Nerve growth factor	Phase 3	Pain due to osteoarthritis of knee or hip, low back pain, cancer pain due to bone metastasis

Data available as of November 30, 2018. Abbreviations: BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; BLYS, B lymphocyte stimulator; CGRP, calcitonin gene-related peptide; MASP-2, mannose-binding protein-associated serine protease 2; TACI, transmembrane activator and CAML interactor; IGF-1R, insulin-like growth factor-1 receptor; VEGF, vascular endothelial growth factor.

( $p = 0.0057$ ) and  $-198 \mu\text{m}$  versus  $-155 \mu\text{m}$ , respectively, in the HARRIER study ( $P < 0.0001$ ).

### ***Eptinezumab (Alder Biopharmaceuticals, Inc.)***

Like the marketed products Emgality and Ajovy, eptinezumab targets CGRP and it is for migraine prevention. In November 2018, Alder announced that they are on track to complete a BLA submission in the first quarter of 2019 that will include chemistry, manufacturing, and controls processes;

positive results from a pharmacokinetic study intended to support the comparability evaluation of the clinical supply for eptinezumab and its planned commercial supply; data from eptinezumab's PROMISE 1 (NCT02559895) and PROMISE 2 (NCT02974153) Phase 3 clinical studies; and long-term safety data.<sup>64,65</sup> The PROMISE 1 and PROMISE 2 studies evaluated the effects of eptinezumab in episodic migraine patients ( $n = 888$ ) or chronic migraine patients ( $n = 1,072$ ), respectively. In PROMISE 1, the primary and key secondary endpoints were met, and the safety and

tolerability were similar to placebo, while in PROMISE 2, the primary and all key secondary endpoints were met, and the safety and tolerability was consistent with earlier eptinezumab studies. Alder announced one-year results from the PROMISE 1 study in June 2018, which indicated that, following the first quarterly infusion, episodic migraine patients treated with 300 mg eptinezumab experienced 4.3 fewer monthly migraine days (MMDs) from a baseline of 8 MMDs, compared to 3.2 fewer MMDs for placebo from baseline ( $p = 0.0001$ ). At one year after the third and fourth quarterly infusions, patients treated with 300 mg eptinezumab experienced further gains in efficacy, with a reduction of 5.2 fewer MMDs compared to 4.0 fewer MMDs for placebo-treated patients.<sup>66</sup> In addition, ~31% of episodic migraine patients achieved, on average per month, 100% reduction of migraine days from baseline compared to ~21% for placebo. New 6-month results from the PROMISE 2 study were also released in June 2018.<sup>67</sup> These results indicated that, after the first quarterly infusion, chronic migraine patients dosed with 300 mg of eptinezumab experienced 8.2 fewer MMDs, from a baseline of 16 MMDs, compared to 5.6 fewer MMDs for placebo from baseline ( $p < .0001$ ). A further reduction in MMDs was seen following a second infusion; 8.8 fewer MMDs for patients dosed with 300 mg compared to 6.2 fewer MMDs for those with placebo. In addition, ~21% of chronic migraine patients achieved, on average, 100% reduction of MMDs from baseline compared to 9% for placebo after two quarterly infusions of 300 mg of eptinezumab.

### **Teprotumumab (Horizon Pharma)**

This human IgG1 mAb targets insulin-like growth factor-1 receptor. Teprotumumab is in development for moderate-to-severe thyroid eye disease, which is commonly associated with Grave's disease (hyperthyroidism). Data from the Phase 3 OPTIC study (NCT03298867) is expected in the second quarter of 2019, and a BLA submission is expected mid-2019.<sup>68</sup> In the OPTIC study, participants receive 8 infusions of teprotumumab or placebo every 3 weeks for a total of 21 weeks. Teprotumumab (10 mg/kg) is administered on Day 1, with 20 mg/kg administered for the remaining 7 infusions. The primary endpoint at week 24 is the proptosis responder rate, defined as the percentage of participants with >2 mm reduction in study eye without deterioration ( $\geq 2$  mm increase) of proptosis in the fellow eye. An open-label extension study (NCT03461211; OPTIC-X) is enrolling by invitation. Teprotumumab was granted Fast Track, Breakthrough Therapy and Orphan Drug designations by FDA.

### **Crizanlizumab (SEG101; Novartis)**

Sickle cell disease, caused by mutations in the gene encoding hemoglobin subunit  $\beta$ , is characterized by production of red blood cells that are misshapen, prone to hemolysis and can occlude the vasculature, causing pain.<sup>69</sup> P-selectin found on endothelial cells and platelets participates in cell-cell interactions that contribute to the pathogenesis of vaso-occlusion and sickle cell-related pain crises. Crizanlizumab, a humanized mAb, binds P-selectin and blocks these interactions. Post-hoc analysis of data from the Phase 2 SUSTAIN study (NCT01895361) showed

that more patients treated with crizanlizumab did not experience a vaso-occlusive crisis (VOC) compared to those treated with placebo (35.8% vs 16.9%), specifically patients with a history of 2–10 VOCs in the previous year.<sup>70</sup> Crizanlizumab was granted Orphan Drug designation in the US and EU for the treatment of sickle cell-related pain crises. Novartis anticipates submitting a BLA in 2019.<sup>71</sup>

### **Satralizumab (SA237; Chugai Pharmaceutical Co., Ltd.)**

This humanized anti-interleukin-6 (IL-6) receptor mAb is undergoing development as a treatment for neuromyelitis optica spectrum disorder (NMOSD), which is a rare autoimmune disease that affects the central nervous system. The constant and variable regions of satralizumab were engineered to give the molecule longer plasma half-life. In October 2018, Chugai announced that positive results from the Phase 3 SakuraSky Study (NCT02028884) were presented at the 2018 Congress of European Committee for Treatment and Research in Multiple Sclerosis held October 10–12, 2018, in Berlin, Germany. In this study, satralizumab (120 mg) or placebo was added to baseline therapy (azathioprine, mycophenolate mofetil and/or corticosteroids). Both treatments were administered SC to patients at week 0, 2, and 4, then subsequent treatment was continued at 4-week intervals. Satralizumab with immunosuppressive therapy significantly reduced the risk of relapse by 62% (hazard ratio = 0.38 [95% confidence interval: 0.16–0.88],  $p = 0.0184$  [stratified log-rank test]) in patients with NMOSD including anti-aquaporin-4 (AQP4) antibody positive (AQP4 Ab positive) and negative (AQP4 Ab negative) patients, achieving the primary endpoint of time to first protocol-defined relapse in the double-blind period. The proportion of patients relapse free at weeks 48 and 96 was 88.9% and 77.6% with satralizumab and 66.0% and 58.7% with placebo, respectively.<sup>72</sup> Satralizumab has been granted US and EU orphan designations for the treatment of NMOSD. According to the Roche pipeline listing, an application submission for satralizumab is anticipated in 2019.

### **Tanezumab (Pfizer Inc., Eli Lilly and Company)**

Therapeutics that block nerve growth factor (NGF) have the potential to ameliorate pain associated with various disorders.<sup>73</sup> The humanized anti-NGF IgG2 antibody tanezumab has been studied extensively in late-stage clinical studies of patients with osteoarthritis pain, cancer pain, and chronic low back pain. In July 2018, Pfizer and Lilly announced positive results from a 16-week Phase 3 study (NCT02697773) evaluating the efficacy and safety of SC administration of tanezumab compared to placebo in patients with osteoarthritis of the knee or hip.<sup>74</sup> In this study, 698 patients were randomized into one of 3 study arms, and they then received injections once every eight weeks. Patients in arm 1, 2 or 3 received two doses of placebo, two doses of tanezumab 2.5 mg, or one dose of tanezumab 2.5 mg followed by one dose of tanezumab 5 mg eight weeks later, respectively. Patients who received two doses of tanezumab experienced a statistically significant improvement in pain, physical function and the patients' overall assessment of their osteoarthritis compared to those receiving placebo. Tanezumab

was granted FDA's Fast Track designation for tanezumab for the treatment of osteoarthritis pain and chronic low back pain. Lilly has indicated that a BLA for tanezumab for osteoarthritis pain may potentially be submitted in 2019.<sup>75</sup>

### Antibodies to watch in 2019: cancer indications

As of November 2018, 33 novel antibody therapeutics were in late-stage clinical studies for cancer indications (Table 4). Antibody therapeutics for solid tumors clearly predominated, with less than 20% of the total developed solely for hematological malignancies. Of the 33 product candidates, polatuzumab vedotin may enter regulatory review by the end of 2018, and at least 7 (isatuximab, spartalizumab, MOR208, oportuzumab monatox, TSR-042, enfortumab vedotin, ublituximab) may enter regulatory review in 2019.

#### Polatuzumab vedotin (DCDS4501A, RG7596; Roche)

In collaboration with Seattle Genetics, Roche is developing polatuzumab vedotin, which is composed of a humanized anti-CD79b IgG1 antibody conjugated to the antimetabolic agent monomethyl auristatin E (MMAE). The antibody's target is highly expressed on B cells of patients with lymphoma. Polatuzumab vedotin was granted FDA's Breakthrough Therapy designation, EMA's PRIME designation, and US and EU Orphan Drug designations for diffuse large B-cell lymphoma (DLBCL). Roche has indicated that, based on positive clinical data from a randomized Phase 2 study (NCT02257567/GO29365),<sup>76</sup> the company anticipates an accelerated submission for polatuzumab vedotin in DLBCL in 2018.<sup>77</sup> The Phase 2 NCT02257567 study evaluated polatuzumab vedotin administered by IV infusion in combination with standard doses of bendamustine (B) and rituximab (R) or obinutuzumab in patients with relapsed or refractory follicular lymphoma (FL) or diffuse DLBCL. Study results indicating that, at a median follow-up of 15 months, rates of PFS and complete response were similar among FL patients. In contrast, the combination of polatuzumab vedotin and BR significantly increased all efficacy outcomes, complete response ( $p = 0.012$ ), median PFS ( $p < 0.0001$ ), and median overall survival ( $p = 0.0008$ ), in the DLBCL group. The combination of polatuzumab vedotin with R-CHP protocol (rituximab, cyclophosphamide, doxorubicin and prednisone) versus R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine and prednisone) in DLBCL patients is currently being investigated in the Phase 3 POLARIX (NCT03274492) study. The primary endpoint is PFS. Secondary outcome measures include PFS, complete response and overall survival. The estimated primary completion date of the study is December 2019.

#### Isatuximab (SAR650984; Sanofi)

This anti-CD38 IgG1 chimeric mAb is being evaluated as a treatment for patients with multiple myeloma (MM). Isatuximab in combination with chemotherapy is being evaluated in three Phase 3 studies (ICARIA, IKEMA, and IMROZ) of MM patients. Sanofi expects results from ICARIA by Q1 2019; positive clinical data may allow marketing application submissions for isatuximab in 2019.<sup>78</sup> In the ICARIA study (NCT02990338), the effects of isatuximab in combination with pomalidomide and low-dose dexamethasone are being compared to those of only the

chemotherapy drugs in patients with refractory or relapsed and refractory MM.<sup>79</sup> The primary endpoint is PFS. Key secondary endpoints include overall response rate and overall survival. The IKEMA (NCT03275285) and IMROZ (NCT03319667) studies are evaluating isatuximab with other chemotherapy combinations (carfilzomib/dexamethasone and bortezomib/lenalidomide/dexamethasone, respectively) in MM patients. Isatuximab was granted US and EU Orphan Drug designations for the treatment of MM.

#### Spartalizumab (PDR001, Novartis)

This humanized IgG4 mAb binds PD-1 with sub-nanomolar affinity and blocks interaction with PD-L1/PD-L2, thus preventing PD-1-mediated inhibitory signaling and leading to T-cell activation. Spartalizumab is being evaluated in the randomized, double-blind, placebo-controlled Phase 3 COMBI-i study (NCT02967692) evaluating the safety and efficacy of spartalizumab combined with dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) versus matching placebo in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600-mutant unresectable or metastatic melanoma. Determination of dose-limiting toxicities, changes in PD-L1 levels and CD8+ cells in the tumor microenvironment, and PFS are the primary endpoints of the study. Key secondary endpoints are overall survival, overall response rate and duration of response. The estimated primary completion date of the study is July 2019. Novartis plans to submit marketing applications for PDR001 in combination with trametinib + dabrafenib for the treatment of metastatic BRAF V600+ melanoma in 2019.<sup>80</sup> Spartalizumab is undergoing evaluation in Phase 2 studies as a treatment for other cancers, including neuroendocrine tumors, nasopharyngeal carcinoma, non-small cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma and colorectal cancer. Spartalizumab was granted US Orphan Drug designation for the treatment of neuroendocrine tumors.<sup>81</sup>

#### MOR208 (MorphoSys)

Formerly known as Xmab<sup>®</sup>5574, MOR208 is a humanized Fc-engineered mAb directed against CD19. The Fc domain contains 2 amino acid substitutions, S239D and I332E, that enhance cytotoxicity by increasing the affinity for activatory FcγRIIIa on effector cells. MOR208 has been shown to induce lysis of leukemia cells that is mediated by natural killer cells.<sup>82</sup> The mAb was granted EU and US Orphan Drug designations for the treatment of chronic lymphocytic leukemia (CLL), as well as FDA's Breakthrough Therapy and Fast Track designations for DLBCL. MOR208 is under clinical investigation as a treatment option in combination with other anti-cancer agents for both of these hematological malignancies. In March 2018, MorphoSys reported results from the Phase 2 L-MIND study (NCT02399085), which evaluated MOR208 combined with lenalidomide in patients with relapsed or refractory DLBCL.<sup>83</sup> A total of 81 patients enrolled in the study, with 68 available for efficacy assessment at the time of data cut-off. With a median observation time of 8.3 months, the data showed an overall response rate of 49%, and a complete response in 31% of the patients. The preliminary PFS rate at 12 months was 50.4% (95% confidence interval 40–67%) and the preliminary median PFS had not been reached (95% confidence interval: 4.3 months-

**Table 4.** Investigational monoclonal antibodies in late-stage clinical studies for cancer indications.

Primary sponsoring company	INN or code name	Molecular format	Target(s)	Most advanced phase	Pivotal Phase 2, Phase 2/3 or 3 indications
TG Therapeutics	Ublituximab	Chimeric IgG1	CD20	Phase 3	Chronic lymphocytic leukemia
ADC Therapeutics Sarl	Loncastuximab tesirine	Humanized IgG1 ADC	CD19	Pivotal Phase 2	Diffuse large B-cell lymphoma
Hoffmann-La Roche	Polatuzumab vedotin	Humanized IgG1 ADC	CD79b	Phase 3	Diffuse large B-cell lymphoma
Pfizer	Utomilumab	Human IgG2	4-1BB (CD137)	Phase 3	Diffuse large B-cell lymphoma
MorphoSys	XMAB-5574, MOR208	Humanized IgG1	CD19	Phase 2/3	Diffuse large B-cell lymphoma
Sanofi	Isatuximab	Humanized IgG1	CD38	Phase 3	Multiple myeloma
Jiangsu HengRui Medicine Co., Ltd	Camrelizumab	Humanized IgG4	PD-1	Phase 3; regulatory review in China	Hodgkin's lymphoma, hepatocellular carcinoma
Actinium Pharmaceuticals	I-131-BC8, lomab-B	Murine IgG1, radio-labeled	CD45	Phase 3	Ablation of bone marrow prior to hematopoietic cell transplantation in AML patients
Tracon	Carotuximab	Chimeric IgG1	Endoglin	Phase 3	Angiosarcoma
Alphamab Oncology	KN035	mAb, single domain	PD-L1	Phase 3	Bile tract carcinoma
Viventia Bio	Oportuzumab monatox	Humanized scFv immunotoxin	EpCAM	Phase 3	Bladder cancer
Bio-Thera Solutions	BAT8001	Humanized IgG1 ADC	HER2	Phase 3	Breast cancer
Synthon Biopharmaceuticals BV	(vic)-trastuzumab duocarmazine	Humanized IgG1 ADC	HER2	Phase 3	Breast cancer
MacroGenics	Margetuximab	Chimeric IgG1	HER2	Phase 3	Breast cancer
Daiichi Sankyo	Trastuzumab deruxtecan	Humanized ADC	HER2	Phase 3	Breast cancer, HER2+ gastric or gastroesophageal junction adenocarcinoma
Five Prime Therapeutics, Zai Lab Limited	Bemarituzumab	Humanized IgG1	FGFR2b	Phase 3	Gastric and gastro-esophageal junction adenocarcinoma
Astellas	Zolbetuximab, claudiximab	Chimeric IgG1	Claudin-18.2	Phase 3	Gastric and gastro-esophageal junction adenocarcinoma
Gilead Sciences	Andecaliximab	Humanized IgG4	MMP9	Phase 3	Gastric cancer or gastroesophageal junction adenocarcinoma
AbbVie	Depatuzumab mafodotin	IgG1 ADC	EGFR	Phase 2b/3	Glioblastoma
Y-mabs Therapeutics	Naxitamab	Humanized mAb	GD2	Phase 3	High risk neuroblastoma and refractory osteomedullary disease
Bristol-Myers Squibb	Relatlimab (BMS- 986016)	Human mAb	LAG-3	Phase 2/3	Melanoma
Biocad	BCD-100	Human mAb	PD-1	Phase 2/3	Melanoma
Novartis	Spartalizumab, PDR001	Humanized IgG4	PD-1	Phase 3	Melanoma
Philogen SpA	L191L2 + L19TNF	scFv conjugates	Fibronectin extra-domain B	Phase 3	Melanoma
Y-mAbs Therapeutics	131I-omburtamab	Murine mAb, radiolabeled	B7-H3	Phase 2/3	Neuroblastoma central nervous system/ leptomeningeal metastases
BeiGene	Tislelizumab (BGB- A317)	Humanized mAb	PD-1	Phase 3; regulatory review in China	Non-small cell lung cancer, Hodgkin's lymphoma
Innovent Biologics (Suzhou) Co. Ltd.	IBI308	Human mAb	PD-1	Phase 3; regulatory review in China	Squamous cell non-small cell lung cancer
CStone Pharmaceuticals	CS1001	Human	PD-L1	Phase 3	Non-small cell lung cancer
AstraZeneca/ MedImmune LLC	Tremelimumab	Human IgG2	CTLA4	Phase 3	Non-small cell lung, head & neck, urothelial cancer
Tesaro, Inc.	TSR-042	Humanized mAb	PD-1	Phase 3	Ovarian cancer
ImmunoGen	Mirvetuximab soravtansine	IgG1 ADC	Folate receptor 1	Phase 3	Ovarian cancer
AbbVie	Rovalpituzumab tesirine	Humanized IgG1 ADC	DLL3	Phase 3	Small cell lung cancer
Seattle Genetics	Enfortumab vedotin	Human IgG1 ADC	Nectin 4	Phase 3	Urothelial cancer

Data available as of November 30, 2018. Abbreviations: ADC, antibody drug conjugate; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DLL3, delta-like protein 3; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor receptor-2; MMP-9, matrix metalloproteinase 9; PD-1, programmed cell death 1; PD-L1, programmed death ligand-1.

not reached). In November 2018, MorphoSys indicated that they are in discussions with the FDA to evaluate possible paths to market, including the possibility of an expedited regulatory submission and potential approval based primarily on the L-MIND study.<sup>84</sup> MOR208 with bendamustine versus rituximab with bendamustine is being evaluated in the Phase 2/3 B-MIND study (NCT02763319) of patients in patients with relapsed or refractory

DLBCL. The primary endpoint of the study is PFS and the primary completion date is March 2020.

#### **Oportuzumab monatox (VB4-845, Vicinium™; Sesen Bio)**

This immunotoxin is composed of a recombinant humanized antibody scFv targeting epithelial cell adhesion molecule

(EpCAM) conjugated to *Pseudomonas aeruginosa* exotoxin A.<sup>85</sup> Once bound to EpCAM expressed by cancer cells, oportuzumab monatox is internalized into the cytoplasm, where it induces apoptosis. Oportuzumab monatox was granted US and EU Orphan Drug designations in 2005, and FDA's Fast Track designation for non-muscle invasive bladder cancer (NMIBC) that is unresponsive to treatment with bacillus Calmette-Guérin (BCG) in August 2018.<sup>86</sup> The efficacy and tolerability of intravesical Vicinium™ is being evaluated in the open-label, multicenter Phase 3 VISTA study (NCT02449239) of NMIBC patients previously treated with BCG. Enrollment was completed in March 2018 with a total of 133 patients with high-grade NMIBC that is either carcinoma in situ (CIS) or papillary with or without CIS, who have been previously treated with BCG. The primary endpoint is the complete response rate in patients with CIS with or without papillary disease. In an analysis assessing pooled CIS patients (n = 77), Vicinium treatment resulted in a complete response rate of 42% at three months.<sup>87</sup> Sesen Bio expects to provide a six-month update from the VISTA study in December 2018, and is on track to report 12-month VISTA study data in mid-2019.<sup>88</sup> Positive results could allow a BLA submission by the end of 2019.

#### **TSR-042 (TESARO, Inc.)**

TESARO is developing anti-PD-1 mAb TSR-042 as a treatment for several types of cancers. In October 2018, TESARO announced results from a Phase 1 dose escalation and cohort expansion study (GARNET; NCT02715284), which is intended to support a BLA submission to the FDA in 2019.<sup>89</sup> The GARNET study is evaluating TSR-042 in patients with advanced solid tumors who have limited available treatment options. In the ongoing cohort expansion portion of GARNET, patients are administered TSR-042 at a dose of 500 milligrams every 3 weeks for the first 4 cycles, and 1000 milligrams every 6 weeks thereafter in four cohorts: microsatellite instability high (MSI-H) endometrial cancer, MSI-H non-endometrial cancer, microsatellite-stable endometrial cancer and non-small cell lung cancer. Among the 25 patients with MSI-H endometrial cancer who had at least one post-baseline tumor assessment, one had a complete response and 12 had partial responses (including 1 unconfirmed response) by immune-related response evaluation criteria in solid tumors (irRECIST) criteria.<sup>89</sup> Of the 13 responses, 12 are ongoing (92%), including three patients with partial responses who have thus far received over 60 weeks of treatment with TSR-042. Three additional patients (12%) had stable disease. TSR-042 is also being evaluated in the Phase 3 FIRST study (NCT03602859), which is comparing platinum-based therapy with TSR-042 and niraparib versus standard of care platinum-based therapy as first-line treatment of Stage III or IV non-mucinous epithelial ovarian cancer.

#### **Enfortumab vedotin (ASG22ME; Seattle Genetics, Inc./Astellas Pharma Inc.)**

This ADC directed against nectin-4 is undergoing evaluation as a treatment for locally advanced or metastatic urothelial cancer. FDA has granted enfortumab vedotin Breakthrough Therapy designation for this disease. Enfortumab vedotin as

monotherapy was evaluated at escalating doses in a Phase 1 study (NCT02091999) of 81 patients with locally advanced or metastatic urothelial cancer. The results of the clinical study showed that, of 71 patients evaluated for response, 41% had an objective response, including three (4%) complete responses and 26 (37%) partial responses. Disease control was achieved in 51 patients (72%), defined as the sum of patients achieving a complete response, partial response or stable disease.<sup>90</sup> Data from the study supported the start of the pivotal single-arm, open-label, multicenter Phase 2 EV-201 study (NCT03219333), which is evaluating the safety and efficacy of enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer who previously received a checkpoint inhibitor (PD-L1 or PD-1) and either previously received platinum-containing chemotherapy (Cohort 1) or are platinum-naïve and cisplatin-ineligible (Cohort 2). The primary endpoint is the objective response rate, and secondary key outcomes measures include duration of response, disease control rate, and PFS. Seattle Genetics and Astellas expect to report top-line data from the EV-201 study in the first quarter of 2019. Positive data from this study could serve as the basis for a BLA submission under the FDA's accelerated approval pathway.<sup>91</sup> Enfortumab vedotin is also under evaluation in the global Phase 3 EV-301 study (NCT03474107) in the same indication. The EV-301 study is intended to support a broader global registration strategy and to serve as the confirmatory randomized trial in the US. The estimated primary completion date is September 2021.

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

The glyco-engineered anti-CD20 antibody ublituximab is currently under clinical investigation in a total of 5 late-stage clinical studies in cancer (CLL, non-Hodgkin's lymphoma) and non-cancer (multiple sclerosis) indications, with the most advanced being the studies for cancer. TG Therapeutics is awaiting pivotal data from all of them. In hematological malignancies, TG Therapeutics is conducting three Phase 3 studies exploring the efficacy of ublituximab in combination with other anti-cancer agents. The UNITY-CLL Phase 3 study (NCT02612311) evaluated the combination of ublituximab and TGR-1202, a PI3K delta inhibitor, versus anti-CD20 obinutuzumab plus chlorambucil in untreated and previously treated CLL patients. The primary and secondary outcome measures are PFS and overall response rate, respectively. TG Therapeutics had announced plans to prepare and potentially submit a marketing application by the end of 2018, but, in September 2018, TG Therapeutics reported that an interim analysis of the overall response rate in UNITY-CLL trial 'could not be conducted at this time as the data were not sufficiently mature to conduct the analysis.'<sup>92</sup> The company will now focus on PFS data, with a readout anticipated in 2019. Another Phase 3 study (NCT02301156) is comparing ublituximab in combination with Ibrutinib to Ibrutinib alone in previously treated CLL patients. The primary outcome measures are overall response rate and PFS. The estimated primary completion date is June 2019. The Phase 2/3 UNITY-NHL (NCT02793583) study is evaluating ublituximab in combination with TGR-

1202 with or without bendamustine in 500 patients with previously treated non-Hodgkin's lymphoma. Overall response rate is the primary outcome measure and the estimated primary completion date is May 2019.

Two Phase 3 studies (ULTIMATE 1, NCT03277261 and ULTIMATE 2, NCT03277248) are evaluating the efficacy and safety of ublituximab compared to teriflunomide in 440 patients with relapsing multiple sclerosis. For both studies, the primary outcome measure is annualized relapse rate and the estimated primary completion date is March 2021.

## Outlook for the near future

Medical care of patients will likely be strongly influenced by the increased number and variety of antibody therapeutics that may be approved in the near future. This is especially the case for cancer patients, who may soon have a substantially larger number of antibody immune checkpoint modulators and ADCs available to them. Of the 33 antibody therapeutics currently in late-stage clinical development for cancer, 11 modulate immune checkpoints and 8 are ADCs. Of the immune checkpoint modulators, 'antibodies to watch' include anti-CTLA4 **tremelimumab** (AstraZeneca), anti-PD-1 **spartalizumab** (Novartis), anti-PD-1 **BCD-100** (Biocad), and radiolabeled anti-B7-H3 **omburtamab** (Y-mAbs Therapeutics), which are all being evaluated in clinical studies with primary completion dates in late 2018 and in 2019. Looking further into the future, results from studies of antibodies targeting immune checkpoints other than CTLA4, PD-1 and PD-L1 are eagerly anticipated. Results of the Phase 3 study (NCT02951156) of the CD137/4-1BB agonist utomilumab (PF-05082566, Pfizer) in combination regimens in patients with relapsed or refractory diffuse large B-cell lymphoma may be available near the study's primary completion date of March 2020. In addition, results of the Phase 2/3 study (NCT03470922) of anti-LAG3 relatlimab (Bristol-Myers Squibb) combined with nivolumab versus nivolumab in patients with previously untreated metastatic or unresectable melanoma may be released near the study's primary completion date of July 2020.

ADC 'antibodies to watch' include **mirvetuximab soravtansine** (ImmunoGen), **trastuzumab duocarmazine** (Synthon BioPharmaceuticals), and **depatuxizumab mafodotin** (AbbVie). Mirvetuximab soravtansine, an ADC that targets  $\alpha$ -folate receptor 1, is undergoing evaluation in the Phase 3 FORWARD I study (NCT02631876) of patients with folate receptor alpha-positive advanced epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. This study has a primary completion date in November 2018, and top-line results from the study are expected in the first half of 2019. The safety and efficacy of anti-HER2 trastuzumab duocarmazine (Synthon BioPharmaceuticals) is being evaluated in the Phase 3 TULIP study (NCT03262935) of patients with human epidermal growth factor receptor 2 (HER2)-positive unresectable locally advanced or metastatic breast cancer. This study has a primary completion date in May 2019. Trastuzumab duocarmazine was granted a Fast Track designation for treating patients diagnosed with HER2-positive metastatic breast cancer that has progressed during or after at least two HER2-targeting treatment regimens

for locally advanced or metastatic disease, or progressed during or after [ado-]trastuzumab emtansine treatment. The anti-epidermal growth factor receptor ADC depatuxizumab mafodotin is being evaluated as a treatment for glioblastoma in two Phase 3 studies, NCT03419403 and NCT02573324, with primary completion dates in September 2019 and March 2020, respectively. In addition, anti-DLL3 rovalpituzumab tesirine (AbbVie) is undergoing evaluation in three Phase 3 studies of small cell lung cancer (SCLC) patients, TAHOE (NCT03061812), MERU (NCT03033511) and M16-292 (NCT03334487), with primary completion dates in September 2019, November 2019, and September 2020. However, AbbVie announced in March 2018 that they will not seek accelerated approval for rovalpituzumab tesirine in third-line relapsed/refractory SCLC based on the magnitude of effect across multiple parameters in the Phase 2 TRINITY study.<sup>93</sup>

We anticipate that a sufficient number of the ~ 225 antibody therapeutics in Phase 2 studies will transition to late-stage studies to keep the total number in the range of 50–65 in 2019 and beyond. For example, the Phase 3 IMAGINE study (NCT03744910) to evaluate the safety and efficacy of anti-IL-6 clazakizumab for the treatment of chronic active antibody-mediated rejection in kidney transplant recipients is due to start in March 2019, and Phase 3 studies to investigate the efficacy and safety of UB-421 monotherapy as substitution for stable antiretroviral therapy in HIV-1 infected adults (NCT03149211) and UB-421 in combination with optimized background therapy regimen in patients with multi-drug resistant HIV-1 infection (NCT03164447) are due to start in July and September 2019, respectively. We look forward to documenting progress made with these and other 'antibodies to watch' in the next installment of this article series.

## Abbreviations

ADC	antibody-drug conjugate
AE	adverse events
ARR	annualized relapse rate
ART	antiretroviral therapy
aTTP	acquired thrombotic thrombocytopenic purpura
BCG	bacillus Calmette-Guérin
BLA	biologics license application
C5	complement component 5
CCR4	CC chemokine receptor 4
CGRP	calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human Use
CIS	carcinoma in situ
CLL	chronic lymphocytic leukemia
CR	complete response
CSCC	cutaneous squamous cell carcinoma
CTCL	cutaneous T-cell lymphoma
DLBCL	diffuse large B-cell lymphoma
EC	European Commission
EMA	European Medicines Agency
EpCAM	epithelial cell adhesion molecule
EU	European Union
FDA	US Food and Drug Administration
FL	follicular lymphoma
HAE	hereditary angioedema
HCL	hairy cell leukemia
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis



IV	intravenous
mAb	monoclonal antibody
MF	mycosis fungoides
MM	multiple myeloma
MMD	monthly migraine days
MSI	microsatellite instability
nAMD	neovascular age-related macular degeneration
NDA	new drug application
NGF	nerve growth factor
NMIBC	non-muscle invasive bladder cancer
NMOSD	neuromyelitis optica spectrum disorder
NMPA	National Medical Products Administration
PD-1	programmed cell death 1 protein
PD-L1	programmed death ligand 1
PFS	progression-free survival
PNH	paroxysmal nocturnal hemoglobinuria
SC	subcutaneous
scFv	single-chain variable fragment
SCLC	small cell lung cancer
SS	Sézary syndrome
US	United States
XLH	X-linked hypophosphatemia

## Disclosure Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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