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PERSPECTIVE



Antibodies to watch in 2018

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ABSTRACT

The pace of antibody therapeutics development accelerated in 2017, and this faster pace is projected to continue through 2018. Notably, the annual number of antibody therapeutics granted a first approval in either the European Union (EU) or United States (US) reached double-digits (total of 10) for the first time in 2017. The 10 antibodies granted approvals are: brodalumab, dupilumab, sarilumab, guselkumab, benralizumab, ocrelizumab, inotuzumab ozogamicin, avelumab, duvalumab, and emicizumab. Brodalumab, however, had already been approved in Japan in 2016. As of December 1, 2017, nine antibody therapeutics (ibalizumab, burosumab, tiltrakizumab, caplacizumab, erenumab, fremanezumab, galcanezumab, romosozumab, mogamulizumab) were in regulatory review in the EU or US, and regulatory actions on their marketing applications are expected by the end of 2018. Based on company announcements and estimated clinical study primary completion dates, and assuming the study results are positive, marketing applications for at least 12 antibody therapeutics that are now being evaluated in late-stage clinical studies may be submitted by the end of 2018. Of the 12 candidates, 8 are for non-cancer indications (lanadelumab, crizanlizumab, ravulizumab, eptinezumab, risankizumab, satralizumab, brolucizumab, PRO140) and 4 are for cancer (sacituzumab govitecan, moxetumomab pasudotox, cemiplimab, ublituximab). Additional antibody therapeutics to watch in 2018 include 19 mAbs undergoing evaluation in late-stage studies with primary completion dates in late 2017 or during 2018. Of these mAbs, 9 are for non-cancer indications (lampalizumab, roledumab, emapalumab, fasinumab, tanezumab, etrolizumab, NEOD001, gantenerumab, anifrolumab) and 10 are for cancer indications (tremelimumab, isatuximab, BCD-100, carotuximab, camrelizumab, IBI308, glembatumumab vedotin, mirvetuximab soravtansine, oportuzumab monatox, L19IL2/L19TNF). Positive clinical study results may enable marketing application submissions in 2018. Brief summaries of these antibody therapeutics are provided in this installment of the ‘Antibodies to watch’ article series.

KEYWORDS

antibody therapeutics; Food and Drug Administration; European Medicines Agency; cancer; immune-mediated disorders

Introduction

The number of antibody therapeutics in late-stage clinical studies sponsored by commercial firms has substantially increased, from 26 to over 50, since the ‘Antibodies to watch’ article series was started in 2010.^{1–10} This has, in turn, driven a sustained increase in the number of antibodies that are granted their first marketing approvals annually in the European Union (EU) or United States (US). Prior to 2014, the annual number of approvals in the EU or US reached 6 in only one year (2009). In contrast, this number was matched or exceeded every year during 2014 to 2017 (6, 9, 6, and 10 approvals, respectively).^{1–5} Notably, the 10 marketing approvals for antibody therapeutics granted in the US during 2017 is the highest annual number of approvals achieved to date.

In this installment of the ‘Antibodies to watch’ article series, we review the antibody therapeutics that were approved in the EU or US in 2017, and provide details of those that, as of December 1, 2017, were being reviewed by either the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA). We also discuss the antibody therapeutics in

late-stage clinical development, focusing on those that might enter regulatory review by the end of 2018 and those that are being evaluated in late-stage clinical studies with primary completion dates that occur by the end of 2018. Due to the substantial amount of information available for these antibodies, we have limited our discussion to recent events and disclosures, and thus not all indications or studies for every molecule are considered here.

Antibody therapeutics approved in the EU or US in 2017

As of December 1, 2017, 10 monoclonal antibodies (mAbs) have received their first marketing approvals in 2017 in either the EU or the US (Table 1). It should be noted that the approvals in the EU or US were not always the first global approval granted. Brodalumab was first approved in Japan in July 2016 for treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma. Moreover, sarilumab was first approved in Canada in January 2017. Of the 10 mAbs approved in the EU or US during 2017, 5 mAbs are for

Table 1. Antibody therapeutics approved in the European Union or United States during 2017*.

International non-proprietary name	Brand name	Target; Format	Indication first approved	Date of first EU approval	Date of first US approval
Brodalumab	Siliq, Lumicef, Kyntheum	IL-17RA; Human IgG2	Plaque psoriasis	7/17/17	2/15/17
Avelumab	Bavencio	PD-L1; Human IgG1	Merkel cell carcinoma	9/18/17	3/23/17
Dupilumab	Dupixent	IL-4R α ; Human IgG4	Atopic dermatitis	9/27/17	3/28/17
Ocrelizumab	Ocrevus	CD20; Humanized IgG1	Multiple sclerosis	EC decision pending	3/29/17
Durvalumab	Imfinzi	PD-L1; Human IgG1	Bladder cancer	In review	5/1/17
Sarilumab	Kevzara	IL-6R; Human IgG1	Rheumatoid arthritis	6/23/17	5/22/17
Guselkumab	Tremfya	IL-23 p19; Human IgG1	Plaque psoriasis	11/23/17	7/13/17
Inotuzumab ozogamicin	Besponsa	CD22; Humanized IgG4; ADC	Acute lymphoblastic leukemia	6/29/17	8/17/17
Benralizumab	Fasenra	IL-5R α ; Humanized IgG1	Asthma	EC decision pending	11/14/17
Emicizumab	Hemlibra	Factor IXa, X; Humanized IgG4, bispecific	Hemophilia A	In review	11/16/17

Table notes: Sarilumab's first global approval was granted in Canada on January 12, 2017; brodalumab's first global approval was granted in Japan on July 4, 2016. *Data available as of December 1, 2017

Abbreviations: ADC, antibody drug conjugate; CD, cluster of differentiation; EC, European Commission; EU, European Union; IL, interleukin; IgG, immunoglobulin G; PD-L1, programmed cell death 1.

immune-mediated disorders (brodalumab, dupilumab, sarilumab, guselkumab, benralizumab), 4 mAbs are for cancer indications (avelumab, ocrelizumab, durvalumab, inotuzumab ozogamicin), and 1 mAb (emicizumab) is for hemophilia.

Brodalumab (Siliq[®], Lumicef[®], Kyntheum[®], AMG-827) is a human IgG2 antibody that targets IL-17 receptor A (IL-17RA) and prevents inflammatory signaling of IL-17A, IL-17F and IL-17C pro-inflammatory cytokines through IL-17RA. Brodalumab was first approved in Japan, under the name Lumicef[®], on July 4, 2016 for patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and psoriatic erythroderma. Brodalumab was granted marketing approvals in the US (Siliq[®]) and the EU (Kyntheum[®]) in February and July 2017, respectively. Brodalumab is indicated for the treatment of adult patients with moderate to severe plaque psoriasis, who are candidates for systemic therapy or phototherapy and who have failed to respond, or have stopped responding to other systemic therapies. The recommended dose is 210 mg subcutaneously (SC) at weeks 0, 1, 2 followed 210 mg every 2 weeks. The efficacy and safety of brodalumab (at 140 mg or 210 mg) compared to placebo and ustekinumab were evaluated on 4373 patients from three Phase 3 studies, AMAGINE-1 (NCT01708590), AMAGINE-2 (NCT01708603), and AMAGINE-3 (NCT01708603). The primary outcome measures were the proportion of patients with superior to 75% improvement in Psoriasis Area and Severity Index (PASI 75), and Static Physician Global Assessment (sPGA) success score (0/1) measuring psoriasis severity based on induration, scaling and erythema at week 12. In the AMAGINE-1 Phase 3 study, at week 12, PASI 75 response rates were higher with brodalumab at a dose of 210 mg (83%) or at 140 mg (60%) compared to 3% with placebo. sPGA scores were also higher in patients receiving brodalumab at 140 mg and 210 mg (54% and 76%, respectively versus 1% of patients with placebo).¹¹

In the AMAGINE-2 and AMAGINE-3 trials, the clinical efficacy of brodalumab was compared to placebo and to ustekinumab. Brodalumab was superior to both treatments regarding primary endpoints. PASI response rates were significantly higher with brodalumab at 210 mg, or 140 mg than with placebo (AMAGINE-2, 86% and 67% and 8%, AMAGINE-2 86%, 69% and 6%, respectively; $P < 0.001$). The sPGA scores were

also significantly higher with brodalumab at 210 mg or 140 mg than with placebo (AMAGINE-2, 79% and 58%, versus 4%; AMAGINE-3, 80% and 60%, versus 4%, respectively; $P < 0.001$).¹²

Avelumab (Bavencio[®], MSB0010718C), a human IgG1 that targets programmed cell death ligand 1 (PD-L1), was first approved in the US on March 23, 2017 as a monotherapy for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC), and in the EU for MCC patients in September 2017. The approvals were based on data from the pivotal Phase 2 Javelin Merkel 200 study (NCT02155647). This study included two parts: Part A for patients who had received prior chemotherapy treatment, Part B for patients where treatment-naïve to systemic therapy for metastatic MCC. The recommended dose is 10 mg/kg every 2 weeks intravenously (IV). In Part A of the study, 88 patients who had previously received at least one chemotherapy treatment were enrolled; the median follow-up period was 10.4 months. The primary endpoint was objective response (complete response (CR) or partial response (PR)). An objective response was achieved by 31.8% of patients treated with avelumab, including 8 complete responses and 20 partial responses.¹³ Part B of the study includes 39 patients who had not received prior systemic therapy. The primary outcome measure is the duration of response (DOR). The estimated primary completion date of the study is September 2019. Avelumab received orphan drug designation from the European Commission and the Australian Therapeutic Goods Administration for MCC. In the US, avelumab received orphan drug and Breakthrough Therapy designations for this indication.

On May 9, 2017, the FDA granted a supplemental, accelerated approval for avelumab for patients with locally advanced or metastatic urothelial carcinoma whose disease has progressed after platinum-based therapy. Avelumab is being evaluated as an investigational agent in four Phase 3 studies with primary completion dates in 2018. These studies include patients with non-small cell lung cancer (NCT02395172), ovarian cancer (NCT02580058), renal cell carcinoma (NCT02684006) and gastric cancer, including gastroesophageal junction adenocarcinoma (NCT02625623). Avelumab was granted orphan drug designation in the US and EU for gastric cancer.

Dupilumab (Dupixent®, REGN668/SAR231893) is a human IgG4 mAb that targets IL-4 receptor (IL4R), thus blocking inflammatory responses mediated by IL-4 and IL-13. The mAb was approved in the US and EU for patients with atopic dermatitis on March 28, 2017 and September 28, 2017, respectively, based on data from LIBERTY Atopic Dermatitis program, which included the SOLO 1, SOLO 2, and CHRONOS studies. In SOLO 1 and SOLO 2, patients received for 16 weeks, weekly SC injections of dupilumab (300 mg) or placebo or the same dose of dupilumab every other week alternating with placebo. In the CHRONOS Phase 3 study (NCT02260986), the efficacy of dupilumab administered concomitantly with corticosteroids was compared to placebo plus corticosteroids. The primary end point was the proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 (higher score is associated with the severity of the disease) and a reduction from baseline of at least 2 points in the score at week 16. At week 16, a significant higher proportion of patients receiving dupilumab (SOLO 1 37%, SOLO 2 36%) as a monotherapy than patients receiving placebo (SOLO 1 10%, SOLO 2 8%) had an IGA score of 0 or 1 and improvement of 2 points or more on the IGA from the baseline score.¹⁴ Similar results were observed for the CHRONOS study, in which 39% of patients treated with dupilumab + corticosteroids, weekly or every two weeks, achieved the co-primary endpoints of IGA 0/1 compared to 12% who received placebo + corticosteroids ($P < 0.0001$).¹⁵ FDA granted dupilumab a Breakthrough Therapy designation for atopic dermatitis.

Dupilumab is being evaluated as an investigational agent in Phase 3 studies of asthma patients and patients with nasal polyps. In September 2017, Regeneron and Sanofi announced that the primary endpoints were met in the Phase 3 LIBERTY ASTHMA QUEST study (NCT02414854) of dupilumab in a broad population of patients with uncontrolled, persistent asthma.¹⁶ Two Phase 3 studies (NCT02912468, NCT02898454) of patients with nasal polyps have primary completion dates in 2018. Dupilumab is also currently under investigation in Phase 2 studies for treatment of eosinophilic esophagitis, and received orphan drug designation from FDA for this indication.

Ocrelizumab (Ocrevus®) is a humanized IgG1 antibody targeting CD20-positive B cells. Such B cells play a role in myelin damage and multiple sclerosis pathogenesis through production of pro-inflammatory cytokines, secretion of autoantibodies, and activation of pro-inflammatory T cells. Ocrelizumab is thought to deplete CD20-positive B cells through three mechanisms: complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and apoptosis after ligation of CD20 on the target cell surface. This mAb was evaluated in Phase 3 studies of patients with rheumatoid arthritis (RA)¹⁷ or systemic lupus erythematosus (SLE),¹⁸ but did not demonstrate a positive outcome in these studies.

Ocrelizumab was granted an approval for the treatment of relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) in the US on March 29, 2017. Ocrelizumab received Breakthrough Therapy and Fast Track designations, and the biologics license application (BLA) was given a priority review by FDA. The safety and efficacy of IV ocrelizumab compared to interferon β -1a were evaluated in patients

with RMS in the Phase 3 OPERA I and OPERA II (NCT01247324 and NCT01412333, respectively) studies. In the ocrelizumab arms, the annualized relapse rate (ARR), the primary endpoint, was lower than the interferon β -1a arms (46% lower for OPERA I and 47% lower for OPERA II; $P < 0.001$).¹⁹ To determine the safety and efficacy in PPMS patients, ocrelizumab was investigated in the Phase 3 ORATORIO trial. The primary endpoint was the percentage of patients with disability progression confirmed at 12 weeks. Compared to placebo, ocrelizumab showed a significant effect on the percentage of patients with disability progression (32.9% with ocrelizumab versus 39.3% with placebo; $P = 0.03$). Furthermore, in patients who received ocrelizumab, a decrease (3.4%) of the total volume of brain lesions seen in magnetic resonance imaging was observed compared with an increase (7.4%) in those who received placebo.²⁰

Durvalumab (Imfinzi®, MEDI4736) is a human IgG1 directed against PD-L1 that blocks the interaction between PD-L1 and their receptors (PD-1, CD80), involved into T cell inhibition. Durvalumab was engineered to prevent cytotoxic effector functions (ADCC or CDC) against PD-L1-positive immune cells. This mAb received accelerated FDA approval for patients with locally advanced or metastatic urothelial carcinoma who progressed after receiving platinum-containing chemotherapy on May 1, 2017. The application was granted a priority review, and Breakthrough Therapy designation. The approval is based on data from the Phase 1/2 Study 1108 (NCT01693562) of 182 patients. In this study, patients were administered 10 mg/kg durvalumab IV every 2 weeks for up to 12 months. Patients in the PD-L1 high subgroup had a higher objective response rate (27.4%) than those in the PD-L1 low/negative subgroup (4.1%).²¹

FDA is reviewing a supplemental BLA for durvalumab for the treatment of patients with locally advanced (Stage III) unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy. The BLA has Priority Review status. Durvalumab was granted a Breakthrough Therapy designation for this indication. The EMA is also reviewing a marketing authorization application for durvalumab as a treatment for Stage III unresectable NSCLC. The marketing applications submitted to both agencies include results from the Phase 3 PACIFIC trial (NCT02125461). Patients received 10 mg/kg durvalumab IV every 2 weeks for up to 12 months. In the durvalumab arm of the study, the median progression free survival was 16.8 months compared to 5.6 months with placebo.²²

Durvalumab was granted Fast Track designation for the treatment of patients with PD-L1-positive metastatic head and neck squamous cell carcinoma by FDA. The Phase 3 EAGLE (NCT02369874) and KESTREL (NCT02551159) studies evaluating the effects of durvalumab in patients with head and neck cancer have primary completion dates in February and March 2018, respectively.

Sarilumab (Kevzara®, SAR153191, REGN88), a human IgG1 antibody targeting IL-6 receptor (IL-6R), was first approved in Canada (February 2017), and subsequently approved in the US (May 2017) and EU (June 2017) for patients with moderately to severely active rheumatoid arthritis (RA) who had an inadequate response or intolerance to one or

more disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX). The approvals were based on data derived from the global SARIL-RA clinical development program, which included the Phase 3 MOBILITY (NCT01061736), TARGET (NCT01709578) and MONARCH (NCT02332590) studies.

In the MOBILITY and TARGET studies, sarilumab was administered in combination with MTX or other DMARDs. These studies met their primary endpoints, which were the improvement of signs and symptoms of RA measured by the percentage of patients achieving American College of Rheumatology 20% (ACR20) at week 24 and the change from baseline in Health Assessment Question Disability Index (HAQ-DI) at week 16. In the MOBILITY study, sarilumab-treated patients achieved significantly higher ACR20 responses rates (66% for sarilumab at 200 mg, 58% at 150 mg) than those who received placebo (33%). Sarilumab also improved physical function measured by HAQ-DI with a decrease in the HAQ-DI score (-0.58 and -0.54 for sarilumab at 200 mg and 150 mg, respectively) compared to placebo (-0.30). Similarly, in the TARGET study, the proportion of patients achieving ACR20 was higher in sarilumab + DMARD group (61% for sarilumab at 200 mg, 56% at 150 mg) than in placebo group (34%). An improvement of physical function was also observed in the sarilumab + DMARD group with -0.50 for patients treated with sarilumab at 150 mg, or -0.49 for 200 mg compared to -0.29 in the placebo + DMARD group.²³

The Phase 3 MONARCH study investigated the clinical efficacy of sarilumab (200 mg every 2 weeks) compared to adalimumab for 24 weeks. The primary outcome measure was change from baseline in 28-joint disease activity score using erythrocyte sedimentation rate (DAS28-ESR) at week 24. Sarilumab demonstrated superiority to adalimumab in the primary endpoint (-3.28 compared to -2.20 with adalimumab; $P < 0.0001$).²⁴

Guselkumab (Tremfya®), a human IgG1 λ mAb, blocks the p19 subunit of IL-23, thereby limiting inflammatory responses. IL-23 is a cytokine involved in Th17 differentiation and maintenance, which allows production of pro-inflammatory cytokines such as IL-17, IL-22 and tumor necrosis factor (TNF) by this T cell subset. On July 13, 2017, guselkumab received a FDA approval for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy based on results from the VOYAGE 1 (NCT02207231), VOYAGE 2 (NCT02207244) and NAVIGATE (NCT02203032) studies. A marketing authorization was granted in the European Union for the use of guselkumab in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy in November 2017.

In the VOYAGE 1 and 2 studies, guselkumab demonstrated superiority to placebo and to adalimumab for the co-primary endpoints. The percentage of patients with an IGA score of 0 or 1 was higher in the guselkumab group (85.1%) than in the placebo group (6.9%) at week 16. In addition, the proportion of patients who achieved at least 90% improvement from baseline in the PASI score (PASI 90) was higher for guselkumab-treated patients (73.3%) versus those who received placebo (2.9%) at week 16. Similarly, a higher percentage of subjects receiving guselkumab achieved IGA 0/1 (85.1%) compared to

adalimumab-treated patients (65.9%). The PASI90 response rate was also greater in the guselkumab group (73.3%) versus adalimumab group (49.7%).^{25, 26} Similar results were observed in the VOYAGE 2 trial.^{26, 27}

In the NAVIGATE study, patients initially received ustekinumab (45 mg or 90 mg) at weeks 0 and 4. At week 16, patients with an inadequate response to ustekinumab were randomized to receive 100 mg guselkumab or to continue with ustekinumab. The primary outcome measure was the number of visits at which participants achieved an IGA response of cleared (0) or minimal (1) and at least a 2 grade improvement (from week 16) from week 28 through week 40. The proportion of patients achieving this measure was significantly greater in the guselkumab-treated patients (31.1%) versus the ustekinumab group (14.3%) at week 28 and week 52 (36.3% vs. 17.3%, respectively).²⁸

Inotuzumab ozogamicin (Besponsa®, CMC-544) is an anti-CD22 humanized IgG4 antibody conjugated to calicheamicin, a cytotoxic drug. This antibody-drug conjugate (ADC) was first approved in the EU on June 30, 2017 for adult patient with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), and subsequently approved in the US on August 17, 2017 for this indication. Inotuzumab ozogamicin received Breakthrough Therapy designation from FDA for ALL, as well as orphan drug designations in the US and EU for this indication.

The approvals for ALL were supported by results from the Phase 3 INOVATE ALL study (NCT01564784) for the treatment of adults with relapsed or refractory ALL. The INOVATE All Phase 3 investigated the safety and efficacy of inotuzumab ozogamicin compared to standard-of-care therapy for ALL patients. The primary outcome measure was the percentage of patients with a CR and overall survival (OS). Patients were randomly assigned to receive either three doses of inotuzumab ozogamicin on day 1 (0.8 mg/m²), day 8 (0.5 mg/m²), and day 15 (0.5 mg/m²) of a cycle or standard-of-care therapy. Treatment cycle 1 lasted for 21 days and subsequent cycles each lasted for 28 days; patients received treatment for up to six cycles. The standard of care was the investigator's choice of FLAG therapy (fludarabine, cytarabine and granulocyte-colony stimulating factor), high dose cytarabine, or cytarabine and mitoxantrone. The CR rate was significantly greater in the inotuzumab ozogamicin-treated patients (80.7%) compared to standard therapy group (29.4%). Moreover, the median OS was 7.7 months for patients who received inotuzumab ozogamicin compared to 6.7 months for those administered the standard-of-care therapy.²⁹

Benralizumab (Fasenra®, MEDI-563), an afucosylated IgG1 mAb targeting the α -subunit of IL-5R found on eosinophils, received FDA approval on November 14, 2017 for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on November 10, 2017, recommending the marketing authorization of benralizumab as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β -agonists. The European Commission's decision regarding marketing authorization

in the EU is pending. Marketing applications for benralizumab are undergoing review in Japan and other countries. The mAb was in-licensed from BioWa, Inc., a wholly-owned subsidiary of Kyowa Hakko Kirin Co., Ltd. by MedImmune.

The safety and efficacy of benralizumab as a treatment for asthma were evaluated in the WINDWARD program, which included six Phase 3 trials, SIROCCO, CALIMA, ZONDA, BISE, BORA and GREGALE. The randomized, double-blinded, parallel-group, placebo-controlled SIROCCO (NCT01928771) and CALIMA (NCT01914757) trials evaluated the efficacy and safety of a regular, SC administration of a fixed 30 mg dose of benralizumab for up to 56 weeks in exacerbation-prone adult and adolescent patients 12 years of age and older. Study results were published in 2016.^{30, 31} In the 28-week randomized ZONDA study (NCT02075255), the effects of 30 mg benralizumab administered SC either every 4 weeks or every 8 weeks (with the first three doses administered every 4 weeks) versus placebo on the reduction in the oral glucocorticoid dose while asthma control was maintained in adult patients with severe asthma. The study's primary outcome measure, percentage reduction in final oral steroid dose compared with baseline while maintaining asthma control, was met. The median final oral glucocorticoid doses from baseline were reduced by 75% in patients who received either dose of benralizumab, compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group ($P < 0.001$ for both comparisons).³²

Emicizumab (Hemlibra[®], emicizumab-kxwh, ACE910, RO5534262), a bispecific IgG4 mAb targeting Factor IXa and X, was approved by FDA on November 16, 2017. The drug, which is administered once a week, was approved to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A who have developed Factor VIII inhibitors. The BLA was granted Priority Review and a Breakthrough Therapy designation. Hemlibra[®] was also granted an orphan drug designation by FDA. Marketing applications for emicizumab are under review in the European Union and Japan; the EMA is reviewing the marketing authorization application under accelerated assessment. Emicizumab was granted an orphan drug designation in Japan for the prevention and reduction of bleeding episodes in patients with congenital factor VIII deficiency with inhibitors. The drug was created by Chugai Pharmaceutical Co., Ltd. and co-developed by Chugai, Roche and Genentech.

The marketing applications for emicizumab include results from the Phase 3 HAVEN 1 (NCT02622321) and interim analysis of the HAVEN 2 (NCT02795767) studies. In the HAVEN 1 study, adult and adolescent patients (12 or older) who had previously received episodic treatment with bypassing agents were randomly assigned in a 2:1 ratio to emicizumab prophylaxis (group A) or no prophylaxis (group B). The primary end point of the study was the difference in bleeding rates between group A and group B. Emicizumab was SC administered at a dose of 3 milligrams per kilogram per week (mg/kg/week) for 4 weeks followed by 1.5 mg/kg/week up to the end of the study. The annualized bleeding rate in group A was reduced by 87% compared to group B (2.9 events vs 23.3 events, $P < 0.001$).³³ The HAVEN 2 study is evaluating the efficacy, safety, and pharmacokinetics of SC administration of emicizumab in hemophilia A pediatric patients with inhibitors.

Antibody therapeutics undergoing regulatory review in the US or EU

As of December 1, 2017, a total of 9 antibody therapeutics were undergoing regulatory review in either the US or EU (Table 2). Of these, 8 (ibalizumab, burosumab, tildrakizumab, caplacizumab, erenumab, fremanezumab, galcanezumab, romosozumab) had not yet received a marketing approval in any other country. One, mogamulizumab, was granted a first global approval in Japan on March 20, 2012.

Ibalizumab, an IgG4 mAb targeting CD4, is being evaluated by the FDA as a treatment for multi-drug resistant human immunodeficiency virus (HIV) infection. The FDA's target action date for the BLA, which received a priority review, is January 3, 2018. Ibalizumab was granted orphan drug and Breakthrough Therapy designations by FDA. Theratechnologies Inc. and TaiMed Biologics, Inc. have an agreement to market and distribute ibalizumab in the US and Canada.

The BLA for ibalizumab includes data from the Phase 3 TMB-301 study (NCT02475629), which was a 24-week open-label study investigating the efficacy and safety of ibalizumab plus optimized background regimen in highly treatment-experienced patients with multidrug resistant HIV. In October 2017, Theratechnologies Inc. announced 48-week efficacy and safety results for ibalizumab in patients infected with multidrug resistant HIV-1 who completed the TMB301 study and

Table 2. Antibody therapeutics in regulatory review in the European Union or United State*.

International non-proprietary name	Brand name proposed	Target; Format	Indication under reviewed	Status in EU	Status in US
Ibalizumab	(Pending)	CD4; Humanized IgG4	HIV infection	NA	In review
Burosumab	(Pending)	FGF23; Human IgG1	X-linked hypophosphatemia	In review	In review
Tildrakizumab	(Pending)	IL-23 p19; Humanized IgG1	Plaque psoriasis	In review	In review
Caplacizumab	(Pending)	von Willebrand factor; Humanized Nanobody	Acquired thrombotic thrombocytopenic purpura	In review	NA
Erenumab	Aimovig	CGRP receptor; Human IgG2	Migraine prevention	In review	In review
Fremanezumab	(Pending)	CGRP; Humanized IgG2	Migraine prevention	NA	In review
Galcanezumab	(Pending)	CGRP; Humanized IgG4	Migraine prevention	In review	In review
Romosozumab	Evenity	Sclerostin; Humanized IgG2	Osteoporosis in postmenopausal women at increased risk of fracture	NA	In review
Mogamulizumab	Poteligeo	CCR4; Humanized IgG1	Cutaneous T cell lymphoma	In review	NA

*Data available as of December 1, 2017

Abbreviations: CGRP, Calcitonin gene-related peptide; CCR4, CC chemokine receptor 4; CD, cluster of differentiation; FGF23, fibroblast growth factor 23; HIV, human immunodeficiency virus; IL, interleukin; IgG, immunoglobulin G; NA, not approved or in review in the EU; not approved or information on review status not available in US.

continued treatment in the Expanded Access Program study (TMB-311; NCT02707861)). A total of 27 patients completed the 24-week treatment period of TMB-301 in the US and entered TMB-311, where patients continued to receive 800 mg ibalizumab every 2 weeks for up to 48 weeks. The virologic suppression observed at week 24 was sustained through week 48; median viral load reduction from baseline was $2.5\log_{10}$ at weeks 24 and 48. In TMB-311, all 15 patients with an undetectable viral load at week 24 maintained suppression to week 48. Another patient in TMB-311 reached less than 50 copies/mL at week 48 after having a detectable viral load at week 24. A total of 17 patients (63%) achieved a viral load less than 200 copies/mL.³⁴

Burosumab (KRN23) is a human IgG1 mAb targeting fibroblast growth factor 23 (FGF23), a hormone that regulates phosphate excretion and active vitamin D production by the kidney. Discovered by Kyowa Hakko Kirin, burosumab is being developed by Ultragenyx and Kyowa Hakko Kirin to treat X-linked hypophosphatemia (XLH), which is characterized by skeletal defects resulting from excess levels of FGF23, as well as tumor-induced osteomalacia. Marketing applications have been submitted in the EU and US. Burosumab was granted Breakthrough Therapy designation in the US, and the BLA was granted a priority review. FDA's Prescription Drug User Fee Act (PDUFA) date is April 17, 2018.

The primary endpoint of increasing serum phosphorus levels was met in the randomized, double-blind, placebo-controlled Phase 3 NCT02526160 study of burosumab in adult XLH patients.³⁵ Patients were randomized 1:1 to receive 1 mg/kg burosumab or placebo every four weeks for 24 weeks; 94% of patients treated with burosumab ($n = 68$) achieved serum phosphorus levels above the lower limit of normal and maintained levels in the low normal range through 24 weeks compared to 8% of patients in the placebo arm ($n = 66$; $P < 0.0001$). A key secondary endpoint of stiffness improvement was also met in the study. A Phase 3 study (NCT02915705) comparing the efficacy and safety of burosumab with oral phosphate/active vitamin D therapy in children (aged 1 to ≤ 12 years) with XLH has a primary completion date in July 2018.

Tildrakizumab (SCH 900222/MK-3222) is a humanized IgG1 mAb targeting IL-23p19. Marketing applications for tildrakizumab as a treatment for moderate to severe plaque psoriasis have been submitted in the EU and US. The BLA for tildrakizumab is based on two Phase 3 trials (reSURFACE 1 and 2) that included over 1,800 patients, some of whom were treated with tildrakizumab for up to 3.5 years. The 52-week, placebo-controlled, parallel design reSURFACE 2 study (NCT01729754) compared the efficacy and safety/tolerability of SC tildrakizumab (100 mg or 200 mg) with 50 mg etanercept in patients with moderate-to-severe chronic plaque psoriasis; participation in an optional long-term evaluation of safety is available to patients. The placebo-controlled reSURFACE 1 study (NCT017223310) has a similar design, but does not include an active comparator arm. The co-primary endpoints were the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 grade score reduction from baseline) at week 12. At the 12 week timepoint in the reSURFACE 2 study, a higher proportion of patients who received either

dose of tildrakizumab achieved PASI 75 compared to those who received etanercept or placebo (66% and 61% for 200 mg and 100 mg tildrakizumab groups, respectively, versus 48% and 6% for the etanercept and placebo groups, respectively). The PGA response was also higher for patients who received tildrakizumab (59% in both the 200 and 100 mg tildrakizumab group versus 48% and 4% for the etanercept and placebo groups, respectively). Results for the co-primary endpoints were similar in the reSURFACE 1 study.³⁶

Caplacizumab (ALX-0081), a bivalent single-domain antibody (Nanobody®) targeting von Willebrand factor, is undergoing regulatory review as a treatment for acquired thrombotic thrombocytopenic purpura (aTTP), a rare, life-threatening blood clotting disorder involving the formation of microclots that lead to low platelet counts, tissue ischemia and organ dysfunction in aTTP patients. The mAb has been granted Fast Track designation in the US and orphan drug designations in the US and EU for the treatment of aTTP. In February 2017, Ablynx announced that a marketing authorisation application (MAA) for caplacizumab had been submitted to EMA. Positive top-line results from the Phase 3 HERCULES study (NCT0255331), a placebo-controlled, randomized study to evaluate the efficacy and safety of caplacizumab in more rapidly restoring normal platelet counts as measure of prevention of further microvascular thrombosis, were announced in October 2017.³⁷ 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 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, there was a statistically significant reduction in time to platelet count response, with, at any given time, patients treated with caplacizumab 50% more likely to achieve platelet count response; a 74% relative reduction in the percentage of patients with aTTP-related death, a recurrence of aTTP, or at least one major thromboembolic event during the study drug treatment period; and a 67% relative reduction in the percentage of patients with aTTP recurrence during the overall study period.³⁷ A 3-year Phase 3 follow-up study (NCT02878603) of patients who completed the HERCULES study is in progress.

Erenumab, (Aimovig™, AMG 334) is an IgG2 mAb that targets the receptor for calcitonin gene-related peptide (CGRP), which is involved in the development of sensitized nociceptive neurons. Marketing applications for erenumab for the prevention of migraine in patients experiencing four or more migraine days per month were submitted in the EU and US by Novartis and Amgen. The companies will co-commercialize erenumab in the US; Amgen has exclusive commercialization rights in Japan and Novartis has exclusive commercialization rights in rest of world. The regulatory submissions include data from four Phase 2 and 3 clinical studies like the STRIVE study (NCT02456740)³⁸ involving more than 2,600 patients

experiencing four or more migraine days per month. Across the studies, erenumab demonstrated a reduction in the number of migraine-affected days, disability and acute medication use for patients with episodic and chronic migraine compared with placebo. FDA's PDUFA target action date is May 17, 2018.³⁹

Fremanezumab (TEV-48125) is an IgG2 mAb targeting CGRP that is undergoing regulatory review for the preventive treatment of migraine.⁴⁰ The BLA submitted to FDA includes data from the Phase 3 HALO program, which included more than 2,000 episodic migraine and chronic migraine patients. Primary and secondary endpoints of the program, which evaluated both monthly and quarterly dose regimens of fremanezumab, were met.

Episodic migraine patients enrolled in the HALO program were randomized in a 1:1:1 ratio to receive SC injections of 225 mg fremanezumab for three months (monthly dose regimen), 675 mg fremanezumab at initiation followed by placebo for two months (quarterly dose regimen), or three monthly doses of matching placebo. The primary efficacy endpoint of study was the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the first dose of fremanezumab. When given monthly, fremanezumab improved the average number of migraine days, relative to baseline, by 41.6% for the duration of the trial (-3.7 days vs. -2.2 days for placebo, $P < 0.0001$). The quarterly SC dose of fremanezumab also decreased migraine days (-3.4 days or 37.0%, $P < 0.0001$). Both dose regimens highly significantly improved migraine in patients on stable doses of other prophylactic medications (-4.0 days for monthly dose vs -2.0 days for placebo, $P = 0.001$; -3.7 days for quarterly dose, $P = 0.006$).^{41, 42}

Chronic migraine patients enrolled in the HALO program were randomized in a 1:1:1 ratio to receive SC injections of 675 mg fremanezumab at initiation followed by monthly 225 mg for two months (monthly dose regimen), 675 mg fremanezumab at initiation followed by placebo for two months (quarterly dose regimen), or three monthly doses of matching placebo. The primary efficacy endpoint was the mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of fremanezumab. Chronic migraine patients treated with fremanezumab experienced statistically significant reduction in the number of monthly headache days of at least moderate severity vs. placebo (-2.5 days) during the 12 week period after first dose, for both monthly (-4.6 days $P < 0.0001$) and quarterly (-4.3 days $P < 0.0001$) dosing regimens.⁴³

Galcanezumab (LY2951742) is an IgG4 mAb targeting CGRP that is undergoing regulatory review for prevention of episodic and chronic migraine in adults.⁴⁴ Results from three Phase 3 studies of patients with episodic or chronic migraine, EVOLVE-1, EVOLVE-2 and REGAIN, were announced in June 2017 at the American Headache Society.⁴⁵ The primary endpoint of statistically significant reductions in the number of monthly migraine headache days compared to placebo at the studied doses (120 mg and 240 mg galcanezumab) was met in the three studies. In the EVOLVE-1, at least a 50% reduction was observed in 62.3%, 60.9% and 38.6% of patients who received 120 mg galcanezumab, 240 mg galcanezumab or

placebo, respectively ($P < 0.001$ for both dosing groups). At least a 75% reduction was observed in 38.8%, 38.5% and 19.3% of patients who received 120 mg galcanezumab, 240 mg galcanezumab or placebo, respectively ($P < 0.001$ for both dosing groups), while 100% reduction was observed in 15.6%, 14.6% and 6.2% of patients who received 120 mg galcanezumab, 240 mg galcanezumab or placebo, respectively ($P < 0.001$ for both dosing groups). The EVOLVE-2 also demonstrated a statistically significantly greater percentage of patients treated with both doses of galcanezumab achieved at least a 50%, 75% and 100% reduction in the number of migraine headache days compared to placebo over the six-month treatment period.⁴⁵ In the placebo-controlled REGAIN study, patients with chronic migraine were administered 120 mg or 240 mg doses of galcanezumab over a three-month treatment period. Patients treated with either dose of galcanezumab experienced a statistically significantly greater decrease in the average number of monthly migraine headache days compared to patients treated with placebo.

Galcanezumab is also being evaluated in a placebo-controlled Phase 3 study (NCT02438826) of patients with chronic cluster headache. Patients are administered galcanezumab by SC injection every 30 days for 12 weeks, then every 30 days for 12 months during a long-term open label extension of the study. The primary outcome measure is mean change from baseline in weekly cluster headache attack frequency. The estimated enrollment is 162 patients, and the primary completion date is March 2018.

Galcanezumab was granted a Fast Track designation for treatment of cluster headache.

Romosozumab (EVENTYTM, AMG785), a humanized IgG2 mAb targeting sclerostin, is being evaluated as a treatment for osteoporosis in women and men. A BLA for romosozumab submitted to the FDA in July 2016 included data from the placebo-controlled Phase 3 FRAME study (NCT01575834) of postmenopausal women with osteoporosis. Participants in the FRAME study received 210 mg romosozumab SC injections once a month for 12 months, followed by 60 mg denosumab SC once every 6 months for 24 months or placebo. Subsequently, data from the Phase 3 ARCH study (NCT01631214), in which postmenopausal women with osteoporosis and a fragility fracture received monthly SC romosozumab (210 mg) or weekly oral alendronate (70 mg), showed serious cardiovascular adverse events more often with romosozumab (50 of 2040 patients [2.5%]) than with alendronate (38 of 2014 patients [1.9%]).⁴⁶ In July 2017, Amgen announced that the FDA issued a complete response letter for the BLA, and asked that the efficacy and safety data from the ARCH study, as well as the Phase 3 BRIDGE study (NCT02186171) evaluating romosozumab in men with osteoporosis, be integrated into the BLA.

Mogamulizumab (KW-0761, Poteligeo[®]) is an IgG1 afucosylated humanized mAb targeting CC chemokine receptor 4 (CCR4) expressed on tumor cells of patients with cutaneous T cell leukemia lymphoma (CTCL), including mycosis fungoides and Sézary syndrome. Afucosylation enhances the antibody-dependent cell-mediated cytotoxicity (ADCC) activity of the mAb. Mogamulizumab was initially approved in Japan in March 2012 for the treatment of patients with relapsed or refractory CCR4-positive adult T cell leukemia-lymphoma (ATL), and then granted marketing authorization in Japan for

the treatment of patients with relapsed or refractory CCR4-positive, peripheral T-cell lymphoma (PTCL) and CTCL in March 2014, and with chemotherapy-naïve CCR4-positive ATL in December 2014.

In October 2017, Kyowa Hakko Kirin announced that a MAA for mogamulizumab, for the treatment of CTCL in adults who have received at least one prior systemic therapy, is under review at EMA.⁴⁷ The MAA includes data from the randomized, open-label, multi-center Phase 3 MAVORIC study (NCT01728805), which evaluated the effects of mogamulizumab versus vorinostat (Zolinza®) in patients with refractory CTCL who failed previous treatment. The study included 372 patients who were randomized to receive either mogamulizumab (1.0 mg/kg weekly x 4 in cycle 1, then every other week until progression) or vorinostat (400 mg orally daily). The primary outcome measure of the study was progression-free

survival (PFS), with the target being a 50% improvement over the reference median PFS for vorinostat (median PFS of 254 days for the mogamulizumab arm versus 169 days for the vorinostat arm).⁴⁸ In April 2017, Kyowa Hakko Kirin announced top-line results from the MAVORIC study indicating the primary endpoint of PFS had been met. In August 2017, mogamulizumab received Breakthrough Therapy designation in the US for mycosis fungoides and Sézary syndrome based on results from the MAVORIC study.

Antibodies to watch in 2018: Non-cancer indications

As of December 1, 2017, 26 investigational (i.e., not approved in any country) antibody therapeutics are undergoing evaluation in late-stage clinical studies of non-cancer indications (Table 3). The companies developing 8 of these mAbs

Table 3. Antibody therapeutics in late-stage clinical studies for non-cancer indications.

Primary sponsoring company	INN or code name	Molecular format	Target	Most advanced phase	Late-stage study indication(s)
Novartis	Crizanlizumab	Humanized IgG2	CD62 (aka P-selectin)	Phase 3	Sickle cell disease
LFB Group	Roledumab	Human IgG1	Rh D	Phase 2/3	Rhesus disease
Shire	Lanadelumab	Human IgG1	Plasma kallikrein	Phase 3	Hereditary angioedema attacks
Prothena Therapeutics Ltd.	NEOD001	Humanized IgG1	Amyloid	Phase 3	Primary systemic amyloidosis
Omeros Corporation	OMS721	Human mAb	MASP-2	Phase 3	Atypical hemolytic uremic syndrome
Alexion Pharmaceuticals Inc.	Ravulizumab (ALXN1210)	Humanized mAb	C5	Phase 3	Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome
AstraZeneca/ MedImmune LLC	Tezepelumab	Human IgG2	Thymic stromal lymphopoietin	Phase 3	Severe uncontrolled asthma
AstraZeneca/ MedImmune LLC	Tralokinumab	Human IgG4	IL-13	Phase 3	Atopic dermatitis
Boehringer Ingelheim Pharmaceuticals, AbbVie	Risankizumab	Humanized IgG1	IL-23 p19	Phase 3	Psoriasis; Crohn's disease
AstraZeneca/MedImmune LLC	Anifrolumab	Human IgG1	IFN α , β , ω receptor 1	Phase 3	Systemic lupus erythematosus
Genentech	Etolizumab	Humanized IgG1	$\alpha 4$ - $\beta 7$ / αE - $\beta 7$ integrin receptor	Phase 3	UC; Crohn's disease
Shire	SHP-647	Human IgG2	Mucosal addressin cell adhesion molecule	Phase 3	UC; Crohn's disease
R-Pharm	Olokizumab	Humanized IgG4	IL-6	Phase 3	Rheumatoid arthritis
AstraZeneca/MedImmune LLC	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
NovImmune SA	Emapalumab	Human IgG1	IFN γ	Phase 2/3	Primary hemophagocytic lymphohistiocytosis
CytoDyn	PRO-140, PA14	Humanized IgG4	CCR5	Phase 2/3	HIV infection
Biogen	Aducanumab	Human IgG1	Amyloid β	Phase 3	Alzheimer's disease
Genentech	Crenezumab	Humanized IgG4	Amyloid β	Phase 3	Alzheimer's disease
Hoffmann-La Roche	Gantenerumab	Human IgG1	Amyloid β	Phase 3	Alzheimer's disease
Alder Biopharmaceuticals	Eptinezumab	Humanized IgG1	CGRP	Phase 3	Migraine prevention, chronic migraine
Regeneron Pharmaceuticals	Fasimab	Human IgG4	NGF	Phase 3	Pain due to osteoarthritis of knee or hip, chronic low back pain
Pfizer; Eli Lilly & Company	Tanezumab	Humanized IgG2	NGF	Phase 3	Pain due to osteoarthritis of knee or hip, chronic low back pain, cancer pain due to bone metastasis
Horizon Pharma USA	Teprotumumab	Human IgG1	IGF-1R	Phase 3	Thyroid eye disease
Genentech	Lampalizumab	Humanized IgG1 Fab	Complement Factor D	Phase 3	Geographic atrophy associated with dry age-related macular degeneration
Novartis Pharmaceuticals Corp.	Brolucizumab	Humanized scFv	VEGF-A	Phase 3	Neovascular age-related macular degeneration

Note: Table includes only commercially developed monoclonal antibody therapeutics that have not previously been approved for any indication; updated December 1, 2017.

Abbreviations: C5, complement component 5; CCR, chemokine receptor; CD, cluster of differentiation; CGRP, calcitonin gene-related peptide; Fab, antigen-binding fragment; FGF, fibroblast growth factor; HIV, human immunodeficiency virus; IFN, interferon; IGF, insulin-like growth factor; IL, interleukin; INN, international non-proprietary name; MASP, mannose-binding protein-associated serine protease; NGF, nerve growth factor; Rh, rhesus; scFv, single-chain variable fragment; VEGF, vascular endothelial growth factor.

(lanadelumab, crizanlizumab, ravulizumab, eptinezumab, risankizumab, satralizumab, brotuzumab, PRO140) have indicated that marketing applications may be submitted in either late 2017 or during 2018. Additional antibody therapeutics for non-cancer indications to watch in 2018 include 9 mAbs undergoing evaluation in late-stage studies with primary completion dates in late 2017 or during 2018. These mAbs are: lampalizumab, roledumab, emapalumab, fasinumab, tanezumab, etrolizumab, NEOD001, gantenerumab, and anifrolumab. Brief descriptions for the antibodies to watch in 2018 for non-cancer indications are provided below. These antibodies are being studied in patients with a wide variety of non-cancer illnesses, including cardiovascular/hemostasis diseases, immune-mediated disorders, infectious disease, neurological disorders, and ophthalmic conditions.

Lanadelumab (SHP643, DX-2930), a human IgG1 mAb that targets plasma kallikrein and thereby prevents production of bradykinin, is in Phase 3 studies designed to assess the mAb's ability to treat hereditary angioedema attacks (HAE), a rare debilitating disease characterized by attacks of swelling that can occur anywhere in the body. The FDA has granted lanadelumab Breakthrough Therapy and orphan drug designations, and lanadelumab has been granted orphan drug designation in the EU, for treatment of hereditary angioedema attacks. In May 2017, Shire reported key results from the 26-week Phase 3 HELP study (NCT02586805), which evaluated the efficacy and safety of lanadelumab in preventing acute angioedema attacks in patients with Type I and Type II HAE.⁴⁹ Patients were administered 300 mg lanadelumab every 2 weeks or every 4 weeks, or 150 mg lanadelumab every 4 weeks, or placebo. The primary and all secondary endpoints for all lanadelumab treatment arms compared to placebo. The monthly attack rate reduction compared to placebo was 87%, 73% and 76% for the 300 mg every 2 weeks, 300 mg every 4 weeks and 150 mg every 4 weeks treatment arms, respectively, with $P < 0.001$ for all analyses.⁴⁹ A Phase 3 open-label, long term safety and efficacy study (NCT02741596) to evaluate lanadelumab in preventing acute angioedema attacks in patients with Type I and Type II HAE has a primary completion date in February 2018. Shire has indicated that their current expectation is for BLA submission in late 2017 to early 2018, and potential marketing application submission in Europe in the first half of 2018, pending discussions with the relevant regulatory agencies.

Crizanlizumab (SEG101), a humanized mAb targeting P-selectin, also known as CD62, is undergoing evaluation as a treatment for sickle cell-related pain crises (SCPC), which are caused by vaso-occlusion in sickle cell disease patients. In the placebo-controlled Phase 2 SUSTAIN study (NCT01895361) of 198 patients (16 to 65 years), 5 mg/kg crizanlizumab administered once every 4 weeks through week 50 reduced the median annual rate of SCPC by 45.3% compared to placebo (1.63 versus 2.98, $p = 0.010$), and the time to first SCPC versus placebo was 2.9 times longer (medians of 4.07 versus 1.38 months, $P = 0.001$) and time to second SCPC was 2.0 times longer than placebo (medians of 10.32 versus 5.09 months, $P = 0.02$).⁵⁰ Crizanlizumab was granted orphan drug designation in the US and EU for the treatment of sickle cell-related pain crises. Novartis expects to submit for regulatory approval in the

US in 2018, assuming results from a pharmacokinetics/pharmacodynamics (PK/PD) comparability to final manufacturing process study (NCT03264989) are suitable.

Ravulizumab (ALXN1210) is a humanized mAb targeting complement component 5 (C5) that is undergoing evaluation in two Phase 3 studies of patients with paroxysmal nocturnal hemoglobinuria (PNH) and two Phase 3 studies of patients with atypical hemolytic uremic syndrome (aHUS). The mAb has been engineered for half-life extension. The dosing regimen of ALXN1210 used in the PNH Phase 3 studies (NCT02946463 and NCT03056040) was informed by the results of two Phase 1/2 studies of PNH patients naive to complement inhibitor therapy in which ALXN1210 treatment resulted in rapid and sustained reduction in plasma lactate dehydrogenase (LDH) levels and improved FACIT-Fatigue score.⁵¹ The Phase 3 NCT02946463 study is assessing ALXN1210 compared to eculizumab (Soliris®) in adult patients with PNH who have not previously used a complement inhibitor. In this study, ALXN1210 is dosed as a single loading dose on day 1, followed by regular maintenance dosing beginning on Day 15, based on weight (≥ 40 to <60 kg: 2400 mg loading, then 3000 mg every 8 weeks; ≥ 60 to <100 kg: 2700 mg loading, then 3300 mg every 8 weeks; ≥ 100 kg: 3000 mg loading, then 3600 mg every 8 weeks). Patients who receive eculizumab are administered induction doses of 600 mg on days 1, 8, 15, and 22, followed by regular maintenance dosing of 900 mg beginning on day 29 and every 2 weeks thereafter. The primary outcome measure of the NCT02946463 study is normalization of LDH levels in a timeframe of 26 weeks, the enrollment is 246 patients, and the estimated primary completion date is December 2017. The Phase 3 NCT03056040 study is assessing ALXN1210 compared to eculizumab in adult patients with PNH who are clinically stable on eculizumab for at least 6 months. For patients who receive ALXN1210, the dose regimen based on weight is the same as used in the NCT02946463 study. Patients who receive both drugs are administered eculizumab with regular maintenance dosing beginning on day 1, then every 2 weeks to Day 183, then a single loading dose of ALXN1210 on Day 183, followed by regular maintenance dosing beginning on day 197, based on weight. The primary outcome measure of the NCT03056040 study is hemolysis as directly measured by percentage change in LDH levels in a timeframe of 26 weeks, enrollment is 197 patients, and the estimated primary completion date is March 2018. Enrollment in these two studies is complete. Alexion expects to report data from these studies in the second quarter of 2018, and a 2018 BLA submission is planned. ALXN1210 has received orphan drug designations in the US and EU for the treatment of patients with PNH.

Enrollment and dosing are ongoing in a single-arm Phase 3 study (NCT02949128) of ALXN1210 administered IV every eight weeks in complement inhibitor treatment-naïve adolescent and adult aHUS patients. Patients receive a single loading dose of ALXN1210 on Day 1, followed by regular maintenance dosing beginning on Day 15, based on weight. The primary outcome measure is the complete thrombotic microangiopathy response in a timeframe of 26 weeks. Enrollment of an estimated 55 patients is expected to be complete in early 2018. Enrollment is also ongoing in a Phase 3 trial (NCT03131219) of ALXN1210 in pediatric patients (up to 18 years) with aHUS.

The estimated enrollment is 16 patients, and the estimated primary completion date is December 2018.

Eptinezumab (ALD403), an IgG1 mAb targeting calcitonin gene-related peptide (CGRP), is being evaluated for migraine prevention. In June 2017, Alder BioPharmaceuticals announced that the primary and key secondary endpoints were met in the placebo-controlled Phase 3 PROMISE 1 study (NCT02559895), which evaluated the effects of eptinezumab in patients with frequent episodic migraine.⁵² Patients enrolled in the study experienced, on average, 8.6 migraines days per month. They received 300 mg, 100 mg, or 30 mg doses of eptinezumab or placebo during the study; results from the 30 mg dose level were not included in the statistical analysis plan. Statistically significant reductions in monthly migraine days from baseline over weeks 1 through 12 were observed for both the 300 mg and 100 mg doses (4.3 monthly migraine days for 300 mg ($p = 0.0001$) and 3.9 days for 100 mg ($p = 0.0179$) compared to an average 3.2 days for placebo). Approximately 1/3 of patients achieved a $\geq 75\%$ reduction in migraine days through 4 and 12 weeks, and an average of 1 in 5 patients had no migraines in any given month from months 1 through 6.

A second Phase 3 study, PROMISE 2 (NCT02974153) is evaluating the safety and efficacy of eptinezumab in patients with chronic migraine. An estimated 1,050 patients are randomized to receive one of two dose levels of eptinezumab or placebo. The primary endpoint is the change in frequency in migraine days from baseline over 12 weeks. Top-line data for that study are expected in the first half of 2018. Alder plans to file a marketing application for eptinezumab in the second half of 2018.

Risankizumab (ABBV066, BI655066) is an IgG1 mAb targeting the p19 subunit of IL-23, which has been implicated in the pathogenesis of psoriasis. In October 2017, AbbVie announced that co-primary endpoints had been met in three Phase 3 clinical trials evaluating risankizumab compared to ustekinumab (Stelara®) and adalimumab (Humira®) for the treatment of patients with moderate to severe chronic plaque psoriasis.⁵³ In the ultIMMa-1 (NCT02684370) and ultIMMa-2 (NCT02684357) studies, the safety and efficacy of risankizumab (150 mg) was compared to placebo or ustekinumab (45 or 90 mg based on patient weight). After 16 weeks of treatment, 75% of patients receiving risankizumab in both studies achieved at least a 90% improvement in the PASI 90 compared to 42% and 48% of patients receiving ustekinumab and 5% and 2% of patients receiving placebo in ultIMMa-1, and ultIMMa-2, respectively. A sPGA score of clear or almost clear was achieved by 88% and 84% of patients administered risankizumab in ultIMMa-1 and ultIMMa-2 at week 16, respectively, compared to 63% and 62% of patients who received ustekinumab and 8% and 5% of patients who received placebo. In the IMMvent study (NCT02694523), patients were administered either risankizumab (150 mg) or adalimumab (80 mg initially followed by 40 mg every two weeks starting one week after the initial dose). At week 16, 72% of patients receiving risankizumab achieved PASI 90 compared to 47% of patients treated with adalimumab, and 84% of risankizumab patients versus 60% of adalimumab patients achieved a sPGA score of clear or almost clear. A BLA submission for psoriasis is planned in 2018, with launch expected in 2019.

Satralizumab (SA237), a humanized IgG2 targeting IL-6R, is undergoing evaluation in two Phase 3 studies of patients with neuromyelitis optica (NMO) or NMO spectrum disorder. The constant and variable regions of the mAb were engineered for half-life extension. Enrollment is ongoing in the placebo-controlled Phase 3 NCT02028884 study, which is evaluating the efficacy and safety of SA237 added to baseline treatment in patients with NMO and NMO spectrum disorder. The primary outcome measure is the time to first relapse up to ~ 30 months from the entry of the first patient into the study. The estimated enrollment is 70 and the estimated primary completion date is July 2018. Enrollment is complete in the placebo-controlled Phase 3 NCT02073279 study, which is evaluating the efficacy and safety of SA237 as monotherapy in patients with NMO and NMO spectrum disorder. The primary outcome measure is the time to first relapse up to ~ 38 months from the entry of the first patient into the study. A total of 95 patients are enrolled, and the estimated primary completion date is October 2018. Satralizumab was granted US and EU orphan designations for the treatment of NMO spectrum disorders. According to the Roche pipeline listing, an application submission for satralizumab is anticipated in 2018.

Brolucizumab (RTH258) is a single-chain variable fragment (scFv) targeting vascular endothelial growth factor (VEGF)-A. The mAb is undergoing evaluation as a treatment for neovascular age-related macular degeneration (nAMD). In June 2017, Novartis announced that the primary efficacy endpoint of non-inferiority to aflibercept (EYLEA®) in mean change in best-corrected visual acuity from baseline to week 48 was met in the Phase 3 HAWK (NCT02307682) and HARRIER (NCT02434328) studies, which included more than 1,800 patients. The two studies compared the efficacy and safety of intravitreal injections of 6 mg brolucizumab or 3 mg brolucizumab (HAWK study only) versus 2 mg aflibercept in patients with nAMD. Of patients receiving 6 mg brolucizumab, 57% (HAWK) and 52% (HARRIER) were maintained exclusively on an every 12 week dosing interval immediately following the loading phase and continuing through week 48.⁵⁴ Key secondary endpoints were also met.⁵⁵ Novartis is developing a competitive, low cost of goods formulation, and expects to complete the PK study with antibody derived from the final manufacturing process to enable filing in 2018.

PRO140, a humanized IgG4 mAb, blocks the human immunodeficiency virus (HIV) co-receptor CCR5 on T cells, thereby preventing viral entry. Two Phase 2/3 studies that are currently recruiting patients, NCT02483078 and NCT02859961, have primary completion dates in October and December 2017, respectively. NCT02483078 is a randomized, double-blind, placebo-controlled trial, followed by single-arm treatment of PRO140 in combination with optimized background therapy in treatment-experienced HIV patients, while the NCT02859961 study is evaluating the effects of shifting clinically stable patients receiving suppressive combination antiretroviral therapy to PRO140 monotherapy. In October 2017, CytoDyn met with FDA to confirm the number and type of evaluable patients required for submission of a BLA for PRO140 as a combination therapy. The agency confirmed that 50 patients will be required for the completion of NCT02483078, and that a total of 300 patients will be required

for the safety analysis in a BLA, which can be provided by all of the company's HIV trials, providing the patients have been on a PRO140 therapy for 24 weeks.⁵⁶ PRO140 received FDA's Fast Track designation, which allows a rolling BLA submission.

Lampalizumab (RG7417, FCFD4514S), a humanized antigen-binding fragment (Fab), inhibits activation and amplification of the alternative complement pathway by binding complement factor D. The efficacy and safety of a 10 mg dose of lampalizumab administered intravitreally every 4 or 6 weeks to patients with geographic atrophy secondary to age-related macular degeneration are being compared with sham injections in two identically-designed Phase 3 studies, NCT02247531 (SPECTRI) and NCT02247479 (CHROMA). In September 2017, Roche announced that lampalizumab did not reduce mean change in geographic atrophy lesion area compared to sham treatment at 1 year, which was the primary endpoint of the study. Further dosing of patients in the SPECTRI study have been interrupted until results from the CHROMA study are evaluated. The enrollment in the CHROMA study is 905 patients, and the estimated primary completion date of the study is December 31, 2017.

Roledumab (LFB-R593) is a human IgG1 anti-rhesus (Rh)D mAb derived from LFB S.A.'s EMABling[®] technology platform, which alters fucosylation, leading to more effective binding of antibodies to effector cells. The antibody is designed to prevent some fetomaternal alloimmunization conditions, i.e., in RhD-negative pregnant women carrying an RhD-positive fetus. The safety, efficacy and immunogenicity of roledumab (300 μ g intramuscular (IM) / IV) are being evaluated in the Phase 2/3 NCT02287896 study, which has an estimated enrollment of 60 women and primary completion date in November 2017. LFB S.A. has indicated that roledumab is currently under clinical development for registration in Europe.

Emapalumab (NI-0501) is a human mAb that targets interferon gamma (IFN γ). It is under investigation as a treatment for primary hemophagocytic lymphohistiocytosis, a hyperinflammatory condition characterized by the overwhelming activation of normal T lymphocytes and macrophages, which leads to clinical and hematologic alterations and death in the absence of treatment. NovImmune SA has received a variety of designations for emapalumab that are intended to facilitate the development of drugs, including Priority Medicines and orphan drug designations in the EU, and Breakthrough Therapy, rare pediatric disease, and orphan drug designations in the US. The Phase 2/3 NCT01818492 study investigating the safety, tolerability, PK and efficacy of multiple IV administrations of emapalumab in children (up to 18 years old) with primary hemophagocytic lymphohistiocytosis is recruiting patients. The primary outcome measure is the overall response rate, the estimated enrollment is 32 patients, and the primary completion date of the NCT01818492 study is December 2017. In addition, a Phase 3 (NCT03312751) study of emapalumab is due to start in January 2018. This study, which has an estimated enrollment of 34, will assess the efficacy, safety, impact on quality of life, and long-term outcome of emapalumab in pediatric patients (up to 18 years old) with primary hemophagocytic lymphohistiocytosis. The primary outcome measure is overall response at week 8 or end of treatment (if earlier), and the estimated primary completion date is June 2019.

Fasinumab (REGN475), a human IgG4 mAb targeting nerve growth factor, is being evaluated in numerous late-stage studies as a treatment for moderate-to-severe osteoarthritis pain of the hip or knee, and chronic low back pain. As listed on clinicaltrials.gov as of December 1, 2017, two Phase 3 studies are recruiting patients and two Phase 3 studies were not yet recruiting patients. Of these studies, the Phase 3 FACT LTS & OA study (NCT02683239), which is a long-term safety and efficacy study of fasinumab, is recruiting an estimated 7000 patients with pain due to osteoarthritis of the knee or hip. This study has a primary completion date in February 2018.

Tanezumab (PF-04383119) is a humanized IgG2 mAb targeting nerve growth factor being investigated as a treatment for chronic low back pain (CLBP), moderate-to-severe osteoarthritis (OA) pain of the hip or knee, and pain due to cancer metastasis. The FDA has granted tanezumab fast-track designation as a treatment for chronic pain in patients with OA and CLBP. Pfizer Inc. and Eli Lilly and Company have a worldwide co-development and co-commercialization agreement for the advancement of the mAb. As of December 1, 2017, patients were being recruited for five Phase 3 studies, and one Phase 3 study designed to characterize the outcomes related to the development of infants up to the age of 15 months who were potentially exposed to tanezumab, placebo or comparator via maternal exposure or in utero in any tanezumab study was not yet recruiting patients. In total, the Phase 3 global clinical development program for tanezumab includes ~7,000 patients with OA, CLBP or cancer pain who did not experience adequate pain relief with approved therapies. Two studies, NCT02528253 and NCT02697773, have primary completion dates in October and November 2017, respectively. The Phase 3 NCT02709486 study, which is evaluating the analgesic efficacy and safety of SC doses of 2.5 mg or 5 mg tanezumab in subjects with OA of the hip or knee, has a primary completion date in June 2018. The studies are investigating SC administration of tanezumab once every eight weeks for treatment periods ranging from 16 to 56 weeks, followed by a 24-week safety follow-up period. The results of these studies are projected to be available in 2018.

Etrolizumab (RH7413) is a humanized mAb that binds the $\beta 7$ subunit of $\alpha 4\beta 7$ and $\alpha E\beta 7$ integrin heterodimers, thereby inhibiting interactions with their ligands MAdCAM-1 and E-cadherin, respectively. The safety and efficacy of etrolizumab are being evaluated in six Phase 3 studies of patients with ulcerative colitis (UC) and 2 Phase 3 studies of patients with Crohn's disease. Of the 6 studies in UC, 2 (NCT02163759 and NCT02171429) have primary completion dates in March 2018. In both of these placebo-controlled studies, the efficacy and safety of etrolizumab in induction of remission in patients with moderately to severely active UC who are naïve to TNF inhibitors and refractory to or intolerant of prior immunosuppressant and/or corticosteroid treatment are being evaluated. Etrolizumab (105 mg) will be administered SC every 4 weeks, and the effects will be compared to those of an active comparator, adalimumab (160 mg) administered SC at week 0; 80 mg SC at week 2; 40 mg SC at weeks 4, 6 and 8. For both studies, the primary outcome measure is the percentage of participants with induction of

remission compared with placebo as determined by the Mayo Clinic Score (MCS) by week 10, and the estimated enrollment is 350 patients.

NEOD001, a humanized IgG1 mAb, targets soluble and insoluble light chain aggregates that cause amyloid light chain (AL) amyloidosis, a disorder characterized by excessive accumulation of protein aggregates in the tissues and organs, including the heart, kidneys and liver. The mAb has been granted orphan drug designation for AL amyloidosis by both the FDA and EMA. In addition, FDA granted NEOD001 Fast Track designation for the potential treatment of AL amyloidosis. In a Phase 1/2 study (NCT01707264), the safety and tolerability of doses of NEOD001 ranging from 0.5 to 24 mg/kg administered to 27 patients with AL amyloidosis and persistent organ dysfunction were evaluated, and the dose recommended for future studies was assessed. Interim data indicated that monthly infusions of NEOD001 were safe and well tolerated; the recommended dose was 24 mg/kg, and the half-life was reported to be ~13–16 days.⁵⁷ The safety and efficacy of NEOD001 administered IV every 28 days at 24 mg/kg is being evaluated in patients with AL amyloidosis who have persistent cardiac dysfunction in the Phase 2b PRONTO (NCT02632786) study. The primary outcome measure of the PRONTO study is cardiac best response as measured by NT-proBNP, a biomarker in cardiac disease, from baseline to 12 months. The study has a primary completion date in January 2018, and topline results of the PRONTO study are expected in the second quarter of 2018.

NEOD001 is also being evaluated in the Phase 3 VITAL study (NCT02312206), which is a randomized, placebo-controlled, global trial assessing NEOD001 treatment in patients with newly diagnosed AL amyloidosis receiving standard-of-care therapy. The dosing regimen is the same as for the PRONTO study (every 28 days at 24 mg/kg). The primary outcome measure of the study is time to composite of all-cause mortality or cardiac hospitalization from the date of randomization until the date of death or cardiac hospitalization, whichever came first, assessed for up to approximately 42 months. The estimated enrollment is 236 patients and the primary completion date is January 2018.

Gantenerumab (RO4909832) is a human mAb targeting fibrillar amyloid- β that is undergoing investigation as a treatment for Alzheimer's disease. The effects of monthly SC administration of 105 mg or 225 mg of gantenerumab to patients with prodromal (i.e., pre-dementia) Alzheimer's disease were evaluated in the placebo-controlled Phase 3 SCarlet RoAD (NCT01224106) study; however, the primary endpoint of the study, mean change from baseline in clinical dementia rating scale sum of boxes total score at week 104, was not met.⁵⁸ Gantenerumab continues to be evaluated in the placebo-controlled Phase 3 Marguerite RoAD (NCT02051608) study in patients with mild dementia due to Alzheimer's disease. The primary outcome measures of the study are mean change from baseline in Alzheimer's disease activity scale-cognitive subscale 13 scores at week 104 and mean change from baseline in Alzheimer's disease cooperative study-activities of daily living scores at week 104. The study also includes an open-label extension for participating patients; the primary outcome measure for this second part of the study is the percentage of participants with adverse events or serious adverse events from

baseline to week 104. Initiated in March 2014, the Phase 3 NCT02051608 study has primary completion date in July 2018. MorphoSys announced in March 2017 that Roche intends to commence preparations for two Phase 3 studies, expected to start later in 2017. As of October 2017, details are not yet available.⁵⁹

Anifrolumab (MEDI-546) is a human IgG1 mAb targeting type-I interferon (IFN) receptor subunit 1 that is being evaluated as a treatment for SLE. The mAb sterically inhibits the binding of IFN ligands to the receptor, thus blocking the formation of a signaling complex.⁶⁰ In a Phase 2b study (NCT01438489) of patients with chronic, moderately-to-severely active SLE with an inadequate response to standard-of-care treatment for SLE, the percentage of participants achieving an SLE responder index response with oral corticosteroids tapering at day 169, a primary outcome measure of the study, was 34.3%, 28.8% and 17.6% for patients who received 300 mg anifrolumab, 1000 mg anifrolumab or placebo, respectively.⁶¹ The results were statistically significant for 300 mg versus placebo ($P = 0.014$). Anifrolumab is undergoing evaluation in two Phase 3 studies with primary completion dates in 2018, NCT02446912 and NCT02446899. Both studies involve placebo-controlled evaluations of the efficacy and safety of two doses of anifrolumab in adult patients (18 to 70 years of age) with moderately to severely active, autoantibody-positive SLE while receiving standard-of-care therapy. For both studies, anifrolumab is administered IV every 4 weeks from Week 0 to week 48 for a total of 13 doses, the primary outcome measure is the effect of anifrolumab compared to placebo on disease activity as measured by the difference in the proportion of subjects who achieve an SLE Responder Index of ≥ 4 at week 52, and the estimated enrollment is 460 patients. The primary completion dates for NCT02446912 and NCT02446899 are July and September 2017, respectively.

Antibodies to watch in 2018: Late-stage antibody therapeutics for cancer indications

As of December 1, 2017, 28 investigational antibody therapeutics are undergoing evaluation in late-stage clinical studies of patients with cancer (Table 4). The companies developing 4 of these mAbs (sacituzumab govitecan, moxetumomab pasudotox, cemiplimab, ublituximab) have indicated that they plan to meet with FDA regarding a BLA submission or may submit a marketing application during 2018. Other anti-cancer antibodies to watch in 2018 include tremelimumab, isatuximab, BCD-100, carotuximab, camrelizumab, IBI308, glembatumumab vedotin, mirvetuximab soravtansine, oportuzumab monatox, and L19IL2/L19TNF. These 10 mAbs are being investigated in late-stage studies with primary completion dates in late 2017 or during 2018. Brief descriptions of the anti-cancer antibodies to watch in 2018 are below.

Sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC) comprising a humanized anti-Trop-2 antibody conjugated to SN38 (active metabolite of the topoisomerase I inhibitor, irinotecan), is undergoing evaluation in pivotal studies as a treatment of late-stage metastatic triple-negative

Table 4. Antibody therapeutics in late-stage clinical studies for cancer indications.

Primary sponsoring company	INN or code name	Molecular format	Target	Most advanced phase	Late-stage study indication(s)
Actinium Pharmaceuticals	I-131-BC8, lomab-B	Murine IgG1, radiolabeled	CD45	Phase 3	Ablation of bone marrow prior to hematopoietic cell transplantation in AML patients
Sanofi	Isatuximab	Humanized* IgG1	CD38	Phase 3	Multiple myeloma
TG Therapeutics	Ublituximab	Chimeric IgG1	CD20	Phase 3	Chronic lymphocytic Leukemia, non-Hodgkin lymphoma, multiple sclerosis
AstraZeneca/ MedImmune LLC	Moxetumomab pasudotox	Murine IgG1 dsFv immunotoxin	CD22	Phase 3	Hairy cell leukemia
MorphoSys	XMAB-5574, MOR208	Humanized IgG1	CD19	Phase 2/3	Diffuse large B-cell lymphoma
Pfizer	Utomilumab	Human IgG2	4–1BB (CD137)	Phase 3	Diffuse large B-cell lymphoma
Hoffmann-La Roche	Polatuzumab vedotin	Humanized IgG1 ADC	CD79b	Phase 3	Diffuse large B-cell lymphoma
Viventia Bio	Oportuzumab monatox	Humanized scFv immunotoxin	EpCAM	Phase 3	Bladder cancer
Seattle Genetics	Enfortumab vedotin	Human IgG1 ADC	Nectin 4	Pivotal Phase 2	Urothelial cancer
Jiangsu HengRui Medicine Co., Ltd	Camrelizumab	Humanized IgG4	PD-1	Phase 2/3	Hepatocellular carcinoma, esophageal carcinoma
MacroGenics	Margetuximab	Chimeric IgG1	HER2	Phase 3	Breast cancer
Synthon Biopharmaceuticals BV	(vic)-trastuzumab duocarmazine	Humanized IgG1 ADC	HER2	Phase 3	Breast cancer
Immunomedics, Inc	Sacituzumab govitecan	IgG1 ADC	TROP-2 (epithelial glyco-protein-1)	Phase 3	Triple-neg. breast cancer
Celldex Therapeutics	Glembatumumab vedotin	Human IgG2 ADC	gpNMB	Pivotal Phase 2	gpNMB+ breast cancer, melanoma
Daiichi Sankyo	DS-8201	Humanized ADC	HER2	Pivotal Phase 2	HER2+ gastric or gastroesophageal junction adenocarcinoma
Gilead Sciences	Andecaliximab	Humanized* IgG4	MMP-9	Phase 3	Gastric cancer or gastroesophageal junction adenocarcinoma
AbbVie	Depatuxizumab mafodotin	IgG1 ADC	EGFR	Phase 2b/3	Glioblastoma
AstraZeneca/ MedImmune LLC	Tremelimumab	Human IgG2	CTLA-4	Phase 3	Non-small cell lung, head & neck, urothelial cancer, hepatocellular carcinoma
Recombio SL	Racotumomab	Murine IgG1	NGcGM3	Phase 3	Non-small cell lung cancer
Regeneron Pharmaceuticals	Cemiplimab	Human mAb	PD-1	Pivotal Phase 2; Phase 3	Cutaneous squamous cell carcinoma; non-small cell lung cancer, cervical cancer
Innovent Biologics (Suzhou) Co. Ltd.	IBI308	Human mAb	PD-1	Phase 3	Squamous cell non-small cell lung cancer
BeiGene	BGB-A317	Humanized mAb	PD-1	Phase 3	Non-small cell lung cancer
AbbVie	Rovalpituzumab tesirine	Humanized IgG1 ADC	DLL3	Phase 3	Small cell lung cancer
ImmunoGen	Mirvetuximab soravtansine	IgG1 ADC	Folate receptor 1	Phase 3	Epithelial ovarian cancer, peritoneal carcinoma, fallopian tube cancer
Biocad	BCD-100	Human mAb	PD-1	Phase 2/3	Melanoma
Novartis	PDR001	Humanized IgG4	PD-1	Phase 3	Melanoma
Philogen SpA	L19IL2/L19TNF	scFv immuno-conjugates	Fibronectin extra-domain B	Phase 3	Melanoma
Tracon	Carotuximab	Chimeric IgG1	Endoglin	Phase 3	Soft tissue sarcoma, angiosarcoma, renal cell carcinoma, wet age related macular degeneration

Note: Table includes only commercially developed monoclonal antibody therapeutics that have not previously been approved for any indication; updated December 1, 2017.

*Identified as humanized in published literature. See Parren PWHI, Carter PJ, Plückthun A. Changes to International Nonproprietary Names for antibody therapeutics 2017 and beyond: of mice, men and more. MABS. 2017 Aug/Sep;9(6):898–906 (doi:10.1080/19420862.2017.1341029) for a review of changes to the World Health Organization and US Adopted Names Council's international non-proprietary name definitions that occurred between 2014 and 2017.

Abbreviations: ADC, antibody-drug conjugate; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DLL3, delta-like protein 3; dsFv, disulfide-stabilized variable fragment; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; gpNMB, glycoprotein non-metastatic gene B; HER2, human epidermal growth factor receptor 2; IL, interleukin; INN, international non-proprietary name; mAb, monoclonal antibody; MMP, matrix metalloproteinase; NGcGM3, Neu-glycolyl-GM3 ganglioside; PD-1, programmed death 1; PD-L1, programmed death ligand 1; scFv, single-chain variable fragment; TROP-2, Tumor-associated calcium signal transducer 2.

breast cancer (TNBC). In November 2017, Immunomedics announced that they were on track to submit a BLA for accelerated approval of sacituzumab govitecan as third-line treatment for metastatic TNBC by the end of March 2018.⁶² The mAb was granted FDA's Breakthrough Therapy designation for metastatic TNBC.

The BLA for sacituzumab govitecan will include data from the Phase 2 NCT01631552 study, in which 110 mTNBC patients were treated with 10 mg/kg sacituzumab govitecan, receiving 14.5 median doses (range 1–88). As determined by local radiologist assessment, the objective response rate (ORR) is 34% (37/110), the clinical benefit rate (CBR: CR+PR+stable

disease > 6 months) is 46%, the Kaplan-Meier (KM) median duration of response and PFS are 7.6 months (95% CI: 4.8 to 11.3) and 5.5 months (95% CI: 4.8 to 6.6), respectively, including 10% (11 patients) with long-term PFS (12 to 30+ months), and the KM median OS is 12.7 months (95% CI: 10.8 to 13.6).^{63, 64} The confirmatory Phase 3 ASCENT trial (NCT02574455) of IMMU-132 is enrolling patients with refractory/relapsed mTNBC after ≥ 2 prior chemotherapies for advanced disease or >1 therapy for patients who progress within 12 months of adjuvant therapy. Patients are randomized 1:1 to receive either 10 mg/kg IV sacituzumab govitecan on days 1 and 8 of 21-day cycles or treatment of physician choice from one of 4 prespecified single-agent regimens (capecitabine, eribulin, vinorelbine or gemcitabine). Treatment is continued until progression requiring discontinuation or unacceptable toxicity. The primary endpoint is PFS. The estimated enrollment is 328 patients.^{63, 65}

Moxetumomab pasudotox (HA22, CAT- 8015) is a recombinant immunotoxin containing the 38-kDa cytotoxic portion of *Pseudomonas* exotoxin A fused to an antibody variable fragment targeting CD22. In February 2016, moxetumomab pasudotox received orphan drug designation for hairy cell leukemia (HCL) in the US. The mAb is currently undergoing evaluation as a treatment for patients with relapsed or refractory HCL in a multicenter, single-arm study Phase 3 trial (NCT01829711). Patients receive moxetumomab pasudotox IV over 30 minutes on days 1, 3, 5 of each 28 day cycle for a maximum of 6 cycles or until disease progression, unacceptable toxicity, initiation of alternate therapy or documented CR. The primary objective of this study is to determine the rate of durable CR; the primary completion date was in May 2017. In a July 2017 pipeline update, AstraZeneca estimated that a BLA may be submitted in 2018.

Cemiplimab (REGN2810, SAR439684), a human antibody that targets programmed death-1 (PD1), is undergoing evaluation as a treatment for metastatic or unresectable cutaneous squamous cell carcinoma (CSCC). The mAb has received FDA's Breakthrough Therapy designation for this indication. Positive preliminary results from a Phase 1 study (NCT02383212) involving CSCC patients were reported at the American Society of Clinical Oncology (ASCO) Annual Meeting in June 2017.⁶⁶ The co-primary objectives were to characterize the safety and tolerability of IV REGN2810 (3 mg/kg Q2W, for up to 48 weeks) and to evaluate the efficacy of REGN2810 by measuring the ORR. Both locally advanced and metastatic CSCC were highly responsive to REGN2810 (combined ORR 46.2%). Sanofi and Regeneron, which have a co-commercialization agreement for the advancement of the mAb, anticipate submitting a BLA for cemiplimab to the FDA in the first quarter of 2018.

Cemiplimab is currently under investigation in EMPOWER-CSCC 1, a single-arm, open label pivotal Phase 2 study (NCT02760498). This study will evaluate the efficiency of cemiplimab as monotherapy in patients with metastatic CSCC and patients with unresectable locally advanced CSCC. The metastatic CSCC patients will be administered either 3 mg/kg cemiplimab every 2 weeks or 350 mg cemiplimab every 3 weeks; patients with unresectable locally advanced CSCC will receive 3 mg/kg cemiplimab every 2 weeks. The primary endpoint is ORR. The effects of cemiplimab are also being evaluated in Phase 3 clinical studies of cervical cancer patients

(NCT03257267) and NSCLC patients (NCT03088540). These studies have estimated primary completion dates in May 2020 and November 2021, respectively.

Ublituximab (LFB-R603, TGT-1101, TGT-1101) is a glycoengineered chimeric mAb targeting CD20. The mAb contains low fucose content, thereby leading to improved FcγRIIIa binding and enhanced ADCC compared to rituximab. Ublituximab is undergoing evaluation in Phase 3 studies for patients with chronic lymphocytic leukemia (CLL).

The multi-center, open-label randomized Phase 3 GENUINE study (NCT02301156) evaluated the safety and efficacy of ublituximab in combination with ibrutinib versus ibrutinib alone in a total of 126 patients with CLL. Patients were administered either 420 mg ibrutinib once daily or ibrutinib plus IV ublituximab at 900 mg on days 1, 8 and 15 for the first cycle and then on day 1 only for cycles 2 through 6. The primary outcome measures are ORR and PFS. The GENUINE study met its ORR primary endpoint.^{67, 68} The combination of ublituximab and ibrutinib demonstrated an ORR of 78% compared with 45% with ibrutinib alone ($P < 0.001$; 11.4 month median follow-up). A trend in improvement of PFS with the combination compared to ibrutinib alone (Hazard Ratio = 0.559) was observed. TG Therapeutics plans to meet with FDA to review the GENUINE Phase 3 data and discuss suitability for filing for accelerated approval.

Ublituximab is also under investigation in the Phase 3 UNITY-CLL study (NCT02612311) to evaluate the efficacy and safety of the combination of ublituximab plus TGR-1202 (PI3K inhibitor), compared to obinutuzumab (anti-CD20 antibody) plus chlorambucil, ublituximab alone or TGR-1202 alone in CLL patients. The primary outcome measure is PFS, and the study has a primary completion date in September 2018. The combination of ublituximab and TGR-1202 with or without bendamustine compared to TGR-1202 alone is also being evaluated in a Phase 2/3 UNITY-NHL study (NCT02793583) of patients with non-Hodgkin's lymphoma (NHL) that has come back or that has not responded to standard treatment. The study has a primary completion date in May 2019.

The clinical development of ublituximab is focused on cancer indications, but it is also undergoing evaluation as a treatment for multiple sclerosis. Two randomized, multi-center, double-blinded Phase 3 studies (NCT03277261 ULTIMATE I and NCT03277248 ULTIMATE II) comparing ublituximab to terflunomide are recruiting patients with relapsing forms of multiple sclerosis. These two studies have primary completion dates in March 2021.

Tremelimumab (CP-675,206) is a human IgG2 antibody targeting the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). In physiological conditions, CD28 interacts with B7 ligands (CD80, CD86), leading to T cell activation, proliferation and CTLA-4 upregulation. CTLA-4 binds B7 ligands with higher affinity than CD28 and terminates T-cell responses. Blocking the CTLA-4 and B7 ligands interaction leads to sustained T cell activation.

Three Phase 3 studies (MYSTIC, ARCTIC, NEPTUNE) are investigating the efficacy and safety of tremelimumab and durvalumab (Imfinzi[®], anti-PDL1 therapy) versus chemotherapy in patients with non-small cell lung cancer (NSCLC). AstraZeneca announced in July 2017 that the primary endpoint of

improving PFS compared to the standard of care (chemotherapy) in patients whose tumors express PD-L1 on 25% or more of their cancer cells was not met in the MYSTIC study (NCT02453282).⁶⁹ This open-label, randomized, multi-center Phase 3 study is evaluating the combination of tremelimumab and durvalumab or durvalumab alone versus chemotherapy in first-line treatment of patients with epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type locally advanced or metastatic NSCLC. Patients received 20 mg/kg durvalumab every 4 weeks for up to 12 months and 1 mg/kg tremelimumab every 4 weeks for up to 4 doses; 20 mg/kg durvalumab every 4 weeks for up to 12 months; or platinum-based chemotherapy.⁷⁰ OS is also a primary endpoint of the MYSTIC study; OS data is expected during the first half of 2018.

The ARCTIC randomized, open-label, multi-center Phase 3 study (NCT02352948) is assessing the clinical activity of tremelimumab in combination with durvalumab in the third-line treatment of NSCLC patients. In Sub-study B, patients with PD-L1-negative tumors were randomly assigned to receive durvalumab in combination with tremelimumab; either durvalumab or tremelimumab alone; or standard-of-care therapy (investigator choice from vinorelbine, gemcitabine and erlotinib). The primary outcome measures are PFS and OS.⁷¹ The estimated enrollment is 597 and the estimated primary completion date is November 2017.

The NEPTUNE study (NCT02542293) is an ongoing randomized, multi-center, open-label, Phase 3 study determining the efficacy and safety of durvalumab in combination with tremelimumab versus chemotherapy in patients with EGFR and ALK wild-type advanced or metastatic NSCLC.⁷² The dose regimen is the same as that used in the MYSTIC study. The primary endpoint is overall survival, the estimated enrollment is 960 and the primary completion date is October 2018.

Tremelimumab is also being evaluated in two Phase 3 studies of patients with metastatic head and neck cancer and one Phase 3 study of patients with urothelial cancer. These studies have primary completion dates during February to April 2018.

The Phase 3 EAGLE (NCT02369874) and KESTREL (NCT02551159) studies are evaluating the clinical efficacy of the tremelimumab + durvalumab combination or durvalumab alone versus chemotherapy for patients with recurrent or metastatic squamous cell carcinoma of the head and neck. In the EAGLE study, patients are randomized to receive durvalumab (10 mg/kg IV for up to 12 months), tremelimumab (1 mg/kg IV) + durvalumab (20 mg/kg IV for up to 12 months) or chemotherapy (cetuximab, taxane, methotrexate, or fluoropyrimidine). The primary endpoint of the EAGLE study is OS.⁷³ This Phase 3, open-label, multi-center has enrolled 736 patients and has an estimated primary completion date in February 2018. First-line treatment will be assessed in the KESTREL study. Patients receive tremelimumab (75 mg every 4 weeks for up to 4 doses) + durvalumab (1500 mg every 4 weeks); durvalumab alone (1500 mg every 4 weeks) or chemotherapy (carboplatin or cisplatin + 5FU + cetuximab).⁷⁴ The primary outcome measures of the KESTREL study are PFS and OS, the estimated enrollment is 823 and the primary completion date is March 2018.

The open label, randomized, multi-center Phase 3 DANUBE study (NCT02516241) is evaluating tremelimumab in combination with durvalumab or durvalumab as monotherapy versus chemotherapy in first-line treatment of patients with stage IV urothelial cancer. Patients receive durvalumab 1500 mg IV every 4 weeks + tremelimumab 75 mg IV every 4 weeks for 4 doses, followed by durvalumab 1500 mg IV every 4 weeks for up to 12 months; durvalumab 1500 mg IV every 4 weeks for up to 12 months or standard-of-care therapy (cisplatin + gemcitabine or carboplatin + gemcitabine) for up to 6 cycles.⁷⁵ The primary outcome measure is PFS, and the estimated enrollment is 1005 patients. The study's primary completion date is April 2018.

Isatuximab (SAR650984) is an anti-CD38 IgG1 chimeric antibody being evaluated for treatment of patients with relapsed and refractory multiple myeloma (MM). ImmunoGen and Sanofi have a license agreement to develop and commercialize isatuximab. Isatuximab received orphan drug designations for multiple myeloma from the FDA and EMA. The efficacy of isatuximab is being evaluated in the open-label, multi-center, randomized Phase 3 ICARA-MM study (NCT02990338). Patients will receive either isatuximab (10 mg/kg on day 1, 8, 15, and 22 in the first cycle; and day 1 and 15 in subsequent cycles) in combination with pomalidomide (on days 1 to 21) plus dexamethasone (on days 1, 8, 15, 22) or the combination of pomalidomide + dexamethasone only.⁷⁶ The primary endpoint of the study is PFS. The estimated enrollment is 300 patients. This Phase 3 study has an estimated primary completion date in May 2018.

BCD-100 is a human antibody targeting programmed cell death-1 (PD-1) developed by BIOCAD. The efficacy, pharmacokinetics, safety and immunogenicity of BCD-100 administration is being investigated in patients with unresectable/metastatic melanoma in the open-label, randomized Phase 2/3 study MIRACULUM study (NCT03269565). Patients receive BCD-100 as monotherapy at doses of either 1 mg/kg every 2 weeks or 1 mg/kg every 3 weeks. The primary outcome measure is the overall response rate (ORR). The estimated enrollment of this study is 126 patients, and the estimated primary completion date in August 2018.

Carotuximab (TRC105) is a chimeric IgG1 antibody targeting endoglin (CD105), a protein highly expressed on angiogenic and proliferative endothelial cells. The mAb binds human CD105 on proliferating endothelium with a K_D of 1–2 ng/mL and induces ADCC of human umbilical vein endothelial cells.⁷⁷ Carotuximab received orphan drug designation for soft tissue sarcoma in the US and EU. The Phase 3 TAPPAS (NCT02979899) is an open-label, randomized clinical trial evaluating TRC105 and pazopanib (a VEGF receptor tyrosine kinase inhibitor) versus pazopanib alone in patients with advanced angiosarcoma. Patients are randomly assigned to receive pazopanib 800 mg daily for adults (and 600 mg for 12–17 years old), and TRC105 (10 mg/kg weekly) or only pazopanib. The study has an adaptive design based on an interim analysis, which will determine the conditional power to meet the PFS endpoint. Based on the conditional power, the data monitoring committee will recommend continued accrual into 1 of 4 zones: 1) Favorable Zone: Continue study as planned (N = 124) to 95 events; 2) Promising Zone: Increase sample size to 200 patients with cutaneous and noncutaneous disease and follow to 170 events ;

3) Enrichment Zone: Enroll patients with cutaneous disease only (N = 170) and follow to 110 events; and 4) Unfavorable Zone: Continue study as planned (N = 124) and follow to 95 events. The primary outcome measure is PFS; OS and ORR are secondary endpoints. The initial enrollment is 124 patients, but may expand up to a maximum of 200 patients.⁷⁸ The estimated primary completion date of the study is September 2018.

Carotuximab received FDA's Fast Track designation for patients with advanced renal cell carcinoma in 2015, and it is undergoing evaluation in the Phase 2 TRAXAR study (NCT01806064) in combination with axitinib versus axitinib as monotherapy in this indication. The primary completion date for the study is December 2017. Tacon Pharma has also developed an ophthalmic formulation of TRC105 for wet age-related macular degeneration in collaboration with Santen Pharmaceutical Company Ltd.

Camrelizumab (INCSHR-1210, SHR-1210) is an IgG4κ humanized antibody targeting PD-1. Incyte Corporation and Jiangsu Hengrui Medicine Co., Ltd have a global license and collaboration agreement for the development and commercialization of this anti-PD1 antibody. The mAb is being evaluated in the Phase 2/3 (NCT02989922) of patients with advanced hepatocellular carcinoma (HCC) in second-line after failure or intolerance to prior systemic treatment. The study has 2 arms in which patients will be intravenous administered 3 mg/kg SHR-1210 on day 1 every 2 weeks or every 3 weeks. The primary outcome measures are the ORR and OS rates at 6 months with duration of response and OS at 2 years as secondary endpoints. The estimated enrollment is 220 patients, and the estimated primary completion date is December 2018. A randomized, open-label Phase 3 study (NCT03099382) is evaluating the efficacy of camrelizumab treatment compared to standard-of-care treatment (docetaxel or irinotecan) in patients with esophageal carcinoma. Patients are randomly assigned to receive either SHR-1210 (200 mg every 2 weeks) or the standard of care (docetaxel 75mg/m² on day 1 every 3 weeks or irinotecan 180 mg/m² on day 1 every 2 weeks). This Phase 3 study has an estimated enrollment of 438 and an estimated primary completion date of June 2018.

IBI308 is a fully human mAb targeting PD-1 developed by Innovent Biologics. The global intellectual property for IBI308 was licensed to Eli Lilly and Company. The mechanism of IBI308 is different from other anti-PD1 drugs because IBI308 has a higher affinity for PD-1 and causes PD-1 endocytosis to activate T cells.⁷⁹ This mAb is undergoing evaluation in the Phase 3 ORIENT-3 study (NCT03150875) study, sponsored by Innovent Biologics (Suzhou) Co. Ltd, of patients with squamous cell NSCLC after failure of first-line platinum-based therapy. This study compares the efficacy of IBI308 at 200 mg every 3 weeks compared to docetaxel (75 mg/m² every 3 weeks). The primary outcome measure is OS. The ORIENT-3 study has an estimated enrollment of 266 and an estimated primary completion date of September 2018.

Glembatumumab vedotin (CDX-011, CR011-vcMMAE) is an IgG2 human antibody targeting transmembrane glycoprotein non-metastatic gene B (gpNMB) conjugated to monomethyl auristatin E, a cytotoxic drug that, when released in cancer cells, may lead to tumor cell death. High expression of gpNMB has been reported in TNBC and in basal-like breast cancer (BLBC)

and correlates with a poor prognosis and increased risk for recurrence. This mAb is currently being investigated in a pivotal Phase 2 METRIC study (NCT01997333) for patients with metastatic breast cancer whose tumor overexpress gpNMB. Overexpression of gpNMB is defined as greater than or equal to 25% of tumor cells testing positive for gpNMB. Patients are randomized (2:1) into 2 arms: glembatumumab vedotin by IV infusion on day 1 of each 21 day cycle or capecitabine on day 1 through 14 of each 21 day cycle. The primary endpoint is PFS. The study enrolled 327 patients. Celldex Therapeutics has announced that topline results for the primary outcome measure should be available in the second quarter of 2018. Glembatumumab vedotin was granted Fast Track designation for advanced, refractory/resistant gpNMB-expressing breast cancer. The mAb is also in development for the treatment of melanoma.

Mirvetuximab soravtansine (IMGN853) is an antibody targeting folate receptor alpha (FRα) that is conjugated to 3–4 molecules of the maytansinoid drug DM4, an anti-mitotic agent. The efficacy and safety of mirvetuximab soravtansine versus chemotherapy is being evaluated in the randomized, open-label, Phase 3 FORWARD I study (NCT02631876) of patients with platinum-resistant epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer. In this 2-arm study, patients will receive either IMGN853 IV at 6 mg/kg every 3 weeks, or chemotherapy (paclitaxel or doxorubicin or topotecan). The primary outcome measure is PFS. The estimated enrollment is 333 and the primary completion date is November 2018. In May 2017, ImmunoGen announced preliminary efficacy data from early-phase monotherapy and combination studies with mirvetuximab soravtansine in patients with FRα-positive epithelial ovarian cancer. In the subset of 36 patients meeting the key eligibility criteria for FORWARD I, the confirmed ORR was 47% (95% CI 30, 65) and median PFS was 6.7 months (95% CI 4.1, 8.3).⁸⁰

Oportuzumab monatox (ViciniumTM, VB4-845) is an anti-epithelial cell adhesion molecule (EpCAM) recombinant humanized antibody scFv fragment conjugated to *Pseudomonas aeruginosa* exotoxin A. Oportuzumab monatox received US and EU orphan drug designations in 2005. An open-label Phase 3 study (NCT02449239) is currently assessing the efficacy of oportuzumab monatox in patients with non-muscle invasive bladder cancer previously treated with intravesical Bacillus Calmette-Guérin immunotherapy. For induction, patients are administered twice-weekly infusions of 30 mg oportuzumab monatox for 6 weeks followed by once weekly for 6 weeks then maintenance dosing of 30 mg once weekly every other week for up to 104 weeks. The primary outcome measure is CR rate. The estimated enrollment is 134 for the study. Eleven Biotherapeutics expects to complete patient enrollment in the first quarter of 2018 and to report topline three-month data in mid-2018.

L19IL2/L19TNF (Daromun) is a fusion protein composed of the scFv of L19 antibody, which targets the extracellular domain B of fibronectin, fused to either human IL2 or human TNF. The two immunocytokines are currently being tested as a mixture in a Phase 3 study (NCT02938299) of patients with malignant melanoma. In this 2-arm study, patients are randomly assigned to receive either multiple intratumoral administrations of a mixture of L19IL2/L19TNF once weekly up to 4 weeks followed by surgical resection of melanoma tumor lesions at week 5 (arm

1), or surgery treatment alone (arm 2). The primary endpoint is the recurrence free survival rate in arm 1 compared to surgery alone. The estimated enrollment is 214, and the estimated primary completion date is December 2018. The study is ongoing in Italy, Germany and Poland, and is due to publish results in 2020. In October 2017, Philogen announced that they will expand the study to include sites in the US.⁸¹

Notable setbacks in 2017

While the focus of the ‘Antibodies to watch’ article series is on molecules that successfully transition from late-stage studies to marketing in the US or EU, it must be noted that not all antibody therapeutics successfully make the required transitions, and not all products that are approved remain on the market. Brief descriptions of 6 antibody therapeutics that had advanced to late-stage clinical studies or beyond but were either terminated in 2017 or sustained a setback in development are provided below.

Catumaxomab (Removab), a full-length mAb targeting EpCAM and the T cell co-receptor CD3, was the first bispecific antibody to be granted a marketing authorization. The product was approved in the EU on April 20, 2009 for treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible, but authorization was withdrawn on June 2, 2017 at the request of Neovil Biotech GmbH, the marketing authorization holder at the time. Marketing of catumaxomab in the EU had ceased in 2014.

XilonixTM (MABp1) is a human IgG1 mAb specific for human IL-1 α that was studied as a treatment for debilitating symptoms of advanced colorectal cancer. A marketing application for this indication was considered by EMA’s CHMP, which adopted a negative opinion, recommending the refusal of a marketing authorization, in May 2017. The opinion was based on study results that did not show clear improvements in lean body mass or quality of life; increased risk of infection in patients who received the drug; and inadequate controls of the manufacturing process. Upon the request of the applicant, XBiotech Germany GmbH, CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorization in September 2017.⁸² Despite the setback, the mAb remains in development. A Phase 1 single arm study evaluating the maximum tolerated dose of Onivyde[®] (Irinotecan liposome injection) and 5-fluorouracil/folinic acid in combination with MABp1 in patients with advanced pancreatic adenocarcinoma and cachexia was initiated in October 2017.⁸³

Sirukumab is a human IgG1 antibody targeting IL-6 that was evaluated in five Phase 3 studies of patients with RA. In September 2016, Janssen submitted a BLA seeking approval of sirukumab for the treatment of moderately to severely active RA, but they announced in September 2017 that they received a complete response letter from the FDA indicating additional clinical data were needed to further evaluate the safety of sirukumab in that patient population. Janssen subsequently decided not to pursue global approvals of sirukumab for the treatment of moderately to severely active RA. Sirukumab was being evaluated in a Phase 3 study (NCT02531633)

of another inflammatory disease, giant cell arteritis. This study, sponsored by GlaxoSmithKline (GSK), was terminated in November 2017 due to GSK’s decision to return rights to sirukumab to Janssen and discontinue sirukumab development in giant cell arteritis. Also in November 2017, a Phase 3 study (NCT02899026) sponsored by GSK of sirukumab in patients with polymyalgia rheumatica, an inflammatory disorder that causes muscle pain and stiffness, was withdrawn prior to enrollment.

MM-302, a HER2 antibody-targeted liposomal doxorubicin, was undergoing evaluation in the Phase 2/3 HERMIONE study as a treatment of HER2-positive metastatic breast cancer in patients who had previously been treated with trastuzumab (Herceptin[®]), pertuzumab (Perjeta[®]) and ado-trastuzumab emtansine (Kadcyla[®]). Merrimack Pharmaceuticals announced in December 2016 that a Data and Safety Monitoring Board recommended that the study be stopped.⁸⁴ There were no new or unexpected safety concerns, but both the treatment and control arms were found to have shorter than expected median progression free survival. Thus, a benefit of MM-302 administration over comparator treatments was unlikely to be demonstrated. The clinical development of MM-302 was subsequently terminated by the company.

Vadastuximab talirine (SGN-CD33A) is an ADC composed of a humanized anti-CD33 mAb with 2 engineered cysteine residues through which pyrrolbenzodiazepine dimer drug moieties are conjugated via a maleimidocaproyl valine-alanine dipeptide linker. The ADC was undergoing evaluation as a treatment of acute myeloid leukemia (AML) in the randomized, double-blind, placebo-controlled Phase 3 CASCADE study. In June 2017, Seattle Genetics, Inc. announced that it was discontinuing the CASCADE study following consultation with the Independent Data Monitoring Committee and after reviewing unblinded data that indicated a higher rate of deaths, including fatal infections in the vadastuximab talirine-containing arm versus the control arm of the study. Seattle Genetics also suspended patient enrollment and treatment in all of its other clinical trials of vadastuximab talirine.⁸⁵

Suptavumab (REGN2222), a human IgG1 mAb targeting respiratory syncytial virus (RSV), was evaluated in the double-blind, placebo-controlled global Phase 3 NURSERY Pre-term study (NCT02325791), which enrolled 1,149 healthy pre-term infants (gestational age of less than 36 weeks, 6 months old or younger at the start of the study). The study included 3 arms in which patients received 30 mg/kg suptavumab as a single dose; 30 mg/kg suptavumab administered as two doses 8 weeks apart; or placebo. Assessment of the primary endpoint occurred through Day 150 of treatment. In August 2017, Regeneron Pharmaceuticals, Inc. announced that the NURSERY study did not meet its primary endpoint of preventing medically-attended RSV infections in infants, and that they planned to discontinue further clinical development of this antibody.⁸⁶

Outlook for the future

The new record for the annual number of novel antibody therapeutics approved in the US or EU set in 2017 (10

mAb products!) was an extraordinary achievement for the biopharmaceutical industry. The people, including scientists, medical professionals and patients, who contributed to the development of brodalumab, dupilumab, sarilumab, guselkumab, benralizumab, ocrelizumab, inotuzumab ozogamicin, avelumab, duvalumab, and emicizumab should be proud of this accomplishment. It may be, however, that 2017 was not unique in this regard. Considering the number of molecules in late-stage clinical studies and in regulatory review as of December 2017, it is certainly possible that 10 or more antibody therapeutics might be granted marketing approvals in 2018. Whatever the outcome, the relevant events will be documented in the next installment of the 'Antibodies to watch' article series.

Abbreviations

ACR	American College of Rheumatology
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
aHUS	atypical hemolytic uremic syndrome
AL	amyloid light chain
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ARR	annualized relapse rate
ATL	adult T cell leukemia lymphoma
aTTP	acquired thrombotic thrombocytopenic purpura
BLA	biologics license application
CCR4	CC chemokine receptor 4
CGRP	calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human Use
CLBP	chronic low back pain
CLL	chronic lymphocytic leukemia
CR	complete response
CSCC	cutaneous squamous cell carcinoma
CTCL	cutaneous T cell leukemia lymphoma
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
C5	complement component 5
DAS28-ESR	28-joint disease activity score using erythrocyte sedimentation rate
DMARDs	disease modifying anti-rheumatic drugs
DOR	duration of response
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EpCAM	epithelial cell adhesion molecule
Fab	antigen-binding fragment
FDA	US Food and Drug Administration
FR α	folate receptor alpha
gpNMB	transmembrane glycoprotein non-metastatic gene B
HAE	hereditary angioedema attacks
HAQ-DI	Health Assessment Question Disability
HCC	hepatocellular carcinoma
HCL	hairy cell leukemia
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
IFN γ ,	interferon gamma

IGA	Investigator's Global Assessment
IM	intramuscular
IV	intravenous
mAb	monoclonal antibody
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MAA	marketing authorisation application
MCC	Merkel cell carcinoma
MCS	Mayo Clinic Score
MM	multiple myeloma
MTX	methotrexate
nAMD	neovascular age-related macular degeneration
NHL	non-Hodgkin's lymphoma
NMO	neuromyelitis optica
NSCLC	non-small cell lung cancer
OA	osteoarthritis
OS	overall survival
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamics
PD-1	programmed death 1
PD-L1	programmed cell death ligand 1
PDUFA	Prescription Drug User Fee Act
PEX	plasma exchange
PFS	progression-free survival
PGA	static Physician Global Assessment
PK	pharmacokinetics
PNH	paroxysmal nocturnal hemoglobinuria
PPMS	primary progressive multiple sclerosis
PTCL	peripheral T cell lymphoma
RA	rheumatoid arthritis; Rh, rhesus
RMS	relapsing multiple sclerosis
RSV	respiratory syncytial virus
SC	subcutaneous
scFv	single-chain variable fragment
SCPC	sickle cell-related pain crises
SLE	systemic lupus erythematosus
TNF	tumor necrosis factor
TNBC	triple-negative breast cancer
UC	ulcerative colitis
XLH	X-linked hypophosphatemia.

Note added in proof

On December 13, 2017, Sanofi and Regeneron announced that a rolling BLA submission for anti-PD-1 cemiplimab in advanced cutaneous squamous cell carcinoma had been initiated. Completion of the BLA submission and an MAA submission to EMA are expected by the end of March 2018. Cemiplimab should thus be included in Table 2 as in review in the US. Sanofi also announced on December 13, 2017 that regulatory filings for anti-CD38 isatuximab for relapsed refractory multiple myeloma are expected in 2018.

Disclosure Statement

The authors declare no conflicts of interest.

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