Antibodies to watch in 2015

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**Abbreviations**: BLA, biologics license application; EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; IL, interleukin; mAb, monoclonal antibody; MTX, methotrexate; PCSK9, proprotein convertase subtilisin/kexin type 9; pharmacokinetic, PK; PA, protective antigen; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

The commercial pipeline of recombinant antibody therapeutics is robust and dynamic. As of early December 2014, a total of 6 such products (vedolizumab, siltuximab, ramucirumab, pembrolizumab, nivolumab, blinatumomab) were granted first marketing approvals in 2014. As discussed in this perspective on antibodies in late-stage development, the outlook for additional approvals, potentially still in 2014 and certainly in 2015, is excellent as marketing applications for 6 antibody therapeutics (secukinumab, evolocumab, mepolizumab, dinutuximab, nivolumab, necitumumab) are undergoing a first regulatory review in the EU or US. Of the 39 novel mAbs currently in Phase 3 studies, a marketing application for one (alirocumab) may be submitted in late 2014, and marketing application submissions for at least 4 (reslizumab, ixekizumab, ocrelizumab, oblitoxaximab) are expected in 2015. Other ‘antibodies to watch’ are those in Phase 3 studies with estimated primary completion dates in late 2014 or 2015, which includes 13 for non-cancer indications (brodalumab, bimagrumab, bococizumab, MABp1, gevokizumab, dupilumab, sirukumab, sarilumab, tildrakizumab, guselkumab, epratuzumab, combination of actoxumab + bezlotoxumab, romosozumab) and 2 (racotumomab and clivatuzumab tetraxetan) undergoing evaluation as treatments for cancer. In addition to the novel antibody therapeutics mentioned, biosimilar infliximab and biosimilar trastuzumab are ‘antibodies to watch’ in 2015 because of their potential for entry into the US market and regulatory review, respectively.

**Introduction**

The highly dynamic late-stage commercial pipeline of recombinant antibody therapeutics now includes nearly 50 molecules. Regulatory actions, marketing application submissions and clinical study completions that might occur for these molecules during late 2014 or 2015 are discussed here. The antibodies are categorized by the highest status achieved, e.g., regulatory review, Phase 3. It should be noted that antibodies in regulatory review, as well as those on the market, may still be undergoing evaluation in Phase 3 studies. Data were collected in October 2014; the literature cited here focuses on articles published during January to October 2014.

To recap the highlights of 2014, as of early December a total of 6 mAbs (vedolizumab, siltuximab, ramucirumab, pembrolizumab, nivolumab, blinatumomab) had been granted their first marketing approval in 2014. Vedolizumab and siltuximab were approved in both the United States (US) and European Union (EU), while ramucirumab, pembrolizumab and blinatumomab were approved in the US, but remained in regulatory review in the EU. Nivolumab was approved in Japan in 2014, and it is in regulatory review in the US and EU. A table of the antibody therapeutics in regulatory review or approved in the US or EU is available on the mAbs web site (www.tandfonline.com/action/newsAndOffers?journalCode=mab20). Based on the timing of application submissions to the regulatory agencies, marketing approvals for 2 additional mAbs (secukinumab, dinutuximab) are possible by the end of 2014.

**Regulatory actions: Projections for 2015**

As of early December 2014, marketing applications for 6 antibody therapeutics are undergoing a first regulatory review in the US or EU (Table 1). Three (secukinumab, evolocumab, mepolizumab) are for non-cancer indications, while 3 (dinutuximab, nivolumab and necitumumab) are for various types of cancer. Regulatory actions on the marketing applications are expected during 2015.

Anti-interleukin (IL)-17 secukinumab has been studied as a treatment for a variety of immune-mediated disorders. The marketing applications currently under review in the US and EU are for psoriasis. In October 2014, the Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration (FDA) unanimously recommended the approval of secukinumab for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. An action by FDA is expected in January 2015. In November 2014, the European Medicines Agency (EMA)’s Committee for Medicinal Products for Human Use (CHMP) recommended that a marketing authorization be granted. An approval by
CI compared with placebo treatment (95% CI 30.9% at 12 weeks, which was significant). Administration every 4 weeks was well tolerated. It was granted evolocumab an orphan drug designation. Recently published results indicated that 420 mg evolocumab may follow later in 2015.

Evolocumab is the first monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) to enter regulatory review. In August 2014, Amgen announced that a biologics license application (BLA) for evolocumab as a treatment of high cholesterol had been submitted. The clinical evaluation for evolocumab includes 22 studies, of which 16 are Phase 3, with a combined planned enrollment of ~30,000 patients. The BLA contained data from 10 studies of patients with heterozygous familial hypercholesterolemia (HoFH); a rare and serious genetic disorder for which FDA granted evolocumab an orphan drug designation. Recently published results indicated that 420 mg evolocumab administered every 4 weeks was well tolerated and reduced LDL cholesterol by 43.9% at 12 weeks, which was significant compared with placebo treatment (95% CI −43.9% to −18.0%; P < 0.0001), in patients with heterogeneous familial hypercholesterolemia receiving stable background lipid-lowering treatment and not on apheresis. Reductions of 60% in LDL cholesterol compared with placebo were observed in patients with heterozygous familial hypercholesterolemia administered evolocumab either 140 mg every 2 weeks or 420 mg monthly. The FDA has set a target action date of August 27, 2015, for the evolocumab application.

The mAb has garnered numerous FDA designations intended to expedite the development and review of drugs for serious or life-threatening conditions, including fast track designations for melanoma, NSCLC and renal cell carcinoma, and breakthrough therapy designations for melanoma and Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab. If approved in the US, nivolumab would be the second PD-1-targeted mAb on the market, following FDA’s September 2014 approval of pembrolizumab (Keytruda®) as a treatment for melanoma, NSCLC and renal cell carcinoma, and breakthrough therapy designations for melanoma and Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab.
for patients with advanced or unresectable melanoma who are no longer responding to other drugs. Pembrolizumab is currently undergoing evaluation in 3 Phase 2/3 or Phase 3 studies that include patients with NSCLC; the estimated primary completion date of one (NCT01905657) is in September 2015.

In October 2014, Eli Lilly and Company announced that a rolling FDA submission had begun for necitumumab in first line squamous NSCLC. The epidermal growth factor receptor (EGFR)-targeted mAb was granted Fast Track designation for NSCLC; thus, the application is expected to receive a priority review. At the American Society of Clinical Oncology annual meeting in May 2014, Lilly presented positive results for the Phase 3 SQUIRE study (NCT00981058) of necitumumab in combination with gemcitabine and cisplatin (GC) as a first-line treatment for stage IV squamous non-small cell lung cancer. The addition of necitumumab to GC chemotherapy was found to statistically significantly improve overall survival, progression-free survival, and disease control rate, and the safety profile of the combined treatment was acceptable.6

Marketing application submissions: Projections for late 2014 and 2015

A total of 39 investigational mAbs, i.e., those not yet in regulatory review or marketed, are currently in Phase 3 studies. A marketing application for one (alirocumab) may be submitted in late 2014, and marketing application submissions for at least 4 (reslizumab, ixekizumab, ocrelizumab, obiltoxaximab) are expected in 2015. These mAbs have been evaluated in studies of cardiovascular-related diseases (alirocumab), respiratory conditions (reslizumab), immune-mediated disorders (mepolizumab, ixekizumab, ocrelizumab) and infectious disease (obiltoxaximab). Arilocomab targets PCSK9 and would compete with evolocumab if both mAbs were to be granted marketing approvals. Alirocumab has been or is being evaluated in at least 14 Phase 3 studies. In the Phase 3 ODYSSEY Mono study (NCT01644474) of hypercholesterolemic patients at moderate cardiovascular risk not receiving statins or other lipid-lowering therapy, alirocumab demonstrated significantly greater LDL-C lowering versus ezetimibe after 24 weeks.7 A 75 mg dose of alirocumab administered every 2 weeks was sufficient to provide ≥ 50% LDL-C reduction in the majority of the patients.7 At the European Society of Cardiology Congress 2014 (www.escardio.org/esc2014), it was reported that an additional 4 studies of patients with hypercholesterolemia, ODYSSEY COMBO II (NCT01644188), ODYSSEY LONG TERM (NCT01507831), ODYSSEY FH I (NCT01623115) and ODYSSEY FH II (NCT01709500), had met their primary endpoints. Regulatory submissions for alirocumab in hypercholesterolemia are expected in the US and EU during the fourth quarter of 2014. Sanofi and Regeneron announced that they intend to use a rare pediatric disease priority review voucher in connection with the BLA submission in the US. If the submission occurs by year end and the application is given priority review, an action by FDA would be expected by mid-2015.

In September 2014, Teva announced positive Phase 3 studies results for anti-IL-5 reslizumab in reducing asthma exacerbations, and indicated that regulatory submissions were planned for the first half of 2015, pending full analysis of the data. The results were from the NCT01287039 study of 489 patients with eosinophilic asthma that evaluated reslizumab at a dose of 3 mg/kg administered intravenously (IV) every 4 weeks for 52 weeks, and the NCT01285323 study that evaluated the same regimen of reslizumab in 464 patients with eosinophilic asthma whose symptoms are inadequately controlled with inhaled corticosteroids. Reslizumab treatment showed clinically relevant and statistically significant reductions in the frequency of clinical asthma exacerbations compared to placebo in both studies (50% and 60%, respectively; p < 0.0001 for both).

Positive results from Phase 3 studies of ixekizumab administered to patients with moderate-to-severe plaque psoriasis were disclosed by Eli Lilly in August 2014, and they indicated that regulatory submissions of ixekizumab are planned for the first half of 2015. In 3 UNCOVER pivotal studies (NCT01777191, NCT01597245, NCT01646177), anti-IL-17A ixekizumab demonstrated superiority on skin clearance compared to both etanercept (Enbrel8), an Fc-fusion protein that targets tumor necrosis factor (TNF), and placebo. Significant improvements were observed in patients receiving ixekizumab as early as the first week of the study and high levels of response to treatment were maintained through the 60-week duration of the therapy.

Three Phase 3 studies evaluating the safety and efficacy of anti-CD20 ocrelizumab in patients with multiple sclerosis are active but not recruiting patients as of October 2014. In one study (NCT01194570), the efficacy and safety of ocrelizumab is being evaluated in adults with primary progressive multiple sclerosis, while 2 studies (NCT01247324, NCT01412333) are comparing the effects of ocrelizumab with interferon β-1a (Rebif®) in patients with relapsing multiple sclerosis. The earliest estimated primary completion date for these studies is October 2017; however, in an update provided in mid-October 2014, Roche indicated that market application submissions in the US and EU are planned in 2015 for ocrelizumab as multiple sclerosis therapy.

Obiltoxaximab targets the anthrax toxin protective antigen, and it is intended for the treatment of inhalation anthrax in patients who have established infection and are symptomatic for anthrax disease, and for prophylaxis. The drug is a potential target for future acquisition into the US Strategic National Stockpile, which is a repository of critical medical supplies for biowarfare preparedness. The safety and tolerability of IV infusion of the mAb were evaluated in 3 pivotal studies that included over 300 healthy volunteers who received the intended therapeutic dose. Intramuscular administration of obiltoxaximab is also being evaluated. Due to the rarity of the infection, efficacy and safety have been studied in animal models of inhalational anthrax and safety has been evaluated in a total of 470 healthy human volunteers. Obiltoxaximab was granted Fast Track and orphan drug designations by the FDA. In September 2014, Elusys Therapeutics indicated that a BLA was in preparation.
Phase 3 studies with projected completion dates in late 2014 or 2015: Non-cancer indications

As listed in Table 2, 27 mAbs are in Phase 3 studies for non-cancer indications. Of these, one (broladumab) is undergoing evaluation in Phase 3 studies that have estimated completion dates in late 2014, and Phase 3 studies for an additional 12 mAb product candidates (bimagrumab, bococizumab, MABp1, gevokizumab, dupilumab, sirukumab, sarilumab, tildrakizumab, guselkumab, epratuzumab, and the combination of actoxumab + bezlotoxumab, romosozumab) have estimated completion dates in 2015.

Top-line results from the Phase 3 AMAGINE-2 (NCT01708603) and AMAGINE-3 studies (NCT01708629) of broladumab, which targets the IL17 receptor, administered to patients with moderate-to-severe plaque psoriasis are expected in late 2014. The AMAGINE-2 and AMAGINE-3 studies are evaluating the efficacy and safety of induction and maintenance regimens of subcutaneous administration of 2 doses (140 mg or 210 mg) broladumab compared with placebo and ustekinumab in patients with moderate to severe plaque psoriasis. Broladumab is also being evaluated in Phase 3 studies as a treatment of psoriatic arthritis.

Bimagrumab targets type II activin receptors, which are involved in the regulation of muscle mass.8 The on-going Phase 2/3 RESILIENT study (NCT01925209) is evaluating the efficacy, safety and tolerability of IV administration of multiple doses of bimagrumab compared to placebo on physical function, muscle strength, and mobility in patients with sporadic inclusion body myositis, a degenerative disease affecting muscular tissues. The study’s primary outcome measure is the change from baseline to Week 52 in the distance a patient can walk in a 6-minute period. The estimated enrollment for the study is 240 patients, and the estimated primary completion date is December 2015.

Bococizumab (PF-04950615) targets PCSK9, and it is undergoing evaluation as a cholesterol-lowering agent. Results were recently reported for a 24-week, placebo-controlled Phase 2 study (NCT01592240) that evaluated the low density lipoprotein cholesterol (LDL-C) lowering effect of bococizumab administered subcutaneously at monthly intervals, or twice monthly intervals in patients with high cholesterol whose LDL-C is ≥80 mg/dL on background treatment with a statin.9 For patients who received drug, the doses administered were 50, 100 or 150 mg bococizumab every 2 weeks or 200 or 300 mg bococizumab every month. Treatment with bococizumab was found to significantly reduce LDL-C across all doses.9 As of October 2014, a total of 6 Phase 3 studies were recruiting patients, although only one has a completion date in 2015. The Phase 3 SPIRE-SI study (NCT02135029) is assessing the efficacy, safety and tolerability of bococizumab in subjects with primary hyperlipidemia or mixed dyslipidemia who are intolerant to statin. In this study, 150 mg bococizumab is administered by subcutaneous injection every 2 weeks for 24 weeks. The primary outcome measure is the percentage change from baseline in fasting LDL-C at week 12. The estimated enrollment is 150 patients, and the estimated primary completion date is November 2015.

MABp1 (Xilonix™) targets IL-1α, a pleiotropic cytokine that mediates inflammation and may act to promote tumor growth and metastasis. Two Phase 3 studies of the mAb are evaluating whether inhibition of IL-1α improves survival or symptoms in patients with colorectal cancer. The open-label Phase 3 NCT 01767857 study of metastatic colorectal cancer patients with cachexia is comparing MABp1 administered IV every 2 weeks with megestrol acetate oral suspension administered daily for as long as the patient is benefiting clinically. All patients are also receiving best supportive care. The primary outcome measure is overall survival, the estimated enrollment is 656, and the estimated primary completion date is December 2016. The second Phase 3 study, NCT02138422, is a double-blind and placebo-controlled study enrolling patients with pathologically confirmed colorectal carcinoma that is metastatic or unresectable and refractory to standard therapy. Xilonix or placebo are administered IV every 2 weeks, and patients are being assessed for improvement in symptoms of muscle loss, fatigue, appetite loss, and pain. The estimated enrollment is 276, the estimated primary completion date is March 2015, and the estimated study completion date is September 2015.

Gevokizumab targets the pro-inflammatory cytokine IL-1β, and the mAb is currently being evaluated in Phase 3 programs in Behçet’s disease uveitis, non-infectious uveitis and pyoderma gangrenosum. Gevokizumab was granted orphan drug designation in the EU and US for Behçet’s disease and non-infectious uveitis, and it has US orphan drug designation for pyoderma gangrenosum. Two Phase 3 studies of gevokizumab in patients with non-infectious uveitis, EYEGUARD™-A (NCT01684345) and EYEGUARD™-C (NCT01747538), as well as a Phase 3 study in patients with Behçet’s disease uveitis, EYEGUARD™-B (NCT01965145), have primary completion dates in December 2014. An additional study in patients with Behçet’s disease uveitis, EYEGUARD™-US (NCT02258867) has an estimated primary completion date of September 2015.

Dupilumab targets the α-subunit of the IL-4 receptor, thereby inhibiting the binding of both IL-4 and IL-13. The human IgG4 mAb is being evaluated as a treatment for asthma and atopic dermatitis. Results of several early phase randomized, double-blind, placebo-controlled studies of dupilumab administered to adults with moderate-to-severe atopic dermatitis, an indication for which dupilumab received breakthrough therapy designation, were recently reported.10 Marked and rapid improvement in atopic dermatitis disease activity was observed in the dupilumab-treated patients, and the side-effect profiles were not dose-limiting.10 The efficacy and long-term safety of 2 doses of dupilumab when administered in combination with topical corticosteroids to adults with moderate-to-severe atopic dermatitis are being evaluated in the Phase 3 study NCT02260986. The primary outcome measure of the study is the proportion of patients with both an Investigator’s Global Assessment of 0 to 1 (on a 5-point scale) at week 16 and a reduction from baseline of ≥2 points at week 16. The estimated enrollment is 700, and the estimated primary completion date is November 2015.
Anti-IL-6 sirukumab is undergoing evaluation as a treatment for rheumatoid arthritis (RA). In a 2-part (proof-of-concept/dose-finding) Phase 2 study (NCT00718718) of patients with active RA despite methotrexate therapy, the primary endpoint (ACR50 at week 12 in Part B) was achieved in the cohort of patients who were administered 100 mg sirukumab every 2 weeks compared to those who received placebo (26.7% vs 3.3%; \( p = 0.026 \)). Sirukumab is currently undergoing evaluation in 5 Phase 3 studies of patients with RA. Three of these studies have primary completion dates in 2015. The double-blind Phase 3 NCT01689532 study is evaluating the safety and efficacy of 50 or 100 mg doses of sirukumab as a single therapy in Japanese patients with moderately to severely RA who have not responded to treatment with methotrexate (MTX) or sulfasalazine. Enrollment is 122 patients, and the estimated primary completion date is May 2015. The Phase 3 SIRROUND-H study (NCT02019472) is investigating the efficacy of 50 or 100 mg sirukumab monotherapy compared with 40 mg adalimumab monotherapy in biologic-naive subjects with active RA who are intolerant to MTX, who are considered inappropriate for treatment with MTX or who are inadequate responders to MTX. Both study drugs are administered subcutaneously. Estimated enrollment is 510 patients, and the estimated primary completion date is December 2015.

Sarilumab targets IL-6 receptor \( \alpha \). The safety and efficacy of sarilumab as a treatment for RA are being investigated in at least 6 ongoing Phase 3 studies. Results of Part A of the completed Phase 2/3 RA-MOBILITY study (NCT01061736) were recently reported. The RA-MOBILITY study was a randomized, double-blind, placebo-controlled, multicenter, 2-part, dose ranging and confirmatory study that evaluated the effects of sarilumab on top of MTX in patients with active RA who are unresponsive or intolerant to treatment with tumor necrosis factor-targeting agents. Doses of 50 or 100 mg sirukumab are administered subcutaneously either every 2 or 4 weeks.

Table 2. Antibody therapeutics in Phase 2/3 or Phase 3 clinical studies of non-cancer indications

| Primary sponsoring company | INN or code name | Molecular format | Target(s) | Current phase | Phase 3 indications |
|----------------------------|------------------|------------------|-----------|--------------|-------------------|
| Novartis                  | Bimagrumbab      | Human IgG1       | Type II activin receptors | Phase 2/3 | Sporadic inclusion body myositis |
| Regeneron                 | Alirocumab       | Human IgG1       | PCSK9     | Phase 3      | Hypercholesterolemia; acute coronary syndrome |
| Pfizer                    | Bococizumab,     | Humanized IgG2   | PCSK9     | Phase 3      | Hypercholesterolemia; hyperlipidemia; reduction of CV events |
|                           | PF-04950615      |                  |           |              |                   |
| Xbiotech                  | MABp1, XilonixTM | Human mAb        | IL-1 \( \alpha \) | Phase 3      | Cachexia in cancer patients |
| Zomax; Servier            | Gevokizumab      | Humanized IgG2   | IL-1 \( \beta \) | Phase 3      | Uveitis; pyoderma gangrenosum |
| Regeneron                 | Dupilumab        | Human IgG4       | IL-4R \( \alpha \) | Phase 3      | Atopic dermatitis; asthma |
| Teva                      | Reslizumab       | Humanized IgG4   | IL-5      | Phase 3      | Eosinophilic asthma |
| AstraZeneca               | Benralizumab     | Humanized IgG1   | IL-5R     | Phase 3      | Asthma; COPD |
| Janssen                   | Sirukumab        | Human IgG1       | IL-6      | Phase 3      | Rheumatoid arthritis |
| Regeneron                 | Sarilumab        | Human IgG1       | IL-6R subunit \( \alpha \) | Phase 3 | Rheumatoid arthritis |
| Chugai/Roche             | SA237            | Humanized IgG2   | IL-6R     | Phase 3 | Neumyelitis optica and NMO Spectrum Disorder |
| Genentech                 | Lebrikizumab     | Humanized IgG4   | IL-13     | Phase 3 | Severe asthma |
| AstraZeneca               | Tralokinumab     | Humanized IgG4   | IL-13     | Phase 3 | Uncontrolled asthma |
| Eli Lilly and Co.         | Ixekizumab       | Humanized IgG4   | IL-17a    | Phase 3 | Psoriasis, psoriatic arthritis |
| Amgen                     | Broladumab       | Human IgG2       | IL-17R    | Phase 3 | Plaque psoriasis; psoriatic arthritis |
| Sun Pharmaceutical        | Tildrakizumab    | Humanized IgG1   | IL-23 p19 subunit | Phase 3 | Plaque psoriasis |
| Janssen                   | Guselkumab       | Human IgG1       | IL-23 p19 subunit | Phase 3 | Plaque-type psoriasis |
| Genentech                 | Ocrelizumab      | Humanized IgG1   | CD20      | Phase 3 | Multiple sclerosis |
| UCB                       | Epratuzumab      | Humanized IgG1   | CD22      | Phase 3 | SLE |
| Merck & Co.               | Actoxumab,       | Human mAbs       | Clostridium difficile enterotoxin A and B | Phase 3 | Clostridium difficile infection |
|                           | + bezlotoxumab   | (MK-3415A)       |           |              |                   |
| Genentech                 | Etrolizumab      | Humanized IgG1   | \( \beta7 \) subunit of \( \alpha 4 \beta7, \alpha E 7 \) integrins | Phase 3 | Ulcerative colitis |
| Boehringer Ingelheim      | Idarucizumab     | Humanized Fab    | Dabigatran | Phase 3 | Reversal of the anticoagulant effects of dabigatran |
| Genentech                 | Lampalizumab     | Humanized IgG1   | Factor D  | Phase 3 | Geographic atrophy secondary to age-related MD |
| Elusys                    | Obiltoxizumab    | Chimeric IgG1    | PA, B. antrachis exotoxin | Phase 3 | Safety/tolerability, intended for inhalational anthrax |
| Amgen                     | Romosozumab      | Humanized IgG2   | Sclerostin | Phase 3 | Postmenopausal osteoporosis, osteoporosis in men |
| Hoffmann-La Roche         | Gantenerumab     | Human IgG1       | Amyloid \( \beta \) | Phase 3 | Alzheimer disease |
| Eli Lilly and Co.         | Solanezumab      | Humanized IgG1   | Amyloid \( \beta \) | Phase 3 | Alzheimer disease; cognition disorders |

Note: Table compiled from information available as of November 5, 2014.
Abbriviations: CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; Fab, antigen-binding fragment; IL, interleukin; INN, international non-proprietary name; MD, macular degeneration; PCSK9, proprotein convertase subtilisin/kexin type 9; PA, protective antigen; SLE, systemic lupus erythematosus.
are inadequate responders to MTX therapy. The signs and symptoms of RA improved over 12 weeks in patients with moderate-to-severe RA who received the drug: 150 mg and 200 mg of sarilumab administered every other week provided the most favorable efficacy, safety and dosing convenience. Of the 6 ongoing Phase 3 studies, 5 have estimated primary completion dates in late 2014 or early 2015: 1) SARIL-RA-ASCERTAIN (NCT01768572); 2) RA-COMPARE (NCT01764997); 3) SARIL-RA-TARGET (NCT01709578); 4) SARIL-RA-EASY (NCT02057250); and 5) SARIL-RA-ONE (NCT02121210). The estimated primary completion dates for these studies are November 2014, December 2014, March 2015, April 2015 and July 2015, respectively. Estimated enrollments range from 120 to 700 patients. A Phase 3 uncontrolled extension study, RA-EXTEND (NCT01146652), evaluating the safety and efficacy of sarilumab in patients with active RA is enrolling by invitation patients who were previously randomized in the sarilumab RA clinical program. The estimated completion date for the extension study is January 2020.

Tildrakizumab (SCH 900222/MK-3222) targets the p19 subunit of IL-23. The mAb was developed by Schering-Plough, which was acquired by Merck & Co. in 2009, and it was then licensed by Merck to Sun Pharmaceutical Industries Ltd in September 2014. Clinical development and regulatory activities will be conducted by Merck, but funded by Sun Pharma. As of October 2014, the safety and efficacy of tildrakizumab are being evaluated in 2 Phase 3 studies that are ongoing but not recruiting patients. Both studies include patients with moderate-to-severe chronic plaque psoriasis and subcutaneously administered drug. The 52-week Phase 3 NCT01729754 study has 4 arms (200 mg tildrakizumab; 100 mg tildrakizumab; 50 mg etanercept; and placebo only), and includes an optional long-term safety extension study. The estimated enrollment is 1050, and the estimated primary completion date is October 2019. The 64-week Phase 3 NCT01722331 study is evaluating the effects of either 200 mg or 100 mg tildrakizumab to placebo; it includes an optional long-term safety extension study. The estimated enrollment is 885, and the estimated primary completion date is June 2015.

Like tildrakizumab, guselkumab targets the p19 subunit of IL-23, and it is being developed as a treatment for psoriasis. In a Phase 1 study of 24 patients with moderate-to-severe psoriasis, inhibition of IL-23 with a single dose of guselkumab resulted in clinical responses. As of October 2014, patients with moderate-to-severe plaque-type psoriasis and an inadequate response to ustekinumab are being recruited for the Phase 3 NAVIGATE study (NCT02203032), which has an estimated enrollment of 800 and an estimated primary completion date of August 2016. Two additional Phase 3 studies, VOYAGE 1 (NCT02207231) and VOYAGE 2 (NCT02207244), are not yet recruiting patients as of October 31, 2014. Both studies are randomized, double-blind, placebo-controlled and active-comparator (anti-TNF adalimumab)-controlled study of guselkumab in patients with moderate-to-severe plaque-type psoriasis. For VOYAGE 1, the estimated enrollment is 750, and the estimated primary completion date is October 2015. For VOYAGE 2, the estimated enrollment is 1000, and the estimated primary completion date is September 2015.

The safety and efficacy of anti-CD22 epratuzumab as a treatment for systemic lupus erythematosus is currently being evaluated in Phase 3 studies. In Phase 2 randomized, controlled studies of epratuzumab (ALLEVIATE-1 and -2) and a long-term extension study (SL0006), epratuzumab treatment produced clinically meaningful and sustained improvements in health-related quality of life, patient and physician global assessments of disease activity, as well as reductions in corticosteroid doses. Two Phase 3 studies, EMBODY 1 (NCT01262365) and EMBODY 2 (NCT01261793), of epratuzumab in patients with moderate-to-severe general systemic lupus erythematosus have estimated study completion dates in 2015. Both studies are multicenter, placebo-controlled, randomized, double-blind studies designed to evaluate the efficacy, safety, tolerability, and immunogenicity of epratuzumab in SLE. Each study involves 4 12-week treatment cycles with drug administered at 600 mg per week or 1200 mg every other week and has an estimated enrollment of 780 patients. The primary completion date for both EMBODY 1 and EMBODY 2 is April 2015.

The Clostridium difficile toxin-targeted antibodies actoxumab (MK-3415) and bezlotoxumab (MK-6072) are being evaluated separately and in combination (as MK3415A) in 2 Phase 3 studies, MODIFY 1 (NCT01241552) and MODIFY 2 (NCT01513239). MODIFY 1 is a Phase 3, randomized, double-blind, placebo-controlled, adaptive design study of the efficacy, safety, and tolerability of a single IV infusion of 10 mg/kg actoxumab, 10 mg/kg bezlotoxumab, and the actoxumab (10 mg/kg) + bezlotoxumab (10 mg/kg) combination in patients receiving antibiotic therapy for Clostridium difficile infection. The estimated enrollment is 1600 patients, and the estimated primary completion date is December 2014. MODIFY 2 is a Phase 3, randomized, double-blind, placebo-controlled study of the efficacy, safety and tolerability of a single IV infusion of 10 mg/kg bezlotoxumab or a combination of 10 mg/kg each of actoxumab + bezlotoxumab in patients receiving antibiotic therapy for C. difficile infection. The estimated enrollment is 1200 patients, and the estimated primary completion date is March 2015.

Romosozumab targets sclerostin, which is an inhibitor of osteoblast activity. The results of a Phase 2 study (NCT00896532) evaluating the efficacy and safety of the drug in postmenopausal women with low bone mass concluded that administration of romosozumab was associated with increased bone mineral density and bone formation and with decreased bone resorption. Romosozumab is being evaluated in 4 ongoing Phase 3 studies of postmenopausal osteoporosis and one Phase 3 study of osteoporosis in men. Two of these studies have completion dates in late 2014 or 2015. A randomized, multiple-dose Phase 3 study (NCT02016716) to evaluate 2 different formulations of romosozumab in postmenopausal women with osteoporosis had an estimated primary completion date in September 2014. An open-label, randomized, teriparatide-controlled Phase 3 STRUCTURE study (NCT01796301) to
evaluate the effect of treatment with romosozumab in postmenopausal women with osteoporosis previously treated with bisphosphonate therapy has an estimated primary completion date in April 2015.

Phase 3 studies with projected completion dates in 2015: Cancer indications

Only 2 (racotumomab and clivatuzumab tetraxetan) of the 12 mAbs for cancer listed in Table 3 have Phase 3 studies with estimated primary completion dates in 2015. Racotumomab comprises the mirror image of the P3 mAb idiotype, which targets tumor-associated antigen N-glycolylneuraminic acid (NeuGc) gangliosides. As an anti-idiotypic mAb, the mechanism of action of racotumomab is like that of a vaccine. Results of a preliminary study of racotumomab as switch maintenance for patients with advanced NSCLC were recently published. Patients received racotumomab-alum (5 immunizations every 2 weeks and reimmunizations every 4 weeks) or placebo; median OS was 8.23 and 6.80 months, respectively [HR, 0.63; 95% confidence interval (CI), 0.46–0.87; P = 0.004], while median progression-free survival (PFS) was 5.33 and 3.90 months (HR, 0.73; 95% CI 0.53–0.99; P = 0.039). The efficacy and safety of active specific immunotherapy with racotumomab with best supportive care compared to best supportive care in patients with advanced NSCLC who have achieved an objective response (partial or complete response) or stable disease with standard first-line treatment are being evaluated in a Phase 3 study (NCT01460472). The primary outcome measures is overall survival from treatment administration until date of death or last censored observation, on average up to 17 months, and the study completion date is September 2015.

Clivatuzumab targets the mucin MUC5AC and has high specificity for pancreatic ductal adenocarcinoma. A Phase 3 study (NCT01956812) of radio-labeled (90Y) clivatuzumab tetraxetan with low-dose gemcitabine compared with placebo and low-dose gemcitabine in metastatic pancreatic cancer patients who have progressed on at least 2 prior therapies for metastatic cancer (1 of which was a gemcitabine-containing regimen) is recruiting patients as of October 2014. The primary outcome measure is overall survival in a time-frame of 24 months, and the estimated primary completion date for the study in July 2015.

Biosimilar antibodies: projections for EU or US approvals in 2015

Numerous companies are developing biosimilar mAbs or fusion proteins, with most focusing on a total of 6 reference products that garner substantial global sales, adalimumab, bevacizumab, etanercept, infliximab, rituximab and trastuzumab. As of October 2014, only one biosimilar mAb has been approved in either the EU or US. Celltrion’s biosimilar infliximab (Remsima®) was first approved in the EU in September 2013. Marketing approval was granted for 6 indications: ankylosing spondylitis, RA, psoriatic arthritis and psoriasis in adults; and Crohn disease and ulcerative colitis in adults, children and adolescents aged 6 to 17 y. Remsima® demonstrated equivalent efficacy to innovator infliximab at week 30, with a comparable pharmacokinetic (PK) profile and immunogenicity, in the Phase 3 PLANETRA study (NCT01217086) of patients with RA. In the Phase 3 PLANETAS study (NCT01220518), the PK profiles of Remsima® and the innovator infliximab were equivalent in patients with active ankylosing spondylitis, and its efficacy and safety profile were comparable to that of innovator infliximab up to week 30. Celltrion announced in early August 2014 that a 351(k) marketing application for Remsima® had been submitted to FDA. Assuming a 10-month review period for a standard review, an action by FDA would be expected by early June 2015.

Celltrion announced in January 2014 that its biosimilar trastuzumab (Herzuma®), had been approved in

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Table 3. Antibody-based therapeutics in Phase 2/3 or Phase 3 clinical studies of cancer indications

| Primary sponsoring company | INN or code name | Molecular format | Target | Current phase | Phase 3 indications |
|----------------------------|------------------|-----------------|--------|--------------|-------------------|
| AstraZeneca | Tremelimunab | Human IgG2 | CTLA4 | Phase 2/3 | Mesotheiloma |
| Merrimack Pharmaceuticals | Mim-302 | scFv | HER2 | Phase 2/3 | Breast cancer |
| CIMA
t, Recombio | Racotumomab | Murine IgG1 | NeuGc gangliosides | Phase 3 | NSCL |
| Daiichi Sankyo | Patritumab | Human IgG1 | HER3 | Phase 3 | NSCL |
| AstraZeneca | MEDI-4736 | Human IgG1 | PD-L1 | Phase 3 | NSCL |
| Genentech | RG7446, MPDL3280A | Human IgG1 | PD-L1 | Phase 3 | NSCL |
| Peregrine | Bavituximab | Chimeric IgG1 | Phosphatidyserine | Phase 3 | NSCL |
| Immunomedics | Clivatuzumab tetraxetan | Humanized IgG1; Y-90 | MUC5AC | Phase 3 | Pancreatic cancer |
| Bristol-Myers Squibb | Elotuzumab | Humanized IgG1 | CD2 | Phase 3 | Multiple myeloma |
| Pfizer | Inotuzumab ozogamicin | Humanized IgG4 ADC | CD22 | Phase 3 | Acute lymphoblastic leukemia |
| AstraZeneca | Moxetumomab pasudotox | Murine dsFv immunotoxin | CD22 | Phase 3 | Hairy cell leukemia |
| Janssen | Daratumumab | Human IgG1 | CD38 | Phase 3 | Multiple myeloma |

Note: Table compiled from information available as of December 5, 2014.

*In-licensed; National Cancer Institute is sponsoring Phase 3 studies.

Abbreviations: CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte-associated protein; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; HGF/SF, hepatocyte growth factor/scatter factor; INN, international non-proprietary name; NSCL, non-small cell lung; PD-L1, programmed death 1 receptor ligand; scFv, single-chain variable fragment.
Korea. Assuming the same strategy used for Remsima®’s approvals is applied, a marketing application for Herzuma® may be submitted in the EU during late 2014 or early 2015, with a 351(k) application submission to FDA potentially following later in 2015. Given that the regulatory review period in the EU for Remsima® was nearly 18 months, an EU approval of Herzuma® in 2015 is possible but unlikely. An additional 15–20 biosimilar antibodies and fusion proteins are in Phase 3 clinical studies, but the estimated primary completion dates for most of these studies occur during late 2015 to 2017. Marketing approvals in the EU or US would thus not be anticipated until 2016 at the earliest.

**Outlook for 2015 and beyond**

As evidenced by the molecules discussed here, the pharmaceutical industry has a highly active late-stage pipeline that is poised to deliver novel severe and novel antibody therapeutic products to the global market in the near future. Continuing the tradition we established in 2009,21–27 mAbs will track the progress of antibody therapeutics in clinical development and regulatory review, and we look forward to reporting updated information in our 2015 mid-year installment of the “Antibodies to watch” series.