

Antibodies to watch in 2014

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Since 2010, *mAbs* has documented the biopharmaceutical industry's progress in transitioning antibody therapeutics to first Phase 3 clinical studies and regulatory review, and its success at gaining first marketing approvals for antibody-based products. This installment of the "Antibodies to watch" series outlines events anticipated to occur between December 2013 and the end of 2014, including first regulatory actions on marketing applications for vedolizumab, siltuximab, and ramucirumab, as well as the Fc fusion proteins Factor IX-Fc and Factor VIII-Fc; and the submission of first marketing applications for up to five therapeutics (secukinumab, ch14.18, onartuzumab, necitumumab, gevokizumab). Antibody therapeutics in Phase 3 studies are described, with an emphasis on those with study completion dates in 2014, including antibodies targeting interleukin-17a or the interleukin-17a receptor (secukinumab, ixekizumab, brodalumab), proprotein convertase subtilisin/kexin type 9 (alirocumab, evolocumab, bococizumab), and programmed death 1 receptor (lambrolizumab, nivolumab). Five antibodies with US Food and Drug Administration's Breakthrough Therapy designation (obinutuzumab, ofatumumab, lambrolizumab, bimagrumab, daratumumab) are also discussed.

Regulatory Actions: Projections for 2014

Regulatory actions by FDA on marketing applications for two Fc-fusion proteins and three mAbs (vedolizumab, siltuximab, ramucirumab) are expected in the first half of 2014 (Table 1). The marketing applications from Biogen Idec for Factor IX-Fc for hemophilia B and Factor VIII-Fc for hemophilia A are undergoing standard reviews at FDA. Both of these recombinant products have orphan drug and fast track designations from FDA.

Vedolizumab, which targets $\alpha 4\beta 7$ exclusively and modulates inflammation in the gastrointestinal tract, is undergoing regulatory review in the US and EU as a treatment for adults with moderate-to-severe active ulcerative colitis (UC) and Crohn disease (CD). The humanized IgG1 has been Fc-engineered to silence effector functions, and it thus does not elicit complement-mediated cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) or cytokine release. Data from four Phase 3 studies, GEMINI I (NCT00783718), GEMINI II (NCT00783692), GEMINI III (NCT01224171) and GEMINI Long-term Safety (NCT00790933), were included in the marketing applications. In the US, the application for UC was given a priority review, while the application for CD was given a standard review.

Marketing applications for siltuximab, a chimeric IgG1 targeting interleukin (IL)-6, as a treatment of patients with multicentric Castleman disease (MCD) who are HIV-negative and human herpes virus-8-negative are undergoing review in the US and EU. Siltuximab has orphan drug designations for the

indication in both regions. Data from a Phase 2 randomized, multi-national, double-blind, placebo-controlled study (NCT01024036) to assess the efficacy and safety of siltuximab plus best supportive care (BSC) compared with best supportive care in MCD patients, and data from two non-randomized supportive studies, were included in the applications.

Ramucirumab, a human IgG1 that targets vascular endothelial growth factor receptor-2, received Fast Track designation from the FDA, which allows rolling submission of the marketing application. The mAb is undergoing regulatory review as monotherapy in second-line gastric cancer, and received priority review designation from FDA. Ramucirumab has been evaluated in two Phase 3 studies (NCT00917384, NCT01170663) of patients with gastric cancer. Data for the Phase 3 randomized, double-blinded study (NCT00917384) of ramucirumab and BSC vs. placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy were included in the marketing applications. Data from the Phase 3 RAINBOW study (NCT01170663) of ramucirumab in combination with paclitaxel for the treatment of advanced gastric cancer will be submitted as part of a separate marketing application. In addition, the ramucirumab is also undergoing evaluation in Phase 3 studies of non-small cell lung cancer (NCT01168973), hepatocellular carcinoma (NCT01140347), colorectal cancer (NCT01183780), and breast cancer (NCT00703326) patients. Top-line results from the studies in colorectal, hepatocellular and lung cancer are expected in 2014.

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Table 1. Therapeutic antibody-based therapeutics in first US or EU regulatory review

Sponsoring company	Name	Molecular format	Target	Location of regulatory review	Designations	Indication under review
Biogen Idec	Factor IX-Fc	Fc-fusion protein	NA	US	S, O, FT	Hemophilia B
Biogen Idec	Factor VIII-Fc	Fc-fusion protein	NA	US	S, O, FT	Hemophilia C
Takeda	Vedolizumab	Humanized IgG1; Fc engineered	$\alpha 4\beta 7$ integrin	US, EU	P (for UC), S (for CD)	Ulcerative colitis, Crohn disease
Janssen	Siltuximab	Chimeric IgG1	IL-6	US, EU	O	Multicentric Castleman disease
Lilly	Ramucirumab	Human IgG1	VEGFR2	US, EU	FT, P	Gastric cancer

Note: Table compiled from information available as of November 1, 2013. Abbreviations: BT, US breakthrough therapy designation; CD, cluster of differentiation; EU, European Union; FT, US fast track designation; IL, interleukin; NA, not applicable; O, orphan drug designation in US and EU; P, priority review by US Food and Drug Administration; S, standard review by US Food and Drug Administration; US, United States; VEGFR, vascular endothelial growth factor receptor.

It should also be noted that regulatory submissions for secukinumab are planned in the EU and US for the second half of 2013. The submissions are expected to be based on results from the Phase 3 FIXTURE study, which is described below in the section “Anti-IL-17a or IL-17R mAbs: Secukinumab, ixekizumab and brodalumab”. If submissions are made by December 31, 2013, a regulatory action would be expected in 2014.

Regulatory Submissions: Projections for 2014

Companies sponsoring antibody therapeutics currently in Phase 3 studies have indicated that they anticipate submission of marketing applications for four of these product candidates (Ch14.18, onartuzumab, necitumumab, gevokizumab) in 2014. United Therapeutics Corporation, which has a cooperative research and development agreement with the National Cancer Institute (NCI) for development of Ch14.18, has indicated that they expect to file marketing application in the US and EU for Ch14.18 as a treatment for neuroblastoma. The chimeric mAb targets GD2, which is a glycolipid found on tumor cells. Phase 3 studies (NCT01041638, NCT00026312) of the effects of CH14.18 on patients with neuroblastoma are being conducted by NCI; studies to demonstrate the comparability of the mAb produced by United Therapeutics Corporation with that produced by NCI are underway.

In their pipeline update as of September 30, 2013, Roche indicated that marketing applications for onartuzumab, also known as MetMab, as a 2nd/3rd -line treatment for metastatic non-small cell lung cancer (NSCLC) are planned to occur in the US and EU in 2014. The combination of onartuzumab and erlotinib (Tarceva®) is undergoing evaluation in two Phase 3 studies (NCT01456325, NCT01887886) of NSCLC patients. Onartuzumab is also being evaluated in a Phase 3 study (NCT01662869) of patients with metastatic HER2-negative and Met-positive adenocarcinoma of the stomach or gastroesophageal junction.

Eli Lilly and Company announced in August 2013 that the Phase 3 SQUIRE study (NCT00981058) of necitumumab had met the primary endpoint of overall survival in patients with stage IV squamous NSCLC, and that the company

anticipates submitting to regulatory authorities before the end of 2014.¹ The SQUIRE study evaluated gemcitabine-cisplatin chemotherapy plus necitumumab to gemcitabine-cisplatin alone as first-line treatment of stage IV squamous NSCLC patients. Necitumumab, a human mAb targeting the epidermal growth factor receptor, has also undergone evaluation as first-line therapy in combination with pemetrexed-cisplatin in a Phase 3 INSPIRE study (NCT00982111) of patients with stage IV squamous NSCLC. Enrollment in the INSPIRE study was halted due to concerns of an increased risk of thromboembolic events.²

In a corporate presentation in September 2013, XOMA noted that top-line data from the first study in the Phase 3 program for gevokizumab in non-infectious uveitis is expected in the first half of 2014, and that success in two of three studies should allow submission of a marketing application to the US FDA. They also proposed exploration of a parallel strategy to submit a marketing application in 2014 by pursuing a Behçet’s uveitis indication. Gevokizumab is a humanized IgG2 targeting IL-1 β .

Anti-IL-17a or IL-17R mAbs in Phase 3: Secukinumab, Ixekizumab and Brodalumab

As indicated in Table 2, three mAbs (secukinumab, ixekizumab, brodalumab) that inhibit IL-17 pathway signaling are currently in Phase 3 studies. These studies have completion dates in 2014. Secukinumab and ixekizumab target the IL-17a ligand, while brodalumab targets the IL-17 receptor. IL-17a is a pro-inflammatory cytokine implicated in the pathogenesis of immune-mediated disorders such as psoriasis.^{3,4}

Results from the Phase 3 FIXTURE (NCT01358578), SCULPTURE (NCT01406938) and ERASURE (NCT01365455) studies of secukinumab (AIN457; Novartis) as a treatment for moderate-to-severe chronic plaque-type psoriasis were announced at the 22nd Congress of the European Association of Dermatology and Venereology held in Istanbul, Turkey in October 2013. The release of additional results for these studies and results for the Phase 3 STATURE study (NCT01412944) is expected in 2014.

The Phase 3 FIXTURE study compared the effects of subcutaneously (s.c.)-administered secukinumab with those of

Table 2. Therapeutic antibodies in Phase 2/3 or Phase 3 clinical studies of non-cancer indications

Sponsoring company	INN or code name	Molecular format	Target(s)	Current phase	Phase 3 indications
Novartis	Bimagrumab, BYM338	Human IgG1	Activin A receptor type IIB	Phase 2/3	Sporadic inclusion bodymyositis
Amgen	Evolocumab, AMG 145	Human IgG2	PCSK-9	Phase 3	Hypercholesterolemia; hyperlipidemia
Regeneron; Sanofi	Alirocumab, REGN-727, SAR236553	Human IgG1	PCSK-9	Phase 3	Hypercholesterolemia; acute coronary syndrome
Pfizer	Bococizumab PF-04950615, RN316	Humanized IgG2	PCSK-9	Phase 3	Hypercholesterolemia; hyperlipidemia
Amgen	Romosozumab, AMG785	Humanized IgG2	Sclerostin	Phase 3	Postmenopausal osteoporosis
Merck	Actoxumab + bezlotoxumab, MK-3415A	Human IgG1	C. difficile enterotoxin A and B	Phase 3	C. difficile Infection
XBioTech, Inc.	MABp1	Human	IL-1 α	Phase 3	Cachexia in cancer patients
Xoma; Servier	Gevokizumab	Humanized IgG2	IL-1 β	Phase 3	Non-infectious uveitis
GlaxoSmithKline	Mepolizumab	Humanized IgG1	IL-5	Phase 3	Asthma; hypereosinophilic syndrome; COPD with eosinophilic bronchitis
Teva	Reslizumab	Humanized IgG4	IL-5	Phase 3	Eosinophilic asthma
AstraZeneca	Benralizumab	Humanized IgG1	IL-5R	Phase 3	Asthma
Janssen	Sirukumab	Human IgG1	IL-6	Phase 3	Rheumatoid arthritis
Regeneron; Sanofi	Sarilumab, SAR153191, REGN88	Human IgG1	IL-6R subunit α	Phase 3	Rheumatoid arthritis
Hoffmann-La Roche	Lebrikizumab	Humanized IgG4	IL-13	Phase 3	Severe asthma
Eli Lilly and Co.	Ixekizumab, LY2439821	Humanized IgG4	IL-17a	Phase 3	Rheumatoid arthritis, psoriatic arthritis, psoriasis
Novartis Pharmaceuticals	Secukinumab	Human IgG1	IL-17a	Phase 3	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis
Amgen; Kyowa Hakko Kirin	Brodalumab, AMG827, KHK4827	Human IgG2	IL-17R	Phase 3	Plaque psoriasis, pustular psoriasis and psoriatic erythroderma
Merck	Tildrakizumab, MK-3222	Humanized IgG1	IL-23 p19 subunit	Phase 3	Plaque psoriasis
Eli Lilly and Co.	Tabalumab, LY2127399	Human IgG4	BlyS	Phase 3	SLE
Genentech	Ocrelizumab	Humanized IgG1	CD20	Phase 3	Multiple sclerosis
UCB	Epratuzumab	Humanized IgG1	CD22	Phase 3	SLE
Hoffmann-La Roche	Gantenerumab	Human IgG1	Amyloid β	Phase 3	Alzheimer disease
Eli Lilly and Co.	Solanezumab	Humanized IgG1	Amyloid β	Phase 3	Alzheimer disease

Note: Table compiled from information available as of November 1, 2013. Abbreviations: BlyS, B lymphocyte stimulator; CD, cluster of differentiation; IL, interleukin; PCSK9, proprotein convertase subtilisin/kexin type 9; SLE, systemic lupus erythematosus.

placebo and etanercept after 12 wk of treatment, and assessed safety, tolerability and long-term efficacy for up to one year in 1,306 patients with moderate-to-severe chronic plaque-type psoriasis. The study had 4 arms: (1) placebo etanercept and placebo secukinumab; (2) 50 mg etanercept and placebo secukinumab; (3) 150 mg secukinumab and placebo etanercept; and (4) 300 mg secukinumab and placebo etanercept. The primary outcome measure was the efficacy of secukinumab compared with placebo as measured by the psoriasis area and severity index (PASI) and investigator's global assessment at 12 wk. Both doses of secukinumab showed superior efficacy compared with etanercept throughout the study.⁵ At week 12, 54% of patients receiving 300 mg secukinumab and 21% of patients administered etanercept achieved PASI 90, indicating at least a 90% reduction in skin redness, thickness and scaling. PASI 100 responses, indicating completely clear skin, were achieved by 24% and 4% of 300 mg secukinumab and etanercept patients, respectively, at week 12. By week 16, 72% of patients receiving 300 mg secukinumab achieved PASI 90. At week 52, PASI 90 responses were achieved by 65% and 33% of patients receiving 300 mg secukinumab and etanercept, respectively. The most common adverse events (AEs) throughout the 52 wk study were nasopharyngitis and headache (12–36 patients per 100 patient years in all groups). Serious AEs were experienced by 6%, 5% and 6% of patients who received 300 mg secukinumab, 150 mg secukinumab and etanercept, respectively.⁵ Results of the FIXTURE study are expected to support marketing applications that may be filed by the end of 2013.

The randomized, double-blind Phase 3 SCULPTURE study was designed to compare a fixed maintenance schedule of once-monthly dosing of secukinumab with dosing as needed to treat relapse. A total of 966 patients with moderate-to-severe chronic plaque psoriasis received induction therapy of 5 once-weekly s.c. injections of either 150 mg or 300 mg secukinumab. At week 8, patients with PASI 75 responses were re-randomized to the same dose once monthly or as needed for relapse. To maintain blinding, patients in the “as needed” cohorts received a placebo if there was no relapse. At week 52, PASI 75 responses were achieved by 78%, 68%, 62% and 52% of patients who received 300 mg once monthly, 300 mg as needed, 150 mg once monthly, and 150 mg as needed, respectively.⁶ PASI 90 responses at week 52 were achieved by 60% and 46% of patients who received 300 mg and 150 mg once monthly, respectively. Substantially lower PASI 90 rates were observed for those who received either dose of secukinumab on an as needed basis. Antidrug antibodies that did not affect clinical efficacy or safety were observed in three patients on monthly doses and two patients on “as needed” therapy.⁶

The randomized, double-blind, placebo-controlled Phase 3 ERASURE study was designed to assess efficacy after 12 wk of treatment, and to assess safety, tolerability and long-term efficacy up to one year in patients with moderate-to-severe chronic plaque psoriasis. A total of 738 patients were administered 300 mg or 150 mg secukinumab or placebo.⁶ At week 12, PASI 75 rates were 81.6%, 71.6% and 4.5% in the 300 mg secukinumab, 150 mg secukinumab and placebo cohorts, respectively. At week

16, 69.8% and 41.6% of patients in the 300 mg secukinumab achieved PASI 90 and PASI 100 responses, respectively. Antidrug antibodies developed transiently in one patient in the 150 mg secukinumab cohort.⁶

In addition to psoriasis, secukinumab is being studied as a treatment for other immune-mediated disorders. On-going Phase 3 studies of secukinumab with estimated primary completion dates in 2014 include the FUTURE 1 study (NCT01392326) of patients with psoriatic arthritis, and the MEASURE 1 study (NCT01358175) of patients with ankylosing spondylitis. The randomized, double-blind, placebo-controlled FUTURE 1 study is designed to assess the efficacy and safety of secukinumab in patients with active psoriatic arthritis who are intolerant to or have had an inadequate response to nonsteroidal antiinflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) or tumor necrosis factor (TNF) inhibitor therapy. Adult patients (18 y or older) are administered either 75 or 150 mg secukinumab or placebo. The primary outcome measure is the proportion of patients achieving American College of Rheumatology (ACR) 20 response criteria, which indicates that a patient's arthritis has improved by 20%, on the two doses of secukinumab compared with placebo, in the subgroup of patients who are TNF-inhibitor naïve, in a 24-wk time frame. In the randomized, double-blind, placebo-controlled MEASURE 1 study, the safety and efficacy of secukinumab in patients with active ankylosing spondylitis who are intolerant to or have had an inadequate response to NSAIDs, DMARDs or TNF inhibitor therapy is being evaluated. Adult patients (18 y or older) will be administered either 75 or 150 mg secukinumab or placebo. The primary outcome measure is the proportion of patients achieving an ASAS 20 response⁷ in the subgroup of patients who are TNF inhibitor-naïve in a 16-wk time frame. The estimated primary completion date for both the FUTURE 1 and MEASURE 1 studies is July 2014.

Two mAbs, ixekizumab and brodalumab, with mechanisms of action similar to secukinumab are also in Phase 3 studies. The IL-17a-targeting ixekizumab (LY2439821; Eli Lilly) is being evaluated in five Phase 3 studies with estimated primary completion dates in 2014. Four of these studies (UNCOVER-1, -2, -3, and -A) are designed to evaluate the effects of ixekizumab in patients with moderate-to-severe psoriasis. The UNCOVER-1 study (NCT01474512) is evaluating 80 mg ixekizumab doses administered in a randomized, double-blind, placebo-controlled induction dosing period followed by a randomized maintenance dosing period and a long-term extension period. The enrollment is an estimated 1,296 patients, and the estimated primary completion date is June 2014. In the UNCOVER-2 (NCT01597245) and UNCOVER-3 (NCT01646177) studies, the effects of 80 mg doses of ixekizumab are being compared with doses of 50 mg etanercept or placebo in patients with moderate-to-severe chronic plaque psoriasis over varied periods of time. Both studies have estimated enrollments of 1,225; the estimated primary completion dates are September and July 2014 for UNCOVER-2 and UNCOVER-3, respectively. The UNCOVER-A study (NCT01777191) is designed to evaluate the pharmacokinetics of ixekizumab after s.c. administration

using either prefilled syringe or auto-injector in patients with moderate-to-severe plaque psoriasis. The fifth Phase 3 study of ixekizumab with an estimated primary completion date in 2014 is the SPIRIT-P1 study (NCT01695239). In this study, the effects of two dosing regimens of 80 mg ixekizumab are compared with doses of 40 mg adalimumab or placebo in patients with active psoriatic arthritis.

Brodalumab (AMG 827/KHK 4827; Amgen/Kyowa Hakko Kirin), which targets the IL-17 receptor, is being evaluated in three Phase 3 studies (AMAGINE-1, -2 and -3) with estimated primary completion dates in 2014. The placebo-controlled AMAGINE-1 study (NCT01708590) is evaluating withdrawal and retreatment of brodalumab in patients with moderate-to-severe plaque psoriasis. Patients are administered either 140 mg or 210 mg of brodalumab or placebo by s.c. injection until week 12. At week 12, patients who received brodalumab are rerandomized to placebo or continued treatment and those who received placebo are assigned to the 210 mg brodalumab cohort. Enrollment for the AMAGINE-1 study is estimated at 600 patients and the estimated primary completion date is March 2014. The AMAGINE-2 (NCT01708603) and AMAGINE-3 (NCT01708629) studies are comparing the effects of induction and maintenance regimens of either 140 mg or 210 mg brodalumab with the effects of 45 mg or 90 mg ustekinumab or placebo in patients with moderate-to-severe plaque psoriasis. For both studies, the primary outcome measures are improvement in PASI and Static Physician Global Assessment (sPGA) score at week 12. Safety outcome measures, e.g., incidence of AEs, presence of anti-drug antibodies, will be evaluated for as long as 5 y. Enrollment of at least 1,800 patients is estimated for each study. The estimated primary completion dates are August 2014 and September 2014 for AMAGINE-2 and AMAGINE-3, respectively.

Results of Phase 2 studies had suggested that ixekizumab and brodalumab might be efficacious as psoriasis treatments.^{8,9} In a randomized, double-blind, placebo-controlled Phase 2 study (NCT01107457) of ixekizumab, 142 patients with chronic moderate-to-severe plaque psoriasis were administered s.c. doses of 10, 25, 75 or 150 mg ixekizumab or placebo at weeks 0, 2, 4, 8, 12 and 16. At week 12, the percentage of patients with reductions in PASI of at least 75% in the 75 mg and 150 mg cohorts were 83% and 82%, respectively. The percentage of patients with reductions in PASI of at least 90% at week 12 in the 75 mg and 150 mg cohorts were 59% and 71%, respectively.⁸ PASI 75 or PASI 90 responses were 8% and 0% in the placebo cohort.

In a randomized, double-blind, placebo-controlled Phase 2 study (NCT00975637) of brodalumab, 198 patients with moderate-to-severe plaque psoriasis were administered s.c. doses of 70, 140 or 210 mg brodalumab at day 1 and weeks 1, 2, 4, 6, 8 and 10 or 280 mg brodalumab monthly or placebo. At week 12, the percentage of patients with reductions in PASI of at least 75% in the 70 mg and 140 mg cohorts were 33% and 77%, respectively. The percentage of patients with reductions in PASI of at least 90% at week 12 in the 70 mg and 140 mg cohorts were 18% and 72%, respectively.⁹ No patients in the placebo cohorts had PASI 75 or PASI 90 responses.

Anti-Proprotein Convertase Subtilisin/Kexin 9 mAbs in Phase 3: Alirocumab, Evolocumab, and Bococizumab

The levels of circulating low-density lipoprotein (LDL) cholesterol are regulated by proprotein convertase subtilisin/kexin type 9 (PCSK9), which enhances degradation of LDL receptors.¹⁰ Blocking the binding of PCSK9 to the receptors interferes with this degradation pathway and leads to reductions in serum LDL cholesterol levels. As of November 1, 2013, three mAbs targeting PCSK9, alirocumab, evolocumab, and bococizumab, are undergoing evaluation in Phase 3 studies.

Top-level data from the first Phase 3 study (NCT01644474) of alirocumab (SAR236553/REGN727; Sanofi/Regeneron Pharmaceuticals) indicating that the study endpoint was met were announced in October 2013. Clinical studies of alirocumab were designed to test the hypothesis that inhibition of PCSK9 will lower LDL cholesterol levels in patients with hypercholesterolemia. As of October 2013, a total of nine Phase 3 studies evaluating the effects of alirocumab on hypercholesterolemia had been initiated, two additional Phase 3 studies in hypercholesterolemia were not yet recruiting and one in acute coronary syndrome was recruiting patients.

Alirocumab administered s.c. or i.v. was evaluated in two single-dose Phase 1 studies of healthy volunteers, and the s.c. administered drug was also evaluated in one multiple-dose study of patients with either familial or non-familial hypercholesterolemia.¹¹ In the single-dose study of i.v. administration, a total of 40 participants received placebo ($n = 10$) or alirocumab at a dose of 0.3, 1.0, 3.0, 6.0, or 12.0 mg/kg ($n = 6$ per dose). In the single-dose study of s.c. administration, 32 participants received placebo ($n = 8$) or 50, 100, 150 or 250 mg ($n = 6$ per dose) of alirocumab. For the groups that received drug i.v., the least-squares mean difference in the change from baseline in LDL cholesterol ranged from -28.1 ± 6.3 to -65.4 ± 8.4 percentage points compared with the placebo group ($P < 0.001$ for all 5 groups). For the groups that received drug s.c., the least-squares mean difference in the change from baseline in LDL cholesterol ranged from -32.5 ± 8.5 to -45.7 ± 7.2 percentage points compared with the placebo group ($P < 0.001$ for all 4 groups).¹¹ The degree and duration of LDL cholesterol lowering were dose-dependent in these two studies. In the multiple-dose Phase 1 study, patients received s.c. administered placebo or alirocumab at doses of 50, 100 or 150 mg on study days 1, 29 and 43. All patients had LDL cholesterol levels > 100 mg/dL and were receiving atorvastatin. The differences in the change from baseline of measured LDL cholesterol were -39.2 , -53.7 and -61.0 percentage points compared with placebo for the groups receiving 50, 100 and 150 mg alirocumab, respectively.¹¹

The results of two randomized, double-blind, placebo-controlled Phase 2 studies of patients with primary hypercholesterolemia who were receiving atorvastatin have been published.^{12,13} In a study of 92 patients with LDL cholesterol ≥ 100 mg/dL, the addition of alirocumab (150 mg/mL) administered as a 1 mL s.c. injection every two weeks from week 0 to week 6 to treatment with either 10 or 80 mg atorvastatin resulted in significantly greater reduction ($P < 0.001$) in LDL

cholesterol compared with atorvastatin alone. The least-squares mean percent change from baseline in LDL cholesterol was -73.2 ± 3.5 , -66.2 ± 3.5 and -17.3 ± 3.5 for the 80 mg atorvastatin plus alirocumab, 10 mg atorvastatin plus alirocumab, and 80 mg atorvastatin plus placebo groups, respectively.¹² In a study of 183 patients with LDL cholesterol ≥ 100 mg/dL, alirocumab was found to further reduce LDL cholesterol by 40% to 72% when added to atorvastatin therapy. The reductions were dependent on the dose and dosing frequency of alirocumab, which was administered s.c. at 50, 100 or 150 mg every two weeks or at 200 or 300 mg every 4 wk.¹³

The effects of alirocumab in patients with heterozygous familial hypercholesterolemia on stable statin dose with or without ezetimibe were assessed in a randomized, double-blind, placebo-controlled, 12-wk Phase 2 study (NCT01266876).¹⁴ A total of 77 patients received 150 mg, 200 mg or 300 mg alirocumab every 4 wk or 150 mg alirocumab every 2 wk or placebo every 2 wk. The least-squares mean change from baseline to week 12 was -10.65% for placebo-treated patients, and -28.9%, -31.54%, -42.53% and -67.90% for patients treated with 150 mg every 4 wk, 200 mg every 4 wk, 300 mg every 4 wk and 150 mg every 2 wk, respectively. The study conclusion was that alirocumab has the potential to provide optimal control of LDL cholesterol in patients with the disease.¹⁴

The on-going Phase 3 ODYSSEY program is designed to evaluate alirocumab in combination with other lipid-lowering agents and as monotherapy. It is expected to enroll over 23,000 patients and involves at least 12 Phase 3 studies. As announced in October 2013, the primary efficacy endpoint of the randomized, double-blind, active-controlled ODYSSEY Mono study (NCT01644474) was met.¹⁵ In this study, 103 patients received either monotherapy with either 10 mg ezetimibe (oral) or alirocumab (s.c. injection), with appropriate matching placebo given in both study arms. The initial dose of alirocumab was 75 mg every two weeks, which was up-titrated to 150 mg at week 12 if the LDL cholesterol level at week 8 was > 70 mg/dL. The majority of patients remained on the original dose. Compared with patients who received ezetimibe, the reduction from baseline to week 24 was significantly greater in those who received alirocumab (15.6% for ezetimibe-treated vs. 47.2% for alirocumab-treated patients, $P < 0.0001$). Treatment emergent AEs were reported by 78% and 69% of patients treated with ezetimibe and alirocumab, respectively. Infections were the most common class of AEs (39% with ezetimibe and 42% with alirocumab). Primary completion dates for eight other Phase 3 studies of alirocumab as a treatment for hypercholesterolemia are expected in 2014 (clinicaltrials.gov number NCT01730053, February 2014; NCT01709513 and NCT01730040, March 2014; NCT01644175, April 2014; NCT01644188, May 2014; NCT01709500, August 2014; NCT01507831, October 2014; NCT01623115, December 2014).

Evolocumab (AMG 145; Amgen), which also targets PCSK9, is undergoing evaluation in the PROFICIO Phase 3 program, which includes 12 studies with an estimated combined enrollment of 27,000 patients with hypercholesterolemia. Seven of the studies have estimated primary completion dates between

September and December 2013. Results from pooled analyses of four Phase 2 studies of evolocumab administered s.c. to patients with high cholesterol were announced in August 2013.¹⁶ The results of each of the 12 wk studies (MENDEL,¹⁷ LAPLACE-TIMI57,¹⁸ RUTHERFORD,¹⁹ and GAUSS²⁰) were published in 2012. In the efficacy analysis of pooled data, treatment with evolocumab resulted in mean reductions of LDL cholesterol from baseline to week 12 of 40% to 59% across drug doses. For comparison, the reductions observed in the placebo groups were 0.1% to 0.5%. AEs were observed in 57% and 49% of patients treated with evolocumab and placebo, respectively. The most frequent AEs were nasopharyngitis and upper respiratory tract infections.

The dose and dosing frequency of evolocumab varied somewhat between the four Phase 2 studies. In the MENDEL (NCT01375777) and LAPLACE-TIMI57 (NCT01380730) studies, patients were assigned to 70 mg, 105 mg or 140 mg every 2 wk or 280 mg, 350 mg, or 420 mg every 4 wk. Patients with hypercholesterolemia in the absence of concurrent lipid-lowering treatment were included in the MENDEL study and the active comparator was ezetimibe,¹⁷ while patients on a stable dose of statin with or without ezetimibe were included in the LAPLACE-TIMI57 study and there was no active comparator in the study.¹⁸ The placebo-controlled RUTHERFORD study (NCT01375751) included patients with heterozygous familial hypercholesterolemia who had LDL cholesterol > 100 mg/dL despite statin therapy with or without ezetimibe; patients received 350 mg or 420 mg evolocumab every 4 wk.¹⁹ In the GAUSS study (NCT01375764), patients with statin intolerance due to muscle-related side effects were administered 280 mg, 350 mg or 420 mg evolocumab, 420 mg evolocumab plus 10 mg ezetimibe or placebo plus 10 mg ezetimibe.²⁰ Each of these studies has a Phase 3 equivalent. The Phase 3 MENDEL-2 (NCT01763827), LAPLACE-2 (NCT01763866), RUTHERFORD-2 (NCT01763918), and GAUSS-2 (NCT01763905) studies have estimated primary completion dates of October 2013.

Patients who completed any of the four Phase 2 studies were eligible to participate in the 52-wk open label OSLER (NCT01439880) study. This extension study enrolled 1,104 patients who were randomized 2:1 to receive evolocumab s.c. at 420 mg every 4 wk with standard of care ($n = 736$) or standard of care alone ($n = 368$) for one year.²¹ At week 52, patients who first received evolocumab in the OSLER study experienced an average of 52% reduction in LDL cholesterol. Patients who received one of six dosing regimens of evolocumab in the parent studies and received evolocumab in the OSLER study had persistent average LDL cholesterol reductions of 50% at the end of the parent study and 52% at 52 wk. LDL cholesterol levels in patients who were administered evolocumab in a parent study but only standard of care in the OSLER study returned to near base-line at 52 wk. AEs and serious AEs occurred in a somewhat percentage of patients receiving evolocumab compared with those who received only standard of care (81% and 7% vs. 73% and 6%, respectively).²¹

The first Phase 3 studies of bococizumab (PF-04950615, RN316; Pfizer) were initiated in October 2013; a total of five Phase 3 studies were started or due to start during the month.

Table 3. Therapeutic antibodies in Phase 3 clinical studies of cancer indications

Sponsoring company	INN or code name	Molecular format	Target	Phase 3 indications
Bristol-Myers Squibb, AbbVie	Elotuzumab	Humanized IgG1	CD2	Multiple myeloma
Pfizer, UCB	Inotuzumab ozogamicin	Humanized IgG4 ADC	CD22	ALL; NHL
AstraZeneca*	Moxetumomab pasudotox, CAT-8015	Murine Fv immunotoxin	CD22	Hairy cell leukemia
ImClone Systems	Necitumumab	Human IgG1	EGFR	NSCL cancer
Amgen	Rilotumumab	Human IgG2	HGF/SF	Gastric or gastresophageal junction adenocarcinoma
Genentech	Onartuzumab	Humanized IgG1 Fab-Fc	cMet	NSCL cancer, gastric cancer
Merck	Lambrolizumab, MK-3475	Humanized IgG4	PD1	Melanoma; NSCL cancer
Bristol-Myers Squibb	Nivolumab, BMS-936558	Human IgG4	PD1	NSCL cancer, renal cell carcinoma, melanoma
United Therapeutics Corporation*	Ch14.18	Chimeric IgG1	GD2	Neuroblastoma
Recombio	Racotumomab	Murine; anti-idiotypic	GM3	NSCL cancer

Note: Table compiled from information available as of November 1, 2013. *In-licensed; National Cancer Institute is sponsoring Phase 3 studies. Abbreviations: ALL, acute lymphoblastic leukemia; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; HGF/SF, hepatocyte growth factor/ scatter factor; NHL, non-Hodgkin lymphoma; NSCL, non-small cell lung; PD1, programmed death 1 receptor; VEGFR2, vascular endothelial growth factor receptor 2.

The Double-Blind, Randomized, Placebo-Controlled, Parallel-Group SPIRE-LDL study (NCT0196896) will evaluate the effects of bococizumab in patients with primary hyperlipidemia or mixed dyslipidemia at risk of cardiovascular events who receive highly effective statins. Patients will be administered 150 mg bococizumab or placebo every 2 wk, by s.c. injection, for 18 mo. The primary outcome measure is Percent Change from Baseline in LDL cholesterol at week 12. Long-term safety and efficacy will also be assessed. Enrollment is estimated at 1600 patients and the estimated primary completion date is December 2014. Of the other four Phase 3 studies, two studies (SPIRE-HF NCT01968980 study of patients with heterozygous familial hypercholesterolemia; SPIRE-HR NCT01968954 study of patients with hyperlipidemia) have estimated primary completion dates of January 2016, and two studies (SPIRE-1 NCT01975376 and SPIRE-2 NCT01975389 studies of high risk patients with high LDL and cardiovascular disease) have estimated primary completion dates in August 2017.

Anti-PD1 mAbs in Phase 3: Lambrolizumab and Nivolumab

Substantial resources are currently being dedicated to the evaluation of antibody-based cancer therapies in Phase 3 studies (Table 3), including those that modulate immune system responses, e.g., by antagonizing a repressor such as programmed death 1 receptor (PD1).²² Blocking PD1 enables

activation of T cells that can target tumors. At least eight antibody-based therapeutics that target PD1 are currently in clinical studies, with two (lambrolizumab, nivolumab) in Phase 3 studies that have estimated primary completion dates in 2014. Notably, lambrolizumab received FDA's Breakthrough Therapy designation for the treatment of patients with advanced melanoma, and nivolumab received FDA's Fast Track designation for non-small-cell lung cancer (NSCLC), renal cell carcinoma and advanced melanoma, in 2013. Phase 1 study results for lambrolizumab²³ and nivolumab²⁴⁻²⁷ administered to patients with advanced cancers have been published.

The effects of two dosing schedules of lambrolizumab (MK-3475; Merck), a humanized IgG4 targeting PD1, are being compared with those of ipilimumab (Yervoy®) in patients with advanced melanoma in a Phase 3 study (NCT01866319) with an estimated primary completion date of December 2014. In this three-arm study, an estimated 645 adult patients (18 y and older) will be administered 10 mg lambrolizumab intravenously (i.v.) once every 2 wk for up to 2 y; 10 mg lambrolizumab i.v. once every 3 wk for up to 2 y; or 3 mg/kg i.v. ipilimumab once every 3 wk for a total of 4 doses. The primary outcome measures are progression-free survival (PFS) assessed for up to 2 y and overall survival (OS) assessed up to 30 mo. Lambrolizumab is also being evaluated in a Phase 2/3 study (NCT01905657) of patients with NSCLC who have experienced disease progression after platinum-containing systemic therapy. The estimated primary completion date for the study in NSCLC is September 2015.

Nivolumab (BMS-936558; Bristol-Myers Squibb) is undergoing evaluation as a treatment for NSCLC in two Phase 3 studies with primary completion dates in 2014. In an open-label, randomized Phase 3 study (NCT01642004), the effects of nivolumab are being compared with those of docetaxel (Taxotere®) in an estimated 264 patients with previously treated advanced or metastatic squamous cell NSCLC. Adult patients (18 y and older) receive 3 mg/kg nivolumab i.v. every 2 wk, or 75 mg/m² i.v. docetaxel every 3 wk until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends. The primary outcome measures are the objective response rate (defined as the number of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of randomized patients) and OS (defined as the time from randomization to the date of death) in a time frame of 24 mo. The estimated primary completion date for the NCT01642004 study is August 2014. A Phase 3 study (NCT01673867) of the same dose of nivolumab in patients with previously treated advanced or metastatic non-squamous cell NSCLC has an estimated primary completion date of November 2014.

mAbs with Breakthrough Therapy Designations

The Food and Drug Administration Safety and Innovation Act, which was signed into law on July 9, 2012, gave the US FDA authority to designate drugs as breakthrough therapies. The designation is intended to expedite the development and review of new drugs with preliminary clinical evidence indicating that the drug may offer a substantial improvement on a clinically significant endpoint over available therapies for patients with serious or life-threatening diseases. The benefits of breakthrough therapy designation include intensive guidance on an efficient drug development program beginning as early as Phase 1, organizational commitment involving senior FDA managers, as well as all the Fast Track designation features.²⁸

As of October 2013, five mAbs (obinutuzumab, ofatumumab, lambrolizumab, bimagrumab, daratumumab) had received breakthrough therapy designations from the US FDA. On November 1, 2013, obinutuzumab became the first drug with the designation to be approved. Ofatumumab (Arzerra®, Genmab/GlaxoSmithKline), which targets CD20 and is marketed in the US and EU for patients with chronic lymphocytic leukemia (CLL) that is refractory to fludarabine and alemtuzumab, has breakthrough therapy designation for use in combination with chlorambucil for the treatment of patients with CLL who have not received prior treatment and are inappropriate for fludarabine-based therapy. As previously noted in this review, lambrolizumab has breakthrough therapy designation for advanced melanoma and is in Phase 3 studies for this indication.

Bimagrumab (BYM338; Novartis) has breakthrough therapy designation for sporadic inclusion body myositis (sIBM). The human IgG1 mAb, which targets type II activin receptors and blocks binding of natural ligands such as myostatin and activin, was derived from a HuCAL library (MorphoSys). A Phase 2/3 study (NCT01925209) evaluating bimagrumab as

a treatment for sporadic inclusion body myositis (sIBM) was initiated in September 2013. Characterized by inflammatory and degenerative mechanisms that cause muscle weakness and loss, sIBM is the most frequently acquired myopathy after age 50.²⁹ Disease progression is slow, with time from onset to first use of a wheelchair in the range of 14–16 y. Bimagrumab received breakthrough therapy and orphan drug designations from the US FDA, and orphan drug designation from the European Medicines Agency, for sIBM. In addition to sIBM, bimagrumab is also being evaluated in clinical studies of mechanically ventilated patients and patients with chronic obstructive pulmonary disease, cancer cachexia, and sarcopenia.

The randomized, double-blind Phase 2/3 study (NCT01925209) will evaluate the efficacy, safety and tolerability of multiple doses of i.v. administered bimagrumab compared with placebo on physical function, muscle strength, and mobility in patients with sIBM. Patients 36 to 85 Years of age with a confirmed diagnosis of sIBM will be administered low, mid or high doses of bimagrumab, or matching placebo, via i.v. infusion from day 1 to week 52, and up to week 104. The primary outcome measure is the change from baseline in 6 min walking distance test meters to week 52. Secondary outcome measures include the change from baseline in lean body mass and change from baseline in quadriceps quantitative muscle testing at week 52. The enrollment is estimated at 240 patients (60 patients per each of 4 study arms) and the estimated study completion date is November 2015.

A Phase 2 study (NCT01423110) evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of bimagrumab showed that the drug substantially benefited sIBM patients compared with treatment with placebo.³⁰ The study enrolled 14 patients in the range of 40–80 y with a confirmed diagnosis of sIBM. The primary outcome measure was the effect of bimagrumab on thigh muscle volume, as determined by magnetic resonance imaging, in a time frame of 8 wk, and the secondary outcome measure was the effect of bimagrumab on muscle function by a “Timed Get Up and Go” test.

Daratumumab (Genmab / Janssen) has breakthrough therapy designation for treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double refractory to a PI and IMiD. As of November 2013, the anti-CD38 mAb was undergoing evaluation in two Phase 1/2 and one Phase 2 study of multiple myeloma patients. The Phase 2 study (NCT01985126), which is in the breakthrough therapy designation indication, was initiated in October 2013 and has a primary completion date of October 2016.

Outlook for 2014

Based on the information available as of November 2013, the development of antibody therapeutics is expected to be robust and dynamic in 2014 and beyond. As has been discussed here, 4–5 mAb product candidates are expected to transition from Phase 3 to regulatory review and 3–4 are anticipated to gain first

marketing approvals in the US or EU during 2014. Study results for some of the 33 mAbs in Phase 3 studies (Tables 2 and 3) are also expected to be announced in 2014.

It should be noted at least three mAbs (dupilumab, clivatuzumab tetraxetan, baviximab) not included in the tables are expected to enter first Phase 3 studies by the end of 2013, which would bring the total number of mAb product candidates in Phase 3 studies to 36 by January 2014. As of November 22, 2013, Phase 3 studies for dupilumab (Regeneron/Sanofi) and clivatuzumab tetraxetan (Immunomedics, Inc.) were not yet recruiting (NCT01949311 and NCT01956812, respectively). Peregrine Pharmaceuticals, Inc. announced that they anticipate

initiating a randomized, double-blind, placebo-controlled Phase 3 study of baviximab plus docetaxel vs. docetaxel alone enrolling approximately 600 patients at sites worldwide. The trial will enroll Stage IIIB/IV non-squamous NSCLC patients who have progressed after standard front-line treatment, but information for the study was not found on clinicaltrials.gov as of November 22, 2013.

Continuing the tradition we established in 2009,³¹⁻³⁵ mAbs will track the progress of antibody therapeutics in clinical development in 2014, and we look forward to reporting updated information in our 2014 mid-year installment of the “Antibodies to watch” series.

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