

# Antibodies to watch in 2013

## Mid-year update

Janice M. Reichert

Editor-in-Chief, *mAbs*; Landes Bioscience; Austin, TX USA

The transitions of antibody therapeutics to late-stage clinical development, regulatory review and the market are proceeding at a rapid pace in 2013. Since late 2012, two monoclonal antibody (mAb) therapeutics (itolizumab, trastuzumab emtansine) received their first approvals, first marketing applications for three mAbs (vedolizumab, ramucirumab, obinutuzumab) were submitted to regulatory agencies, and five mAbs (brodalumab, MABp1, moxetumomab pasudotox, tildrakizumab, rilotumumab) entered their first Phase 3 studies. The current total of commercially-sponsored antibody therapeutics undergoing evaluation in late-stage studies is 30. Recently announced study results for farletuzumab, naptumomab estafenatox, and tabalumab indicate that clinical endpoints were not met in some Phase 3 studies of these product candidates.

Early 2013 proved to be a sufficiently busy period for antibody therapeutics developers that this mid-year update to *mAbs* annual coverage of antibodies in late-stage development<sup>1-4</sup> was needed. A total of five antibody therapeutics (itolizumab, trastuzumab emtansine, vedolizumab, ramucirumab, obinutuzumab) transitioned to either the market or regulatory review. Biocon announced in January 2013 that the marketing application for itolizumab (Alzumab) had been authorized by the Drugs Controller General of India. Itolizumab is a humanized mAb that targets CD6, which is predominantly expressed by T cells and a subset of B cells. In the 52-week TREAT-PLAQ study conducted in India, interim results indicated that patients with psoriasis area severity index (PASI) of > 20 at baseline had PASI 75-response (i.e., improvement from baseline of  $\geq 75\%$ ) rates of 43% and 54% at week 12 and 28, respectively. Patients in the fixed dose treatment arm of the study received 1.6 mg/kg every two weeks for 12 weeks followed by 1.6 mg/kg every four weeks for 16 weeks; those in the induction dose arm received 0.4 mg/kg every two weeks for 12 weeks followed by 1.6 mg/kg every four weeks for 16 weeks. Biocon is reportedly planning to launch itolizumab in India as a treatment for moderate-to-severe psoriasis in the July–September 2013 quarter. The company has indicated that itolizumab has also shown promising efficacy in other autoimmune disorders, including rheumatoid arthritis (RA) and multiple sclerosis (MS).

In February 2013, trastuzumab emtansine (Kadcyla<sup>TM</sup>; Genentech/Roche) was approved by the US Food and Drug Administration (FDA) as a treatment for human epidermal growth factor receptor (HER)2-positive metastatic breast cancer. Trastuzumab emtansine is an antibody-drug conjugate (ADC) comprising trastuzumab (Herceptin<sup>®</sup>; Genentech/Roche) linked to ImmunoGen's DM1 maytansinoid drug. The ADC is the third anti-HER2 monoclonal antibody (mAb) on the US market.

The parental trastuzumab was first approved in 1998 and anti-HER2 pertuzumab (PERJETA<sup>TM</sup>; Genentech/Roche) was first approved in 2012 as treatments for HER2-positive metastatic breast cancer. In the European Union, trastuzumab and pertuzumab are approved, and trastuzumab emtansine is undergoing regulatory review. Trastuzumab emtansine is approved for patients who were previously treated with trastuzumab and taxanes. It is currently also undergoing evaluation in the Phase 3 MARIANNE study (NCT01120184) of trastuzumab emtansine and pertuzumab vs. trastuzumab plus a taxane in patients with metastatic breast cancer; the Phase 3 TH3RESA study (NCT01419197) of trastuzumab emtansine compared with treatment of physician's choice in patients with HER2-positive metastatic breast cancer who have received at least two prior regimens of HER2 directed therapy; and the Phase 3 KATHERINE study (NCT01772472) of trastuzumab emtansine vs. trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor present pathologically in the breast or axillary lymph nodes following preoperative therapy, which was initiated in April 2013. In addition, the safety and efficacy of the mAb are being evaluated in an adaptive Phase 2/3 study (NCT01641939) of patients with previously treated, locally advanced or metastatic HER2-positive gastric cancer, including adenocarcinoma of the gastroesophageal junction.

In early March 2013, Takeda Pharmaceutical Company announced that they submitted a marketing authorization application to the European Medicines Agency for vedolizumab, a gut-selective, anti- $\alpha 4\beta 7$  humanized mAb intended as a treatment for adults with moderate-to-severe active ulcerative colitis (UC) and Crohn disease (CD). The application included data from four Phase 3 clinical studies, GEMINI I, GEMINI II, GEMINI III and GEMINI Long-term Safety, that evaluated the efficacy and

\*Correspondence to: Janice M. Reichert; Email: janice.reichert@landesbioscience.com  
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safety of vedolizumab in moderately to severely active CD and UC patients who had failed to respond to treatment with at least one conventional or anti-tumor necrosis factor drug.

In late April 2013, Lilly announced that they received Fast Track designation from the FDA for ramucirumab, a human IgG1 that targets vascular endothelial growth factor receptor-2, and that they initiated a rolling submission of a licensing application of the mAb as monotherapy in second-line gastric cancer. Fast Track designation is given to drugs intended to treat serious diseases and fill an unmet medical need. The review of Fast Track drugs can be expedited by a rolling submission in which completed sections of the application are reviewed by FDA as they are submitted, i.e., FDA does not wait for the entire application to be submitted before beginning the review. Lilly expects to complete the submission process by the end of 2013. Ramucirumab has been evaluated in two Phase 3 studies (NCT00917384, NCT01170663) of patients with gastric cancer. In addition, the mAb 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. The primary completion date for the study in breast cancer is March 2013, with primary completion dates scheduled in 2014 for the other studies.

In mid-May 2013, Roche announced that obinutuzumab had been granted breakthrough therapy designation by FDA, and that marketing applications had been submitted in the US and European Union. Obinutuzumab is a type II anti-CD20 IgG1 antibody with reduced fucosylation. The marketing applications were based on data from the 3-arm, Phase 3 CLL11 study (NCT01010061), which compared the combination of either obinutuzumab or rituximab and chlorambucil to chlorambucil alone in patients with previously untreated chronic lymphocytic leukemia. The benefits of the breakthrough therapy designation includes all those provided by the fast track program, but also more intensive FDA guidance on the drug's development program. Obinutuzumab is also undergoing evaluation as a treatment for lymphoma. Three Phase 3 studies are on-going: (1) GADOLIN (NCT01059630), which compares bendamustine with the combination of bendamustine and obinutuzumab in patients with rituximab-refractory, indolent non-Hodgkin lymphoma; (2) GOYA (NCT01287741), which compares obinutuzumab in combination with CHOP chemotherapy to rituximab with CHOP in previously untreated patients with CD20-positive diffuse large B cell lymphoma; and (3) GALLIUM (NCT01332968), which compares obinutuzumab in combination with chemotherapy compared to rituximab with chemotherapy (CHOP, CVP or bendamustine) followed by obinutuzumab or rituximab maintenance in patients with untreated advanced indolent non-Hodgkin lymphoma. The primary completion dates for these studies are January 2015, November 2016 and March 2022, respectively.

### First Phase 3 Studies for Five mAbs

A total of 30 mAbs that were either developed or in-licensed by companies are currently undergoing evaluation in late-stage

studies (Tables 1 and 2). Five of these (brodalumab, MABp1, moxetumomab pasudotox, tildrakizumab, rilotumumab) transitioned into Phase 3 studies during the period from late 2012 to April 2013. Brodalumab (AMG827, Amgen; KHK4827, Kyowa Hakko Kirin), a human IgG2 targeting the interleukin (IL)-17 receptor, is undergoing evaluation in three Phase 3 studies (AMAGINE-1, -2, and -3) of patients with psoriasis. The AMAGINE-1 study (NCT01708590) is evaluating the efficacy, safety, and effect of withdrawal and retreatment with brodalumab in patients with moderate-to-severe plaque psoriasis. In this study, either of two doses (140 mg or 210 mg) or placebo is administered subcutaneously (SC) every two weeks until week 12, when patients are rerandomized to placebo or continued treatment. Patients are retreated at return of disease. The estimated primary completion date for the study is March 2014. In the AMAGINE-2 (NCT01708603) and AMAGINE-3 (NCT01708603) studies, the efficacy and safety of induction and four maintenance regimens of brodalumab compared with placebo and ustekinumab in patients with moderate-to-severe plaque psoriasis is being evaluated. These studies have estimated primary completion dates of August and September 2014, respectively.

A first Phase 3 study (NCT01767857) of MABp1 (Xilonix, XBiotech, Inc.), a human mAb targeting IL-1 $\alpha$ , was recruiting patients as of March 2013. The study will evaluate overall survival of metastatic colorectal cancer patients with cachexia who are administered the mAb as a monotherapy. The effects of MABp1 administered intravenously (IV) every two weeks, plus best supportive care will be compared with those of megestrol acetate administered daily plus best supportive care. The difference between the study arms in median overall survival from baseline to 18 mo will be compared. The study has an estimated primary completion date of April 2014.

The recombinant immunotoxin moxetumomab pasudotox (CAT-8015, AstraZeneca) is undergoing evaluation in a Phase 3 study (NCT01829711) of patients with relapsed/refractory hairy cell leukemia. The study is sponsored by the National Cancer Institute (NCI); the mAb is currently licensed to AstraZeneca. In 2004, NCI licensed moxetumomab pasudotox to Genencor, Inc. The mAb was then acquired in 2005 by Cambridge Antibody Technology, which was itself acquired by AstraZeneca in 2006. Moxetumomab pasudotox comprises a mouse disulfide stabilized variable fragment with the variable heavy domain fused with a 7-mer linker and the *Pseudomonas aeruginosa* exotoxin A PE38 fragment. In the Phase 3 study, patients will receive 40  $\mu$ g/kg of the immunotoxin administered IV over 30 min on days 1, 3, 5 of each 28 d cycle until complete response, progressive disease, initiation of alternate therapy or unacceptable toxicity is observed. Initiated in March 2013, the study's estimated primary completion date is December 2014.

Two Phase 3 studies of tildrakizumab (SCH900222/MK-3222, Merck), a humanized mAb targeting the p19 subunit of IL-23, are recruiting patients. Initiated in December 2012, NCT01722331 is a 64-week study to evaluate the efficacy and safety/tolerability of SC administration of tildrakizumab in patients with moderate-to-severe chronic plaque psoriasis. Patients receive 100 mg or

**Table 1.** Therapeutic antibodies in Phase 3 clinical studies of non-cancer indications

Sponsoring company	INN or code name	Molecular type	Target(s)	Current phase	Phase 3 indications
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
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 $\alpha$	Phase 3	Cachexia in cancer patients
Xoma; Servier	Gevokizumab	Humanized IgG2	IL-1 $\beta$	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
Janssen Research & Development LLC	Sirukumab	Human IgG1	IL-6	Phase 3	Rheumatoid arthritis
Regeneron; Sanofi	Sarilumab, SAR153191, REGN88	Human IgG1	IL-6R subunit $\alpha$	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	Psoriasis, psoriatic arthritis, plaque psoriasis
Novartis Pharmaceuticals	Secukinumab	Human IgG1	IL-17a	Phase 3	Rheumatoid or 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-LaRoche	Gantenerumab	Human IgG1	Amyloid $\beta$	Phase 3	Alzheimer disease
Eli Lilly and Co.	Solanezumab	Humanized IgG1	Amyloid $\beta$	Phase 3	Alzheimer disease

Note: Table compiled from information available as of April 25, 2013. Abbreviations: CD, cluster of differentiation; IL, interleukin; PCSK9, proprotein convertase subtilisin/kexin type; SLE, systemic lupus erythematosus.

200 mg tildrakizumab at week 0 and week 4, and then every 12 weeks until study end or participant discontinuation. The comparator is placebo. In the 54-week NCT01729754 study in the same indication, patients receive the same doses of tildrakizumab, but the study includes 50 mg etanercept as well as placebo as comparators. Both studies are followed by an optional long-term safety extension study. The two Phase 3 studies have estimated primary completion dates of June and July 2015, respectively.

Rilotumumab (Amgen) is a human IgG2 targeting human hepatocyte growth factor/scatter factor (HGF/SF) that blocks binding of HGF/SF to its receptor MET, thereby inhibiting the MET signaling pathways. The mAb is undergoing evaluation in a Phase 3 study (NCT01697072) of chemotherapy (epirubicin, cisplatin and capecitabine) with rilotumumab or placebo for untreated advanced MET-positive gastric or gastroesophageal junction adenocarcinoma. Rilotumumab or placebo is

**Table 2.** Therapeutic antibodies in Phase 2/3 or Phase 3 clinical studies of cancer indications (continued)

Sponsoring company	INN or code name	Molecular type	Target(s)	Current phase	Phase 2/3 or 3 indications
Active Biotech	Naptumomab estafenatox, ABR-217620	Murine Fab immunotoxin	5T4	Phase 2/3	Renal cell carcinoma
Amgen	Rilotumumab	Human IgG2	HGF/SF	Phase 3	Gastric or gastroesophageal junction adenocarcinoma
Morphotek	Farletuzumab	Humanized IgG1	Folate receptor $\alpha$	Phase 3	Ovarian cancer
Bristol-Myers Squibb, Abbott	Elotuzumab	Humanized IgG1	CD2	Phase 3	Multiple myeloma
Pfizer, UCB	Inotuzumab ozogamicin	Humanized IgG4 ADC	CD22	Phase 3	ALL; NHL
AstraZeneca*	Moxetumomab pasudotox, CAT-8015	Murine Fv immunotoxin	CD22	Phase 3	Hairy cell leukemia
ImClone Systems	Necitumumab	Human IgG1	EGFR	Phase 3	NSCL cancer
Bristol-Myers Squibb	Nivolumab, BMS-936558	Human IgG4	PD1	Phase 3	NSCL cancer, renal cell carcinoma, melanoma
Genentech	Onartuzumab	Humanized IgG1 Fab-Fc	$\psi$ Met	Phase 3	NSCL cancer, gastric cancer
CIMAB; Laboratorio Elea S.A.C.I.F. y A	Racotumomab	Murine	GM3	Phase 3	NSCL cancer

Note: Table compiled from information available as of April 25, 2013. \*In-licensed; National Cancer Institute is sponsoring the Phase 3 study in hairy cell leukemia patients. Abbreviations: ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; HGF/SF, hepatocyte growth factor/ scatter factor; NHL, non-Hodgkin lymphoma; NSCL, non-small cell lung; VEGFR2, vascular endothelial growth factor receptor 2.

administered IV at doses of 15 mg/kg every 21 d. The primary outcome measure is overall survival in a time-frame of three years. Initiated in October 2012, the estimated primary completion date for the study is December 2015.

### Clinical Endpoints Missed in Studies of Three mAbs

Recently announced results for three late-stage studies of two mAbs for cancer (farletuzumab, naptumomab estafenatox) and tabalumab, a mAb treatment for autoimmune disorders, indicate that clinical endpoints were not met. Farletuzumab (MORAb-003, Morphotek/Eisai) is a humanized IgG1 mAb that targets human folate receptor  $\alpha$ , which is overexpressed in most epithelial ovarian cancers, as well as some forms of endometrial, breast, renal, lung and colorectal cancers. The primary endpoint of progression-free survival (PFS) was not met in the Phase 3 FAR-131 study (NCT00849667) of farletuzumab in combination with carboplatin and a taxane in patients with platinum-sensitive epithelial ovarian cancer in first relapse. Patients received placebo or farletuzumab at either 1.25 mg/kg or 2.5 mg/kg weekly for ~six cycles. Although the primary endpoint was not met, a trend toward improved PFS was observed in some patient subsets in a post-hoc analysis. The mAb is also in development as a treatment for other cancers. The safety and efficacy of farletuzumab in combination with a platinum containing doublet in chemotherapy-naïve subjects with stage IV adenocarcinoma of the lung are being evaluated in a Phase 2 study (NCT01218516).

As announced in January 2013 by Active Biotech AB, initial results of a Phase 2/3 study (NCT00420888) of naptumomab estafenatox (ABR-217620, ANYARA) in combination with interferon  $\alpha$  as a treatment for advanced renal cell carcinoma indicated that the study did not achieve its primary clinical endpoint of overall survival in the intention-to-treat cohort. A confounding factor was the presence of high levels of pre-formed anti-drug antibodies found in a majority of patients in this, but not previous, studies. A doubling of PFS and overall survival occurred in the 25% of patients who had low or normal levels of base-line IL-6 and expected levels of anti-drug antibodies. Naptumomab estafenatox is composed of an antigen-binding fragment (Fab) that targets metastasis-associated 5T4 fused to a mutated form of Staphylococcal enterotoxin A (SEA/E-120).

Phase 3 studies of tabalumab (LY2127399, Eli Lilly and Co.) as a treatment for RA have been discontinued due to lack of efficacy. Tabalumab, a human IgG4 targeting B-lymphocyte stimulator, was being evaluated in five Phase 3 studies of RA patients. The Phase 3 program in systemic lupus erythematosus (SLE) will continue. Tabalumab in combination with bortezomib and dexamethasone is also being evaluated in a Phase 2/3 study (NCT01602224) of patients with previously treated multiple myeloma.

### Late-Stage Pipeline Update

Historically, ~50% of mAbs in the commercial clinical pipeline have been studied as cancer agents; however, ~67% of the current cohort of mAbs at Phase 3 is in studies for non-cancer indications (Table 1). These 20 mAbs are human or humanized, with

more than half (55%) targeting an interleukin or an interleukin receptor. The mAbs are being developed as treatments for immunological disorders such as RA, SLE, MS and psoriasis, but also for hypercholesterolemia, cachexia and Alzheimer disease.

Reflecting the overall greater challenge of demonstrating safety and efficacy in cancers, the molecular types of the 10 mAbs in late-stage studies of cancer (Table 2) are more diverse than those for non-cancer indications. Of particular note is the inclusion of a toxin in three molecules (naptumomab estafenatox, moxetumomab pasudotox, inotuzumab ozogamicin) and use of less than a full-length sequence for three molecules (naptumomab estafenatox, moxetumomab pasudotox, onartuzumab). The majority (70%) of the 10 product candidates are in studies of solid tumors, with the remainder undergoing evaluation as treatments for hematological cancers. The number of anti-cancer mAbs at Phase 3 is likely to increase in the next 3–5 y as more ADCs move into and through the clinical pipeline.<sup>5</sup> *mAbs* will continue to track the progress of antibody therapeutics in clinical study throughout 2013, and we look forward to reporting on results that may be released during the year in “Which are the antibodies to watch in 2014?,” our next installment of this series.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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