Which are the antibodies to watch in 2013

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The start of the new year signals that it is time for mAbs’ annual review of the therapeutic monoclonal antibodies (mAbs) in active Phase 2/3 or Phase 3 clinical studies. The entire clinical pipeline currently includes ~350 mAbs, but most of these are in early development. As of the beginning of 2013, our “Antibodies to watch” list includes 28 single mAbs and one mAb mixture that are undergoing evaluation in Phase 3 studies for inflammatory or immunological disorders, cancers, high cholesterol, osteoporosis, Alzheimer disease and infectious disease. In alphabetical order, the 28 mabs are alirocumab, AMG 145, elotuzumab, epratuzumab, farletuzumab, gantenerumab, gevokizumab, inotuzumab ozogamicin, itolizumab, lebrikizumab, mepolizumab, naprtumomab estafenatox, nevitumomab, nivolumab, obinutuzumab, ocirelizumab, onartuzumab, racotumomab, ramucirumab, reslizumab, romosozumab, sarilumab, secukinumab, sirukumab, solanezumab, tabalumab and vedolizumab. The mixture of actoxumab and bezlotoxumab is being evaluated in two Phase 3 studies as a treatment for Clostridium difficile infection.

Historically, mAbs that target antigens relevant to cancer have comprised ~50% of the mAb clinical pipeline, but the majority (19/29; 66%) of the antibodies to watch in 2013 are for non-cancer indications (Table 1). Of the 19 product candidates, all are either humanized (11 mAbs) or human (7 single mAbs and the mAb mixture) full-length mAbs; three are IgG2, four are IgG4, with the remainder IgG1. Four antigens, amyloid beta, proprotein convertase subtilisin/kexin type 9 (PCSK9), interleukin (IL)-5, IL-17a, are the targets of two mAbs each.

The IgG2 AMG 145 and IgG1 alirocumab, both of which target PCSK9, are undergoing assessments of safety and efficacy in patients with hypercholesterolemia. A Phase 2/3 study to determine the safety, tolerability, and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia was initiated in March 2012 and is due for completion in May 2013. Results from several Phase 1 and 2 studies of AMG 145 have recently been reported.1-4 In July 2012, Sanofi and Regeneron announced the initiation of the ODYSSEY program, which is a series of Phase 3 clinical trials of alirocumab. As of mid-November 2012, a total of eight Phase 3 studies of alirocumab were listed as recruiting on clinicaltrials.gov: ODYSSEY Mono (alirocumab compared with ezetimibe in patients with hypercholesterolemia), ODYSSEY Combo I and II (evaluates alirocumab in combination with lipid modifying therapy in patients with hypercholesterolemia at high cardiovascular risk), ODYSSEY High FH (evaluates alirocumab in combination with lipid modifying therapy in patients with familial hypercholesterolemia), ODYSSEY FH1 (evaluates alirocumab in patients with familial hypercholesterolemia that is not adequately controlled), ODYSSEY Alternative (evaluates alirocumab in patients with hypercholesterolemia and cardiovascular risk who are intolerant to statins), ODYSSEY Outcomes (compares the effect of alirocumab with placebo on the occurrence of cardiovascular events in patients who have experienced an acute coronary syndrome event), and ODYSSEY Long-term (evaluated the long-term safety and tolerability of alirocumab in patients with hypercholesterolemia and cardiovascular risk). The completion dates for these studies are between November 2013 (ODYSSEY Mono) and March 2018 (ODYSSEY Outcomes).

Two anti-IL-5 mAbs, IgG1 mepolizumab and IgG4 reslizumab, are in multiple Phase 3 studies that are actively recruiting patients. Mepolizumab is currently undergoing evaluation in six Phase 3 studies; patients with asthma are being recruited for four studies, while patients with hypereosinophilic syndrome and patients with chronic obstructive pulmonary diseases and eosinophilic bronchitis are each being recruited for one study. The completion dates for these six studies range from March 2013 to December 2016. Patients are currently being recruited for a total of four Phase 3 studies of the safety and efficacy of reslizumab as a treatment for eosinophilic asthma. These four studies have estimated completion dates between June 2013 and January 2015.

IL-17a is the target of IgG4 ixekizumab and IgG1 secukinumab. Ixekizumab is undergoing evaluation as a treatment for moderate to severe psoriasis in three Phase 3 studies, UNCOVER-1, -2 and -3. These three studies have estimated completion dates between February 2018 and April 2019. Japanese patients with moderate to severe psoriasis are being recruited for an additional Phase 3 study of ixekizumab. A Phase 3 study of patients with active psoriatic arthritis was planned but had not yet started recruiting patients as of mid-November 2012. The safety and efficacy...
Several of the antibodies to watch in 2013 are undergoing evaluation as cancer treatments (Table 2). Seven of the ten are full-length, unmodified mAbs; inotuzumab ozogamicin is an antibody-drug conjugate (ADC), onartuzumab comprises a Fab-Fc fusion and naptumomab estafenatox is a Fab-based immunotoxin. Naptumomab estafenatox combined with interferon (IFN)-α vs. IFN-α alone in renal cell carcinoma patients was evaluated in a Phase 2/3 study (NCT00420888). Active Biotech has indicated that they expect results of the study results to be presented in the first quarter of 2013. Several Phase 3 studies of ramucirumab are due for completion in

| Sponsoring company | INN or code name | Molecular type | Target(s) | Current phase | Phase 2/3 or 3 indications |
|--------------------|------------------|----------------|-----------|---------------|---------------------------|
| Amgen              | AMG 145          | Human IgG2     | PCSK-9    | Phase 2/3     | High cholesterol          |
| Janssen            | Bevaximab        | Humanized IgG1 | Sclerostin| Phase 3       | Postmenopausal osteoporosis|
| Teva               | Reslizumab       | Humanized IgG4 | IL-5      | Phase 3       | Eosinophilic asthma       |
| Genentech          | Lebrikizumab     | Humanized IgG4 | IL-13     | Phase 3       | Asthma                    |
| Eli Lilly and Co.  | Ixekizumab (LY2439821) | Humanized IgG4 | IL-17a     | Phase 3       | Psoriasis                 |
| Novartis Pharmaceuticals | Secukinumab | Human IgG1 | IL-17a     | Phase 3       | Rheumatoid or psoriatic arthritis; ankylosing spondylitis; psoriasis |
| Millennium Pharmaceuticals | Vedolizumab | Humanized IgG1 | alpha4/beta7 integrin | Phase 3 | Ulcerative colitis; Crohn disease |
| Eli Lilly and Co.  | Tabalumab, LY2127399 | Human IgG4 | BLyS      | Phase 3       | SLE; rheumatoid arthritis, MM |
| Genentech          | Rituximab        | Humanized IgG1 | CD6       | Phase 3       | Plaque psoriasis          |
| 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         |

Table compiled from information available as of November 15, 2012. IL, interleukin; MM, multiple myeloma; PCSK9, proproteinconvertasesubtilisin/kexin type; SLE, systemic lupus erythematosus.
Table 2. Therapeutic antibodies in Phase 2/3 or Phase 3 clinical studies of cancer indications

| Sponsoring company               | INN or code name                  | Molecular type | Target(s)         | Current phase | Phase 2/3 or 3 indications               |
|----------------------------------|-----------------------------------|----------------|-------------------|---------------|------------------------------------------|
| Active Biotech                   | Naptumomabestafenox (ABR-217620) | Murine Fab immunotoxin | ST4             | Phase 2/3     | Renal cell carcinoma                     |
| ImClone LLC                      | Ramucirumab                       | Human IgG1     | VEGFR2            | Phase 3       | Gastric; liver, breast, colorectal, NSCL cancers |
| Morphotek                        | Farletuzumab                      | Humanized IgG1 | Folate receptor α | Phase 3       | Ovarian cancer                           |
| Genentech; Roche Pharma          | Obinutuzumab                      | Humanized IgG1 | CD20             | Phase 3       | Diffuse large B cell lymphoma, CLL, NHL  |
| Bristol-Myers Squibb, Abbott     | Elotuzumab                        | Humanized IgG1 | CD2              | Phase 3       | Multiple myeloma                         |
| Pfizer; UCB                      | Inotuzumabozogomicin              | Humanized IgG4 ADC | CD22            | Phase 3       | ALL; NHL                                 |
| ImClone LLC                      | Necitumumab                       | Human IgG1     | EGFR             | Phase 3       | NSCL cancer                              |
| Bristol-Myers Squibb             | Nivolumab (BMS-936558)            | Human IgG4     | PD1              | Phase 3       | NSCL cancer, renal cell carcinoma        |
| Genentech                        | Onartuzumab                       | Humanized IgG1 Fab-Fc | cMet         | Phase 3       | NSCL cancer; gastric cancer              |
| CIMAB; Laboratorio Elea S.A.C.I.F. y A | Racotumomab                      | Murine          | GM3              | Phase 3       | NSCL cancer                              |

Table compiled from information available as of November 15, 2012. ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; VEGFR2, vascular endothelial growth factor receptor 2.

2013. A Phase 3 study (NCT00917384) of ramucirumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy and the Phase 3 REACH study (NCT01140347) of ramucirumab as second-line treatment in hepatocellular carcinoma patients following first-line therapy with sorafenib have estimated completion dates in January and August 2013, respectively. Ramucirumab is also in Phase 3 studies as a treatment for breast, colorectal and non-small cell lung cancers.

Phase 3 study results of farletuzumab in ovarian cancer may be released in 2013. In March 2012, Morphotek announced that a Phase 3 study (NCT00849667) of farletuzumab in combination with carboplatin and taxane in patients with platinum-sensitive ovarian cancer in first relapse had reached its randomization target of 1080 patients; the final data collection date for primary outcome measures was estimated as September 2012. A previous Phase 3 study (NCT00738699) of farletuzumab in combination with paclitaxel therapy in patients with platinum-resistant or refractory relapsed ovarian cancer did not meet pre-specified criteria for continuation following interim futility analysis and was terminated.

The Phase 3 SQUIRE study (NCT00981058) of gemcitabine-cisplatin chemotherapy plus neicitumumab vs. gemcitabine-cisplatin chemotherapy alone in the first-line treatment of patients with Stage IV squamous non-small cell lung cancer has an estimated primary completion date of September 2013. Enrollment of the Phase 3 INSPIRE study (NCT00982111) of pemetrexed-cisplatin chemotherapy with neicitumumab compared with the chemotherapy alone in the first-line treatment of patients with Stage IV nonsquamous non-small cell lung cancer was stopped because of safety concerns related to thromboembolism in the experimental study arm. Two Phase 2 studies of neicitumumab as a treatment for solid tumors have estimated completion dates in July 2013.

mAbs looks forward to tracking the clinical study results that may be released during the year, but we also anticipate the first marketing approval of at least one therapeutic antibody in 2013. Trastuzumab emtansine, which is composed of trastuzumab (Herceptin®) conjugated to a cytotoxic drug, was given a ‘priority review’ designation by the US Food and Drug Administration; a decision on the marketing application is expected by February 26, 2013. The ADC is also undergoing regulatory review by the European Medicines Agency. Results of a Phase 2 study of trastuzumab emtansine as first-line treatment in previously untreated patients with HER2-positive metastatic breast cancer indicated that the ADC provided significant improvement in progression-free survival compared with the control treatment (trastuzumab plus docetaxel) and had a favorable safety profile.²
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