mAbs 6:4, 799–802; July/August 2014; © 2014 Landes Bioscience

Antibodies to watch in 2014
Mid-year update

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Keywords: monoclonal antibodies, clinical studies, cancer, immune-mediated disorders, Food and Drug Administration, European Medicines Agency

The commercial pipeline of monoclonal antibodies is highly dynamic, with a multitude of transitions occurring during the year as product candidates advance through the clinical phases and onto the market. The data presented here add to that provided in the extensive "Antibodies to watch in 2014" report published in the January/February 2014 issue of *mAbs*. Recent phase transition data suggest that 2014 may be a banner year for first approvals of antibody therapeutics. As of May 2014, three products, ramucirumab (Cyramza®), siltuximab (Sylvant®) and vedolizumab (Entyvio™), had been granted first approvals in the United States, and four additional antibody therapeutics (secukinumab, dinutuximab, nivolumab, pembrolizumab) are undergoing regulatory review in either the US or the European Union. Other notable events include the start of first Phase 3 studies for seven antibody therapeutics (dupilumab, SA237, etrolizumab, MPDL3280A, bavituximab, clivatuzumab tetraxetan, blinatumomab). Relevant data for these product candidates are summarized, and metrics for antibody therapeutics development are discussed.

First Approvals for Three mAbs

As of May 21, three monoclonal antibody (mAb) therapeutics had been granted their first approval in 2014. Ramucirumab (Cyramza®), siltuximab (Sylvant®) and vedolizumab (Entyvio™) were approved by the Food and Drug Administration (FDA) on April 21, April 23 and May 20, 2014, respectively. Ramucirumab, which targets human vascular endothelial growth factor receptor-2, is indicated for the treatment of advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single-agent after prior fluoropyrimidine-or platinum-containing therapy. The dosage is 8 mg/kg administered intravenously (iv) every 2 wk for these indications. Ramucirumab is undergoing regulatory review by the European Medicines Agency (EMA); it has orphan drug designation in the European Union (EU) for treatment of gastric cancer and hepatocellular carcinoma. Ramucirumab is undergoing evaluation in Phase 3 studies that are active but not recruiting patients with non-small cell lung cancer (NCT01168973), hepatocellular carcinoma (NCT01140347), colorectal cancer (NCT01183780) or breast cancer (NCT00703326).

Anti-interleukin (IL)-6 siltuximab is indicated in the US for treatment of patients with multicentric Castleman disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. Dosing is 11 mg/kg given over 1 h by iv infusion every 3 wk. On March 20, 2014, the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, which recommended the granting of a marketing authorization for siltuximab for the treatment of adult patients with MCD who are HIV negative and hHHV-8 negative. A decision on the EU marketing application by the European Commission is normally issued 67 d from adoption of the CHMP opinion. Siltuximab received orphan drug designation as a treatment for MCD in both the US and EU.

Vedolizumab is approved to treat adult patients with moderate to severe ulcerative colitis (UC) and adult patients with moderate to severe Crohn disease (CD) when one or more standard therapies (corticosteroids, immunomodulators, or tumor necrosis factor blocker medications) have not resulted in an adequate response. The humanized IgG1 mAb, which targets α4β7 integrin, is Fc-engineered to silence effector functions. On March 20, 2014, CHMP adopted a positive opinion for vedolizumab for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor antagonist and adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor antagonist.

Antibodies in First Regulatory Review

As of May 1, 2014, at total of four antibodies were undergoing their first regulatory review in the US, EU or Japan (**Table 1**). Marketing applications for secukinumab are being reviewed by both the FDA and EMA. Dinutuximab, also known as ch14.18,

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Submitted: 05/19/14; Accepted: 05/19/14; Published Online: 05/19/14
http://dx.doi.org/10.4161/mabs.29282

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

Sponsoring company	Name	Molecular format	Target	Location of regulatory review	Designations	Indication under review
Novartis	Secukinumab	Human IgG1	IL-17a	US, EU	S	Psoriasis
United Therapeutics Europe Ltd	Dinutuximab	Chimeric IgG1	GD2	EU	O (EU, US)	Brain cancer
Ono Pharma./Bristol-Myers Squibb	Nivolumab	Human IgG4	PD1	Japan	O (Japan)	Melanoma
Merck	Pembrolizumab	Humanized IgG4	PD1	US	P, BT	Melanoma

Note: Table compiled from information publically available as of May 21, 2014. Abbreviations: BT, US breakthrough therapy designation; CD, cluster of differentiation; EU, European Union; FT, US fast track designation; GD, disialoganglioside; IL, interleukin; INN, international non-proprietary name; NA, not applicable; O, orphan drug designation; P, priority review by US Food and Drug Administration; PD, programmed cell death; S, standard review by US Food and Drug Administration; US, United States.

is undergoing review in the EU as a treatment for neuroblastoma. The marketing authorization applicant is United Therapeutics Europe Ltd. Dinutuximab has been designated an orphan drug in both the EU and US.

Two programed cell death (PD)-1 immune checkpoint inhibitors, nivolumab and pembrolizumab, are in regulatory review. ONO Pharmaceutical Co., Ltd. announced their submission of the first application for manufacturing and marketing approval of nivolumab for treatment of malignant melanoma in December 2013. Nivolumab has orphan drug designation in Japan for this indication. Bristol-Myers Squibb has a strategic license agreement with ONO for development and commercialization rights outside of Japan, Korea and Taiwan, where ONO retains all rights to develop and commercialize the antibody. FDA has granted nivolumab Breakthrough Therapy designation for the treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant and brentuximab. Nivolumab is undergoing evaluation in Phase 3 studies of patients with squamous or non-squamous non-small cell lung cancer, renal cell carcinoma and squamous cell carcinoma of the head and neck, as well as early-stage studies of patients with hematological malignancies such as HL.

Anti-PD1 pembrolizumab, the mAb formerly known as lambrolizumab, is undergoing regulatory review in the US as a treatment for unresectable or metastatic melanoma. The marketing application was granted a priority review and the FDA's first action deadline is October 28, 2014. FDA granted pembrolizumab Breakthrough Therapy designation for the treatment of patients with advanced melanoma. Pembrolizumab is also undergoing evaluation in a Phase 3 study of patients with non-small cell lung cancer.

Antibodies New to Phase 3

Between October 2013 (when the "Antibodies to watch in 2014"[1] article was written) and mid-May 2014, seven antibody therapeutics entered their first Phase 3 study (**Table 2**). Three (dupilumab, SA237, etrolizumab) are for non-cancer indications and four (MPDL3280A, bavituximab, clivatuzumab tetraxetan, blinatumomab) are for cancer indications.

A Phase 3 open-label extension study (NCT01949311) to assess the long-term safety and efficacy of repeat doses of dupilumab, a human IgG4 targeting IL-4 receptor α, in adults with moderate-to-severe atopic dermatitis who have previously participated in controlled studies of dupilumab began enrolling patients by invitation only in February 2014. Another Phase 3 study, an open-label extension study (NCT02134028) to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in a previous dupilumab asthma study, was not yet open for participant recruitment as of May 15 but due to start in May 2014.

SA237 was designed to have pH-dependent binding to soluble IL-6R. The mAb will thus release bound IL-6R in the lysosome, and then recycle via the FcRn-mediated salvage pathway. A Phase 3 study (NCT02028884) to evaluate the efficacy and safety of SA237 as add-on therapy in patients with neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD) began recruiting patients in February 2014. A second Phase 3 study (NCT02073279) to evaluate the efficacy and safety of SA237 as monotherapy in patients with NMO and NMOSD is due to start in June 2014, and thus not yet open for participant recruitment as of May 15, 2014.

The safety and efficacy of etrolizumab, a humanized IgG1 mab targeting the β7 subunit of α4β7 and αEβ7 integrins, is being evaluated in a Phase 3 program in inflammatory bowel disease. A Phase 3 study (NCT02100696) of etrolizumab administered to ulcerative colitis (UC) patients who are refractory to or intolerant of tumor necrosis factor inhibitors began recruiting patients in May 2014. Two additional Phase 3 studies in UC patients, NT02118584 and NCT02136069, are due to start recruiting participants in June and September 2014, respectively.

Of the four mAbs in **Table 2** that target antigens relevant in cancer, two (MPDL3280A, bavituximab) are undergoing evaluation as treatments for non-small cell lung cancer (NSCLC). The Phase 3 "OAK" study (NCT02008227) of MPDL3280A, an Fc-engineered anti-PD-L1 antibody, compared with docetaxel in patients with locally advanced or metastatic NSCLC who have failed platinum therapy began recruiting patients in February 2014. The Phase 3 SUNRISE study (NCT01999673) of bavituximab plus docetaxel vs. docetaxel alone in patients with late-stage

Table 2. Therapeutic antibodies that recently* entered first Phase 3 clinical studies

Sponsoring company	INN or code name	Molecular format	Target(s)	Phase 3 indications
Regeneron, Sanofi	Dupilumab	Human IgG4	IL-4 receptor α	Atopic dermatitis
Chugai/Roche	SA237	Humanized IgG2; Fc engineered	IL-6 receptor	Neuromyelitis optica and NMO Spectrum Disorder
Hoffmann-La Roche	Etrolizumab	Humanized IgG1	β7 subunit of α4β7 and αEβ7 integrins	Ulcerative colitis
Genentech/ Roche	MPDL3280A	Human IgG1; Fc engineered	PD-L1	Non-small cell lung cancer
Peregrine	Bavituximab	Chimeric IgG1	Phosphatidyl-serine	Non-small cell lung cancer
Immunomedics	Clivatuzumab tetraxetan	Humanized IgG1; radio-labeled	MUC1/PAM4	Pancreatic cancer
Amgen	Blinatumomab	Murine; bispecific tandem single chain Fv	CD19, CD3	Acute lymphocytic leukemia

*December 2013-April 2014; table compiled from information publically available as of May 15, 2014. Abbreviations: CD, cluster of differentiation; Fc, crystallizable fragment; Fv, variable fragment; IL, interleukin; INN, international non-proprietary name; PD, programmed cell death

non-squamous NSCLC began recruiting patients in December 2013. Bavituximab, a chimeric IgG1 mAb that targets phosphatidylserine, was given US Fast Track designation for NSCLC.

Radioimmunoconjugate (90Y)-clivatuzumab tetraxetan plus gemcitabine is being compared with placebo plus gemcitabine in the Phase 3 PANCRIT-1 study (NCT01956812) in metastatic pancreatic cancer. The study began recruiting patients in January 2014. Clivatuzumab tetraxetan, a humanized IgG1 mAb that targets a mucin glycoprotein, was given US Fast Track and orphan drug designations for pancreatic cancer.

The bispecific T-cell engager blinatumomab targets the tumor-associated antigen CD19 and CD3, which is a receptor on T cells. The Phase 3 TOWER study (NCT02013167) of blinatumomab vs investigator's choice of chemotherapy in adult patients (18 y and older) with relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL) began recruiting patients in January 2014. The TOWER study is sponsored by Amgen. Blinatumomab is also undergoing evaluation in studies sponsored by the National Cancer Institute (NCI). Combination chemotherapy with or without blinatumomab in treating patients with newly diagnosed BCR-ABL-negative B lineage ALL is being evaluated in an NCI-sponsored Phase 3 study (NCT02003222) that is currently recruiting patients who are in the age range of 35 to 70 y. NCI is also sponsoring a Phase 3 study (NCT02101853) that will evaluate how well blinatumomab works in treating younger patients (1 y to 30 y) with relapsed B-Cell ALL. Due to start in April 2014, this study was not yet recruiting patients as of May 15, 2014.

Imminent First Phase 3 Studies

Initiation of first Phase 3 clinical studies for two mAbs, daratumumab and MEDI4736, was anticipated in May, but the studies were not yet recruiting as of May 15, 2014. A Phase 3 study (NCT02076009) will compare daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in relapsed or refractory multiple myeloma. Daratumumab (Genmab, Janssen), a human IgG1 mAb targeting CD38, was granted Breakthrough Therapy designation from FDA for the 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.

The Phase 3 PACIFIC study (NCT02125461) will evaluate the effects of MEDI4736 (MedImmune) as sequential therapy in patients with locally advanced, unresectable non-small cell lung cancer (Stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy. A human IgG1 mAb that targets PD-L1, MEDI4736 contains a triple mutation in the Fc that abrogates Fc-mediated effector function.[2]

Antibody Therapeutics Development Metrics

The development of drugs, including antibody therapeutics, is a time-consuming, risky business. For 19 antibody drugs approved in the US during the past decade (2004–2013), the average period from initiation of clinical studies to first US approval was 8.3 y. Compared with this average for all 19 products, cancer treatments had shorter (7.7 y, n = 9), and those for immune-mediated disorders had longer (9.1 y, n = 8), average development periods. A table of antibody therapeutics approved in the US and EU can be found on the *mAbs* website (www.landesbioscience.com/journals/mabs/about).

Positive outcomes from clinical development programs are not guaranteed; discontinuation due to safety, efficacy or commercial reasons may occur at any phase of the process. Antibody therapeutics are generally recognized as having higher phase transition rates compared with small molecule drugs,[3] but nonetheless discontinuations do occur. For non-murine, canonical antibodies (i.e., monospecific full-length IgG) developed in their lead therapeutic area, the Phase 1 to 2, Phase 2 to 3, Phase 3 to regulatory review, and review to approval transition rates currently are 76%,

43%, 75% and 94%, respectively. Based on this data, canonical antibody therapeutics, which are the majority of antibody therapeutics in clinical development, thus have an approval success rate of 23%. Other formats, however, may have substantially higher rates. For example, the approval success rate for antibody-drug conjugates (ADCs) is 35%, based on the current Phase 1 to 2, Phase 2 to 3, Phase 3 to regulatory review, and review to approval transition rates of 62%, 57%, 100% and 100%, respectively. It should be noted that the clinical experience with canonical antibodies is ~10 times that of ADCs (~500 vs 50 molecules), and that many antibodies have entered clinical study recently. Thus, success rates may change as additional knowledge is gained and the fates (approval or discontinuation) of these molecules are determined in the future.

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