

Antibodies to watch in 2010

Janice M. Reichert

Tufts Center for the Study of Drug Development; Boston, MA USA

Monoclonal antibodies (mAbs) are a burgeoning class of therapeutics, with more than 25 approved in countries worldwide. Novel molecules are entering clinical study at a rate of nearly 40 per year, and the commercial pipeline includes approximately 240 mAb therapeutics in clinical studies that have not yet progressed to regulatory approval or been approved. Of particular interest are the 26 mAbs that are currently at Phase 3, when safety and efficacy data critical to approval is established. Phase 3 study lengths are typically two to four years, so results for some studies might be announced in 2010, but data from others might not be presented until 2014.

This overview of the 26 candidates provides a brief description of the background and the on-going Phase 3 studies of each mAb. Additional mAbs that have progressed to regulatory review or been approved may also be in Phase 3 studies, but these, as well as Fc fusion proteins, have been excluded. Due to the large body of primary literature about the 26 candidates, only selected references are given, with a focus on recent publications and articles that were relevant to Phase 3 studies. Current as of October 2009, the results presented here will serve as a baseline against which future progress can be measured.

Introduction

Monoclonal antibodies (mAbs) are a burgeoning class of therapeutics,¹ with more than 25 approved in countries worldwide. Novel molecules are entering clinical study at a rate of nearly 40 per year, and the commercial pipeline includes approximately 240 mAb therapeutics in clinical studies that have not yet progressed to regulatory approval or been approved. Of particular interest are the 26 mAbs that are currently at Phase 3, when safety and efficacy data critical to approval is established. Phase 3 study lengths are typically 2 to 4 years, so results for some studies might be announced in 2010, but data from others might not be presented until 2014.

The 26 mAbs are currently in Phase 3 studies for a variety of indications (Tables 1, 3 and 5), although most (85%) are being evaluated primarily as treatments for cancer (13 mAbs) or immunological disorders such as rheumatoid arthritis, psoriasis and Crohn disease (9 mAbs). Four candidates (15%) are in studies as treatments for 'non-traditional' indications such as prevention of infection and neurological diseases. It is important to note that many of the 26 candidates have been (or are being) studied in a variety of indications, and may also be in studies at less advanced phases. More than half (58%) are humanized mAbs,

with six (23%) human and the remainder chimeric or murine molecules. The 26 mAbs are predominately full-size molecules; only one (naptumomab estafenatox) is an antigen binding fragment (Fab).

This overview of the 26 candidates provides a brief description of the background and the ongoing Phase 3 studies of each mAb. Additional mAbs that have progressed to regulatory review or been approved may also be in Phase 3 studies, but these, as well as Fc fusion proteins, have been excluded. Due to the large body of primary literature about the 26 candidates, only selected references are given, with a focus on recent publications and articles that were relevant to Phase 3 studies. Current as of October 2009, the results presented here will serve as a baseline against which future progress can be measured.

Anticancer Antibodies in Phase 3 Studies

A total of 13 of the 26 mAbs are undergoing evaluation in Phase 3 studies as treatments for cancer (Table 1). Nine are unmodified antibodies, three are conjugated to either a toxin or cytotoxic drug, and one is radio-labeled. Most (92%) are full-size mAbs; one is a Fab. Of the unmodified molecules, eight (89%) are IgG1 and one is IgG2. The anti-cancer mAbs currently in Phase 3 studies target a total of 11 antigens. Two mAbs each target human epidermal growth factor receptor (HER2), and insulin-like growth factor-1 receptor (IGF-1R). There is limited overlap with the targets for mAbs already on the market in the US (Table 1); only three mAbs (zalutumumab, trastuzumab-DM1 and pertuzumab) in Phase 3 target the same antigen as one of the ten products approved as of October 2009. Four of the candidates were designated by the FDA as orphan drugs, and two have FDA's fast track designation; these designations entitle the companies developing these candidates to benefits such as increased access to FDA resources, which might facilitate the clinical study phase.

Naptumomab estafenatox. Naptumomab estafenatox (ABR-217620; Active Biotech Research) is currently being studied in a Phase 2/3 study as a treatment for advanced renal cell carcinoma (RCC). The molecule targets tumor associated antigen 5T4, and comprises a Fab conjugated to a mutated variant of the superantigen staphylococcal enterotoxin E (SEA/E-120). Results of a dose-escalation, pharmacokinetic (PK) and pharmacodynamic (PD) study indicated that the monotherapy maximum tolerated dose was 15 µg/kg for renal cell carcinoma patients, and 26 µg/kg for non-small cell lung cancer patients and pancreatic cancer patients, who were administered five daily boluses in 3-month

Correspondence to: Janice M. Reichert; Email: janice.reichert@tufts.edu

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Table 1. Antineoplastic antibodies in Phase 3 studies

Sponsoring company	International non-proprietary name	Description	Indication of Phase 3 study	FDA designations for phase 3 study indication
Active Biotech Research	Naptumomab estafenatox	Anti-5T4 Fab; conj. to staph. enterotoxin A	Advanced renal cell carcinoma	
Wyeth	Inotuzumab ozogamicin	Anti-CD22 IgG4; conj. to calicheamicin	Follicular non-Hodgkin lymphoma	
Biogen idec	Galiximab	Anti-CD80 IgG1; primatized	Follicular non-Hodgkin lymphoma	
Medarex/Bristol-Myers Squibb	Ipilimumab	Anti-CTLA-4 IgG1	Advanced melanoma	FT, O
Genmab	Zalutumumab	Anti-EGFR IgG1	Head and neck cancer	FT
Morphotek	Farletuzumab	Anti-folate receptor α IgG1	Ovarian cancer	O
Genentech	Trastuzumab-DM1	Anti-HER2 IgG1 conj. to DM1	Locally advanced or metastatic breast cancer	
Genentech	Pertuzumab	Anti-HER2 IgG1	Metastatic breast cancer	
Merck, Pierre Fabre	Dalotuzumab	Anti-IGF-1R IgG1; humanized	Metastatic colorectal cancer	
Pfizer	Figitumumab	Anti-IGF-1R IgG2	Refractory lung cancer	
Wilex AG	WX-G250	Anti-carbonic anhydrase ix IgG1; chimeric	Non-metastatic renal cell carcinoma	O
Bradmer Pharmaceuticals	Anti-tenascin 131I-mAb-81C6	Anti-tenascin IgG2b; murine, radiolabeled	Glioblastoma multiforme	O
Imclone Systems/Eli Lilly	Ramucirumab	Anti-VEGF-R2 (KDR) IgG1	Metastatic gastric or gastroesophageal junction adenocarcinoma; breast cancer	

CTLA, cytotoxic T-lymphocyte-associated antigen; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; FT, fast track designation; HER2, human epidermal growth factor receptor; IGF-1R, insulin-like growth factor-1 receptor; O, orphan drug designation; International non-proprietary naming convention: -umab, human; -zumab, humanized; -ximab, chimeric or primatized; -momab, murine; Data current as of October 2009.

cycles.² Dose-limiting toxicities were fever, hypotension, acute liver toxicity and vascular leak syndrome. Fourteen patients (36%) had stable disease on day 56 of the study.

In an ongoing Phase 2/3 study (NCT00420888), the safety and efficacy of naptumomab estafenatox are being assessed in adult (18 years or older) RCC patients treated with a combination of naptumomab estafenatox and interferon (IFN) α . The results will be compared with those for patients treated with IFN α only. Patients receiving the experimental therapy are administered either 10 μ g/kg or 15 μ g/kg naptumomab estafenatox as a 5 minute intravenous (iv) bolus on four consecutive days on an 8-week cycle that will be repeated three times. These patients also receive 3, 6 and 9 million international units subcutaneous (sc) or intramuscular (im) injections of IFN α three times per week. Patients in the control arm of the study receive the IFN treatment only. The primary outcome measure is time to death assessed every 12 weeks through a maximum of 18 months of study treatment. Secondary outcome measures include progression-free survival (PFS) time, objective tumor response rate, best overall response and duration of response. The study is expected to enroll 526 patients, and the estimated completion date is August 2011.

Inotuzumab ozogamicin. Inotuzumab ozogamicin (CMC-544; Wyeth) targets CD22 on B cells, and comprises an IgG4 covalently linked to the DNA-binding cytotoxic agent

N-acetyl- γ -calicheamicin dimethyl hydrazide through the acid-labile linker 4-(4'-acetylphenoxy) butanoic acid.³ After binding to CD22, the molecule is internalized, and the calicheamicin portion then binds to the minor groove of DNA, leading to DNA-strand breaks and ultimately apoptosis. Preclinical studies indicated that the candidate significantly reduced levels of CD22 and CD55 in Daudi and Raji cells, as well as in cells obtained from patients with B cell malignancies; however, CD20 levels remained constant or increased for 12 h.⁴ These observations suggested that the anti-CD22 inotuzumab ozogamicin and anti-CD20 rituximab combination might be an efficacious treatment for B cell malignancies.

The combination of inotuzumab ozogamicin and rituximab is being compared to a drug regimen selected by investigators in an ongoing Phase 3 study (NCT00562965) of adult patients (18 years or older) with follicular non-Hodgkin lymphoma. The active comparator could be rituximab combined with cyclophosphamide, vincristine and prednisone/prednisolone or rituximab combined with fludarabine, Novantrone and dexamethasone. The primary outcome measure is assessment of efficacy as measured by PFS; demonstration of superiority of the combination of inotuzumab ozogamicin and rituximab compared to the investigator-selected drug regimen is a goal. Secondary outcome measures include assessment of safety, tolerability and population

PK of the inotuzumab ozogamicin and rituximab combination and evaluation of factors affecting drug metabolism. Enrollment is estimated at 978 patients, and a study completion date of September 2014 is estimated.

Galiximab. Galiximab (Biogen Idec), an anti-CD80 primatized IgG1, is undergoing evaluation as a treatment for NHL.⁵ The CD80 antigen is a costimulatory molecule of the B7 family. The mAb has been studied as monotherapy in a Phase 1/2 study,⁶ and in combination with rituximab in a Phase 1/2 study,⁷ of adult patients (18 years or older) with relapsed or refractory follicular lymphoma. In both studies, galiximab was dosed iv at 125, 250, 375 or 500 mg/m² weekly for four weeks. The mean serum half-life was 25.8 days for the 500 mg/m² dose.⁷ Study results indicated that galiximab could be safely administered either alone or in combination with rituximab, and provided evidence of biologic activity. No patients developed anti-drug antibodies during the study periods.

As of October 2009, one Phase 3 study of galiximab in combination with rituximab had been terminated and one Phase 3 study was open. The Targeted Antibody Therapy with Rituxan and Galiximab Efficacy Trial (TARGET study; NCT00363636) was expected to enroll 742 adult patients with relapsed or refractory follicular non-Hodgkin lymphoma; however, the study was prematurely ended in October 2009 after a strategic review of the program determined that the trial would likely not support an approval, although safety was not a concern.⁸ The clinical benefit of the combination of mAbs was to be compared to that of rituximab alone. Patients receiving the experimental treatment were administered iv galiximab at 500 mg/m² in combination with an iv rituximab dose of 375 mg/m² weekly for four weeks. Patients in the comparator arm of the study were administered the rituximab dose in combination with placebo at the same intervals.

The second Phase 3 study of the galiximab-rituximab combination (NCT00384150) involves retreatment of patients who participated in study NCT00363636, and who demonstrated a response to treatment with a time to progression of six months or greater. As of October 2009, the study is enrolling patients by invitation only; an estimated 345 adult patients are expected to participate. The treatment regime is the same galiximab-rituximab combination administered in the TARGET study. The primary outcome measures involve safety, e.g., adverse event (AE) rates, development of anti-drug antibodies during a study period of approximately two years. Secondary outcome measures include PK and further characterization of the efficacy profile of the mAb combination. Biogen Idec is evaluating options following discontinuation of the TARGET study.⁸

Ipilimumab. Ipilimumab (MDX-010; Medarex/Bristol-Myers Squibb), an anti-CTLA4 IgG1, is being studied as part of multiple regimens administered to melanoma patients, e.g., as a single agent, in combination with dacarbazine, and in combination with MDX-010 vaccine. Clinical benefit appears to be associated with “immune-related adverse events” (irAE), including severe rash, colitis, hepatitis and hypophysitis.⁹ In a Phase 1/2 study of 88 adult patients with metastatic melanoma, single doses of up to 20 mg/kg ipilimumab administered iv over 90 minutes, and multiple doses of 10 mg/kg, were well-tolerated; however, 72% of

patients reported an irAE (58% Grade 1 or 2, 14% Grade 3 or 4).¹⁰ In a Phase 2 study of ipilimumab alone or with dacarbazine, disease control and long-term survival were assessed in patients with advanced melanoma who had not previously been treated with chemotherapy agents. Patients were administered 3 mg/kg ipilimumab only every four weeks or ipilimumab with up to six 5-day courses of dacarbazine at 250 mg/m² per day. At least 10% of patients treated with either regimen were alive after follow up periods of two to more than four years; efficacy of the mAb appeared to be augmented by addition of dacarbazine.¹¹

A study of the effect of ipilimumab in adult metastatic melanoma and ovarian carcinoma patients who had previously been immunized with cancer vaccines of various types was initiated in 2000.¹² Patients were administered a single 3 mg/kg dose of ipilimumab. Extensive tumor necrosis was observed in patients who had previously been vaccinated with irradiated, autologous granulocyte-macrophage colony-stimulating factor-secreting tumor cells. These encouraging results prompted further evaluation of ipilimumab administered in combination with cancer vaccines. In a series of two trials, ipilimumab was administered in conjunction with two gp100 melanoma antigen peptides.¹³ In the first study, patients were administered 3 mg/kg iv ipilimumab and 1 mg sc of each of the two peptides. Subsequent doses at 3 week intervals included either 3 or 1 mg/kg ipilimumab. Doses were escalated to a maximum of 9 mg/kg ipilimumab in the second study. In a combined analysis, the overall objective response rate was 17%, and the majority (62%) of patients developed irAEs.

Ipilimumab is currently being evaluated in three Phase 3 studies of melanoma. A Phase 3 study of the candidate as monotherapy (NCT00636168) will evaluate efficacy in preventing recurrence of high-risk stage III melanoma after complete resection. Adult patients are administered 10 mg/kg iv ipilimumab every 21 days until week 24, then every 12 weeks until week 156 or progression, or iv placebo on the same schedule. Enrollment is estimated at 950 patients; the estimated completion date is September 2014. The combination of ipilimumab and dacarbazine is being compared to dacarbazine and placebo in an ongoing Phase 3 study (NCT00324155) of adult patients with untreated unresectable stage III or IV melanoma. Patients are administered 10 mg/kg iv ipilimumab every 3 weeks for 10 weeks, then one dose every 12 weeks starting at week 24 in combination with iv dacarbazine at 850 mg/m² every 3 weeks for 22 weeks or until disease progression. Active comparator is given on the same schedule. The primary outcome measure is overall survival (OS). Enrollment is estimated at 500 patients; the estimated completion date is December 2010.

An ongoing, 3-arm, Phase 3 study (NCT00094653) is designed to evaluate ipilimumab monotherapy, ipilimumab in combination with gp100 melanoma vaccine (MDX-1379) and MDX-1379 monotherapy in adult patients with previously treated, unresectable stage III or IV melanoma. Patients are administered ipilimumab iv at 3 mg/kg every three weeks for 4 doses alone or in combination with sc MDX-1379, or receive sc MDX-1379 alone every three weeks for four doses. The primary outcome measure is best objective response (OR) rate at 24 weeks. Enrollment is estimated at 750 patients; the estimated

completion date of January 2009 was not updated as of October 2009.

Zalutumumab. Zalutumumab (HuMax-EGFr; Genmab) is a human IgG1 targeting the epidermal growth factor receptor (EGFr). The mAb binds to EGFr domain III, and inhibits activation by restricting conformational flexibility and, upon achieving bivalent binding, separating kinase domains sufficiently to suppress EGFr transphosphorylation.¹⁴ In a Phase 1/2 study of 28 patients with advanced squamous cell carcinomas of the head and neck (SCCHN), zalutumumab was administered iv over 60 min in doses ranging from 0.15 to 8 mg/kg. On day 28, this dose was followed by 4 weekly infusions of the same amount.¹⁵ Clearance data indicated saturation of compartments at the 4 and 8 mg/kg doses. The candidate was found to be safe and well-tolerated at the doses given, with rash as the most frequently reported AE, and preliminary data on tumor response was thought to be encouraging.

Two Phase 3 studies of zalutumumab are ongoing. The efficacy of zalutumumab in combination with best supportive care (BSC) is being compared to BSC alone in a Phase 3 study (NCT00382031) of adult patients with non-curable SCCHN who have failed standard platinum-based chemotherapy. Zalutumumab is administered as individual iv doses titrated weekly in combination with BSC. The primary outcome measure is OS, with secondary measures of safety and time to progression. The estimated enrollment is 273 patients, and the estimated study completion date is March 2010. The Danish Head and Neck Cancer Group, a permanent working group of the Danish Society for Head and Neck Oncology, is sponsoring a Phase 3 study (NCT00496652) of the importance of zalutumumab to patients' outcome after primary curative radiotherapy for SCCHN. Patients are administered radiotherapy totaling 66–68 Gray (Gy) fractionated at 2 Gy per day for six days per week, and weekly cisplatin at 40 mg/m² during radiotherapy to stage 3 and 4. Patients in the experimental arm are additionally administered 8 mg/kg zalutumumab the week before start of radiotherapy and every week during radiotherapy. The aim of the study is to determine whether locoregional control increases and disease-specific survival or OS is improved with the addition of zalutumumab. Tolerability and acute and late toxicity of the treatment will also be assessed over a 5 year time frame. An estimated 600 patients will be enrolled, and the estimated completion date is November 2015.

Farletuzumab. Farletuzumab (MORAb-003; Morphotek) targets human folate receptor alpha, an antigen that is overexpressed in ovarian cancer and associated with parameters of biologically aggressive cancer. Results from preclinical evaluation in cynomolgus macaques indicated that the half-life was 239 h and 289 h as determined from two animals, and the estimated no observed adverse effect level for four female animals was greater than 136.8 mg/kg over 28 days.¹⁶ No macaque anti-drug responses were observed during the study period. Farletuzumab is currently in a Phase 2 study in patients with ovarian cancer who have relapsed after platinum-based chemotherapy and a Phase 2 study of platinum-resistant or refractory, relapsed ovarian cancer patients.

The efficacy and safety of farletuzumab in combination with carboplatin and taxane is being evaluated in a Phase 3 study (NCT00849667) of patients with platinum-sensitive ovarian cancer who are in first relapse. Patients are administered farletuzumab iv at either 1.25 or 2.5 mg/kg weekly (day 1 and week 1 of each 21-day cycle) in combination with carboplatin and taxane. Patients in the placebo comparator arm will receive 0.9% saline as placebo in combination with carboplatin and taxane. The primary outcome measure is PFS within three years. The estimated enrollment is 900 patients, and the study completion date is estimated at September 2012.

Trastuzumab-DM1. The immunoconjugate trastuzumab-MCC-DM1 (T-DM1; Genentech/ImmunoGen) targets the HER2, which is a transmembrane receptor tyrosine kinase.¹⁷ The parent trastuzumab molecule (trastuzumab) was first approved for treatment of HER2-positive (HER2⁺) metastatic breast cancer by FDA in 1998. Trastuzumab is currently approved for use with a single agent (paclitaxel, docetaxel or vinorelbine) or in combination with paclitaxel and carboplatin, or docetaxel and carboplatin.¹⁷

The second-generation molecule T-DM1 comprises trastuzumab conjugated to the maytansinoid cytotoxin DM1 through the thioether linker SMCC. Studies suggest that the immunoconjugate undergoes proteolytic degradation in the lysosome, and lysine-MCC-DM1 is a major active metabolite.¹⁸ It is important to note that clinical benefit to patients from treatment with either trastuzumab or its immunoconjugate is dependent on the accurate assessment of the patient's HER2 status. In a Phase 2 study, T-DM1 was iv administered at 3.6 mg/kg doses every three weeks to patients who had progressed on HER2-directed therapy and received chemotherapy.¹⁹ Study results indicated that the candidate was well-tolerated and had activity as a single agent for treatment of HER2⁺ metastatic breast cancer. No cardiac-specific toxicity was observed.

In the two-arm, open label, Phase 3 EMILIA study (NCT00829166), trastuzumab-MCC-DM1 is being compared to the combination of capecitabine and lapatinib in patients with HER2⁺ locally advanced or metastatic breast cancer in adult patients (18 years or older) who have received prior treatment with trastuzumab. Patients are administered iv repeating doses of trastuzumab-DM1; exact dosing information is not currently available. The primary outcome measures are incidence, nature and severity of AEs, and PFS as determined by independent review of tumor assessments. Secondary outcome measures include duration of survival, OR (confirmed at least 28 days after initial documentation of response), and duration of OR (defined as first occurrence of a documented objective response until the time of disease progression). Initiated in March 2009, the study is expected to enroll 580 patients, and has an estimated primary completion date of August 2013.

Pertuzumab. Anti-HER2 pertuzumab (RO4368451, rhMAB 2C4; Genentech) targets an epitope within the HER2 dimerization domain and thereby inhibits ligand-activated signaling from HER2/HER1 and HER2/HER3 heterodimers. The candidate has been studied in combination with docetaxel in patients with advanced solid tumors.²⁰ The Phase 1b study evaluated docetaxel

at 60 or 75 mg/m² doses administered in combination with a fixed dose of pertuzumab (1,050 mg), as well as the combination of docetaxel at two doses levels (75 or 100 mg/m²) after a fixed dose of 420 mg pertuzumab with a loading dose of 840 mg. The drugs were iv administered every three weeks. Of the combinations, a docetaxel dose of 75 mg/m² and 420 mg pertuzumab following a loading dose of 840 mg was recommended as the Phase 2 dose.

Pertuzumab was also evaluated in a Phase 2 study of patients with HER2⁺ metastatic breast cancer.²¹ This study included patients who had previously been administered 1 to 3 trastuzumab-based regimens, and had a left ventricular ejection fraction (LVEF) of 55% or greater. A total of 11 adult patients were administered iv doses of either 8 or 6 mg/kg trastuzumab and 840 mg pertuzumab, followed by 6 mg/kg trastuzumab and 420 mg pertuzumab every three weeks until 64 cycles had been given. The effects of the treatment were assessed every three and six weeks, respectively. The study results suggested that the combination therapy may have clinical benefit, but cardiac toxicity was associated with the treatment. The majority of the cardiotoxicity was asymptomatic and reversible.

The Phase 3 CLEOPATRA study (NCT00567190) is evaluating the clinical benefit of the combination of pertuzumab, trastuzumab and docetaxel compared to the combination of trastuzumab, docetaxel and a placebo in adult patients (18 years or older) with previously untreated HER2⁺ metastatic breast cancer. The study is expected to enroll 800 patients who will receive iv repeating doses of the experimental and comparator combination of drugs; exact dosing information is not currently available. The primary outcome measures are PFS as determined by independent review facility assessment. Secondary outcome measures include OS, incidence of congestive heart failure and asymptomatic LVEF events, LVEF measurements over the duration of the study, and incidence and severity of AEs and serious AEs. Initiated in December 2007, the study has an estimated primary completion date of March 2012.

Dalotuzumab. Dalotuzumab (MK-0646; Merck, Pierre Fabre) is an anti-IGF-1R IgG1 antibody. The antigen regulates cellular proliferation and apoptosis, modulates cancer cell growth, adhesion and motility, and is overexpressed in a number of cancers, e.g., colorectal and lung cancer.²² Studies have indicated that there are multilayered interactions between EGFR and IGF-1R that can contribute to the development of resistance to monotherapy directed toward these targets.²³ As a consequence, MK-0646 is being studied in combination with anti-EGFR cetuximab and chemotherapy. A Phase 2 study assessed the tolerability of MK-0646, cetuximab and irinotecan treatment in patients with metastatic colorectal cancer.²⁴ Patients were administered MK-0646 either 10 mg/kg weekly or 15 mg/kg on day 1 followed by 7.5 mg/kg every alternate week. These patients also received a loading dose of 400 mg/m² cetuximab followed by 250 mg/m² weekly, and irinotecan until disease progression was observed. The combination therapy was found to be tolerable, and no concerning overlapping toxicities were highlighted.

The efficacy of this three drug combination is under evaluation in an ongoing Phase 2/3 study (NCT00614393) of adult

patients with colorectal cancer. In experimental arm A, patients receive iv 10 mg/kg MK-0646 over 60–120 min once weekly; in experimental arm B, patients receive a loading dose of iv 15 mg/kg MK-0646 followed by 7.5 mg/kg MK-0646 once every alternate week, with placebo given on weeks when MK-0646 infusions are not scheduled. Cetuximab and irinotecan are dosed as in the Phase 2 study. The primary outcome measures include OS and PFS; secondary outcome measure is the OR rate of the experimental three-drug combination therapy compared to the OR of the cetuximab-irinotecan combination alone. Enrollment is estimated at 1,112 patients; the estimated completion date is August 2014.

Figitumumab. Anti-IGF-1R IgG2 figitumumab (CP-751,871; Pfizer) is undergoing Phase 2 studies as a treatment for lung, prostate, breast and colorectal cancers and Ewing's sarcoma. Phase 3 studies of figitumumab in combination with chemotherapy in patients with various types of lung cancers are ongoing. In a Phase 2 study of figitumumab with paclitaxel and carboplatin, previously untreated, locally advanced, or metastatic non-small-cell lung cancer (NSCLC) patients were administered 10 to 20 mg/kg of figitumumab either with or without the chemotherapy combination every three weeks for up to six cycles.²⁵ The mAb candidate in combination with paclitaxel and carboplatin was well-tolerated and the investigational combination/chemotherapy combination hazard ratio for PFS was 0.8–0.56, according to censorship, which suggests that the investigational combination demonstrated efficacy.

The combination of figitumumab and erlotinib is being compared to erlotinib alone in the Phase 3 ADVIGO 1018 study (NCT00673049) of patients with advanced NSCLC of non-adenocarcinoma histology. Erlotinib is a small molecule inhibitor of EGFR. Adult patients in the experimental arm of the study are administered 20 mg/kg iv figitumumab and 150 mg/day erlotinib; the mAb is infused on days 1 and 2 of each three week cycle. Patients in the active comparator arm of the study receive 150 mg/day erlotinib alone. The primary outcome measure is OS over a 24 month time frame; secondary outcome measures include assessment of safety and tolerability of multiple doses of the mAb, PFS and efficacy in terms of OR rate over 16 months, and level of anti-drug antibody response. The estimated enrollment is 600 patients, and the estimated completion date is June 2011.

Figitumumab in combination with paclitaxel and carboplatin was also being studied in a Phase 3 study (ADVIGO 1016; NCT00596830) of adult patients with locally advanced or metastatic NSCLC. Initiated in March 2008, enrollment of new patients was suspended in October 2009 as a result of a recommendation from the study's Data Safety Monitoring Committee. Study data on serious AEs indicated more events, including fatalities, had occurred in patients who were randomized to receive the investigational combination of drugs. Further analysis of the study data is ongoing. A Phase 3 study (ADVIGO 1017; NCT00907504) of figitumumab in combination with gemcitabine and cisplatin is scheduled to start in January 2010.

WX-G250. WX-G250 (Wilex) is a chimeric IgG1 mAb that targets carbonic anhydrase IX, an antigen that is highly expressed

in renal cell carcinoma (RCC), and may play a role in oncogenesis and tumor progression.²⁶ The candidate has been studied as monotherapy,²⁷ and in combination with low dose interleukin (IL)-2 in patients with RCC,²⁸ and is currently being evaluated as monotherapy in a Phase 3 study of RCC patients. The Phase 2 study of WX-G250 as monotherapy was conducted in 2000.²⁷ Adult patients (42 to 77 years of age) with primary RCC were administered weekly iv doses of 50 mg WX-250 for 12 weeks; those with stable disease or response could be administered treatment for eight additional weeks. The treatment was well-tolerated and the median survival was 15 months.

The ongoing Phase 3 ARISER study (NCT00087022) is evaluating adjuvant WX-G250 treatment compared to placebo in patients with clear cell RCC and high-risk of recurrence. Adult patients are administered a loading dose of 50 mg iv WX-250 over 15 min in week 1 and weekly doses of 20 mg during weeks 2–24. A total of 864 patients have been recruited. Primary outcome measures are evaluation of disease-free survival and OS. The estimated completion date is September 2013. A radiolabeled (iodine-124) version of WX-250 was also studied for pre-surgical detection of RCC (NCT00606632).

mAb 81C6. The radiolabeled (iodine-131), murine anti-tenascin mAb 81C6 (Bradmer Pharmaceuticals) is undergoing evaluation as a treatment for malignant glioma. The I-131 mAb is administered into a surgically created resection cavity (SCRC), and treatment is followed by external beam radiotherapy and chemotherapy. In a pilot study, the dose of radioactivity delivered was patient-specific, and designed to achieve a 44-Gy boost to the 2-cm SCRC margin in adult patients with newly diagnosed malignant gliomas.²⁹ Patients were further treated with external beam radiotherapy (55–60 Gy approximately one month after administration of I-131 81C6) and chemotherapy (temozolomide, lomustine, irinotecan and etoposide administered in a serial manner) for 10–12 months. The study regimen was well-tolerated, and median OS for patients with glioblastoma multiforme was 90.6 weeks after a median follow-up time of 151 weeks.

A similar regimen is being evaluated in the ongoing Phase 3 GLASS-ART study (NCT00615186) of I-131 81C6 in combination with external beam radiation and temozolomide compared to treatment with external beam radiation and temozolomide only in adult patients with newly diagnosed glioblastoma multiforme. The primary outcome measure is OS and the secondary outcome measure is PFS. The estimated enrollment is 760 patients, and the estimated completion date is December 2013.

Ramucirumab. Ramucirumab (IMC-1121B; ImClone Systems/Eli Lilly), an anti-vascular endothelial growth factor receptor 2 (VEGFR2) IgG2, is currently in Phase 2 studies as a treatment for NSCLC, RCC and melanoma, as well as prostate, liver, colorectal, ovarian, fallopian tube, peritoneal and brain cancer. The mAb is currently in Phase 3 studies of patients with breast cancer and gastric or gastro-esophageal junction adenocarcinoma. Limited results from Phase 1 or 2 studies have been reported. Phase 1 dose-escalating studies have been performed in patients with advancing solid malignancies who were administered 6 to 20 mg/kg ramucirumab iv weekly, or every 2 or 3 weeks.³⁰ The mAb was well-tolerated, but dose-limiting toxicities

were observed in the patients who received the highest dose levels (16 mg/kg weekly doses and 20 mg/kg administered every 3 weeks). A good correlation was observed between dose level and anti-vascular effect.

Two Phase 3 studies of ramucirumab are currently recruiting participants. In a placebo-controlled Phase 3 study (NCT00703326), ramucirumab in combination with docetaxel is being compared to docetaxel only in previously untreated patients with HER2-negative, unresectable, locally-recurrent or metastatic breast cancer. On day 1, adult patients are administered iv docetaxel at 75 mg/m² as a 1 h infusion followed by either iv ramucirumab at 10 mg/kg or placebo as a 1 h infusion. Each cycle is repeated every 21 days during the study period. The primary outcome measure is PFS, and the secondary outcome measure is OS, in a time-frame of 36 months. The estimated enrollment is 1,113 patients, and the estimated completion date is August 2015.

Ramucirumab is also being evaluated in a placebo-controlled Phase 3 study (NCT00917384) of patients with metastatic gastric or gastroesophageal junction adenocarcinoma. The mAb candidate is administered iv at 8 mg/kg doses every two weeks in combination with appropriate treatment (best supportive care) selected by the investigator. Outcomes of patients in the experimental arm of the study will be compared to those of patients who received placebo and BSC. The primary outcome measure is OS, and the secondary outcome measures are PFS, OR rate, duration of response, quality of life, safety profile, PK profile, and immunogenicity, over a 40 month time frame. The estimated enrollment is 615 patients, and the estimated completion date is November 2012.

Immunological Antibodies in Phase 3 Studies

Of the 26 mAbs, a total of nine candidates are undergoing evaluation in Phase 3 studies as treatments for immunological disorders (Table 3). All the candidates are unmodified, full-size antibodies; eight (89%) are IgG1 and one (11%) is IgG4. The mAbs in Phase 3 studies for immunological diseases target a total of seven antigens. Two mAbs each target CD3 and IL5. As with the anti-cancer mAbs, there is limited overlap with the targets for mAbs already on the market in the US products or undergoing FDA review (Table 4). Otelixizumab and teplizumab are humanized mAbs that both target CD3, which is also targeted by muromonab-CD3 (a murine mAb) that was approved in the US in 1986. In addition, ocrelizumab targets CD20, which is also targeted by the approved product rituximab. Four of the candidates were designated by the FDA as orphan drugs, and two have FDA's fast track designation.

Vedolizumab. Vedolizumab (Takeda/Millennium), an anti-alpha4beta7 integrin mAb, is being evaluated as a treatment for Crohn disease and ulcerative colitis (UC). Expression of the alpha4beta7 integrin is restricted to subsets of leukocytes; vedolizumab selectively inhibits binding of these leukocytes to the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on endothelial cells, and fibronectin.³¹ In a placebo-controlled trial initiated in December 2000, adult patients with active UC were

administered 0.5 mg/kg, 2.0 mg/kg or placebo on days 1 and 29.³² At six weeks, the clinical remission rates were 33, 32 and 14%, respectively, for the three cohorts of patients. The same protocol was utilized in a study of patients with Crohn disease.³³ As assessed on day 57, clinical responses were 53, 49 and 41% for patients who received 2.0, 0.5 mg/kg vedolizumab and placebo, respectively.

Vedolizumab was also evaluated in a placebo-controlled Phase 2 study of patients with active UC who were administered four doses of drug over 85 days and then monitored for 253 days.³⁴ Patients were iv administered the drug at 2, 6 or 10 mg/kg doses, or placebo, on days 1, 15, 29 and 85. From day 29 to day 253, the percentage of patients who responded was consistently greater than 50% as assessed by partial Mayo score (a noninvasive outcome measure); placebo responses were in the 22–33% range.

Three ongoing Phase 3 studies are now evaluating the safety and efficacy of vedolizumab in UC and Crohn disease. In the placebo-controlled GEMINI I study (NCT0078718), adult patients (18 to 80 years) with moderate to severe UC are administered vedolizumab (exact dosing information not provided) at weeks 0, 2, 6 and then 4- or 8-week intervals for up to 1 year. The primary outcome measures are proportion of patients with clinical response at week 6, and clinical remission at week 52. Enrollment is estimated at 826; the estimated completion date is October 2011. The placebo-controlled GEMINI II study (NCT00783692) has a similar design, and will establish the safety and efficacy of vedolizumab for the induction and maintenance of clinical response and remission in patients with moderate to active Crohn disease. An estimated 1,059 patients will participate; the estimated completion date is September 2011. GEMINI III (NCT00790933) is an open-label study of vedolizumab to assess long-term safety and efficacy in patients with UC and Crohn disease. Adult patients are administered vedolizumab every four weeks for up to 100 weeks. The primary outcome measures include the determination of AEs and serious AEs. Enrollment is estimated at 1,500 patients; the estimated completion date is October 2013.

Belimumab. The anti-B lymphocyte stimulator (BLyS) IgG1 belimumab (Human Genome Sciences, GlaxoSmithKline) is currently in Phase 3 studies as a treatment for systemic lupus erythematosus (SLE). BLyS is a member of the tumor necrosis factor cytokine family; the soluble ligand binds to any of three receptors on B lymphocytes, and contributes to differentiation, homeostasis and selection of these cells.³⁵ The antigen is overexpressed in SLE patients, and changes in BLyS concentration correlate with increased disease activity. Safety, tolerability, biologic activity and efficacy of the mAb in combination with standard of care were assessed in a Phase 2 placebo-controlled study of adult patients with active SLE.³⁶ Patients were iv administered 1, 4 or 10 mg/kg belimumab or placebo over 2 hours on days 0, 14 and 28, and then every 28 days for 52 weeks, in addition to the standard of care for SLE. Belimumab was found to be well-tolerated and biologically active. The reduction of SLE disease activity or flares in the patients administered belimumab compared to those who received placebo was not significant; however, response was significantly better in serologically active SLE patients who received belimumab.

The safety, tolerability and impact on quality of life of treatment of SLE patients with belimumab were evaluated in the placebo-controlled Phase 3 BLISS-52 study (NCT00424476). Adult patients were administered 1 or 10 mg/kg belimumab or placebo on days 0, 14, 28 and every 28 days through 48 weeks in addition to standard therapy. The primary outcome measure was the percentage of subjects with a reduction of greater than or equal to four points from baseline in their safety of estrogens in lupus erythematosus national assessment (SELENA)-systemic lupus erythematosus disease activity index (SLEDAI) score at 52 weeks. A total of 865 patients are enrolled. Initiated in early 2007, this study was due for completion in mid-2009; no published results were available as of October 2009.

The regimens of belimumab administered at 1 or 10 mg/kg doses on the same dosing schedule for 72 weeks duration were also assessed in the Phase 3 BLISS-76 study (NCT00410384). Adult SLE patients are evaluated at 52 and 76 weeks for a reduction of greater than or equal to four points from baseline in their SELENA-SLEDAI score (primary and secondary outcome measures, respectively). Enrollment is estimated at 819 patients, and the estimated study completion date is February 2010. Preliminary results of the BLISS-76 study have indicated that the 10 mg/kg dose met the primary efficacy endpoint.³⁷ The proportion of patients with at least a four point reduction in SELENA-SLEDAI score by week 52 was 46.9%, 42.8% and 35.6% for patients who received 10 mg/kg, 1 mg/kg and 0 mg/kg (placebo) belimumab, respectively. The results were statistically significant for the 10 mg/kg dose ($p = 0.0062$ compared to placebo). Patients who participated in either the BLISS-52 or -76 are eligible to enroll in Phase 3 studies (NCT00712933 and NCT00724867) that will evaluate the long-term safety and efficacy in SLE patients. Both studies have an estimated completion date of December 2010.

Ocrelizumab. Ocrelizumab (Genentech), an anti-CD20 IgG1 mAb, is currently in three Phase 3 studies of patients with rheumatoid arthritis and a Phase 3 study of patients with SLE. CD20 is the target of four marketed antibodies (Table 2), although three of the four are treatments for only cancer. Rituximab is the exception; the product is FDA-approved for rheumatoid arthritis (RA) and used off-label for SLE.³⁸ The effects of ocrelizumab administration on RA patients with moderate-to-severe disease who were already receiving methotrexate (MTX) were examined in a Phase 1/2 ACTION study.³⁹ In the Phase 2 portion of the study, patients were randomized into a total of six cohorts that received 10, 50, 200, 500 or 1,000 mg infusions of ocrelizumab or placebo on day 1 and day 15. At week 24, the American College of Rheumatology (ACR) criteria for 20% improvement was met by 42, 35, 45, 50 and 50% of patients who received the 10, 50, 200, 500 or 1,000 mg doses, respectively. In contrast, 22% of patients who received placebo had an ACR20 response rate. At 72 weeks, serious AEs had been reported by 17.9 and 14.6% of patients who received drug and placebo, respectively.

Various regimens of ocrelizumab treatment are being evaluated in three ongoing Phase 3 studies of RA patients. In the STAGE (NCT00406419) and SCRIPT (NCT00476996) placebo-controlled studies, adult patients are iv administered 200

Table 2. FDA approved antineoplastic monoclonal antibodies

Generic name	Trade name	Target and type	Indication under review or first approved	FDA approval year
Ofatumumab	Arzerra	Anti-CD20; human IgG1	Chronic lymphocytic leukemia	2009
Tositumomab-I131	Bexxar	Anti-CD20; murine IgG2a	Non-Hodgkin lymphoma	2003
Ibritumomab tiuxetan	Zevalin	Anti-CD20; murine IgG1	Non-Hodgkin lymphoma	2002
Rituximab	Rituxan	Anti-CD20; chimeric IgG1	Non-Hodgkin's lymphoma	1997
Gemtuzumab ozogamicin	Mylotarg	Anti-CD33; humanized IgG4	Acute myeloid leukemia	2000
Alemtuzumab	Campath-1H	Anti-CD52; humanized IgG1	Chronic myeloid leukemia	2001
Panitumumab	Vectibix	Anti-EGFR; human IgG2	Colorectal cancer	2006
Cetuximab	Erbix	Anti-EGFR; chimeric IgG1	Colorectal cancer	2004
Trastuzumab	Herceptin	Anti-HER2; humanized IgG1	Breast cancer	1998
Bevacizumab	Avastin	Anti-VEGF; humanized IgG1	Colorectal cancer	2004

Note: Information current as of October 1, 2009; CD, cluster of differentiation; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; VEGF, vascular endothelial growth factor.

Table 3. Antibodies in Phase 3 studies of immunological disorders

Sponsoring company	International non-proprietary name	Description	Indication of Phase 3 study	FDA designations for Phase 3 study indication
Millennium/Takeda	Vedolizumab	Anti-alpha4beta7 integrin IgG1	Moderate-to-severe Crohn disease; ulcerative colitis	
Human Genome Sciences, GlaxoSmithKline	Belimumab	Anti-B-lymphocyte stimulator IgG1	Systemic lupus erythematosus	FT
Genentech	Ocrelizumab	Anti-CD20 IgG1	Rheumatoid arthritis; systemic lupus erythematosus	
Immunomedics/UCB	Epratuzumab	Anti-CD22 IgG1	Systemic lupus erythematosus	FT
Tolerx	Otelixizumab	Anti-CD3 IgG1	Type 1 diabetes mellitus	O
Macrogenics, Eli Lilly	Teplizumab	Anti-CD3 IgG1	Type 1 diabetes mellitus	O
Abbott	Briakinumab	Anti-IL12/23 IgG1	Plaque psoriasis	
GlaxoSmithKline	Mepolizumab	Anti-IL5 IgG1	Hypereosinophilic syndrome	O
Ception Therapeutics	Reslizumab	Anti-IL5 IgG4	Eosinophilic esophagitis	O

CD, cluster of differentiation; FDA, US Food and Drug Administration; FT, fast track designation; O, orphan drug designation; International non-proprietary naming convention: -umab, human; -zumab, humanized; Data current as of October 2009.

or 500 mg ocrelizumab or placebo on days 1 and 15. A repeat course is administered at weeks 24 and 26, and the primary outcome measure (percentage of patients with ACR20 response) is assessed at weeks 24 and 48. The difference between the two studies is the patient population studied—the STAGE study includes patients with active RA who are continuing MTX treatment, and the SCRIPT study includes patients with active RA who do not have a response to anti-tumor necrosis factor α . Each study has an estimated enrollment of 1,000 patients, and estimated completion dates in 2010.

Ocrelizumab is also being evaluated in patients with RA who have inadequate response to MTX in the ongoing, placebo-controlled Phase 3 FEATURE study (NCT00673920). Adult patients are iv administered 200 mg ocrelizumab on days 1 and 15, 400 mg ocrelizumab on day 1 and placebo on day 15, or placebo on days 1 and 15. All patients receive concomitant MTX. The primary outcome measure is the percentage of patients with

ACR20 response at week 24. Enrollment is estimated at 300 patients; the estimated completion date is November 2011.

The safety and efficacy of two doses of ocrelizumab is being evaluated in Phase 3 studies of patients with active SLE who do not have moderate-to-severe glomerulonephritis (BEGIN study; NCT00539838). Patients 16 years or older are administered drug or placebo in combination with immunosuppressive medication and corticosteroids; information on the exact dose of ocrelizumab was not provided. The primary outcome measures include the percentage of patients who achieve a complete or partial response at week 48. Estimated enrollment in the BEGIN study is 423, and the estimated completion date is October 2009.

Two additional Phase 3 studies of ocrelizumab as a treatment for patients with RA (FILM study; NCT00485589) or lupus nephritis (BEGIN study; NCT00539838) were interrupted in October 2009 after a safety review of data revealed an apparent imbalance in opportunistic infections among

Table 4. Monoclonal antibodies in FDA review or approved as treatments for immunological indications

Generic name	Trade name	Target and type	Indication under consideration or first approved	FDA approval year
Eculizumab	Soliris	Anti-C5; humanized IgG2/4	Paroxysmal nocturnal hemoglobinuria	2007
Muromonab-CD3	Orthoclone Okt3	Anti-CD3; murine IgG2a	Reversal of kidney transplant rejection	1986
Basiliximab	Simulect	Anti-IL2R; chimeric IgG1	Prevention of kidney transplant rejection	1998
Daclizumab	Zenapax	Anti-IL2R; humanized IgG1	Prevention of kidney transplant rejection	1997
Efalizumab	Raptiva	Anti-CD11a; humanized IgG1	Psoriasis	2003*
Tocilizumab	Actemra*	Anti-IL6R; humanized IgG1	Rheumatoid arthritis	Pending
Ustekinumab	Stelara	Anti-IL12/23; human IgG1	Psoriasis	2009
Canakinumab	Ilaris	Anti-IL1 β ; human IgG1	Muckle-Wells syndrome	2009
Omalizumab	Xolair	Anti-IgE; humanized IgG1	Asthma	2003
Natalizumab	Tysabri	Anti- α 4 integrin; humanized IgG4	Multiple sclerosis	2004
Golimumab	Simponi	Anti-TNF α ; human IgG1	Rheumatoid and psoriatic arthritis, ankylosing spondylitis	2009
Certolizumab pegol	Cimzia	Anti-TNF α ; humanized Fab, pegylated	Crohn disease	2008
Adalimumab	Humira	Anti-TNF α ; human IgG1	Rheumatoid arthritis	2002
Infliximab	Remicade	Anti-TNF α ; chimeric IgG1	Crohn disease	1998

Note: Information current as of October 1, 2009; *Proposed trade name; *Voluntarily withdrawn from US market in April 2009; C5, complement 5; CD, cluster of differentiation; FDA, US Food and Drug Administration; IL, interleukin; TNF, tumor necrosis factor.

Table 5. Antibodies in Phase 3 studies as treatments for non-traditional indications

Sponsoring company	International non-proprietary name	Description	Indication of Phase 3 study	FDA designations for Phase 3 study indication
Biosynexus	Pagibaximab	Anti-lipoteichoic acid IgG1	Prevention of staphylococcal sepsis in very low birth weight neonates	O
Lilly	Solanezumab	Anti-amyloid beta IgG1	Alzheimer disease	
Wyeth, Janssen	Bapineuzumab	Anti-amyloid beta IgG1	Alzheimer disease	FT
Pfizer	Tanezumab	Anti-nerve growth factor IgG2	Pain associated with osteoarthritis of the knee or hip; lower back pain	

FDA, US Food and Drug Administration; FT, fast track designation; O, orphan drug designation; International non-proprietary naming convention: -zumab, humanized; -ximab, chimeric or primatized; Data current as of October 2009.

ocrelizumab-treated patients in these clinical trials. (Biogen Idec SEC report) Based on the review, the FILM study in MTX-naïve RA patients was placed on clinical hold. The BELONG study was closed.

Epratuzumab. Epratuzumab (hLL2; Immunomedics) targets CD22 on B cells. The candidate has been in clinical studies for SLE and a variety of cancer indications since 1997. Epratuzumab has been studied as a treatment for B cell malignancies such as acute lymphoblastic leukemia, non-Hodgkin lymphomas, and Waldenström macroglobulinemia. The technetium-99 labeled form of epratuzumab has also been studied for the detection and staging of patients with non-Hodgkin lymphoma. However, the current commercial focus is on development of the candidate as a treatment for SLE.

In a preliminary open label Phase 2 study, 12 adult patients (18 years or older) with moderately active SLE were administered 360 mg/m² epratuzumab iv every two weeks for four doses, and were evaluated at weeks 6, 10, 18 and 32.⁴⁰ The drug was well

tolerated and improvement was observed in all patients for at least 12 weeks. Two Phase 3 studies (NCT00111306, NCT00383214) of epratuzumab as a treatment for SLE were initiated in 2005. The studies were terminated early due to interruptions in the supply of epratuzumab, but the data collected was reported in 2008.⁴¹ Patients were administered 360 (n = 34) or 720 (n = 10) mg/m² epratuzumab or placebo (n = 30) for up to four cycles. The first treatment cycle included four weekly infusions at weeks 0, 1, 2 and 3, while subsequent cycles included two infusions administered one week apart every 12 weeks. Patients were followed for at least six months. The proof-of-concept analysis suggested that treatment with drug resulted in clinically meaningful efficacy, although the number of patients who were administered epratuzumab as per the protocol was limited.

An open label, retreatment Phase 3 study (NCT00383513) of patients who participated in either of the two terminated Phase three studies is currently ongoing. Adult patients are administered 360 mg/m² iv doses of epratuzumab on 12 week maintenance

cycles beginning with two consecutive weekly infusions. The primary outcome measure is assessment of safety over 4 years, and the secondary outcome measures include assessment of efficacy, tolerability and immunogenicity over 4 years. The estimated enrollment is 30 patients and the estimated completion date is February 2010.

Otelixizumab. Otelixizumab (TRX4, ChAglyCD3; Tolerx, GlaxoSmithKline), a humanized, aglycosylated IgG1 mAb, targets CD3 on T cells. Aglycosylation reduces binding of the antibody to Fc receptors (FcR) and complement. Studies on the mechanism of action of antibody immunotherapy on clonal islet reactive T cells suggested that the anti-CD3 ChAglyCD3 antibody modulated surface expression of CD3 and T cell activity, but did not deplete auto-reactive cells.⁴² Modulation of cytokine release was moderate and selective, with an observed decrease in release of IFN γ and IL-5 and an increase in secretion of IL-10. Type 1 diabetes mellitus is an autoimmune disease characterized by destruction of pancreatic islet beta cells and subsequent reduction in insulin production; preclinical and clinical studies of anti-CD3 antibodies have demonstrated a protective effect.⁴³

In a placebo-controlled Phase 2 study initiated in 2000, otelixizumab was administered to a total of 80 patients (12 to 39 years) with type 1 diabetes mellitus of recent onset.⁴⁴ The first nine patients received 24 mg otelixizumab iv over 2–4 hours followed by 8 mg infusions on each of the next five days. Four patients developed severe headache or vomiting, and so the remaining 71 patients received 8 mg iv otelixizumab on each of six days. Patients were followed for 18 months. Residual beta-cell function was found to be better maintained in the treatment compared to the placebo cohorts at 6, 12 and 18 months. Insulin dose did not increase in the treatment cohort, whereas the dose did increase in the placebo cohort. Transient side effects were reported by patients who received otelixizumab, e.g., fever after the start of infusions, rash and acute mononucleosis-like syndrome.

Otelixizumab is undergoing evaluation in the Phase 3 DEFEND-1 study (NCT00678886) as a treatment for patients with newly diagnosed Type 1 diabetes mellitus. The objective of the study is to determine if an 8-day series of infusions will lead to improvement in insulin secretion compared to placebo. Information on the amount of otelixizumab in a dose was not provided. Patients between the ages of 12 and 45 years are eligible to participate in the study. After treatment with the regimen of either otelixizumab or placebo, patients will have follow-up visits weekly for the first month, biweekly for the following three months, and then monthly visits for the remainder of one year. An additional three visits will occur in the second year of the study. The primary outcome measure is the amount of C-peptide during a mixed meal stimulation test as assessed at 12 months, and the secondary outcome measure is average daily insulin use, HbA1c, and incidence of abnormal blood glucose level. The estimated enrollment is 240 patients, and the estimated study completion date is December 2010.

Teplizumab. Teplizumab [MGA031, hOKT3 γ 1 (Ala-Ala); MacroGenics, Eli Lilly] targets CD3, and has reduced binding to FcR as a consequence of two single amino acid substitutions to the Fc portion of the molecule. This feature was expected to

reduce the T cell activation and cytokine release observed with a murine anti-CD3 antibody.⁴³ In a Phase 1/2 study initiated in May 1999, patients (7.5 to 30 years) with recently diagnosed type 1 diabetes were randomized into four cohorts. The first cohort of 12 patients were administered iv doses of teplizumab daily for 14 days according to the following schedule: 1.42 μ g/kg on day 1, 5.67 μ g/kg on day 2, 11.3 μ g/kg on day 3, 22.6 μ g/kg on day 4, and 45.4 μ g/kg on days 5 to 14.⁴⁵ The second cohort of 9 patients were administered higher iv doses of teplizumab (0.46 mg/m² on day 1, 0.919 mg/m² on day 2, 1.818 mg/m² on days 3 to 12) due to the development of anti-idiotypic antibodies in the first group of patients.⁴⁶ Two control groups of 12 and nine patients did not receive antibody treatment; the study was not placebo-controlled. Preliminary results were reported for the cohorts of 12 patients who were followed for 1 year, when 67% (9/12) of patients who were administered drug maintained or improved insulin production compared to 17% (2/12) of patients who did not receive the mAb treatment.⁴⁵ The most common side effects were mild and moderate fever and anemia (9/12 patients), as well as rash (7/12 patients). Results for all patients indicated that treatment with a single course of teplizumab can prevent loss of insulin production for 1 year, and the effects persist for at least two years.⁴⁶

In a Phase 2b study of patients who had been diagnosed with type 1 diabetes recently (within six weeks of enrollment), teplizumab was administered iv over 30 min to six patients according to the following schedule: 0.46 mg/m² on day 1, 0.919 mg/m² on day 2, 1.818 mg/m² on days 3 to 12.⁴⁷ However, the frequency and severity of AEs in this study compared to the earlier Phase 1/2 study prompted a hold; subsequent examination of the antibody preparation indicated that the protein concentration was approximately 40% greater compared to what had been administered previously. The study was terminated, but the patients who received drug were followed for up to five years. The results supported the previous finding of a trend toward reduced loss of C-peptide and lower use of insulin over two years in patients administered teplizumab, and suggested that treatment preserved insulin production for up to five years. However, the increased doses were associated with greater AEs without improved efficacy.⁴⁷

The safety and efficacy of teplizumab as a treatment for recent-onset type 1 diabetes is currently being evaluated in a Phase 2/3 study, an extension of this study, as well as a Phase 3 study. In the placebo-controlled, Phase 2/3 Protégé study (NCT00385697), three dosing regimens of teplizumab are administered to cohorts of patients who are 8 to 35 years of age. Patients are administered iv doses daily for 14 days, and receive two courses of this treatment. Information on the exact doses was not provided. The primary outcome measures include assessment of total daily insulin usage and HbA1c levels over 12 months, and secondary outcome measures include C-peptide secretory responses over 24 months. Enrollment was 554 patients, and the estimated completion date is June 2011. Patients who completed the Protégé study were eligible for the Protégé extension study (NCT00870818), in which an additional two courses of treatment are administered and patients are followed for up to three years. The primary objective of the study is assessment of long-term safety; the secondary objective

is assessment of long-term efficacy. Enrollment is by invitation, and an estimated 530 patients will participate. The estimated completion date is June 2014. The Phase 3 Protégé Encore study (NCT00920582) has the same design as the Protégé study. An estimated 400 patients will participate, and the estimated completion date is June 2012.

Briakinumab. The anti-IL-12/23 mAb briakinumab (ABT-874; Abbott) is currently being evaluated in five Phase 3 studies of patients with moderate-to-severe chronic plaque psoriasis. Originally isolated from a phage display library, the mAb targets the p40 subunit that is common to both IL12 and IL23.⁴⁸ The safety and efficacy of briakinumab as a treatment for moderate-to-severe chronic plaque psoriasis was evaluated in a placebo-controlled Phase 2 study.⁴⁹ Adult patients were administered placebo, or single or multiple subcutaneous (sc) doses of briakinumab on the following schedules: one dose of 200 mg at week 0, 200 mg every week for 4 weeks, 100 mg every other week for 12 weeks, 200 mg every other week for 12 weeks, 200 mg every week for 12 weeks. The percentage of patients who achieved a 75% reduction in their psoriasis area and severity index (PASI) at week 12 ranged from 63 to 93% for the five cohorts that received briakinumab compared to 3% for the cohort that received placebo. Treatment was well-tolerated; the most common AE was injection site reaction.

The safety and efficacy of two dosing regimens of briakinumab were evaluated in a placebo controlled Phase 3 study (NCT00570986). In one arm of the study, adult patients with moderate-to-severe chronic plaque psoriasis were administered 200 mg briakinumab at week 0 and 4, 100 mg at week 8; after re-randomization at week 12, patients received 100 mg every four weeks. Placebo was administered on the same schedule. In the second active comparator arm, patients were administered 100 mg briakinumab every 12 weeks. The primary outcome measures were the proportion of patients who achieved a Physician's Global Assessment (PGA) of clear or minimal at weeks 12 and the proportion of those who maintained this score at week 52, and the number of patients who achieved a 75% reduction in their PASI score from baseline to week 12. A total of 1,465 patients participated, and the study was completed in mid-2009; however, no published results were available as of October 2009.

The effects of briakinumab were compared to those of etanercept in two placebo-controlled Phase 3 studies (NCT00691964, NCT00710580). Adult patients with moderate-to-severe chronic plaque psoriasis were administered 200 mg briakinumab at week 0 and 4, and 100 mg at week 8. Patients in the active comparator arm received sc injections of 50 mg etanercept twice weekly, and those in the placebo arm received sc injections on the same schedules. The primary outcome measures were the proportion of patients who achieved a PGA of clear or minimal at week 12 and the number of patients who achieved a 75% reduction in their PASI score from baseline to week 12. A total of 347 and 350 patients participated in NCT00691964 and NCT00710580, respectively. Both studies were complete as of mid-2009, but no results had been published as of October 2009. Long-term safety, efficacy and tolerability are being assessed in an ongoing Phase 3 open label continuation study (NCT00626002) of patients

who completed a preceding psoriasis study of briakinumab. Adult patients are administered 100 mg briakinumab sc every 4 weeks for approximately 160 weeks. An estimated 2,000 patients are enrolled, and the study has an estimated completion date of December 2010.

The safety and efficacy of briakinumab are being compared to those of MTX in an ongoing Phase 3 study (NCT00679731) of patients with moderate-to-severe plaque psoriasis. Adult patients are administered regimens of either 200 mg sc briakinumab at week 0 and 4, followed by 100 mg at week 8 and every four weeks thereafter or MTX at doses of 5 to 25 mg weekly. The primary outcome measures are the proportion of patients who achieve a 75% reduction in their PASI score from baseline to week 24 and week 52, and the proportion of patients who achieve a PGA of clear or minimal at week 24 and 52. A total of 317 patients are enrolled and the estimated primary completion date is November 2009.

Mepolizumab. Mepolizumab (SB-240563; GlaxoSmithKline), an anti-IL5 IgG1 mAb, is undergoing evaluation in an open label Phase 3 study as a treatment for hypereosinophilic syndrome (HES), which consists of heterogeneous autoimmune disorders characterized by elevated levels of eosinophils that damage organs and tissues.⁵⁰ IL-5 regulates eosinophil development and may contribute to the pathogenesis of the disease, thus making the cytokine an attractive target for antibody therapeutics. The US FDA has designated mepolizumab an orphan drug for HES.

In a placebo-controlled Phase 2 study of the safety and efficacy of mepolizumab, adult HES patients (18 to 85 years) were first stabilized clinically on prednisone (20 to 60 mg per day) or equivalent monotherapy.⁵¹ Patients were then administered either 750 mg mepolizumab (n = 43) or placebo (n = 42) iv every 4 weeks during a 36 week period, with the last dose at week 32. The dose of prednisone or equivalent was adjusted as required based on the blood eosinophil count and HES symptoms. Reduction of prednisone dose to 10 mg or less per day for eight or more consecutive days, which was the primary end point, was achieved by 84% of patients administered mepolizumab and 43% of those who received placebo. Serious AEs occurred in 7 and 5 patients in the mepolizumab and placebo cohorts, respectively.

HES patients who participated in the Phase 2 study were eligible to enroll in an ongoing, open label extension Phase 3 study (NCT00097370) to evaluate the long term safety, efficacy and optimal dosing frequency of 750 mg mepolizumab. The primary outcome measure is the frequency of all AEs. Secondary outcome measures include maintenance of durable effect on prednisone dose use, durable effect in reducing blood eosinophil count, and proportion of patients achieving a prednisone use level of 10 mg or less for 2 or 3 month periods. Enrollment is estimated at 85 patients, and the estimated completion date is December 2009. In addition, access to mepolizumab is being made available to patients with life-threatening HES, and who have failed at least 3 standard therapies, through a compassionate use Phase 3 study (NCT00244686). Patients 12 years or older are eligible to participate in the study. The primary outcome measure is the incidence and severity of AEs, and the secondary outcome measures are changes in end organ assessments, peripheral blood

eosinophil levels, disease control and HES medications. An estimated 75 patients will enroll; the estimated completion date is March 2011.

Reslizumab. Reslizumab (SCH55700, CTx55700; Ception Therapeutics), an anti-IL5 mAb, was originally developed by Schering Plough via grafting of human IL5 antigen recognition sites of a rat antibody onto consensus regions of a human IgG4 framework.⁵² The mAb has US orphan designation as a treatment for eosinophilic esophagitis (EE) in pediatric patients, and is currently undergoing evaluation in a Phase 2/3 and a Phase 3 study of patients with the disorder, which is an allergic inflammatory disease characterized by elevated levels of eosinophils, and infiltration of these cells in the esophagus. Reslizumab has been evaluated in two studies of patients with eosinophilic gastroenteritis⁵³ and hypereosinophilic syndrome,⁵⁴ diseases that are also characterized by high levels of eosinophils that infiltrate of tissues. In these studies, each of which included four patients administered one or more 1 mg/kg iv doses of reslizumab, eosinophil levels decreased from baseline for up to 12 weeks in a total of six patients, but a rebound effect was observed. Studies of purified eosinophils from patients and normal donors suggested that rebound eosinophilia was the result of a transient increase in IL5.⁵⁵

The safety and efficacy of three iv doses of reslizumab were compared to placebo in a Phase 2/3 study (NCT00538434) of 226 pediatric patients (5 to 18 years). Patients were administered 1, 2 or 3 mg/kg doses of reslizumab on day 0 of each of four 28 day cycles, or saline as a control. The primary outcome measures were esophageal eosinophil counts and EE global assessment at 15 weeks. The study was completed in October 2009, but no results are available yet. Patients who received at least two doses of reslizumab while participating in NCT00538434 were eligible to continue treatment in an open label extension, Phase 3 study (NCT00635089). Patients are administered 1 mg/kg of drug monthly. The primary outcome measure is the safety profile of reslizumab as assessed at four months, and the secondary outcome measure is the profile of treatment response durability at four months. Enrollment is estimated at 212 patients; the estimated completion date is October 2009, although on October 30, 2009 the study was noted as enrolling patients by invitation.

Antibodies in Phase 3 Studies for Non-Traditional Indications

A total of four of the 26 mAbs are undergoing evaluation in Phase 3 studies as treatments for non-traditional diseases (Table 5), i.e., indications that are not classified as cancer or immunological disorders, which historically have been the focus of mAb development efforts.¹ All four candidates are unmodified, full-size antibodies; three (75%) are IgG1 and one (25%) is IgG2. One mAb targets an infectious agent, and three are for neurological disorders (Alzheimer disease and pain). There is no overlap of the targets with those of FDA-approved products or any mAbs undergoing FDA review (Table 6). One of the candidates is designated by the FDA as an orphan drug and one has FDA's fast track designation.

Pagibaximab. Pagibaximab (BSYX-A110; Biosynexus) is an anti-lipoteichoic acid IgG1 mAb developed for the prevention of staphylococcal sepsis in very-low-birth-weight (VLBW) neonates. The mAb targets a highly-conserved component in the staphylococcal cell wall. In preclinical studies, pagibaximab administered at a dose of 80 mg/kg significantly increased survival of suckling rats with sepsis caused by coagulase-negative staphylococci (CoNS), and significantly increased survival in a lethal suckling rat model of *Staphylococcus aureus* sepsis.⁵⁶

The safety and pharmacokinetics of pagibaximab were first assessed in eight healthy subjects in 2001.⁵⁷ Adults (18 years or older) subjects were administered a single iv dose of either 3 or 10 mg/kg pagibaximab. The half-life of the mAb was approximately 33 days, and the single dose was well-tolerated. Pagibaximab was then evaluated in a placebo-controlled, dose escalation Phase 1/2 study in VLBW neonates.⁵⁶ Patients were administered two doses of 10, 30, 60 or 90 mg/kg iv pagibaximab, with doses administered 2 weeks apart, or placebo. Serum half-life was 20.5 days +/- 6.8 days; no evidence of immunogenicity was detected. Morbidity and mortality were similar in the five cohorts.

In a placebo-controlled Phase 2 study, VLBW neonates (mean birth weight 992 g, mean gestational age of 28 weeks) were administered three doses seven days apart of 60 or 90 mg/kg iv pagibaximab or placebo.⁵⁸ A total of 88 subjects were administered at least one dose. Staphylococcal sepsis was confirmed in 0, 20 and 13% of subjects who received 90 mg/kg pagibaximab, 60 mg/kg pagibaximab and placebo, respectively. The treatment appeared safe and well-tolerated at either dose level.

The safety and efficacy of pagibaximab in preventing staphylococcal sepsis is currently being evaluated in a placebo-controlled Phase 2b/3 study (NCT00646399) of VLBW neonates. Eligible infants are less than 48 hours old, with a birth weight of between 600 and 1,200 g and an estimated gestational age of 33 weeks or less. Subjects are administered iv pagibaximab at 100 mg/kg or placebo on days 0, 1, 2, 9, 16 and 23. The primary outcome measures are safety, PK and efficacy in a time frame of 0 to 35 days. Presence of neonatal sepsis will be assessed by clinical signs and symptoms and a blood culture positive for *Staphylococcus aureus* or two blood cultures positive for CoNS. An estimated 1,550 subjects will be enrolled, and the estimated completion date is April 2011.

Solanezumab. Solanezumab (LY2062430; Eli Lilly), an anti-amyloid beta IgG1 mAb, is undergoing evaluation as a treatment for mild-to-moderate Alzheimer disease. The mAb binds to soluble amyloid beta protein and may alter the equilibrium between amyloid beta in the blood and central nervous system.⁵⁹ In a Phase 2 study, 52 patients were iv administered 100 or 400 mg solanezumab either once a week or every four weeks or placebo on the same schedule, for 12 weeks.⁶⁰ Levels of amyloid beta plaque in the brain, blood and cerebrospinal fluid were assessed. The treatment was well-tolerated, and increased levels of amyloid protein were detected in blood and cerebrospinal fluid. During the 12 week study period, no change was observed in the patients' cognitive scores or levels of brain amyloid beta plaque, as measured by single photon emission tomography scanning.

Table 6. Antibodies in FDA review or approved as treatments for non-traditional indications

Generic name	Trade name	Target and type	Indication under consideration or first approved	FDA approval year
Raxibacumab	ABThrax*	Anti- <i>B. anthracis</i> PA; human IgG1	Anthrax infection	Pending
Abciximab	Reopro	Anti-GPIIb/IIIa; chimeric IgG1 Fab	Prevention of blood clots in angioplasty	1994
Denosumab	Prolia*	Anti-RANK-L; human IgG2	Bone loss	Pending
Motavizumab	Numax*	Anti-RSV; humanized IgG1	Prevention of respiratory syncytial virus infection	Pending
Palivizumab	Synagis	Anti-RSV; humanized IgG1	Prevention of respiratory syncytial virus infection	1998
Ranibizumab	Lucentis	Anti-VEGF; humanized IgG1 Fab	Macular degeneration	2006

Note: Information current as of November 1, 2009; *Proposed trade name; FDA, US Food and Drug Administration; GP, glycoprotein; PA, protective antigen; RANK-L, receptor activator of NF κ B ligand; RSV, respiratory syncytial virus; TNF, tumor necrosis factor.

The effect of solanezumab on the progression of Alzheimer disease is currently being evaluated in two placebo-controlled Phase 3 studies, Expedition and Expedition 2 (NCT00905372 and NCT00904683, respectively). Adults (55 years and older) with mild-to-moderate Alzheimer disease are administered 40 mg solanezumab or placebo iv every four weeks for 80 weeks. The primary outcome measures are the change from baseline to week 80 in the Alzheimer disease assessment scale-cognitive subscore (ADAS-Cog11) and the Alzheimer disease cooperative study-activities of daily living (ADCS-ADL) inventory. The estimated enrollment is 1,000 patients, and the estimated study completion date is July 2012.

Bapineuzumab. Bapineuzumab (AAB-001; Wyeth/Janssen), an IgG1 mAb that targets the N-terminus of amyloid beta, is currently being evaluated in a total of six Phase 3 studies, and an additional three Phase 3 studies are planned. Of the ongoing Phase 3 studies, three include patients who carry the apolipoprotein E (ApoE) ϵ 4 allele and three include patients who do not carry this allele that increases the risk for development of late-onset Alzheimer disease. In a Phase 2 study designed to assess the safety and tolerability of bapineuzumab, 234 patients with mild-to-moderate Alzheimer disease were administered 0.15, 0.5, 1.0 or 2.0 mg/kg bapineuzumab or placebo iv every 13 weeks for a total of six doses over the 18-month study period.⁶¹ A statistically significant result was not obtained on the pre-specified efficacy endpoints of ADAS-Cog and Disability Assessment Scale for Dementia (DAD). In a post-hoc efficacy analysis, data relative to the ApoE4 carrier status was evaluated. Statistically significant changes from baseline to week 78 in cognitive and functional endpoints were observed in bapineuzumab-treated patients who were non-carriers of ApoE ϵ 4. These patients also showed significantly less brain volume reduction, which is associated with disease progression, compared to patients who received placebo. The treatment was generally well-tolerated; vasogenic edema was reported in 12 patients treated with bapineuzumab and none treated with placebo.

The safety and efficacy of bapineuzumab is being evaluated in two placebo-controlled Phase 3 studies (NCT00574132 and NCT00667810) of patients with mild-to-moderate Alzheimer disease who are not ApoE4 carriers. The studies were initially designed to include three dosing regimens (0.5, 1.0 and 2.0 mg/kg), but the highest dose was discontinued based on a review of vasogenic edema occurrence during the Phase 3 program.⁶²

Both studies are continuing to evaluate the two lower doses; an estimated 1,000 adult patients (55 to 88 years) will participate in each of these 18 month studies. The primary outcome measures for NCT00574132 and NCT00667810 are cognitive and functional measures, and ADAS-Cog and DAD, respectively. The estimated completion dates are June 2011 and April 2011 for NCT00574132 and NCT00667810, respectively.

Three ongoing, placebo-controlled Phase 3 studies (NCT00575055, NCT00676143, NCT00909675) are evaluating the safety and efficacy of bapineuzumab as a treatment for mild-to-moderate Alzheimer disease in patients who are ApoE4 carriers. For NCT00575055 and NCT00676143, adult patients (55 to 88 years) are administered 0.5 mg/kg bapineuzumab or placebo. An estimated 800 patients will participate in each of these 18 month studies. Dosing information was not available for the NCT00909675 study. The primary outcome measures for NCT00575055 are cognitive and functional; the estimated completion date is June 2011. The primary outcome measures for both NCT00676143 and NCT00909675 are ADAS-Cog and DAD; the estimated completion date is April 2011 for both studies.

Patients who participated in either NCT00574132 (non-carriers of ApoE4) or NCT00575055 (ApoE4 carriers) are eligible to enroll in the ongoing Phase 3 study (NCT00937352) of the long-term safety and tolerability of the bapineuzumab. Adult patients are administered 0.5 or 1.0 mg/kg iv bapineuzumab every 13 weeks for 2.5 years. The primary outcome measures include clinically important changes in safety assessment results such as vital signs, weight, brain magnetic resonance imaging, and physical and neurological examinations. The estimated enrollment is 1,350, and the estimated completion date is June 2012.

Tanezumab. Tanezumab (PF-4,383,119, RN624; Pfizer) is an IgG2 antibody that targets nerve growth factor, which modulates nociceptor function. The mAb is currently being evaluated in a total of eight Phase 3 studies of patients with pain due to a variety of causes, with an additional three Phase 3 studies planned. Tanezumab was developed by Rinat Neuroscience Corp., which was acquired by Pfizer in 2006.

A randomized, double-blind study of patients with chronic knee osteoarthritis examined the safety and efficacy of tanezumab compared to placebo.⁶³ Patients (n = 79) were administered 0.1 or 0.3 mg/kg tanezumab or placebo, and then were followed through day 181. The endpoint of summed pain

intensity difference for days 2–14 did not show statistically significant differences between the groups. A post-hoc analysis of mean change from baseline during days 2–56 in daily walking pain indicated a significant difference between both groups of patients who received tanezumab and the group that received placebo. More AEs were experienced in the tanezumab-treated patients.

In a Phase 2 study of patients with chronic low back pain (CLBP), the safety and efficacy of tanezumab was compared to those of naproxen.⁶⁴ Patients were administered tanezumab iv at 0.2 mg/kg on day 1 with oral placebo (twice per day on days 1–85), an iv placebo administered on day 1 with oral naproxen (500 mg twice per day on days 1–85), or iv and oral placebo administered on the same schedule. The primary outcome measure was average low back pain intensity (aLBPI; score of 1–10) at week 6. The mean change in aLBPI was greater in the group that received tanezumab (-3.37) compared to the groups that received naproxen (-2.54) or placebo (-1.96). A secondary outcome measure was percentage of patients who had a 50% or greater reduction in aLBPI. This level of improvement was achieved by 57, 34 and 20% of patients who received tanezumab, naproxen and placebo, respectively. The efficacy results were statistically significant. Altered peripheral sensation AEs were reported in 11.4%, 3.4% and 2.4% of patients who received tanezumab, naproxen and placebo, respectively.

The safety and efficacy of tanezumab is being assessed in a placebo-controlled Phase 3 study (NCT00733902) of patients with osteoarthritis of the knee. Adult patients (18 years or older) are administered 2.5, 5 or 10 mg tanezumab or placebo every eight weeks. The primary outcome measures are western Ontario and McMaster Universities (WOMAC) physical function and pain index, and patient assessment of osteoarthritis at week 16. The estimated enrollment is 697, and the estimated study completion date is November 2009.

A Phase 3 study (NCT00744471) of the same design is evaluating tanezumab as a treatment for osteoarthritis of the hip. Enrollment is estimated at 600 patients, and the estimated study completion date is April 2010. Patients who participated in either NCT00733902 or NCT00744471 are eligible to enroll in a Phase 3 extension study (NCT00809783) that will assess safety over 1 year. Patients with either osteoarthritis of the knee or hip are administered 2.5, 5 or 10 mg tanezumab. The primary outcome measures are hematology, electrocardiogram, clinical chemistry and AEs in a 1 year time frame. Secondary outcome measures are WOMAC pain, physical function and stiffness. An estimated 2,400 patients will participate, and the estimated primary completion date is June 2012.

The effects of tanezumab on peripheral nerve function in patients with osteoarthritis are being evaluated in an ongoing, placebo-controlled Phase 3 study (NCT00863772). Adult patients (18 years or older) are administered 5 or 10 mg iv tanezumab or placebo every eight weeks for the duration of the study. The primary outcome measure is the change from baseline in a composite measure of nerve conductance and heart rate response to deep breathing during a time frame of six months. The secondary outcome measures are intra-epidermal nerve

fiber density, WOMAC subscales, patient's global assessment of arthritis, tanezumab levels in plasma and anti-drug antibodies in the serum in a time frame of six months. The estimated enrolment is 369 patients, and the estimated study completion date is October 2010.

The long-term safety of tanezumab in patients with chronic low back pain is currently being evaluated in an ongoing Phase 3 study (NCT00924664). Adult patients (18 years or older) are administered 10 or 20 mg iv tanezumab every eight weeks for three administrations, followed by sc administrations of tanezumab every eight weeks for four administrations over a period of 64 weeks. Primary outcome measures include AEs, change in baseline to various time points throughout the study in the brief pain inventory short form pain scores and pain interference with function composite score, and time to discontinuation due to lack of efficacy. An estimated 1,040 patients will be enrolled, and the estimated study completion date is June 2011.

The safety and efficacy of tanezumab alone or in combination with non-steroidal anti-inflammatory drugs (NSAIDs) is also being compared to the effects of NSAIDs analgesics such as naproxen, celecoxib and diclofenac in a total of three Phase 3 studies. In an ongoing Phase 3 study (NCT00809354), adult patients (18 years or older) with osteoarthritis of the knee or hip are randomized into five treatment arms that receive interventions as follows: (1) 5 mg iv tanezumab every eight weeks through week 48 and either naproxen (oral, 500 mg twice daily for 56 weeks) or celecoxib (oral, 500 mg twice daily for 56 weeks); (2) 10 mg iv tanezumab every 8 weeks through week 48 and either naproxen (oral, 500 mg twice daily for 56 weeks) or celecoxib (oral, 500 mg twice daily for 56 weeks); (3) 5 mg iv tanezumab every eight weeks through week 48 and oral placebo; (4) 10 mg iv tanezumab every eight weeks through week 48 and oral placebo; (5) iv and oral doses of placebo as per the schedule for tanezumab and NSAID dosing. The primary outcome measures are WOMAC physical function and pain subscales, and patient global assessment of osteoarthritis within a 16 week time frame. The estimated enrollment is 2,500, and the estimated study completion date is November 2010.

In a similar Phase 3 study (NCT00863304), adult patients with osteoarthritis of the knee or hip are administered 5 or 10 mg iv tanezumab at weeks 0 and 6, naproxen (1,000 mg daily for 16 weeks), or placebo dosed to match the route of administration and schedule of tanezumab and naproxen. The primary outcome measures are WOMAC physical function and pain subscales and patient global assessment of osteoarthritis at 12 and 16 weeks. The estimated enrollment is 800 and the estimated study completion date is June 2010.

The analgesic efficacy and safety of tanezumab in combination with diclofenac is being evaluated in a Phase 3 study (NCT00864097) of patients with osteoarthritis of the knee or hip. Adult patients are randomized into four treatment arms that receive interventions as follows: (1) 2.5 mg iv tanezumab every eight weeks through week 16 and oral diclofenac SR at 75 mg twice daily for 32 weeks; (2) 5 mg iv tanezumab every eight weeks through week 16 and oral diclofenac SR at 75 mg twice daily for 32 weeks; (3) 10 mg iv tanezumab every eight weeks

through week 16 and oral diclofenac SR at 75 mg twice daily for 32 weeks; (4) oral diclofenac SR at 75 mg twice daily for 32 weeks. The primary outcome measures are WOMAC physical function and pain subscales, and patient global assessment of osteoarthritis at 24 weeks. The estimated enrollment is 600, and the estimated study completion date is September 2010.

Cautionary Tale

Despite the dedicated efforts to development these candidates, not all will gain approval success. Based on historical data, the rate for the transition from Phase 3 to US approval is currently 82% for humanized mAbs.¹ Using this value as a benchmark, an estimated 21 of the 26 mAb candidates currently in Phase 3 might be approved by the FDA. The recent termination of late-stage studies of lumiliximab provides an example of the pitfalls of therapeutics development. Anti-CD23 lumiliximab (Biogen Idec) is a 'primatized' antibody, i.e., composed of human constant regions with variable regions derived from cynomolgus macaque. The technology to engineer these antibodies was developed by IDEC (now Biogen Idec), and has been applied to at least four antibodies that entered clinical study (lumiliximab, galiximab, keliximab, clenoliximab).

Lumiliximab was undergoing evaluation in a Phase 2/3 study of patients with chronic lymphocytic leukemia (CLL). Since the candidate had previously shown a favorable safety profile as a treatment for allergic disorders, and preclinical studies indicated the mAb might be active against primary CLL cells, a Phase 1 study of the candidate in 47 adult patients (47 to 80 years) with relapsed or refractory CLL was performed.⁶⁵ Patients received lumiliximab at 125, 250, 375 or 500 mg/m² weekly for four weeks; 500 mg/m² three times during week 1, then 500 mg/m² weekly for three additional weeks; or 500 mg/m² three times a week for four weeks. The treatment appeared to be well-tolerated and have clinical activity. The half-life of the candidate was approximately 7 to 10 days for doses of 375 mg/m² and above; no anti-drug antibodies were detected in 15 patients evaluated at the end of the study.

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Possibilities in 2010 and Beyond

The candidates currently sponsored by commercial firms in Phase 3 studies, when safety and efficacy data critical to approval is established, are the mAbs to watch in 2010, although the cast of candidates will change over time as some progress to regulatory review, others are terminated and new candidates enter the phase. There are over 100 mAb candidates currently in Phase 2 studies that, depending on study results, might be eligible for Phase 3 studies in the near future. Many of the mAbs now at Phase 3 target unique antigens, and may represent novel options for treatment of diseases with unmet medical need. The information presented here will serve as an aid to track progress of the candidates in 2010 and beyond.

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