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Antibody-based therapeutics to watch in 2011

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This overview of 25 monoclonal antibody (mAb) and five Fc fusion protein therapeutics provides brief descriptions of the candidates, recently published clinical study results and on-going Phase 3 studies. In alphanumeric order, the 2011 therapeutic antibodies to watch list comprises AIN-457, bapineuzumab, brentuximab vedotin, briakinumab, dalotuzumab, epratuzumab, farletuzumab, girentuximab (WX-G250), naptumomab estafenatox, necitumumab, obinutuzumab, orelizumab, pagibaximab, pertuzumab, ramucirumab, REGN88, reslizumab, solanezumab, T1h, teplizumab, trastuzumab emtansine, tremelimumab, vedolizumab, zalutumumab and zanolimumab. In alphanumeric order, the 2011 Fc fusion protein therapeutics to watch list comprises aflibercept, AMG-386, atacicept, Factor VIII-Fc and Factor IX-Fc. Commercially-sponsored mAb and Fc fusion therapeutics that have progressed only as far as Phase 2/3 or 3 were included. Candidates undergoing regulatory review or products that have been approved may also be in Phase 3 studies, but these were excluded. Due to the large body of primary literature about the candidates, only selected references are given and results from recent publications and articles that were relevant to Phase 3 studies are emphasized. Current as of September 2010, the information presented here will serve as a baseline against which future progress in the development of antibody-based therapeutics can be measured.

Introduction

The pharmaceutical and biotechnology industry is currently investing substantial resources in the development of antibody-based therapeutic products. Novel monoclonal antibodies (mAbs) have been entering clinical study at a rate of over 40 per year since 2007 and new products are being approved at a steady pace.¹ Hundreds of mAbs, as well as novel Fc fusion proteins that are composed of binding peptides or proteins fused to the Fc domain of immunoglobulin G, are undergoing clinical study as potential treatments for disease. By the end of 2010, a total of 30 of these candidates (25 mAb and five Fc fusion protein) were in Phase 2/3 or Phase 3 clinical studies sponsored by commercial firms, and these are included on the 2011 antibody-based therapeutics to watch list.

A total of 26 mAbs in commercially-sponsored Phase 2/3 or Phase 3 clinical studies were included on the 2010 antibodies to watch list.² In alphanumeric order by mAb name, these candidates were: 131-I mAb 81C6, bapineuzumab, belimumab, briakinumab, dalotuzumab, epratuzumab, farletuzumab, figitumumab, galiximab, girentuximab

(WX-G250), inotuzumab, ozogamicin, ipilimumab, mepolizumab, naptumomab estafenatox, orelizumab, orelizumab, pagibaximab, pertuzumab, ramucirumab, reslizumab, solanezumab, tanezumab, teplizumab, trastuzumab emtansine, vedolizumab and zalutumumab.

Nine of the 26 mAbs on the 2010 list were not included in the 2011 version for various reasons. Two mAbs (belimumab and ipilimumab) advanced to regulatory review, all studies of two mAbs (galiximab and 131-I mAb 81C6) were suspended or terminated and development of five (figitumumab, inotuzumab, ozogamicin, mepolizumab, orelizumab and tanezumab) reverted to Phase 2 studies. New to the 2011 list are eight mAbs that entered a first Phase 3 clinical study or re-entered a Phase 3 study since September 2009. In alphanumeric order by mAb name, these are: AIN-457, brentuximab vedotin, necitumumab, obinutuzumab, REGN88, T1h, tremelimumab and zanolimumab. Two (trelimumab and zanolimumab) were previously in Phase 3 studies that were terminated prior to 2009, and so were not on the “antibodies to watch in 2010” list. As a consequence of these changes to the 2010 list, there

are 25 “antibodies to watch” in 2011. The complete list of the 25 mAbs in alphanumeric order by target appears in **Tables 1, 3 and 5**.

Information about mAbs that are in regulatory review or approved for marketing by the United States Food and Drug Administration (US FDA) are listed in **Tables 2, 4 and 6** for comparison. Two mAbs, catumaxomab and nimotuzumab, that are approved for marketing outside of the US should also be noted. **Catumaxomab** (Removab®; Fresenius Biotech GmbH, Trion Pharma) is a mouse/rat-derived, bispecific mAb that targets the epithelial cell adhesion molecule (EpCAM) on tumor cells and CD3 on T cells.³ The product was approved for marketing in the European Union in April 2009 for treatment of patients with malignant ascites. Catumaxomab is in an on-going Phase 3 study [NCT00822809] as a treatment of malignant ascites due to epithelial cancer.

Nimotuzumab (BIOMab-EGFR, Thera-CIM; Biocon, YM Biosciences, Oncosciences) is a humanized IgG1 mAb that targets the epithelial growth factor receptor (EGFR).⁴ The product is approved for marketing in a number of

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Table 1. Monoclonal antibodies in Phase 3 studies as treatments for cancer indications

Sponsoring company	International non-proprietary name	Target and type	Indication of Phase 3 study	FDA designations for Phase 3 study indication
Active Biotech Research	Naptumomab estafenatox	ST4; Fab conj. to staph. enterotoxin A	Advanced renal cell carcinoma	
Wilex AG	Girentuximab	Carbonic anhydrase ix; IgG1	Non-metastatic renal cell carcinoma	O
TenX Biopharma/Genmab	Zanolimumab	CD4; IgG1	Cutaneous T-cell lymphoma	FT, O
Glycart/Genentech/Biogen Idec	Obinutuzumab	CD20; IgG1	Chronic lymphocytic leukemia	
Seattle Genetics	Brentuximab vedotin	CD30; IgG1; conjugated to monomethyl auristatin E	Hodgkin lymphoma	FT, O
Pfizer	Tremelimumab	CTLA-4; IgG2	Metastatic melanoma	
Genmab	Zalutumumab	EGFR; IgG1	Head and neck cancer	FT
ImClone	Necitumumab	EGFR; IgG1	Non-small cell lung cancer	
Morphotek	Farletuzumab	Folate receptor α ; IgG1	Ovarian cancer	O
Genentech	Trastuzumab emtansine	HER2; IgG1 conj. to DM1	Locally advanced or metastatic breast cancer	
Genentech	Pertuzumab	HER2; IgG1	Metastatic breast cancer	
Merck, Pierre Fabre	Dalotuzumab	IGF-1R; IgG1	Metastatic colorectal cancer	
Imclone Systems/Eli Lilly	Ramucirumab	VEGFR2; IgG1	Metastatic gastric or gastroesophageal junction adenocarcinoma; breast cancer; hepatocellular carcinoma	

Information current as of September 1, 2010. CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte-associated antigen; EGFR, epidermal growth factor receptor; Fab, antigen-binding fragment; 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; VEGFR2, vascular endothelial cell growth factor receptor 2. International non-proprietary naming convention: -umab, human; -zumab, humanized; -ximab, chimeric; -momab, murine.

Table 2. Monoclonal antibodies in FDA review or approved as treatments for cancer indications

International non-proprietary name	Trade name	Target and type	Indication under review or first approved	FDA approval year
Ofatumumab	Arzerra	CD20; human IgG1	Chronic lymphocytic leukemia	2009
Tositumomab-I131	Bexxar	CD20; murine IgG2a	Non-Hodgkin lymphoma	2003
Ibritumomab tiuxetan	Zevalin	CD20; murine IgG1	Non-Hodgkin lymphoma	2002
Rituximab	Rituxan	CD20; chimeric IgG1	Non-Hodgkin's lymphoma	1997
Gemtuzumab ozogamicin	Mylotarg	CD33; humanized IgG4	Acute myeloid leukemia	2000 ^a
Alemtuzumab	Campath-1H	CD52; humanized IgG1	Chronic myeloid leukemia	2001
Ipilimumab	Pending	CTLA-4; human IgG1	Advanced melanoma	Pending (PDUFA action date Dec. 25, 2010)
Panitumumab	Vectibix	EGFR; human IgG2	Colorectal cancer	2006
Cetuximab	Erbitux	EGFR; chimeric IgG1	Colorectal cancer	2004
Trastuzumab	Herceptin	HER2; humanized IgG1	Breast cancer	1998
Bevacizumab	Avastin	VEGF; humanized IgG1	Colorectal cancer	2004

Information current as of September 1, 2010. ^aVoluntarily withdrawn from US market. CD, cluster of differentiation; EGFR, epidermal growth factor receptor; CTLA, cytotoxic T-lymphocyte-associated antigen; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor; PDUFA, Prescription Drug User Fee Act; VEGF, vascular endothelial growth factor. International non-proprietary naming convention: -umab, human; -zumab, humanized; -ximab, chimeric; -momab, murine.

Table 3. Monoclonal antibodies in Phase 3 studies as treatments for immunological indications

Sponsoring company	International non-proprietary name	Target and type	Indication of Phase 3 study	FDA designations for Phase 3 study indication
Millennium/Takeda	Vedolizumab	$\alpha 4 \beta 7$ integrin; IgG1	Moderate-to-severe Crohn disease; ulcerative colitis	
Tolerx	Otelixizumab	CD3; IgG1	Type 1 diabetes mellitus	O
Macrogenics/Eli Lilly	Teplizumab*	CD3; IgG1	Type 1 diabetes mellitus	O
Biocon/CIMAB SA	T1h	CD6; humanized IgG1	Psoriasis	
Immunomedics/UCB	Epratuzumab	CD22; IgG1	Systemic lupus erythematosus	FT
Cephalon	Reslizumab	IL-5; IgG4	Eosinophilic esophagitis	O
Regeneron	REGN88	IL-6R; human IgG1	Ankylosing spondylitis, rheumatoid arthritis	
Abbott	Briakinumab**	IL-12/23; IgG1	Plaque psoriasis	
Novartis	AIN-457	IL-17A; human IgG1	Uveitis	

Information current as of September 1, 2010. CD, cluster of differentiation; FDA, US Food and Drug Administration; FT, fast track designation; IL, interleukin; O, orphan drug designation. International non-proprietary naming convention: -umab, human; -zumab, humanized. *Note added in proof: In a press release issued in October 2010, Lilly announced that the primary endpoint in the PROTÉGÉ study (NCT00385697) had not been met and enrollment and dosing in the PROTÉGÉ and PROTÉGÉ Encore (NCT00920582) studies were suspended. **Note added in proof: In a press release issued in October 2010, Abbott announced that marketing applications for briakinumab were filed in the US and Europe during the third quarter of 2010.

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

International non-proprietary name	Trade name	Target and type	Indication under consideration or first approved	FDA approval year
Belimumab	Pending	B-lymphocyte stimulator; human IgG1	Systemic lupus erythematosus	Pending (PDUFA action date Dec. 9, 2010)
Eculizumab	Soliris	C5; humanized IgG2/4	Paroxysmal nocturnal hemoglobinuria	2007
Muromonab-CD3	Orthoclone Okt3	CD3; murine IgG2a	Reversal of kidney transplant rejection	1986 [#]
Basiliximab	Simulect	IL2R; chimeric IgG1	Prevention of kidney transplant rejection	1998
Daclizumab	Zenapax	IL2R; humanized IgG1	Prevention of kidney transplant rejection	1997 [#]
Efalizumab	Raptiva	CD11a; humanized IgG1	Psoriasis	2003 [#]
Tocilizumab	Actemra	IL6R; humanized IgG1	Rheumatoid arthritis	2010
Ustekinumab	Stelara	IL12/23; human IgG1	Plaque psoriasis	2009
Canakinumab	Ilaris	IL1 β ; human IgG1	Muckle-Wells syndrome	2009
Omalizumab	Xolair	IgE; humanized IgG1	Asthma	2003
Natalizumab	Tysabri	$\alpha 4$ integrin; humanized IgG4	Multiple sclerosis	2004
Golimumab	Simponi	TNF; human IgG1	Rheumatoid and psoriatic arthritis, ankylosing spondylitis	2009
Certolizumab pegol	Cimzia	TNF; humanized Fab, pegylated	Crohn disease	2008
Adalimumab	Humira	TNF; human IgG1	Rheumatoid arthritis	2002
Infliximab	Remicade	TNF; chimeric IgG1	Crohn disease	1998

Information current as of September 1, 2010. [#]Voluntarily withdrawn from US market. C5, complement 5; CD, cluster of differentiation; FDA, US Food and Drug Administration; IL, interleukin; PDUFA, Prescription Drug User Fee Act; TNF, tumor necrosis factor. International non-proprietary naming convention: -umab, human; -zumab, humanized; -ximab, chimeric; -momab, murine.

countries, e.g., India, Cuba, Argentina, Columbia, Ivory Coast, Gabon, Ukraine, Peru and Sri Lanka as a treatment for patients with squamous cell carcinoma of the head and neck; Cuba, Argentina, Philippines and Ukraine as a treatment for glioma in pediatric and adult patients and China for patients with

nasopharyngeal cancer. Nimotu-zumab is in commercially-sponsored, ongoing Phase 3 studies in patients with glioblastoma multiforma (NCT00753246) and patients with advanced nasopharyngeal cancer (NCT01074021).

With six products in FDA review or approved and five candidates in Phase 3

studies, Fc fusion protein therapeutics are a growing class of antibody-based molecules that have been included on the 2011 watch list. In alphanumeric order, the 2011 Fc fusion protein therapeutics to watch list comprises aflibercept, AMG-386, atacicept, Factor VIII-Fc and Factor IX-Fc (Table 7). For comparison,

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

Sponsoring company	International non-proprietary name	Target and type	Indication of Phase 3 study	FDA designations for Phase 3 study indication
Biosynex	Pagibaximab	Lipoteichoic acid; IgG1	Prevention of staphylococcal sepsis in very low birth weight neonates	O
Lilly	Solanezumab	Amyloid beta; IgG1	Alzheimer disease	
Pfizer, Janssen	Bapineuzumab	Amyloid beta; IgG1	Alzheimer disease	FT

Information current as of September 1, 2010. FDA, US Food and Drug Administration; FT, fast track designation; O, orphan drug designation. International non-proprietary naming convention: -zumab, humanized; -ximab, chimeric.

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

International non-proprietary name	Trade name	Target and type	Indication under consideration or first approved	FDA approval year
Raxibacumab	Pending	<i>B. anthracis</i> PA; human IgG1	Anthrax infection	Pending
Abciximab	Reopro	GP1Ib/IIla; chimeric IgG1 Fab	Prevention of blood clots in angioplasty	1994
Denosumab	Prolia	RANK-L; human IgG2	Bone loss	2010
Motavizumab	Pending	RSV; humanized IgG1	Prevention of respiratory syncytial virus infection	Pending
Palivizumab	Synagis	RSV; humanized IgG1	Prevention of respiratory syncytial virus infection	1998
Ranibizumab	Lucentis	VEGF; humanized IgG1 Fab	Macular degeneration	2006

Information current as of September 1, 2010. FDA, US Food and Drug Administration; GP, glycoprotein; PA, protective antigen; RANK-L, receptor activator of NFκB ligand; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; VEGF, vascular endothelial cell growth factor.

Table 7. Fc fusion protein therapeutics in Phase 3 studies for any indication

Sponsoring company	International non-proprietary or code name	Description	Indications of Phase 3 study	FDA designations for Phase 3 study indication
Regeneron/Sanofi-aventis/Bayer	Aflibercept	Extracellular domains of VEGFR1 and VEGFR2 fused to Fc of human IgG1	Ovarian cancer with symptomatic malignant ascites, prostate, small cell lung, colorectal and pancreatic cancers; wet age-related macular degeneration; central retinal vein occlusion	FT (for symptomatic malignant ascites)
Amgen	AMG 386	Angiopoietin-1 and -2 binding peptide fused to Fc of human IgG1	Epithelial ovarian, primary peritoneal or fallopian tube cancers*	
ZymoGenetics/Merck Serono	Atacicept	Extracellular domain of transmembrane activator and calcium-modulating ligand interactor fused with Fc of human Ig	Systemic lupus erythematosus	
Biogen Idec/Swedish Orphan Biovitrum	Factor VIII-Fc	Factor VIII fused to Fc of human IgG1	Severe hemophilia A	
Biogen Idec/Swedish Orphan Biovitrum	Factor IX-Fc	Factor IX fused to Fc of human IgG1	Hemophilia B-associated hemorrhagic events	O

Data current as of September 2010. *Five separate Phase 3 studies, with one in each indication. **Single Phase 3 study [NCT01204749] in which patients may have any of these indications; listed on clinicaltrials.gov as not yet open for participation as of September 2010. FDA, United States Food and Drug Administration; FT, fast track; O, orphan drug; VEGFR, vascular endothelial growth factor receptor.

information about Fc fusion proteins that are in regulatory review or approved for marketing by the FDA are listed in Table 8.

Commercially-sponsored mAb and Fc fusion protein therapeutics that have progressed only to Phase 2/3 or Phase 3 were included. Candidates undergoing

regulatory review or products already on the market may also be in Phase 3 studies, but these were excluded. MABs in development sponsored solely by academic, government and non-profit organizations were also excluded. Due to the large body of primary literature about the 30 candidates on the 2011 watch list, only selected

references are given, and results from recent publications and articles that were relevant to Phase 3 studies are emphasized. Current as of September 2010, the information presented here will serve as a baseline against which future progress in the development of antibody-based therapeutics can be measured.

Table 8. Fc fusion protein therapeutics approved in the US as treatments for any indication

International non-proprietary name	Trade name	Description	Indication under review or first approved	Year of first FDA approval
Belatacept	Pending	Extracellular domain of CTLA-4 fused to Fc of a human IgG1	Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants	Pending
Abatacept	Orencia	Extracellular domain of CTLA-4 fused to Fc of a human IgG1	Moderate-to-severely active rheumatoid arthritis	2005
Rilonacept	Arcalyst	Extracellular domain of interleukin-1 receptor fused to Fc of human IgG1	Cryopyrin-associated periodic syndromes	2008
Alefacept	Amevive	Extracellular domain of LFA-3 fused to Fc of a human IgG1	Treatment of adults with moderate-to-severe plaque psoriasis	2003
Etanercept	Enbrel	Extracellular domain of tumor necrosis factor receptor fused to Fc of human IgG1	Moderate-to-severely active rheumatoid arthritis	1998
Romiplostim	NPlate	Thrombopoietin-binding peptide fused to Fc of human IgG1	Thrombocytopenia in chronic immune thrombocytopenic purpura patients	2008

Data current as of September 2010.

Eight New mAbs in Phase 3 Clinical Studies

Of the eight mAbs that entered (or re-entered) Phase 3 clinical studies recently, five (zanolimumab, obinutuzumab, brentuximab vedotin, tremelimumab, necitumumab) are potential treatments for cancer indications (Table 1) and three (T1h, REGN88, AIN-457) are being studied as treatments for immunological disorders (Table 3). Four of these mAbs target antigens that are unique compared to those targeted by mAb products already on the market or in regulatory review. The antigens are: CD4 (target of zanolimumab), CD30 (target of brentuximab vedotin), CD6 (target of T1h) and interleukin (IL)-17A (target of AIN-457).

Zanolimumab (HuMax-CD4, MDX-CD4; TenX Biopharma) is a human IgG1 mAb that targets CD4 on the surface of T cells. The mAb has been shown to inhibit or deplete T cells through a variety of mechanisms such as alteration of T-cell receptor signal transduction, Fc-dependent CD4 receptor down-modulation and antibody dependent cellular cytotoxicity (ADCC).⁵ Zanolimumab has been evaluated as a treatment for a variety of diseases characterized by T-cell disorders, including rheumatoid arthritis, psoriasis and lymphoma. The current focus of Phase 3 clinical development is on cutaneous T-cell lymphomas (CTCLs), which are rare lymphomas presenting primarily in the skin and include mycosis fungoides

and Sézary syndrome.⁶ Zanolimumab was designated a Fast Track candidate as a treatment for CTCL patients who have failed current therapy and an Orphan drug specifically for treatment of mycosis fungoides by the FDA.

Zanolimumab was assessed in two Phase 2 studies as a treatment for early (Hx-CD4-007; NCT00071071) and late (Hx-CD4-008; NCT00071084) stage CTCL.⁷ Initiated in 2003, both of these multicenter Phase 2 studies were non-randomized, uncontrolled (i.e., no placebo arm was included), open label and single group assignment. Prior to enrollment, patients in both studies had been previously treated with at least one treatment regimen and had failed or relapsed. For both studies, patients were administered intravenous (iv) doses of zanolimumab over 15 min on a weekly basis. Seventeen infusions were given over 16 weeks, with a follow up visit four weeks later. Response rates, duration of responses, relief of symptoms and the safety profile of the mAb were evaluated in the 38 mycosis fungoides patients and nine Sézary syndrome patients who enrolled in the two studies. The studies were designed as single arm evaluations of 280 mg doses of zanolimumab, but data review indicated that T-cell depletion might be inadequate. Additional study arms with doses of 560 mg for mycosis fungoides patients and 980 mg for Sézary syndrome patients were then added.

The Hx-CD4-007 (NCT00071071) study included 25 early stage (IB-IIA) mycosis fungoides patients, 11 and 14 of which were administered 280 and 560 mg doses of zanolimumab, respectively.⁷ The Hx-CD4-008 (NCT00071084) study included a total of 22 patients dosed as follows: nine late stage (IIB-IVB) mycosis fungoides and four Sézary syndrome patients received 280 mg doses of zanolimumab and four late stage (IIB-IVB) mycosis fungoides and five Sézary syndrome patients received 980 mg doses of zanolimumab.⁷ An objective response, based on composite assessment of the index lesion disease severity score, was obtained by 13 mycosis fungoides patients (3 of 20 at 280 mg dose level, 7 of 14 at 560 mg dose level and 3 of 4 at 980 mg dose level). One of four and one of five Sézary syndrome patients who were administered 280 mg or 980 mg doses of zanolimumab, respectively, obtained an objective response. The response rate of 56% in the high dose group was obtained with a median response of 81 weeks. Increased titers of anti-drug antibodies were observed in only one patient. Adverse events (AEs) included inflammatory skin reactions and infections; nine infections were deemed drug-related although no dose relation was apparent.

A Phase 3 study (Hx-CD4-110; NCT00127881) of zanolimumab as a treatment for mycosis fungoides started by Genmab in 2005 was discontinued in 2008 due to slow enrollment and a need

by the company to reserve resources at that time. TenX Biopharma acquired the mAb in 2010 and re-initiated enrollment in the study, which is designed as non-randomized, open label, dose escalation, followed by open label and single arm. Adult patients (18 years or older) with mycosis fungoides (Stage IB-IVB) or Sézary syndrome who are refractory or intolerant to bexarotene and one other standard therapy will receive 12 weekly infusions. The primary outcome measure is efficacy as measured by physician's global assessment (PGA); the estimated date for final data collection for the PGA is February 2011.

Obinutuzumab (RO5072759, GA101; Genentech/Roche), a glyco-engineered anti-CD20 IgG1 mAb, is undergoing evaluation in combination with other drugs in two Phase 3 studies as a treatment for non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Obinutuzumab differs from the marketed anti-CD20 ofatumumab and rituximab in its mechanisms of action. The mAb is a Type II antibody and so has a distinct effector function profile that includes reduced binding to C1q and lower levels of CDC but potent induction of cell death through caspase-independent apoptosis.⁸ Enhanced activity was correlated with a modified elbow hinge residue (valine at Kabat position 11 instead of leucine).⁹ Obinutuzumab also contains a glyco-engineered Fc region, with bisected, complex, non-fucosylated oligosaccharides attached to asparagines 297, that allows the mAb to bind with increased affinity to FcγRIII.⁹

Obinutuzumab is being evaluated as a monotherapy in an on-going open-label, dose-escalating Phase 1/2 study with a randomized Phase 2 part (NCT00517530) of patients with CD20⁺ malignant disease. The study was initiated in September 2007 and results for the first 12 patients were reported in December 2008.¹⁰ Obinutuzumab was administered by iv infusion at a flat dose on days 1, 8 and 22 and subsequently every three weeks for a total of nine infusions. The dose was escalated according to a 3 + 3 design; doses ranging from 50–800 mg were administered to patients who had follicular NHL (nine patients), diffuse large B-cell lymphoma (one patient), CLL (one patient)

or Waldenstrom macroglobulinemia (one patient). No dose-limiting toxicity was observed. The most common AEs were infusion-related reactions; six minor infections were observed. The pharmacokinetics of the mAb showed a dose-dependent increase in exposure, but significant inter- and intra-patient variability was noted. At the time of the report, 7 of 12 patients had responded to treatment by day 85. The objective response rate (ORR) was 58%, with complete response in three patients (25%) and partial response in four patients (33%).¹⁰

Obinutuzumab in combination with chlorambucil is undergoing evaluation in a Phase 3 study (NCT01010061) of adult (18 years and older) patients with previously untreated CLL. The open label, randomized study will have three arms: (1) 1 g doses of obinutuzumab iv administered on days 1, 8 and 15 in cycle 1 and on day 1 of cycles 2–6 in combination with 0.5 mg/kg chlorambucil administered orally on day 1 and 15 of each cycle; (2) 375 mg/m² rituximab iv administered on day 1 in cycle 1 and 500 mg/m² on day 1 of cycles 2–6 in combination with chlorambucil administered as in arm 1; (3) chlorambucil only administered as in arm 1. The primary outcome measure is progression-free survival as assessed every two weeks while patients are on study treatment, 28 days after last dose and at intervals for at least 5 years of follow-up. Secondary outcome measures include response rates, duration of response and disease-free survival in patients with complete response, overall survival, molecular remission, minimal residual disease, safety profile, pharmacokinetics of obinutuzumab and patient reported outcomes. The estimated enrollment is 786 patients and the estimated study completion date is February 2022.

A second Phase 3 study (NCT01059630; GADOLIN) is investigating the efficacy and safety of obinutuzumab in combination with bendamustine in adult patients with rituximab-refractory, indolent NHL. This open label, randomized study will compare results for the combination of drugs with those observed for patients treated with bendamustine alone. No dosing information is currently available. The primary outcome measure is

progression free survival. Secondary outcome measures include overall survival, complete response, overall response and best response. An estimated 360 patients will be enrolled and the estimated primary completion date is January 2015.

Brentuximab vedotin (SGN-35; Seattle Genetics, Millennium) is a chimeric IgG1 immunoconjugate that targets CD30, which is expressed at high levels on activated lymphocytes. The immunoconjugate comprises Seattle Genetic's mAb cAC10 (SGN-30) conjugated to the anti-tubulin agent monomethyl auristatin E through a peptide linker that is selectively cleaved after internalization into cells.¹¹

Results for Phase 1 studies of brentuximab vedotin have been reported. A Phase 1 dose escalation study included 45 patients (42 with Hodgkin lymphoma, two with systemic anaplastic large cell lymphoma and one with angioimmunoblastic T-cell lymphoma) who were administered immunoconjugate at doses ranging from 0.1–3.6 mg/kg as 2 h iv infusions every three weeks.¹² The observed maximum tolerated dose was 1.8 mg/kg on this dosing schedule and the terminal elimination half-life was 5.0 ± 1.8 days at the 1.8 mg/kg dose. AEs that occurred in 20% or more of patients were fatigue, pyrexia, nausea and diarrhea. Neutropenia related to dose level was observed. One patient administered 3.6 mg/kg who developed febrile neutropenia died 14 days after the first dose. Of 28 patients who received doses of 1.2 mg/kg or greater and could be evaluated, 46% obtained an objective response; seven patients (25%) obtained a complete remission rate.

A more frequent schedule of brentuximab vedotin doses was evaluated in a dose escalation Phase 1 study with a 3 + 3 design. A total of 17 adult patients (25–27 years) who had been pretreated (median of four prior therapies, with 65% having received an autologous stem cell transplant) were administered brentuximab vedotin weekly at doses of 0.4, 0.6, 0.8 and 1 mg/kg.¹³ Grade 1/2 rash, nausea and peripheral neuropathy were the most common AEs; Grade 3 diarrhea occurred in one patient. Three (of four) and four (of six) patients who received the 0.8 and 1.0 mg/kg doses, respectively, obtained a complete response, with an observed time

to response of approximately eight weeks for patients in the 1 mg/kg dose group.

A total of seven heavily pretreated patients who were administered brentuximab vedotin during one of three Phase 1 studies experienced relapse and were retreated with the immunoconjugate. Results of the case series, which included six Hodgkin lymphoma patients and one anaplastic large cell lymphoma patient, were reported in 2010.¹⁴ The adult patients (28–39 years) were administered IV infusions of brentuximab vedotin at doses of 1 mg/kg once per week or 1.8 mg/kg every three weeks; the seven patients experienced eight retreatments. Treatment related AEs were Grade 1/2. Of AEs that occurred in more than one patient, three patients developed upper respiratory tract infection and peripheral sensory neuropathy was observed in two patients. Objective responses were observed in six retreatments (two complete responses and four partial responses) and occurred 5–13 weeks after the start of retreatment.

Top-line results were reported in September 2010 for a pivotal Phase 2 study (NCT00848926) of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma who had previously received autologous stem cell transplants.¹⁵ Patients (12 years and older) were administered 1.8 mg/kg doses of brentuximab vedotin every three weeks for up to 16 total doses. Of 102 patients who participated in the study, 75% achieved an objective response. The mean duration of response was greater than 6 months.

Brentuximab vedotin is currently being evaluated in a randomized, double-blind placebo-controlled Phase 3 AETHERA study (NCT01100502; SGN35-005). The immunoconjugate and best supportive care (BSC) is being compared to placebo and BSC in the treatment of patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant. Adult patients (18 years or older) are administered either 1.8 mg/kg doses of brentuximab vedotin or placebo by iv infusion every 21 days. The primary outcome measure is progression-free survival and secondary outcome measures are overall survival, incidence of adverse events and laboratory abnormalities and incidence of anti-therapeutic antibodies.

The estimated enrollment is 322 patients and the primary completion date is estimated to be June 2013.

The safety of brentuximab vedotin is being evaluated in an open label, non-randomized Phase 2/3 study (NCT01196208) in patients with progressive Hodgkin lymphoma. Adult patients (18 years and older) are administered 1.8 mg/kg doses of brentuximab vedotin by iv infusion every 21 days. The primary outcome measures are the incidence of AEs and laboratory abnormalities through 1 month after last dose. Enrollment is by invitation to patients who are randomly allocated to placebo in the Phase 3 SGN35-005 study (NCT01100502).

Tremelimumab (CP-675,206; Pfizer), a human IgG2 mAb, targets the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) that acts as a negative regulator for T cells, thereby modulating the duration and intensity of an immune response.¹⁶ Tremelimumab has been, or is being, evaluated in clinical studies of patients with a variety of cancers,¹⁷ including metastatic bladder, prostate, pancreatic, non-small cell lung and colorectal cancer, as well as renal cell and hepatocellular carcinoma and gastric and esophageal adenocarcinoma. Reports for small Phase 2 studies in refractory metastatic colorectal cancer (47 patients)¹⁸ and advanced gastric and esophageal adenocarcinoma (18 patients)¹⁹ indicated that the activity of tremelimumab was not clinically meaningful in the patient populations studied. Patients received 15 mg/kg iv doses of tremelimumab every 90 days until progression in both studies. Results of a Phase 2 study of tremelimumab in 246 patients with advanced refractory or relapsed melanoma that used the same dose regimen was recently reported.²⁰ The objective response rate was 6.6%, the clinical benefit rate was 21% and median overall survival was 10.0 months. Grade 3/4 AEs included diarrhea, fatigue and colitis.

A Phase 3 study (A3671009; NCT 00257205) of tremelimumab as a treatment for surgically incurable metastatic melanoma patients who had received no prior chemo- or biochemo-therapy for treatment of metastatic disease was initiated in November 2005 but later

terminated. The open label, randomized parallel assignment study compared tremelimumab with either dacarbazine or temozolomide. Patients were administered 15 mg/kg iv tremelimumab every 90 days or the physician's choice of 1,000 mg/m² IV dacarbazine every 21 days or 200 mg/m² oral doses of temozolomide on days 1–5 and then every 28 days. The primary outcome measure was overall survival. Between March 2006 and July 2007, 328 patients were randomized to tremelimumab (324 treated) and 327 to chemotherapy (319 treated).²¹ The study was discontinued after interim analysis showed that the experimental treatment would not demonstrate superiority over the chemotherapy: overall survival by intent-to-treat was 11.8 months in the tremelimumab arm and 10.7 months in the chemotherapy arm.^{17,21} A retrospective analysis later indicated response in some patient subgroups and a biomarker that will be used for future studies was identified. In 2010, Debiopharma and Pfizer agreed to co-develop the mAb, with Debiopharma assuming responsibility for initiating a Phase 3 study of tremelimumab in melanoma patients.

Necitumumab (IMC-11F8) is a human IgG1 mAb that targets epidermal growth factor receptor (EGFR). The safety, pharmacokinetics, preliminary antitumor activity and immunogenicity of necitumumab were evaluated in a Phase 1 study of patients with advanced solid malignancies who were administered 100 mg to 1 g of necitumumab. The maximum tolerated dose was established as 800 mg; the half-life was approximately 7 days at this dose.²² The most common drug-related toxicity was mild skin toxicity that was dose-related. Target trough concentrations were achieved by all patients who were administered 600 mg or more of necitumumab. Anti-drug antibodies were not detected in the patients. Based on the results of this study, a dose of 800 mg (flat dose) either weekly or biweekly was recommended for additional study.

The safety and efficacy of necitumumab combined with 5-FU/FA and oxaliplatin as first line therapy were evaluated in a Phase 2 study in patients with unresectable, locally advanced or metastatic colorectal cancer.²³ Patients

were administered 800 mg (flat dose) of necitumumab on each cycle's day 1, followed by a combination of 85 mg/m² oxaliplatin, 400 mg/m² folinic acid and 5-fluorouracil 400 mg/m² bolus followed by a 2,400 mg/m² as a 46 h continuous infusion. Treatment cycles were repeated every two weeks until toxicity necessitated discontinuation or the patient's disease progressed. Preliminary results indicated a 60% partial response rate (6 of 10 patients who had response assessments). Skin rash was the most common AE.

Necitumumab is being evaluated in two Phase 3 studies in patients with non-small cell lung (NSCL) cancer. The Phase 3 INSPIRE study (NCT00982111) is an open label, randomized, active control study of necitumumab administered in combination with pemetrexed-cisplatin chemotherapy compared to pemetrexed-cisplatin chemotherapy in adult patients (18 years or older) with advanced non-squamous Stage IIIB or IV NSCL cancer. Patients in the experimental arm of the study are administered 800 mg necitumumab on days 1 and 8, as well as 500 mg/m² of pemetrexed on day 1 and 75 mg/m² cisplatin on day 1 of every three week cycle. Patients in the active control arm are administered the chemotherapy agents but no mAb. All patients also receive oral folic acid and intramuscular (im) vitamin B12. The chemotherapy regimens will continue for a maximum of six cycles; administration of necitumumab continues until progressive disease (determined by radiographic assessment), toxicity requiring cessation, protocol non-compliance or withdrawal of consent. The primary outcome measure is percentage of patients with an overall survival within a 30 month time frame. Secondary outcome measures include progression-free survival, objective response rate, time to treatment failure, safety profile and immunogenicity within a 30 month time frame. The enrollment is estimated at 947 patients and the estimated date of final data collection is October 2011, with an estimated study completion date of May 2012.

The open label, randomized Phase 3 SQUIRE study (NCT00981058) is evaluating the safety and efficacy of necitumumab and gemcitabine-cisplatin as

first-line treatment of patients with Stage IV squamous non-small cell lung cancer. Adult patients (18 years or older) randomized to the experimental arm of the study are administered 800 mg necitumumab IV on days 1 and 8, 1,250 mg/m² of gemcitabine on days 1 and 8 and 75 mg/m² IV cisplatin on day 1 of every three week cycle. The chemotherapy regimens will continue for a maximum of six cycles; administration of necitumumab continues until progressive disease (determined by radiographic assessment), toxicity requiring cessation, protocol non-compliance or withdrawal of consent. The primary outcome measure is overall survival time within a 31 month time frame. Secondary outcome measures include progression-free survival, objective response rate, time to treatment failure and adverse events within a 31 month time frame. An estimated 947 patients will be enrolled, and the estimated date of final data collection is November 2011, with an estimated study completion date of July 2013.

T1h (Biocon/CIMAB SA), a humanized IgG1 mAb targeting CD6, is undergoing evaluation in Phase 3 studies in psoriasis patients. CD6 is a co-stimulatory receptor on T cells and T1h binds in the membrane-distal domain (SRCR1) of its target.²⁴

Phase 2 studies have or are, evaluating T1h in combination with methotrexate as a treatment for active rheumatoid arthritis and T1h as a single agent in active moderate-to-severe psoriasis. In a dose-finding, single-blind, randomized Phase 2 study, 40 patients with moderate-to-severe psoriasis were administered three different IV doses of T1h once a week, biweekly or every four weeks for eight weeks.²⁵ Patients were then followed for an additional 24 weeks. One dose cohort received 1.6 mg/kg; information on the doses administered to the two other cohorts was not available. The primary endpoints were safety and pharmacokinetics. T1h was well-tolerated; chills and pyrexia were the most common AEs. One patient developed anti-drug antibodies. The mAb's half life was in the range of 11.72–18.51 days across the three dosing regimens. The mean PASI scores at 12 weeks were significantly different compared with baseline scores (22.32–6.23, $p < 0.0001$). PASI50 and 75

responses were 72.5 and 45% respectively, over all patients, with the best response observed in the cohort of patients who were administered 1.6 mg/kg T1h every two weeks. A PGA score of clear or minimum at 12 weeks was obtained by 65% (26/40) of patients.

In March 2010, Biocon reported that T1h had entered a pivotal Phase 3 study of patients with psoriasis. No specific information about the study design or results was available as of September 2010.

REGN88 (SAR-153191; Regeneron Pharmaceuticals/Sanofi-aventis) is a human IgG1 mAb that targets the IL-6 receptor. The mAb is undergoing a Phase 2/3 study in patients with rheumatoid arthritis (RA) and Phase 3 long term evaluations of REGN88 in RA patients and in patients with ankylosing spondylitis.

Results from three Phase 1 studies indicated that subcutaneous REGN88 was well-tolerated in patients with RA who received concomitant methotrexate (MTX).²⁶ A total of 107 patients participated in the three studies. Study 801 included 15 patients with well-controlled RA who received a single dose of 50 mg, 100 mg, 200 mg REGN88 or placebo. Study 803 evaluated the same amounts of single doses in 32 patients with active RA. Study 802 included 60 patients with well-controlled RA who received a single dose of 50 mg, 100 mg, 150 mg, 200 mg REGN88 or placebo weekly or biweekly for five weeks. In these three studies, no dose limiting toxicities were observed. Dose-related reductions in high-sensitivity C-reactive protein (hsCRP), serum amyloid A, erythrocyte sedimentation rate and serum hepcidin were observed after administration of REGN88 in patients with active RA. After a single 200 mg dose of REGN88, HsCRP was suppressed for two weeks.

The randomized, double-blind, placebo-controlled Phase 2/3 study (MOBILITY; NCT01061736) is evaluating REGN88 on top of MTX in adult (18–75 years) patients with active RA who are inadequate responders to MTX therapy. The study is designed with two parts. In Part A, patients are randomized to one of five dosing regimens or placebo comparator. In Part B, two dosing regimens

based on Part A data will be selected and evaluated along with a placebo comparator. The five Part A regimens involve subcutaneous administration of REGN88 on top of MTX, with the doses of REGN88 as follows: 100 mg REGN88 every week (regimen 1); 150 mg REGN88 every week (regimen 2); 100 mg REGN88 biweekly (regimen 3); 150 mg REGN88 biweekly (regimen 4); 200 mg REGN88 biweekly (regimen 5). The primary outcome measure in Part A is the percentage of patients who achieve the American College of Rheumatology (ACR) criteria for improvement ACR20 in a time frame of 12 weeks and the primary outcome measure in Part B is the percentage of patients who achieve ACR20 in a time frame of 24 weeks. The number of patients who will be enrolled is estimated at 1,740 and the estimated completion date is May 2013.

Patients who participated in the Phase 2/3 MOBILITY study are being invited to enroll in an uncontrolled Phase 3 (NCT01146652) long term evaluation of REGN88's safety and efficacy. Adult patients (18 years and older) will be administered 150 mg REGN88 every week on top of disease-modifying antirheumatic drugs (DMARDs) for a maximum of 260 weeks, with a follow up of six weeks after treatment is discontinued. The primary outcome measure is the number of patients with adverse events in a time frame of 266 weeks; secondary outcome measures include the percentages of patients who achieve ACR20 and disease activity score (DAS)28 up to a maximum of 260 weeks and patients European League Against Rheumatism (EULAR) response up to a maximum of 260 weeks. An estimated 1,500 patients will be enrolled and the study completion date is August 2015.

The Phase 3 extension study (NCT01118728) for long term evaluation of REGN88 in patients with ankylosing spondylitis is enrolling only patients who participated in the dose-ranging Phase 2 ALIGN study (NCT0161723). The primary objective of the ALIGN study is evaluation of the efficacy of REGN88 using the Assessment in Ankylosing Spondylitis working group response criteria (ASAS20), with secondary objectives of assessment of a higher level of response (ASAS40),

partial remission, disease activity, range of motion, changes in magnetic resonance imaging score, safety and tolerability and pharmacokinetic profile in ankylosing spondylitis patients. The dose levels to be evaluated are the same as in Part A of the Phase 2/3 MOBILITY study of REGN88 in RA patients; administration is subcutaneous. The time frame for assessments is 12 weeks. The estimated enrollment is 300 adult (18–75 years) patients with ankylosing spondylitis and the estimated study completion date is February 2011.

For the extension study (NCT01118728) of REGN88 in ankylosing spondylitis, enrollment is estimated at 270 patients who will be administered 150 mg REGN88 subcutaneously every week. The primary outcome measure is adverse events in a time frame of first dose up to the end of study participation (maximum of 266 weeks), and the secondary outcome measure is the percentage of patients who obtain ASAS20 in a time frame that is up to a maximum of 260 weeks. The estimated study completion date is March 2016.

AIN-457 (Novartis), a human IgG1 mAb that targets IL-17A, is being evaluated in three on-going Phase 3 studies in patients with various types of uveitis, which is characterized by inflammation, swelling and irritation in the middle, vascular layer of the eye. Each of the Phase 3 studies has an associated extension trial that is either on-going or planned.

AIN-457 was evaluated in an open label Phase 2 study in patients with non-infectious uveitis.²⁷ The study included 11 patients with posterior segment uveitis and five patients with anterior uveitis. The mAb was iv administered at a dose of 10 mg/kg once at baseline and once three weeks later and patients were evaluated over approximately 9 months. The response criteria were met by 73% (8 of 11) of patients with posterior segment uveitis and 60% (3 of 5) patients with anterior uveitis. The average gain in visual acuity was approximately 11.5 and 4.8 letters for patients with posterior segment uveitis and patients with anterior uveitis, respectively.

In the on-going Phase 3 SHIELD study (NCT00995709), the safety and efficacy of AIN-457 is being evaluated in Behçet

syndrome patients with posterior or panuveitis. The syndrome involves multisystem inflammation and has unknown etiology. AIN457 is being compared to placebo, and both are adjunctive to standard of care immunosuppressive therapy. Adult patients (18 years or older) are subcutaneously administered 300 mg AIN-457 biweekly, 300 mg AIN-457 monthly or placebo. The primary outcome measure is determination of effectiveness in reducing the rate of posterior segment uveitis exacerbations secondary to Behçet disease as assessed by visual acuity, anterior chamber cells and vitreous haze at time frames of one to eight weeks, week 12, week 22 and week 24. Secondary outcome measures include determination of whether treatment with AIN-457 reduced the need for standard of care immunosuppressive medications and assessment of safety. A 38 week extension study [NCT01093846] is enrolling patients from the SHIELD study by invitation and has an estimated primary completion date of March 2011.

The on-going, dose-ranging, placebo-controlled Phase 3 ENDURE study (NCT01032915) is assessing the safety and efficacy of AIN-457 in patients with quiescent non-infectious intermediate, posterior or panuveitis. Adult patients (18 years or older) are subcutaneously administered 300 mg AIN-457 weekly for three weeks, 300 mg AIN-457 at baseline and week 2, 150 mg AIN-457 at baseline and week 2 or placebo weekly for three weeks. The primary outcome measure is recurrence of active intermediate, posterior or panuveitis defined by either a ≥ 2 step increase in vitreous haze with or without an increase in anterior chamber cell grade or decrease in best corrected visual acuity of ≥ 10 ETDRS letters after baseline. Secondary outcome measures include a change in immunosuppressive medication score from baseline to week 24 and the mean change in best corrected visual acuity from baseline to week 24. Enrollment is estimated at 232 patients and the estimated primary completion date is April 2011. A 38 week extension study (NCT01090310) was not yet open for participant recruitment as of September 2010.

In the on-going, dose-ranging, placebo-controlled Phase 3 INSURE study (NCT01095250), AIN-457 is being

compared to placebo in inducing and maintaining uveitis suppression in adults (18 years and older) with active non-infectious, intermediate, posterior or panuveitis requiring immunosuppression. Patients are subcutaneously administered AIN-457 at doses of 300 mg biweekly, 300 mg every four weeks or 150 mg every four weeks. The placebo comparator is administered subcutaneously every two weeks. The primary outcome measure is the mean change in vitreous haze grade in the study eye from baseline to 28 weeks or at time of rescue if earlier. Secondary outcome measures include the proportion of responders with no recurrence of active intermediate, posterior or panuveitis in the study eye at 28 weeks, mean change in best corrected visual acuity from baseline to 28 weeks, and change in immunosuppressive medication score from baseline to week 28. Enrollment is estimated at 208 patients and the estimated primary completion date is June 2011. A 34 week extension study (NCT01090310) was not yet open for participant recruitment as of September 2010.

Updates on Anticancer Antibodies in On-going Phase 3 Studies

In addition to the five anticancer mAbs already discussed, eight more (naptumomab estafenatox, girentuximab, zalutumumab, farletuzumab, trastuzumab emtansine, pertuzumab, dalotuzumab, ramucirumab) are in on-going Phase 3 studies (Table 1). Two are immunoconjugates and 5 of the 8 mAbs target antigens that are unique compared to those targeted by mAb products already on the market or in regulatory review (Table 2), i.e., the antigens 5T4 (target of naptumomab estafenatox), carbonic anhydrase ix (target of girentuximab), folate receptor α (target of farletuzumab), insulin-like growth factor-1 receptor (target of dalotuzumab) and vascular endothelial cell growth factor receptor 2 (target of ramucirumab).

Naptumomab estafenatox (ABR-217620; Active Biotech Research) is an immunoconjugate composed of an antigen-binding fragment (Fab) that targets metastasis-associated 5T4 conjugated to a mutated form of Staphylococcal enterotoxin A (SEA/E-120). The Fab bound 5T4

antigen on the human renal cell cancer cell line Caki-2 with an affinity in the order of 1.6 nM, with approximately 180,000 binding sites per cell.²⁸ In an assay of the cytotoxic activity of SEA-activated T-cell cultures, the immunoconjugate induced 5T4-dependent, superantigen antibody dependent cellular cytotoxicity (ADCC) of Caki-2 cells with an EC_{50} of 20 pM. Naptumomab estafenatox was produced in *E. coli* at levels on the order of 50–100 mg/L.²⁸

A Phase 2/3 study (NCT00420888) of naptumomab estafenatox in combination with interferon alpha ($IFN\alpha$) as a treatment for advanced renal cell carcinoma (RCC) is on-going but not recruiting participants. Active Biotech Research announced in June 2009 that patient enrollment in the Phase 3 study was complete, and analysis of the final survival data for ANYARA would be analyzed after 384 events. The date for presentation of the results was estimated to be in the first half of 2011. The primary outcome measure for the study is time to death and secondary outcome measures include progression-free survival time, objective tumor response rate, best overall response and duration of response.

Girentuximab (WX-G250; WILEX), a chimeric IgG1 mAb that targets carbonic anhydrase IX, is currently being evaluated in a Phase 3 study as a treatment for non-metastatic kidney cancer. Results of a Phase 1/2 study of the combination of girentuximab with low-dose ($IFN\alpha$) in patients with progressive metastatic renal cell carcinoma indicated that the combination therapy was safe, well-tolerated and demonstrated clinical benefit in the patient population.²⁹ The Phase 3 ARISER study (NCT00087022) of girentuximab as monotherapy in patients with clear renal cell cancer is on-going but not recruiting patients. WILEX announced in July 2010 that a total of 324 relapses had been reported as of the end of June 2010, and that the next milestone in the study was the occurrence of a total of 343 relapses. An interim analysis after the 343th relapse was planned.

Zalutumumab (HuMax-EGFr; Genmab), a human IgG1 that targets the epidermal growth factor receptor (EGFR), is undergoing evaluation in a Phase 3 study (ZALUTE; NCT00382031) that

is active but not recruiting patients with non-curable squamous cell carcinoma of the head and neck (SCCHN) who have failed standard platinum-based chemotherapy. Top line results from the ZALUTE study were recently reported.³⁰ A total of 286 adult patients (18–75 years; median age 57 years) were randomized in a ratio of 2:1 to either zalutumumab monotherapy (191 patients) or best supportive care (BSC; 95 patients). The initial dose of zalutumumab was 8 mg/kg, and then individually-titrated doses, with a maximum exposure of 16 mg/kg, were administered weekly until disease progression. Most patients (60%) received the highest zalutumumab dose. The median overall survival (OS) was 6.7 months and 5.2 months for patients administered zalutumumab with BSC compared to those who received BSC only, respectively. The difference in OS, which was the primary endpoint of the study, was not statistically significant ($p = 0.065$). The median progression free survival was 9.9 months for patients who were administered zalutumumab and BSC and 8.4 months for those who received BSC only; the difference was clinically meaningful ($p = 0.001$). Non-compliance with the study protocol that might have affected results was noted: 28% of BSC-treated patients and 14% of zalutumumab-treated patients received other anti-cancer therapies that were not permitted by the protocol.

Zalutumumab is also undergoing evaluation in a Phase 3 study (NCT00496652) sponsored by the Danish Head and Neck Cancer Group, a permanent working group of the Danish Society for Head and Neck Oncology, that is currently recruiting previously untreated patients. The study is examining the safety and efficacy of the combination of zalutumumab with radiotherapy. Enrollment is estimated at 600 patients and the estimated study completion date is November 2015.

Farletuzumab (MORAb-003; Morphotek) is a humanized IgG1 mAb that targets human folate receptor alpha, which is overexpressed in most epithelial ovarian cancers (EOC). Results of a Phase 1 study in 25 heavily pretreated patients with platinum-refractory or platinum-resistant EOC were recently reported.³¹ The study evaluated

farletuzumab doses of 12.5, 25, 37.5, 62.5, 100, 200 and 400 mg/m² that were administered IV on days 1, 8, 15 and 22 of a five week cycle. Most patients (23 of 25) received at least four doses of mAb. No dose-limiting toxicities were observed and the maximum tolerated dose was not encountered. The mean terminal half-life estimates from samples taken on day 22 ranged from 120.9 (lowest dose cohort; n = 1) to 260.0 h (highest dose cohort; n = 3). The most common treatment related AEs were hypersensitivity reactions (60% of patients), fatigue (48% of patients) and diarrhea (16% of patients); no serious or severe treatment related AEs or treatment related myelotoxicity or neurotoxicity was observed. Markedly increased levels of human anti-human antibody levels were observed in two patients (one at baseline and one on day 15); most patients did not exhibit anti-drug antibodies at any point.

Results of a Phase 2 study of farletuzumab administered as a single agent or in combination with carboplatin and taxane in 54 patients with platinum-sensitive relapsed EOC patients were recently reported.³² Patients received weekly doses of mAb alone or with the chemotherapy agents administered every 21 days for six cycles, followed by farletuzumab maintenance. Normalization of CA125, a biomarker used to assess disease progression and objective response rate were the primary endpoints of the study. The duration of a second response was compared to each patient's own first response. Of patients who received the combination therapy and whose first progression-free interval was less than 12 months (n = 12), CA125 was normalized in 92%, 64% had either a complete or partial response and 100% had stable disease, a complete response or partial response. Of patients who received the combination therapy and whose first progression-free interval was 12 months or greater (n = 32), CA125 was normalized in 84%, 71% had either a complete or a partial response and 90% had stable disease, a complete response or a partial response.

The Phase 3 study (NCT00849667) of farletuzumab in combination with carboplatin and taxane in patients with platinum-sensitive ovarian cancer who are

in first relapse is currently recruiting participants. The estimated enrollment is 900 patients and the estimated study completion date is September 2012.

Trastuzumab emtansine (T-DM1, trastuzumab-MCC-DM1; Genentech/ImmunoGen) is a humanized IgG1 immunoconjugate that targets the human epidermal growth factor receptor (HER)-2. Naked trastuzumab, i.e., the unconjugated antibody, was first approved by the FDA for treatment of HER2-positive (HER2⁺) metastatic breast cancer in 1998. Trastuzumab was conjugated to the maytansinoid cytotoxin DM1 to form an immunoconjugate that is internalized, undergoes proteolytic degradation in the lysosome and releases lysine-MCC-DM1 is a major active metabolite.

In a Phase 1 study, 24 patients with HER2⁺ metastatic breast cancer who had previously been treated with a median of four prior chemotherapeutic agents were administered 0.3–4.8 mg/kg trastuzumab emtansine on an every three weeks schedule.³³ The maximum tolerated dose was 3.6 mg/kg and the half-life at this dose was 3.5 days, with peak levels less than 10 ng/mL. Drug related AEs of grade 2 or less included thrombocytopenia, fatigue, nausea and anemia. At the 3.6 mg/kg dose, clinical benefit rate among 15 patients was 73% and the confirmed response rate in nine patients with measurable disease was 44%.

Roche announced on July 7, 2010 that the company had submitted a marketing application for accelerated approval to the FDA based on results of a Phase 2 study (TDM4374g; NCT00679211). The 110 metastatic breast cancer patients (34–77 years) who enrolled in this study were HER2⁺ and had received prior anti-HER2 treatments, as well as chemotherapy. Patients were iv administered 3.6 mg/kg doses of trastuzumab emtansine every three weeks. The objective response rate was 32.7% and the clinical benefit rate was 44.5%; these rates increased to 39.5% and 52.6%, respectively, in the cohort of treated patients whose HER2⁺ status was retrospectively confirmed.³⁴ The mAb treatment regimen was well-tolerated and no dose-limiting cardiotoxicity or new safety signals were observed. On August 27, 2010, Roche announced that

the FDA had issued a "Refuse to File" letter stating that the trials of trastuzumab emtansine did not meet the standard for accelerated approval because all available treatment choices approved for metastatic breast cancer, regardless of HER2 status, had not been exhausted in the study population.

Data from the Phase 3 EMILIA study (NCT00829166) and the Phase 3 MARIANNE study (NCT01120184) will be used to support future marketing applications. In the two-arm, open label EMILIA study, trastuzumab emtansine 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. Initiated in March 2009, the study is expected to enroll 580 patients, and has an estimated primary completion date of August 2013.

The 3-arm Phase 3 MARIANNE study (NCT01120184) of the combination of pertuzumab and trastuzumab-DM1 or trastuzumab-DM1 as the only active drug compared to the combination of trastuzumab and a taxane in patients with HER2⁺ progressive or recurrent locally advanced or previously untreated metastatic breast cancer was initiated in July 2010. Patients are randomized into 1 of 3 treatment arms: Arm A, combination of trastuzumab administered iv and either docetaxel or paclitaxel; Arm B, combination of 840 mg pertuzumab administered IV on day 1 of cycle 1 followed by 420 mg doses every three weeks in subsequent cycles and 3.6 mg/kg trastuzumab-DM1 administered IV every three weeks; Arm 3, 3.6 mg/kg trastuzumab-DM1 administered IV every three weeks and a placebo replacement for pertuzumab. Arms B and C are blinded, but Arm A is open label. The primary outcome measures are progression free survival up to approximately 48 months after the study start and incidence of adverse events up to approximately 78 months after study start. Secondary outcome measures include the one-year survival rate, the overall survival rate up to approximately 78 months after

study start and time-to-treatment failure up to approximately 48 months after study start. Enrollment is estimated at 1,092 and the estimated study completion date is July 2017.

Pertuzumab (RO4368451, rhMAB 2C4; Genentech), a humanized anti-HER2 IgG1 mAb that targets HER2, is undergoing evaluation as a combination with other drugs in two Phase 3 studies in patients with HER2⁺ metastatic breast cancer. Pertuzumab and trastuzumab bind to domain II and IV, respectively, of HER2. Preclinical experiments with the combination of pertuzumab and trastuzumab indicated that the two mAbs can bind simultaneously to HER2⁺ tumor cells *in vivo* and they do not compete for binding.³⁵ The mAb combination was also shown to promote tumor regression in tumor xenograft models. These results suggested that the combination may be more efficacious than the single agents.

The combination of pertuzumab and trastuzumab was evaluated in a single-arm, two stage Phase 2 study of patients with HER2⁺ metastatic breast cancer that progressed during prior trastuzumab therapy.³⁶ Adult patients (25–85 years) were administered trastuzumab *iv* either as a 4 mg/kg loading dose, then 2 mg/kg every week or as an 8 mg/kg loading dose, then 6 mg/kg every three weeks. They were also administered pertuzumab *iv* as an 840 mg loading dose, then 420 mg every three weeks. A total of 66 patients were enrolled and treatment continued until progression of the disease or the patient experienced excessive toxicity. The mAb combination was well-tolerated and AEs were mild to moderate. The objective response rate was 24.2%, clinical benefit was observed in 50% and the median progression-free survival was 5.5 months. A total of 17 patients (25.8%) experienced stable disease for 6 months or more.

A Phase 2 study of pertuzumab in HER2-negative metastatic breast cancer patients indicated limited efficacy of the mAb administered as a single agent to this patient population.³⁷ Patients were administered a loading dose of 840 mg, followed by doses of either 420 mg or 1,050 mg every three weeks. A total of 6 of 78 patients (7.7%) responded or had stable disease for 6 months or more.

Pertuzumab is undergoing evaluation in two studies of mAb combinations: the Phase 3 MARIANNE study (NCT01120184) of the combination of pertuzumab and trastuzumab-DM1 and the Phase 3 CLEOPATRA study (NCT00567190), which is evaluating the safety and efficacy 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. Dose amounts for the CLEOPATRA study have not been provided. The CLEOPATRA study is expected to enroll 808 patients who will receive *iv* repeating doses of the experimental and comparator combination of drugs; exact dosing information is not currently available. Initiated in December 2007, the study has an estimated primary completion date of March 2012.

Dalotuzumab (MK-0646; Merck, Pierre Fabre), a humanized IgG1 mAb that targets insulin-like growth factor-1 receptor, was included on the 2010 version of the “Antibodies to watch” list based on classification of an on-going Phase 2/3 study in colorectal cancer as Phase 3, but the decision to proceed to Phase 3 had not been made as of September 2010. The mAb is in on-going Phase 1/2 or Phase 2 studies as a treatment for a variety of cancers, including Stage IIIB or IV metastatic non-squamous lung cancer; extensive stage small cell lung cancer; metastatic hormone receptor-positive, HER2-negative breast cancer; and advanced pancreatic cancer.

Preliminary results from a Phase 1 study of escalating doses of dalotuzumab in combination with gemcitabine or gemcitabine and erlotinib in patients with advanced, previously untreated pancreatic cancer were recently reported.³⁸ The study had two arms that each included two dose levels of dalotuzumab: Arm A, dalotuzumab administered at either 5 or 10 mg/kg doses on days 1, 8, 15 and 22 in combination with 1,000 mg/m² gemcitabine administered on days 1, 8 and 15; Arm B: dalotuzumab and gemcitabine dosed as in Arm A in combination with 100 mg erlotinib administered daily. The statistical design of the study was 3 + 3 and cycles were repeated every four

weeks. With 22 patients enrolled and a median of two cycles (range 1–8) administered, grade 3 or 4 hematologic toxicity was noted as common (neutropenia in nine patients, thrombocytopenia in six patients). Grade 3 hyperglycemia, fatigue and ALT were observed in two, two and three patients, respectively. Dose limiting toxicities were experienced by two patients in Arm B who were administered 10 mg/kg dalotuzumab with gemcitabine and erlotinib. Antitumor activity (six patients with partial responses, three patients with stable disease) was noted in the preliminary results.

The combination of dalotuzumab, cetuximab and irinotecan is under evaluation in an on-going Phase 2/3 study (NCT00614393) of adult patients (18 years and older) with KRAS wild-type metastatic colorectal cancer. The primary outcome measures include overall survival and progression-free survival; a secondary outcome measure is the objective response rate of patients to the experimental 3-drug combination therapy compared to that of the cetuximab-irinotecan combination alone. Enrollment is estimated at 1,112 patients. Initiated in December 2007, the estimated study completion date is January 2014.

Ramucirumab (IMC-1121B; ImClone Systems/Eli Lilly), a human IgG1 mAb that targets the vascular endothelial growth factor receptor-2 (VEGFR2), is currently in Phase 2 studies as a treatment for a variety of cancers, including colorectal, prostate, liver, non-small cell lung and ovarian cancers, as well as melanoma and recurrent glioblastoma multiforme. The mAb is currently in three Phase 3 studies of patients with breast cancer (NCT00703326), gastric cancer or gastroesophageal junction adenocarcinoma (NCT00917384) and hepatocellular carcinoma (NCT01140347). Three additional Phase 3 studies of ramucirumab with or without paclitaxel in metastatic gastric adenocarcinoma (NCT01170663), in second line metastatic colorectal cancer (NCT01183780) and in second line non-small cell lung cancer (NCT01168973) are planned but not yet open for patient enrollment.

Results of a Phase 2 study (NCT00515697) of ramucirumab in

patients with metastatic renal cell carcinoma following VEGFR2 tyrosine kinase inhibitor therapy were reported at the 2010 American Society of Clinical Oncology annual meeting.³⁹ Patients with progressive disease or intolerance to either sorafenib (NEXAVAR®; Onyx Pharmaceuticals/Bayer Healthcare Pharmaceuticals), sunitinib (SUTENT®; Pfizer) or both were IV administered 8 mg/kg ramucirumab biweekly and received tumor assessments every six weeks. A total of 40 patients were enrolled and 39 were treated. Grade 1–2 headache (23% of patients), Grade 1–3 fatigue (18% of patients and Grade 1 nausea (13%) were the most common therapy-related AEs. Nineteen patients (49%) had stable disease that lasted for more than 5 months; preliminary median progression free survival was 6 months.

Three Phase 3 studies of ramucirumab are currently recruiting participants. In an on-going Phase 3 study (TRIO-012; 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. Patients are administered 75 mg/m² docetaxel as a 1 h IV infusion, followed by administration of either 10 mg/kg ramucirumab or placebo as a 1 h IV infusion. The primary outcome measure is progression free survival (PFS) in a time-frame of up to 36 months. The estimated enrollment is 1,113 patients. Initiated in August of 2008, the estimated study completion date is August 2015.

Ramucirumab is also being evaluated in an on-going Phase 3 study (NCT00917384) as a treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy. Patients are administered IV 8 mg/kg ramucirumab doses every two weeks in combination with best supportive care (BSC) 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 overall survival and the secondary outcome measures include PFS, duration of response, quality of life, safety profile,

pharmacokinetic profile and immunogenicity, over a 40 month time frame. Initiated in October 2009, enrollment is estimated at 615 patients and the estimated study completion date is November 2012.

Initiated in August 2010, a third on-going Phase 3 study (REACH; NCT01140347) is evaluating the safety and efficacy of ramucirumab and BSC compared to placebo and BSC as second-line treatment in patients with hepatocellular carcinoma after first-line therapy with sorafenib. Adult patients (18 years and older) are iv administered 8 mg/kg ramucirumab or placebo biweekly. The primary outcome measure is overall survival in a time frame of 27 months. The estimated enrollment is 544 patients and the estimated study completion date is December 2012, with final data collection for the primary outcome measure estimated to be November 2011.

Update on Antibodies for Immunological Diseases in On-Going Phase 3 Studies

In addition to the three mAbs in Phase 3 studies of patients with immunological disorders already discussed (T1h, REGN88 and AIN-457), six more (vedolizumab, orelizumab, teplizumab, epratuzumab, reslizumab and briakinumab) are in on-going Phase 3 studies (Table 3). Three of the six mAbs target antigens that are unique compared to those targeted by mAb products already on the market or in regulatory review (Table 4), i.e., $\alpha 4\beta 7$ integrin (target of vedolizumab), CD22 (target of epratuzumab) and IL-5 (target of reslizumab). Although the target is technically not different than that of the murine muromonab-CD3, orelizumab and teplizumab are engineered anti-CD3 antibodies in clinical studies for a unique indication (Type 1 diabetes mellitus).

Vedolizumab (MLN0002, LDP-02; Takeda/Millennium), a humanized IgG1 mAb that targets $\alpha 4\beta 7$ integrin, is being evaluated as a treatment for ulcerative colitis (UC) and Crohn disease (CD). The mAb blocks binding of lymphocytes to the mucosal addressin cell adhesion molecule-1 (MAdCAM-1), thereby inhibiting lymphocyte trafficking.

The safety and efficacy of the mAb in UC and CD patients is under investigation in three on-going Phase 3 studies: GEMINI I (NCT0078718), GEMINI II (NCT00783692) and GEMINI III (NCT00790933). Enrollment in the Phase 3 studies is limited to patients who have failed at least one conventional therapy.

The safety profile of vedolizumab based on findings from nine Phase I and Phase 2 studies of vedolizumab were recently reported.⁴⁰ A total of 579 patients or health volunteers participated in the studies. Of these, 415 subjects were iv administered single or multiple doses (two to four) of vedolizumab in amounts ranging from 0.15–10 mg/kg. Of those treated with vedolizumab, 84% reported AEs; the most common AEs were headache, nausea, exacerbation of UC, abdominal pain, fatigue and nasopharyngitis. Of placebo-treated subjects, 87% reported AEs.

In the randomized, placebo-controlled GEMINI-I study (NCT0078718), adult patients (18 to 80 years) with moderate-to-severe UC are administered vedolizumab at weeks 0, 2, 6 and then four or eight week intervals for up to 1 year. Dosing information was not provided as of September 2010. 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 study completion date is August 2012.

The randomized, placebo-controlled GEMINI II study (NCT00783692), which has the same dosing regimen as GEMINI I, is evaluating the safety and efficacy of vedolizumab for the induction and maintenance of clinical response and remission in adult patients (18–80 years) with moderate-to-active Crohn disease. The primary outcome measure is the proportion of patients in clinical remission at weeks 6 and 52. Enrollment is estimated at 1,059 patients; the estimated study completion date is December 2012.

GEMINI III (NCT00790933) is a non-randomized, open-label study of vedolizumab to assess long-term safety and efficacy in patients with UC and Crohn disease who participated in GEMINI I, GEMINI II or the Phase 2 NCT00619489 (C13004) study. 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 in a maximum time frame of 100 weeks. Enrollment is estimated at 1,500 patients; the estimated study completion date is November 2013.

Otelixizumab (TRX4, ChAglyCD3; Tolerx, GlaxoSmithKline), a humanized IgG1 mAb, targets CD3 on T cells. The mAb contains a humanized gamma1 heavy chain and a rat/human chimeric lambda light chain and has no glycosylation site in the Fc domain, which limits its Fc-mediated functions. Results of the Belgian Diabetes Registry study, an 18-month, double-blind, randomized, placebo-controlled Phase 2 study that evaluated otelixizumab administered over 6 days to recent-onset Type 1 diabetic patients, were reported in 2005.⁴¹ Pharmacokinetics and anti-drug antibody response to otelixizumab from this study were recently reported.⁴² A total of 40 patients received otelixizumab and 40 received placebo. Otelixizumab was iv administered over 2–4 h for six consecutive days. The first 9 patients received 24 mg otelixizumab or placebo on the first day, followed by 8 mg per day. Four of the nine experienced headache or vomiting after the first infusion; these four were later shown to have received study drug. The remaining 71 patients received 8 mg per day of otelixizumab or placebo for six consecutive days. The terminal half-life was estimated at 1.5 days and dose-dependent accumulation was observed. Anti-drug antibodies were assessed by enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (SPR), which had greater sensitivity compared with the ELISA method. Using SPR, antibody responses were observed in all patients starting on day 8 after initiation of treatment. By days 22 to 29, neutralizing antibodies were detected in a significant proportion of patients.

A total of 80 patients participated in the original Belgian Diabetes Registry study, and 73 consented to the 48 month extension study [NCT00627146] of the otelixizumab- and placebo-treated groups.⁴³ The primary study endpoint was the change in insulin dose over 48 months and this

was compared in 31 and 33 patients in the placebo- and otelixizumab-treated groups, respectively. The mean daily insulin dose increased steadily for patients who received placebo, but initially decreased for those treated with otelixizumab and then increased to a level slightly above the start values. The effect varied with the age and initial residual beta cell function of the patients.

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 study is ongoing and enrollment was complete as of September 2010. The study's objective is to determine if administration of otelixizumab in an 8 day series of infusions leads to improvement in insulin secretion in patients (12–45 years) compared to infusions of placebo. The amount of a dose was not provided as of September 2010. After treatment, patients have follow-up visits weekly for the first month, biweekly for the following 3 months and then monthly visits for the remainder of 1 year. Three additional follow up visits 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 measures are average daily insulin use, HbA1c and incidence of abnormal blood glucose level at 6, 12, 18 and 24 months. The estimated enrollment is 240 patients and the estimated primary completion date is December 2010.

A confirmatory Phase 3 study (DEFEND-2; NCT01123083) in the same patient population was initiated in May 2010. The primary and secondary outcome measures are the same as for the DEFEND-1 study. The enrollment for DEFEND-2 is estimated at 240 and the estimated primary completion date is December 2010.

Teplizumab [MGA031, hOKT3 γ 1 (Ala-Ala); MacroGenics, Eli Lilly] is a humanized IgG1 mAb that targets CD3 and has been engineered to have reduced binding to FcR. The 4-arm, controlled Phase 2/3 study PROTÉGÉ study (NCT00385697) of teplizumab in children and adults with recent on-set Type 1 diabetes is on-going but not recruiting

participants. Patients (8–35 years) are administered one of three dose levels of teplizumab or placebo daily for 14 days and receive two courses of this treatment. Dose amounts were not provided as of September 2010. The primary outcome measure is successful compared with unsuccessful clinical response; assessment of total daily insulin usage and HbA1c levels over 12 months is used to determine clinical response. The secondary outcome measures include C-peptide secretory responses over 24 months. Enrollment is an estimated 554 patients and the estimated study completion date is June 2011.

Longer-term safety and efficacy data from patients who complete the PROTÉGÉ trial are being collected in the observational Phase 3 PROTÉGÉ Extension study (NCT00870818). The primary outcome measures include the number and percentage of subjects who experience a serious AE, AE of special interest (e.g., opportunistic infection, lymphoproliferative disease) or other Immediately Reportable Event during the 3 year study period. Secondary outcome measures include determination of the efficacy of teplizumab by measuring patient's total daily insulin usage and HbA1c levels. Estimated enrollment is 530 patients and the estimated study completion date is June 2014.

The Phase 3 PROTÉGÉ Encore study (NCT00920582) of teplizumab in children and adults with recent-onset Type 1 diabetes is designed to capture patient-reported outcome measures, as well as safety and efficacy data. The Protégé Encore study includes the same patient population and four-arm study design as the Protégé study. An estimated 400 patients will participate and the estimated study completion date is June 2012.

Epratuzumab (hLL2; Immunomedics/UCB) is a humanized IgG1 mAb that targets CD22 on B cells. The mAb has been studied for systemic lupus erythematosus (SLE) and a variety of cancer indications since 1997. Commercial development is currently focused on epratuzumab as a treatment for SLE.

Results from a randomized, double-blind, placebo-controlled, dose and dose regimen-ranging Phase 2 study (NCT00624351) of epratuzumab in

serologically-positive SLE patients with active disease were reported in June 2010.⁴⁴ Adult patients (18 years and older) were randomized into a placebo arm or 1 of 5 experimental arms of the study. The study population included 227 patients (mean age 38.8 years, 94% female). Those in the experimental arms received cumulative doses (cd) ranging from 200–3,600 mg epratuzumab as follows: Arm 1, 600 mg infusions for each of four weeks (cd 2,400 mg); Arm 2, 100 mg infusions at weeks 0 and 2 and placebo at weeks 1 and 3 (cd 200 mg); Arm 3, 400 mg infusions at weeks 0 and 2 and placebo at weeks 1 and 3 (cd 800 mg); Arm 4, 1,200 mg infusions at weeks 0 and 2 and placebo at weeks 1 and 3 (cd 2,400 mg); Arm 5, 1,800 mg infusions at weeks 0 and 2 and placebo at weeks 1 and 3 (cd 3,600 mg). The primary endpoint was a combined responder index of clinical disease activity at week 12, which was defined as reduction of all baseline British Isles Lupus Assessment Group (BILAG) A to B/C/D and BILAG B to C/D in all body systems, no BILAG worsening in other organ systems, and no deterioration in Systemic Lupus Erythematosus Disease Activity Index or Physicians Global Assessment and with no increase in corticosteroid or immunosuppressive use over baseline. Responder rates were 21.1, 30.8, 26.3, 45.9, 40.5 and 23.7% in the placebo, 100 mg biweekly, 400 mg biweekly, 600 mg weekly, 1,200 mg biweekly and 1,800 mg biweekly groups, respectively. The responder rates were statistically greater in the 600 mg weekly group compared to placebo ($p = 0.03\%$). Epratuzumab was well-tolerated and the incidence of serious adverse events and infusion reactions was similar between epratuzumab- and placebo-treated patients.

An open label, retreatment Phase 3 study (NCT00383513) of SLE patients who participated in either of two Phase 3 studies (NCT00111306, NCT00383214) that were terminated due to an interruption of drug supply is on-going but not recruiting patients. Adult patients (18 years and older) are iv administered 360 mg/m² epratuzumab on 12 week maintenance cycles beginning with two consecutive weekly infusions. The primary outcome measure is assessment of

safety over a time frame of 4 years and the secondary outcome measures include assessment of efficacy, tolerability and immunogenicity over 4 years. Initiated in June 2006, the estimated enrollment is 30 patients and the estimated study completion date is February 2014. In June 2010, UCB indicated that it will initiate two Phase 3 studies of epratuzumab in patients with moderate-to-severe lupus in the second half of 2010.

Reslizumab (CEP-38072, CTx55700, SCH55700; Cephalon, Inc.) is a humanized anti-IL5 IgG4 mAb that is now sponsored by Cephalon after their acquisition of Ception Therapeutics in April 2010. The safety and efficacy of reslizumab is being evaluated in one Phase 3 extension study (NCT00635089) in pediatric patients with eosinophilic esophagitis, which is an allergic inflammatory disease characterized by elevated levels of eosinophils and infiltration of these cells in the esophagus. Only patients who participated in the Phase 2/3 NCT00538434 (Res-5-002) study were eligible to participate in the Phase 3 study, which was not recruiting patients as of September 2010.

Top-line results from a double-blind, placebo-controlled Phase 2 study [NCT00587288] of reslizumab in adult patients with poorly controlled eosinophilic asthma were announced in April 2010 by Cephalon.⁴⁵ A total of 106 patients were IV administered 3 mg/kg or placebo once every 28 days for four cycles. The primary endpoint was improvement in asthma control as assessed by changes in scores on the Asthma Control Questionnaire (ACQ) at week 15. ACQ scores were improved in patients who received reslizumab compared to those who received placebo ($p = 0.054$). Differences that were statistically significant were seen in secondary outcome measures such as reduction in sputum eosinophil counts ($p = 0.006$) and improvement in indices for assessment of airway obstruction, bronchoconstriction or broncodilation (FEV1, $p = 0.002$ and FVC, $p = 0.004$) for patients who received reslizumab compared to those who received placebo. Reslizumab was generally well-tolerated, with AEs comparable between the two groups. The most common AE associated

with administration of reslizumab compared to placebo was nasopharyngitis.

Top-line results from the Phase 2/3 study [NCT00538434; Res-5-002] were announced by Ception Therapeutics and Cephalon in November 2009.⁴⁶ A total of 226 pediatric patients (between 5 and 18 years) with poorly controlled eosinophilic esophagitis were iv administered 1, 2, 3 mg reslizumab or placebo on day 0 of each 28 days cycle (± 7 days) for four treatment cycles. There were statistically significant reductions in peak esophageal eosinophils at all dose levels compared to placebo ($p < 0.0001$).

In the on-going Phase 3 extension study (NCT00635089), pediatric patients (5 years and older) are iv administered 1 mg/kg reslizumab monthly. The primary outcome measure is the safety profile of reslizumab in a time frame of approximately 4 months and the secondary outcome measure is the profile of treatment response durability in a time frame of approximately 4 months. Enrollment is estimated at 190 patients and the estimated study completion date is January 2011.

Briakinumab (ABT-874; Abbott) is a human IgG1 mAb that targets the p40 subunit that is common to both IL12 and IL23. The safety and efficacy of the mAb in patients with moderate-to-severe chronic plaque psoriasis were evaluated in four Phase 3 studies that were completed as of September 2010.

The Phase 3 NCT00570986 study evaluated two dosing regimens compared to placebo. In regimen 1, adult patients (18 years and older) were administered briakinumab at doses of 200 mg at week 0 and week 4, 100 mg at week 8, then at week 12, Arm 1 was rerandomized to 100 mg every four weeks. In regimen 2, patients were administered briakinumab at doses of 100 mg every 12 weeks, with the regimen not used for weeks 0–11 of the study. A total of 1,465 patients participated and the study was completed in mid-2009; no published results were available as of September 2010.

The Phase 3 NCT00691964 and NCT00710580 studies compared the effects of briakinumab to etanercept and placebo in patients with moderate-to-severe chronic plaque psoriasis. The route

of administration was subcutaneous for active drugs as well as placebo. Adult patients were administered 200 mg briakinumab at week 0 and 4 and 100 mg at week 8. Patients in the active comparator arm were administered 50 mg etanercept twice weekly. 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 September 2010.

The Phase 3 NCT00679731 study of briakinumab compared with methotrexate was conducted in patients with moderate-to-severe plaque psoriasis. Adult patients are administered regimens of either 200 mg subcutaneous briakinumab at week 0 and 4, followed by 100 mg at week 8 and every four weeks thereafter or methotrexate at doses of 5–25 mg weekly. A total of 317 patients are enrolled and the estimated primary completion date was November 2009; no published results were available as of September 2010.

The long-term safety, efficacy and tolerability of briakinumab are being assessed in a Phase 3 open label continuation study (NCT00626002) in patients with moderate-to-severe psoriasis who completed a preceding psoriasis study of the mAb. Adult patients (18 years and older) are subcutaneously administered 100 mg briakinumab every four weeks for approximately 160 weeks. The study was on-going but not recruiting patients as of September 2010. A total of 2,301 patients are enrolled and the estimated primary completion date is April 2011.

Updates on Other Antibodies in On-Going Phase 3 Studies

A total of three of the 25 novel mAbs in Phase 3 studies are undergoing evaluation as treatments for indications that are not cancer or immunological disorders (Table 5). All three candidates are unmodified, full-size IgG1 antibodies. One mAb targets an infectious agent and two are for Alzheimer disease (AD). There is no overlap of the targets with those of FDA-approved products or any mAbs undergoing FDA review (Table 6). Pagibaximab is designated by the FDA as an orphan drug

and bapineuzumab has FDA's Fast Track designation.

Pagibaximab (BSYX-A110; Biosynex) is a chimeric IgG1 mAb developed for the prevention of staphylococcal sepsis in very-low-birth-weight (VLBW) neonates. The mAb targets lipoteichoic acid, a highly-conserved component in the staphylococcal cell wall.

A pharmacokinetic (PK) model and dosing regimen developed to attain pagibaximab serum levels at or greater than 500 µg/mL for 35 days in VLBW infants who would participate in future Phase 3 studies were recently described.⁴⁷ Based on data from serum antibody levels from 100 VLBW infants administered 10–90 mg/kg pagibaximab or placebo for 1–3 doses, the PK model described a two compartment model with linear central compartment elimination. The PK parameters were (mean ± SE): clearance (mL/h) 0.446, volume of distribution (V) 175, V2 138, C0int 12.3 and elimination rate constant (Ke) 0.000836, with a t1/2 of 15.4 days. A dosing regimen of 100 mg/kg daily for 3 days and then weekly for three weeks was developed using the model and this regimen was prospectively evaluated based on analysis of samples obtained for 35 days from VLBW infants administered pagibaximab. The prospective analysis confirmed that the model-based dosing regimen maintained serum levels at or greater than 500 µg/mL in the infants.

The safety, efficacy and pharmacokinetics of 6 doses of pagibaximab in VLBW neonates for the prevention of staphylococcal sepsis is currently being evaluated in a Phase 2b/3 study (NCT00646399). Infants up to 48 h old with a birth weight of between 600 and 1,200 g and an estimated gestational age of 33 weeks or less 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, pharmacokinetics and efficacy in a time frame of 0–35 days. Neonatal sepsis will be assessed by the presence of clinical signs and symptoms and a blood culture positive for *Staphylococcus aureus* or two blood cultures positive for coagulase negative Staphylococci. An estimated 1,550 subjects will be enrolled and the estimated study completion date is May 2011.

Solanezumab (LY2062430; Eli Lilly), a humanized IgG1 mAb that targets soluble amyloid beta, is undergoing evaluation as a treatment for mild-to-moderate AD. In binding its target, the mAb may alter the equilibrium between amyloid beta in the blood and central nervous system.

Results for a study of the effects of a single dose of solanezumab in patients with mild-to-moderate AD were recently published.⁴⁸ A total of 19 patients were administered single doses of 0.5, 1.5, 4.0 and 10.0 mg/kg solanezumab. Gadolinium-enhanced magnetic resonance imaging of the brain and analyses of the cerebrospinal fluid (CSF) at baseline and 21 days after dosing were done to assess safety. Concentrations of solanezumab and amyloid β in the plasma and CSF were determined and cognitive evaluations were performed. Administration of single doses of solanezumab was generally well-tolerated, although two of four patients administered 10 mg/kg infusion reactions experienced infusion reactions. A dose-dependent change in plasma and CSF amyloid beta was observed; cognitive scores did not change.

The safety and efficacy of solanezumab administration in AD patients is currently being evaluated in two Phase 3 studies, Expedition and Expedition 2 (NCT00905372 and NCT00904683, respectively). In each study, adults (55 years and older) with mild-to-moderate AD are administered 400 mg solanezumab or placebo once 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 Expedition study is on-going but not recruiting patients, while the Expedition 2 study was recruiting patients as of September 2010. The estimated enrollment in each study is 1,000 patients; the estimated study completion date is August 2012 and September 2012 for the Expedition and Expedition 2 studies, respectively.

An open label, uncontrolled Phase 3 extension study (Expedition Ext; NCT01127633) for continued efficacy and safety monitoring of patients who

participated in either the Expedition or Expedition 2 study through 80 weeks was planned, but not yet open for participant recruitment as of September 2010. In the Expedition Ext study, patients will be iv administered 400 mg solanezumab once every four weeks for 100 weeks. The primary outcome measures are vital signs, laboratory values and electrocardiograms that are statistically different between the treatment groups in a time frame of 104 weeks. The estimated enrollment is 1,275 patients and the estimated study completion date is July 2014.

Bapineuzumab (AAB-001; Pfizer/Janssen Alzheimer Immunotherapy) is a humanized IgG1 mAb that targets the N-terminus of amyloid beta and is currently being evaluated in seven Phase 3 studies. Of these, three are extension studies.

The results of a placebo-controlled, multiple ascending dose Phase 2 study [NCT00112073] of bapineuzumab's safety and efficacy in mild-to-moderate AD patients were reported in 2009.⁴⁹ A total of 234 adults were randomized to receive 6 iv doses of 0.15, 0.5, 1.0 or 2.0 mg/kg bapineuzumab or placebo that were given 13 weeks apart over a period of 78 weeks. Treatment differences between the patients who received bapineuzumab compared to those who were administered placebo were observed only in the 79 patients who were non-carriers of the APOE $\epsilon 4$ allele. For these patients, statistically significant differences were seen in the Alzheimer disease assessment scale-cognitive subscale (ADAS-Cog; $p = 0.026$), neuropsychological test battery ($p = 0.006$), mini-mental state examination ($p = 0.043$) and the clinical dementia rating-sum or boxes ($p = 0.040$), but not on the disability assessment of dementia (DAD; $p = 0.137$). Reversible vasogenic edema (VE) was detected by MRI in 9.7% (12/124) of patients treated with bapineuzumab and none of those who received placebo. VE rates increased with increasing doses of bapineuzumab. Ten of the 12 patients who experienced VE were APO $\epsilon 4$ carriers. Other AEs in bapineuzumab-treated vs. placebo-treated patients included back pain (12.1 vs. 5.5%), anxiety (11.3 vs. 3.6%) and vomiting (9.7 vs. 3.6%).

Phospho-tau (P-tau) protein has been identified as a biomarker of active loss of brain cells in AD patients. The effects of bapineuzumab on P-tau and total tau levels in cerebrospinal fluid (CSF) were reported at the Alzheimer's Association International Conference on Alzheimer's Disease in 2010.⁵⁰ Pooled analyses of two randomized, double-blind, placebo-controlled, multiple-ascending-dose Phase 2 studies indicate that bapineuzumab may decrease P- and total tau in the CSF of Alzheimer patients.

The effects of bapineuzumab in patients with mild-to-moderate AD who are not ApoE4 carriers are being evaluated in two placebo-controlled Phase 3 studies (NCT00574132 and NCT00667810). As of September 2010, dosing information was not available for these studies. An estimated 1,300 and 1,000 adult patients (50–88 years) will participate in NCT00574132 and NCT00667810, respectively. The primary outcome measures for NCT00574132 and NCT00667810 are cognitive and functional measures and ADAS-Cog and DAD, respectively. The estimated completion dates are August 2012 and June 2014 for NCT00574132 and NCT00667810, respectively.

A long-term Phase 3 study [NCT00996918] of patients who participated in NCT00667810 was initiated in December of 2009. Patients are administered 0.5 or 1.0 mg/kg bapineuzumab. The primary outcome measures include incidence and severity of treatment emergent AEs, clinically important changes in vital signs and physical and neurological examinations during a time frame of 2 years. The estimated enrollment is 1,000 patients and the estimated study completion date is June 2016.

Two on-going Phase 3 studies (NCT00575055, NCT00676143) are evaluating the safety and efficacy of bapineuzumab compared to placebo as a treatment for mild-to-moderate AD in adult patients (50–88 years) who are Apo $\epsilon 4$ carriers. As of September 2010, dosing information was not available for these studies. The primary outcome measures for NCT00575055 are cognitive and functional in a time frame of 18 months; the estimated enrollment is

1,000 patients and the primary completion date is February 2012. The primary outcome measures for NCT00676143 are ADAS-Cog and DAD in a time frame of 78 weeks; the estimated enrollment is 800 patients and the study completion date is June 2013.

Two Phase 3 extension studies (NCT937352, NCT00998764) are assessing the long-term safety and tolerability of the bapineuzumab in patients with mild-to-moderate AD. Initiated in July 2009, patients who participated in either NCT00574132 (non-Apo $\epsilon 4$ carriers) or NCT00575055 (Apo $\epsilon 4$ carriers) are being invited to enroll in NCT937352. The effects of iv administration of 0.5 or 1.0 mg/kg bapineuzumab every 13 weeks for 2.5 years in adult (55 years or older) AD patients are being evaluated. The primary outcome measures include clinically important changes in safety assessment results in a time frame of 2.5 years or when the marketing application is submitted (whichever comes first). The estimated enrollment is 1,350 patients and the estimated primary completion date is June 2012.

NCT00998764 is the extension of the Phase 3 NCT00676143 study of AD patients who carry the Apo $\epsilon 4$ allele. Patients are administered 0.5 mg/kg bapineuzumab in this non-randomized, open label, single assignment study. The primary outcome measures include incidence and severity of treatment emergent AEs and clinically important changes in vital signs in a time frame of 2 years. The estimated enrollment is 800 patients and the estimated study completion date is June 2015.

Two mAbs New to Regulatory Review

Belimumab and ipilimumab first entered US regulatory review in 2010. Human Genome Sciences, sponsor of belimumab, announced on June 10, 2010 that a biologics license application (BLA) had been filed with the FDA. Bristol-Myers Squibb announced on August 19, 2010 that a BLA for ipilimumab had been accepted for review by FDA. Both BLAs were granted FDA's priority review designation. The due dates for FDA's first actions are

December 9, 2010 for belimumab's BLA and December 25, 2010 for ipilimumab's BLA. Marketing applications for belimumab and ipilimumab are also undergoing review at the European Medicines Agency.

Belimumab (Human Genome Sciences, GlaxoSmithKline), a human IgG1 mAb that targets B lymphocyte stimulator (BLyS), is undergoing FDA review as a treatment for systemic lupus erythematosus (SLE) as of September 2010. A member of the tumor necrosis factor cytokine family, the soluble ligand BLyS binds to any of three receptors on B lymphocytes and contributes to differentiation, homeostasis and selection of these cells. The antigen is overexpressed in SLE patients and changes in BLyS concentration correlate with increased disease activity.

The BLA includes results from the Phase 3 BLISS-52 study (NCT00424476) and the Phase 3 BLISS-76 study (NCT00410384). The results of BLISS-52 were presented at the American College of Rheumatology (ACR) annual meeting in October 2009. Results of BLISS-76 as well as additional data from the BLISS-52 study were presented in June 2010 at the 2010 Congress of the European League Against Rheumatism (EULAR). Additional data from both studies were presented at the International Congress on SLE in June 2010.⁵¹⁻⁵³ In these studies, patients were iv administered placebo or belimumab at 1 or 10 mg/kg doses on days 0, 14, 28 and every 28 days through either 48 (BLISS-52 study) or 72 weeks (BLISS-76). Final assessments occurred at week 52 and week 76 for the BLISS-52 and BLISS-76 studies, respectively.

In the BLISS-52 study, a clinically and statistically significant improvement was shown in the SLE responder index (SRI) response rate at week 52 for patients who were administered belimumab and standard of care compared to those who received placebo and standard of care.⁵² The response rate was 57.6% for the 10 mg/kg belimumab group (n = 290; p = 0.0006) and 51.4% for the 1 mg/kg belimumab (n = 288; p = 0.013) compared to 43.6% for the placebo group (n = 287). There was a statistically significant (p < 0.05) difference in the number

of responders in the 10 mg/kg belimumab group compared to the placebo group at week 16 that was sustained through week 52. For the 1 mg/kg group, the improvement was statistically significant at week 24 and sustained through week 52.

In BLISS-76, based on an intention-to-treat analysis of the data, statistically significant improvement over placebo was observed in belimumab-treated patients at week 52.⁵³ The SRI was 43.2% for the 10 mg/kg belimumab group (n = 273; p = 0.017), 40.6% for the 1 mg/kg belimumab (n = 271, p = 0.089) and 33.5% for the placebo group (n = 275) at week 52. At week 76, the difference between the groups was not statistically significant (38.5% for 10 mg/kg belimumab, 39.1% for 1 mg/kg belimumab and 32.4% for placebo, with p = 0.13 and p = 0.11 for the 10 mg/kg and 1 mg/kg belimumab groups, respectively compared with placebo).

Two long-term continuation studies (NCT00712933 and NCT00724867) of belimumab are enrolling by invitation only SLE patients who participated in either the BLISS-52 or -76 studies. Patients will be administered the same belimumab regimen as in the BLISS-52 and -76 studies and the primary outcome measure of both studies is the evaluation of long-term safety of belimumab in SLE patients until the belimumab is approved. The estimated study completion date is December 2010 for both studies.

Ipilimumab (MDX-010, BMS-734016; Medarex/Bristol-Myers Squibb) is a human IgG1 mAb that targets CTLA4 IgG1. The product candidate is in FDA review as a treatment for advanced melanoma in adults who have been previously treated for the disease. Ipilimumab has been or is being studied in over 50 clinical studies of patients with a variety of cancers, including prostate, pancreatic, urothelial, lung, brain, breast, colorectal and renal cancer, as well as lymphoma and chronic myeloid leukemia. In melanoma patients, the mAb has been studied as a single agent,^{54,55} in combination with dacarbazine,⁵⁶ and in combination with a glycoprotein (gp) 100 vaccine.⁵⁷ Clinical benefit appears to be associated with "immune-related adverse events" (irAE) that often affect the skin and gastrointestinal tract.

Results of the 3-arm, randomized, double-blind Phase 3 study (NCT00094653) of ipilimumab in HLA-A*0201-positive patients with unresectable stage III or IV melanoma who had experienced disease progression while being treated for metastases were published in 2010.⁵⁷ A total of 676 patients were assigned to receive 3 mg/kg ipilimumab and gp100 (n = 403), 3 mg/kg ipilimumab alone (n = 137) or gp100 alone (n = 136). The median overall survival was 10.0 and 10.1 months for the ipilimumab + gp100 and ipilimumab alone groups, respectively, compared with 6.4 months for the gp100 alone group. The differences between both the ipilimumab-treated groups compared with the gp100-treated group were statistically significant. The most common AEs were immune-related and occurred in approximately 60% of ipilimumab-treated patients and 32% of gp100-treated patients. A total of 14 deaths were study drug related; 7 of these deaths were associated with irAEs.

Ipilimumab is in two Phase 3 studies in melanoma patients (NCT00324155, NCT00636168) and two Phase 3 studies in prostate cancer patients (NCT00861614, NCT01057810) as of September 2010. In the 2-arm Phase 3 study NCT00324155, the combination of ipilimumab and dacarbazine is being compared to dacarbazine and placebo in adult patients (18 years and older) with untreated stage III or IV melanoma. Patients in Arm 1 are IV administered 10 mg/kg ipilimumab every three weeks for ten weeks, then one dose ipilimumab every 12 weeks starting at week 24, in addition to IV doses of dacarbazine at 850 mg/m² every three weeks for 22 weeks or until disease progression. Patients in Arm 2 receive placebo and the same regimen of dacarbazine. The primary outcome measure is overall survival, which is assessed at every visit; secondary outcome measures include progression-free survival, disease control rate, best overall response rate and survival at 1, 1.5 and 2 years. The enrollment is estimated at 500 patients and the estimated study completion date is November 2011.

The effects of ipilimumab as adjuvant immunotherapy are being compared with placebo in a Phase 3 study (NCT00636168) of patients with high

risk stage III melanoma. The study will determine if ipilimumab is effective in preventing or delaying reoccurrence and prolonging survival after complete resection of this type of melanoma. During the induction phase of Arm 1, adult patients (18 years or older) are iv administered 10 mg/kg ipilimumab every 21 days for four cycles; in the maintenance phase starting at week 24, patients are then administered 10 mg/kg ipilimumab every 12 weeks until week 156 or progression. Patients in Arm 2 receive iv placebo on the same schedule. The primary outcome measure is recurrence-free survival. The estimated enrollment is 950 patients and the estimated study completion date is September 2014.

Fc Fusion Proteins in Phase 3 Studies

A total of five candidates composed of the Fc of a human IgG1 antibody fused to a peptide or protein with specificity toward one or two targets are in Phase 3 clinical studies. Two (aflibercept, AMG 386) of these Fc fusion proteins are being studied as cancer treatments, one (atacept) is undergoing evaluation in systemic lupus erythematosus patients and two (Factor IX-Fc, Factor VIII-Fc) are intended as treatments for hemophilia (Table 7). Information for marketed Fc fusion proteins is shown in Table 8. The addition of an Fc to a recombinant protein increases the serum half-life of the resulting molecule through the interactions of the Fc with the neonatal FcR (FcRn).⁵⁹ The Fc fusion proteins typically have shorter half-lives compared with full-size human or humanized mAbs, which may be due to lower affinity of the Fc fusion proteins for FcRn.⁵⁹

Aflibercept (VEGF Trap, AVE-0005, BAY86-5321; Regeneron/Sanofi-aventis/Bayer) is composed of the extracellular domains of the vascular endothelial growth factor receptors (VEGFR)-1 and -2 fused to the Fc of a human IgG1 and binds to VEGF-A isoforms as well as placental growth factor. Designed to interfere with angiogenesis, the candidate is in Phase 3 studies as a potential treatment for a variety of cancers and ocular disorders.

In a Phase 1 study, 47 patients with advanced solid tumors were iv administered doses of 0.3, 1, 2, 3, 4, 5 or 7 mg/kg aflibercept every two weeks.⁶⁰ The apparent terminal half life was 1.70 days in patients who received the 0.3 mg/kg dose and ranged from 5.51–7.43 days in patients who received doses in the 3.0–7.0 range. No anti-aflibercept antibodies were detected in any patient. In patients who received 7 mg/kg aflibercept, dose limiting toxicities were rectal ulceration and proteinuria. Grade 3 hypertension was also observed in patients in the 4, 5 and 7 mg/kg dose groups.

The effects of iv administration of 4 mg/kg aflibercept every two weeks to 22 patients with recurrent or metastatic urothelial cancer were evaluated in a Phase 2 study.⁶¹ Grade 3 toxicities included fatigue, hypertension, proteinuria, pulmonary hemorrhage and pain. Limited single-agent activity was observed in the patient population. Modest or limited activity was also observed when aflibercept was administered as a single agent at 4 mg/kg doses every two weeks to patients with recurrent or metastatic gynecologic soft-tissue sarcomas⁶² or platinum- and erlotinib-resistant adenocarcinoma of the lung.⁶³ Evidence of activity was observed for the 4 mg/kg aflibercept every 2 week regimen in patients with radioactive iodine-refractory, positron emission tomography positive thyroid carcinoma,⁶⁴ recurrent inoperable stage III or stage IV melanoma of cutaneous or ocular origin⁶⁵ and recurrent temozolomide-resistant glioblastoma.⁶⁶

Four on-going Phase 3 studies are evaluating aflibercept in combination with a chemotherapy agent in patients with colorectal, non-small cell lung, prostate or pancreatic cancer. Dosing information for these studies was not provided as of September 2010. Specifically, aflibercept is being evaluated in combination with irinotecan and 5-FU in patients with metastatic colorectal cancer who failed on an oxaliplatin-based regimen [VELOUR; NCT00561470]; with docetaxel in patients with locally advanced or metastatic non-small cell lung cancer who failed one platinum-based therapy [VITAL; NCT00532155]; with docetaxel and prednisone in patients with

metastatic androgen-independent prostate cancer [VENICE; NCT00519285]; and with gemcitabine in patients with metastatic pancreatic cancer [VANILLA; NCT00574275]. In addition, a Phase 2/3 study [NCT00327444] of aflibercept administered every two weeks to advanced ovarian cancer patients with recurrent symptomatic malignant ascites was completed in October 2009.

Aflibercept is also undergoing evaluation as a potential treatment for ocular diseases. In a Phase 1 study, 21 patients with neovascular age-related macular degeneration (AMD) were administered a single intraocular injection of 0.05, 0.15, 0.5, 1.0, 2.0 or 4.0 mg aflibercept.⁶⁷ Assessment for the primary end point occurred at six weeks, with follow-up continuing until week 12. At the end of the 6 week period, the mean decrease in excess foveal thickness was 104.5 μ m and the mean increase in visual acuity was 4.43 for all patients. For patients who received either 2 or 4 mg doses of aflibercept, the mean increase in best-corrected visual acuity (BCVA) was 13.5 letters.

The safety and efficacy of repeated dosing of aflibercept are being investigated in two Phase 3 studies (VIEW 1 and VIEW 2) of patients with wet age-related macular degeneration. These are non-inferiority studies that will compare results for aflibercept with those for ranibizumab (Lucentis®, Genentech). In the 4 arm VIEW 1 study [NCT00509795], adult patients (50 years and older) in arms 1 and 2 are administered either 0.5 or 2.0 mg aflibercept every four weeks for 1 year, then the same dose is administered as frequently as every four weeks but no less frequently than every 12 weeks. Patients in arm 3 are administered 2.0 mg aflibercept at weeks 4 and 8, then every eight weeks for the first year. Thereafter, dosing is as frequently as every four weeks but no less frequently than every 12 weeks. The active comparator (arm four) is ranibizumab administered every four weeks during the first year, then dosed as frequently as every four weeks but no less frequently than every 12 weeks. The primary outcome measure is the proportion of subjects who maintain vision at week 52 (i.e., prevention of moderate vision loss) within a time frame of 52 weeks. The

secondary outcome measures include mean change from baseline in BCVA as measured by ETDRS letter score at week 52 and the proportion of subjects who gain at least 15 letters of vision at week 52. The estimated enrollment, which occurred at sites in the US and Canada and is complete, is 1,200 patients and the estimated study completion date is December 2011.

Patients who participate in VIEW 1 through week 96 and have neovascular AMD in the study eye are eligible to participate in the Phase 3 extension study [NCT00964795]. An estimated 960 patients invited to participate are intravitreally administered 2 mg aflibercept at a minimal interval of every four weeks and a maximum interval of every 12 weeks at the discretion of the investigator. The estimated study completion date is September 2013. The on-going VIEW 2 [NCT00637377] has the same design as VIEW 1, but is being conducted at sites in Europe, Asia Pacific, Japan and Latin America by Bayer. A total of 1,211 patients were recruited; the estimated study completion date is August 2011.

Two on-going Phase 3 studies (COPERNICUS and GALILEO) are evaluating the safety, efficacy and tolerability of repeated intravitreal administration of aflibercept in patients with macular edema due to central retinal vein occlusion (CRVO). In the COPERNICUS study (NCT00943072), adult patients (18 years and older) receive monthly 2.0 mg injections of aflibercept or placebo until evaluation at week 24. The primary outcome measure is improvement in visual acuity compared to baseline after 6 months of treatment and the secondary outcome measures are visual acuity and retinal thickness by optical coherence tomography (OCT) in a time frame of 24 weeks. The estimated enrollment is 165 patients and the estimated study completion date is August 2012.

In the placebo-controlled GALILEO study [NCT01012973], patients in the experimental arm receive intravitreal injections of aflibercept every four weeks during weeks 0–20, every four weeks during weeks 24 to 52 plus additional injections of either aflibercept or placebo on week 60 and 68 at re-assessment. Patients in the placebo arm receive sham

treatment every four weeks during weeks 0 to 20, reassessment and sham injection every four weeks during weeks 24–48, an injection of aflibercept at week 52 unless the investigator declines for medical reasons, reassessment and either injection of aflibercept or placebo at weeks 60 and 68, with a final visit at week 76. The primary outcome measure is the proportion of patients who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at week 24. The secondary outcome measures include change from baseline in BCVA score at 24 weeks, absolute change from baseline in central retinal thickness as assessed by OCT at week 24 and the proportion of patients progressing to anterior segment neovascularization of the optic disc or neovascularization of the retina elsewhere requiring pan-retinal photocoagulation at week 24. The estimated enrollment is 165 patients and the estimated study completion date is March 2012.

AMG 386 (2xCon4[C]; Amgen), a “peptibody” composed of a peptide that binds angiopoietins Ang-1 and Ang-2 fused with a human IgG1 Fc, selectively inhibits the interactions of Ang-1 and Ang-2 with their receptor, Tie2, thereby affecting angiogenesis. In an assessment of AMG 386 as a competitive inhibitor of angiopoietin-Tie2 interaction by ELISA, AMG 386’s IC₅₀ was 0.023 nM and 0.9 nM for human Ang2-Tie2 and Ang1-Tie2, respectively.⁶⁸ A Phase 3 study [TRINOVA-1; NCT01204749] of AMG 386 or placebo in combination with weekly paclitaxel in patients with ovarian cancer, primary peritoneal cancer and fallopian tube cancer was planned as of September 2010.

AMG 386 has been or is being, evaluated in Phase 2 studies in patients with a variety of cancers, including HER2-negative breast, metastatic colorectal, hepatocellular, epithelial ovarian or primary peritoneal cancer, as well as renal cell carcinoma and metastatic gastric, gastroesophageal junction or distal esophageal adenocarcinoma. The peptibody is one of at least five drugs undergoing evaluation in the I-SPY 2 Phase 2 study (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis 2;

NCT01042379) of neoadjuvant and personalized adaptive novel agents to treat breast cancer sponsored by the Foundation for the National Institutes of Health. The study uses a Bayesian adaptive design developed in cooperation with the FDA, which allows investigators to graduate, discontinue and add drugs throughout the study period. As of September 2010, five investigational drugs were included: AMG 386, conatumumab (AMG 655; Amgen), figitumumab (Pfizer), neratinib (HKI-272; Pfizer) and veliparib (ABT-888; Abbott). The stated purpose of the study is “to further advance the ability to practice personalized medicine by learning which new drug agents are most effective with which types of breast cancer tumors and by learning more about which early indicators of response (tumor analysis prior to surgery via magnetic resonance imaging (MRI) images along with tissue and blood samples) are predictors of treatment success.”⁶⁹ AMG 386 will be iv administered to patients in the I-SPY 2 study at doses of 15 mg/kg every week during 12 weekly treatment cycles post-randomization.

In Phase 1 studies, AMG 386 administered iv at doses of 0.3, 1, 3, 10 or 30 mg/kg was well-tolerated in patients with advanced solid tumors and the elimination half-life was in the range of 3.1–6.3 days.^{70,71} The exposure-response relationships of AMG 386 administered to advanced ovarian cancer patients at 3 or 10 mg/kg doses in combination with weekly paclitaxel in a Phase 1 and a Phase 2 study indicated an association between exposure and progression-free survival, but that the maximum benefit was not reached at the 10 mg/kg dose of AMG 386.⁷² In the Phase 2 study [NCT00479817], 161 patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer were randomized to receive weekly IV doses of 3 mg/kg or 10 mg/kg in combination with 80 mg/m² paclitaxel given weekly on a three weeks on, one week off schedule or paclitaxel alone.⁷³ Grade 3 or higher AEs that occurred more frequently in patients who received AMG 386 included hypokalemia, peripheral neuropathy, anorexia, neutropenia and dyspnea. The primary endpoint of the study was median progression-free survival, which was 7.2, 5.7 and

4.6 months in the 10 mg/kg AMG 386, 3 mg/kg AMG 386 and paclitaxel alone groups, respectively. The study conclusion was that the peptibody was tolerable in this patient population and showed promising evidence of antitumor activity with a dose-response effect.

In the planned TRINOVA-1 Phase 3 study [NCT01204749], the effects of AMG 386 or placebo in combination with weekly paclitaxel will be evaluated in patients with ovarian, primary peritoneal and fallopian tube cancer. Dosing information was not provided as of September 2010. The primary outcome measure is progression-free survival in a time frame of 8 months on average and the secondary outcome measures include overall survival in a time frame of 20 months on average, objective response rate from baseline (if subject has measurable disease) until objective response (radiologic) and duration of response from baseline until progression. The study start date is October 2010. The enrollment is estimated at 900 patients; the estimated primary completion date for final primary outcome measure data is July 2013 and the estimated study completion date is April 2017.

Atacept (TACI-Ig; ZymoGenetics/MerckSerono) comprises the extracellular domain of transmembrane activator and calcium-modulating ligand interactor (TACI) fused to the Fc of human IgG1. The candidate is in Phase 2/3 studies as a treatment for generalized systemic lupus erythematosus (SLE), which is characterized by the presence of antibodies to self-antigens such as chromatin. B cells are thought to play a key role in the pathogenesis of the disease.⁷⁴ Atacept binds to B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), two members of the tumor necrosis factor superfamily that are overexpressed in the sera of patients with autoimmune disorders,⁷⁵ and thus interferes with B-cell signal transduction induced by these two ligands. In Phase 2 studies, the effects of atacept administration were investigated in patients with multiple sclerosis, optic neuritis and lupus nephritis, but these studies had been terminated as of September 2010. One Phase 2 study in rheumatoid arthritis patients was completed and one was recruiting patients as of September 2010.

Results from two dose-escalating Phase 1b studies of either subcutaneous or iv administration of atacept in SLE patients were recently reported.^{76,77} In the study of subcutaneous administration, 49 patients (age range 23–64) with mild-to-moderate SLE received placebo or atacept as follows: single doses of 0.3 mg/kg, 1 mg/kg, 3 mg/kg or 9 mg/kg atacept with 6 week follow-up period; multiple doses of 1 mg/kg or 3 mg/kg atacept once a week for four weeks with a nine week follow-up period.⁷⁶ Atacept-treated patients reported more mild injection site reactions than those who received placebo. No statistical differences were observed in the AEs between the placebo-and atacept-treated patients. Dose-dependent reductions in immunoglobulin levels and in mature and total B-cell numbers were observed. A trend toward improvement in disease activity in atacept-treated patients was observed.

In the Phase 1b study of iv administered atacept, 24 patients (21–66 years) with mild-to-moderate SLE were administered placebo, single doses of 3, 9 or 18 mg/kg atacept or two doses of 9 mg/kg atacept over three weeks.⁷⁷ Patients who received a single dose were followed for six weeks and those who received two doses were followed for nine weeks after dosing. Atacept was well-tolerated at a total dose up to 18 mg/kg. Reductions in mature B-cell counts and decreases in immunoglobulin levels were observed. In the studies of both sc and iv administration, atacept displayed multiphasic PK in SLE patients and had similar biological activity profiles.⁷⁸ Bioavailability was approximately 30–40% in both studies.

The on-going Phase 2/3 study [NCT00624338] is intended to evaluate the effects of subcutaneously administered atacept compared to placebo in SLE patients. Patients (16 years and older) will be administered placebo or atacept (75 or 150 mg) twice a week for four weeks and then once a week for 48 weeks. The primary outcome measure is the proportion of patients experiencing a new flare as defined by a British Isles Lupus Assessment Group (BILAG) score of A or B during the 52 week treatment period. The secondary outcome measures are the time to new flare after randomization

and proportion of patients with new flare within the first 24 weeks after randomization. The estimated enrollment is 510 patients and the estimated study completion date is October 2012.

Factor VIII-Fc (rFVIII-Fc; Biogen Idec/Swedish Orphan Biovitrum), comprising recombinant Factor VIII fused with a human IgG1 Fc, is undergoing investigation for the prevention and treatment of bleeding in previously treated patients with severe hemophilia A. The candidate received orphan drug product designation in Europe in September 2010. A recombinant Factor VIII (ReFacto®)/Factor VIII-Fc cross-over study in two Factor VIII-deficient dogs demonstrated that the half-life of Factor VIII-Fc by chromogenic assay was approximately twice that of ReFacto® (15–16 h vs. 7–8 h).⁷⁹ Whole blood clotting times were corrected to the normal range of 10–20 min after 125 IU dose and remained in that range for approximately 90–120 h. Anti-Factor VIII antibodies were measurable in both dogs by 168 h.

The safety, tolerability and PK of a single iv dose of Factor VIII-Fc in these patients was evaluated in a two-arm Phase 1 study [NCT01027377] of 16 male patients (12 years and older) who were iv administered either (1) a single low dose of recombinant Factor VIII (ADVATE; Baxter) followed by a single 25 international units (IU)/kg dose of Factor VIII-Fc; or (2) a single high dose of recombinant Factor VIII (ADVATE; Baxter) followed by a single 65 international units (IU)/kg dose of Factor VIII-Fc. PK assessments were done after administration of the recombinant Factor VIII and the study drug. The primary outcome measure was safety in a time frame of 78 weeks and the secondary outcome measures were PK parameters, comparison of the PK of recombinant Factor VIII with that of Factor VIII-Fc and determination of the pharmacodynamics activity of Factor VIII over time for both doses of Factor VIII-Fc. The final study data was collected in July 2010. Factor VIII-Fc was well-tolerated and had a prolonged half-life compared to recombinant Factor VIII;⁸⁰ no additional data was available as of September 2010.

The safety, PK and efficacy of Factor VIII-Fc in male patients (12 years and older)

with severe hemophilia A will be investigated in a three-arm Phase 2/3 study [A-LONG; NCT01181128] that was not yet open for participant recruitment as of September 2010. In two arms of the study, patients will be iv administered either low dose or high dose Factor VIII-Fc as a prophylactic agent. Patients in the third study arm will receive Factor VIII-Fc on demand. The primary outcome measures are clinically notable changes from baseline in physical examinations, vital signs, lab values, incidence of AEs and inhibitor development and the annual number of either spontaneous or traumatic bleeding episodes in a time frame of 156 weeks. The secondary outcome measures include the total annualized Factor VIII-Fc consumption per subject, evaluation of PK parameter estimates of Factor VIII-Fc and recombinant Factor VIII at baseline and at week 12–28 and evaluation of subjects' response to treatment in a time frame of 156 weeks. The estimated enrollment is 150 patients; the study completion date was not given as of September 2010.

Factor IX-Fc (rFIXFc; Biogen Idec/Swedish Orphan Biovitrum), comprising recombinant Factor IX fused with a human IgG1 Fc, is in a Phase 2/3 study [B-LONG; NCT01027364] for prevention and treatment of bleeding in previously treated patients with hemophilia B. The candidate has US orphan drug product designation for the control and prevention of hemorrhagic episodes in patients with hemophilia B and it also has orphan drug status in Europe. In preclinical studies of two Factor IX-deficient dogs administered 140 IU/kg, the terminal half-life of Factor IX-Fc was 47.5 h when the data were analyzed using WinNonLin and 38.5 h when based on activity data.⁸¹ The whole blood clotting activity in the dogs was corrected to approximately normal levels through 144 h after dosing. The terminal half-life of Factor IX-Fc was approximately 47 h in cynomolgus monkeys.

The safety and PK of Factor IX-Fc in previously treated hemophilia B patients was investigated in an open-label, dose-escalation Phase 1/2 study [NCT00716716]. A total of 14 adult (18 years and older) males were iv administered a single dose of 1, 5, 12.5, 25, 10 or 100 IU/kg Factor IX-Fc. The Factor IX-Fc

was well-tolerated; no drug related serious AEs, but two AEs (headache, altered taste) were reported as related to Factor IX-Fc dosing. The half-life of Factor IX-Fc was 52.5 ± 9.2 h.⁸² No additional data was available as of September 2010.

The Phase 2/3 B-LONG study will investigate the safety, PK and efficacy of iv administration of Factor IX-Fc to male hemophilia B patients who are 12 years or older. Low and high doses of Factor IX-Fc, as well as use of the candidate for on-demand treatments and in surgical settings, will be compared. The primary outcome measures include safety, tolerability and number of breakthrough bleeding episodes in a time frame of 156 weeks. The secondary outcome measures include evaluation of the patients' response to treatment and consumption of Factor IX-Fc in a time frame of 156 weeks. The estimated enrollment is 75 patients and the estimated study completion date is January 2013.

Possibilities in 2011 and Beyond

In addition to the sponsoring companies, patients and the medical community are eagerly awaiting the outcome of the Phase 3 clinical studies of the 30 mAb and Fc protein therapeutics discussed here. In 2011, the cast of candidates on the watch list will change as some progress to regulatory review, others revert to earlier phases or are terminated and new candidates enter Phase 3. With approximately 140 and 120 novel mAbs in Phase 1 and 2 studies, respectively, as well as a dozen Fc fusion protein therapeutics in either Phase 1 or 2 studies, a variety of antibody-based candidates should be eligible for Phase 3 study in the future. The information presented here will serve as a baseline against which progress of the candidates can be measured in 2011 and beyond.

Note Added in Proof

In a press release issued in October 2010, Lilly announced that the primary endpoint in the PROTÉGÉ study (NCT00385697) had not been met and enrollment and dosing in the PROTÉGÉ and PROTÉGÉ Encore (NCT00920582) studies were suspended. In a press release issued in October 2010, Abbott announced that marketing applications for briakinumab

were filed in the US and Europe during the third quarter of 2010.

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