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CD19 as an attractive target for antibody-based therapy

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Despite progress in the treatment of B cell disorders, novel treatment approaches are still highly needed. CD19 is a pan-B cell marker that is recognized as a potential immunotherapy target for B cell disorders, including blood-borne malignancies and autoimmune diseases. Although initial attempts to target CD19 were unsuccessful, a new wave of investigational agents is currently in development. These agents are based on novel antibody-based technologies and formats that appear to better exploit CD19's therapeutic potential, and some promising clinical study data has already been reported. This review provides an overview and the rationale for the most advanced CD19-targeting programs in development.

Introduction

Monoclonal antibodies have emerged as a valuable approach for the treatment of cancer. This is most evident in the case of B cell malignancies, where CD20 antibodies have revolutionized the standard of care. Rituximab, a chimeric anti-CD20 antibody, represents a major breakthrough in the treatment of B cell malignancies. It is highly effective in non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) either as monotherapy or in combination with chemotherapy regimens.[1] Nevertheless, many patients relapse or progress while being treated with rituximab. Moreover, certain B cell malignancies [acute lymphocytic leukemia (ALL) and multiple myeloma] do not express CD20 and are consequently not amenable to CD20 modulation. Therefore, there is still a need to expand beyond CD20 and identify novel targets for the treatment of B cell leukemias and lymphomas.

Additional B cell markers such as CD19, CD22, CD79B and CD37 have the potential to fill the therapeutic void presented by rituximab relapse or refractory disease.[2-4] CD19 is emerging as a promising target due to several factors. It is expressed on a variety of B cell lymphomas and leukemias and on normal B cells, but it is not found on hematopoietic stem cells, plasma cells, and other healthy tissues. CD19 has a broader expression profile than that of CD20 and it is thought to be a better target for antibody-drug conjugates (ADC) compared with CD20, which suffers from inefficient internalization. CD19 was also shown to be expressed in cases where rituximab is ineffective due to CD20 downregulation or other factors.[5,6] Lastly, because CD19-targeting agents have a mode of action that is distinct from that of anti-CD20 antibodies, they could complement existing rituximab regimens.

Conventional antibodies targeting CD19 demonstrate limited activity in preclinical models, despite high CD19 expression and antibody internalization.[5,7,8] This has led to the evaluation of CD19 in the context of novel immunotherapy approaches such as bispecific antibodies, ADCs, Fc- engineered antibodies and chimeric-antigen receptor (CAR)-transduced T cells (**Table 1**). As several of these programs have already generated promising results in clinical trials, CD19 antibody-based therapy has the potential to become a valuable addition to the armamentarium of hematology drugs.

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CD19 Programs in development

Blinatumomab (Amgen): Phase 2 (pivotal). Blinatumomab is currently the most advanced CD19 program, with two pivotal Phase 2 studies in progress. It belongs to a novel class of bispecific antibodies, bispecific T-cell engager (BiTE), that redirect T cells to attack cancer cells.[9,10] It comprises two scFvs that bind CD3 and CD19, respectively. Upon simultaneous binding of both targets, blinatumomab brings a T cell and a target cell in close proximity, which leads to T cell activation and subsequent killing of the target cell.

Blinatumomab and other BiTE antibodies have demonstrated potent activity in various preclinical models.[11,12] In in vitro killing assays using peripheral blood mononuclear cells (PBMC), blinatumomab had an EC_{50} of 50 pg/ml compared with 11–50 ng/ml for rituximab.[12] In in vivo xenograft models, blinatumomab completely prevented tumor formation at cumulative doses of 5 or 0.5 μg per animal.[13]

In clinical studies, blinatumomab has been evaluated in NHL and ALL. To mitigate side effects and maintain prolonged exposure to this rapidly-cleared antibody, blinatumomab is given as a continuous infusion, typically for a 4–8 week period. In the Phase 1 NHL trial, blinatumomab demonstrated objective responses across a variety of NHL subtypes.[14] In the 22 patients who received the highest dose of the drug (60 $\mu g/m^2$/day), a response rate of 82% was observed, including a complete

Table 1. CD19 immunotherapy programs in development

Sponsor	Program	Class	MOA	Phase	Indications
Amgen	Blinatumomab	Bispecific scFv- CD19xCD3 (BiTE)	T cell recruitment	2	ALL, DLBCL
Sanofi-Aventis	SAR3419	Antibody-drug conjugate	Delivery of toxic payload	2	DLBCL, ALL
Medimmune (AstraZeneca)	MEDI-551	Glyco-engineered antibody	Enhanced ADCC	2	DLBCL, CLL, MS
Montefiore Medical Center	Combotox	scFv immunotoxins (CD19, CD22)	Delivery of toxic payload	1	ALL
NCI	DT2219ARL	Bispecific immunotoxin- CD19/CD22	Delivery of toxic payload	1	B cell malignancies
Morphosys/Xencor	MOR-208/Xmab5574	Fc engineered antibody	Enhanced ADCC	1	CLL
Xencor/Amgen	XmAb-5871	Fc engineered antibody	B cell inhibition via CD32B	1	RA, SLE
Bristol-Myers Squibb	MDX-1342	Glyco-engineered antibody	Enhanced ADCC	1 (on hold)	CLL, RA
NCI	CD19-CAR	Chimeric antigen receptor (CAR)	Engineered T cells (CD28)	1	NHL, CLL
University of Pennsylvania	CART19	Chimeric antigen receptor (CAR)	Engineered T cells (4-1BB)	1	CLL
Seattle Genetics	SGN-19A	Antibody-drug conjugate	Delivery of toxic payload	Preclinical	
Affimed	AFM11	Tetravalent bispecific antibody - CD19xCD3	T cell recruitment	Preclinical	
Glenmark	GBR401	Naked antibody	ADCC	Preclinical	
Macrogenics	CD19xCD3 DART	Bispecific scFv- CD19xCD3 (DART)	T cell recruitment	Preclinical	

ADCC, antibody-dependent cell-mediated cytotoxicity; ALL, acute lymphoblastic leukemia; BiTE, bispecifc T cell engager; CAR, chimeric antigen receptors; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; DART, dual-affinity re-targeting; DLBCL, diffuse large B cell lymphoma; MS, multiple sclerosis; NHL, non-Hodgkin lymphoma; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

response (CR) rate of 45%. Interestingly, blinatumomab had activity in patients with bulky disease and resulted in massive T cell infiltration according to repeated biopsies. The study was expanded to enroll diffuse large B cell lymphoma (DLBCL) patients based on initial signs of clinical activity.

Blinatumomab was evaluated in a Phase 2 trial as consolidation treatment in ALL patients with minimal residual disease (MRD).[15] MRD status is defined by the presence of a detectable amount of leukemia cells in the bone marrow in the absence of active disease in the blood. MRD is associated with disease aggressiveness and poor prognosis.[16,17] In the trial, MRD status was evaluated using patient-specific PCR-based assays that could detect 1 tumor cell in 10^4 bone marrow cells. Of 20 patients enrolled in the trial, 80% experienced a MRD response (defined as no evidence of MRD). At a median follow-up of 405 d, the probability for relapse-free survival was 78%.

Another Phase 2 trial evaluated blinatumomab in relapsed/refractory ALL. In this dose ranging study, patients were assigned to one of three regimens of blinatumomab. The antibody generated a complete response (with or without hematologic recovery) in 17 (68%) of 25 evaluable patients. Strikingly, all responders also achieved a MRD response, implying that their bone marrow had no detectable presence of leukemic cells.[18]

The most common adverse events associated with blinatumomab were flu-like symptoms, which were typically observed in the first 48 h following treatment initiation. Blinatumomab's safety profile was manageable in the ALL studies, which utilized relatively low doses (5–15 μg/m^2/day). In the NHL trial, however, investigators encountered a high degree of CNS toxicities that were reversible upon drug discontinuation. These side effects might be prevented using a lower starting dose in high-risk patients (low B:T cell ratio).

Blinatumomab is currently being evaluated in two pivotal trials in ALL. The first trial is a single arm Phase 2 study initiated in 2010 that is expected to enroll 130 patients and could lead to approval in Europe. The primary endpoint is conversion to MRD-negative status, based on PCR tests. Results are expected in the later part of 2013. The second pivotal trial is a Phase 2 trial in relapsed/refractory ALL. This single arm, 65-patient trial, was initiated in late 2011. The primary endpoint is complete response rate after 2 cycles and results are expected in 2013. Additional studies evaluate blinatumomab in pediatric ALL and DLBCL, which is an aggressive subtype of NHL.

SAR3419 (Sanofi/Immunogen): Phase 2. SAR3419 is an anti-CD19 ADC currently in Phase 2 studies. The molecule is composed of the humanized antibody huB4 conjugated to the maytansine derivative DM4 via a cleavable disulfide linker.[19] Upon binding to CD19 on the surface of cells, SAR3419 is internalized and delivers its toxic payload into the cell, resulting in inhibition of microtubule assembly and cell death.

Based on robust preclinical activity in various xenograft models of NHL, including superiority over rituximab,[20] SAR3419 advanced into clinical testing in 2007. It was evaluated in two Phase 1 trials employing two dosing regimens (every 3 weeks and weekly) in NHL patients. In the every 3 weeks dosing trial, objective responses were seen in 6 (17%) out of 35 evaluable patients who received doses in the range of 10–270 mg/m^2.[21] Of note, 20 (57%) additional patients experienced tumor shrinkage. In the weekly dosing trial, 44 patients received 10–70 mg/m^2 of SAR3419. Of 21 patients who received the maximum tolerated dose (55 mg/m^2), 7 (33%) achieved a response.[22]

SAR3419 is not associated with severe hematologic or gastrointestinal toxicities, which are maytansine's primary toxicities. The most clinically-relevant dose limiting toxicity was ocular toxicity primarily in the form blurred vision. To minimize incidence of ocular toxicity, a modified schedule (4 weekly doses of 55 mg/m^2 followed by every 2 weeks dosing of 55 mg/m^2) has been evaluated. This optimized regimen resulted in decreased incidence of ocular toxicities with similar activity in the form of a 29% response rate in 21 evaluable patients.[23]

SAR3419 is currently being evaluated in three Phase 2 trials. Two trials are evaluating SAR3419 as monotherapy in DLBCL and ALL patients, respectively. The third trial is evaluating SAR3419 in combination with rituximab in DLBCL patients who are rituximab pre-treated.

MEDI-551 (AstraZeneca): Phase 2. MEDI-551 is an Fc-engineered humanized CD19 antibody with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). Because the antibody is produced in a fucosyltransferase-deficient cell line, it is afucosylated and therefore has increased binding to FcγRIIIA.[24] MEDI-551 was found to mediate strong ADCC against multiple cell lines and had potent activity in various in vivo models. Compared with rituximab in vivo, MEDI-551 exhibited superior growth inhibition in some models, although it was comparable or inferior to rituximab in others.[25]

MEDI-551 entered two Phase 1 studies in patients with B cell malignancies and scleroderma, respectively. The B cell malignancy study included NHL, CLL and multiple myeloma patients who received MEDI-551 at doses of 0.5–12 mg/kg. Of 34 evaluable patients, 9 (26.5%) achieved an objective response.[26] MEDI-551 appeared to have a benign safety profile and no maximum-tolerated dose was reached. The most frequent adverse events were infusion reaction and nausea, which were predominantly grade 1/2, although some grade 3 adverse events were observed.

Two large randomized Phase 2 trials comparing MEDI-551 to rituximab are currently on-going. One trial is evaluating the combinations of MEDI-551 and bendamustine vs. rituximab and bendamustine in 156 relapsed/refractory CLL patients. The second trial is in 170 rituximab-pretreated DLBCL patients, where either MEDI-551 or rituximab is added to salvage chemotherapy prior to autologous stem cell transplant. Another Phase 2 trial is evaluating MEDI-551 compared with interferon-β-1a for the treatment of multiple sclerosis.

Combotox (Montefiore Medical Center): Phase 1. Combotox is a mixture of two immunotoxins that target CD19 and CD22, respectively. Both immunotoxins are scFv antibodies fused to deglycosylated ricin A chain. Combotox and each immunotoxin demonstrated potent activity in in vitro and in vivo models of B cell leukemia.[27,28]

Combotox has been evaluated in two Phase 1 trials in adult and pediatric ALL, respectively. In the pediatric Phase 1, Combotox was given to 17 patients, 3 of which achieved a complete response.[29] In the adult ALL study, 1 out of 17 patients achieved a partial response.[30] Dose limiting toxicities in both studies included vascular leak syndrome, liver enzyme elevation and pancreatitis. Antibodies against the immunotoxins were observed in only 7–18% of patients, which may be due to the short exposure to Combotox and patients' dysfunctional immune system. A Phase 1 evaluating the combination of Combotox and cytarabine in ALL patients started in June 2011.

DT2219ARL (Scott and White Hospital and Clinic): Phase 1. DT2219ARL, a bispecific immunotoxin targeted to CD19 and CD22, is composed of two scFv antibodies and a truncated form of a diphtheria toxin. Upon binding and internalization, the immunotoxin leads to strong inhibition of protein synthesis. In preclinical testing, DT2219ARL demonstrated anti-cancer activity using in vitro and in vivo of B cell malignancies.[31] A Phase 1 for DT2219ARL in B cell malignancies was initiated in 2009 and was to be completed in April 2012. No study results have been released as of June 2012.

MOR-208/XmAb-5574 (Morphosys/Xencor): Phase 1. XmAb-5574 is an Fc-engineered anti-CD19 antibody with enhanced FcγRIIIA binding, which results in improved ADCC activity. In contrast to MEDI-551 and MDX-1342, XmAb-5574's Fc modification involves changes in the protein sequence of the Fc domain rather than the glycosylation pattern.[32] In preclinical studies, XmAb-5574 demonstrated in vitro and in vivo anticancer effect primarily mediated by ADCC.[33,34] Administration of XmAb-5574 to monkeys led to an immediate and dose-related B cell depletion that was not observed with a conventional anti-CD19 antibody.[35]

XmAb-5574 entered Phase 1 in CLL in December 2010. In May 2012, Morphosys and Xencor announced the study completed enrollment of 30 relapsed/refractory CLL patients.[36] According to the announcement, no dose-limiting toxicity was observed and the study protocol was amended to include a period of extended dosing for patients responding to treatment. Results from the study are expected in the fourth quarter of 2012.

XmAb-5871 (Xencor/Amgen): Phase 1. XmAb-5871 is a humanized, Fc-engineered, anti-CD19 antibody for the treatment of autoimmune diseases. The antibody's Fc domain selectively binds FcγRIIB (CD32B), an inhibitory receptor on B cells which leads to suppression of B cell activity upon co-engagement.[37] Therefore, XmAb-5871 exploits the physiologic inhibitory role of FcγRIIB to regulate the immune system. Notably, XmAb-5871 is not expected to cause general B cell depletion, which could confer a better safety profile compared with B cell depleting antibodies such as rituximab, belimumab or other anti-CD19 antibodies. In preclinical models, XmAb-5871 inhibited antigen-specific B cell activation in vitro and demonstrated robust activity in vivo in mice engrafted with PBMC from lupus patients.[38] XmAb5871 entered Phase 1 study in October 2011.

MDX-1342 (Bristol-Myers Squibb): Phase 1 (suspended). MDX-1342 is an Fc-engineered human anti-CD19 antibody with enhanced ADCC. Similarly to MEDI-551, it is an afucosylated antibody produced in a fucosyltransferase-deficient cell line.[39] In preclinical testing, the antibody was active in murine lymphoma models and demonstrated profound B cell depletion in monkeys.[39]

MDX-1342 entered clinical testing in 2008. Two Phase 1 studies evaluated the antibody's safety and efficacy in CLL and

rheumatoid arthritis. Preliminary results from the CLL study included early signs of activity in the form of 1 partial response (PR) out of 9 evaluable patients. A decrease in WBC and CD20+ cells was observed across several doses.[40] This program appears to be terminated because both Phase 1 studies have been put on clinical hold without any further disclosure and the program no longer appears on the pipeline of Bristol-Myers Squibb.

SGN-CD19A (Seattle Genetics) – Preclinical. SGN-CD19A is an anti-CD19 ADC currently in preclinical testing. It is composed of a humanized antibody conjugated to monomethyl auristatin E (MMAE) via a protease-sensitive peptide-based linker. Upon binding of target cells, SGN-CD19A internalizes into cells and releases its payload, leading to microtubule destabilization and cell death. In preclinical testing, SGN-CD19A demonstrated robust anti-cancer activity in multiple models, including in vivo models of rituximab-resistant cells.[5] According to Seattle Genetics' website, SGN-CD19A is expected to enter Phase 1 during 2012.[41]

AFM11 (Affimed): Preclinical. As a bispecific antibody targeting CD3 and CD19, AFM11 is designed to recruit T cells for killing CD19 positive cells. It is constructed based on the RECRUIT TandAb format, which entails a tetravalent structure with two binding sites for each antigen.[42] This enables bivalent binding to both the effector target (CD3) and the therapeutic target (CD19), leading to superior killing activity compared with a conventional bivalent format.

In preclinical testing, AFM11 demonstrated potent in vitro killing activity using PBMC or T cells as effector cells, without any cytotoxicity toward non-target cells. In an in vivo model, AFM11 led to a dose-dependent anti-tumor effect using PBMC as effector cells.[43] AFM11 is expected to enter Phase 1 during 2013.

GBR401 (Glenmark): Preclinical. GBR 401 is a humanized anti-CD19 monoclonal antibody currently in preclinical testing. It depletes CD19 positive cells primarily via ADCC. GBR401 had profound activity in SCID mice adoptively transferred with human PBMC.[44] GBR401 started IND-enabling studies in 2011 and is expected to enter clinical study in 2012.[45]

CD19xCD3 DART (Macrogenics): Preclinical. Dual-affinity re-targeting (DART) antibodies represent a novel and diverse class of bispecific antibodies. A DART molecule comprises 2 variable regions with each consisting of a V_H and a V_L domain, which is a format similar to BiTE antibodies. In contrast to BiTE antibodies, a DART antibody is encoded by 2 different polypeptide chains that contain a V_H domain from one Fv fused to a V_L domain from the other Fv.[46] A cysteine residue is engineered into each polypeptide chain to create a disulfide link that provides structural stability. To date, more than 60 DART molecules have been produced, including different variants that involve fusing DARTs to Fc or IgG.[47]

A CD19xCD3 DART was designed for optimal recruitment of T cells for killing CD19-positive cells. Like blinatumomab, it is a bivalent antibody capable of co-engaging a T cell and a target cell simultaneously. Using PBMC as effector cells, CD19xCD3 DART demonstrated potent lysis of CD19-positive cells in a target-specific manner.[48] Interestingly, compared with the same Fv sequences incorporated into a BiTE format, CD19XCD3 DART was 16–60 fold more potent. A 2nd generation CD19xCD3 DART with improved cross-reactivity to non-human primates and a more frequent dosing regimen is currently in preclinical development.

CD19-targeted chimeric-antigen receptors. Chimeric-antigen receptors (CARs) are T cells that are genetically modified to express a targeting moiety (most commonly antibodies) on their surface. These targeting moieties confer the desired specificity toward cells that express a given target, regardless of T cell receptor (TCR) specificity.[49,50] Typically, the antibody is fused with an intracellular signaling domain of the TCR complex (CD3-zeta chain). Upon binding target cells via the antibody moiety, CARs undergo activation that leads to proliferation, cytokine production, and lysis of target cells. Importantly, as a cellular treatment, CARs have the potential to replicate and expand in vivo upon chimeric receptor engagement, which could result in durable anti-tumor effect.

The 1st generation of CARs that entered the clinic demonstrated disappointing activity stemming from insufficient persistence in the body, loss of antigen receptor expression, low efficacy and suboptimal cytokine production.[51-53] This result prompted the development of 2nd generation CARs that are currently in clinical development. To overcome some of the limitations of 1st gen CARs, 2nd generation versions include endodomains of co-stimulatory molecules such as CD28, 4–1BB (also known as CD137) and OX40.

Typical production of CARs involves collecting peripheral T cells from a patient, genetically engineering the cells to express the chimeric receptor and expansion ex vivo. The cells are then injected into patients following lymphodepletion in combination with IL-2 in some cases. There are currently over 10 clinical trials evaluating CD19-targeting CARs,[54] some of which have already demonstrated profound and sustained anti-cancer activity. Two programs that have recently generated positive data are described below.

Anti-CD19-CAR (National Cancer Institute): Phase 1. Anti-CD19-CAR is generated by retroviral transduction of an anti-CD19 antibody fused to CD3 zeta chain and CD28 endodomain as a co-stimulatory factor. Preclinical testing using a murine version of the CAR demonstrated robust anti-lymphoma activity.[55]

A Phase 1 study recruited 8 patients with relapsed B cell malignancies (NHL or CLL) who were given autologous anti-CD19-CAR.[56] Patients were lymphodepleted with cyclophosphamide and fludarabine prior to CAR administration, which were given as a single infusion followed by IL-2 every 8 h until dose limiting toxicity was noted.

Of 8 evaluable patients, 6 achieved an objective response (1 CR, 5 PR), with duration of response of 6–18 mo and some still ongoing at the time of publication. One patient died of influenza shortly after CAR administration and was consequently excluded from the efficacy analysis. Because patients received lymphodepleting treatment and IL-2, it is difficult to assess the exact contribution of anti-CD19-CAR to the responses.

Interestingly, one of the responding patients had been previously treated with anti-CD19-CAR and reported as a case study.[57]

This patient, who had originally achieved a PR with a duration of 7 mo with the first CAR treatment, experienced a more durable PR (18 mo, ongoing at the time of publication) following retreatment with anti-CD19-CAR.

The most common toxicity was B cell depletion and hypogammaglobulinemia, which were expected given the expression of CD19 on B cells. In addition, every patient experienced multiple grade 3/4 adverse events, including hypotension, fever, renal failure and capillary leak syndrome. These toxicities generally peaked during the first 8 d after CAR-transduced T cell infusion and resolved over time. There appeared to be a correlation between cytokines level (IFNγ and TNF) and toxicity.

CART19 (University of Pennsylvania): Phase 1. CART19 is produced by transducing patients' unselected peripheral T cells with a CD19 antibody and the co-stimulatory molecule 4–1BB (CD137) signaling domain. In preclinical testing, incorporation of 4–1BB's signaling domain led to improved persistence and potency in mice.[58] 4–1BB was also chosen over CD28 as a stimulatory molecule to avoid enhanced IL-2 and TNF-α secretion associated with CD28 incorporation.

In a Phase 1 study, CART19 was given to 3 patients with CLL over a period of 3 d.[59,60] Patients had undergone lymphodepletion with bendamustine/rituximab or pentostatin/ cyclophosphamide. Patients were not given IL-2. All three patients experienced durable responses, including two CRs that were ongoing at the time of publication. Impressively, CART19 cells expanded and persisted in the blood and bone marrow of patients for a follow-up of six months. Moreover, it appears that a subset of CART-19 acquired features of central memory cells 4 mo following administration. Because patients received lymphodepleting treatments, CART19's exact contribution to the responses cannot be accurately assessed. The most common side effect was lymphopenia, which is expected given the expression of CD19 on B cells. Other toxicities included tumor lysis syndrome, fever, rigors, chills, liver enzyme elevation and cardiac dysfunction. Most adverse events were transient or manageable with corticosteroid therapy.

Summary

CD19 immunotherapy is emerging as a promising approach for B cell malignancies, as well as inflammatory diseases. With five anti-CD19 therapeutics in commercial clinical development to date, CD19 is one of the top five targets for antibody-based therapies developed by the pharmaceutical industry.[61] Even more noteworthy is the number of different antibody-based approaches being employed for this target, including bispecific antibodies, ADCs, Fc-engineered antibodies and CARs. Consequently, the importance of CD19 immunotherapy is not only in the direct clinical value, but also in validating novel antibody technologies. As numerous anti-CD19 programs have demonstrated clinical activity, it is likely that several of these agents will eventually receive regulatory approval. As each program has a different clinical profile, actual use of the different agents across the relevant indications is still hard to predict. Blinatumomab, a bispecific T cell engaging antibody is expected to be the first CD19 agent to reach the market in 2014 for the treatment of ALL.

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